# Obstructive Sleep Apnea and Cardiovascular Disease

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# Disclosure

In the past 24 months, I have not had any financial relationships with any ineligible companies.

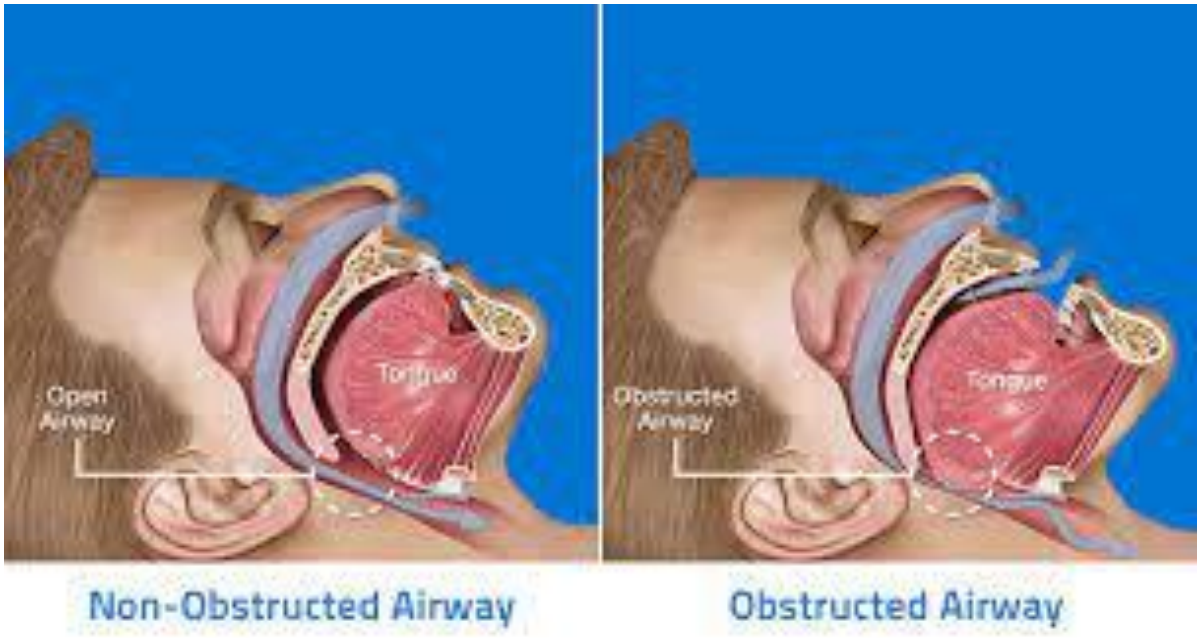
# Objectives

- Review the epidemiology and pathophysiology of obstructive sleep apnea (OSA)
- Review the literature regarding OSA and cardiovascular disease (CVD)

# Obstructive Sleep Apnea

| | |
|---|---|
| **Definition of OSA** | Repetitive and reversible upper airway obstruction occurring during sleep |
| **Hypopnea** | Reduced airflow during sleep |
| **Apnea** | Absent airflow during sleep |
| **Physiologic Manifestation** | Cortical arousal (determined by EEG) or oxygen desaturation >3% from baseline |
| **Diagnostic Threshold** | Greater than 5 events per hour |

