
Non-restorative Sleep

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Speaker:

1. I do not have any potential conflicts of interest to disclose, **OR**

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4. This talk presents material that is related to one or more of these potential conflicts, and the following objective references are provided as support for this lecture:

1. Principle and Practice of Sleep Medicine – Section on Pharmacology

2.

3.

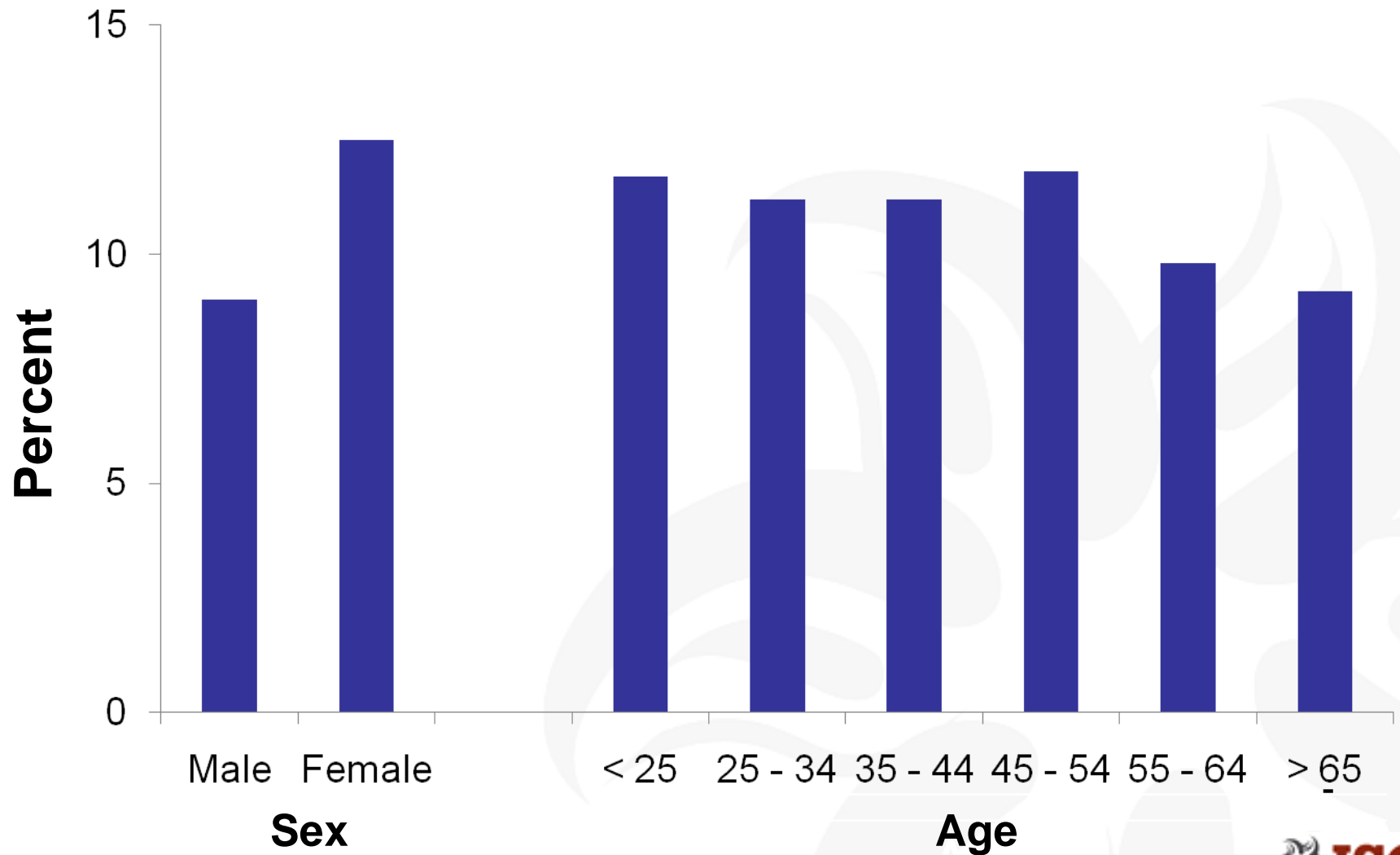
Non-restorative sleep

- The term “nonrestorative sleep” as a component of insomnia is used in the 3 major diagnostic and coding manuals for sleep (i.e. ICD, ICSD, and DSM-IV)
- Various operational definitions of “nonrestorative” sleep have been used

Prevalence of NRS

- **“How frequently are you bothered by the following problem:**
 - **Your sleep is not refreshing, you don’t feel rested even if the duration of your sleep is normal.”**
 - **NRS = 3 to 4 days/week or more**
- **NRS Population prevalence = 10.8%**

Prevalence of NRS by Sex and Age



Classic Insomnia and NRS

- Classic insomnia symptoms defined by “period lasting two weeks or longer in the past 12 months” of:
 - “nearly every night it took you two hours or longer before you could fall asleep” - DIS
 - “you woke up nearly every night and took an hour or more to get back to sleep” - DMS
 - “you woke up nearly every morning at least two hours earlier than you wanted to” - EMA
- NRS assessed based on frequency during past 12 months with:
 - difficulty getting up in the morning
 - waking up not feeling rested
 - had not slept long enough even when having enough time in bed
 - not feeling refreshed after sleep

NRS and Traditional Nocturnal Symptoms of Insomnia

Insomnia Symptom	Conditional Prevalence of NRS; % +/- se
DIS	55.7 +/- 4.1
DMS	53.7 +/- 3.3
EMA	50.2 +/- 4.4
DIS-DMS	66.4 +/- 4.4
DIS-EMA	63.2 +/- 6.5
DMS-EMA	59.2 +/- 4.8
DIS-DMS-EMA	73.4 +/- 1.9
None	10.0 +/- 0.6

Prevalence (%) and Adjusted Odds Ratios for NRS With Associated Factors

Factor	% with NRS	OR
Regular difficulty getting started	39.8	5.42
Global sleep dissatisfaction	52.6	3.28
Bad night's sleep \geq 2/wk	38.8	3.04
DSM-IV Bipolar	40.7	1.90
Nighttime awakenings, > 2 nights/wk	20.0	1.73
DSM-IV Depressive	42.9	1.72
DSM-IV Anxiety	12.9	1.68
Extra sleep on days off, > 3 hours	18.9	1.58
Sleep latency > 60 min	28.3	1.55
Nighttime sleep duration \geq 9 hrs	8.9	1.47

Prevalence of NRS and Associated Features

Variable	Subjects with NRS, %	Crude OR *(95% CI)	Adjusted OR † (95% CI)
Sleep Latency, min			
≤ 15	7.1	1.0	1.0
16-30	12.8	1.9‡ (1.76-2.13)	1.30‡ (1.13-1.49)
31-60	18.5	2.99‡ (2.66-3.35)	1.38‡ (1.15-1.66)
>60	28.3	5.20‡ (4.53-5.96)	1.55‡ (1.19-2.01)
Nighttime sleep duration, hrs			
<5	25.7	4.25‡ (3.55-5.09)	0.66† (0.46-0.94)
≥5 to <6	17.3	2.57‡ (2.22-2.99)	0.72† (0.55-0.94)
≥6 to <7	14.0	2.00‡ (1.78-2.25)	1.03 (0.85-1.24)
≥7 to <8	9.5	1.28‡ (1.14-1.44)	0.95 (0.80-1.13)
≥8 to <9	7.5	1.00	1.00
≥ 9	8.9	1.20 (1.00-1.43)	1.47‡ (1.12-1.92)

Prevalence of NRS and Associated Features

Variable	Subjects with NRS, %	Crude OR *(95% CI)	Adjusted OR † (95% CI)
Extra Sleep on wk/end & days off, hrs			
0	7.9	1.00	1.00
≤1	11.5	1.51‡ (1.32-1.74)	1.15 (0.95-1.38)
>1 to ≤2	14.4	1.95‡ (1.73-2.20)	1.31§ (1.11-1.55)
>2 to ≤3	16.1	2.22‡ (1.90-2.61)	1.31† (1.05-1.63)
>3	18.9	2.70‡ (2.29-3.18)	1.58‡ (1.26-1.99)
Global sleep dissatisfaction			
Satisfied	7.1	1.00	1.00
Dissatisfied	52.6	14.42‡ (13.05-15.93)	3.28‡ (2.70-3.99)
Frequency of bad night's sleep			
Never	7.6	1.00	1.00
1 Time/wk	32.2	5.78‡ (5.04-6.63)	2.41‡ (1.98-2.93)
≥2 Nights/wk	38.8	7.71‡ (6.73-8.82)	3.04‡ (2.42-3.82)
Stressful event in the last 12 mo			
Absent	8.2	1.00	1.00
Present	20.7	2.93‡ (2.67-3.23)	1.43‡ (1.26-1.62)

Prevalence and Inter-Correlations of 12-Month Sleep Problems in the Part II NCS-R

