Hypoxic burden in Obstructive sleep apnea

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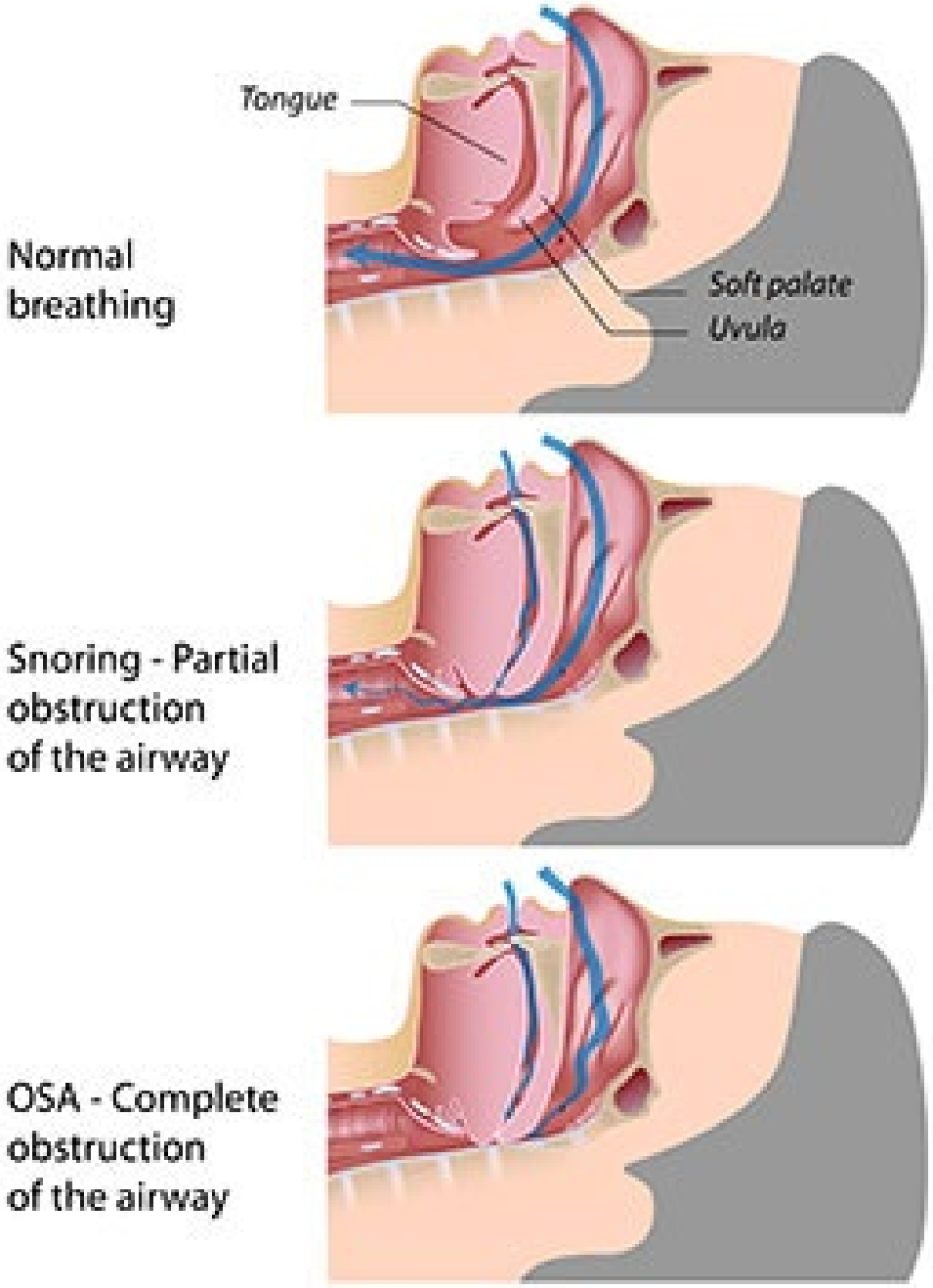


Apnea (무호흡) : 10s, 90% reduction

Hypopnea (저호흡) : 30%, 3% or 4% Spo2

AHI : Apnea + Hypopnea index

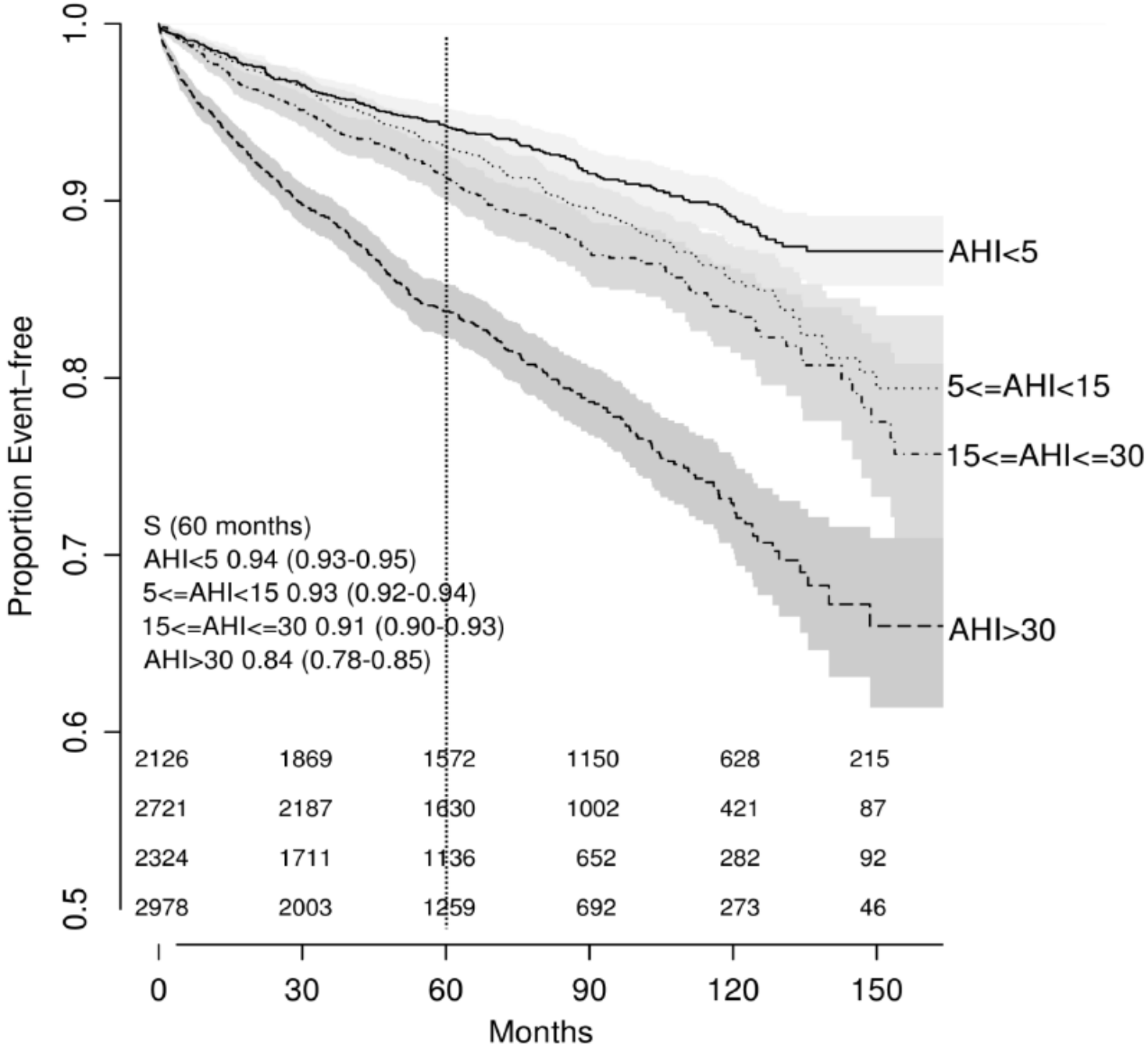
RERA(Respiratory effort-related arousal)

RDI : AHI + RERA index

ODI (Oxygen desaturation index)

T90, TST90 (total sleep time, under 90%)

OSA and Cardiovascular disease



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

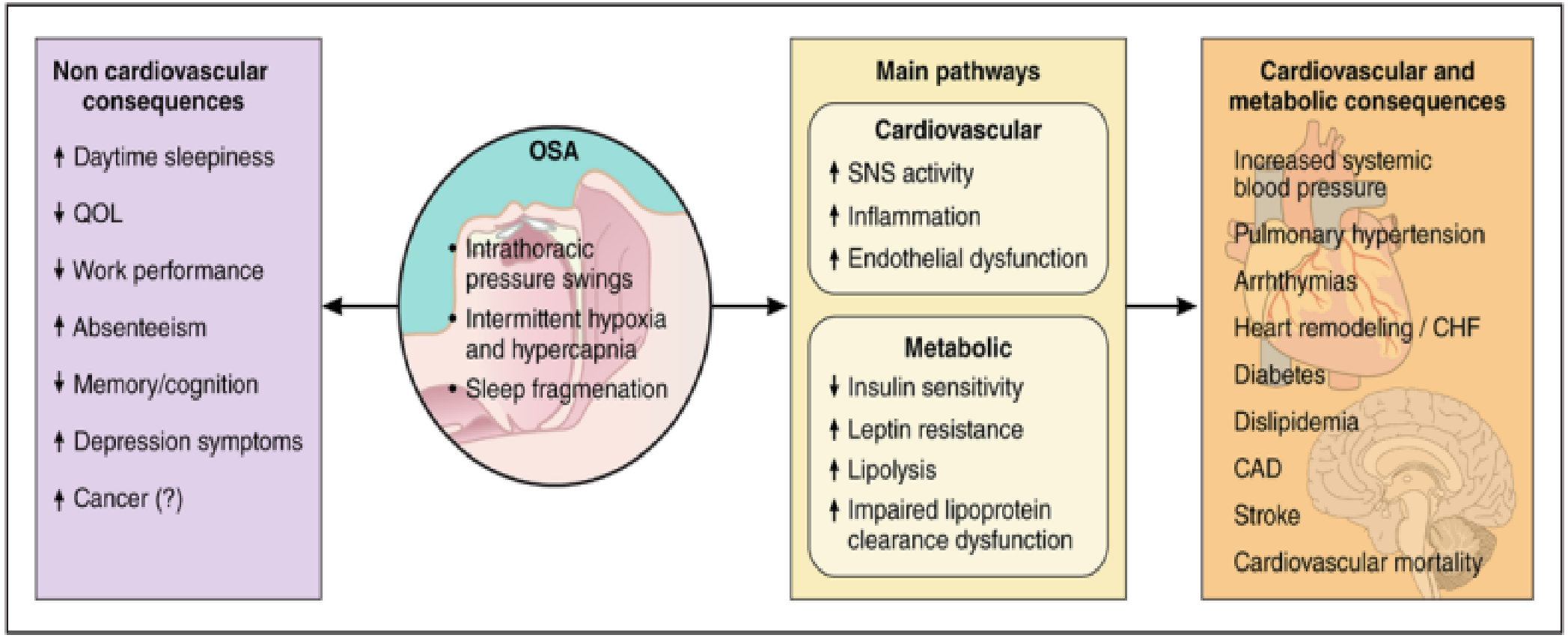


Figure 1. Proposed consequences of obstructive sleep apnea (OSA).

CAD indicates coronary artery disease; CHF, congestive heart failure; QOL, quality of life; and SNS, sympathetic nervous system.

Short period

Compliance ▲▲

Long period

Compliance ▲

- **EDS(졸림)** : Low in Heart failure, A.fib
  High in asthma
  AHI correlation.

- **QOL(quality of life)** : sleep related QOL (more improved)

- **CAR crash**
  Disease severity(AHI) and rates of crashes is **inconclusive**.

  Recent, SHHS ; AHI(4% hypopnea) : **OR 1.15**, CI 1.07-1.26

  AHI 10증가 < **sleeping one hour less per night**

- **HTN**

  Severe OSA (AHI 3%, >30)
  more strongly than BMI 30, Male sex

- **CHD(Coronary heart disease)**

  AHI>10, OR 3.1,
  (DM과 비슷, HTN, hyperlipidemia보다 높다) (Peker et al)

  AHI >14, OR 4.5 (HTN, DM, BMI 5증가와 비슷)
  (**Smoking aOR 1.6 보다 높다**) (Mooe et al)

