Daytime Sleepiness, Sleep Apnea and Obesity

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Hershey
Excessive Daytime Sleepiness

• Is there an “epidemic”? 
• Is obesity a major factor in this “epidemic”? 
## Excessive Daytime Sleepiness

**“Sleeping Too Much”**

<table>
<thead>
<tr>
<th>Source</th>
<th>Year</th>
<th>Age</th>
<th>Total</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Karacan</td>
<td>1976</td>
<td>18-70</td>
<td>.3%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bixler</td>
<td>1979</td>
<td>18-80</td>
<td>4.2%</td>
<td></td>
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</tr>
<tr>
<td>Ford</td>
<td>1989</td>
<td>18-65+</td>
<td>3.2%</td>
<td>2.8%</td>
<td>3.5%</td>
</tr>
</tbody>
</table>
# Excessive Daytime Sleepiness

**“Daytime Sleepiness”**

<table>
<thead>
<tr>
<th>Source</th>
<th>Age</th>
<th>Total</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maertikanen</td>
<td>1992</td>
<td>36-50</td>
<td>6.9%</td>
<td>12.0%</td>
</tr>
<tr>
<td>Hublin</td>
<td>1996</td>
<td>33-60</td>
<td>6.7%</td>
<td>11.0%</td>
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<tr>
<td>Ohayon</td>
<td>1997</td>
<td>15-100</td>
<td>5.5%</td>
<td>6.6%</td>
</tr>
<tr>
<td>Bixler</td>
<td>2000</td>
<td>20-100</td>
<td>8.6%</td>
<td>10.1%</td>
</tr>
</tbody>
</table>
Sleepiness in Patients with Sleep Apnea

• Young *et.al.*, 1993
  – Complaint of EDS (age=30-60)
    • Women 22.6% of AHI≥5
    • Men 15.5% of AHI ≥5

• Bixler *et.al.*, 2005
  – Complaint of EDS (age=20-100)
    • 17.6% of AHI≥15

• Kapur *et.al.*, 2005
  – Complaint of EDS (age>40 x≈65)
    • 16.6% of AHI≥5
    • ESS>10 is higher
## Prevalence of Sleepiness by Apnea-Hypopnea Index Category

<table>
<thead>
<tr>
<th>AHI</th>
<th>No.</th>
<th>ESS score &gt;10</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5</td>
<td>3463</td>
<td>21.4%</td>
</tr>
<tr>
<td>5-15</td>
<td>1831</td>
<td>26.7%</td>
</tr>
<tr>
<td>15-30</td>
<td>749</td>
<td>29.6%</td>
</tr>
<tr>
<td>≥30</td>
<td>400</td>
<td>40.2%</td>
</tr>
</tbody>
</table>

*Kapur et al., 2005*
Obesity is Independently Associated with Daytime Sleepiness

- 73 Obese patients & 45 Controls both without SDB

- Obese patients compared to controls:
  - Sleepier during the day
  - Less sleepy during the night

Vgontzas et al. 1998, Arch. Int. Med
Daytime Sleep Latencies in Obese and Healthy Controls
Prevalence of EDS (BMI)

Bixler et al. 2005, JCEM
### Studies on the independent association of EDS and obesity

<table>
<thead>
<tr>
<th>Human Studies</th>
<th>Sample</th>
<th>n</th>
<th>Control</th>
<th>n</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vela Bueno</td>
<td>1984</td>
<td>PWS without EDS</td>
<td>9</td>
<td>None</td>
<td>0</td>
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<tr>
<td>Vgontzas</td>
<td>1996</td>
<td>PWS without EDS</td>
<td>8</td>
<td>None</td>
<td>0</td>
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<tr>
<td>Vgontzas</td>
<td>1998</td>
<td>Obese without SDB</td>
<td>73</td>
<td>Normal weight without SDB</td>
<td>45</td>
</tr>
<tr>
<td>Punjabi</td>
<td>1999</td>
<td>SDB patients</td>
<td>741</td>
<td>N/A</td>
<td>0</td>
</tr>
<tr>
<td>Resta</td>
<td>2001</td>
<td>Obese patients</td>
<td>161</td>
<td>Normal weight</td>
<td>40</td>
</tr>
<tr>
<td>Resta</td>
<td>2003</td>
<td>Obese without SDB</td>
<td>78</td>
<td>Normal weight</td>
<td>40</td>
</tr>
<tr>
<td>Bixler</td>
<td>2005</td>
<td>Population cohort</td>
<td>1741</td>
<td>N/A</td>
<td>0</td>
</tr>
<tr>
<td>Resnik</td>
<td>2006</td>
<td>Population cohort</td>
<td>3130</td>
<td>N/A</td>
<td>0</td>
</tr>
<tr>
<td>Theorell-Haglow</td>
<td>2006</td>
<td>Population cohort</td>
<td>5508</td>
<td>N/A</td>
<td>0</td>
</tr>
</tbody>
</table>

