



Sleep & Obesity

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Outline

- Purpose of sleep
- How it works?
- Sleep Duration:
 - Sleep deprivation
 - Metabolic role of sleep
- Causes of Obesity
- Obesity & sleep
 - Interaction in appetite regulation
 - Impact on sleep quality
 - Sleepiness

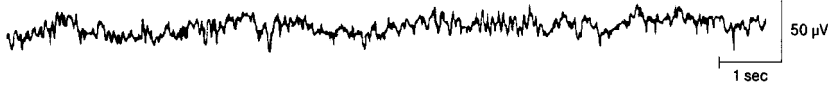
~~Obesity, Sleep & Sleep disordered breathing~~

~~• STOP BANG~~

~~• Treatment of SDB peri-operatively~~

Normal human sleep

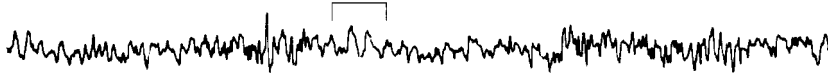
Awake: low voltage – random, fast



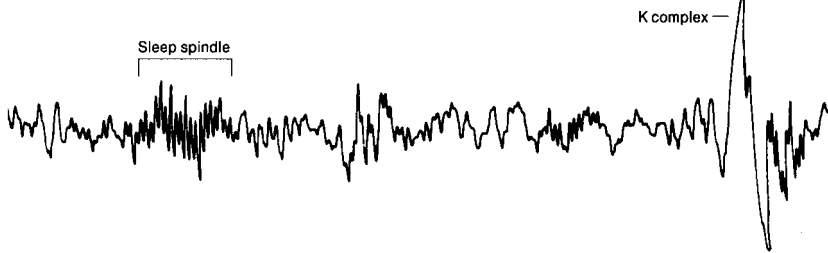
Drowsy: 8 to 12 cps – alpha waves



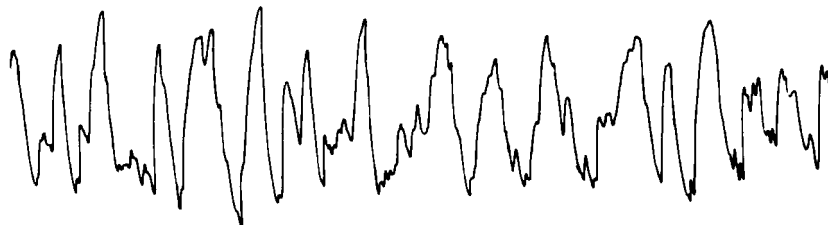
Stage 1: 3 to 7 cps – theta waves



Stage 2: 12 to 14 cps – sleep spindles and K complexes



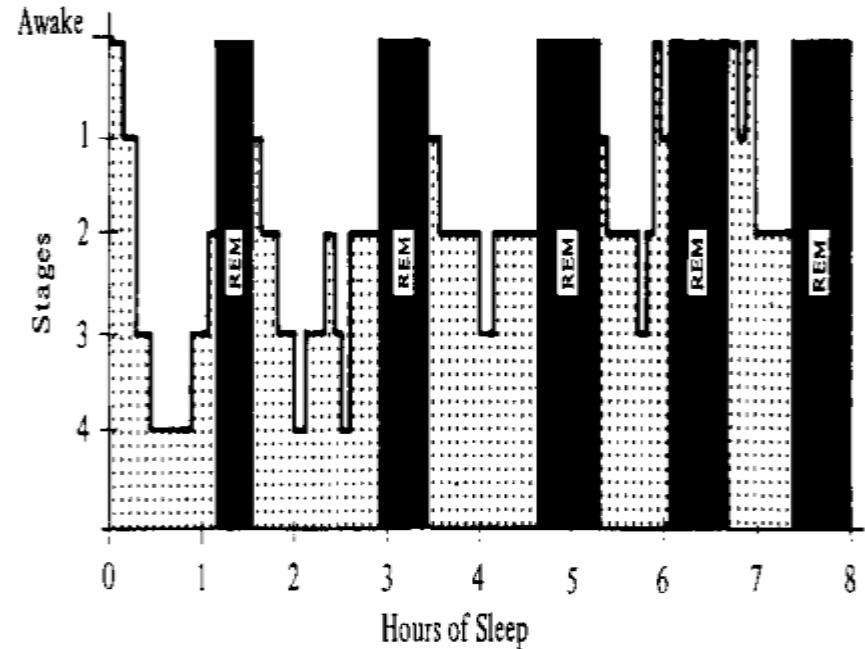
Delta sleep: (stages 3 and 4) 1/2 to 2 cps – delta waves >75 μV



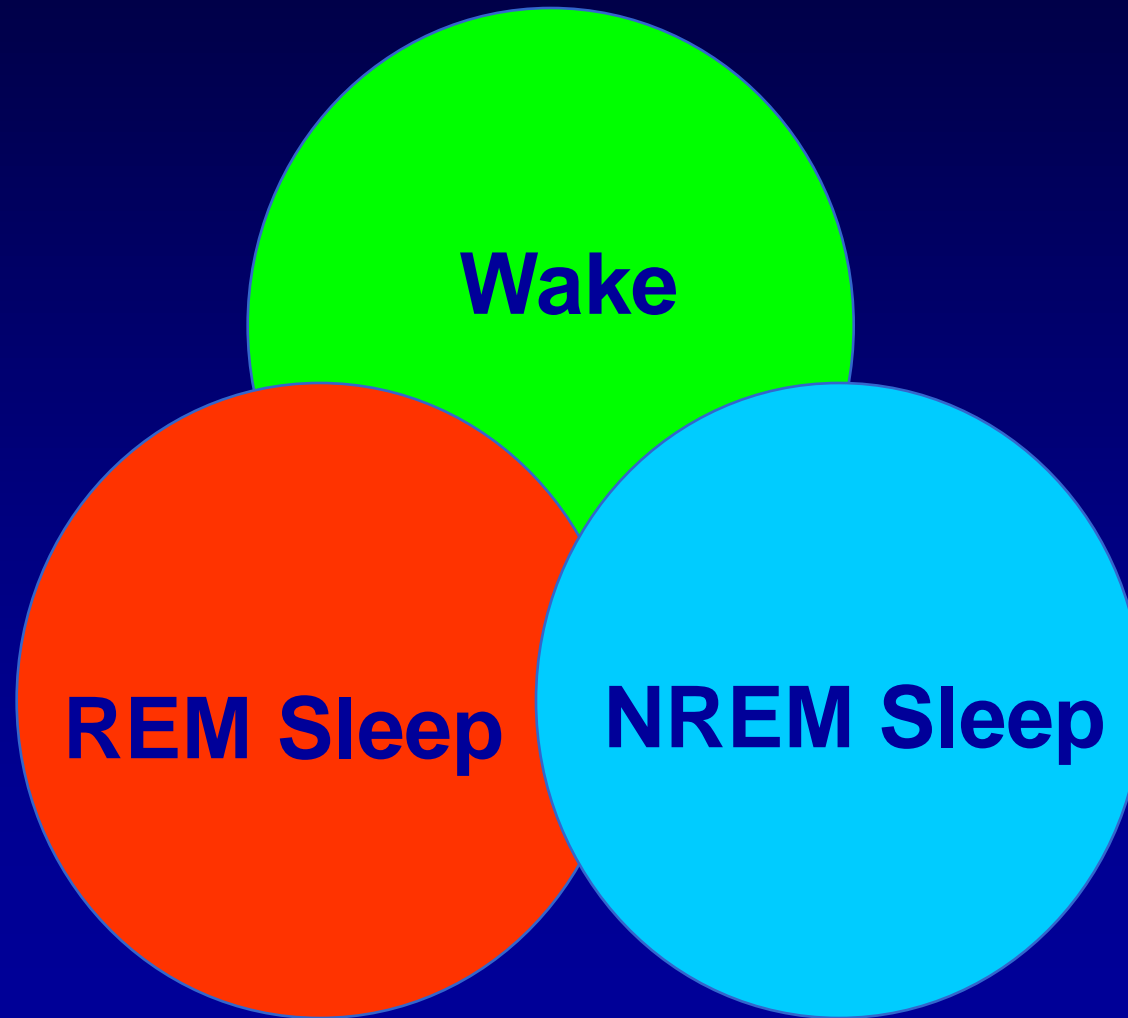
REM sleep: low voltage – random, fast with sawtooth waves

