Sleep Disorders in Patients with Chronic Kidney Disease

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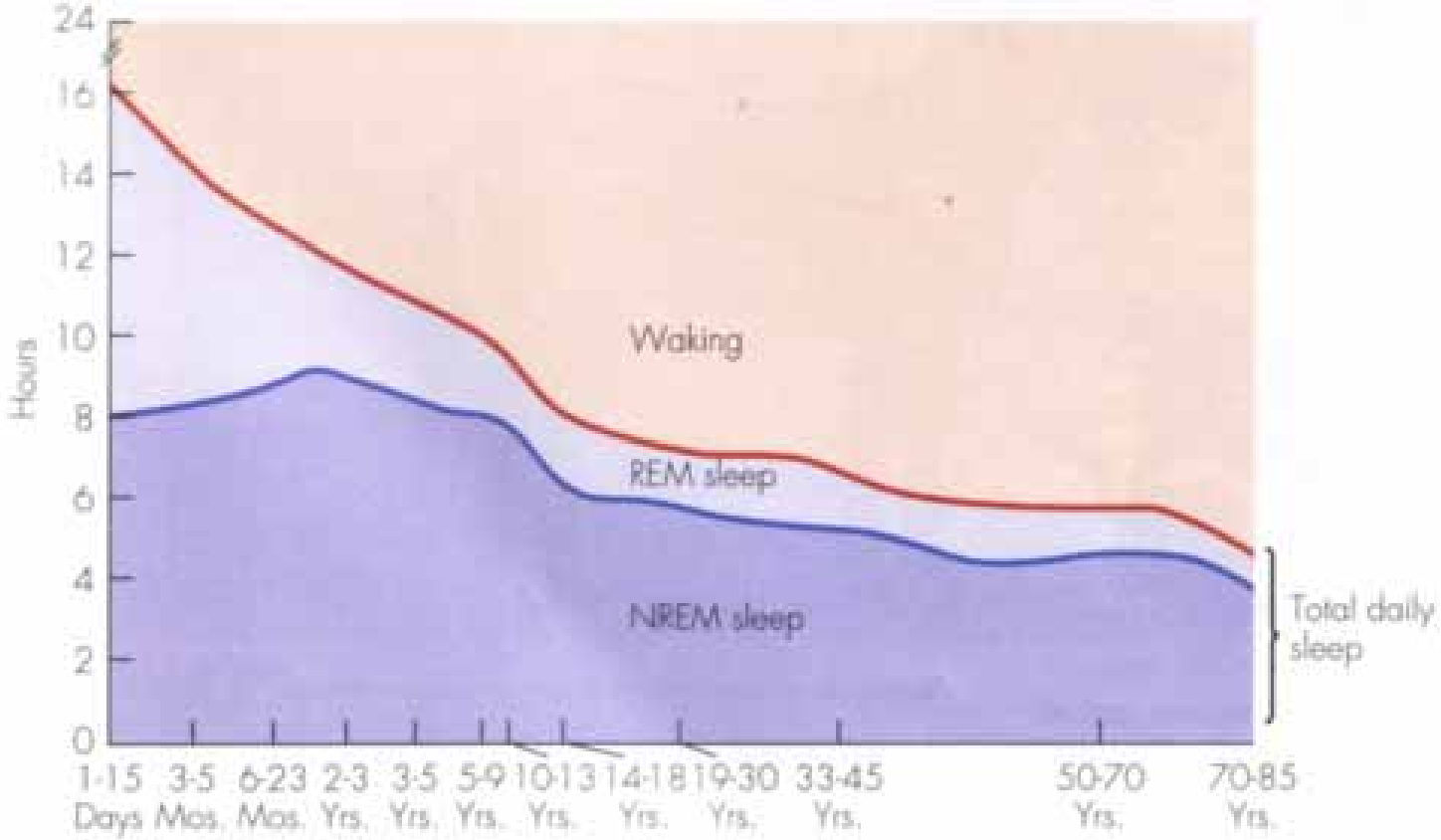
University of Toronto, Canada

- Sleep – significance

- The most frequent sleep problems in CKD patients
- Restless legs syndrome (RLS)/Periodic limb 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?

Evolutionary theory, energy conservation

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
- Sleep need is individual

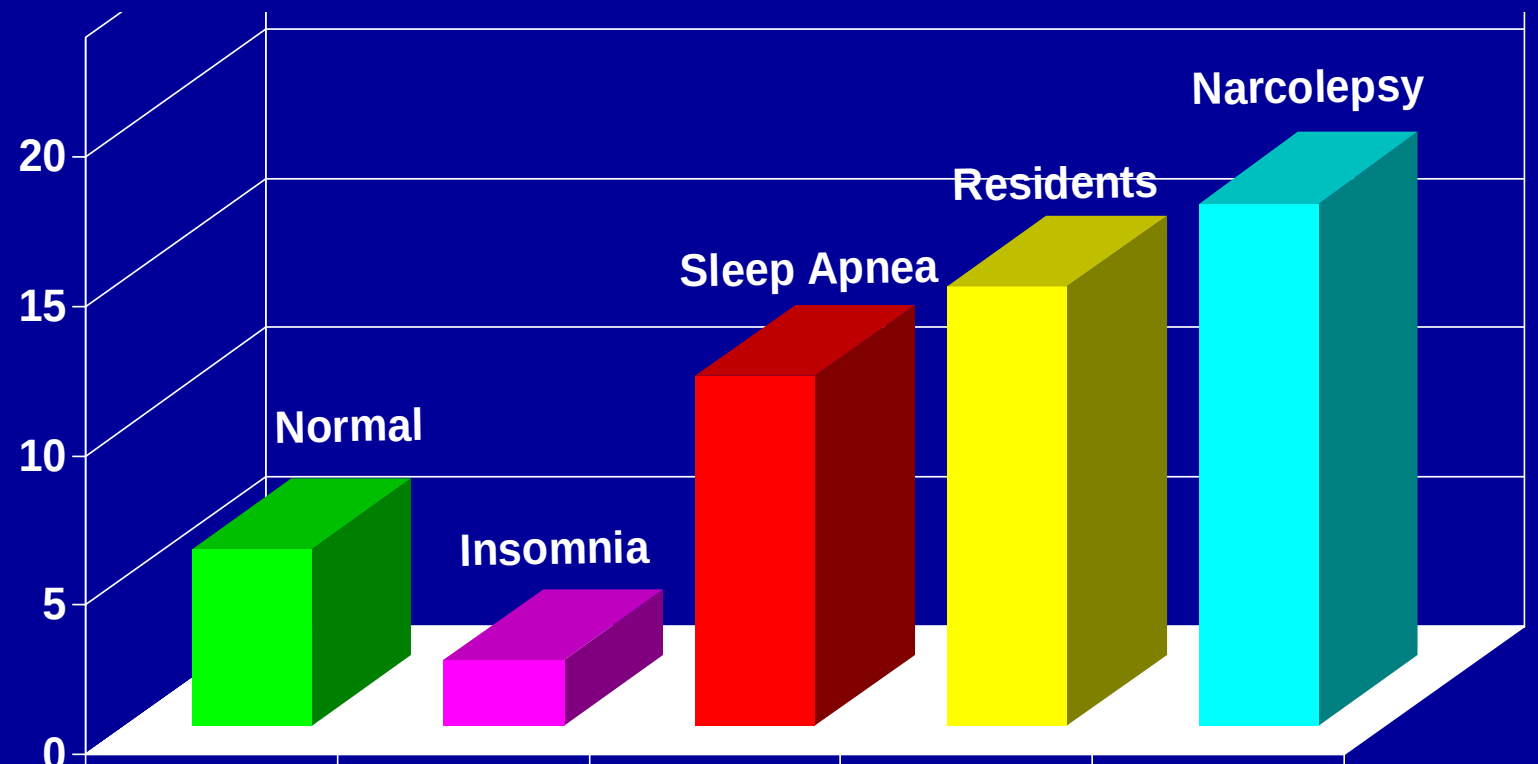
Sleep disorders

- Sleep deprivation
- Individual consequences, quality of life
- Socio-economical consequences, health care utilization, accidents etc.

Consequences of Chronic Sleep Deprivation

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

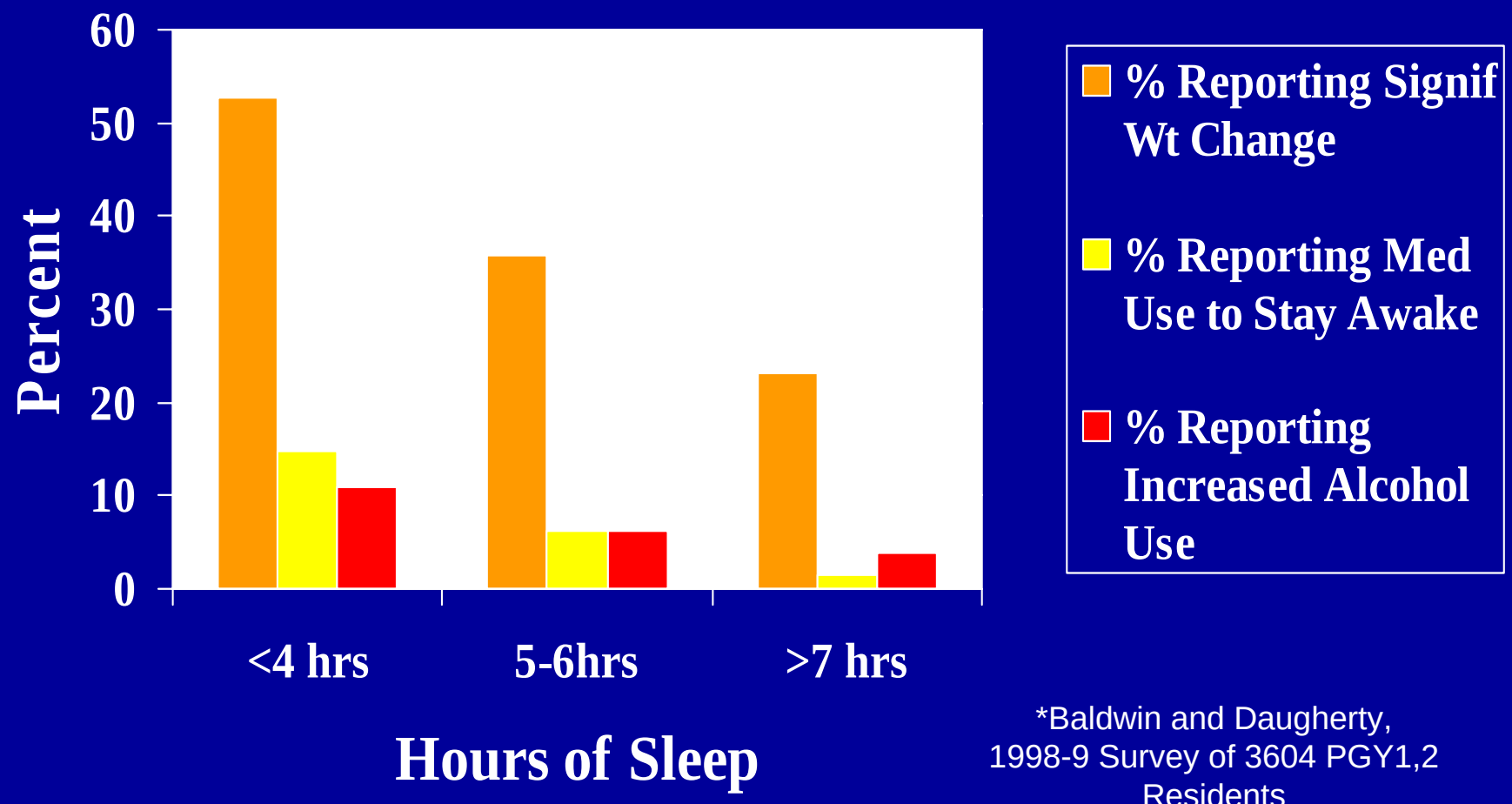
Epworth Sleepiness Scale



	Normal	Insomnia	Sleep Apnea	Residents	Narcolepsy
Mean	5.90	2.20	11.70	14.70	17.50

Sleepiness in residents is equivalent to that found in patients with serious sleep disorders. Mustafa and Strohl, unpublished data. Papp, 2002

Adverse Health Consequences by Average Daily Hours of Sleep*

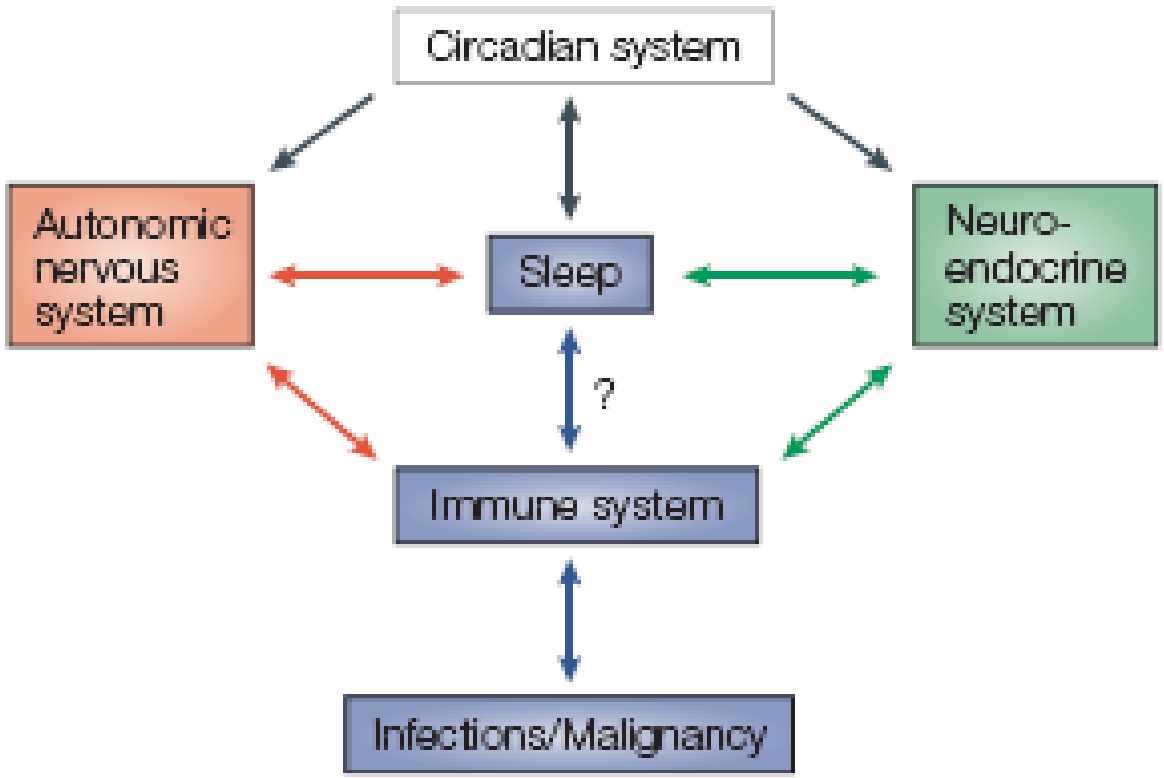


*Baldwin and Daugherty, 1998-9 Survey of 3604 PGY1,2 Residents

Sleep and the Immune System

- Sleep deprivation is correlated with a significant reduction in cellular immunity
- Can cause reductions in NK cells, T-cells, and monocyte function
- Men with just four hours of sleep a night for four straight nights after receiving a flu shot produced half the antibodies as the control group (Weintraub, 2004)

Cytokines and sleep



NATURE REVIEWS | IMMUNOLOGY VOLUME 4 | JUNE 2004 |

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)

