

ABC (Altogether to Beat Cushing's syndrome)
"Viaggio alla (ri)scoperta della sindrome di Cushing"
Sorrento, 27 – 30 maggio 2014

17:00-18:00

SESSIONE 4: IL CUSHING DOPO LA GUARIGIONE

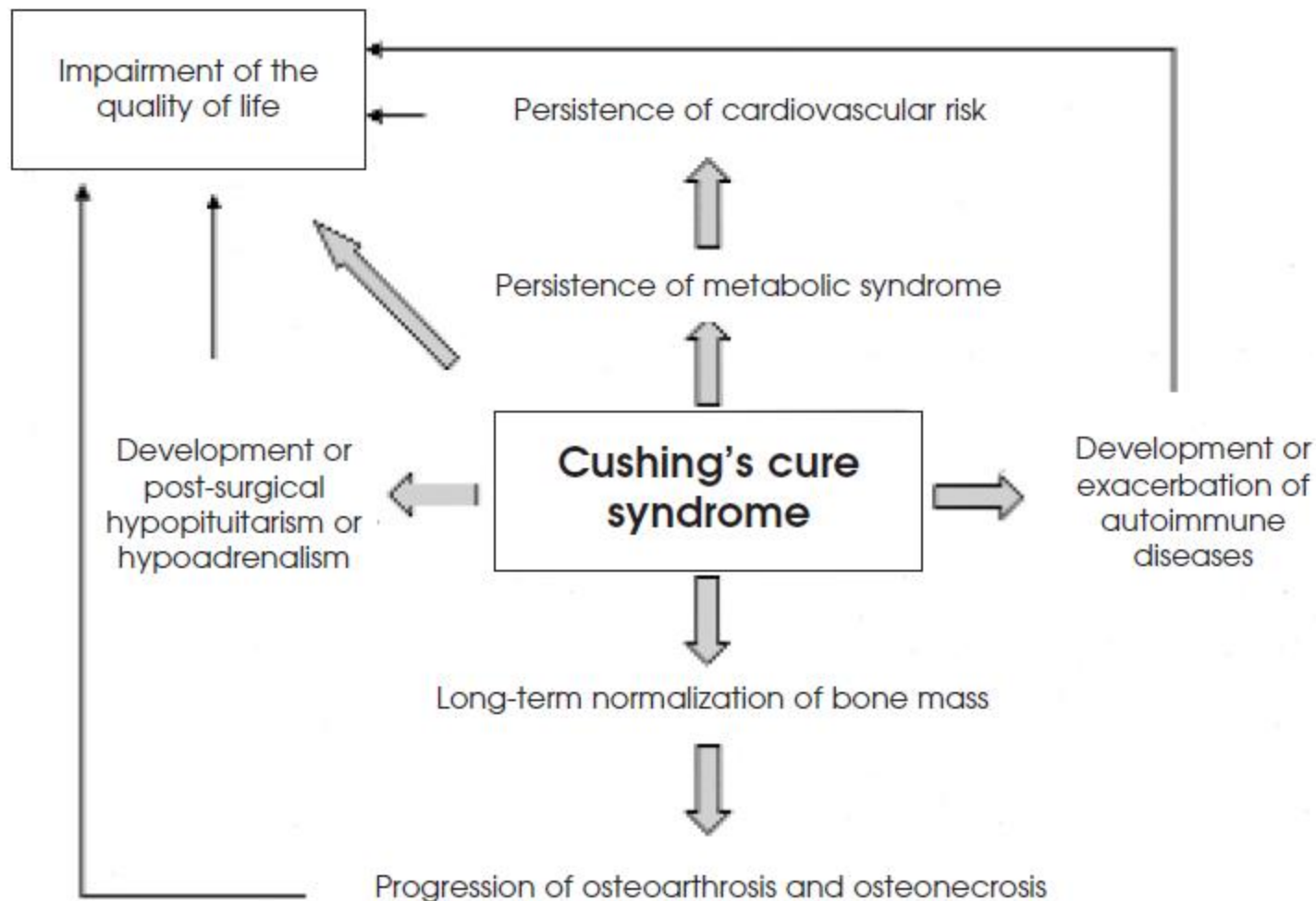
>> Moderatori: Dario Giugliano, Andrea Isidori

IL DANNO RESIDUO PSICHICO ED ESTETICO

Laura Trementino

Clinica di Endocrinologia
Università Politecnica della Marche
Ancona, ITALY

“Residual” morbidity in CS after cure



“Residual” cognitive/psychiatric damage in CS after cure

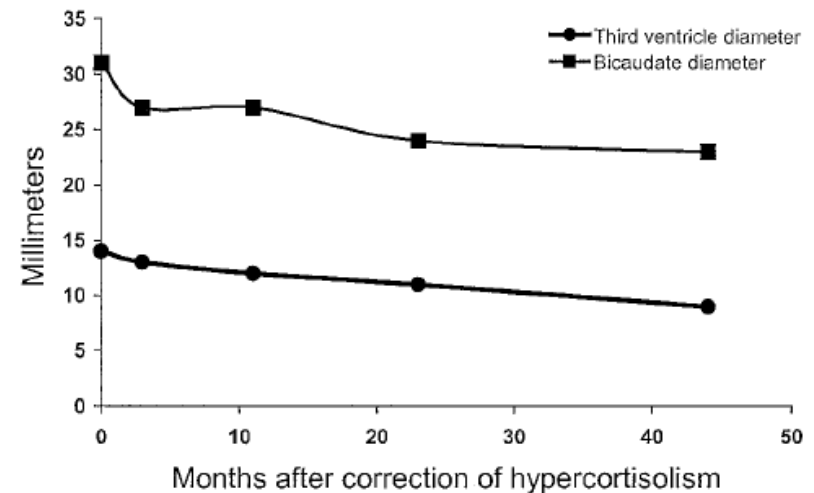
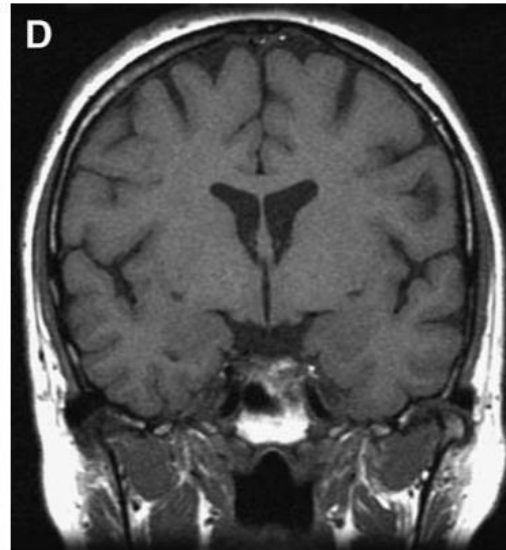
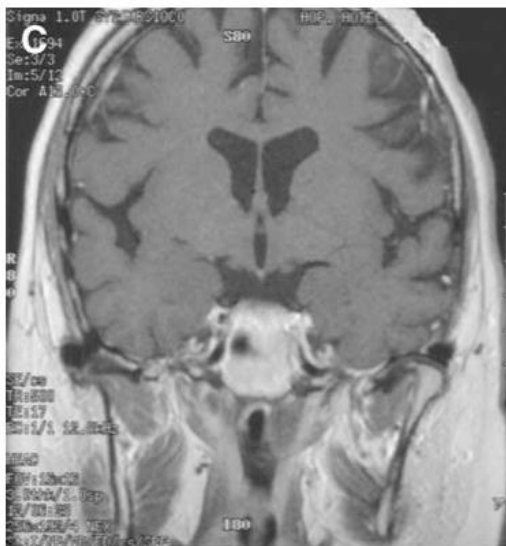
- Morphological/functional abnormalities
- Cognitive function
- Psychiatric disorders
- QoL

