# Aspetti metabolici correlati ai disturbi del sonno

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ORDINE DEI MEDICI CHIRURGHI
E DEGLI ODONTOIATRI
DELLA PROVINCIA DI PARMA

**I Martedì dell'Ordine**

2 ottobre 2012

# Menù
# relazione tra:

- OSA e obesità
- OSA e alterazioni metaboliche
- OSA e diabete mellito di tipo 2
- Riduzione del sonno e alterato metabolismo glucidico

✓Associazione tra i fenomeni
✓Relazioni fisiopatologiche
✓Beneficio dagli studi di intervento

# L’obesità è considerata il fattore di rischio principale per l’insorgenza e la progressione di OSA

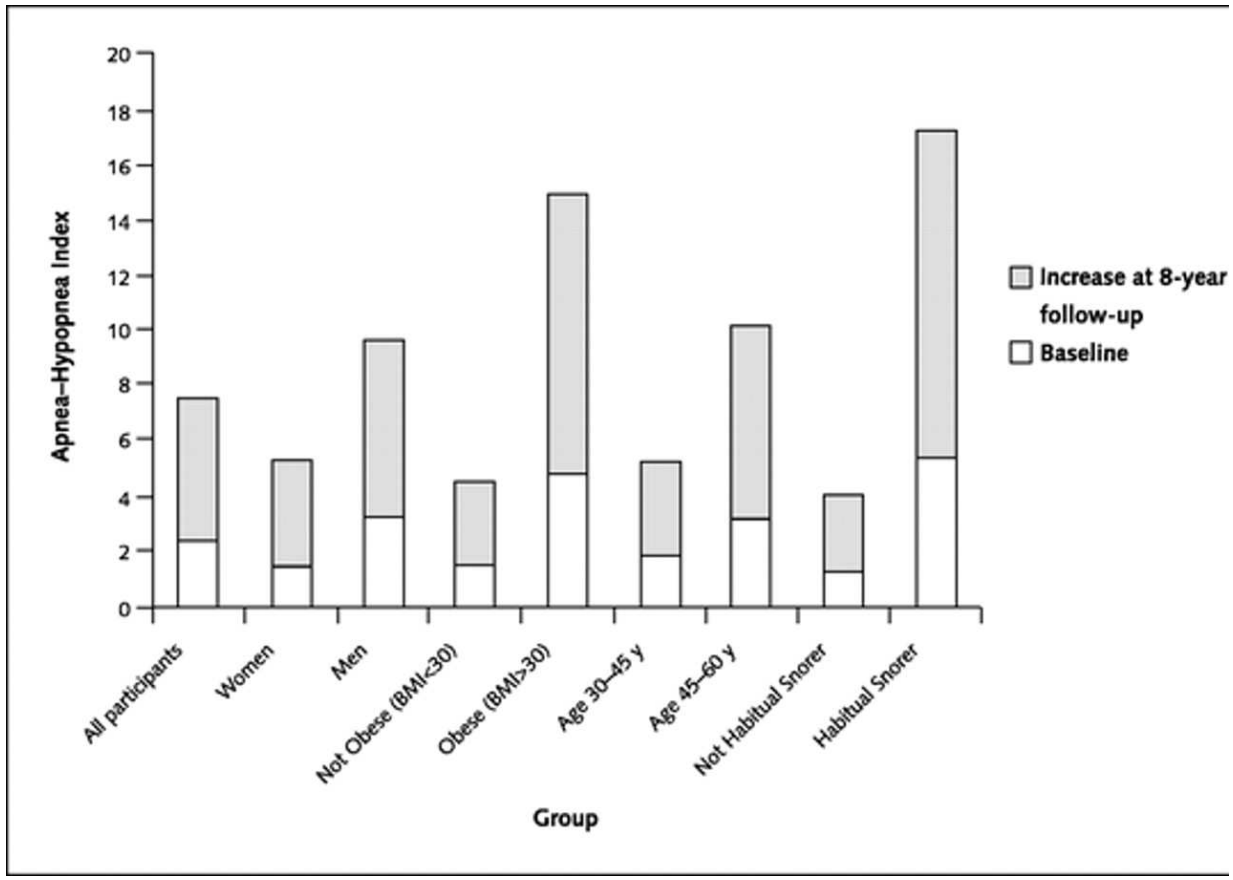
J Intern Med 1997; 241:11-18
JAMA 2004; 291:2013-6

# OSA in obesi
# dati epidemiologici

- Prevalenza di OSA nella popolazione generale è variabile,  dipende dall'età, dal sesso e dal BMI, circa del 24% nei maschi e del 9% nelle femmine
- Prevalenza di OSA negli obesi varia dal 42 al 48% negli uomini e dall'9 al 38% nelle donne
- Prevalenza di obesità in OSA oltre 70%

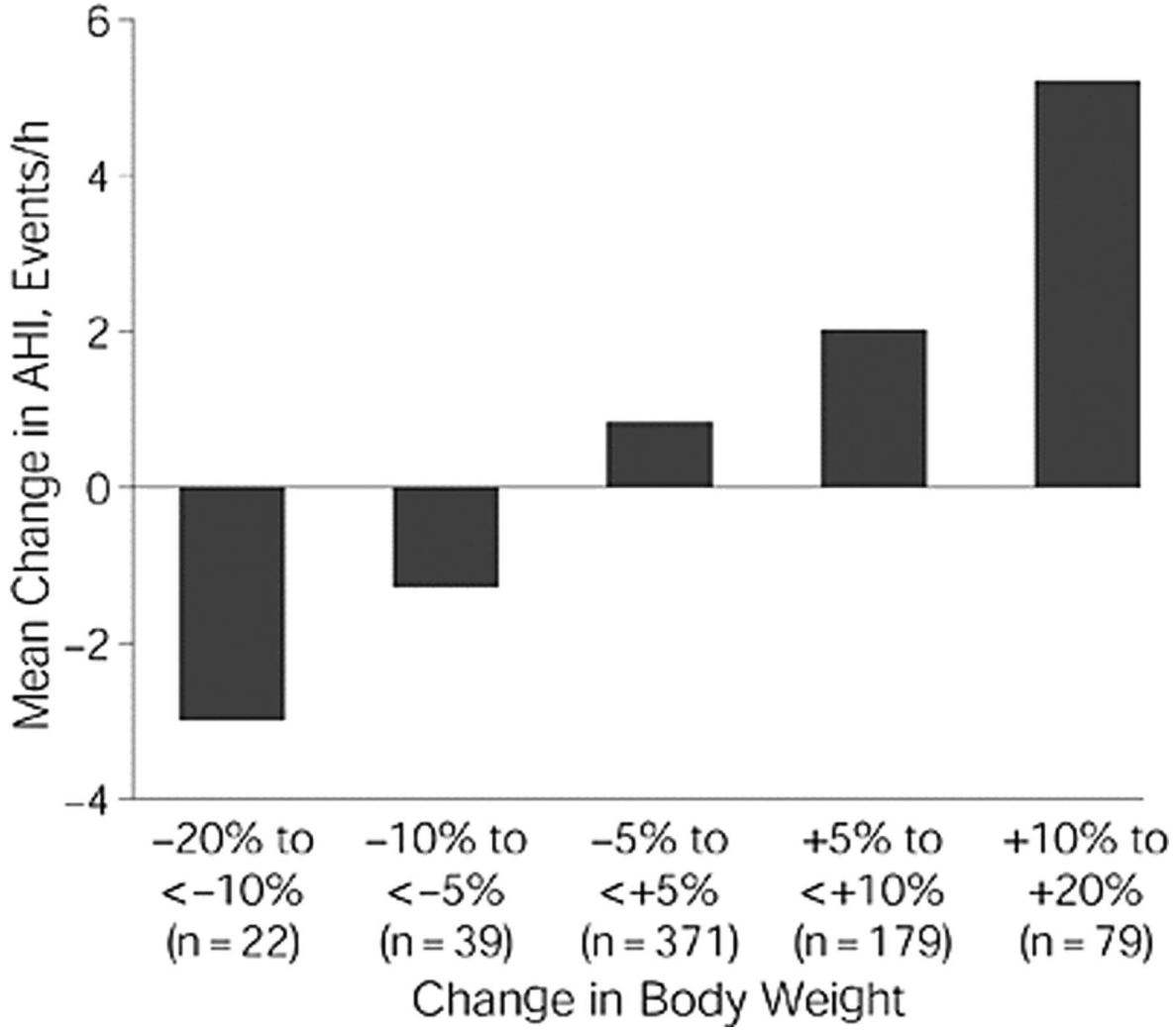
Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S. The occurrence of sleep-desordered breathing among middle-aged adults. N Engl J Med 328: 1230-1235, 1993.
Kyzer S, Charuzi I. Obstructive sleep apnea in the obese. World J Surg 22: 998-1001, 1998

# Mean apnea–hypopnea index at baseline and the increase 8 years later in 282 participants in the Wisconsin Sleep Cohort.




Subgroup analysis showed greater progression of disease in patients who were obese, 45 to 60 years of age, or habitual snorers at baseline. Sex did not correlate with disease progression. Data from Young T et al. Epidemiology of obstructive sleep apnea: a population health perspective. Am J Respir Crit Care Med. 2002;165:1217-39

# The mean change in apnea-hypopnea index (AHI) was related in a dose-response fashion to change in body weight during 4 years of follow-up.

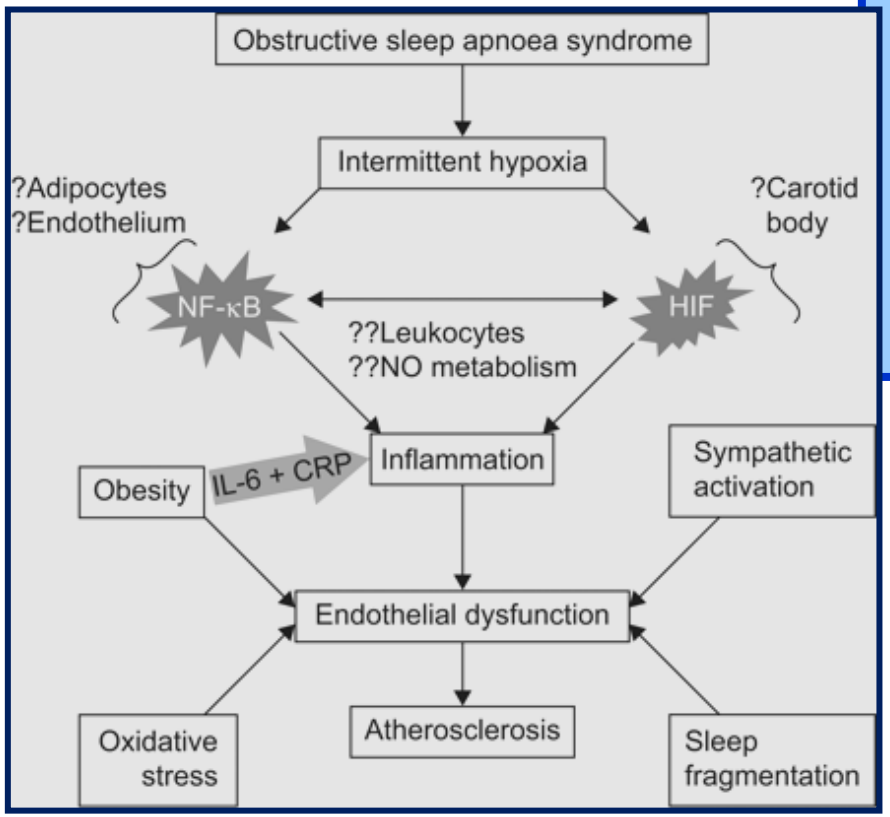



Leinum C J et al. Nutr Clin Pract 2009;24:675-687

# Relazione obesità e OSAS

1. Fattore meccanico: depositi di grasso a livello di vie aeree, torace, grasso viscerale
2. Fattore ormonale: leptina, grelina
3. Fattore infiammatorio: citochine (TNF-α, IL-6, PCR)

# Available Evidence of Chronic Inflammatory Status in Human Obstructive Sleep Apnea Syndrome



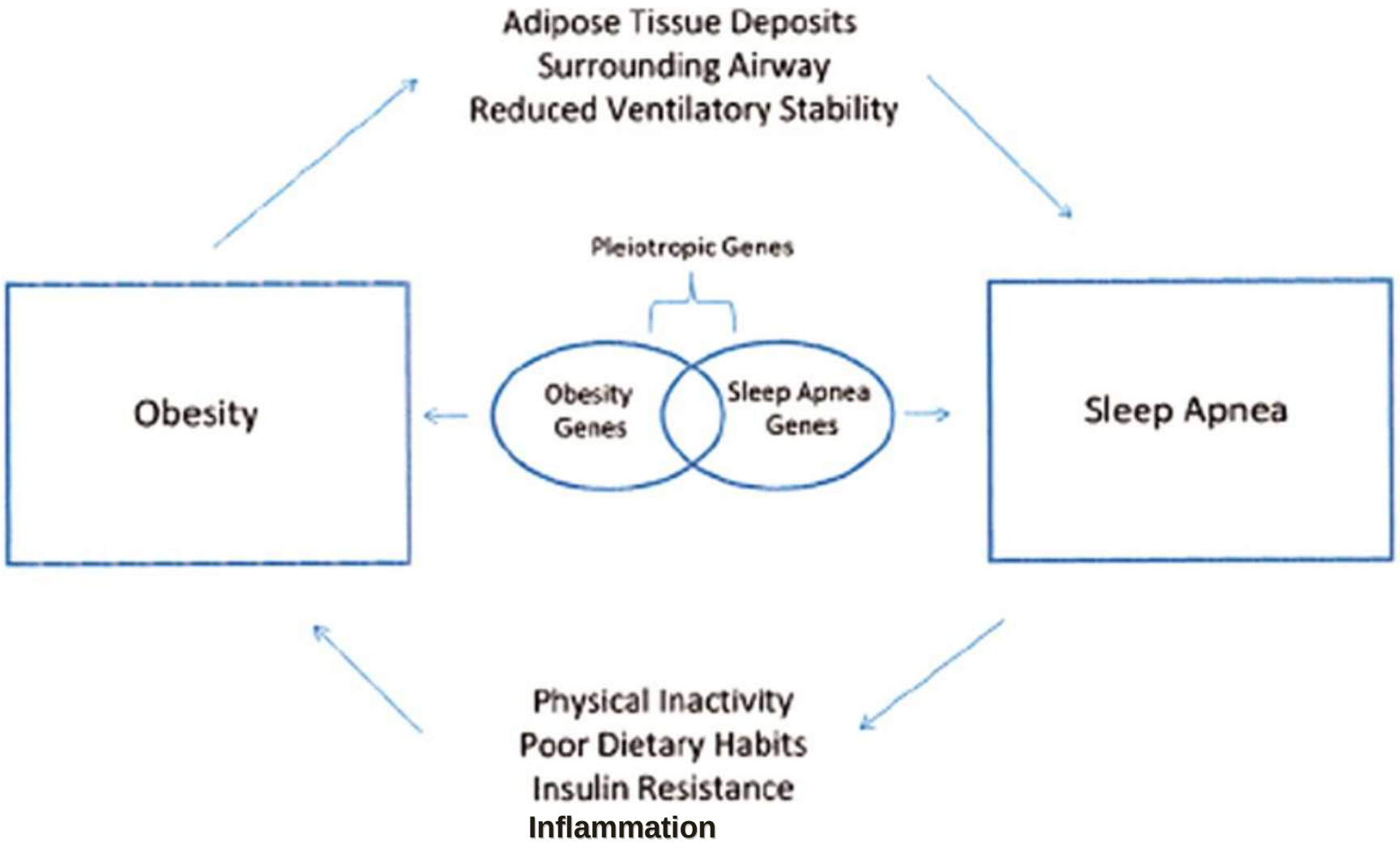

## Local inflammation—upper airways

| | |
|---|---|
| Interleukin 6 | ↑ |
| CD4+ cells | ↑ |
| CD4+/CD25+ cells | ↑ |
| CD8+-activated cells | ↑ |
| Neutrophils | ↑ |
| Macrophages | ↓ |

## Systemic inflammation—peripheral blood

| | |
|---|---|
| C-reactive protein | ↑ |
| Tumor necrosis factor | ↑ |
| Interleukin 6 | ↑ |
| Reactive oxygen species | ↑ |
| Nitric oxide | ↓ |

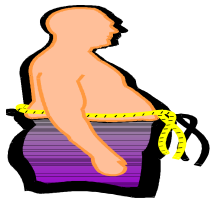
# The potential mechanisms that mediate the relationship between sleep-disordered breathing and obesity.

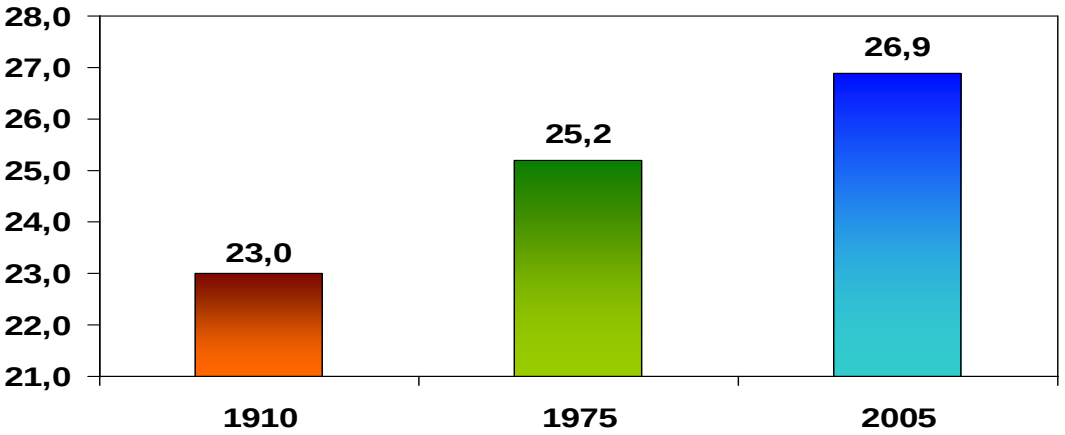



Leinum C J et al. Nutr Clin Pract 2009;24:675-687

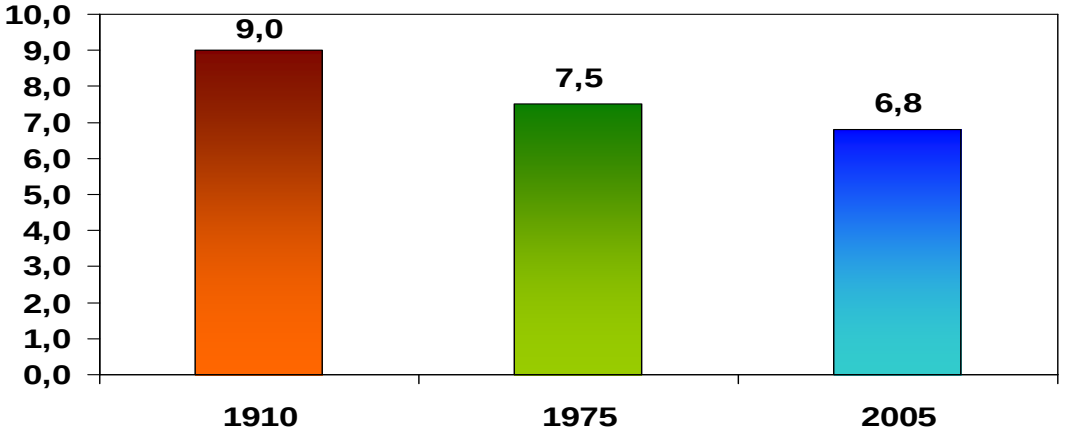
# Obesity Epidemic and Sleep Duration

## BMI in US adults



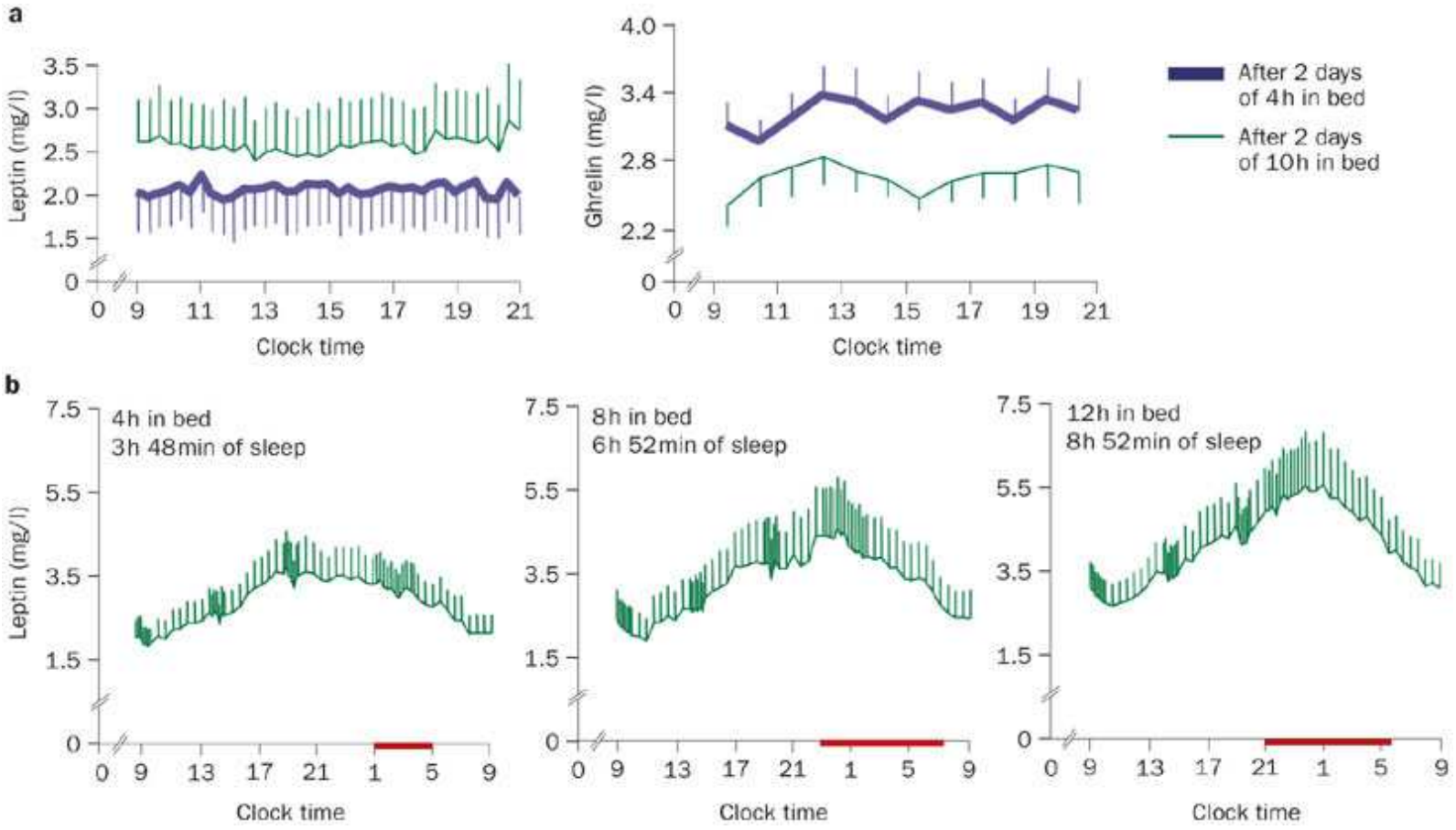



## Sleep duration in US adults



# Effect of sleep duration on leptin and ghrelin levels

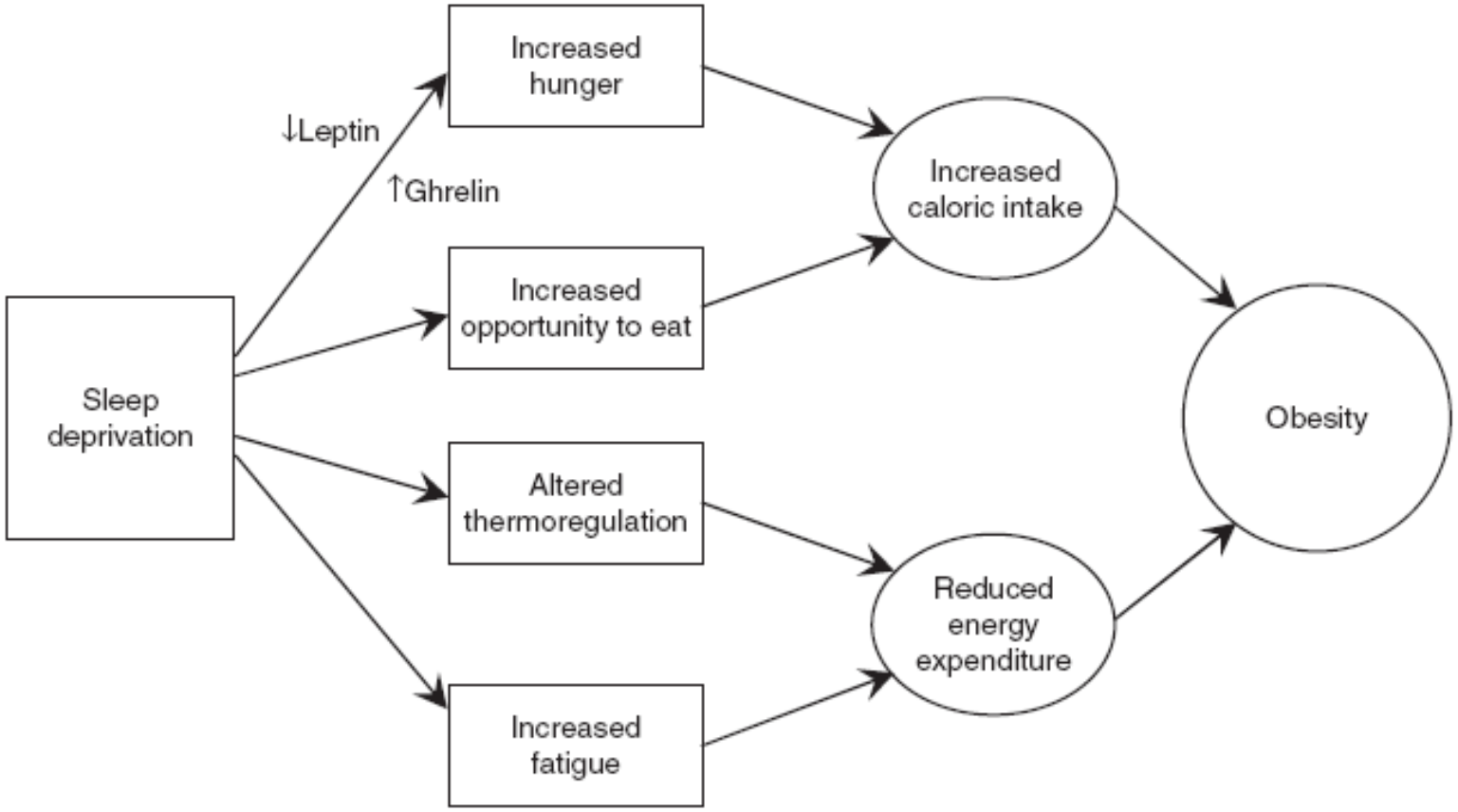
Risultati: restrizione del sonno in giovani uomini è associata a riduzione dei livelli di leptina, aumento dei livelli di grelina e aumento della fame e dell'appetito



