Mild autonomous cortisol secretion in adrenal incidentalomas: why should we care?

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Disclosures

- NIH NIDDK: funding for research
- Data Safety and Monitoring Board: Adrenas (fee to institution)
- Elsevier point of care: writer
- Dynamed: reviewer
- Consulting: Sparrow, Spruce, Corcept, Recordati, HRA Pharma, Lantheus (fee to institution)

Objectives

- Definition of MACS
- Prevalence of MACS
- Diagnosis of MACS
- Consequences of MACS
- Management of MACS

Outline

1. To review the epidemiology of mild autonomous cortisol secretion (MACS)
2. To define and diagnose MACS and review diagnostic pitfalls of tests used in its diagnosis
3. To summarize evidence on the clinical consequences of treated and untreated MACS

Outline

- **Definition of MACS**
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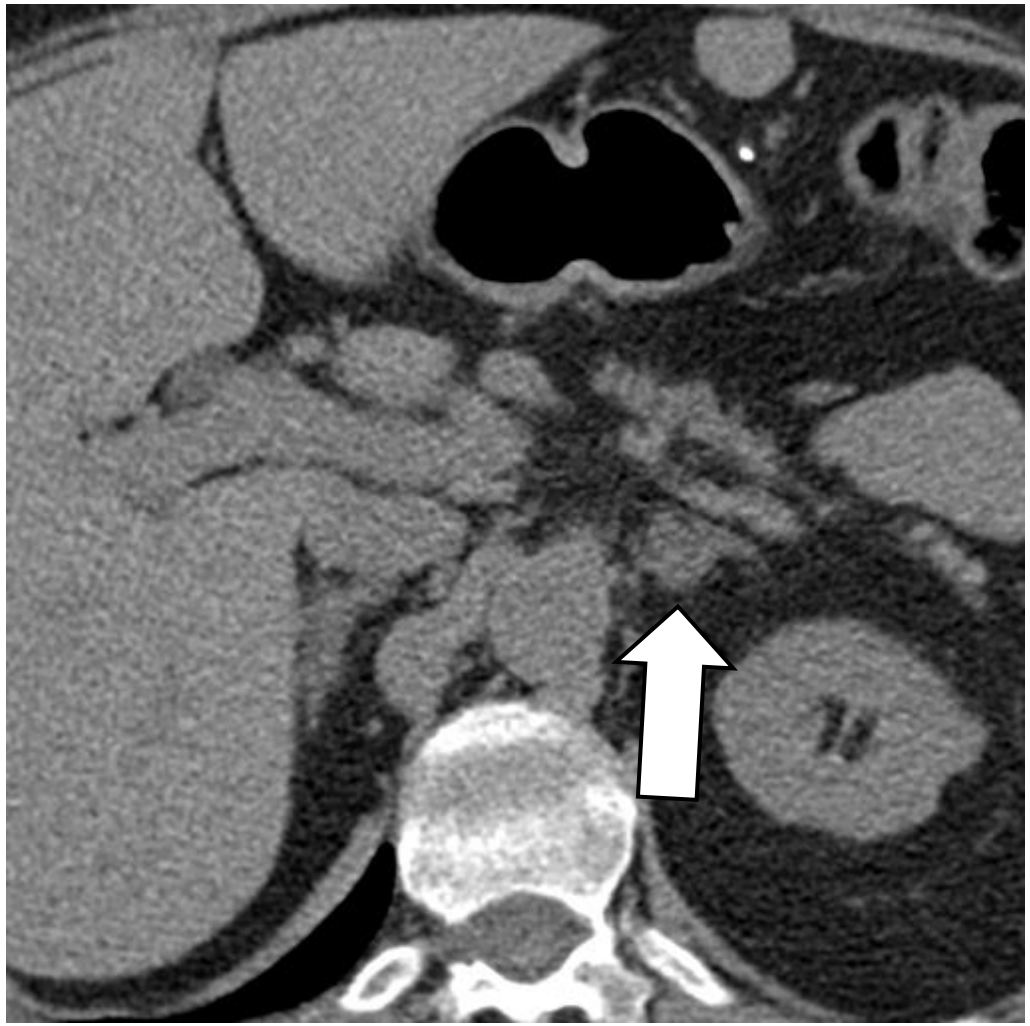
Definition of mild autonomous cortisol secretion (MACS)

- Cortisol following the 1 mg Dexamethasone suppression test is **>1.8 mcg/dL**
- Patient **without** overt features of Cushing syndrome
- Adrenal adenoma/macronodular hyperplasia (very rarely – micronodular hyperplasia)
- ACTH independence
- “Subclinical Cushing syndrome” – no longer to be used.

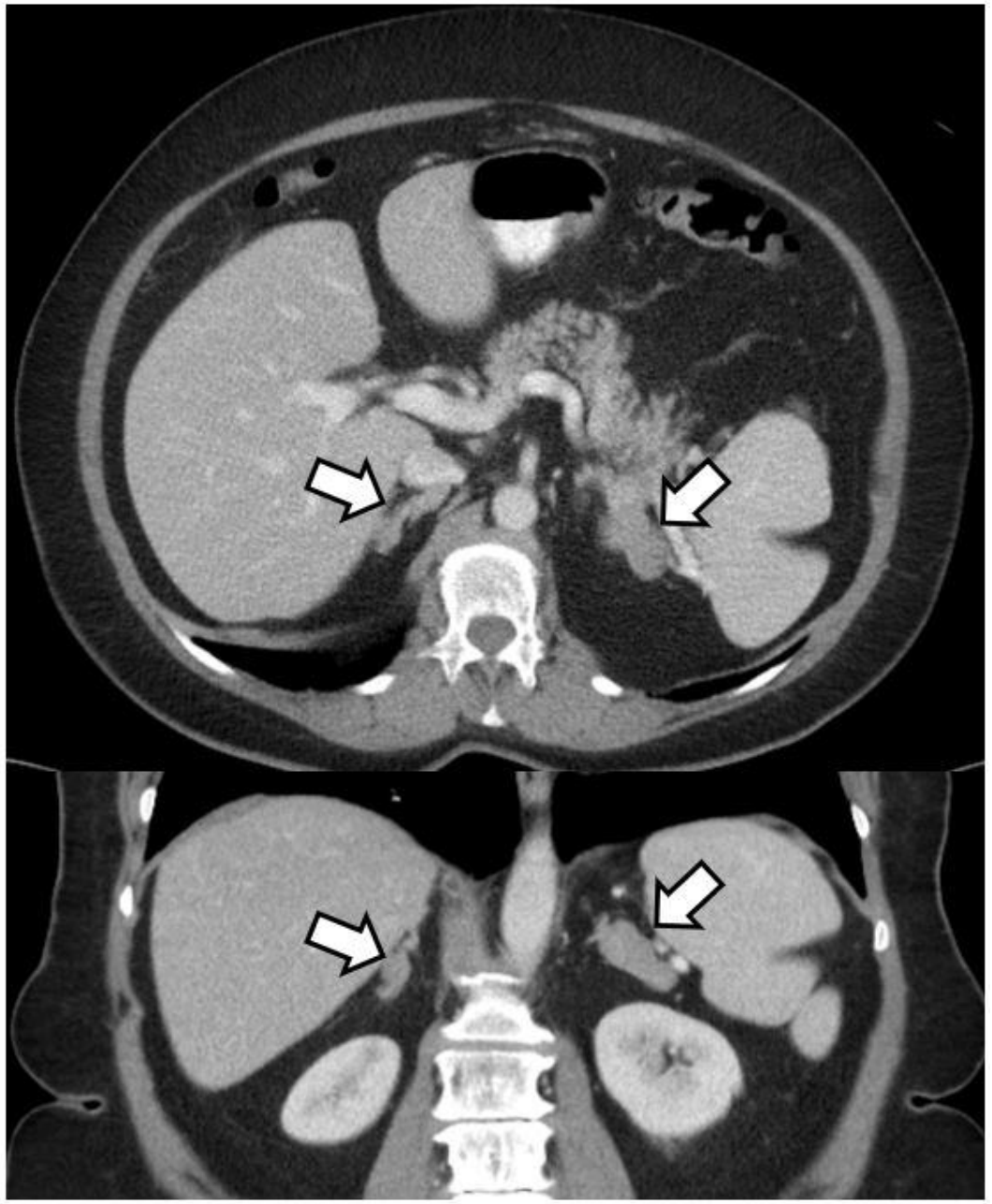
- Fassnacht et al.Management of adrenal incidentalomas: European Society of Endocrinology Clinical Practice Guideline in collaboration with the European Network for the Study of Adrenal Tumors (PMID: 27390021)
- Vaidya et al. The evaluation of incidentally discovered adrenal mass (PMID: 30817193)



Coronal images from an unenhanced and contrast enhanced CT scan showed a lipid rich adrenal mass of 2.2 x 1.4 cm left adrenal mass (Unenhanced HU of 6)

- 54-yr-old woman
- Weight gain of 50 pounds over 5-7 years
- Prediabetes (HbA1C=6%, not on medications)
- Hypertension (metoprolol tartrate, nifedipine)
- Osteoporosis (2 years ago)
- Incidental discovery of adrenal mass 2 months prior
- Physical exam: BMI 39.8 kg/m^2, BP 138/86 mmHg, no features of Cushing syndrome.

Biochemical Testing	**Result**	**Ref. range**
1-mg overnight DST, cortisol, mcg/dL	**2.3**	<1.8
ACTH, pg/mL	**<5**	7.2-63
DHEA-S, mcg/dL	**26**	15-200
Aldosterone, ng/dL	8	<21
Plasma renin activity, ng/mL/h	4.1	2.9-10.8
Urine free cortisol, mcg/24h	7.5	3.5-45



- 66-yr-old woman
- Weight gain of 30 pounds over 1 year
- Dyslipidemia (simvastatin)
- Hypertension (4 medications), hypokalemia
- Incidental discovery of bilateral adrenal masses
- Physical exam: BMI 39.6 kg/m^2, BP 142/72 mmHg, no features of Cushing syndrome.

Biochemical Testing	Result	Ref.range
1 mg DST, mcg/dL	**4.7**	<1.8
8 mg DST, mcg/dL	**3.2**	<1
ACTH, pg/mL	**<5**	7.2-63
DHEA-S, mcg/dL	**26**	<15-157
Aldosterone, ng/dL	**11, 13**	<21
Plasma renin activity, ng/mL/h	**<0.6**	2.9-10.8
Urine metanephrines, mcg/24 h	51	<400
Urine normetanephrines, mcg/24h	273	<900
Urine free cortisol, mcg/24h	8	3.5-45

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Outline

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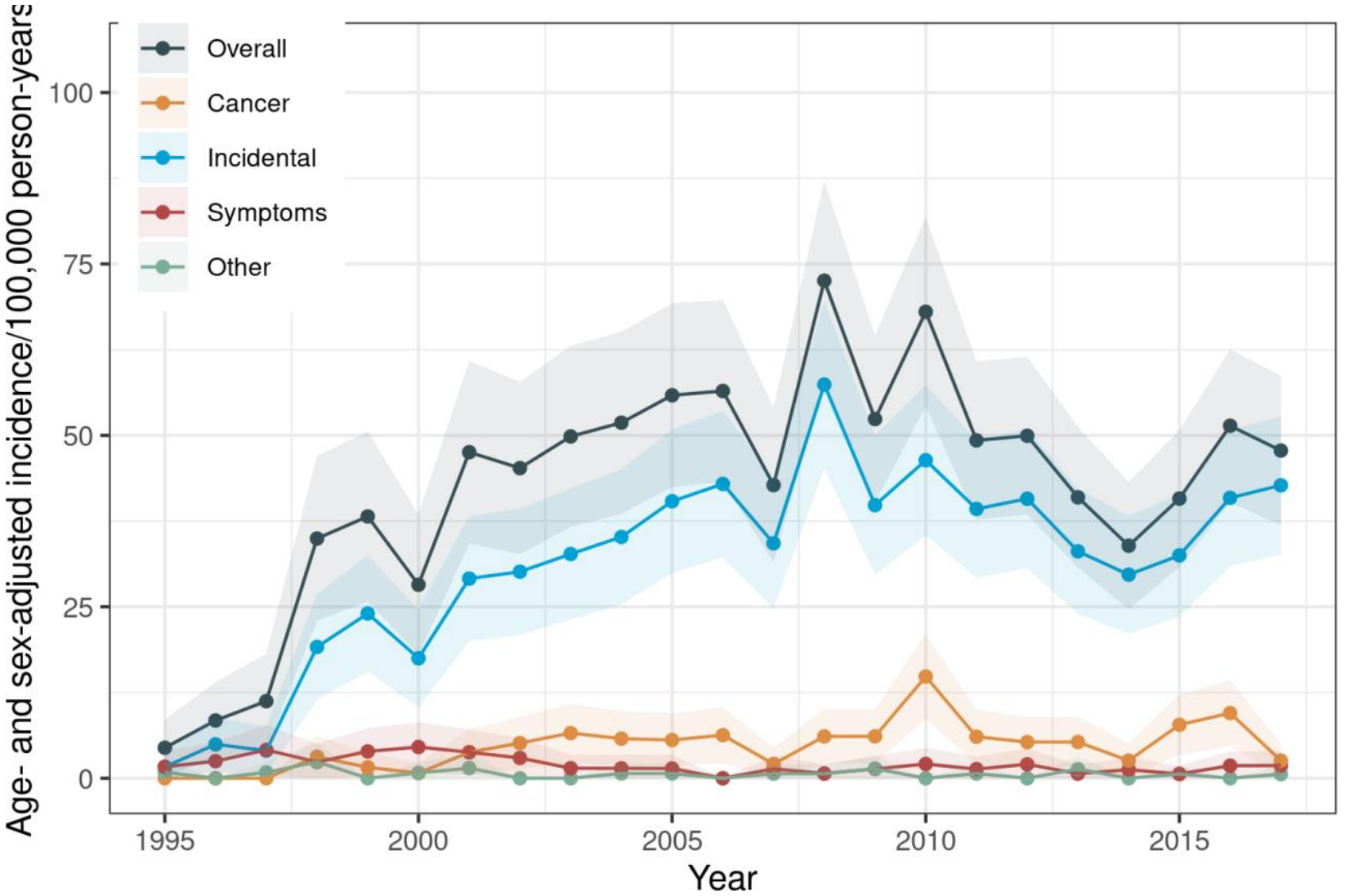
Epidemiology (population)



A population based- study of patients with adrenal tumors
Olmsted County, MN, 1995-2017.

