Sleep Disorders in the Elderly

Dott.ssa Federica Moscucci

Sleep

- Sleep is associated with well being, health and mortality
- Sleep is a vital physiological process with important restorative functions that are essential for optimal daytime functioning

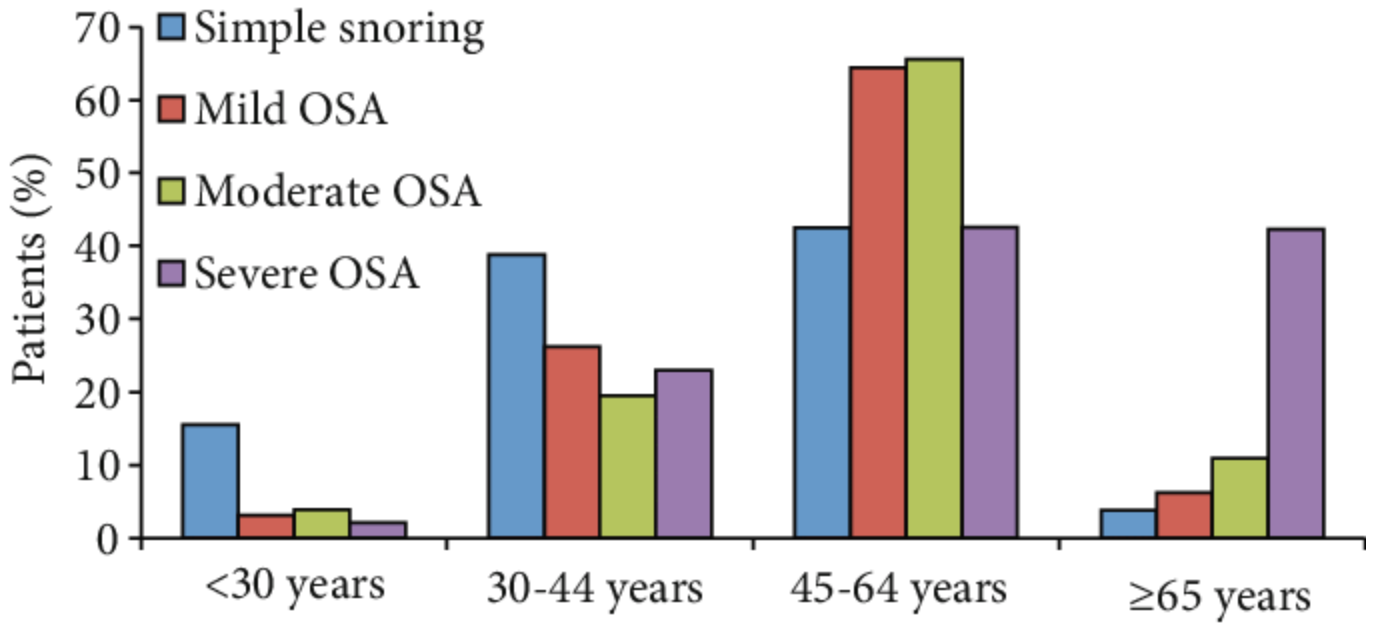
Background

- By 2025 62 million Europeans will be over the age of 65
- Annual direct costs associated with insomnia $15.4 billion

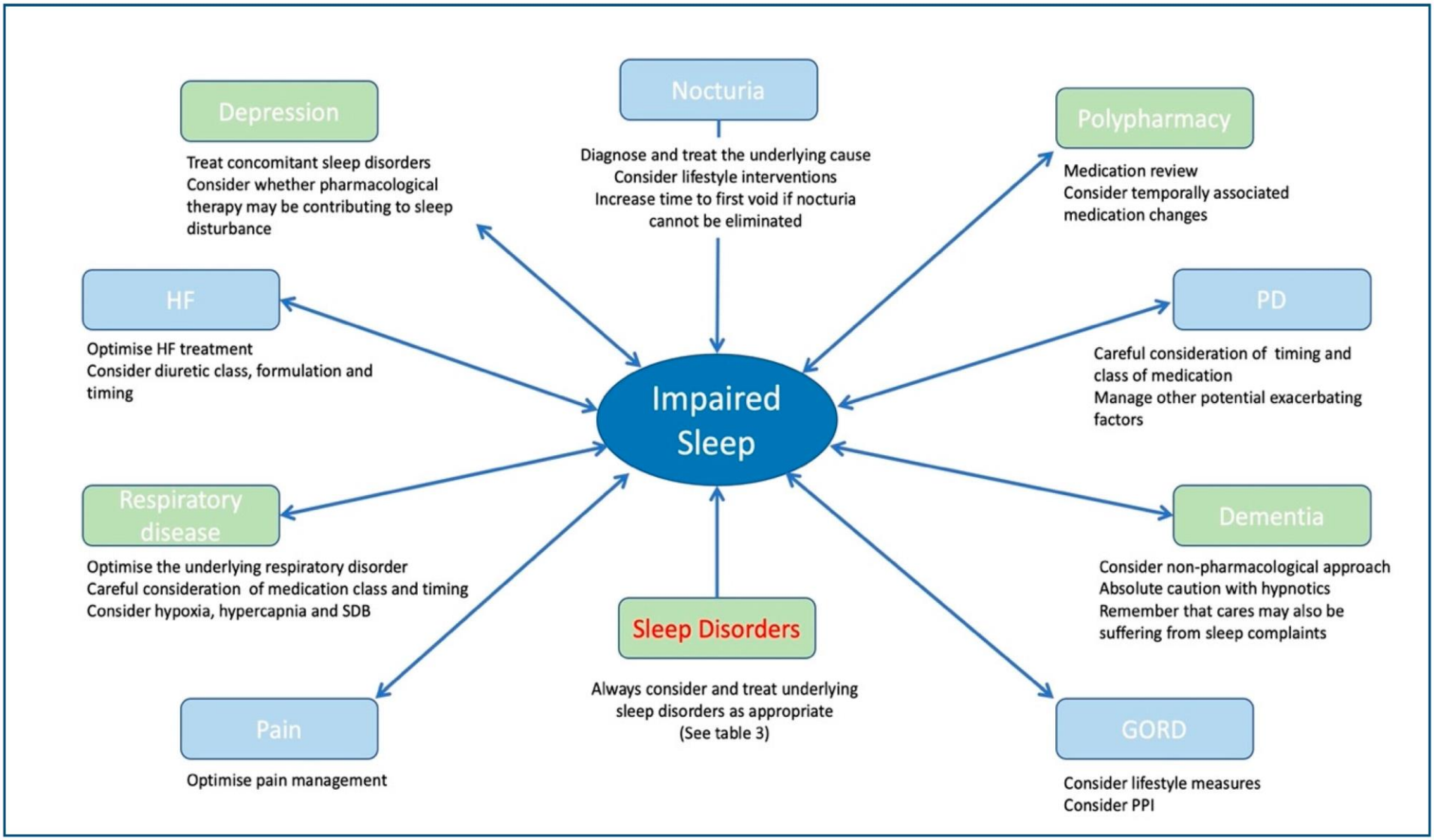
Sleep Disorders: Insomnia

- Difficulty initiating sleep, maintaining sleep and/or unrestorative sleep leading to daytime impairments
- Affects 20-50% in western countries adult population
- Reported more in elderly women than men
- Up to 57% of noninstitutionalized elderly have problems with chronic insomnia

Normal sleep is affected by significant distress such as impairment in occupational or other important areas of functioning or social processes



Total sleep time may not necessarily decrease with age but the way in which sleep is consolidated becomes altered and one study showed that healthy elderly persons were less sleepy and performed better in tests of alertness and attention than young subjects after sleep deprivation


Impaired Sleep
Depression
Treat concomitant sleep disorders
Consider whether pharmacological therapy may be contributing to sleep disturbance
Nocturia
Diagnose and treat the underlying cause
Consider lifestyle interventions
Increase time to first void if nocturia cannot be eliminated
Polypharmacy
Medication review
Consider temporally associated medication changes
HF
Optimise HF treatment
Consider diuretic class, formulation and timing
PD
Careful consideration of timing and class of medication
Manage other potential exacerbating factors
Respiratory disease
Optimise the underlying respiratory disorder
Careful consideration of medication class and timing
Consider hypoxia, hypercapnia and SDB
Dementia
Consider non-pharmacological approach
Absolute caution with hypnotics
Remember that cares may also be suffering from sleep complaints
Sleep Disorders
Always consider and treat underlying sleep disorders as appropriate
(See table 3)
Pain
Optimise pain management
GORD
Consider lifestyle measures
Consider PPI

A New Vital Sign

- Sleep disturbances affect not only nighttime sleep quality but are also a risk factor for daytime sleepiness which may negatively affect participation in physical exercise and ultimately functional ability
- Screening for sleep disorders as a new vital sign as sleep/sleepiness is emerging as an important aspect of health promotion and disease prevention.

Insomnia

- Chronic insomnia is associated with a wide range of health problems: mental disorders, discomfort, anxiety, substance abuse.
- Chronic insomnia can increase risk for new onset depression with persons with persistent insomnia 3 x more likely to develop depression within a 1 year period
- Possible causality between short sleep duration and development of diabetes mellitus in community dwelling middle and older age adults

Evidence based Standards of Care to Manage Insomnia

- Benzodiazepines and nonbenzodiazepines are effective in the management of chronic insomnia. However benzodiazepines, nonbenzodiazepines and antidepressants pose a risk of harm
- Benzodiazepines: Not recommended due to BEERs listing
- Benzodiazepines have a greater risk of harm than nonbenzodiazepines
- Melatonin is effective in the management of chronic insomnia in subsets of the chronic insomnia population and there is no evidence that melatonin poses a risk of harm (based on a small number of studies)
- Chronic insomnia is associated with older age
- Relaxation therapy and cognitive/behavioral therapy are effective in the management of chronic insomnia in subsets of the chronic insomnia population.

