Cushing's Disease in Children: Growth and Bones

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Rome March 19th 2016

Cushing's syndrome

Definition

Clinical syndrome

- **Characterised** by weight gain, growth failure, osteoporosis, hypertension, virilisation etc.
- **Caused** by excess circulating glucocorticoid (cortisol-like) hormone concentrations due to endogenous secretion or exogenous administration

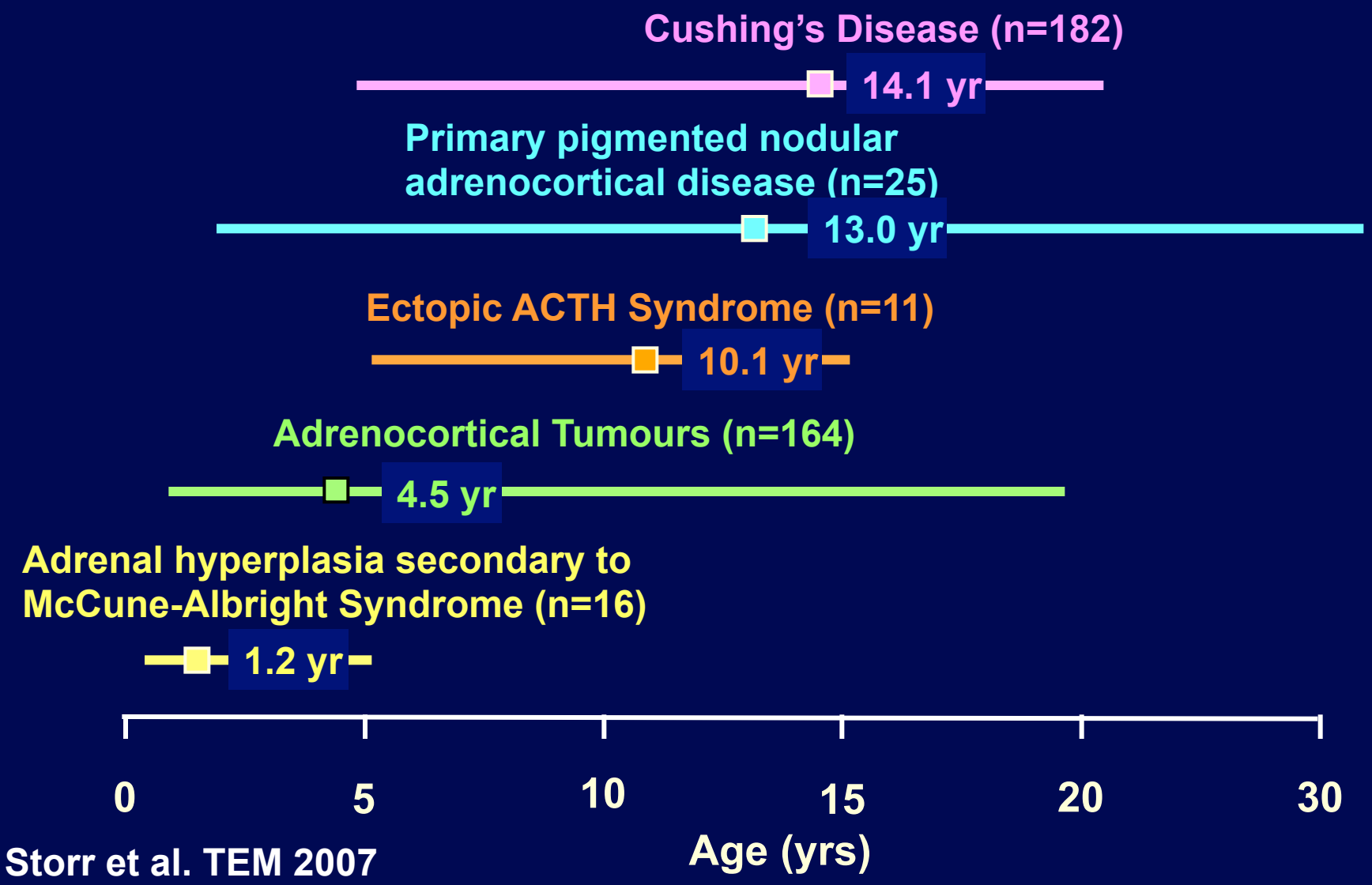
10-year old patient with Cushing's disease

Typical features:

- plethora
- striae
- weight gain
- osteoporosis
- abnormal bone-age
- growth failure
- virilisation

Paediatric Cushing's Syndrome

Literature Review of Aetiology vs Age (n=398 cases)



Storr et al. TEM 2007

Paediatric Cushing's Disease

- Rare, diagnosis is difficult
- After age 5y Cushing's disease predominates
- Growth failure critical feature
- Male predominance pre-pubertally
- Adenoma almost always a microadenoma
- Low visibility rate in pituitary MRI, but a high rate of tumour localisation by BSIPSS
- Diagnostic tests similar to adults, but more likely to have exaggerated response to CRH

(Storr et al EJE 2011)

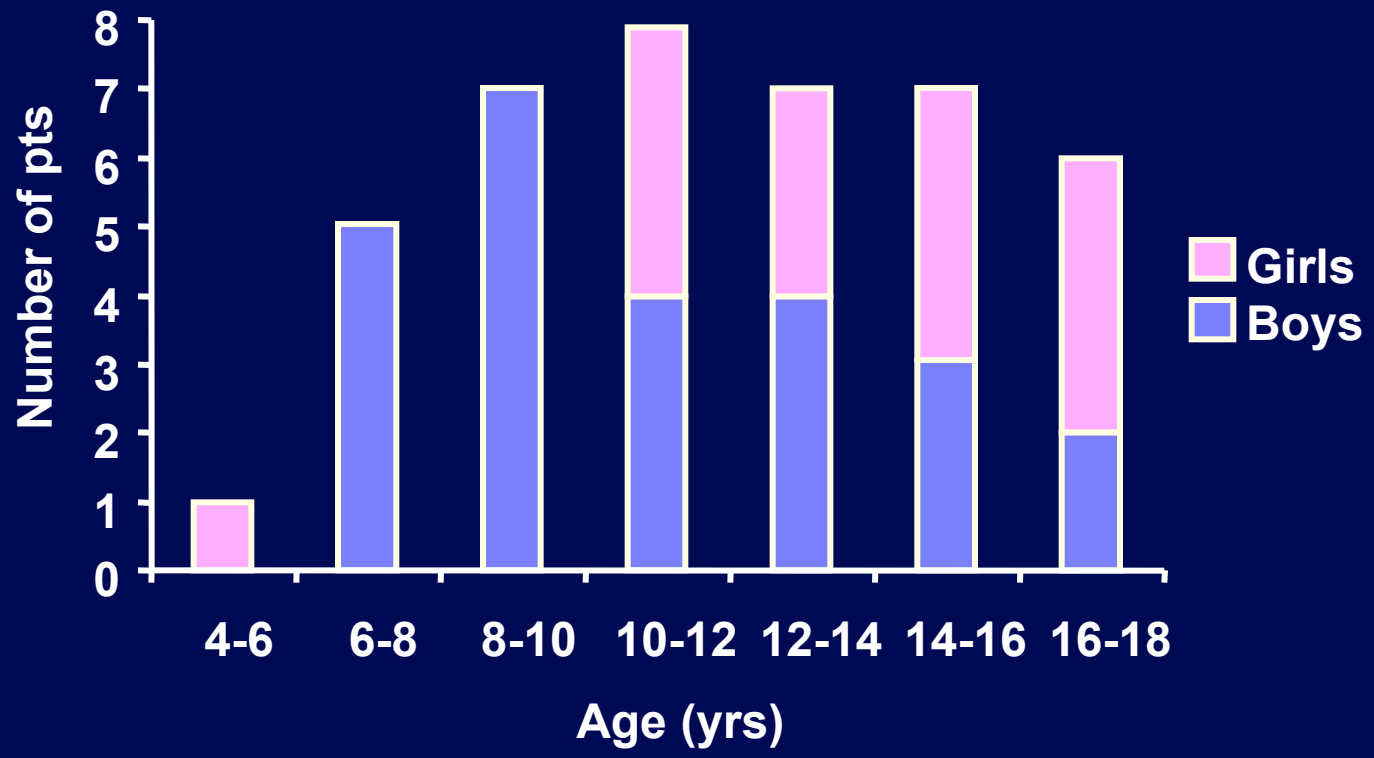
Paediatric Cushing's disease: Clinical features at diagnosis (n=47)

Storr HL & Savage MO Eur J Endocrinol, 2015

Major symptoms	Patients (n)	% of total
Weight gain	46	98 ←
Short stature	22	45 ←
Facial changes	47	100 ←
Pre-pub virilisation	21/24	88 ←
Fatigue	28	60 ←
Emotional lability/ depression	28	60 ←
Hirsutism	25	53
Headaches	24	51
Striae	21	45 ←
Hypertension	21	45
Acne	19	40 ←