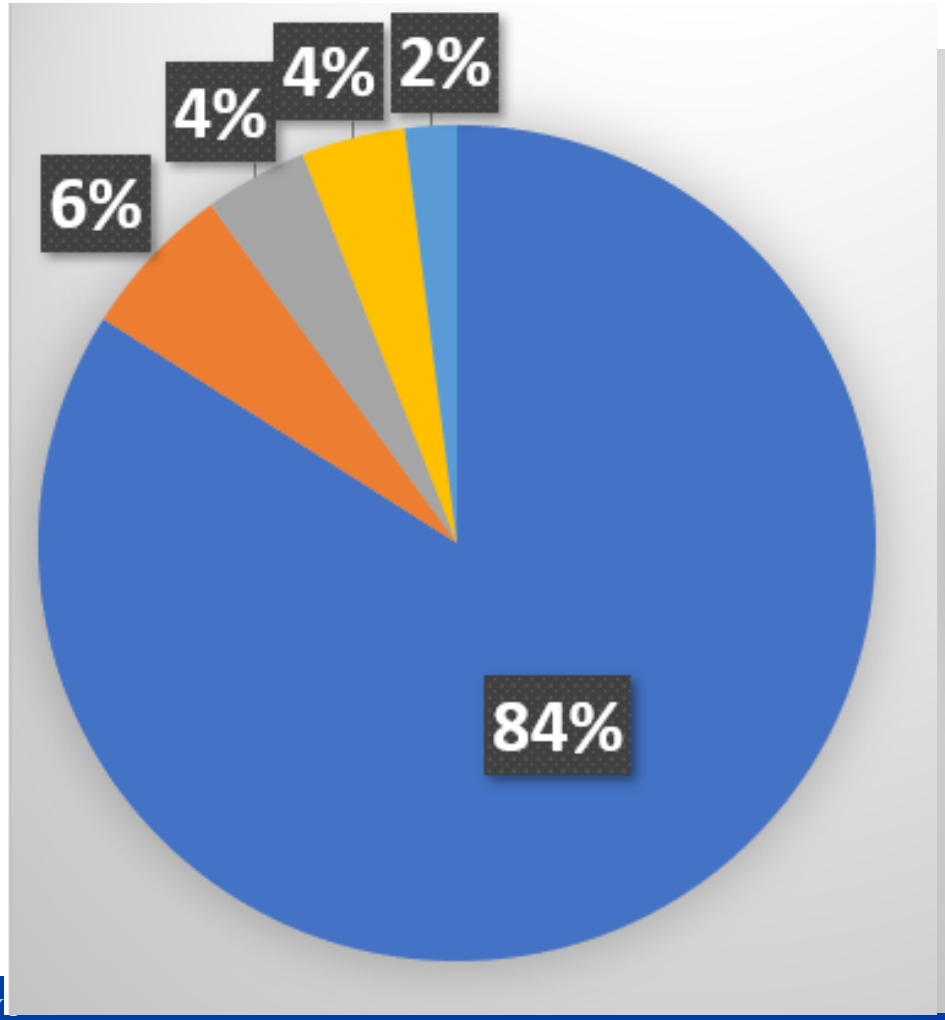
10-fold increase in the **incidence** of adrenal tumors

Parallel to the increase in the **number of abdominal CT scans**

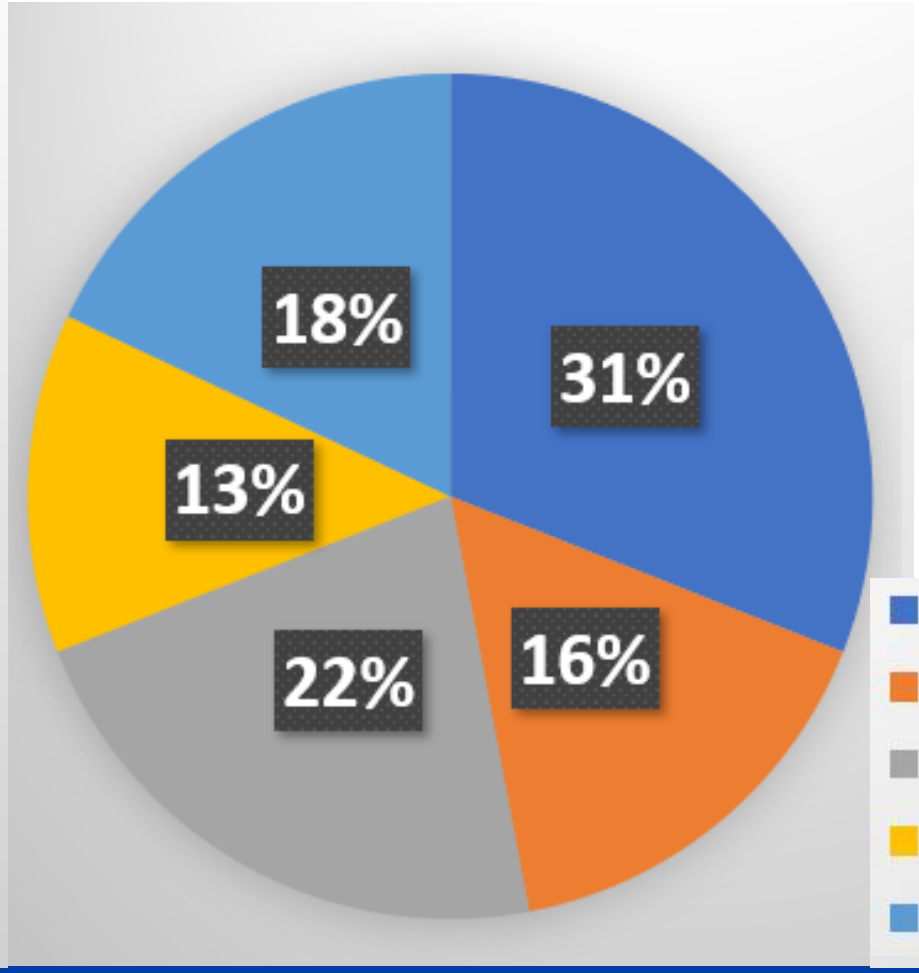
• Ebbehoj A et al. Epidemiology of adrenal tumours in Olmsted County, Minnesota, USA: a population-based cohort study. Lancet DE 2020 PMID 33065059

Etiology of adrenal mass based on size

All-comers:

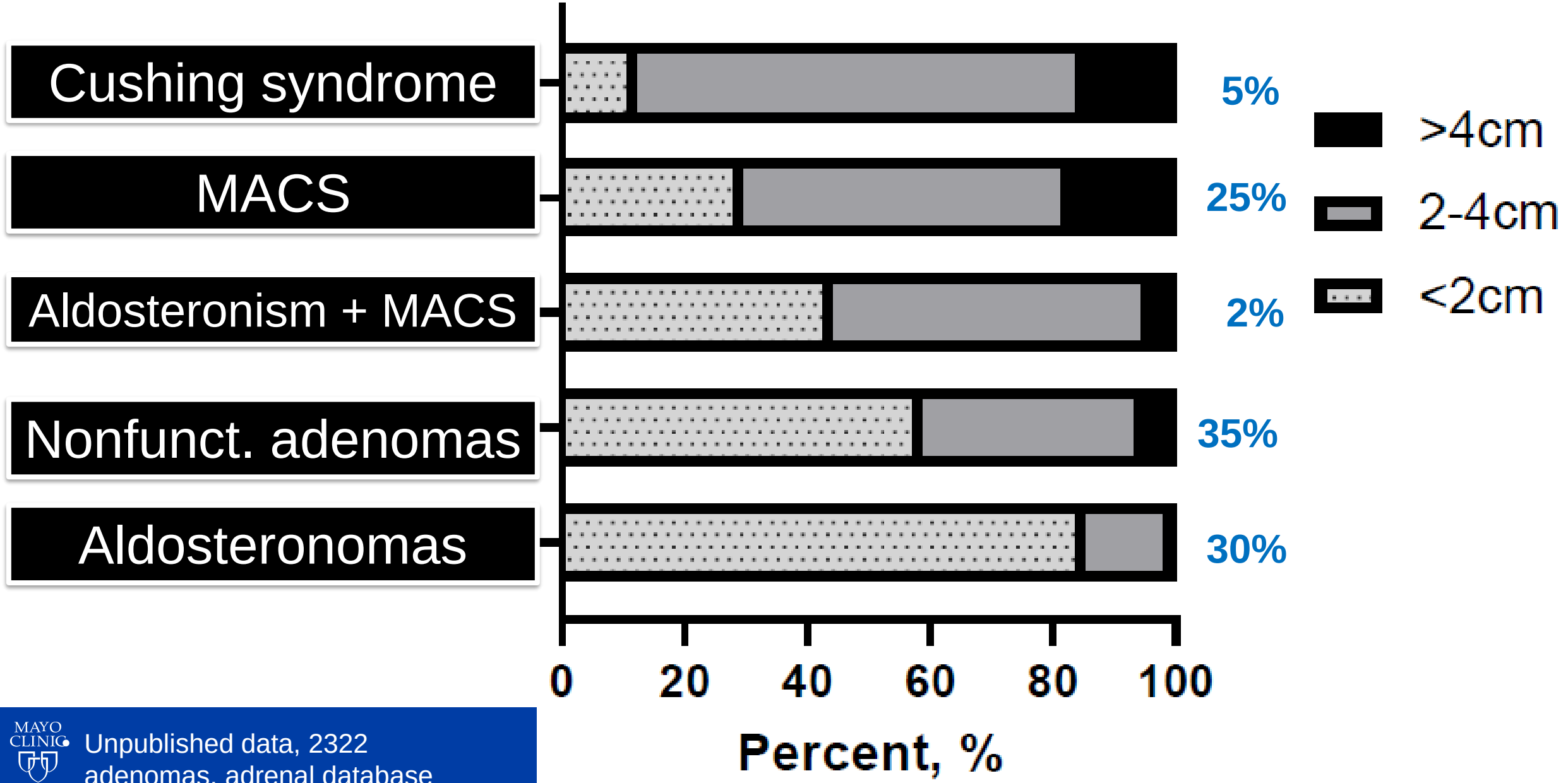


Size ≥ 4 cm



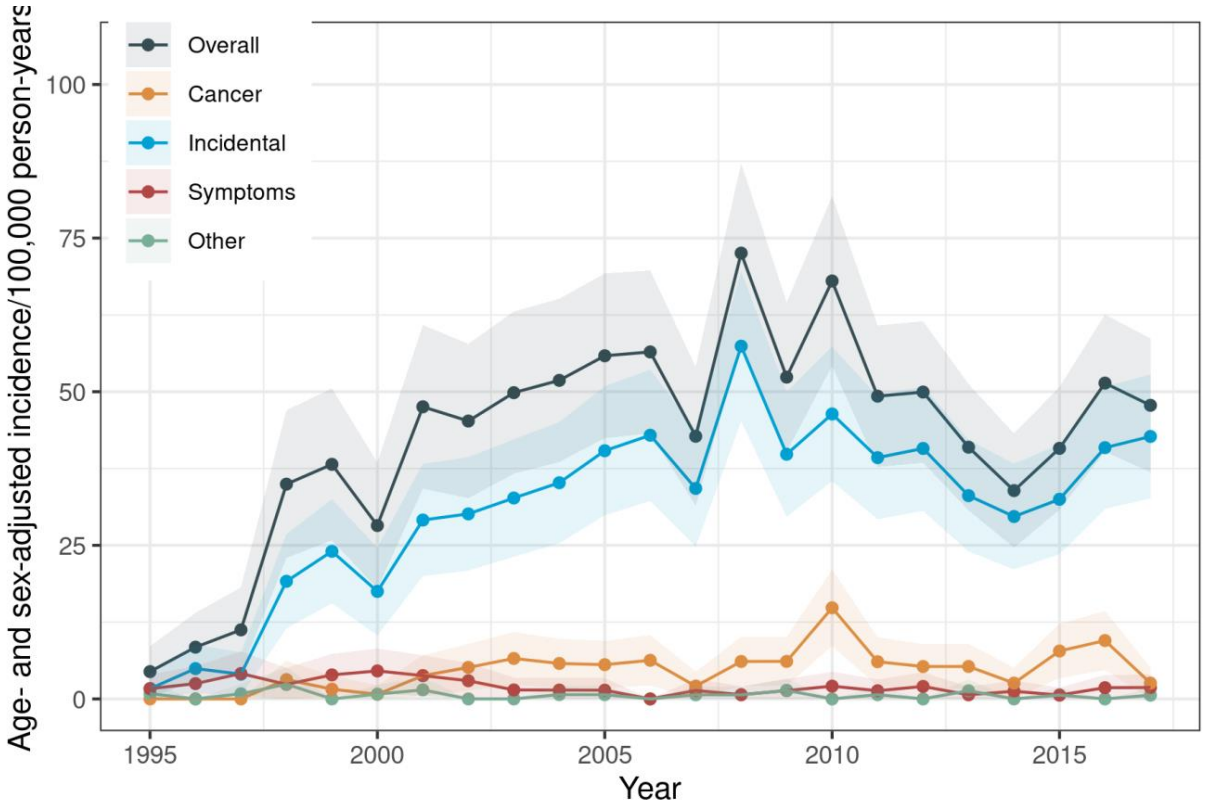
Mantero et all, 2000, Iniguez et al, 2017, Mayo Clinic adrenal database, Eurine ACT study

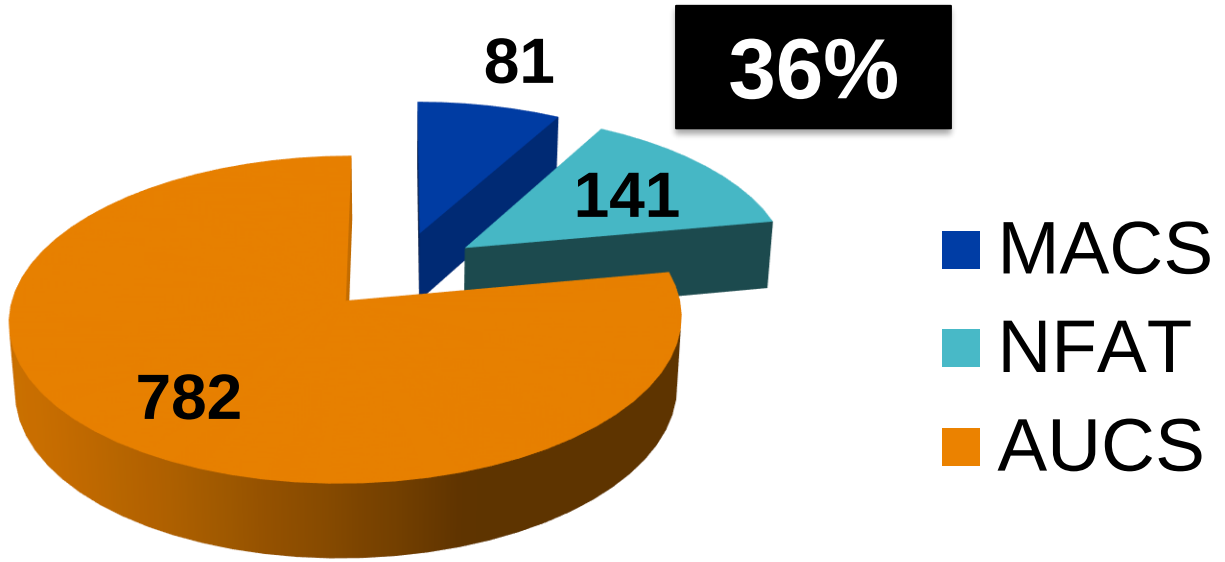
Prevalence of MACS in a tertiary center



Unpublished data, 2322 adenomas, adrenal database

Prevalence of MACS in a population:





