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Endogenous Hypercortisolism (Cushing from A to Z) Epidemiology, Classification and Clinical Presentation

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Cushing's Syndrome - October 2008

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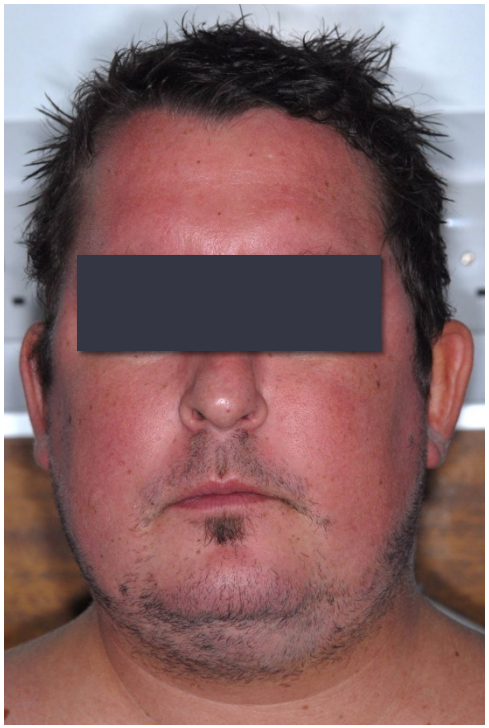

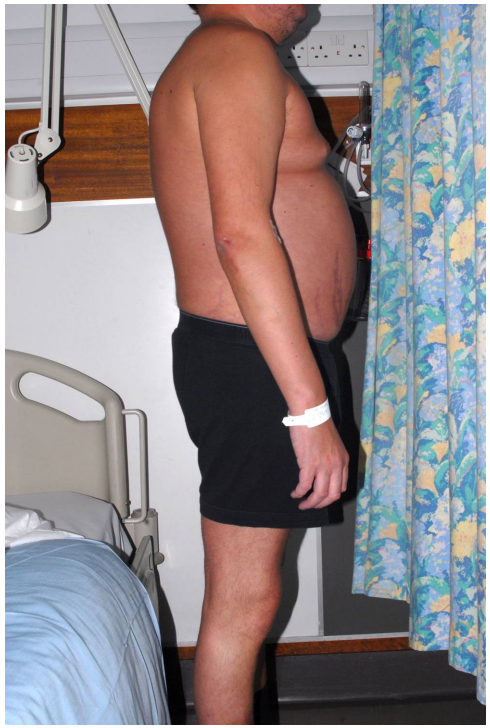

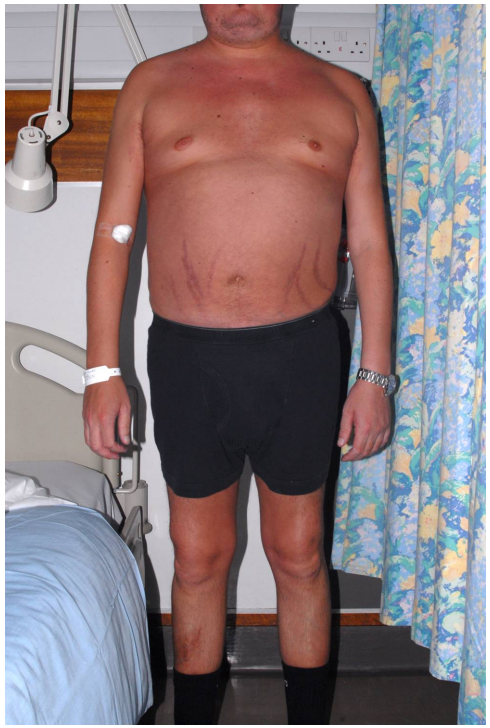

- All biochemistry consistent with Cushing's disease
- No history of cyclical disease, MRI – 3mm microadenoma
- BIPSS – positive gradient
- Transsphenoidal Surgery November 2008 – warned likely to feel worse for several months if successful