BMI = Body-mass index  EDS = Excessive daytime sleepiness  PSG = Polysomnography  PWS = Prader-Willi syndrome  SDB = Sleep disordered breathing  

Vgontzas et al. 2008, Archives of Physiology and Biochemistry
Sleep alterations during high-fat induced obesity in mice

Jenkins 2006, Physiol. Behav
Effects of Weight Loss on Sleep in mice

Summary

High Fat Group

Light Period

REM sleep

NREMS sleep

Wake

Dark Period

Regular Food Group

Light Period

REM sleep

NREMS sleep

Wake

Dark Period

Guan, SLEEP 2008
Diabetes

- Diabetes reported by history
  - or
- Fasting blood sugar $\geq 126$ mg/dl

*Bixler et al. 2005, JCEM*
Prevalence of EDS in diabetic and nondiabetics in a general random sample of 1,741 men and women.

OR=2.2(1.4,3.4), P=0.0003
Prevalence of OSA and EDS in women with Polycystic Ovary Syndrome

Vgontzas et al. 2001, JCEM
Exercise and Sleep Apnea

- 1104 men and women, 30-60 years
- Sleep assessed in the sleep lab
- Exercise assessed by questionnaire
- Adjusting for BMI, age, sex and other
- Apnea Hypopnea Index 5.3 - 0 hours of exercise
- Apnea Hypopnea Index 2.8 - >7 hours of exercise

Wisconsin Sleep Cohort Study
Peppard and Young, 2004
Exercise and Sleepiness

- 1106 patients with sleep apnea
- AHI $\geq 5$ + symptoms
- Sleepiness (Epworth), Activity (Physical Activity Questionnaire)
- Logistic regression – logAHI, depression, lack of regular exercise

*Basta et al. 2008, JCSM*
Exercise and Sleepiness (cont’d)

• In mild to moderate sleepiness: depression and logAHI in both sexes

• In severe sleepiness
  – in men, exercise strongest predictor, followed by depression and minSaO\textsubscript{2}
  – in women, logAHI – women exercise significantly less than men and are heavier (BMI 39.8 vs 35.4)