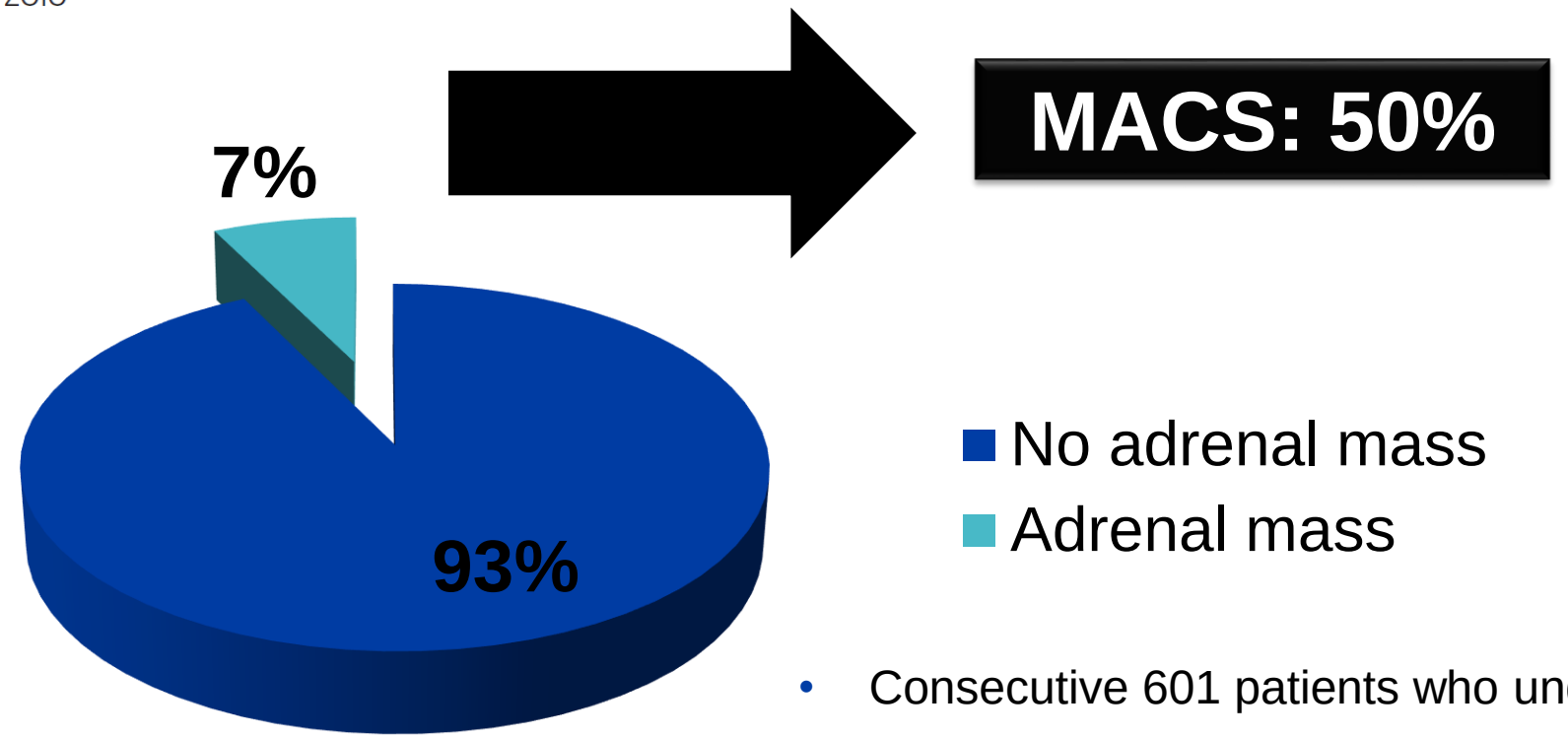
- **Three subgroups based on 1 mg DST:**
- MACS: cortisol >1.8 mcg/dl
- NFAT: cortisol ≤1.8 mcg/dl
- Adenoma with unknown cortisol secretion (AUCS): N/A

- Ebbehoj A et al. Epidemiology of adrenal tumours in Olmsted County, Minnesota, USA: a population-based cohort study. Lancet DE 2020 PMID 33065059

Prevalence of MACS in a radiological cohort:

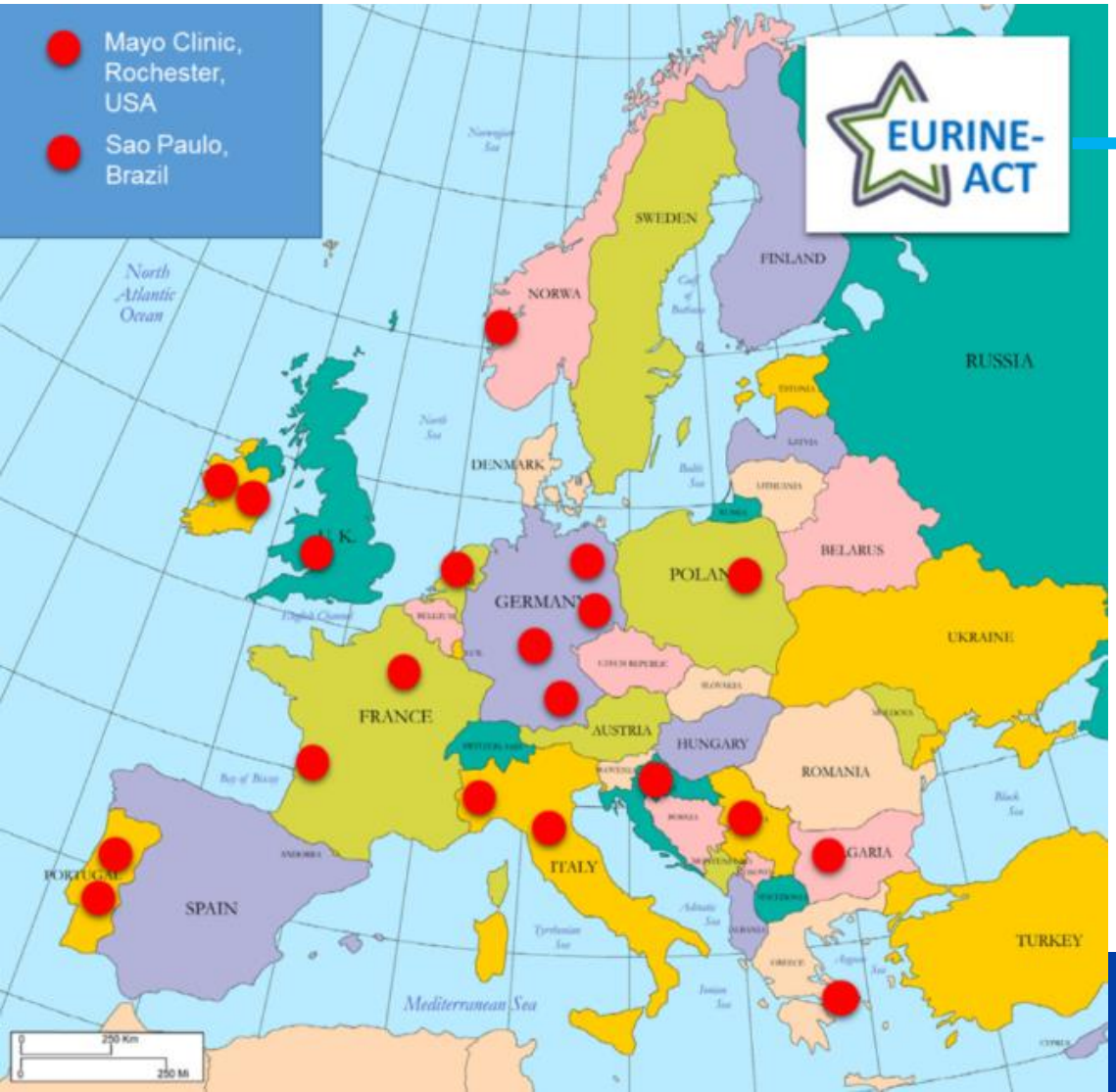
Adrenal Incidentalomas are Tied to Increased Risk of Diabetes: Findings from a Prospective Study

Giuseppe Reimondo,[1,†] Elena Castellano,[2,†] Maurizio Grosso,[3] Roberto Priotto,[3] Soraya Puglisi,[1] Anna Pia,[1] Micaela Pellegrino,[2] Giorgio Borretta,[2,‡] and Massimo Terzolo[1,‡]



- Consecutive 601 patients who underwent abdominal CT
- No suspected adrenal disease, no malignancy

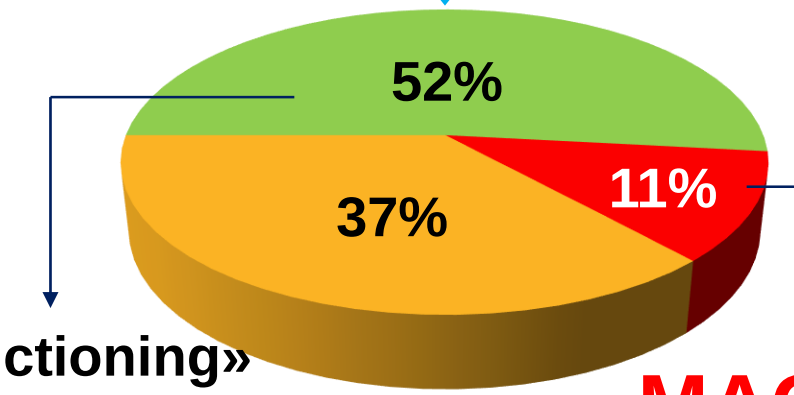
The EURINE-ACT project and MACS



N=2,020 newly diagnosed adrenal tumours:

- **88%** Benign adrenocortical adenomas
- **5%** Adrenocortical carcinomas
- **4%** Other benign adrenal tumours
- **3%** Other malignant adrenal tumours

N=1,201 underwent 1mgDST



DST>5

«nonfunctioning» adenomas (NFA)

DST 1.8-5

MACS:48%

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Management of adrenal incidentalomas: European Society of Endocrinology Clinical Practice Guideline in collaboration with the European Network for the Study of Adrenal Tumors

Martin Fassnacht[1,2], Wiebke Arlt[3,4], Irina Bancos[3,4,5], Henning Dralle[6], John Newell-Price[7,8], Anju Sahdev[9], Antoine Tabarin[10], Massimo Terzolo[11], Stylianos Tsagarakis[12] and Olaf M Dekkers[13,14]

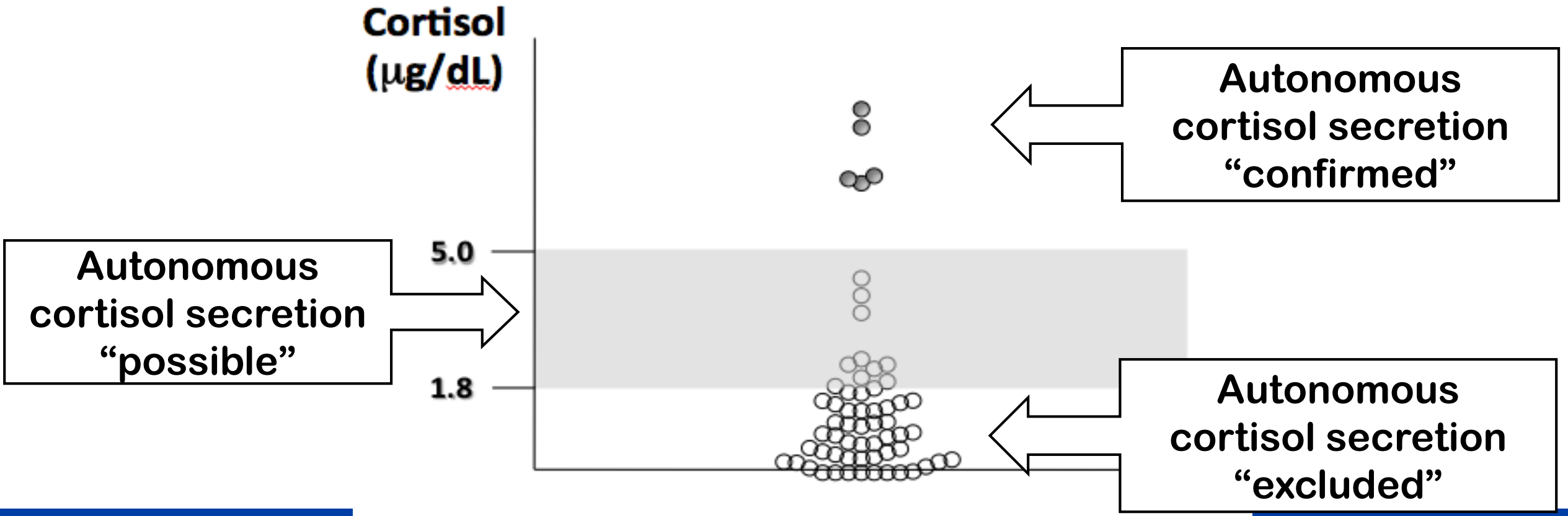
- R.3.2 We recommend that all patients with AI undergo a **1-mg overnight DST** to exclude cortisol excess (XXOO).

