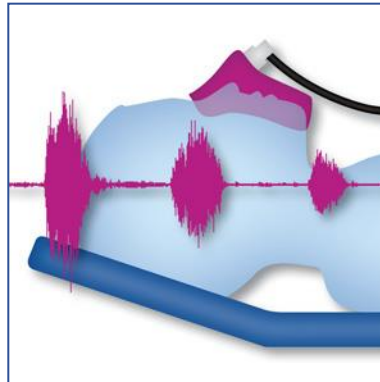


Pneumo Update Europe 2017

9-10 June, Vienna

Sleep Disordered Breathing



Walter McNicholas, Ireland

Objectives

- Most important/relevant publications during 2016 and 2017 in:
 - Obstructive Sleep Apnoea
 - Obesity Hypoventilation Syndrome
 - OSA-COPD overlap
- Highly selected as >2000 publications during 2016 on sleep apnoea alone.

Obstructive Sleep Apnoea

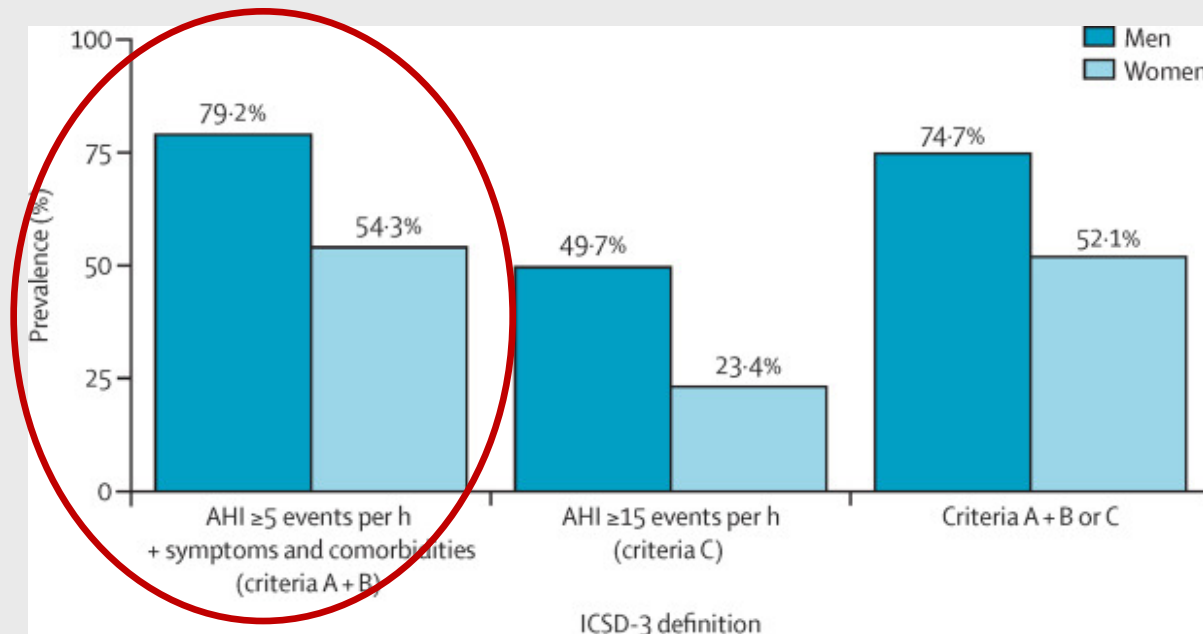
State of the Art

- OSA is highly prevalent and increasing
- Represents one of the most common chronic respiratory disorders
- Increasing recognition that traditional diagnostic criteria based on AHI and sleepiness are outdated
- Traditional gold standard diagnosis based on sleep laboratory testing progressively being replaced by limited ambulatory testing

Lévy P et al. Nature Reviews Disease Primers 2015; 1:1-20.

Prevalence of OSA in the middle to old age general population.

Data from the HypnoLaus cohort (2121 participants) having home PSG

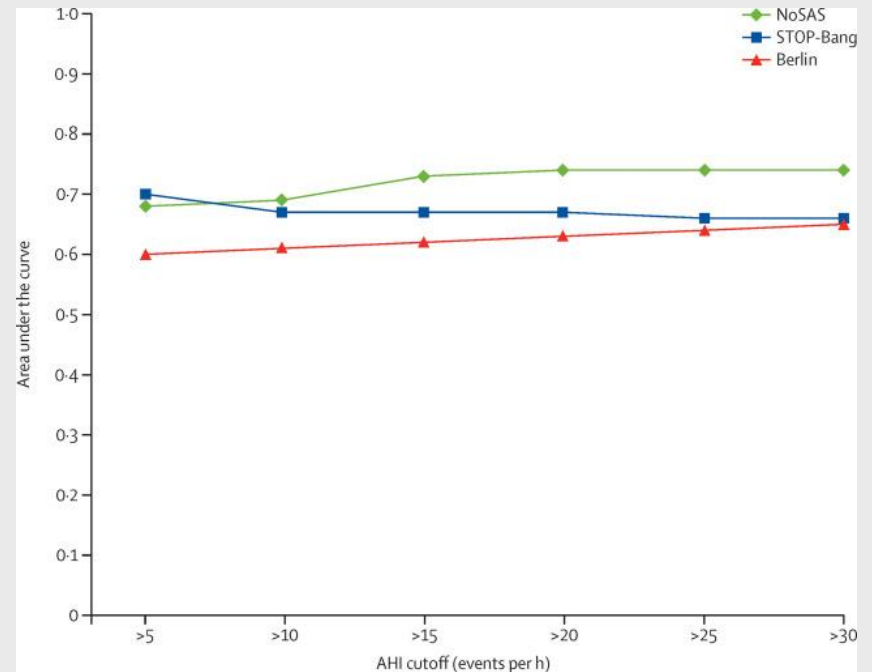
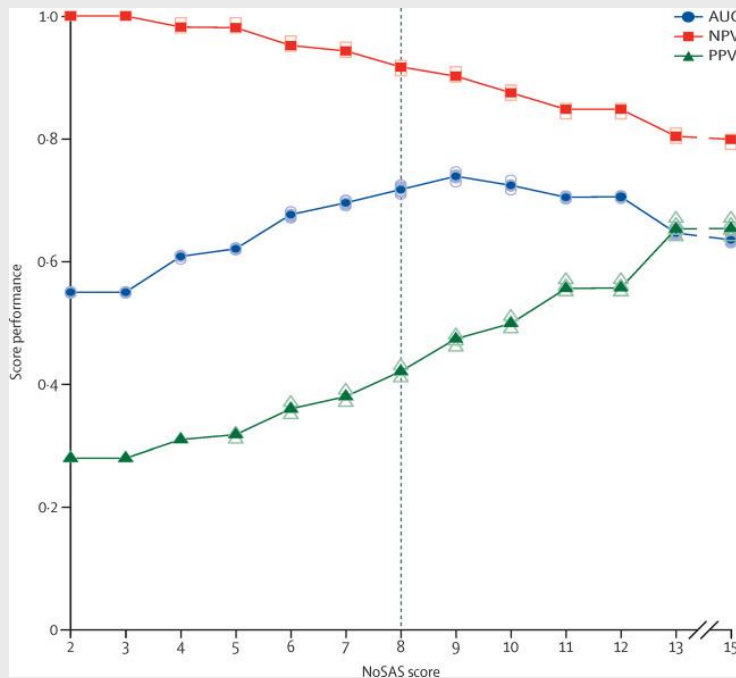


Message: Criteria for the clinical syndrome of OSA are very highly prevalent in this older population.

Heinzer R et al. Lancet Respir Med. 2016 Feb;4(2):e5-6

The NoSAS score for screening of sleep-disordered breathing

- HypnoLaus cohort
- Score based on snoring, BMI, neck circumference, age > 55yr, male sex.
- Comparison of NoSAS with a separate Brazilian cohort also performed well



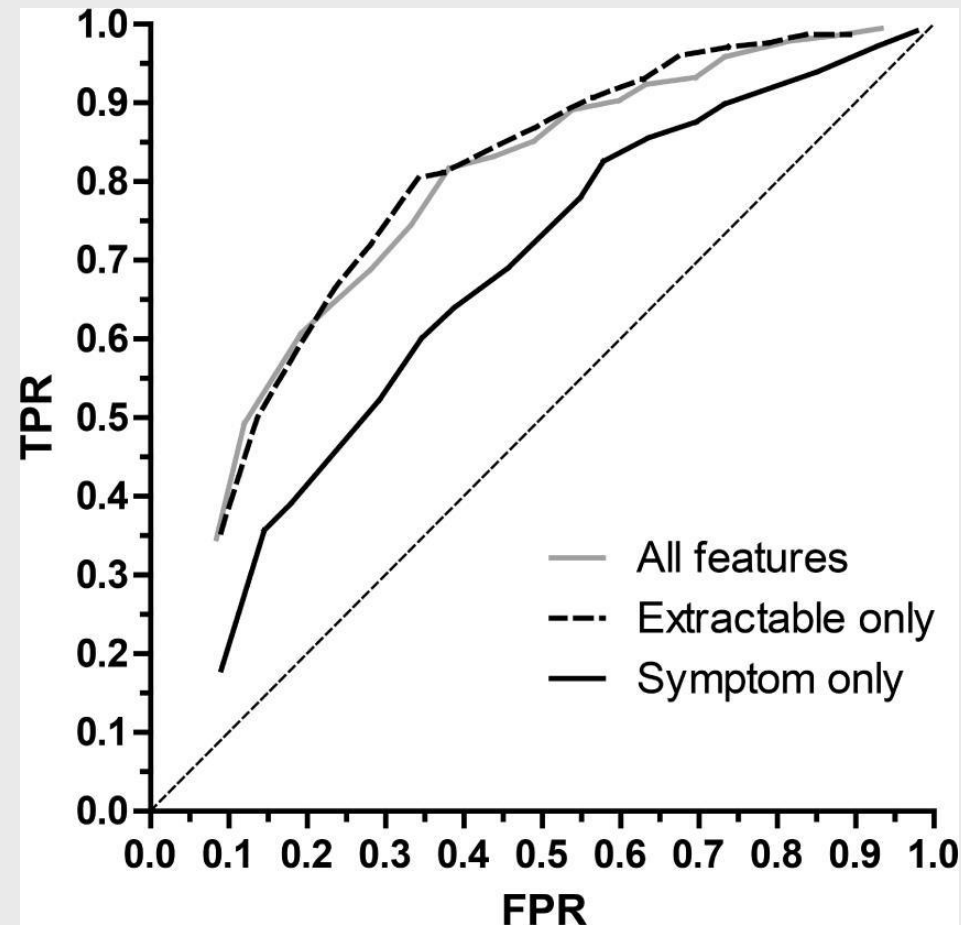
- **Message:** Screening score based on snoring and readily available objective measures provides a good prediction of likely OSA

Marti-Soler H et al. Lancet Respir Med. 2016 Sep;4(9):742-8

Clinical Prediction Models for OSA: Importance of Medical History over Symptoms.

- PSG in 1,922 patients in sleep laboratory
- Self-reported symptoms compared with information from medical records

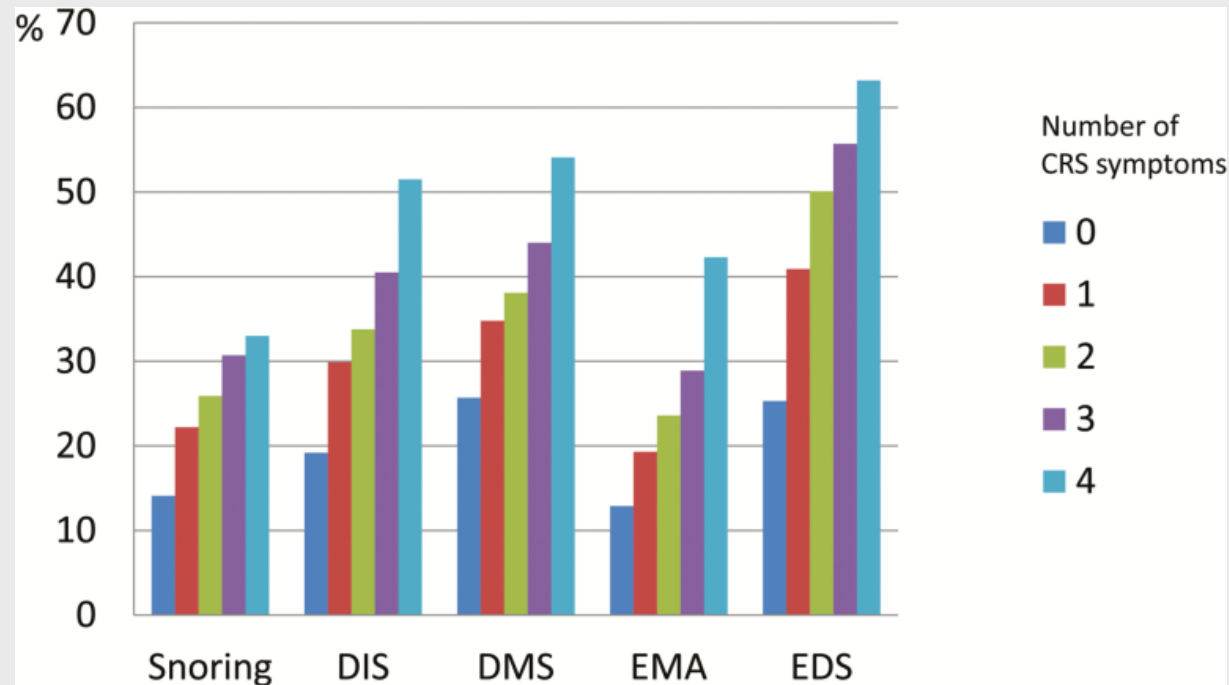
MESSAGE: Variables such as age, sex, BMI, and medical history are superior to classic symptoms of snoring and sleepiness for predicting OSA.



Ustun B et al. J Clin Sleep Med. 2016 Feb;12(2):161-8

Chronic Rhinosinusitis Impairs Sleep Quality: the GA²LEN Study.

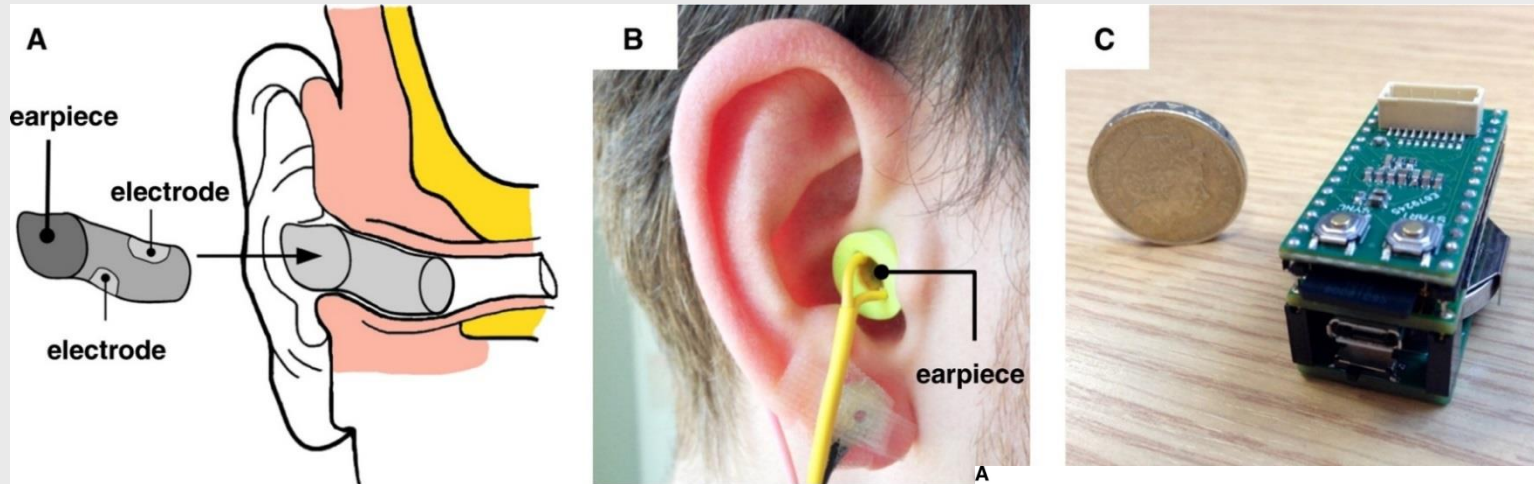
- 45,000 random adults in Sweden - 8.4% had chronic rhinosinusitis (CRS).
- Sleep complaints increased with CRS severity, and significantly different between CRS4 and CRS0 after adjustment for confounding variables



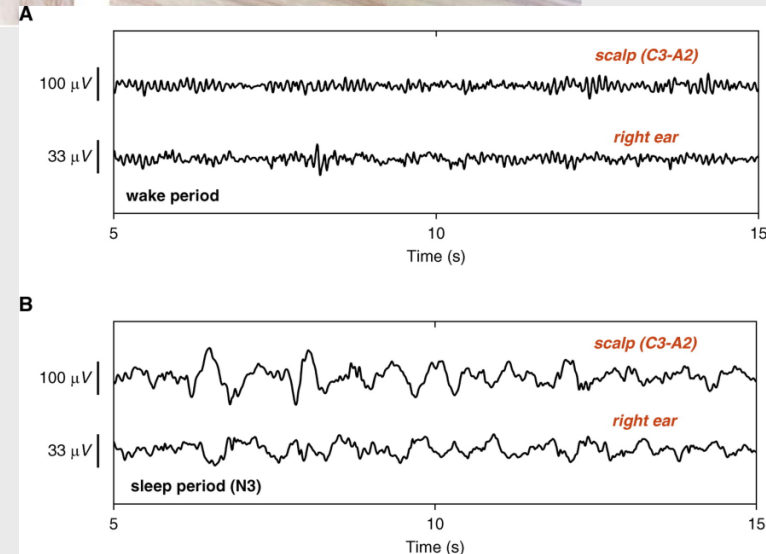
Message: Chronic rhinosinusitis is associated with sleep disturbance and OSA-related symptoms.

