



Look both ways down a one way street

Bobby Collins  
"On the Inside"



## Pathophysiology and Consequences of OSA

The Health and Medical  
Consequences of OSA

Is OSA a Systemic Disorder?

## Overview

- Cardiac Disease:
  - Hypertension
  - Arrhythmias – especially A-fib
  - Coronary Artery Disease
  - Congestive Heart Failure
  - Pulmonary Hypertension
- Neurologic Disease:
  - Stroke                      Cognitive Impairment
  - Pain                              Psych Issues: Anxiety / Depression
- Endocrine Disease:
  - Obesity                      Diabetes
- GI:
  - GERD

## 238 OSA Patients

- Medical Care:      Mean Cost \$2,720
- Control:              Mean Cost \$1,384

Magnitude of Cost Correlates to Severity

Kapur, et al  
SLEEP, vol 22, 1999

## Metabolic Syndrome (originally known as Syndrome X)

Consists of 3 of the 5 features

- Abdominal Obesity (increased waist circumference and "gut")
- Increase in triglyceride levels
- Reduced HDLs
- Hypertension
- Impaired fasting glucose

### Snoring – Insomnia and Metabolic Syndrome

- Diagnosed in 14% of the 115 participants who remained after 3 years (started with 290)
- Predictors of developing Metabolic Syndrome:  
 Difficulty falling asleep: OR 1.81  
 Unrefreshing sleep: OR 1.71  
 Loud snoring: OR 2.30

### Metabolic Syndrome

- Predicts Diabetes Type II
- Relates to morbidity and mortality from:  
 Cardiovascular Disease  
 Cancer  
 Arthritis

"Self-reported Sleep Quality is Associated With the Metabolic Syndrome" SLEEP 2007;30(2):219-223

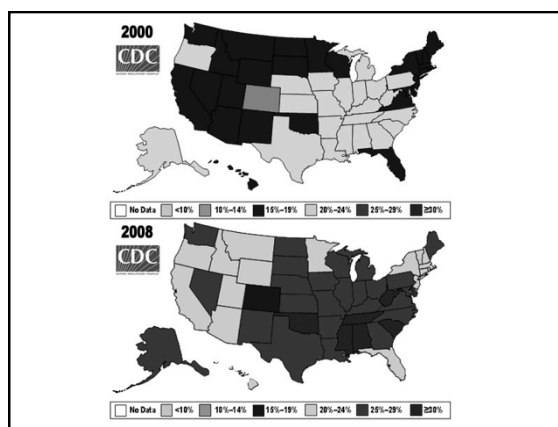
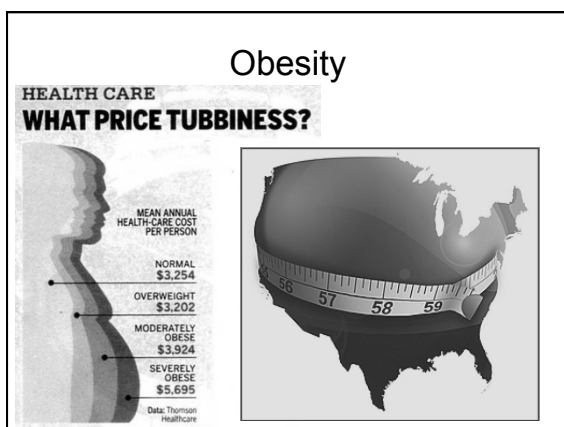
### Sleep and Obesity

