Obesity, Diabetes and **Obstructive Sleep Apnea Syndrome (OSAS)**

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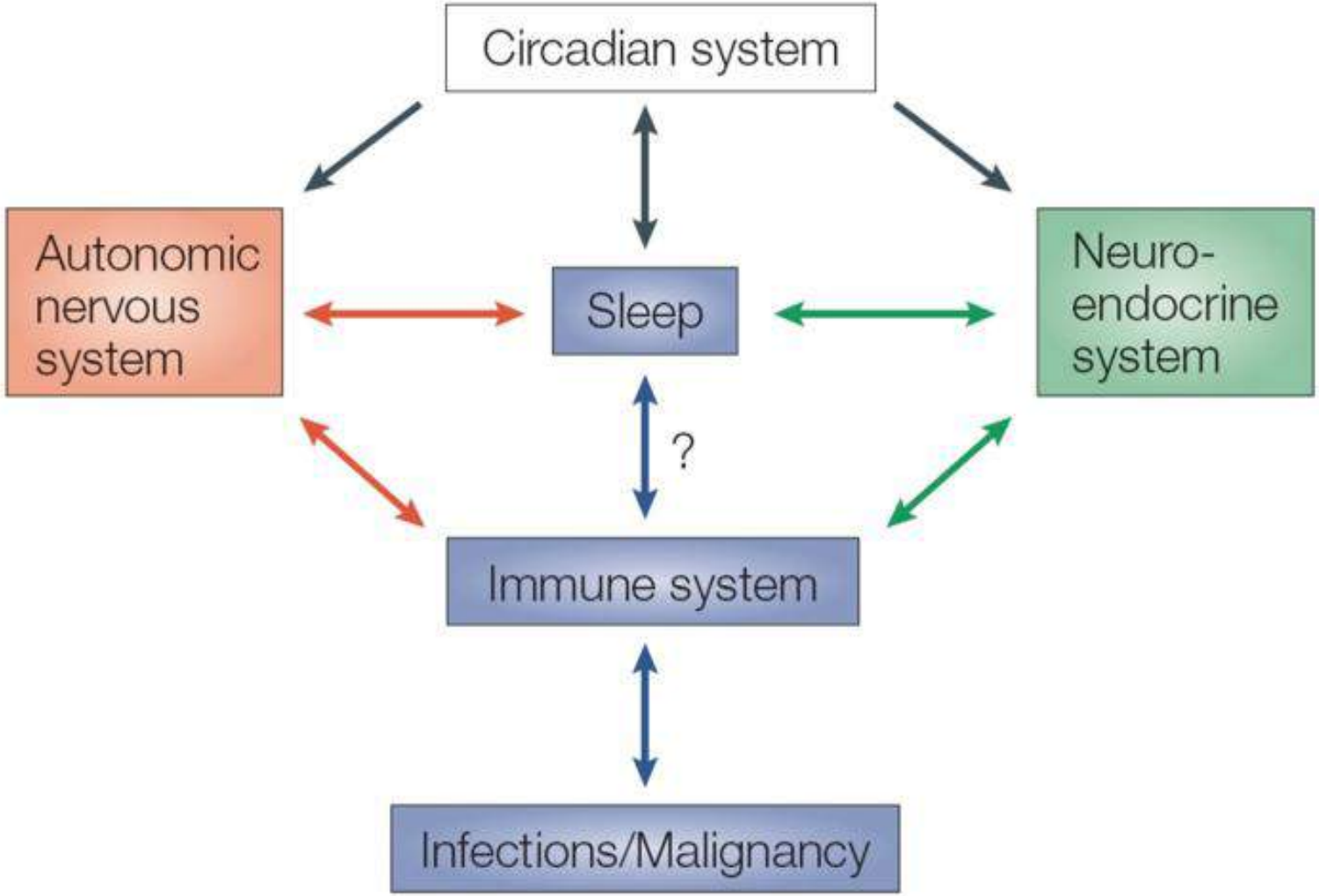
- **Sleep and metabolism**
- **Obstructive sleep apnea (OSA)**
- **OSA and type-2 diabetes**
- **The modern treatment of OSA – impact**

OIVAUNI
UNIKLINIKKA

Our Health

- Our comprehensive well-being is based on regular physical activity, healthy eating and restoring sleep.

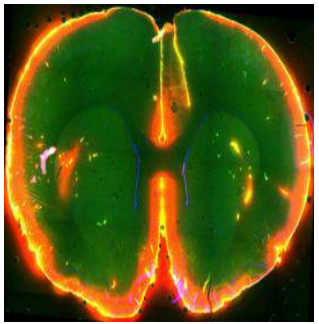

Circadian system
Autonomic nervous system
Sleep
Neuro-endocrine system
?
Immune system
Infections/Malignancy

Significance of sleep

Why we sleep

➢ no accepted universal theory

Lulu Xie et al. Science 2013: Sleep Drives Metabolite Clearance from the Adult Brain



Vital function of sleep

- repair of cell damage
- memory and cognitive function
- supplementation of brain cell energy storage
- clearance of brain metabolites

Consequences of sleep deprivation

- stress mechanisms ↗
- subclinical inflammation ↗
- glucose- and lipid metabolism ↘
- immune system ↘
- appetite ↗

Significance of sleep

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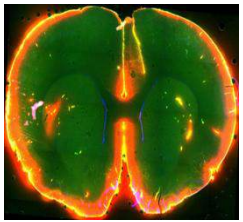
- no accepted universal theory



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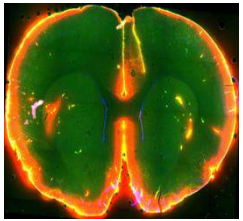
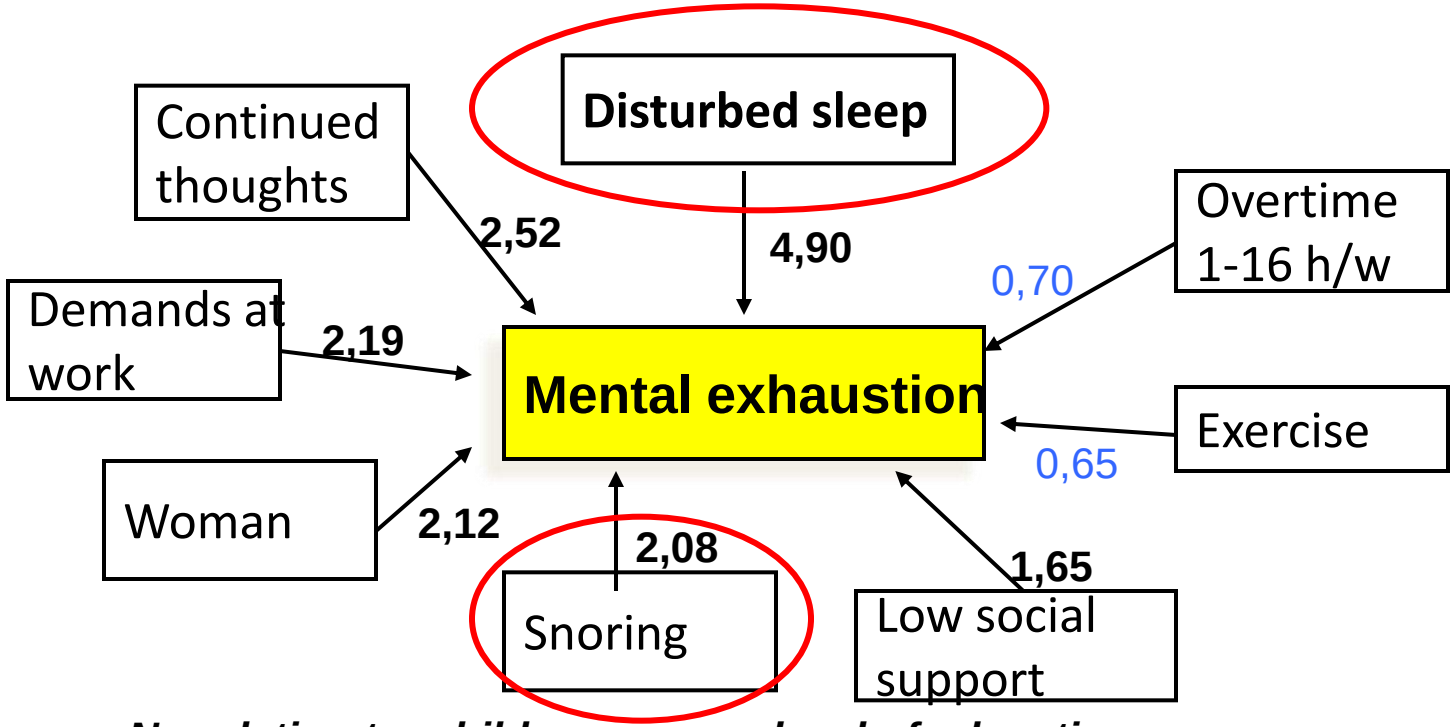


Lulu Xie et al. Science 2013: Sleep Drives Metabolite Clearance from the Adult Brain