# Obstructive Sleep Apnea




https://www.centralavedentalny.com/blog/what-is-obstructive-sleep-apnea

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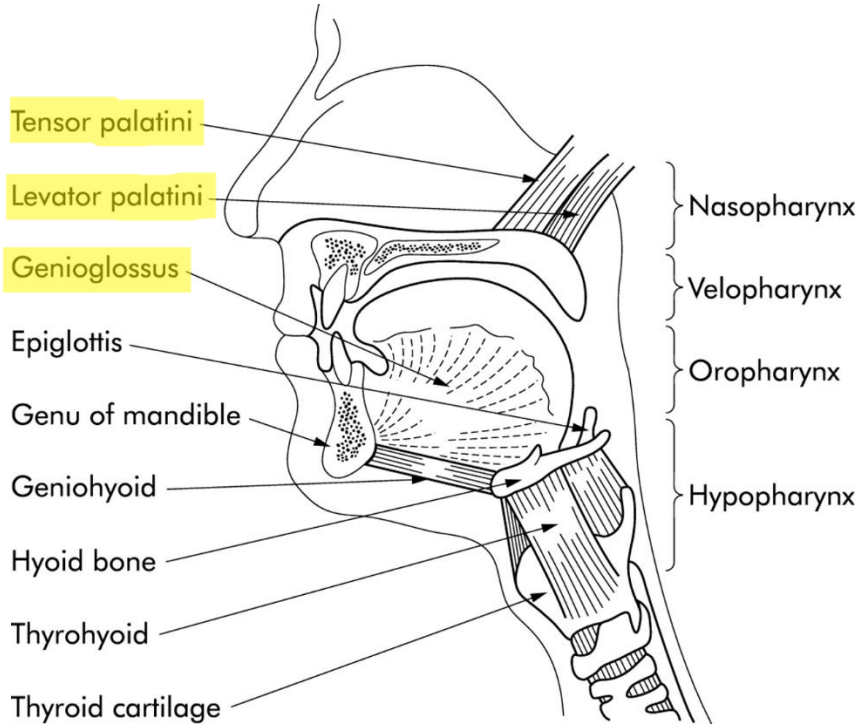
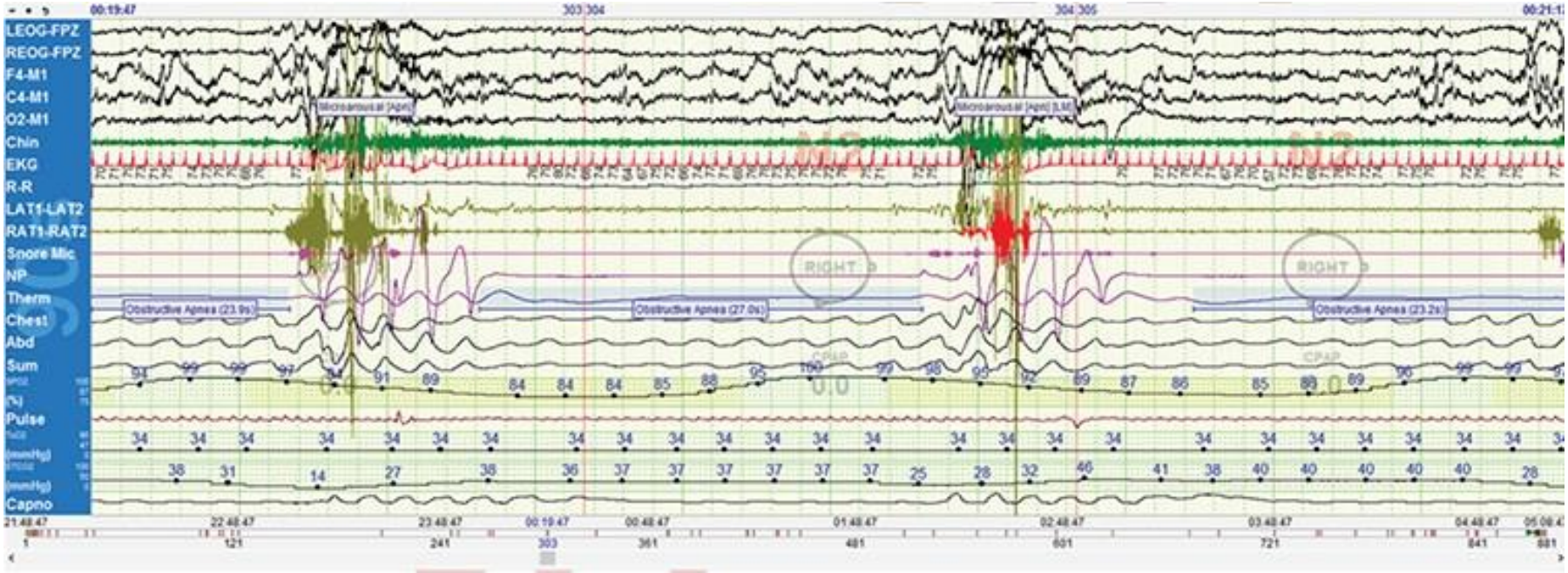
# Obstructive Sleep Apnea




Poothrikovil et al

# Obstructive Sleep Apnea

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# Epidemiology

- Sleep disordered breathing (SDB) is underrecognized throughout the world
  - 22 million Americans are estimated to have sleep apnea
  - 80% of cases with moderate to severe obstructive sleep apnea are undiagnosed

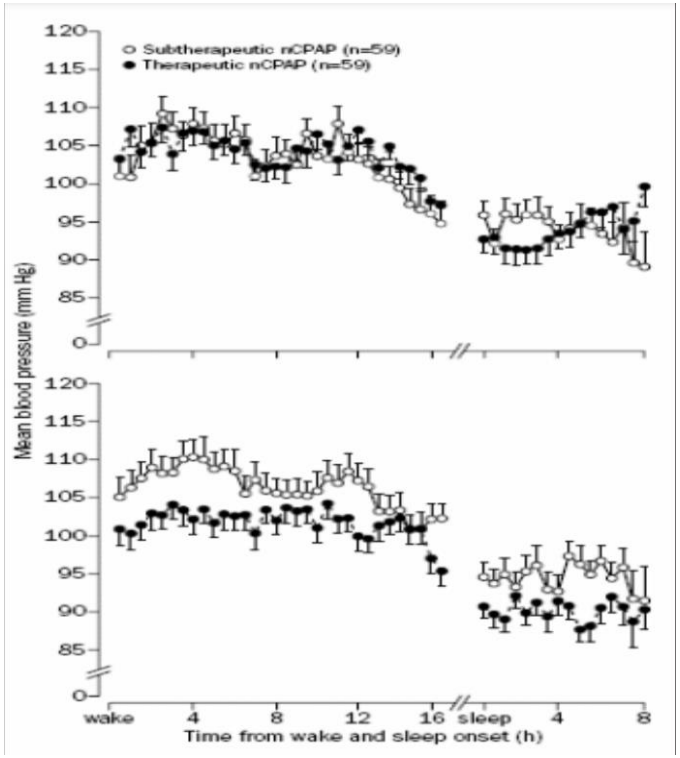
- Lancet Resp Medicine, Zhang et al (Aug 2025)
  - Global burden of obstructive sleep apnea will significantly increase over the next 3 decades
  - Prevalence of OSA will increase from 34.3% to 46.2% in the next 30 years (total case volume of 76.6 million cases)

