Sleep Apnea in Allergic Diseases

James J. Herdegen, MD
Section Director, Sleep Medicine
Rush University Medical Center

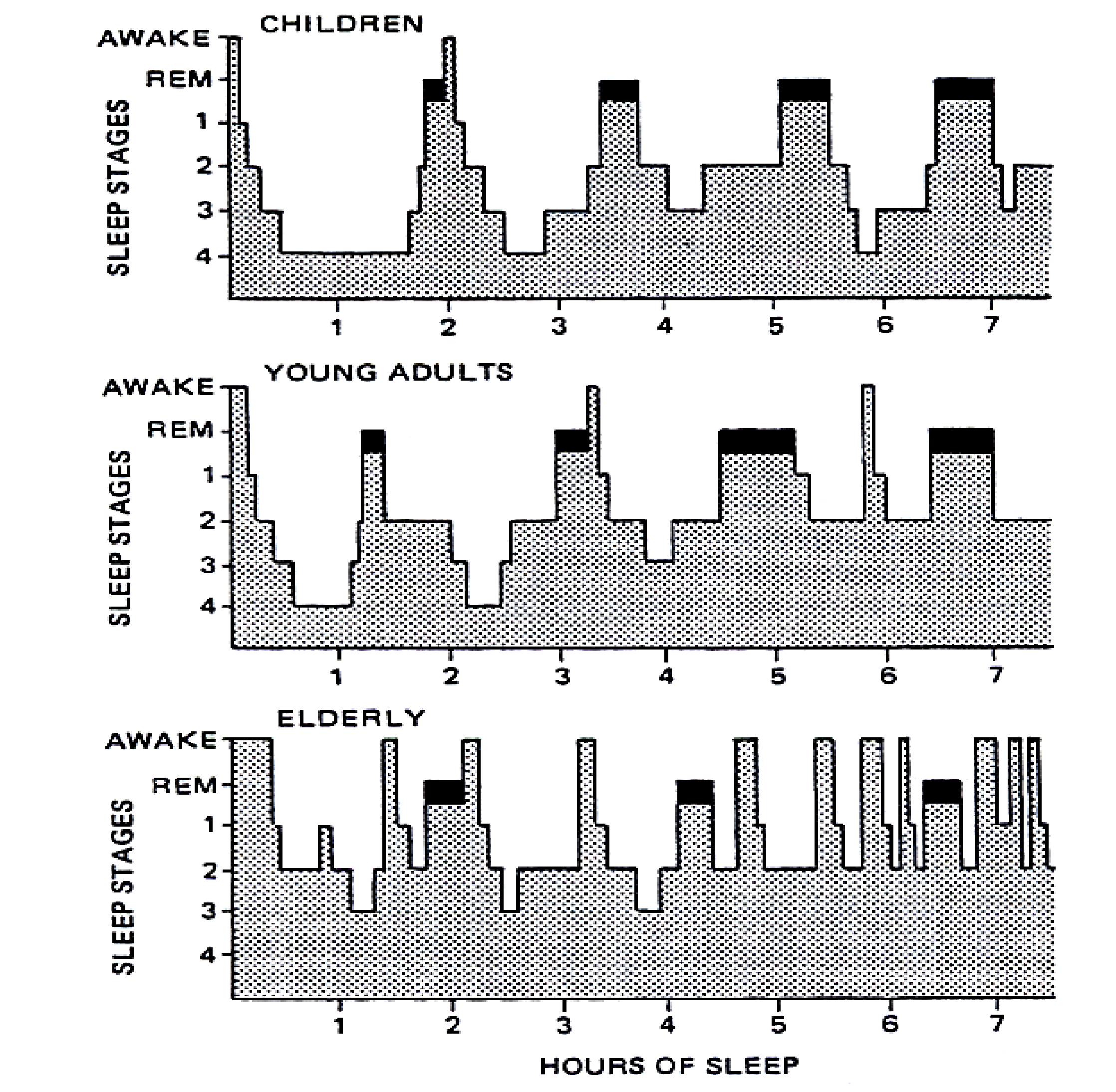
- I have no relevant financial relationship(s) with ineligible companies to disclose

Sleep Apnea in Allergic Diseases

- Lecture Overview
  - Normal Sleep
  - Sleep Apnea and Inflammation
  - Allergic Diseases Affecting Sleep
  - Allergic Diseases Associated with Sleep Apnea
  - Sleep Apnea Treatment and Allergic Response

Normal Sleep and Age-Related Changes

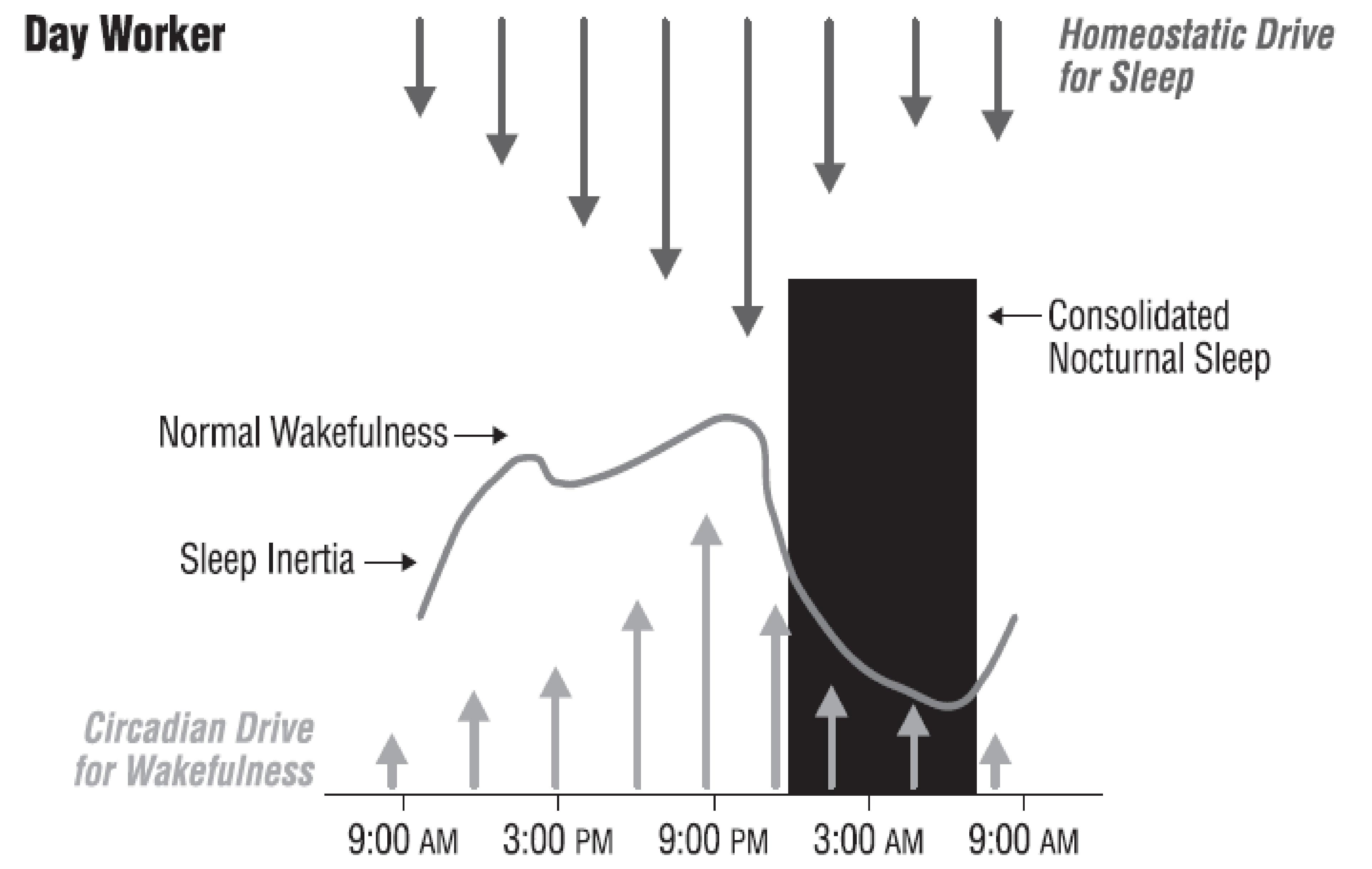
Sleep Cycle Pattern Over Life Span



Sleep Needs Over Live Span

- Infants 2-12 Mo 14-15 Hr
- Toddler 18 Mo-3 Yr 12-14 Hr
- Children 3-5 Yr 11-13 Hr
- Children 5-12 Yr 9-11 Hr
- Adolescents 8.5-9.5 Hr
- Adults 7.9 Hr

2 Process (Homeostatic and Circadian) Model of Sleep

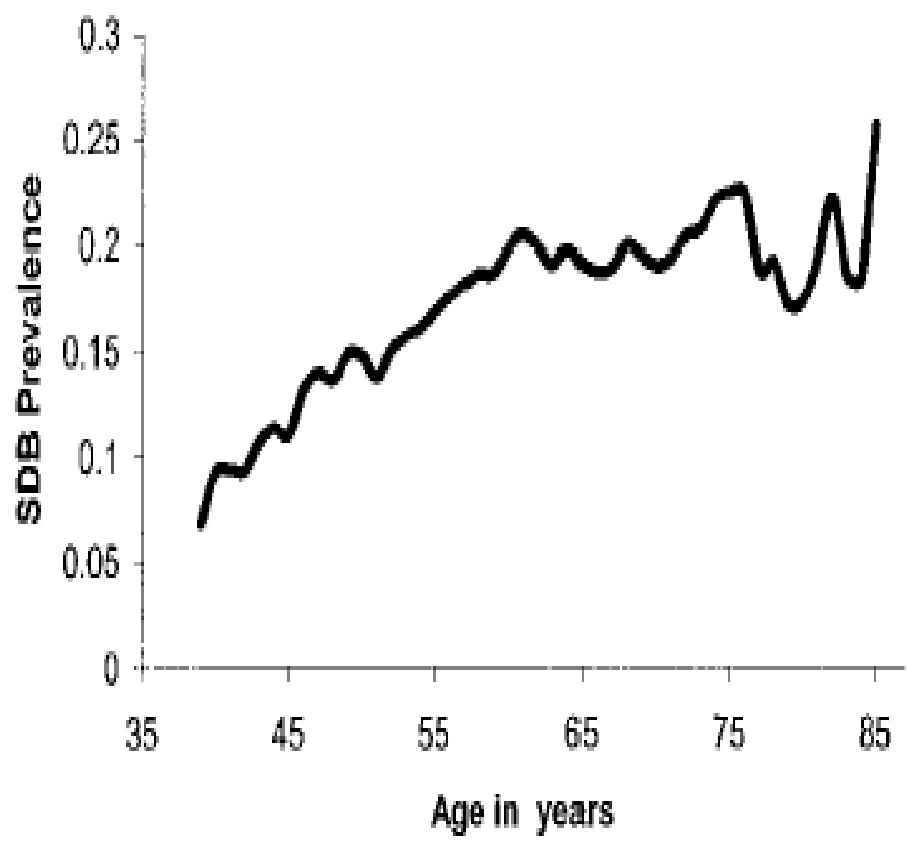


Prevalence of Sleep-Disordered Breathing

Young T et al. AJRCCM 2002;165:1217-1239; Punjabi NM Proc Am Thorac Soc 2008;5(2):136-143

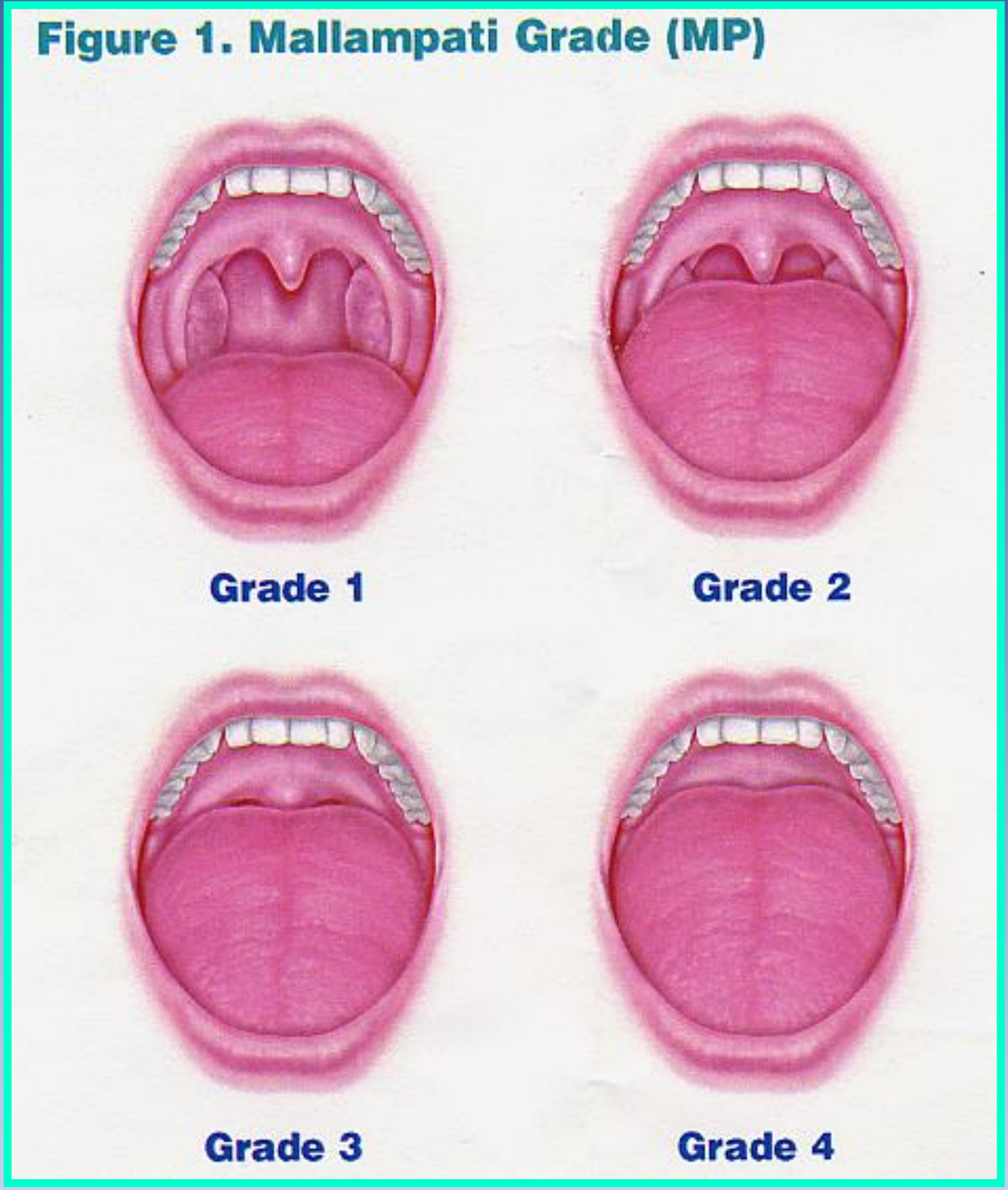
TABLE 1. PREVALENCE OF OBSTRUCTIVE SLEEP APNEA FROM THREE STUDIES WITH SIMILAR DESIGN AND METHODOLOGY