Consequences of sleep deprivation

- stress mechanisms ↗
- subclinical inflammation ↗
- glucose- and lipid metabolism ↘
- immune system ↘
- appetite ↗
- mood and motivation ↘

Prediction of mental exhaustion



No relation to: children, age, or level of education

Average sleep length globally

United Kingdom

Average time slept work nights- **6h 49m**
Average sleep needed to function best- **7h 20m**
Less sleep than needed on workdays- **51%**
Good night sleep every/almost every night- **42%**
Schedule/Routine allows adequate sleep- **82%**

Average number of pillows- **2**
Make bed everyday/almost everyday- **80%**
Change sheets once a week or more- **68%**
Air out bedroom once a week or more- **93%**

Say "I feel more relaxed in my bed if my room has a fresh, pleasant scent"- **86%**
Lavender is a relaxing scent- **64%**
Jasmine is a relaxing scent- **60%**

Germany

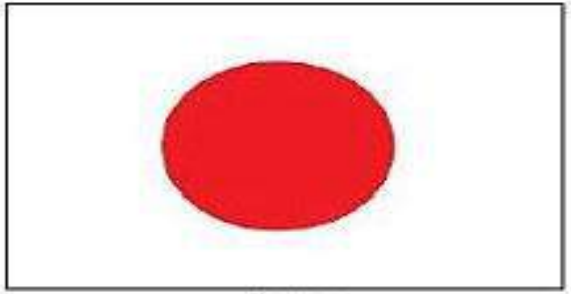
Average time slept work nights- **7h 1m**
Average sleep needed to function best- **7h 31m**
Less sleep than needed on workdays- **66%**
Good night sleep every/almost every night- **40%**
Schedule/Routine allows adequate sleep- **72%**

Average number of pillows- **2**
Make bed everyday/almost everyday- **79%**
Change sheets once a week or more- **22%**
Air out bedroom once a week or more- **100%**

Say "I feel more relaxed in my bed if my room has a fresh, pleasant scent"- **90%**
Lavender is a relaxing scent- **46%**
Jasmine is a relaxing scent- **30%**

Worldwide around 6 - 7h

Average sleep length globally



Japan

Average time slept work nights- **6h 22m**
Average sleep needed to function best- **6h 58m**
Less sleep than needed on workdays- **56%**
Good night sleep every/almost every night- **54%**
Schedule/Routine allows adequate sleep- **66%**

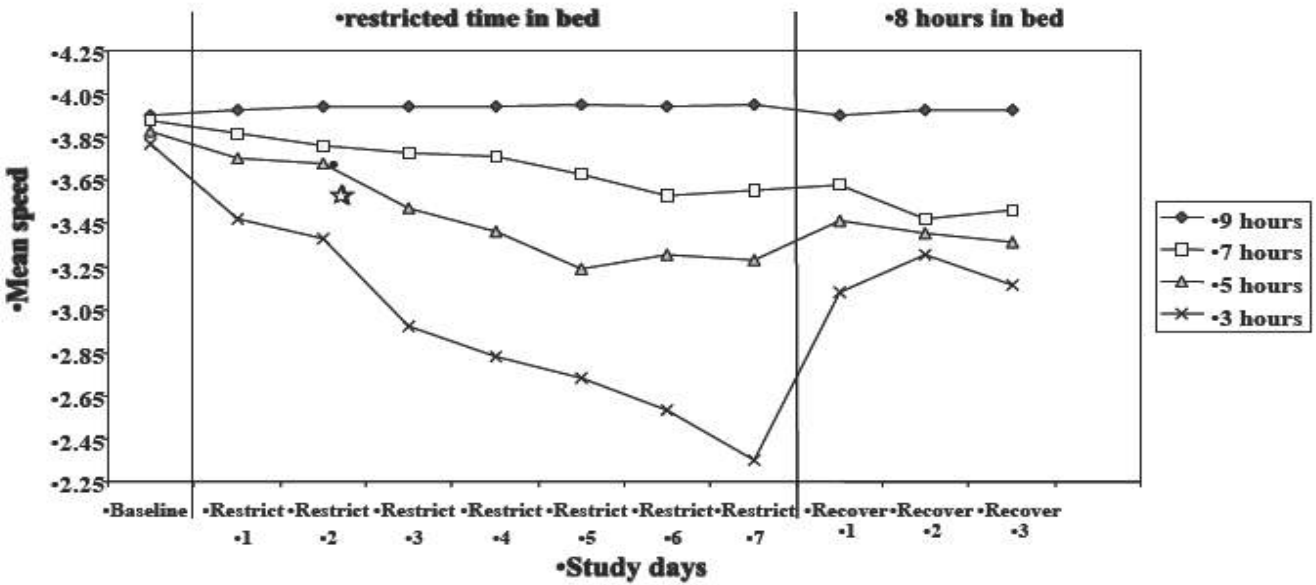
Average number of pillows- **1**
Make bed everyday/almost everyday- **44%**
Change sheets once a week or more- **40%**
Air out bedroom once a week or more- **86%**

Say "I feel more relaxed in my bed if my room has a fresh, pleasant scent"- **41%**
Lavender is a relaxing scent- **41%**
Jasmine is a relaxing scent- **38%**

Worldwide around 6 - 7h

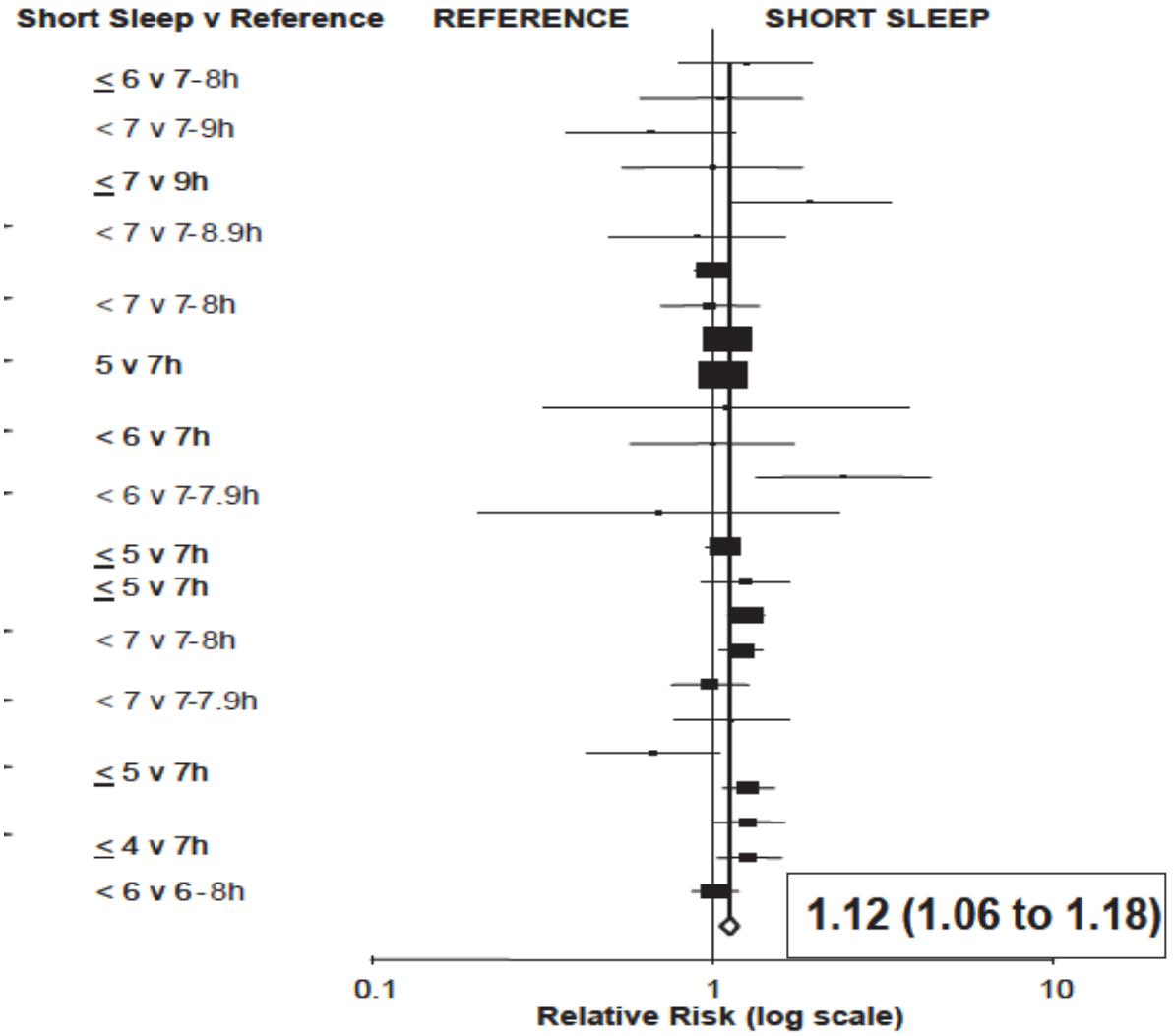
Immediate consequences of sleep deprivation

