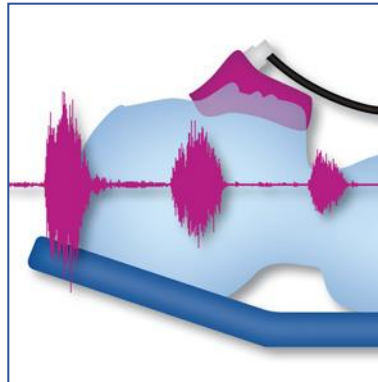


# **Pneumo Update Europe 2016**

**24-25 June, Prague**

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## **Sleep Disordered Breathing**



**Walter McNicholas, Ireland**

# Objectives

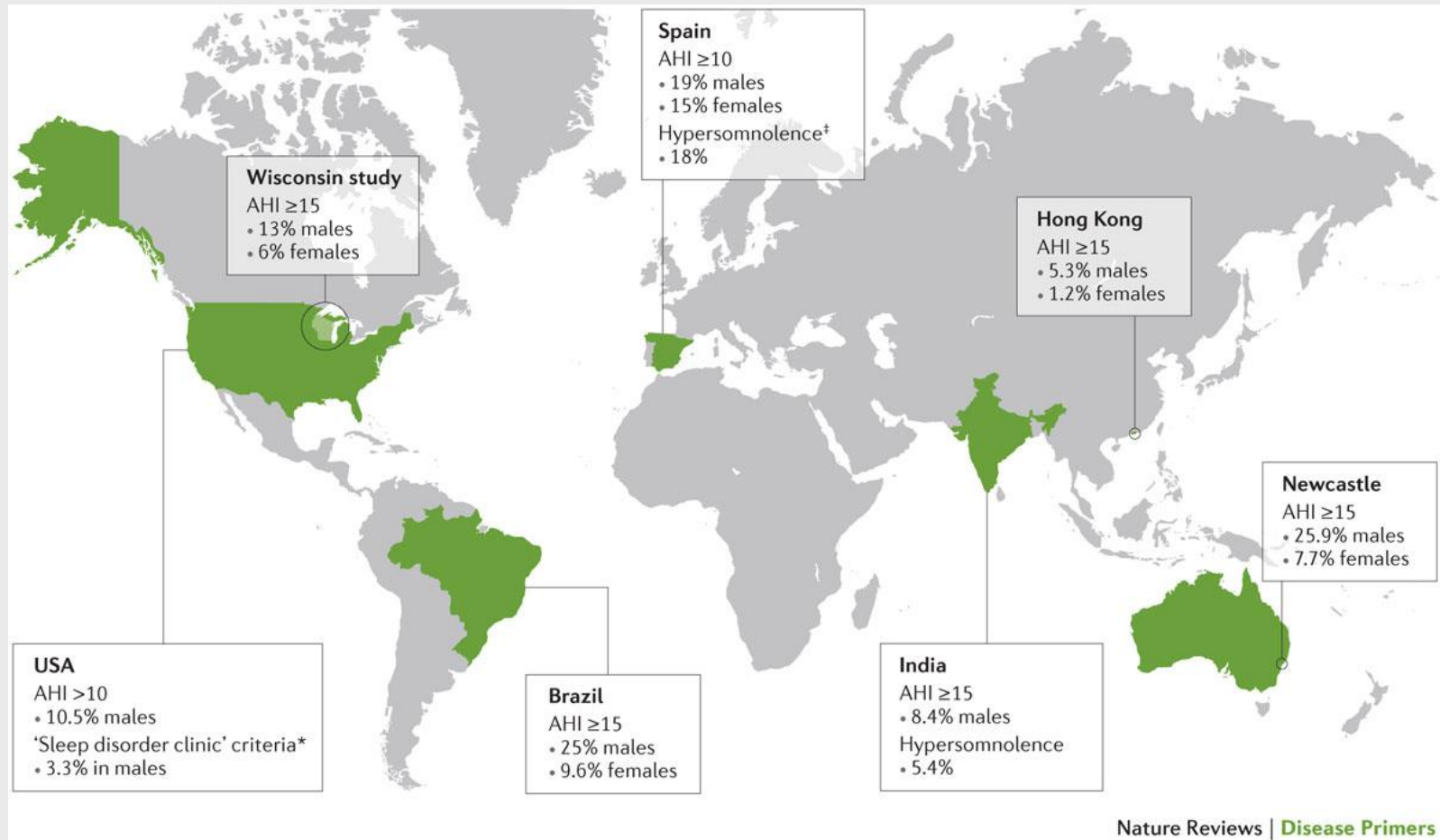
- Epidemiology and clinical significance
- Diagnosis
  - Screening questionnaires
  - Limited ambulatory sleep studies
- Co-morbidities
- Management options
- Outcomes
- Driving Risks

# **Epidemiology and Clinical Significance**

# State of the Art

- Obstructive Sleep Apnoea is highly prevalent and reports indicate increasing prevalence over past 3 decades
- Rising prevalence of obesity is likely to be an important contributing factor

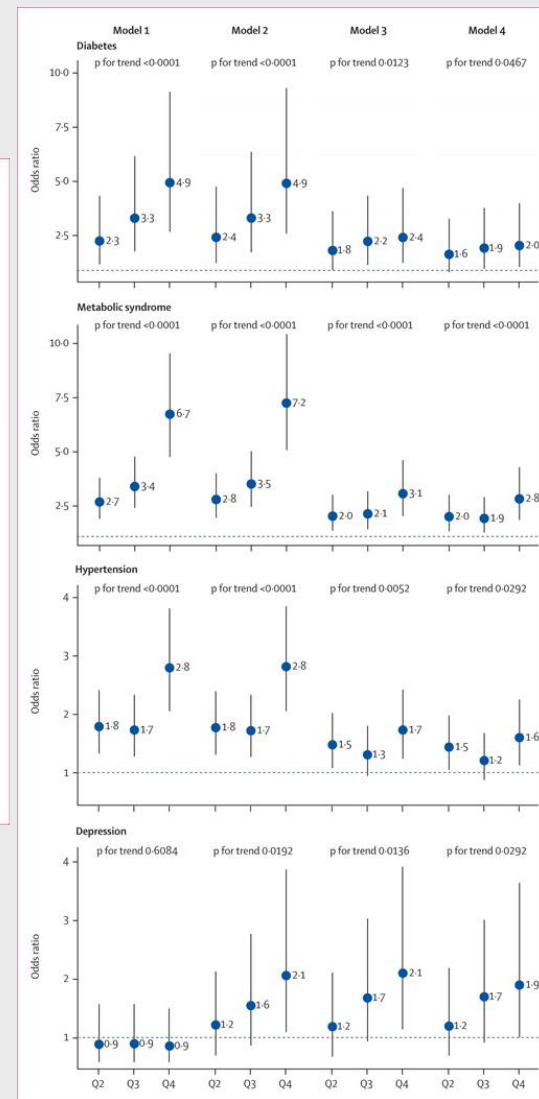
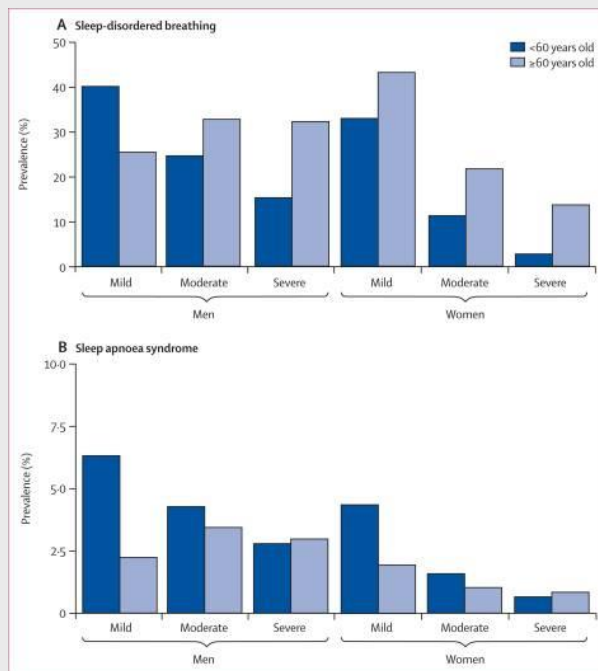
# Global prevalence of sleep apnoea



Lévy, Kohler, McNicholas *et al.* (2015) Obstructive sleep apnoea syndrome  
*Nat. Rev. Dis. Primers* doi:10.1038/nrdp.2015.15

# Prevalence of sleep-disordered breathing in a Swiss general population: the HypnoLaus study.

- 2121 middle-aged adults
- Sleep-disordered breathing (AHI) highly prevalent but clinically significant OSA much less so.
- Upper quartile for AHI (>20.6) was associated independently with
  - prevalent hypertension (OR 1.60,  $p=0.029$ ),
  - diabetes (2.00,  $p=0.0467$ ),
  - metabolic syndrome (2.80,  $p<0.0001$ ),
  - depression (1.92,  $p=0.029$ ).

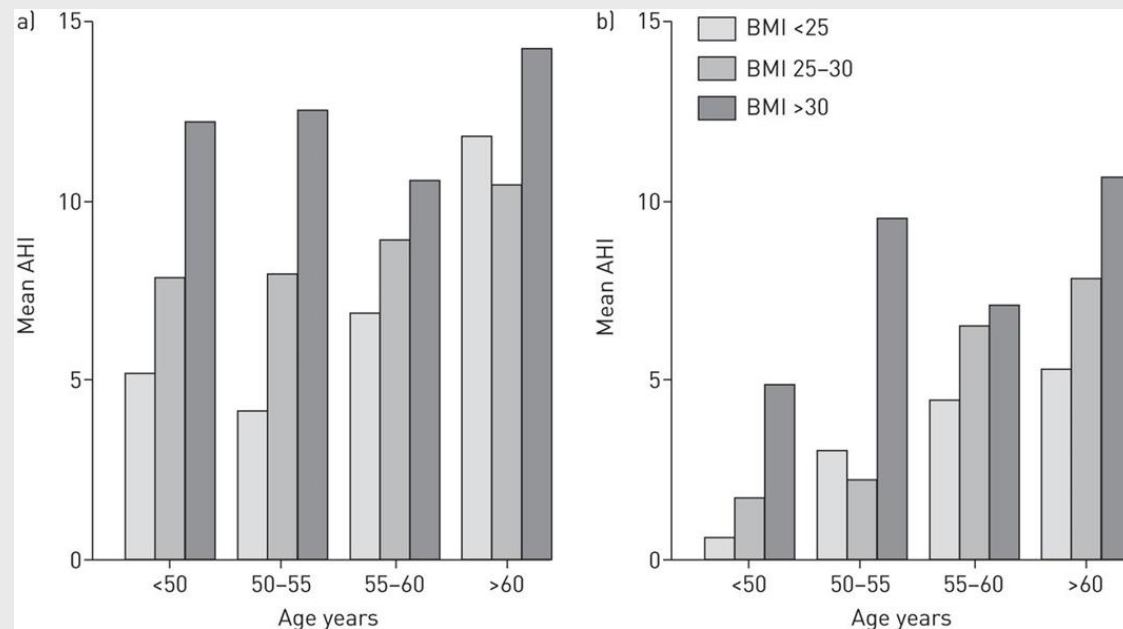


**Conclusion:** Sleep-disordered breathing is highly prevalent but associated co-morbidities evident only in severe category.

Heinzer R et al. *Lancet Respir Med.* 2015; 3(4): 310–318

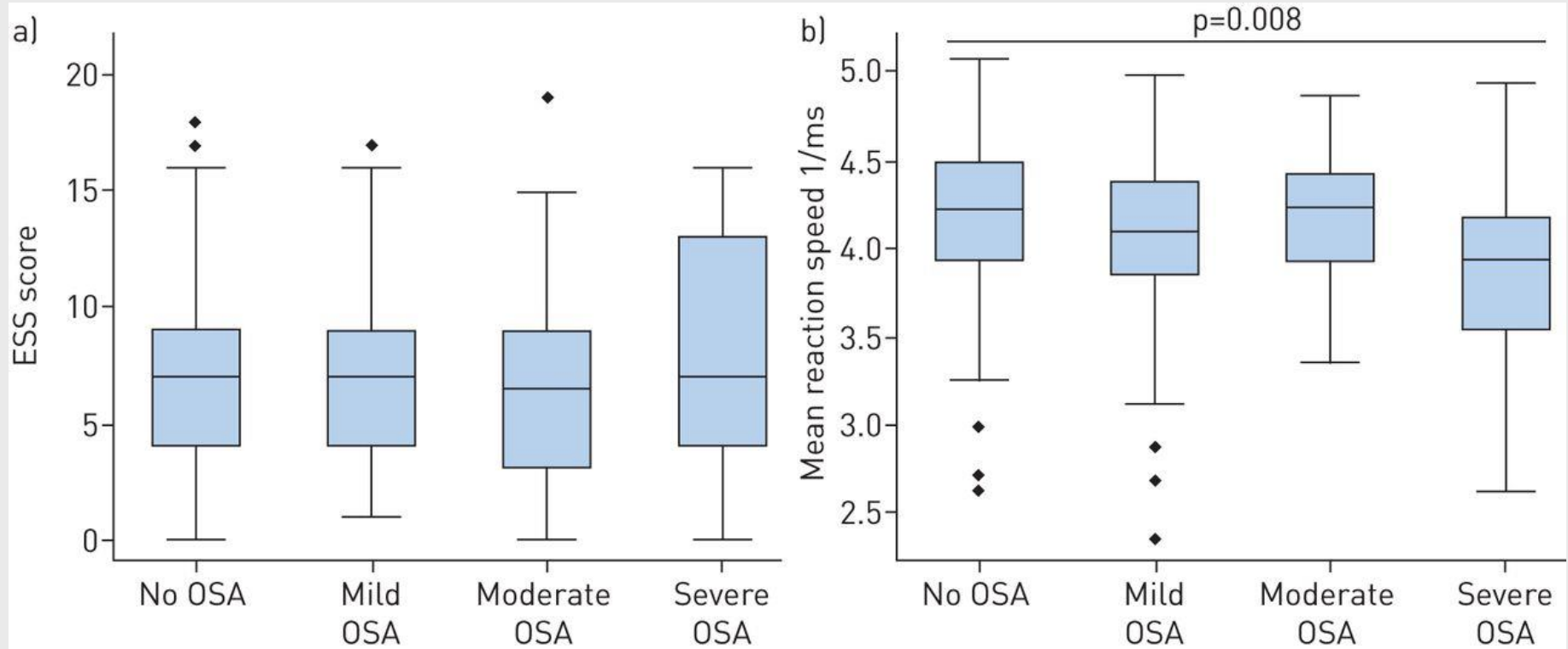
# OSA in the general population: highly prevalent but minimal symptoms.

- 415 middle-aged Icelanders from general population.
  - 56.9% no OSA (AHI <5)
  - 24.1% mild OSA (AHI 5-14.9),
  - 12.5% had moderate OSA (AHI 15-29.9)
  - 2.9% had severe OSA (AHI  $\geq 30$ )
  - 3.6% were already diagnosed and receiving OSA treatment.
- No relationship between AHI and subjective sleepiness or other symptoms
- Relationship with Psychomotor Vigilance Testing found only with AHI  $\geq 30$ .



