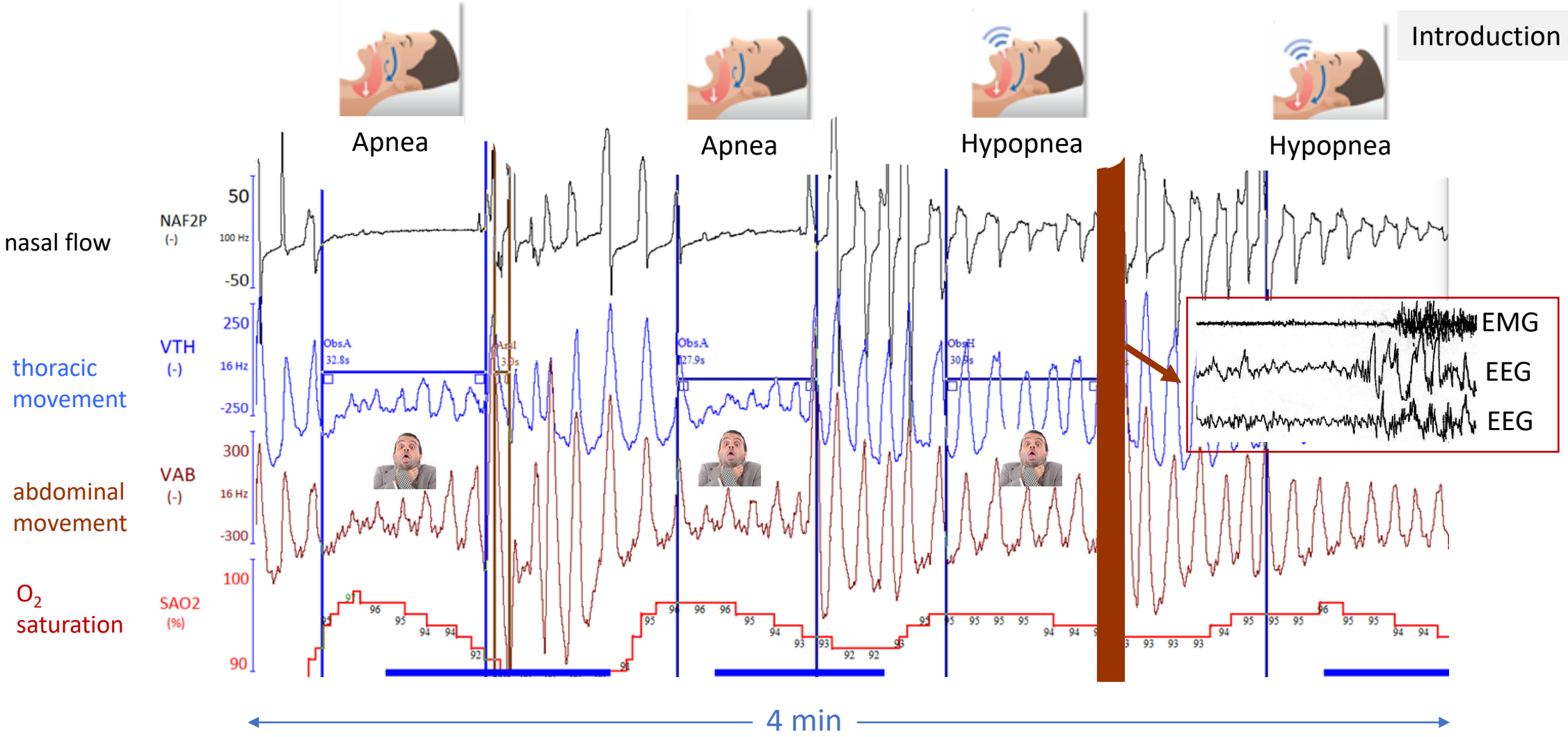
Obstructive sleep apnoea (OSA) in the elderly:

a great challenge for the future!

Prof. B. Buyse, MD, PhD
Louvain University Center for Sleep and wake disorders (LUCS)
Dept of Pulmonology UZ Leuven – KU Leuven, Belgium



Grading	
Mild	AHI 5-14 / h sleep
Moderate	AHI 15-29 / h sleep
Severe	AHI ≥30 / h sleep

large intrathoracic pressure swings

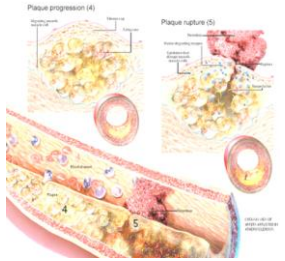
temporary O_2 desaturation /reoxygenation

arousal

Excessive daytime sleepiness, depression, cognitive dysfunction, etc…

Hypertension,
Insulin resistance, …

Mortality, cardio-vascular morbidity, metabolic dysfunction, etc…



Intermediate mechanisms

sympathetic activation
oxidative stress
inflammation, …

3 stress components:

- **large intrathoracic pressure swings**
- **temporary O_2 desaturation /reoxygenation**
- **arousal**

Excessive daytime sleepiness, depression, cognitive dysfunction, etc…

Hypertension,

Mortality, cardio-vascular morbidity, metabolic dysfunction, etc…

These data are predominantly obtained in (younger) middle aged subjects

Extrapolation?

Elderly

sympathetic activation

inflammation, …

3 stress components:

large intrathoracic pressure swings

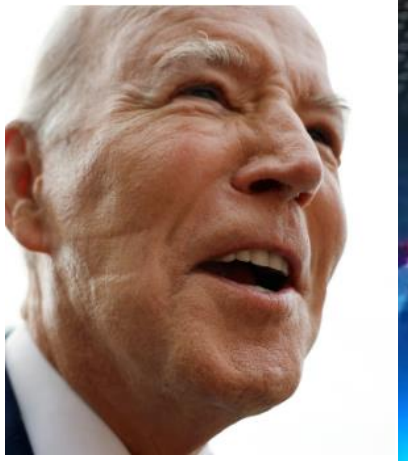
temporary O_2 desaturation /reoxygenation

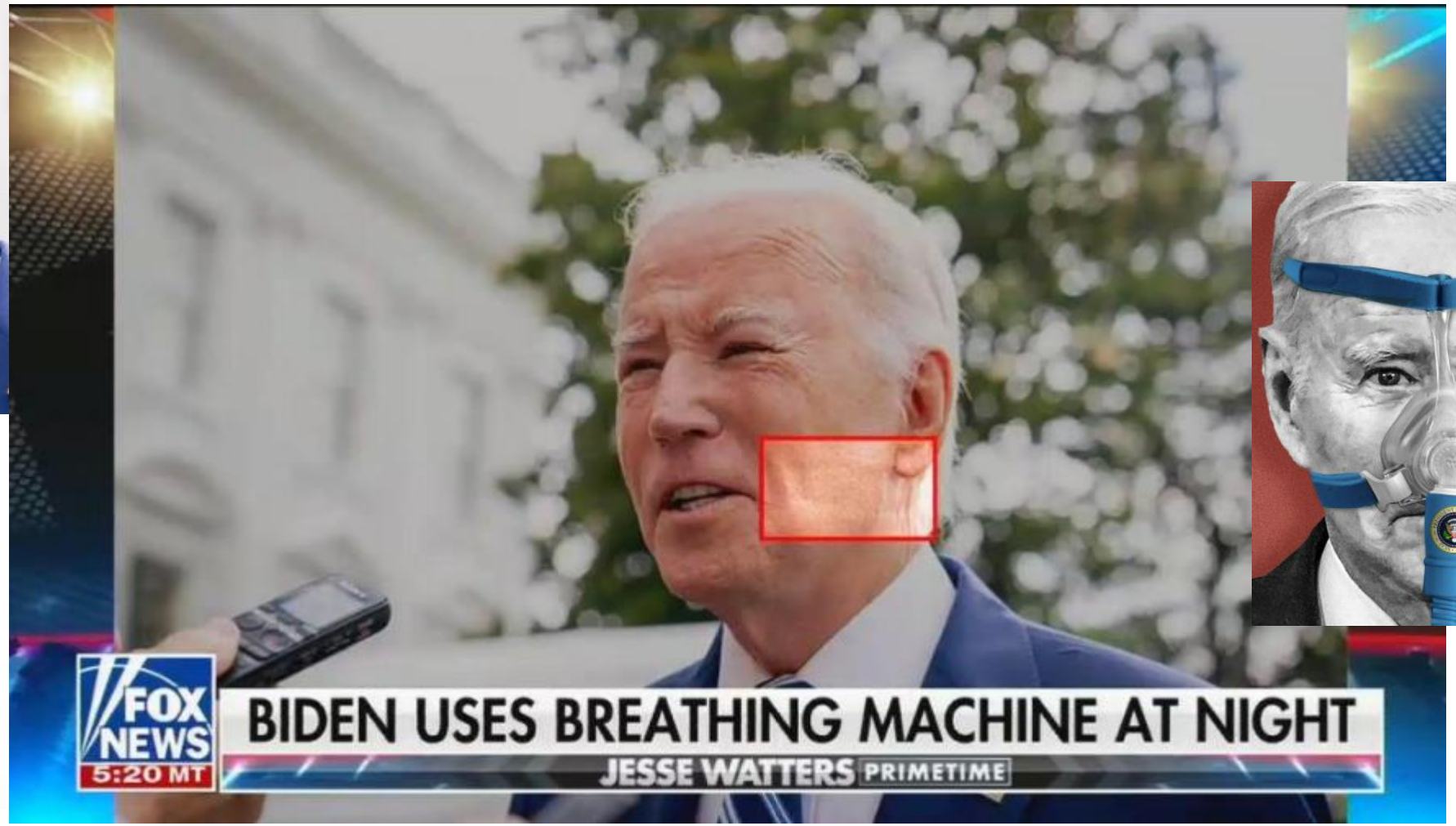
arousal

CNN health

28 jun 2023 — President Joe **Biden** has recently begun using a **CPAP** machine to treat sleep **apnea**

> 80 yrs old



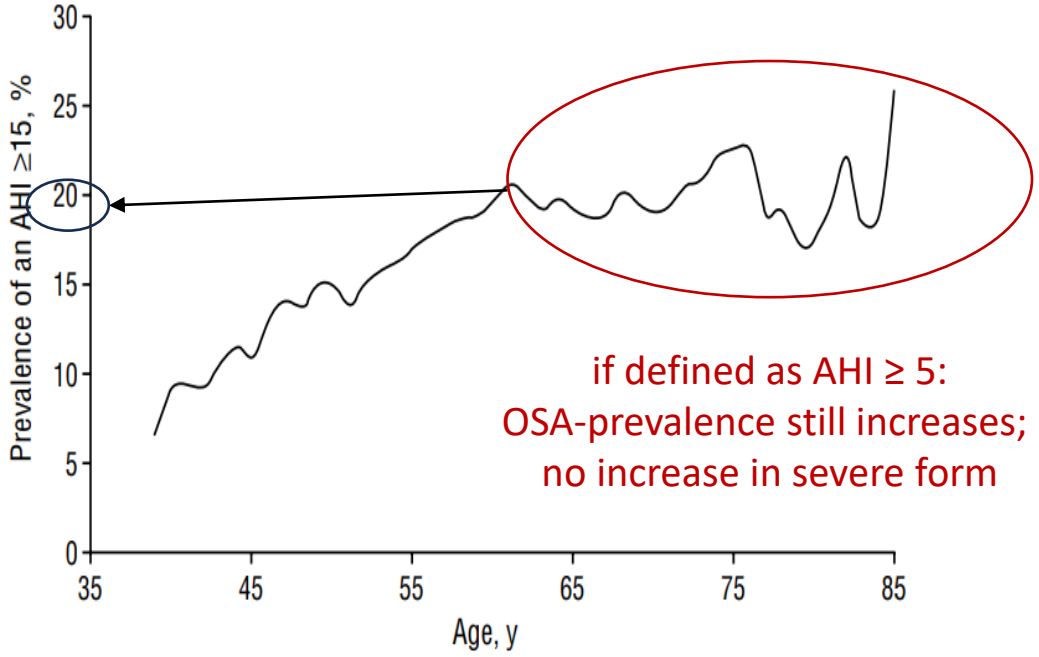


OSA in the elderly: a great challenge for the future ?