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

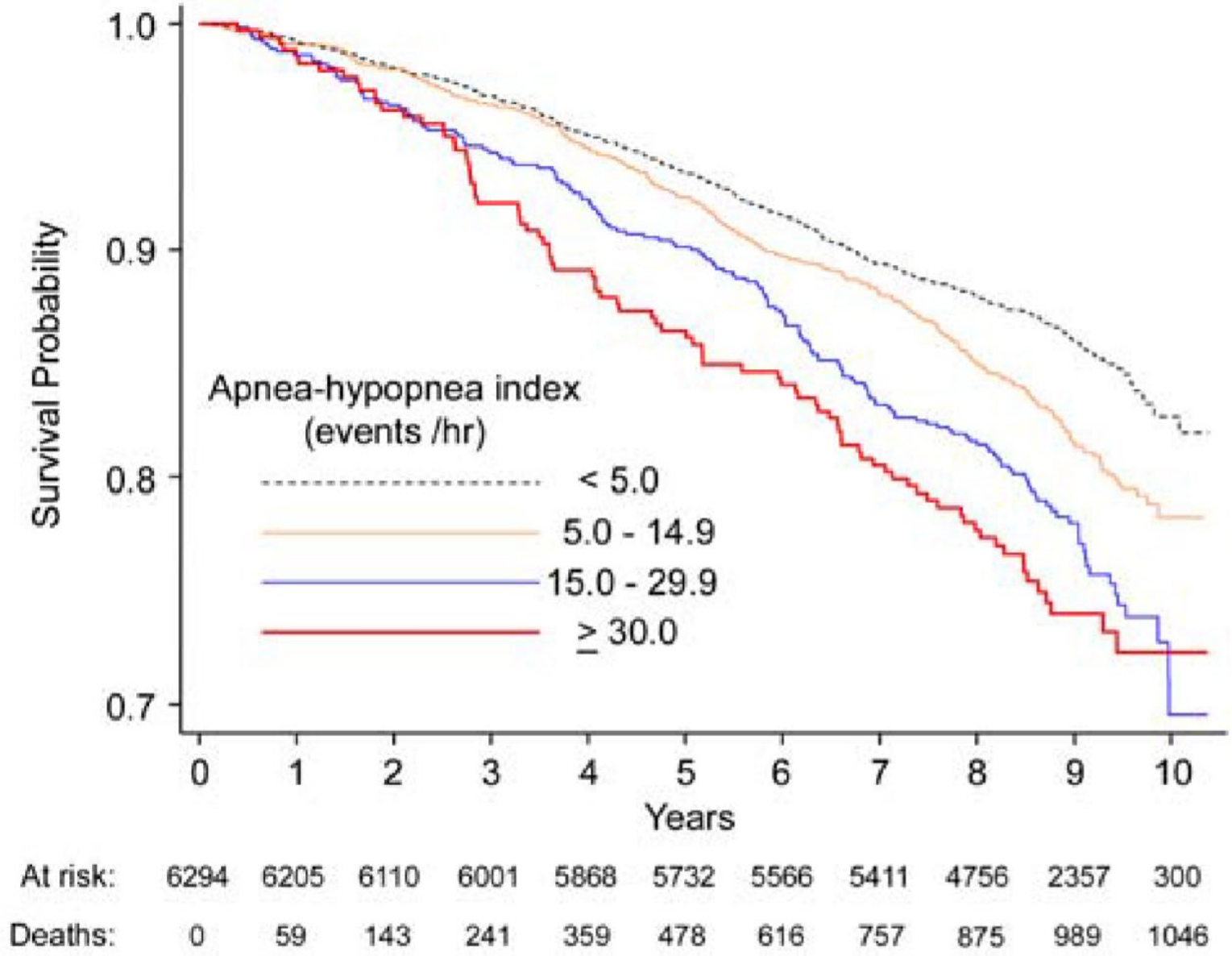
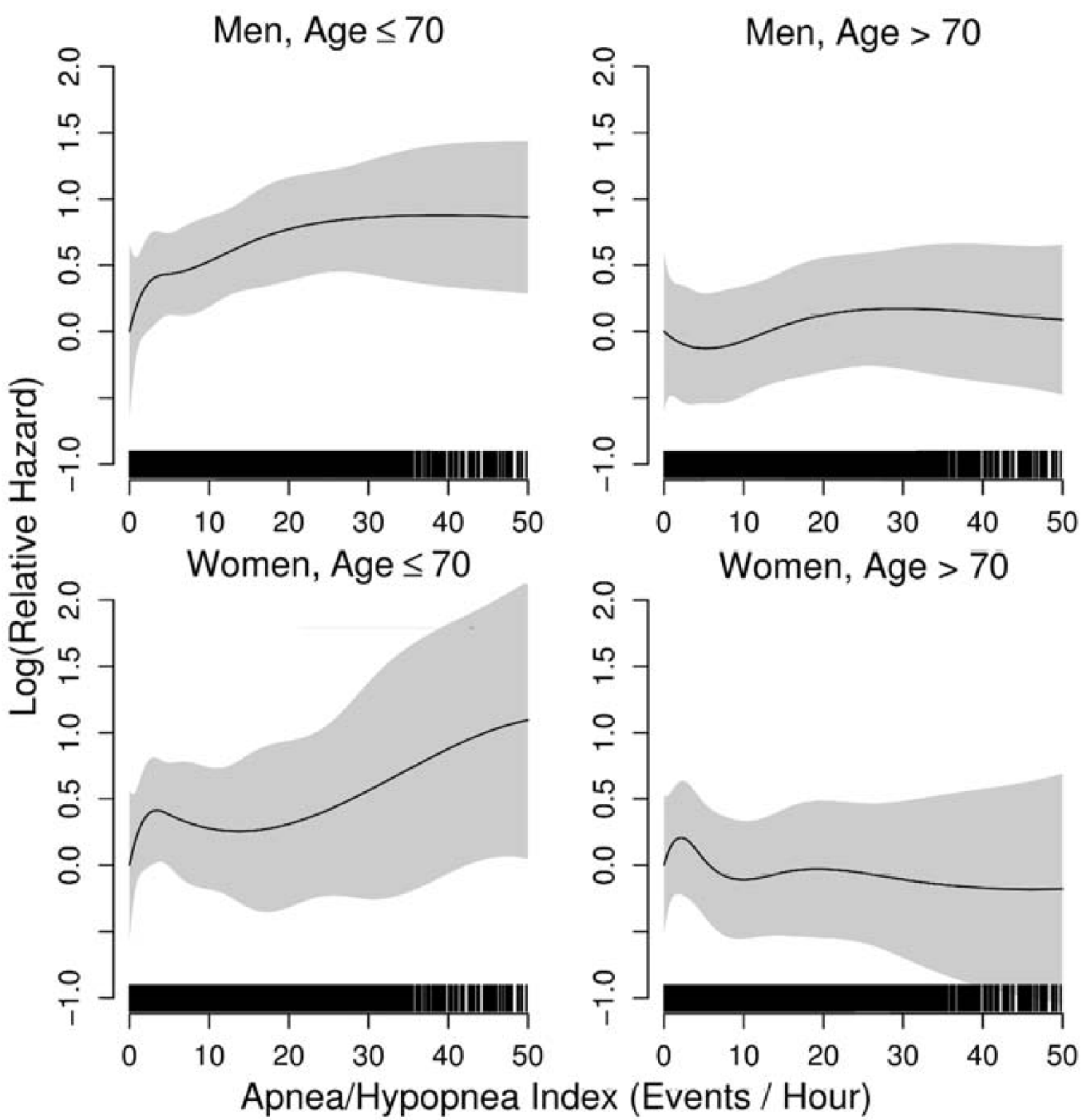


Figure 1. Kaplan-Meier survival curves across categories of the apnea–hypopnea index (AHI).

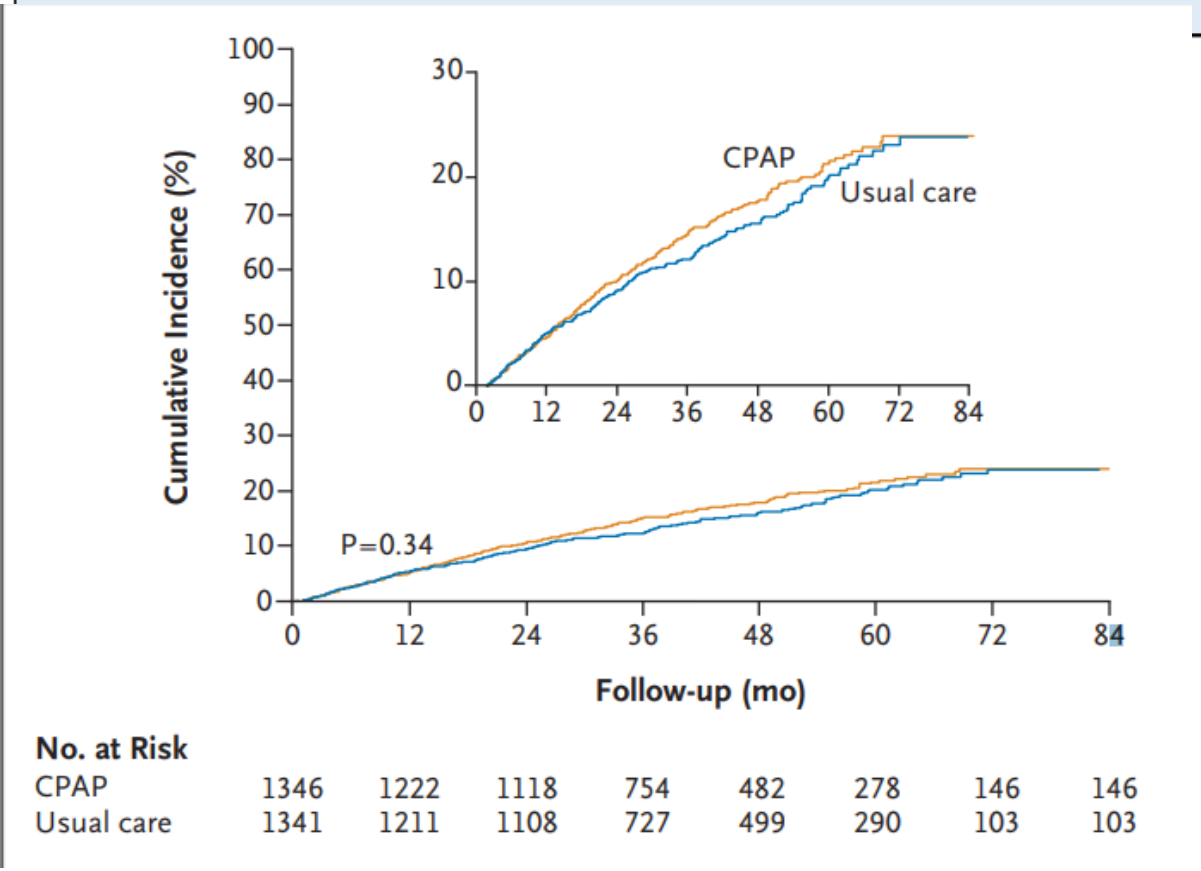
Table 3. Adjusted hazard ratios (95% confidence intervals) for all-cause mortality associated with sleep-disordered breathing,stratified by sex and age in the Sleep Heart Health Study.

막으로 저장한 프리젠테이션

Apnea–Hypopnea Index (Events/h)	*N*	Person–Years	Deaths	Mortality Rate[a]	Model 1[b]	Model 2[c]	Model 3[d]
Men ≤70 y							
<5.0	985	8,220	91	11.1	1.00	1.00	1.00
5.0–14.9	694	5,697	82	14.4	1.10 (0.81–1.48)	1.16 (0.85–1.58)	1.24 (0.90–1.71)
15.0–29.9	322	2,623	47	17.9	1.37 (0.96–1.95)	1.44 (1.00–2.08)	1.45 (0.98–2.14)
≥30.0	168	1,355	28	20.7	1.67 (1.09–2.55)	1.88 (1.19–2.95)	2.09 (1.31–3.33)
Men >70 y							
<5.0	277	2,055	125	60.8	1.00	1.00	1.00
5.0–14.9	282	2,176	111	51.0	0.86 (0.67–1.11)	0.89 (0.69–1.16)	0.92 (0.70–1.20)
15.0–29.9	140	1,029	67	65.1	1.18 (0.87–1.58)	1.25 (0.92–1.70)	1.23 (0.90–1.68)
≥30.0	74	517	36	69.6	1.16 (0.80–1.69)	1.25 (0.85–1.83)	1.27 (0.86–1.86)
Women ≤70 y							
<5.0	1641	13,902	90	6.5	1.00	1.00	1.00
5.0–14.9	527	4,448	40	9.0	1.00 (0.68–1.45)	0.99 (0.66–1.47)	0.97 (0.64–1.48)
15.0–29.9	161	1,350	14	10.4	1.11 (0.63–1.96)	1.12 (0.62–2.02)	1.15 (0.63–2.11)
≥30.0	63	537	8	14.9	1.73 (0.84–3.58)	1.75 (0.82–3.74)	1.76 (0.77–3.95)
Women >70 y							
<5.0	526	4,149	171	41.2	1.00	1.00	1.00
5.0–14.9	294	2,382	86	36.1	0.77 (0.60–1.00)	0.78 (0.60–1.02)	0.77 (0.58–1.00)
15.0–29.9	104	821	37	45.1	0.98 (0.68–1.40)	0.99 (0.69–1.42)	0.89 (0.61–1.31)
≥30.0	36	261	14	53.6	1.09 (0.62–1.89)	1.10 (0.63–1.92)	1.14 (0.65–2.01)


Men, Age ≤ 70
Men, Age > 70
Women, Age ≤ 70
Women, Age > 70
Log(Relative Hazard)
−1.0
0.0
0.5
1.0
1.5
2.0
0
10
20
30
40
50
Apnea/Hypopnea Index (Events / Hour)

Trial (Ref. #)	Patient Group	OSA Diagnosis	Intervention (n)	Follow-Up, Mean	Primary Outcome: MACE	Higher Adherence Subgroup, >4 h per Night	Daytime Sleepiness at Baseline
SAVE (135)	Prevalent CVD	ODI >12/h	CPAP vs control (1,346/1,341)	43 months	HR: 1.10 (95% CI: 0.91-1.32)	HR: 0.52 (95% CI: 0.30-0.90) for stroke	ESS <15 Severe sleepiness excluded
RICCADSA (136)	Revascularized CVD	AHI >15/h	CPAP vs control (122/122)	57 months	HR: 0.80 (95% CI: 0.46-1.41)	HR: 0.29 (95% CI: 0.10-0.86) MACE	ESS <10 Nonsleepy
ISAAC (137)	Acute coronary syndrome	AHI >15/h	CPAP vs control (631/631)	40 months	HR: 0.89 (95% CI: 0.68-1.17)	HR: 0.08 (95% CI: 0.52-1.23) MACE	ESS <10 Nonsleepy



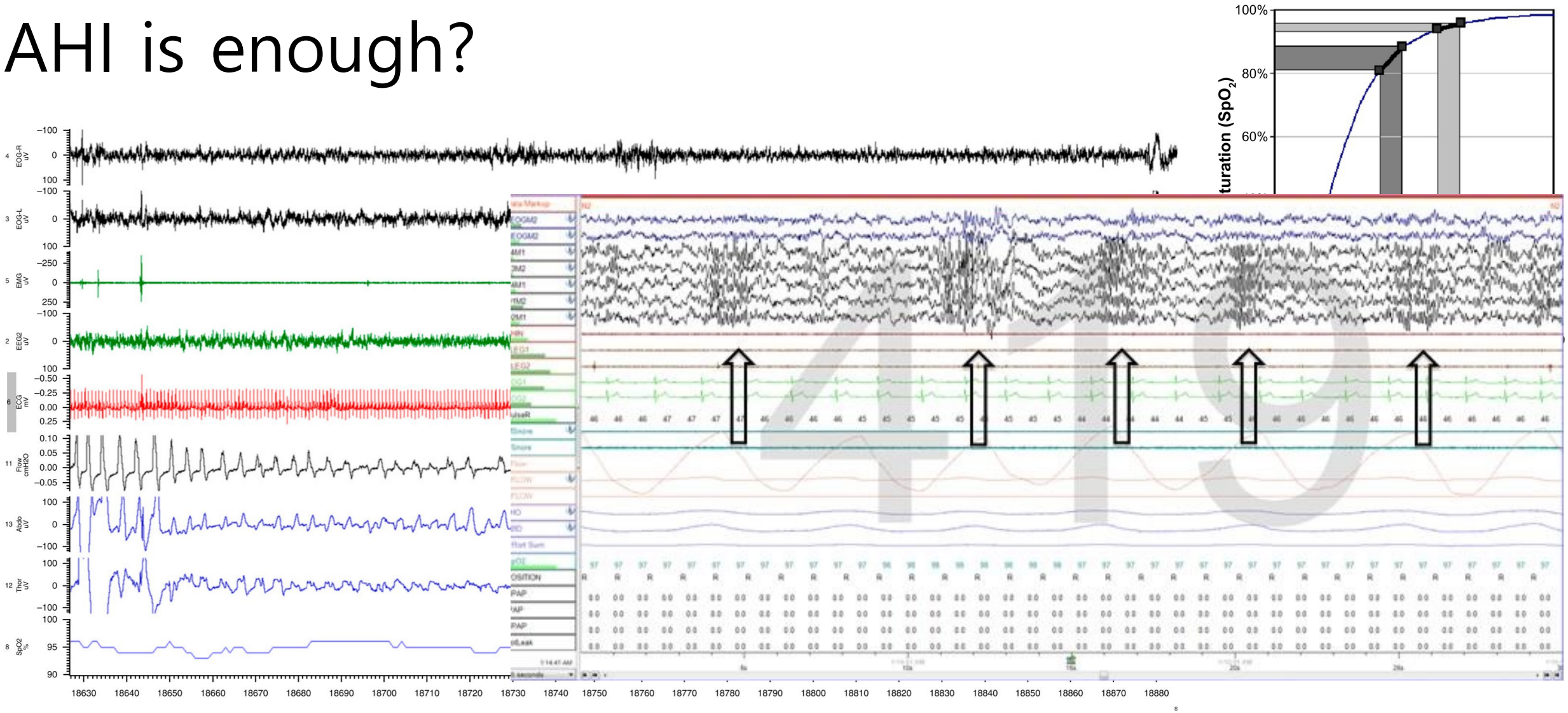
ODI : Oxygen desaturation index (4% from baseline)

