Società Italiana dell'Ipertensione Arteriosa
Lega Italiana contro l'Ipertensione Arteriosa

EVENTO FORMATIVO INTERREGIONALE SIIA
PIEMONTE | LIGURIA | VALLE D'AOSTA
Torino, 29 novembre 2025

UNIVERSITÀ DI TORINO

S. Luigi Gonzaga

LA SINDROME DI CUSHING

Massimo Terzolo

Medicina Interna, AOU San Luigi Gonzaga
Dipartimento di Scienze Cliniche e Biologiche
Università di Torino

2023 - 2027
DEPARTMENT OF EXCELLENCE
Ministero dell'Università e della Ricerca

ens@t
european network for the study of adrenal tumors
Center of Excellence

- Adrenocortical carcinoma
- Adrenal incidentaloma
- Adrenal research center

DECLARATION OF INTERESTS

Massimo Terzolo

Consulting: Corcept Therapeutics,

Esteve Rare Diseases, Recordati Rare Diseases,

Speaking fees: Esteve Rare Diseases

Cushing syndrome

Definition

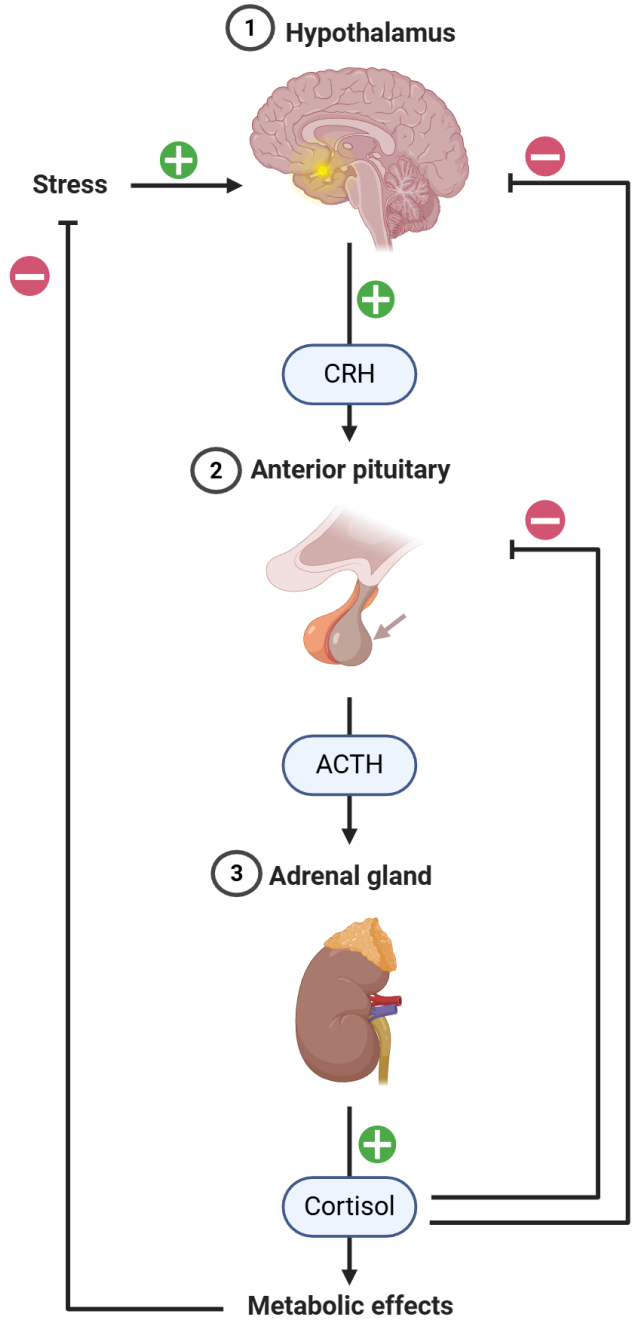
constellation of signs and symptoms caused by excessive exposure to exogenous or endogenous glucocorticoid hormones

Epidemiology

- rare disorder, incidence of 1.8 to 3.2 million cases per year
- median age at diagnosis of 40 years
- predominance among women ♀

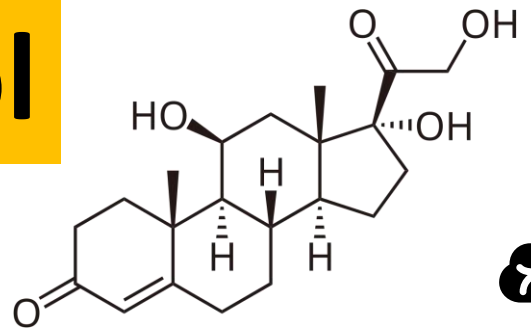
Mortality

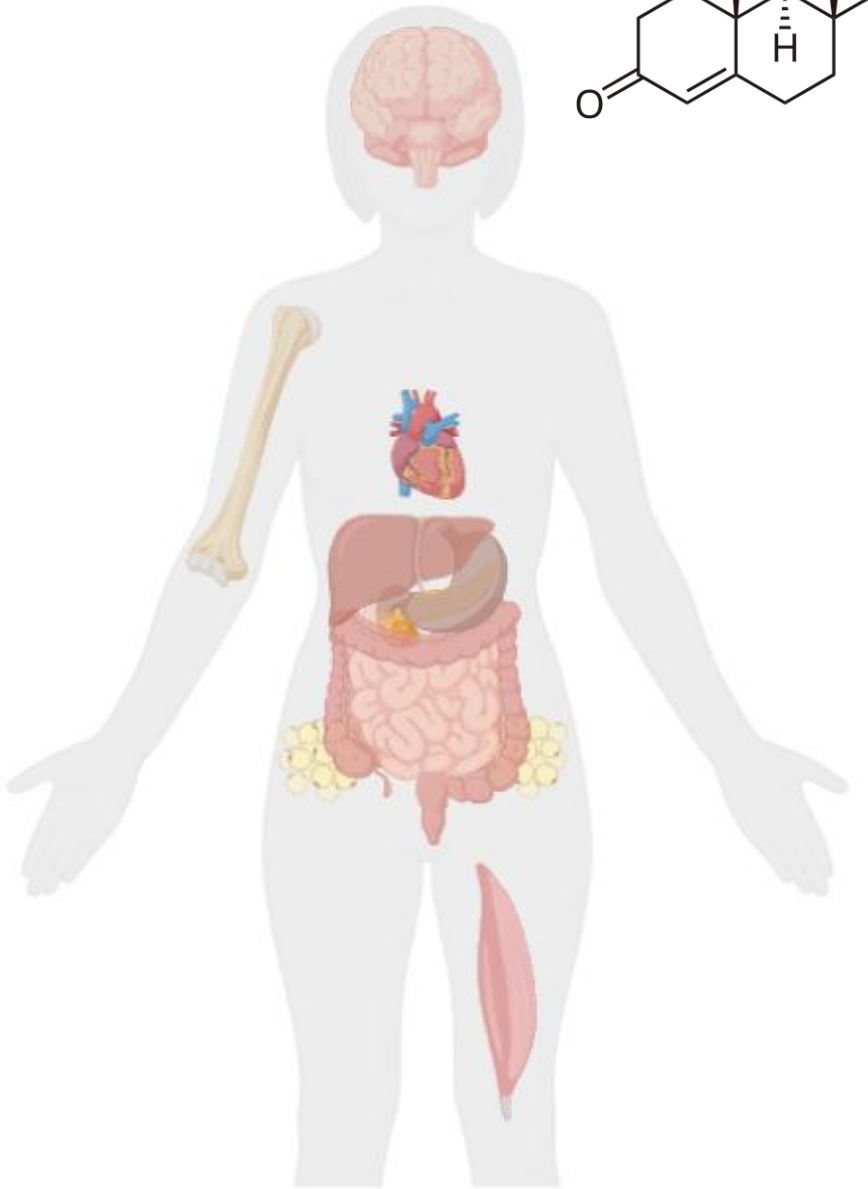
2.1-fold to 17.9-fold increase in mortality compared with the general population



