



2023 Patient 2023 Patient Conference Co-Hosted with Adrenal Insufficiency United

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Why do patients with Cushing syndrome
often feel so lousy?

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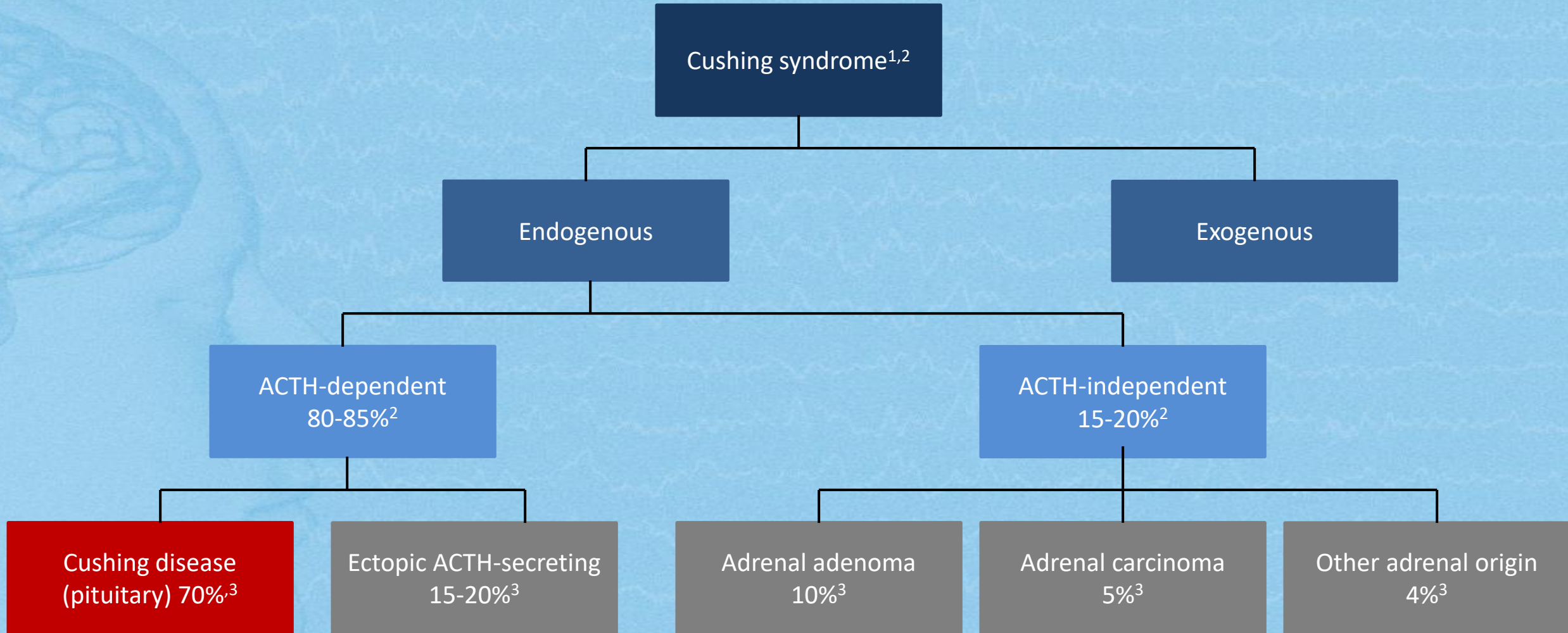
Disclosures

- Received research grants to Barrow Neurological Institute from Crinetics, Ascendis, Corcept, Sparrow and Amryt
- Served as an occasional advisory board member for Novo Nordisk, Ascendis, Corcept, Ipsen, Amryt, Strongbridge, Crinetics, Recordati and Xeris
- Served as occasional speaker for Recordati, Novo Nordisk and Corcept

What is Cushing syndrome?

*A clinical state of prolonged exposure to
too much cortisol*

What is the difference between Cushing syndrome (CS) *and* Cushing disease (CD)?



1. Rubenstein G, et al. *Best Pract Res Clin Endocrinol Metab* 2019 33(2):101270.

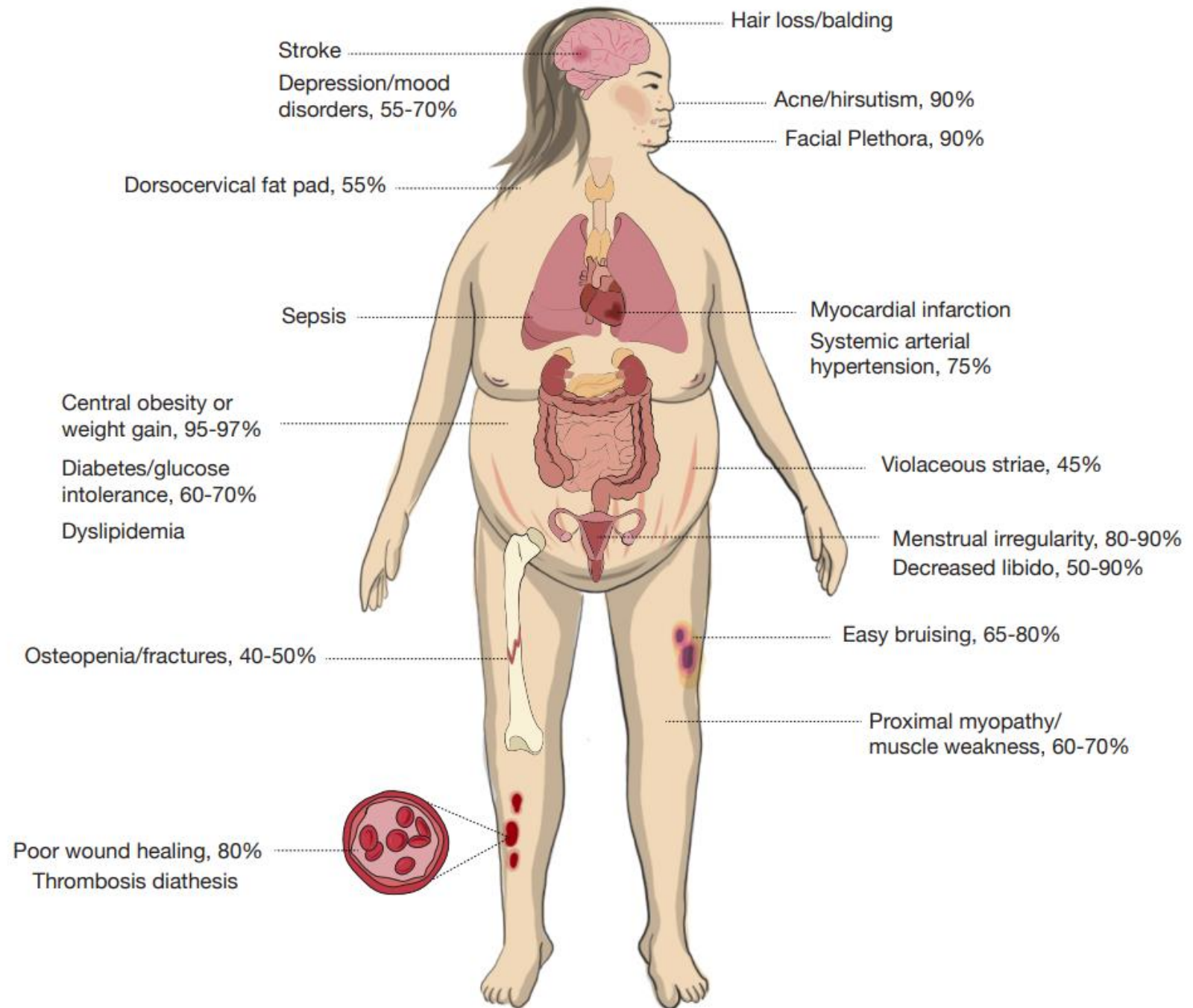
2. Arnaldi D, et al. *J Clin Endocrinol Metab*. 2003;88(12):5593-5602.

