Determinants of normal puberty

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European Society of Human Reproduction and Embryology

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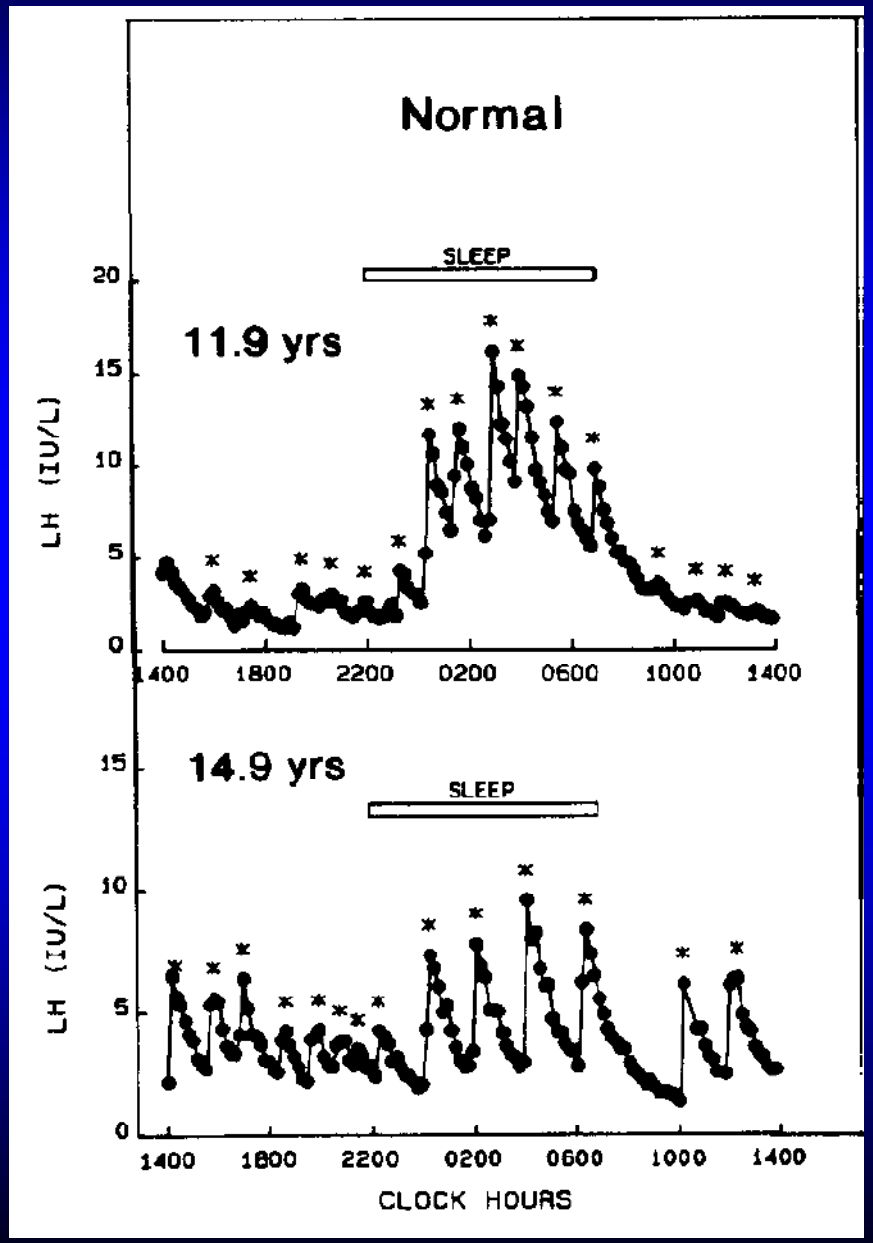
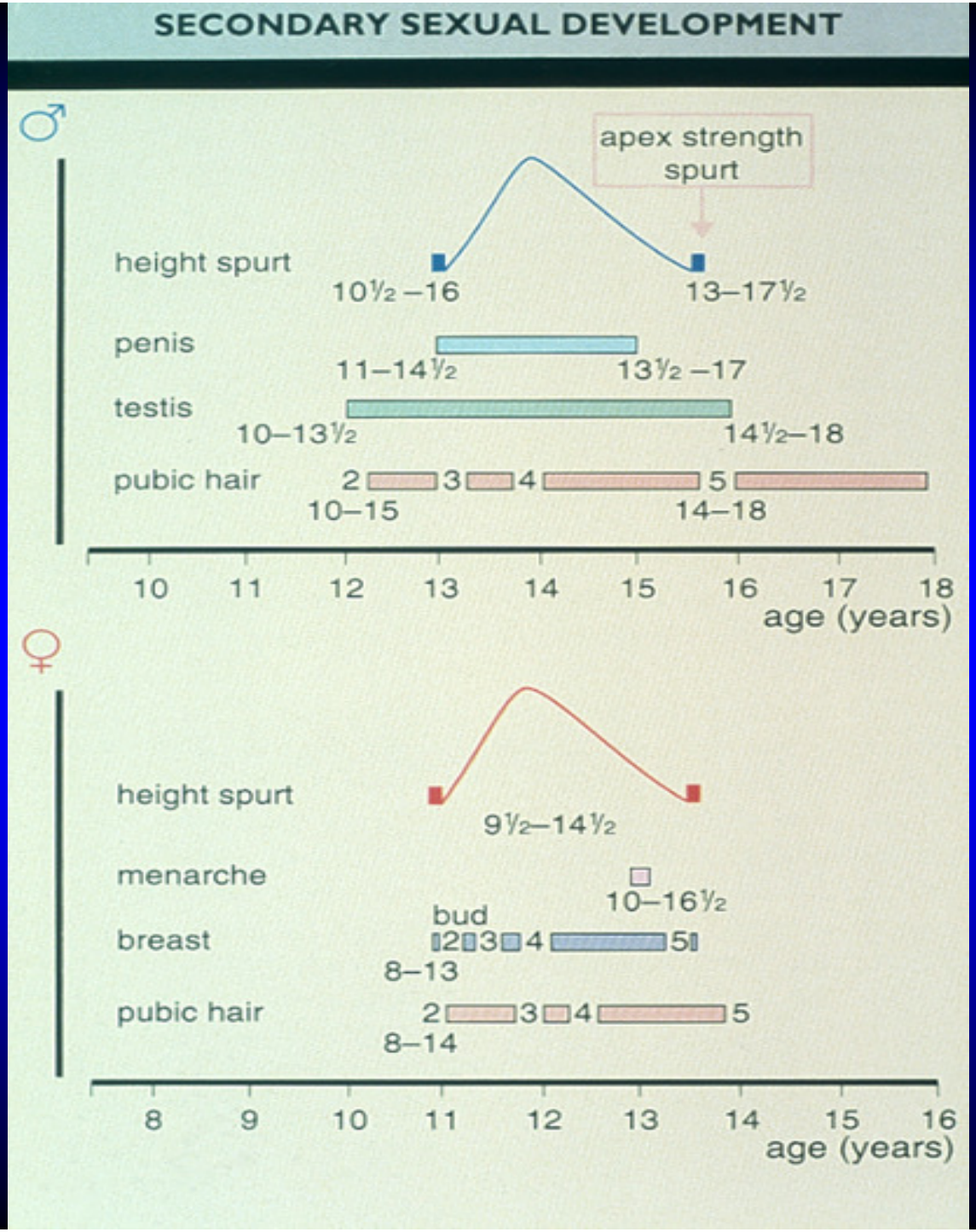
Determinants of normal puberty

- Endocrinology of puberty
- Timing of puberty
- Thelarche, pubarche and adrenarche

