Sleep Disorders in Patients with Chronic Kidney Disease

Istvan Mucsi
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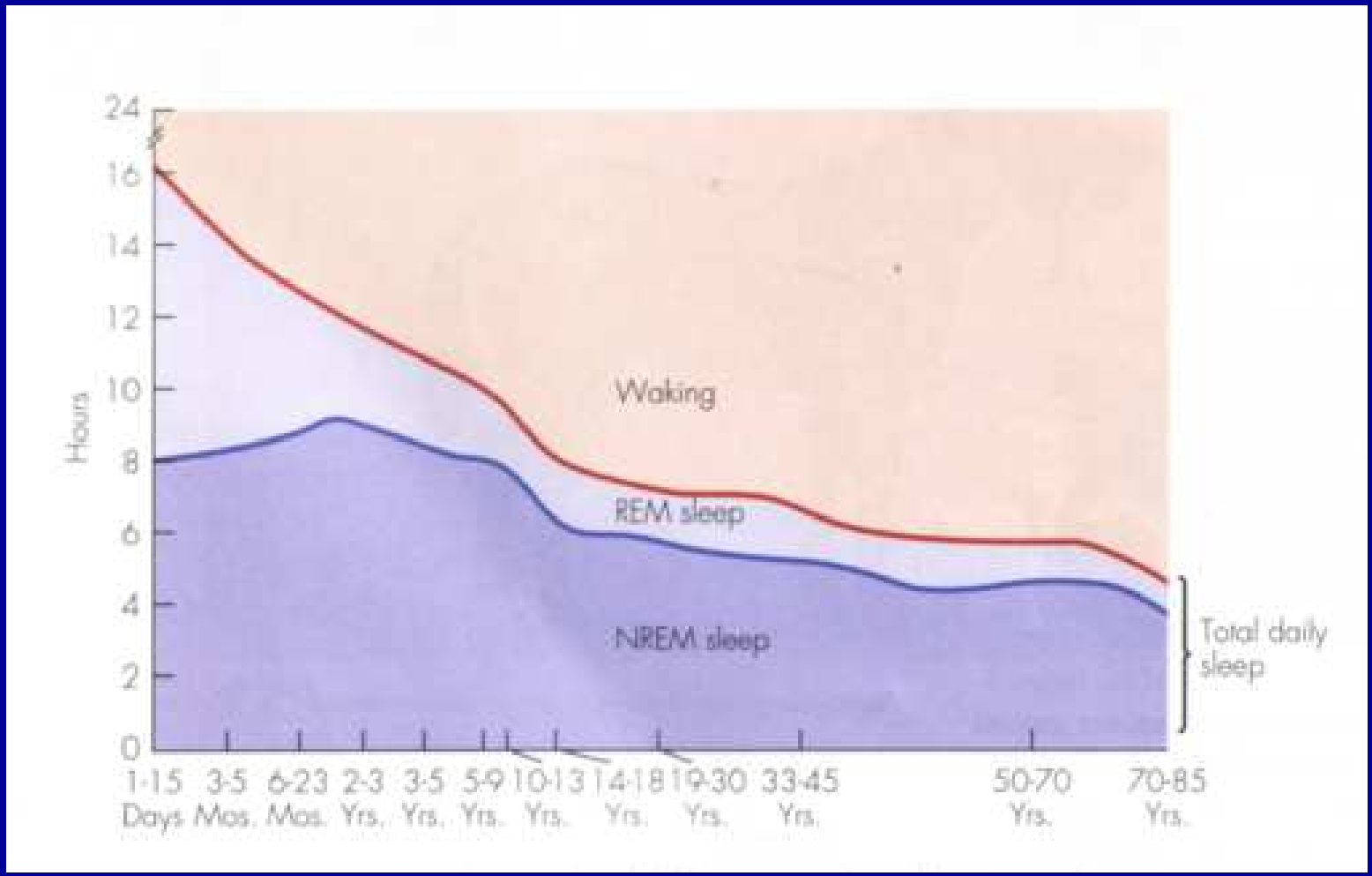
University of Toronto, Canada

Why sleep?

My wife is a sleep specialist …

- Sleep – significance
- Sleep disorders in CKD

- Restless legs syndrome (RLS)/Periodic leg movements in sleep (PLMS)
- Sleep disordered breathing - Obstructive sleep apnea syndrome (OSAS)

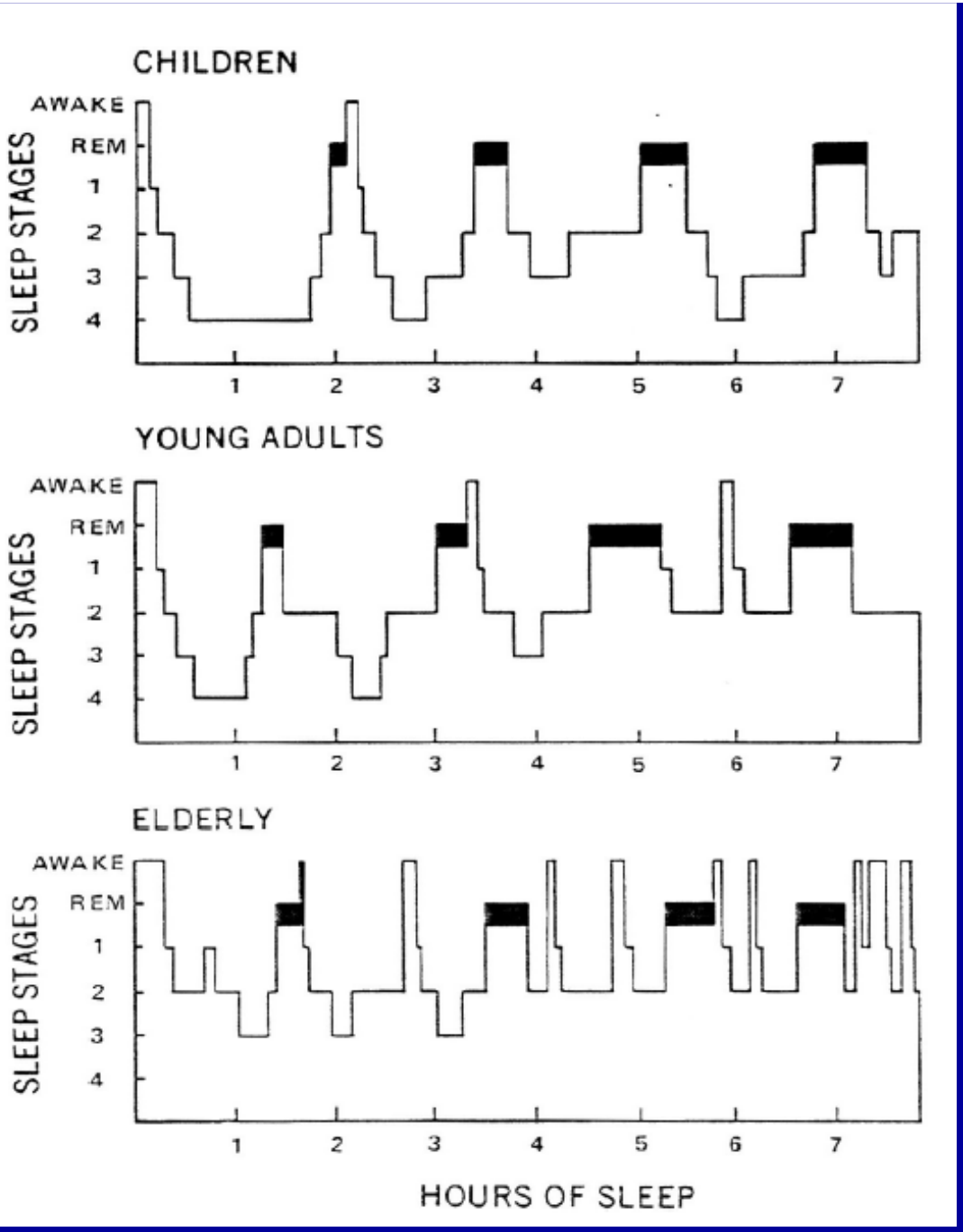

24
16
14
12
10
8
6
4
2
0
Hours
Waking
REM sleep
NREM sleep
Total daily sleep
1-15 Days
3-5 Mos.
6-23 Mos.
2-3 Yrs.
3-5 Yrs.
5-9 Yrs.
10-13 Yrs.
14-18 Yrs.
19-30 Yrs.
33-45 Yrs.
50-70 Yrs.
70-85 Yrs.

Why do we sleep?

Repair and Restoration Theory

- sleep enables the body and brain to repair after activity during the day – homeostatic balance
- memory

- Sleep deprivation leads to irritability, impaired concentration and hallucinations



C. R. Soldatos & T. J. Paparrigopoulos

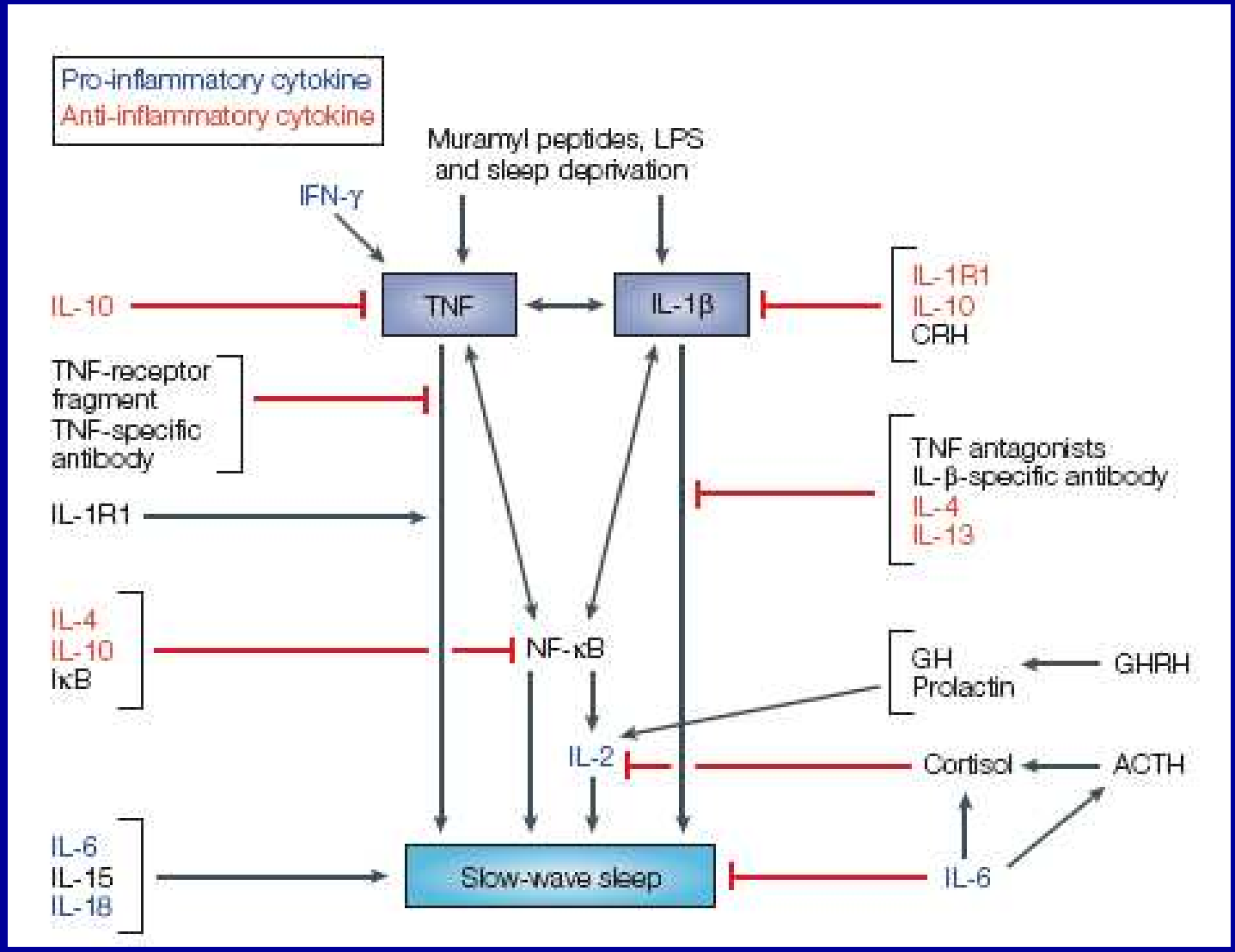
International Review of Psychiatry, August 2005; 17(4): 213–228

Consequences of Chronic Sleep Deprivation

Sleep is a vital and necessary function, and sleep needs (like hunger and thirst) must be met.

