OBSTRUCTIVE SLEEP APNEA AND DIABETES MELLITUS

The content of this Telehealth presentation, in its enduring state, will expire on 11/20/2016 from this date on CNE's can no longer be awarded.

Measures have been taken, by the Utah Department of Health, Bureau of Health Promotions, to ensure no conflict of interest in this activity.

OBSTRUCTIVE SLEEP APNEA AND DIABETES MELLITUS

Krishna M. Sundar, MD
Associate Professor (Clinical), Pulmonary Division
Medical Director, Sleep-Wake Center
University of Utah

DM and OSA – two common diseases

Diabetes mellitus

- 25.8 million of US population has DM (8.3%)
- 18.8 million (diagnosed)
- 7 million (undiagnosed)
- Pre-diabetes 79 million

- Costs of DM care 245 billion
- 176 billion in direct costs
- 69 billion in decreased productivity

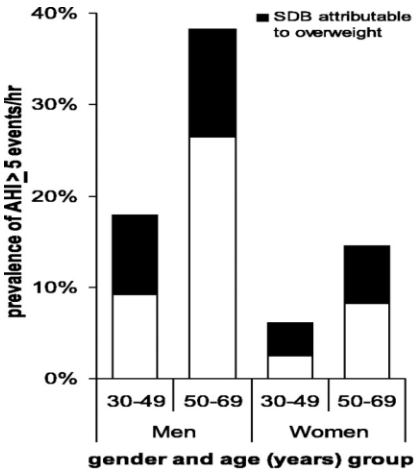
Obstructive sleep apnea

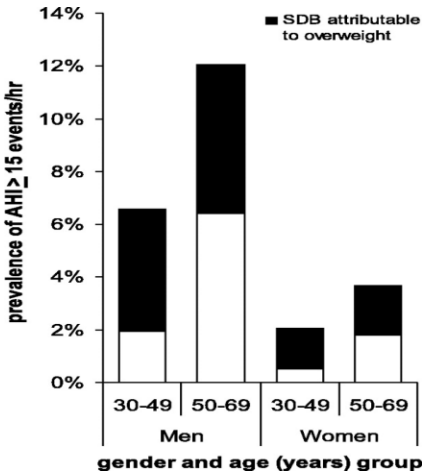
Young T. Wisconsin Sleep Cohort Study NEJM 1993

Prevalence OSA in middle aged adults

9% in women (2%)

24% in men (4%)





Questions about the DM and OSA relationship

- Does OSA predispose to DM, if so what level of risk does untreated OSA pose?

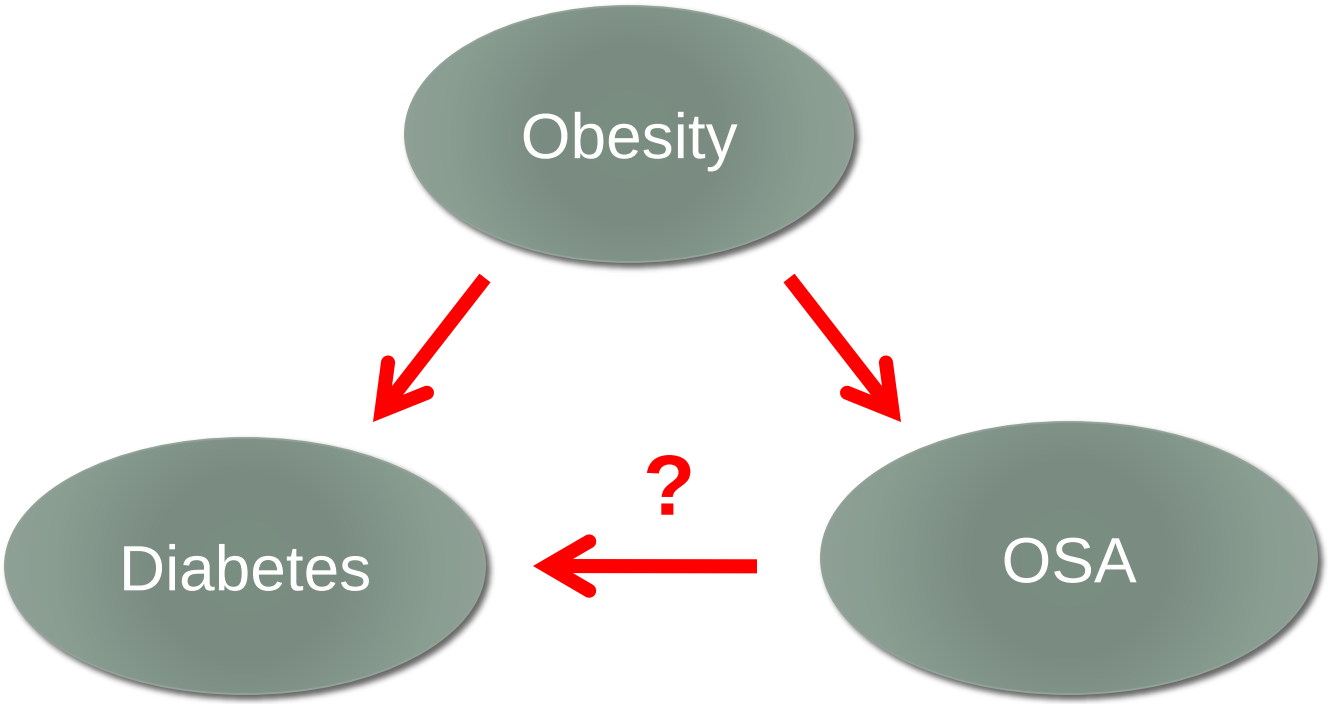
If so, treatment of OSA could reduce the staggering burden of DM

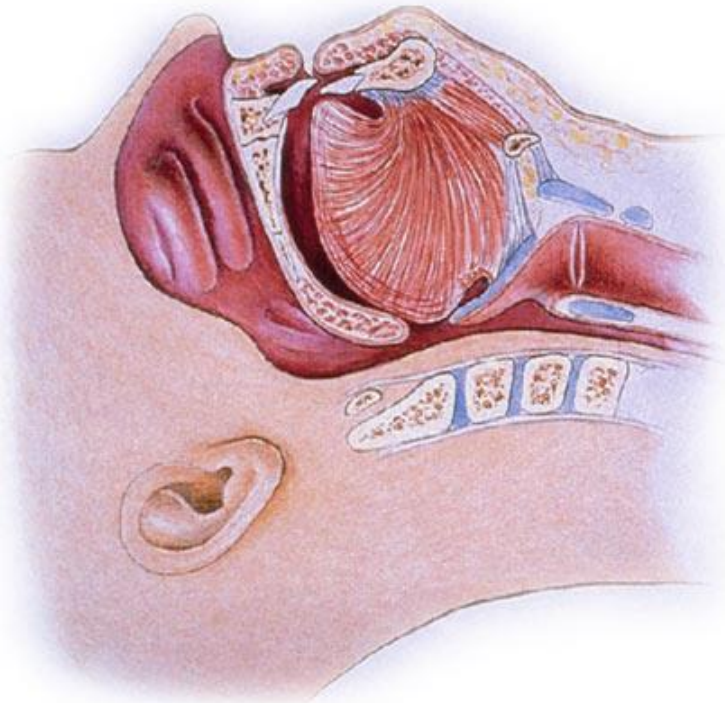
- Does treatment of OSA in established DM lead to improved outcomes from DM?

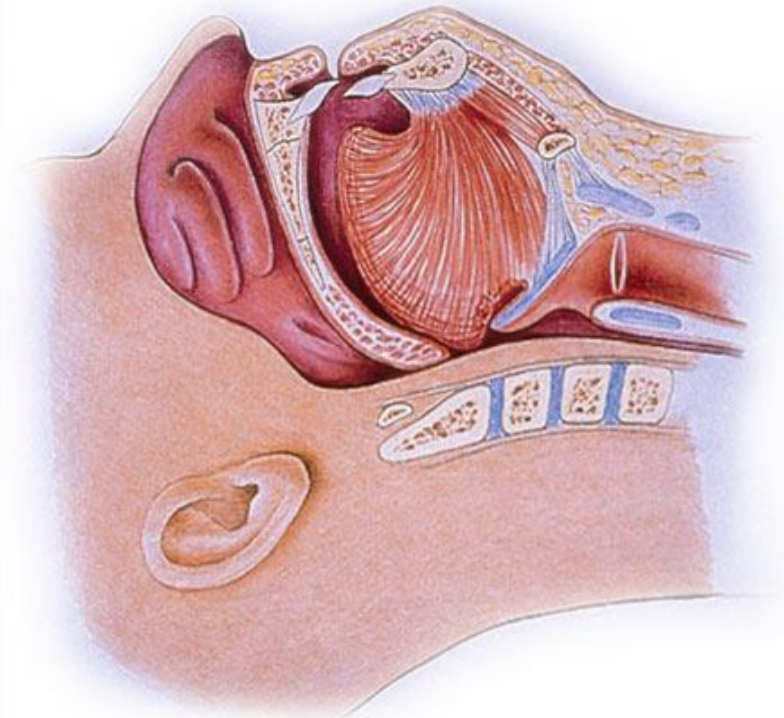
Improvement in DM outcomes can lead reduced costs of care of DM

