Sleep Disorders and the Cardiovascular System

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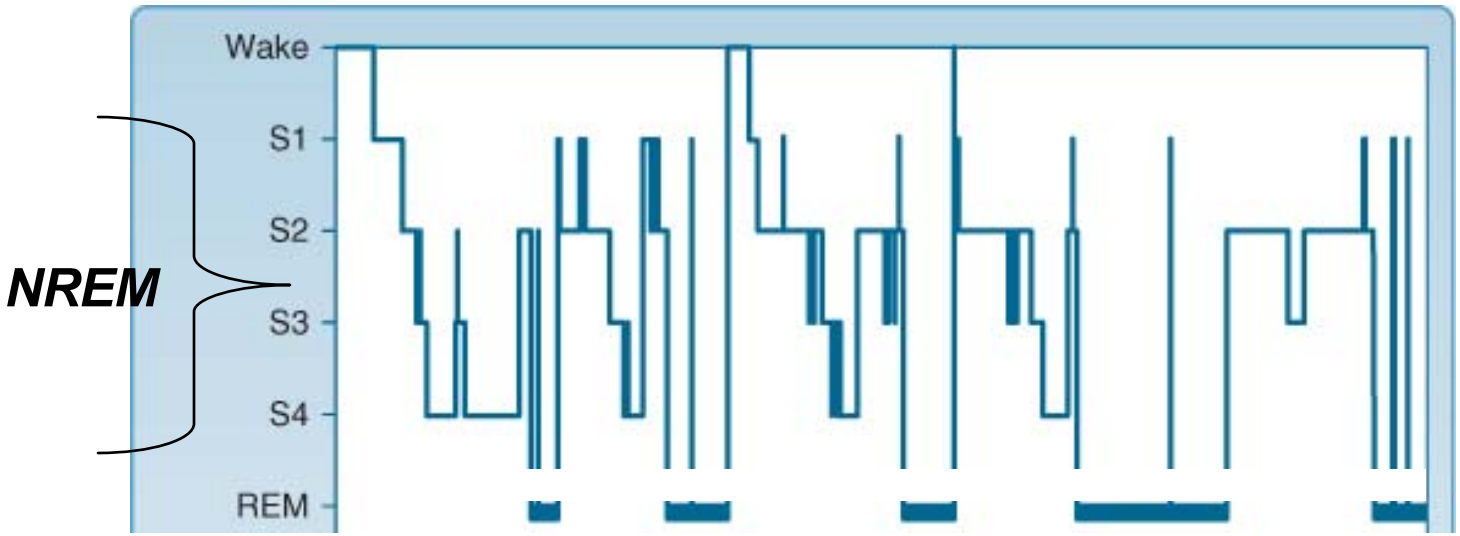
Disclosures

Grant / Research Support from

- ResMed Foundation
- Restore Medical

Normal Sleep

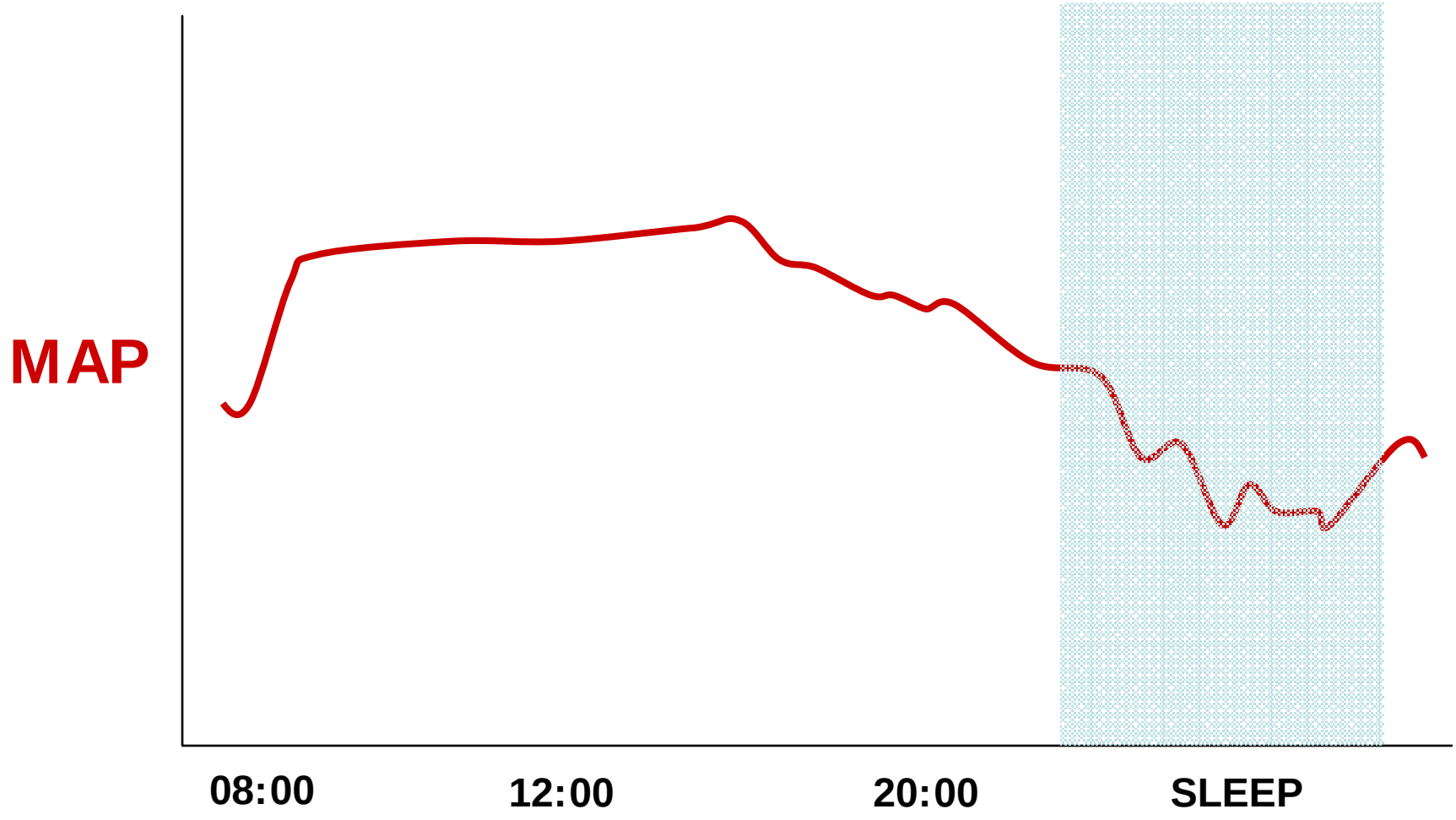


Sleep in the Healthy

- Non-REM (~75%)
  - ⇧ parasympathetic, ⇩ sympathetic
  - Cardiovascular quiescence and stability
  - Reduced blood pressure and heart rate

24 Hour Blood Pressure in Normals

"*Dipping*"



Sleep in the Healthy

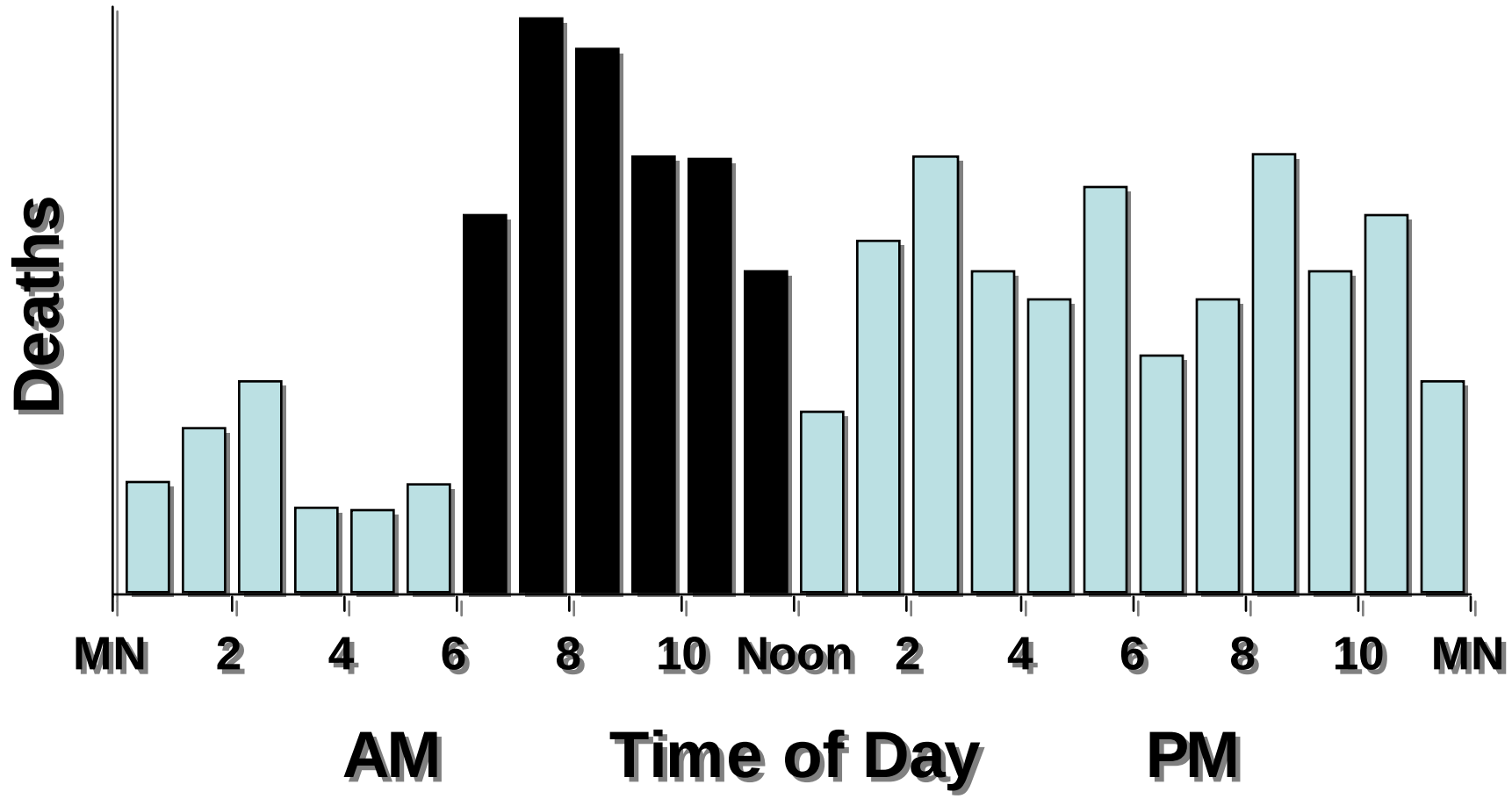
Rapid eye movement (REM) ~25%

- EEG looks awake--“paradoxical sleep”
- Brain electrical discharges may directly impact sympathetic tone and cardiac activity
- Irregular heart and breathing rhythm
- Modest hypoventilation and oxyhemoglobin desaturation

Dreams and Cardiovascular Homeostasis

- Anger and fear commonly elicited
- Emotion has been implicated in cardiac events during the day
- May be mediated by autonomic (sympathetic) tone

