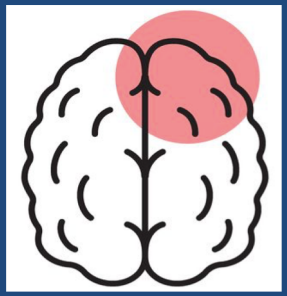
Sleep problems
in
Cerebrovascular disease

Pongsakorn Tanayapong, MD



Nov 13, 2020

Why sleep is important in Stroke?

- Stroke is one of the leading causes of morbidity and mortality.

- Sleep disorders are highly prevalent in general population and particularly in stroke patients.
  - SDB: prevalent in 50-70% of stroke patients
  - Insomnia:
  - Sleep-related movement disorders:

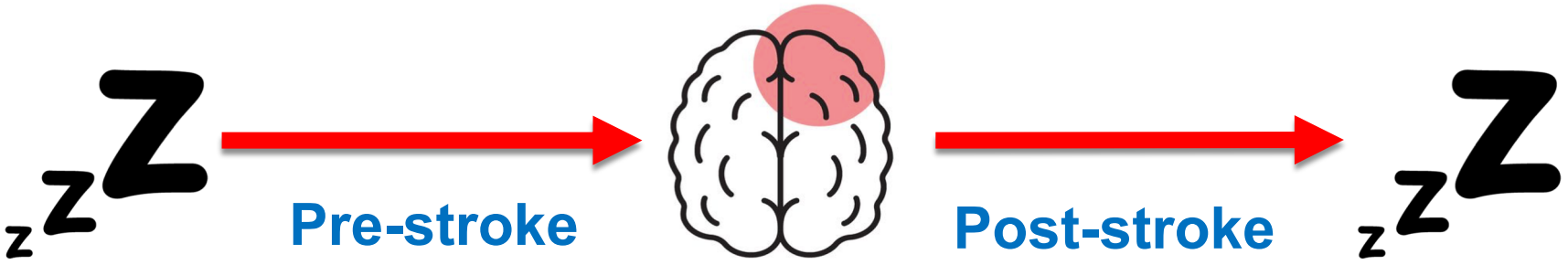
} 20-50% of stroke patients

Johnson KG, et al. *J Clin Sleep Med* 2010;6(2):131-137

Outline

- Pre-stroke phase
  - Are sleep disorders (SDB, insomnia, RLS/PLMS) **risks** of stroke?
  - Do treatment of sleep disorders **prevent** stroke?

- Post-stroke phase
  - **Frequency** of sleep disorders after stroke and the **impact** on outcome

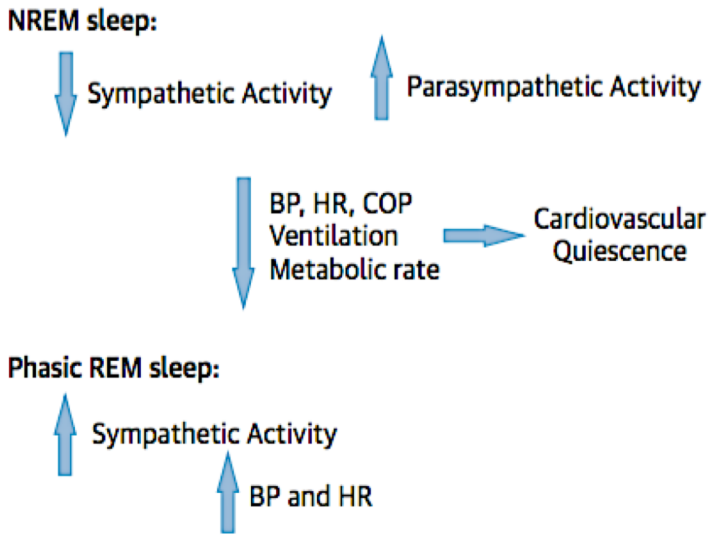


Sleep disturbances and Stroke

- Along with the brain and other organs or physiological streams, **the cardiovascular system achieves homeostatic restoration during sleep**, mainly through autonomic circulatory control.

  - **NREM sleep**
    - Vagal dominance (reduced BP and HR) and stable breathing
    - Cardiovascular-neural restoration in response to distress during wakefulness

  - **REM sleep**
    - Abrupt irregular swings in sympathovagal balance (abrupt change in BP and HR)
    - Acting as phasic loads on the resting cardiovascular system



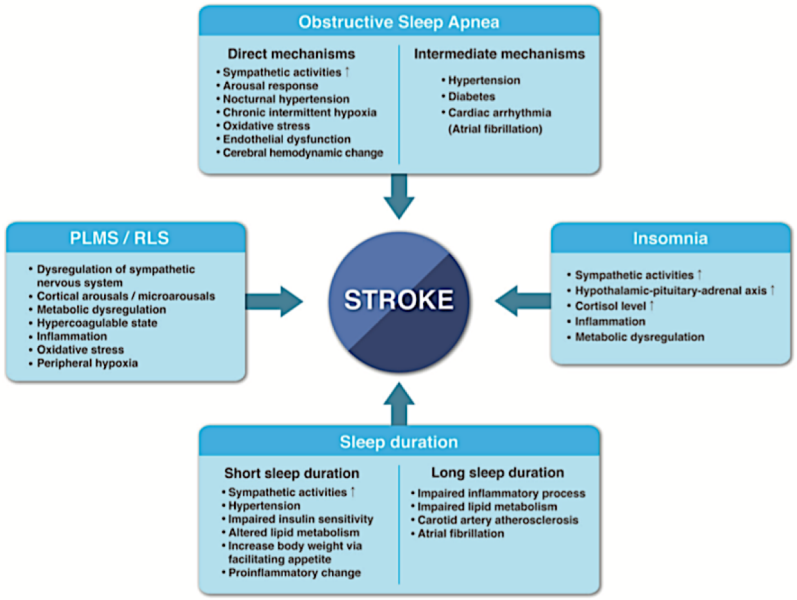
Koo DL, et al. Journal of Stroke 2018;20(1):12-32

Sleep disturbances and Stroke

- Any causes of **sleep deprivation** or **fragmentation**, not only impair cardiovascular restoration but also **impose a stress on the cardiovascular and cerebrovascular systems.**

- Sleep deprivation
  - e.g., sleep restriction

- Sleep fragmentation
  - defined by cortical EEG arousals
  - e.g., sleep apnea, insomnia, PLMS
  - associated with overshoots in sympathetic activity



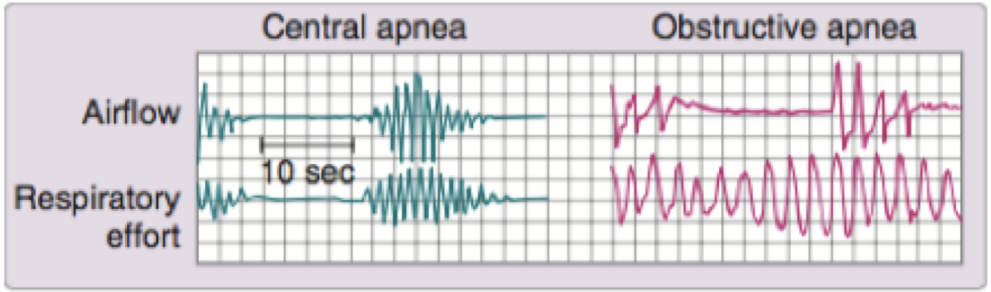
Koo DL, et al. Journal of Stroke 2018;20(1):12-32

Sleep-disordered breathing and Stroke

- **Obstructive sleep apnea (OSA)**
  - Repetitive reduction (hypopnea) or cessation (apnea) of air flow during sleep
  - Due to **upper-airway collapse** despite continued activity of inspiratory thoracic pump muscles

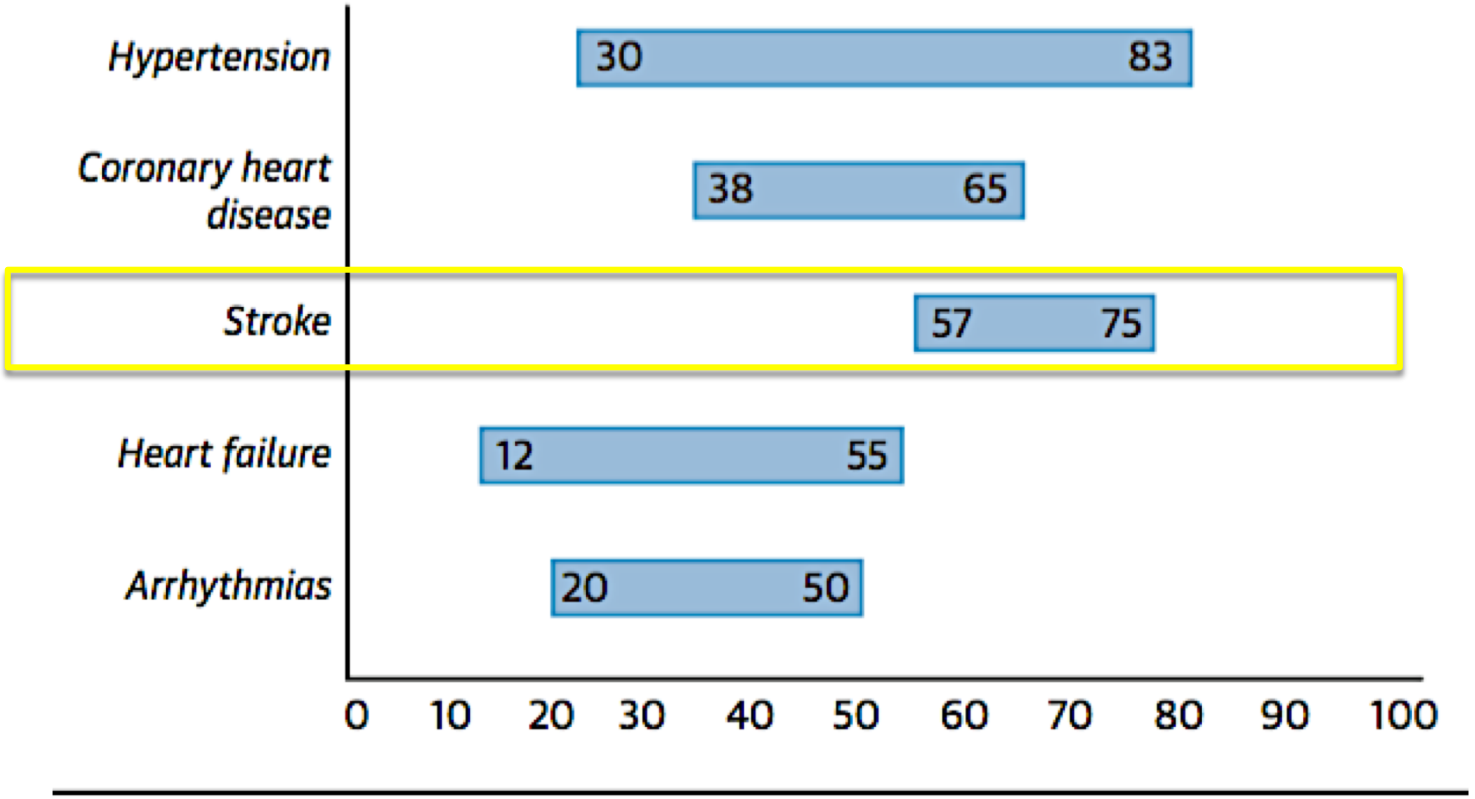
- **Central sleep apnea (CSA)**
  - Repetitive reduction or cessation in both airflow and ventilatory effort
  - Due to **a transient reduction by the pontomedullary pacemaker** in the generation of breathing rhythm

- No consistent data: UARS (OSA subtype), sleep-related hypoventilation, sleep-related hypoxemia



