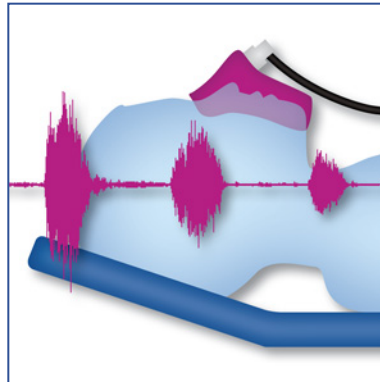


# **Pneumo Update Europe 2018**

**15 - 16 June, Budapest**

## **Sleep Disordered Breathing**



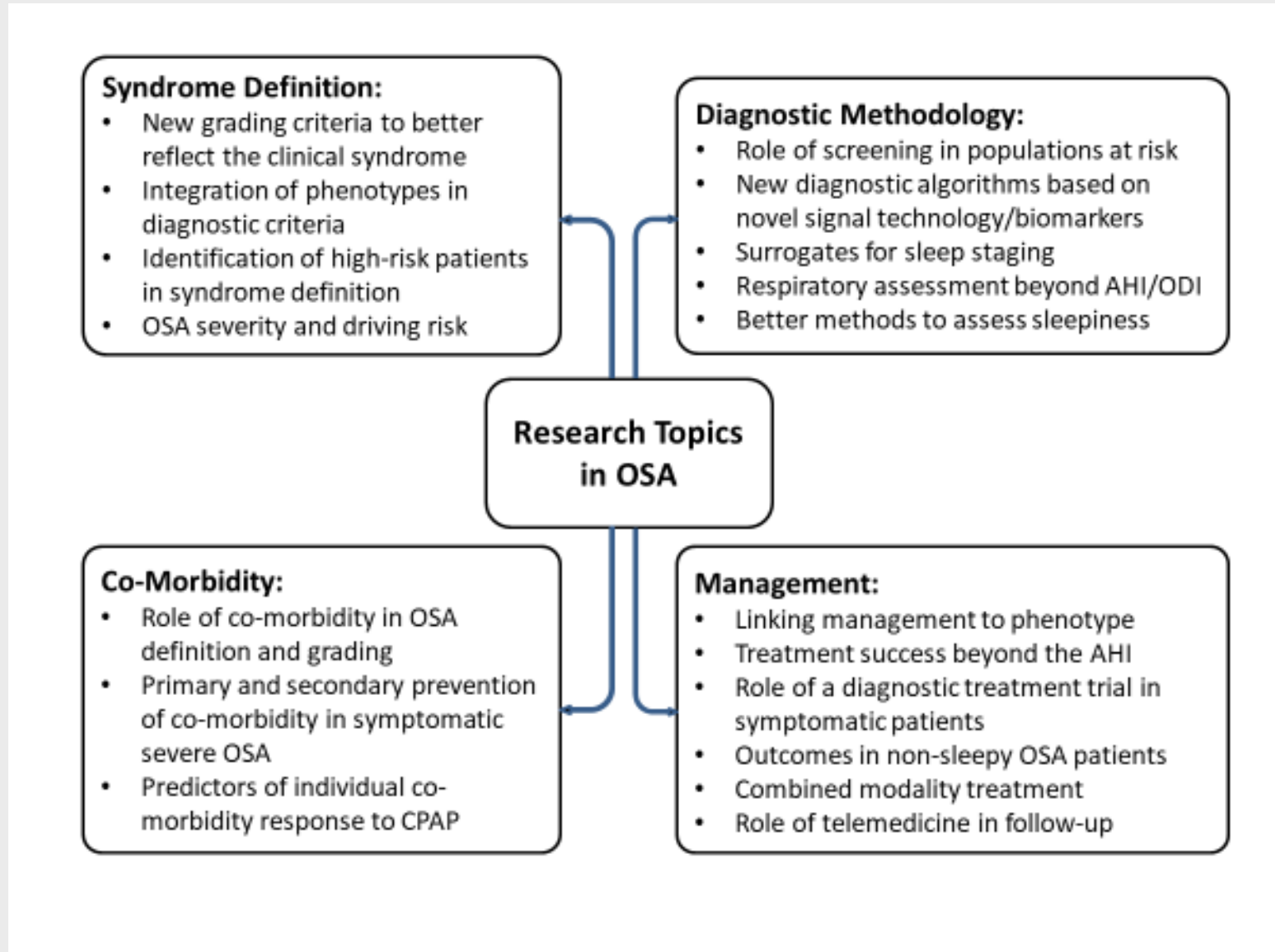
**Walter McNicholas, Ireland**

# **Obstructive Sleep Apnoea**

# State of the Art

- Diagnostic Criteria established over 30 years ago and last major revision in 1999
- Recent prevalence figures of 30-50% in adult males call into question these criteria
- CPAP's pre-eminent place in management is being questioned by increasing understanding of complex pathophysiology and recent negative outcome studies

# Challenges in the Diagnosis and Management of OSA



*McNicholas WT et al. Lancet Respiratory Medicine 2018*

# **Pathogenesis and Diagnosis**

# Genetic Basis of OSA

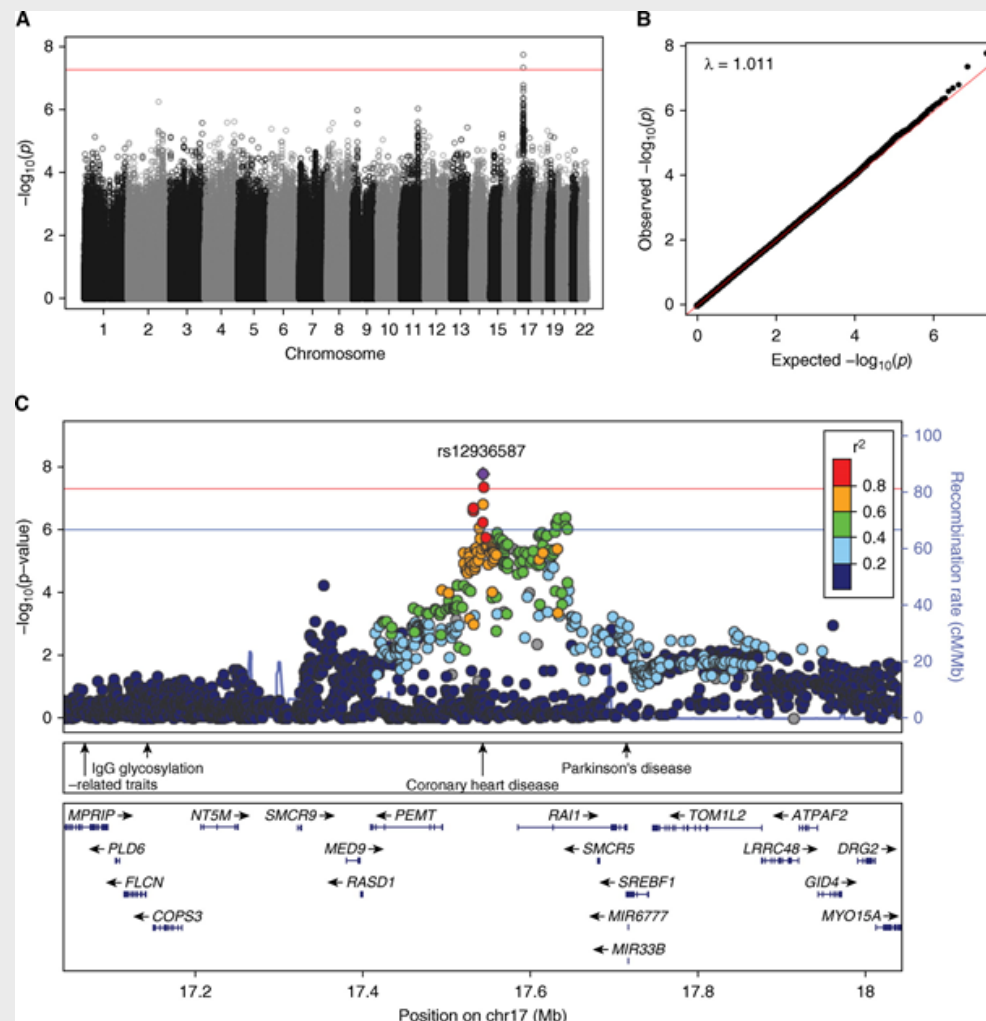
## **Background:**

Increasing evidence that narrowed oropharyngeal airway in OSA has a genetic/hereditary basis

# Multiethnic Meta-Analysis Identifies *RAI1* as a Possible OSA-related Quantitative Trait Locus in Men.

- Genome-wide association tests in 19,733 multi-ethnic participants.
- rs12936587 on chromosome 17 identified as a possible quantitative trait locus for NREM AHI in men ( $N = 6,737$ ;  $P = 1.7 \times 10^{-8}$ ) but not in women ( $P = 0.77$ ).

**Message:** Report supports genetic basis for OSA in men.



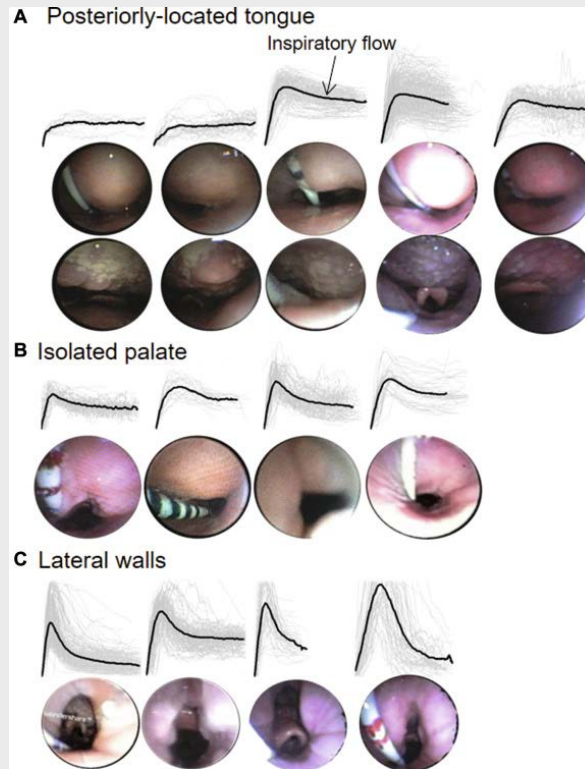
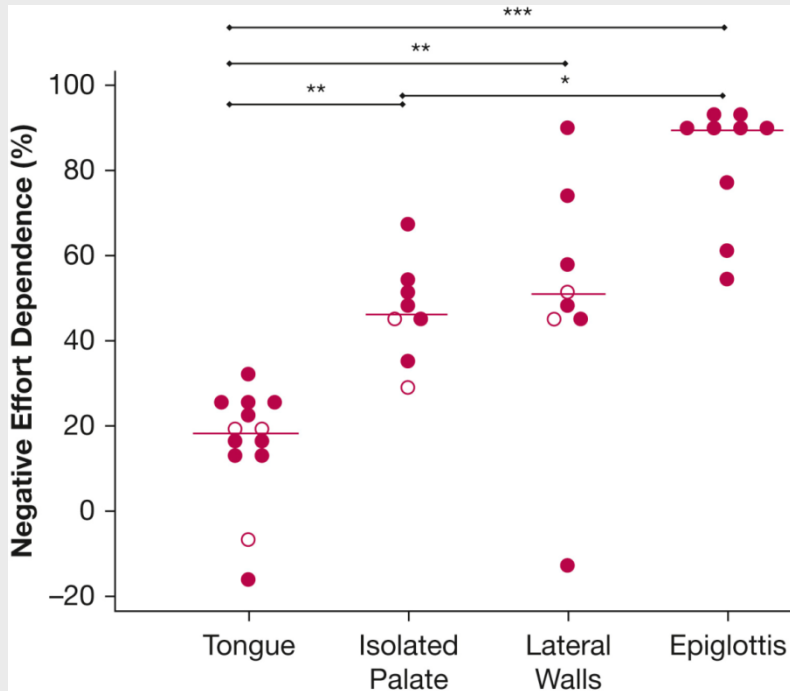
Chen H et al. Am J Respir Cell Mol Biol. 2018;58(3):391-401

# **Non-invasive assessment of Pharyngeal Collapsibility**



# Airflow Shape is associated with the Pharyngeal Structure causing OSA

- 31 OSA patients underwent sleep endoscopy, and nasal flow and pharyngeal pressure recordings
- Negative effort dependence and inspiratory flow differed with site of obstruction

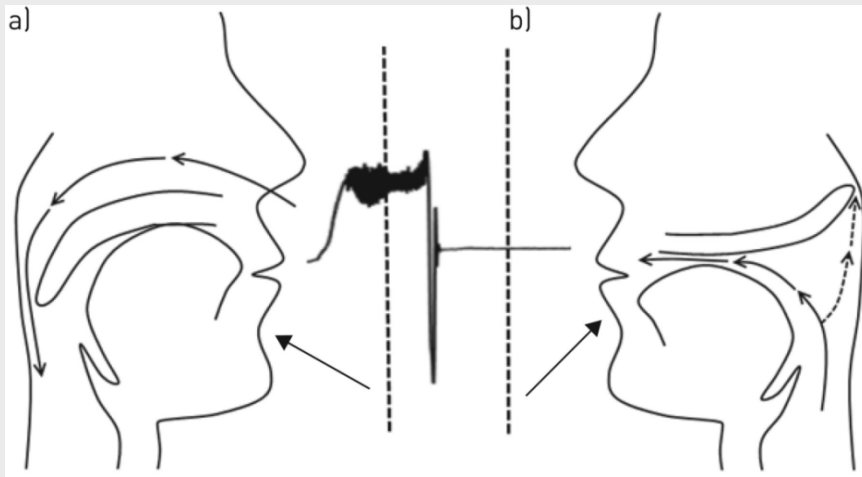


**Message:** Flow shape analysis may be a noninvasive tool to help determine the pharyngeal structure causing collapse

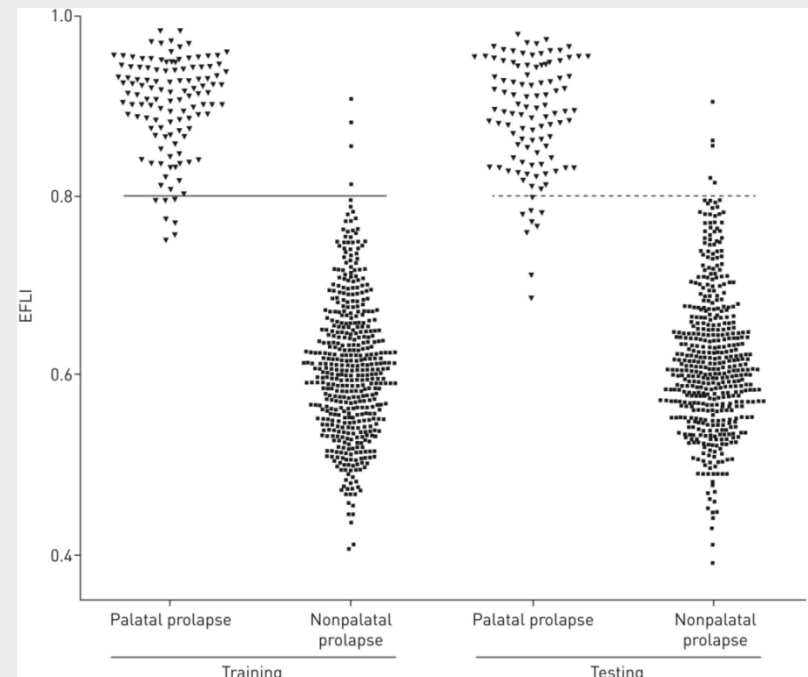
Genta PR et al. CHEST 2017;(3):537–546

# Palatal prolapse as a signature of expiratory flow limitation and inspiratory palatal collapse in OSA

- Palatal prolapse assessed during sleep endoscopy compared to an expiratory flow limitation index (EFLI) determined from flow and peak epiglottic pressure
- A cut-off value of EFLI  $>0.8$  detected the presence of palatal prolapse and EFL with an accuracy of  $>95\%$  and  $82\%$ , respectively. The proportion of breaths with palatal prolapse predicted isolated inspiratory palatal collapse with  $90\%$  accuracy. EFLI derived from nasal pressure gave similar results.



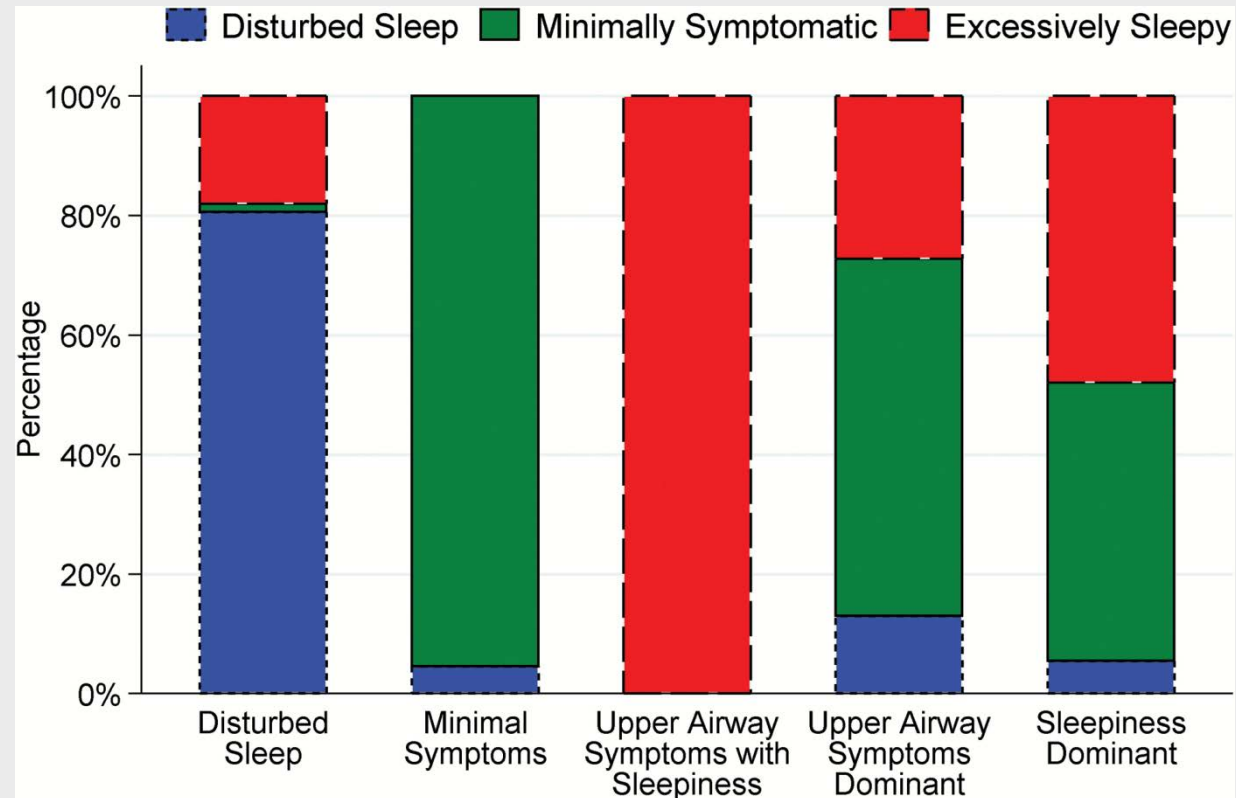
**Message:** Non-invasive assessment can assess upper airway functional abnormality predisposing to OSA



Azarbarzin A et al. *European Respiratory Journal* 2018 51: 1701419

# Recognizable clinical subtypes of OSA across international sleep centers: a cluster analysis

- 972 patients,  $AHI \geq 15$ , in Sleep Apnea Global Interdisciplinary Consortium (SAGIC)
- Analysis of 18 self-reported symptom variables, hypertension, cardiovascular disease, and diabetes

