Hypoxic Burden as the New Frontier in Sleep Apnea

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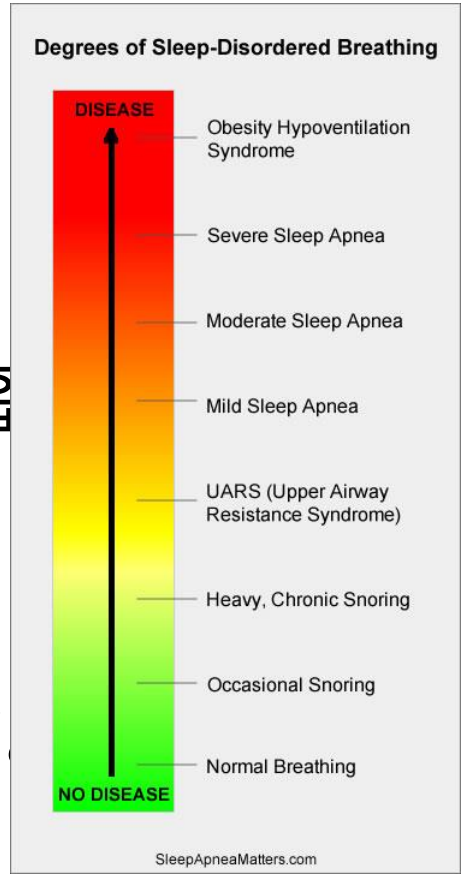
   - Obstructive sleep apnea (폐쇄성수면무호흡증)
   - Pathophysiology & Comorbid disease

2) Traditional metrics : **AHI**, ODI, T90

3) New metrics : **Hypoxic burden, Hear rate response**, etc

4) Clinical application & Importance

수면호흡장애



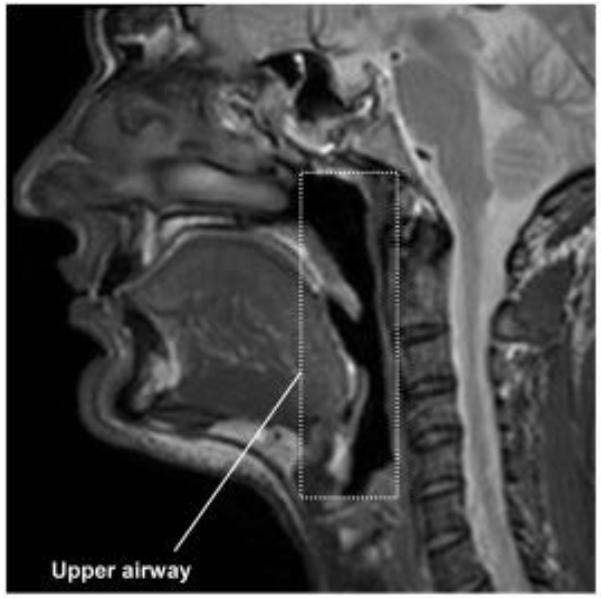
- 잠을 자는 동안 **상기도의 저항이 증가**하면서 일어나는 호흡
- 단순코골이 (Simple snoring)
- 저산소증(Sleep-related hypoxemia or nocturnal hypoxemi
- **수면무호흡증후군(Sleep apnea syndrome)**
  - 폐쇄성 수면무호흡증 (Obstructive sleep apnea, OSA)
  - 중추성 수면무호흡증 (Central sleep apnea, CSA) → 호흡노력없음
- 수면 관련 저환기증후군(sleep-related hypoventilation syndromes)

J Sleep med, 2022;19(3):133-138
Circulation. 2021;144:e56–e67

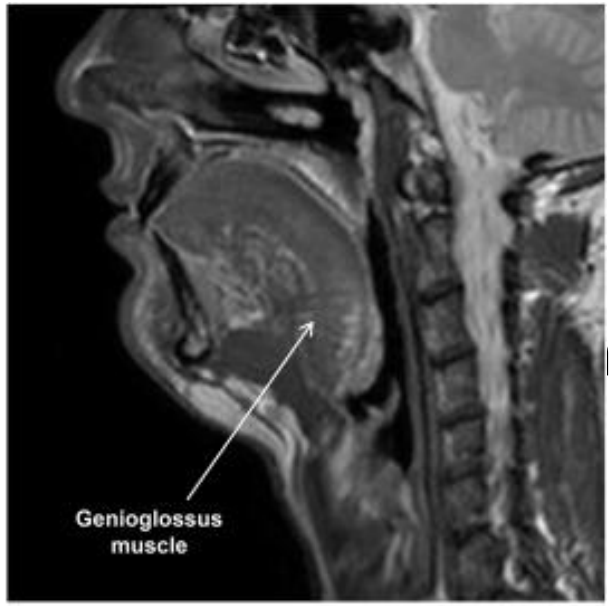
Obstructive sleep apnea (폐쇄성 수면무호흡증)

- 수면 중 상기도의 **반복적인 폐쇄**
  : Partial or Complete cessation of breathing

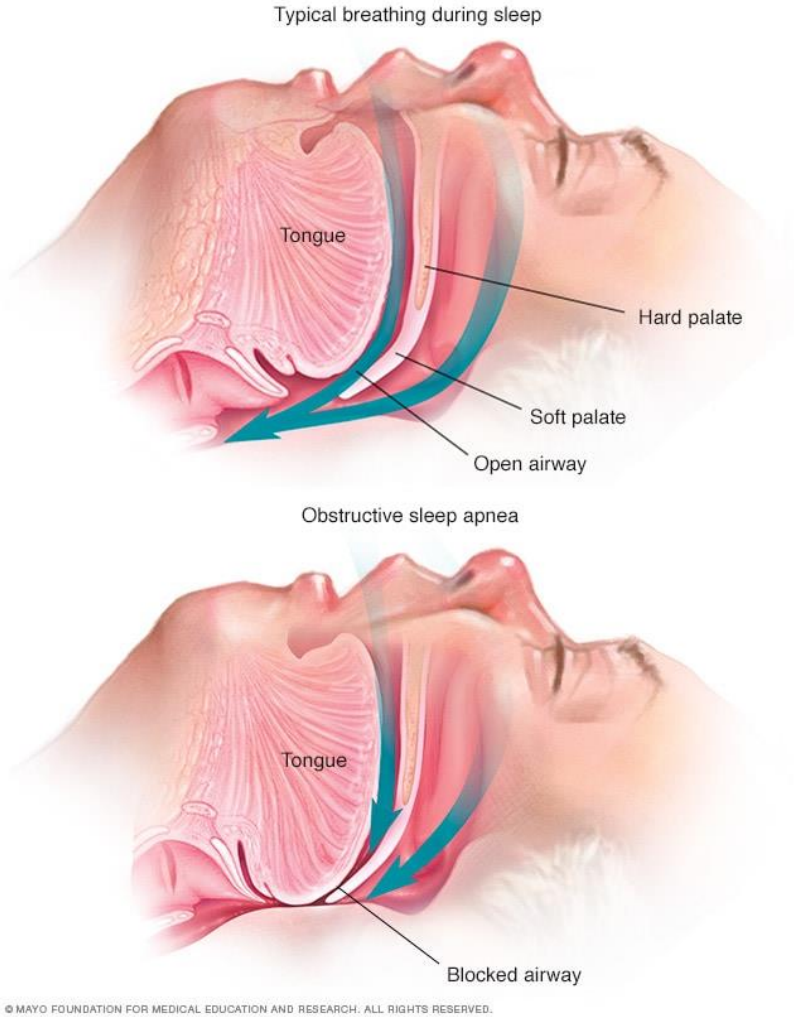
- Obstructive sleep apnea (OSA)
  : **20-30% of men, 10-15% of women**
  → 점차 증가하고 있다.



Healthy individual



Obstructive sleep apnoea



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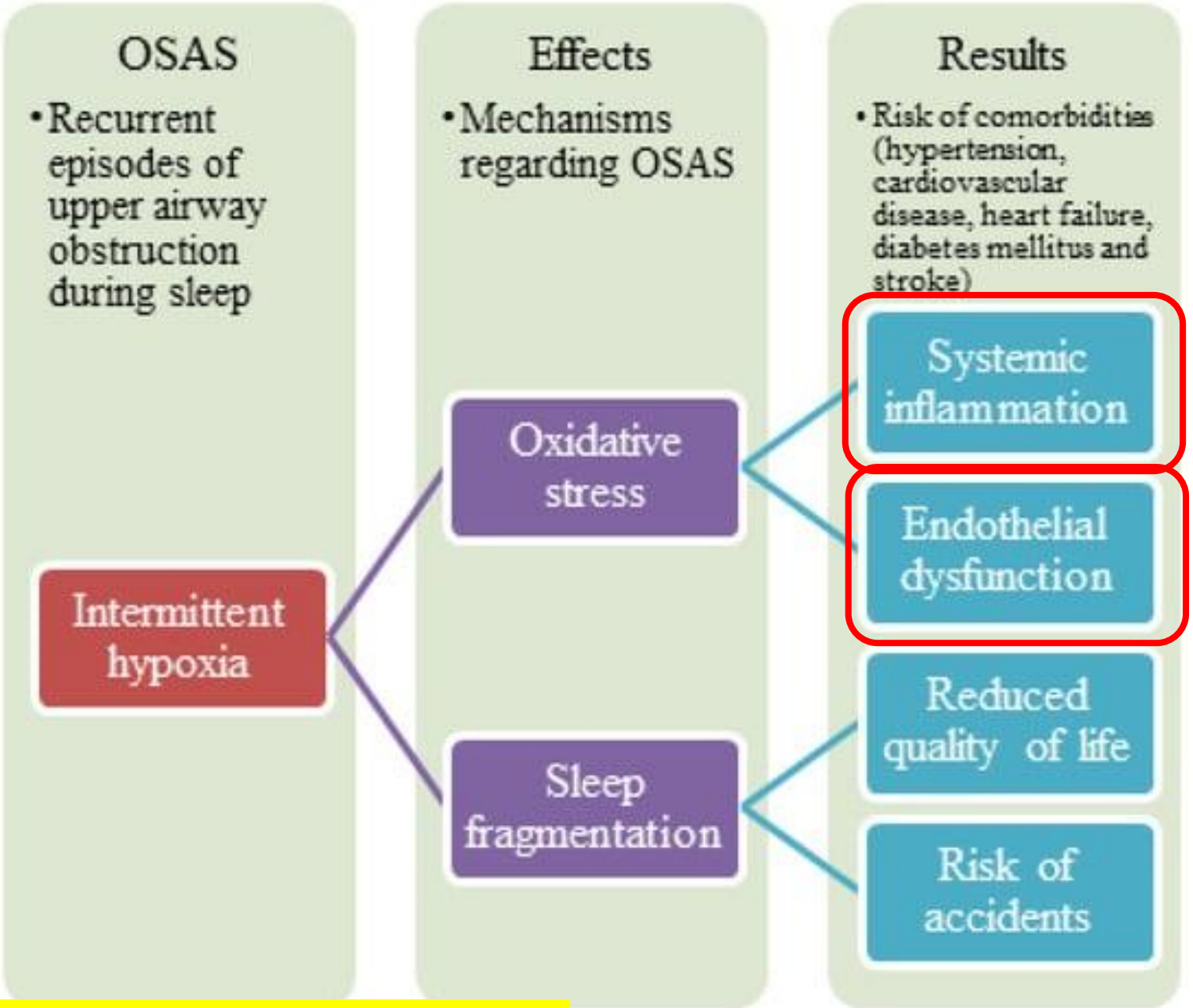


Chronic intermittent hypoxia

P Fiedorczuk et al, J. Clin. Med. **2023**, 12(1),

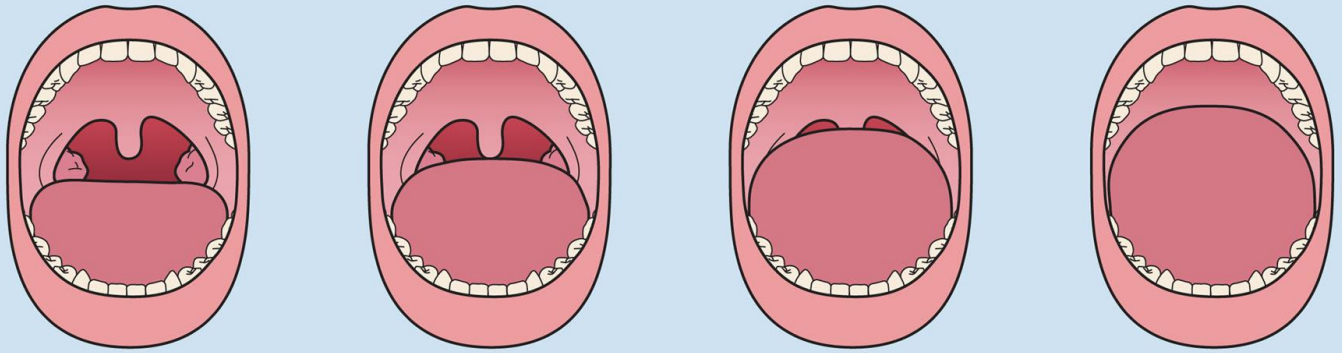
Signs and Symptoms

- Excessive daytime sleepiness
- Morning headaches
- Memory impairment
- Irritability and/or changes in affect
- Difficulty concentrating
- Nocturia
- Decreased libido and erectile dysfunction

Exam Findings

- Obesity
- Increased neck circumference
- Mallampati score ≥3*
- Craniofacial abnormalities

The Mallampati Score



CLASS I Complete visualization of the soft palate

CLASS II Complete visualization of the uvula

CLASS III Visualization of only the base of the uvula

CLASS IV Soft palate is not visible at all

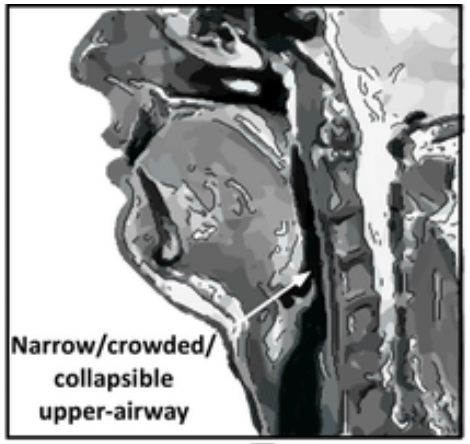
Risk factor

Male
Older age
Obestiy

Race (Asian,African-american)
Family history

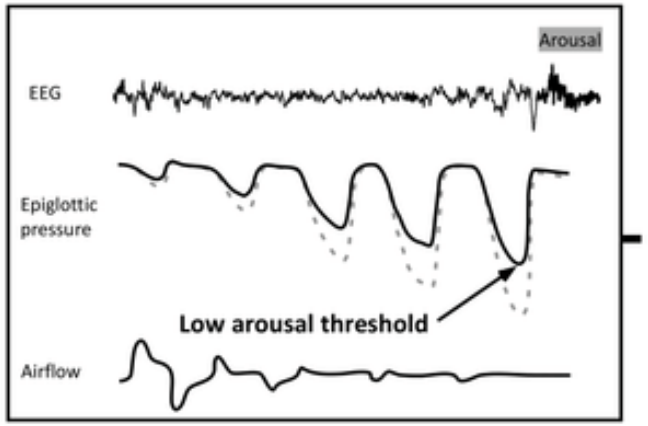
Yerem et al, Circulation, 2021

Pathophysiology

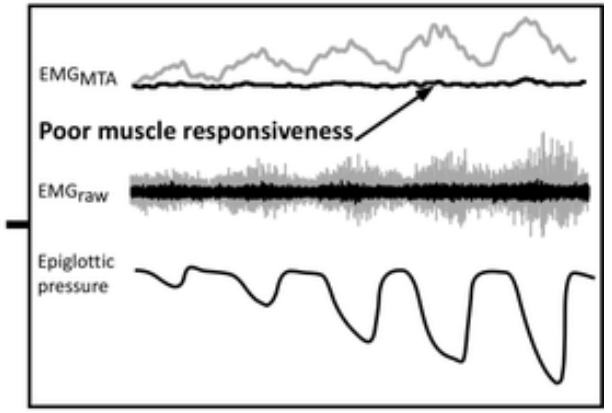


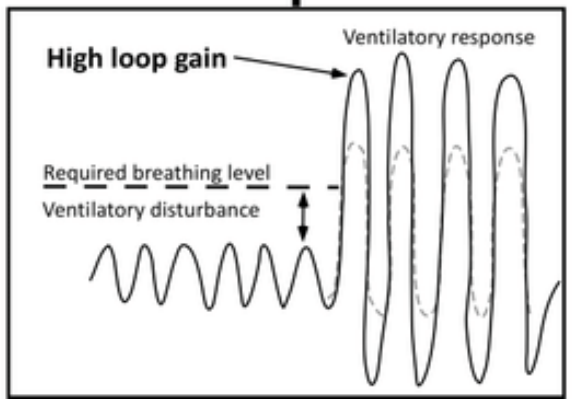
Anatomical factor

→CPAP, Surgery, Oral appliance
Positional therapy, Weight loss



OSA

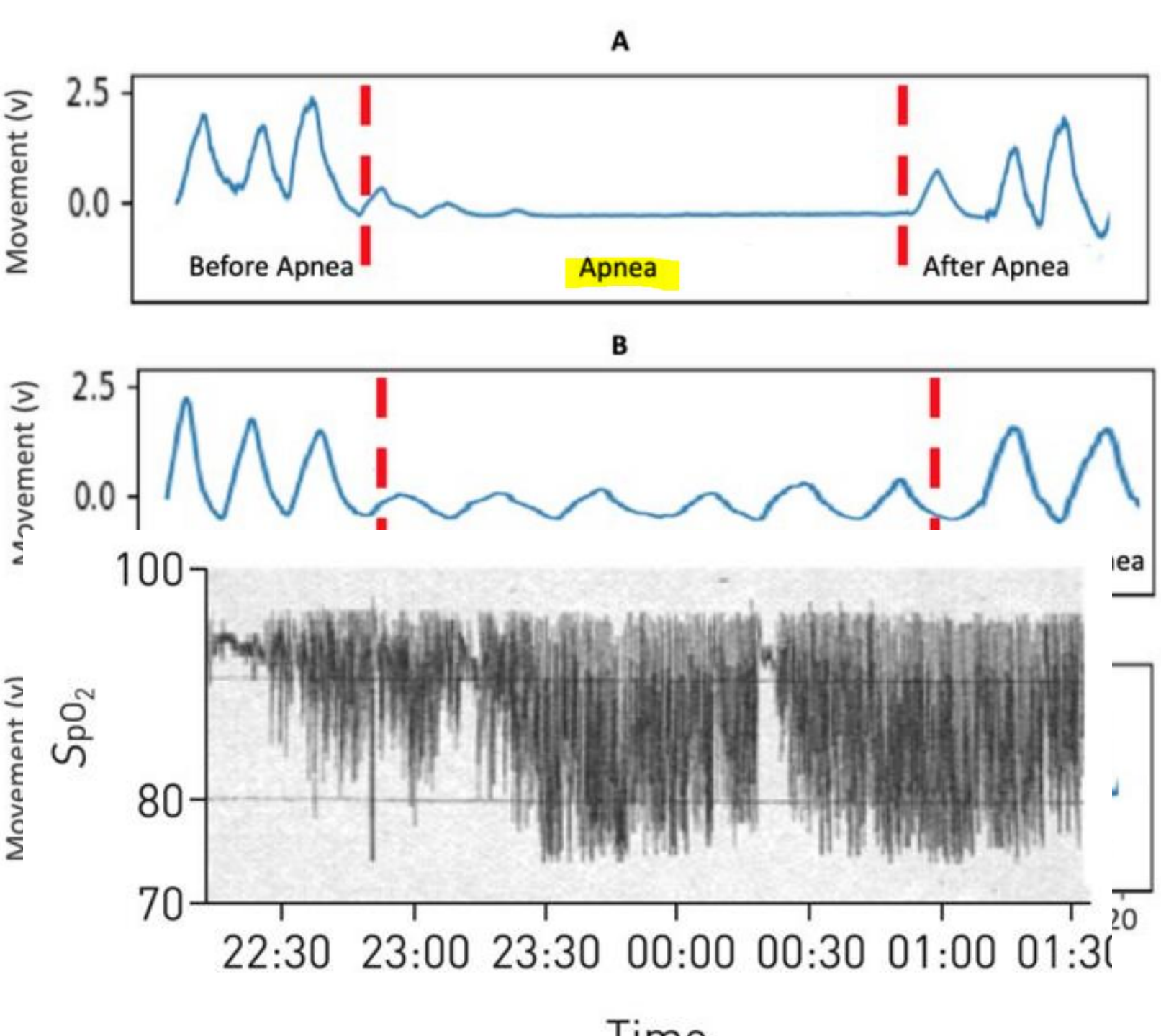




Non-anatomical factor

약 70%

Chest. 2018;153(3):744-755.
Curr Sleep Med Rep 2018;4:231–242



10s, 90% reduction

흡) : 30%, 3% Spo2 저하

+ Hypopnea index

흡지수 (시간당 몇번)

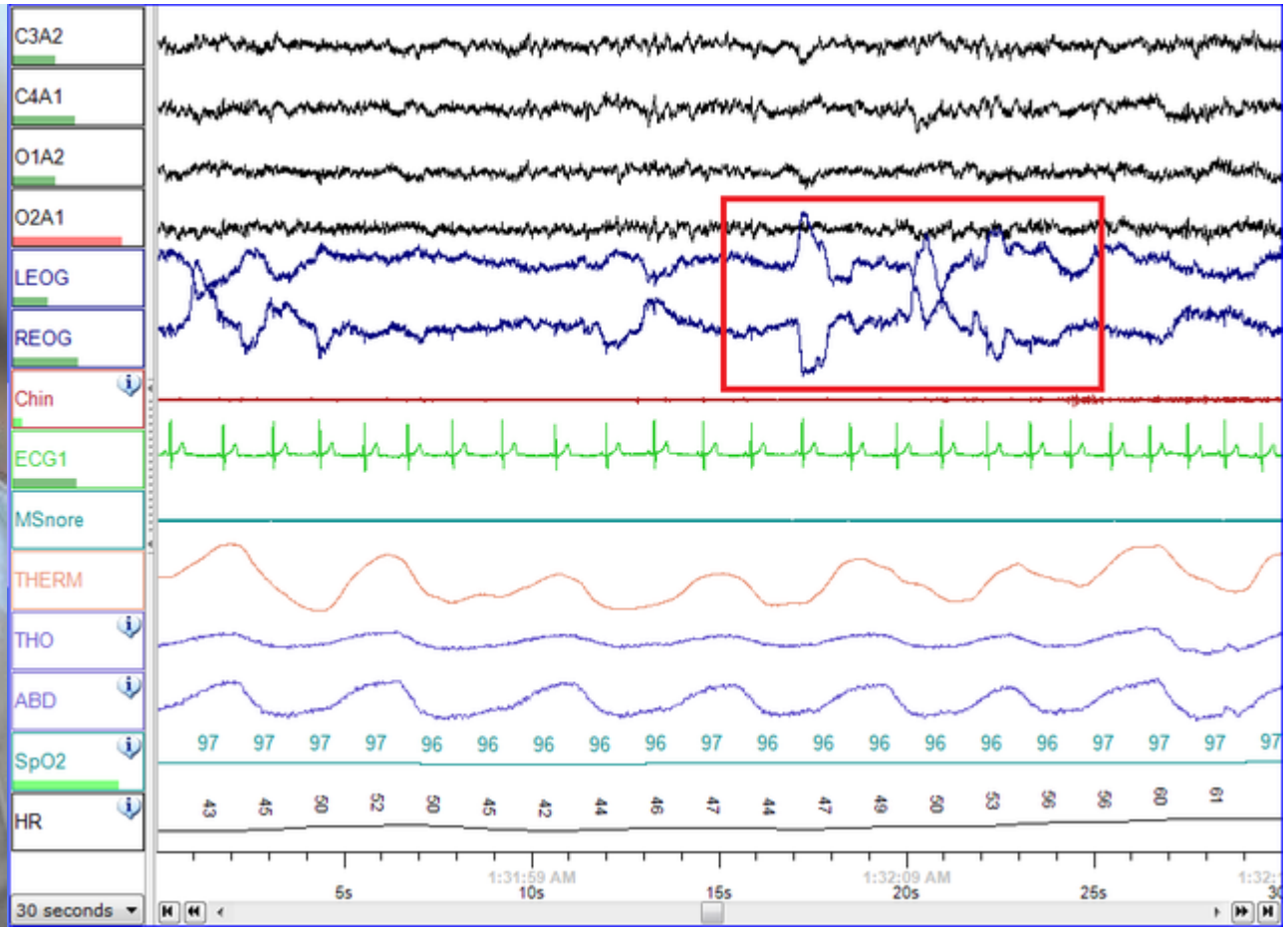
effort-related arousal)

ERA index

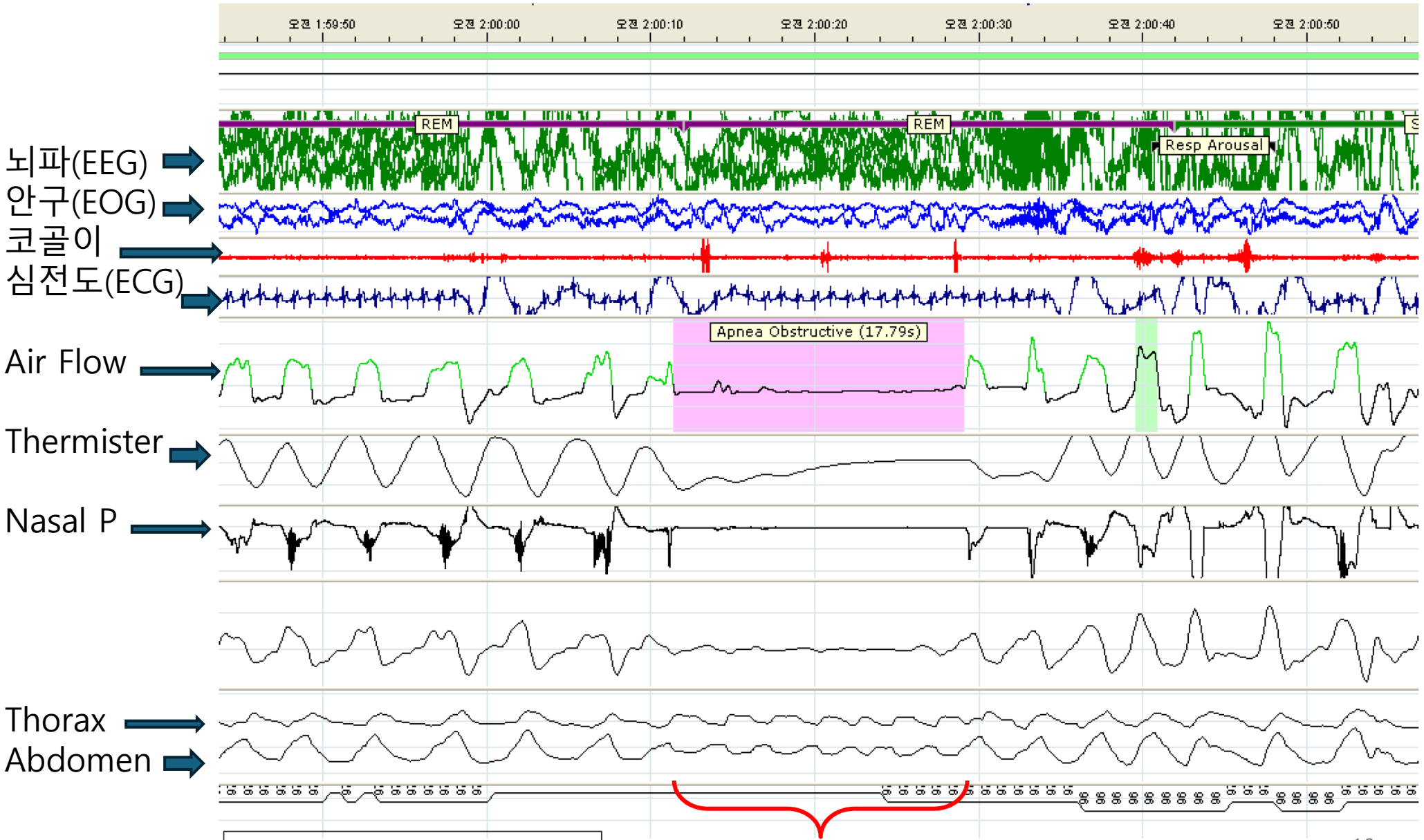
saturation index)

l sleep time, under 90%)

Polysomnography (수면다원검사)



수면다원검사(Polysomnography)



수면무호흡증의 중증도 분류

* **무호흡-저호흡지수(Apnea-hypopnea index, AHI)**

1시간동안 발생하는 무호흡 + 저호흡

경증(mild) : 5 이상 15미만
중등도(moderate) : 15이상 30미만
중증(severe) : 30이상

RDI(Respiratory disturbance index) : AHI + RERA index.
ODI (Oxygen desaturation index) : 산소포화도가 떨어진 횟수
T90, TST90, TSao90 (total sleep time, under 90%) (시간)

Azarbazin et al, EHR, 2019

Q1-2 양압기 급여대상자 및 진단기준은?

○ (급여대상자) 수면무호흡(G47.3), 신생아의 원발성 수면무호흡(P28.3), 신생아의 기타 무호흡(P28.4)의 상병으로 아래 진단기준에 해당되어 양압기가 필요하다고 전문의로부터 진단받아 공단에 신청하여 등록된 자가 해당 됩니다.

○ (진단 기준) 다음의 어느 하나에 해당하는 경우입니다.

- (일반) 제Ⅰ형 수면다원검사(Level Ⅰ) 결과 무호흡·저호흡 지수(AHI, Apnea Hypopnea Index)가 15 이상이거나
  - 또는 10 이상이면서 다음의 어느 하나에 해당 할 것
    1) 불면증, 2) 주간졸음, 3) 인지기능 감소, 4) 기분장애
  - 또는 5 이상이면서 다음의 어느 하나에 해당 할 것
    1) 고혈압, 2) 빈혈성 심장질환, 3) 뇌졸중 기왕력, 4) 산소포화도가 85% 미만

OSA & Cardiovascular disease

- **Hypertension**
  - **30-50%** have comorbid OSA
  - Resistant hypertension → **80%** may have OSA
  - CPAP adherence → Nocturnal BP reduction

- **Atrial fibrillation**
  - OSA(Independent risk factor) : Hypoxia & hypercapnia → intrathoracic pressure change
    → sympathetic tone increasing → autonomic dysregulation
    → Atrial remodeling, atrial fibrosis
  - CPAP → improved A.fib burden

- **Pulmonary HTN**
  - OSA prevalence 70-80%
  - Hypoxia induced pulmonary arteriolar vasoconstriction
  - PAP 25~30mmHg (35 이상은 다른 질환이 대부분 동반)

J Am Heart Assoc. 2019;8:e010440
JAMA. 2013;310:2407–2415
Am J Respir Crit Care Med. 2006

OSA & Cardiovascular disease

- **Coronary artery disease**
  - Repetitive hypoxemia & reoxygenation → oxidative stress
  - Coronary artery calcification, Plaque instability, Plaque vulnerability → CV event & death 2배

- **Cerebrovascular disease**
  - Independent risk factor incident Stroke / Stroke recurrence
  - **CPAP tiral after stroke → recovery & secondary prevention (no high level)**

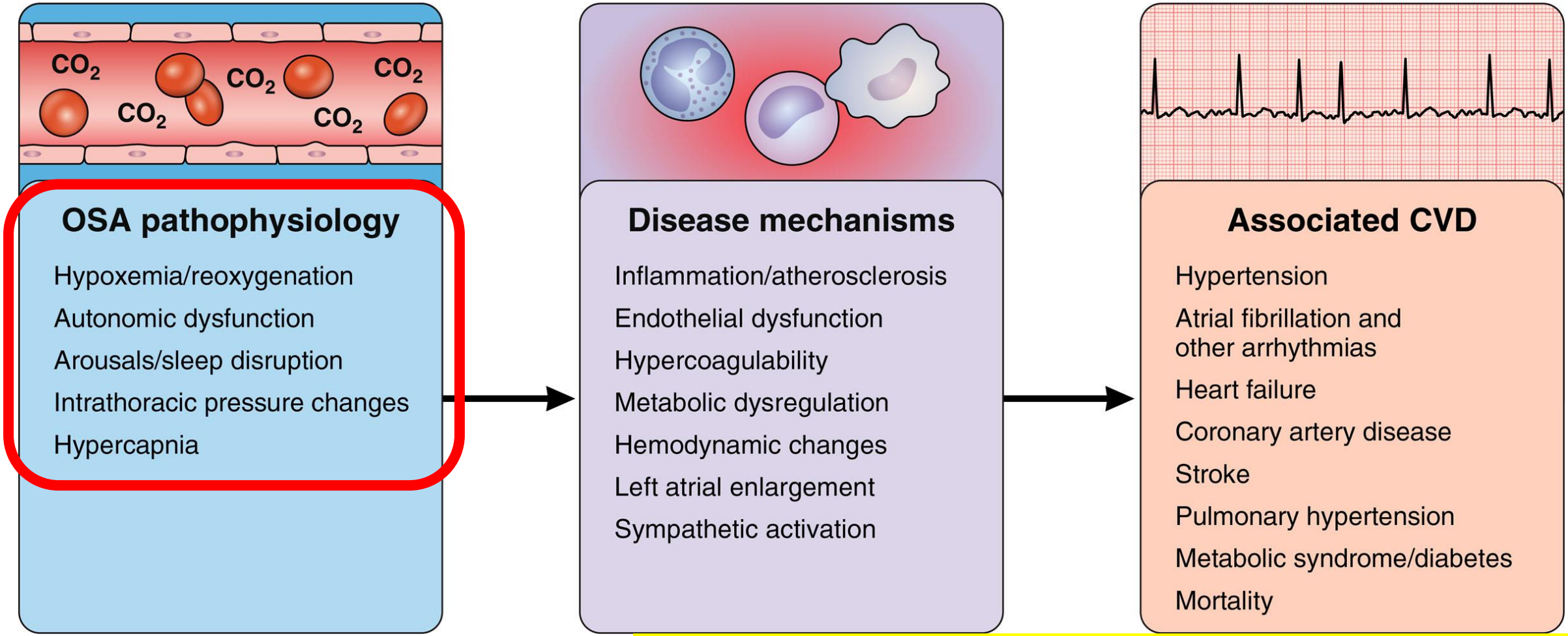
- **Heart failure**
  - Symtomatic HF → 40-60% Sleep-disordered breathing
  - **Central sleep apnea dominant (70%)**
  - CPAP → No significant effects on either LV EF & hospitalization

Clin Sleep Med. 2011;7:616–621.

