Co-Morbidities Associated with OSA

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OSAS and Cardiovascular Diseases

- **OSA has been shown to increase the risk for**
  - **Systemic Hypertension**
  - **Pulmonary vascular disease**
  - **Ischemic heart disease**
  - **Cerebral vascular disease**
  - **Congestive heart failure**
  - **Arrhythmias**
- **However, a causal relationship remains controversial**

OSAS and Cardiovascular Diseases

- **Many risk factors for OSA are also known risk factors for cardiovascular disease**
  - **Age**
  - **Male gender**
  - **Obesity**
- **OSA is also associated with conditions that are known to increase the risk for CV disease**
  - **Diabetes mellitus**
  - **Hypertension**
- **Therefore, it is difficult to prove whether OSA independently causes CV disease**

OSAS and Systemic Hypertension

- **"Dipping" phenomenon: In normal individuals, sleep is associated with a reduced BP when compared with wakefulness**
- **Systolic and diastolic BP may decline as much as 10-15%**
- **Sleep apnea has been found to blunt the dipping of BP during sleep**
- **Disordered breathing during sleep has been found be associated with acute peripheral vasoconstriction and rise in BP during sleep**

(Golbin JM et al. Proc Am Thorac Soc 2008; 5: 200-206)

OSAS and Systemic Hypertension

- Several studies have shown that OSA increases the relative risk for hypertension
- Wisconsin Sleep Cohort Study
- Sleep Heart Health Study
- Canadian population based study
- Study from Spain

OSAS and Systemic Hypertension

- 709 participants of the Wisconsin Sleep Cohort Study
- A dose-response association between SDB at baseline and the presence of hypertension four years later
- This was independent of known confounding factors
- This study suggested that SDB is likely to be a risk factor for hypertension

(Peppard PE et al. N Engl J Med 2000; 342: 1378-84)

OSAS and Systemic Hypertension

- **Sleep Heart Health Study (a cross sectional analysis >6000 patients) showed a linear relationship between mean systolic and diastolic BP and OSA severity[1]**
- **A Canadian population based study had shown[2]**

  Each apneic event /hour increased the odds for hypertension by 1%

  Each 10% reduction in nocturnal O_2 saturation increased the likelihood of hypertension developing by 13%

([1]Nieto FJ et al. JAMA 2000; 283: 1829-36. [2]Lavie P et al. BMJ 2000; 320: 479-82)

OSAS and Systemic Hypertension

- A prospective cohort study of 2470 participants aged > 40 years without baseline hypertension or not on antihypertensive medication
- A significant relationship between the risk of developing hypertension and increasing baseline AHI
- This association was lost after adjustment for BMI
- A modest influence of an AHI greater than 30 on hypertension could not be excluded

(O'Connor GT et al. The Sleep Heart Health Study Am J Respir Crit Care Med 2009; 179: 1159-64)

OSAS and Systemic Hypertension

- A study of 1180 subjects (30-70yrs.) in Spain
- Randomly sampled and followed up for 7.5 years for incidental hypertension
- The risk of developing hypertension significantly increased with higher respiratory disturbance index(RDI)
- The significance was lost once adjusted for age and BMI.

(Cano-Pumarega I et al . Am J Respir Crit Care Med 2011; 184: 1299-1304)

OSAS and Systemic Hypertension

- CPAP has been shown to acutely attenuate sympathetic drive and nocturnal BP in OSA[1]
- Observational studies from uncontrolled and highly selected populations have suggested improvements in BP control with CPAP[2]
- A meta-analysis of 12 placebo-controlled randomised trials (n=572) found a statistically pooled reduction in mean BP of 1.69 mm Hg with CPAP treatment[3]
- Most of these trials were limited to normotensive individuals

([1]Dimsdale JE et al. Hypertension 2000; 35: 144-47. [2]Pepperell JE et al. Lancet 2002; 359: 204-10. [3]Haentjens et al. Arch Intern Med 2007; 167: 757-64)