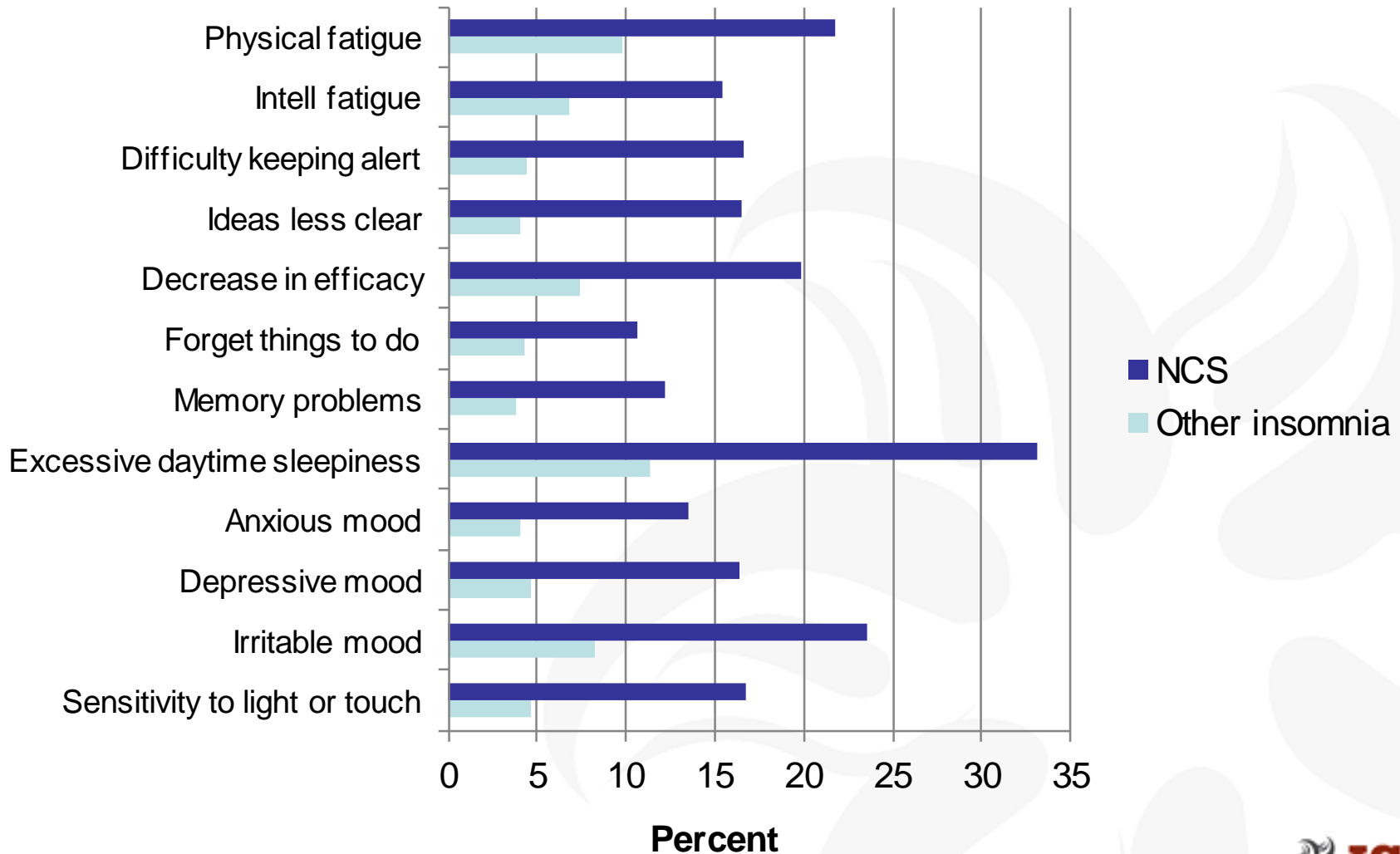
	Prevalence		Inter-Correlations			
	%	(se)	DIS	DMS	EMA	NRS
Difficulty Initiating Sleep (DIS)	16.4	(.6)	-	-	-	-
Difficulty Maintaining Sleep (DMS)	19.9	(.8)	.76 ^b	-	-	-
Early Morning Awakening (EMA)	16.7	(.7)	.66 ^b	.84 ^b	-	-
Non-Restorative Sleep (NRS)	25.0	(.8)	.68 ^b	.70 ^b	.65 ^b	-
Any	36.3	(1.0)				

^aTetrachoric correlations.

^bSignificant at the .05 level, two-sided test.

Part II NCS-R (n = 5692)

Percentage of Individuals With NRS and Other Insomnia Complaints Who Report Daytime Symptoms



Ohayon, 2005

Association of Sleep Problems with Role Functioning

		Daytime Sleepiness	Days Out of Role	Reduced Quantity	Reduced Quality	Extreme Effort
DIS	net	-1.2	2.0	0.8	0.6	0.7
	pure	10.4	1.8	1.6	1.0	1.7
DMS	net	6.1	1.3	0.5	0.4	0.4
	pure	18.1	-0.4	0.1	-0.1	-0.5
EMA	net	7.3	0.6	0.1	0.0	0.4
	pure	12.4	-0.5	0.1	0.4	0.0
NRS	net	29.8	2.2	1.5	1.0	1.5
	pure	42.2	2.0	1.6	1.2	1.4

NCS-R (n = 5692), RED= p<0.05

net = adjusted for sex, age, race-ethnicity, education, marital status, occupation, no. children, DSM-IV diagnoses.

pure = includes only sub-sample without any DSM-IV diagnosis

b = adjusted mean differences on impairment scales versus those without sleep problems

Associations with nonrestorative sleep

- Ohayon, 2005

- Sleep initiation problems
- Sleep maintenance problems
- Younger
- More women
- Increased stress
- Anxiety (OR = 1.68)
- Depression (OR = 1.72)
- Increased sleepiness
- Reduced sleep duration
- Other sleep disorders

Ohayon MM. Arch Intern Med 2005;165:35–41.

- Roth, 2006

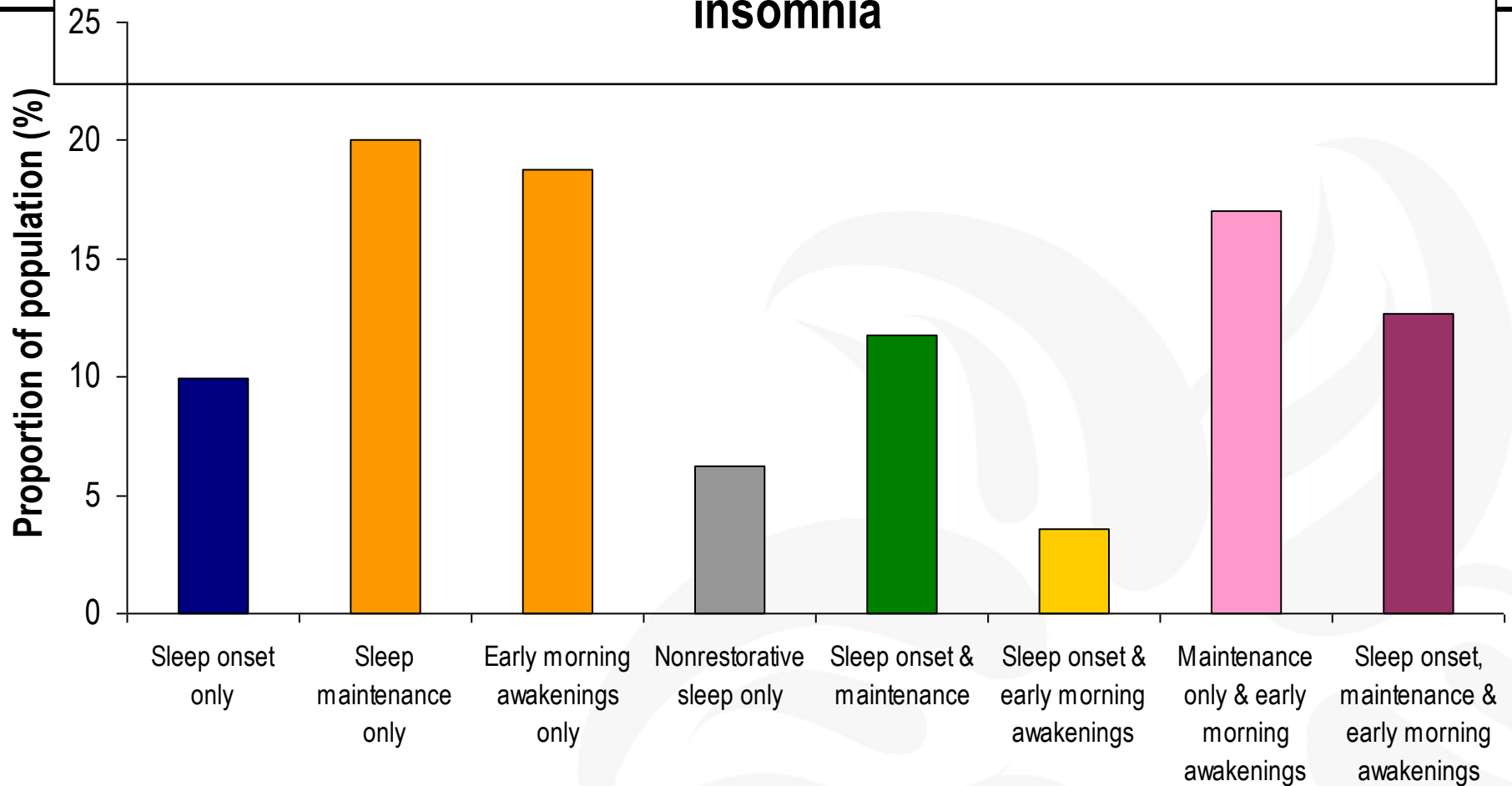
- Sleep initiation problems
- Sleep maintenance problems
- Younger
- Gender?
- Increased stress (post-traumatic stress disorder)
- Anxiety (OR = 4.1)
- Depression (OR = 6.1)
- Increased sleepiness
- Sleep duration?
- Other sleep disorders?

Roth T et al. Biol Psychiatry 2006;60:1364–71.