Am J Respir Crit Care Med. 2016;194:613–620.

Eur J Heart Fail. 2007;9:251–257
J Am Heart Assoc. 2018
J Clin Sleep Med. 2019;15:301–334

OSA & Cardiovascular disease



MACE (Major adverse cardiovascular event)

Yerem et al, Circulation, 2021

What is Ideal metrics?

Ideal Metrics(Biomarker)	Comment
Sensitive for disease	Screening test, Diagnostic utility
Specific for disease	Few false positives avoid unnecessary PSG
Dose responsive, correlates with disease severity	Could quantify disease burden, Prioritize therapy
Treatment responsive	Use as a metric for adequacy of therapy or adherence to CPAP
Involvement in important causal pathway	Reliable surrogate outcome measure, predicting disease complications
Easily measured	Would not require major expertise to assess
Inexpensive	Allow high throughput in clinic or research
Panel of metrics	Assess multiple pathway, e.g. inflammation, oxidative stress, autonomic

Sleep to sleep variation

SB montesi et al, CHEST, 2012 Jul;142(1):239-245

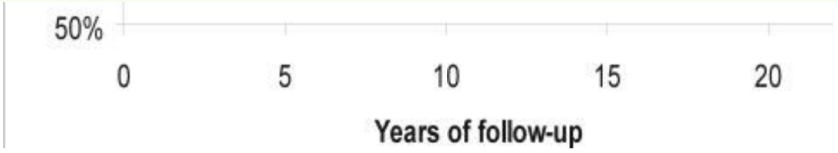
OSA(AHI) → Cardiovascular disease

A.

B.

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

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



A: Mortality

B: CPAP 치료환자는 제외

- Wisconsin cohort
- 1,522 patients → 18yrs f/u
- AHI correlation
- Severe OSA!

SLEEP. 2008 Aug 1;31(8):1071–1078.

AHI & Cardiovascular disease

- Sleep Heart health study
- Prosepctive corhort

- 1995-1998 in New York
- 40세 이상, 6,441 patients

- 6,294 patient
  (53.3% women)

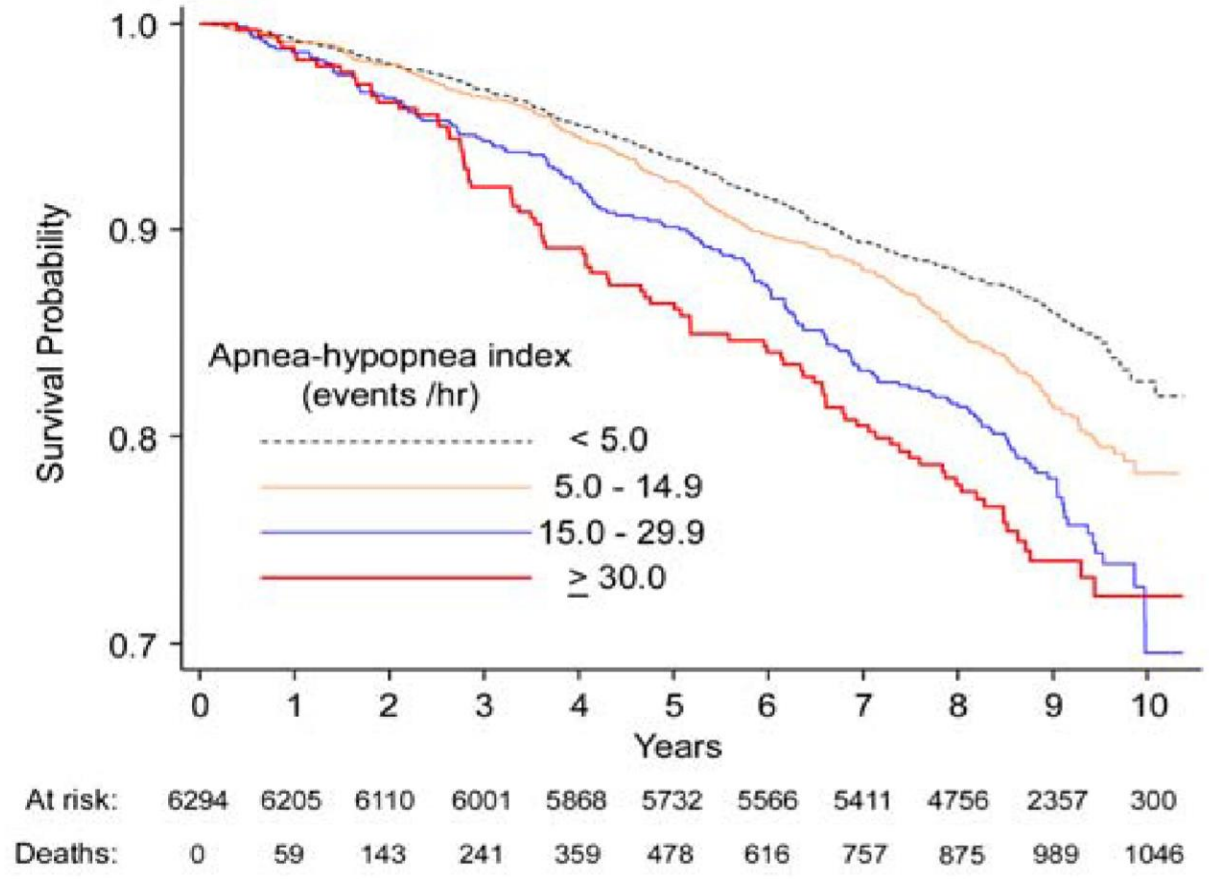
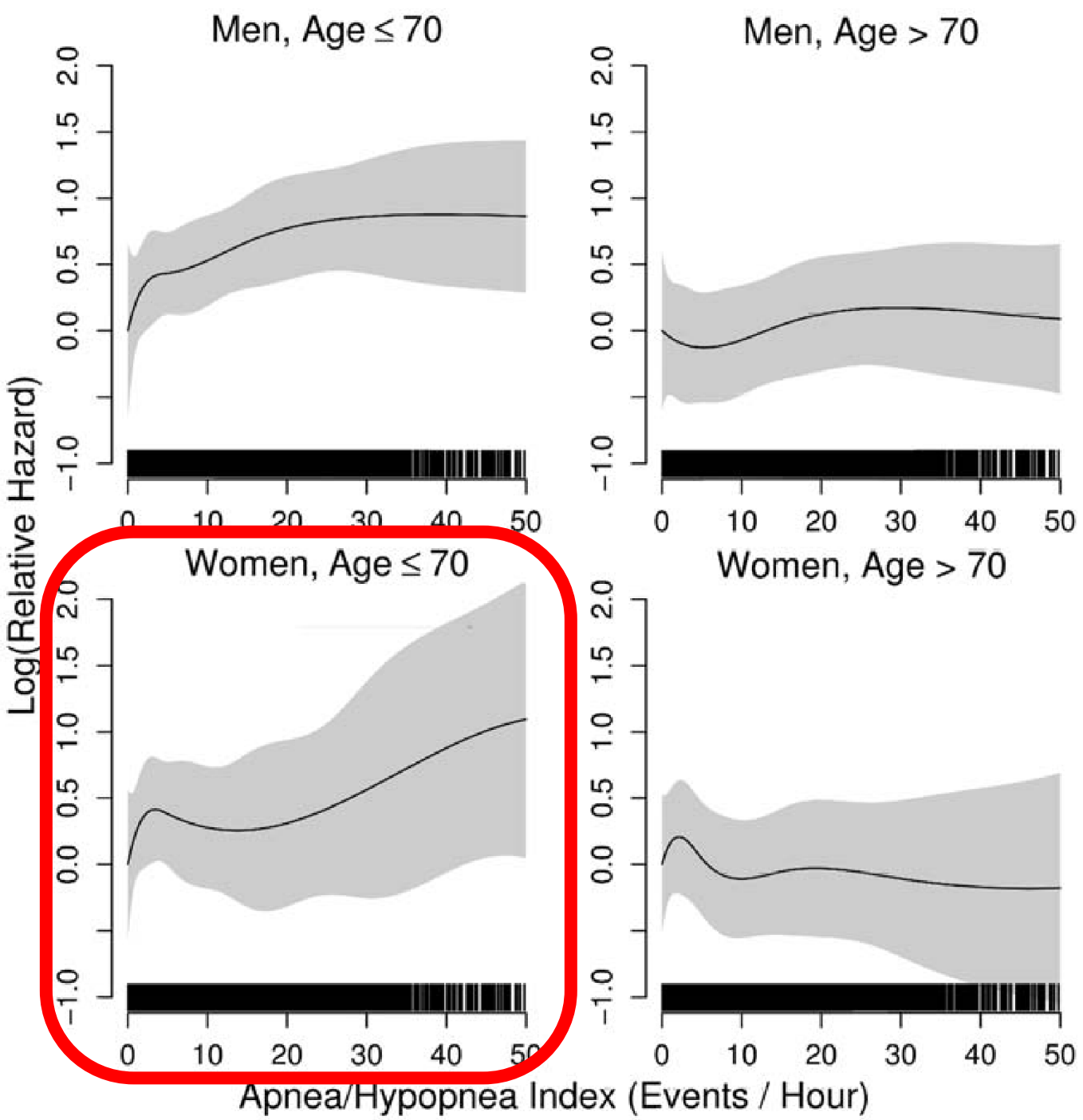


Figure 1. Kaplan-Meier survival curves across categories of the apnea–hypopnea index (AHI).

Naresh et al, PloS Med, 2009



In Old age group

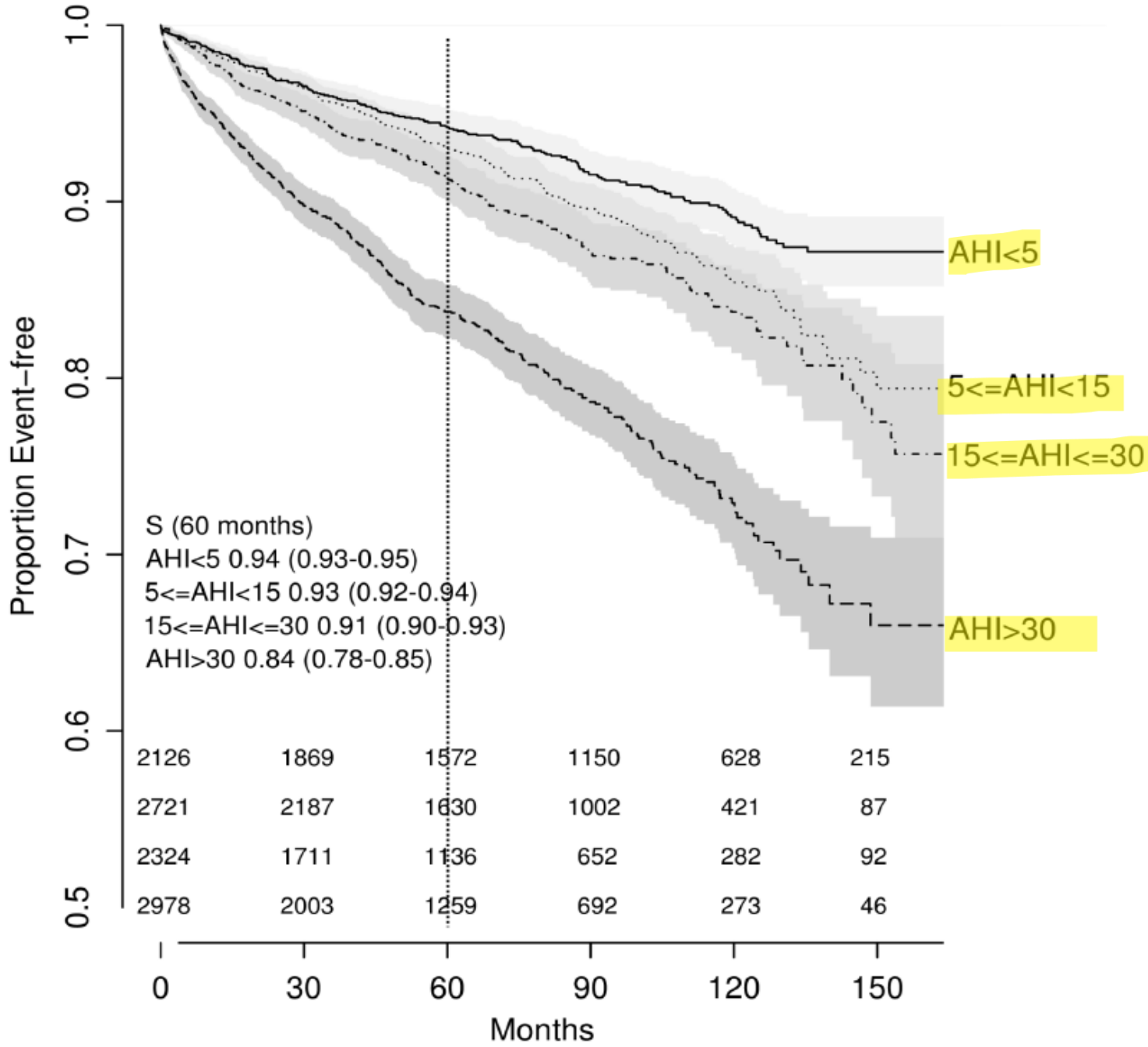
AHI → No correlation with comorbidity

Naresh et al, PloS Med, 2009

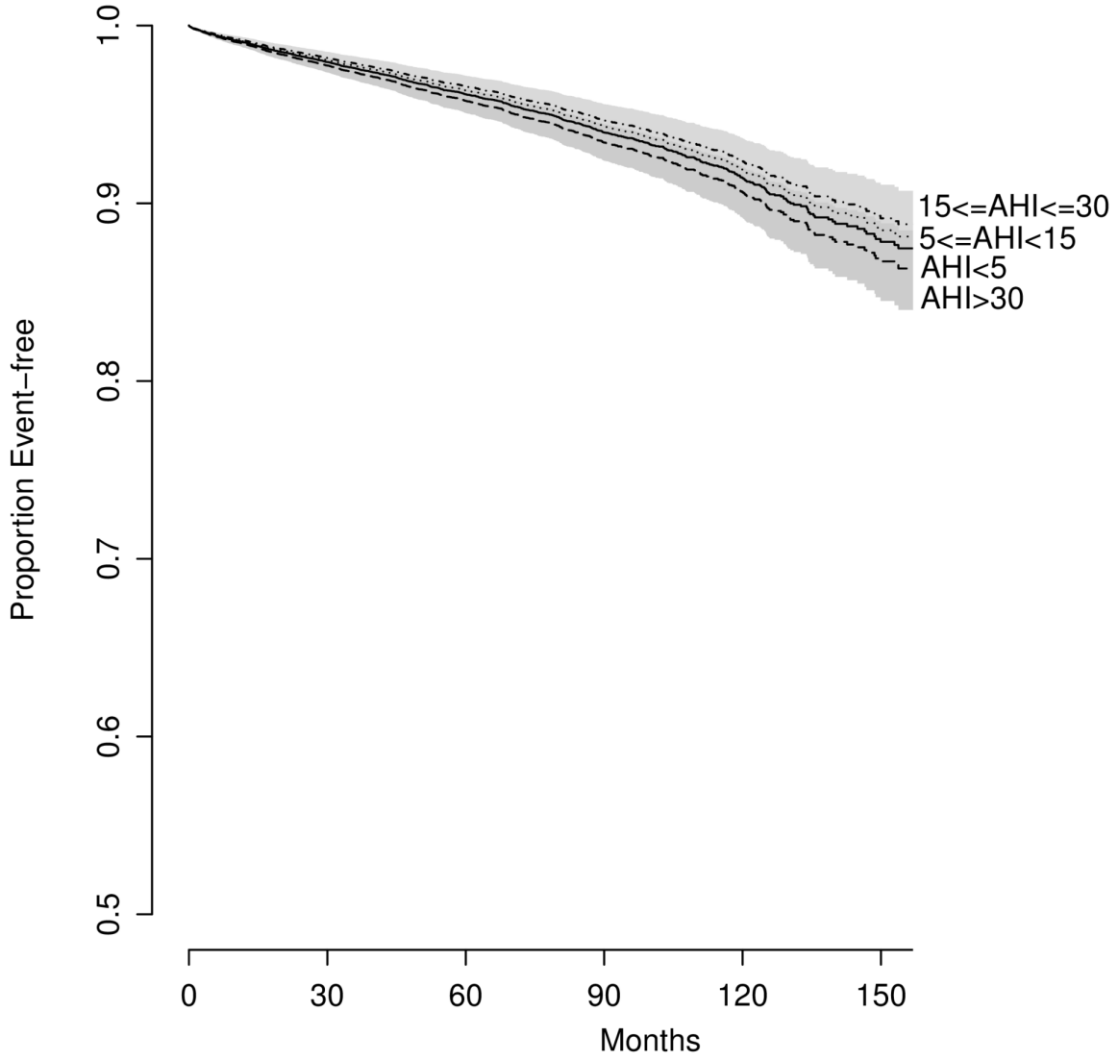
OSA and Cardiovascular disease

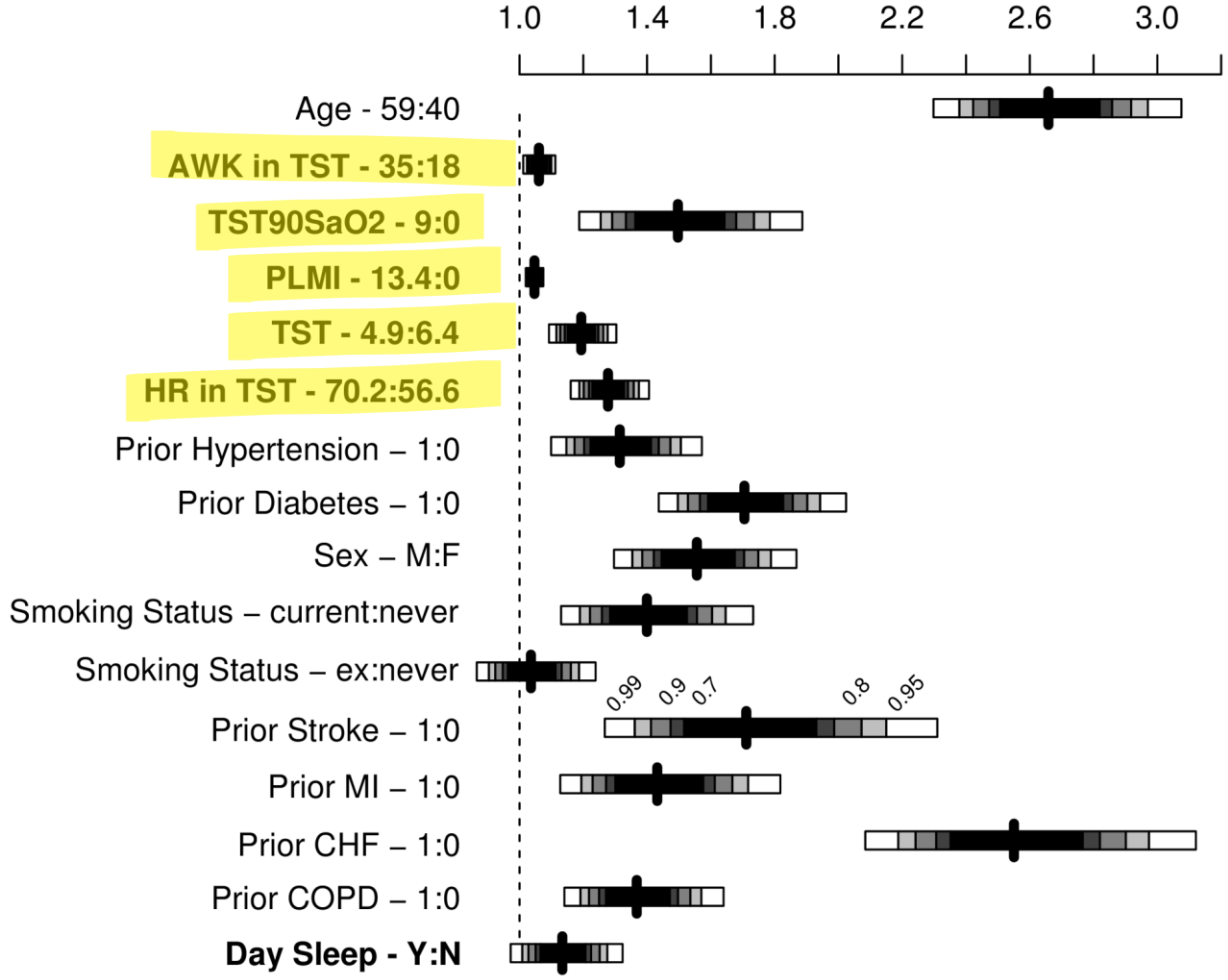
- Canada
- 1990-2010

- Myocardial infarction, Stroke, Heart failure, resvascularization procedure, Any cause of deah



Tetyana et al, PLoS Med. 2014 Feb 4;11(2)



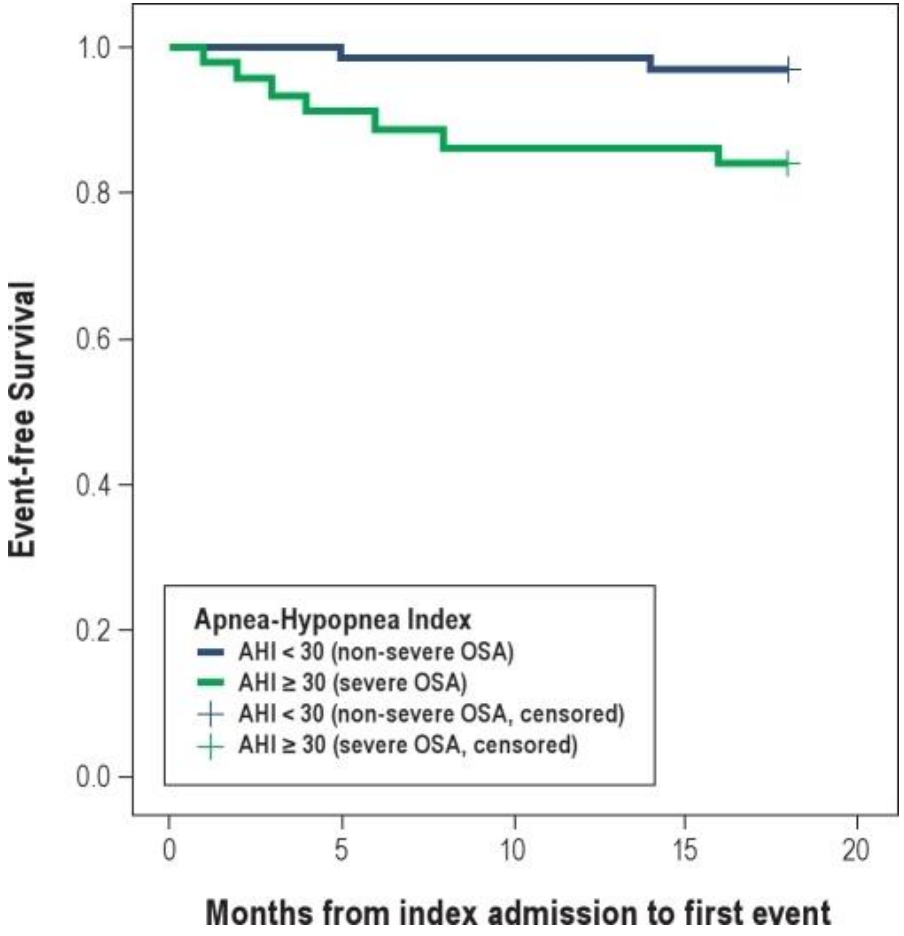


Fully adjusted model

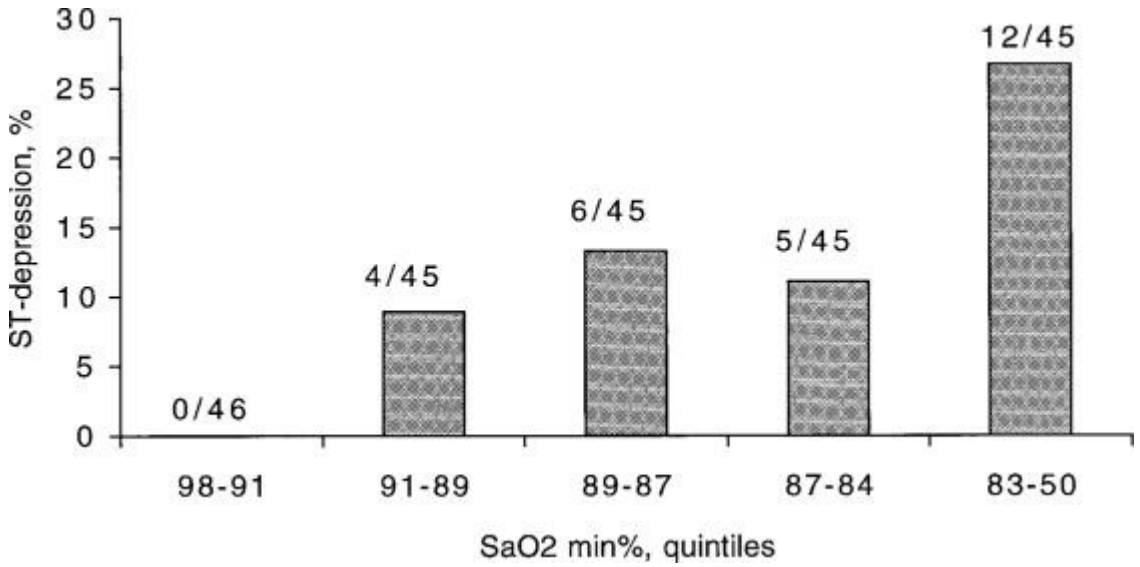
Multivariable Cox regression model

Tetyana et al, PLoS Med. 2014 Feb 4;11(2)

OSA & Myocardial infarction?



AHI > 30, ST-Elevation MI



Lowest SpO2 → (ST-Depression MI)

Chest . 2000;Jun;117(6)
J Clin Sleep Med. 2011;7:616–621

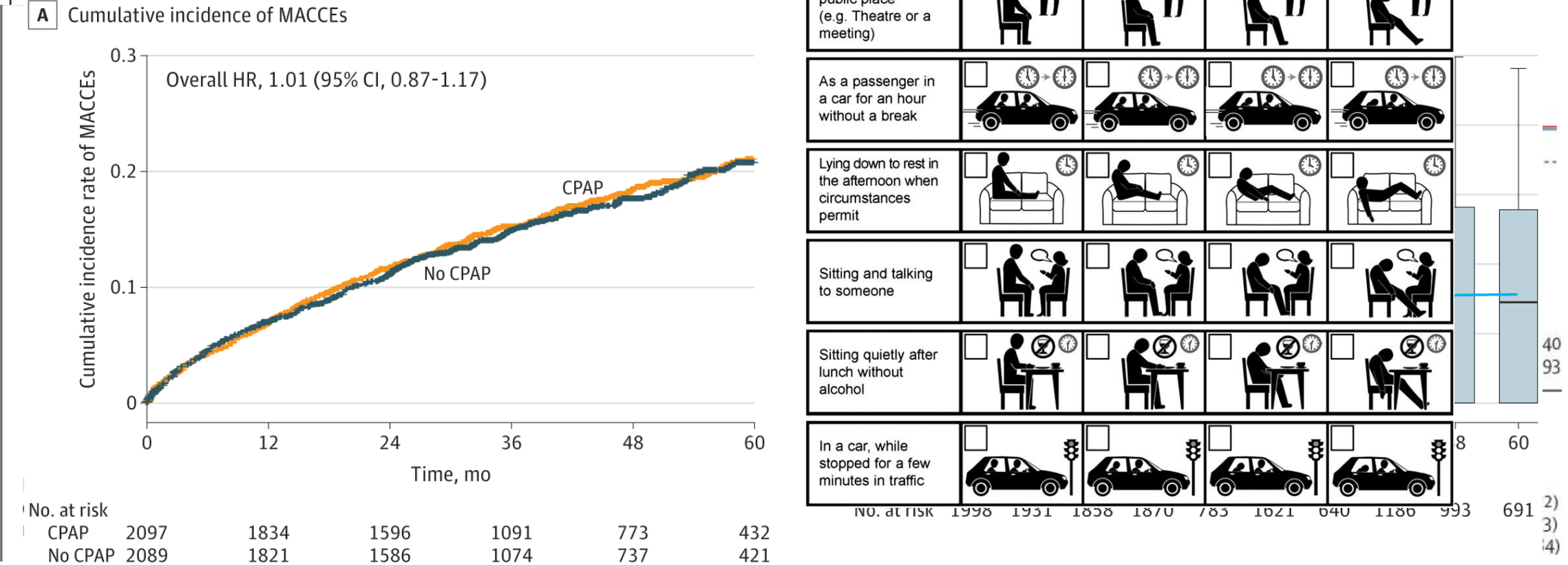
Trial (Ref. #)	Patient Group	OSA Diagnosis	Intervention (n)	Follo M	Daytime Sleepiness at Baseline
SAVE (135)	Prevalent CVD	ODI >12/h	CPAP vs control (1,346/1,341)	43 m	ESS <15 Severe sleepiness excluded
RICCADSA (136)	Revascularized CVD	AHI >15/h	CPAP vs control (122/122)	57 m	ESS <10 Nonsleepy
ISAAC (137)	Acute coronary syndrome	AHI >15/h	CPAP vs control (631/631)	40 m	ESS <10 Nonsleepy

Pictorial Epworth Sleepiness Scale

Name: _____ Date: ___/___/___ Hospital No: _____ Date of Birth: ___/___/___

In contrast to just feeling tired, how likely are you to doze off or fall asleep in the following situations? Even if you have not done some of these things recently, try to work out how they would affect you. **Use the following scale to choose the most appropriate number for each situation.**

Situation (✓ Please tick box)	0 No chance of dozing	1 Slight chance	2 Moderate chance	3 Definitely would doze
Sitting and reading				
Watching TV				
Sitting inactive in a public place (e.g. Theatre or a meeting)				
As a passenger in a car for an hour without a break				
Lying down to rest in the afternoon when circumstances permit				
Sitting and talking to someone				
Sitting quietly after lunch without alcohol				
In a car, while stopped for a few minutes in traffic				