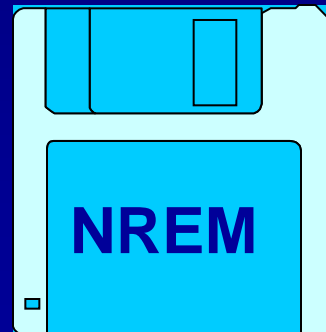
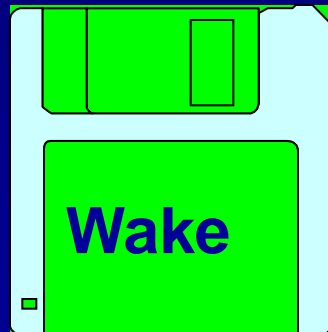
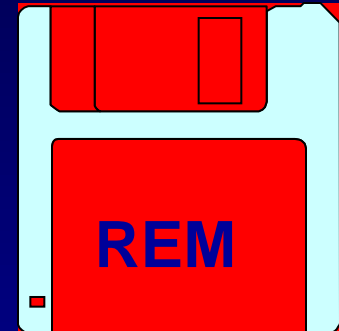
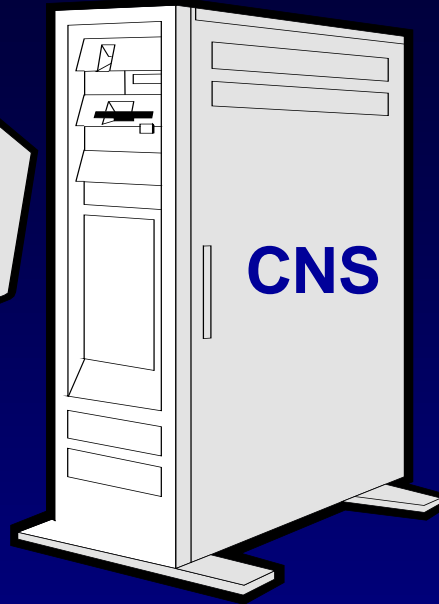
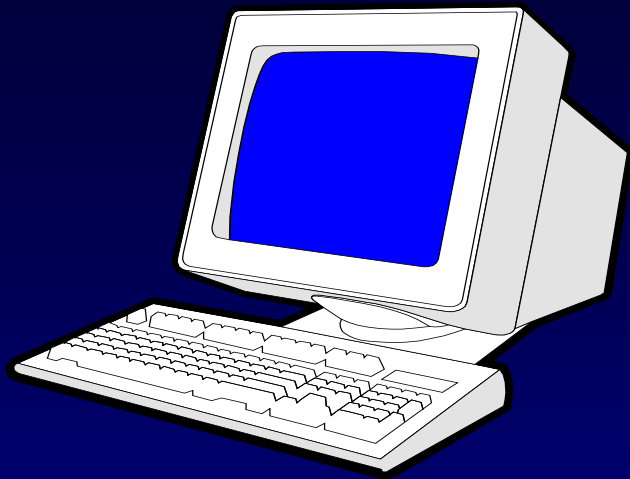


SEQUENCES OF STATES AND STAGES OF SLEEP ON A TYPICAL NIGHT



States of Being



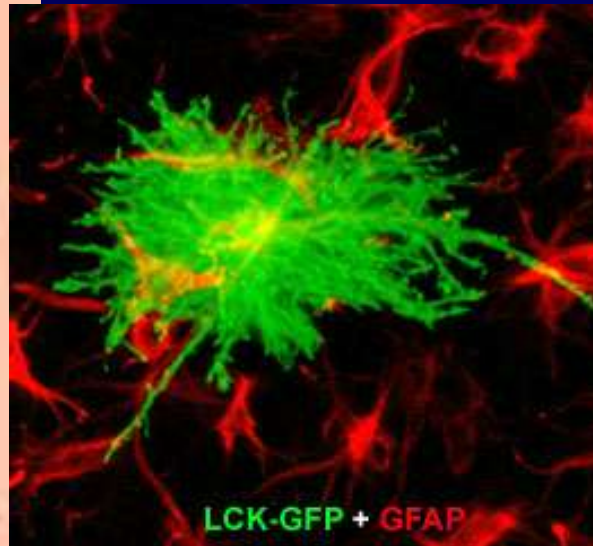


Downside of wakefulness to CNS

- Wakefulness = interacting & acquiring data from environment:
- Waking plasticity costs:
 - Energy (O_2 consumption increases)
 - Space requirements (fills up our RAM?)
 - Saturates our capacity to learn;
- Total sleep deprivation is fatal



Function of sleep: glimmer of light?



Synapses by the bucketload

Wakefulness: interacting with environment & acquiring information

- ***How?***

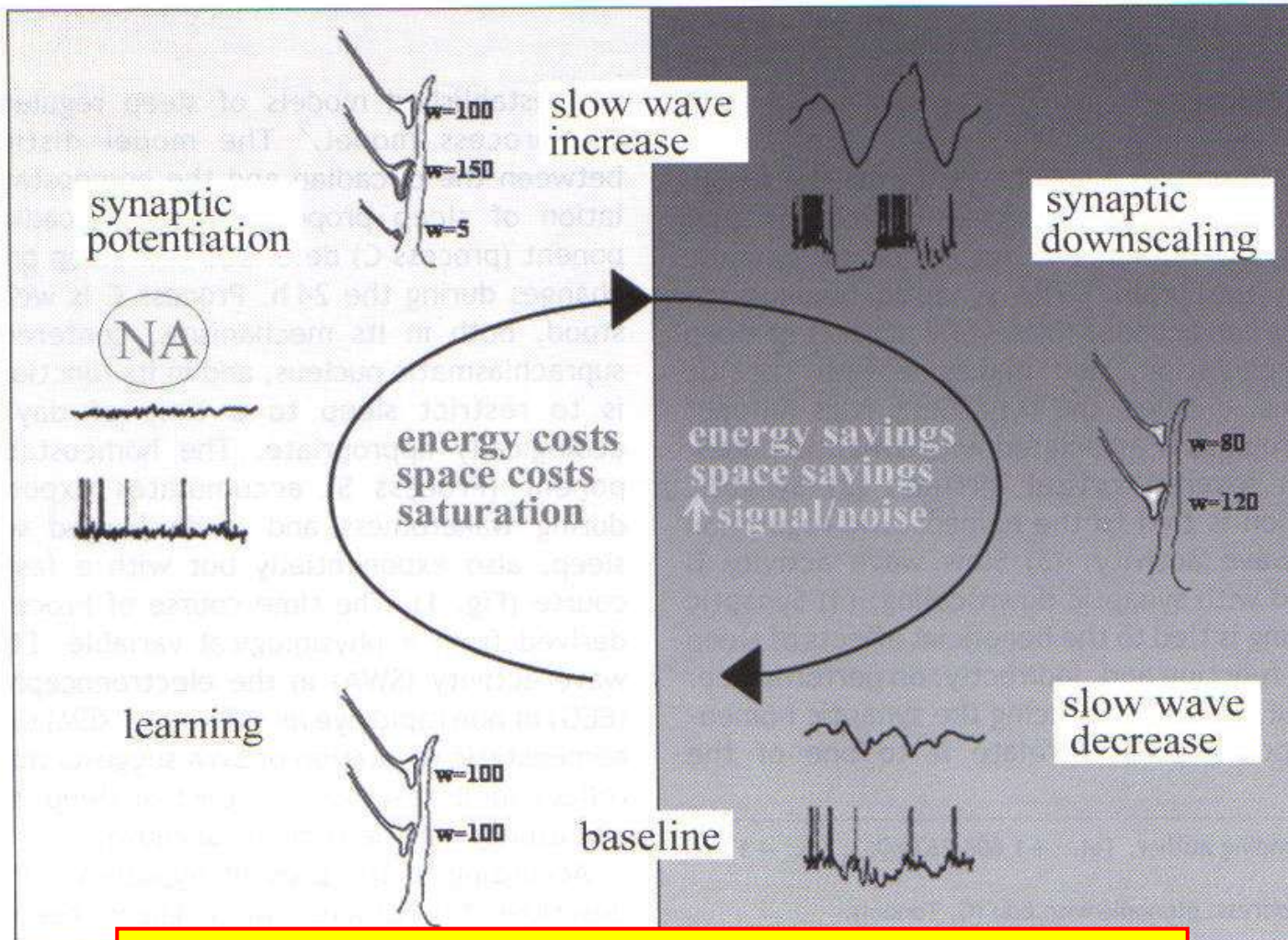
- Activated EEG
- Storage of information favoured by milieu (increased NAdr and other neurotransmitters)
- Information storage requires synaptic strength to be increased (long term potentiation).