Sudden Cardiac Death

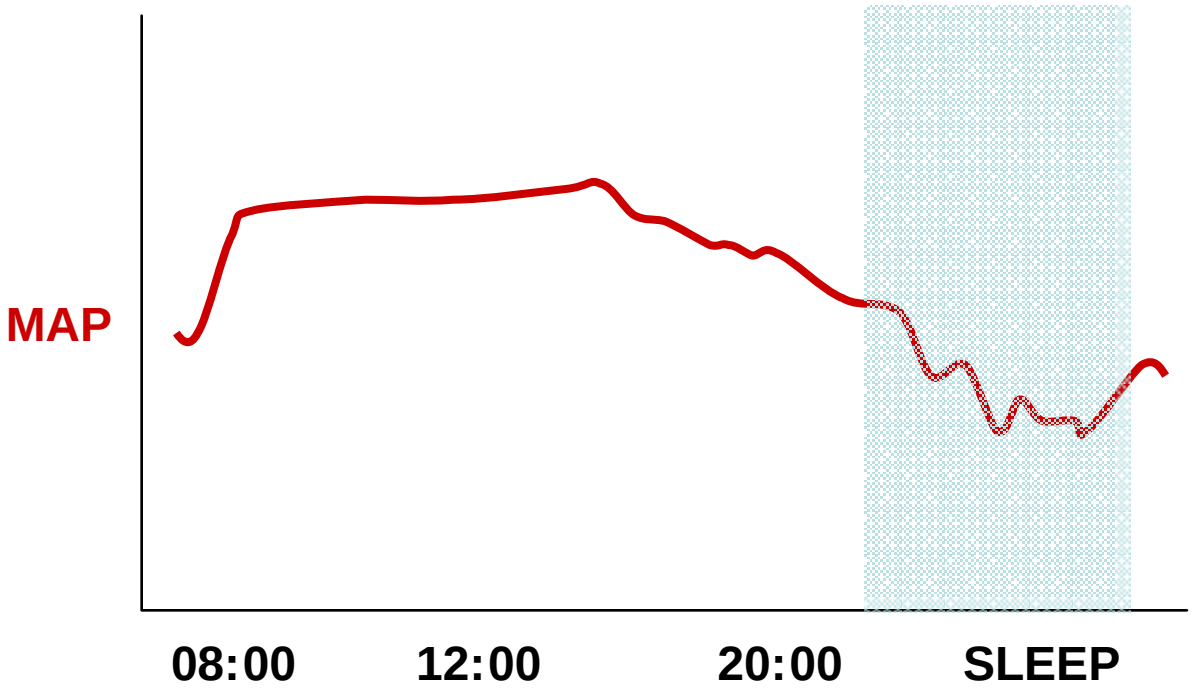


Muller JE, et al. Circulation, 1987
Willich SN, et al. Am J Cardiol, 1987

Non-Dipping of BP

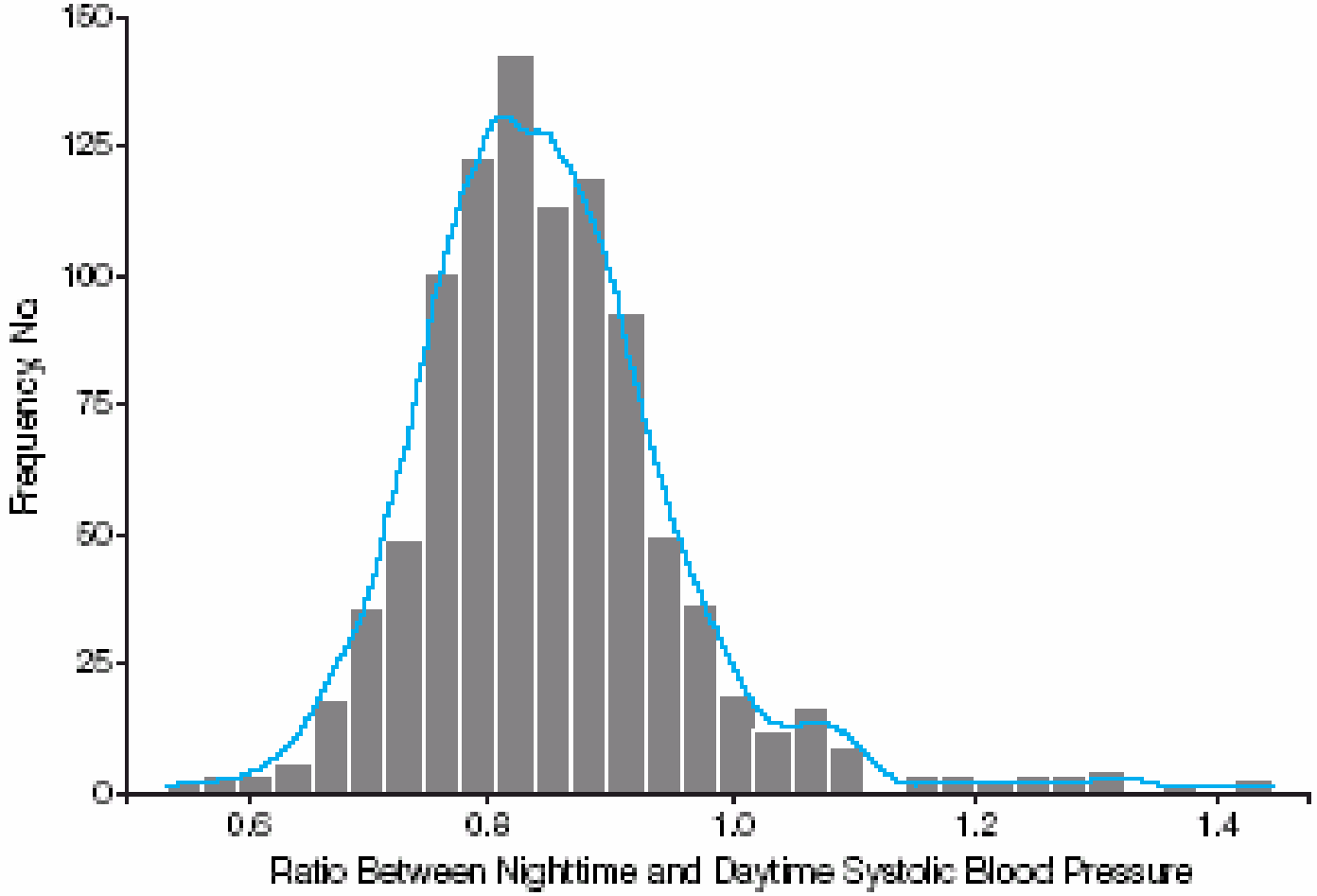
- Implicated in
  - Incident stroke
  - Diurnal hypertension
  - Drug resistant hypertension
  - Heart failure
  - Mortality

Loss of Normal BP Dip



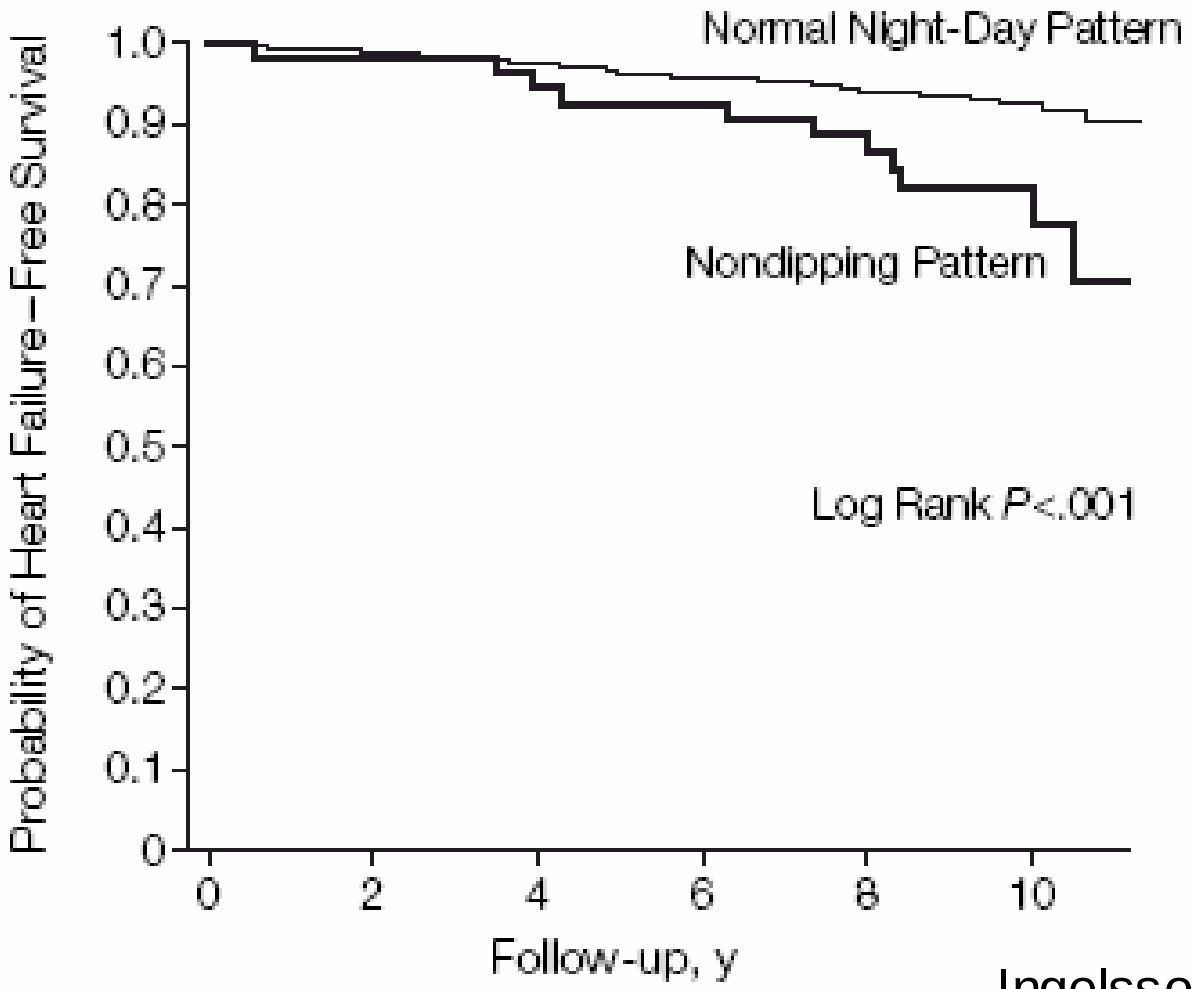
- Less BP dip
- Greater 24 hr BP load

Non-Dippers
Incident Heart Failure



Ingelsson, *JAMA*, 2006

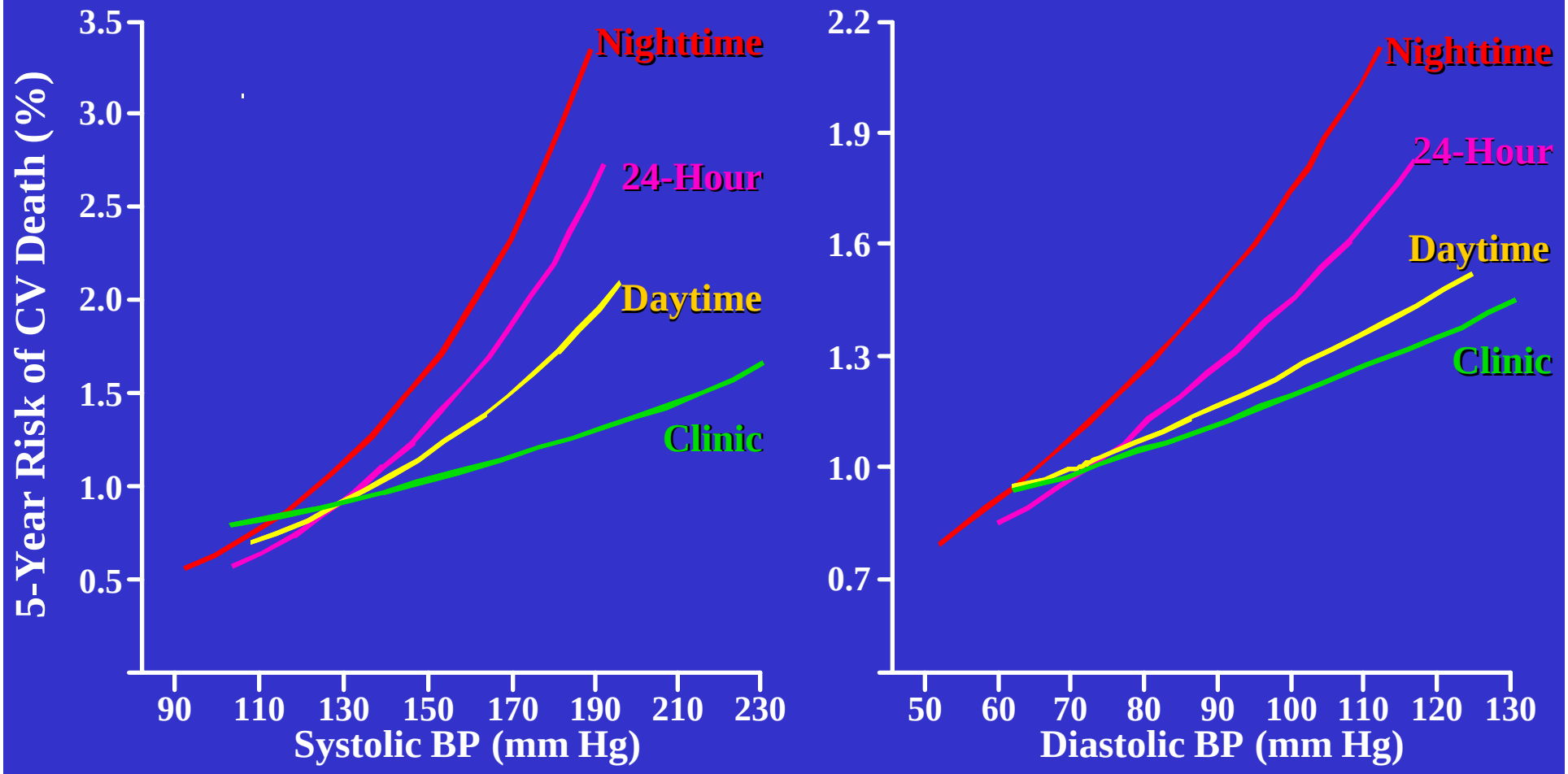
Heart Failure



Ingelsson, JAMA, 2006

Adjusted 5-year risk of CV death in the study cohort of 5292 patients for CBPM and ABPM

N = 5292



Dolan et al. Hypertension. 2005; 46:156-161

Sleep Duration / Debt

Effects on

- CV Homeostasis
- Hypertension
- Intermediary Factors (glucose metabolism)
- Mortality

Societal Sleep Debt

- NSF Sleep in America Poll
- Less sleep, more work
- 1 to 2 hours less sleep per night over past 40 yrs
- Truncates cardioprotective effects of (NREM) sleep; relative greater “load” of daytime stressors, sympathetic excitation

Sleep Debt and HTN

- Cross-sectional analyses; self report of sleep duration
  - NHANES I (National Health and Nutrition Examination Survey)
  - Sleep Heart Health Study

TABLE 3. HRs (95% CI) of Hypertension Incidence Over the Follow-Up Period by Sleep Duration at Baseline

Hours of Sleep	Model 1*	Model 2†	Model 3‡	Model 4§
Ages 32 to 86 y				
≤5 h	1.76 (1.37 to 2.56)	1.51 (1.17 to 1.95)	1.44 (1.11 to 1.85)	1.32 (1.02 to 1.71)
6 h	1.11 (0.91 to 1.35)	1.07 (0.88 to 1.31)	1.06 (0.87 to 1.29)	1.01 (0.82 to 1.23)
7 to 8 h	1.00	1.00	1.00	1.00
≥9 h	1.32 (0.99 to 1.75)	1.18 (0.88 to 1.57)	1.13 (0.85 to 1.51)	1.12 (0.84 to 1.50)
Ages 32 to 59 y				
≤5 h	2.10 (1.58 to 2.79)	1.84 (1.38 to 2.46)	1.74 (1.30 to 2.32)	1.60 (1.19 to 2.14)
6 h	1.18 (0.94 to 1.48)	1.14 (0.91 to 1.43)	1.13 (0.90 to 1.41)	1.05 (0.83 to 1.31)
7 to 8 h	1.00	1.00	1.00	1.00
≥9 h	0.98 (0.64 to 1.50)	0.91 (0.59 to 1.39)	0.91 (0.59 to 1.40)	0.92 (0.60 to 1.41)
Ages 60 to 86 y				
≤5 h	1.05 (0.63 to 1.75)	0.86 (0.51 to 1.46)	0.86 (0.51 to 1.47)	0.85 (0.50 to 1.45)
6 h	0.90 (0.58 to 1.38)	0.88 (0.57 to 1.36)	0.85 (0.55 to 1.32)	0.86 (0.56 to 1.33)
7 to 8 h	1.00	1.00	1.00	1.00
≥9 h	1.54 (1.03 to 2.30)	1.36 (0.90 to 2.06)	1.32 (0.87 to 2.01)	1.31 (0.86 to 1.99)

*Model 1, unadjusted.