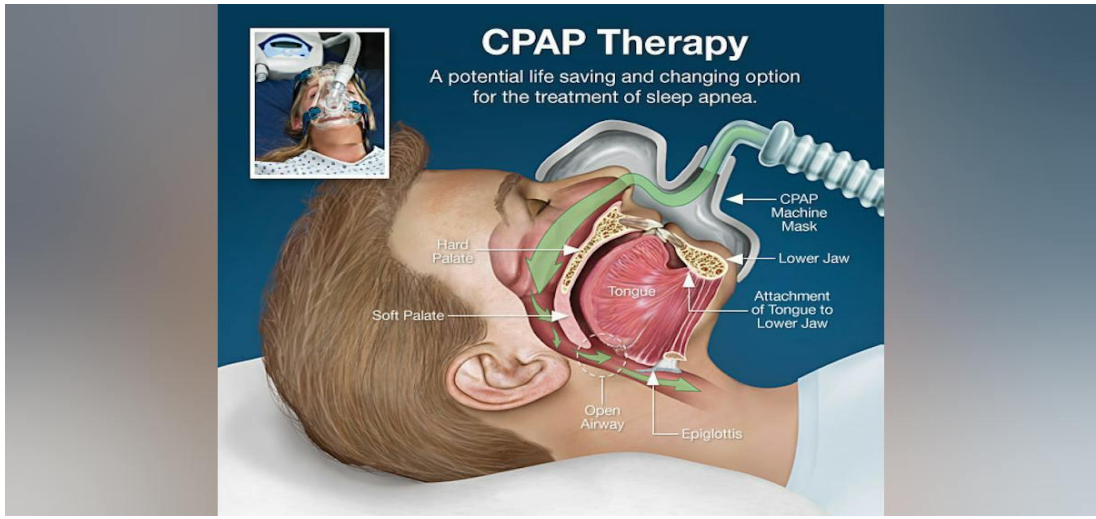
NEJM, 2016
Lancet 2020
AJRCCM 2016

Outcome	CPAP Group (N=1346)					Usual-Care Group (N=1341)					Adjusted Difference in Change from Baseline (95% CI)†	P Value
	Baseline		End of Study		Change from Baseline	Baseline		End of Study		Change from Baseline		
	no. of patients with data	*value*	*no. of patients with data*	*value*		*no. of patients with data*	*value*	*no. of patients with data*	*value*			
Blood pressure — mm Hg												
Systolic	1341	132±16	1166	132±16	0.7±17‡	1333	131±16	1158	132±16	1.5±17	−0.4 (−1.5 to 0.8)	0.55
Diastolic	1341	80±11	1166	79±16	−0.9±11	1333	79±11	1158	79±10	−0.1±11	−0.7 (−1.4 to 0.0)	0.05
Epworth Sleepiness Scale score	1346	7.3±3.6	1221	4.2±3.5	−3.1±4.1	1341	7.5±3.6	1188	6.8±4.4	−0.7±4.3	−2.5 (−2.8 to −2.2)	<0.001
Hospital Anxiety and Depression Scale												
Anxiety score	1341	4.6±3.7	1220	3.8±3.6	−0.8±3.6	1336	4.6±3.6	1190	4.2±3.6	−0.4±3.5	−0.4 (−0.6 to −0.2)	0.002
Depression score	1341	5.1±3.9	1220	4.3±3.6	−0.8±4.0	1336	5.2±3.9	1190	5.1±3.8	−0.1±3.8	−0.8 (−1.0 to −0.5)	<0.001
SF-36§												
Physical-component summary score	1335	45.4±7.7	1218	46.9±8.0	1.3±7.5	1332	45.1±7.8	1189	45.9±8.1	0.6±7.6	0.9 (0.3 to 1.4)	0.002
Mental-component summary score	1332	52.6±8.6	1218	53.6±8.0	1.0±8.9	1332	52.3±8.7	1189	52.4±8.8	0.0±8.9	1.2 (0.6 to 1.8)	<0.001
EQ-5D utility score¶	—	—	1252	0.8±0.3	—	—	—	1229	0.8±0.3	—	0.02 (0.00 to 0.05)	0.03

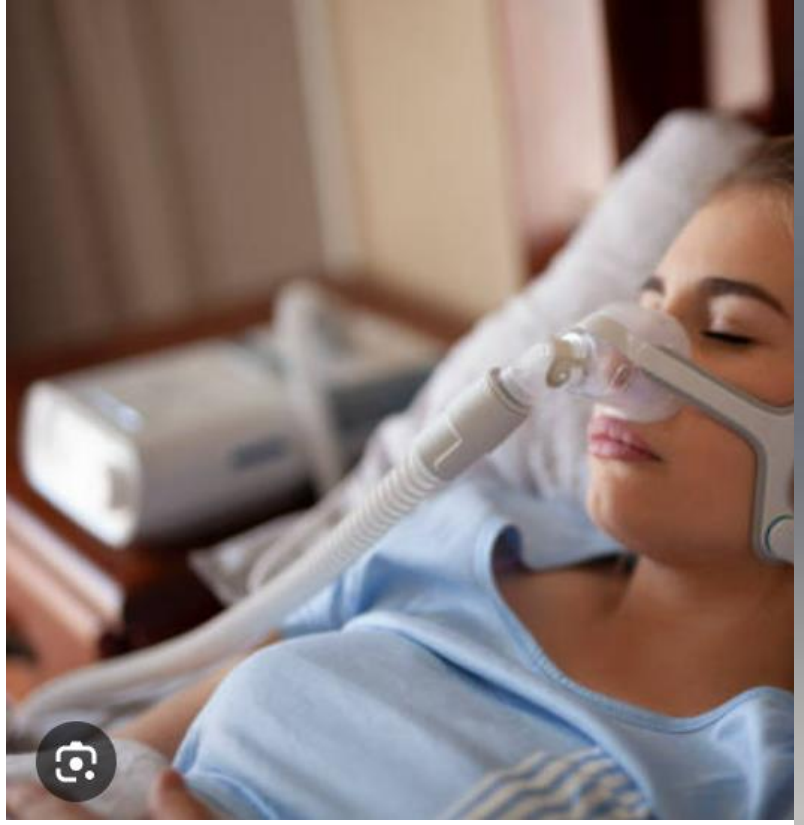
PAP therapy (positive airway pressure)

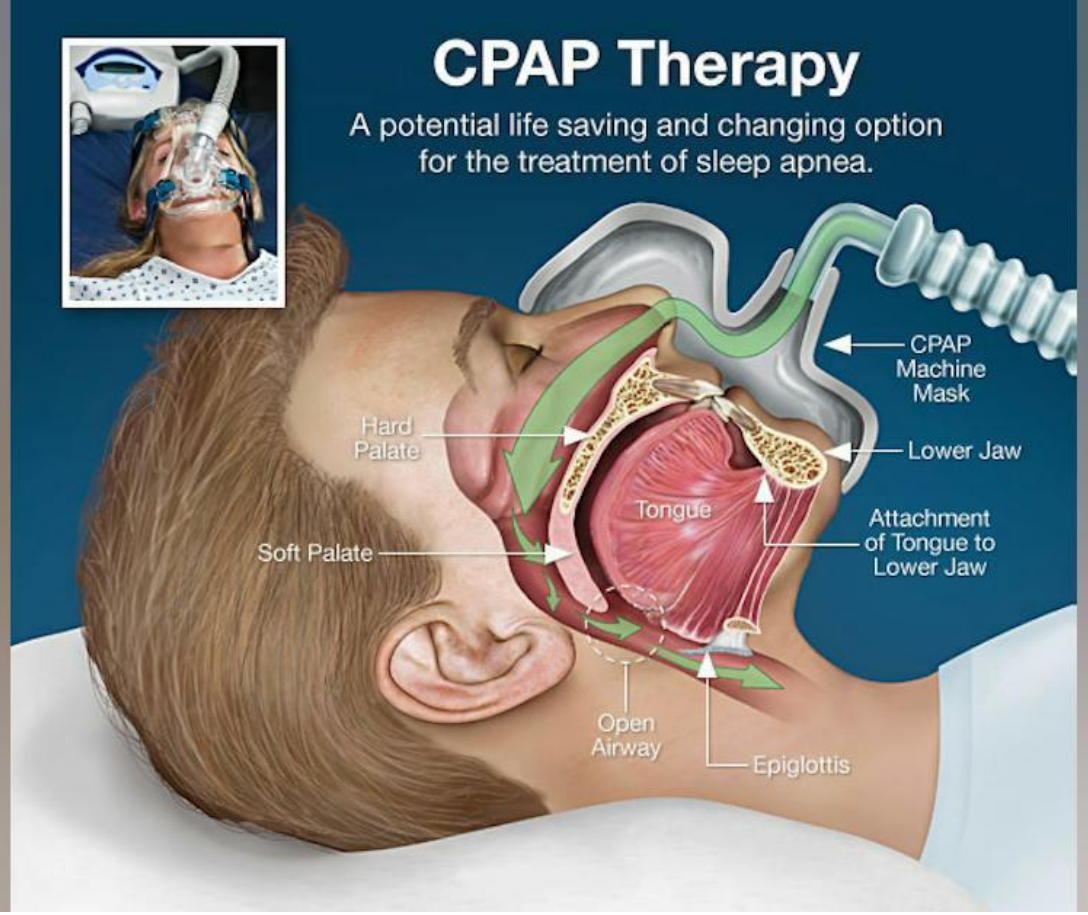
- High quality of evidence

Reduces frequency of respiratory events during sleep
Decrease daytime sleepiness
Improve systemic blood pressure
Lower the risk of traffic accidents
Improve quality of life



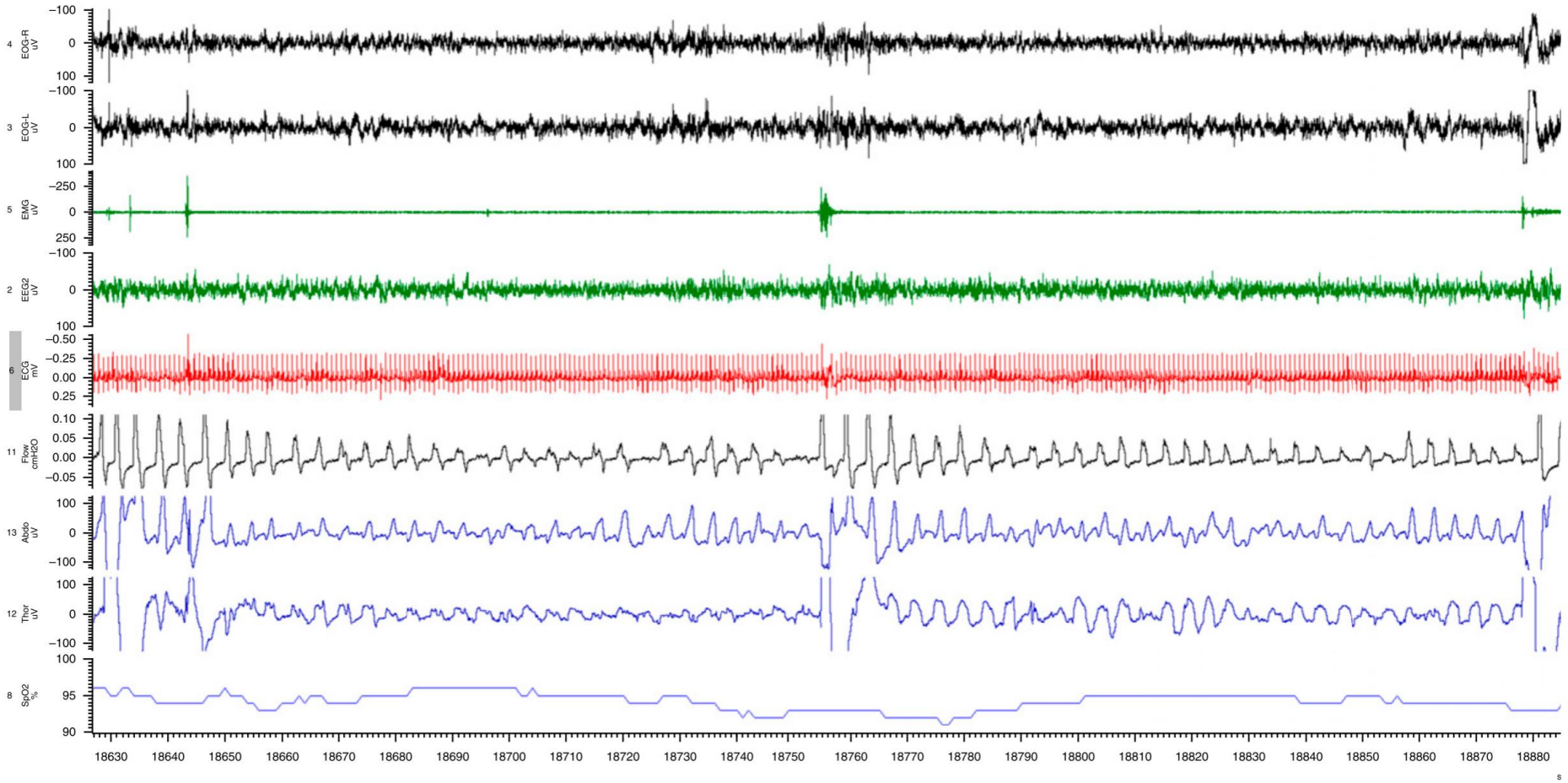
But) Unsuccessful → <u>primary or secondary cardiovascular outcomes!</u>

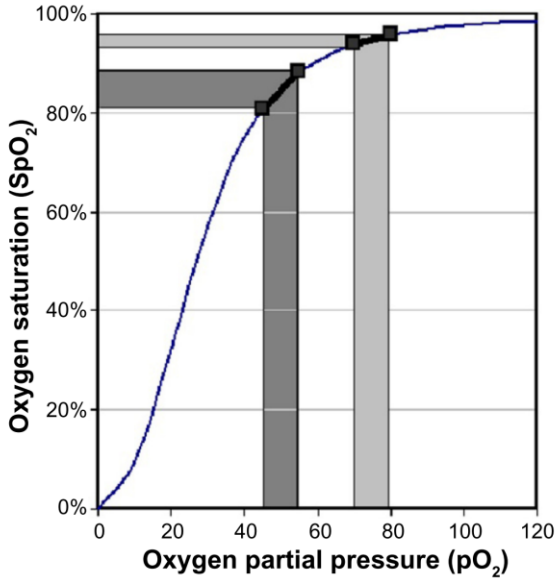




Positive airway pressure therapy (PAP therapy)
: **Adherence 40~60%**

AHI & ODI is enough?





- Cardiovascular event ← Chronic intermittent hypoxia = AHI ??
- Under estimation?(prolonged hypoventilation), (Supplemental oxygen?)
  Over estimation? (hypopnea), Alpha intrusion?

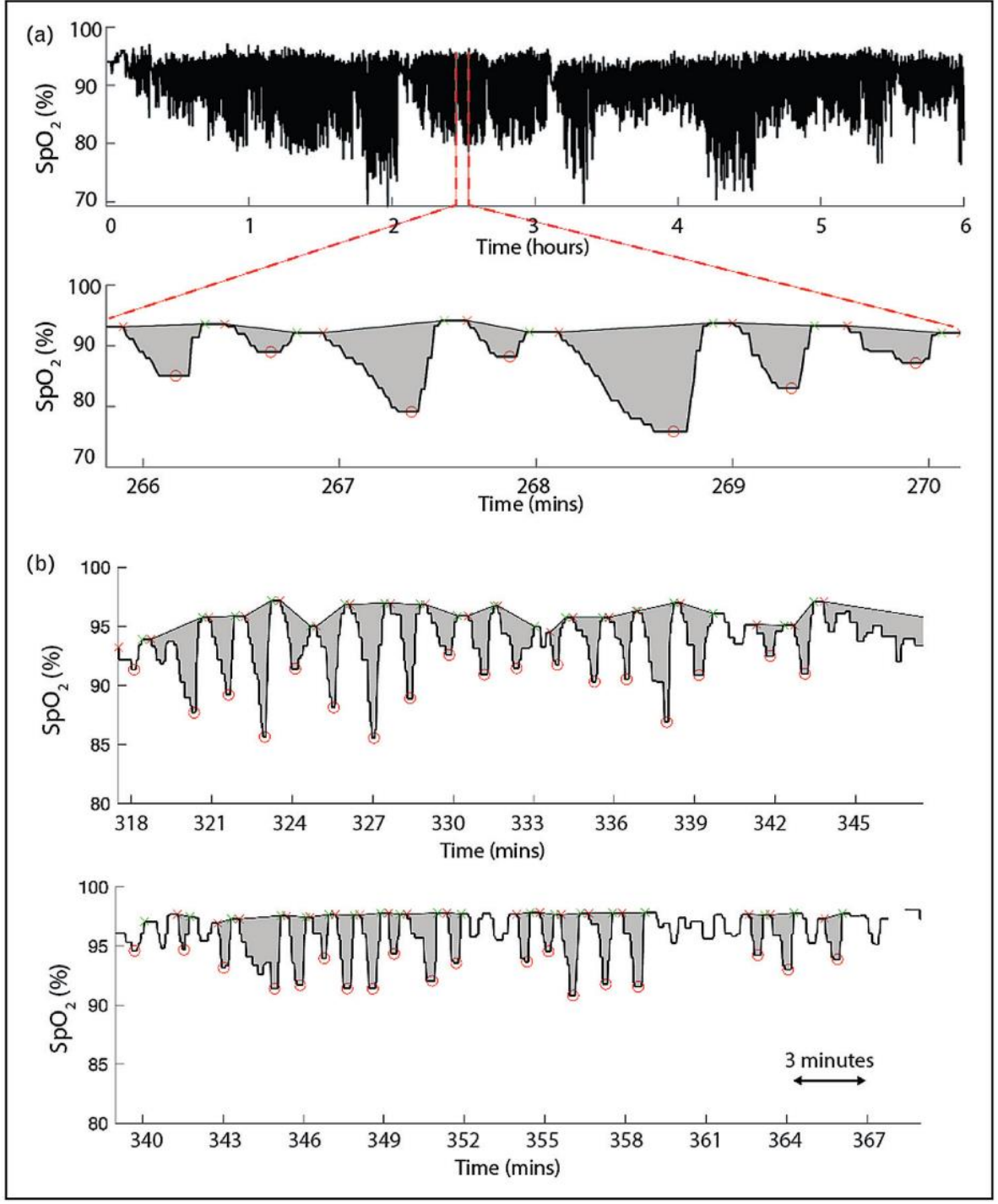
AHI is not enough

- AHI : Anthropometric / Demograp
  Underlying disease

  Severity of individual respirato
  (duration & depth) & Sleep fra

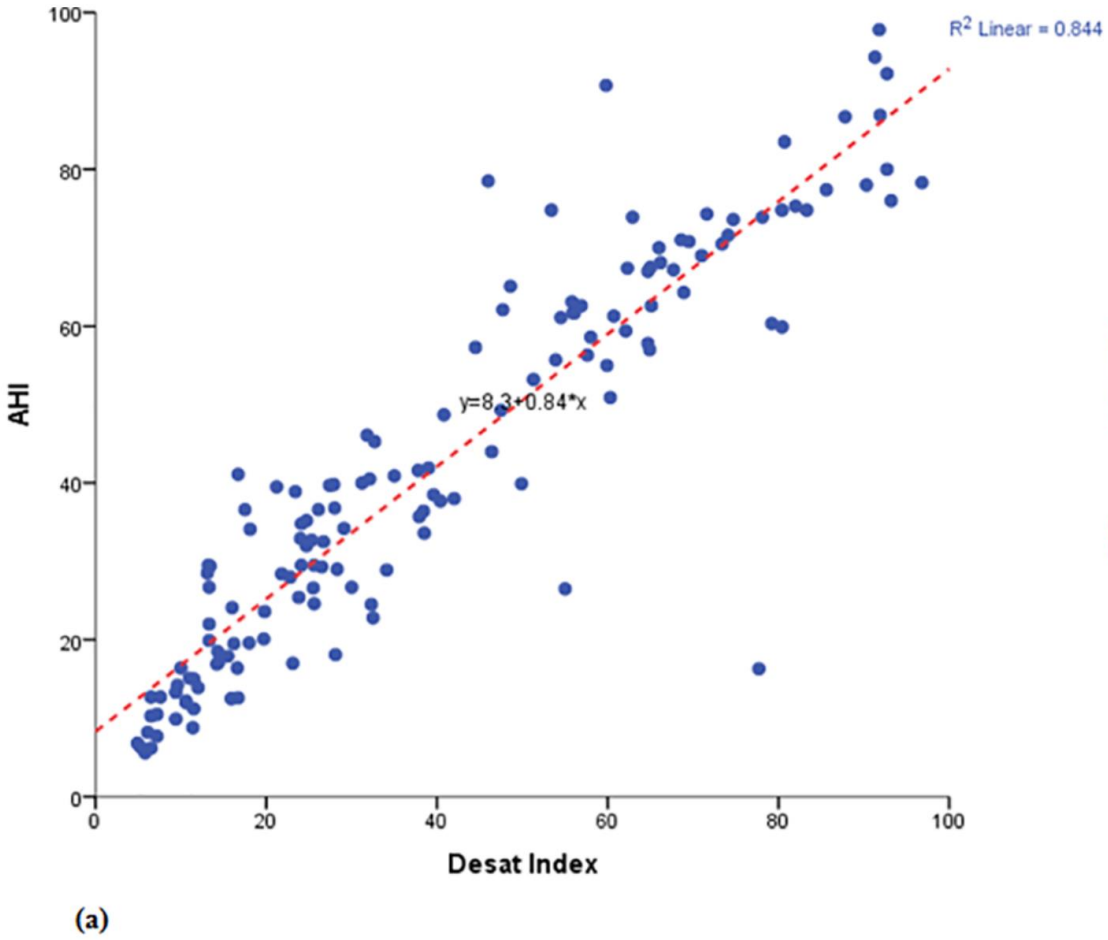
- **Longer & Deeper respiratory eve**
  → Larger acute cardiovascular res
  (Surges in Heart rate & Blood p

  → Longer & deeper oxygen desa



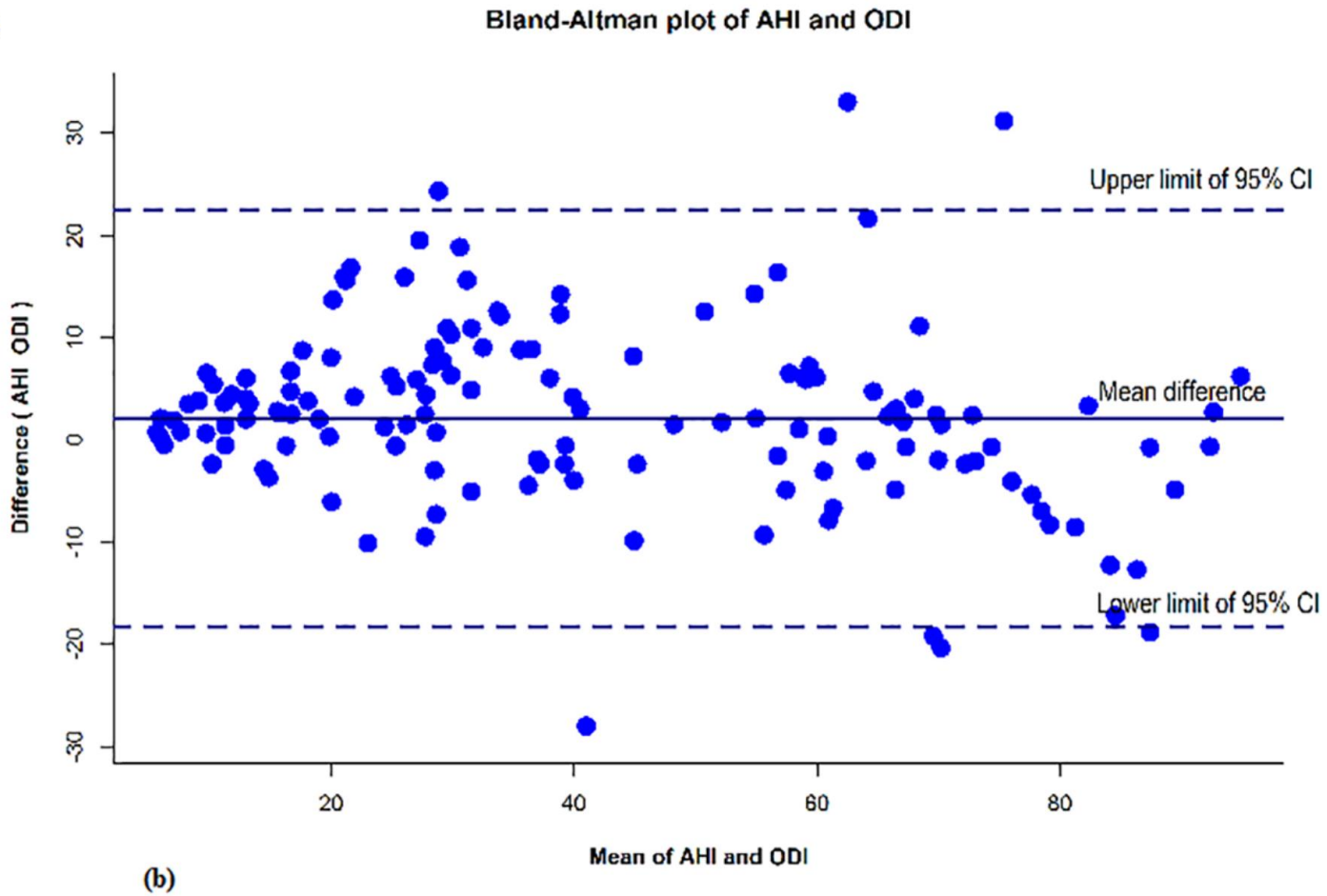
Oxygen desaturation index (ODI)

a) Room air



(a)

b)



(b)

Time, Depth 반영이 안된다

T90: Time spent with SpO2 <90

Table 4. Association Between SA and Other Sleep Measures and Carotid Intima-Media Thickness

	Model 1: β±SE	*P* Value	Model 2: β±SE	*P* Value	Model 3: β±SE	*P* Value
SA (AHI ≥15 events/h)	0.011±0.010	0.264	−0.002±0.010	0.807	−0.005±0.010	0.642
Arousal index (events/h)	0.0004±0.0004	0.332	0.0001±0.0004	0.793	0.00004±0.0004	0.918
Sleep maintenance efficiency, %	−0.0003±0.0004	0.361	−0.00008±0.0004	0.835	0.000004±0.0004	0.992
≥0.64% sleep time with Sp_{0_2} <90%, %	0.021±0.009	0.018	0.009±0.009	0.346	0.007±0.010	0.444
Total sleep duration, min	−0.00004±0.0001	0.478	0.00000±0.0001	0.997	0.000005±0.0001	0.923
Slow-wave sleep, (N3) %	−0.0007±0.0005	0.197	−0.0005±0.0005	0.340	−0.0006±0.0005	0.279

Model 1: adjusted for demographic factors (continuous age, race/ethnicity, and sex). Model 2: additionally adjusted for pack-years smoked and body mass index. Model 3: additionally adjusted for alcohol use, the presence of hypertension and diabetes mellitus, serum total cholesterol, serum triglyceride level, and HMG-CoA reductase (statin) use. AHI indicates apnea-hypopnea index; SA, sleep apnea; and Sp_{0_2}, oxygen saturation.

Depth 반영이 안된다

Ying et al, Stroke, 2019

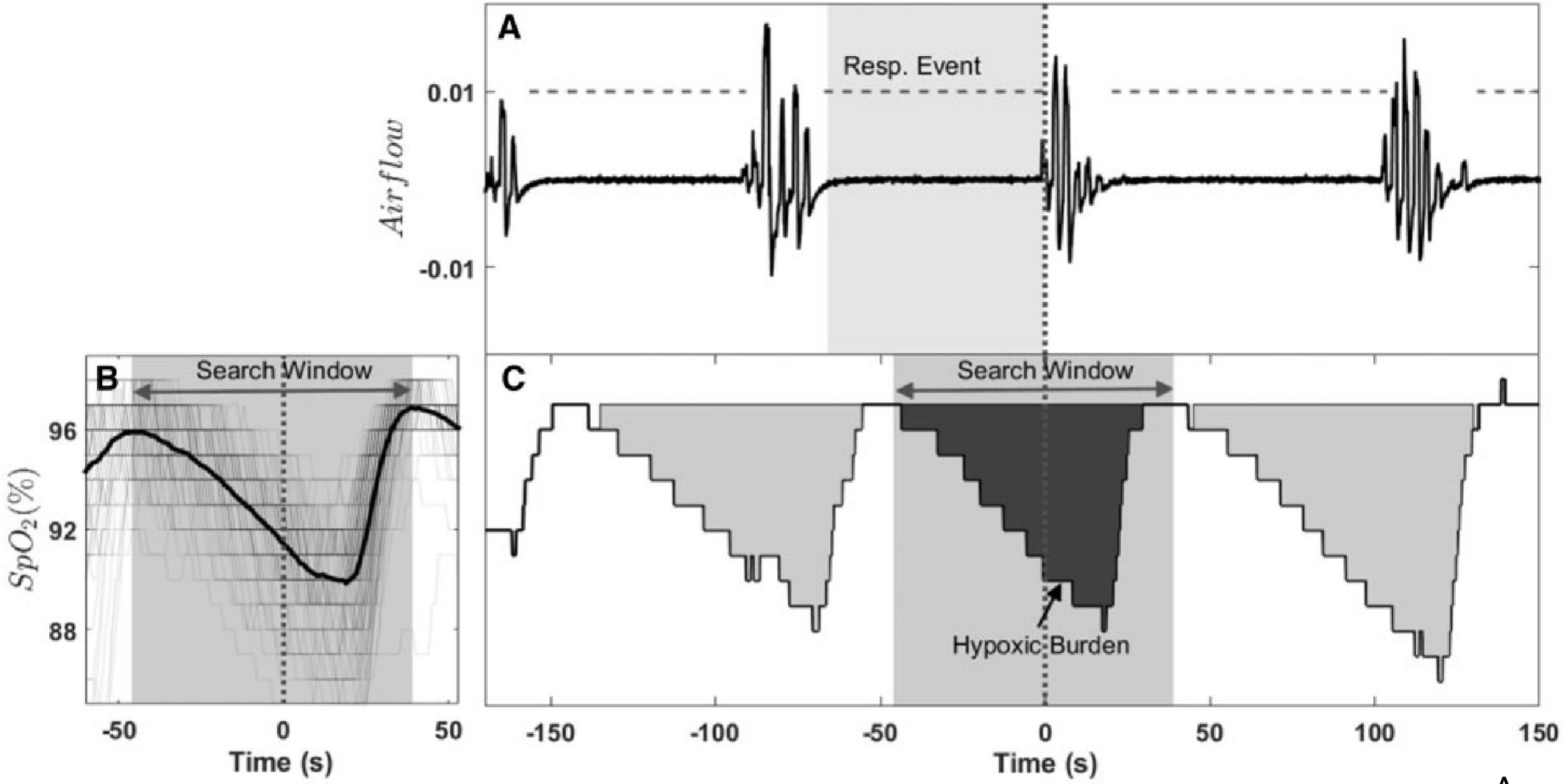
Table 1 Polysomnographic Metrics of Measuring Severity of OSA

Classification	Metrics	Pathophysiological Backgrounds	Complications Associated with OSA
Conventional and widely used	AHI	intermittent hypoxia	EDS,[13,14] CVD and all-cause mortality,[15] hypertension[16]
	ODI, T90, LSpO2		subclinical atherosclerosis,[25] all-cause mortality in HF,[26] postoperative complications[27–29]
	SIT		hypoxemia in sleep disorders[34]
Novel and promising	Hypoxic burden	intermittent hypoxia	CVD mortality,[15] BP,[35] and risk of incident HF[36]
	Obstruction severity		CVD and all-cause mortality[42]
	hypoxia load		CVD risk,[44] BP[45]
Emerging and potential	ApEn of oxygen saturation	indirect metric, mainly quantification of data regularity	Hypoxemia,[48,49] Associated with AHI[60]
	flow:drive ratio	pharyngeal obstruction	
	CPC, HRV, ORP	sympathetic activation, arousability	effect of CPAP titration,[54,58] CVD risk[52,57]
	Expiratory time constant	product of airway resistance and lung compliance	severe sleep apnea[61]

Wenhao et al, Nature and Sciece of sleep, 2020

Hypoxic burden

- **<u>Area under the oxygen desaturation curve</u>** from a pre-event baseline saturation. (%mintue) / per hour of sleep)



Azarbazin et al, EHR, 2019

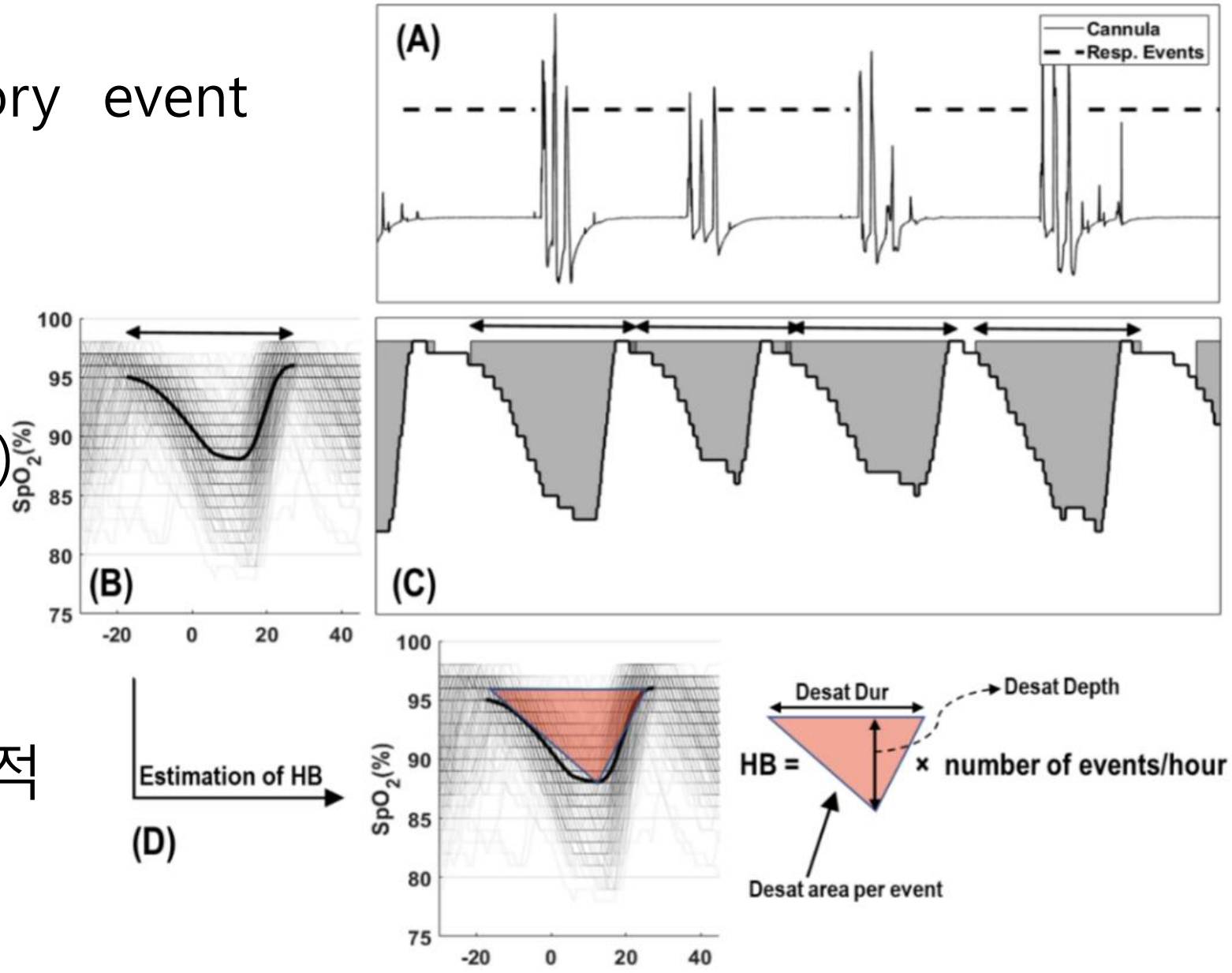
(A) HB : based on Respiratory event

(B) Subject-specific
search window

Peak SpO2 (Event 전/후)