Slide Courtesy of John Newell-Price

Patient Progress

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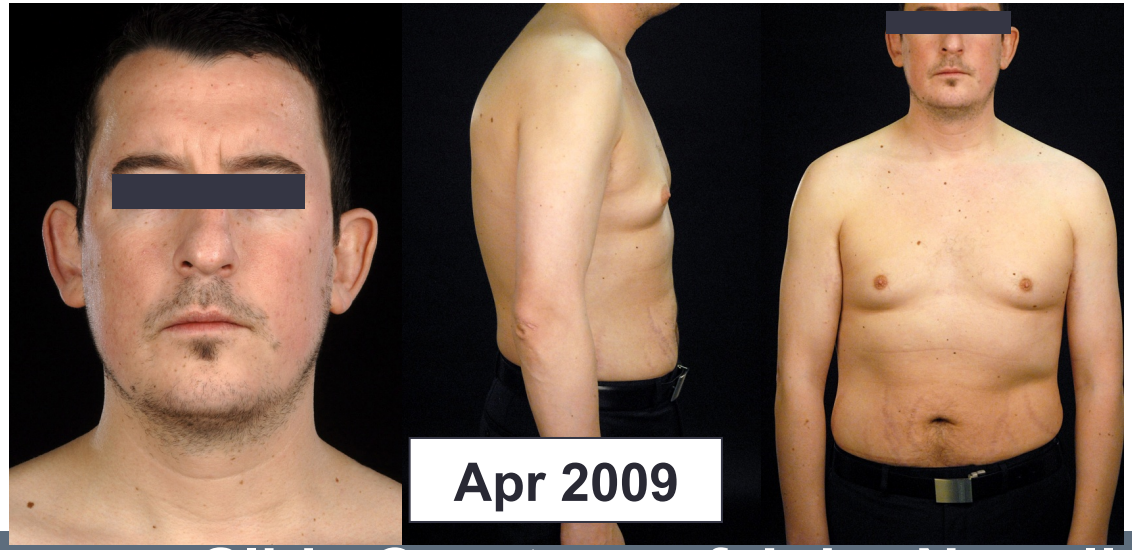
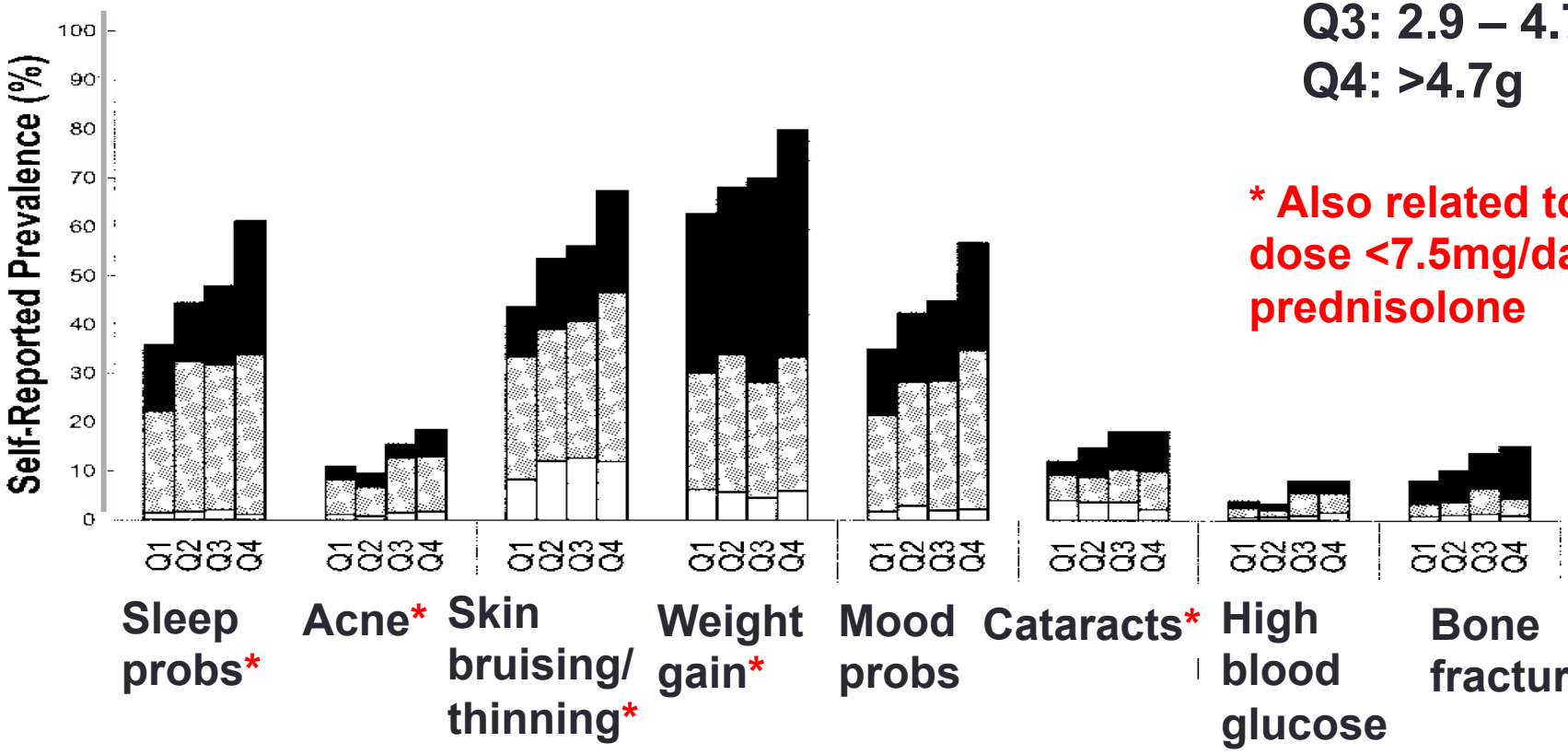


Slide Courtesy of John Newell-Price

Epidemiology: Exogenous Cushing's in patients on Glucocorticoids

N = 2167 – SE were common affecting at least 90% of subjects

Q1: <1.7g
Q2: 1.7 – 2.8g
Q3: 2.9 – 4.7g
Q4: >4.7g



*** Also related to low dose <7.5mg/day prednisolone**

Curtis et al Arthritis and Rheumatism 2006 55: 420 - 426

Incidence & Prevalence of Endogenous Cushing's Syndrome

Etxabe 1994 (49 patients over 18 years)

- Incidence: 2.4 / million.yr
- Prevalence: 39 / million
- F:M – 15:1

Lindholm 2001 (Incidence 2.3 / million.yr)

- Cushing's disease: N=99; 1.2 – 1.7 / million.yr
- Adrenal adenoma: N=37; 0.6 / million.yr
- Adrenal adenocarcinoma: N=11; 0.2 / million.yr
- Ectopic ACTH: N=6; 0.1 / million.yr

Etxabe Clinical Endo 1994 40: 479 – 484; Lindholm JCEM 2001 86: 117 - 123

Other Epidemiological Data – Sex, Age at Surgery and SMR

	N	M/F	Age (range) at surgery	No of deaths	SMR (95% CI)
Cured post TSS	45	14/31	38.5 (15 – 69.5)	1	0.31 (0.01 – 1.72)
Unilateral adrenalectomy	25	3/22	35.8 (3.7 – 77.7)	3	3.95 (0.81 - 11.5)
Not cured at initial pituitary surgery	20	7/13	46.4 (25.2 – 63.6)	6	5.06 (1.86 - 11.0)