OSA and Resistant Hypertension

- Resistant hypertension is (RHTN) defined as uncontrolled blood pressure ≥ 140/90 mmHg on an optimally dosed three-drug regimen, ideally including a diuretic
- Increased levels of aldosterone in OSA
- Significant correlation between aldosterone levels and severity of OSA
- 41 patients with RHTN: 96% of men and 65% of women an AHI of ≥10
- Aldosterone may cause chronic parapharyngeal fluid retention

Kumar N et al. Integrated Blood Pressure Control. 2013; 6: 139-151;
Logan AG et al. J Hypertens 2001; 19: 2271-2277

OSAS and Systemic Hypertension

- **The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC-VII) now lists sleep apnea as a significant cause of secondary hypertension**

**(US Department of Health and Human Services. The National Heart, Lung, and Blood Institute: The seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. 2003.
Available at: http://www.nhlbi.nih.gov/guidelines/hypertension/ Accessed September 20, 2010)**

OSAS and Pulmonary Hypertension

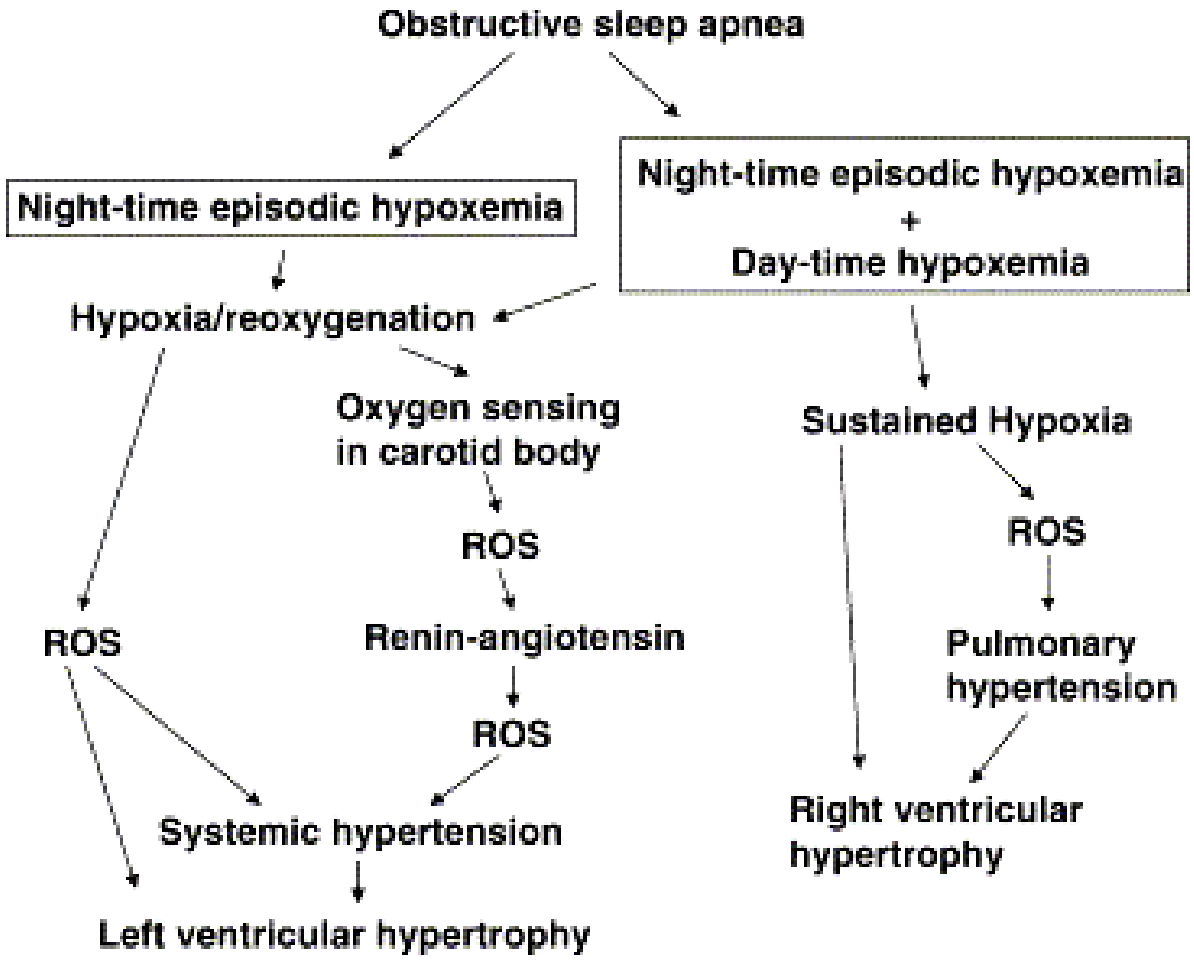
- **Pulmonary hypertension is defined as a mean pulmonary arterial pressure >25 mm Hg at rest or > 30 mm Hg with exercise as measured by right heart catherisation**
- **The prevalence of PH in OSA is reported to vary from 17 to 52%**
- **However, there are no population based data to know the prevalence of PH in OSA**