T90 : SpO2 < 90%

R. Doug McEvoy, NEJM, 2016

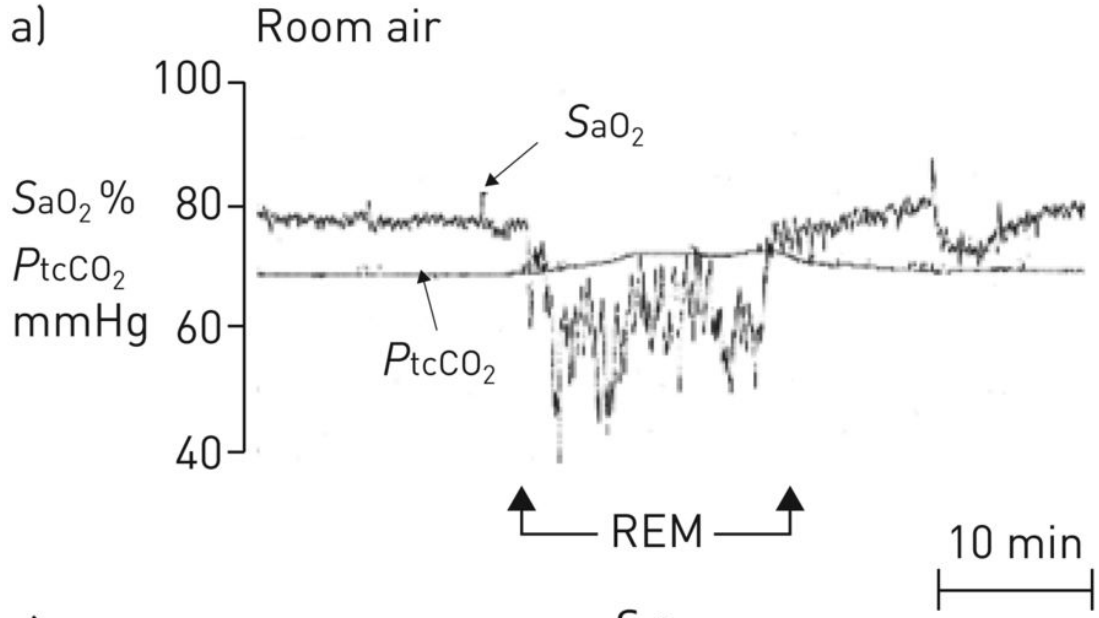
Outcome	CPAP Group (N=1346)					Usual-Care Group (N=1341)					Adjusted Difference in Change from Baseline (95% CI)†	P Value
	Baseline		End of Study		Change from Baseline	Baseline		End of Study		Change from Baseline		
	no. of patients with data	*value*	*no. of patients with data*	*value*		*no. of patients 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

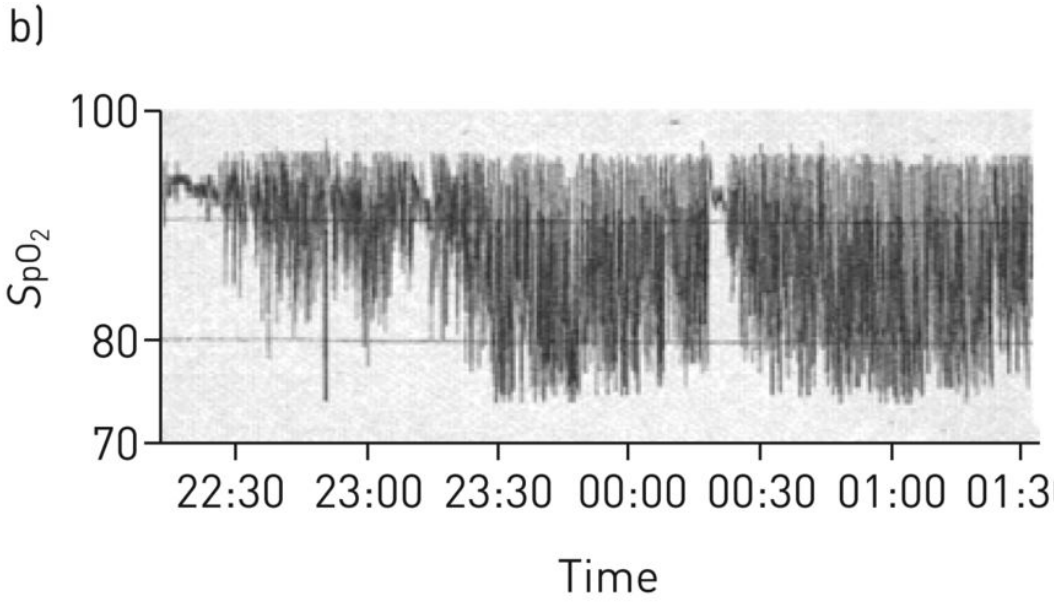
AHI is enough?

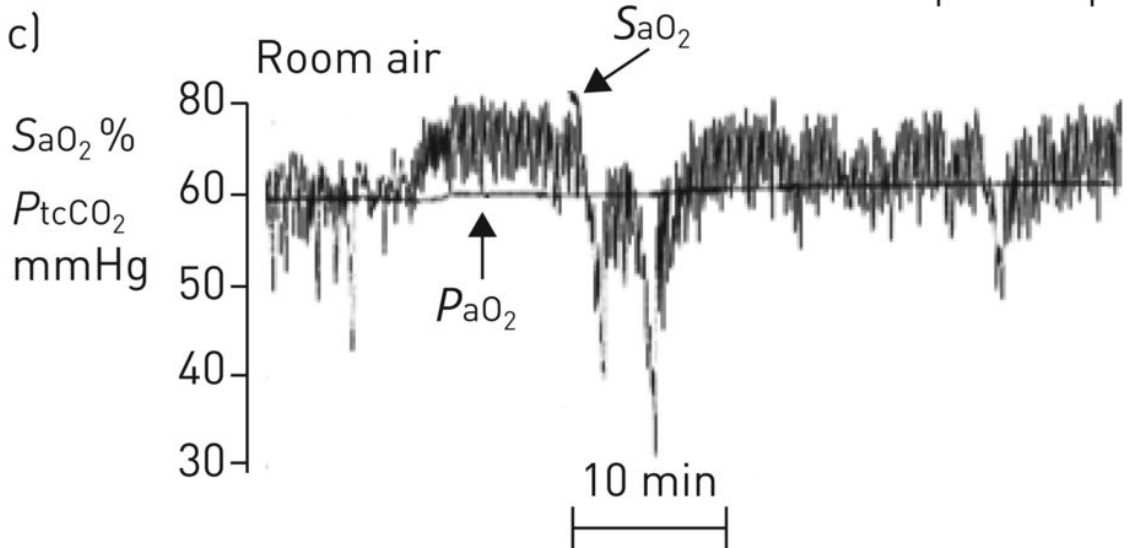


- Hypoxic burden = AHI ??
- Under estimation?(prolonged hypoventilation),
  Over estimation? (hypopnea), supplemental oxygen?, Alpha intrusion?

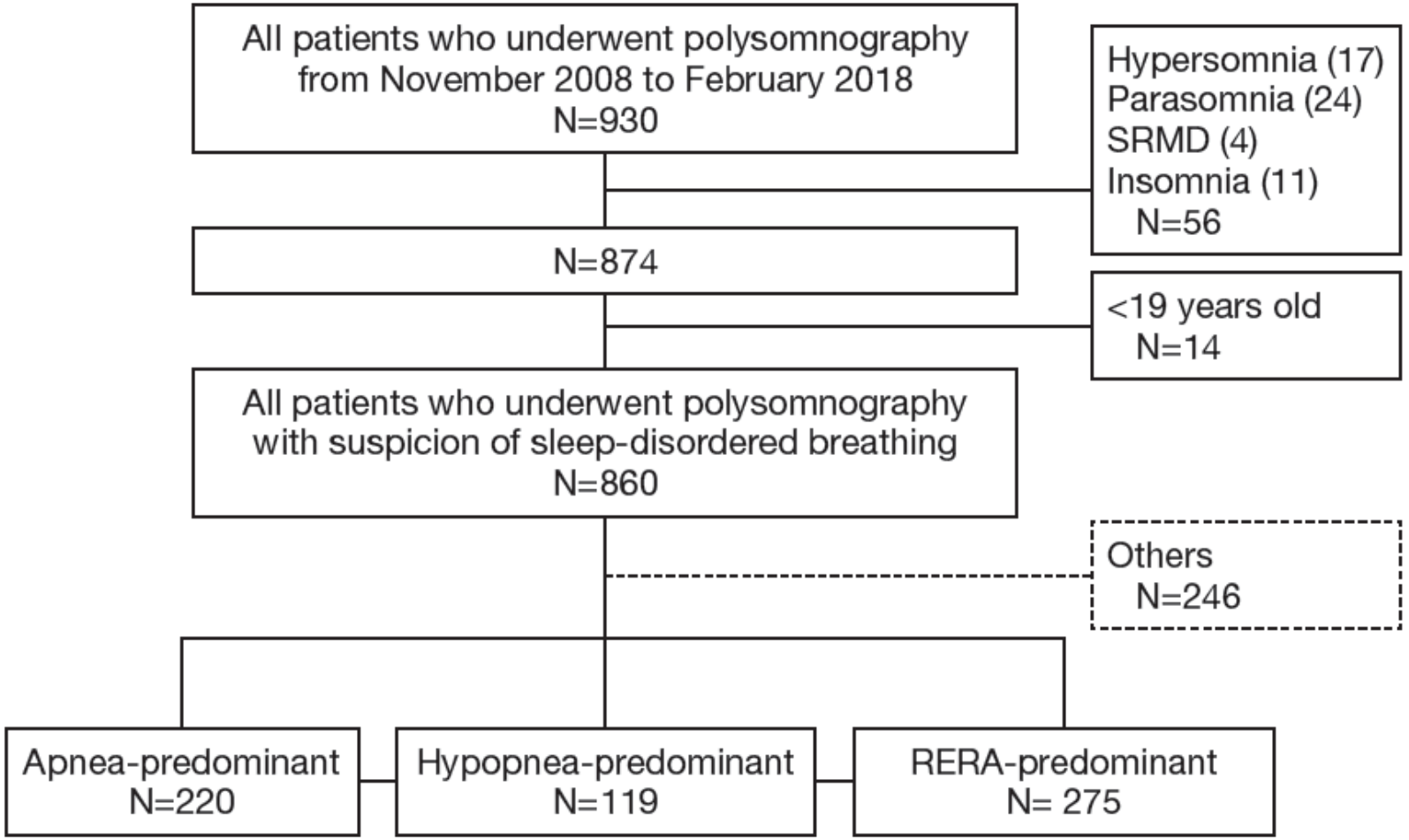
OSA & COPD overlap syndrome







Apnea > Hypopnea??



Park S, JTD 2020

Variables	Apnea-predominant group (n=220)	Hypopnea-predominant group (n=119)	RERA-predominant group (n=275)	P value
Age, years	48.5±12.6[a]	54.5±14.9[b]	46.3±15.8[a]	0.002
Male, (%)				
Epworth Sle				
Anthropome				
Height, m				
Weight, kg				
Body mass index, kg/m^2	27.7±4.1[b]	27.7±4.9[b]	24.6±3.6[a]	<0.001
Neck circumference, cm	38.1±4.9[b]	36.9±3.9[a]	36.7±5.4[a]	0.019
Smoking history				
Never smoker, (%)	91 (44.0)[a]	66 (60.0)[b]	171 (63.8)[b]	<0.001
Ever smoker, (%)	69 (33.3)[b]	29 (26.4)[a]	69 (25.7)[a]	0.164
Current smoker, (%)	47 (22.7)[b]	15 (13.6)[a]	28 (10.4)[a]	0.001
Quantity, pack years	14.4±18.4[b]	10.2±17.8[b]	8.1±15.4[a]	<0.001
Comorbidities				
Hypertension, (%)	109 (52.4)[b]	63 (56.3)[b]	90 (33.5)[a]	<0.001
Diabetes, (%)	46 (22.3)[b]	25 (22.7)[b]	26 (9.7)[a]	<0.001
Hyperlipidemia, (%)	51 (24.8)[a]	41 (37.6)[b]	41 (15.3)[a]	<0.001
Heart failure, (%)	10 (4.9)[a]	17 (15.5)[b]	9 (3.4)[a]	<0.001
Coronary artery diseases, (%)	24 (11.7)[a]	23 (20.9)[b]	24 (9.0)[a]	0.005
Cerebrovascular diseases, (%)	14 (6.8)	6 (5.5)	8 (3.0)	0.144

- Apnea dominant : Apnea index / RDI > 50%
- Hypopnea dominant : Hypopnea index / RDI > 50%
- RERA dominant : RERA index / RDI > 50%

Park S, JTD 2020

Variables	N=614	Coronary artery diseases		Heart failure	
		Odds ratio, 95% confidence interval	p value	Odds ratio, 95% confidence interval	p value
Age, years	48.7±14.8	1.06 (1.04-1.08)	**<0.001**	1.10 (1.07-1.14)	**<0.001**
Males, (%)	472(76.9)	1.43 (0.83-2.49)	0.199	2.49 (1.25-4.97)	0.010
BMI, kg/m²	26.3±4.3	1.10 (1.04-1.16)	**0.001**	1.10 (1.03-1.18)	**0.008**
Neck circumference, cm	37.2±5.0	1.04 (0.99-1.09)	0.093	1.02 (0.95-1.10)	0.538
Smoking, pack year	10.8±17.2	1.02 (1.01-1.03)	0.002	1.00 (0.98-1.02)	0.866
Hypertension, (%)	262(42.7)	8.84 (4.54-17.23)	**<0.001**	11.59 (4.04-33.22)	**<0.001**
Hyperlipidemia, (%)	133(21.7)	23.30 (12.37-43.90)	**<0.001**	14.70 (6.51-33.18)	**<0.001**
Diabetes, (%)	97(15.8)	4.95 (2.89-8.46)	**<0.001**	6.01 (3.00-12.06)	**<0.001**
Apnea index	18.0±24.0	1.00 (0.99-1.01)	0.994	0.99 (0.98-1.01)	0.418
Hypopnea index	9.8±11.8	1.03 (1.01-1.05)	**0.002**	1.03 (1.01-1.05)	**0.006**
RERA index	8.44±6.5	0.98 (0.94-1.02)	0.264	0.91 (0.84-0.97)	0.005

Table 3 Logistic regression model predicting the risk for coronary artery disease based on severity of the hypopnea index

Hypopnea index	N	Coronary artery disease	Model 1		Model 2		Model 3	
			Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value
<5.0	284	22 (7.7%)	1.00		1.00		1.00	
5.0–14.9	187	23 (12.3%)	1.70 (0.92–3.15)	0.093	1.54 (0.81–2.92)	0.407	0.92 (0.44–1.94)	0.824
15.0–29.9	107	18 (16.8%)	2.44 (1.25–4.76)	0.009	2.08 (1.04–4.17)	0.040	1.31 (0.58–2.96)	0.516
≥30.0	36	8 (22.2%)	3.79 (1.52–9.42)	0.004	3.06 (1.16–8.05)	0.023	1.31 (0.40–4.27)	0.657

Model 1: hypopnea index. Model 2: hypopnea index, age, sex, and smoking (pack years). Model 3: hypopnea index, age, sex, smoking (pack years), BMI, hypertension, hyperlipidemia, and diabetes. 95% CI, 95% confidence interval.