- Mechanistic bases of OSA – DM relationship

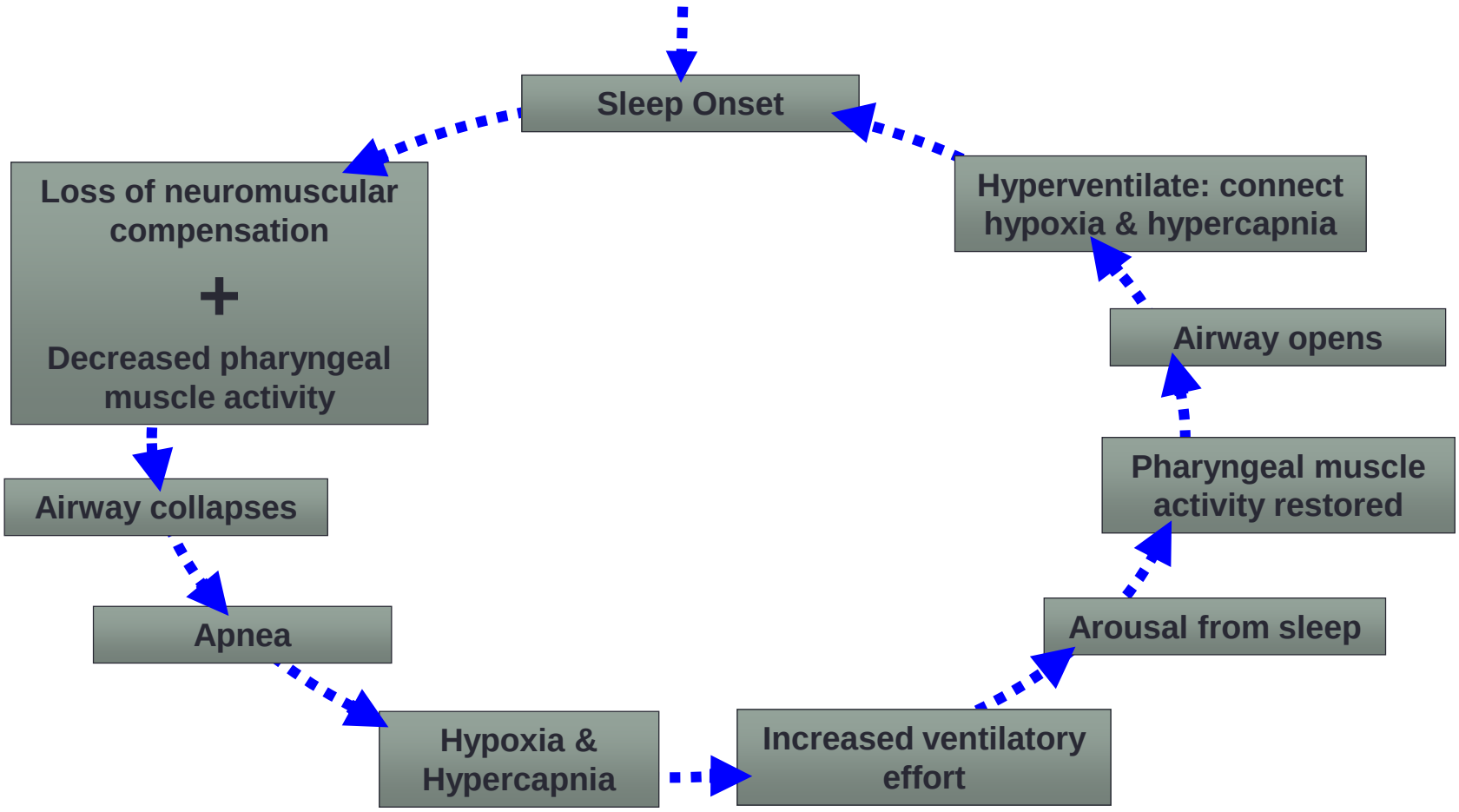
Obstructive Sleep Apnea and Diabetes: Cause or Association?