Sleep restriction and performance
N = 66; age 25-55 y; PVT-test

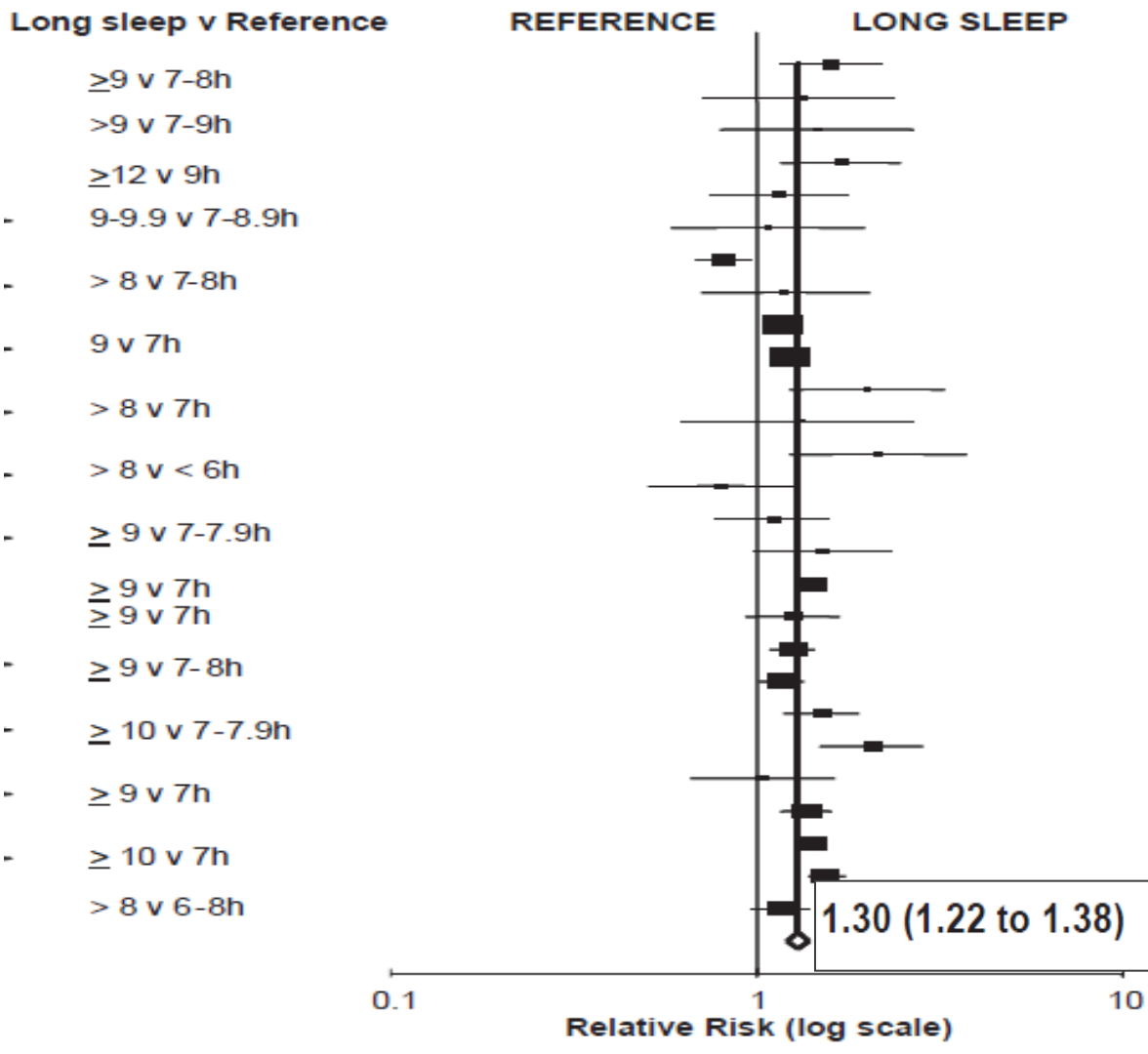


•Belenky G et al. J Sleep Research 2003; 12: 1-12

Risk of death associated with **short duration** of sleep compared to the reference group in 25 population cohorts from 15 published prospective studies including 1,381,324 participants and 112,163 events



Risk of death associated with **long duration** of sleep compared to the reference group in 27 population cohorts from 16 published prospective studies including 1,382,999 participants and 112,566 events



Mortality and OSA

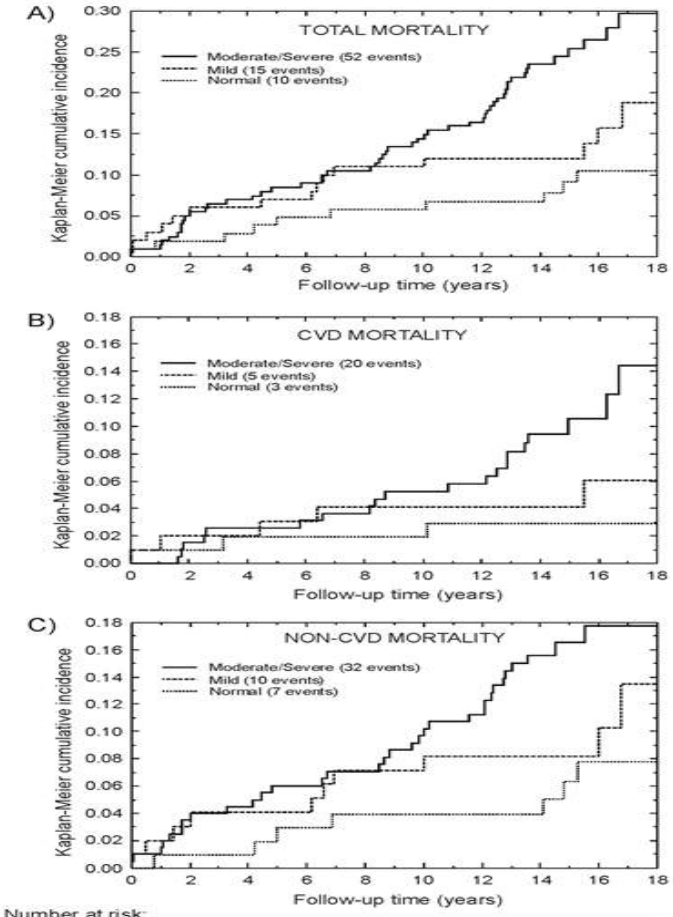


Figure 2: Total mortality (A), cardiovascular mortality (B) and non-cardiovascular mortality (C). Patients with moderate to severe sleep apnea showed significantly higher mortality than the patients with normal recordings. All cases were followed at least 12 years and 10 months, the longest follow-up time being 17.2 years.

•Muraja-Murro A., Sleep Breath 2013

OSA and cardiovascular diseases

- OSA in 83% of patients with hypertension[1]
  - poor response to antihypertension treament
- OSA in 76% patients with heart failure[2]
- OSA in 62% patients with atrial flimmer[3]
- OSA OR 5.16 for stroke[4]

[1] Logan et al. Hypertension 2001
[2] Oldenburg et al. Eur J Heart Fail 2007
[3] Stevenson et al. Eur Heart J 2010
[4] Capampangan et al. Neurologist 2010

Long-term consequences of sleep debt

- **Sleep deprivation → central obesity, type-2 diabetes and metabolic syndrome**

- **Epidemiological and laboratory studies**
- [1] Spiegel ym. Lancet 1999; 354: 1435-1439, [2] Spiegel ym. J Clin Endocrinol Metab 2004; 89: 5762-5771, [3] Knutson ym. Sleep Med Rev 2007; 11: 163-178, [4] Fogelholm ym. Int J Obes 2007; 31: 1713-1721, [5] Tuomilehto ym. Sleep Med 2008; 9: 221-227, [6] Tuomilehto ym. Diabetes Obes Metab 2008; 10: 468-475.

- **Two or three nights' consecutive wakefullness or partial ≥6 nights sleep debt → glucose tolerance ⇩ ,insulin resistance ⇧ visceral fat ⇧**

Sleep disorders are major burden – insomnia, sleep apnea and sleep medication

Trends in Outpatient Visits for Insomnia, Sleep Apnea, and Prescriptions for Sleep Medications among US Adults: Findings from the National Ambulatory Medical Care Survey 1999-2010

Earl S. Ford, MD, MPH; Anne G. Wheaton, PhD; Timothy J. Cunningham, ScD; Wayne H. Giles, MD, MS; Daniel P. Chapman, PhD; Janet B. Croft, PhD

Division of Population Health, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, GA

Study Objective: To examine recent national trends in outpatient visits for sleep related difficulties in the United States and prescriptions for sleep medications.

Design: Trend analysis.

Setting: Data from the National Ambulatory Medical Care Survey from 1999 to 2010.

Participants: Patients age 20 y or older.