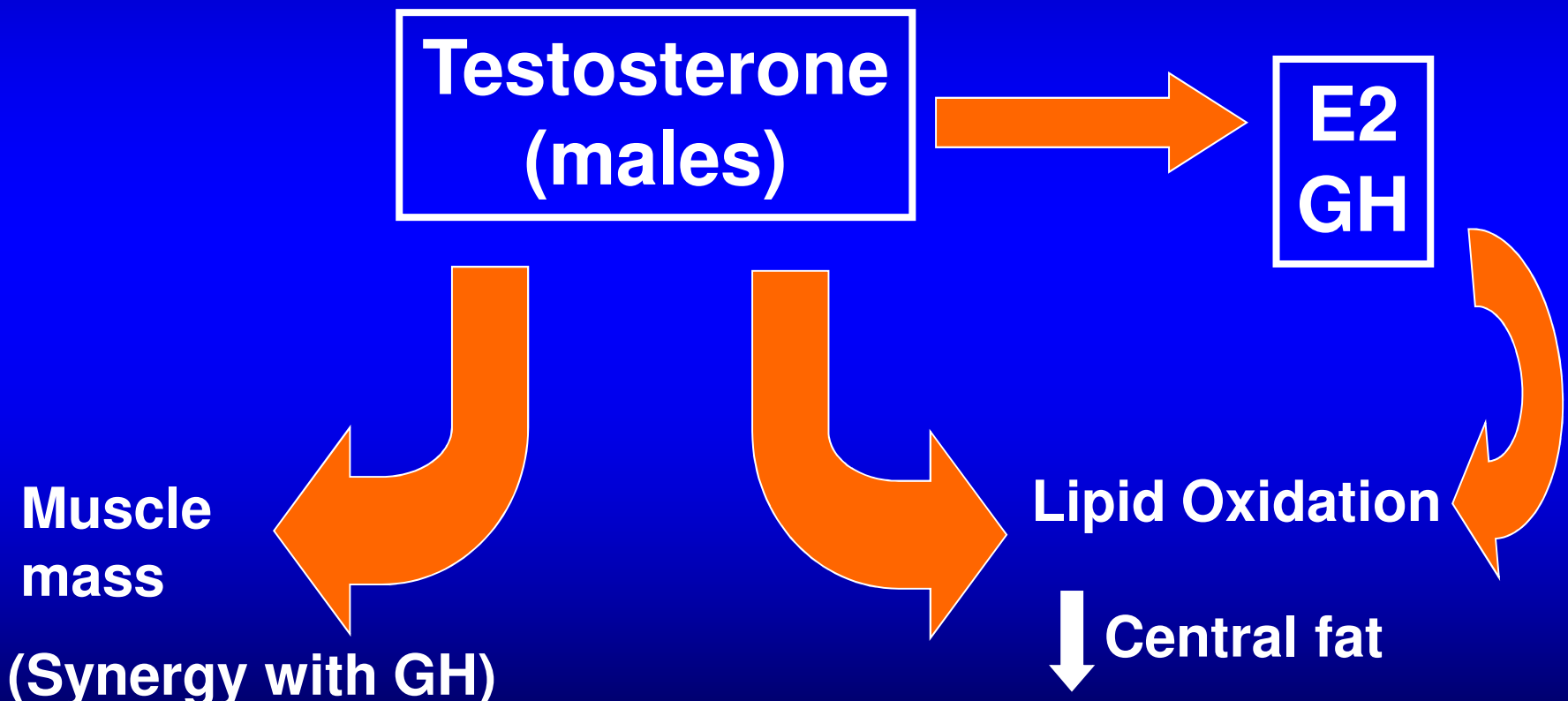
Luteinizing hormone (LH) pulsatility



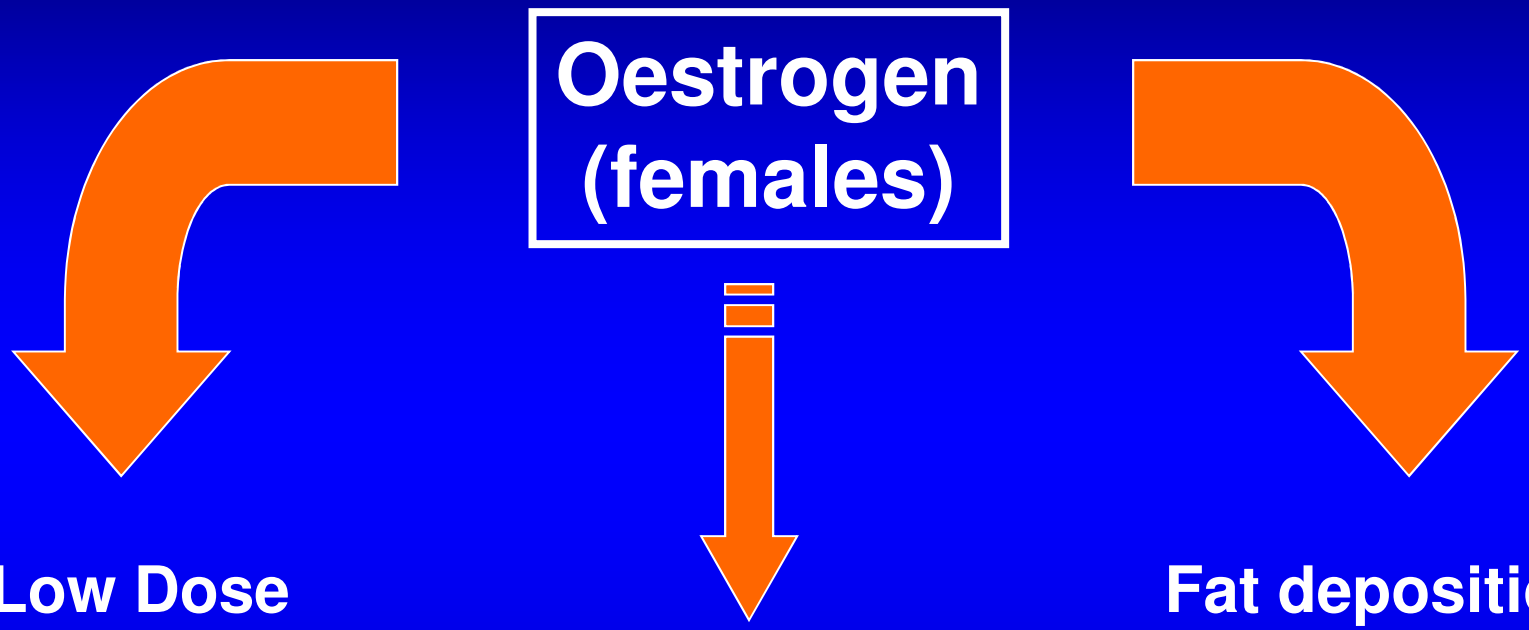
Apter D, 1994, JCEM


SECONDARY SEXUAL DEVELOPMENT
♂
apex strength spurt
height spurt
10½–16
13–17½
penis
11–14½
13½–17
testis
10–13½
14½–18
pubic hair
2
3
4
5
10–15
14–18
10 11 12 13 14 15 16 17 18
age (years)
♀
height spurt
9½–14½
menarche
10–16½
bud
breast
2
3
4
5
8–13
pubic hair
2
3
4
5
8–14
8 9 10 11 12 13 14 15 16
age (years)