Prevalence of insomnia symptoms by nosology and in total population

	DSM (%)	ICD (%)	RDC (%)	Total populati on (%)
Sleep onset	38.2	62.0	41.2	12.5
Sleep maintenance	61.4	76.1	63.4	23.6
Early morning awakenings	51.8	51.7	52.4	23.2
Nonrestorative sleep	6.5	5.8	7.3	1.8

Prevalence of clusters of sleep symptoms by any insomnia

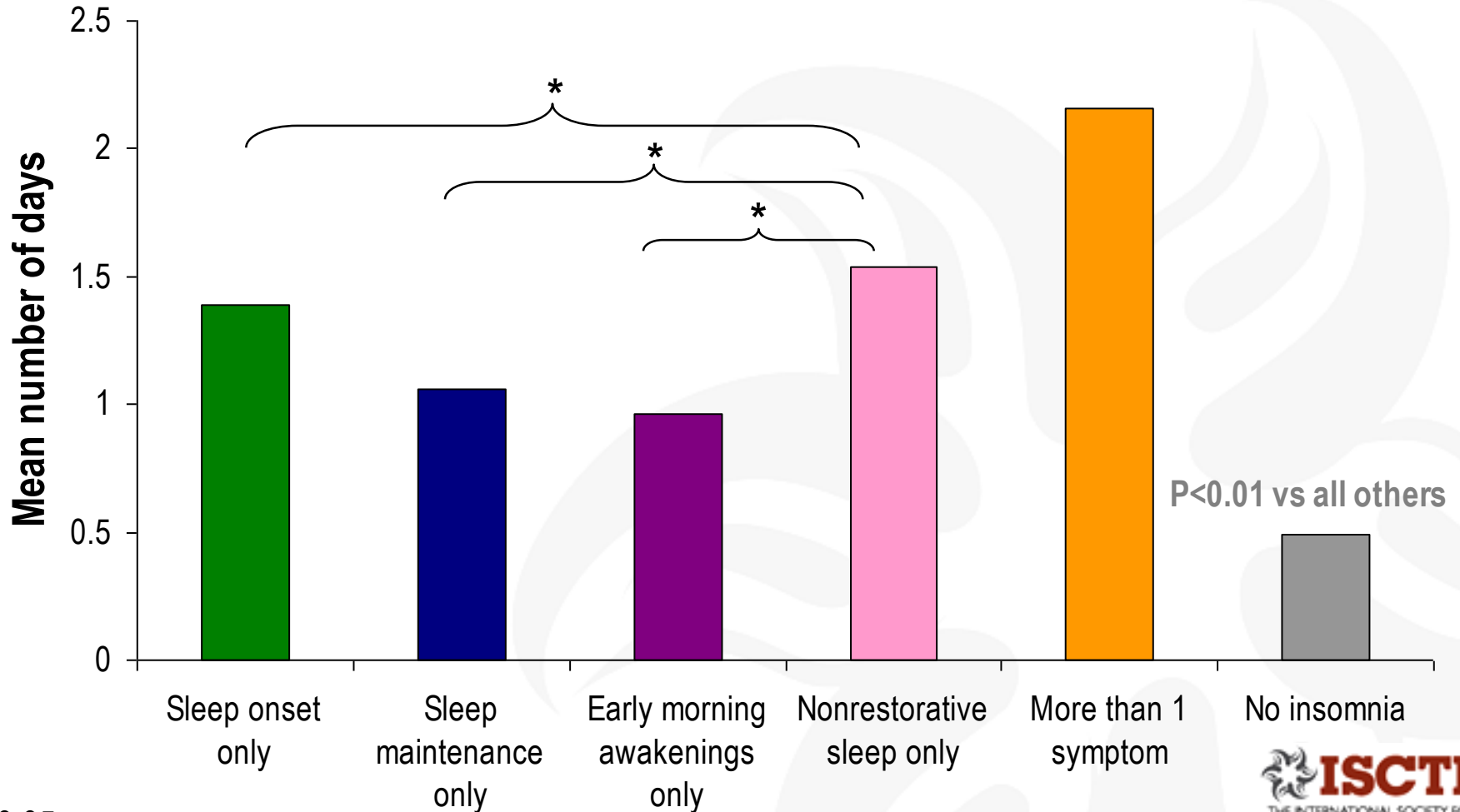


Population attributable risk proportion (PARP)

PARP

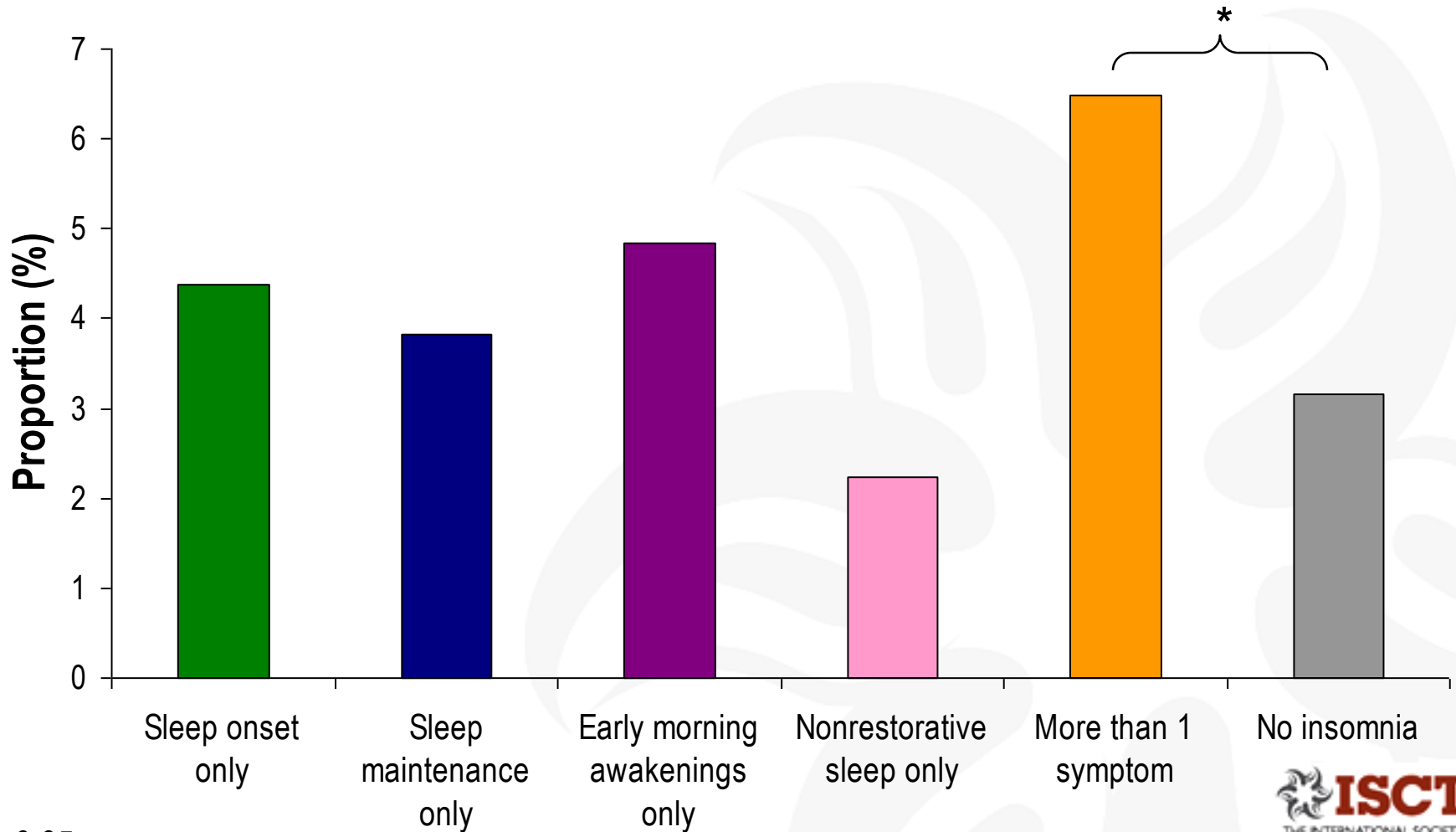
	Accidents (%)	Days out of role/30 days (%)
Any insomnia	9.8	29.1
Chronic obstructive pulmonary disease	0.5	3.5
Diabetes	0.3	-1.5
Osteoarthritis	-0.1	2.6
Gastroesophageal reflux disease	0.9	4.0
Sleep apnea	-0.6	1.1
Neuropathic pain	2.6	2.9
Chronic heart failure	0.3	2.3
Climacteric symptoms	0.3	2.1
Hypertension	3.9	6.2
Major depressive disorder	1.5	3.9
Rheumatoid arthritis	-0.1	0.7
All of the above disorders	18.0	52.0

Impairment by insomnia symptom: days out of role due to physical/mental health (past 30 days)



*P<0.05

Impairment by insomnia symptom: prevalence of falls (past 12 months)



*P<0.05

Subject selection and cohort assignment

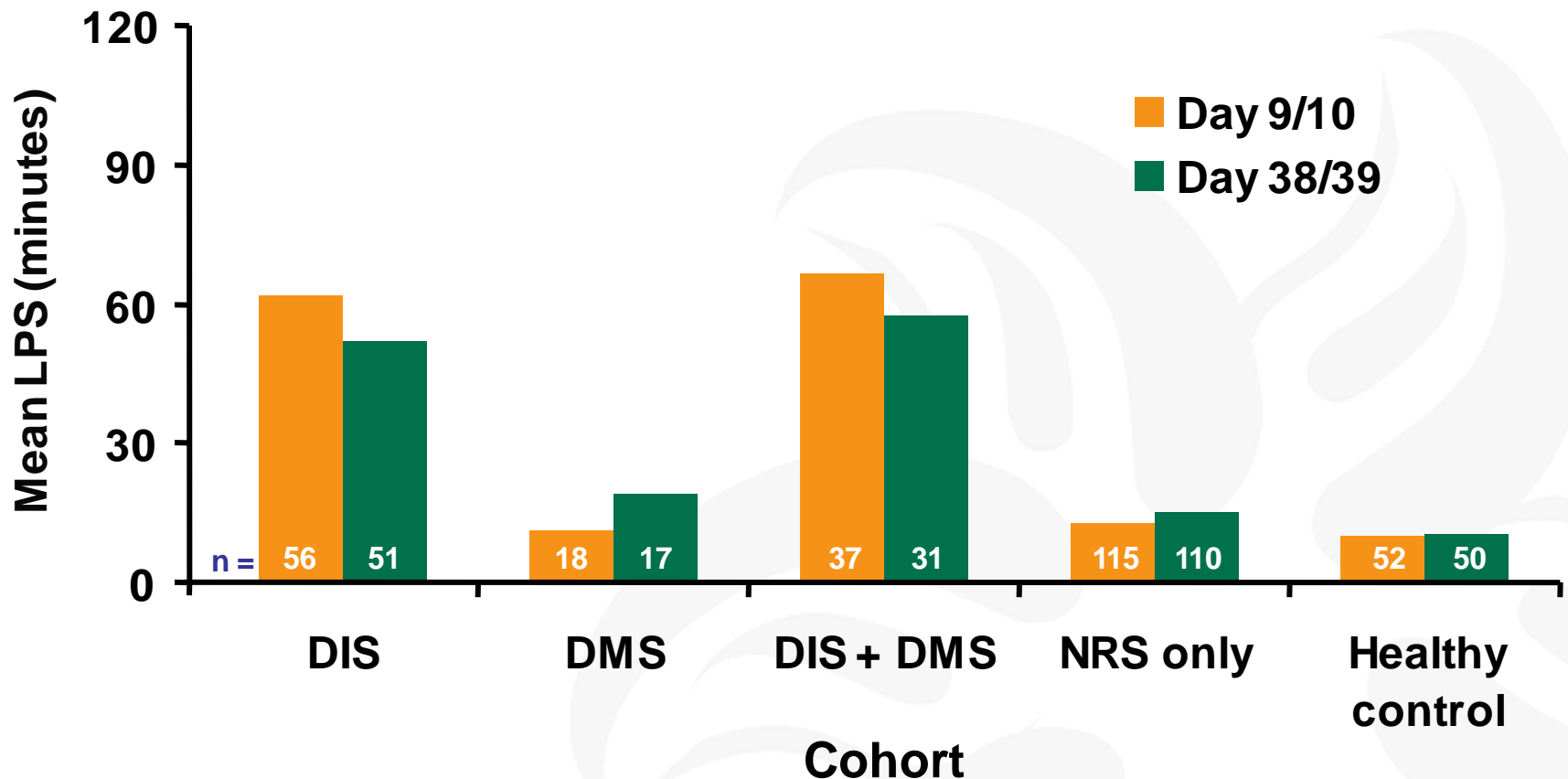
- Enrollment – subjects reporting symptoms consistent with NRS:
 - Regularly (≥ 3 times per week) awakening unrestored or unrefreshed, causing significant distress or impairment in social, occupational, or other important areas of daytime functioning, for at least the past 3 months
- Cohort assignment, based initially on self-reported symptoms:
 - DIS (sleep latency typically ≥ 30 minutes)
 - DMS (time awake after sleep onset typically ≥ 60 minutes)
 - DIS and DMS
 - NRS only – neither DIS nor DMS
- Healthy volunteers without sleep disorders formed a control group
- Exclusions: subjects with PSG evidence of respiratory or limb movement disorders or any parasomnia