• Insulin resistance/visceral adiposity strong determinants of sleepiness in sleep apneics
<table>
<thead>
<tr>
<th>Study Authors</th>
<th>Year</th>
<th>Sample Description</th>
<th>Sample n</th>
<th>Control Description</th>
<th>Control n</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feinberg</td>
<td>1993</td>
<td>Type 2 diabetes mellitus patients without treatment</td>
<td>2</td>
<td>None</td>
<td>0</td>
<td>Subjective EDS is associated with undiagnosed diabetes</td>
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<tr>
<td>Vgontzas</td>
<td>2001</td>
<td>PCOS patients</td>
<td>53</td>
<td>Normal weight</td>
<td>452</td>
<td>Subjective sleepiness is increased in women with PCOS compared to controls</td>
</tr>
<tr>
<td>Bixler</td>
<td>2005</td>
<td>Population cohort</td>
<td>1741</td>
<td>N/A</td>
<td>0</td>
<td>Subjective EDS is associated with diabetes independently of BMI, SDB, depression and age</td>
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<tr>
<td>Resnik</td>
<td>2006</td>
<td>Population cohort</td>
<td>3130</td>
<td>N/A</td>
<td>0</td>
<td>Subjective daytime fatigue is associated with less physical activity</td>
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<tr>
<td>Tasali</td>
<td>2006</td>
<td>Obese PCOS patients</td>
<td>40</td>
<td>None</td>
<td>0</td>
<td>Subjective daytime sleepiness is associated with PCOS</td>
</tr>
<tr>
<td>Theorell-Haglow</td>
<td>2006</td>
<td>Population cohort</td>
<td>5508</td>
<td>N/A</td>
<td>0</td>
<td>Subjective fatigue is associated with less physical activity</td>
</tr>
<tr>
<td>Basta</td>
<td>2008</td>
<td>Patients with SDB</td>
<td>1106</td>
<td>N/A</td>
<td>0</td>
<td>Subjective sleepiness is significantly reduced in obese apneic men that exercise regularly</td>
</tr>
<tr>
<td>Barcelo</td>
<td>2008</td>
<td>SDB patients with and without EDS</td>
<td>44</td>
<td>Normal weight without SDB</td>
<td>23</td>
<td>Objective and subjective EDS is associated with insulin resistance in patients with SDB independently of obesity</td>
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<tr>
<td>Hayashino</td>
<td>2008</td>
<td>Population cohort</td>
<td>4540</td>
<td>N/A</td>
<td>0</td>
<td>EDS or dozing/sleeping while driving is associated with diabetes</td>
</tr>
</tbody>
</table>

BMI = Body-mass index  
EDS = Excessive daytime sleepiness  
PSG = Polysomnography  
PCOS = Polycystic Ovary Syndrome  
SDB = Sleep disordered breathing  

Vgontzas et al. 2008, Archives of Physiology and Biochemistry
EDS and Depression

Bixler et al. 2005, JCEM
EDS
(Variables Evaluated)

- Age & $\text{Age}^2$
- $\text{BMI} & \text{BMI}^2$
- Diabetes or FBS $\geq 126$
- OA/HI $\geq 15$
- % Sleep Time
- Interactions:
  - Age
  - BMI
- Depression
- Asthma/Allergies
- Hypertension
- Race
- Alcohol
- Smoking
## Risk Factors For EDS

<table>
<thead>
<tr>
<th>Parameter</th>
<th>ES</th>
<th>P</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression</td>
<td>10.6</td>
<td>&lt;0.001</td>
<td>6.85</td>
</tr>
<tr>
<td>Log BMI</td>
<td>4.3</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>+ 1 SD</td>
<td></td>
<td></td>
<td>1.45</td>
</tr>
<tr>
<td>+ 2 SD</td>
<td></td>
<td></td>
<td>2.10</td>
</tr>
<tr>
<td>Age</td>
<td>3.6</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>+ 1 SD</td>
<td></td>
<td></td>
<td>0.61</td>
</tr>
<tr>
<td>+ 2 SD</td>
<td></td>
<td></td>
<td>0.38</td>
</tr>
<tr>
<td>Typical sleep duration</td>
<td>3.2</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>+ 1 SD</td>
<td></td>
<td></td>
<td>0.76</td>
</tr>
<tr>
<td>+ 2 SD</td>
<td></td>
<td></td>
<td>0.58</td>
</tr>
<tr>
<td>Diabetes / glucose &gt; 126</td>
<td>2.3</td>
<td>0.019</td>
<td>1.87</td>
</tr>
<tr>
<td>Smoke</td>
<td>1.9</td>
<td>0.060</td>
<td>1.53</td>
</tr>
<tr>
<td>OHI&gt;15</td>
<td>1.2</td>
<td>0.255</td>
<td>1.70</td>
</tr>
</tbody>
</table>