Physiological effects of Testosterone



Physiological effects of Oestrogen

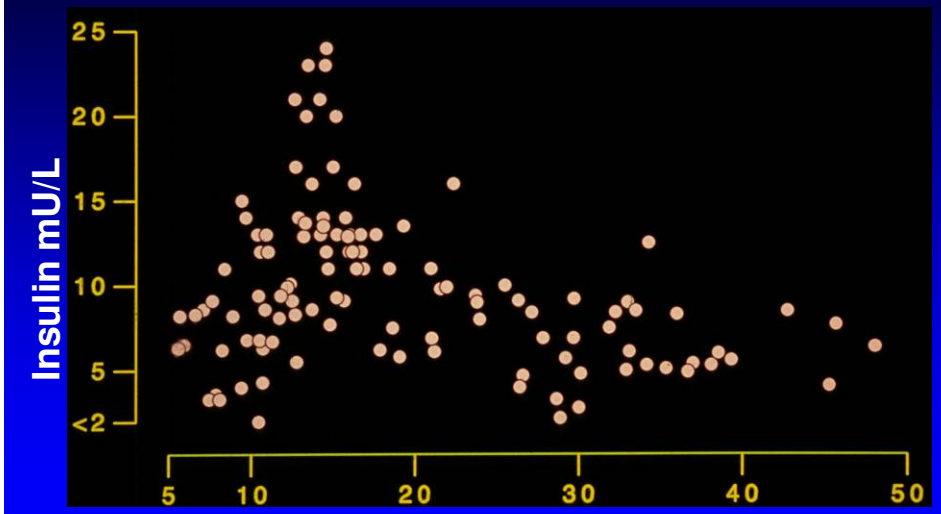


Low Dose
Primes GH release

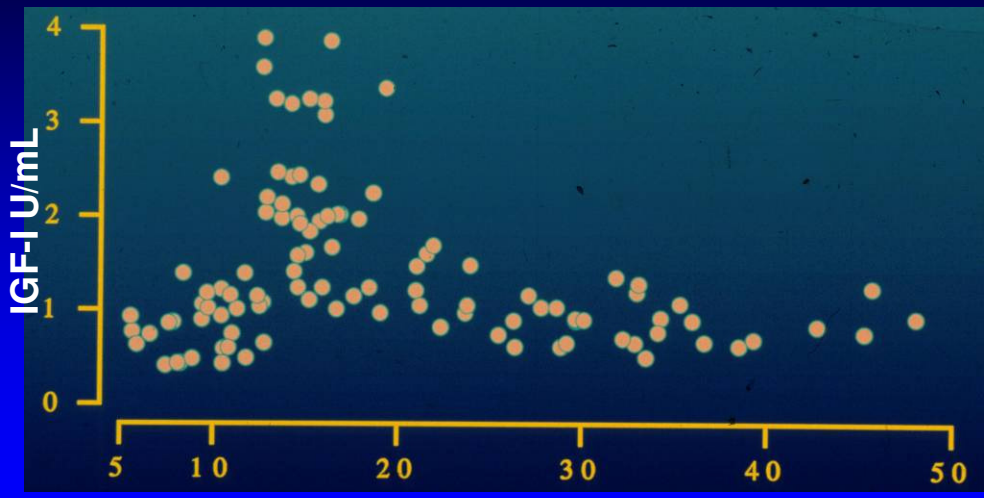
High Dose
Blocks GH action
↑ GH Levels

Fat deposition
Gynoid distribution
E2 sensitive lipase
↓ lipid oxidation

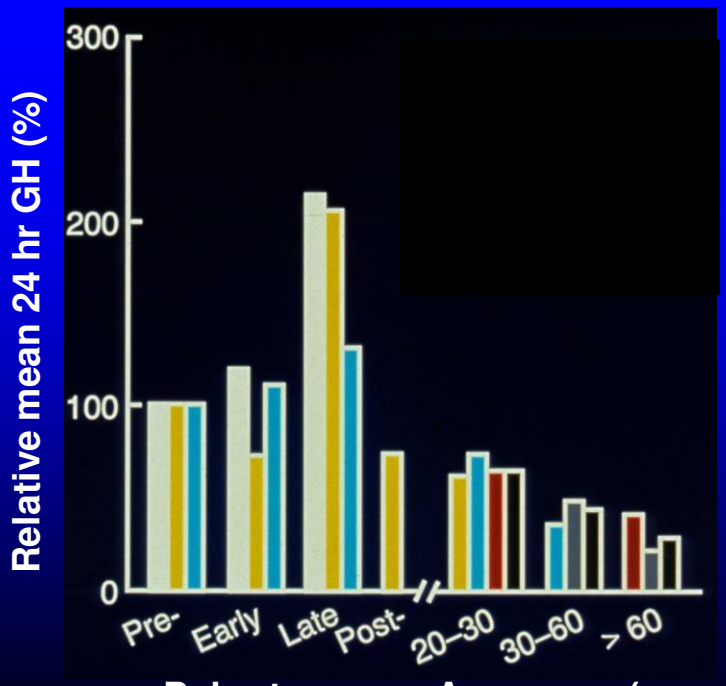
Fasting insulin



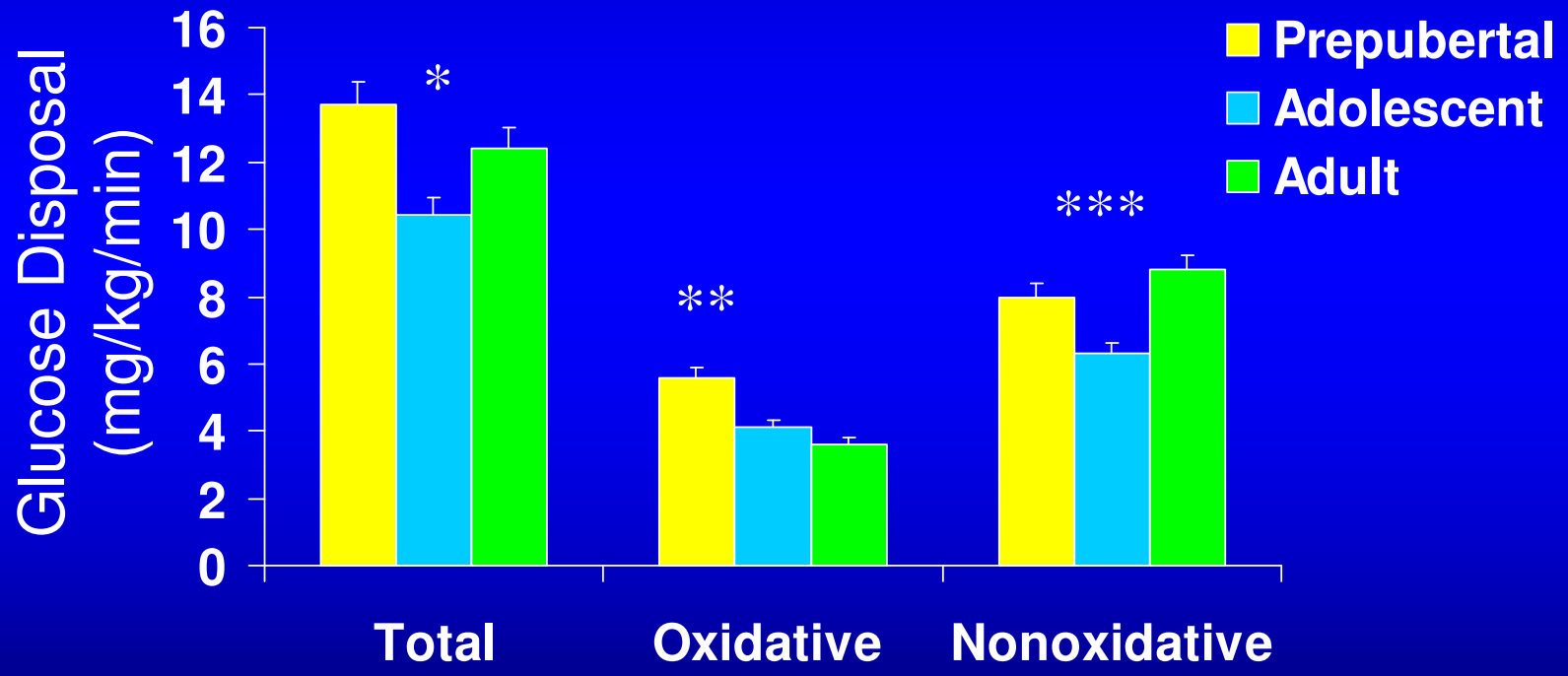
IGF-I



Growth Hormone

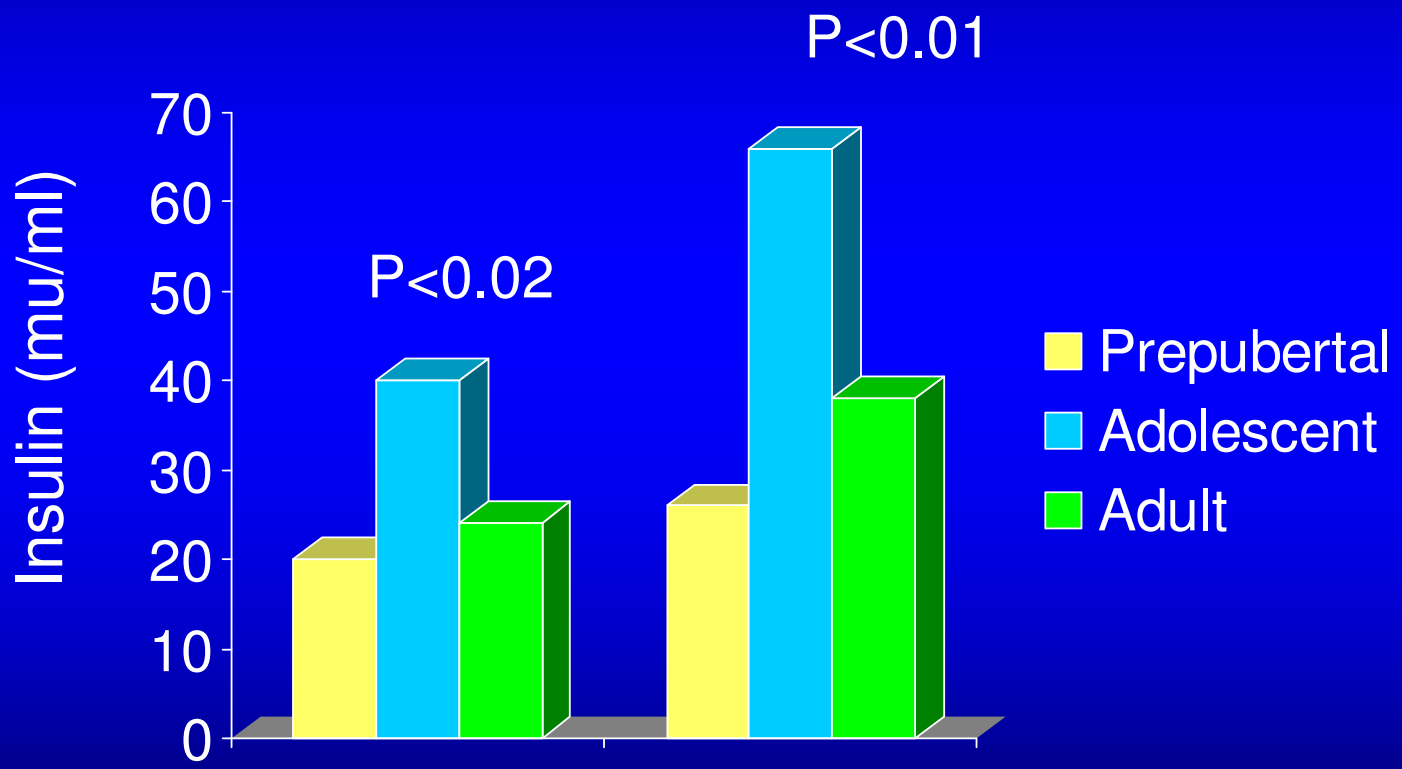


Insulin Resistance of Puberty



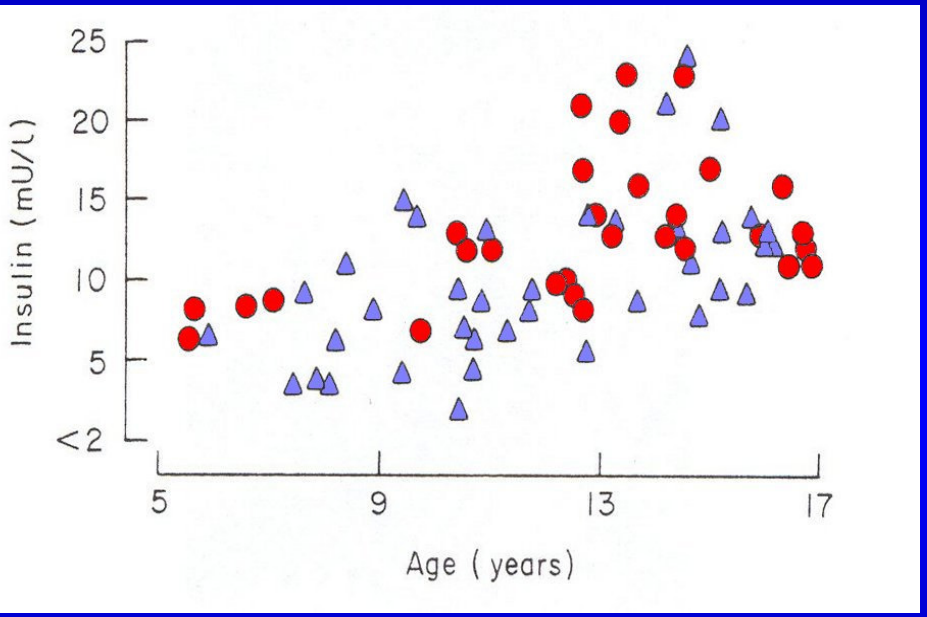
Arslanian S & Kalhan S: Diabetes 43: 908, 1994

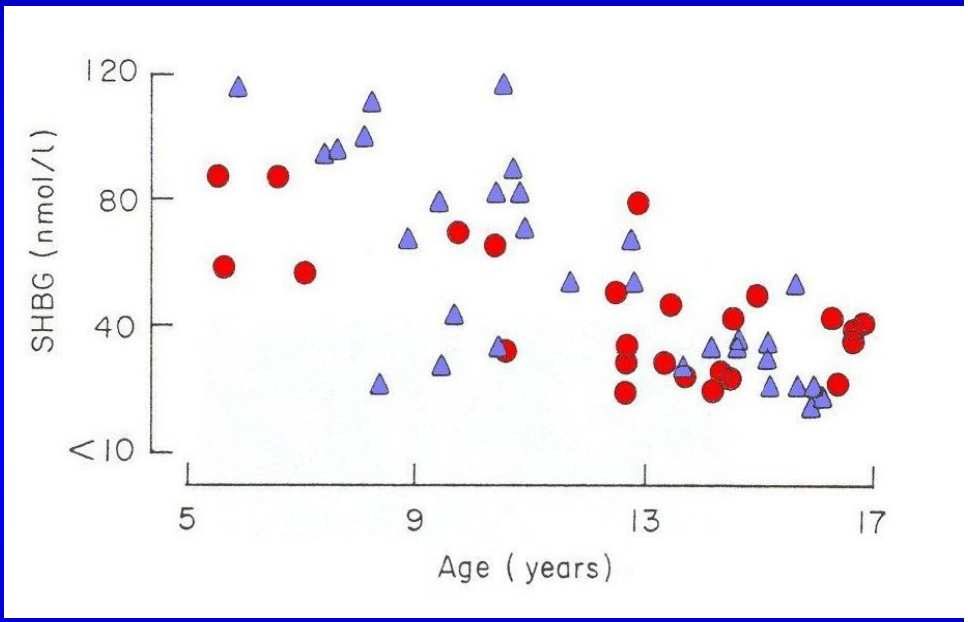
Increased Insulin Secretion In Puberty



Caprio et al J Pediatr 114: 963, 1989

Insulin levels and SHBG





● Females
▲ Males

Holly et al. Clin Endocrinol 1989;31:277-284

Insulin resistance of puberty

- 25-30% decrease insulin sensitivity
- Glucose uptake by muscle
- Post absorptive proteolysis
- Protein sparing 1g/Kg/d of FFM