Loss of Brain Volume in Endogenous Cushing's Syndrome and Its Reversibility after Correction of Hypercortisolism

	Sex (M:F)	Mean age (yr \pm SD)	Third ventricle diameter ^a (mm)	Bicaudate diameter (mm)	Subjective evaluation ^b
CD (n = 21)	8:13	37.3 \pm 11.1	5.61 \pm 2.33 ^c (21)	15.81 \pm 4.88 ^c (19)	1.69 \pm 1.03 ^d (21)
ACS (n = 17)	1:16	45.4 \pm 12.0	6.00 \pm 1.83 ^c (16)	18.30 \pm 3.51 ^c (15)	1.94 \pm 0.83 ^d (17)
Pooled CS (CD + ACS; n = 38)	9:29	41.3 \pm 12.0	5.78 \pm 2.10 ^c (37)	16.90 \pm 4.45 ^c (34)	1.80 \pm 0.94 ^d (38)
OST (n = 18)	4:14	35.4 \pm 8.4	3.68 \pm 1.24 (17)	12.82 \pm 3.80 (17)	0.17 \pm 0.38 (18)
NST (n = 20)	3:17	37.3 \pm 12.8	3.08 \pm 1.13 (19)	12.74 \pm 2.47 (17)	0.10 \pm 0.31 (20)

Mean follow-up 39.7 \pm 34.1 months

	Third ventricle diameter (mm)	Bicaudate diameter (mm)	Subjective evaluation scale of atrophy
Initial value	5.48 \pm 2.48 ^a	17.14 \pm 4.69	1.70 \pm 1.09
Following correction of hypercortisolism	3.95 \pm 1.96 ^b	14.09 \pm 3.69 ^c	1.23 \pm 1.05 ^d



Children Experience Cognitive Decline Despite Reversal of Brain Atrophy One Year After Resolution of Cushing Syndrome

Cerebral volumes (ml)	Control (n = 10)	Cushing baseline (n = 11)	Cushing 1-yr follow-up (n = 11)	P value Cushing baseline <i>vs.</i> control	P value Cushing baseline <i>vs.</i> 1-yr follow-up
Total cerebrum	1119 ± 116	947 ± 94	1050 ± 74	<0.001	<0.001
Lateral ventricle	10.8 ± 4.2	21.4 ± 12.5	14.5 ± 11.6	0.02	0.001
Temporal lobe	175.1 ± 20.1	160.0 ± 20.8	171.7 ± 20.1	0.11	<0.001
Hippocampus	8.2 ± 0.7	7.7 ± 0.9	8.1 ± 0.8	0.19	0.08
Amygdala	7.4 ± 0.8	6.1 ± 0.8	6.1 ± 0.8	0.004	0.60

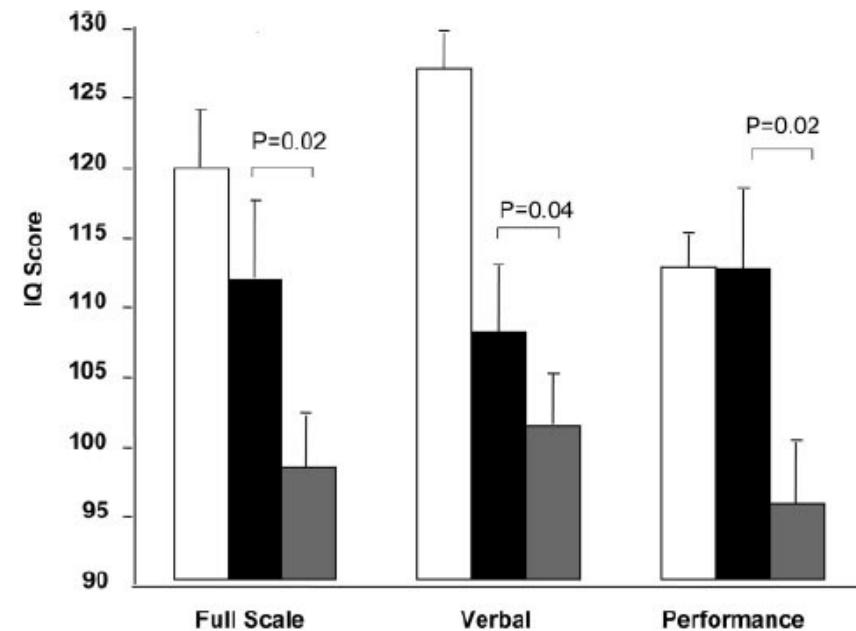
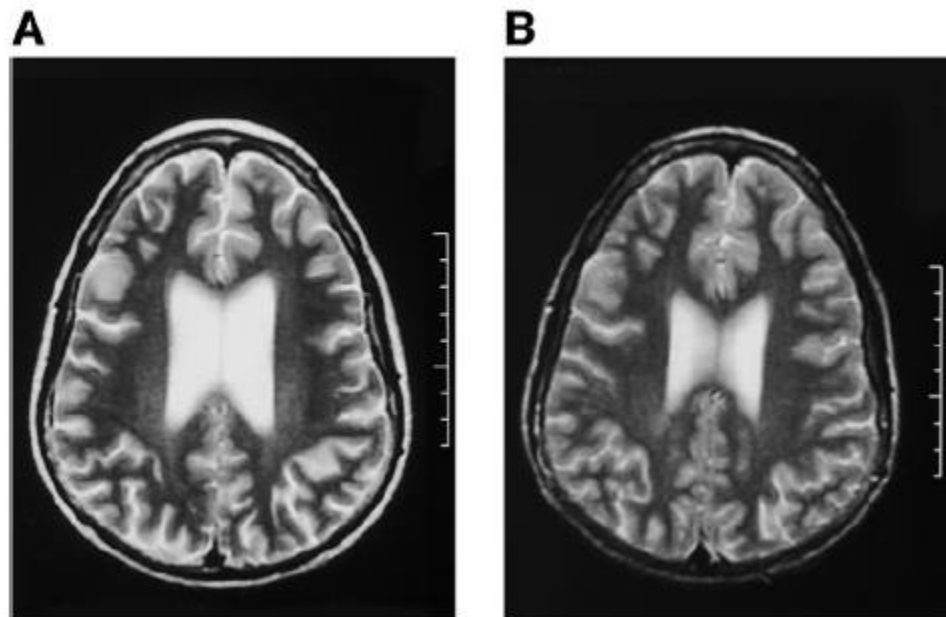
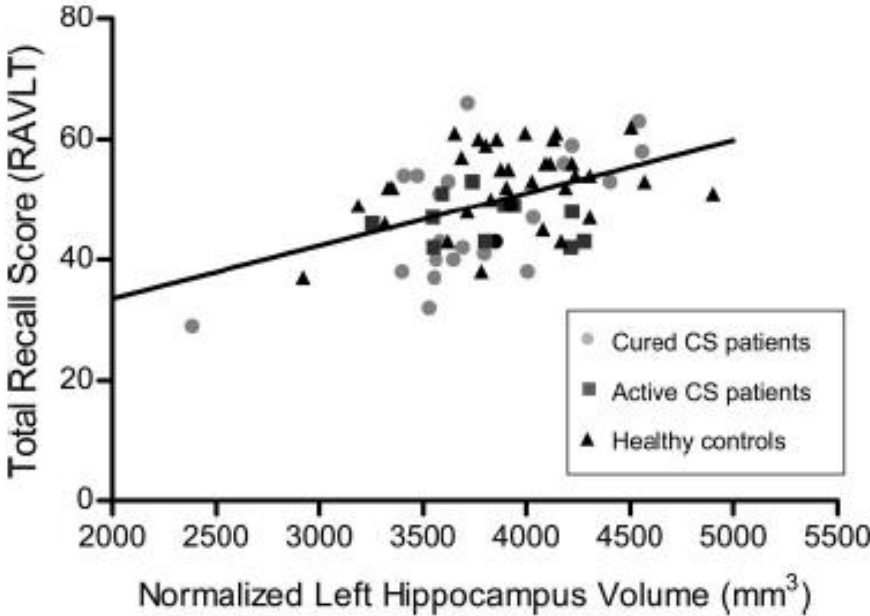