Table 1 Conclusions from the Agency for Healthcare Research and Quality Evidence Report/technology Assessment Regarding the Manifestations and Management of Chronic Insomnia. Review of Insomnia Pharmacotherapy Options for the Elderly: Implications for Managed Care Population Health Management Vol 12, no. 6, 2009

Normal Sleep

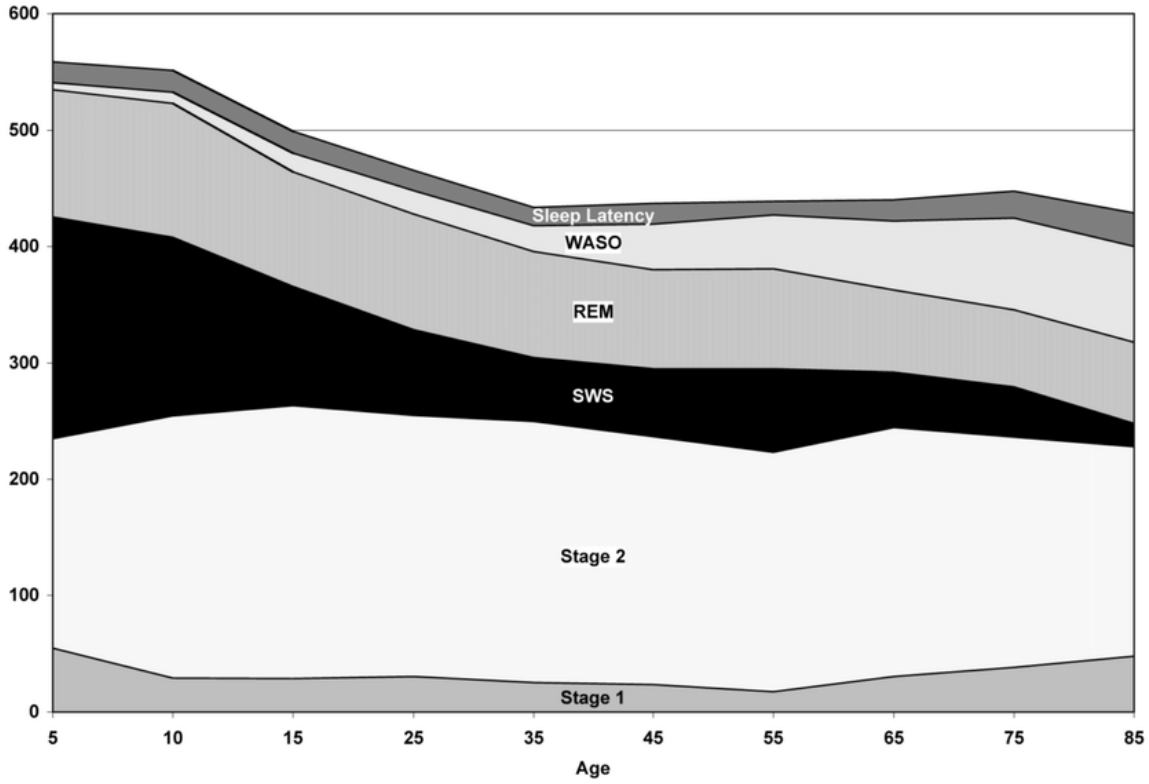
- Circadian rhythm- 24 hour dark/light cycle needs to be activated for sleep by entry of light via the eye
- Increased daylight exposure and physical activity may help normalize circadian rest/activity rhythm.

Benefits of Physical Activity

- Decreased risk of CV disease and osteoporosis
- Decreased blood pressure
- Increased glucose tolerance and insulin responsiveness
- Increased mental acuity
- Psychological well being

Sleep Architecture

Normal sleep progresses through several stages in a predictable pattern.



Stages of sleep

- **Non REM sleep**

N1 Stage 1 — **Transition stage**
Light sleep
Reduced brain-wave activity
Slow eye movement

N2 Stage 2 — **Muscle relaxation**

- **Non REM sleep**

Decreased body temperature

- **Awake- "alert brain", muscles relatively tense**

Reduced heart rate
Sleep spindles on EEG
K complexes on EEG

N3 Stages 3 and 4 (slow wave sleep) — **Deep sleep**
High voltage, low frequency brain waves
Restorative sleep

REM sleep — **Rapid eye movements**
Vivid dreaming
Increased brain activity
increased heart rate
Increased respiratory rate
Active inhibition of voluntary muscles

Age Related Changes in Sleep Architecture

- Meta analysis of 65 studies of healthy adults showed men more affected by aging than women with a decreased total sleep time, decreased percent of N3 and REM sleep and increased percent of N2 and wake time after sleep onset.
- Women with increased sleep latency compared to men. Also with shorter and poorer sleep
- Women used hypnotics at a greater frequency than men

Predictable Age Related Changes in Sleep Architecture

- Sleep fragmentation
- Reduced sleep efficiency
- Decreased quality of sleep
- Decrement in amplitude of low frequency delta on EEG

- True sleep disorders are rare in healthy older adults- elderly with poor sleep often have comorbidities
- When controlled for comorbidity changes in sleep quality, high rates of insomnia become less.
- **Elderly person with insomnia often display poor sleep maintenance rather than problems with sleep initiation.**

Sleep and Aging

- Nocturnal secretion of endogenous melatonin gradually decreases with age
- In every decade except for ages 30-39 the prevalence of insomnia is increased in women with prevalence of insomnia being 40% in women

SLEEP CYCLES CHANGE WITH AGE

	Age 20	Age 40	Age 60	Age 70	Age 80
Time to fall asleep	16 minutes	17 minutes	18 minutes	18.5 minutes	19 minutes
Total sleep time	7.5 hours	7 hours	6.2 hours	6 hours	5.8 hours
Time in regular sleep	47%	51%	53%	55%	57%
Time in slow wave sleep	20%	15%	10%	9%	7.5%
Time in REM sleep	22%	21%	20%	19%	17%
Time asleep while in bed	95%	88%	84%	82%	79%

JamesClear.com

Source: Sleep, Nov. 1, 2004, pp. 1255-73

- During hospitalization the prevalence of sleep deprivation seems to increase for multiple reasons: environmental factors, circadian dysregulation, acute clinical problems.
- These complaints of insomnia can persist for several months post discharge

- Men- sleep time decreased on average of 27 minutes per decade from mid life until the 8th decade
- An association between the need for institutionalization and the presence of insomnia has been demonstrated in healthy males

- Many factors that impair sleep in older adults can be diagnosed and treated
- True sleep disorders are rare in healthy older adults. Elderly with poor sleep often have comorbidities

- In older patients, continuously decreased sleep homeostasis may contribute to the inability to maintain long sleep episodes, irregular mealtimes, decreased bright light exposure, nocturia and increased mobility and decreased exercise
- 50% of men and 70% of women over the age of 75 have no regular physical activity
- During the late decades of life, sleep evolves even further
- Elderly persons with insomnia often display poor sleep maintenance rather than problems with sleep initiation

Elderly Spend More Time in Lighter Stages of Sleep

- Decreased slow wave sleep
- Increased fragmentations of entire sleep cycle
- REM sleep may decrease overall
- Take longer to initiate sleep
- Decreased total sleep time
- Have early morning awakening
- Increased need to nap during the day
- Tend to fall asleep during the daytime faster
- Elderly women maintain sleep better with aging but with menopause have increased subjective complaints of insomnia

Evaluation of Sleep Disorders

- History
  1. Multidisciplinary approach
  2. Past sleep history
  3. Detailed inventory of specific sleep complaints in the presence of bed partner
  4. Inquiry regarding alcohol, tobacco, caffeine and other meds (dose, time)

Hypnogram

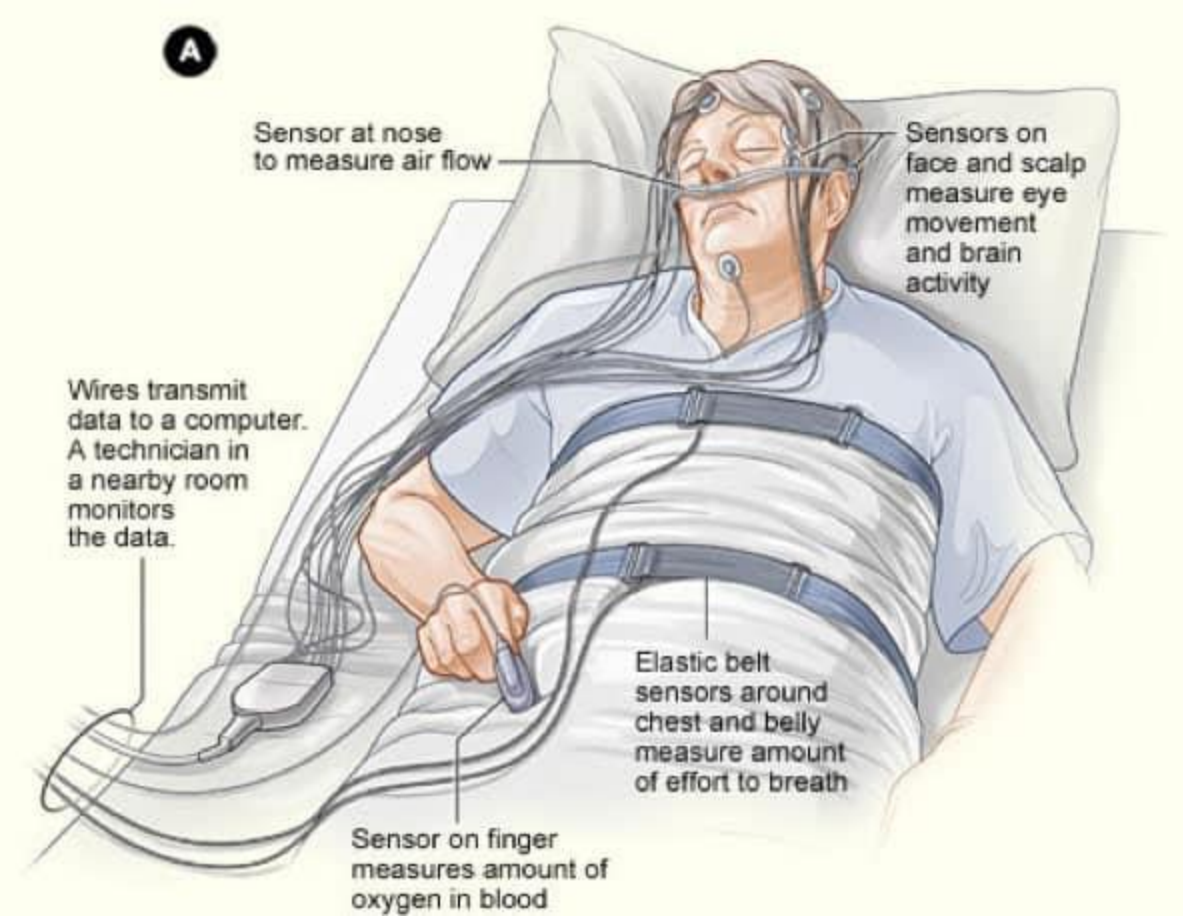
- Displays distribution of sleep stages across the night
- Healthy adults – NREM, N1, N2, N3 followed by a period of REM
- REM occurs about 90 minutes into sleep
- Reduction in N3 and increased in REM as night progresses
- Punctuated by brief arousals and awakenings

Examples of Sleep-Related Questions That Can Help to Screen for Sleep Problems in the Geriatric Patient

- Do you have difficulties falling asleep or maintaining sleep?
- Do you feel excessively sleepy, tired or fatigued during the day?
- What is your sleep schedule during the weekdays and on weekends?
- How many hours do you sleep during the night?
- How long does it take you to fall asleep after deciding to go to sleep?
- How many times do you wake up during a typical night?
- Do you feel refreshed when you wake up in the morning?
- Do you have loud snoring and do you stop breathing at night?
- Do you have restless ness or crawling or acning sensations in your legs when trying to fall asleep?
- Do you repeatedly kick your legs during sleep?
- Do you act out your dreams?