Arnardottir ES et al.  
*Eur Respir J*  
2016;47(1):194-202

# OSA in the general population: highly prevalent but minimal symptoms.



**Conclusion:** Moderate-to-severe OSA is found in almost 20% of a general population, but most were asymptomatic and did not have impaired vigilance.



# Take-Home Message

- Obstructive sleep apnoea is one of the most prevalent chronic respiratory disorders
- All respiratory practitioners will regularly encounter patients with OSA in their daily clinical practice
- Clinically significant OSA represents only a small proportion of patients with „significant“ AHI on sleep studies
- Major challenge to reliably screen for clinically significant cases

# Diagnosis

# Screening Questionnaires

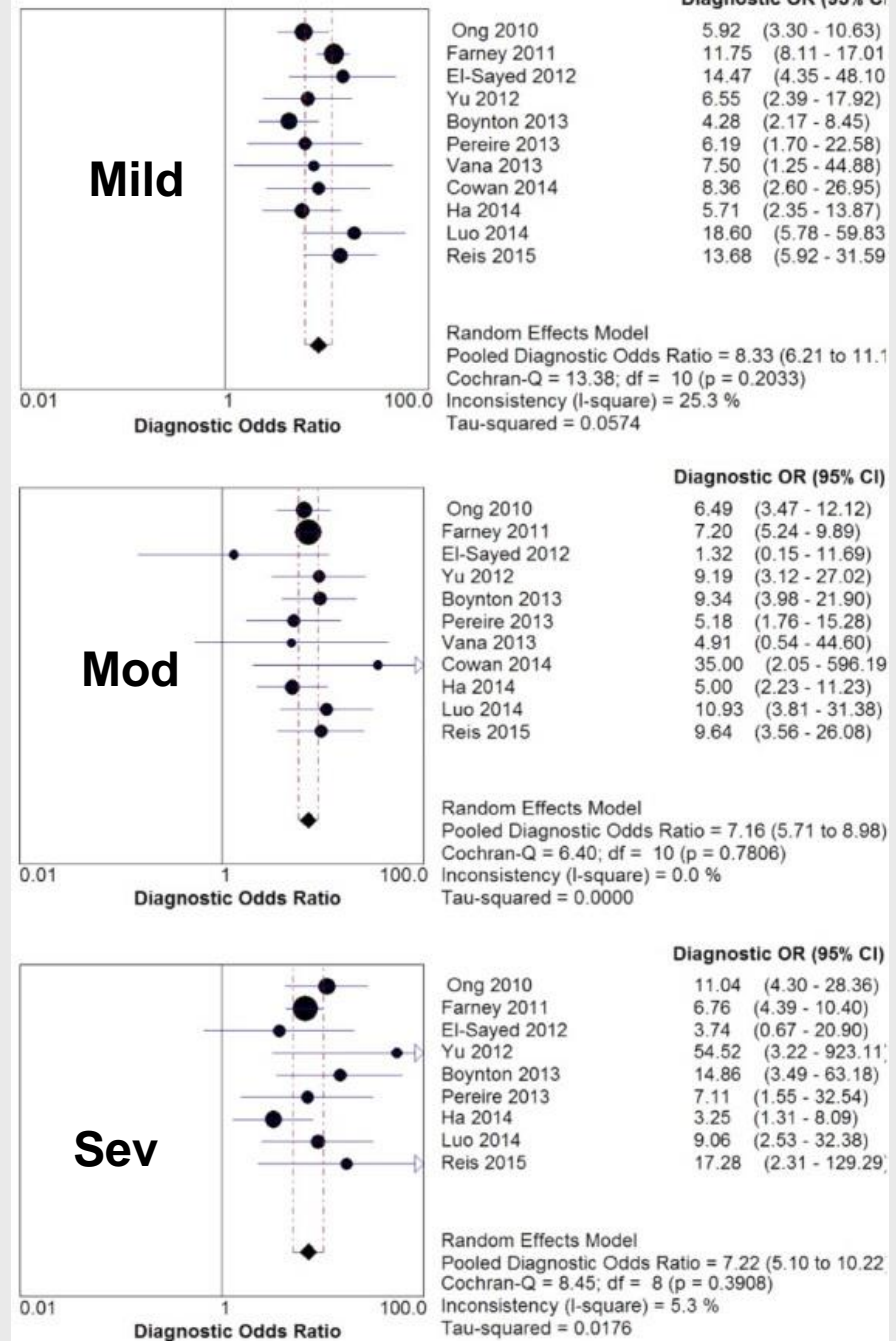
- **Berlin, STOP, STOP-BANG**
- Sensitivity v specificity
- Applicability to different populations
- Complexity of questionnaire

# Systematic Review of STOP-Bang Questionnaire as a Screening Tool for OSA

- **STOP-Bang:** 8-point questionnaire – snoring, apnoea, sleepy, weight, BP, age>50, male sex
- 17 studies with 9,206 patients having PSG - sleep clinic and surgical populations.
- **Sleep clinic:** Sensitivity 90%, 94% and 96% for AHI  $\geq 5$ , AHI  $\geq 15$ , and  $\geq 30$ ; Negative predictive value (NPV) - 46%, 75% and 90%.
- Diagnostic accuracy improved with progressively increasing SBQ scores.
- **Surgical clinic:** Probability of severe OSA with a STOP-Bang score of 3 was 15%; increased to 25%, 35%, 45% and 65%, with increasing score to 4, 5, 6 and 7/8.

# Validation of the STOP-Bang Questionnaire as a Screening Tool for OSA in Different Populations

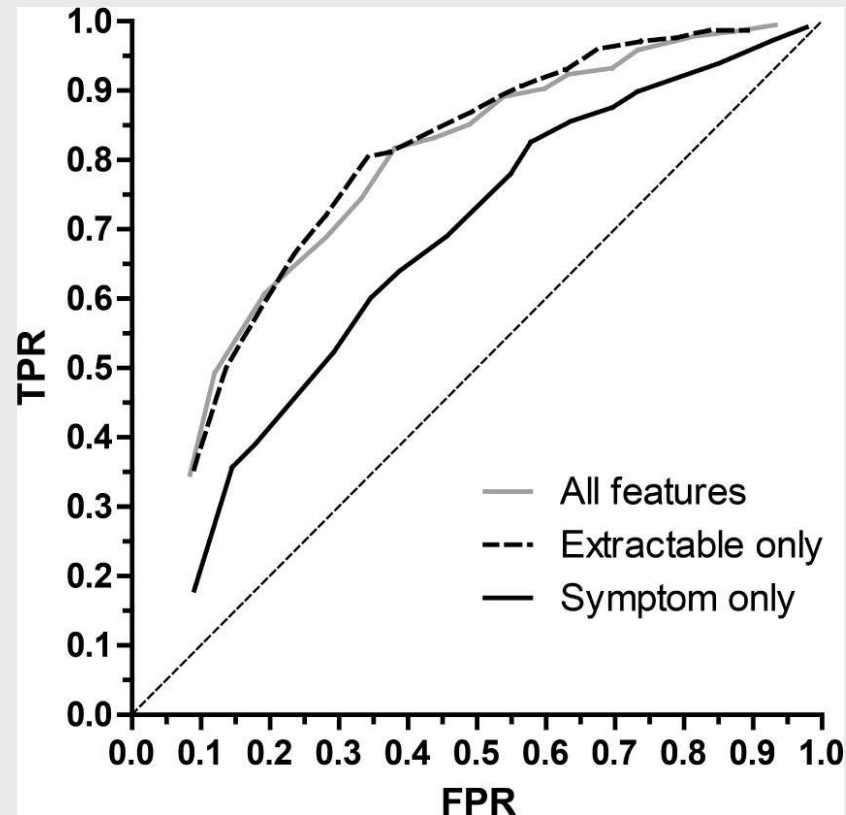
**Message:** STOP-Bang has high sensitivity but relatively low specificity. Specificity can be increased by using higher SBQ scores



# Clinical Prediction Models for Sleep Apnea: Importance of Medical History over Symptoms.

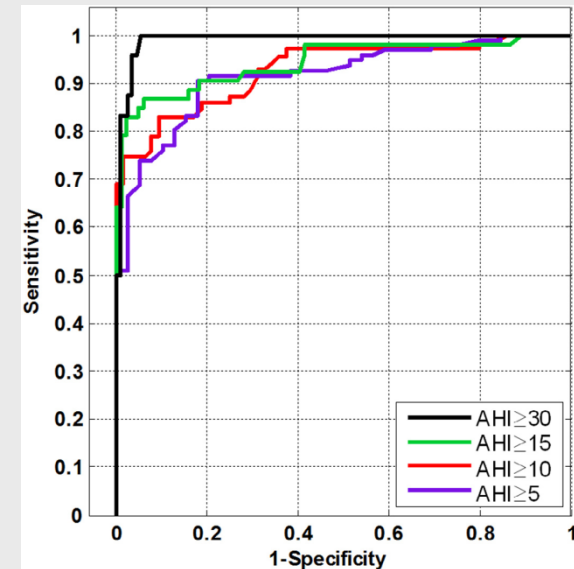
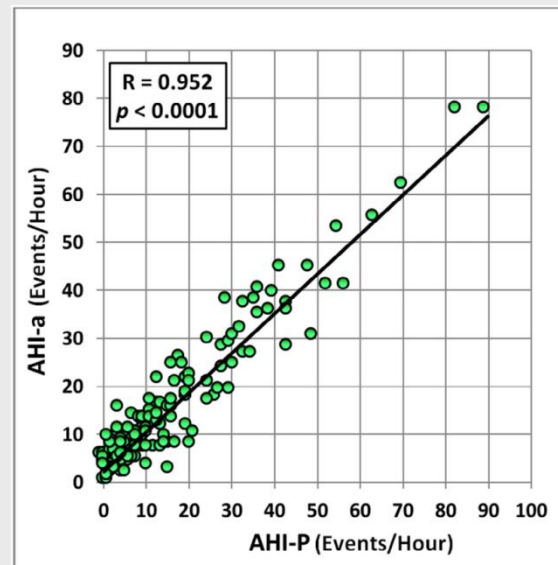
- Sophisticated Machine learning method
- PSG in 1,922 patients in sleep laboratory
- Compared self-reported symptoms with self-reported medical information on demographics and co-morbidities
- Model performance using only medical history features was superior to model performance using symptoms alone, and similar to model performance using all features. Sensitivity 64.2% and specificity 77%.

**CONCLUSION:** 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*

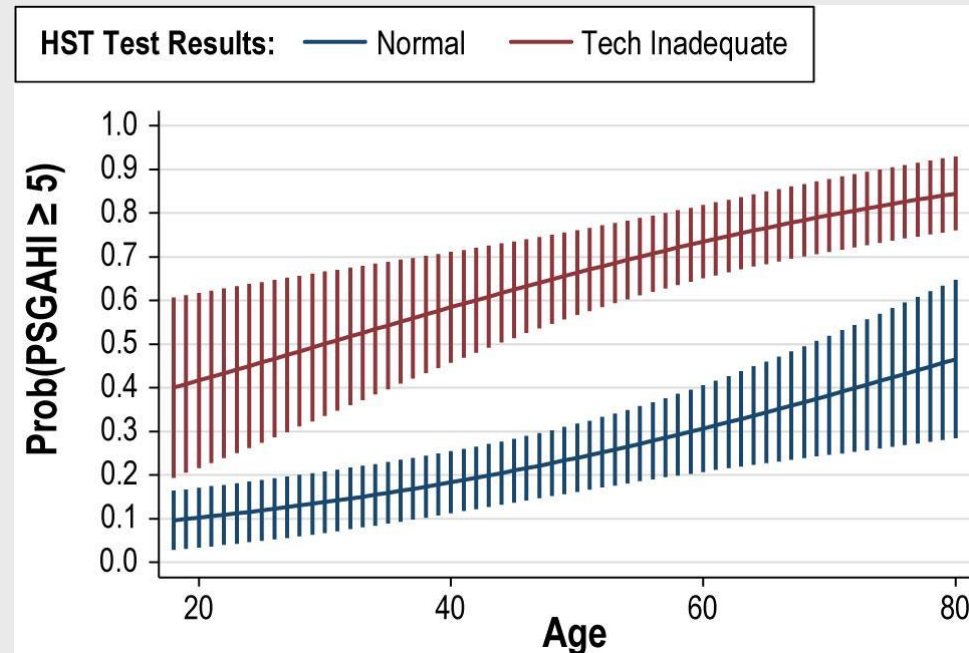
# Comparison of in-laboratory and home diagnosis of OSA using a cordless portable acoustic device.



Alshaer H et al. Sleep Med. 2015 Dec 2. pii: S1389-9457 [Epub ahead of print]

# Predictors of OSA on PSG after a Technically Inadequate or Normal HomeSleep Test.

- 1,157 patients having Home Sleep Test (HST): 111 technically inadequate and 127 negative studies proceeded to PSG.
- Normal HST is highly predictive of normal PSG/mild OSA, particularly in younger age, but technically inadequate studies require further testing.



Zeidler MR et al. J Clin Sleep Med. 2015;11(11):1313-8.



# An Economic Evaluation of Home Versus Laboratory-Based Diagnosis of OSA

- 373 USA patients at high pre-test risk for moderate to severe OSA.
- Randomized to either home sleep study followed by unattended CPAP autotitration, or laboratory sleep study and CPAP titration.
- From the payer perspective, average costs for the laboratory path were \$1,840 compared to \$1,575 for the home path ( $P=0.02$ ).
- From the provider perspective, average costs for the laboratory path were \$1,697 compared to \$1,736 in the home path ( $P=0.66$ ).
- The provider operating margin was \$142 ( $P < 0.01$ ) in the laboratory arm, compared to a loss of -\$161 ( $P < 0.01$ ) in the home arm.

## CONCLUSIONS:

- For payers, home-based management is cheaper.
- For providers, home-based management is slightly more expensive and loses money
- **Caution:** Cost calculations may be different in other countries.

*Kim RD et al. Sleep 2015 Jul 1;38(7):1027-37.*

# Take-Home Message

- The search for a reliable predictive screening questionnaire continues and traditional symptoms show poor correlation with AHI
- The choice of limited ambulatory systems continues to grow and advancing technologies play an important role
  - Watch the future!