# OSA and CVD

- OSA is independently associated with
  - HTN
  - Stroke
  - CAD
  - HF
  - Atrial fibrillation

- Metabolic disorders
  - T2DM
  - Obesity
  - NAFLD

# OSA and CVD




Initiation of CPAP (no change in BP)

4 weeks of CPAP: reduction in BP

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# OSA and CVD

**Table 6**—Mortality Risk* With Untreated Sleep-Disordered Breathing (n = 1396)**

| Baseline AHI category | All-cause mortality Hazard Ratio (95% CI) | Cardiovascular mortality Hazard Ratio (95% CI) |
|---|---|---|
| None: 0 - < 5 | Reference | Reference |
| Mild: 5 - < 15 | 1.4 (0.7, 2.6) | 1.3 (0.4, 4.1) |
| Moderate: 15 - < 30 | 1.7 (0.7, 4.1) | 1.5 (0.3, 7.3) |
| Severe: ≥30 | 3.8 (1.6, 9.0) | 5.2 (1.4, 19.2) |
| | P trend = 0.004 | P-trend = 0.03 |

*Hazard ratios adjusted for age, age$^2$, sex, body mass index, and body mass index$^2$

**126 persons who reported usual use of continuous positive air pressure (CPAP) ≥ 4 nights per week were excluded from sample

AHI denotes number of apnea and hypopnea events per hour of sleep, CI denotes confidence interval

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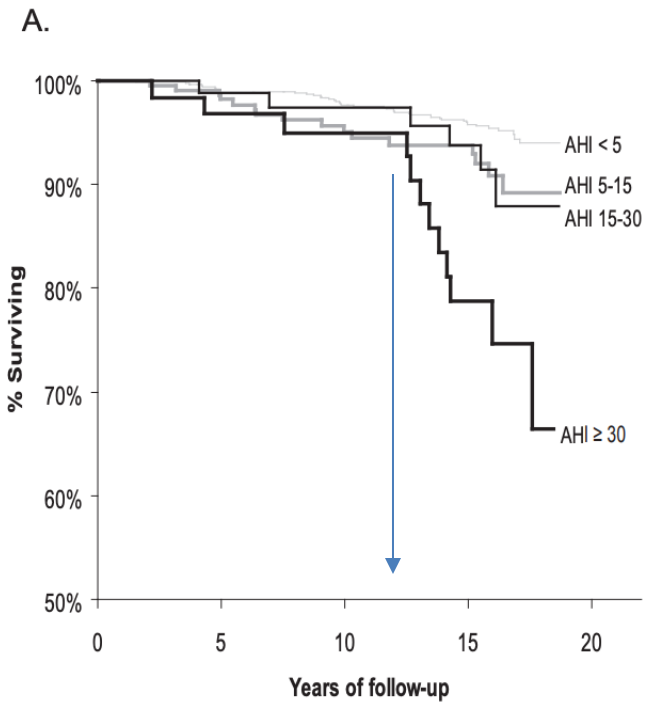
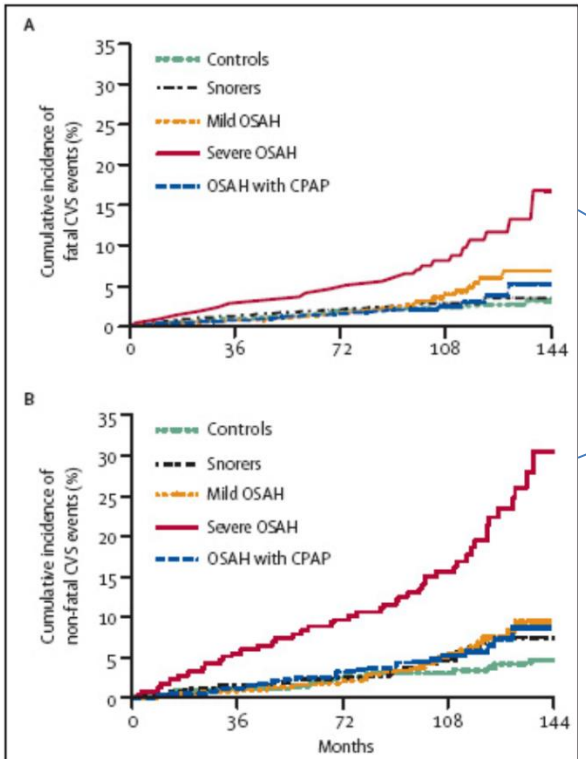
# OSA and Mortality




