Deutsches Cushing Register

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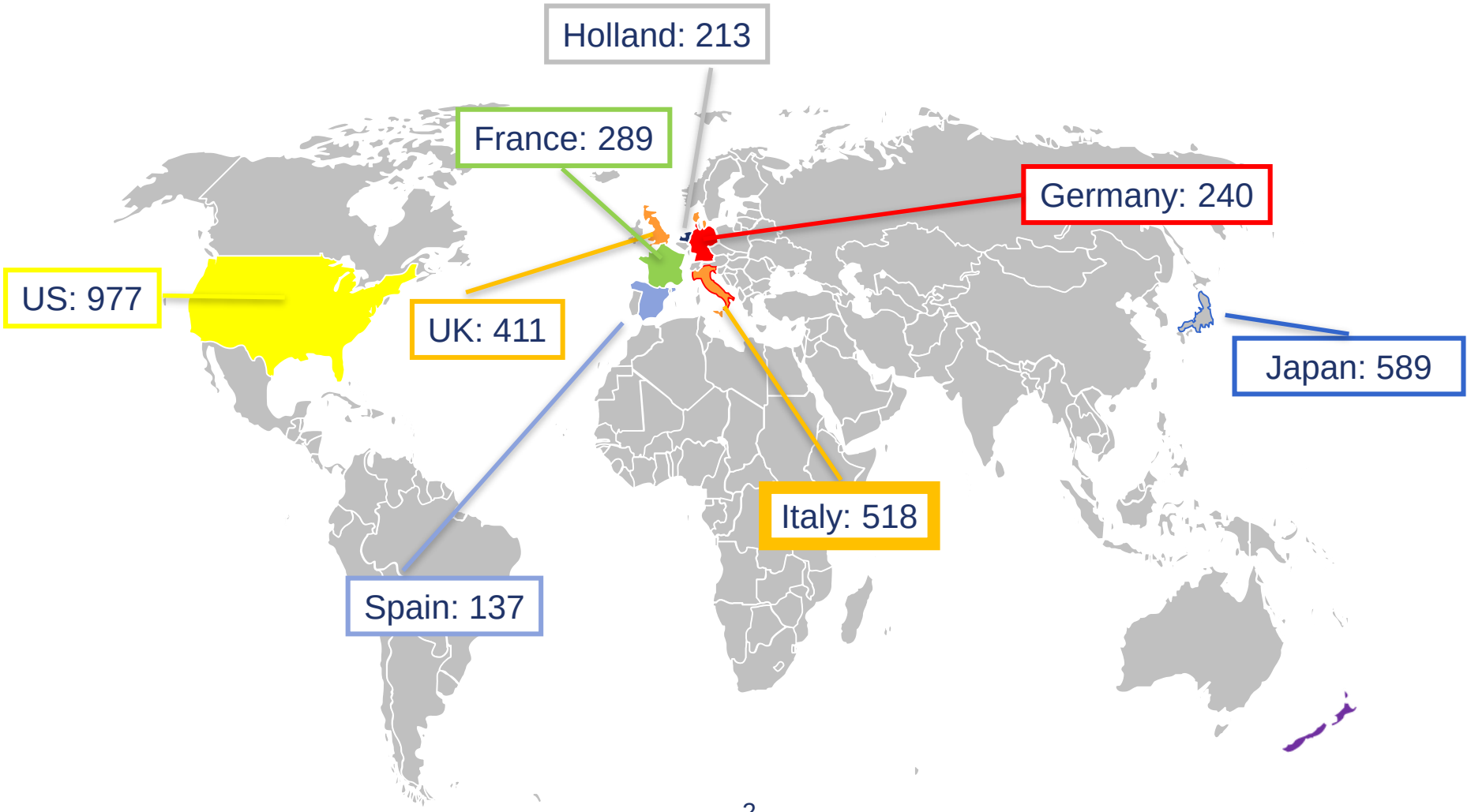
Custodes

DISCRIMINATORY VALUE OF CLINICAL FEATURES IN CUSHING'S SYNDROME: WHAT HAS CHANGED?

Alltogether to Beat Cushing's Syndrome
Naples 5th-7th of May, 2015

M. Reincke & Co-workers
Medizinische Klinik und Poliklinik IV
Ludwig-Maximilians-Universität München

Cushing's syndrome: Where is the science going on? PubMed listed publication (1900-2015)



Overview: Cushing

- **Introduction**
- German Cushing Registry
- Automatic Face Recognition
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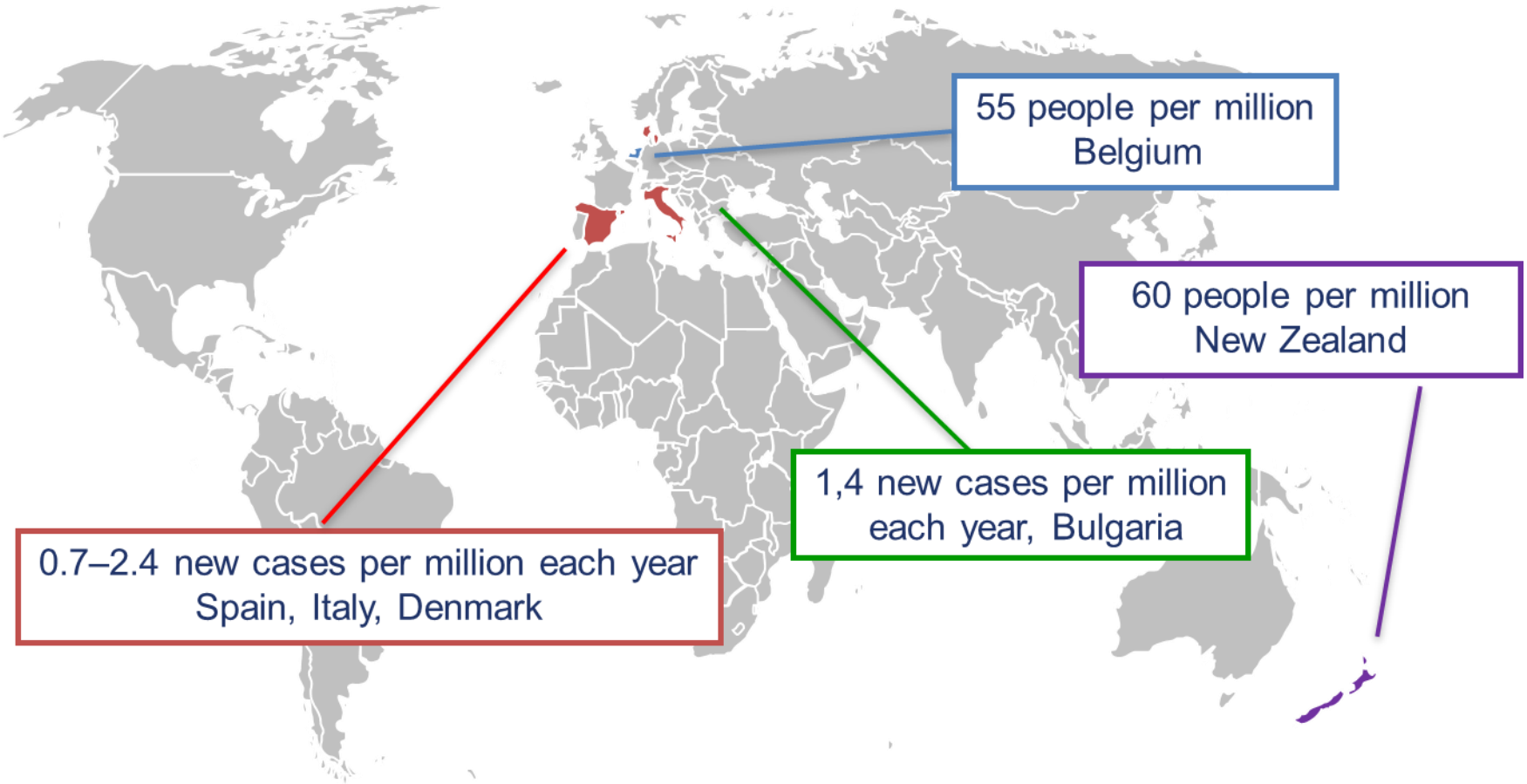
- Conclusions

Cushing disease: a Rare Condition



[1]Etxabe J & Vazquez JA. Clin Endocrinol 1994;40:479-484; [2]Ambrosi B et al. Excerpta Medica 1991;159–168; [3]Lindholm J et al. J Clin Endocrinol Metab 2001;86:117–123; [4]Daly AF et al. J Clin Endocrinol Metab 2006;91:4769–4775 ; [5]Bolland MJ *et al. Clin Endocrinol (Oxf)* 2011;75:436–442

Cushing syndrome in Diabetes and Obesity

Author	Disease	N	N (%) Screening	N (%) confirmation
Leibowitz et al. 1996	**DM, HbA1c>9; Obesity**	90	4 (4,4%)	3 (3,3%)
Catargi et al. 2003	**DM, HbAa1c>8; Obesity**	200	52 (26%)	4 (2%)
Caetano et al. 2007	**DM2, overweight**	103	8 (7,8%)	0 (0%)
Reimondo et al. 2007	**New DM2**	100	5 (5%)	1 (1%)
Newton et al. 2008	**DM2**	171	32 (18,7%)	1 (0,6%)
Mullan et al. 2010	**DM2, HBA1c >7, BMI>25**	201	47 (23%)	0 (0%)
Baid et al. 2009	**Overweight, obesity**	369	n.a.	0 (0%)
Fierabracci et al. 2010	**Morbid obesity**	783	n.a.	6 (0,8%)
	Total	2017	148 (17,1%)	15 (0,7%)