†Model 2, adjusted for daytime sleepiness, depression, physical activity, alcohol consumption, salt consumption, smoking, pulse rate, and gender.

‡Model 3, adjusted for the variables in model 2 plus education, age, and ethnicity.

§Model 4, adjusted for the variables in model 3 plus overweight/obesity and diabetes.

Gangwisch, 2006

Sleep Heart Health Study

Table 2—Odds ratios (95% Confidence Intervals)* for Hypertension by Reported Usual Sleep Duration

Usual sleep duration, h/night	Model 1 Unadjusted	p < .0001	Model 2 Adjusted for age, sex, race, and AHI	p < .0001	Model 3 Adjusted for all covariates in Model 2 plus BMI	P < .0001
< 6	1.86 (1.54 – 2.26)		1.67 (1.36 – 2.05)		1.66 (1.35 – 2.04)	
6 to < 7	1.25 (1.08 – 1.44)		1.20 (1.03 – 1.39)		1.19 (1.02 – 1.39)	
7 to < 8	1.0 (referent)		1.0 (referent)		1.0 (referent)	
8 to < 9	1.31 (1.15 – 1.49)		1.19 (1.04 – 1.36)		1.19 (1.04 – 1.37)	
≥9	1.75 (1.42 – 2.15)		1.31 (1.05 – 1.63)		1.30 (1.04 – 1.62)	

*Odds ratios are for the presence of hypertension, from categorical logistic regression models using 7 to < 8 hours of sleep per night as the referent category. P values reflect the overall significance level of the effect of sleep duration on hypertension, based on the likelihood ratio chi² with 4 degrees of freedom. AHI refers to apnea-hypopnea index.

Gottlieb, 2006

Sleep and Mortality: A Population-Based 22-Year Follow-Up Study

Christer Hublin, MD, PhD[1]; Markku Partinen, MD, PhD[2]; Markku Koskenvuo, MD, PhD[3]; Jaakko Kaprio, MD, PhD[3,4]

Table 10—Age and Sex Adjusted Risk of Total Mortality (Hazard Ratio and 95% Confidence Interval) in 1982-2003 by Age-Groups (Age at Entry to the Follow-Up). All Three Variables Measured in 1981 and Mutually Adjusted in the Same Model

	All N = 21268	24-39 Years N = 11747	40-54 Years N = 5759	55 Years Or More N = 3762
Sleep Length				
short	1.27 (1.16-1.39)	1.84 (1.48-2.27)	1.28 (1.07-1.55)	1.15 (1.03-1.29)
average	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
long	1.27 (1.17-1.38)	1.40 (1.12-1.76)	1.15 (0.95-1.39)	1.25 (1.12-1.39)
Sleep Quality				
sleeping well	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
sleeping fairly well	1.06 (0.98-1.14)	1.22 (1.02-1.46)	1.10 (0.95-1.28)	0.96 (0.87-1.07)
sleeping fairly poorly/poorly	1.17 (1.04-1.31)	2.00 (1.50-2.66)	1.22 (0.96-1.54)	1.05 (0.91-1.21)
Use Of Hypnotics And/Or Tranquilizers				
no	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
infrequent	1.07 (0.93-1.23)	1.58 (1.12-2.21)	1.33 (1.04-1.71)	0.88 (0.73-1.06)
frequent	1.70 (1.45-1.99)	2.72 (1.82-4.08)	2.01 (1.50-2.70)	1.49 (1.23-1.80)

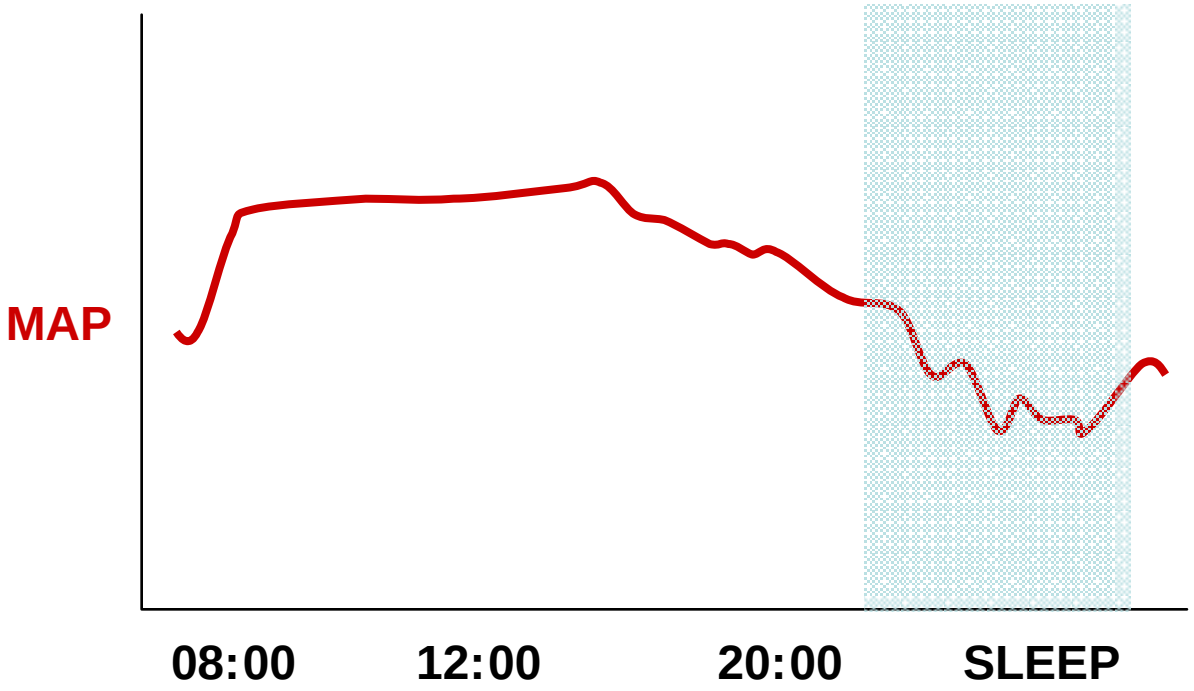
* short = < 7 □

Sleep 2007

Sleep Loss/Debt:

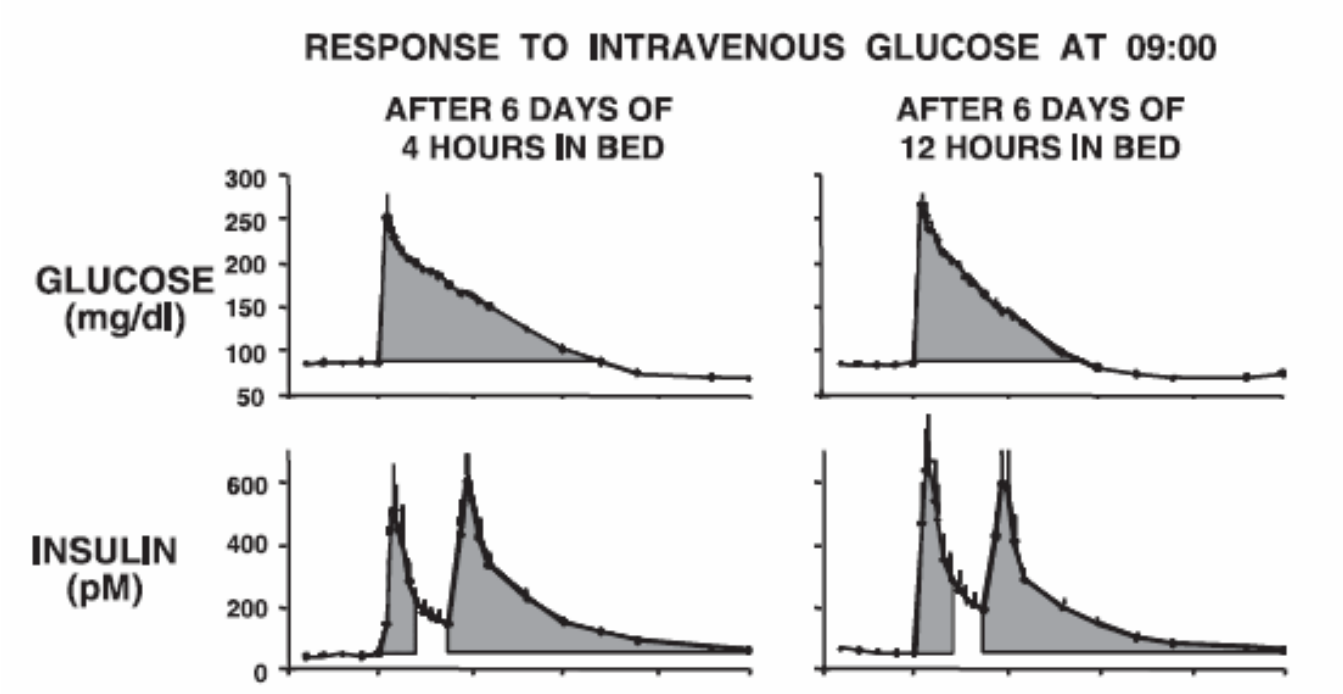
Intermediary Mechanisms

Loss of Normal BP Dip



- Less BP dip
- Greater 24 hr BP load
- More daytime stressors

Decreased Insulin Sensitivity

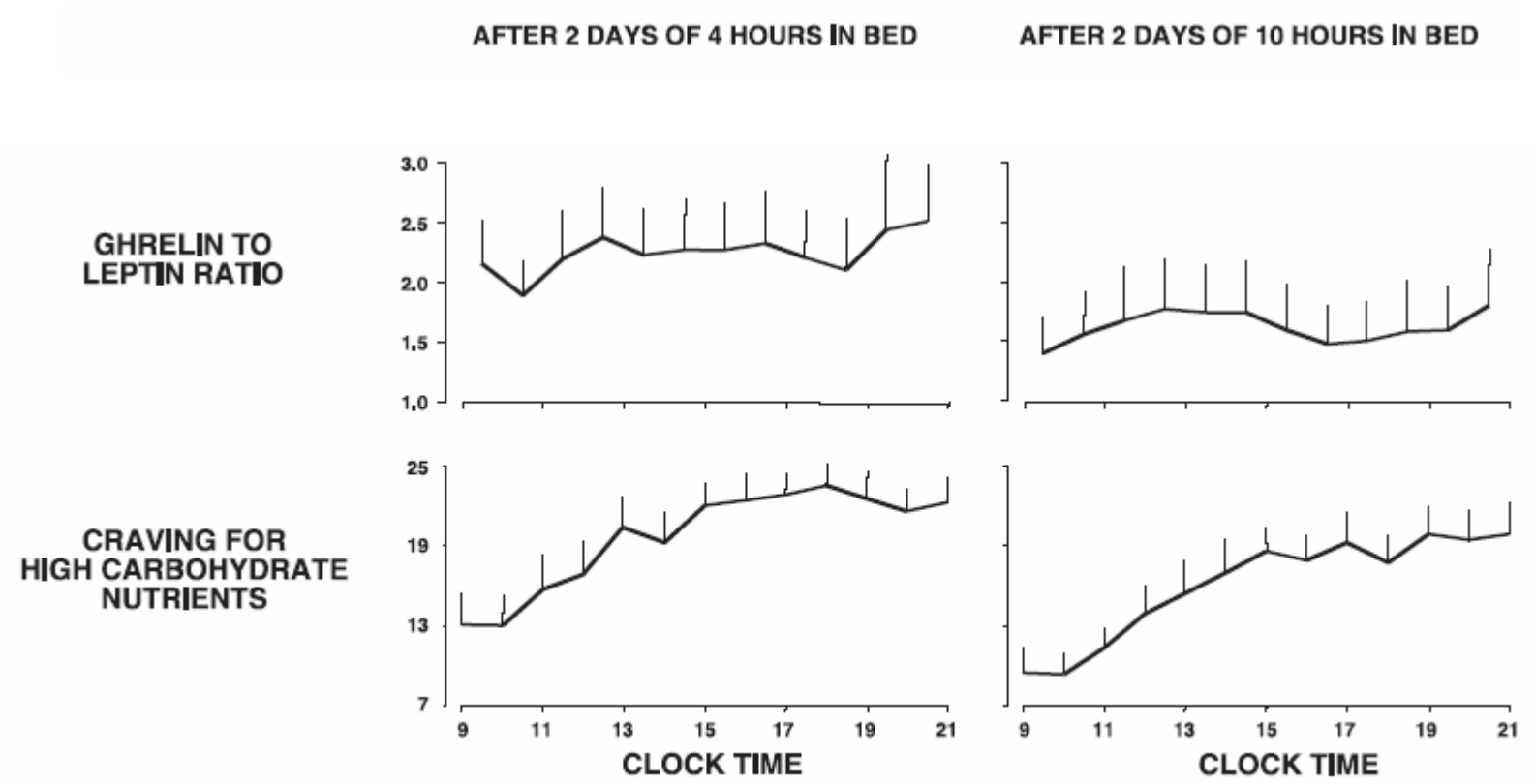


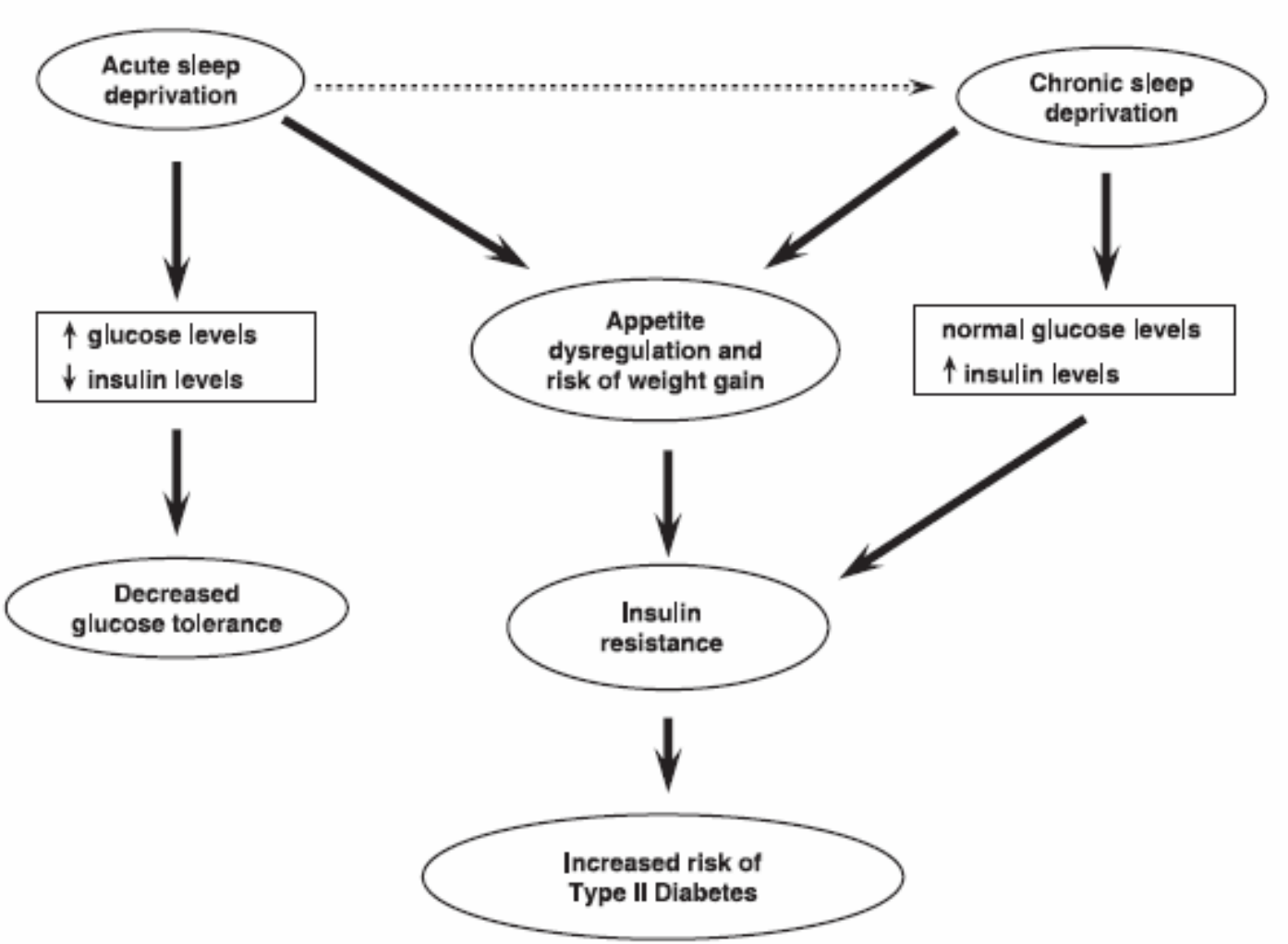
Spiegel, 2005

Leptin-satiety hormone
Ghrelin-appetite hormone

Leptin knockout mice

Appetite Hormone Dysregulation





Spiegel, 2005

PEDIATRICS®

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Shorter Sleep Duration Is Associated With Increased Risk for Being Overweight at Ages 9 to 12 Years

Julie C. Lumeng, MD[a,b], Deepak Somashekar, BS[a], Danielle Appugliese, MPH[c], Niko Kaciroti, PhD[a], Robert F. Corwyn, PhD[d], Robert H. Bradley, PhD[e]

National Institute of Child Health and Human Development Study of Early Child Care and Youth Development (NICHD-SECCYD)

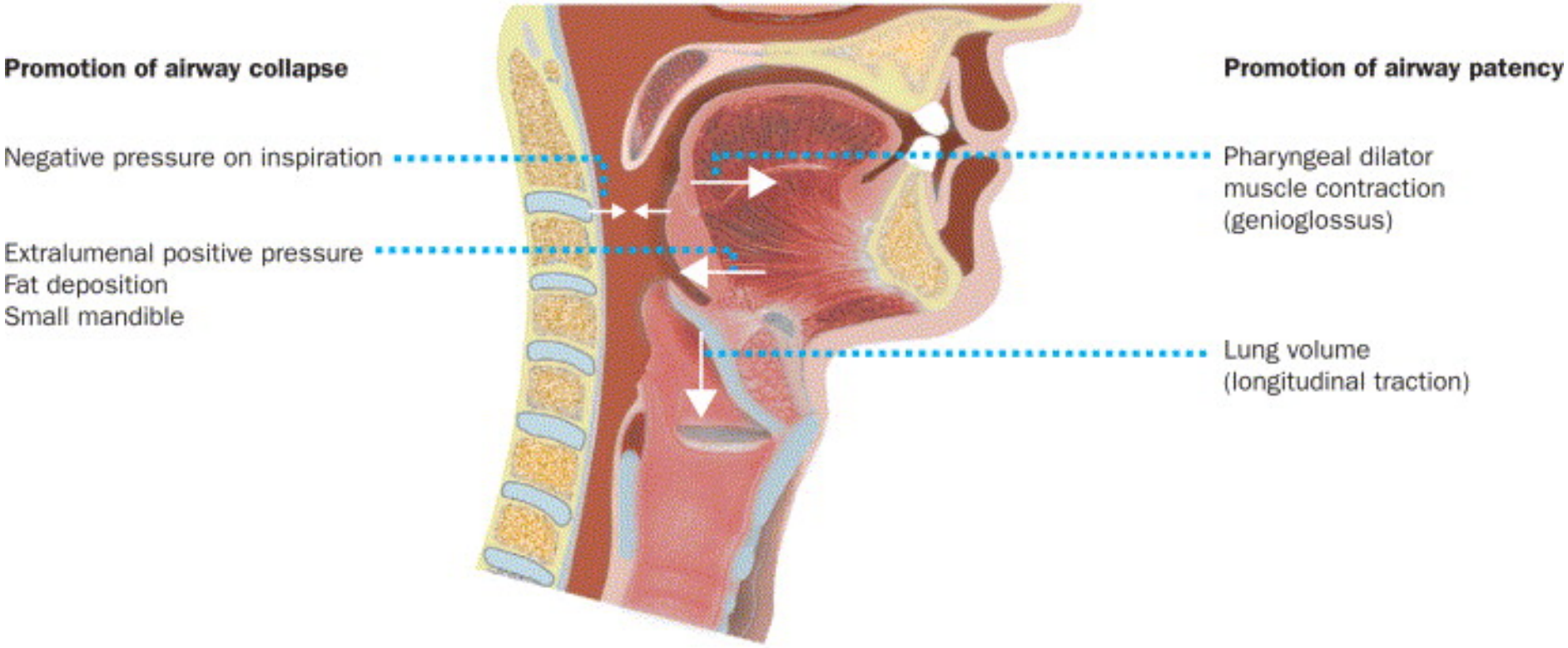
TABLE 4 Sleep Duration Between 3rd and 6th Grades and Overweight in 6th Grade ($N = 706$)

Characteristic	OR (95% CI)
Sleep duration in 3rd grade, h	0.60 (0.36–0.99)[a]
Change in sleep duration between 3rd and 6th grades, h	0.68 (0.44–1.06)
Gender (female vs male)	0.82 (0.40–1.71)
Race (other vs white)	1.42 (0.54–3.73)
Maternal education, y	0.84 (0.72–0.99)[a]
BMI *z* score at 3rd grade	127.4 (48.0–337.8)[b]

[a] $P < .05$.
[b] $P < .001$.

Obstructive Sleep Apnea (OSA)