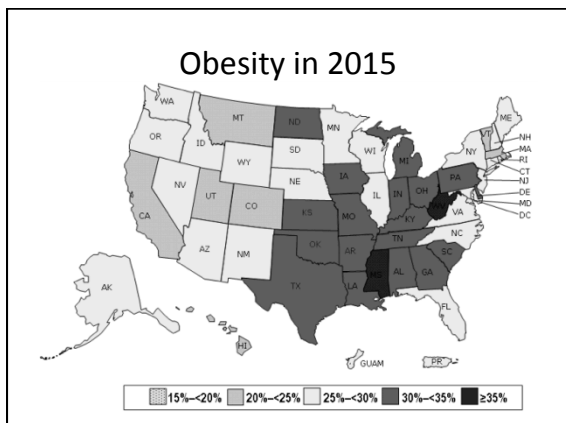
### SLEEP and OBESITY

Followed 500 Young Adults for 13 Years

*Results:* Association Between Short Sleep Duration and Obesity That Diminishes After Age 34

SLEEP July 21, 2004

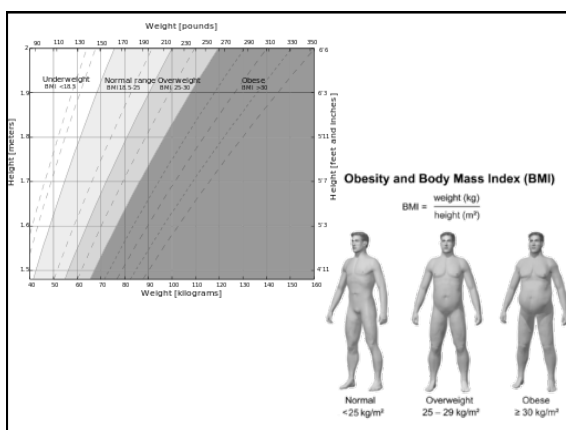




### Inadequate Sleep as a Risk Factor for Obesity

7 Hours sleep critical  
 <7 hours sleep more likely to be obese as compared to those who slept 7 hours  
 >7 hours not an issue

Sleep 2005;28(10):1289-96



### Too Little, Too Much Sleep Linked to Premature Death

- Sleep < 6 Hrs and > 8 Hrs linked to premature death
- Sleep 9 Hrs or more leads to premature death but for different reasons - possibly linked to ill health
- Short Sleep 12% higher risk for death
- Long sleep 30% greater risk for death

Sleep May 2010

### Sleep and Inflammation

### With Sleep Deprivation May Also Have

- Increased Interferon - IL-6 - TNF $\alpha$
- Increased risk of OSA
- Increased Sleepiness
- Both IL-6 and TNF $\alpha$   $\Rightarrow$  Decrease neurogenesis

### CPAP improves Inflammation (So Do Oral Appliances)

- Both have been found to reduce markers for inflammation
- Inflammation associated with the multi-morbidities of sleep disorders

J Inflamm (Lond) 2013;10:13 (CPAP)  
J Clin Sleep Med 2014;10(3):255-262 (OAs)

### OSA and Hypertension

### OSA and Hypertension

- 50% of OSA patients have hypertension
- 30% of hypertensive patients have OSA

Somers VK, White DP, et al  
Circulation 2008;118:1080-1111

### OSA and Hypertension

- Both prevalent: HTN 30% of the population - 40 to 70% of OSA patients also have HTN
- Obliteration of “dipping”
- Associated with hypoxia - Increased Sympathetic tone - may persist after resolution of hypoxia

### OSA and Reverse Dipping

- Cannot determine with office or home monitoring of BP – nocturnal BP may be elevated
- More critical in Mod-Severe OSA
- Leads to cognitive decline (white matter loss), stroke and mortality
- Also see increased C-reactive
- Associated with increased sympathetic tone

J Hypertension 2014, 32:1964-1966

### Odds Ratio for Hypertension Associated with SDB

- No Events Odds Ratio 1.42
- 1 to <5 AHI Odds Ratio 1.42
- 5 to < 15 AHI Odds Ratio 2.03
- 15 or More AHI Odds Ratio 2.89

NE J of Medicine Vol 342, #19 (May 11, 2000)  
P1378-1384

### Association of Sleep Duration With Hypertension

- Odds Ratio Based on Hours of Sleep:

