Sleep, Inflammation, & Metabolism: Sleep-Worthy Connections!

Aric A. Prather, PhD
Department of Psychiatry
University of California, San Francisco

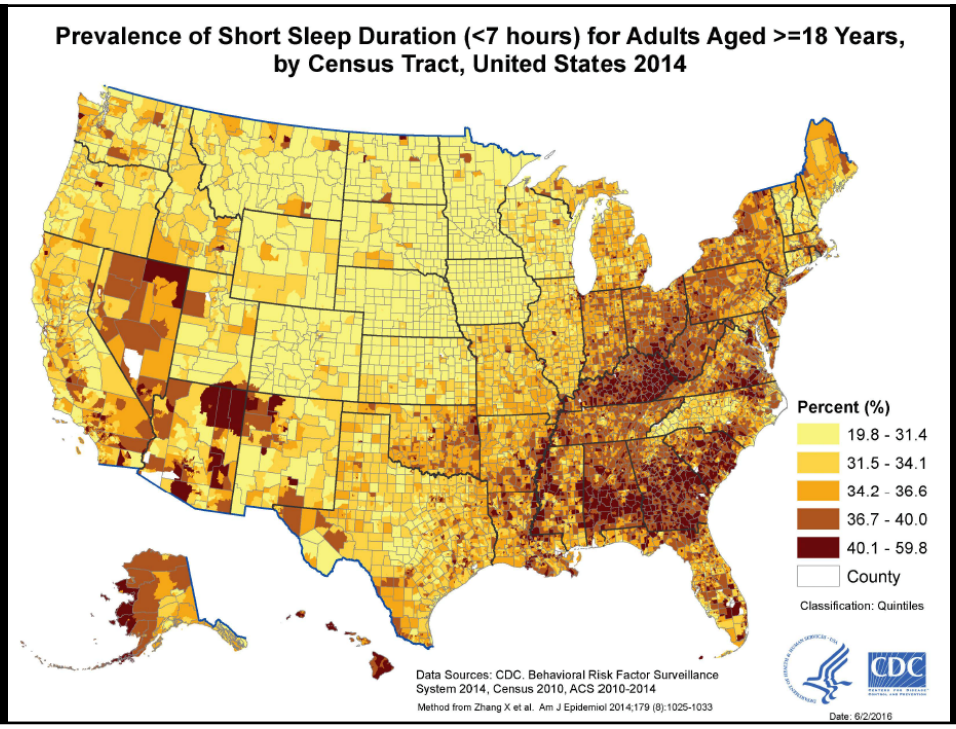
Follow me on : @AricPrather

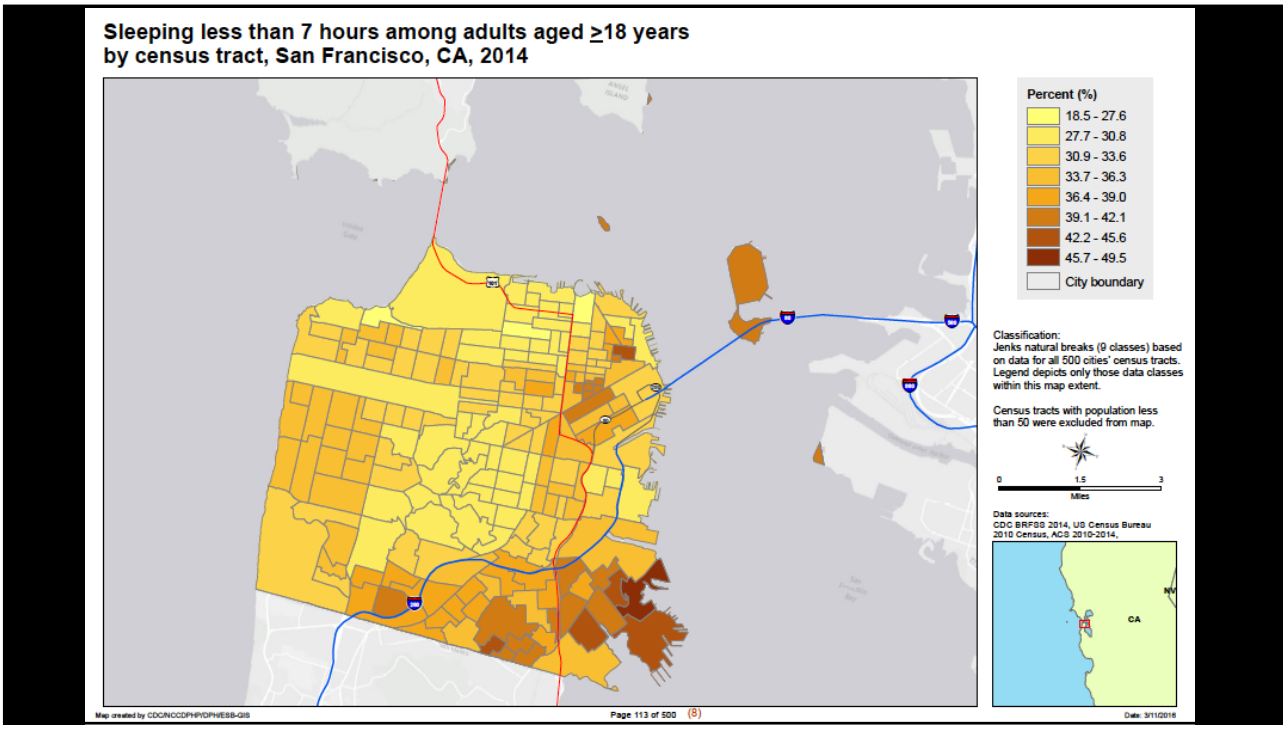
Outline:

1. Laying the foundation:
   - What is sleep and how is it measured?
2. Sleep and metabolism: sleep less, weigh more?
3. Sleep and inflammatory functioning: a central pathway to disease?
4. Rest and recovery: sleep interventions to improve metabolic health?
5. Your questions and my "answers"

Sleep: Who Does It?

If you live to 75, approximately 219,000 hours will be spent asleep.



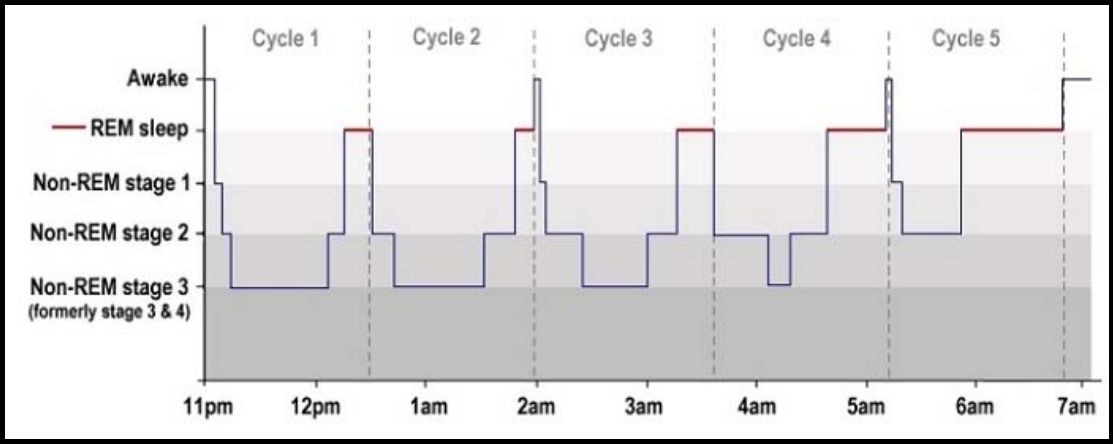


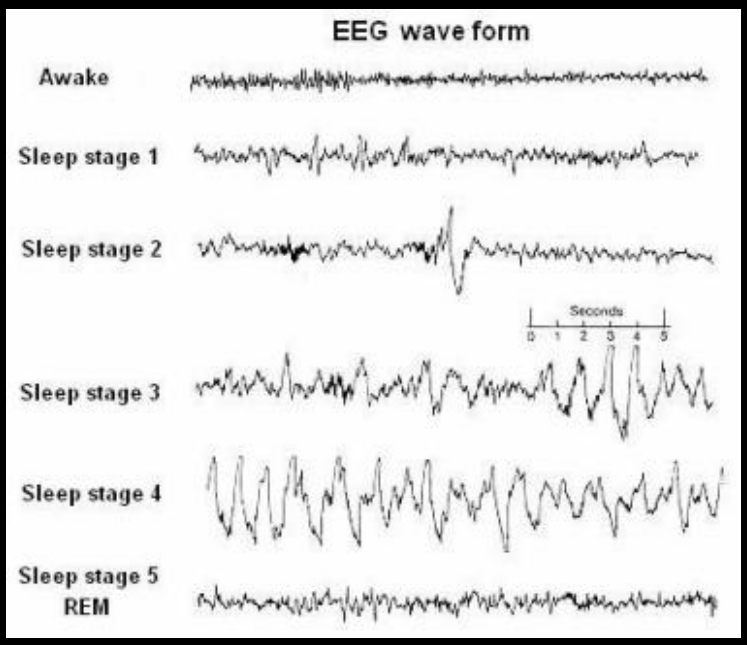
What is sleep?

A useful definition:

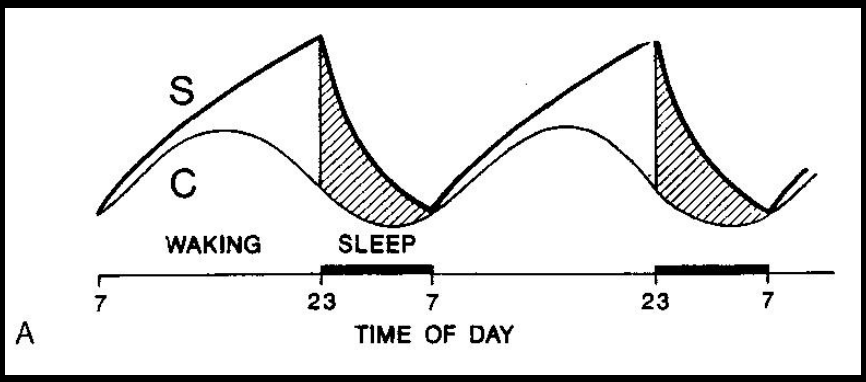
Sleep is a naturally recurring state of mind and body, characterized by altered consciousness, relatively inhibited sensory activity, inhibition of nearly all voluntary muscles, and reduced interactions with surroundings.