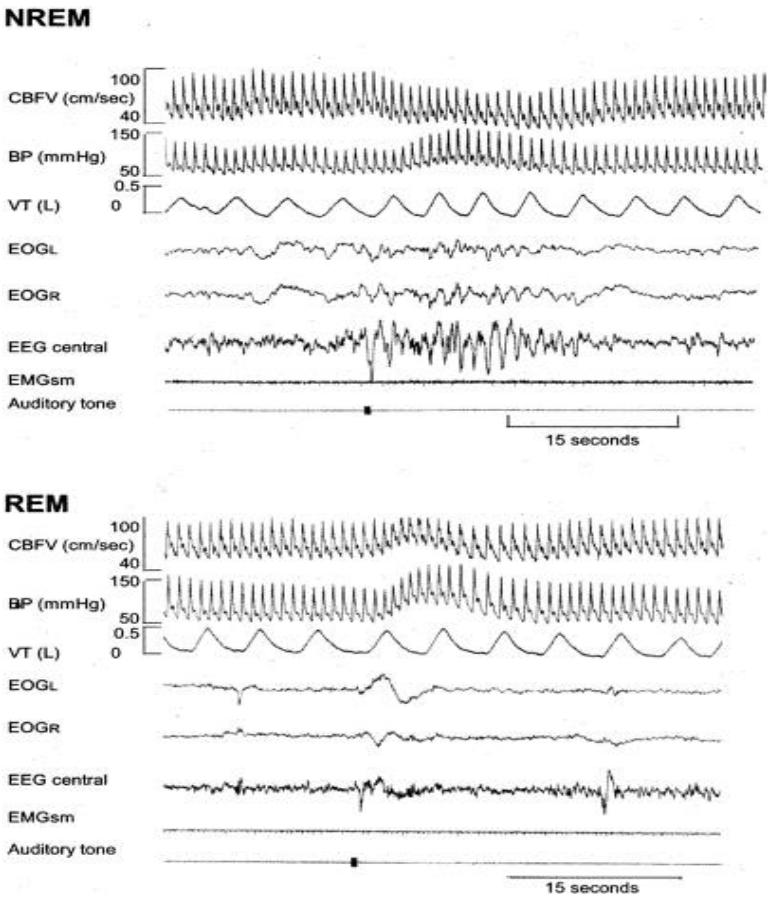


Pathophysiology of Sleep Apnea

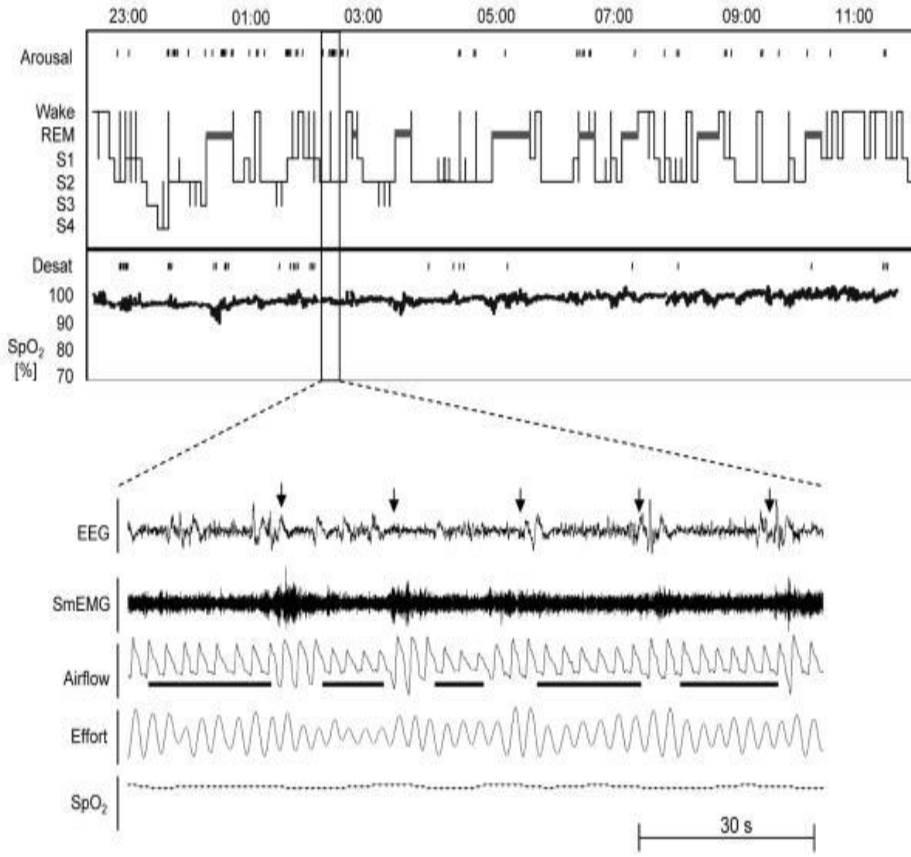


Physiologic consequences

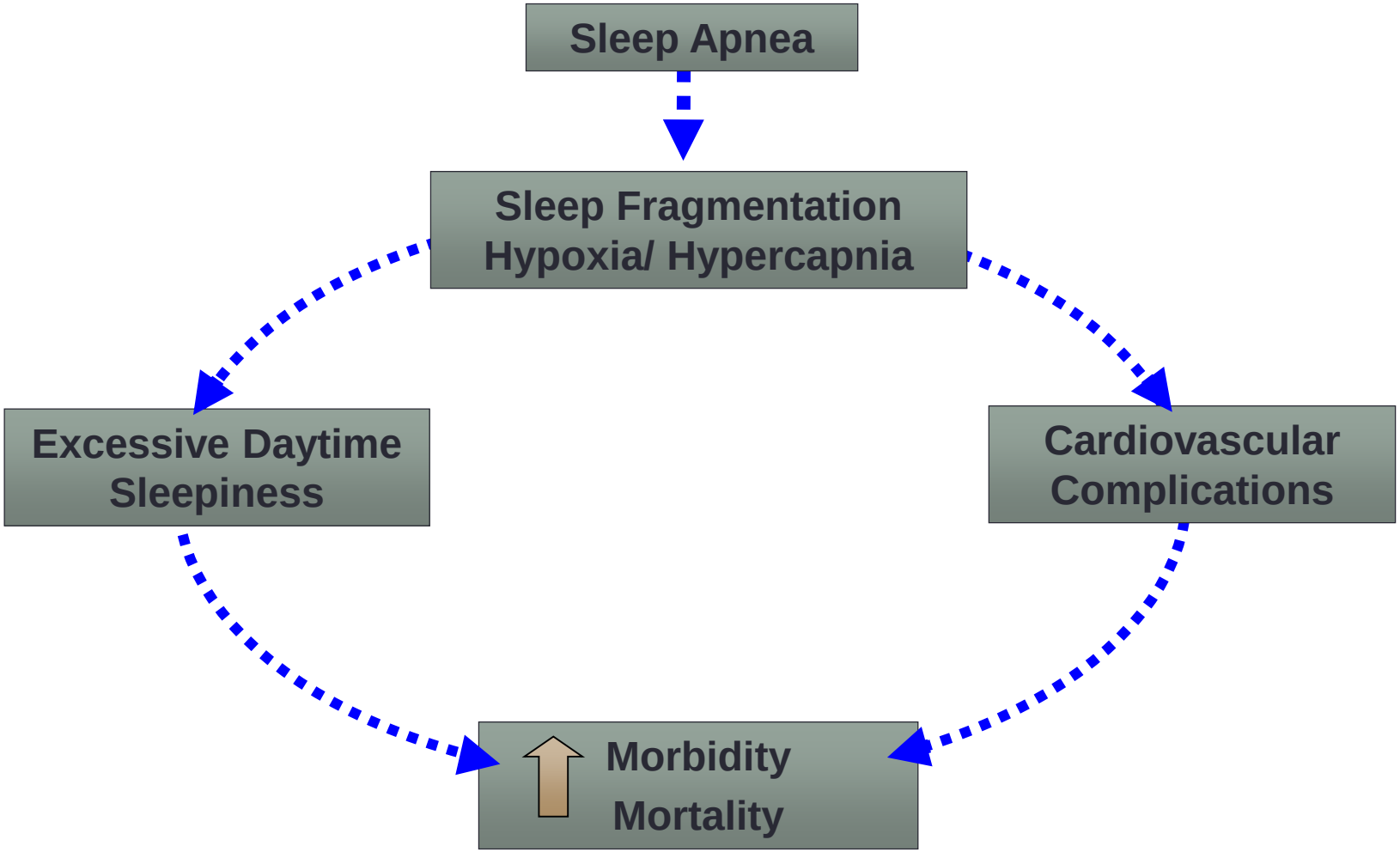
AROUSALS



DISORDERED OXYGENATION



Clinical Consequences



Categorization of OSA

- Based on apneas-hypopneas/hour
- APNEA-HYPOPNEA INDEX

Mild – 5-15/hr

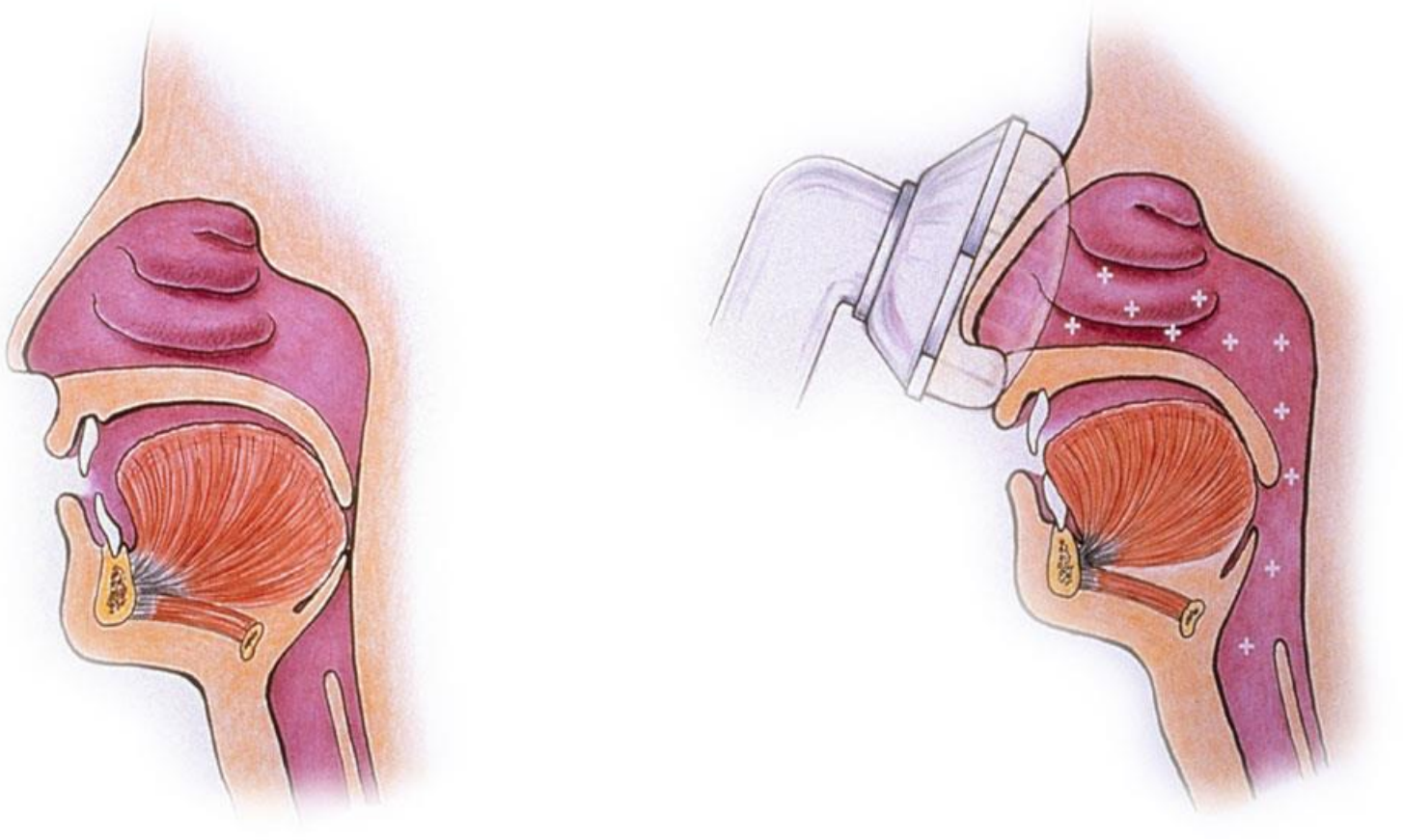
Moderate – 15-30/hr

Severe > 30/hr

Two key events that define the impact of OSA

- Arousals
- Hypoxemia

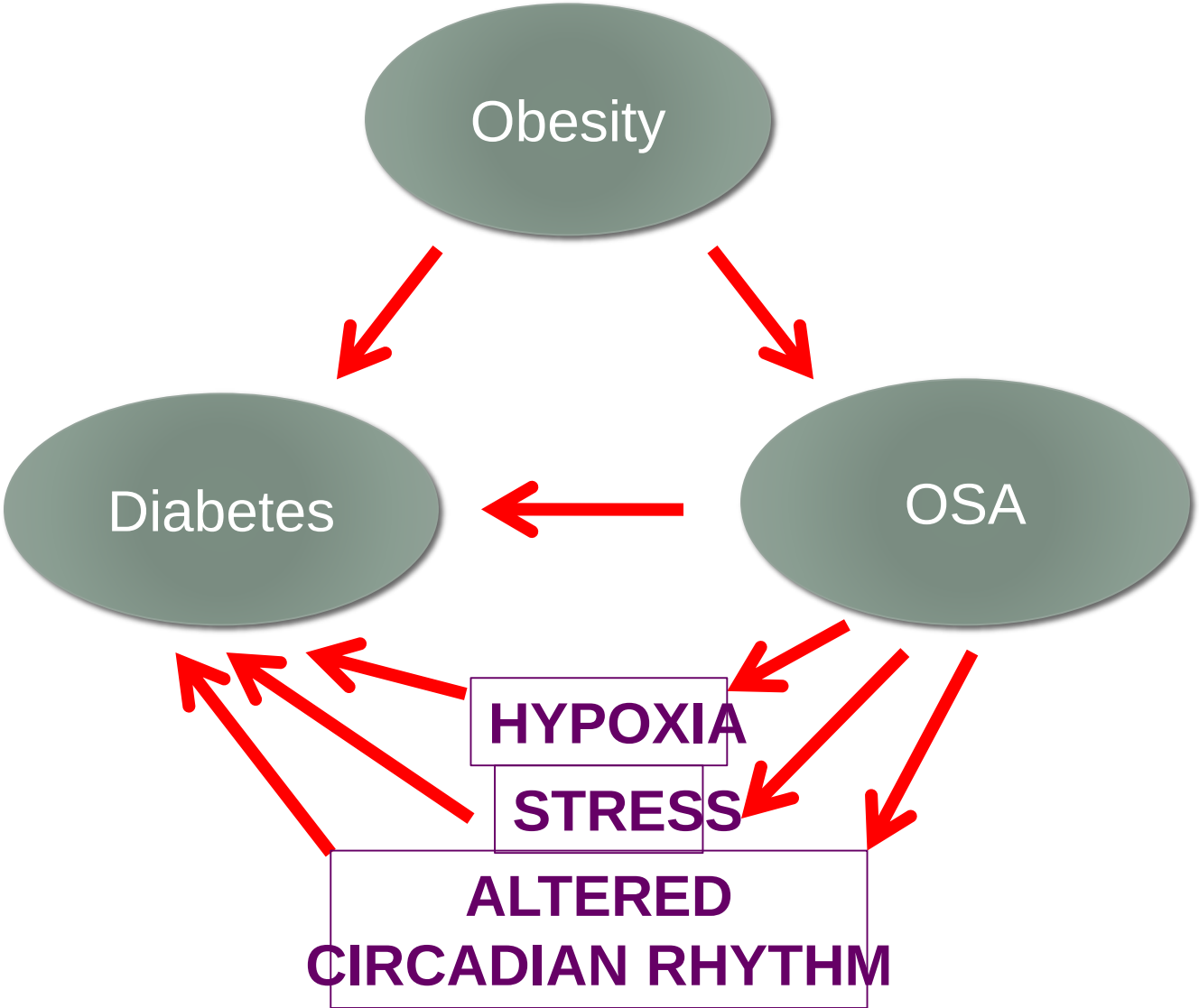
Positive Airway Pressure



Treatment of OSA

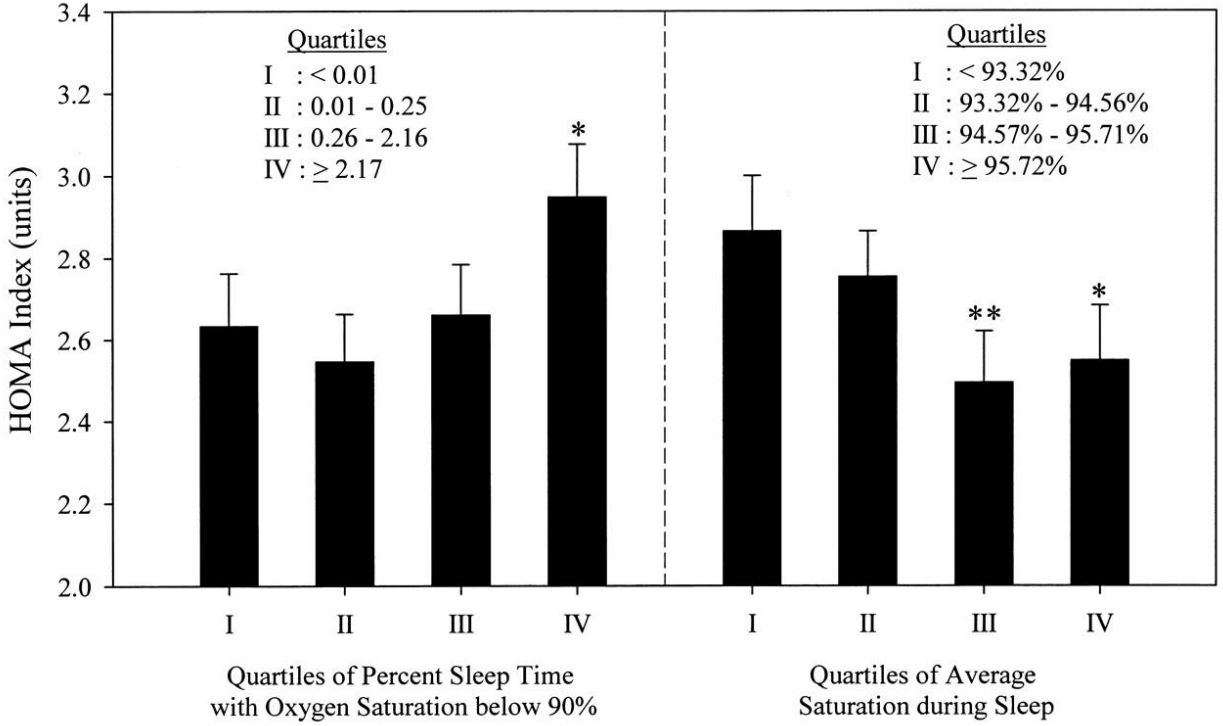
- Weight loss
- Avoidance of alcohol, sedatives, opiates
- Positional therapy
- Dental appliances
- Upper airway surgery

Obstructive Sleep Apnea and Diabetes: Cause or Association?