Labs

- Polysomnography specifically with complaints of sleep stage abnormalities (restless leg syndrome, unusual behaviors and sleep disordered breathing)



Tests

- MSLT- multiple sleep latency tests
- Objective assessment of daytime sleepiness
- EES- Epsworth Sleepiness Scale

Primary Sleep Disorders

- Sleep apnea
- Restless leg syndrome

Repetative/continuous leg jerks every 20-40 seconds during sleep
5-6% of population affected
Treatment- benzodiazepines, sinemet, dopamine agonists, opiates, iron replacement

Chronic Medical Conditions Impacting Sleep

- Medical Condition

  Diabetes

- Increased incidence of obstructive sleep
- apnea
- Increased incidence of sleep disordered
- breathing
- Autonomic neuropathy leading to
- Ventilatory disorders

Chronic Medical Conditions Impacting Sleep

- Medical Condition

  Dementia

- Delayed sleep induction
- Prolonged wake time after arousal from sleep
- Increased activity during periods of wakefulness
- “Sundowning”
- Increased daytime sleepiness compared with age matched controls

Chronic Medical Conditions Impacting Sleep

- Medical Condition

  Depression

- Exaggerated behavioral disturbances
- Insomnia
- Increased number of awakenings
- Chronic Pain
- Decreased sleep time
- Delayed sleep onset
- Increased nighttime awakenings
- Increase in depressive symptoms

Chronic Medical Conditions Impacting Sleep

- Medical Condition

Parkinson's Disease

Decreased total sleep time

Malignancies

Excessive fatigue

Leg restlessness

Insomnia

Decreased sleep efficiency

Excessive sleepiness

Chronic Kidney Disease and incontinence

Restless leg syndrome

Periodic limb movement

Sleep apnea

Chronic Medical Conditions Impacting Sleep

- Medical Condition

  Chronic Obstructive Pulmonary Disease

- Reduction in arteriolar oxygenation
- Decline in baseline oxygen
- More frequent in blue bloaters
- Decline in ventilatory response to hypoxia
- Exaggerated breath to breath variability
- Exaggerated increase in respiratory frequency sleep disordered breathing
- Hypopneas (partial respiration)
- Apneas (complete cessation of respirations)

The Effect of Chronic Disorders on Sleep in the Elderly p.29

Medications with Negative Effect on Sleep

- Bronchodilators
- Corticosteroids
- Decongestants
- Diuretics
- Stimulating antidepressants
- Antihistamines (increased delirium, do not use with narrow angle glaucoma as it increases intraocular pressure)

Nonpharmacologic Treatment

- Cognitive behavioral treatment has been successful
- Very solid data that support sleep hygiene interventions

Treatments

- **Nonpharmacologic**
- **Light treatment-** exposure to very bright light during the day and darkness at night can consolidate rest and activity patterns in persons with AD
- **Evening light exposure**- effective in consolidating rest/activity rhythms of AD patients and help them sleep better at night. Also helps to fall asleep later and wake up later
- **Study**- Would person light treatment devices be effective for reliably stimulating the circadian system- made goggles for light. Measured melatonin levels. Results- light induced nocturnal melatonin suppression and light induced circadian phase shifts utilize the same retinal neural apparatus and follow similar stimulus/response function

One Study Bright Light Treatment

- BP decreased with sleep at night,
- Limit naps to 30 minutes in early afternoon for elderly
- Timed bright light treatment (light is regarded as the strongest cure for the synchronization and stabilization of circadian rhythms and melatonin regulation.
- It may even reduce behavioral symptoms in person with dementia.
- No consensus on the best time of day for administering bright light therapy for dementia/depression
- Side effects: Headache, nausea, dry eye, dry skin.

Benzodiazapines in the Elderly

- Prolonged sedation
- Increased risk of falls/fractures
- Postural instability
- 1 study showed a 60% risk of hip fracture

Zolpidem

- If used dose should be 5mg and for a short, limited period of time
- Concern about abuse/dependency
- Concern about confusion, hallucinations

Depression and Insomnia

- Early morning awakening-symptom most consistently related to depression over time
- Strongest predictor of future depression among those not depressed at baseline was sleep disturbance at baseline

Depression and Insomnia

- Alteration in sleep architecture in depression
- Depression increases the risk of poor sleep quality and poor sleep quality is a predictor for future depressive episodes
- One study found that those getting 7 hours of sleep or less were more likely to develop a depressive disorder than those getting more than 7 hours of sleep a day

Anxiety and Insomnia

- Poor sleep can be a consequence of anxiety disorder
- Important symptom of general anxiety disorder (most common among older adults)
- Panic attacks- One study found that both short and long sleepers were more likely to have depression or anxiety disorder
- Persons with depression spent more time in bed than non-depressed
- Persons with depressive disorder and comorbid anxiety disorder reported a substantially shorter total sleep time than other elderly persons.
- Poor sleep quality reported in 40-90% of patients with depression

Insomnia and Dementia

- Most frequent cause of insomnia in demented patients is a medical condition or side effect of a medication
- Sundowning- marked increase in agitation, confusion and wandering in late afternoon or evening.
- Treatment for sundowning- stimulate the circadian system improving sleep hygeine

Dementia and Sleep

- Complete cessation of breathing (apnea) or partial decreases in breathing (hypopnea).
- Sleep apnea in demented patients in greater prevalence than in age matched controls
- More episodes of apnea.
- Apnea increases with severe dementia.
- Association with increased sleep disorders and apolipoprotein E, chronic hypoxia in AD leads to increased B secretase activity and production of B amyloid protein.
- Treatment of OSA in early stages of dementia may slow the progress of the disease by modulating cholinergic activity that influences upper airway opening. Impaired cholinergic transmission in AD leads to cholinergic respiratory disturbances.
- Donepezil will increase REM sleep (when apnea episodes are more frequent)
- One study showed that donepezil significantly improved apnea/hypopnea index and O2 sat levels

Dementia and Sleep

- Longer sleep duration may be an early sign of dementia
- AD patients suffer from sleep disturbances- sleep fragmentation, longer periods on intra sleep wakefulness.
- Problems for caregivers
- Community based longitudinal studies showed that excessive daytime sleepiness was associated with a 2 times risk of incident dementia
- As dementia progresses the symptoms of poor sleep become more severe.
- Patients become sleepier during the daytime
- Increases in neurocognitive impairment, end organ dysfunction, chronic health condition and increased mortality

REM Sleep

- REM sleep- dreaming/inhibition of voluntary muscle activity
- Disorder – vigorous dream, enacting behavior, nightmares, exacerbated by beta blockers, antidepressants, neurological diseases.
- In Lewy body dementia- 50-80%

Pain and Insomnia

- One study showed that pain in 2 or more sites was independently associated with a 16-41% greater likelihood of having sleep difficulties
- Persons with more severe pain had a more than 2 times likelihood of having trouble getting to sleep on 1 or more days per week than those with the lowest pain severity score
- There was strong and consistent association between more severe and disseminated chronic pain and heterogeneous sleep complaints.
- Dysfunction of the hypothalmic pituitary adrenal axis has been found to be associated with increased risk of developing chronic widespread pain
- Severity and distribution of pain was strongly associated with sleep disturbances
- Consistent association were not found between individual sites of pain and sleep difficulties
- Diffuse distribution of pain is an important factor in the association between pain and sleep
- After adjustment for use of psychiatric meds and daily analgesics the association between pain and sleep difficulties decreased modestly.

Restless Leg Syndrome

- Strong evidence emerging that it is modulated by presence of genes with autosomal dominant transmission and high penetrance
- Reports a significantly worse executive function in untreated restless leg syndrome patients than age matched controls
- Little evidence to support drug treatment for suppression of Periodic Leg Movements in the elderly.

Restless Leg Syndrome

- Creeping sensation in lower extremities
- Tingling, cramping or even very painful sensations usually inn the lower extremities
- Intense urge to move or message legs usually occurs when patients go to bed and cause sleep onset insomnia

Restless Leg Syndrome

- Iron deficiency
- RA
- Renal failure
- Peripheral neuropathy
- Excessive caffeine intake

Specific Geriatric Issues

- **Menopause**
- Associated with prolonged sleep latency, decreased REM sleep and decreased total sleep time
- Menopause plays a pivotal role in modulating both the presence and severity of OSA (progesterone/estrogen dysfunction) Progesterone is a respiratory stimulant. Estrogen affects body fat distribution.

REMS Sleep Disorder Behavior

- Loss of normal muscle atonia which normally occurs during REM sleep
- Persons with this disorder may display a variety of movements during REM sleep including walking, thrashing limbs or engaging in complex activity

Narcolepsy

- Excessive daytime somnolence and fatigue
- Sleep attacks (irresistible urge to sleep)
- Hypnogogic hallucinations
- Sleep paralysis
- Cataplexy

The Wisconsin Sleep Cohort Study

- Demonstrated that a transition into menopause was associated with a significant increased likelihood of having OSA independent of known confounding factors.
- In post menopausal women a functional or physiological difference rather than upper airway anatomy may account for observed differences in severity and prevalence of apnea between pre and post menopausal women.

Pathophysiology of the cardiovascular consequences of OSA

The **intermittent hypoxia** observed in OSA leads to **oxidative stress**, **increased sympathetic activation**, **endothelial dysfunction**, **blood pressure surges**, an increase in the levels of circulating **inflammatory markers** and **hypercoagulability**.

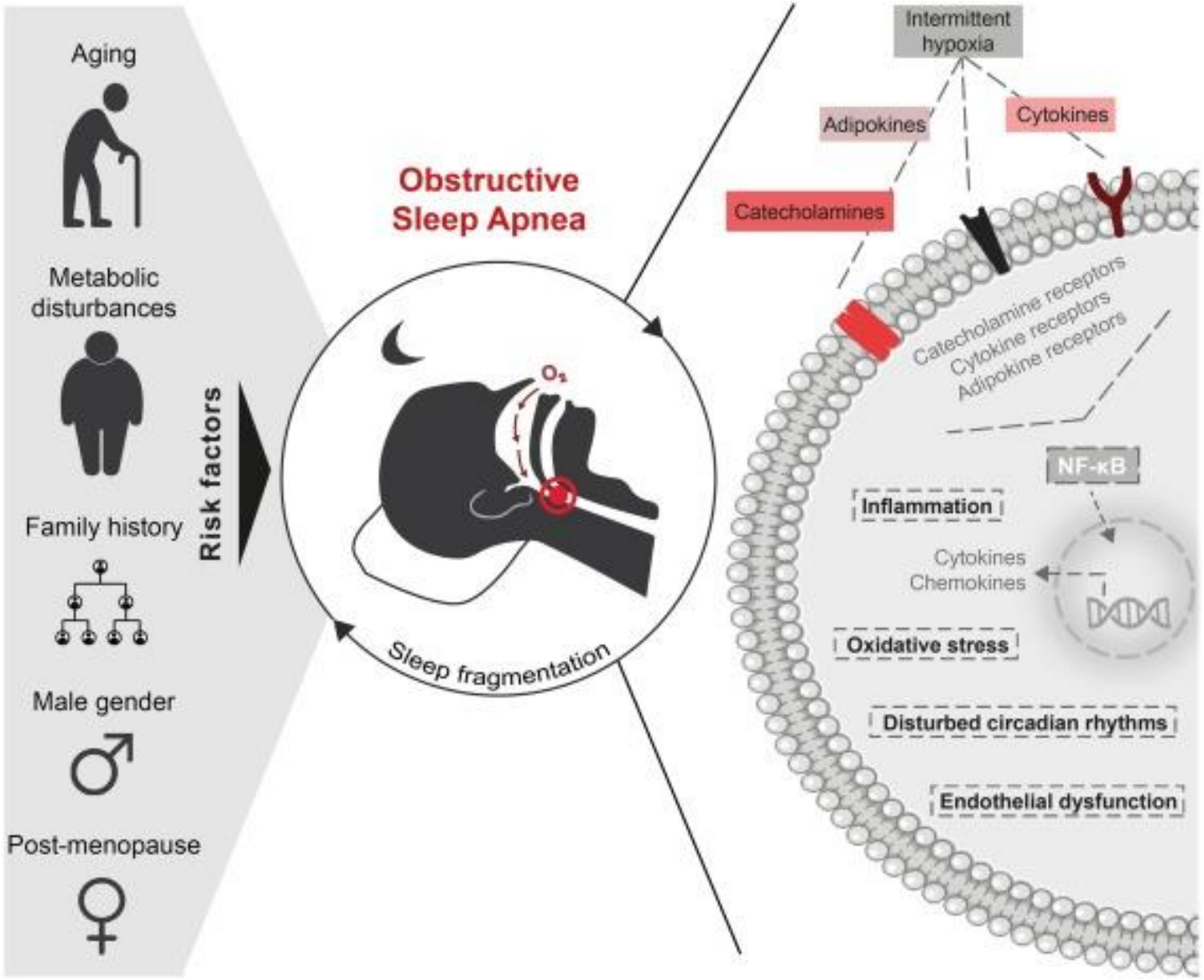
Large negative intrathoracic swings generated by obstructed breathing efforts also place considerable **mechanical stress** on the **heart and great vessels**.