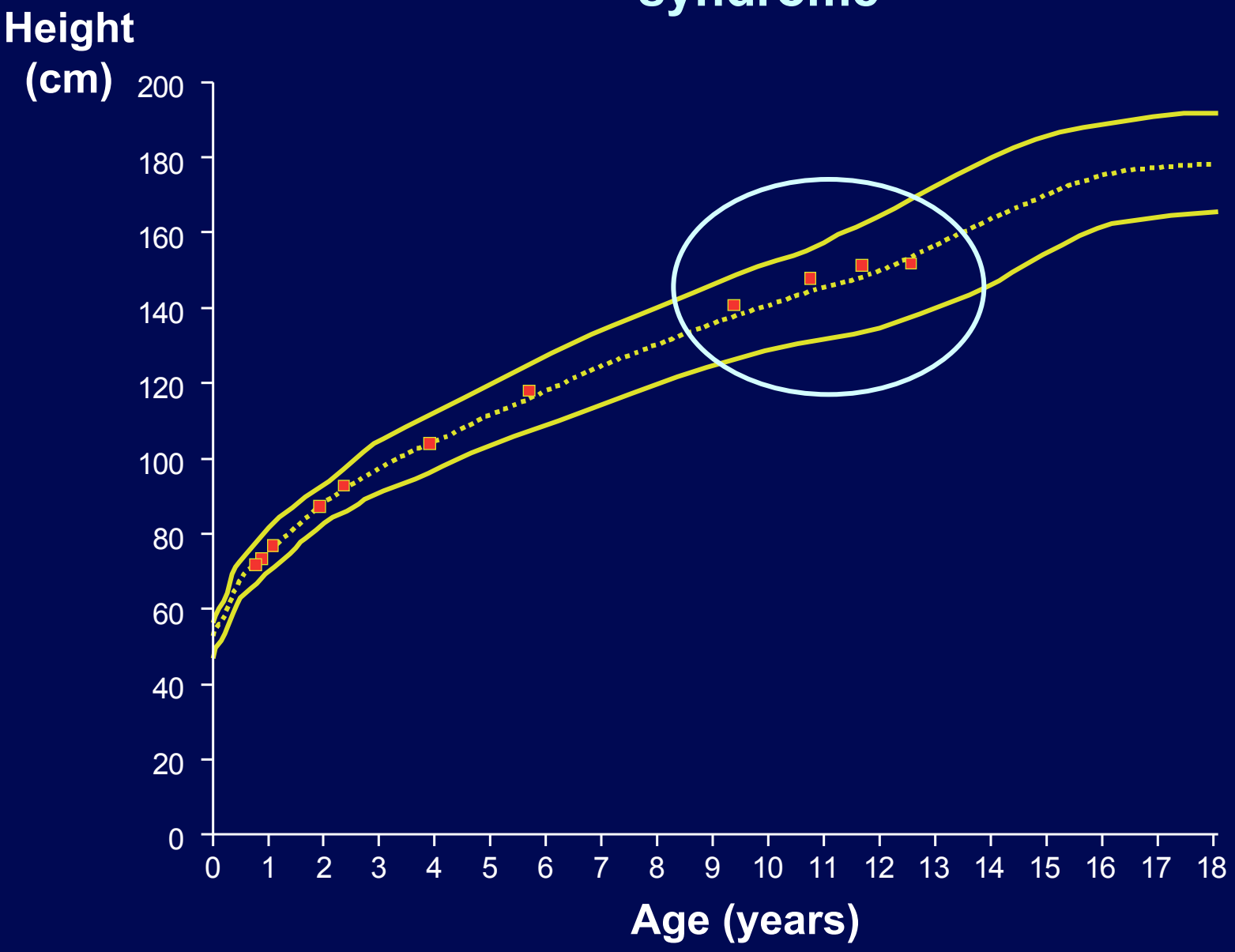
Sex incidence and age of diagnosis of CD

- In adults, CD has a female preponderance
- 126 patients: 31 (24.6%) M, 95 (75.4%) F



41 paediatric patients: 26 (63%) M, 15 (37%) F (P=0.0001)

Growth in a child with features suggestive of Cushing's syndrome



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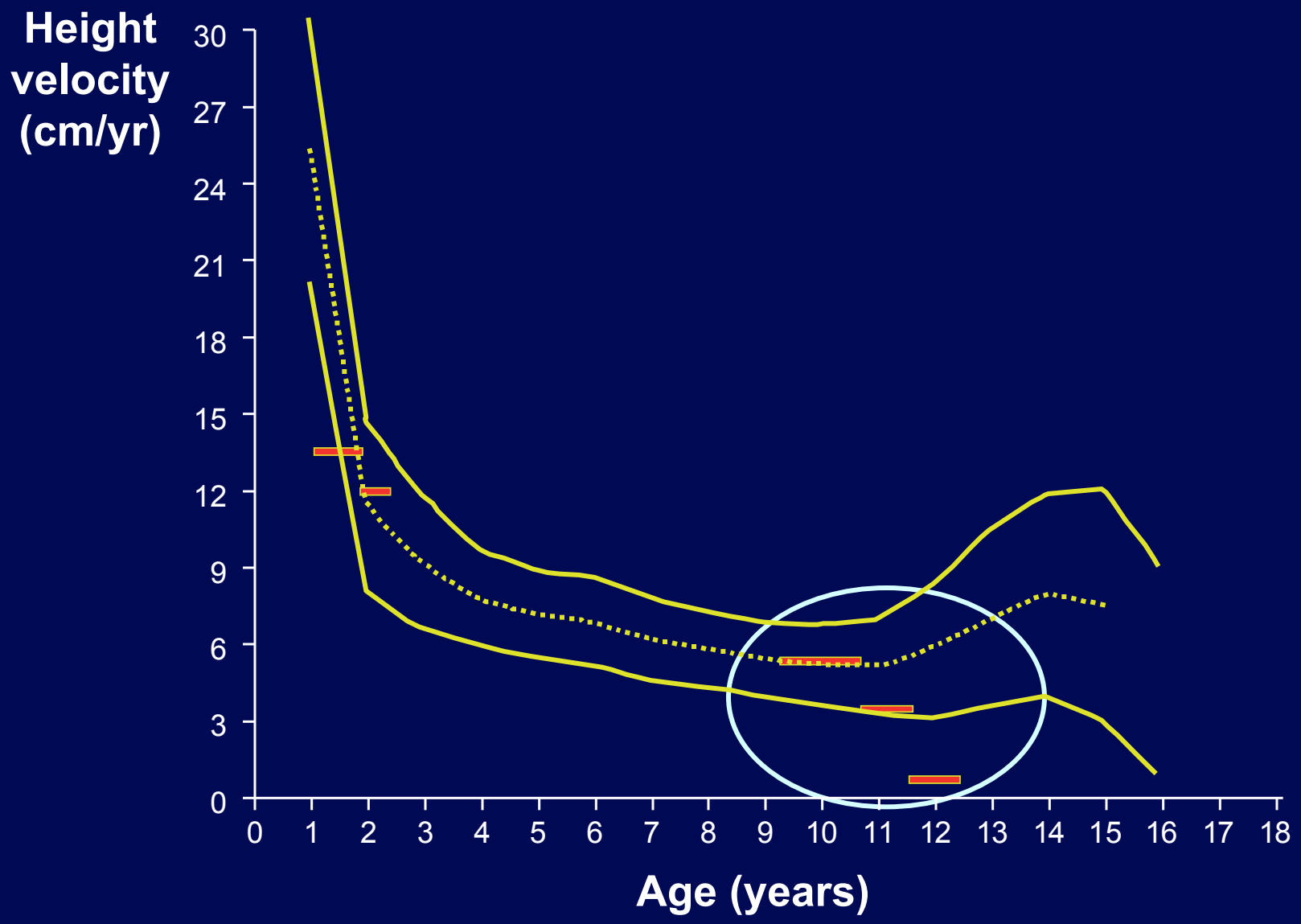


GROWTH HORMONE DEFICIENCY IN PAEDIATRIC CUSHING'S DISEASE

- 59 children with Cushing's syndrome (CD=50)
- Growth retardation in 83%
- Normal bone age in 81%
- Mean height before surgery -1.3 SDS
- Mean height at one year -1.2 SDS

(Magiakou et al NEJM 1994)

GH SECRETION IN PAEDIATRIC CUSHING'S SYNDROME

- 14 patients with Cushing's syndrome, 14 normals
- GH assayed ever 20 mins for 24h
- Slight catch-up growth in absence of GH
- Subnormal GH secretion maintained at 3, 6 and 12 months

- CONCLUSIONS: Persistent GH suppression is consistent with some growth

(Magiakou et al 1994)