Subject demographics

	Cohort					Total (n=278)
	DIS (n=56)	DMS (n=18)	DIS + DMS (n=37)	NRS only (n=115)	Healthy control (n=52)	
Gender, n (%)						
Male	23 (41)	3 (17)	16 (43)		14 (27)	101 (36)
Female	33 (59)	15 (83)	21 (57)		38 (73)	177 (64)
Age, mean (SD)	31.8 (10.0)	44.8 (10.0)	39.7 (10.7)		30.2 (9.4)	32.5 (10.3)
Race, n (%)						
White	27 (48)	6 (33)	16 (43)	51 (44)	40 (77)	140 (50)
Black	8 (14)	8 (44)	17 (46)	13 (11)	2 (4)	48 (17)
Hispanic	11 (20)	2 (11)	4 (11)	39 (34)	7 (13)	63 (23)
Other	10 (18)	2 (11)	0 (0)	12 (10)	3 (6)	27 (10)

PSG results:

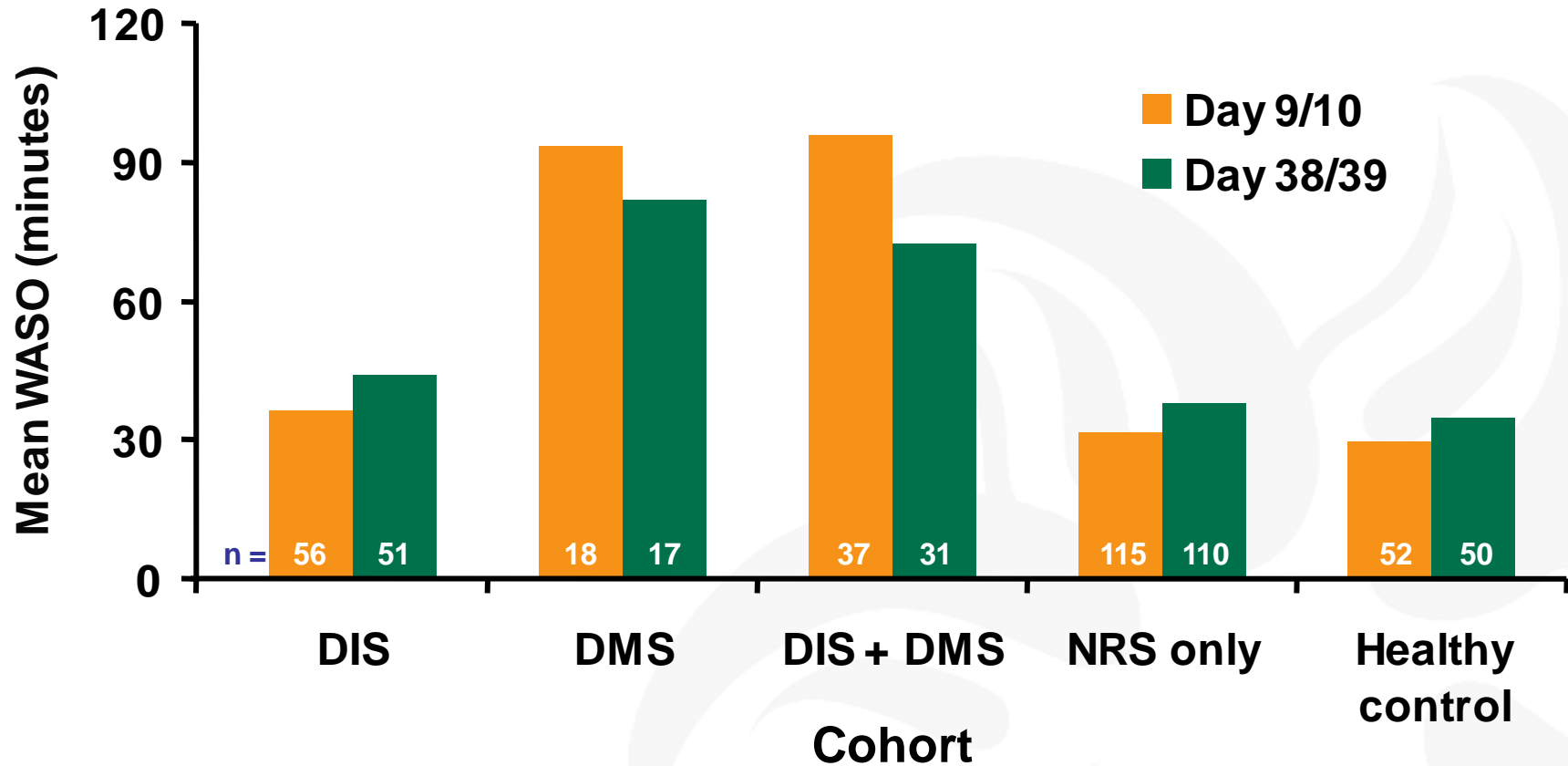
Latency to persistent sleep



- Subjects with NRS-only had mean LPS similar to the healthy control group

PSG results:

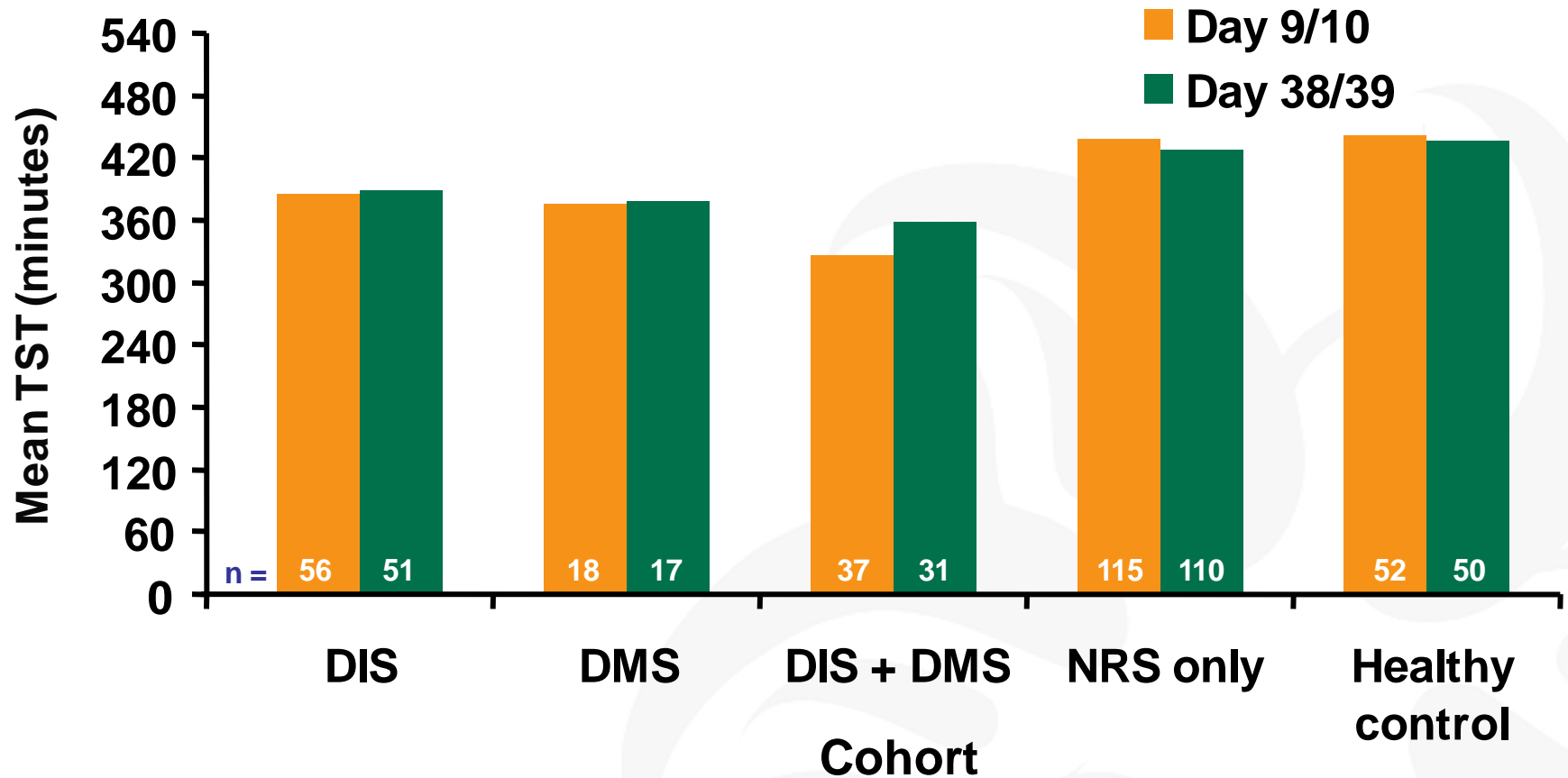
Wake after sleep onset



Subjects with NRS-only had mean WASO similar to the healthy control group

PSG results:

Total sleep time



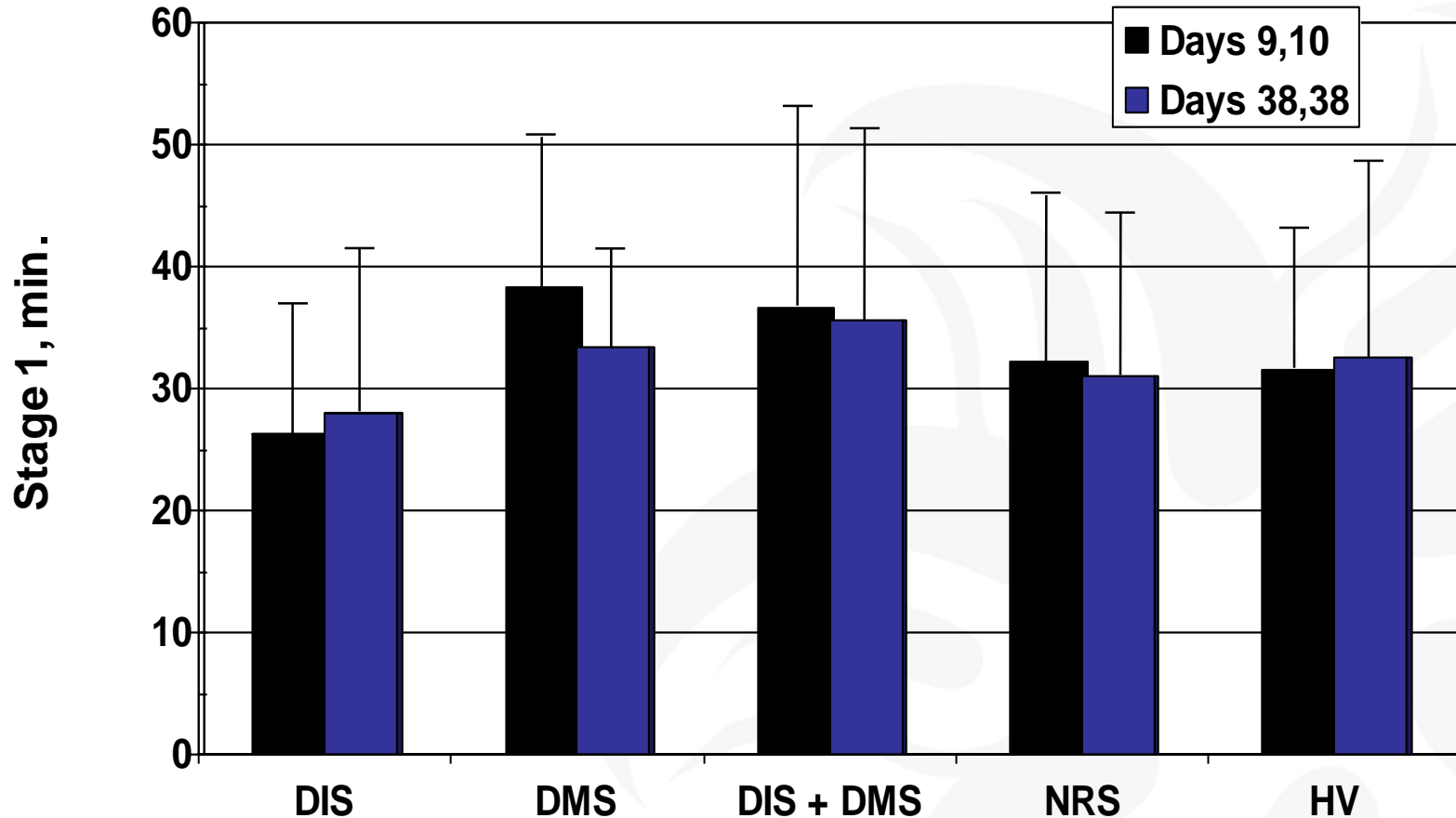
Subjects with NRS-only had mean TST similar to the healthy control group

Consistency of diagnostic classification

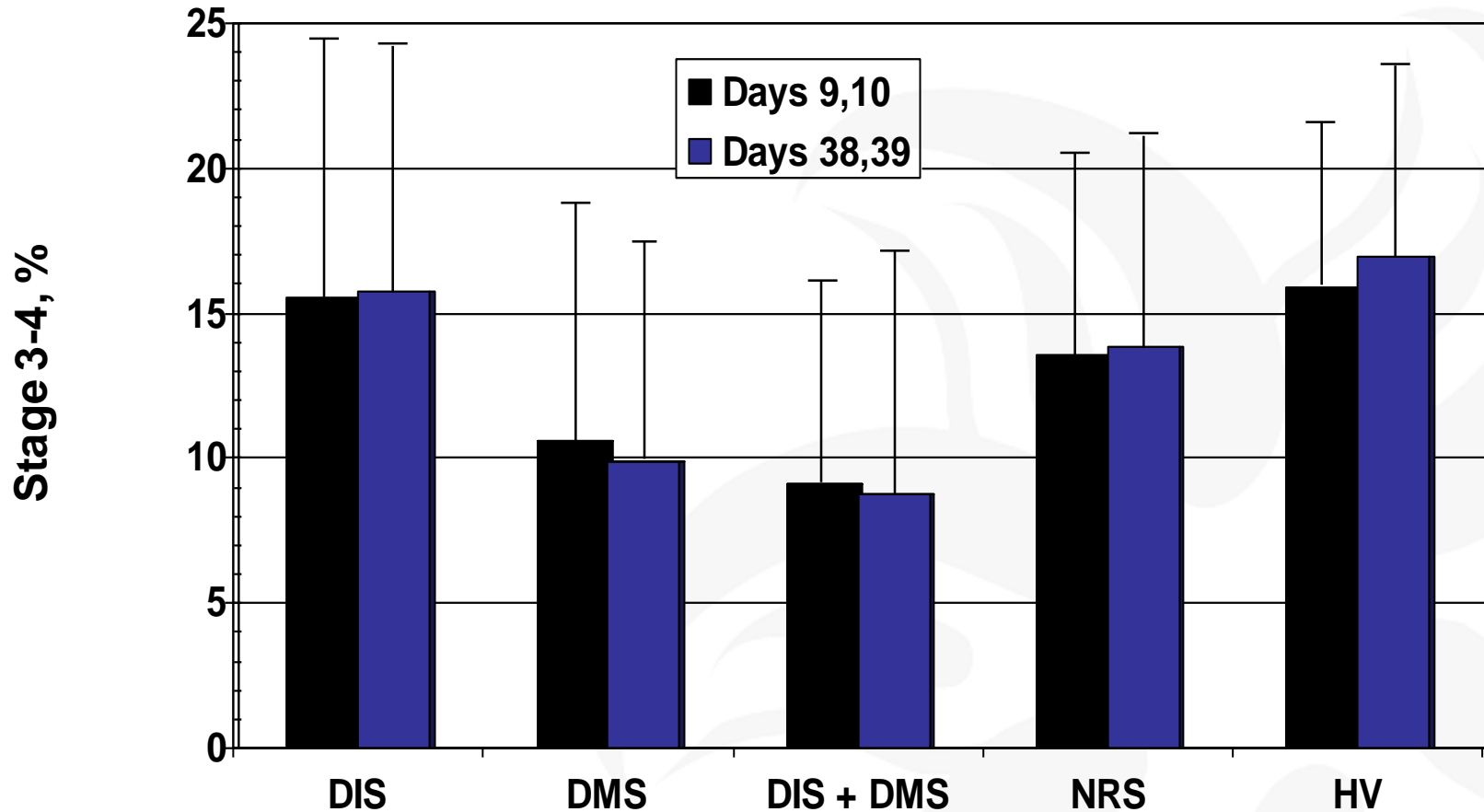
Cohort	DIS	DMS	DIS + DMS	NRS only	Healthy control
PSG-confirmed cohort size on Days 9/10, n	56	18	37	115	52
Subjects retaining the same PSG classification at Days 38/39, n (%)	30 (59)	10 (59)	12 (39)	86 (78)	43 (86)

A higher proportion of NRS-only and healthy control subjects than subjects with DIS and/or DMS retained the same objective cohort classification at Day 38/39 PSG as at Day 9/10 PSG