Prototypical Hypnogram



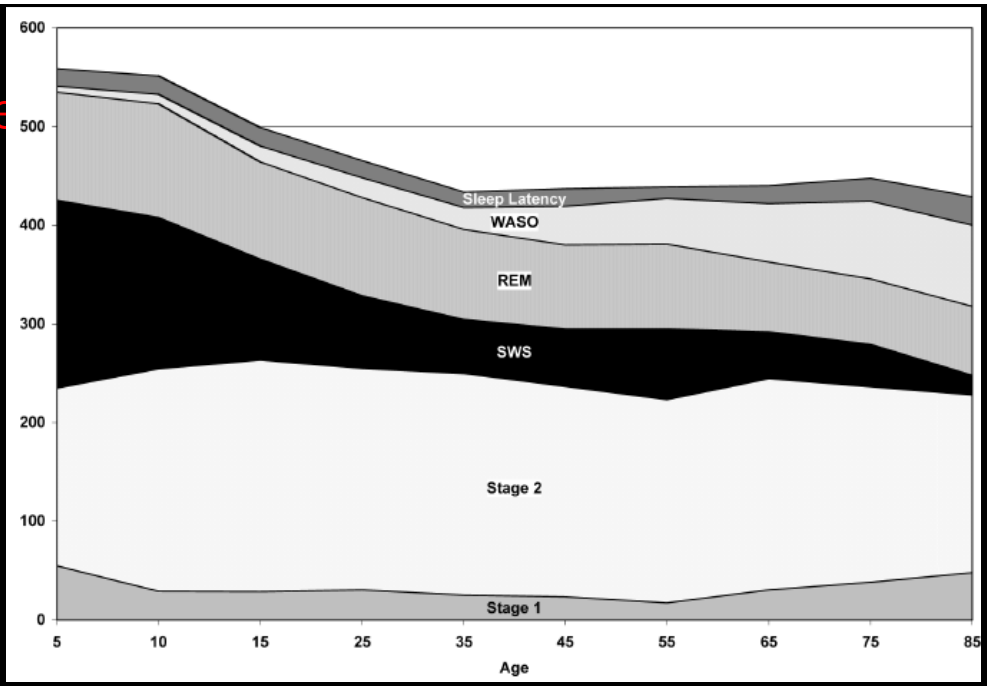


How is sleep regulated: two process model

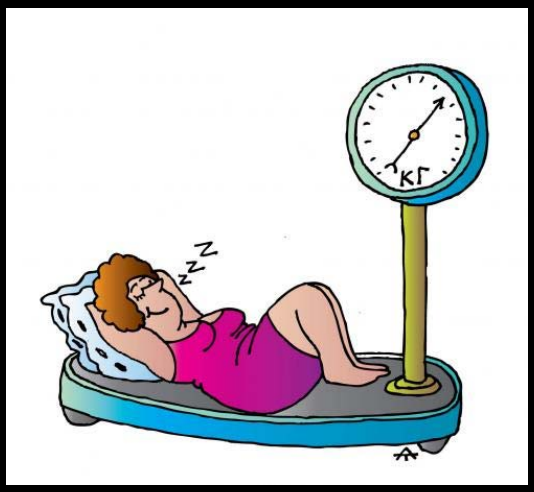


S= Homeostatic Sleep Drive; C= Circadian rhythm

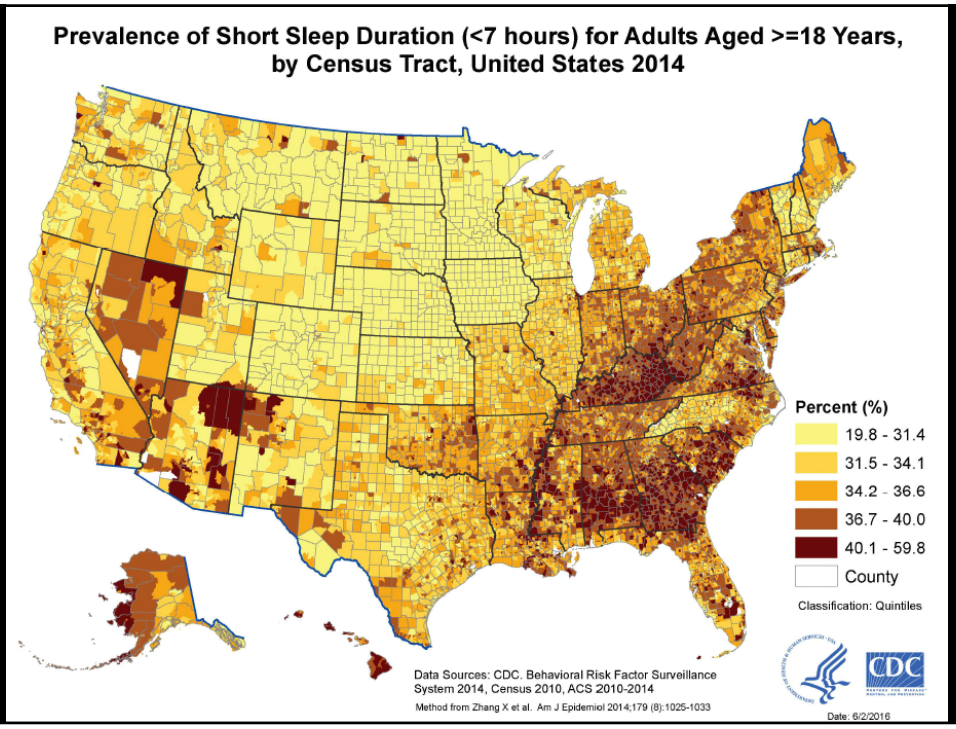
Sle



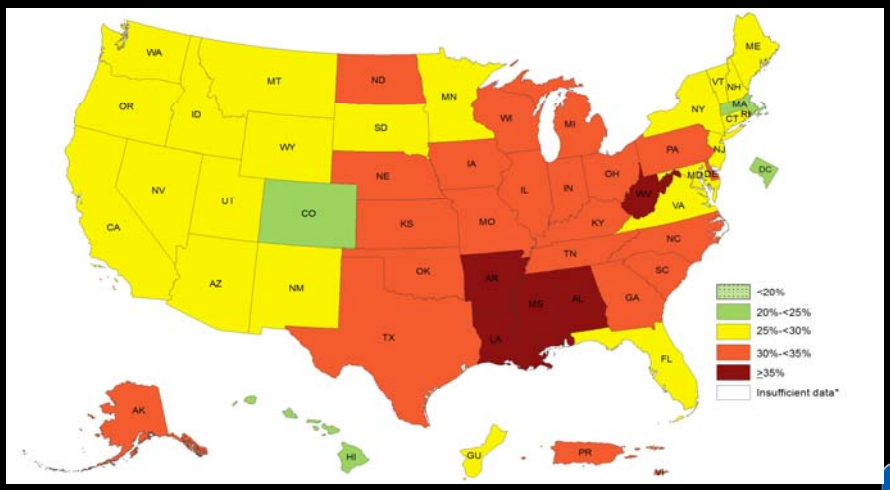
Ohayon et al. , 2004




SLEEP


Prevalence of Short Sleep Duration (<7 hours) for Adults Aged >=18 Years, by Census Tract, United States 2014
Percent (%)
19.8 - 31.4
31.5 - 34.1
34.2 - 36.6
36.7 - 40.0
40.1 - 59.8
County
Classification: Quintiles
Data Sources: CDC. Behavioral Risk Factor Surveillance System 2014, Census 2010, ACS 2010-2014
Method from Zhang X et al. Am J Epidemiol 2014;179 (8):1025-1033
CDC
Date: 6/2/2016

Prevalence of Self-Reported Obesity Among U.S. Adults by State and Territory, BRFSS, 2016



*Sample size <50 or the relative standard error (dividing the standard error by the prevalence) ≥ 30%.

Sleep and obesity: epidemiologic evidence

Contents lists available at ScienceDirect

Sleep Medicine

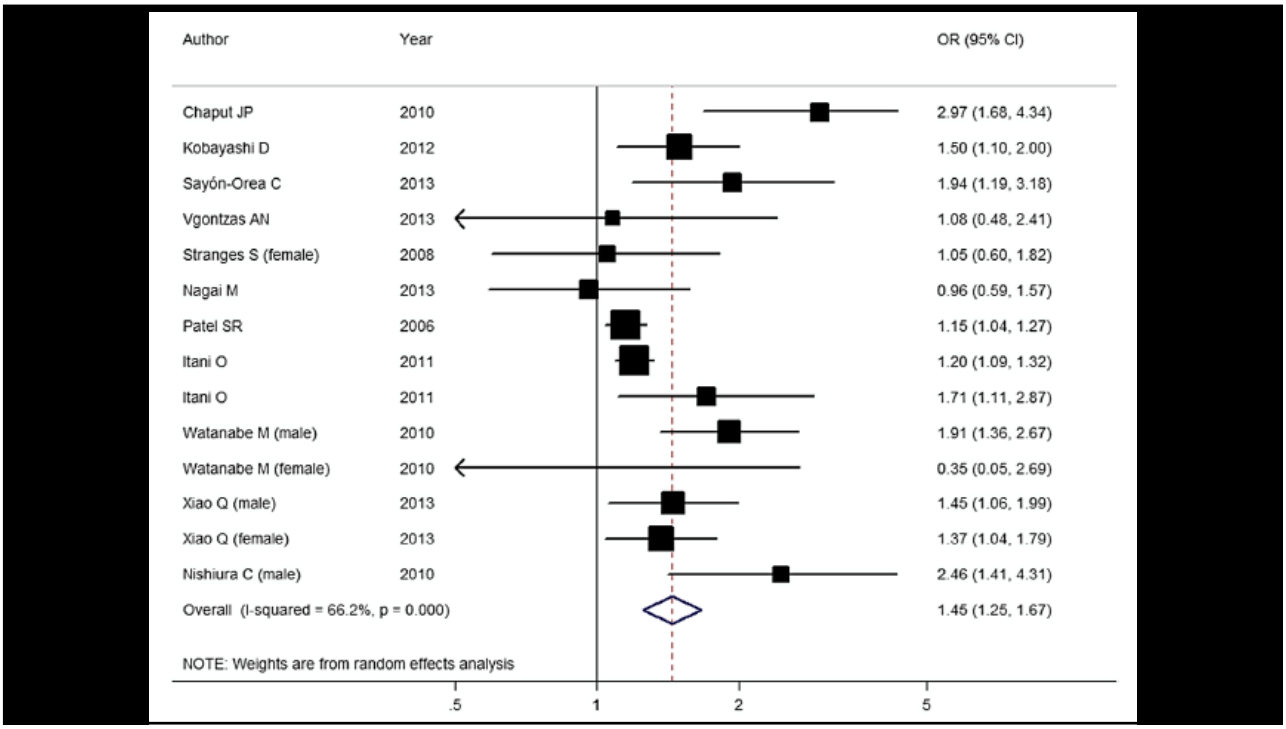
journal homepage: www.elsevier.com/locate/sleep