Sleep Heart Health Study: 2656 subjects underwent sleep study and glucose tolerance testing

Odds ratio for impaired glucose tolerance was 1.5-2.0 in the individuals spending the highest quartile of sleep time below 90% saturation or the lowest quartile of average saturation during sleep



Punjabi NM, Shahar E, Redline S, Gottlieb DJ, Givelber R, Resnick HE. Sleep-disordered breathing, glucose intolerance, and insulin resistance: the Sleep Heart Health Study. *Am J Epidemiol* 160(6):521-530, 2004.

Habitual snoring linked to DM in women

(Valham et al Sleep Med 2010)

Questions on SDB in the North Sweden component of WHO trends and monitoring of CVD 1999-2004 study (7905 subjects; 4047 W; 3858 M)

25-79 yr old women had 58% increased DM risk with habitual snoring and if they had witnessed apnea, 3-fold risk of DM independent of age, smoking, BMI or waist circumference.

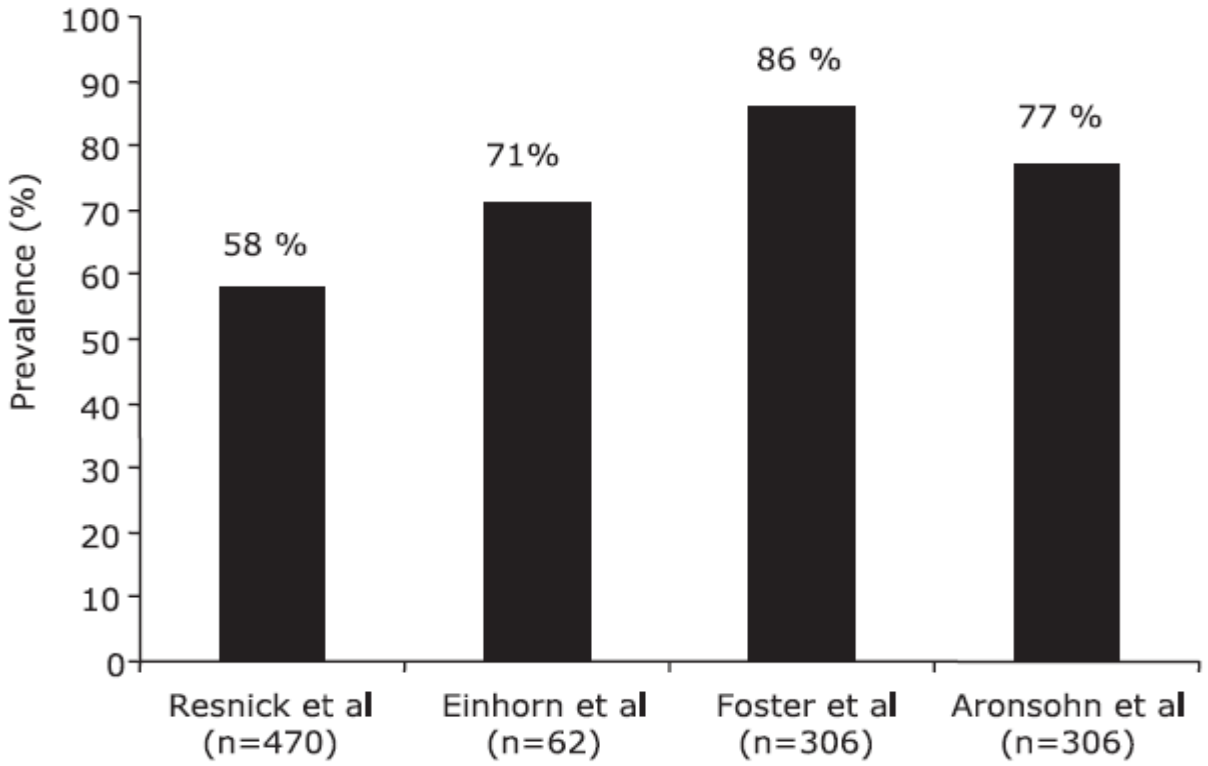
Univariate logistic regression analysis

	Women			Men		
	OR	95% CI	*p*-value	OR	95% CI	*p*-value
Non-snoring	1			1		
Unknown snoring pattern	1.62	0.98–2.69	0.060	1.43	0.82–2.49	0.204
Habitual snoring	2.25	1.49–3.38	<0.001	0.98	0.70–1.39	0.923
No witnessed sleep apnea	1			1		
Unknown apnea pattern	1.85	1.27–2.70	0.001	1.25	0.87–1.80	0.224
Witnessed sleep apnea	4.66	1.93–11.2	0.001	1.53	0.85–2.76	0.158
Non-smoker	1			1		
Current smoking	0.62	0.38–1.02	0.062	0.72	0.44–1.19	0.201
Age 25–44 (years)	1			1		
45–54	1.23	0.59–2.56	0.579	2.95	1.29–6.72	0.010
55–64	3.61	1.99–6.55	<0.001	8.71	4.13–18.3	<0.001
65–74	6.13	3.47–10.83	<0.001	13.0	6.26–27.0	<0.001
75–79	7.73	3.39–17.65	<0.001	28.6	12.5–65.5	<0.001
Body mass index (kg/m^2)	1.11	1.08–1.14	<0.001	1.10	1.06–1.14	<0.001
Waist circumference (cm)	1.06	1.04–1.07	<0.001	1.04	1.03–1.06	<0.001

Prevalence of OSA in DM (73%)

(Pamidi et al Best Pract Res Clin Endocrinol Met 2010)

- Highest in Sleep-AHEAD study – obese DM (86%).
- Lowest in SHHS – 58% (65+, self-reported DM, hypopnea definition of 4%)



Prevalence of DM in OSA

(Pamidi et al Best Pract Res Clin Endocrinol Met 2010)

- **Higher prevalence of Type 2 DM in OSA**

Unadjusted OR 4.06-11.2

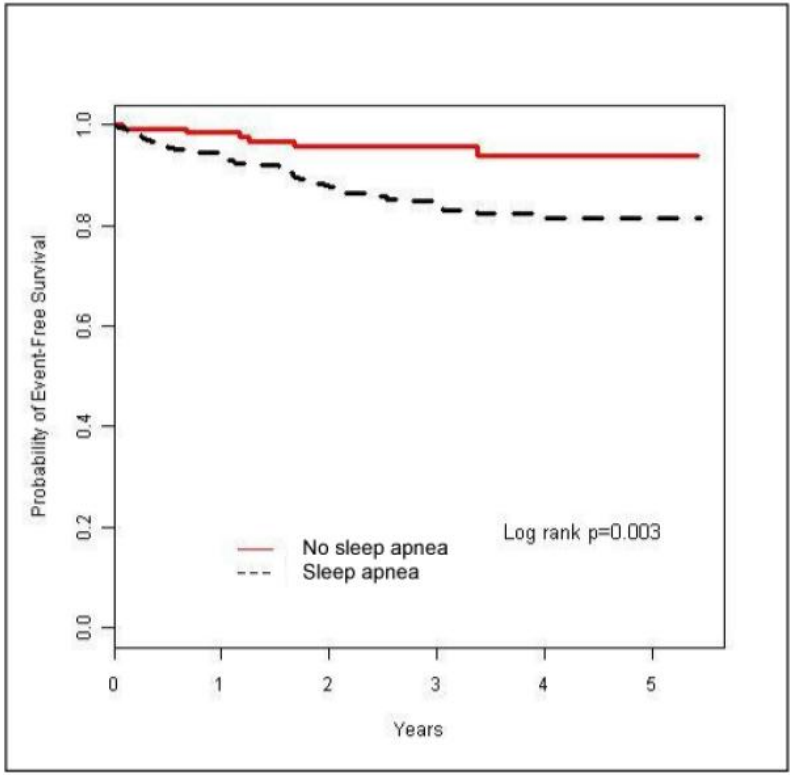
Adjusted OR 1.3-13.4

- **Higher incidence of T2DM with increasing severity of** OSA (Botros et al Am J Med 2009 & Wisconsin sleep cohort – AHI>15, DM prevalence 15%; AHI<5, fewer than 3% had DM)
- **Longitudinal follow –up studies looking at causality**

- Wisconsin sleep cohort (1387 patients, after adjustment for age, sex and body habitus, OR for DM in 4 years was **1.62** with AHI≥15/h compared to AHI with AHI of 5/hr but not statistically significant) (Reichmuth AJRCCM 2005)
- Busselton Health study even though showing independent association, sample sizes and incident DM was small (Marshall et al J Clin Sleep Med 2009)

544 nondiabetic subjects assessed for sleep disorders were then followed for a median of 2.7 years

OSA was associated with subsequent risk of diabetes when corrected for age, race, baseline glucose, BMI, and change in BMI



Botros N, Concato J, Mohsenin V, Selim B, Doctor K, Yaggi HK. Obstructive sleep apnea as a risk factor for type 2 diabetes. *Am J Med* 122(12):1122-1127, 2009.