Less than 6 Hours: 1.66

6 to 9 Hours: 1.19

Over 9 Hours: 1.30

Hypertension defined as > 140/90 or using medication

Ideal Hours of Sleep: 7-8

Association of Usual Sleep Duration With Hypertension: The Sleep Heart Health Study SLEEP 2006;29(8):1009-1014

### SNORING AND BLOOD PRESSURE

INCREASED INCIDENCE OF RISK

MOSTLY IN AGE 50 OR LESS

Europ Respir J 1998

### Long-term Effect of CPAP in Hypertensive Patients with Sleep Apnea

- Looked at non-sleepy patients with OSA
- Treatment over 1 year
- Results: small decrease in BP
- Results only evident in patients who use CPAP 5.6 hrs or more

Am J Resp Crit Care Med April 2010

### Effect of Oral Appliance Therapy on Sleep Apnea and Hypertension

Followed 102 Patients with OSA

38 with average BP 149/93 AHI 21.6

64 with average BP 123/76 AHI 17.8

Post-OA Treatment

Hypertensive Group average BP 137/84

Non-Hypertensive Group average BP 122/75

Abstract IADR March 12, 2004

### Oral Appliances Reduce BP In OSA Patients

- Increased Oxygen Levels
- 50% Decrease in RDI
- In 4 Weeks: Decreased BP = To CPAP

Sleep 2004;27(5):934-941

### Dietary Nitrate and Hypertension

- 250 ml Beetroot Juice daily
- Compared two groups of n-34 in treated and non-treated patients
- Saw significant reduction in BP in treatment group

Hypertension 2015 Feb 65:320-27

## Diabetes and Sleep Disorders

## SNORING: A Risk Factor for TYPE II Diabetes

Increased Risk: 1.48 to 2.25

Am J Epidem 2002;155(5):387-393

## SRBD - Insulin Resistance and Glucose Intolerance

Increased CVD Associated With  
Increased Risk For Type II Diabetes

Am J Epidem 2004;160(6):521-530

## Sleep Disruption and Diabetes Type 2

- Sleep disruption disturbs the body's ability to regulate blood sugar
- 18 million Americans have Diabetes type 2
- 3 nights of sleep disruption led to a 25% decrease in the ability to regulated blood sugar

Proceedings of the National Academy  
of Sciences - online

## Sleep Restriction (Insomnia) and Diabetes

- Chronic sleep restriction - less than 6 hours a night
  - Deterioration of:
    - Memory
    - Adverse effects on endocrine function
- Increased Risk for:
- Obesity
  - Diabetes

Roth T. J Clinical Sleep Med 2009, Vol 5 No 2 p S4

## Too Little Sleep = Increased Risk for Diabetes

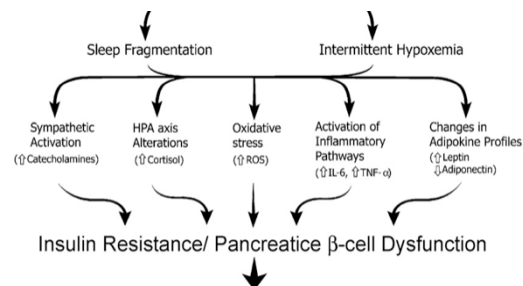
- Less than 6 hours of sleep – prone to abnormal blood sugar
- If sleep less than 6 hrs – 4.5 times more likely to develop abnormal blood sugar in 6 years vs those who slept longer

## Diabetes on Upward Trajectory

- 2011 - 366 million world wide - up 30% from 2010
- 2010 - 285 million world wide

Diabetes Atlas

## SLEEP APNEA



## Risk for Diabetes based on Degree and Duration of Obesity

- Degree & Duration of excess BMI (obese) higher correlation to risk for developing Type II Diabetes
- Elevated BMI alone - risk lower