#1 Determinant of Upper Airway Collapse = Fat deposition

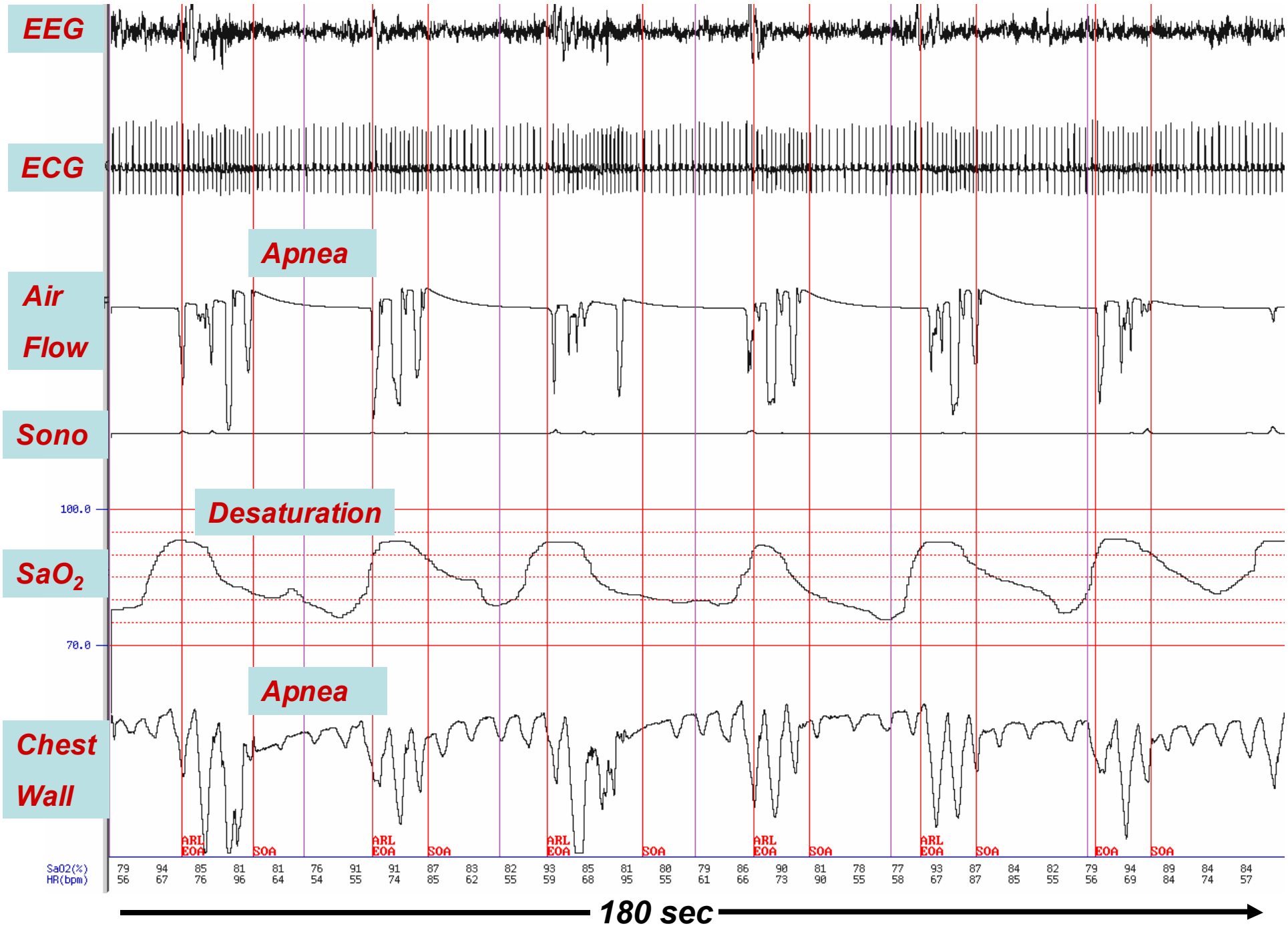


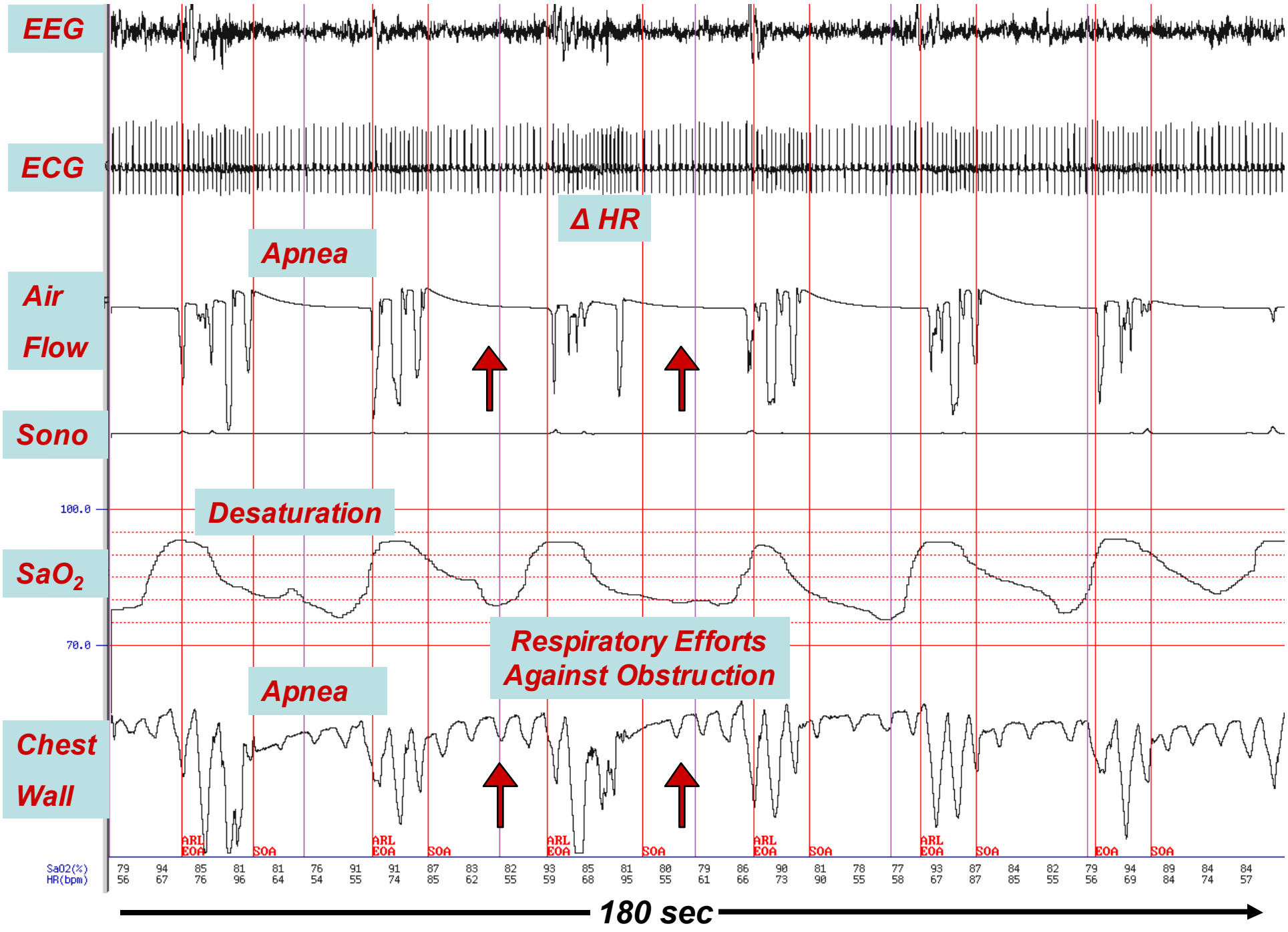
Malhotra and White, *Lancet*, 2002

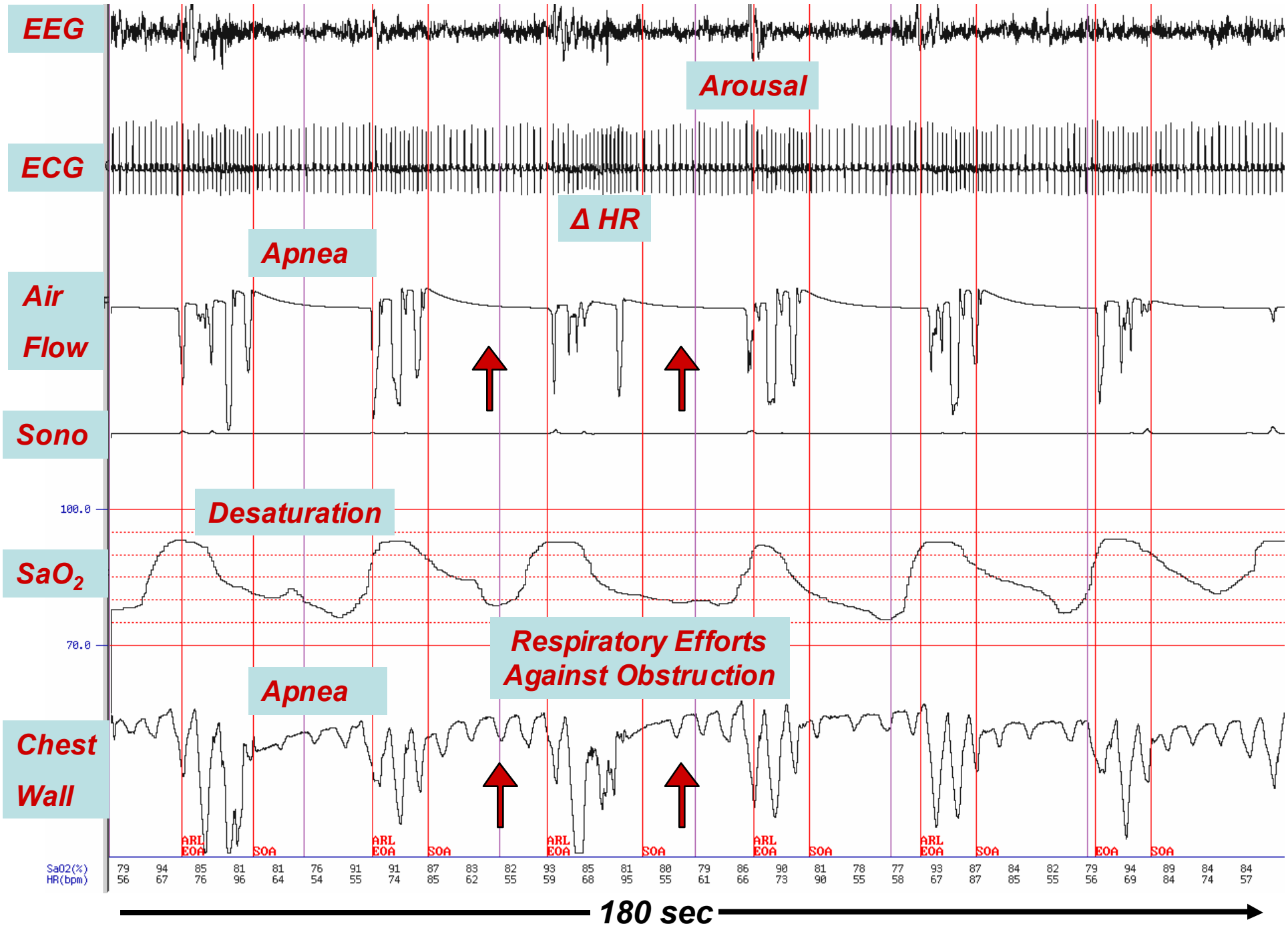
OSA

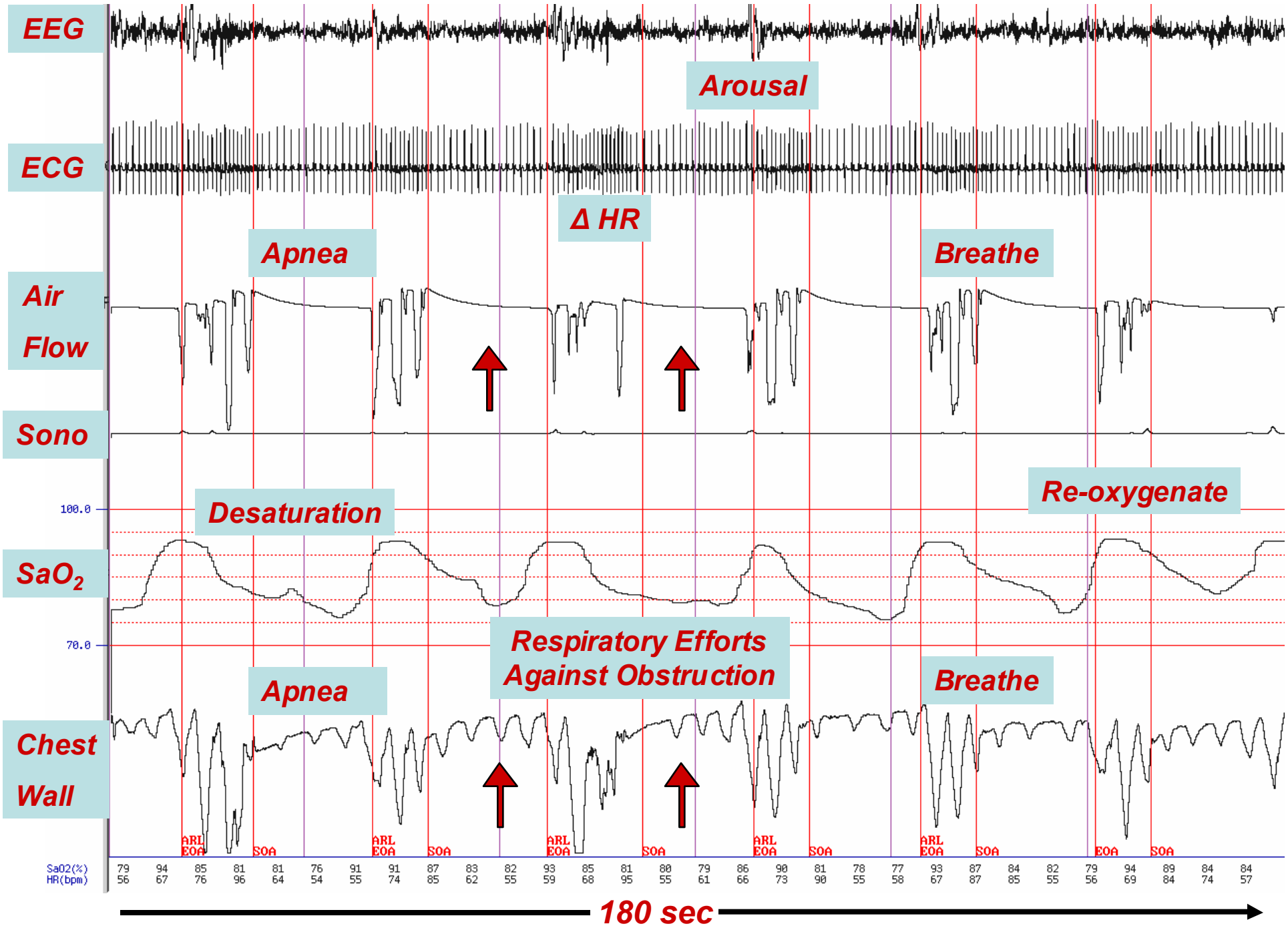
- Repetitive
  - arousals from sleep (up to 500 per night)
  - episodes of de-oxygenation/re-oxygenation
- Severity graded by the apnea-hypopnea index (AHI)
- Treatment: CPAP by mask, wt loss