FIG. 2. IQ scores were based on the Wechsler Intelligence Scale (16, 17) for healthy age- and sex-matched control subjects (□), and children with Cushing's syndrome before treatment (■) and 1 yr after surgery and correction of hypercortisolism (▒). The T bars indicate SE values.

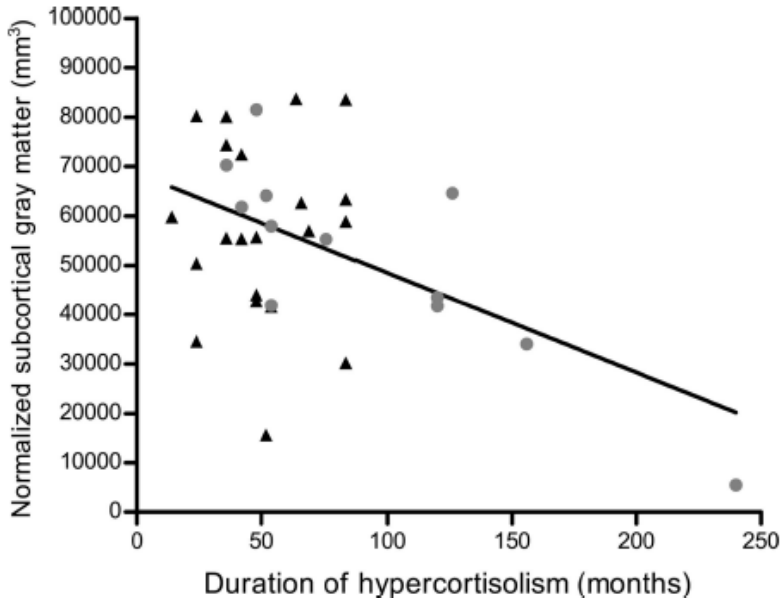
Verbal and Visual Memory Performance and Hippocampal Volumes, Measured by 3-Tesla Magnetic Resonance Imaging, in Patients with Cushing's Syndrome

TABLE 2. Memory performances and HV in CS patients and controls

	CS patients (n = 33)	Controls (n = 34)	P
Left HV (mm ³)	3781.34 ± 423.94	3924.53 ± 405.97	NS
Right HV (mm ³)	3893.32 ± 357.94	4025.63 ± 357.29	NS
Rey5	12.09 ± 1.89	13.23 ± 1.15	0.01
Retention index	9.12 ± 2.93	11.14 ± 2.39	0.01
Total recall score	46.97 ± 8.46	52.32 ± 6.06	0.01
Recognition-A	12.85 ± 1.75	13.95 ± 1.33	0.01
Recognition-B	7.36 ± 3.71	9.50 ± 2.87	0.02
Fig-Rey-Im	18.86 ± 7.07	22.23 ± 6.43	NS
Fig-Rey-delayed	18.50 ± 6.90	22.34 ± 6.62	0.04



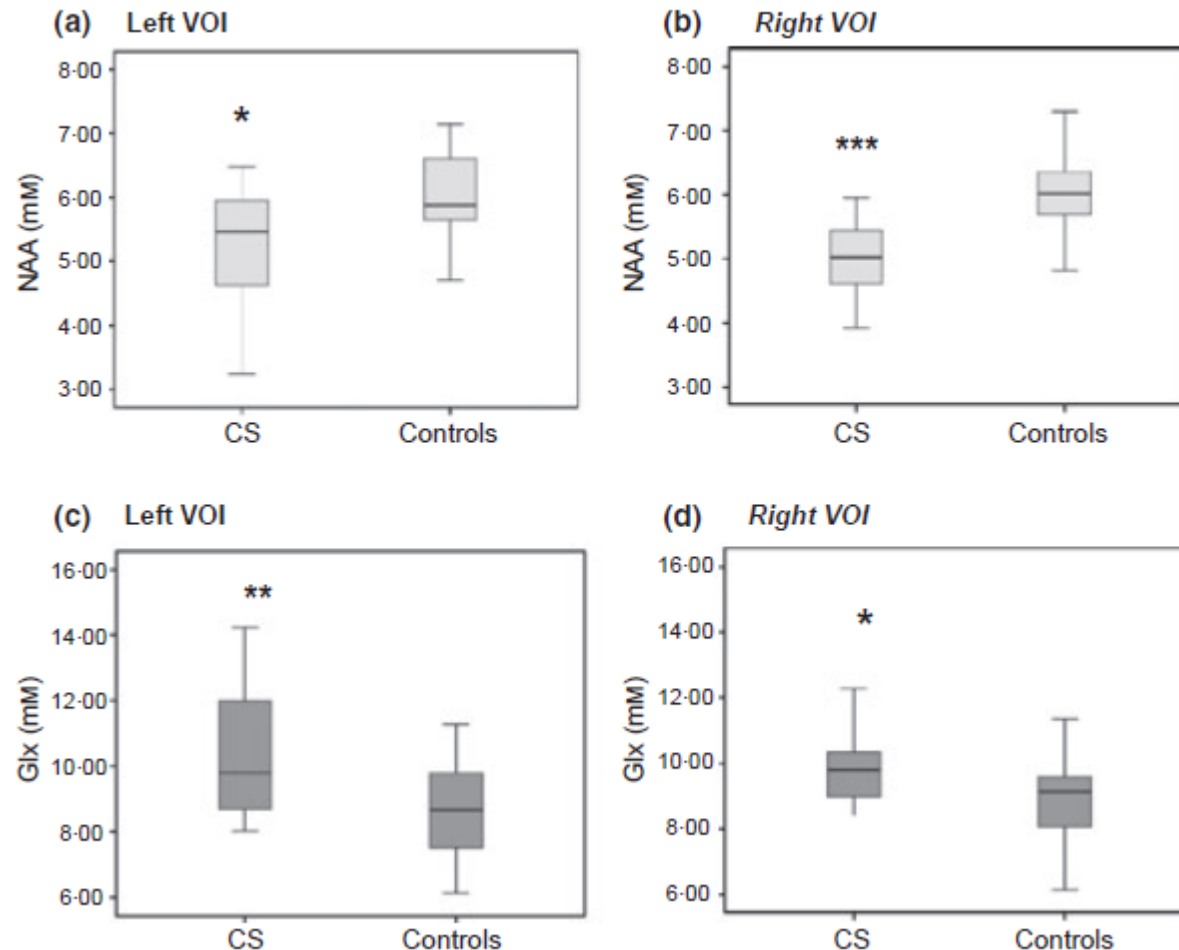
Mean time of remission 7.3 ± 2.4 years (22/33)



Hippocampal dysfunction in cured Cushing's syndrome patients, detected by ^1H -MR-spectroscopy