Lindholm JCEM 2001 86: 117 - 123

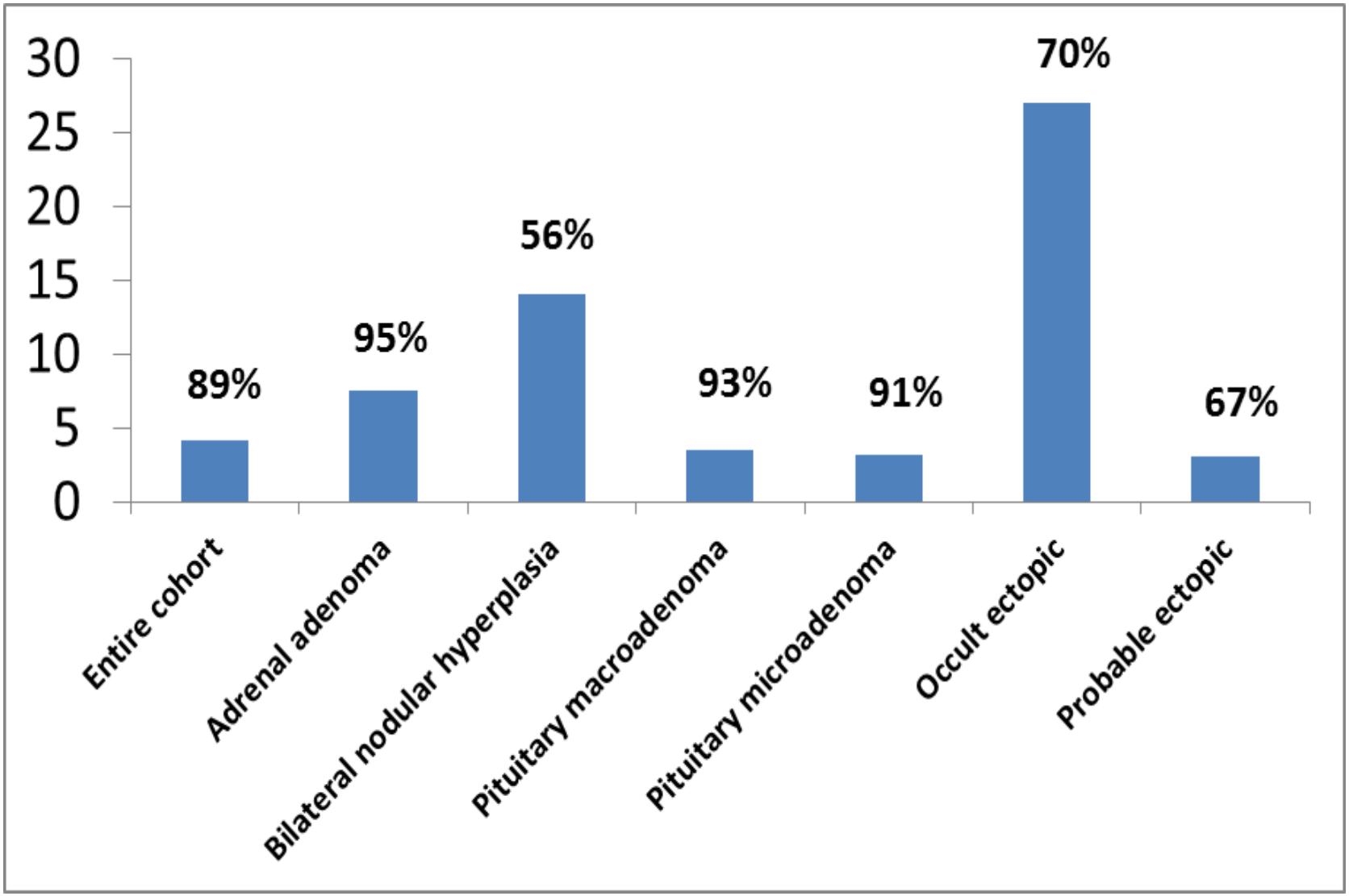
Other Epidemiological Data – Duration of symptoms prior to diagnosis and follow up

Prevalence in New Zealand 79/million; Incidence 1.8/million/year

	Entire cohort n=253	Adrenal adenoma n=37	Bilateral nodular hyperplasia n=9	Pituitary macro adenoma n=30	Pituitary micro adenoma n=158	Occult ectopic n=10	Probable ectopic n=9
Duration of symptoms Years (range)	2 (0 – 21)	0.1 (0 – 21)	0.2 (0 – 10)	0.2 (0 – 17)	0.2 (0 – 20)	0.1 (0 – 3)	0.1 (0 – 3)
Duration of follow up Years (range)	6.4 (0 – 46)	3.1 (0 – 18)	5.7 (1.5 – 39)	6.9 (0 – 30)	7.5 (0 – 46)	6.8 (0 – 28)	8.1 (0 – 16)

Bolland Clinical Endo 2011 75: 436 - 442

SMR in relation to biochemical cure



Bolland Clinical Endo 2011 75: 436 - 442

Incidence of Cushing's syndrome in special cohorts

- Type 2 Diabetes Mellitus: 0.7% in 813 patients
  - (Terzolo JCEM 2012)
- Obesity: 0% in 369 patients
  - (Baid JCEM 2009)
- Osteoporosis: 5% in 219 patients
  - (Chiodini Annals Intern Med 2007)
- Hypertension: 2% of 1020 patients
  - (Omura Hypertension Res 2004)
- Adrenal incidentaloma: 1% of elderly patients have autonomous cortisol secretion
  - (Terzolo JCEM 2002)

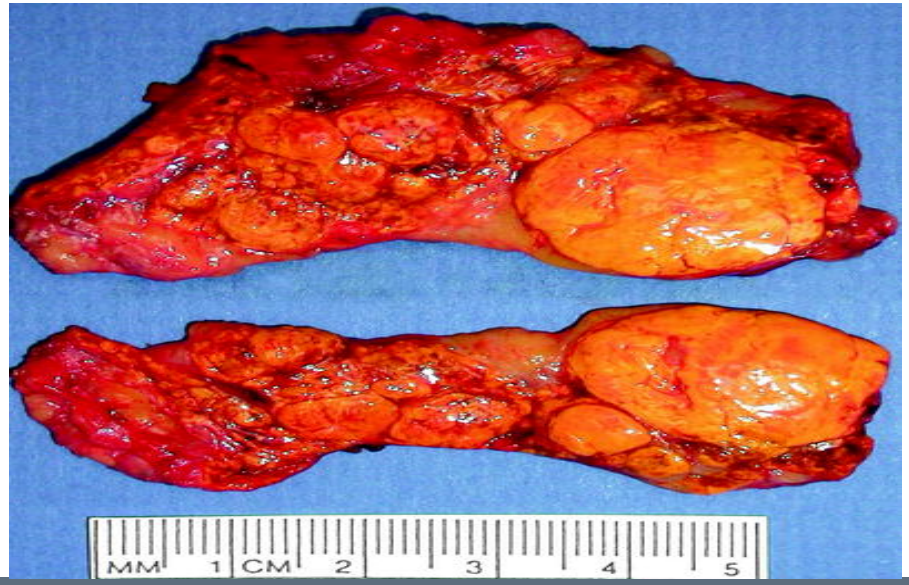
Classification of Cushing's syndrome

Cause of Cushing's syndrome	%	F:M
ACTH-dependent		
Cushing's disease	70%	3.5:1*
Ectopic ACTH syndrome	10%	1:1
Unknown source of ACTH	5%	5:1
ACTH-independent		
Adrenal adenoma	10%	4:1
Adrenal carcinoma	5%	1:1
Macronodular hyperplasia (AIMAH)	<2%	1:1
Primary pigmented nodular adrenal disease	<2%	1:1
McCune Albright syndrome	<2%	1:1

Newell-Price Lancet 2006 367: 1605 - 1617

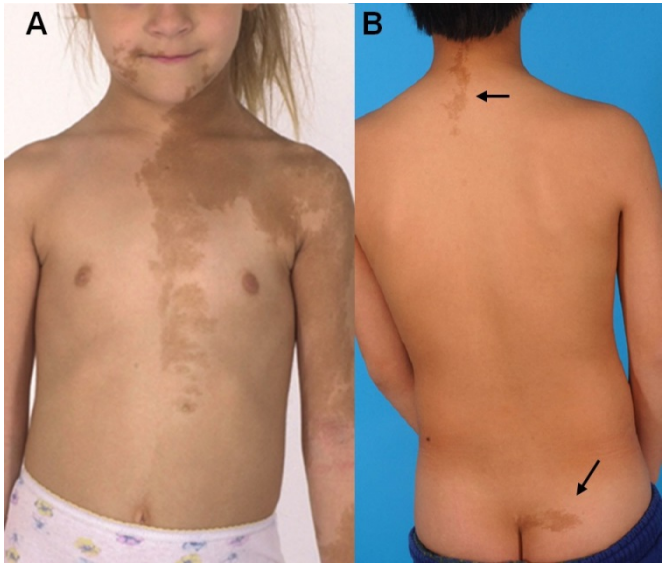
ACTH-independent Macronodular Adrenal Hyperplasia