Increase in mortality with severe OSA begins 10-15 years after diagnosis

# OSA and CVD




Increase in CV events (fatal and non fatal) with untreated severe OSA

# Intermittent Hypoxia

- Intermittent hypoxia (IH) is the main mechanism associated with cardiovascular and metabolic complications of OSA

- Primarily studied in animal models mimicking the repetitive oxygen desaturation cycle seen in OSA
  - intima-media thickness increased in the aorta after exposure to IH
  - generates atrial remodeling and arrythmias
  - responsible for increase in myocardial sensitivity to ischemia/reperfusion
  - induces remodeling (hypertrophy, apoptosis and fibrosis) as well as contractile dysfunction –> leading to heart failure

# Sympathetic activation

- During sleep, parasympathetic system predominates
- Patients with OSA have an increase in circulating or urinary catecholamines that directly correlates with AHI
- 1-2 weeks of IH showed signs of increased sympathetic activation (decrease in baroreflex sensitivity)
- Cortical arousals without hypoxia also cause sympathetic activation

# Treatment of OSA and CV risk

- 4 major RCT's evaluating the effect of CPAP as a treatment for OSA in regards to cardiovascular risk
  - Barbe et. al (primary prevention, no prior CV event)
  - RICCADSA
  - SAVE
  - ISAAC

- All 4 failed to demonstrate a reduction in cardiovascular outcomes with the use of PAP in patients with OSA for either primary or secondary prevention of CVD

- Applying these RCT's to all patients with OSA is highly flawed

# Limitations of RCTs

- Limited PAP adherence
  - Average of 3-5 hours per night across all 4 trials
  - Post hoc analysis demonstrating benefit in those who are more adherent to PAP may be confounded by “healthy user” effect

- Each of these trials were performed in ”non-sleepy” patients
  - CPAP has previously been established to improve daytime sleepiness and has shown a reduction in car/workplace accidents
  - Would be unethical to withhold CPAP in a patient with OSA who exhibits excessive daytime sleepiness
  - Non-sleepy patients are less adherent to PAP

# Limitations of RCTs

- PAP for primary prevention
  - Short term follow up in Barbe et al (4 years) probably underestimates the benefit of CPAP
- PAP for secondary prevention
  - Effect of PAP likely outweighed by the benefits of other CV therapies such as antihypertensives, statins, etc.
- OSA is a heterogenous disease
  - Patient with AHI of 15, daytime sleepiness and significant nighttime hypoxemia is at much greater CVD risk than patient with AHI of 15, no hypoxemia and not sleepy

# Limitations of RCTs

- Recruitment
  - Patients were recruited from non-sleep clinic settings
  - Racial and ethnic inclusion not representative of US population
  - Limited inclusion of women

- Despite the lack of “gold standard” RCT’s demonstrating benefit of CPAP on CV risk reduction, observational studies, systematic reviews and meta-analyses continue to elucidate which patients may benefit most from CPAP usage

# Other Literature

Original Investigation | Pulmonary Medicine

## Positive Airway Pressure, Mortality, and Cardiovascular Risk in Older Adults With Sleep Apnea

Diego R. Mazzotti, PhD; Lemuel R. Waitman, PhD; Jennifer Miller, PhD, APRN-NP, ACNPC-AG; Krishna M. Sundar, MD; Nancy H. Stewart, DO, MS; David Gozal, MD, MBA, PhD; Xing Song, PhD; for the Greater Plains Collaborative

### Key Points

**Question** Is positive airway pressure therapy associated with lower mortality and incidence of major adverse cardiovascular events among Medicare beneficiaries with obstructive sleep apnea?

**Findings** In this cohort study of 888 835 older adults with obstructive sleep apnea in the central US, participants with evidence of positive airway pressure therapy initiation had significantly lower all-cause mortality and major adverse cardiovascular events incidence risk when compared with those without evidence of therapy.

**Meaning** These results might inform future trials assessing the importance of obstructive sleep apnea therapies toward minimizing cardiovascular risk and mortality in older adults.

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# Other Literature

ERJ OPEN RESEARCH
REVIEW
M. BRADICICH ET AL.