Archives of Pediatrics and Adolescent Medicine (Sept 5 online)

## Diabetes Type 3

- Insulin disappears early in Alzheimer's disease
- Found the Brain produces Insulin
- Cells in the brain of these patients are resistant to Insulin – neurons in the brain are deprived of glucose

Suzanne de la Monte at Brown Univ  
J of Alzheimer's Disease Nov 2007

## GERD and Sleep Disorders Mainly Sleep Breathing Disorders but also Impacts Insomnia

## Relationship of GERD and SRBD

- Mechanism: Negative inspiratory pressure and inflammation (obesity)  
Increased intra-thoracic pressure effects the phrenoesophageal ligament → connected to the esophageal sphincter
- Other Relationships: Asthma, allergy, nasal airway obstruction

## Incidence of GERD

- 7% of adults have daily symptoms
- 20% of adults have symptoms once weekly
- Obesity a key factor  
Gastroenterology 1997;112:1448-56
- Despite medication only 49% had symptoms controlled
- 54% of events during sleep - 62% followed by an awakening – 90% associated with sleep disruption  
J Clin Sleep Med 2007;3(5):505-513

## Types of GERD

- Symptomatic / Acidic
- Non-Acidic / Silent Reflux  
More common with PPI therapy – symptoms may persist despite treatment

Orr WC, Craddock A, Goodrich S.  
Acidic and non-acidic reflux during sleep under conditions of powerful  
Acid suppression  
Chest 2007;131(2):460-5

## GERD and Asthma

- GERD makes Asthma symptoms worse
- Asthma an inflammatory condition
- With GERD Asthma worse plus:  
Chronic cough  
Voice changes  
Asthma worse at night / lying down  
From Everyday Health Aug 2010

## Sleep Position and GERD

- No difference in GERD supine or on the left side
- On the right side - ↑ GERD  
From Am J of Gastroenterology  
(1999) 94, 2069-2073
- Peak Gastric secretion 10 PM to 2 AM

## Treatment of GERD

- Suspected: Do OTC trial x two weeks
- Medications for GERD:  
H-2 blockers – block Histamine – symptom Tx  
Treat heartburn but not **esophagitis**  
PPIs (proton pump inhibitors)  
Block acid production – preventives  
Take before meals – at bedtime?  
Proton Pump Inhibitors (prevent acids from staying in the stomach) - Reglan

## Medications

- | <u>H-2 blockers</u>    | <u>PPIs</u>                     |
|------------------------|---------------------------------|
| • Nizatidine (Axid)    | • Aciphex (Rabeprazole)         |
| • Pepcid (Famotidine)  | • Nexium<br>(Esomeprazole)      |
| • Tagamet (Cimetidine) | • Prevacid<br>(Lansoprazole)    |
| • Zantac (Ranitidine)  | • Prilosec (Omeprazole)         |
|                        | • Protonix (Pantoprazole)       |
|                        | • Dexilant<br>(Dexlansoprazole) |

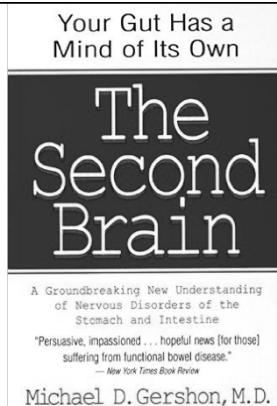


### Association of PPI With Risk of Dementia (Claims Data Analysis)

- Cohort observational study from 2004 to 2011
- Over 73,000 participants 75 years and older who were free of Dementia at baseline
- All took PPIs (...azole) meds
- At mean age of 83.8 there was significantly increased risk of incident dementia
- Use of PPI = increased  $\beta$ -amyloid
- What does this mean?