Nieman et al., Nat Rev Dis Primers, 2025

Cortisol





GC RECEPTORS ARE UBIQUITOUS

CNS actions:
mood, behavior, sleep regulation

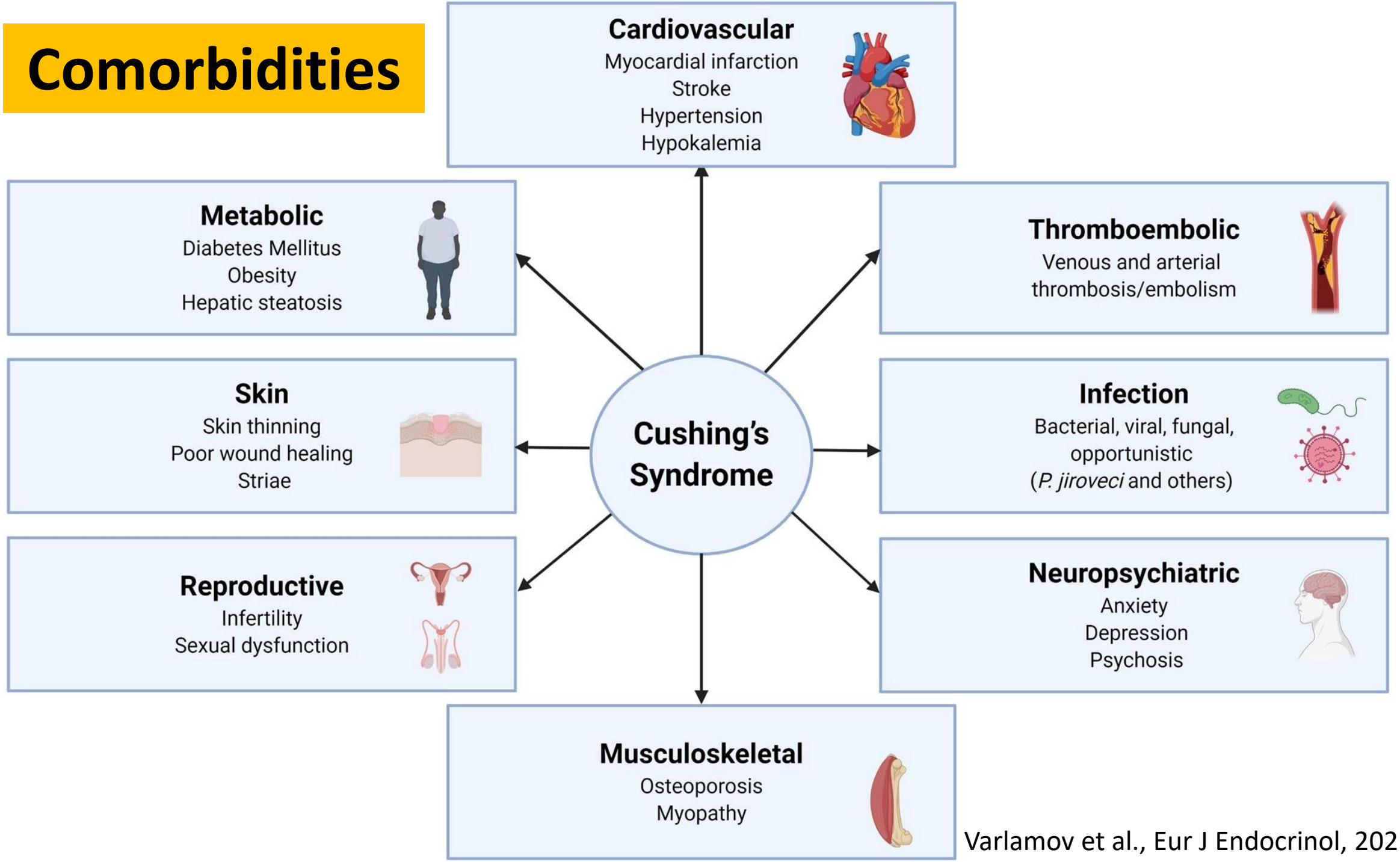
Metabolism:
carbohydrate, protein, and lipid metabolism; body fat distribution