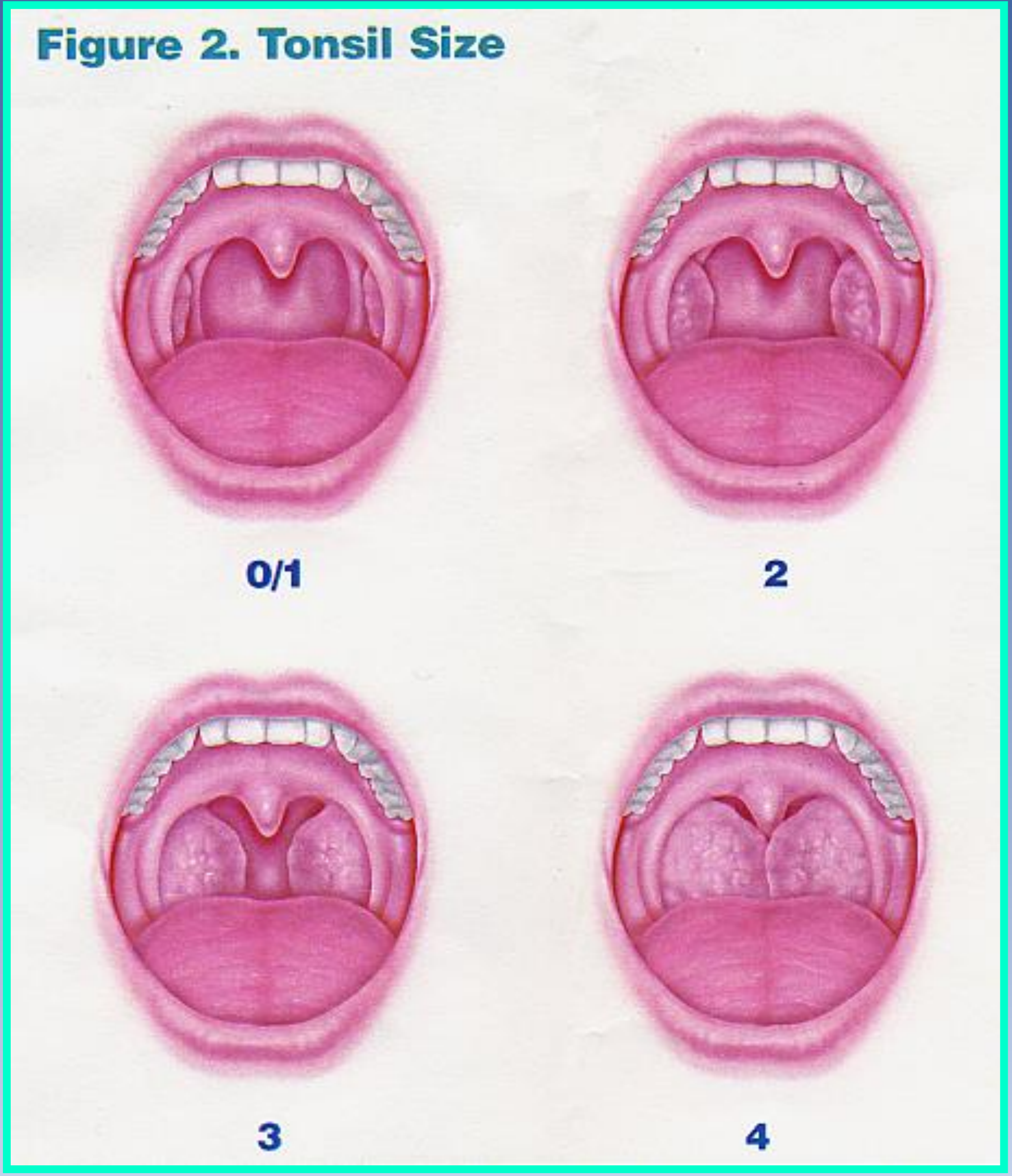
Study Location	n	Age Range (years)	Estimated Prevalence of AHI ⩾ 5 events/hour (% [95% CI]) Men	Women	Estimated Prevalence of AHI ⩾ 15 events/hour (% [95% CI]) Men	Women
Wisconsin*	626	30–60	24 (19–28)	9 (6–12)	9 (6–11)	4 (2–7)
Pennsylvania†	1,741	20–99	17 (15–20)	Not given	7 (6–9)	2 (2–3)
Spain‡	400	30–70	26 (20–32)	28 (20–35)	14 (10–18)	7 (3–11)



- With changing obesity patterns: Wisconsin cohort OSA estimates were revised to 34% of Men, 17.1% women ages 30-70 (AHI > 5); With EDS 14% men, 5% women
- 2015 Swiss study (n=2000): 49% men, 23.4% women had moderate-severe OSA (AHI ≥ 15)
- Assuming 10% US has OSA=30M, currently 4-5M on treatment for OSA in US

Sleep Apnea Risk: Airway Anatomy

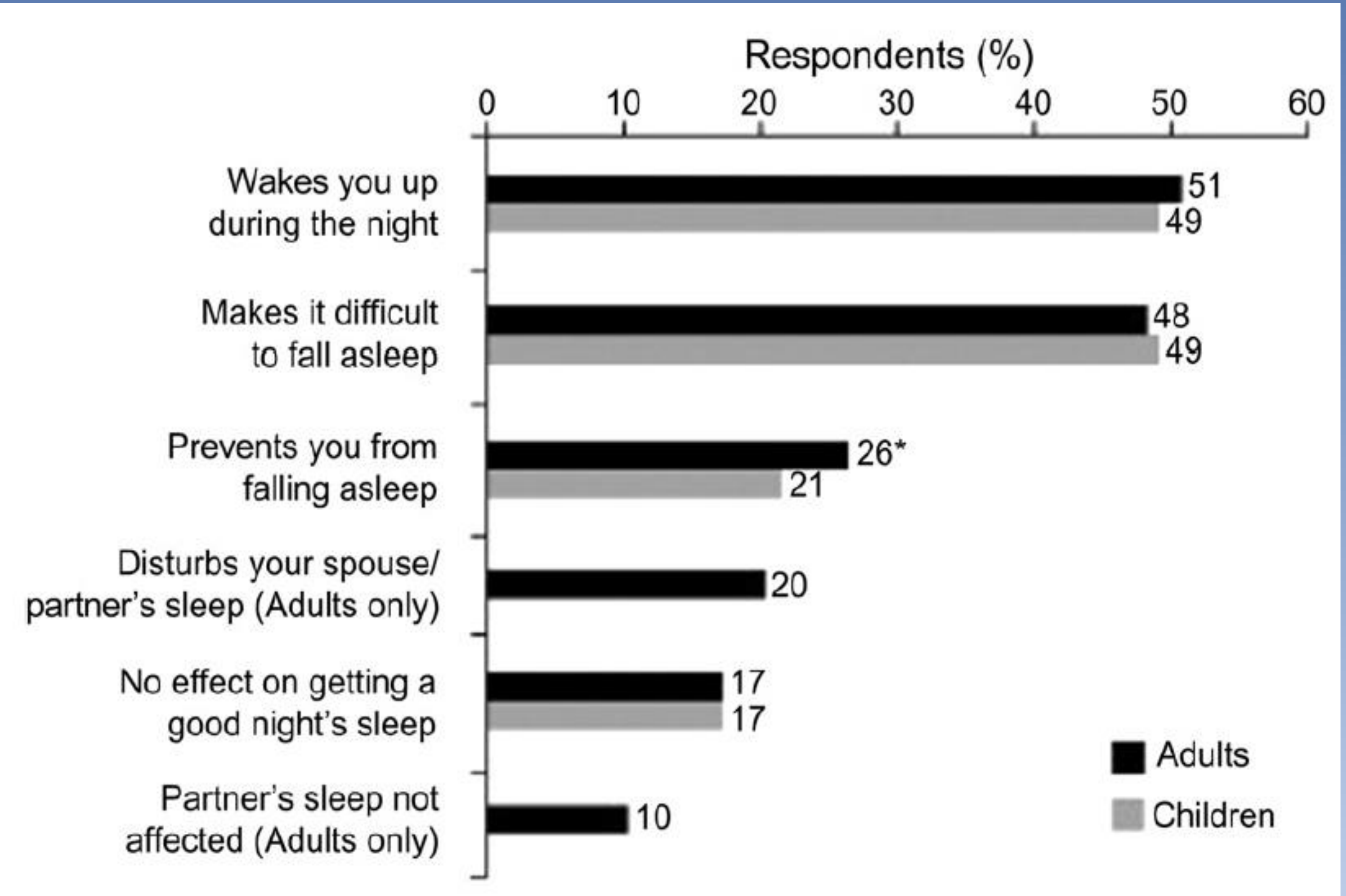




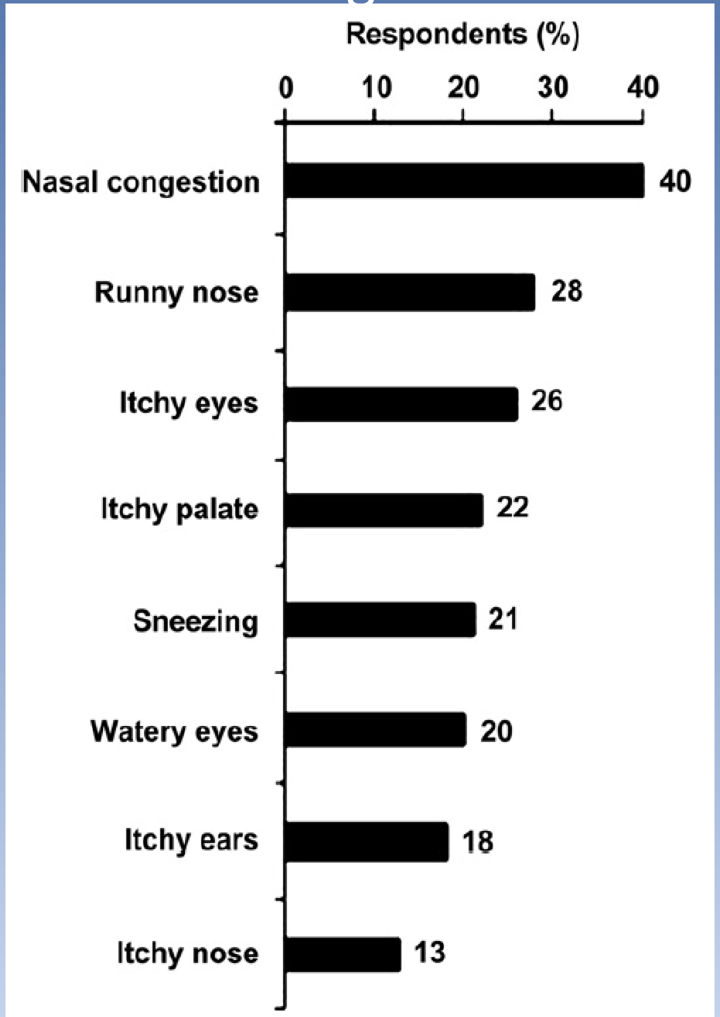
Sleep and Allergic Rhinitis

Soose RJ Otolaryngol Clin N Am 2011;44:625-635

Survey: Impact of Nasal Congestion on Sleep N=2355 Patients with Allergic Rhinitis



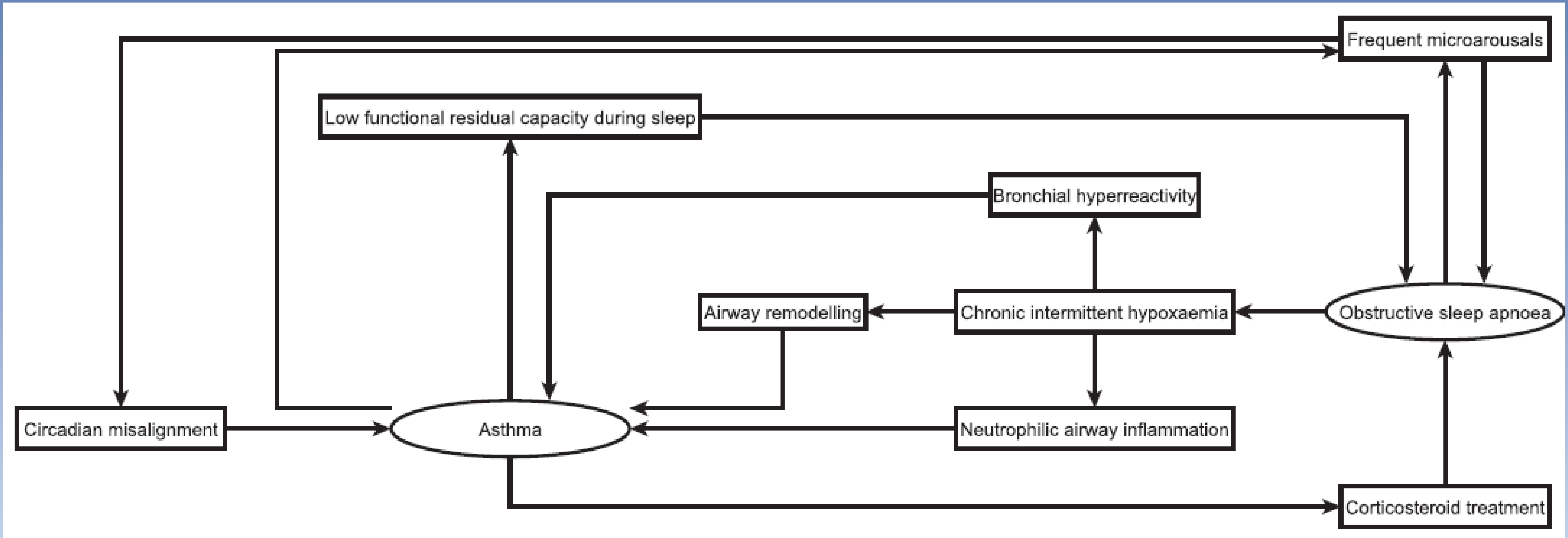
Reported Severe Symptoms in Patients with Allergic Rhinitis



Proposed Bi-directional Link: OSA and Asthma

Wang R et al. Sleep Med Rev 2022;61:101564

Influencing Factors:
Circadian Clock: PEFR, FEV-1 lowest at night, Peak of eosinophils, neutrophils at **4 AM**
Chronic Intermittent Hypoxia: Increase airway inflammation, bronchial epithelial proliferation
Sleep Fragmentation: Increased collapsibility of upper airway



Asthma and OSA in Adults and Children: Intermittent Hypoxia and Airway Inflammation

