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Sleep disturbances in relation to diabetes

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JW Goethe on the importance of sleep

"Der Schlaf heilt bei mir vieles"

JW Goethe, An Charlotte v. Stein, 3.4.1715

Sleep, stress and diabetes

- People sleep less today than 100-150 years ago, due to changes in working and private life
- Both subjective sleep problems and diabetes are public health problems on the increase according to population-based surveys and screening studies
- **The Gender Paradox:** Women report more sleep problems and use more hypnotic drugs, but men run a higher risk for adverse health effects associated with insomnia (OSA could be a mediator)
- Increased psychosocial stress load can be counterbalanced by rest and sleep (restitution)

Åkerstedt T, Nilsson PM, J Internal Med 2004

Sleep complaints and illness
- a gender paradox?

Biology?

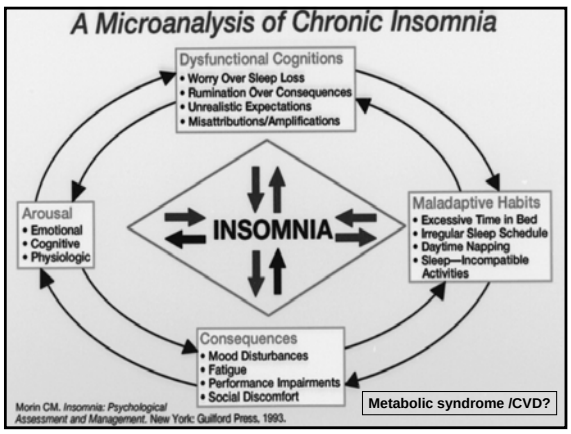
Evolution?

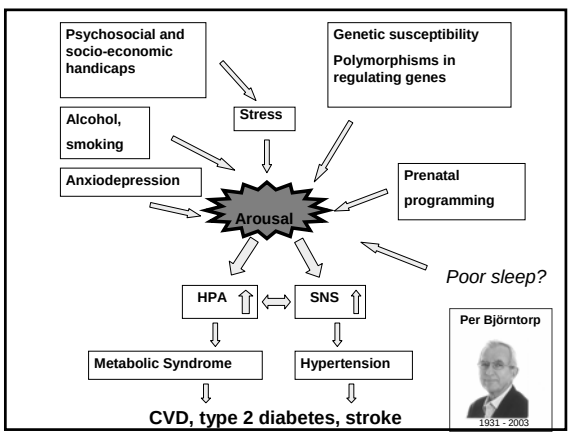
Genetics?

Gender?

Lifestyle?

Social?

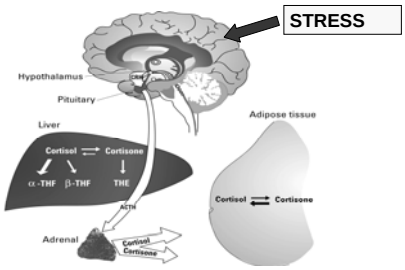




Increased glucocorticoid receptor activity due to:

1) Increased central drive in the HPA axis

2) Locally produced cortisol in liver and adipose tissue



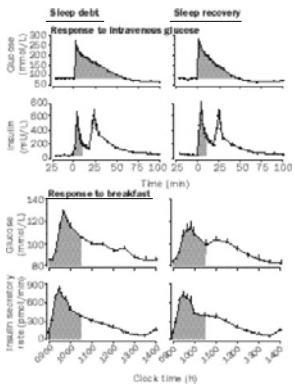
Per Björntorp 2003 (†)

Unhealthy lifestyle and sleep disturbances leading to obesity

Impact of sleep deprivation on metabolism

- Experimental sleep deprivation in healthy, young, male volunteers
- Negative impact on glucose metabolism and endocrine variables
- Short-sleeping men show a metabolic and endocrine profile that resembles the one found in elderly subjects

Karen Spiegel, Eve van Cauter, Lancet 1999



Mean (SE) profiles of blood glucose and serum insulin during intravenous glucose tolerance test, and glucose and insulin responses to breakfast

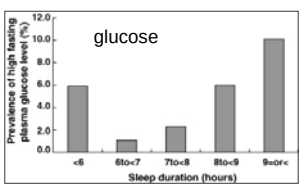
The Lancet 1999; **354**:1435-39

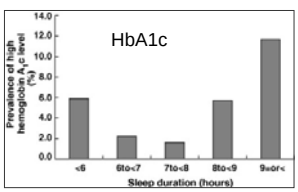
Association between sleep duration and hemoglobin A1c level in Japan

The distributions of the analyzed subjects by gender and age classification

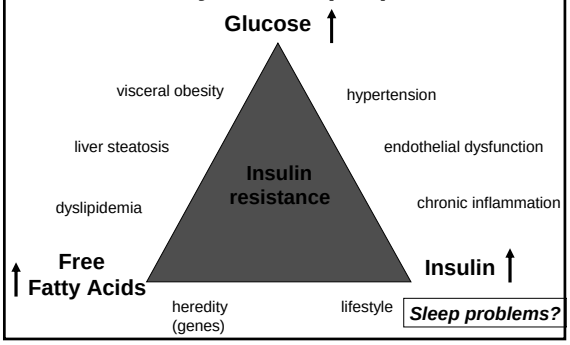
Age classification	Male *N* (%)	Female *N* (%)	Total *N* (%)
20–39	57(14.0)	86(13.1)	143(13.5)
40–49	61(15.0)	81(12.3)	142(13.4)
50–59	99(24.4)	163(24.8)	262(24.7)
60–69	94(23.2)	189(28.8)	283(26.6)
70–	95(23.4)	137(20.9)	232(21.8)
Total	406(100.0)	656(100.0)	1062(100.0)

Nakajima H, et al. Sleep Medicine, 2007

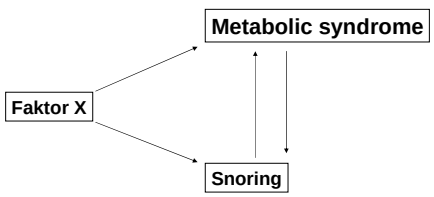




Cornerstones in the Insulin Resistance Syndrome (IRS)



Could there be a faktor X? Which one?