J Thorac Dis 2015;7(8):1373-1384

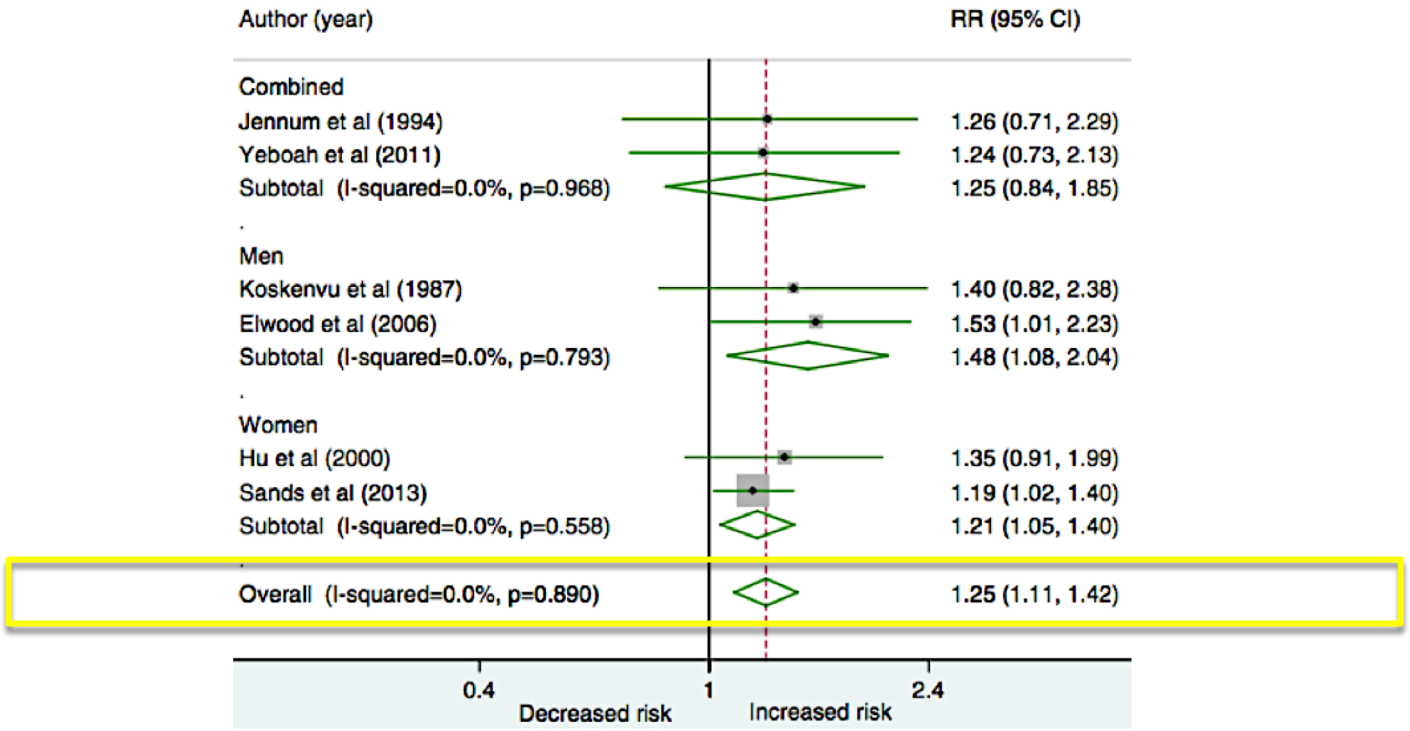
Prevalence (%) of OSA in CVD



The lower limit is invariably using an AHI of ≥15/h, indicating presence of moderate-to-severe OSA. The upper part of the range relates to a lower threshold of ≥5/h. CVD = cardiovascular disease; OSA = obstructive sleep apnea.

Javaheri S, et al J Am Coll Cardiol 2017;69:841–58

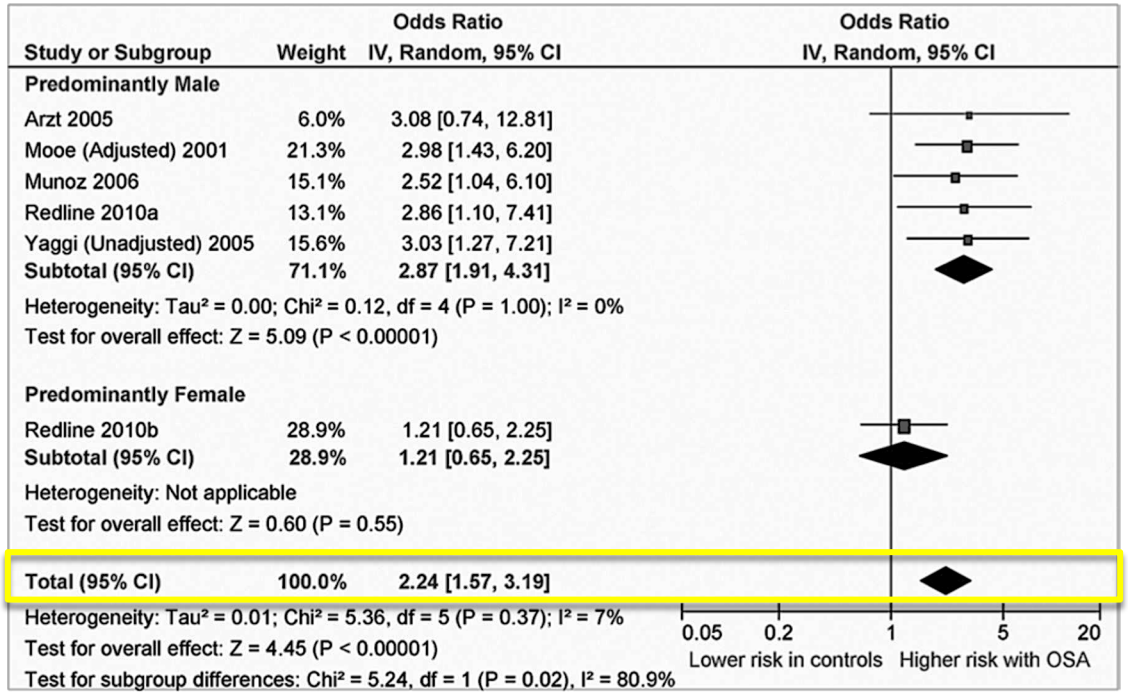
SDB – as a stroke risk (Surrogate marker: Snoring)



- A meta-analysis (n > 100,000) showed that habitual snorers, who snore more than three nights per week, **carry a 25% additional risk for stroke** compared to non-snorers (**pooled relative risk 1.25**; 95% CI 1.11–1.42)

Li M, et al. Int J Cardiol 2015; 185: 46-9

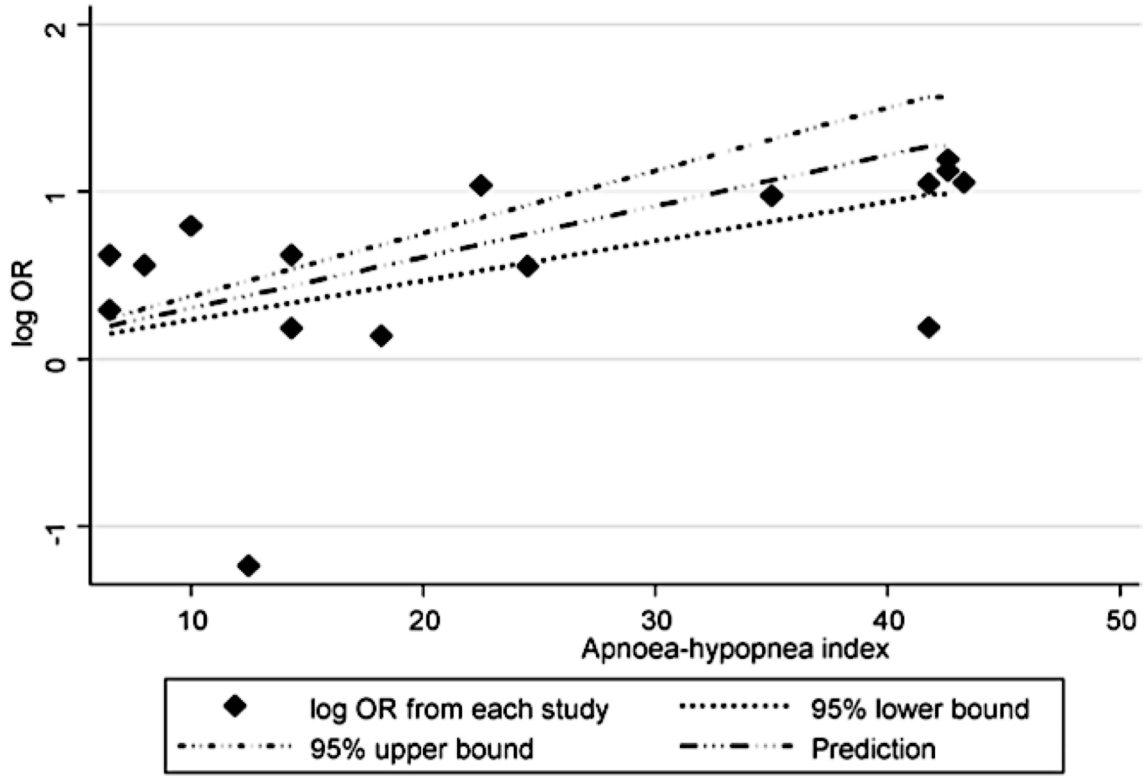
SDB – as a stroke risk



- **OR 2.24** A meta-analysis of prospective cohort studies of 8,435 participants, **OSA was associated with incident stroke**(OR 2.24; 95% CI 1.57–3.19).

Loke YK, et al Circ Cardiovasc Qual Outcomes 2012;5:720–28

Dose-response relationship: Severity of SDB and Stroke risk

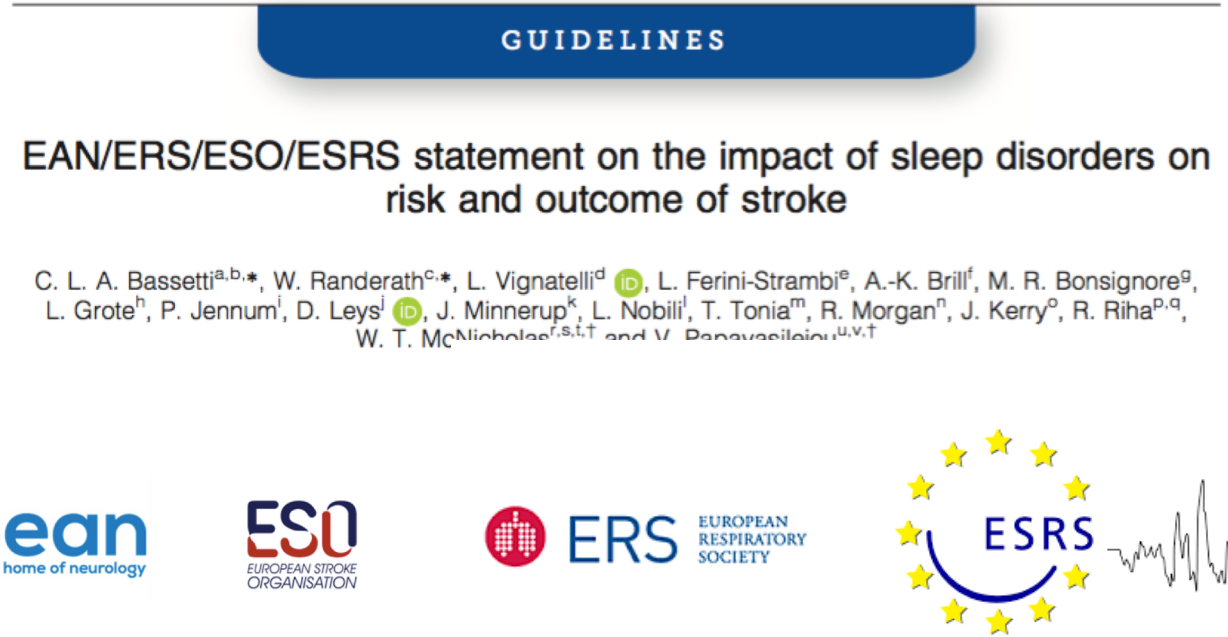


- **3.6%:1AHI** This meta-analysis showed that each **10-unit increase in the AHI** is associated with **a relative increase of 36% in the odds of having a cerebrovascular event** with OR of 1.36 (1.26–1.43).