Original Article

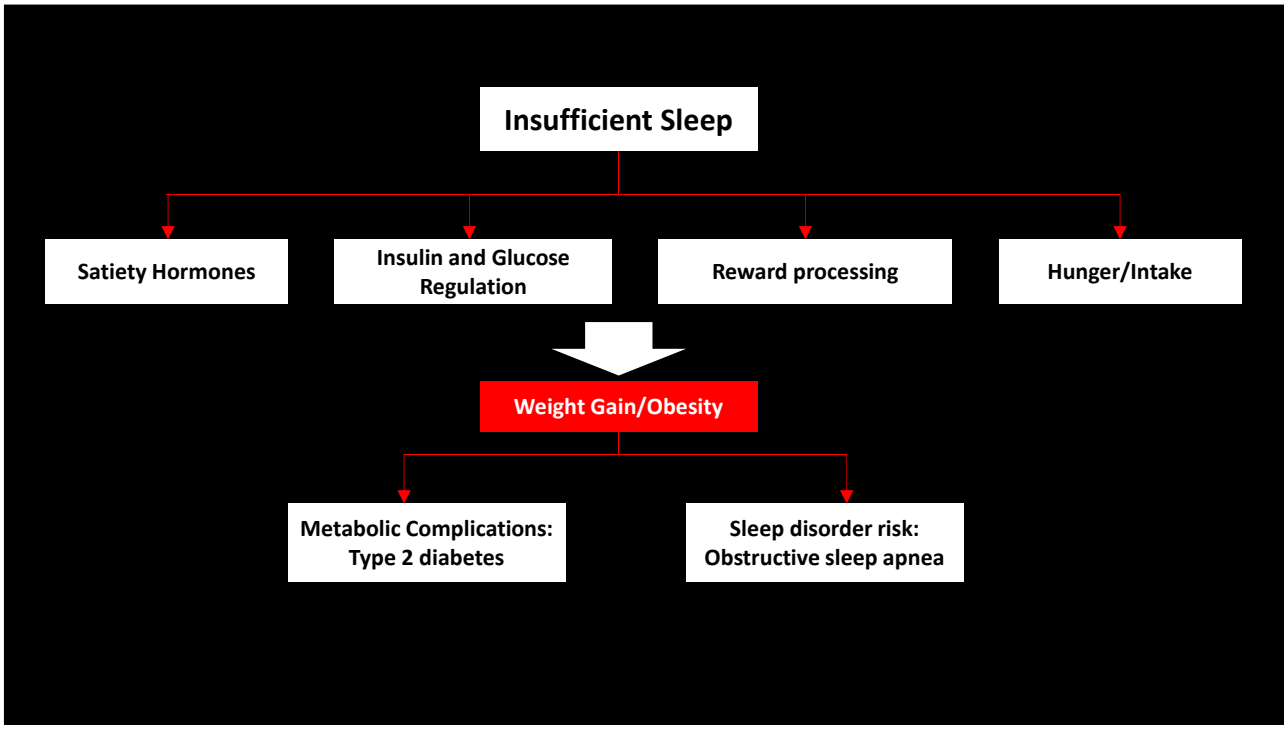
Sleep duration and obesity among adults: a meta-analysis of prospective studies

Yili Wu *, Long Zhai, Dongfeng Zhang

Department of Epidemiology and Health Statistics, Qingdao University Medical College, Qingdao, China



How could sleep affect weight?



What regulates hunger?

- Hypothalamus- makes the distinction if the body is rich or poor in energy.
- Full:
  - High glucose→ insulin binds hypothalamus
  - High fat (lipid)→ leptin bind hypothalamus
    - Leptin is released from fat cells (adipocytes)
- Hungry:
  - Stomach releases ghrelin that binds hypothalamus

How do we test whether sleep affects these things?

Sleep deprivation: total sleep deprivation or partial deprivation (e.g., reducing from 8 hours to 4 hours).

Sleep and satiety hormones

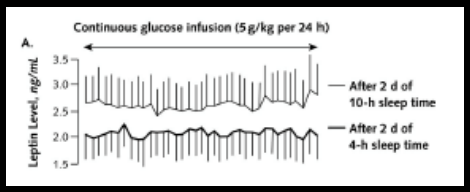
Sleep and satiety hormones

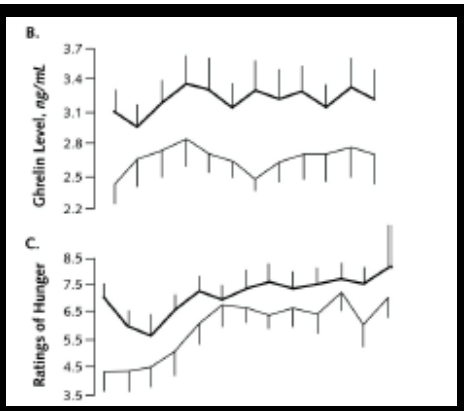
- Experimental sleep loss results in reduction in leptin levels
  - Consistent in well-controlled trials, particularly when it comes to rhythm amplitude of the 24-hours.
- Increases in ghrelin
- Concomitant increases in subjective hunger.

Brief Communication: Sleep Curtailment in Healthy Young Men Is Associated with Decreased Leptin Levels, Elevated Ghrelin Levels, and Increased Hunger and Appetite

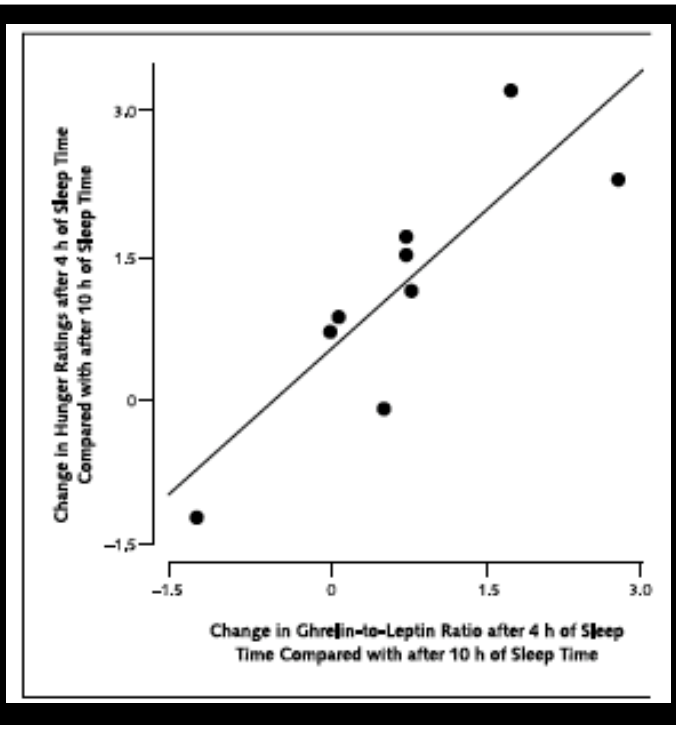
Karine Spiegel, PhD; Esra Tasali, MD; Plamen Penev, MD, PhD; and Eve Van Cauter, PhD

12 healthy men, BMI=23
Cross over design
2 nights of 10 hr; 2 nights of 4 hrs





Spiegel et al., *Annals of Internal Med,* 2004



Spiegel et al., 2004

Sleep and satiety hormones

- Experimental sleep loss results in reduction in leptin levels
  - Consistent in well-controlled trials, particularly when it comes to rhythm amplitude of the 24-hours.
- Increases in ghrelin
- Concomitant increases in subjective hunger.
- Of note, findings across studies have been mixed (possibly due to heterogeneity in samples, sampling times, and control of dietary intake)

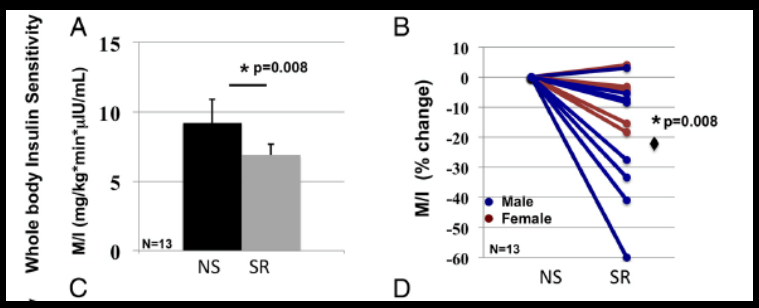
Sleep and insulin sensitivity/glucose metabolism