Long-term follow-up of self-reported sleep compalints in middle-aged women in Göteborg, Sweden

- In total 1462 women were followed between 1968 and 2000.
- The diabetes incidence was 8.7% (n= 126). No statistical association was shown for an association between sleep complaints and diabetes risk.
- Subjective sleep complaints correlated with increasing waist-to-hip ratio (WHR).
- There was an inverse association between WHR, BMI and sleep duration

Björkelund C, *et al.* Diabetes Care 2005

Sleep disturbances and risk
- chronic inflammation as mediator

- Chronic, low-grade inflammation is associated with biological ageing and impaired immune function
- Interleukin 6 (IL-6) is a cytokine of importance for the inflammatory response
- IL-6 increases with abdominal obesity and the metabolic syndrome, but also in subjects with severe sleep complaints
- This could support the notion that chronic sleep deprivation facilitates inflammatory processes, and thereby increases the risk of developing both CVD and type-2 diabetes

Vgontzas et al. 2002-2004

Men **Prediction of total mortality**

Problems	N	Deaths	Age adjustment	Full adjustment	p-value
None	10770	1184	1.0	1.0	
Difficulties falling asleep	895	141	1.52 (1.28-1.81)	**1.33** (1.11-1.58)	0.0017
Early wake-up	915	129	1.17 (0.97-1.40)	**1.22** (1.02-1.47)	0.033
Combination	951	189	1.90 (1.63-2.21)	**1.76** (1.51-2.06)	0.0001

Adjustment for (1) age only, or for (2) age, BMI, cholesterol, systolic BP, smoking and alcohol problematic drinking at baseline (full adjustment).

Nilsson PM, et al. J Internal Med 2001;250:521-9

The incidence of diabetes in middle-aged men is related to resting heart rate and sleep disturbances

Nilsson PM, Rööst M, Engström G, Hedblad G.
Diabetes Care 2004;27:2464-2469

Sleep problems and prospective risk of type 2 diabetes in Malmö (1)

- Rationale: Sleep deprivation has experimentally been shown to negatively influence glucose metabolism in young, healthy volunteering men (Spiegel K, *et al.,* Lancet 1999)
- Design: A 15-years follow-up of 6,599 healthy middle-aged, non-diabetic men from a population-based screening study (MPP) in 1974-1980, were followed-up for incident diabetes (n= 281)
- Diabetes status at follow-up (Malmö Diet Cancer study 1992-1994) was assessed from questionnaire data (including drug use) in all subjects, and from fasting blood glucose in a minority (n= 1,551)

Nilsson PM, et al. Diabetes Care 2004;27:2464-69

Sleep problems and prospective risk of type 2 diabetes in Malmö (2)

Incident diabetes		Multiple logistic regression	p-value
No	Yes		
6318	281		
No sleep problems		Reference	---
Difficulties in falling asleep or regular use of hypnotics		1.52 (10.5-2.20)	0.025
Both types of sleep problems		1.78 (0.96-3.32) *	0.070
Heart rate (per 10 beats/min)		1.13 (0.99-1.30)	0.068

*** p for trend 0.007**

adjustment for age, BMI, log glucose, social class, family history of diabetes, lifestyle, and follow-up time

Nilsson PM, et al. Diabetes Care 2004;27:2464-69

Sleep problems and prospective risk of type 2 diabetes in Malmö (3)

- Results: Difficulties in falling asleep or regular use of hypnotics, RR 1.52 (95%CI 1.05-2.20), and resting heart rate, RR (per 10 beats/min) 1.13 (0.99-1.30) were predictive of incident diabetes after full adjustment for age, BMI, log glucose, social class, family history of diabetes, lifestyle, and follow-up time
- Interpretation: Sleep disturbances is a marker for increased risk of diabetes in middle-aged men independent of other risk factors. In association with elevated heart rate this could be markers of increased sympathetic nervous activation or the obstructive sleep apnoea (OSA) syndrome - not measured
- The same independent association has not been shown for women

Nilsson PM, et al. Diabetes Care 2004;27:2464-69

Why does sleep disturbance increase the risk of diabetes mellitus, and is there really a gender difference?

Nilsson PM. Sleep Med. 2007 Aug 1;
[E-pub ahead of print]

Summary

- Different sleep patterns and self-report of sleep disturbances have been associated with increased risk for cardiovascular disease, but also experimentally for impaired glucose metabolism and epidemiologically for development of type 2 diabetes (Eve van Cauter, Lancet 1999, Nilsson 2004, etc.)
- In the population-based Malmö Preventive Project (MPP) an increased risk of diabetes was predicted after 15 years by sleep complaints and use of hypnotic drugs, adjusted for other risk factors.
- This could represent the negative influence of sleep disturbances per se, or the association with abdominal obesity and obstructive sleep apnoea (OSA) syndrome
- Randomised intervention studies are needed to prove causality

PN 2007