Table 1. clinical characteristic of CS patients at the time of spectroscopy

	Cushing patients ($n = 18$)
Age	44.8 ± 12.5
Years of education	12.6 ± 3.8
Males/females	3/15
Adrenal/pituitary origin	3/15
Previous radiotherapy	4/18
Hydrocortisone replacement therapy	3/18
Urinary cortisol level (nmol/24 h)	149 ± 80
Mean time of hormonal cure (years)	8.5 ± 3.2
Mean duration of hypercortisolism (years)	4.7 ± 2.6



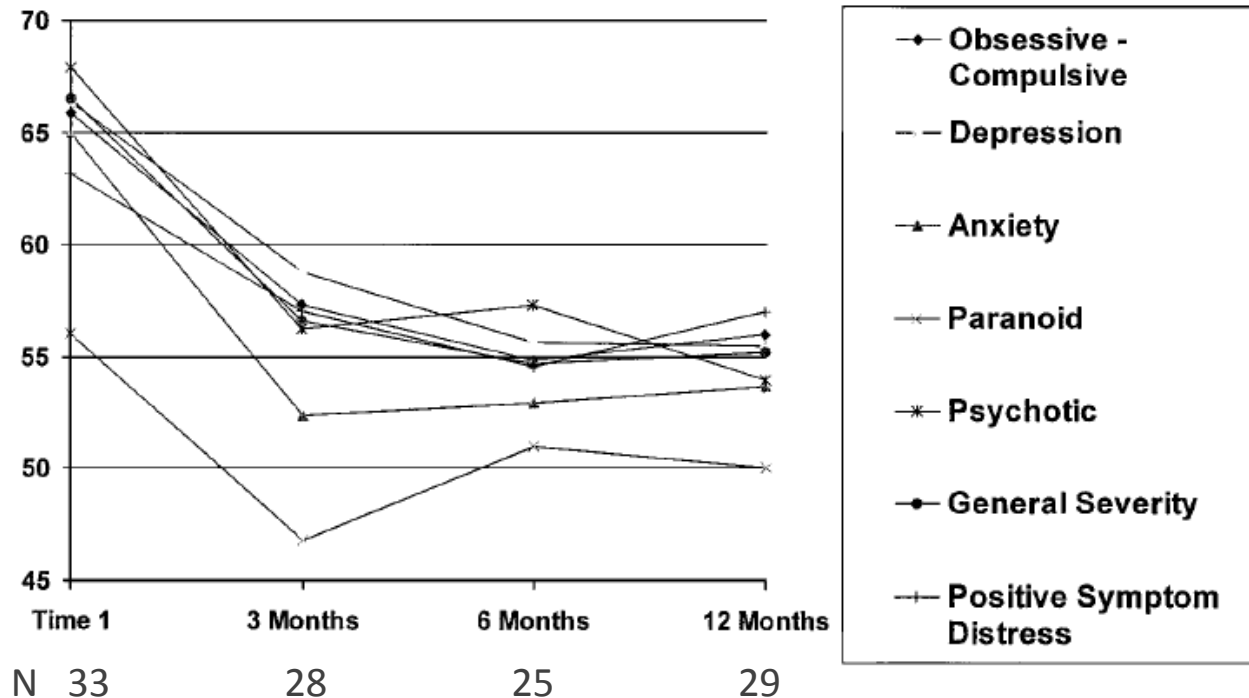
- **No differences in left and right total hippocampal volumes between CS and controls**
- **No correlations between NAA or Glx and duration of hypercortisolism**

Summary of studies on cognitive function in CS in remission

Study	Subjects	Main variables	Design	Time at evaluation	Main findings
(118) Mauri et al., 1993	25 CD 60 controls	Memory, learning, visual scanning, divided attention, motor speed, information-processing speed and verbal fluency	Prospective	Pre- and post treatment (8 of 25 patients re-evaluated 6 months after treatment)	Eight patients re-tested 6 months after treatment showed significant improved memory and attention but not in other cognitive functions compared with controls
(56), USA Dorn et al., 2000	29 CD 3 EAS 1 CPAA 17 controls	Memory, learning, problem solving, motor speed, visual construction ability and IQ	Prospective	Pre-treatment and at 3, 6 and 12 months after treatment	No significant improvement in cognitive functioning. Trend of lower IQ at baseline. For some subscales of IQ there was a positive relationship with recovery of the HPA axis and a negative relationship with duration of CS
(57), Canada Forget et al., 2002	9 CD 4 CPAA 13 controls	Attention, visual processing, visuospatial processing, memory, reasoning and verbal fluency	Prospective	Pretreatment and 1 year after treatment	Visual processing and verbal fluency improved after treatment but no other cognitive functions
(119) Hook et al., 2007	27 CD	Memory, learning, attention, working memory and verbal fluency	Prospective	Pretreatment and at 3–5, 6–12 and 13–18 months after treatment	Memory, learning and verbal fluency improved after treatment while attention and working memory did not
(60), The Netherlands Tiemensma et al., 2010	74 CD 74 controls 54 NFPA	Global cognitive functioning, memory, learning, working memory and verbal fluency	Cross-sectional	Mean \pm s.d. duration of remission 13 ± 13 years (range 1–51 years)	Patients with CD had worse global cognitive functioning, memory, learning, working memory and verbal fluency compared with patients with NFPA
(61), Spain Resmini et al., 2012	25 CD 7 CPAA 1 EAS 34 controls	Visual and verbal memory	Cross-sectional	11 of 33 patients had active CS. Mean \pm s.d. duration of remission for the remaining 22 was 5.5 ± 3.7 years	Memory performance did not differ between active CS and CS in remission. Verbal and visual memory worse in CS patients (active and in remission pooled) in comparison to controls
(49), Sweden Authors, 2012	43 CD 12 CPAA 55 controls	Working memory, attention, information-processing speed, verbal fluency, reading speed, alerting, orienting and executive control	Cross-sectional	Median (interquartile range) duration of remission was 13 (5–19) years	Attention, spatial orienting, alerting, working memory, verbal fluency and reading speed all worse in comparison with controls, independent of scores for depression and anxiety and fatigue