Bone remodelling

Cardiovascular function, blood pressure regulation, stress response

Sodium–potassium balance and immune response

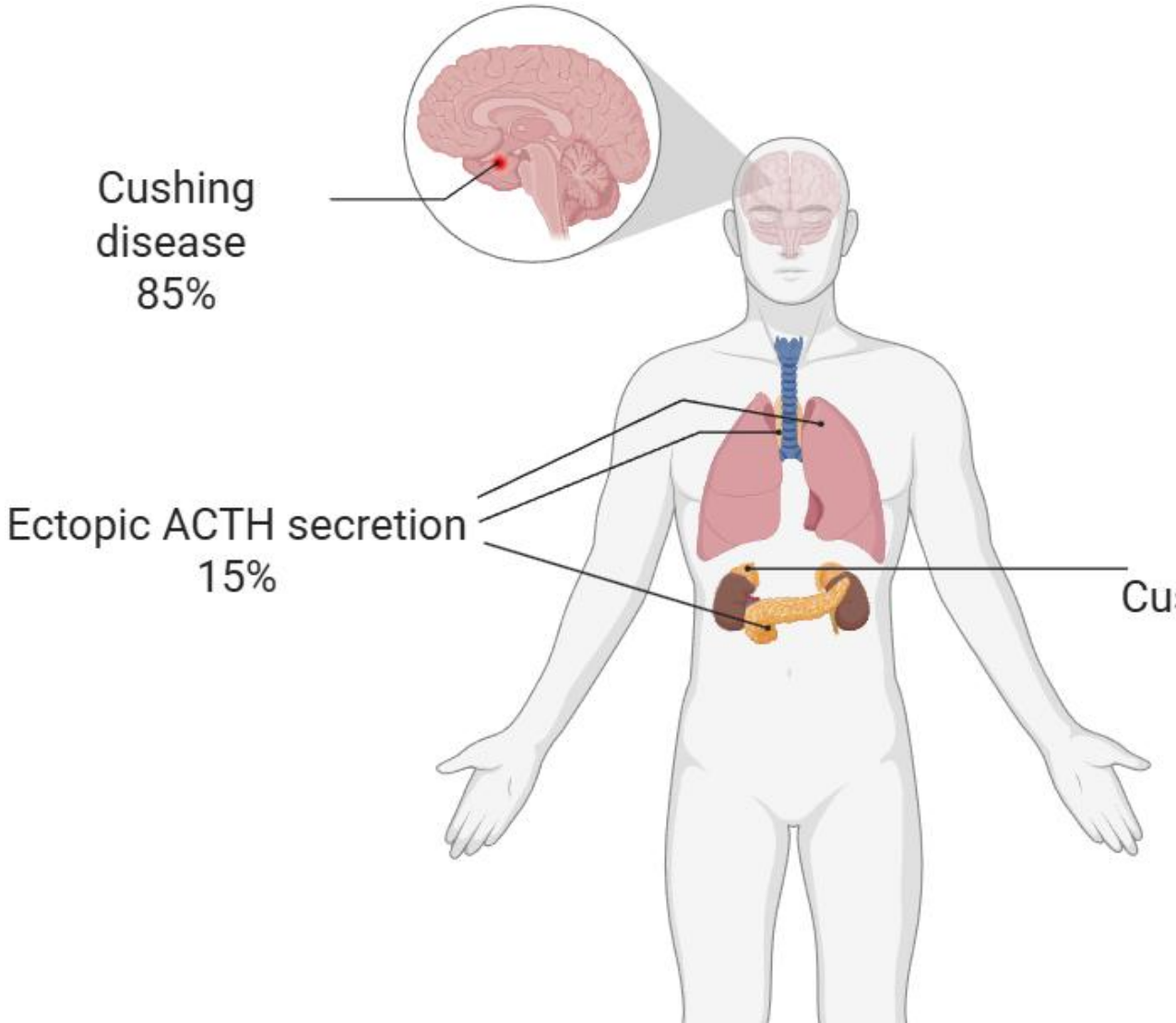
Comorbidities



Varlamov et al., Eur J Endocrinol, 2021

Causes of Cushing syndrome

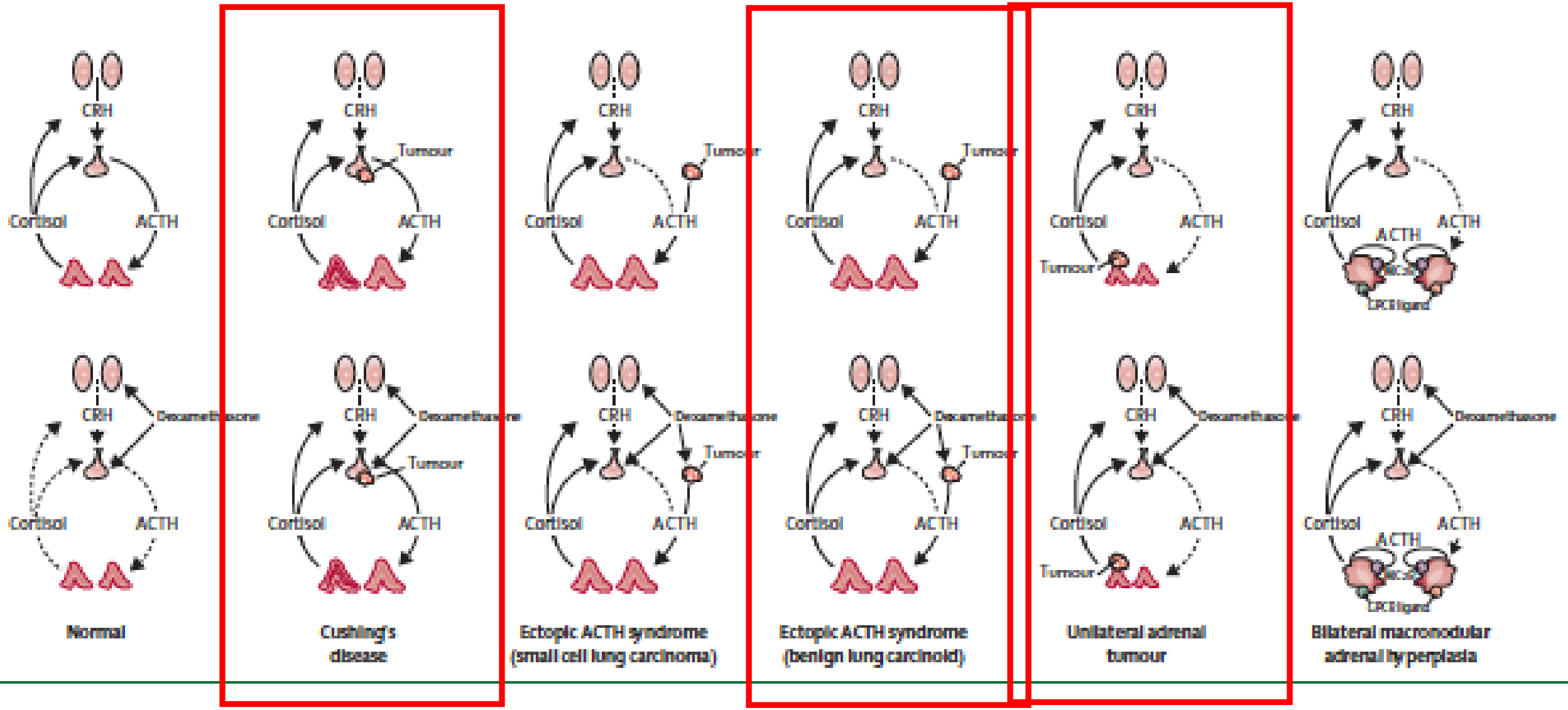
ACTH DEPENDENT 65-85%



ACTH INDEPENDENT 15-35%

Nieman et al., Nat Rev Dis Primers, 2025

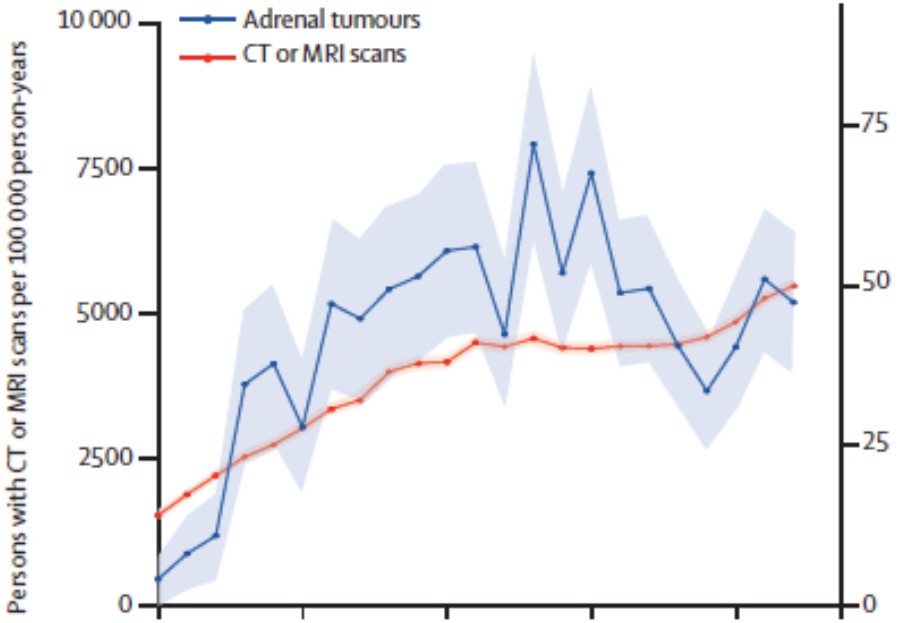
Cushing Syndrome



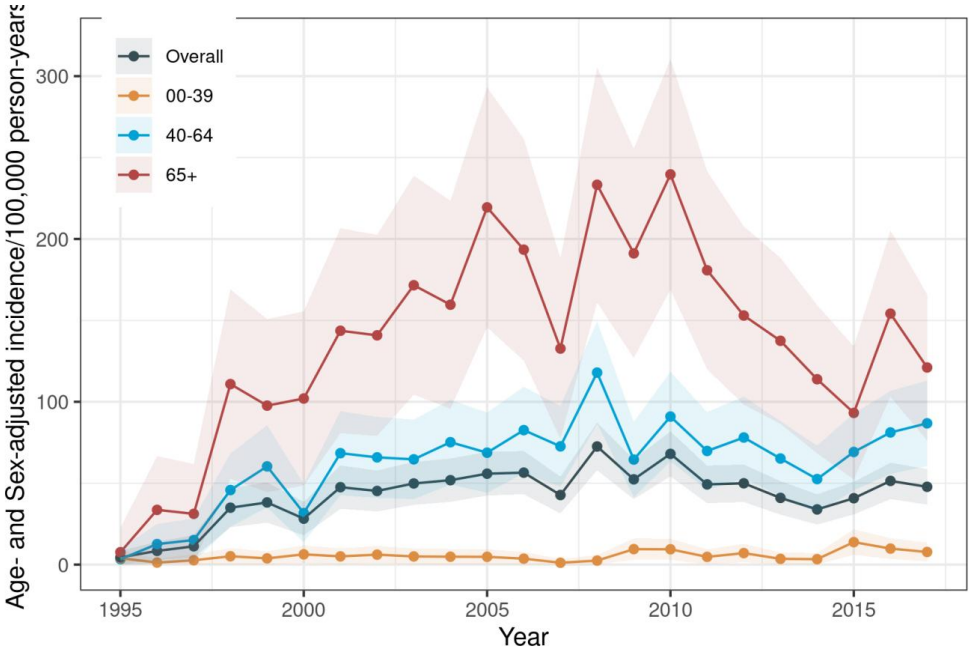
Epidemiology of adrenal tumours in Olmsted County, Minnesota, USA: a population-based cohort study

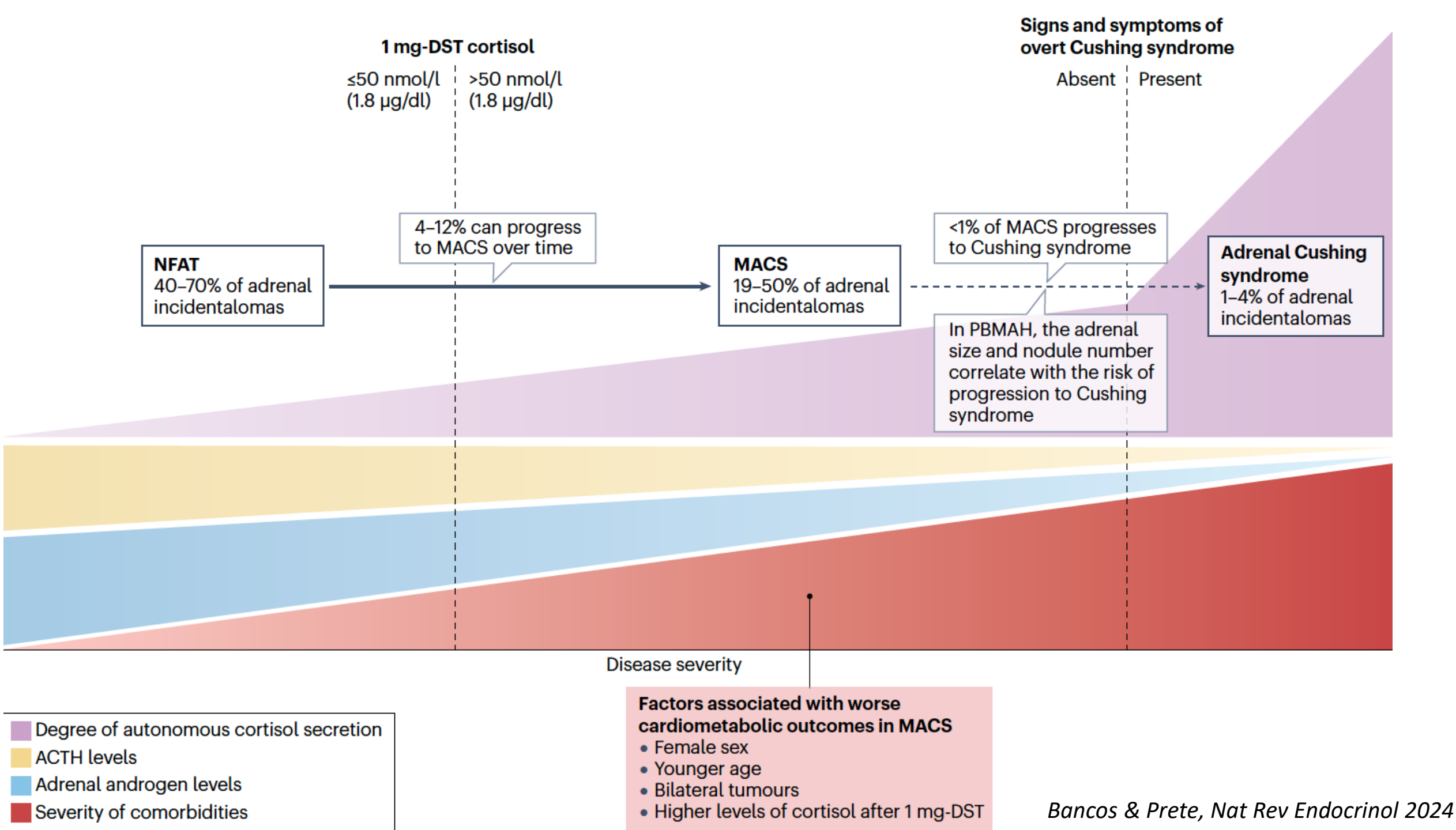
Andreas Ebbehoj, Dingfeng Li, Ravinder J Kaur, Catherine Zhang, Sumitabh Singh, Taoran Li, Elizabeth Atkinson, Sara Achenbach, Sundeep Khosla, Wiebke Arlt, William F Young, Walter A Rocca, Irina Bancos

Lancet Diabetes Endocrinology, 2020



- **Incidence of adrenal tumors increased by 10 times..**
- **in parallel with the increase of cross-sectional imaging studies**
- **particularly in subjects > 40 yrs**
- **tumors were mostly small, benign, adenomas**
- **without overt hormone excess**