Cushing‘s syndrome: S&S in textbooks

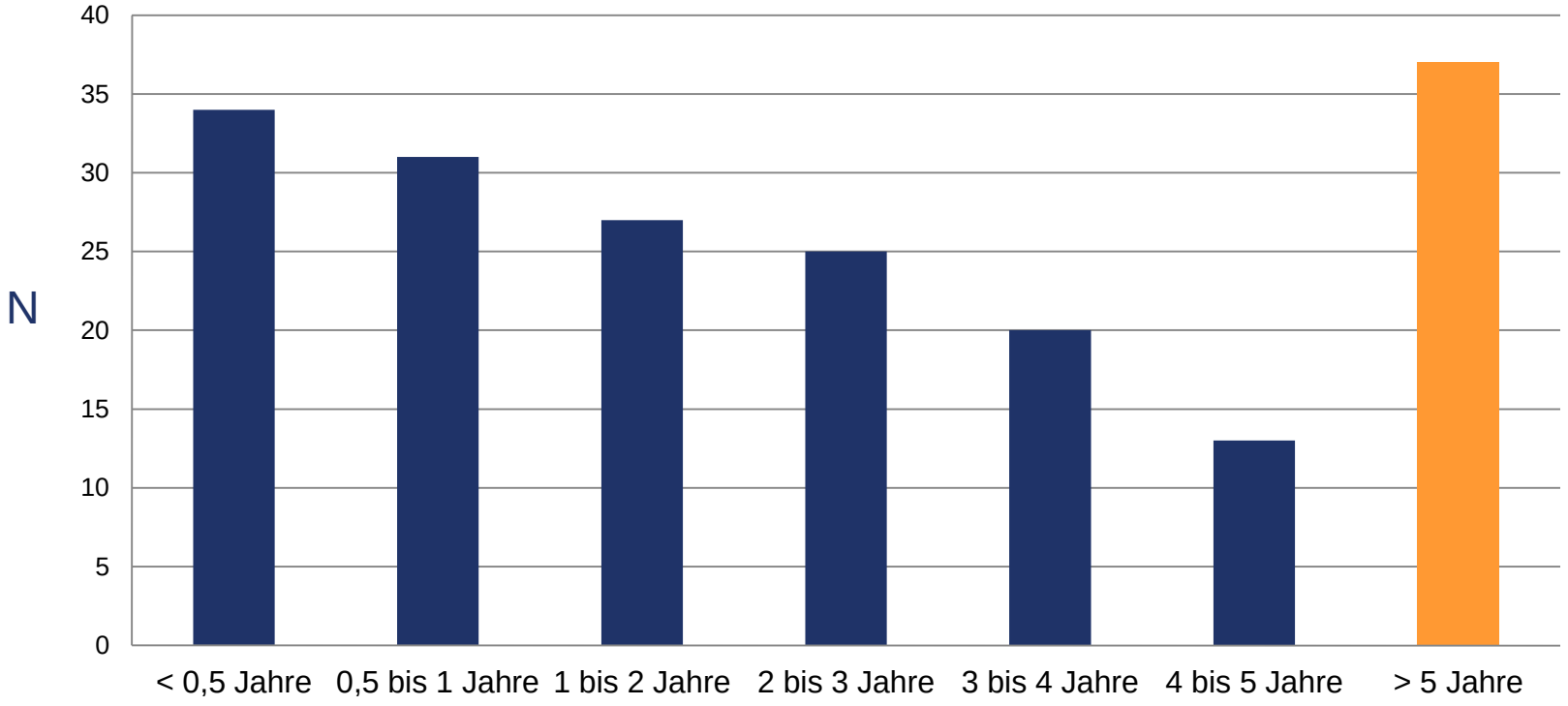
Unspecific/low discriminatory value	Prevalence (%)
Obesity	40–80
Diabetes mellitus	25–50
Hirsutism	30–50
Hypertension	50
Osteoporotic fracture	40–50
Specific/high discriminatory value	
Skin changes (atrophy, rubeosis, plethora, ecchymosis, wide violaceous striae, acne, skin infections)	100
Truncal obesity	80–100
Moon face	50–95
Myopathy	30–90
Oligomenorrhea/impotence	30–85
Mental disturbances	50–80

Metabolic syndrome

Nieman LK *et al. J Clin Endocrinol Metab* 2008;93:1526–1540

3 years prior | 6 month prior | 1 month prior surgery

Time from first symptoms to diagnosis: the LMU expierence



The median time elapsed between onset of symptoms and final diagnosis was 2.0 yrs. (range < 1 month to 15.7 yrs.).
In male patients it was 1.6 yrs. (range < 1 month to 15.2 yrs.), in female 2.0 yrs. (range < 1 month to 15.2 yrs.).
About 20% of patients were diagnosed after more than 5 years (CD 61%; AC 33%; EC 6%).

Gesamtzahl: 187 Patienten

Disriminatory value of signs and symptoms of Cushing syndrome the past, the presence and the future

Discriminant index	own series[2] 2000 - 2012	ERCU-SYN[2] ? - 2012	Ross and Linch[2] 1960-1982
n	73	481	
Osteopenia	na	5,6	-
Recurrent infections	3,9	-	-
Red striae	2,8		2,5
Amenorrhea	2,7	2,3	1,6
Abdominal fat distribution	2,6	-	-
Plethora	2,5	-	3,0
Muscle weakness	2,4	3,7	8,0
Hirsutism	2,1	2,2	2,8
Hypertension	1,6	1,9	-
Loss of libido	1,4	1,1	-
Oedema	1,0	-	2,9
Depression	0,9	0,6	-

Schneider et al. Clin Endo 2012





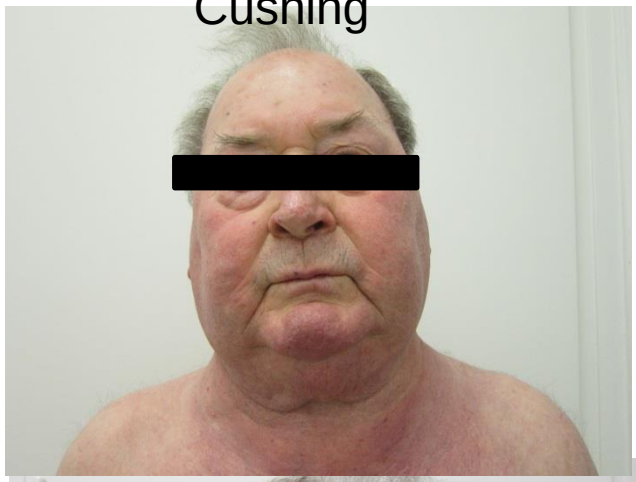




Cushing

Cushing

No Cushing









Overview: Cushing

- Introduction
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Why start a Cushing Registry in 2012?

	Pheo	Primary Aldo.	Cushing
Rare Disease?	+	+	+
Sufficient screening test?	+	-	-
Subtype testing accuracy?	+	-	-
Overall diagnostic accuracy?	++	--	--
Excellent surgical outcome?	+	+	(+)
Pathophysiology elucidated?	++	++	-
Medical treatment	(+)	++	(+)

Goals of a Cushing's Registry

Custodes

- To build a cohort of sufficient epidemiologic strength for studies of high evidence
- To investigate long-term morbidity and mortality
- To identify patients with high risk for adverse events
- To identify those factors that contribute to persistence of Cushing associated co-morbidities despite biochemical cure
- To define better diagnostic tests for Cushing syndrome
- To build a network for IIT in the treatment of CS

Case-control study, 1: 2 matching, significance α=0.05

	Sample size					
Odds ratio	**250**	**300**	**500**	**750**	**1000**	**1500**
1.1	0.065	0.068	0.079	0.095	0.109	0.14
1.3	0.164	0.188	0.282	0.394	0.497	0.667
1.5	0.323	0.376	0.565	0.739	0.851	0.957
1.7	0.498	0.572	0.789	0.923	0.974	0.998
1.9	0.652	0.731	0.914	0.983	0.997	1
2.1	0.771	0.841	0.969	0.997	1	1
2.3	0.854	0.910	0.989	0.999	1	1
2.5	0.909	0.950	0.997	1	1	1
2.7	0.944	0.973	0.999	1	1	1

Power Calculation

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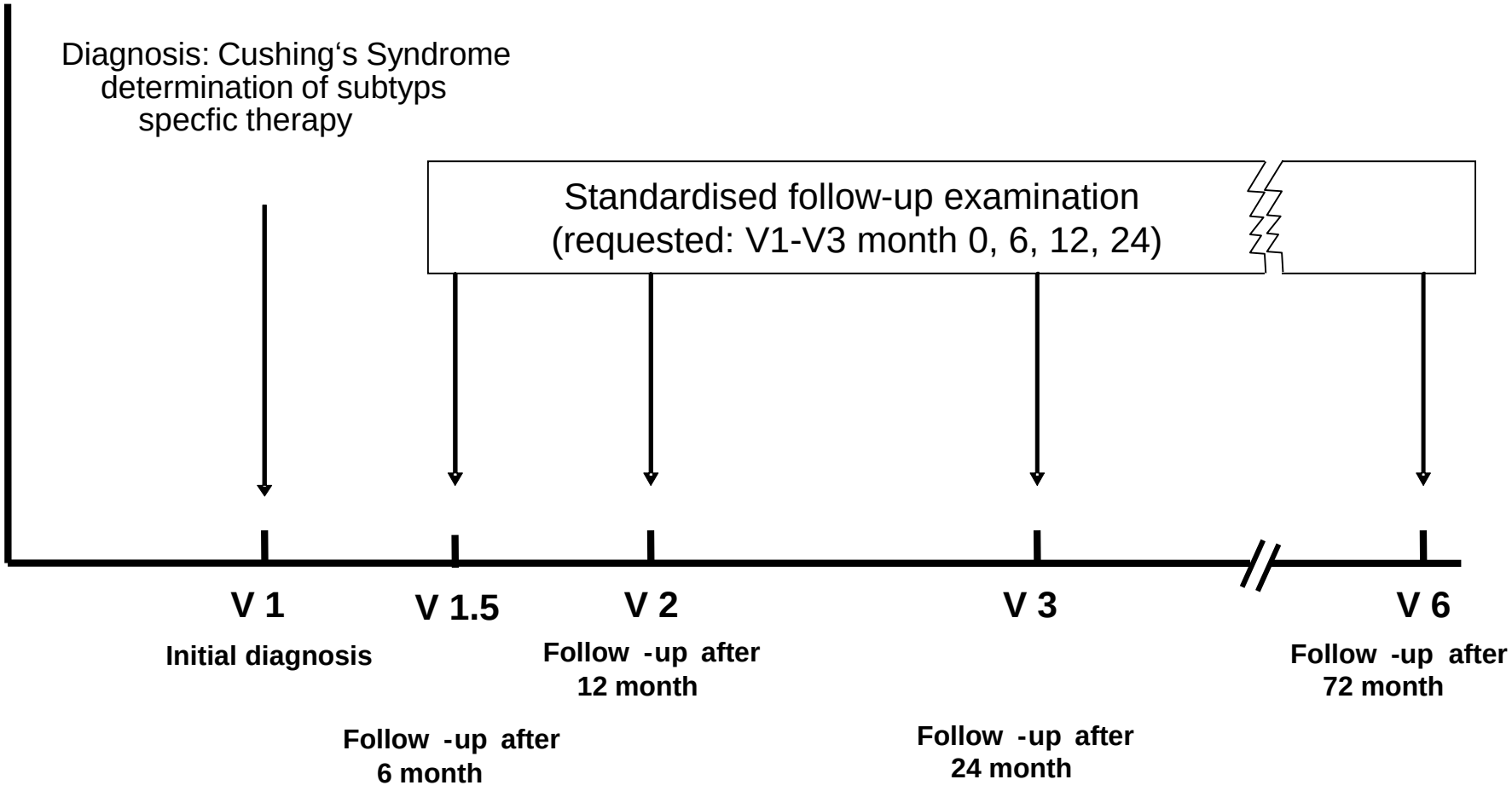
Custodes