JAMA Neurol online Feb 15, 2016

Published in  
1998



CARDIOVASCULAR  
PATHOPHYSIOLOGY  
RELATED TO

SNORING  
SLEEP APNEA

The Relationship of:

Cardiovascular Disease  
To  
Sleep Disordered Breathing

### Sleep Duration and CVD Results of National Health Interview Study

- Short (< 5 hr) and long ( $\geq$  9 hr) sleep durations independently associated with CVD
- This is independent of all factors
- Compared to 7 Hrs. sleep duration

SLEEP Vol 33, No 8, 2010

### CONSEQUENCES OF SRBD

- Neurocognitive  
Ability to Concentrate, Memory Issues,  
Mood Swings, Sleepiness, Tired
- Cardiovascular  
Hypertension, Atrial Fibrillation

### Other Sleep Disorders Associated with CVD

- Insomnia
- RLS – now termed “Willis-Ekborn disease”

• Both have association with hypertension, CVD and heart failure

Insomnia and the risk of incident heart failure  
 Eur Heart J 2103;35:1382-42

Association of RLS and CVD in Sleep Heart Health study  
 Neurology 2008;70(1):35-42

### RLS and CV Disease

- Patients with RLS have:
  - higher BP
  - faster heart rate
  - increased sympathetic tone
- Also RLS disrupts sleep – or is it PLMs?
- Has to be > 3 years duration to be significant

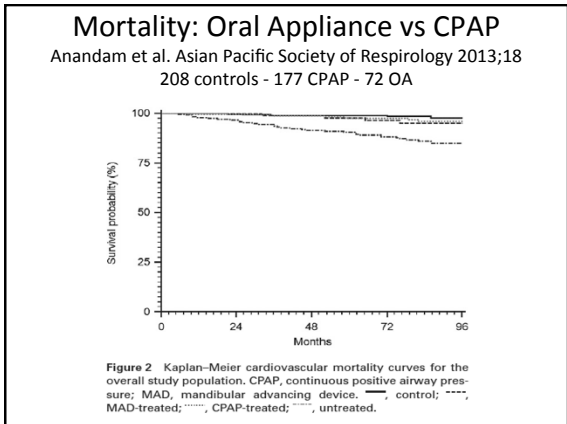
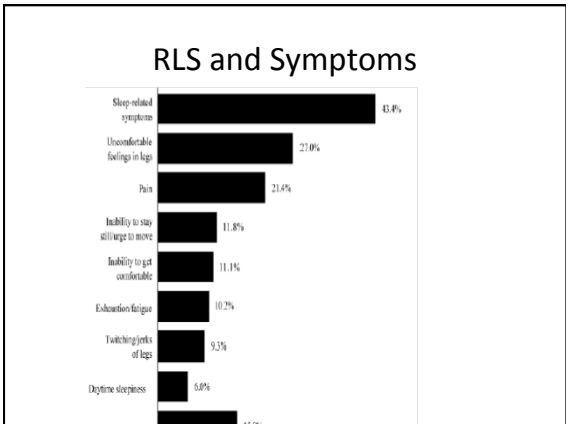
### RLS / CV Disease hazard ratios

<u>Group</u>	<u>Hazard Ratio</u>
• Any RLS	• 1.46
• Symptoms < 3yr	• 0.98
• Symptoms > 3yr	• 1.72

Circulation Sept 11, 2012 (online)

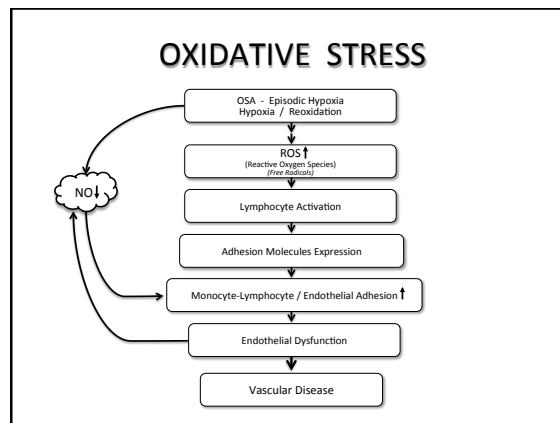
### Willis-Ekborn disease (RLS)