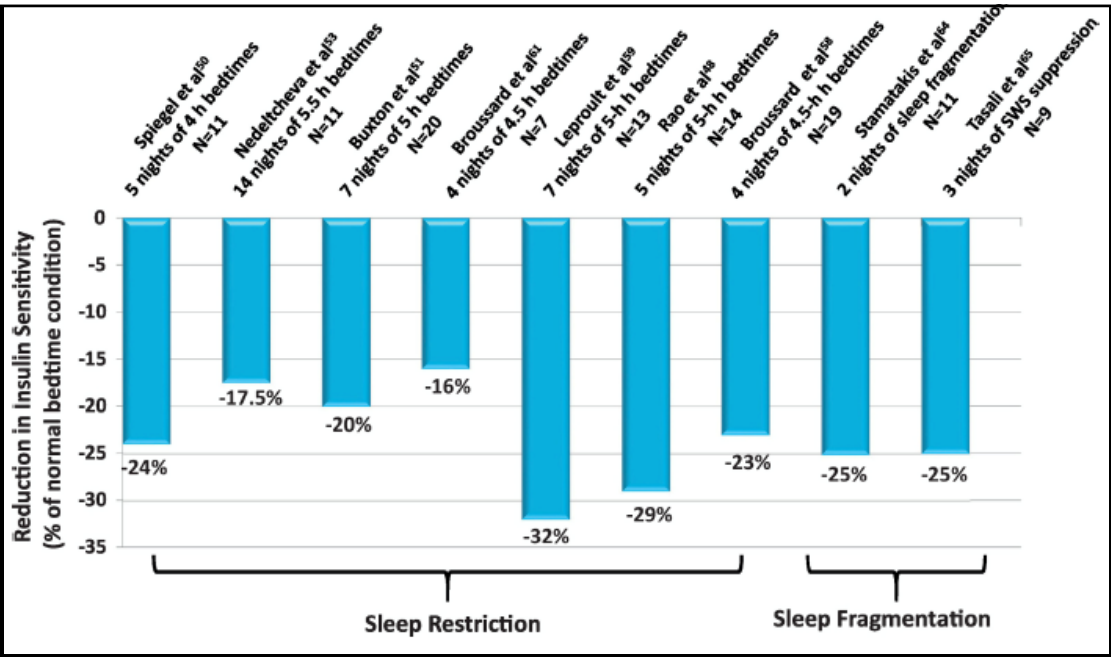
- Fairly consistent evidence that acute and prolonged sleep loss results in impaired glucose tolerance and decreased insulin sensitivity under both intravenous and oral glucose tolerance testing

Reutrakul & Van Cauter, *Metabolism,* in press

Sleep and insulin sensitivity

- Rao et al., 2015 (13 healthy participants; randomized cross over design)
- 5 nights of 4 hours in bed vs. 5 nights of 8 hours in bed.
- Hyperinsulinemic-euglycemic clamp





Reutrakul & Van Cauter, *Metabolism,* in press

Role of slow wave sleep?

- Fragmentation studies (suppressing slow wave sleep specifically)
- Tasali et al., 2008 (3-nights of SWS suppression)
  - 25% reduction in insulin sensitivity
  - 23% reduction in glucose tolerance (via IVGTT).
- One study tested SWS suppression vs. REM suppression (Herzog et al. 2013); demonstrated that decrease insulin sensitivity is specific to SWS.

More than about the amount of sleep: timing

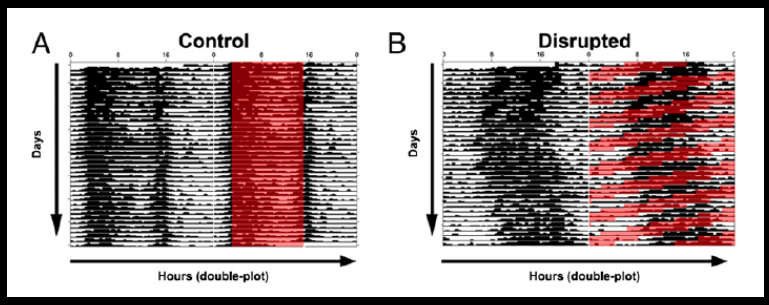
PNAS

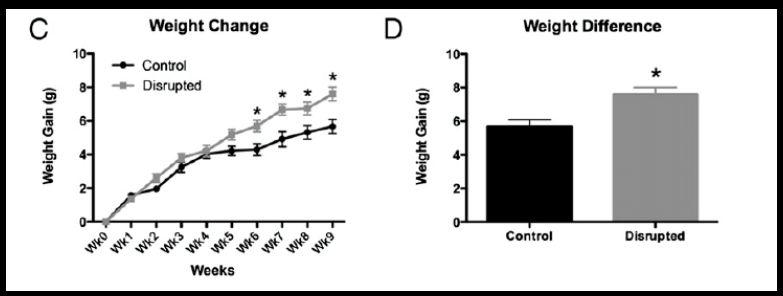
Disruption of circadian clocks has ramifications for metabolism, brain, and behavior

Ilia N. Karatsoreos[a,1], Sarah Bhagat[a], Erik B. Bloss[b], John H. Morrison[b], and Bruce S. McEwen[a,1]

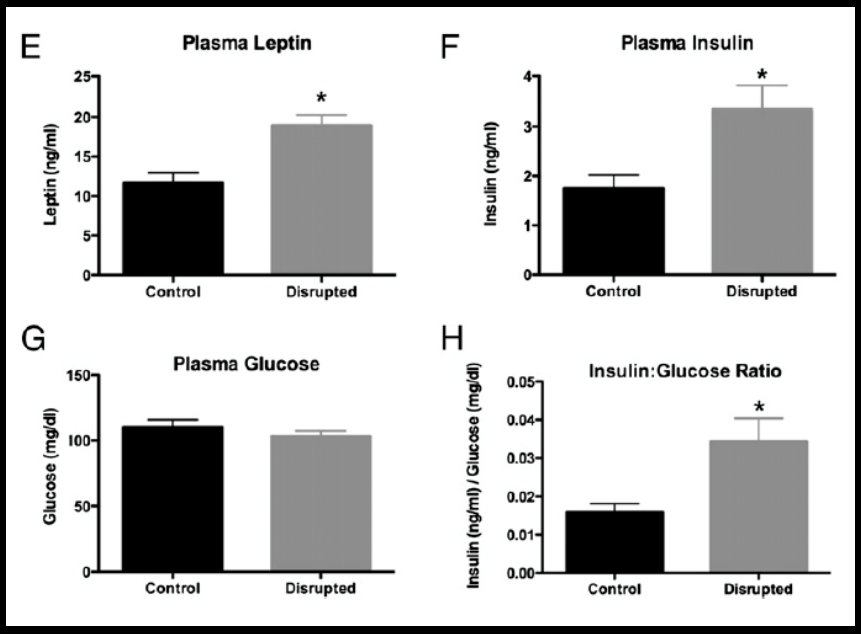
[a]Laboratory of Neuroendocrinology, The Rockefeller University, New York, NY 10065; and [b]Fishberg Department of Neuroscience and Kastor Neurobiology of Aging Laboratories, Mount Sinai School of Medicine, New York, NY 10029

Contributed by Bruce S. McEwen, December 14, 2010 (sent for review August 15, 2010)





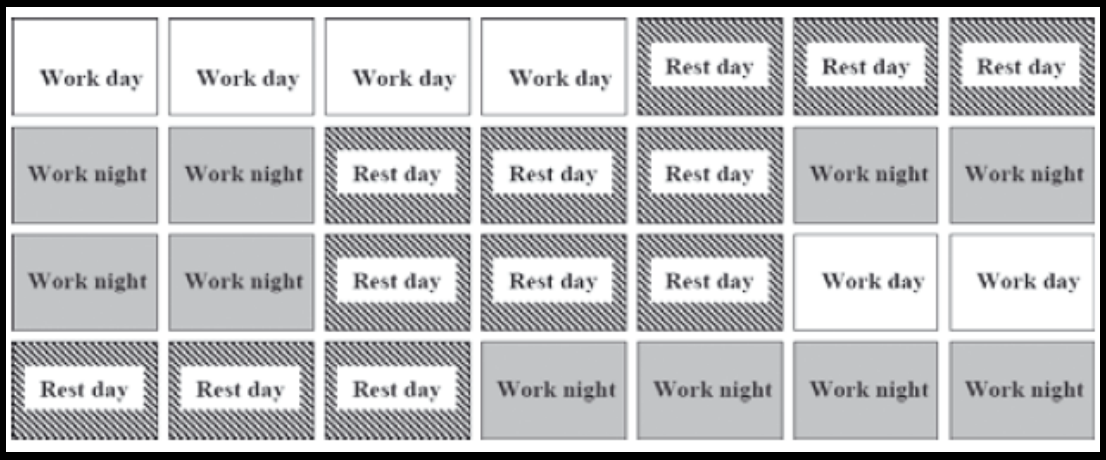
Karatsoreos et al., *PNAS*, 2011



Karatsoreos et al., *PNAS*, 2011

Shift work

- Estimated that more than 2 million Americans are shift workers.



In a sample of 474 rotating shift workers, compared to over 800 day workers; Significantly higher WHR and HOMA-IR as well as fasting insulin and triglycerides

Sookoian et al., 2007

How does sleep stack up to traditional risk factors for type 2 diabetes?

- Recent meta-analysis:
  - 36 Prospective Studies
  - Short sleep duration (≤5 hours): RR=1.48 (95% CI 1.25-1.76).
  - Poor sleep quality: RR=1.40 (95% CI 1.21-1.63)
  - Obstructive sleep apnea: RR= 2.02 (95% CI 1.57-2.61).
  - Being overweight: RR=2.99 (95% CI 2.42-3.72)
  - Family history: RR=2.33 (95% CI 1.79-2.79)
  - Being physically inactive: RR=1.20 (95% CI 1.11-1.32)

Anothaisintawee et al., *Sleep Medicine Reviews,* 2016

Beyond metabolic effects

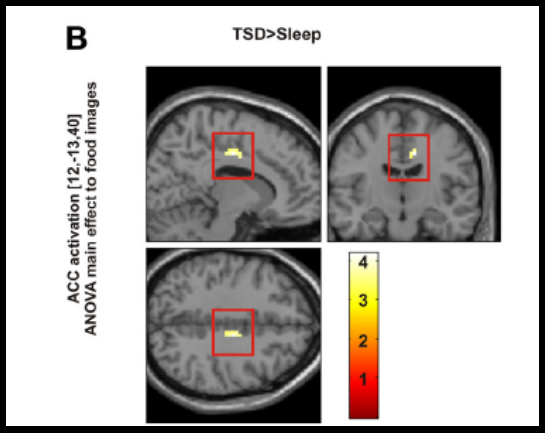
A sleepy brain is a hungry brain

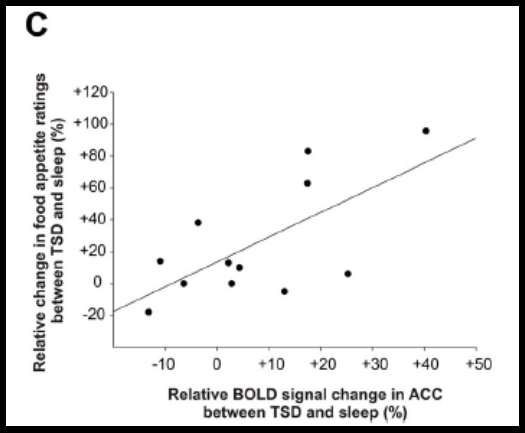
- Exposure to food cues engages reward circuity in the brain
- These effects are more pronounced under periods of sleep deprivation.
- Like under periods of stress, under sleep loss we tend to crave high caloric (often sweet or salty) foods.