Synaptic potentiation?

- Presynaptic neurone fires leading to either depolarization or firing of post synaptic neuron;
- The neuromodulatory milieu signals the occurrence of salient events and strengthens the synapse;
- Repeated use of a “pathway” during wakefulness progressively strengthens the synapse (this has an energy requirement).

What might be happening to the CNS?

Tononi & Cirelli, Brain Res Bull 2003; 62:143-150.

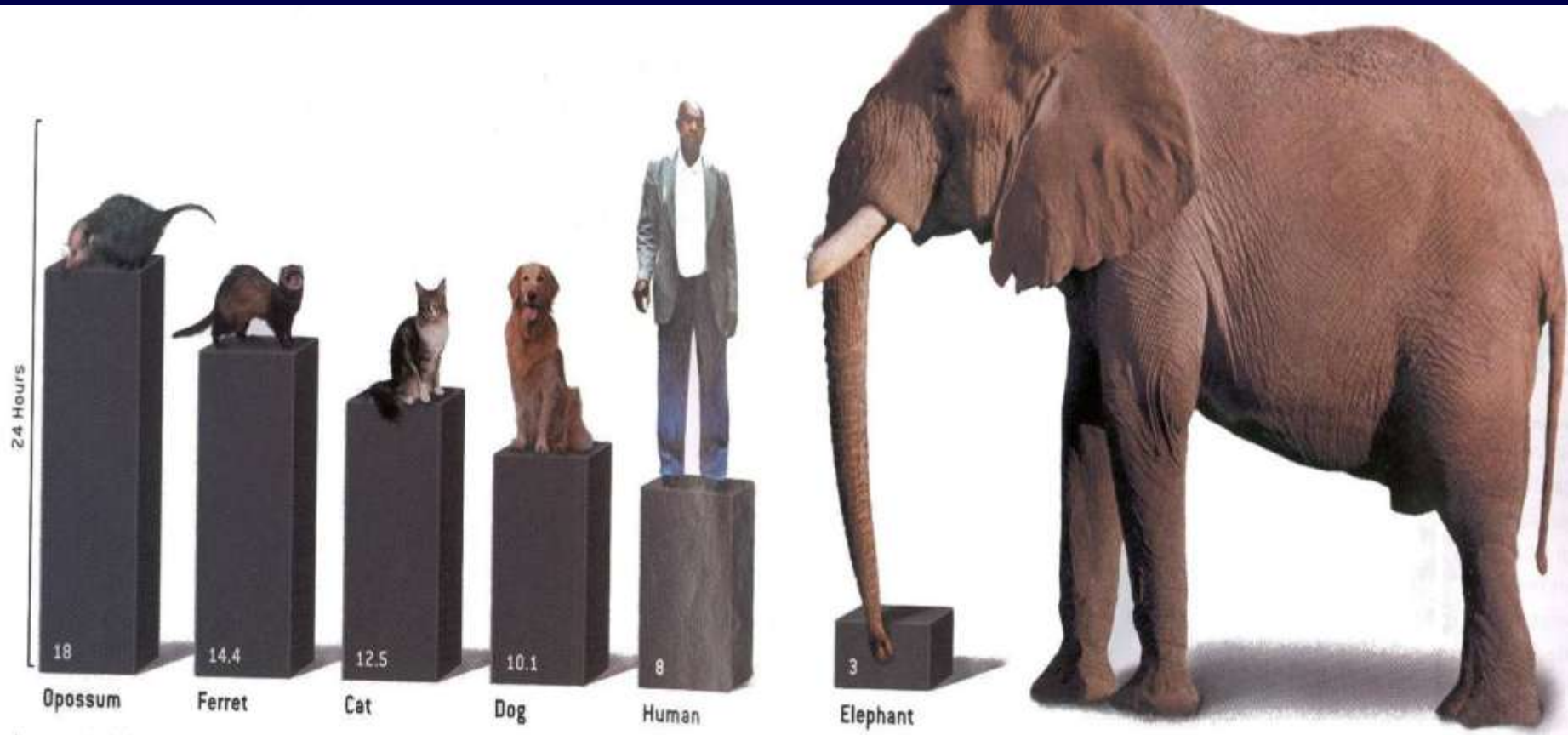


The synaptic homeostasis theory

Getting stuck in a rut: an example of synaptic potentiation?



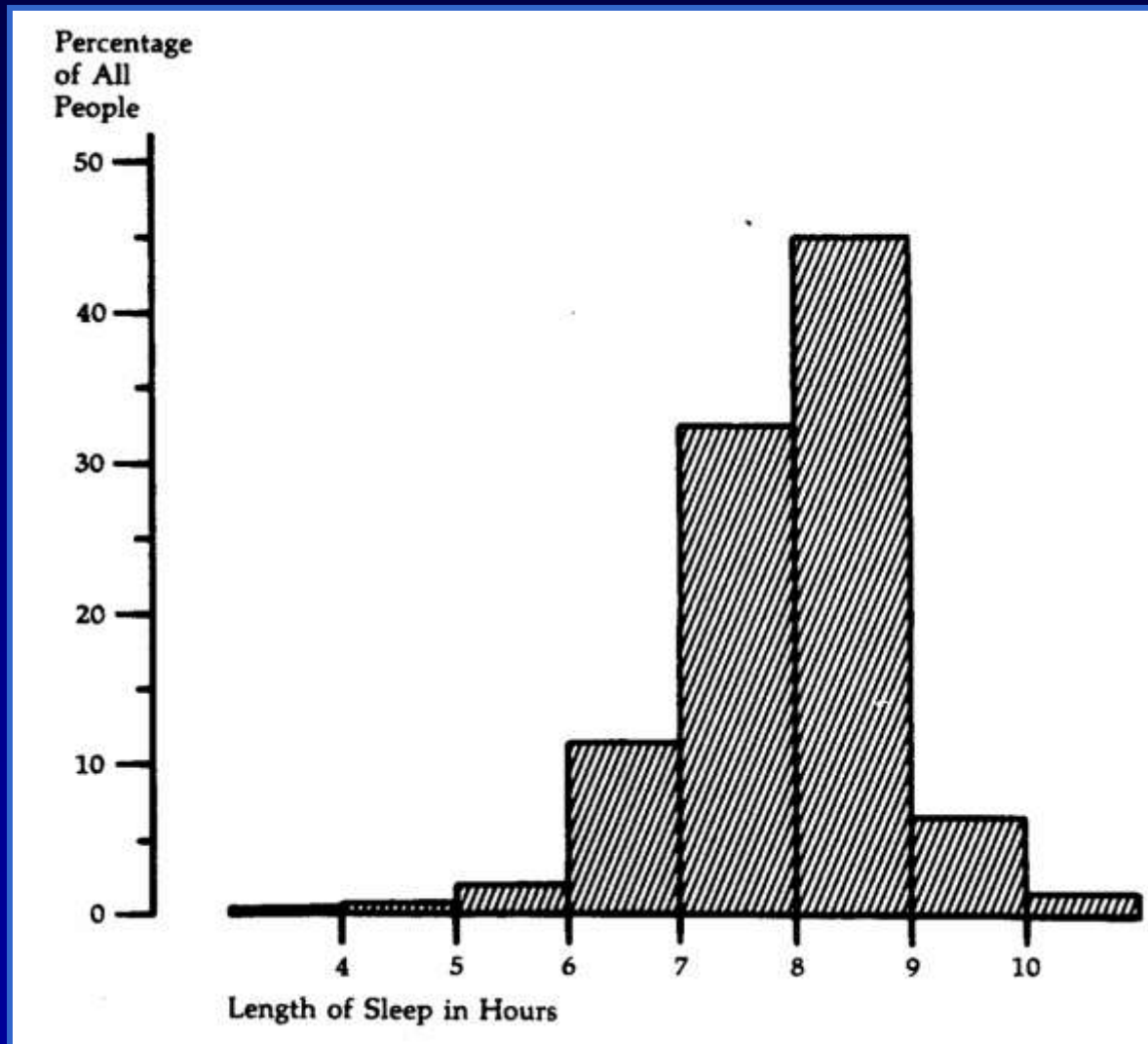
Sleep across mammalian species



Seigel 2003

Optimal duration of sleep?