Effect of CPAP treatment
Methodologies used to understand impact

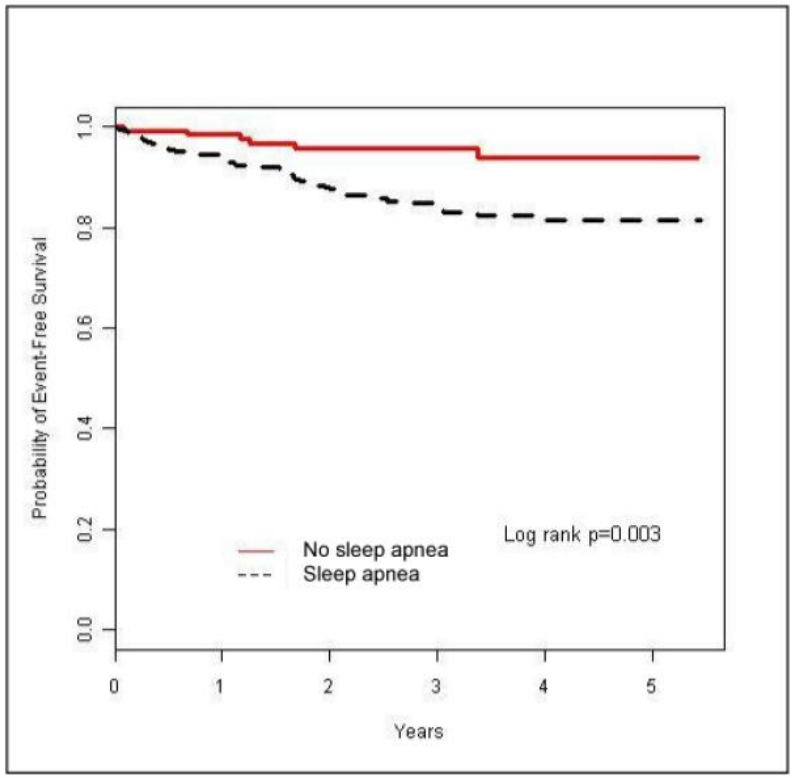
- Risk of developing DM

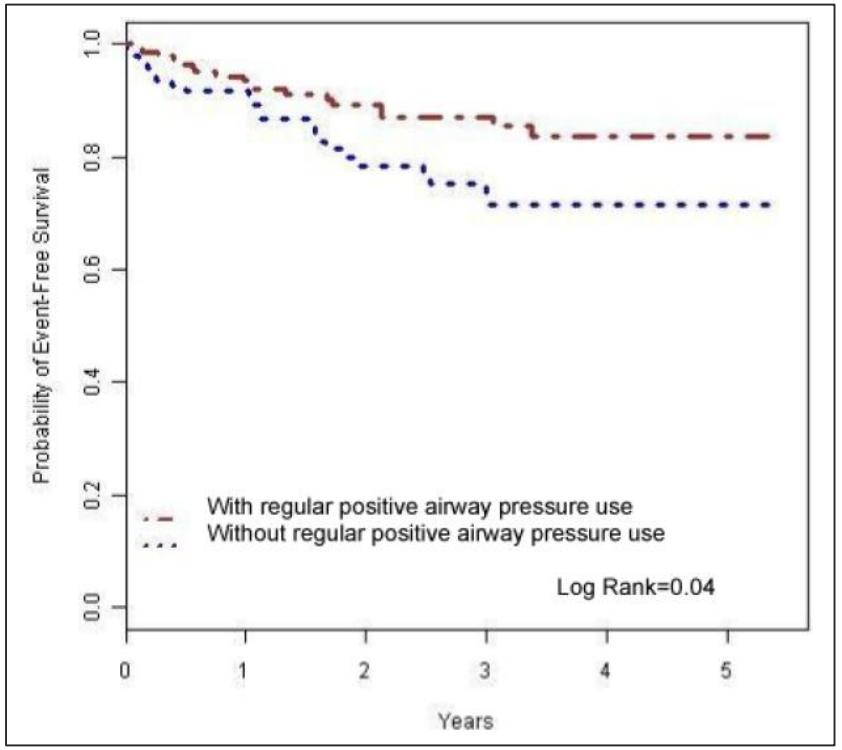
- Effects on glucose metabolism
  - Insulin levels
  - Insulin resistance
  - Glucose levels and HbA1C
  - Insulin sensitivity

- Risk of diabetic complications following CPAP treatment for OSA in DM

544 nondiabetic subjects assessed for sleep disorders were then followed for a median of 2.7 years

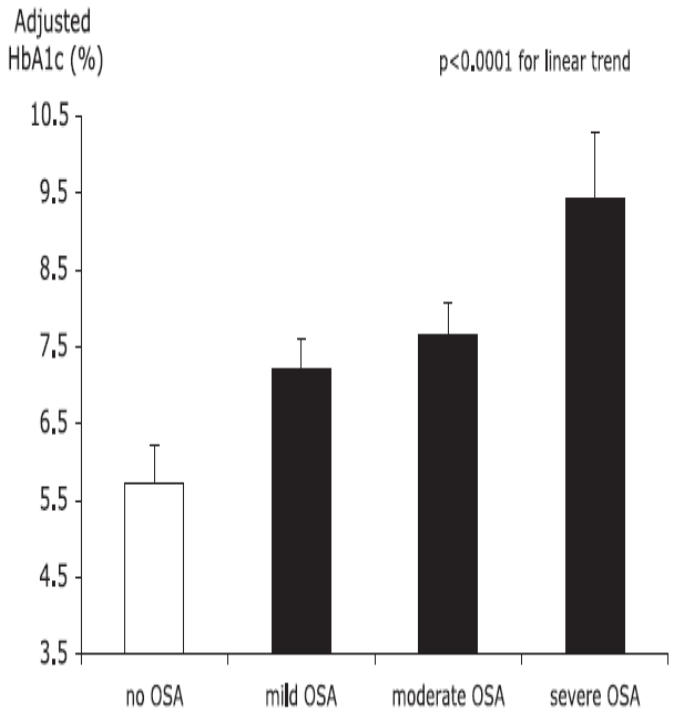
Use of CPAP was associated with a decreased risk of developing diabetes.





Botros N, Concato J, Mohsenin V, Selim B, Doctor K, Yaggi HK. Obstructive sleep apnea as a risk factor for type 2 diabetes. *Am J Med* 122(12):1122-1127, 2009.

HbA1C with and without CPAP



- Effect of CPAP therapy on HbA1C
  - Babu et al (Arch Intern Med 2005) showed benefit in 25 obese DM with >4 hours of CPAP in 3 months
  - 4 other studies showed no improvement in HbA1C

Aronsohn et al AJRCCM 2010

Effect of CPAP on glucose tolerance or insulin sensitivity

- Majority of studies done in obese men
- Out of 21 studies, 9 reported positive findings and 12 were negative
- Methods used ranged from

- HOMA index
- OGTT
- Gold standard hyper-insulinemic euglycemic clamp technique rarely used.

Randomized studies on effect of CPAP in DM

Table 1. Randomized Controlled Trials on the Effect of CPAP on Glucose Metabolism

Study	Study Sample	Observation Period	Age (SD) BMI (SD)	Measurement of Glucose Metabolism	Main Findings
Coughlin et al., 2007	34 non-diabetic OSA patients	6 weeks	49.0 (8.3) 36.1 (7.6)	HOMA	No improvement of HOMA
West et al., 2007	42 diabetic OSA patients	3 months	56.2 (9.9) 36.7 (4.8)	HOMA, HbA1c Euglycemic clamp	No improvement of HOMA, HbA1c, or euglycemic clamp
Lam et al., 2010	61 non-diabetic OSA patients	1 week RCT 12 weeks uncon-trolled	46.3 (10.2) 27.5 (3.7)	HOMA Insulin sensitivity SITT	No improvement of HOMA Significant higher insulin sensitivity after one week

Note: Values are mean (SD); BMI, body-mass-index (kg/m^2); HOMA, homeostasis model assessment derived from the fasting glucose and insulin to characterize insulin resistance; HbA1c, glycated hemoglobin; OSA, obstructive sleep apnea; RCT, randomized controlled trial; SITT, short insulin tolerance test.

But were they sufficiently powered?

Table 1. Randomized Controlled Trials on the Effect of CPAP on Glucose Metabolism

Study	Study Sample	Observation Period	Age (SD) BMI (SD)	Measurement of Glucose Metabolism	Main Findings
Coughlin et al., 2007	34 non-diabetic OSA patients	6 weeks	49.0 (8.3) 36.1 (7.6)	HOMA	No improvement of HOMA
West et al., 2007	42 diabetic OSA patients	3 months	56.2 (9.9) 36.7 (4.8)	HOMA, HbA1c Euglycemic clamp	No improvement of HOMA, HbA1c, or euglycemic clamp
Lam et al., 2010	61 non-diabetic OSA patients	1 week RCT 12 weeks uncon-trolled	46.3 (10.2) 27.5 (3.7)	HOMA Insulin sensitivity SITT	No improvement of HOMA Significant higher insulin sensitivity after one week

Note: Values are mean (SD); BMI, body-mass-index (kg/m^2); HOMA, homeostasis model assessment derived from the fasting glucose and insulin to characterize insulin resistance; HbA1c, glycated hemoglobin; OSA, obstructive sleep apnea; RCT, randomized controlled trial; SITT, short insulin tolerance test.

P=0.08 P=0.2

Other notable features of DM-OSA relationship

- CPAP therapy seems to reduce glucose variability at night (Pallayova et al Diabetes Res Clin Pract 2008)
- Higher proportion of central apneas in patients with DM than those without (Sanders et al Sleep Med 2003)
- DM related retinopathy strongly associated with OSA (West Diabetes Med 2010) with some suggestion of improvement of visual improvement (macular edema) with CPAP (Mason et al Respiration 2012)
- 4 fold risk of Restless Legs syndrome in DM patients (Merlino et al 2007)

Diabetes and sleep duration:

- A sleep duration of 6 hours or less, or 9 hours or more is associated with increased prevalence of type II diabetes and impaired glucose tolerance

Gottlieb *et al.*, 2005

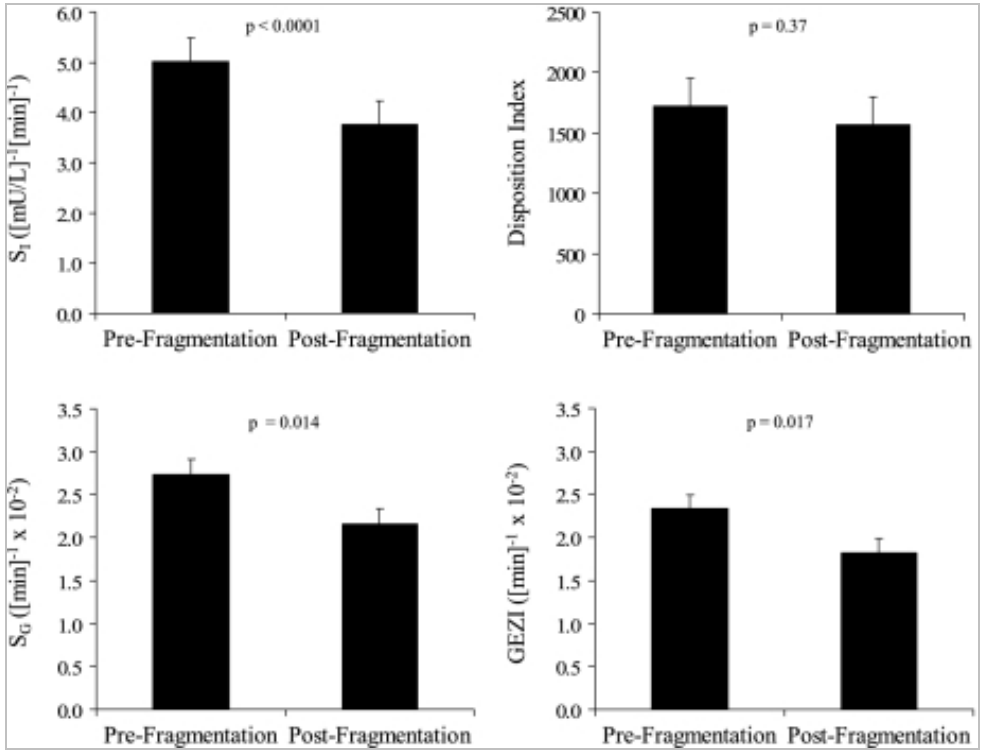
- Healthy individuals restricted to four hours of sleep in a clinical study had impaired insulin secretion after a glucose challenge.