FINAL HEIGHT IN IN PAEDIATRIC CUSHING'S DISEASE

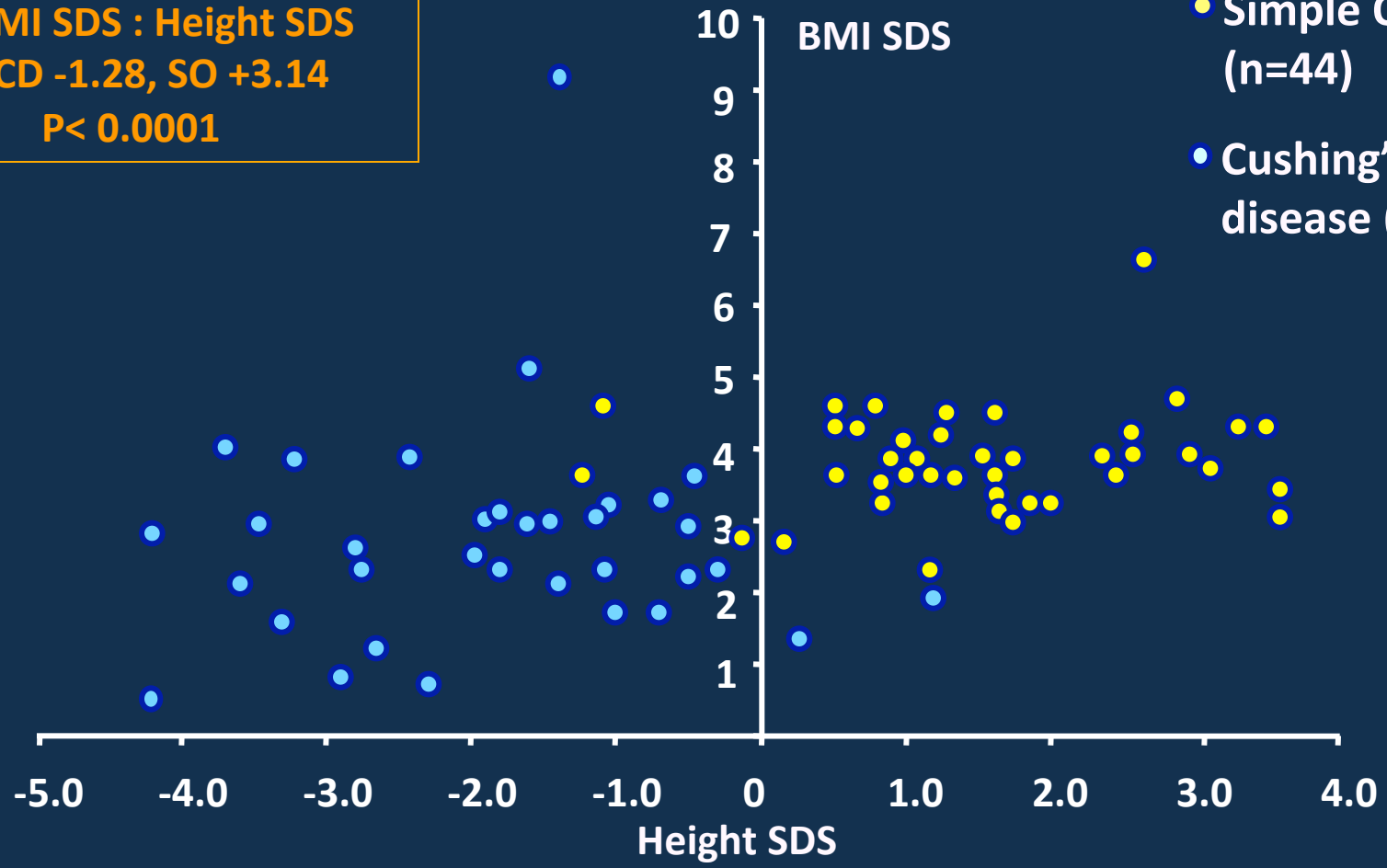
- 10 children with Cushing's syndrome
- Height SDS at presentation -1.7±1.3
- Adult height SDS after cure -1.3±0.9
- MPH-Adult height = 8.9cm

- CONCLUSION: LACK OF CATCH-UP COMPROMISES FINAL HEIGHT

(Magiakou et al JCEM 1994)

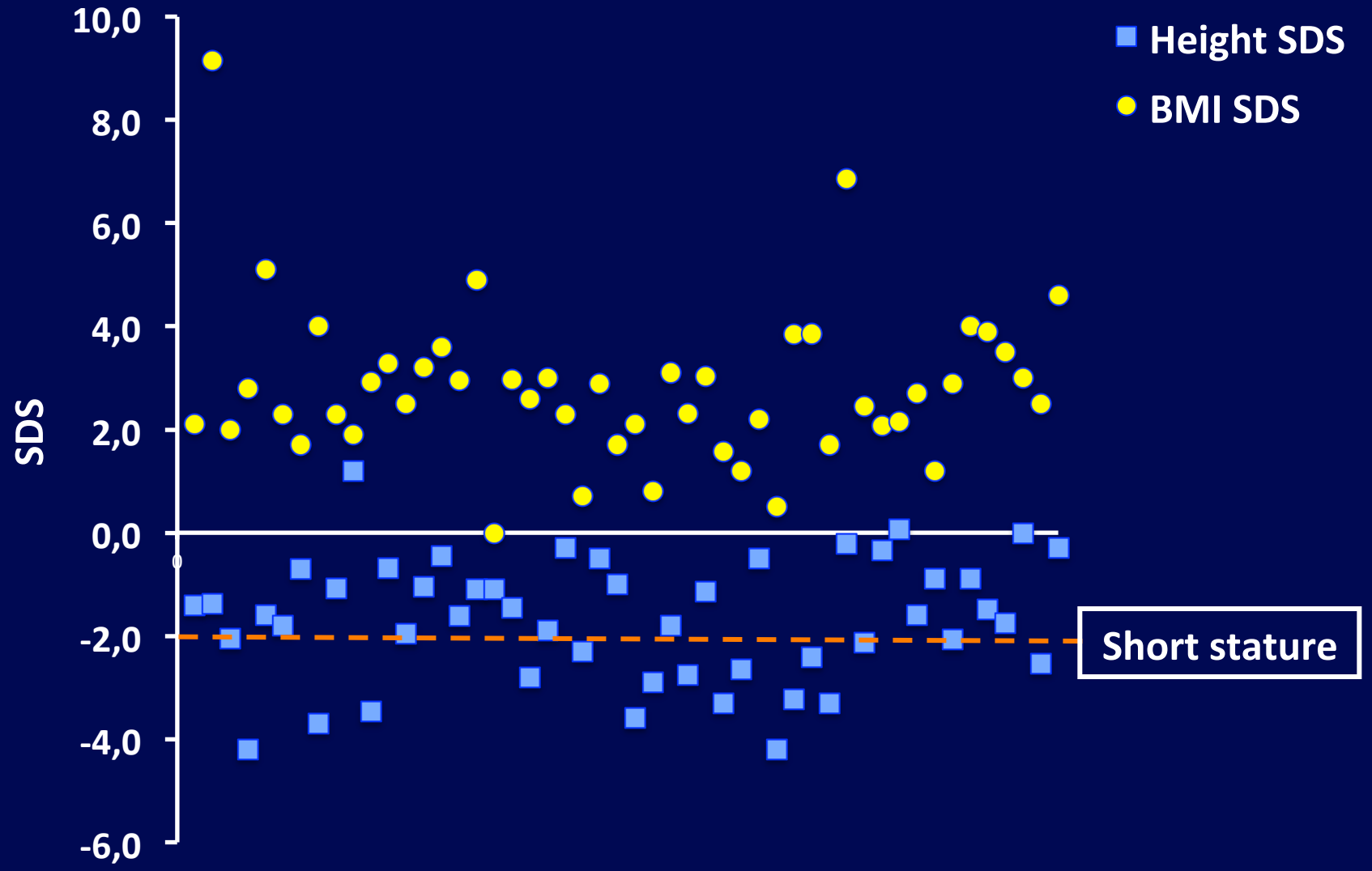
Height and BMI SDS values in children with Cushing's disease and simple obesity

BMI SDS : Height SDS
CD -1.28, SO +3.14
P< 0.0001

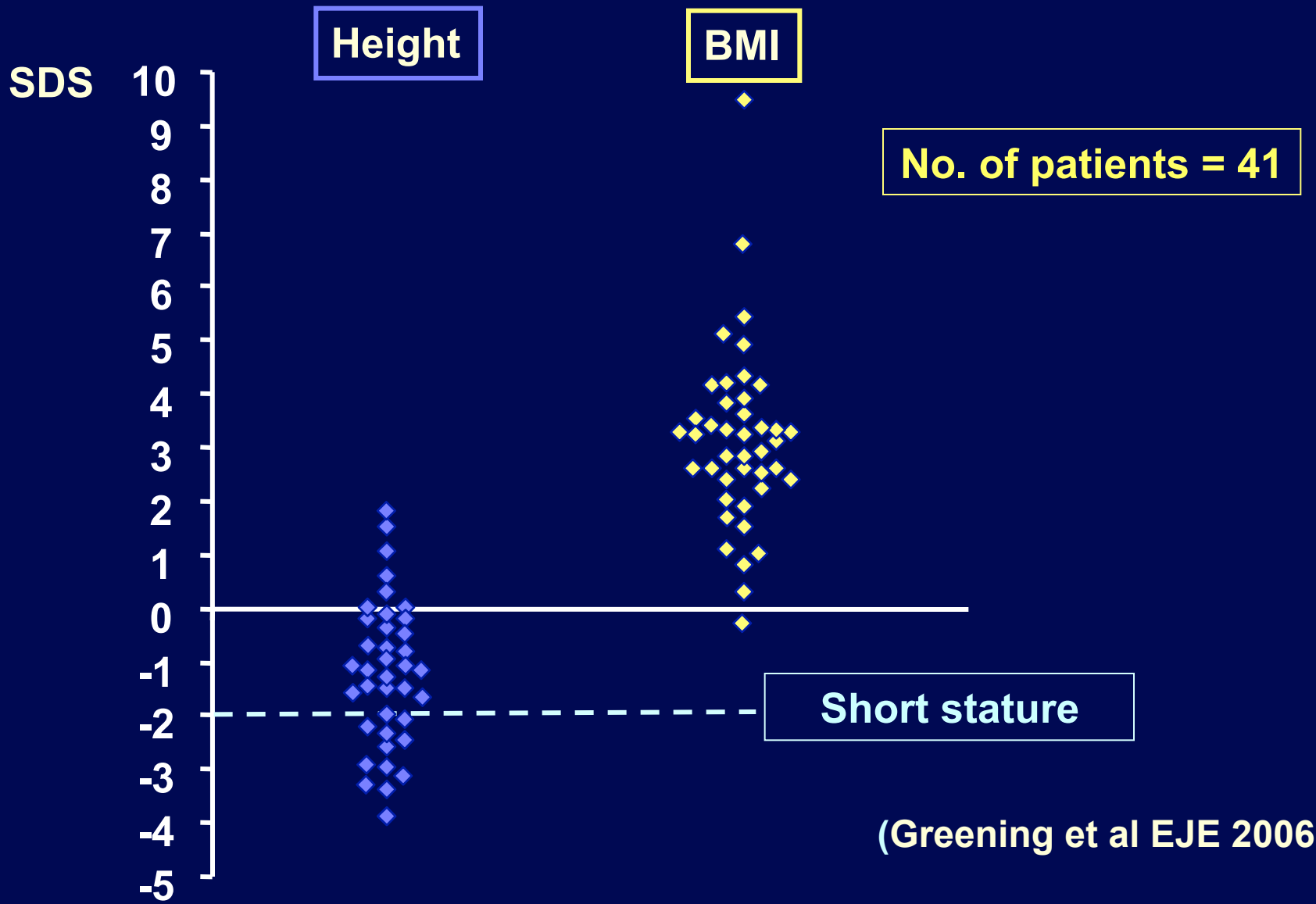


Greening JE et al (2006). J Endocrinol Invest. 29 (10) 885-887.