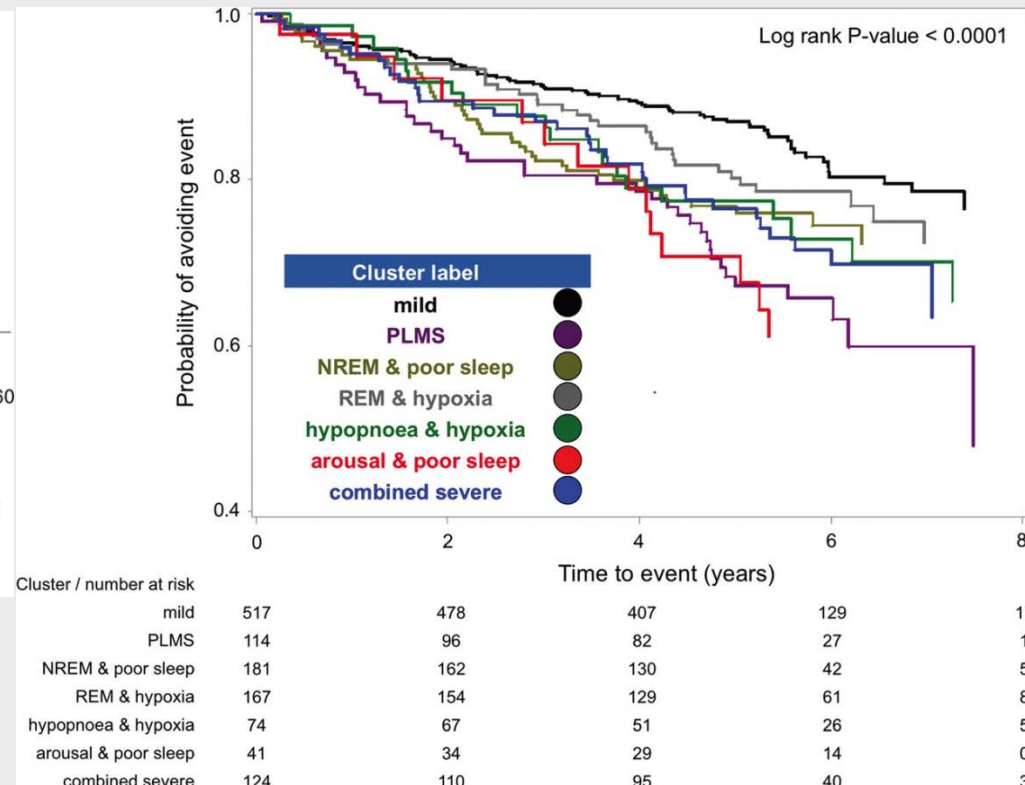
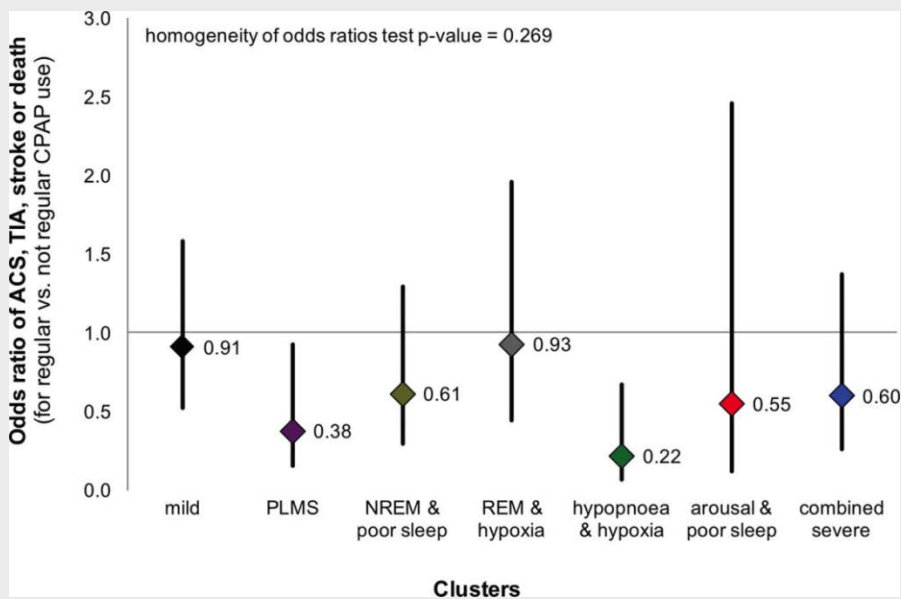


**Message:** This study identifies distinct clinical phenotypes in OSA

*Keenan BT et al. Sleep, Volume 41, (3) 1 March 2018, zsx214*

# Polysomnographic phenotypes and their cardiovascular implications in OSA

- 1247 US veterans – can PSG data identify OSA phenotypes (clusters)
- Associations between phenotypes and cardiovascular outcomes

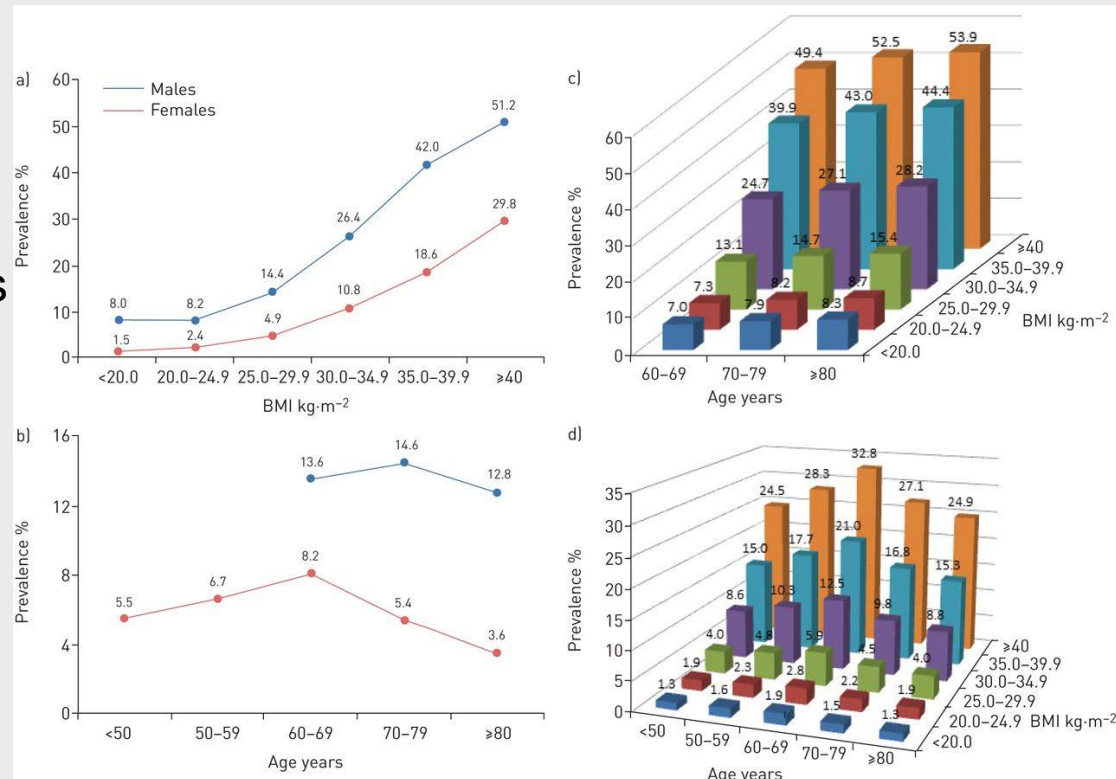


**Message:** PSG data can predict likelihood of future CV events better than AHI

Zinchuk AV *et al.* *Thorax* 2018;**73**:472-480

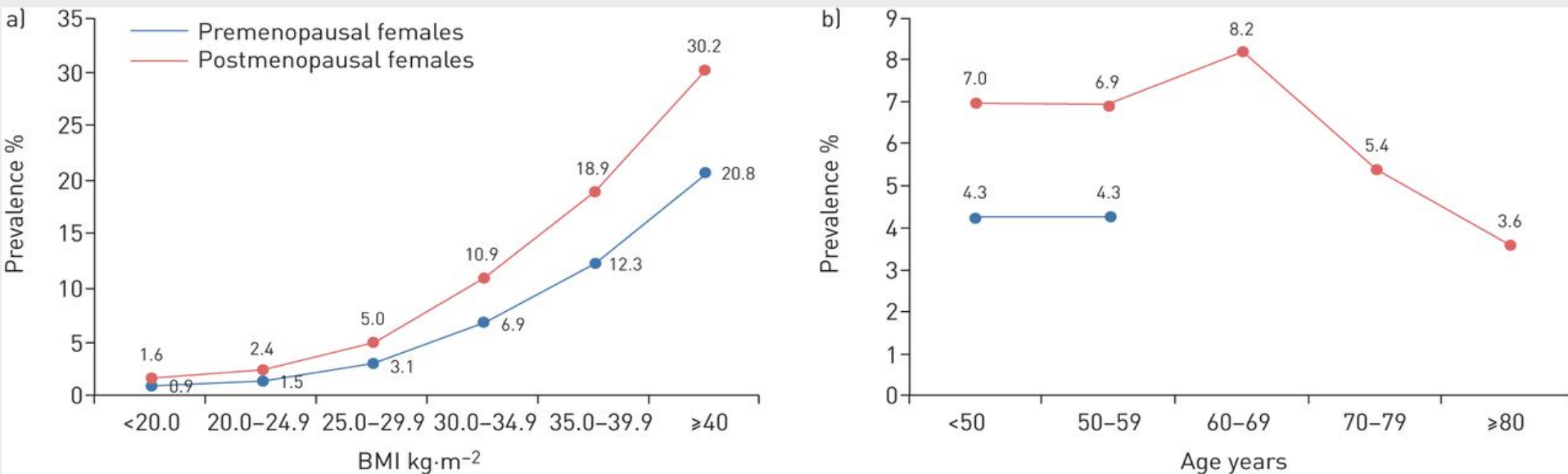
# Sex differences in the associations of OSA with epidemiological factors.

- 143,326 females (48–93 years) from the Nurses' Health Study and 22,896 males from the Health Professionals Follow-up Study (65–101 years).
- OSA prevalence 6.4% in females and 13.8% in males.
- Associations of OSA with physical inactivity, hypertension and daytime sleepiness stronger in females.
- Associations with waist circumference and witnessed apnoea stronger in males.
- **Message: Clinical manifestations differ in males and females with OSA.**



Huang T et al, *Eur Resp J* Mar 2018, 51 (3) 1702421

# Sex differences in the associations of OSA with epidemiological factors.



Huang T et al, *Eur Resp J* Mar 2018, 51 (3) 1702421

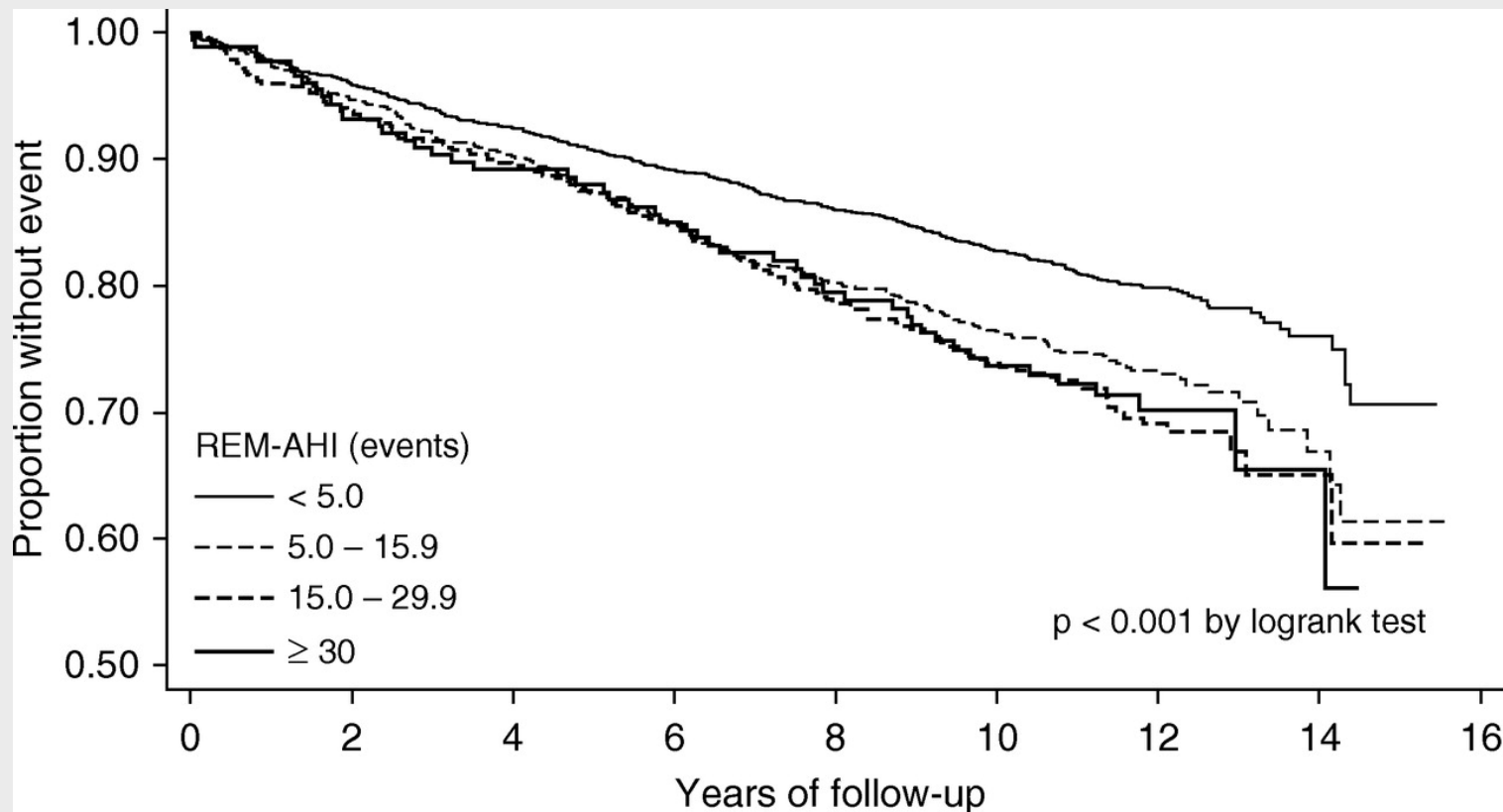
# Take Home Messages

- Growing evidence of genetic basis to OSA
- Non-invasive physiological measurements can predict upper airway obstruction
- Important differences between males and females with OSA – genetics, clinical presentations



# OSA during REM Sleep and Cardiovascular Disease – SHHS.

**Severe OSA present only during REM sleep is associated with recurrent cardiovascular events in people with prevalent cardiovascular disease**

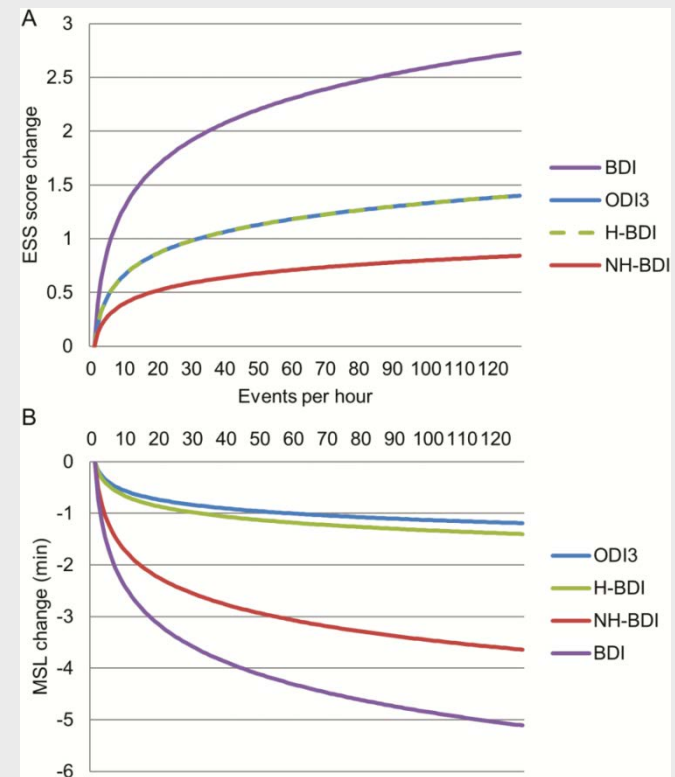
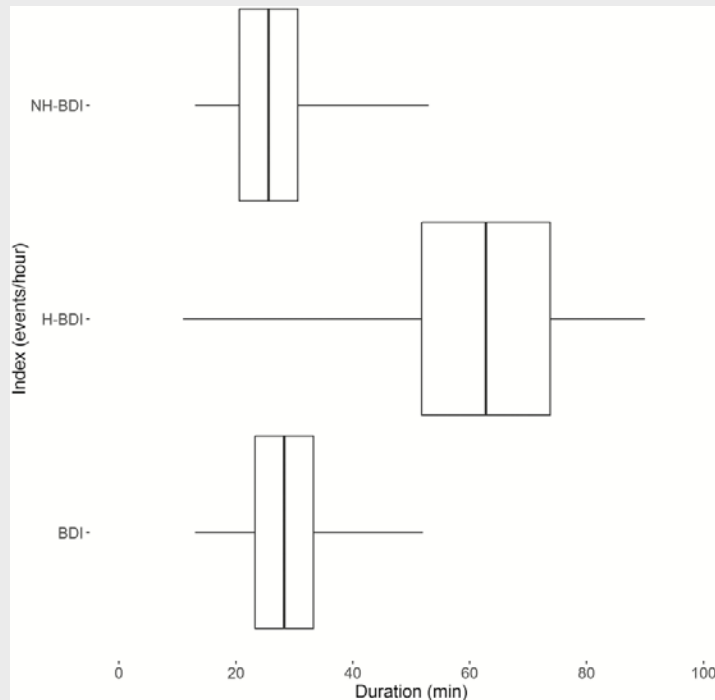


*Aurora et al. Am J Respir Crit Care Med. 2018;197(5):653-660*



# Breathing Disturbances Without Hypoxia Are Associated With Objective Sleepiness in OSA

- 1022 subjects (Wisconsin Cohort) – automated PSG analysis for RDI and hypoxia
- Subjective (ESS) and objective sleepiness (MSLT), and hypertension (BP>140/90)
- Hypoxia associated events correlated more with hypertension and ESS but non hypoxia events associated more with MSLT.

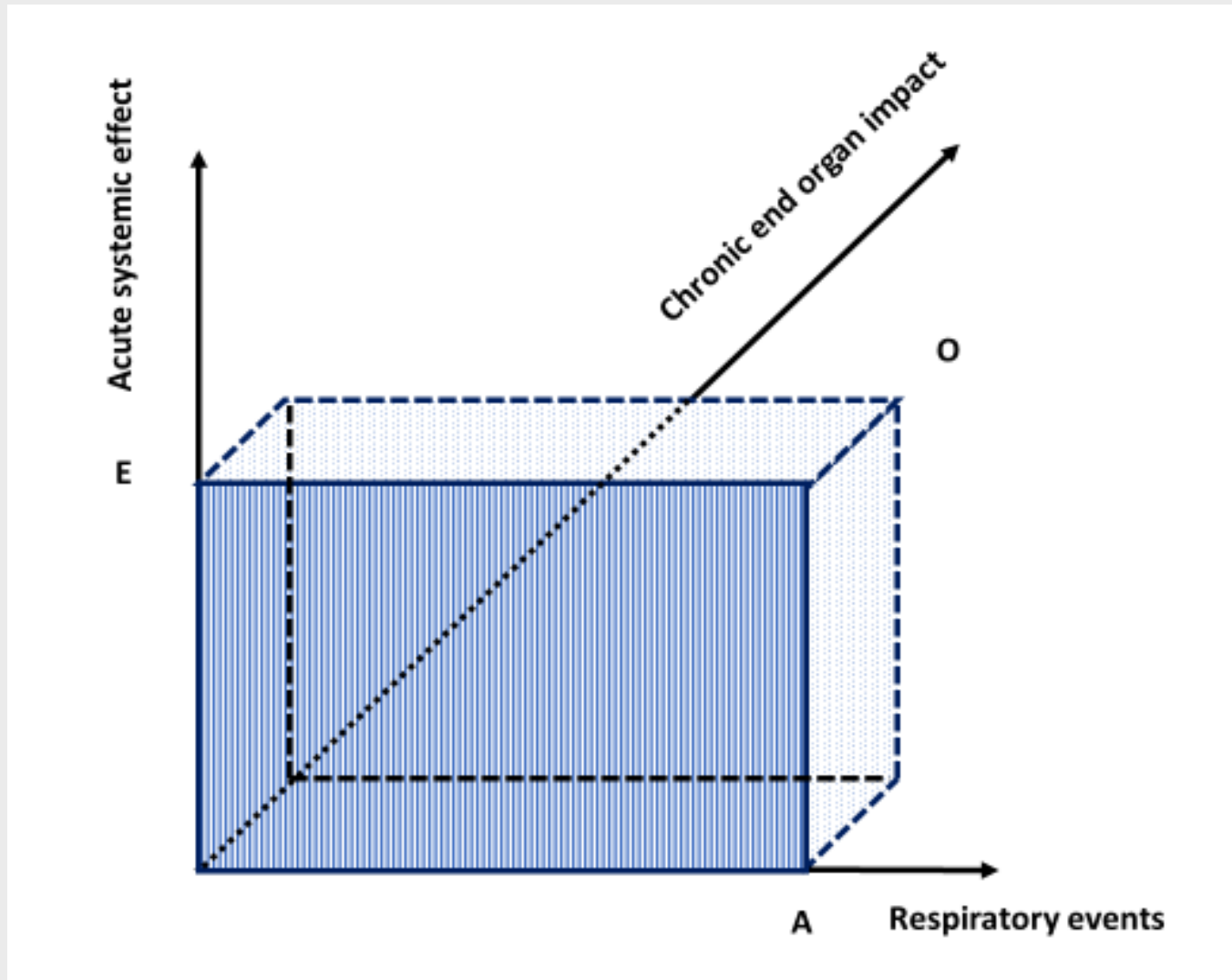


**Koch H et al. Sleep, Volume 40, Issue 11, 1 November 2017, zsx152**

# Take Home Message

- Study supports growing evidence that cardiometabolic co-morbidities are principally driven by hypoxia
- ***Speculation:*** The finding that non hypoxic events are associated with objective sleepiness could indicate that heightened arousal sensitivity is a mechanism producing earlier termination of apnoea but also more sleep fragmentation