OSAS and Pulmonary Hypertension

- In a study of patients with OSA with no clinically significant cardiac and pulmonary disease, 41% had PH
- There was no difference in AHI, BMI, smoking history and lung function between patients with PH and those without PH*
- A placebo-controlled randomised cross-over trial of CPAP and sham CPAP over 12 weeks has been reported in 23 patients with OSA**
- CPAP therapy reduced PASP in all patients with OSA, more so in those with PH at baseline

(* Sajkov D et al. Am J Respir Crit Care Med 1994; 149: 416-22.
** Arias MA et al. Eur Heart J 2006; 27: 1106-13)

Role of Reactive Oxygen Species in Cardiovascular Changes in OSAS



(Suzuki YJ et al. Free Radical Biology and Medicine 2006;40:1683-1692)

Cardiac Arrhythmias and Cardiovascular Mortality

- **SHHS showed that, compared with subjects with respiratory disturbance index (RDI) <5, those with severe OSA (RDI >30) had higher rates of atrial fibrillation, non sustained VT, ectopic ventricular beats and Ventricular arrhythmias**
- **Bradyarrhythmias are also commonly reported in OSA, may correlate with severity and can occur with a structurally normal heart**
- **However, a causative role for sleep apnea in serious arrhythmias or sudden death has not been proven**