Supportive data:

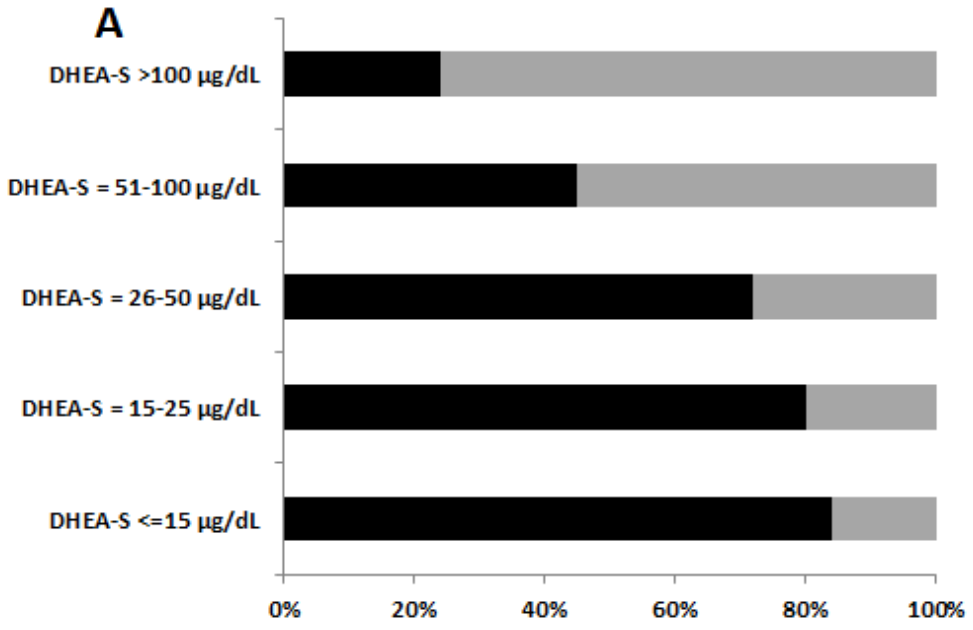
1. ACTH (low)
2. DHEAS (low)
3. Repeat DST

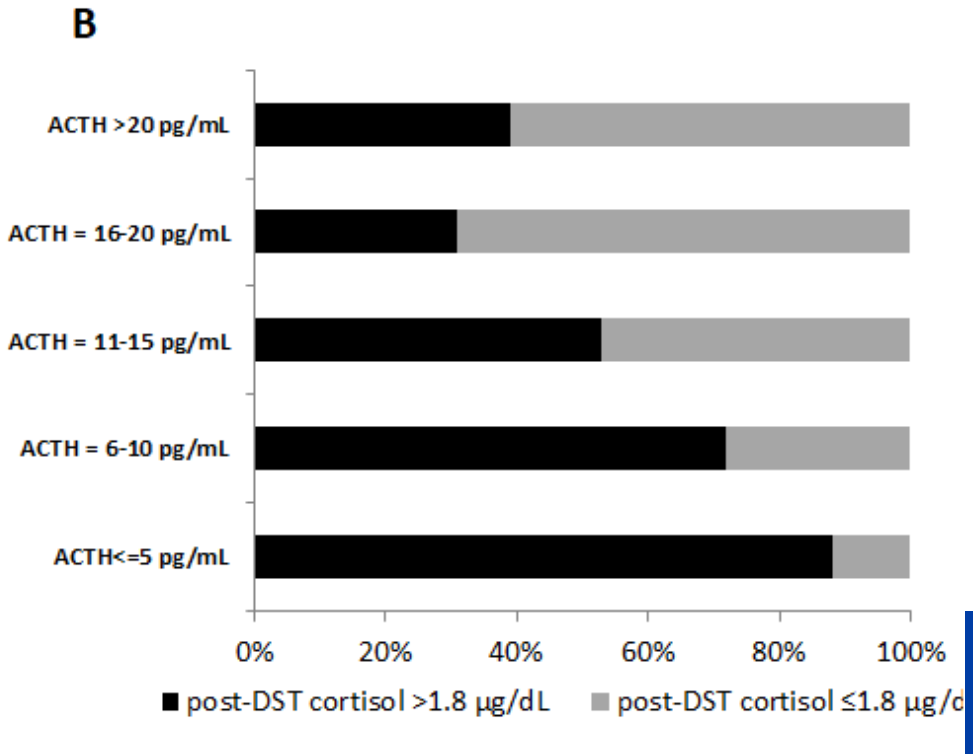
Other tests:

1. 24hour urine cortisol – almost always within normal ranges
2. *Midnight salivary cortisol* – frequently normal



ACTH and DHEAS?





Biomedicines. 2021 Jun 28;9(7):741. doi: 10.3390/biomedicines9070741.

Diagnostic Accuracy of Dehydroepiandrosterone Sulfate and Corticotropin in Autonomous Cortisol Secretion

Lindsay E Carafone [1], Catherine D Zhang [2], Dingfeng Li [2], Natalia Lazik [2], Oksana Hamidi [2 3], Maria Daniela Hurtado [2 4], William F Young Jr [2], Melinda A Thomas [2], Benzon M Dy [5], Melanie L Lyden [5], Trenton R Foster [5], Travis J McKenzie [5], Irina Bancos [2]

- ACTH>**20** pg/mL and DHEAS >**100** mcg/dL → MACS is very unlikely
- ACTH<**10** pg/mL and DHEAS <**40** mcg/dL → MACS is very likely

Interpretation of Abnormal Dexamethasone Suppression Test is Enhanced With Use of Synchronous Free Cortisol Assessment

Natalia Genere,[1,2] Ravinder Jeet Kaur,[2] Shobana Athimulam,[2,3] Melinda A. Thomas,[2] Todd Nippoldt,[2] Molly Van Norman,[4] Ravinder Singh,[4] Stefan Grebe,[4] and Irina Bancos[2,4]

- Cross-sectional study of
  - adult volunteers (n=168; 47 women on OCP, 66 women not on OCP, 55 men)
  - patients undergoing evaluation for hypercortisolism (n=196; 16 women on OCP).
- **Measurements:**
  - post-DST dexamethasone
  - free cortisol (mass spectrometry)
  - total cortisol (immunoassay)

JCEM 2021, PMID: 34648626

Interpretation of Abnormal Dexamethasone Suppression Test is Enhanced With Use of Synchronous Free Cortisol Assessment

Natalia Genere,[1,2] Ravinder Jeet Kaur,[2] Shobana Athimulam,[2,3] Melinda A. Thomas,[2] Todd Nippoldt,[2] Molly Van Norman,[4] Ravinder Singh,[4] Stefan Grebe,[4] and Irina Bancos[2,4]

- **Adequate dexamethasone concentrations (≥0.1 mcg/dL)**
  - 97.6% volunteers
  - 96.3% patients
- **False positive post-DST total cortisol (>1.8 mcg/dL), only if optimal dexamethasone concentrations:**
  - Volunteers: 25.5% of women volunteers on OCP
  - Patients: only in the range of 1.8 and 5 mcg/dL
  - OCP use was the only factor associated with false positive results

MAYO CLINIC JCEM 2021, PMID: 34648626

Diagnosis of MACS (summary)

- 1mg dexamethasone suppression test
  - Dexamethasone concentrations(if concerned about compliance/absorption)
  - Free cortisol (if on OCP)
- ACTH/DHEAS
  - Helpful to assess for severity of MACS
  - If available → avoid 1mgDST?
- Repeat DST
  - if dexamethasone concentrations were low/undetectable
  - 8 mg DST
- Other tests: not likely to be helpful
  - 24h urine cortisol: usually normal
  - Midnight salivary cortisol – frequently normal

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Annals of Internal Medicine REVIEW

Natural History of Adrenal Incidentalomas With and Without Mild Autonomous Cortisol Excess

A Systematic Review and Meta-analysis

Yasir S. Elhassan, MBBS; Fares Alahdab, MD; Alessandro Prete, MD; Danae A. Delivanis, MD, PhD; Aakanksha Khanna, MD; Larry Prokop, MLS; Mohammad H. Murad, MD, MPH; Michael W. O'Reilly, PhD; Wiebke Arlt, MD, DSc; and Irina Bancos, MD

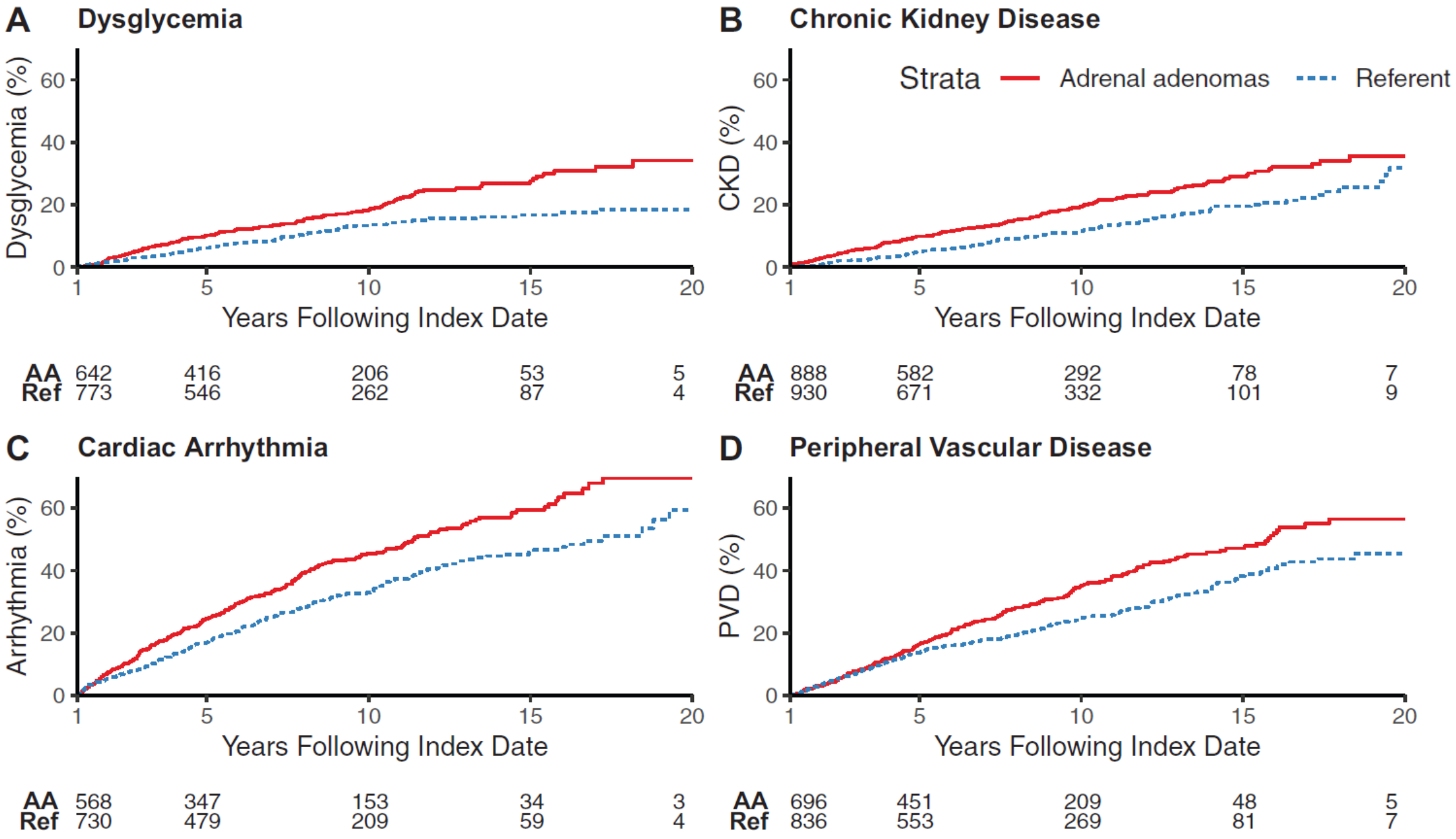
- **32** studies
- **4121** patients with NFAT or MACS
- 61.5% women
- mean age 60.2 years
- mean follow-up **50.2 months**
- **Heterogeneous** definitions of MACS

MACS: increased CV risk and mortality

- **New or worsening hypertension**
  - NFAT:10% vs MACS:**22%**
- **New or worsening obesity**
  - NFAT:9% vs MACS:**21%**
- **New or worsening dyslipidemia**
  - NFAT:11% vs MACS:**12.5%**
- **New or worsening DM2**
  - NFAT:5% vs MACS:**14%**

- **Cardiovascular events**
  - Prevalence
    - NFAT – 8.7%
    - MACS – 6.3%
  - **Incidence**
    - **NFAT – 6.4%**
    - **MACS – 15.5%**
- **Mortality?**
  - Discrepant data, variable follow up
  - Increased with increasing DST

Elhassan Y, Annals of internal medicine 2019, Debono et al JCEM 2014, Di Dalmazi et al, 2014, Lancet, Zhang JCEM 2021



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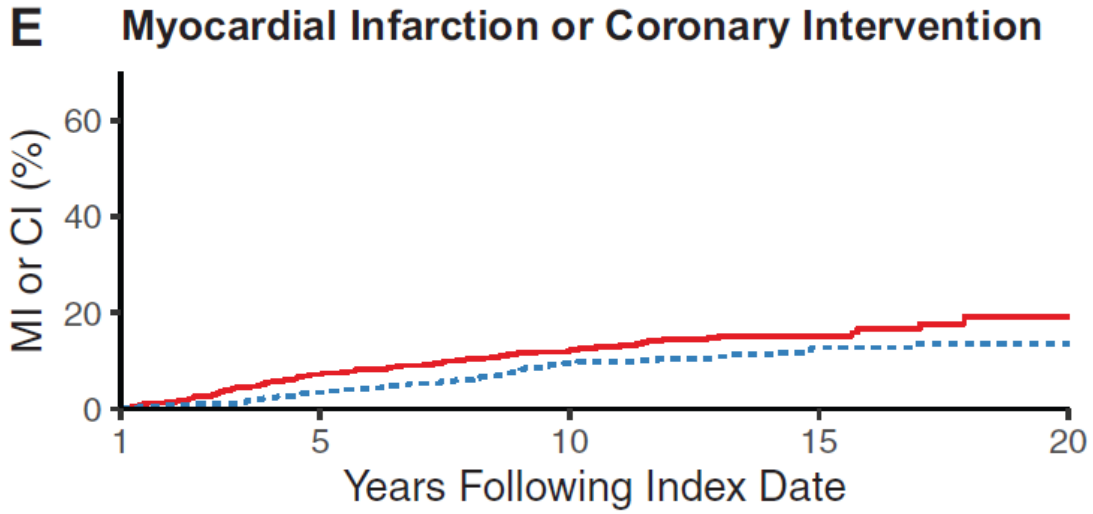
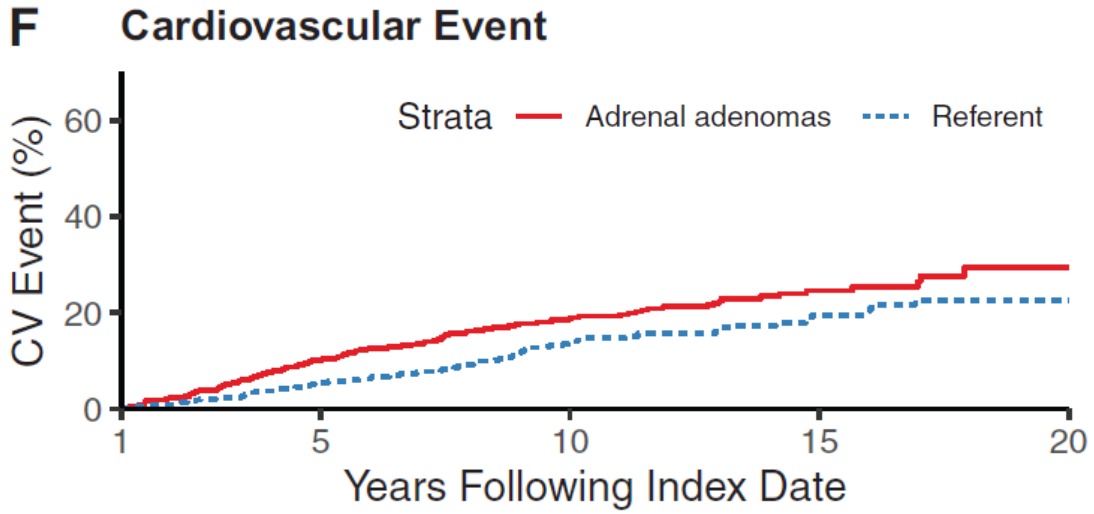
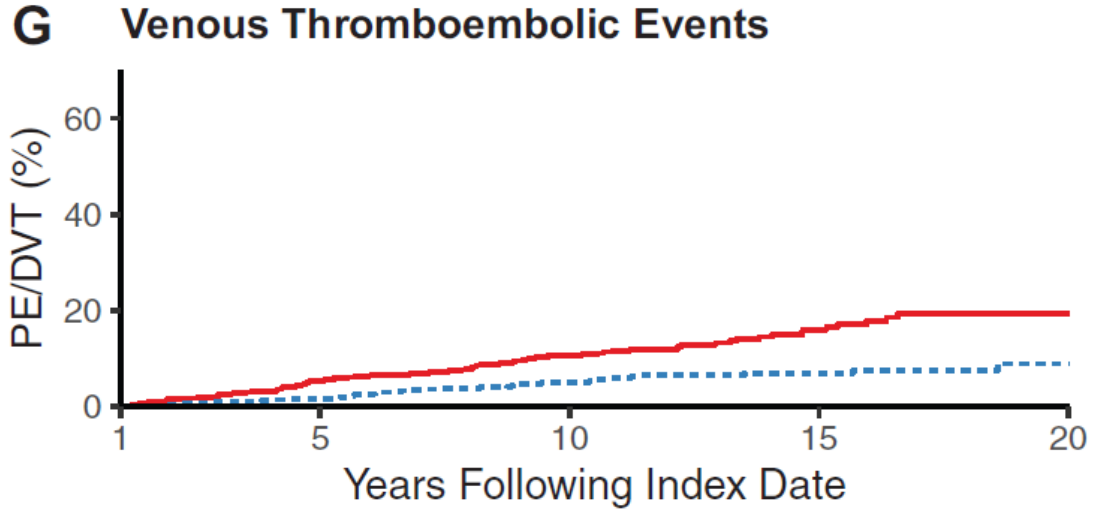
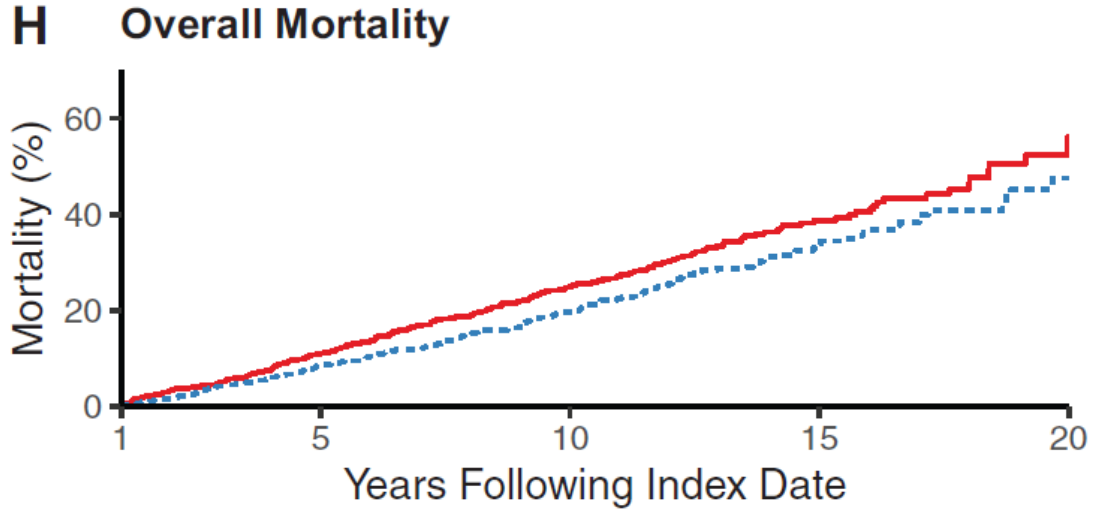
Zhang JCEM 2021