Puberty

16% mature height

Doubling of LBM

Puberty

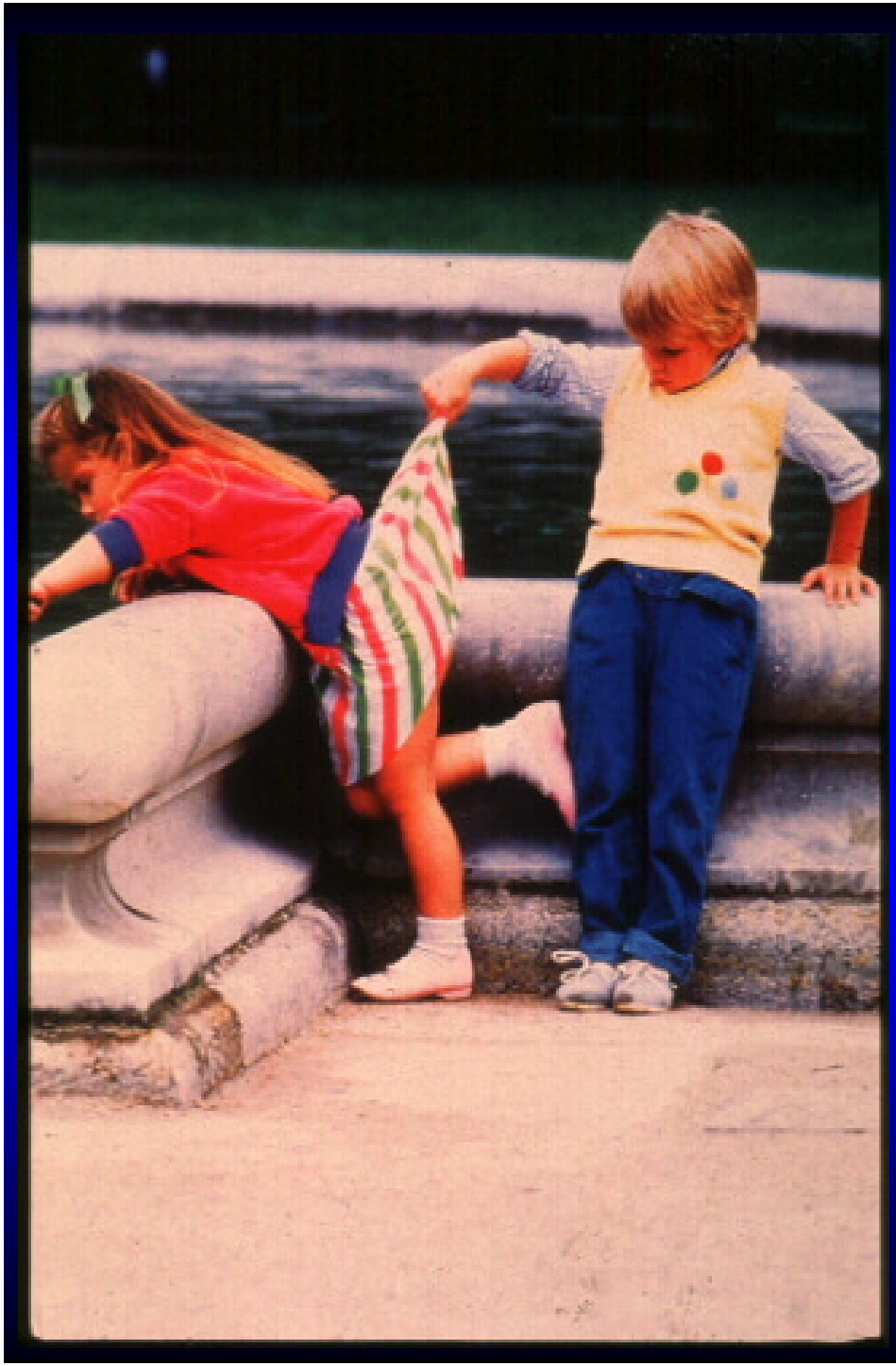
16% Mature height

42% (Males)

47% (Females)

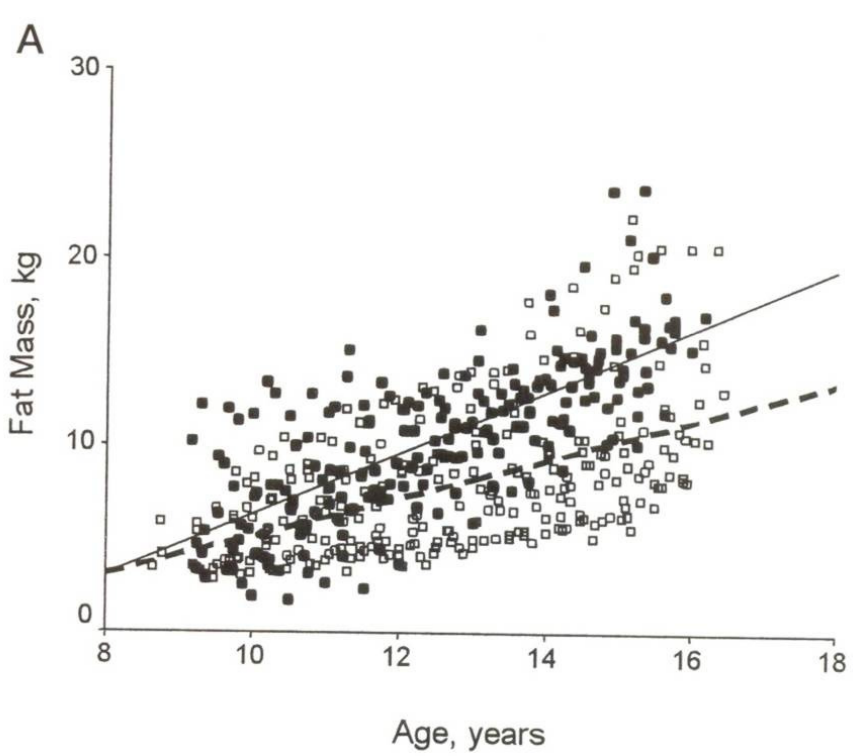
} Adult weight

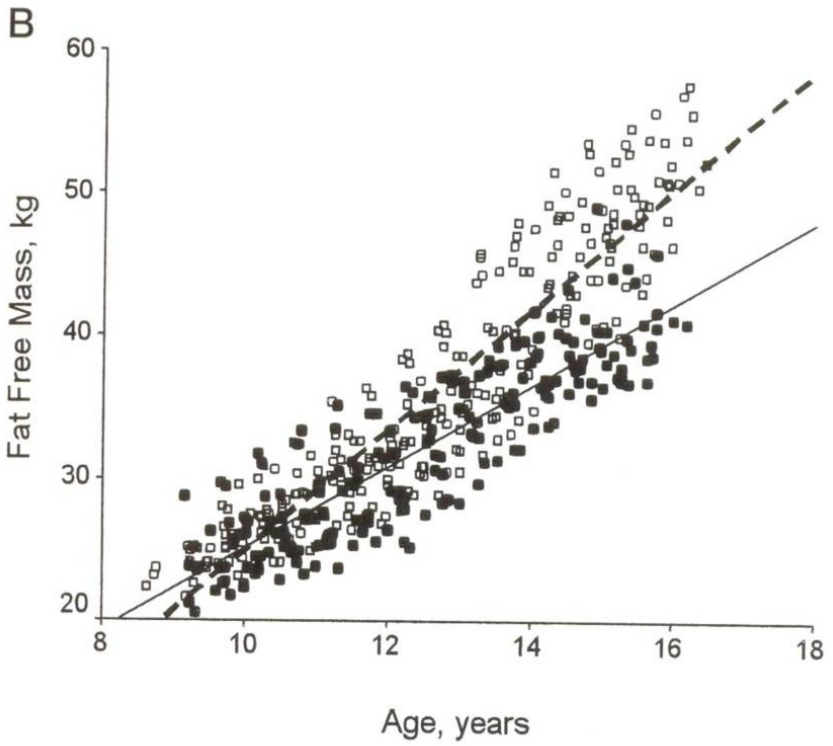
Doubling of LBM



Gender differences?