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

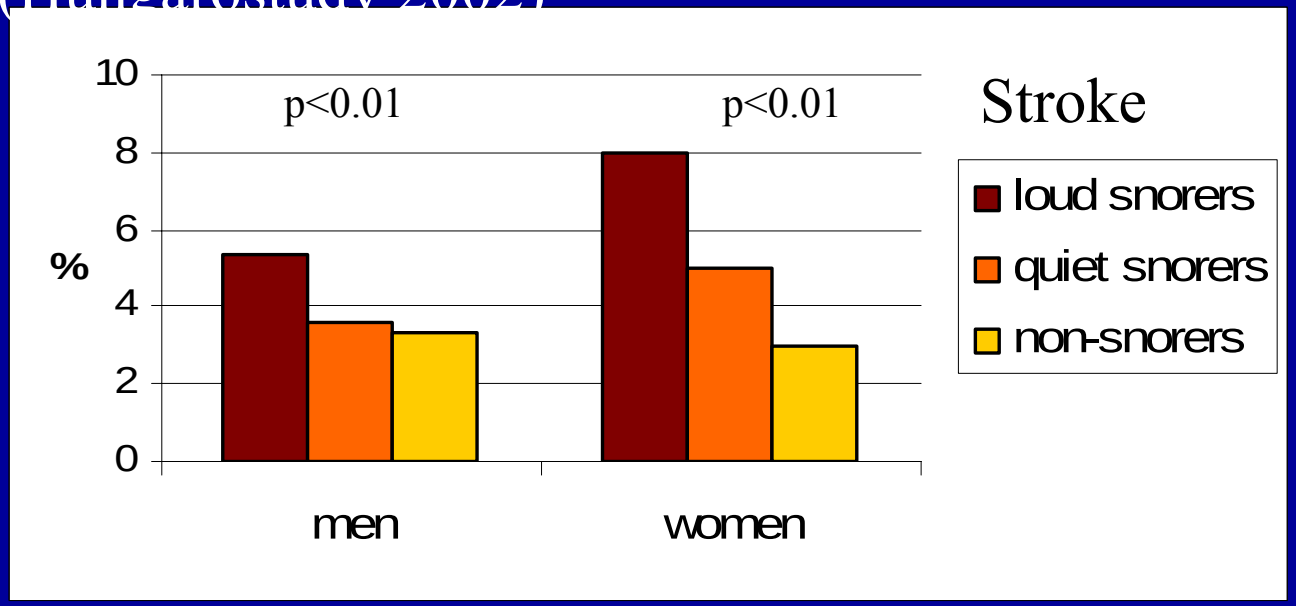
CAD

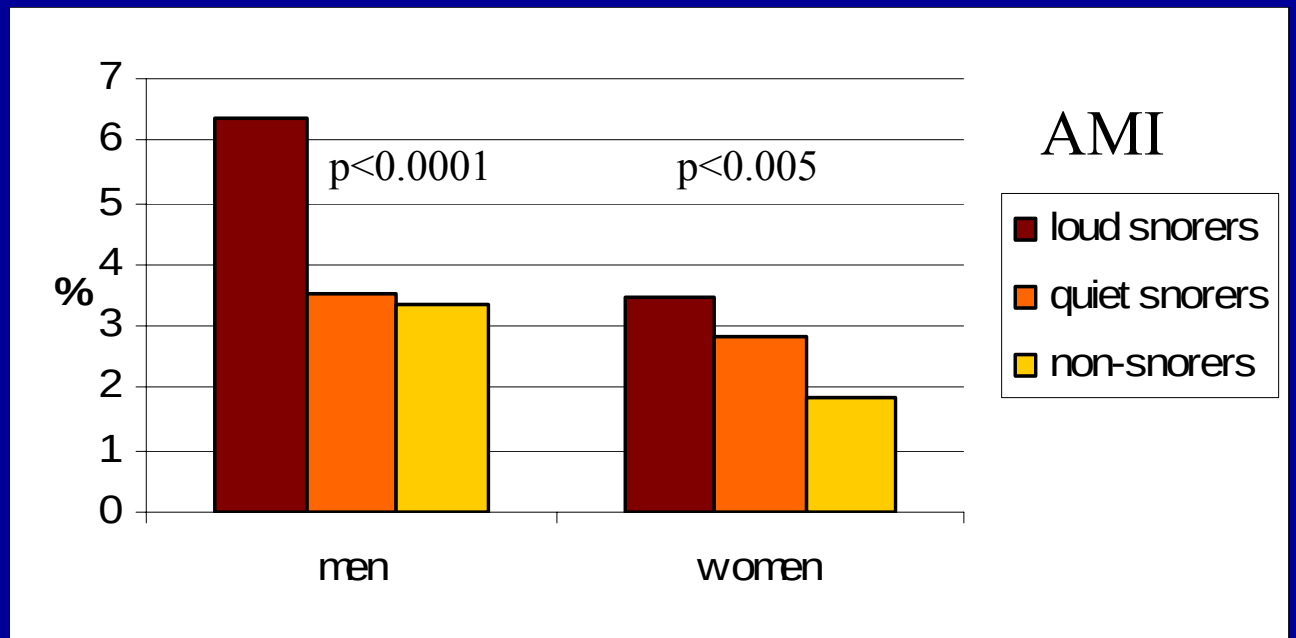
Cerebrovascular disease

Modifying factors

Obesity
Gender
Age
Metabolic syndrome
Smoking
Medications

Snoring and cardiovascular disease (n= 12600) (Hungarostudy 2002)





Sleep disorders in CKD – why is it important?

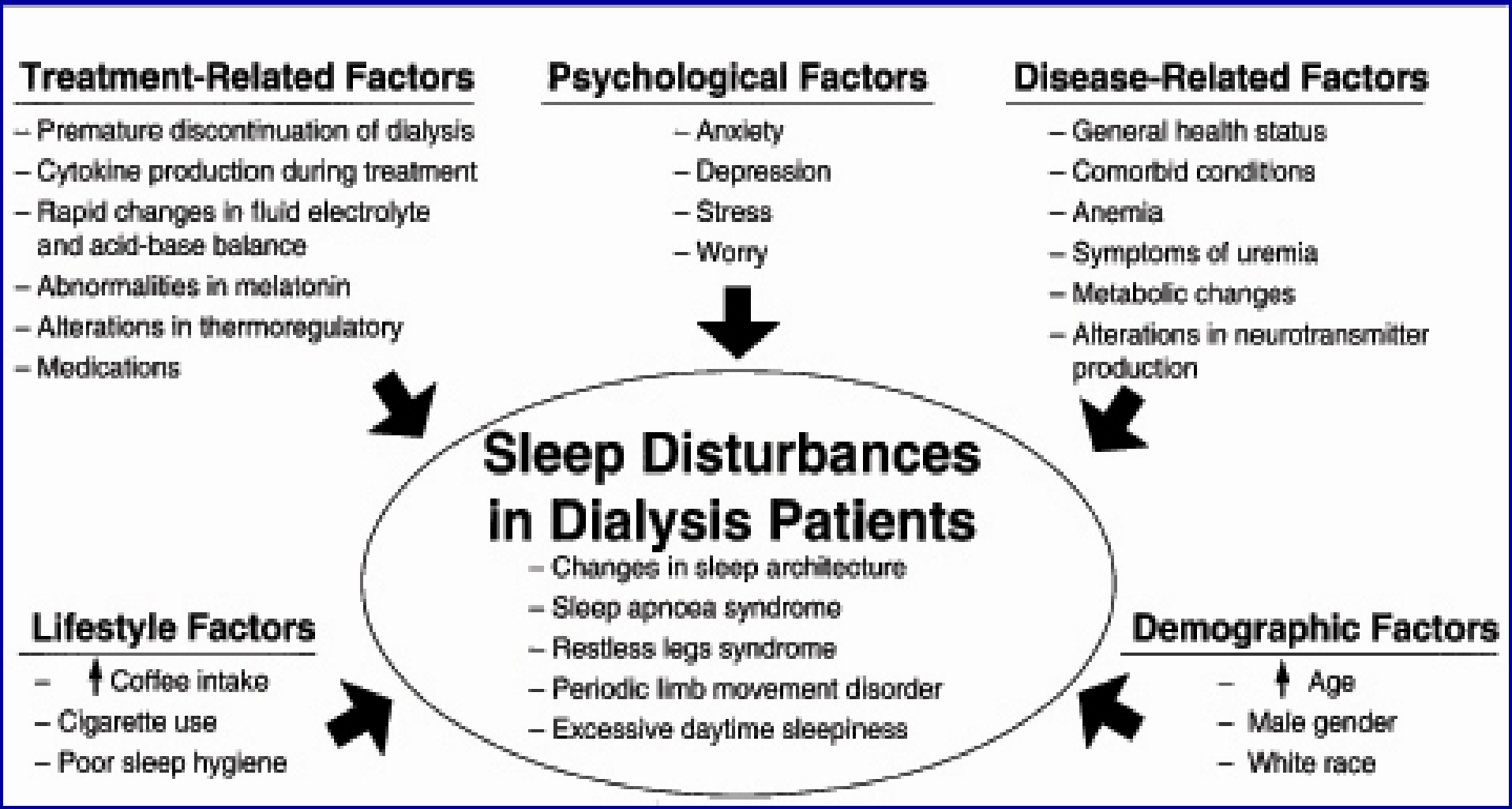
- Sleep problems are one of the most common complaints of patients in the dialysis unit
- Sleep Apnea Syndrome (SAS) may contribute to the pathogenesis of hypertension, CV morbidity
- Sleep disorders may impair quality of life
- Poor sleep have been shown to be a predictor of morbidity and mortality 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 20-80%
- 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



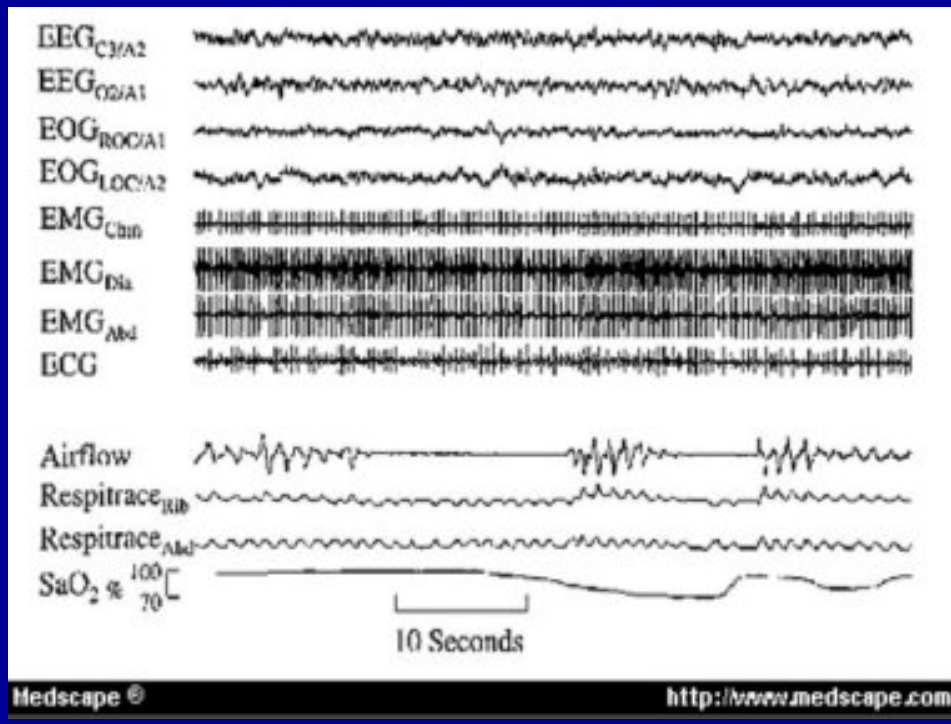
K. Parker., Sleep Medicine Reviews, Vol. 7, No. 2, pp 131-143, 2003

Diagnostic tools to detect sleep problems

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

Polysomnography

- neurophysiologic variables
- electrooculography, EEG, submental myogram) – sleep stages
- Respiration
- ECG
- Limb movements
- Body position
- Video



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

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 patients[4]
- There is no data regarding the association of RLS, poor sleep and QoL after renal transplantation

[1] Winkelman et al. (1995)

[2] Mucsi et al. (2004)

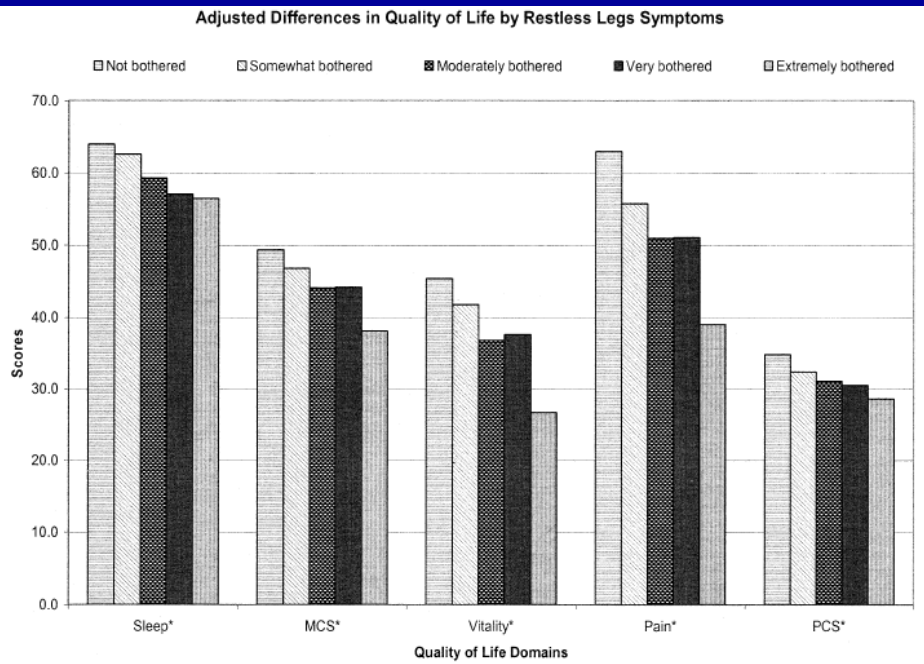
[3] Molnar et al. (2005)

[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-
r index, Karnofsky Index, and center. *All $P < 0.0001$ for adjusted comparison of
ıptoms of restless legs.

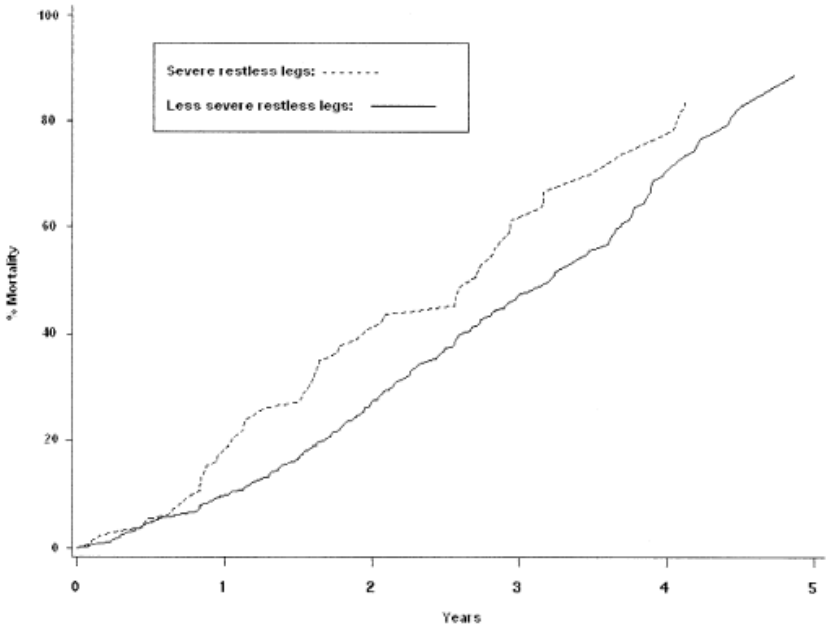
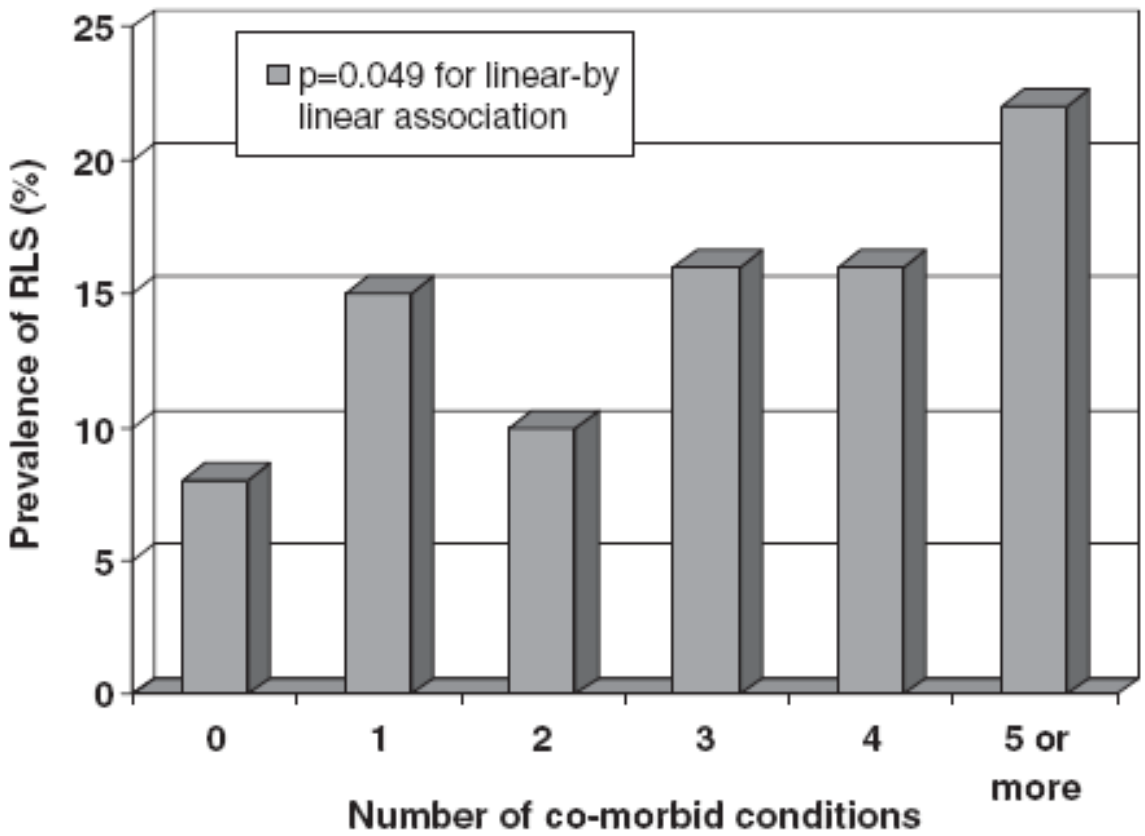


Fig 2. Crude cumulative mortality according to severe symptoms of restless legs.