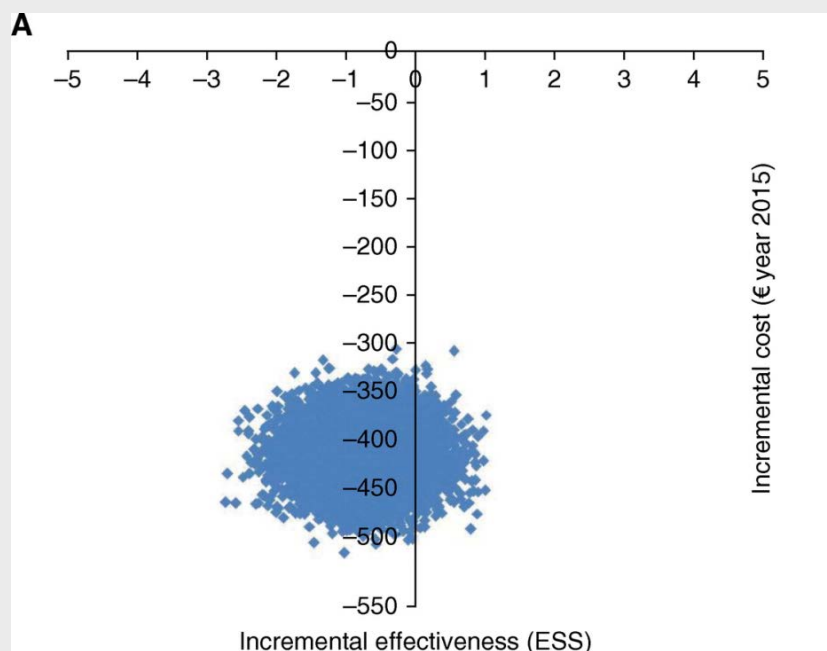
# 3-dimensional model of OSA disease severity



*Randerath W et al. Eur Resp J 2018*

# Polysomnography Is Not Necessary for the Management of Most Patients with Suspected OSA.

- Effectiveness of home respiratory polygraphy (HRP) protocol assessed by ESS is not inferior to that of PSG
- Efficacy assessed by HRQL and ABPM similar between protocols
- Cost effectiveness relationship favours HRP (savings average €416)



**Message: Home studies are as effective as SLAB PSG and cheaper.**

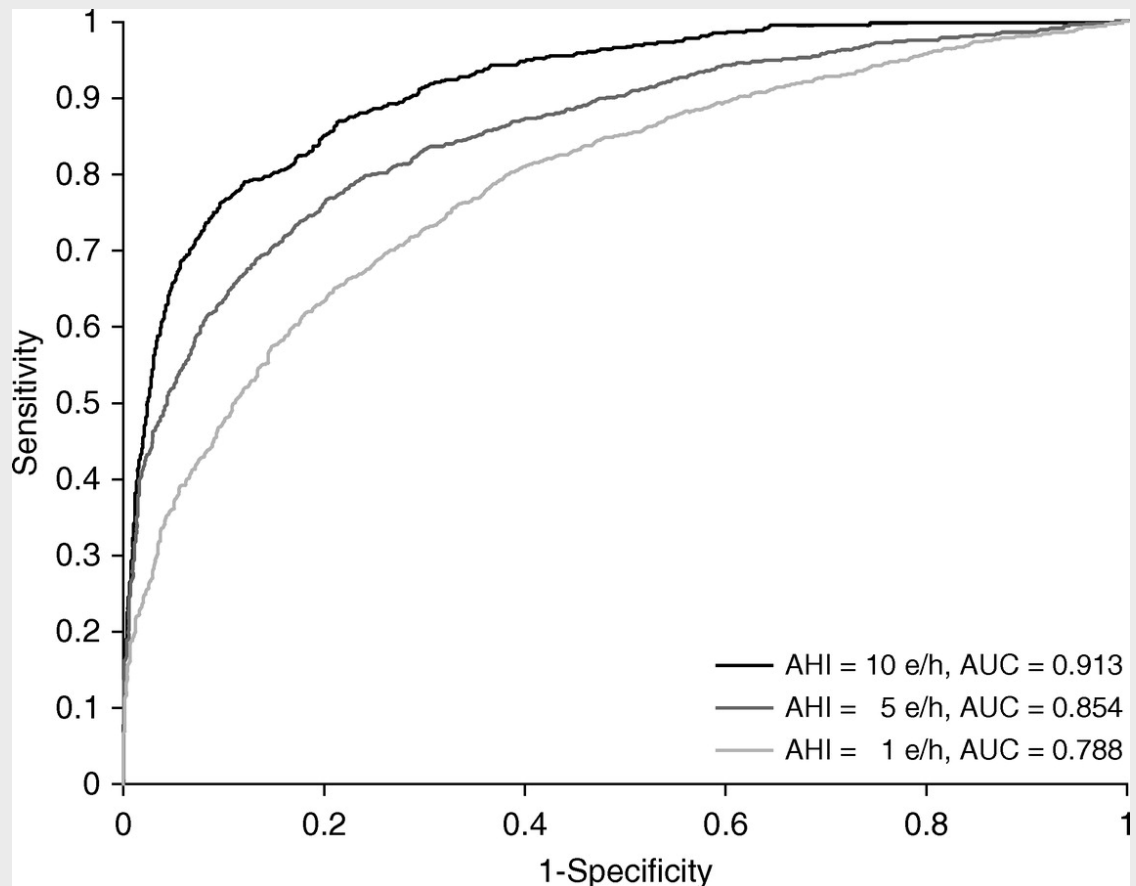
***Corral et al. Am J Respir Crit Care Med. 2017;196(9):1181-1190.***

# Nocturnal Oximetry–based Evaluation of Habitually Snoring Children.

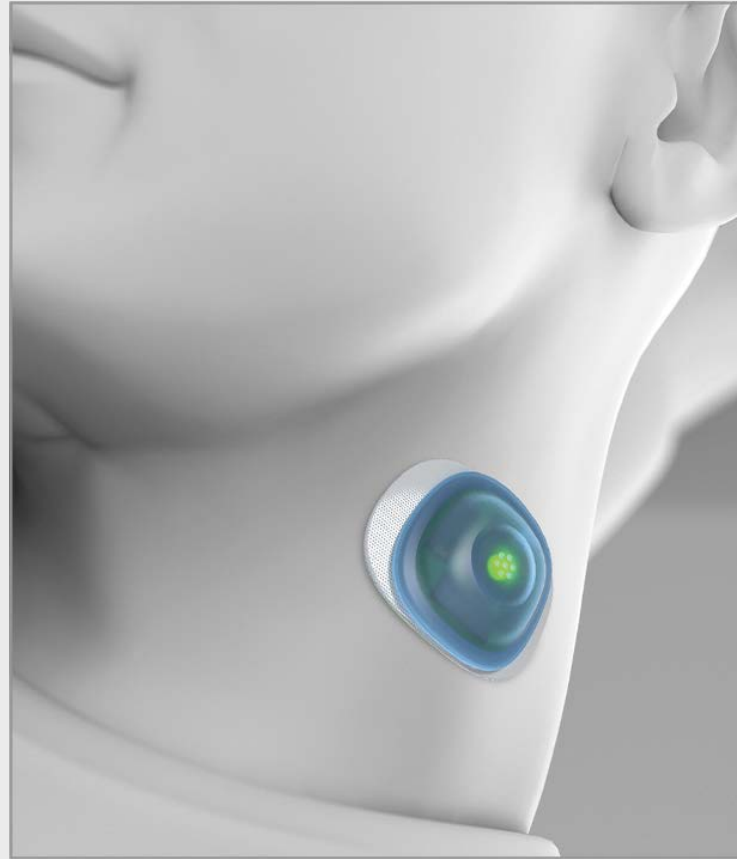
- 4191 children from 13 sleep laboratories worldwide
- Automated neural network algorithm of single-channel nSpO<sub>2</sub> recordings
- High agreement with AHI from PSG (correlation coefficient, 0.785)

**Message: Oximetry is a suitable screening tool for OSA in children especially for more severe disease**

*Hornero et al. Am J Respir Crit Care Med. 2017 Dec 15;196(12):1591-1598*



# In-home, Over-the-counter OSA Sensor on the Horizon.

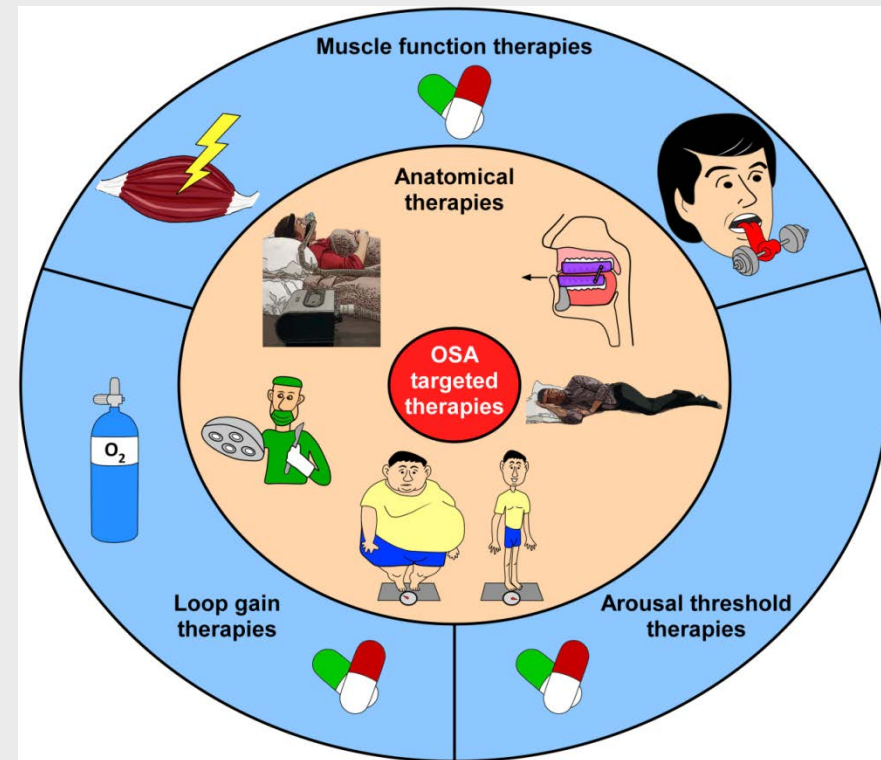
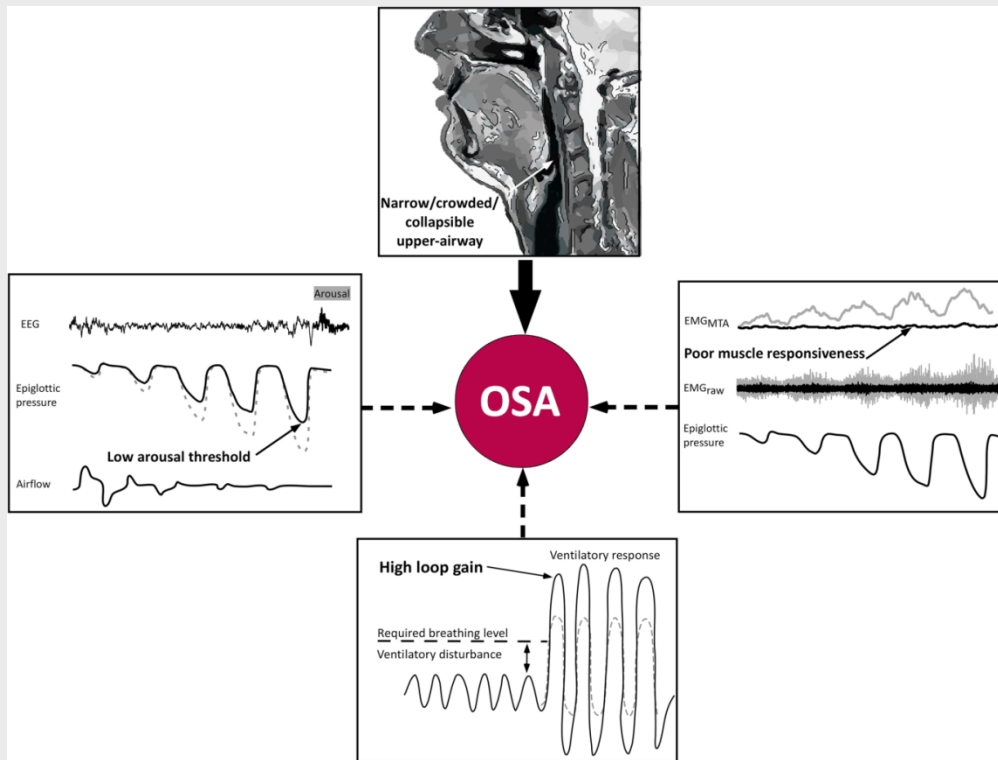


[Abbasi](#) J. *JAMA*. 2017;317(22):2271.

# Treatment of OSA

- CPAP has been the cornerstone of OSA therapy for decades
- Increasing recognition of the role of other factors relating to respiratory control, muscle function, and arousal has increased the potential role of other management options
- Personalised approach to management that recognises the range of potential factors in optimum choice of management - single or multiple options.

# Personalized Management Approach for OSA



Carberry J et al. CHEST 2018; 153, Issue 3, Pages 744–755



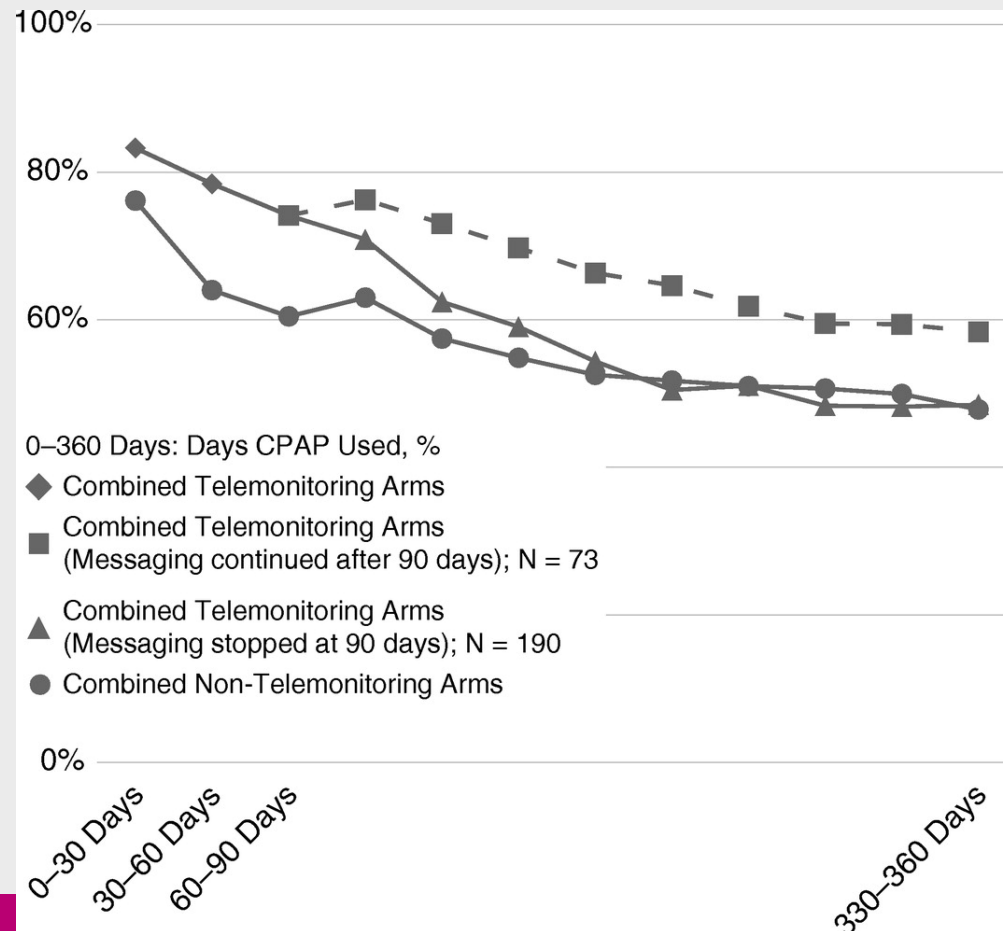
# CPAP

# Effect of Telemedicine Education and Telemonitoring on CPAP Adherence in OSA.

- 556 OSA patients prescribed CPAP randomised to 1] usual care, 2] Tel-Ed, 3] Tel-TM, 4] Tel-Ed and Tel-TM. Monitored for 90 days.
- Tel-TM improved CPAP adherence but not Tel-ED; ESS reduction similar.

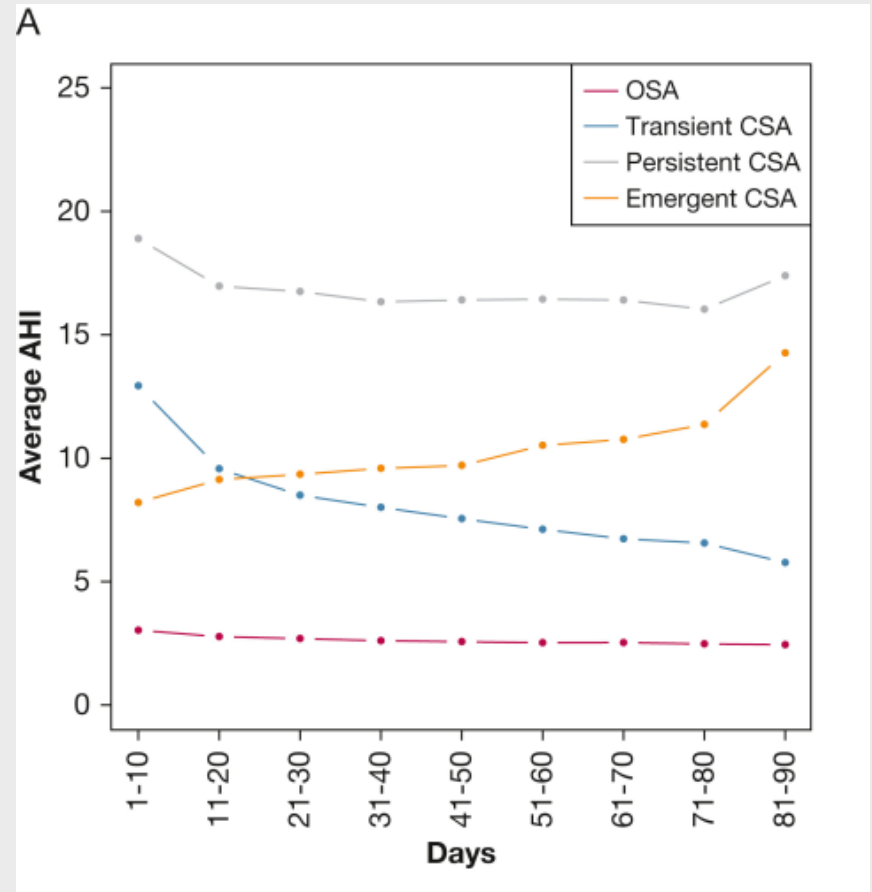
**Message: Telemedicine education and telemonitoring improve CPAP compliance but do not produce greater improvements in sleepiness**

*Hwang et al. Am J Respir Crit Care Med. 2018; 197(1):117-126.*



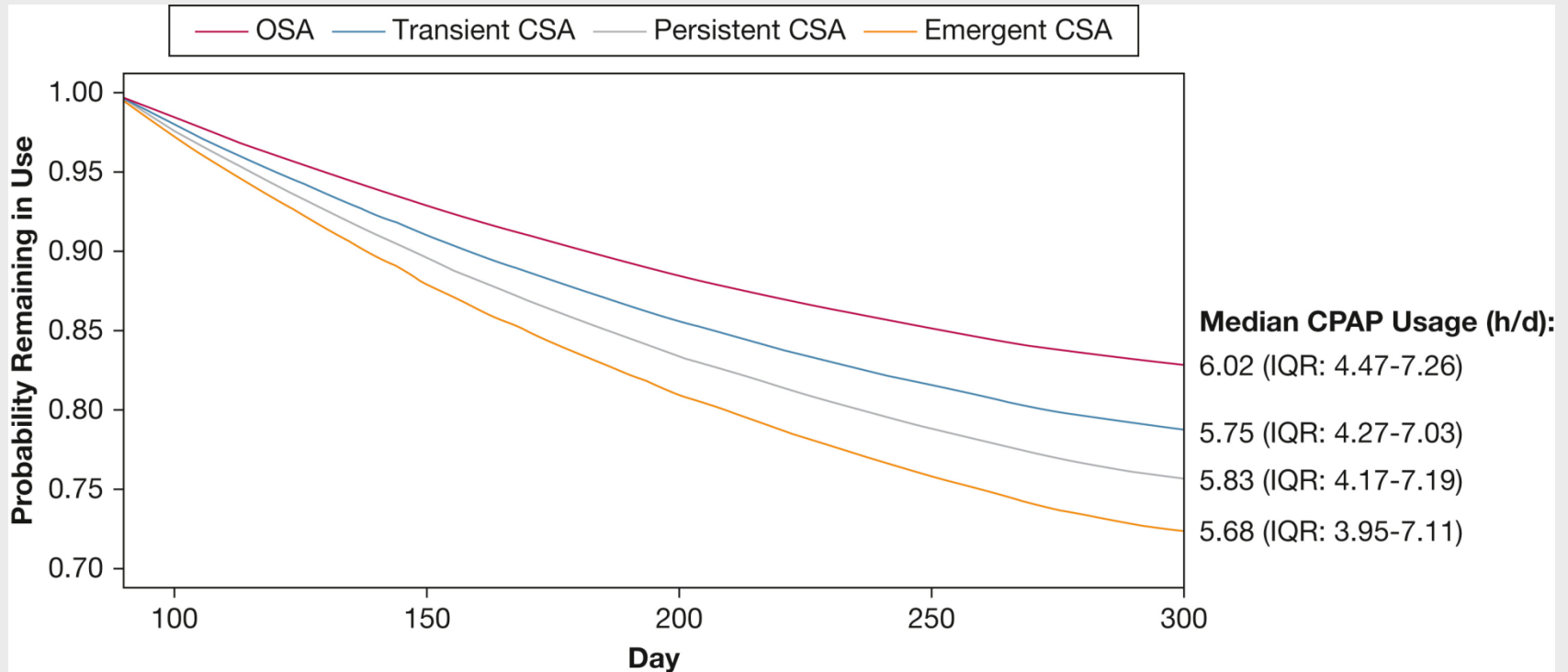
# Trajectories of Emergent Central Sleep Apnea During CPAP Therapy