# Co-Morbidities

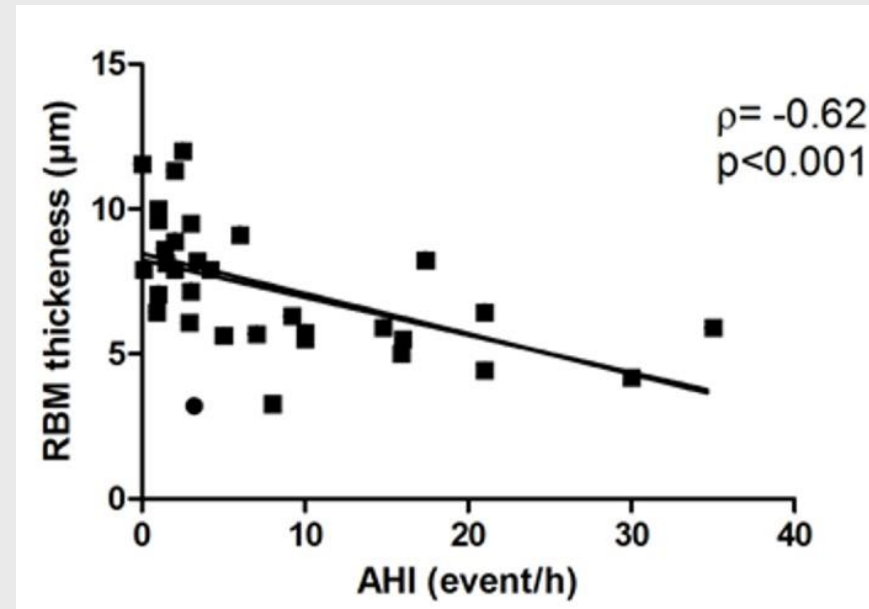
# Asthma and COPD

Asthma is an independent  
risk factor for future OSA:  
*Pneumo Update 2015*

What about reverse relationship – ie  
potential impact of OSA on asthma?

# OSA Modulates Airway Inflammation and Remodelling in Severe Asthma

- 55 patients with resistant asthma and nocturnal symptoms.
- Sputum analysis and bronchial biopsies for assessment of reticular basement membrane (RBM) thickness, smooth muscle area, vascular density and inflammatory cell infiltration.
- 27/55 patients (49%) had OSA (AHI;  $14.2 \pm 1.6$ )
  - Higher sputum neutrophils and higher levels of IL-8 and matrix metalloproteinase 9.
  - RBM thinner in OSA than non-OSA ( $5.8 \pm 0.4$  vs.  $7.8 \pm 0.4$   $\mu\text{m}$ ,  $p < 0.05$ ). RBM thickness negatively correlated with AHI ( $\rho = -0.65$ ,  $p < 0.05$ ).
  - OSA and non-OSA patients similar in age, sex, BMI, lung function, asthma control findings and treatment.



## CONCLUSION:

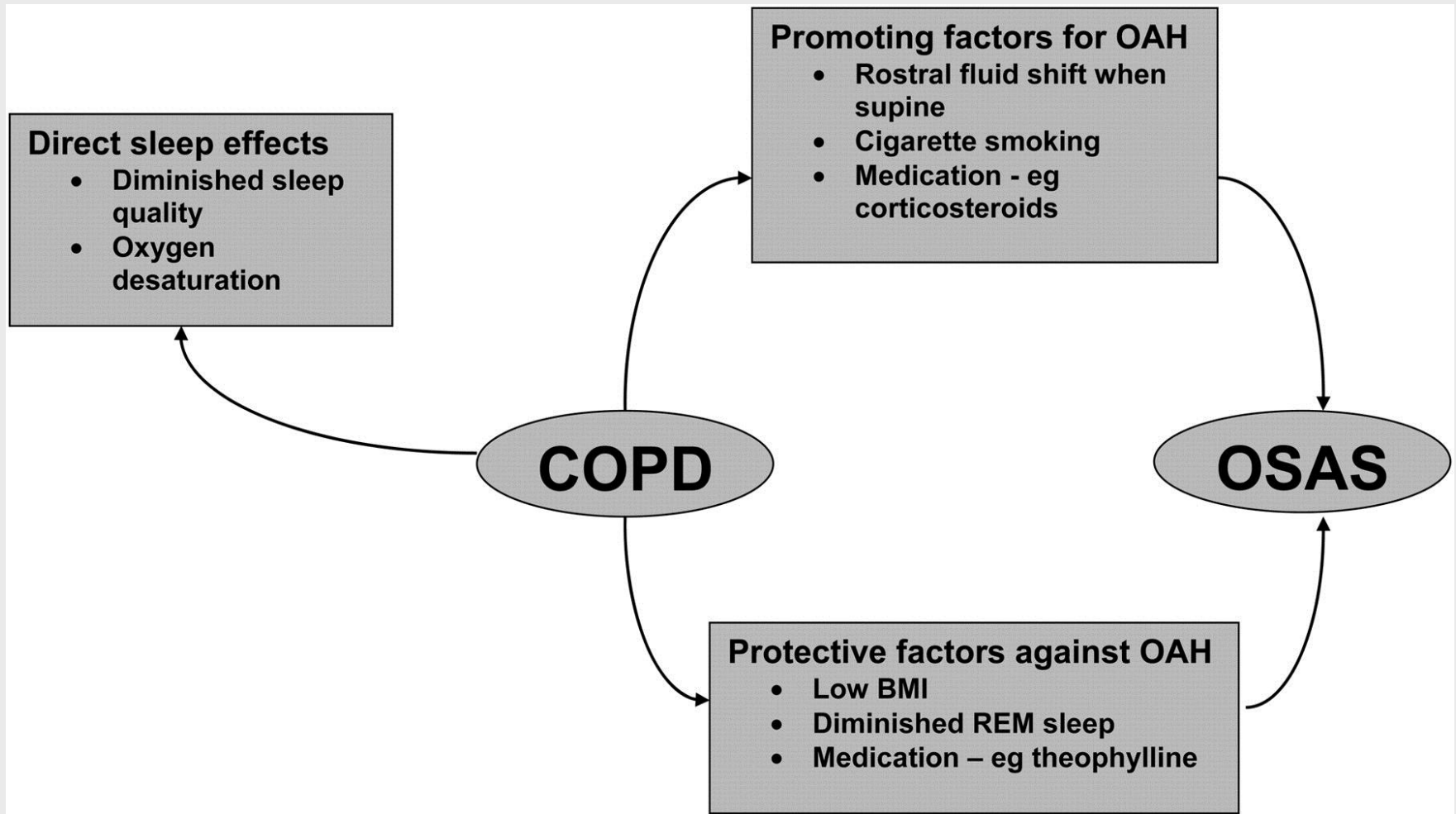
Mild OSA in patients with severe asthma is associated with increased neutrophils in sputum and changes in airway remodelling.

# Long-term CPAP therapy improves asthma control in patients with asthma and OSA.

- 152 asthmatics with OSA started CPAP and followed average 5.7 years later.
- Self-reported asthma severity and rescue inhaler use decreased significantly ( $p < 0.001$ ).

*Kauppi P et al Sleep Breath. 2016 Apr 7. [Epub ahead of print]*

# Pathophysiological interactions between COPD and OSA



McNicholas WT. Pulmonary Perspective. AJRCCM 2009

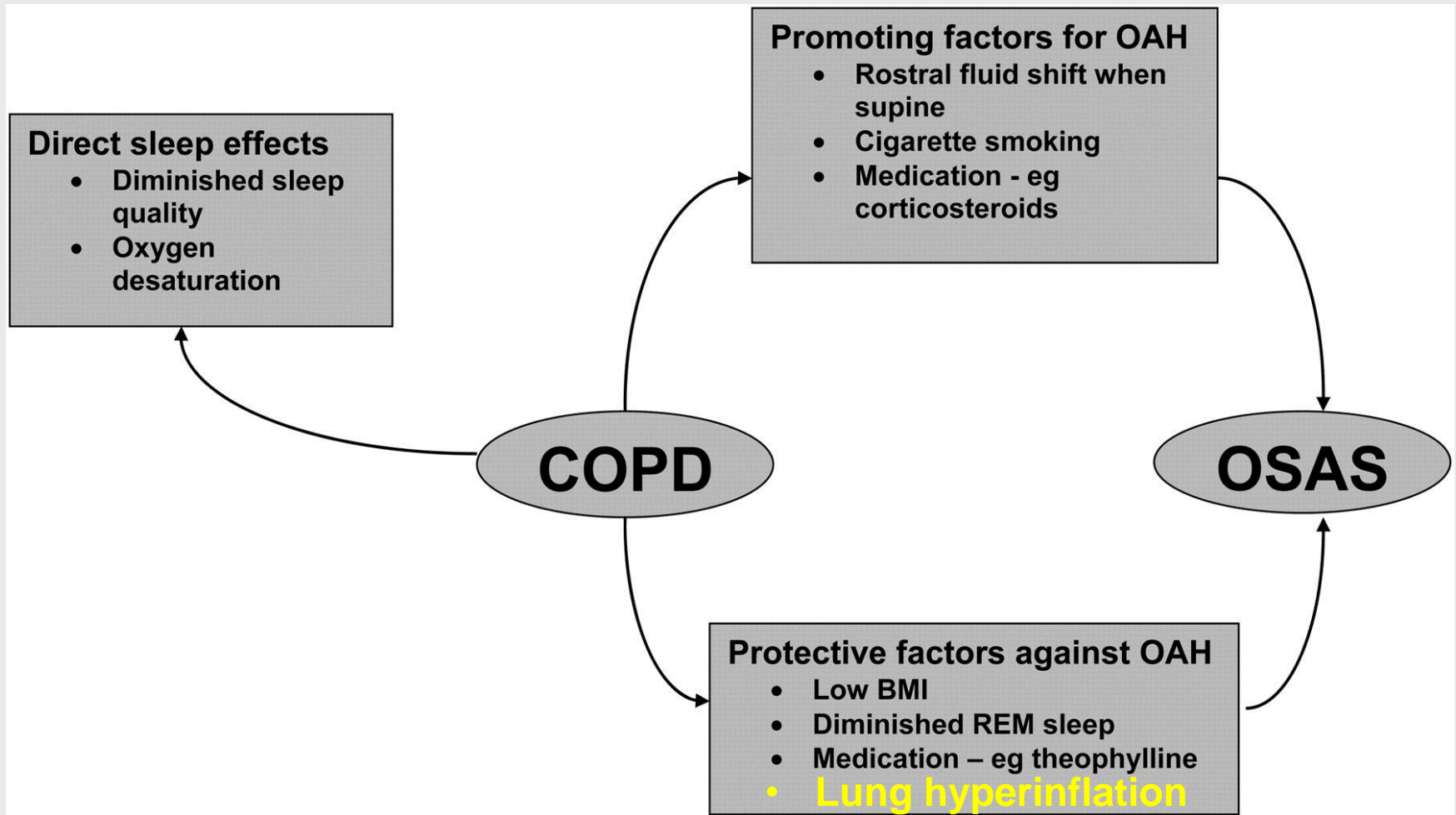


# Role of Hyperinflation

- Background: Lung inflation increases upper airway size and stability and may ameliorate OSA severity
- 51 smokers, average BMI 32, had PSG, PFT, volumetric chest CT
- 29 had OSA (AHI  $18 \pm 12$  events/hr) and were younger and heavier
- Inverse correlation between AHI and CT% emphysema and CT% gas trapping in the full group and also those with OSA.
- Multiple regression analysis showed CT% emphysema and CT% gas trapping, gender, and BMI were independent predictors of AHI.
- ***Conclusion: Lung hyperinflation is associated with less severe OSA as measured by AHI***