3. Tritos NA, et al. *Nat Rev Endocrinol*. 2011;7(5):270-289.

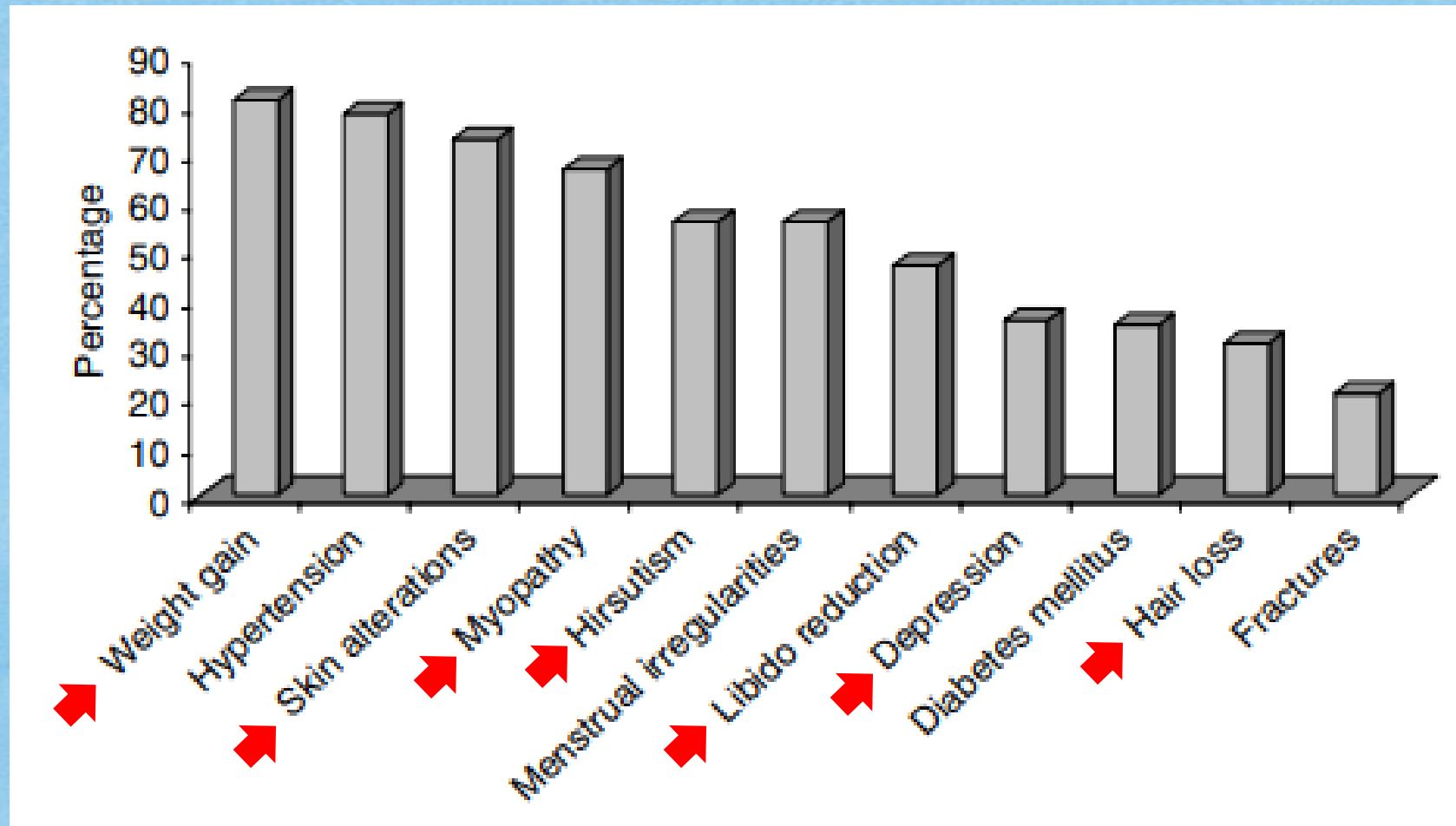
Incidence and prevalence of CS

- Incidence of CD: 1.2 to 2.4 per million people per year in newly diagnosed cases
- Prevalence: 1.2-5.6% of all pituitary tumors
- Female: male 3-4:1
- Peak incidence: 3rd-4th decade of life (very rare in childhood and adolescents)
- Incidence of other causes of CS:
 - 0.6 per million people per year for adrenal adenoma
 - 0.2 per million people per year for adrenal carcinoma

Clinical features of CS



Distribution of symptoms in patients with CS



What is defined as QoL? *The concepts*

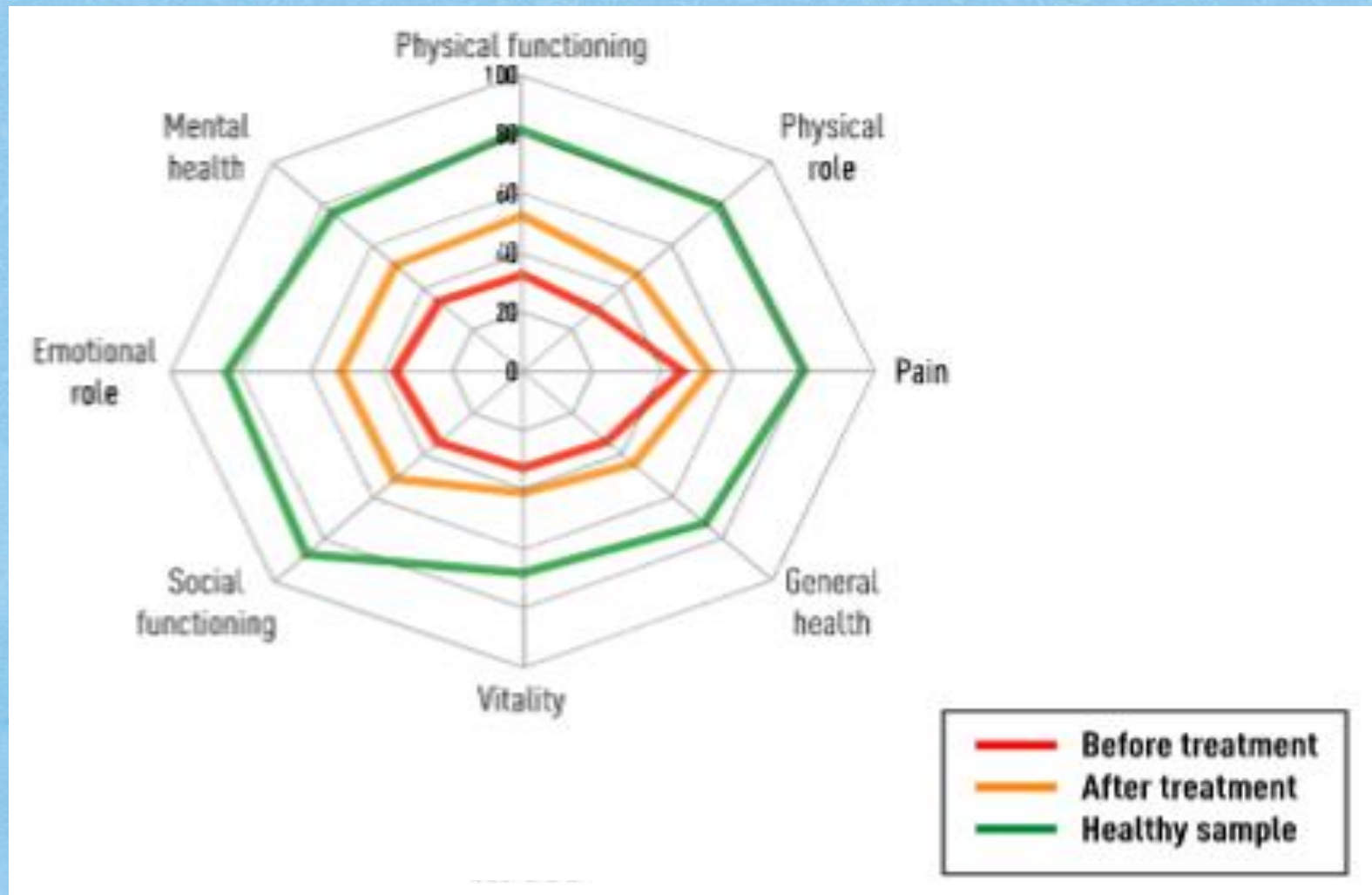
- WHO definition: “an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns” OR “a patient-reported measure that reflects their individual definition of well-being (including patients' expectations and physical, emotional and social aspects)”
- Clinicians’ and researchers’ definition: “those aspects of self-perceived well-being that are related to or affected by the presence of disease or treatment”

How is QoL measured?

Santos A, et al. Front Endocrinol (Lausanne). 2019 Dec 11;10:862.

Questionnaire list	
Generic quality of life questionnaires	<p>Notingham Health Profile (NHP)</p> <p>Short Form-36 (SF-36)</p> <p>Short Form-12 (SF-12) (SF-36 in a short form)</p> <p>Psychological General Well Being Scale (PGWBS)</p> <p>EuroQoL-5D (EQ-5D)</p> <p>World Health Organization Quality of Life BREF (WHOQoL-BREF)</p>
Disease-specific quality of life questionnaires	<p>CushingQoL</p> <p>Tuebingen Cushing's disease quality of life inventory (Tuebingen CD-25)</p>
Specific domains: Depression	<p>Hospital Anxiety and Depression Scale (HADS)</p> <p>Beck Depression Inventory-II (BDI-II)</p>
Anxiety	<p>Hospital Anxiety and Depression Scale (HADS)</p> <p>Beck Anxiety Inventory (BAI)</p> <p>State Trait Anxiety Inventory (STAI)</p>
Fatigue	<p>Checklist individual strength Questionnaire (CIS)</p> <p>Modified Fatigue Impact Scale (MFIS)</p>
Self-esteem	<p>Rosenberg's questionnaire</p>
Sexual function	<p>Female Sexual Function Index (FSFI)</p> <p>International Index of Erectile Function (IIEF-5)</p>
Pain	<p>Mc Gill Pain Questionnaire</p>
Fatigue	<p>Checklist Individual Strength Questionnaire</p>
Sleep	<p>Pittsburgh Sleep Quality Index (PSQI)</p> <p>Insomnia Severity Index</p>

Impaired QoL in CS



Most common symptoms still present in patients in remission of CS after surgery (n = 343, F/U ~12 yrs)

Symptom	Percentage of patients reporting the symptoms (%)	Symptom	Percentage of patients reporting the symptoms (%)
Fatigue	41.3	Bulging abdomen	29.3
Forgetfulness	35.7	Anxiety	28.4
Trouble sleeping	33.3	Facial hair	27.6
Depression	31.2	Feelings of sadness	27.6
Weight gain	30.4	Mood swings	27.4
Decreased muscle strength or weakness	30.4	Decreased ability to exercise	27.0

Why do patients with CS still do not feel well after surgery?