Spiegel *et al.* 2008

- Other studies showed similar effects of less severe—5.5 hr of sleep curtailment.

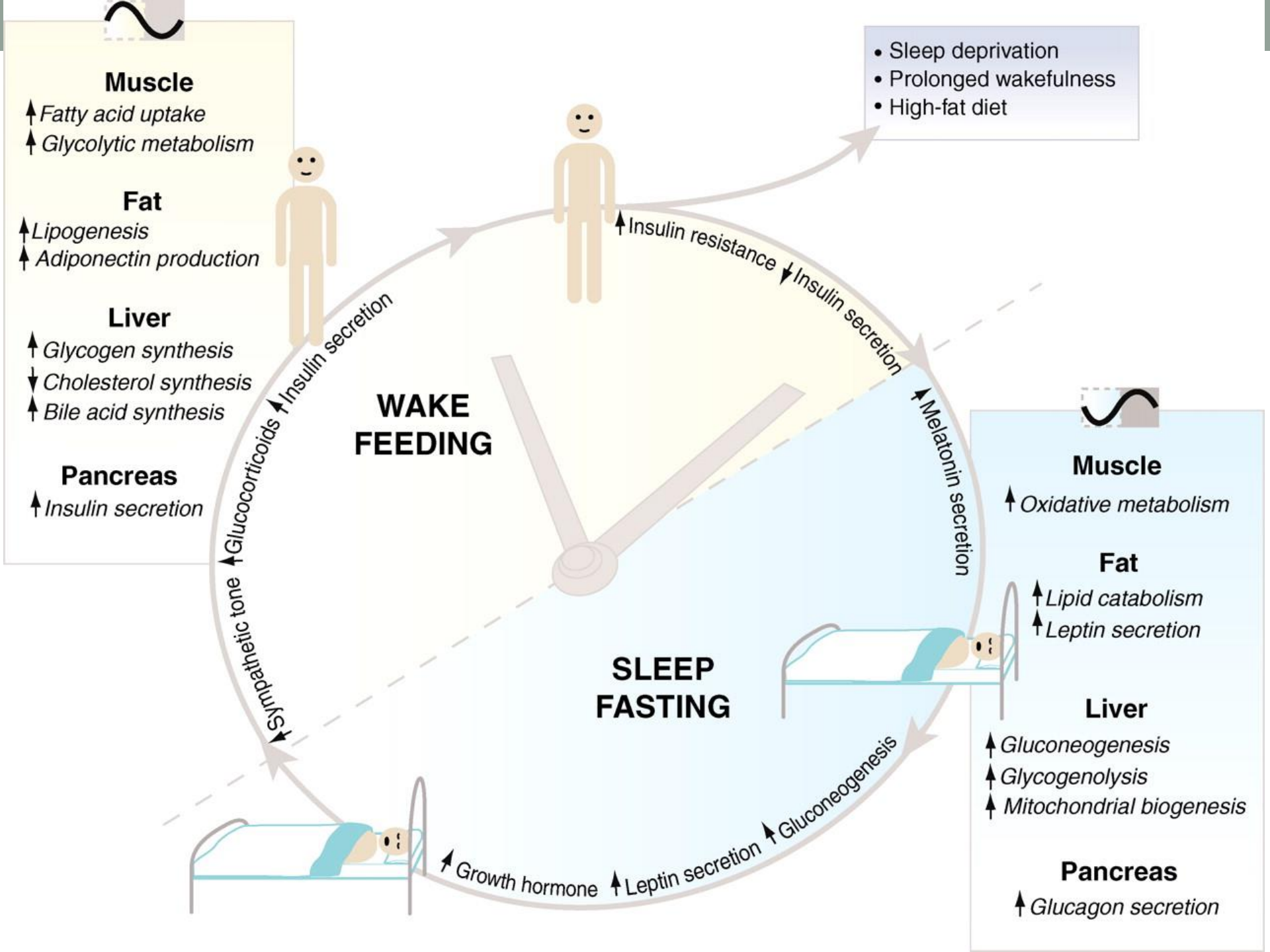
Sleep quality: without a change in total sleep time, interrupted sleep impairs insulin sensitivity and glucose disposal

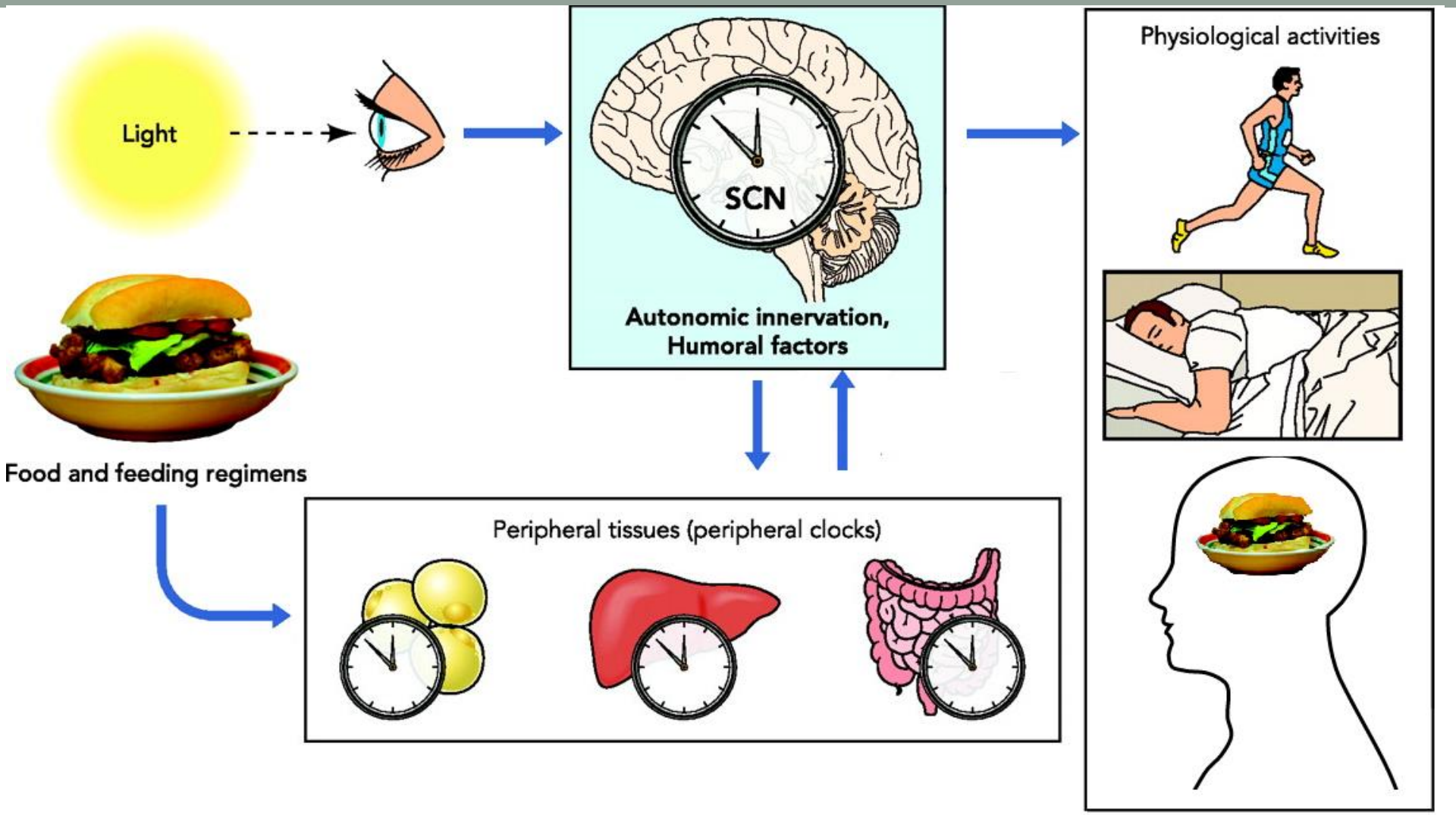
Sleep was disrupted in 11 healthy volunteers with auditory and mechanical stimuli, resulting in more stage 1 and 2 sleep but markedly decreased slow wave sleep.



AM cortisol and sympathetic activation were higher after sleep interruption.

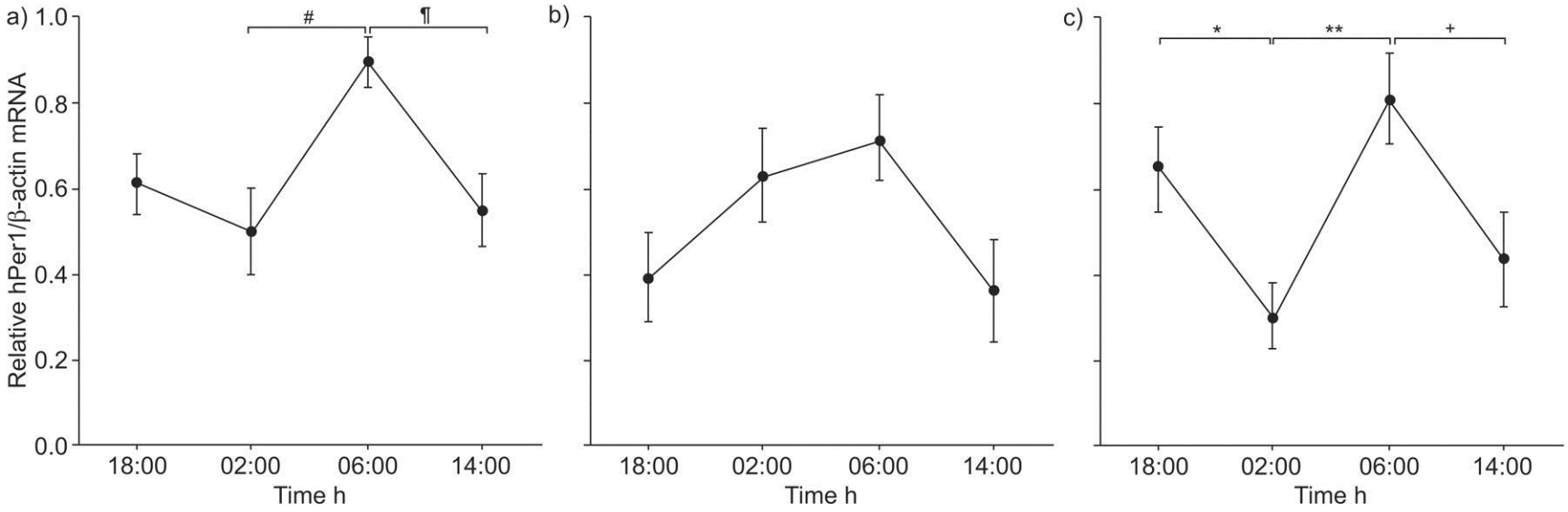
- Stamatakis KA, Punjabi NM. Chest. 2010 Jan;137(1):95-101.