*Krachman et al. Ann ATS 2016 IN Press*

# Pathophysiological interactions between COPD and OSA

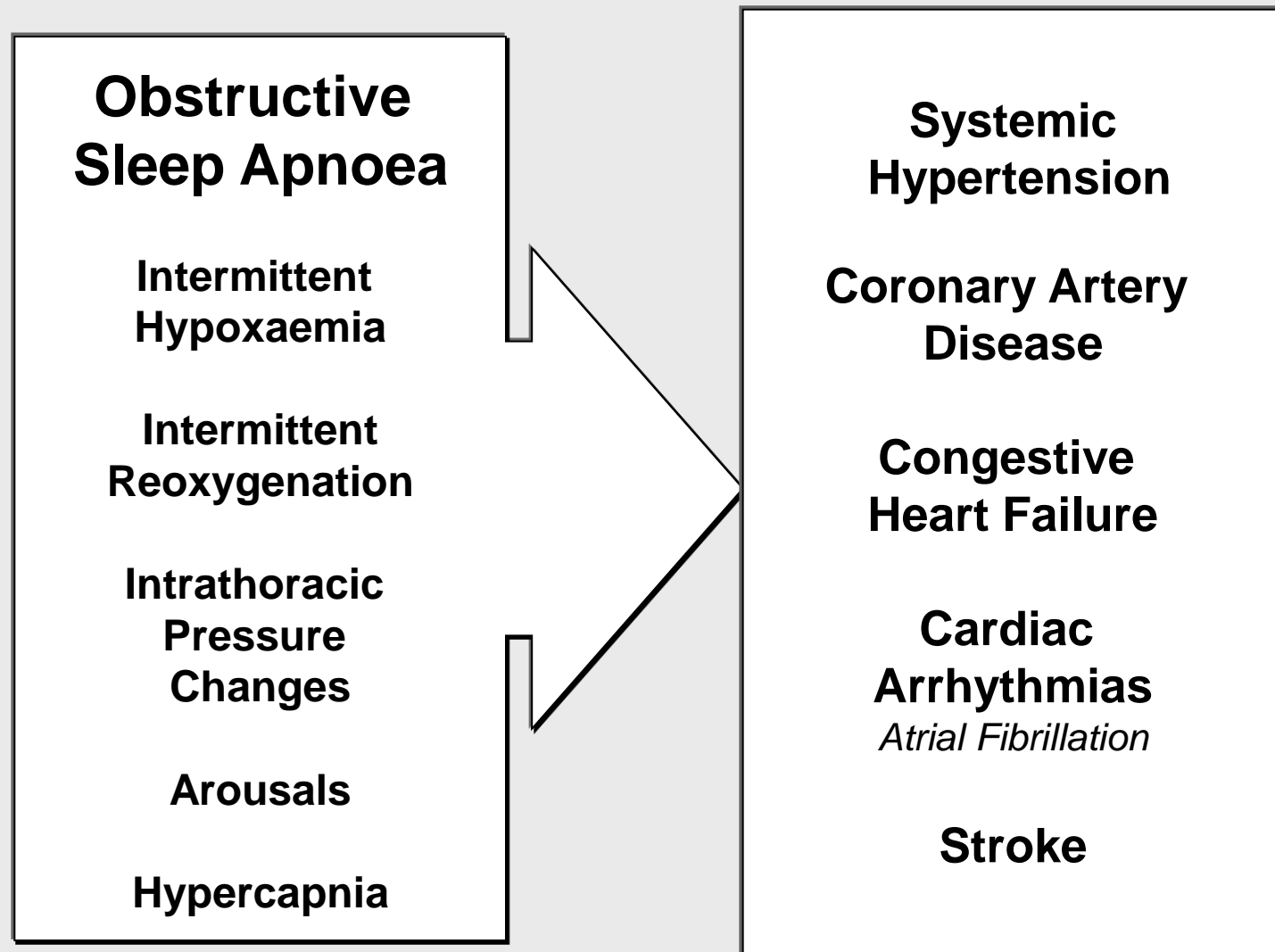


McNicholas WT. Pulmonary Perspective. AJRCCM 2009

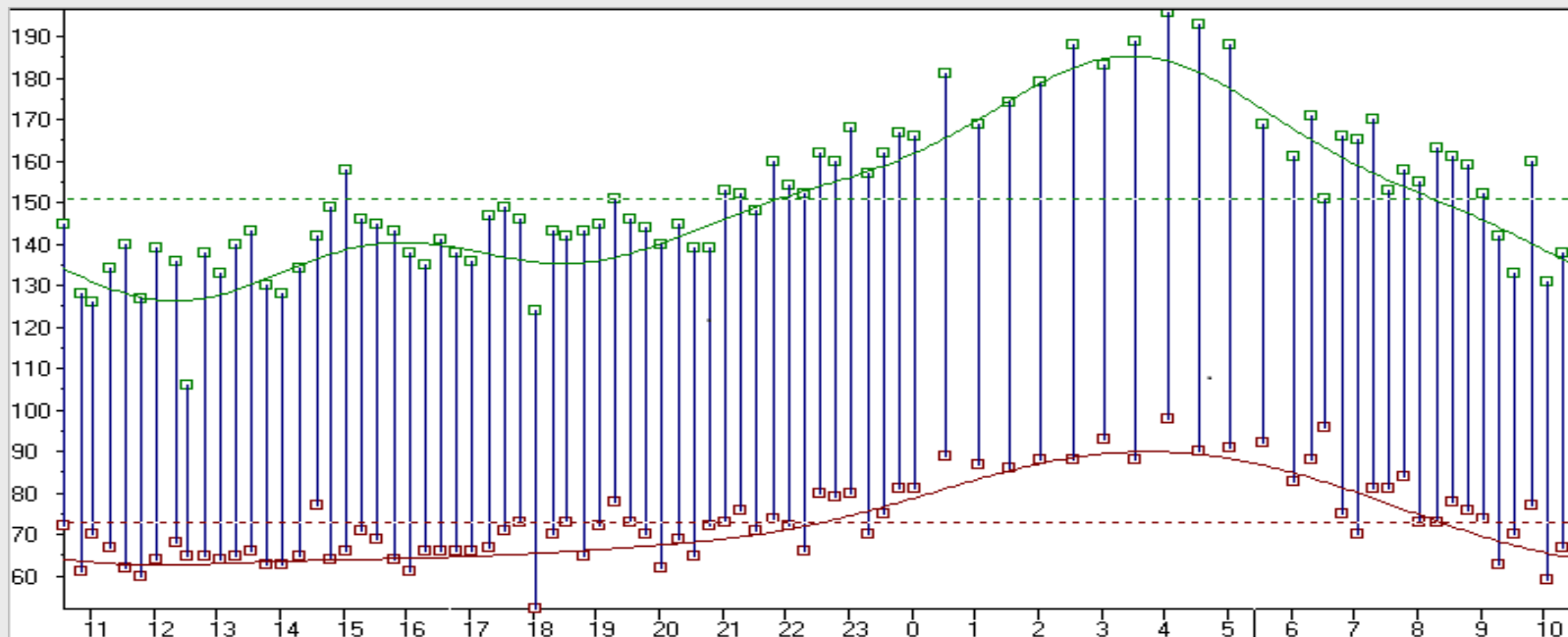
# Take-Home Message

- Growing evidence of relationship between asthma and OSA, which may be bi-directional
- Uncertainties regarding relationships between COPD and OSA – some COPD factors protective
  - Hyperinflation, low BMI

# OSAS and Cardiovascular Disease – *putative associations*



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

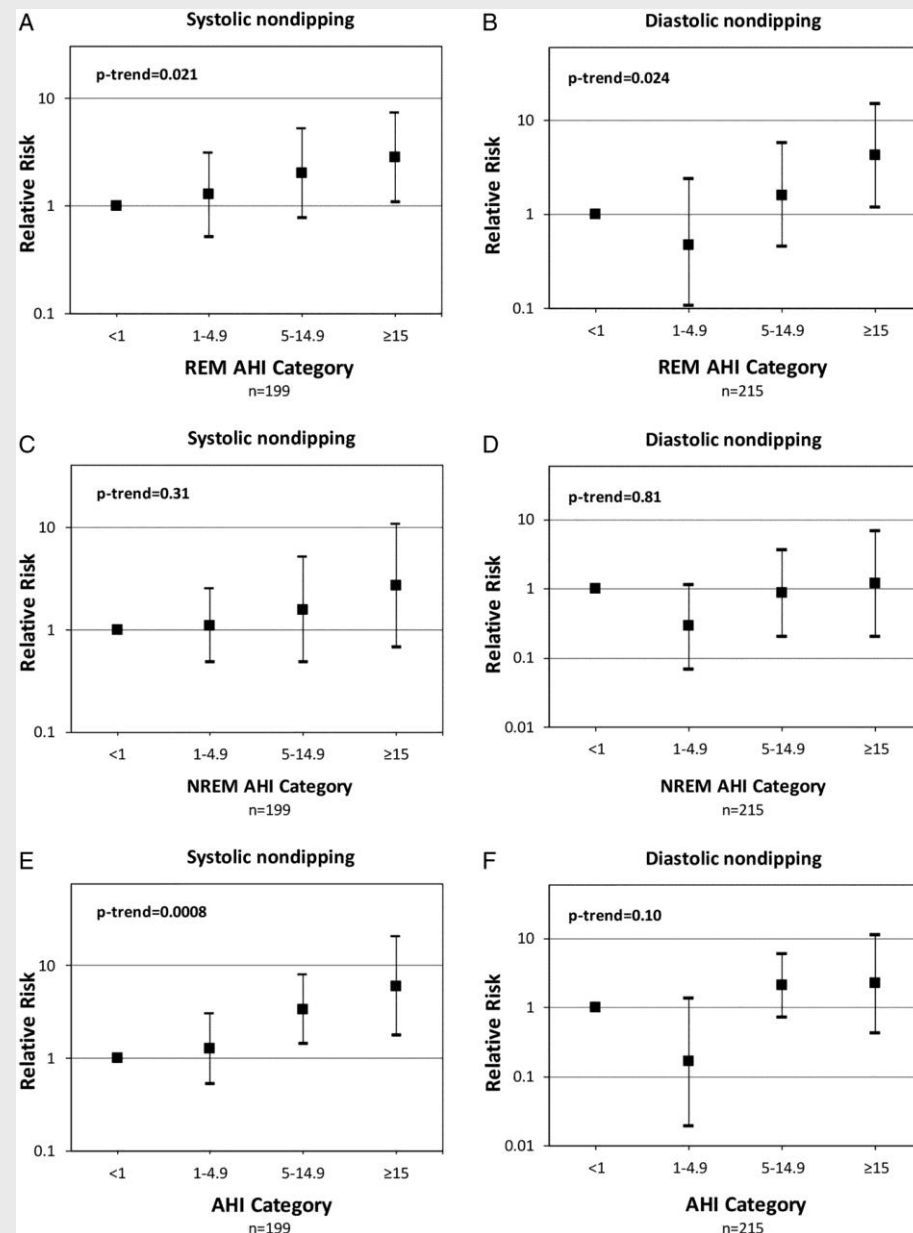


Strong association with drug-resistant hypertension

# OSA in REM sleep and incident non-dipping nocturnal BP

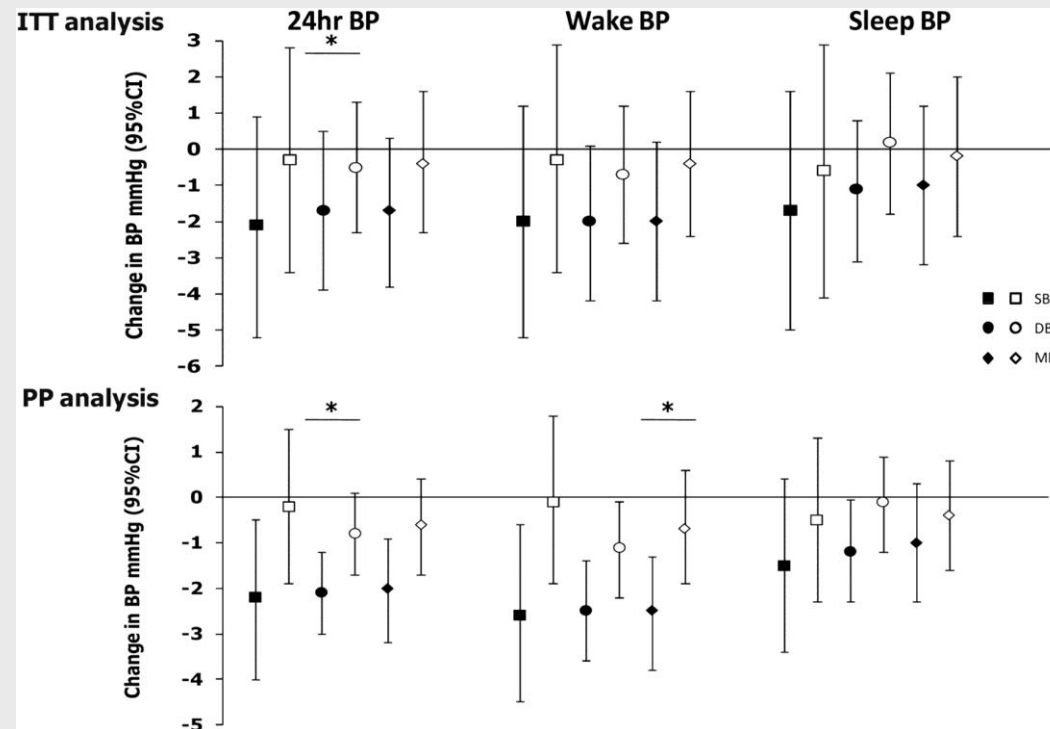
- 269 non-hypertensive adults from the Wisconsin Cohort Study followed for average 6.6 years - OSA defined by baseline AHI.
- Dose-response greater risk of developing systolic and diastolic non-dipping BP with greater severity of OSA in REM sleep but not in NonREM.
- In patients with REM AHI >15, relative risk of incident systolic non-dipping was 2.84 and incident diastolic non-dipping was 4.27.

**CONCLUSION:** In a population-based sample, REM OSA is independently associated with incident non-dipping of BP.



# Fixed-pressure CPAP versus auto-adjusting CPAP: comparative efficacy on blood pressure in OSA

- 322 OSA patients (mean AHI 43) randomised to CPAP or APAP for 4 months
- Significant reduction in mean 24hr BP on ABPM: -1.7 mmHg with CPAP vs -0.5 mmHg with APAP
- Limitations: Study not confined to hypertensive patients so benefits may be underestimated



**Conclusion:** CPAP is somewhat superior to APAP in reducing BP among OSA patients.

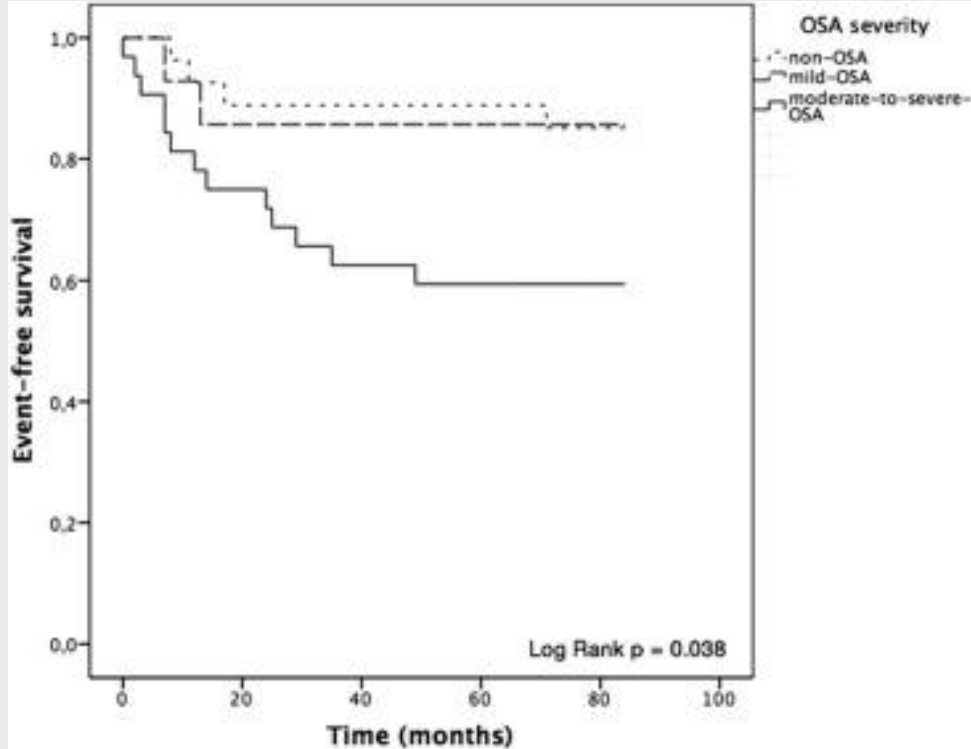
# Coronary Heart Disease

## Effect of OSA in Acute Coronary Syndrome

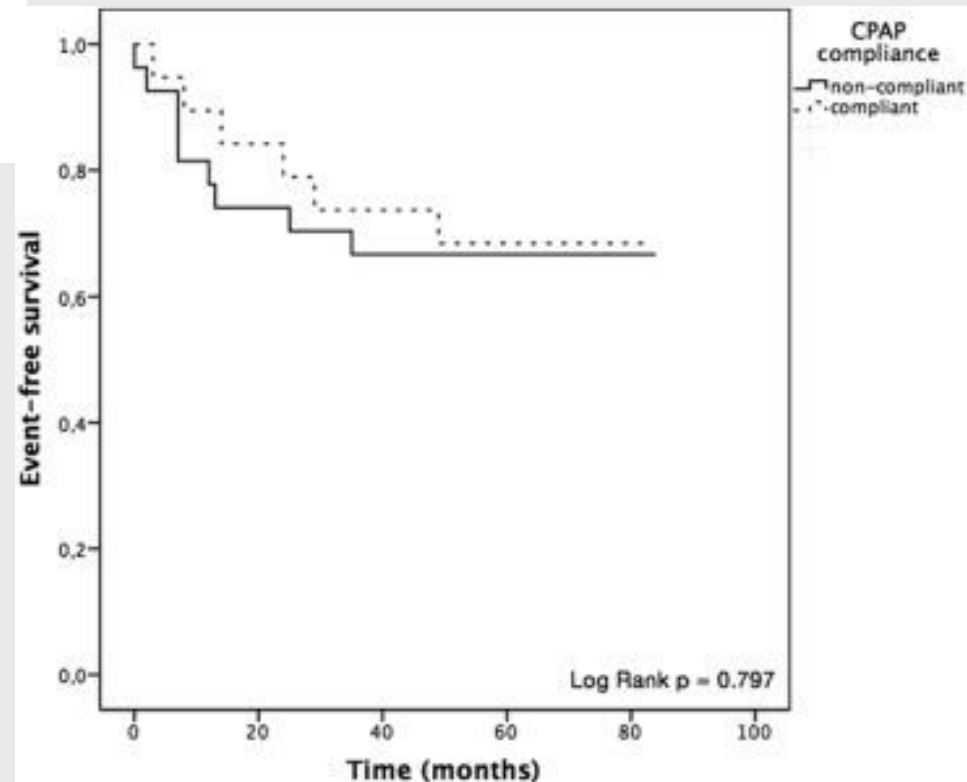
- 73 patients admitted to CCU with acute coronary syndrome had sleep study.
- AHI >15 (s-OSA) in 32 patients - Age and cardiovascular risk factors similar between groups.
- After a median follow-up of 75 months, s-OSA had a higher incidence of death for any cause, myocardial infarction, and myocardial revascularization (hazard ratio 3.58,  $p = 0.035$ ).