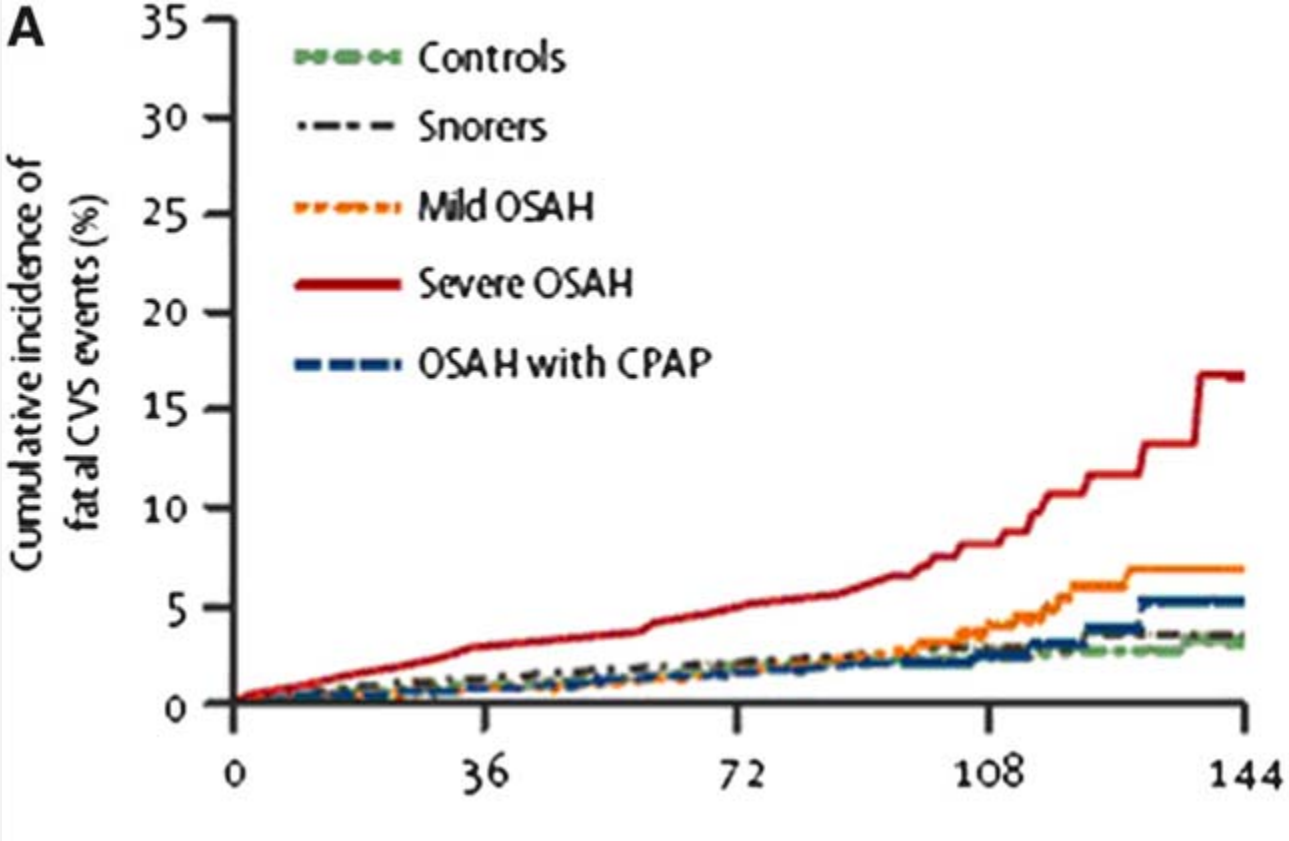
(Mehra R et al. Am J Respir Crit Care Med 2006; 173: 910-16. Grimm W et al Am J Cardiol 2000; 86: 688-92)

OSAS and Heart Failure

- There is a close link between OSA and heart failure (HF) by their close association with aging and obesity
- The Framingham study had shown that increasing BMI is directly correlated with incident HF (may be mediated in part by OSA)
- Incident atrial fibrillation, an important risk factor for HF is also associated with the degree of oxyhemoglobin desaturation in OSA