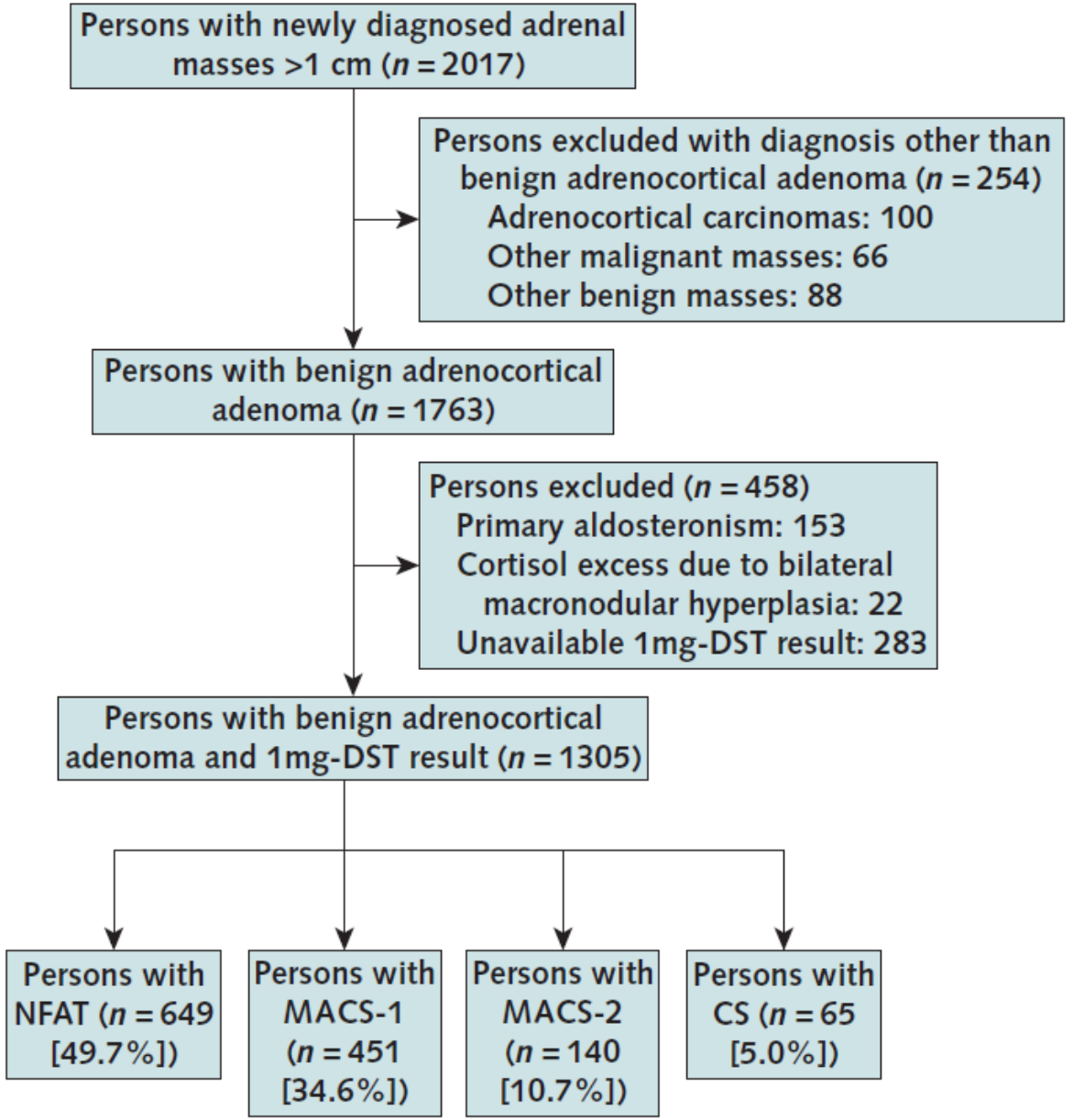
Annals of Internal Medicine

ORIGINAL RESEARCH

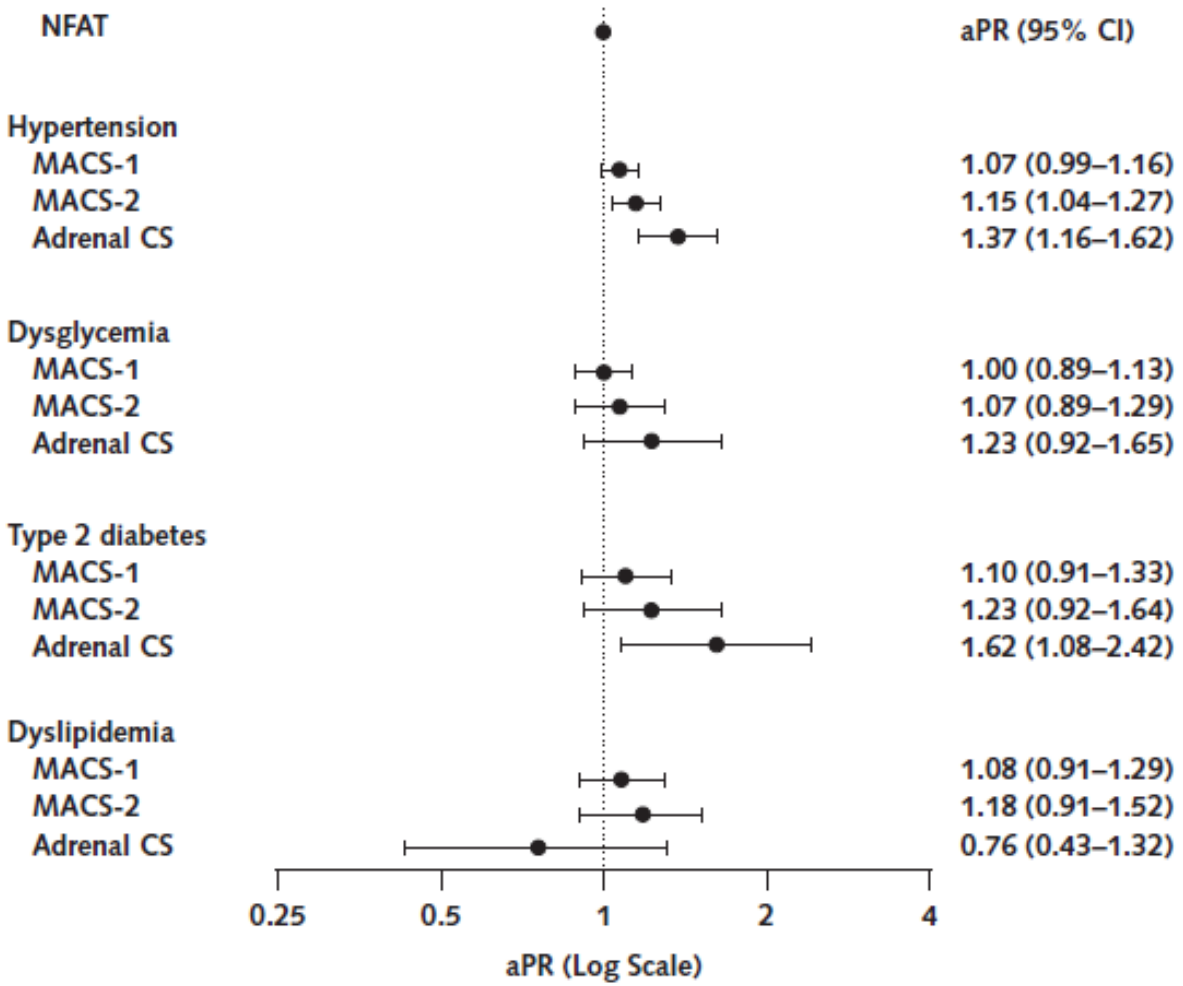
Cardiometabolic Disease Burden and Steroid Excretion in Benign Adrenal Tumors

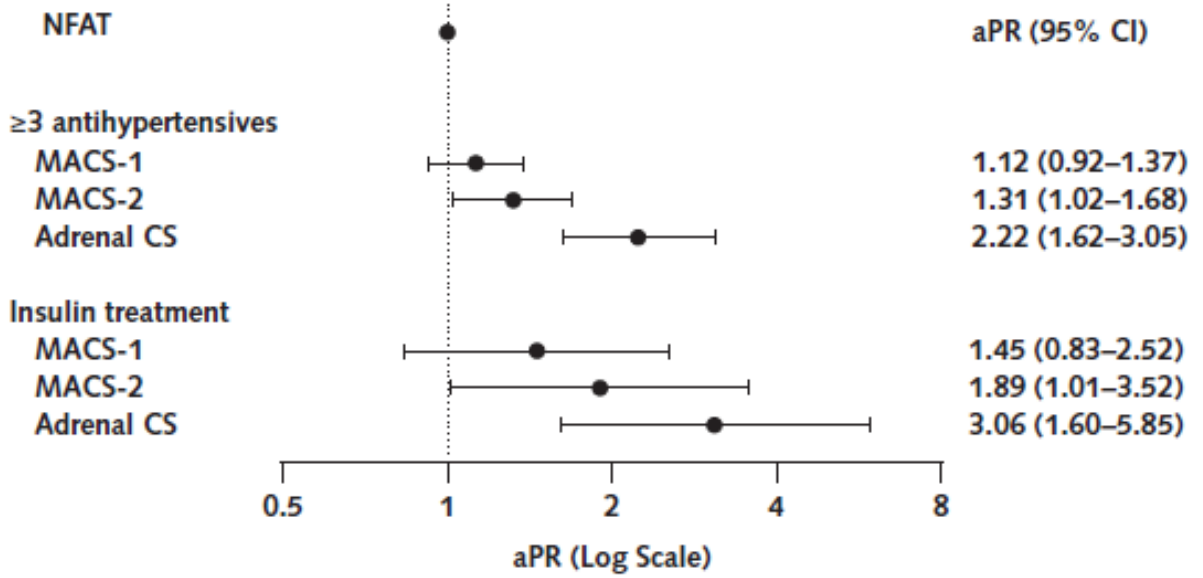
A Cross-Sectional Multicenter Study

- Considerations:
  - Comparison to NFAT (no controls)
  - Cortisol assays varied (accuracy of MACS-1 vs MACS-2 designation)



Hypertension and Diabetes: risk is proportional to degree of cortisol autonomy/excess





Prete et al, Annals of Internal Medicine, 2022

Fractures in MACS

Study	Design	MACS	LS BMD z-score	FN BMD z-score	Prevalence of vertebral fractures (%)	Criteria of MACS diagnosis
Chiodini et al 2004	Cross-sectional	21	-0.78 ± 0.29	NA	66.6	1mg DST >3
Chiodini et al 2009	Cross-sectional	85	-1.04 ± 1.84	-0.37± 1.06	70.6	1mg DST >3
Chiodini 2009	Cross-sectional	22	-0.73 ± 1.43	-0.63 ± 1.01	72.7	1mg DST >3
Eller-Vainicher et al 2012	Cross-sectional	34	-0.31 ± 1.17	-0.29 ± 0.91	82.4	1mg DST >3
Morelli et al 2013	Cross-sectional	41	-0.66 ± 0.45	-0.6 ± 0.3	46.3	1mg DST >3
Morelli et al 2016	Cross-sectional Longitudinal	216	NA	NA	65.7	1mg DST >2

Athimulam S et al, Curr Opin Endocrinol Diabetes Obes, 2019

Fractures in adenomas

Risk of bone fractures after the diagnosis of adrenal adenomas: a population-based cohort study