- May experience more flare-ups of underlying chronic conditions
- Steroid withdrawal symptoms
- Persistent muscle weakness and easy fatigued limiting physical ability
- Persistent difficulty to lose weight
- Lack of understanding by providers of how patients are feeling (even if lab results normalized)

Factors that worsen QoL and contribute to persistence of symptoms in patients with CS

Delay to diagnosis



More pronounced symptoms

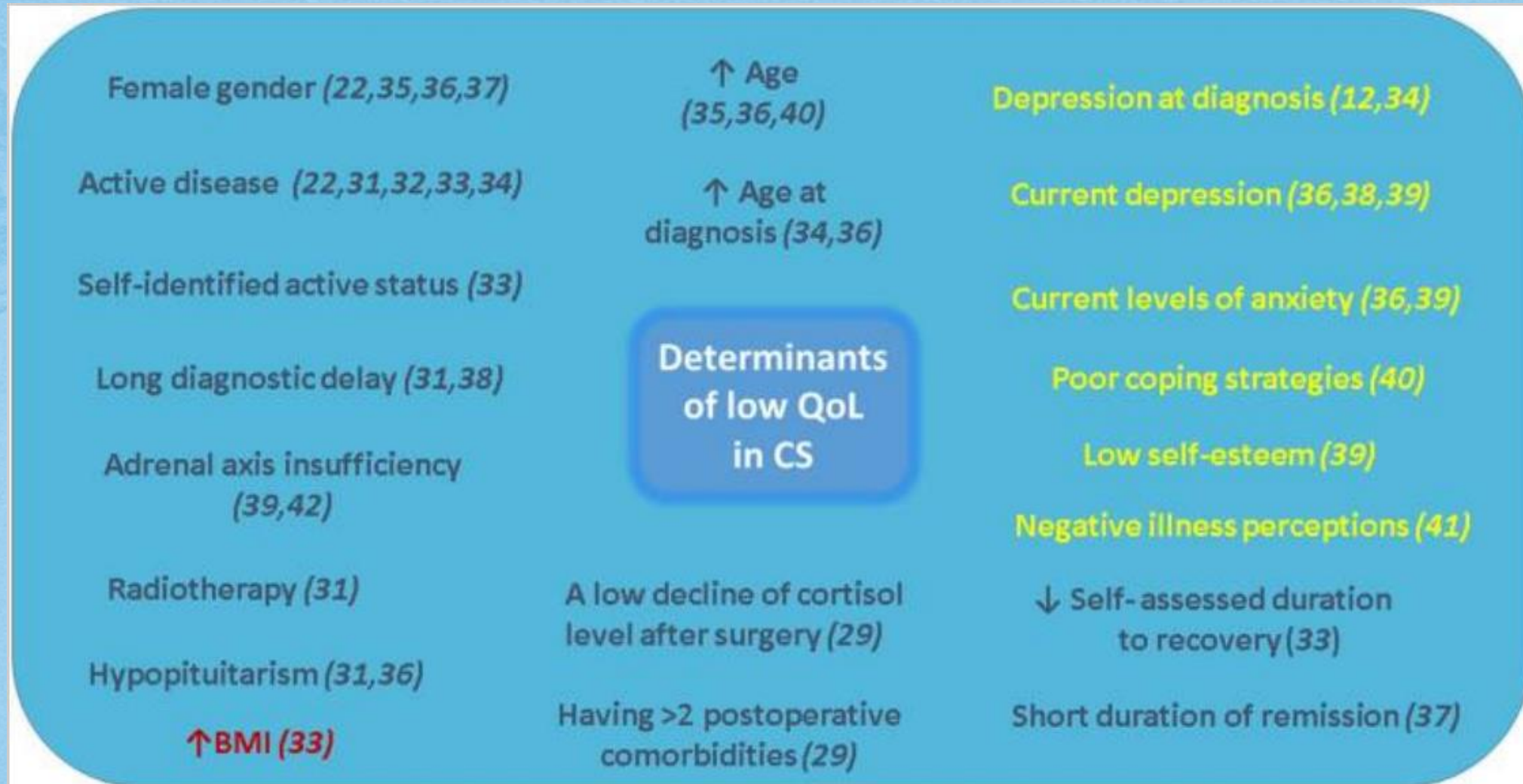


Affects social and family relationships and professional performance

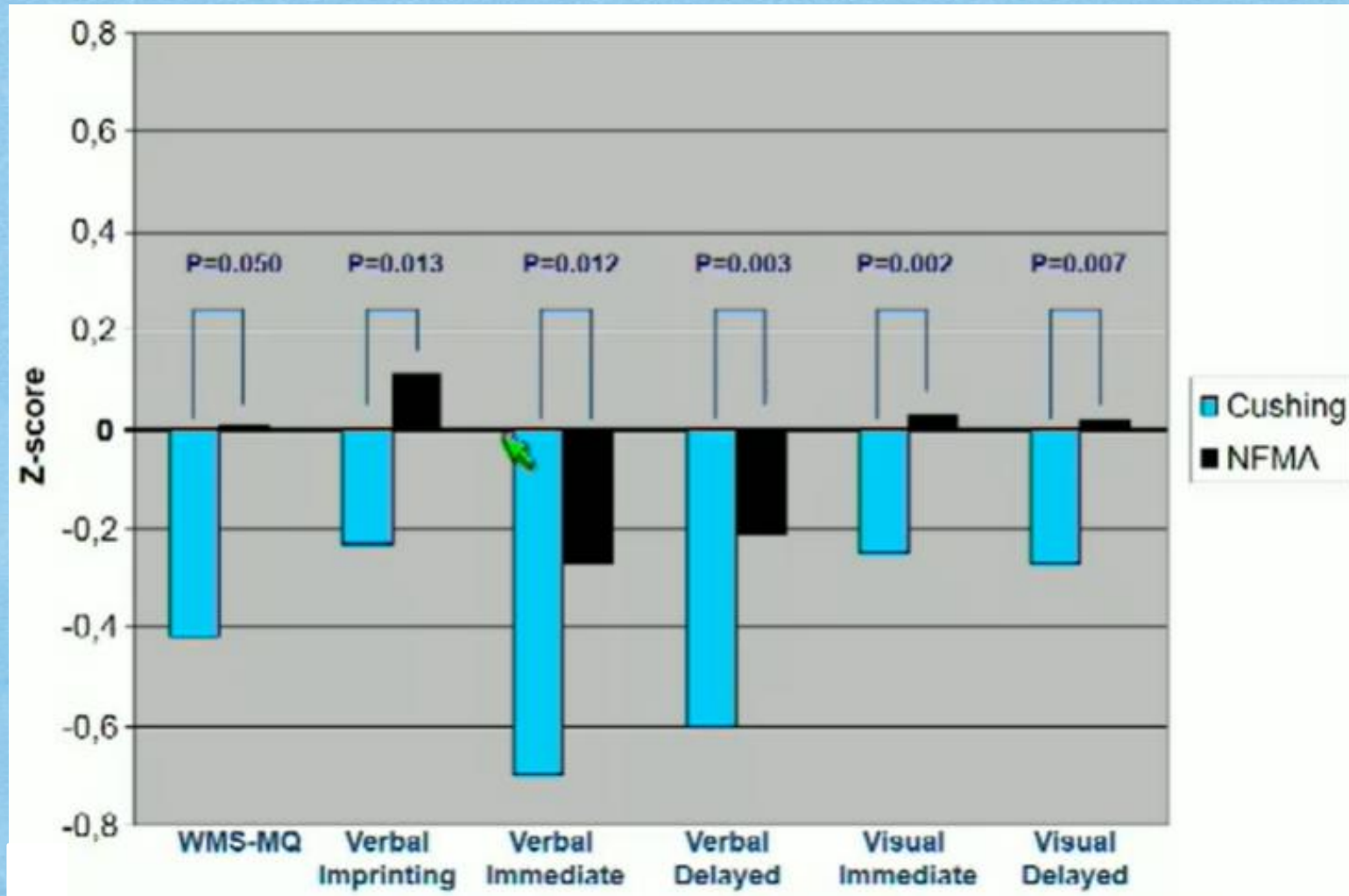
Data from ERCUSYN:

- *delay to diagnosis ~ 2 years*
- *only 47% of patients were employed (mean age 44 years)*
- *high degree of absenteeism*

Factors causing impaired QoL in CS



Impaired cognitive functioning (memory) after long-term remission of CD



*More depression
and anxiety*

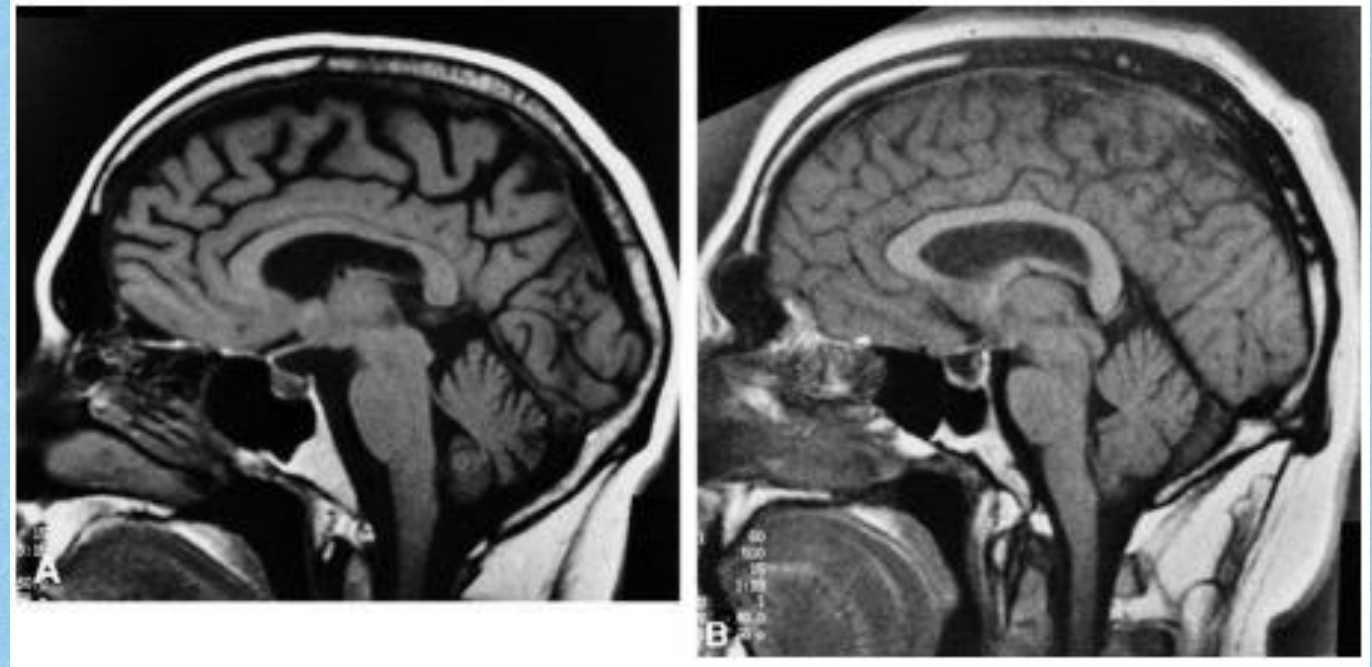
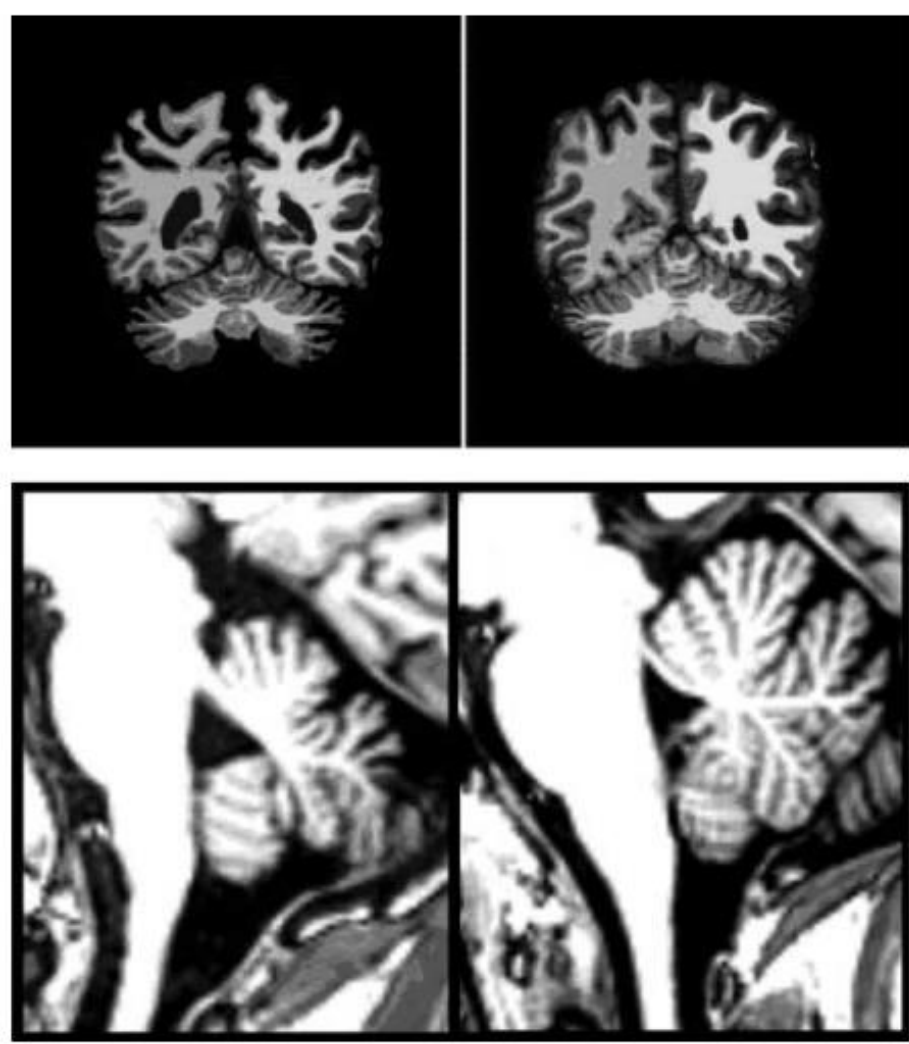


*More maladaptive
personality traits*

Neuropsychological dysfunction in CS

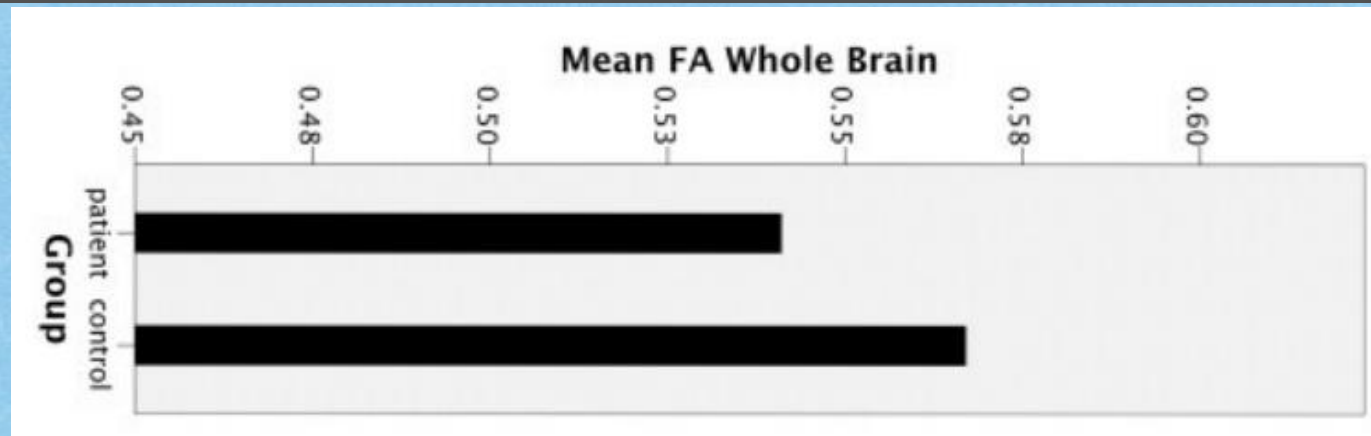
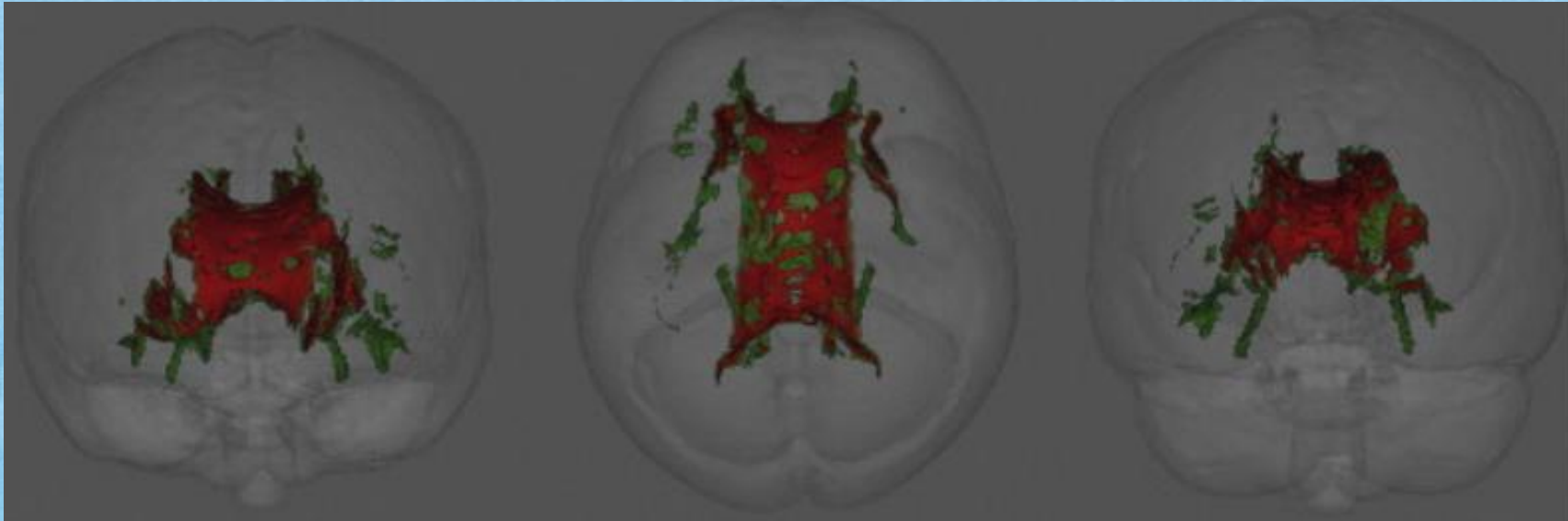
- Brain regions for cognitive and emotional functioning are rich in glucocorticoid receptors → vulnerable
- Volumetric reduction of these structures has been described in active CS that do not revert to normal after biochemical remission
- Deficits in cognitive function:
 - memory
 - verbal learning
 - language
 - spatial information
 - working memory, executive function and mental fatigue