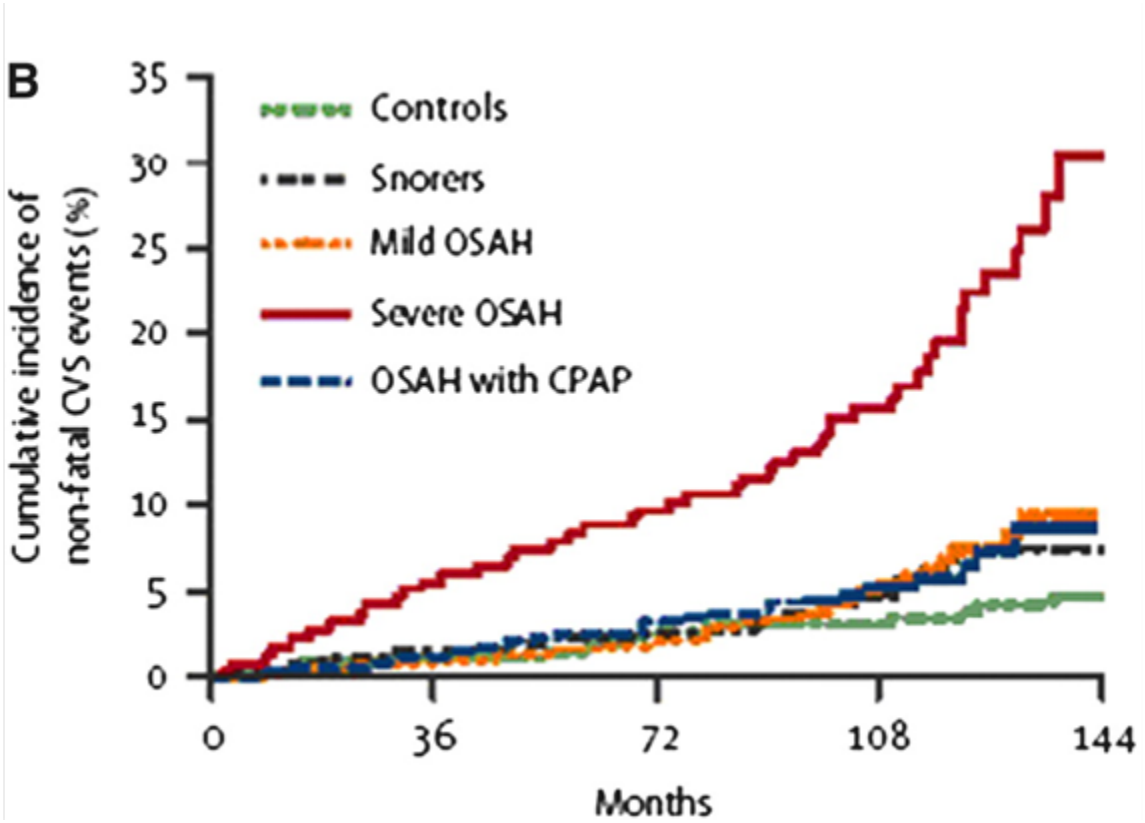
(Sin DD et al. Am J Respir Crit Care Med 1999; 160: 1101-06. Kenchaiah S et al. N Engl J Med 2002; 347: 305-13. Gami AS J Am Coll Cardiol 2007; 49: 565-71)

Men with Fatal CV Events (More than 10 Years Follow-up)



(Marin JM et al. Lancet 2005;365:1046-53)

Men with Non-fatal CV Events (More than 10 Years Follow-up)



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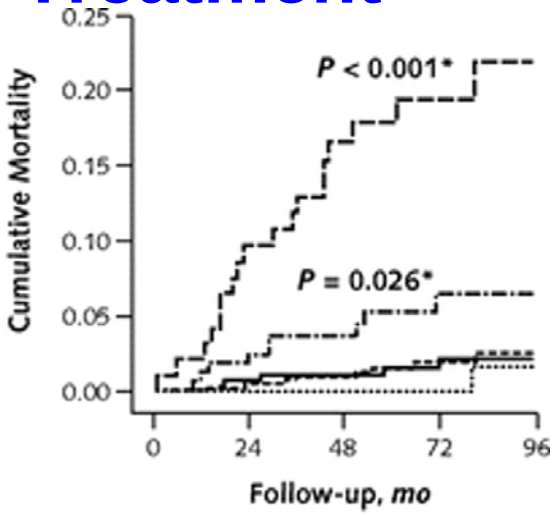
CV Mortality in Women with OSA with or without CPAP Treatment



Patients at risk, *n*

AHI <10 (control group)	277	255	198	102	23
AHI of 10–29 and treated with CPAP	155	140	102	55	18
AHI ≥30 and treated with CPAP	419	381	280	148	48
AHI of 10–29 and untreated	166	146	102	49	12
AHI ≥30 and untreated	93	78	55	28	7

— AHI <10
····· AHI of 10–29 and treated with CPAP
---- AHI of 30 and treated with CPAP
–·– AHI of 10–29 and untreated
– – – AHI of 30 and untreated