## Cardiovascular effects of obstructive sleep apnoea and effects of continuous positive airway pressure therapy: evidence from different study models

Matteo Bradicich [1], Martino F. Pengo [2], Joerg Steier [3] and Esther Irene Schwarz [1,4]

[1]Department of Pulmonology, University Hospital Zurich, Zurich, Switzerland. [2]Department of Cardiovascular, Neural and Metabolic Sciences, IRCCS Istituto Auxologico Italiano and Department of Medicine and Surgery, University of Milano-Bicocca, Milan, Italy. [3]Lane Fox Respiratory Unit and Sleep Disorders Centre, Guy's and St Thomas' NHS Foundation Trust and Centre for Human Applied Physiological Science, Faculty of Life Sciences and Medicine, King's College London, London, UK. [4]Centre of Competence Sleep and Health, University of Zurich, Zurich, Switzerland.

# Other Literature

*Results and conclusions* There is high-level evidence of a causal relationship between OSA and arterial hypertension and endothelial dysfunction, as well as on higher MACE incidence among subgroups of patients with untreated OSA. The cardiovascular effects of OSA depend on the severity of OSA, symptoms, phenotype and comorbidities. The blood pressure-lowering effect of CPAP is mainly observed in uncontrolled and treatment-resistant hypertension. The MACE risk reduction in OSA depends on good long-term CPAP adherence. Younger, sleepy patients with more severe OSA, higher hypoxaemic burden and without overt cardiovascular end-organ disease may particularly benefit from CPAP treatment in terms of cardiovascular risk reduction. Randomised controlled trials of CPAP or other effective OSA treatments in primary cardiovascular prevention and in patients at highest risk are lacking.

# Other Literature

ORIGINAL ARTICLE

## Cardiovascular Benefit of Continuous Positive Airway Pressure in Adults with Coronary Artery Disease and Obstructive Sleep Apnea without Excessive Sleepiness

Ali Azarbarzin[1], Andrey Zinchuk[2], Andrew Wellman[1], Gonzalo Labarca[1], Daniel Vena[1], Laura Gell[1], Ludovico Messineo[1,3], David P. White[1], Daniel J. Gottlieb[1,4], Susan Redline[1], Yüksel Peker[1,5,6,7,8*], and Scott A. Sands[1*]

[1]Division of Sleep and Circadian Disorders, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts; [2]Pulmonary, Critical Care, and Sleep Medicine, Yale Medicine, Yale University, New Haven, Connecticut; [3]Adelaide Institute for Sleep Health, Flinders Health and Medical Research Institute, Flinders University, Bedford Park, Adelaide, South Australia, Australia; [4]Medical Service, VA Boston Healthcare System, Boston, Massachusetts; [5]Department of Pulmonary Medicine, Koc University, Istanbul, Turkey; [6]Department of Molecular and Clinical Medicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden; [7]Department of Clinical Sciences, Respiratory Medicine, and Allergology, Faculty of Medicine, Lund University, Lund, Sweden; and [8]Division of Pulmonary, Allergy, and Critical Care Medicine, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania

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# Other Literature

**Measurements and Main Results:** The CPAP-related reduction in risk increased progressively with increasing pretreatment ΔHR (interaction hazard ratio [95% confidence interval], 0.49 [0.27 to 0.90] per SD increase in ΔHR; $P < 0.05$). This means that in patients with a ΔHR of 1 SD above the mean (i.e., 10 beats/min), CPAP was estimated to reduce cardiovascular risk by 59% (6% to 82%) ($P < 0.05$), but no significant risk reduction was estimated in patients with a mean ΔHR (6 beats/min; CPAP risk reduction, 16% [−53% to 54%]; $P = 0.6$).

**Conclusions:** The protective effect of CPAP in patients with CAD and OSA without excessive sleepiness was modified by the ΔHR. Specifically, patients with higher ΔHR exhibit greater cardiovascular benefit from CPAP therapy.

**Keywords:** heart rate response; sleepiness; sleep apnea; cardiovascular; clinical trial

# Other Literature

## The hypoxic burden of sleep apnoea predicts cardiovascular disease-related mortality: the Osteoporotic Fractures in Men Study and the Sleep Heart Health Study

**Ali Azarbarzin[1]*, Scott A. Sands[1], Katie L. Stone[2,3], Luigi Taranto-Montemurro[1], Ludovico Messineo[1], Philip I. Terrill[4], Sonia Ancoli-Israel[5,6], Kristine Ensrud[7], Shaun Purcell[1,8], David P. White[1], Susan Redline[1], and Andrew Wellman[1]**

[1]Division of Sleep and Circadian Disorders, Brigham and Women's Hospital and Harvard Medical School, Sleep Disordered Breathing Lab, 221 Longwood Avenue, Boston, MA 02115, USA; [2]Research Institute, California Pacific Medical Center, 550 16th Street, 2nd Floor, San Francisco, CA 94158, USA; [3]Department of Epidemiology and Biostatistics, University of California, San Francisco, 550 16th St, San Francisco, CA 94158, USA; [4]School of Information Technology and Electrical Engineering, The University of Queensland, Brisbane, Australia; [5]Department of Psychiatry, University of California San Diego, 9500 Gilman Drive La Jolla, CA 92093, USA; [6]Department of Medicine, University of California San Diego, 9500 Gilman Drive La Jolla, CA 92093, USA; [7]University of Minnesota and Minneapolis Veterans Affairs Health Care System, 1 Veterans Dr, Minneapolis, MN 55417, USA; and [8]Stanley Center for Psychiatric Research, Broad Institute of MIT & Harvard, 415 Main St, Cambridge, MA 02142, USA