Loke YK, et al Circ Cardiovasc Qual Outcomes 2012;5:720–28

SDB – as a stroke risk

- 6 SR/MA of prospective cohorts:
  - OSA approximately **doubles** the risk for stroke (RR ranging from 2.02 - 2.24) in untreated OSA patients over a follow-up period of 3–10 years.


GUIDELINES

EAN/ERS/ESO/ESRS statement on the impact of sleep disorders on risk and outcome of stroke

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Bassetti CLA, et al Eur J Neurol 2020;0:1–20

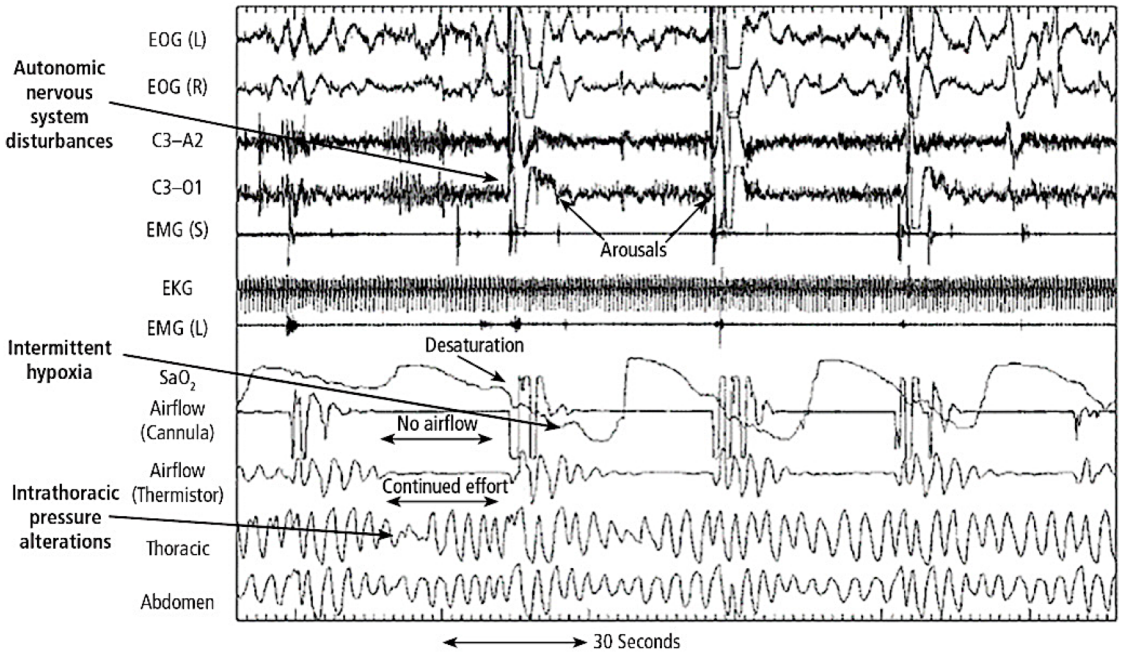
Mechanisms contributing SDB to stroke

- **Indirect mechanisms** via other shared risk factors
  - hypertension, arrhythmia (AF)

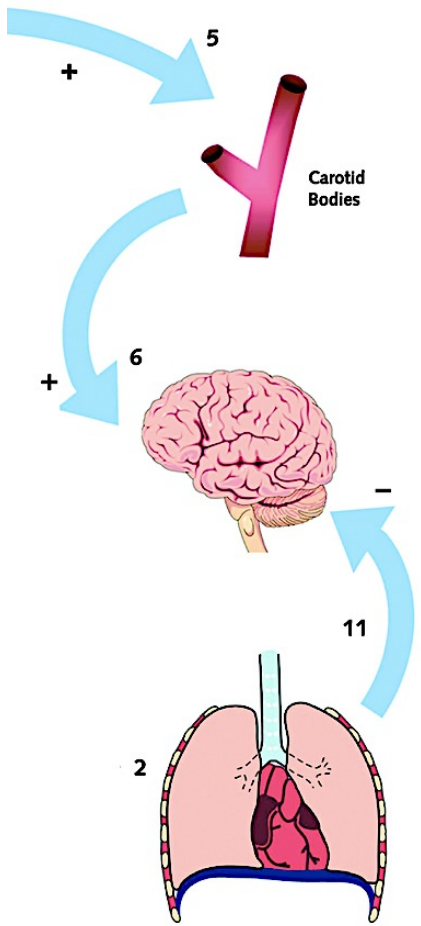
- **Direct mechanisms**
  - Intermediate mechanisms linking SDB with cardiovascular/cerebrovascular disease
    - Sympathetic activation, Inflammation, Hypercoagulability, Endothelial dysfunction
  - Effect of SDB on cerebral circulation
    - Reduction of cerebral blood flow
    - Changes in cerebral autoregulation

- **Additional mechanisms**
  - PFO, snoring

Mechanisms contributing SDB to stroke



C3–A2 and C3–01 = brain waves via electroencephalogram; EKG = electrocardiogram; EMG = electromyogram for sleep (S) and leg (L) movement; EOG = electrooculogram for left (L) and right (R) eye movement; SaO_2 = oxygen saturation



- **Consequences of SDB**
  - Arterial blood gas abnormalities
  - Arousals
  - Large negative intrathoracic pressure swings
  - Reoxygenation

Eckert DJ, et al. 2009; 51 (4): 313-323

Consequences of SDB: (1) Arterial blood gas abnormalities

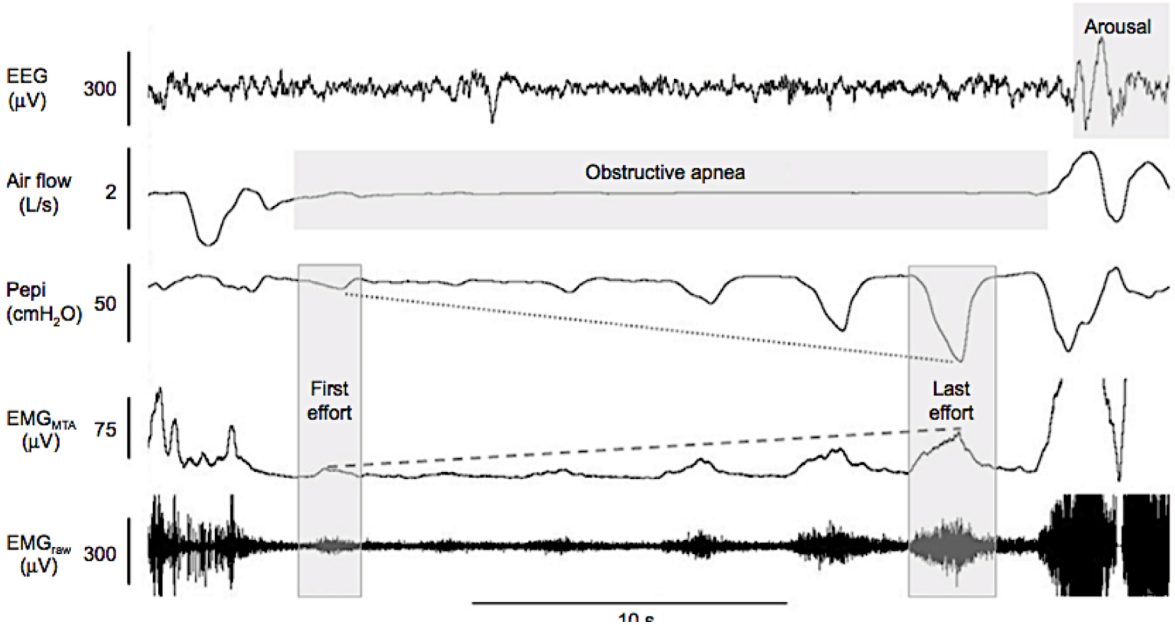
- Hypoxemia and hypercapnia
  - stimulate chemoreceptors, triggering reflex increases in sympathetic activity

- Apnea: a lack of lung inflation (Pulmonary stretch receptors)
  - Lung inflation normally attenuates sympathetic activity mediated by vagal afferents.

Eckert DJ, et al. 2009; 51 (4): 313-323

Consequences of SDB: (2) Arousals

- Arousal
  - a protective role serving to terminate the apneic events by
    - reopening the airway in response to collapse/negative intrathoracic pressure (OSA)
    - increase ventilatory rate in response to hypercapnia (CSA, OSA)
  - detrimental effects on sleep stability; i.e., shift to lighter sleep stages
  - Normally sympathetic nerve traffic is progressively reduced during deepening stages of NREM sleep.