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

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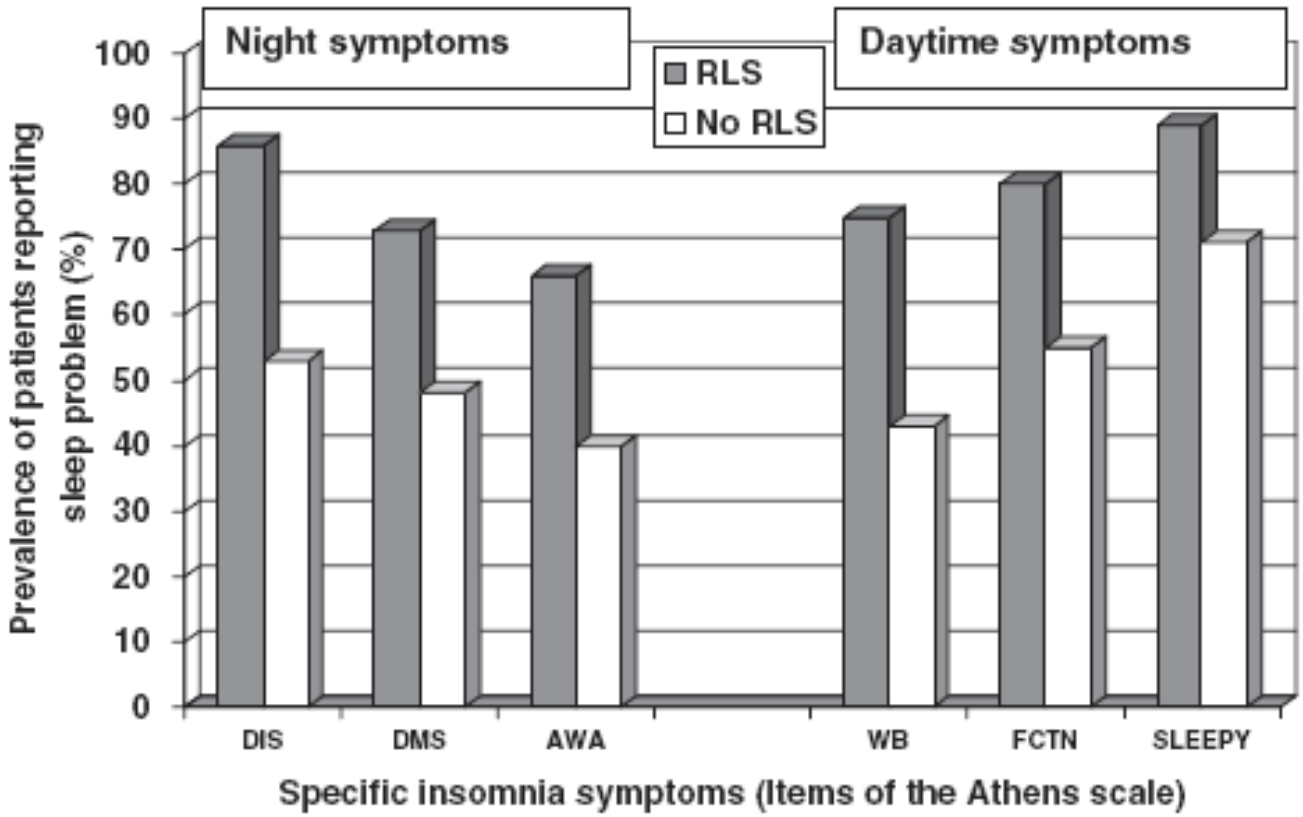

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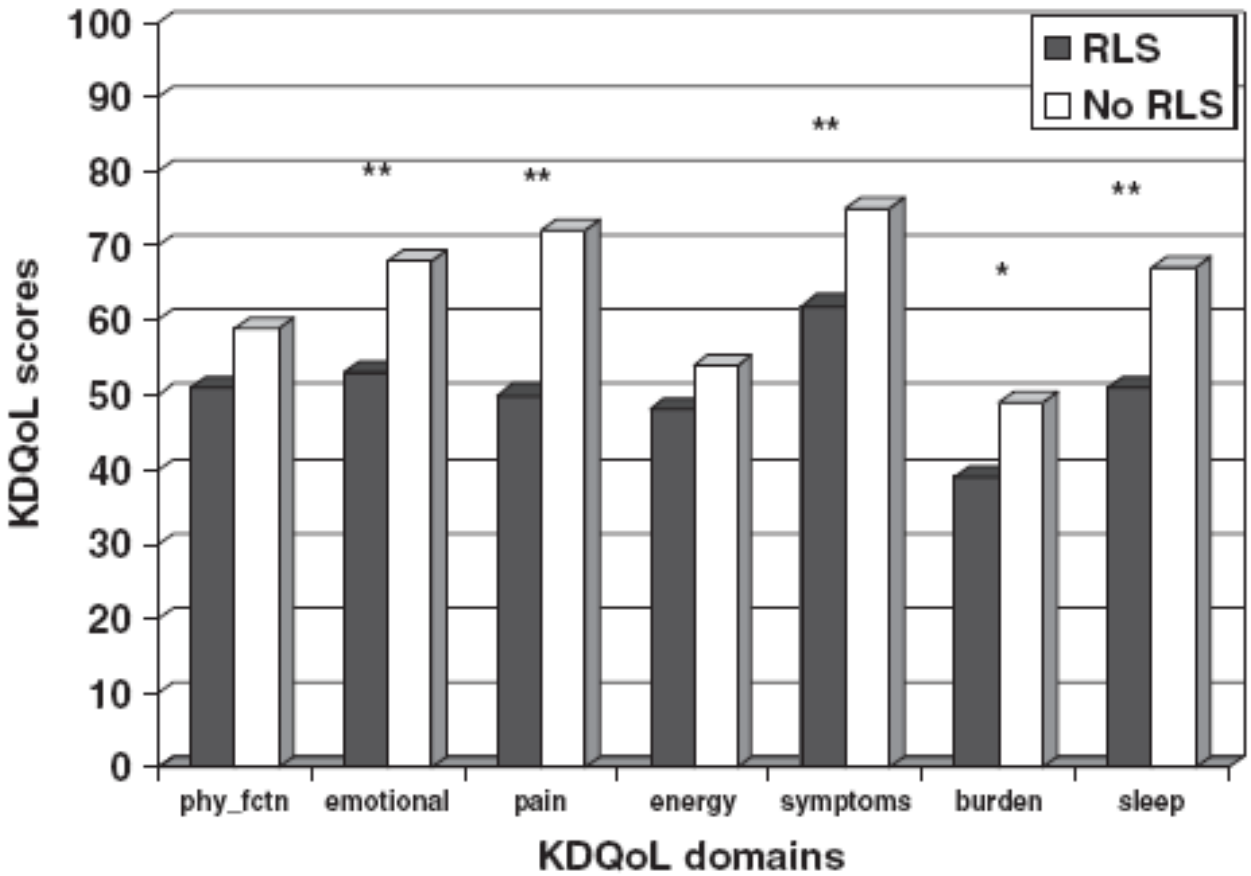
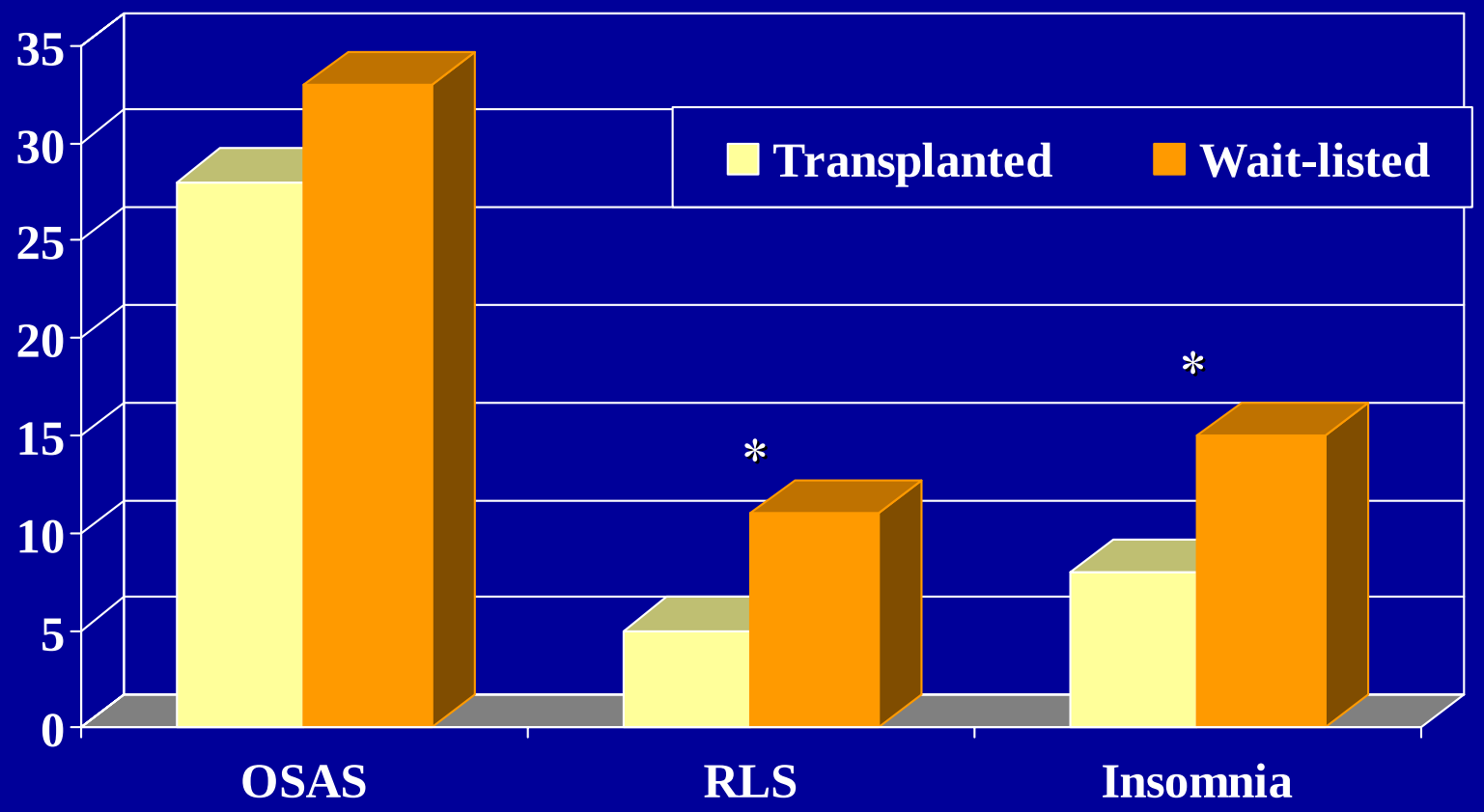


Nephrol Dial Transplant (2005) 20: 571–577

Prevalence of sleep disorders in Hungarian dialysis and transplanted patients



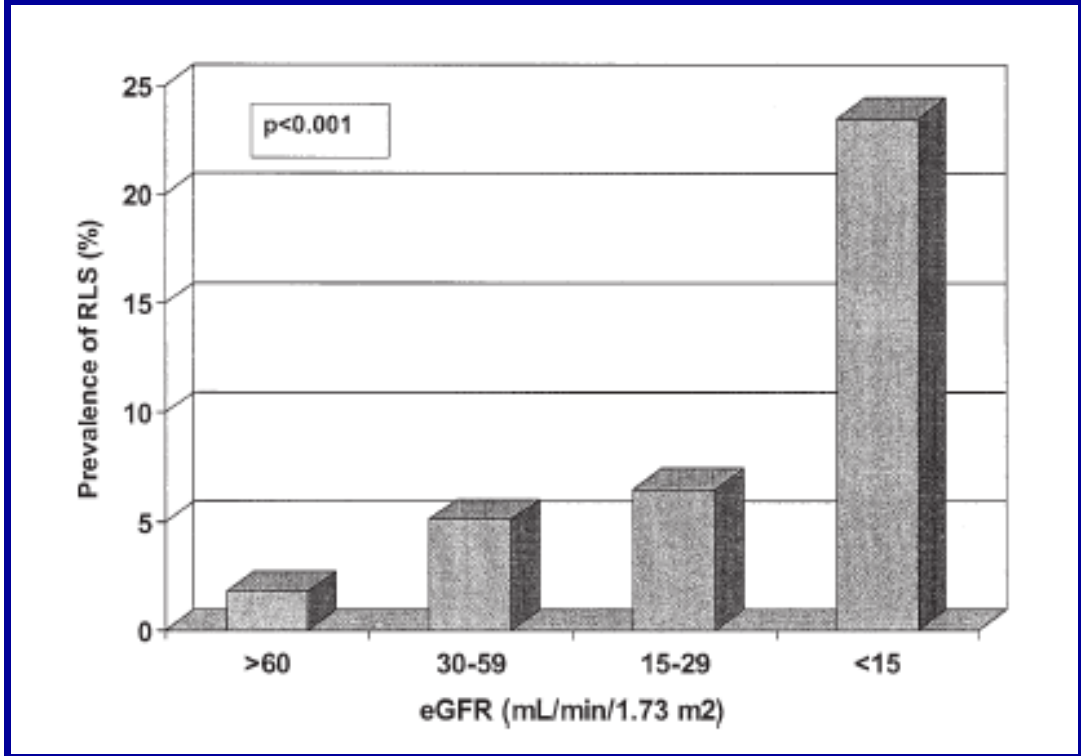
*: P<0.001, Khi-square test

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

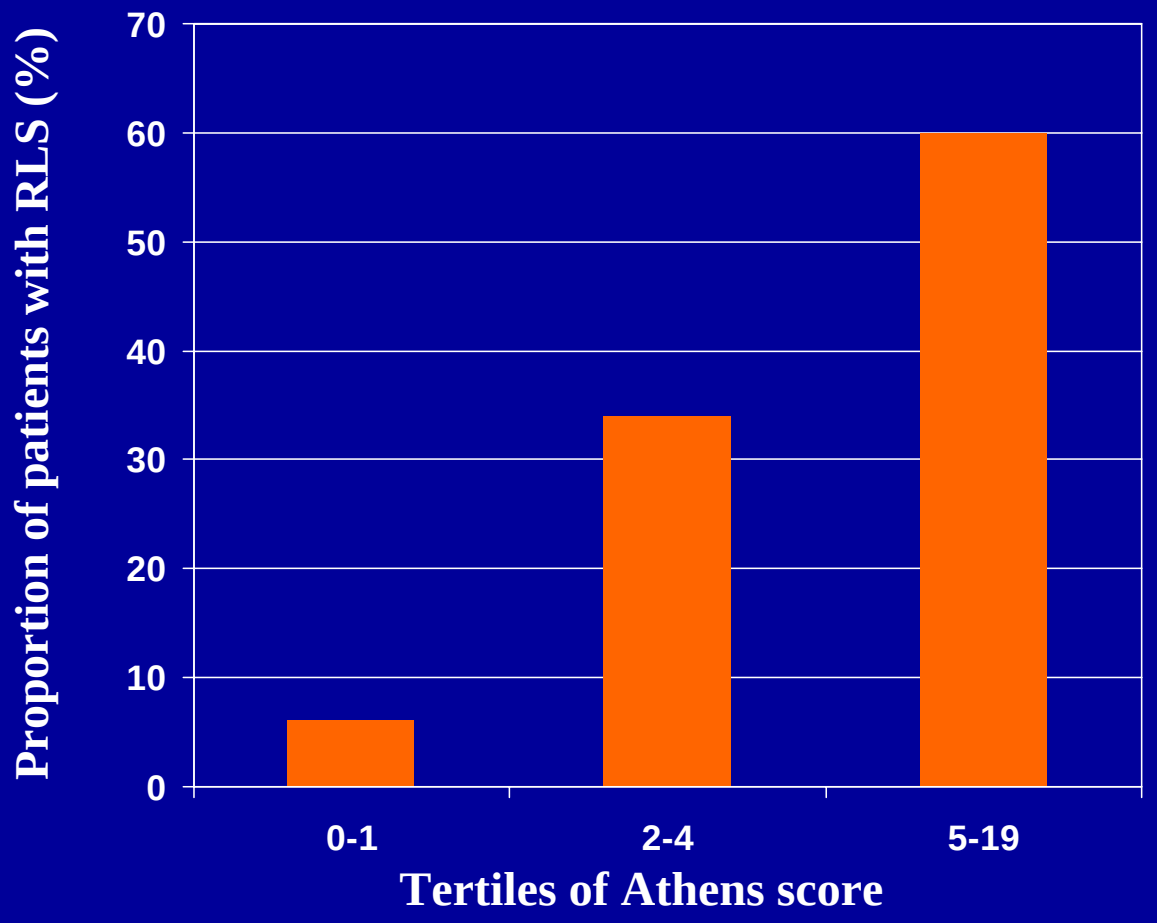
Table 2. Characteristics of Patients With or Without RLS in the Tx Group