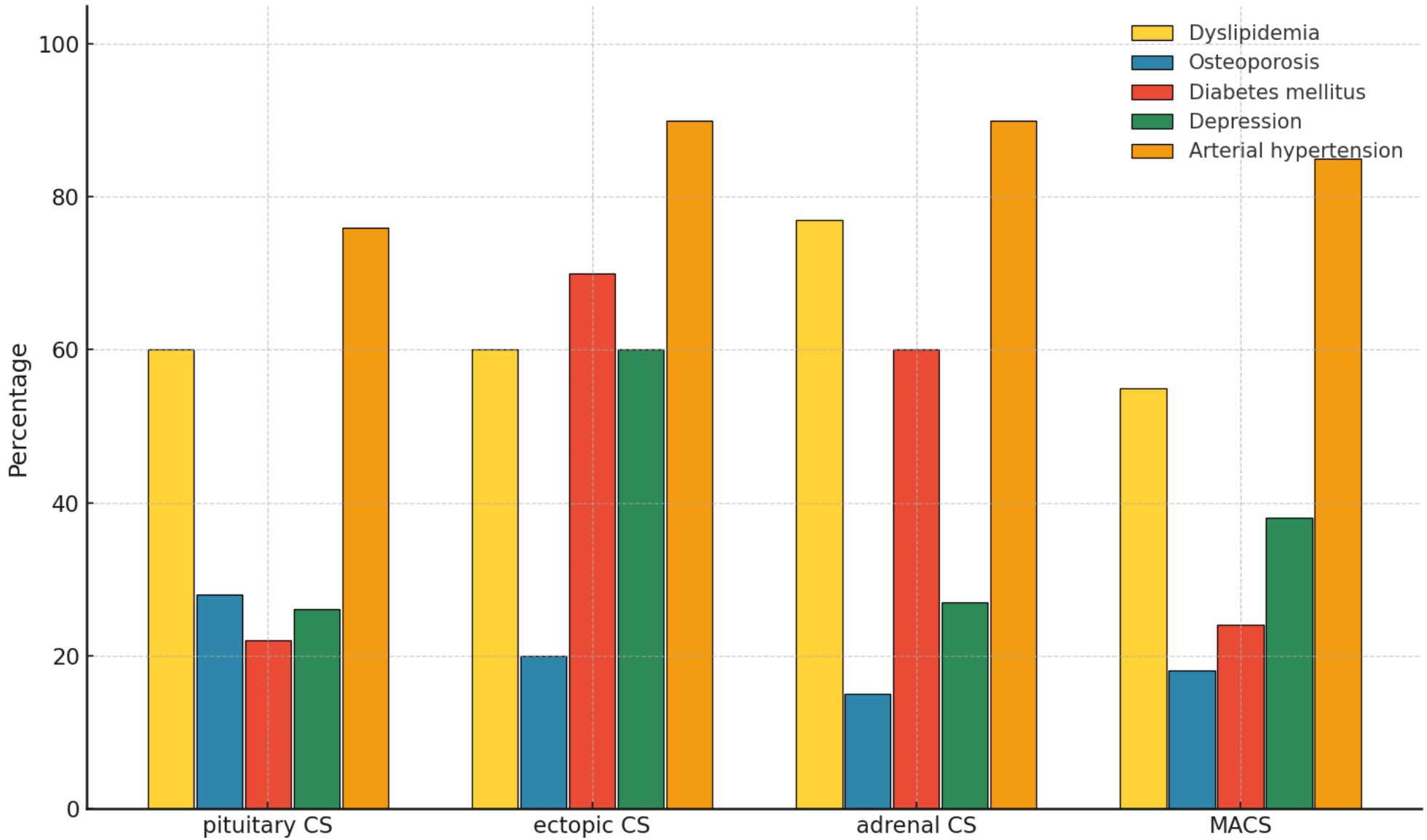




Bancos & Prete, Nat Rev Endocrinol 2024

The clinical context

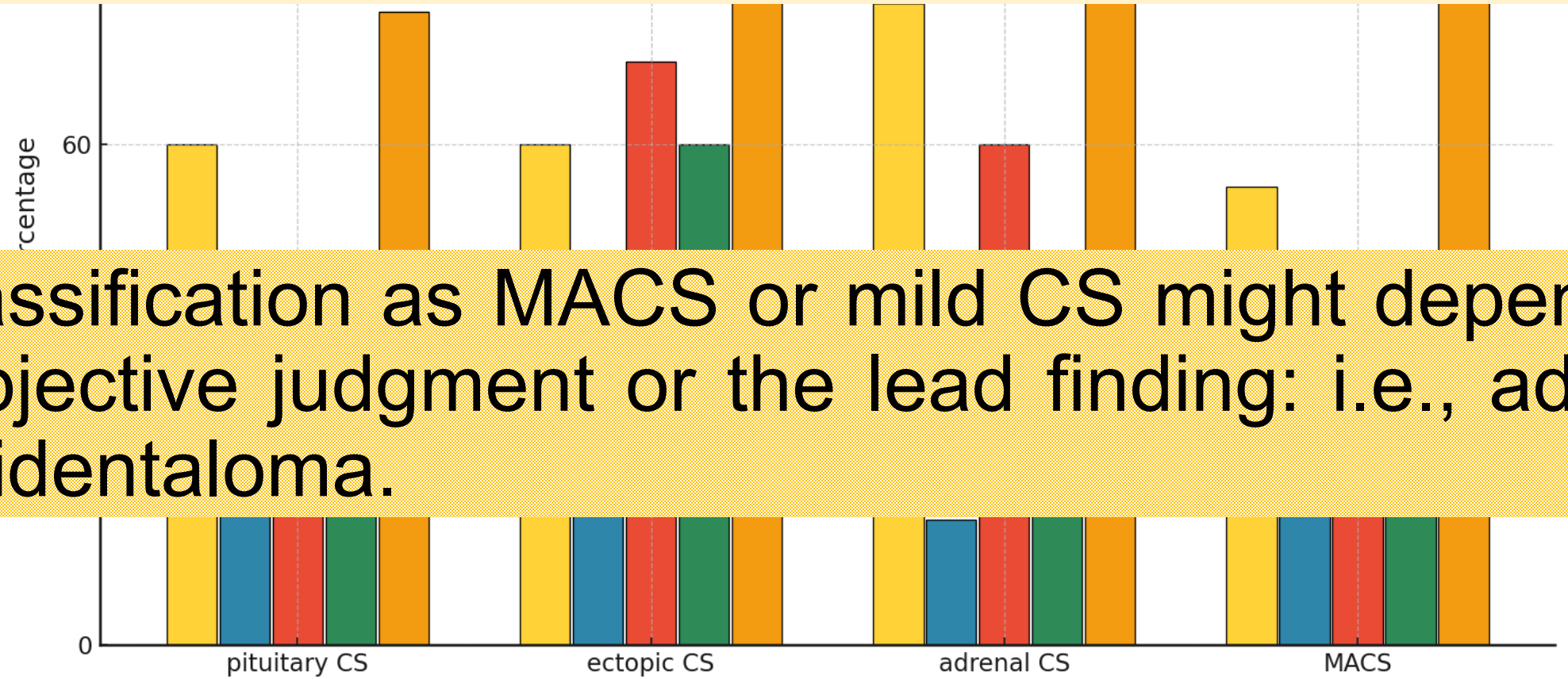
Braun LT et al. EJE 2024; 191:473 - 9



The clinical context

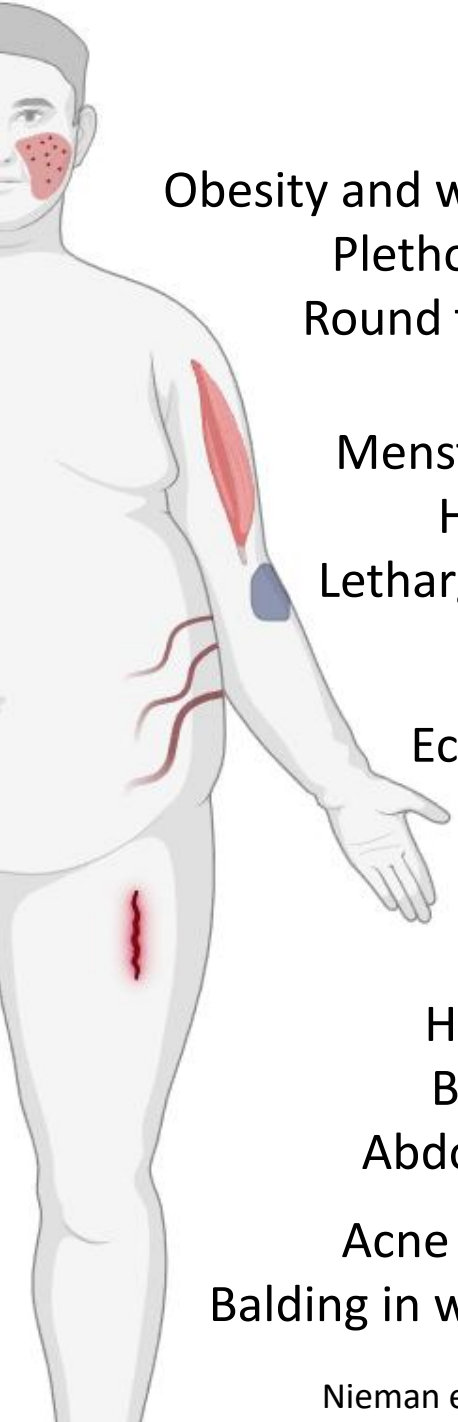
Braun LT et al. EJE 2024; 191:473 - 9

Patients with milder forms of CS and MACS overlap substantially.



Classification as MACS or mild CS might depend on subjective judgment or the lead finding: i.e., adrenal incidentaloma.

Clinical presentation



Obesity and weight gain (97%),
Plethora (94%),
Round face (88%),

Menstrual changes (84%),
Hirsutism (81%),
Lethargy and/or depressior
(62%),

Ecchymoses (62%),
Dorsal fat pad
(54%)
Edema (50%),

Headache (47%),
Backache (43%),
Abdominal pain (21%),

Acne (21%),
Balding in women (13%)

The possible presence of Cushing's syndrome (CS) is suggested by certain symptoms and signs. Unfortunately, none of these are pathognomonic, and many are nonspecific.
The concomitance of multiple progressive features, their severity and occurrence at unusual ages suggest the diagnosis of CS.