- Sensorimotor neurologic disorder
- Genetic – prevalence 12-15% and 2-3% have significant symptoms that require medication
- Neurotransmitter Dopamine in basal ganglion may be faulty OR
- Ferritin (Iron) levels may be low (<45-50µg/L) in the brain (blood levels may be normal)



## OXIDATIVE STRESS

The Initiating  
Factor  
In Cardiovascular Disease



## OXIDATIVE STRESS DUE TO HYPOXIA

- Leads to Neuronal Injury in Wake Promoting Areas of the Brain (Residual Sleepiness)
- Gradual Development of OSA Influences the Amount of Neuronal Injury

Sleep 2004;27(4):194-201

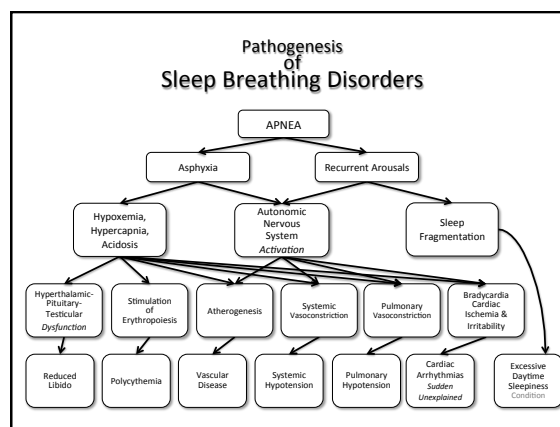
## Increased Oxidative Stress and Altitude

- Related to hypoxia at high altitude
- Measure total plasma glutathione
- Assessed by measuring:  
thiobarbituric acid reactive substances  
urine 8-isoprostaglandin

## Reduce Oxidative Stress

- N-acetylcysteine (anti-oxidant) leads to production of L-cysteine and glutathione (may also impact Dopamine)
- Monitor oxygen (pulse oximetry)
- Current diagnostic criteria for minimal O<sub>2</sub> levels is 88% for adults and 90% for children (ICSD3)

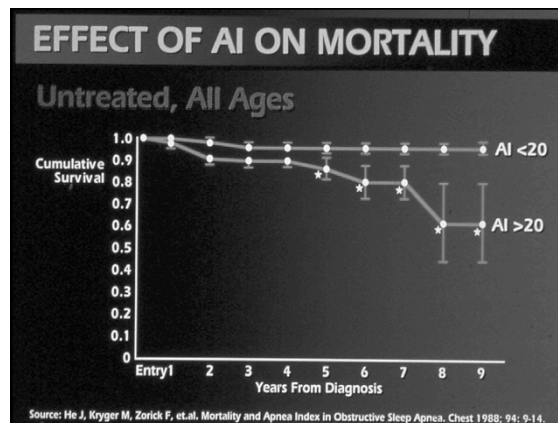
Chest 2014;145(2):423  
Chest 2013;143(2):444-451



## Consequences Cardiovascular

- Systemic Hypertension
- Heart Failure
- Cardiac Arrhythmias
- Myocardial Ischemia
- Cerebrovascular Disease
- Pulmonary Hypertension / Cor Pulmonale

“Sleep-Disordered Breathing and CVD”  
Sleep 2007;30(3):291-304

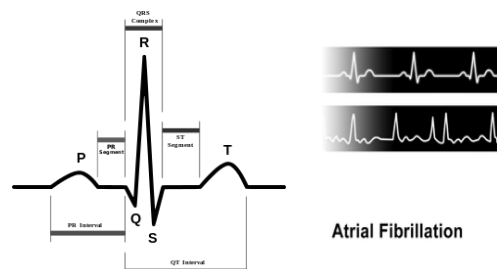


## Atrial Fibrillation and OSA

The Mayo Clinic Reports that  
Patients with Atrial Fibrillation  
Are Twice as Likely to Have OSA