(C) Summation

(D) Event 깊이, 지속시간,면적



Azarbine et al, 2023, Animed

Example) Hypoxic burden (algorithm)

- 한시간에 20번의 Event

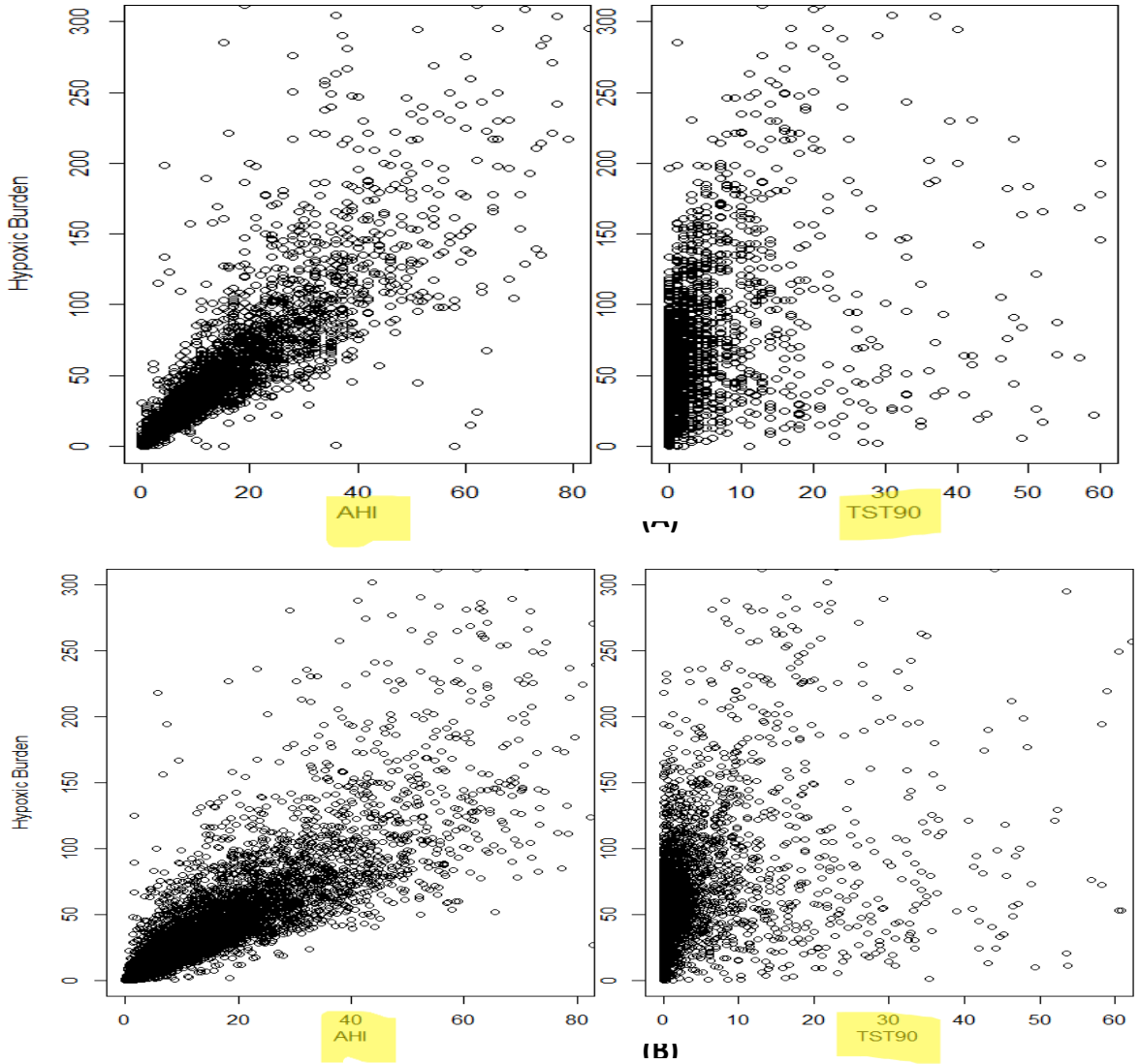
- 평균적으로 SpO2 8% 만큼 30초간 감소

→½ x 0.5 x 8 = 2%분

시간당 20번의 이벤트 → HB = 2 x 20 = 40%min/hour

SpO2 로 확인하는 지표 → Useful in Home sleep test!

Hypoxic burden / Traditional metrics correlation



Home sleep apnea test

Figure S3: Scatter plots of hypoxic burden (HB) versus apnea-hypopnea index (AHI) and the sleep time below 90% oxygen saturation (TST90) f or MrOS study (panel A) and SHHS study (panel B). The association between hypoxic burden and AHI weakens as AHI increases. Also, the hyp oxic burden and TST90 are poorly correlated in both studies.

Azarbazin et al, EHR, 2019

삼성전자, 갤럭시 워치 '수면 승인 획득

2025/06/06

삼성전자가 갤럭시 워치 시리즈를 활용해 개발한 '수면 무호흡 기능(SI

갤럭시 워치 수면무호흡 삼성전자 제공 [뉴스락]

만, 미국
못해 증상

미한다.
내는 인

필수적으로

혈액 내
관 질환

애플, 韓 홀대 여전… '수면 무호흡증' 기능 식약처 허가 신청도 안해

아주경제 원문 | 기사전송 2024-11-14 17:01 최종수정 2024-11-14 18:17

AI챗으로 요약

0 0

늦장 AI에 이어 헬스케어 기능 탑재 허가도 불투명

애플워치. [사진=애플]

애플이 애플워치 시리즈 10에 탑재한 수면 무호흡증 감지 기능과 관련해 국내 허가를 위한 절차조차 밟지 않은 것으로 파악됐다. 애플이 지난 9월 아이폰16 시리즈 출시를

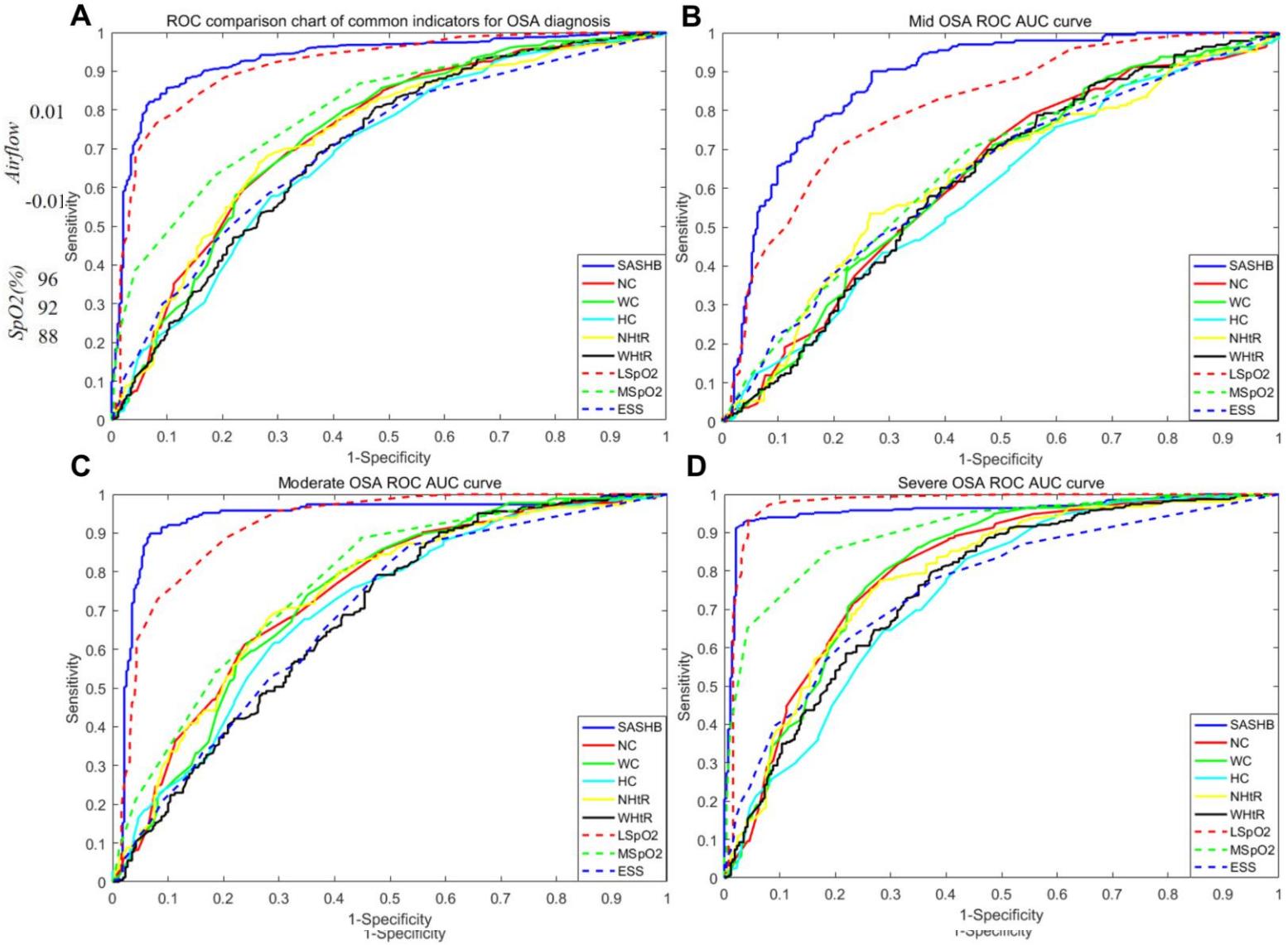
Hypoxic burden → OSA predictive models

- Shanghai 2019-2020
- 2,303 patients

- Test (n=1,200)
  Validation (n=1,103)

- Sensitivity/Specificity
  75.7% / 90.1%

- Mild OSA (AUC 0.878)
  Moderate (AUC 0.938)
  Severe (AUC 0.959)



Hypoxic burden → CV risk prediction?

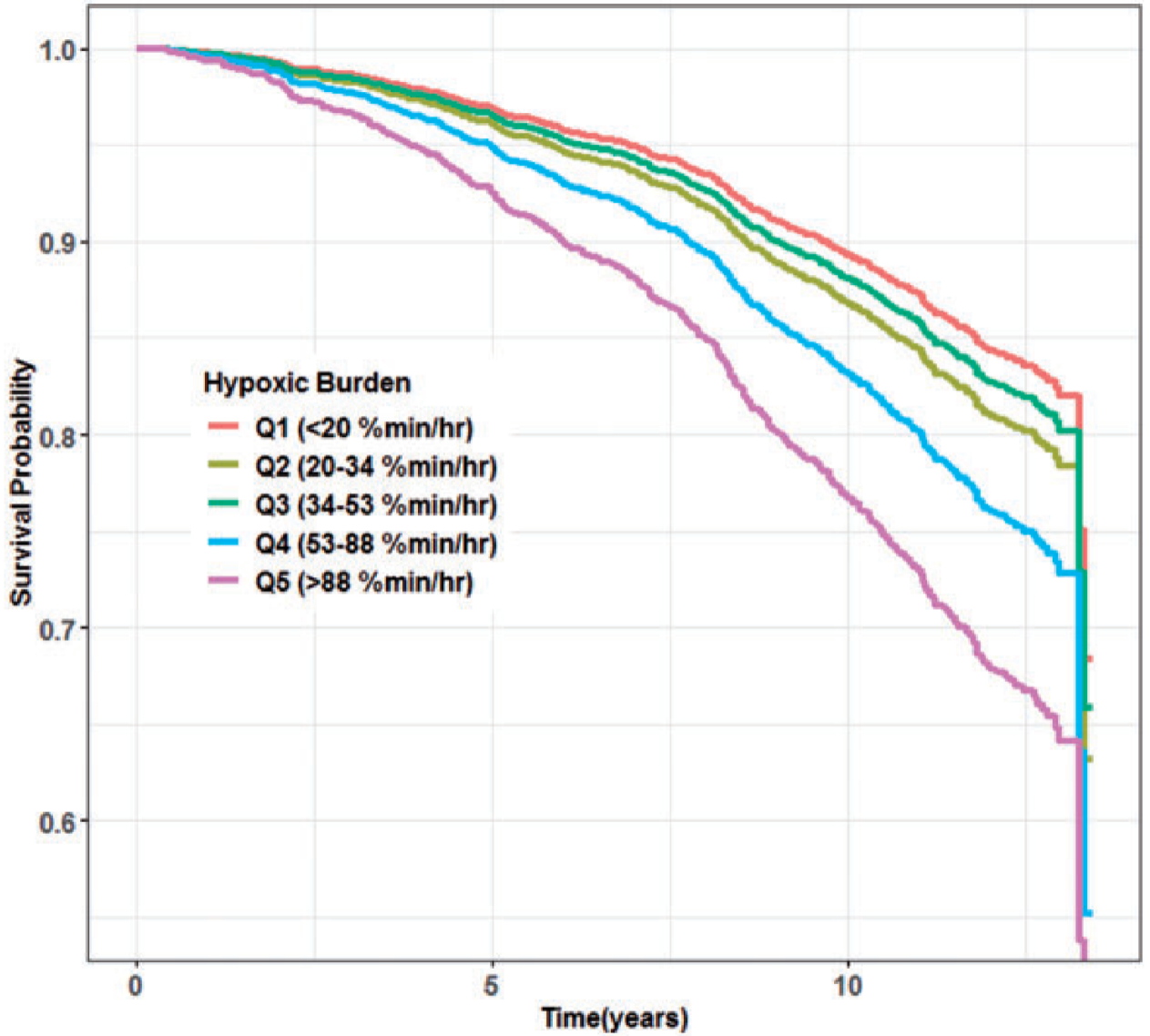
- Two cohort
  (1) MrOS sleep study
  (2) Sleep Heart Health Study

- (1) 2743 men
  (2) 5111(중년이상, 52.8% women)

- All-cause mortality
  CVD-related mortality

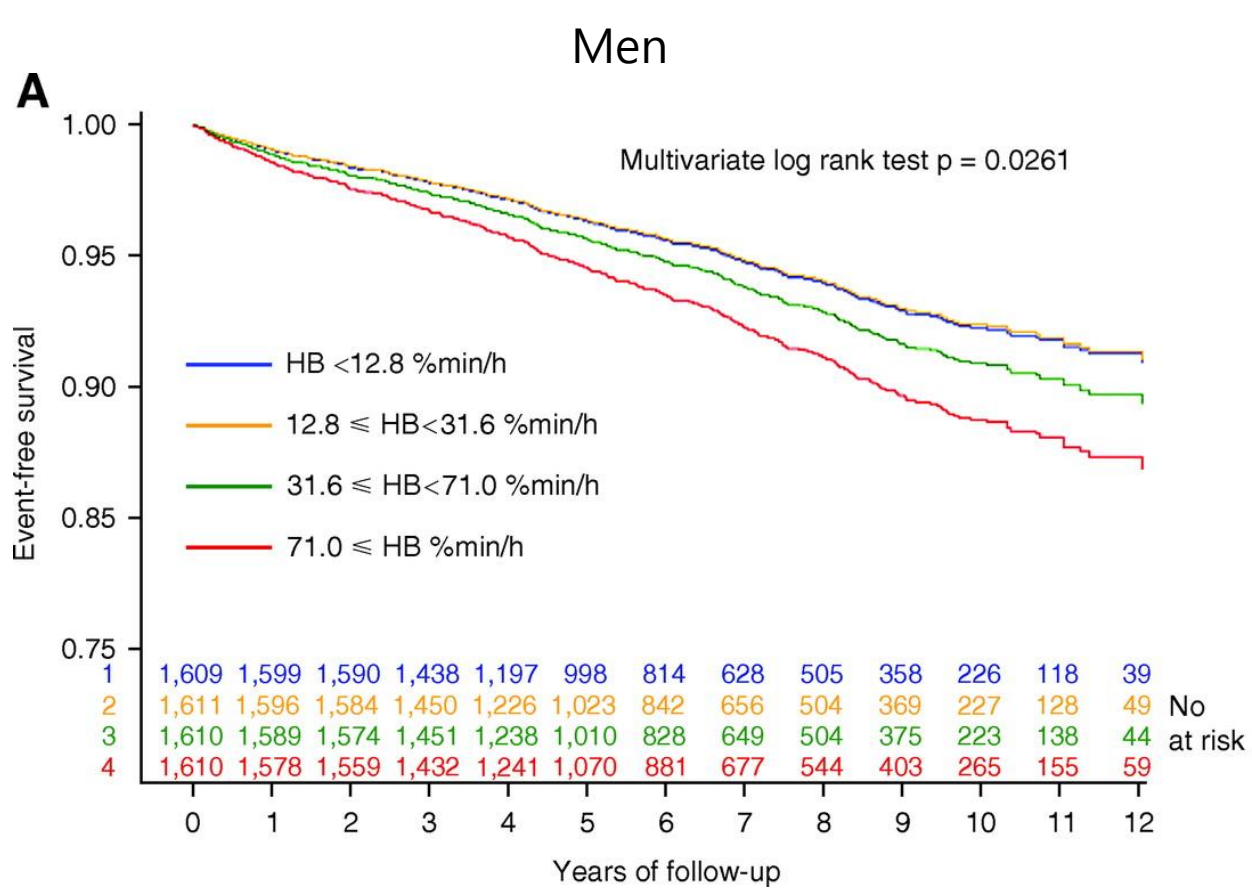
- (1) HR 1.81 (CI 1.25-2.62) Q3
  2.73 (CI 1.71-4.36) Q4

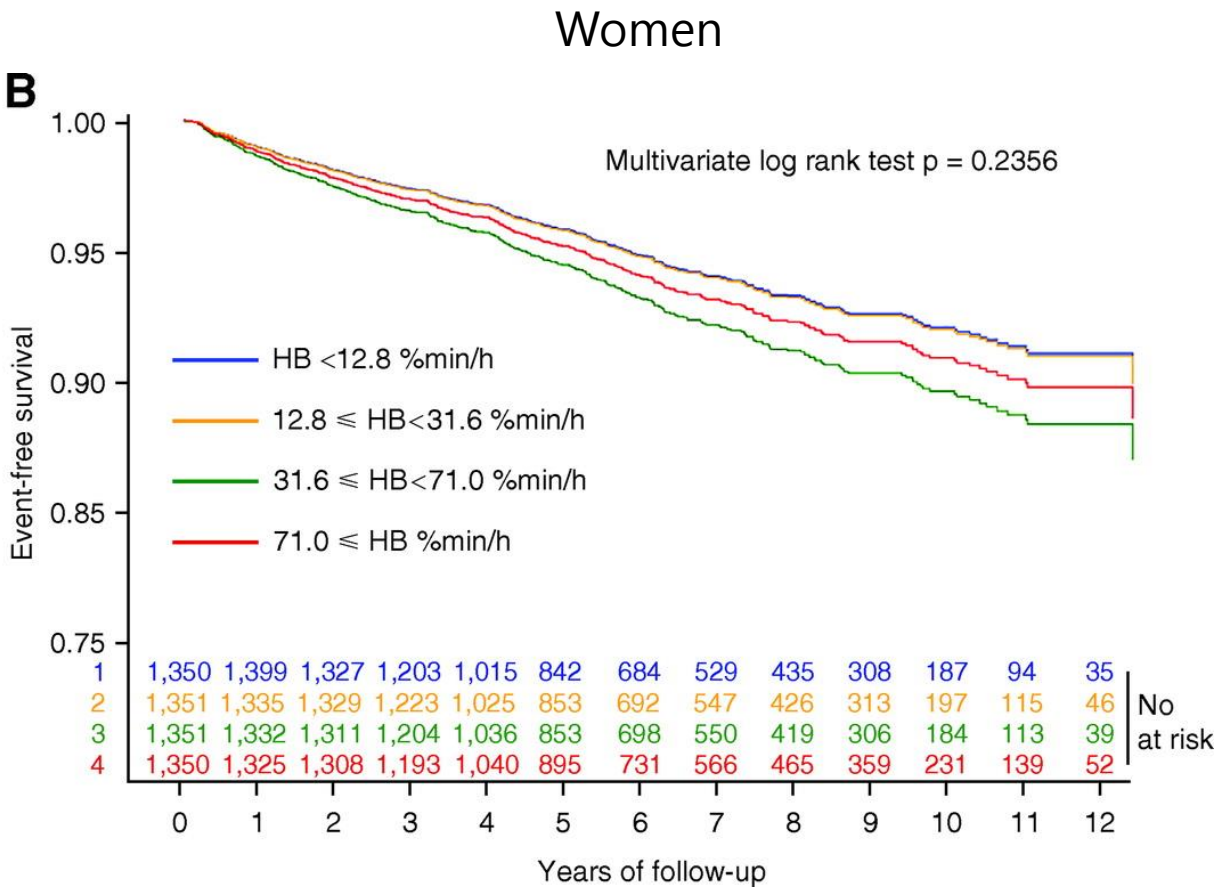
- (2) HR 1.96 (CI 1.1 – 3.43) Q4



Azarbazin et al, EHR, 2019

Hypoxic burden → CV risk prediction?

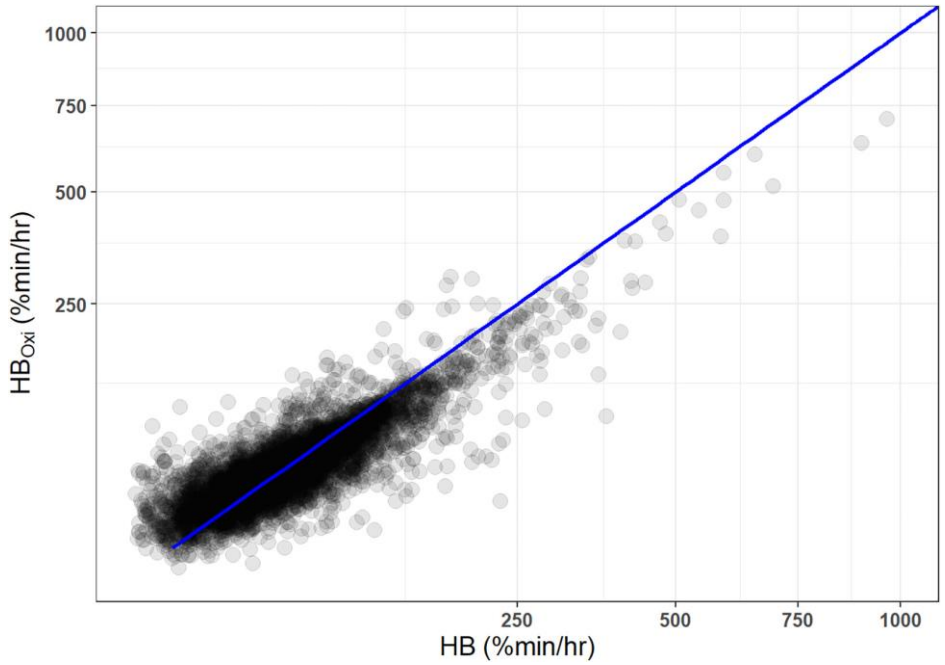


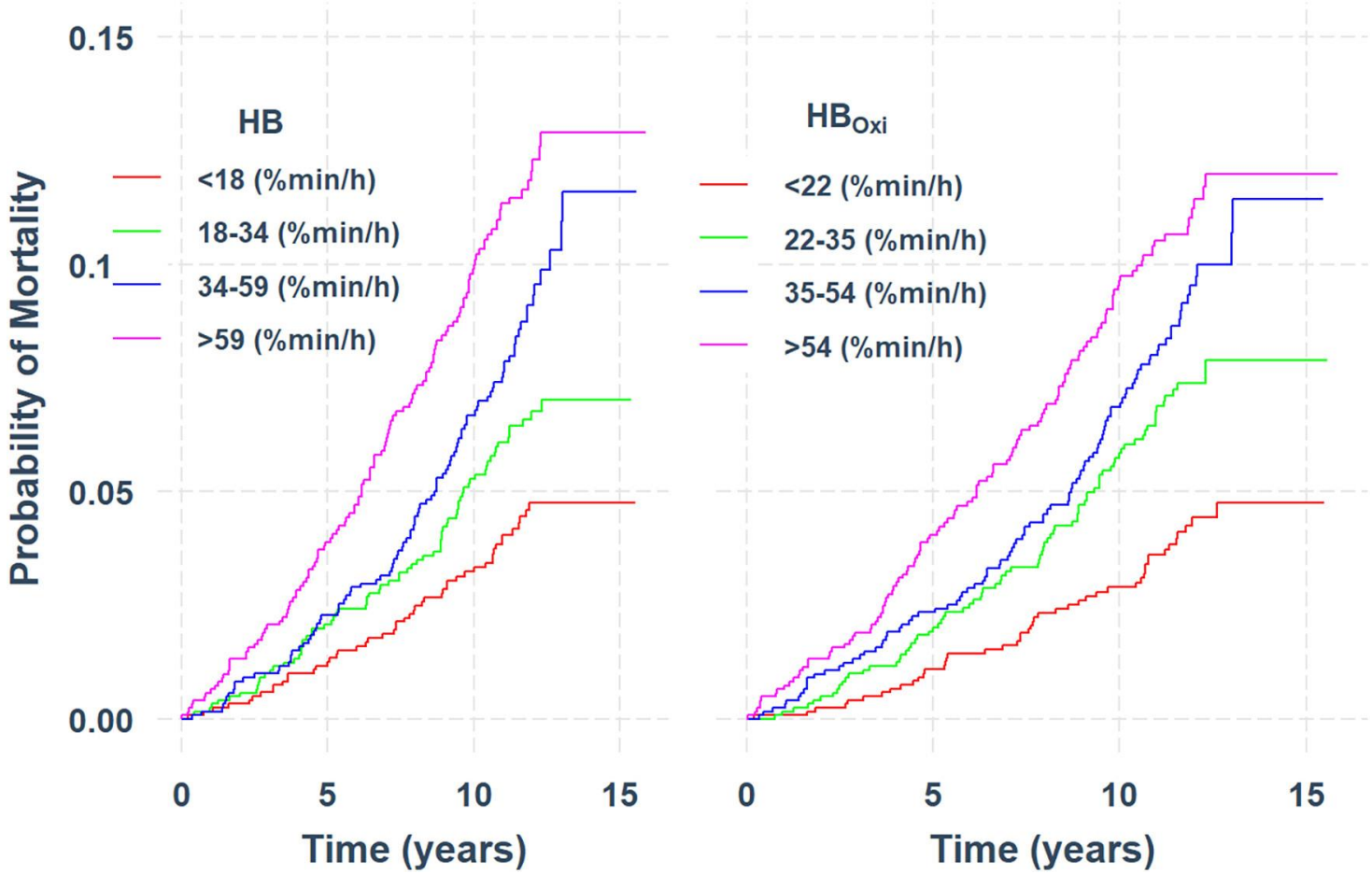


- Pays de la Loire Sleep cohort : 5,358 patients
- HR 1.27 (1.19-1.36) : 1.21 (1.07-1.38)

Trzepizur W et al, Am J Respir Crit Care Med. 2022

Manually & Automatically calculated HB





Neda Esmael et al, AJRCCM. 2023

Hypoxic burden & Blood pressure

- Especially uncontrolled or resistant form

Kim et al(2019) ;

High DBP (1SD HB → 0.9% increase DBP)

Not SBP

Not-using anti-hypertensive drug

: 1SD increase → 1.1% increase SBP

1.9% increasd DBP

Hypoxic burden & Stroke

- Inconclusive (variation in mean age & nature of prevention)

	Hazard ratio (95% CI)		
	Model 1	Model 2	Model 3
Indices of OSA severity			
ln AHI	1.45 (1.15–1.84)**	1.18 (0.93–1.50)	1.20 (0.93–1.55)
ln SASHB	1.46 (1.24–1.72)***	1.25 (1.04–1.51)*	1.28 (1.05–1.57)*
ln MAI	1.44 (1.01–2.05)*	1.20 (0.86–1.68)	1.21 (0.86–1.71)
ln 3%ODI	1.30 (1.09–1.55)**	1.13 (0.95–1.33)	1.13 (0.95–1.35)
ln T90	1.11 (1.06–1.16)***	1.06 (1.01–1.12)*	1.06 (1.01–1.12)*
Indices of HRV			
ln SDNN	0.97 (0.59–1.61)	1.19 (0.73–1.95)	1.23 (0.75–2.04)
ln RMSSD	1.36 (0.93–1.98)	1.43 (0.99–2.07)	1.43 (0.99–2.07)
ln LF	0.36 (0.21–0.64)***	0.47 (0.26–0.85)*	0.47 (0.26–0.86)*
ln HF	3.35 (1.48–7.61)**	2.78 (1.25–6.17)*	2.77 (1.25–6.16)*
ln LF/HF ratio	0.59 (0.43–0.81)**	0.66 (0.48–0.90)**	0.66 (0.48–0.90)**

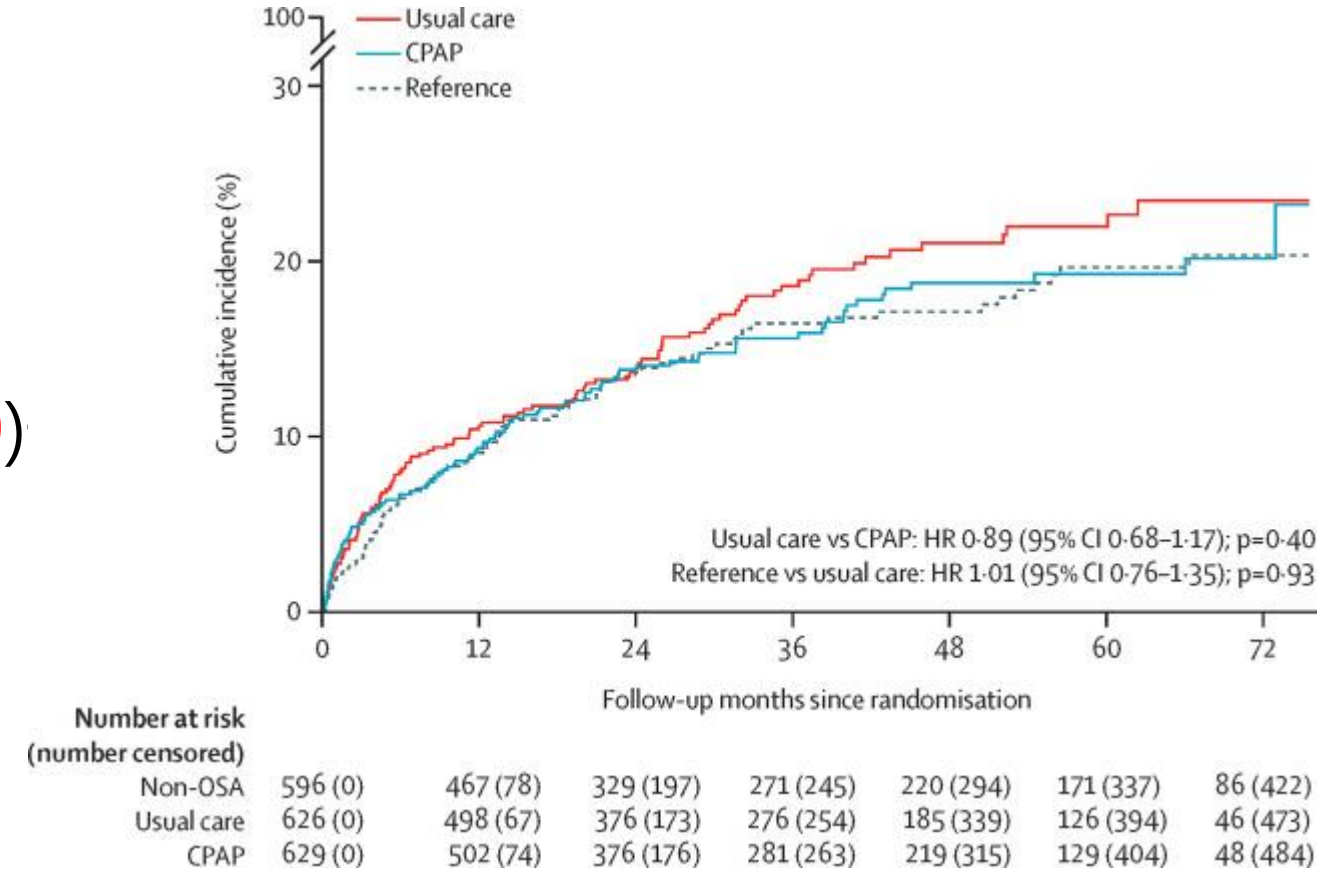
Model 1: unadjusted. Model 2: adjusted for age, gender, body mass index, alcohol intake, smoking status, diabetes, hypertension, history of cardiac disease and study site. Model 3: model 2, additionally adjusted for positive airway pressure adherence. AHI: apnoea–hypopnoea index; SASHB: sleep apnoea specific hypoxic burden; MAI: micro-arousal index; ODI: oxygen desaturation index; T90: percentage of sleep time with oxygen saturation <90%; SDNN: standard deviation for the mean of value of all normal-to-normal R-R intervals; RMSSD: root mean square of successive differences in normal-to-normal R-R intervals; LF: normalised low frequency power; HF: normalised high frequency power. *: p<0.05; **: p<0.01; ***: p<0.001.