Fat mass and Fat free mass in boys and girls



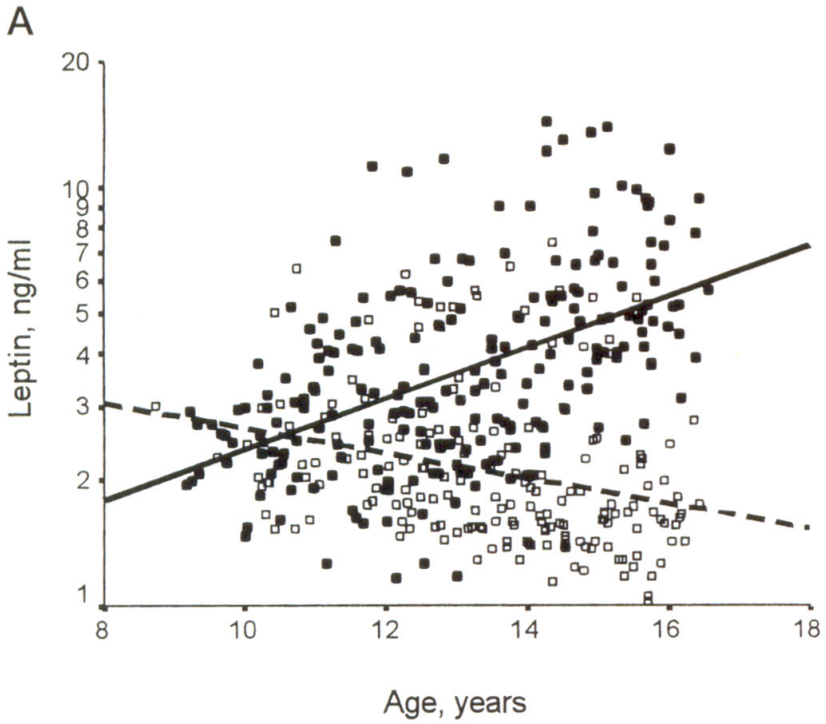


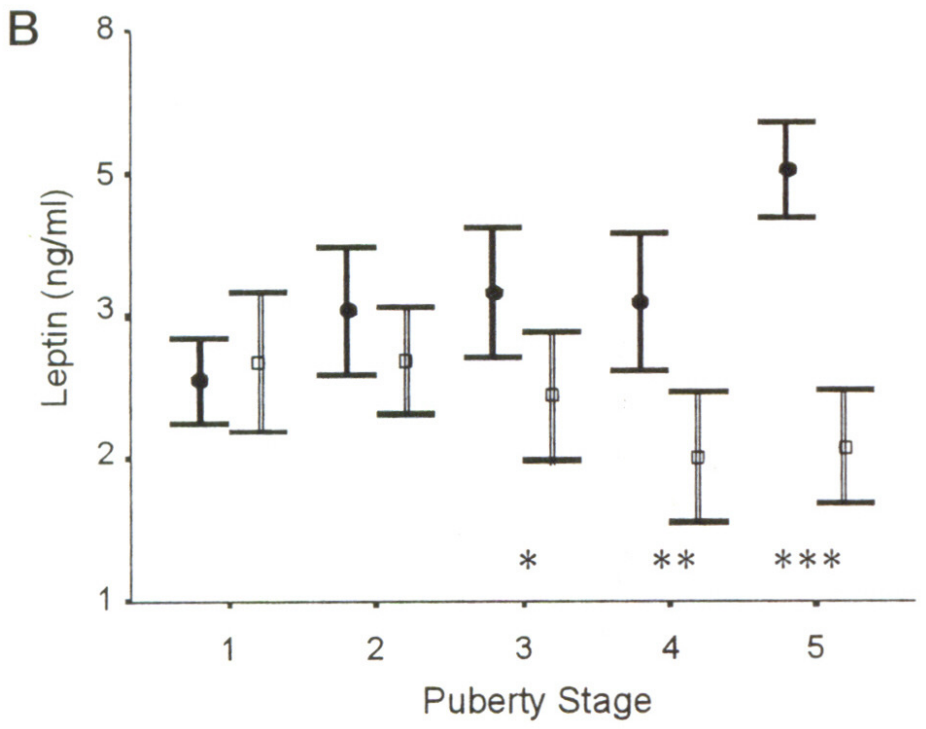
Boys □ and ---
Girls ● and —

Boys □ and ---
Girls ● and —

Ahmed et al. JCEM 1999;84:899-905

Sex differences in leptin levels plotted against age and pubertal stage

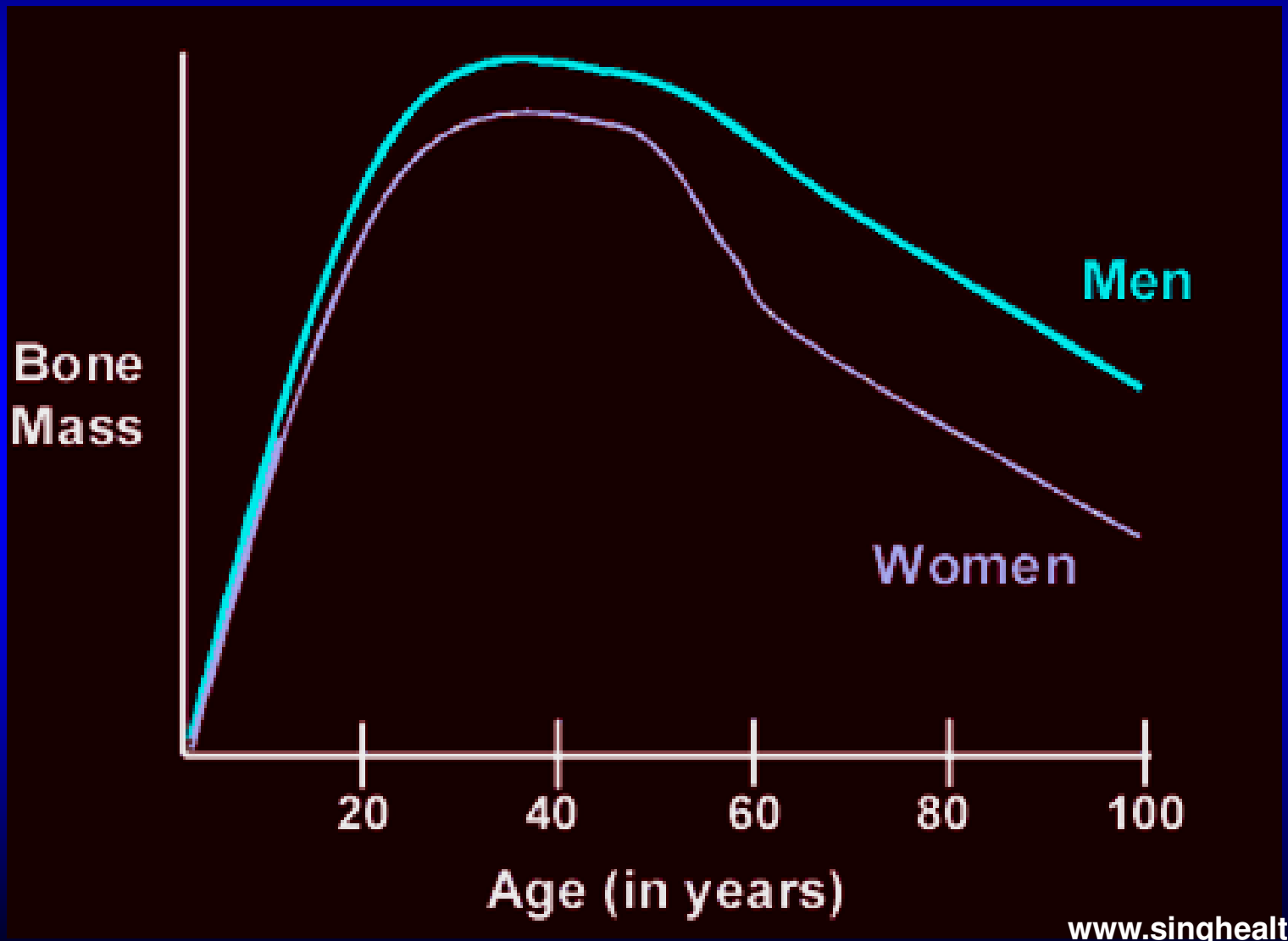




Boys □ and ---
Girls ● and —

Ahmed et al. JCEM 1999;84:899-905

Peak Bone Mass



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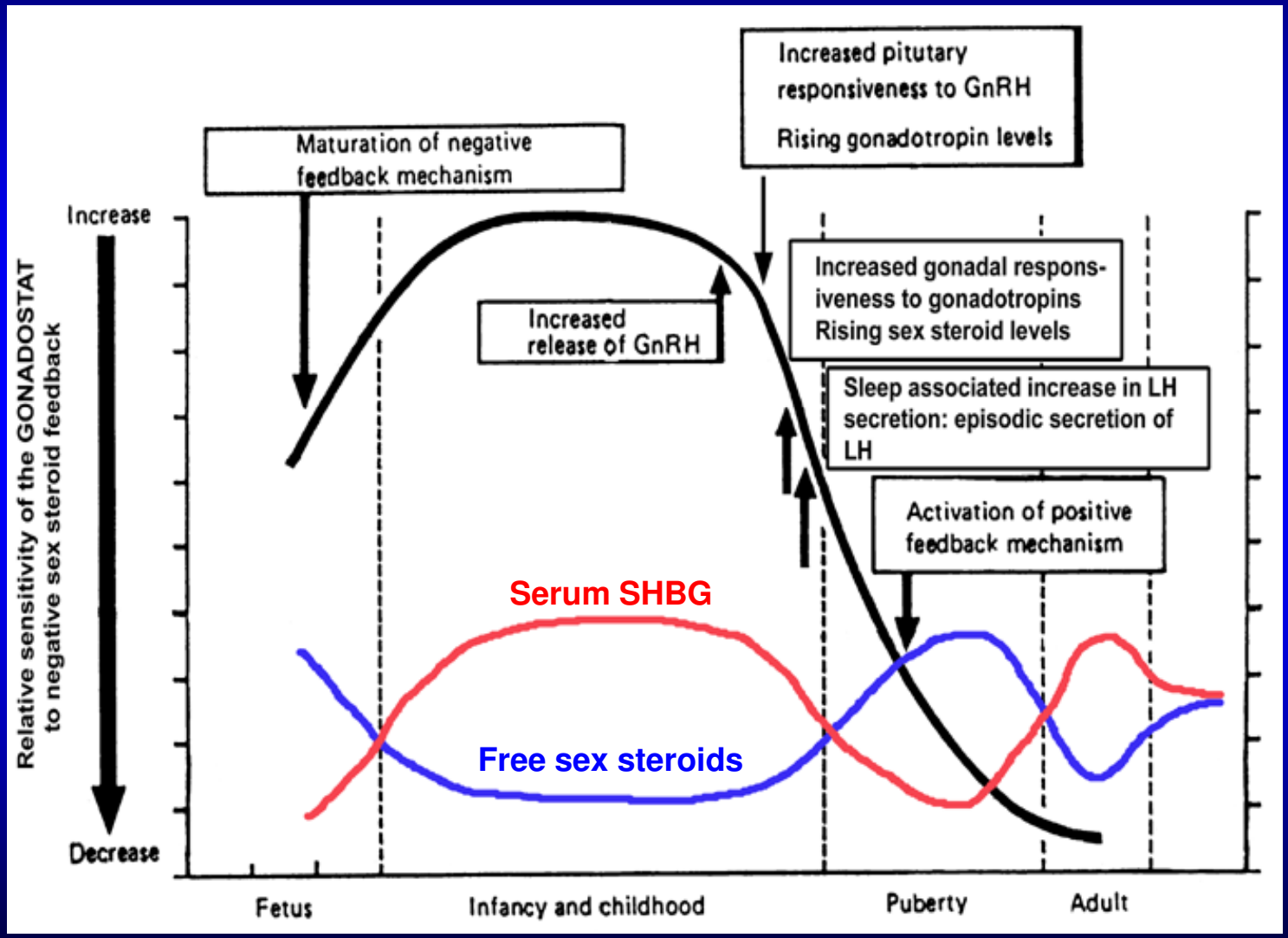
GONADOSTAT theory of regulation of LH control and timing of puberty



Grumbach et al; Control of the Onset of Puberty 1974

Genetic inheritance of puberty

Mean difference in age at menarche	
Unrelated women	18.6 months
Sisters	12.9
DZ twins	12.0
MZ twins	2.2