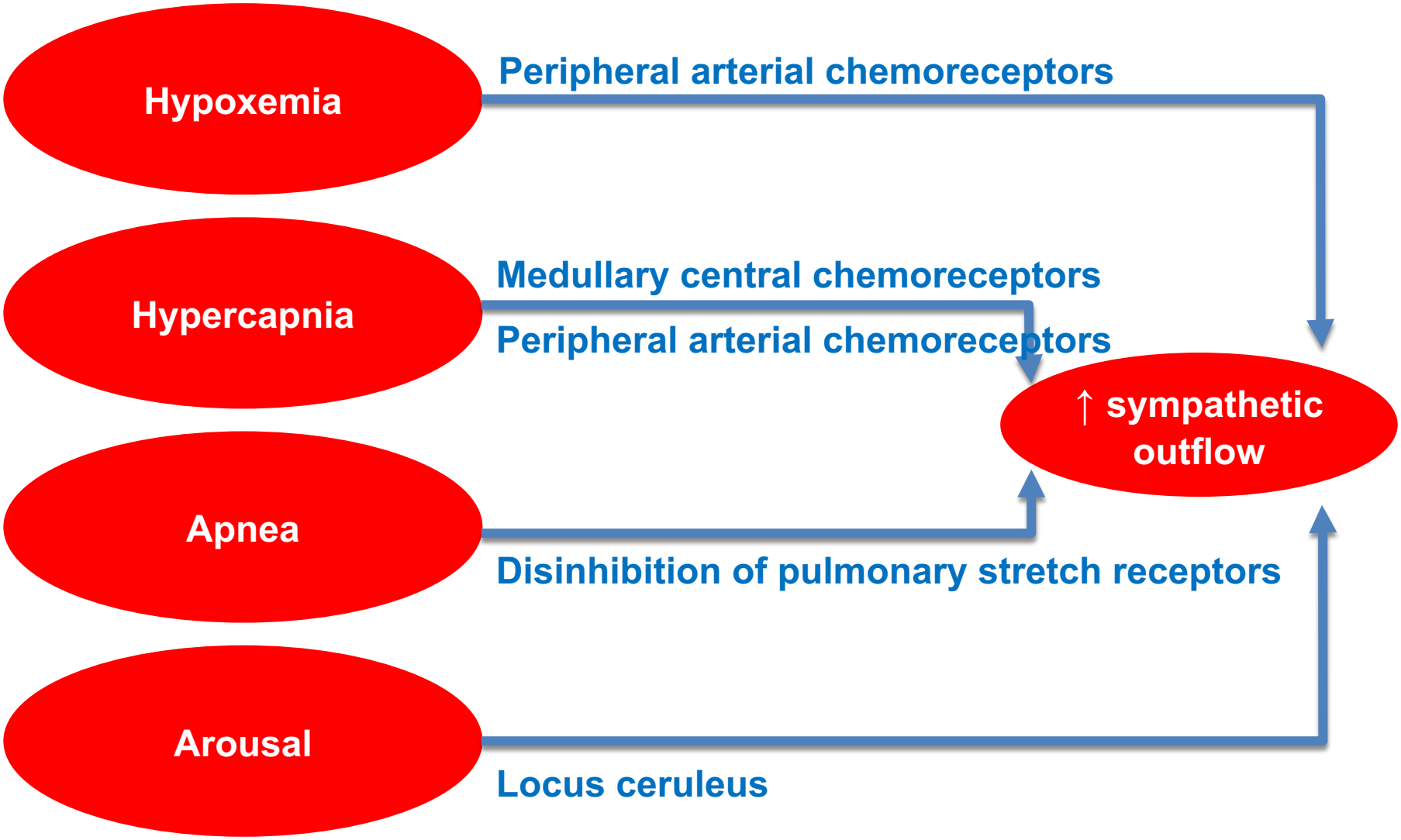
Arousals

Negative intrathoracic pressure

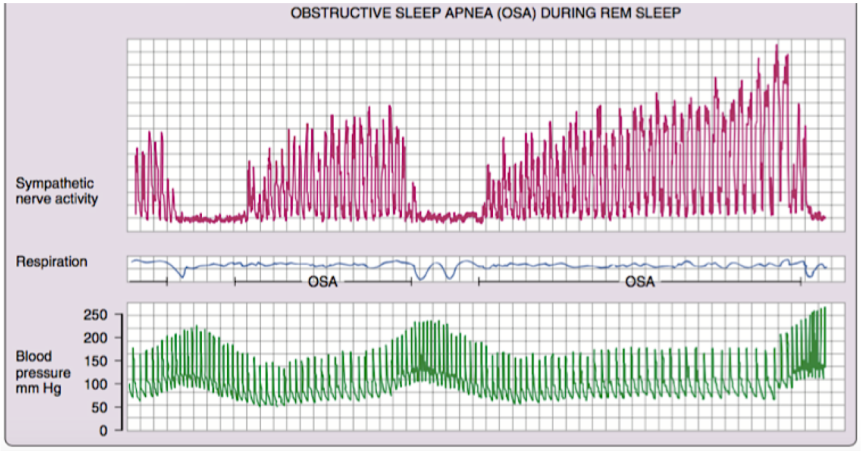
Osman AM, et al, Nature and Science of Sleep 2018:10 21–34

Eckert DJ, et al. 2009; 51 (4): 313-323

Sympathetic nervous system activation in SDB



Sympathetic nervous system activation in OSA



- During REM sleep, the repetitive hypoxemia and hypercapnia trigger chemoreflex-mediated **sympathetic activation** and **vasoconstriction**.
  - During apnea, blood pressure can reach levels from 130/60 mm Hg during wakefulness to a peak of 220/130 mm Hg.
  - At the end of apneas, the baroreflex inhibits sympathetic traffic, causing decreased blood pressure.

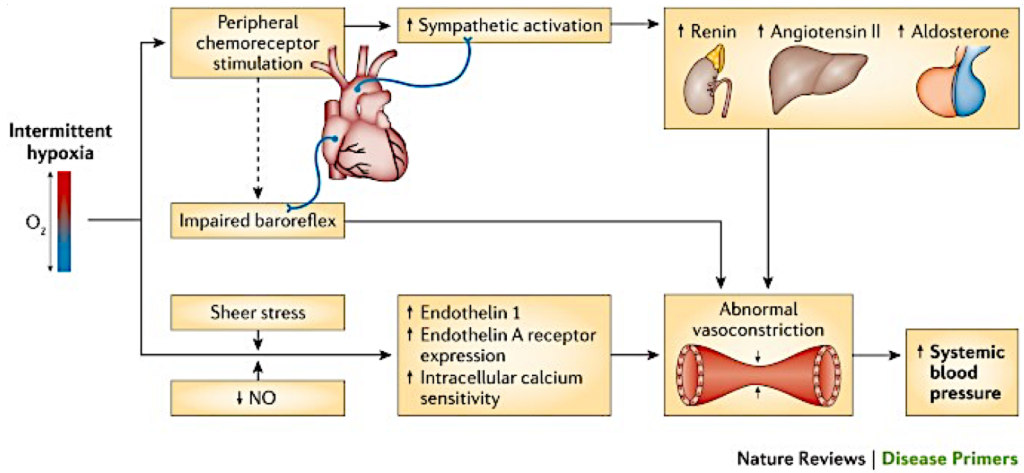
Somers VK, et al. *J Clin Invest* 1995; 96: 1897-904

Kryger MH, et al. Principles and Practice of Sleep Medicine, 6th edition, Philadelphia, PA : Elsevier, 2017; 155-66

Sympathetic nervous system activation in OSA

- Nighttime sympathetic activation
  - contributes to a **blunted response to nocturnal dipping** (the normal decline in blood pressure during sleep where blood pressure falls by at least 10-15% of the awake value)
  - **carries over into daytime wakefulness**

- Sympathetic activation leads to **hypertension**.



Loredo JS, et al. Stroke. 2004; 27: 1097-103

Lévy, P et al. Nat Rev Dis Primers. 2015; 1: 15015

Consequences of SDB: (3) large negative intrathoracic pressure swings

- Large negative intrathoracic pressure swings
  - generated during obstructive events in OSA due to inspiratory effort against a closed upper airway
  - increases the transmural pressure of the intrathoracic vascular structures, including aorta, pulmonary vascular bed, ventricles, and particularly **thin-walled atria that are vulnerable to surrounding negative pressure**
  - activates ion channels of atria, enabling development of atrial arrhythmia, specifically **atrial fibrillation (AF)**

Kryger MH, et al. Principles and Practice of Sleep Medicine, 6th edition, Philadelphia, PA : Elsevier, 2017; 155-66

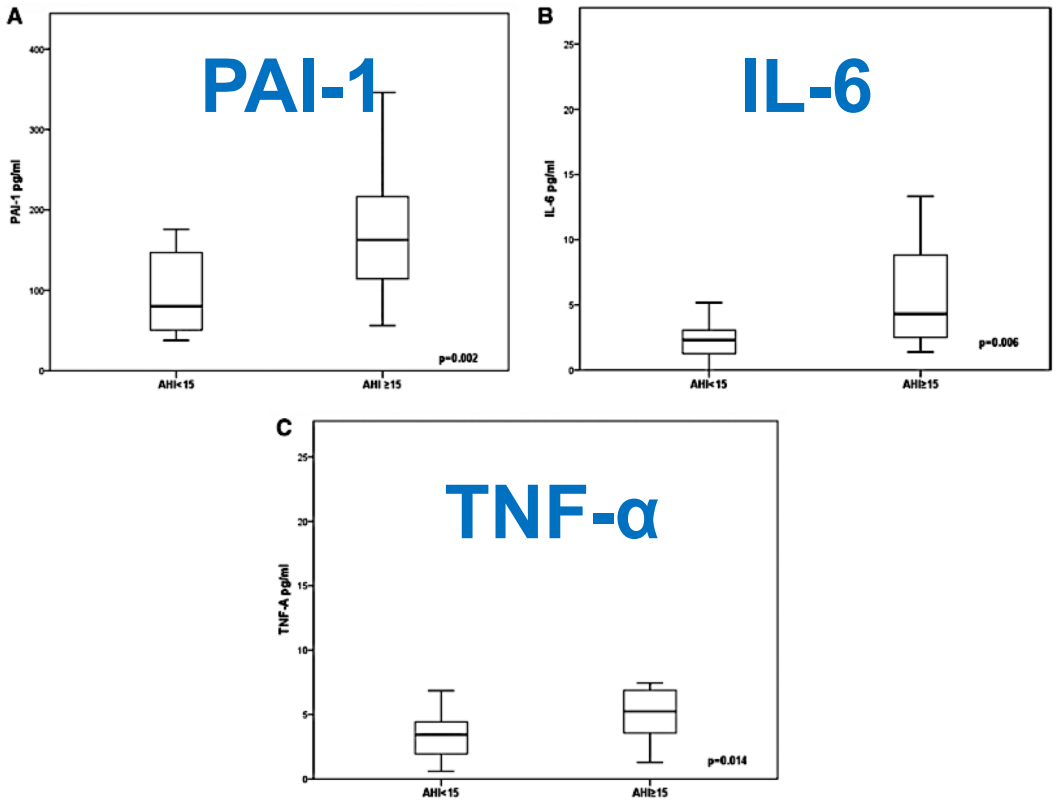
Consequences of SDB: (4) reoxygenation

- Rapid reoxygenation at the end of apnea causes **production of free radicals**, leading to oxidative stress and up-regulation of nuclear factor-kappaB.

- This process triggers **inflammatory cascade**, causing **hypercoagulability** and **endothelial dysfunction**.

Prabhakar NR, et al. Ann N Y Acad Sci 2009; 1177: 162-8

Hypercoagulability and Inflammation in OSA after acute stroke



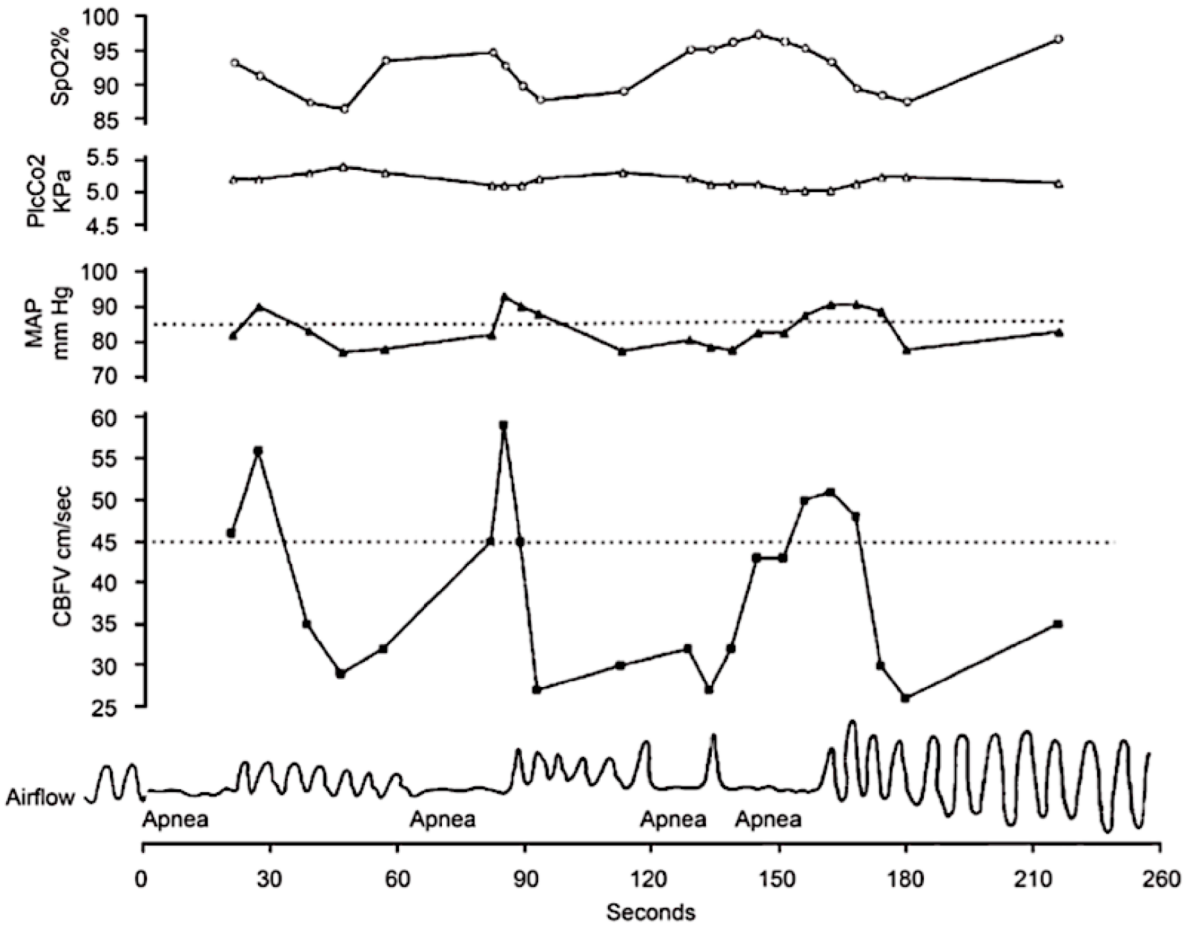
- Observational study showed **hypercoagulability** and **increased platelet aggregation** related to OSA increase risk of blood vessels' blockage.
- 43 patients underwent a nocturnal respiratory assessment during the first 48 hours after stroke symptoms onset.
- **PAI-1** was significantly higher in patients with an AHI≥15(mean of 176.64±74.52 versus 98.48±52.58 pg/ml, P=0.003).
- **IL-6** (6.64±5.27 versus 3.14±2.05 pg/ml, P=0.006), and **TNF-α** (6.39±5.00 versus 3.57±1.87 pg/ml, P=0.022) were also higher.