Wang R et al. Sleep Med Rev 2022;61:101564

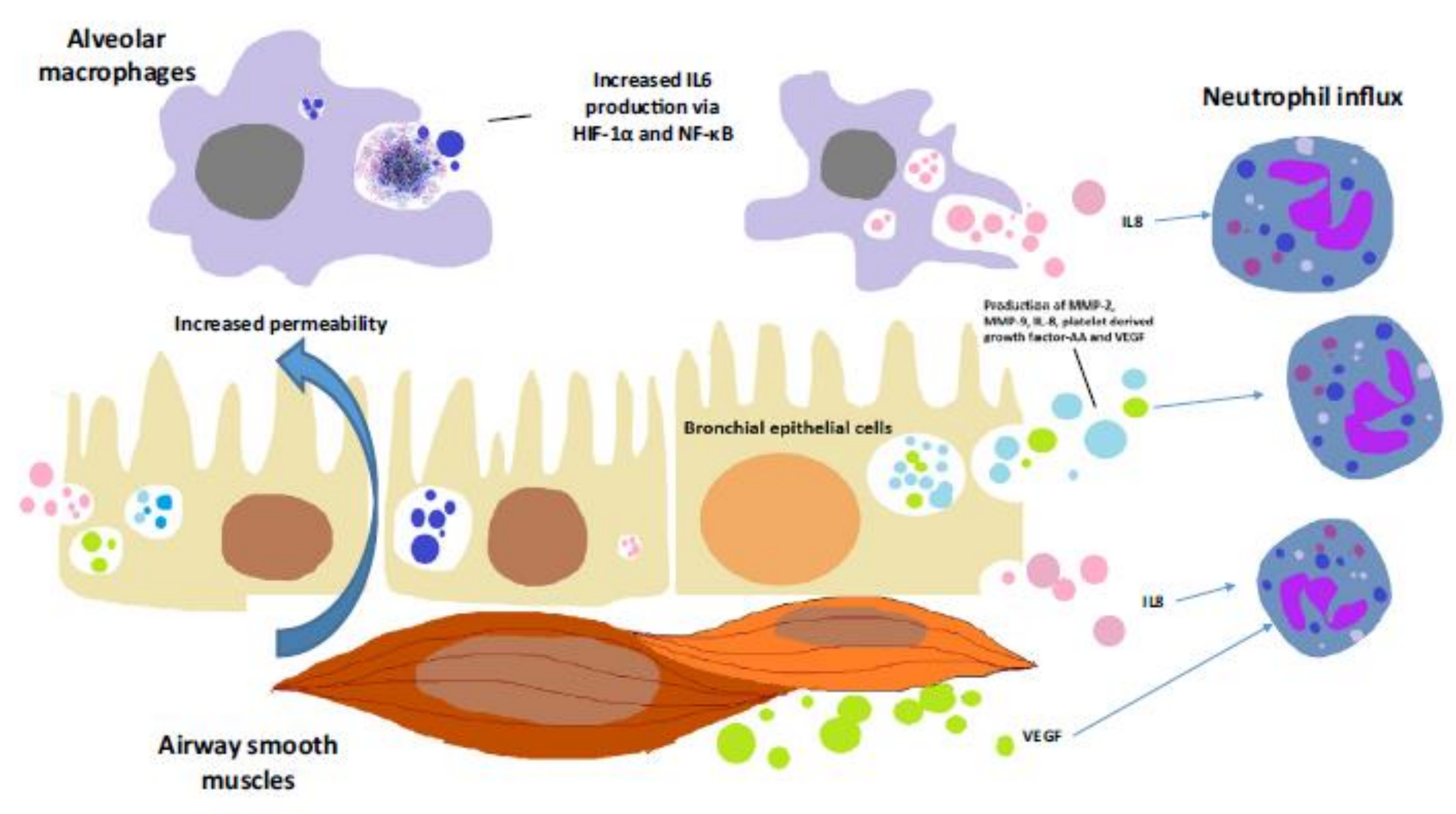
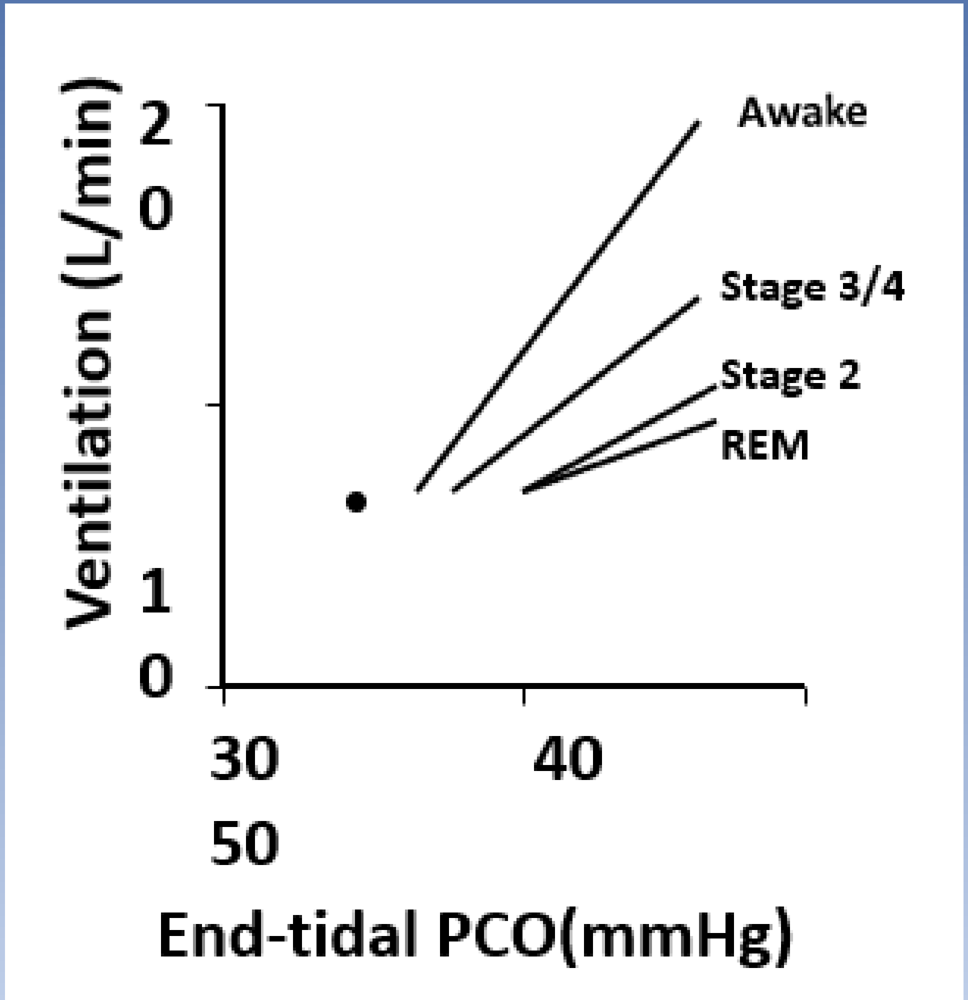


Fig. 2. The effect of intermittent hypoxaemia in the airways.

Sleep and Circadian Rhythm Influence

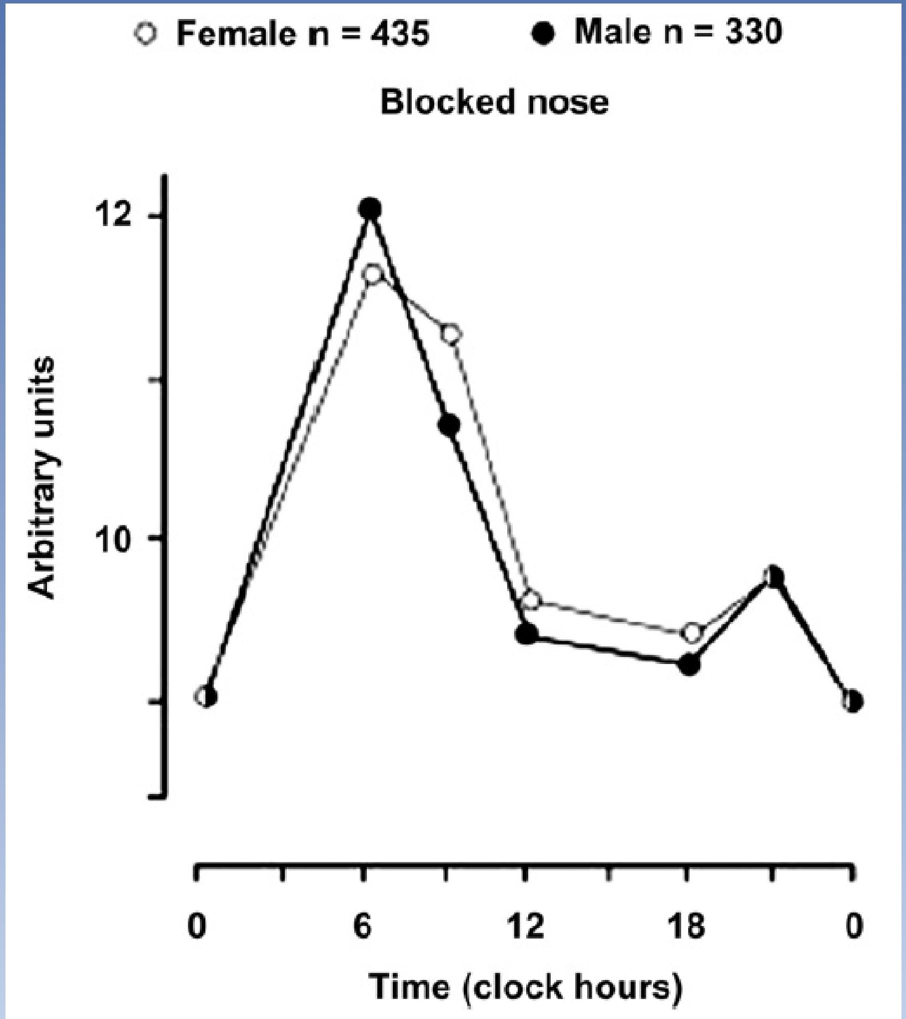
Sleep Stage and CO2 Response

Douglas NJ Clin Chest Med 1985



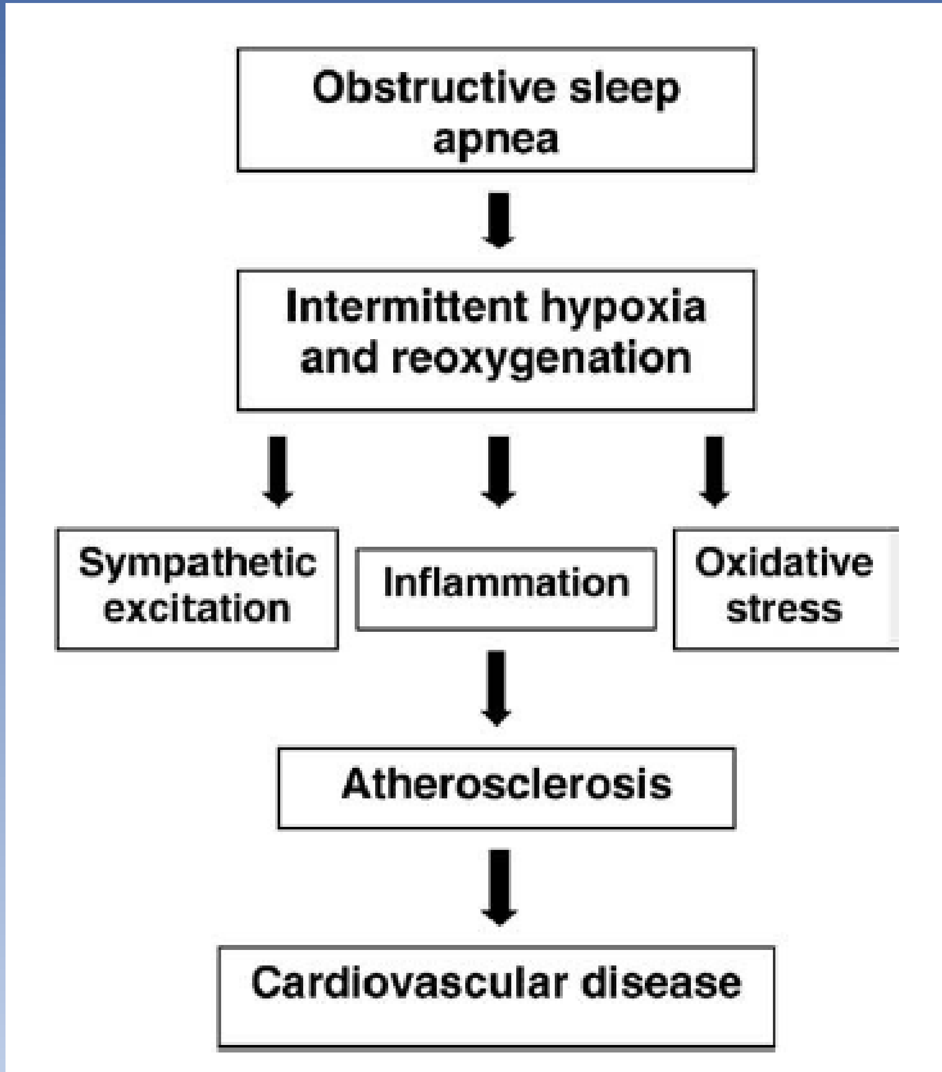
Circadian Variation of Nasal Congestion

Craig TJ Am J Otolaryngol 2008;29:211



Sleep Apnea and Inflammation

McNicholas WT Progress in Cardiovascular Diseases 2009;51:392-399



Inflammatory Biomarkers in Sleep Apnea

- C-Reactive Protein
- TNF-alpha
- IL-8
- IL-6
- Cell Adhesion Molecules

Rhinitis, Sinusitis and Upper Airway Disease: Role of Inflammatory Mediators

Zheng M et al. Curr Opin Allergy Clin Immunol 2018;18:16-25

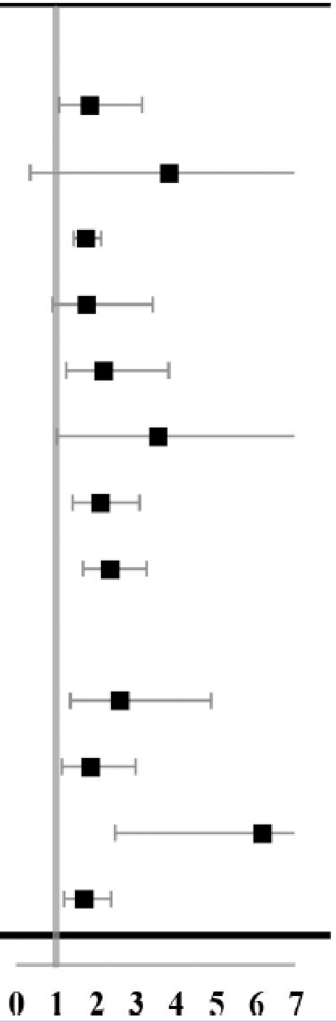
Table 1. The effect of inflammatory mediators on sleep and nose

Mediators	Effect on sleep	Effect on nose	References
Histamine	Regulates the sleep–wake cycle and arousal	Slightly increases congestion and rhinorrhea	[92]
CysLTs	Increases slow-wave sleep and leads to sleep disruption	Increases eosinophil presence and function, congestion and rhinorrhea,	[93,94]
IL-1β	Increases REM sleep and decreases time in REM sleep, and decreases latency to sleep onset	Upregulates the late-phase response of allergic rhinitis and increases congestion	[95,109]
IL-4	Increases REM sleep and decreases time in REM sleep, and decreases latency to sleep onset	Major Th2 cytokine and increases congestion	[95,110]
IL-10	Increases REM sleep and decreases time in REM sleep, and decreases latency to sleep onset	Unknown	[95]
IL-6	Improves circadian rhythm and regulates the sleep–wake cycle and increases slow wave sleep, as the 'sleep factor'. Promotes mucosal thickening of upper airway and increases the risk of OSA. sIL-6R reflects the severity of OSA	Promotes Th2 cell phenotypes and increases congestion	[99,24,111]
TNF-α	Promotes mucosal thickening of upper airway and increases the risk of OSA	Promote Th2 cell phenotypes and increases congestion	[24,33]
Prostaglandin D2	Promotes sleep. Increases both REM and NREM sleep	Increases congestion	[112,113]
Bradykinin	Increases sleep apnea	Increases congestion and rhinorrhea	[23,113]
Substance P	Increases REM latency and arousal	Increases congestion	[113]

Allergic Rhinitis and Sleep Outcomes: Meta-analysis

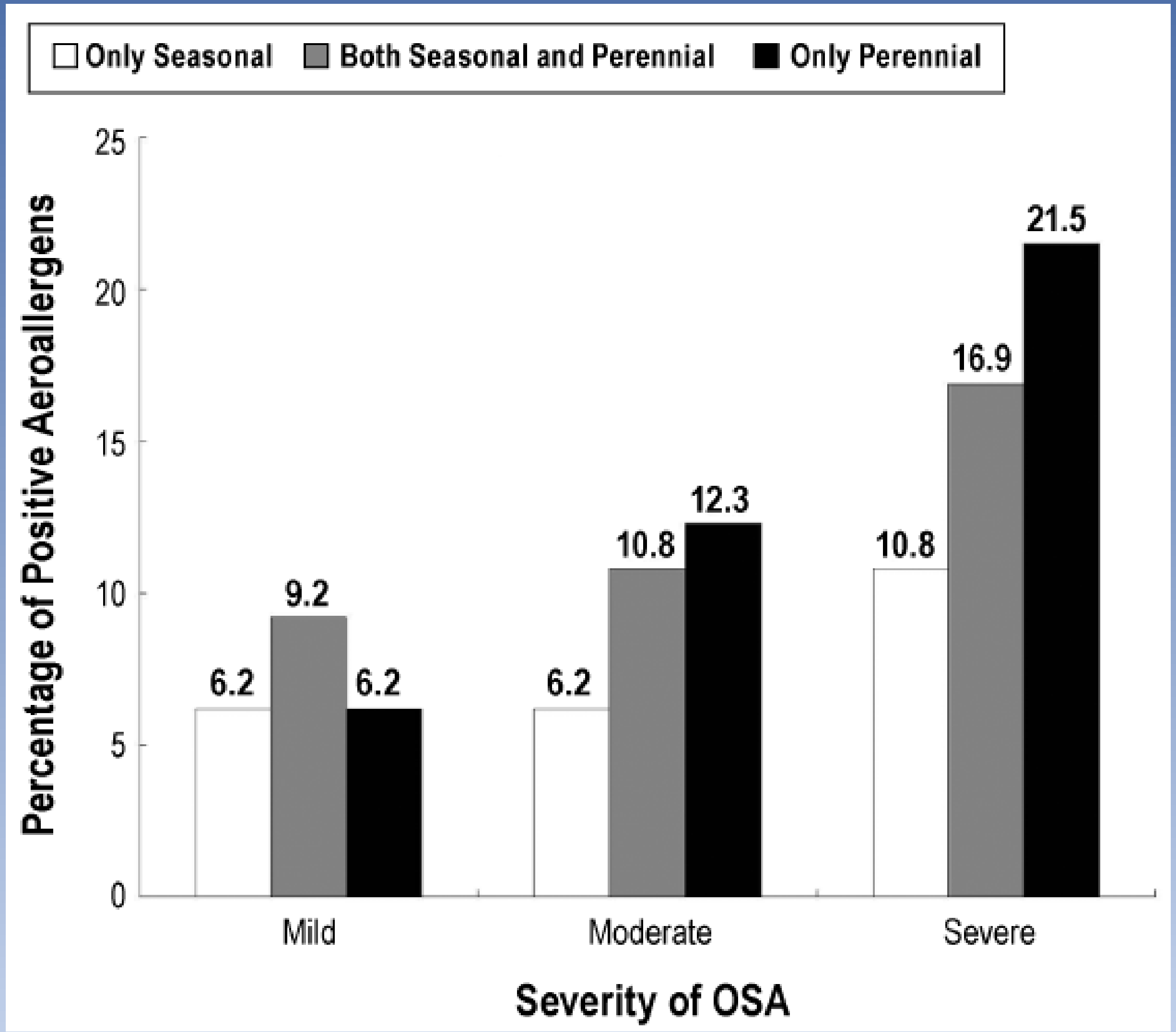
Liu J et al. PLOS One 2020;15:e0228533

	No. of studies	Sample size	No. of AR cases	OR (95% CI)
Nocturnal dysfunction				
Insomnia	1	5,556	1,797	1.84 (1.07, 3.16)
Nocturnal sweating	2	6,556	2,726	3.82 (0.35, 41.24)
Nocturnal enuresis	3	664,220	332,184	1.75 (1.44, 2.13)
Sleep bruxism	1	175	65	1.76 (0.91, 3.42)
Restless sleep	3	8,022	2,073	2.20 (1.26, 3.82)
SDB	2	523	122	3.55 (1.03, 12.31)
OSA	7	11,943	3,343	2.09 (1.41, 3.10)
Snoring	9	32,981	6,552	2.34 (1.68, 3.28)
Daytime dysfunction				
Difficulty to wake up	1	175	65	2.58 (1.36, 4.89)
Daytime sleepiness	3	4,074	1,419	1.85 (1.14, 3.00)
Morning headache	1	175	65	6.16 (2.48, 15.27)
Sleeping pills	1	5,556	1,797	1.69 (1.20, 2.38)