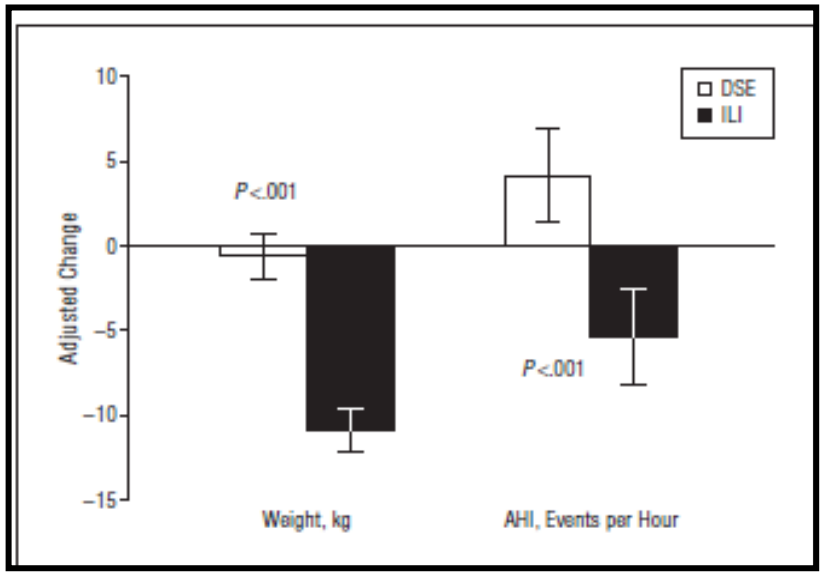

Spiegel K *et al*. (2009) Effects of poor and short sleep on glucose metabolism and obesity risk *Nat Rev Endocrinol* doi:10.1038/nrendo.2009.23

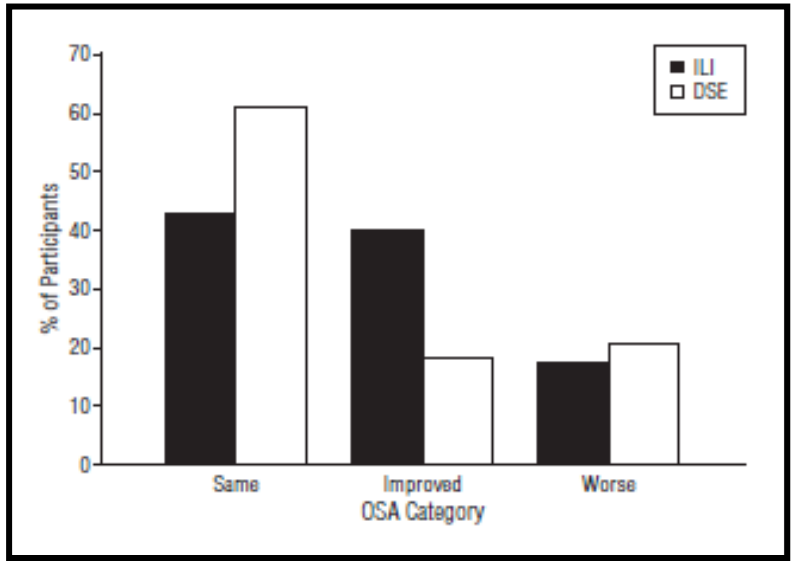
# Potential mechanisms by which sleep deprivation may predispose to obesity.

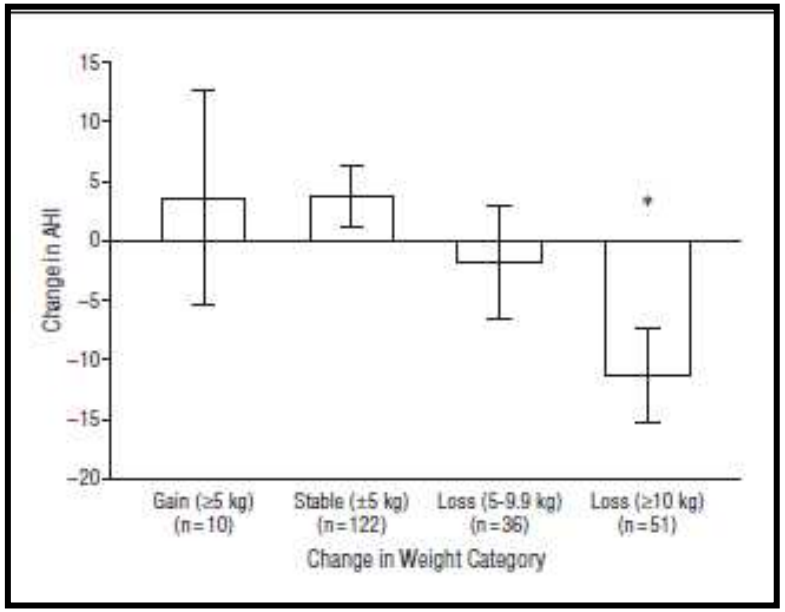
Patel SR,Hu FB. Short Sleep Duration and Weight Gain: A Systematic Review. *Obesity* (2008) 16 3, 643-653.



# CALO PONDERALE e OSA



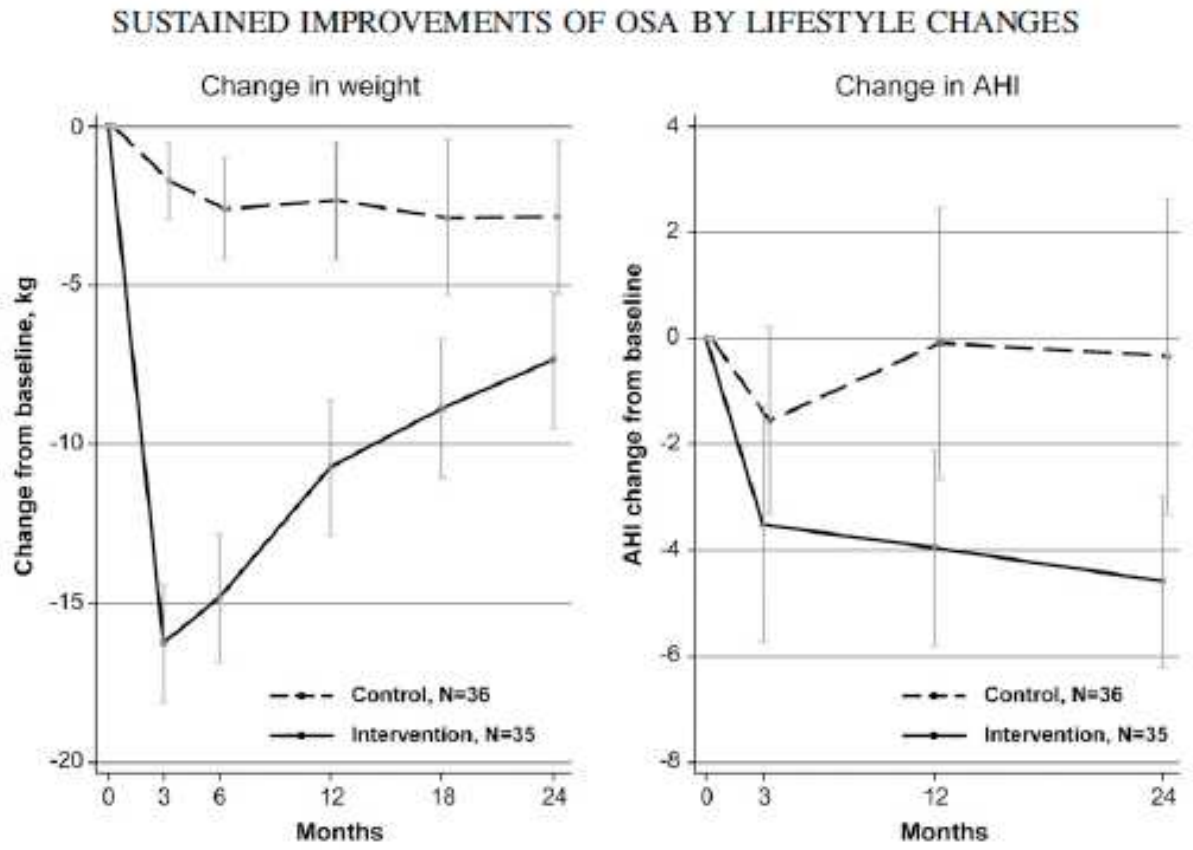




264 soggetti OSA moderata, DMT2, randomizzati in 2 gruppi
Intensive Lifestyle Intervention and Diabetes Support Education
Seguiti per 12 mesi
The Sleep AHEAD Study

*Arch Intern Med 169,17:1619-1626 2009*

## CALO PONDERALE e OSA




*Am J Clin Nutr 2010; 92: 688-96*

# CALO PONDERALE e OSA

## Association Between Weight Loss Achieved By Bariatric Surgery and Obstructive Sleep Apnea Severity

| | | | | | BMI | | | AHI | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Study | No. of Patients | Follow-up, mo | Year of Study | Type of Surgery | Baseline | Follow-up | Reduction (% Change) | Baseline | Follow-up | Reduction (% Change) |
| Rasheid et al[81] | 11 | 3-21 | 1998-2001 | GBP | 62 | 40 | −22 (−35.5) | 56 | 23 | −33 (−68.9) |
| Haines et al[82] | 101 | 6-42 | 1998-2005 | GBP | 56 | 38 | −18 (−22.2) | 51 | 15 | −35 (−70.6) |
| Valencia-Flores et al[83] | 29 | 13.7 | 1999-2002 | GBP | 56.5 | 39.2 | −17.3(−30.7) | 53.7 | 8.6 | −45.1 (−83.9) |
| Lankford et al[84] | 15 | 12 | 2002-NA | GBP | 48 | 32 | −16 (−33.4) | 32 | 11 | −21 (−65.7) |
| Dixon et al[50] | 25 | 17 | 1999-2002 | GBP | 52.7 | 37.2 | −15.5 (29.5) | 61.6 | 13.4 | −48.2 (−78.3) |
| Guardiano et al[85] | 8 | 28 | NA | GBP | 49 | 34 | −15 (−30.7) | 55 | 14 | −41 (−74.6) |
| Busetto et al[86] | 17 | 17 | NA | IGB | 55.8 | 48.6 | −7.2 (−12.9) | 52.1 | 14 | −38.1 (−73.2) |
| Charuzi et al[91] | 46 | 46 | 1978-1986 | GBP and VBG | 47.5 | 32.1 | −15.4(−32.5) | 58.8 | 7.8 | −51 (−86.8) |
| Scheuller et al[88] | 15 | 12-144 | NA | GBP and VBG | 160[a] | 105[a] | −55[b] (−65.6) | 97 | 11.3 | −85.7 (−88.4) |
| Sugerman et al[89] | 40 | 69.6 | 1980-1990 | GBP,VBG, and HG | 56 | 40 | −16 (−28.6) | 64 | 26 | −38 (−59.4) |
| Pillar et al[90] | 14 | 90 | NA | GBP | 45 | 35 | −10 (−22.3) | 40 | 24 | −16 (−40) |
| Summers et al[99] | 1 | 6 | NA | VBG | 54 | 37 | −17 (−31.5) | 40 | <5 | −36 (−90) |
| Lettieri et al[98] | 24 | 12 | 2003-2005 | GBP | 51.0 | 32.1 | −18.9(−37.1) | 47.9 | 24.5 | −23.4 (−48.8) |
| Buchwald et al[92] | 1195 | ~24 | 1990-2003 | GBP,VBG, HG, and BPD | NA | NA | −14 | NA | NA | −33 |
| Angrisani et al[93] | 1 | 60 | 2000 | GBP and VBG | ~43.4 | ~35.5 | −7.9 (−28.3) | NA | <5 | 100% resolved |
| Skroubis et al[94] | 4 | 29.3 | 1994-2005 | GBP and BPD | ~45 | ~26 | −19 (−42.3) | NA | <5 | 100% resolved |
| Nelson et al[95] | 9 | 21 | 1999-2005 | GBP | 51 | 37 | −14 (−27.5) | NA | NA | 77% resolved |
| Nelson et al[96] | 85 | 12-148 | 1985-2004 | GBP | 61 | 37 | −24 (−39.4) | NA | NA | 48% resolved |
| Cleator et al[97] | 20 | 12 | 1997-2002 | Ileogastrostomy | 42.3 | 36 | −6.3(−14.9) | NA | NA | 85% improved |

Romero-Corral A et al. Chest 2010;137:711-719

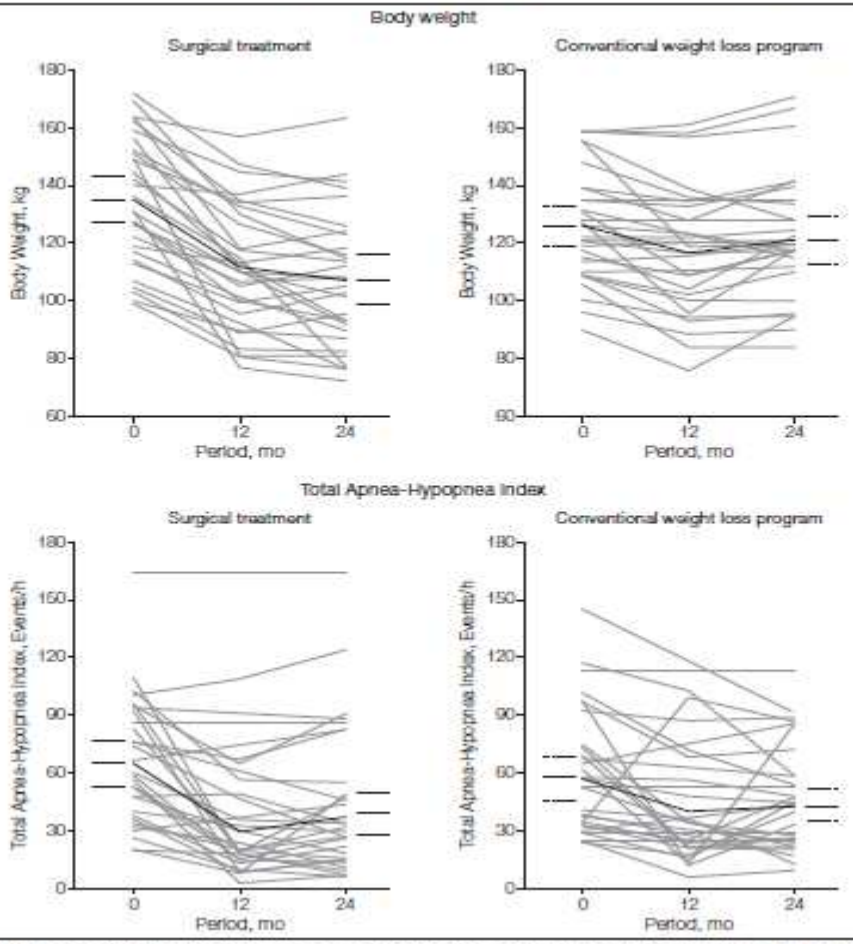
JAMA, September 19, 2012—Vol 308, No. 11 1149

# Surgical vs Conventional Therapy for Weight Loss Treatment of Obstructive Sleep Apnea

## A Randomized Controlled Trial

John B. Dixon, MBBS, PhD, FRACGP
Linda M. Schachter, MBBS, PhD
Paul E. O'Brien, MD, FRACS
Kay Jones, MT&D, PhD
Mariee Grima, BSc, MDiet
Gavin Lambert, PhD
Wendy Brown, MBBS, PhD, FRACS
Michael Bailey, PhD, MSc
Matthew T. Naughton, MD, FRACP

**Figure 2.** Weight and Apnea-Hypopnea Index at Baseline, 12 Months, and 2 Years



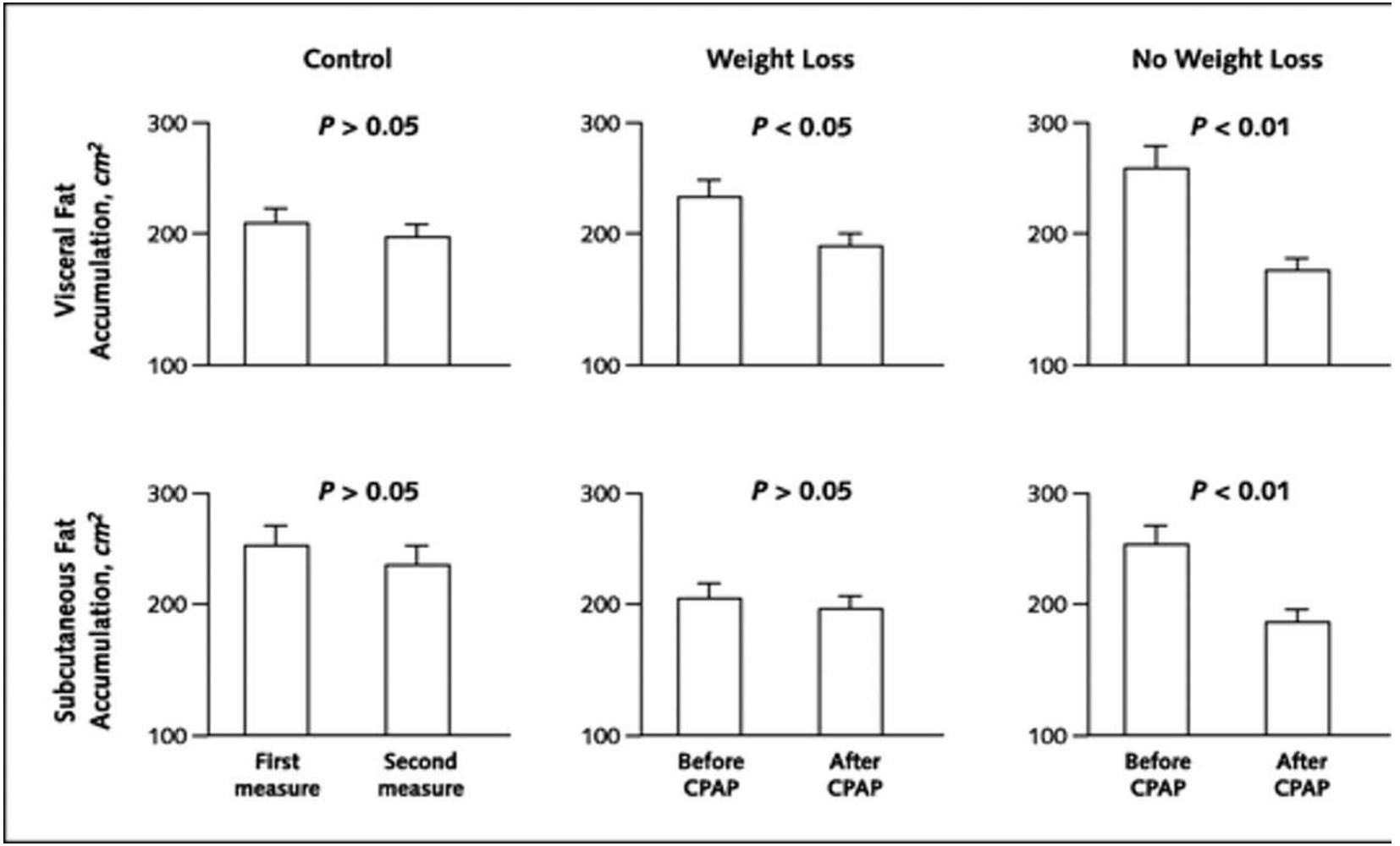

Mean values are indicated by thickened lines and 95% CIs are shown for baseline and 2 years by the dashed

- 60 obesi BMI>40 OSAS severe
- 30 terapia medica
- 30 chirurgica bariatrica
- Calo ponderale di 5,1 kg e di 27,8 kg rispettivamente

Conclusioni: l'utilizzo della chirurgia bariatrica non comporta una riduzione maggiore di OSA nonostante il maggior calo ponderale

# E la terapia con C-PAP migliora l’obesità?

# Changes in body fat after long-term treatment with continuous positive airway pressure (CPAP)




Caples S M et al. Ann Intern Med 2005;142:187-197

Annals of Internal Medicine

# Osa e resistenza insulinica

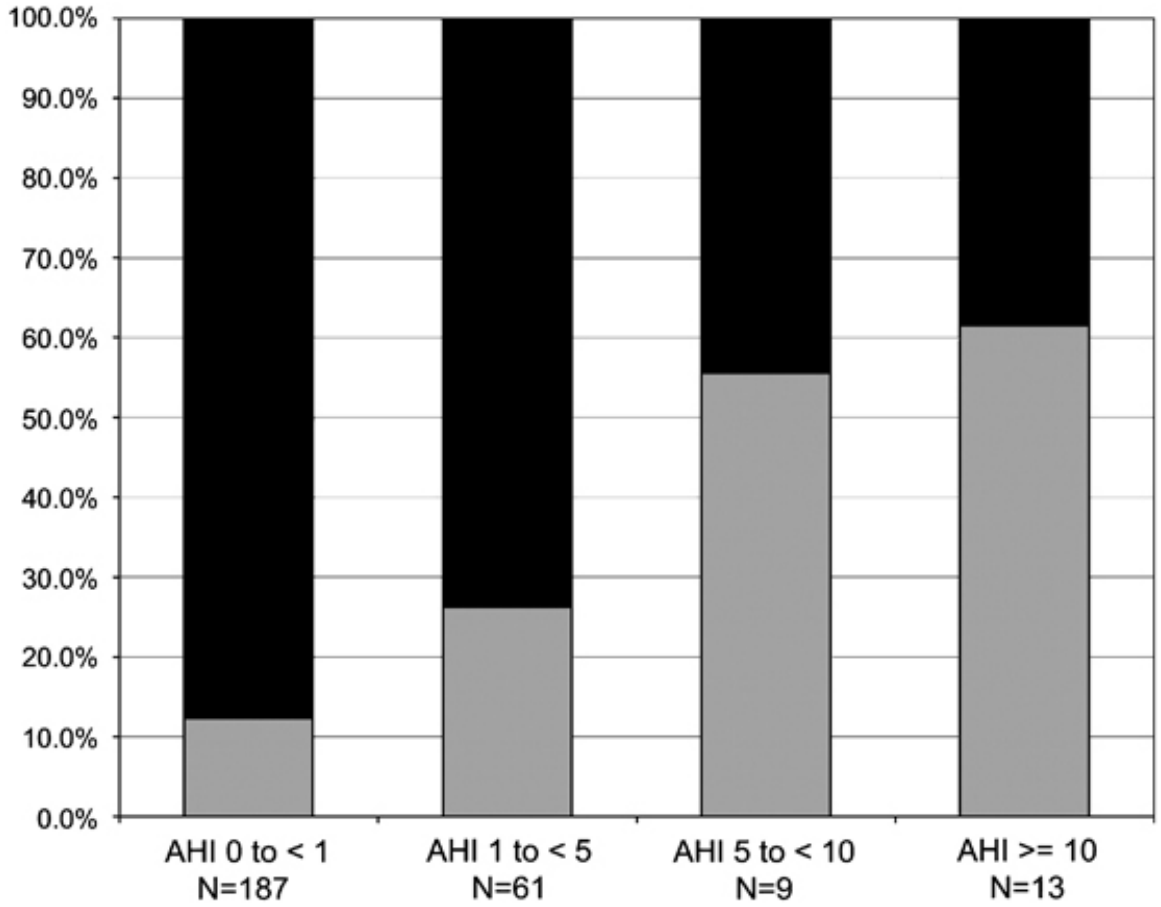
- OSA è associata con lo sviluppo di Resistenza Insulinica

- OSA aggrava la Resistenza Insulinica

- I soggetti che presentano OSA hanno più probabilità di avere la sindrome metabolica e le persone con sindrome metabolica presentano un rischio maggiore per OSA

# Prevalence of the metabolic syndrome in increasingly severe categories of sleep-disordered breathing, as defined by increasing levels of the apnea-hypopnea index (AHI).