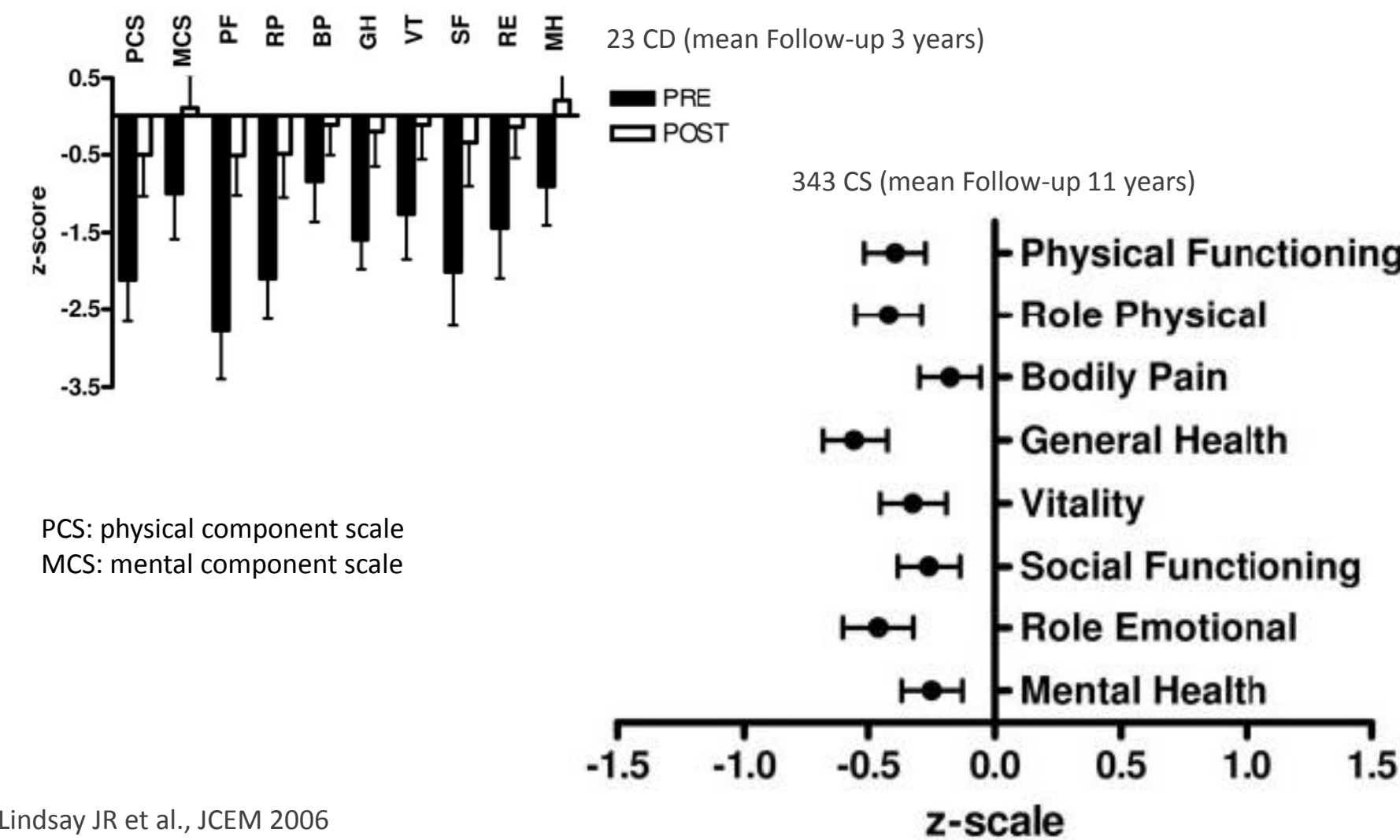
- **Cognitive function is not only temporarily affected at short-term follow-up but seems to be a permanent state**
- **Patients with CS in remission have impairment in various domains of cognitive function (not only in hippocampal function)**

The Longitudinal Course of Psychopathology in Cushing's Syndrome after Correction of Hypercortisolism

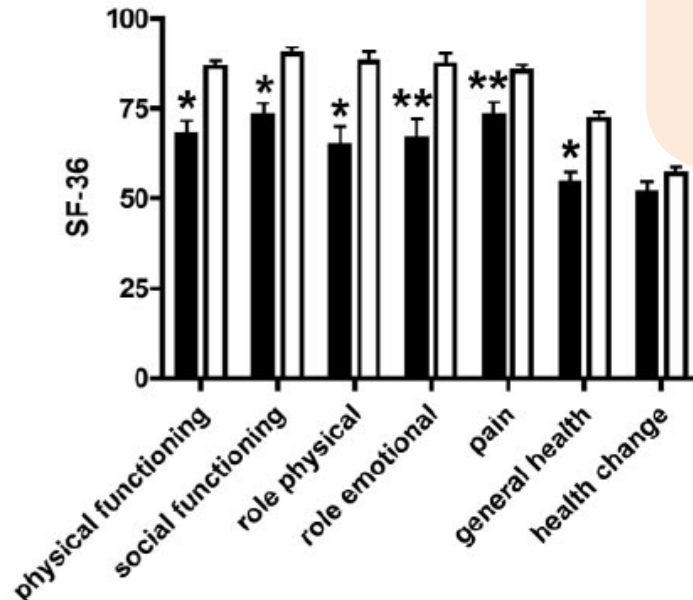
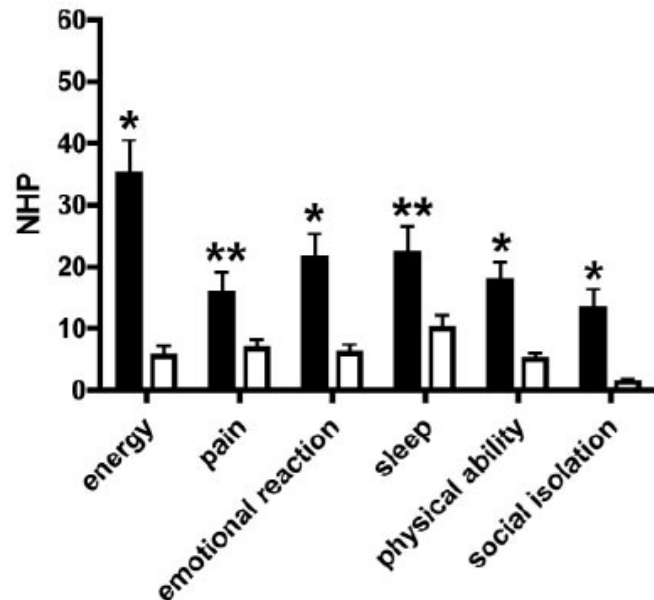
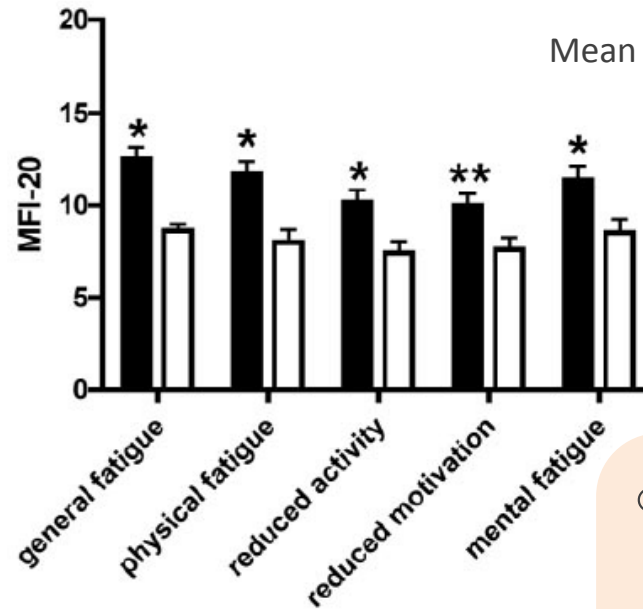
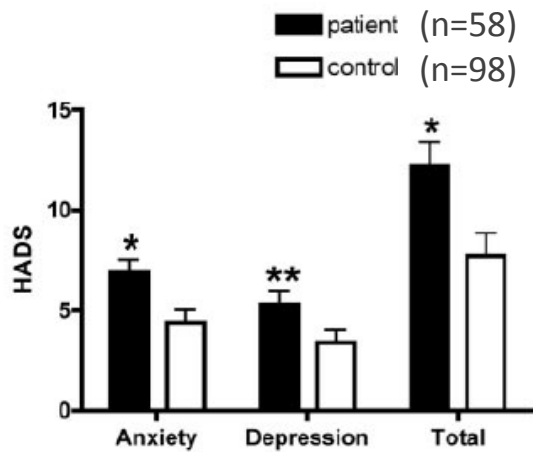


1. After cure, **overall psychopathology decreased significantly** (but frequency of suicidal ideation and panic increase)
2. **No correlations** between psychopathology and **HPA recovery** (but inverse correlation with baseline cortisol levels at months 6 and 12)
3. **No correlations** between **previously psychopathology** and **after cure**