	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

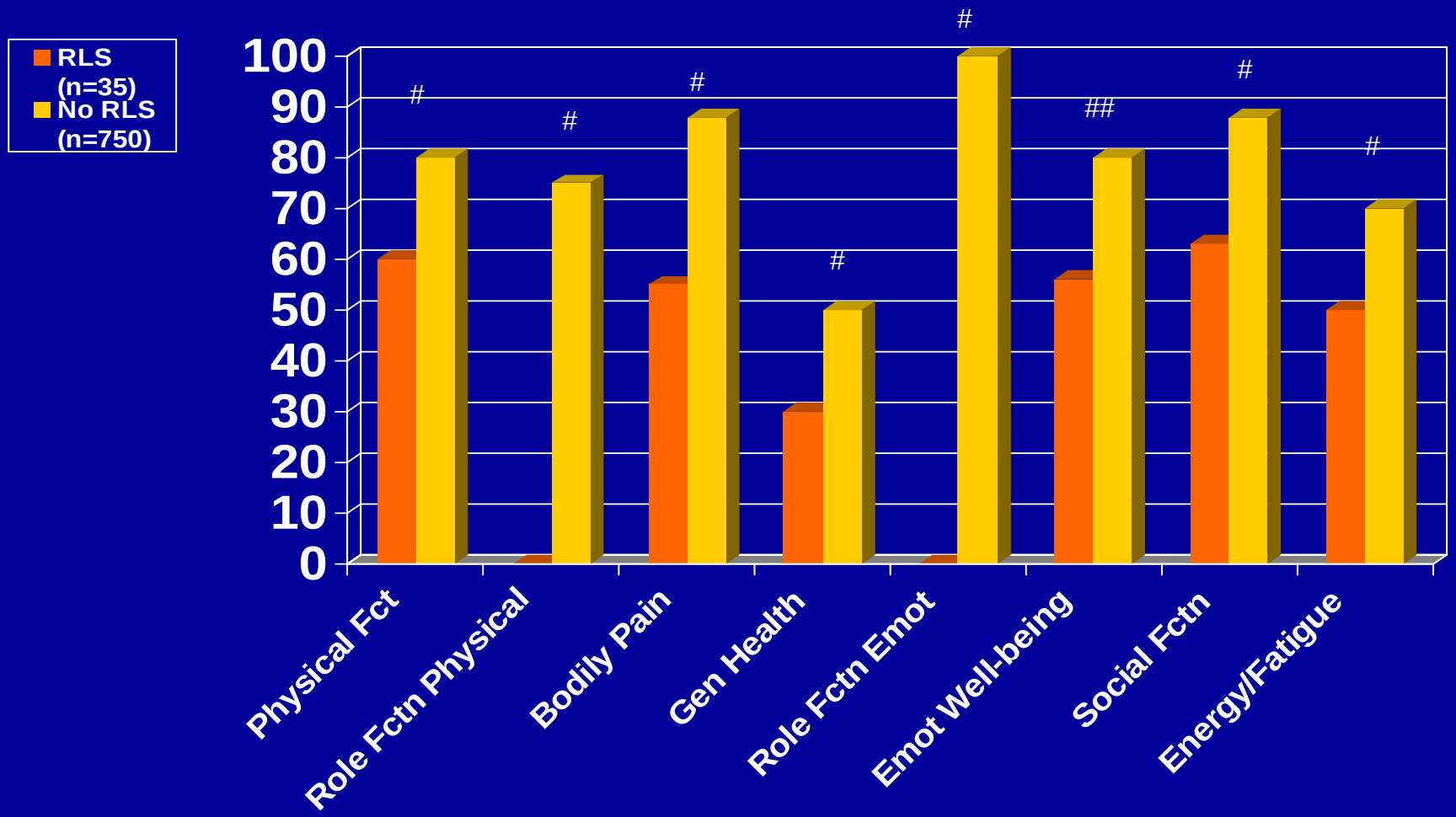
RLS and Overall Sleep Quality



Restless Legs Syndrome, Insomnia and Quality of Life after Renal Transplantation

M. Zs. Molnar et al. (in press, JPR)

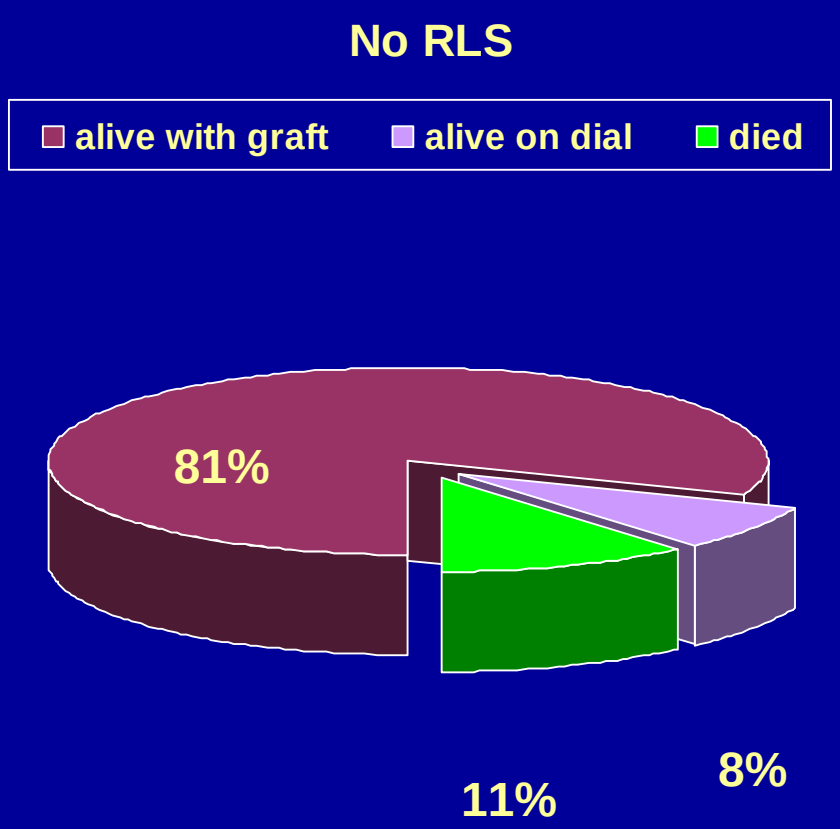
SF-36 QoL Scores with and without RLS*

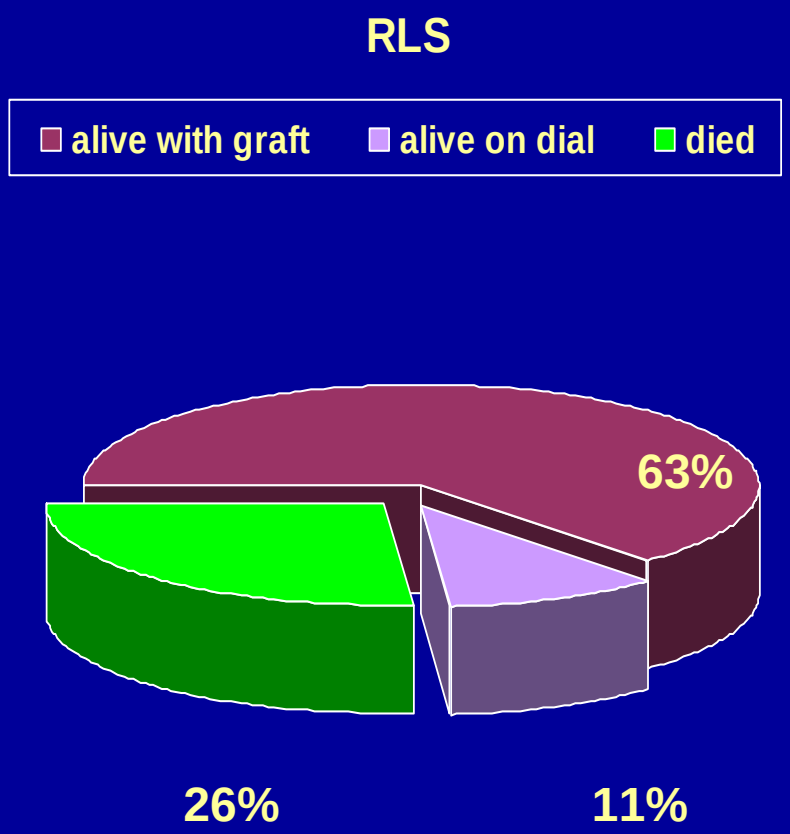


Restless Legs Syndrome, Insomnia and Quality of Life after Renal Transplantation

M. Zs. Molnar et al. (in press, JRR)

Restless legs syndrome is associated with mortality in kidney transplanted patients





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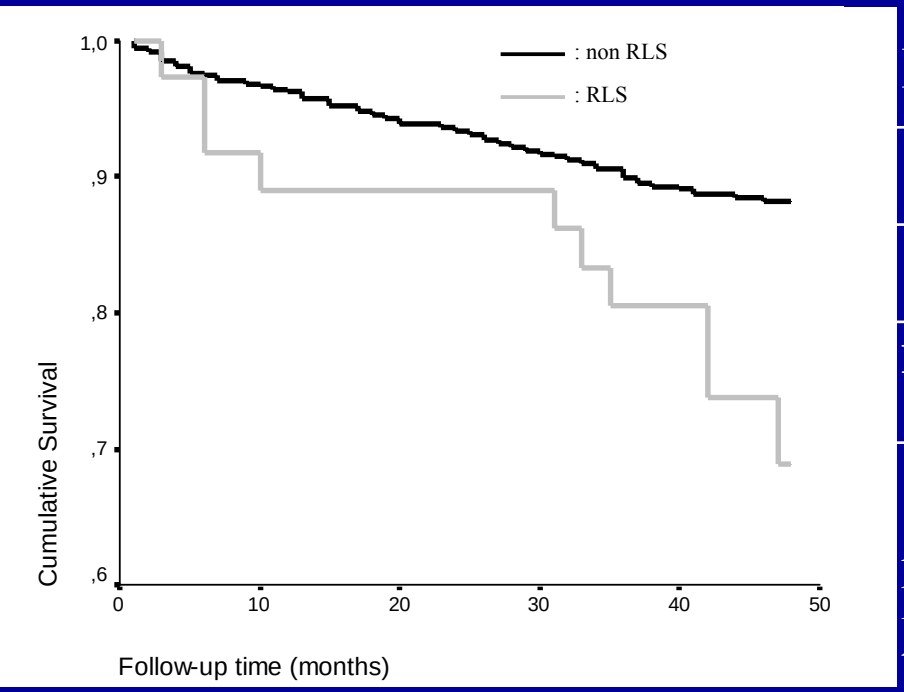


Multivariate Cox-modell

	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

M. Zs. Molnar et al. (AJKD 2007)

Periodic limb movements in sleep

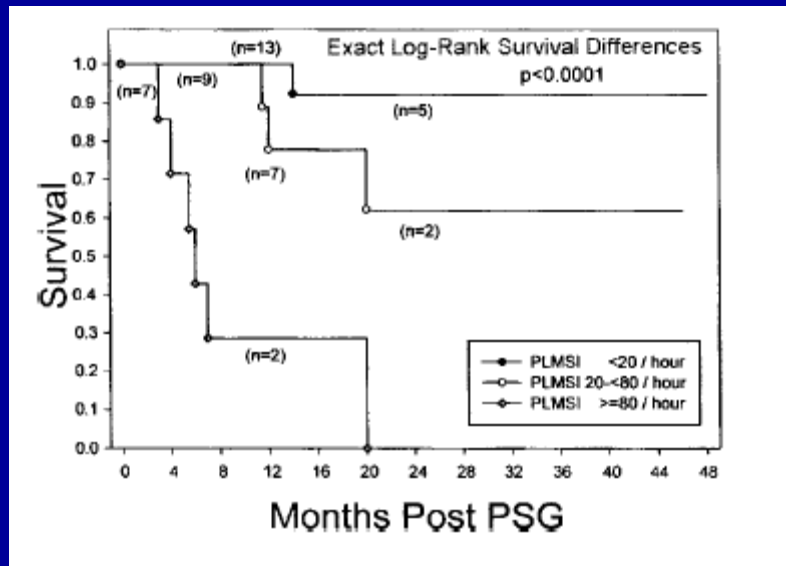
Overlap with RLS

Regular leg movements during sleep

Sleep fragmentation

Hypersomnia

Predictor of mortality in dialysis patients (Benz at al; AJKD; 2000)



Clinical management of RLS in CKD

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

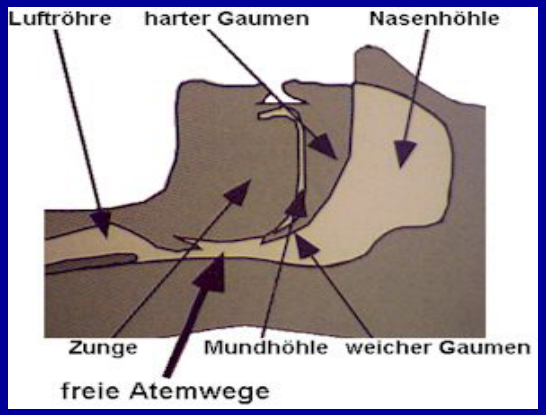
Sleep apnea syndrome

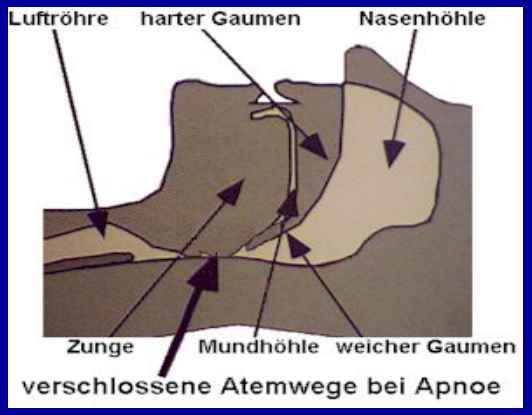
- intermittent episodes of breathing cessation during sleep,
  - airway collapse (obstructive sleep apnoea, OSA)
  - cessation of respiratory effort (central SA)
  - or both (mixed SA)
- The severity of the SAS is usually characterized by the number of apneic events per hour of sleep (AHI, RDI) (RDI>5 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

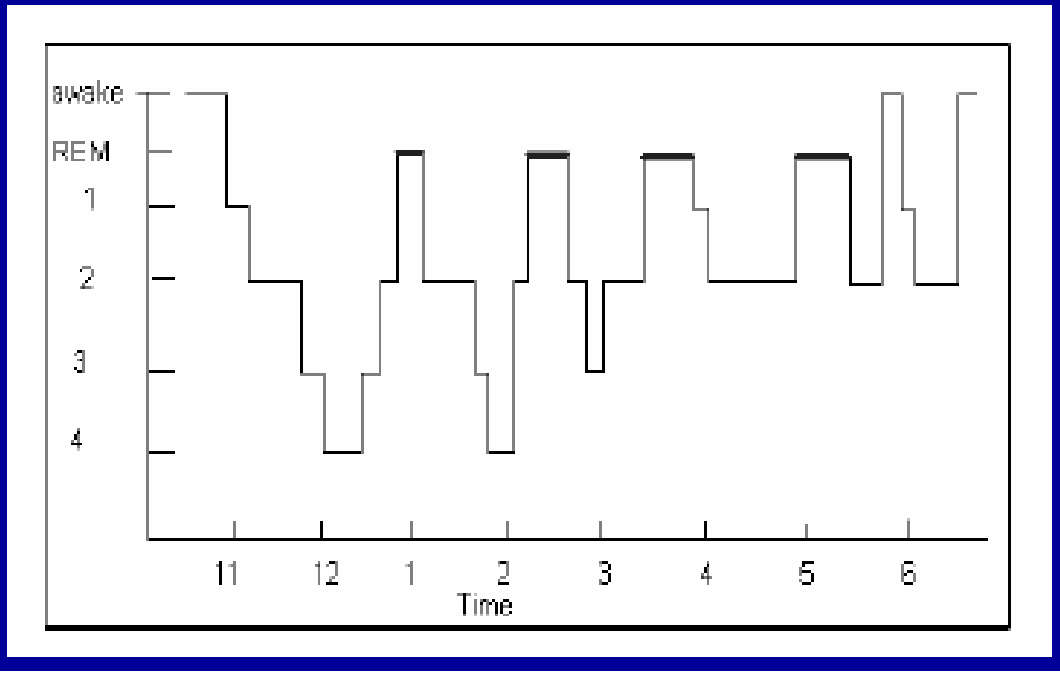
- Upper airway obstruction
- Anatomical problems
- Decreased muscle tone ↓
  +
  weakness of pharyngeal wall

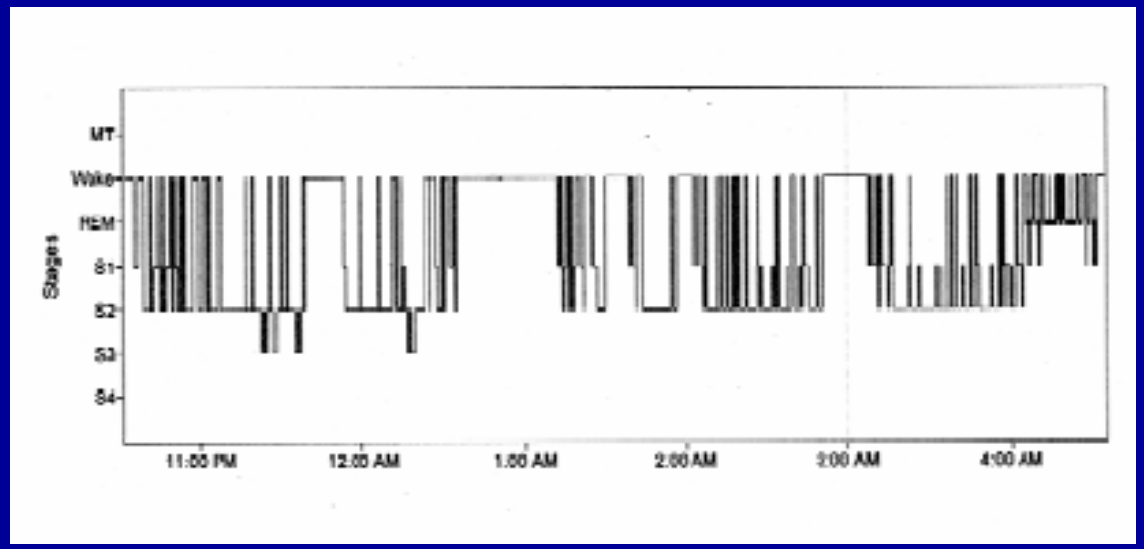
} Dynamic collapse during inspiration





Apnea leads to micro-arousals and fragmented sleep





Clinical features of sleep apnea

- Snoring and daytime sleepiness
- Non-restorative sleep and other sleep-related symptoms
- Daytime consequences: daytime sleepiness, tiredness, headaches, naps, neuropsych symptoms
- Medical consequences: cardiovasc, sex, diab.