Nieman et al., Nat Rev Dis Primers, 2025

Hypertension in CS

Hypertension is usually an **early comorbidity of CS**

Prevalence of hypertension in CS **around 80%,** irrespective of sex. It reaches **88% in ectopic CS**

A **non-dipping blood pressure profile** is observed in **>50%** of patients with CS, **also in normotensive patients**

Hypertension persists even after achieving disease remission in 30–40% of cases

De Martino MC et al. 2024

Pathophysiology of CS-related hypertension

DIRECT MECHANISMS

Enhanced mineralocorticoid activity

Cortisol ↑ → saturated 11β-HSD2 → MR effect ↑
→ Na^+ retention, ↑ plasma volume, hypokalemia

Activation of the **renin-angiotensin system**

Cortisol ↑ → up-regulation AT1 receptors
→ pressor response

Impaired cardiac **sympathetic autonomic** modulation
Enhances vascular responsiveness to **vasoconstrictors**

INDIRECT MECHANISMS

Metabolic Syndrome

Central Obesity
Insulin resistance

Obstructive sleep apnea

De Martino MC et al. 2024

Who should be assessed for Cushing syndrome ?

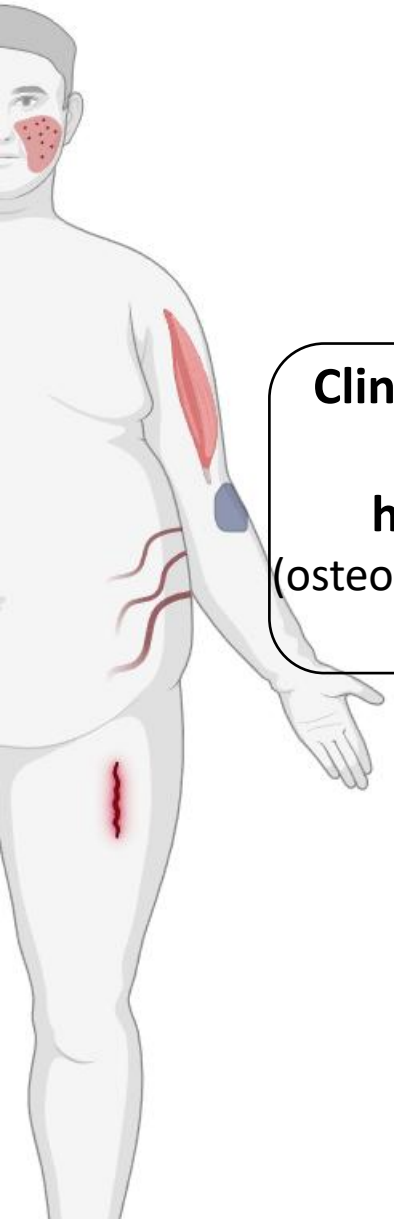
- ✓Metabolic syndrome
- ✓Osteoporosis
- ✓Adrenal Incidentaloma
- ✓Growth failure

with:

- ➢A specific Cushingoid sign
- ➢Unusual presentation for age
- ➢Unusual severity
- ➢Progressive & uncontrolled conditions

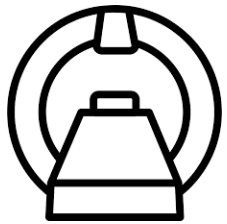
Demographic characteristics

Young patients (<40 y) or onset in childhood



Clinical characteristics suggestive of hypercortisolism
(osteoporosis in young obese subjects)

RED FLAGS
for CS in hypertensive patients



Radiological findings

Incidentally detected adrenal or pituitary lesions

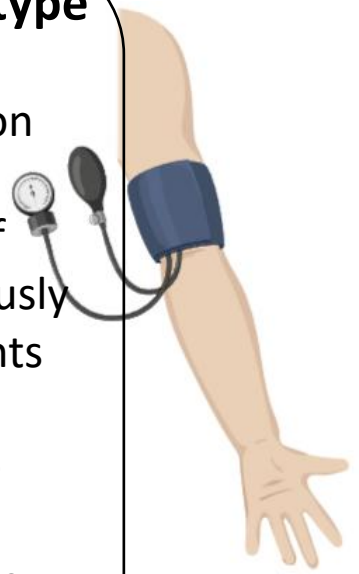
Hypertension phenotype

Resistant hypertension

Acute worsening of hypertension in previously well-controlled patients

Non-dipping profile

Presence of extensive hypertension-mediated organ damage



De Martino MC et al. 2024

Diagnosis of CS

At least 2 tests if clinical suspicion high

Clinical Suspect based on RED flags

N.B.
Consider **pseudo-Cushing** in: depression, alcohol misuse, severe obesity, intense exercise

24-h UFC

Reflects the overall daily cortisol exposure

Cave: requires a complete and accurate collection

LNSC

Assesses the physiological cortisol nadir

Cave: do not use in shift workers

1-mg overnight DST

Evaluates the physiological ability to suppress ACTH

Cave: Measure dex levels to avoid false-positive results

If ≥2 tests are concordantly abnormal → proceed with etiologic evaluation

If results are discordant → repeat testing / reassess interfering conditions

Screening tests used in hypertensives

Journal of Endocrinological Investigation (2024) 47:3029–3038
https://doi.org/10.1007/s40618-024-02387-2

ORIGINAL ARTICLE

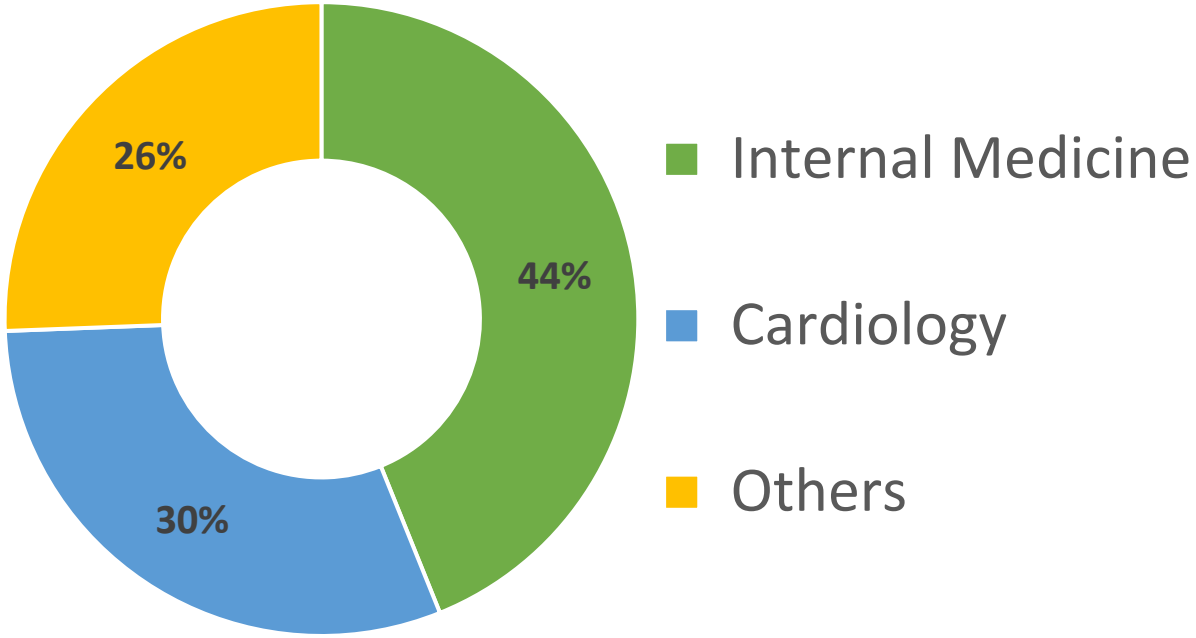
Screening of hypercortisolism among patients with hypertension: an Italian nationwide survey

G. Di Dalmazi[1,2] · J. Goi[3] · J. Burrello[3] · L. Tucci[1,2] · A. F. G. Cicero[4] · C. Mancusi[5] · E. Coletti Moia[6] · G. Iaccarino[5] · C. Borghi[4] · M. L. Muiesan[7] · C. Ferri[8] · P. Mulatero[3]

Aim

investigate screening and management of hypercortisolism among patients with hypertension in Italy using a 10-item questionnaire