Long-Term Impaired Quality of Life in Cushing's Syndrome despite Initial Improvement after Surgical Remission

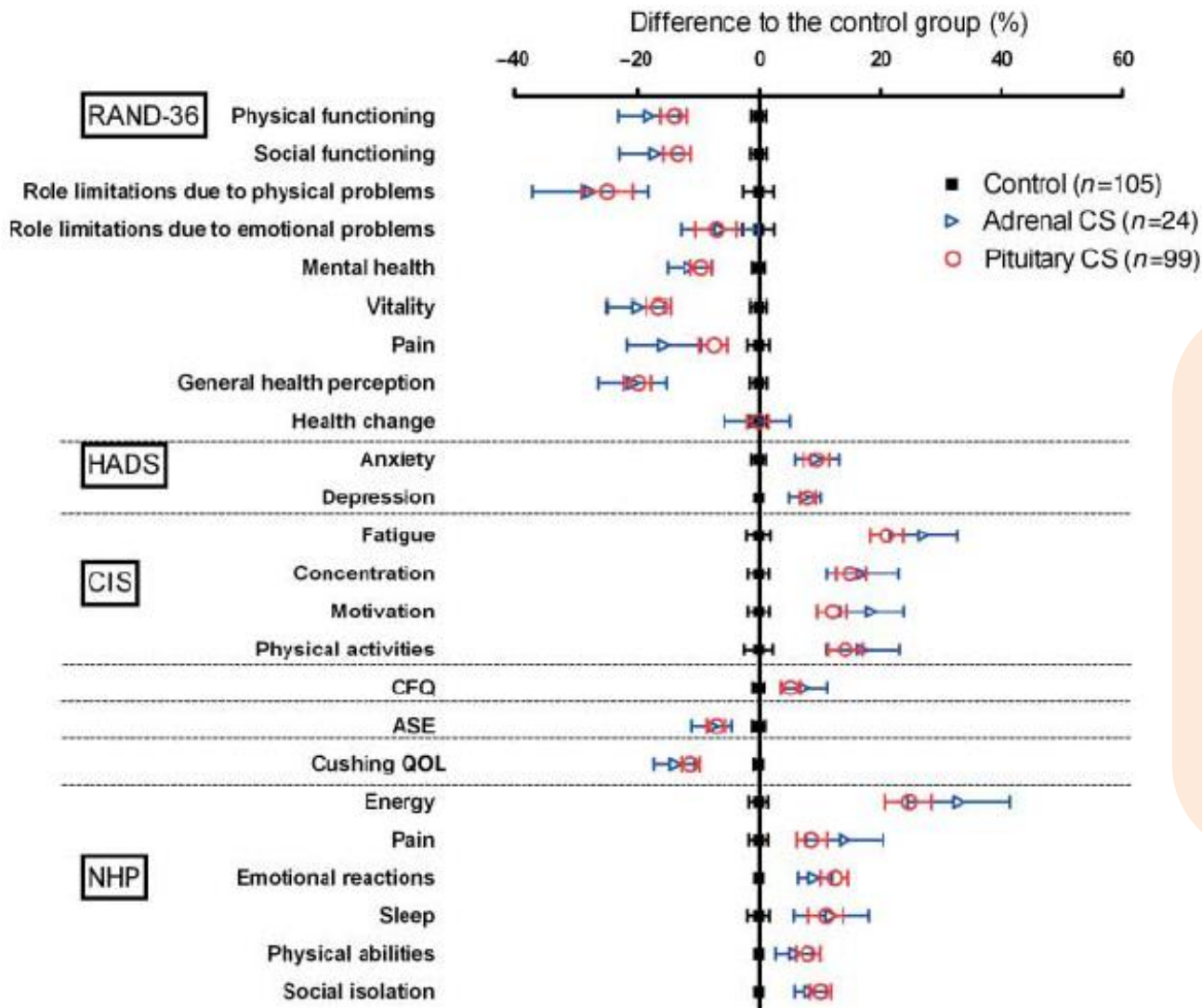


Quality of Life in Patients after Long-Term Biochemical Cure of Cushing's Disease



○ Hypopituitarism was an important independent predictor of reduced QoL

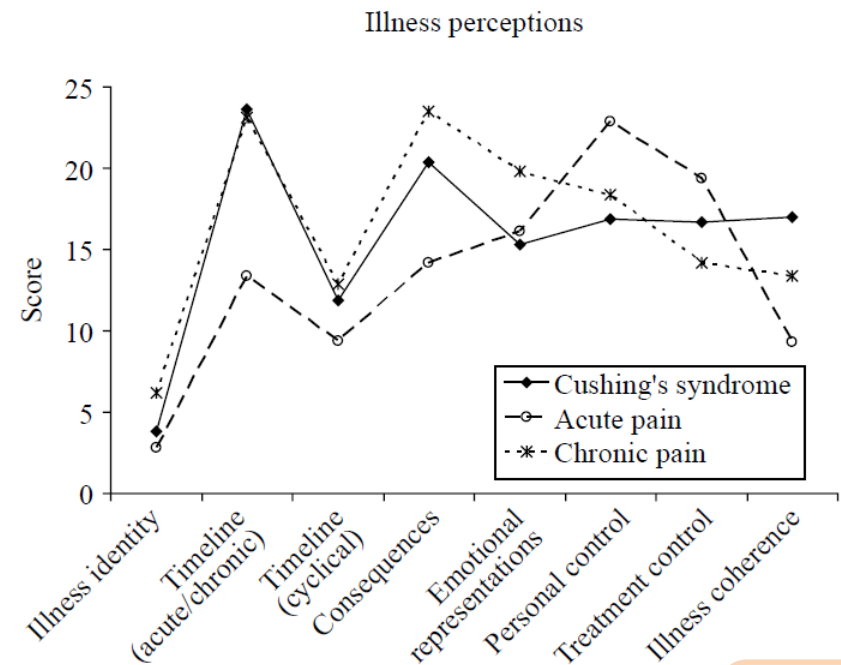
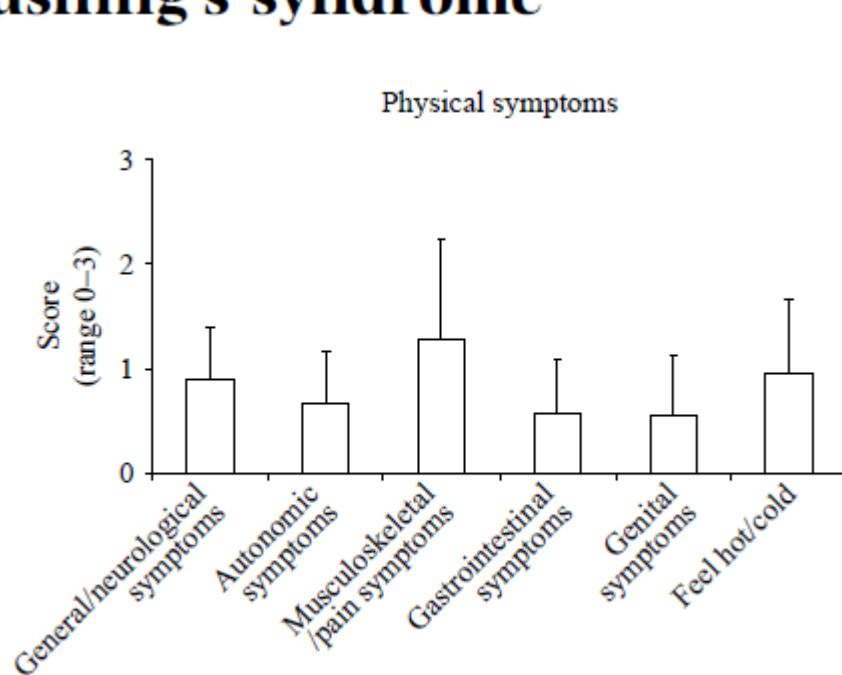
Impaired quality of life in patients in long-term remission of Cushing's syndrome of both adrenal and pituitary origin: a remaining effect of long-standing hypercortisolism?