(Campos-Rodriguez F et al. Ann Intern Med 2012;156:115-122)

CV Mortality in Women with OSA with or without CPAP Treatment

- **Severe OSA is associated with cardiovascular death in women and adequate CPAP treatment may reduce this risk**

(Campos-Rodriguez F et al. Ann Intern Med 2012;156:115-122)

OSAS and Metabolic Syndrome

- **OSA has been independently associated with metabolic syndrome**
- **It has been suggested that OSA may contribute to the development of metabolic syndrome**
- **Chronic intermittent hypoxia and sleep deprivation with sleep loss may play a role to trigger inflammation**
- **OSA may be a risk factor for metabolic syndrome**

Core Components of Metabolic Syndrome

- **Abdominal obesity**
- **Insulin resistance or glucose intolerance**
- **Hypertension**
- **Low serum high-density lipoprotein**
- **Elevated serum triglyceride**

(Metabolic syndrome: three of these five criteria)

(Tasali E and Ip MSM. Proc Am Thorac soc 2008; 5: 207-217)

Features associated with Metabolic Syndrome

- Pro inflammatory state
- Pro Thrombotic state
- Hyperleptinemia
- Hypoadiponectinemia
- Hyperuricemia
- Endothelial dysfunction
- Microalbuminuria

OSA and Type2 Diabetes Mellitus

- **Population and clinical based studies have indicated an independent association between OSA and altered glucose metabolism**
- **However, obesity is a major confounder in this relationship**
- **Clinicians are urged to evaluate the risk of OSA in type 2 Diabetes mellitus**
- **Conversely, to assess glucose tolerance in patients with known OSA**

(Tasali E et al. Obstructive sleep apnea and type 2 diabetes: interacting epidemics. Chest 2008, 133, 496-506)

CPAP for Metabolic Syndrome

- **In a double-blind placebo-controlled randomised trial, patients were treated for the obstructive sleep apnea syndrome with 3 months of continuous positive airway pressure (CPAP) followed by 3 months of sham CPAP or vice versa with a wash period of one month in between.**

(Sharma SK et al. N Engl J Med 2011; 365: 2277-86)

Study Overview

CPAP therapy lowered blood pressure and ameliorated metabolic abnormalities.

(Sharma SK et al. N Engl J Med 2011;365:2277-2286)

OSAS and Incident Stroke

- **The incidence of stroke was studied in a geographically diverse, community-based sample of male and female participants in the SHHS, a multicenter prospective study**
- **Based on 8 years of prospective data from this study, it has been observed that modest to severe levels of sleep apnea are associated with an approx. three-fold increased risk of ischemic stroke in men**

(Redline S et al. Am J Respir Crit Care Med 2010; 182: 269-77)

OSA and Neurocognitive Deficits

- **Neurocognitive deficits occur with a high frequency in OSA**
- **These deficits can affect any cognitive domain including learning, memory and attention**
- **It has been suggested that severe sleep apnea can increase the risk of dementia in the elderly**

OSA and Neurocognitive Deficits

- **Impaired mood, reduced vigilance, impaired concentration and reduced memory**
- **Impaired performance in surgical skills, anesthesia administration, intubation and EKG interpretation**

(Weinger MB and Ancoli-Israel. JAMA 2002; 287: 955-957)

OSA and Erectile Dysfunction

- **Erectile dysfunction (ED) is common in patients with OSA**
- **In a prospective study of non-diabetic men under the age of 60 years with newly diagnosed OSA, ED was present in 45.6% and 27.2% had diminished libido***
- **The oxygenation nadir has the greatest association with the development of ED****
- **Treatment of OSA with CPAP has been found to improve erectile function***

(*Dombrowsky J et al. Sleep. 2012;35:A0574
****Budweiser S et al. J Sex Med. 2009;6:3147-3157)**

Other Medical Consequences

- Daytime sleepiness
- Loss of alertness
- Memory deficits
- Reduced vigilance
- Impaired executive function
- Increased risk for automobile and occupational accidents
- Decreased quality of life