Together these changes create an environment that has the potential to **promote atherosclerosis** and **increase the risk of coronary artery disease** (CAD) and **stroke**.

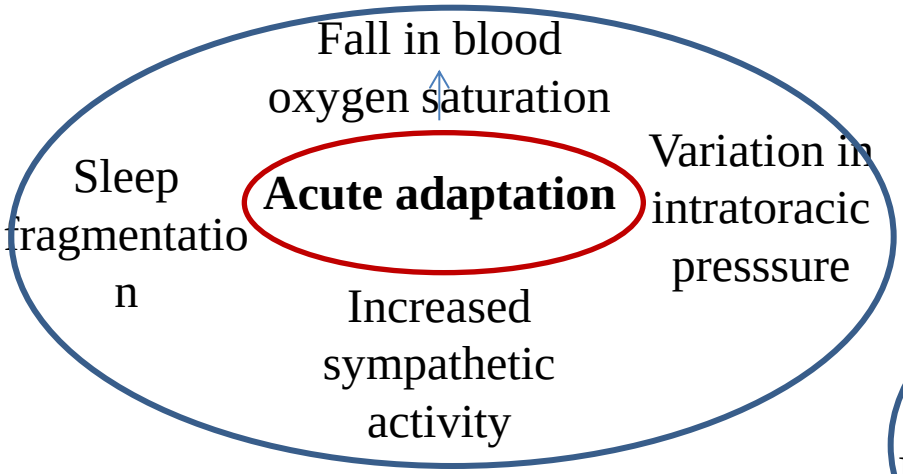
J Thor Dis 2018 Dec;10(Suppl 34):S4189-S4200.

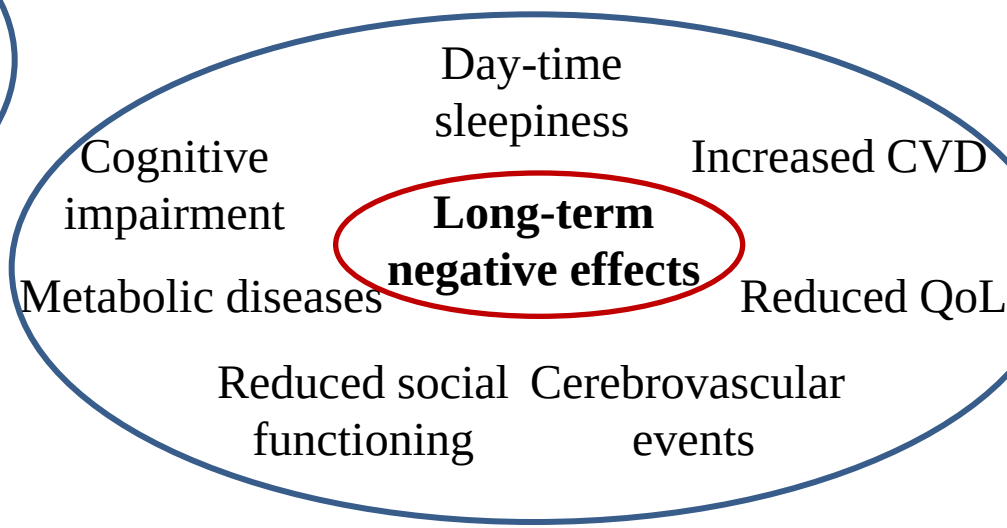
Nat Rev Cardiol 2010;7:677-85.

Lancet Respir Med 2013;1:61-72.


Aging
Metabolic disturbances
Family history
Male gender
Post-menopause
Risk factors
Obstructive Sleep Apnea
O_2
Sleep fragmentation
Intermittent hypoxia
Adipokines
Cytokines
Catecholamines
Catecholamine receptors
Cytokine receptors
Adipokine receptors
NF-κB
Inflammation
Cytokines
Chemokines
Oxidative stress
Disturbed circadian rhythms
Endothelial dysfunction

OSAs and CV disease: a vicious circle





OSA ⟷ premature death.

JAMA. 2020;323(14):1389-400
JAMA. 2017;317(4):415-33

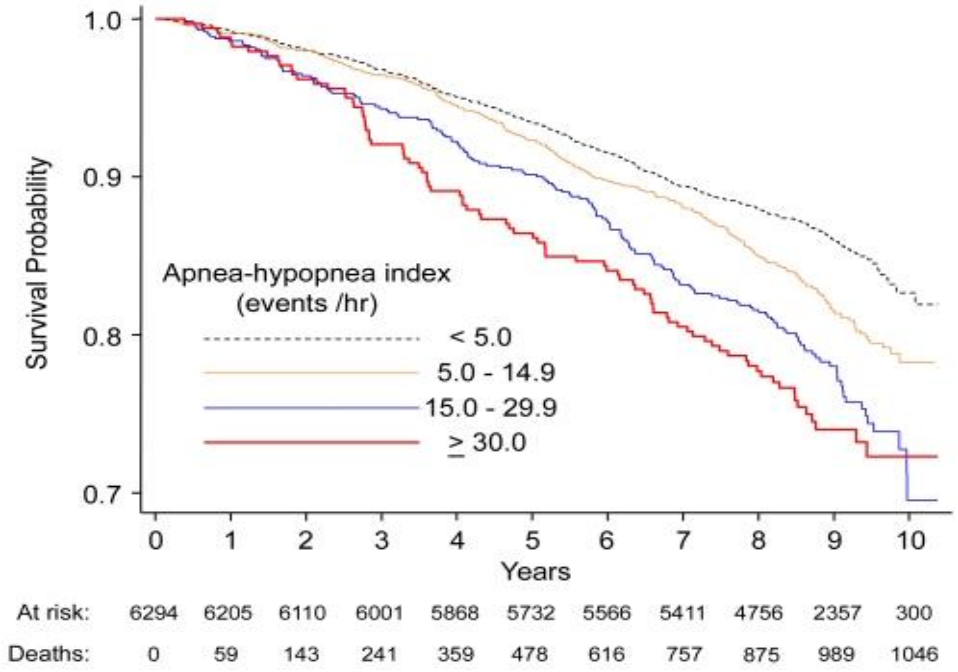
Causal and Risk factor

- OSA acts not only as a risk factor for CVD but also as a **worsening factor** in outcomes related to CVD.
- However, as OSA and CVD **share several comorbidities and risk factors**, the demonstration of a causative link between these two conditions has been extremely hard.

The present systematic review and meta-analysis provide evidence for a positive association between OSAS and the risk of CVDs, despite the severity of OSAS. The relative risk of CVDs increases continuously with the increment in AHI.

Sleep Medicine Volume 71, July 2020, Pages 39-46

Sleep Heart Health Study:



Associazione significativa (dopo correzione per fattori di confondimento) per AHI≥30 in popolazione maschile tra 40 e 70 anni

Am J Respir Crit Care Med . 2009 Jun 15;179(12):1159-64.

Courtesy of prof Mauro Contini, IRCCS Cardiologico Monzino

Sleep Apnea

- Most important and frequently occurring in the elderly
- Repetitive upper airway obstruction, arousals, O2 desaturation, daytime sleepiness, snoring, impairment of cognition
- Hard to establish a diagnosis due to lack of normative data in the apnea/hypoxic index

Age Related Respiratory Physiology

- Decreased airway size
- Change in elastin to collagen ratio
- Decreased elastic recoil of lung
- Decreased O2 diffusion capacity
- Premature airway closure causing decreased ventilatory/perfusion mismatch
- Increased alveolar/arterial O2 gradient
- Small airway closure with air trapping
- Increased rigidity of thoracic cage leading to more diaphragmatic and abdominal breathing
- Decreased vital capacity
- Increased residual volume and functional residual capacity but a decrease vital capacity and inspiratory reserve volume

Lung volume changes- an increased lung volume can apply a caudal traction force on the trachea and larynx inducing longitudinal tension on the upper airway reducing intraluminal pressure to close and reopen the airway and decrease pressure exerted on the airway walls by surrounding tissue. Studies have shown that increases in end expiratory lung volume can protect the upper airway from this collapse.

Increased Risks for Obstructive Sleep Apnea

- Hypothyroidism
- Acromegaly
- Disease states affecting the upper airway
- Obesity
- Thick Neck
- Crowded oropharyngeal inlet
- Presence of retognathia
- Mactognathia

Overweight

Table 5. Model-based[a] Prevalence Estimates of Moderate to Severe Sleep-Disordered Breathing With Concomitant Daytime Sleepiness, Wisconsin Sleep Cohort Study, Wisconsin, 1988–2011

Body Mass Index[b] by Age, years	Estimated Prevalence of AHI[c] ≥15 and ESS Score >10	
	%[d]	95% CI
	Men	
30–49		
<25	0.39	0.10, 0.87
25–29.9	1.6	0.74, 2.66
30–39.9	7.7	4.7, 11.3
≥40	35.9	20.2, 56.6
50–70		
<25	1.2	0.44, 2.5
25–29.9	3.7	2.3, 5.1
30–39.9	11.5	8.4, 14.8
≥40	28.7	19.7, 38.1
	Women	
30–49		
<25	0.045	0.008, 0.140
25–29.9	0.19	0.048, 0.44
30–39.9	0.95	0.36, 1.9
≥40	6.0	2.8, 10.6
50–70		
<25	0.48	0.15, 1.09
25–29.9	1.46	0.77, 2.33
30–39.9	4.7	3.1, 6.6
≥40	13.3	9.1, 18.6

Am J Epidemiol. 2013;177(9):1006–1014

Quick Look

Current knowledge

Obstructive sleep apnea (OSA) and chronic obstructive pulmonary disease (COPD) alone have been estimated to have high prevalence of Metabolic syndrome (MetS), in which systemic inflammation plays an important role. But clinical studies about the frequency of MetS in overlap syndrome (OSA in combined with COPD) and the status of systemic inflammation in patients with overlap syndrome is rare.