- US telemonitoring of 133,000 patients with OSA started on CPAP
- 3.5% developed central sleep apnoea on CPAP
- Emergence of CSA on CPAP associated with more CPAP discontinuation
- Patients older, higher residual AHI, more mask leaks



Liu et al. Chest 2017;152(4):751-760

# Trajectories of Emergent Central Sleep Apnea During CPAP Therapy



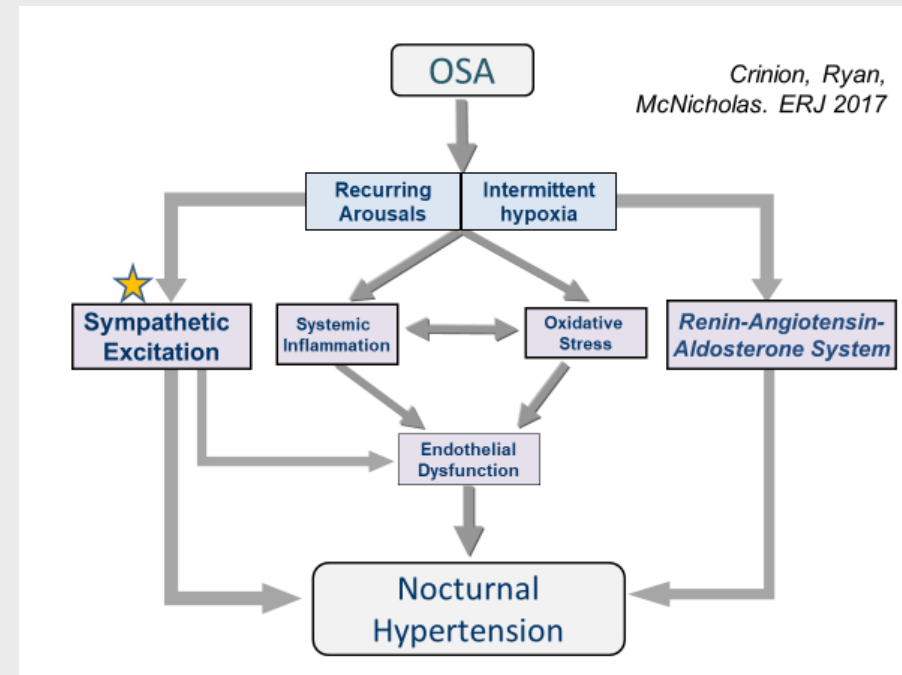
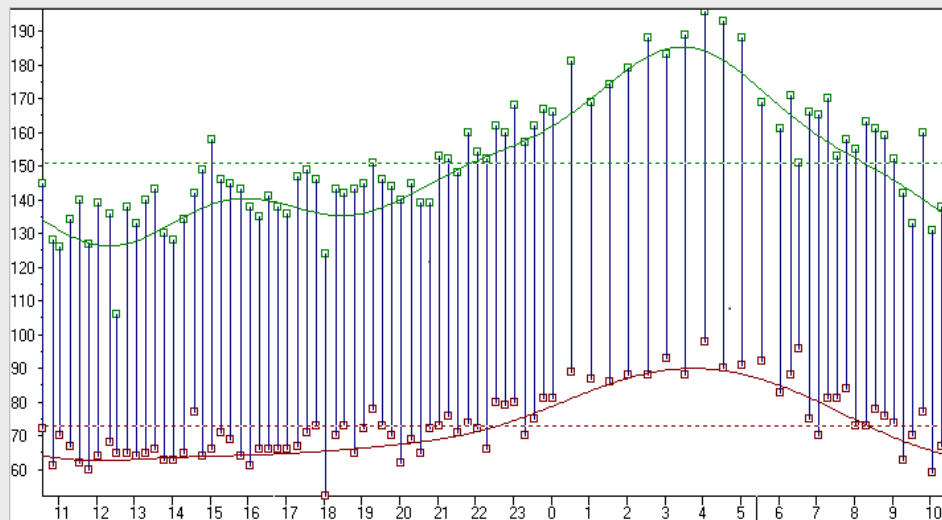
**Message:** CPAP emergent CSA is more likely in older patients and diminishes compliance

*Liu et al. Chest 2017;152(4):751-760*

# Association of PAP Therapy with Cardiovascular Events and Death in OSA.

- **Background:** SAVE trial concluded that CPAP therapy in non-sleepy OSA patients was ineffective in secondary prevention of cardiovascular morbidity and mortality but was limited by poor treatment compliance. (*McEvoy et al. NEJM 2016*).
- However, small but significant reduction in blood pressure.
- Recent meta-analysis of reports on cardiovascular outcomes of CPAP therapy concluded that CPAP does not prevent cardiovascular events or death. [Yu J et al. JAMA. 2017;318\(2\):156-166.](#)

# Diurnal BP Pattern in OSA – loss of normal nocturnal dipping

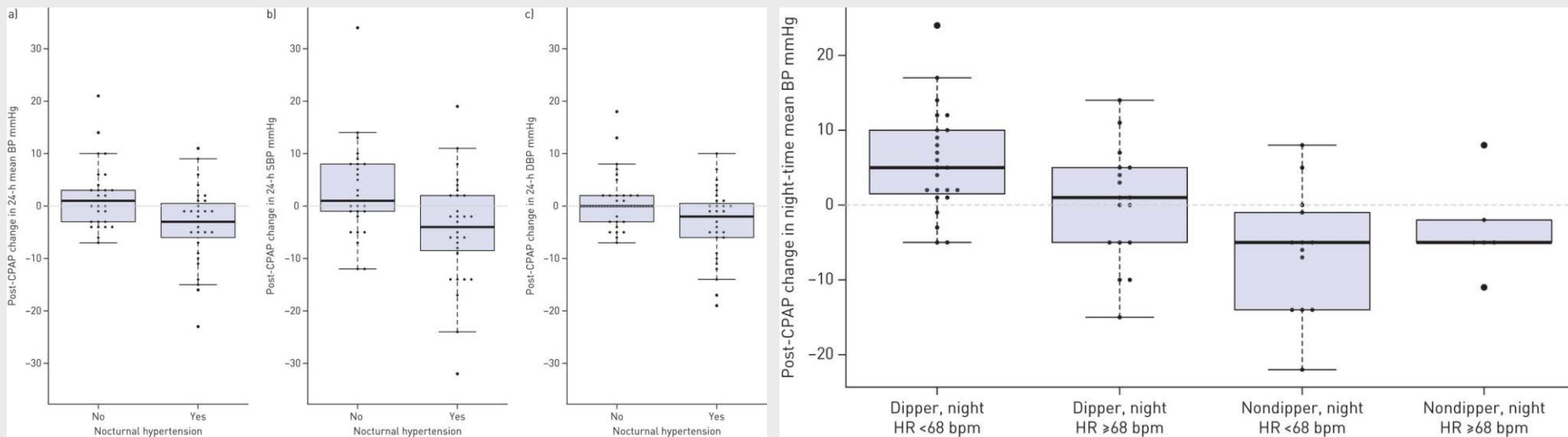


Strong association with drug-resistant hypertension

*Crinion, Ryan, McNicholas. Eur Resp J 2017. 49 (1): 1601818*

# BP response to CPAP in OSA: predictive value of 24-h ambulatory BP monitoring

- 88 patients with severe OSA having 24-hr ABPM, biomarkers and HR measured at baseline and after 6 months CPAP
- Baseline nocturnal hypertension and low HR predicted the best BP response to CPAP.

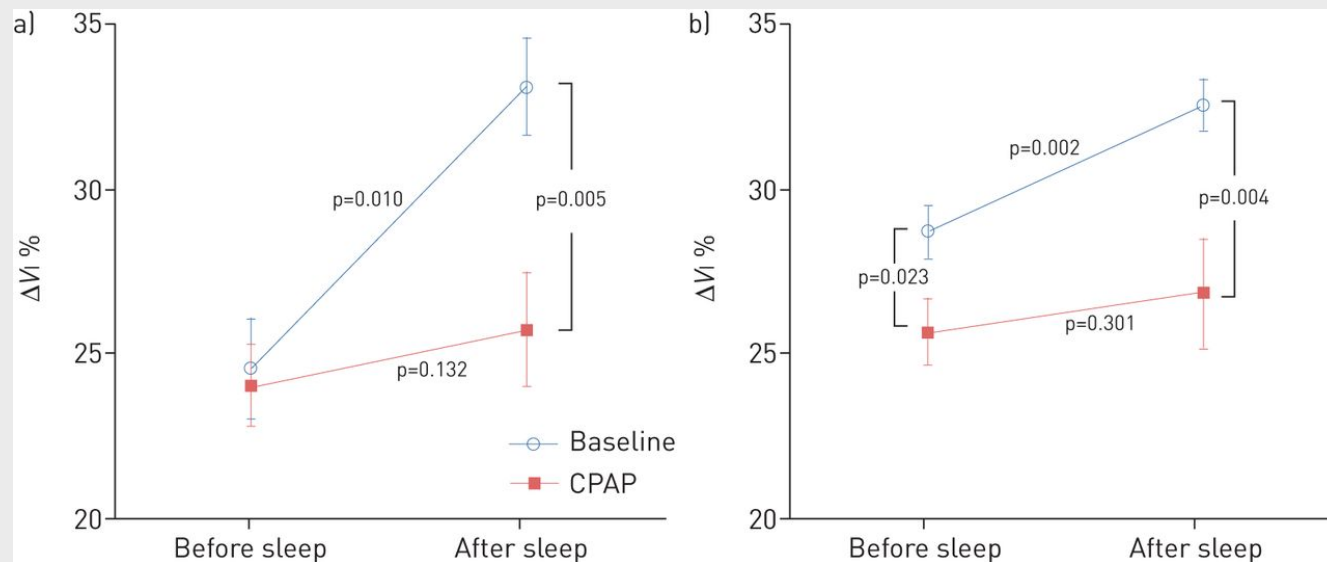


**Message: 24-hr BP monitoring helps predict BP response to CPAP**

*Castro-Grattoni AL et al. European Respiratory Journal 2017 50: 1700651*

# Effect of CPAP on determinants of BP control

- 32 OSA patients with newly diagnosed HTN randomised to CPAP/ sham.
- Assess effects of CPAP on peripheral chemosensitivity, RAAS activity, sympathetic tone, and endothelial biomarkers in patients with isolated nocturnal hypertension or day–night sustained hypertension.
- CPAP reduced nocturnal increase in chemosensitivity only in isolated nocturnal hypertension patients



**Message:** CPAP benefits to BP control mechanisms seen only in isolated nocturnal hypertension

*Casitas R et al. European Respiratory Journal 2017 50: 1701261*

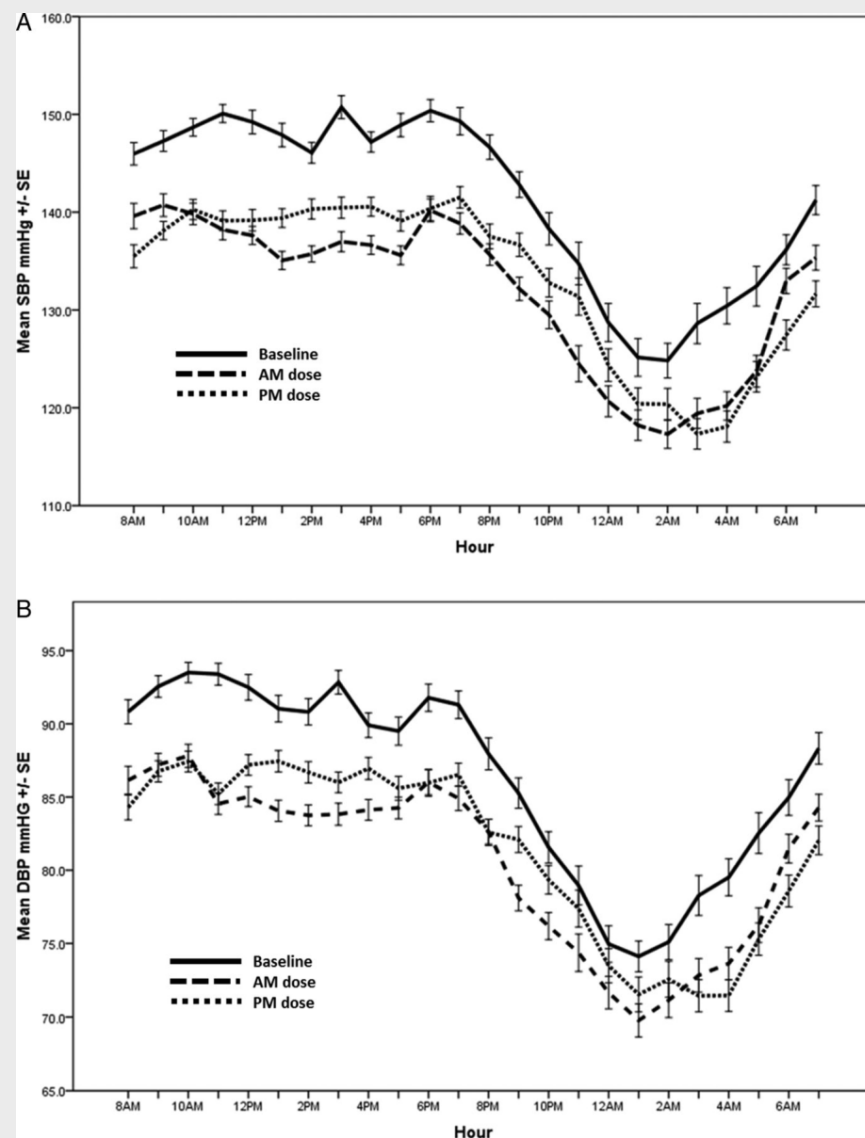


# Chronotherapy for hypertension in OSA - RPCT

- 85 patients AHI>15 and HTN given perindopril in AM or PM
- AM perindopril produced greater reduction in daytime BP and similar reduction in sleep BP as PM perindopril
- Addition of CPAP caused further reductions in BP, similar with AM and PM medication

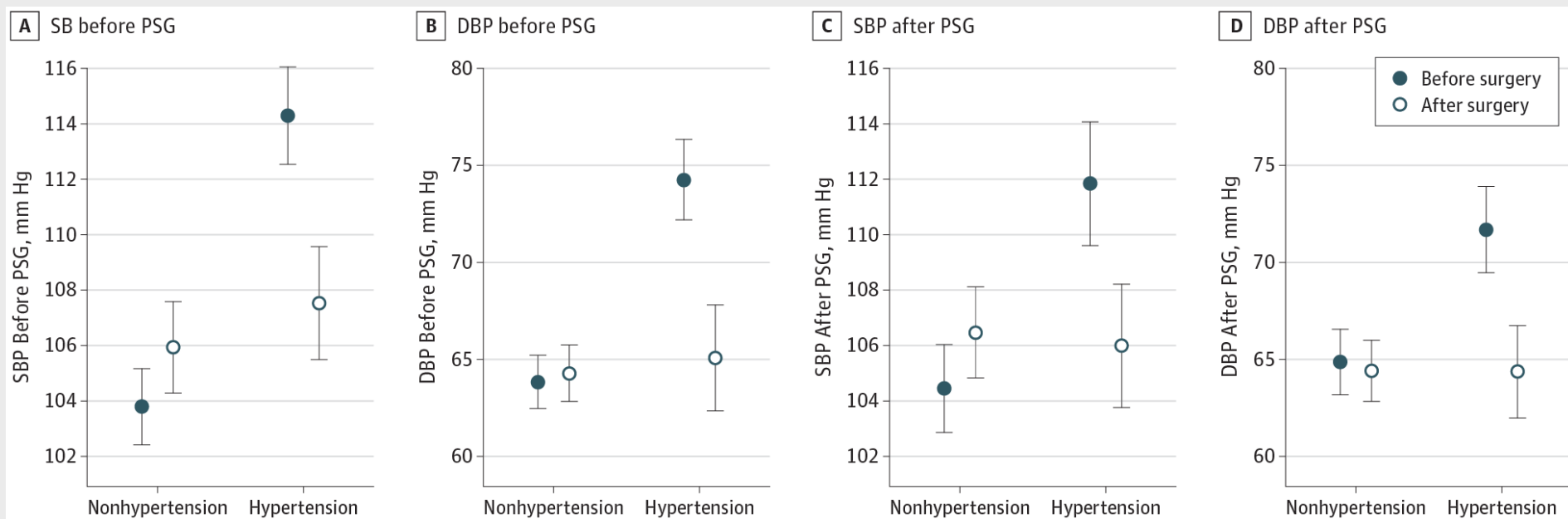
**Message:** AM BP medication superior to PM and CPAP addition added further benefit.

Serinel Y et al. *Thorax* 2017;**72**:550-558



# BP post Adenotonsillectomy in Hypertensive and Nonhypertensive Children with OSA

- 204 non-obese children with OSA undergoing adenotonsillectomy.
- Hypertensive children showed improvement in systolic and diastolic BP

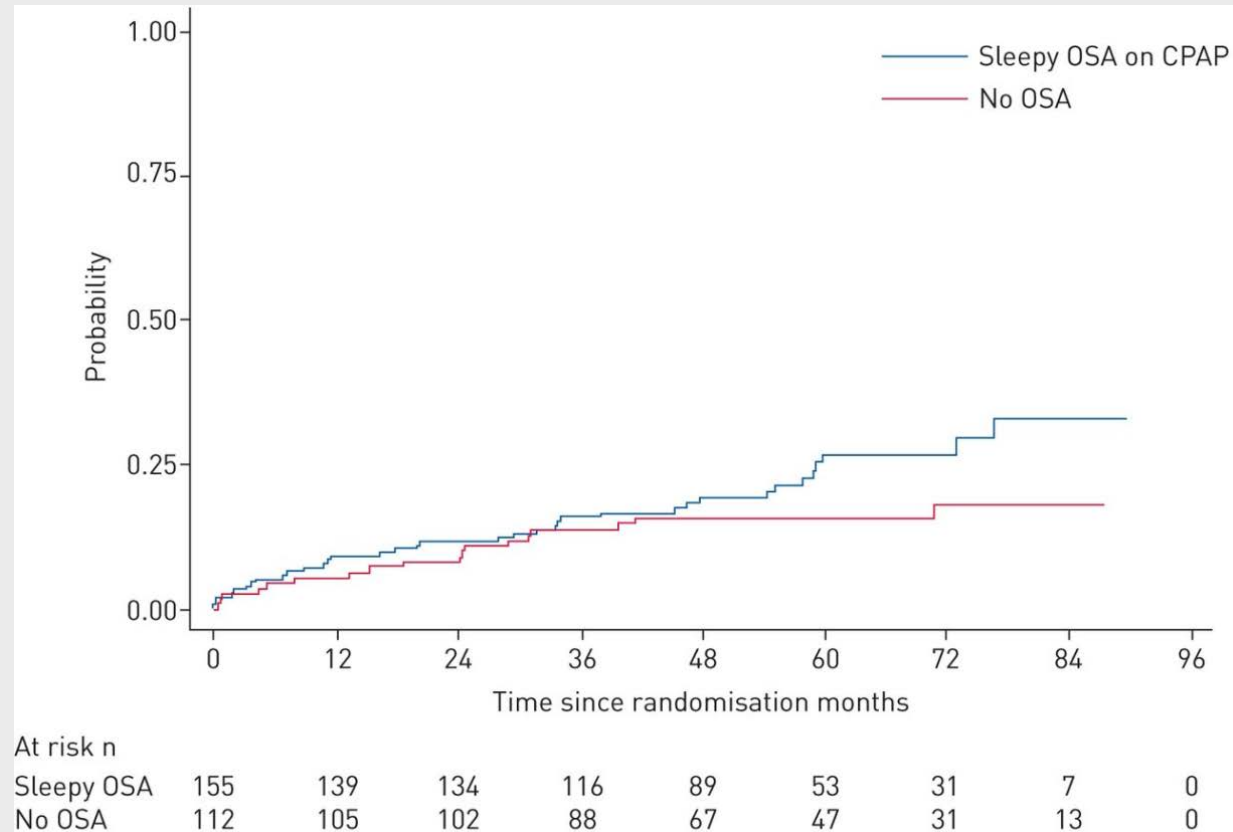


**Message:** Hypertensive children with OSA should be screened for adenotonsillar hypertrophy and have surgery where appropriate

[Lee CH et al.](#) *JAMA Otolaryngol Head Neck Surg.* 2018;144(4):300-307.