Sleep Apnoe Syndrome

Predictors, correlates

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

Consequences

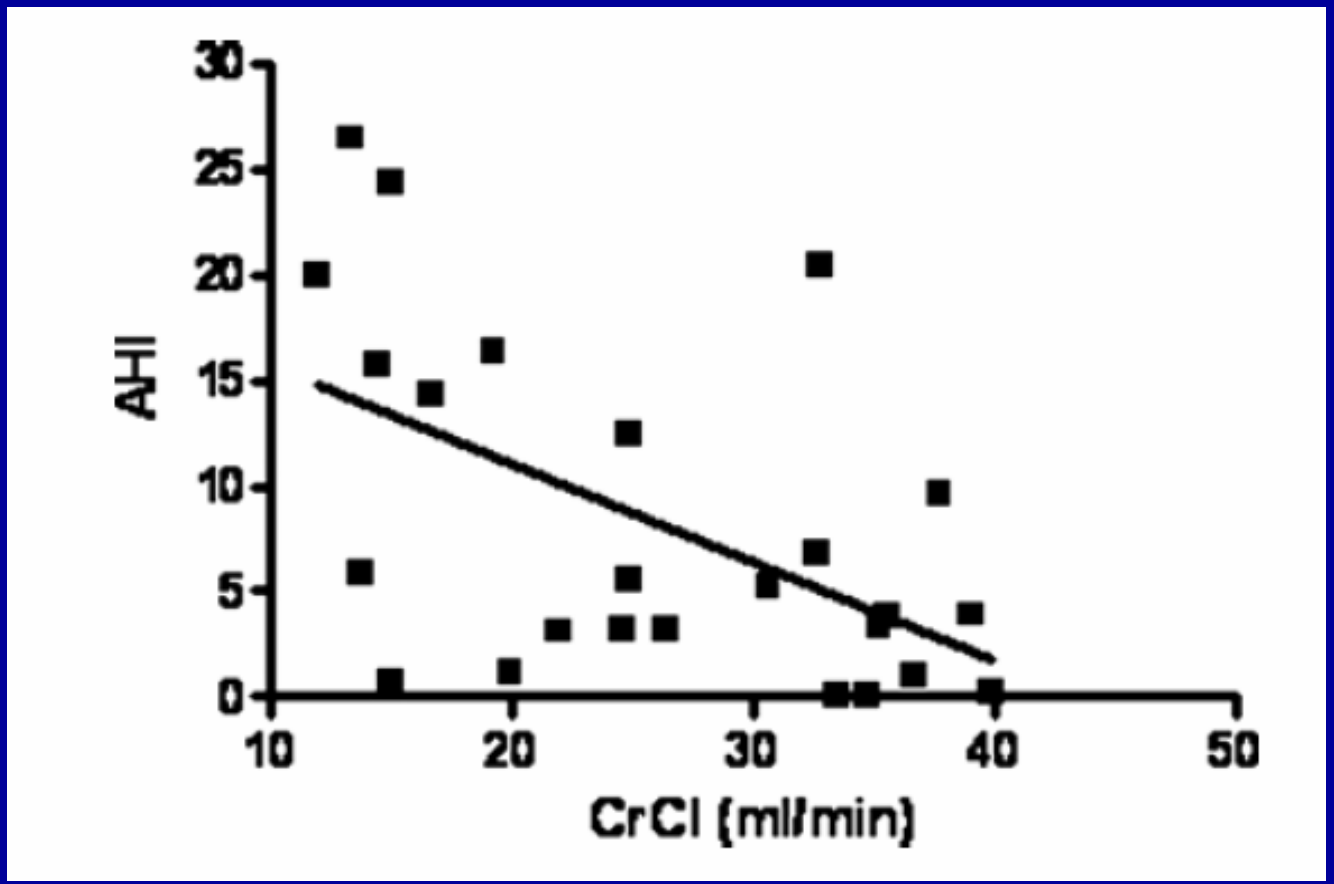
- Daytime seleepiness
- Accidents
- Cognitive impairment
- Depression
- Sexual dysfunction
- Hypertension, LVH, CAD, arrhytmias
- Impaired QoL
- Increased morbidity, mortality?

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)

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

Sleep Apnea in Patients on Conventional Thrice-Weekly Hemodialysis: Comparison with Matched Controls from the Sleep Heart Health Study

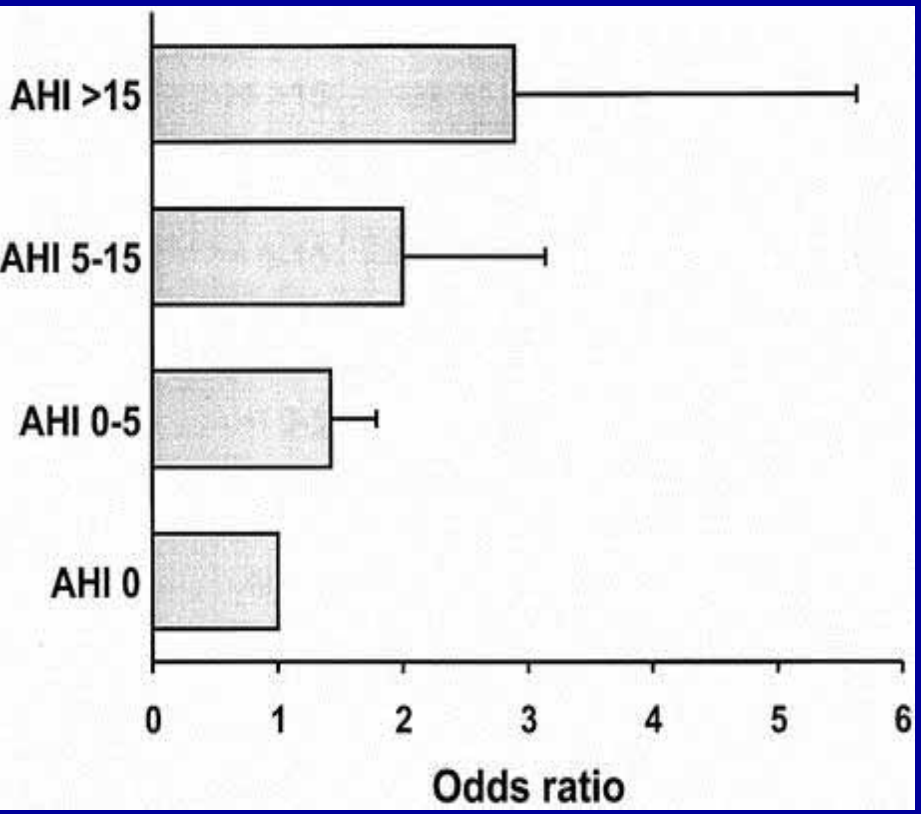
Mark L. Unruh,* Mark H. Sanders,† Susan Redline,‡ Beth M. Piraino,* Jason G. Umans,§ Terese C. Hammond,‖ Imran Sharief,¶ Naresh M. Punjabi,** and Anne B. Newman††

Table 2. Sleep parameters of HD and population control samples[a]

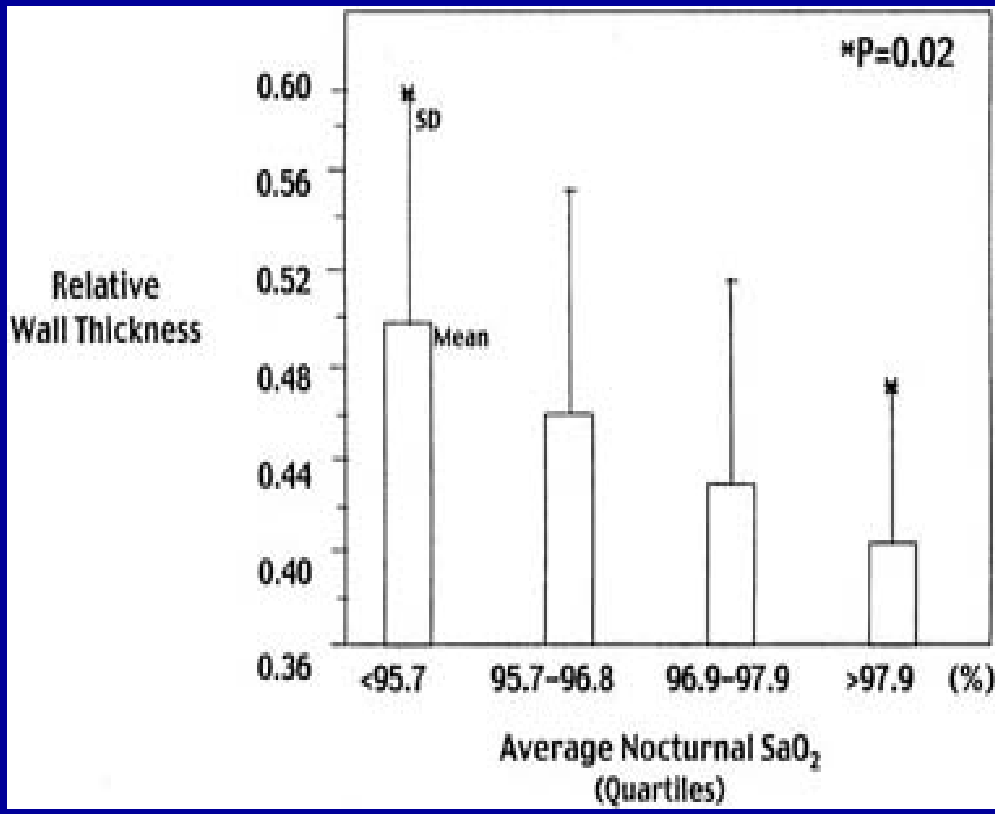
Variable	HD Population (n = 46)	Matched Controls (n = 137)	p[b]
Sleep time (min)	319.5 ± 106.3	378.9 ± 67.3	<0.001
Sleep efficiency (sleep time/total time in bed)	78.1 ± 15.3	81.3 ± 10.4	NS
Stage 1 sleep (%)[c]	5.0 ± 3.4	5.5 ± 3.65	NS
Stage 2 sleep (%)	57.6 ± 14.3	58.4 ± 11.5	NS
Stage 3 to 4 sleep (%)[c]	23.4 ± 12.2	14.3 ± 10.7	<0.001
REM sleep (%)	13.6 ± 8.2	21.7 ± 6.2	<0.001
Arousal index (arousals/h)[d]	25.1 ± 14.6	17.1 ± 8.0	<0.001
Respiratory disturbance index[d]	27.2 ± 19.3	15.2 ± 14.9	<0.001
Hypoxemic index[d,e]	7.2 ± 20.8	1.84 ± 8.4	<0.001
Lowest oxygen saturation, NREM[c]	83.6 ± 7.1	86.7 ± 5.3	<0.01
Lowest oxygen saturation, REM[c]	81.2 ± 9.7	85.9 ± 6.4	<0.001
Epworth Sleepiness Scale	9.0 ± 4.7	8.0 ± 4.3	NS