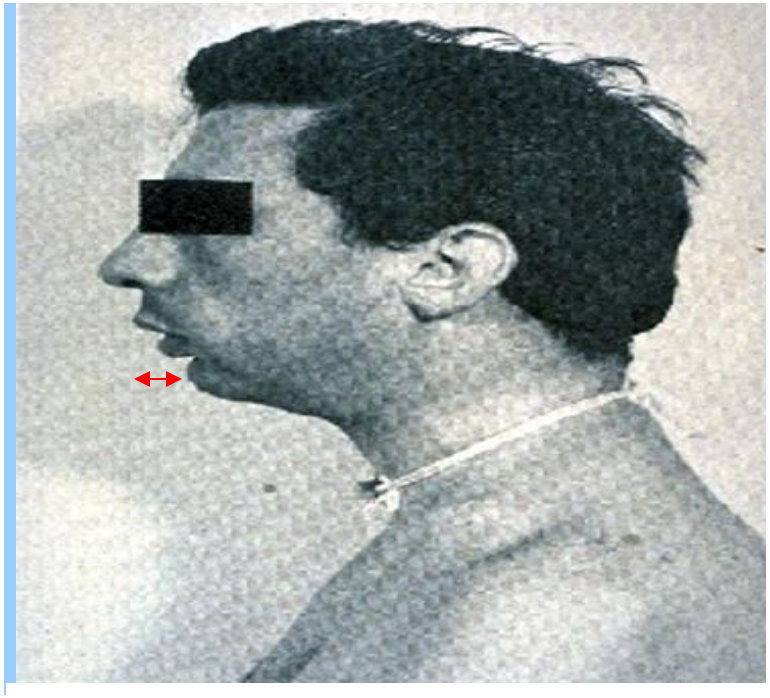
What this paper contributes to our knowledge

This study shows that MetS is frequent in patients with overlap. Overlap syndrome indicates a higher cardiometabolic risk and higher levels of systemic inflammation. Mechanisms mediating the associations need further investigation.

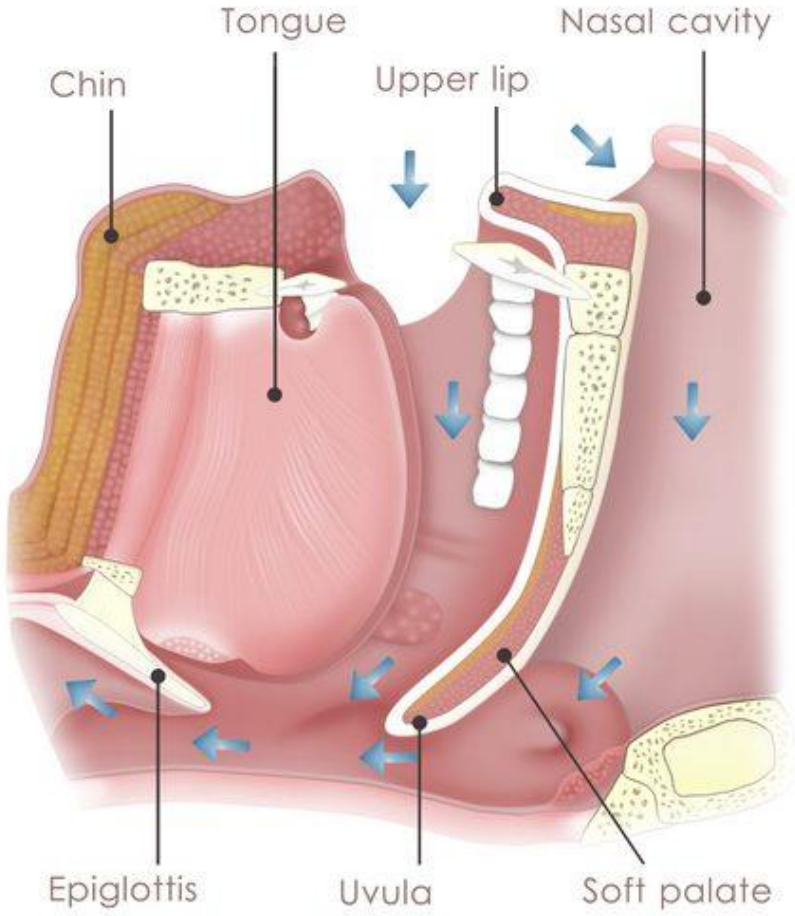
Clin Respir J. 2020;14:1159–1165.

Who has Obstructive Sleep Apnoea

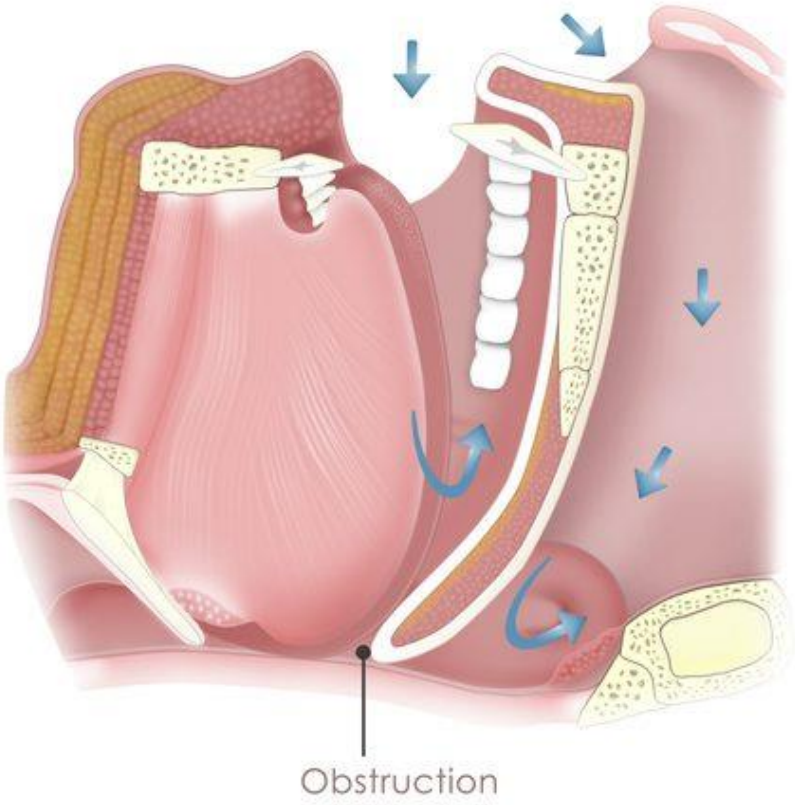
- Large Neck circumference



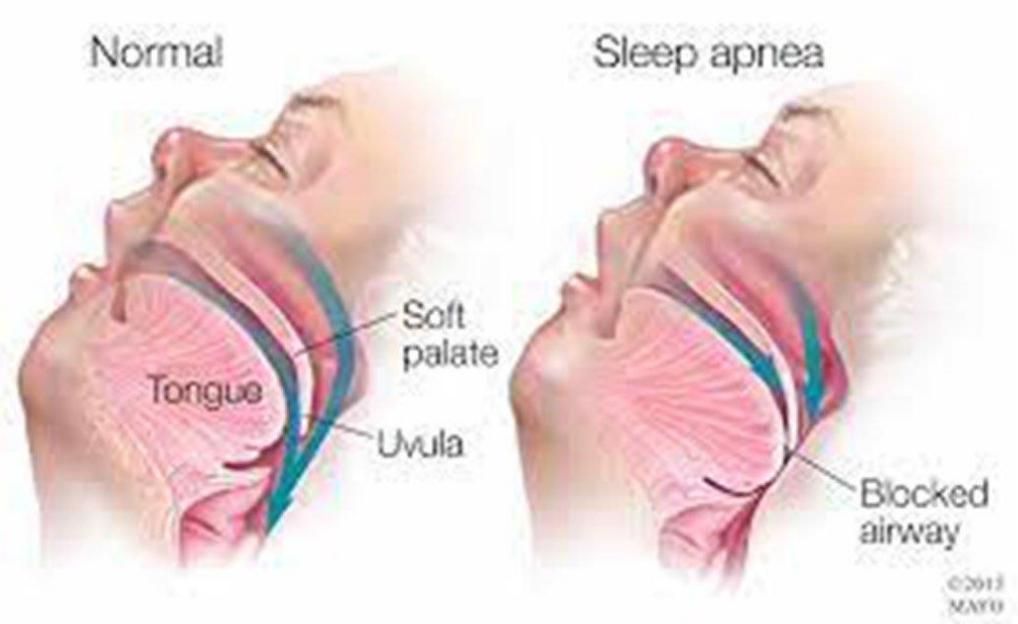
- Lower Mandibular Retraction

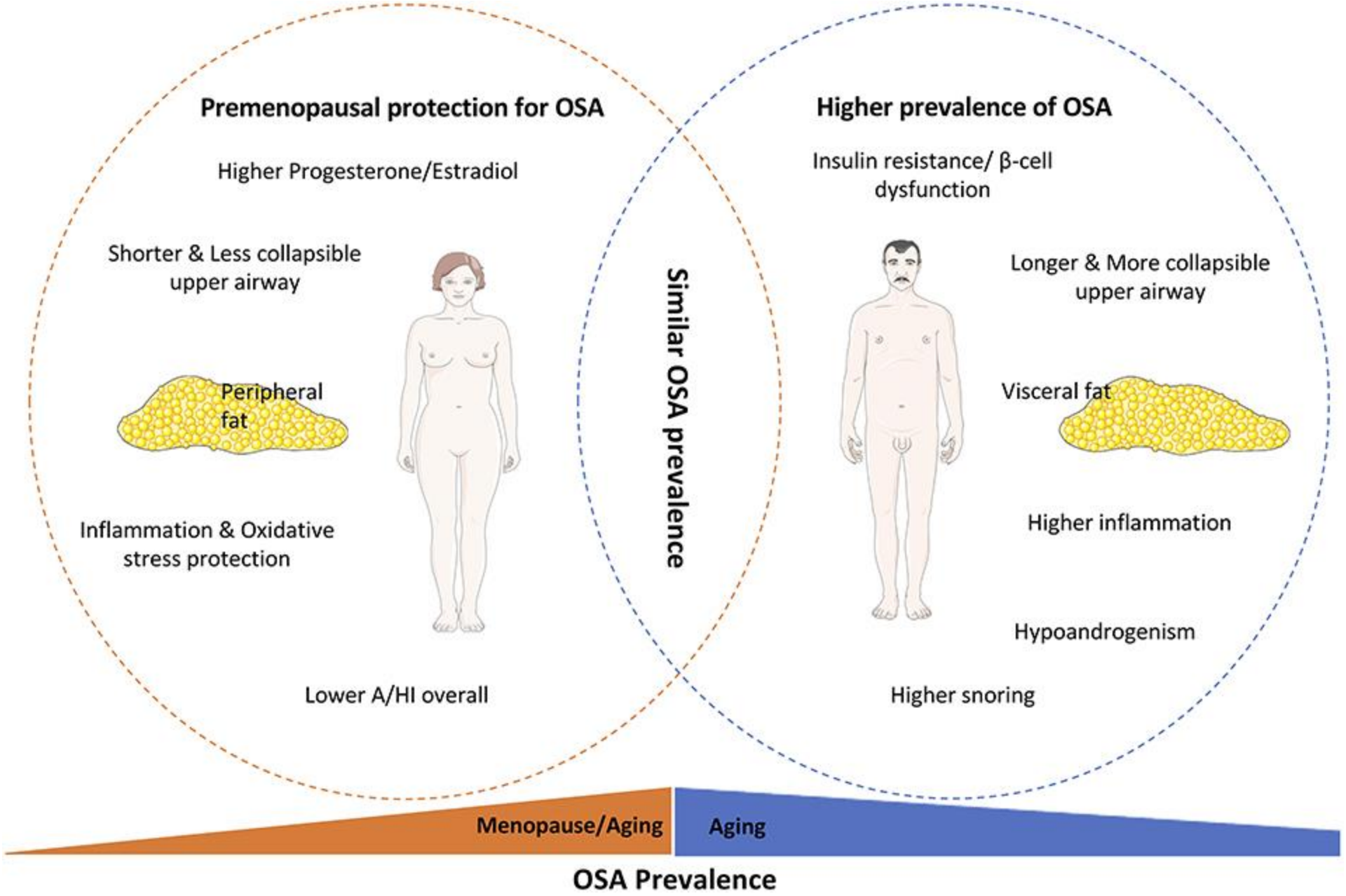


Open airway during sleep



Sleep apnea present with obstruction


Normal
Sleep apnea
Soft palate
Tongue
Uvula
Blocked airway
©2013 MAYO


Premenopausal protection for OSA
Higher Progesterone/Estradiol
Shorter & Less collapsible upper airway
Peripheral fat
Inflammation & Oxidative stress protection
Lower A/HI overall
Similar OSA prevalence
Higher prevalence of OSA
Insulin resistance/ β-cell dysfunction
Longer & More collapsible upper airway
Visceral fat
Higher inflammation
Hypoandrogenism
Higher snoring
Menopause/Aging
Aging
OSA Prevalence

Glucose Metabolism in MeTS in OSAS patients

Our study showed that treatment of OSAS by PAP therapy offers beneficial effect on glucose metabolism, not only in diabetic patients, but also **in obese and normal-weighted OSAS patients**. Although data regarding overall effects of PAP therapy on glycemic control present contradictory results in the literature, it should be emphasized that duration and adherence to PAP therapy were main determinants for beneficial outcome of treatment.