60-80% of the variance is familial

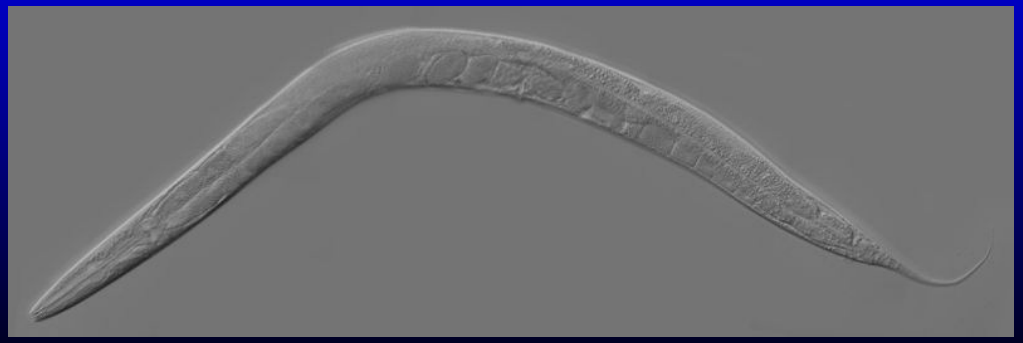
Petri 1935
Parent 2003

Age at Menarche

nature genetics

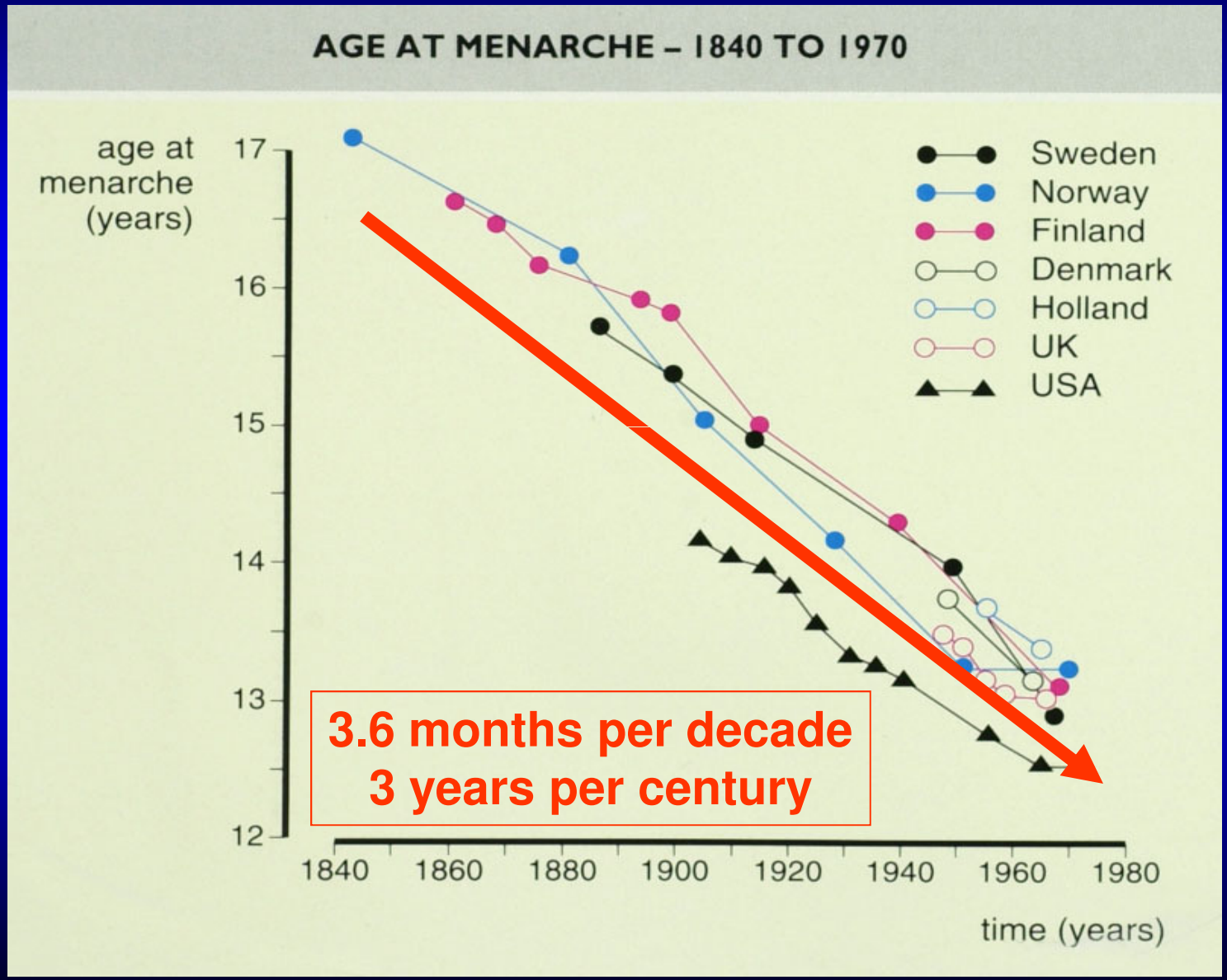
- He et al.
- Perry et al.
- Ong et al.
- Sulem et al.

- ***LIN28B*** **shows similar sequence homology to the heterochronic gene** ***lin-28*** **in** ***C. elegans*** **(Guo** ***et al***, ***Gene***, **2006).**
- **Mutations in** ***lin-28*** **produce abnormal rapid tempo of development through larval stages and adult cuticle development (Ambros** ***et al***, ***Science***, **1984).**
- **Enhanced** ***lin-28*** **expression delays larval progression (Moss** ***et al***, ***Cell***, **1997).**
- ***LIN28B*** **and** ***LIN28*** **encode potent and specific regulators of microRNA preprocessing (Viswanathan** ***et al***, ***Science***, **2008), and regulate cell pluripotency and cancer growth (Guo** ***et al***, **2006).**