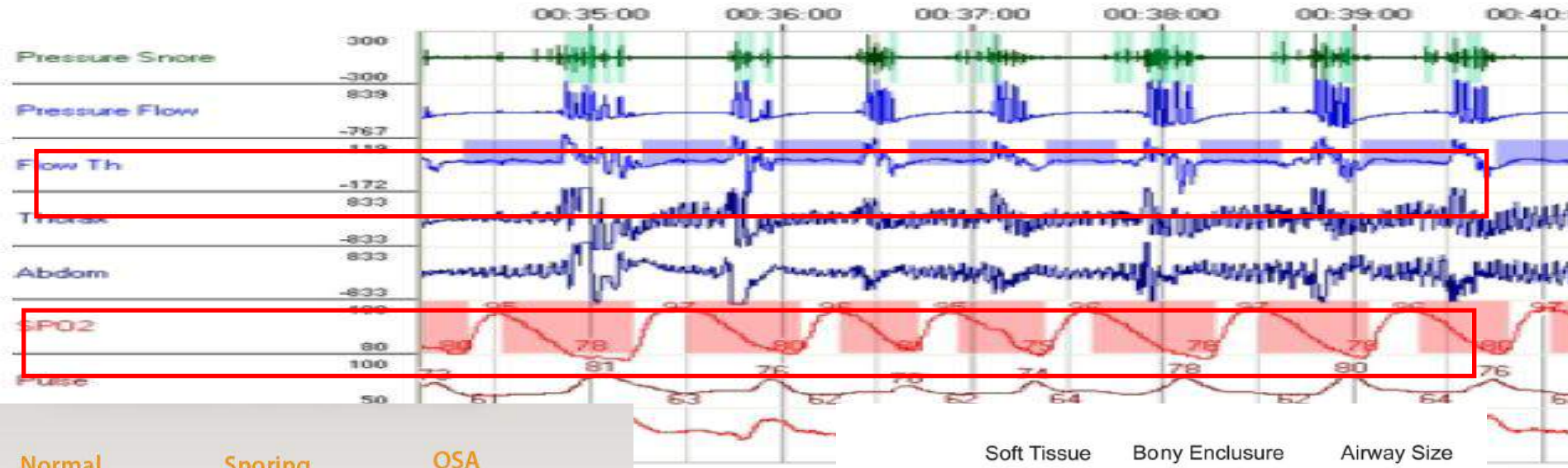
Measurements and Results: The number of office visits with insomnia as the stated reason for visit increased from 4.9 million visits in 1999 to 5.5 million visits in 2010 (13% increase), whereas the number with any sleep disturbance ranged from 6,394,000 visits in 1999 to 8,237,000 visits in 2010 (29% increase). The number of office visits for which a diagnosis of sleep apnea was recorded increased from 1.1 million visits in 1999 to

Office visits

1999-2010

- **OSA +442% (5.8 mi)**
- **Other disorders +266% (12.1 mi)**
- **Sleep medication +293% (20.8 mi)**
- **benzodiazepine +430%**

Obstructive sleep apnea



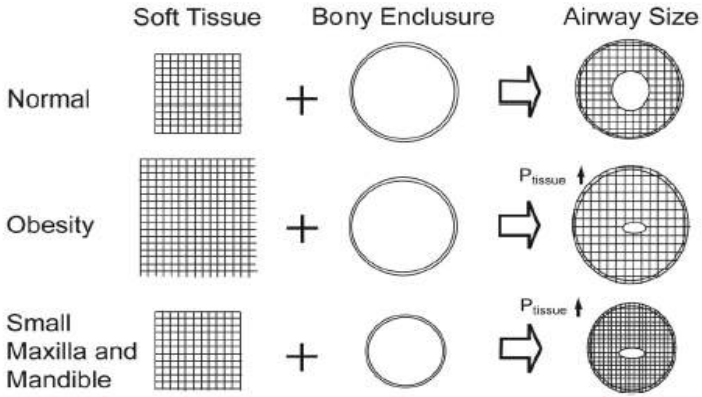
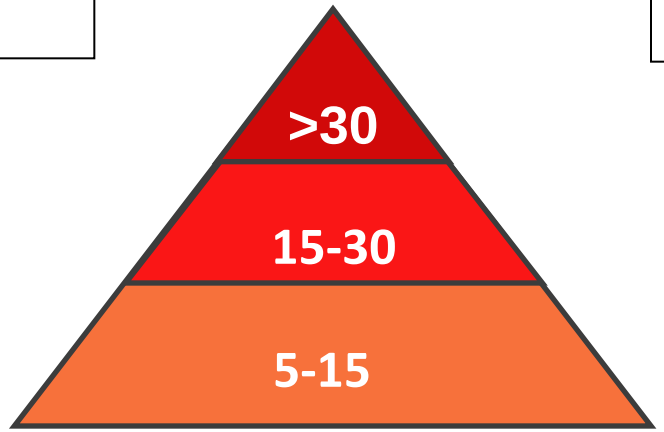


Fig. 5. Interaction of soft tissue and bony enclosure determines airway size. Schematic explanations for the mechanical model of the pharyngeal airway. P_{tissue} is the pressure surrounding the collapsible tube. (From Reference 9, with permission.)

Classification of OSA

- Sleep recording - mandatory
- **A**pnea-**H**ypopnea **I**ndex **(AHI)** events/h

Severity		Proportion
Severe	>30	10%
Moderate	15-30	30%
Mild	5-15	60%



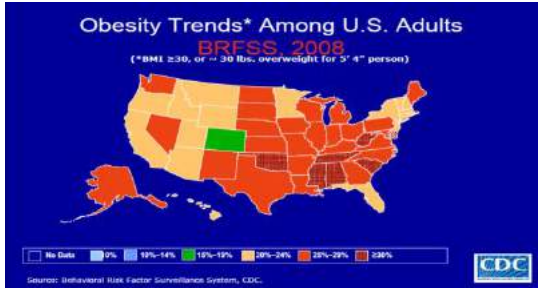
How common is OSA?

- **Obstructive sleep apnea (OSA)**
  - **OSAS 2-4% of population**

TABLE 1. PREVALENCE OF OBSTRUCTIVE SLEEP APNEA FROM THREE STUDIES WITH SIMILAR DESIGN AND METHODOLOGY

Study Location	n	Age Range (*years*)	Estimated Prevalence of AHI ≥ 5 events/hour (% [95% CI]) Men	Estimated Prevalence of AHI ≥ 5 events/hour (% [95% CI]) Women	Estimated Prevalence of AHI ≥ 15 events/hour (% [95% CI]) Men	Estimated Prevalence of AHI ≥ 15 events/hour (% [95% CI]) Women
Wisconsin*	626	30–60	24 (19–28)	9 (6–12)	9 (6–11)	4 (2–7)
Pennsylvania†	1,741	20–99	17 (15–20)	Not given	7 (6–9)	2 (2–3)
Spain‡	400	30–70	26 (20–32)	28 (20–35)	14 (10–18)	7 (3–11)

Definition of abbreviation: AHI = apnea–hypopnea index.
* Young and coworkers (11).
† Bixler and coworkers (15, 16).
‡ Durán and coworkers (17).



- **80-90% undiagnosed**

OSA – risk factors

- Obesity is most important single risk factor (Wolk et al 2003)
- Approximately **70%** of OSA patients are obese (Malhotra and White 2002)

Acta Odontologica Scandinavica, 2011; 69: 137–143

informa
healthcare

ORIGINAL ARTICLE

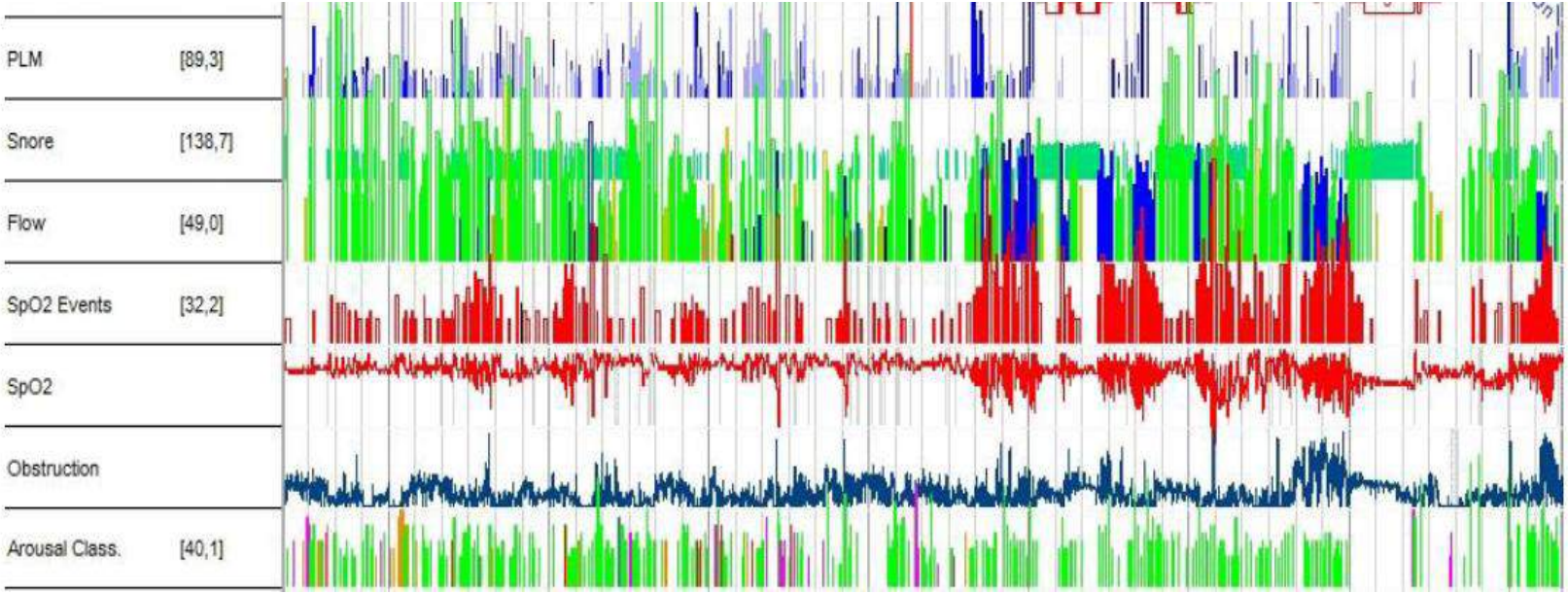
Risk factors for sleep-disordered breathing: the role of craniofacial structure