- Bimodal age distribution – 1st year and 5th & 6th decades
- Sporadic with some familial clustering
- Equally distributed between genders
- Association with MEN1 and FAP
- GIP, Vasopressin, β adrenergic, LH/HCG, 5HT4, Angiotensin



McCune Albright Syndrome

- Sporadic heterogenous disorder with activating mutation in GNAS1

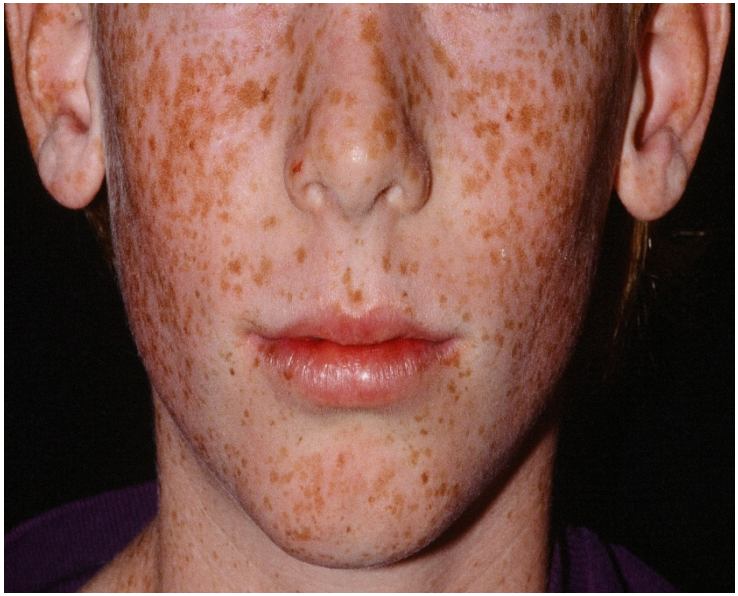


- Polyostotic fibrous dysplasia
- Café au lait patches
- Endocrinopathy
  - Precocious puberty
  - Thyroid nodules
  - GH secreting pituitary tumours and prolactinomas
  - Cushing's syndrome

PPNAD / Carney Complex

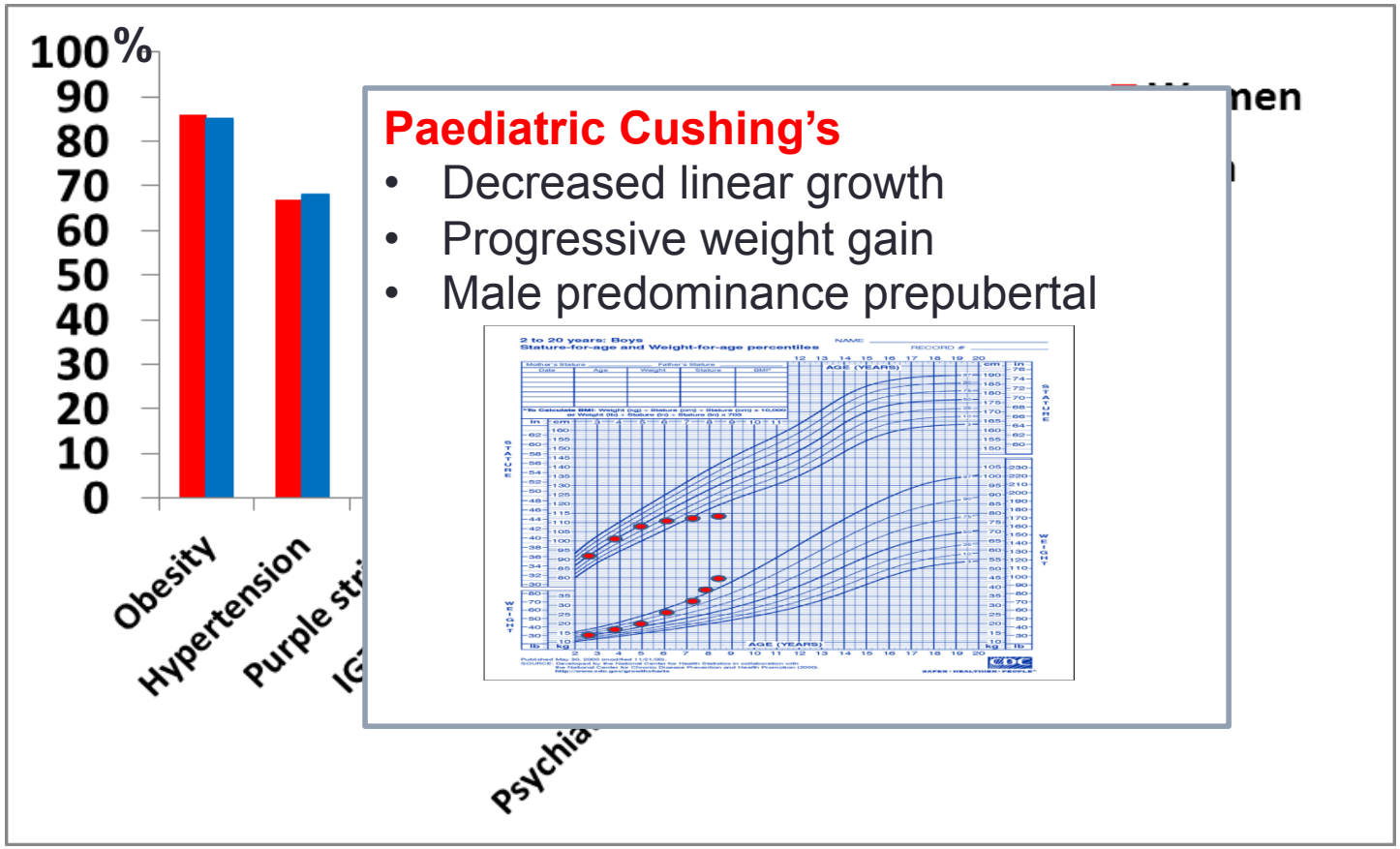
- Occurs in late adolescence / early adulthood
- Autosomal dominant
- Inactivating mutation of PRKARIα

- Spotty skin pigmentation
- Cardiac, skin or mucosal myxomas
- Endocrinopathy
  - Cushing's syndrome
  - Sertoli cell tumour / ovarian cyst
  - GH / prolactin secreting tumours
  - Thyroid adenoma