Mean Follow-up 13.3 ± 10.4 years

- QoL remains impaired in patients in long-term remission of CS regardless of aetiology, hormonal deficiencies and treatment strategies

Negative illness perceptions are associated with impaired quality of life in patients after long-term remission of Cushing's syndrome



Mean time of remission 16 ± 12 years (N=52)

	Physical symptom checklist	EQ-5D mobility	EQ-5D self-care	EQ-5D activity	EQ-5D pain	EQ-5D anxiety	EQ-5D VAS	Cushing QoL
Illness identity	0.625 [†]	0.327*		0.329*		0.319*	-0.382*	-0.659 [†]
Timeline (acute/chronic)							-0.326*	-0.339*
Timeline (cyclical)								
Consequences				0.317*			-0.411 [†]	-0.316*
Emotional representations	0.413 [†]	0.313*				0.591 [†]		-0.629 [†]
Personal control			-0.348*				0.347*	
Treatment control		-0.348*			-0.412 [†]		0.486 [†]	0.326*
Illness coherence		-0.353*						
Psychological attributions	0.412 [†]	0.336*						-0.327*
Risk factors								
Behavioral attributions								

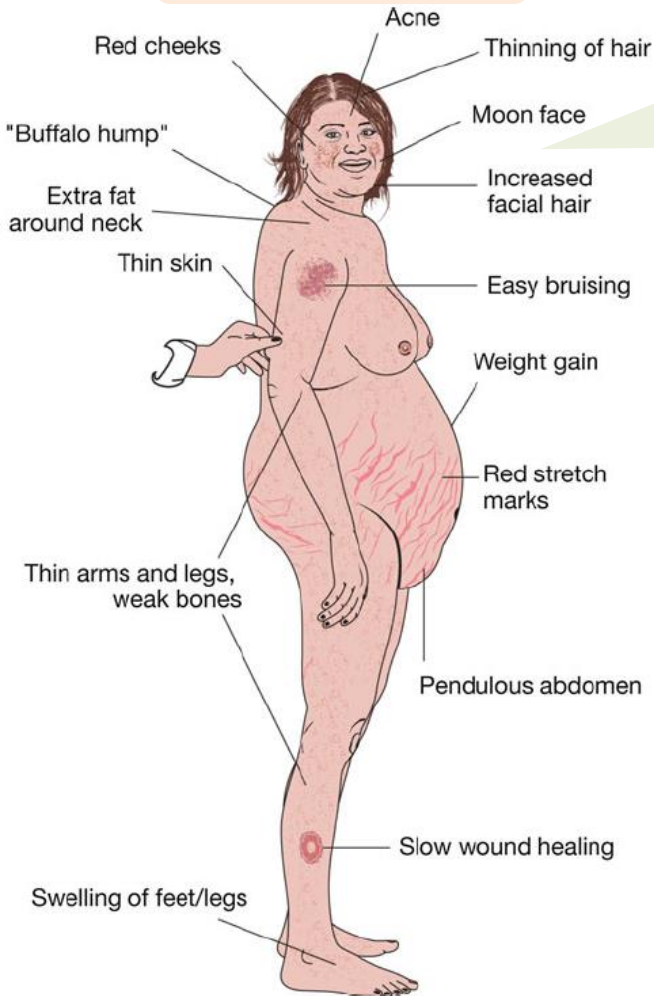
Quality of life in children and adolescents one-year after cure of Cushing syndrome: A prospective study

N= 40 CS	Pre-tx CS	Post-tx CS	Pre- vs. post-Rx (p value)
Physical summary score	37.2 (\pm 15.8)	47 (\pm 11)	<0.001
Psychosocial summary score	45.2 (\pm 7.8)	49.2 (\pm 10)	<0.049
Physical function	66.9 (\pm 28)	87.2 (\pm 18.1)	<0.001
Role physical	70.3 (\pm 37)	86.3 (\pm 27.8)	<0.01
Global health perception	64.6 (\pm 20)	58 (\pm 16.8)	<0.14
Bodily pain	56.1 (\pm 29.2)	77.1 (\pm 23.6)	<0.001
Role-emotional/behavior	85.9 (\pm 22.3)	87.4 (\pm 25.4)	<0.82
Parent-impact-time	72.2 (\pm 25.8)	84.7 (\pm 22.3)	<0.02
Parent-impact-emotional	40.1 (\pm 22.5)	63.8 (\pm 25)	<0.001
Self-esteem	61.7 (\pm 18.7)	71 (\pm 22.7)	<0.001
Mental health	67.2 (\pm 16)	76.4 (\pm 14.6)	<0.012
Behaviour	80.8 (\pm 16.5)	75.2 (\pm 18)	<0.25

- Incomplete recovery of adrenal function 1-year after treatment was associated with impaired scores
- WASI IQ scores declined and a correlation was noted between age at first evaluation and IQ score changes

“Residual” aesthetic damage in CS after cure

Active CS



What is the longitudinal
course of CS signs after
hypercortisolism
remission?



Fig. 1 Signs and symptoms of Cushing's disease

Symptoms	% of patients with symptoms		
	Prior to treatment (n= 40)	1-yr post-treatment (n=40)	Adults post-treatment* (n=343;cross-sectional data)
Weight gain	97.6	34.1	30.4
Round face	97.6	19.5	8.1
Headache	94.9	62.5	--
Bulging abdomen	92.7	21.9	29.3
Fatigue	92.5	67.4	41.3
Acne	92.3	36.6	7.2
Mood swings	92.1	42.8	27.4
Fat pad neck/shoulder	87.8	20	9
Increased irritability	87.2	39	21.3
Feelings of frustration	85	63.4	23.1
Feeling of being fat & ugly	82.5	36.5	21.6
Ruddy or red complexion	81.6	19.5	10.5
Anger	80	52.3	15.6
Decreased muscle strength	76.9	43.9	30.4
Feelings of sadness	76.9	39	27.6
Facial hair	75	46.1	27.6
Purple stretch marks	72.5	29.3	13.5
Irregular menses	70.6	35.9	11.3
Trouble sleeping	70	40	33.3
Bruise easy	69.2	28.6	24.3



Keil MF et al., Clin Endoc 2009

* from Nieman LK, Ann N Y Acad Sci 2002

Drawings Reflect a New Dimension of the Psychological Impact of Long-Term Remission of Cushing's Syndrome

TABLE 3. Symptoms and severity ratings

	Drawing 2	Drawing 3
Fat accumulation in general (%)	97.8	59.5
Fat accumulation, moon facies (%)	87.0	28.6
Fat accumulation, truncal fat (%)	87.0	35.7
Skin lesions (%)	27.2	2.4
Hirsutism/changes in hair (%)	37.0	19.0
Emotion in general (%)	58.7	56.0
Emotion, negative (%)	30.1	4.4
Emotion, positive (%)	69.9	95.6
Severity rating (range 1–5)	3.4 (1)	2.1 (1)

Data are expressed as mean (SD) unless mentioned otherwise.