- 40-70 million Americans experience either chronic or intermittent sleep-related problems
- Untreated sleep disorders have a profound impact nationally in terms of reduced quality of life, lower productivity, increased morbidity and mortality, and decreased public safety
- Lack of awareness among health care professionals and the public

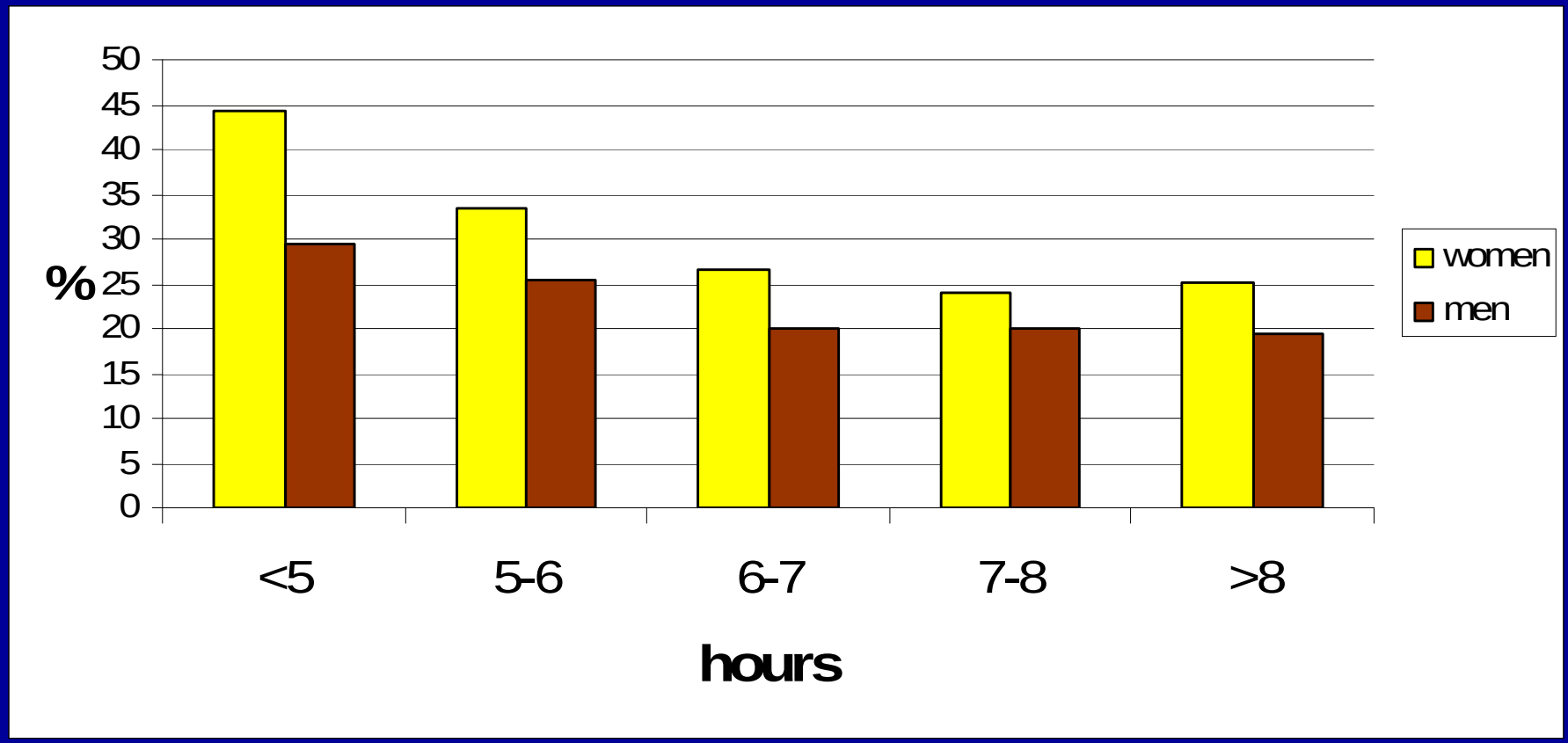
Cytokines and sleep



Sleep and the Cardiovascular System

- Sleep deprivation increases concentrations of cytokines and C-reactive protein
- This inflammation can lead to endothelial damage, leading to possible stroke or heart disease
- Blood pressure and heart rate are higher following sleep deprived nights (Voelker, 1999)
- Sleep deprivation increases risk of heart disease in women (Josefson, 2003)

SLEEP TIME AND HYPRTENSION




Sleep in CKD

Sleep disorders in CKD – why is it important?

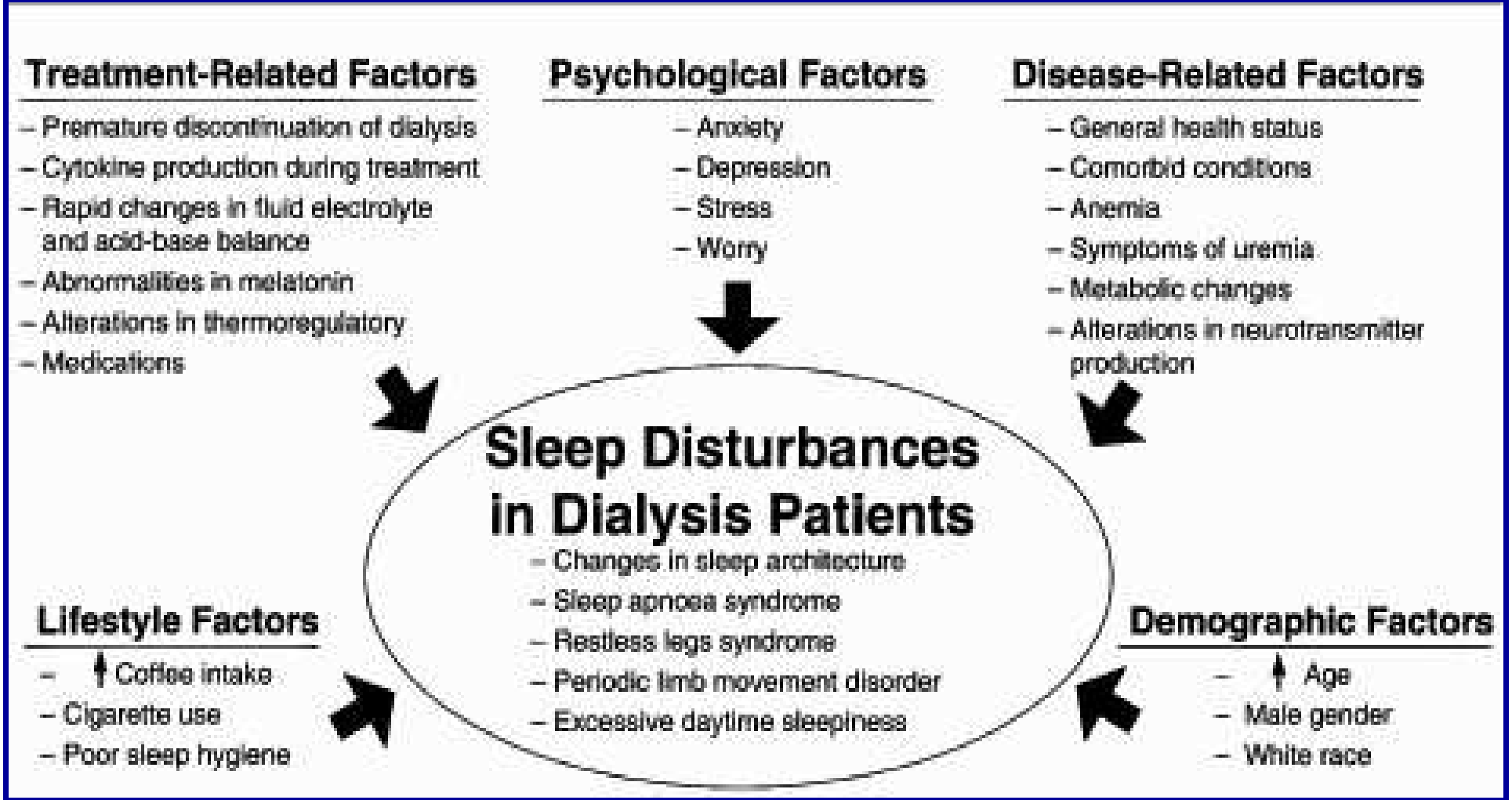
- Sleep problems are one of the most common complaints of patients in the dialysis unit
- Sleep Apnea Syndrome (SAS) may contribute to the pathogenesis of hypertension, CV morbidity
- Sleep disorders may impair quality of life
- Poor sleep is a predictor of morbidity and mortality in this patient population
- Sleep disorders are treatable – successful treatment may improve clinical outcomes

Sleep disorders in dialysis patients (30-80%)

- Insomnia
  - 4-29% vs 15-70%
- Sleep apnea syndrome (SAS)
  - 2-4% vs 20-70%
- Restless legs syndrome (RLS)
  - 5-15% vs 15-80%

Little is known about sleep problems in „predialysis” and transplanted patients

Factors contributing to sleep disturbances in patients on dialysis



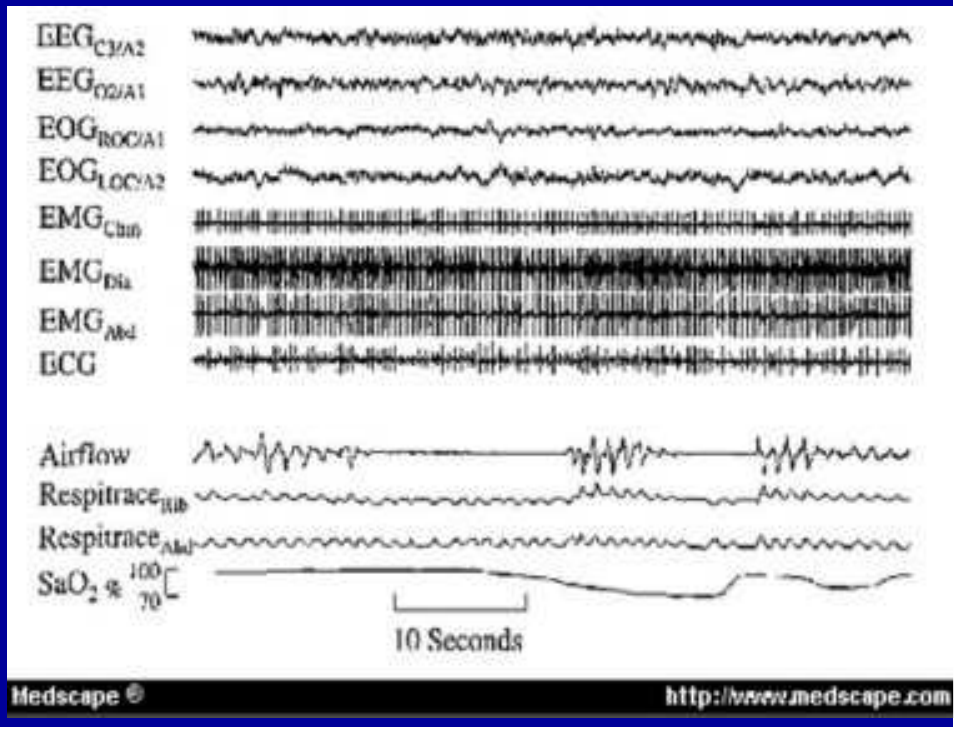
K. Parker., Sleep Medicine Reviews, Vol. 7, No. 2, pp 131-143, 2003

Diagnostic tools to detect sleep problems

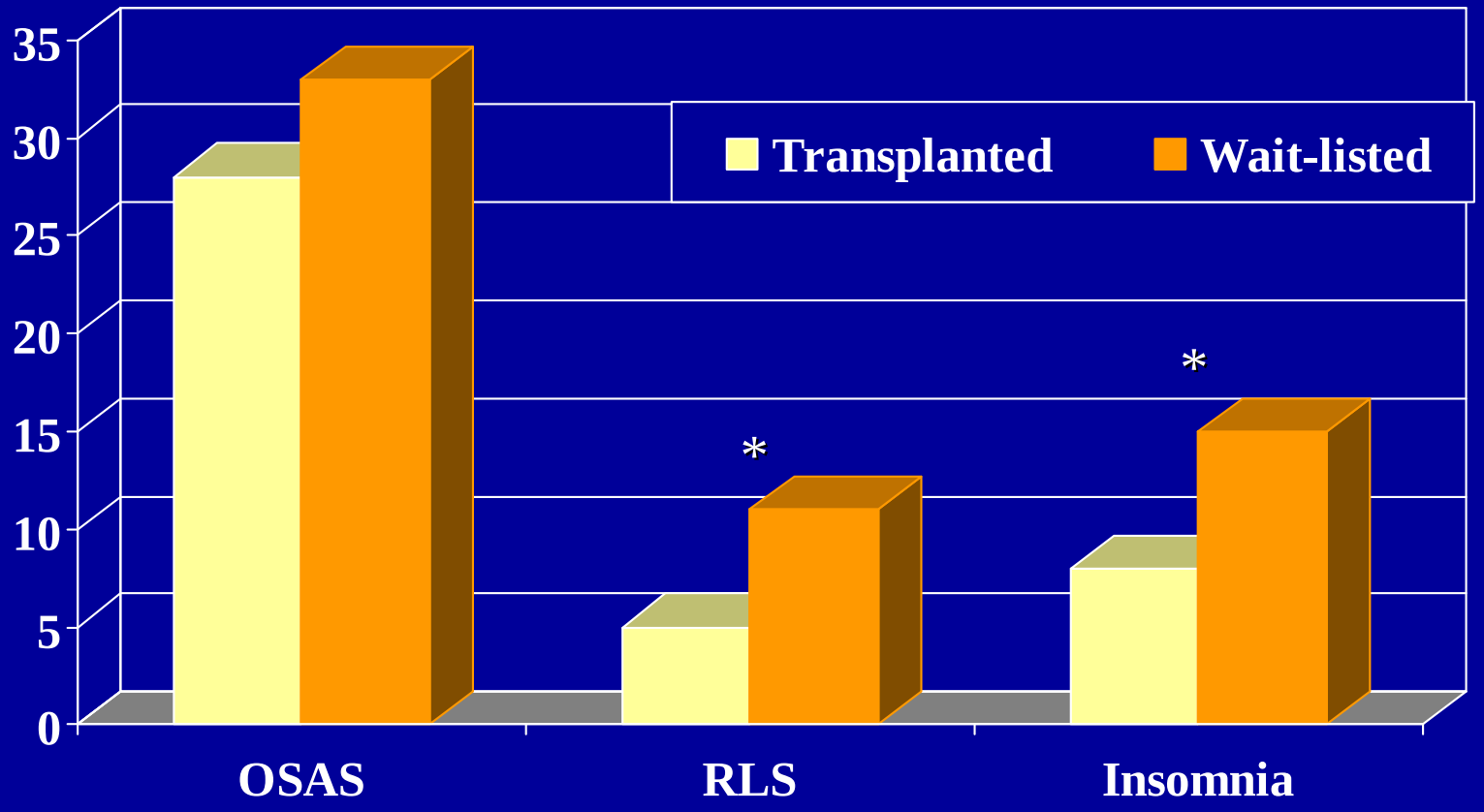
- Clinical interview
- Sleep diaries
- Self administered questionnaires
  - Insomnia: Pittsburgh Sleep Quality Index, Athen Insomnia Scale
  - SAS: Berlin Questionnaire
  - RLS: Restless Legs Syndrome Questionnaire
  - Epworth Sleepiness Scale
- Actigraphy
- Polysomnography (SAS, PLMS)
  - MSLT, MWT – daytime effects