82 centers:
30% excellence, **78.790 patients**,
average 600 patients/year



Screening tests used in hypertensives

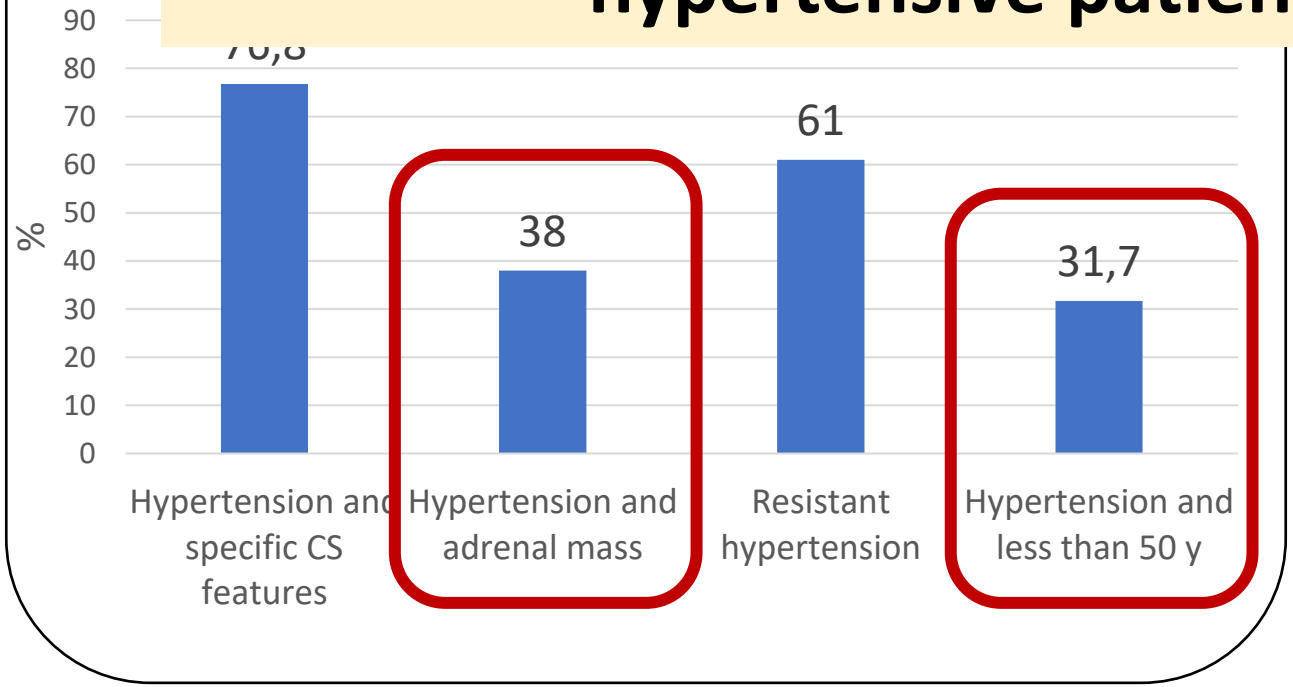
Journal of Endocrinological Investigation (2024) 47:3029–3038
https://doi.org/10.1007/s40618-024-02387-2

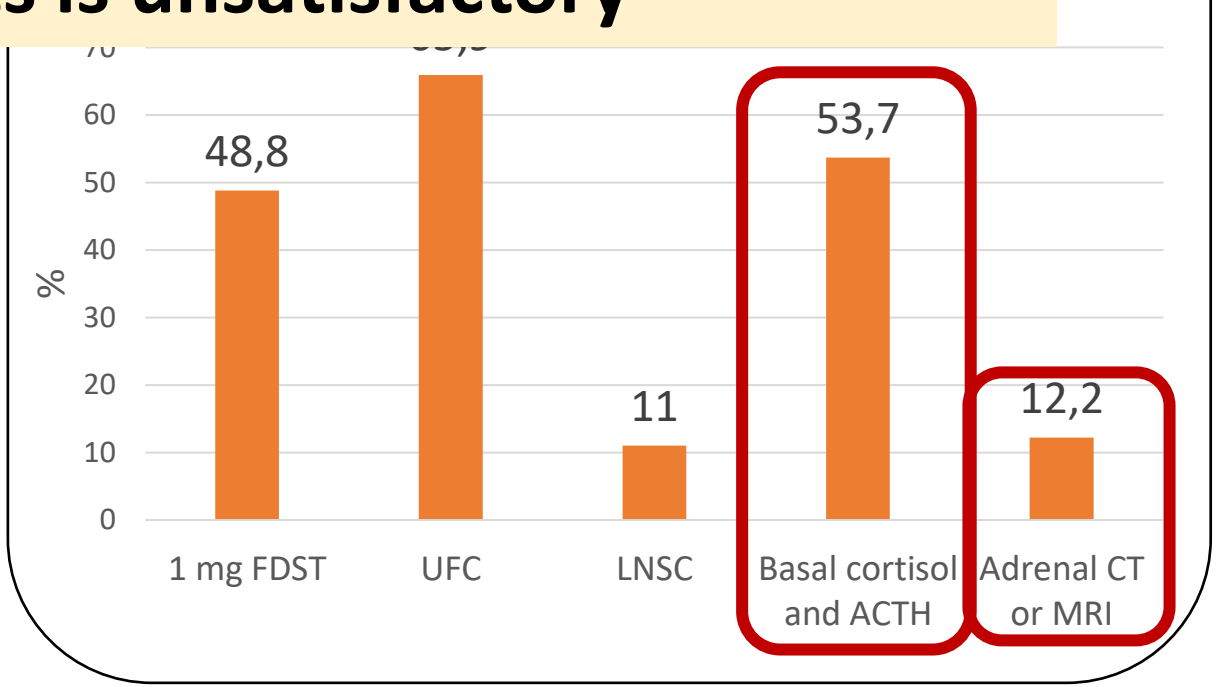
ORIGINAL ARTICLE

Screening of hypercortisolism among patients with hypertension: an Italian nationwide survey

G. Di Dalmazi[1,2] · J. Goi[3] · J. Burrello[3] · L. Tucci[1,2] · A. F. G. Cicero[4] · C. Mancusi[5] · E. Coletti Moia[6] · G. Iaccarino[5] · C. Borghi[4] · M. L. Muiesan[7] · C. Ferri[8] · P. Mulatero[3]

Conclusion: Current screening of hypercortisolism among hypertensive patients is unsatisfactory





53-yr-old man

On March 2024, diagnosis of HTN that is not controlled despite multiple poli-drug regimens. Progressive weight gain and dyslipidemia.

On Feb. 2025, admission to the ER for a hypertensive crisis with severe hypokalemia. Dismissed after treatment.

On April 2025, Cushing syndrome is suspected.

ENDOCRINE WORK-UP

- Morning cortisol: **19.1 μg/dL** (n.v.: 5 – 25)
- Morning ACTH: **43 pg/mL** (n.v.: 6– 60)

Cushing syndrome excluded ?

ENDOCRINE WORK-UP

- Morning cortisol: **19.1 μg/dL** (n.v.: 5 – 25)
- Morning ACTH: **43 pg/mL** (n.v.: 6– 60)
- 24-h UFC: **1701 μg/24h** (n.v.: 10 – 90)
- 1-mg DST: **45.7 μg/dL** (n.v.: <1.8)
- Night-time salivary cortisol: **27 – 20 - 43 ng/dL** (n.v.: <2.8)

Cushing syndrome confirmed !

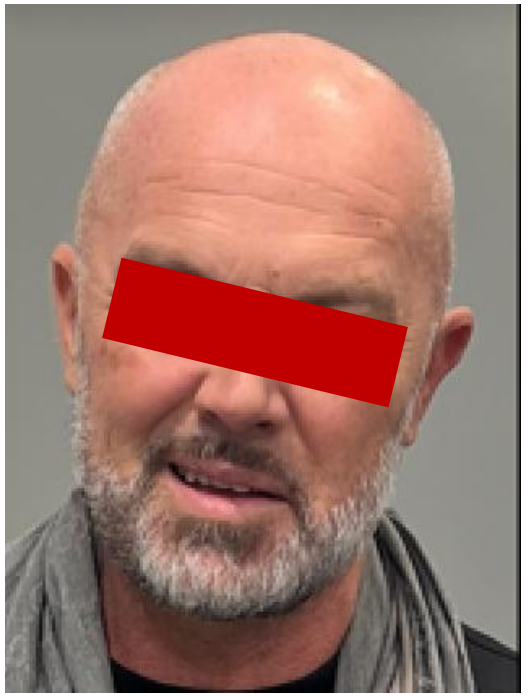
On medical treatment

Morning cortisol: 8.1 μg/dL (n.v.: 5 – 25)

Morning ACTH: 113 pg/mL (n.v.: 6– 60)

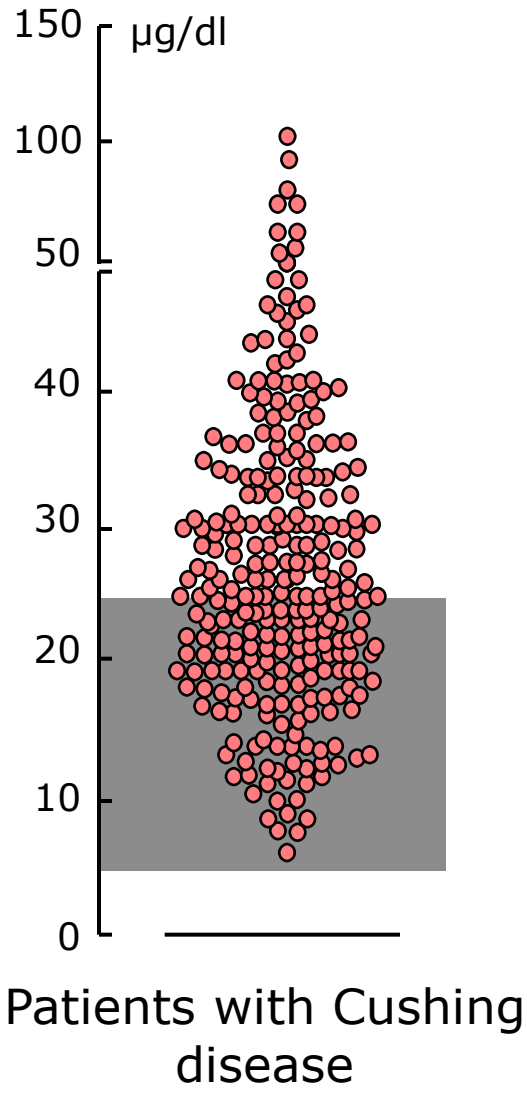
24-h UFC: 22 μg/24h (n.v.: 10 – 90)

Night-time salivary cortisol: 2.5 – 1.8 ng/dL (n.v.: <2.8)