J Am Soc Nephrol 17: 3503–3509,

SAS - HTN



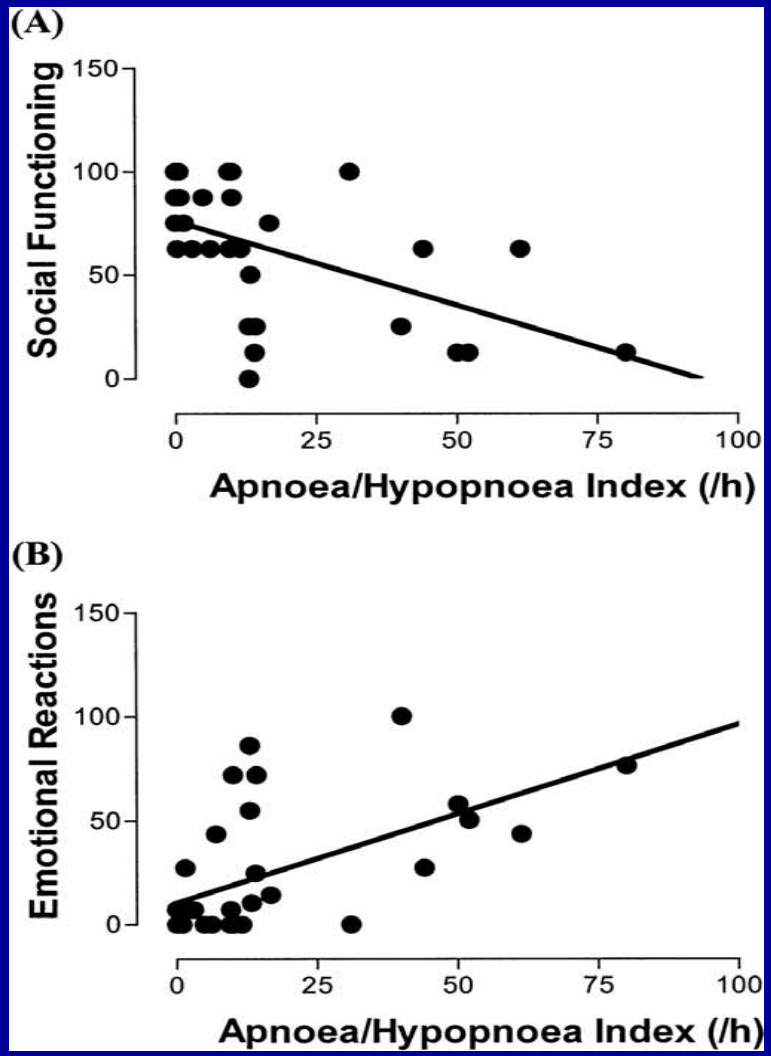
SAS - LVH



Peppard PE et al:N Engl J Med. 2000; 342: 1378–1384

Zoccali et al.: Kidney Int 53: 1078–1084, 1998

SAS and quality of life in dialysis patients



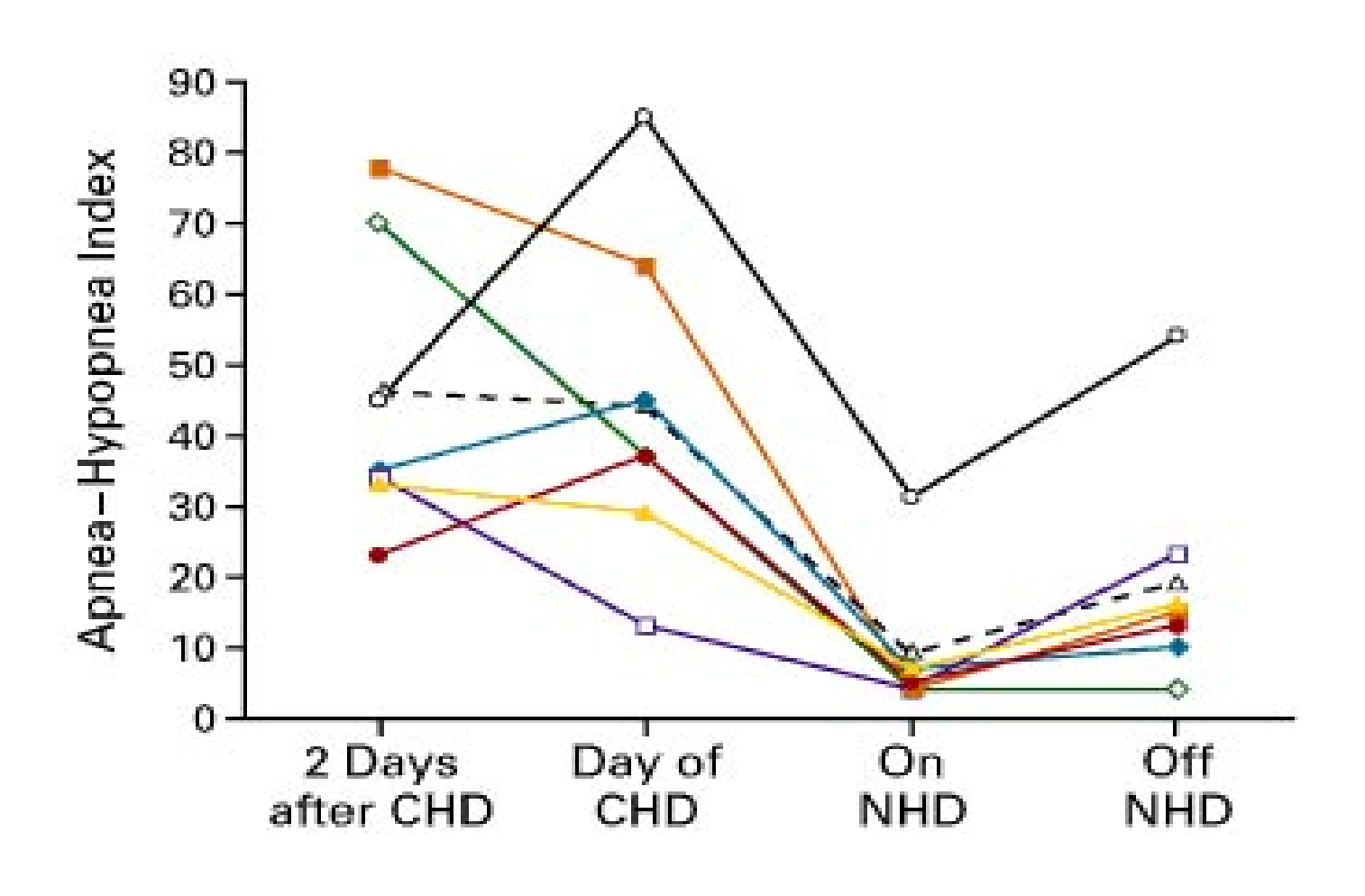
Sanner et al.: NDT, 2002

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

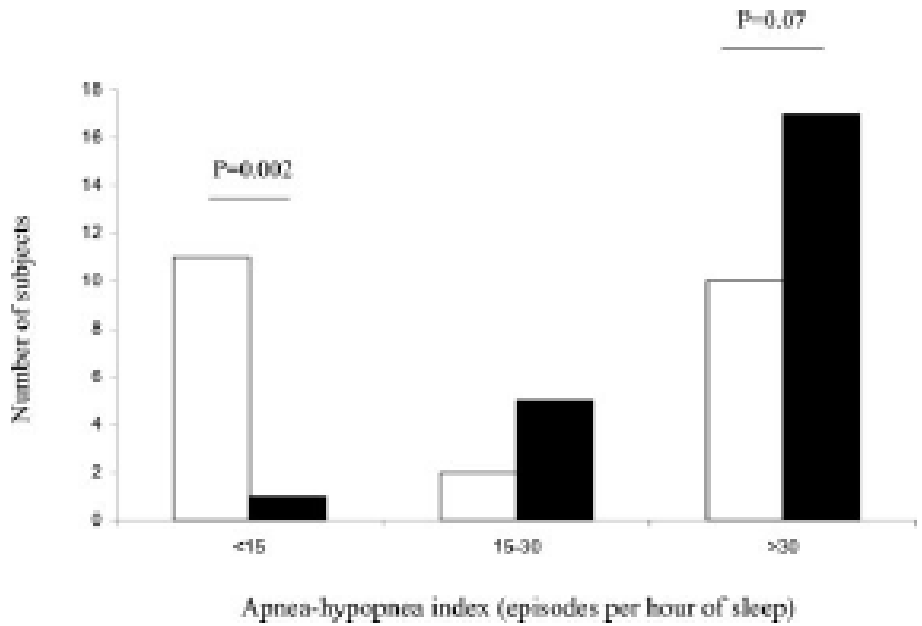
SAS and Nocturnal Home Hemodialysis

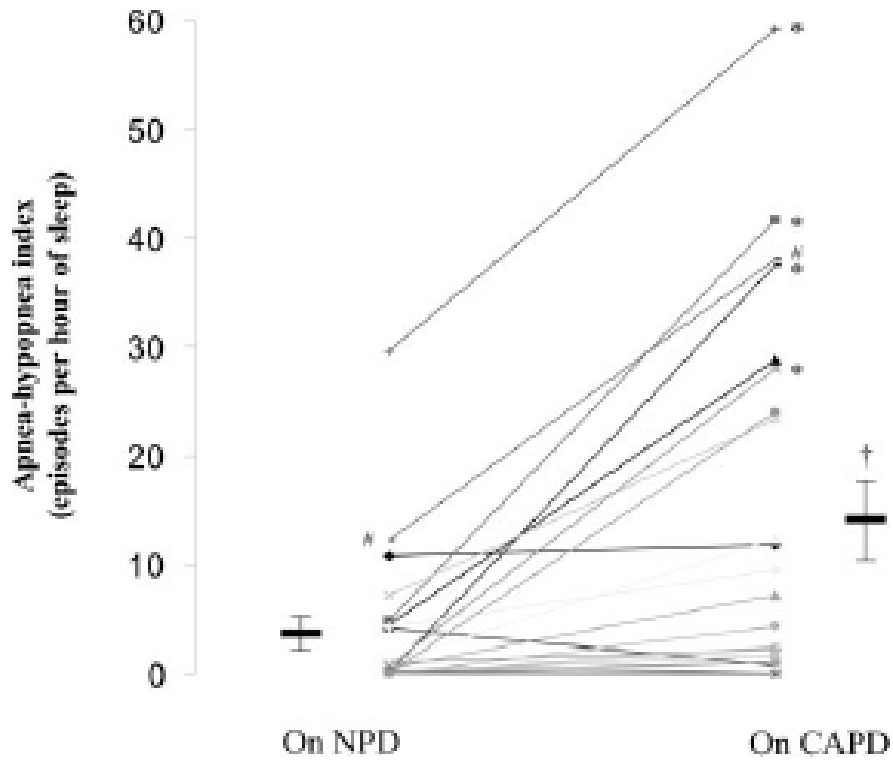


Hanly PJ, Pierratos A. N Engl J Med 2001; 344(2): 102±107.

Alleviation of Sleep Apnea in Patients with Chronic Renal Failure by Nocturnal Cycler–Assisted Peritoneal Dialysis Compared with Conventional Continuous Ambulatory Peritoneal Dialysis

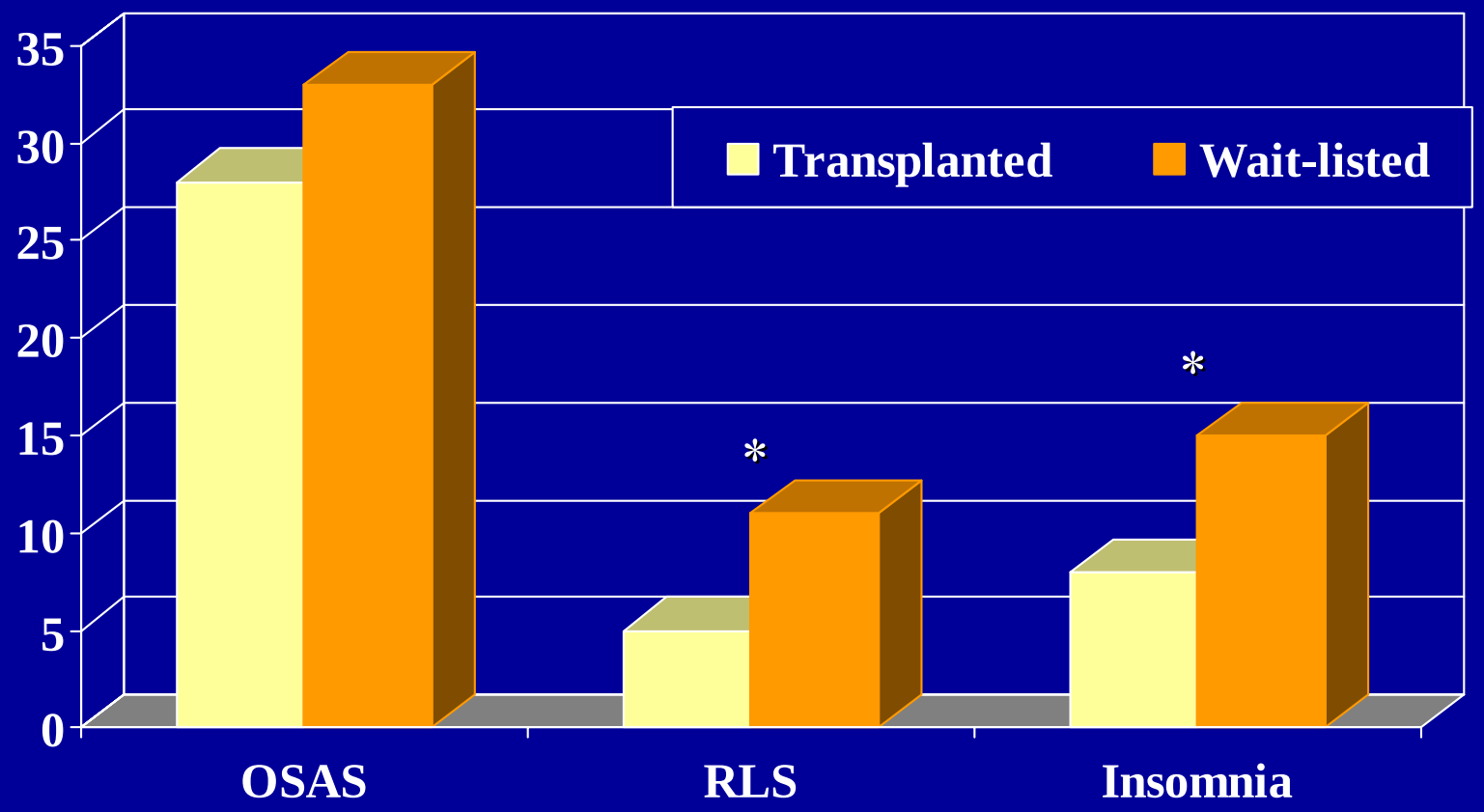
Sydney C.W. Tang,*† Bing Lam,‡ Pui Pui Ku,‡ Wah Shing Leung,§ Chung Ming Chu,§ Yiu Wing Ho,† Mary S.M. Ip,‡ and Kar Neng Lai*





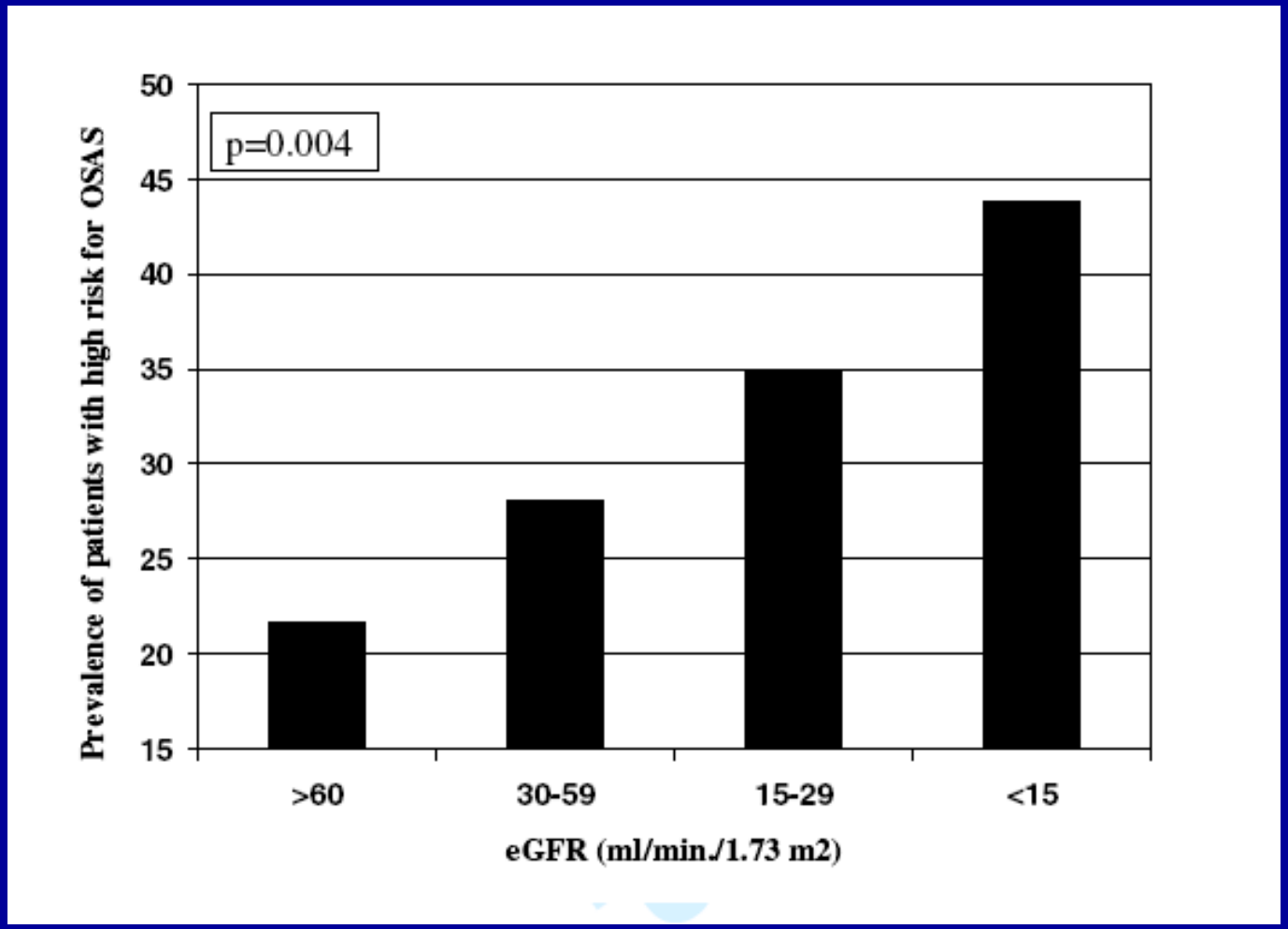
J Am Soc Nephrol 17: 2607–2616, 2006.

Prevalence of sleep disorders in Hungarian dialysis and transplanted patients



*: P<0.001, Khi-square test

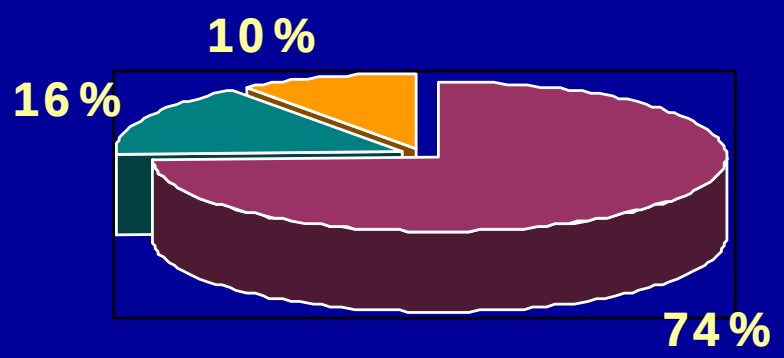
High risk of OSAS and renal function in Tx patients



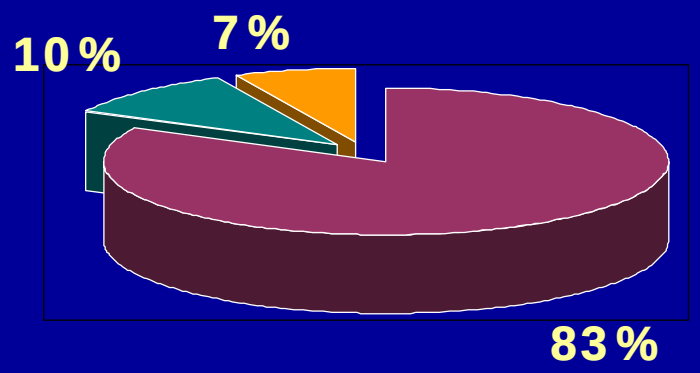
Molnar et al: NDT 2007

Outcome during 4 years

High risk of OSAS

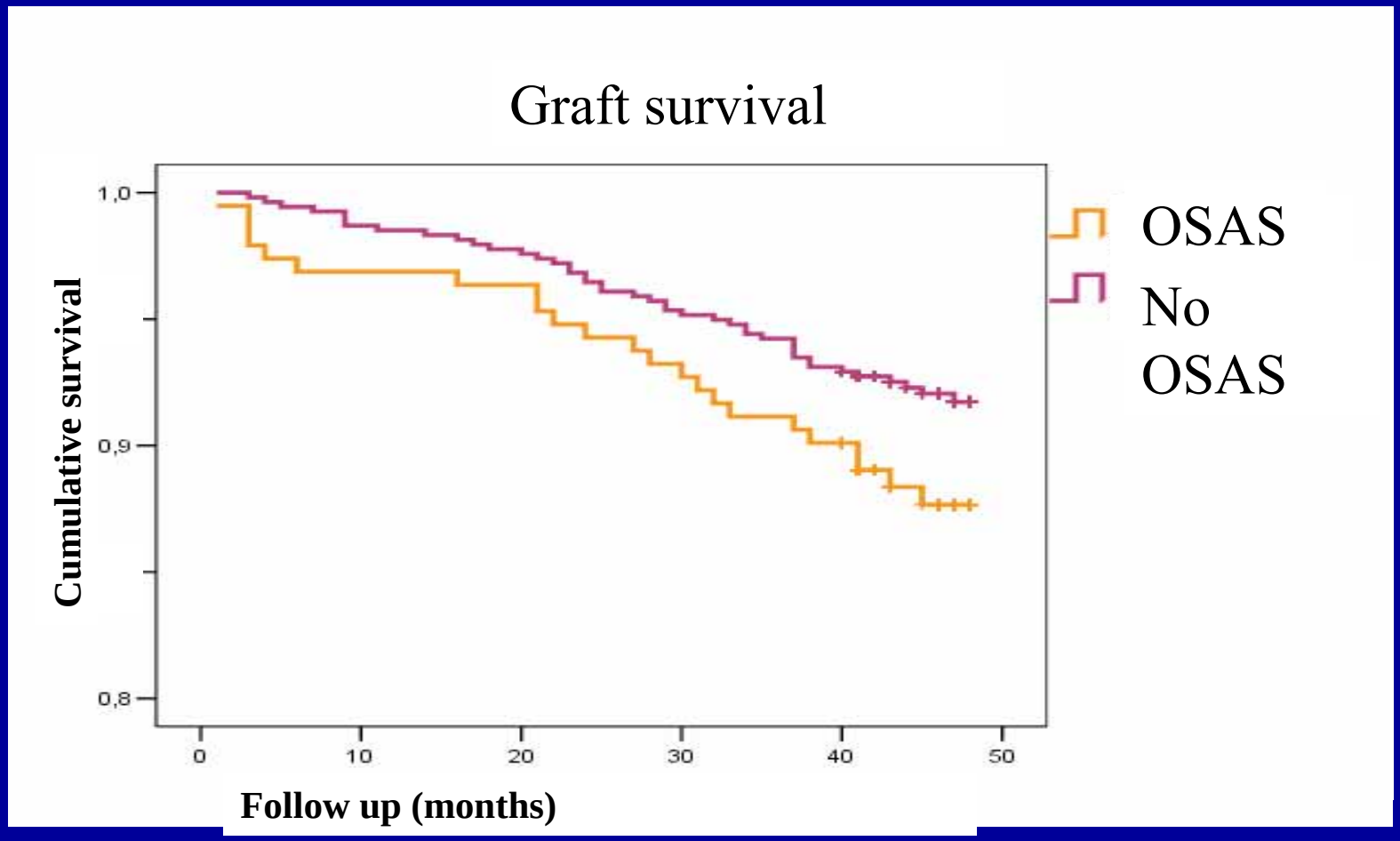


Low risk of OSAS



living with graft | died | living on dial

High risk of OSAS and graft failure



Insomnia

- Difficulties falling or staying asleep, pooor sleep quality, short sleep duration
- Multi-causal
- Lifestyle important
- Role of psychological disturbances (anxiety, depression)
- Depression –early morning awakening
- Other sleep disturbances?