Thank you

Vallabhbhai Patel Chest Institute

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The National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) Report

- **Recommends five variables with set threshold values for each variable for clinical identification of Metabolic Syndrome**
    1. **Hypertension**
    2. **Insulin resistance or glucose intolerance**
    3. **Low serum high-density lipoprotein (HDL) cholesterol**
    4. **Elevated serum triglyceride**
    5. **Abdominal obesity**
- **Subjects meeting three of these five criteria are classified as having metabolic syndrome**

(JAMA 2001;285:2486–2497)

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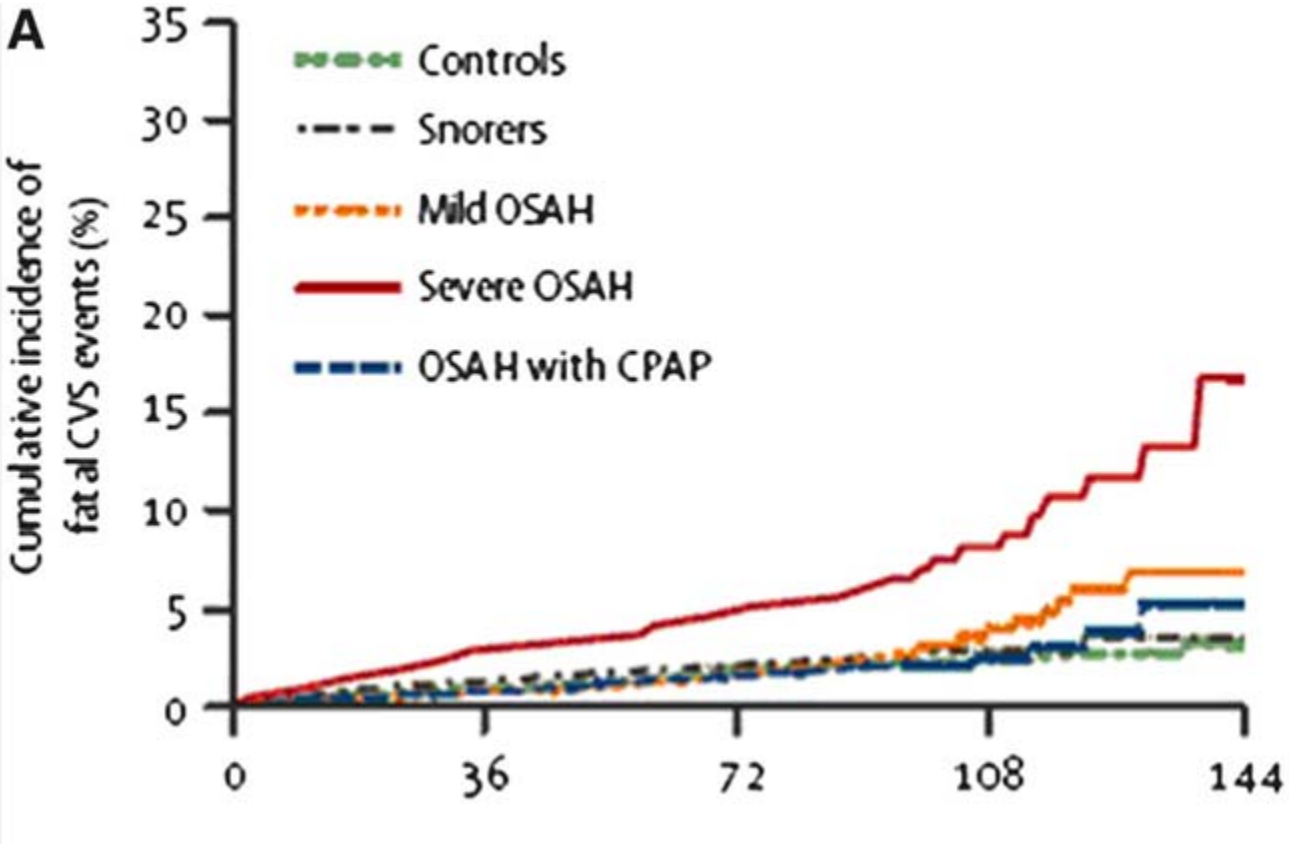