Acute Pathophysiologic Cardiovascular Mechanisms









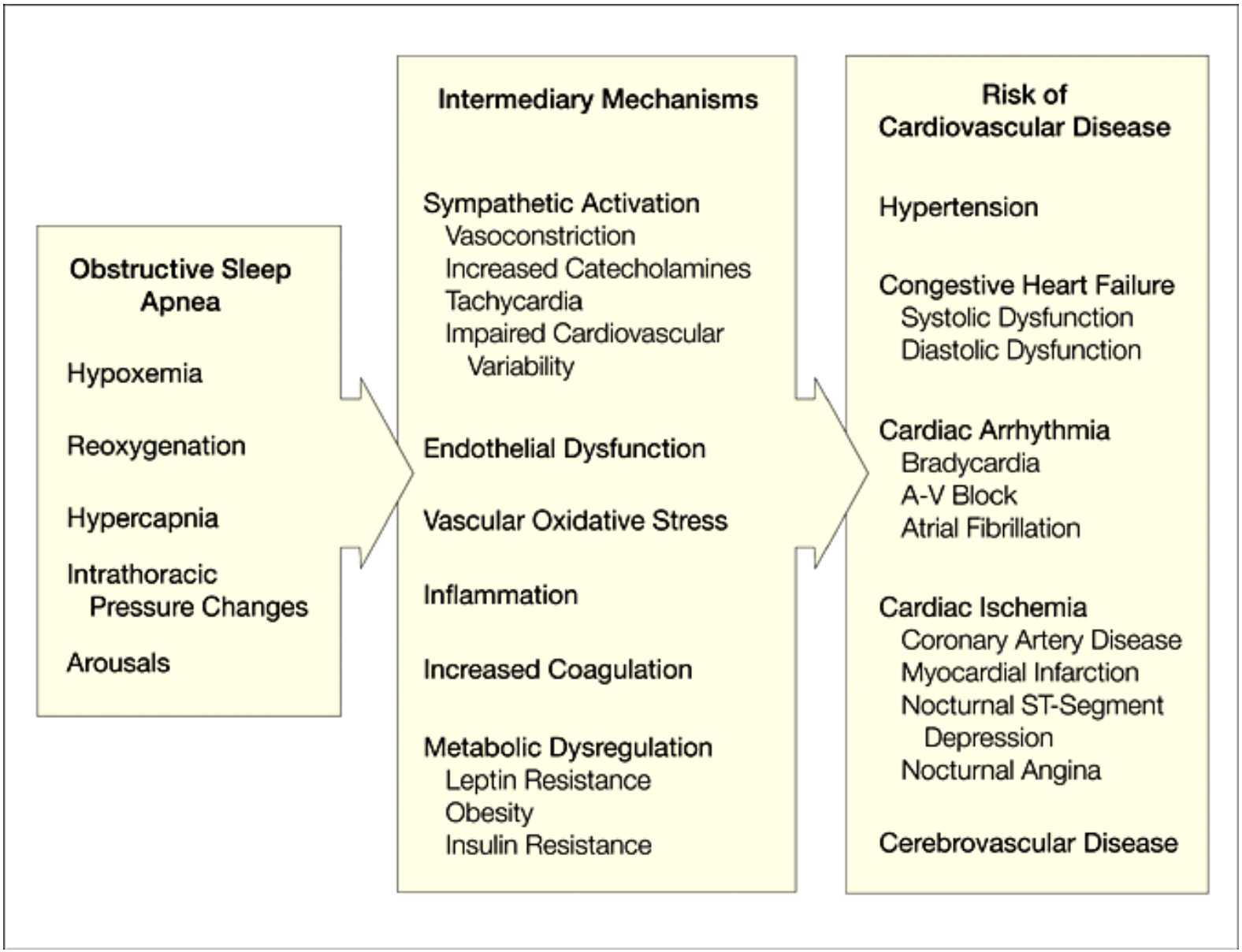
High Risk of Traffic Accidents

TABLE 2. RELATION BETWEEN SLEEP APNEA AND TRAFFIC ACCIDENTS.*

APNEA–HYPOPNEA INDEX†	CASE PATIENTS (N=102)	CONTROLS (N=152)	UNADJUSTED OR (95% CI)	ADJUSTED OR (95% CI)‡
	no. of patients (%)			
≥5	29 (28.4)	7 (4.6)	8.2 (3.4–19.6)	11.1 (4.0–30.5)
≥10	21 (20.6)	6 (3.9)	6.3 (2.4–16.2)	7.2 (2.4–21.8)
≥15	17 (16.7)	5 (3.3)	5.8 (2.1–16.5)	8.1 (2.4–26.5)

TABLE 3. RISK OF A TRAFFIC ACCIDENT ACCORDING TO THE PRESENCE OR ABSENCE OF SLEEP APNEA AND ALCOHOL INTAKE ON THE DAY OF THE ACCIDENT.

VARIABLE	APNEA–HYPOPNEA INDEX ≥10	APNEA–HYPOPNEA INDEX <10	OR (95% CI)*
Case patients			
Alcohol consumed on day of accident	11	24	11.2 (3.8–32.9)
No alcohol consumed on day of accident	8	49	4.0 (1.3–12.0)
Controls	6	146	1.0