Parameters Median (min-max) Mean ± SD	All patients $n = 280$ (100%)	OSAS moderate AHI < 30 $n = 76$ (27%)	OSAS severe AHI ≥ 30 $n = 204$ (73%)	p value
OSAS (AHI)	*49.0 ± 25.4*	*22.8 ± 3.2*	*58.8 ± 23.1*	*< 0.001*
Age (years)	56.4 ± 12.7	56.7 ± 10.1	56.3 ± 13.5	0.858
BMI (kg/m^2)	32.8 ± 6.7	31.1 ± 4.8	33.4 ± 7.2	*0.009*
All glucose levels (mg/dL)	98 (90–111)	93 (87–108)	101 (92–113)	*0.003*
Glucose levels (mg/dL)[a]	96 (90–105)	91 (84–101)	98 (91–106)	*0.002*
All C-peptide levels (nmol/L)	1.0 (0.8–1.4)	0.9 (0.7–1.1)	1.1 (0.8–1.5)	*< 0.001*
C-peptide levels (nmol/L)[a]	1.0 (0.8–1.4)	1.0 (0.7–1.2)	1.1 (0.8–1.5)	*0.016*
All HbA1c (%)	5.8 (5.5–6.4)	5.8 (5.4–6.3)	5.8 (5.5–6.4)	0.839
HbA1c (%)[a]	5.7 (5.4–5.9)	5.8 (5.3–6.0)	5.7 (5.4–5.9)	0.700

Sleep Breath (2020) 24:1389–1395

Intern Med 58: 3227-3234, 2019

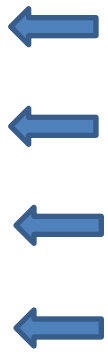
Arterial Hypertension and OSA

link between arterial hypertension (AH) and OSA is the most widely studied

Table 1 Prevalence of hypertension in obstructive sleep apnoea

Study	Sample size and gender	Methodology	Definition of hypopnoea	OR for hypertension when AHI >10–15 events/hr
Young *et al.* [1997] (22)	1,069 adults (30–60 years); M: 617; F: 452	Attended PSG	50% reduction in airflow for a minimum of 10 s with oxygen desaturation of ≥4%	1.8 (95% CI, 1.3–2.4)
Lavie *et al.* [2000] (27)	2,677 adults (20–85 years); M: 1,949; F: 728	Attended PSG	50% reduction in airflow for a minimum of 10 s with oxygen desaturation of ≥4% or an arousal	1.12 (95% CI, 0.75–1.56)
Bixler *et al.* [2000] (25)	1,741 adults (20–100 years); M: 741; F: 1,000	Attended PSG	50% reduction in airflow for a minimum of 10 s with oxygen desaturation of ≥4%	6.8 (95% CI, 2.02–26.36)
Nieto *et al.* [2000] (23)	6,132 adults (≥40 years); F: 3,238; M: 2,894	Home unattended PSG	30% reduction in airflow for a minimum of 10 s with oxygen desaturation of ≥4%	1.37 (95% CI, 1.03–1.83)

PSG, polysomnography.



J Thorac Dis 2018;10(Suppl 34):S4189-S4200

Arterial Hypertension and OSA (2)

Animal and human studies suggest **sympathetic nervous system activation** caused by hypoxemia and/or arousal from sleep as a potential mechanism linking sleep disordered breathing and hypertension

Journal of Thoracic Disease, Vol 10, Suppl 34 December 2018

The episodes of hypoxia stimulates peripheral **chemoreceptors** and there is a release of inflammatory markers: hypoxia-inducible factor 1, nuclear factor kappa, vasoconstrictive endothelin-1, interleukins (ILs) 1, 2, and 6, tumor necrosis factor alpha (TNFα), and interferon gamma (IFNγ)

The C-reactive protein (CRP), IL-6 and IL-8 released during hypoxemic/apneic episodes have been associated with increasing **carotid intima medial thickness** which is a precursor for HTN

CPAP therapy also improves endothelial damage by increasing NO production and reducing the stress on the endothelium by decreasing oxidative and inflammatory processes

In OSA patients, sympathetic stimulation causes the release of catecholamines, as well as an activation of the renin-angiotensin system, which causes high BP resulting in RHTN

CPAP therapy is a key in the treatment of RHTN with underlying OSA.

Sleep Med Disord. 2020;4(3):67-76. Epub 2020 Nov 23

Sleep Medicine Reviews 58 (2021) 101446

Contents lists available at ScienceDirect

Sleep Medicine Reviews

journal homepage: www.elsevier.com/locate/smrv

CLINICAL REVIEW

Efficacy of continuous positive airway pressure (CPAP) in patients with obstructive sleep apnea (OSA) and resistant hypertension (RH): Systematic review and meta-analysis

Gonzalo Labarca [a, b, *], Alexia Schmidt [a], Jorge Dreyse [c], Jorge Jorquera [c], Daniel Enos [a, d], Gerard Torres [e], Ferran Barbe [e]

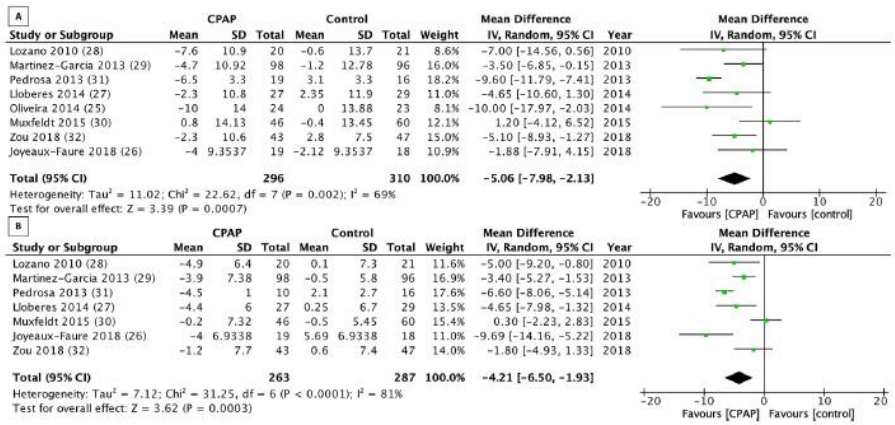


Fig. 3. Changes in 24-h blood pressure. A) Forest plot showing changes in 24-h systolic blood pressure (8 studies, 606 participants), B) Forest plot showing changes in 24-h diastolic blood pressure (7 studies, 550 participants).

Conclusion

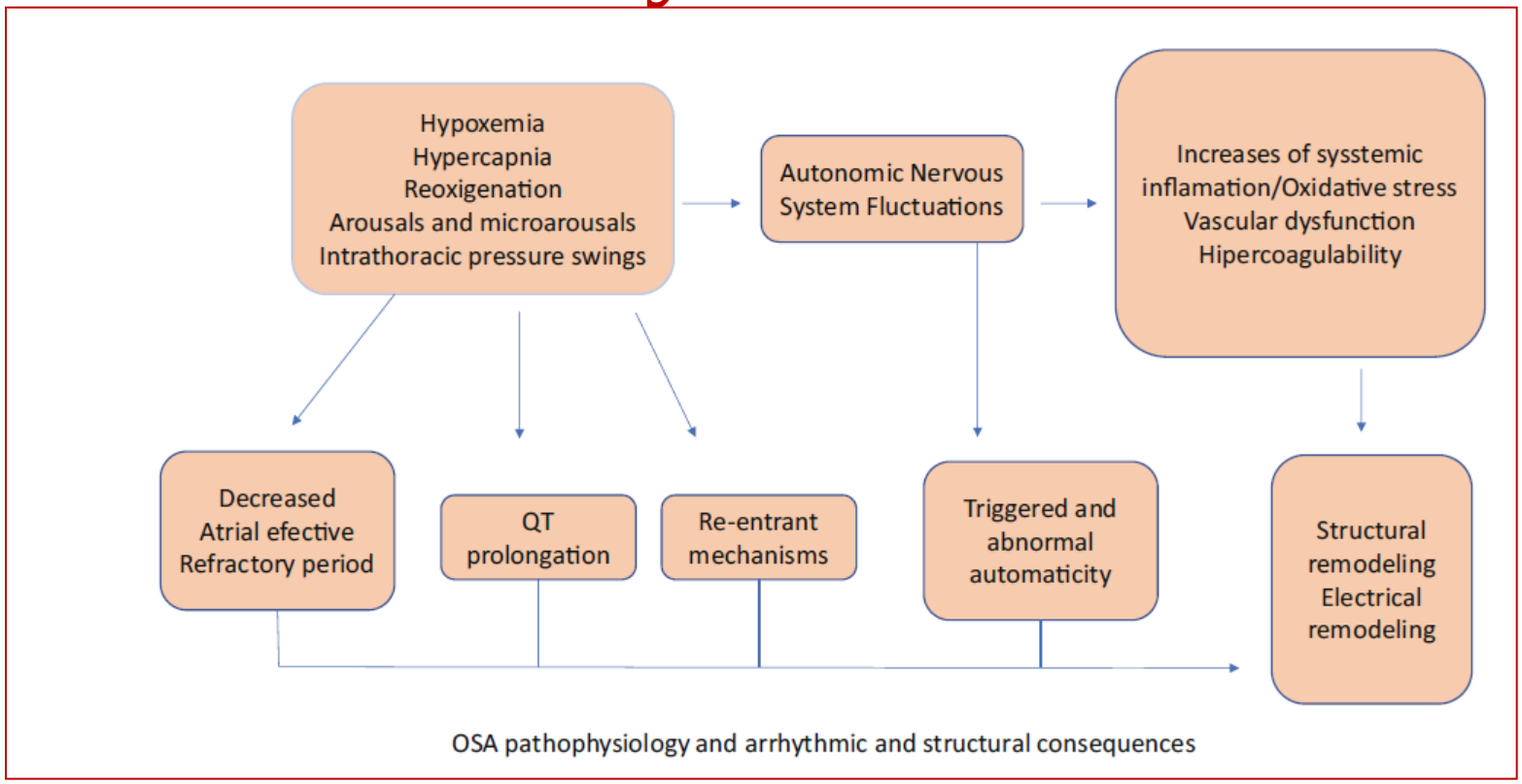
Although CPAP therapy was associated with clinically significant changes in 24-h SBP and 24-DBP, the quality of the evidence was moderate or low for most outcomes, and the evidence is not sufficient to support the benefits of this therapy in all patients with OSA and RH. There was also a different pattern of responses in the changes in SBP and DBP as measured using ABPM. These findings should guide future studies to improve the selection of patients for research and clinical practice.