Height and BMI SDS values at diagnosis in paediatric Cushing's syndrome n=52



Height and BMI SDS values at diagnosis in paediatric Cushing's disease



(Greening et al EJE 2006)

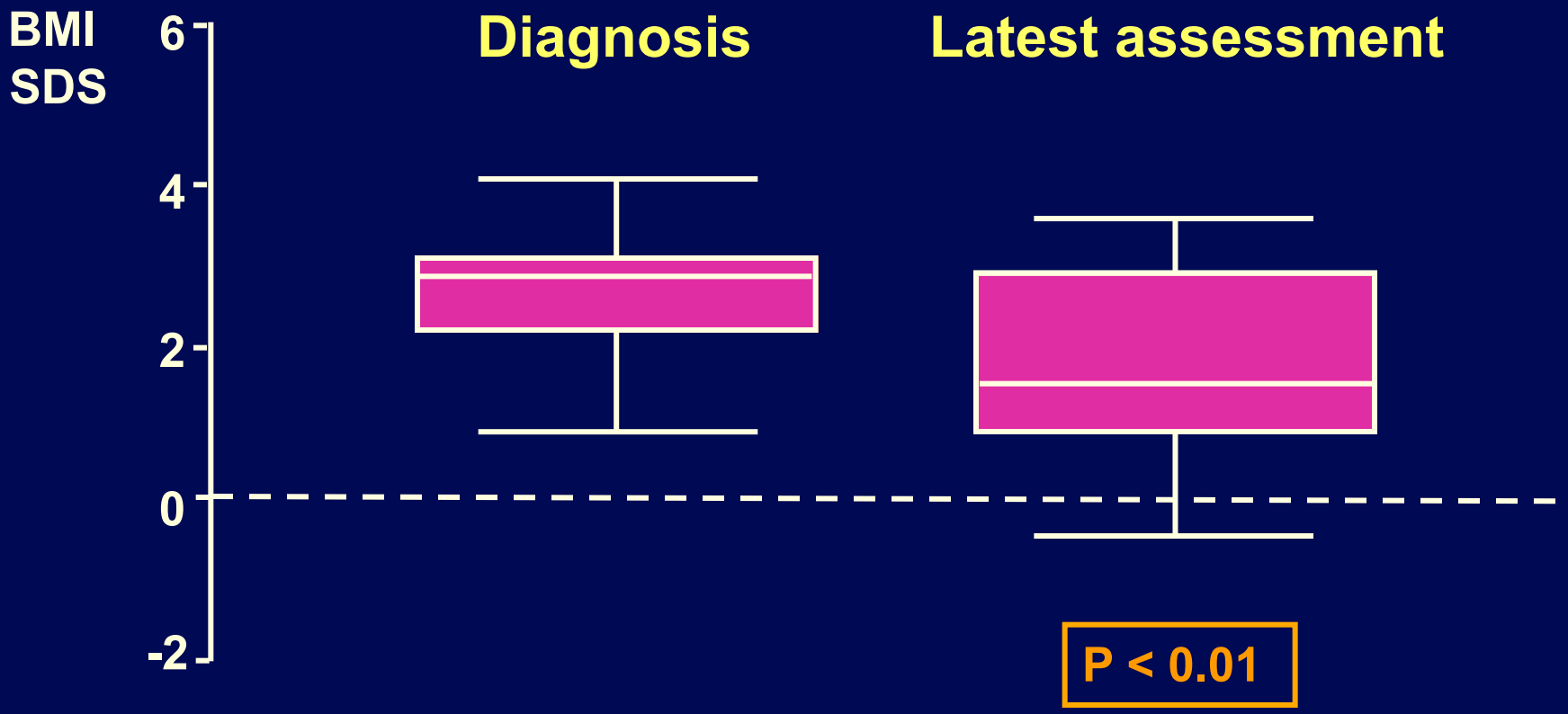
GROWTH HORMONE DEFICIENCY IN PAEDIATRIC CUSHING'S DISEASE

- Growth failure a symptom in 74%
- 9/10 patients without catch-up growth after successful therapy
- Impaired GH secretion permanent
- 9/10 patients received GH therapy
- 3/10 received GnRH to arrest or delay puberty

(Savage et al 2003)

BMI SDS at diagnosis and latest assessment (n=14)

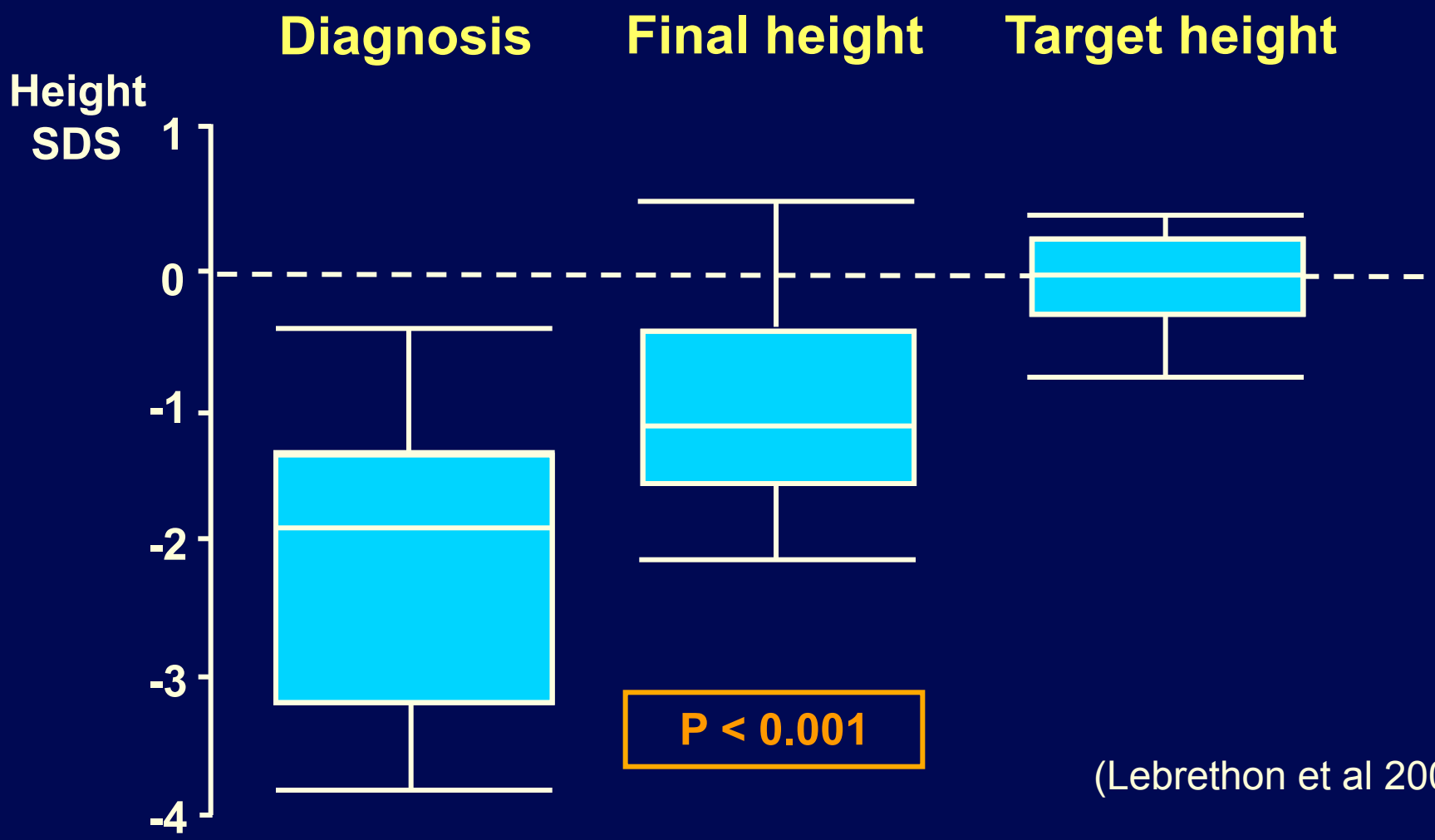
Interval 3.9 yrs (0.5-10.7)



(Davies JH et al. 2005 Clin Endocrinol. 62:466-472)