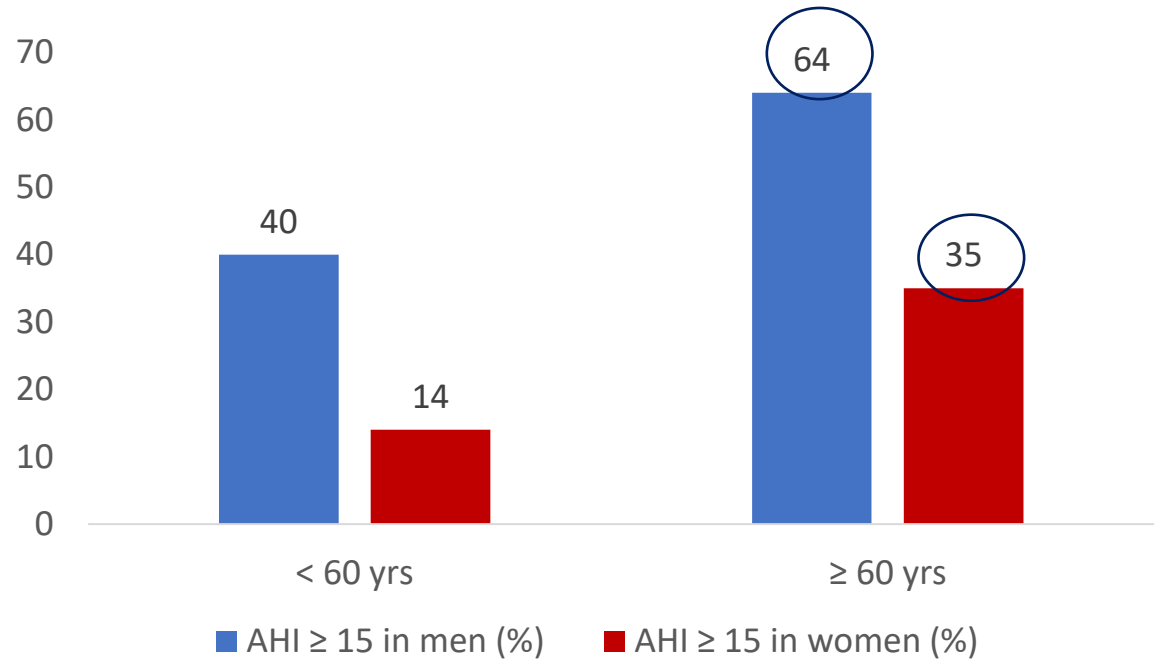
- Prevalence?
- Health outcome impact?
  - Impact on mortality and on “hard” cardio-vascular outcomes
  - Impact on excessive daytime sleepiness
  - Impact in cognition
- Treatment (CPAP) possible?

OSA in the elderly: **prevalence** in the community **= High**

SHSS: n = 6441 (at least 40yrs)



Swiss population study: n = 2121 (40-80yrs)



<u>Difference in prevalence between different studies can be attributed to</u>

- use of modern (more sensitive) diagnostic machinery
- change in methodology e.g. more liberal definition of hypopnoea 4% desaturation versus 3% or arousal

Young et al (SHHS). Arch Intern Med 2002

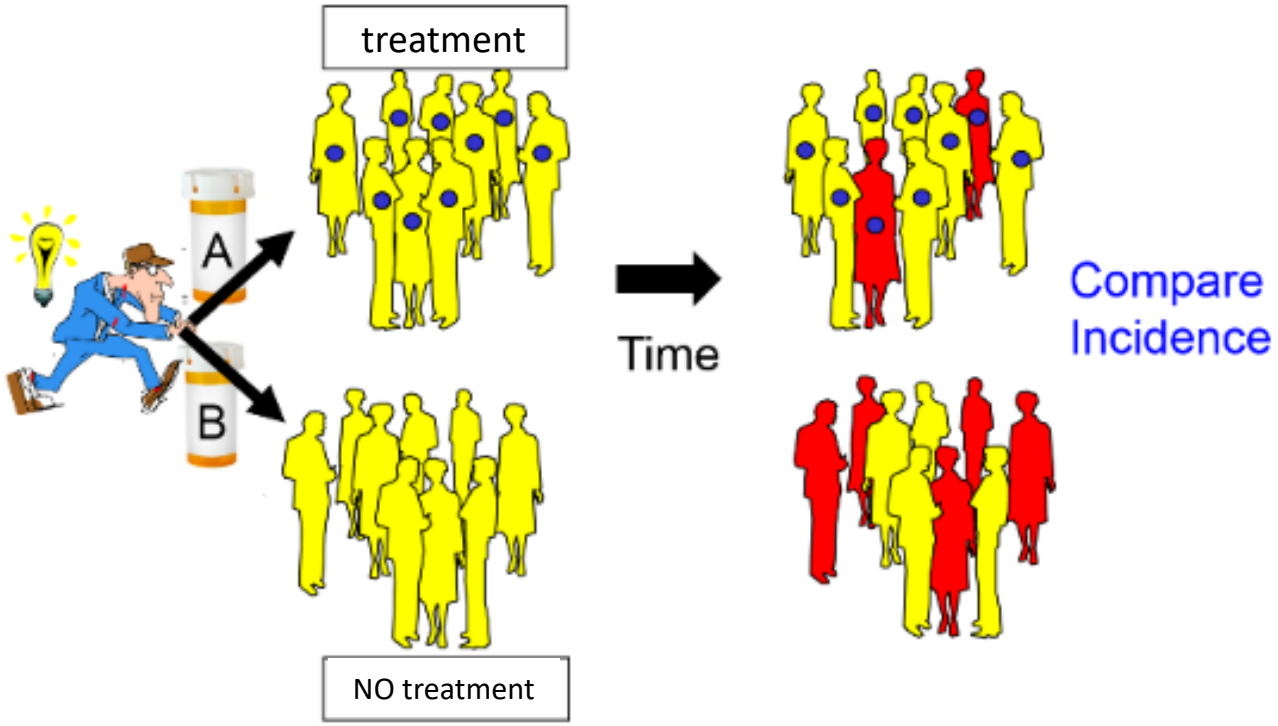
Adapted from Heinzer et al. Lancet Respir Med 2015

OSA in the elderly: a great challenge for the future ?

- Prevalence: high!
- Health outcome impact?

OSA in the elderly: **health impact?**

- Studies only including elderly (≥ 65 yrs old)



Interventional studies (CPAP)

interventional studies provide insight into causal associations

OSA in the elderly: **reversible health impact?**

1. Impact on mortality and on “hard” cardio-vascular outcomes,

2. Impact on excessive daytime sleepiness,

3. Impact on cognition.

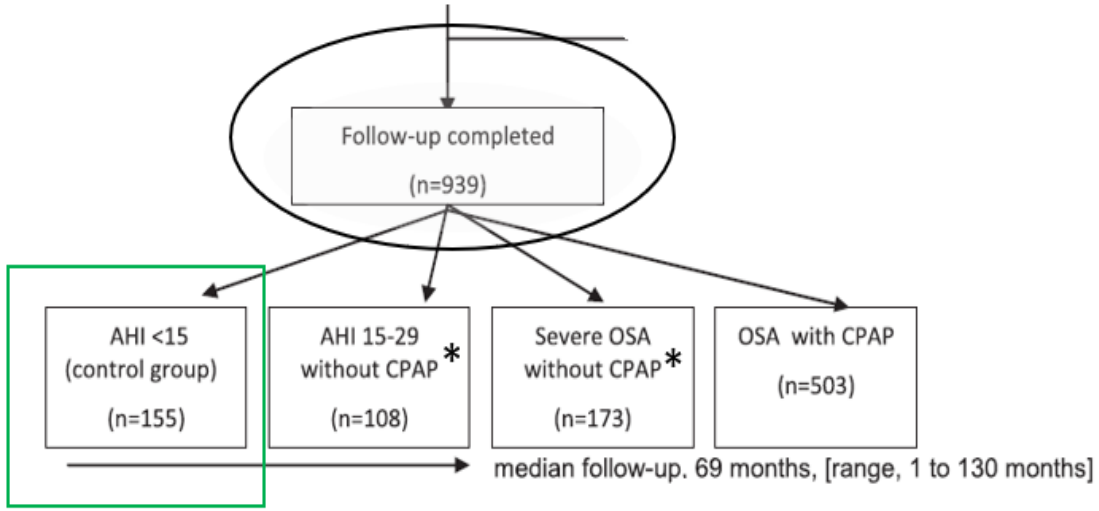
OSA in the elderly: 1. CPAP-impact on mortality and on “hard” cardio-vascular outcomes?

No RCT’s available

Review of large observational studies

OSA in the elderly: 1. CPAP-impact on mortality and on “hard” cardio-vascular outcomes?

CPAP prescription if:
AHI ≥ 30 regardless of symptoms
AHI between 15 and 29 with symptoms
(especially daytime hypersomnia (ESS>10))



Bias: healthy survival effect,
you need RCT’s to proof causality

But this is reflection
of what happens in
a real clinical setting!