Practice points

1. CPAP therapy in patients with obstructive sleep apnea and resistant hypertension improves 24-h systolic and diastolic blood pressure. However, this benefit is different between daytime and nighttime blood pressure.
2. The principal benefit of CPAP therapy in this population is related to nighttime systolic and diastolic blood pressure.
3. Patients with both diseases reported different response patterns based on other variables, such as age, body mass index, the prevalence of type 2 diabetes mellitus at baseline, and CPAP adherence.

Sleep Med Rev. 2021 Jan 28;58:101446.

Arrhythmias (2)



Curr Cardiol Rep. 2021 Feb 20;23(3):20.

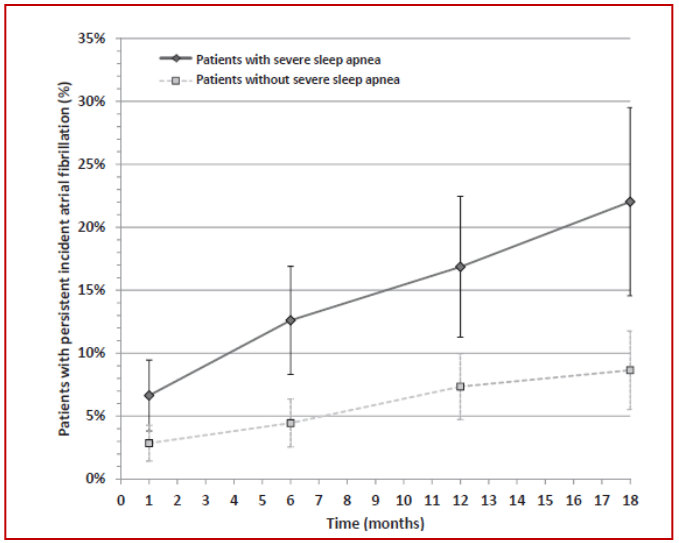
Arrhythmias (3)

- Both **bradyarrhytmias** and **ventricular arrhythmias** are more prevalent in patients with OSA, with a prevalence of 18% and 14-74%, respectively.

(J Thorac Dis. 2018;10(Suppl 34):S4189-S200.)

- OSA acts as a consistent and well-recognized risk factor for the *onset, progression and persistence* of **atrial fibrillation**

(Heart Rhythm. 2020;17(2):195-202)



Heart Rhythm. 2020;17(2):195-202

Table 2 Co-primary end points

Variable	Patients with severe sleep apnea	Patients without severe sleep apnea	Difference (95% CI) (%); *P*
Main analysis—first co-primary end point (FAS)	n = 172	n = 381	
Significant AF at 12 mo	43 (25.0)	53 (13.9)	11.1 (3.7 to 18.4); *P* = .002
Sensitivity analysis—first co-primary end point (mITT)*†	n = 321	n = 698	
Significant AF at 12 mo	80 (24.9)	92 (13.2)	11.7 (6.4 to 17.1); *P* < .001
Main analysis—second co-primary end point (mITT)†	(n = 312)	(n = 712)	
Major serious adverse events at 18 mo‡	27 (8.7%)	42 (5.9)	2.8 (−0.8 to 6.3); *P* = .065§
Death	16 (5.1)	17 (2.4)	2.7 (0.05 to 5.4); *P* = .023§
Myocardial infarction	2 (0.6)	3 (0.4)	0.2 (−0.8 to 1.2); *P* = .33
Stroke	3 (1.0)	2 (0.3)	0.7 (−0.5 to 1.8); *P* = .12
Reintervention	8 (2.6)	20 (2.8)	−0.2 (−2.4 to 1.9); *P* = .59

Heart Rhythm. 2020;17(2):195-202

Arrhythmias (3)

- OSAS and Sick Sinus Syndrome (SSS)
- OSAS and Atrial flutter/Atrial fibrillation
- OSAS and VT/Sudden Cardiac Death

Conclusion

OSAS is a highly prevalent illness in western countries and is clearly related to an increase in cardiovascular mortality and morbidity. Cardiac arrhythmias are triggered by a repetitive hypoxemia, hypercapnia, acidosis, intrathoracic pressure fluctuations, reoxygenation, and arousals during apnea-hypopnoea episodes. An early diagnosis and treatment of these patients can reduce further cardiovascular morbidity and mortality.

Curr Cardiol Rep. 2021 Feb 20;23(3):20.

Pulmonary hypertension

- Pulmonary hypertension (PH) coexists in about 10-20% of patients with moderate-to-severe OSA and, on the other hand, the prevalence of OSA in patients with PH ranges from 70 to 80%.

- OSA in turn leads to subsequent worsening of pulmonary vascular resistance and is associated to increased mortality especially in patients with severe PH

J Am Heart Assoc. 2019;8(1):e0

Coronary Artery disease

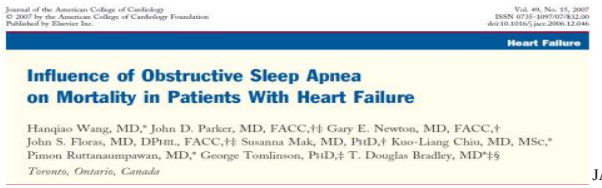
- However, longitudinal studies showed discordant results, with the **association between OSA and incident CAD being weakened after correction for common risk factors** and being confirmed only in some groups, i.e. in younger male subgroup as shown in the SHHS.

J Thorac Dis. 2018;10(Suppl 34):S

- On the other hand, in patients with pre-existent CAD, the presence of **OSA increases CV**

OSA nello scompenso cardiaco: impatto prognostico

La sopravvivenza è migliore nei soggetti senza apnee del sonno o con forme di lieve entità, rispetto ai pazienti con OSA non trattata

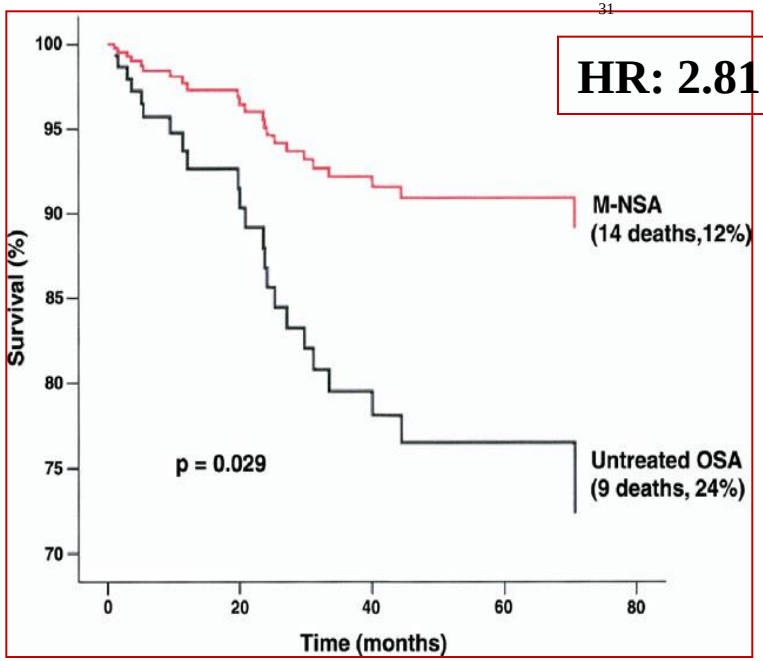

Heart Failure

Influence of Obstructive Sleep Apnea on Mortality in Patients With Heart Failure

Hanqiao Wang, MD,* John D. Parker, MD, FACC,†‡ Gary E. Newton, MD, FACC,† John S. Floras, MD, DPHIL, FACC,†‡ Susanna Mak, MD, PHD,† Kuo-Liang Chiu, MD, MSC,* Pimon Ruttanaumpawan, MD,* George Tomlinson, PHD,‡ T. Douglas Bradley, MD*†§