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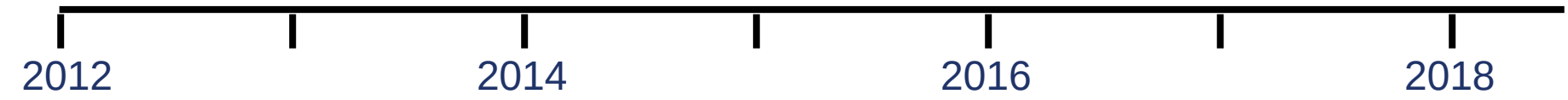
Retrospective data entry (Cohort 1:**>400**)

Clinical, biochemical, metabolic and cardiovascular characterization of retrospective patients invited to (annual) follow up (Cohort 2: **140**)

Prospective recruitment of newly diagnosed patients with CS (Cohort 3: **65**)

Intervention trials



Participating centers:

- Ziemssenstraße, MK IV, München
- MPI f. Psychiatrie, München
- Uni Düsseldorf
- Uni Dresden
- Uni Würzburg
- Uni Tübingen
- Uni Essen
- Uni Erlangen
- Berlin (Praxis Quinkler)
- Berlin (Endokrinologikum)

End points of the cohort study:

Hypothesis-driven data base:

- cardiovascular morbidity
- metabolic comorbidity
- psychiatric comorbidity
- musculoskeletal comorbidity

Standardized follow-up examination of CS patients:

- Medical history and clinical examination
- Quality of life questionnaires
- Measurements (*blood pressure, muscle power, gripp strength, ECG, bioelectrical impedance, thyroid ultrasound, intima-media thickness, BMD)*
- laboratory findings, biomaterial deposition (plasma, tumor, saliva, urine, hair)

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Custodes

- **Diagnosis of CS**

  Schneider et al. Clin Endo 2013
  Schneider et al. ECED 2013
  Johar et al. JCEM 2014

- **Surgical Outcome**

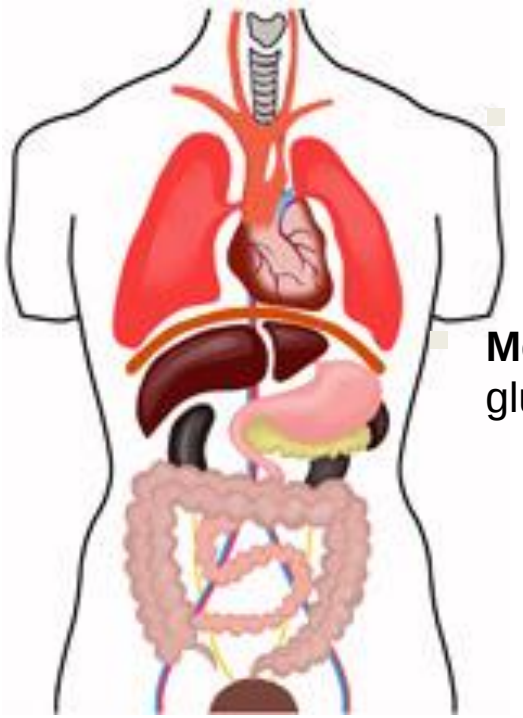
  Dimopoulou et al. EJE 2013
  Ritzel et al. JCEM 2013
  Osswald et al. EJE 2014
  Di Dalmazi et al. JCEM 2014
  Berr et al., JCEM 2015

- **Subtype differentiation**

  Ritzel et al. EJE 2015
  Di Dalmazi et al. 2014

- **Genetics of CS**

  Beuschlein et al. NEJM 2014
  Di Dalmazi et al. JCEM 2014
  Reincke et al. Nat Gen 2015
  Perez-Rivas et al., JCEM 2015



- **CNS:** Anxiety, depression, impaired quality of life
- **Cardiovascular co-morbidities:** MI, heart failure, stroke, AF
- **Metabolic co-morbidities:** glucose intolerance, lipid abnormalities,
- **Musculosceletal co-morbidities** Osteoporosis, sarcopenia

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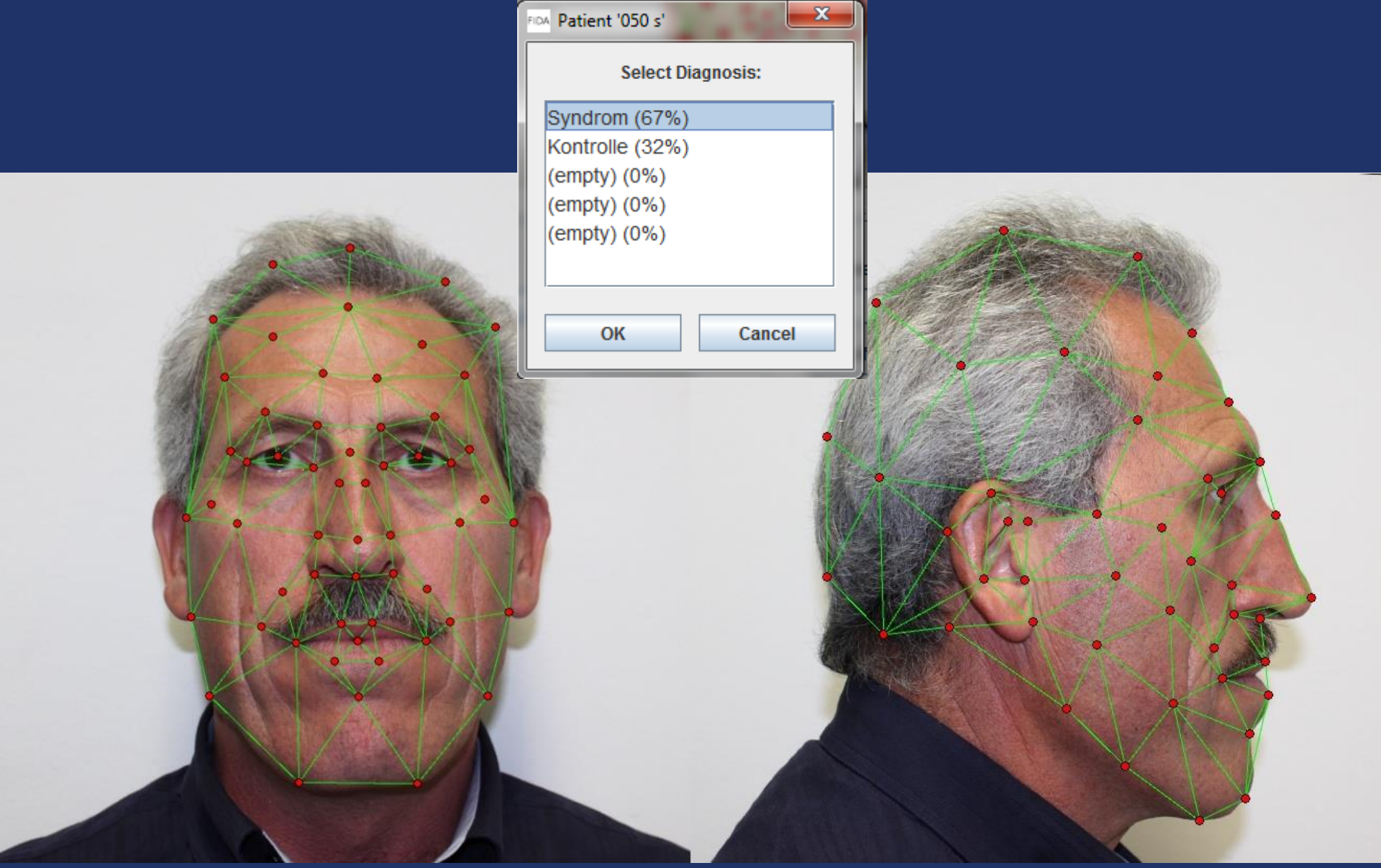
Screening with for endocrine diseases with face classification: the experience with acromegaly

- Initial study
- Subjects:
- N=57 acromegalics, N=60 age- and sex-matched controls
- frontal and side photographs with digital camera
- Face classification based on
  - Texture (Gabor wavelets)
  - Geometry of landmarks
- Calculation of correct classification rate using the leave-on-out method