Polysomnography

- neurophysiologic variables (electrooculography, EEG, submental myogram) – sleep stages
- Measurment of resp. effort
- Art. O2 sat., pCO2 – transdermal pulsoxymetry
- ECG
- Limb movements

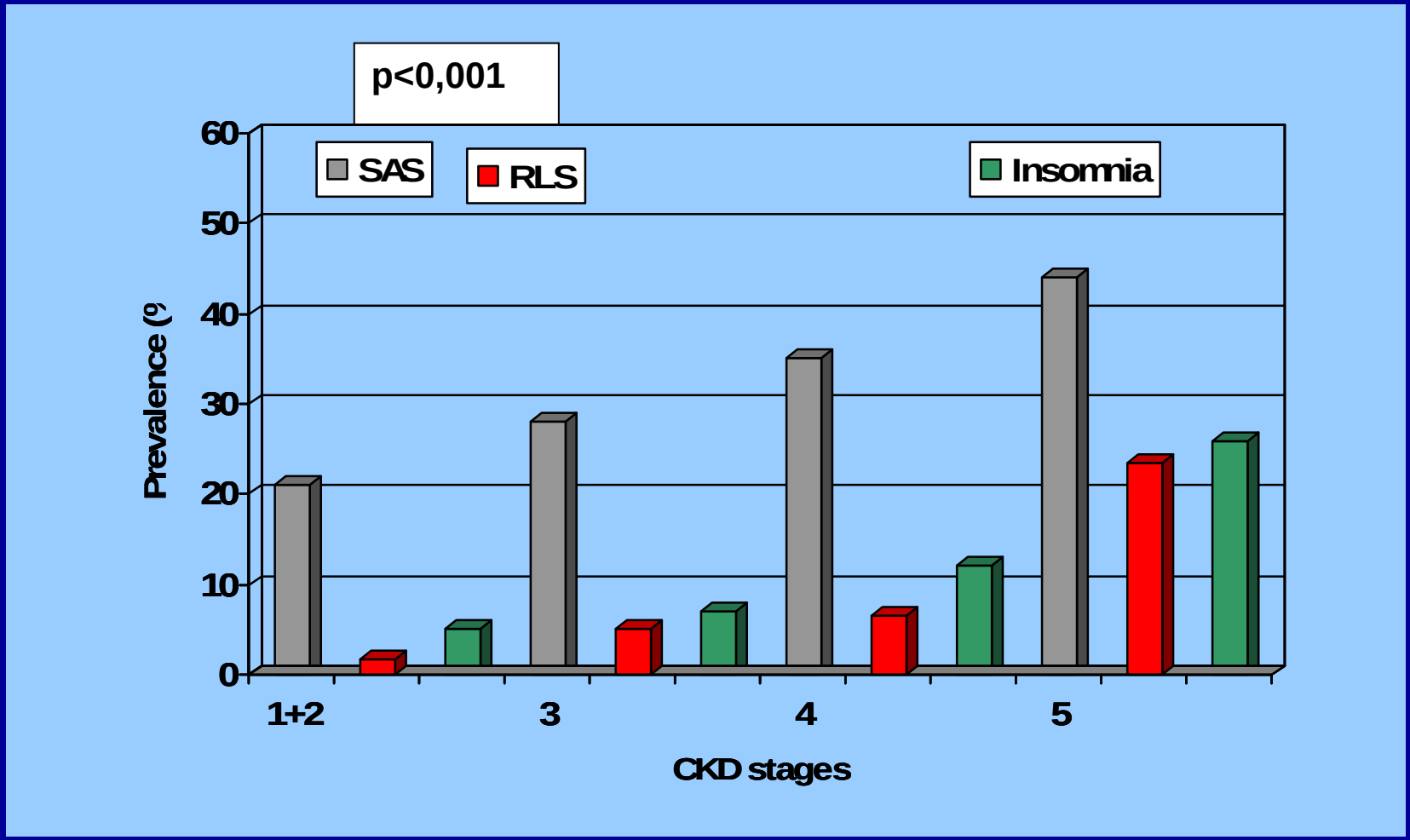


Prevalence of sleep disorders in Hungarian dialysis and transplanted patients



*: P<0.001, Khi-square test

Sleep problems and renal function in transplant patients (n=920)

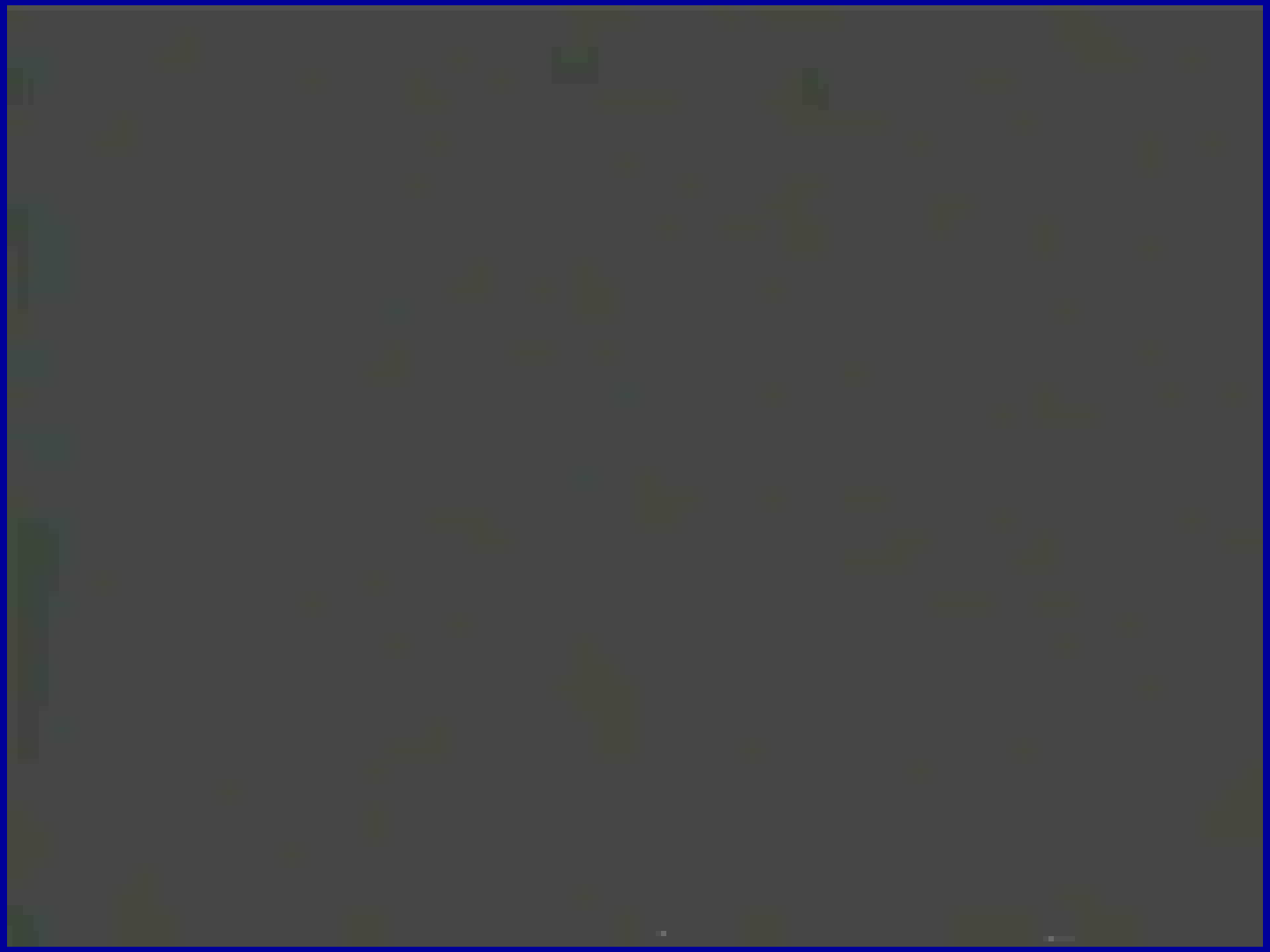



Restless legs syndrome

Restless legs syndrome (RLS)

- Restless legs syndrome (RLS) is characterized by an urge to move the legs that is often hard to resist and is usually but not always associated with disagreeable leg sensations
- Main symptoms:
  - 1. An urge to move the legs, usually accompanied or caused by uncomfortable and unpleasant sensations in the legs.
  - 2. The unpleasant sensations begin or worsen during rest or inactivity
  - 3. The unpleasant sensations are partially or totally relieved by movement
  - 4. The unpleasant sensations are worse in the evening or night than during the day or only occur in the evening or night

RLS



Restless Legs Syndrome

Predictors, etiology

- Altered CNS dopamin metabolism
- Iron deficiency (cerebral versus peripheral)
- Uremia – uremic toxins?
- Anemia
- Neuropathy

Consequences

- Fragmented sleep, „intitiation” insomnia
- Fatigue, tiredness
- Daytime sleepiness
- Impaired QoL
- Incr. mortality?

- Prevalence of RLS: 12-20% in dialysed[1,2] and 4.5% in kidney transplanted populations[3]
- RLS is associated with increased risk of

insomnia and impaired quality of life (QoL) in dialysed and transplanted patients[4]

[1] Winkelman et al. (1995)

[2] Mucsi et al. (2004)

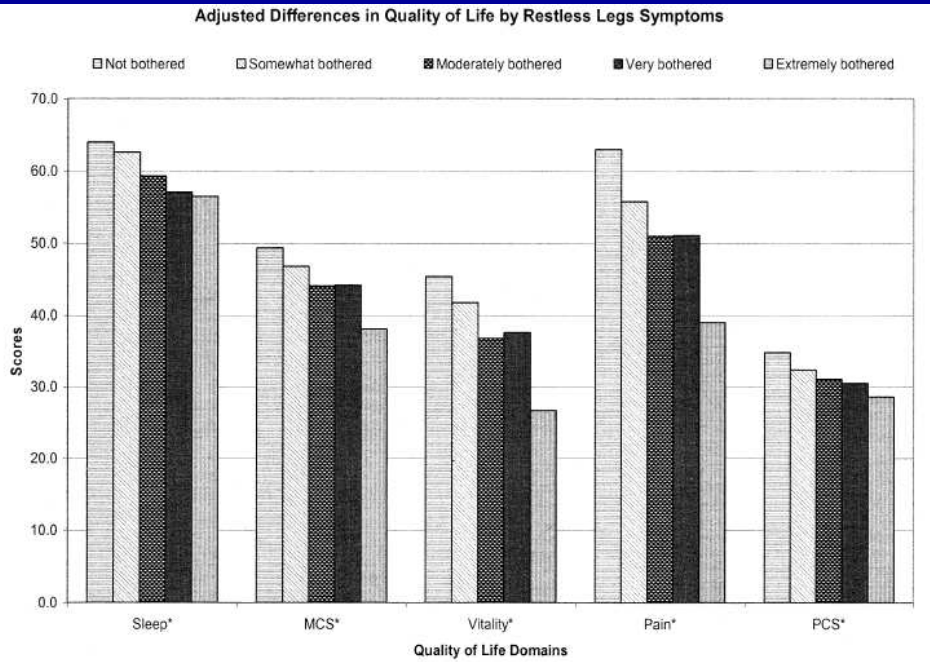
[3] Molnar et al. (2005)

[4] Unruh et al. (2004)

RLS in dialysis patients predicts mortality

Table 3. Adjusted Hazards of Severe Symptoms of Restless Legs and by Category of Restless Legs Symptom

	Severe Restless Legs Symptoms	Category of Restless Legs Symptom
Unadjusted hazard	1.31 (1.00-1.73)	1.06 (0.97-1.15)
Model 1, adjusted for age and race	1.42 (1.07-1.87)	1.07 (0.98-1.16)
Model 2, model 1 and adjusted for ICED, Karnofsky	1.39 (1.05-1.84)	1.06 (0.98-1.16)
Model 3, model 2 adjusted for clustering of clinics	1.39 (1.08-1.79)	1.06 (0.98-1.16)



of restless legs symptom adjusted for age, race, sex, dialysis mode, insulin- index, Karnofsky Index, and center. *All $P < 0.0001$ for adjusted comparison of ptoms of restless legs.