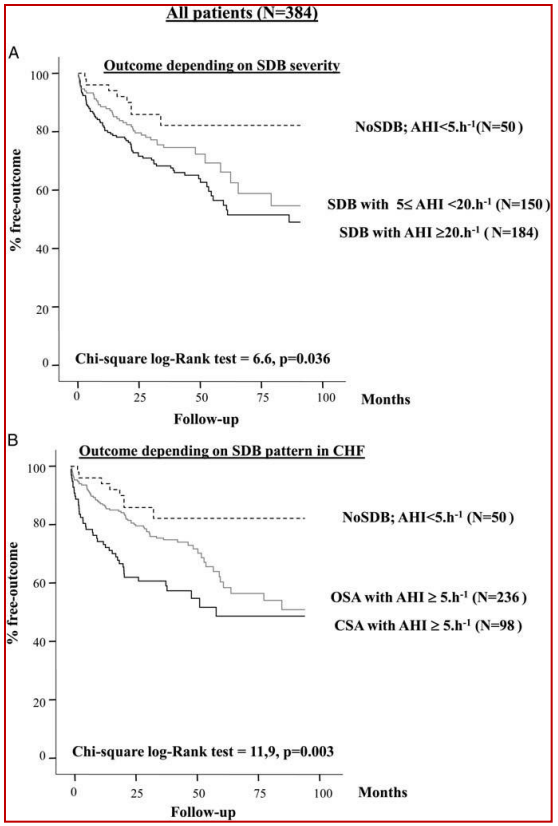
Toronto, Ontario, Canada

JACC 2007;49:1625-31

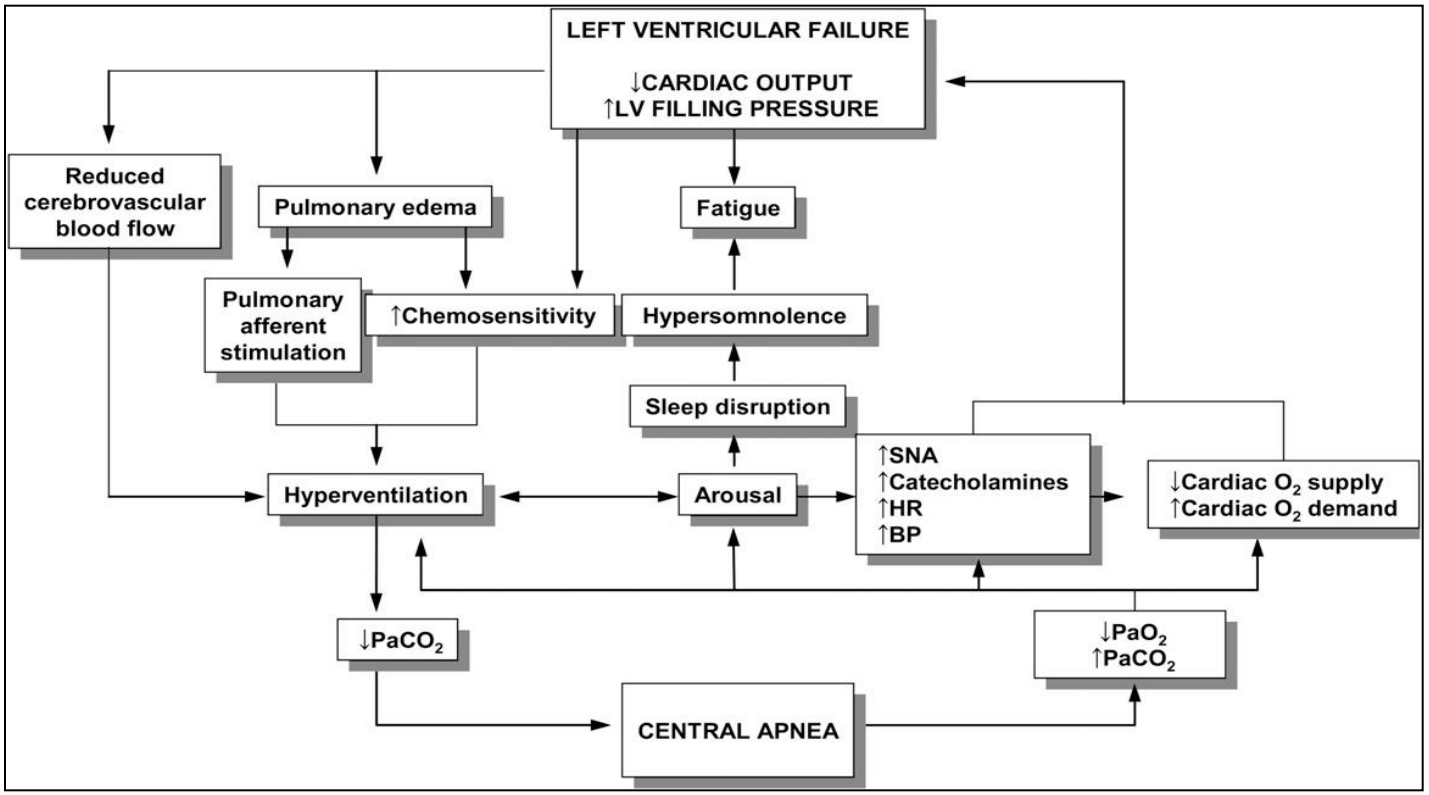


M-NSA: Mild to No Sleep Apnea

Eur J Heart Fail 2012;14:1009-19



CSA nello scompenso cardiaco: le conseguenze



Yumino D and Bradley TD Proc Am Thorac Soc 2008;5:226-36

Courtesy of prof Mauro Contini, IRCCS Cardiologico Monzino

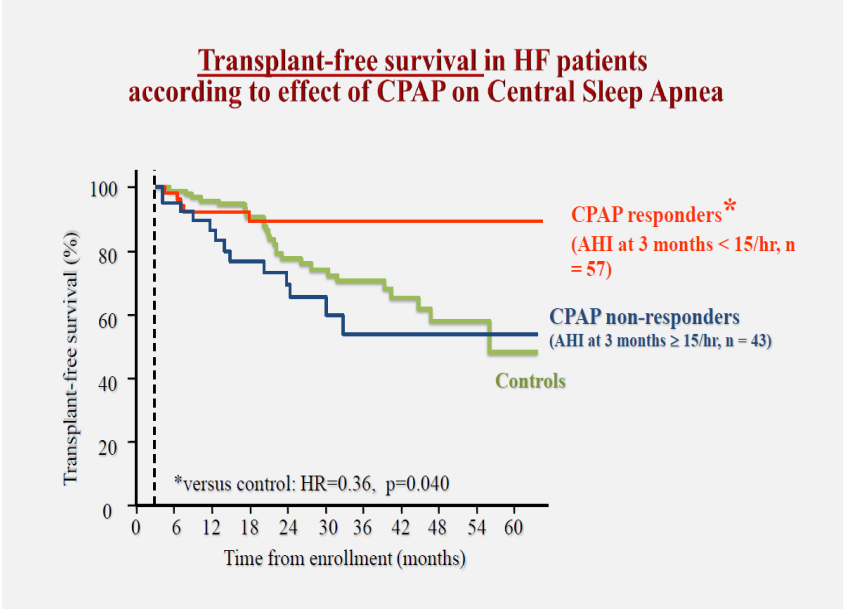
Trattamento di CSA/CSR nello scompenso cardiaco: prognosi

Studio CANPAP (Canadian Continuous Positive Airway Pressure for Patients with Central Sleep Apnea and Heart Failure). Analisi post-hoc: 210 pazienti

Circulation

American Heart Association

Suppression of Central Sleep Apnea by Continuous Positive Airway Pressure and Transplant-Free Survival in Heart Failure: A Post Hoc Analysis of the Canadian Continuous Positive Airway Pressure for Patients With Central Sleep Apnea and Heart Failure Trial (CANPAP)



Arzt M. et al. Circulation. 2007;115:3173-3180

Courtesy of prof Mauro Contini, IRCCS Cardiologico Monzino

Trattamento di CSA/CSR nello scompenso cardiaco: prognosi

ASV (Adaptive Servo Ventilation)

Courtesy of prof Mauro Contini, IRCCS Cardiologico Monzino

Trattamento di CSA/CSR nello scompenso cardiaco: prognosi

ASV (Adaptive Servo Ventilation)

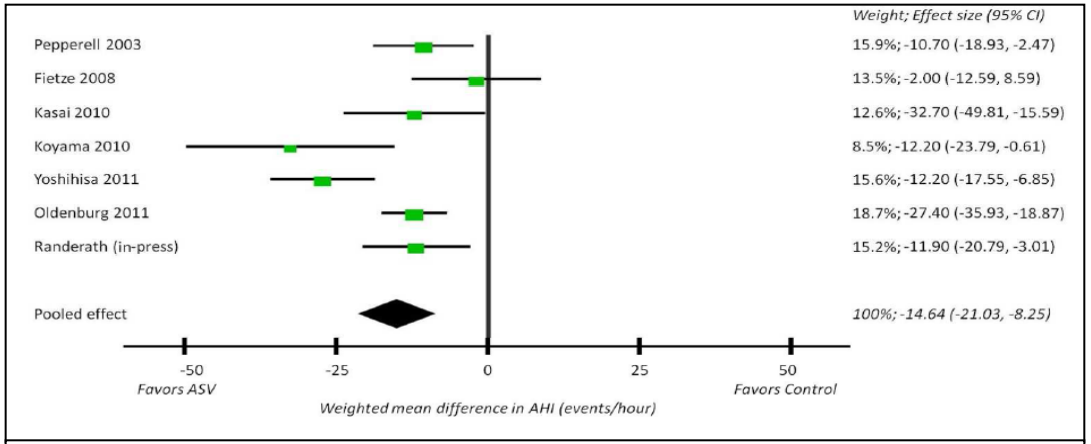
CHEST

Official publication of the American College of Chest Physicians

Adaptive servo-ventilation for treatment of sleep-disordered breathing in heart failure: A systematic review and meta-analysis

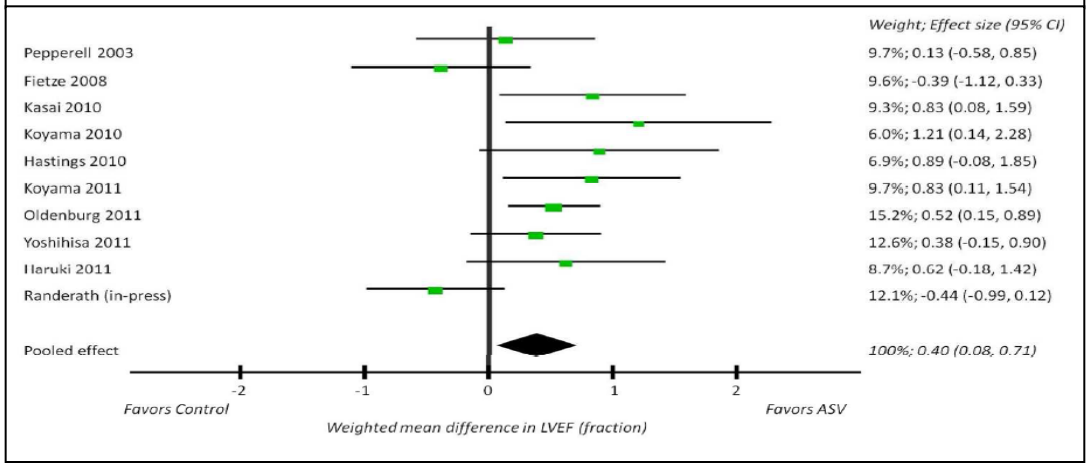
Bhavneesh K. Sharma, Jessie P. Bakker, David G. McSharry, Akshay S. Desai, Shahrokh Javaheri and Atul Malhotra

AHI



Trattamento delle apnee centrali del sonno nello scompenso cardiaco con ASV: una metanalisi mostra una riduzione dell'AHI e un miglioramento della FE

LVEF



Sharma BK et al. CHEST 2012;142:1211-21

Courtesy of prof Mauro Contini, IRCCS Cardiologico Monzino

Central Sleep Apnea

- Cheyne stokes respirations, waxing and waning of breathing and apnea
- Treatment

  CPAP,

  Wt loss,

  Decreased alcohol intake,

  Avoid supine position during sleep,

  Avoid benzodiazepines.

Sleep Heart Study

- Large epidemiological study
- Prevalence of SDB (sleep disturbed breathing) with increased age
- About 20% of subjects greater than age 60 had an RDI (respiratory distress index) greater than 15 hrs. even healthy non-obese
- Asymptomatic for OSA men affect more than women

Elderly have a decreased (substantially) ventilatory response to hypercapnia and hypoxemia possibly related to a physiological decline in the ability to interpret and integrate information from the peripheral and central chemoreceptors and from mechanoreceptors to generate an appropriate neuronal feedback response

Physiology and Anatomy of Sleep Apnea in the Elderly

- Upper airway- smaller caliber

  Studies found that all upper airway dimensions

  decreased with age

  collapse easier

  increased deposition of parapharyngeal fat

  Increased pharyngeal collapsibillity during sleep

*Some contradictions

Decreased ability of ginioglossus muscle (major pharyngeal dilator muscle) to respond to increase in pharyngeal negative pressure) impaired in aging

Definitions

- Apnea- complete cessation of breathing
- Hypopnea- partial decreases in breathing
- Sleep apnea in demented patients in greater prevalence than in age matched controls
- Apnea increases with severe dementia

Complications of moderate to severe OSA in the elderly

Neurocognitive	Cardiovascular	Cerebrovascular
Increased risk of cognitive decline (growing body of evidence).	Increased risk of incident heart failure. Association with ischemic heart disease is equivocal.	Increased risk of incident ischemic stroke (independent of other atherosclerotic risk factors).

Future Directions

Systematic studies are needed to develop a step-wise approach to diagnosing OSA in elderly that combines clinical data in tandem with PSG/HST.
Perform validation studies of the use of Epworth Sleepiness Scale to measure sleepiness in the elderly and the STOP-BANG to screen for OSA in the elderly.
Identify the subgroup of vulnerable elderly OSA patients who could benefit the most from treatment, with the aim of delaying neurocognitive decline and preventing cardiovascular events related mortality.
Evaluate the therapeutic and economic costs and benefits of CPAP in older adults particularly in those with mild OSA.
Determine the impact of non-PAP therapies on cardiovascular and neurocognitive outcomes in the elderly.

CPAP

- Gold standard of treatment
- Good long term compliance is difficult

Treatments of OSA

- CPAP- symptomatic treatment, not curative
- Avoid substances that may worsen sleep apnea (alcohol, sedating compounds, nicotine)
- Weight loss, even moderate can decrease symptoms
- Sleep position (avoid lying in supine position)