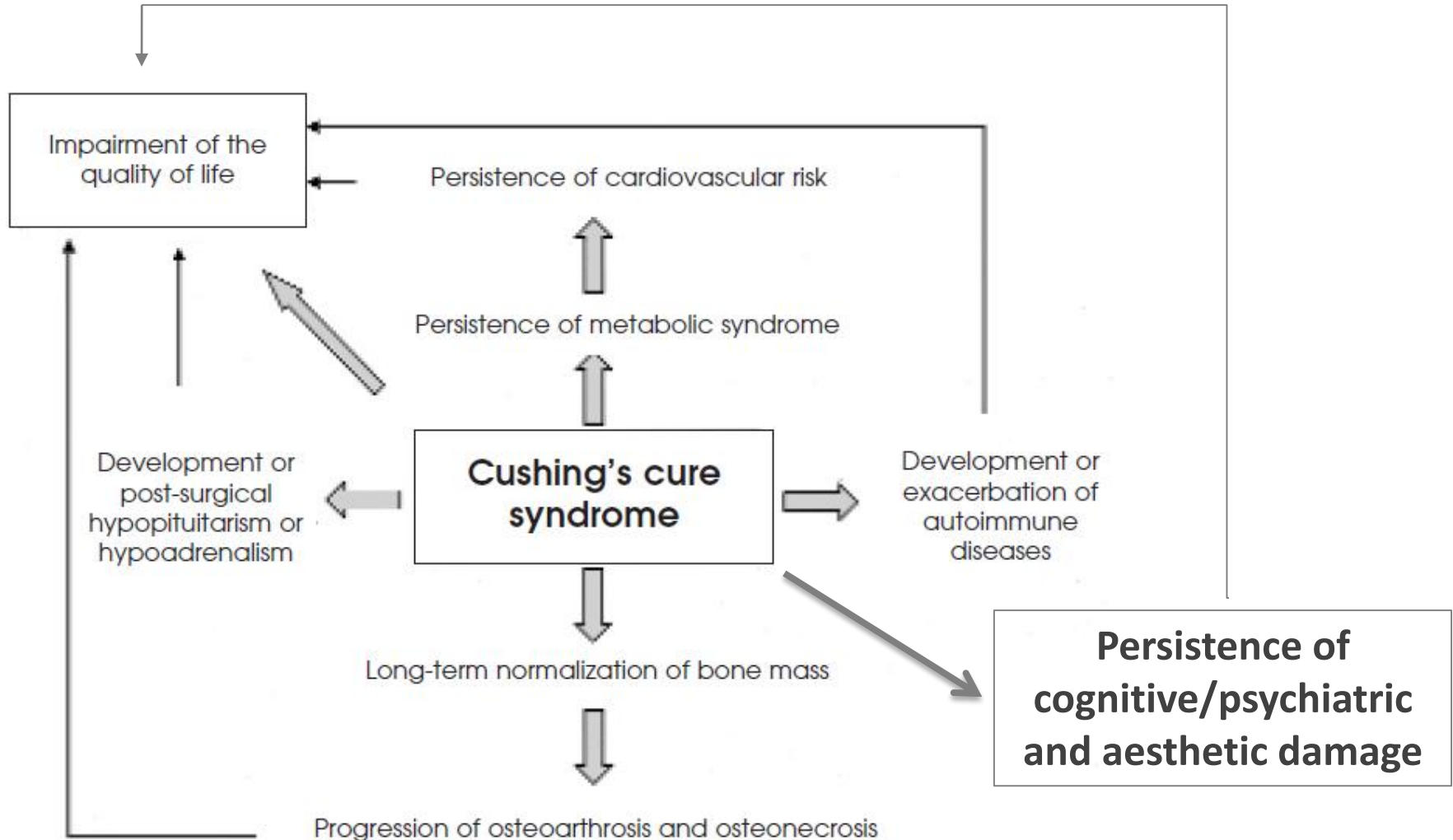
Evaluation of depression, quality of life and body image in patients with Cushing's disease

	Patients with remission (n = 32) Mean \pm SD	Patients without remission (n = 8) Mean \pm SD	Healthy controls (n = 40) Mean \pm SD	<i>p</i>
BDI	12.81 \pm 12.75	18.88 \pm 10.86	9.41 \pm 7.87	0.04
SF-36				
Physical functioning	21.88 \pm 5.35	18.63 \pm 5.61	24.68 \pm 3.03	0.002
Role physical	6.44 \pm 1.93	5.63 \pm 1.99	6.98 \pm 1.57	0.11
Bodily pain	8.19 \pm 2.92	6.81 \pm 3.52	11.04 \pm 9.75	0.04
General health	17.01 \pm 5.37	11.88 \pm 3.68	19.03 \pm 3.07	0.002
Socialfunctioning	7.75 \pm 2.52	7.00 \pm 2.14	8.24 \pm 2.32	0.13
Role emotional	5.10 \pm 1.19	4.25 \pm 1.28	5.16 \pm 1.30	0.16
Mental health	20.09 \pm 6.24	20.00 \pm 5.90	21.22 \pm 4.45	0.86
Vitality	15.25 \pm 5.78	13.63 \pm 5.15	16.08 \pm 4.25	0.51
MBSRQ				
Appearance evaluation	3.28 \pm 0.96	2.99 \pm 0.49	3.59 \pm 0.82	0.06
Appearance orientation	3.58 \pm 0.94	3.19 \pm 0.54	3.70 \pm 0.72	0.12
Fitness evaluation	3.49 \pm 0.88	2.79 \pm 0.46	3.79 \pm 0.69	0.003
Fitness orientation	3.18 \pm 0.68	2.77 \pm 0.61	3.16 \pm 0.58	0.28
Health evaluation	3.19 \pm 0.78	3.06 \pm 1.08	3.69 \pm 0.68	0.009
Health orientation	3.67 \pm 0.74	3.59 \pm 0.83	3.51 \pm 0.67	0.46
Body areas satisfaction	3.31 \pm 1.09	2.56 \pm 0.86	3.78 \pm 0.66	0.001
The mean item score	3.40 \pm 0.66	3.02 \pm 0.33	5.9 \pm 0.49	0.01



Mean time from remission 47.5 months

“Residual” morbidity in CS after cure



REVIEW

MANAGEMENT OF ENDOCRINE DISEASE

Cushing's syndrome: a structured short- and long-term management plan for patients in remission

Oskar Ragnarsson and Gudmundur Johannsson

Long-term management

Evaluate biochemical and/or clinical signs of recurrence of CS at least annually.
Assess menstrual cycle, sexual functions and pituitary function tests at least yearly and initiate adequate hormone replacement when indicated.
Consider evaluation of possible growth hormone deficiency 1–2 years postoperatively.
For patients with remaining adrenal insufficiency, avoid supraphysiological GC replacement doses.
Evaluate cardiovascular risk profile yearly and treat hypertension, hyperglycaemia and dyslipidemia when present.
Evaluate bone health regularly and treat osteoporosis when indicated.
Assess potential cognitive impairments and/or psychiatric disorders annually by evaluating subjective complaints of fatigue, memory impairments, concentration difficulties, attention deficits, anxiety and/or depressed mood.
When cognitive dysfunction is present, rule out treatable causes such as hypopituitarism, other endocrine disorders, hormonal overtreatment, vitamin deficiencies, depression and/or anxiety.
Support patients with cognitive impairment and discuss coping strategies and social support

As prolonged exposure to cortisol excess leads to worse and less reversible outcomes **early detection and appropriate intervention are critical features in the long-term management of patients with Cushing's syndrome**



Thank you!