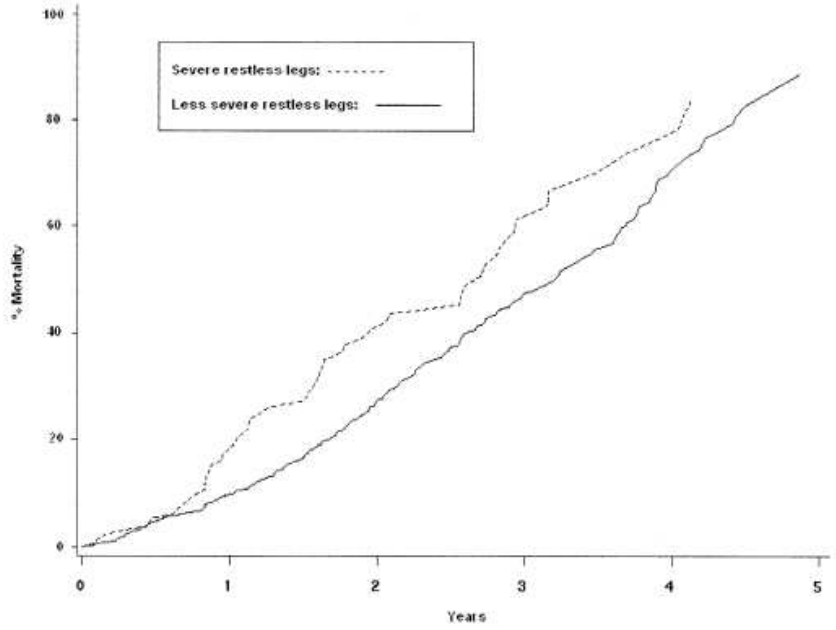
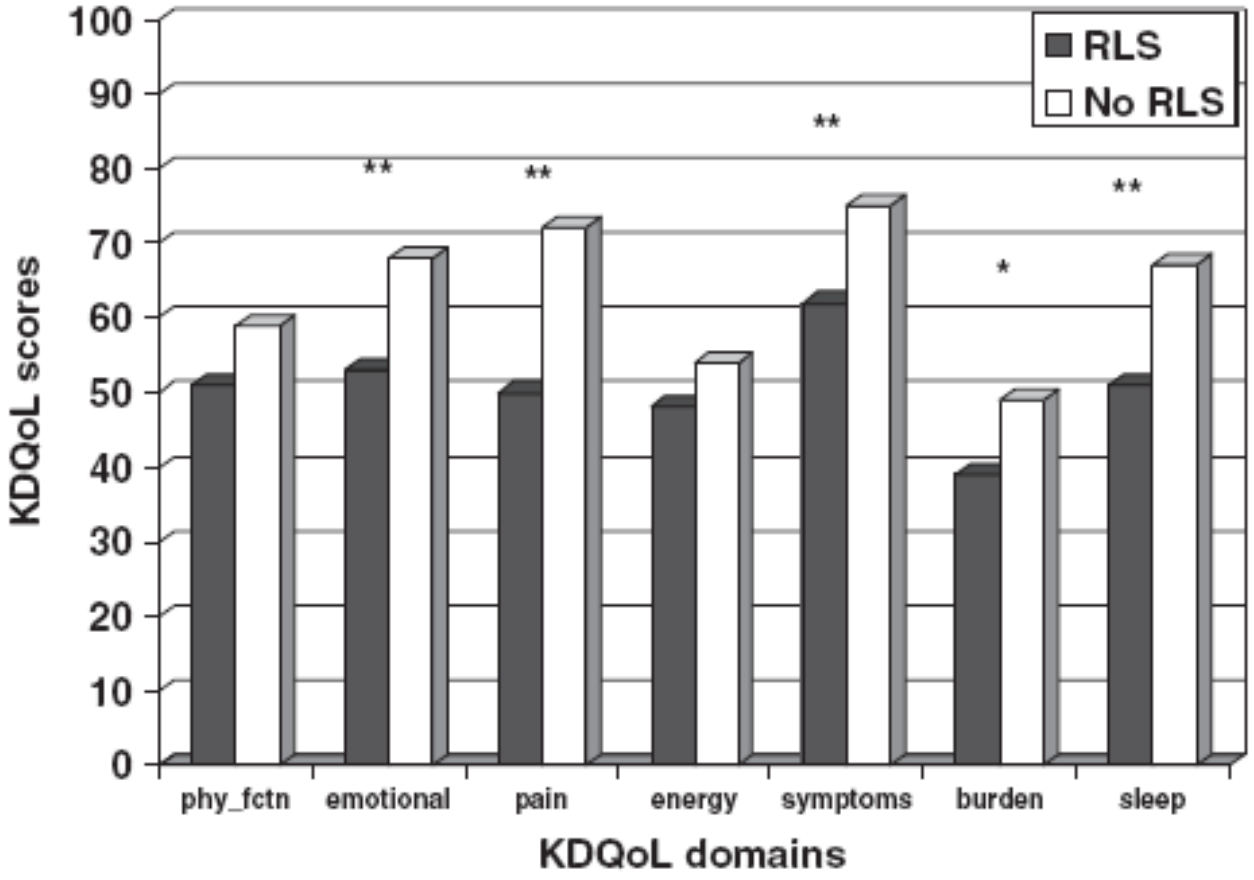


Fig 2. Crude cumulative mortality according to severe symptoms of restless legs.

Unruh et al; AJKD; 2004

Restless legs syndrome, insomnia and quality of life in patients on maintenance dialysis

Istvan Mucsi[1–3], Miklos Zsolt Molnar[1,2,4], Csaba Ambrus[2,4], Lilla Szeifert[1], Agnes Zsofia Kovacs[1], Rezső Zoller[1], Szabolcs Barótfi[1], Adam Remport[5] and Marta Novak[1,6]



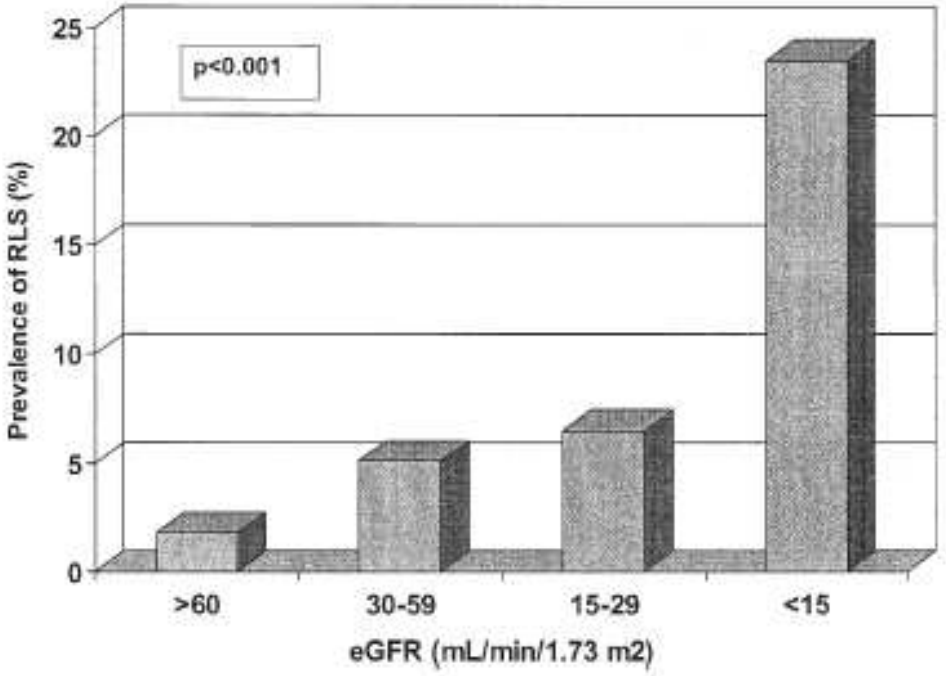
Nephrol Dial Transplant (2005) 20: 571–577

Restless Legs Syndrome in Patients After Renal Transplantation

Miklos Zsolt Molnar, MD, Marta Novak, MD, Csaba Ambrus, MD, Lilla Szeifert, Agnes Kovacs, Judit Pap, Adam Remport, MD, and Istvan Mucsi, MD, PhD

Table 2. Characteristics of Patients With or Without RLS in the Tx Group

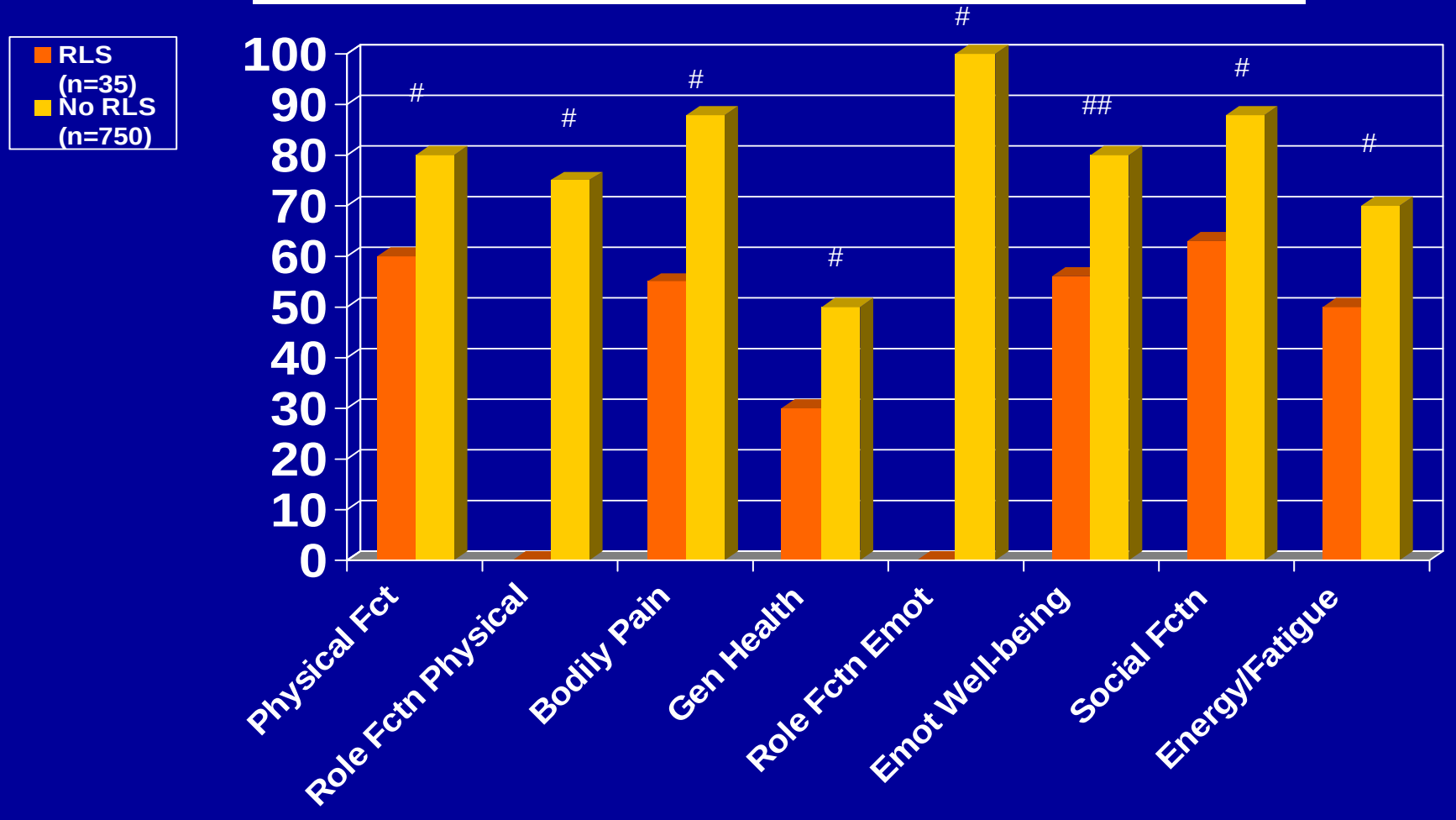
	RLS (n = 39)	No RLS (n = 777)	*P*
Age (y)	51 ± 11	48 ± 13	NS
Male	59	59	NS
eGFR (mL/min)	42 ± 19	50 ± 23	<0.05
Number of comorbid conditions, median (range)	3 (0-7)	2 (0-7)	<0.05
Immunosuppressive drugs			
Steroids	74	87	<0.05
Cyclosporin A	77	69	NS
Tacrolimus	18	18	NS
Mycophenolate mofetil	56	64	NS
Imuran	13	12	NS
Diabetes	11	17	NS
Serum albumin (g/dL)	4.08 ± 0.37	4.16 ± 0.33	NS
Serum phosphorus (mg/dL)	3.4 ± 1.3	3.4 ± 0.8	NS
Serum Hb (g/dL)	12.7 ± 2.0	13.3 ± 1.9	<0.05
Serum transferrin (mg/dL)	243 ± 52	247 ± 52	NS
Iron deficiency TSAT<20%	26	11	<0.05
Time since transplantation (mo)	69 ± 53	58 ± 45	NS



American Journal of Kidney Diseases, Vol 45, No 2 (February), 2005: pp 388–396

Restless legs syndrome, insomnia, and quality of life after renal transplantation

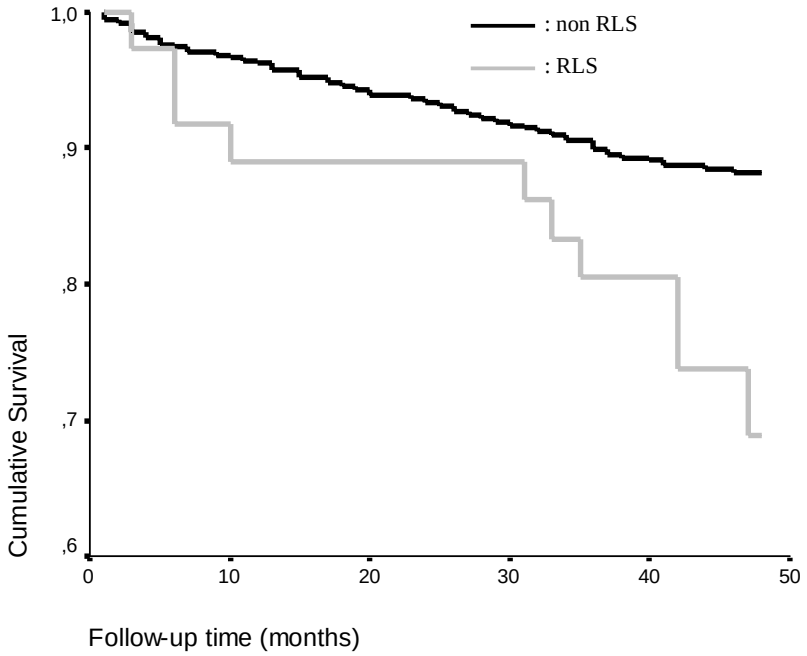
Miklos Zsolt Molnar[a,b,c], Marta Novak[a,d], Lilla Szeifert[a], Csaba Ambrus[b,c], Andras Keszei[e], Agnes Koczy[a], Anett Lindner[a], Szabolcs Barotfi[f], Andras Szentkiralyi[a], Adam Remport[g], Istvan Mucsi[a,c,h,*]



Journal of Psychosomatic Research 63 (2007) 591–597

Restless Legs Syndrome and Mortality in Kidney Transplant Recipients

Miklos Zsolt Molnar, MD, PhD,[1,2,3] Andras Szentkiralyi, MD,[1] Anett Lindner, MD,[1] Maria Eszter Czira, MD,[1] Lilla Szeifert, MD,[1] Agnes Zsofia Kovacs, MD,[1] Katalin Fornadi, MD,[4] Andras Szabo, MD, DSc,[5] Laszlo Rosivall, MD, DSc,[6] Istvan Mucsi, MD, PhD,[1,2,6,7] and Marta Novak, MD, PhD[1,8]



Multivariate Cox-modell

	Mortality		
	HR	**95% CI**	**p**
Presence of RLS	**2**	**1.03-3.95**	**0.04**

Adjusted for: age, gender, eGFR, albumin, hemoglobin, CRP, diabetes, hypertonia and transplant vintage

American Journal of Kidney Diseases, Vol 50, No 5 (November), 2007: pp 813-820

Clinical management of RLS in CKD

- Adequate dialysis/ renal transplantation
- Iv iron/ anemia management (Dose?)
- Drugs
  - Ropirinole, pramipexole, carbidopa/levodopa,
  - Benzodiazepines - efficacy??
  - Gabapentin, carbamazepine – efficacy??