Bengtsson C et al. Sleep. 2017 Jan 1;40(1). doi:10.1093/sleep/zsw021

Wearable In-Ear Encephalography Sensor for Monitoring Sleep



- Pilot study of 4 healthy adult males during daytime naps
- Good agreement between sensor and conventional scalp electrodes in identifying nonREM sleep
- Further more extensive studies required to evaluate clinical utility.

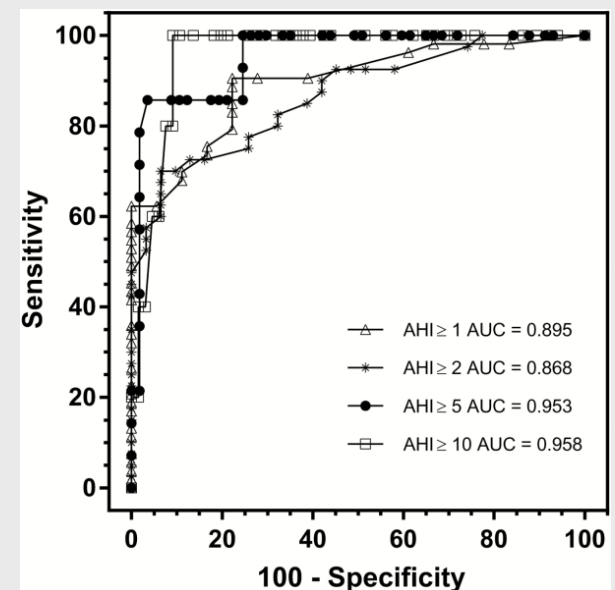
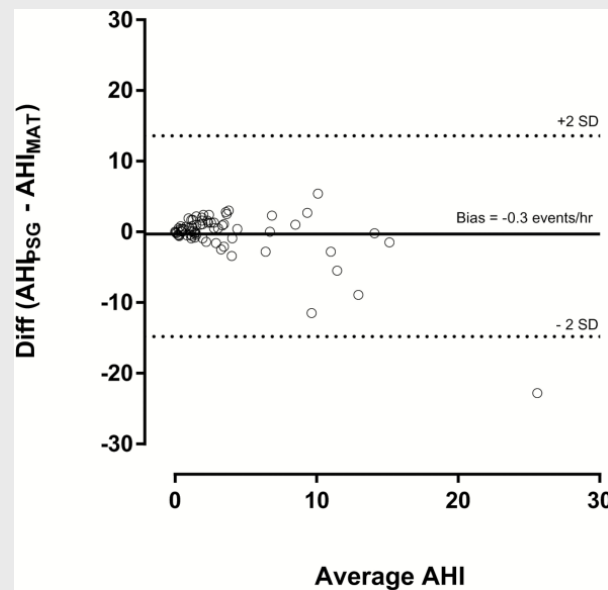
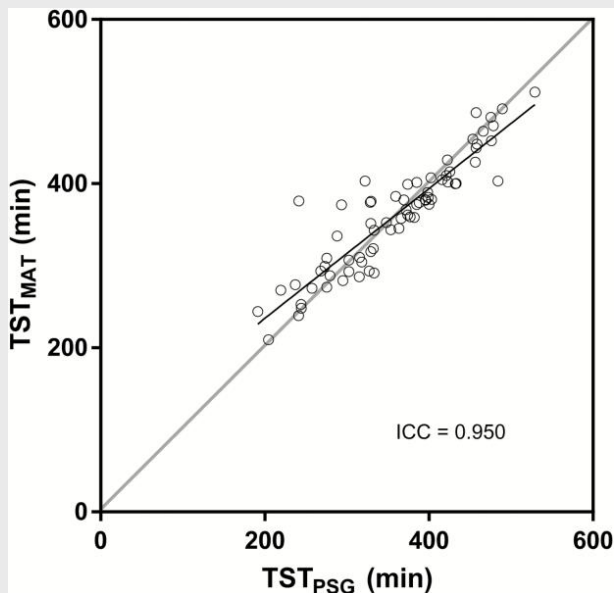


Looney D et al. Ann Am Thorac Soc 2016;13 No 12:2229–2233

Sonomat v PSG and Measurement of Partial Upper Airway Obstruction in Children With Sleep-Disordered Breathing.

- 76 children, simultaneous PSG and Sonomat
- Good agreement in sleep time and SDB variables
- Also permits quantification of partial upper airway obstruction

Message: Sonomat gives good measure of sleep quality and OSA severity



Norman MB et al. *Sleep*. 2017 Mar 1;40(3). doi: 10.1093/sleep/zsx017.

Take-Home Message

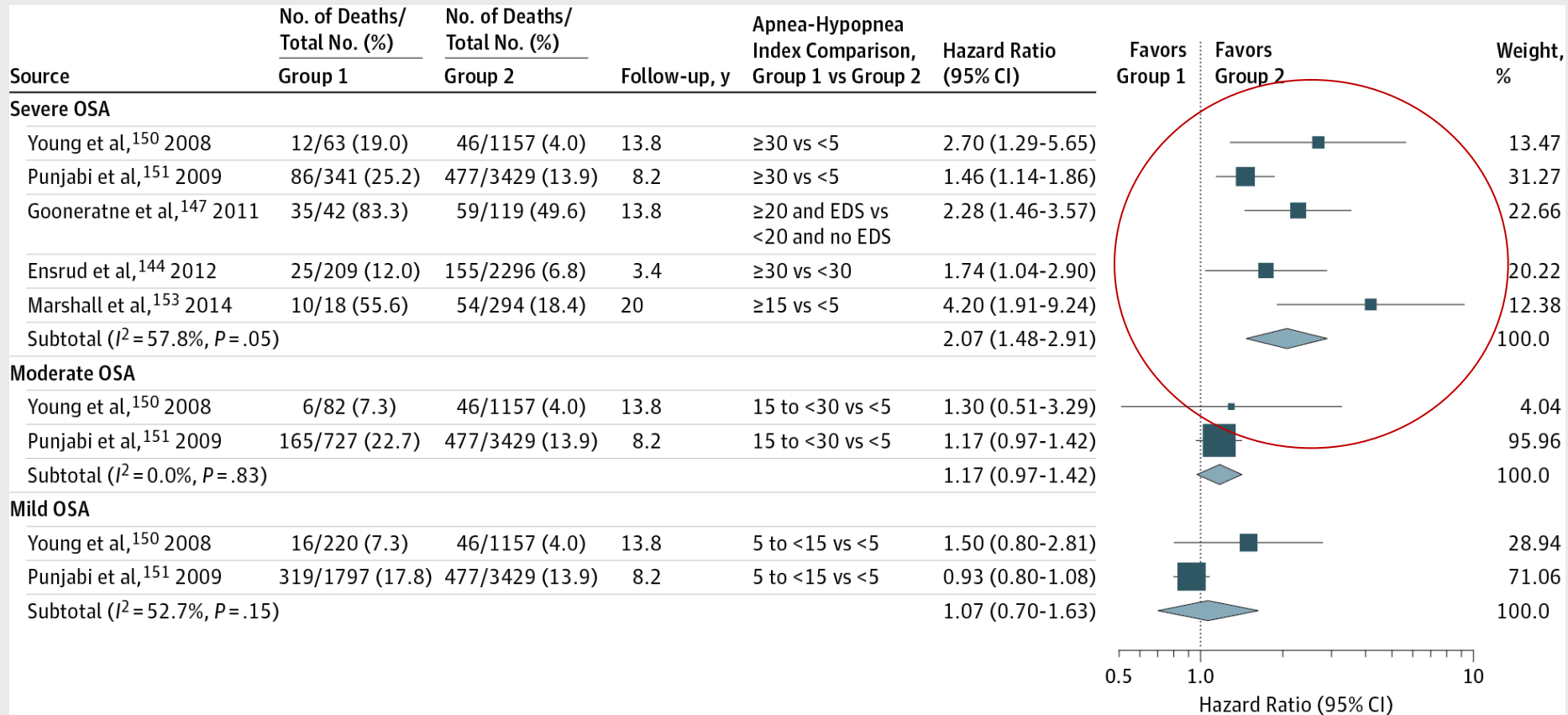
- Sleep apnoea is highly prevalent and current population estimates call into question existing diagnostic criteria
- High prevalence figures make sleep laboratory studies impractical for most patients
- Accurate screening tools necessary to help identify patients requiring further investigation
- Growing interest in novel, minimally invasive technology for ambulatory assessment

OSA co-morbidities

Screening for OSA in Adults.

US Preventive Services Task Force.

Association Between AHI and All-Cause Mortality, by OSA Severity



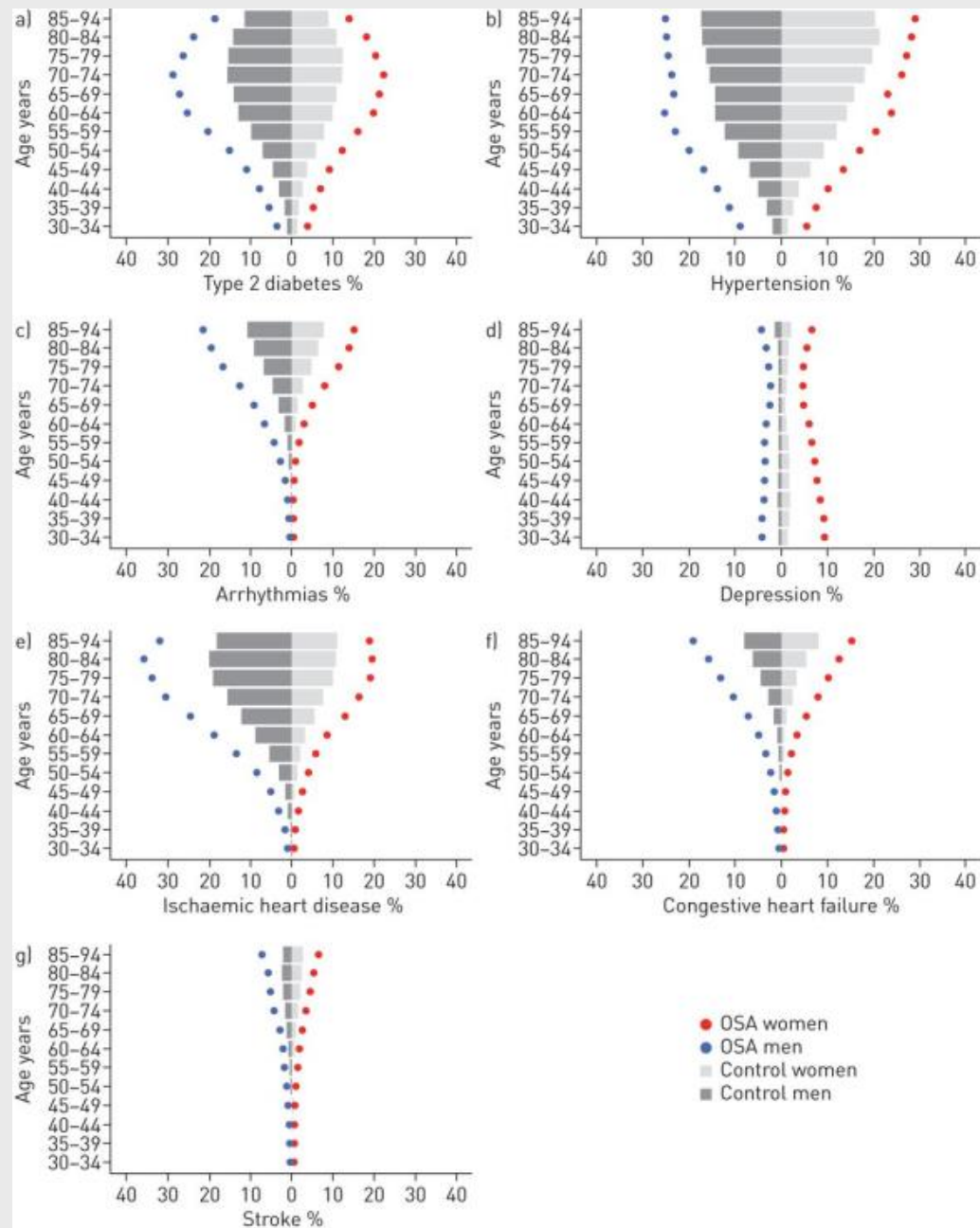
Message: Only severe OSA is an independent risk factor for death

Jonas DE. JAMA. 2017 Jan 24;317(4):415-433

Effect of sex and age on OSA comorbidity: analysis from a nationwide US health claims database.

- ~1.7 million OSA patients and equal number of matched controls
- Co-morbidities more prevalent in OSA in a fully adjusted model
- Prevalence increased with age, although depression showed opposite trend

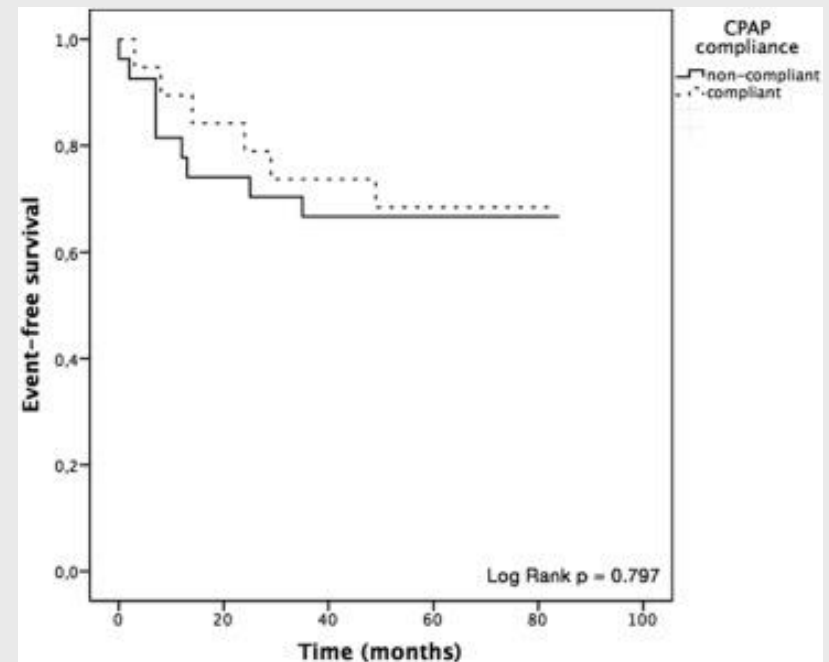
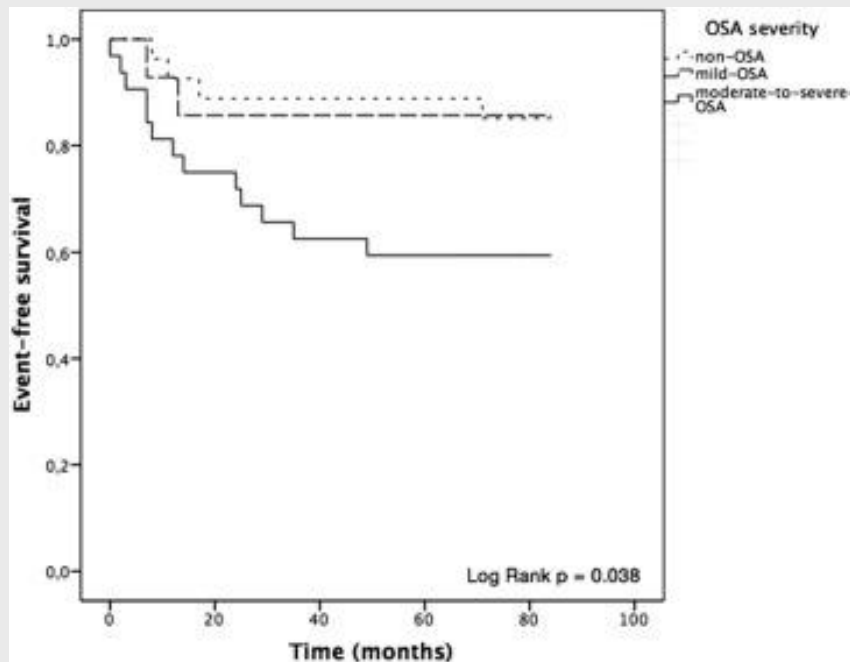
Message: OSA is an independent risk factor for co-morbidities



Mokhlesi B et al. *Eur Respir J.* 2016; 47(4):1162-9

Effect of OSA in Acute Coronary Syndrome

- Long-term follow-up of 73 patients admitted to CCU with acute coronary syndrome who had a sleep study
- OSA (AHI >5) in 46 patients (63%) and AHI >15 in 32 patients. OSA and non-OSA patients similar.