Park S, JTD 2020

Hypopnea

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

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

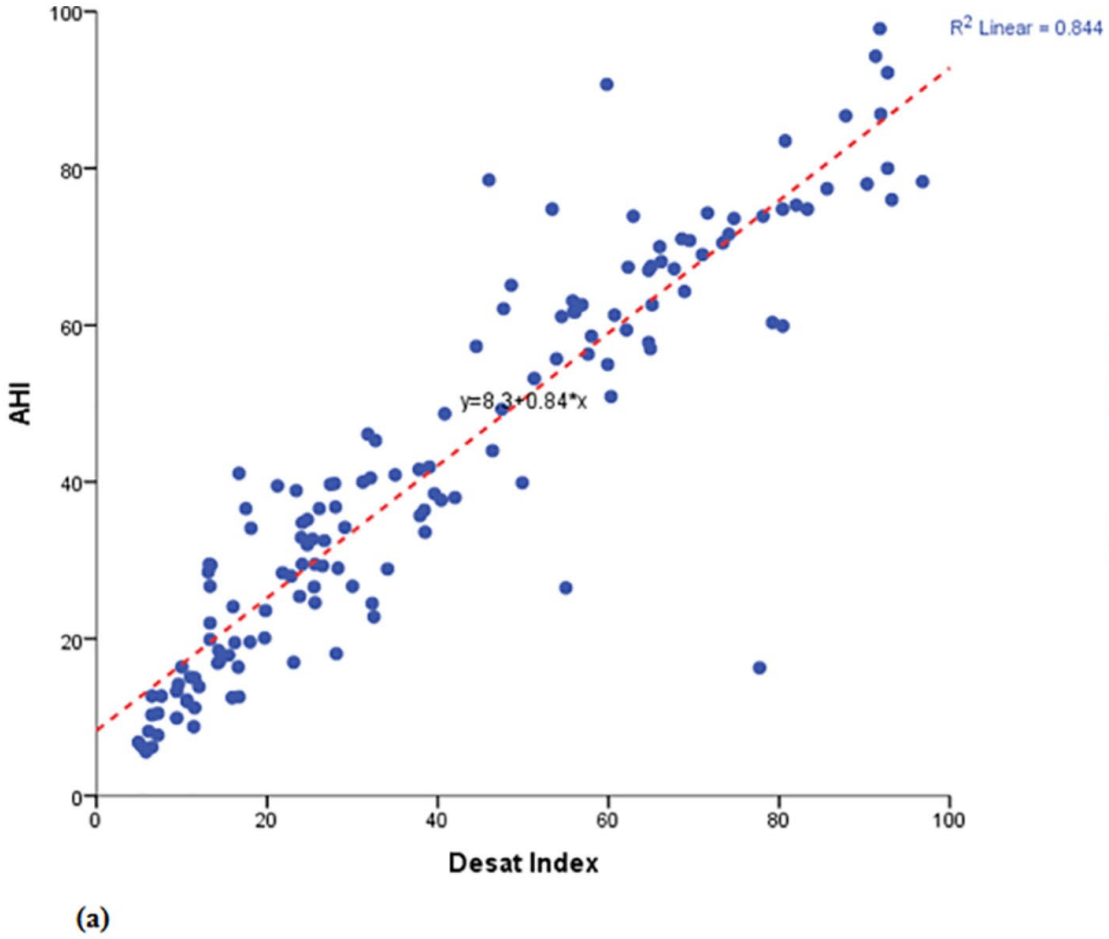
1999
- AASM Hypopnea taskforce (Chicago Criteria) defines hypopnea to as 50% reduction in AF or clear AF amplitude reduction with 3% oxygen desaturation and/or arousal (30)

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)

Oxygen desaturation index (ODI)

a) Room air

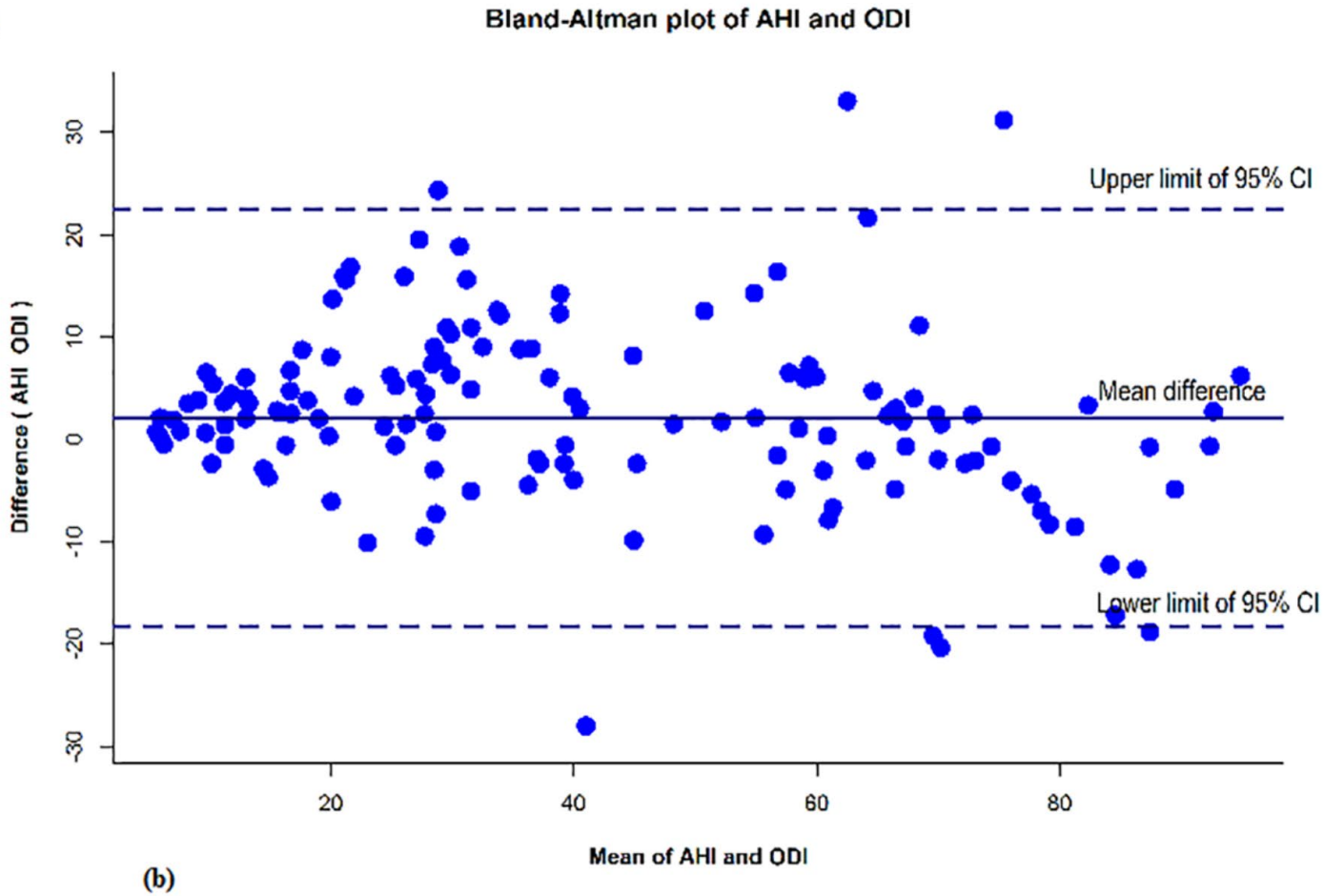


(a)

30

10 min

b)



(b)

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.

Ying et al, Stroke, 2019

T90: Time spent with SpO2 <90

Table 5. Association Between SA and Other Sleep Measures and Carotid Intima-Media Thickness by Dichotomized Age

	Model 1: β±SE, *P* Value	*P* Interaction	Model 2: β±SE, *P* Value	*P* Interaction	Model 3: β±SE, *P* Value	*P* Interaction
SA (AHI ≥15 events/h)		0.041		0.058		0.072
Age <68 y	0.034±0.014, 0.018		0.022±0.015, 0.125		0.019±0.015, 0.200	
Age ≥68 y	−0.006±0.014, 0.658		−0.014±0.014, 0.299		−0.016±0.014, 0.242	
Arousal index (events/h)		0.389		0.641		0.499
Age <68 y	0.0009±0.0006, 0.115		0.0006±0.0006, 0.335		0.0005±0.0006, 0.341	
Age ≥68 y	0.0002±0.0005, 0.688		0.0002±0.0005, 0.724		0.00002±0.0005, 0.969	
≥0.64% sleep time with Spo2 <90%, %		0.045		0.089		0.106
Age <68 y	0.042±0.013, 0.001		0.032±0.01, 0.021		0.028±0.014, 0.038	
Age ≥68 y	0.006±0.013, 0.664		0.0007±0.013, 0.955		−0.001±0.013, 0.928	

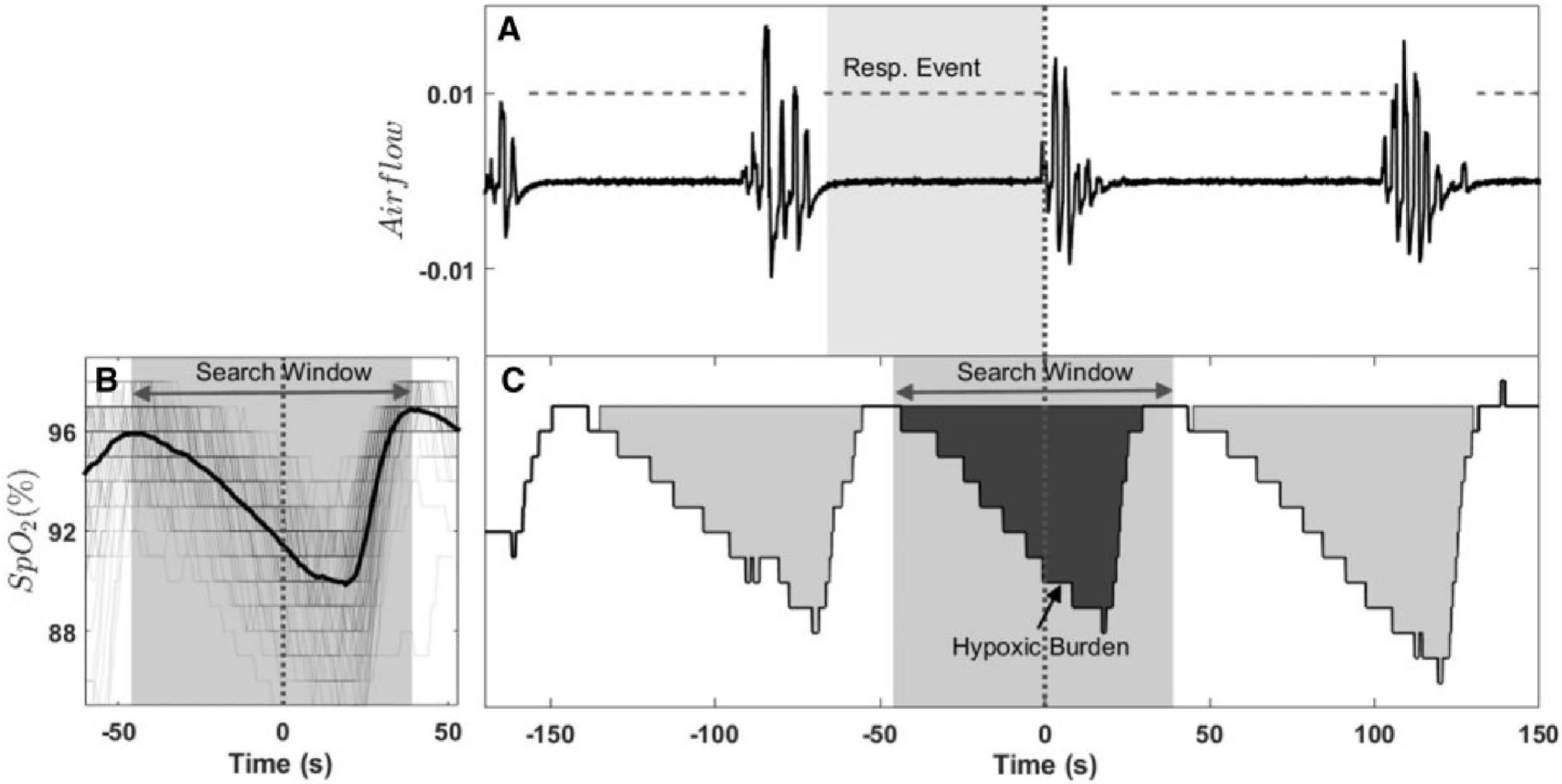
Wenhao et al, Nature and Sciece of sleep, 2020

Table 1 Polysomnographic Metrics of Measuring Severity of OSA

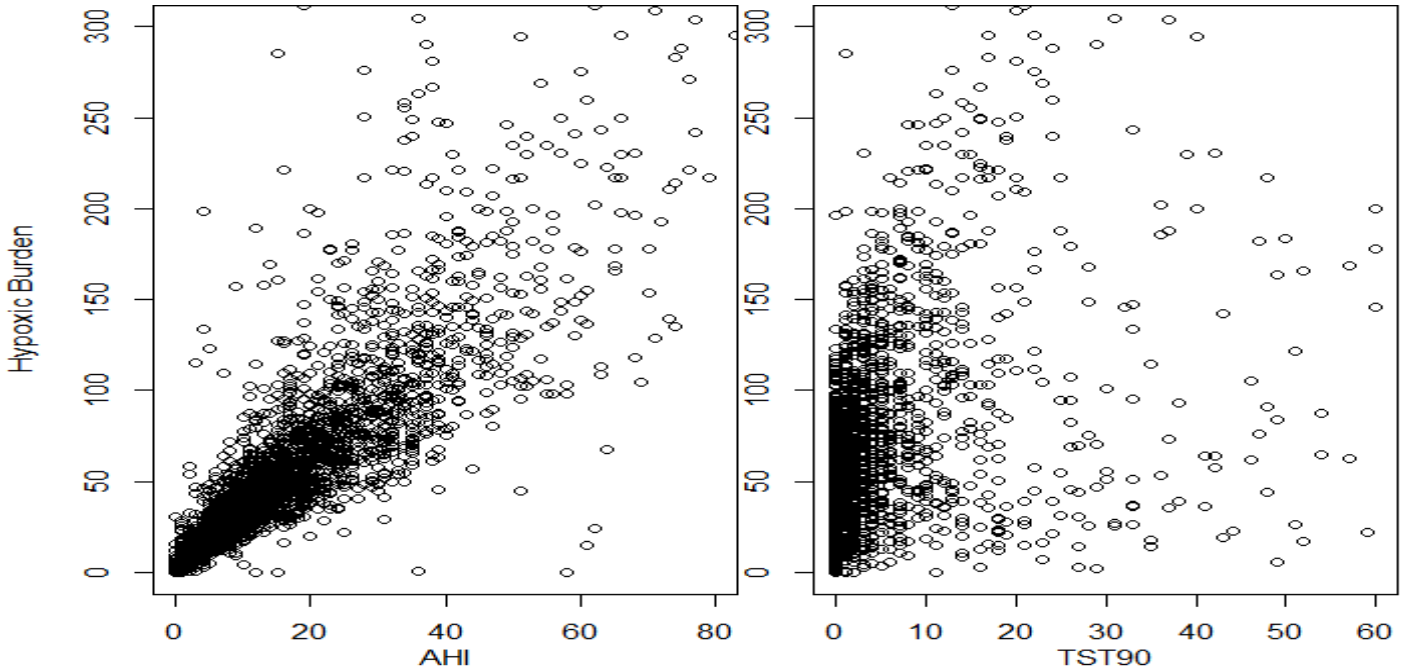
Classification	Metrics	Pathophysiological Backgrounds	Complications Associated with OSA
Conventional and widely used	AHI	intermittent hypoxia	EDS,[13,14] CVD and all-cause mortality,[15] hypertension[16]
	ODI, T90, LSpO2		subclinical atherosclerosis,[25] all-cause mortality in HF,[26] postoperative complications[27–29]
	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