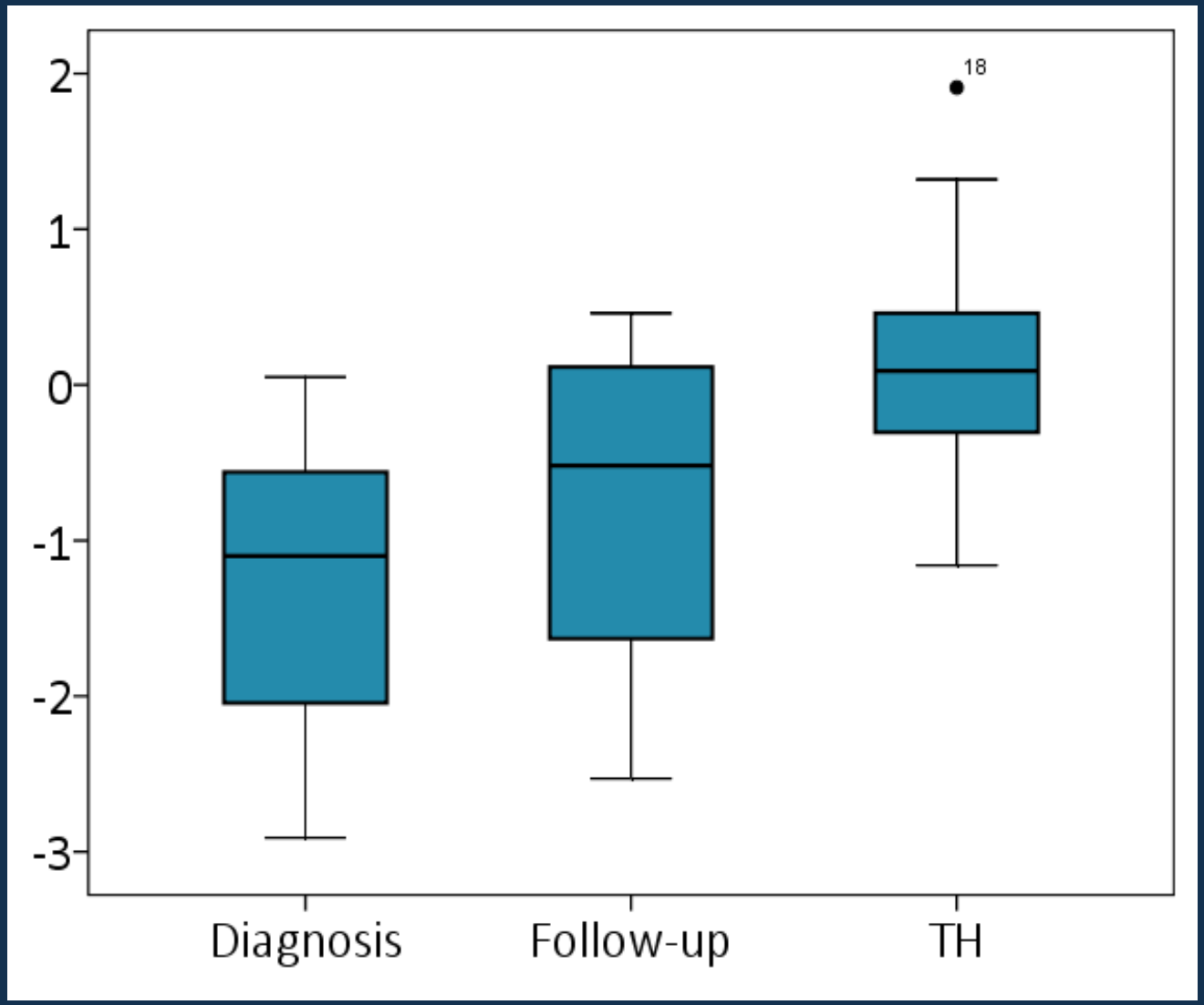
Height SDS at diagnosis, final or latest height and target height (n=14)

Interval 3.9 yrs (0.5-10.7)



(Lebrethon et al 2000)

Height SDS at diagnosis, final or latest height and target height



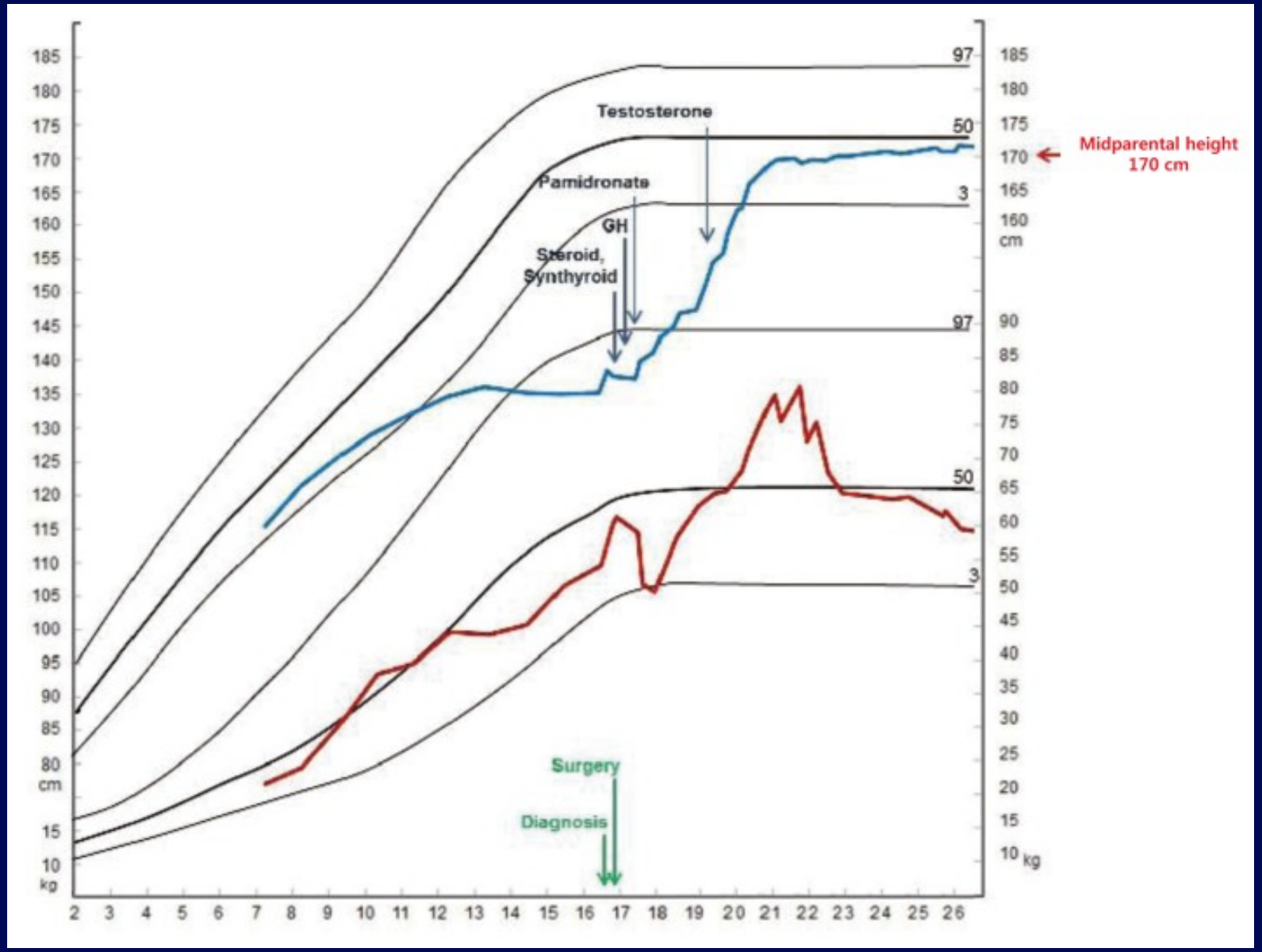
Storr, ESPE, 2014

GROWTH HORMONE DEFICIENCY AFTER RADIOTHERAPY IN PAEDIATRIC CUSHING'S DISEASE

- 12 patients received external beam RT after failed surgery
- 11/12 'cured', usually within 12 months
- At one year, GHD in 5/6
- At 9 years, 3/4 were GH sufficient
- CONCLUSIONS: Short-term GH deficiency is common in these patients, although eventually it may recover

(Chan et al 2007)

GROWTH IN A CHILD WITH CS ON FULL REPLACEMENT



(Jeong et al 2014)

EARLY REPORT OF OSTEOPOROSIS IN CHILDHOOD CS

- **Identical twins aged 15 years**
- **One with Cushing's disease**
  - **Bone density -3.2 vs -0.1SD**
- **After 27 months**
  - **Bone density -1.9 vs 0**
  - **Final height -21cm**

CONCLUSION: Persistent OP and long-term growth retardation remain important factors in paediatric CD

Leong et al 1998

BONE DENSITY IN PAEDIATRIC CUSHING'S SYNDROME

- 35 children with Cushing's disease
- 16 with follow-up scans ("up to 18 months")
- Bone density at entry
  - -1.6 (spine) vs -1.04 (hip)
- At follow-up
  - +0.84 (spine) vs +1.05 (hip)
- Osteopenia in 38% (spine) and 23% (hip)

- CONCLUSIONS: Osteoporosis is significant but not severe, and is reversible

(Lodish et al 2010)

BONE DENSITY BEFORE AND AFTER CURE IN CUSHING'S DISEASE

- 8 patients at diagnosis
- BMD -1.04 SDS (negative correlation with midnight cortisol)

- 11 patients after cure (4.5 years)
- BMD -0.38 SDS

- **"These findings show variability of BMD at diagnosis and near normal BMD after cure of paediatric CD, suggesting that with appropriate replacement of pituitary hormone deficiency normal peak bone mass is achievable"**

(Scommegna et al 2005)

BONE DENSITY AFTER TREATMENT OF CHILDHOOD CS

- 16 year-old male with Cushing's disease
- Bone age = 11y
- Bone density -6.1, -4.5 SDS
- Age 26y, Bone density -4.3, -3.0 SDS

Jeong et al 2014

RENAL STONES IN CHILDREN WITH CS

139 patients

19.4% with evidence of renal stones (radiographic or history)

1% in general population

Correlated with urinary free cortisol

(Rahman et al 2016)

BONE AGE IN PAEDIATRIC CUSHING'S SYNDROME

- 93 children with Cushing's disease, 31 with ACTH-independent disease
- Bone age assessed before and after surgery
- Bone age
  - Normal 76%
  - Advanced 21% (correlated with adrenal androgens)
  - Delayed 3%
- After one year remission, bone age decreased

- CONCLUSIONS: Bone age is rarely delayed and often normal or advanced.