Ifergane G, et al. Stroke. 2016;47:1207-1212

Effect of SDB on cerebral circulation

- Reduction of cerebral blood flow
- Changes in cerebral autoregulation

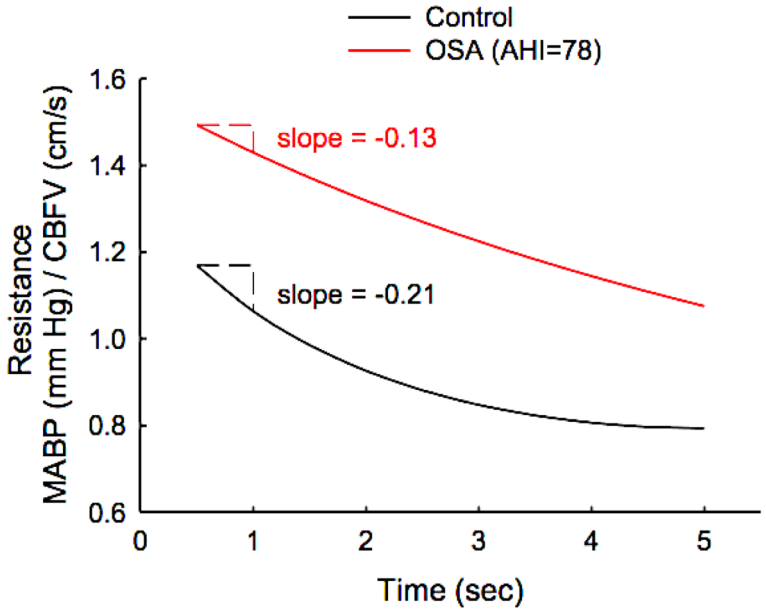
Reduction of cerebral blood flow



- Mean arterial pressure (MAP) and cerebral blood flow velocity (CBFV)
  - increase during obstructive apneas
  - **drop precipitously with apnea termination**
- In patients with repetitive apneas, the subsequent hemodynamic changes can be profound, esp. **a compromise in perfusion.**

Balfors EM, et al. Am J Respir Crit Care Med 1994;150:1587–91

Changes in cerebral autoregulation



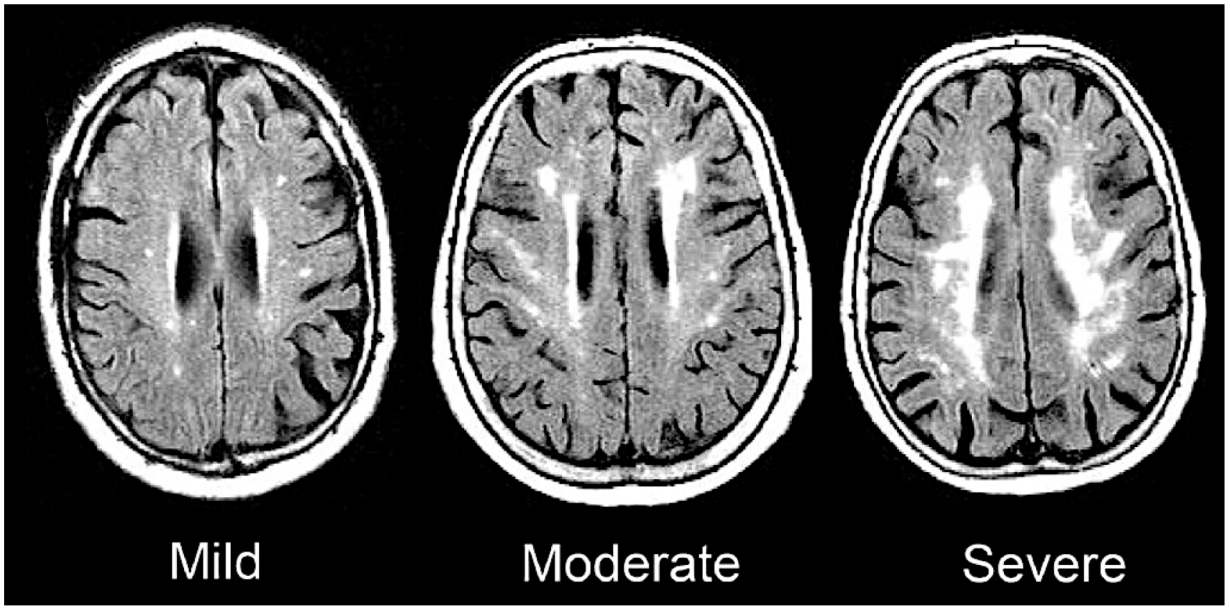
- The increased resistance (38%) in the patients with OSA after an orthostatic hypotension challenge (obtained by having individuals stand from a squatting position)
  - indicates **impaired autoregulatory mechanisms** responsible for dilating cerebral arteries.

Urbano F, et al. J Appl Physiol. 2008;105:1852–1857

Durgan DJ, et al.J Am Heart Assoc. 2012;1:e000091

Cerebral hemodynamic changes

- Moderate to severe OSA is **an independent risk factor** for **white matter change** in middle-aged and older individuals.



Kim H, et al *SLEEP* 2013;36(5):709-15

Additional mechanisms

- **Patent foramen ovale (PFO)**
  - PFO has been suggested to be the mediator for paradoxical embolism giving rise to cardioembolic stroke.
  - **Large swing in intrathoracic pressure** has been a postulated mechanism that OSA induce right-to-left shunting through PFO.

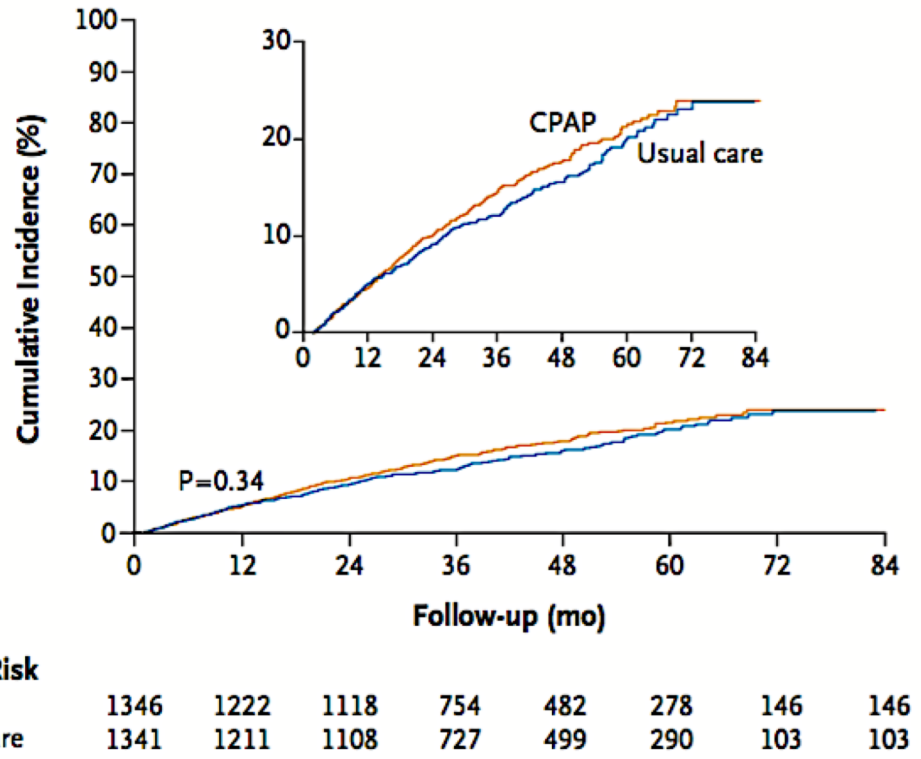
Beelke M, et al. Sleep Med 2003; 4(3):219-23

- **Snoring**
  - Vibrations from snoring in OSA with mechanical energy transmission could potentially be involved in intimal injury or **endothelial damage** to the carotid artery, resulting in atherosclerosis or even introducing plaque rupture.

Lee SA, et al. Sleep 2008; 31: 1207-13

Does treatment of SDB prevent stroke?

- 4 SR, 4 studies (including SAVE and RICCADSA trials):
  - CPAP treatment is not associated with stroke risk reduction in OSA patients; however, **patients adherent to CPAP therapy (>4hr per day) may benefit.**
    - **SAVE**
      - **Hazard ratio=0.56; 95%CI, 0.32-1.00; p=0.05**
    - **RICCADSA**
      - **Adjusted HR=0.29; 95%CI, 0.10-0.86; p=0.0026**



No. at Risk								
CPAP	1346	1222	1118	754	482	278	146	146
Usual care	1341	1211	1108	727	499	290	103	103

Bassetti CLA, et al Eur J Neurol 2020;0:1–20

McEvoy RD, et al N Engl J Med 2016;375:919-31

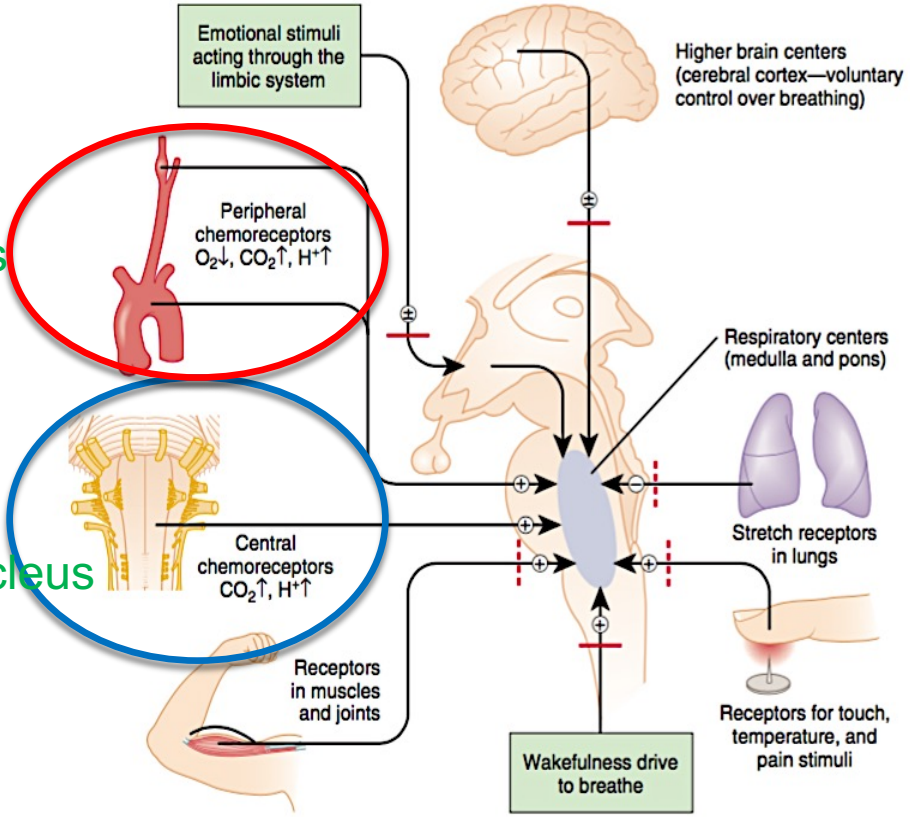
Peker Y, et al Am J Respir Crit Care Med 2016;194:613-20

Stroke - as a SDB cause

- With the absence of behavioral influences on breathing during sleep, the breathing is regulated only by **brainstem neurons**, peripheral chemoreceptors and respiratory muscle afferents.