A sleepy brain is a hungry brain

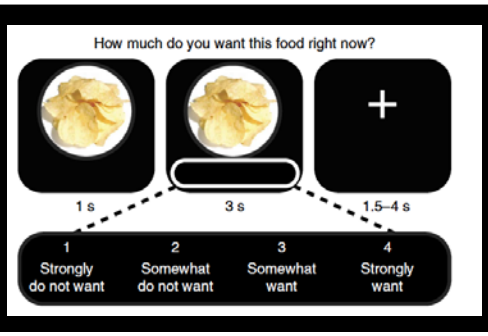
Benedict et al., 2012

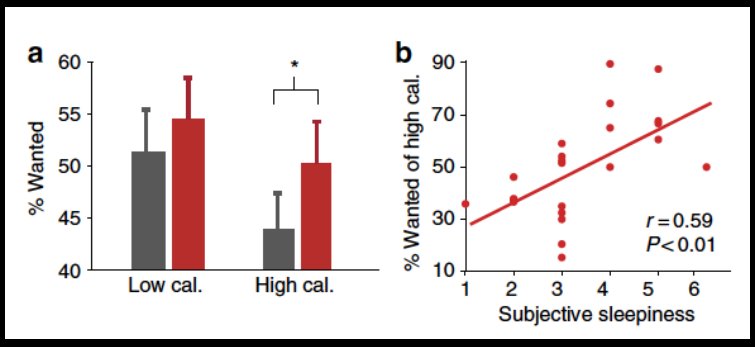
A sleepy brain is a hungry brain



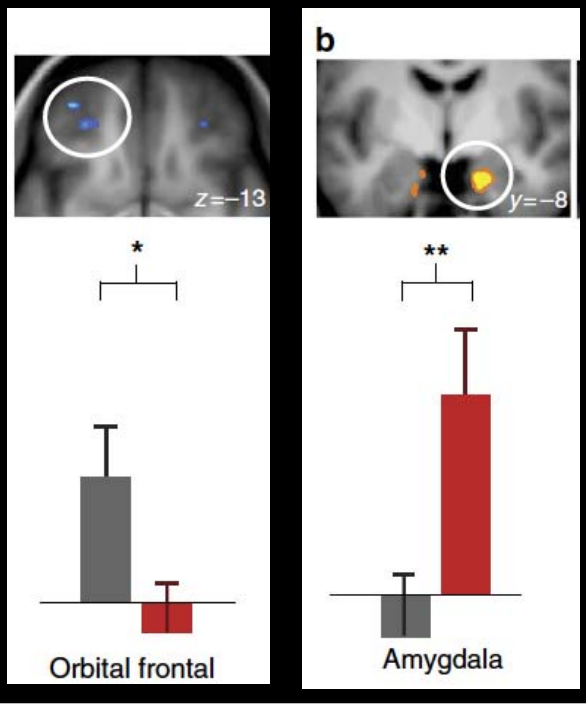


Benedict et al., 2012





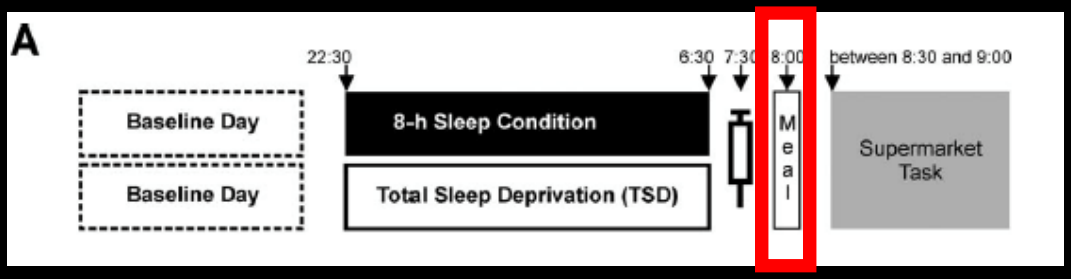
Greer et al., *Nature Comm.*, 2013



Greer et al., *Nature Comm.*, 2013

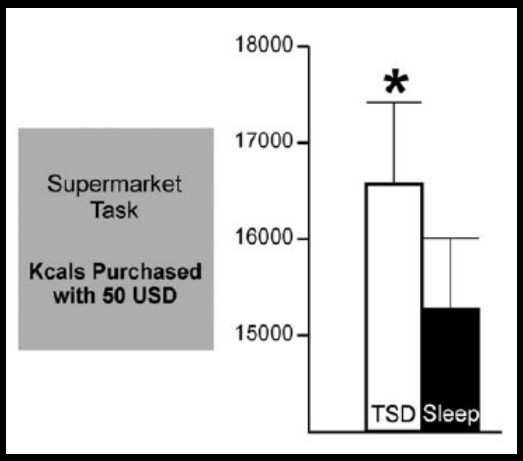
What does it mean for daily life?

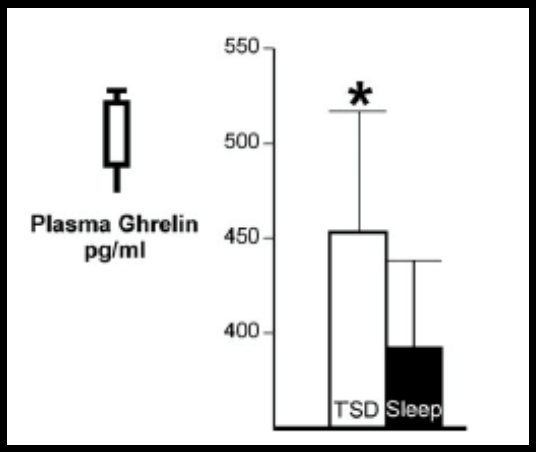
- Recruited 14 healthy, non-obese men
- Cross-over design



Chapman et al., *Obesity,* 2013

What does it mean for daily life?





Chapman et al., 2013

Sleep and Soda

Short and sweet: Associations between self-reported sleep duration and sugar-sweetened beverage consumption among adults in the United States

Aric A. Prather, PhD [a,b,*], Cindy W. Leung, ScD, MPH [b], Nancy E. Adler, PhD [a,b], Lorrene Ritchie, PhD, RD [c], Barbara Laraia, PhD, MPH, RD [b,d], Elissa S. Epel, PhD [a,b]

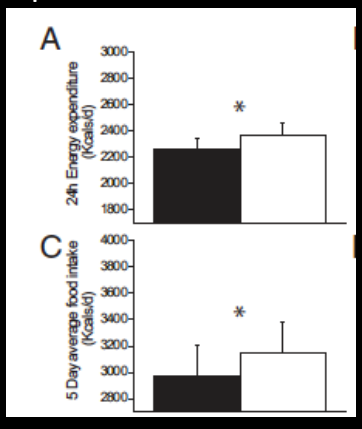
Sleeping 6 or fewer hrs/night

=

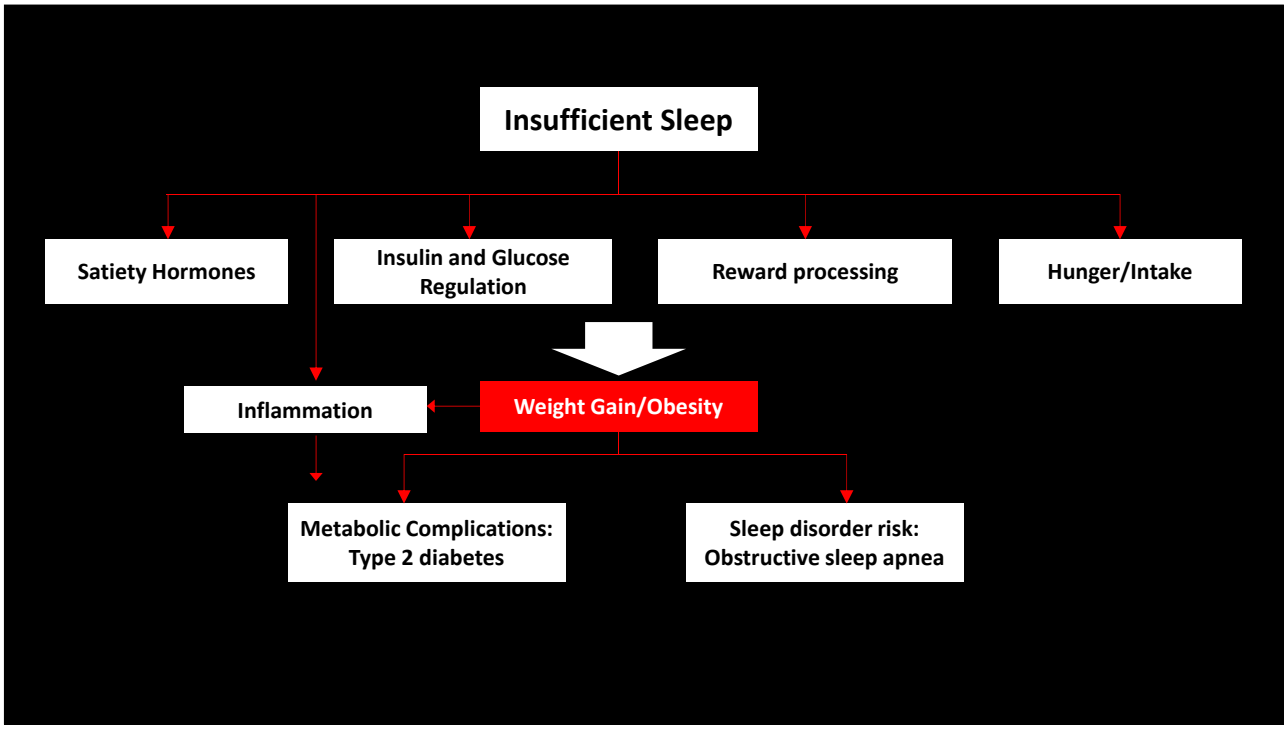
11-21%
more sugar-sweetened beverage consumption