# Effect of OSA in Acute Coronary Syndrome

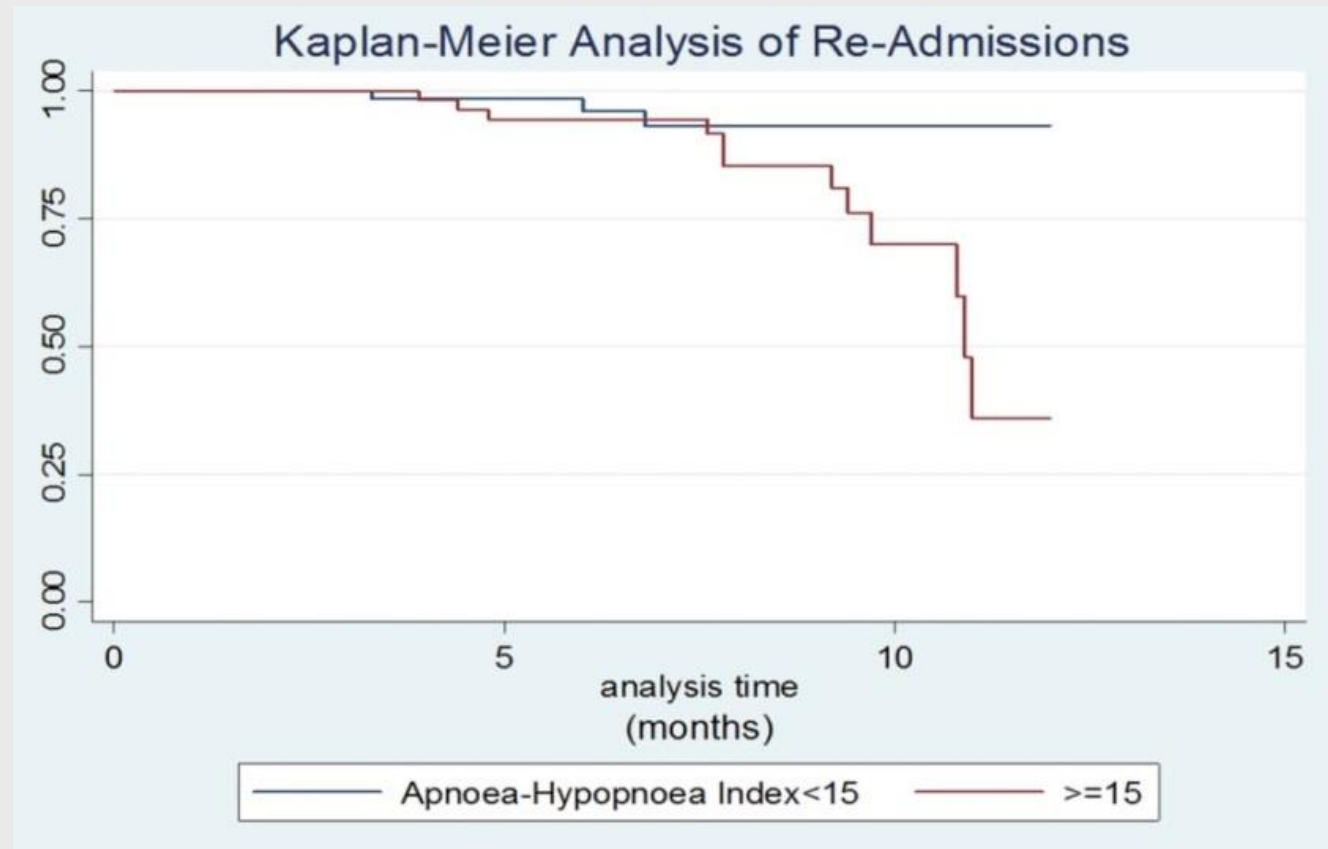


**Conclusion:** OSA is highly prevalent in patients with ACS and associated with worse outcome.



# Sleep apnoea and unscheduled re-admission in patients undergoing coronary artery bypass surgery

138 patients had sleep study before CABG: AHI  $\geq 15$  in 69 (50%)

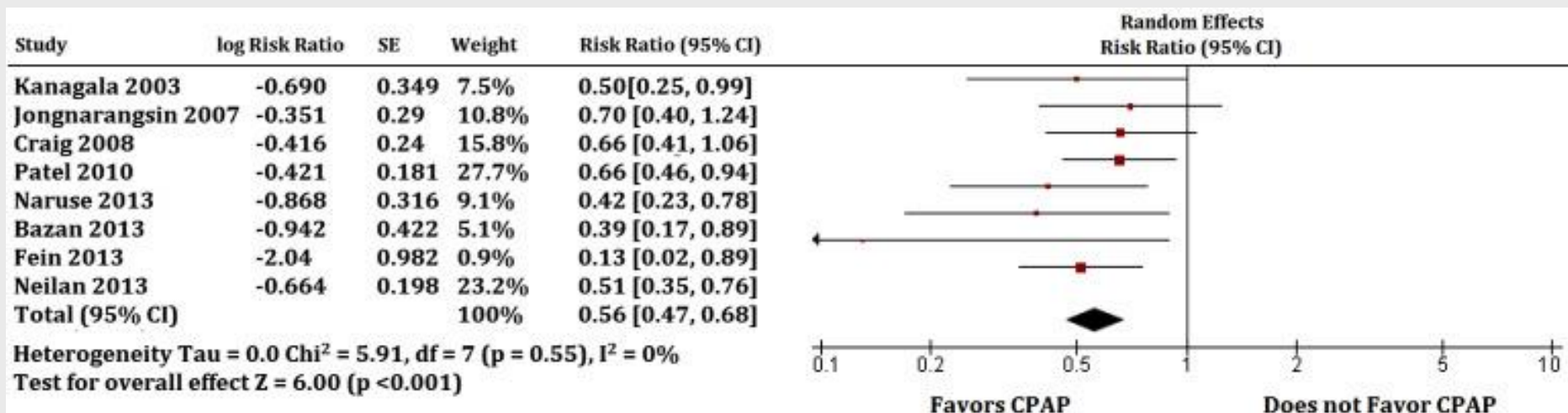


**CONCLUSIONS:** Sleep apnoea was highly prevalent and predictive of unscheduled re-admissions in patients scheduled for CABG.

*Zhao L et al. Atherosclerosis 2015;242(1):128-34.*

# Meta-Analysis of CPAP as a Therapy of Atrial Fibrillation in OSA

- 8 studies on OSA (1 RCT) with 698 CPAP users and 549 non-CPAP users.
- CPAP treated patients had a 42% lower risk of AF ( $p < 0.001$ ).
- Benefits of CPAP greater for younger, obese, and male patients ( $p < 0.05$ ).



Qureshi WT et al. Am J Cardiol. 2015 Dec 1;116(11):1767-73

# Effect of CPAP on Glycemic Control in Patients with OSA and Type 2 Diabetes. *A Randomized Clinical Trial*

- 50 OSA patients with poorly controlled type 2 diabetes
- After 6 months, the CPAP group achieved a greater decrease in HbA1c levels compared with controls.
- Insulin resistance and serum levels of IL-1 $\beta$ , IL-6 and adiponectin improved in the CPAP group compared with controls.

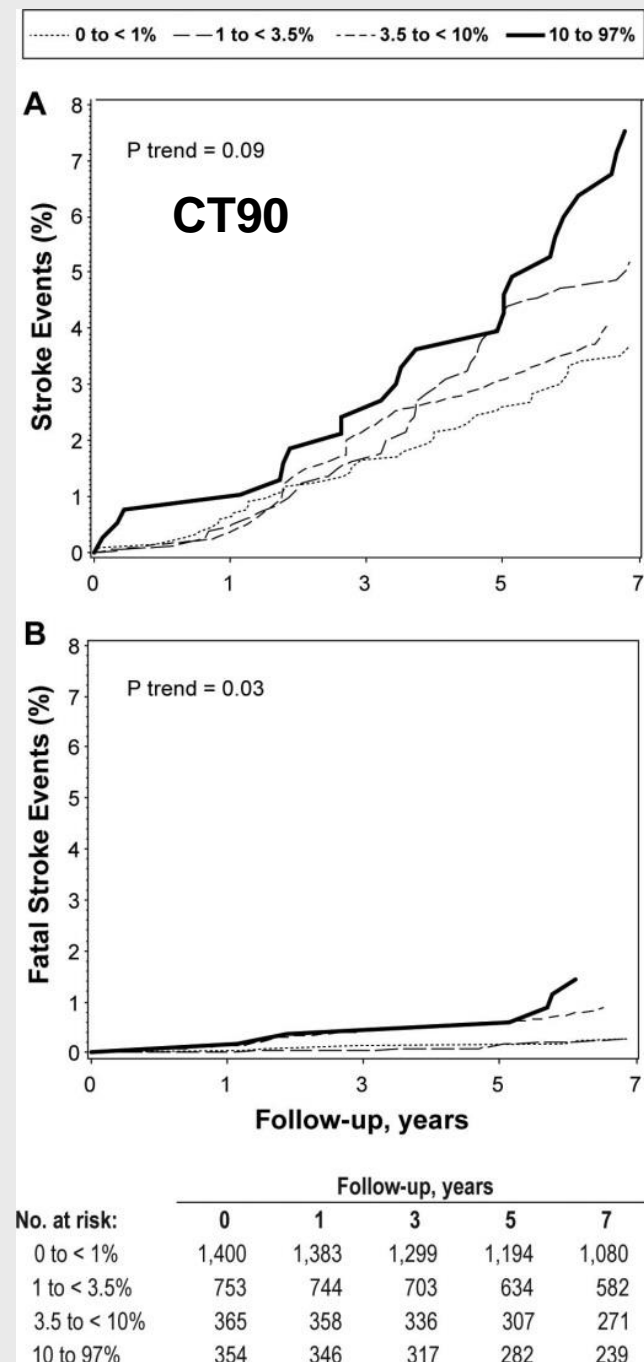
**CONCLUSIONS:** Among patients with sub-optimally controlled type 2 diabetes and OSA, CPAP therapy resulted in improved glycemic control and insulin resistance.

*Martínez-Cerón E et al. Am J Respir Crit Care Med. 2016 Feb 24. [Epub ahead of print]*

# Sleep Disordered Breathing and Risk of Stroke in Older Community-Dwelling Men

- 2,872 elderly men having PSG.
- 156 (5.4%) had stroke during average 7.3 yrs follow-up.
- Severe nocturnal hypoxemia (CT90 >10%) had a 1.8-fold increased risk of incident stroke (RR vs normal saturation was 1.83; P = 0.02).
- AHI not associated with incident stroke.

**CONCLUSIONS:** Older men with severe nocturnal hypoxemia are at significantly increased risk of incident stroke.



# Can CPAP Reduce the Risk of Stroke in Patients with OSA? *A Systematic Review and Meta-Analysis*

- 8 relevant studies: one RCT, 5 cohort studies, and 2 studies using administrative health data.
- CPAP therapy associated with lower incidence of stroke and cardiac events in cohort studies; RR 0.27 [0.14-0.53] and 0.54 [0.38-0.75] respectively.
- Association not evident in the RCT and the studies using administrative data.

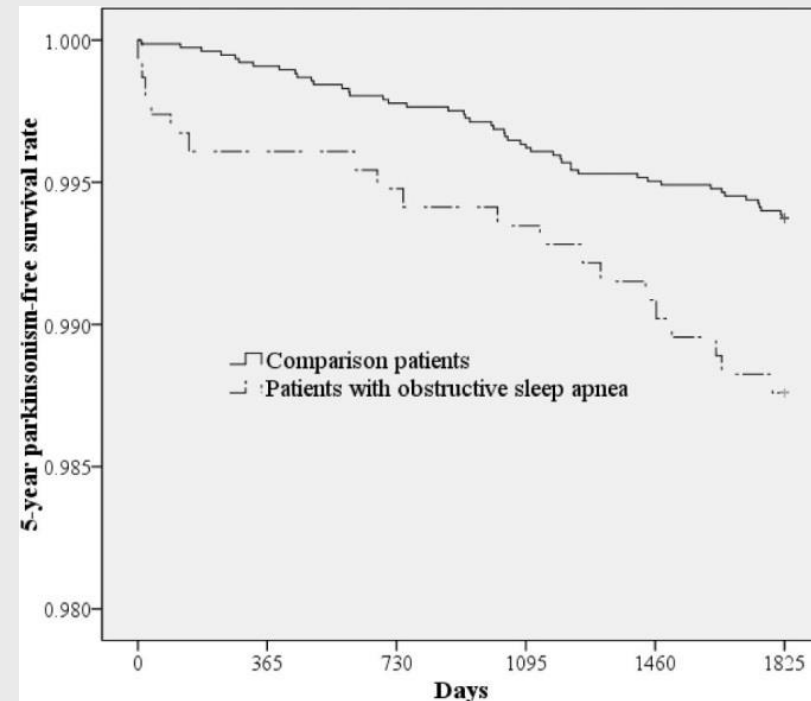
## **CONCLUSIONS:**

- CPAP therapy in patients with OSA may decrease the risk of stroke, although evidence not clear-cut. Effect more pronounced for stroke than for cardiac events.

Kim Y et al. *PLoS One*. 2016;11(1):e0146317

# A 5-Year Follow-up Study on the Relationship between OSA and Parkinson Disease

- Retrospective cohort study based on a Health Insurance Database.
- 1,532 patients with OSA as the study cohort and 7,660 patients randomly selected as the control cohort.
- Parkinson disease developed in 1.24% of OSA and 0.63% of control subjects over 5-years - hazard ratio (HR) 2.26.
- Relationship significant only in females (HR 3.54).



**CONCLUSIONS:** Females with OSA are at significant risk of developing Parkinson disease during 5-y follow-up.

*Sheu JJ et al. J Clin Sleep Med. 2015;11(12):1403-8*

# Effect of Sleep-Disordered Breathing on Cognitive Performance in a Community Cohort of Young School-Aged Children

- 1,010 5-7 year-old snoring and non-snoring schoolchildren had PSG and neurocognitive assessments.
- Subdivided into 4 groups based on AHI, followed by comparisons of cognitive functioning.
- DAS Verbal ( $p < .001$ ) and Nonverbal performance ( $p = .002$ ), as well as IQ ( $p < .001$ ) scores differed significantly across the groups, with higher AHI showing worse performance.
- Children with higher AHI ( $>5/\text{hrTST}$ ) were significantly more impaired than all three lower AHI groups.