How much sleep do we need?



Teenage sleep this century

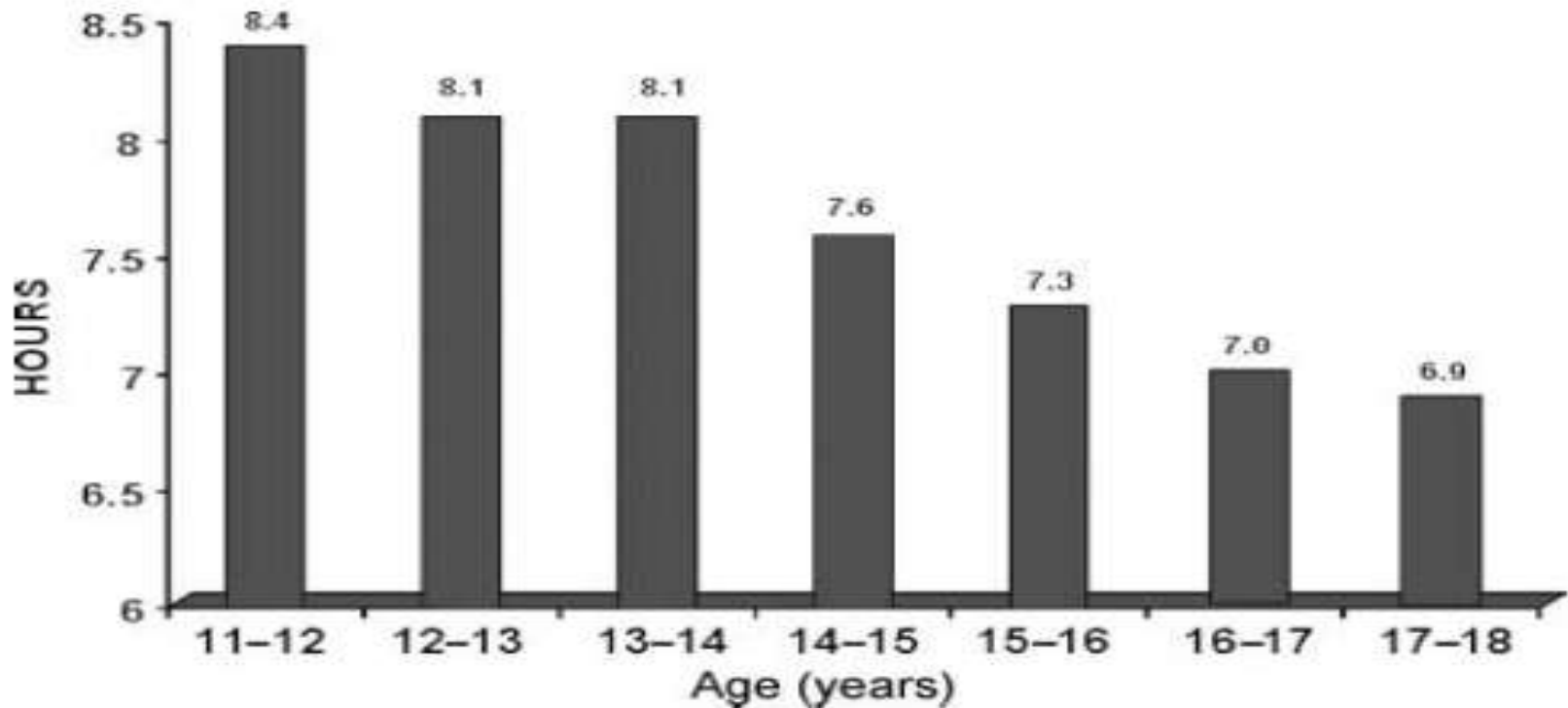


Figure 3 Self-reported sleep duration (hours) by age for the US children aged 11–18 years (14).



3

TEMPORARY INSANITY II

Effects of Sleep deprivation

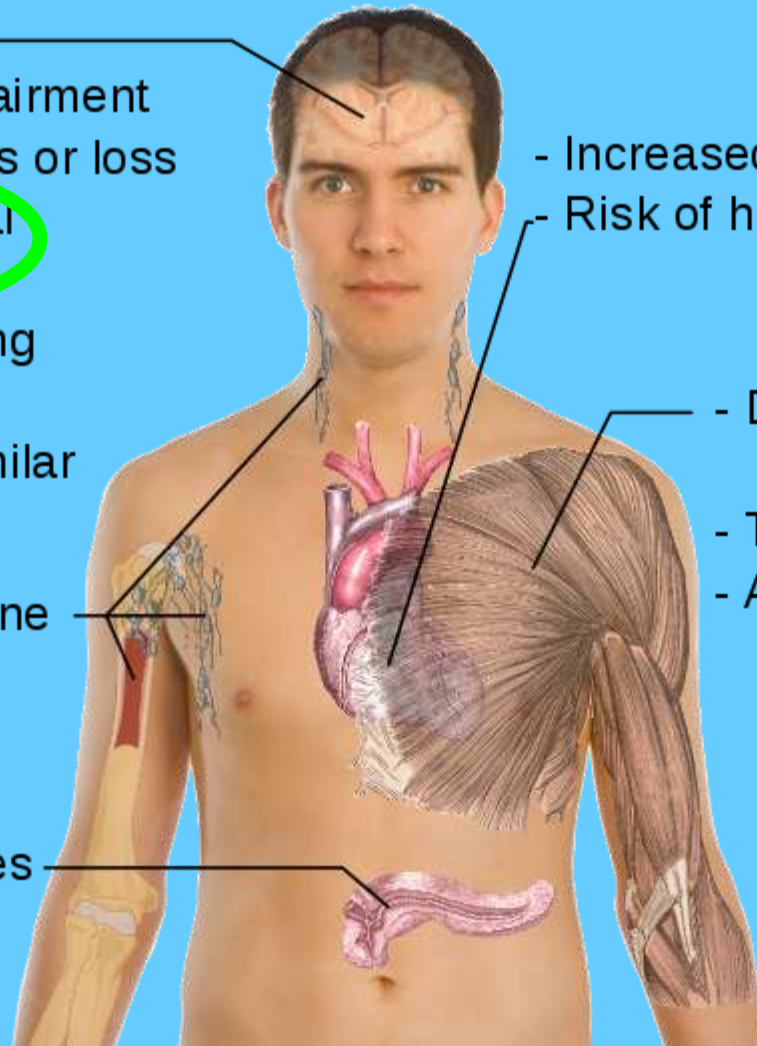
- Irritability
- Cognitive impairment
- Memory lapses or loss
- Impaired moral judgement
- Severe yawning
- Hallucinations
- Symptoms similar to ADHD
- Impaired immune system
- Risk of diabetes Type 2

- Increased heart rate variability
- Risk of heart disease

- Decreased reaction time and accuracy
- Tremors
- Aches

Other:

- Growth suppression
- Risk of obesity
- Decreased temperature



Effects of reduced sleep

- Adverse health outcomes:
 - Total mortality
 - Stroke and coronary artery disease
 - NIDDM
 - Hypertension
 - Respiratory disease
 - Obesity – children & adults
- Putative mechanisms:
 - Behavioural:
 - Increased intake
 - Reduced exercise
 - Hormonal:
 - Decreased leptin
 - Increased ghrelin
 - Altered thermoregulation

Carter et al, BMJ 2011;342:d2712 (doi:1136/bmj.d2712)

Neuroendocrine role of sleep

- Sleep modulates neuro-endocrine function & glucose metabolism
- Shortened sleep duration increases risk of obesity & weight gain.