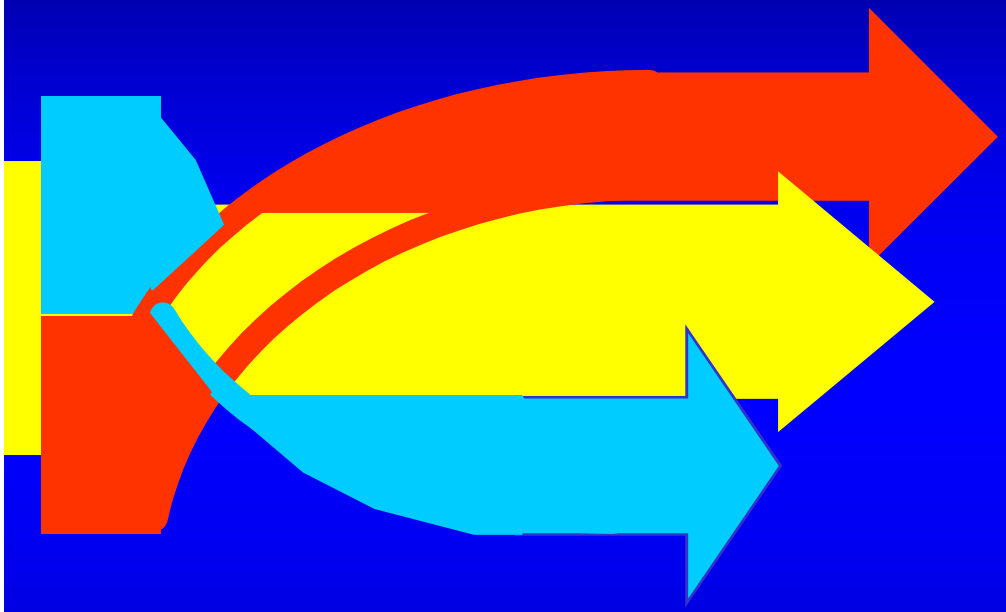


Caenorhabditis elegans

Historical trends in age at menarche



Early maturation



Birth *2 years* *5 to 8 years*

- ↑ Childhood Ht BMI
- ↑ Childhood Ht gain
- Earlier puberty

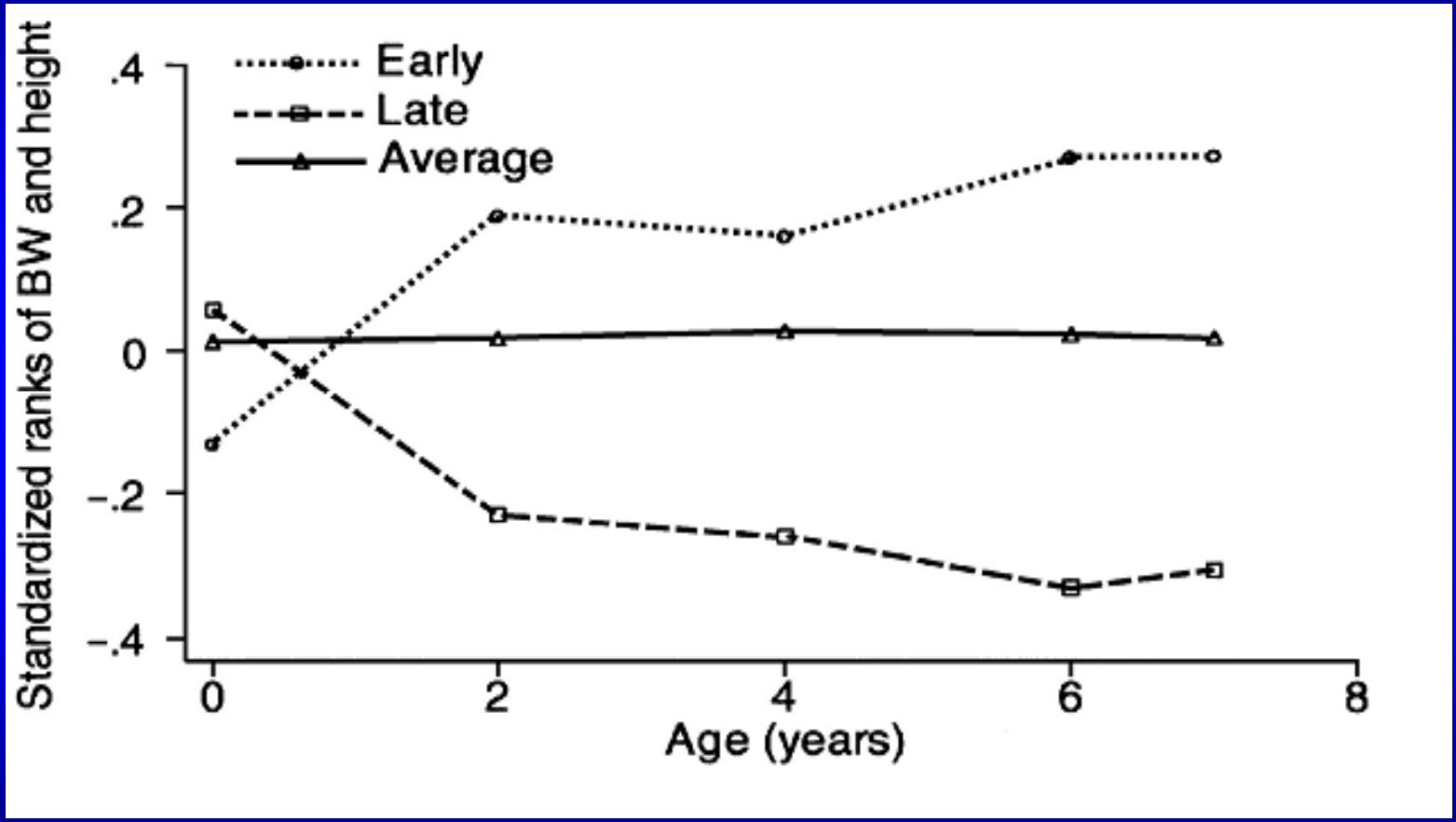
  0.6 y boys

  0.7 y girls
- ↓ Pubertal Ht gain

He & Kalbery Ped Res 2001;49:244-251

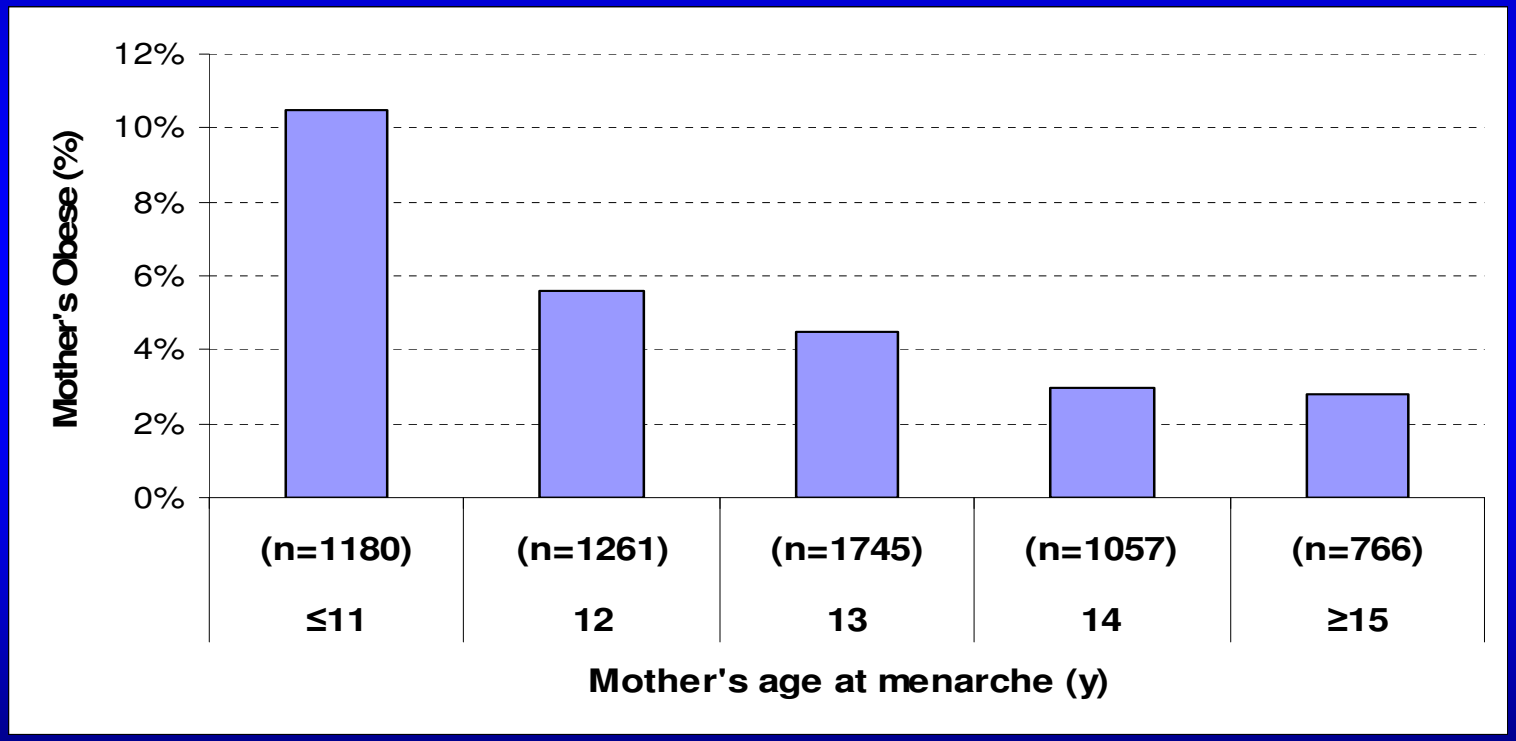
Rapid infancy growth → Earlier puberty

MRC 1946 Birth Cohort



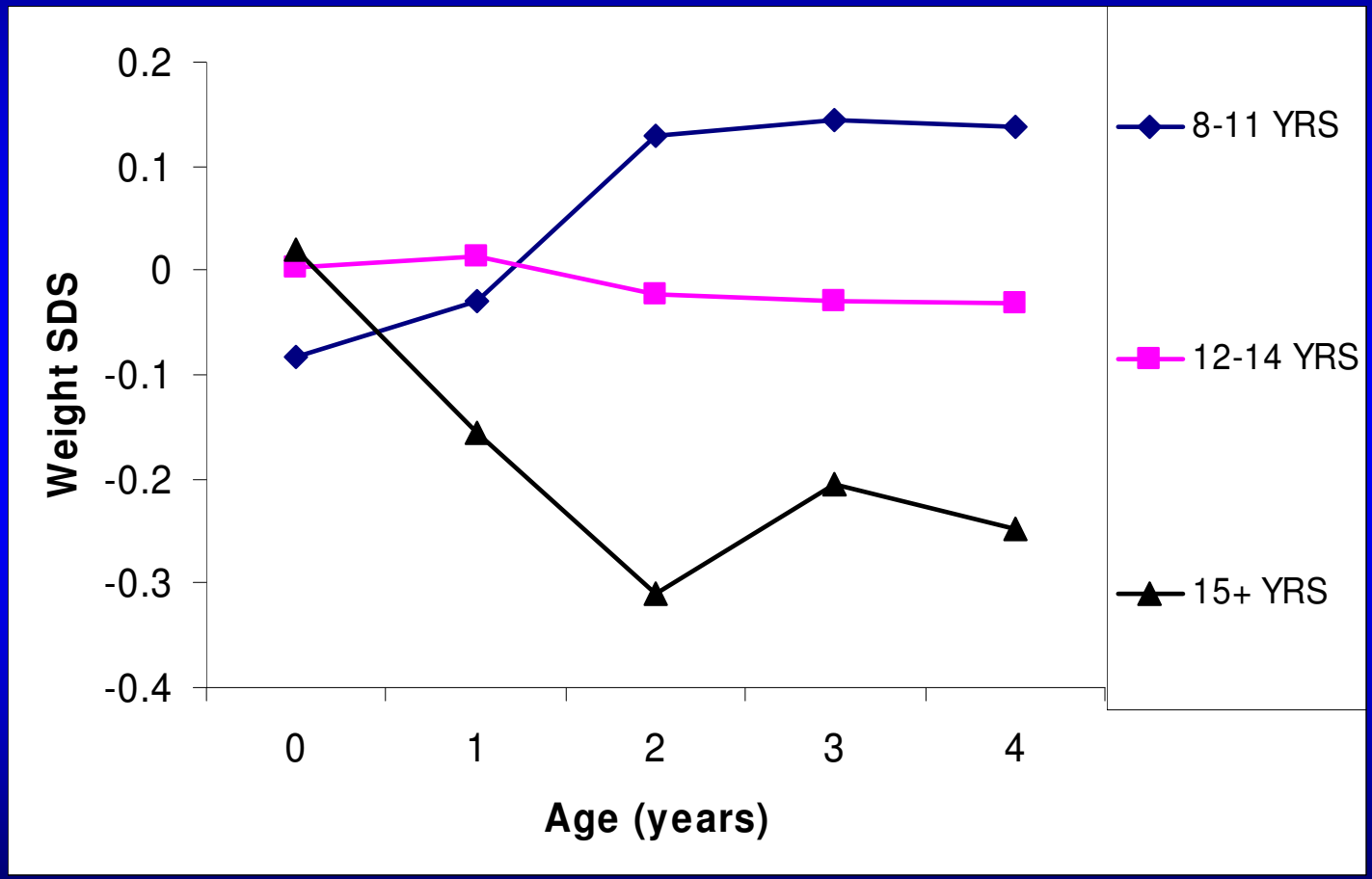
dos Santos Silva et al. Int J Epidemiology 2002