*Bixler et al. 2005, JCEM*
<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Sample Description</th>
<th>Sample Size</th>
<th>Control Description</th>
<th>Control Size</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vgontzas</td>
<td>2000</td>
<td>Primary hypersomnia and psychiatric hypersomnia patients</td>
<td>82</td>
<td>controls without sleep disorders</td>
<td>50</td>
<td>Psychogenic hypersomnia is associated with subjective but not objective daytime sleepiness</td>
</tr>
<tr>
<td>Bardwell</td>
<td>2003</td>
<td>Patients with SDB</td>
<td>60</td>
<td>None</td>
<td>0</td>
<td>Depression is independently associated with subjective fatigue in SDB patients</td>
</tr>
<tr>
<td>Bixler</td>
<td>2005</td>
<td>Population cohort</td>
<td>1741</td>
<td>N/A</td>
<td>0</td>
<td>Depression is the strongest risk factor associated with subjective EDS in a general random sample</td>
</tr>
<tr>
<td>Hasler</td>
<td>2005</td>
<td>Population cohort</td>
<td>591</td>
<td>N/A</td>
<td>0</td>
<td>Anxiety is a significant predictor of subjective EDS</td>
</tr>
<tr>
<td>Theorell-Haglow</td>
<td>2006</td>
<td>Population cohort</td>
<td>5508</td>
<td>N/A</td>
<td>0</td>
<td>Psychological distress is the most prominent risk factor for subjective EDS and fatigue in women</td>
</tr>
<tr>
<td>Bardwell</td>
<td>2007</td>
<td>Patients with SDB</td>
<td>56</td>
<td>None</td>
<td>0</td>
<td>Depression is independently associated with subjective fatigue in SDB patients</td>
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<tr>
<td>Dixon</td>
<td>2007</td>
<td>Bariatric obese patients</td>
<td>1055</td>
<td>N/A</td>
<td>0</td>
<td>Depression is associated with subjective sleepiness in severely obese patients</td>
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<tr>
<td>Pallesen</td>
<td>2007</td>
<td>Population cohort</td>
<td>231</td>
<td>N/A</td>
<td>0</td>
<td>Depression is significantly related to subjective sleepiness</td>
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<td>Bartlett</td>
<td>2008</td>
<td>Population cohort</td>
<td>3300</td>
<td>N/A</td>
<td>0</td>
<td>Depression is associated with chronic subjective sleepiness</td>
</tr>
<tr>
<td>Basta</td>
<td>2008</td>
<td>Patients with SDB</td>
<td>1106</td>
<td>N/A</td>
<td>0</td>
<td>Depression is a significant predictor of subjective sleepiness in obese apneics</td>
</tr>
</tbody>
</table>

EDS = Excessive daytime sleepiness  SDB = Sleep disordered breathing  
Vgontzas et al. 2008, Archives of Physiology and Biochemistry
EDS in Obese Children with SDB

- 150 children
- 9 hour PSG
- Subjective measures of EDS
- IL-6, TNFα, sIL-6R, TNFR1, CRP, leptin and adiponectin

Tsaoussoglou et. al. 2010 JCEM
SDB in Obese Children: EDS

![Graph showing % EDS for different groups: Lean Controls, Overweight/Obese Controls, Overweight/Obese mild SDB, Overweight/Obese moderate SDB. The graph indicates a significant increase in % EDS from Lean Controls to Overweight/Obese moderate SDB.](image-url)
# Prevalence and Risk Factors of Excessive Daytime Sleepiness in a Community Sample of Young Children: The Role of Obesity, Asthma, and Anxiety/Depression and Sleep