Sleep Apnea is Commonly Associated With Allergic and Non-Allergic Rhinitis

Zheng M et al. J Clin Sleep Med 2017;13:959-966

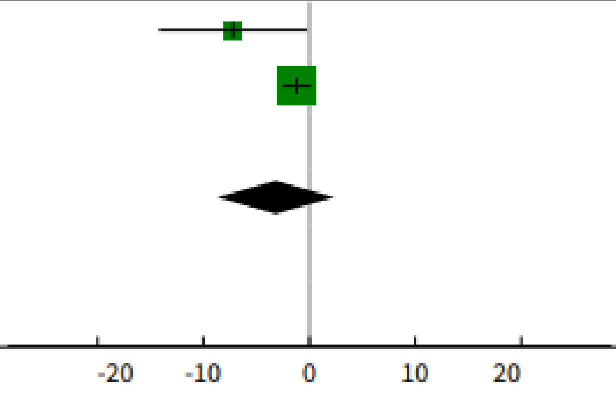


Anti-Inflammatory Medications for Sleep Apnea in Children: Nasal Corticosteroids

Kuhle S et al Cochrane Database of Systematic Reviews 2020;1:CD007074

Analysis 1.1. Comparison 1 Corticosteroids versus placebo, Outcome 1 Apnoea/hypopnoea index.

Study or subgroup	Corticosteroids N	Corticosteroids Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Brouillette 2001	13	-5 (3.5)	12	2.2 (11.9)		32.94%	-7.2[-14.2,-0.2]
Chan 2015	24	1.7 (1.5)	26	2.9 (3.1)		67.06%	-1.2[-2.53,0.13]
Total ***	**37**		**38**			**100%**	**-3.18[-8.7,2.35]**
Heterogeneity: Tau²=11.4; Chi²=2.73, df=1(P=0.1); I²=63.32%							
Test for overall effect: Z=1.13(P=0.26)							



Anti-Inflammatory Medications for Sleep Apnea in Children: Nasal Corticosteroids

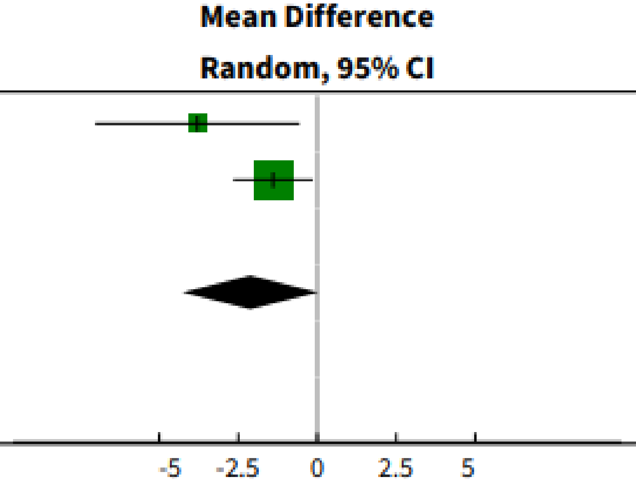
Kuhle S et al Cochrane Database of Systematic Reviews 2020;1:CD007074

Analysis 1.2. Comparison 1 Corticosteroids versus placebo, Outcome 2 Desaturation index.

Study or subgroup	Corticosteroids N	Corticosteroids Mean(SD)	Placebo N	Placebo Mean(SD)	Weight	Mean Difference Random, 95% CI
Brouillette 2001	13	-4.1 (4.7)	12	-0.3 (3.5)	29.96%	-3.8[-7.03,-0.57]
Chan 2015	24	1.1 (1)	26	2.5 (3.1)	70.04%	-1.4[-2.66,-0.14]
Total ***	**37**		**38**		**100%**	**-2.12[-4.27,0.04]**

Heterogeneity: Tau²=1.31; Chi²=1.84, df=1(P=0.18); I²=45.64%

Test for overall effect: Z=1.93(P=0.05)



Anti-Inflammatory Medications for Sleep Apnea in Children: Nasal Corticosteroids

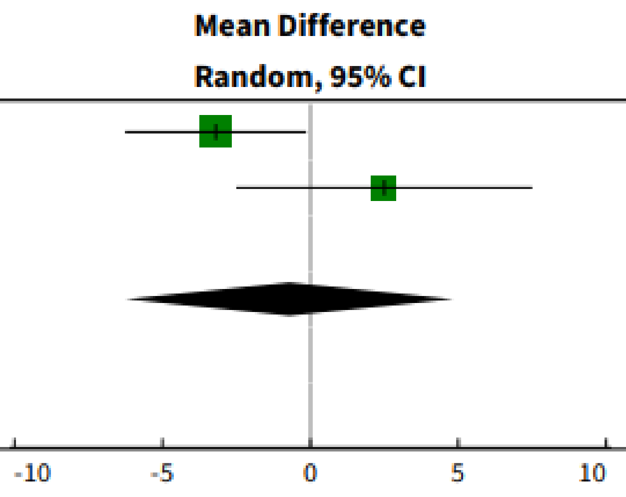
Kuhle S et al Cochrane Database of Systematic Reviews 2020;1:CD007074

Analysis 1.3. Comparison 1 Corticosteroids versus placebo, Outcome 3 Respiratory arousal index.

Study or subgroup	Corticosteroids		Placebo		Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)		Random, 95% CI
Brouillette 2001	13	-3.4 (4)	12	-0.2 (3.8)	56.3%	-3.2[-6.26,-0.14]
Chan 2015	24	13.1 (11.3)	26	10.6 (5.6)	43.7%	2.5[-2.51,7.51]
Total ***	**37**		**38**		**100%**	**-0.71[-6.25,4.83]**

Heterogeneity: Tau^2=11.76; Chi^2=3.63, df=1(P=0.06); I^2=72.42%

Test for overall effect: Z=0.25(P=0.8)



Anti-Inflammatory Medications for Sleep Apnea in Children: Montelukast

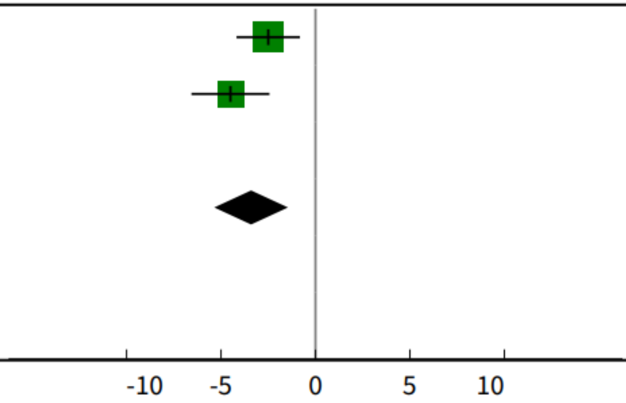
Kuhle S et al Cochrane Database of Systematic Reviews 2020;1:CD007074

Analysis 2.1. Comparison 2 Montelukast versus placebo, Outcome 1 Apnoea/hypopnoea index.

Study or subgroup	Montelukast		Placebo		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI		Random, 95% CI
Goldbart 2012	23	3.6 (2.3)	23	6.1 (3.4)		54.69%	-2.5[-4.18,-0.82]
Kheirandish-Gozal 2016	28	4.2 (2.8)	29	8.7 (4.9)		45.31%	-4.5[-6.56,-2.44]
Total ***	**51**		**52**			**100%**	**-3.41[-5.36,-1.45]**

Heterogeneity: Tau^2=1.08; Chi^2=2.17, df=1(P=0.14); I^2=53.99%

Test for overall effect: Z=3.42(P=0)



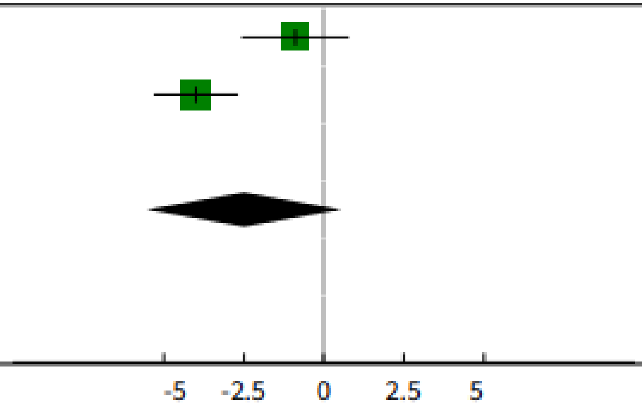
Favours experimental   Favours control

Anti-Inflammatory Medications for Sleep Apnea in Children: Montelukast

Kuhle S et al Cochrane Database of Systematic Reviews 2020;1:CD007074

Analysis 2.2. Comparison 2 Montelukast versus placebo, Outcome 2 Desaturation index.

Study or subgroup	Montelukast		Placebo		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI		Random, 95% CI
Goldbart 2012	23	2.2 (2.3)	23	3.1 (3.4)		48.51%	-0.9[-2.58,0.78]
Kheirandish-Gozal 2016	28	2.8 (1.8)	29	6.8 (3.1)		51.49%	-4[-5.31,-2.69]
Total ***	**51**		**52**			**100%**	**-2.5[-5.53,0.54]**
Heterogeneity: Tau²=4.22; Chi²=8.15, df=1(P=0); I²=87.72%							
Test for overall effect: Z=1.61(P=0.11)							



Favours experimental | Favours control

Anti-Inflammatory Medications for Sleep Apnea in Children: Montelukast

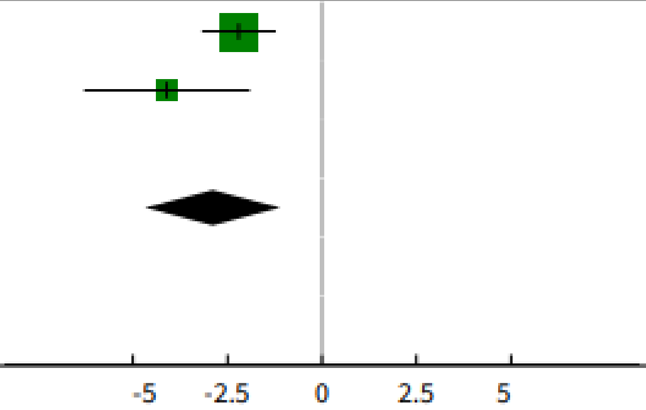
Kuhle S et al Cochrane Database of Systematic Reviews 2020;1:CD007074

Analysis 2.3. Comparison 2 Montelukast versus placebo, Outcome 3 Respiratory arousal index.

Study or subgroup	Montelukast N	Montelukast Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Goldbart 2012	23	11.4 (1.3)	23	13.6 (2)		63.84%	-2.2[-3.17,-1.23]
Kheirandish-Gozal 2016	28	2.5 (2.6)	29	6.6 (5.4)		36.16%	-4.1[-6.29,-1.91]
Total ***	**51**		**52**			**100%**	**-2.89[-4.68,-1.1]**

Heterogeneity: Tau^2=1.06; Chi^2=2.42, df=1(P=0.12); I^2=58.61%

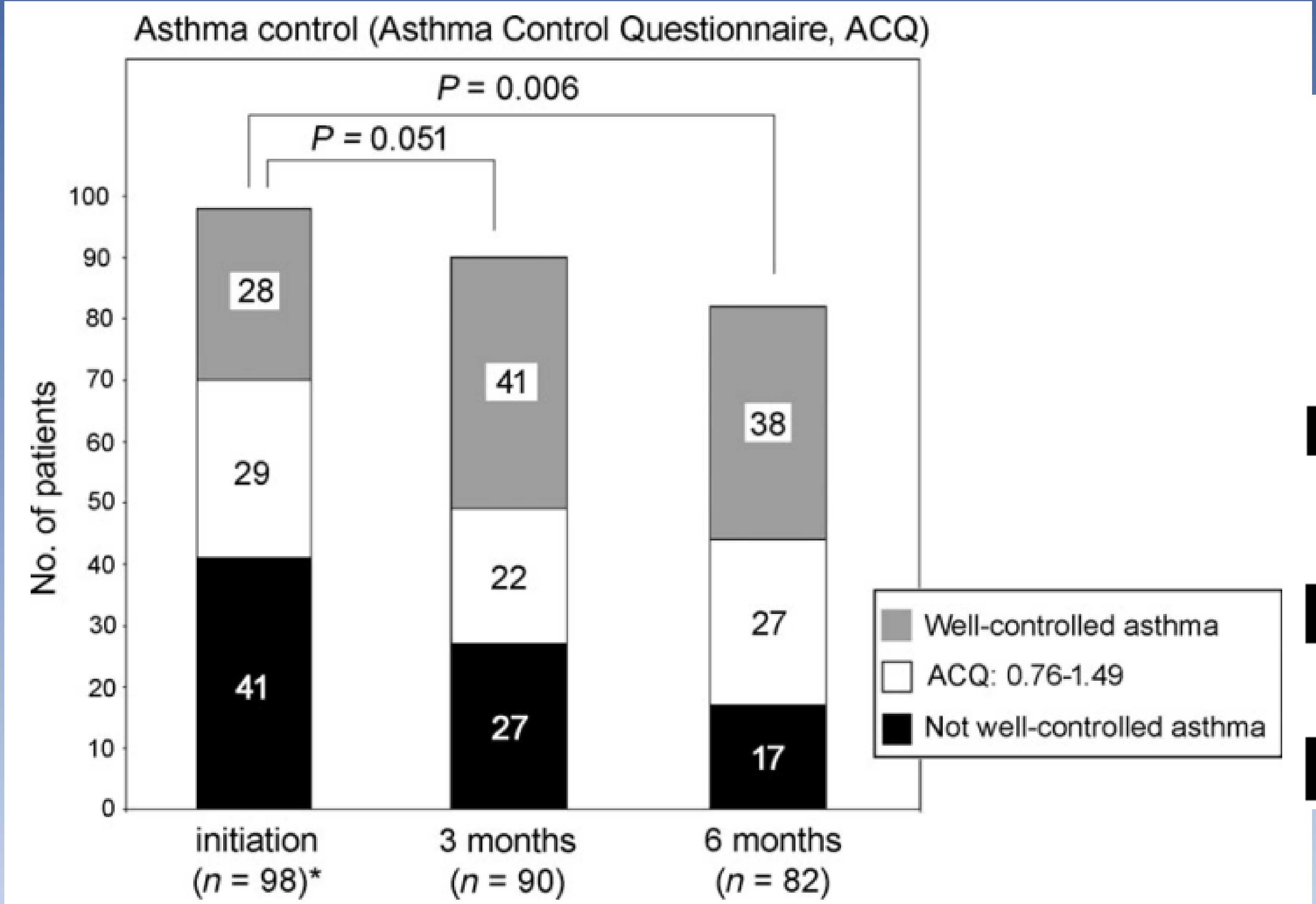
Test for overall effect: Z=3.16(P=0)