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# Other Literature


**Aims** Apnoea–hypopnoea index (AHI), the universal clinical metric of sleep apnoea severity, poorly predicts the adverse outcomes of sleep apnoea, potentially because the AHI, a frequency measure, does not adequately capture disease burden. Therefore, we sought to evaluate whether quantifying the severity of sleep apnoea by the 'hypoxic burden' would predict mortality among adults aged 40 and older.

**Methods and results** The samples were derived from two cohort studies: The Outcomes of Sleep Disorders in Older Men (MrOS), which included 2743 men, age 76.3 ± 5.5 years; and the Sleep Heart Health Study (SHHS), which included 5111 middle-aged and older adults (52.8% women), age: 63.7 ± 10.9 years. The outcomes were all-cause and Cardiovascular disease (CVD)-related mortality. The hypoxic burden was determined by measuring the respiratory event-associated area under the desaturation curve from pre-event baseline. Cox models were used to calculate the adjusted hazard ratios for hypoxic burden. Unlike the AHI, the hypoxic burden strongly predicted CVD mortality and all-cause mortality (only in MrOS). Individuals in the MrOS study with hypoxic burden in the highest two quintiles had hazard ratios of 1.81 [95% confidence interval (CI) 1.25–2.62] and 2.73 (95% CI 1.71–4.36), respectively. Similarly, the group in the SHHS with hypoxic burden in the highest quintile had a hazard ratio of 1.96 (95% CI 1.11–3.43).

**Conclusion** The 'hypoxic burden', an easily derived signal from overnight sleep study, predicts CVD mortality across populations. The findings suggest that not only the frequency but the depth and duration of sleep related upper airway obstructions, are important disease characterizing features.



**Keywords** Sleep apnoea • CVD mortality • Hypoxic burden • Polysomnography • Apnoea–hypopnoea index


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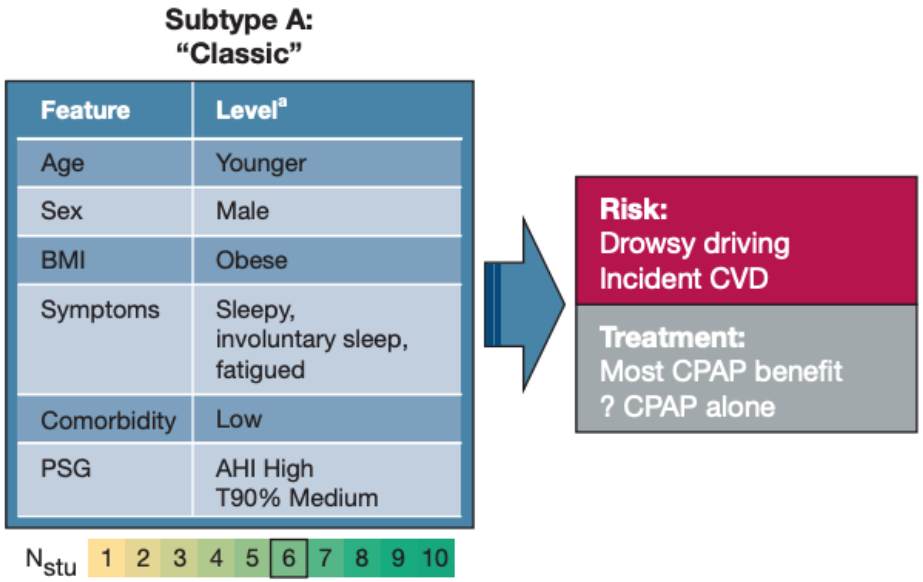
# Beyond the AHI: Precision Medicine

- Comorbidity clusters
- Anatomical variants
  - Absence of complete concentric collapse
- PSG clusters
  - Hypoxemia
  - Arousals
- “Symptom based” clusters
  - Excessively sleepy
  - Disturbed sleep (maintenance insomnia)
  - Minimally symptomatic