Clinical Presentation

(N = 280 patients; 233/47)



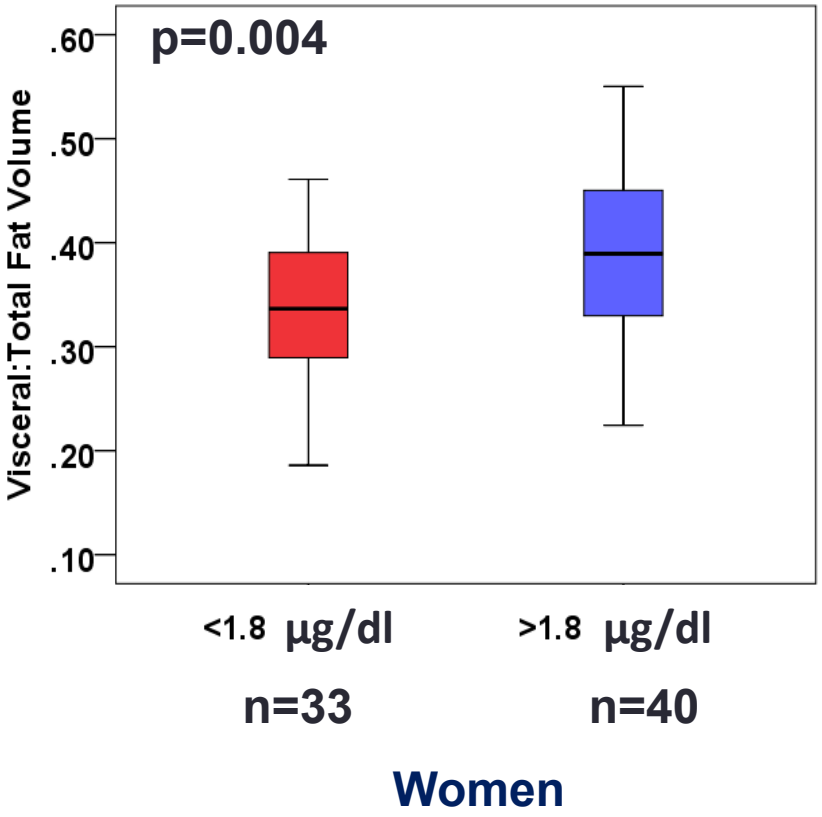
Pecori Giraldi JCEM 2003; 88: 1554 - 1558

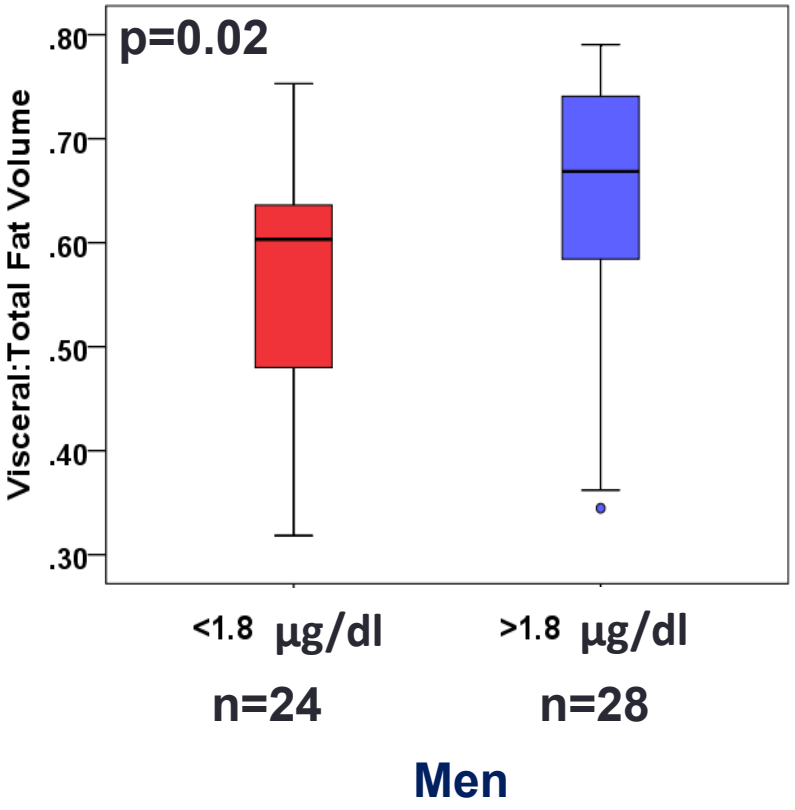
Clinical Presentation – Metabolic Complications

	Women	Men
Hypokalaemia	12%	41%
Impaired Glucose Tolerance	42%	47%
Dyslipidaemia	37%	59%
Thromboembolic events	9%	12%
Carotid Plaques	22%	28%
Symptomatic fractures	9%	29%
Fatty Liver *	30%	60%

Zilio Clinical Endo 2014 80: 403 – 410; Liu Int J of Endo 2015*

Increased Visceral Fat associated with Mild Endogenous Hypercortisolism

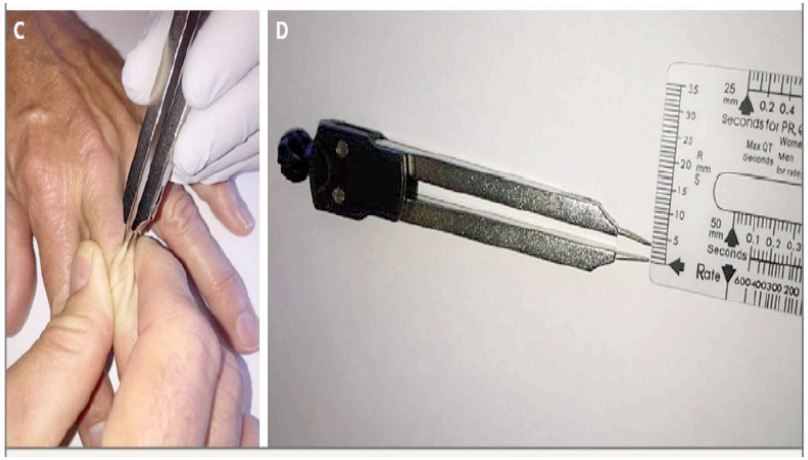




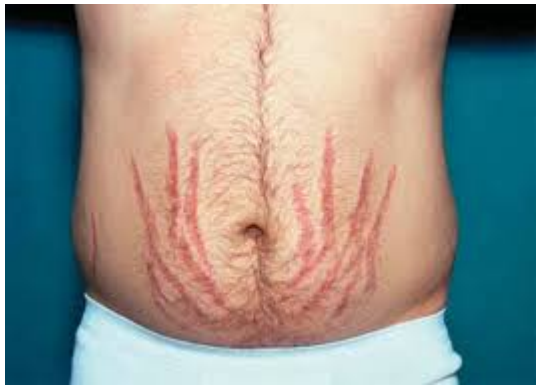
- Significant accumulation of visceral fat within 6 months in those with dexamethasone cortisol >1.8µg/dl