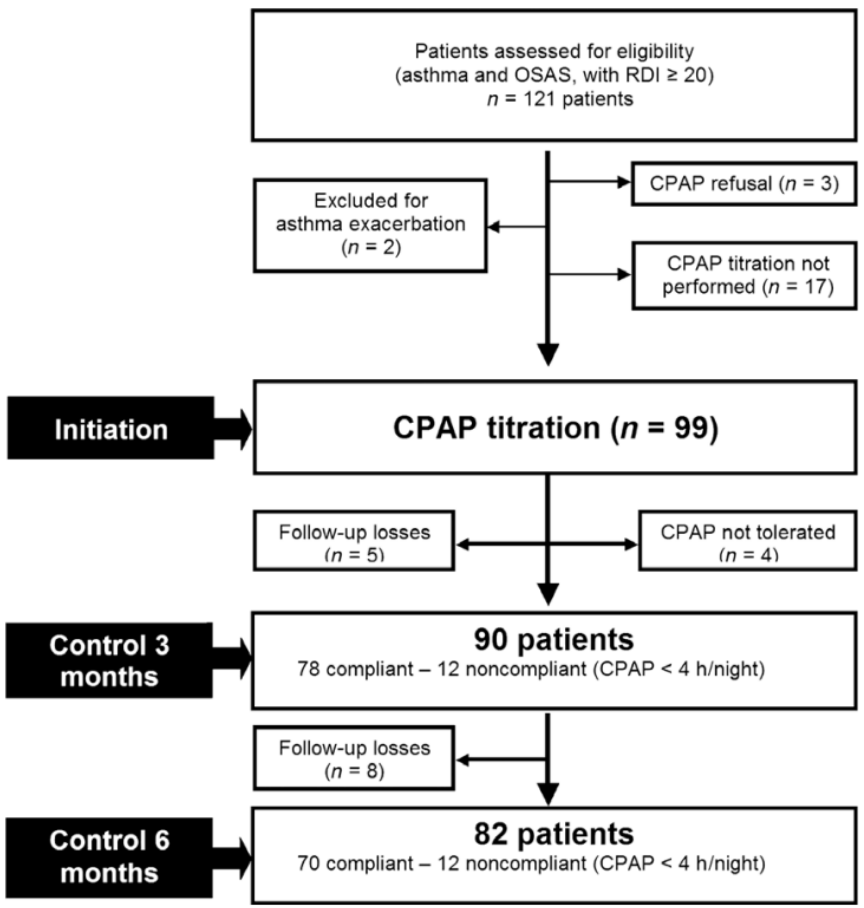


Favours experimental — Favours control

CPAP Therapy and Effect on Asthma: Improved Control

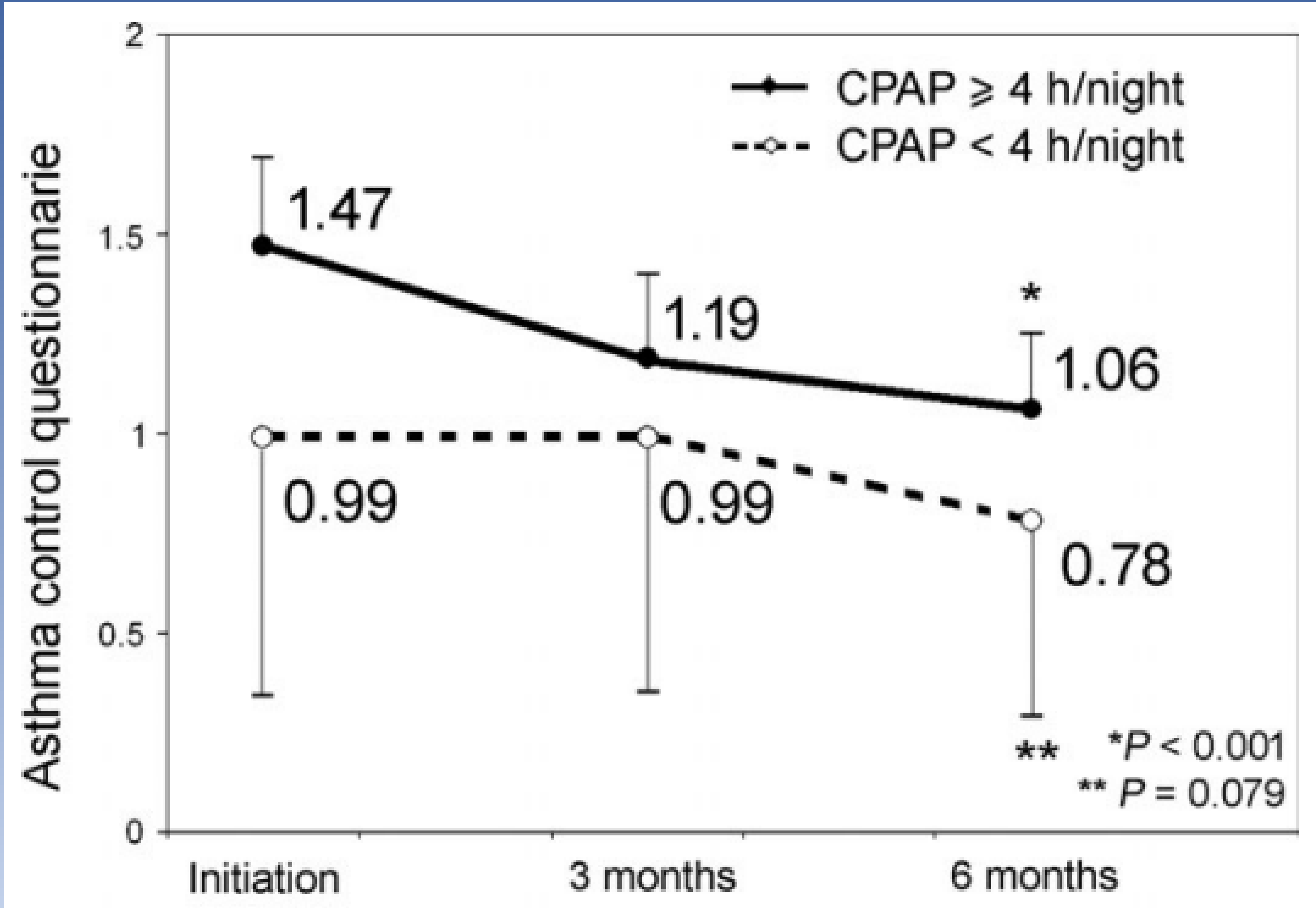
Serrano-Pariente J et al. Allergy 2017;72:802-12





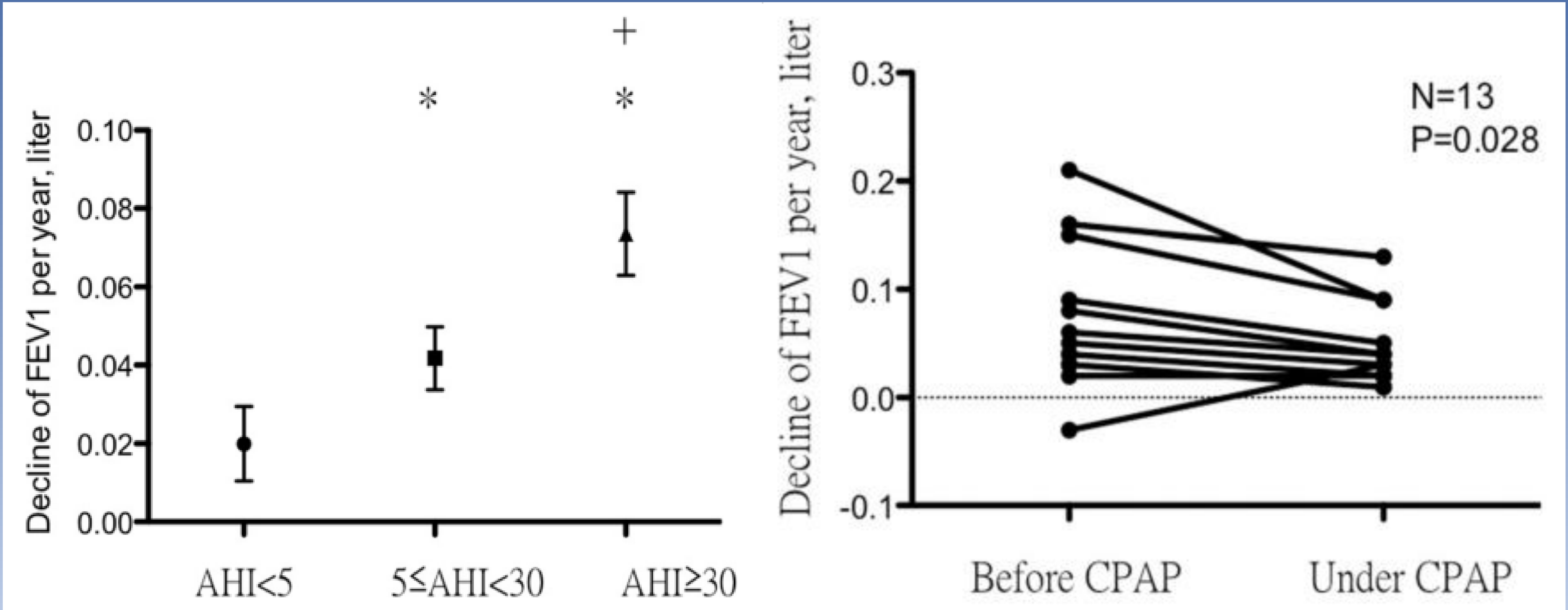
CPAP Therapy and Effect on Asthma: Compliance Effect

Serrano-Pariente J et al. Allergy 2017;72:802-12



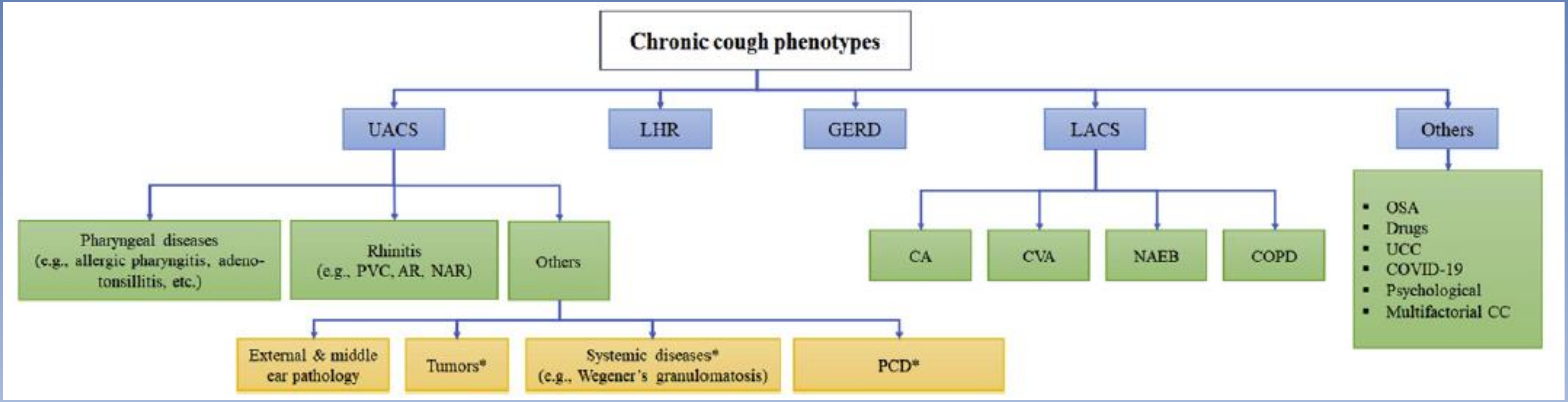
OSA, Asthma, FEV-1 Decline: CPAP Effect

Wang T-Y et al BMC Pulm Med 2017;17:55



Chronic Cough: Phenotypes and Presentations

Rouadi PW et al. World Allergy Organization Journal 2021;14:100618



Chronic Cough and Sleep Apnea

Wang T-Y et al. Cough 2013;9:24

Characteristics	OSA n = 99	Non-OSA n = 32	*p*-value
Age	52.2±11.6	48.3±13.1	0.105
Male, n (%)	75 (75.8)	17 (53.1)	0.025
BMI	28.9±4.1	24.9±4.3	0.000
Epworth Sleepiness Scale	12.9±4.5	12.8±5.5	0.884
Total AHI, /h	53.6±24.7	10.1±4.3	0.000
Pulmonary function test			
FEV_1/FVC	83.7±8.4	82±12.5	0.394
FEV_1 (% predicted)	82.6±20.1	82.6±17.5	0.993
FVC (% predicted)	82.4±17.9	86.8±22.3	0.278
Chronic cough	39 (39.4)	4 (12.5)	0.005
Upper airway cough syndrome	79 (79.8)	23 (71.9)	0.340
Gastro-esophageal reflux disease	43 (43.4)	5 (15.6)	0.006
Asthma	18 (18.2)	5 (15.6)	1.000

Characteristics	OSA with CPAP treatment n = 18	OSA without CPAP treatment n = 21	*p*-value
Age	49.8±9.5	57.1±10.8	0.055
Male, n (%)	16 (88.9)	14 (66.7)	0.139
BMI	29.2±5.4	29.1±3.4	0.602
Pulmonary function test			
FEV_1/FVC	78.9±12.5	85.3±6.0	0.193
FEV_1 (% predicted)	76.6±23.5	85.4±16.8	0.317
FVC (% predicted)	79.4±19.5	86.2±16.6	0.367
Epworth Sleepiness Scale	12.9±4.1	13.4±5.3	0.618
Improved cough, n (%)	12 (66.7)	2 (9.5)	0.010

Chronic Rhinosinusitis (CRS) and Sleep

Mahdavinia M et al Expert Rev Anti Infect Ther 2017;15:457-465

- CRS affects more than 10M Americans, limiting productivity, significant QOL loss and high financial burden (60B/year)
- CRS patients commonly have poor sleep complaints (60-75%) compared to general population (8-18%)
- The Pittsburgh sleep quality index (PSQI) questionnaire was used to determine that 75% of CRS patients report abnormal scores
- Some studies found that functional endoscopic sinus surgery improved sleep symptoms (reduction in PSQI) and resulted in a mild reduction of AHI

Chronic Rhinosinusitis: GA²LEN Study

Bengtsson C et al. Sleep 2017;40:1-6

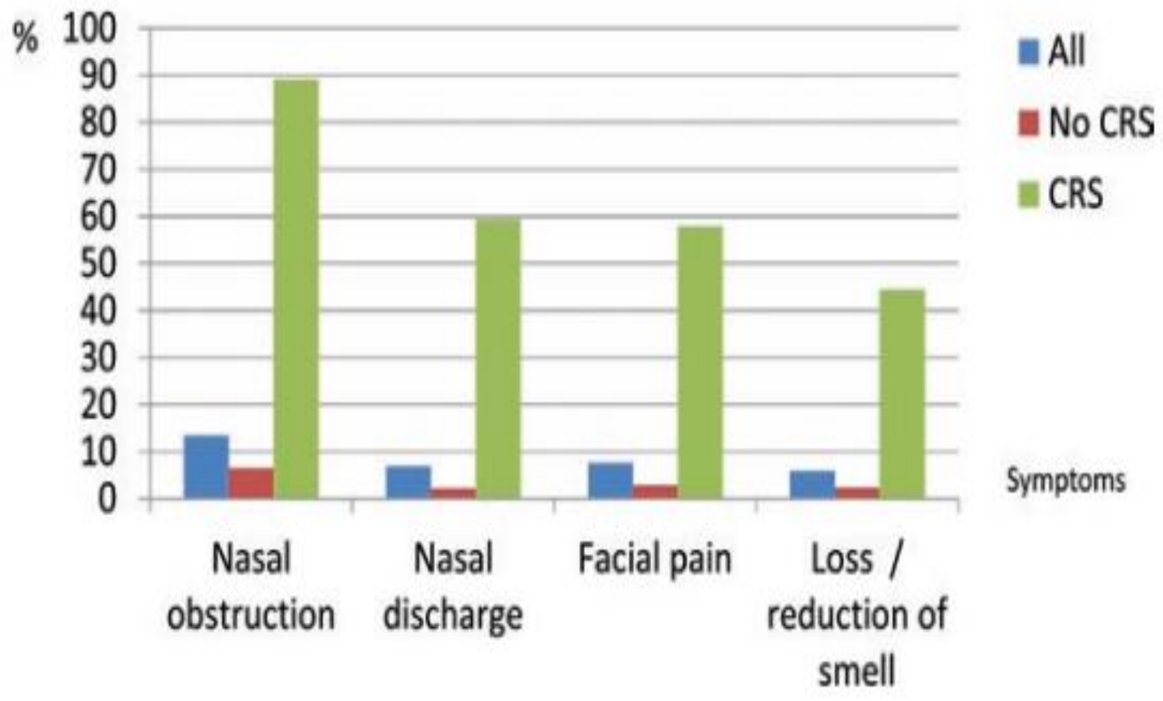


Figure 1—Prevalence of chronic rhinosinusitis (CRS) symptoms in the total population and among subjects with and without CRS.