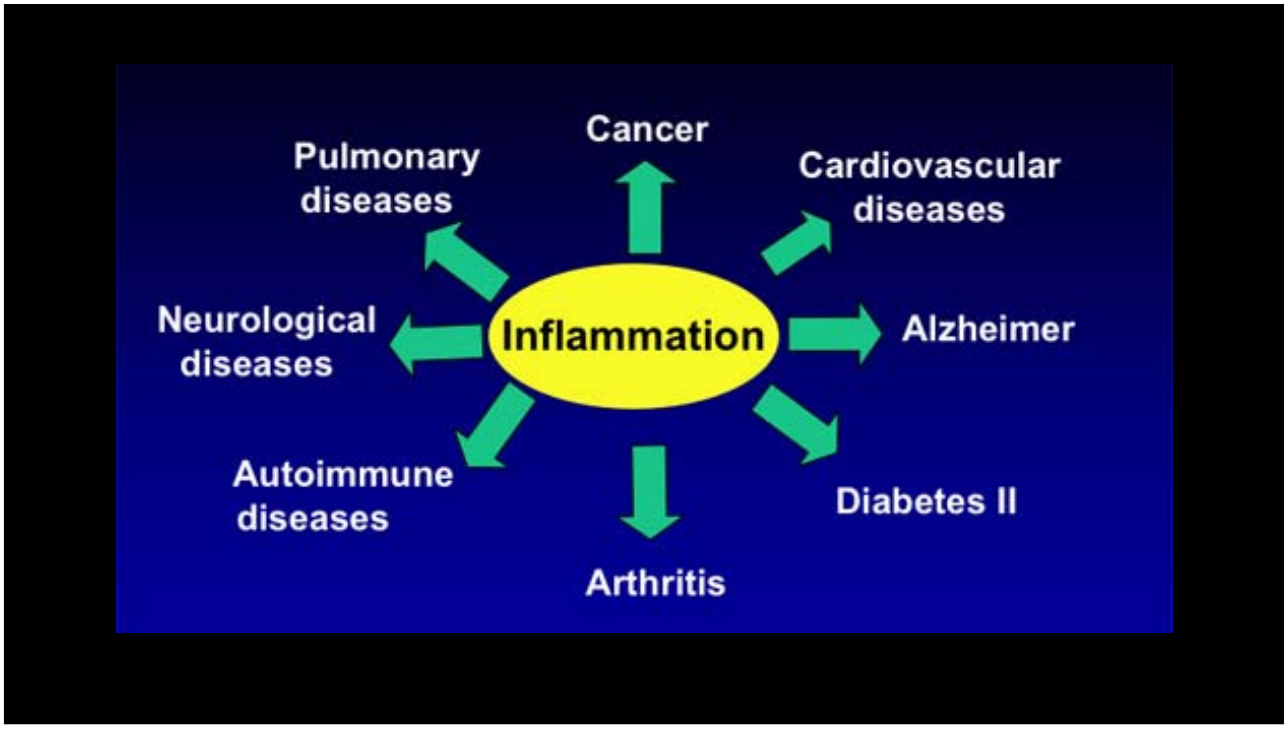
Why does this happen?

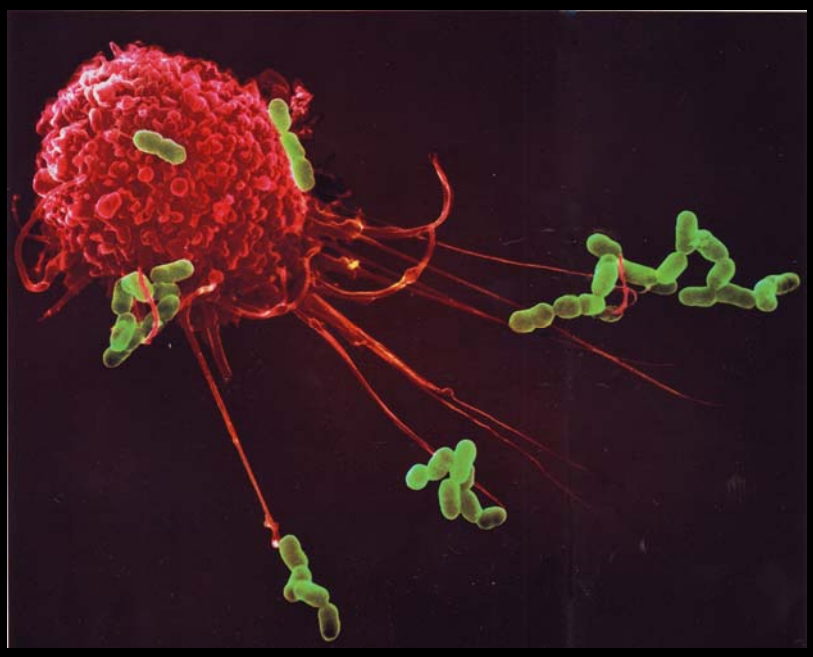
- One leading hypothesis is that this is an adaptive process to obtain/utilize energy to maintain wakefulness.
- However, when food is readily available…
- Participants consume more calories than is justified by increased energy expenditure

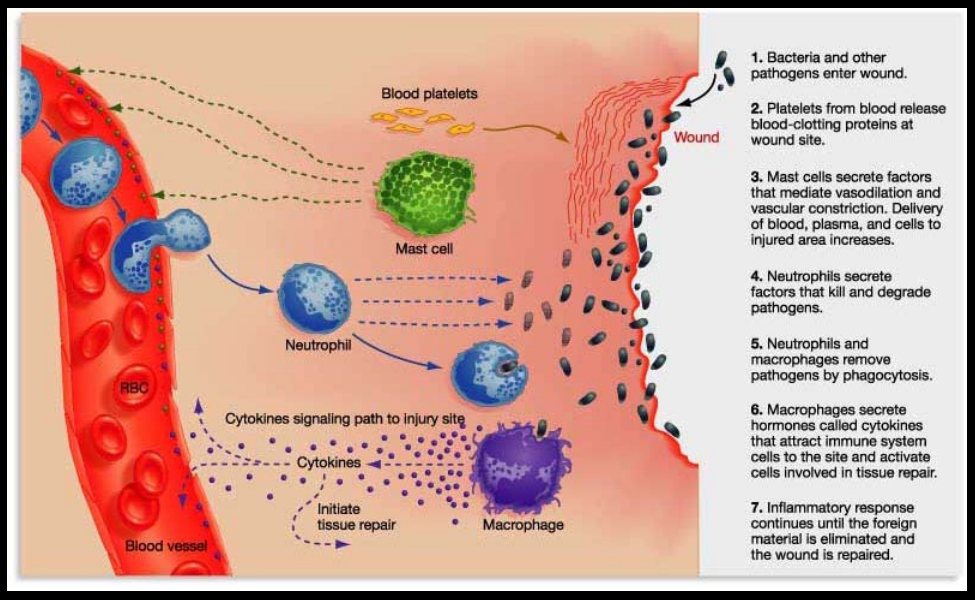


Markwald et al., PNAS, 2013


Insufficient Sleep
Satiety Hormones
Insulin and Glucose Regulation
Reward processing
Hunger/Intake
Inflammation
Weight Gain/Obesity
Metabolic Complications: Type 2 diabetes
Sleep disorder risk: Obstructive sleep apnea

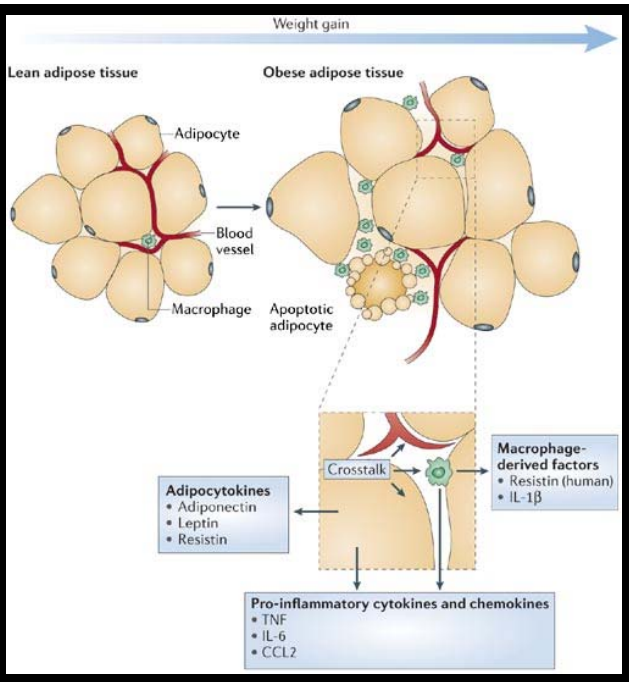

Cancer
Pulmonary diseases
Cardiovascular diseases
Neurological diseases
Inflammation
Alzheimer
Autoimmune diseases
Diabetes II
Arthritis




Blood platelets
Wound
Mast cell
Neutrophil
RBC
Cytokines signaling path to injury site
Cytokines
Initiate tissue repair
Macrophage
Blood vessel
1. Bacteria and other pathogens enter wound.
2. Platelets from blood release blood-clotting proteins at wound site.
3. Mast cells secrete factors that mediate vasodilation and vascular constriction. Delivery of blood, plasma, and cells to injured area increases.
4. Neutrophils secrete factors that kill and degrade pathogens.
5. Neutrophils and macrophages remove pathogens by phagocytosis.
6. Macrophages secrete hormones called cytokines that attract immune system cells to the site and activate cells involved in tissue repair.
7. Inflammatory response continues until the foreign material is eliminated and the wound is repaired.