Black bars represent the percentage of subjects without the metabolic syndrome; gray bars represent with the metabolic syndrome




Verhulst SL et al. Is sleep-disordered breathing an additional risk factor for the metabolic syndrome in obese children and adolescents?. *International Journal of Obesity* (2009) 33**,** 8-13

# Sindrome Z

Ian Wilcox et al

Thorax 1998; 53 suppl 3 S25-28

Syndrome X + OSA =

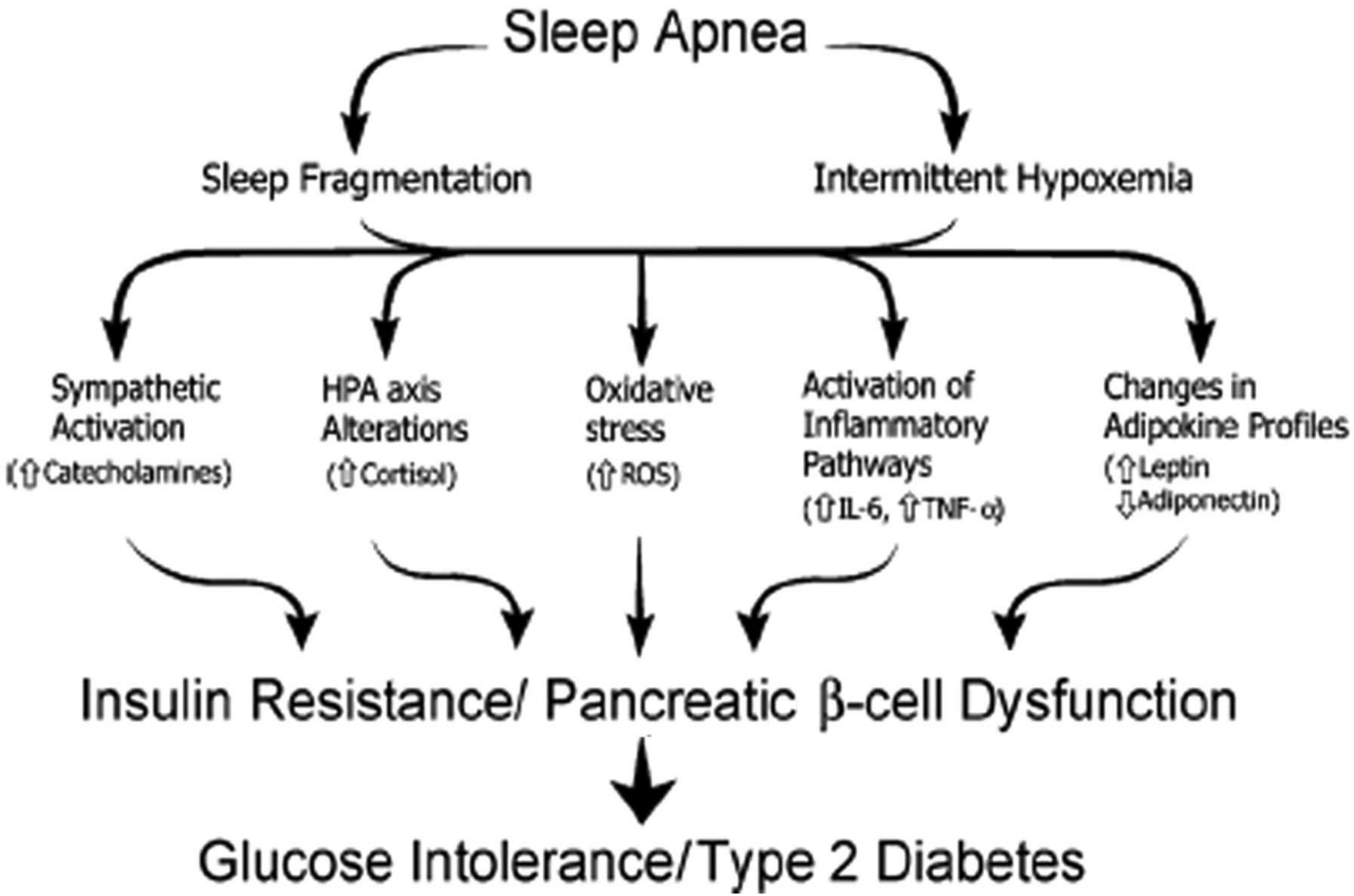
“Syndrome Z” the interaction of sleep apnea, vascular risk factors and heart disease.

# Gli studi sul metabolismo glucidico nei pazienti con OSA hanno evidenziato:

**…….un'associazione robusta tra OSA e resistenza insulinica, alterata tolleranza glucidica ed il rischio di sviluppare diabete indipendentemente dalla presenza di obesità**

—Homa index, Clamp iperinsulinemico, ivGTT
—Controllato per età, sesso, BMI, circonferenza vita, percentuale di grasso corporeo
—Evidenze da studi prospettici: molto poche !
—Studi di intervento CPAP per lo più negativi (compliance !!!)

# The potential mechanisms of glucose intolerance and insulin resistance in patients with sleep-disordered breathing.

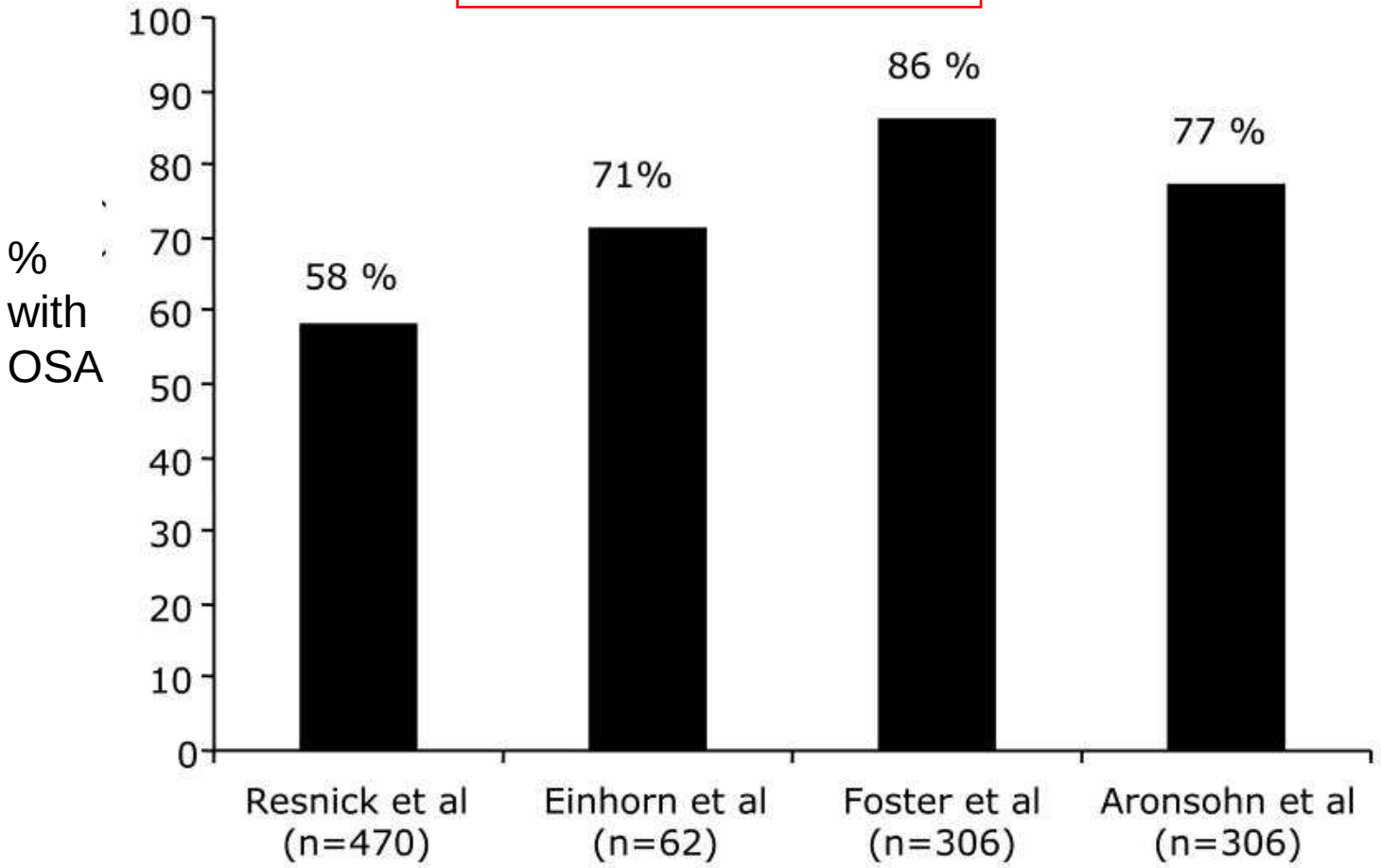



Diabetes Res Clin Prac. 2008;81:2-12.179

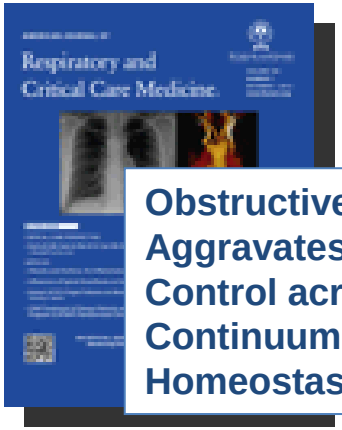
# OSA e Diabete tipo 2

## Prevalenza elevata di OSA nei pazienti con DMT2

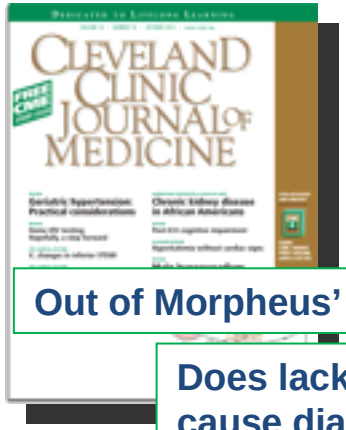
Most were undiagnosed



# Sleep apnea and diabetes risk*: the evidence*

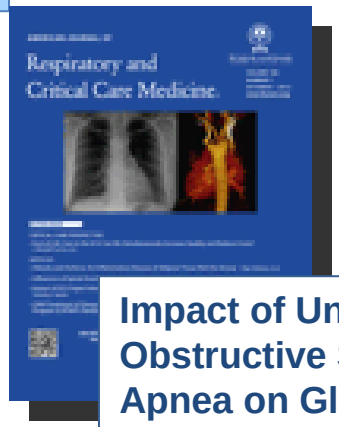



Obstructive Sleep Apnea Aggravates Glycemic Control across the Continuum of Glucose Homeostasis

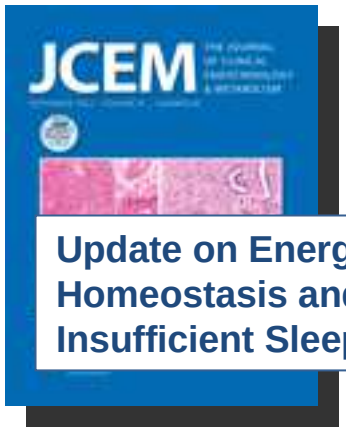



Out of Morpheus' embrace

Does lack of sleep cause diabetes?

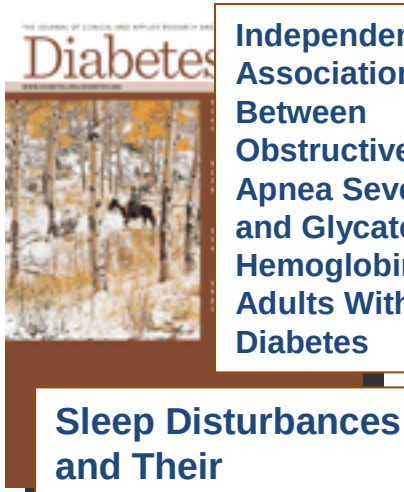



Impact of Untreated Obstructive Sleep Apnea on Glucose Control in Type 2 Diabetes




Update on Energy Homeostasis and Insufficient Sleep


Cross-Sectional Associations Between Measures of Sleep and Markers of Glucose Metabolism Among Subjects With and Without Diabetes
The Coronary Artery Risk Development in Young Adults (CARDIA) Sleep Study



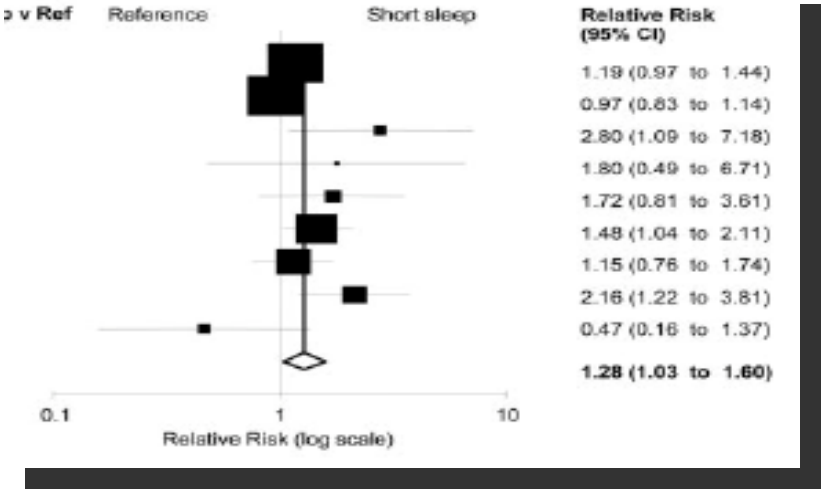

Independent Association Between Obstructive Sleep Apnea Severity and Glycated Hemoglobin in Adults Without Diabetes

Sleep Disturbances and Their Relationship to Glucose Tolerance in Pregnancy

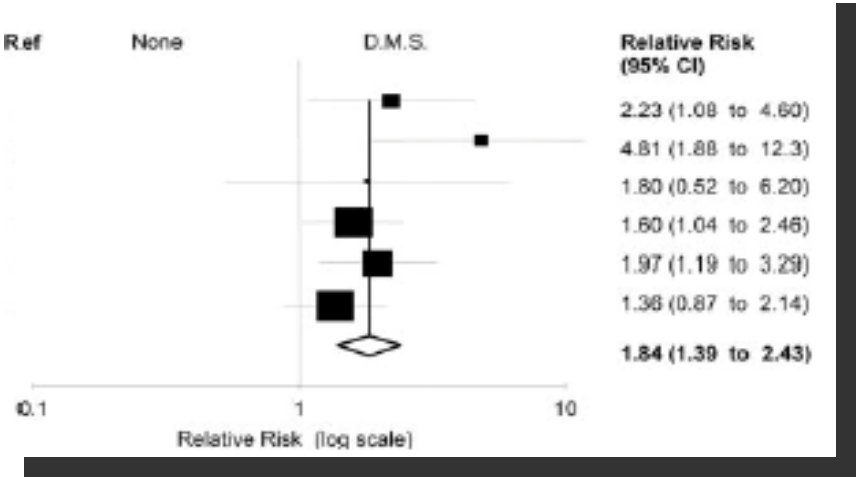
# Quantity and Quality of Sleep and Incidence of Type 2 Diabetes

Cappuccio FP et al. Diabetes Care 33:414-420,2010

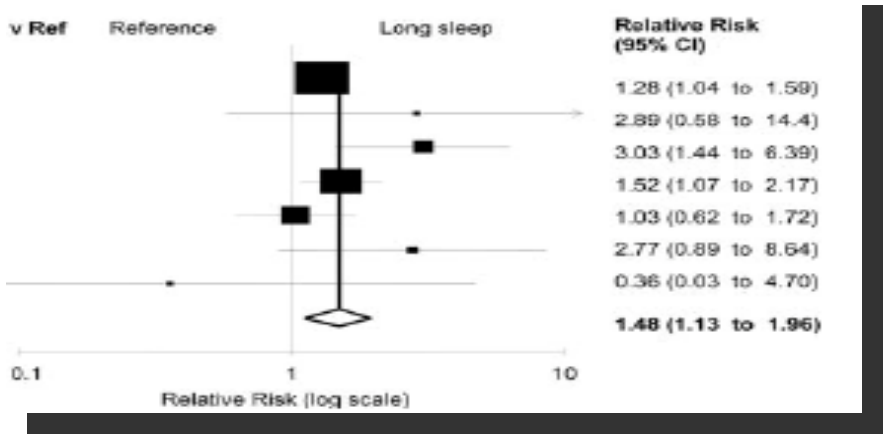
Short sleep duration and incidence of diabetes




Difficulty staying asleep and incidence of diabetes




Difficulty falling asleep and incidence of diabetes




Poor sleepers had
% increased odds
of developing diabetes

# Possibili meccanismi patogenetici

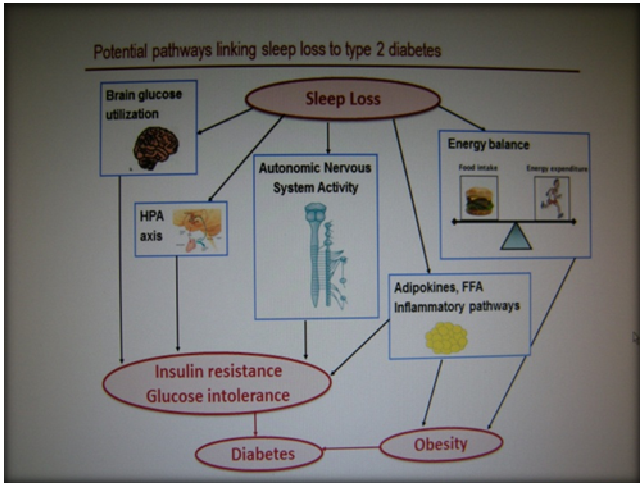
- **Riduzione dell'utilizzazione di glucosio cerebrale**
  → studi con *PET*

- **Aumentati livelli serali di cortisolo**
→ *Ridotta S.I. alla mattina*

- **Aumentata secrezione di grelina e di GH durante lo stato di veglia**
→ *Ridotto glucose disposal*

- **Alterazioni della bilancia simpato-vagale**
→ *A favore dell'attività simpatica*

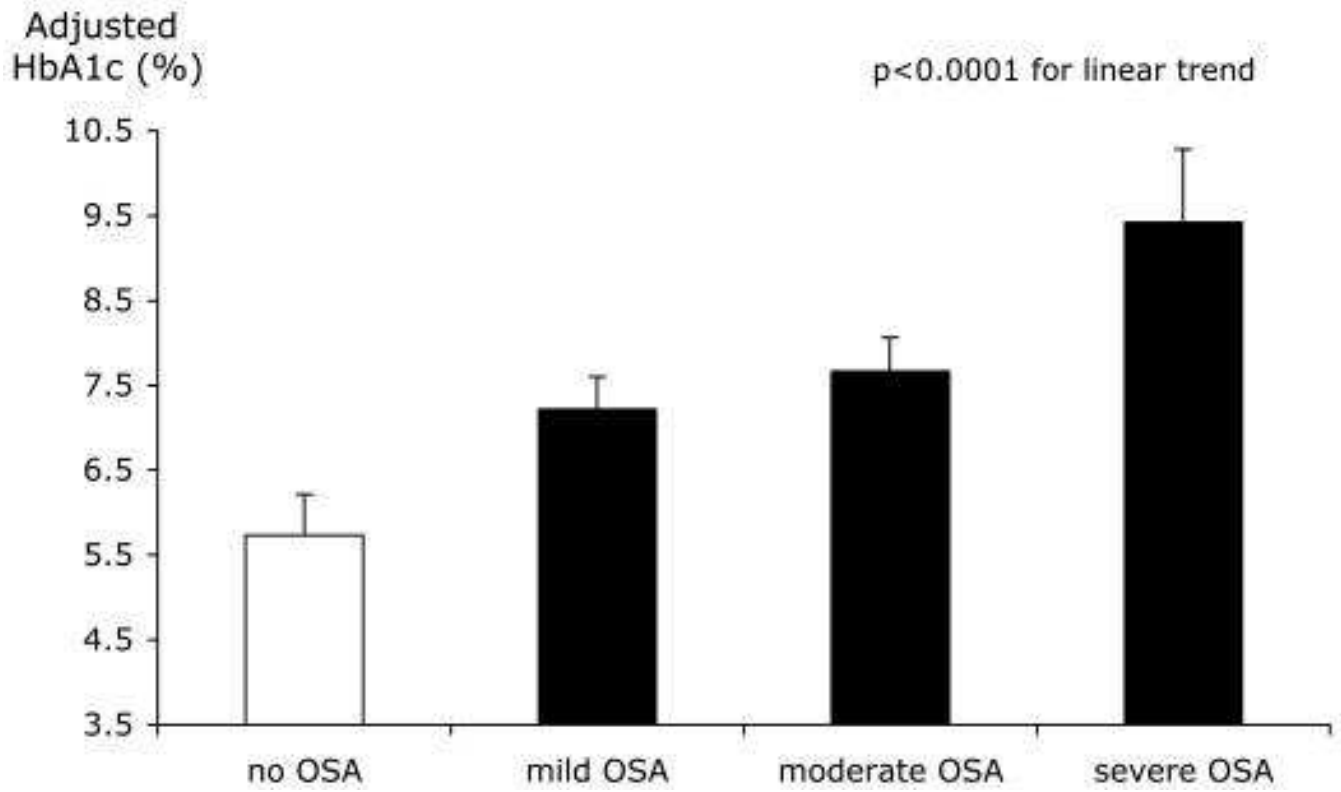
- **Infiammazione**
→ *CRP, IL-6, TNF α sono elevati*



# Inoltre……..

- Relazione tra OSA e compenso glicemico, HbA1c più elevata in OSA di grado severo.Aronshn RS et al Am J Resp Crit Care Med 181, 507-513, 2010
- Retinopatia preproliferativa e maculopatia molto più frequenti in diabetici con OSA. West SD et al Diabet Med 27, 423-430, 2010
- D'altra parte nella retinopatia proliferativa la desaturazione di O2 è predittore oltre all' età e a HbA1c Shipa et al AmJ Ophtalmol 2010

# Association between OSA severity and HbA1c




Adjusting for effects of age, sex, race, BMI, number of diabetes medications, levels of exercise, years of diabetes, and total sleep time on PSG

*Conclusions*: In patients with type 2 diabetes, increasing severity of OSA is associated with poorer glucose control, independent of adiposity and other confounders

Aronsohn et al AJRCCM 2009

# Effect of C-PAP treatment on glucose metabolism

**Table 2** | Effect of CPAP treatment on glucose metabolism

| Population of patients | Positive effect reported | No effect reported |
|---|---|---|
| ***Patients with T2DM***[a] | | |
| Total number of studies | 5[49–53] | 1[54] |
| Total number of patients | 102 | 42 |
| ***Nondiabetic patients***[b] | | |
| Total number of studies | 4[55–58] | 7[59–65] |
| Total number of patients | 109 | 225 |

[a]Improvement of glucose metabolism in patients with T2DM was defined as decreased $HbA_{1C}$ level and/or decreased postprandial glucose level by continuous glucose monitoring, and/or improved insulin sensitivity by hyperinsulinemic euglycemic clamp, and/or improved insulin sensitivity by fasting HOMA index. [b]Improvement of glucose metabolism in nondiabetic patients was defined as improved insulin sensitivity by hyperinsulinemic euglycemic clamp, and/or improved insulin sensitivity by fasting HOMA index, and/or decreased fasting glucose and insulin levels. Abbreviations: CPAP, continuous positive airway pressure; HOMA, homeostasis model assessment; T2DM, type 2 diabetes mellitus.