Schneider et al. JCEM 2011



Schneider et al. JCEM 2011

Results

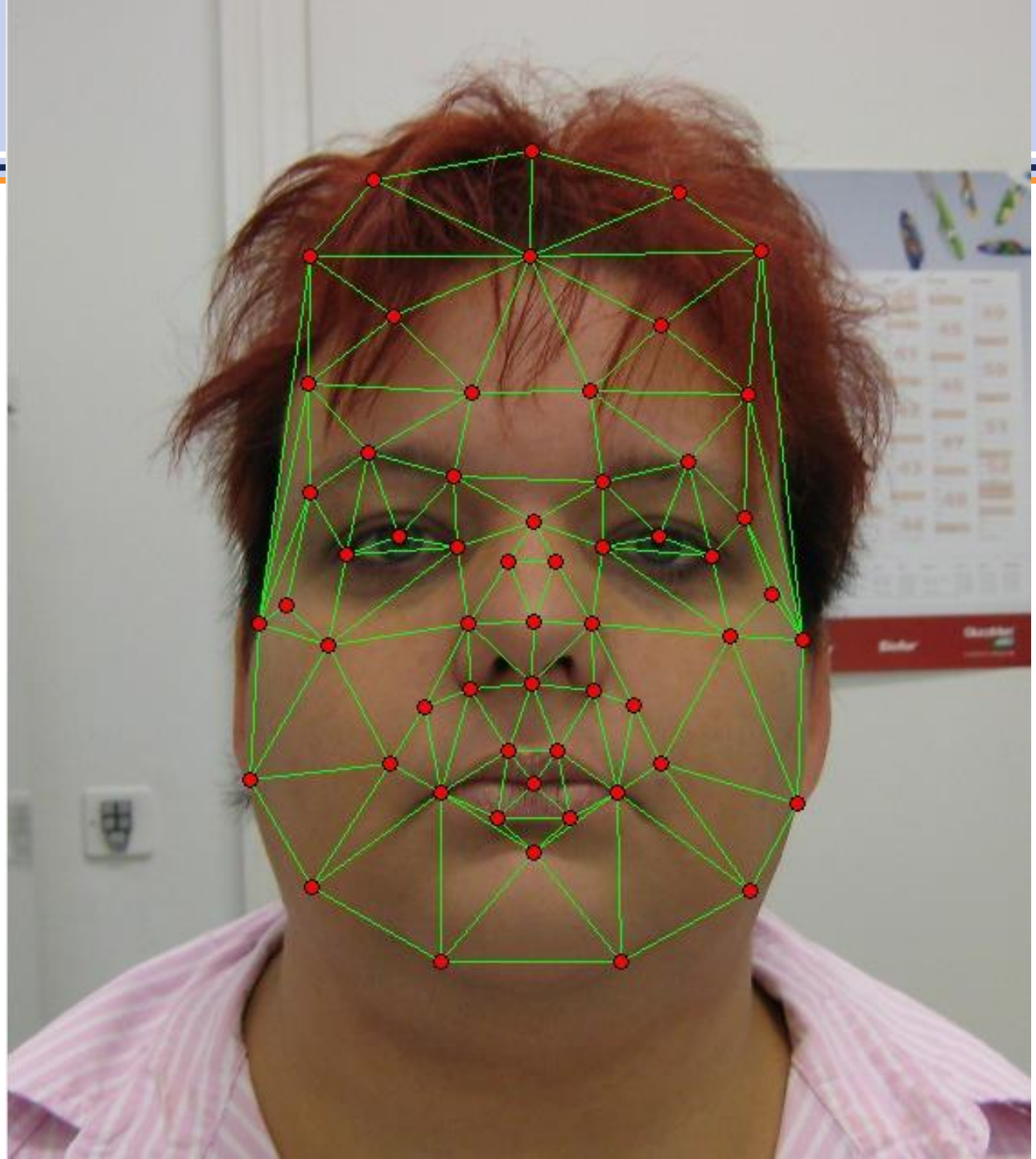
correct classification rates (%)	*Software*[1]	*Experts*[2]	*Internists*[3]
Overall	**81.9**	**72.1**	**64.9**
Acromegaly	**71.9**	**63.2**	**42.1**
Controls	**91.5**	**80.8**	**87.0**

Schneider et al. JCEM 2011

Proof-of-principle study in women with Cushing‘s syndrome

- Subjects:
- N=20 women with Cushing‘s syndrome
- N=40 age- and sex-matched controls

- frontal and side photographs with digital camera
- Face classification based on
  - Texture (Gabor wavelets)
  - Geometry of landmarks
- Calculation of correct classification rate using the leave-one-out method



Results

Classification Accuracy (%)	*n*	FIDA[a]
Overall	**60**	**91.7**
Patients / *Sensitivity*	**20**	85.0
Endogenous CS	**12**	**75.0**
- *Central CS*	**8**	**62.5**
- *Adrenal CS*	**4**	**100**
Iatrogenic CS	**8**	**100**
Controls / *Specifity*	**40**	95.0

Schneider et al., JCEM (2011)
Schneider et al., ECED(2013)

Ongoing prospective study on Cushing‘s syndrome

Recruitment targets:

- 50 patients with Cushing‘s syndrome
- 100 age-, sex- and BMI-matched controls referred for exclusion of Cushing‘s syndrome
- Recording of clinical parameters, face classification and biochemical parameters

Aim:

- Determining classification rates with face classification and establishment of a Clinical Prediction Score for the presence of Cushing‘s syndrome

Preliminary results

- Included subjects
- 56 Patients (40 women, 16 men)
- 60 controls (30 women, 30men)

Preliminary results

	Controls m N=30	Patients m N=16	Controls f N=30	Patients f N=40
BMI	BMI	BMI	BMI	BMI
Mean	32.9	27.7	34.2	29.9
p	0.0045		0.009	
Age (y)	Age (y)	Age (y)	Age (y)	Age (y)
Mean	43.5	53.5	43.4	55.5
p	0.060		0.0008	

1:1-matching by BMI: Preliminary results

BMI-matched		Patients	Controls
Correct classification rates (%)	Women N=54	70.4	74.0
	Men N=32	68.8	75.0

DISSAPPOINTING!

All patients		Patients	Controls
Correct classification rates (%)	Women N=70	72.5	53.3
	Men N=46	43.8	90.0

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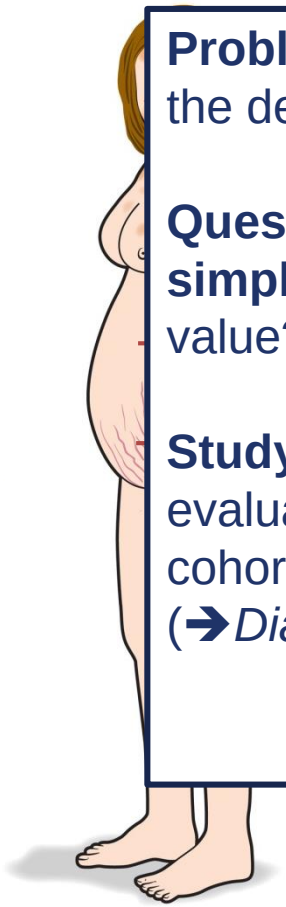
Cushing's syndrome – development of a *Diagnostic Score*



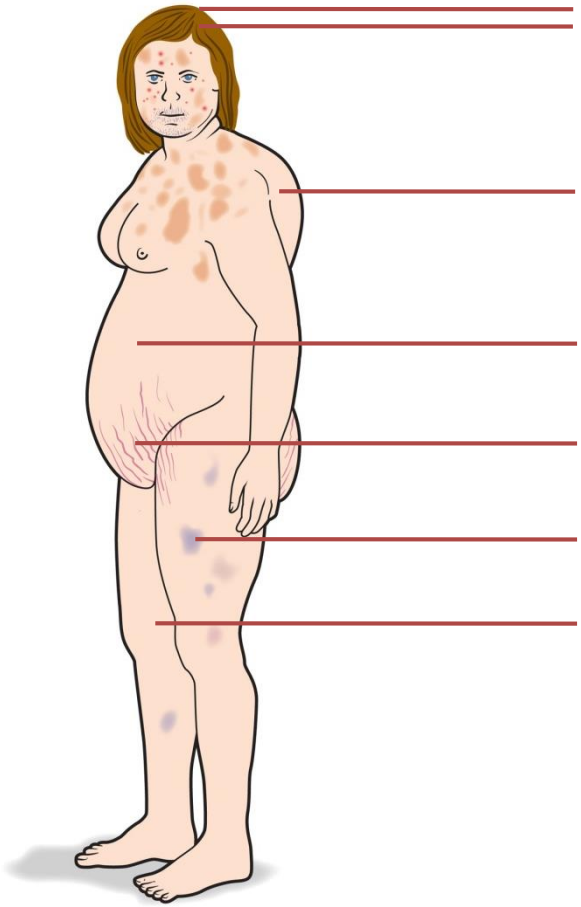
Problem: Single signs and symptoms do not have the desired discriminatory power

Question: is there the potential to develope a **simple**, diagnostic score with **good** predictive value?

Study: prospective, multicentric, standardized evaluation of all relevant parameters in a large cohort with adequate statistical power (➔*Diagnostikstudie*)

Impaired glucose toelrance, metabolic syndrome,
Hyperlipidemia
Immunosuppression, osteoporosis

Cushing syndrome - signs and symptoms



Cognitive deficits, depression

Moon face

Buffalo hump

Central obesity

Striae rubrae (>1 cm width, purple)

Easy brusising, impaired wound healing

Proximal myopathy

Arteriell hypertension
Impaired glucose tolerance, metabolic syndrome,
Hyperlipidemia
Immunosuppression, osteoporosis

The German Cushing Registry *Diagnostic Study*: -study outline-

- Investigation of the prevalence of signs and symptoms of Cushing‘s syndrome *versus* rule-out Cushing cases.

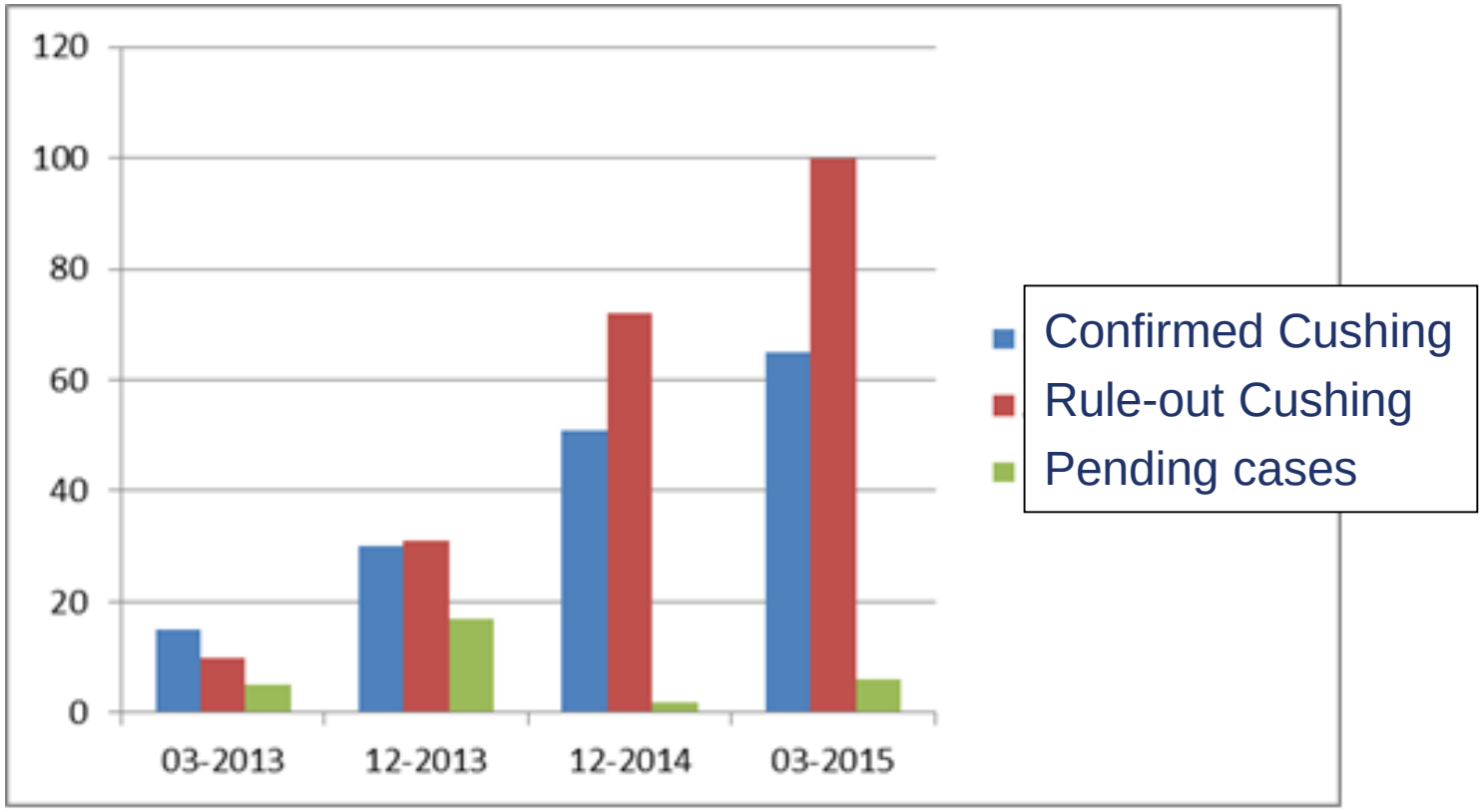
150 patients reffered for evaluation of Cushing‘s syndrome