* 0-<4 h/day

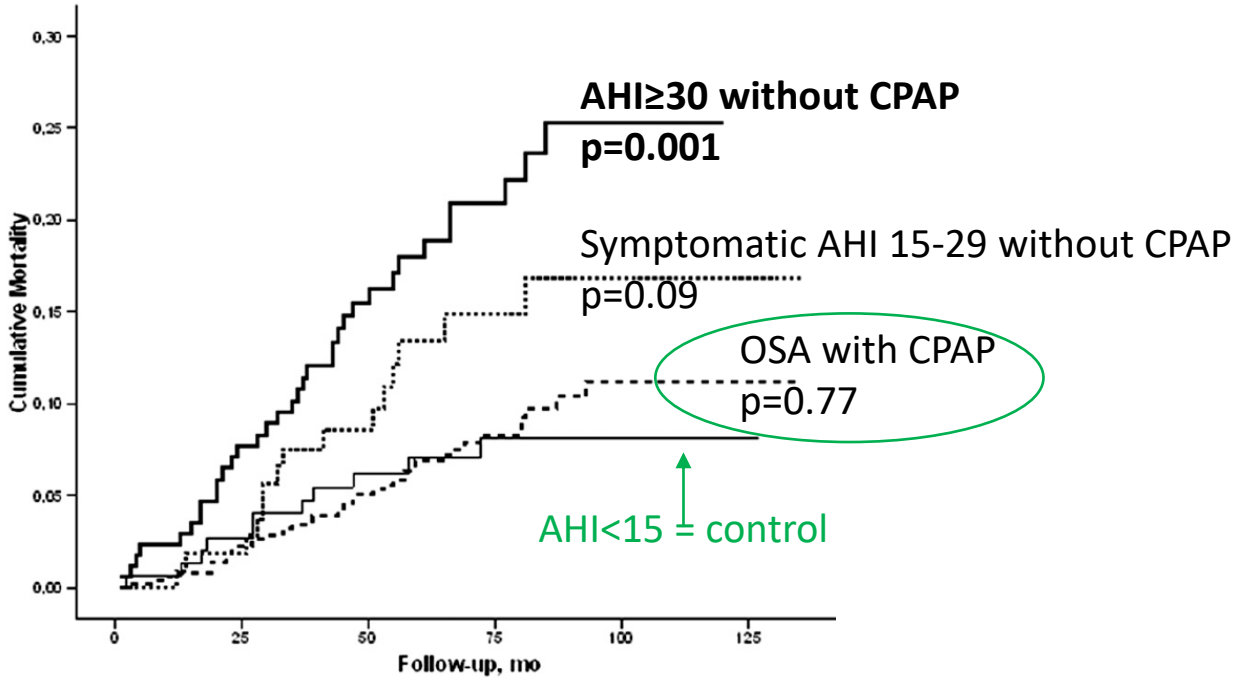
Prospective, observational study of consecutive patients aged ≥ 65 yrs

Martinez-Garcia et al. AJRCCM 2012

OSA in the elderly: 1. CPAP-impact on mortality and on "hard" cardio-vascular outcomes?

Variable	Fully Adjusted† HR (95% CI)	*P* Value
Age	1.06 (1.03–1.11)	0.002
Sex	1.64 (0.86–3.13)	0.13
Type of sleep study (PSG)	1.25 (0.61–2.59)	0.55
Sleep clinic	1.64 (0.87–3.01)	0.13
BMI	1.04 (0.99–1.07)	0.06
Smoked (⩾30 pack-years)	1.53 (0.92–2.56)	0.11
ESS	1.03 (0.99–1.08)	0.13
Dyslipidemia	0.83 (0.55–1.25)	0.37
Diabetes mellitus	2.25 (1.47–3.43)	0.0001
Previous CVE	2.22 (1.44–3.42)	0.0001
AHT	1.12 (0.68–1.85)	0.66
OSA group		
AHI < 15	1	
AHI 15–29 without CPAP	1.38 (0.73–2.64)	0.32
OSA with CPAP	0.93 (0.46–1.89)	0.84
AHI ⩾ 30 without CPAP	2.25 (1.41–3.61)	0.001

Primary end-point:
death from stroke, heart failure and myocardial infarction

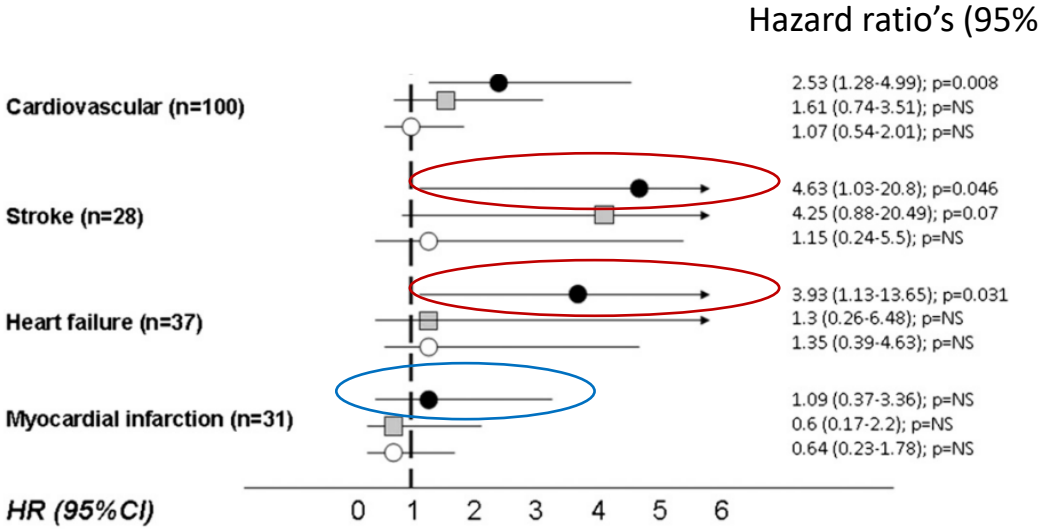


Martinez-Garcia et al. AJRCCM 2012

OSA in the elderly: 1. CPAP-impact on mortality and on “hard” cardio-vascular outcomes?

- ● Severe OSA (AHI≥30) without CPAP
- ■ Moderate symptomatic OSA without CPAP
- ○ OSA with CPAP

<u>Mortality due to:</u>



Note: the risk of death from stroke has also been adjusted for the presence of atrial fibrillation

Cause of cardio-vascular death: stroke/heart failure, not myocardial infarction

Martinez-Garcia et al. AJRCCM 2012

OSA in the elderly: 1. CPAP-impact on mortality and on “hard” cardio-vascular outcomes?

CPAP prescription if:
AHI ≥ 30 regardless of symptoms
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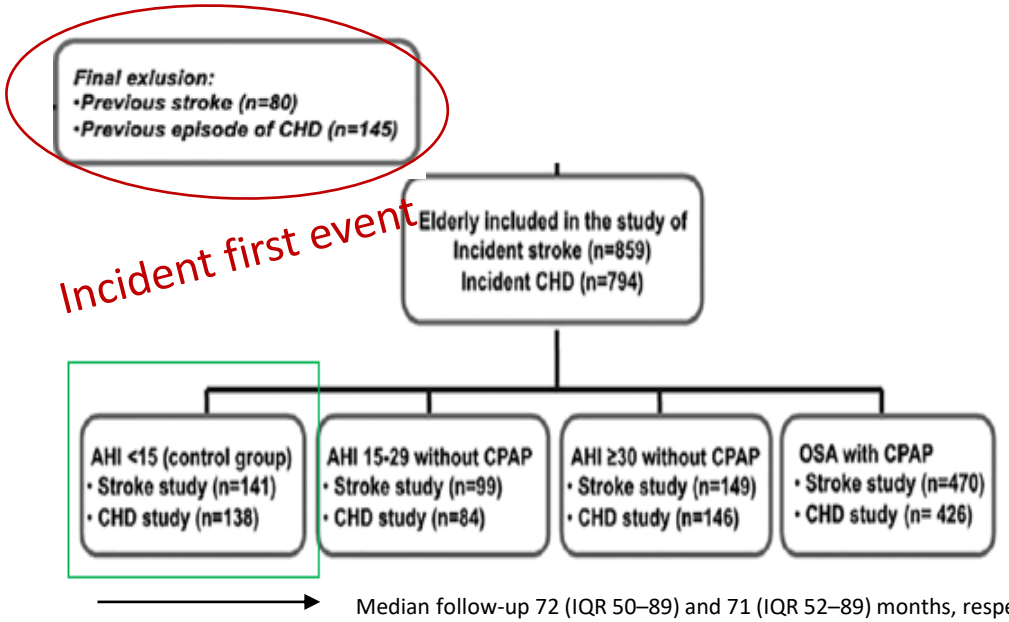
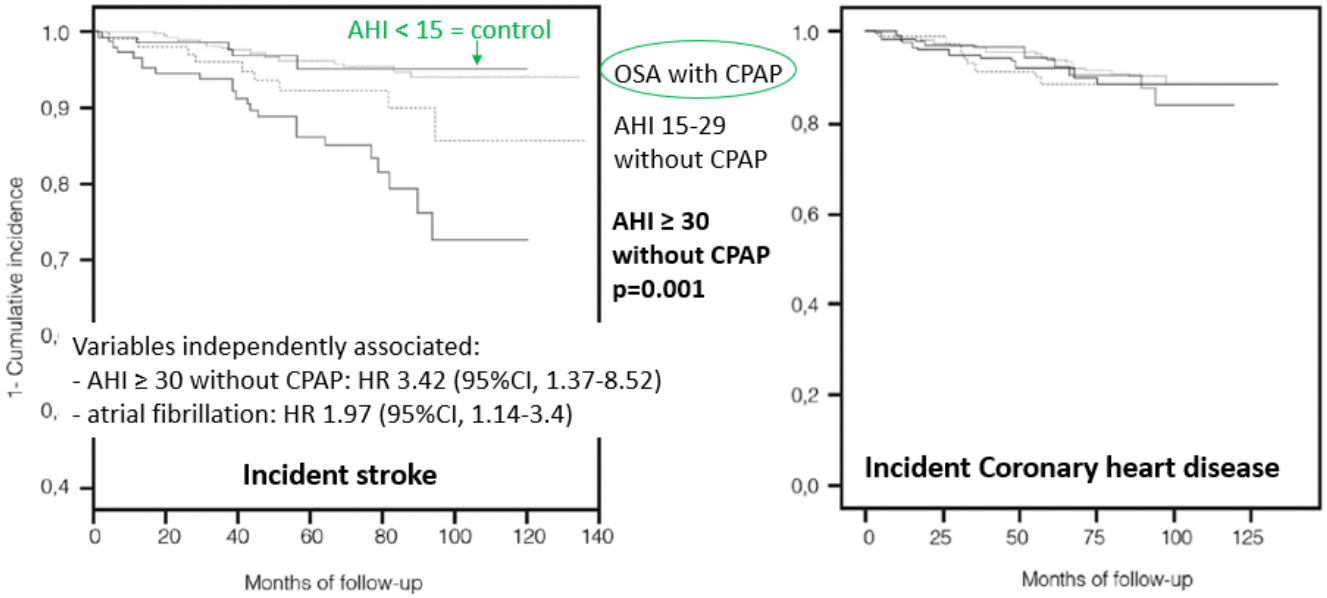


Median follow-up 72 (IQR 50–89) and 71 (IQR 52–89) months, respectively.