Muscle
Fatty acid uptake
Glycolytic metabolism
Fat
Lipogenesis
Adiponectin production
Liver
Glycogen synthesis
Cholesterol synthesis
Bile acid synthesis
Pancreas
Insulin secretion
• Sleep deprivation
• Prolonged wakefulness
• High-fat diet
Insulin resistance
Insulin secretion
Melatonin secretion
WAKE
FEEDING
SLEEP
FASTING
Sympathetic tone
Glucocorticoids
Insulin secretion
Growth hormone
Leptin secretion
Gluconeogenesis
Muscle
Oxidative metabolism
Fat
Lipid catabolism
Leptin secretion
Liver
Gluconeogenesis
Glycogenolysis
Mitochondrial biogenesis
Pancreas
Glucagon secretion



Modified from http://physiologyonline.physiology.org/content/26/4/225/F1.large.jpg

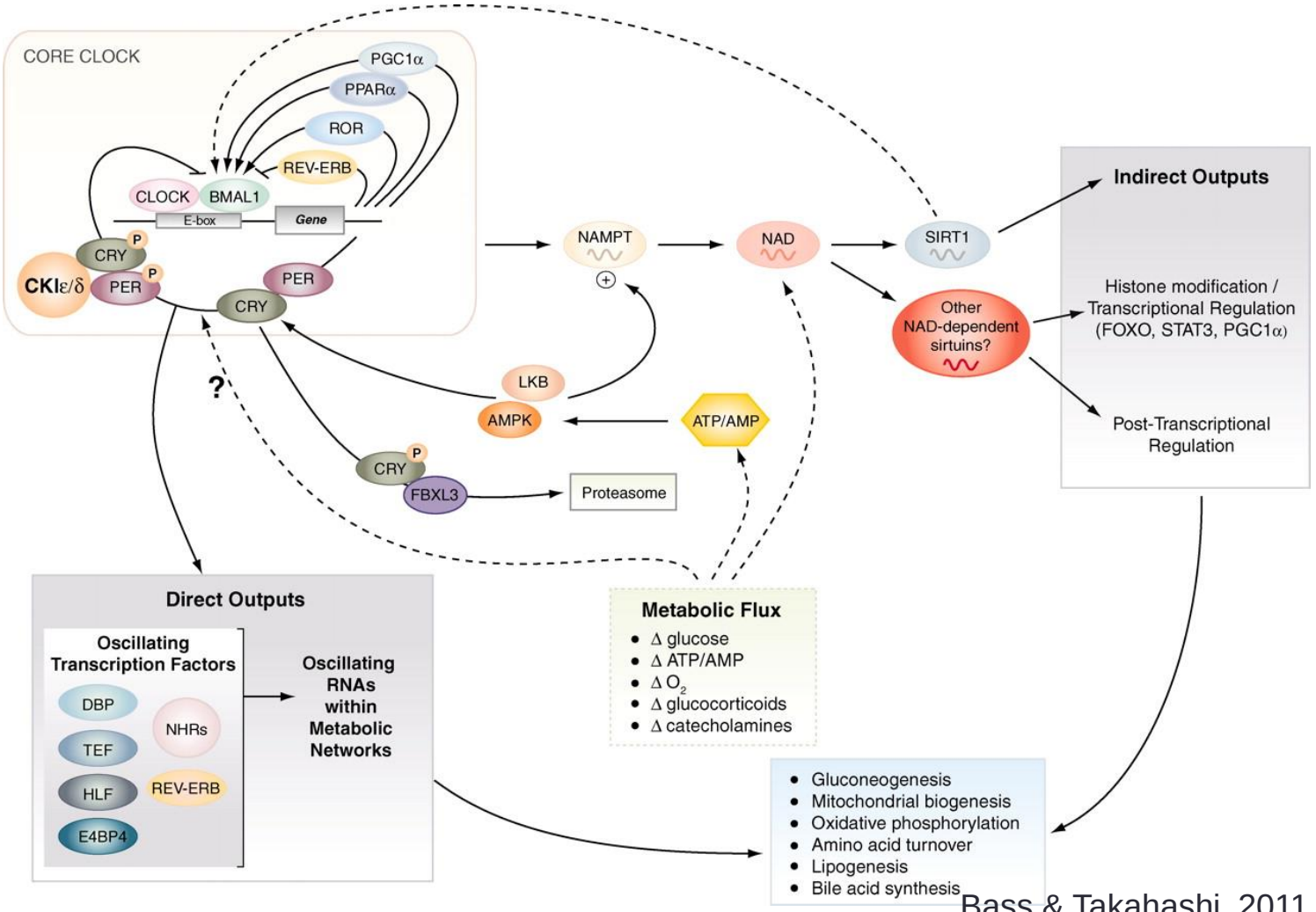
Do OSA patients have disrupted circadian rhythms?



Controls OSA OSA after CPAP

These altered rhythms correlate with changes in cortisol, sympathetic tone, blood pressure, cytokine levels, and many more.

Relationship between clock genes and metabolic regulatory pathways



Bass & Takahashi, 2011

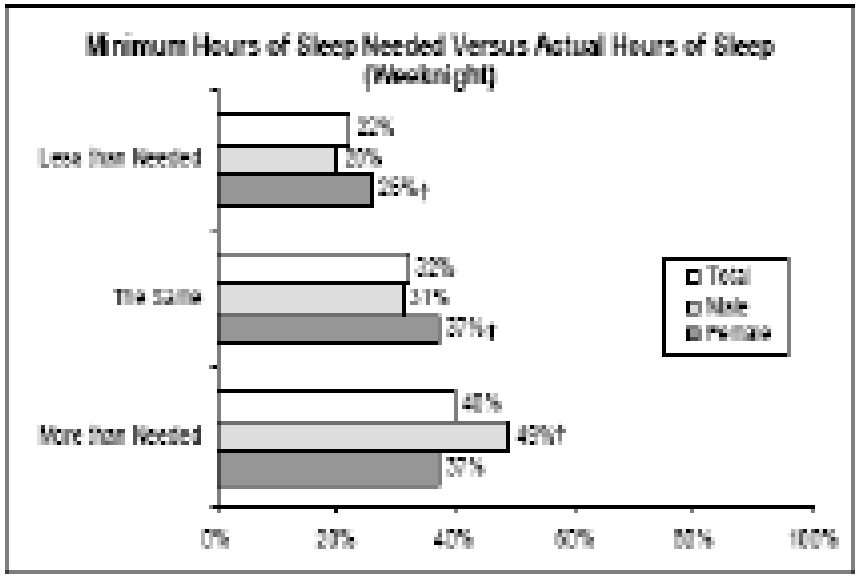
Voluntary Sleep Loss

- "Sleep in America 2005" poll
  - National Sleep Foundation
- Adults average 6.9 hours of sleep

Number of Hours Slept per Night on Weekdays (past two weeks)

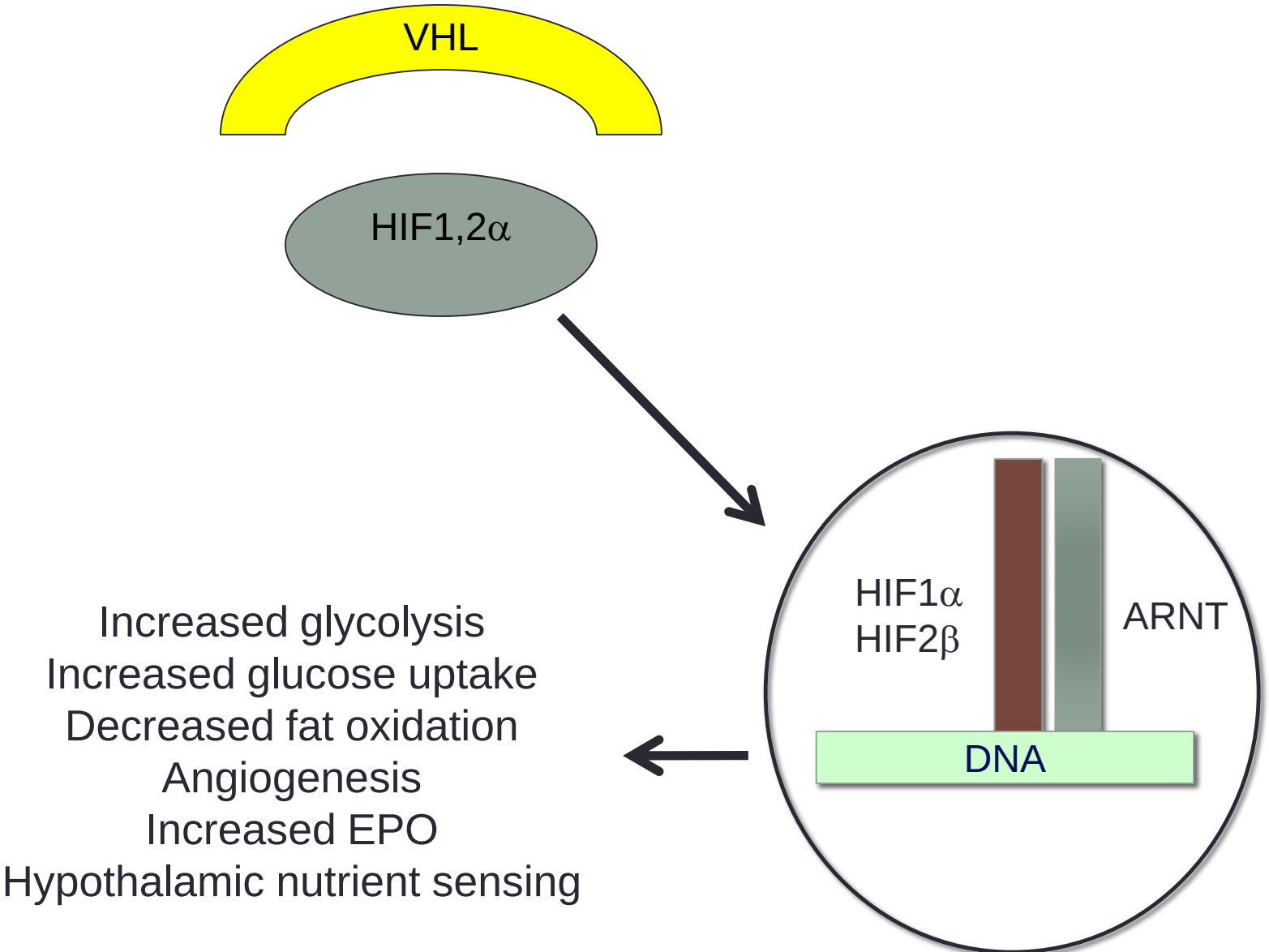
	1998	2001	2002	2005
	a	b	c	d
Less than 6 hours	12%	13%	15%a	16%abc
6 to 6.9 hours	23c	18	24c	24c
7 to 7.9 hours	28	31	29	31
8 or more hours	35bcd	38bcd	30c	28
Mean (# of hours)	na	7.0	6.9	6.8
Median (# of hours)	na	7.0	7.0	7.0