RIITTA PAHKALA[1], RIIKKA PUUSTINEN[1], HENRI TUOMILEHTO[2], JARI AHLBERG[3] &

The craniofacial profile in normal-weight patients was more convex (P < 0.000) and the mandible more retrusive (P = 0.004) than in overweight subjects. In addition, distal molar occlusion (P = 0.005) was more prevalent in normal-weight subjects, and their overjet and overbite were increased as compared to overweight patients (P = 0.009 and 0.006, respectively). Similarly, cross bite was detected significantly more often in normal-weight subjects (P = 0.052).

of Clinical Medicine, Otorhinolaryngology, Kuopio University Hospital, Kuopio, Finland and University of Eastern Finland, Finland, and [3]Institute of Dentistry, Department of Stomatognathic Physiology and Prosthetic Dentistry, University of Helsinki, Helsinki, Finland

OSA and obesity – vicious cycle

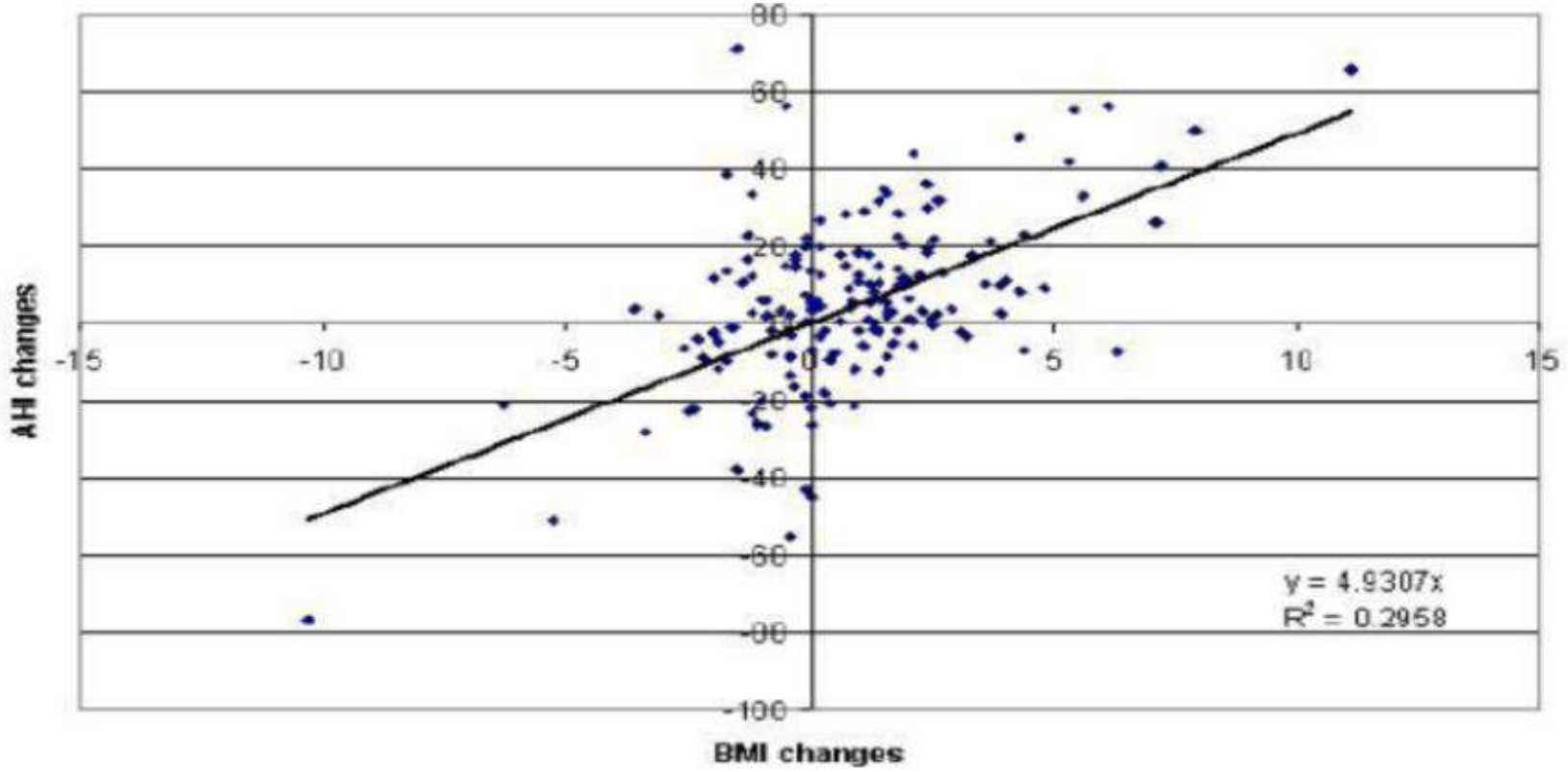


Tuomilehto H et al., Sleep Med Rev 2013

How to suspect OSA?

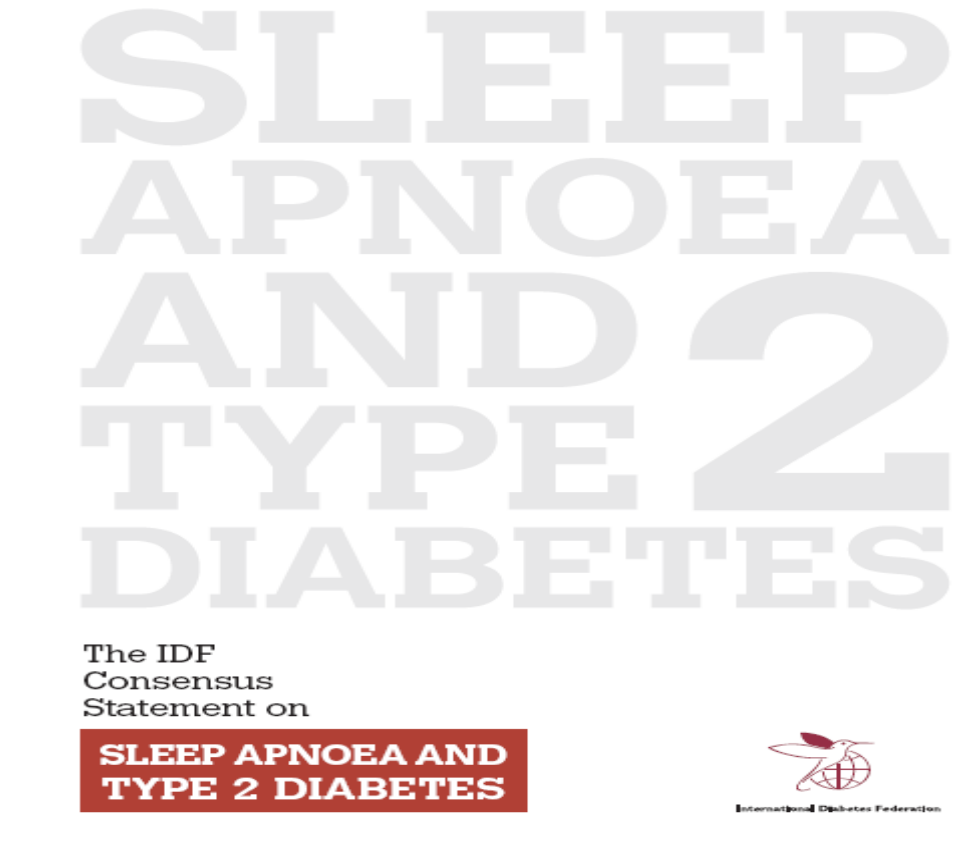
- Snoring
- Breathing pauses
- Nocturia
- Submental space
- Occlusion (over-jet)
- Obesity
- Central obesity
- Gender
- Age
- Daytime sleepiness?!
  - young adults!!??

OSA has natural tendency to worsen…



Berger et al. Eur Respir J 2009;33:338-45

OSA and type-2 diabetes



Recent research demonstrates the likelihood of a relationship between sleep-disordered breathing (SDB) and type 2 diabetes. Whilst the exact nature of the relationship between the two conditions remains uncertain, the association between them has important implications for public health and for individuals. Additionally, both type 2 diabetes and SDB are strongly associated with cardiovascular disease (CVD). SDB is increasingly considered as a condition to be treated for the prevention of CVD. When type 2 diabetes is already present, the treatment of SDB is even more relevant, because people with diabetes are already at high risk of CVD.