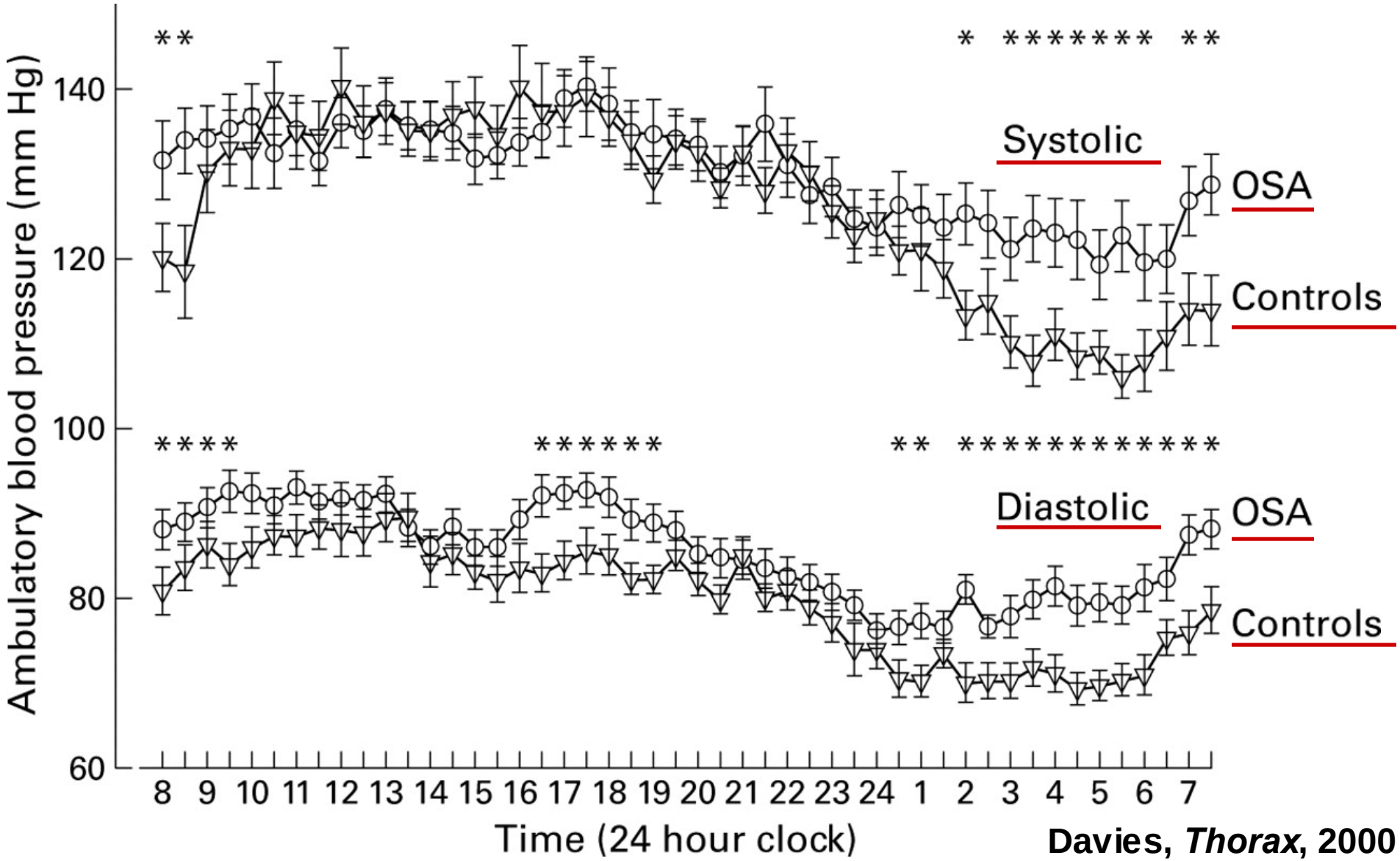


Shamsuzzaman, *JAMA* 2003

Clinical Cardiovascular Disease

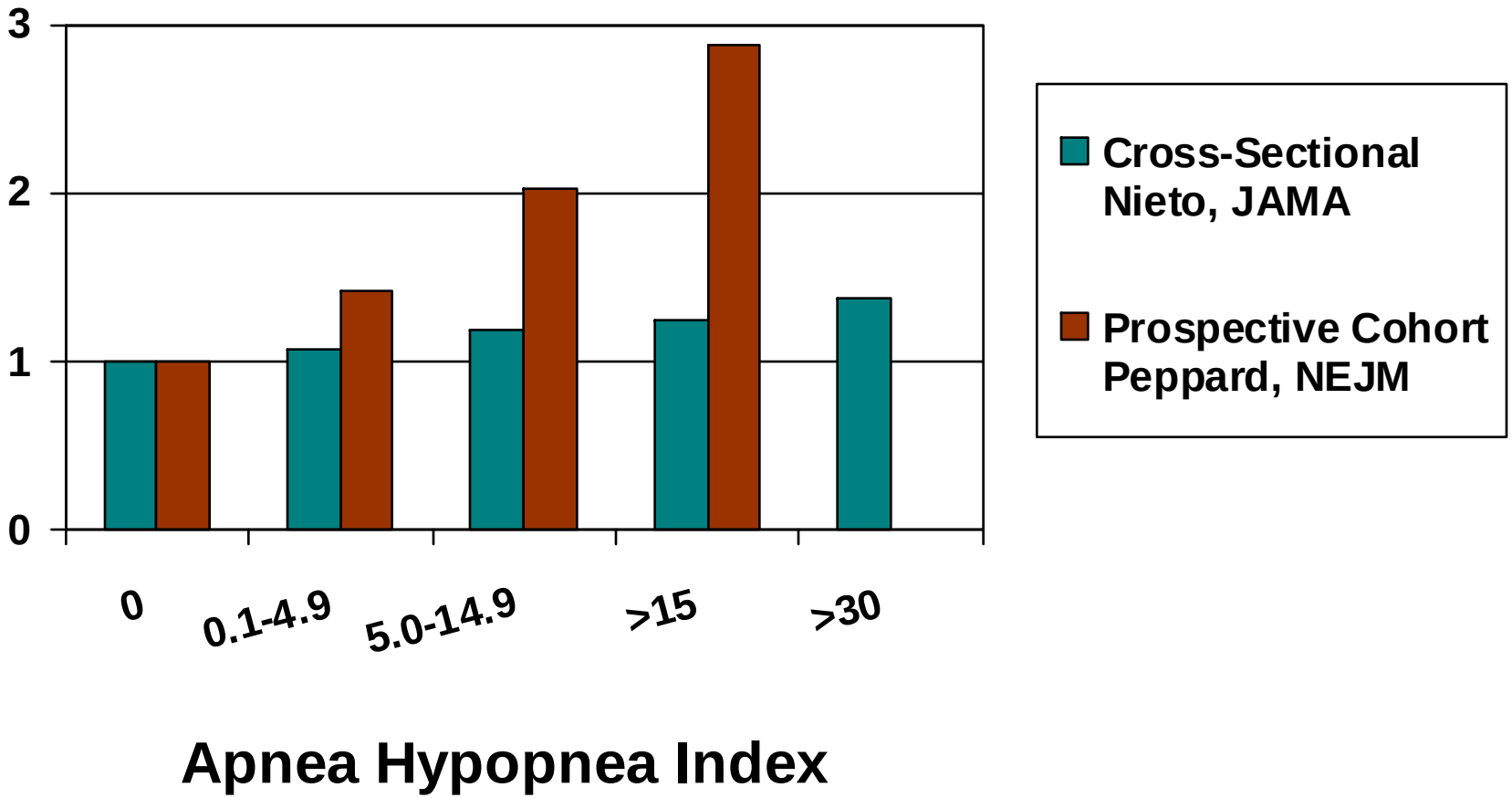
Systemic Hypertension

24hr BP—loss of dipping



Davies, *Thorax*, 2000

Odds Ratio of HTN
Impact of Milder OSA

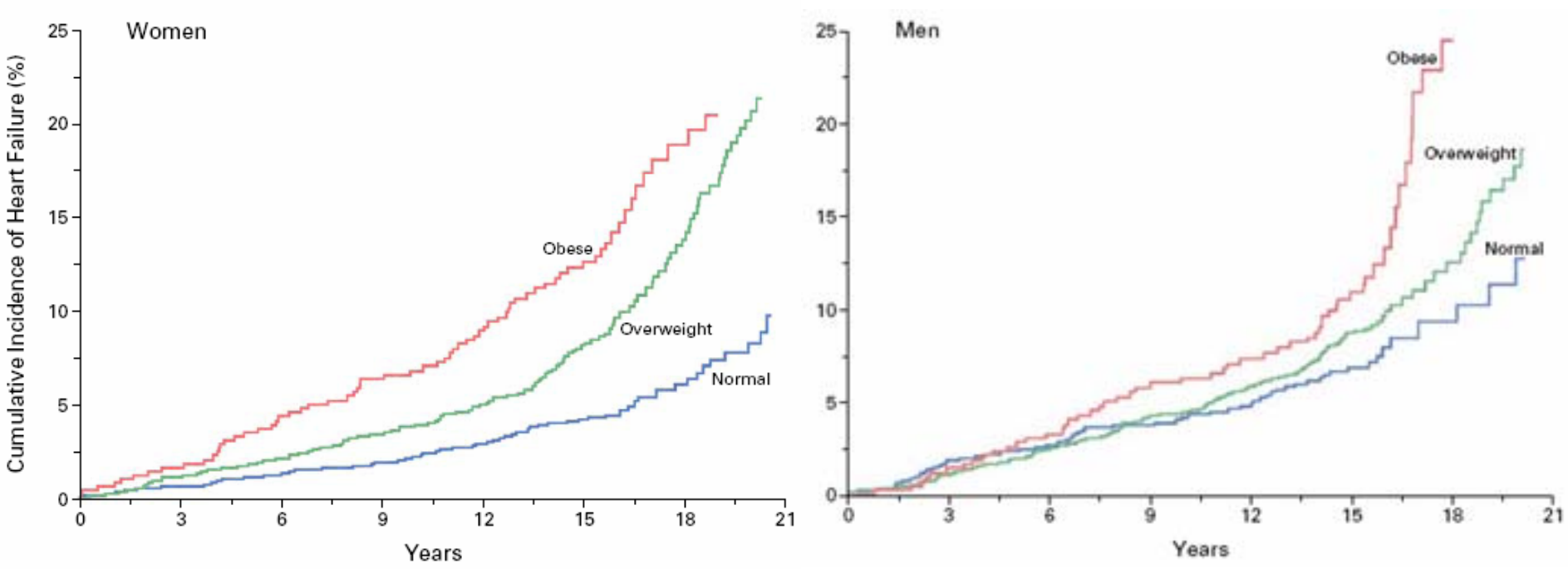


Heart Failure

A Top Medicare Expenditure

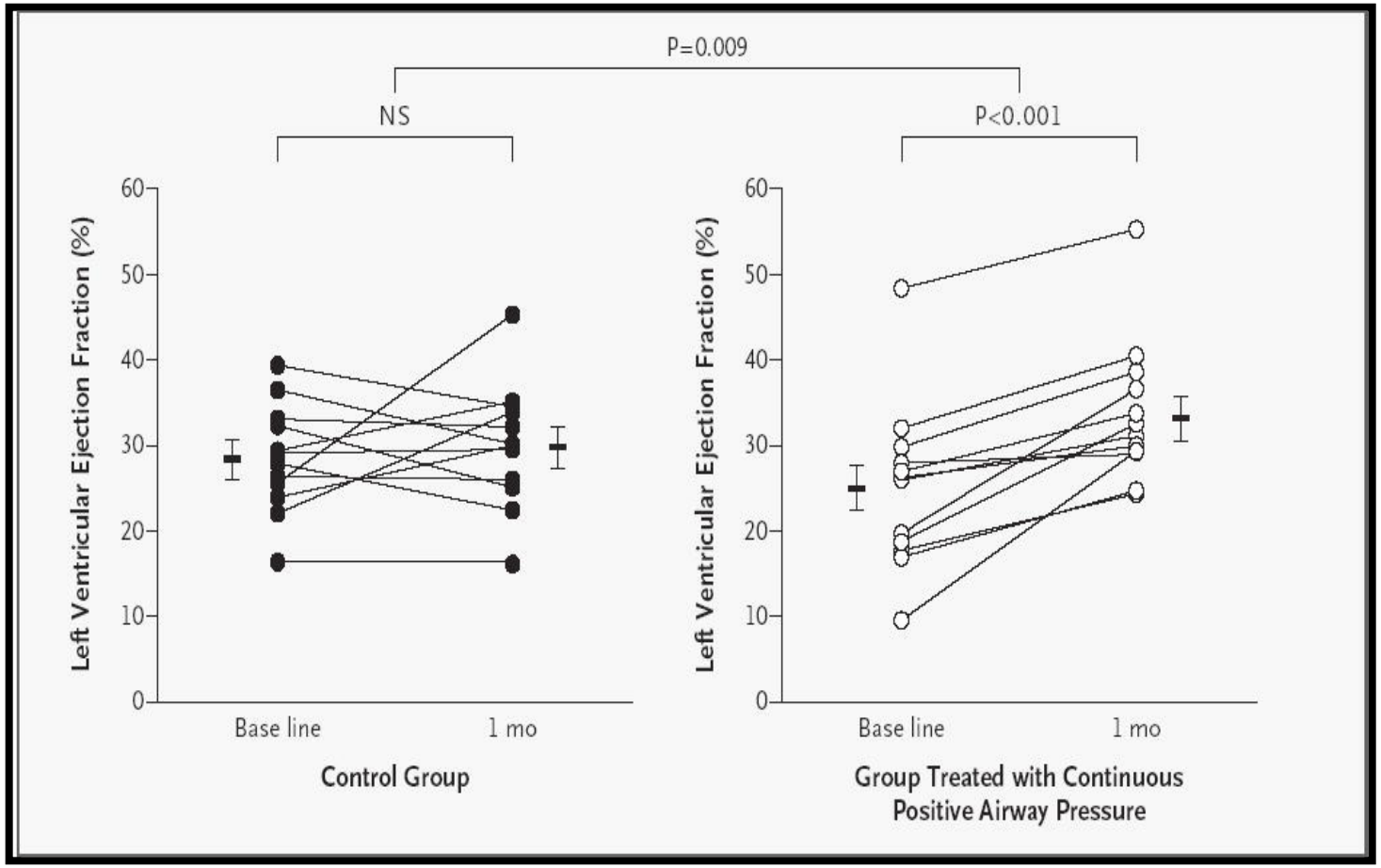
Obesity As A Risk Factor for Heart Failure