Debono et al JCEM 2013 98: 2383 - 2391

Clinical Presentation – Anti – Anabolic Features

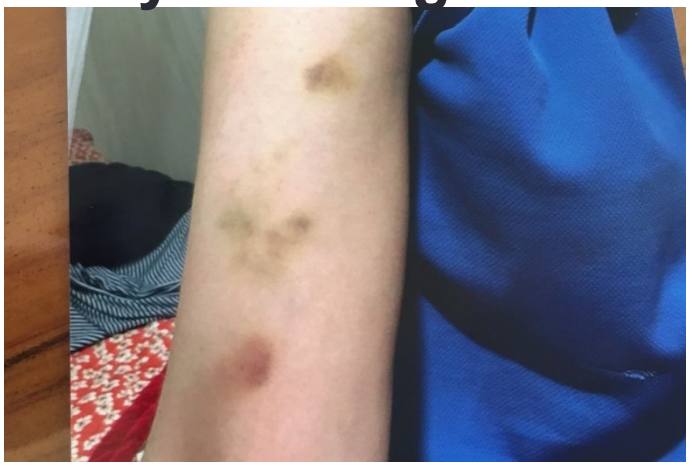


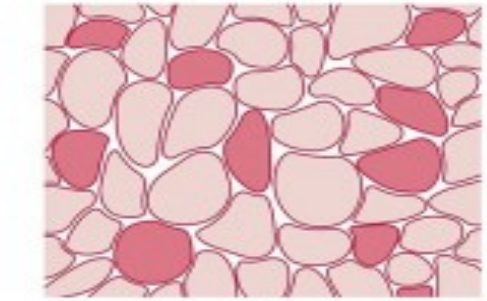
Thin skin



Purple striae

Easy Bruising

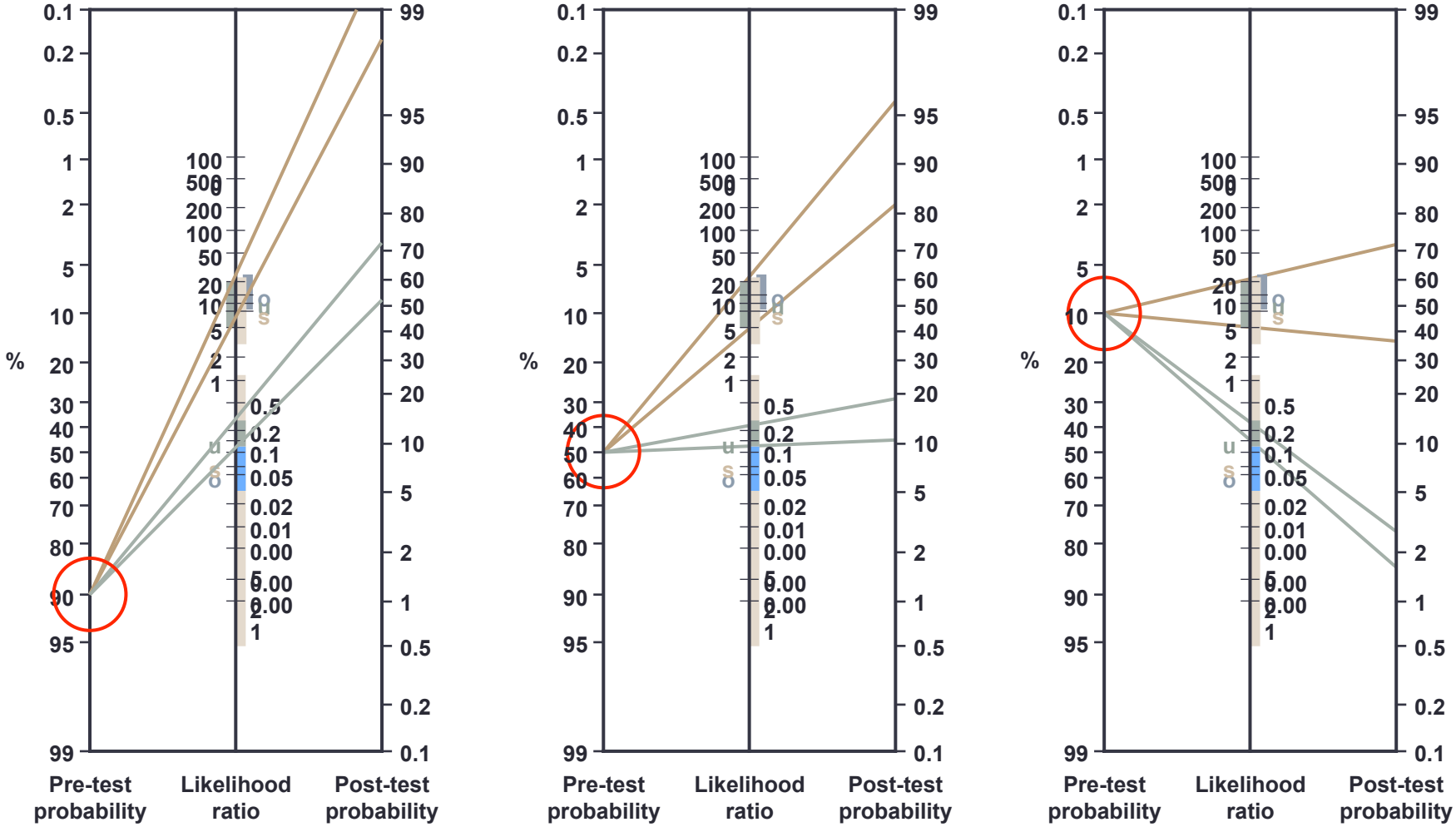




Type 2 muscle atrophy

Fagan nomogram can be used to estimate the post-test probability of Cushing's syndrome for selected tests