Hormonal effects of sleep deprivation

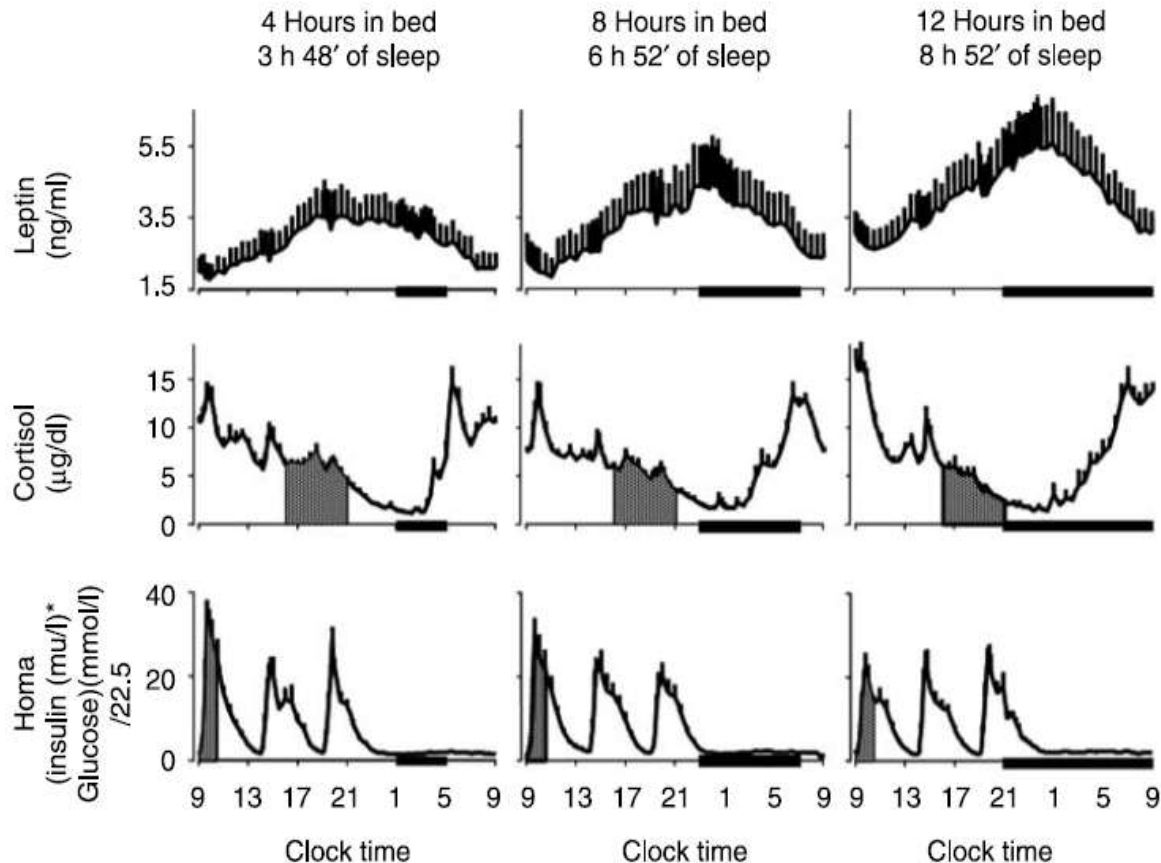
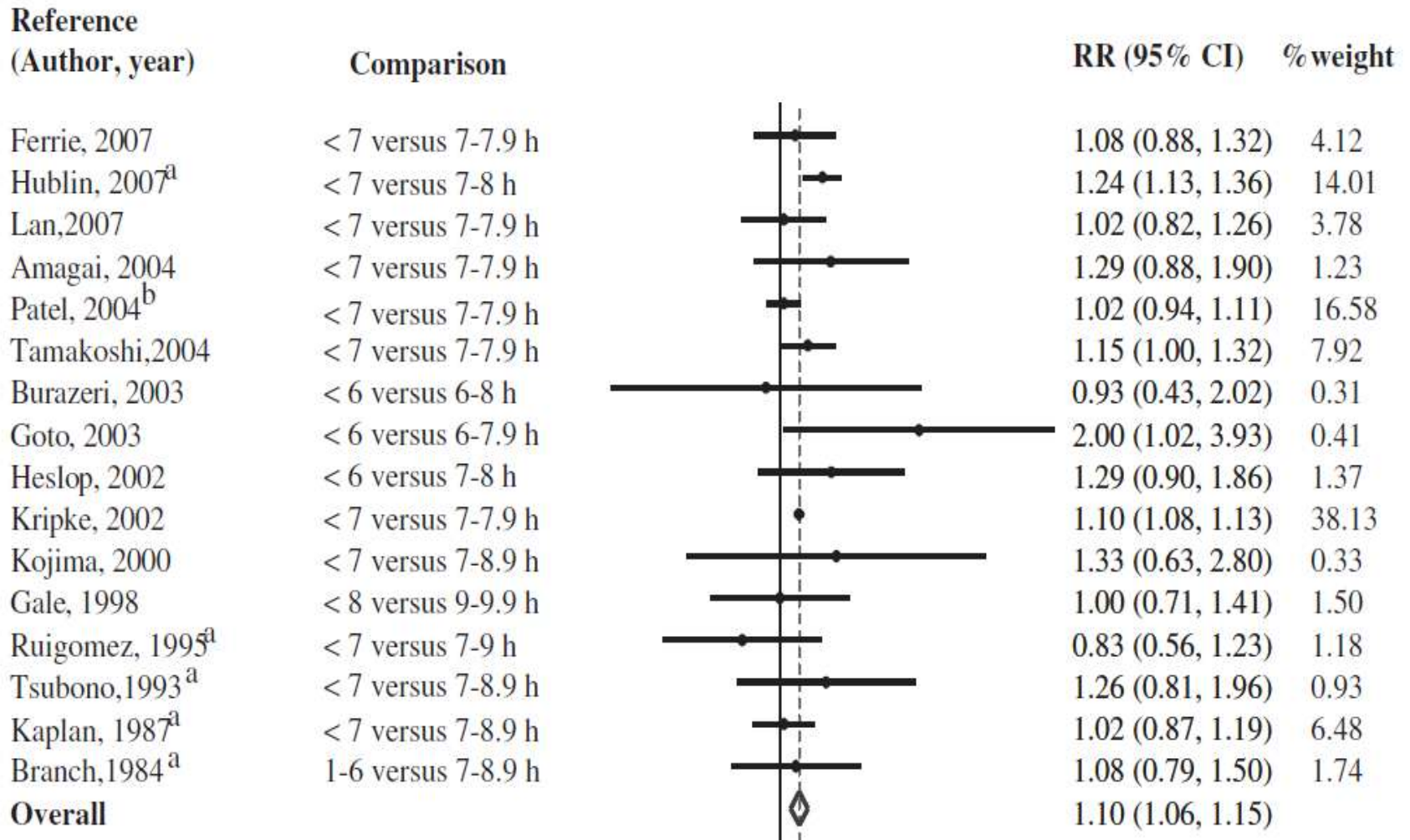


Figure 4 Mean (\pm s.e.m.) 24-h leptin, cortisol, and HOMA profiles with 4-, 8-, and 12-h bedtimes. Note that the relative synchronization of the leptin and cortisol profiles in the study with 8-h bedtimes was intermediate between that observed with 4-h bedtimes and that observed with 12-h bedtimes. Similarly, the HOMA response to breakfast gradually increased from the 12-h bedtime condition to the 4-h bedtime condition, with an intermediate response during the 8-h bedtime condition. Black bars, Sleep periods. (Copied with permission from Ref. (22)).