Spiegel K *et al*. (2009) Effects of poor and short sleep on glucose metabolism and obesity risk *Nat Rev Endocrinol* doi:10.1038/nrendo.2009.23

# Riassumendo:

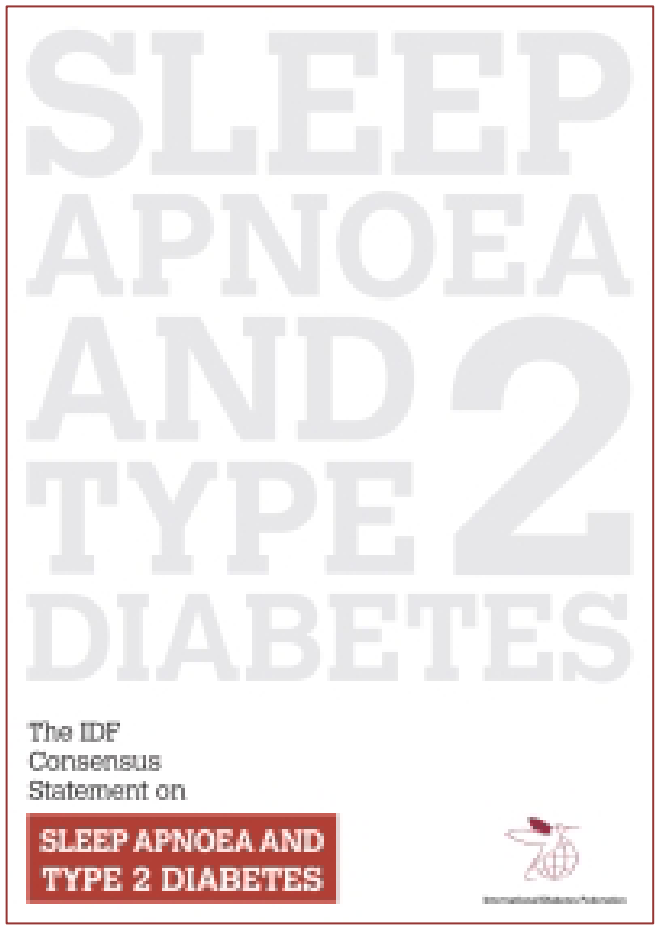
- ✓ OSA sono frequenti nell'obesità, che costituisce il principale fattore predisponente l'insorgenza e la progressione di OSA, il calo ponderale significativo migliora OSA
- ✓OSA sono associate con resistenza insulinica, alterata tolleranza glucidica, e rischio di DMT2, indipendentemente da obesità

- ✓ OSA ha un'elevata prevalenza nei pazienti con DMT2 può essere una comorbidità misconosciuta

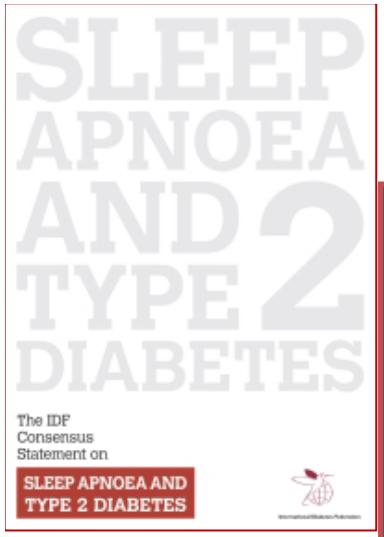
- ✓OSA non riconosciute e non trattate possono peggiorare il controllo glicemico e richiedere terapie farmacologiche più aggressive

- ✓Sono necessari trials clinici più consistenti per verificare gli effetti del trattamento dell'OSA (C-PAP) sull'obesità e sul controllo glicemico

- ✓La durata e la qualità del sonno sono fattori di rischio potenzialmente modificabili, che potrebbero avere importanti implicazioni cliniche nella prevenzione e nel trattamento dell'obesità e del diabete




**IDF Consensus Statement**
on Sleep Apnoea and Type 2 Diabetes 2008 ha analizzato i legami tra OSA ed alterazioni del metabolismo glucidico e i legami tra OSA e malattie cardiovascolari




# Raccomandazioni per la *PRATICA CLINICA*

**Nei centri del sonno-**

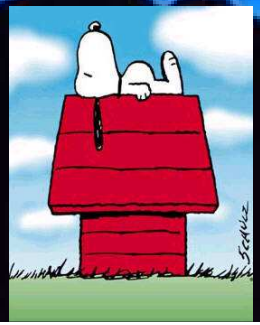
Pazienti con OSA dovrebberro essere indagati di routine per markers di disturbi metabolici e di rischio cardiovascolare. I test di base dovrebbero comprendere:

- Circonferenza vita
- Pressione arteriosa
- Profilo lipidico
- Glicemia

**Nei Servizi di Diabetologia**

- Nella valutazione di tutti i soggetti con diabete di tipo 2 e/o con sindrome metabolica dovrebbe essere considerata la possibilità di OSA
- Nei diabetici tipo 2 dovrebbero essere sistematicamente indagati i sintomi di OSA: russamento, apnee osservate durante il sonno, sonnolenza diurna.
- Si dovrebbe fare riferimento ad uno specialista in fase precoce per stabilire una diagnosi per i benefici indotti dalla terapia sull'ipertensione e sulla qualità di vita.
- La terapia dell'OSA dovrebbe essere focalizzata sulla riduzione del peso corporeo nei soggetti obesi e sovrappeso. La C-PAP è attualmente il miglior trattamento per OSA da moderata a severa e dovrebbe essere considerata dove appropriato

# Grazie per l’attenzione



*Rationale*: Obstructive sleep apnea (OSA), a treatable sleep disorder that is associated with alterations in glucose metabolism in individuals without diabetes, is a highly prevalent comorbidity of type 2 diabetes. However, it is not known whether the severity of OSA is a predictor of glycemic control in patients with diabetes.
*Objectives*: To determine the impact of OSA on hemoglobin A1c (HbA1c), the major clinical indicator of glycemic control, in patients with type 2 diabetes.
*Methods*: We performed polysomnography studies and measured HbA1c in 60 consecutive patients with diabetes recruited from outpatient clinics between February 2007 and August 2009.
*Measurements and Main Results*: A total of 77% of patients with diabetes had OSA (apnea–hypopnea index [AHI] ≥5). Increasing OSA severity was associated with poorer glucose control, after controlling for age, sex, race, body mass index, number of diabetes medications, level of exercise, years of diabetes and total sleep time. Compared with patients without OSA, the adjusted mean HbA1c was increased by 1.49% ($P = 0.0028$) in patients with mild OSA, 1.93% ($P = 0.0033$) in patients with moderate OSA, and 3.69% ($P < 0.0001$) in patients with severe OSA ($P < 0.0001$ for linear trend). Measures of OSA severity, including total AHI ($P = 0.004$), rapid eye movement AHI ($P = 0.005$), and the oxygen desaturation index during total and rapid eye movement sleep ($P = 0.005$ and $P = 0.008$, respectively) were positively correlated with increasing HbA1c levels.
*Conclusions*: In patients with type 2 diabetes, increasing severity of OSA is associated with poorer glucose control, independent of adiposity and other confounders, with effect sizes comparable to those of widely used hypoglycemic drugs.

## Sleep duration and cardiometabolic risk: A review of the epidemiologic evidence

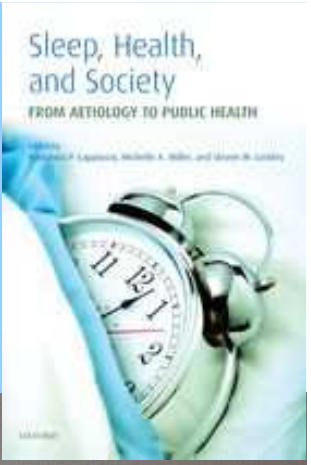
Kirsten L. Knutson

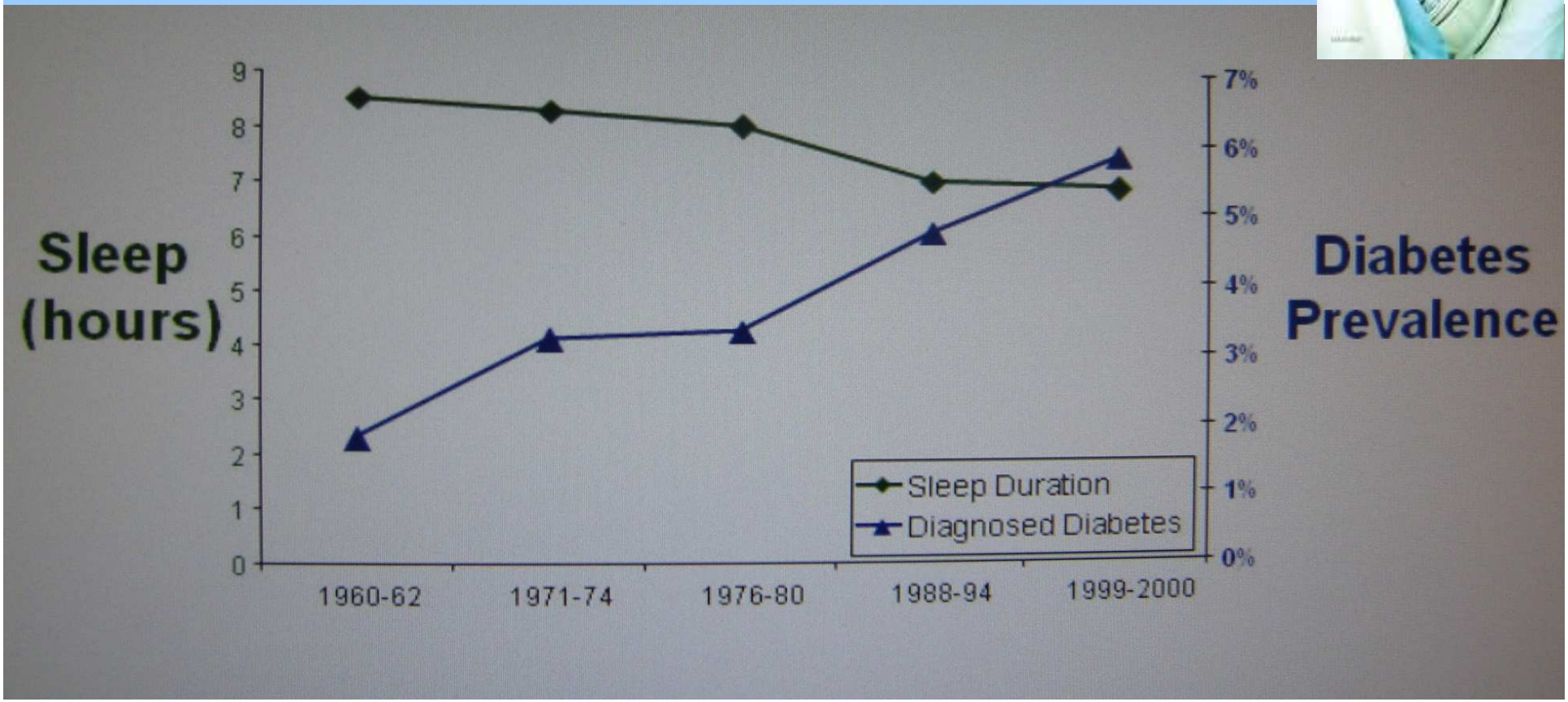




Schematic representation of possible mechanistic pathways linking disturbed or insufficient sleep to obesity, diabetes, cardiovascular disease (CVD) and hypertension (HTN).

# Sleep Duration and Diabetes in the U. S. 1960-2000




From Knutson and Broussard in Sleep,Health & Society 2010

# Incidence of Diabetes in Middle-Aged Men Is Related to Sleep Disturbances

Table 1—*Baseline and 15-year follow-up data on clinical characteristics of initially nondiabetic men and incidence of diabetes in relation to self-report of difficulty in falling asleep and regular use of hypnotics*

| | Neither type of sleep disturbance | Difficulty falling asleep or regular use of hypnotics | Both types of sleep disturbance | Whole study sample |
|---|---|---|---|---|
| n | 5,826 | 615 | 158 | 6,599 |
| At baseline | | | | |
| Age (years) | 44.3 ± 4.1 | 46.2 ± 2.7§ | 46.3 ± 2.5§ | 44.5 ± 4.0 |
| Systolic blood pressure (mmHg) | 125.7 ± 13.7 | 126.6 ± 15.5 | 126.4 ± 14.4 | 125.8 ± 13.9 |
| Diastolic blood pressure (mmHg) | 85.0 ± 9.2 | 86.1 ± 10.0 | 86.4 ± 10.0 | 85.1 ± 9.3 |
| Use of antihypertensive medication (%) | 2.8 | 5.7‖ | 5.7 | 3.2 |
| Heart rate (bpm) | 69.3 ± 10.4 | 69.7 ± 10.5 | 69.5 ± 10.8 | 69.4 ± 10.4 |
| Fasting whole blood glucose (mmol/l) | 4.8 ± 0.5 | 4.7 ± 0.5 | 4.7 ± 0.5 | 4.8 ± 0.5 |
| BMI (kg/m$^2$) | 24.5 ± 3.0 | 24.6 ± 3.1 | 24.2 ± 3.1 | 24.5 ± 3.0 |
| Current smoker (%) | 40.5 | 53.2§ | 57.6§ | 42.1 |
| Use of smokeless tobacco (%)* | 2.5 | 3.4 | 5.1‖ | 2.7 |
| Low physical activity (%) | 48.2 | 61.5§ | 57.6¶ | 49.7 |
| Social class | | | | |
| Nonmanual worker (%) | 44.1 | 36.9§ | 32.9‖ | 43.1 |
| Manual worker (%) | 52.4 | 56.4 | 53.2 | 52.8 |
| Other classifications (%) | 3.5 | 6.7§ | 13.9§ | 4.1 |
| Diabetes heredity (%)† | 11.9 | 12.7 | 14.6 | 12.0 |
| Follow-up | | | | |
| Follow-up time (years) | 14.7 ± 2.4 | 15.2 ± 2.5 | 15.1 ± 2.5 | 14.8 ± 2.4 |
| Change in BMI from baseline (kg/m$^2$) | 1.78 ± 1.88 | 1.90 ± 2.14¶ | 2.01 ± 2.20¶ | 1.80 ± 1.91 |
| Low physical activity (%) | 25.0 | 25.4 | 25.9 | 25.1 |
| Diabetes at follow-up (%) | 3.9 | 7.0† | 8.2¶ | 4.3 |
| $HbA_{1c}$ (%)‡ | 4.87 ± 0.71 | 5.11 ± 0.93§ | 4.89 ± 0.44 | 4.89 ± 0.73 |

Data are means ± SD or proportions. *Based on 4,229 men; †a positive family history of diabetes in first-degree relatives; ‡based on 1,549 men, e.g., 1,362, 148, and 39 men in respective category; §$P < 0.001$; ‖$P < 0.01$; ¶$P < 0.05$; $P$ values indicate significant age-adjusted (except for age) differences from the reference group, e.g., with neither type of sleep disturbance.

# Sleep disordered breathing and cancer mortality: results from the Wisconsin Sleep Cohort Study

F. Javier Nieto1, Paul E Peppard2, Terry Young3, Laurel Finn4, Khin Mae Hla5 and Ramon Farré6

## Abstract

Rationale: Sleep disordered breathing (SDB) has been associated with total and cardiovascular mortality, but an association with cancer mortality has not been studied. Results from in vitro and animal studies suggest that intermittent hypoxia promotes cancer tumor growth. The goal of the present study was to examine whether SDB is associated with cancer mortality in a community-based sample.

Methods: We used 22-year mortality follow-up data from the Wisconsin Sleep Cohort sample (n=1522). SDB was assessed at baseline with full polysomnography. SDB was categorized using the apnea-hypopnea index (AHI) and the hypoxemia index (percent sleep time below 90% oxyhemoglobin saturation). The hazards of cancer mortality across levels of SDB severity were compared using crude and multivariate analyses.

Measurements and Main Results: Adjusting for age, sex, body mass index, and smoking, the SDB was associated with total and cancer mortality in a dose-response fashion. Compared to normal subjects, the adjusted relative hazards of cancer mortality were 1.1 [95% confidence interval (CI), 0.5-2.7] for mild SDB (AHI 5-14.9), 2.0 (95% CI, 0.7-5.5) for moderate (AHI 15-29.9), and 4.8 (95% CI, 1.7-13.2) for severe SDB (AHI≥30) (p-trend=0.0052). For categories of increasing severity of the hypoxemia index, the corresponding relative hazards were 1.6 (95% CI, 0.6, 4.4), 2.9 (95% CI, 0.9-9.8), and 8.6 (95% CI, 2.6-28.7).

Conclusions: Our study suggests that baseline SDB is associated with increased cancer mortality in a community-based sample. Future studies that replicate our findings and look at the association between sleep apnea and survival after cancer diagnosis are needed.

# Prevalence of OSA in various populations

**Table 1** | Prevalence of OSA in various populations

| Population of patients | Prevalence of OSA (%) |
|---|---|
| ***General population*** | |
| Patients with OSA (AHI >5) and excessive daytime sleepiness[81] | 2–7 |
| Patients with OSA (AHI >5)[82] | 17 |
| ***Patients with endocrine disorders*** | |
| Obese patients[82] | 41–58 |
| Morbidly obese patients[37] | 50–98 |
| Patients with diabetes mellitus[38–40] | 17–97 |
| Patients with polycystic-ovary syndrome[41,42] | 44–70 |
| Patients with acromegaly[43] | 19–23 |
| Patients with hypothyroidism[43] | 50–100 |
| Patients with Cushing syndrome[43] | 18–32 |

Abbreviations: AHI, apnea–hypopnea index; OSA, obstructive sleep apnea.

Spiegel K *et al.* (2009) Effects of poor and short sleep on glucose metabolism and obesity risk
*Nat Rev Endocrinol* doi:10.1038/nrendo.2009.23

# Potential Mechanisms of Vascular Disease Associated With Obstructive Sleep Apnea

PARISH JM, SOMERS VK *Mayo Clin Proc. 2004;79(8):1036-1046*

## Increased daytime sympathetic activity

- Increased resting heart rates
- Decreased R-R interval variability
- Increased blood pressure variability

## Endothelial dysfunction

- Increased endothelin-1 activity
- Blunted vasodilation to cholinergic stimulation
- Increased intercellular adhesion molecule 1, vascular cell adhesion molecule 1, and E-selectin
- Increased adhesion of leukocytes to vascular endothelium

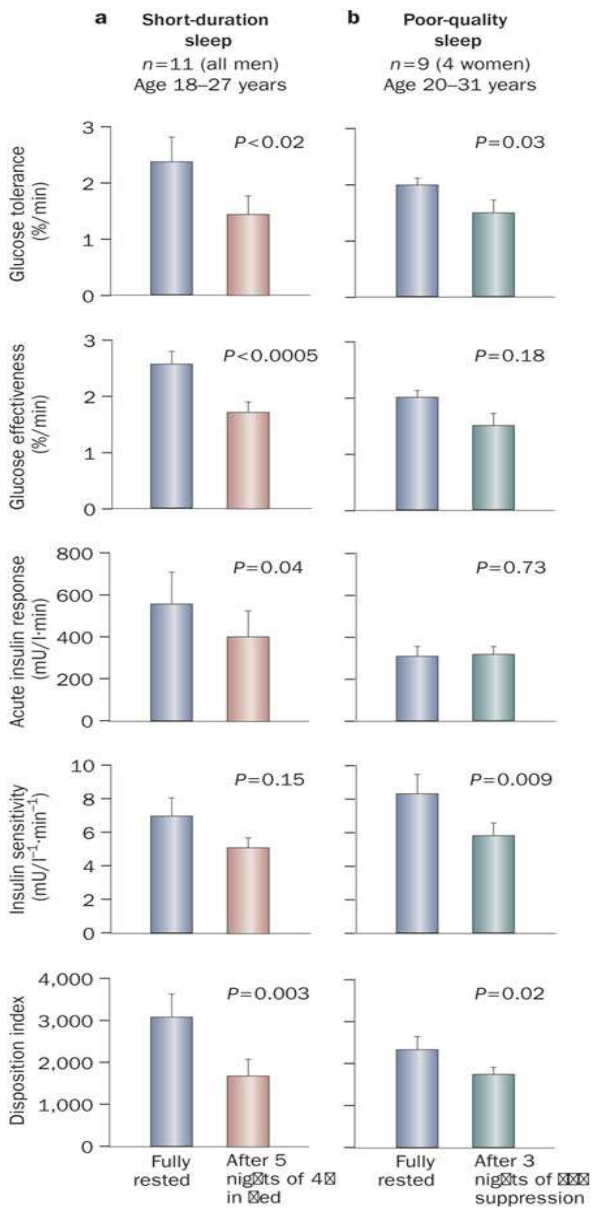
## Increases in inflammatory mediators

- C-reactive protein
- Interleukin 6
- Oxidative stress by oxygen free radicals

## Increases in prothrombotic factors

- Fibrinogen
- Platelet activation and aggregation
- Plasminogen activator inhibitor