ERJ 2021

AHI base CPAP therapy → No benefit (CV risk)

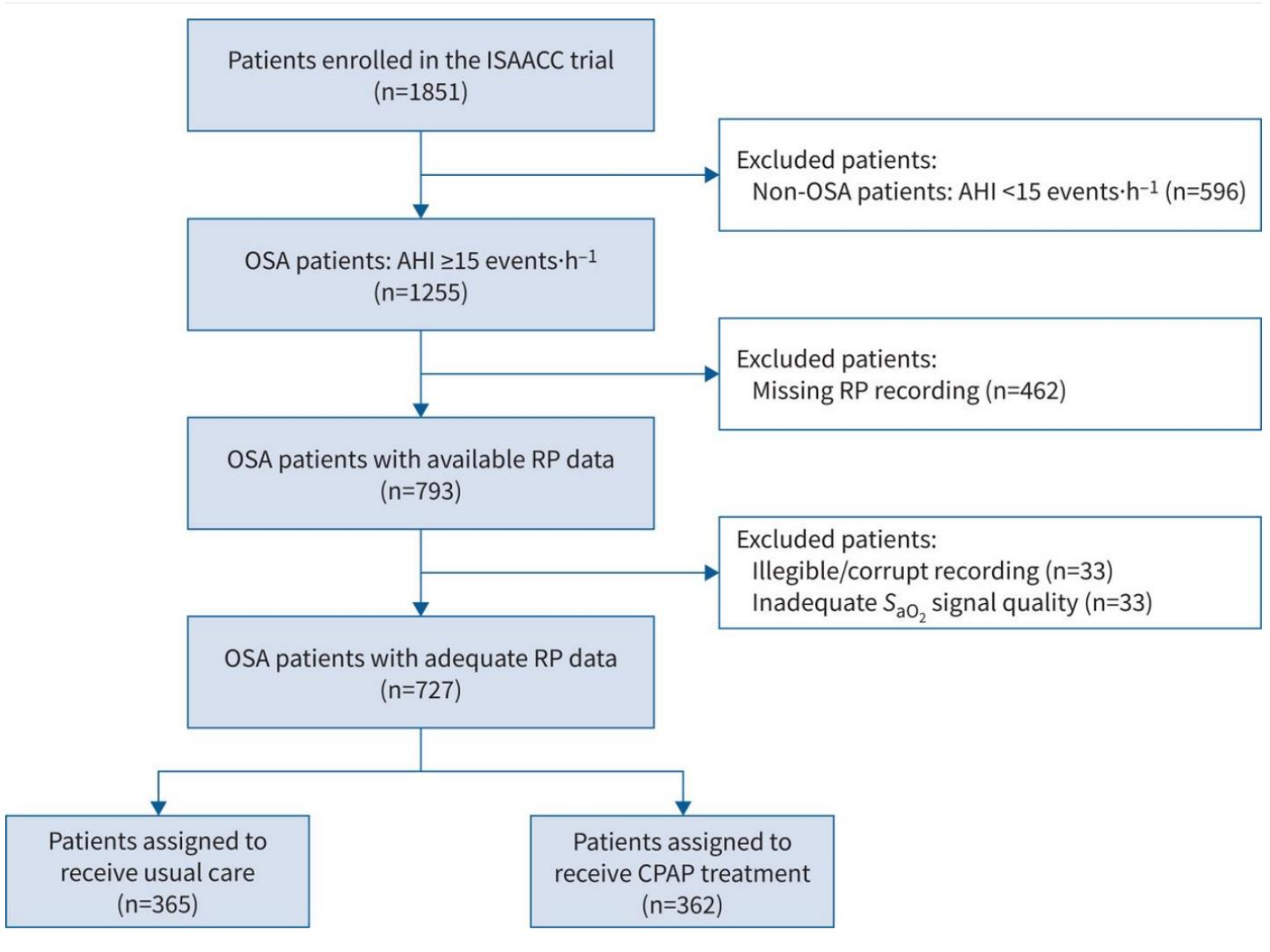
- ISAACC trial
- Spain, 15 hospitals
- AHI 15이상 환자를 대상
- Non-sleepy patients (ESS <10)
- CPAP 633 / Usual care 631
- F/U : 3.35yr

- **HR 1.01 (0.76 – 1.35)**



Manuel et al, Lancet Respiratory medicine, 2020

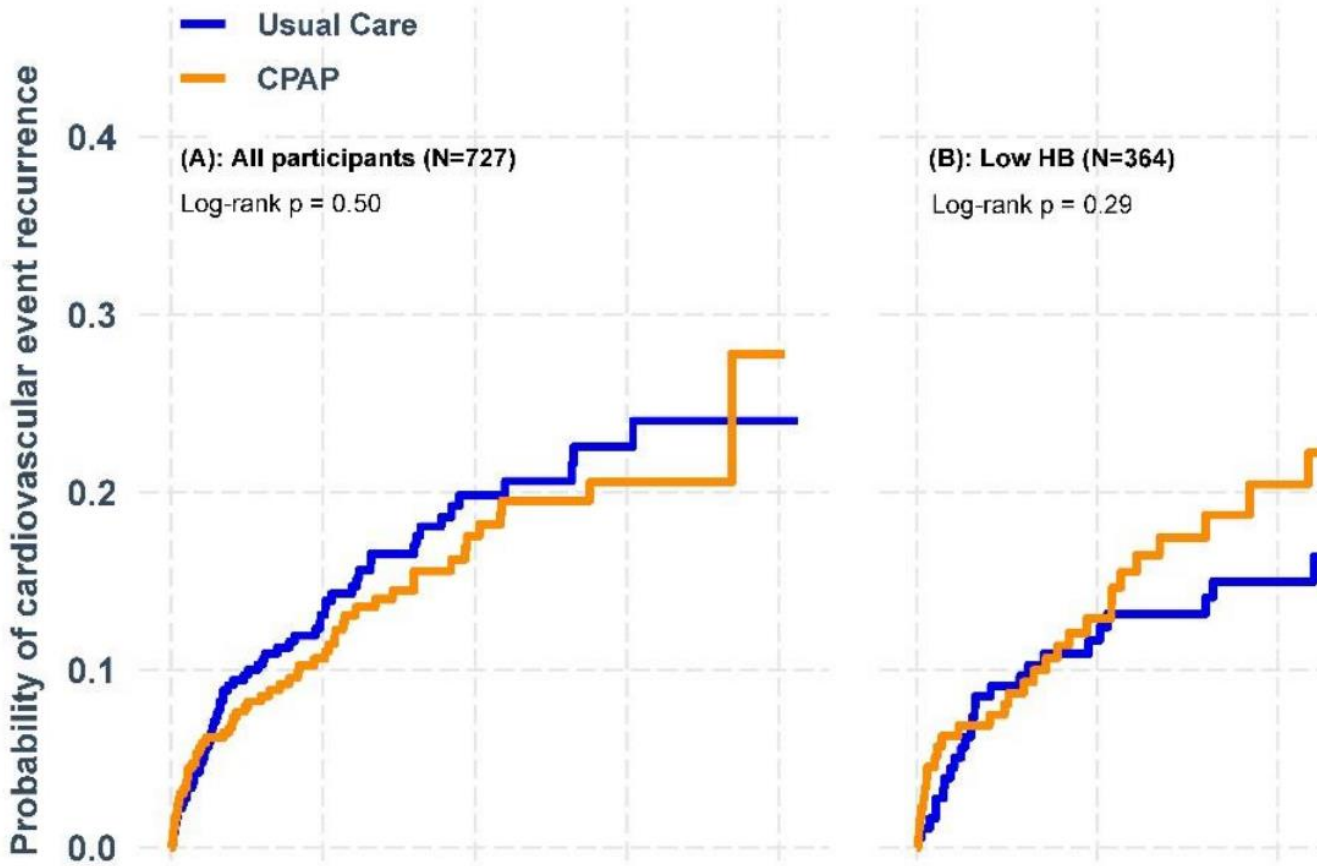
Hypoxic burden → CPAP treatment?

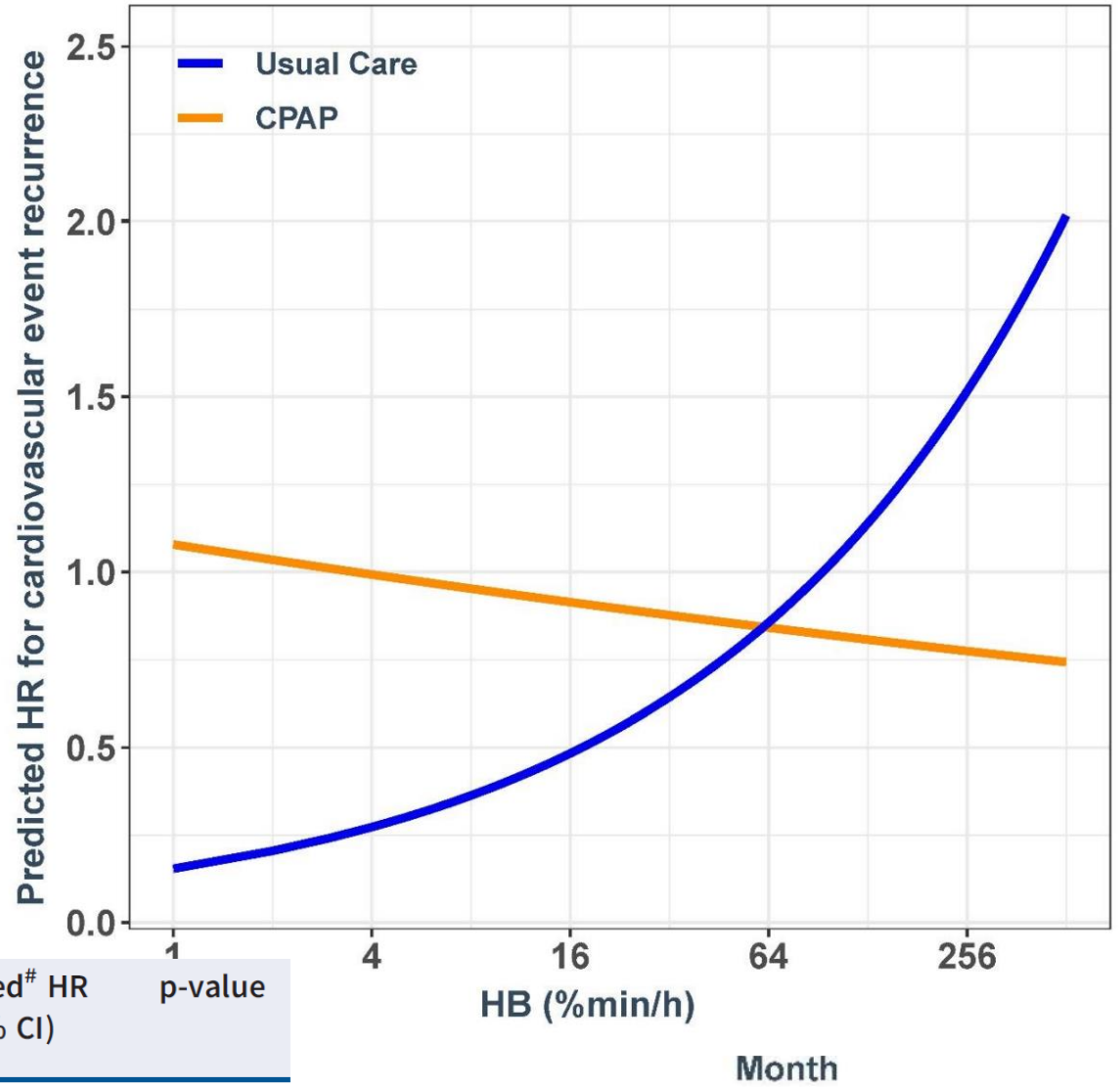


- RCT
- Post hoc analysis of ISAACC trial

- **High HB / Low HB** 73.1%min/h

Lucia Pinilla et al, ERJ, 2023 62(6) : 2300828





	Events	Follow-up (months)	Unadjusted HR (95% CI)	p-value	Adjusted[#] HR (95% CI)	p-value
Low HB						
Usual care	18 (9.6)	34.91 (16.78–55.95)	Reference		Reference	
CPAP	22 (12.4)	25.96 (14.32–47.57)	1.36 (0.73–2.54)	0.331	1.36 (0.72–2.55)	0.339
High HB						
Usual care	31 (17.4)	24.6 (12.85–47.04)	Reference		Reference	
CPAP	19 (10.3)	34.29 (17.50–58.45)	0.52 (0.29–0.92)	**0.025**	0.53 (0.30–0.95)	**0.034**

Lucia Pinilla et al, ERJ, 2023 62(6) : 2300828

New Metrics for OSA & Comorbidity

Report	Type of study and cohort	Main CV outcomes related to HB
Azarbarzin A. *et al.* 2019 [27]	Observational, longitudinal study MrOS and SHHS cohorts	HB was defined for the first time and OSA severity quantified with this term was independently associated with CV mortality.
de Chazal P. *et al.* 2020 [30]	Review	AHI may oversimplify the complexity of OSA and poorly correlates to CV consequences. Parameters such as HB can better predict CVR and other comorbidities.
Kim JS. *et al.* 2020 [40]	Cross-sectional study MESA cohort	High HB was related to higher BP, specifically with increased DBP overall and SBP and DBP among non-hypertension medication users. HB was similarly associated with DBP in both NREM and REM sleep.
Azarbarzin A. *et al.* 2020 [38]	Observational, longitudinal study MrOS and SHHS cohorts	Incident HF was more strongly and consistently associated with the HB than the traditional AHI.
Azarbarzin A. *et al.* 2021 [36]	Observational, longitudinal study MESA and SHHS cohorts	HB together with ΔHR, may be useful for the identification of OSA patients with high CVR. There is an association of a high ΔHR with nonfatal and fatal CVD and all-cause mortality, moderated by the severity of OSA (higher HB).
O'Donnell C. *et al.* 2021 [29]	Review	HB seems to be better correlated with the end-organ consequences of OSA than AHI.
Trzepizur W. *et al.* 2022 [37]	Observational, longitudinal study Pays de la Loire Sleep cohort	HB and T90 were better associated with major adverse CV events than AHI and ODI. This marker could be utilized in clinical practice to identify OSA patients at higher CVR.
Javaheri S. and Javaheri S., 2022 [31]	Review	There may be other metrics to quantify the severity of OSA in the HF population, including HB. HB is currently under investigation, however more investigation is needed before clinical application.
Blekic N. *et al.* 2022 [35]	Review	HB is a parameter that results in a better assessment of CV OSA patients. It would be included for improving classification of OSA patients with higher future CVR.
Martinez-Garcia MA. *et al.* 2023 [32]	Review	A threshold of HB >60 %min/h is established to identify OSA with higher risk of CV morbidity and mortality. Soon, this measure could be incorporated in sleep laboratories and could play a role in clinical therapeutic decisions in patients with OSA.
Trzepizur W. *et al.* 2023 [39]	Observational, longitudinal study Pays de la Loire Sleep cohort	HB predicted incident venous thromboembolism. Thus, patients with more severe nocturnal hypoxia are more likely to have incident venous thromboembolism.
Redline S. *et al.* 2023 [14]	Review	HB was related with higher BP and had stronger relation with CV mortality and major incidents of CV events.
Peker Y. *et al.* 2023 [17]	Review	HB have demonstrated to be better predictors of adverse CVD outcomes and response to OSA treatment.
Solano-Pérez E. *et al.* 2023 [33]	Review	HB has not yet been assessed in the pediatric population. Evaluating HB in children with OSA could be an interesting advance to predict the risk of the disease and may improve the choice of the treatment.
Esmaeili N. *et al.* 2023 [41]	Observational, longitudinal study SHHS cohort	The oximetry-derived HB, a novel method to quantify the HB automatically was assessed and it highly correlated with manual-scored HB and was associated with EDS, HBP and CVD mortality in a similar way as previously reported.
Pack AI. 2023 [34]	Review	HB and ΔHR, that may provide information on who with OSA is at most risk for CV consequences.

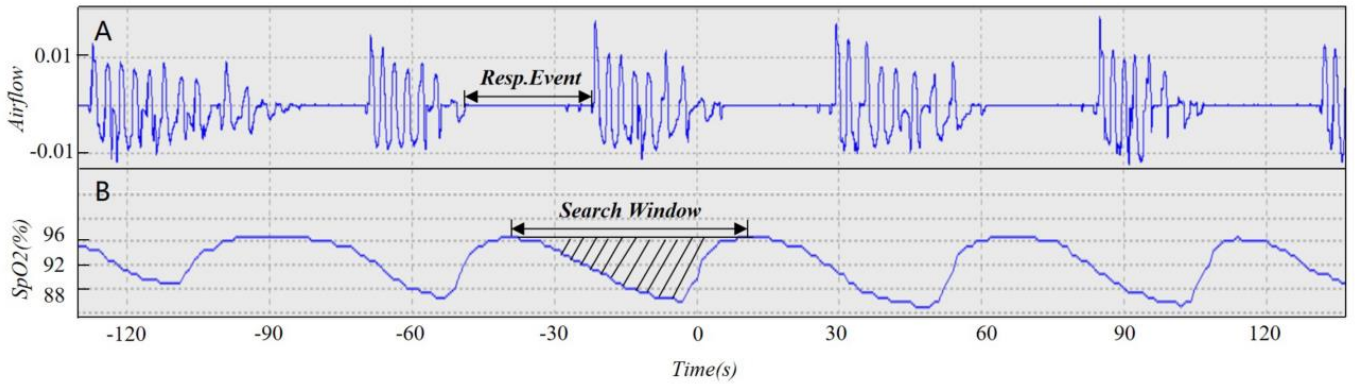
Hypoxic burden

- 1) Index-based hypoxic burden measure : AHI, ODI
  (Oxygen desaturation index)

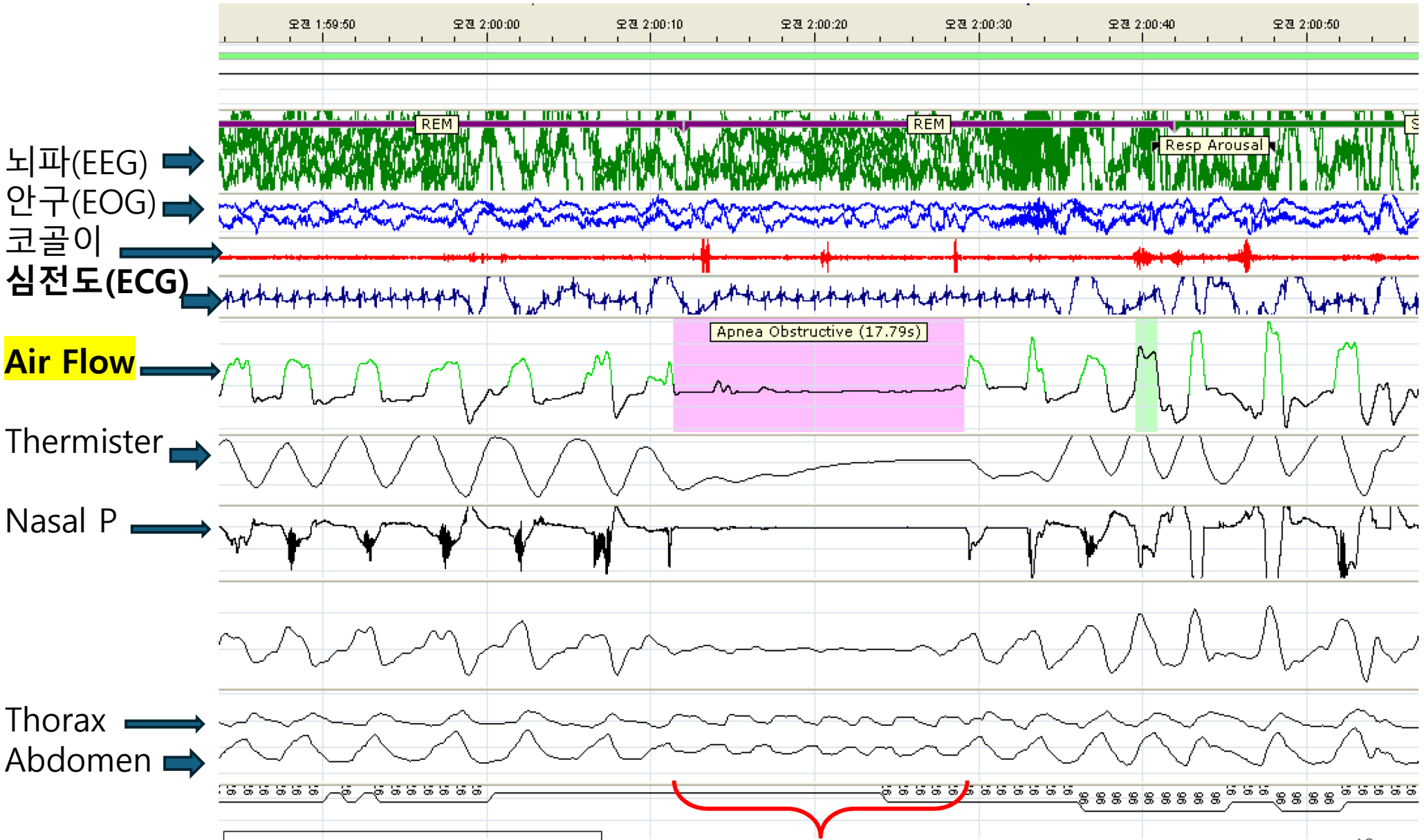
- 2) Time based hypoxic burden measures : T90
  (Time below SpO2 90%)

- 3) Area based hypoxic burden measures : Hypoxic burden

  Duratio & Depth



수면다원검사(Polysomnography)



Hypopnea

1979
- Block et al. first describe hypopnea using 4% oxygen desaturation (13)

1988
- Gould et al. describe "Sleep Hypopnea Syndrome" (15)

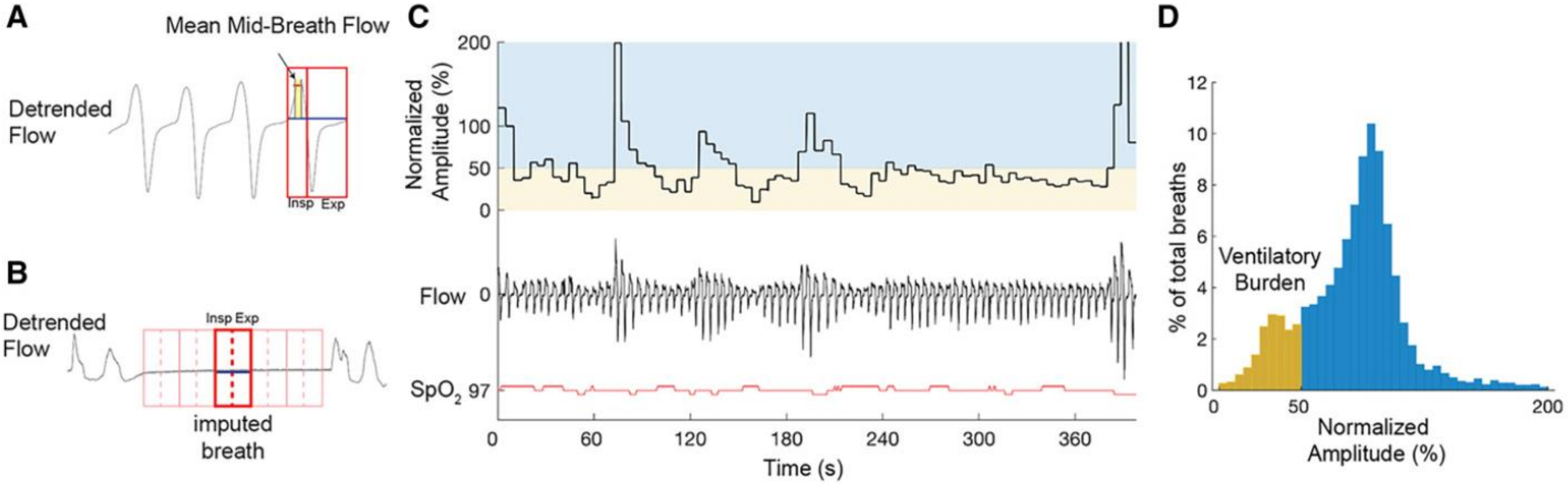
1999
- AASM Hypopnea taskforce (Chicago Criteria) defines hypopnea to as 50% reduction in AF or clear AF amplitude reduction with 3% oxygen desaturation and/or arousal (30)

2007
- AASM Scoring Manual (v 1.0) sets 2 rules for hypopneas: "*Recommended*" (30% AF reduction + 4% oxygen desaturation) and "*Alternative*" (3% oxygen desaturation and/or arousal) (31))

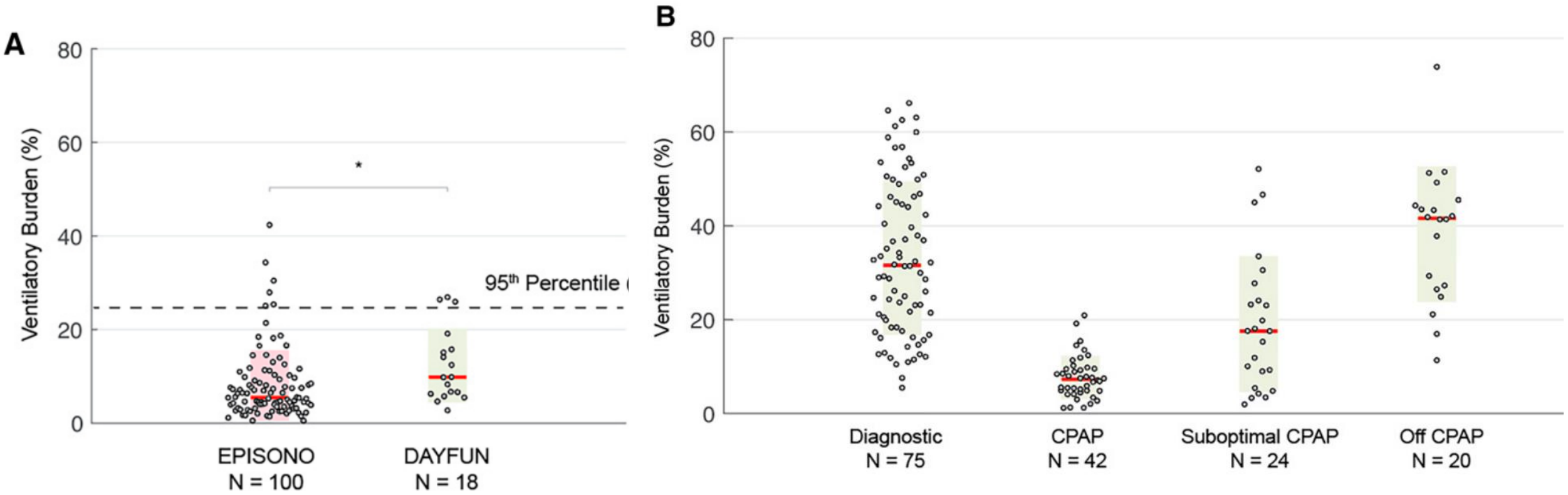
2012
- AASM changes "*Recommended*" to 30% AF reduction + 3% oxygen desaturation and/or arousal; adds an "*Option*" to report hypopneas with a 4% desaturation (26)

Ventilatory burden

- Proportion of overnight breaths with less than 50% normalized amplitude

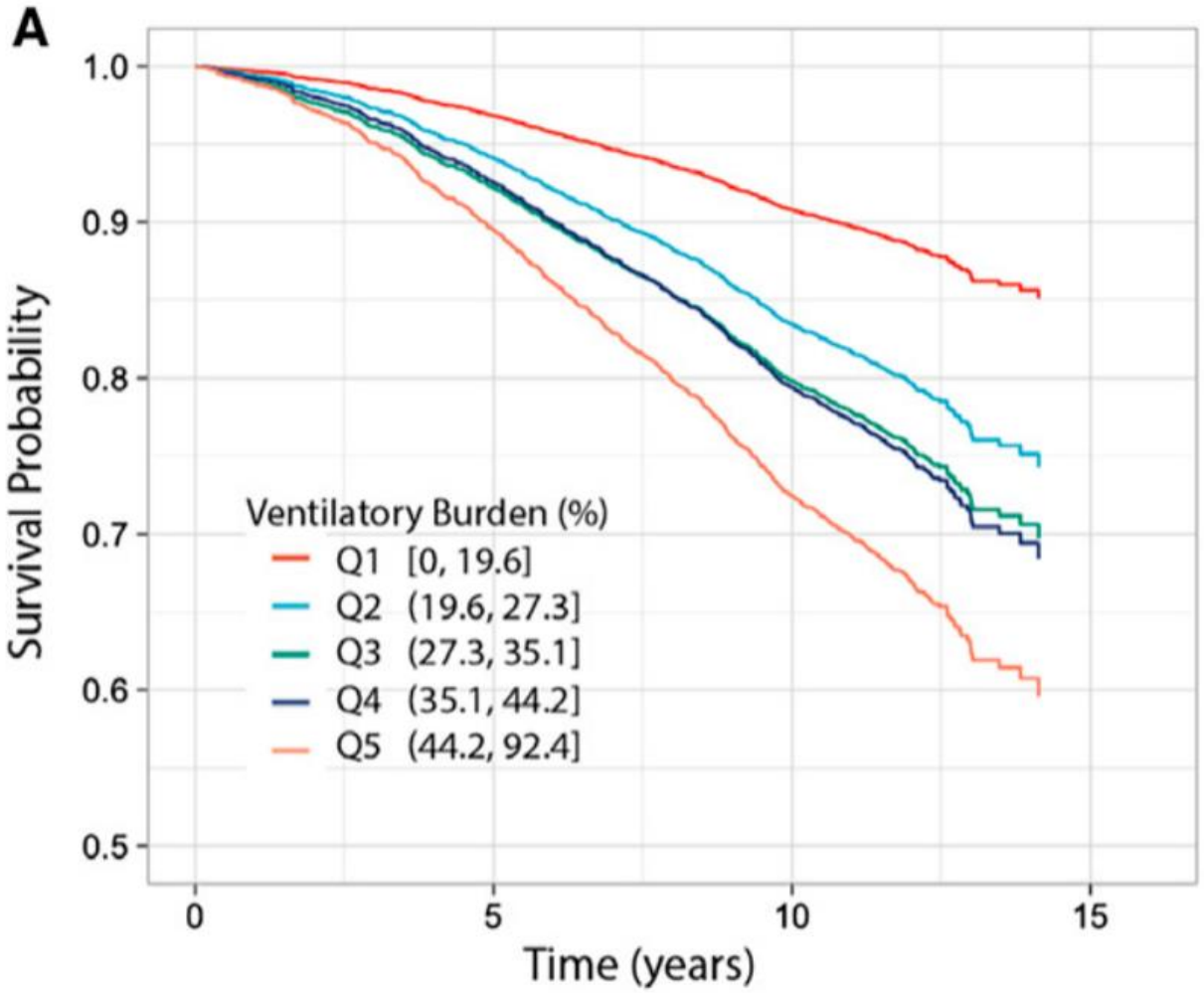


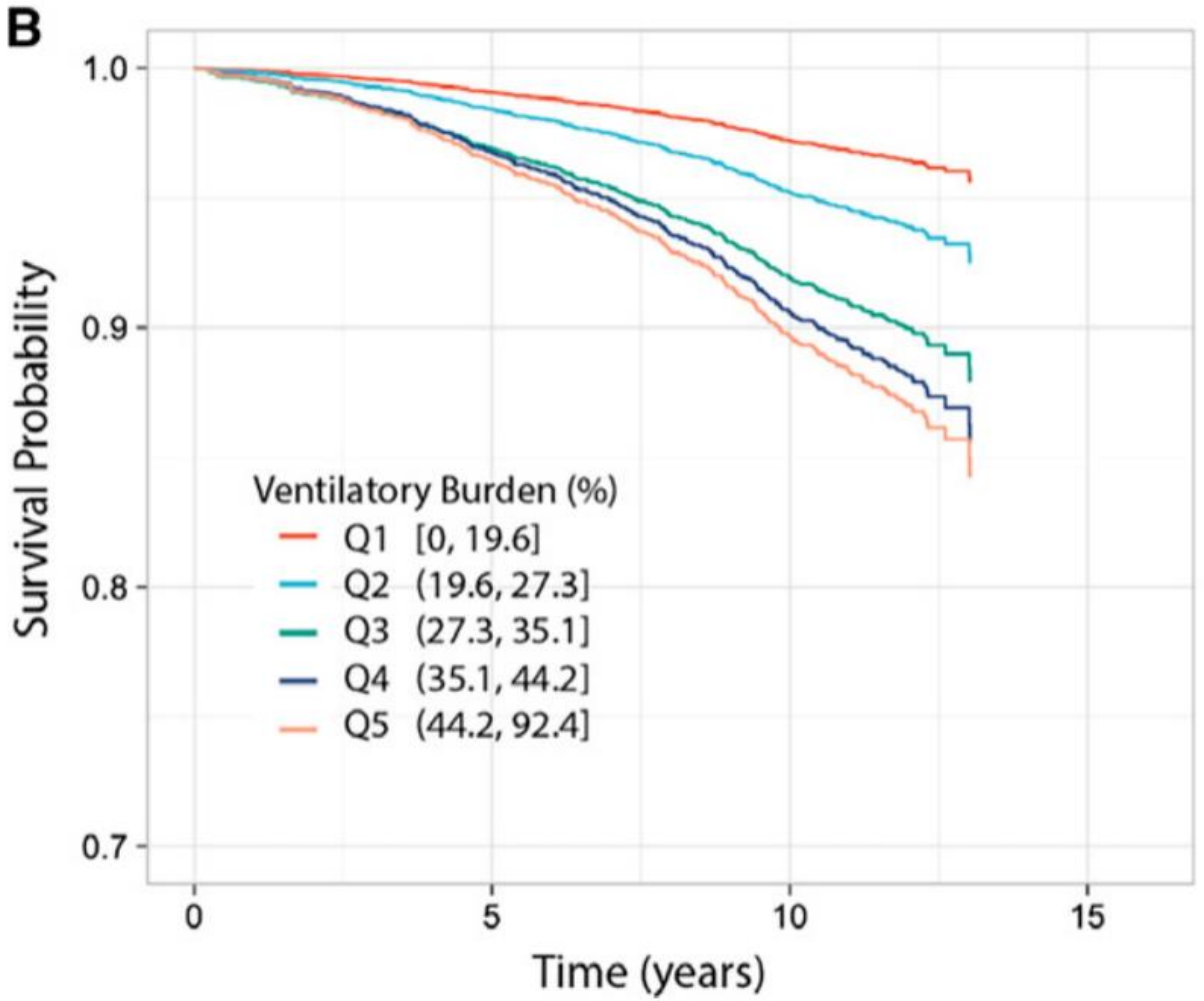
Parekh et al, AJRCCM, 2023



- A : Normal group
- B : CPAP / Suboptimal CPAP / Off CPAP (2일 뒤)