Biomarkers of inflammation

- Proinflammatory cytokines
  - Interleukin (IL)-6, IL-1β, and tumor necrosis factor (TNF)-α
- Sources:
  - Activated immune cells (e.g., macrophages)
  - Adipose tissue (especially visceral fat)
  - Muscle cells (myocytes)
- Acute phase proteins
  - C-reactive protein (released by the liver in response to increasing IL-6)

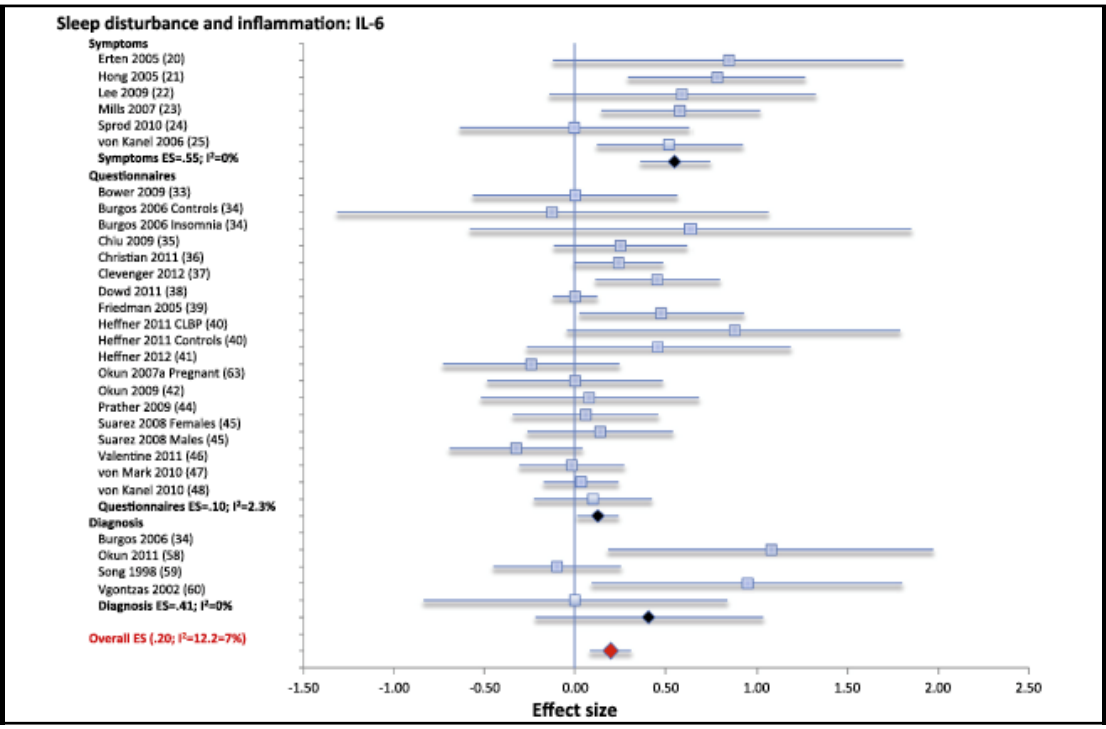


Tilg & Moschen, Nature Reviews Immunol, 2006

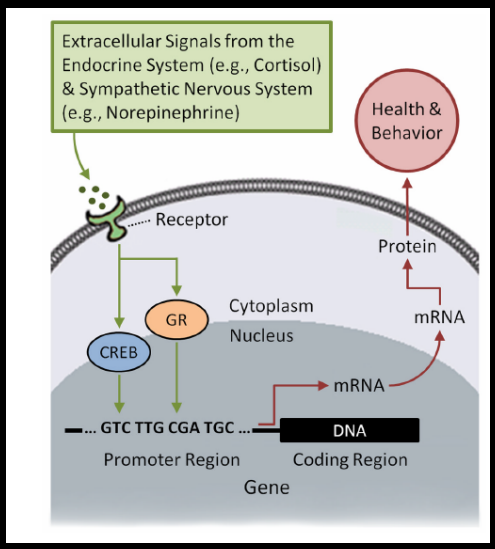
Does sleep affect inflammation?

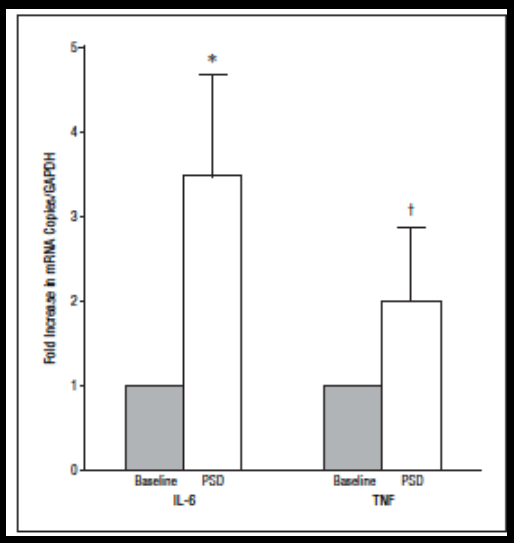
Sleep and inflammation

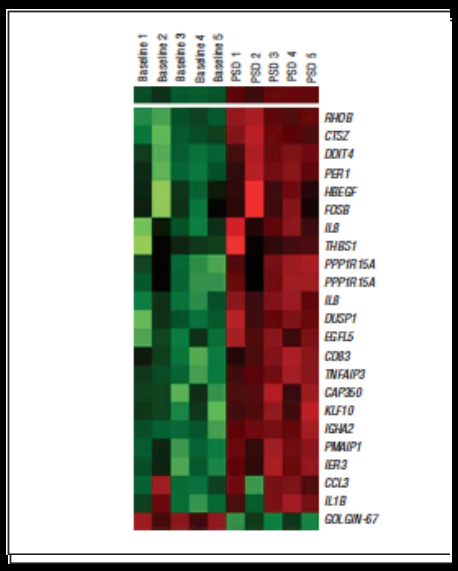
- Small effects of short sleep duration and larger effects for long sleep duration on higher inflammation.
- Also, evidence that sleep disturbances (symptoms, insomnia) are also related to elevated inflammation



Experimental sleep loss and inflammatory genes

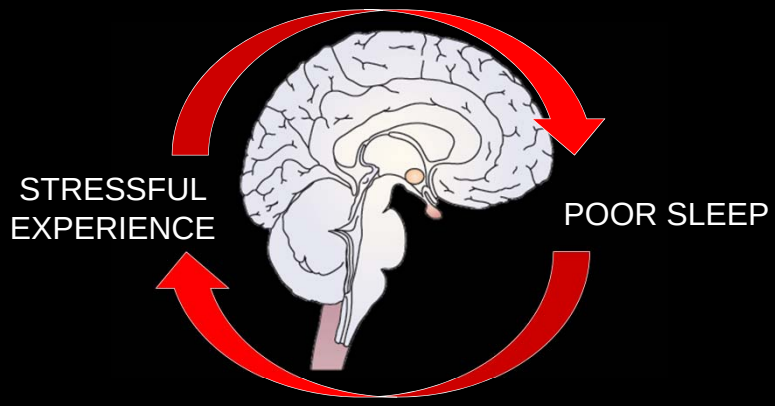






Irwin et al, *JAMA Inter Med,* 2006

Sleep-Stress: Recursive processes



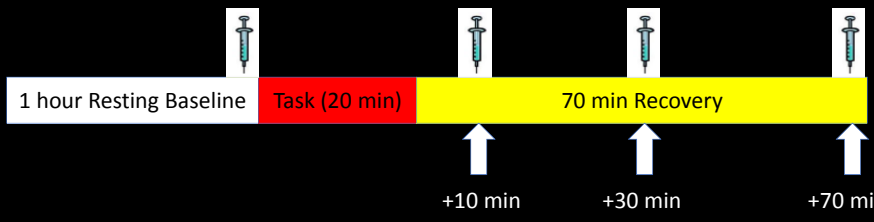
48 postmenopausal women

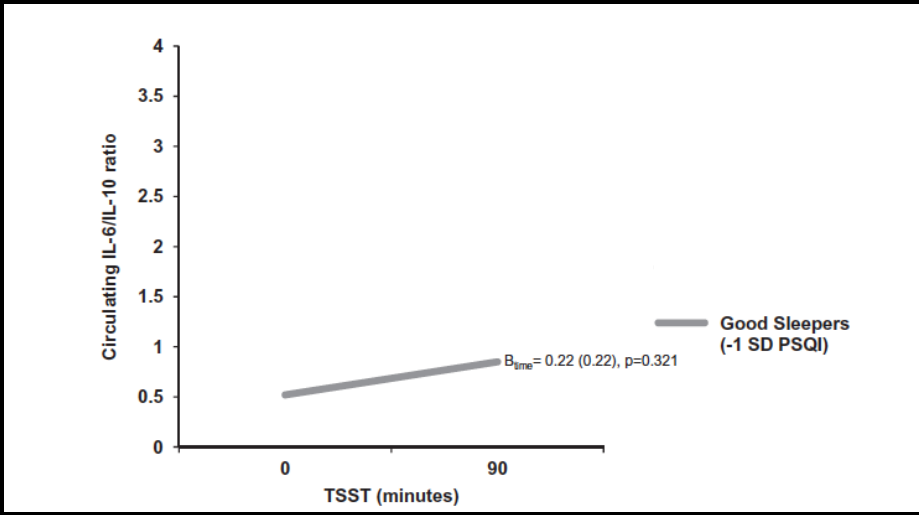
Free of chronic medical conditions and medications

Global Sleep Quality assessed by self-report

Carried out Trier Social Stress Task (TSST): Speech & Serial Subtraction

Blood assayed for interleukin (IL)-6 and IL-10. Outcome: IL-6/IL-10.





Prather et al., *Brain, Behavior, & Immunity,* 2013

What can be done??

Do sleep improvements lead to better biological outcomes?