## CONCLUSIONS:

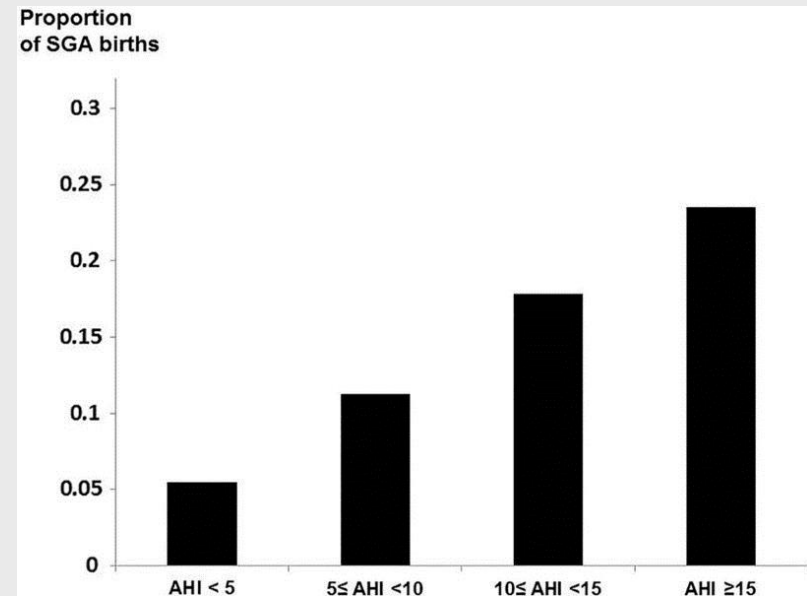
- OSA has a deleterious impact on neurocognitive functioning in a severity graded manner.

*Hunter SJ et al. Am J Respir Crit Care Med. 2016 Mar 1. [Epub ahead of print]*



# Maternal sleep-disordered breathing and the risk of delivering small for gestational age (SGA) infants: a prospective cohort study

- Multicentre pregnancy cohort study. Participants evaluated for SDB based on symptoms and home PSG in the third trimester.
- 234 subjects, BMI 23(4). Delivery of small for gestational age (SGA) infants in 27 (12%).
- Third trimester SDB symptoms showed trend towards association with delivering an SGA infant (OR 2.36. CI, 0.85-6.54,  $p=0.10$ )).
- Odds of delivering an SGA infant higher with PSG diagnosis of maternal SDB (AHI  $\geq 10$ ); OR 2.65 ( $p=0.02$ ).



**CONCLUSIONS:** Objectively measured SDB in the third trimester associated with delivery of SGA infants.

# Take-Home Message

- Body of evidence continues to grow regarding independent relationships between OSA and various co-morbidities
  - Cardiovascular
  - Endocrine and Metabolic
  - Neurological/Neuropsychological

# Management options for obstructive sleep apnoea

- CPAP
- Lifestyle
  - Weight, exercise
- Mandibular advancement
- Surgical options
  - Upper airway
  - Bariatric surgery
- Hypoglossal nerve stimulation

# CPAP

# CPAP Vignettes

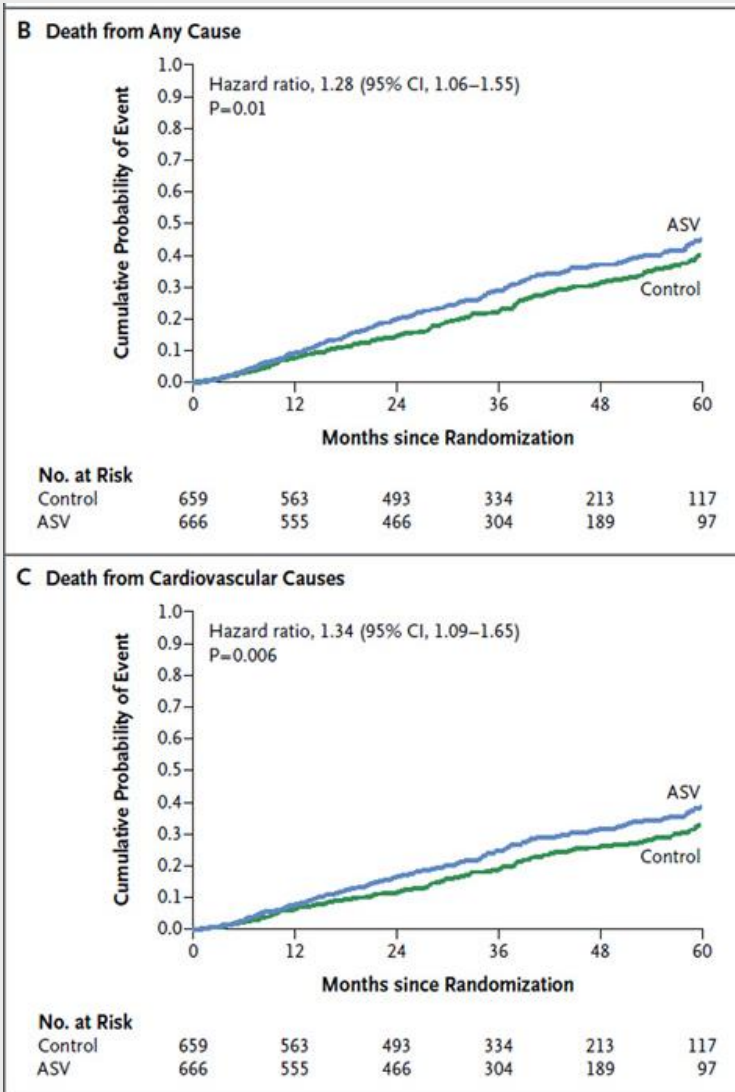
- Cost-effectiveness analysis of a telemedicine-based strategy for the management of OSA: a multicentre randomised controlled trial. Isetta V et al. (Spanish Sleep Network). Thorax. 2015 Nov;70(11):1054-61.
  - **A telemedicine-based strategy had lower total costs due to savings on transport and less lost productivity (indirect costs).**
- Effectiveness of alternative care providers in the management of OSA. Pendharkar SR et al. J Sleep Res. 2016 Apr;25(2):234-40.
  - **Follow-up of CPAP therapy by Allied Health Professionals is as effective as physician care with most patients discharged to primary care after 2-3 visits**
- Self-Efficacy Enhances the Association between CPAP therapy and Adherence. Dzierzewski J et al. J Clin Sleep Med. 2016 Feb;12(2):169-76.
  - **In patient only with high self-efficacy beliefs, there was a significant positive relationship between CPAP therapy and adherence.**
  - **Message: A positive attitude helps!**

# Adaptive Servo-Ventilation for Central Sleep Apnea in Systolic Heart Failure (SERVE-HF).

- 1325 patients with left ventricular ejection fraction  $\leq 45\%$ , AHI  $\geq 15$  and predominantly central events, randomly assigned to standard treatment and adaptive servo-ventilation (ASV) or standard treatment alone (control).
- All-cause mortality and cardiovascular mortality significantly higher in the ASV group than in the control group (hazard ratio for death from any cause, 1.28;  $P=0.01$ ; and hazard ratio for cardiovascular death, 1.34;  $P=0.006$ ).

*Cowie M et al. N Engl J Med. 2015;373(12):1095-105.*

# Adaptive Servo-Ventilation for Central Sleep Apnea in Systolic Heart Failure (SERVE-HF).



## CONCLUSIONS:

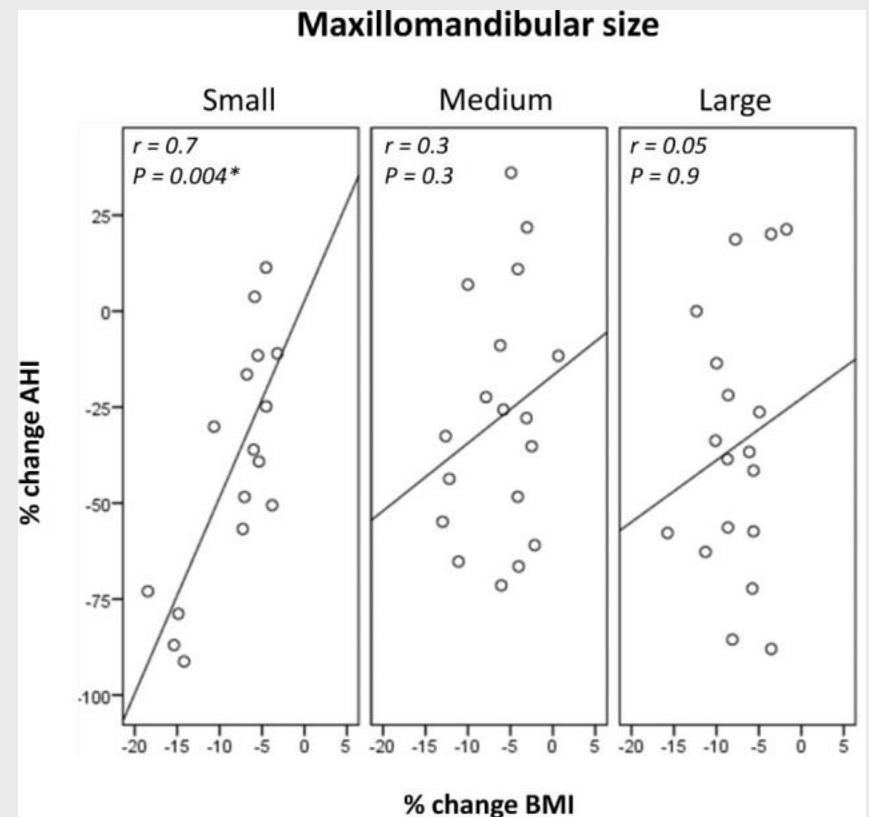
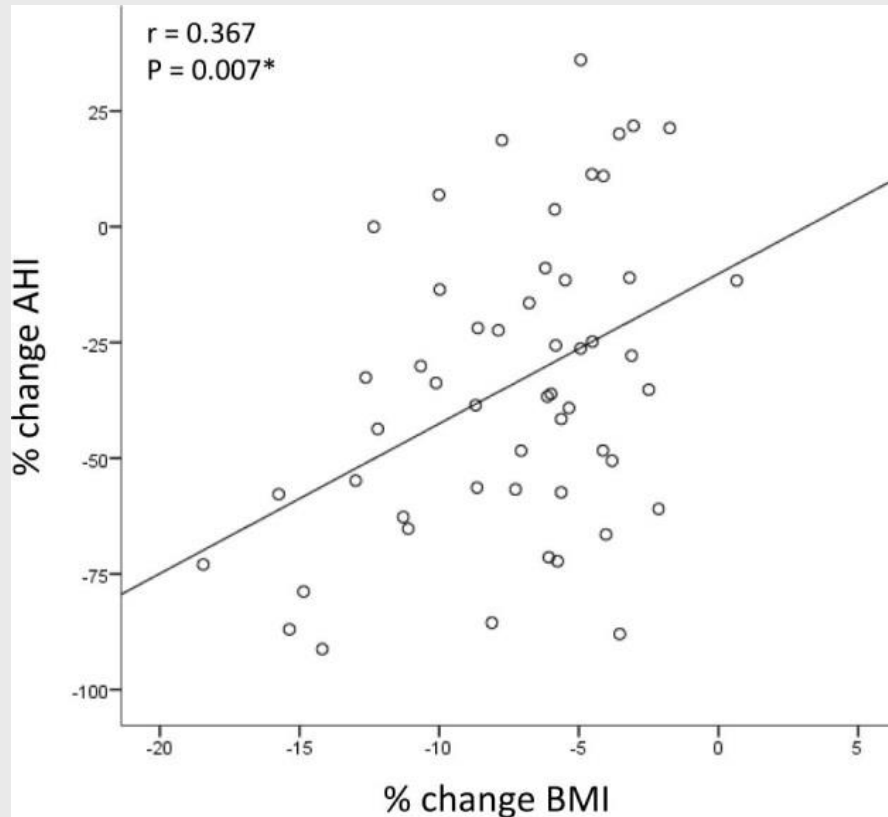
All-cause and cardiovascular mortality were both increased with ASV therapy in patients with CHF and CSA.

ASV not indicated in CHF patients with co-existing central sleep apnoea

Does not necessarily apply to patients with CHF and OSA

*Cowie M et al. N Engl J Med. 2015; 373(12): 1095-105.*

# Maxillomandibular Volume Influences the Relationship between Weight Loss and Improvement in OSA



**CONCLUSION:** A small skeletal maxillomandibular volume predicts the greatest benefit to AHI from weight loss.

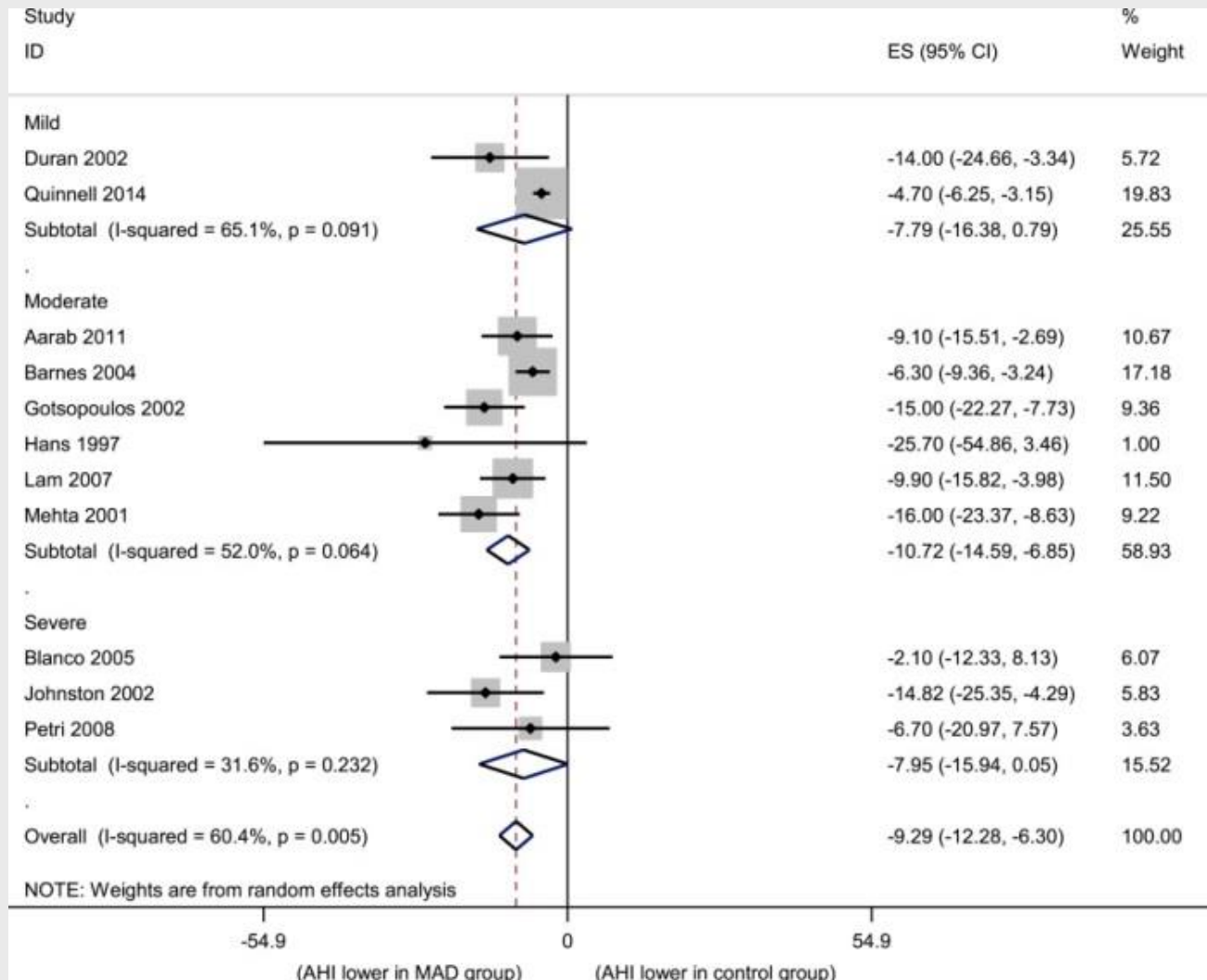
*Sutherland K et al. Sleep 2016;39(1):43-9*