(Lodish et al 2014)

SKELETAL MATURATION IN PAEDIATRIC CUSHING'S DISEASE

- 17 patients (12 male)
- Bone age by TW3 RUS
- Delay = CA-BA
- Bone age delay in 15/17 patients (mean 2.0y)
- Positive correlation with duration of symptoms
- Negative correlation with height SDS

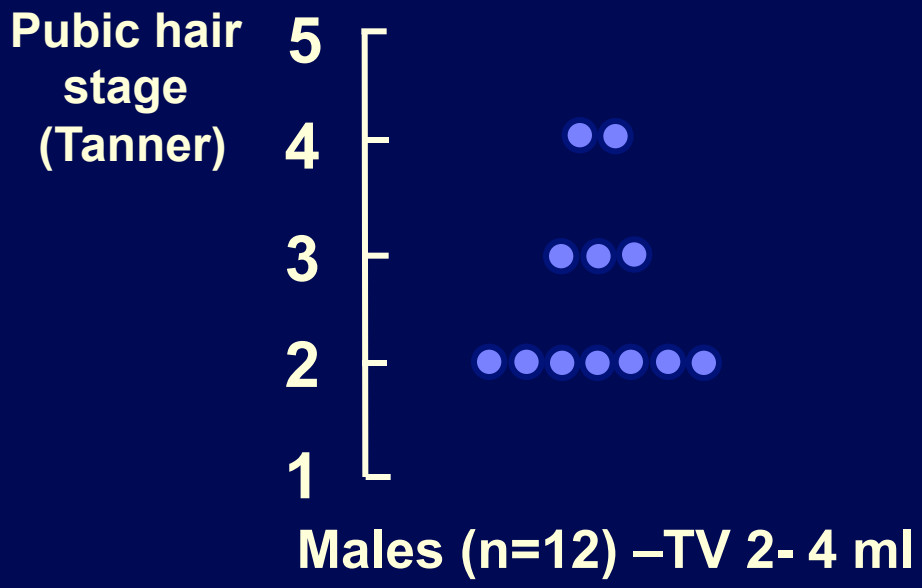
- **CONCLUSIONS: Bone age delay is a common feature of paediatric Cushing's disease**

(Peters et al 2007)

Abnormal virilisation in a 6.2 yr old prepubertal boy with Cushing's disease

Abnormal pubertal development caused by virilisation: 16/21 (76%) cases

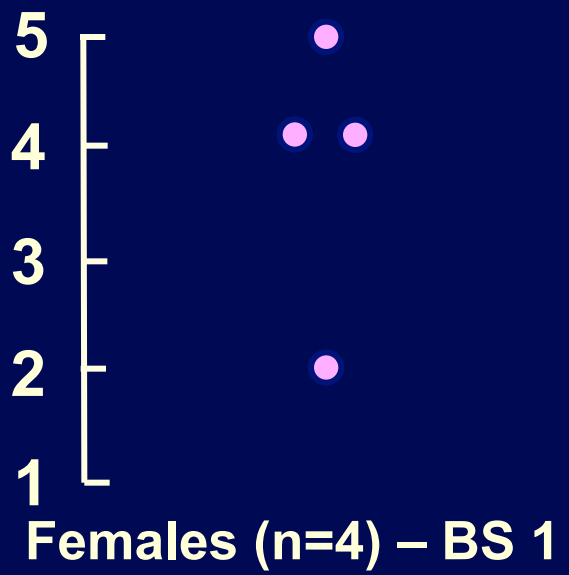
Males:	**Advanced pubic hair stage (2-4) for testicular volume (TV 2-4ml) (NR 6·8 –12·6 ml)***



*Zachmann (1964), Tanner (1969), Tanner (1970)

Abnormal pubertal development caused by virilisation: 16/21 (76%) cases

Females:	**Advanced pubic hair stage (2-5) for breast stage (BS 1) (14% PH 2; 0% PH 5)***



Females (n=4) – BS 1

*Zachmann (1964), Tanner (1969), Tanner (1970)

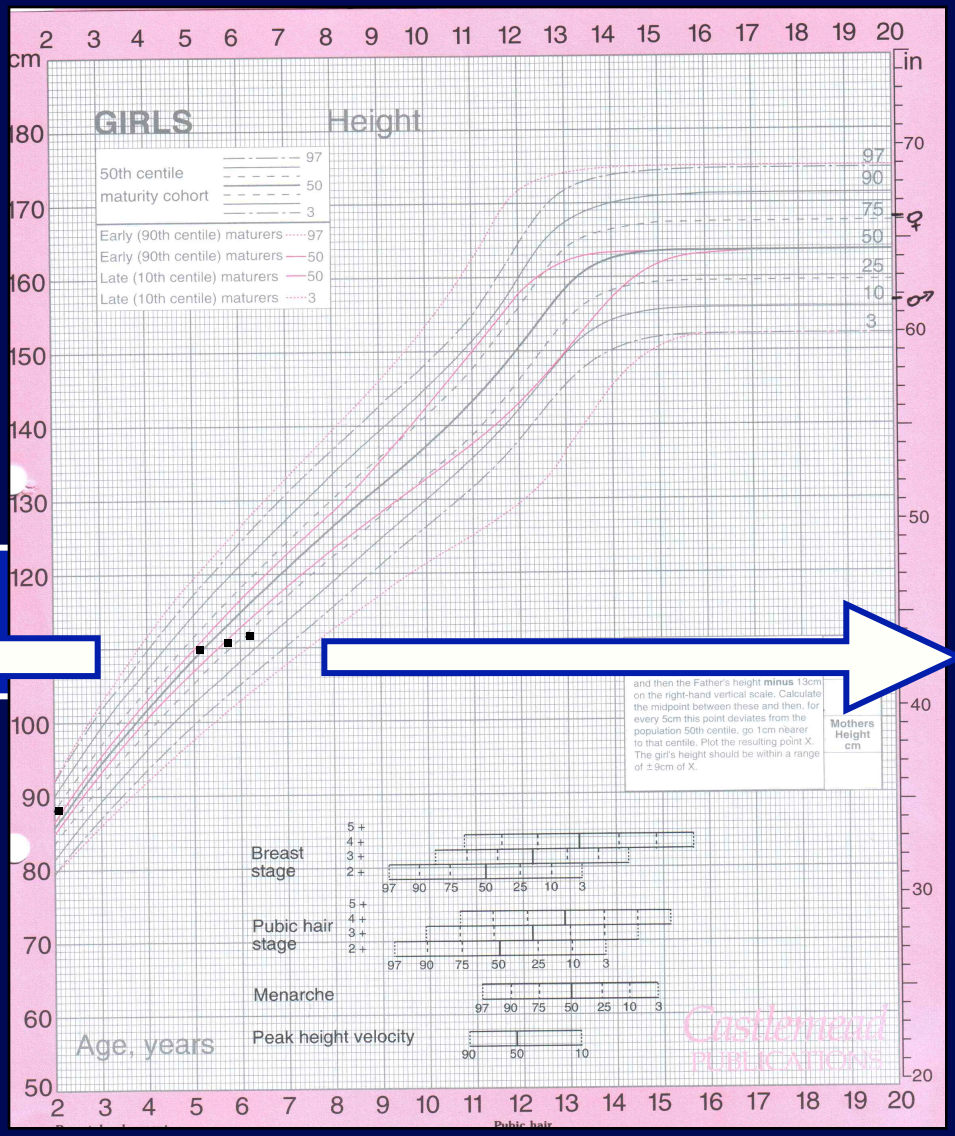
VIRILISATION IN PAEDIATRIC CUSHING'S DISEASE

- 27 patients, mean age 13.4y
- *Mean* DHEA-S, testosterone and androstenedione normal
- SHBG inversely related to BMI
- Abnormal virilisation in 13 (11 male)
  - A4, testosterone, DHEA-S elevated; SHBG low
- In puberty low levels of LH and FSH in both sexes

- CONCLUSION: Virilisation common and gonadotrophins often suppressed

(Dupuis et al 2007)

Influences of hypercortisolaemia and adrenal androgens on growth in Cushing's syndrome



Hypercortisolaemia
BA delay

Adrenal Androgens
BA advance

CONCLUSIONS 1

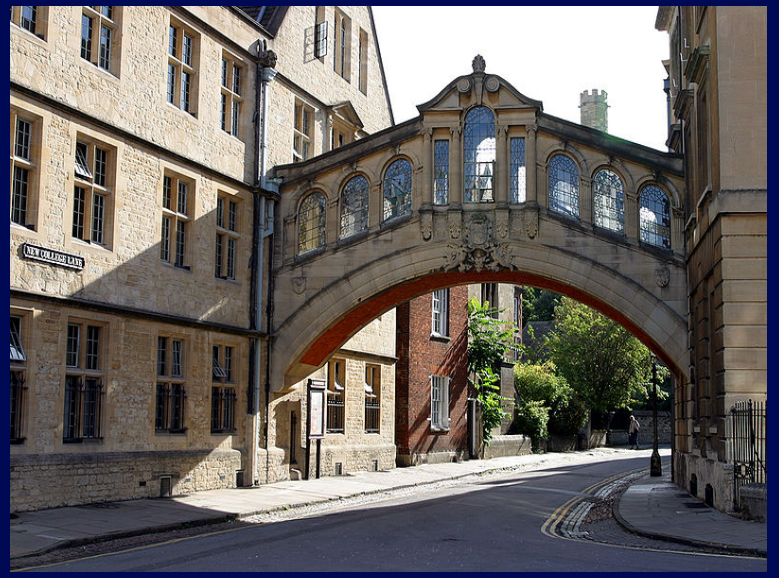
- Children with Cushing's syndrome often present with growth failure
- This is mainly attributable to GH deficiency
- Cure of the Cushing's will lead to some return of growth, but this is far from normal
- After treatment, near-normal height can be produced with early GH therapy

CONCLUSIONS 2

- Skeletal maturation may be normal, advanced or delayed dependent on the interplay between hypercortisolaemia and virilisation