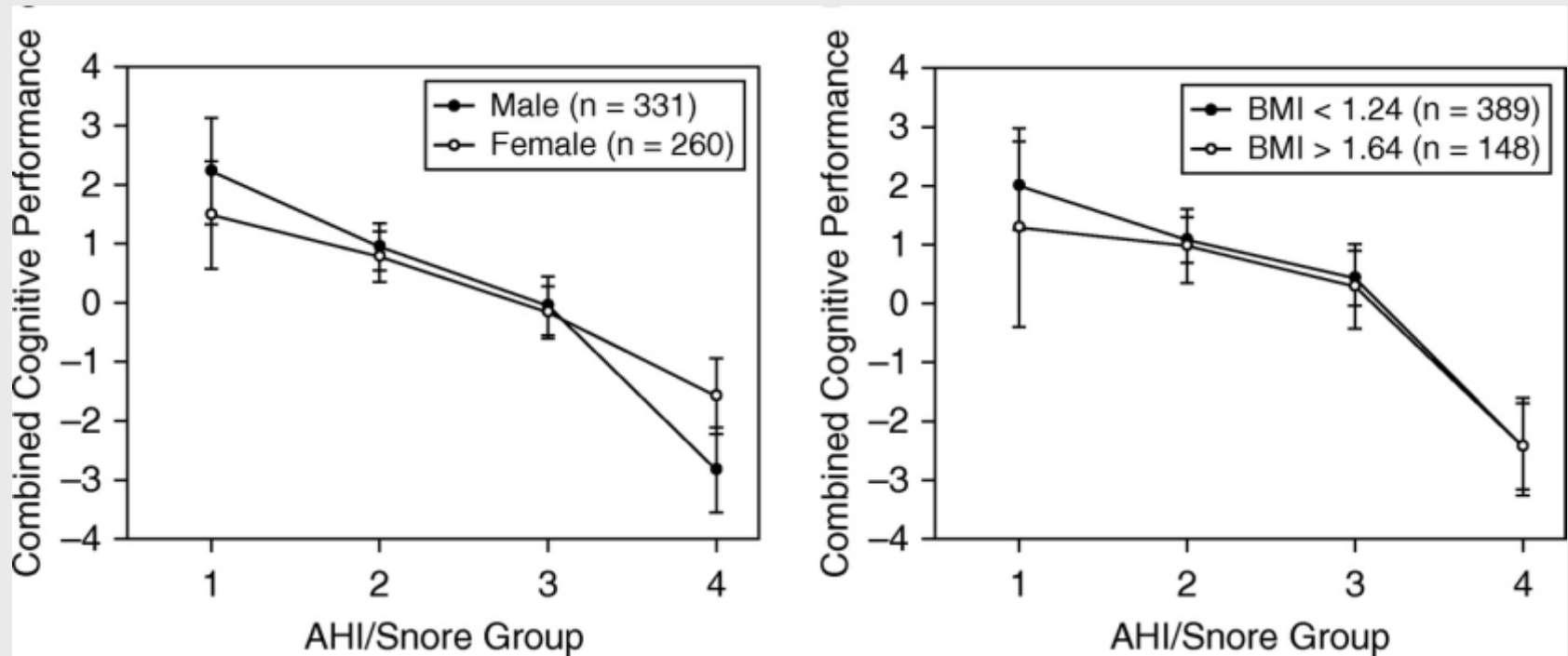


Message: OSA is associated with recurrent cardiovascular events but CPAP therapy doesn't prevent.

Leão S et al. Am J Cardiol 2016; 117(7):1084-7.

Sleep-disordered Breathing affects Cognitive Performance in School-aged Children

- 1010 schoolchildren 5-7yr had PSG and neurocognitive assessment; 4 subgroups by AHI
- Cognitive performance declined with increasing SDB severity



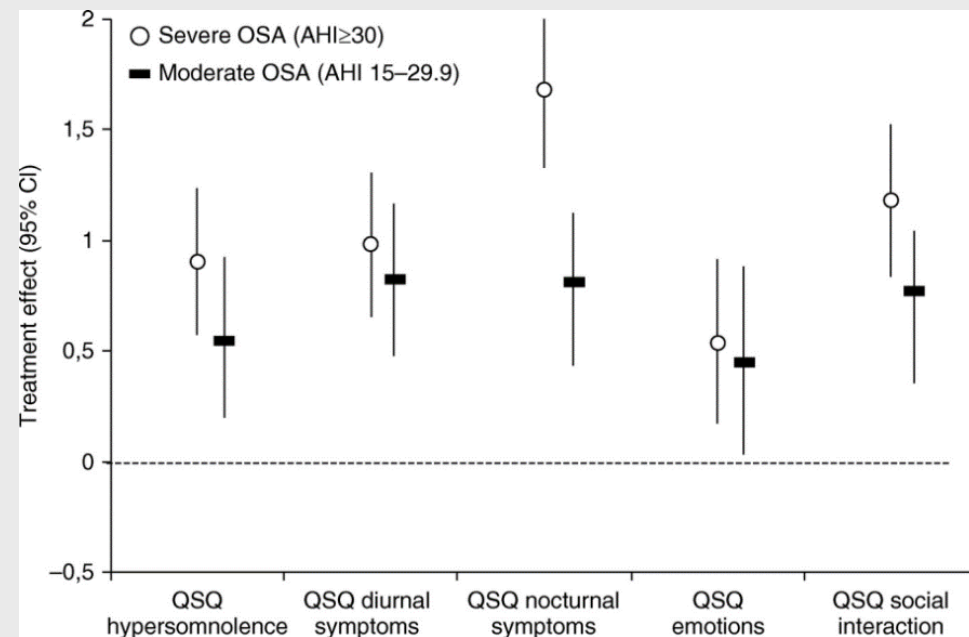
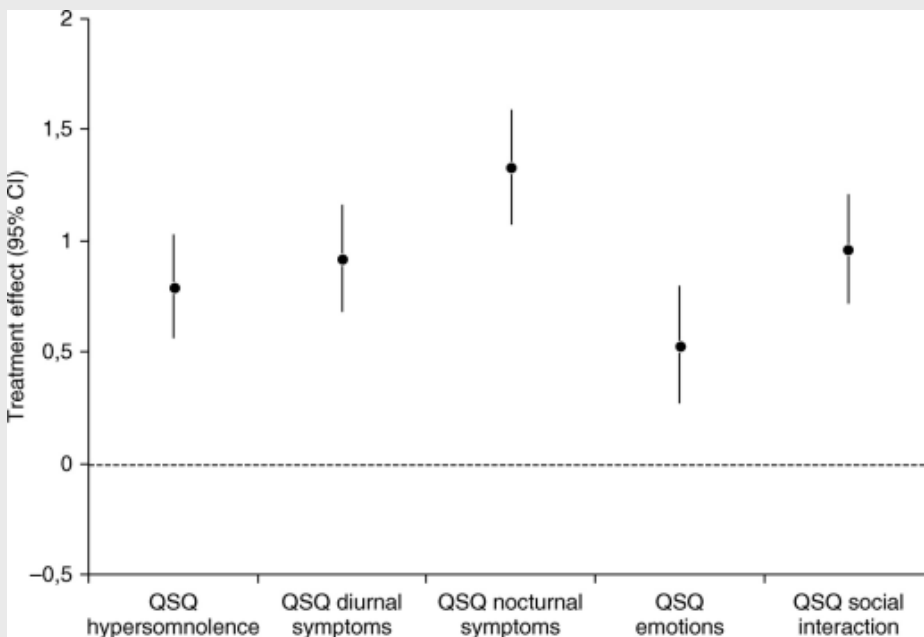
Message: SDB is associated with impaired cognition in a dose dependant fashion.

Hunter SJ et al. Am J Respir Crit Care Med. 2016;194(6):739-47

CPAP Therapy

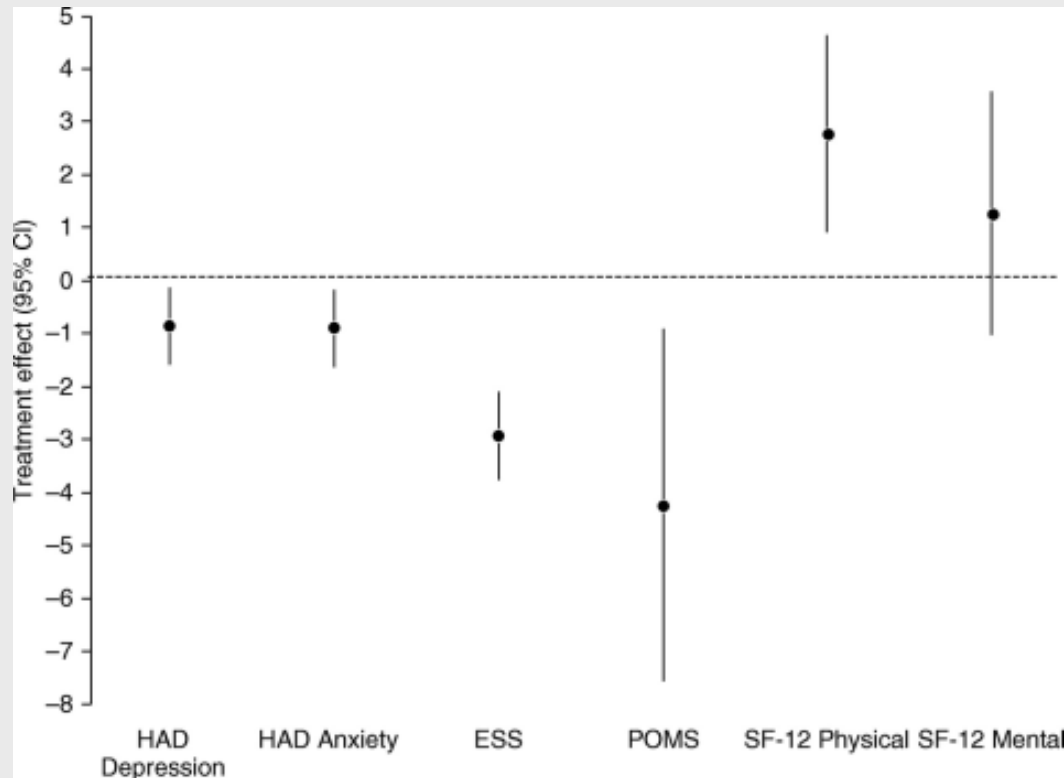
CPAP Improves Quality of Life in Women with OSA

- 307 women, AHI>15, randomized to CPAP or usual care for 3 months.
- QoL changes based on the Quebec Sleep Questionnaire, ESS, mood, anxiety, depression.



Campos-Rodriguez et al. Am J Respir Crit Care Med. 2016;194(10):1286-1294

CPAP Improves Quality of Life in Women with OSA



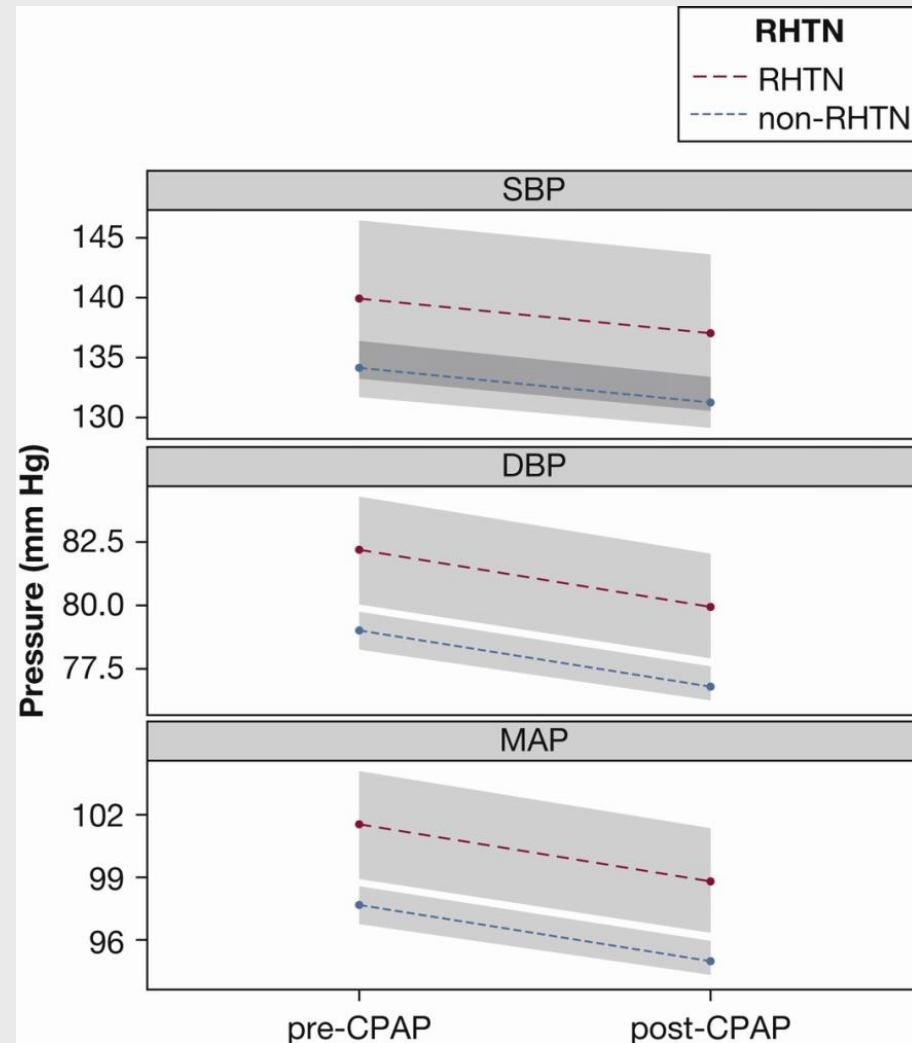
Message: CPAP benefits a wide range of HRQOL measures in women with OSA

Campos-Rodriguez et al. Am J Respir Crit Care Med. 2016;194(10):1286-1294

Longitudinal Effect of CPAP on BP in Resistant and Nonresistant Hypertension

- 894 clinic patients with OSAS and hypertension (15%, resistant HTN)
- Follow up after 1-yr CPAP therapy
- Significant reductions in BP with no difference between resistant and non-resistant HTN in response.

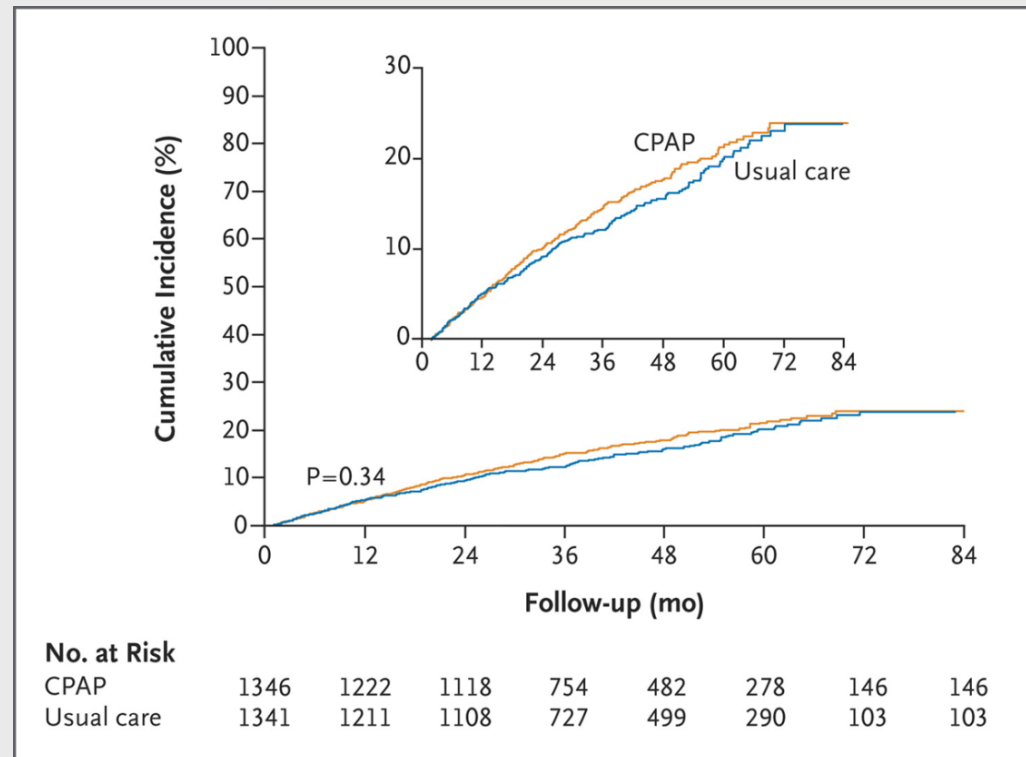
Message: Long-term CPAP therapy reduces BP in hypertensive patients



Harneet K. Walia et al, CHEST 2016; 149(3):747-755

CPAP for Prevention of Cardiovascular Events in OSA – SAVE trial.

- 2717 patients with *pre-existing coronary or cerebrovascular disease*, AHI >15, and ESS <10 randomised to CPAP or usual care – followed for ~3.7yrs.
- No significant difference in cardiovascular morbidity or mortality
- Average compliance only 3.3hrs
- CPAP treated patients showed a significant drop in ESS and in diastolic BP

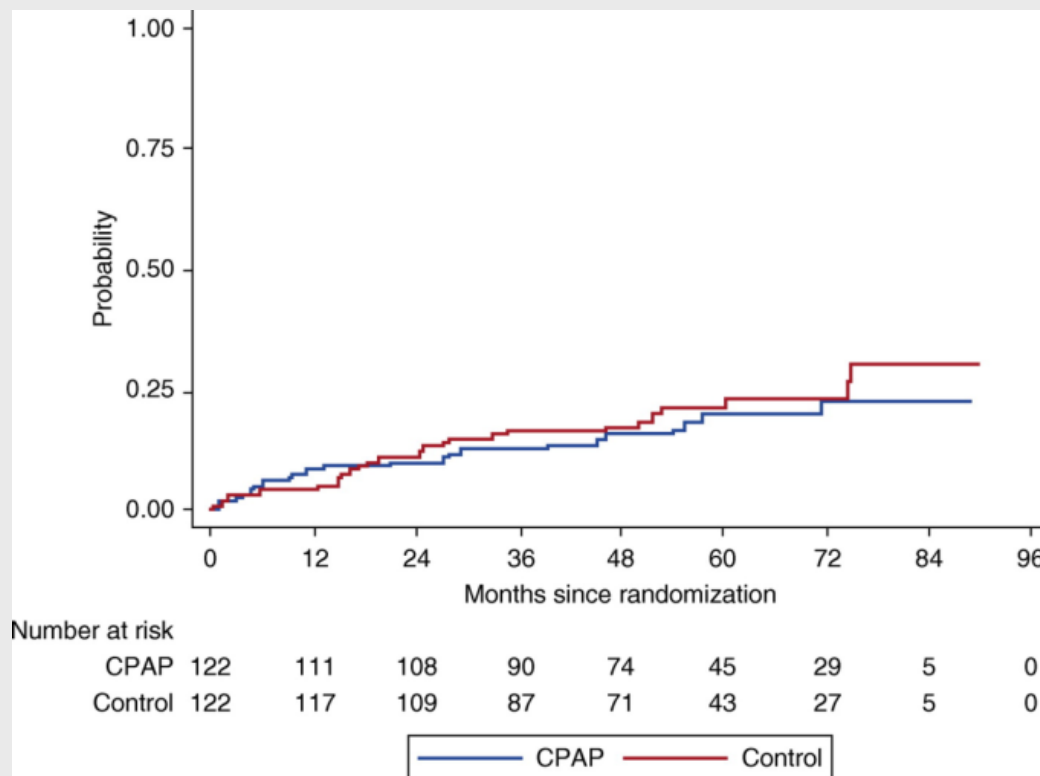


Message: CPAP ineffective in secondary prevention of CVD but poor CPAP compliance is an important limitation

McEvoy RD et al. N Engl J Med. 2016 Sep 8;375(10):919-31.