- Experimental settings:
  - Recovery sleep
- Intervention settings:
  - Sleep Extension protocols
  - Cognitive behavioral therapy for insomnia
  - Pharmacologic intervention

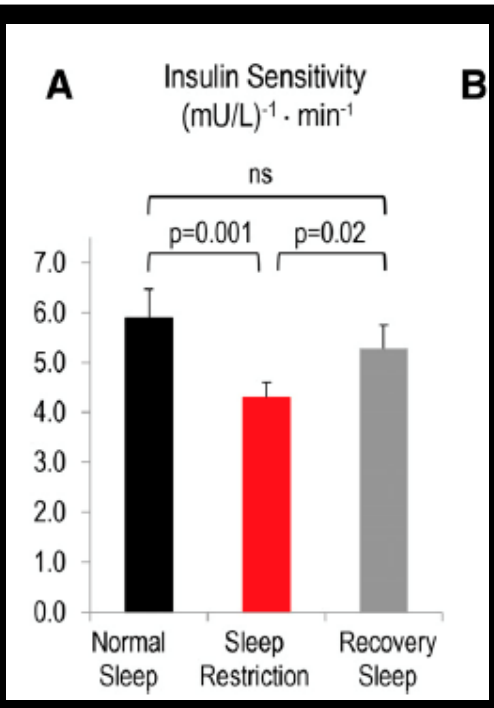
Sleep and Insulin Resistance: hope?

Two Nights of Recovery Sleep Reverses the Effects of Short-term Sleep Restriction on Diabetes Risk

Josiane L. Broussard,[1] Kristen Wroblewski,[2] Jennifer M. Kilkus,[3] and Esra Tasali[3]

Diabetes Care 2016;39:e40–e41 | DOI: 10.2337/dc15-2214

4 nights of 8.5 hr TIB, 4 nights of 4.5 hr TIB, 2 nights 12 and 10 hr TIB



Broussard et al., 2016

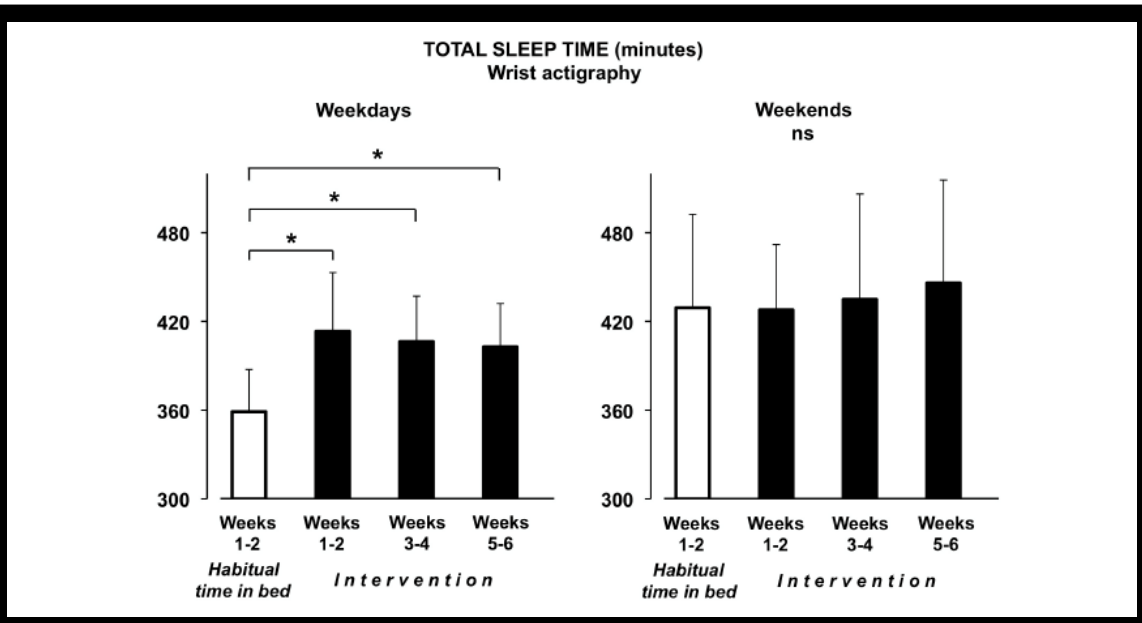
BENEFIT OF SLEEP EXTENSION ON FASTING INSULIN SENSITIVITY

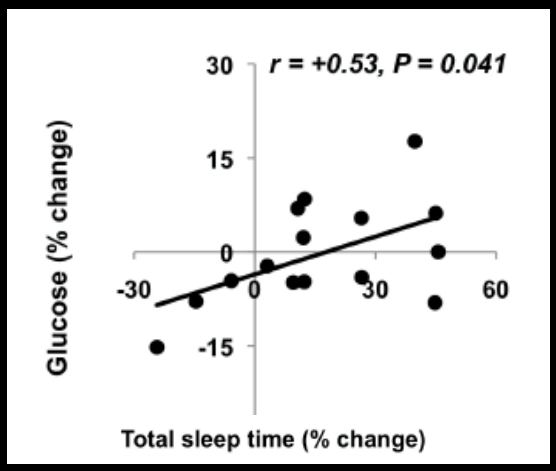
Beneficial Impact of Sleep Extension on Fasting Insulin Sensitivity in Adults with Habitual Sleep Restriction

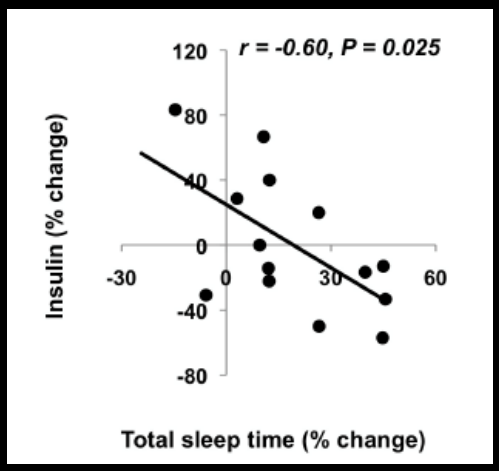
Rachel Leproult, PhD[1]; Gaétane Deliens, PhD[1,2]; Médhi Gilson, MS[1]; Philippe Peigneux, PhD[1]

[1]Neuropsychology and Functional Neuroimaging Research Unit and [2]CO3-Consciousness, Cognition & Computation Group, Center for Research in Cognition and Neurosciences and the ULB Neuroscience Institute, Université Libre de Bruxelles (ULB), Brussels, Belgium

- 16 healthy non-obese participants (all reported sleeping <7 hours/night on weekdays)
- 2 weeks of habitual sleep time, and 6 weeks of extension (1 hour more in bed per night).


TOTAL SLEEP TIME (minutes)
Wrist actigraphy
Weekdays
Weekends
ns
*
*
*
480
420
360
300
Weeks 1-2
Weeks 1-2
Weeks 3-4
Weeks 5-6
Habitual time in bed
Intervention


r = +0.53, P = 0.041
Glucose (% change)
Total sleep time (% change)
30
15
0
-15
-30
0
30
60


r = -0.60, P = 0.025
Insulin (% change)
Total sleep time (% change)
120
80
40
0
-40
-80
-30
0
30
60

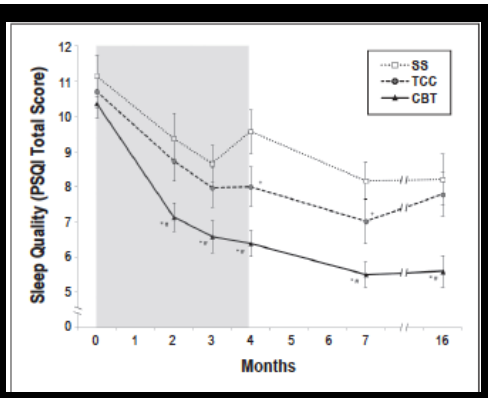
Cognitive behavioral therapy for insomnia

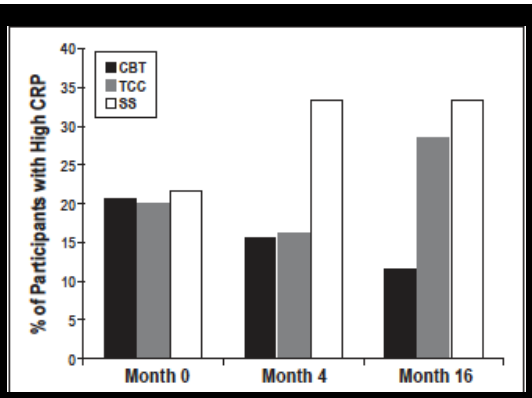
- First line treatment for insomnia
- Combination of sleep hygiene, sleep restriction, stimulus control, and cognitive therapy targeting maladaptive sleep beliefs.
- https://www.ucsfhealth.org/clinics/neuro_psych_sleep/

CBT VS. TAI CHI FOR LATE LIFE INSOMNIA AND INFLAMMATORY RISK

Cognitive Behavioral Therapy vs. Tai Chi for Late Life Insomnia and Inflammatory Risk: A Randomized Controlled Comparative Efficacy Trial

Michael R. Irwin, MD[1]; Richard Olmstead, PhD[1]; Carmen Carrillo, MPH[1]; Nina Sadeghi, BS[1]; Elizabeth C. Breen, PhD[1]; Tuff Witarama, BS[1]; Megumi Yokomizo, BS[1]; Helen Lavretsky, MD[1]; Judith E. Carroll, PhD[1]; Sarosh J. Motivala, PhD[1]; Richard Bootzin, PhD[2]; Perry Nicassio, PhD[1]





Pharmacologic intervention

- One study of Zolpidem (Ambien; 10mg) administration on glucose regulation in response to OGTT in 12 men (Gramaglia et al., 2014)
- Compared to baseline, 15 days of treatment resulted in a 86% increase in glucose area under the curve with no effect on insulin- suggestive of impaired insulin sensitivity due to treatment.
- More studies are needed.

How can you improve sleep?

- Create an ideal sleep environment
  - Keep the bedroom quiet, cool, and dark
  - Keep your smart phone out of the bedroom
  - Don't consume caffeine or exercise near bedtime and avoid excessive alcohol
  - Avoid long naps, especially if having sleep problems
  - Avoid using excess mental energy worrying

If you could do two things..

Set a routine wake up time 7-days a week

If it is clear that you can't sleep, leave the bedroom until sleepy

Protect your sleep…

YOUR METABOLISM IS COUNTING ON YOU

THANK YOU
(and sleep well.)

QUESTIONS?
aric.prather@ucsf.edu