Type-2 diabetes in OSA - Prevalence

Table 1
Studies examining the prevalence and incidence of type 2 diabetes (T2DM) in patients with obstructive sleep apnea (OSA).

Author/year	Sample	OSA diagnosis	Diabetes definition	Adjusted covariates	Main Findings
Meslier et al.[51] (2003)	595 men referred to sleep disorders center	AHI ≥ 10 494 with OSA 101 without OSA	Self-report; Fasting glucose > 126 mg/dl; OGTT 2-h post-load glucose ≥ 200 mg/dl	None	Higher prevalence of T2DM in OSA
Reichmuth et al.[43] (2005)*	1387 (779 men); Wisconsin Sleep Cohort, United States 4-year follow-up (n = 987)	AHI ≥ 5	Physician diagnosis; Fasting glucose ≥ 126 mg/dl	Age, sex, body habitus	Higher prevalence of T2DM in moderate to severe OSA; Adjusted OR = 2.30 (CI = 1.28–4.11) Higher incidence of T2DM in moderate to severe OSA; Unadjusted OR = 4.06 (CI = 1.86–8.85) Adjusted OR = 1.62 (CI = 0.67–3.65)
Seicean et al.[42] (2008)	2588 (1196 men); Sleep Heart Health Study, United States	AHI [illegible]	[illegible] glucose [illegible] mg/dl; [illegible] 2-h post [illegible] glucose [illegible] 200 mg/dl	Age, sex, BMI, race, waist	Higher prevalence of T2DM in OSA; Adjusted OR = 1.7 (CI = 1.1–1.6)
Tamura et al.[44] (2008)	129 Japanese patients with OSA	AHI [illegible]	[illegible]-report; [illegible] glucose > 12[illegible] mg/dl; OGTT 2-h post-load glucose ≥ 200 mg/dl	Sex, BMI	Higher prevalence of T2DM with increasing severity of OSA
Ronksley et al.[40] (2009)	2149 (1346 men); Calgary Health Region, Canada	AHI ≥ 5 (limited PSG) 1717 with OSA 432 without OSA	Self-report; Use of diabetes medications	Age, sex, BMI, neck size, smoking status	Higher prevalence of T2DM in severe OSA; Adjusted OR = 2.18 (CI = 1.22–3.89)
Mahmood et al.[45] (2009)	1008 (468 men); referred to sleep disorders center	AHI ≥ 5 745 with OSA 263 without OSA	Medical chart review; Self-report; Use of diabetes medications	Age, sex, race, BMI, oxygen parameters	Higher prevalence of T2DM in OSA; Unadjusted OR = 1.8 (CI = 1.3–2.6) **Adjusted OR = 1.3 (0.9–2.0)**
Marshall et al.[39] (2009) *	399 (294 men); Busselton Health Study, Australia 4-year follow-up	AHI ≥ 5 (limited PSG) 94 with OSA 278 without OSA	Physician diagnosis; Use of diabetes medications; Fasting glucose ≥ 126 mg/dl;	Age, sex, BMI, waist, mean blood pressure, HDL cholesterol	Higher prevalence of T2DM in moderate to severe OSA; Unadjusted OR = 4.37 (CI = 1.12–17.12) **Adjusted OR = 1.98 (0.41–9.55)** Higher incidence of T2DM in moderate to severe OSA; Unadjusted OR = 11.20 (CI = 1.88–66.75) Adjusted OR = 13.45 (CI = 1.59–114.11)
Botros et al.[41] (2009) *	544 individuals; VA Connecticut Sleep Center, United States 2.7 year follow-up	AHI ≥ 8 (full PSG) 402 with OSA 142 without OSA	Physician diagnosis; Fasting glucose ≥ 126 mg/dl;	Age, sex, race, BMI, baseline fasting glucose, weight change	Higher incidence of T2DM with increasing severity of OSA; Adjusted HR per quartile of OSA severity = 1.43 (CI = 1.10–1.86)

* includes prospective analysis; **Bold type indicates non-significant findings**, OR = odds ratio; CI = 95% confidence interval; HR = hazard ratio.

40%

OSA and type-2 diabetes - incidence

- **A recent study demonstrated that even after controlling for multiple confounders, initial OSA severity and its physiologic consequences predicted up to 30% higher risk for incident diabetes.**

Kendzerska T, Gershon A, Hawker G, Tomlinson G, Leung R. Obstructive Sleep Apnea and Incident Diabetes: A Historical Cohort Study. Am J Respir Crit Care Med Jun 2014, Epub.

OSA and type 2 diabetes - mechanism

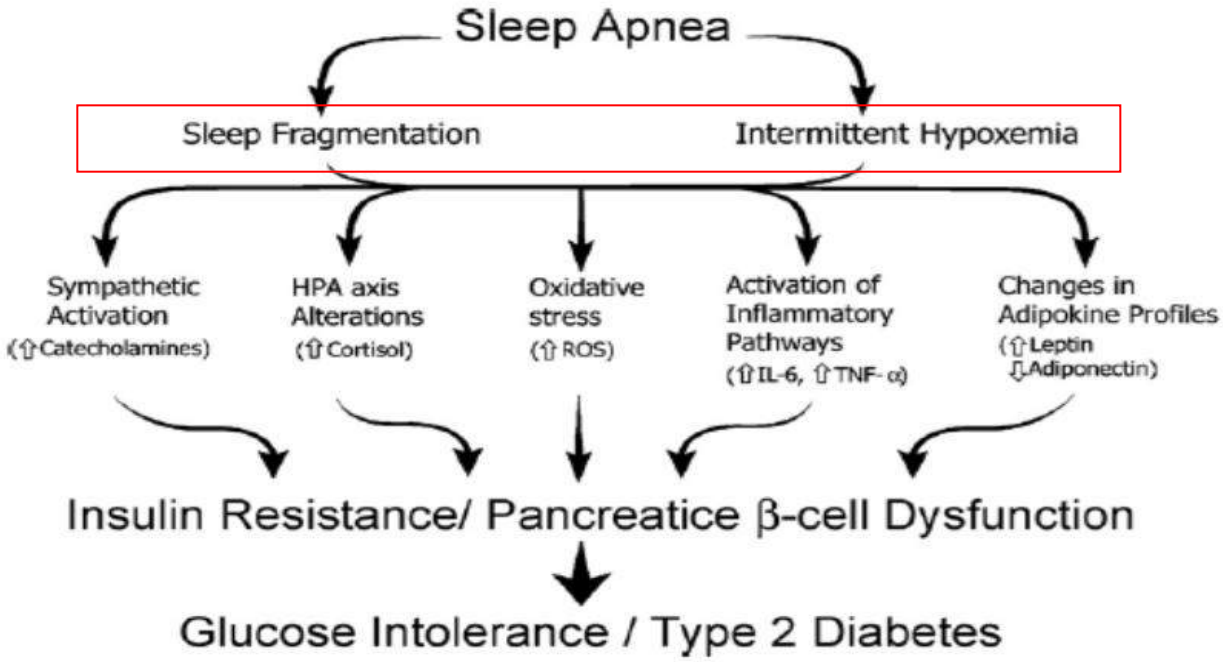


Fig. 1 – Potential mechanisms linking sleep apnoea to glucose intolerance.