# Outcomes in coronary artery disease patients with sleepy OSA on CPAP

- Revascularised coronary artery disease patients with AHI >15 and ESS >9 (N=155) treated with CPAP compared with 112 similar patients without OSA. Both groups followed long term.
- No difference in time to onset of first major adverse cardiovascular and cerebrovascular event.
- **Limitation:** Observational and “positive” finding based on the premise that OSA patients expected to have worse outcome.

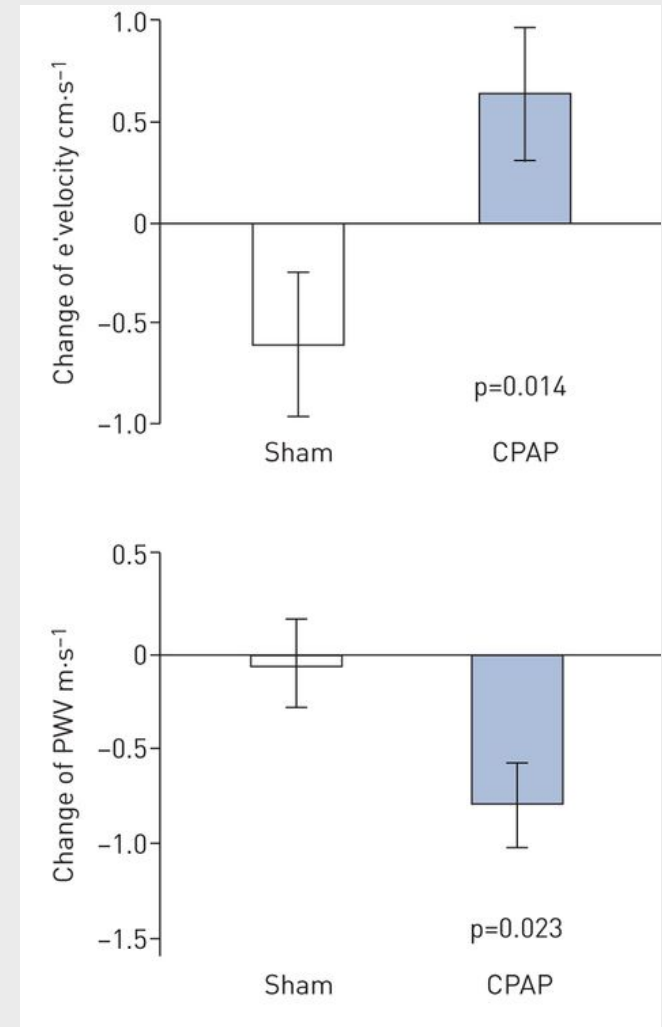


*Peker Y et al. European Respiratory Journal 2017 50: 1700749*

# Effects of CPAP on left ventricular diastolic function

- 3-month randomised sham-controlled trial in 52 patients with severe OSA.
- CPAP increased the early diastolic mitral annular (e') velocity, pulse wave velocity, 24-h mean diastolic BP, and night-time diastolic BP.
- **Message: CPAP improves measures of LV function and also BP**

*Shim CY et al. Eur Resp J 2018; 51: 1701774*



# **ATS Report:** Morbidity and Mortality of CHF Patients with CSA treated by ASV (FACE)

- **Background:** SERVE-HF trial demonstrated increased mortality in CHF patients with CSA treated with ASV – RCT (*Cowie et al. N Engl J Med. 2015;373(12):1095-105*).
- 391 CHF patients with CSA (69%) or CSA-OSA (31%) treated with ASV and followed for two years. 76% had AHI>30.
- 66% compliant with ASV and outcomes compared to non-compliant patients
- ASV associated with improved outcomes overall but ischaemic cardiomyopathy worse
- Benefits of ASV particularly seen in non-ischemic CHF and more hypoxaemic patients

**Message: Benefits of ASV may be confined to specific sub-populations of CHF patients**

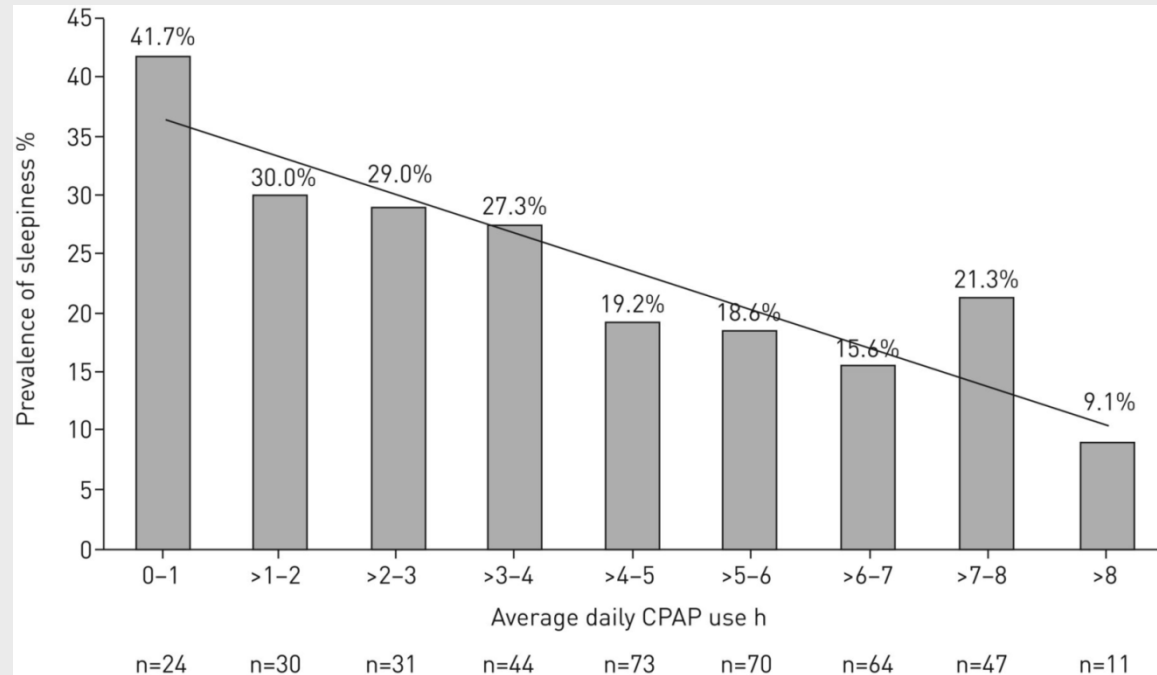
*Pepin JL et al. ATS Conference 2018.*

# Predictors of sleepiness in OSA at baseline and after 6 months of CPAP therapy

- 1105 OSA patients randomised to active/sham CPAP for 6 months
- All had baseline and follow-up MWT
- Younger age, depression, and higher AHI predicted baseline sleepiness
- Active CPAP associated with reduced sleepiness, especially >4hr/night but high baseline sleepiness associated with more residual sleepiness.

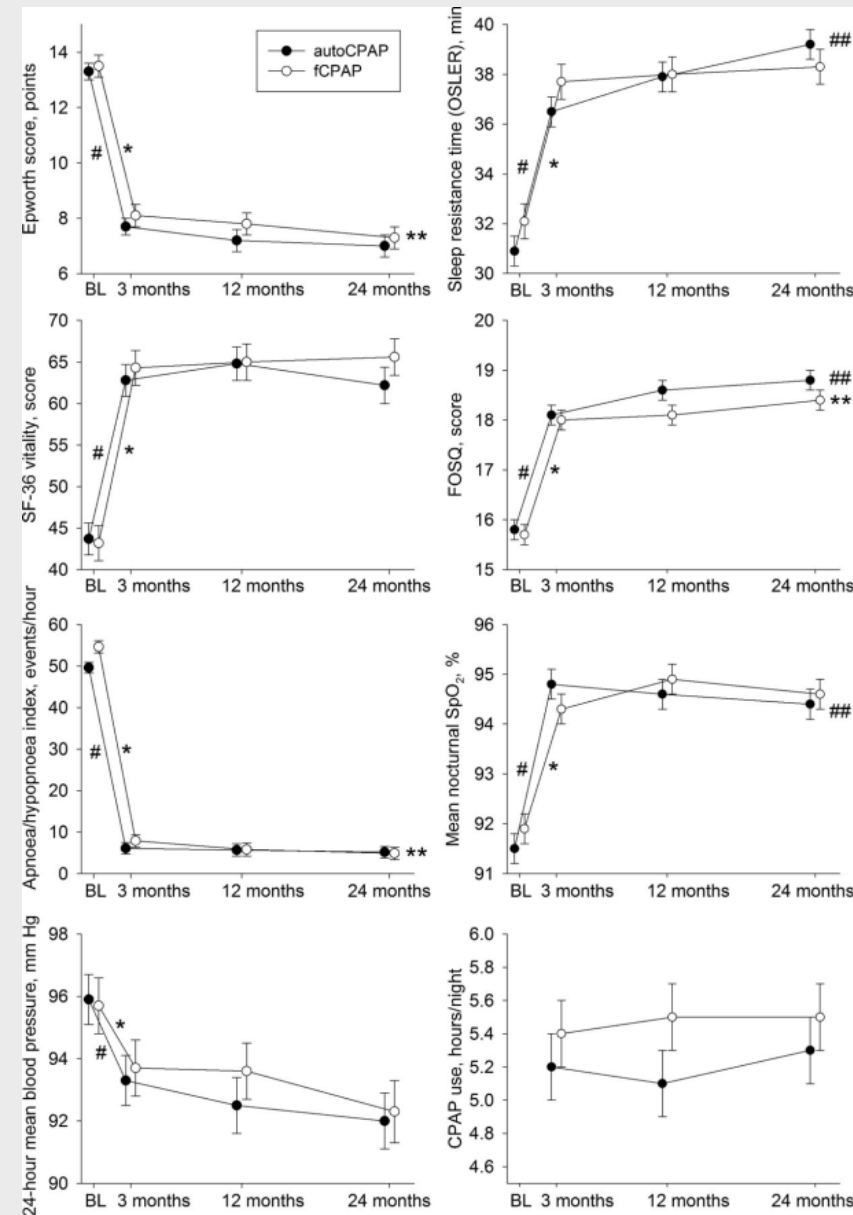
**Message: CPAP improves subjective and objective sleepiness**

*Rohit Budhiraja R et al.  
European Respiratory  
Journal 2017 50: 1700348*



# Auto-adjusted vs fixed CPAP for OSA

- 208 OSA patients randomised to APAP (5-15) or CPAP (P90) over 2 years
- Subjective (ESS) and objective sleepiness (Osler test) similar
- BP changes also similar and also OSA-related costs
- **Message: CPAP and APAP equally effective in reducing sleepiness, BP, and have similar costs**

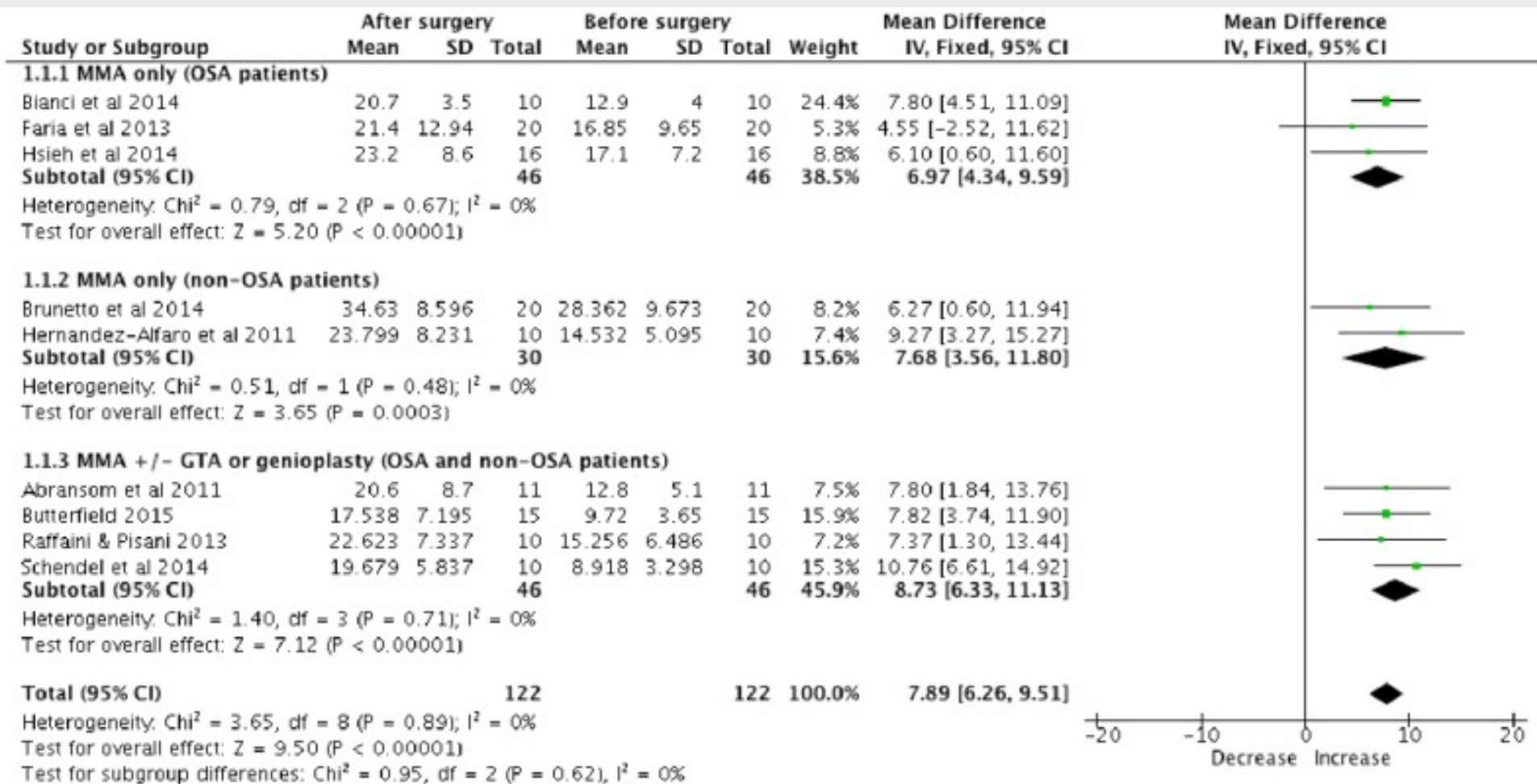


Bloch KE et al. *Thorax* 2018;**73**:174-184

# Other OSA Therapies



# Pharyngeal volume changes after maxillomandibular advancement surgery. Overview of systematic reviews



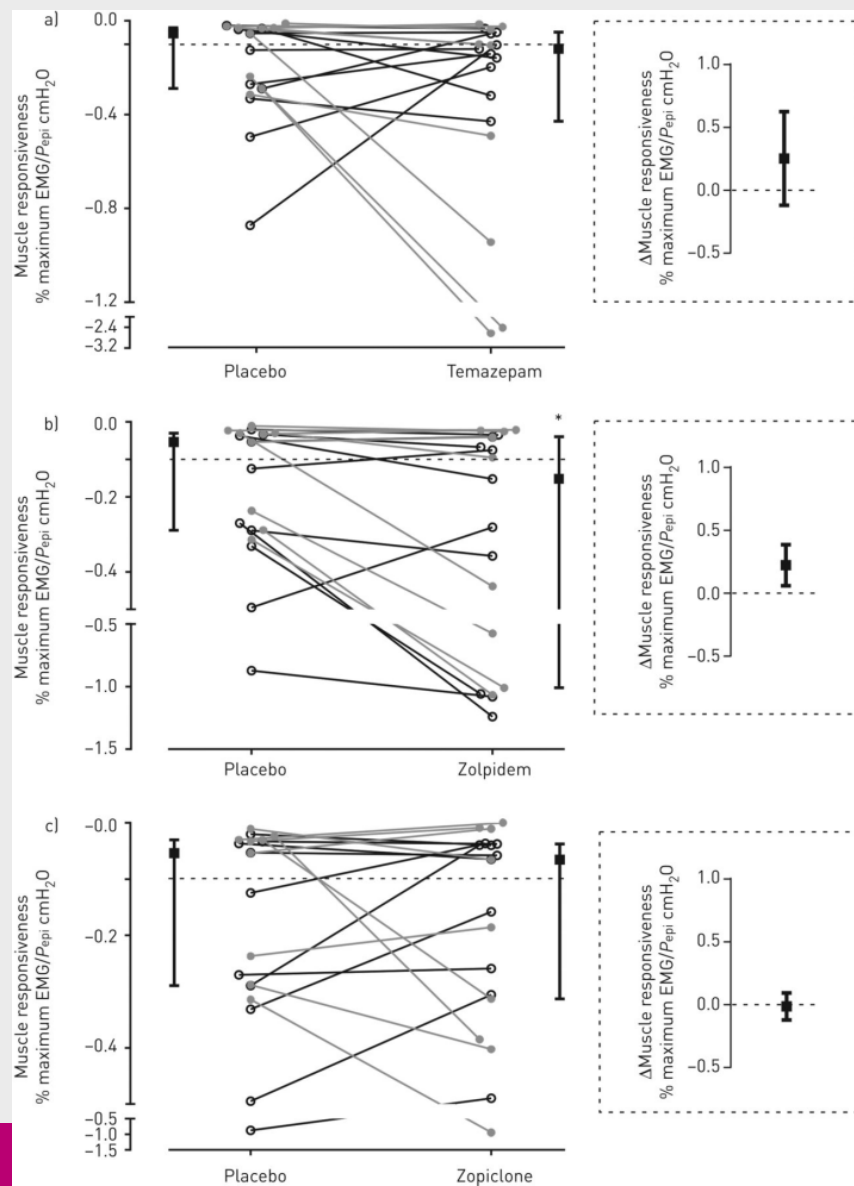
**Message:** Maxillomandibular advancement surgery produces consistent increases in pharyngeal volume in OSA and nonOSA patients.

*Tan et al. PLoS1 July 27, 2017.*

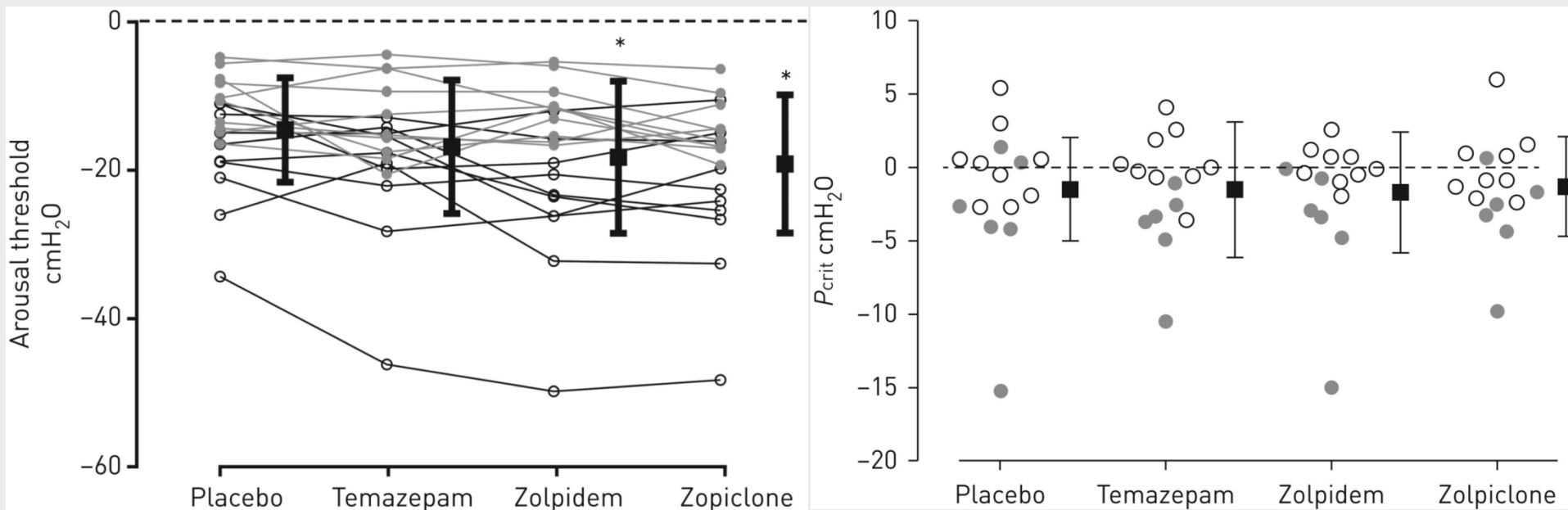
# Role of common hypnotics on the phenotypic causes of OSA: paradoxical effects of zolpidem

- Effects of 3 hypnotics on respiratory arousal threshold, genioglossus muscle responsiveness and upper airway collapsibility during sleep in 21 subjects with/without OSA.
- Muscle activity increased during airway narrowing with zolpidem and differential effects on arousal threshold but no change in upper airway collapsibility during sleep.