N=8631 patients; 9% CS

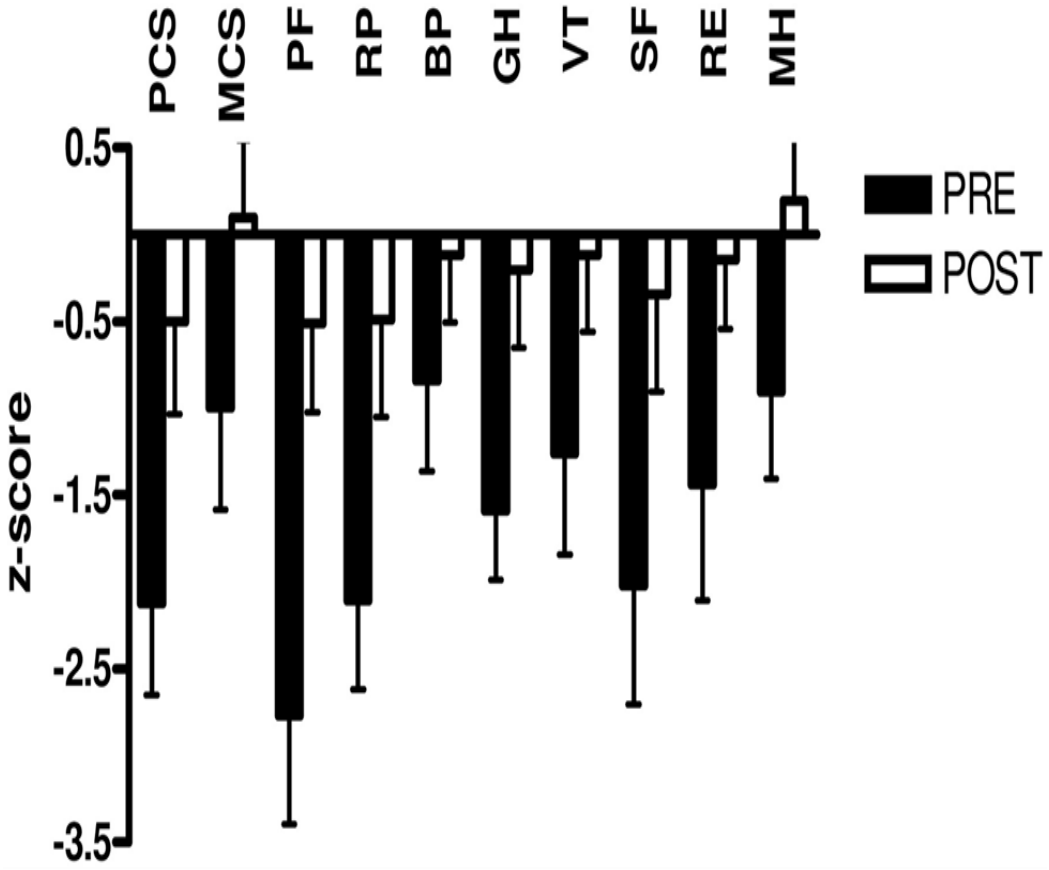


o, overnight dexamethasone suppression test;
s, late-night salivary cortisol; u, UFC