OSA in people with type-2 diabetes

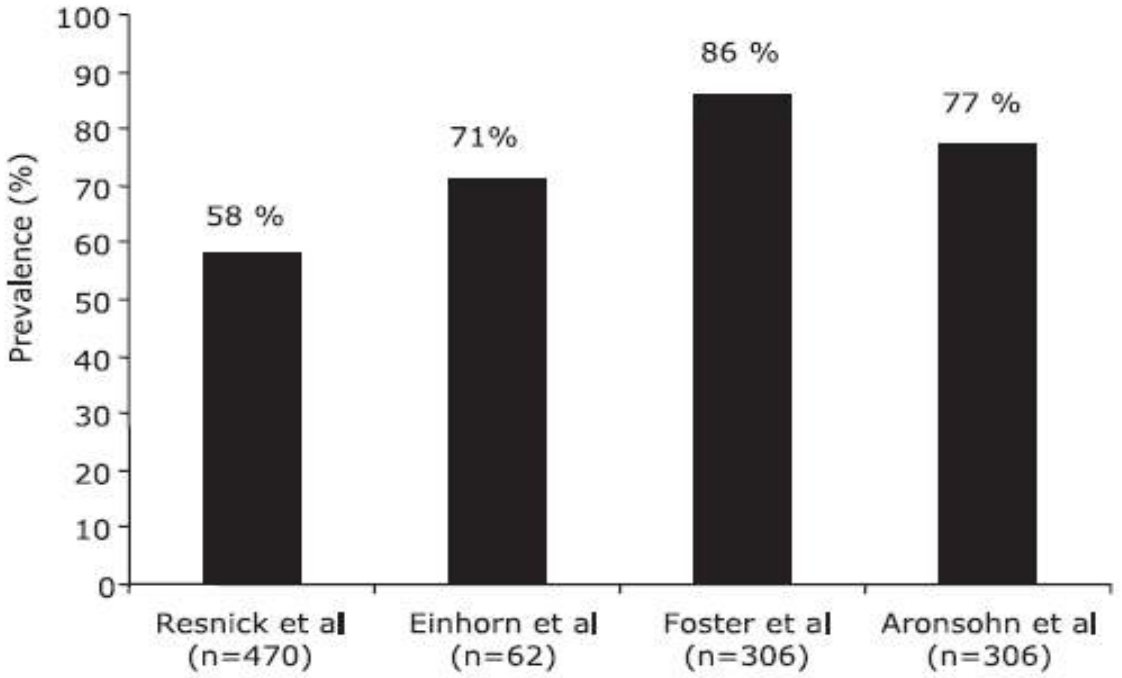
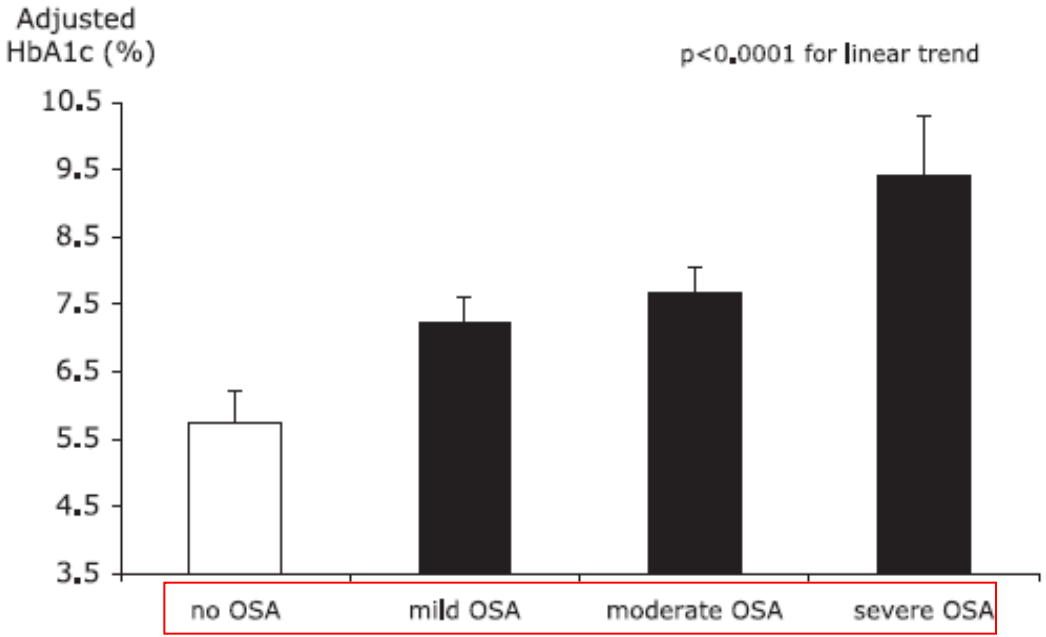


Fig. 1. Prevalence of OSA by polysomnography in patients with Type 2 Diabetes.

75%

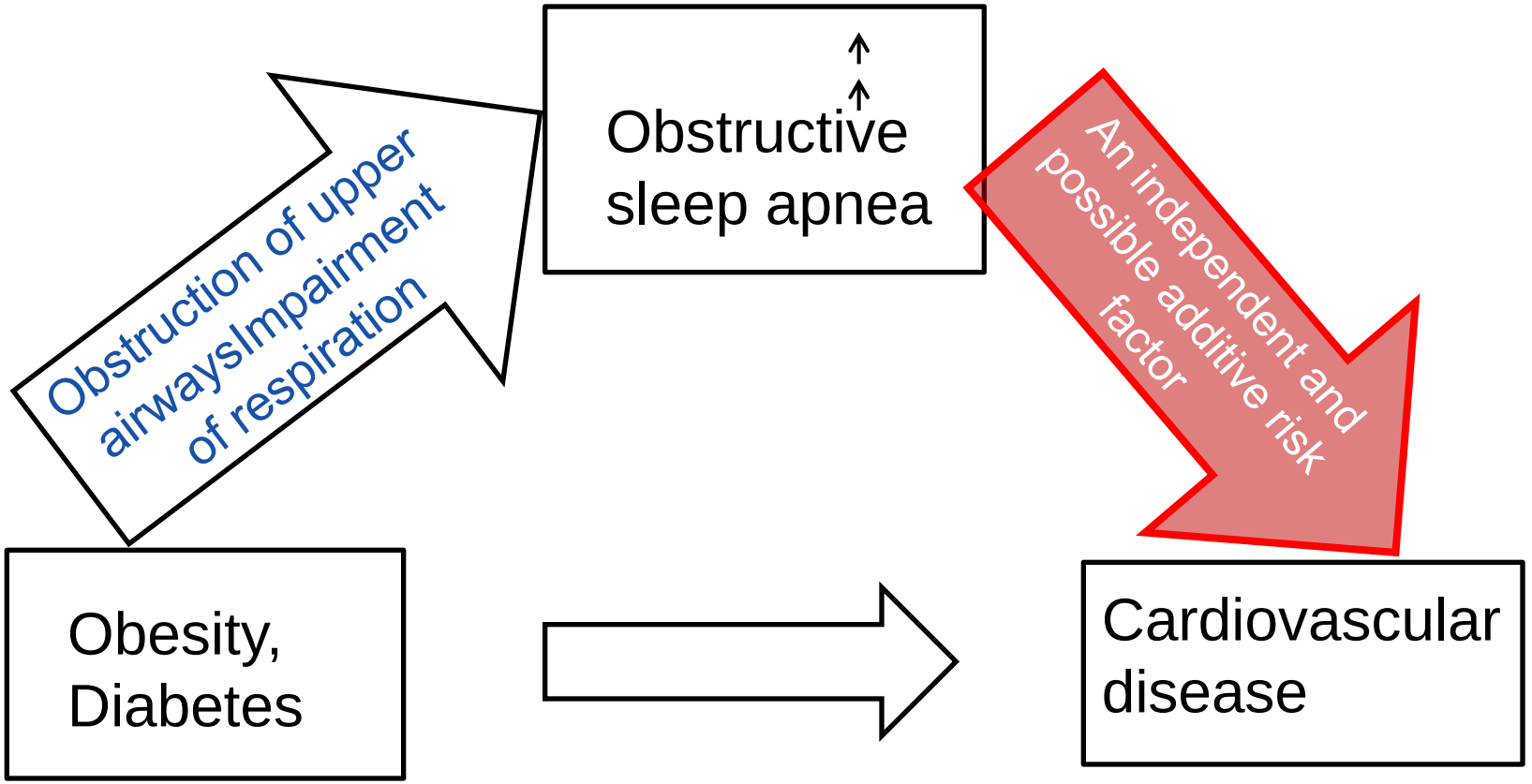
•Pamidi et al. 2010

The impact of OSA on glycaemic control in type-2 diabetes



Aronsohn et al. 2010

Fig. 2. Adjusted mean hemoglobin A1c (HbA1c) values for patients with no, mild, moderate and severe obstructive sleep apnea (OSA). Data were adjusted for age, sex, race, body mass index, number of diabetes medications, level of exercise, years of diabetes, and total sleep time on polysomnogram. Bars represent SEM. Adapted from Aronsohn et al.[36].



- Synergistic and possibly additive!!