OSAS

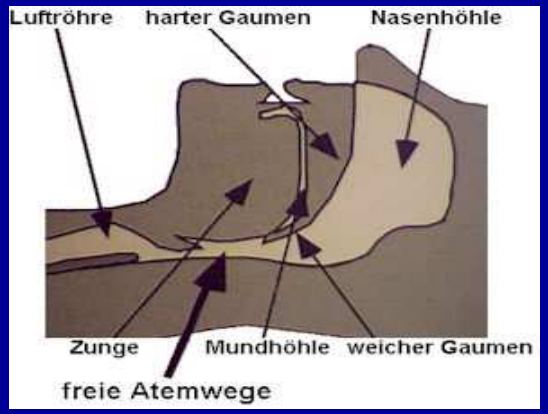
Sleep apnea syndrome

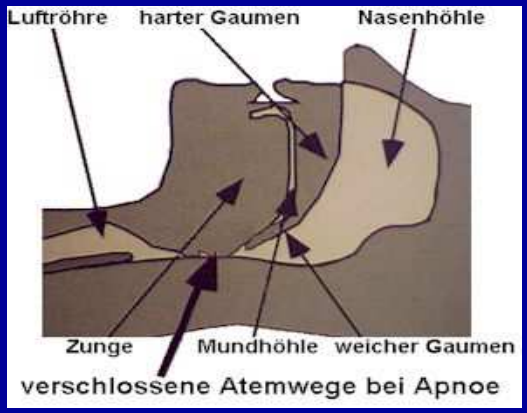
- intermittent episodes of breathing cessation during sleep,
  - airway collapse (obstructive sleep apnoea, OSA)
  - cessation of respiratory effort (central SA)
  - or both (mixed SA)
- The severity of the SAS is usually characterized by the number of apneic events per hour of sleep (AHI, RDI) (RDI>5 is considered pathological), severity of desaturation and by the presence and severity of daytime sleepiness.
- SAS is associated with disturbances of sleep initiation and maintenance as well as daytime sleepiness.
- A potential link is suggested between SAS and HTN, CAD, CHF and arrhytmias

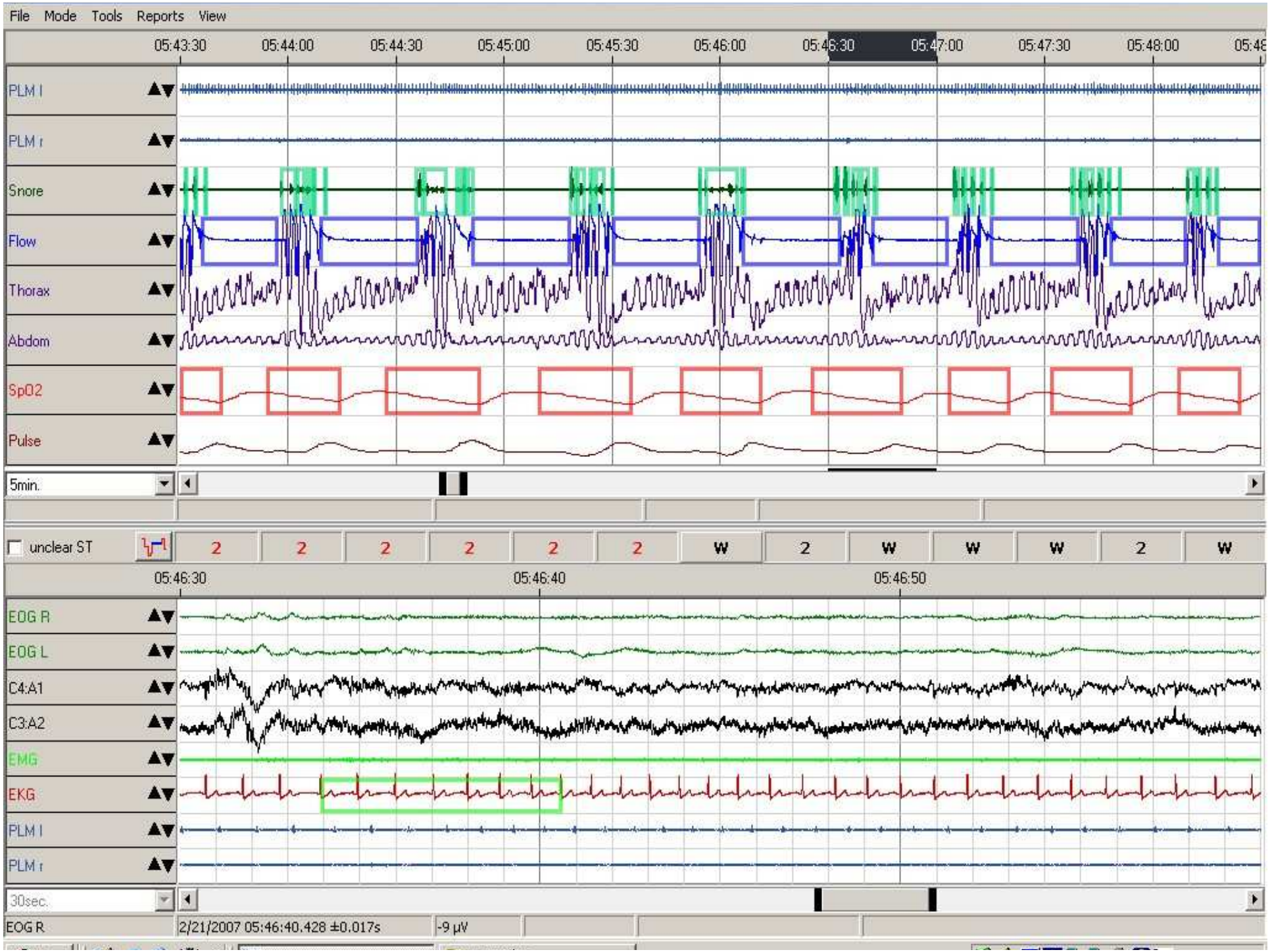
OSAS

- Upper airway obstruction
- Anatomical problems
- Decreased muscle tone ↓
  +
  weakness of pharyngeal wall

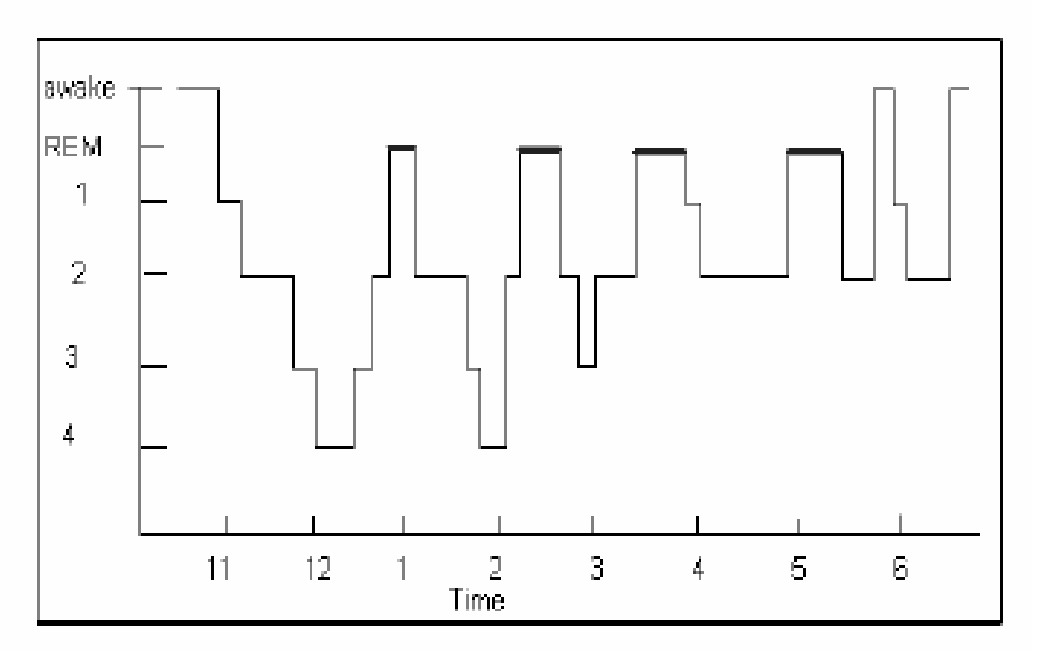
} Dynamic collapse during inspiration

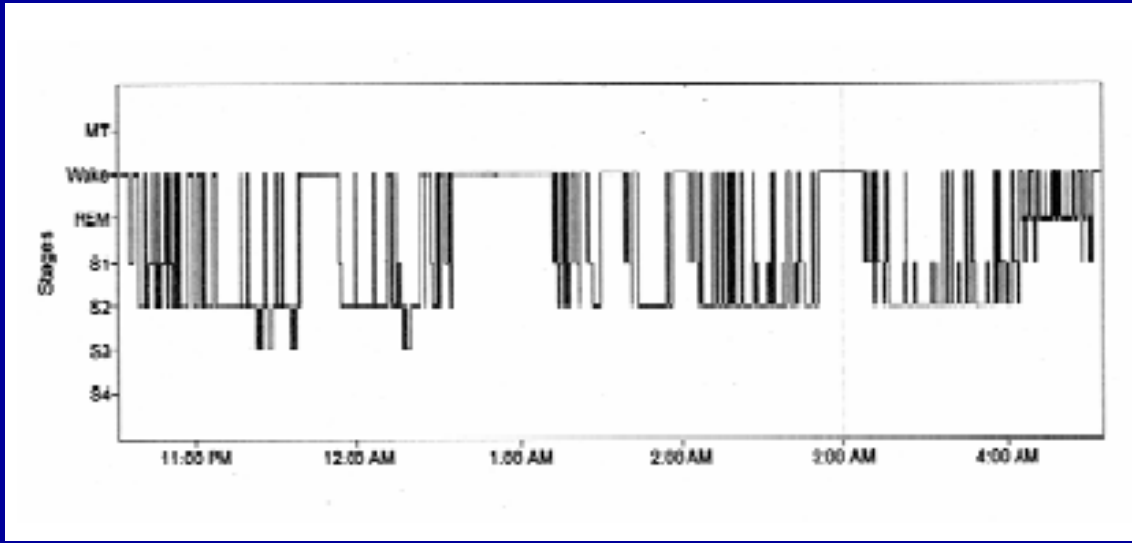





File Mode Tools Reports View
05:43:30
05:44:00
05:44:30
05:45:00
05:45:30
05:46:00
05:46:30
05:47:00
05:47:30
05:48:00
PLM l
PLM r
Snore
Flow
Thorax
Abdom
SpO2
Pulse
5min.
unclear ST
2 2 2 2 2 2 W 2 W W W 2 W
05:46:30
05:46:40
05:46:50
EOG R
EOG L
C4:A1
C3:A2
EMG
EKG
PLM l
PLM r
30sec.
EOG R
2/21/2007 05:46:40.428 ±0.017s
-9 µV

Apnea leads to micro-arousals and fragmented sleep





Sleep Apnoe Syndrome

Predictors, correlates

- Age
- Obesitas (BMI, neck circumference)
- Male gender/menopause
- Alcohol
- Uremic toxins?
- Anemia
- Altered metabolic state

Consequences

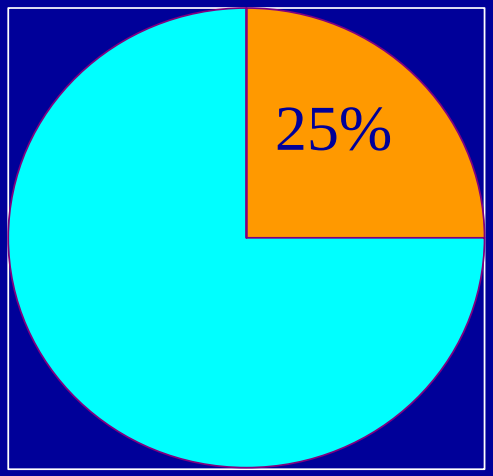
- Daytime seleepiness
- Accidents
- Cognitive impairment
- Depression
- Sexual dysfunction
- Hypertension, LVH, CAD, arrhytmias
- Impaired QoL
- Increased morbidity, mortality?