Effects of CPAP on Cardiovascular Outcomes in Coronary Artery Disease Patients with Non-sleepy OSA – RICCADSA Trial

- 244 patients with *pre-existing coronary disease*, AHI >15 and ESS <10 randomised to CPAP or usual care – followed ~4.7yr
- No improvement in cardiovascular outcomes with CPAP.
- Significant benefit from CPAP in those using >4 hrs/night: HR 0.29 (CI 0.10-0.86; P=0.026)



Message: CPAP is ineffective overall in the secondary prevention of CHD but appears to benefit compliant patients

Peker Y et al. Am J Respir Crit Care Med. 2016 Sep 1;194(5):613-20

Take-Home Message

- Taken together, these data support OSAS as an independent contributor to cardiovascular co-morbidity but cast doubt on the benefit of CPAP in the secondary prevention of cardiovascular disease.
- However, data also suggest that CPAP compliant patients do benefit.

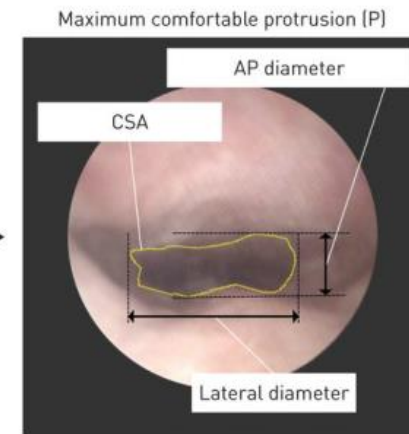
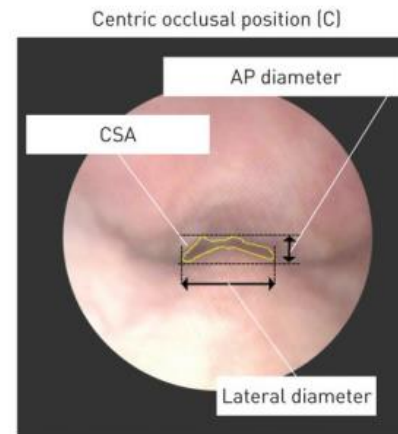
Non-CPAP therapies

Endoscopy evaluation to predict oral appliance outcomes in OSA.

- 61 patients with AHI >15
- Baseline AHI and CSA expansion ratio of the velopharynx were independent predictors of OA response

Message: Endoscopy evaluation can help predict OA success

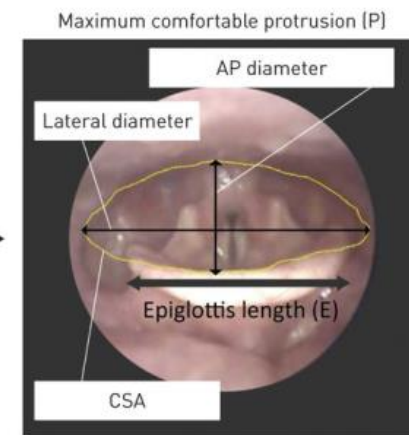
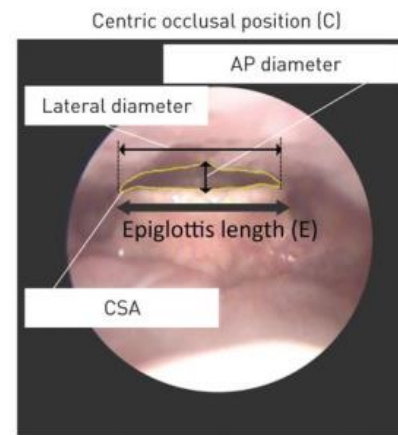
a) Velopharynx



$$\text{CSA expansion ratio} = \frac{\text{CSA (P)}}{\text{CSA (C)}}$$

Lateral and AP expansion ratios are calculated by the same method

b) Oro/hypopharynx



$$\text{CSA expansion ratio} = \frac{\text{CSA (P)/E (P)}^2}{\text{CSA (C)/E (C)}^2}$$

$$\text{Lateral expansion ratio} = \frac{\text{Lateral diameter (P)/E (P)}}{\text{Lateral diameter (C)/E (C)}}$$

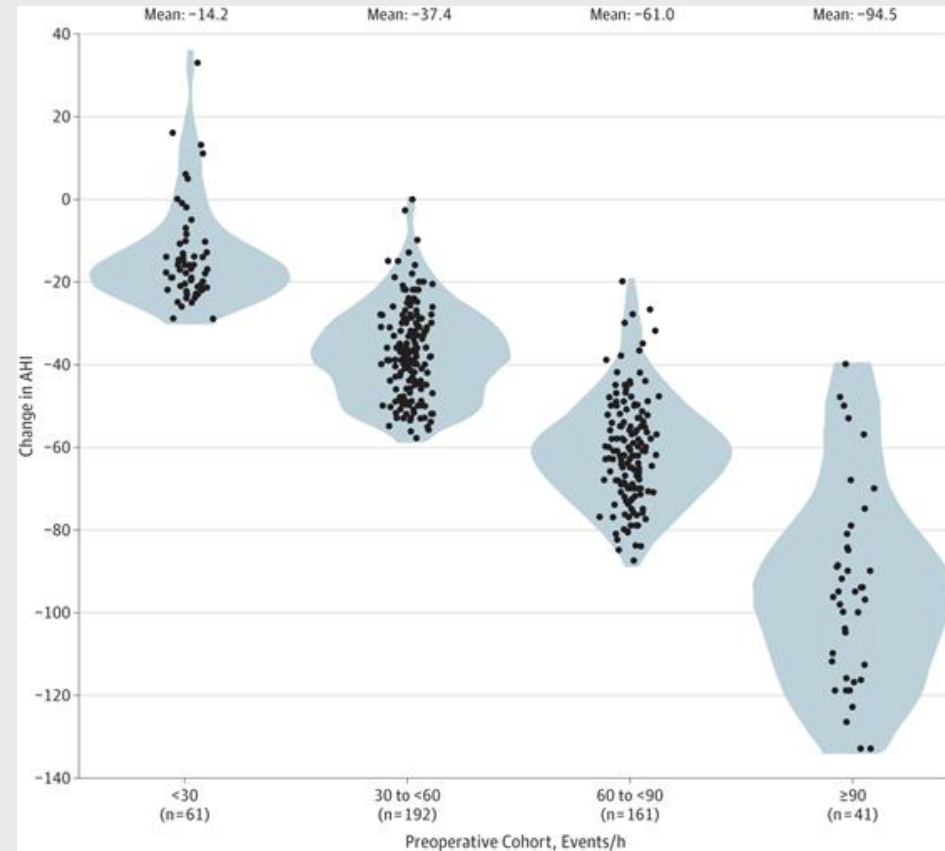
AP expansion ratio is calculated by the same method

Okuno K et al. *Eur Respir J.* 2016;47(5):1410-9

Maxillomandibular Advancement for Treatment of OSA. A Meta-analysis.

- 45 studies (518 patients); most had some form of prior surgery for OSA
- Substantial reduction in AHI across all severity levels
- ESS fell from 13.5 [5.2] to 3.2 [3.2]; $P < .001$
- Preoperative AHI <60 was the factor best associated with surgical cure.

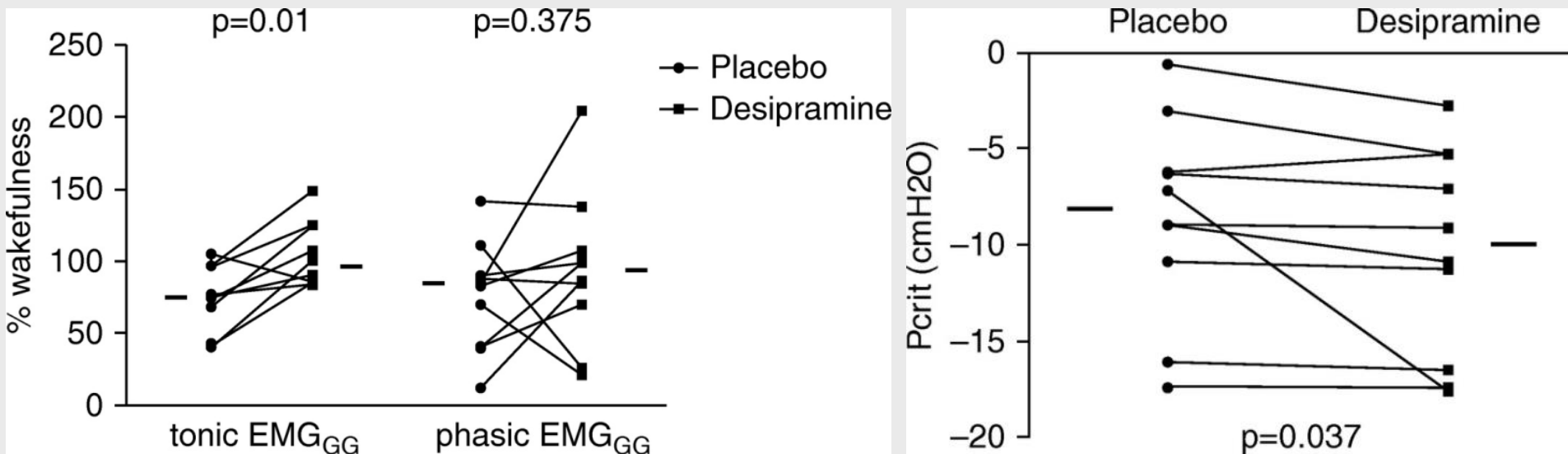
Message: MMA surgery is an effective option for OSA even in patients who had prior surgery.



Zaghi S et al. JAMA Otolaryngol Head Neck Surg. 2016;142(1):58-66.

Desipramine increases genioglossus activity and reduces upper airway collapsibility during non-REM sleep in healthy subjects.

- 17 healthy adults comparing Desipramine v placebo - RPCT.
- Desipramine increased phasic genioglossus EMG and reduced Pcrit.



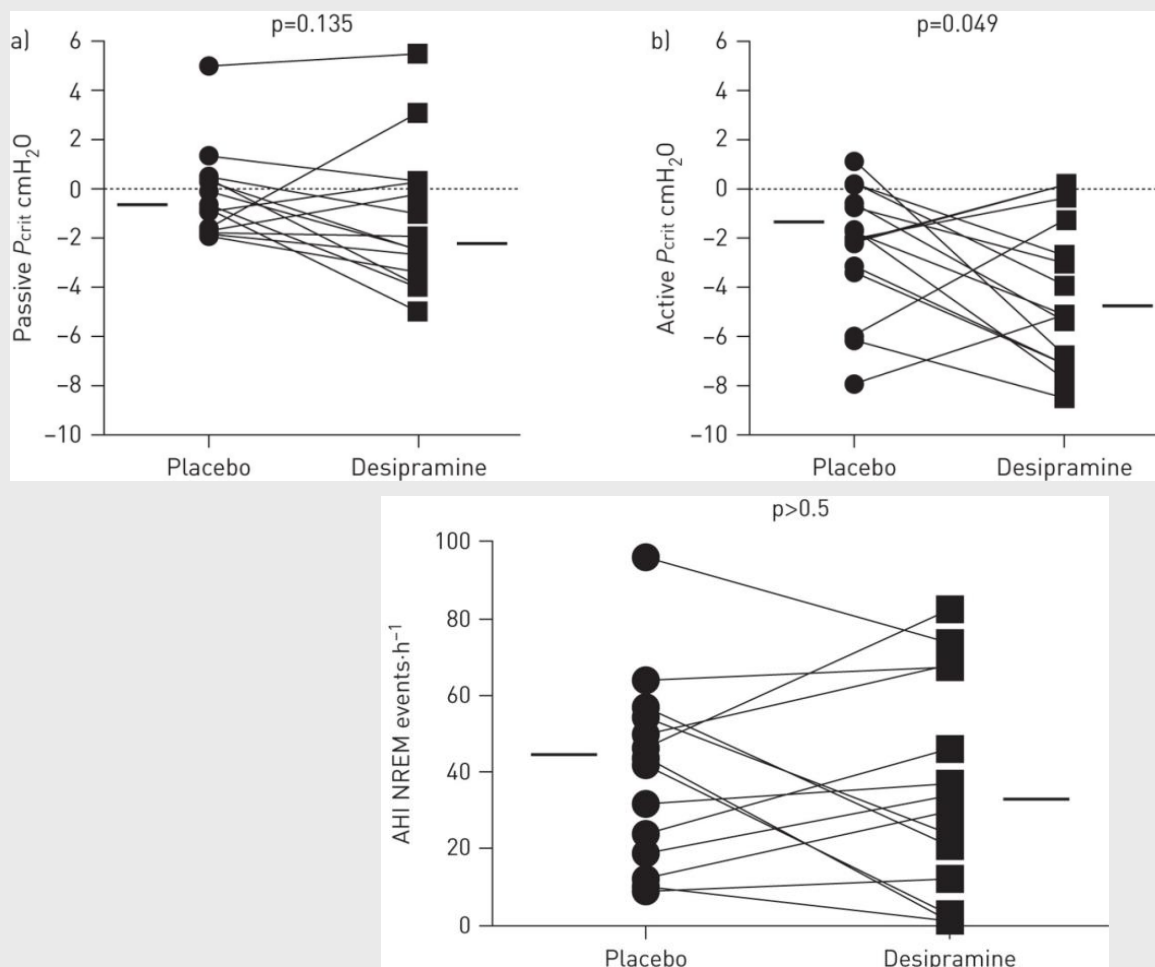
Message: Desipramine reduces upper airway collapsibility and protects against OSA

Taranto-Montemurro L et al. Am J Respir Crit Care Med. 2016;194(7):878-885

Desipramine improves upper airway collapsibility and reduces OSA severity in patients with minimal muscle compensation.

- RPCT of desipramine in 14 OSA patients with AHI >15
- Desipramine reduced active but not passive Pcrit, and also AHI in patients with low muscle compensation.

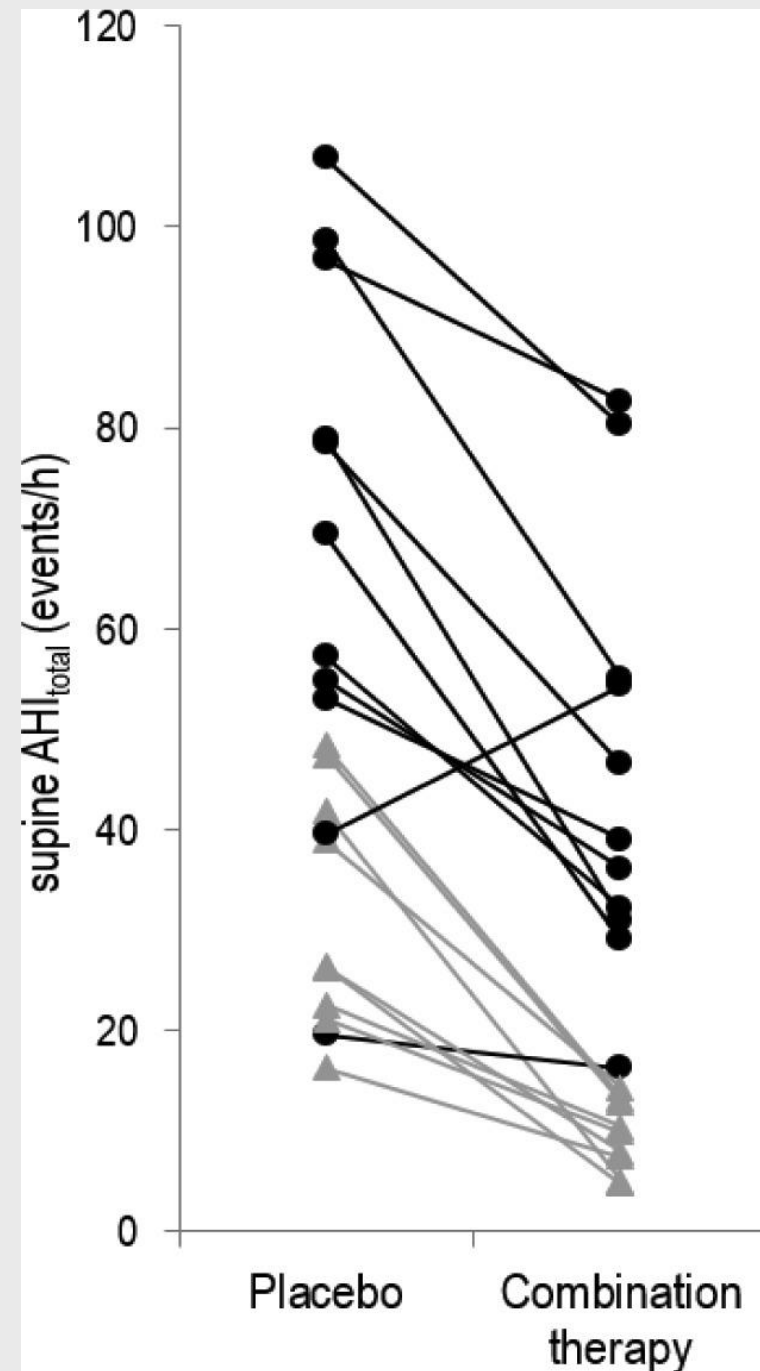
Message: Desipramine can benefit selected patients with OSA.