Treatment of insomnia

- Sleep hygiene, lifestyle
- Combined approach

- Pharmacotherapy

- Non-pharmacological treatment:
  psychotherapy, relaxation, cognitive-behavioral therapy, light therapy


Our research

- Sleep disorders in dialysis patients (n=78)
- Sleep disorders – HRQoL in the FMC Hungary network (n=cca 1000)
- Transqol-HU (WL – Tx): cross-sectional and prospective
- Hungarostudy 2002 (nationally representative survey)
- Sleep disorders – HRQoL in CKD patients (HRRH: 130 pts; DOPPS Canada; Budapest 340 pts)
- OSAS and hypertension in the family practice (Ontario: 60 pts; Hungary: recruiting)
- Malnutrition-inflammation complex syndrome, anemia, depression and sleep disorders in kidney transplanted patients (in progress: cca. 500 pts enrolled, 57 PSG)

HUNGAROSTUDY 2002

N=12.643

Cross - sectional survey enrolling a large, nationally representative sample of the Hungarian population

- clustered, stratified sampling
- Home interview with a battery of questionnaires
- Athens Insomnia Scale for insomnia
- Sociodemographic characteristics

TransQol-Hu 2002

- Waitlisted dialysis patients vs kidney transplanted patients in Budapest

- RLS - RLS Questionnaire (Allen and Earley, 2001)
- Insomnia - Athens insomnia scale (Soldatos et al., 2000)
- OSAS - Berlin Questionnaire (Netzer et al., 1999)
- Depression - CES-D (Radloff, 1977)
- QoL - KDQoL-SF (Hays et al., 1995)

- Baseline in 2002 – 4 yrs follow up since

TransQol-Hu 2002

Transplanted

N=959

- age: 49±12 years (18-76 years)
- Median Tx time: 61 mos (1-311 months)
- male: 59%
- diabetes: 17%
- Hb: 132 ±19 g/l
- albumin: 42 ±3 g/l
- eGFR 50 ±22 ml/min

Waiting list

N= 214

- age: 49±12 years (23-79 years)
- Median dial time: 35 mos (3-213 mos)
- male: 62%
- diabetes: 14.5%
- Hb: 113 ±15 g/l
- albumin: 41 ±4 g/l
- Kt/V: 1.27 ± 0.26

MICS-Sleep 2007

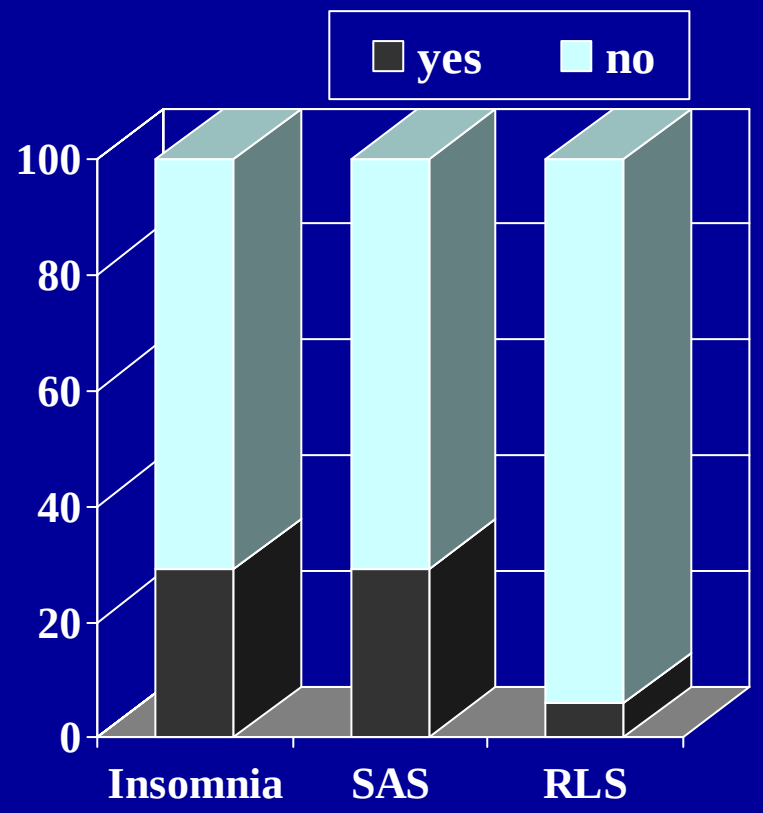
- Cca 1100 kidney transplanted patients in Budapest

- Malnutrition, inflammation – alb, pre-albumin,cholesterol, CRP, SGA, Il1, Il4, Il6, Il10, TNF-alpha, leptin, adiponectin
- Depression - CES-D (Radloff, 1977) + structured interview in a sample of consecutive patients
- Sleep – PSG in cca 100 pts +
  - Athens insomnia scale (Soldatos et al., 2000)
  - Berlin Questionnaire (Netzer et al., 1999)
  - RLS Questionnaire (Allen and Earley, 2001)

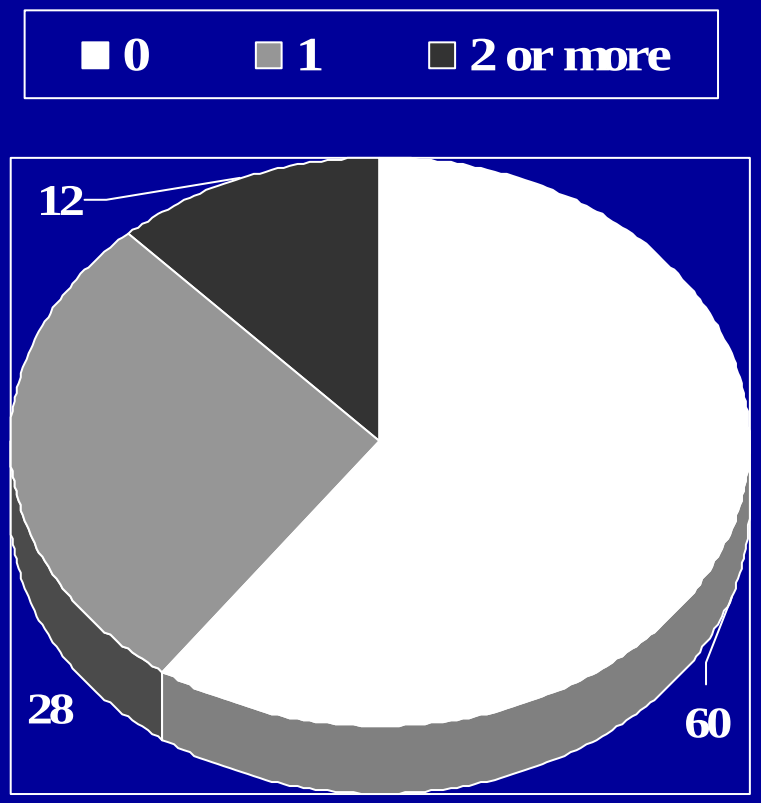
- Baseline in 2007 – 5 yrs follow up planned

Sleep problems in predialysis patients
(Humber River Regional Hospital, Toronto; n=128)