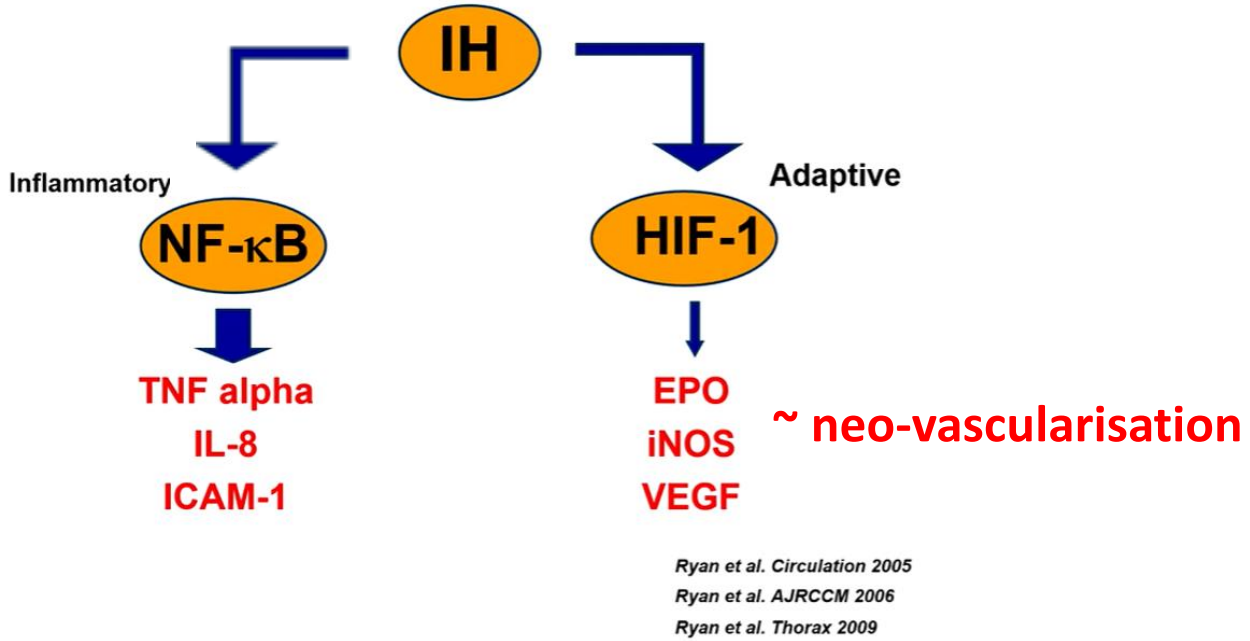


Post-hoc analysis of the previous prospective observational interventional study of consecutive patients aged ≥ 70 yrs

Catalan-Serra et al. Stroke 2019

Preconditioning hypoxia hypothesis

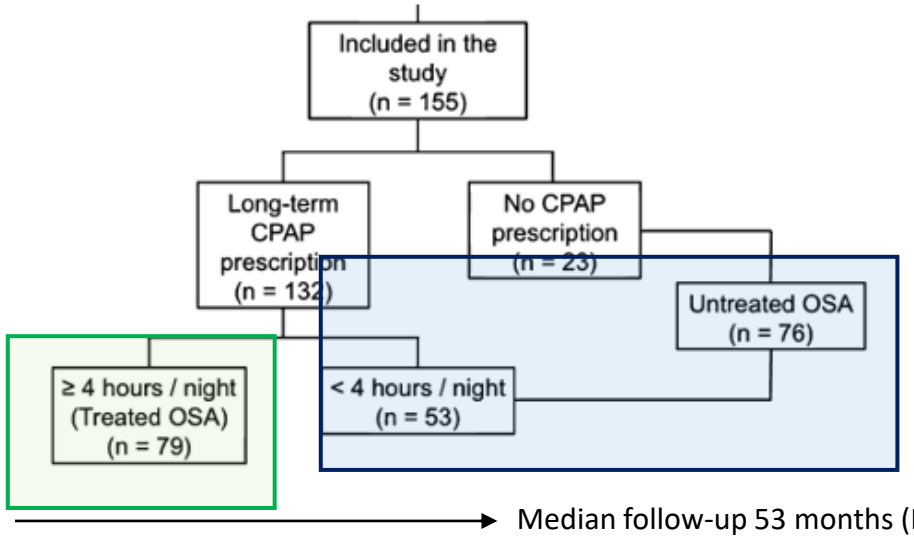
Hypoxic preconditioning refers to exposure of organisms, systems, organs, tissues or cells to moderate hypoxia/ischemia that is able to result in a resistance to subsequent severe hypoxia/ischemia in tissues and cells.



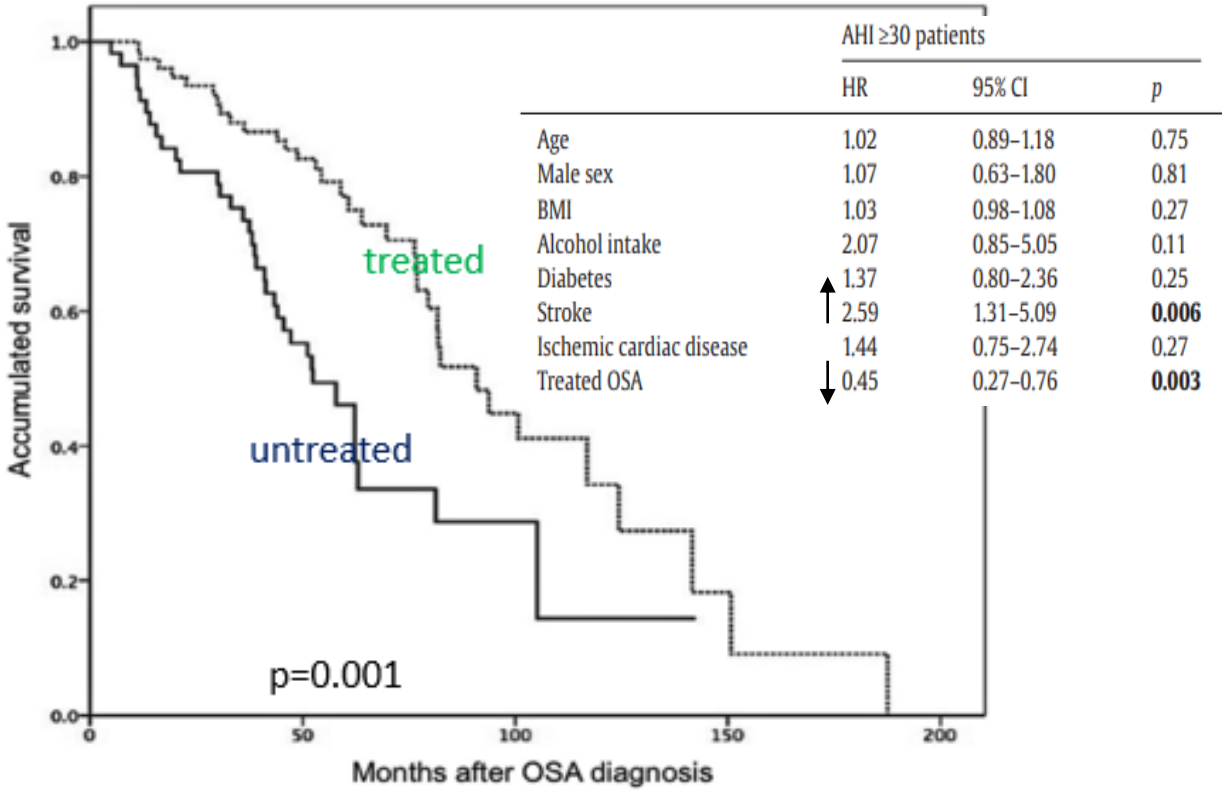
These different effects of OSA on cerebrovascular and coronary disease in the elderly may be explained by different adaptive mechanisms on intermittent hypoxia, which may trigger the formation of collateral vessels in the heart, but not in the brain.

OSA in the **VERY** elderly: 1. CPAP-impact on mortality and on "hard" cardio-vascular outcomes?

<u>CPAP prescription if:</u>
AHI ≥ 30
(AHI between 20 and 29 decided by the sleep specialist on an individual base)



Population with AHI≥30 (86% of total group)



AHI ≥30 patients	HR	95% CI	*p*
Age	1.02	0.89–1.18	0.75
Male sex	1.07	0.63–1.80	0.81
BMI	1.03	0.98–1.08	0.27
Alcohol intake	2.07	0.85–5.05	0.11
Diabetes	1.37	0.80–2.36	0.25
Stroke ↑	2.59	1.31–5.09	**0.006**
Ischemic cardiac disease	1.44	0.75–2.74	0.27
Treated OSA ↓	0.45	0.27–0.76	**0.003**

Retrospective, observational study of consecutive patients aged ≥ 80yrs

Lopez-Padilla et al. Sleep Med 2016

OSA in the elderly: **reversible health impact?**

1. Impact on mortality and “hard” cardio-vascular outcomes

   Consider to treat **severe** (AHI≥30/h) **OSA,**

   in ≥ 80 yrs old: limited evidence

J. Sleep Res. (2009) 18, 397–403

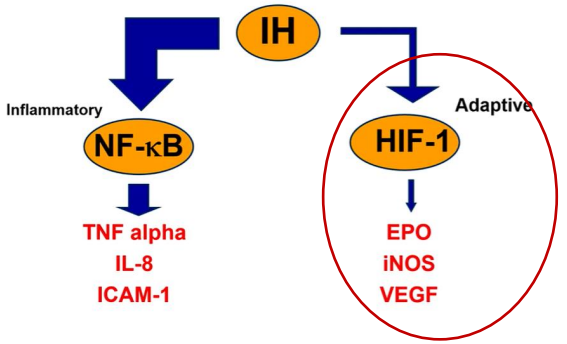
Sleep apnoea

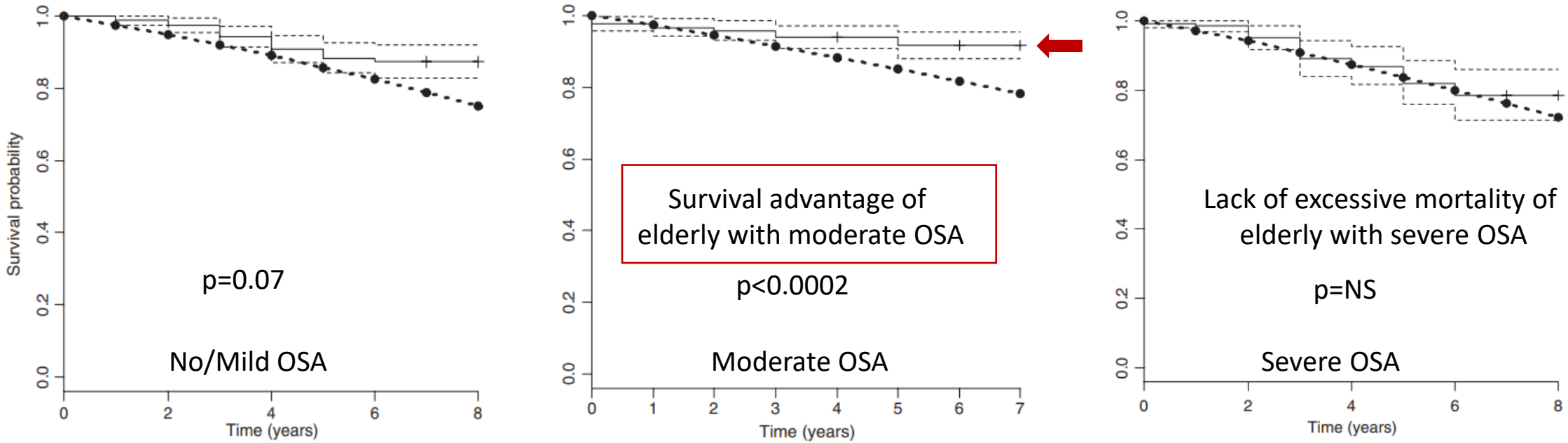
doi: 10.1111/j.1365-2869.2009.00754.x

Unexpected survival advantage in elderly people with moderate sleep apnoea

PERETZ LAVIE and LENA LAVIE

Lloyd Rigler Sleep Apnea Research Laboratory, Ruth and Bruce Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel





= expected survival curve based on age-sex-ethnicity matched national mortality data

OSA in the elderly: **reversible health impact?**

1. Impact on mortality and “hard” cardio-vascular outcomes

   Consider to treat **severe** (AHI≥30/h) **OSA,**

    *in ≥ 80 yrs old: limited evidence*

2. Impact on excessive daytime sleepiness (EDS)

Introductory remarks

The clinical picture of OSA in elderly is different from that seen in younger patients.
EDS due to OSA seems less prominent in elderly:
- less debilitating?
- suggesting the possibility of differential susceptiblity and/or disorder?