Taranto-Montemurro L et al. *Eur Respir J.* 2016;48(5):1340-1350

Combination of Supplemental Oxygen and a Hypnotic Improves OSA in Patients with Mild to Moderate Upper Airway Collapsibility

Edwards BA et al. *Sleep* 2016 Nov 1; 39(11): 1973–1983

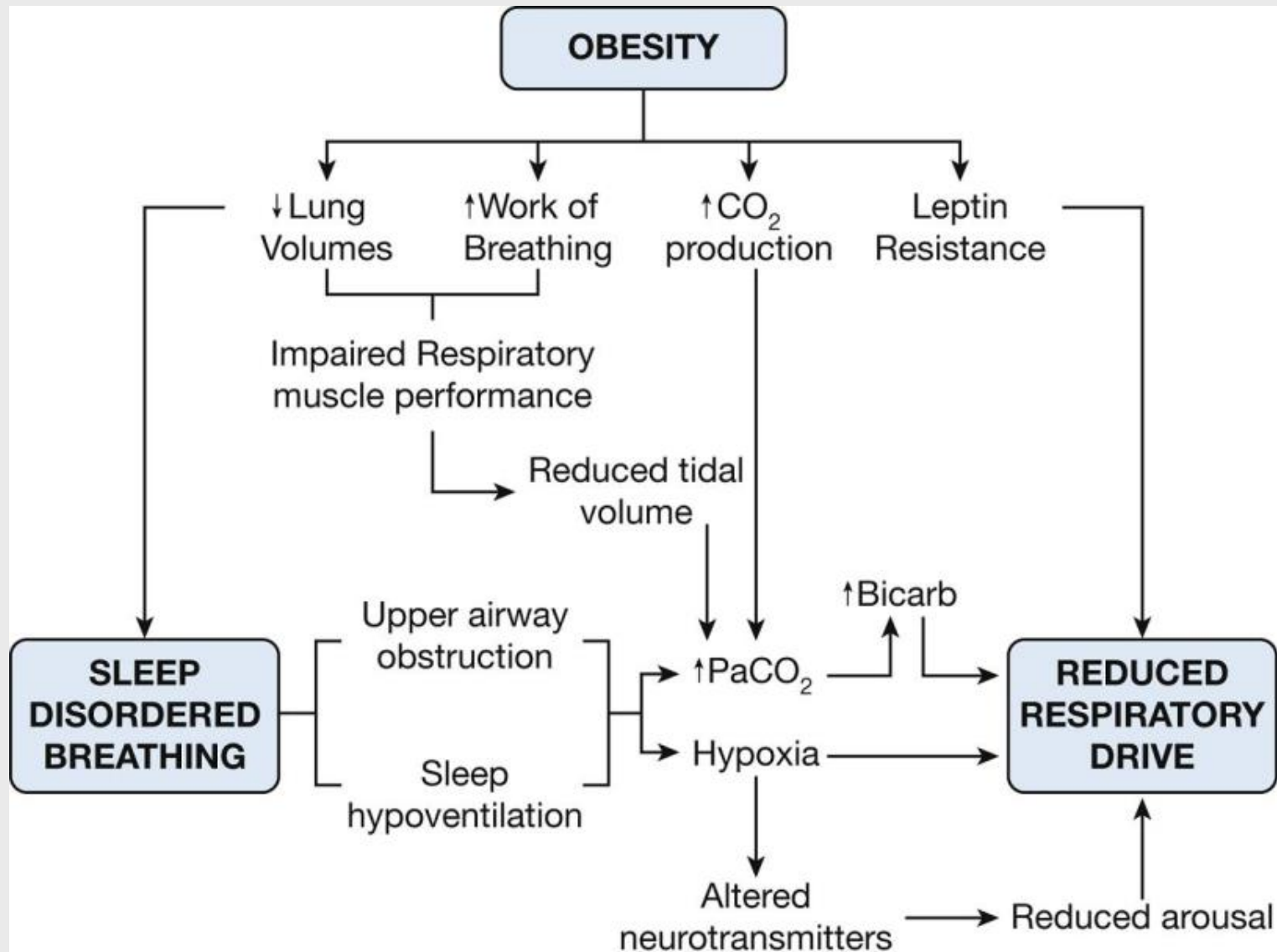


Take-Home Message

- Efficacy of oral appliance therapy can be predicted by prior endoscopic evaluation
- Maxilo-mandibular advancement surgery is efficacious but has limited availability
- Encouraging developments for pharmacological therapy in selected patients with OSA

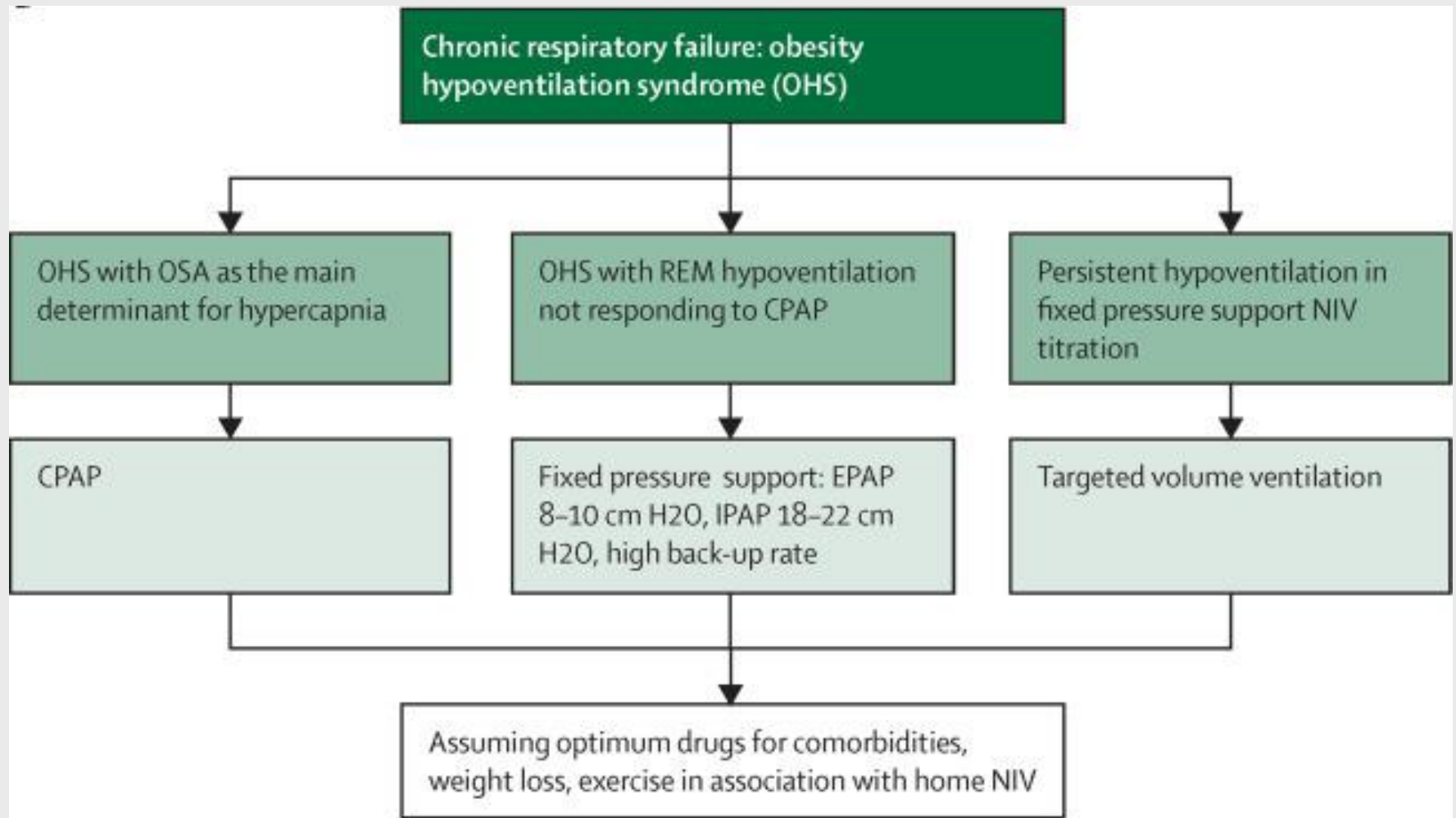
Obesity Hypoventilation

Impact of Obesity on Breathing during Sleep



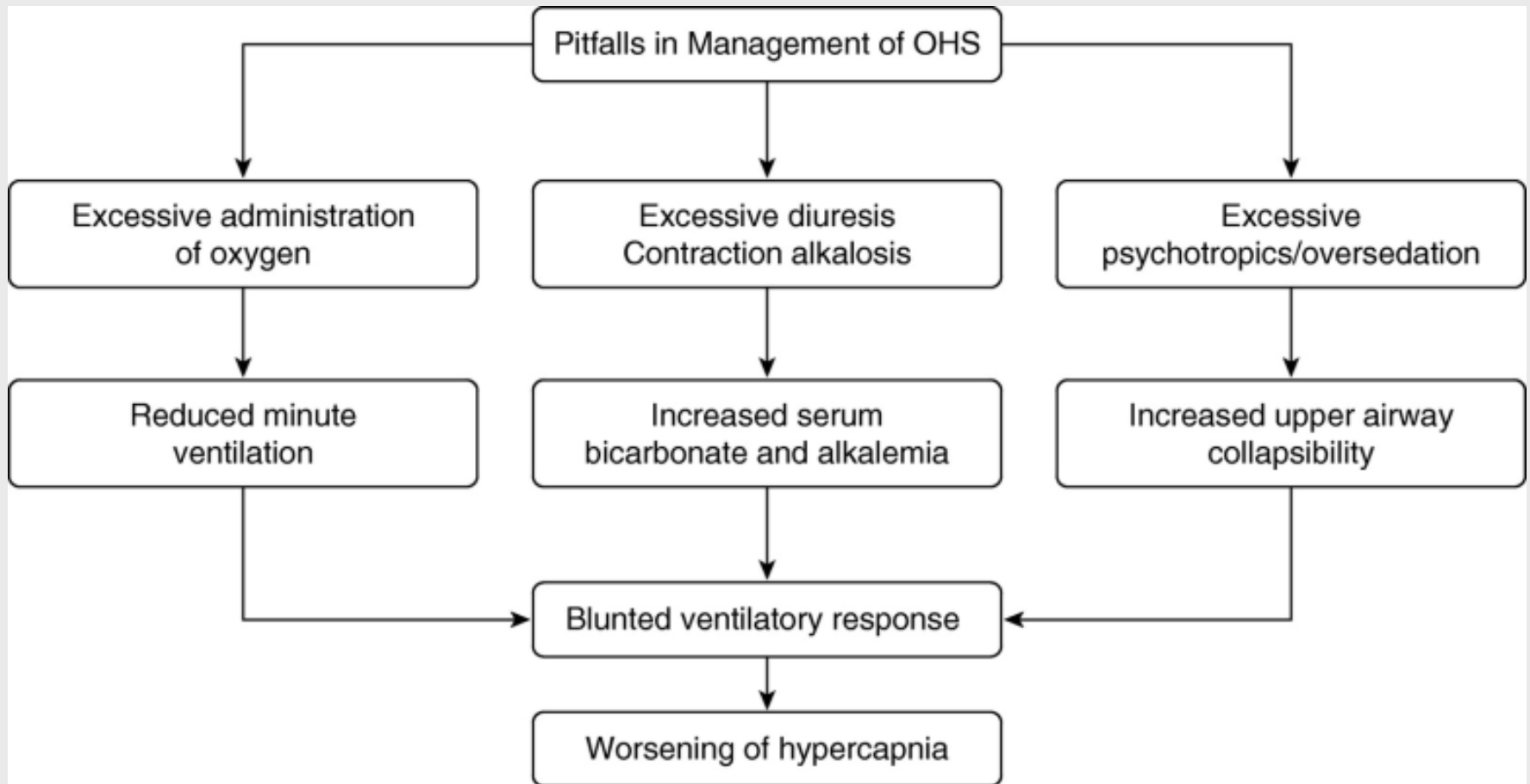
Piper A. Chest 2016;149(3):856-68.

Prevention and care of respiratory failure in obese patients



Pépin JL et al. Lancet Respir Med 2016 May;4(5):407-18.

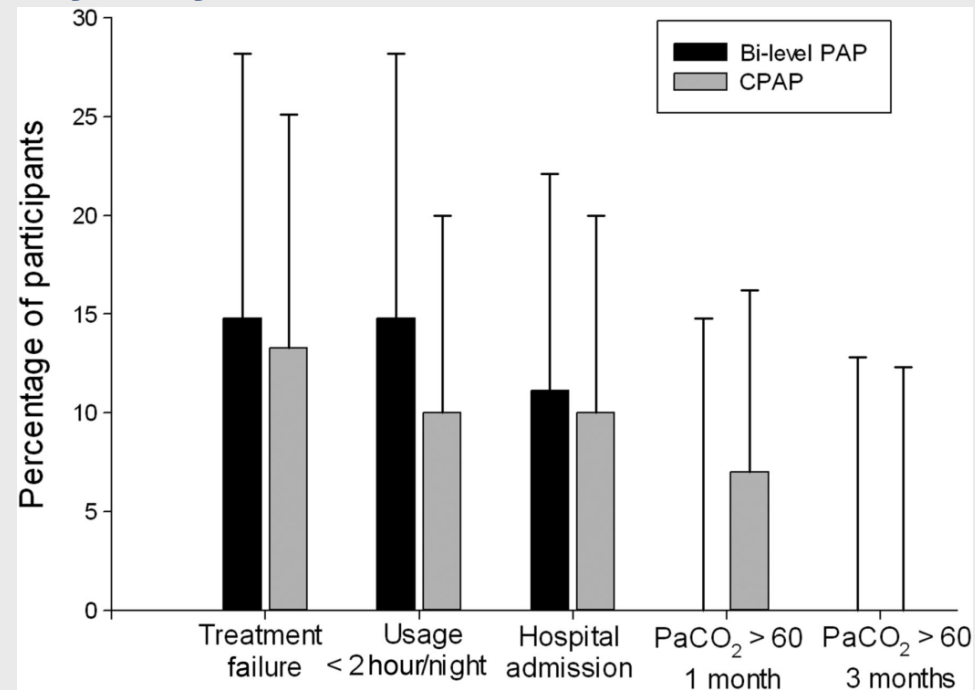
Avoiding Management Errors in Patients with Obesity Hypoventilation Syndrome



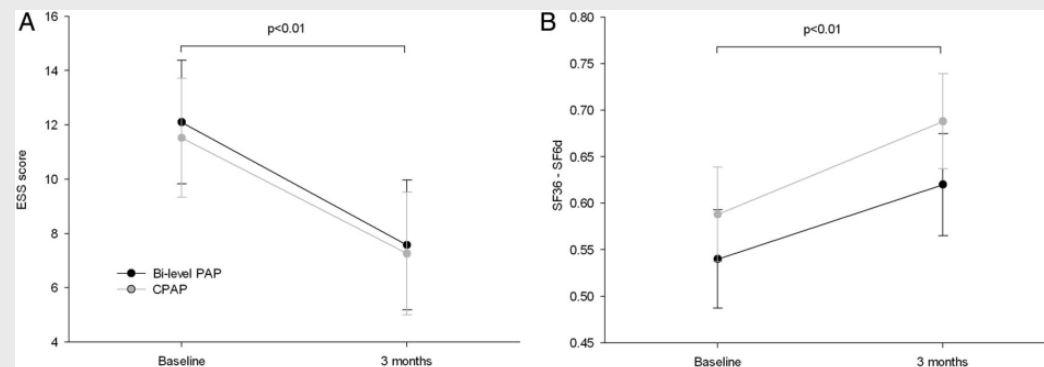
Manthous C et al. Ann Am Thorac Soc 2016 Jan;13(1):109-14.