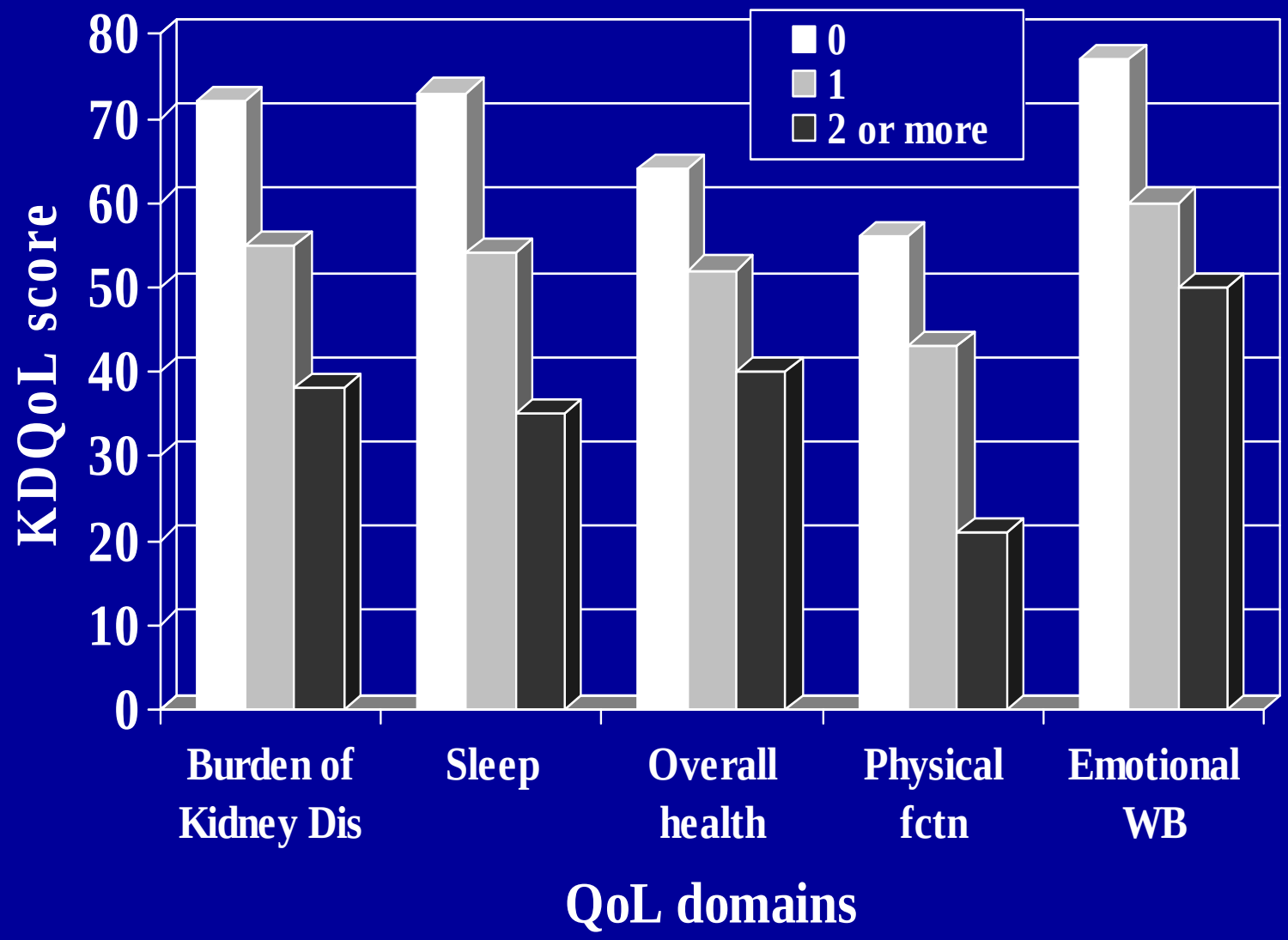
Prevalence of specific sleep problems



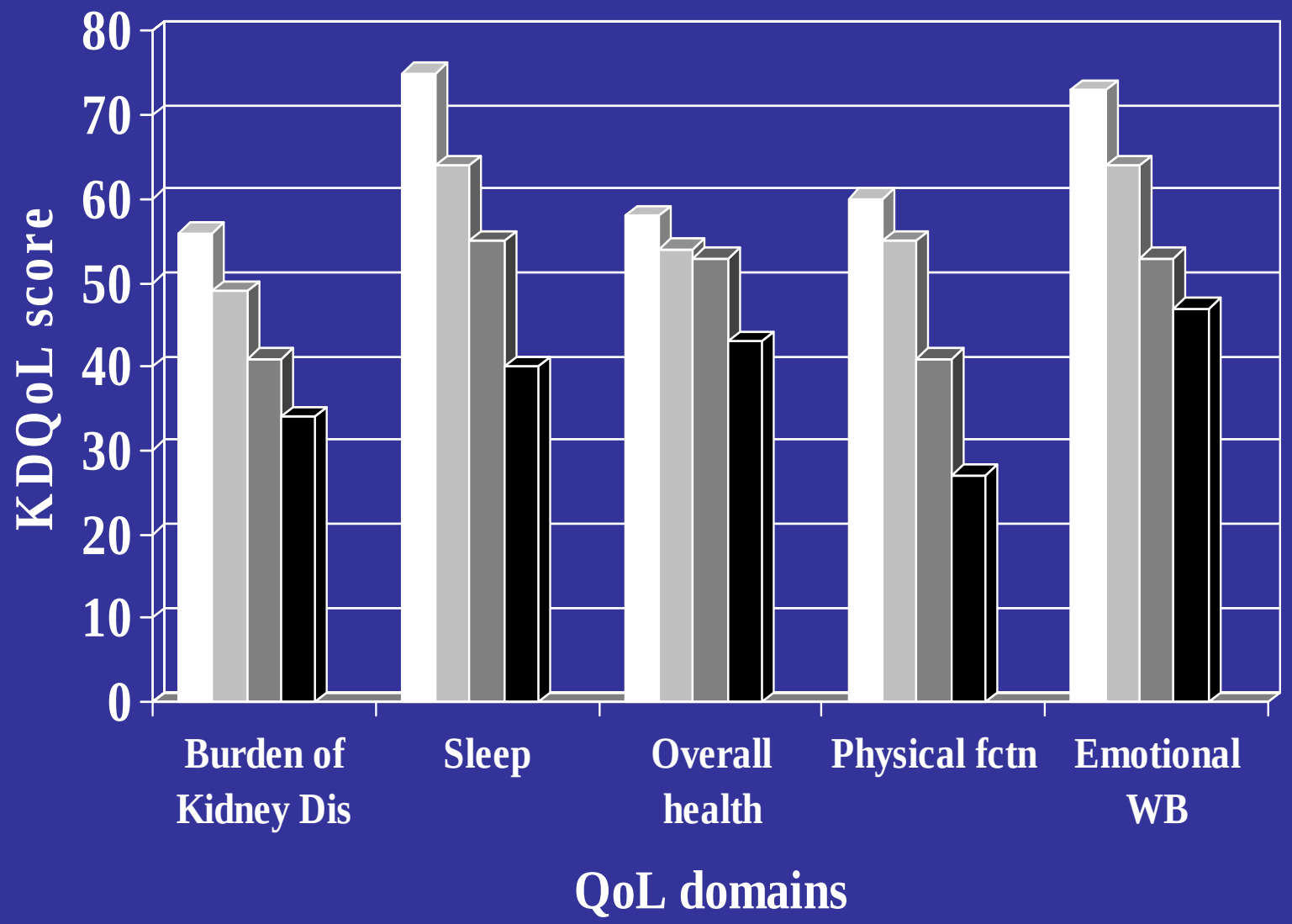
Frequency of sleep problems



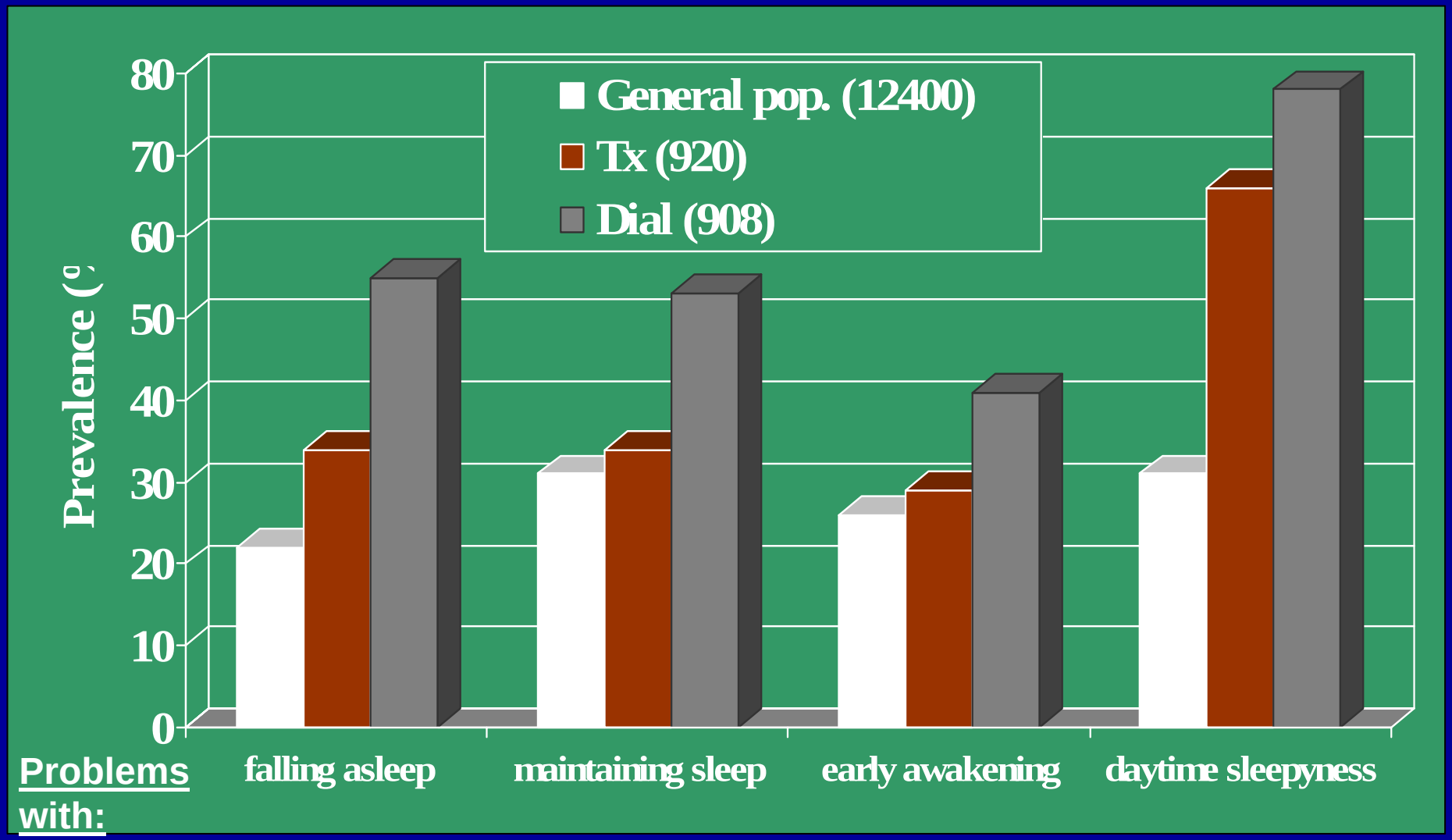
The presence of sleep problems and Health Related Quality of Life in predialysis patients (n=128)



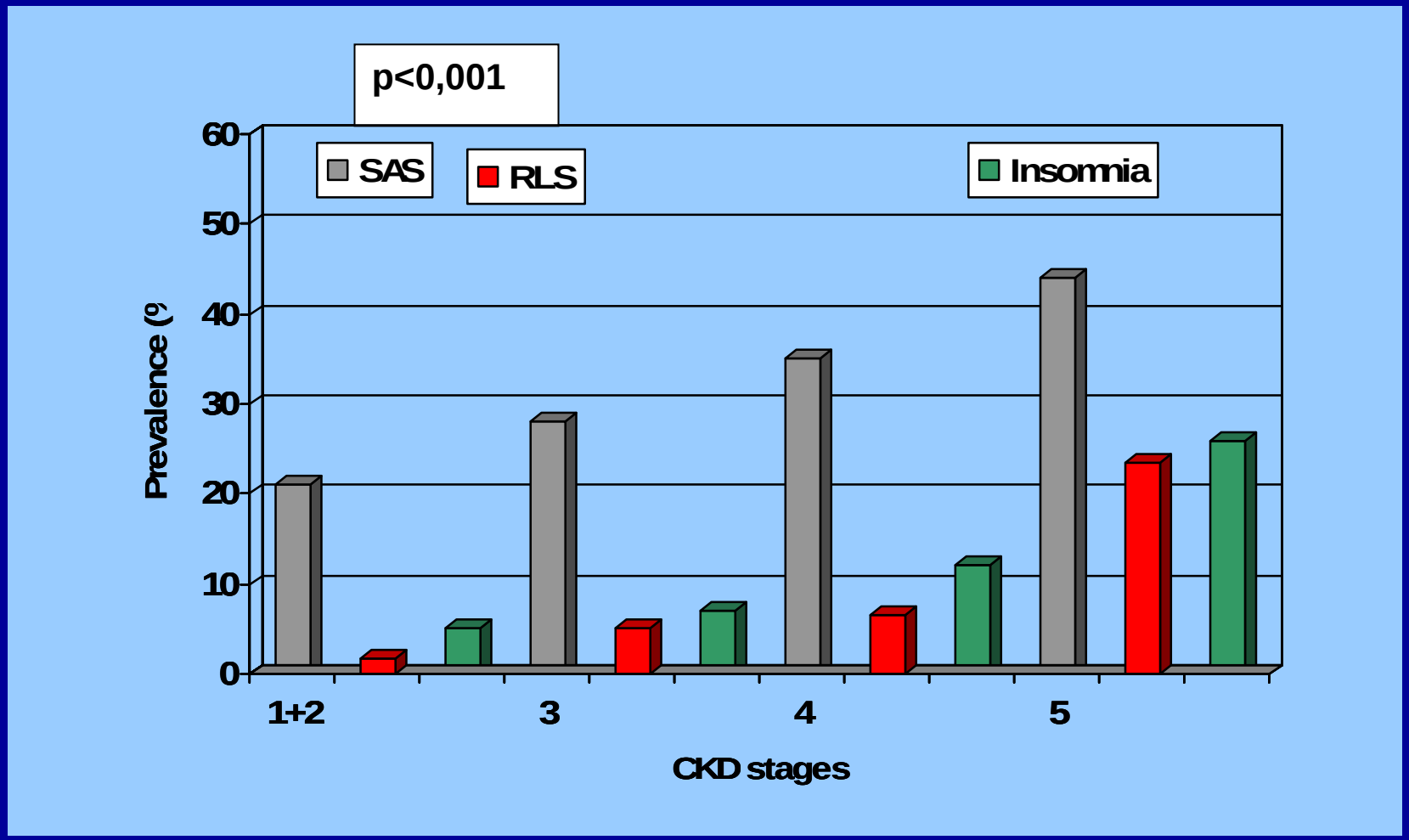
Daytime sleepiness and Health Related Quality of Life in dialysis patients (n=908)



Sleep complaints in transplanted vs dialysis patients vs the general population



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



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 RLS and insomnia these conditions is the lower in transplanted patients (not 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

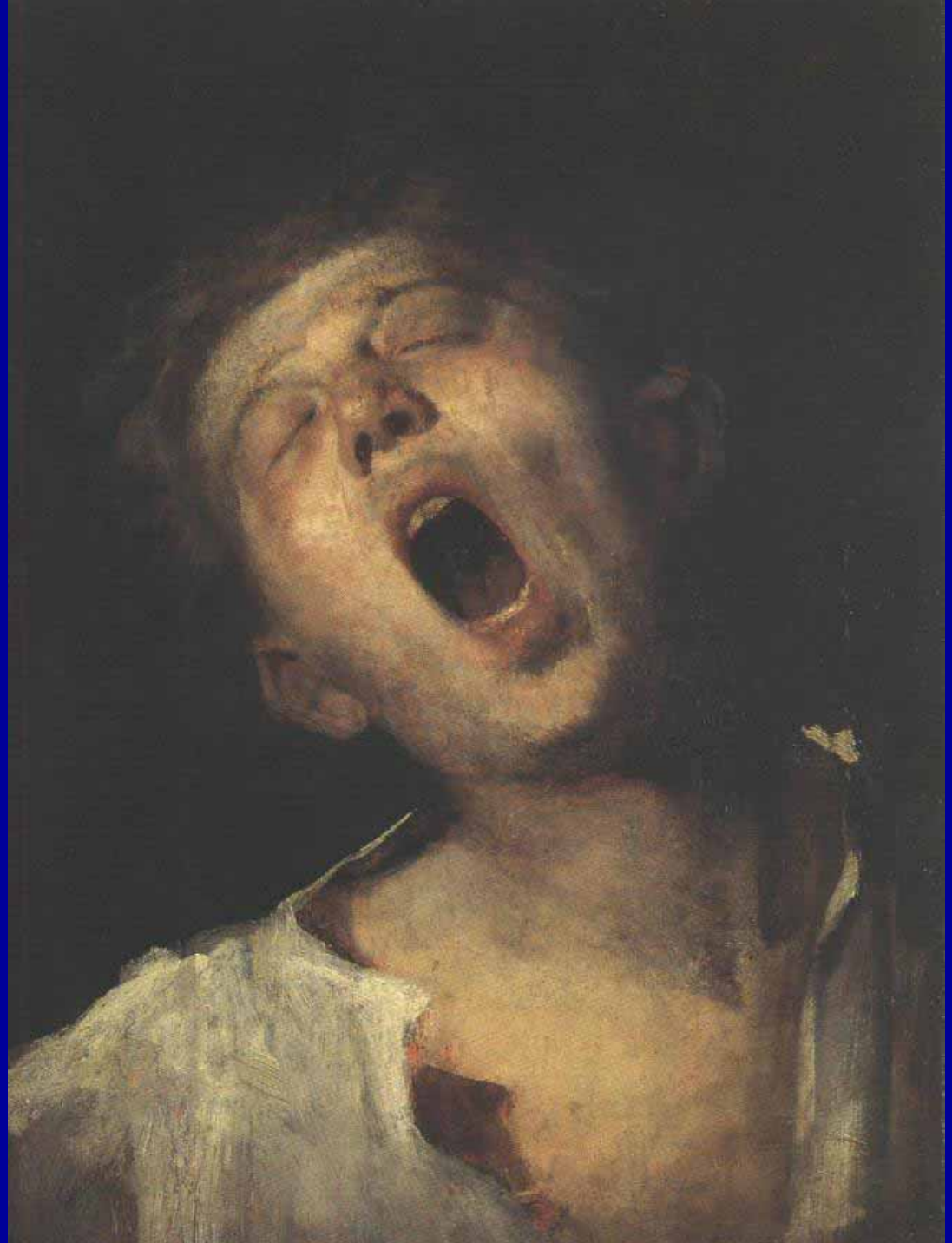
Conclusions

- Sleep disorders are frequent in the CKD population
- Sleep disorders underdiagnosed and un(der)treated
- Effect of sleep disorders on quality of life and other outcomes (co-morbidity?, survival?)
- Management of these treatable disorders and may improve QoL of renal patients

Yawning Apprentice

Mihály Munkácsy

(1844 – 1900)



THANK YOU!

Sleep Heart Health Study

- Multicentrikus, populáció szintű vizsgálat
- N=6,132 (életkor >=40 év, 52.8% nő)
- Kardiovaszkuláris morbiditás és mortalitás közti kapcsolat elemzése
- Hypertonia prevalenciája és a vérnyomás az AHI index-szel arányosan nőtt

JAMA 2000;283:1829-1836

Korrigált esély hányados (OR)
Hypertonia és AHI index: Sleep Heart Health Study, 1995-1998

Variables	No. of Subjects	Adjusted for Demographics† OR (95% CI)	OR Adjusted for Demographics†‡		
			BMI OR (95% CI)	BMI, Neck, Waist-to-Hip Ratio OR (95% CI)	BMI, Neck, Waist-to-Hip Ratio, Alcohol Use, Smoking OR (95% CI)
Apnea-hypopnea index per hour					
<1.5	1691	1.00	1.00	1.00	1.00
1.5-4.9	1598	1.25 (1.08-1.44)	1.12 (0.96-1.30)	1.11 (0.95-1.29)	1.07 (0.91-1.26)
5-14.9	1751	1.57 (1.35-1.81)	1.28 (1.09-1.48)	1.24 (1.06-1.45)	1.20 (1.01-1.42)
15-29.9	719	1.73 (1.43-2.10)	1.32 (1.08-1.61)	1.26 (1.03-1.55)	1.25 (1.00-1.56)
≥30	373	2.27 (1.76-2.92)	1.60 (1.23-2.08)	1.47 (1.12-1.92)	1.37 (1.03-1.83)
P (trend)		.0001	.0001	.0008	.005

Sleep Heart Health Study Korrigált esély hányados az AHI quartilisek szerint

	AHI Quartile				
	I	II	III	IV	p Value
Quartile range	0-1.3	1.4-4.4	4.5-11.0	>11.0	
Coronary heart disease	1.0	0.92	1.20	1.27	0.004
		(0.71-1.20)	(0.93-1.54)	(0.99-1.62)	
Heart failure	1.0	1.13	1.95	2.38	0.002
		(0.54-2.39)	(0.99-3.83)	(1.22-4.62)	
Cardiovascular disease	1.0	0.98	1.28	1.42	0.0003
		(0.77-1.24)	(1.02-1.61)	(1.13-1.78)	

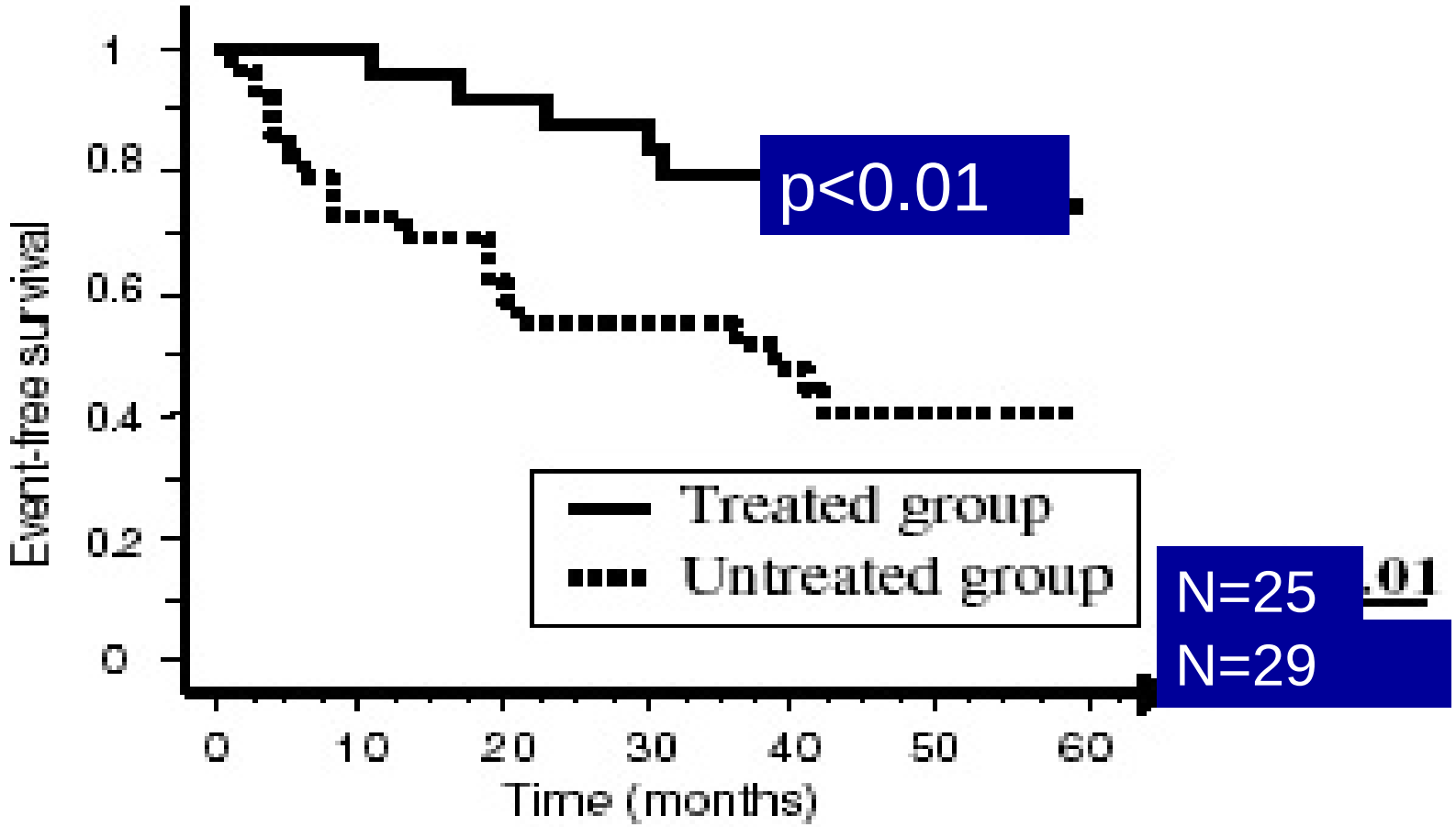


Fig. 1 Kaplan–Meier analysis: event-free survival in the groups with and without treatment for obstructive sleep apnea.