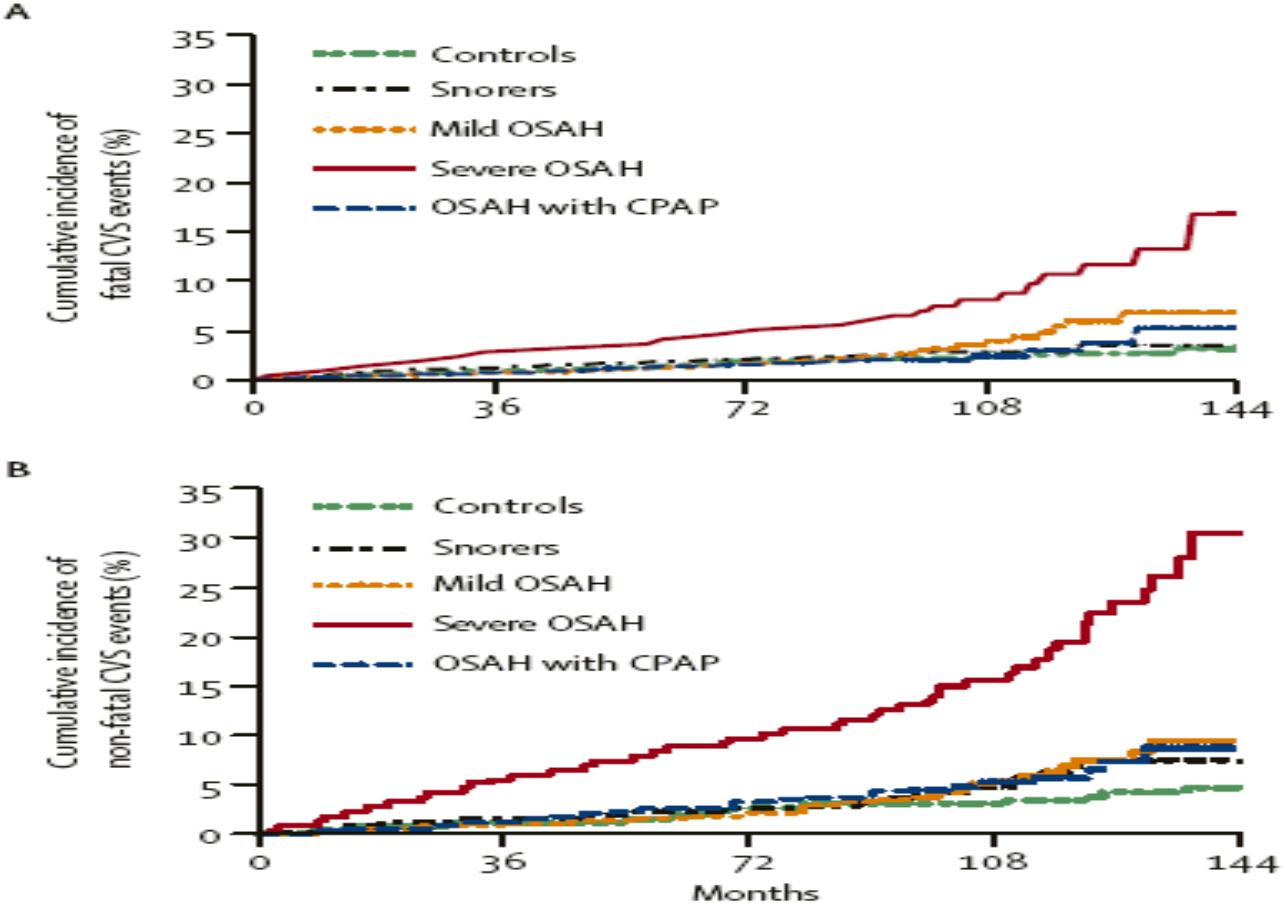
Pack A. 2009

OSA and type 2 diabetes – problem?

- Most patients with type-2 diabetes have OSA
- Most patients are undetected and untreated
  - for type-2 diabetes or OSA or both
- In patients with type-2 diabetes untreated OSA leads to unsatisfactory glycaemic control
- Both diseases are independent risk factors for CVD
- VERY HIGH RISK OF CVD – type-2 diabetes with OSA
- Economically expensive

Treatment of severe OSA:
Continuous positive airway pressure - CPAP

Mortality and CPAP



Marin JM et al.
Lancet. 2005;365:1046-53.

The impact of treating OSA in diabetics

RESULTS

Using CPAP was associated with significantly lower blood pressure at 5 years and increasingly lower HbA_{1c} levels over 5 consecutive years compared with untreated OSA patients. At 5 years, the HbA_{1c} level in the CPAP-treated group was 8.2% (66.0 mmol/mol) vs. 12.1% (108.4 mmol/mol) in the control group ($P < 0.03$). Use of CPAP significantly increased patients' health status by 0.27 quality-adjusted life years (QALYs) per patient over 5 years ($P < 0.001$) and NHS management costs by £4,141 per patient over 5 years; the cost per QALY gained with CPAP was £15,337.

CONCLUSIONS

Initiating treatment with CPAP in OSA patients with T2D leads to significantly lower blood pressure and better controlled diabetes and affords a cost-effective use of NHS resources. These observations have the potential for treatment modification if confirmed in a prospective study.

Clinical Outcomes and Cost-effectiveness of Continuous Positive Airway Pressure to Manage Obstructive Sleep Apnea in Patients With Type 2 Diabetes in the U.K.

Diabetes Care 2014;37:1263–1271 | DOI: 10.2337/dc13-2539

Weight loss as a treatment of OSA – Sustained 5% weight loss

Progression of the disease

The mean AHI at the 5-year visit was 6.3 in patients with successful weight reduction and 14.6 in patients with unsuccessful weight reduction, (P=0.001).

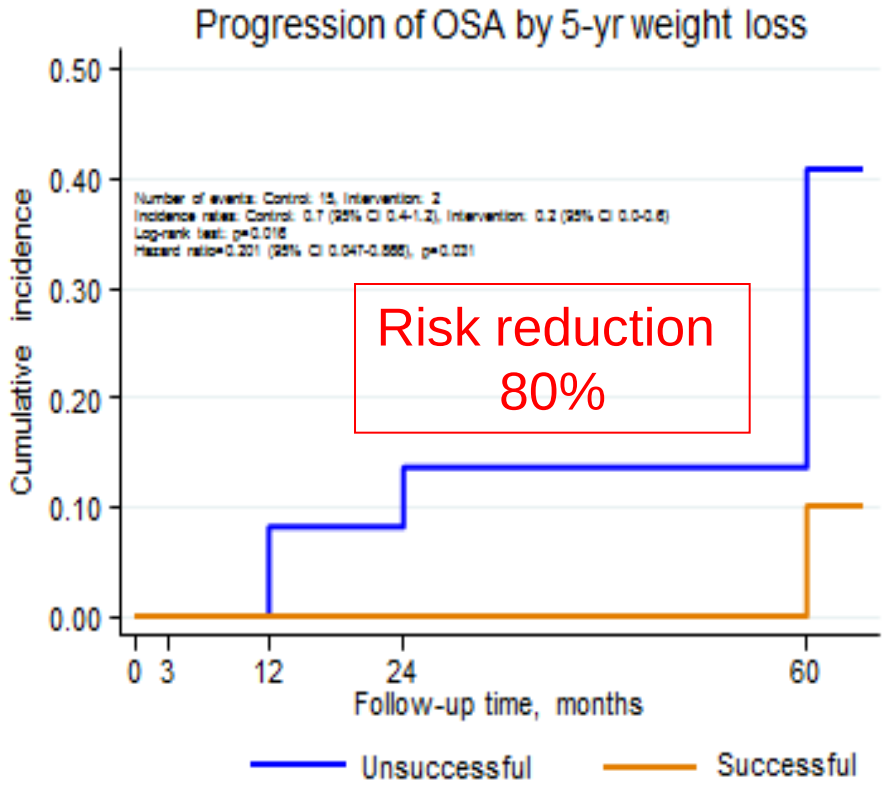
Successful weight loss group

2 participants to moderate OSA

Unsuccessful weight loss group

18 to moderate OSA

2 to severe OSA



Tuomilehto et al. JAMA Intern Med 2013

Tuomilehto et al. Sleep Med 2014

5% weight loss – additional metabolic benefits

	Unsuccessful Group	Successful Group	Difference	P	P adj
Number of patients with follow-up data	37	20			
Number of cured patients (%)	4 (11)	10 (50)	39	0.001	0.003
AHI-total	5.2 (9.7)	-3.5 (5.5)	-8.8	<0.001	0.002
AHI-supine	5.7 (29.9)	-1.7 (15.6)	-7.4	0.35	0.12
AHI-other position than supine	3.7 (6.3)	-3.5 (4.3)	-7.1	0.009	0.058
Percentage of supine recording	0.9 (28.5)	-1.1 (18.5)	-2.0	0.81	0.49
Mean SaO_2 (%)	-0.8 (1.7)	-0.3 (1.4)	0.5	0.23	0.22
Mean SaO_2 below 90%, (min)	26.8 (65.5)	-9.0 (26.6)	-35.8	0.04	0.11
Heart rate (beats/min)	2.9 (5.8)	-1.9 (5.0)	-4.8	0.056	0.062
Weight, kg	2.2 (6.2)	-10.9 (5.3)	-13.1	<0.001	<0.001
BMI, kg/m^2	0.7 (2.1)	-3.7 (1.7)	-3.4	<0.001	<0.001
Waist circumference, cm	2.5 (6.3)	-9.0 (6.4)	-11.5	<0.001	<0.001
Plasma glucose, mmol/l	0.04 (1.2)	-0.1 (0.4)	0.06	0.58	0.039
Plasma insulin, mU/l	5.2 (10.4)	-4.5 (7.6)	-9.7	0.001	0.001
Serum cholesterol, mmol/l	0.01 (1.2)	0.3 (0.7)	0.29	0.34	0.85
HDL cholesterol, mmol/l	0.04 (0.3)	0.2 (0.2)	-0.2	0.007	0.011
Serum triglycerides, mmol/l	0.1 (1.0)	-0.4 (0.6)	-0.5	0.055	0.011
Serum alanine aminotransferase, u/l	4.5 (26.6)	-10.7 (19.5)	-15.2	0.03	0.012
Systolic blood pressure, mm Hg	0.7 (14.1)	0.3 (25.7)	-0.4	0.96	0.74
Diastolic blood pressure, mm Hg	0.0 (9.0)	-3.3 (9.7)	-3.3	0.45	0.81
SOS, points	16.3 (25.2)	19.7 (20.2)	3.4	0.61	0.50