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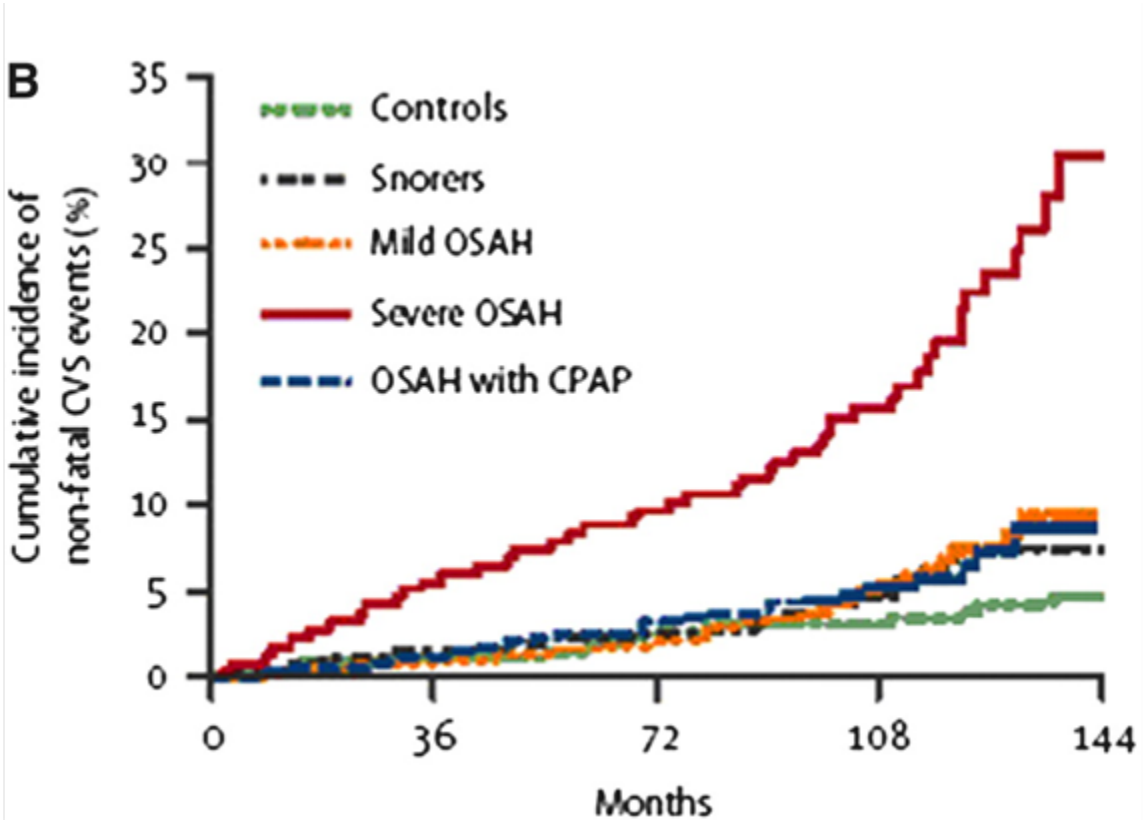

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Acute cardiovascular stressors in OSAS

- **Repetitive episodes of upper airway narrowing and/or occlusion**
  - **Hypoxemia**
  - **Re oxygenation**
  - **Swings in intra thoracic pressure**
  - **Central nervous arousals**
- **These effects are cumulative over time leading to disruption of CV homeostatic mechanisms**
  - **Daytime abnormalities in sympathetic nervous system function and heart rate variability**

(Golbin JM et al. Proc Am Thorac Soc 2008; 5: 200-06)