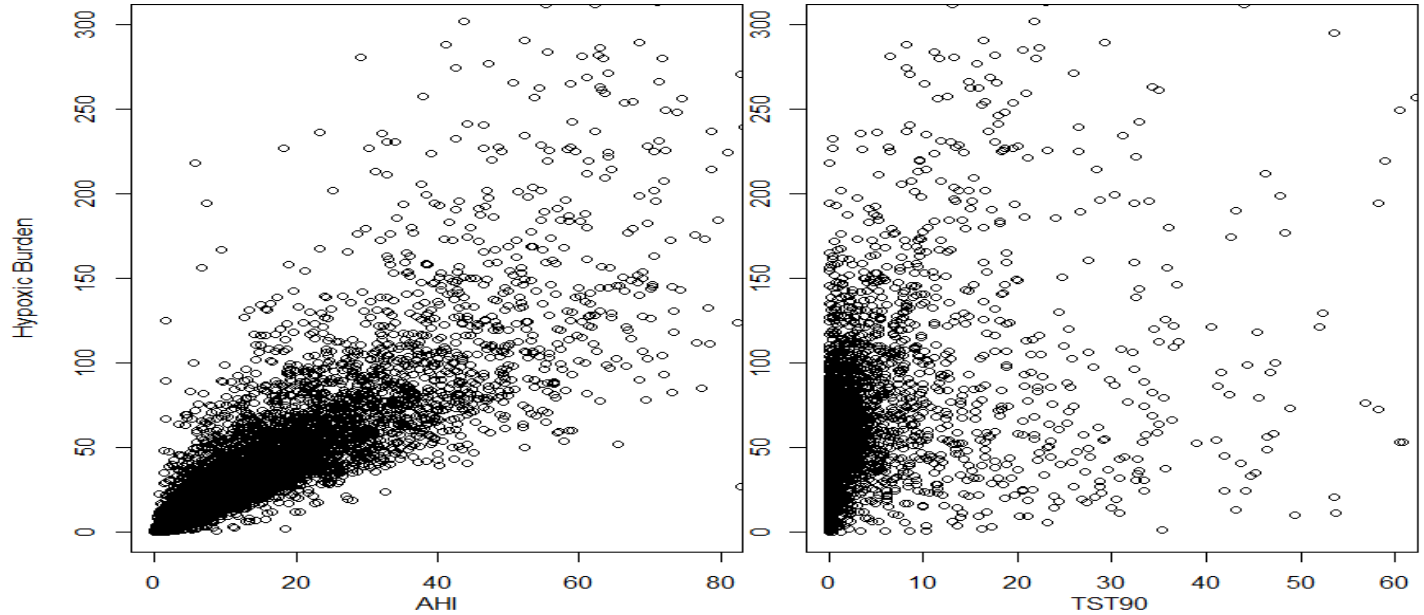
Hypoxic burden



Azarbazin et al, EHR, 2019

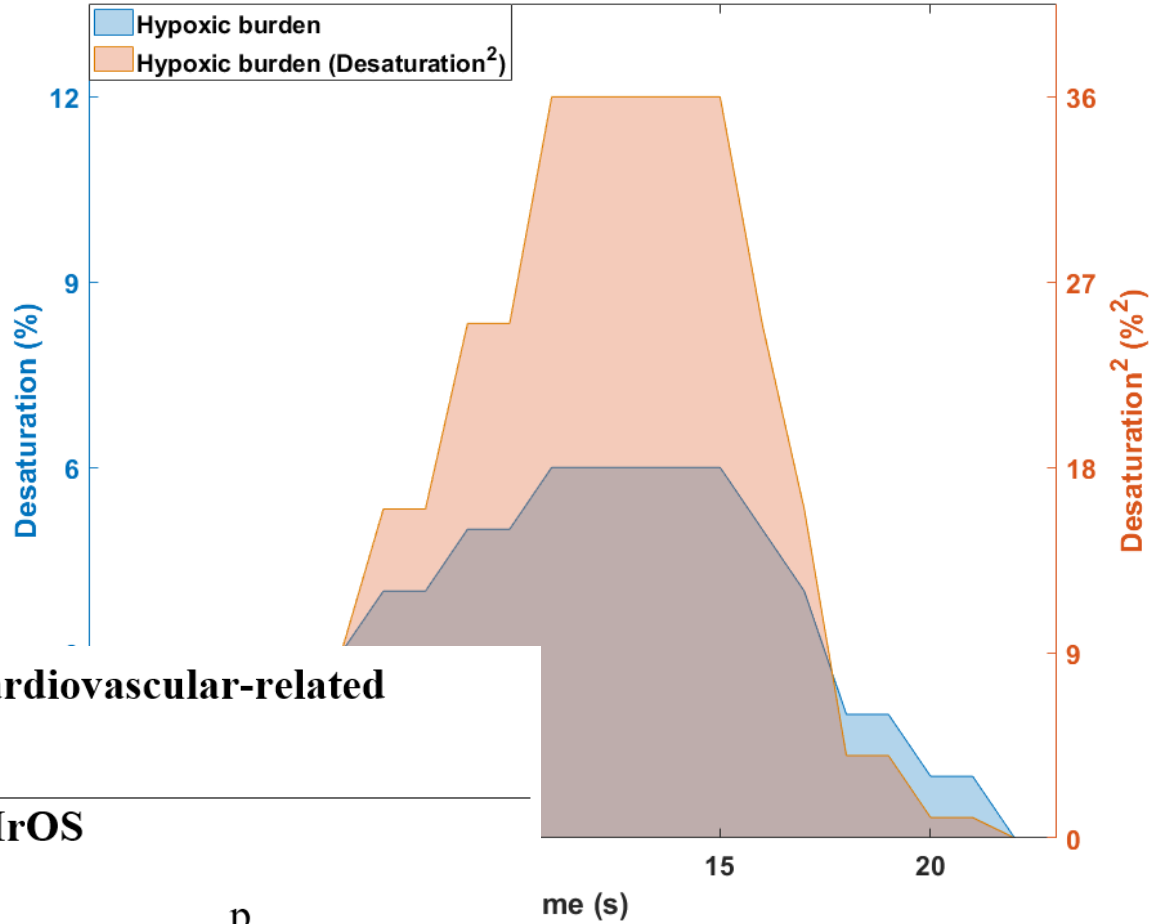


(A)



(B)

Azarbazin et al, EHR, 2019



ɔ account for the impact of desaturation depth on cardio
tion resulted in diminished area for small desaturations a

Table S7: Associations of three modifications of hypoxic burden and cardiovascular-related mortality in MrOS.

Transformation	MrOS	
	HR (95% CI)	p
Square root	1.79 (1.28, 2.50)	0.0007
None	1.86 (1.33, 2.61)	0.0003
Square	1.81 (1.33, 2.47)	0.0002

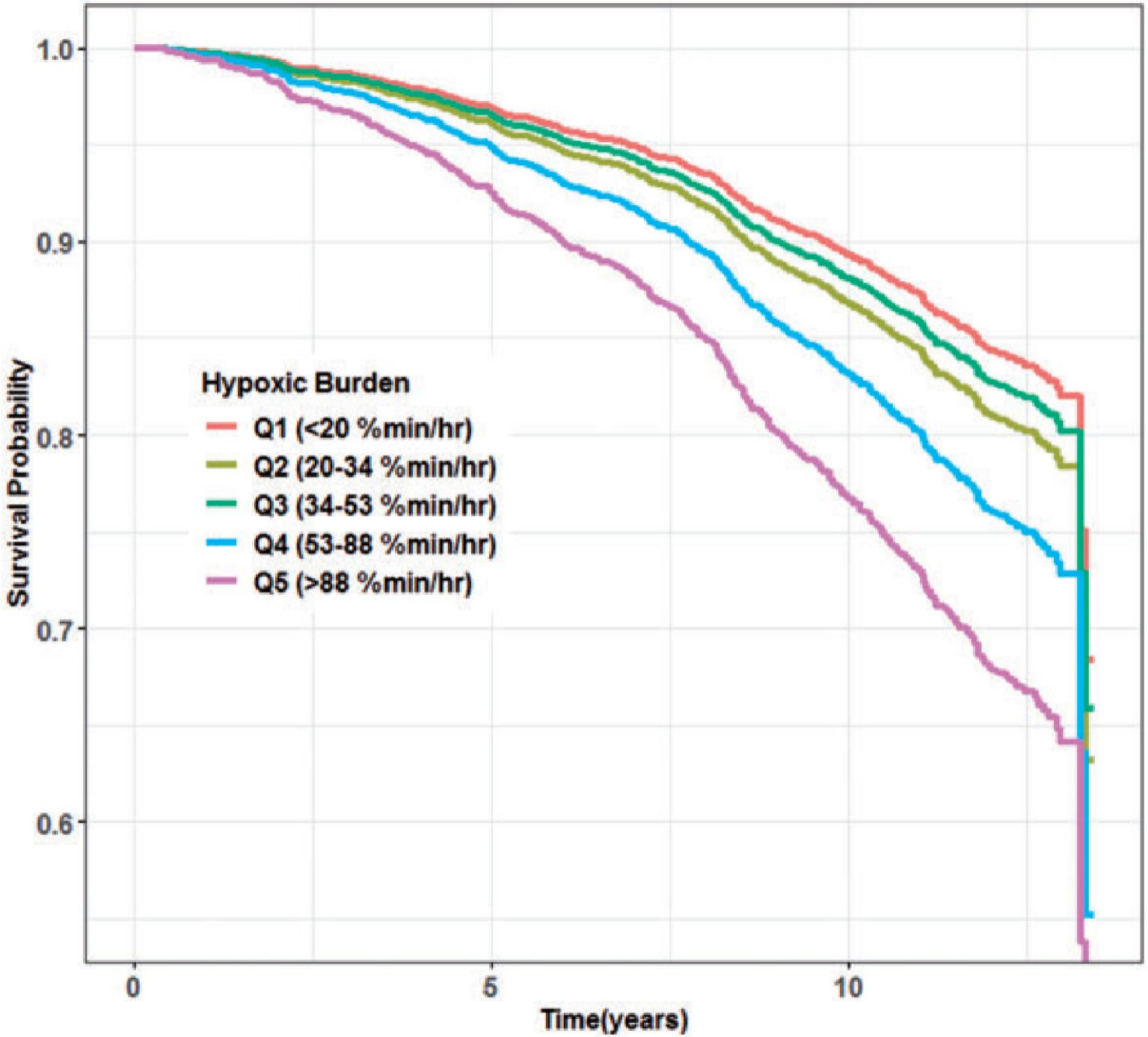
The transformed versions of hypoxic burden were modeled separately. Each model was adjusted for age, BMI, race, total sleep time, COPD, smoking, alcohol consumption, renal failure, and AHI.

Azarbazin et al, EHR, 2019

	Alive
Age (years), mean (SD)	74.3
BMI (kg/m^2)	27.2
Race, *n* (%)	
Caucasian	1312
African American	54
Other race	107
Alcohol, *n* (%)	
<1 glasses/week	660
1–13 glasses/week	725
14+ glasses/week	88
Congestive heart failure, *n* (%)	49
Cardiovascular disease (including congestive heart failure), *n* (%)	459
Hypertension, *n* (%)	658
Stroke, *n* (%)	34
Diabetes, *n* (%)	159
Renal failure, *n* (%)	5
Chronic obstructive pulmonary disease, *n* (%)	60
Smoking status, *n* (%)	
Never	613
Former	836
Current	24
Statin use, *n* (%)	631
Total sleep time (TST), *n* (%)	
>5–8 h	1221
≤5 h	224
>8 h	28
Apnoea–hypopnoea index (events/h)	15.7
TST90 (%TST)	3.23
Hypoxic burden (%min/h)	53.3
Q1 (≤20 %min/h), *n* (%)	324
Q2 (20–34 %min/h), *n* (%)	304
Q3 (34–53 %min/h), *n* (%)	324
Q4 (53–88 %min/h), *n* (%)	283
Q5 (>88 %min/h), *n* (%)	238

Table 3 Hypoxic burden predicts cardiovascular-related mortality in MrOS and SHHS

Covariates	Hypoxic burden quintiles	MrOS HR (95% CI)	SHHS HR (95% CI)
Model 0: none	Q_1	1.00	1.00
	Q_2	1.24 (0.89, 1.72)	**1.67 (1.06–2.65)***
	Q_3	1.10 (0.78, 1.54)	**2.30 (1.49–3.57)*****
	Q_4	**1.64 (1.20, 2.24)****	**2.71 (1.76–4.16)*****
	Q_5	**2.31 (1.71, 3.12)*****	**3.88 (2.56–5.88)*****
Model 1: anthropometric[a], sleep duration, smoking, alcohol[b], non-CVD medical history[c]	Q_1	1.00	1.00
	Q_2	1.22 (0.87, 1.70)	1.41 (0.88–2.24)
	Q_3	1.12 (0.80, 1.58)	1.25 (0.80–1.96)
	Q_4	**1.44 (1.05, 1.97)***	1.51 (0.97–2.35)
	Q_5	**1.75 (1.28, 2.40)*****	**1.62 (1.04–2.51)***
Model 2a: Model 1 + AHI	Q_1	1.00	1.00
	Q_2	1.29 (0.92, 1.81)	1.45 (0.91–2.31)
	Q_3	1.26 (0.88, 1.79)	1.34 (0.85–2.12)
	Q_4	**1.77 (1.23, 2.54)****	**1.69 (1.05–2.70)***
	Q_5	**2.61 (1.65, 4.14)*****	**2.03 (1.17–3.50)***
Model 2b: Model 1 + ODI	Q_1	1.00	1.00
	Q_2	1.25 (0.89, 1.75)	1.43 (0.90–2.28)
	Q_3	1.18 (0.83, 1.68)	1.31 (0.83–2.06)
	Q_4	**1.57 (1.09, 2.26)***	**1.63 (1.04–2.57)***
	Q_5	**2.10 (1.31, 3.34)****	**1.92 (1.16–3.15)***
Model 3: Model 2a + MinSat + TST90	Q_1	1.00	1.00
	Q_2	1.30 (0.93, 1.82)	1.50 (0.94–2.39)
	Q_3	1.29 (0.91, 1.85)	1.41 (0.89–2.25)
	Q_4	**1.83 (1.27, 2.64)****	**1.78 (1.10–2.86)***
	Q_5	**2.77 (1.73, 4.42)*****	**2.09 (1.20–3.63)****
Model 4: Model 3 + cardio-metabolic diseases[d]	Q_1	1.00	1.00
	Q_2	1.19 (0.85, 1.68)	1.48 (0.93–2.37)
	Q_3	1.26 (0.88, 1.81)	1.34 (0.85–2.14)
	Q_4	**1.81 (1.25, 2.62)****	1.61 (1.00–2.61)
	Q_5	**2.73 (1.71, 4.36)*****	**1.96 (1.11–3.43)***