# Mandibular Advancement Devices for OSA

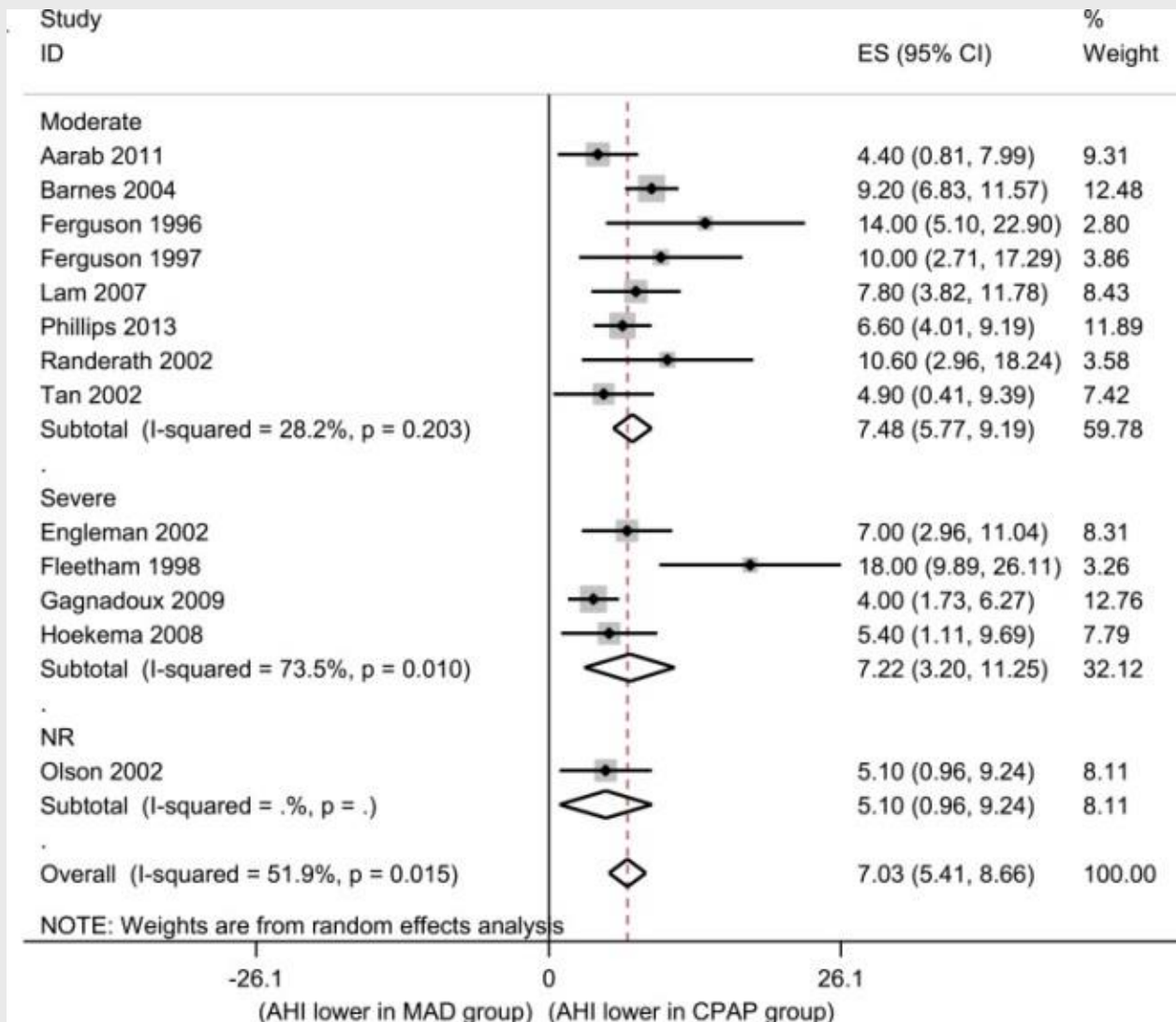
- Particularly appropriate for mild OSA but also as a second line option in CPAP failures.
- Trade-off vs CPAP between lower efficacy but higher compliance.
- Possible now to objectively measure compliance
- Growing evidence of efficacy in ameliorating co-morbidities.

# Meta-analysis of randomised controlled trials of mandibular advancement devices and CPAP for OSA



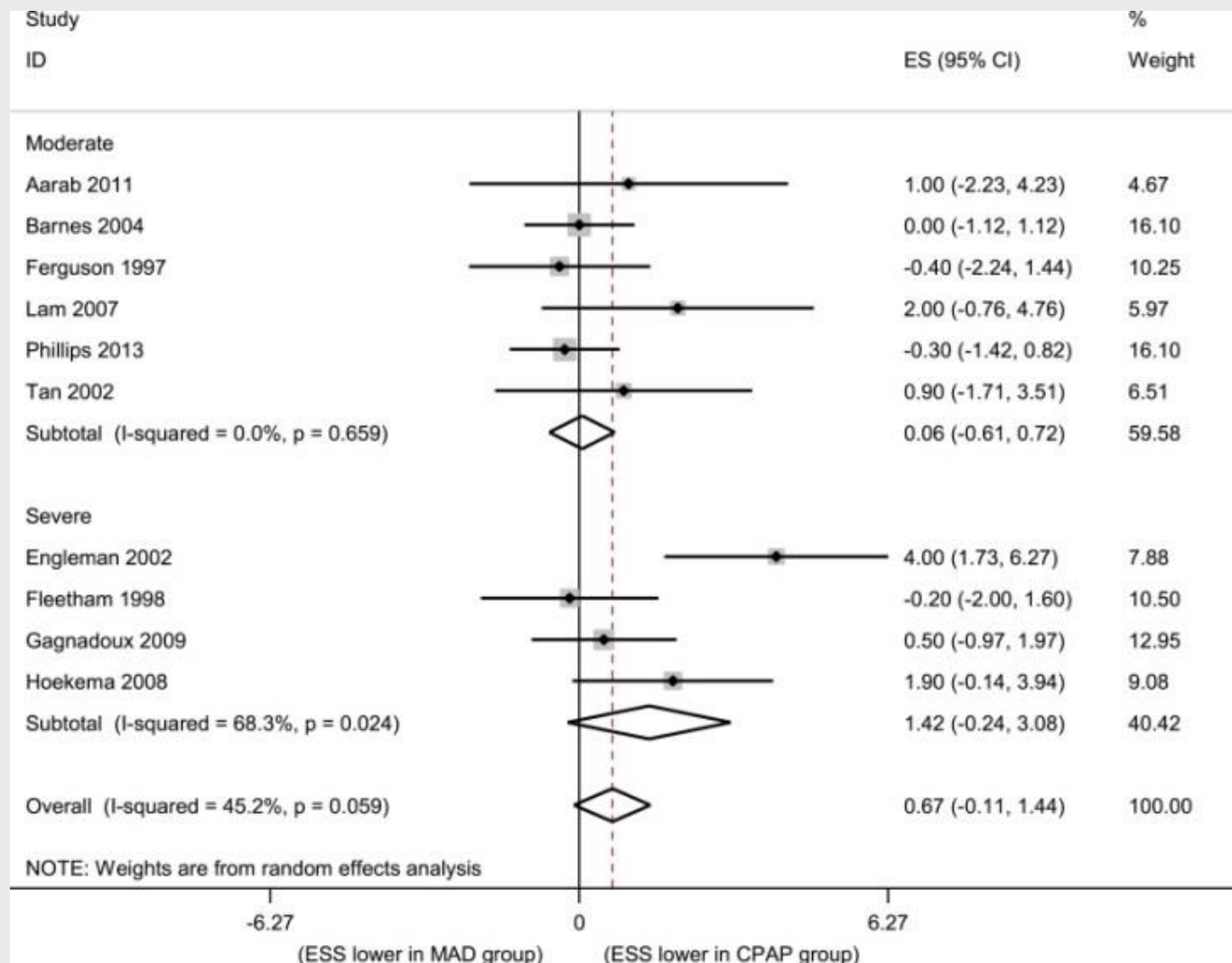
Sharples L et al. Sleep Med Rev. 2016;27:108-24.

# Meta-analysis of randomised controlled trials of mandibular advancement devices and CPAP for OSA



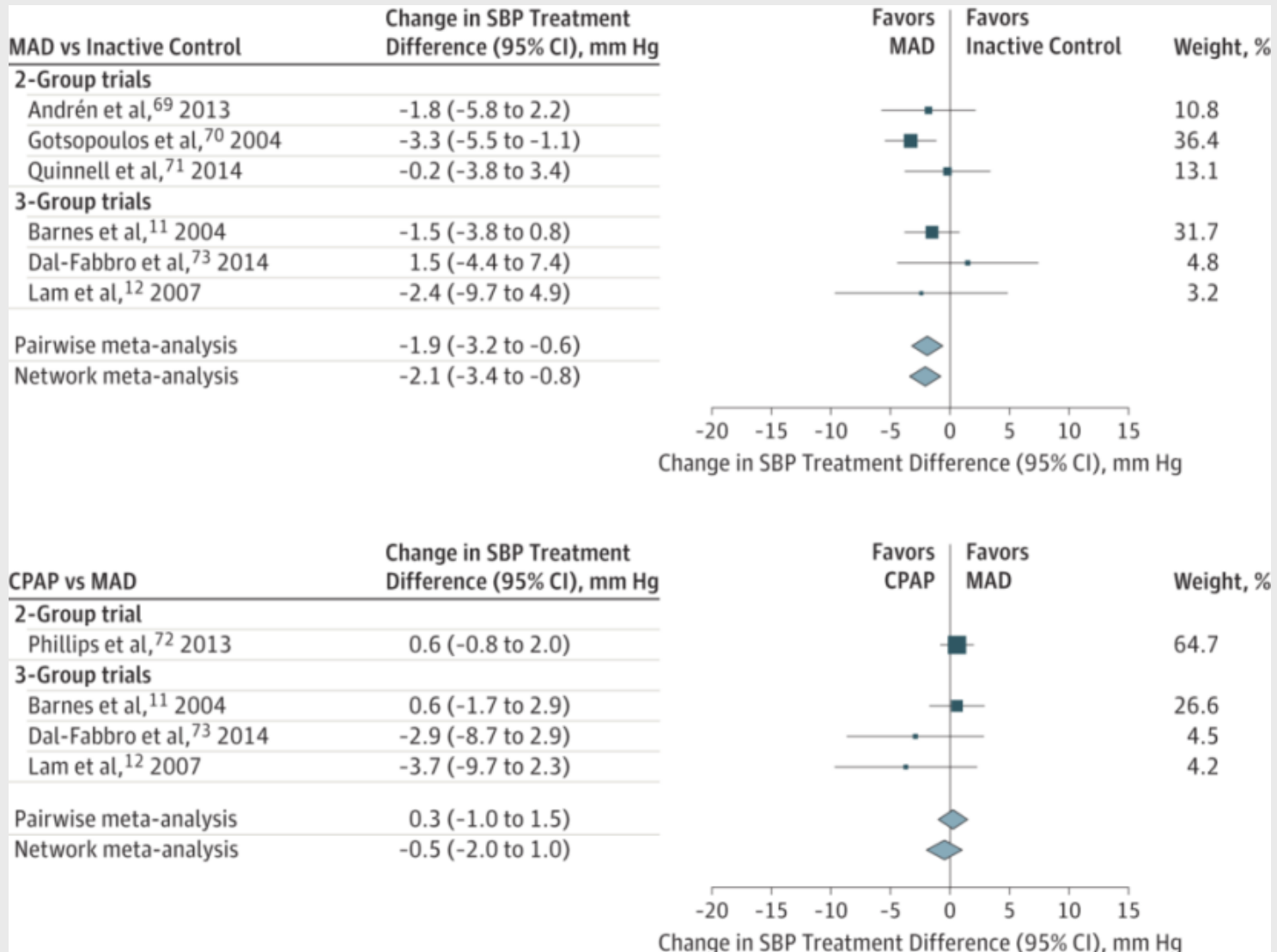
Sharples L et al. Sleep Med Rev. 2016;27:108-24.

# Meta-analysis of randomised controlled trials of mandibular advancement devices and CPAP for OSA



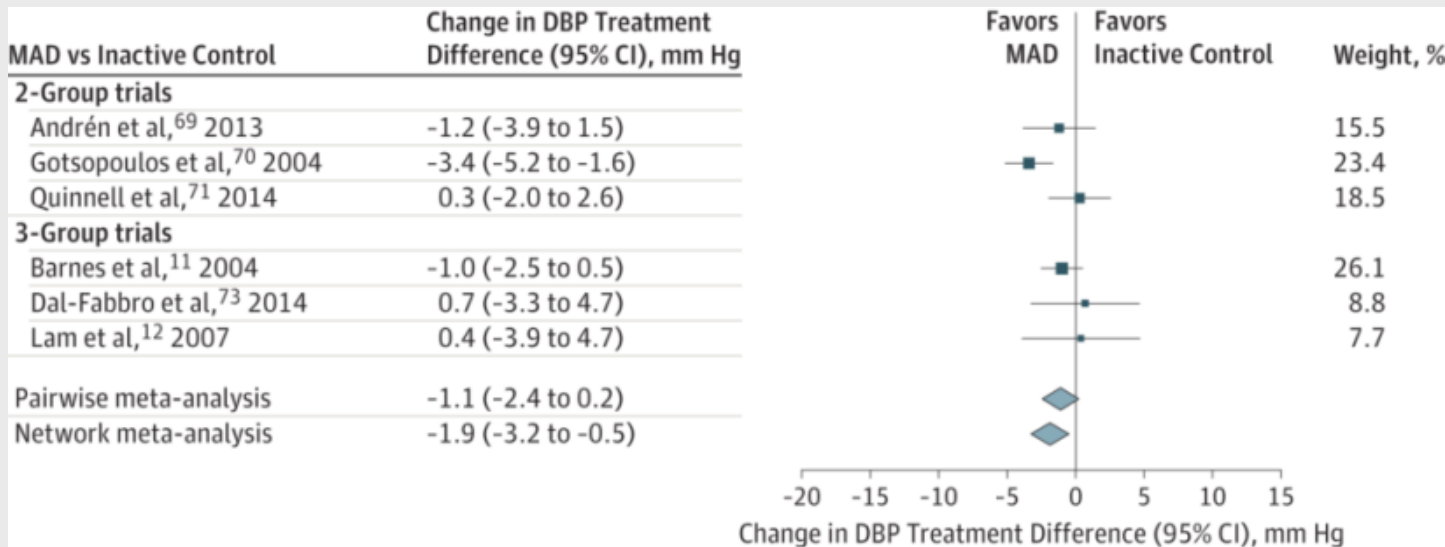
Sharples L et al. Sleep Med Rev. 2016;27:108-24.