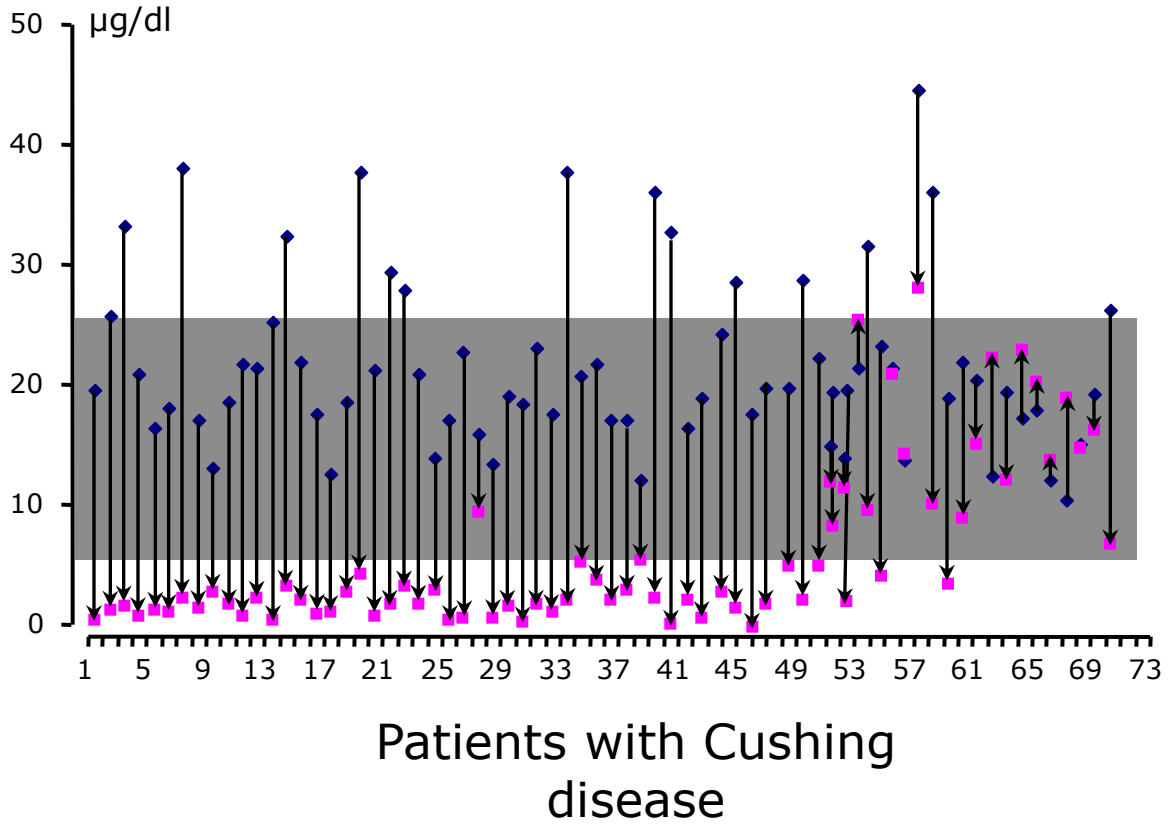


Morning cortisol

Diagnosis

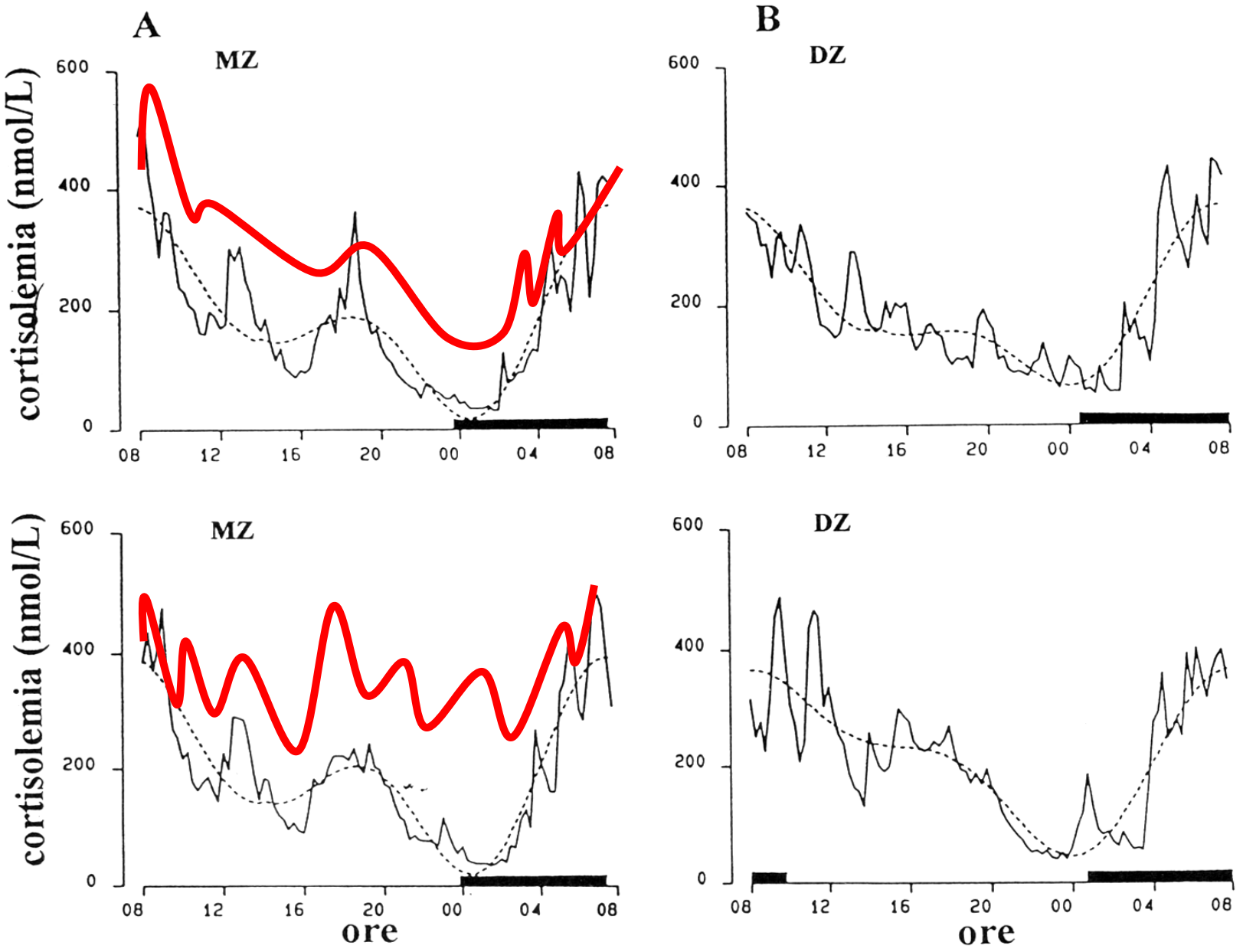


Remission



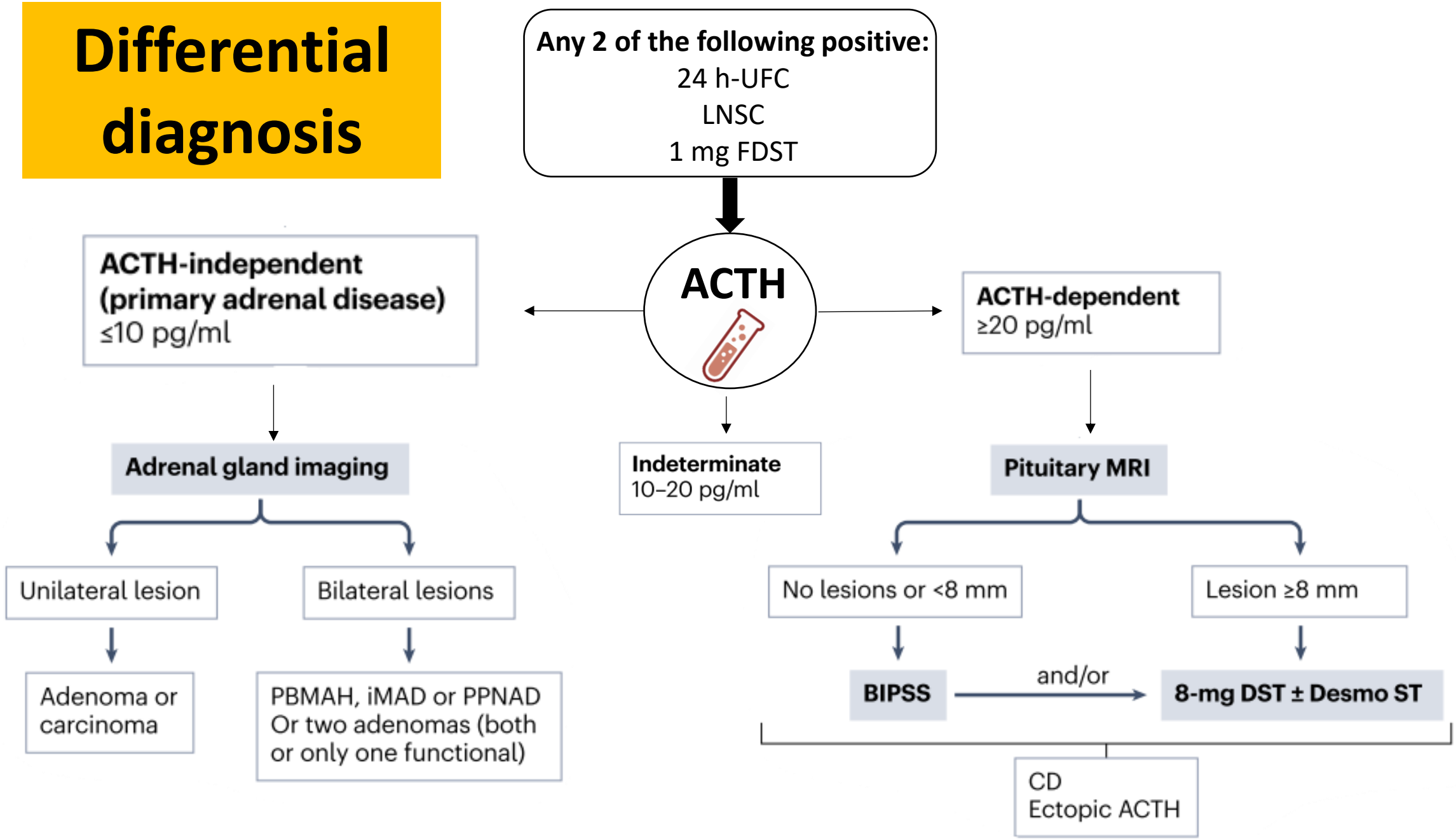
Courtesy of Pecori-Giraldi

Circadian cortisol rhythm



Linkowski P. Pharmacopsychiatry 1994

Differential diagnosis



Nieman et al., Nat Rev Dis Primers, 2025

Management and therapy of CS

N.B. Requires referral to an **experienced center** with endocrine, imaging and surgical expertise