Parekh et al, AJRCCM, 2023





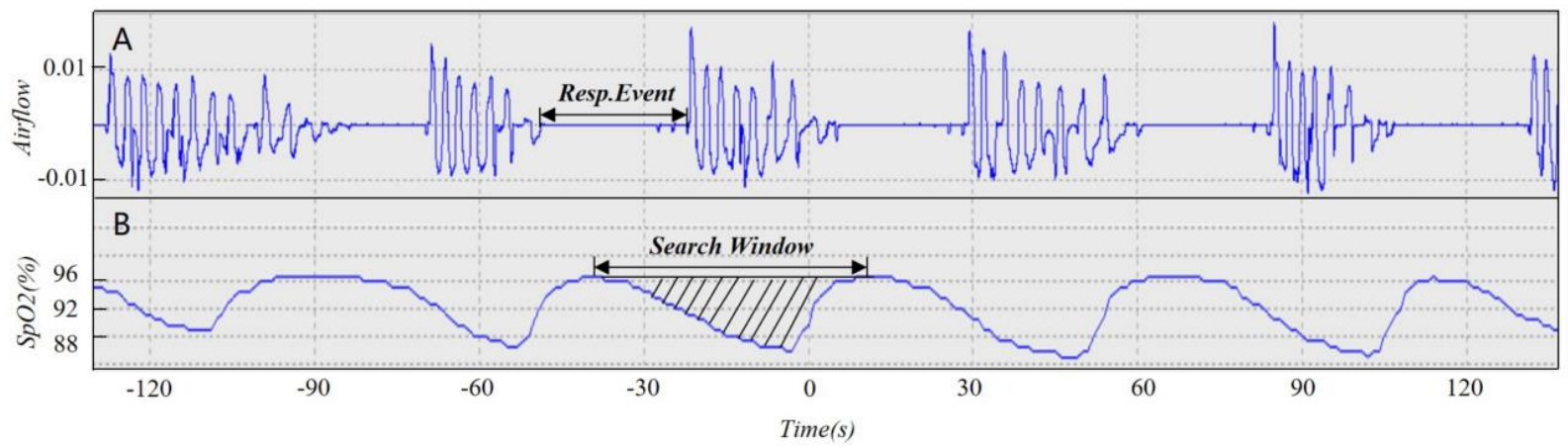
A : All-cause mortality

B : Cardiovascular mortality

SHHS(Sleep heart health study) cohort

Parekh et al, AJRCCM, 2023

Table 3. Relationship between Apnea–Hypopnea Index, Hypoxic Burden, Ventilatory Burden, and Cardiovascular Disease and All-Cause Mortality in SHHS



		All-Cause Mortality				Cardiovascular Disease Mortality					
		Unadjusted		Adjusted		Unadjusted		Adjusted			
		HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	C	
	Q5	3.32 (2.65, 4.15)		1.87 (1.47, 2.37)		3.67 (2.34, 5.76)		1.73 (1.10, 2.73)			
Model 4: VB + HB	VB		**<0.001**		**<0.001**		**<0.001**		0.04		0.86*†‡
	Q1	—	**0.63***†‡	—	**0.79***†‡	—	**0.65***†‡	—			
	Q2	1.64 (1.28, 2.09)		1.40 (1.09, 1.81)		1.52 (0.93, 2.50)		1.25 (0.76, 2.07)			
	Q3	1.90 (1.50, 2.41)		1.39 (1.07, 1.78)		2.39 (1.50, 3.80)		1.53 (0.96, 2.45)			
	Q4	1.85 (1.46, 2.36)		1.33 (1.03, 1.70)		2.92 (1.86, 4.60)		1.89 (1.19, 2.98)			
	Q5	2.49 (1.97, 3.13)		1.66 (1.29, 2.11)		2.89 (1.83, 4.59)		1.69 (1.06, 2.69)			
	HB		**<0.001**		**0.002**		**<0.001**		0.09		
	Q1	—		—		—		—			
	Q2	1.49 (1.16, 1.91)		1.31 (1.00, 1.69)		1.71 (1.06, 2.74)		1.26 (0.78, 2.03)			
	Q3	1.81 (1.42, 2.29)		1.45 (1.13, 1.88)		2.27 (1.44, 3.56)		1.69 (1.07, 2.66)			
	Q4	2.50 (1.99, 3.15)		1.65 (1.29, 2.11)		2.96 (1.91, 4.58)		1.60 (1.02, 2.49)			
	Q5	2.69 (2.14, 3.38)		1.73 (1.33, 2.22)		2.44 (1.56, 3.83)		1.24 (0.78, 1.99)			

	Q5	3.32 (2.65, 4.15)		1.87 (1.47, 2.37)		3.67 (2.34, 5.76)		1.73 (1.10, 2.73)			
	VB		**<0.001**		**<0.001**		**<0.001**		0.2		**0.83**
	Q1	—		—		—		—			
	Q2	1.64 (1.28, 2.09)		1.40 (1.09, 1.81)		1.52 (0.93, 2.50)		1 (0.82, 2.11)			
	Q3	1.90 (1.50, 2.41)		1.39 (1.07, 1.78)		2.39 (1.50, 3.80)		8 (0.99, 2.64)			
	Q4	1.85 (1.46, 2.36)		1.33 (1.03, 1.70)		2.92 (1.86, 4.60)		0 (0.98, 2.51)			
	Q5	2.49 (1.97, 3.13)		1.66 (1.29, 2.11)		2.89 (1.83, 4.59)		5 (0.91, 2.27)			
	HB		**<0.001**		**0.002**		**<0.001**		0.056		**0.85***
	Q1	—		—		—		—			
	Q2	1.49 (1.16, 1.91)		1.31 (1.00, 1.69)		1.71 (1.06, 2.74)		9 (0.80, 2.09)			
	Q3	1.81 (1.42, 2.29)		1.45 (1.13, 1.88)		2.27 (1.44, 3.56)		9 (1.14, 2.82)			
	Q4	2.50 (1.99, 3.15)		1.65 (1.29, 2.11)		2.96 (1.91, 4.58)		4 (1.11, 2.69)			
	Q5	2.69 (2.14, 3.38)		1.73 (1.33, 2.22)		2.44 (1.56, 3.83)		3 (0.90, 2.26)			
	VB		**<0.001**		**<0.001**		**<0.001**		**0.02**		**0.85***
	Q1	—		—		—		—			
	Q2	1.64 (1.28, 2.09)		1.40 (1.09, 1.81)		1.52 (0.93, 2.50)		8 (0.78, 2.10)			
	Q3	1.90 (1.50, 2.41)		1.39 (1.07, 1.78)		2.39 (1.50, 3.80)		9 (1.01, 2.54)			
	Q4	1.85 (1.46, 2.36)		1.33 (1.03, 1.70)		2.92 (1.86, 4.60)		4 (1.23, 3.05)			
	Q5	2.49 (1.97, 3.13)		1.66 (1.29, 2.11)		2.89 (1.83, 4.59)		1.69 (1.06, 2.69)			
Model 4: VB + HB	VB		**<0.001**		**<0.001**		**<0.001**		0.04		0.86*†‡
	Q1	—	**0.63***†‡	—	**0.79***†‡	—	**0.65***†‡	—			
	Q2	1.64 (1.28, 2.09)		1.40 (1.09, 1.81)		1.52 (0.93, 2.50)		1.25 (0.76, 2.07)			
	Q3	1.90 (1.50, 2.41)		1.39 (1.07, 1.78)		2.39 (1.50, 3.80)		1.53 (0.96, 2.45)			
	Q4	1.85 (1.46, 2.36)		1.33 (1.03, 1.70)		2.92 (1.86, 4.60)		1.89 (1.19, 2.98)			
	Q5	2.49 (1.97, 3.13)		1.66 (1.29, 2.11)		2.89 (1.83, 4.59)		1.69 (1.06, 2.69)			
	HB		**<0.001**		**0.002**		**<0.001**		0.09		
	Q1	—		—		—		—			
	Q2	1.49 (1.16, 1.91)		1.31 (1.00, 1.69)		1.71 (1.06, 2.74)		1.26 (0.78, 2.03)			
	Q3	1.81 (1.42, 2.29)		1.45 (1.13, 1.88)		2.27 (1.44, 3.56)		1.69 (1.07, 2.66)			
	Q4	2.50 (1.99, 3.15)		1.65 (1.29, 2.11)		2.96 (1.91, 4.58)		1.60 (1.02, 2.49)			
	Q5	2.69 (2.14, 3.38)		1.73 (1.33, 2.22)		2.44 (1.56, 3.83)		1.24 (0.78, 1.99)			

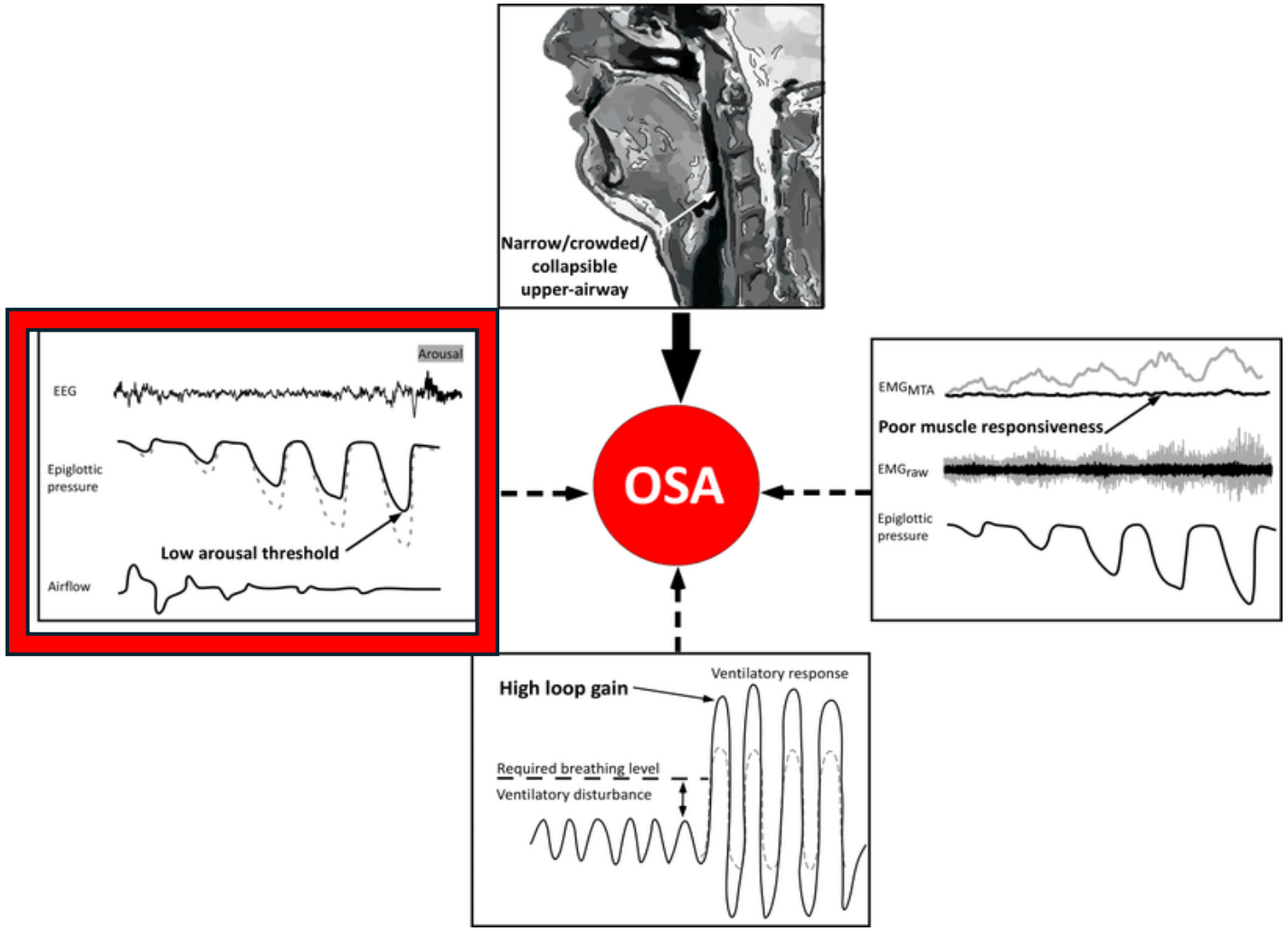
Definition of abbreviations: AHI = apnea–hypopnea index (4% desaturation); C = concordance statistic; HB = hypoxic burden; HR = hazard ratio; *P* = global *P* value; Q1–Q5 = quintiles; SHHS = Sleep Heart Health Study; VB = ventilatory burden. Bold *P* values indicate significance. Bold C (concordance values) indicate significant models ($P < 0.05$).
Adjusted models included age, body mass index, sex, race, smoking status, time in bed, baseline hypertension, and previous history of congestive heart failure and stroke as covariates.

- 전체 사망률: AHI(0.77) < HB(0.78) < VB(0.79) ≈ VB+HB(0.79)
- 심혈관질환 사망률: AHI(0.83) < HB(0.85) ≈ VB(0.85) < VB+HB(0.86)

Parekh et al, AJRCCM, 2023

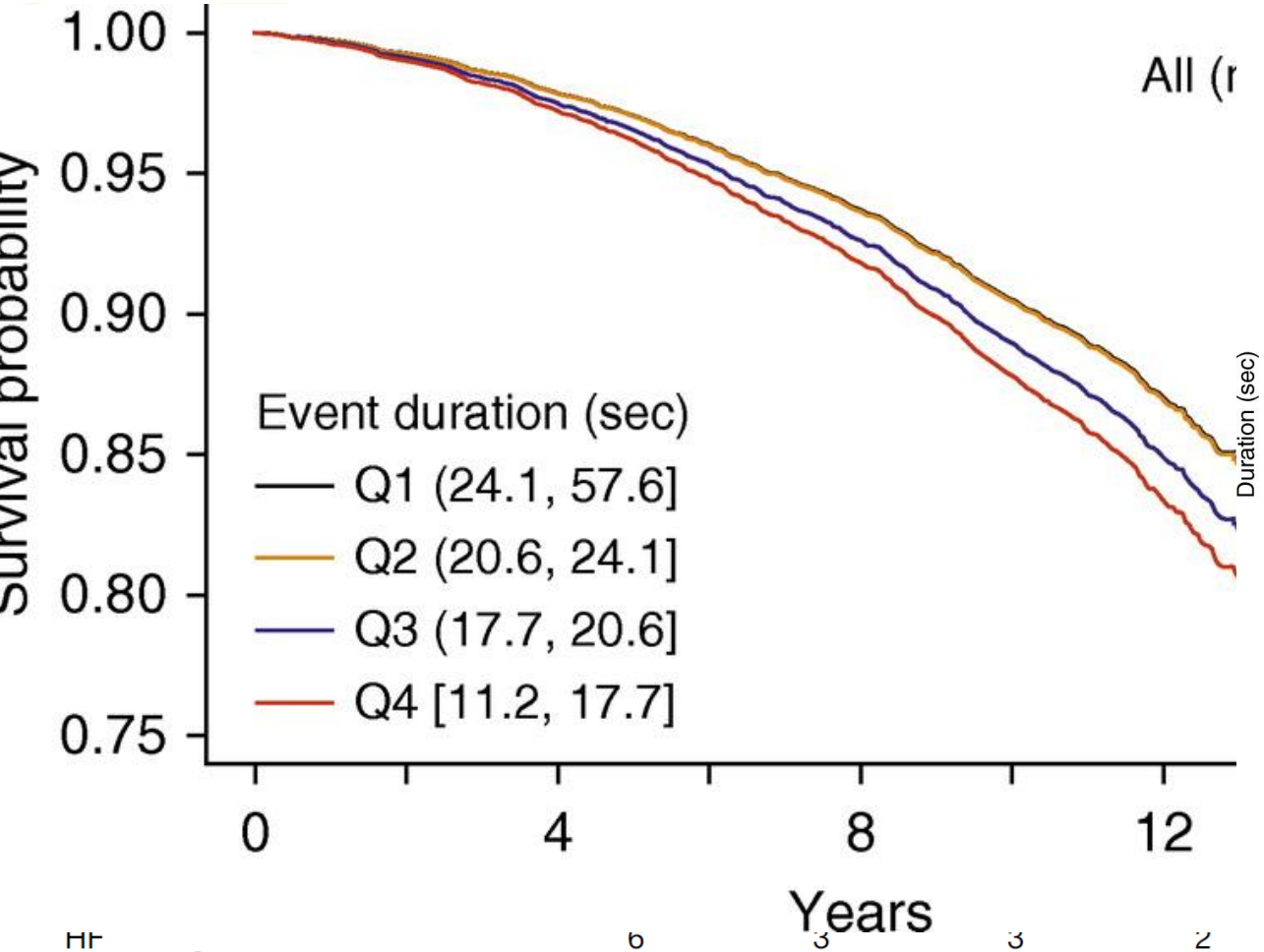
AHI + AHI duration combination

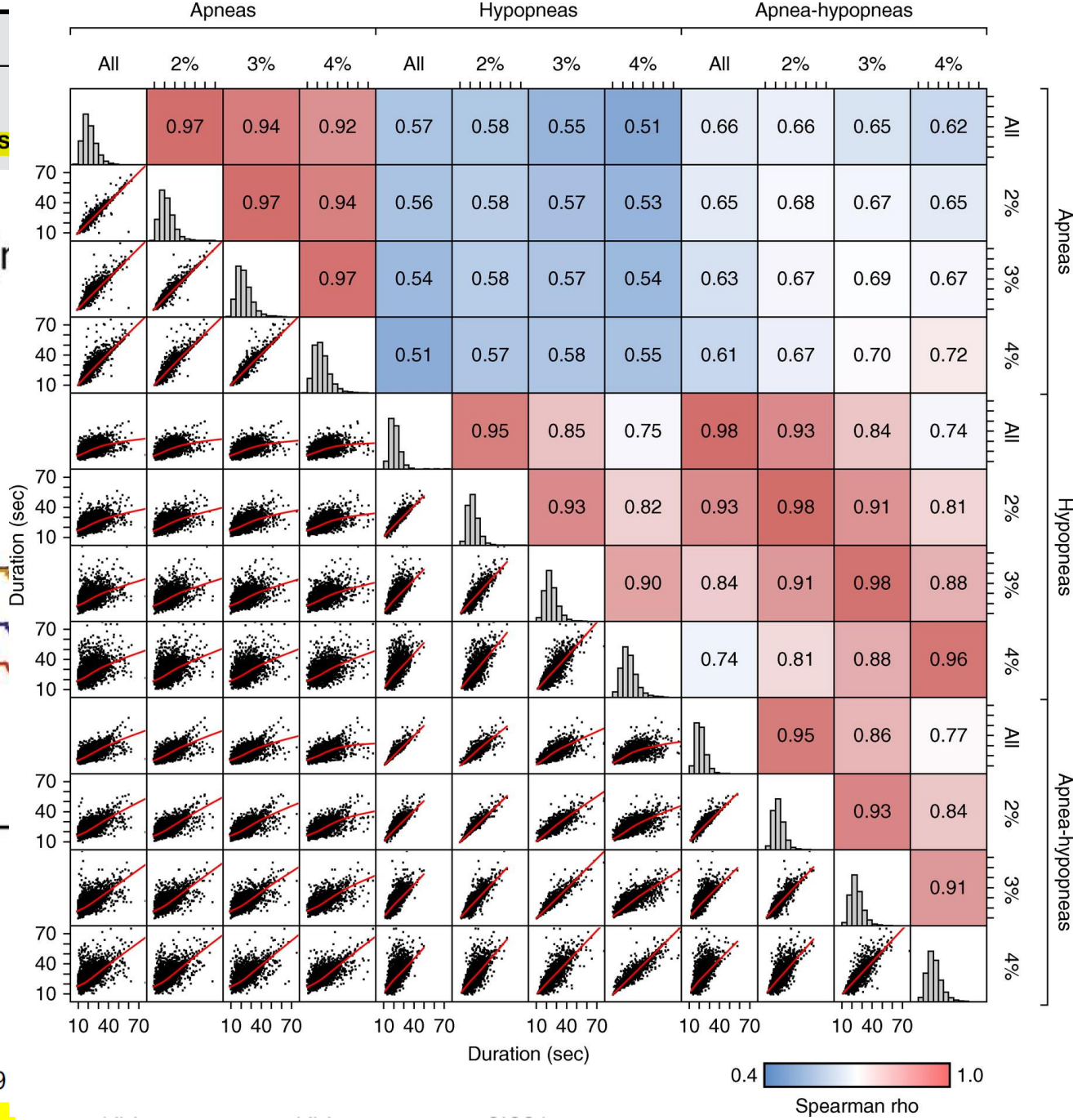
- AHI : Event / Hour
  → Ignore **hypoxemia depth**
- Short event
  → Greater arousability d/t low ar
  Increased sensitivity of the res
- **<u>Short-duration event → Hypers</u>**
- SHHS / 5,712 patients
  → 11yrs f/u



Am J Respir Crit Care Med. 2019 Apr 1;199(7):903-912

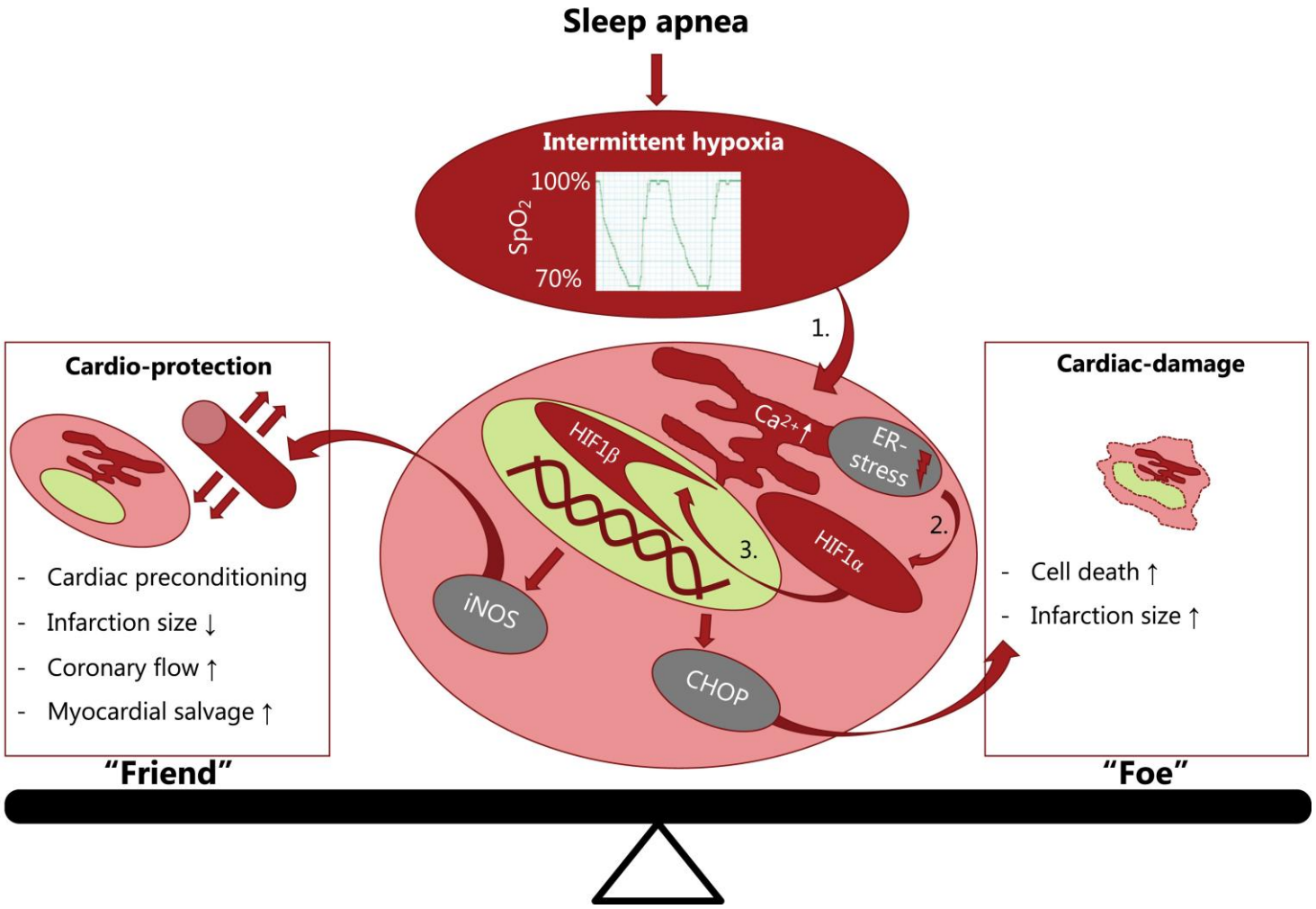
	Quartiles			
	Q1 (Longest)	Q2	Q3	Q4 (Shortes
HR	6	3	3	2
Any CVD§	20	14	14	11
Outcomes				
Deaths	385	301	315	286
Follow-up time, person-years	14,171	14,461	14,534	14,659
Mortality rate per 1,000 person-years	27.2	20.8	21.7	19.5





Am J Respir Crit Care Med. 2019 Apr 1;199(7):903-912

Intermittent hypoxia
→ Cardioprotective effect?



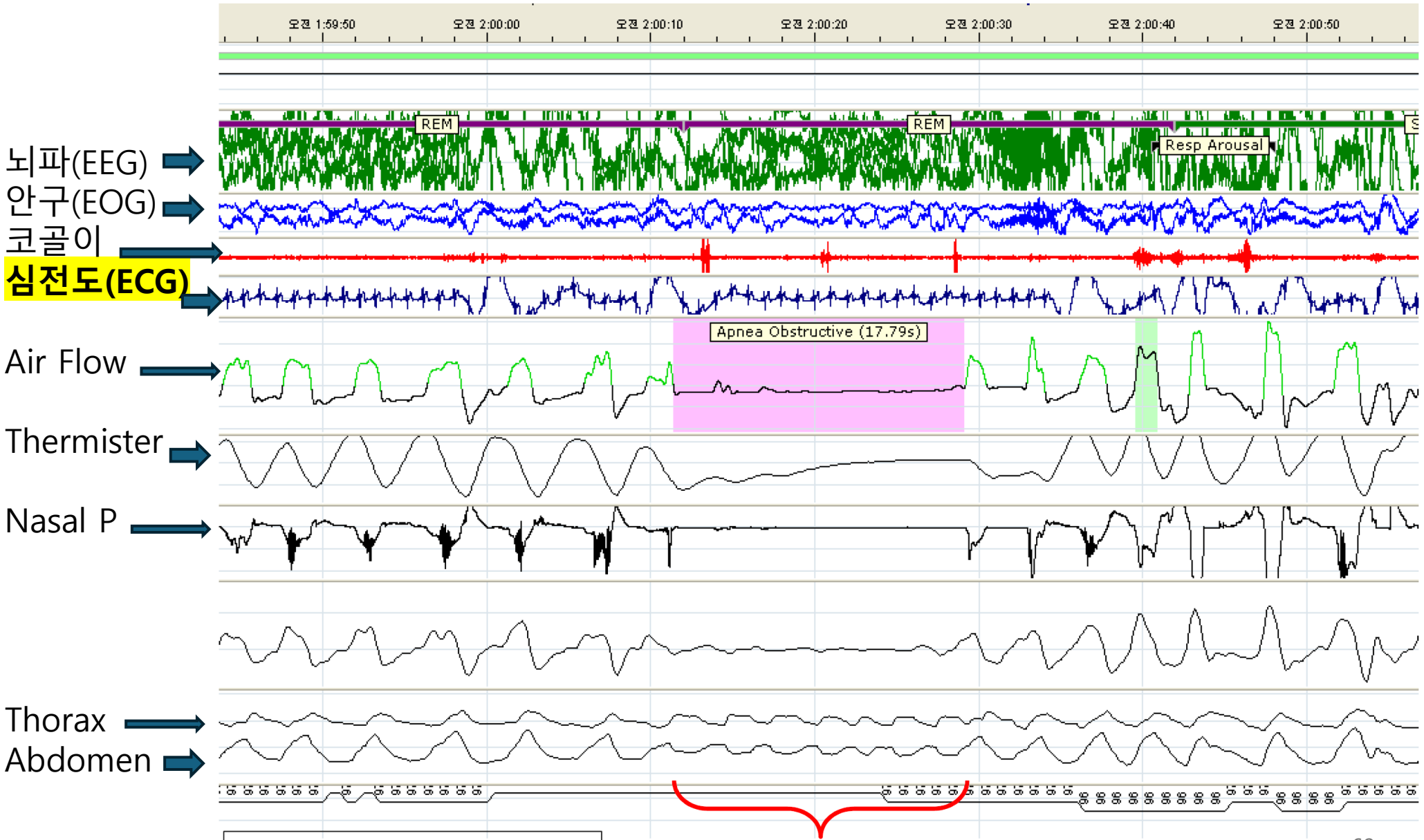
Linz, Dominik et al. CJC, 2020, V36, Issue 6, 809 - 812