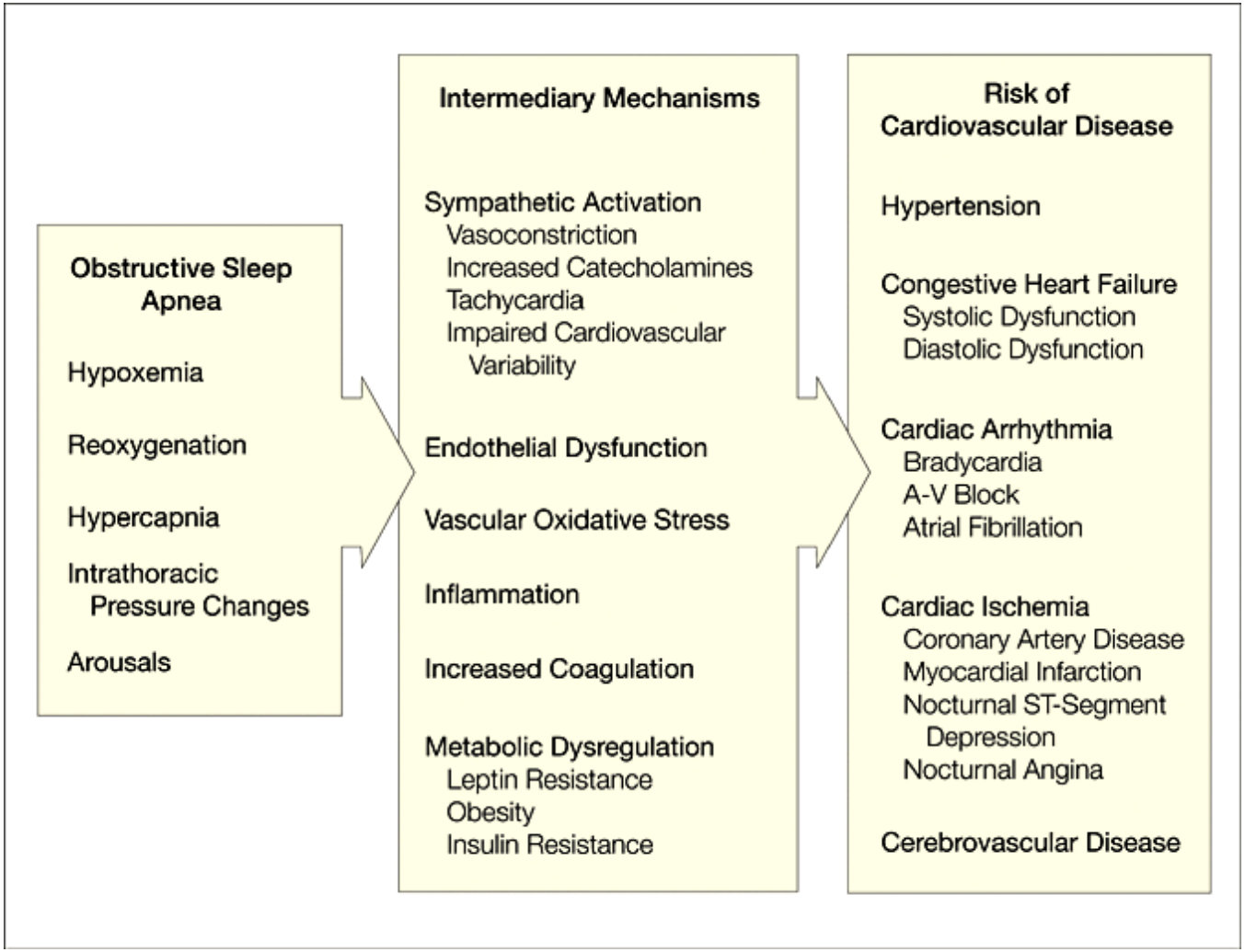
# Results from intravenous glucose-tolerance tests in healthy individuals when fully rested and after sleep manipulations




**Experimental reduction of the duration or quality of sleep has deleterious effect on glucose metabolism**

Spiegel K *et al*. (2009) Effects of poor and short sleep on glucose metabolism and obesity risk *Nat Rev Endocrinol*

# Intermediary Mechanisms Associated With Obstructive Sleep Apnea That Potentially Contribute to Risk of Cardiovascular Disease



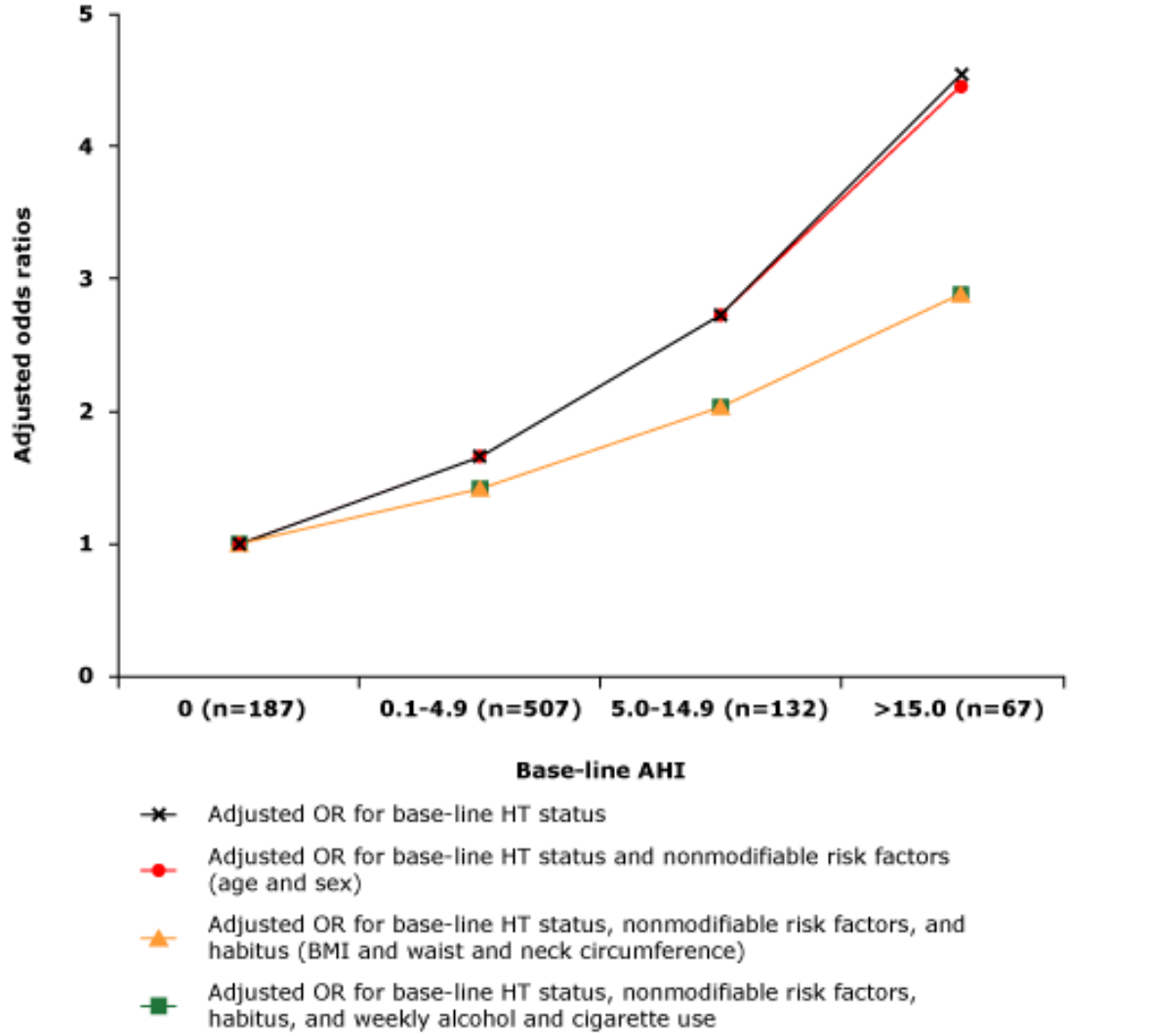

Abnormalities associated with obstructive sleep apnea may be intermediary mechanisms that contribute to the initiation and progression of cardiac and vascular pathology. These mechanisms may interact with each other, thus potentiating their pathophysiological implications.



**Shamsuzzaman, A. S. M. et al. JAMA 2003;290:1906-1914.**

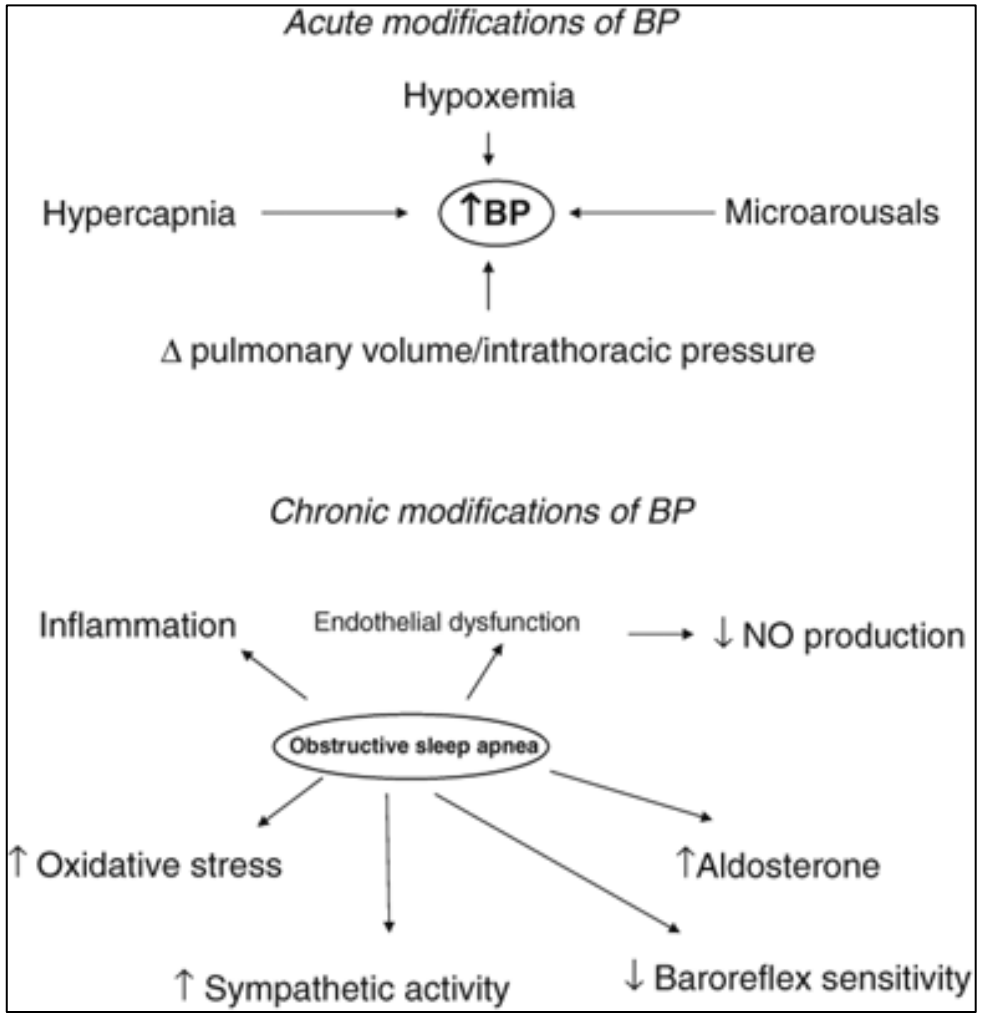
JAMA

## Hypertension and AHI




*Data from: Peppard, PE, Young, T, Palta, M, Skatrud, J. Prospective study of the association between sleep-disordered breathing and hypertension. N Engl J Med 2000; 342:1378.*

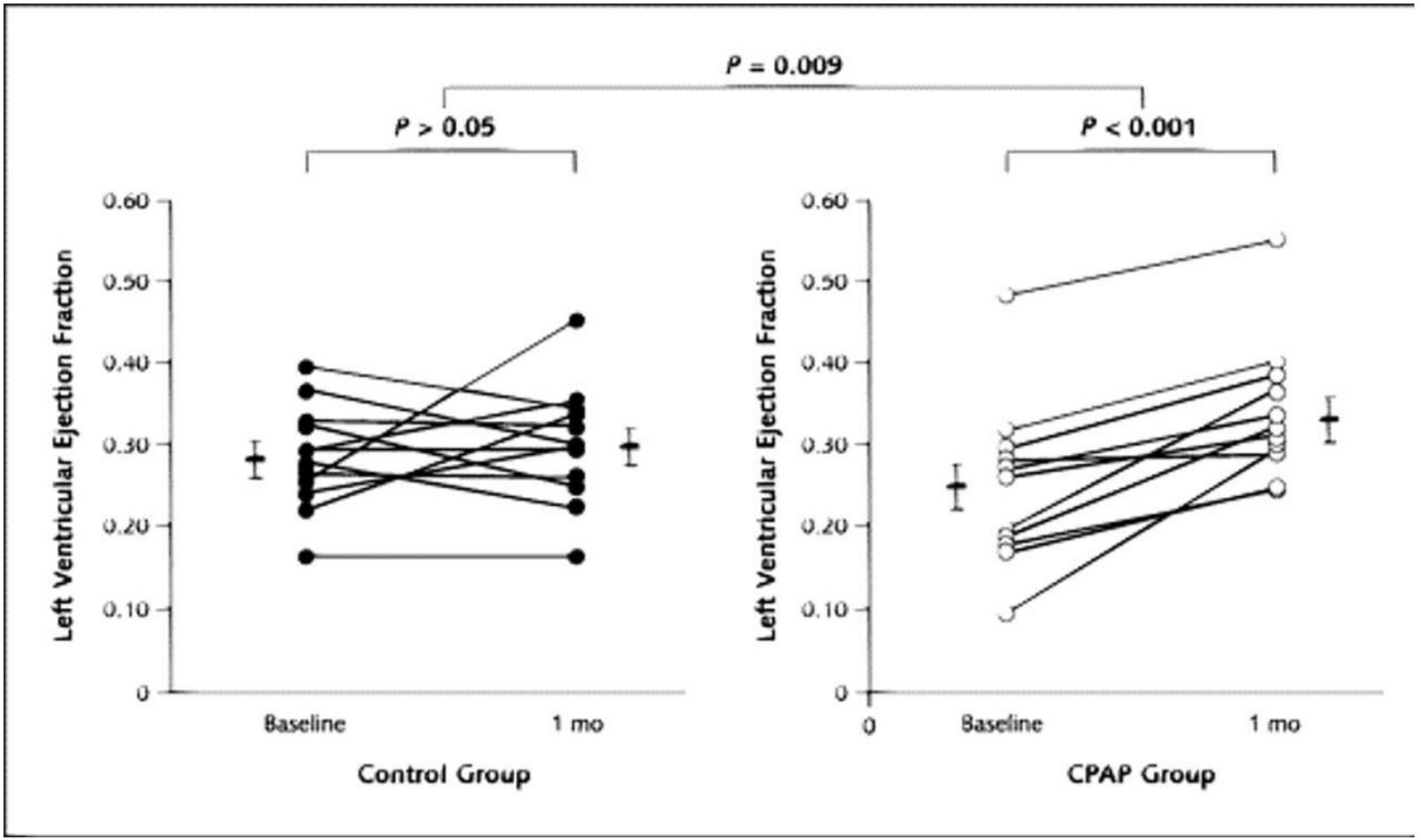
# Mechanisms of hypertension related to obstructive sleep apnoea syndrome (OSAS)




J-P Baguet, et al. Hypertension and obstructive sleep apnoea syndrome: current perspectives
*Journal of Human Hypertension* (2009) 23, 431-443

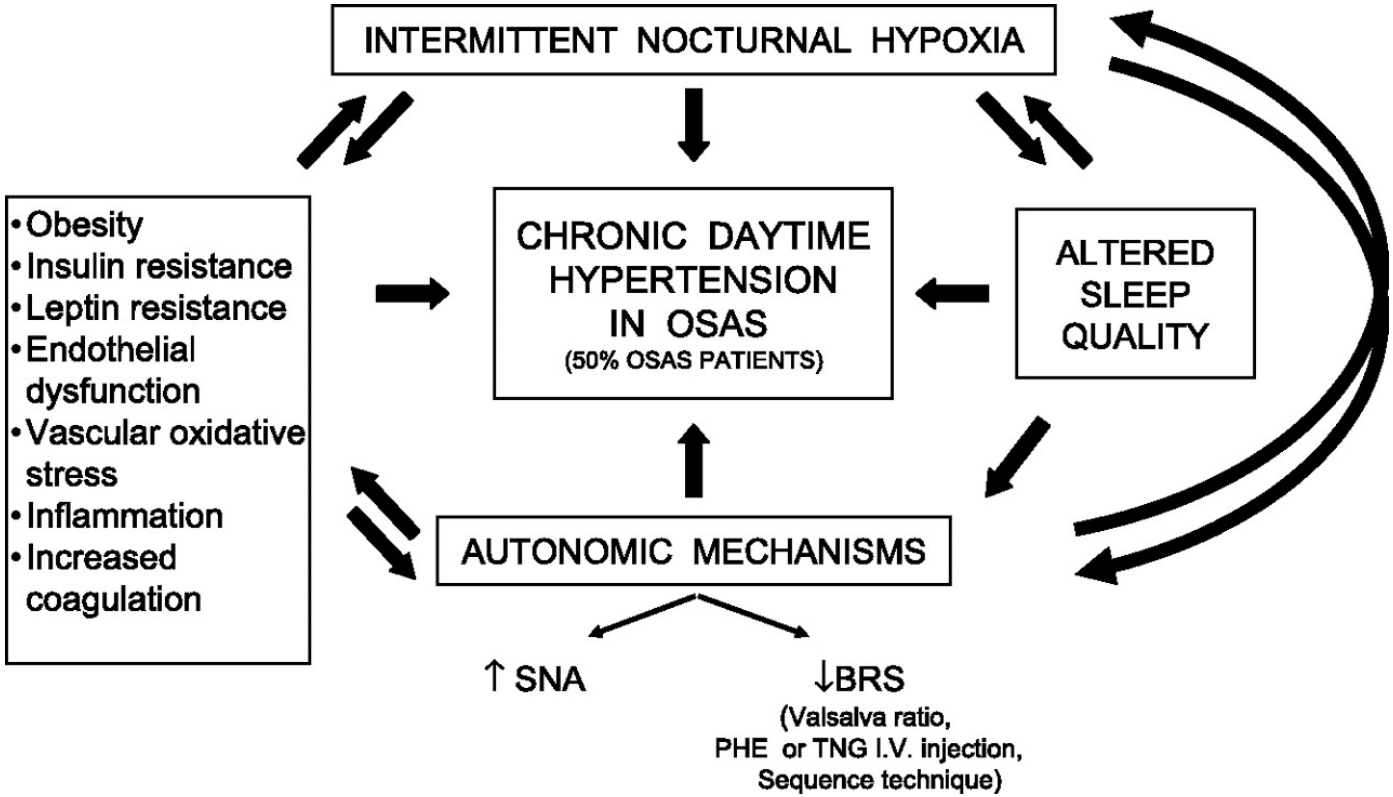
Left ventricular ejection fraction at baseline and at 1 month in persons with congestive heart failure and obstructive sleep apnea who received continuous positive airway pressure (CPAP) (right) or no treatment (left).

Ann Intern Med. 2005;142:187-197




In patients in the treatment group, the ejection fraction increased from a mean of 0.25±0.028 to 0.338±0.024 (P< 0.001). The left ventricular ejection fraction did not change significantly in the control group.

**Mechanisms suggested to be involved in appearance of chronic daytime hypertension in obstructive sleep apnea syndrome (OSAS) patients, and their possible interactions**



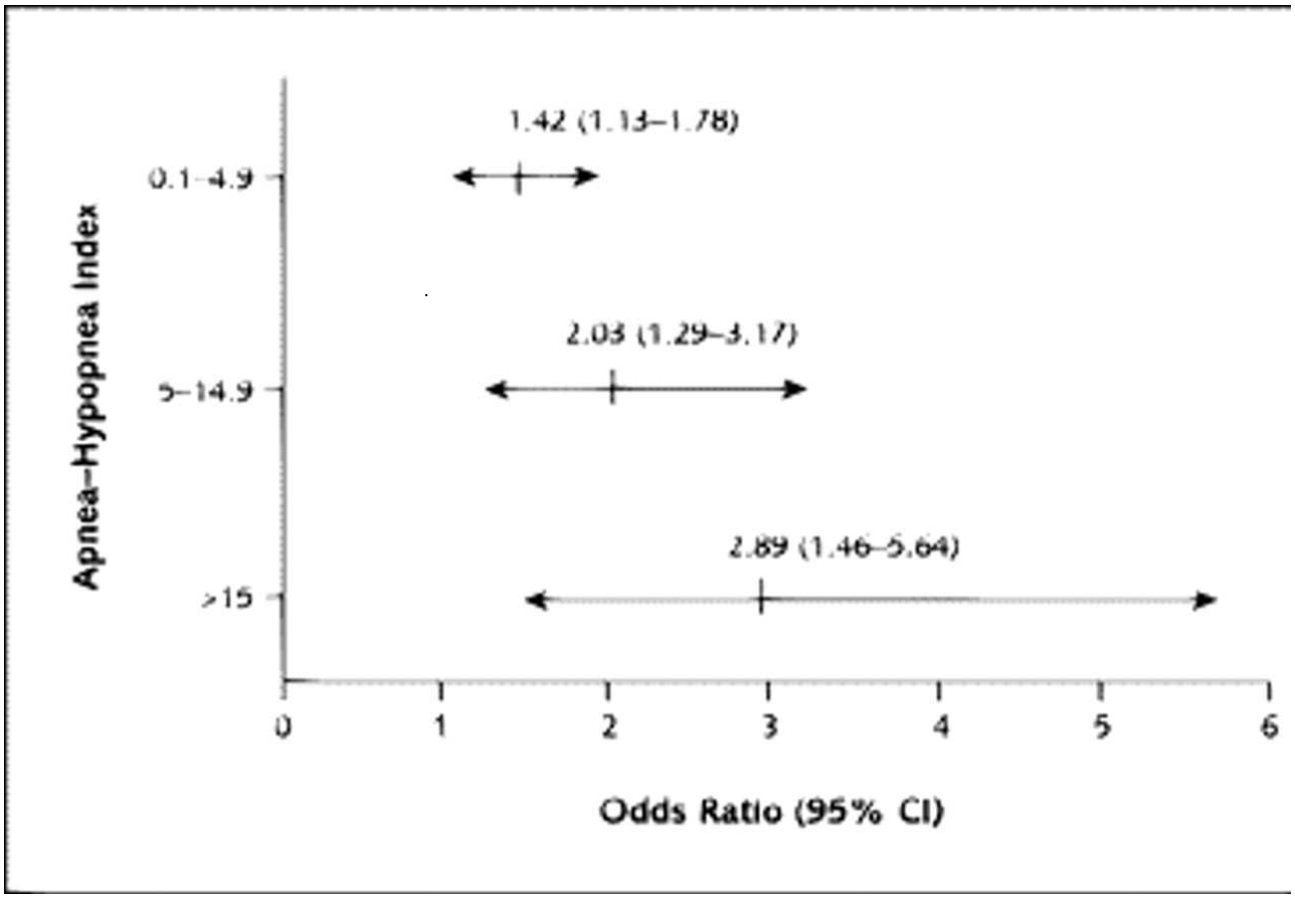

**Parati, G. et al. Am J Physiol Regul Integr Comp Physiol 293: R1671-R1683 2007; doi:10.1152/ajpregu.00400.2007**



AJP - Regulatory, Integrative and Comparative Physiology

# Obstructive sleep apnea and risk for hypertension

Ann Intern Med. 2005;142:187-197




Each increment in the severity of sleep apnea, represented by the apnea–hypopnea index, confers an increase in the odds ratio for developing hypertension.