CPAP vs non-invasive ventilation for initial treatment of obesity hypoventilation

- 60 OHS patients randomised to nocturnal Bi-level PAP (BPAP) or CPAP for 3 months.
- No difference in treatment failure between groups (BPAP=14.8% vs CPAP=13.3%).
- Treatment adherence (average >5 hr/night) and wake PaCO_2 were similar after 3 months



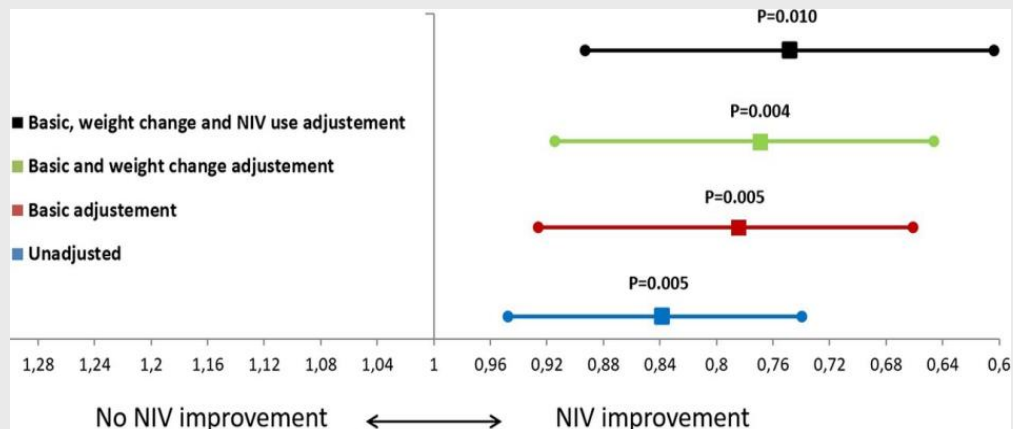
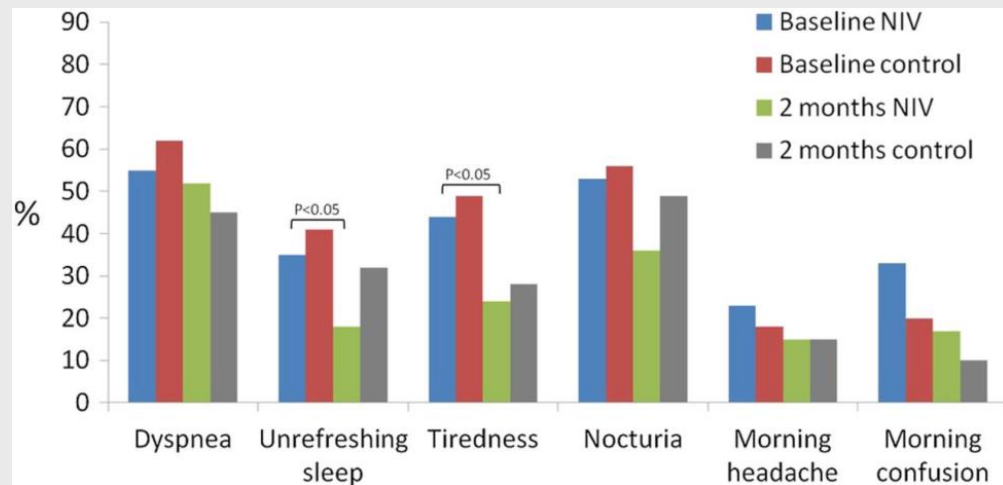
MESSAGE: In newly diagnosed OHS, Bi-level PAP and CPAP resulted in similar improvements in ventilatory failure, HRQoL and adherence.



Howard ME et al. *Thorax*. 2017;72(5):437-44.

Non-invasive ventilation in obesity hypoventilation without severe OSA.

- 86 OHS patients with $AHI < 30$ randomised to NIV or lifestyle modification; followed for 2 months.
- NIV led to greater improvement in:
 - $PaCO_2$ (-6.0 vs -2.8 mmHg; $p < 0.001$)
 - Serum bicarbonate (-3.4 vs -1.0; $p < 0.001$)
- Sleepiness, some HRQOL and PSG variables improved more with NIV.



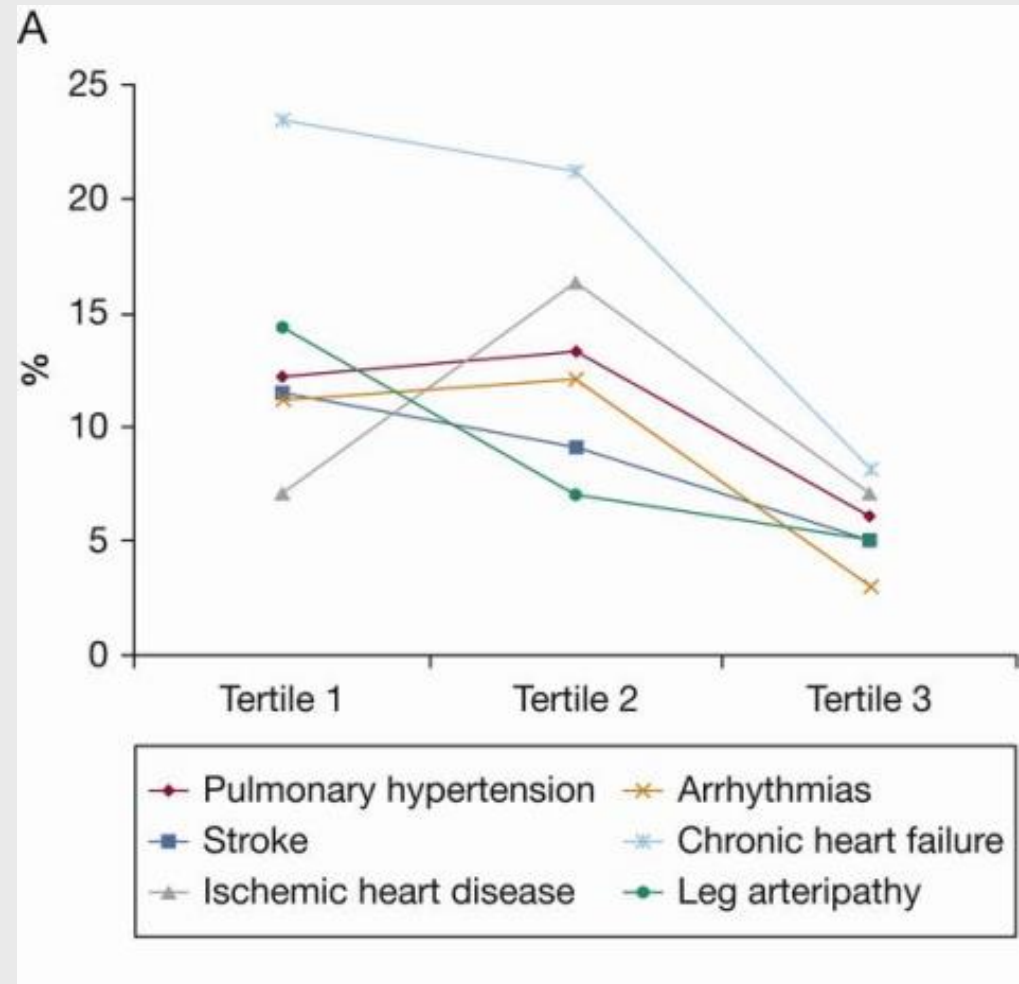
MESSAGE: NIV superior to lifestyle modification in improving daytime $PaCO_2$, sleepiness and sleep quality.

Masa JF et al. Thorax. 2016 Oct;71(10):899-906

Protective Cardiovascular Effect of Sleep Apnea in Obesity Hypoventilation

- 302 patients with OHS comparing OSA severity with cardiovascular morbidity (CVM).
- Prevalence of CVM decreased with increasing severity of OSA.
- Chronic heart failure (CHF) had the strongest negative association with the highest ODI tertile.

MESSAGE: In OHS, the highest OSA severity phenotype is associated with reduced risk of CVM.



Masa JF et al. Chest. 2016;150(1):68-79.

Take-Home Message

- Obesity can have major adverse effects on breathing, particularly during sleep, and independent of sleep apnoea
- CPAP appears to have similar efficacy as NIV in the management of SDB
- Severe sleep apnoea appears to have a protective effect on cardiovascular morbidity in OHS patients

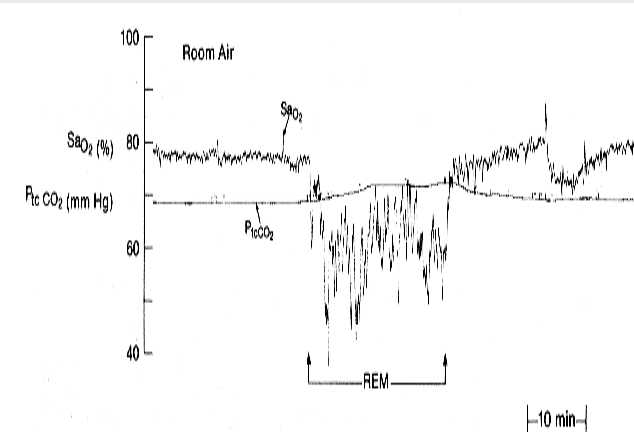
OSA-COPD Overlap

State of the Art

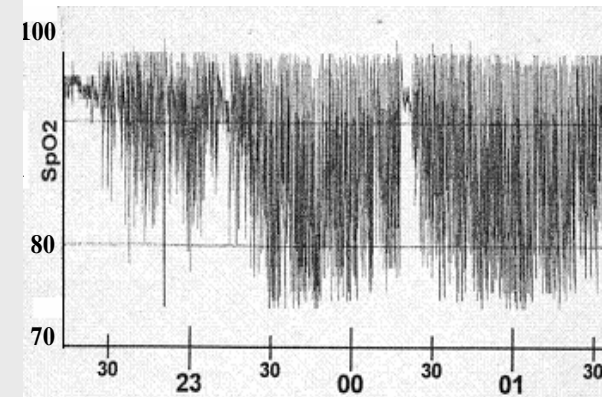
- Sleep-disordered breathing with associated hypoxaemia has long been recognised in patients with COPD
- Given recognised high prevalence of OSA in general population, COPD-OSA overlap likely to be common based on chance association alone
- Inconsistent findings from various reports about whether one condition may predispose to the other
- Different phenotypes may influence predisposition

Oxygen Saturation in COPD, Overlap Syndrome and OSA.

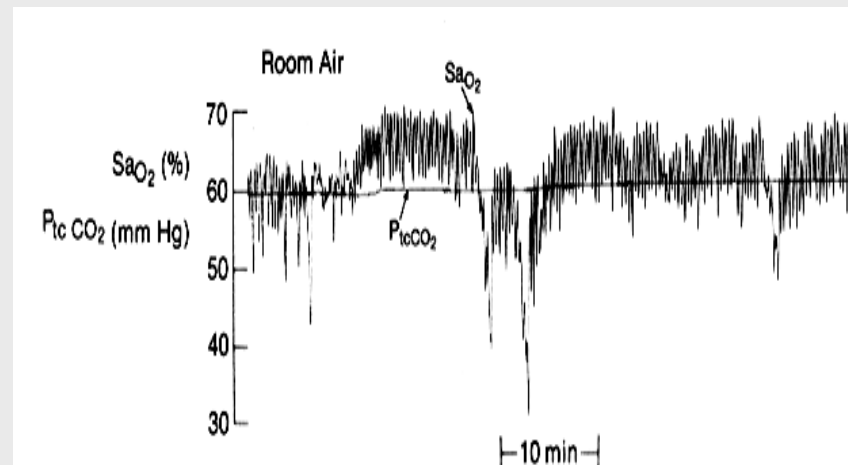
COPD



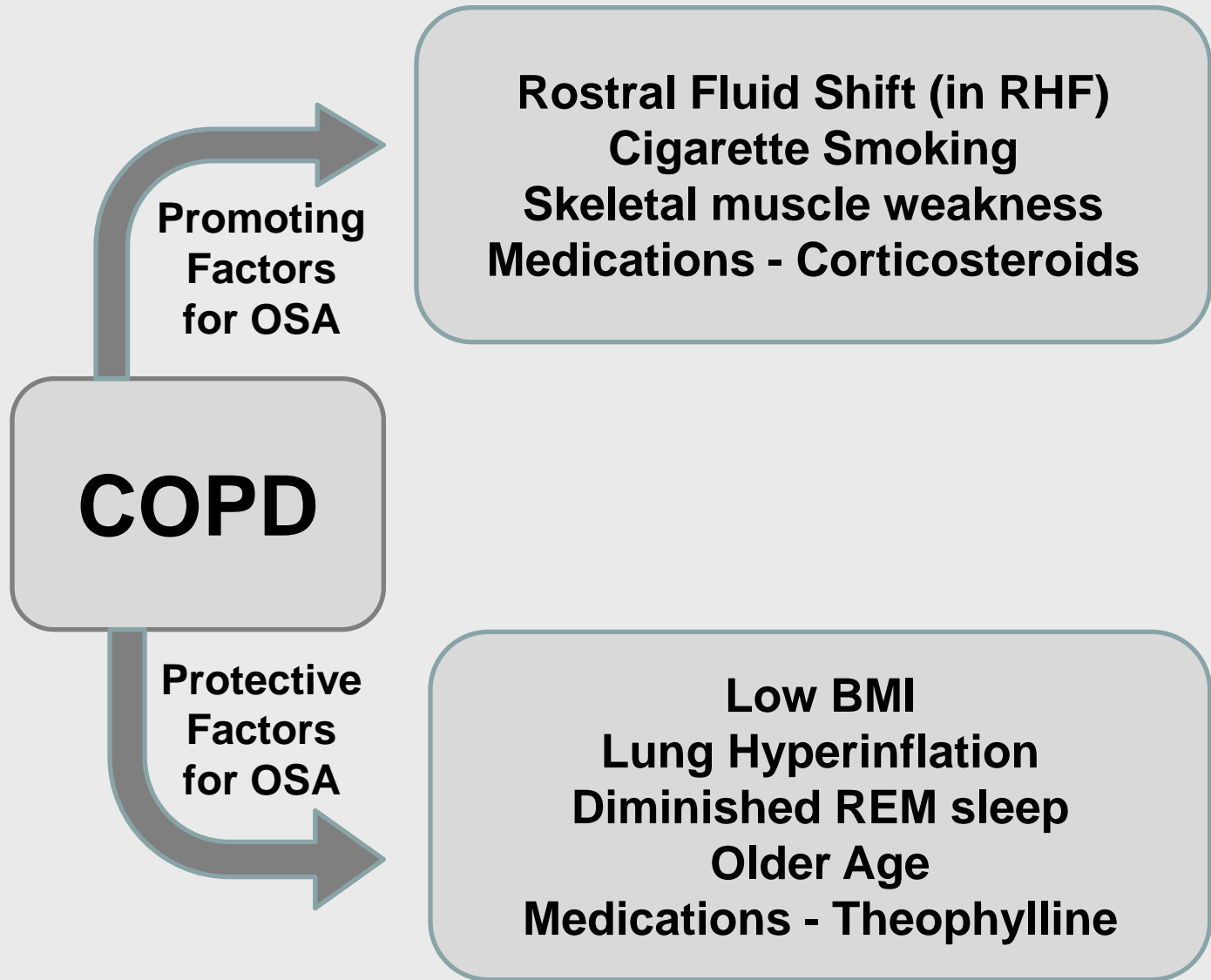
OSA



Overlap syndrome



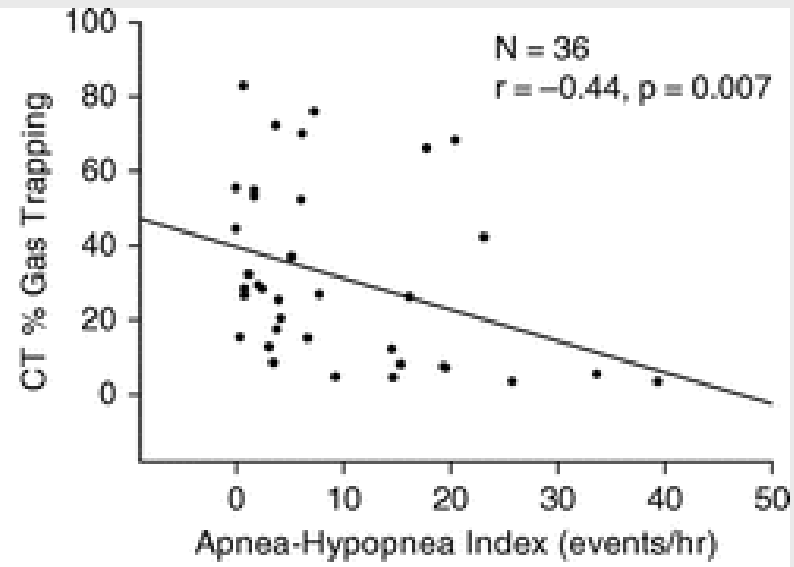
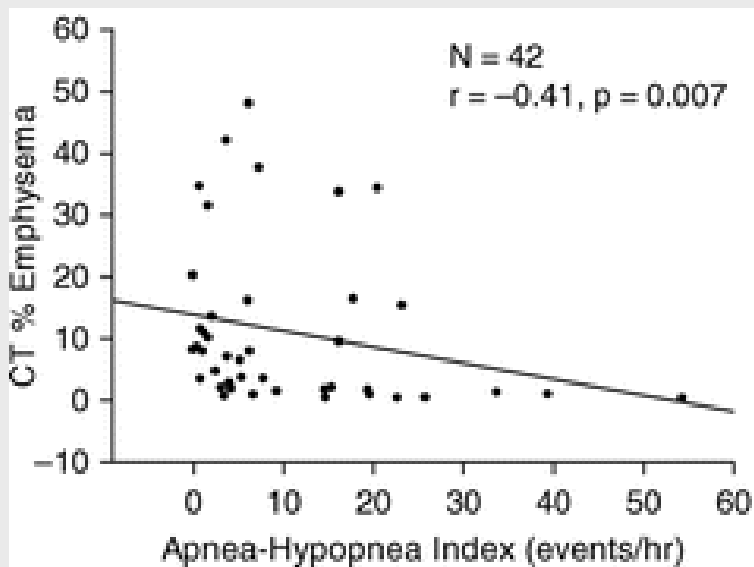
McNicholas WT. *Chest*. 2017 Apr 22. pii: S0012-3692(17)30742-0.



McNicholas WT. Chest. 2017 Apr 22. pii: S0012-3692(17)30742-0.

Effect of Emphysema Severity on AHI in Smokers with OSA: Role of Hyperinflation

- 51 smokers, ~BMI 32, all had PSG
- 29 had OSA (AHI 18 ± 12 events/hr) - younger and heavier
- Inverse correlation between AHI and CT% emphysema/CT% gas trapping.
- Multiple regression analysis showed CT% emphysema and CT% gas trapping, gender, and BMI as independent predictors of AHI.