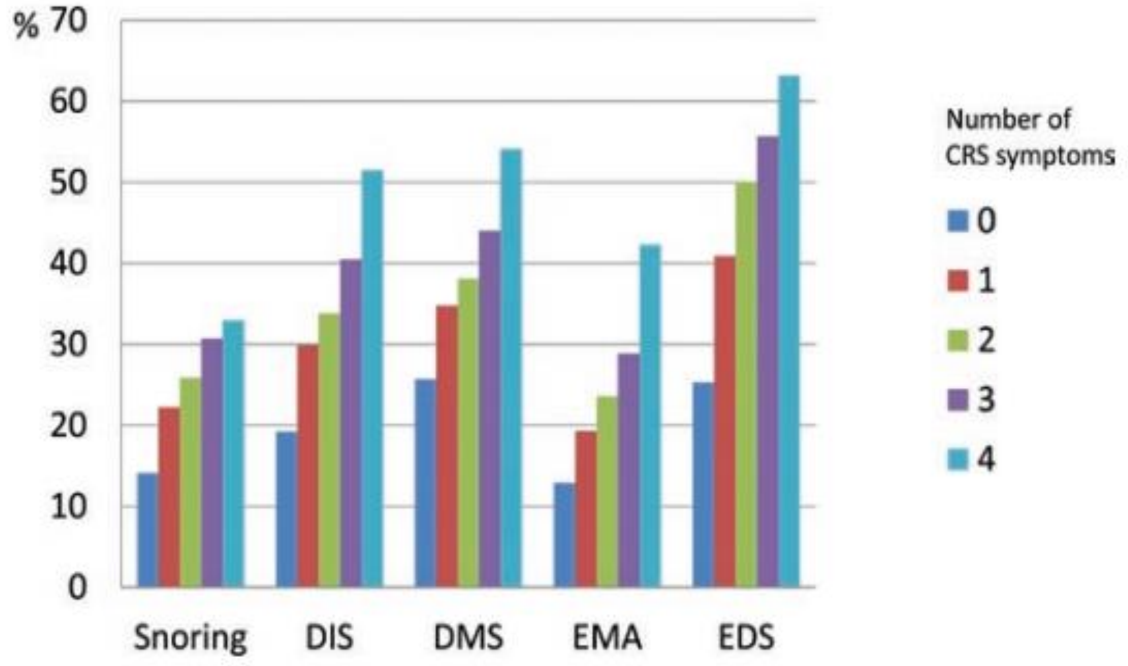


Figure 2—Prevalence of sleep problems in relation to the number of chronic rhinosinusitis (CRS) symptoms. DIS = Difficulties inducing sleep; DMS = Difficulties maintaining sleep; EMA = Early morning awakening; EDS = Excessive daytime sleepiness.

Swedish Questionnaire study of 26,647 participants, 2,249 patients with CRS

Chronic Urticaria and Sleep

Ates H et al. J Cosmet Dermatol 2022;21:4072-4079

- **21 patient study with chronic urticaria compared to 19 controls**
  - Greater degree of sleepiness (ESS $\geq$ 10): 52.4% vs. 5.3%
  - Greater prevalence of all 4 symptoms of sleep apnea (snoring, witnessed apneas, sleepiness, fatigue): 47.6% vs. 0%
  - Greater prevalence of sleep apnea (AHI $\geq$ 5): 44.4% vs. 5.3%
  - Chronic Urticaria Quality-of-Life Questionnaire (sleep problem subset): positive correlation with sleep latency

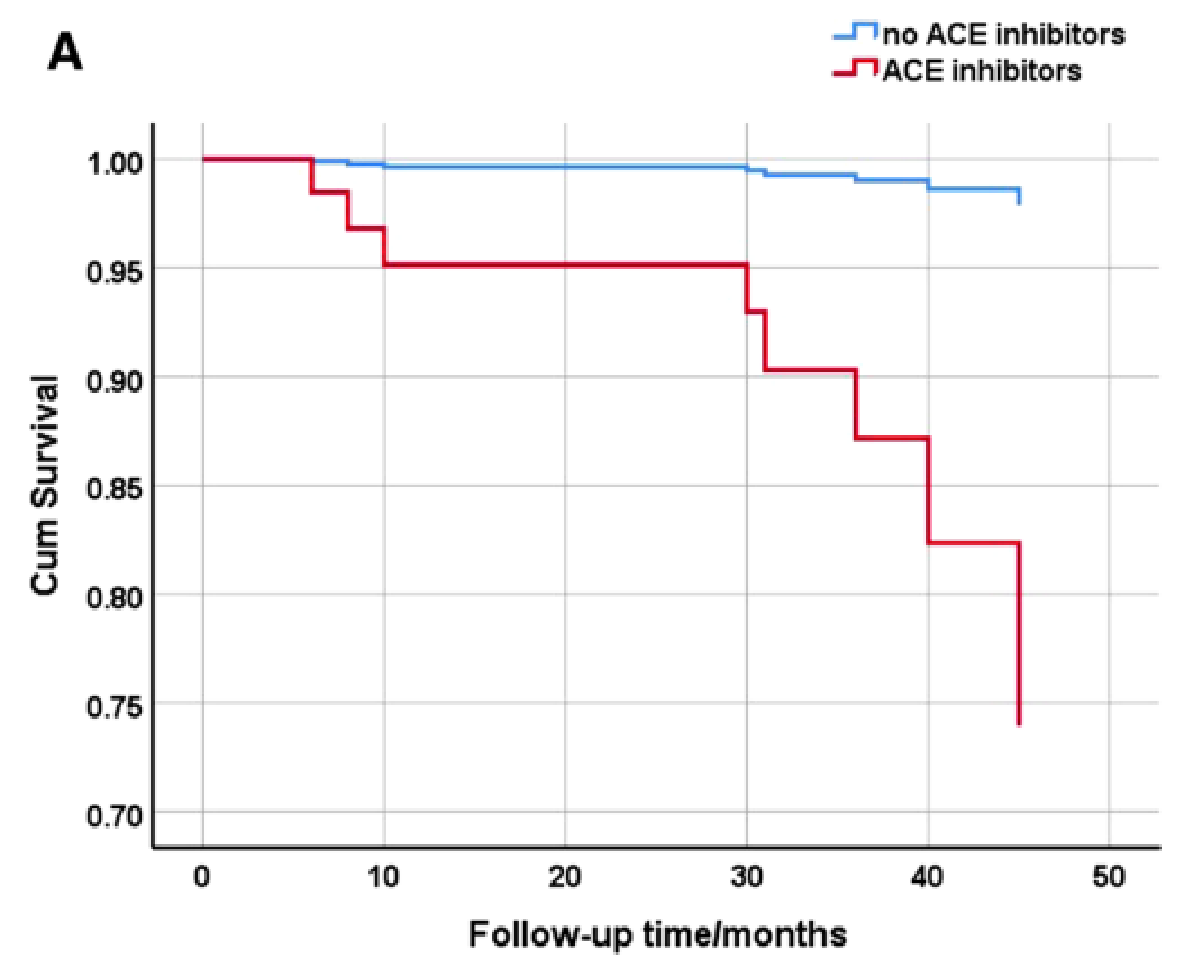
OSA and ACE Inhibitors: AHI, Cough, Mortality

Cicolin A et al. Mayo Clin Proc 2006;8:53-55
Lao M et al. BMC Pulm Med 2022;22:99

TABLE 1. **Individual Values of the AHI in the Study Patients During Treatment With ACE Inhibitors and 1 Month After Substituting ACE Inhibitors With Diuretics***

Patient	ACE inhibitor–induced cough	AHI (No. of episodes per hour)	
		ACE inhibitor	Diuretics
1	Yes	24.80	9.00
2	Yes	10.20	1.90
3	Yes	13.10	5.40
4	Yes	52.60	37.00
5	Yes	60.00	39.90
6	No	18.30	8.90
7	No	26.00	26.00
8	No	38.00	38.00
9	No	64.00	67.30
Mean ± SD		34.1 ±20.4	25.9±21.7†

*Data were analyzed with the Wilcoxon signed rank test. ACE = angiotensin-converting enzyme; AHI = apnea-hypopnea index.
†*P*=.03.



Positive Airway Pressure Therapy

PAP Options: CPAP, Travel CPAP, BiLevel, Auto-CPAP, Auto-Bilevel, Adaptive-Servo Ventilation (ASV), Cflex, Biflex, EPR, VPAP, S, ST, iVAPS

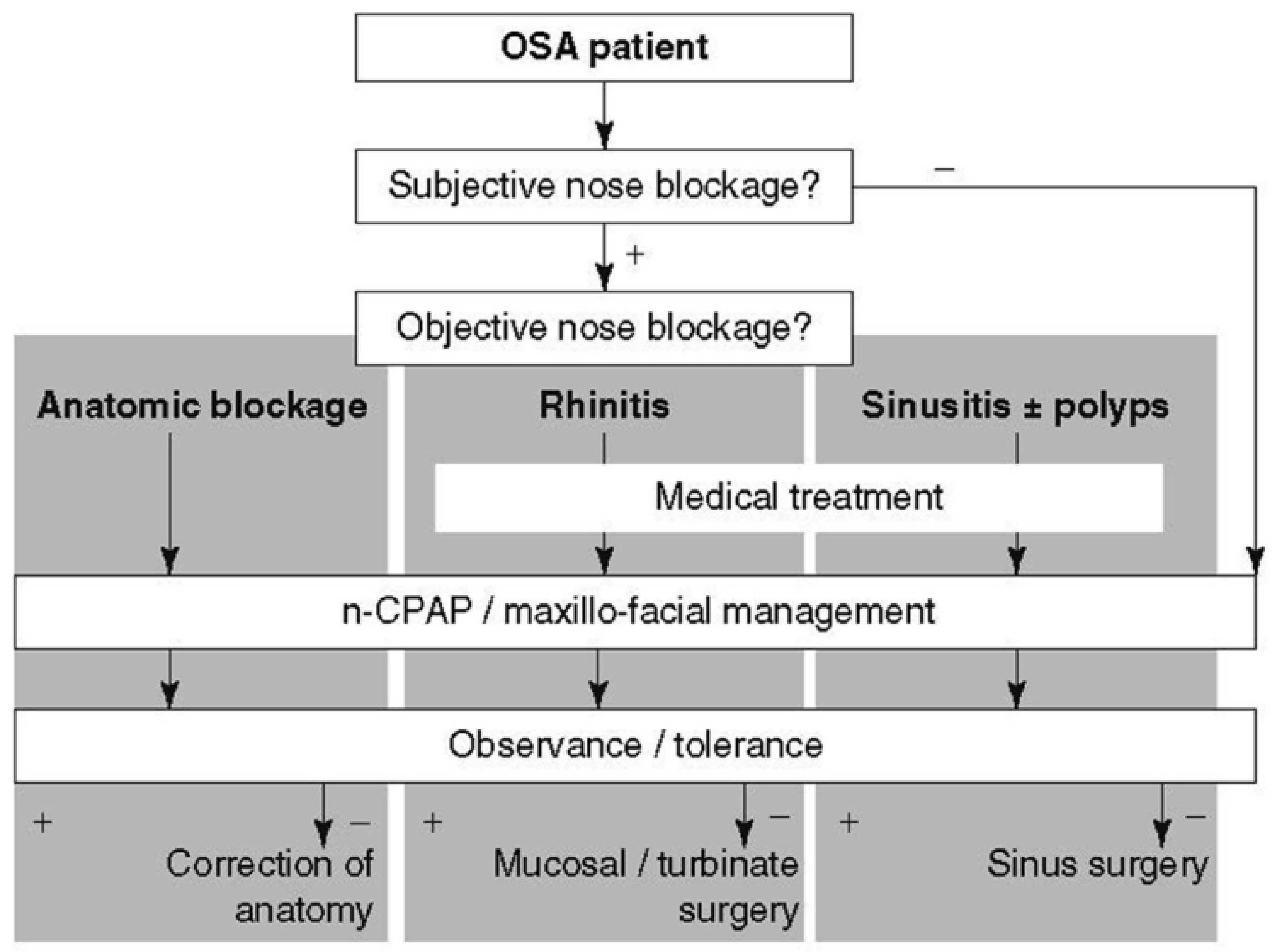



Mask Interfaces



PAP Use: Anticipating Tolerance, Alternative Rx

Shusterman D. et al J Allergy Clin Immunol Pract 2017;5:628-39



PAP Side Effects: Rhinitis, Sinusitis-Better or Worse?