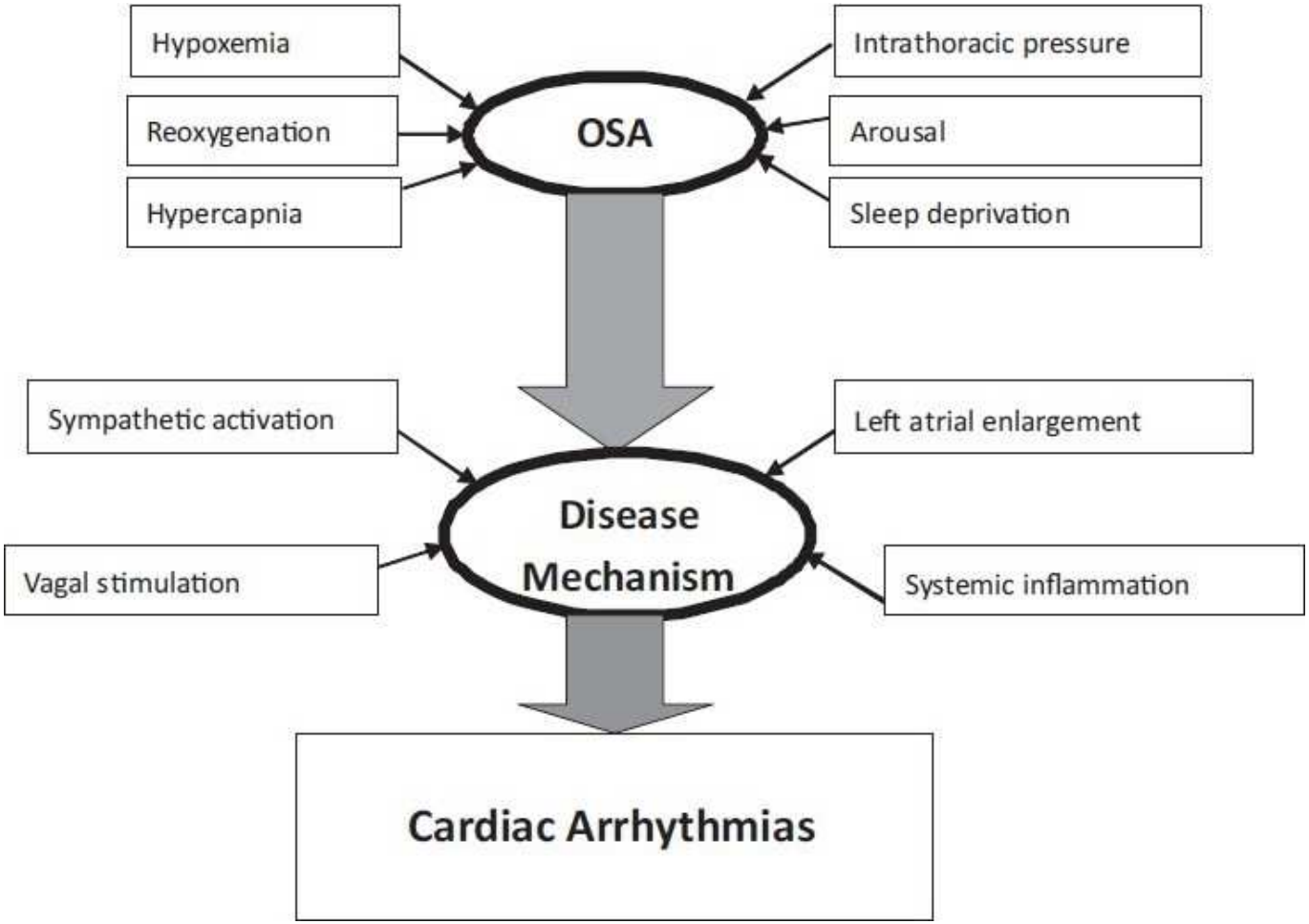
# Tissue-specific effects of intermittent hypoxia

Eur Respir J 2009; 33: 1195–1205

| Tissue | Mechanism | Effects |
|---|---|---|
| **Carotid body** | Oxygen sensing by HIF-1α | Enhanced sympathetic activity |
| | | Increased blood pressure |
| | | Decreased baroreflex sensitivity |
| **Endothelium** | Activation of NF-κB | Inflammatory cytokine production |
| | | Surface adhesion molecule expression |
| | | Increased apoptotic endothelial cells? |
| | | Decreased circulating endothelial progenitor cells? |
| **Adipose tissue** | Activation of NF-κB | Dysregulation of adipokine production |

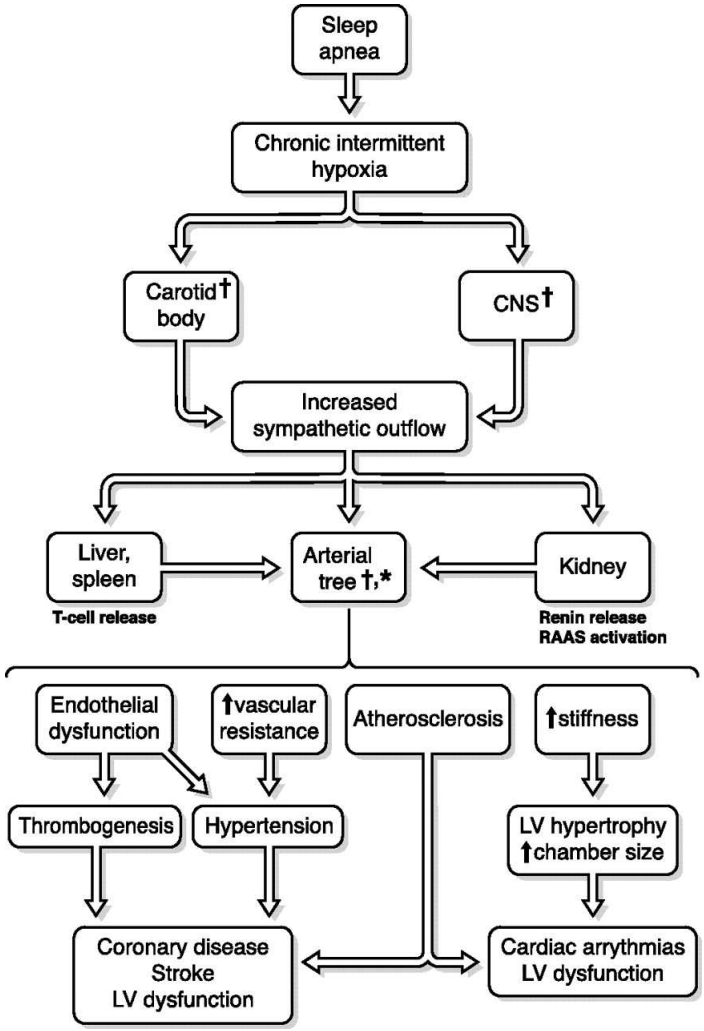
HIF: hypoxia-inducible factor; NF-kB: nuclear factor-kB.

Schematic representation of various pathophysiological mechanisms relating to arrhythmias in obstructive sleep apnea (OSA)




From: Hersi AS. Obstructive sleep apnea and cardiac arrhythmias. Ann Thorac Med 2010;5:10-7

# Putative mechanisms by which OSA activates the sympathetic nervous system, initiating a cascade of events that results in cardiovascular disease



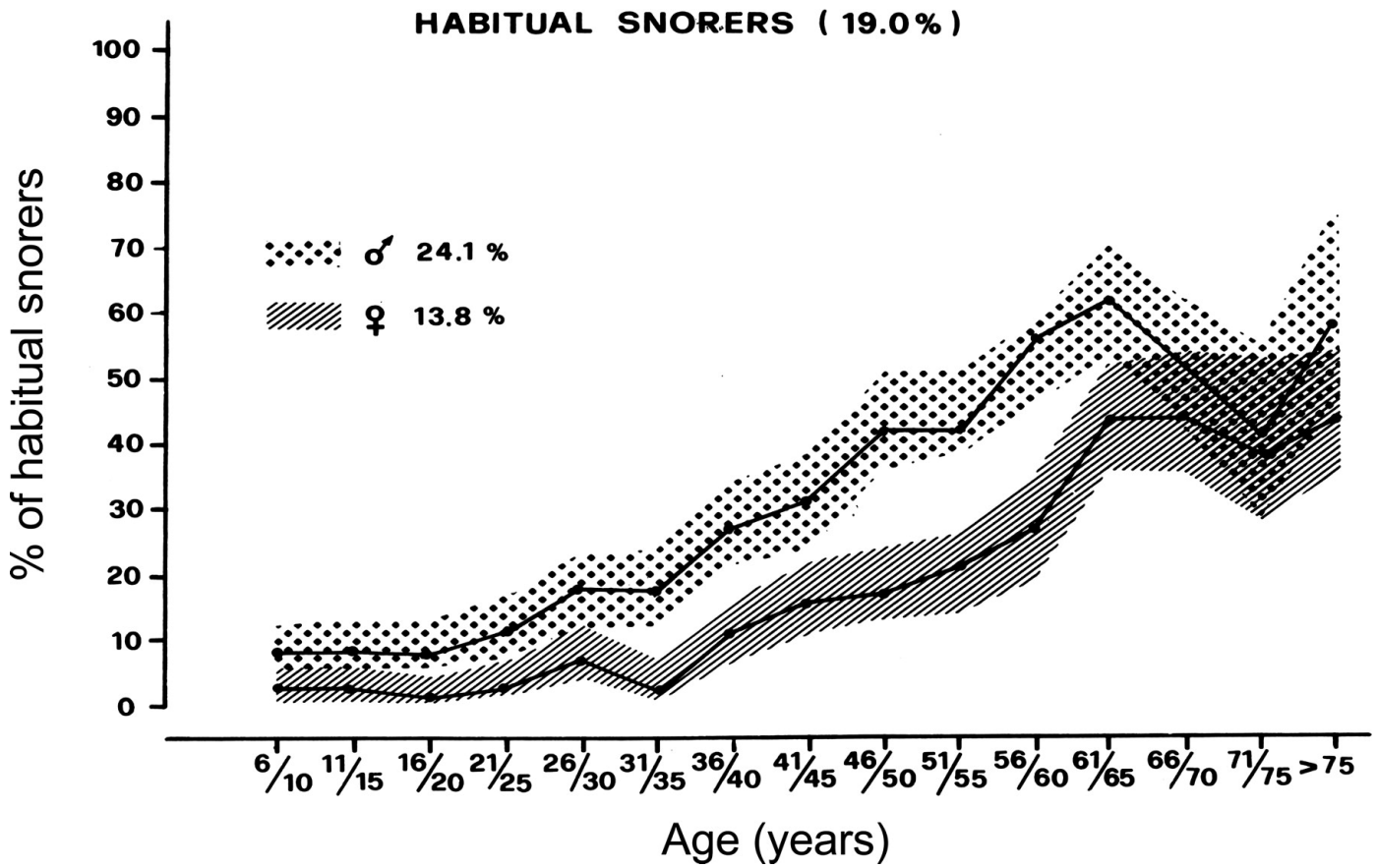

**Dempsey, J. A. et al. Physiol. Rev. 90: 47-112 2010; doi:10.1152/physrev.00043.2008**



Physiological Reviews

## Prevalence of habitual snorers by age and gender

Increasing age is reported on horizontal axis, and differently shaded areas refer to males and females

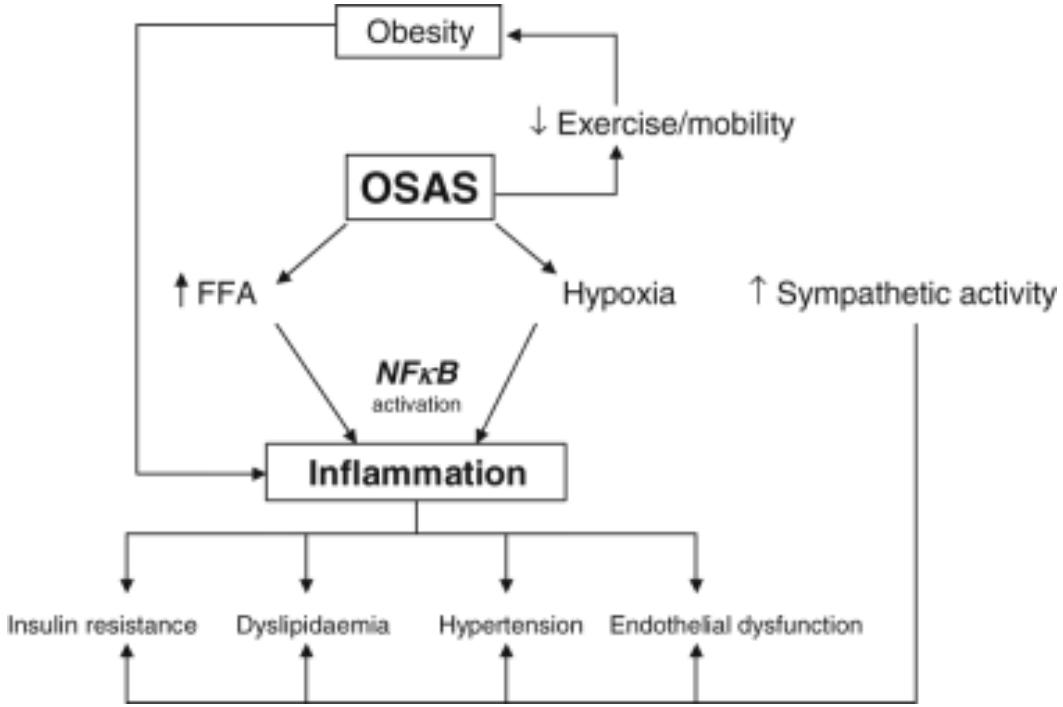



**Parati, G. et al. Am J Physiol Regul Integr Comp Physiol 293: R1671-R1683 2007; doi:10.1152/ajpregu.00400.2007**



AJP - Regulatory, Integrative and Comparative Physiology

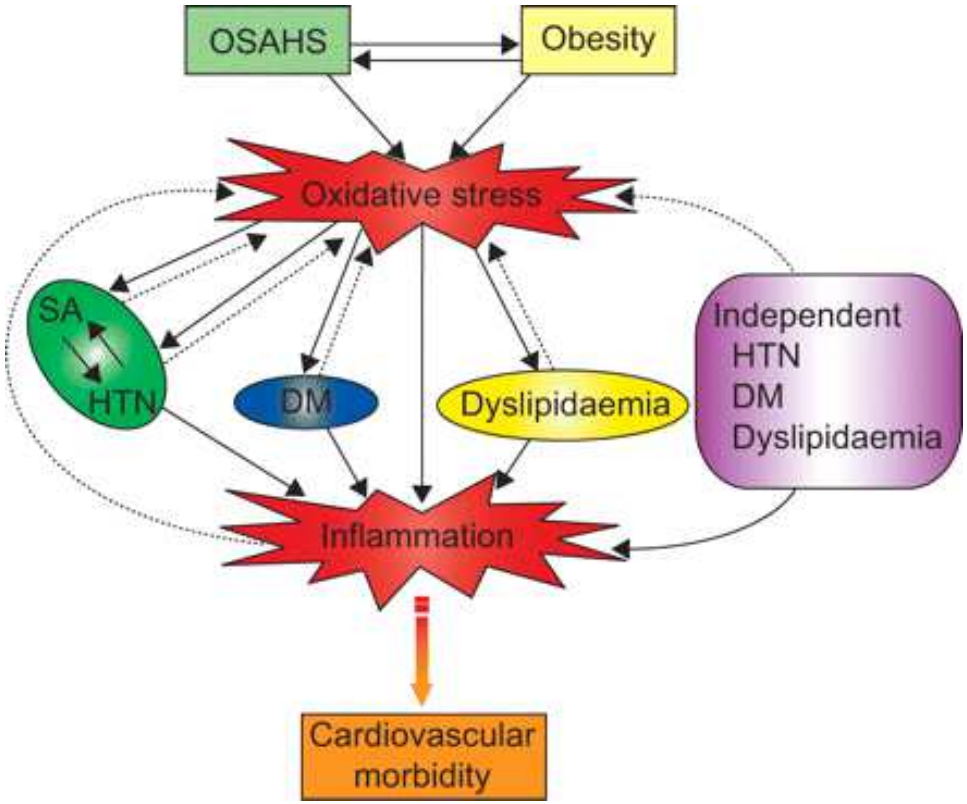
# Correlation between obstructive sleep apnoea syndrome (OSAS), obesity, inflammation, insulin resistance, type 2 diabetes mellitus and hypertension




FFA, free fatty acid; NF $\kappa$ B, nuclear factor kappa

Alam I et al, Obesity Reviews 8, 119–127, 2007

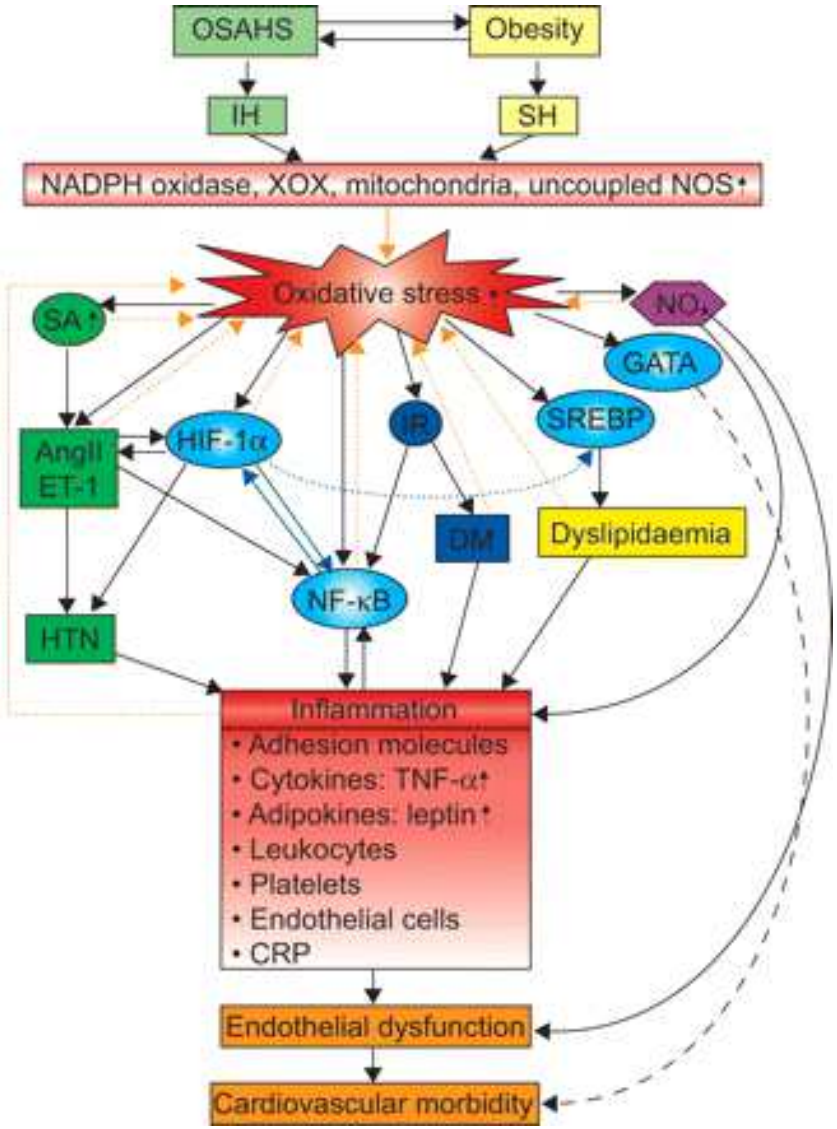
# Central role played by oxidative stress and inflammation in obstructive sleep apnoea/hypopnoea syndrome (OSAHS) and the development of associated conditions and comorbidities




ERJ 2009, 33 , 1467-1484

Associated conditions and comorbidities can be induced by oxidative stress or develop independently. Once these conditions and comorbidities develop, regardless of the initiating factors, they elicit a series of intricate interactions with various transduction pathways, promoting oxidative stress and inflammation. The enhanced oxidative stress exacerbates inflammation, which in turn further exacerbates oxidative stress, generating a vicious cycle, eventually leading to cardiovascular morbidity. SA: sympathetic activation; HTN: hypertension; DM: type 2 diabetes.

A tentative model suggestive of oxidative stress as a unifying paradigm in obstructive sleep apnoea/hypopnoea syndrome (OSAHS) and the development of conditions and comorbidities that aggregate with OSAHS.
These include obesity, hypertension, inflammation, sympathetic activation, type 2 diabetes and dyslipidaemia, all of which have an oxidative stress component.




IH: intermittent hypoxia;
SH: sustained hypoxia;
NADPH: reduced nicotinamide adenine dinucleotide phosphate;
XOX: xanthine oxidase;
NOS: nitric oxide synthase;
SA: sympathetic activation;
NO: nitric oxide;
GATA: GATA transcription factor;
Ang: angiotensin;
ET: endothelin;
HIF: hypoxia-inducible factor;
IR: insulin resistance;
SREBP: sterol regulatory element binding protein;
DM: type 2 diabetes;
NF: nuclear factor;
HTN: hypertension;
TNF: tumour necrosis factor;
CRP: C-reactive protein.
Orange dotted arrows: oxidative stress induced by the various conditions and comorbidities, further augmenting oxidative stress and, consequently, inflammation.

ERJ 2009, 33 , 1467-1484

## Clinical features of obstructive sleep apnea-hypopnea

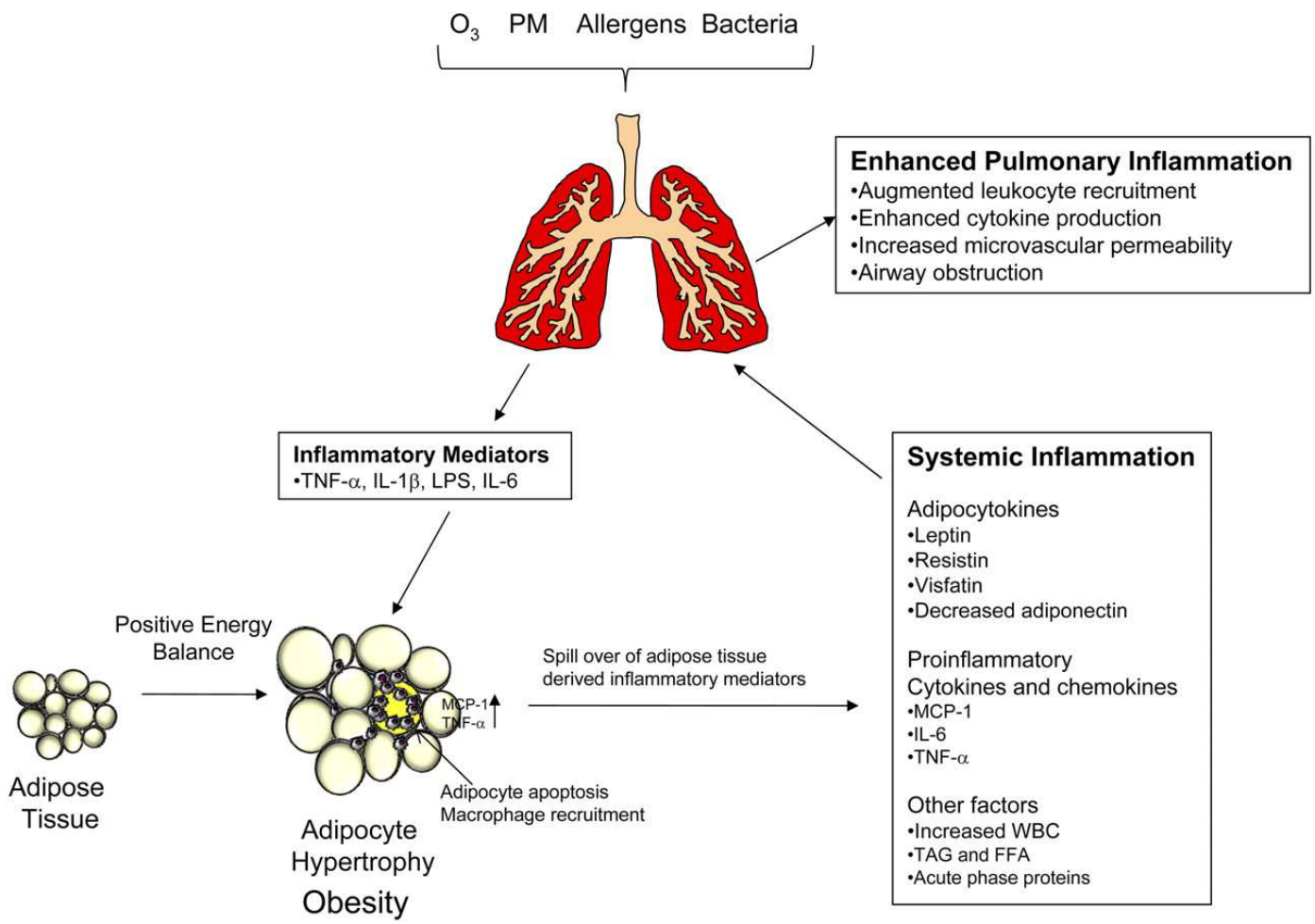
| | |
|---|---|
| Daytime sleepiness | Obesity |
| Nonrestorative sleep | Large neck circumference |
| Witnessed apneas by bed partner | Systemic hypertension |
| Awakening with choking | Hypercapnia |
| Nocturnal restlessness | Cardiovascular disease |
| Insomnia with frequent awakenings | Cerebrovascular disease |
| Lack of concentration | Cardiac dysrhythmias |
| Cognitive deficits | Narrow or "crowded" airway |
| Changes in mood | Pulmonary hypertension |
| Morning headaches | Cor pulmonale |
| Vivid, strange, or threatening dreams | Polycythemia |
| Gastroesophageal reflux | |

# Showing the severity and incidence of obstructive sleep apnoea (OSA)

| Apnoea-hypnoea index | Severity of OSA | Incidence (%) |
|---|---|---|
| AHI < 5 $h^{-1}$ | Normal | Š |
| AHI 5Š15 $h^{-1}$ | Mild disease | Men: 17Š26<br>Women: 9Š28 |
| AHI 15Š30 $h^{-1}$ | Moderate disease | Men: 15<br>Women: 5 |
| AHI > 30 $h^{-1}$ | Severe disease (upper airway resistance syndrome) | Men: 7Š14<br>Women: 2Š7 |