- Population based study, 1995-2017
- Population: 1004 patients with adenoma and 1004 referent subjects
- Overt hormone excess was excluded
- Duration of follow up: median of 6.8 years (0-22)
- Prevalence of fractures: patients vs referent subjects
  - Overall: 48% vs 41% (p=0.003)
  - Vertebral: 6.4% vs 3.6% (p=0.004)
  - Combined osteoporotic site: 17% vs 13% (p=0.04)

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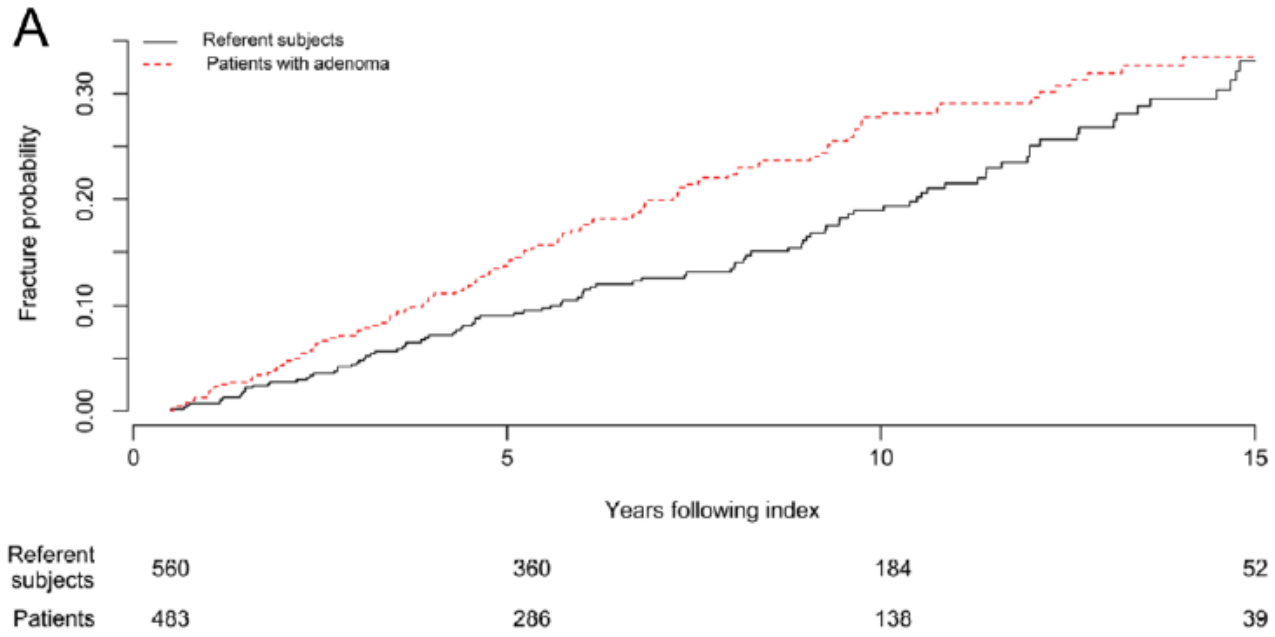
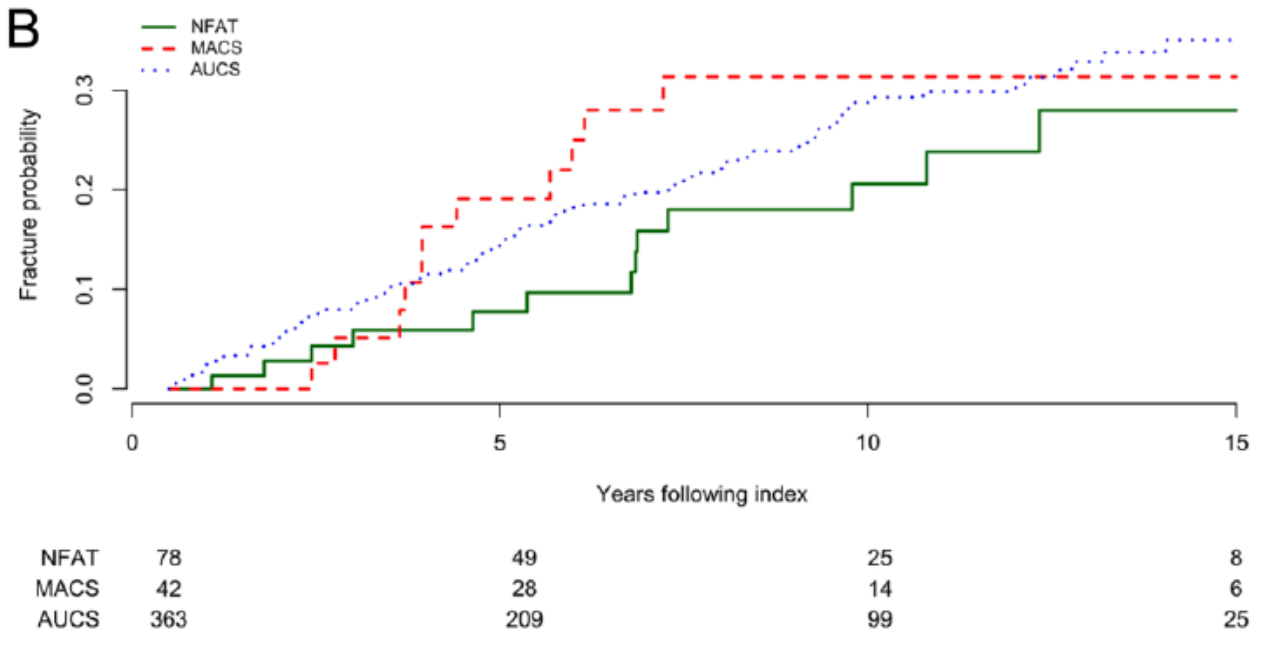
Li et al, EJE, 2021

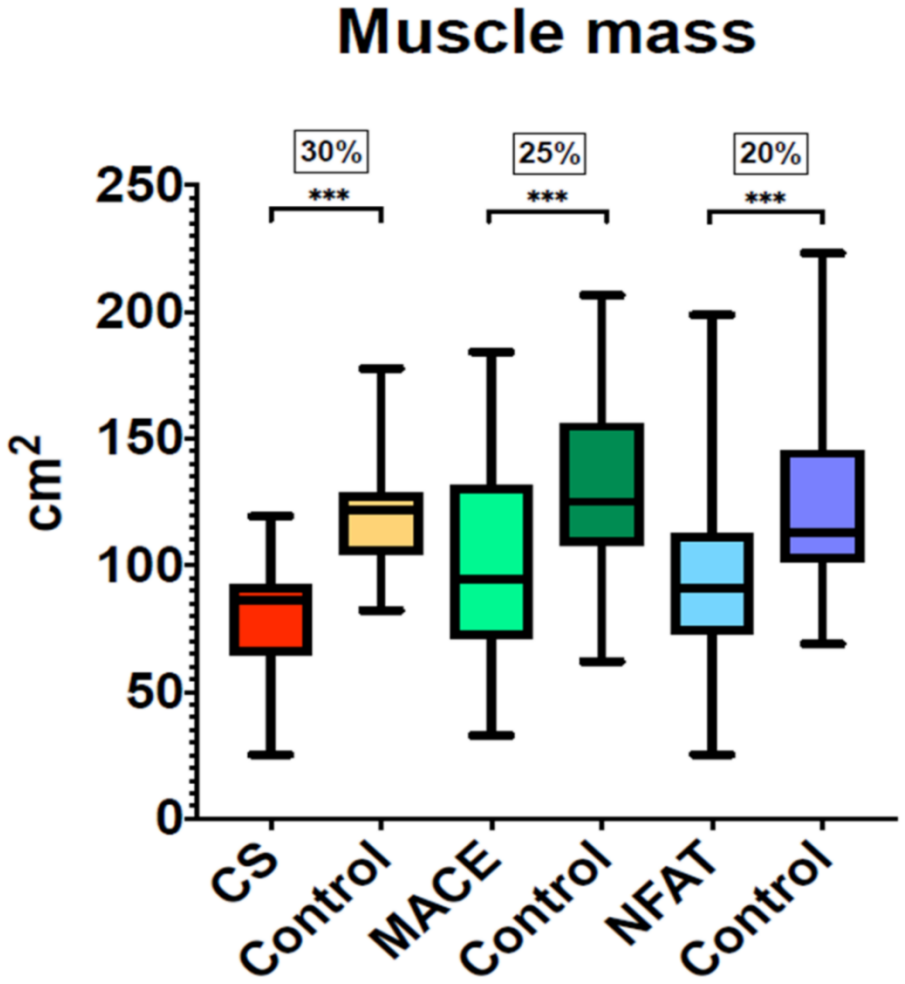
Fractures in adenomas

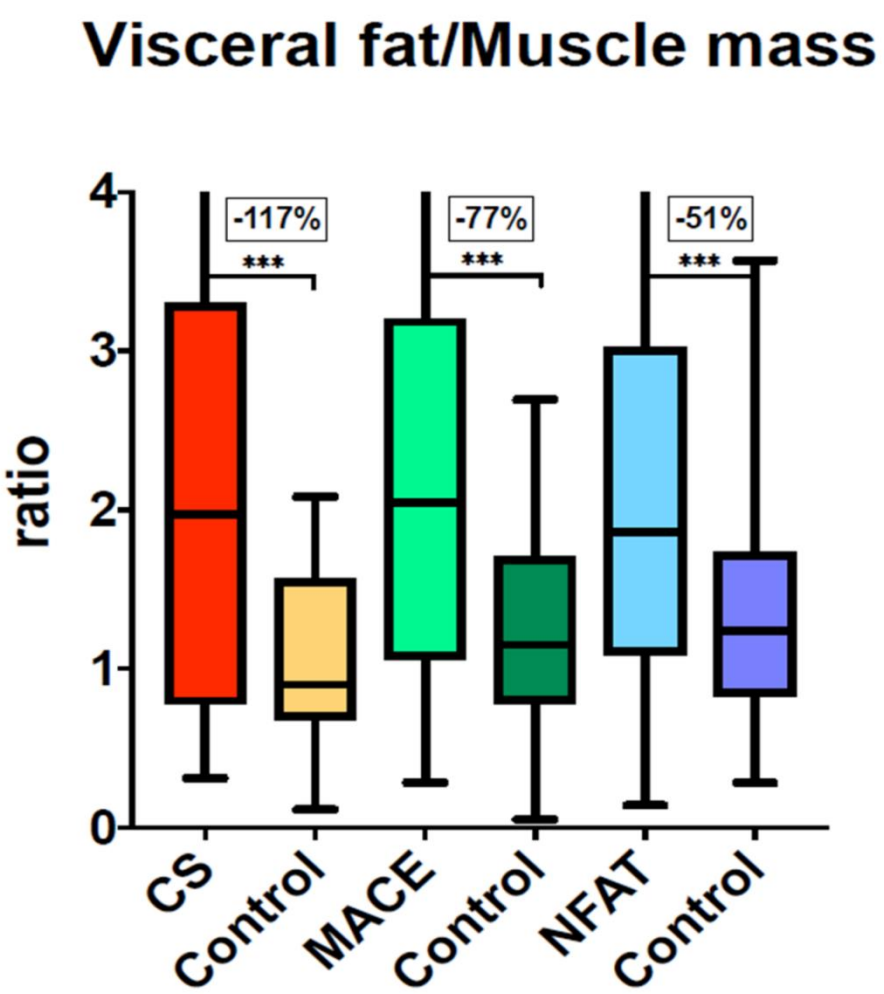
- Incidence of fractures:
  - Overall: Hazard ratio of **1.27** (95%CI 1.07-1.52)
  - No significant differences between subgroups (small sample size)
    - 10 year estimate of cumulative incidence of fracture
      - **30% MACS**
      - **19% NFAT**





Abnormal body composition in MACS





Delivanis D EJE 2021

Patients with MACS “age” quicker: frailty

Frailty in Patients With Mild Autonomous Cortisol Secretion is Higher Than in Patients with Nonfunctioning Adrenal Tumors

Sumitabh Singh, Elizabeth J Atkinson, Sara J Achenbach, Nathan LeBrasseur, Irina Bancos ✉

The Journal of Clinical Endocrinology & Metabolism, Volume 105, Issue 9, September 2020, dgaa410,
https://doi.org/10.1210/clinem/dgaa410
Published: 06 July 2020 **Article history** ▾

- Retrospective study, 2013-2018
- Population:

✓168 patients with MACS (1 mg DST cortisol 1.9-5.0 mcg/dl)

✓275 with NFAT (1 mg DST cortisol ≤1.8 mcg/dl)

- Frailty index (range: 0-1) using a 47-variable deficit model

Frail: (age and sex adjusted)

- MACS: **24%**
- NFAT: **18%**

Median age:

- MACS: 66 (30-91) years
- NFAT: 59 (21-84) years

Prevalence of deficits in patients with MACS and NFAT			
	DST<1.9 µg /dl N=275	**DST=1.9-5.0 µg /dl N=168**	P value
Symptoms			
Weakness in arms/legs	10.8%	20.7%	0.006
Fall easily	2.3%	6.9%	0.02
Sleep difficulty	14.9%	26.3%	0.005
Activity of Daily living			
Climbing two flights of stairs “No, can’t do at all” “Yes, with difficulty” “Yes, with no difficulty”	 8.6% 27.5% 63.9%	 14.7% 30.2% 55.1%	0.07

Singh S, JCEM, 2020

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- Definition of MACS
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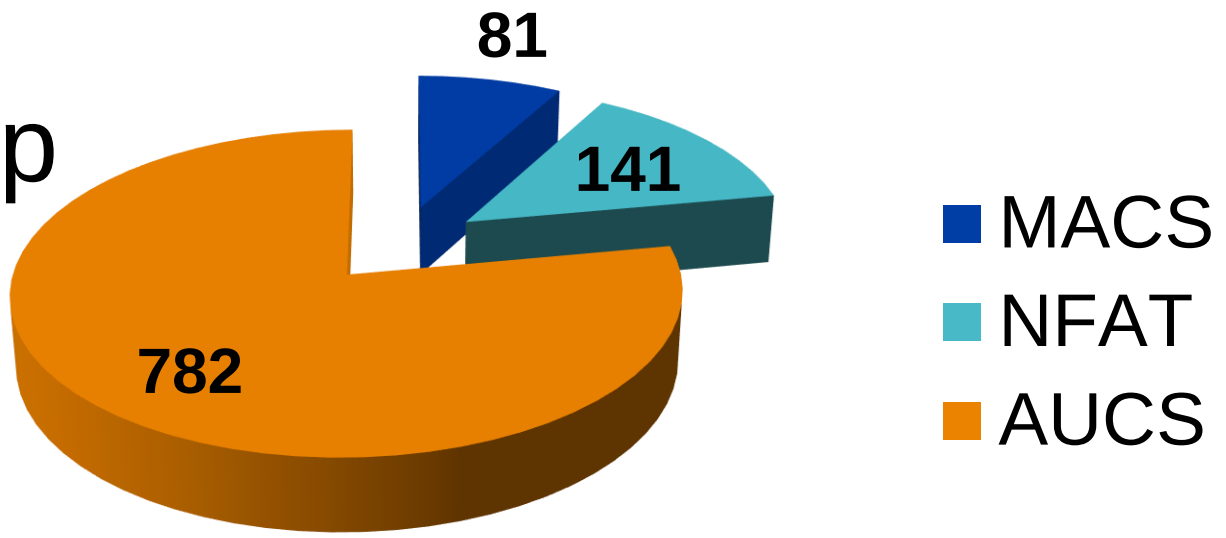
- **Management of MACS**