Standardized clinical and biochemical evaluation, histology or follow-up (3-12 months)

Confirmed Cushing‘s syndrome
N=50

Definitive exclusion of Cushing‘s syndrome
N=100

Total prospective cases in 4 German centers



Including subclinical cases, excluding cosecretory cases and unclassified cases

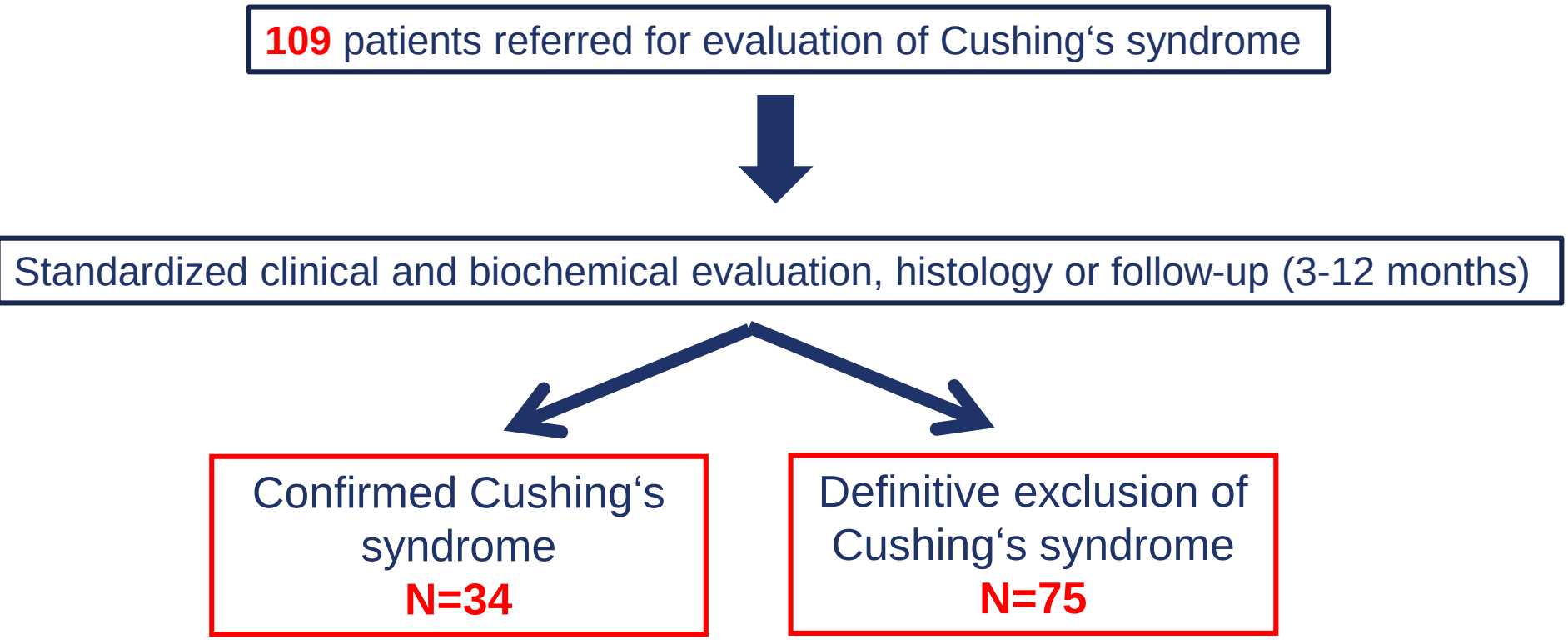
Cushing patients by centers and entity

	Cushing‘s syndrome				Rule-out Cushing‘s syndrome
Centers	**Total (2012-2015)**	**Cushing‘s Disease**	**Adrenal Cushing‘s syndrome**	**Ectopic Cushing‘s**	
München 1 (LMU)	44	31	8	5	87
München 2 (MPI)	0				2
Würzburg	2	1	1		0
Dresden	4	4			11
Düsseldorf	0				0
Tübingen	15	15			0
Total	**65**	**51**	**9**	**5**	**100**

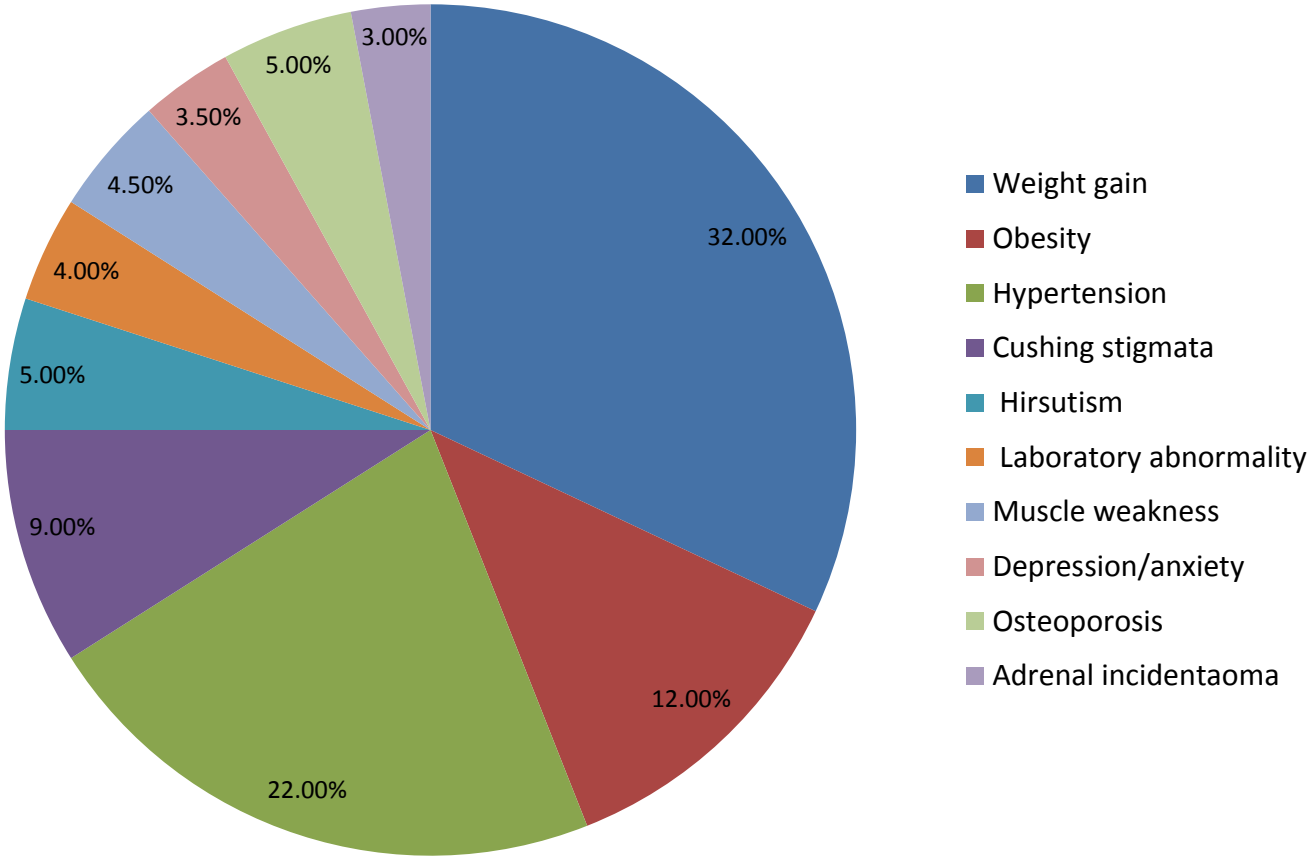
Anmerkung: inkl. Subklinische Patienten, exklusive unklare Fälle, Cosektretion etc.

The German Cushing Registry Diagnostic Study: Interim Analysis

- Investigation of the prevalence of signs and symptoms of Cushing‘s syndrome versus rule-out Cushing cases.