? Mediated in Part by OSA



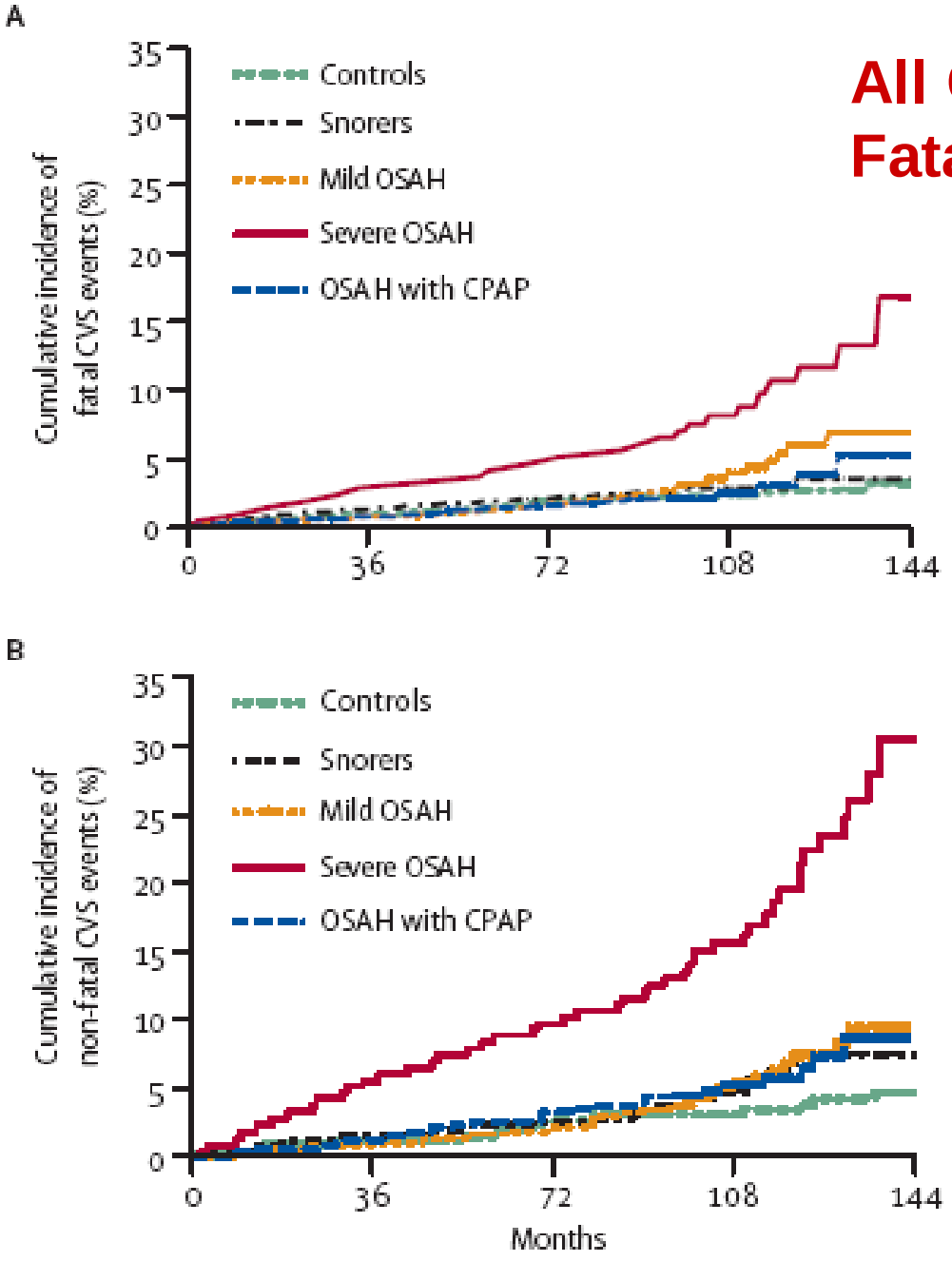
Kenchaiah et al, *NEJM*, 2002

OSA Treatment May Improve Heart Failure Indices



Kaneko, et al. *N Engl J Med* 2003

All Cardiovascular Events Fatal and Non-Fatal



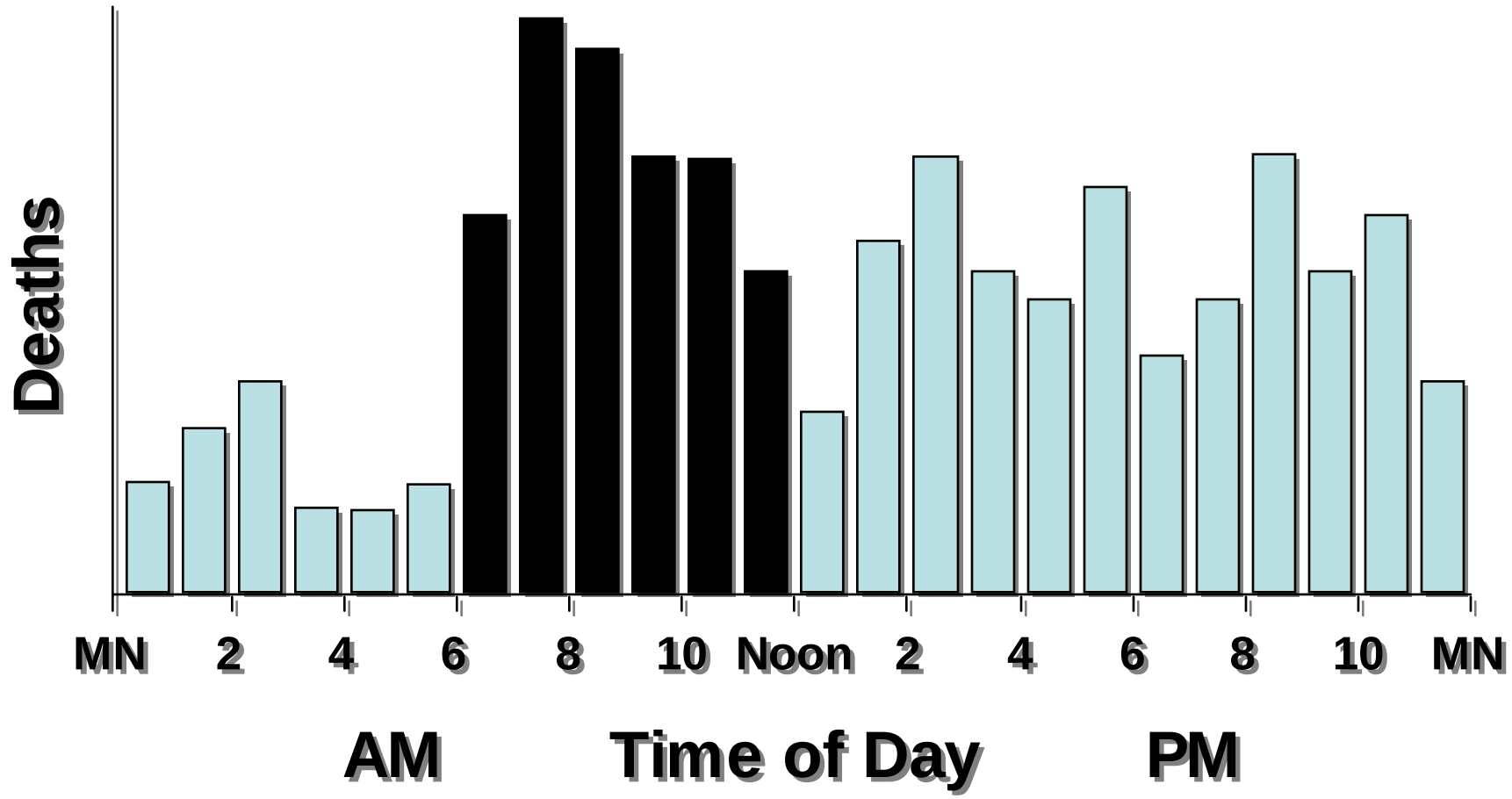
Observational Cohort

>1600 men (50 yo) followed for 10.1 years

36% of patients with severe OSA refused CPAP

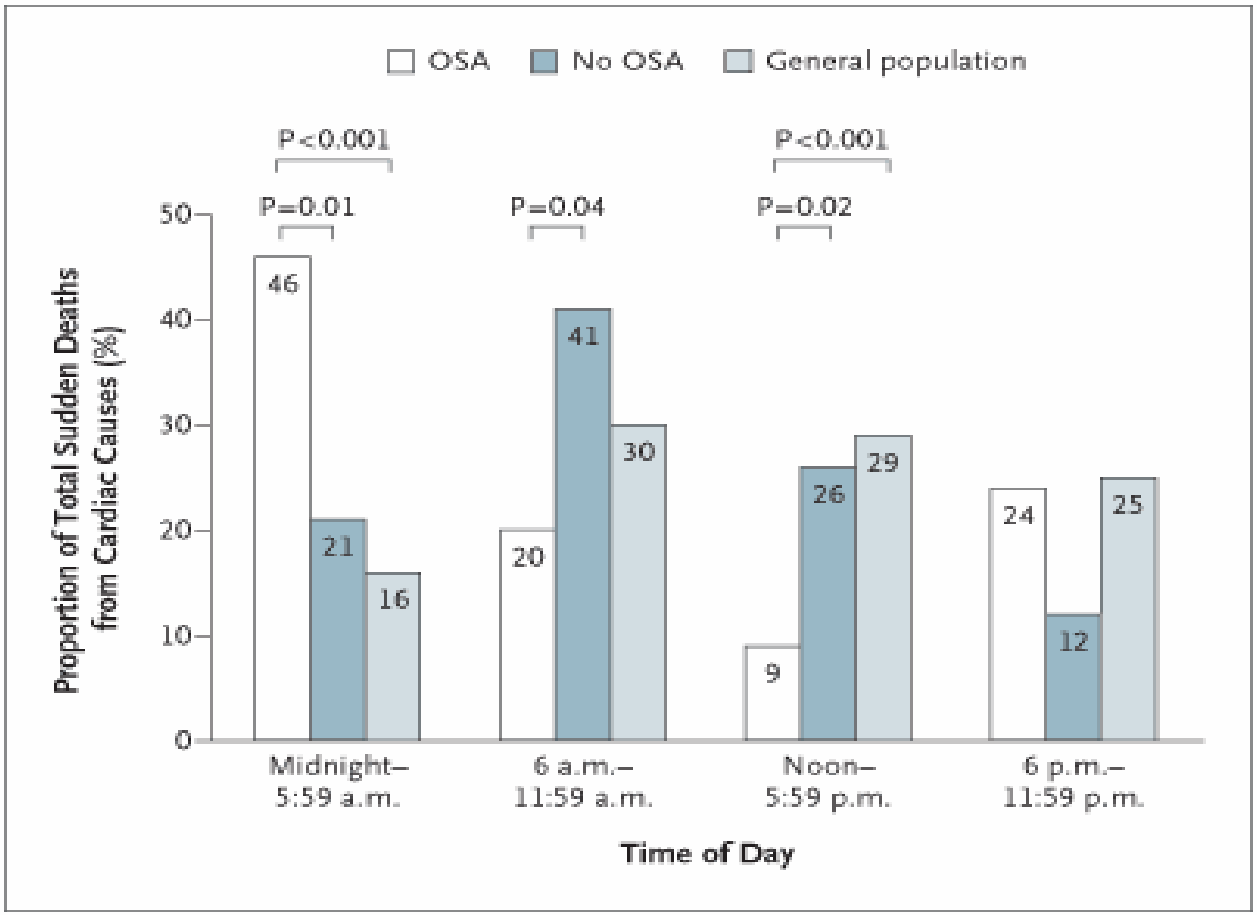
Marin, *Lancet*, 2005

Sudden Cardiac Death



Muller JE, et al. Circulation, 1987
Willich SN, et al. Am J Cardiol, 1987

OSA and Sudden Cardiac Death

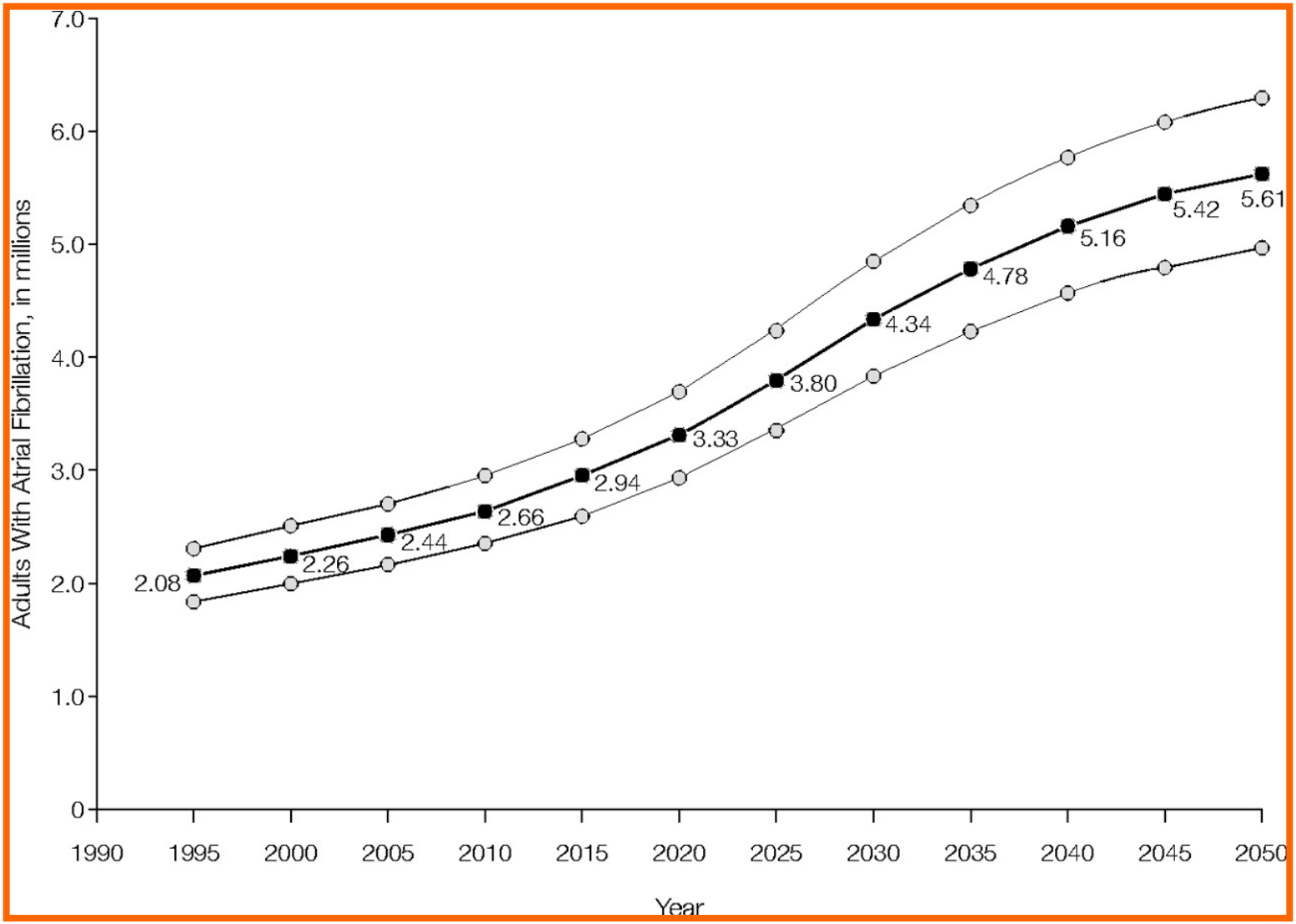


Gami, *NEJM*, 2005

OSA and Atrial Fibrillation

- The most common sustained arrhythmia (5 million)
- A major risk factor for stroke

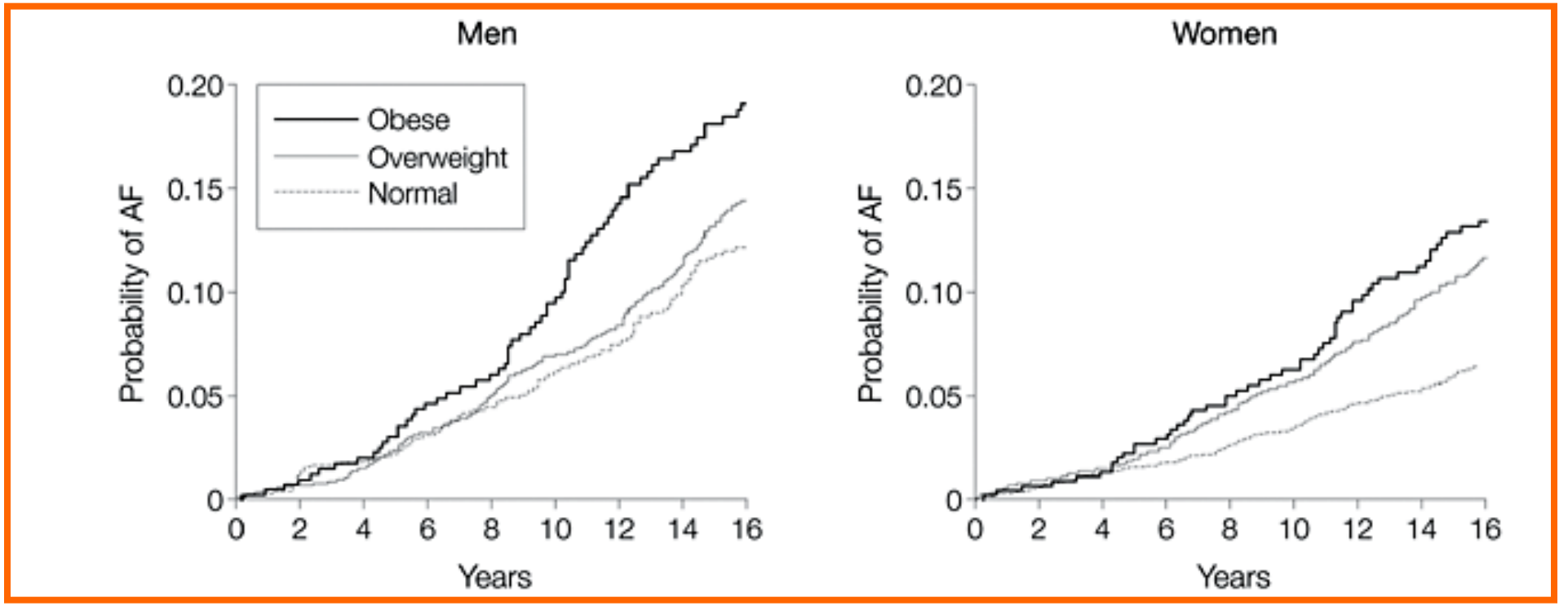
Prevalence of AF will double by 2050



Go, Hylek, Phillips, et al. JAMA 2001

Obesity As A Risk Factor for A Fib

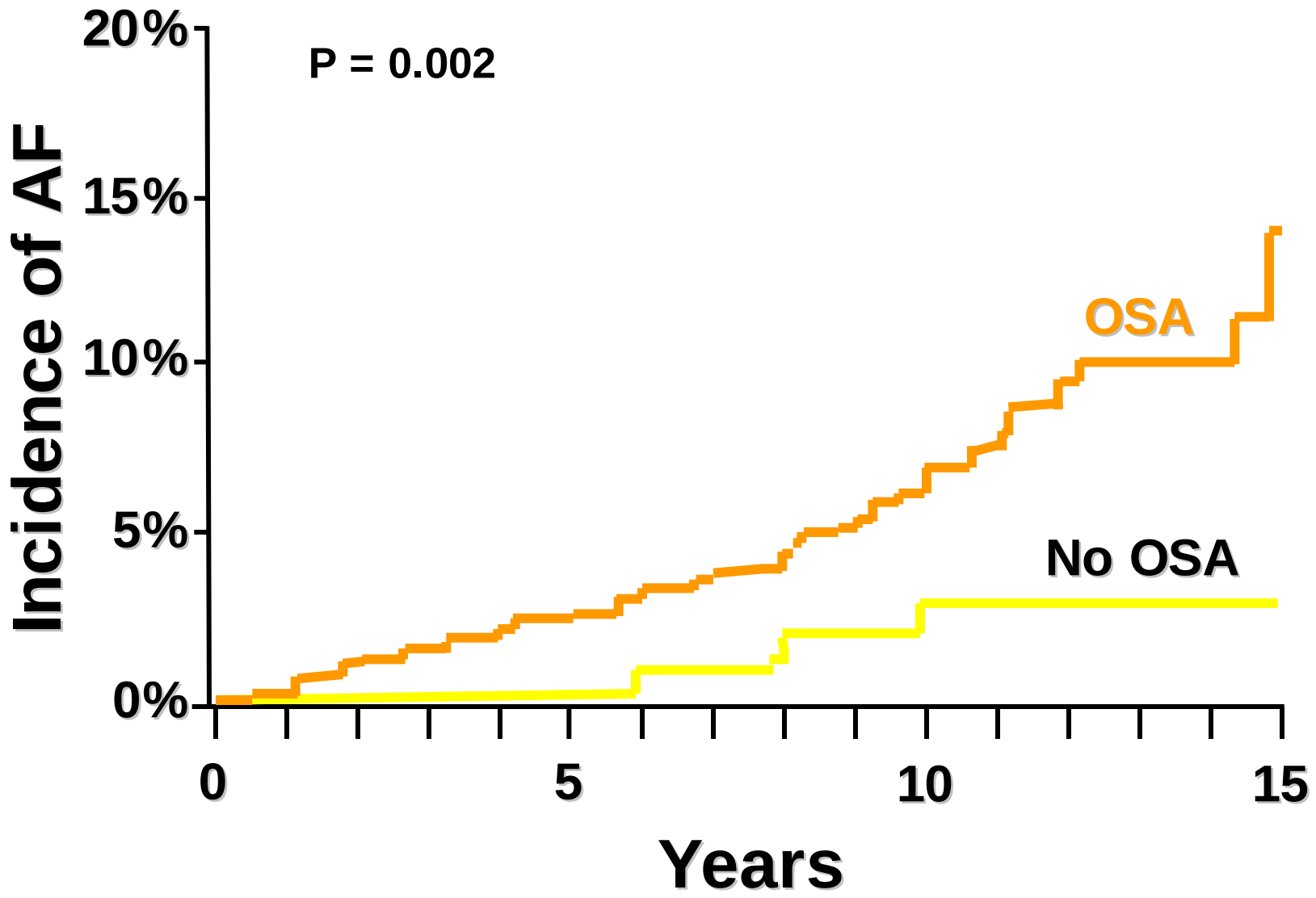
? Mediated in Part by OSA



Left Atrial Size Correlates with BMI

Wang, Parise, Levy JAMA 2004

Incidence of AF by OSA Status



C-reactive Protein, Obstructive Sleep Apnea, and Cognitive Dysfunction in School-aged Children

David Gozal[1,2], Valerie McLaughlin Crabtree[1], Oscar Sans Capdevila[1,2], Lisa A. Witcher[1], and Leila Kheirandish-Gozal[1,2]

- OSA may impair neurocognitive function in children
- May be mediated by inflammation