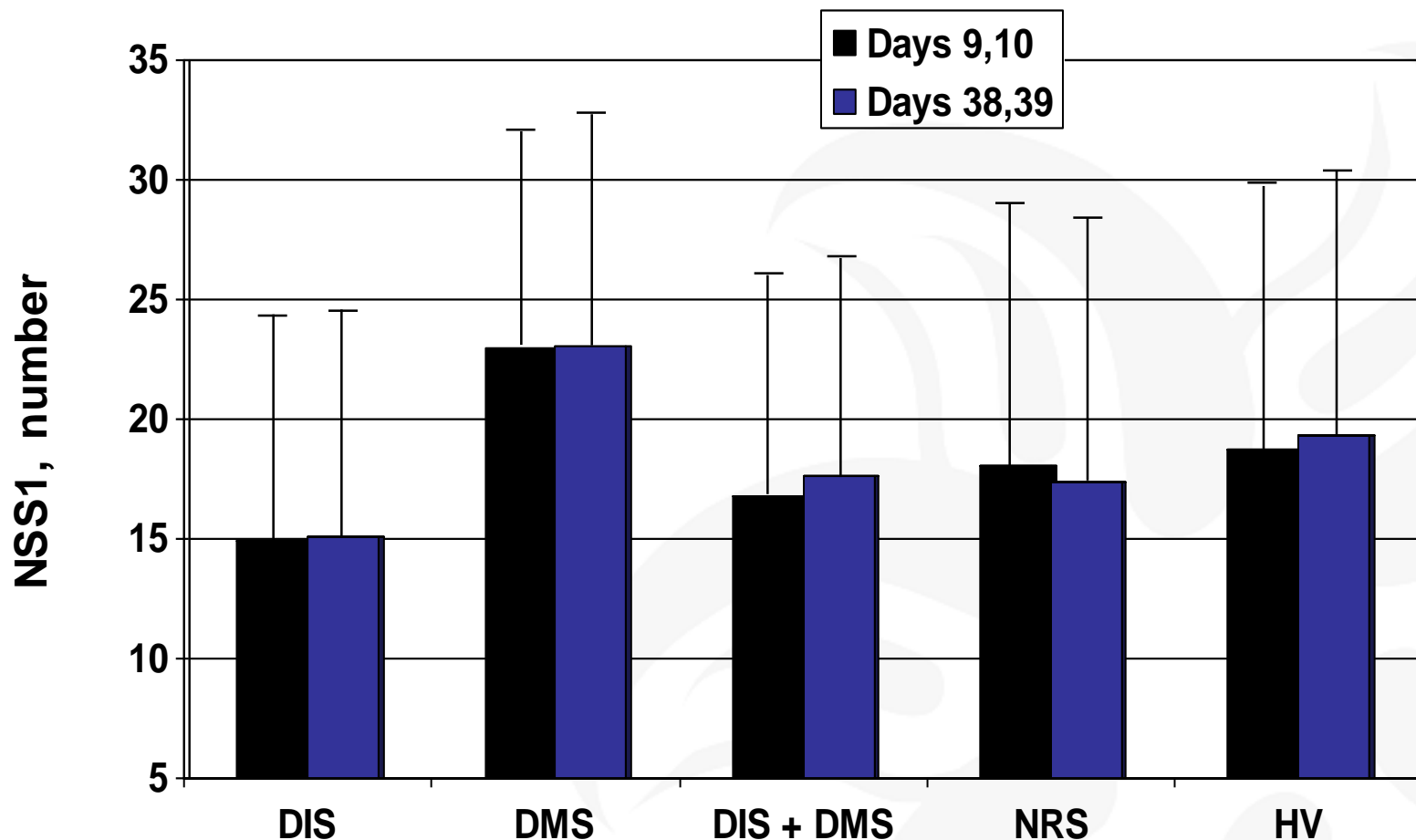
Time in Stage 1 Sleep



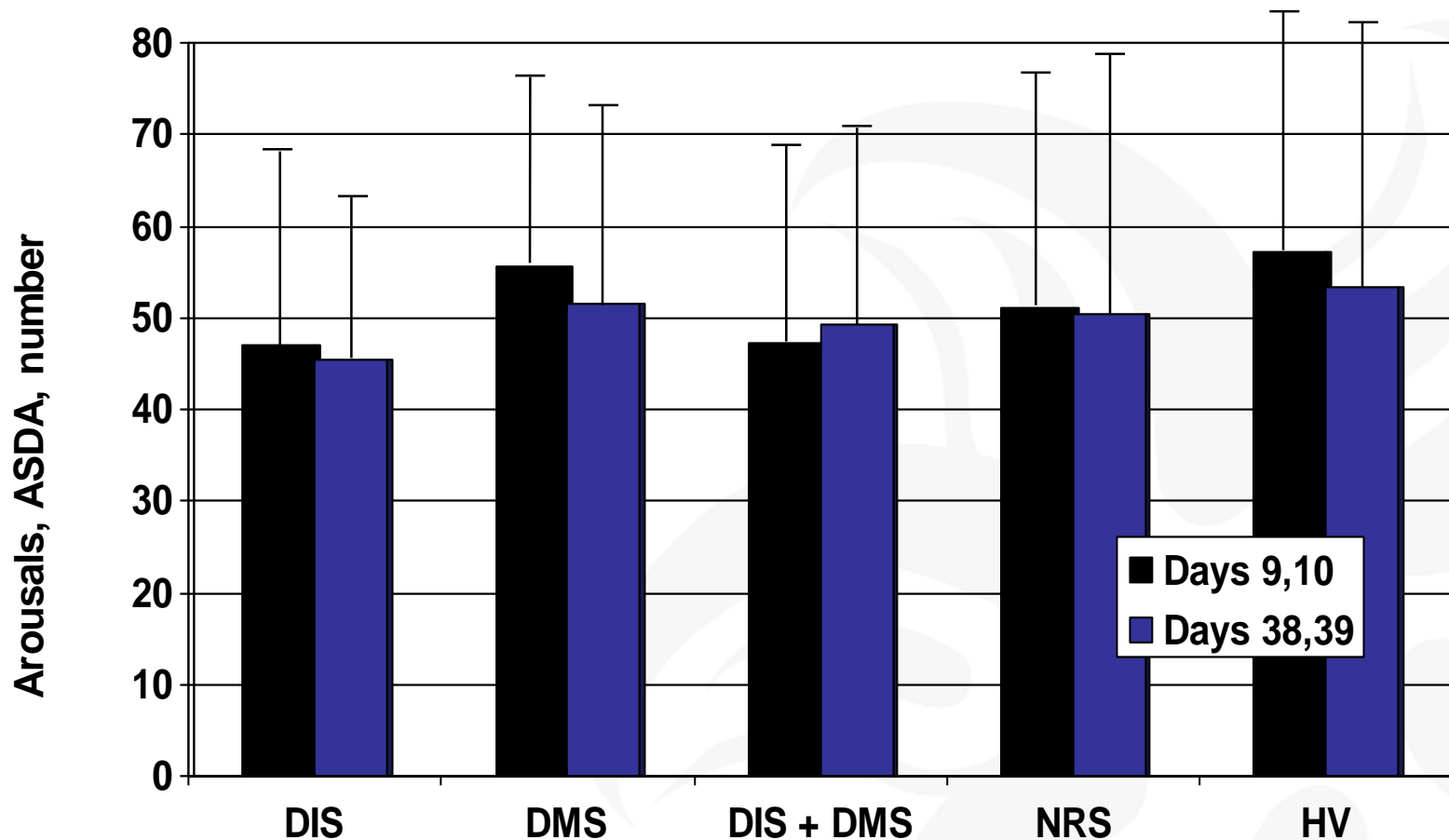
Time in Stage 3-4 Sleep



Number of Shifts to Stage 1 Sleep



Number of ASDA Arousals



Hierarchy in the Arousal Response

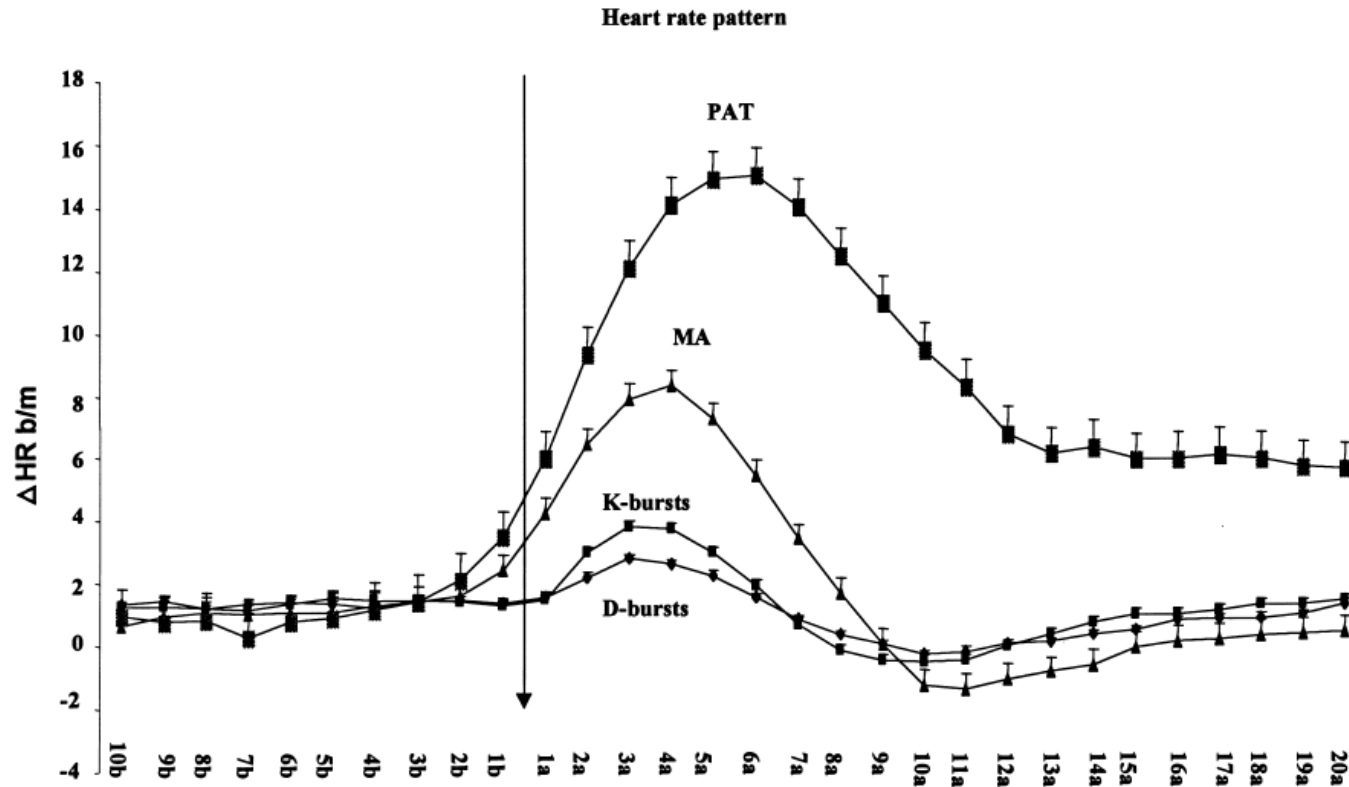
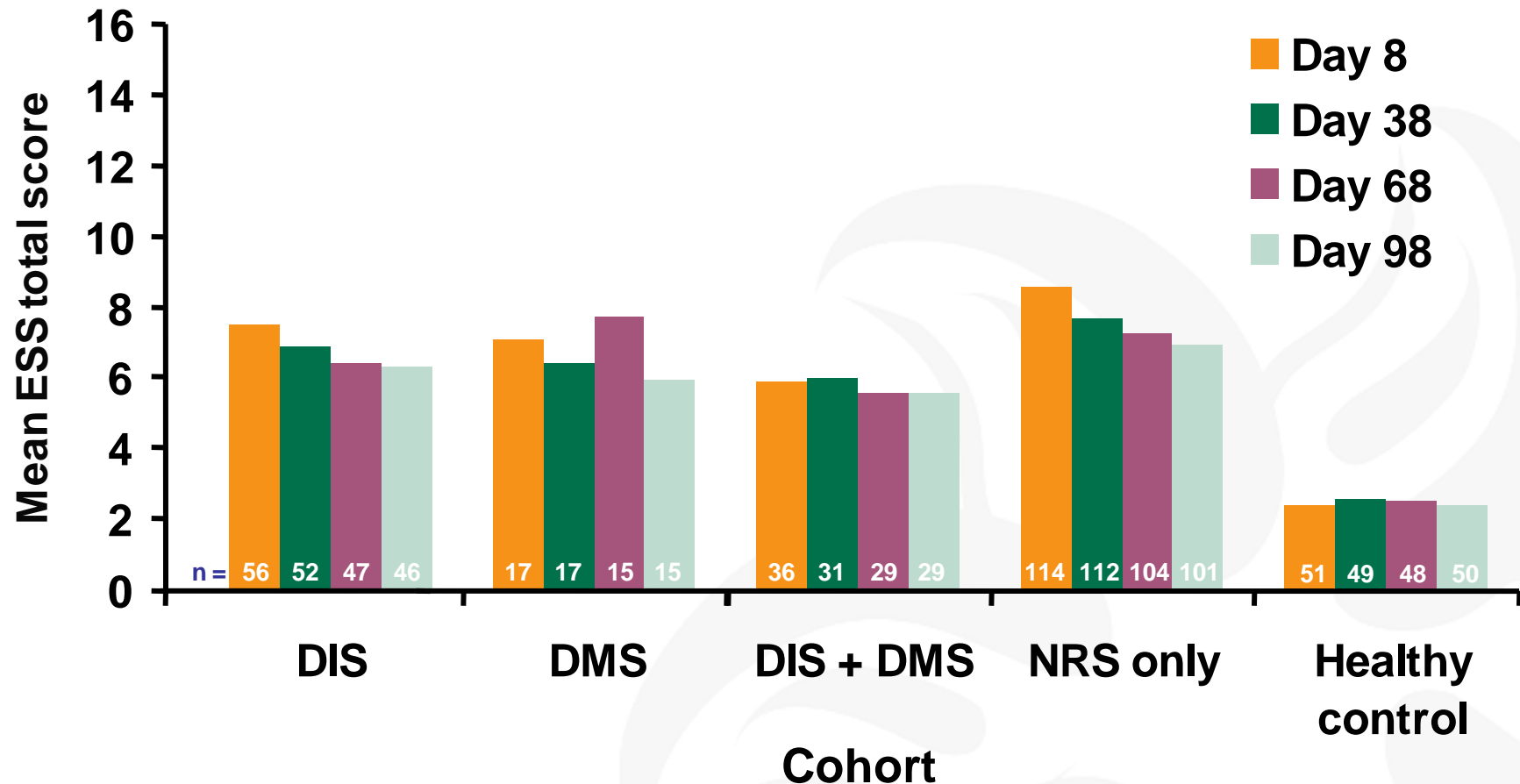