Peak Troponin-T & OSA

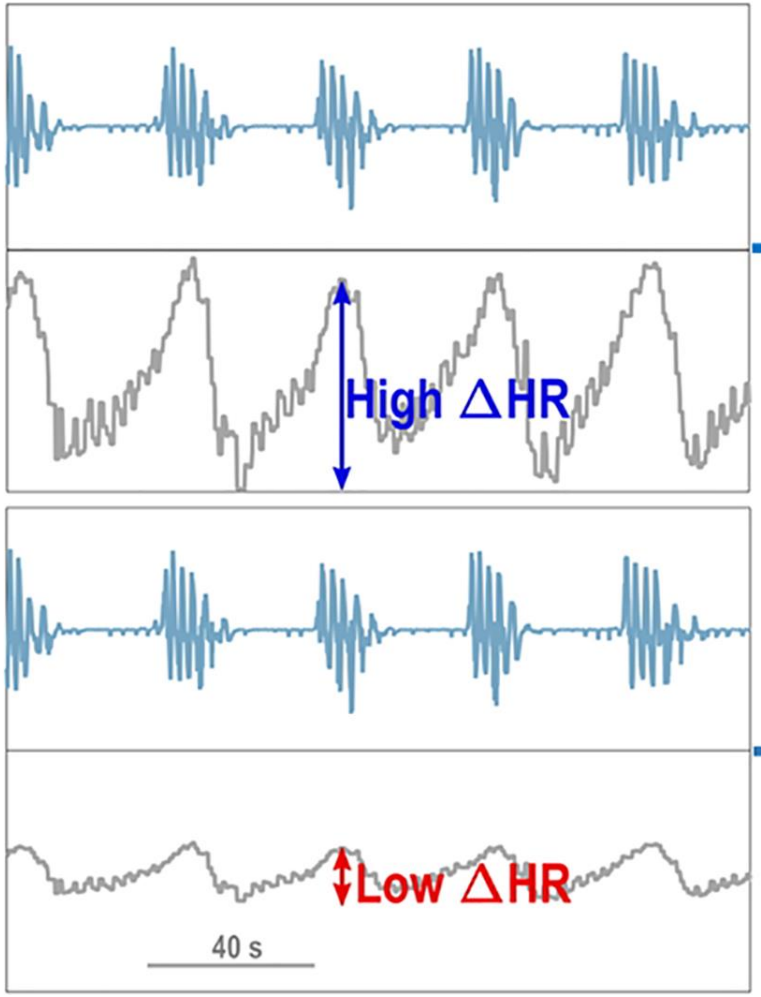
Characteristic	Overall (*N*=78)	Non-OSA (*N*=31)	OSA (*N*=47)	*P*-value
Predictor variable		Partially adjusted for age, gender, and race	Additionally adjusted for smoking, hyperlipidemia, hypertension, cardiovascular disease history, diabetes mellitus, baseline creatinine	
		OR (CI, *P*-value)	OR (CI, *P*-value)	
Model 1 AHI (continuous)		0.949 (0.905–0.995, 0.030)	0.918 (0.856–0.984, 0.015)	
Model 2 AHI > 4 (dichotomous)		0.376 (0.126–1.120, 0.079)	0.217 (0.045–1.038, 0.056)	
Model 3 Mild OSA (AHI≥5)		0.598 (0.156–2.291, 0.452)	0.409 (0.061–2.745, 0.357)	
Moderate OSA (AHI≥ 15)		0.484 (0.108–2.170, 0.343)	0.281 (0.036–2.190, 0.226)	
Severe OSA (AHI≥ 30)		0.093 (0.010–0.886, 0.039)	0.038 (0.002–0.610, 0.021)	

Sleep Breath (2013) 17:819–826

수면다원검사(Polysomnography)



ΔHR → SBP reduction prediction

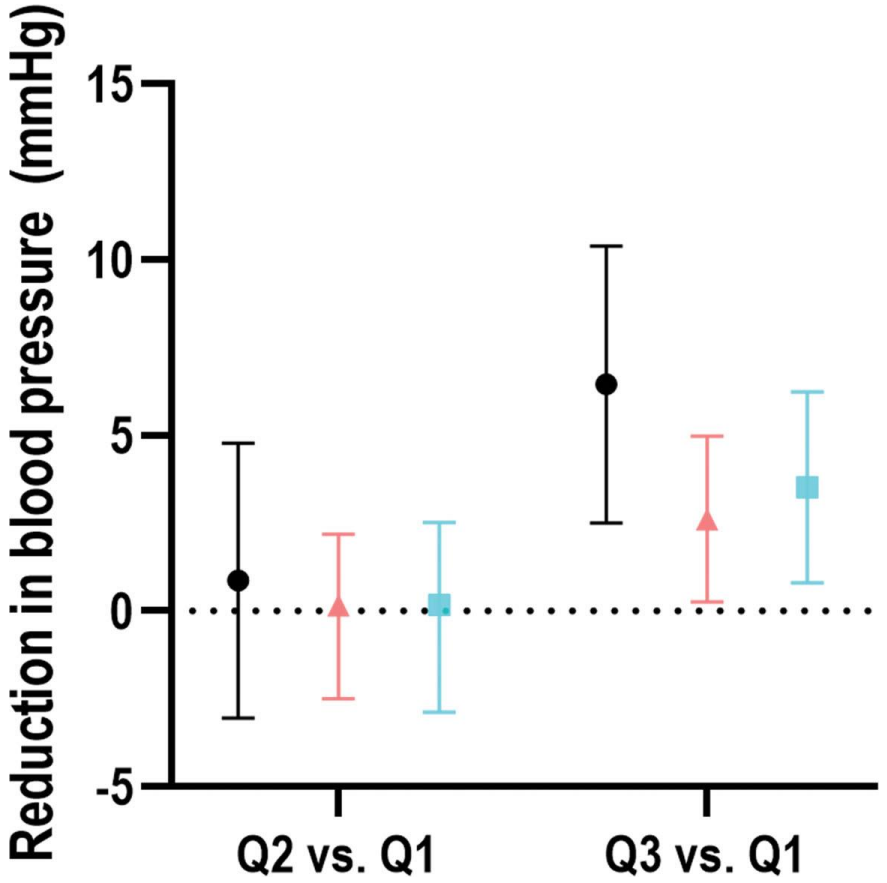


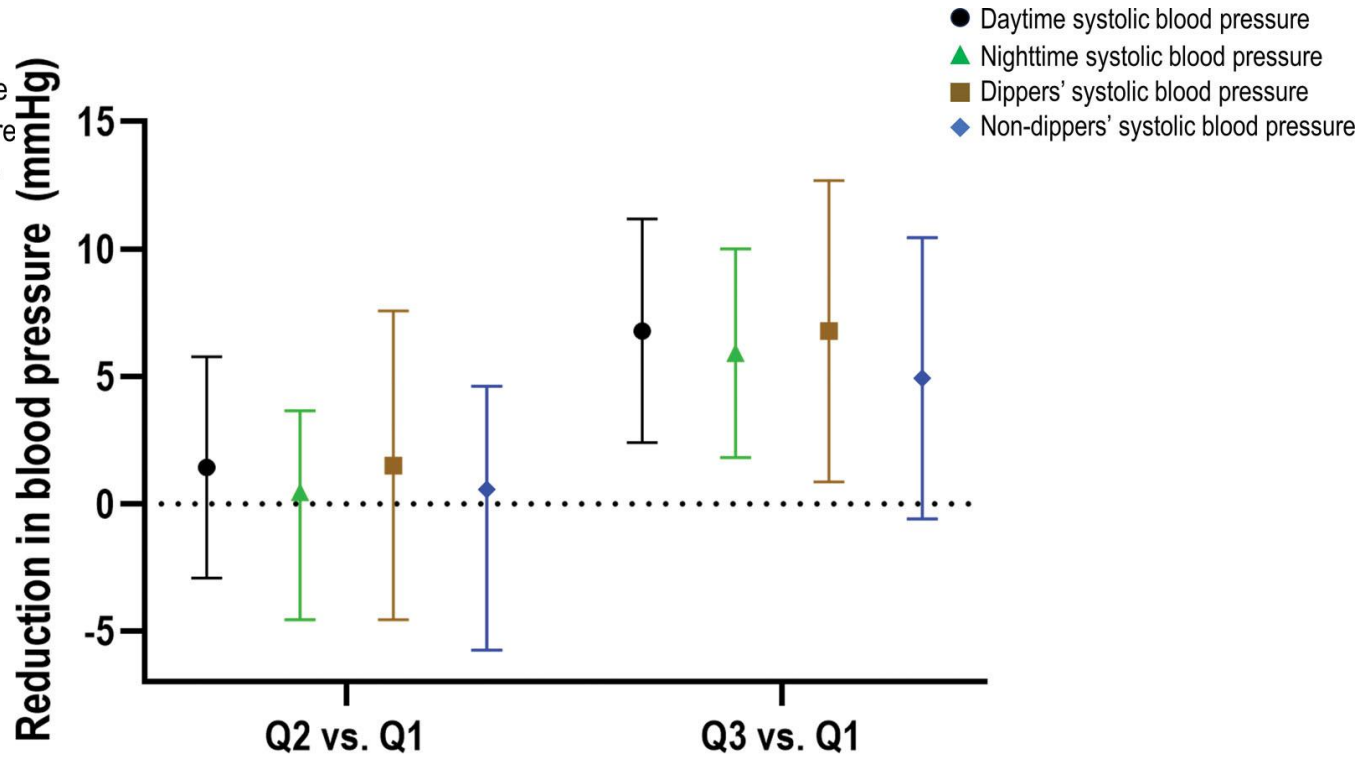
OSA is treated with CPAP or NSO for 3 months

Blood pressure ↓

No change in blood pressure

Ludovico et al, Hypertension, 2024





High ΔHR

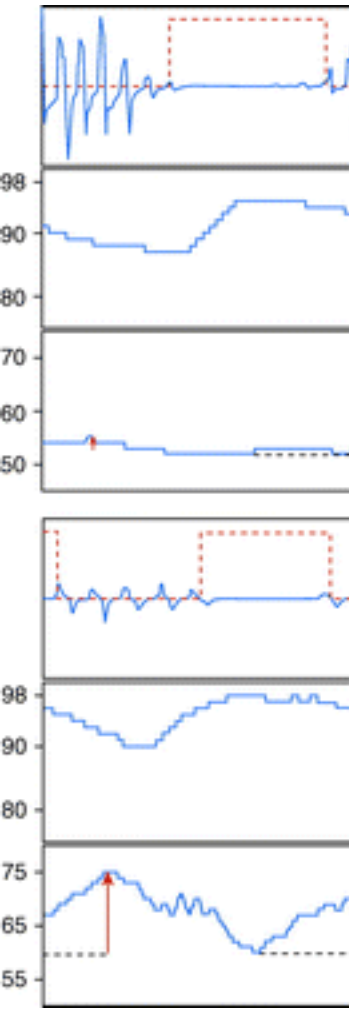
→ Predicted a more **favorable BP response to therapy**

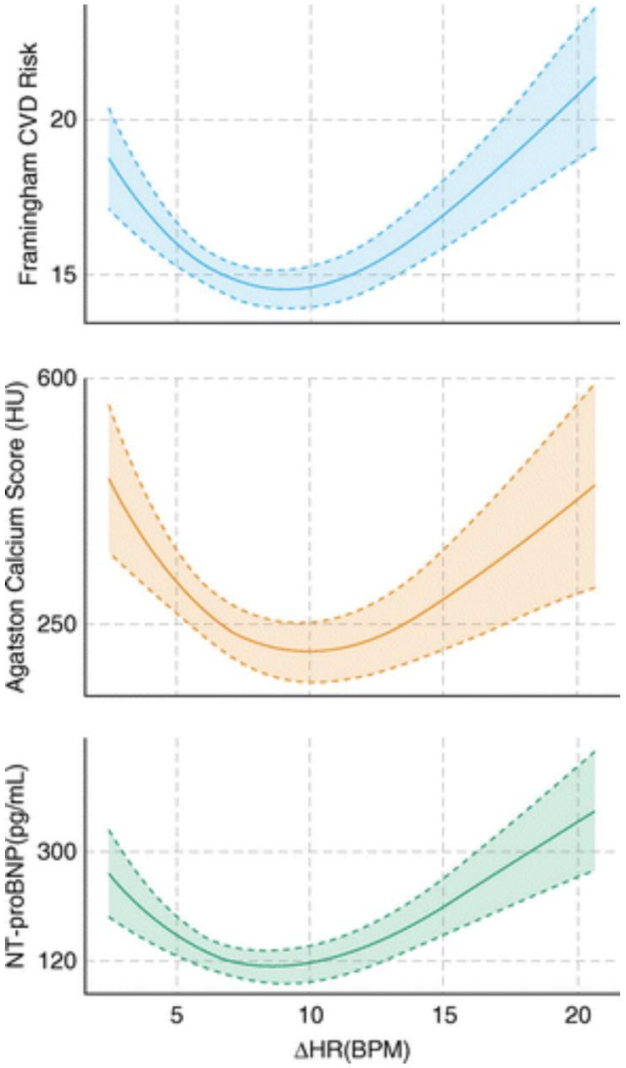
Greater reduction Hypoxic burden

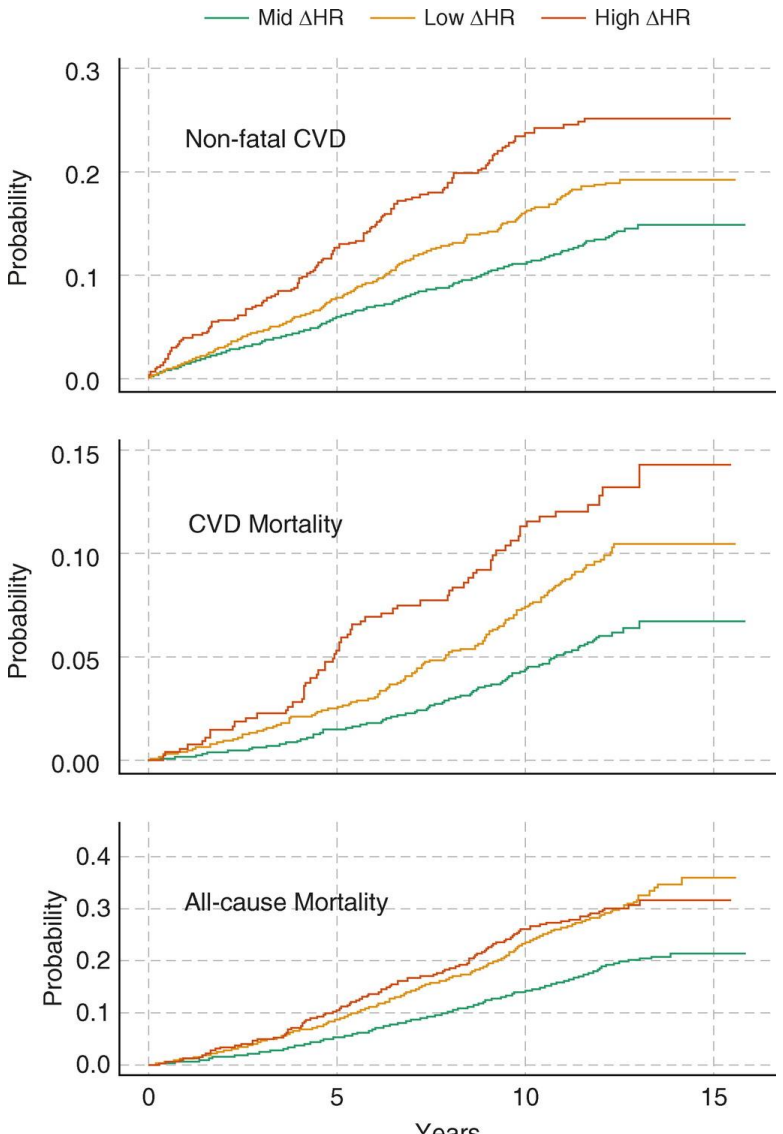
→ Improvement in SBP

Ludovico et al, Hypertension, 2024

ΔHR → Cardiovascular comorbidity







- MESA cohort
- SHHS cohort

Modreate-Severe OSA

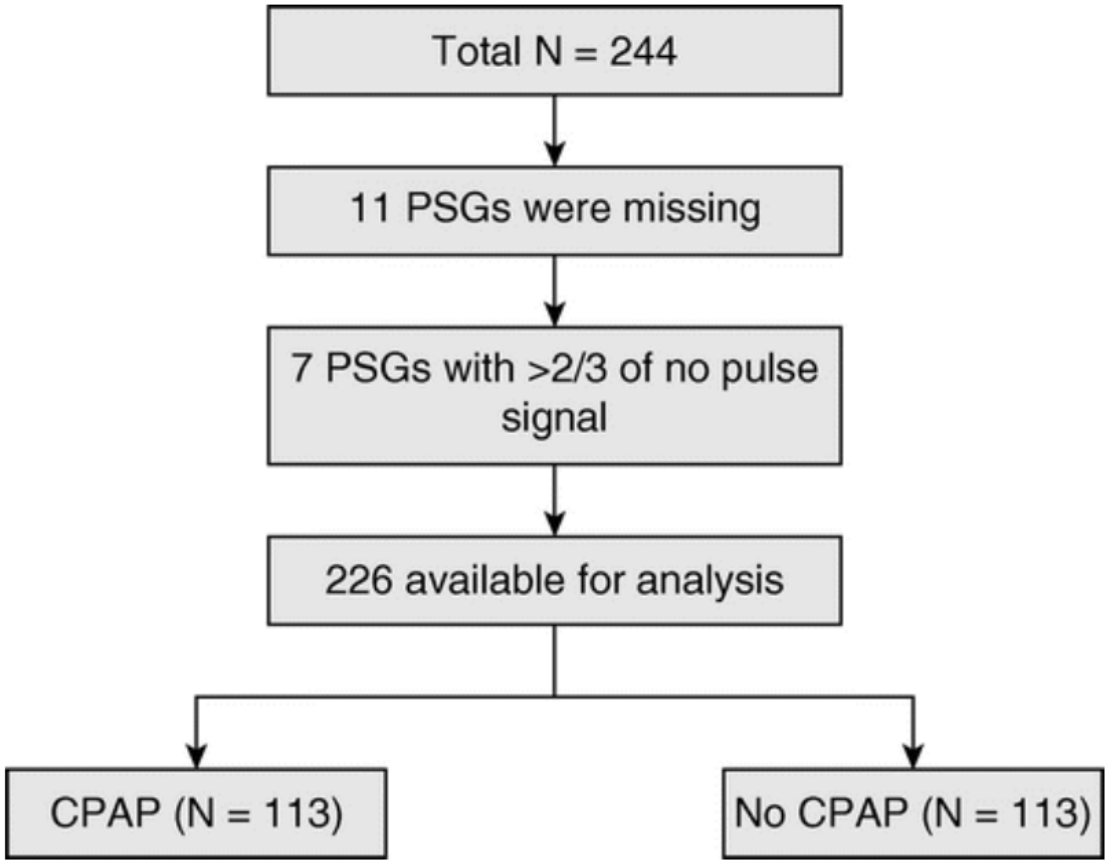
Azarbazin et al, AJRCCM 2019

High ΔHR → CPAP benefit?

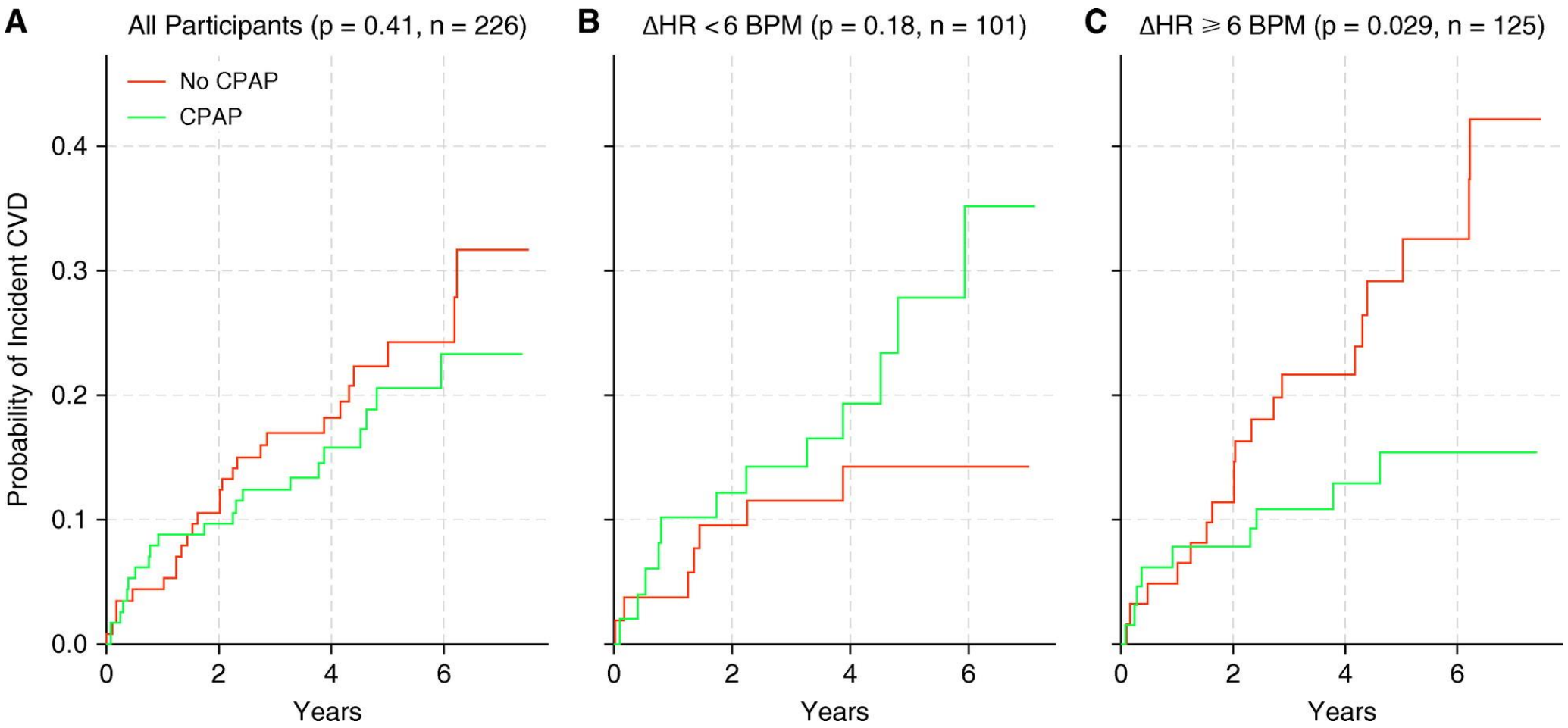
- RICACADSA RCT
- Post hoc analysis

- CPAP-related protection

- Primary outcome
  - Repeat revascularization
  - Myocardial infarction
  - Stroke
  - Cardiovascular mortality



Azarbazine et al, AJRCCM, 2021



- Patients with higher ΔHR exhibit greater cardiovascular benefit from CPAP therapy.

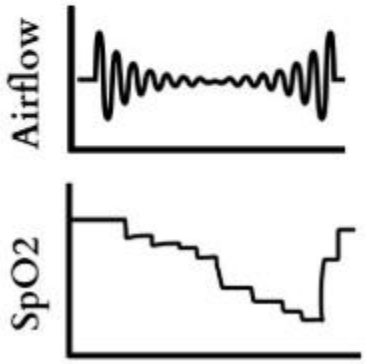
Azarbazine et al, AJRCCM, 2021

CURRENT MANAGEMENT

OSA

BIOMARKERS

Apnea/hypopnea index-
AHI

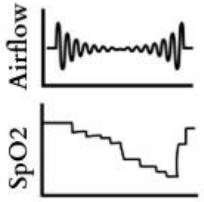


PROPOSED MANAGEMENT

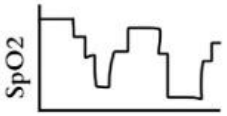
OSA

BIOMARKERS

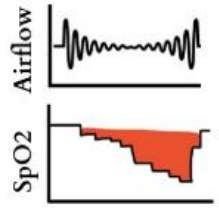
AHI



ODI
T90



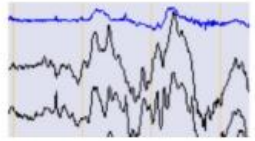
Hypoxic
burden



PATHOPHYSIOLOGY

Intermittent hypoxia

Sleep fragmentation



Changes in intrathoracic
pressure

CLINICAL
PHENOTYPES

HETEROGENEITY
OF THE DISEASE

Cluster analysis : Symptom subtype?

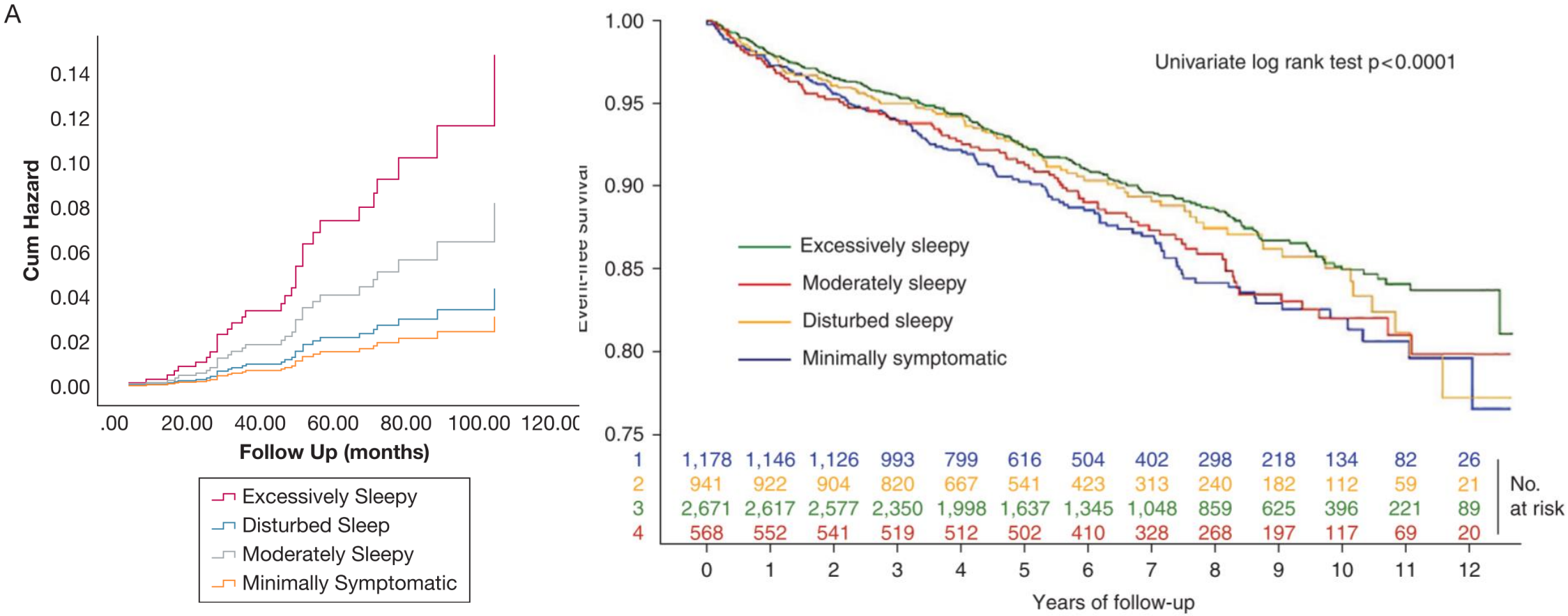


Figure 2 – *Cumulative incidence of cardiovascular mortality among different latent class analyses. (A) SHHS = Sleep Heart Health Study Icelandic Sleep Apnea Cohort.*

CHEST, 2021
AJRCCM. 2022

ERJ OPEN RESEARCH
ORIGINAL RESEARCH ARTICLE
D.R. MAZZOTTI ET AL.

OSA symptom subtypes and hypoxic burden independently predict distinct cardiovascular outcomes

Diego R. Mazzotti[1,2], Ulysses J. Magalang[3], Brendan T. Keenan[4], Jesse Mindel[3], Magdy Younes[5], Thomas Penzel[6], Allan I. Pack[4] and Philip de Chazal[7]

[1]Division of Medical Informatics, Department of Internal Medicine, University of Kansas Medical Center, Kansas City, KS, USA. [2]Division of Pulmonary Critical Care and Sleep Medicine, Department of Internal Medicine, University of Kansas Medical Center, Kansas City, KS, USA. [3]Division of Pulmonary, Critical Care and Sleep Medicine, Department of Internal Medicine, The Ohio State University Wexner Medical Center. [4]Division of Sleep Medicine, Department of Medicine, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, USA. [5]Sleep Disorders Centre, University of Manitoba, Winnipeg, Manitoba, Canada. [6]Interdisciplinary Sleep Medicine Center, Charite Universitatsmedizin, Berlin, Germany. [7]Charles Perkins Centre and School of Biomedical Engineering, University of Sydney, Sydney, NSW, Australia.

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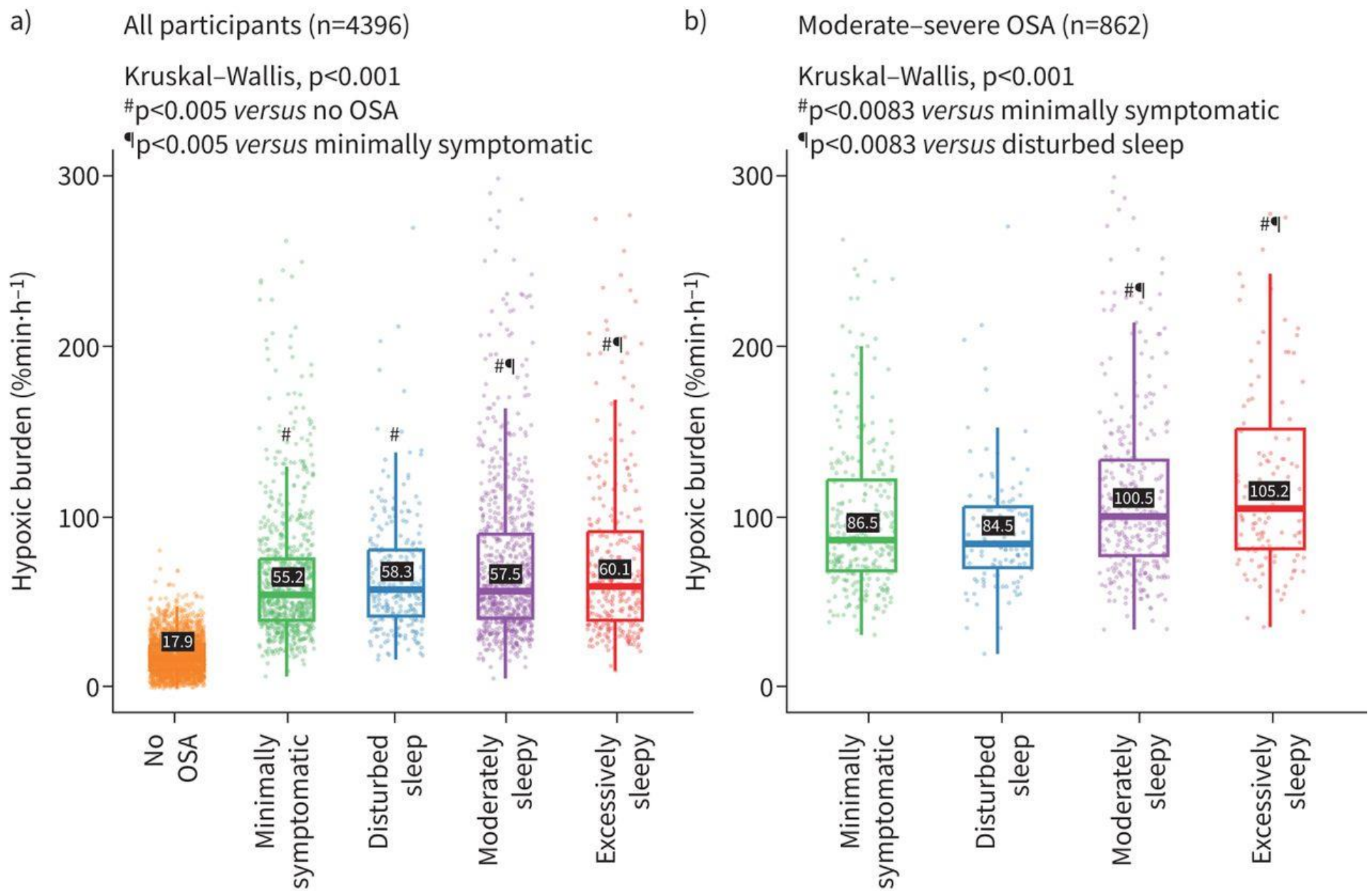