# CPAP vs Mandibular Advancement Devices and Blood Pressure in OSA Patients



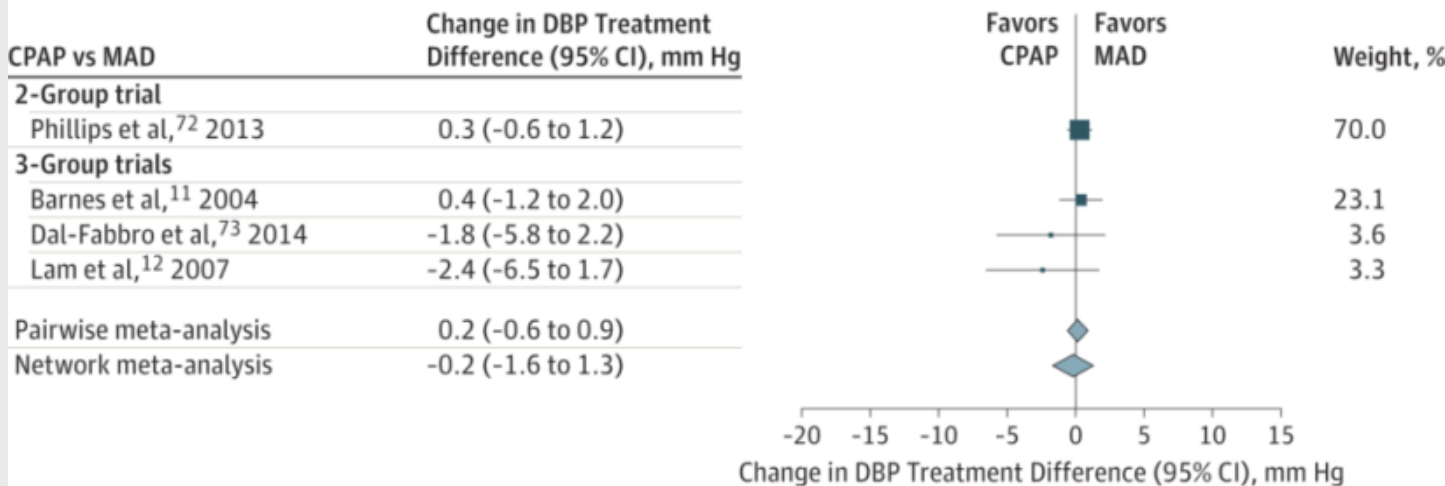
Bratton D et al. JAMA. 2015; 314(21): 2280-93

# CPAP vs Mandibular Advancement Devices and Blood Pressure in OSA Patients



## CONCLUSIONS:

Among OSA patients, both CPAP and MADs were associated with reductions in BP.



Meta-analysis did not identify significant difference between BP outcomes associated with these therapies.

Bratton D et al. JAMA. 2015; 314(21): 2280-93

# Surgical Options

# Maxillomandibular Advancement for Treatment of OSA: Systematic Review and Meta-analysis

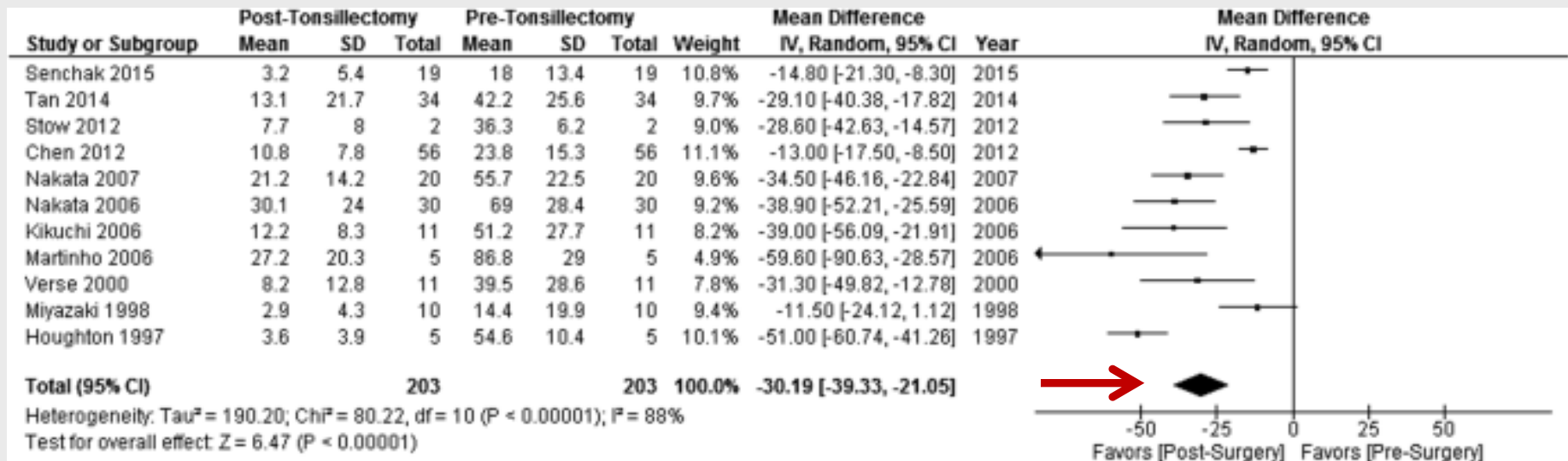
- Outcomes:
  - surgical success (%patients with >50% reduction of AHI to <20),
  - OSA cure (post-MMA AHI <5).
- 45 studies with 518 patients.
- AHI reduced by 47.8 (25.0) after surgery (80% improvement).
- Improvements also seen in:
  - postoperative minimum SaO<sub>2</sub> (70.1% to 87.0%;  $P < .001$ )
  - Epworth Sleepiness Scale score (13.5 to 3.2;  $P < .001$ )
- Surgical success and cure rates were 389 (85.5%) and 175 (38.5%).
- Preoperative AHI <60 was the factor most strongly associated with the highest surgical cure rate.

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



# Tonsillectomy for adult OSA

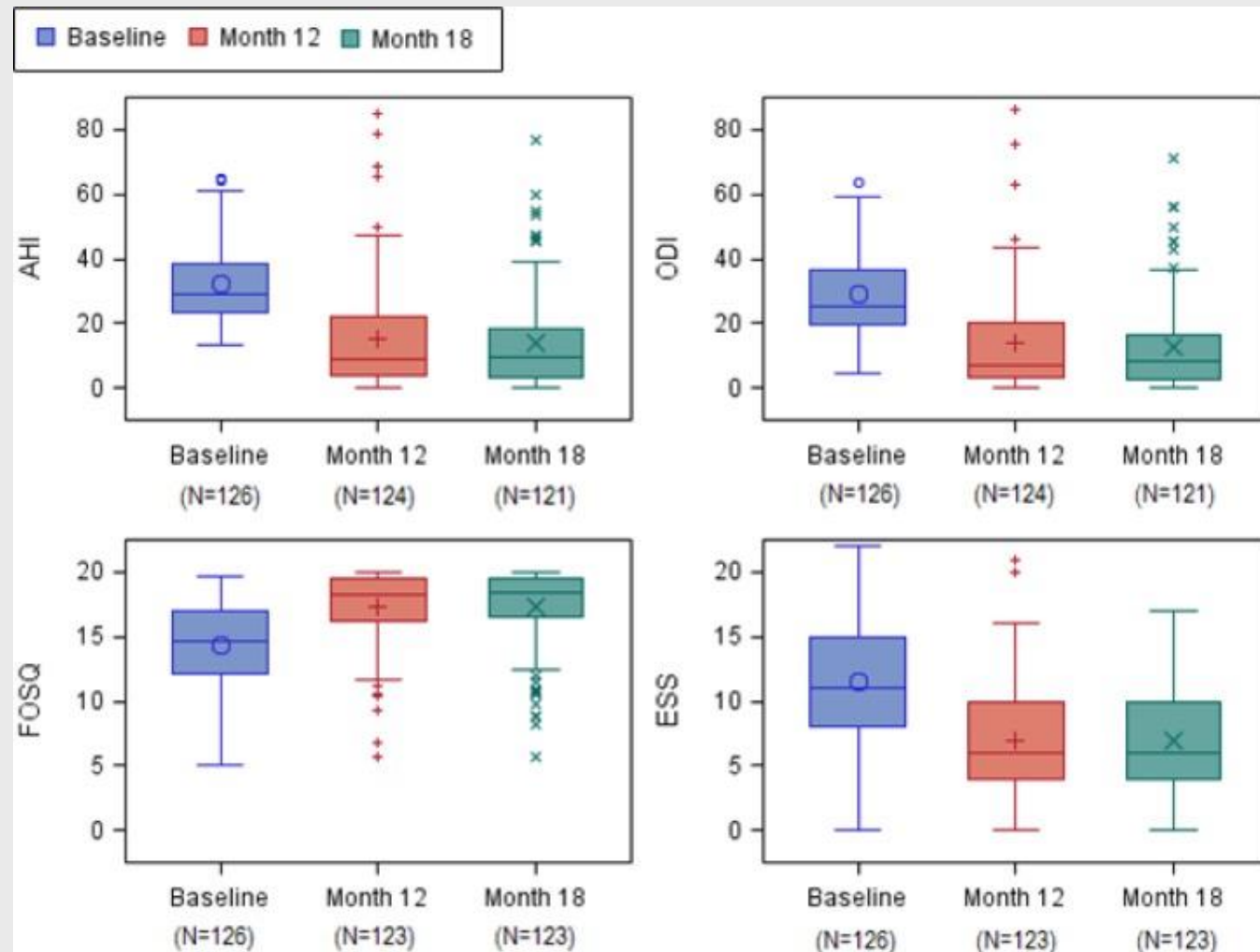
- 17 studies: 216 adult patients; BMI,  $29.0 \pm 6.1$  kg/m<sup>2</sup>; AHI  $40.5 \pm 28.9$ /hour) . Tonsil size varied considerably.



**Conclusion: Isolated tonsillectomy can be successful as treatment for adult OSA, especially among patients with large tonsils and mild to moderate OSA.**

Macario Camacho *Laryngoscope*. 2016 Mar 22. doi: 10.1002/lary.25931. [Epub ahead of print]

# Hypoglossal Nerve Stimulation for OSA: Durability of Treatment Effect at 18 Months.



**CONCLUSION:**  
Hypoglossal nerve stimulation maintains improvement in objective severity and symptom control at 18 months' follow-up.

# Take-Home Message

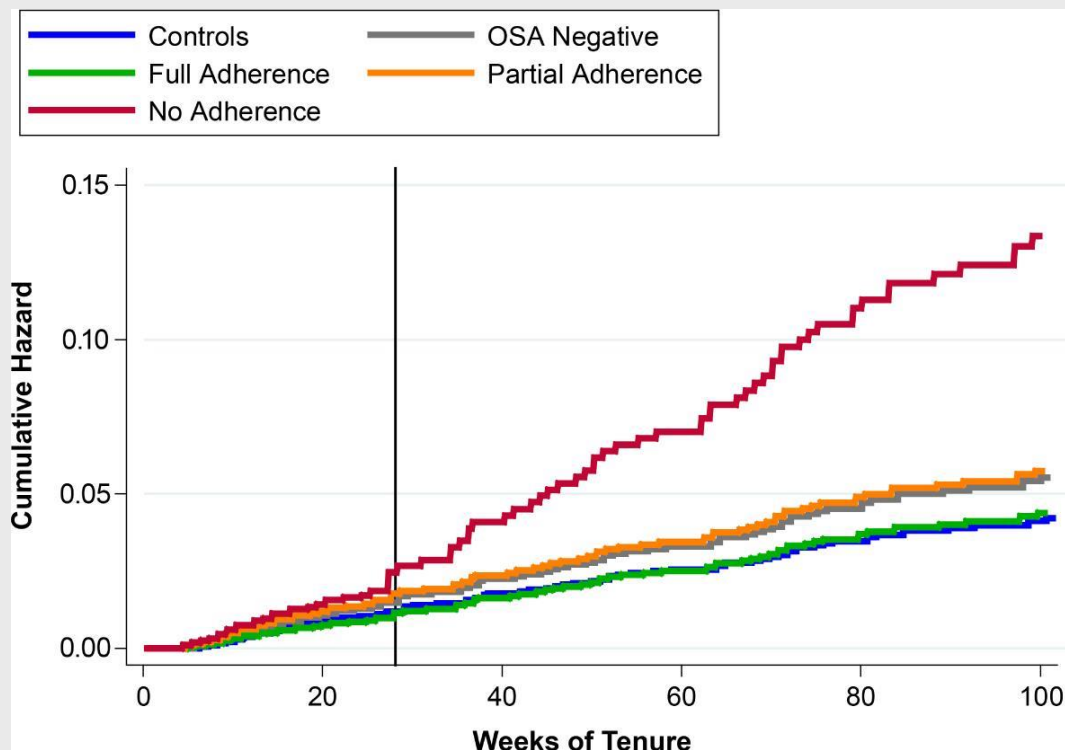
- While CPAP remains firmly the treatment of choice for symptomatic moderate and severe OSA, recent reports enhance the evidence base for alternatives:
  - Mandibular advancement devices: comparative efficacy to CPAP in symptom relief and co-morbidities
  - Surgical alternatives
  - Hypoglossal stimulation

# Driving Accident Risk in Sleep Apnoea

- Untreated patients with OSA are about 3 times more likely to have a driving accident than the general population, which normalises with treatment
- New driving regulations introduced by the European Union that specify criteria for OSA patients to hold a driving license:
  - Patients with moderate to severe OSA associated with sleepiness should not drive until effective treatment is demonstrated.
  - Mandatory for all member states from Jan 1, 2016

# Nonadherence with Employer-Mandated OSA Treatment and Increased Risk of Serious Truck Crashes

- US trucking industry study comparing OSA+ and OSA- patients from PSG studies with matched control drivers.
- DOT-reportable crashes/100,000 miles compared between groups with CPAP treatment stratified by adherence.



## Conclusions:

- Untreated OSA is a substantial risk factor for MVA in truck drivers
- CPAP compliant drivers have same accident risk as controls

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