Circulation: J of the Am Heart Assoc

ECG and A-fib  
P wave (represents depolarization) is  
absent



## Atrial Fibrillation

Odds Ratio for A-fib in people with  
OSA = 4.02

In a Cardiology Practice:  
49% of OSA patients  
32% no OSA

## OSA and the Recurrence of A-fib

- Untreated OSA patients - higher recurrence of A-fib after cardioversion when no treatment (CPAP)
- Using CPAP lower recurrence rate

Circulation 2003;107:2589-2594

## Severe Sleep Apnea Increases Mortality

6,400 middle age men over 8 years

Major (severe) sleep apnea 46% more likely to die from any cause

From: Johns Hopkins Univ Nov 2011

“Want to hear something funny?”



## ENDOTHELIAL FUNCTION AND OSA

Related to NO Levels Which  
Decrease in OSA

Results: Impairment of Vasodilation

Am J Resp and Crit Care Med 2004 Vol 169 p348-353

## Endothelial Dysfunction

40-50% have OSA

OSA patients worse outcome of  
disease

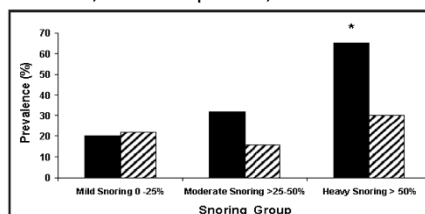
## Snoring and Carotid Atherosclerosis

- OSA promotes vascular endothelial dysfunction and atherosclerosis
- Sympathetic activation
- Increased reactive oxygen species (ROS)
- Increased inflammatory mediators

Sleep Sept 2008;31(9):1207-13

## Snoring and Atherosclerosis

Lee S, et al Sleep 2008;31:1207-13



**Figure 2**—Prevalence of carotid and femoral atherosclerosis. Prevalence of carotid atherosclerosis (black columns) and femoral atherosclerosis (shaded columns) by snoring group. Note that the prevalence of carotid atherosclerosis increased progressively across the 3 groups [\*P < 0.04 (X<sup>2</sup>)]. However, the prevalence of femoral atherosclerosis did not differ between groups.

**OSA – Inflammation – CVD  
Leads To:**

- Increased MVA, Daytime Somnolence, Cognitive Dysfunction
- Increased BP – Arrhythmias – Athleroscolosis

Related to: Inflammatory Response  
Increased Cytokines & C-Reactive  
Proteins  
Front Biosci 2004;9:2892-900

**Summary: Sleep Apnea &  
Metabolic Syndrome**

- Elevated Blood Pressure
- Higher Sympathetic Drive
- Diminished baroreflex sensitivity

Sleep 33(9):1193-1199

Note: AHI defined as 15 or >

**Insomnia and CVD**

- Hypertension present
- Elevated resting heart rate

Nature and Science 2010:2 71-78

**Neurocognitive: Causes of  
neurocognitive impairment in OSA**

- Sleep Fragmentation
- Sleep Related Hypoxia - gives rise of neuronal injury

**Cognitive Decline  
linked to Metabolic Syndrome**

- Increased Triglycerides
- Low HDL
- Diabetes
- Decline in global cognitive function
- Decline in memory

Neurology Feb 2, 2011

**The Sleep Heart Health Study**

- Study to Investigate the OSA and SDB as risk factors for CV Disease
- 6,600 Adult Participants
- Sufficient Evidence for assessing OSA and SDB as risk factors for major CV events - includes myocardial infarction and stroke

### DASH Diet for Hypertension (Dietary Approaches to Stop Hypertension)

- More fruits / vegetables
- Low fat dairy
- Whole grains
- Poultry / fish
- Nuts
- Reduce sweets / red meat / sugary drinks