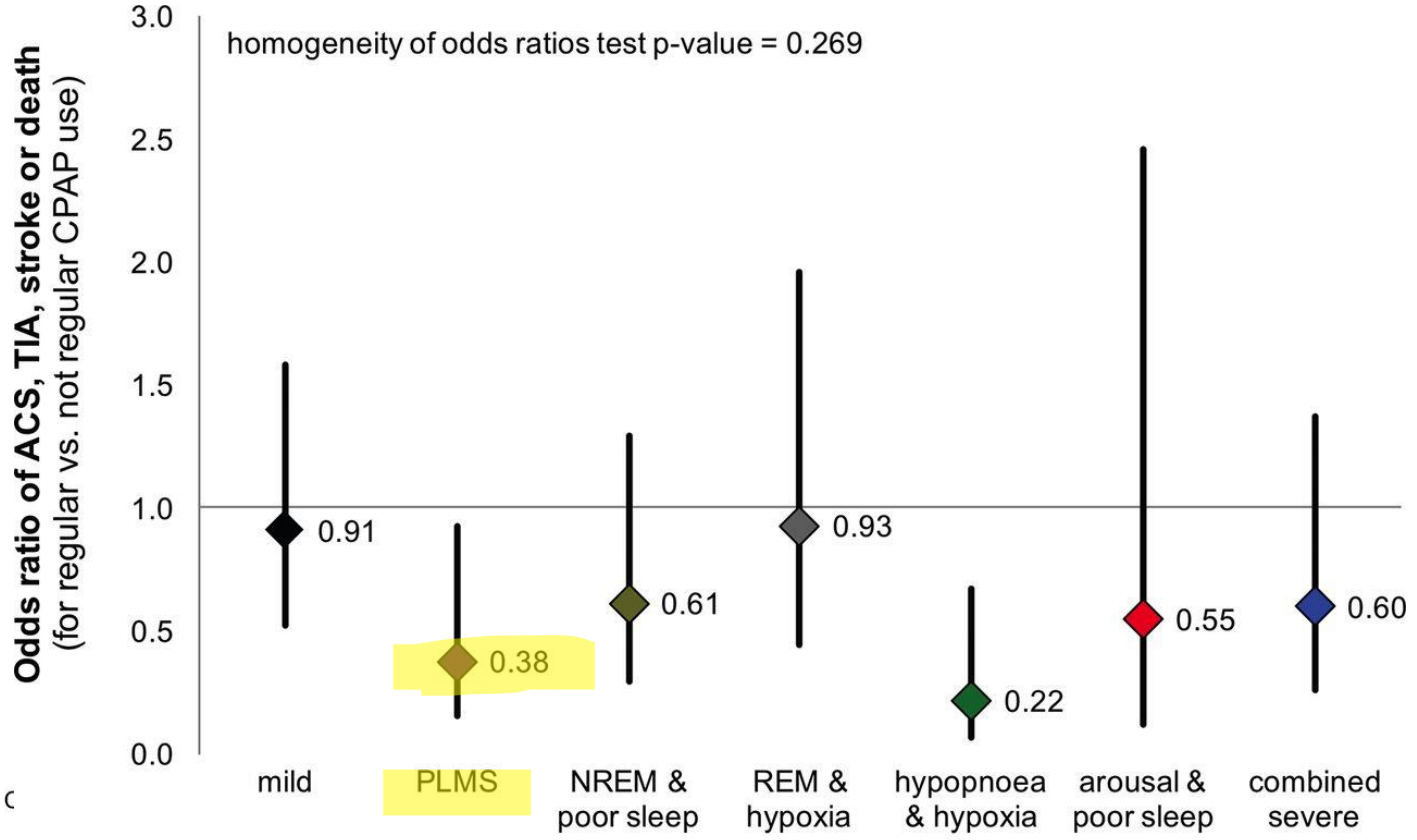
Diego et al, ERJ, 2025

Model	Variable	CV mortality		MACE	
		HR (95% CI)	p-value[#]	HR (95% CI)	p-value[#]
Model B1:	Symptom subtypes	Overall p=0.697		**Overall p<0.001**	
Symptom subtypes	No OSA	1.00 (reference)	-	1.00 (reference)	-
+ Clinical covariates[¶]	Minimally symptomatic	0.86 (0.59–1.27)	0.448	0.85 (0.70–1.03)	0.098
	Disturbed sleep	0.66 (0.35–1.26)	0.206	0.84 (0.62–1.13)	0.251
	Moderately sleepy	0.84 (0.57–1.23)	0.369	0.95 (0.79–1.15)	0.613
	Excessively sleepy	0.95 (0.54–1.66)	0.858	**1.56 (1.22–2.00)**	**<0.001**
Model B2:	Hypoxic burden (log scale)	1.04 (0.86–1.24)	0.697	0.98 (0.90–1.07)	0.657
Hypoxic burden					
+ Clinical covariates[¶]					
Model B3:	Symptom subtypes	Overall p=0.336		**Overall p<0.001**	
Symptom subtypes	No OSA	1.00 (reference)	-	1.00 (reference)	-
+ Hypoxic burden	Minimally symptomatic	0.69 (0.43–1.11)	0.126	0.86 (0.68–1.09)	0.220
+ Clinical covariates[¶]	Disturbed sleep	0.52 (0.26–1.06)	0.072	0.86 (0.61–1.19)	0.356
	Moderately sleepy	0.66 (0.41–1.07)	0.095	0.97 (0.77–1.22)	0.815
	Excessively sleepy	0.75 (0.40–1.41)	0.378	**1.59 (1.20–2.11)**	**0.001**
	Hypoxic burden (log scale)	1.22 (0.95–1.56)	0.116	0.98 (0.87–1.11)	0.775
Model C1:	Symptom subtypes	Overall p=0.870		**Overall p<0.001**	
Symptom subtypes	No OSA	1.00 (reference)	-	1.00 (reference)	-
+ Clinical covariates[¶]	Minimally symptomatic	0.95 (0.62–1.47)	0.825	0.91 (0.74–1.13)	0.385
+ Other OSA severity measures[+]	Disturbed sleep	0.72 (0.37–1.41)	0.341	0.89 (0.65–1.22)	0.471
	Moderately sleepy	0.93 (0.60–1.44)	0.732	1.02 (0.83–1.25)	0.855
	Excessively sleepy	1.07 (0.58–1.95)	0.835	1.67 (1.28–2.17)	<0.001
Model C2:	Hypoxic burden (log scale)	1.41 (1.02–1.94)	0.037	1.05 (0.91–1.21)	0.529
Hypoxic burden					
+ Clinical covariates[¶]					
+ Other OSA severity measures[+]					
Model C3:	Symptom subtypes	Overall p=0.415		**Overall p<0.001**	
Symptom subtypes	No OSA	1.00 (reference)	-	1.00 (reference)	-
+ Hypoxic burden	Minimally symptomatic	0.72 (0.45–1.16)	0.181	0.89 (0.7–1.12)	0.308
+ Clinical covariates[¶]	Disturbed sleep	0.54 (0.27–1.09)	0.087	0.86 (0.62–1.21)	0.392
+ Other OSA severity measures[+]	Moderately sleepy	0.70 (0.44–1.14)	0.153	0.99 (0.79–1.25)	0.942
	Excessively sleepy	0.83 (0.44–1.54)	0.549	1.62 (1.23–2.15)	<0.001
	Hypoxic burden (log scale)	1.63 (1.13–2.35)	0.009	1.05 (0.89–1.23)	0.584

Diego et al, ERJ, 2025

OSA → Heterogenous subtype

- Cluster analysis (K-means)
- Determining Risk of Vascular Events by Apnea Monitoring (DREAM) study cohort
  2041 Veterans
- 2000-2004 → 2012
- 271 patients
  : ACS, TIA, Stroke, Death
- PLMS
  (Periodic limb movement during sleep)

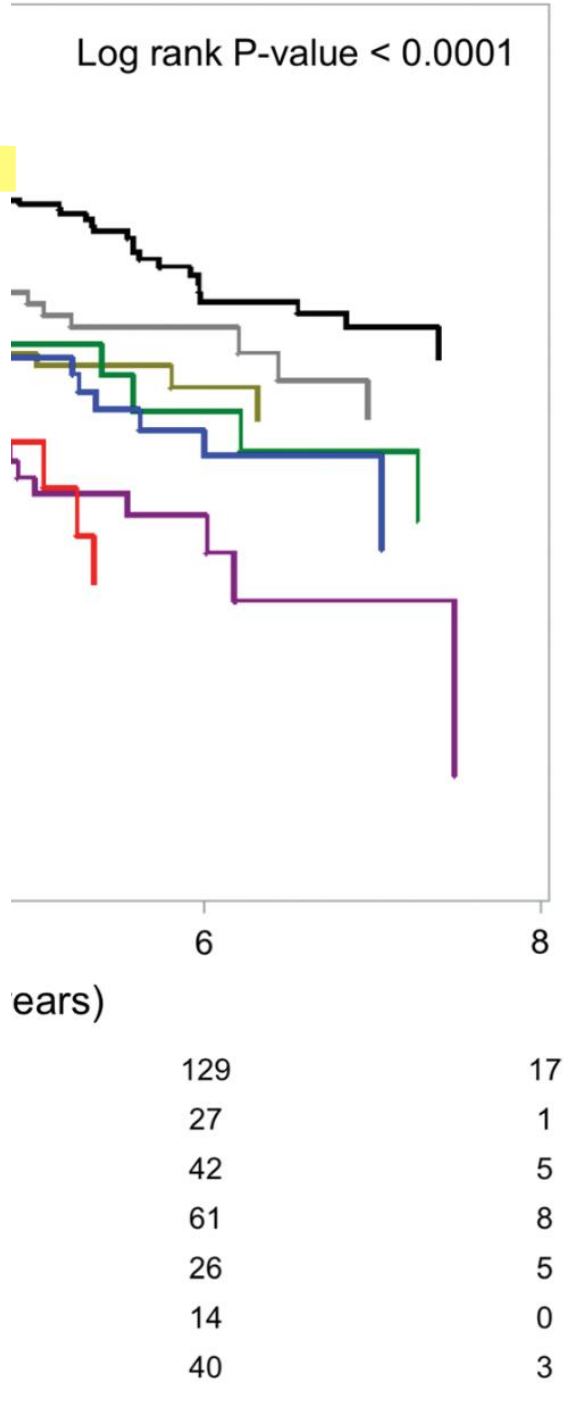


REM & hypoxia	167	154	129	61	8
hypopnoea & hypoxia	74	67	51	26	5
arousal & poor sleep	41	34	29	14	0
combined severe	124	110	95	40	3

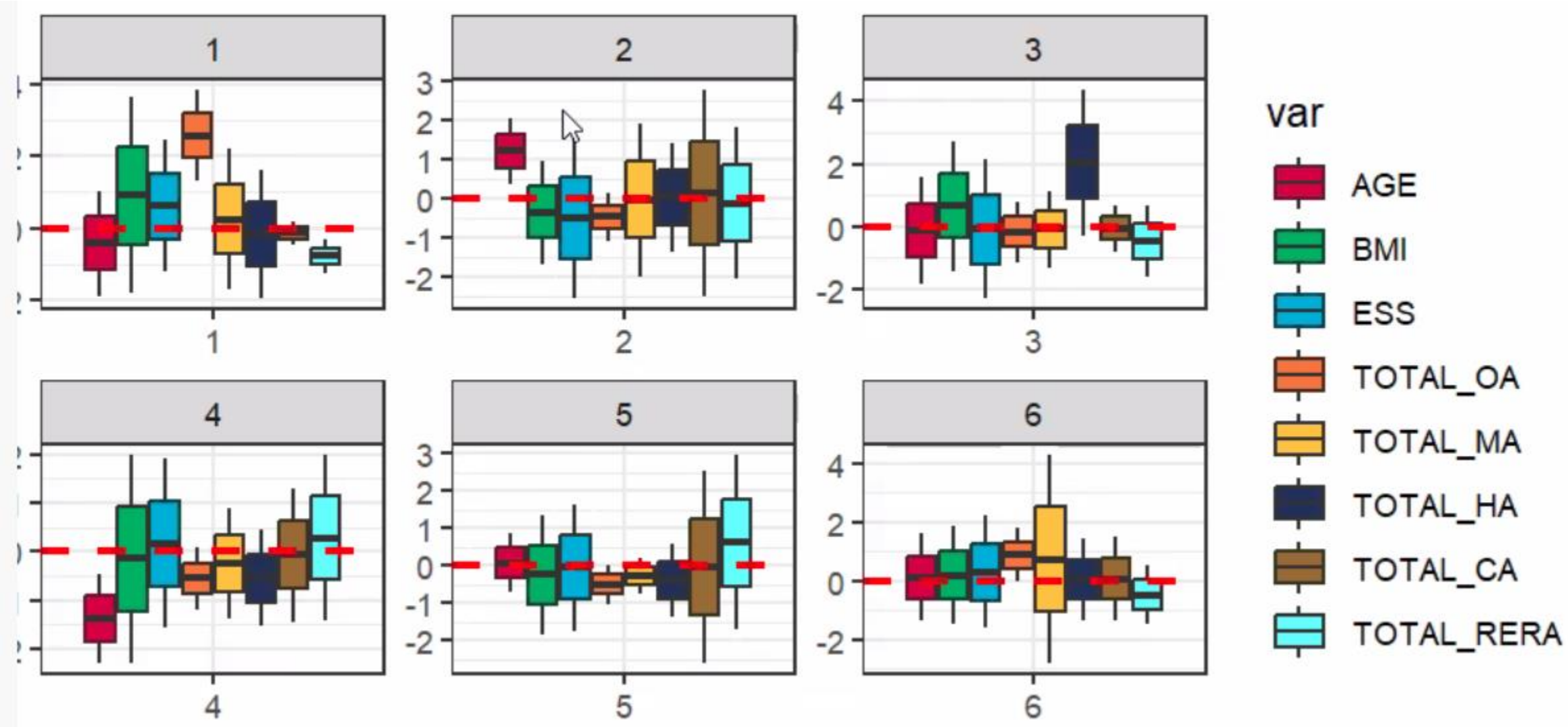
Zinchuk et al, Thorax 2018;73:472-480

Table 3 Polysomnographic characteristics of OSA clusters (ranked by AHI, A–G) grouped according to domain (breathing disturbance, hypoxaemia, sleep architecture disturbance and autonomic dysregulation)*

Cluster/variable	(A) Mild	(B) PLMS	(C) NREM and poor sleep	(D) REM and hypoxia	(E) Hypopnoea and hypoxia	(F) Arousal and poor sleep	(G) Combined severe
N	533	119	186	168	75	42	124
			Mean±SD or median (IQR)				
AHI	3.6 (9.0)	9.9 (18.6)	19.3(30.6)	18.9(24.5)	44.2 (39.0)	67.8 (30.4)	83.9 (28.0)
			Breathing disturbance				
Total apnoea index	3.9 (5.5)	5.0 (11.6)	13.0 (26.2)	13.5 (18.3)	13.8 (22.3)	61.6 (29.4)	77.9 (28.9)
Total hypopnoea Index	3.0 (12.8)	6.0 (16)	4.0 (11.0)	7.0 (17.0)	32.0 (51.0)	3.5 (11.0)	1.0 (6.0)
% Obstructive apnoeas	66±37	79±29	82±29	89±17	89±24	87±24	80±26
% Combined apnoeas	46±33	49±31	58±31	55±26	63±26	32±22	81±20
% Apnoeas with arousal only	32±34	32±33	30±30	18±22	9±17	65±23	7±9
REM: NREM apnoea ratio	3.4±7.5	2.3±5.3	**0.8±3.6**	**8.1±15.7**	0.3±1.1	0.1±0.4	0.1±0.2
Apnoea D4: apnoea arousal ratio	1.4±4.1	1.2±2.7	0.8±1.6	3.1±4.3	7.2±10.8	**0.1±0.1**	**4.4±8.4**
			Hypoxaemia				
T<90% O_2 Index	0.00 (0.02)	0.02 (0.10)	0.01 (0.10)	**0.09 (0.23)**	**0.14 (0.36)**	0.00 (0.04)	**0.20 (0.41)**
>4% Desaturation index	4.1 (8.8)	8.7 (15.1)	18.5 (24.8)	19.8 (22.0)	57.1 (37.5)	21.0 (41.1)	**74.2 (30.1)**
Lowest nocturnal O_2 % saturation	86.1±4.2	82.7±6.7	84.7±5.0	72.8±7.6	78.8±6.8	**87.1±4.2**	77.7±7.0
			Sleep architecture disturbance				
Sleep efficiency	77.7±14.5	69.8±17.5	**54.7±17.9**	79.6±13.6	68.2±16.7	56.4±22.8	68.8±16.6
Stage 1 %	15.2 (8.9)	21.1 (12.2)	**40.9 (20.3)**	16.5 (10.7)	23.2 (15.4)	40.8 (23.4)	40.6 (25.4)
Stages 3 and 4 %	1.5 (8.4)	0.2 (4.8)	**0.0 (0.0)**	0.0 (6.6)	0.0 (0.0)	**0.0 (0.0)**	0.0 (0.0)
REM %	12.0 (12.7)	6.4 (14.0)	**0.0 (6.4)**	12.3 (10.6)	0.0 (2.7)	**0.0 (0.0)**	0.0 (0.0)
Stage shift index	23.8±10.2	27.3±12.2	**47.9±23.1**	24.7±12.4	33.1±18.2	57.3±29.1	45.4±28.0
			Autonomic dysregulation				
Total arousal index	25.9±12.1	40.7±21.5	65.1±23.6	37.3±19.8	60.1±25.0	88.5±27.4	91.7±27.3
% Spontaneous arousals	66±22	43±20	50±21	43±23	28±16	19±11	13±10
PLMS index	0.0 (6.2)	64.7 (32.3)	0.0 (7.6)	0.0 (4.9)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)



Cluster analysis in WSCH sleep cohort



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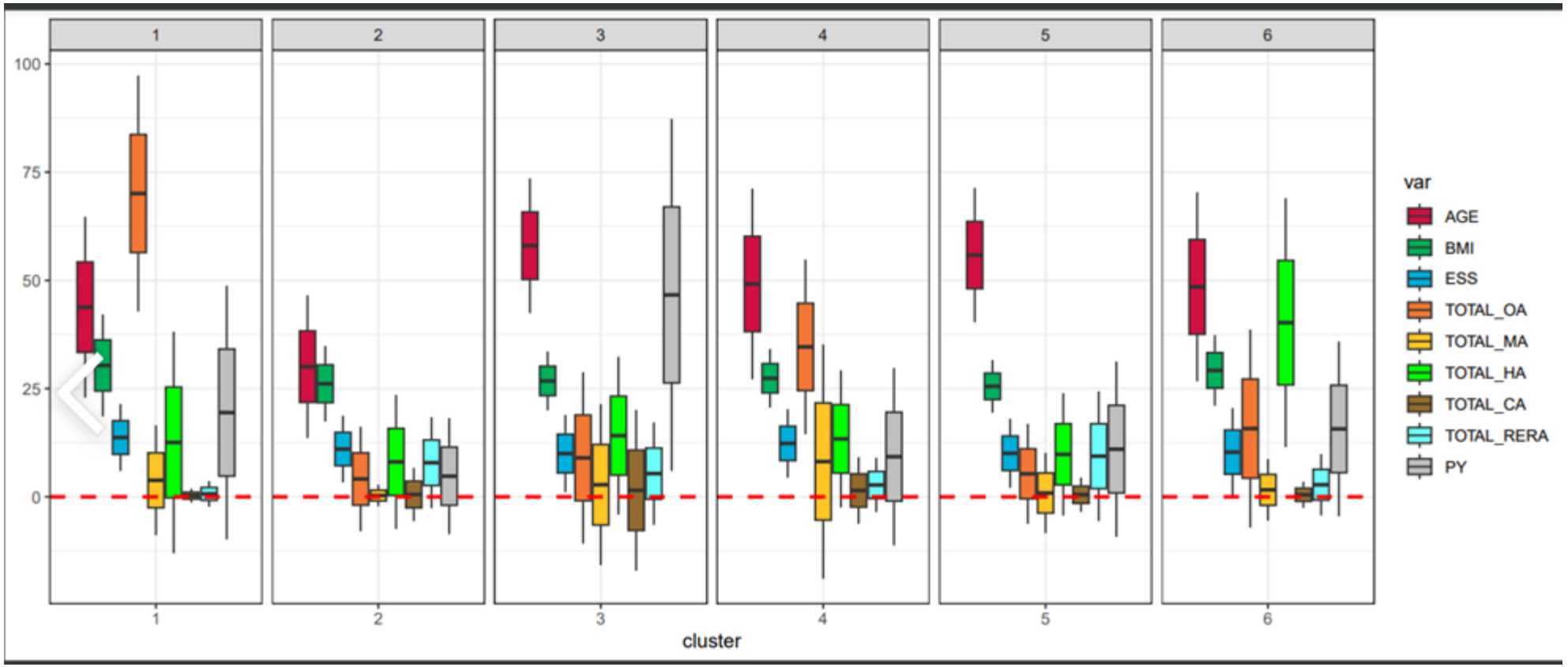

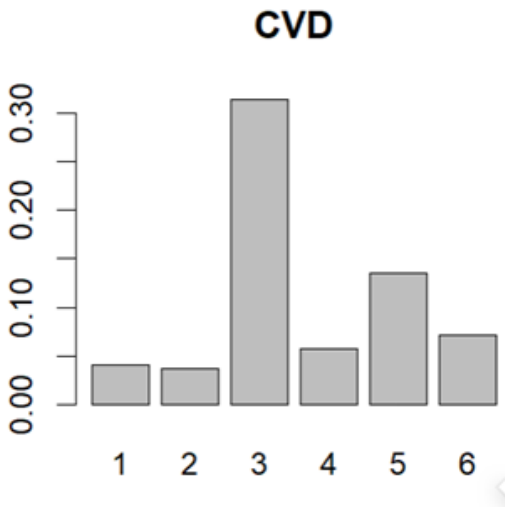

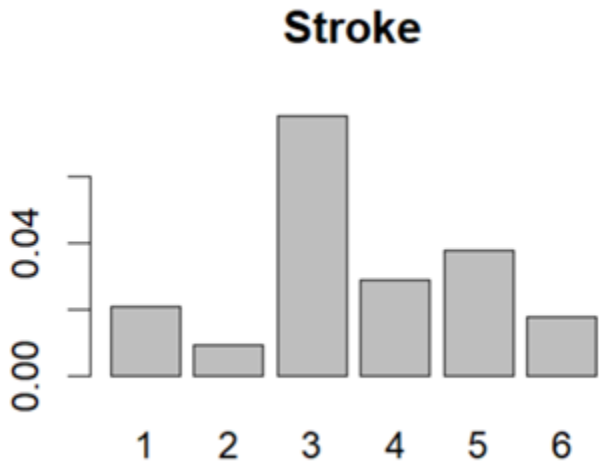

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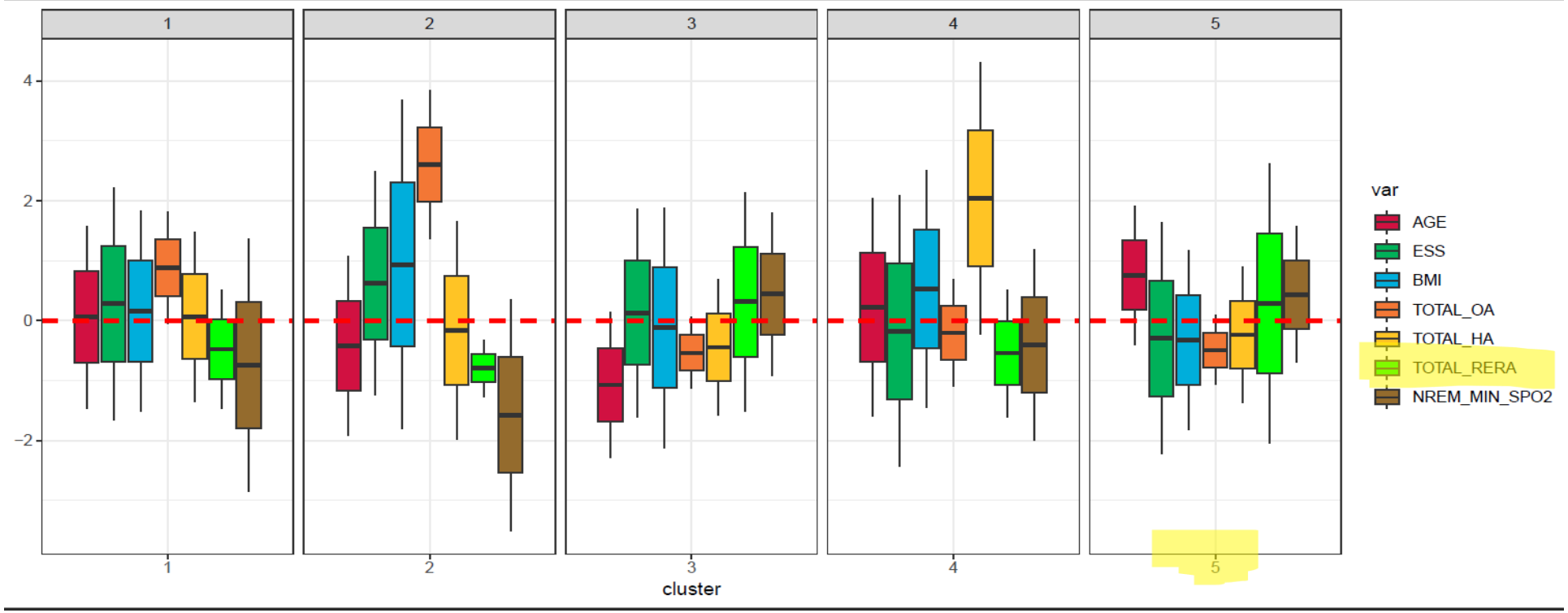
Cluster analysis in WSCH sleep cohort



	Estimate	Std. Error	z value	Pr(>|z|)
(Intercept)	-5.477	0.587586	-9.3212	1.15E-20
cluster2	0.021842	0.514694	0.042437	0.96615
cluster3	0.701385	0.415249	1.68907	0.091206
cluster4	0.601557	0.384931	1.562766	0.118108
cluster5	0.634783	0.308389	2.058383	0.039553
AGE	0.048926	0.008927	5.480971	4.23E-08
PY	0.018479	0.003939	4.691903	2.71E-06

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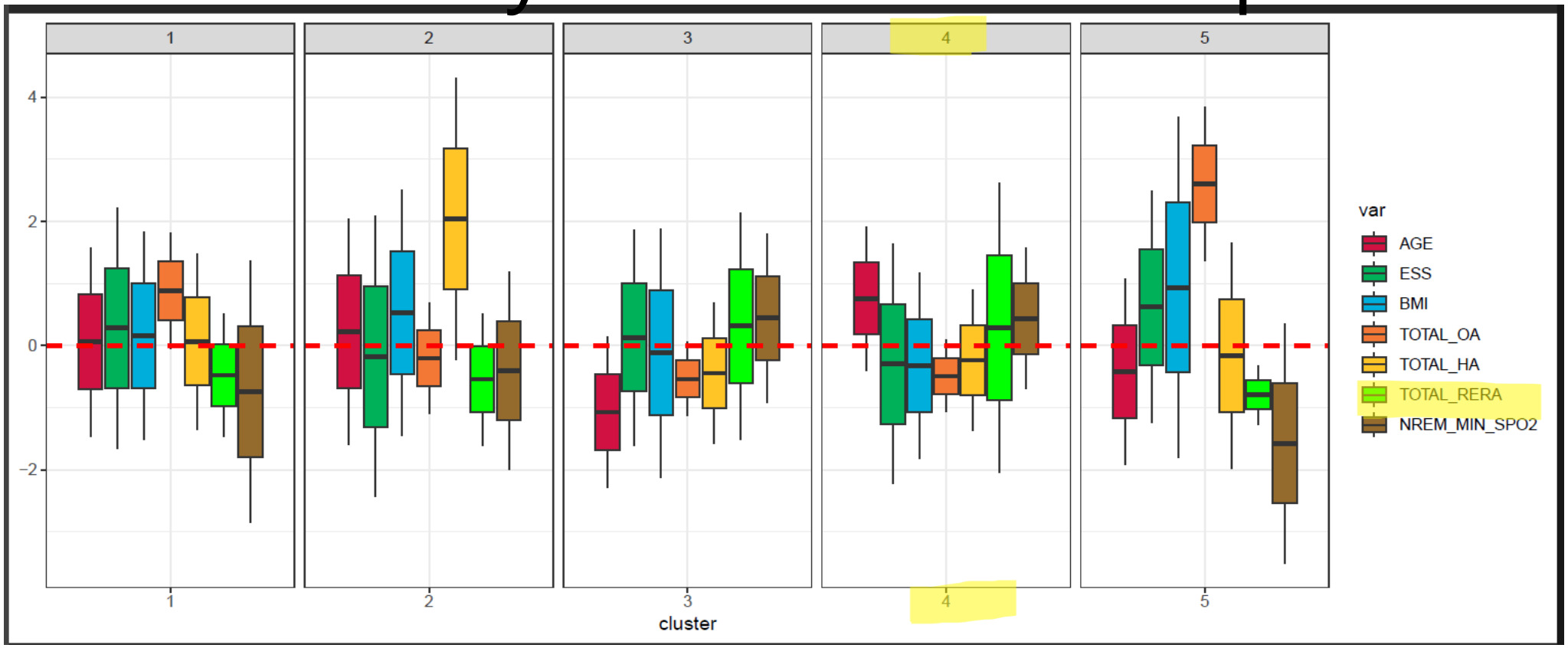
Cluster analysis in WSCH sleep cohort



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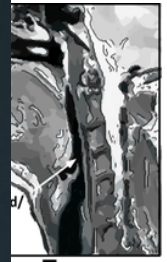
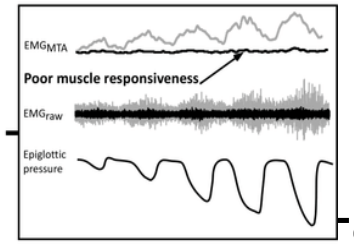
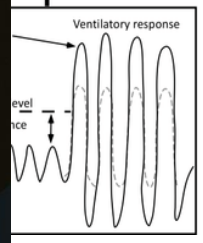


Anatomical factor

→CPAP, Surgery, Oral appliance
Positional therapy, Weight loss

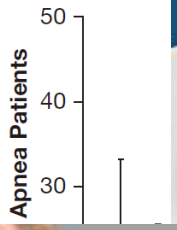


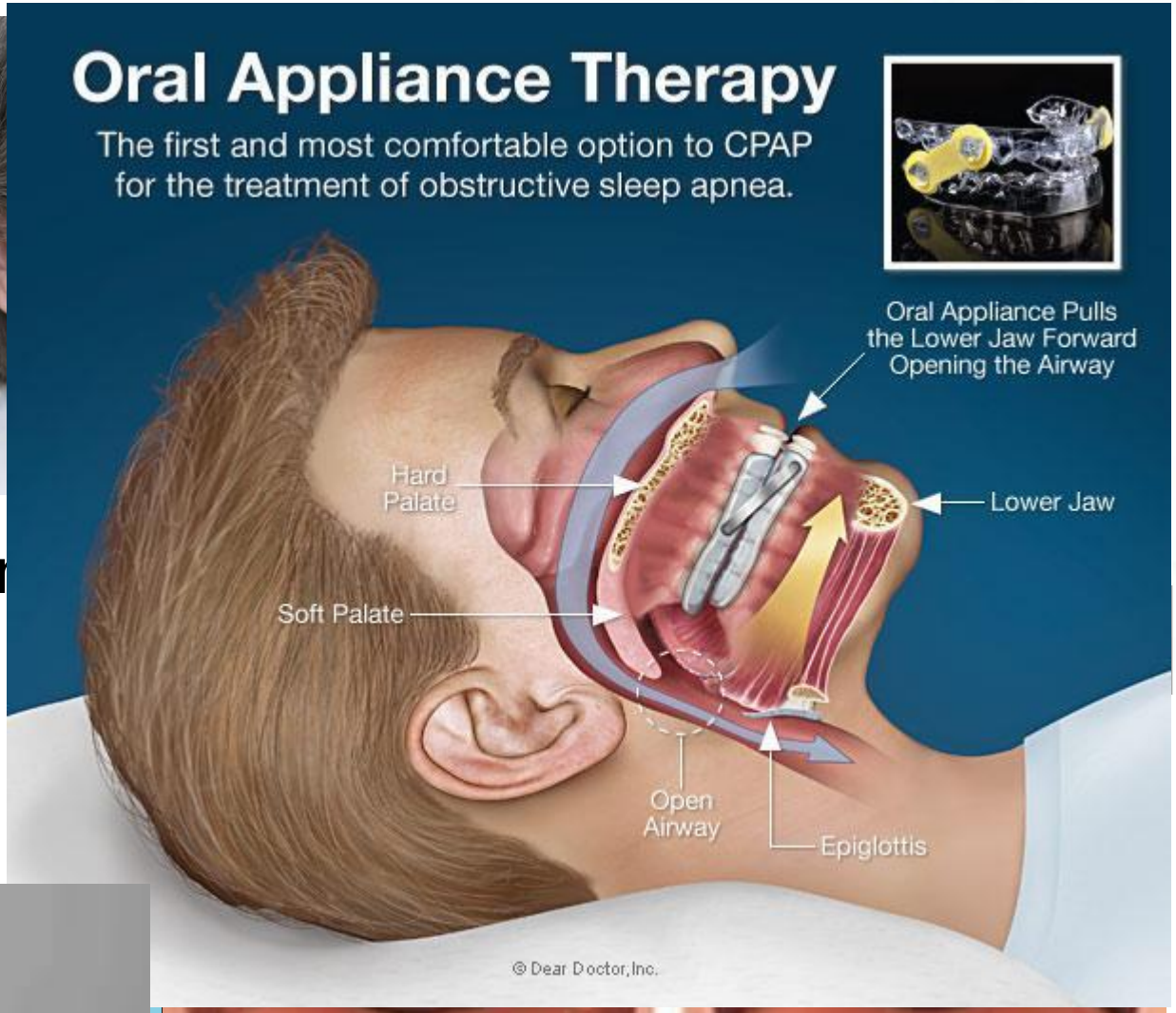
OSA

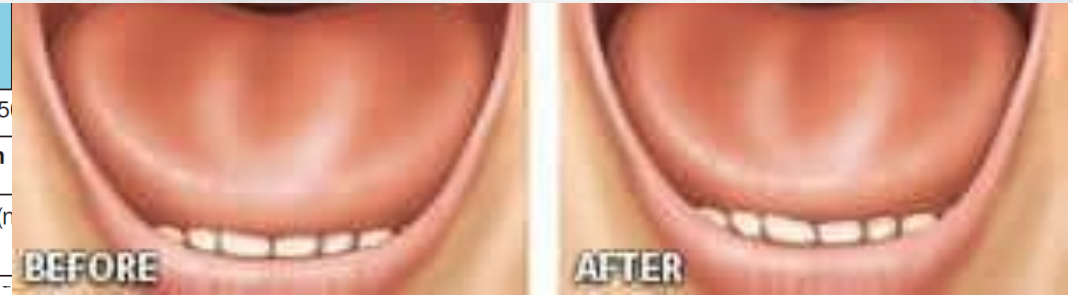


Non-anatomical factor

약 70%





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감 사 합 니 다