Smaller cerebellar and cerebral cortex volumes in active CS

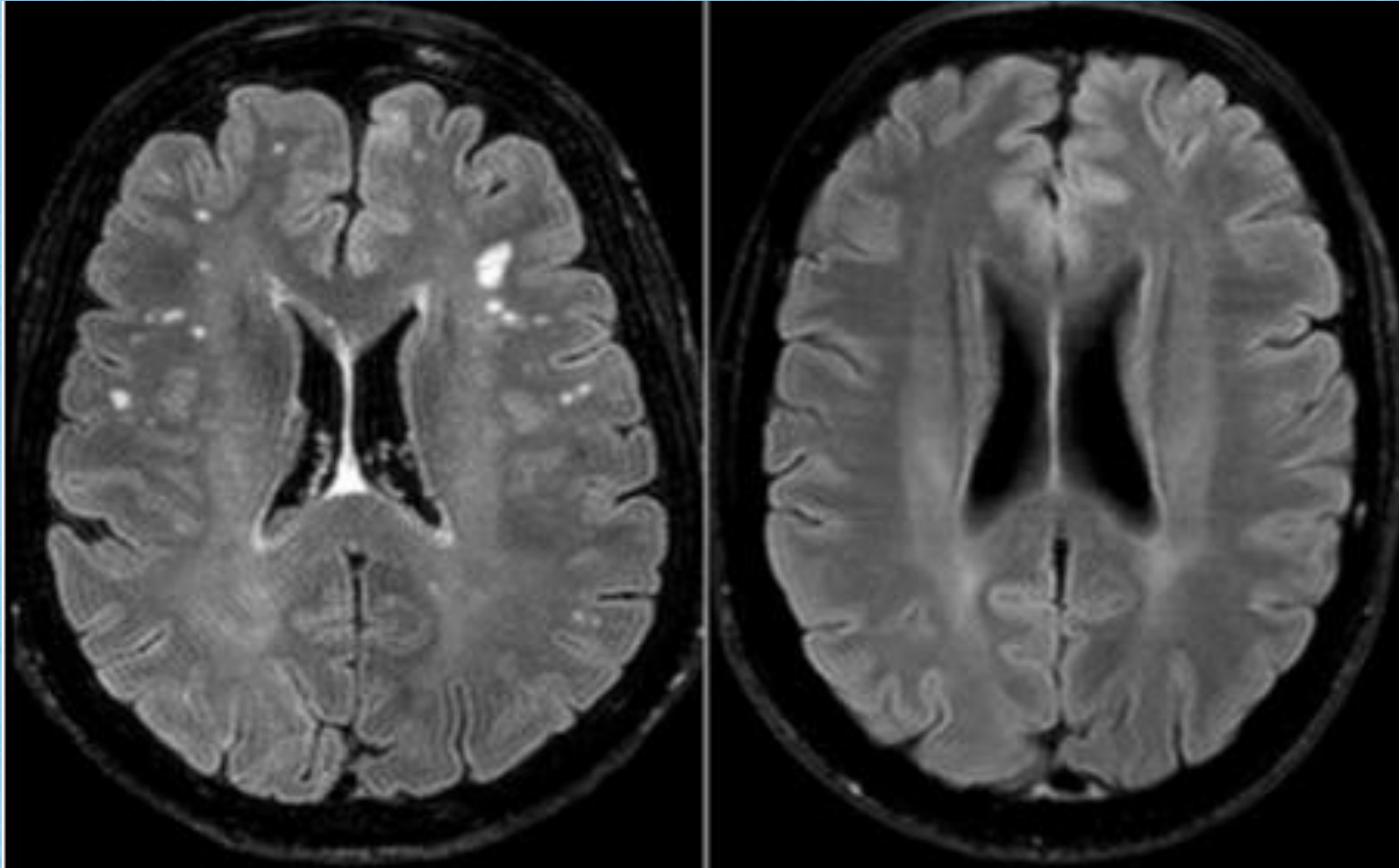


Simmons NE, et al. Surgical Neurology 2000 53 72–76.

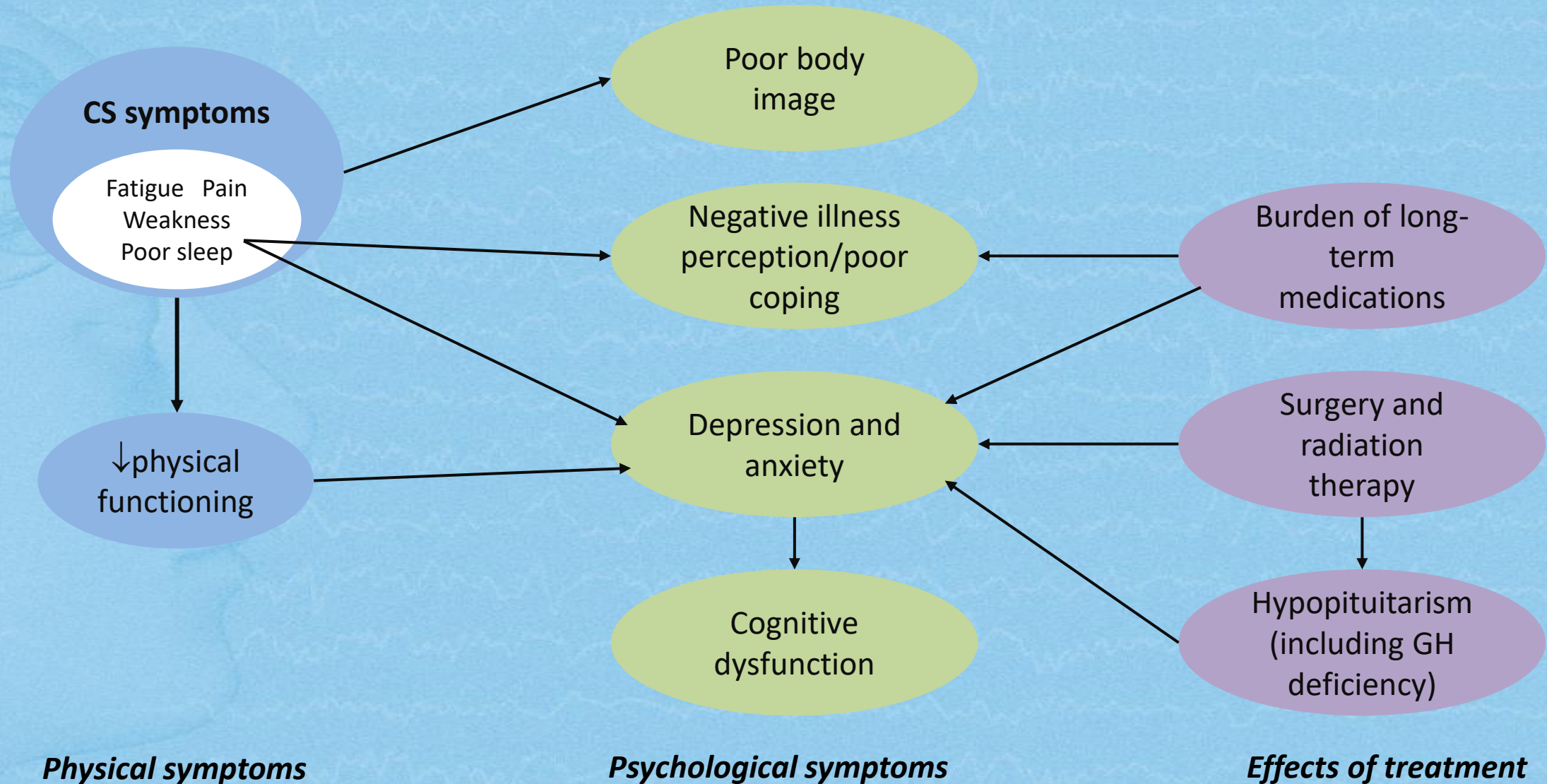
Reductions of white matter integrity in patients with long-term remission of CD