Leading Symptoms



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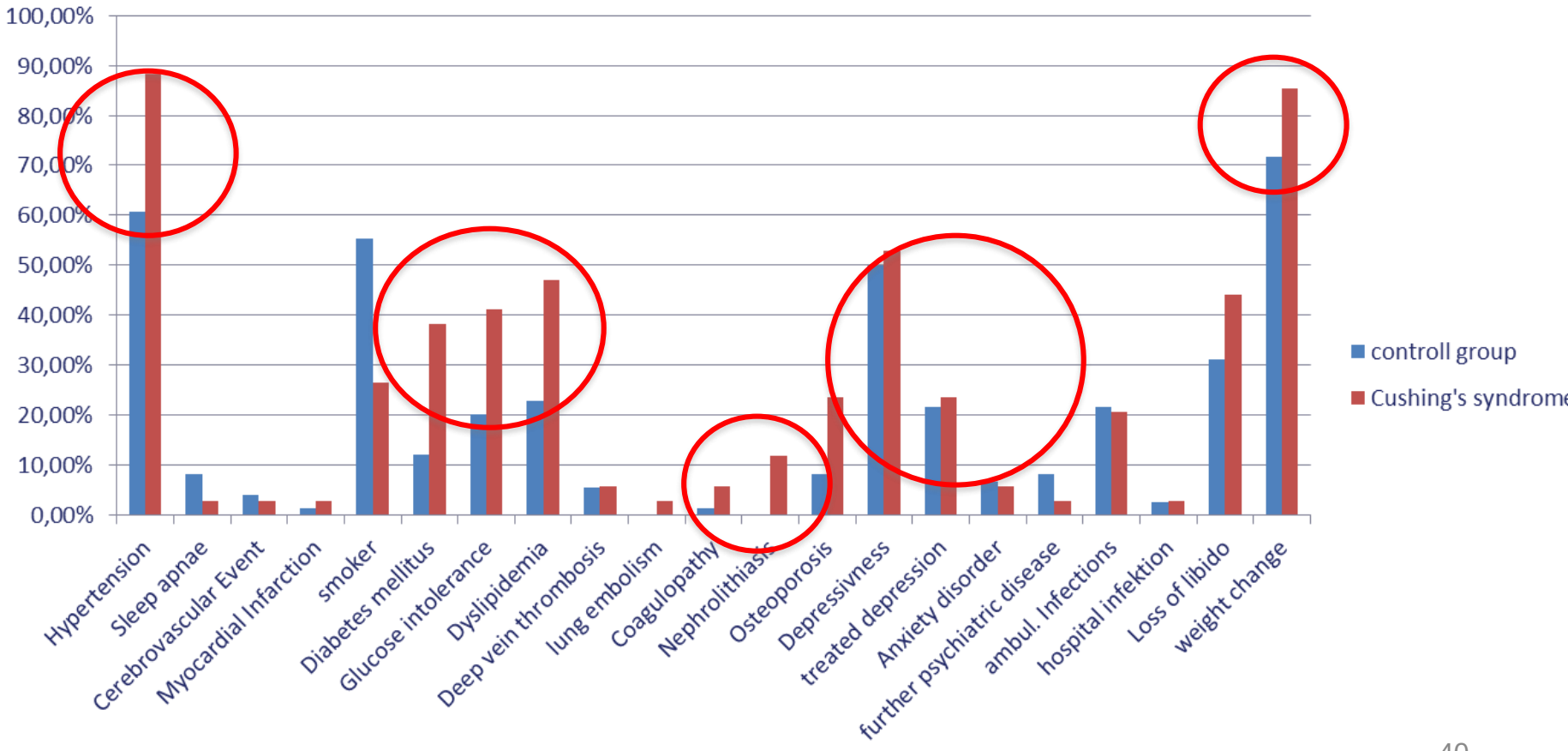
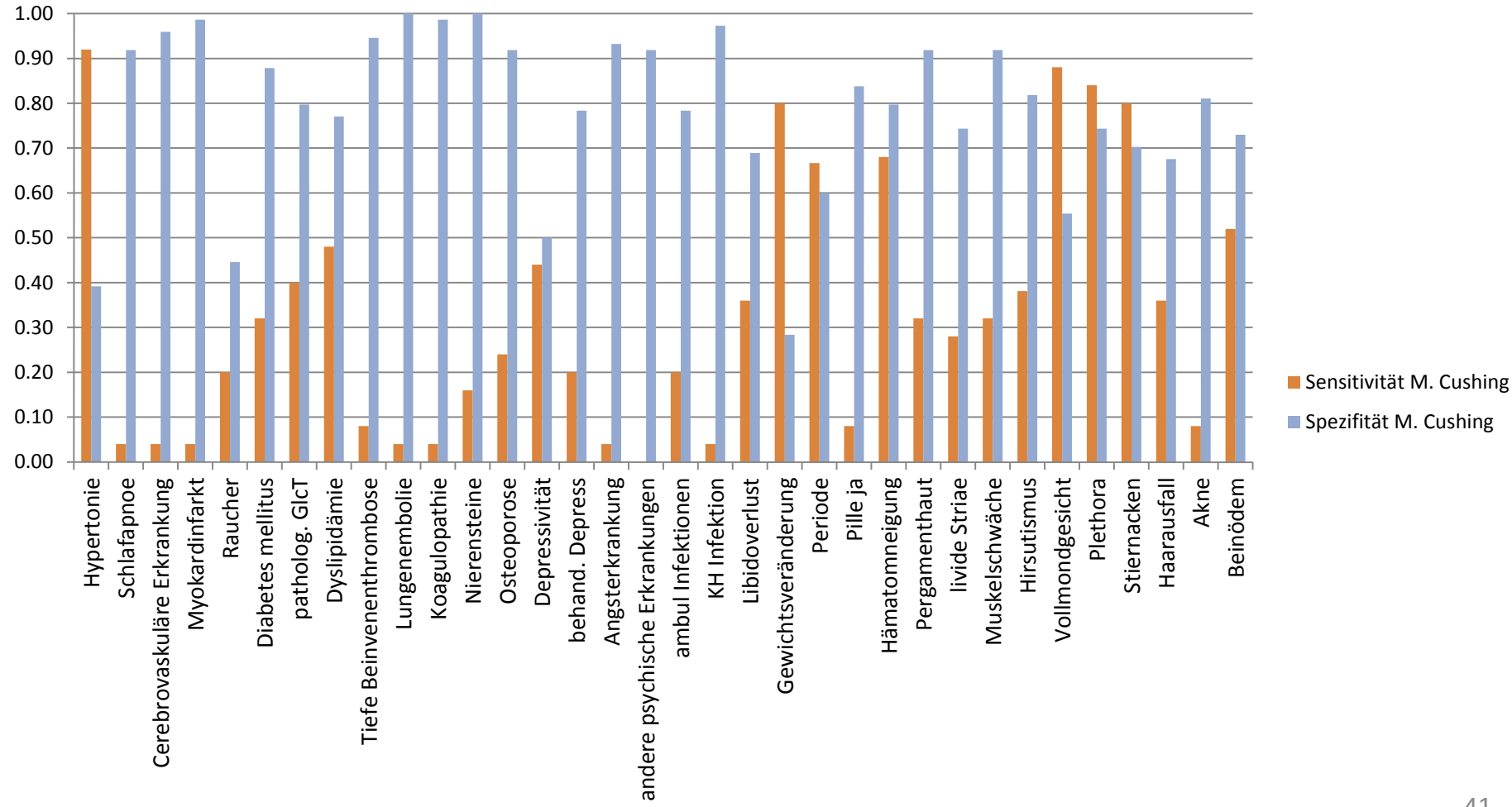
Parameter	Controll group	Cushing ‘s syndrome (total)	P value	Cushing ‘ s disease	Adrenal Cushing ‘s syndrome
No.	75	34		28	6
sex (% female)	68 %	64 %		64 %	67 %
age (years)	43,3	45,6	0.32	44,1	46,8
BMI (kg/m2)	32,6	30,4	0.22	30,1	29,8
Blood pressure sys	141	153	0.002*	151	152
Blood pressure dia	89	98	0.007*	96	99
Diabetes rate	12 %	38 %		32 %	50 %