### Sleep Apnea and Medical Specialists

- Cardiology
- Psychiatry
- Neurology
- Anesthesiology
- Urology
- Endocrinology
- ENT
- GI
- Pulmonary Medicine
- And of Course - Dentistry

### Sleep Disorders and Dentistry

- Sleep Bruxism
- Periodontal Disease
- Orofacial Pain
- TMD / TMJ
- Headaches

### Orofacial pain - Painful Conditions diagnosed by Sleep Complaints

- Myofascial pain TMD
- Headaches
- Trigeminal Neuralgia
- Glossopharyngeal Neuralgia
- Atypical Odontalgia
- Burning Mouth Syndrome

### OSA and Periodontal Disease

- N = 687
- 46.6% had OSA
- 60% with periodontitis had OSA
- Looked at high AHI, mouth breathing during sleep, smoker, male prevalence

Seo WH, Cho ER, Thomas RJ, et al  
J Perio Res 2013 Aug;48(4):500-6

### Periodontitis and SDB in Hispanic Community

- Finds association between SDB and Perio disease
- Most pronounced in young adults
- Study looked at 12,469 participants age 18 to 74

Sleep 2015;38(8):1195-1203

**Sleep Disorders (SD) and  
Burning Mouth Syndrome (BMS)**

- SD have an increased risk of BMS
- Implies: management of SD can improve symptoms of BMS by eliminating systemic inflammatory cytokines
- Underlying mechanism unclear

Chun-Feng Lee, et al  
Sleep Medicine July 2014

**Sleep and Pain / Pain and Sleep**

- Both impact one another
- Cannot treat one without considering the other
- The question is: Which one do you treat first?
- Managing sleep disorders will enhance pain management

**Cardiovascular and Sleep-Related  
Consequences of TMJ Disorders**

NHLBI Workshop  
December 3-4, 2001

Co-morbid complaints such as problems with sleep, blood pressure and breathing not uncommon for this group of TMD patients

**Pain**

“an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage”

**Orofacial / Musculo-Ligamentous Pain**



**Persistent pain after endodontic therapy**

JADA 2014;145(3):270-272

**Asma A. Khan, BDS, PhD; William Maixner, DDS, PHD;  
Pei Feng Lim, BDS, MS  
CLINICAL PROBLEM**

**Odontogenic pain resolves after Endo  
Non-Odontogenic pain persists**



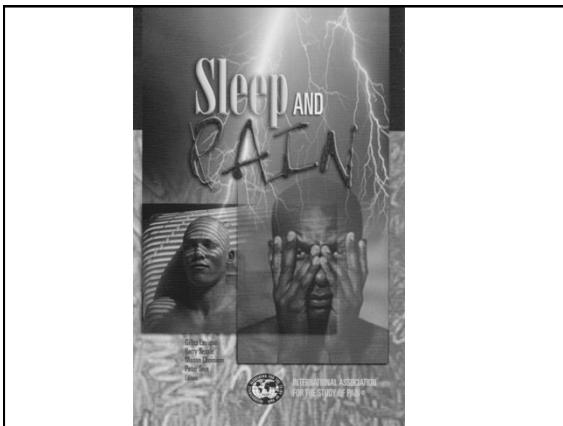
### Sleep Loss / REM Sleep Loss and Pain

- Loss of 4 hours sleep and specifically REM sleep deprivation → Hyperalgesia the next day
- Key Points:
  - Sleep loss increases pain
  - Medications that decrease sleep may increase pain

Sleep 2006 Feb 1;29(2):145-51

### Pain and Sleep Reciprocal Relationship

- Disrupted sleep a consequence of pain
- Pain is seen with sleep disruption
- When treating a painful condition - manage the sleep
- Odds ratio increases for association of insomnia and pain as severity of pain increases



“It is more important to know what sort of a patient has a disease than what sort of a disease a patient has”

William Osler, MD