EDS must not be considered a physiological situation: it “is NOT normal at this age”.
However it should not be assumed that it is associated to OSA.

Zalai et al. Sleep Medicine 2017 and Iannella et al. Eur Arch Oto-Rhino-Laryngology 2019 and Posada et al. J Clin Med 2020

OSA in the elderly: CPAP-impact on **excessive daytime sleepiness**

RCT's available !

Epworth Sleepiness Scale (ESS)

Chance of Dozing
- 0 = no chance of dozing
- 1 = slight chance of dozing
- 2 = moderate chance of dozing
- 3 = high chance of dozing

Situation	Chance of Dozing
Sitting and reading	☐
Watching TV	☐
Sitting inactive in a public place (e.g. a theatre or a meeting)	☐
As a passenger in a car for an hour without a break	☐
Lying down 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	☐
Total:	☐

> 10 = pathological

Validated in elderly

Higher scores indicate more severe symptoms

Labarca et al. Chest 2020 (systematic review and meta-analysis)

OSA in the elderly: CPAP-impact on the Epworth Sleepiness Scale (ESS) after 3 months

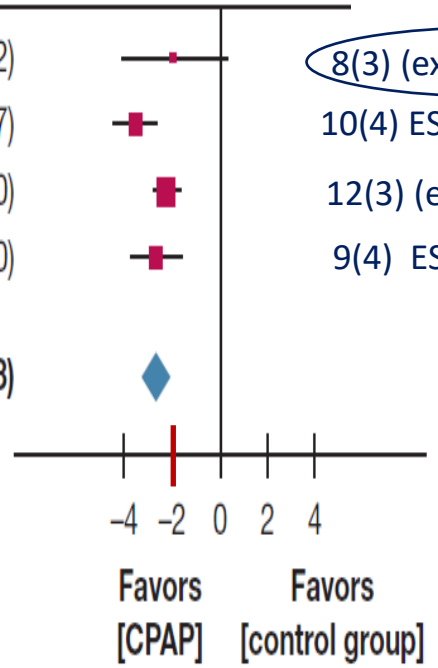
Severe OSA

(Moderate to) severe OSA

Study or Subgroup	CPAP Mean	CPAP SD	CPAP Total	Control Group Mean	Control Group SD	Control Group Total	Weight	Mean Difference IV, Random, 95% CI
Dalmases 2015	−1.5	4.4659	17	0.38	1.14	16	8.2%	−1.88 (−4.08 to 0.32)
Martinez-Garcia 2015	−3.58	4	115	−0.1	2.85	109	27.0%	−3.48 (−4.39 to −2.57)
McMilian 2014	−3.8	0.4	138	−1.6	3	140	40.3%	−2.20 (−2.70 to −1.70)
Ponce 2019	−3.5	3.0718	73	−0.9	3.0718	72	24.5%	−2.60 (−3.60 to −1.60)
Total (95% CI)			**343**			**337**	**100.0%**	**−2.62 (−3.30 to −1.93)**

Heterogeneity: $Tau^2 = 0.24$; $\chi^2 = 6.21$, df = 3 ($P = .10$); $I^2 = 52\%$

Test for overall effect: $z = 7.50$ ($P < .00001$)



Baseline ESS in the CPAP arm

8(3) (excluded ESS≥12)

10(4) ESS≥10 37%

12(3) (excluded ESS<9)

9(4) ESS≥10 38%

Clinical significant threshold for ESS ~ amelioration in daytime sleepiness (Patil et al. J Clin Sleep Med 2019): reduction of at least 2 points

Labarca et al. Chest 2020 (systematic review and meta-analysis)

OSA in the **very** elderly: CPAP-impact on the Epworth Sleepiness Scale (ESS) after 3 months

Table 2
Changes in sleep-related symptoms between groups in an Intention-to-treat principle adjusted for baseline measurements.

Variables	CPAP treatment (n = 47)			Conservative treatment (n = 50)			Intergroup Differences (CI95%)	P value
	Baseline	Follow-up	Intragroup differences	Baseline	Follow-up	Intragroup differences		
Snoring, %	98%	37%	−61%	98%	97%	−1%	−58 (−45, −82%)	<0.001
Witnessed apneas, %	69%	31%	−38%	87%	86%	−1%	−35 (−27, −53%)	0.006
Nightmares, %	36%	28%	−8%	38%	36%	−2%	−6 (12, −14%)	NS
Choking, %	19%	9%	−10%	20%	11%	−9%	−1 (12, −11%)	NS
Nocturia	2.4 (1.2)	2 (1.5)	−0.4 (1.4)	2.1 (0.8)	2.1 (0.8)	0 (0.4)	−0.3 (0.8, −1.5)	NS
ESS	9.2 (3.5)	7.5 (3.7)	−1.7 (3.6)	9.4 (3.9)	9.1 (3.9)	−0.3 (3.9)	1.2 (0.2, −2.6)	NS

ESS≥10 45%

ESS≥10 54%

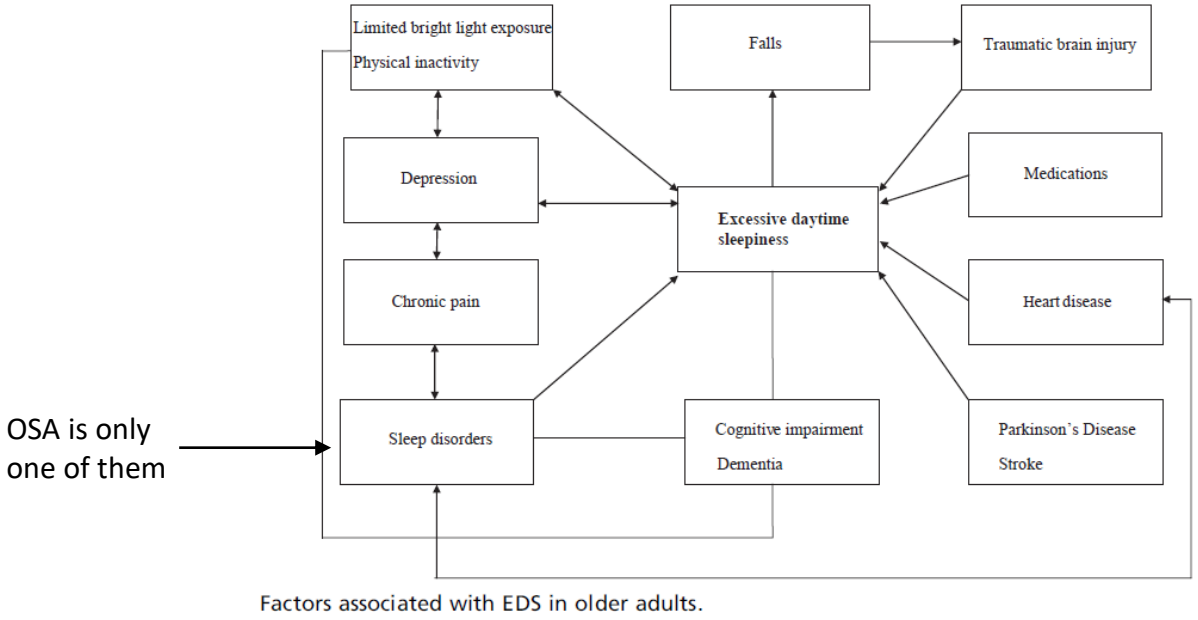
Clinical significant threshold for ESS ~ amelioration in daytime sleepiness (Patil et al. J Clin Sleep Med 2019): reduction of at least 2 points

A post-hoc pooled analysis of 2 RCT's in patients with (moderate to) severe OSA (*Martinez-Garcia 2015, Ponce 2019)* only including ≥ 80 yr old subjects

Martinez-Garcia et al. Sleep Medicine 2022

Why in the **very** elderly no impact on excessive daytime sleepiness

These patients present limited light exposure, a more sedentary lifestyle and a large number of comorbidities and ongoing treatments which might affect the quality or quantity of sleep, inducing a increased hypersomnolence, not correctable with CPAP.



Factors associated with EDS in older adults.

These patients appear to be less compliant with CPAP (see later).

Zalai et al. Sleep Med Clin 2017

OSA in the elderly: **reversible health impact?**

1. Impact on mortality and “hard” cardio-vascular outcomes

   Consider to treat **severe** (AHI≥30/h) **OSA,**

    *in ≥ 80 yrs old: limited evidence*

2. Impact on excessive daytime sleepiness (EDS)

   Treat **somnolent (moderate to) severe** (AHI+/-30 or more /h) **OSA,**

    *in ≥ 80 yrs old: limited evidence **not** to treat*

! Other reasons for EDS than OSA

3. Impact on cognition

a) on cognitive aging

Research has posited that the combination of OSA and advanced age leads to cognitive impairments greater than either factors alone

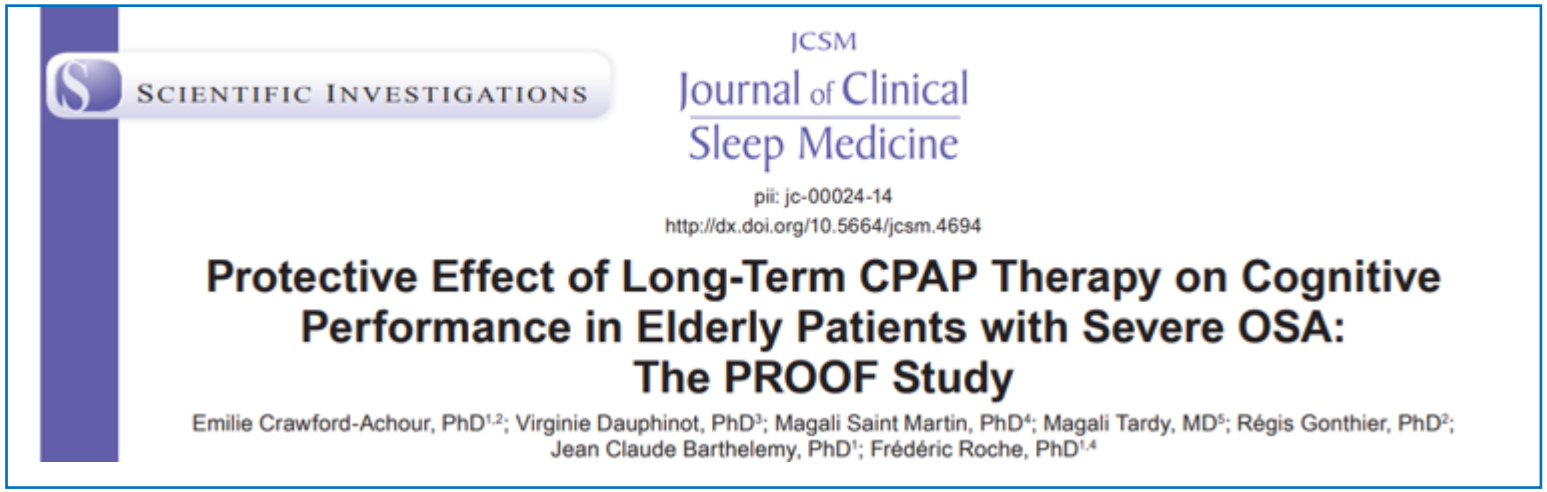
b) on dementia

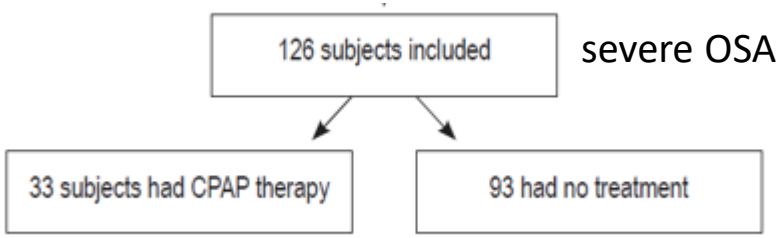
Very short-term!