# Cluster A

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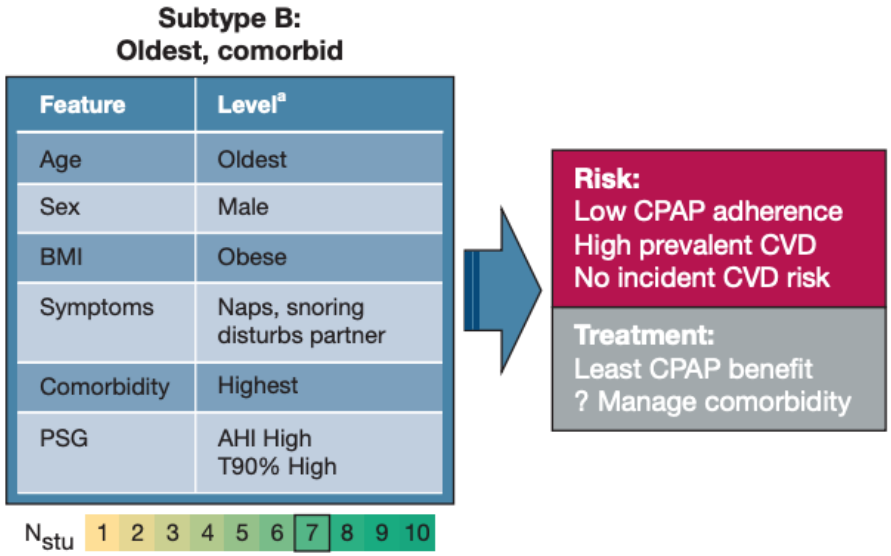
# Cluster B


Subtype B:
Oldest, comorbid
Feature
Level[a]
Age
Oldest
Sex
Male
BMI
Obese
Symptoms
Naps, snoring disturbs partner
Comorbidity
Highest
PSG
AHI High
T90% High
Nstu 1 2 3 4 5 6 7 8 9 10
Risk:
Low CPAP adherence
High prevalent CVD
No incident CVD risk
Treatment:
Least CPAP benefit
? Manage comorbidity

# Cluster C

**Subtype C:**
**Female, insomnia**

| Feature | Level[a] |
|---|---|
| Age | Middle age |
| Sex | Female |
| BMI | Overweight-obese |
| Symptoms | Difficulty falling asleep, early awakening, nonrestorative sleep |
| Comorbidity | Medium |
| PSG | AHI Medium<br>T90% Medium |

$N_{stu}$ 1 2 3 4 5 6 **7** 8 9 10

**Risk:**
Low CPAP adherence
? Lower incident Stroke

**Treatment:**
Medium CPAP benefit (apneic symptoms, restful sleep)
? CBTi + CPAP

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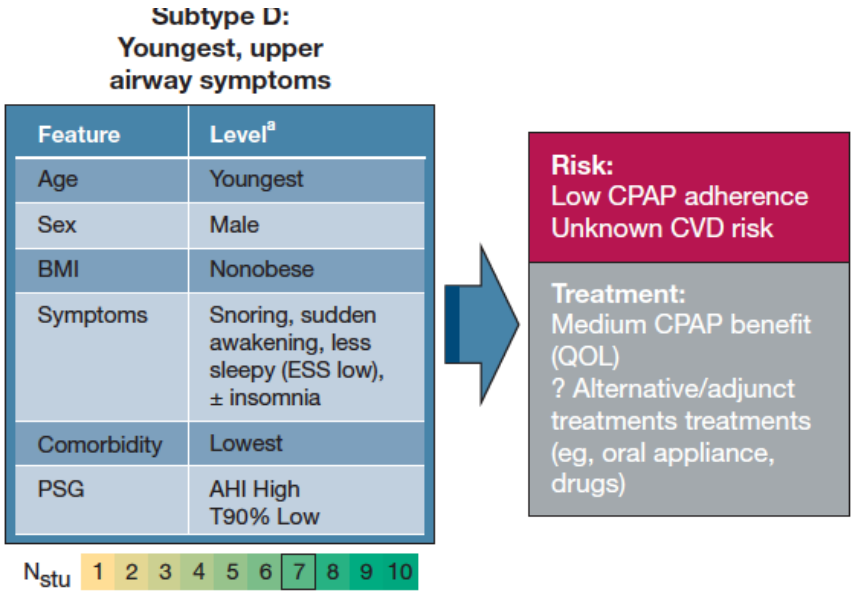
# Cluster D

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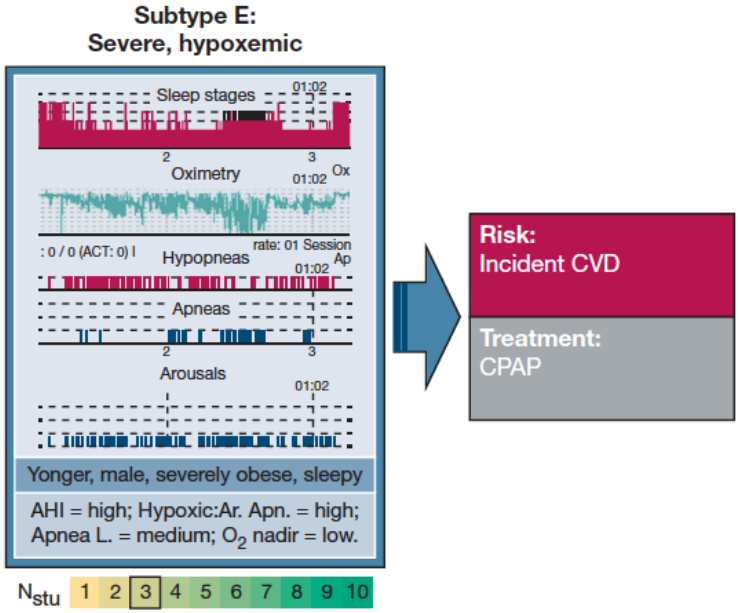
# Cluster E