Alam I et al, Obesity Reviews 8, 119–127, 2007

## Fig. 1. Overview of the influence of obesity on inflammation in the lung

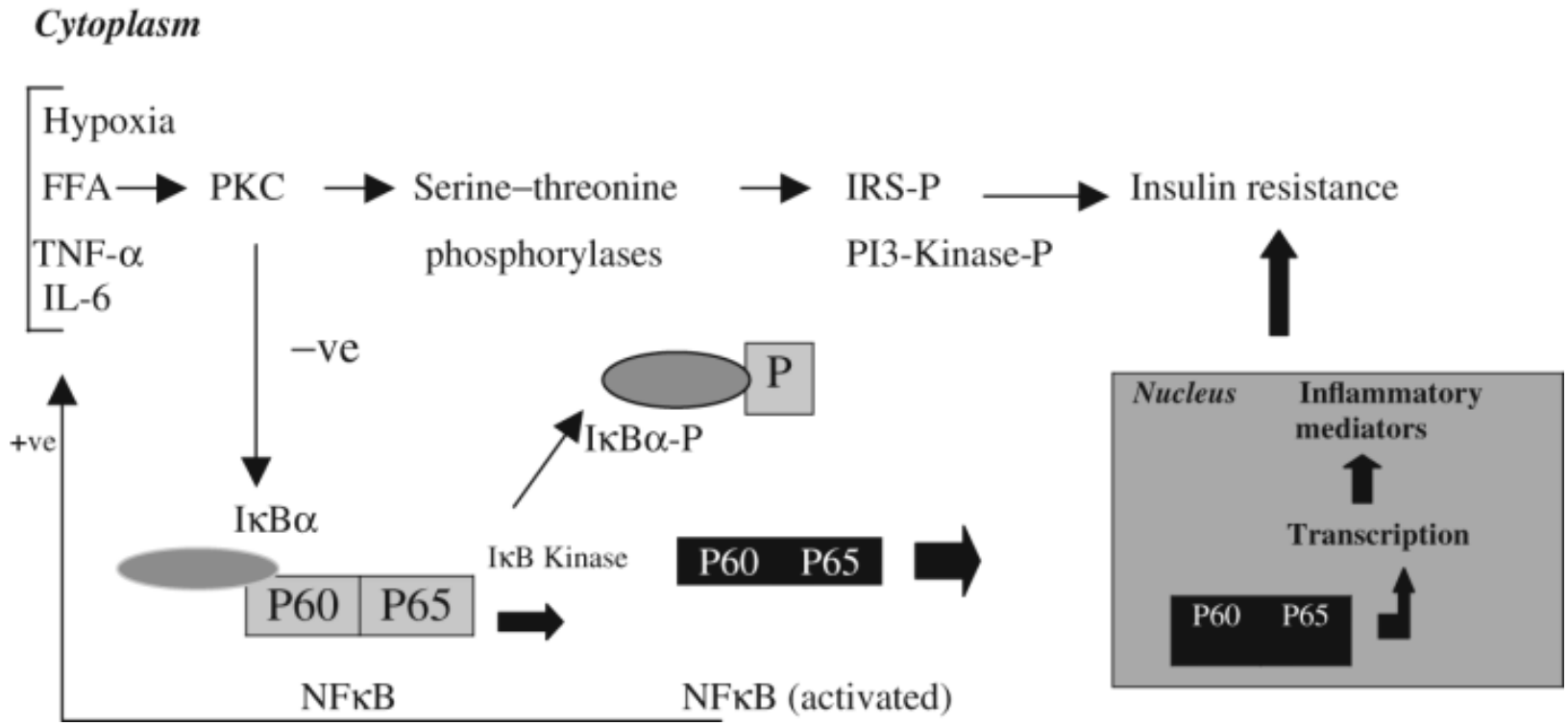



**Mancuso, P. J Appl Physiol 108: 722-728 2010;**
**doi:10.1152/japplphysiol.00781.2009**



Journal of Applied Physiology

## Pathway for insulin resistance: FFA and TNF-α, the IRS and PI3-kinase. Nuclear factor kappa B (NFκB) kept in an inactive form by inhibitor kappa B alpha (IκBα). IκB knase phosphoyralates IκBα. Activated NFκB enters nucleus and initiates transcription




FFA, free fatty acid; IL-6, interleukin-6; IRS, insulin receptor substrate; PKC, protein kinase C; TNF-$\alpha$, tumour necrosis factor alpha.

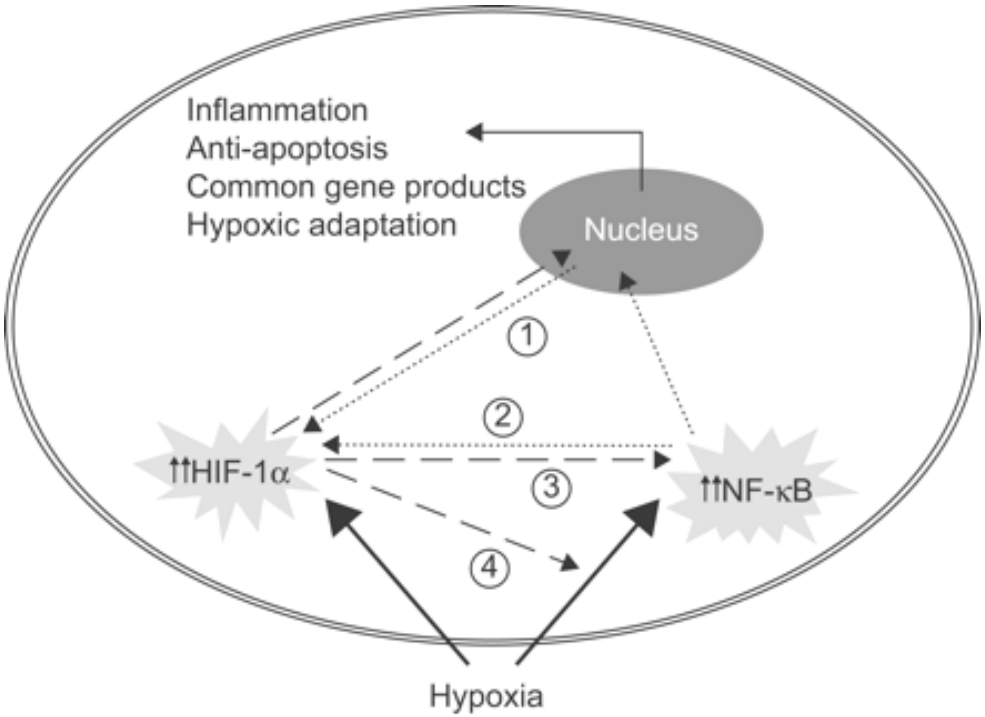
Alam I et al, Obesity Reviews 8, 119–127, 2007

# Prevalence studies of cardiac arrhythmias and obstructive sleep apnea

| Studies | Subjects | Outcomes/Prevalence |
|---|---|---|
| Tilkian *et al.*[45] | 15 | Marked sinus arrhythmia in14 patients<br>Extreme sinus bradycardia in 6<br>Asystole in 5<br>Second-degree atrioventricular block in 2<br>Ventricular arrhythmias--complex premature ventricular beats in 10<br>Ventricular tachycardia in 2 patients |
| Guilleminault *et al.*[22] | 400 | Bradyarrhythmias in 18% of patients<br>Sustained ventricular tachycardia in 2%<br>Sinus arrest in 11%<br>Second-degree atrioventricular block in 8%<br>Frequent premature ventricular contractions in 19% |
| Flemons *et al.*[39] | 263 | Complex ventricular ectopy (including ventricular tachycardia) in 1.3% of patients<br>Frequent ventricular premature beats (>30/h) in 2.6%<br>Second-degree atrioventricular block in 1.3%<br>Sinus arrest in 5.2% patients |
| Becker *et al.*[46] | 239 | Sinus arrest and atrioventricular (AV) block in 30% of patients |
| Mooe *et al.*[47] | 121 | Atrial fibrillation (AF) in 32% of patient with apnea–hypopnea index (AHI) >5 or =5 and in 18% patients with AHI <5<br>Atrial fibrillation in 39% of patients with oxygen desaturation index (ODI) >5 or =5 and in 18% of patients with ODI <5 |
| Javaheri *et al.*[48] | 81 | Atrial fibrillation in 32% of patients |
| Simantirakis *et al.*[50] | 23 | Rhythm disturbances in 48% of patients |
| Gami *et al.*[51] | 524 | OSA more prevalent in patients with AF (n = 151) than in high-risk patients with multiple other cardiovascular diseases |
| Porthan *et al.*[52] | 115 | Sleep apnea syndrome common in lone AF |
| Mehra *et al.*[18] | 566 | Atrial fibrillation in 4.8% of patients<br>Nonsustained ventricular tachycardia in 5.3%<br>Complex ventricular ectopy in 25.0% of patients |

From: Hersi AS. Obstructive sleep apnea and cardiac arrhythmias. Ann Thorac Med 2010;5:10-7

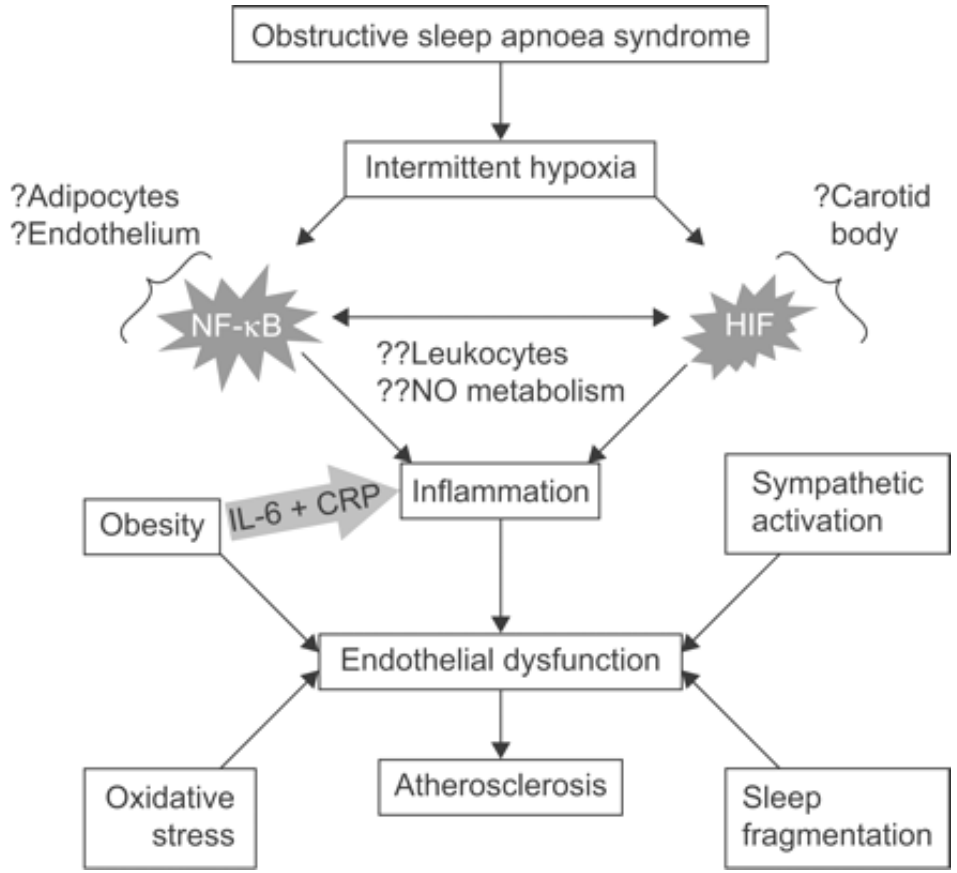
# Interaction between hypoxia-inducible factor (HIF)-1a and nuclear factor (NF)-kB in hypoxia.




Tissue hypoxia leads to the activation of the transcription factors HIF-1a and NF-kB. Activation of HIF-1a facilitates an adaptive response to hypoxia, whereas upregulation of NF-kB leads to inflammatory and anti-apoptotic gene expression. HIF-1a and NF-kB also share some gene products, e.g. inducible nitric oxide synthase. NF-kB regulates basal levels of HIF-1 gene expression and upregulation of HIF-1 transcription occurs through a NF-kB-dependent mechanism (1 and 2).
Conversely, hypoxic induction of NF-kB transcription is dependent on the presence of HIF-1a (3) and HIF-1a is directly involved in regulating apoptosis through the modulation of NF-kB signalling

Eur Respir J 2009; 33: 1195–1205

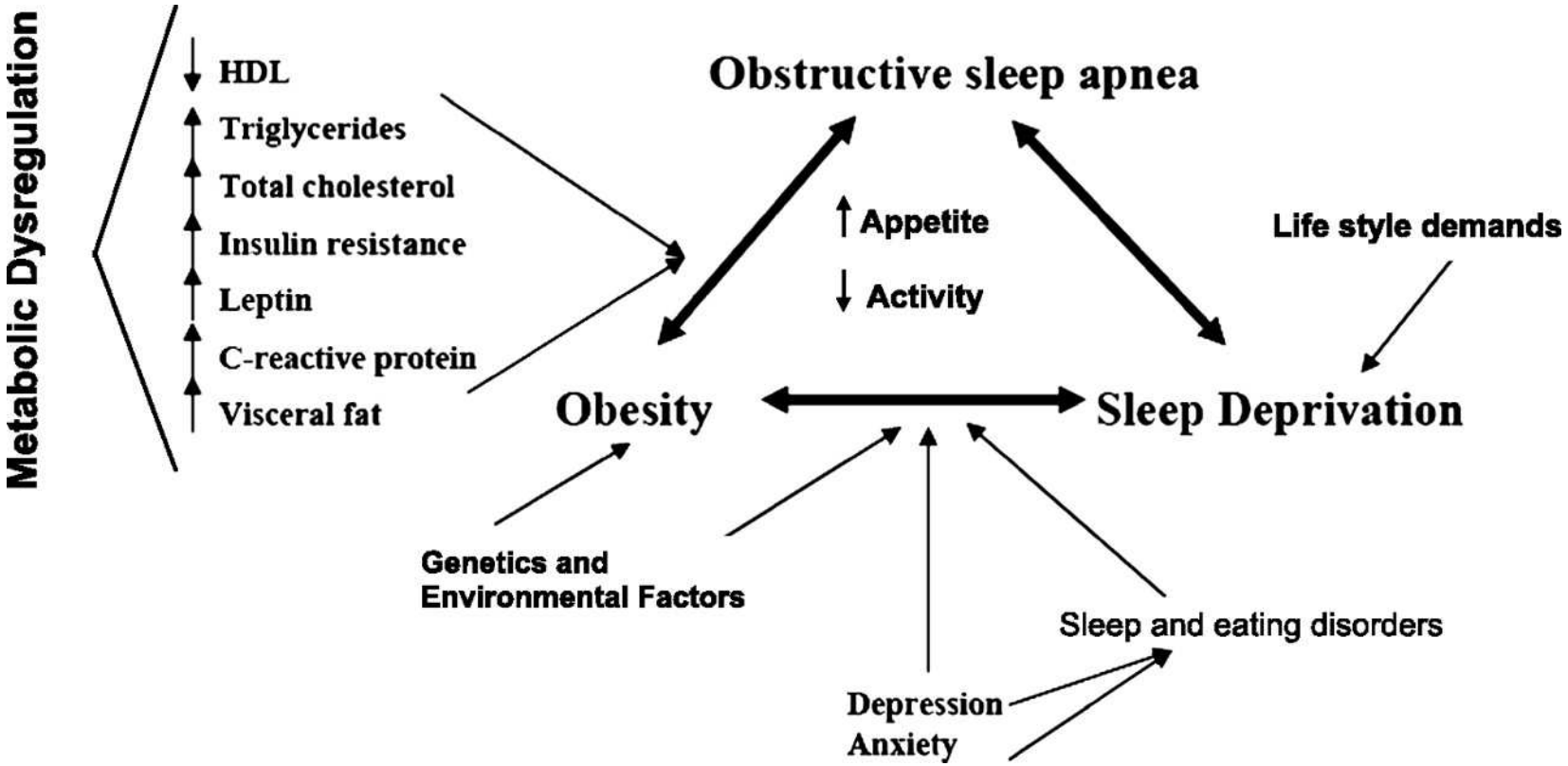
Activation and interaction of inflammatory pathways in response to intermittent hypoxia in obstructive sleep apnoea syndrome (OSAS).
Proposed mechanisms by which OSAS predisposes to the development of endothelial dysfunction and cardiovascular disease include sympathetic excitation, vascularendothelial dysfunction, oxidative stress and inflammation.




Intermittent hypoxia activates inflammatory mechanisms directly through the hypoxia-sensitive transcription factors nuclear factor (NF)-kB and hypoxiainducible factor (HIF)-1.
The co-existence of obesity in many OSAS patients augments the pro-inflammatory state through increased production of interleukin (IL)-6 and C-reactive protein (CRP) by adipose tissue.
There are differences in the response to intermittent hypoxia between body tissues, with NF-kB having its largest apparent influence in endothelial cells, and adipocytes and HIF-1 playing a key role in the carotid body response. Activation of leukocytes and nitric oxide (NO) involvement in the inflammatory response to intermittent hypoxia in OSAS may be regulated by cross-talk between the NF-kB and HIF-1 pathways.

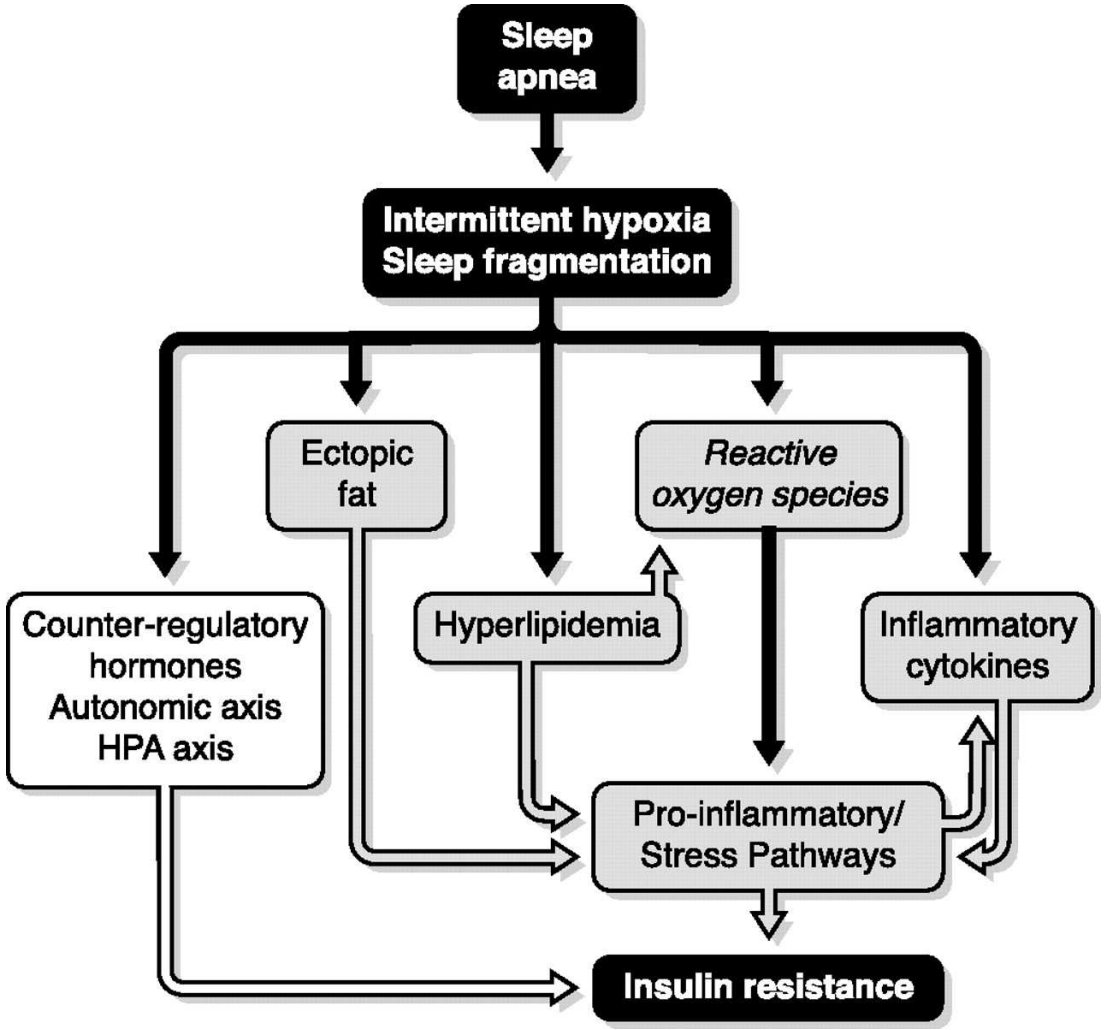
Eur Respir J 2009; 33: 1195–1205

# Interaction between obstructive sleep apnea, obesity, sleep deprivation, and metabolic abnormalities.



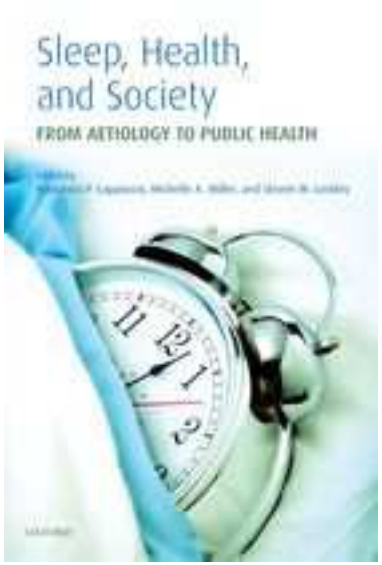

Romero-Corral A et al. Chest 2010;137:711-719

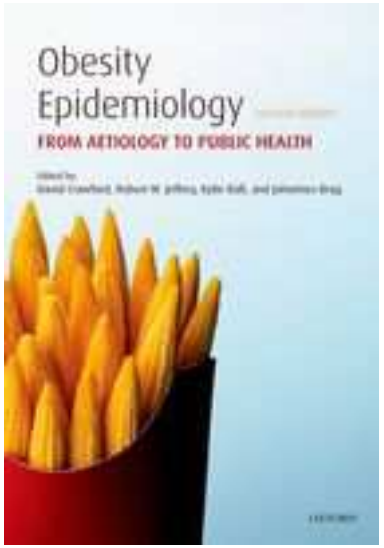
# Putative pathways for the physiological disturbances of intermittent hypoxia and sleep fragmentation to cause insulin resistance through activation of "classical" (white) or "lipotoxic" (grey) pathways



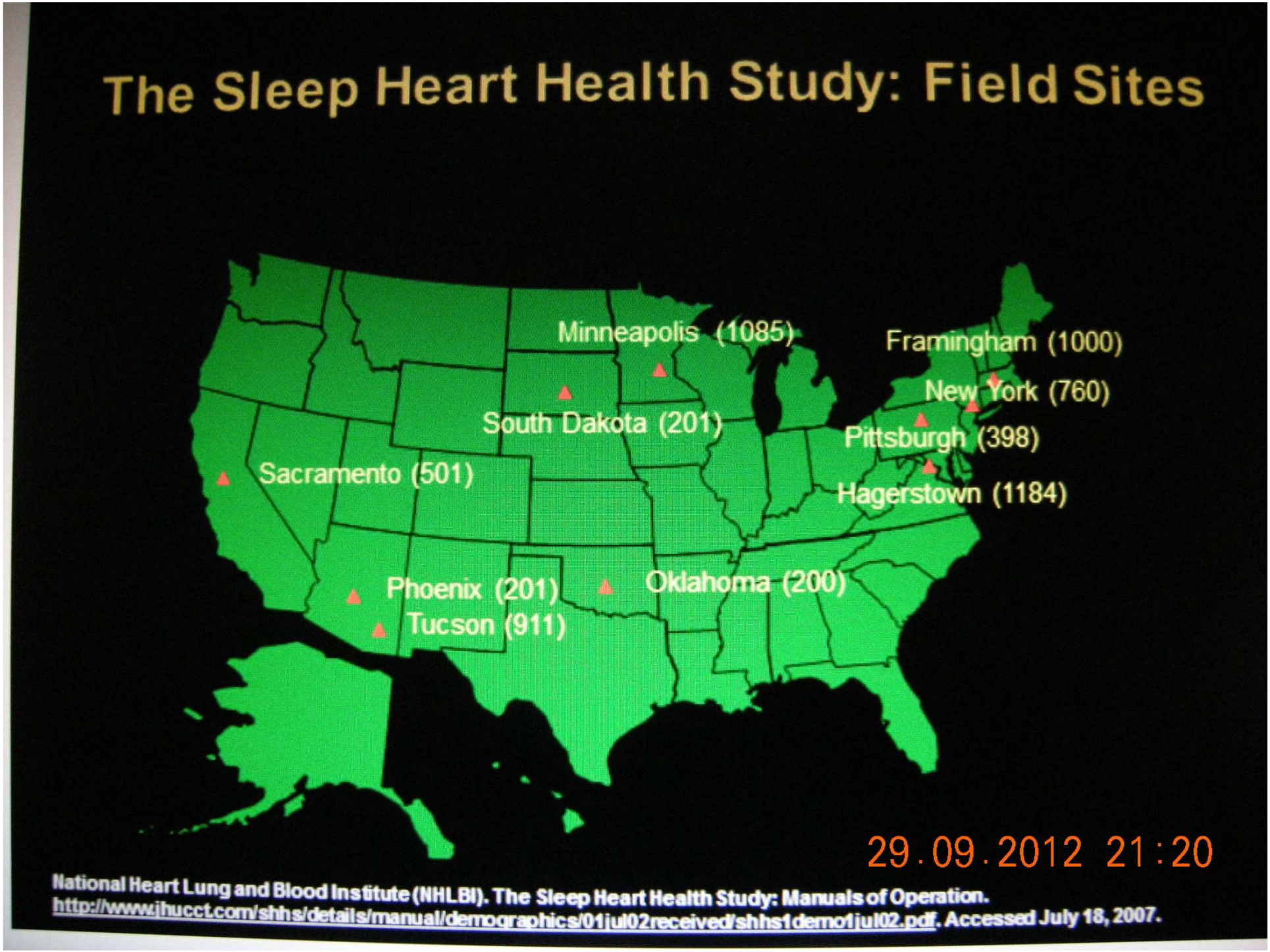

Dempsey, J. A. et al. Physiol. Rev. 90: 47-112 2010;
doi:10.1152/physrev.00043.2008

Physiological Reviews


Sleep, Health,
and Society
FROM AETIOLOGY TO PUBLIC HEALTH


Obesity
Epidemiology
FROM AETIOLOGY TO PUBLIC HEALTH

# The Sleep Heart Health Study: Field Sites




29.09.2012 21:20

National Heart Lung and Blood Institute (NHLBI). The Sleep Heart Health Study: Manuals of Operation. http://www.jhucct.com/shhs/details/manual/demographics/01jul02received/shhs1demo1jul02.pdf. Accessed July 18, 2007.