MANAGEMENT GOALS

Reduce comorbidities and mortality | Remove the source | Normalize cortisol levels

SURGERY =

first-line treatment for ALL forms of Cushing syndrome

- **Adrenalectomy (adrenal Cushing)**
- **Transsphenoidal surgery (Cushing disease)**
- **Surgical resection of the tumor (EAS)**

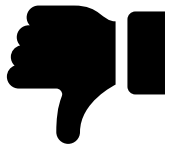
Bilateral adrenalectomy: when to consider it

Metastatic or occult ectopic ACTH syndrome not controlled by medical therapy

Cushing disease not responding to surgery or radiotherapy

Provides **immediate control** of hypercortisolism

Requires **lifelong glucocorticoid + mineralocorticoid replacement**



Blood Pressure Improvement After Treating CS

Retrospective chart review of 75 hypertensives with cured CS (72 ACTH-dependent CS; 3 adrenal adenomas).

About 80% of hypercortisolemic patients showed remission or improvement in blood pressure within 10 days of surgical cure.

By one year, a total of ~90% had improved or normalized blood pressure

PREDICTIVE FACTORS FOR REMISSION

Younger age

Lower preoperative BMI

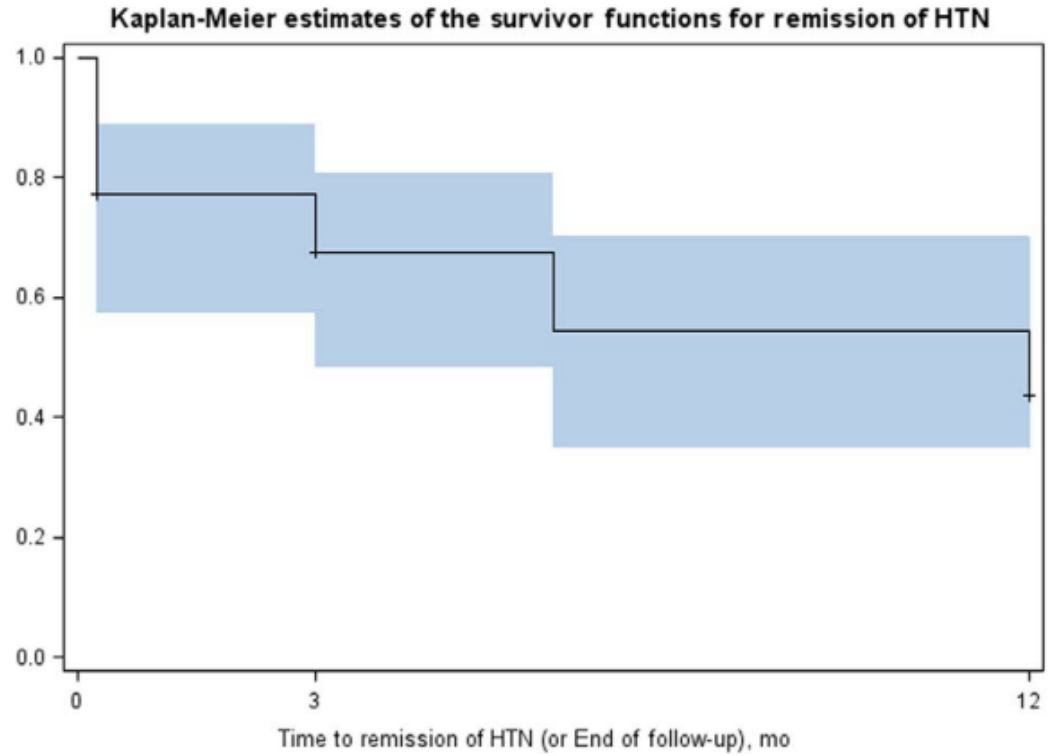
Received: 1 August 2019 | Revised: 17 October 2019 | Accepted: 10 November 2019

DOI: 10.1111/cen.14129

ORIGINAL ARTICLE

Remission of hypertension after surgical cure of Cushing's syndrome

Smita Jha[1,2,3] | Ninet Sinaii[4] | Raven N. McGlotten[1] | Lynnette K. Nieman[1]



Only 44% achieve **complete remission** at 12 months →

long-term follow-up remains essential

Long-term outcomes after remission of CS

Systematic review; papers from 2000 to 2022.
Inclusion Criteria: studies with at least 15 adult patients (≥18 years) with of CS of adrenal, pituitary or ectopic origin **and** median follow-up of ≥ 4 years of disease activity or ≥ 4 years of remission.

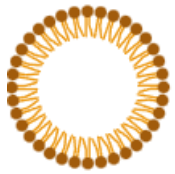
The Journal of Clinical Endocrinology & Metabolism, 2024, **109**, e901–e919
https://doi.org/10.1210/clinem/dgad453
Advance access publication 3 August 2023
Mini-Review
ENDOCRINE SOCIETY

Long-Term Consequences of Cushing Syndrome: A Systematic Literature Review

Soraya Puglisi,[1] Anna Maria Elena Perini,[1] Cristina Botto,[1] Francesco Oliva,[2] and Massimo Terzolo[1]

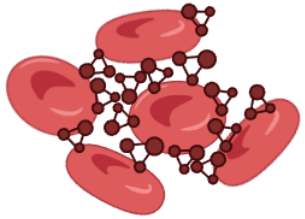
Hypertension
(30-40% remain hypertensive)

Glucose profile



Lipid profile

Body composition



Prothrombotic state

Bone quality

Fatigue and mood disorders

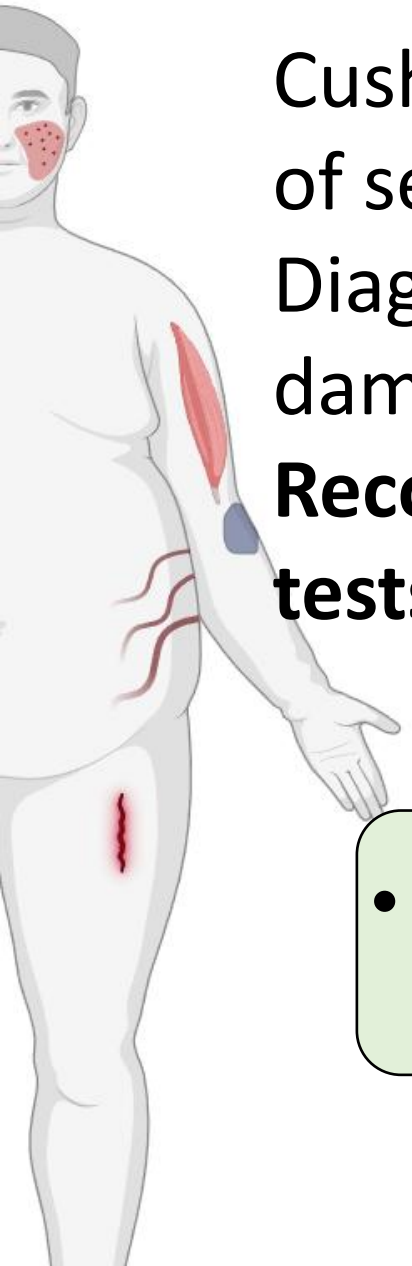
improve after CS remission but often persist

MORTALITY

Overall mortality remains **higher than in the general population**, even after biochemical remission (Standardized Mortality Ratio 1.32)

Remission of CS does not mean equal full recovery of comorbidities.
So…
Careful, long-term cardiovascular and metabolic follow-up is mandatory

To sum up



Cushing syndrome is a rare but crucially underdiagnosed cause of severe and resistant hypertension.

Diagnosis is often delayed for years (~3 years), allowing CV damage to progress.

Recognizing red-flag features, choosing the **right screening tests**, and **referring patients** early can change prognosis.

- Treating hypercortisolism markedly improves blood pressure, metabolic health, and long-term CV risk

Department
Clinical and
Biological Sciences

UNIVERSITÀ DI TORINO

S. Luigi Gonzaga

ens@t
european network for the study of adrenal tumors
Center of Excellence

- Adrenocortical carcinoma
- Adrenal incidentaloma
- Adrenal research center

2023 - 2027
DEPARTMENT OF EXCELLENCE
Ministero dell'Università e della Ricerca

SAN LUIGI adrenal GROUP

Massimo Terzolo
Giuseppe Reimondo
Soraya Puglisi
Vittoria Basile
Erika Messina
Marianna Torchio
Paola Perotti
Laura Saba
Chiara Longo

THANK YOU FOR YOUR ATTENTION