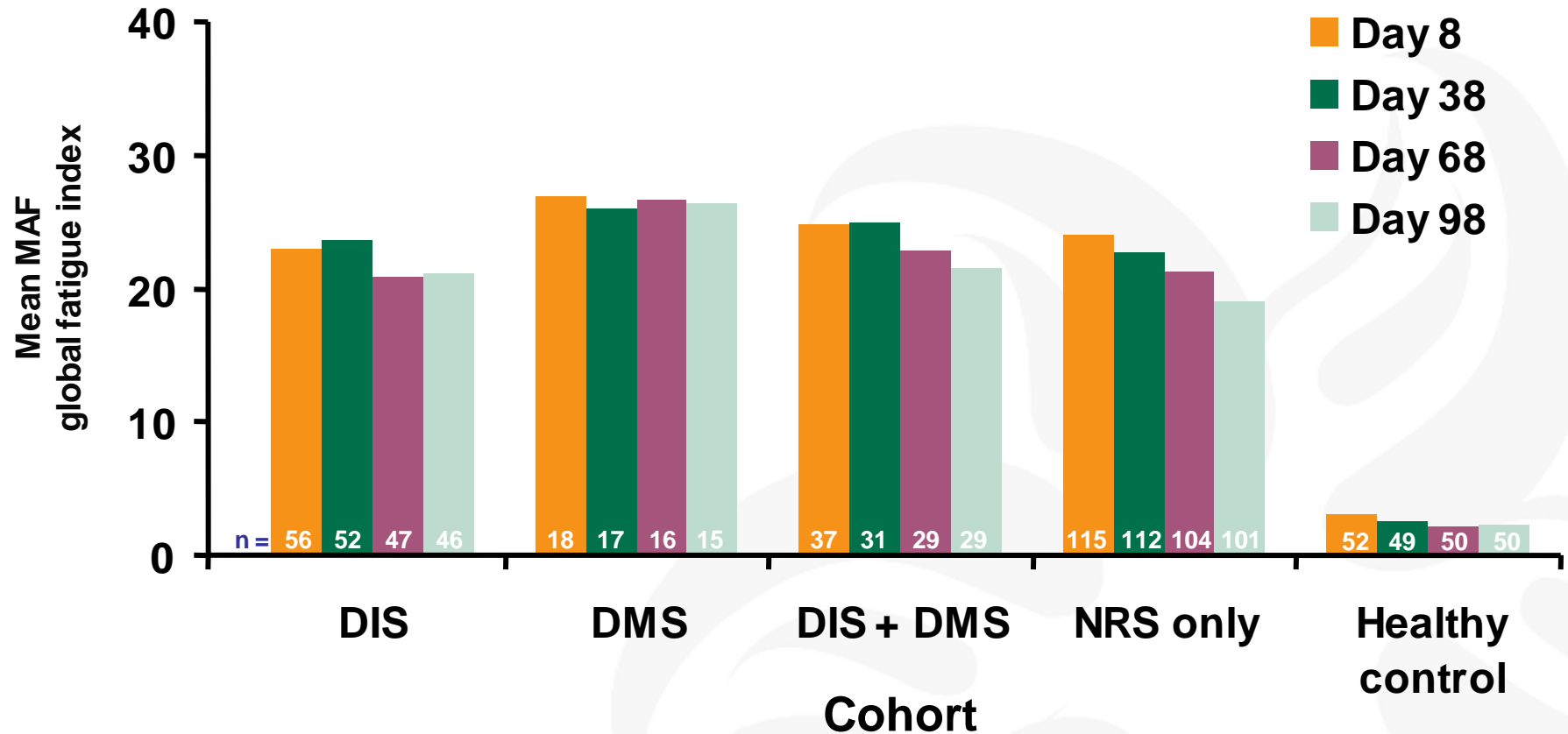
Fig. 2. Overtime heart rate changes in pre-arousal and post-arousal periods for the 4 types of arousal. The arrow indicates the onset of the arousal. For all 4 arousal types a typical pattern of heart rate response was seen, consisting of a tachycardia from the first to the sixth to seventh beats followed by a bradycardia. During MA and PAT, the rise in HR started at the first and second beats before the onset. The bradycardia was less evident during PAT, for which HR does not return to pre-arousal values.

Subjective daytime symptom assessments: Epworth Sleepiness Scale



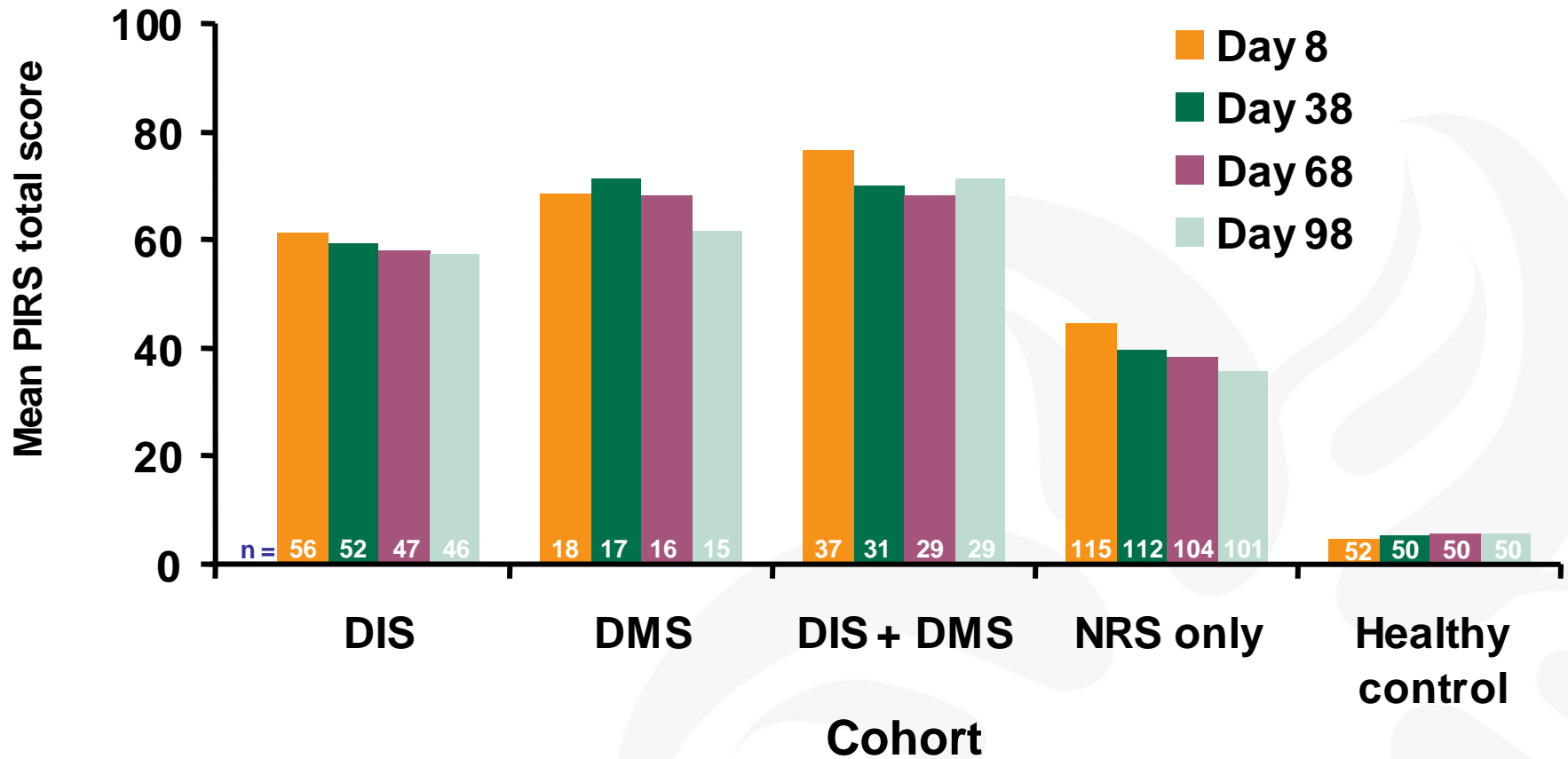
Subjects with NRS-only had mean sleepiness scores at least as high as those with DIS and/or DMS, and higher than healthy controls