Amelioration ~

TMT-A and B
Digit Symbol

OSA in the elderly: CPAP-impact on a) cognitive aging?





severe OSA

evaluated between 2002-2003

re-assessed between 2009-2012
+/-10 years later

CPAP prescription:
at the discretion of the physician

Prospective, observational study of consecutive patients aged ≥ 65yrs

Crawford-Achour et al. J Clin Sleep Med 2015

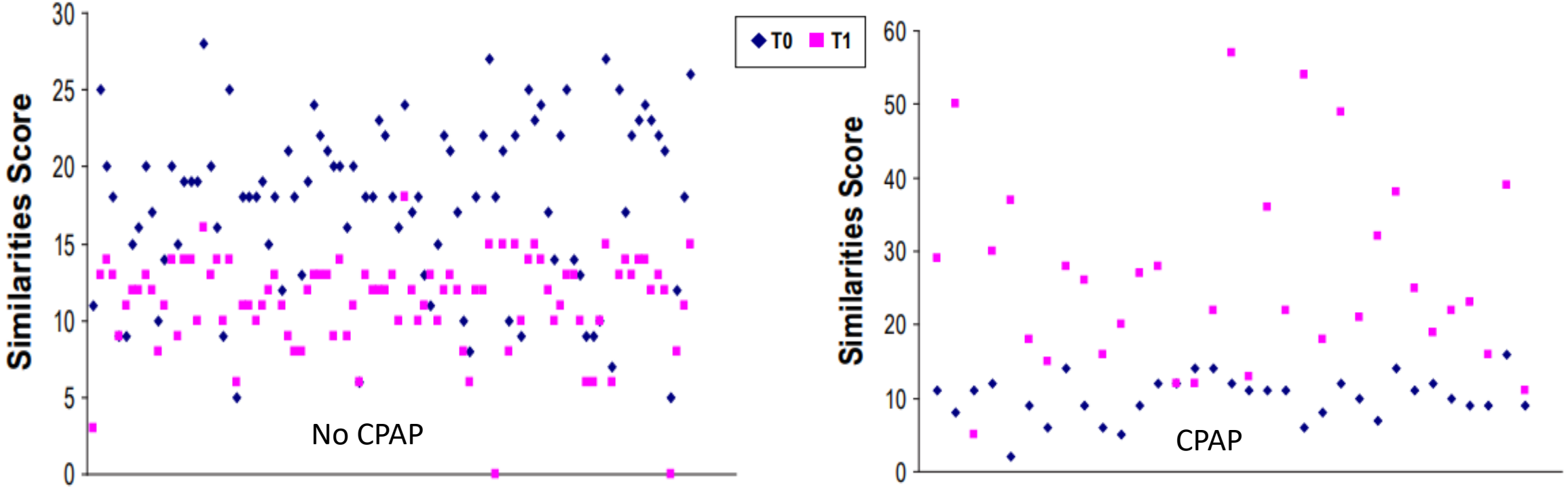
OSA in the elderly: CPAP-impact on a) cognitive aging? in severe OSA

	Non-Treated Patients (n = 93)			Treated Patients (n = 33)			p-value as a function of treatment and effect of time	
	Mean value at T0	Mean value at T1	p value (within-subject time)	Mean value at T0	Mean value at T1	p value (within-subject time)		
MMSE	28.75 (0.12)	28.51 (0.15)	0.13	28.77 (0.2)	28.84 (0.24)	0.78	0.30	
VAS of memory complaint	2.52 (0.21)	3.01 (0.19)	0.04	2.52 (0.34)	2.67 (0.32)	0.69	0.45	
Delayed total recall (Grober and Buschke test)	15.43 (0.12)	15.36 (0.22)	0.71	15.65 (0.2)	15.61 (0.36)	0.85	0.91	
Delayed free recall (Grober and Buschke test)	12.21 (0.25)	11.19 (0.32)	< 0.0001 worsening	12 (0.41)	12 (0.53)	ns	0.02	Episodic memory
Benton test	12.48 (0.17)	12.3 (0.18)	0.34	12.87 (0.28)	12.58 (0.3)	0.48	0.78	
TMT A	44.5 (1.35)	49.77 (1.78)	0.002	41.32 (2.22)	51.74 (2.92)	< 0.0001	0.09	
TMT B	96.86 (3.79)	107.42 (4.81)	0.03	81.49 (6.23)	103.34 (7.92)	< 0.0001	0.19	
Stroop (words)	98.71 (1.34)	89.9 (1.38)	< 0.0001	98.87 (2.3)	92.58 (2.27)	< 0.0001	0.28	
Stroop (colors)	69.20 (1.13)	63.02 (1.19)	< 0.0001	70.19 (1.86)	63.71 (1.96)	< 0.0001	0.85	
Semantic fluency	31.56 (0.84)	30.63 (0.83)	0.20	30.32 (1.39)	29.65 (1.37)	0.53	0.85	
Alphabetic fluency	19.96 (0.72)	19.93 (0.82)	0.96	19.55 (1.18)	20.26 (1.34)	0.47	0.54	
Similarities (WAIS III)	17.71 (0.52)	11.53 (0.72)	< 0.0001 worsening	10.45 (0.85)	25.13 (1.18)	< 0.0001 ameliorating	< 0.0001	Executive function (abstract thinking)

Crawford-Achour et al. J Clin Sleep Med 2015

OSA in the elderly: CPAP-impact on a) cognitive aging?

" These results are of considerable importance as the PAQUID (Personnes agées QUID) French epidemiological study has shown that the similarities test was one of the more specific tests correlated with later occurrence of dementia.
Thus, treating the sleep apnea population could be a way to delay the occurrence of cognitive impairment."



Crawford-Achour et al. J Clin Sleep Med 2015 and Fabrigoule et al. Brain 1998

OSA in the elderly: CPAP-impact on b) dementia?

Moderate to severe OSA — **Mild-to-moderate Alzheimer disease (AD)** — Severe OSA

13.3+/-5.2 months ⟵ evaluation after ⟶ 4.1+/-3.1 yrs

Variable	CPAP+ (n = 5) Mean (SD)		CPAP− (n = 5) Mean (SD)		Effect size
	End of RCT	Follow-Up	End of RCT	Follow-Up	
HVLT	15.2 (7.2)	14.0 (7.9)	13.8 (6.4)	12.8 (4.9)	0.1
WAIS**	19.3 (2.5)	17.0 (8.2)	15.4 (4.6)	12.3 (7.4)	−1.9
Trails A	86.6 (120.1)	96.2 (115.3)	67.6 (26.9)	100.0 (64.5)	0.5
Trails B	95.8 (25.8)	87.8 (71.1)	247.8 (96.3)	249.6 (78.9)	−0.3
WCST	43.6 (13.4)	33.6 (25.4)	35.8 (9.4)	28.8 (22.2)	0.7
Stroop	8.0 (4.1)	18.8 (16.0)	5.3 (3.0)	2.8 (12.1)	−0.8
FAS Letter	24.6 (16.3)	25.4 (26.3)	26.4 (16.2)	19.8 (9.8)	−0.7
FAS Animal	13.2 (9.2)	11.4 (12.6)	11.6 (6.1)	9.2 (5.5)	−0.1
Digit Cancel	18.4 (9.0)	16.2 (14.3)	13.7 (1.5)	11.0 (5.8)	−0.2

Benefit on psychomotor speed

Benefit on executive function

Impact op MMSE=NS (EF 0.1)

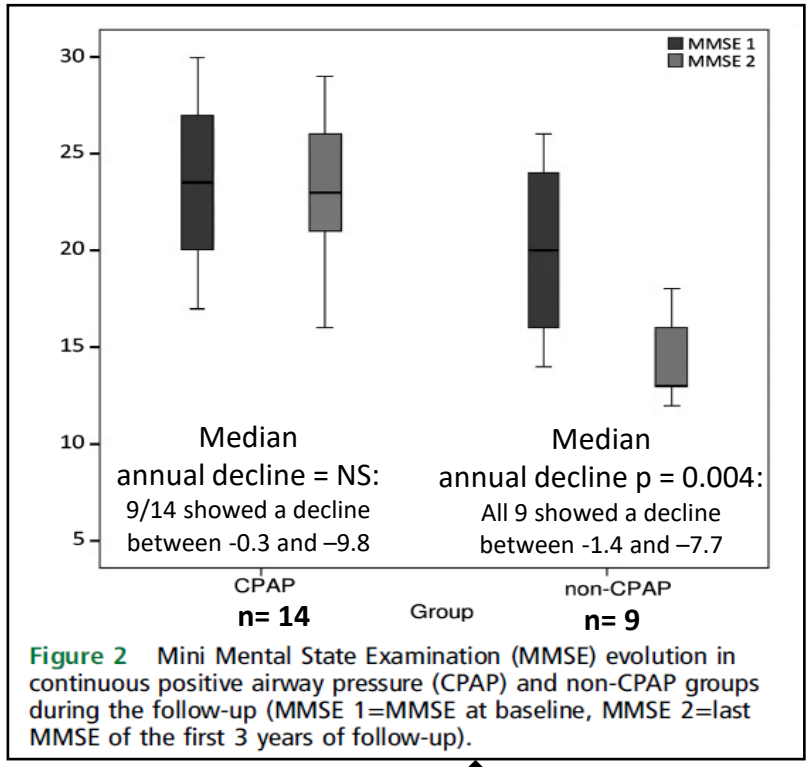


Figure 2 Mini Mental State Examination (MMSE) evolution in continuous positive airway pressure (CPAP) and non-CPAP groups during the follow-up (MMSE 1=MMSE at baseline, MMSE 2=last MMSE of the first 3 years of follow-up).