CKD specific factors potentially contributing to the pathogenesis of SAS

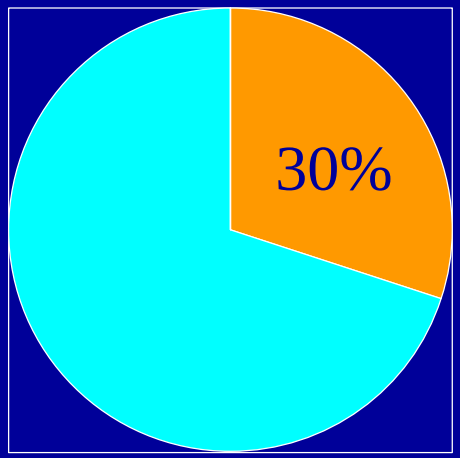
- Hypocapnia, acid-base disorders
- Uremic toxins – effects on CNS
- Soft tissue edemea
- Anemia
- Endocrine problems (menopause – gender difference)
- Dialysis modality (HD-cytokines, type of PD)

Prevalence of OSA in CV diseases

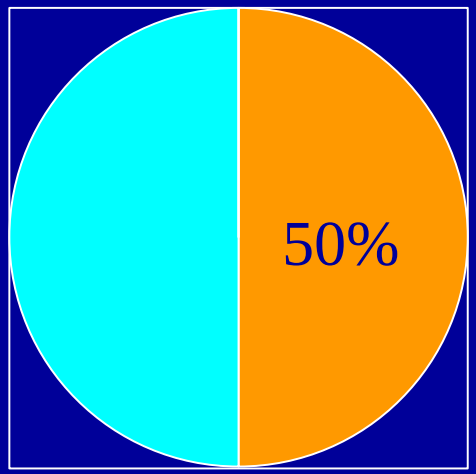
CHF



CAD



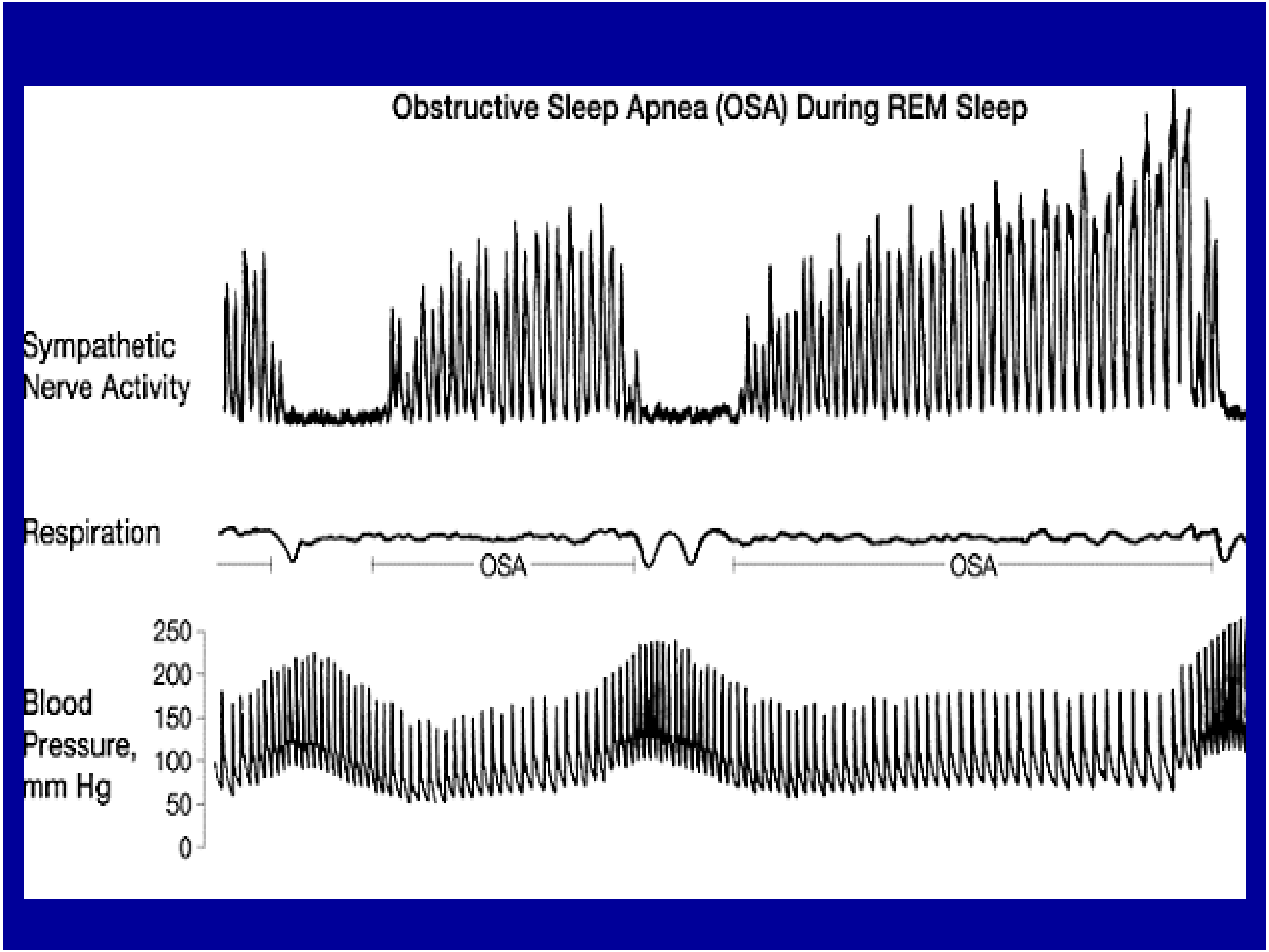
HTN

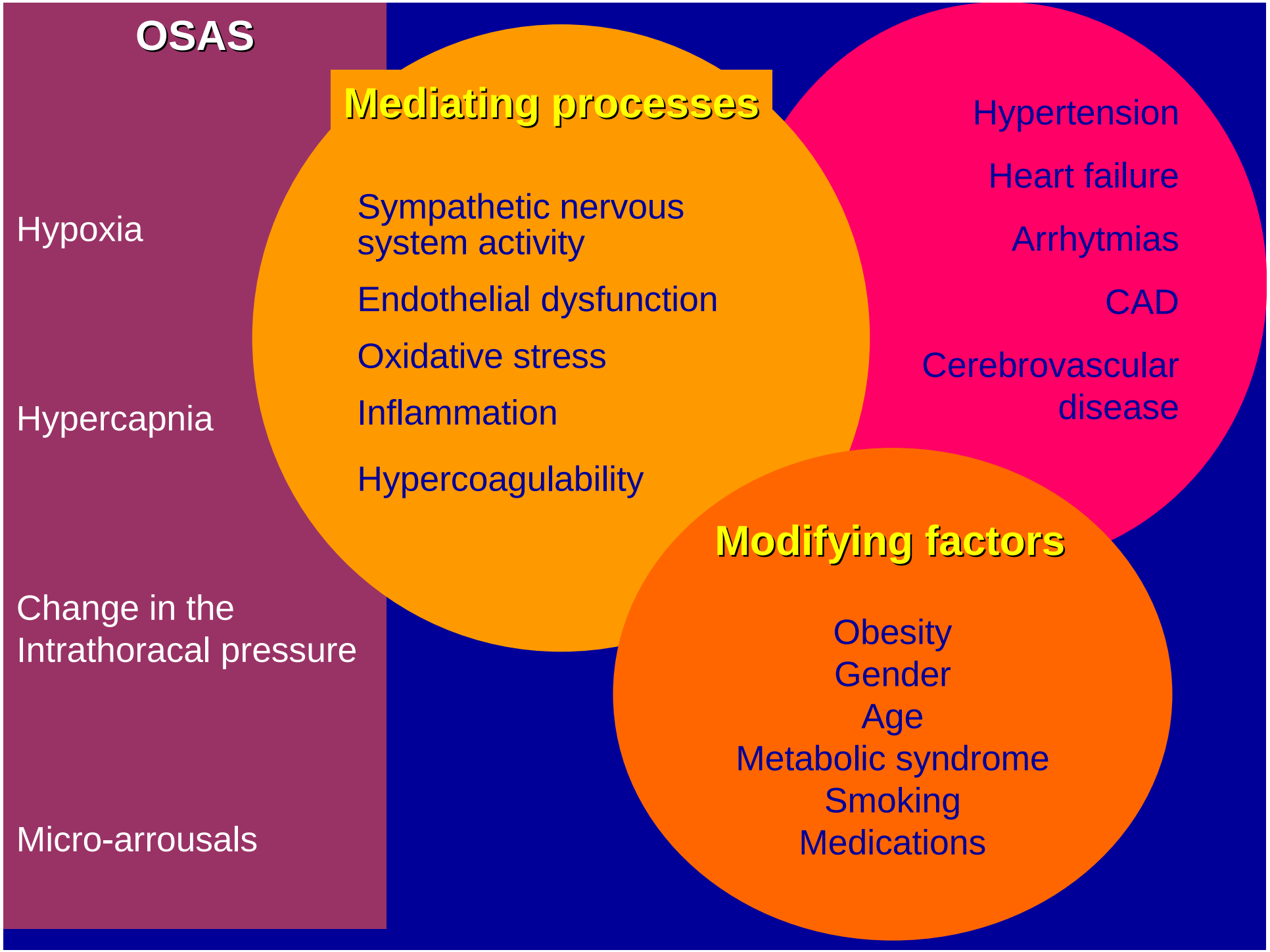


Physiologic non-REM sleep

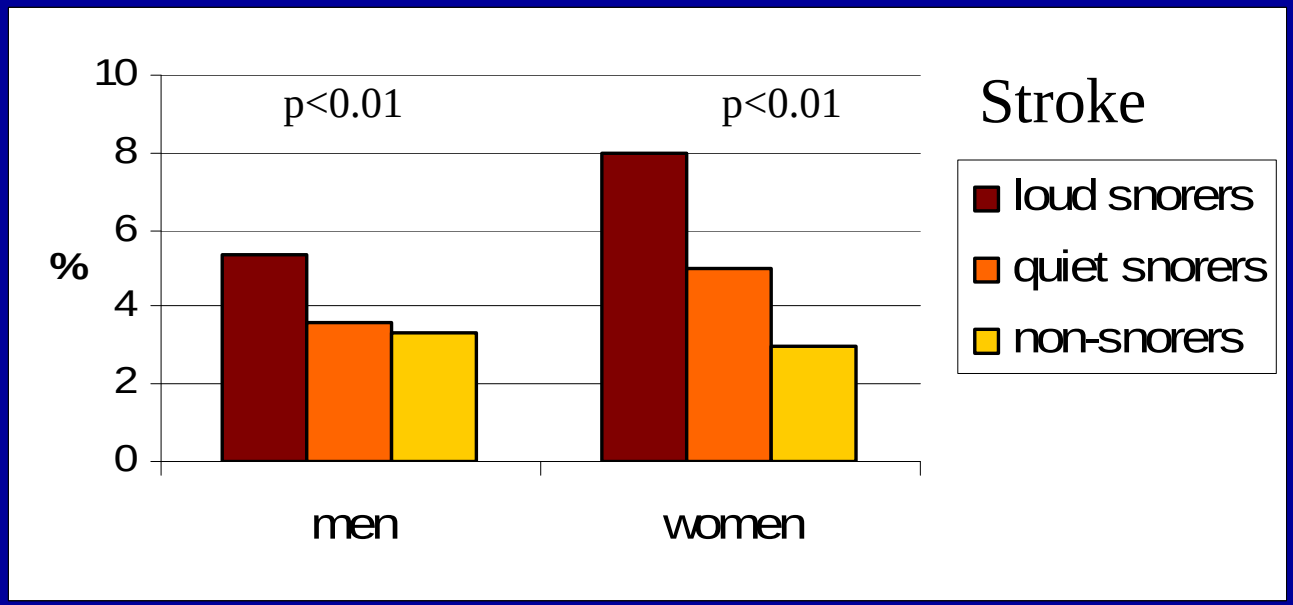
- Sympathetic nerve activity
- BP
- HR
- PVR
- Stroke volume

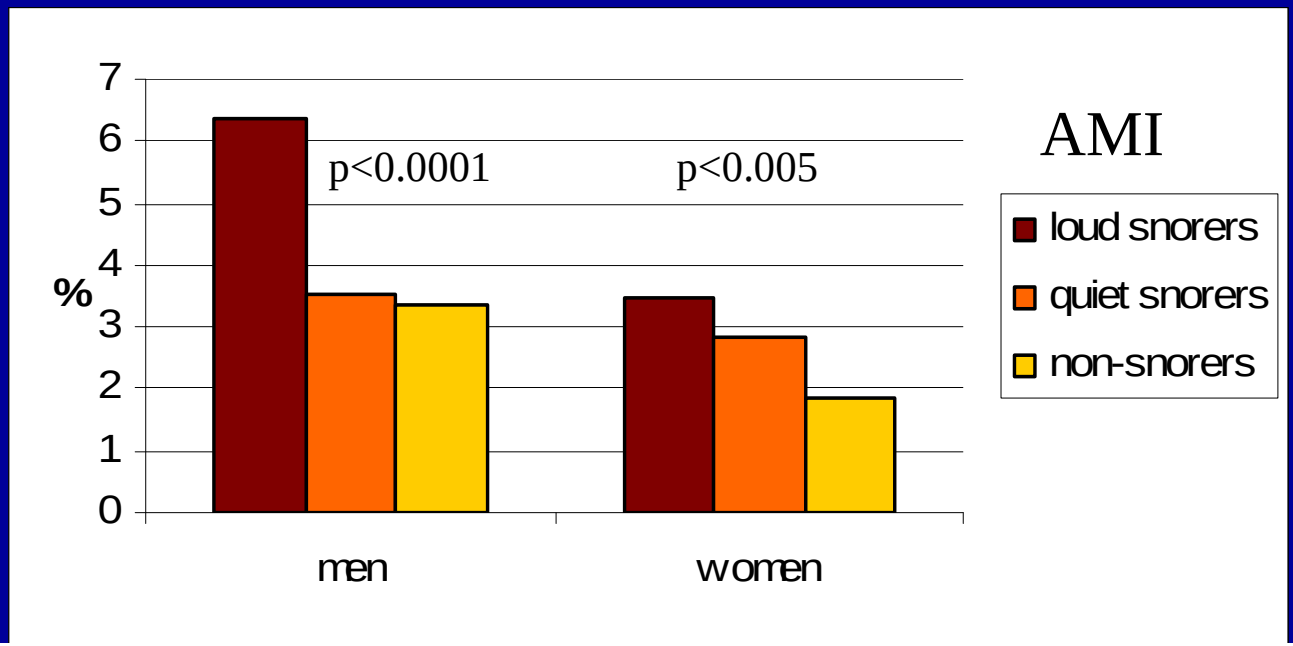
- Parasympathetic activity


Obstructive Sleep Apnea (OSA) During REM Sleep
Sympathetic Nerve Activity
Respiration
OSA
OSA
Blood Pressure, mm Hg
250
200
150
100
50
0