<table>
<thead>
<tr>
<th>RISK FACTORS for those with and w/o EDS</th>
<th>Univariate</th>
<th>ES</th>
<th>P</th>
<th>ORs</th>
<th>CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Health</strong></td>
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<td></td>
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<tr>
<td>Heartburn</td>
<td></td>
<td>.35</td>
<td>.008</td>
<td>3.1</td>
<td>1.4,7.2</td>
</tr>
<tr>
<td>Asthma</td>
<td></td>
<td>.35</td>
<td>.006</td>
<td>2.4</td>
<td>1.3,4.3</td>
</tr>
<tr>
<td>Asthma medication</td>
<td></td>
<td>.41</td>
<td>.002</td>
<td>2.9</td>
<td>1.5,5.7</td>
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<tr>
<td>Waist (cm)</td>
<td></td>
<td>.43</td>
<td>.001</td>
<td>1.04</td>
<td>1.01,1.06</td>
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<td><strong>Objective Sleep</strong></td>
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<tr>
<td></td>
<td></td>
<td>NS</td>
<td></td>
<td></td>
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</tr>
<tr>
<td><strong>Subjective Sleep</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trouble falling asleep</td>
<td></td>
<td>.59</td>
<td>&lt;.001</td>
<td>1.7</td>
<td>1.4,2.3</td>
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<tr>
<td>Restless sleep</td>
<td></td>
<td>.46</td>
<td>&lt;.001</td>
<td>1.6</td>
<td>1.3,2.0</td>
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<tr>
<td>Wakes often during the night</td>
<td></td>
<td>.56</td>
<td>&lt;.001</td>
<td>1.8</td>
<td>1.4,2.3</td>
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<tr>
<td><strong>Psychological</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression and/or anxiety</td>
<td></td>
<td>.48</td>
<td>&lt;.001</td>
<td>2.9</td>
<td>1.6,5.1</td>
</tr>
</tbody>
</table>

*Calhoun et al. Sleep (2011)*
## Significant Predictors of EDS

<table>
<thead>
<tr>
<th></th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
<th>Model 4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>P</td>
<td>OR</td>
<td>P</td>
<td>OR</td>
</tr>
<tr>
<td>Waist*</td>
<td>0.003</td>
<td>1.04</td>
<td>0.01</td>
<td>1.04</td>
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<td>Asthma</td>
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<td>2.1</td>
<td>.04</td>
<td>2.1</td>
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<tr>
<td>Depression/Anxiety</td>
<td>.01</td>
<td>2.5</td>
<td>.05</td>
<td>1.9</td>
</tr>
<tr>
<td>Trouble falling asleep</td>
<td></td>
<td></td>
<td>.03</td>
<td>1.4</td>
</tr>
</tbody>
</table>
Sleepiness vs. Fatigue
Phenomenology

• Synonyms – general public

• In a continuum – sleep patients by “fatigue” may mean a milder form of “sleepiness”

• Two distinct states with different pathophysiology?
Sleepiness vs Fatigue

• “Sleepiness is a subjective feeling of physical and mental tiredness associated with increased sleep propensity” e.g. sleep apnea, narcolepsy, sleep deprivation

• “Fatigue is a subjective feeling of physical and mental tiredness not associated with increased sleep propensity” e.g. chronic insomnia, sleep disturbance in the elderly, depression

Vgontzas et al. 2002, Metabolism
Sleepiness vs Fatigue
Pathophysiology

• Cytokine hypersecretion not associated with HPA axis activation leads to sleepiness and deep sleep e.g. sleep deprivation

• Cytokine hypersecretion associated with HPA axis activation leads to fatigue and poor sleep e.g. sleep disturbances in elderly, insomnia

Vgontzas et al. 2006, NYAS
Infection and Sleep

• Sleepiness is a common symptom of infectious disease
• Sleep loss leads to disease (Hippocrates)
• Bed rest and sleep, an ancient remedy to combat infections
Proinflammatory Cytokines and Sleep in Animals

• IL-1, TNFα injected I.C.V. or systemically in rabbits, rats and cats increases NREM sleep and amplitude of EEG slow wave and suppresses REM

• IL-1 or TNFα receptor antagonists or IL-1β antibodies reduce sleep in rabbits

Kreuger et al.
Cytokines and Disorders of Excessive Daytime Sleepiness

- 5%-9% of the general population complain of EDS
- Sleep apnea
- Narcolepsy
- Idiopathic hypersomnia
- TNFα, IL-1β, IL-6

Vgontzas et al. 1997, JCEM
Cytokines and disorders of EDS

**A**

- **TNFα**
  - Normal: ∼1 pg/mL
  - Obstructive Sleep Apnea: ∼2.5 pg/mL
  - Narcolepsy: ∼2.5 pg/mL
  - Idiopathic Hypersomnia: ∼1.5 pg/mL

**B**

- **IL-6**
  - Normal: ∼1 pg/mL
  - Obstructive Sleep Apnea: ∼1.5 pg/mL
  - Narcolepsy: ∼3 pg/mL
  - Idiopathic Hypersomnia: ∼1 pg/mL