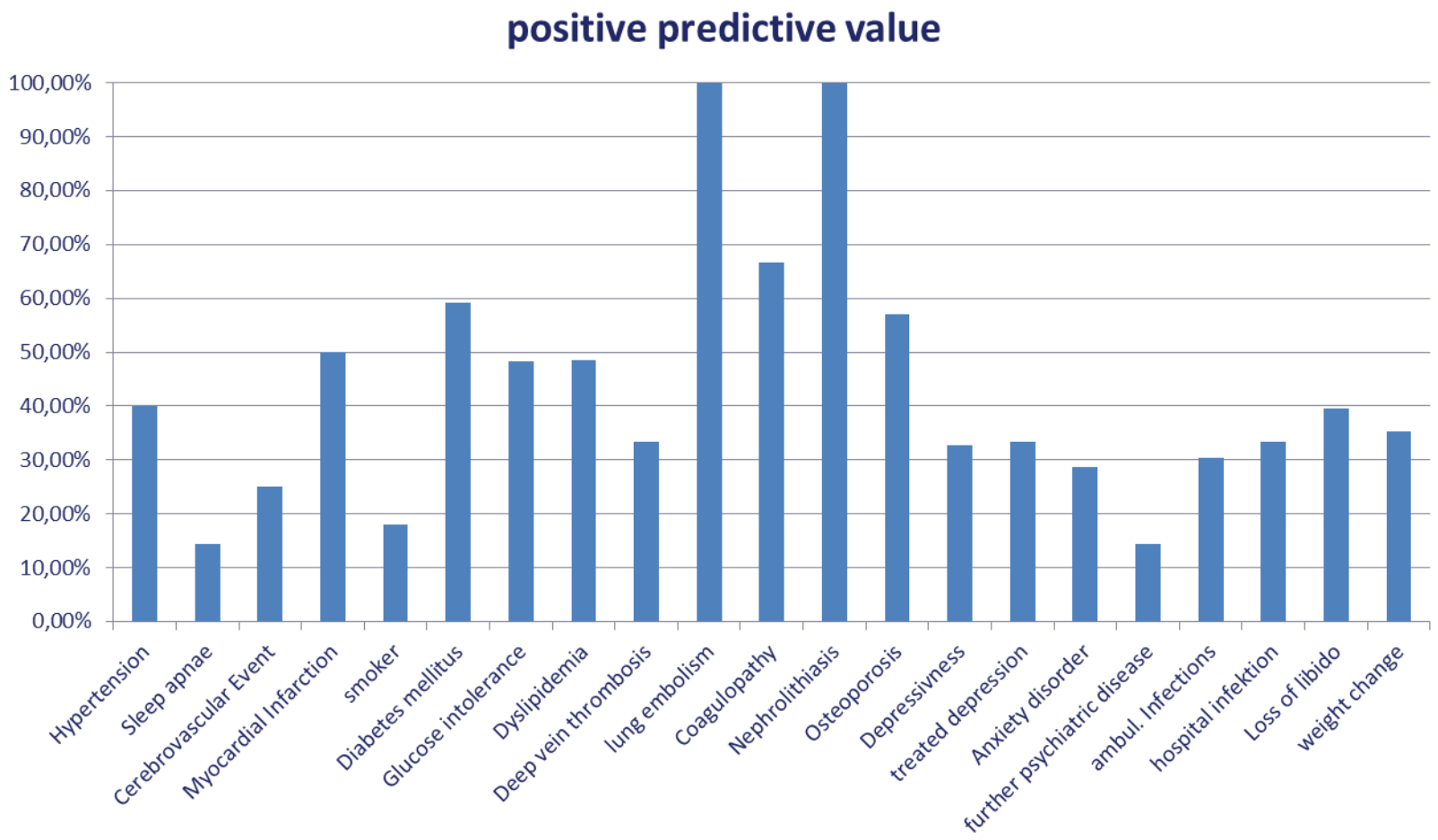
Prevalence, patient‘s history



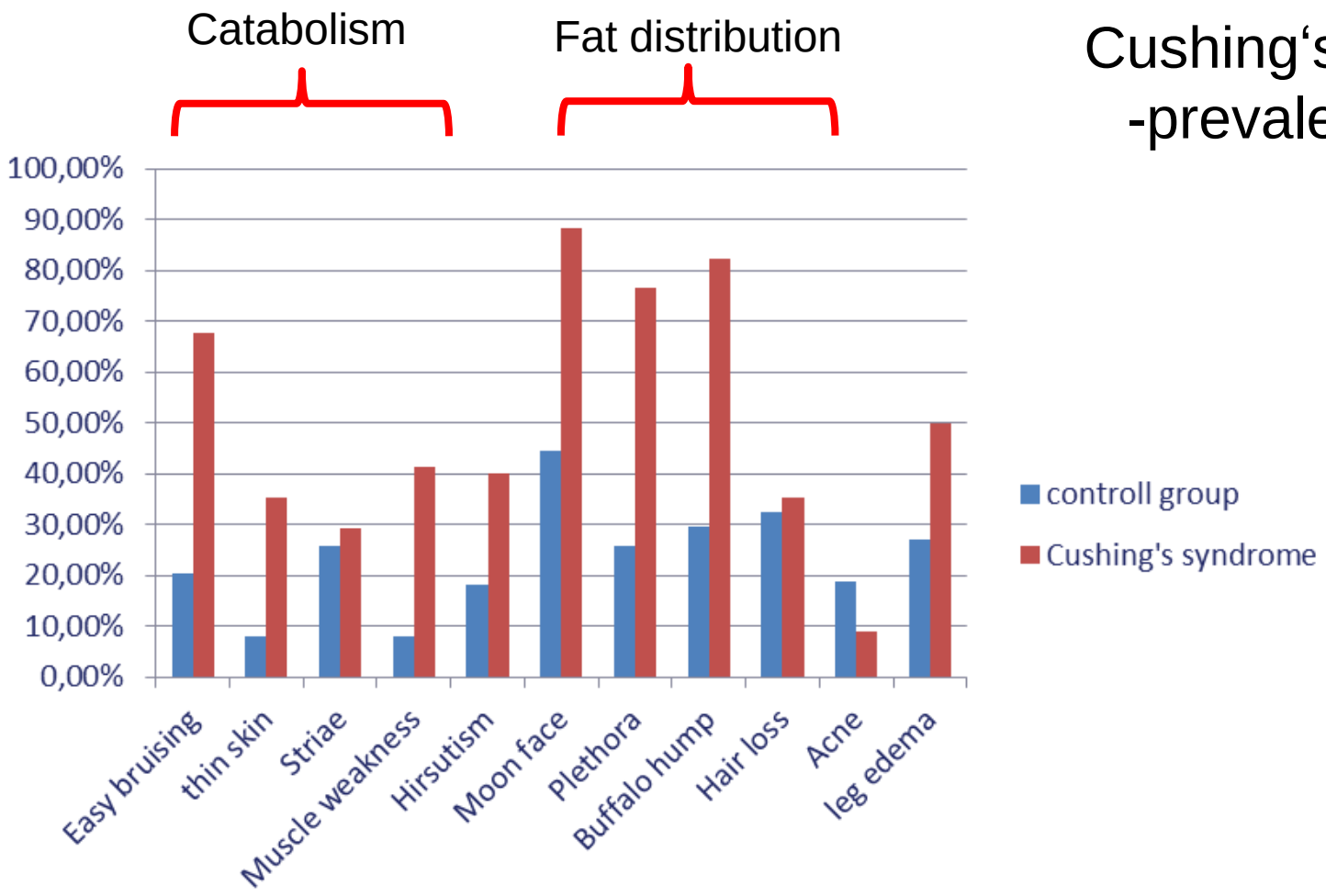
Sensitivity and specificity, patient‘s history