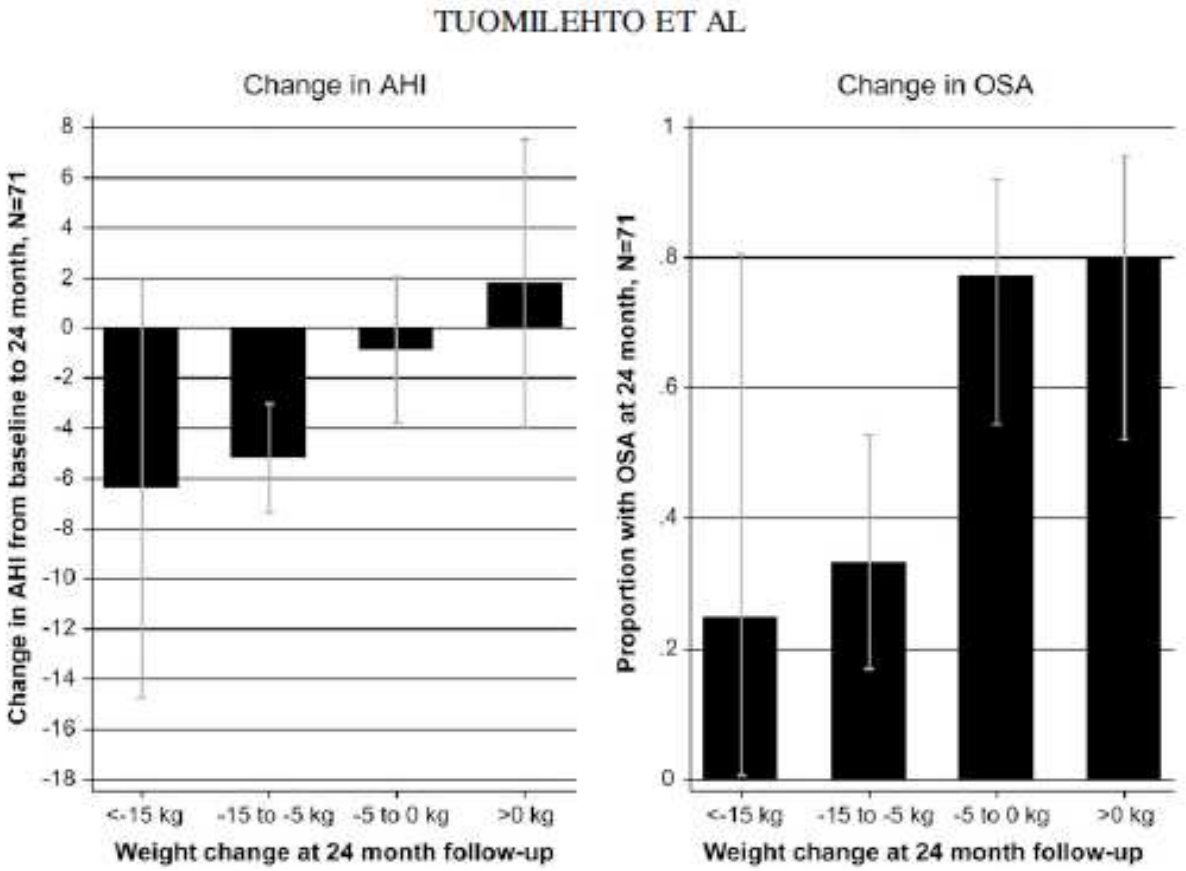
## CALO PONDERALE e OSA

**Table 1. Participants' Characteristics at Baseline[a]**

| Variable | All[b] (n=264) | Diabetes Support and Education[b] (n=139) | Intensive Lifestyle Intervention[b] (n=125) | *P* Value |
|---|---|---|---|---|
| Age, y | 61.2 (6.5) | 61.3 (6.4) | 61.2 (6.6) | .94 |
| Female, % | 59.1 | 56.8 | 61.6 | .43 |
| Race/ethnicity, % | | | | .99 |
| African American | 18.6 | 18.8 | 18.4 | |
| American Indian/Native American | 1.1 | 0.7 | 1.6 | |
| Asian/Pacific Islander | 1.9 | 2.2 | 1.6 | |
| Hispanic | 3.8 | 3.6 | 4.0 | |
| Other | 1.5 | 1.5 | 1.6 | |
| White | 73.0 | 73.2 | 72.8 | |
| BMI | 36.7 (5.7) | 36.5 (5.7) | 36.8 (5.8) | .43 |
| Weight, kg | 102.4 (18.3) | 102.0 (17.1) | 102.9 (19.6) | .67 |
| Height, cm | 167.1 (9.7) | 167.2 (9.8) | 166.9 (9.6) | .62 |
| Waist circumference, cm | 115.8 (13.2) | 115.7 (12.1) | 115.8 (14.4) | .81 |
| Neck circumference, cm | 41.3 (4.2) | 41.5 (4.1) | 41.1 (4.3) | .52 |
| Apnea-hypopnea index | 23.2 (16.5) | 23.5 (15.0) | 22.9 (18.0) | .26 |
| Obstructive apnea index | 12.7 (13.1) | 12.4 (11.8) | 13.0 (14.3) | .98 |
| Central apnea index | 0.4 (1.0) | 0.5 (1.1) | 0.4 (0.9) | .54 |
| Hypopnea index | 10.1 (8.2) | 10.6 (8.3) | 9.4 (7.9) | .05 |
| Oxygen desaturation index, ≥4% | 19.4 (14.9) | 20.2 (13.7) | 18.6 (16.1) | .06 |
| Fasting plasma glucose, mg/dL | 151.0 (41.5) | 152.9 (43.8) | 148.9 (38.8) | .39 |
| Hemoglobin $A_{1c}$, % | 7.2 (1.0) | 7.3 (1.1) | 7.1 (0.9) | .06 |
| Self-reported No. of years with diabetes | 7.4 (7.1) | 7.5 (6.3) | 7.3 (7.9) | .19 |

Am J Clin Nutr 2010; 92: 688-96

## CALO PONDERALE e OSA




Am J Clin Nutr 2010; 92: 688-96

American Journal of
EPIDEMIOLOGY

# Snoring as a Risk Factor for Type II Diabetes Mellitus: A Prospective Study

TABLE 2. Adjusted relative risk of type II diabetes among women in the Nurses' Health Study who were followed up between 1986 and 1996, according to snoring status in 1986

| | No. of cases | Person-years of follow-up | Relative risk | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | Adjusted for age | | Adjusted for age and body mass index* | | Multivariate-adjusted† | |
| | | | RR‡ | 95% CI‡ | RR | 95% CI | RR | 95% CI |
| No snoring | 237 | 176,679 | 1.00§ | | 1.00 | | 1.00 | |
| Occasional snoring | 1,297 | 428,686 | 2.12 | 1.85, 2.44 | 1.48 | 1.29, 1.70 | 1.41 | 1.22, 1.63 |
| Regular snoring | 423 | 58,915 | 4.99 | 4.31, 5.96 | 2.25 | 1.91, 2.66 | 2.03 | 1.71, 2.40 |
| *p* for trend | | | <0.0001 | | <0.0001 | | <0.0001 | |

* Weight (kg)/height (m)$^2$.

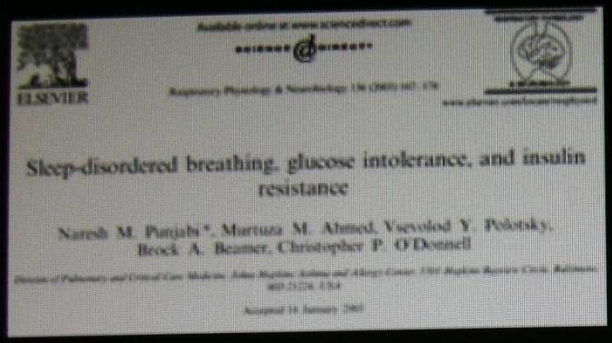
† Adjusted for age, history of high cholesterol, history of high blood pressure, time period, smoking, body mass index (eight categories), physical activity, alcohol use, postmenopausal hormone use, family history of diabetes, usual sleeping position, number of hours of sleep per day, and years of shift-work.

‡ RR, relative risk; CI, confidence interval.

§ Reference category.

Am J Epidemiol 155,5,2002

# Sleep Apnea and and Diabetes Risk: The Evidence

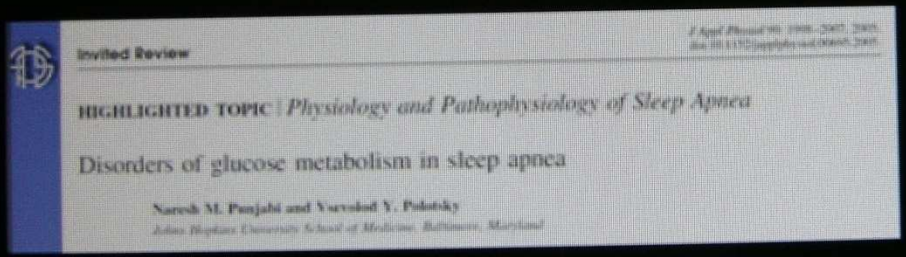


ELSEVIER

Sleep-disordered breathing, glucose intolerance, and insulin resistance

Naresh M. Punjabi *, Murtuza M. Ahmed, Vsevolod Y. Polotsky, Brock A. Beamer, Christopher P. O'Donnell

Accepted 16 January 2003



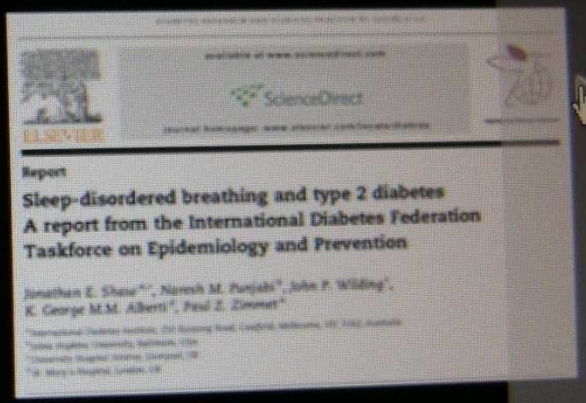
Invited Review

HIGHLIGHTED TOPIC | *Physiology and Pathophysiology of Sleep Apnea*

Disorders of glucose metabolism in sleep apnea

Naresh M. Punjabi and Vsevolod Y. Polotsky

*Johns Hopkins University School of Medicine, Baltimore, Maryland*



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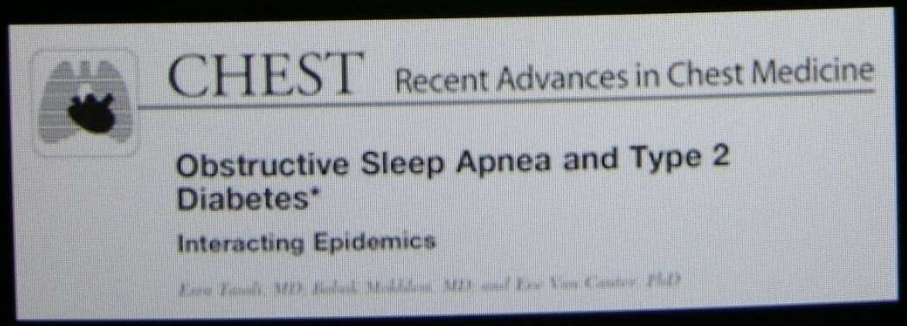
Report

**Sleep-disordered breathing and type 2 diabetes**
**A report from the International Diabetes Federation Taskforce on Epidemiology and Prevention**



CHEST Recent Advances in Chest Medicine

**Obstructive Sleep Apnea and Type 2 Diabetes***

Interacting Epidemics

*Esra Tasali, MD, Babak Mokhlesi, MD, and Eve Van Cauter, PhD*

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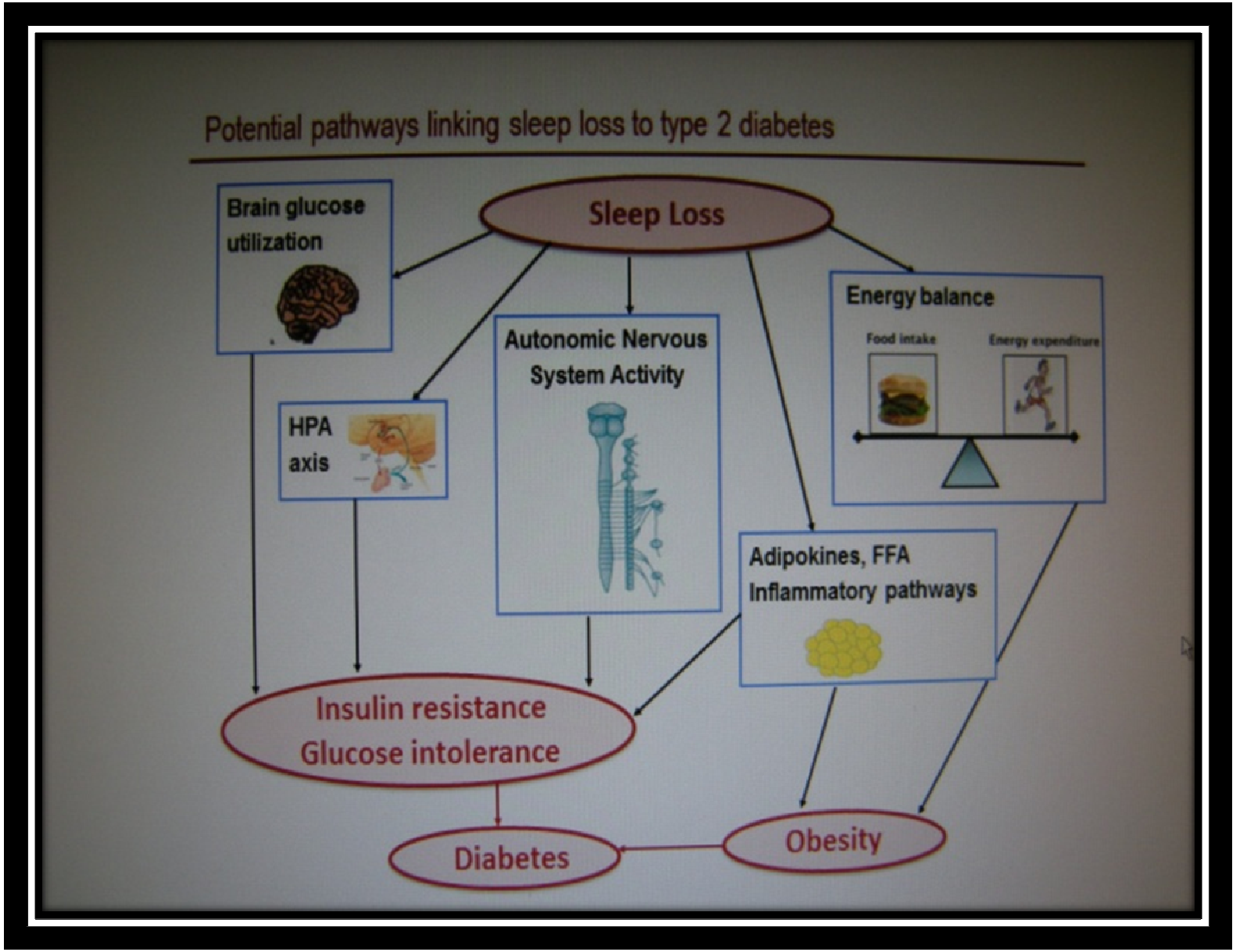
Potential pathways linking sleep loss to type 2 diabetes
Brain glucose utilization
Sleep Loss
Energy balance
Food intake
Energy expenditure
Autonomic Nervous System Activity
HPA axis
Adipokines, FFA Inflammatory pathways
Insulin resistance Glucose intolerance
Diabetes
Obesity

# Population-Based Studies Linking OSA Defined by Polysomnography to Altered Glucose Metabolism and Type 2 Diabetes*

| Study/Year | Study Sample | Measures of Glucose Metabolism | Main Findings |
|---|---|---|---|
| Stoohs et al48/1996 | 50 (34 women) healthy subjects, United States | *In vivo* insulin action by insulin suppression test | Elevated insulin resistance in OSA (AHI ≥ 10) is entirely dependent on BMI |
| Elmasry et al73/2001 | 116 hypertensive men, Sweden | Fasting glucose, fasting insulin, and HbA1c | Higher prevalence of severe OSA (AHI ≥ 20) in diabetic patients than normoglycemic subjects (36% vs 14.5%, respectively). The severity of OSA is associated with indices of glucose metabolism in normoglycemic subjects independently of central adiposity and antihypertensive use |
| Punjabi et al74/2002 | 155 men, United States | OGTT and HOMA | Increasing severity of AHI and oxygen desaturations were associated with worsening glucose tolerance and insulin resistance after adjustment for BMI and percentage of body fat |
| Ip et al75/2002 | 270 (197 men) Chinese individuals | Fasting insulin and HOMA | AHI and minimum oxygen saturation are independent determinants of insulin resistance |
| Punjabi et al76/2004 | Sleep Heart Health Study, United States, 2,656 (1,214 men) participants | Fasting and 2-h glucose during OGTT, and HOMA | AHI and average oxygen saturation are independently associated with both fasting and 2-h glucose levels; independent link between degree of insulin resistance and severity of OSA |
| Reichmuth et al11/2005† | Wisconsin Sleep Cohort, United States, 1,387 (779 men) participants, 4-yr follow-up in 987 subjects | Diabetes diagnosed by physician and/or fasting glucose concentration of ≥ 126 mg/dL | More prevalent diabetes with OSA (AHI ≥ 15): OR, 2.3 (95% CI, 1.28–4.11) after adjustment for age, gender, and body habitus; no independent relationship between incident diabetes and OSA at 4-yr follow-up |
| Lam et al77/2006 | 255 (150 men) Chinese individuals | Fasting glucose | Association between OSA and fasting glucose after adjustment for age, gender, BMI, smoking, and alcohol use; adjusted OR for fasting glucose concentration of ≥ 110 mg/dL, 2.74 (95% CI, 1.16–6.49) for AHI ≥ 5 vs < 5 |
| Okada et al78/2006 | 207 Japanese men | HbA1c and fasting glucose | Higher levels of HbA1c and fasting glucose in sleep apnea patients (AHI ≥ 15) compared to nonapneic subjects with similar BMI |
| Sulit et al79/2006 | Cleveland Family Study, United States, 394 (177 men) subjects | OGTT | Threshold dose response for measures of hypoxic stress (≥ 2% time spent < 90% oxygen saturation) and glucose intolerance; adjusted OR, 2.33 (95% CI, 1.38–3.94) |

# Population-Based Studies Linking Snoring to Altered Glucose Metabolism and Type 2 Diabetes*

| Study/Year | Study Sample | Measures of Glucose Metabolism | Main Findings |
|---|---|---|---|
| Norton and Dunn 1985 | 2,629 (1,411 men) participants, Canada | Self-reported diabetes | Association between snoring and its frequency, and the presence of diabetes |
| Jennum et al 1993 | 804 men and women who were 70 yr old, Denmark | OGTT | Snoring was associated with abnormal glucose tolerance after adjustment for gender, BMI, physical activity, and alcohol and tobacco use |
| Grunstein et al 1995 | Swedish Obese Subjects Cohort, 3,034 (1,324 men) participants; age range, 37–57 yr | Fasting glucose and insulin | Loud snoring and witnessed apneas were associated with higher fasting insulin levels after adjustment for body fat distribution |
| Enright et al 1996 | Cardiovascular Health Study, 5,201 (43% men) participants aged ≥ 65 yr | Self-reported diabetes, hypoglycemic medication use, fasting glucose, or OGTT | Snoring and observed apneas were independently associated with diabetes in elderly women **but not in elderly men** |
| Elmasry et al 2000† | 2,668 Swedish men; age range, 30–69 yr | Self-reported diabetes | Habitual snoring is an independent risk factor for incident diabetes at 10-yr follow-up; obese men who reported snoring at baseline were seven times more likely to have diabetes develop |
| Al-Delaimy et al 2002† | US Nurses Health Study, 69,852 female nurses; age range, 30–55 yr | Diabetes based on composite criteria using clinical and laboratory findings | Regular snoring is independently associated with twofold increased risk of developing diabetes at 10-yr follow-up |
| Renko et al 2005 | 593 (245 men) participants, of whom 553 had no prior diagnosis of diabetes, Finland | OGTT | Habitual snoring was independently associated with diabetes and decreased insulin sensitivity; habitual snorers, compared to nonsnorers, had twice the risk of having diabetes |
| Shin et al /2005 | 2,719 nondiabetic, nonobese Korean men | OGTT | Habitual snoring was independently associated with elevated postload 2-h glucose and insulin levels |
| Joo et al 2006 | 6,981 (3,362 men) nonobese participants; age range, 40–69 yr; Korea | HbA1c | Frequent snoring is independently associated with elevated HbA1c levels (> 5.8%) |
| Thomas et al 2006 | 8,325 (2,550 men); age range, 50–85 yr; China | Diabetes defined by fasting glucose concentration of ≥ 7 mmol/L or hypoglycemic medication use | Snoring was an independent predictor of diabetes after controlling for potential confounders including central adiposity |
| Lindberg et al 2007 | 6,799 Swedish women; age range, 20–99 yr | Self-reported diabetes | "Snoring and excessive daytime sleepiness" is an independent risk factor for diabetes |
| Onat et al 2007 | 119 (61 men) Turkish patients | HOMA | Habitual snoring and witnessed apneas were associated with metabolic syndrome **but not with insulin resistance** |

# OSA e Resistenza insulinica

- Svatikova et al. Curr Diab Rep 2005: Interactions between OSA and the metabolic syndrome
- Vgontzas et al. Sleep Med Rev 2005: SA is a manifestation of the metabolic syndrome
- Punjabi et al .J Appl Physiol 2005: Disorder of glucose metabolism in SA (Review)
- Gruber et al. Cardiovasc Diabetol 2006: OSA is independently associated with the metabolic syndrome but not insulin resistance state
- Lam et al. Respir Med 2006: OSA and the metabolic syndrome in community-based Chinese adults in Hong Kong