Carberry JC et al. *Eur Resp J* 2017 50: 1701344



# Role of common hypnotics on the phenotypic causes of OSA: paradoxical effects of zolpidem

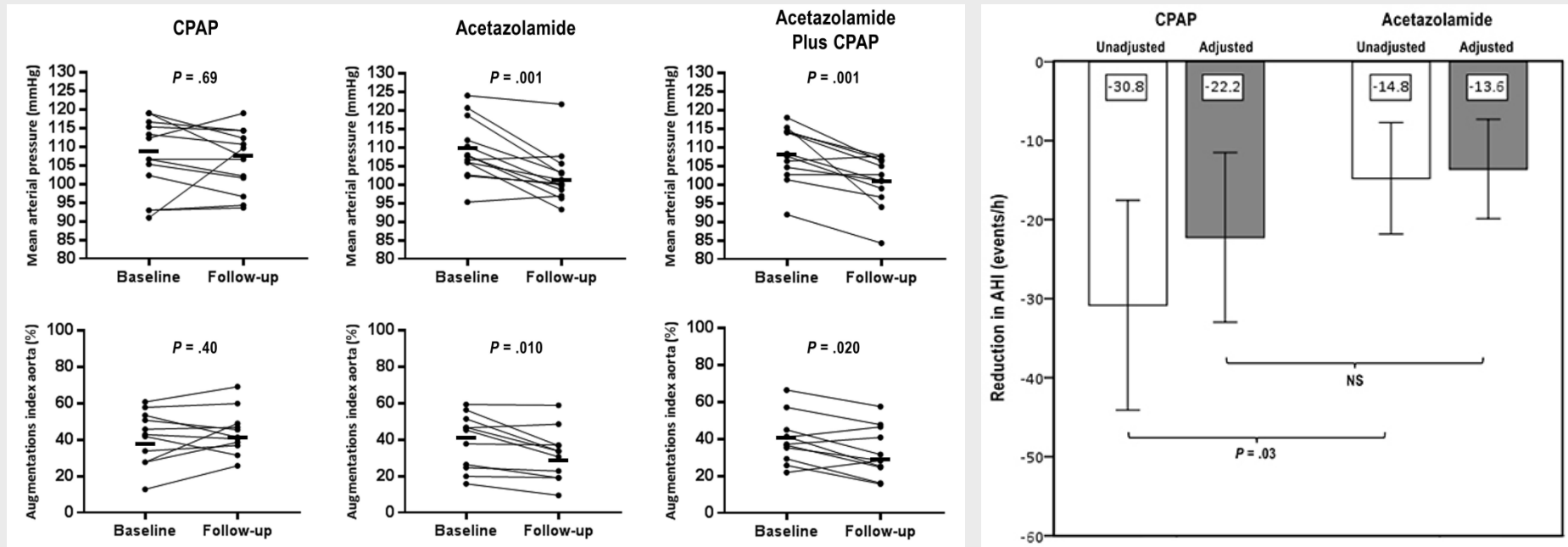


**Message: Zolpidem selectively benefits genioglossus muscle responsiveness but no significant changes in P<sub>crit</sub> or arousal threshold**

*Carberry JC et al. Eur Resp J 2017 50: 1701344*

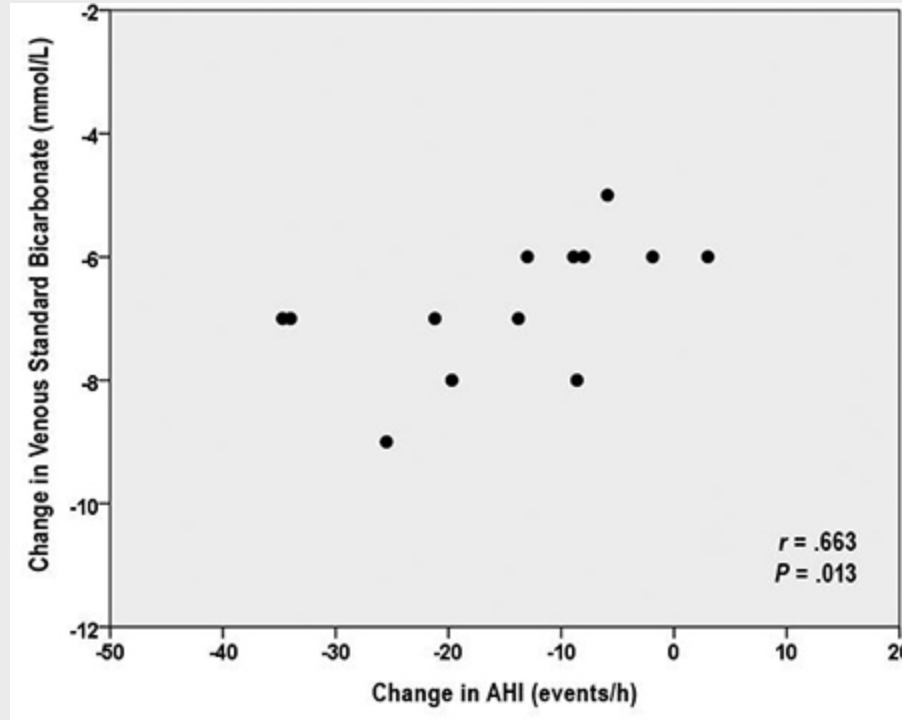
# Acetazolamide reduces blood pressure and SDB in hypertensive OSA patients

- 13 male hypertensive patients with  $AHI > 15$  given acetazolamide (250mg tid), CPAP, or both for two weeks.
- AZT and AZT/CPAP significantly reduced mean arterial BP compared to CPAP and all therapies reduced AHI.



Eskandari D et al. [J Clin Sleep Med.](#) 2018 Mar 15;14(3):309-317

# Acetazolamide reduces blood pressure and SDB in hypertensive OSA patients

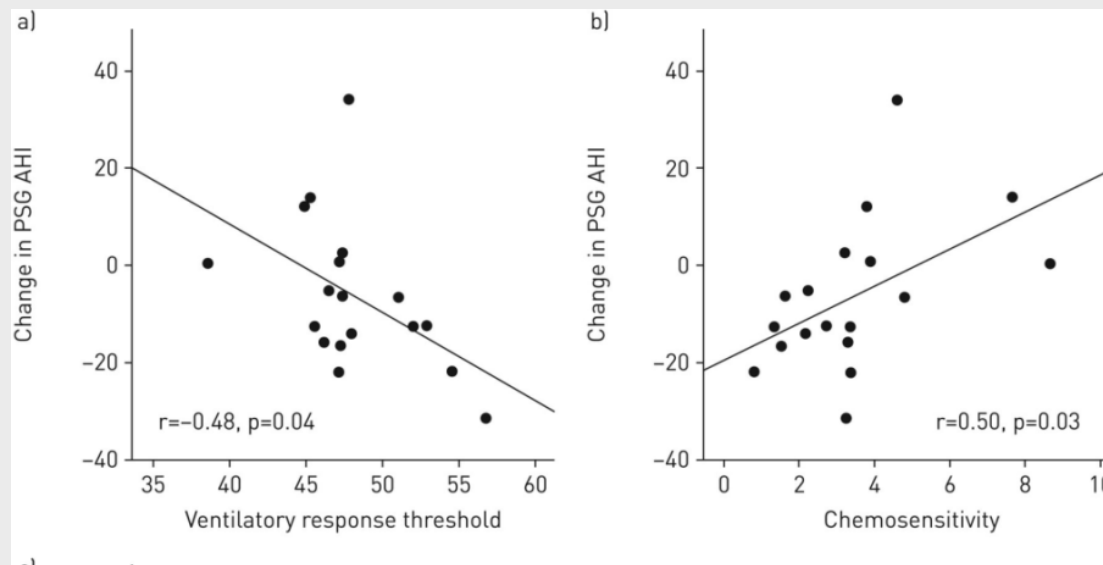


**Message:** A combination of carbonic anhydrase inhibition and CPAP therapy may provide benefits on top of AHI reduction in hypertensive OSA patients.

Eskandari D et al. [J Clin Sleep Med](#). 2018 Mar 15;14(3):309-317

# Predicting response to oxygen therapy in OSA patients by testing awake ventilatory chemoreflex

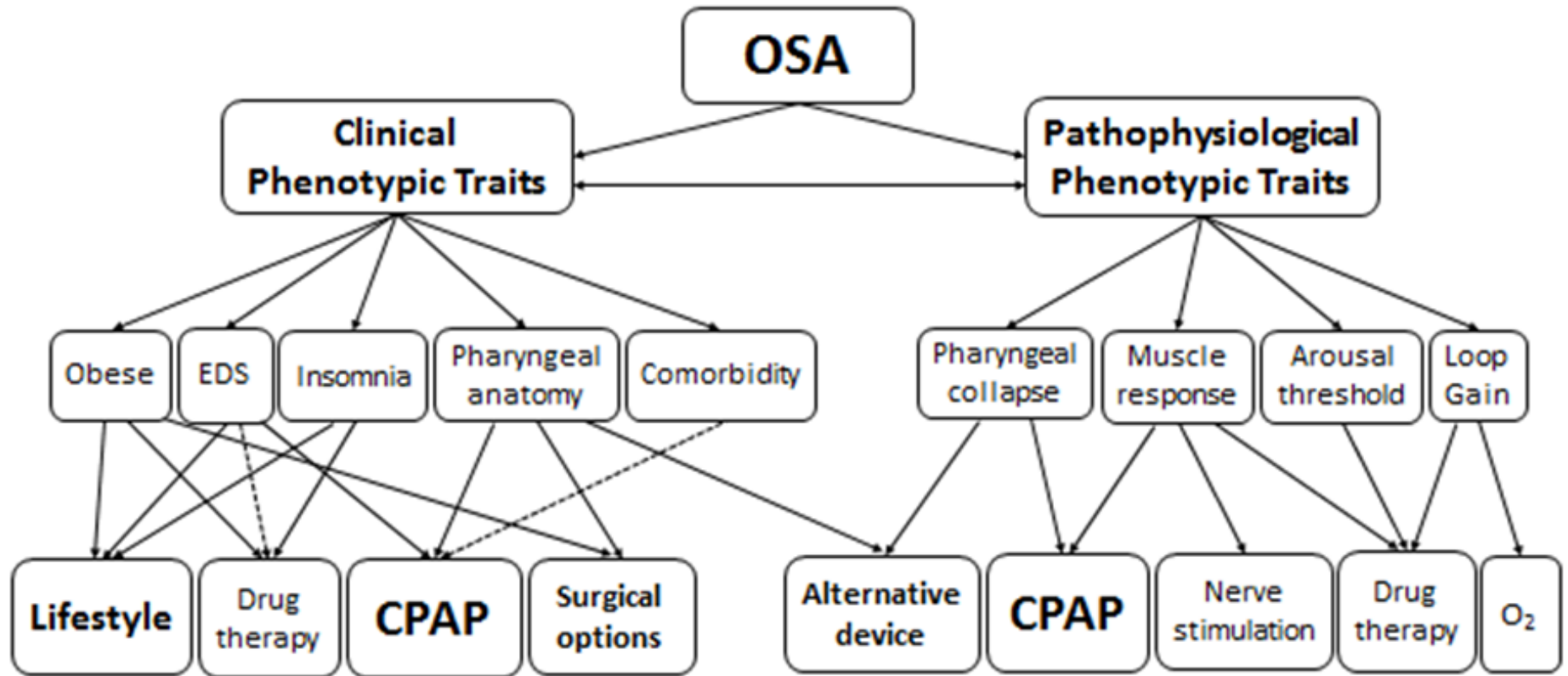
- 20 patients with OSA given 2 months of O<sub>2</sub> treatment.
- AHI changes correlated with baseline CO<sub>2</sub> ventilatory response threshold (VRT) and chemosensitivity.



**Message: Data provide further evidence of significant role for respiratory control mechanisms in pathophysiology of OSA**

*Wang D et al. Eur Resp J 2018; 51: 1701587*

# Personalised Management of OSA

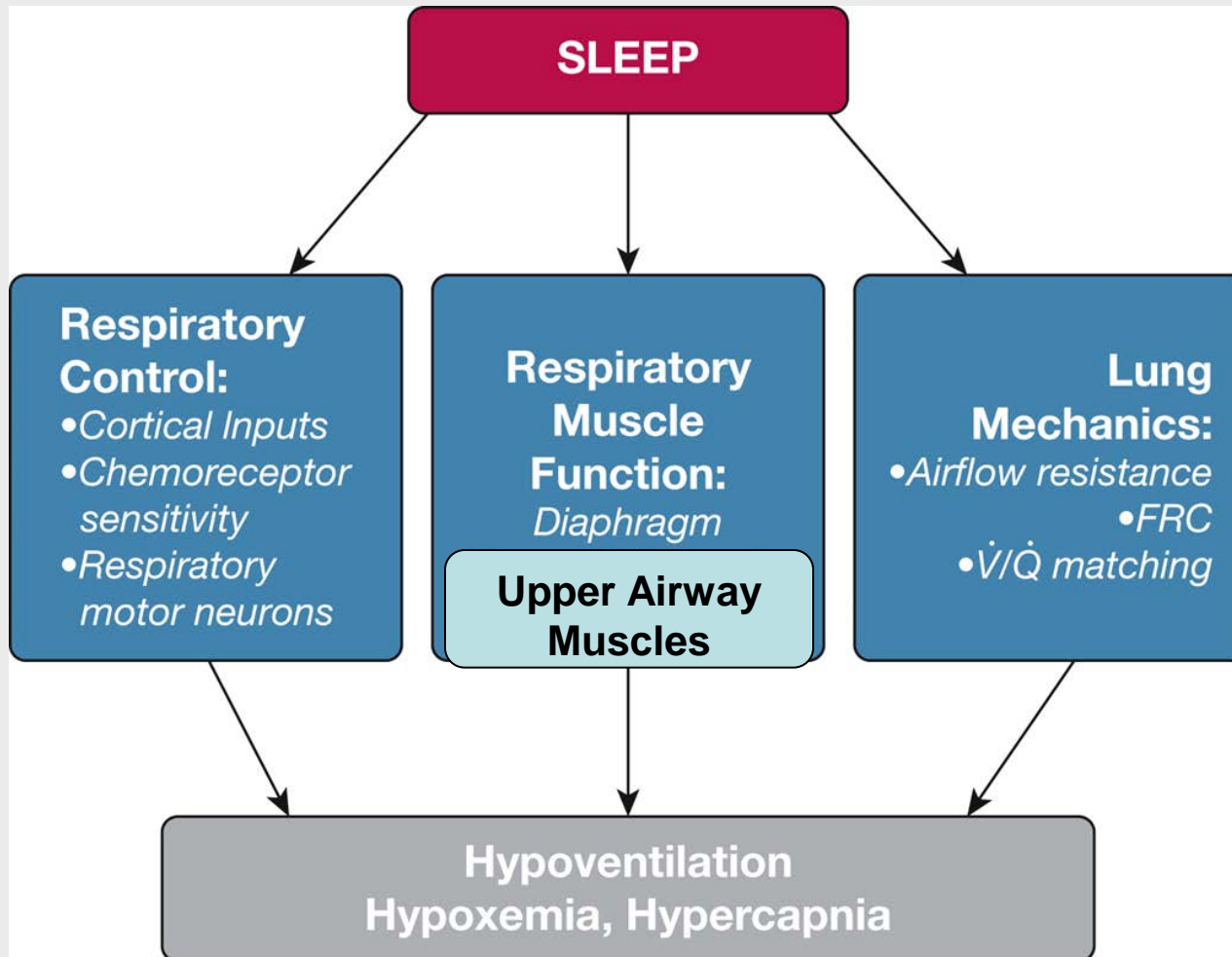


*Randerath et al. ERJ 2018*

# **Non-Apnoeic Respiratory Sleep Disorders**



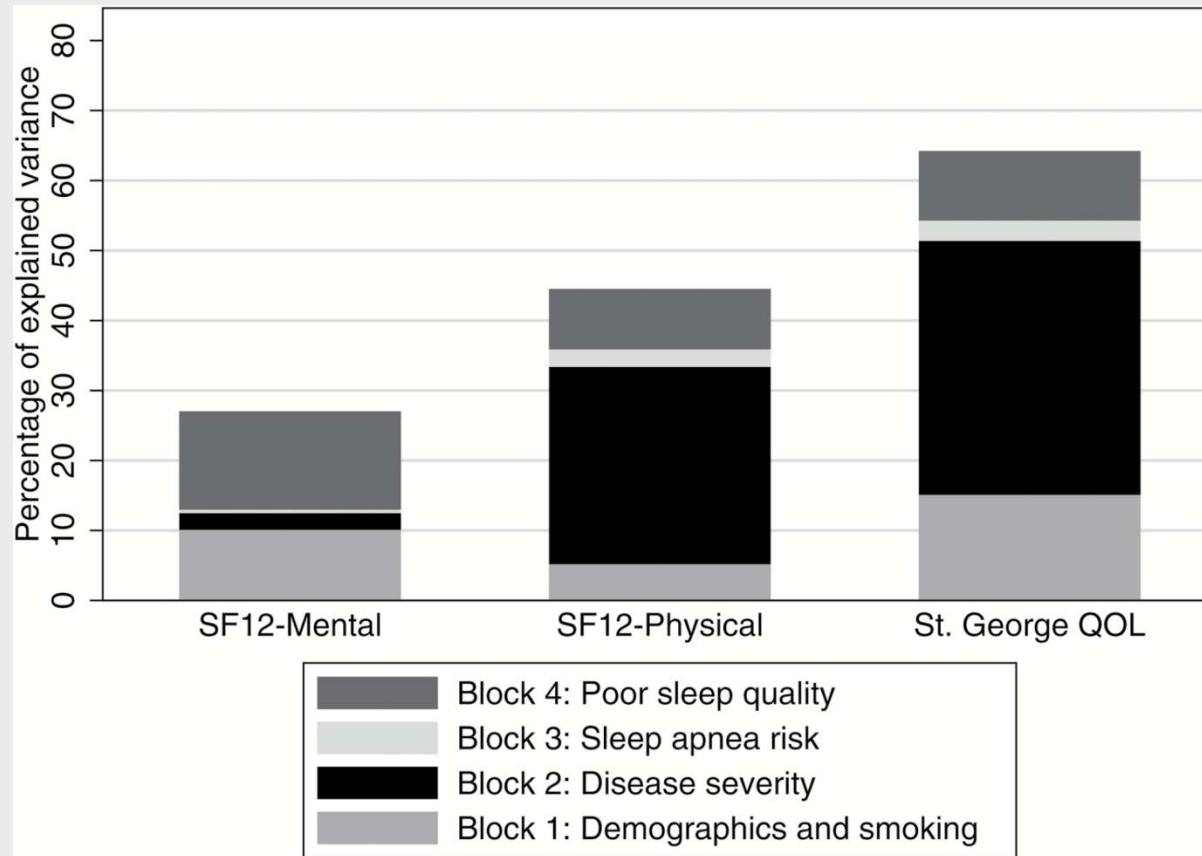
# Impact of Sleep on Respiration



McNicholas WT. Chest. 2017 Dec;152(6):1318-1326.

# **COPD and Sleep**

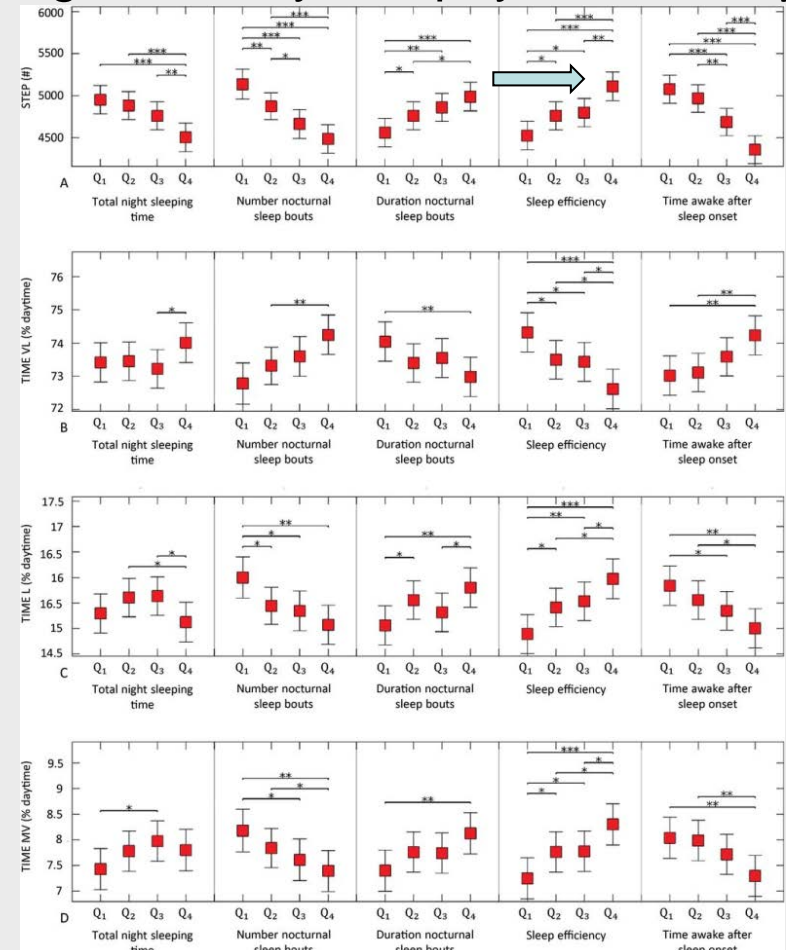
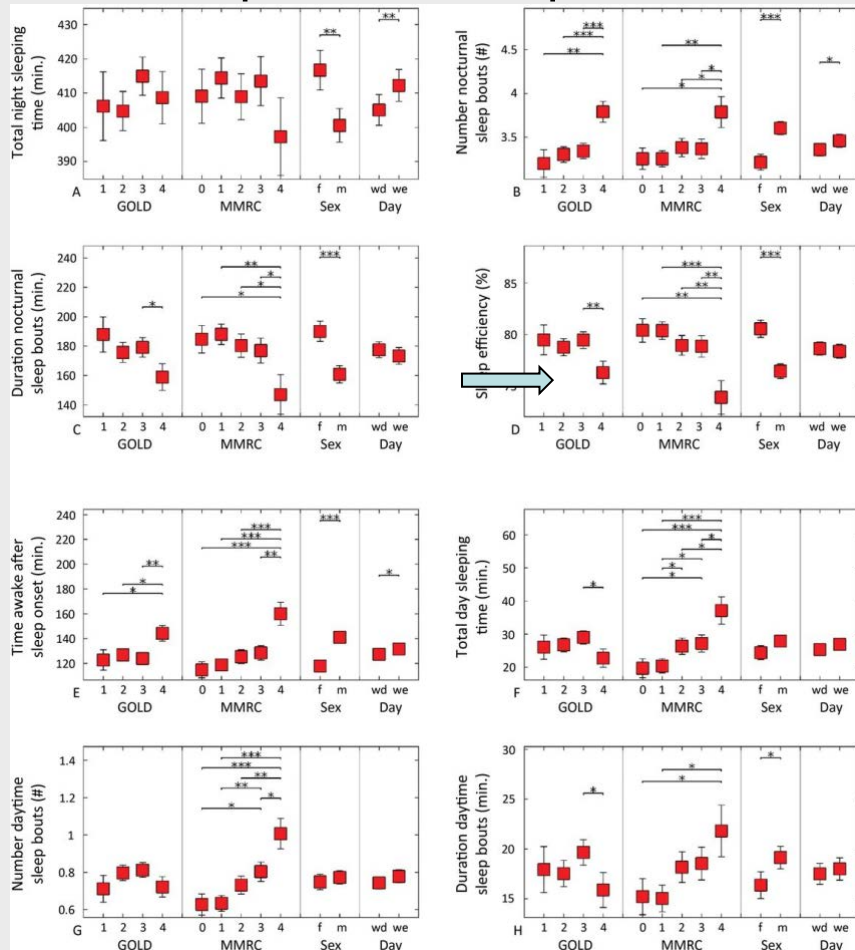
# Sleep disruption as a predictor of quality of life in COPD.