OSAS
Hypoxia
Hypercapnia
Change in the Intrathoracal pressure
Micro-arrousals
Mediating processes
Sympathetic nervous system activity
Endothelial dysfunction
Oxidative stress
Inflammation
Hypercoagulability
Hypertension
Heart failure
Arrhytmias
CAD
Cerebrovascular disease
Modifying factors
Obesity
Gender
Age
Metabolic syndrome
Smoking
Medications

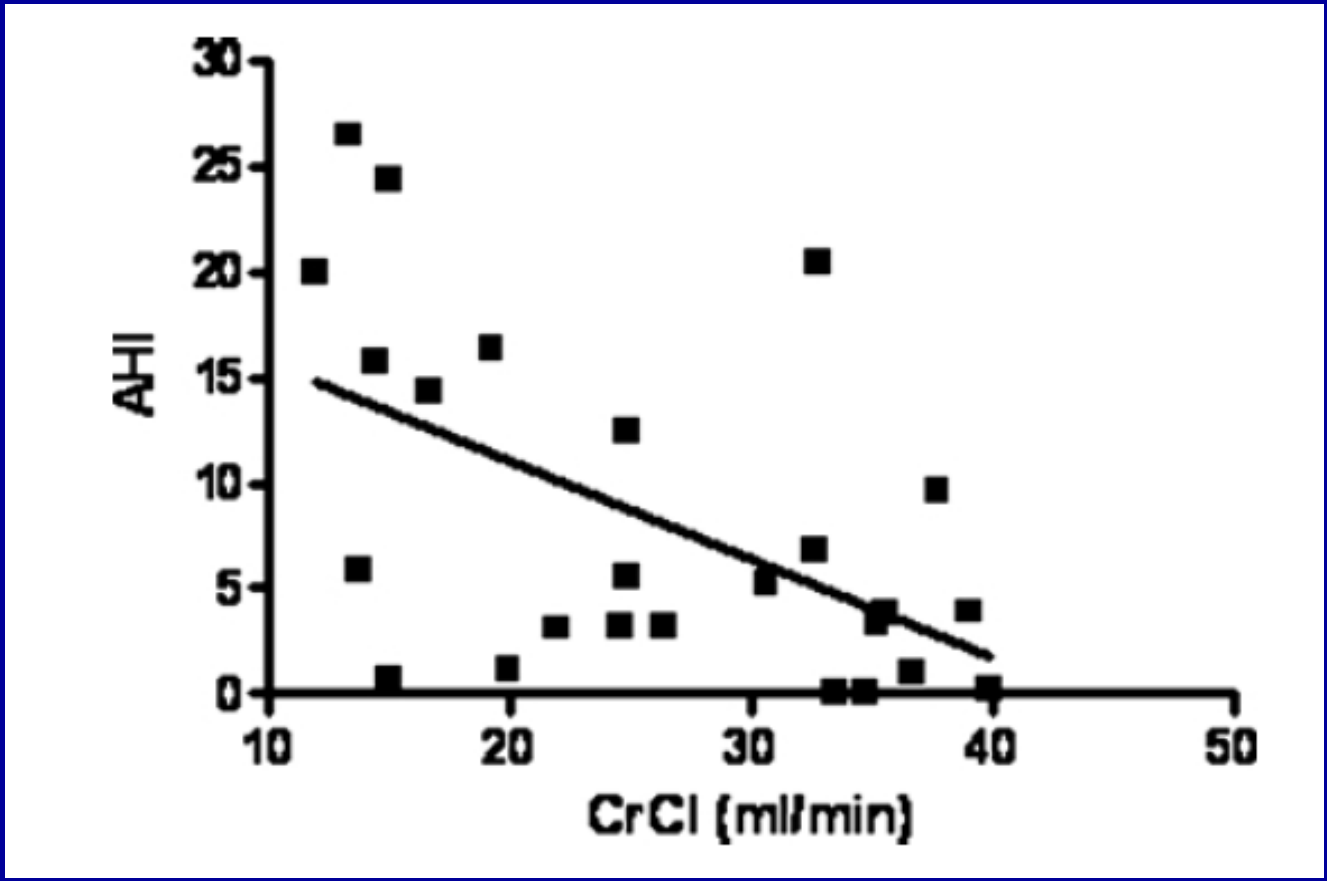
Snoring and cardiovascular disease (n= 12600)





Sleep-Disordered Breathing in Nondialyzed Patients with Chronic Renal Failure

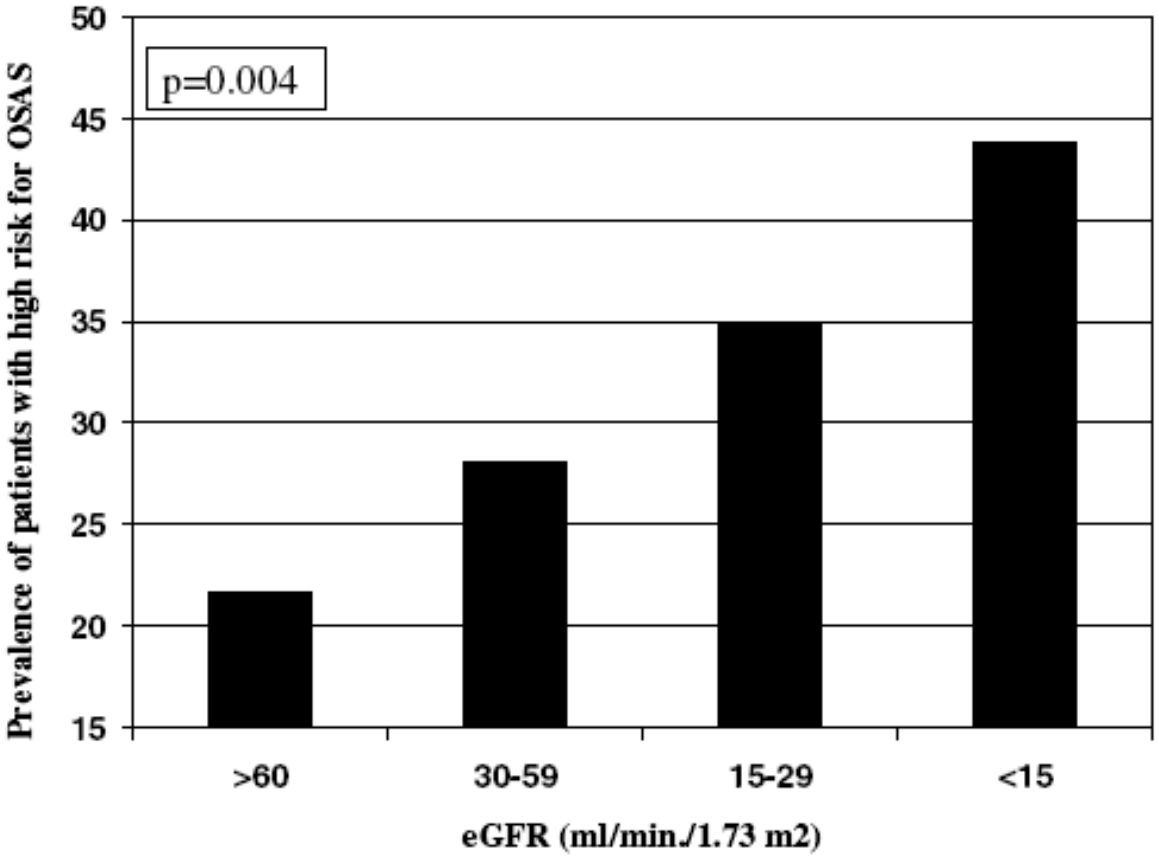
Nikolaos Markou · Maria Kanakaki · Pavlos Myrianthefs · Dimitrios Hadjiyanakos · Dimosthenis Vlassopoulos · Anastasios Damianos · Konstantinos Siamopoulos · Miltiadis Vasiliou · Stavros Konstantopoulos



Lung (2006) 184:43–49

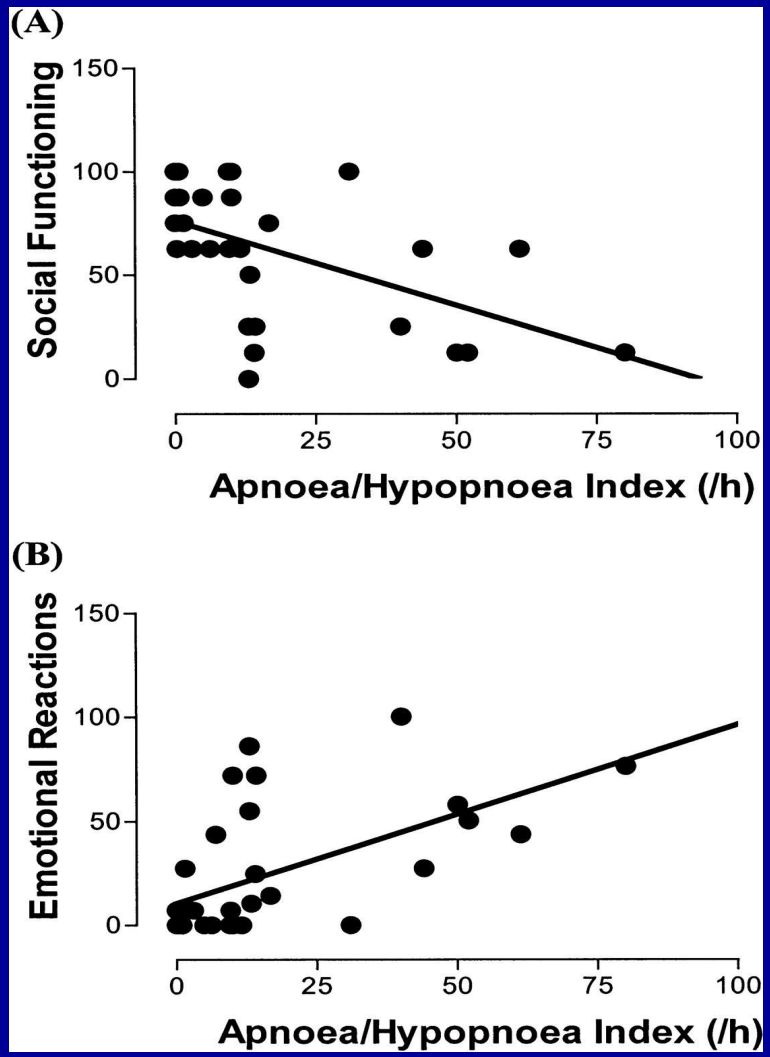
High prevalence of patients with a high risk for obstructive sleep apnoea syndrome after kidney transplantation—association with declining renal function

Miklos Zsolt Molnar[1,2,3], Andras Szentkiralyi[1], Anett Lindner[1], Maria Eszter Czira[1], Andras Szabo[4], Istvan Mucsi[1,2,5] and Marta Novak[1,6]



Nephrol Dial Transplant (2007)

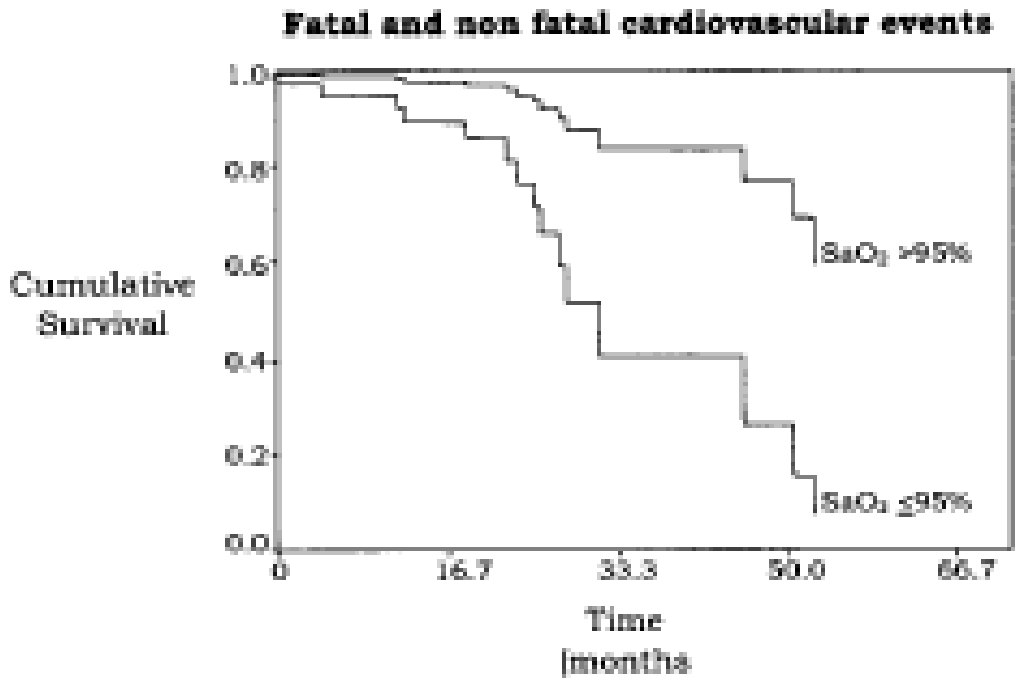
SAS and quality of life in dialysis patients



Sanner et al.: NDT, 2002

Nocturnal Hypoxemia Predicts Incident Cardiovascular Complications in Dialysis Patients

CARMINE ZOCCALI, FRANCESCA MALLAMACI, and GIOVANNI TRIPEPI
CNR, Centre of Clinical Physiology and Division of Nephrology, Ospedali Riuniti, Reggio Calabria, Italy.