* indicates statistically significant differences.
Cytokines, Sleep Apnea and Obesity

IL-6 (pg/ml)

AM
PM

TNFα (pg/ml)

AM
PM

Vgontzas et al. 2000, JCEM
Obesity Related Sleepiness and Fatigue
The Interaction of the Stress System and Cytokines
Body Mass Index

Plasma IL-6 (pg/ml)

$r_{xy} = .636$

Vgontzas et al. 1997, JCEM
Both IL-6 and TNFα correlate with BMI

Vgontzas, 2000
Obesity – HPA axis

• Obesity – HPA axis hyperactive – depression?
  
  *Björntorp, 2000*

• Obesity – lower UFC levels – non depressed

  *Pasquali, 2000*
Obesity – HPA axis

• Study I 45 obese men with and without apnea and non-obese controls 4-night sleep lab recording 24h plasma measures of cortisol

• Study II 38 obese men with and without sleep apnea and non-obese controls 4-nights in the sleep lab – CRH in the evening

Vgontzas et al. 2007, JCEM
Obesity - Sleep - Sleepiness

Two subtypes

• **Sleepiness** - Non depressed - deep sleep – HPA hypoactivity

• **Fatigue** - depression - poor sleep – HPA hyperactivity
Obese patients

Hyperarousal
(↓ % Sleep time)

Hyperarousal
(↑ % Sleep time)

Psychological Distress

Fatigue

EDS

Insulin Resistance

HPA ↑

Cytokines ↑

Cytokine Antagonists (etanercept) in Sleep Apnea and EDS

- 8 obese men with symptomatic apnea (A/HI > 20 plus EDS and/or hypertension) in a placebo-controlled pilot study
- 7-week study, 3 weeks of placebo followed by 3 weeks of Enbrel
- Polysomnography, respiration, MSLT, IL-6, CRP, adiponectin, FBS, insulin

Vgontzas et al., 2004, JCEM
The effects of Napping on Alertness, Cortisol and IL-6

- 41 young men and women
- 20 total sleep deprivation
- 21 2-hour nap following a night of sleep loss
- 7 night sleep lab protocol
- 24-hour blood draw, MSLT and PVT, pre and post sleep deprivation

Vgontzas et al. 2007, Am. J. Physiology
MSLT values before and after sleep deprivation in the no nap (top) and the nap condition (bottom)
IL-6 levels before and after sleep deprivation in the no nap (top) and the nap condition (bottom)
Weight Loss and Apnea

• Effect of diet on moderate/severe apnea
  
  Johansson et al 2009, BMJ
  
  Kansanen et al 1998, Clinical Physiology

• Effect of diet on mild apnea

  Tuomilehto et al 2009, Am J Respir Crit Care Med

• Diet and exercise improve Neurobehavioral and cardiometabolic outcomes

  Barnes et al 2009, JCSM
  
  Kansanen et al 1998, Clinical Physiology
Weight Loss, Sleep Apnea and EDS

- Weight loss (bariatric surgery) improves both Apnea and EDS

Dixon et al. 2005, Int J Obesity
Varela et al 2007, Obes Surg
Fritscher et al 2007, Respiration
Conclusions

EDS, OSA and Obesity

• Multifactorial
• Consider obesity, diabetes, depression, physical activity
• Weight loss, exercise, emotional stress and inflammation, useful interventions in the treatment of EDS
Acknowledgements

- Sleep Research and Treatment Center, Hershey
  - A. Vgontzas, M.D.
  - E.O. Bixler, Ph.D.
  - H-M Lin, Ph.D.
  - A. Kales, M.D.
  - M. Basta, M.D.
  - B. Pejovic, M.D.
  - I. Kritikou, M.D.
  - M. Karataraki, PsychD.
  - M. Tsaoussoglou, B.Sc.

- PREB NIH, Bethesda
- G. P. Chrousos, M.D.
- E. Zoumakis, Ph.D.
- D. Papanicolaou, M.D.
- P. Prolo, M.D.