*Zeidler M et al. Sleep 41(5), May 2018, zsy044*

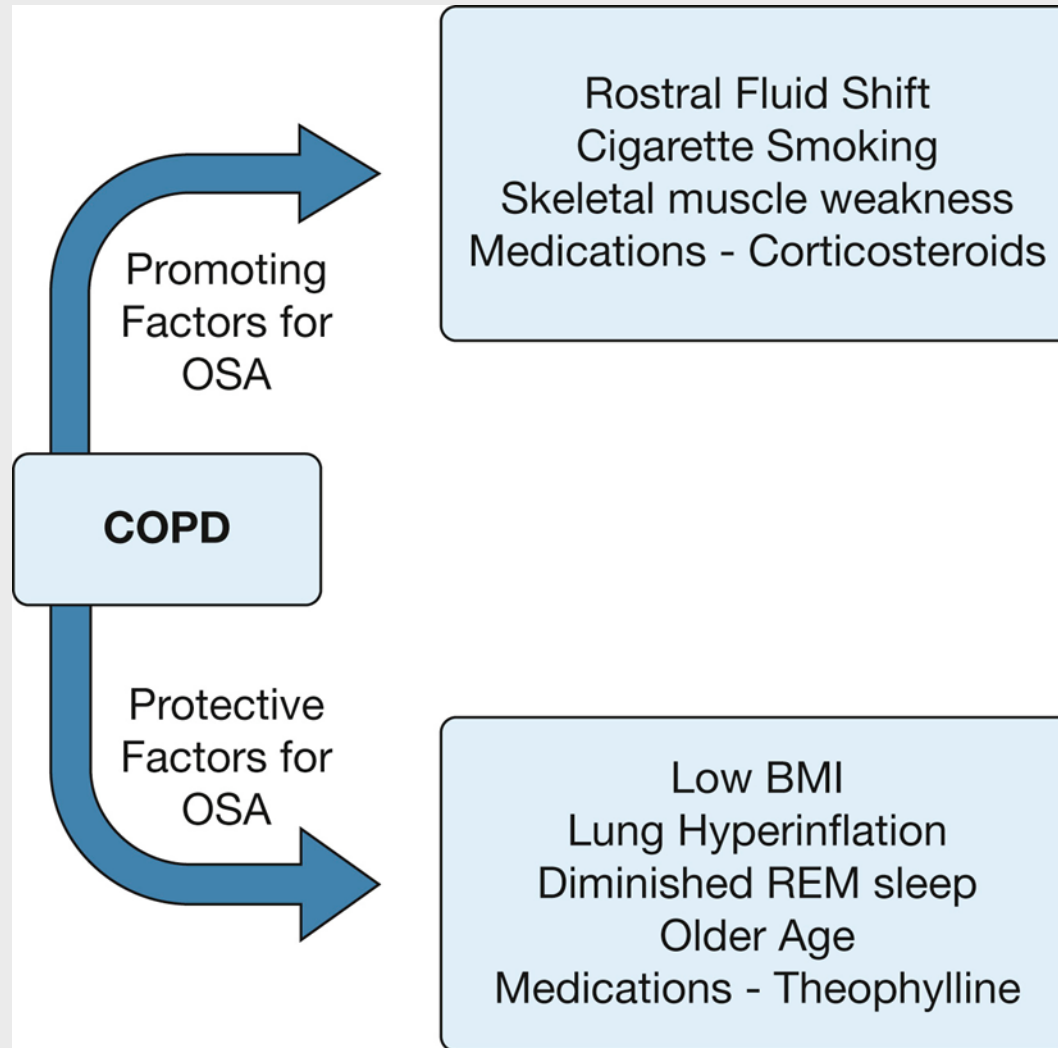
# Analysis of nocturnal sleep actigraphy in COPD and association with daytime physical activity

Multicentre study of 932 COPD patients - More severe COPD associated with worse sleep; better sleep associated with greater daytime physical activity



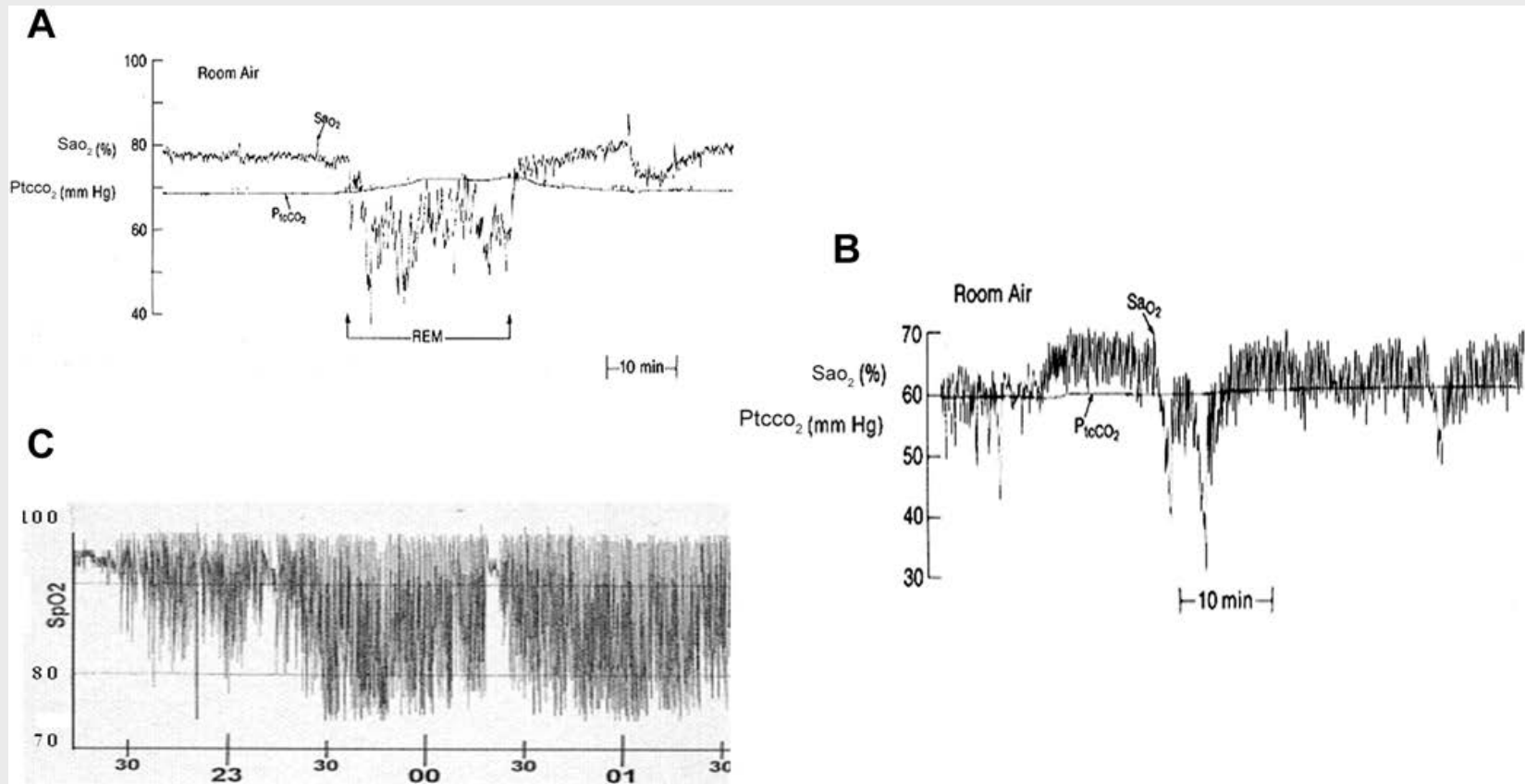
Spina G et al. Thorax 2017;72:694-701.

# COPD-OSA Interactions



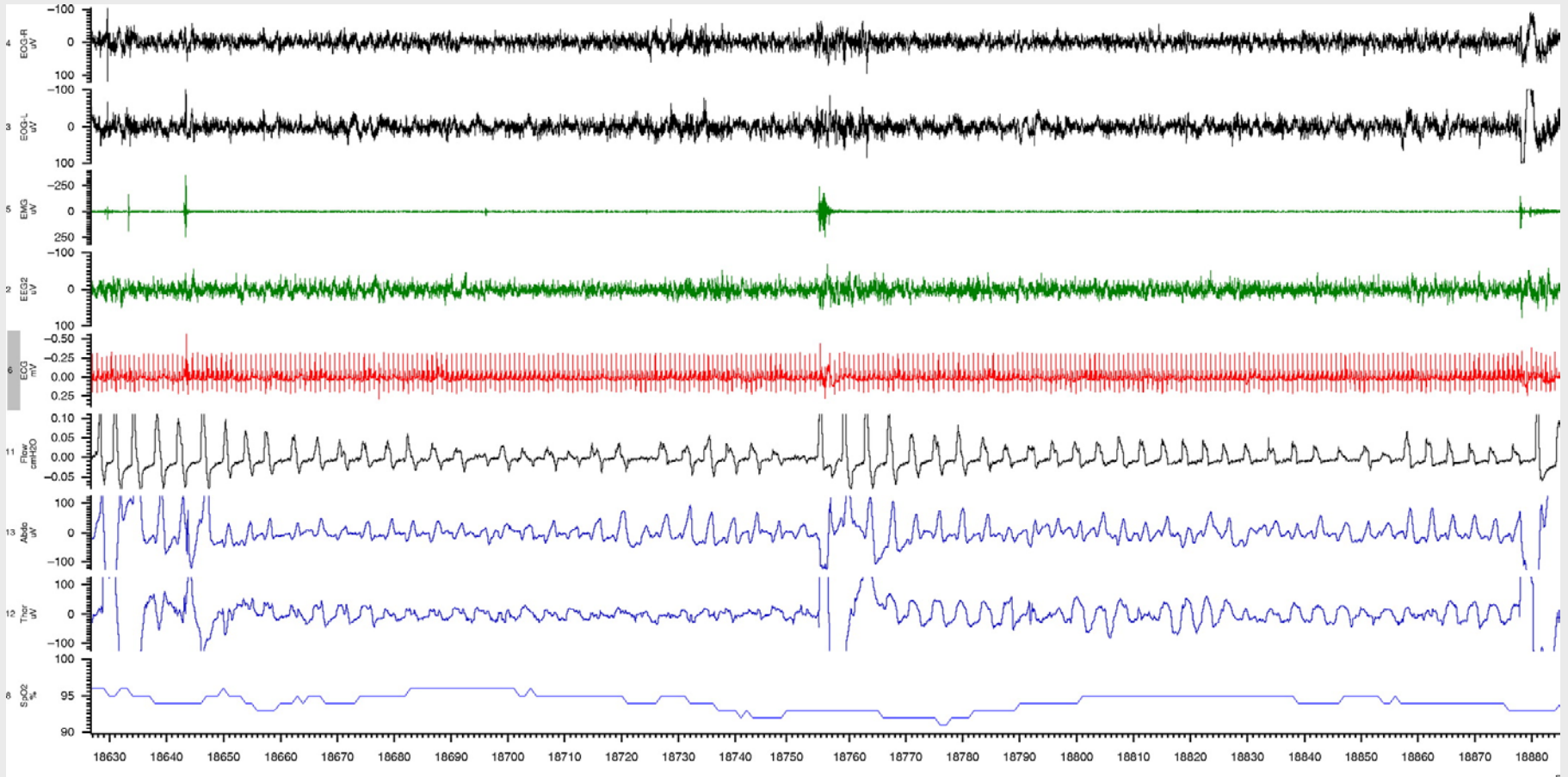
*McNicholas WT. Chest. 2017 Dec;152(6):1318-1326.*

# Oxygen desaturation patterns in OSA, COPD and Overlap.



McNicholas WT. *Chest*. 2017 Dec;152(6):1318-1326.

# Research Priorities in Pathophysiology of SDB in COPD. ATS Document



**Malhotra et al. AJRCCM 2018;197:289–299**

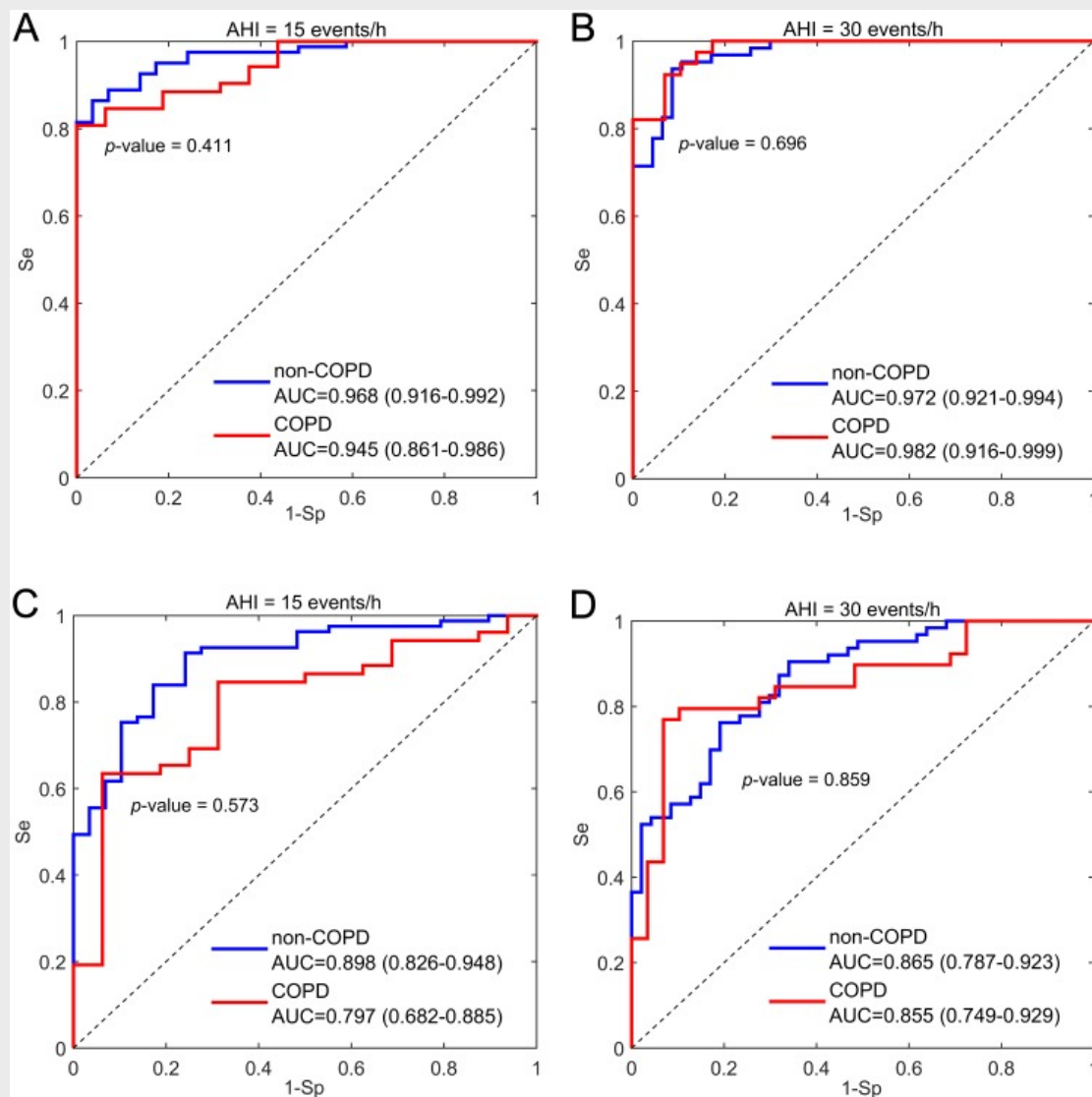
# Pneumo Update Europe 2018



# Oximetry in screening for OSA in COPD

- COPD patients from Pulmonary Clinic and non-COPD patients from Sleep Clinic, all with clinical features suggestive of OSA – 407 total.
- Sleep lab and home oximetry analysed using a specially developed automated analysis system
- **Message:** Oximetry shows similar ability to predict OSA in COPD and non COPD patients but home testing is less accurate

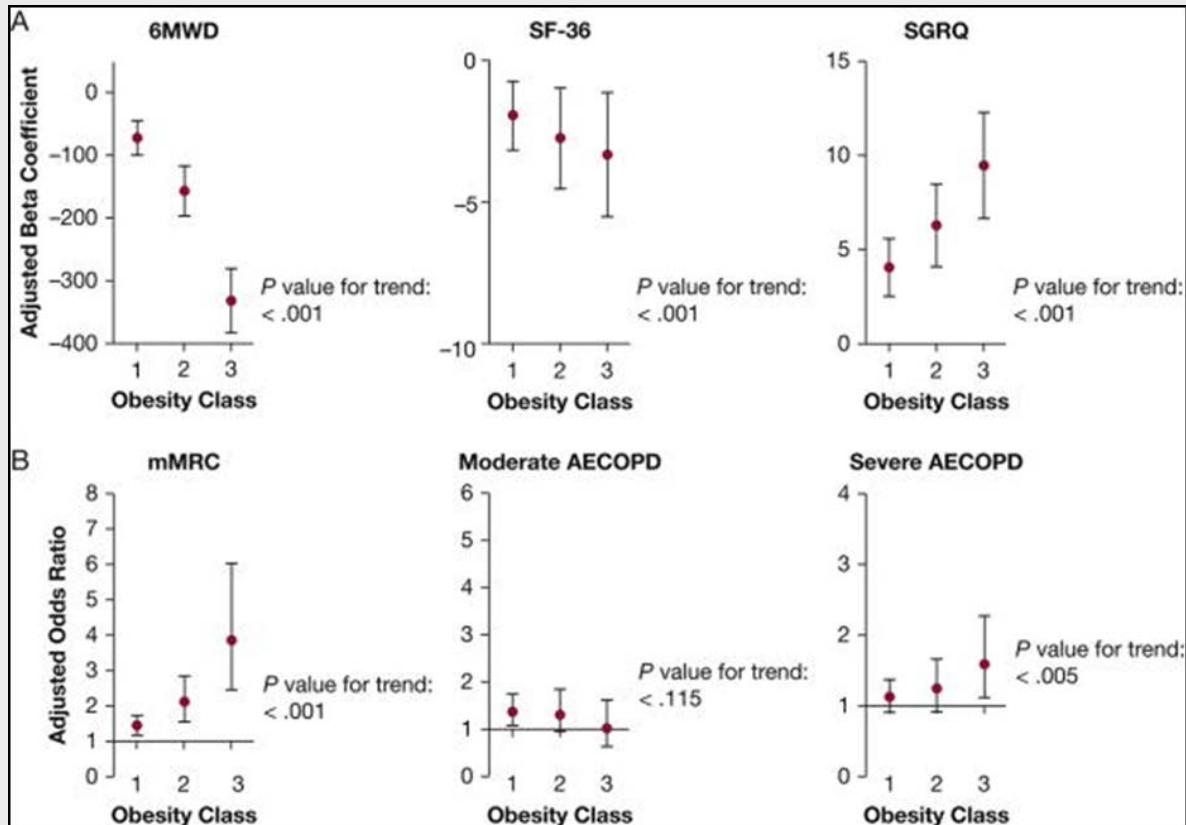
*Andres-Blanco et al. PLoS ONE 12(11): e0188094*





# 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



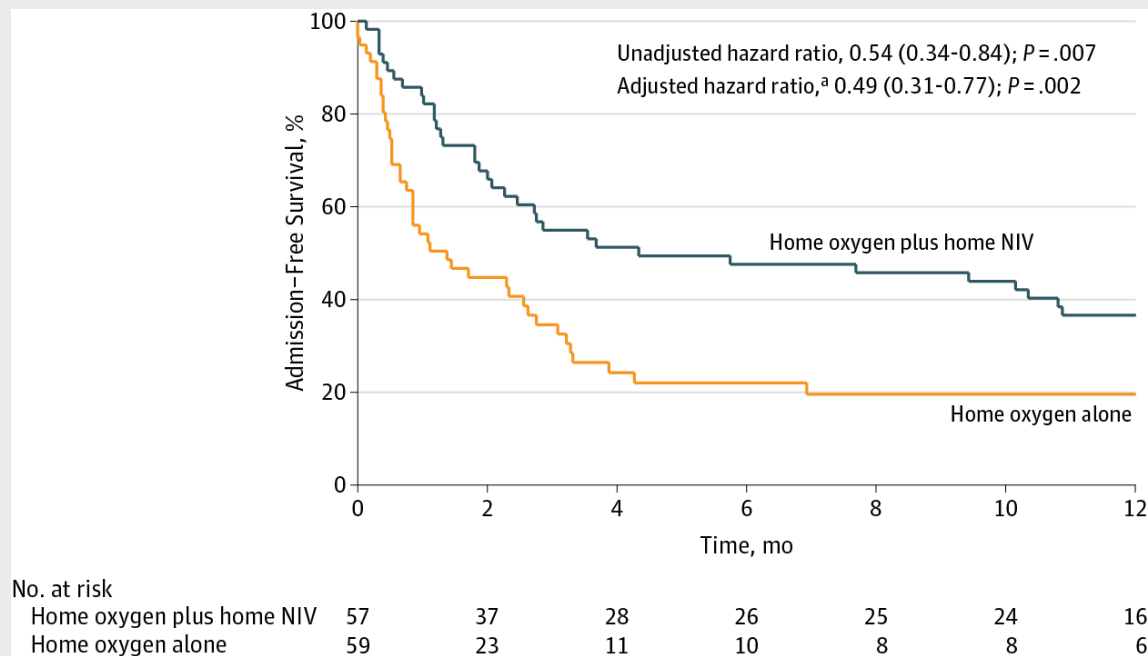
**Message:** Obesity is an independent risk factor for a range of COPD outcomes.