Subjective daytime symptom assessments: Multidimensional Assessment of Fatigue



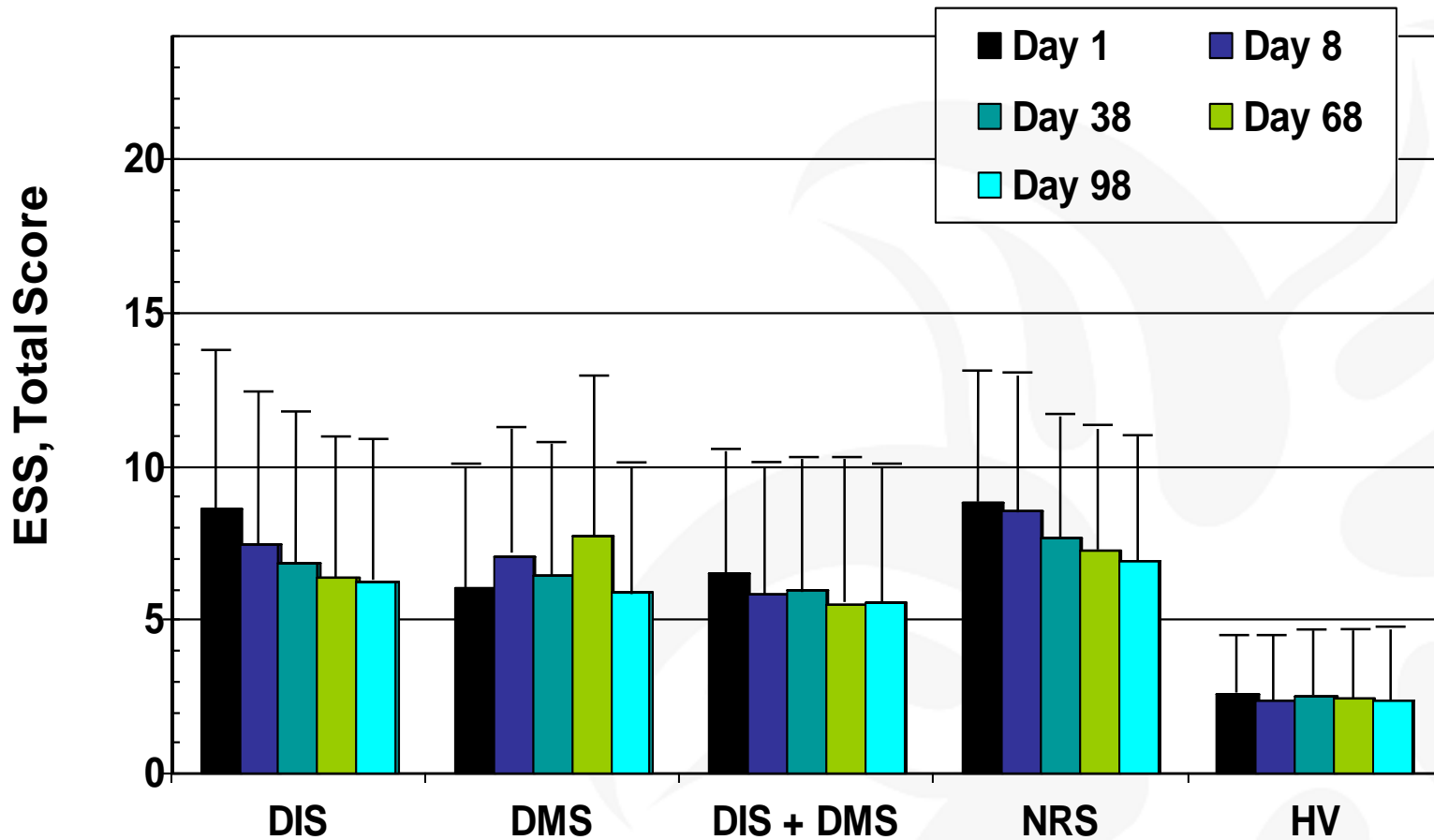
Subjects with NRS-only had mean fatigue scores comparable to those with DIS and/or DMS, and higher than healthy controls

Subjective daytime symptom assessments: Pittsburgh Insomnia Rating Scale

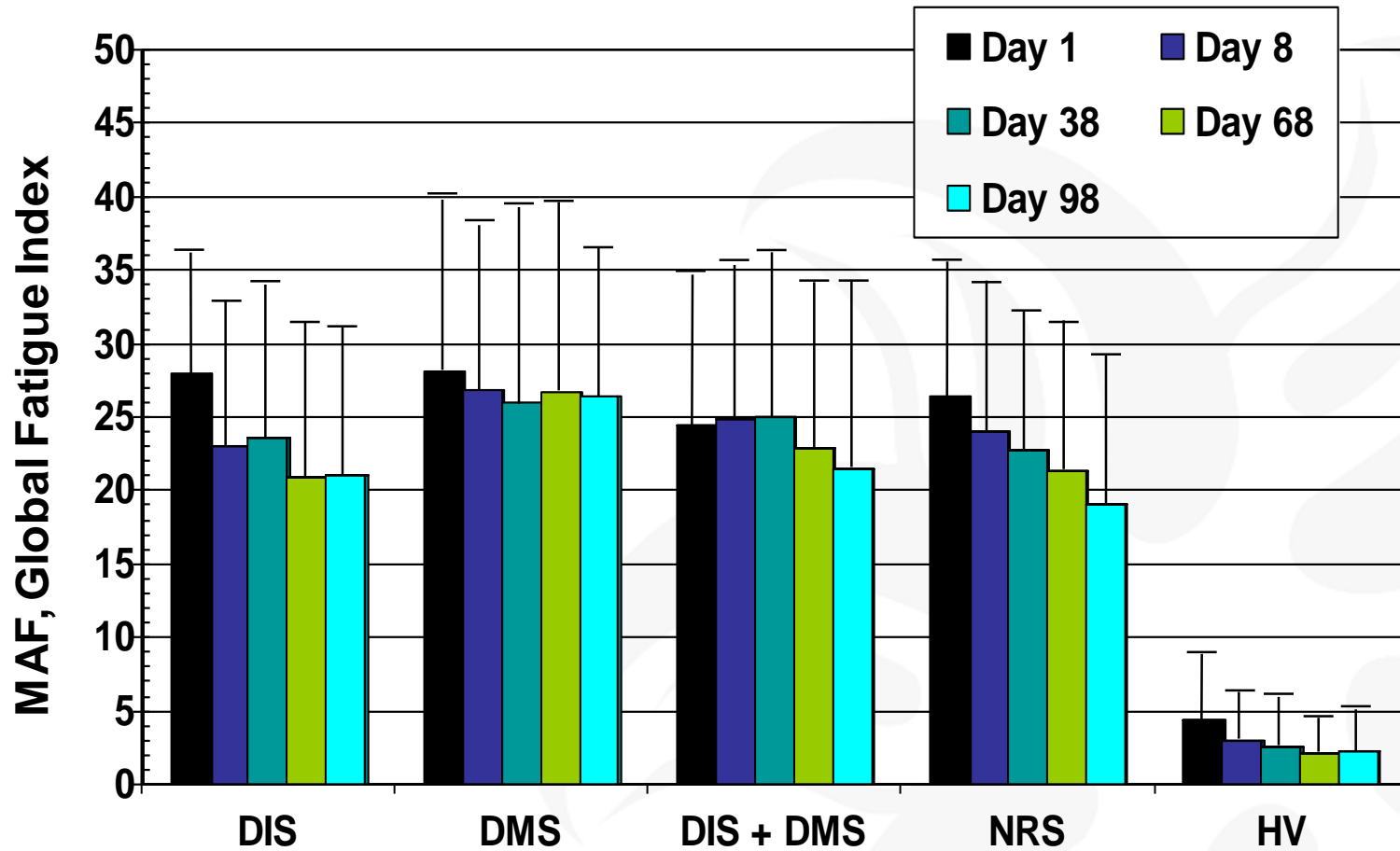


Subjects with NRS-only had higher mean PIRS total scores than healthy controls, approaching scores of subjects with DIS and/or DMS

Epworth Sleepiness Scale (ESS)



Multidimensional Assessment of Fatigue



Persistence of daytime symptoms

Subjects with NRS

- Month 1 subjective and PSG assessments revealed persistent daytime symptoms in the NRS-only cohort, occurring in the continued absence of PSG-measured sleep problems
 - Mean values for all subjective and PSG endpoints were similar at Days 38/39 to Days 9/10 within each cohort
 - A high proportion of subjects with NRS-only (78%) retained the same categorization following Day 38/39 PSG as that confirmed by Day 9/10 PSG
- Subjective complaints persisted over the 3-month study period
 - Mean scores on daytime symptom questionnaires and scales remained similar from Day 8 through Day 98, within each cohort

Unanswered Questions

- Is NRS a single entity?
- Is there “primary” and “secondary” NRS?
 - Sleep deprived?
 - Psychiatric disorders
 - Major depression?
 - Anxiety disorders (e.g., PTSD)?
 - Periodic limb movement disorder?
 - Obstructive sleep apnea?
 - Other sleep disorders?
 - Fibromyalgia?