Patients in remission of CS have more severe white matter lesions than controls

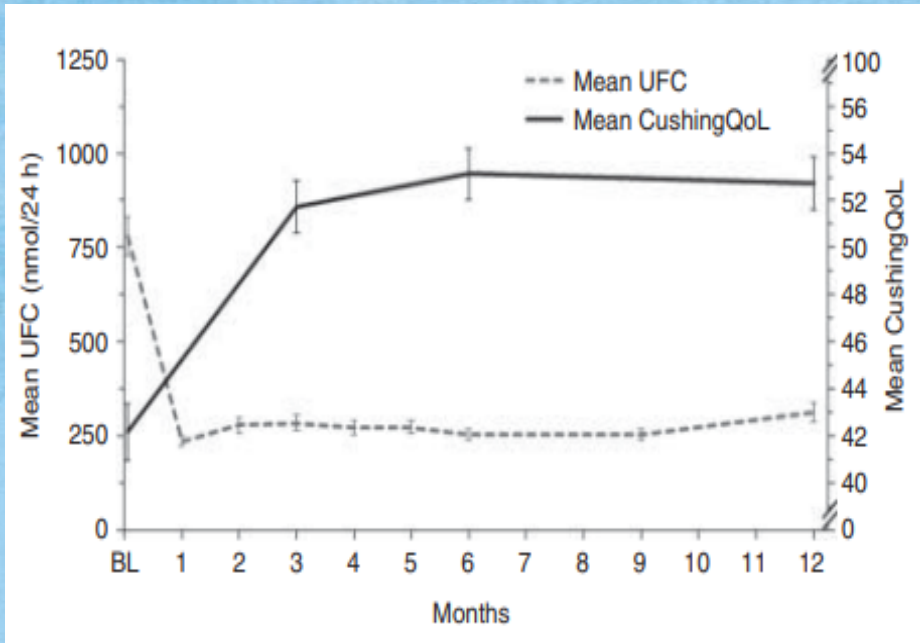


Effects of physical and psychological symptoms and treatments on QoL in patients with CS



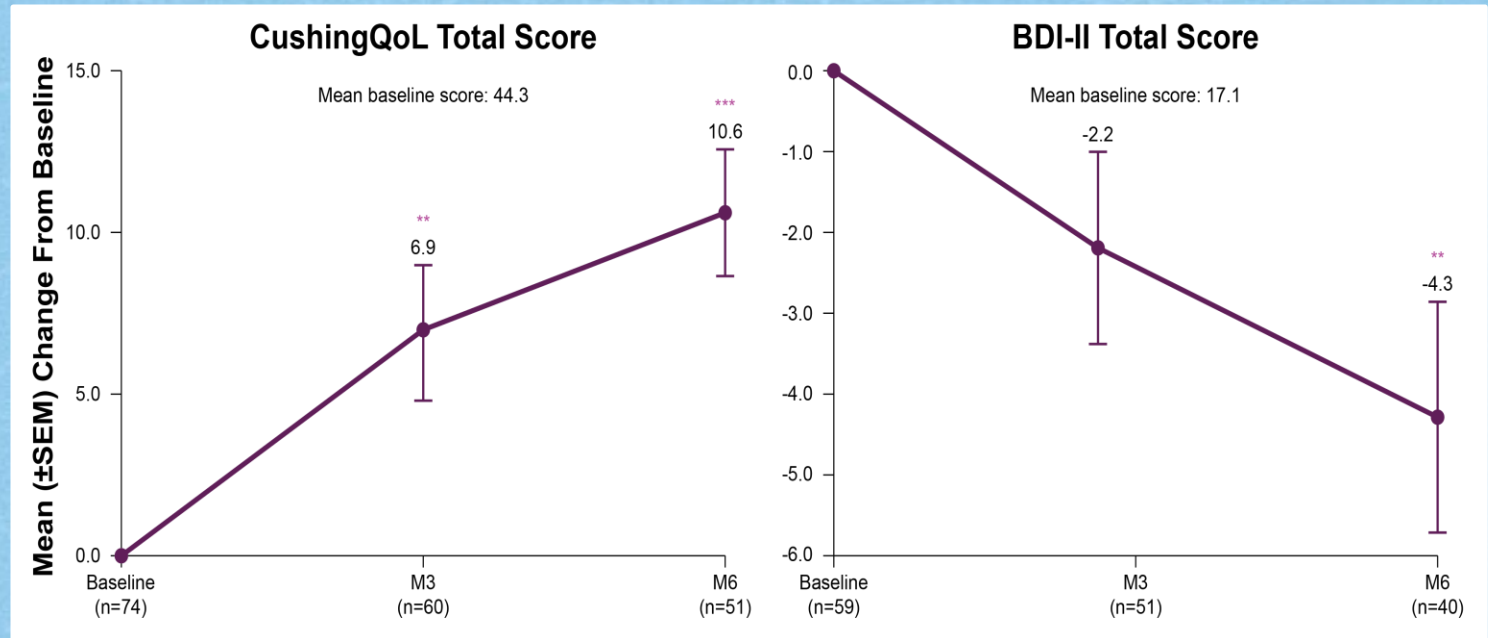
Medical therapy can improve QoL in patients with CS:

Pasireotide and Levoketoconazole



Pasireotide

Webb SM, et al. Eur J Endocrinol. 2014 Jul;171(1):89-98.

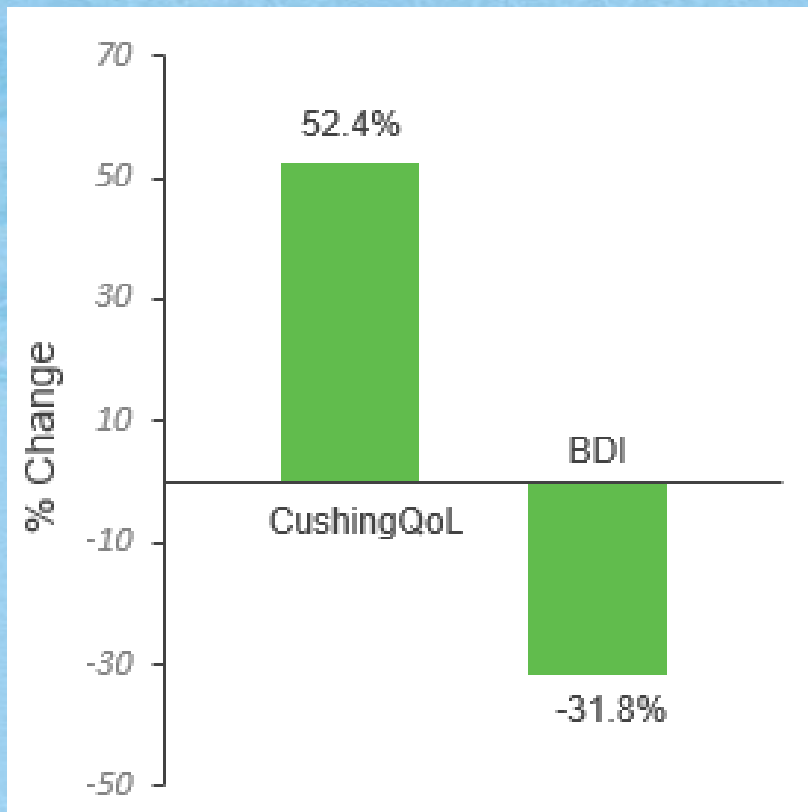


Levoketoconazole

Fleseriu M, et al. Lancet Diabetes Endocrinol. 2019 Nov;7(11):855-865.