Prospective, observational studies of patients aged ≥ 65yrs with AD

Cooke et al. J Clin Sleep Med 2009

Troussière et al. J Neurol Neurosurg Psychiatry 2014

OSA in the elderly: **reversible health impact?**

1. Impact on mortality and “hard” cardio-vascular outcomes

   Consider to treat **severe** (AHI≥30/h) **OSA,**

    *in ≥ 80 yrs old: limited evidence*

2. Impact on excessive daytime sleepiness (EDS)

   Treat **somnolent (moderate to) severe** (AHI+/-30 or more /h) **OSA,**

    *in ≥ 80 yrs old: limited evidence **not** to treat*

   ! Other reasons for EDS than OSA

3. Impact on cognition

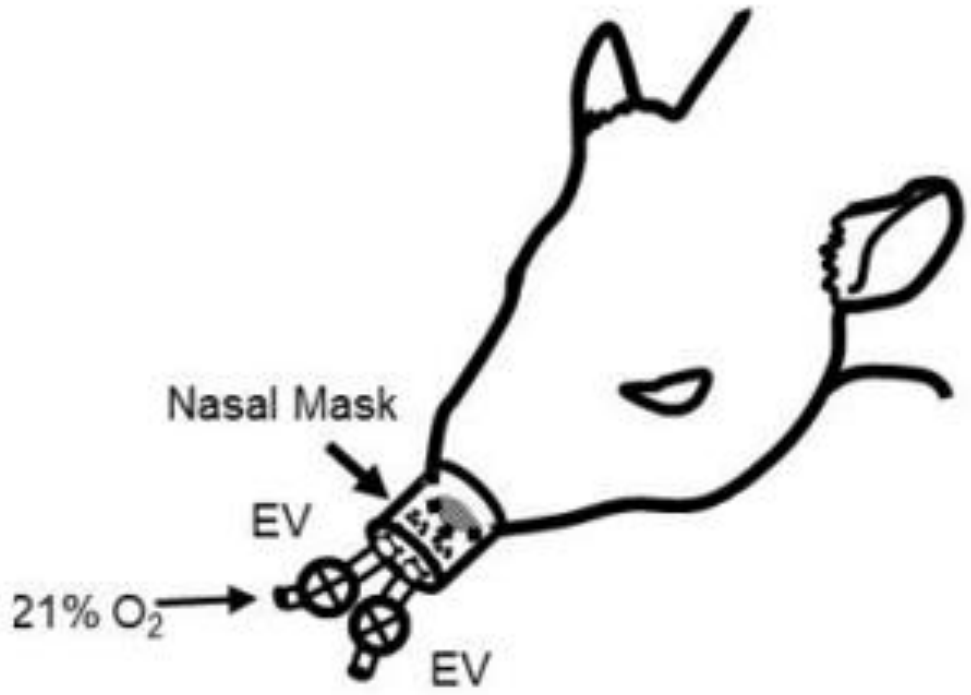
   a) on cognitive aging

      Consider to treat **severe** (AHI≥30/h) **OSA**

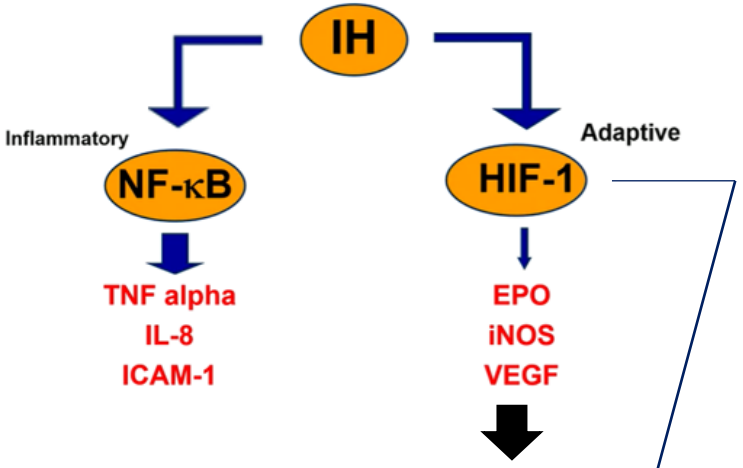
   b) on **mild-to-moderate** dementia

      Consider to treat **severe** (AHI≥30/h) **OSA**

Adaptive and maladaptive processes induced by intermittent hypoxia (IH) in the brain



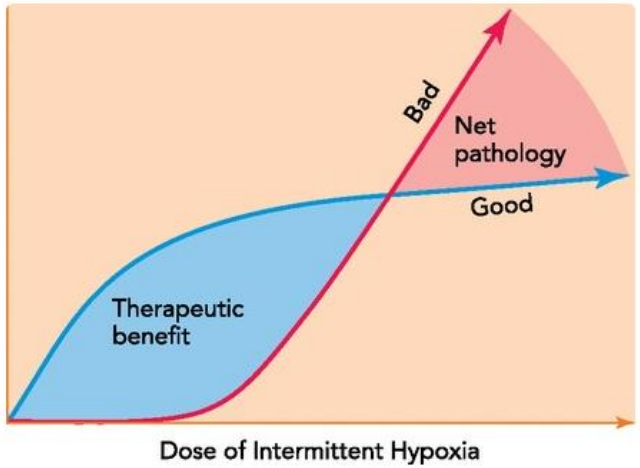
Adaptive and maladaptive processes induced by intermittent hypoxia (IH) in the brain and severity



Precondition hypoxia hypothesis

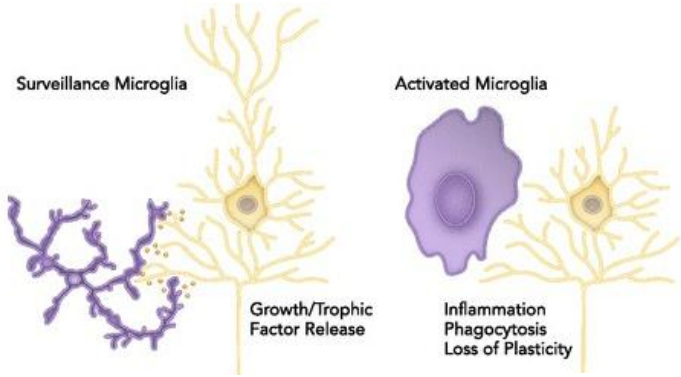
Neo-vascularisation in the heart

↑ Growth/Trophic factor release
~
neuroprotection,
↑ in synaptic strenght (i.e. neuroplasticity)



Low-dose IH exposures do not elicit detectable pathology ("bad").

Although high-dose IH still elicits functional benefits, it shifts the balance from net benefit to unacceptable pathology.



Low-dose IH High-dose IH

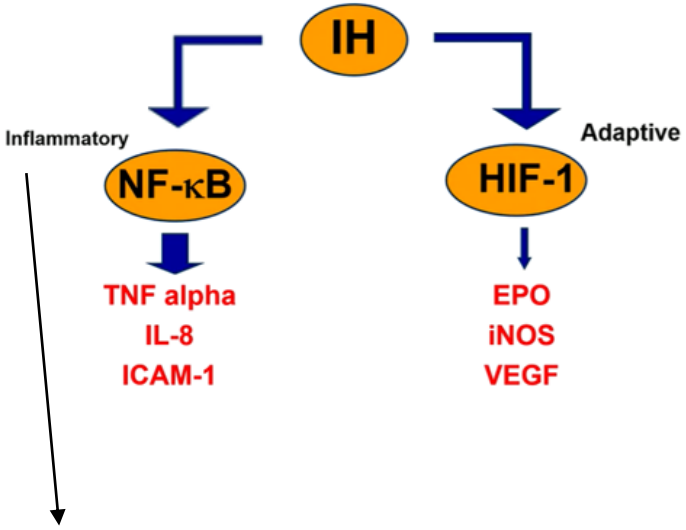
In the healthy CNS with no, or "low-dose" IH, microglia are in a "surveillance mode" that promotes neuron viability and function by releasing growth/trophic factors

In contrast, high doses of IH may activate microglia to a toxic, pro-inflammatory phenotype that triggers neuronal apoptosis and undermines synaptic plasticity.

Studies suggest that mild, short and lower frequency is acknowledged to generate beneficial and adaptive responses in the brain, but finding an optimal IH dose is key to developing effective therapy strategies.

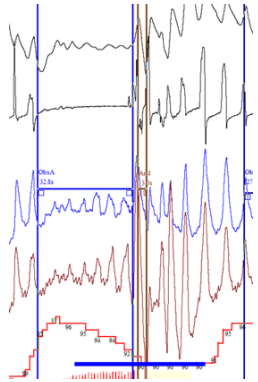
Adapted from Dale et al. Physiology (Bethesda) 2014

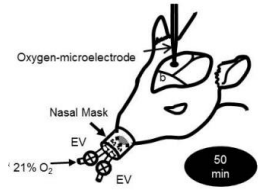
Adaptive and maladaptive processes induced by intermittent hypoxia (IH) in the brain and age

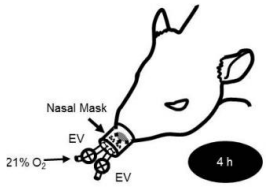


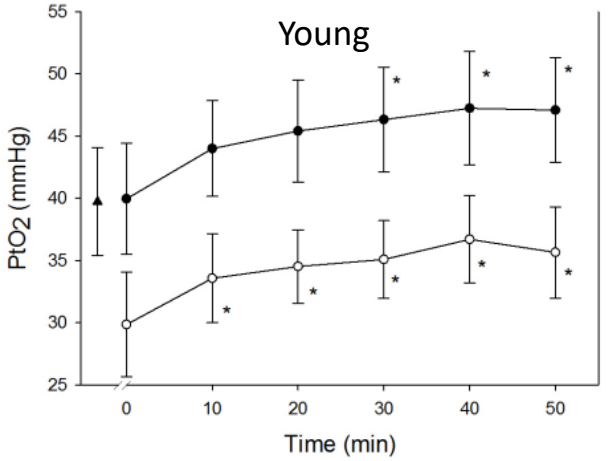
Brain Tissue Hypoxia
and
Oxidative Stress

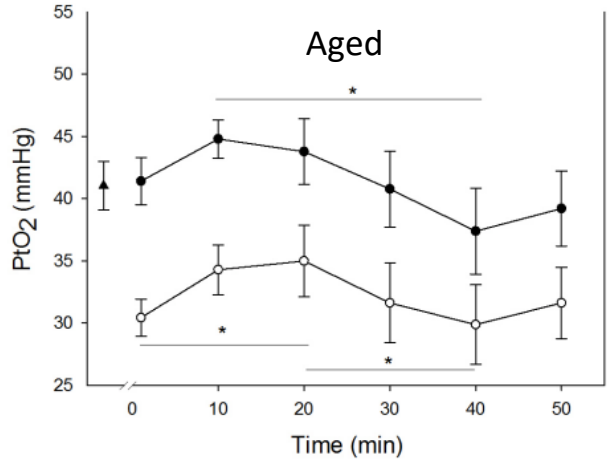
induced by OSA is different in **young** and **aged** rats