Base = Total sample (n=1506)
Letters mean they are statistically significant at the 95% confidence interval.
na = Not available
Q3



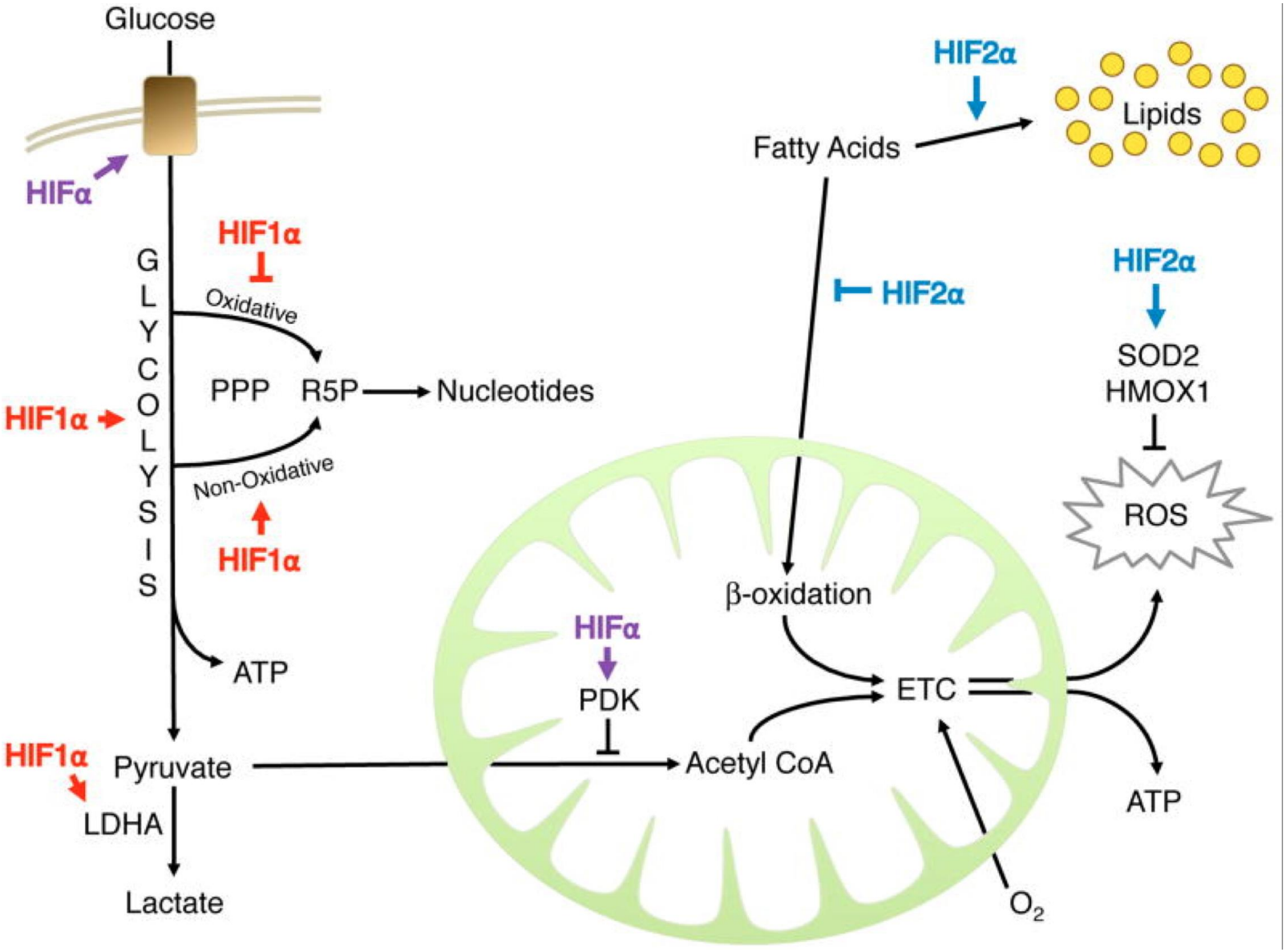
Base = Total sample (n=1, 506)
Note: Up arrow= mean the percentage is significantly higher than the percentage for the comparison group.
Don't know/Refused = 6%
Q8 & 26

Mechanisms for hypoxia-induced regulation



HIF-1 and 2 and Metabolism

(Majumdar et al. Mol. Cell 40:294 (2010)



Other important pathways activated in OSA

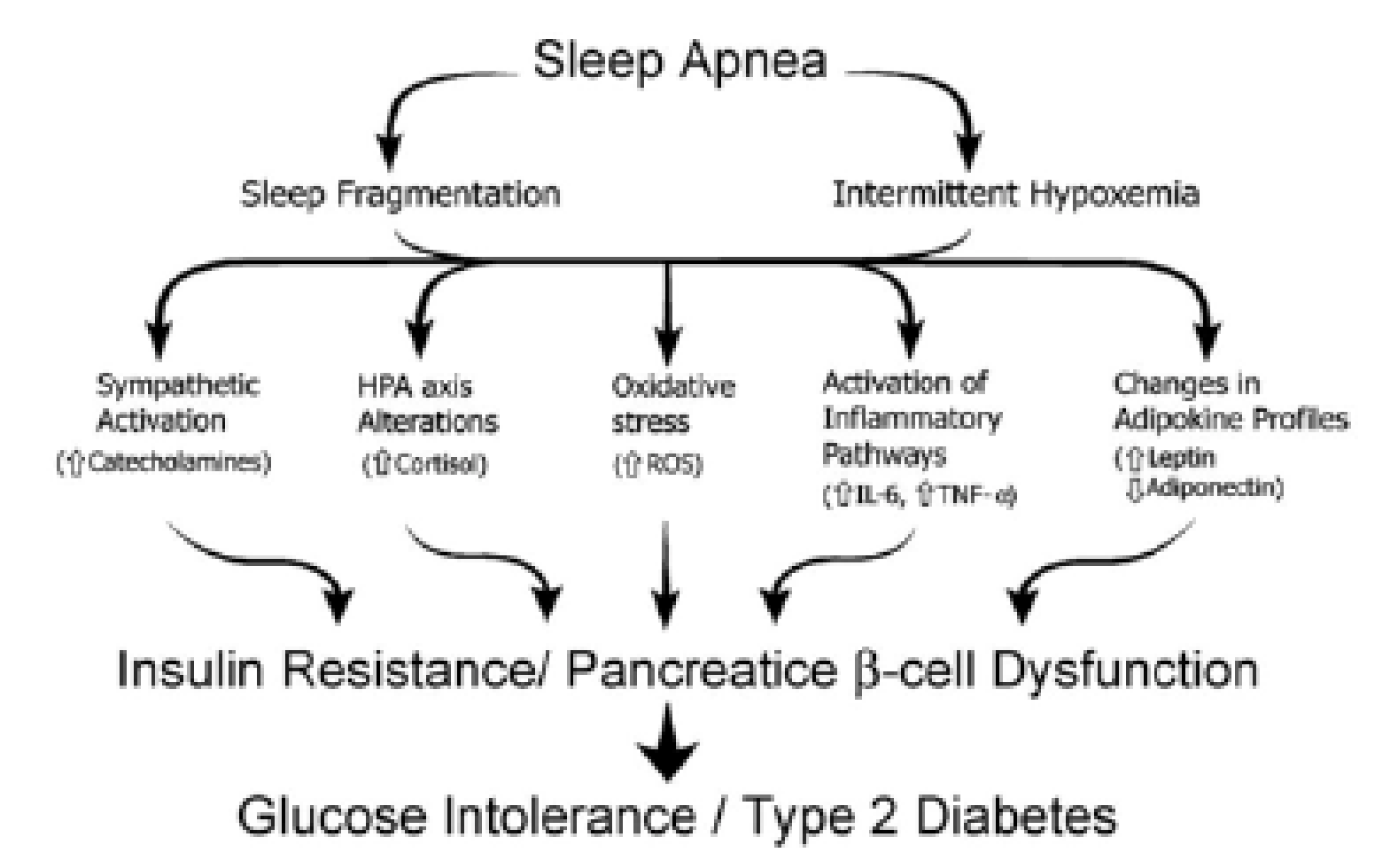
- Sympathetic nervous system activation
  - Also during the wake state
  - Main trigger is hypoxia

- Hypothalamic-pituitary-adrenal axis dysfunction
  - Elevated cortisol levels impair insulin sensitivity

- Systemic inflammation
  - Sympathetic activation and intermittent hypoxemia (hsCRP, TNF-α, interleukin levels)

- Adipokines (elevated levels of leptin)

Linkage Between OSA and DM



Diabetes Research and Clinical Practice; vol.8 (i) pages 2-12

Conclusions

- Current evidence strongly supports an independent association between OSA and insulin resistance and glucose tolerance, causality remains to be determined (Pamidi 2010)
- It is noteworthy to urge clinicians to systematically evaluate risk of OSA in type 2 diabetic patients and conversely, to assess glucose tolerance in patients with known OSA (Tasali et al Chest 2008)

> “the International Diabetes Federation Taskforce on Epidemiology and Prevention strongly recommends that health professionals working in both type 2 diabetes and SDB adopt clinical practices to ensure that a patient presenting with one condition is considered for the other” International Diabetes Federation Taskforce on Epidemiology and Prevention 2008