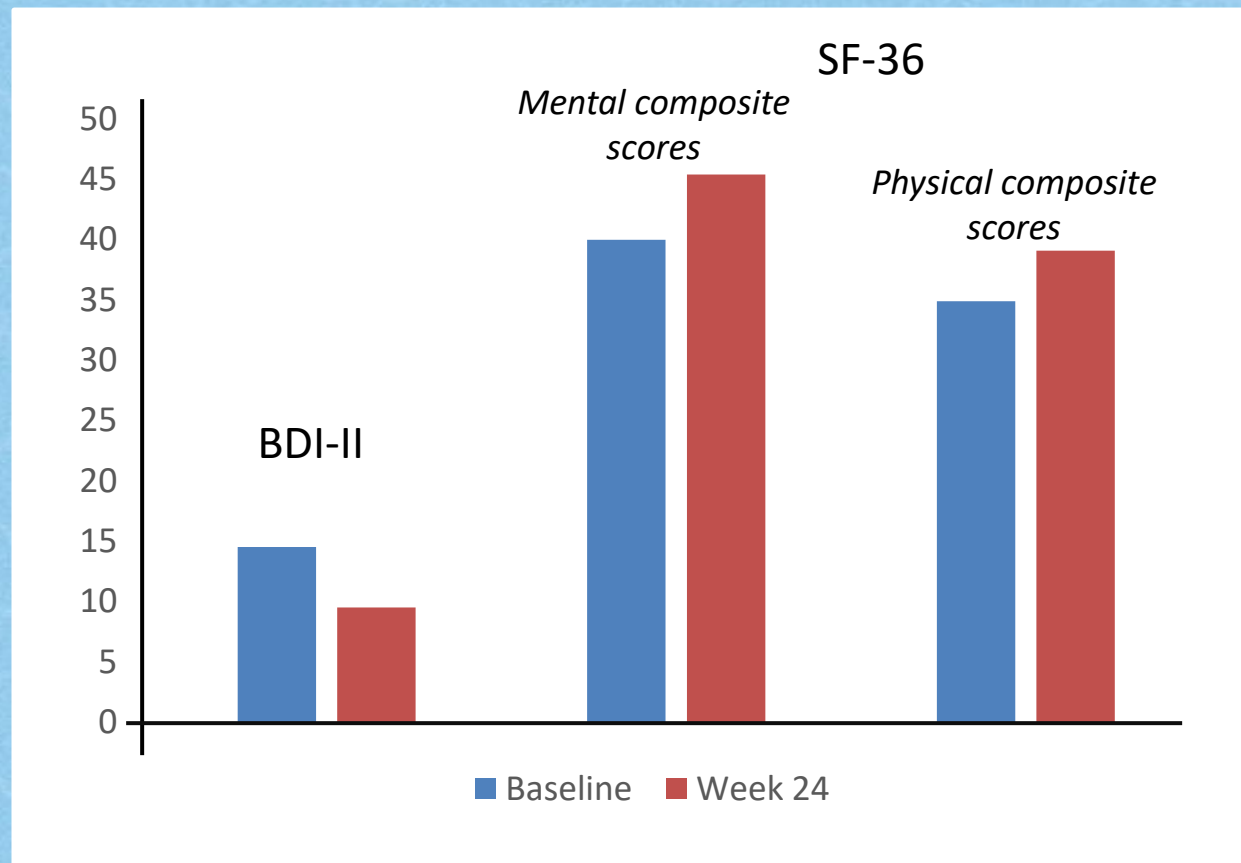
Medical therapy can improve QoL in patients with CS:

Osilodrostat and Mifepristone



Osilodrostat

Pivonello R, et al. Lancet Diabetes Endocrinol. 2020 Sep;8(9):748-761.



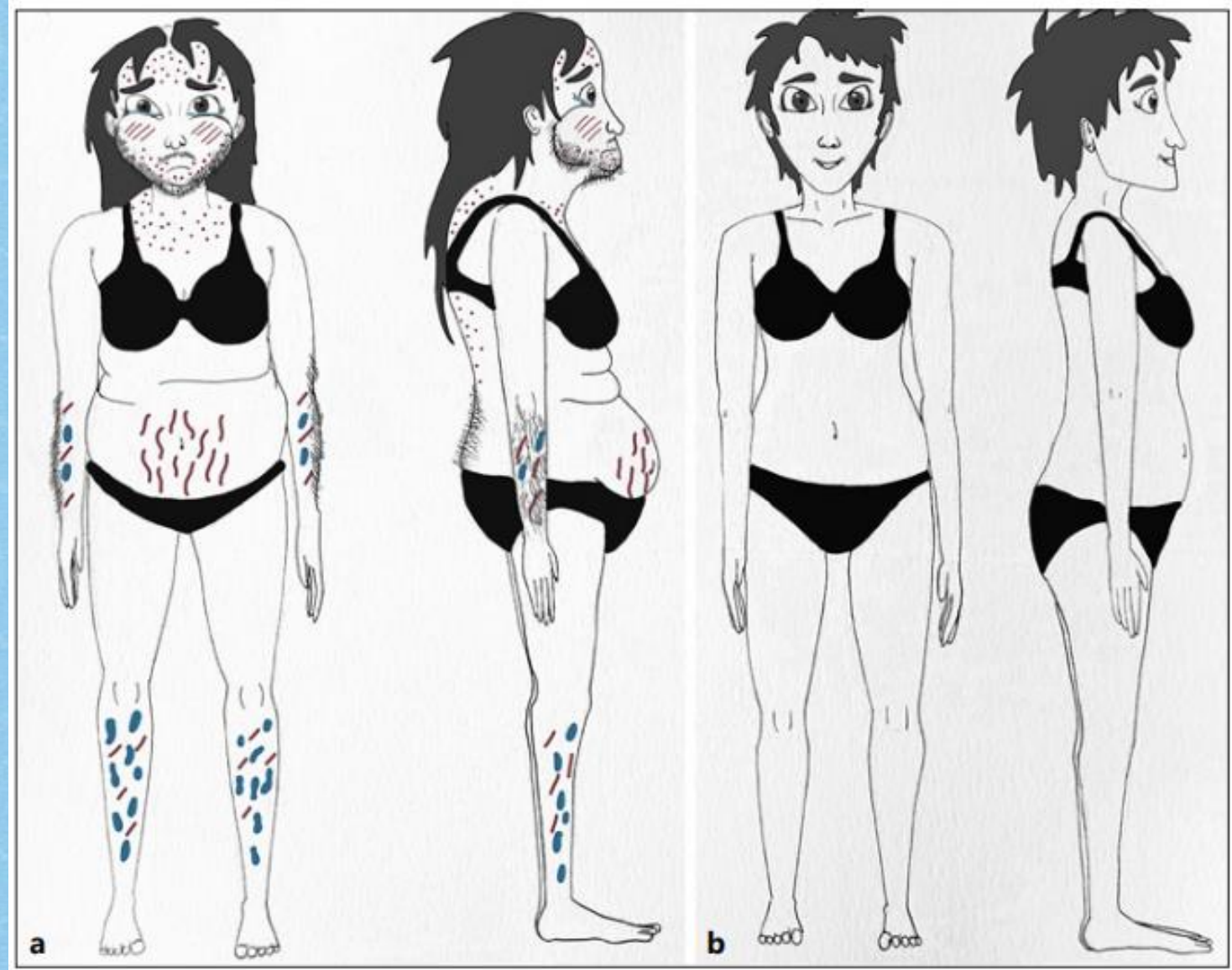
Mifepristone

Fleseriu M, et al. J Clin Endocrinol Metab. 2012 Jun;97(6):2039-49.

Psychological phases of adaptation

- *1st phase:* uncertainty and confusion “What’s going on?”
- *2nd phase:* bewildered, negation and sense of overwhelm “What is this disease?”
- *3rd phase:* opposition/isolation “This cannot be happening to me!”
- *4th phase:* anger “This is not fair to me!”
- *5th phase:* sadness, sense of acceptance and/or adaptation “I have this disease now, so how do I cope with it?””