What are the options in patient diagnosed with MACS

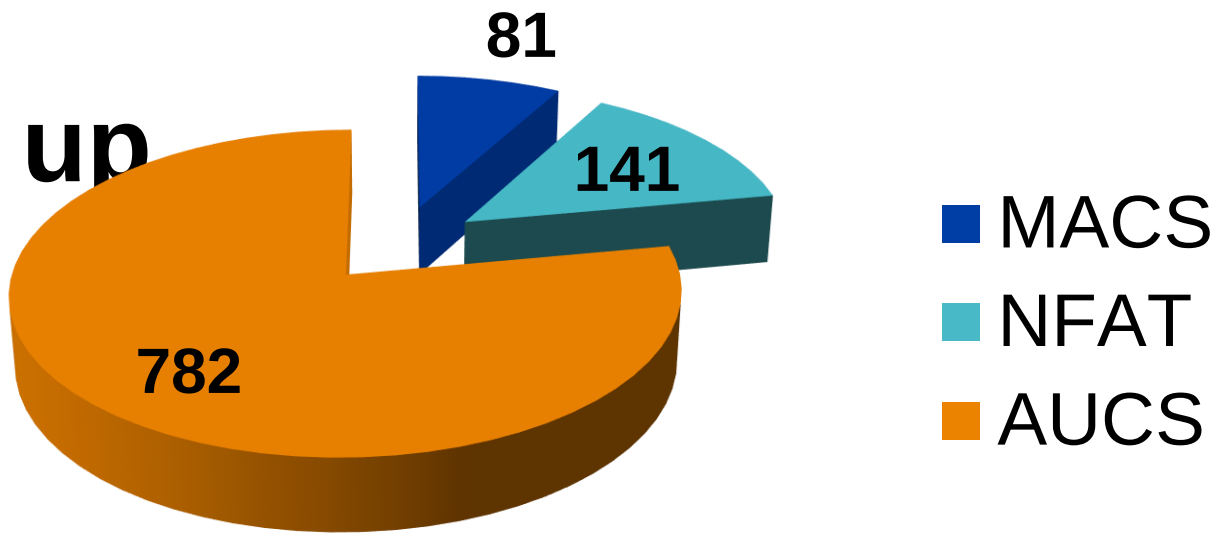
- Adrenalectomy
- Conservative follow up
- Medical therapy



Improve diagnosis of MACS!

What are the options in patient diagnosed with MACS

- Adrenalectomy
- **Conservative follow up**
- Medical therapy



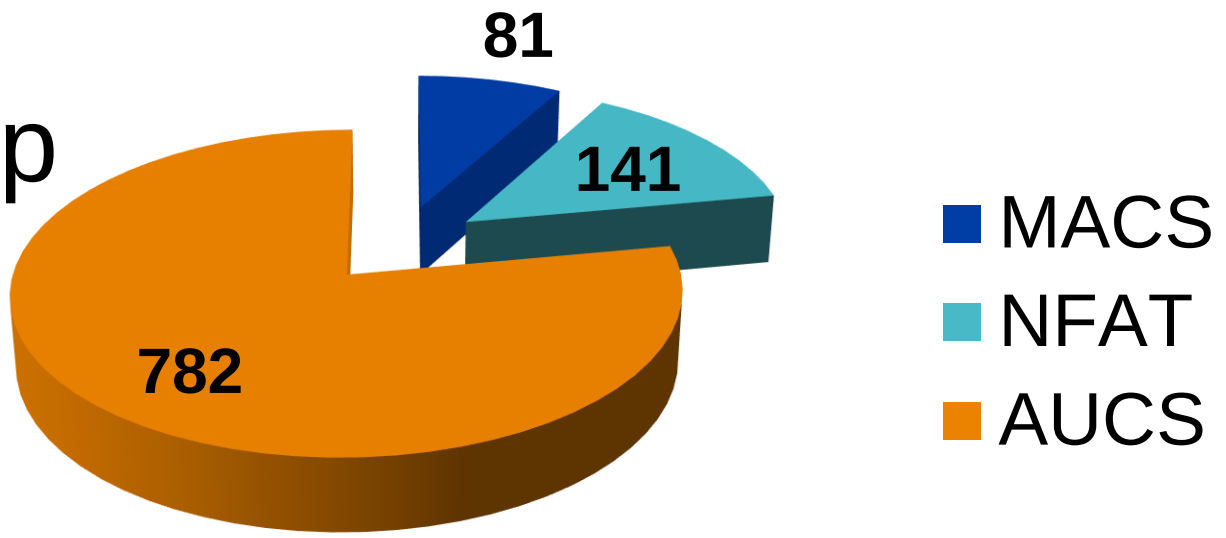
Improve diagnosis of MACS!

Follow up of MACS

- **Patients with MACS are at risk for**
  - Worsening of cardiovascular comorbidities
  - Abnormal body composition
  - New cardiovascular events
  - New fractures
  - Higher frailty (accelerated aging)
  - Higher mortality

What are the options in patient diagnosed with MACS

- Adrenalectomy
- Conservative follow up
- **Medical therapy**



Improve diagnosis of MACS!

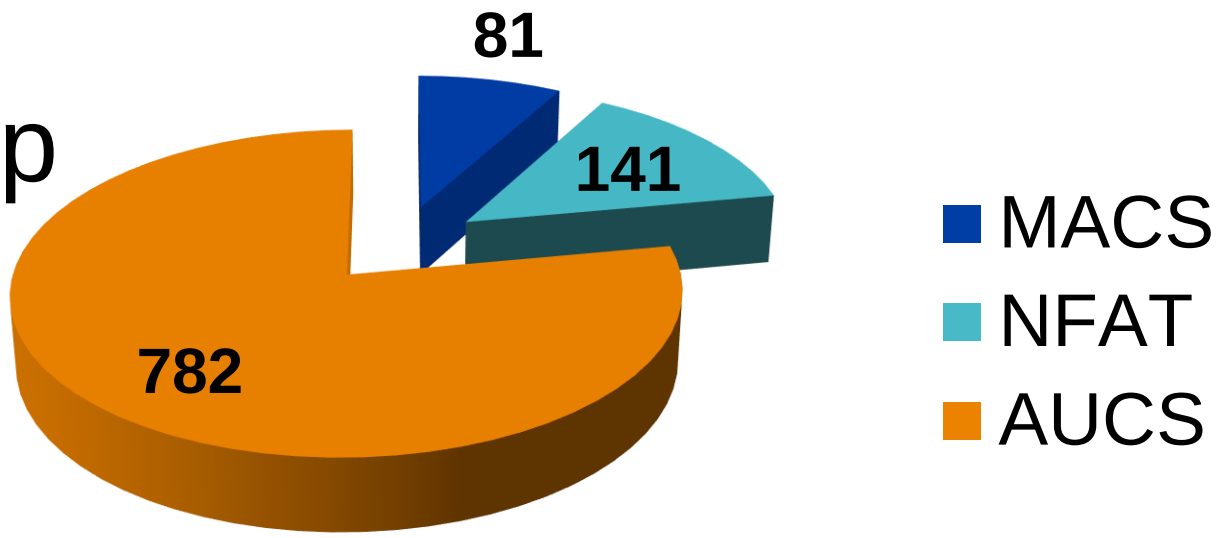
What are the options in patient diagnosed with MACS

- Adrenalectomy
- Conservative follow up
- **Medical therapy**

- Expensive/unaffordable
- Side effects
- Require intensive monitoring
- May play a role to understand the effect of MACS on comorbidities (short term use)
- May play a role in bilateral adrenal disease
- More high quality data are needed

What are the options in patient diagnosed with MACS

- **Adrenalectomy**
- Conservative follow up
- Medical therapy



Improve diagnosis of MACS!

THERAPY OF ENDOCRINE DISEASE

Improvement of cardiovascular risk factors after adrenalectomy in patients with adrenal tumors and subclinical Cushing's syndrome: a systematic review and meta-analysis

Irina Bancos[1], Fares Alahdab[2], Rachel K Crowley[3], Vasileios Chortis[4,5], Danae A Delivanis[1], Dana Erickson[1], Neena Natt[1], Massimo Terzolo[6], Wiebke Arlt[4,5], William F Young Jr[1] and M Hassan Murad[2]

- What is the benefit of adrenalectomy?
  - **23 studies reporting - 584 patients with MACS**
  - Outcomes:
    - Categorical: Hypertension, DM2, Obesity, Dyslipidemia
    - Continuous: SBP/DBP, BMI, HbA1C, Lipids
  - Studies used different definitions of MACS

Improvement of cardiovascular risk factors after adrenalectomy in patients with adrenal tumors and subclinical Cushing's syndrome: a systematic review and meta-analysis

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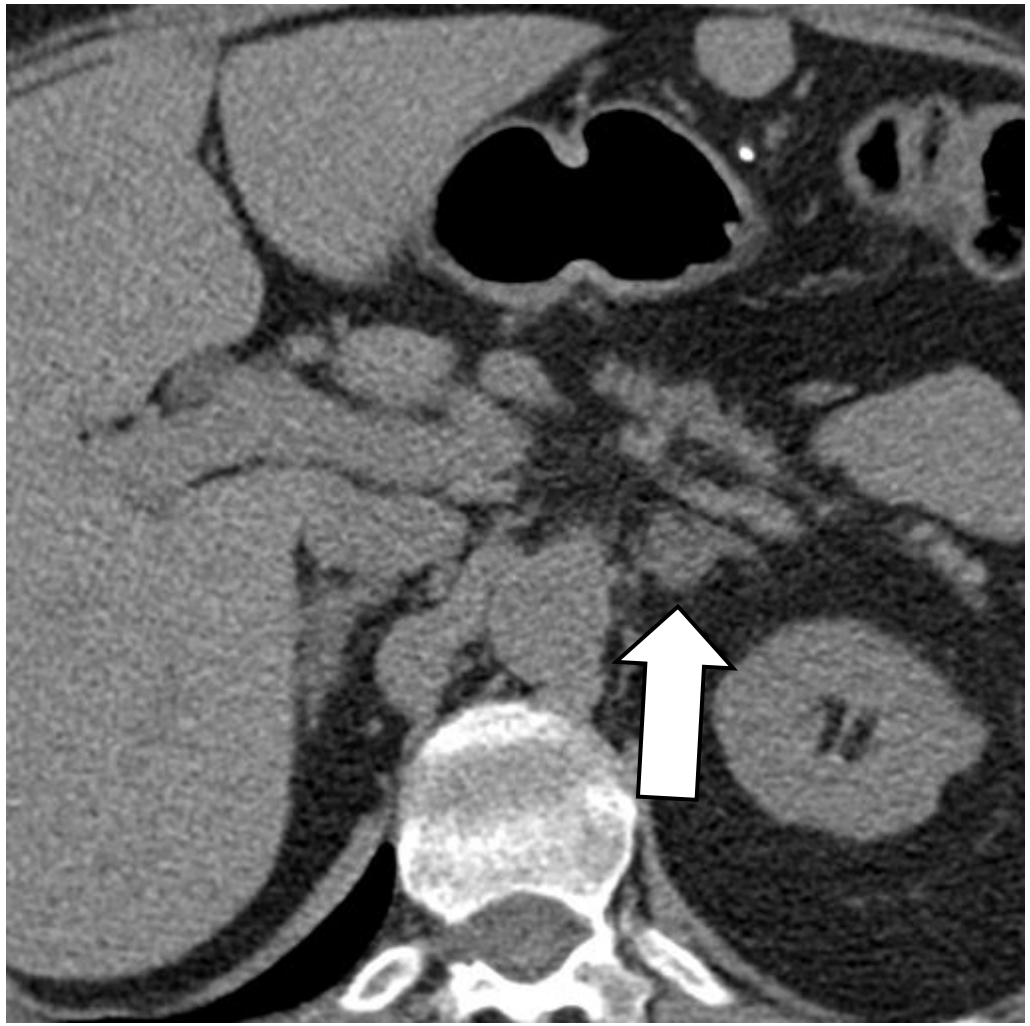
Outcome	Number of studies	% improved	Difference in means	CI 95% lower limit	CI 95% upper limit	I^2 (%)
Hypertension ($n=265$)	21	60.5%		50%	71%	72
Diabetes mellitus type 2 ($n=120$)	20	51.5%		39%	64%	59
Dyslipidemia ($n=102$)	13	24%		13%	35.5%	58
Obesity ($n=128$)	16	45%		32%	57%	64
Systolic blood pressure (mmHg)	8		−12.72	−18.33	−7.1	61
Diastolic blood pressure (mmHg)	7		−9.34	−14.83	−3.85	76
BMI (kg/m^2)	7		−1.96	−3.32	−0.59	68
Fasting glucose (mmol/L)	4		−7.99	−13.9	−2.09	27
HbA1c (SMD)*	3		−0.96	−1.43	−0.49	53
LDL cholesterol (mg/dL)	2		−0.12	−37.7	37.5	53
HDL cholesterol (mg/dL)	3		2.9	−3.4	9.2	53
Triglycerides (mg/dL)	3		−23	−36.7	−9.2	0

Summary

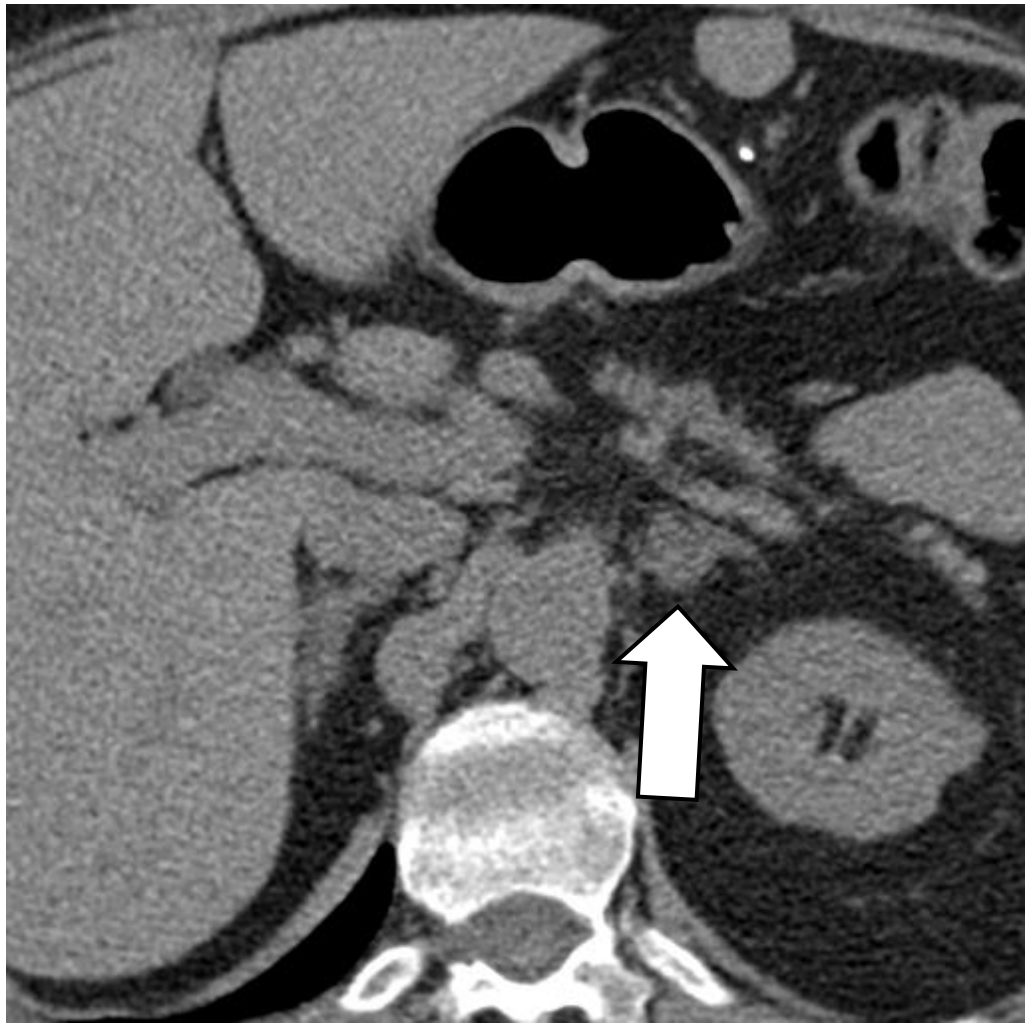
- **Adrenalectomy:**
  - Improvement in cardiovascular risk factors **is variable**
- **No adrenalectomy**:
  - As a group patients with MACS worsen their cardiovascular risk factors
  - Individually, contribution of glucocorticoid excess / autonomy to development/progression of comorbidities is difficult to estimate
  - Role of intensive management of comorbidities, and proactive screening?