Neuroendocrine role of sleep

- Sleep modulates neuroendocrine function & glucose metabolism
 - Shortened sleep duration increases risk of obesity & weight gain.
- Sleep Deprivation:
 - ↓ glucose tolerance
 - ↓ insulin sensitivity
 - ↑ symp'vagal balance
 - ↓ evening [cortisol]
 - ↑ [ghrelin]
 - ↓ [leptin]
 - ↑ hunger
 - ↑ appetite

Sleep duration & mortality

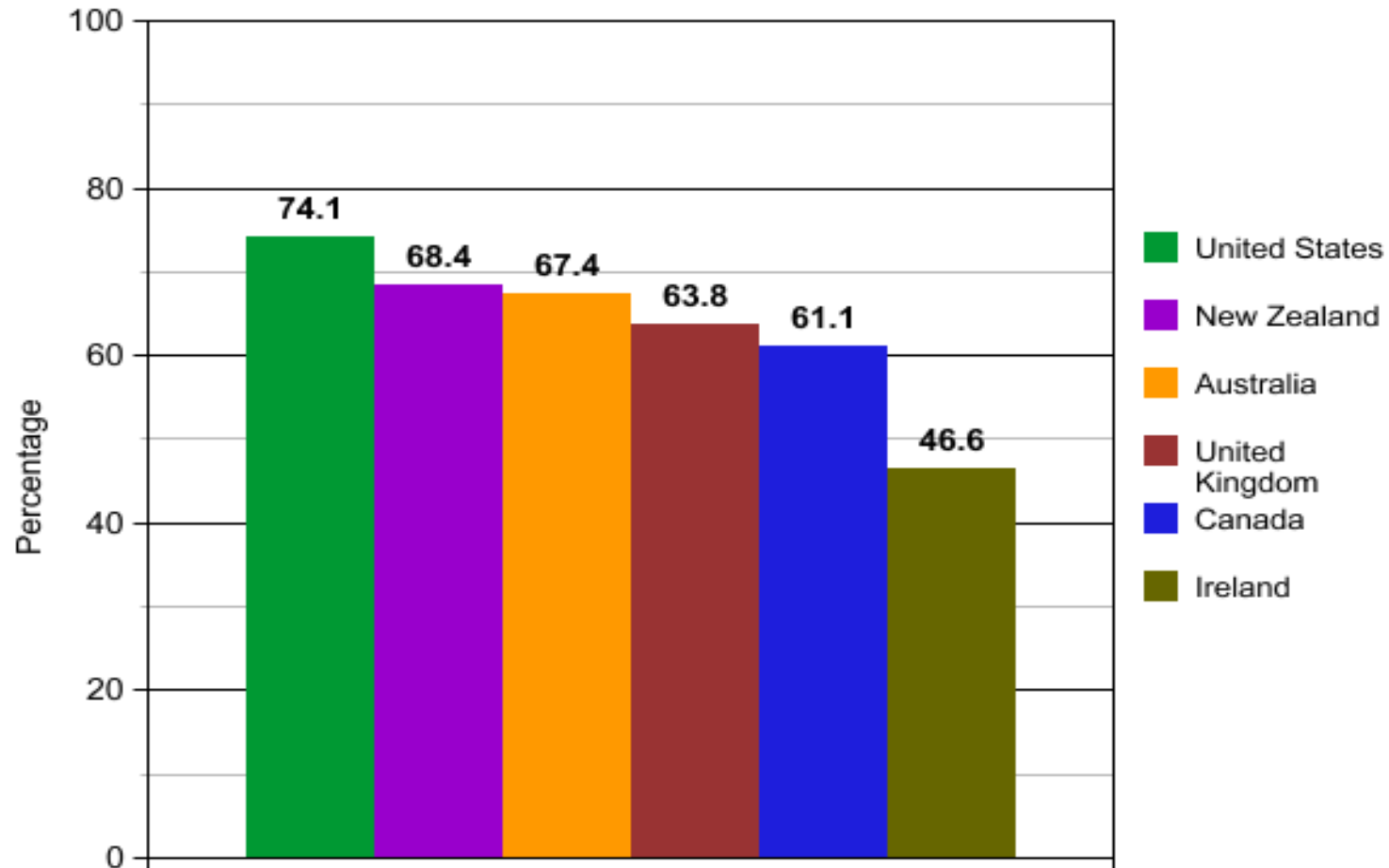


Sleep restriction: Mechanism of action?

- Glucose tolerance circadian & varies in different sleep stages
- Desensitisation of leptin receptors (PYY, GLP1 & CCK) – no satiety feedback
- Increased sympathoadrenal activity: increased cortisol, thyrotrophin & catechols – decreased insulin release
- Increased inflammatory cytokines
- Increased orexin system activity (animals) which promotes feeding.

Obesity epidemic

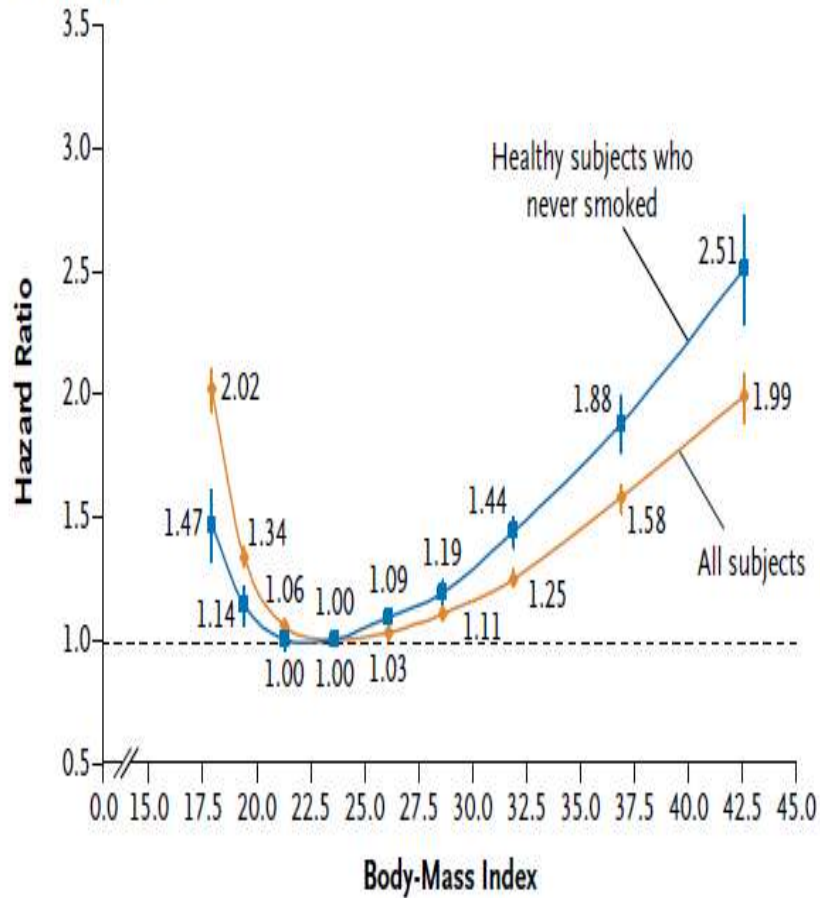
Prevalence of overweight people in the Anglosphere