Carotid bodies

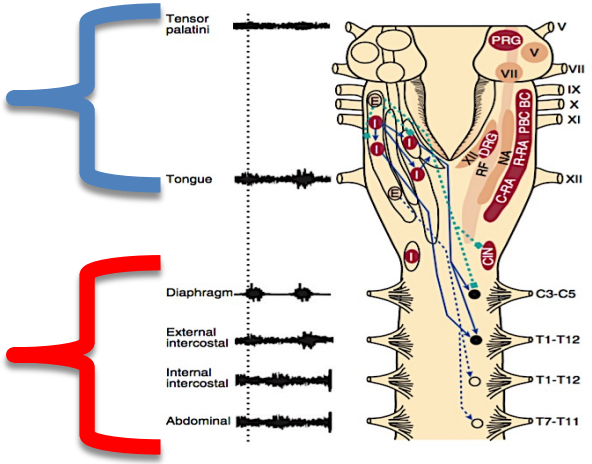
Retrotrapezoid nucleus

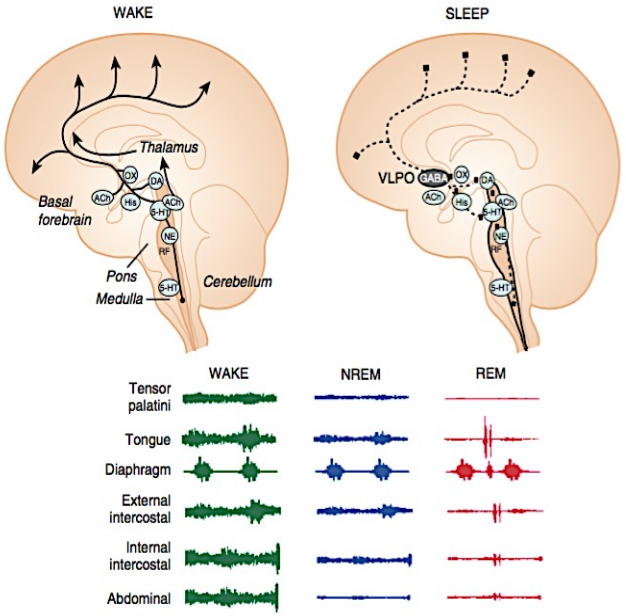


Kryger MH, et al. Principles and Practice of Sleep Medicine, 6th edition, Philadelphia, PA : Elsevier, 2017; 155-66

Stroke - as a SDB cause

Upper-airway neuromotor control





Respiratory neuromotor control

- Brainstem is thought to be critical for controlling both **ventilatory regulation** and **upper-airway tone**.

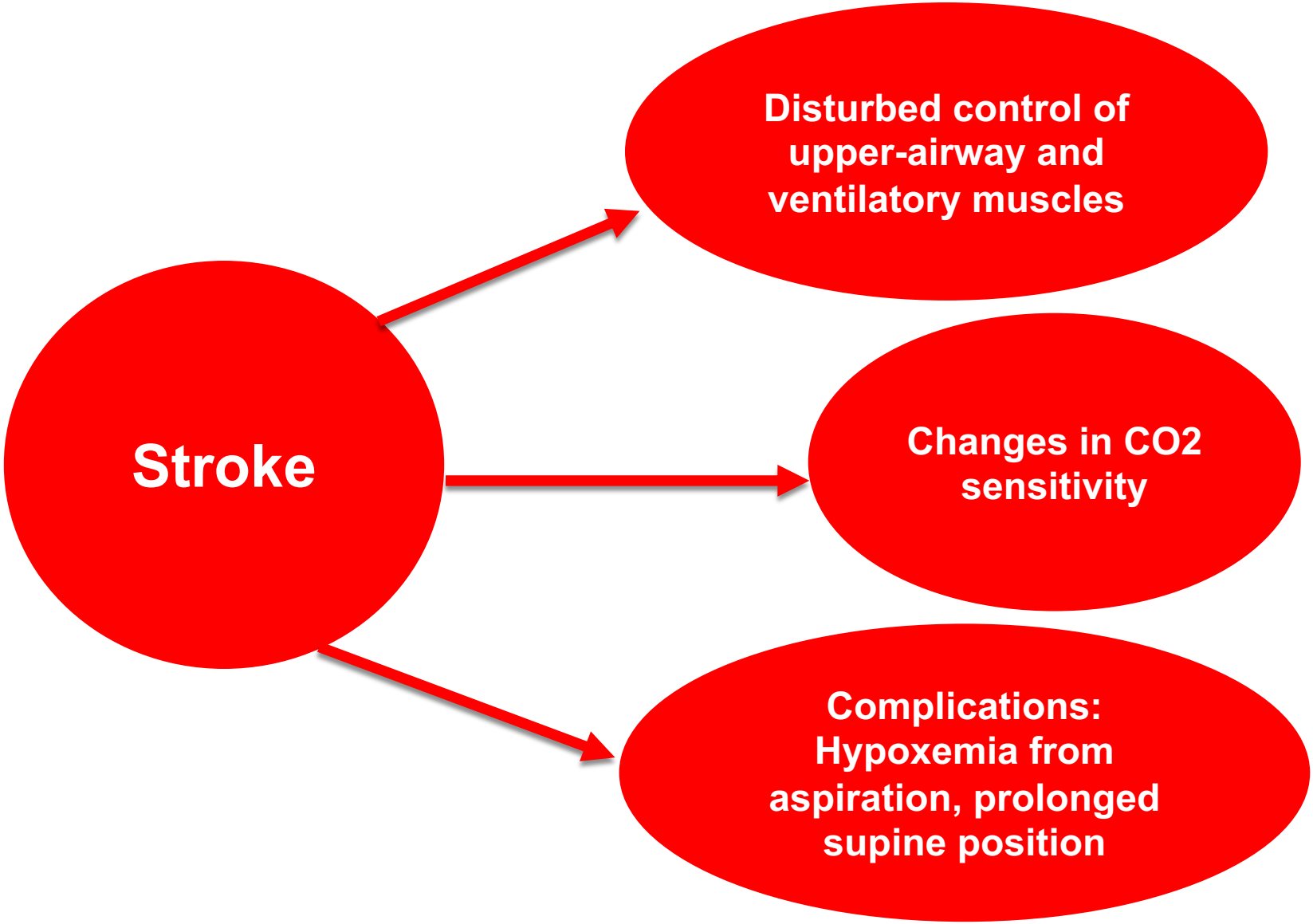
Saper CB, et al. Hypothalamic regulation of sleep and circadian rhythms. Nature 2005; 437:1257–63

Stroke - as a SDB cause

- Stroke may cause SDB through multiple complex mechanisms.
  - 1.**A disturbed control of upper-airway and respiratory muscles**
    - due to supra- or infratentorial stroke potentially favoring OSA.
  - 2.**Changes in CO2 sensitivity**
    - directly to central chemoreceptor, which medulla contains
  - 3.**Stroke complications**:
    - hypoxemia from aspiration, prolonged supine position, rostral fluid shifting from extremity edema

Alexiev F, et al, J Thorac Dis 2018;10(Suppl 34):S4244-S4252

Stroke - as a SDB cause



Post-stroke SDB prevalence

- The prevalence of SDB in stroke survivors, or after TIA, is high at **72%** for **an AHI >5/h** in a meta-analysis published in 2010.

- An important limiting factor is determining whether there was preexisting SDB prior to the stroke and how this may influence post-stroke acute SDB pathophysiology.

- OSA
  - the predominant form of post-stoke SDB
  - **30%** of stroke patients present with **severe OSA**.
  - OSA severity is typically unchanged 3 months post-stroke.

Bassetti CLA, et al Eur J Neurol 2020;0:1–20

Johnson KG, et al J Clin Sleep Med 2010;6:131-7

Post-stroke SDB prevalence

- CSA
  - Only **7%** of the SDB was primarily **central apnea**.
  - CSA can be noted, esp. soon after stroke, but tends to decrease with time.
    - The incidence of CSA increases in larger strokes and those associated with mass effect (increased cranial pressure leading to a reduction in cerebral blood volume, which would precipitate hypocapnia, leading to unstable ventilatory control and CSA)
  - may partly explain a spontaneous decrease in CSA after 3 months

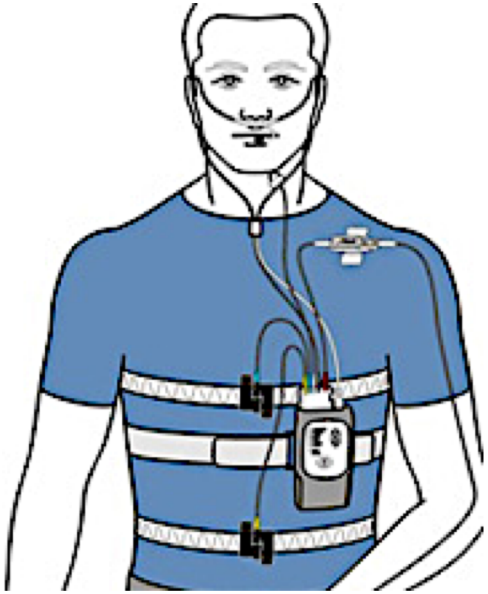
- Most studies published did not find any relationship between topography of stroke and frequency/severity of SDB.

- A few reports suggested an association between central SDB and supra-/infratentorial stroke and obstructive SDB and infratentorial stroke.

Johnson KG, et al J Clin Sleep Med 2010;6:131-7
Bassetti CLA, et al Eur J Neurol 2020;0:1–20
Alexiev F, et al J Thorac Dis 2018;10(Suppl 34):S4244-S4252

Post-stroke SDB prevalence

- **Portable cardiorespiratory polygraphy** is sufficient.



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Bassetti CLA, et al Eur J Neurol 2020;0:1–20

Johnson KG, et al J Clin Sleep Med 2010;6:131-7

SDB and stroke outcome

- 2 SR/MA, 5 studies:
  - 1. OSA is a **risk factor for recurrence** of stroke or TIA.
  - 2. OSA in stroke patients may be associated with **an increase in all cause mortality** and **worsen the neurological outcome**.

Bassetti CLA, et al Eur J Neurol 2020;0:1–20

Mechanisms for worsening neurological outcomes

- First, regions with compromised blood flow –ischemic penumbra – surrounding the infarcted core, may further injured by such **hemodynamic changes** or **tissue hypoxia**, which may lead to worse stroke recovery.