Coronal images from an unenhanced and contrast enhanced CT scan showed a lipid rich adrenal mass of 2.2 x 1.4 cm left adrenal mass (Unenhanced HU of 6)

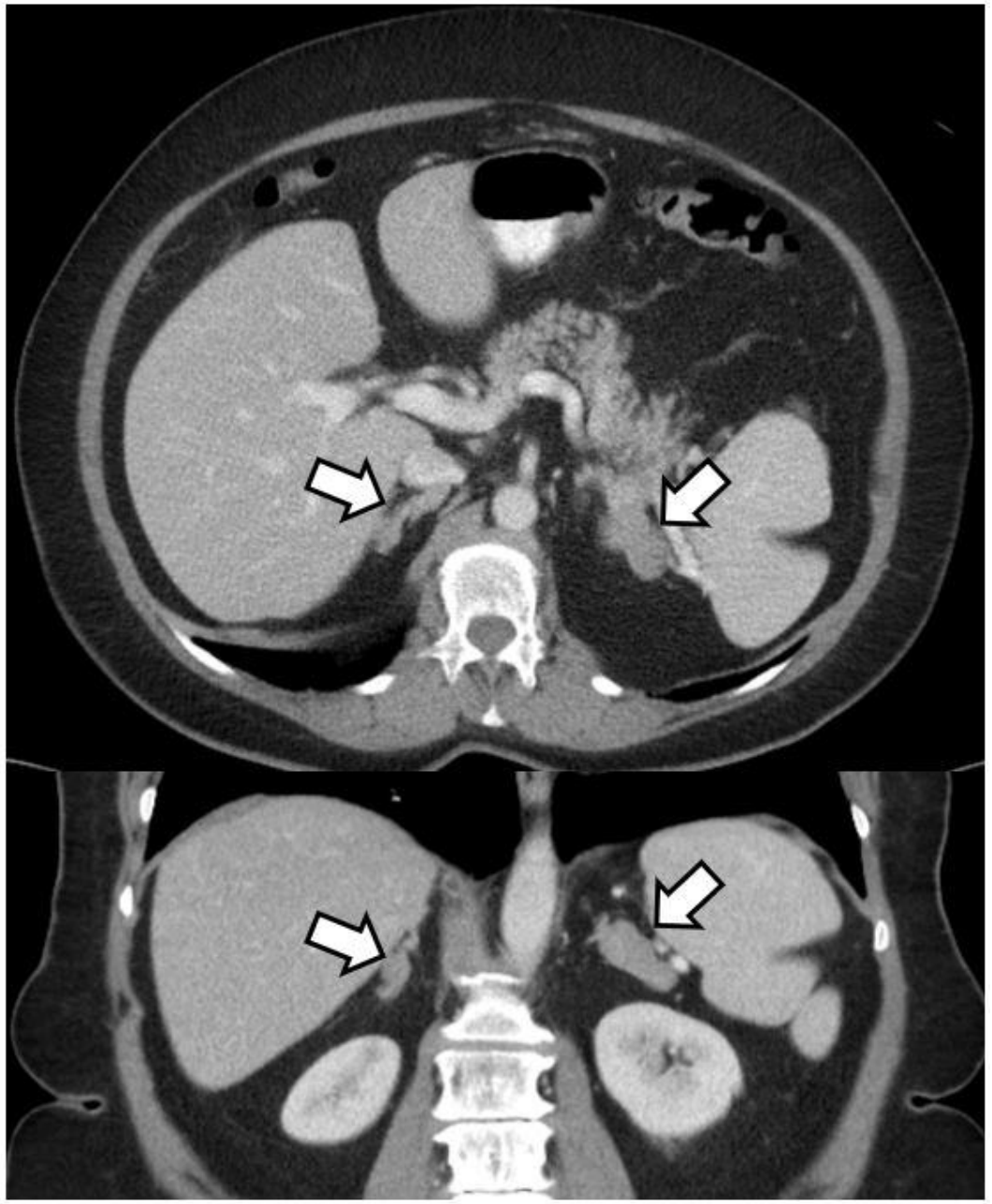
- 54-yr-old woman
- Weight gain of 50 pounds over 5-7 years
- Prediabetes (HbA1C=6%, not on medications)
- Hypertension (metoprolol tartrate, nifedipine)
- Osteoporosis (2 years ago)
- Incidental discovery of adrenal mass 2 months prior
- Physical exam: BMI 39.8 kg/m^2, BP 138/86 mmHg, no features of Cushing syndrome.

Biochemical Testing	**Result**	**Ref. range**
1-mg overnight DST	**2.3**	<1.8
ACTH, pg/mL	**<5**	7.2-63
DHEA-S, mcg/dL	**26**	15-200
Aldosterone, ng/dL	8	<21
Plasma renin activity, ng/mL/h	4.1	2.9-10.8
Urine free cortisol, mcg/24h	7.5	3.5-45



Coronal images from an unenhanced and contrast enhanced CT scan showed a lipid rich adrenal mass of 2.2 x 1.4 cm left adrenal mass (Unenhanced HU of 6)

- Unilateral adrenalectomy
- Postoperative adrenal insufficiency: postop day 1 cortisol of 5.7 mcg/dL
- Hydrocortisone therapy
- Significant glucocorticoid withdrawal necessitating hydrocortisone adjustment
- 6 months later:
  - HPA axis recovery → hydrocortisone stopped
  - 15 pounds weight loss
  - Hypertension improved
  - HbA1C 6% → 5.8%



- 66-yr-old woman
- Weight gain of 30 pounds over 1 year
- Dyslipidemia (simvastatin)
- Hypertension (4 medications), hypokalemia
- Incidental discovery of bilateral adrenal masses
- Physical exam: BMI 39.6 kg/m^2, BP 142/72 mmHg, no features of Cushing syndrome.

Biochemical Testing	Result	Ref.range
1 mg DST, mcg/dL	**4.7**	<1.8
8 mg DST, mcg/dL	**3.2**	<1
ACTH, pg/mL	**<5**	7.2-63
DHEA-S, mcg/dL	**26**	<15-157
Aldosterone, ng/dL	**11, 13**	<21
Plasma renin activity, ng/mL/h	**<0.6**	2.9-10.8
Urine metanephrines, mcg/24 h	51	<400
Urine normetanephrines, mcg/24h	273	<900
Urine free cortisol, mcg/24h	8	3.5-45

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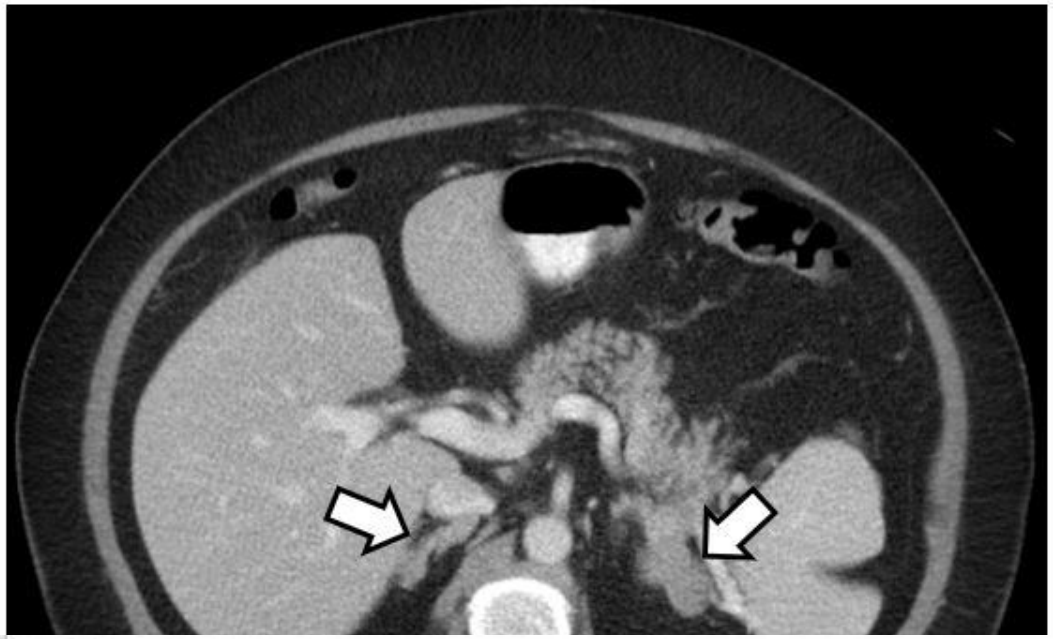
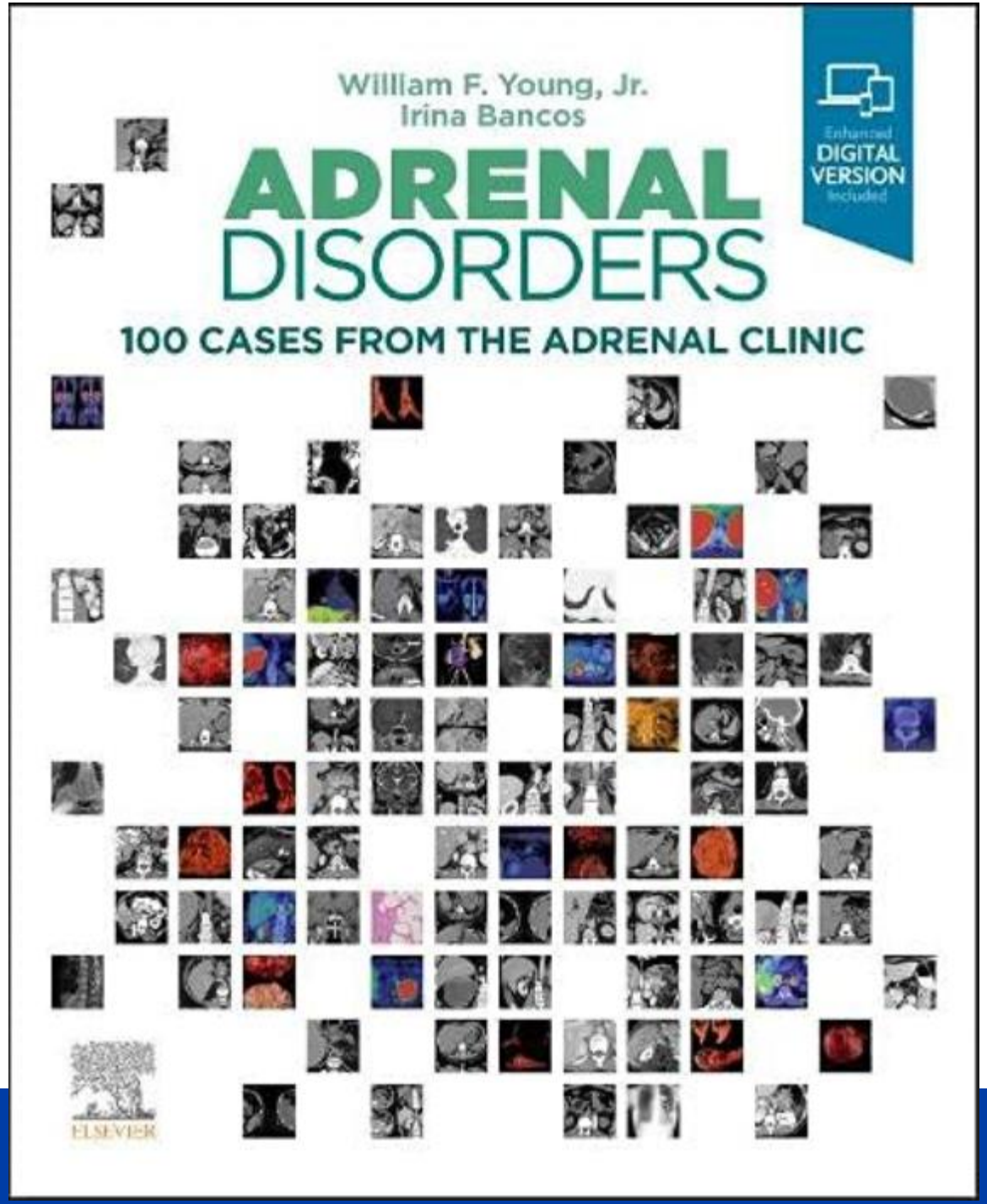


- Bilateral adrenalectomy
- Permanent primary adrenal insufficiency
- Fludrocortisone +Hydrocortisone
- Hypokalemia – resolved
- Hypertension – improved, decreased medications from 4 to 2 medications (30 months follow up)

Outline

- Definition of MACS — **1 mg DST >1.8 mcg/dL + no CS**
- Prevalence of MACS — **30-50% of adrenal adenomas**
- Diagnosis of MACS — **1 mg DST, low ACTH/DHEAS**
- Consequences of MACS — **Cardiovascular, bone, frailty**
- Management of MACS — **Adrenalectomy: adrenal insufficiency, GWS**

  Conservative: management of comorbidities



Thank you!

MAYO CLINIC

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- Several cases presented are also included in the “Adrenal Disorders: 100 cases from the adrenal clinic”
- Any profit from the book → 100% to adrenal research at Mayo Clinic