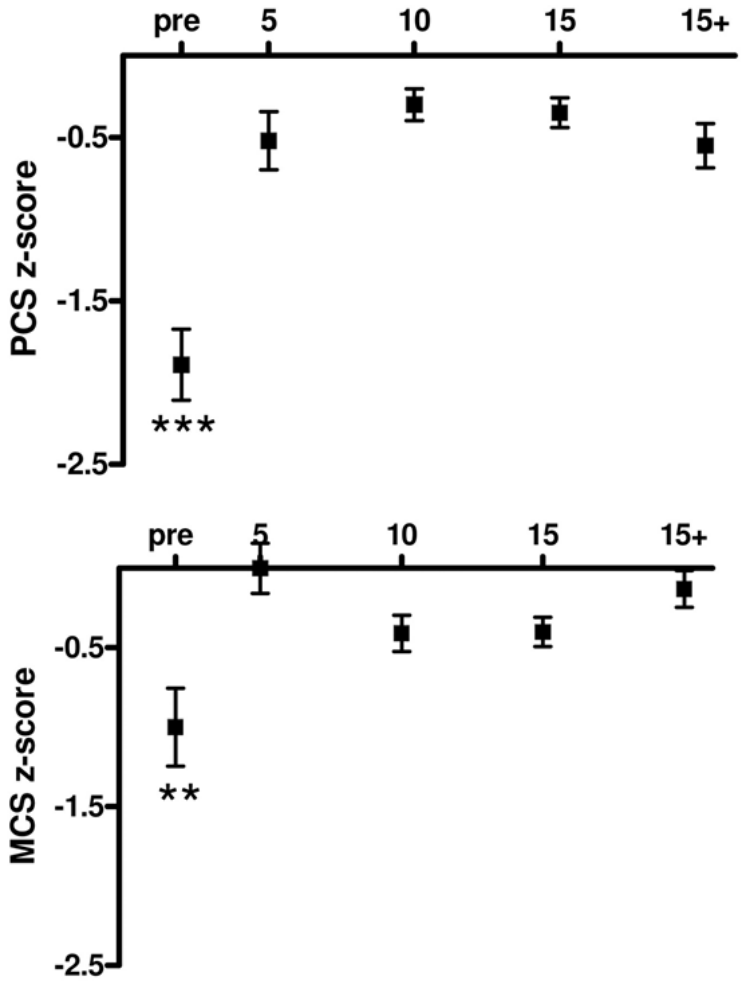
Elamin MB JCEM 2008;93:1553–1562

Quality of Life

N=23 patients before and after TSS



N=343 patients in remission

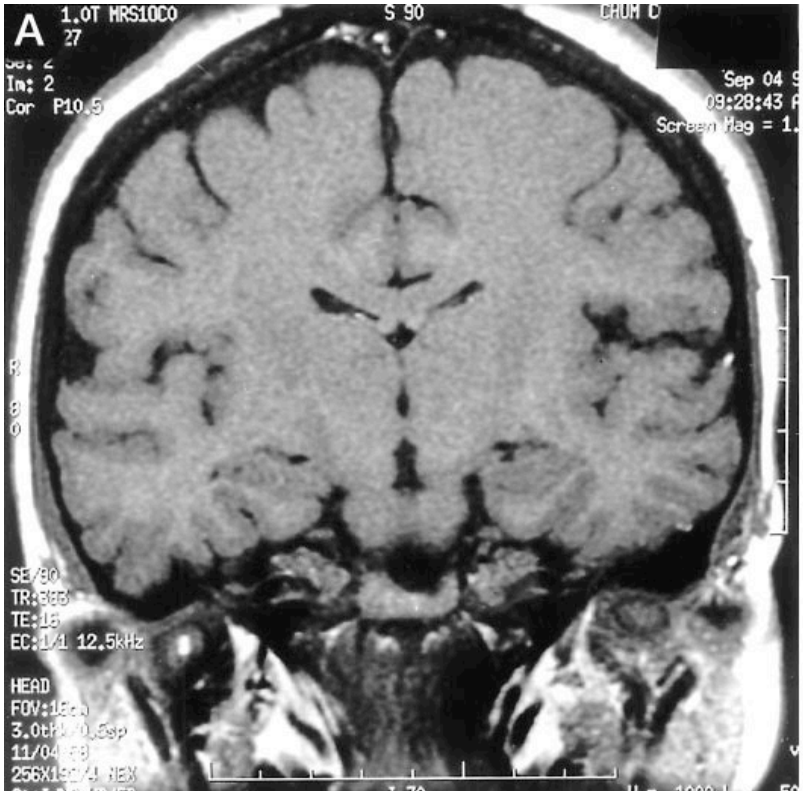


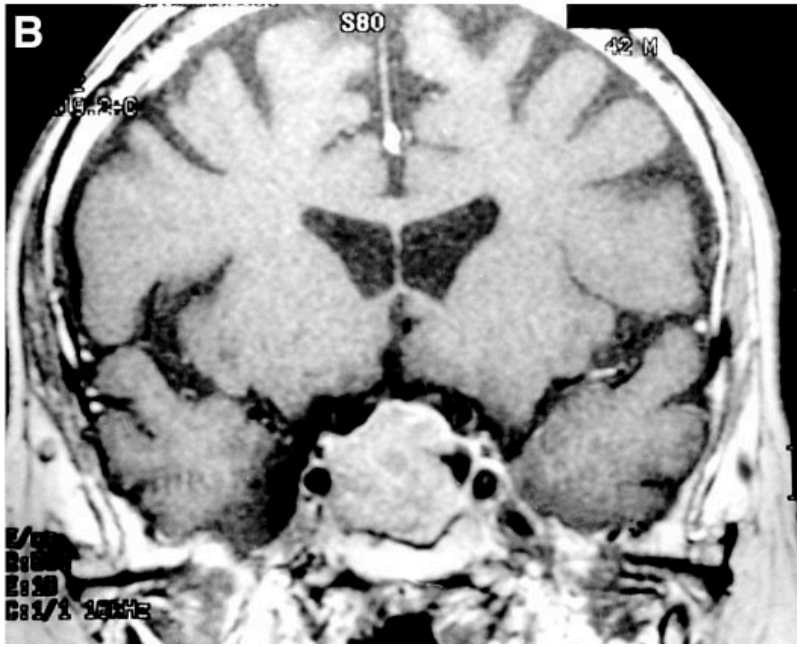
Lindsay JCEM 2006; 91: 447 - 453

Neuropsychiatric disease

N=38 patients

Increased risk for depression, anxiety, mania, neurocognitive effects

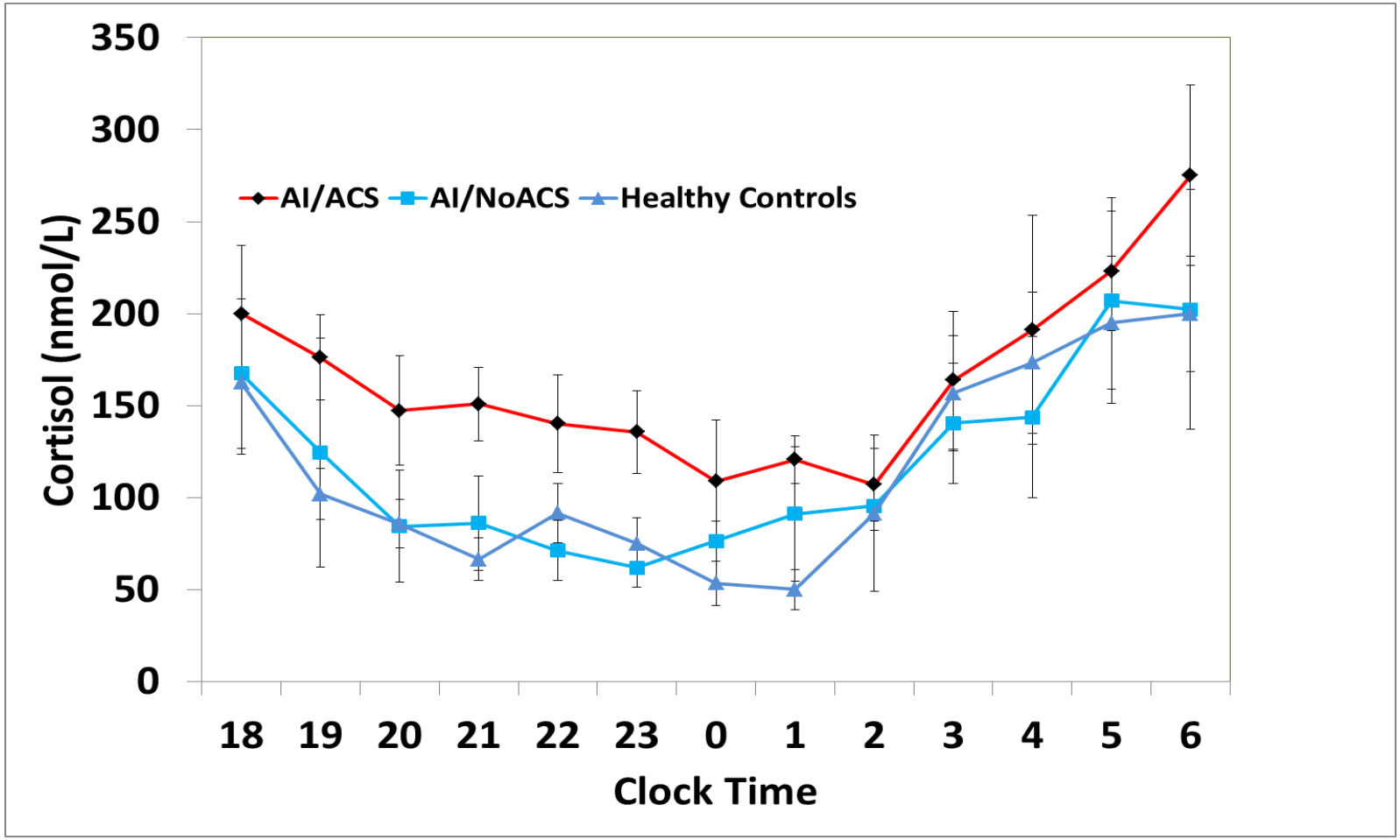




Normal

Loss of brain volume

Loss of Cortisol Rhythm – Increased Nocturnal Cortisol Exposure in Adrenal Tumours with Hypercortisolism



Debono JCEM 2017; 102: 3461 - 3469

Conclusion

- Cushing's syndrome is a fascinating disorder presenting insidiously with anti-anabolic features
- It is a rare disease but making the diagnosis is crucial as impacts on patient morbidity and mortality
- Random screening results in a high rate of false positive tests with risk of mismanagement
- A high pretest probability increases one's possibility of diagnostic accuracy