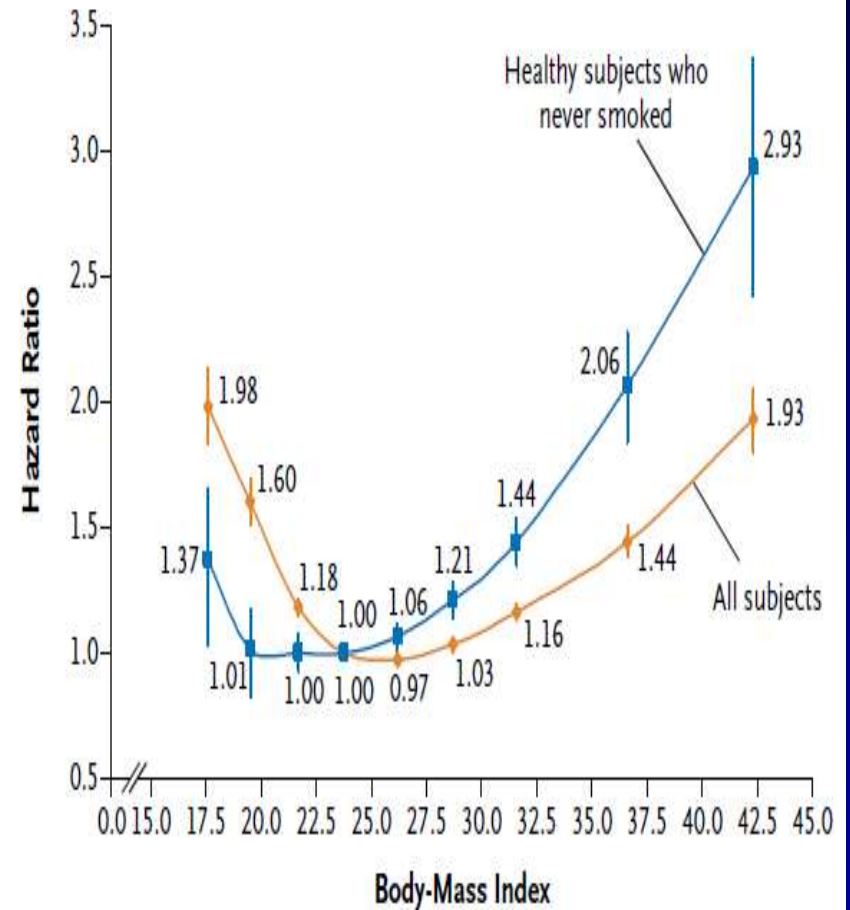
SOURCE: World Health Organization, 2007

Weight kills

A White Women

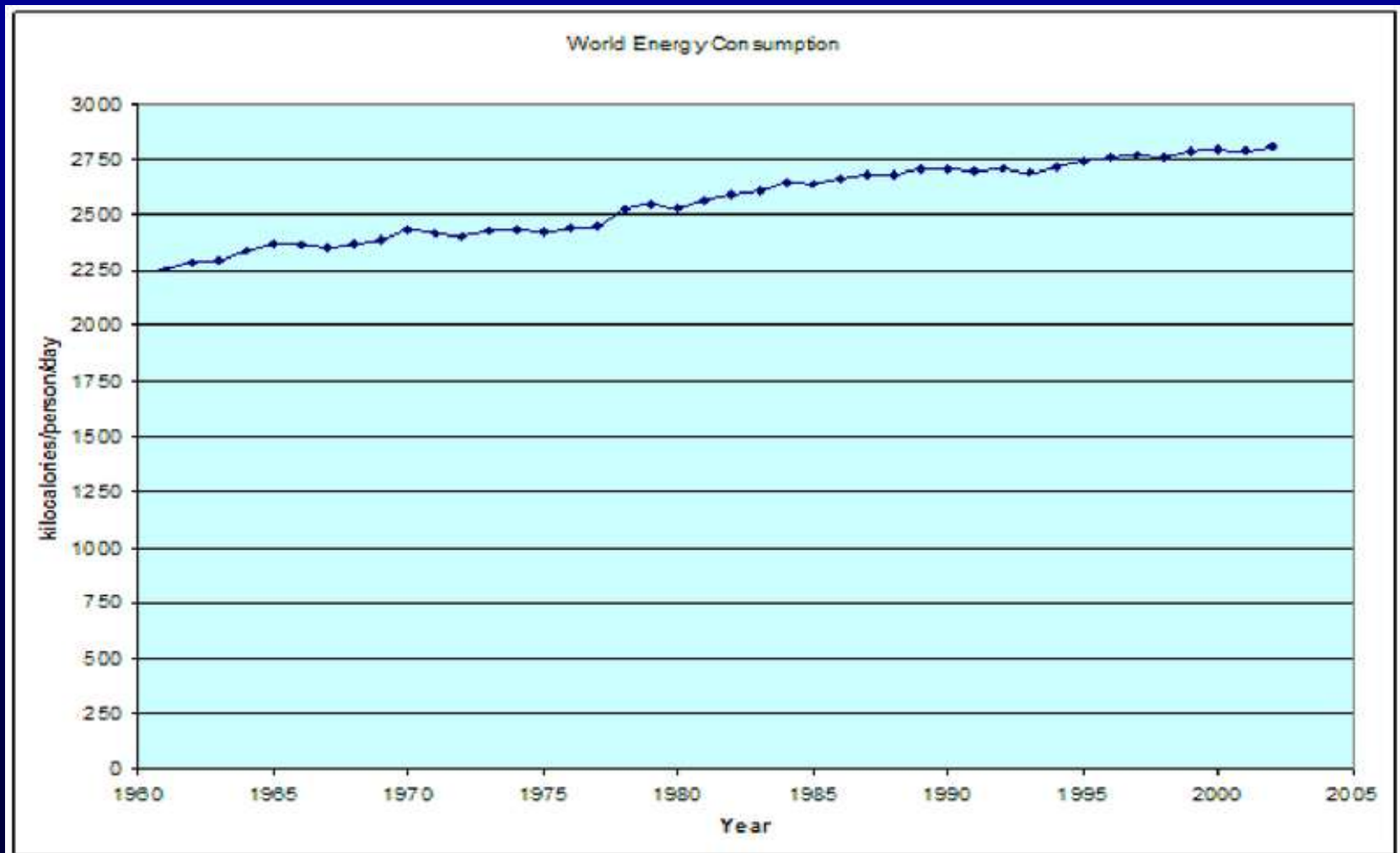


B White Men



Similar data for Afro-American women - Boggs et al NEJM 2011; 365:901

Too many calories



Why look for other explanations?

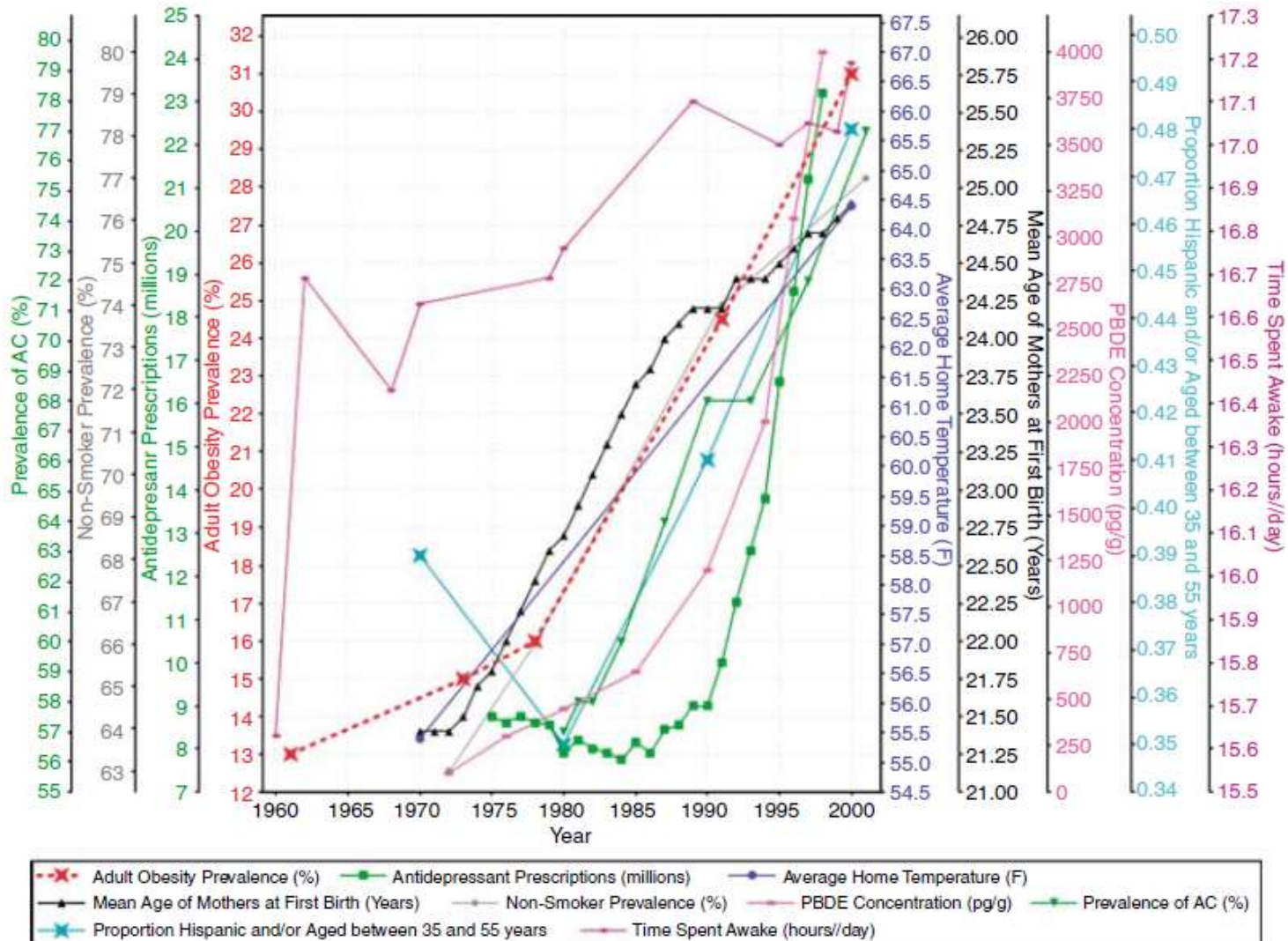


Why look for other explanations?