Positive predictive value, patient‘s history



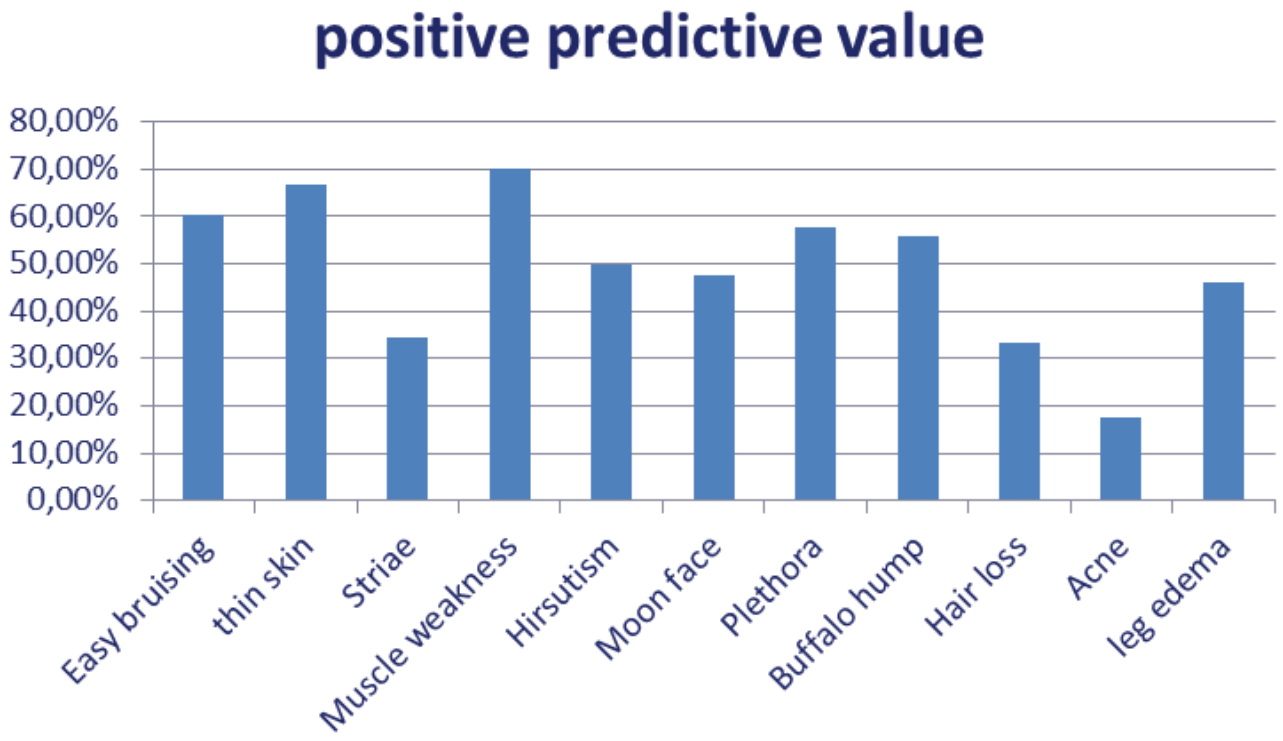
Cushing‘s signs -prevalence-



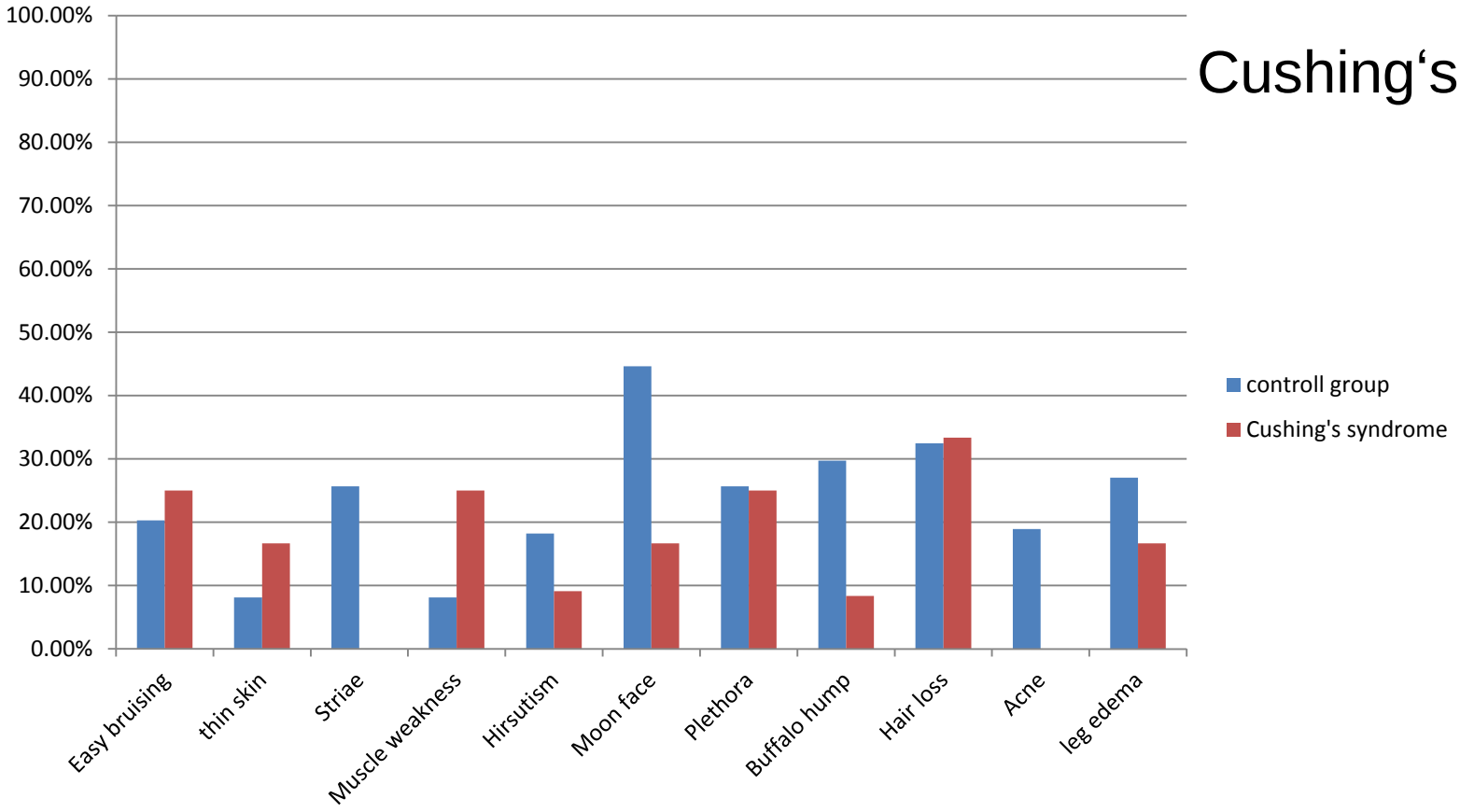
Catabolism

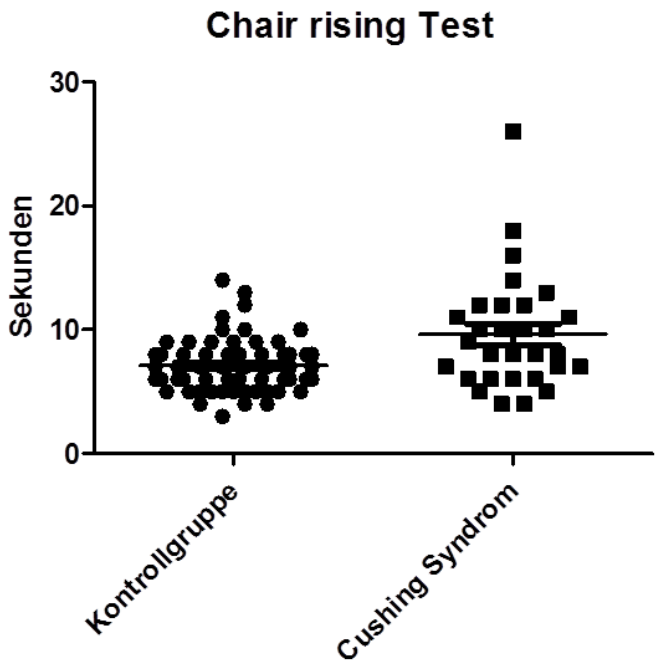
Fat distribution

Cushing‘s signs

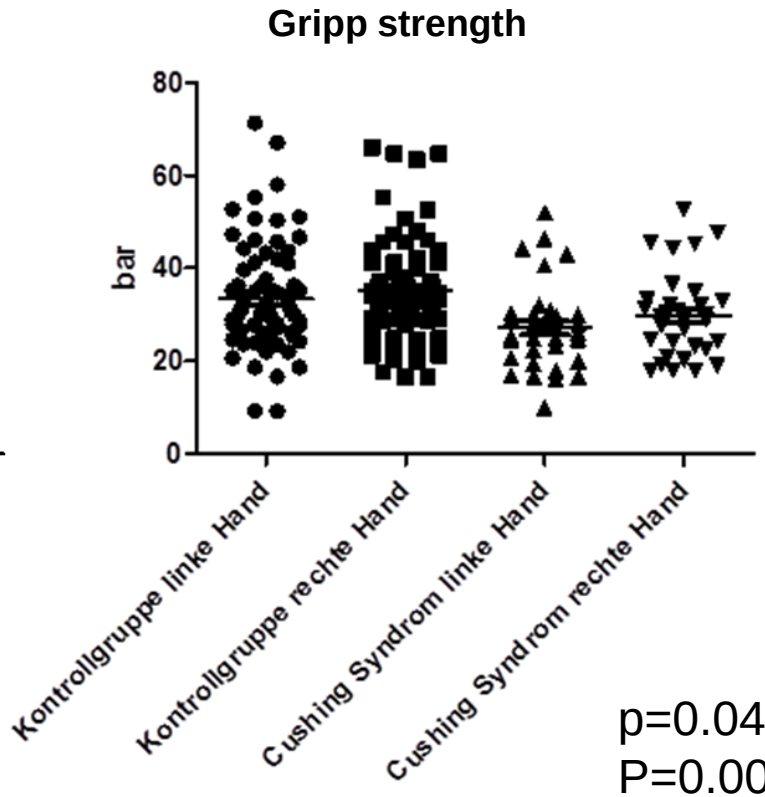


Subclinical Cushing ‘s syndrome (n=17)





p=0.0052



p=0.044 (right)
P=0.009 (left)

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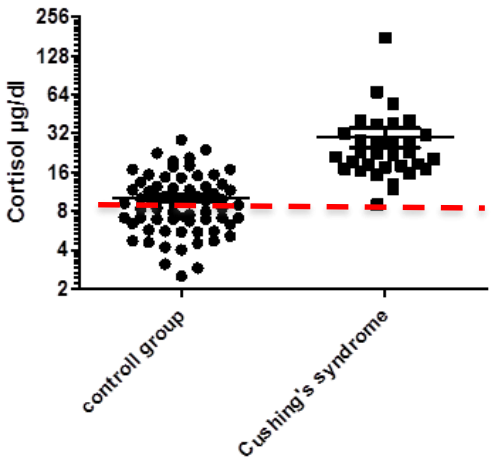
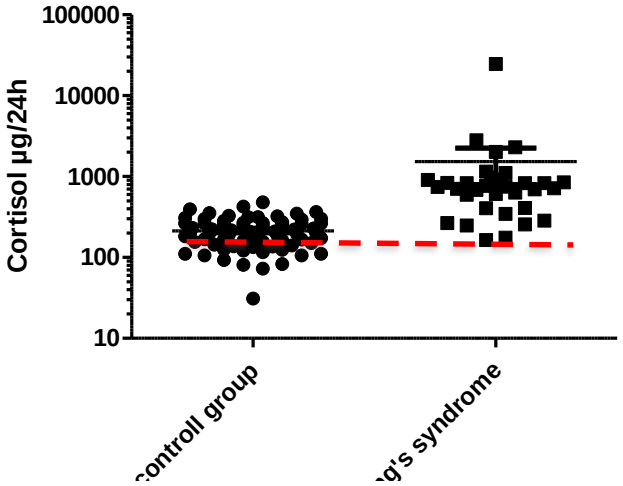
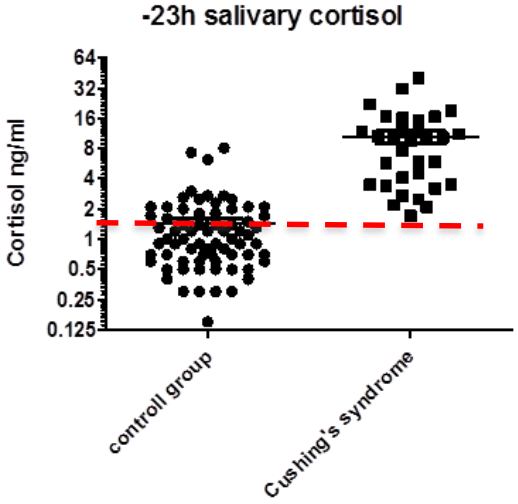
-morning cortisol



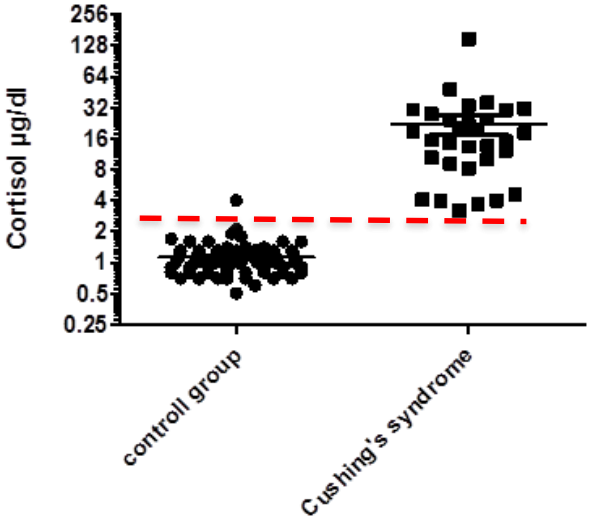
-24h-urinary cortisol



-23h salivary cortisol



-1mg DST



German Cushing‘s Registry

- Is in intresting tool to study prospectively clinical aspects of a rare disease

Discriminatory value of S&S in Cushing‘s

- Increasingly difficult in times of the ‚*obesity tsunami*‘

Automatic face recognition for Cushing‘s syndrome

- Interim results disappointing

Diagnostic scoring system for Cushing‘s syndrome

- Might be feasable!

Deutsches Cushing Register

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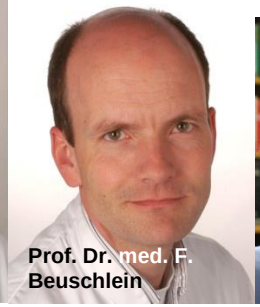
Custodes

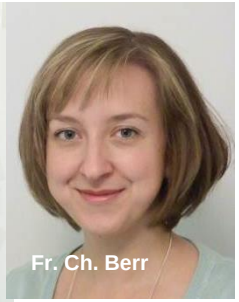
Studienleiter



Studienleiter

Tumorgewebe

Ärztin

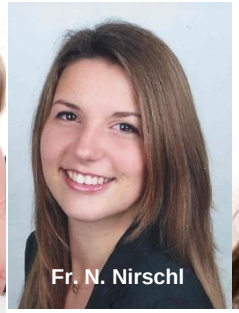


Ärztin

Leiter Endokrinologisches Labor

Psychosomatik

Koordination



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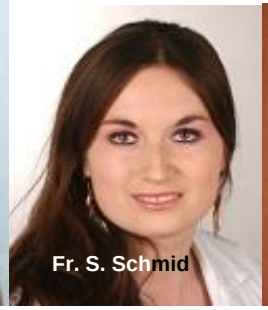

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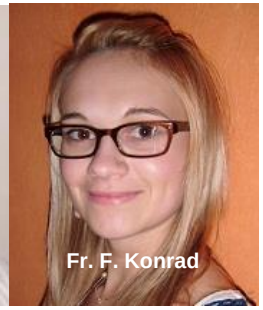

Koordination

Hr. Dr. med. M. Treitl

Radiologe

Chirurgie

Doktorandin

MPI für Psych

MPI für Psych

Substudien

Phase III Studien

Phase III Studien

MPI für Psychiatrie

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Custodes

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