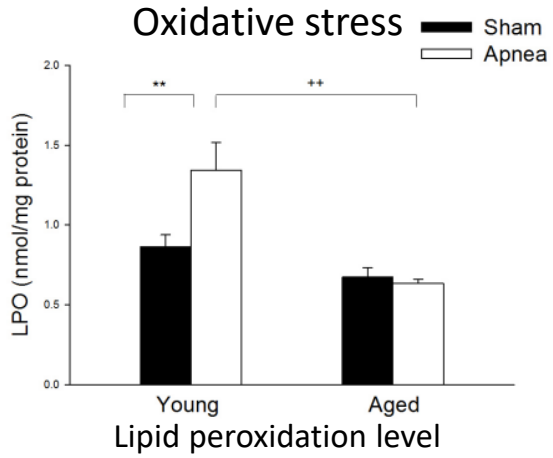


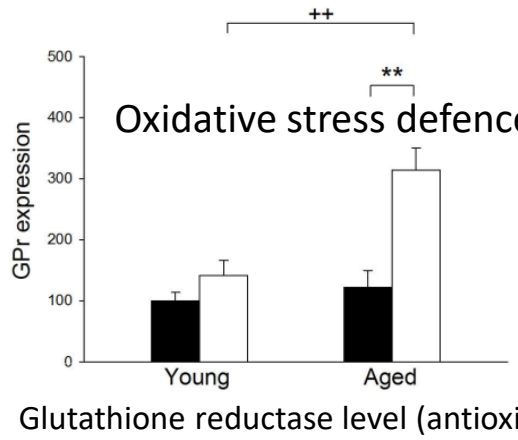












Results are expressed as percentage of increase over young sham rats

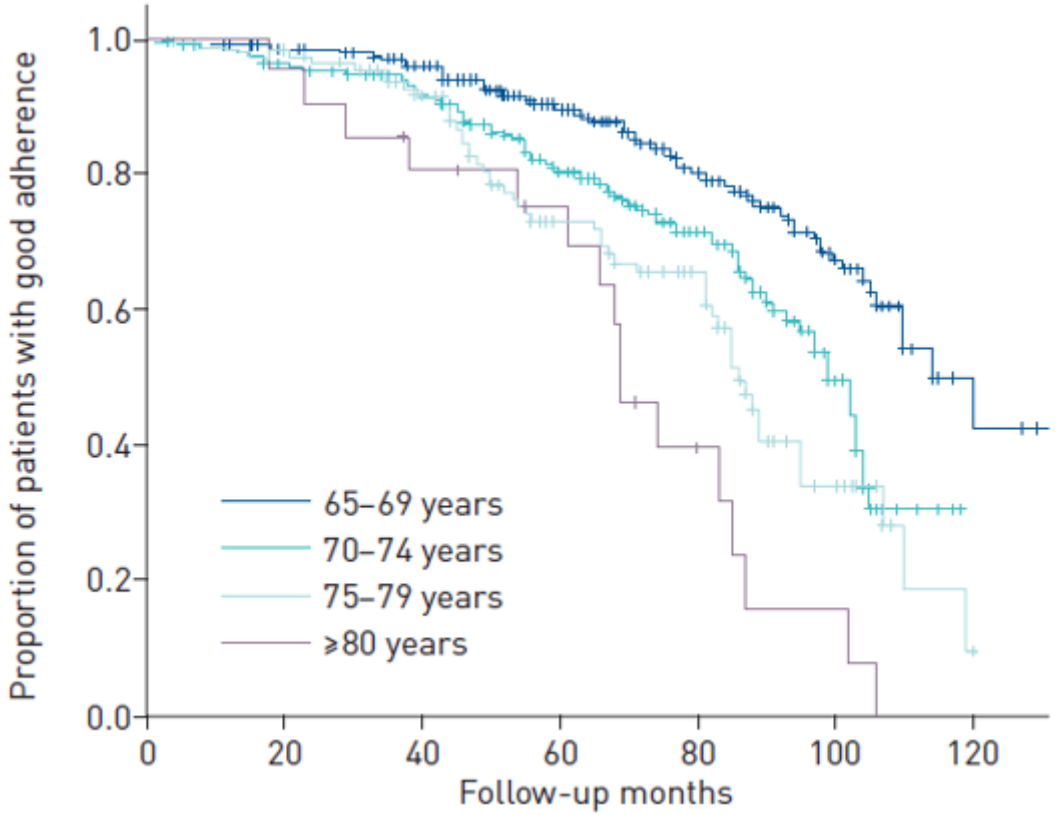
Adapted from Dalmases et al. Sleep 2014

OSA in the elderly: a great challenge for the future ?

- Prevalence?
- Health outcome impact?
  - Impact on mortality and on “hard” cardio-vascular outcomes
  - Impact on excessive daytime sleepiness
  - Impact in cognition

- Treatment (CPAP) possible?

In a clinical cohort of elderly there was a progressive decrease in adherence to CPAP with advancing age



Kaplan-Meier curves according to age group for the proportion of patients with a good CPAP adherence of at least 4 h / day
Log-rank p<0.05 for any comparison between two curves

The low adherence has many causes, including

- a greater number of comorbidities (especially stroke)
- neurocognitive impairment,
- difficulties with self-fitting the mask (f.i. caused by osteoarthritis,…)
- lack of family support,
- decrease in the quality or quantity of sleep.

Martinez-Garcia et al. ERJ Open Res 2019

Conclusion

1. Impact on mortality and "hard" cardio-vascular outcomes

   Consider to treat **severe** (AHI≥30/h) **OSA,**

   in ≥ 80 yrs old: limited evidence

2. Impact on excessive daytime sleepiness (EDS)

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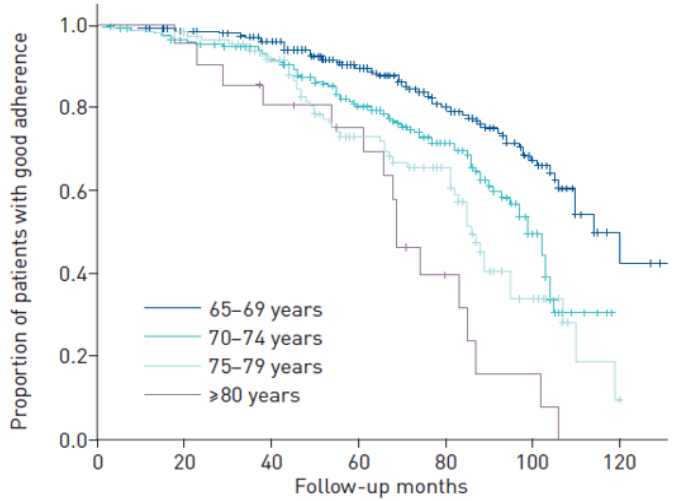
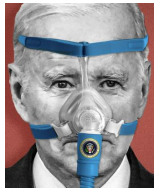


The prescription of CPAP in elderly OSA patients should be individualized

Focus on severe (AHI≥30/h) OSA and somnolent (moderate to) severe OSA if other reasons for somnolence are ruled out

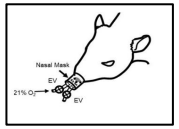
Be rather reluctant in the "≥ 80 year old"

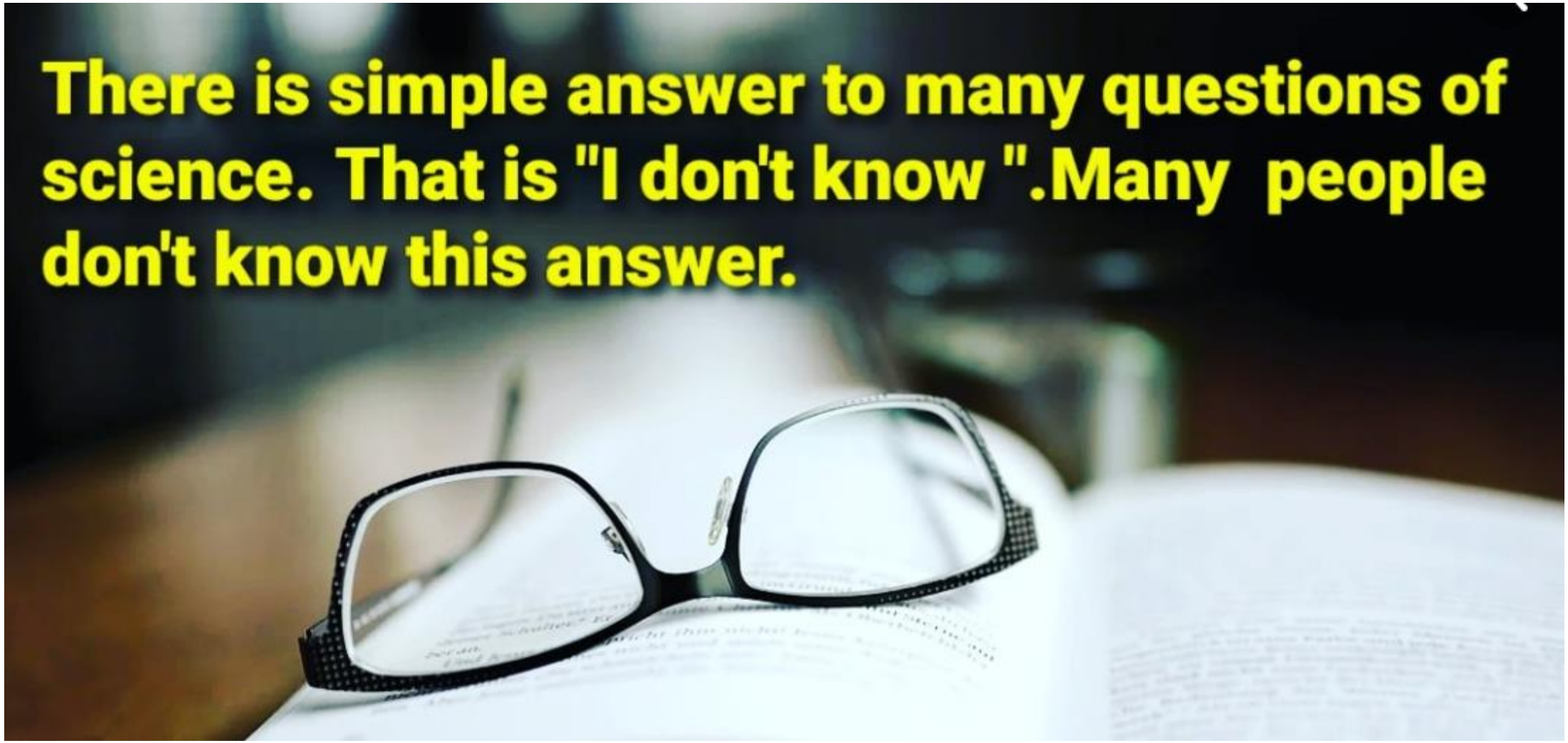


Larger clinical trials are needed!

Unexpected survival advantage in elderly people with moderate sleep apnoea

PERETZ LAVIE and LENA LAVIE




There is simple answer to many questions of science. That is "I don't know ".Many people don't know this answer.