Subjective impression of
body image with active
Cushing syndrome and 2
years after successful
surgery, as drawn by a 20-
year-old graphic designer

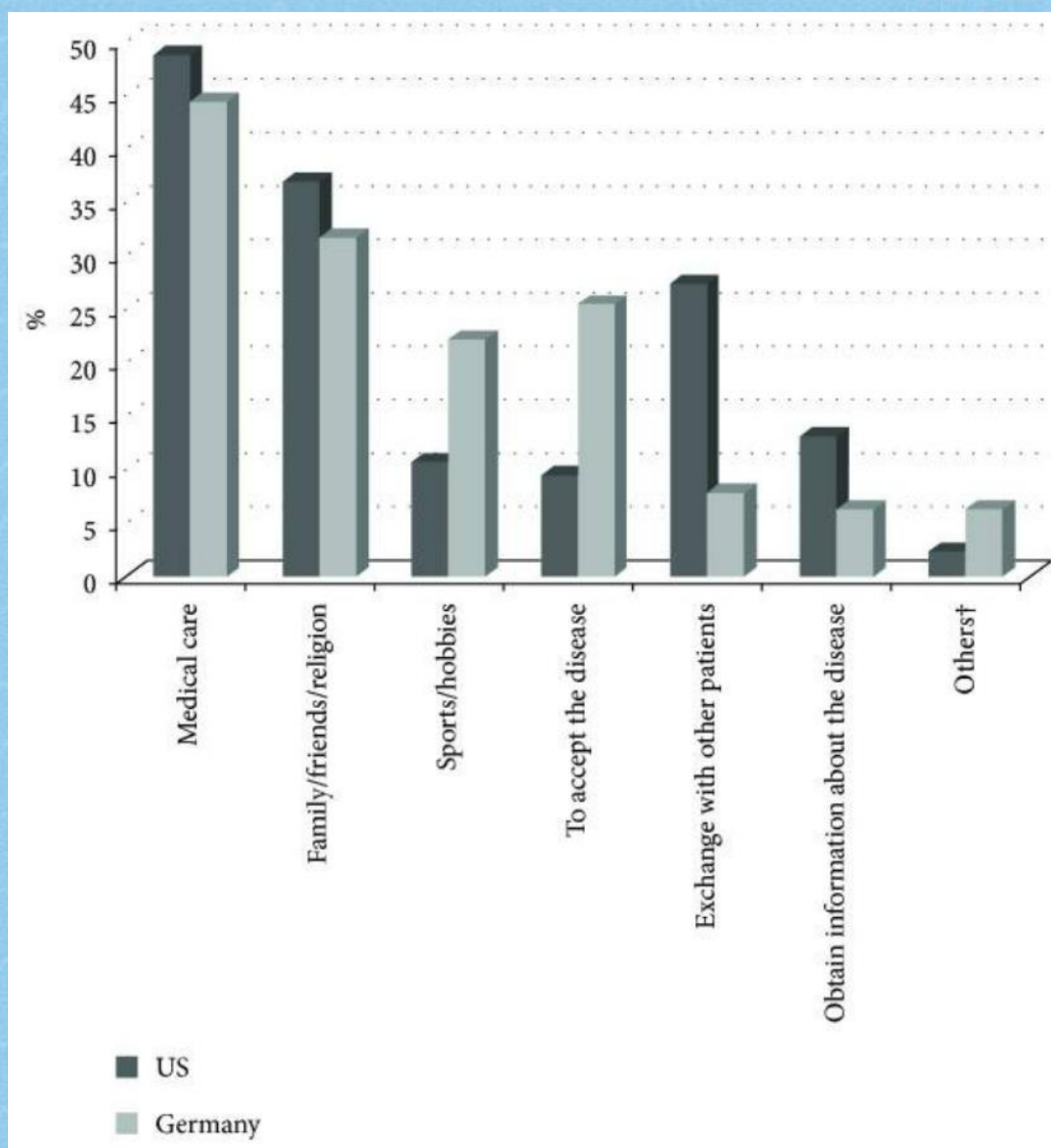


Strategies to improve QoL of CS patients

- Treat all comorbidities and refer to appropriate specialists
- Setting patient expectations
- Provide printed information to help patients understand CS
- Empathetic relationship with patient
- Educational programs
- Maintaining healthy lifestyle

Survey of support needs of patients with CS in remission

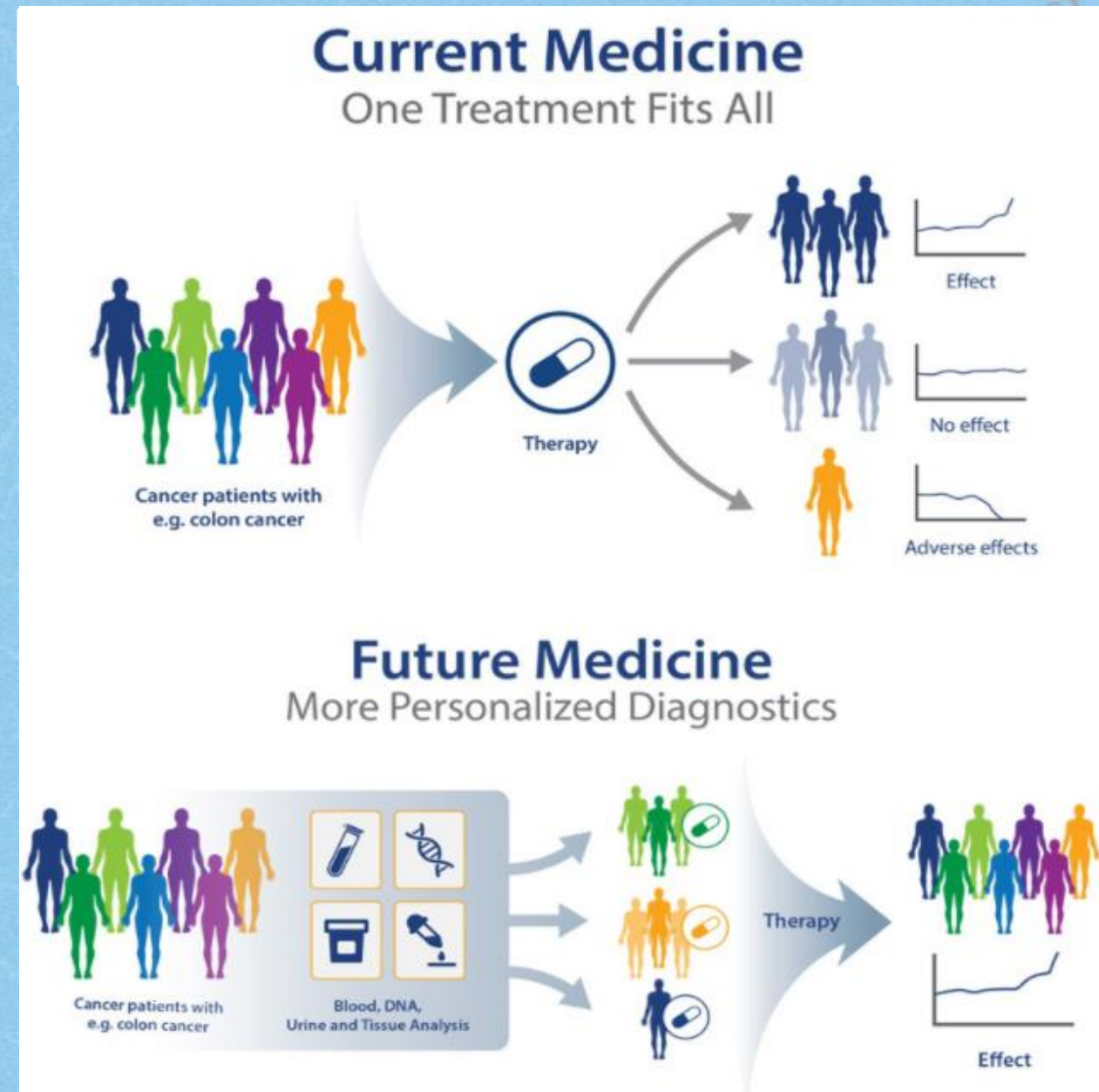
- 84 German and 71 US patients
- Explored patient's needs through a questionnaire



Psychosocial needs of CS patients: *a psychological perspective*

- Raise awareness among other health professionals to reduce delay to diagnosis
- Encourage patients to share their psychological issues
- Need for focus groups and individualized education programs to empower patients
- Involve family, friends and partners
- Provide individualized education programs
- Consider joining a support group

“Personalized medicine” in a multidisciplinary approach to reduce both physical and psychosocial stressors is the most appropriate strategy to improve QoL in CS patients



Take home messages (1)

- Psychological alterations occur often in CS patients and are important factors of ↓QoL
- QoL tends to be poorer in CS patients compared to healthy controls and patients with other pituitary disorders
- Even if some improvement occurs after successful treatment, full recovery is not observed and comorbidities may persist

Take home messages (2)

- Psychological assessments and interventions should be part of the management plan
- Patient education and self-management interventions can help improve health perception and QoL
- Group programs have shown promising results, but few are available
- Appropriate treatment to reduce depressive symptoms is necessary to improve QoL

Ode to a Cushie

It's amazing how sickness can take over your life,
It makes it so hard to be a mom and wife.
Your body hurts all over, bones constantly break,
Your blood pressure's high, hands and fingers shake.
Your face is red and puffy, your belly's big and round,
So many changes can happen, even the way you sound.

Diabetes, weight gain, some people will stare
And don't get me started on the loss of your hair.
Medication, radiation, and of course the shots!
I didn't know all the symptoms, but there seems to be lots!
Balance is off, and there's memory loss,
What's coming next? Well, it's a coin toss

See, Cushing's disease is not common, not fair
So much is unknown, it's incredibly rare.
1 in a million is what doctors say, I should probably buy lotto tickets today!
Decisions to make in finding a cure,
Brain surgery, adrenal removal? Nothing's for sure.
So this my friends is just a short list, as I'm sure there are many more
Symptoms I have missed.

So if you know someone that seems fat and lazy,
Remember, not everyone's path is made of daisies.
Do what you can to understand
Because I can tell you, this is not what they planned.
A smile, a hug is all that it takes, to show your support
With the progress we'll make.

JS, Cushing disease patient

THANK YOU FOR YOUR ATTENTION!