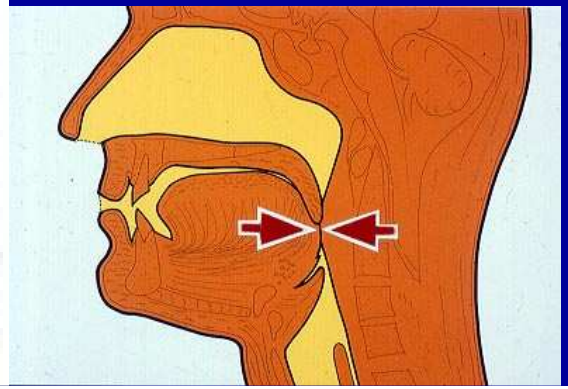


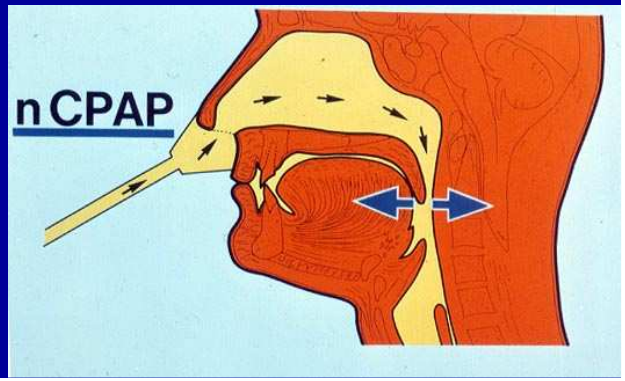
J Am Soc Nephrol 13: 729–733, 2002

Clinical management of SAS in CKD

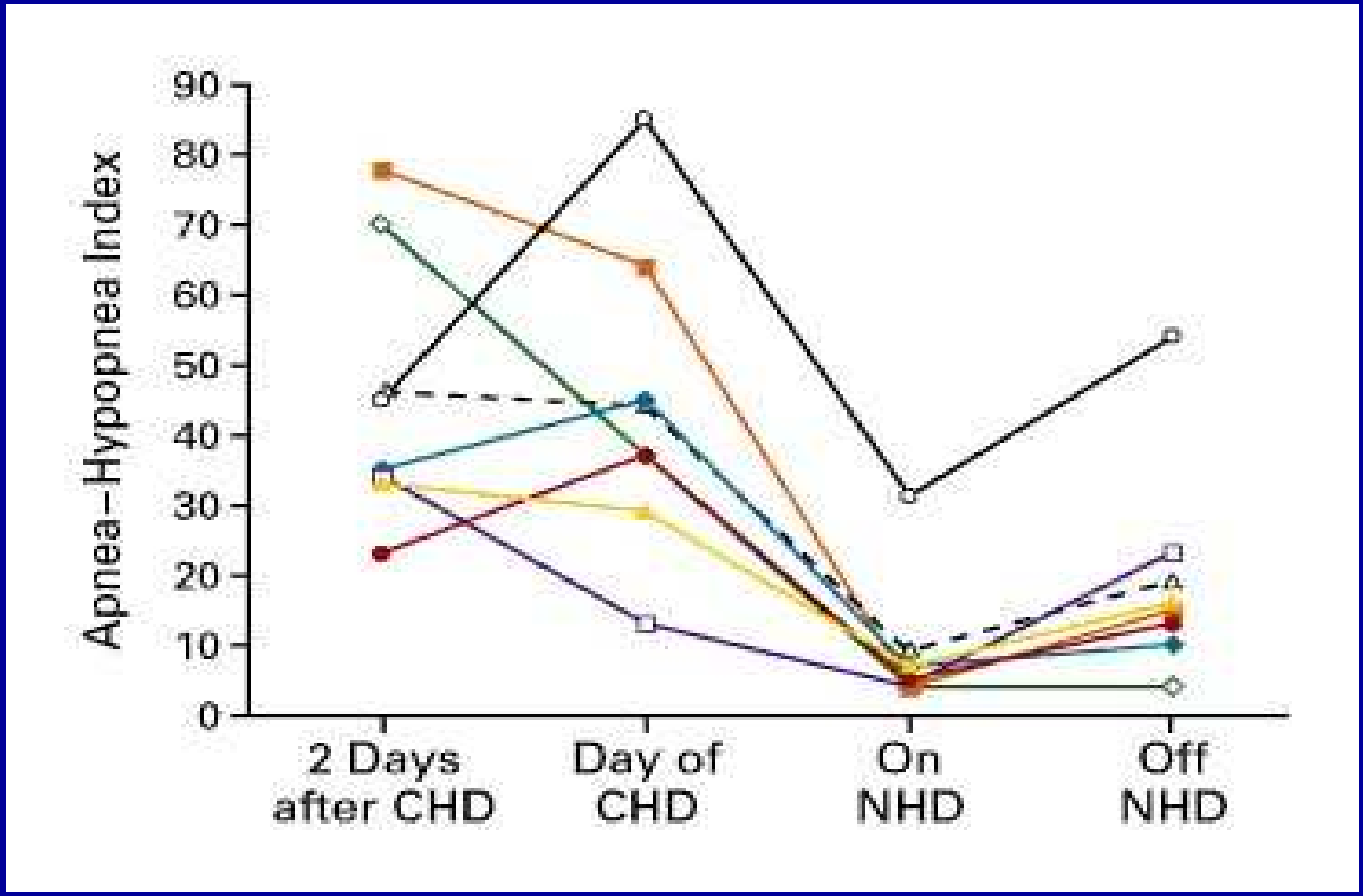
- Weight loss life style changes
- CPAP
  - Long term effects?
  - Compliance?
- Oral devices, Sx
- Transplantation?
- Intensified dialysis

photo courtesy of the American Sleep Apnea Association



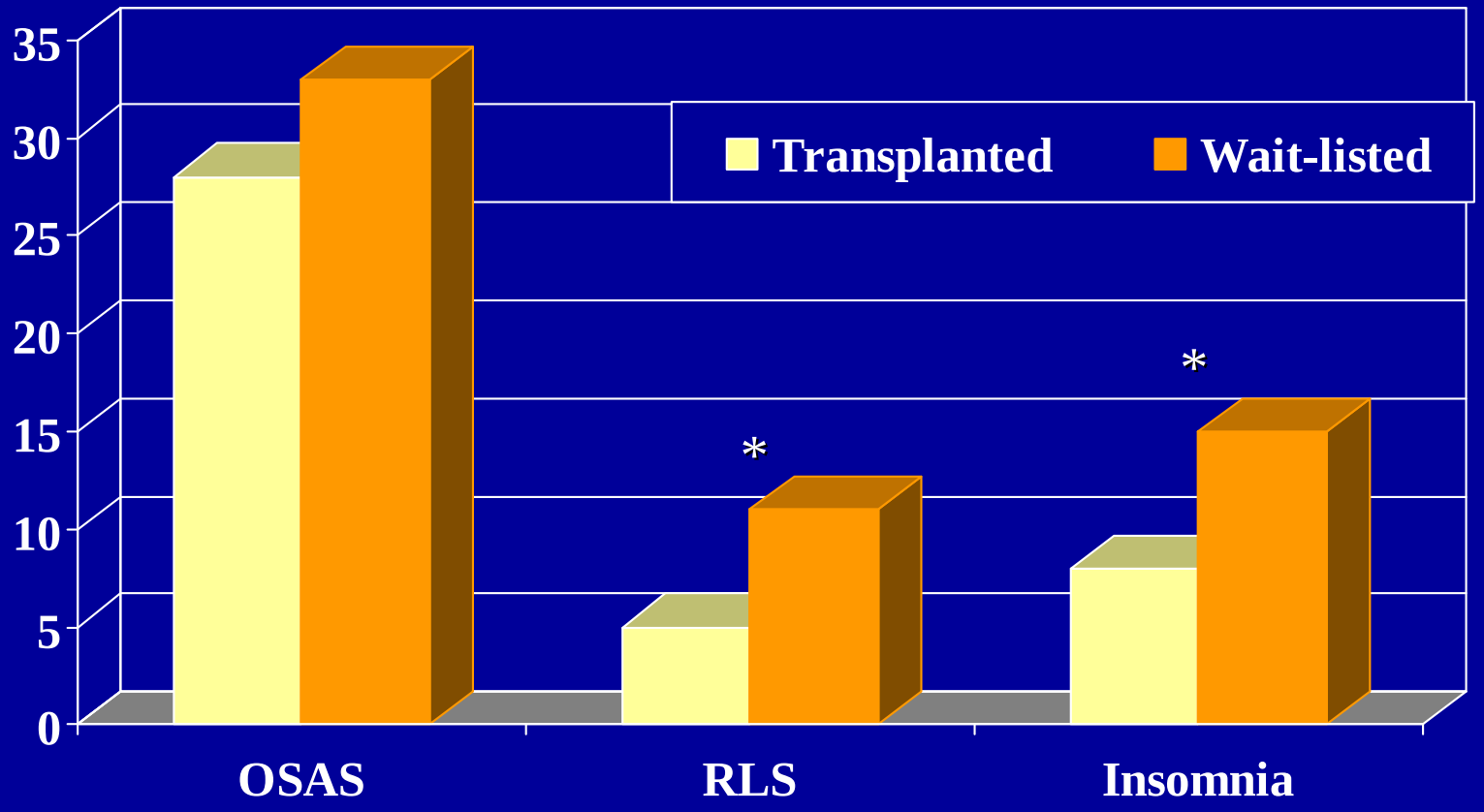

nCPAP

SAS and Nocturnal Home Hemodialysis



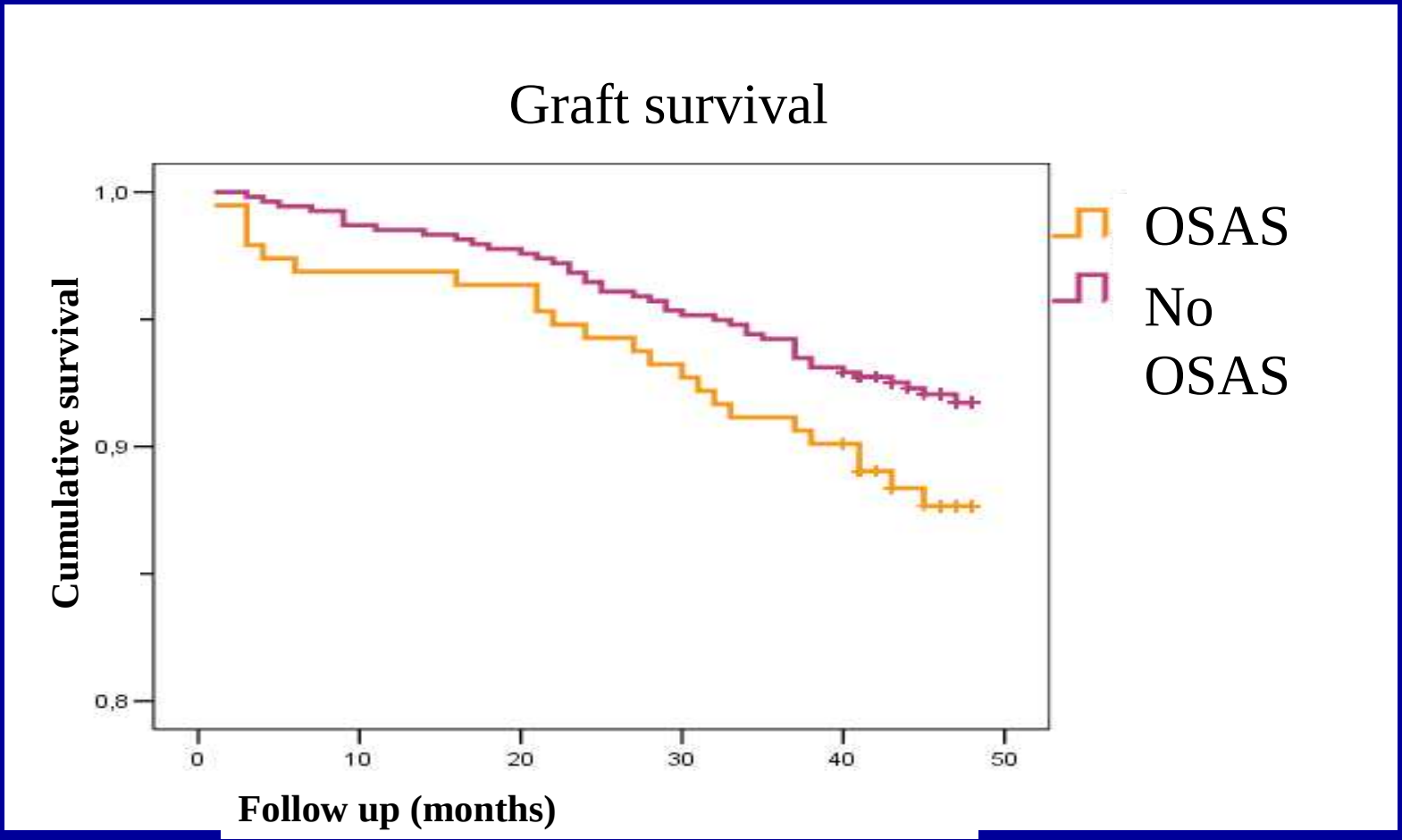
Hanly PJ, Pierratos A. N Engl J Med 2001; 344(2): 102±107.

Prevalence of sleep disorders in Hungarian dialysis and transplanted patients



*: P<0.001, Khi-square test

High risk of OSAS and graft failure



Sleep disorders in CKD patients - summary

- The prevalence of sleep disorders is much higher in patients with CKD than in the average population
- The prevalence of these conditions is the lowest in transplanted patients (except OSAS)
- Age, gender, renal function and co-morbidity is associated with sleep disorders in kidney transplanted patients

Sleep disorders in CKD patients - summary

- Patients with sleep disorders have more fatigue/daytime sleepiness, increased illness intrusiveness and impaired QoL
- OSAS is a predictor of graft loss, RLS is associated with mortality in transplanted patients

Conclusions

- Sleep disorders are underdiagnosed and un(der)treated in the CKD population
- Close collaboration between sleep specialists and nephrologists

may improve management of these treatable disorders and may improve QoL of renal patients


Calpp

Yawning Apprentice

Mihály Munkácsy

(1844 – 1900)

THANK YOU!