Durgan DJ, et al *J Am Heart Assoc* 2012;1(4):e000091

- Second, during acute phase of stroke, selectively vasodilated cerebral vessels in normal brain tissues caused by hypercapnia during apnea steal blood away from regions with bereft cerebrovascular supply, '**Reversed Robin Hood Syndrome**'.

Alexandrov AV, et al Stroke 2007;38:3045-8

SDB treatment in stroke patients

- A sleep study might be considered for patients with an ischemic stroke or TIA on the basis of **the very high prevalence of sleep apnea in this population**.

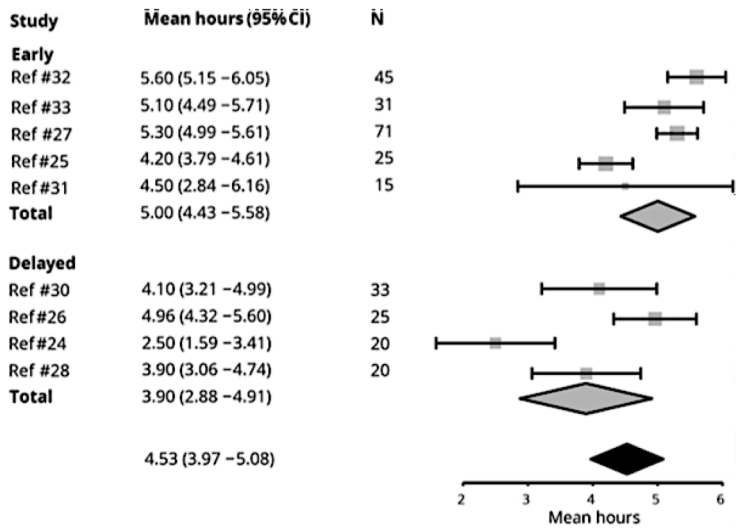
- Treatment with CPAP might be considered for patients with ischemic stroke or TIA and sleep apnea given **the emerging evidence in support of improved outcomes** *(Class IIb; Level of Evidence B)*.

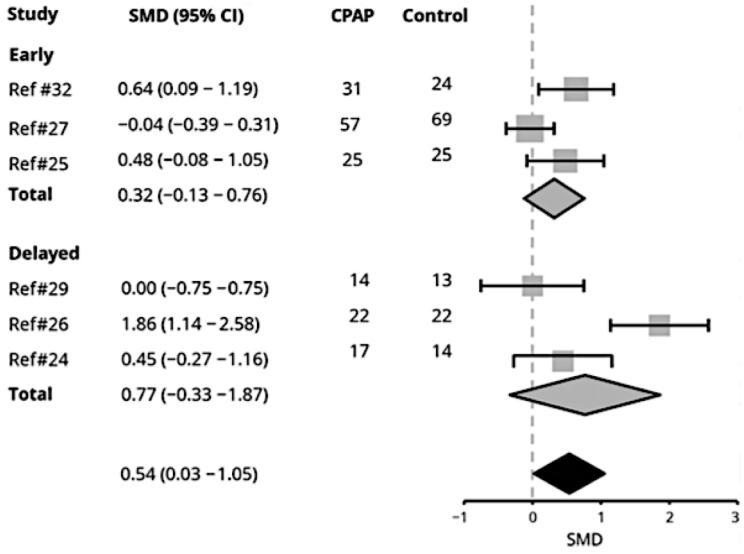
American Heart Association | American Stroke Association®

Kernan WN, et al *Stroke*. 2014;45:2160-236

SDB treatment and stroke outcome

- 2SR, 9 studies:
  - CPAP is feasible in stroke survivors with OSA and may **improve neurological recovery, sleepiness and depressive symptoms**.
  - Acceptance of CPAP in the acute stroke setting within trials was mostly limited due to underlying extremity or facial paresis, dysphagia, aphasia, or neglect but, **once accepted, compliance can be satisfactory.**





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Brill AK, et al Neurology 2018; 90; e1222-30

Conclusions: SDB and Stroke

- OSA
  - is an independent risk factor for stroke
  - doubles the risk for stroke
  - Postulated mechanism:
    - Intermittent hypoxia-mediated elevation of oxidative stress and systemic inflammation, hypercoagulability, impairment of cerebral autoregulation, elevated sympathetic activity
    - Shared risk factors: HT, AF

- The relationship may be bidirectional: SDB as cause (risk factor) for stroke, but also as a potential consequence of stroke.
  - The prevalence of sleep apnea post-stroke has been reported to be up to 70%.
  - CSA can occur in up to 7% during the post-stroke phase.

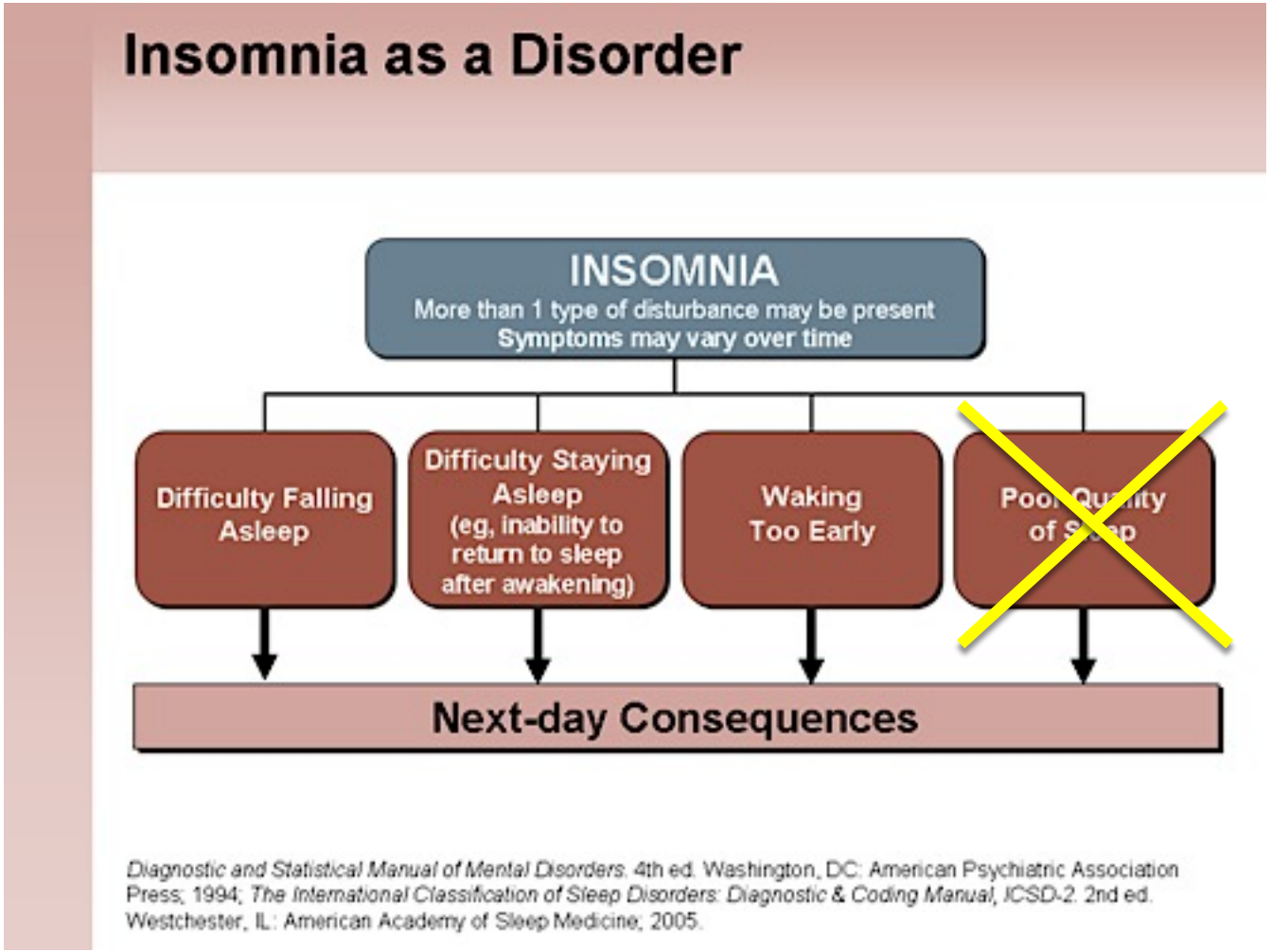
Conclusions: SDB and Stroke

- CPAP may reduce stroke risk, especially in treatment-compliant patients.
- The prevalence of OSA is high in stroke patients and can be assessed by polygraphy.
- Severe OSA is a risk factor for recurrence of stroke and may be associated with stroke mortality, whilst CPAP may improve stroke outcome.

Non-apnea and Stroke

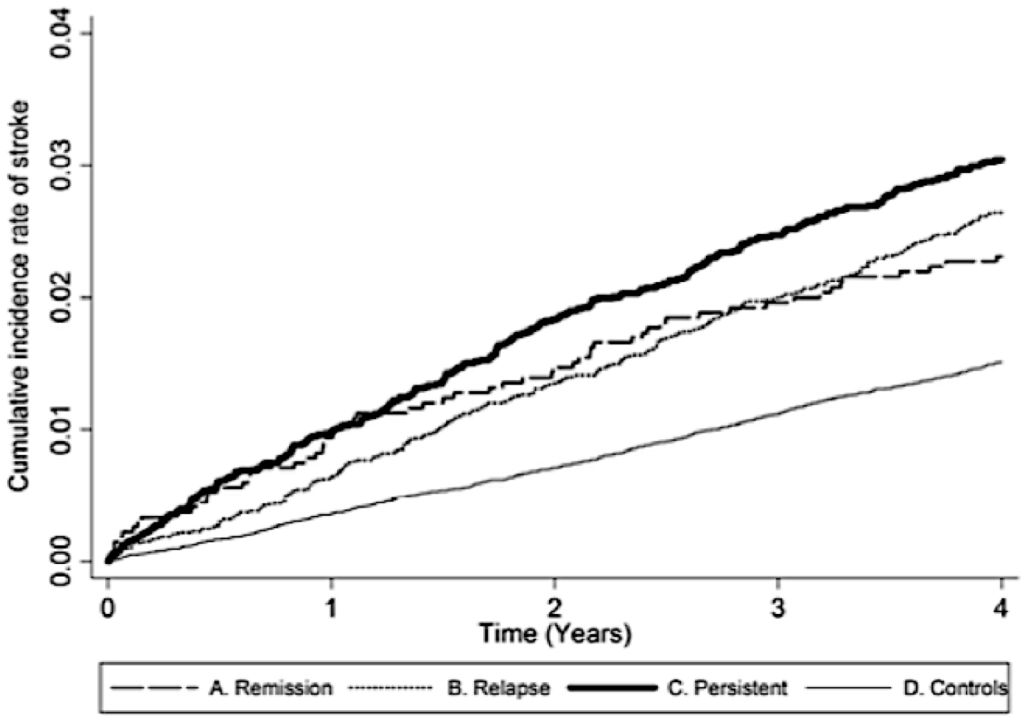
- Insomnia
- RLS/PLMS

Insomnia and Stroke



Despite adequate opportunity and circumstances

Insomnia and Stroke



- A large 4-yr follow-up cohort of 21,438 subjects with insomnia
- **54%** Insomniacs vs non-insomniacs
  - **adjusted HR for stroke 1.54 (1.38–1.72)**
- Limitation
  - based on subjective measures to define insomnia
  - reduce the accuracy of exposure identification (overestimated SL and WASO)

Wu MP, et al. Stroke 2014;45:1349-1354

Is insomnia an independent risk factor for stroke?

- Insomnia slightly increases the risk for cardiovascular events, but **risk for stroke is uncertain**.