Azarbazin et al, EHR, 2019

Alternative metrics

- Approximate entropy (ApEn)
- Arousal intensity
- Odds ratio product (ORP)
- Cardiopulmonary coupling(CPC)
- Apnea-hypopnea event duration

1. Approximate entropy (ApEn)

- Based on chaos theory
- ApEn : Small value → Regularity & Predictability
  Large value → Complexity & Variability

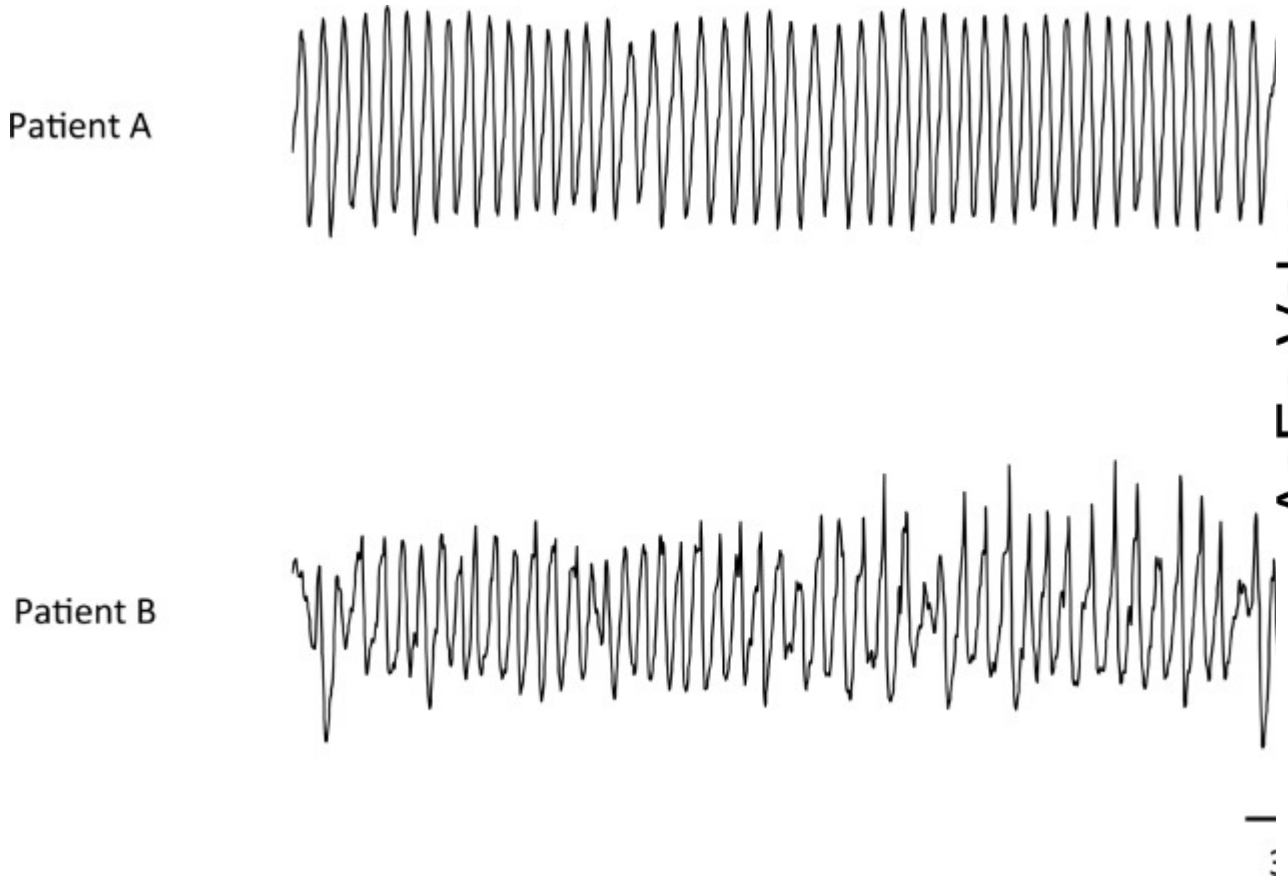
- Measure of system complexibity
- Applied in clinical cardiovascular studies

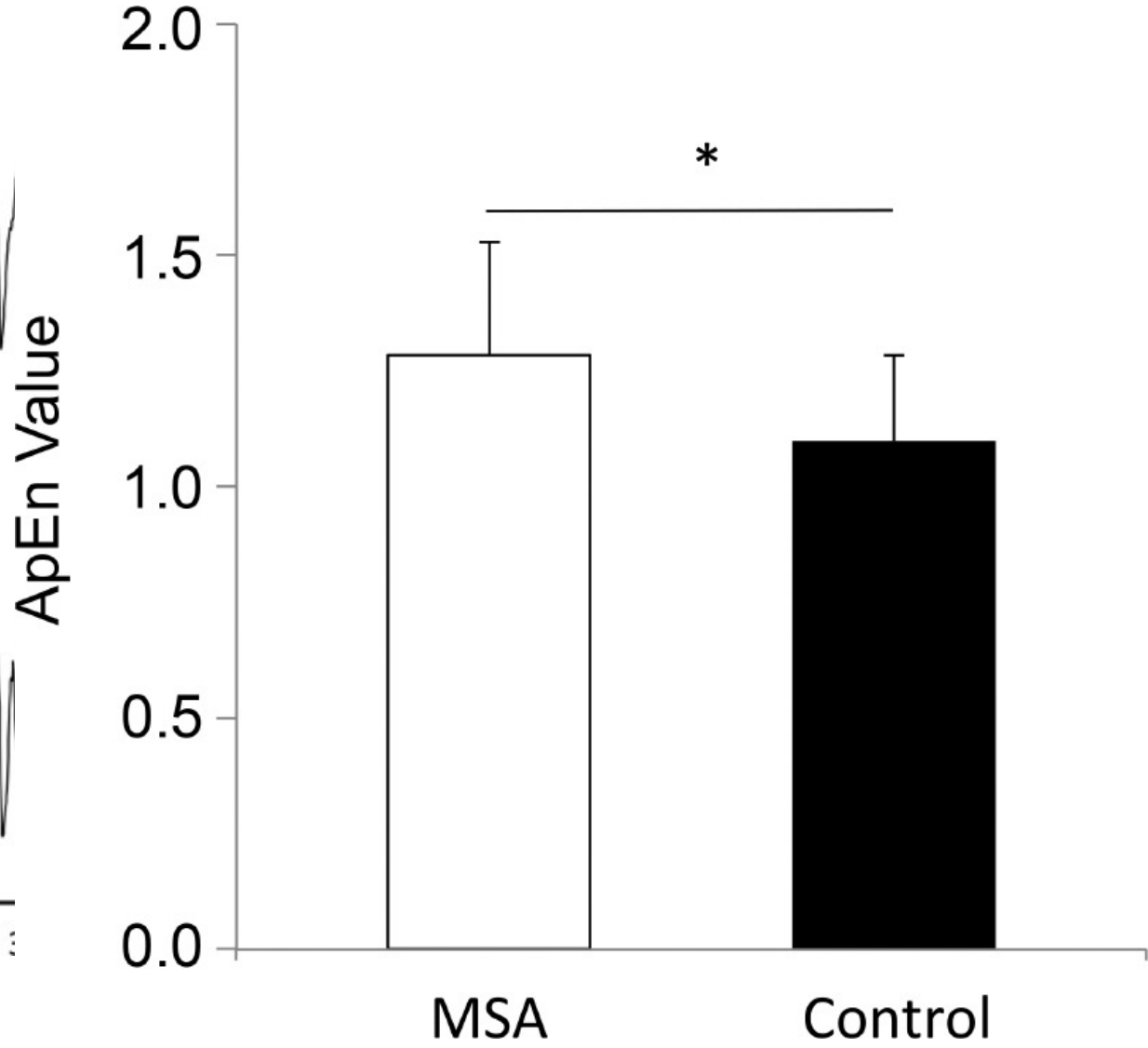
- Improved by CPAP
- Acteazoamide

$$\mathrm{ApEn}(N,m,r) = \phi_m(r) - \phi_{m+1}(r)$$

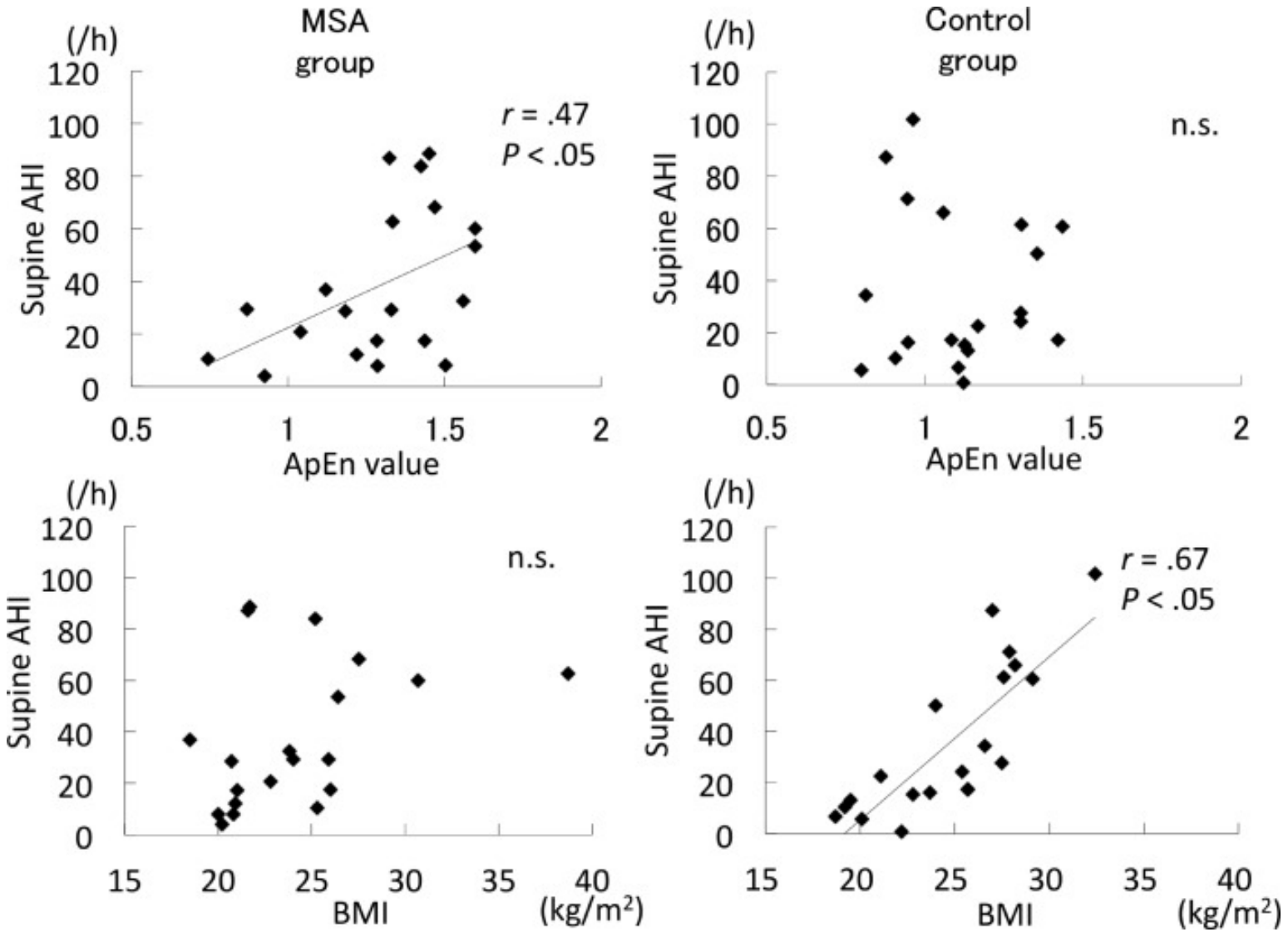
$$\phi_m(r) = (N-(m-1))^{-1} \sum_{i=1}^{N-(m-1)} log\, C_{m,i}(r)$$

- Multiple system atrophy (MSA)