Skirko JR et al. JAMA Otolaryngol Head Neck Surg 2020;146:523-529

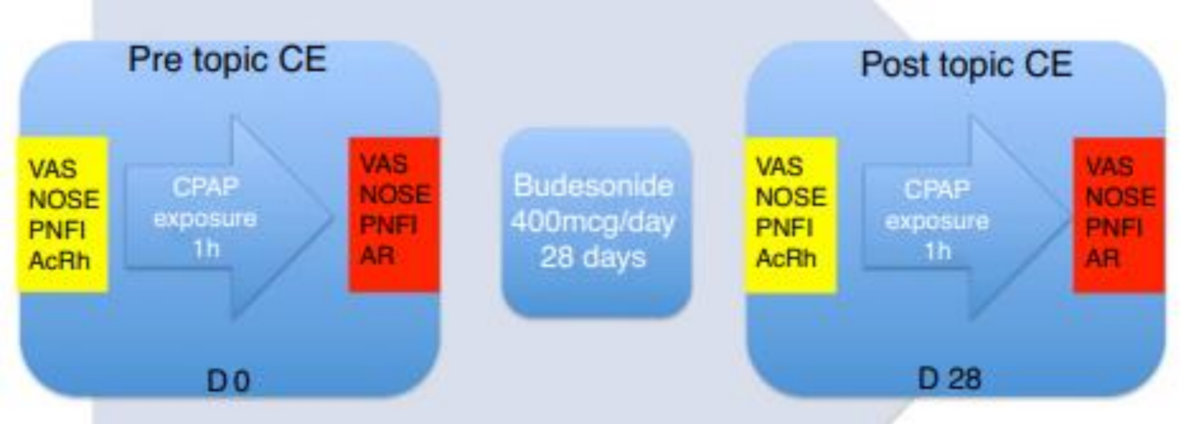
- CPAP side effect present 15-45% of patients: skin irritation, dry mouth, air leak, mask discomfort, claustrophobia, nasal symptoms
- Nasal complaints can occur in 44-65% of CPAP users: nasal obstruction, rhinorrhea, nasal dryness, sneezing
- Early nasal evaluation important: the best predictor of CPAP adherence is usage within the first 7-14 days of therapy initiation
- CPAP improved subjective nasal congestion but less in patients with baseline allergic rhinitis

Table 3. Adjusted Nasal Change Scores by Rhinitis Status[a]

	Rhinitis, mean (95% CI) score		
Adjusted change	Allergic	Nonallergic	No rhinitis
NOSE	−3 (−12 to 7)	−10 (−17 to −4)	−17 (−28 to −6)
VAS	−9 (−21 to 2)	−9 (−16 to −2)	−24 (−36 to −12)

CPAP, Nasal Corticosteroids and Nasal Patency

Balsalobre L et al. Braz J Otorhinolaryngology 2021;87:326-332



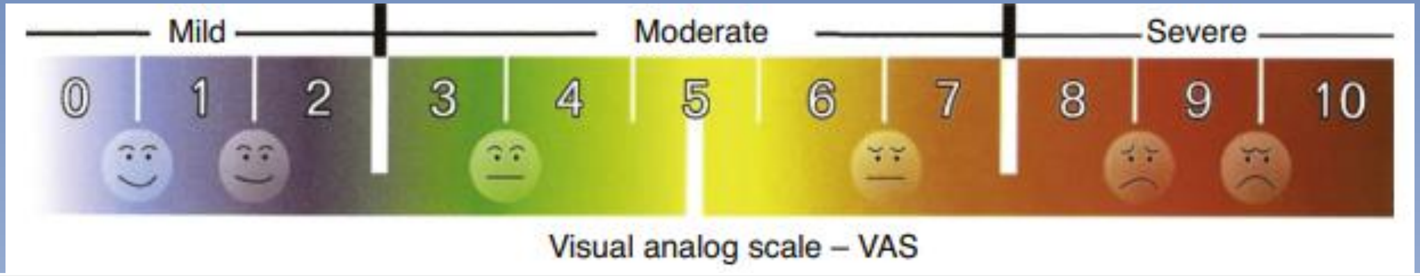


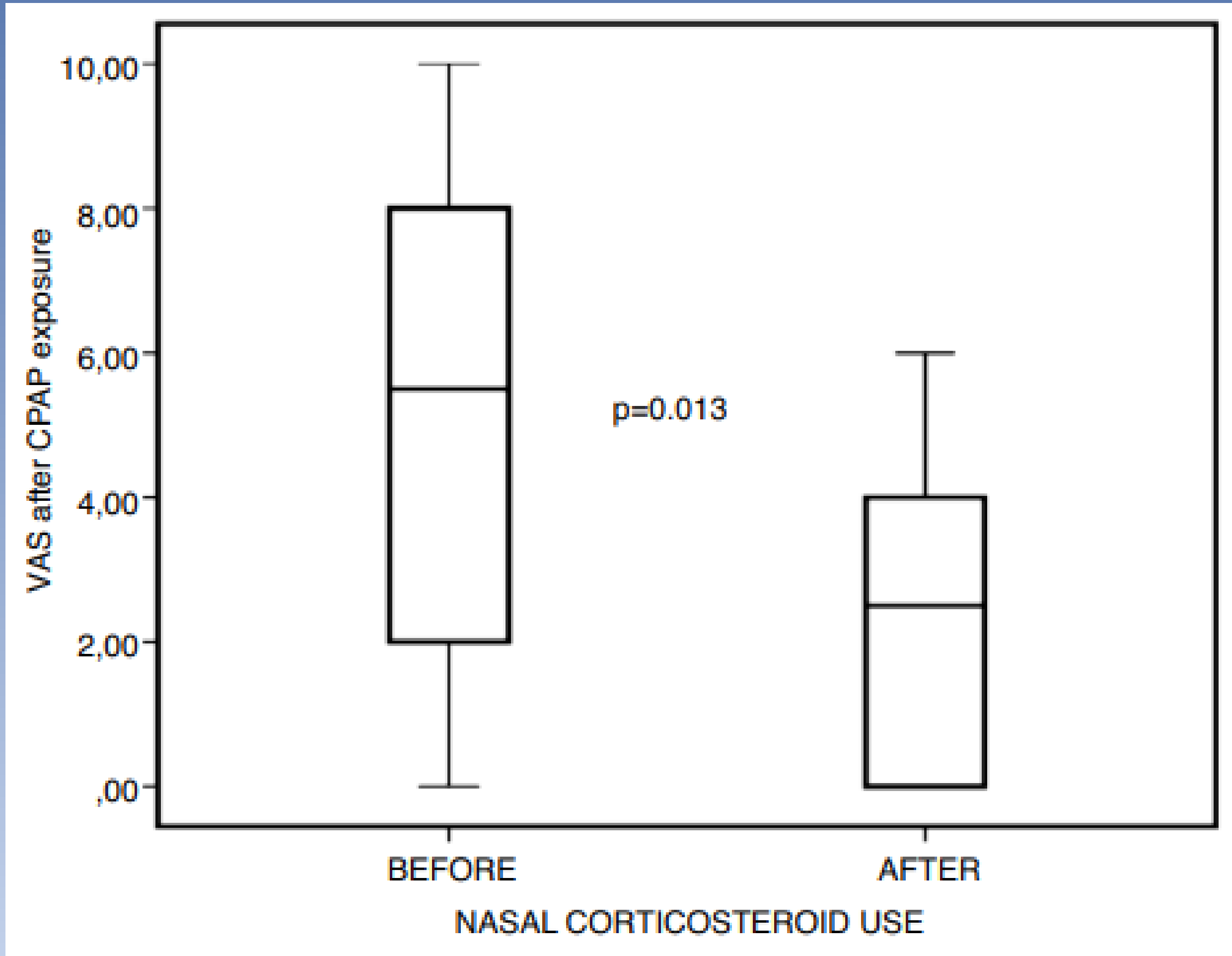
Table 1 Nasal Obstruction Symptom Evaluation (NOSE) scale.

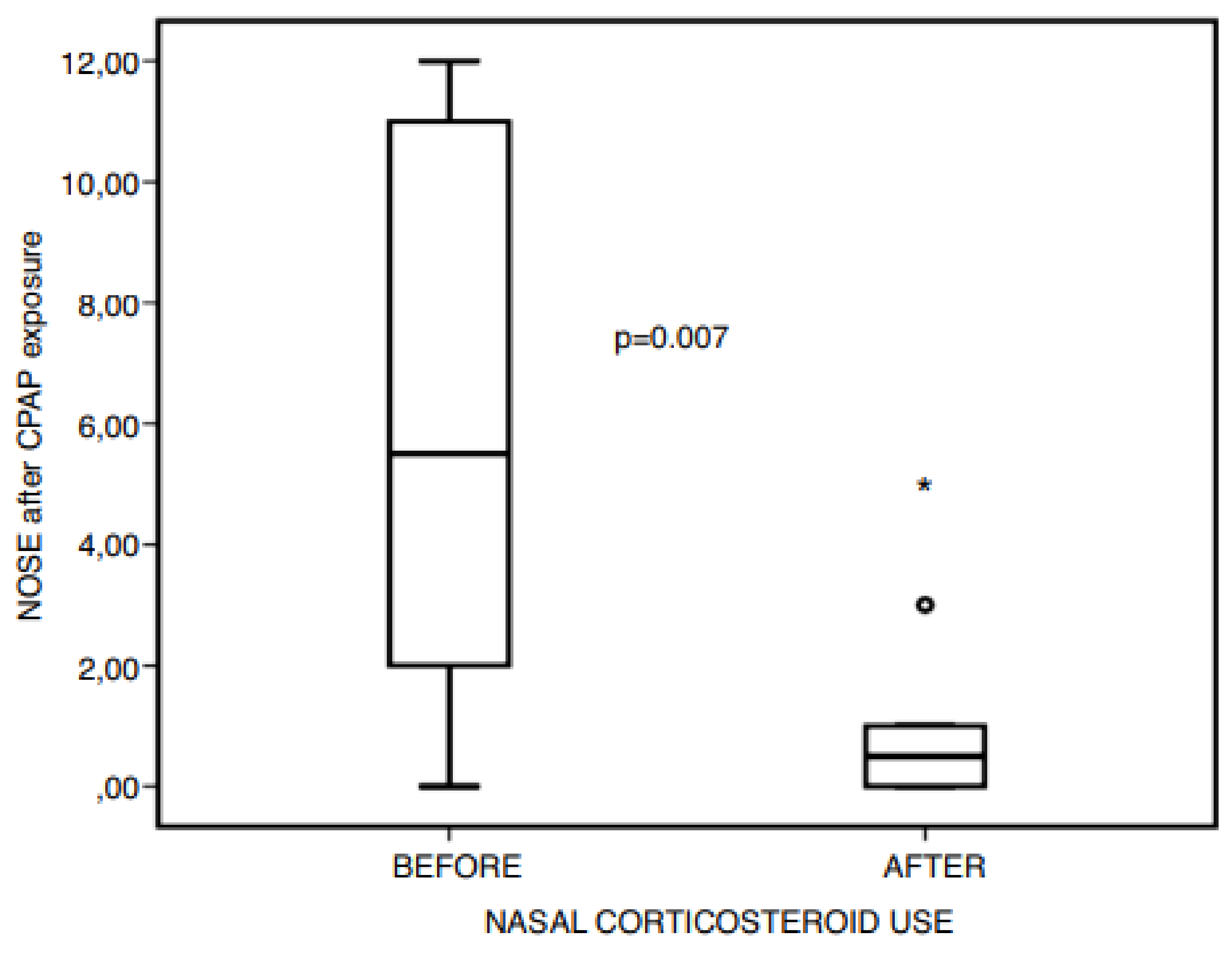
	Not a problem	Very mild problem	Moderate problem	Fairly bad problem	Severe problem
1. Nasal congestion or stuffiness	0	1	2	3	4
2. Nasal blockage or obstruction	0	1	2	3	4
3. Trouble breathing through my nose	0	1	2	3	4
4. Trouble sleeping	0	1	2	3	4
5. Unable to get enough air through my nose during exercise or exertion	0	1	2	3	4

CPAP, Nasal Corticosteroids and Nasal Patency

Balsalobre L et al. Braz J Otorhinolaryngology 2021;87:326-332

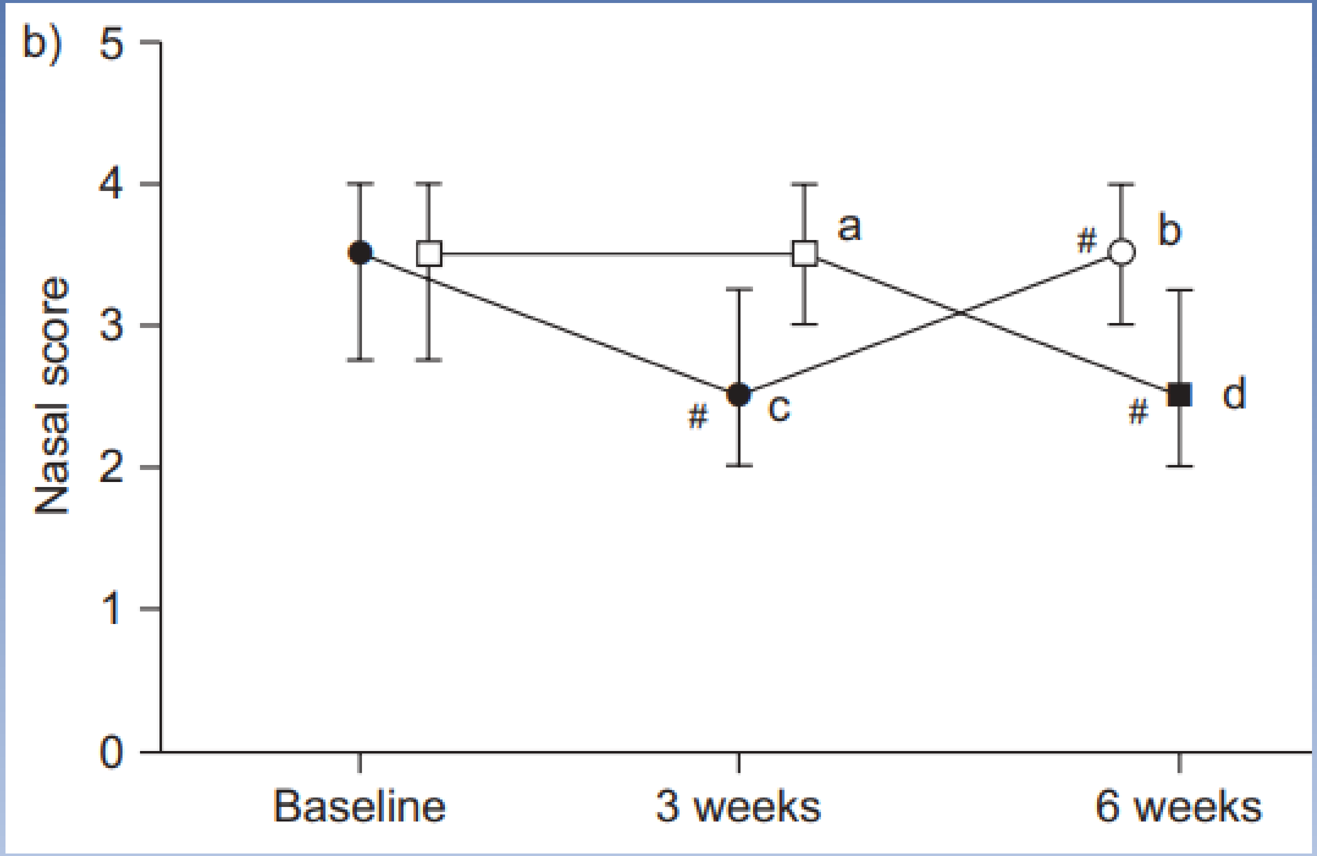
10 patients treated for 28 days demonstrated subjective and objective (incr. nasal cavity volume, incr. peak nasal inspire flow)