**Question:** Could occult OSA be a contributing factor?

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

# Home NIV with Oxygen vs Oxygen alone on Readmission or Death after a COPD Exacerbation

- 124 COPD patients with persistent hypercapnia after AECOPD randomised to NIV+O<sub>2</sub> or O<sub>2</sub>. Co-morbid obesity and OSA excluded
- Primary end-point: time to readmission or death



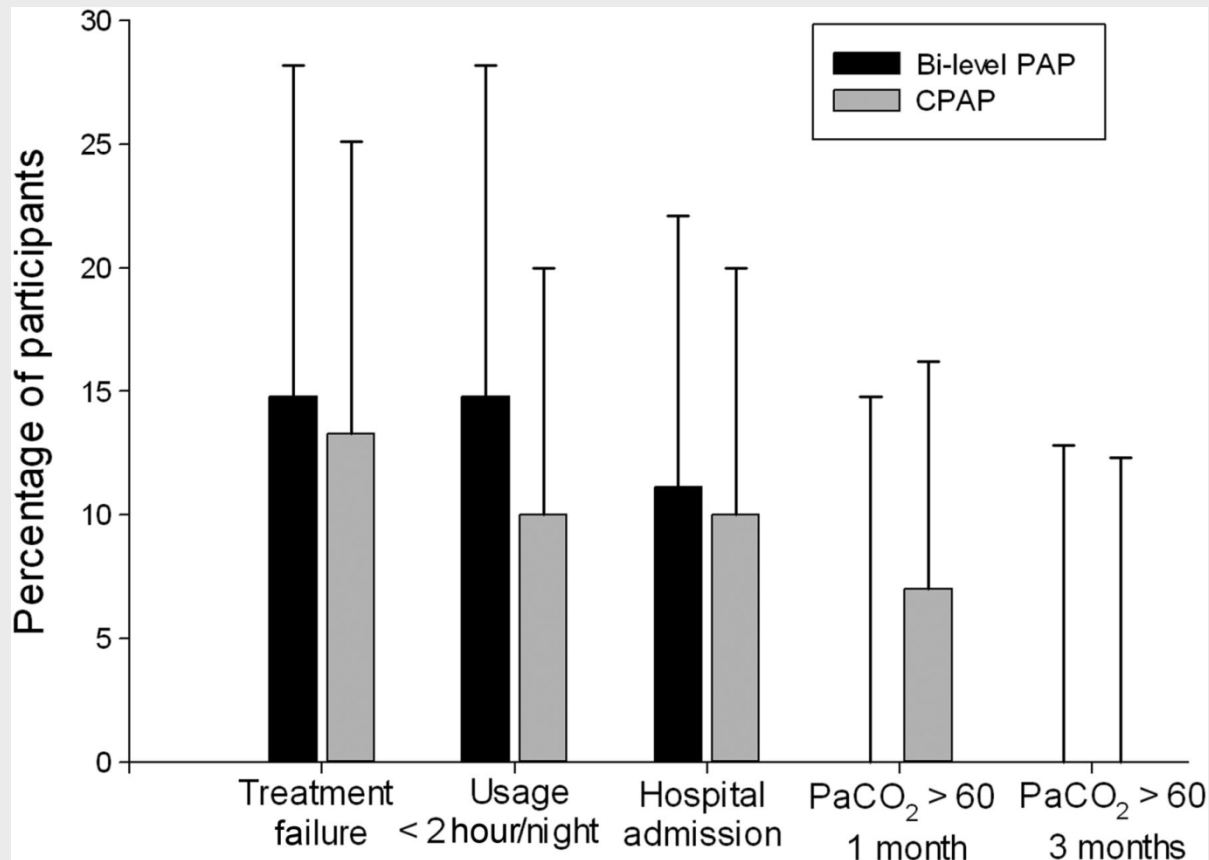
**Message: Adding home NIV to oxygen therapy in COPD patients with persistent hypercapnia following an exacerbation prolonged the time to readmission or death.**

*Murphy P et al. JAMA. 2017;317(21):2177-2186*

# **Obesity-Hypoventilation Disorders**

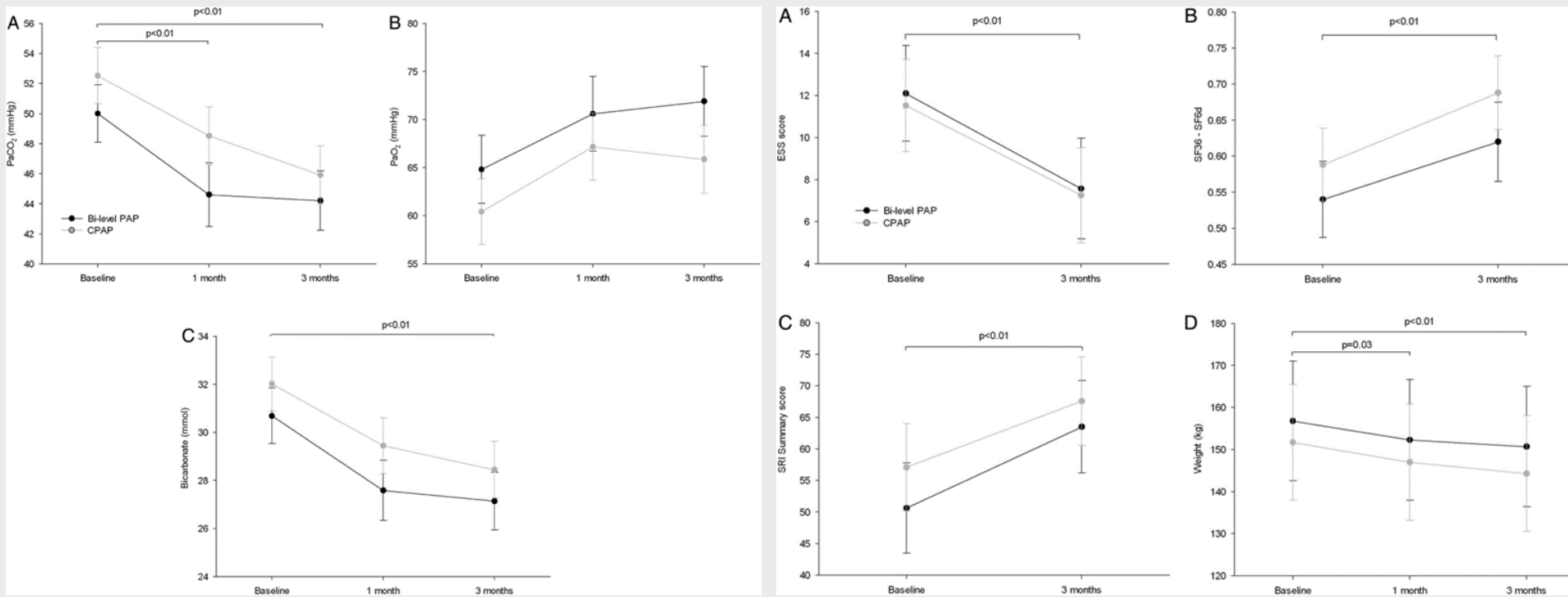
# CPAP vs non-invasive ventilation for initial treatment of obesity hypoventilation syndrome

- 60 patients with OHS randomised to Bi-PAP or CPAP for 3 months
- No difference in treatment failure or adherence, ESS or HrQoL



Howard ME et al. *Thorax* 2017;**72**:437-444

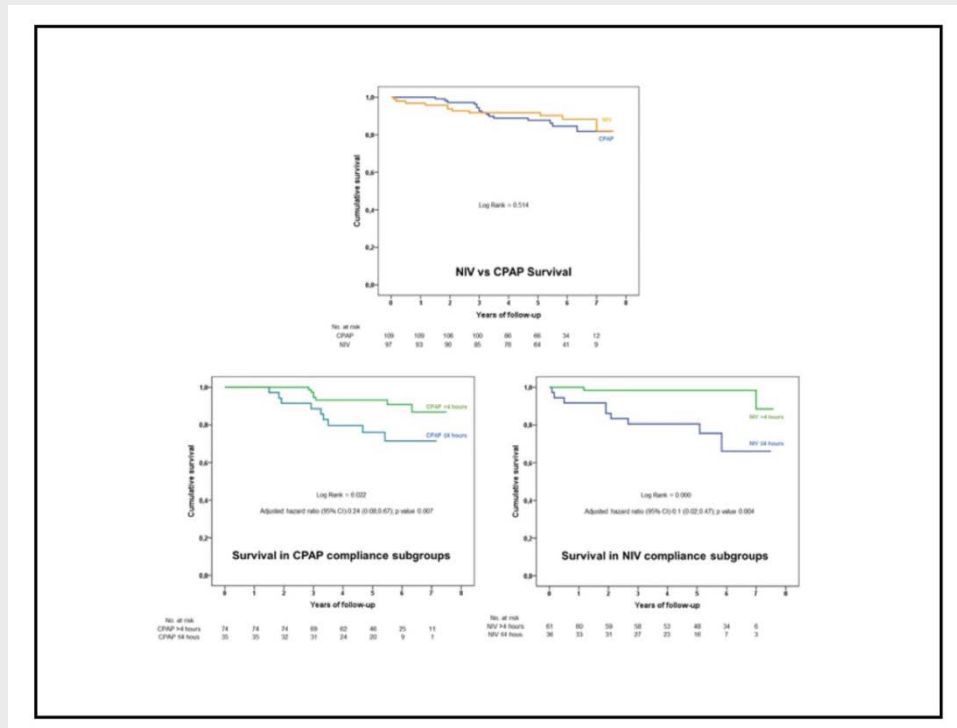
# CPAP vs non-invasive ventilation for initial treatment of obesity hypoventilation syndrome



**Message: CPAP and NIV produces similar outcomes in OHS relating to adherence, symptomatic benefit and  $\text{PaCO}_2$  reduction.**

# **ATS Report:** CPAP vs NIV for long-term treatment of OHS with OSA: Pickwick Trial

- 215 patients with OHS and OSA (AHI>30) randomised to NIV or CPAP and followed for median 5.4 years
- No difference in outcomes between two groups



## Message: CPAP and NIV have similar long-term outcomes

*Sanchez Quiroga MA et al. ATS Conference 2018.*

# Echocardiographic changes with non-invasive ventilation and CPAP in obesity hypoventilation syndrome

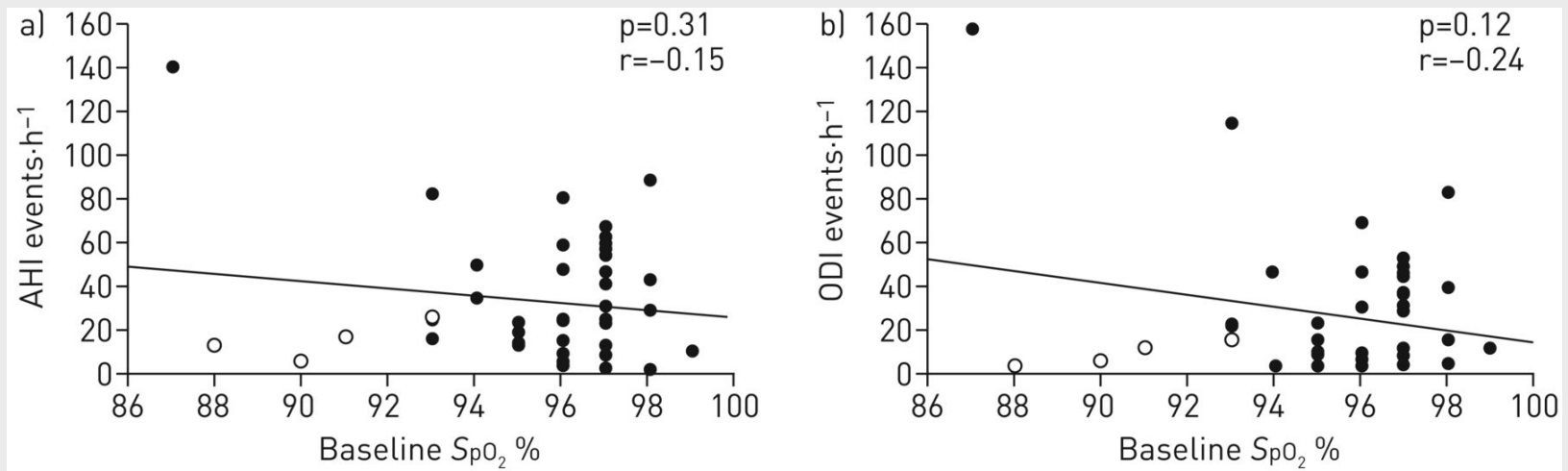
NIV superior to CPAP in improving PHT, LV hypertrophy and 6-minute walk distances

	Baseline, mean (SD)			Intragroup differences, mean (95% CI)			P value of intergroup differences	
	NIV n=71	CPAP n=80	Control n=70	NIV	CPAP	Control	Unadjusted	Adjusted
Systolic PAP, mm Hg	41 (9.2)	38 (12)	41 (10)	-3.4 (-5.3 to -1.5)***	0.02 (-1.7 to 1.7)	-0.44 (-2.7 to 1.9)	0.021† 0.008‡	0.040† 0.033‡
DT, ms	232 (71)	218 (63)	212 (58)	-1.3 (-18 to 16)	-13 (-31 to 4)	15 (0.3 to 30)*	0.015§	0.021§
LVEF, %	66 (7.6)	62 (11)	63 (7.9)	-1.9 (-4.1 to 0.23)	1.6 (-0.6 to 3.8)	0.49 (-1.2 to 2.1)	0.027‡	NS
Septum, mm	13 (2.1)	12 (2.4)	13 (2.6)	-0.52 (-0.96 to -0.08)*	0.29 (-0.08 to 0.67)	0.15 (-0.16 to 0.46)	0.003† 0.017‡	0.033† 0.031‡
LVPW, mm	12 (2)	11 (2)	12 (2.5)	-0.38 (-0.76 to 0)*	0.29 (-0.35 to 0.41)	0.20 (-0.20 to 0.60)	0.042†	0.011†
LV mass, g	225 (52)	211 (63)	237 (73)	-13 (-24 to -2.1)*	5.5 (-5.1 to 16)	8 (-3.1 to 19)	0.016† 0.008‡	0.006† NS
LV mass index, g/m <sup>2</sup>	108 (27)	98 (29)	102 (37)	-5.7 (-11 to -4.4)**	2.9 (-2.1 to 8)	3.5 (-1.5 to 8.6)	0.017† 0.014‡	0.013† NS

**Corral J et al. Thorax 2018;73:361-368**

# OSA and related comorbidities in incident Idiopathic Pulmonary Fibrosis

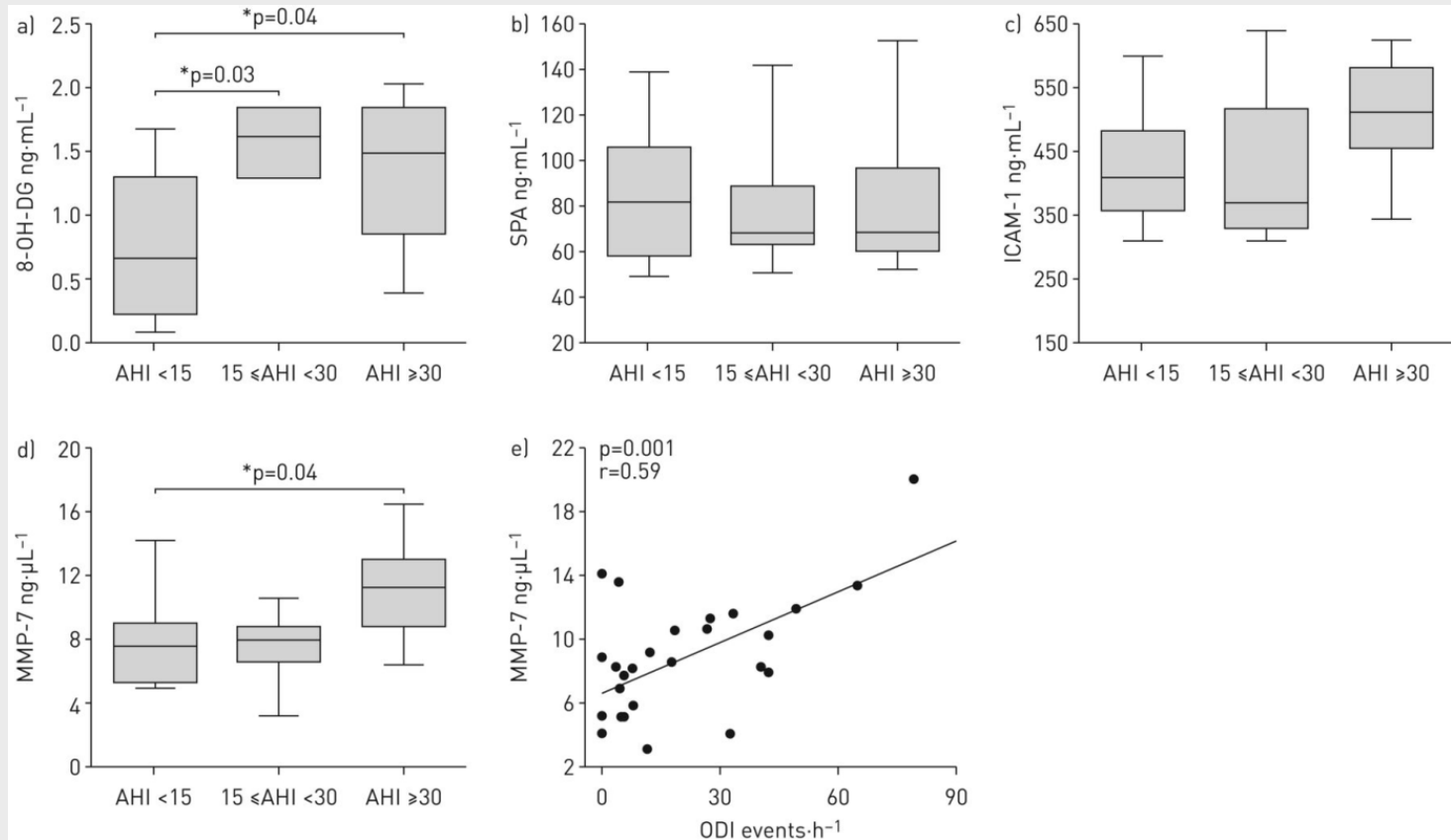
- 45 patients with newly diagnosed IPF had PSG, coronary artery calcification from HRC T, and biomarkers.
- 18 pts had AHI >15 and no correlation of AHI/ODI with BMI, baseline SaO<sub>2</sub> or PFT
- Cardiovascular comorbidity more common in severe OSA and IHD independently associated. Coronary artery calcification also greater in severe OSA.
- 8-OH-DG and MMP-7 serum levels highest in patients with severe OSA



*Gille T et al. European Respiratory Journal 2017 49: 1601934*



# OSA and related comorbidities in incident Idiopathic Pulmonary Fibrosis



**Message:** Severe OSA independently predicts ischaemic heart disease in incident IPF and is associated with higher levels of IPF biomarkers

*Gille T et al. European Respiratory Journal 2017 49: 1601934*

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