- ***The Big Two:***
 - Reduced physical activity
 - Altered diet via “food marketing/availability”
- **Conclusive supporting data?**
 - Surprisingly few studies demonstrate a consistent relationship
 - e.g.: Children’s obesity prevention by increasing
 - physical activity – no change in wt
 - No correlation between weight & access to
 - vending machines

Increasing obesity: Less travelled roads

(Keith et al, *Int J Obes* 2006;30:1585)



Increasing obesity: Less travelled roads

(Keith et al, Int J Obes 2006;30:1585)

- Increase in obesity in US a 100+ yr trend
Supportive, not conclusive evidence for:
 1. Use of anti-depressants (?role of other drugs)
 2. Maternal Age at time of first child & mothers age at time of individual's birth
 3. Ambient indoor winter temperature
 4. Endocrine disruptors – DBPE
 5. In US prevalence of air conditioning
 6. % of non-smokers
 7. Age of population
 8. Duration of sleep

Drugs linked with obesity

- Psychotropic medications
 - Atypical antipsychotics
 - Anti-depressants – data not conclusive SSRIs
- Anti-diabetics:
 - Insulin
 - Sulphonylureas
 - Thiazolidinediones (TZE) – promote adipocyte proliferation (newer agents)
- Anti-histamines
- Anticonvulsants
- Anti-hypertensives – β - blockers (1.2kg)
- Anti-retrovirals & antiproteases

Population studies of sleep restriction & obesity

- Impact greatest in children
- Clear impact in younger adults
- Less clearcut in middle aged and older
- At all ages abnormal leptin/ghrelin ratios

Sleep restriction metabolic effects

- Mostly mediated via effect on sympathetic nervous activity (?):
 - Decreased leptin release & decreased insulin sensitivity
 - Suppresses β cells leading to inadequate compensation for decreased insulin sensitivity

Effects of SWS on metabolism

- Decreased brain glucose consumption
- Growth hormone release from pituitary increases
- Corticotrophin release decreases
- Decreased sympathetic activity
- Increased vagal activity

SWS & glucose metabolism

- SWS only suppressed (acoustic stimuli) for 3 nights to <10% of normal SWS;
 - Insulin sensitivity decreased 25%
 - Glucose tolerance by 23%
 - *(Tasali et al, Proc Natl Acad Sci 2008;105:1044)*
- Reduced SWS in OSA and NIDDM

Leptin resistance

- Obese individuals have high rather than low leptin despite ample energy stores
- Increased [CRP] in obesity & leptin binds to CRP
- Total and partial sleep deprivation increase [CRP]

Diabetes and sleep

- Diabetics report more sleepiness
- Diabetics sleep less than controls
- Diabetics have poorer sleep quality

Obese individuals also have more sleepiness, arousals, poorer sleep quality and less refreshing sleep

OSA & NIDDM – Cause or association?

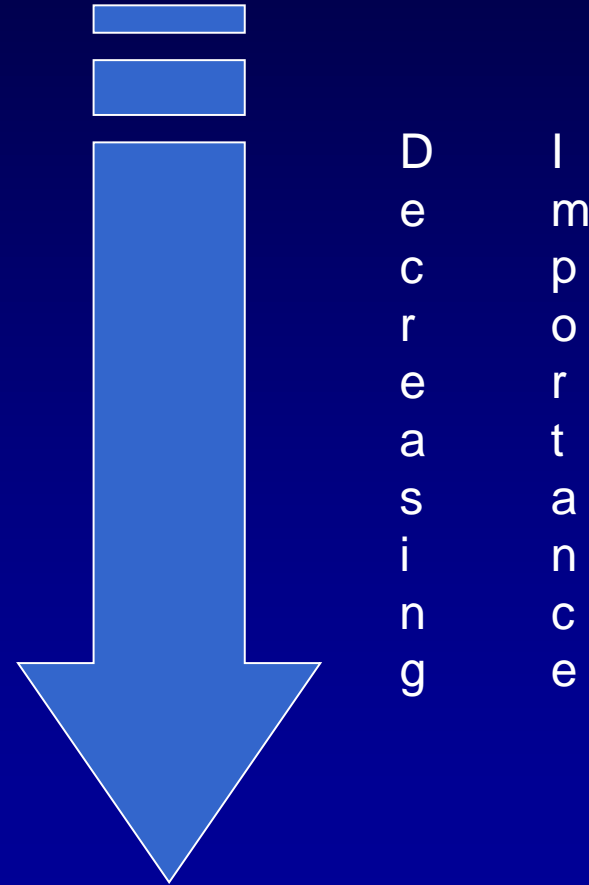
- Screen of NIDDM population for AHI >5/hr
 - 84% had OSA by this definition but not SAHS syndrome
 - *(Sleep AHEAD – Foster et al, Diabetes Care 2009;32:1017)*
- Dose dependent effect on HbA₁C:
 - 77% of diabetics had OSA
 - Mild OSA 1.49% increase (p<0.003)
 - Moderate OSA 1.93% increase (p<0.0033)
 - Severe OSA 3.69% increase (p<0.0001)
 - *(Aronhson et al AJRCCM 2010;181:507)*

OSA & NIDDM – Cause or association?

- Multiple studies (+)ve 10/12 to date
- Association proven
- Causality remains unproven though clearly intertwined and probably not just “a passenger in the same car”
- CPAP improves markers of glucose control but no evidence it “treats” diabetes

Associations of EDS in general population

- Depression
- BMI (independent)
- Age
- Sleep duration
- Diabetes
- OSA



Ockham's Razor blunted?: Sleep, obesity & sleepiness

- *Plurality should not be assumed unnecessarily*

William of Ockham

Quodlibeta (c.1324) No 5,
Question 1, Art 2





DELTA

Delta
Air Lines



Silly & Sad facts about Obesity

- Direct costs of obesity in Australia in 2005 were AUD\$21 billion;
- Overweight/obese Australians receive AUD\$36.5 billion in subsidies
- There is an extremely strong correlation between the weight of the 7.6% of Australian obese dogs & their owners weight (does not apply to cats!).

Never as simple as it seems?



The Message: Sleep long & stay thin

Questions please?



High REM Sleep

≥ 3 hours of REM sleep/day

Platypus

Ornithorhynchus anatinus



8 REM, 14 Total

Thick-tailed Opossum

Lutreolina crassicaudata



6.6 REM, 18 Total

Ferret

Mustela nigripes



6 REM, 14.5 Total

Big Brown Bat

Eptesicus fuscus



3.9 REM, 19.7 Total

European Hedgehog

Erinaceus europaeus



3.5 REM, 10.1 Total

Armadillo

Dasyurus novemcinctus



3 REM, 17 Total

Human

Homo sapiens



2 REM, 8 Total

Low REM Sleep

≤ 1 hour of REM sleep/day

Guinea Pig

Cavia porcellus



1 REM, 9.5 Total

Sheep

Ovis aries



0.6 REM, 5.9 Total

Giraffe

Giraffa camelopardalis



0.5 REM, 4.5 Total

Guinea Baboon

Papio papio



1 REM, 9.5 Total

Horse

Equus caballus



0.5 REM, 3 Total

Bottlenose Dolphin

Tursiops truncatus



<0.2 REM, 10 Total

Consequences of too little sleep

- Increased total mortality
- Increased risk of CVA & CHD
- Increased risk of NIDDM
- Increased risk of hypertension
- Increased risk of respiratory disorders
- Increased risk of obesity
- Increased risk of self rating health poor

Sustainable hypothesis?

- It would neatly explain the loss of cognitive function in sleep deprivation, insomnia and non-refreshing sleep.
- *(and rigidity of thought with age*
- *– no detectable SWS in 50% males >60yrs!)*