- Prospective studies evaluating the association of insomnia with stroke risk are scarce and all available studies are **based on subjective measures** to define insomnia, thus reducing the accuracy of exposure identification.

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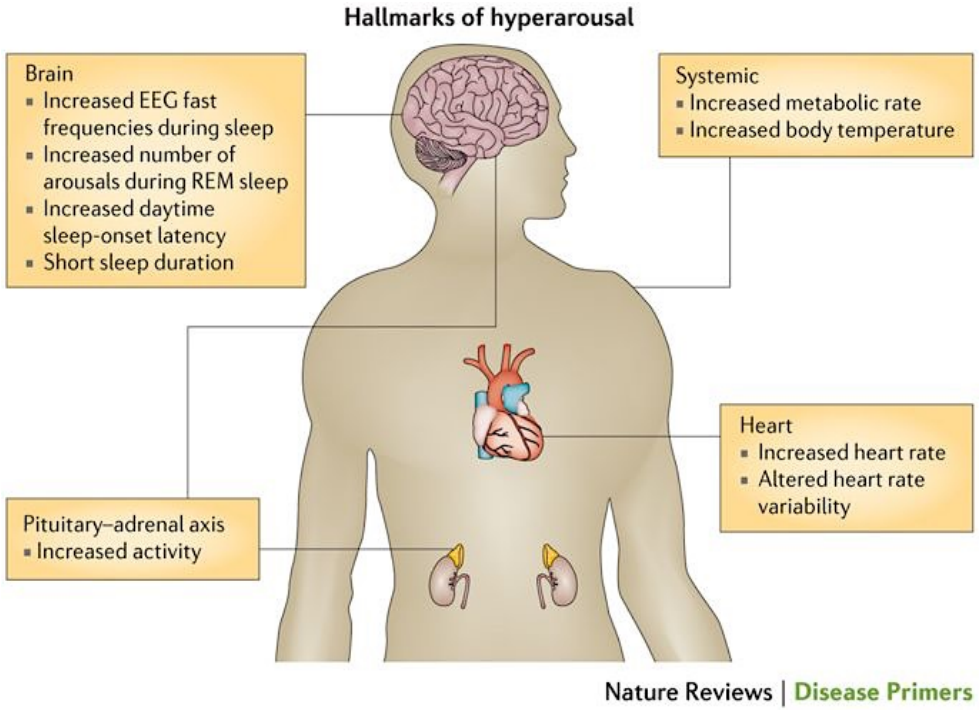
Mechanism of Insomnia for Stroke

- Elevated sympathetic and hypothalamic-pituitary-adrenal axis activity has been proposed as a mechanism for the cardiovascular effect of insomnia.



Vgontzas AN, et al. Sleep Med Rev 2013; 17: 241-54

Does treatment of insomnia prevent stroke?

- Treatment of insomnia with BDZ/non-BDZRs is linked to **an increased risk** of cognitive dysfunction, dementia and mortality and **possibly also stroke**, especially in high dosage and long-term use.

- This effect may be related also to **an indication bias**: patients who are in a worse general or neurological condition suffer more frequently from insomnia and may receive BDZ/non-BDZRs more frequently.

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RLS/PLMS and Stroke

CRE:https://www.shutterstock.com.au

RLS ”URGE” Criteria

- Awake sensory phenomenon with voluntary motor response (chronic sensorimotor disorder)
  - URGE to move leg, usually with dysesthesia
  - REST is worse
  - Getting up for relief
  - EVENING worse or at night

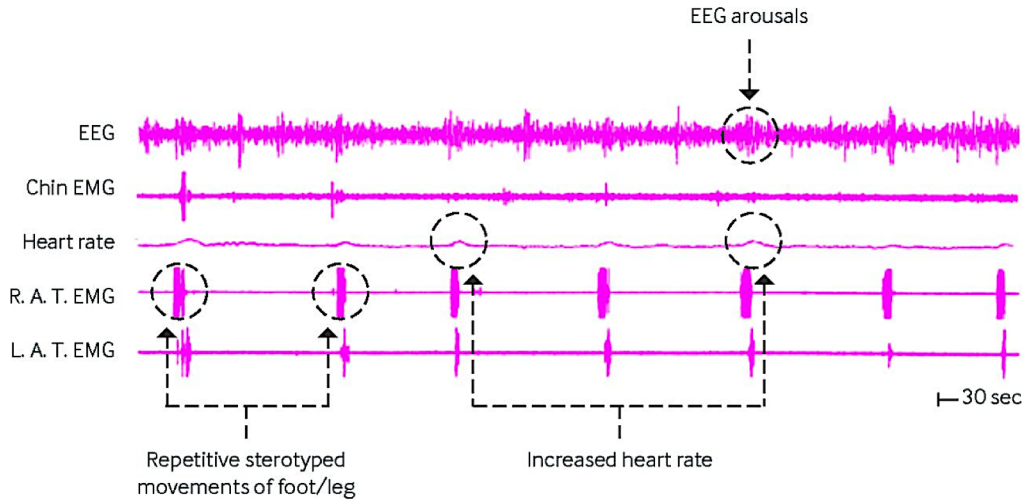
- Supportive features
  - Associated with PLMS (70-90% with PLMS > 5/hr)
  - A family history of RLS
  - Response to dopaminergic therapy

CRE:Levente Gyori / shutterstock.com

Hening WA, et al. Sleep Med 2009; 10: 976-81

Periodic limb movement in sleep

- PLMS
  - periodic episodes of repetitive, highly stereotyped limb movements during sleep
  - mostly occur in the lower extremities
  - may be associated with
    - **Cortical (EEG) arousals**
    - **Autonomic arousals**
      - measured by significant HR and BP surges
      - more frequent than cortical arousals
      - A mechanism for possible increased cardiovascular and cerebrovascular disease risk



Garcia-Borreguero D, et al. Circulation 2011; 124: 1223-31

Koo BB, et al. Circulation 2011; 124: 1223-31

Koo DL, et al. Journal of Stroke 2018;20(1):12-32

RLS/PLMS and Stroke

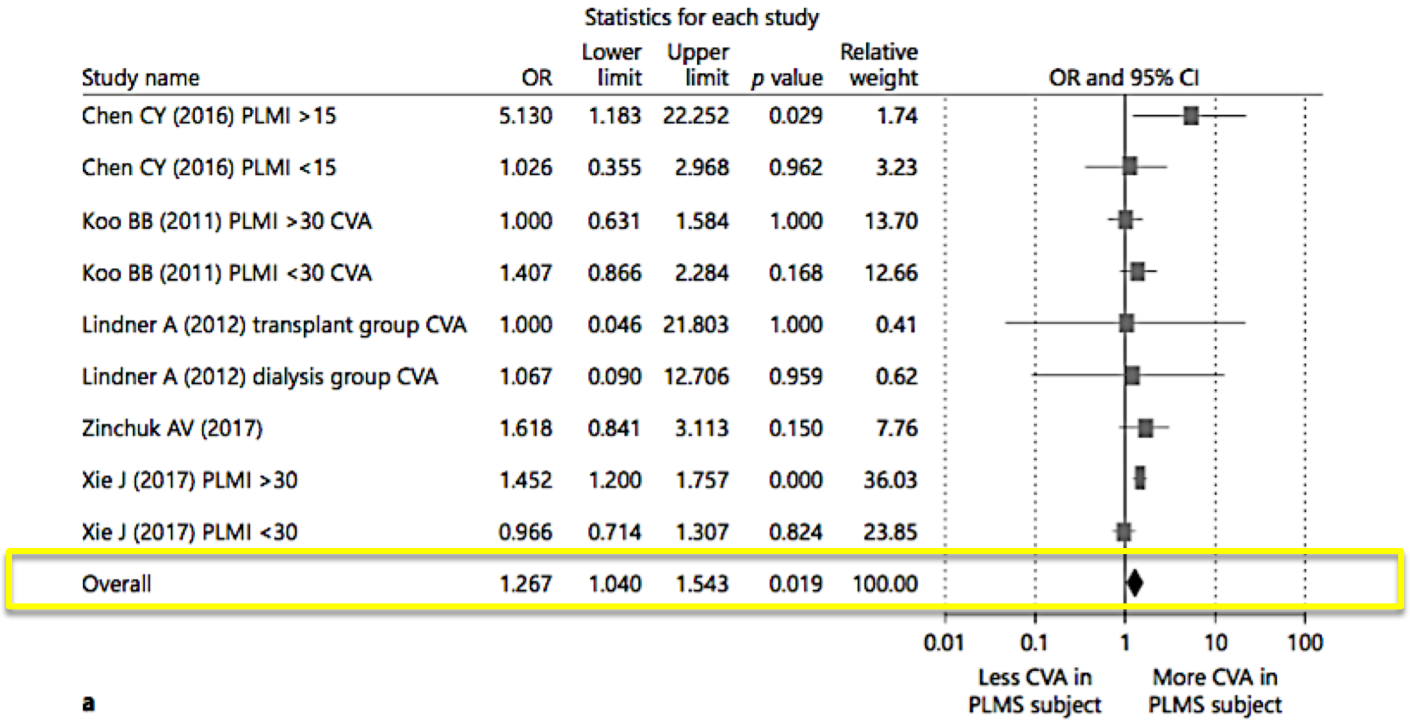
- Multiple clinic-based and population-based studies have shown an increased prevalence of **mood and anxiety disorders** in individuals with RLS.

- Large population-based studies have found positive associations between RLS and **cardiovascular disease, including stroke**. **Repetitive surges in heart rate and blood pressure associated with PLMS** are a potential mediator in the physiology of these relationships.

Earley CJ et al. Sleep Med 2010; 11: 807-15

Ferini-Strambi L et al. J Neurol 2014; 261: 1051-68

Is RLS/PLMS an independent risk factor of stroke?



Study name	OR	Lower limit	Upper limit	*p* value	Relative weight
Chen CY (2016) PLMI >15	5.130	1.183	22.252	0.029	1.74
Chen CY (2016) PLMI <15	1.026	0.355	2.968	0.962	3.23
Koo BB (2011) PLMI >30 CVA	1.000	0.631	1.584	1.000	13.70
Koo BB (2011) PLMI <30 CVA	1.407	0.866	2.284	0.168	12.66
Lindner A (2012) transplant group CVA	1.000	0.046	21.803	1.000	0.41
Lindner A (2012) dialysis group CVA	1.067	0.090	12.706	0.959	0.62
Zinchuk AV (2017)	1.618	0.841	3.113	0.150	7.76
Xie J (2017) PLMI >30	1.452	1.200	1.757	0.000	36.03
Xie J (2017) PLMI <30	0.966	0.714	1.307	0.824	23.85
Overall	1.267	1.040	1.543	0.019	100.00

- An increased prevalence of stroke in patients with PLMS compared to controls (**OR 1.267**, within 8years of a diagnosis of PLMS) was found.

Lin TC, et al. Cerebrovasc Dis 2018; 46: 1–9

Is RLS/PLMS an independent risk factor of stroke?

- Current evidence does not suggest an increased risk of stroke in patients with RLS.

- **PLMS may represent an independent risk factor for stroke**.

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Does treatment of RLS/PLMS prevent stroke?

- No systematic reviews were found.
- No primary studies were found.

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Conclusions

- OSA increases the risk of stroke and worsens its outcome.
- CPAP possibly has a favorable effect on both
  - stroke risk
    - primary prevention
  - outcome
    - improved stroke recovery in the short term
    - reduce risk of recurrent stroke in long term (secondary prevention)
- Non-apnea sleep disorders, such as insomnia, PLMS may be associated with an increased stroke risk and a worse outcome.
- Evidence suggests a bidirectional relationship between sleep and stroke.
- The pathophysiological base of the associations and the possibilities of improving prevention and outcome through sleep-related interventions require further evaluation.