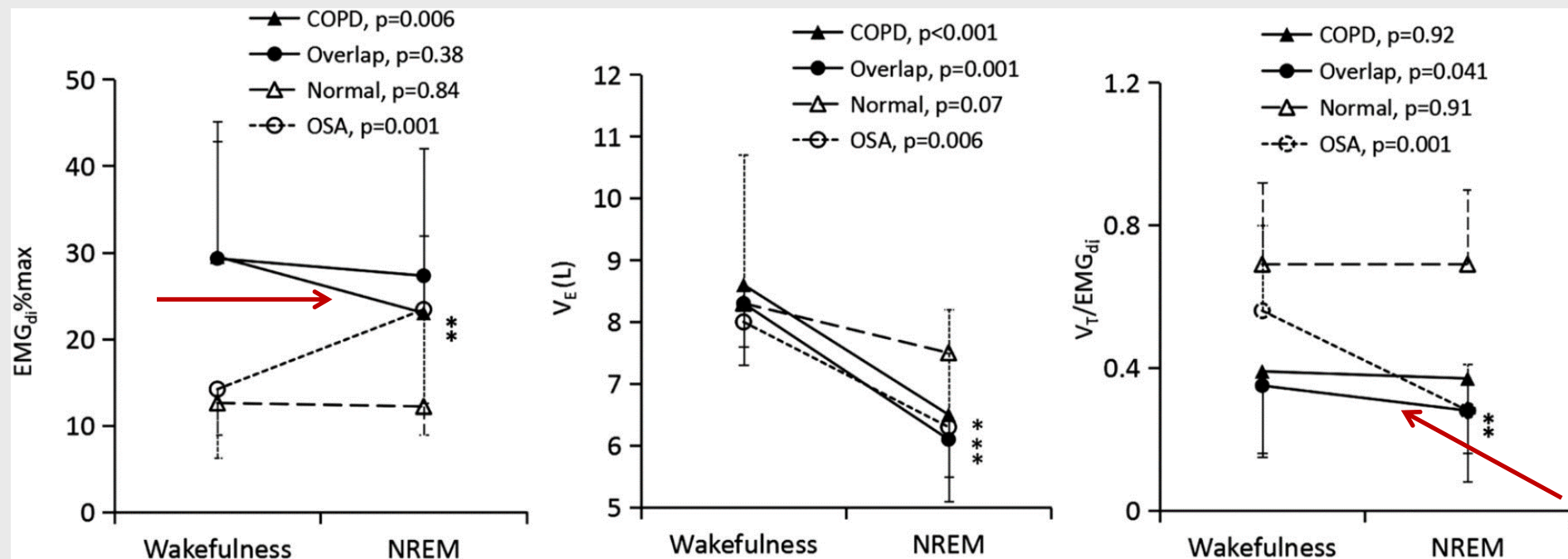


Message: Hyperinflation protects against OSA

Krachman SL et al. Ann Am Thorac Soc. 2016;13(7):1129-35

Coexisting OSA may compensate for sleep related reduction in neural respiratory drive in patients with COPD

EMG_{di} and airflow recorded during PSG in 12 healthy subjects, 14 OSA patients, and 35 COPD (16 with COPD-OSA overlap).

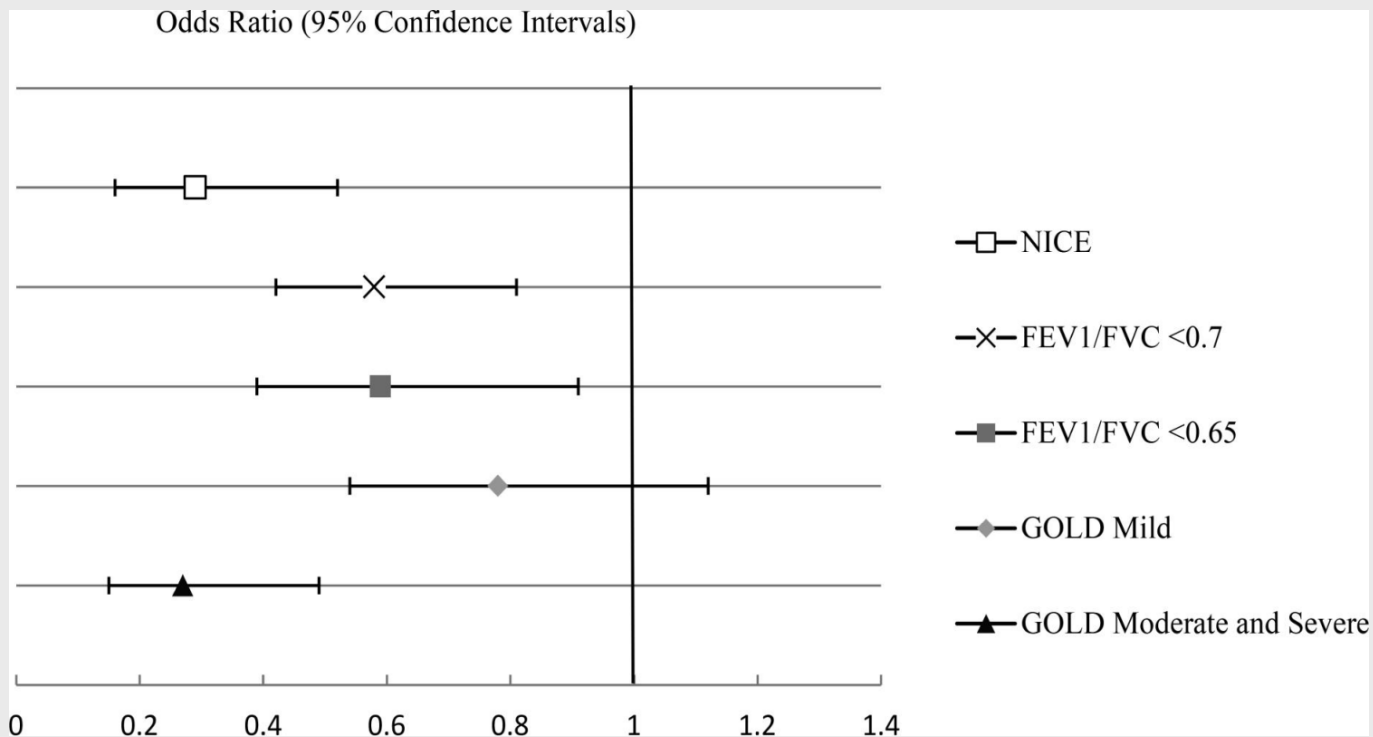


MESSAGE: Hypoventilation during nonREM sleep in COPD alone is due to reduction of neural respiratory drive, but in overlap syndrome is due to increased upper airway resistance.

He BT et al. Thorax. 2017 Mar;72(3):256-262

Sleep Apnea and Obstructive Airway Disease in Older Men.

853 community dwelling older men had home PSG and spirometry.
OSA Dx based on AHI >15

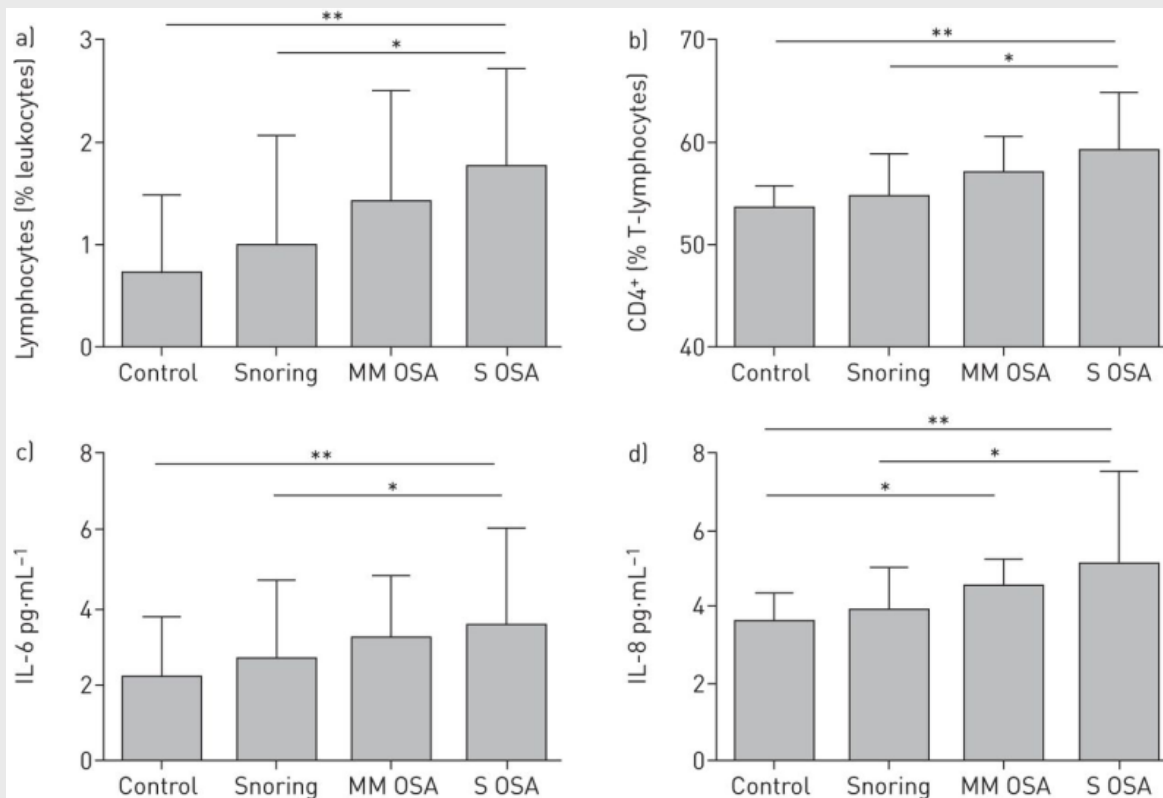


Message: OSA is less prevalent in older men with OAD than in those without, even after adjustment for BMI

Zhao YY et al. Sleep 2016. Jul 1;39(7):1343-51

Upper airway and systemic inflammation in OSA

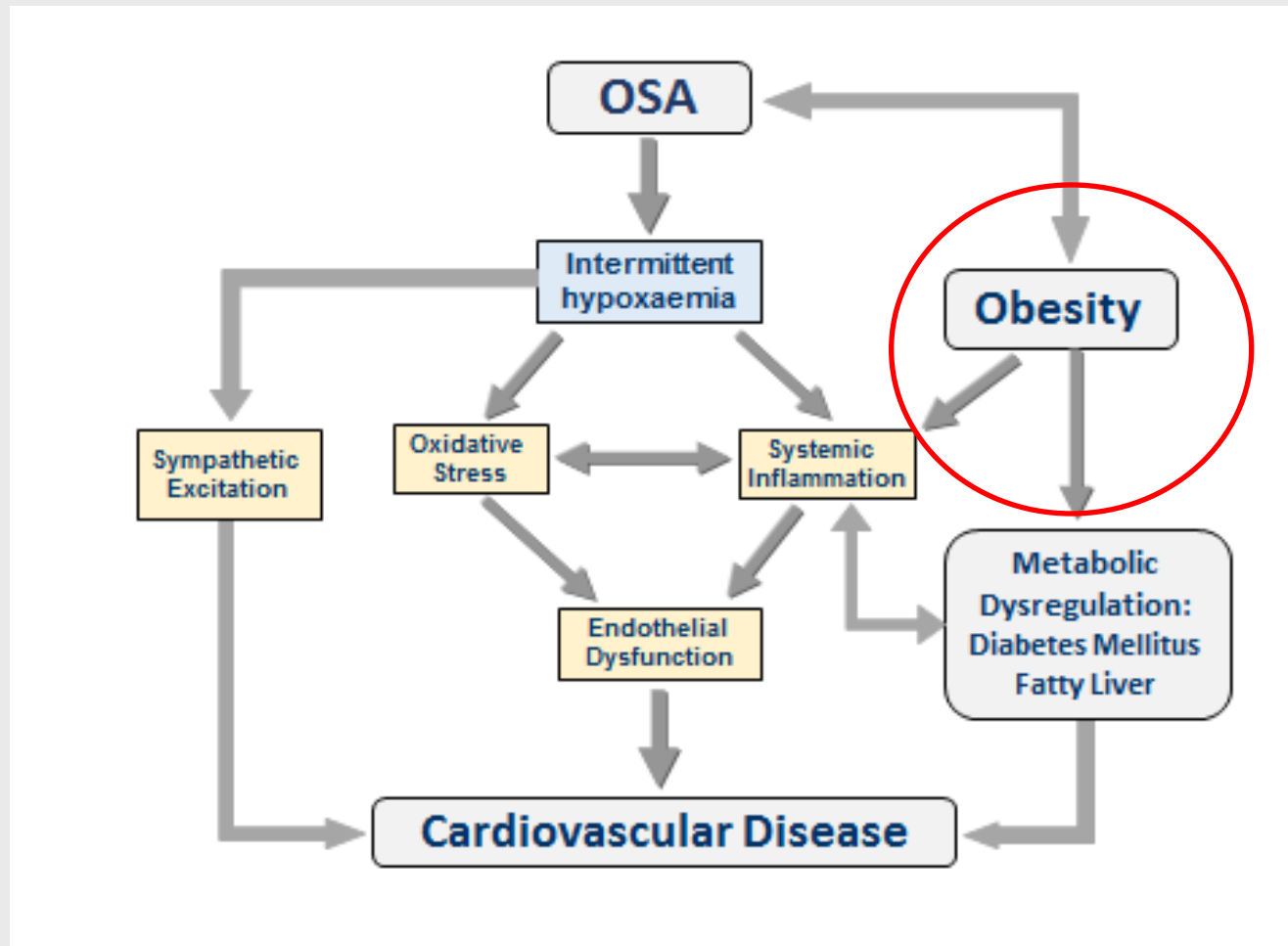
- 138 patients evaluated for OSA, followed for one year; 89 OSA (AHI>5); 28 snorers, 26 healthy controls.
- Pharyngeal lavage demonstrated elevated lymphocytes, IL-6 and IL-8 in OSA which correlated with AHI and fell after treatment.
- No correlation with systemic inflammatory markers.



Message: OSA results in upper airway inflammation, which may have relevance for COPD in the overlap syndrome.

Vicente E et al. Eur Respir J. 2016 Oct;48(4):1108-1117

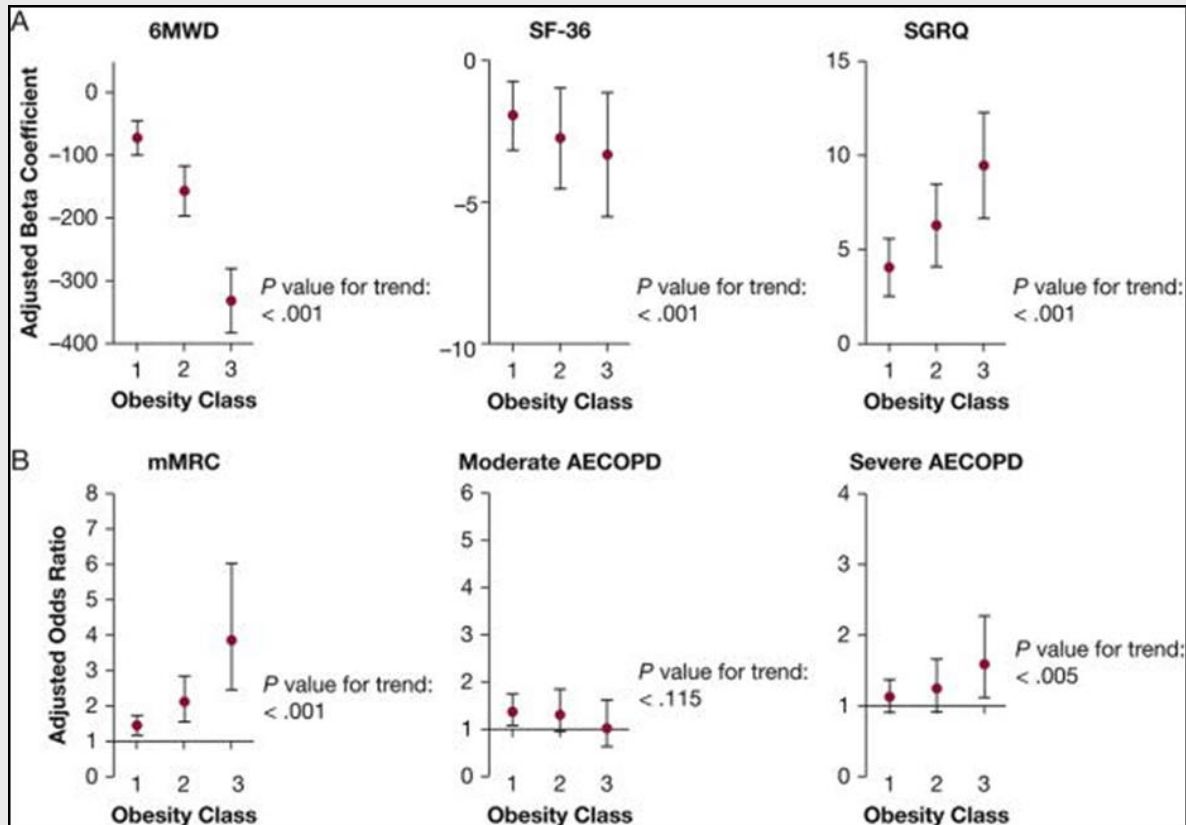
Basic Mechanisms of Cardiovascular Disease in OSA



McNicholas WT et al. *Lancet Respir Med.* 2016 Oct;4(10):826-834

Obesity Is Associated With Increased Morbidity in Moderate to Severe COPD

- 3,631 participants from the prospective COPDGene study with spirometry-confirmed COPD
- Increasing obesity independently associated with worse respiratory-specific and general quality of life measures