- Osteoporosis is often present but mild, and is usually reversible

With grateful acknowledgements to Helen Storr and Martin Savage



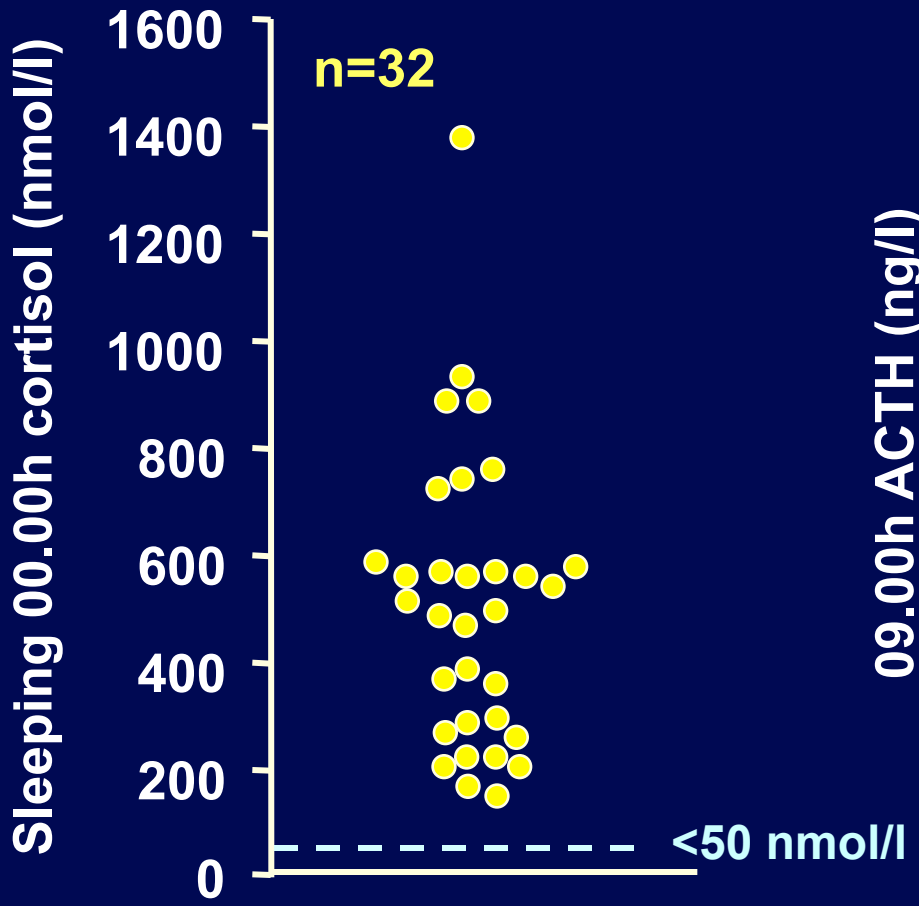
CATCH-UP GROWTH IS DISEASE-DEPENDENT?

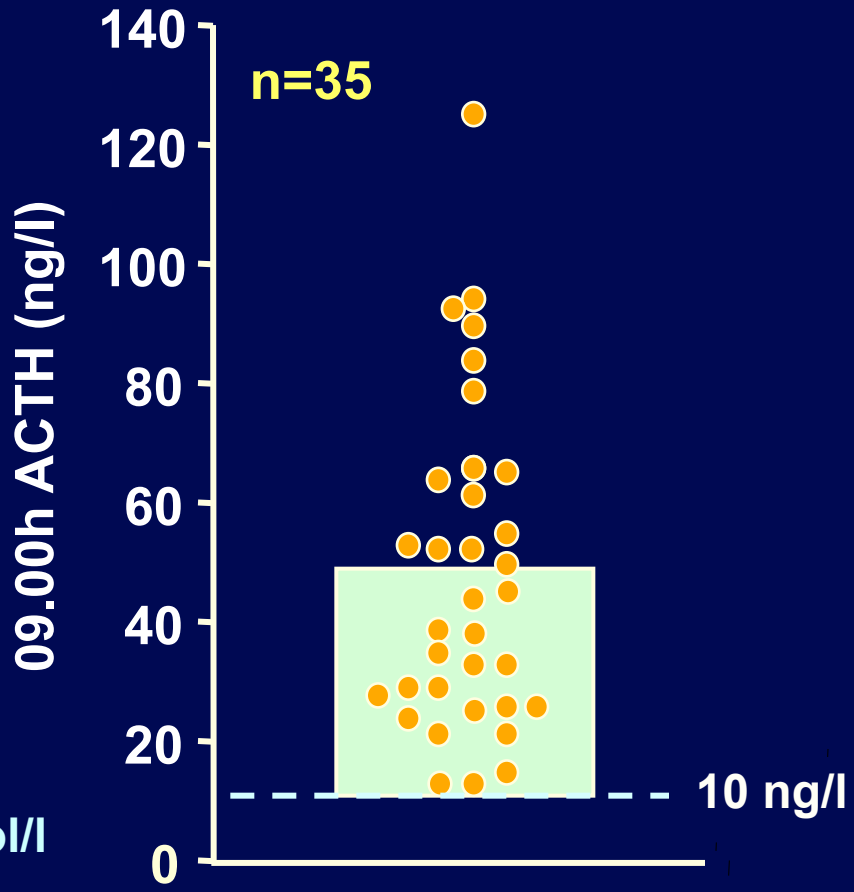
- 18 children with Cushing's disease
- 19 children with PPNAD
- Mean follow-up ~1 year, no GH treatment
- Change in height SDS
  - +0.32 vs. +0.74 ($P<0.05$)

- CONCLUSIONS: Cushing's disease patients show less spontaneous catch-up growth

(Gourgari et al 2014)

Midnight serum cortisol and 09.00 h plasma ACTH in paediatric Cushing's disease





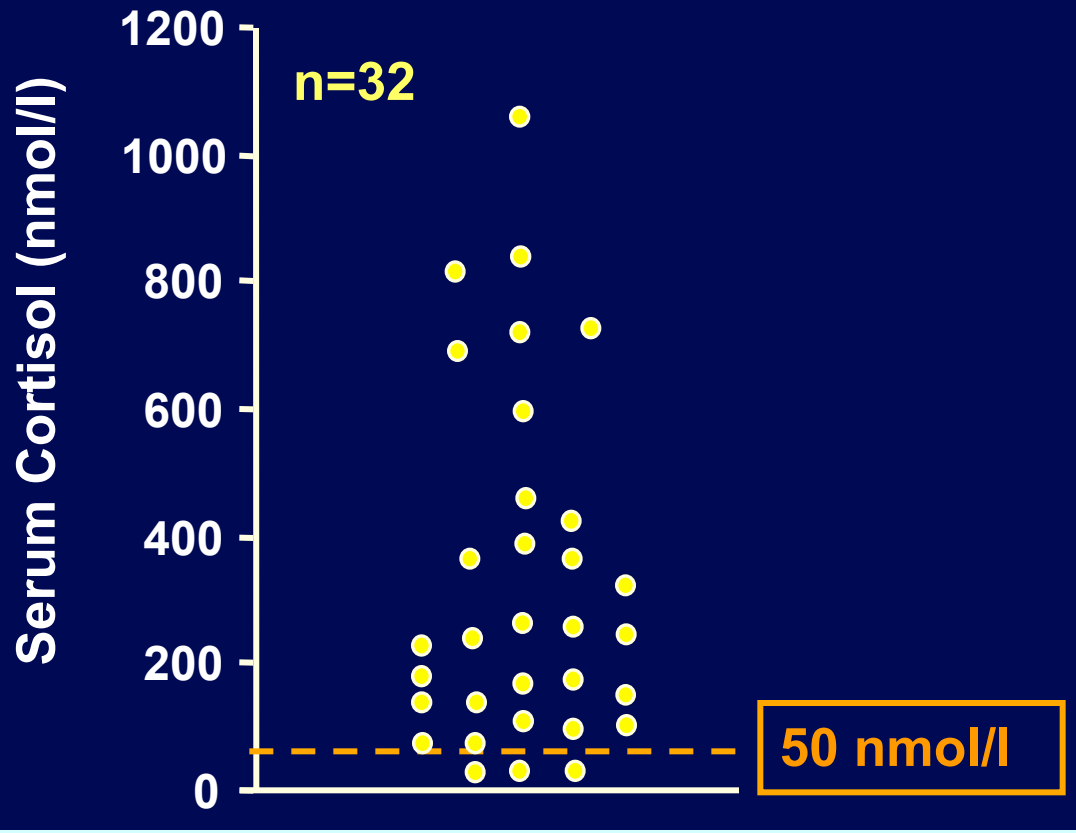
(Storr et al EJE 2011)

Paediatric Cushing's disease: Clinical features at diagnosis (n = 41)

Major symptoms	Patients (n)	% of total
Facial changes	41	100
Weight gain	36	98
Pre pu		76
Fatigu		61
Hirsuti		59
Striae		49
Hypertension	20	49
Acne	18	44
Short stature (Ht ≤ -2 SD)	20	49
Mean length of history	2.5 ± 1.7 yr (0.3-6.6 yr)	
History ≥ 2yr	27 (66%)	

Osteoporosis (Scommegna et al 2005)
Delay in bone age (Peters et al 2007)

Low dose dexamethasone suppression test (LDDST; 0.5mg 6hrly for 48h)



Cortisol non-suppressed to <50 nmol/l in 92% paediatric CD patients

(Storr et al EJE 2011)

Investigations of Cushing's syndrome

Diagnosis of Cushing's syndrome

- Urinary free cortisol x 3
- Serum cortisol circadian rhythm
- Low dose dexamethasone suppression test (LDDST)