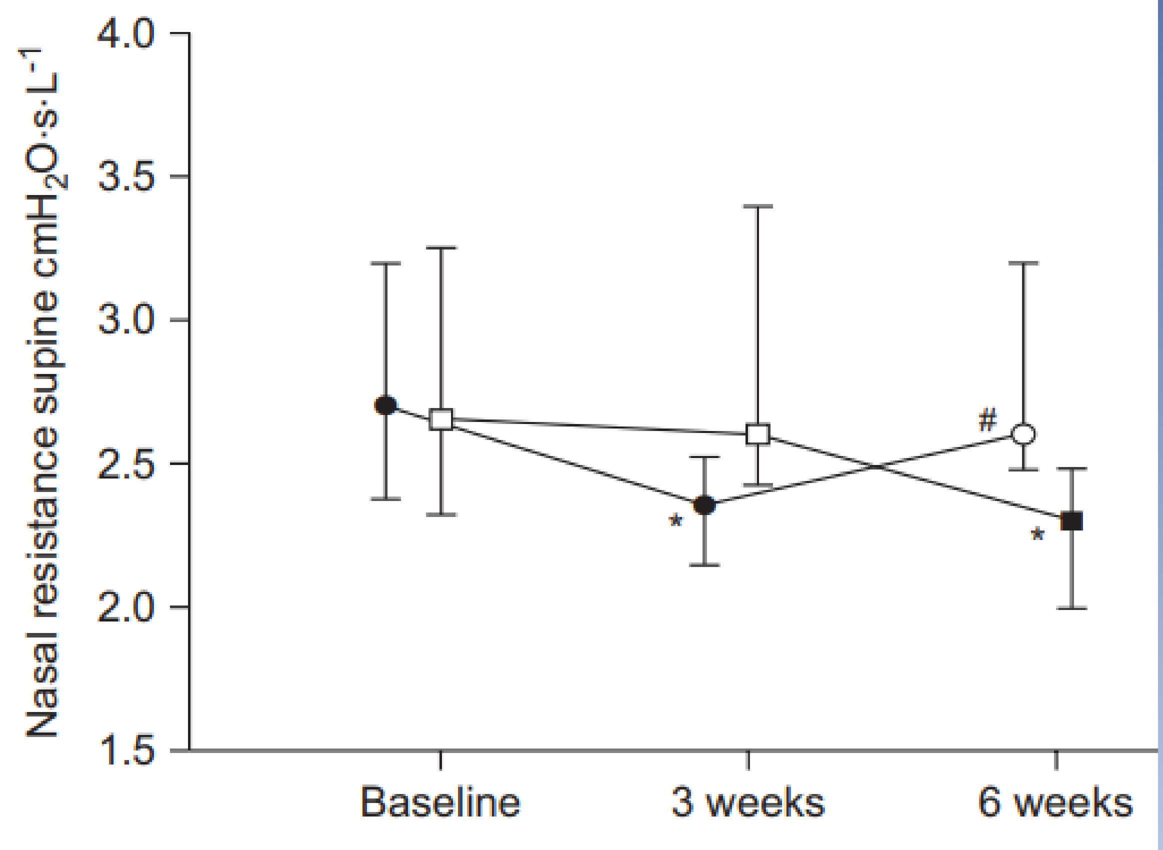




CPAP, Nasal Inflammation, Heated Humidity: A Crossover Study

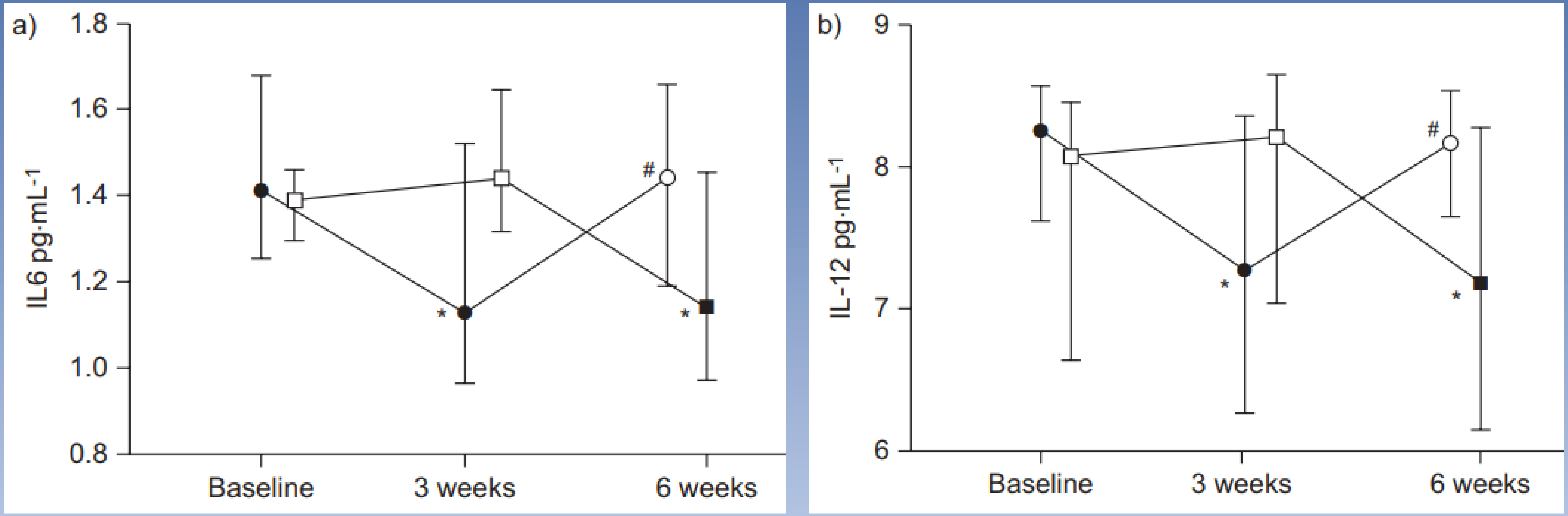
Koutsourelakis I et al. Euro Respir J 2011;37:587-594





CPAP, Nasal Inflammation, Heated Humidity: A Crossover Study

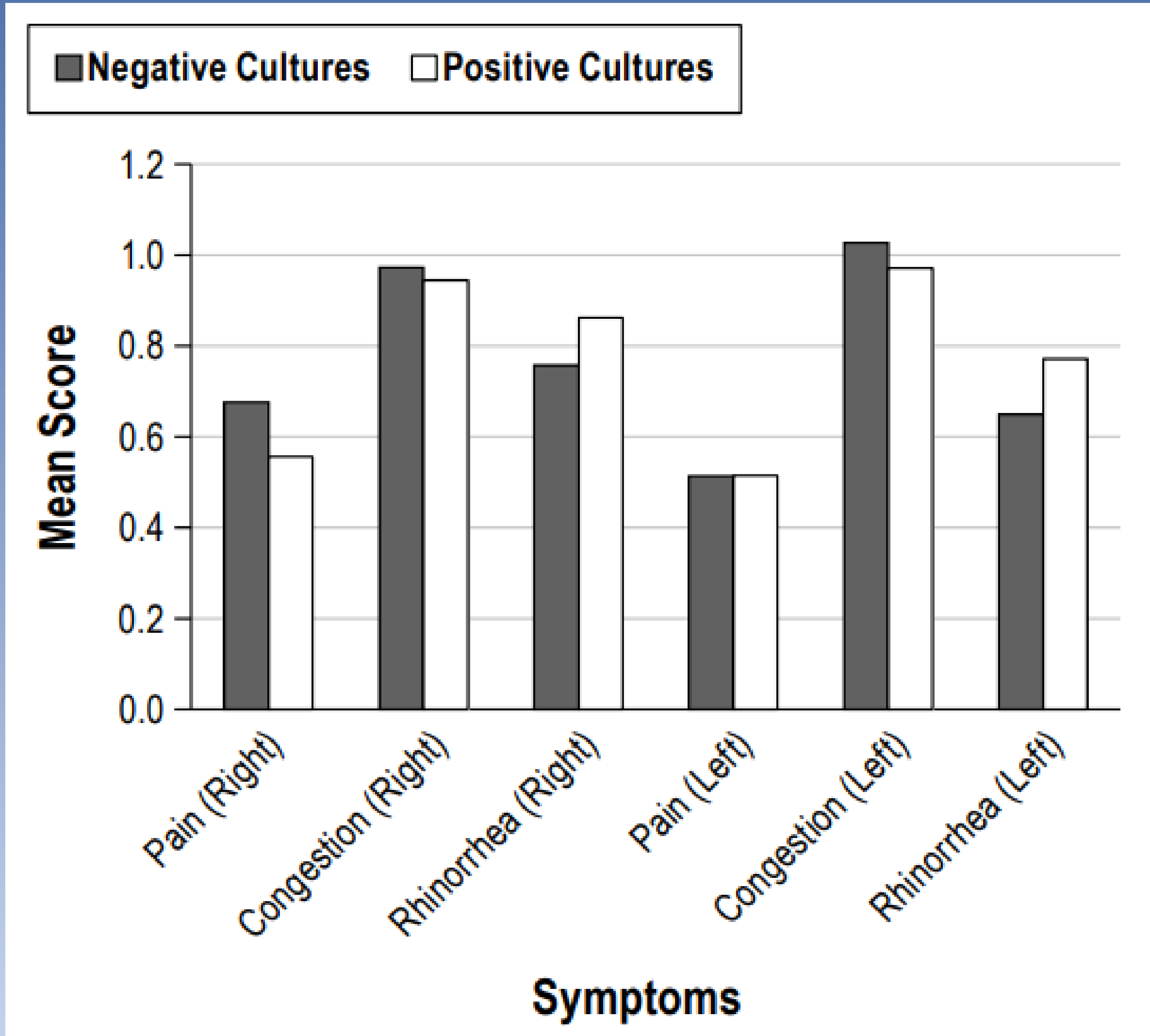
Koutsourelakis I et al. Euro Respir J 2011;37:587-594

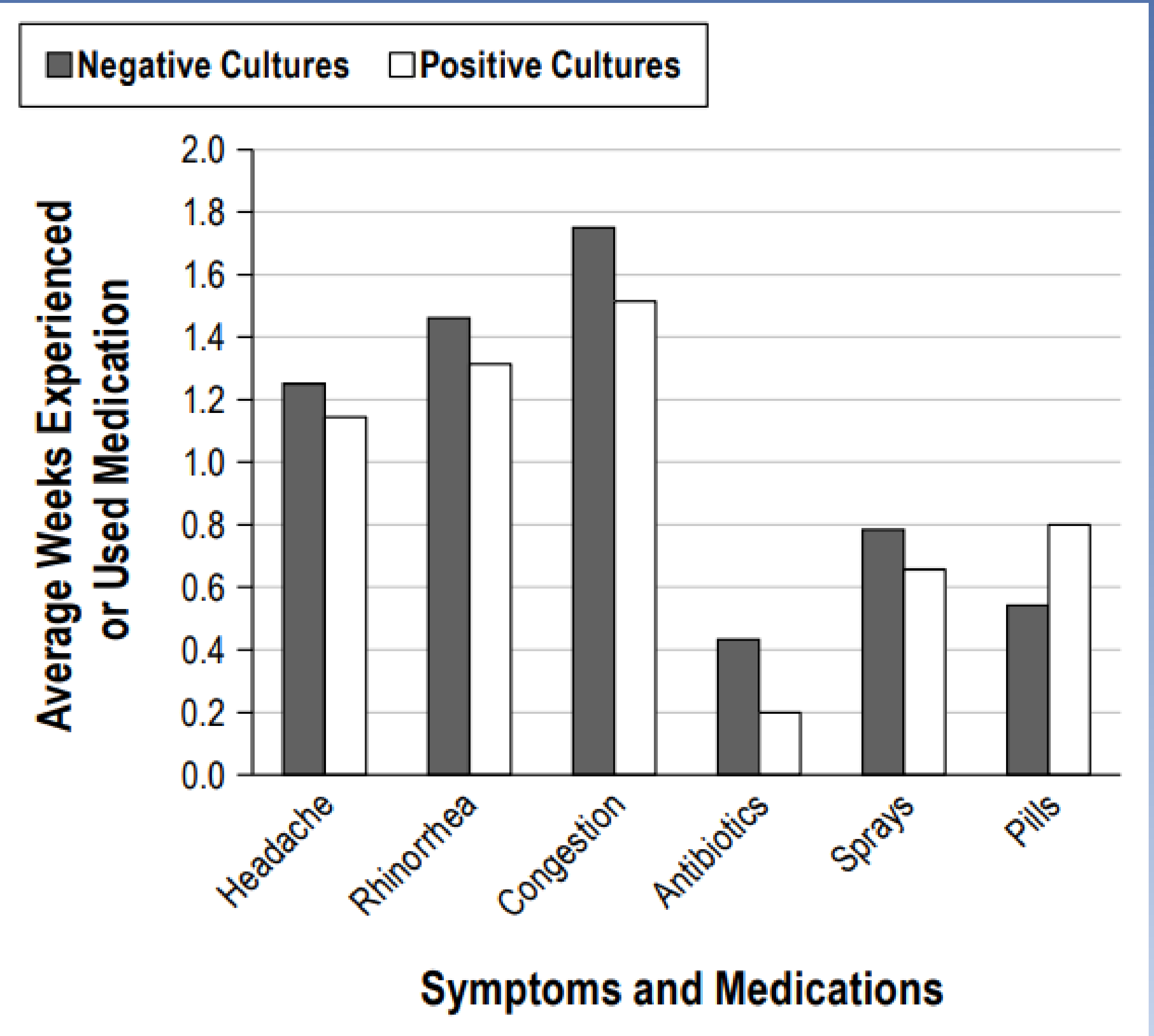


CPAP, Bacterial Colonization, Chronic Rhinosinusitis

Chin CJ et al J Clin Sleep Med 2013;9:747-750

(+) CPAP reservoir culture, while common, does not seem to lead to increased symptomatology of CRS



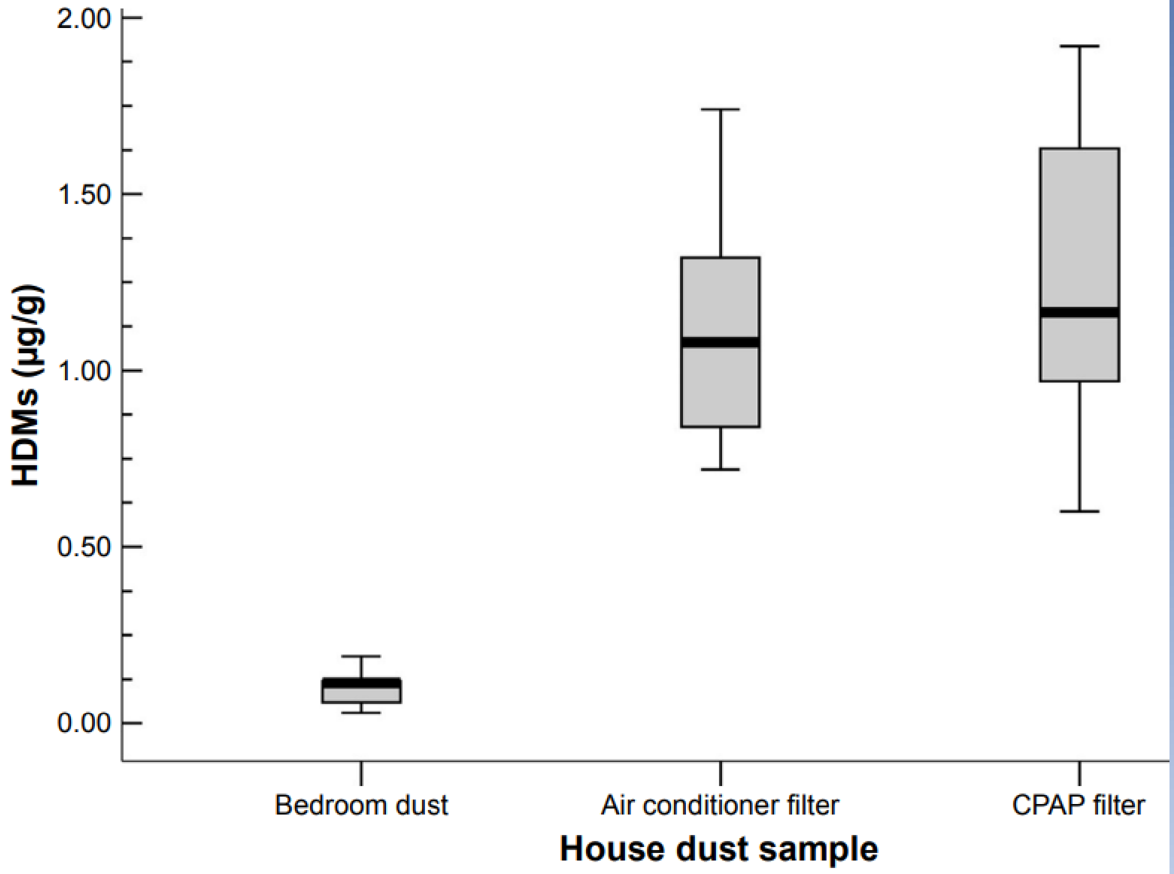


CPAP, Nasal Symptoms, Allergic Rhinitis

Yang Q et al Therapeutics and Clinical Risk Management 2018;14:1507-1513

CPAP associated with a higher incidence and worsening of allergic rhinitis, HDM differences in CPAP filter not seen

Parameter examined	CPAP	Non-CPAP	*P*-value
Onset of nasal symptom			
Within one year	5.7% (18/316)	0 (0/100)	0.031
Within one to two years	2.5% (5/200)	1.0% (1/100)	0.662
Within two to three years	1.0% (1/98)	0 (0/100)	0.495
HDM skin prick test	100% (24/24)	100% (1/1)	1.000
Exacerbation of nasal symptom			
Within one year	0.6% (2/316)	0 (0/100)	1.000
Within one to two years	7.5% (15/200)	0 (0/100)	0.005
Within two to three years	3.1% (3/98)	0 (0/100)	0.238
HDM skin prick test	100% (20/20)	–	–
Nasal symptom unchanged	1.9% (6/316)	6.0% (6/100)	0.073
HDM skin prick test	100% (6/6)	100% (6/6)	1.000
AR incidence	15.8% (50/316)	7.0% (7/100)	0.025



Sleep Apnea-Allergic Disease Summary

- Both sleep apnea and allergic diseases are common, associated with significant life impairment and health cost utilization
- Sleep disturbances are common in patients with allergic diseases
- There appears to be a bi-directional association between sleep apnea and upper airway disease such as asthma, allergic rhinitis and chronic rhinosinusitis
- The treatment of sleep apnea or airway disease may have a positive effect on the other
- Early identification and intervention for upper airway disease may improve CPAP tolerance
- CPAP side effects are common but interventions such as nasal steroids and heated humidity can help minimize side effects