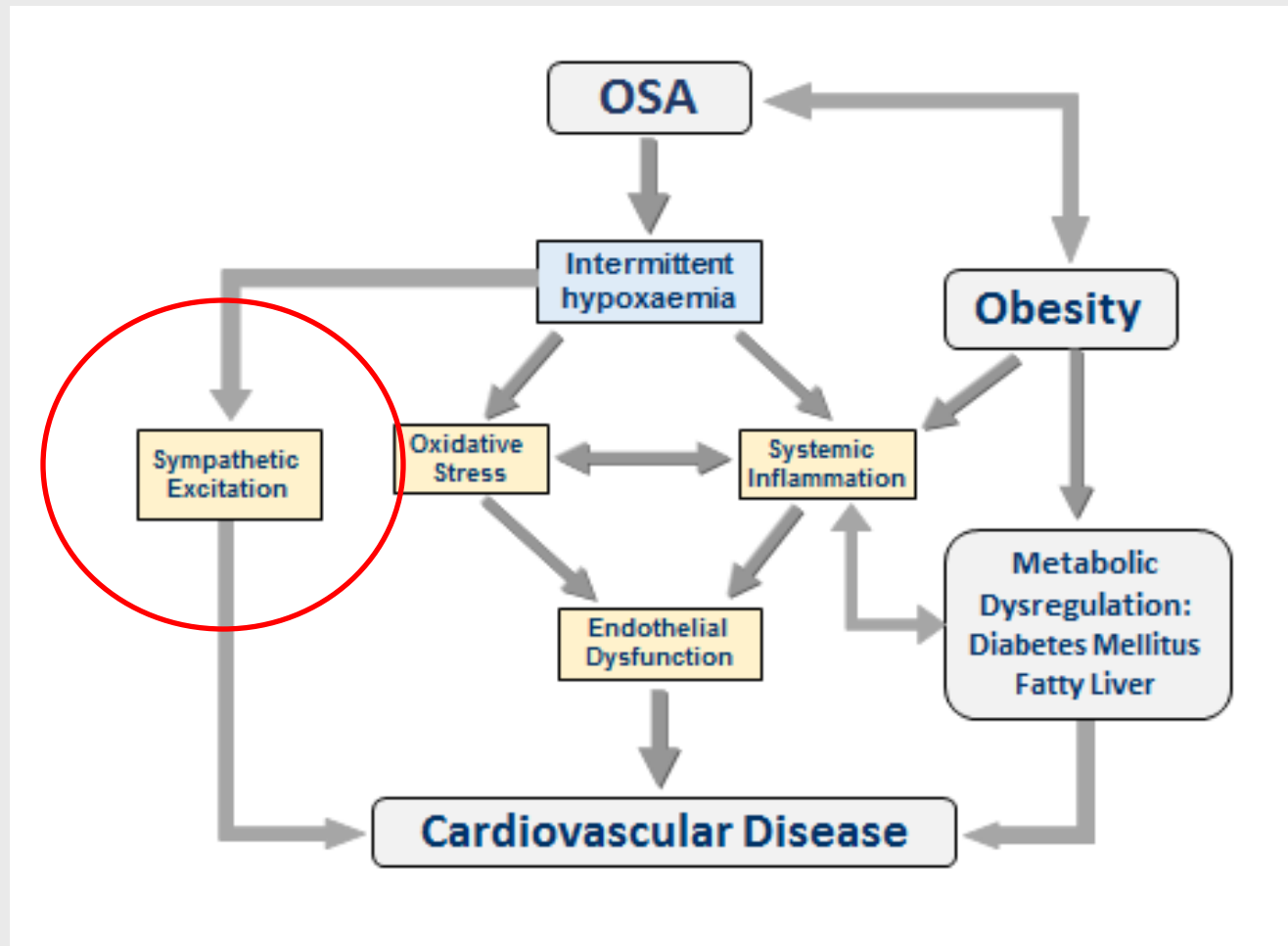


Message: Obesity is an independent risk factor for a range of COPD outcomes.

Question: Could occult OSA be a contributing factor?

*Lambert A et al.
Chest. 2017;151:68-77*

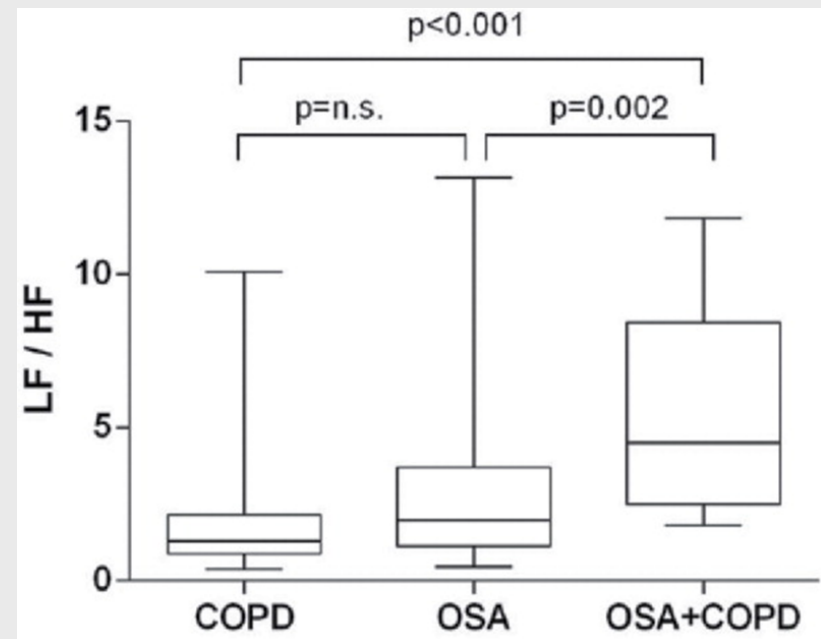
Basic Mechanisms of Cardiovascular Disease in OSA



McNicholas WT et al. *Lancet Respir Med*. 2016 Oct;4(10):826-834

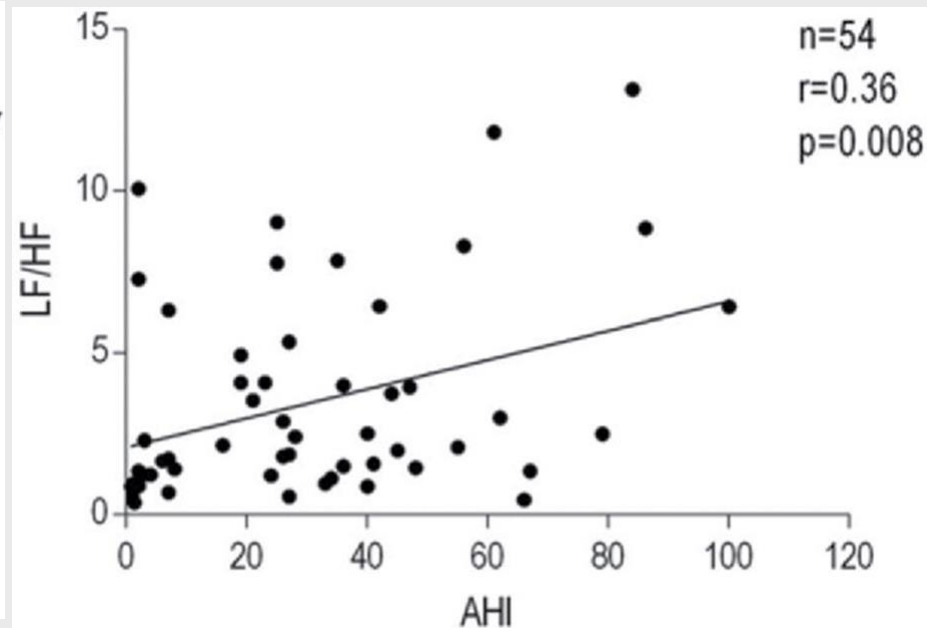
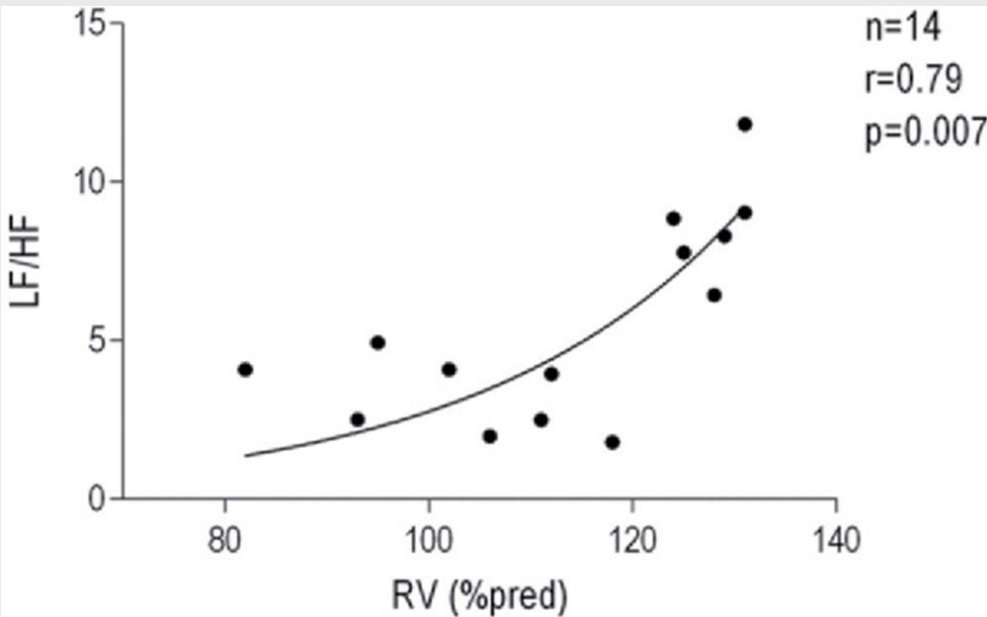
Cardiac Sympathetic Hyperactivity in Patients with COPD and OSA.

- 14 patients with severe OSA (AHI>30) and COPD compared with patients having COPD or OSA alone.
- Cardiac sympathetic activity assessed by heart rate variability
- High frequency power was lower and low frequency power greater in overlap patients compared with COPD or OSA alone ($P<0.01$)
- Overlap patients had higher LF/HF ratio as compared with patients in OSA and COPD groups ($p < 0.01$).



Taranto-Montemurro L et al. COPD 2016 Dec;13(6):706-711

Cardiac Sympathetic Hyperactivity in Patients with COPD and OSA.

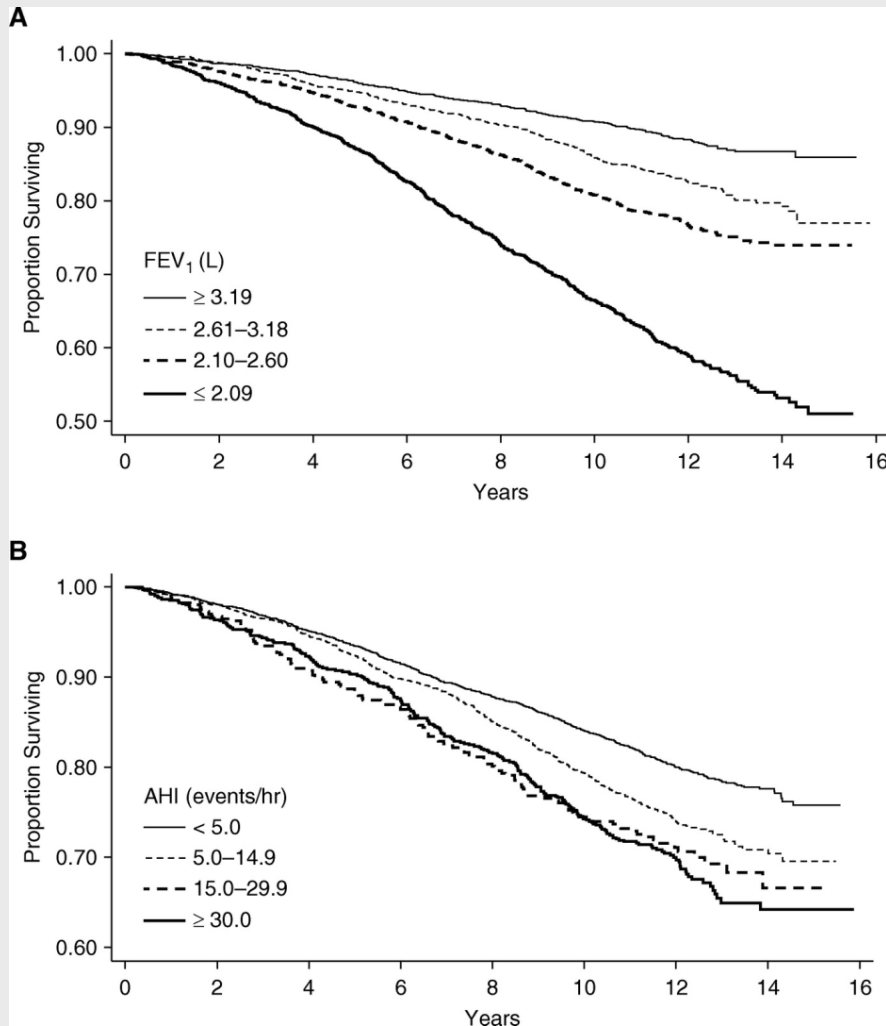


Message: Patients with both OSA and COPD have higher sympathetic modulation of heart rate compared with those with OSA or COPD alone.

Taranto-Montemurro L et al. COPD 2016 Dec;13(6):706-711

Lung Function and Sleep-disordered Breathing Effects on All-Cause Mortality

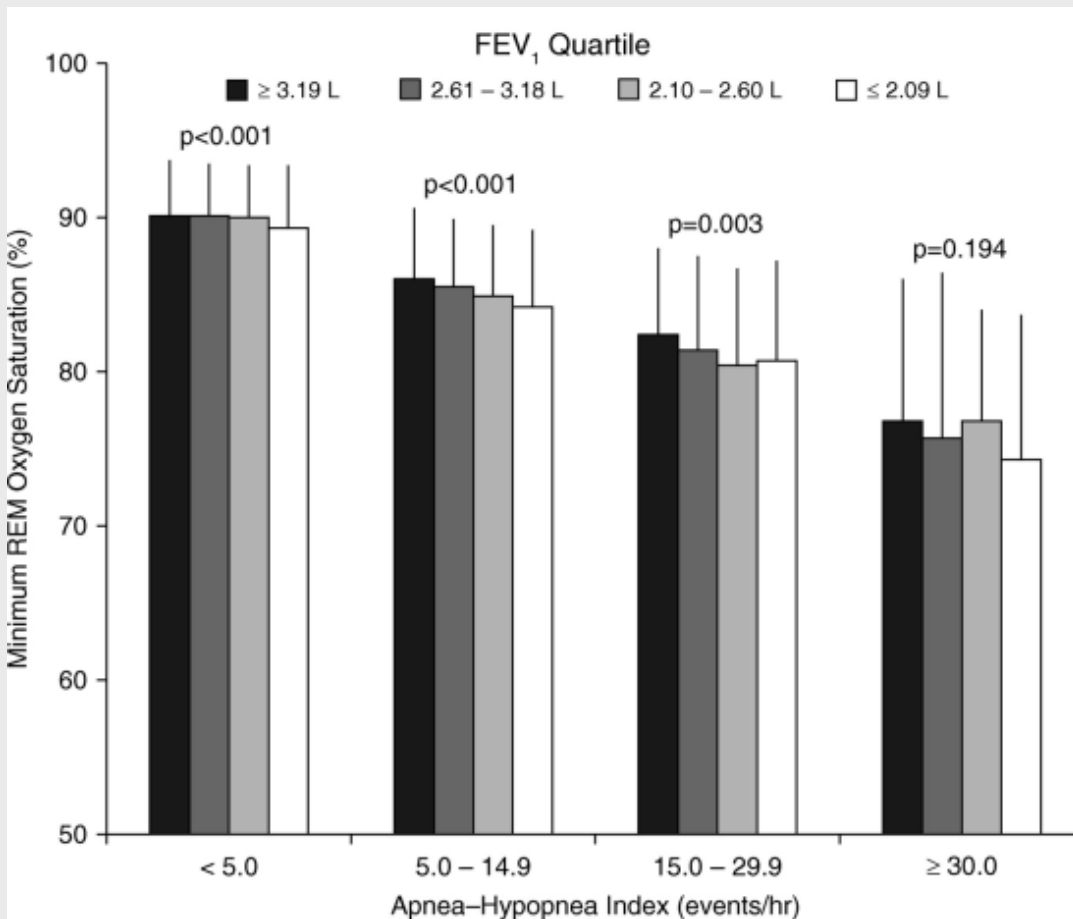
6173 subjects, Sleep Heart Health Study - home PSG



- For every 200-ml decrease in FEV₁, mortality increased by 11% in those without SDB
- In contrast, for every 200-ml decrease in FEV₁, mortality increased by 6% in those with SDB
- Furthermore, the incremental influence of lung function on all-cause mortality was less with increasing severity of SDB.

Putchala N et al. Am J Respir Crit Care Med 2016;194:1007-1014

Lung Function and Sleep-disordered Breathing Effects on All-Cause Mortality



Message:

- Contrary to the *a priori* hypothesis, impairment in lung function has less of an impact on mortality as SDB severity increases.
- A greater impact of AHI on nocturnal hypoxaemia than airflow obstruction could be a factor.
- Survival bias could have been a confounding factor.

Putcha N et al. Am J Respir Crit Care Med 2016;194:1007-1014

Take-Home Message

- COPD phenotype is likely to have a major impact on predisposition to OSA
- Interaction between cell and molecular mechanisms in both COPD and OSA that likely influence susceptibility to co-morbidities, but specific evidence is lacking
- Interaction also influences outcomes/survival
- Practical importance in recognising overlap syndrome – e.g. benefits of pressure support

List of Abbreviations

- AHI – apnoea/hypopnoea frequency per hour
- BMI – body mass index
- BP – blood pressure
- COPD – chronic obstructive pulmonary disease
- CPAP – continuous positive airway pressure
- ESS – Epworth sleepiness score
- OSA – obstructive sleep apnoea
- PSG – polysomnography (sleep studies)
- HRQOL – health related quality of life
- REM – rapid eye movement
- RHF – right heart failure
- SDB – sleep disordered breathing

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