- Plasma ACTH
- CRH test
- Pituitary MRI scan
- Inferior petrosal sinus catheterisation with CRH
- DEXA scan for bone mineral density

Recommendations

All the investigations and their results are discussed with paediatric and adult endocrinologists in consultation

Paediatric Cushing's syndrome

Hypothalamus

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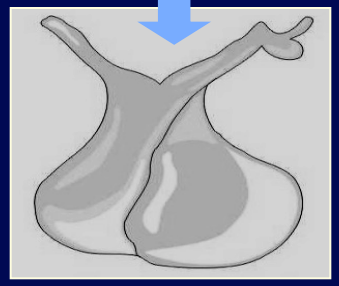
CRH
+AVP



Pituitary

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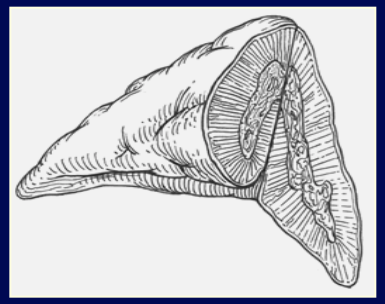
ACTH



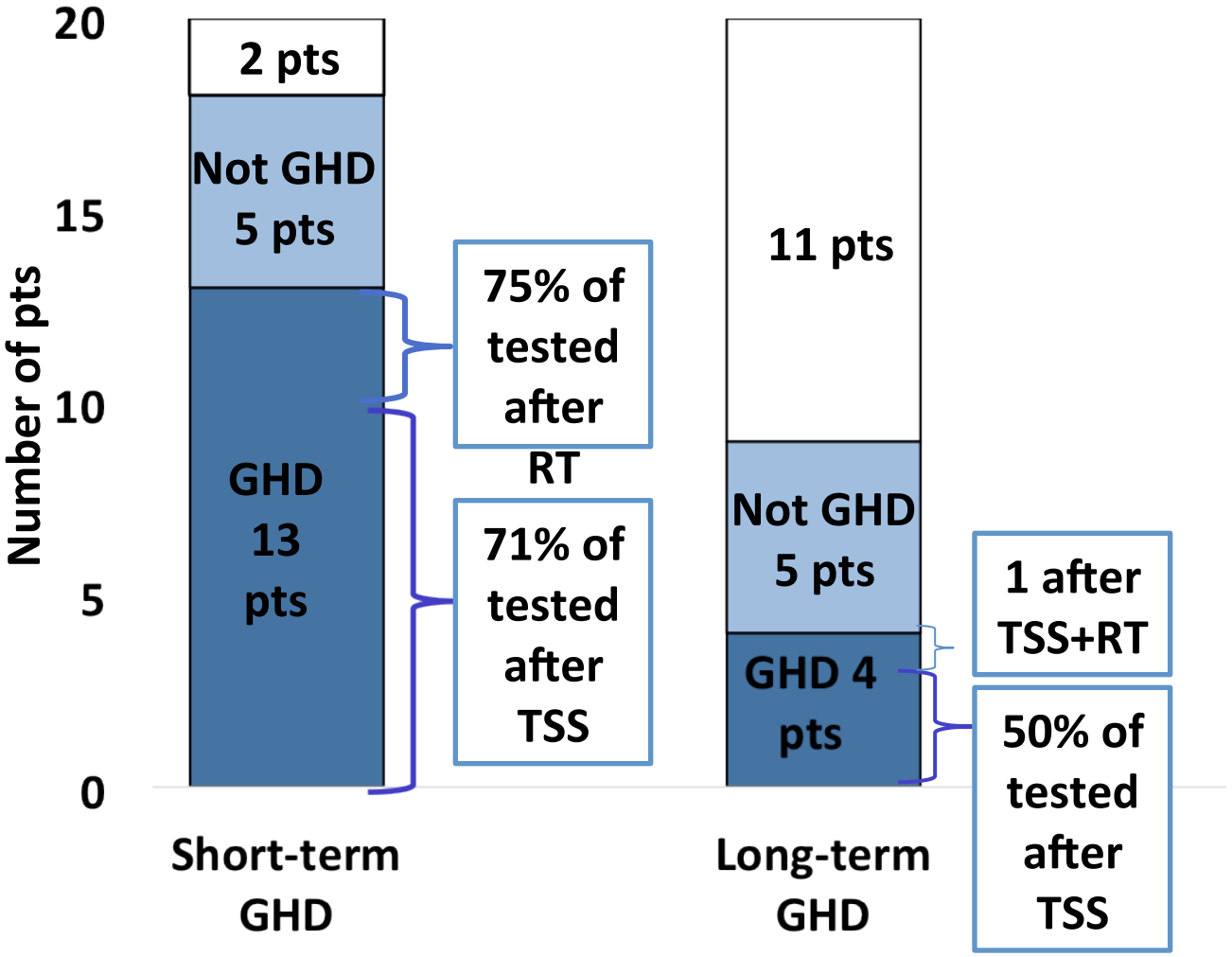
Adrenal

Cortisol

Two groups:

- ACTH - Independent
- ACTH - Dependent

Growth hormone status



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(Lodish et al 2014)

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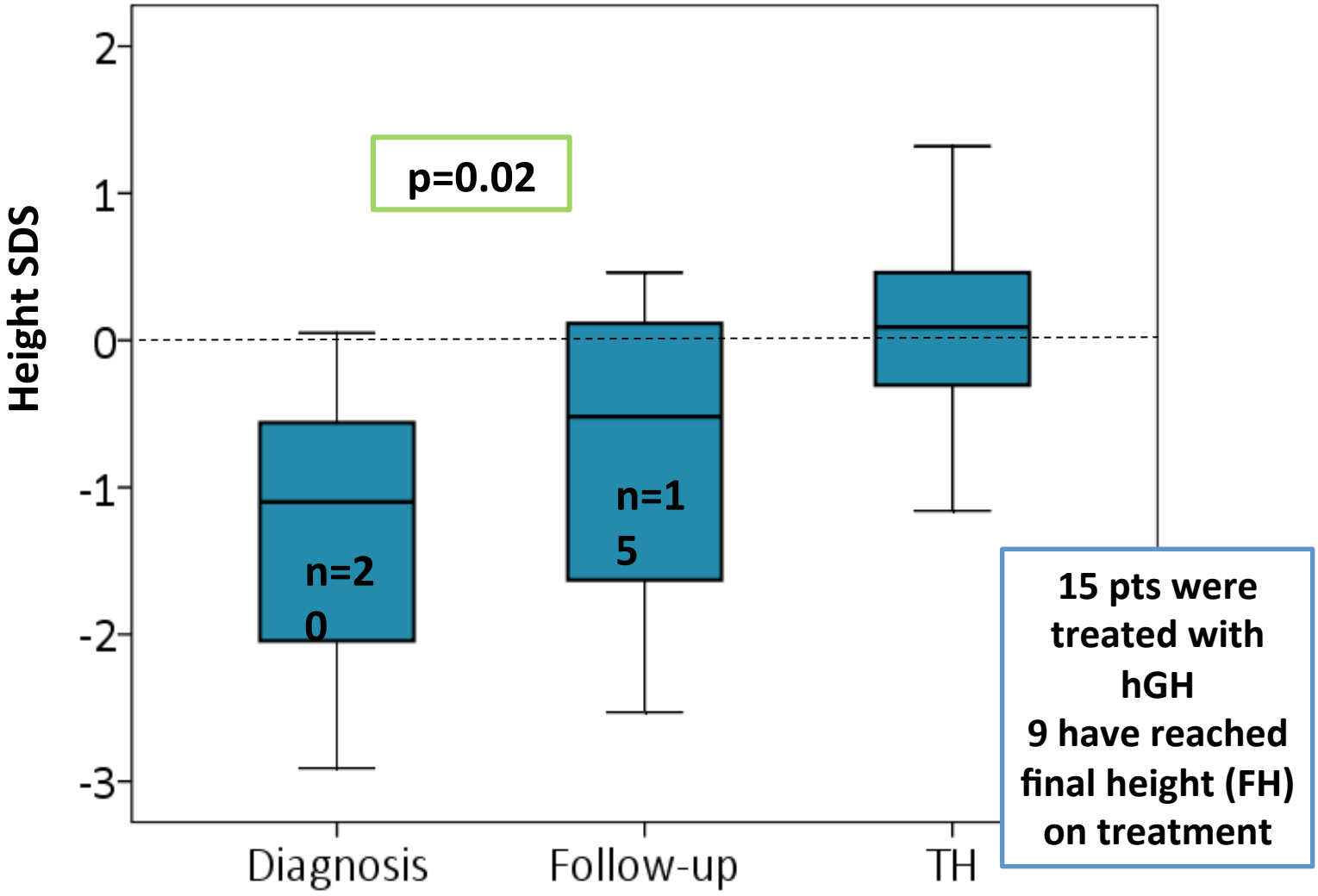

BONE AGE IN PAEDIATRIC CUSHING'S SYNDROME

- 14 children with Cushing's disease, 14 controls
- GH sampled every 20 minutes for 24 hours at 0,3, 6 and 12 months after surgery
- Mean GH pulse amplitude and total area significantly suppressed
- Suppression continued at all time points in spite of some resumption of growth
- CONCLUSIONS: GH remains subnormal after cure in spite of some growth

(Magiakou et al 1994)

Paediatric Cushing's Syndrome
Bart's and The London School of Medicine and Dentistry
1982 - 2010

All patients: n = 56; Age 0.5–17.8 yr

Diagnosis	n	F:M	Mean Age
Cushing's Disease	41	15F 26M	13.2 yr
Primary nodular adrenocortical hyperplasia	7	3F 4M	12.7 yr
Adrenocortical tumour	6	N/A	N/A
Ectopic ACTH syndrome	1	1F	17.7 yr
Exogenous glucocorticoid therapy	1	1M	7.0 yr