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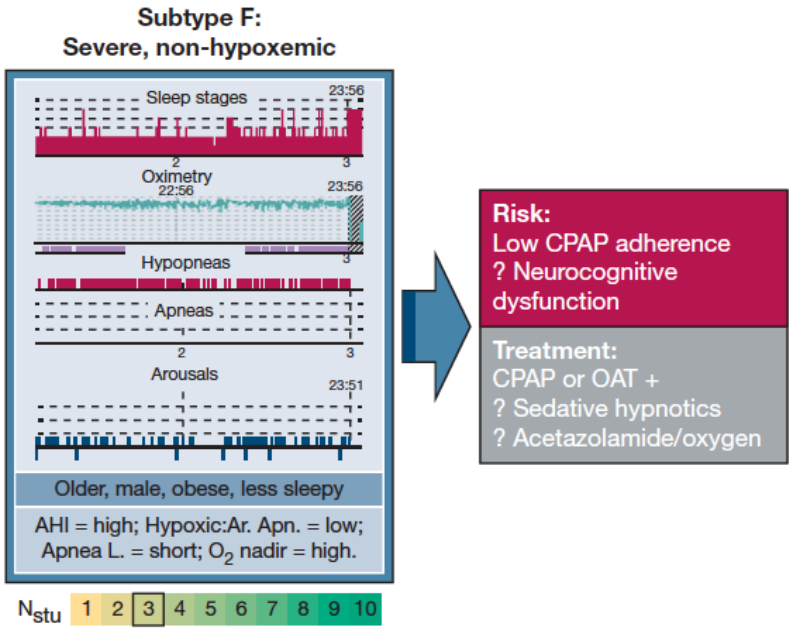
# Cluster F


Subtype F:
Severe, non-hypoxemic
Sleep stages
23:56
2
3
Oximetry
22:56
23:56
Hypopneas
Apneas
2
3
Arousals
23:51
Older, male, obese, less sleepy
AHI = high; Hypoxic:Ar. Apn. = low;
Apnea L. = short; $O_2$ nadir = high.
$N_{stu}$ 1 2 3 4 5 6 7 8 9 10
Risk:
Low CPAP adherence
? Neurocognitive dysfunction
Treatment:
CPAP or OAT +
? Sedative hypnotics
? Acetazolamide/oxygen

# Where do we go from here?

- Early diagnosis
- Reframing the use of CPAP as “primary prevention” for CVD due to OSA
- Further studies to determine which “phenotypic clusters” of OSA benefit the most from CPAP
- Inpatient sleep medicine

# Clinical Pearls in Cardiology

- Heart failure patients with severe sleep disordered breathing do not exhibit classical daytime sleepiness
  - Redeker et al (SLEEP 2010)
- Daytime sleepiness and severity of nocturnal hypoxemia are probably more important than the AHI
- PAP for primary prevention is probably more useful than secondary prevention
  - Identify and treat prior to the onset of CAD, CHF, afib
- Nasal interface is preferred over full facemask for PAP use
  - Don’t give up on them! Try a different mask, daytime sensitization

# Thank You


- Gottlieb, D. Punjabi, N. *Diagnosis and Management of Obstructive Sleep Apnea.* Journal of the American Medical Association. 2020 Apr 14; 323 (14) 1389-1400
- Pepperell et al. *Ambulatory blood pressure after therapeutic and subtherapeutic nasal continuous positive airway pressure for obstructive sleep apnoea: a randomized parallel trial. The Lancet. 359;9302 (Jan 2002) 204-210*
- Young et al. *Sleep Disordered Breathing and Mortality: Eighteen-Year Follow-up of the Wisconsin Sleep Cohort.* SLEEP. 31;8, 2008
- Marin et al. Long-term cardiovascular outcomes in men with obstructive sleep apneoea-hypopnea with or without treatment with continuous positive airway pressure; an observational study. Lancet 2005; 365: 1046-53
- St Onge et al. *Multidimensional Sleep Health: Definitions and Implications for Cardiometabolic Health: A Scientific Statement From the American Heart Association. Circ Cardiovasc Qual Outcomes. May 2025: 18:e000139*
- Cappuccio, F. Miller, M. *Sleep and Cardio-Metabolic Disease. Curr Cardiol Rep* (2017) 19:110
- Zinchuk et al. Phenotypic Subtypes of OSA: A Challenge and Opportunity for Precision Medicine. CHEST. 2020 Feb;157(2): 403-420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