Nakayama et al, J Clin Sleep med, 2018



Nakayama et al, J Clin Sleep med, 2018

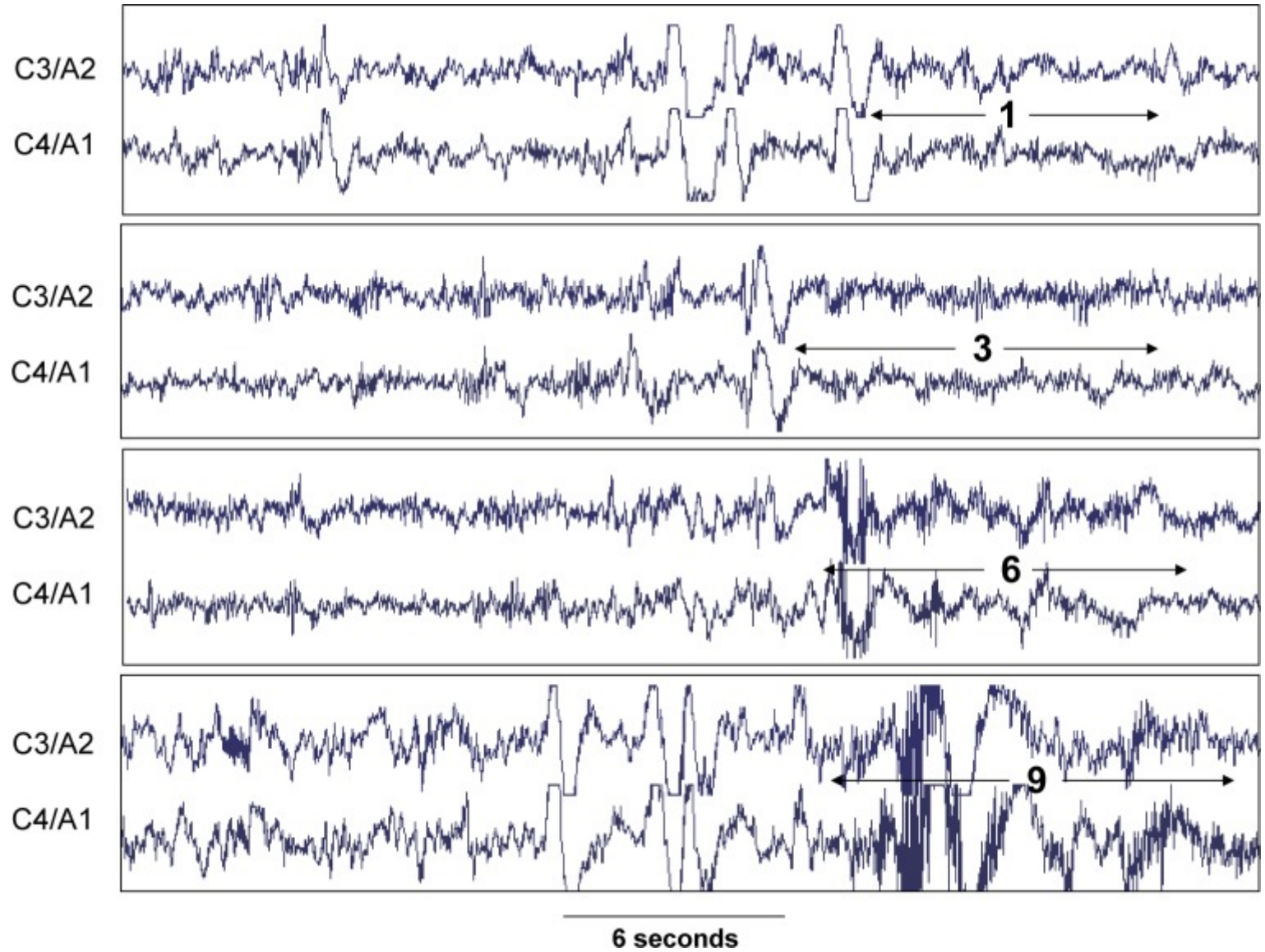
2. Arousal intensity & Heart rate

- Arousal from sleep → can vary in intensity
  (Not captured by traditional EEG criteria)

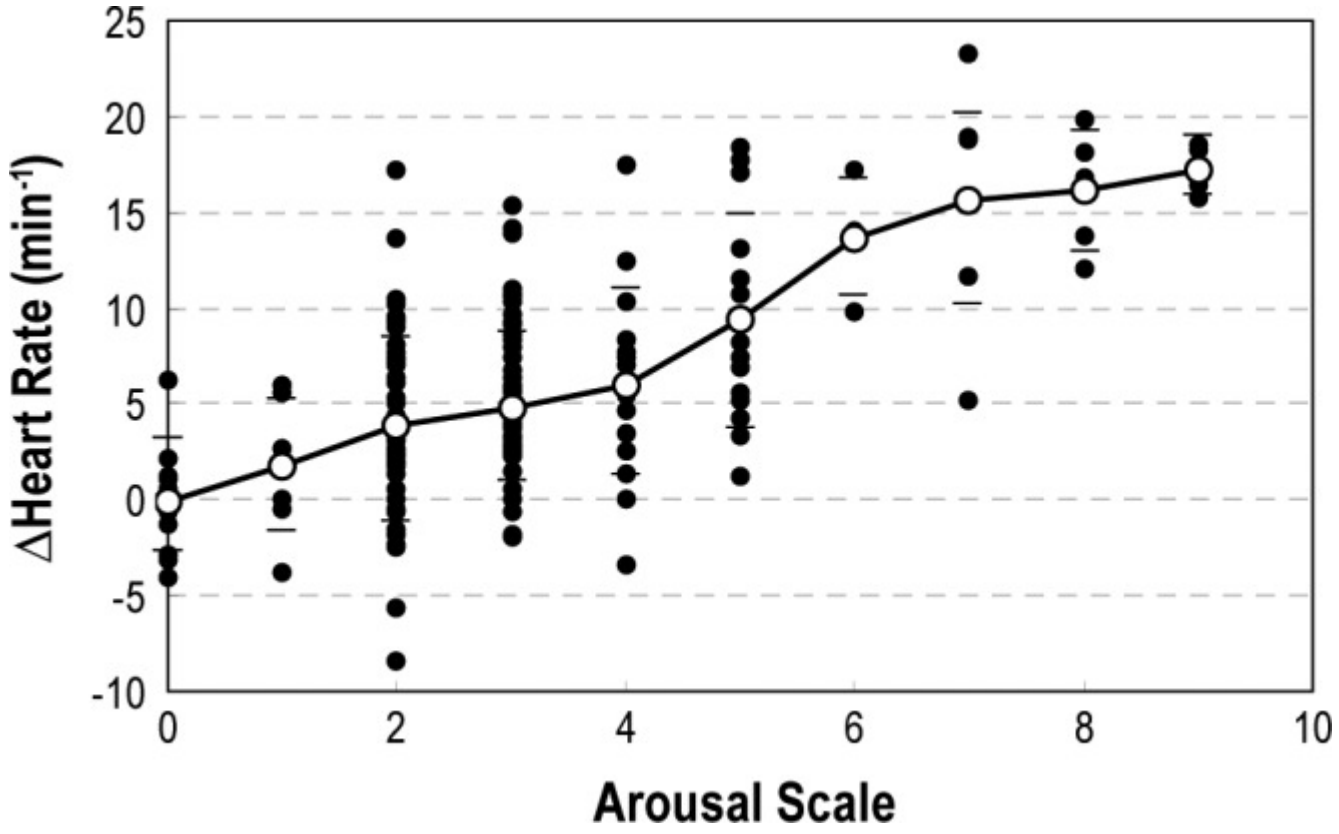
- Frequent arousal ; Cognitive impairment

- Average arousal intensity
  → Positively associated with arousal duration, time to arousal
  Rate of change in epiglootic pressure
  Negatively with BMI

- High arousal intensity → prone to respiratory control instability


C3/A2
C4/A1
1
C3/A2
C4/A1
3
C3/A2
C4/A1
6
C3/A2
C4/A1
9
6 seconds

- Frequent arousal
- Arousal-related tachycardia



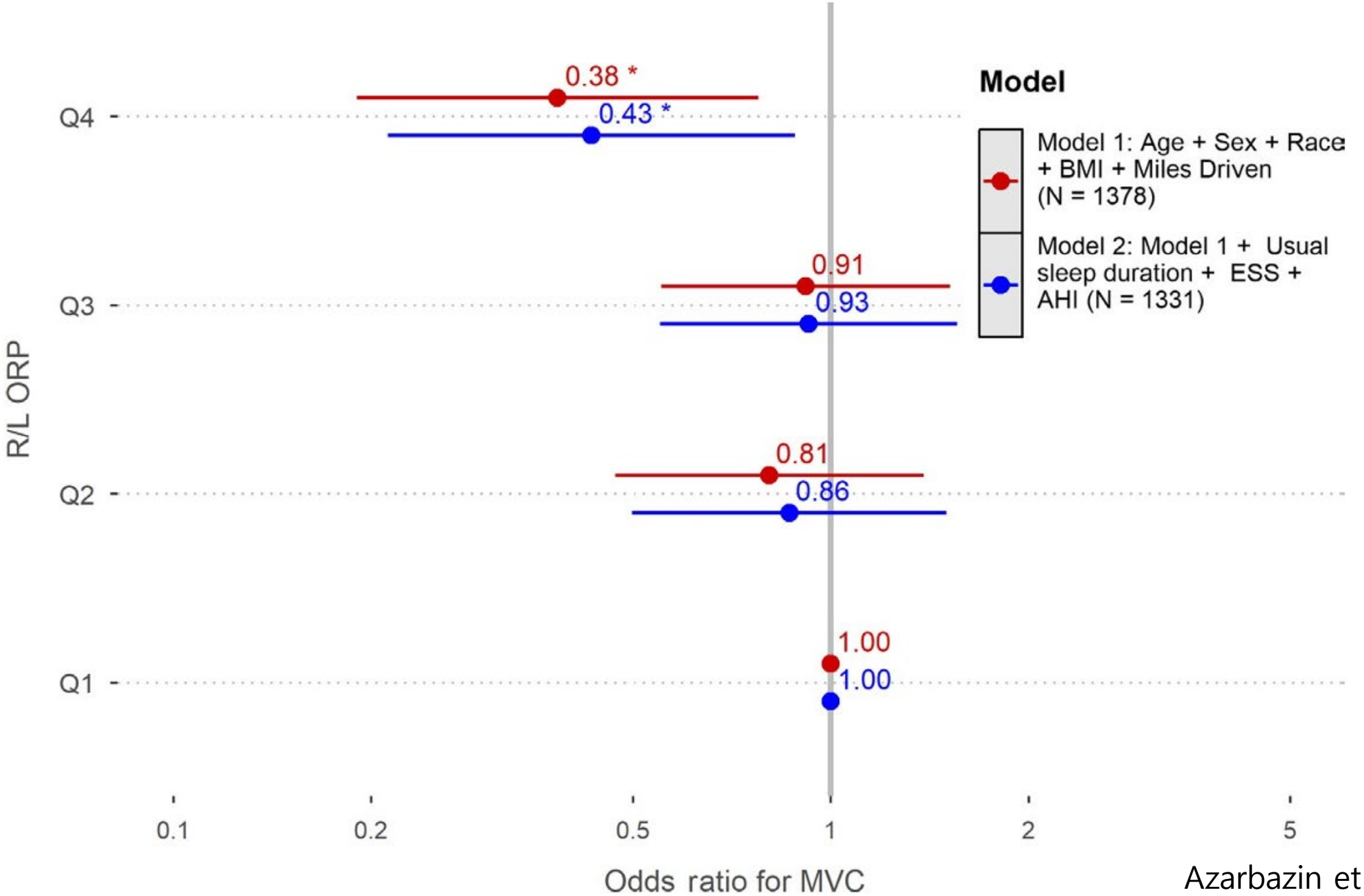
Azarbazin et al, Sleep 2014

3. Odds ratio product (ORP)

- Quantifies sleep depth
- Analyses of the EEG by using various power spectral measure.
- ORP : 0 ~ 1 → Sleep
  2~ 2.5 → Wakefulness
- Overlap in ORP value and different stages of sleep.
- Night to night variability

	R/L ORP Quartiles			
	Q1 (0.12–0.86)	Q2 (0.87–0.90)	Q3 (0.91–0.93)	Q4 (0.94–0.98)
Age (year)	62.4 (10.2)	63.9 (9.68)	64.7 (9.50)	67.5 (8.84)
Sex				
Male	264 (68.9%)	226 (71.5%)	257 (68.4%)	185 (61.1%)
Female	119 (31.1%)	90 (28.5%)	119 (31.6%)	118 (38.9%)
BMI (kg/m^2)	30.8 (5.76)	30.0 (4.81)	29.3 (4.78)	29.5 (5.08)
Race				
White	346 (90.3%)	286 (90.5%)	347 (92.3%)	282 (93.1%)
Black	22 (5.74%)	20 (6.33%)	16 (4.26%)	16 (5.28%)
Other	15 (3.92%)	10 (3.16%)	13 (3.46%)	5 (1.65%)
Apnea–hypopnea Index (events/hr)	17.4 (14.3)	16.5 (13.9)	17.0 (13.1)	14.7 (11.6)
Epworth Sleepiness Scale	8.26 (4.68)	8.61 (4.48)	8.32 (4.39)	7.31 (3.86)
Usual sleep duration (hr)	7.08 (1.11)	7.13 (1.14)	7.03 (1.12)	7.17 (1.16)
Miles driven per year (thousands)	11.0 (7.96)	11.4 (12.7)	10.6 (9.60)	8.96 (7.26)

Azarbazin et al, J Sleep Res 2020



Azarbazin et al, J Sleep Res 2020

4. Cardiopulmonary coupling

- During sleep, using a single-lead EKG signal
- Normal-to-normal sinus interbeat interval series & corresponding electrocardiogram-derived respiration signal.
- Fourier-based technique
- NREM sleep : spontaneous abrupt transitions; High & Low hz
- To track cardiopulmonary interaction dynamically. (NREM)

5. AHI duration

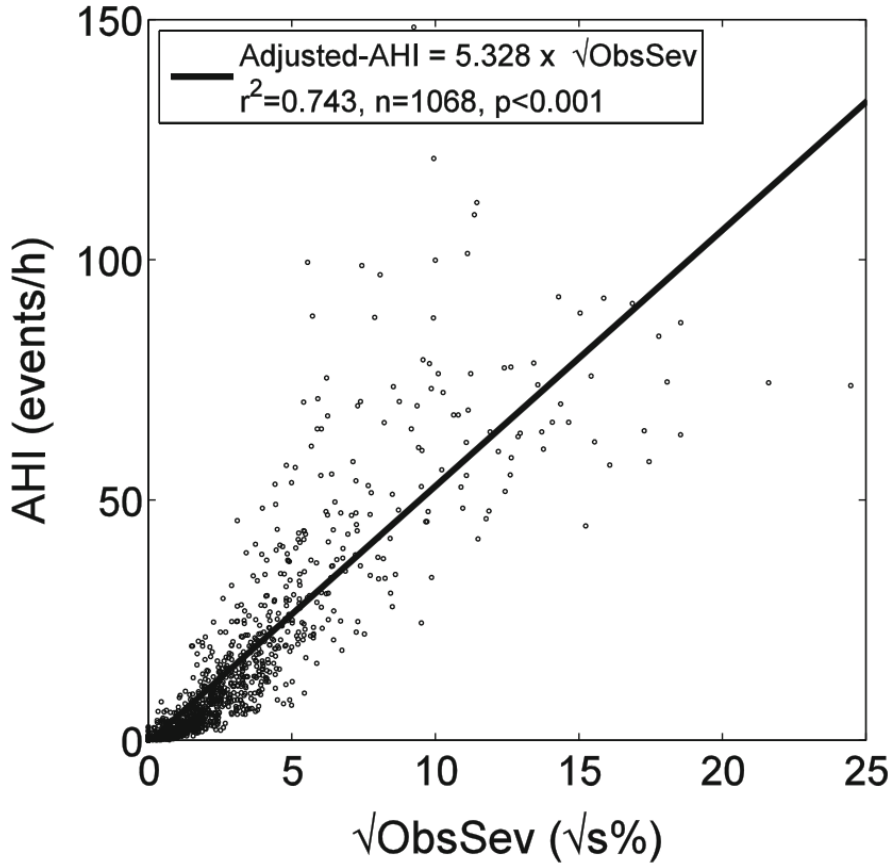
- Duration of the respiratory events & overall mortality in SHHS.

- Short respiratory event : Low arousal threshold
  Unstable ventilatory control
  → Mortality in men & women (HR 1.31)

- Short duration → less hypoxic burden ?

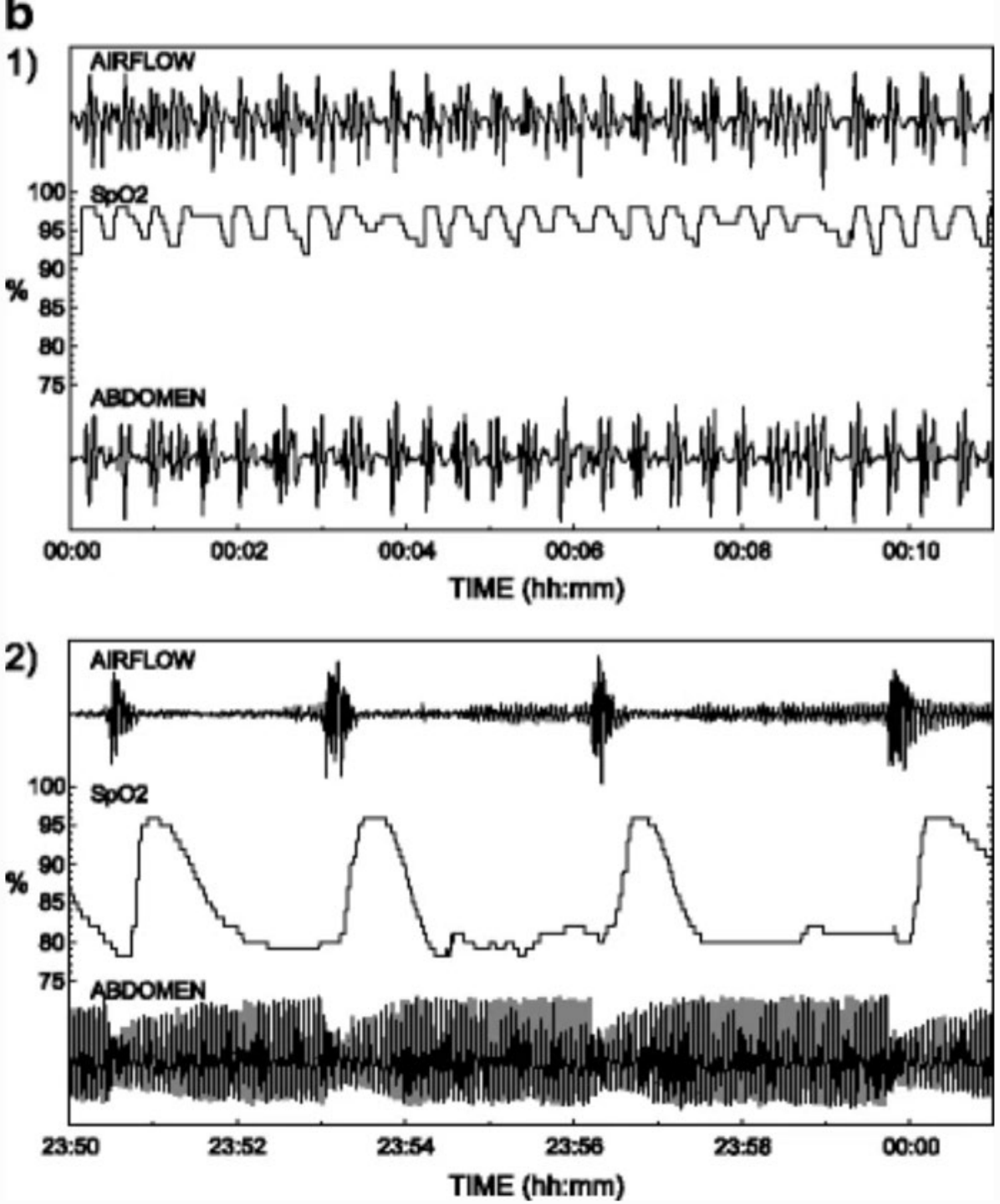
Adjusted AHI

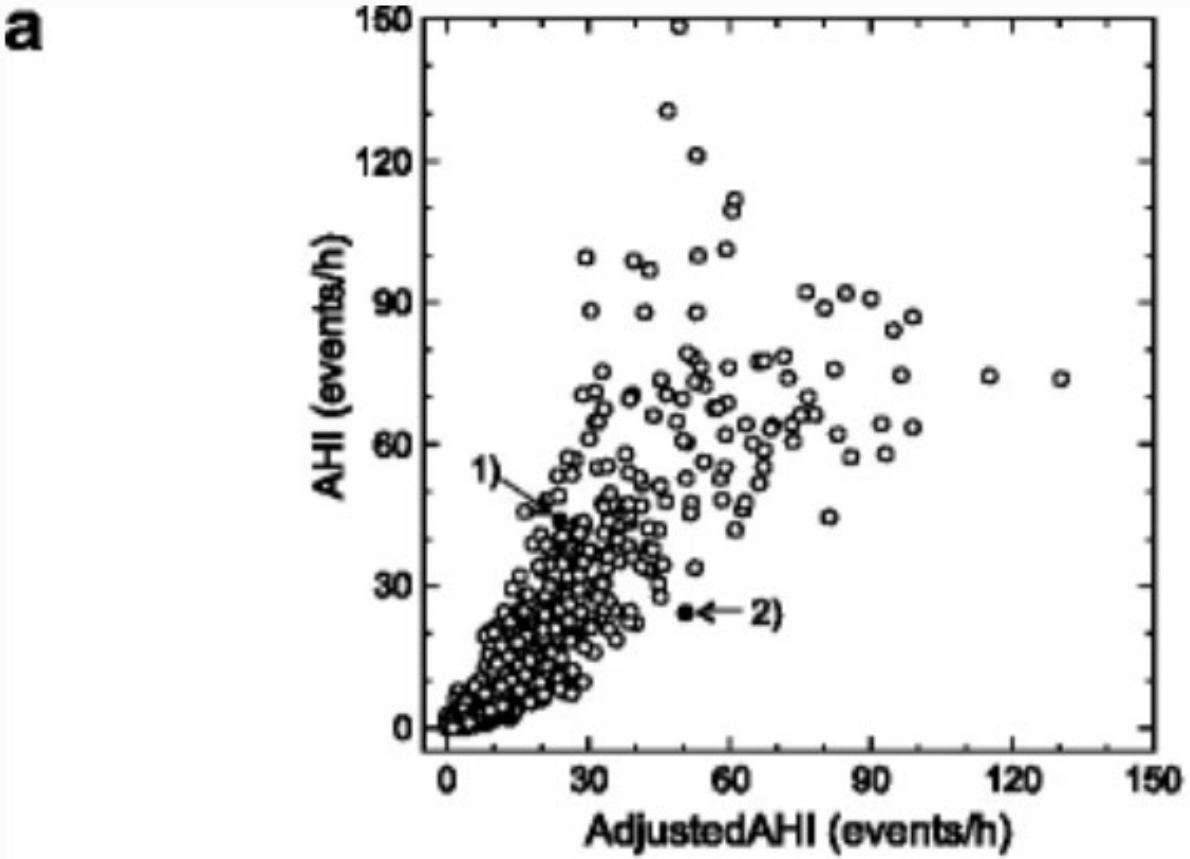
→ AHI + Event duration



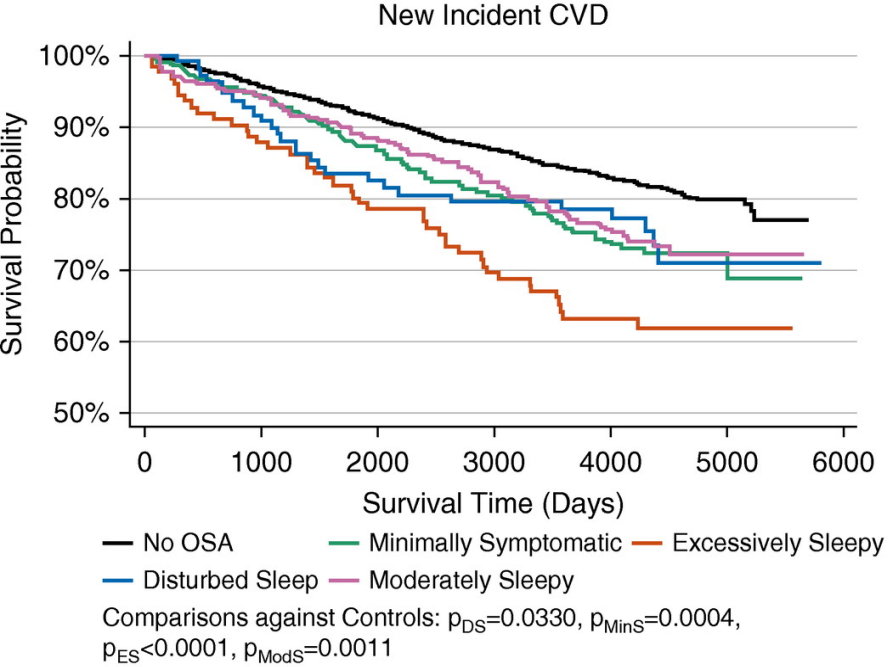
$$\text{Obstruction severity} = \frac{\sum_{n=1}^{L} n(\text{HypDur}_n \times \text{DesArea}_n) + \sum_{n=1}^{L} n(\text{ApDur}_n \times \text{DesArea}_n)}{\text{Index time}},$$

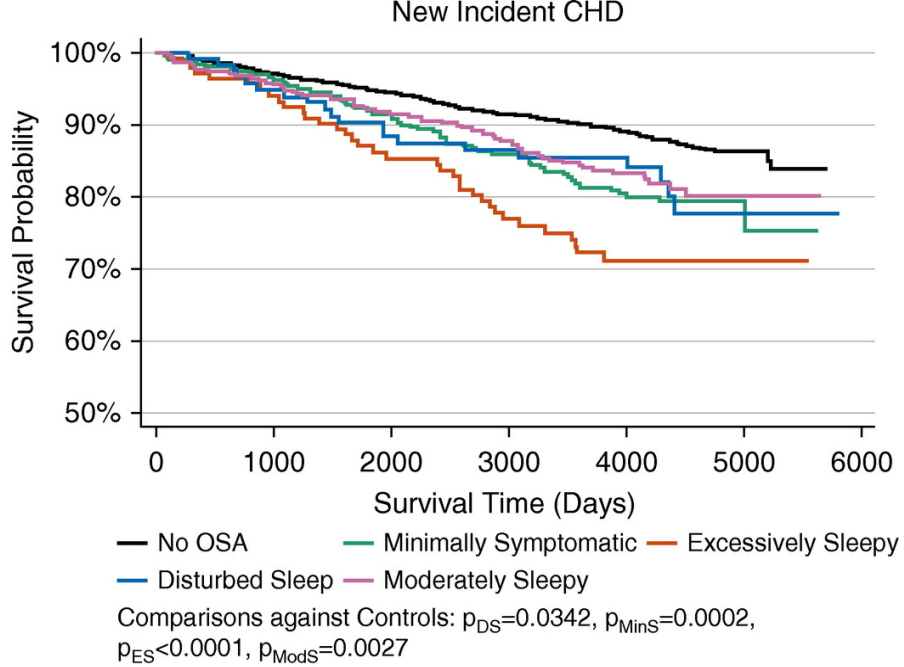
A.Muraja et al, Sleep breath, 2014



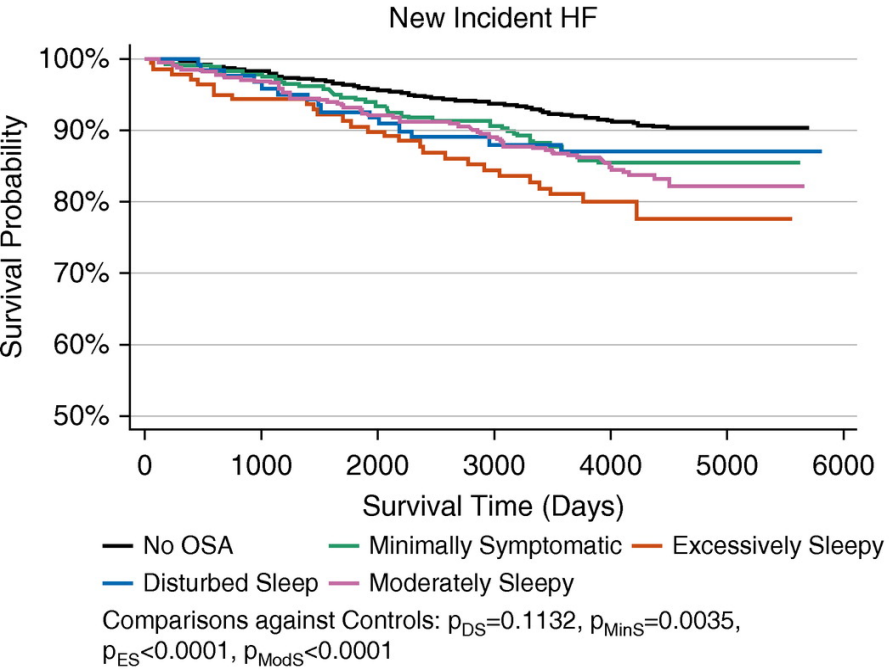


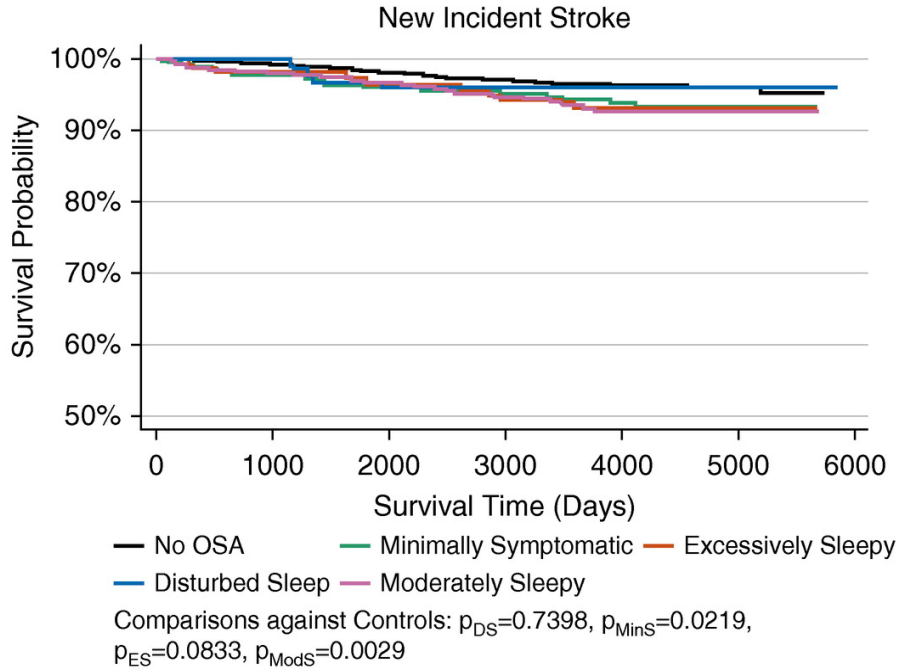
A.Muraja et al, Sleep breath, 2014





Symptom subtype





Death from CVD

Diego et al, AJRCCM 2019

Summary

- Symptom vs Cardiovascular outcome

- AHI, ODI, T90
- Hypoxic burden

- Other metrics

- Subtype(Symptom, Blood test, biomarker) & Cluster analysis