Age at menarche & obesity in ALSPAC mothers



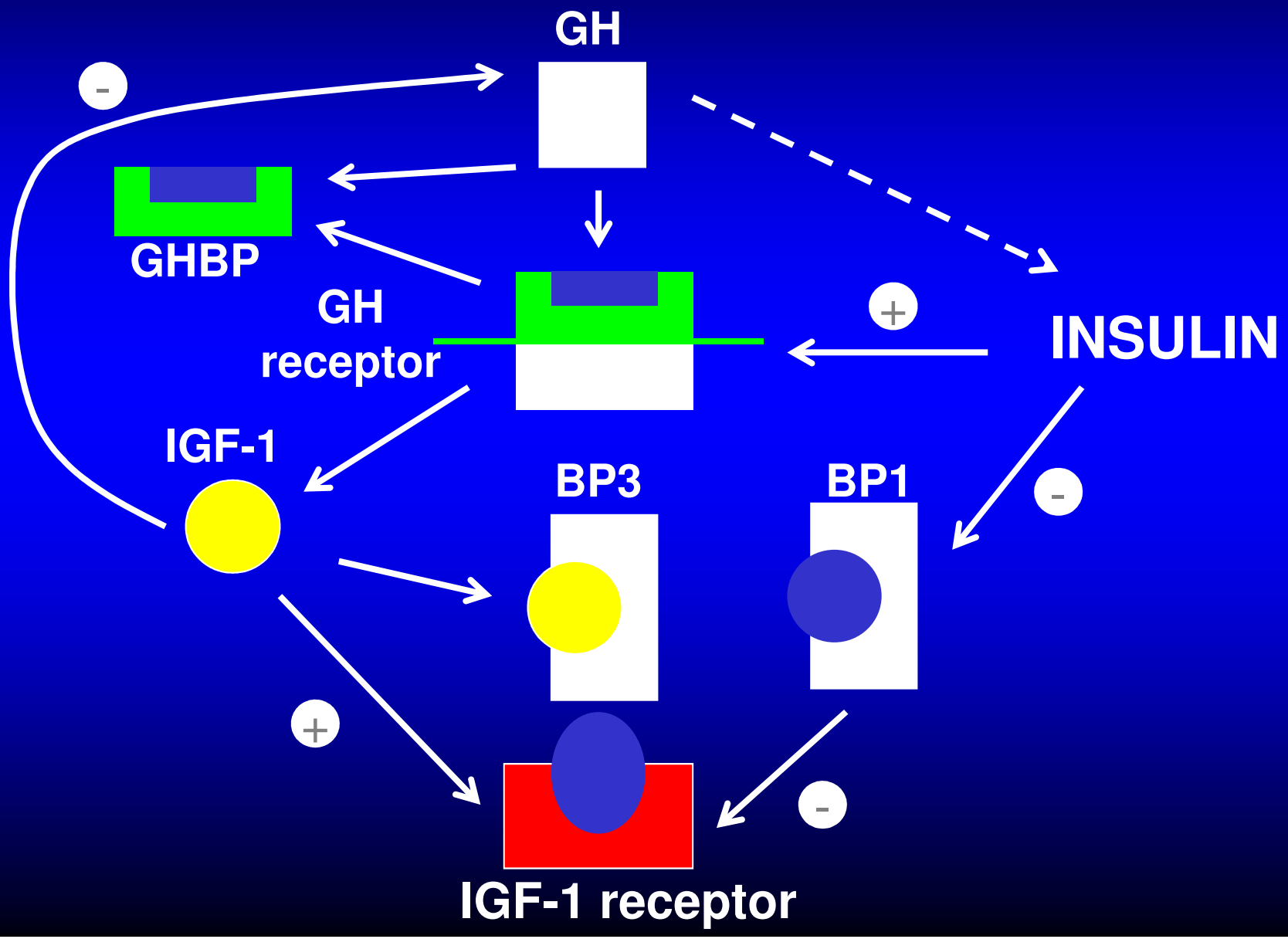
Ong et al. PLoS Medicine 2007

Offspring postnatal weight gain by mother's age at menarche

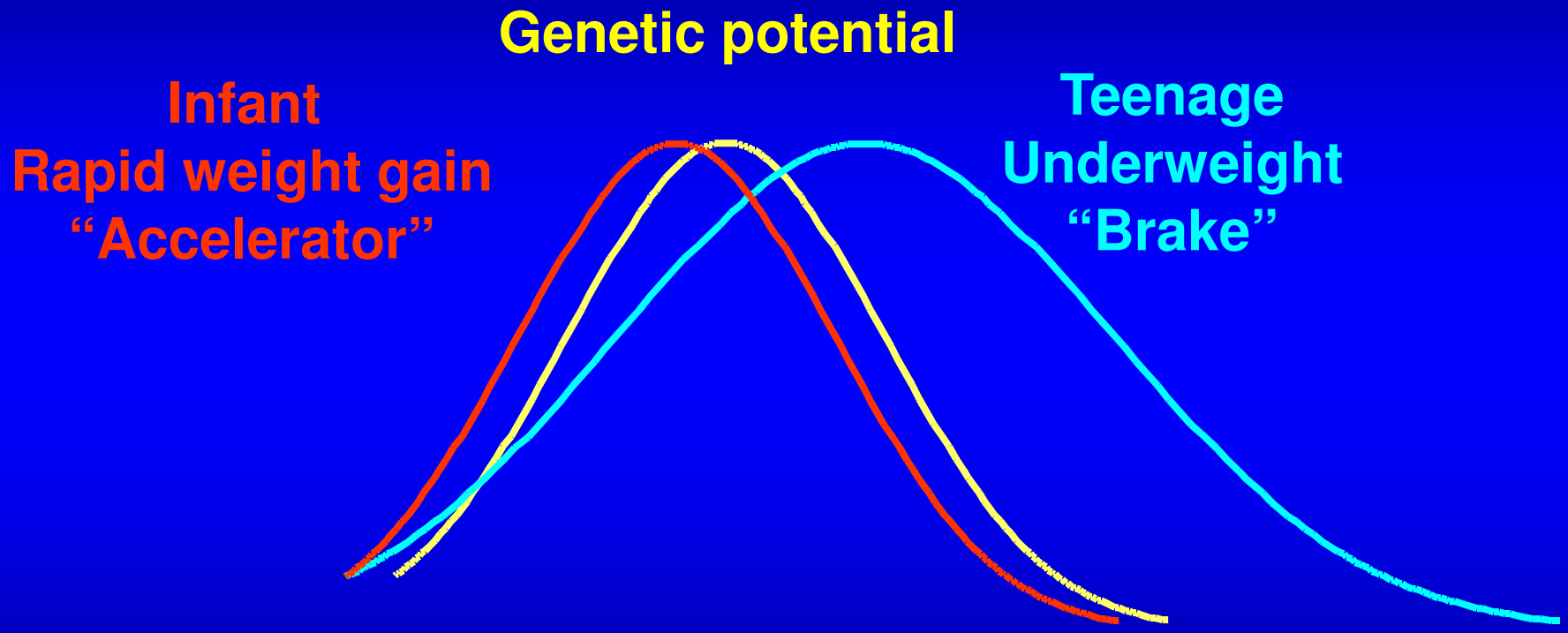


ALSPAC data

Growth Hormone-Insulin Interaction



Hypothesis:
Age-specific effects of weight on puberty



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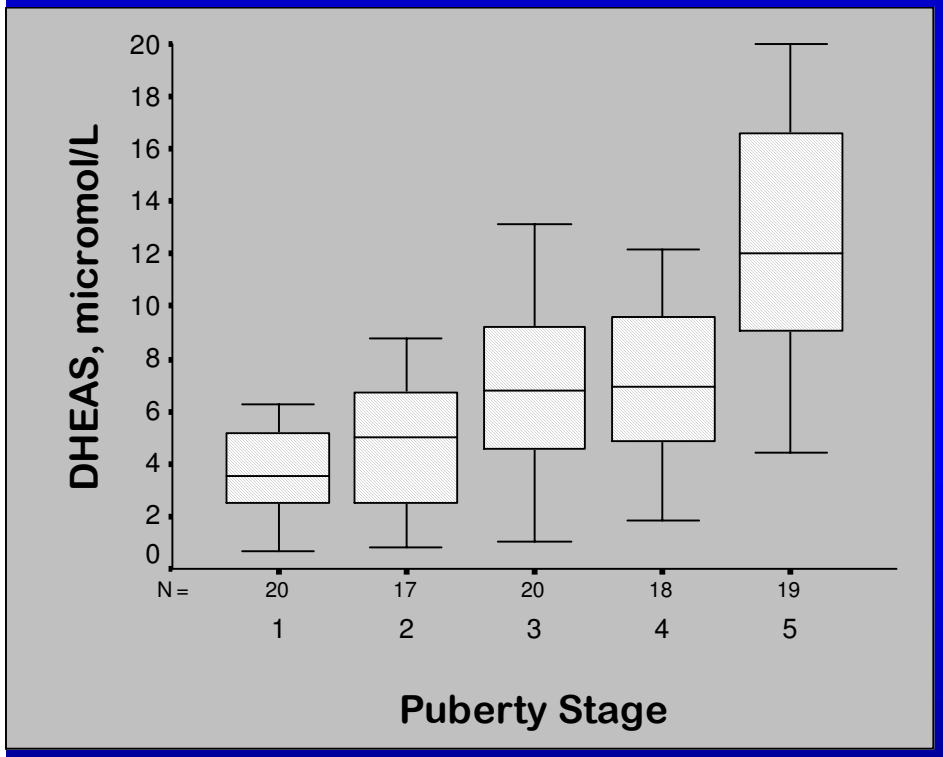
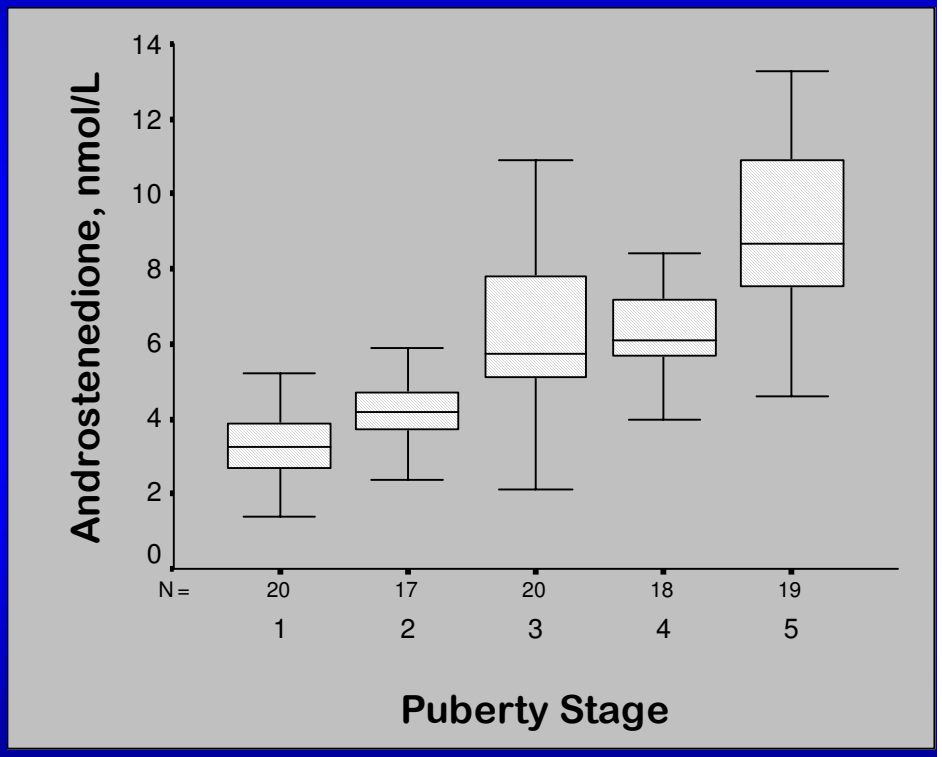
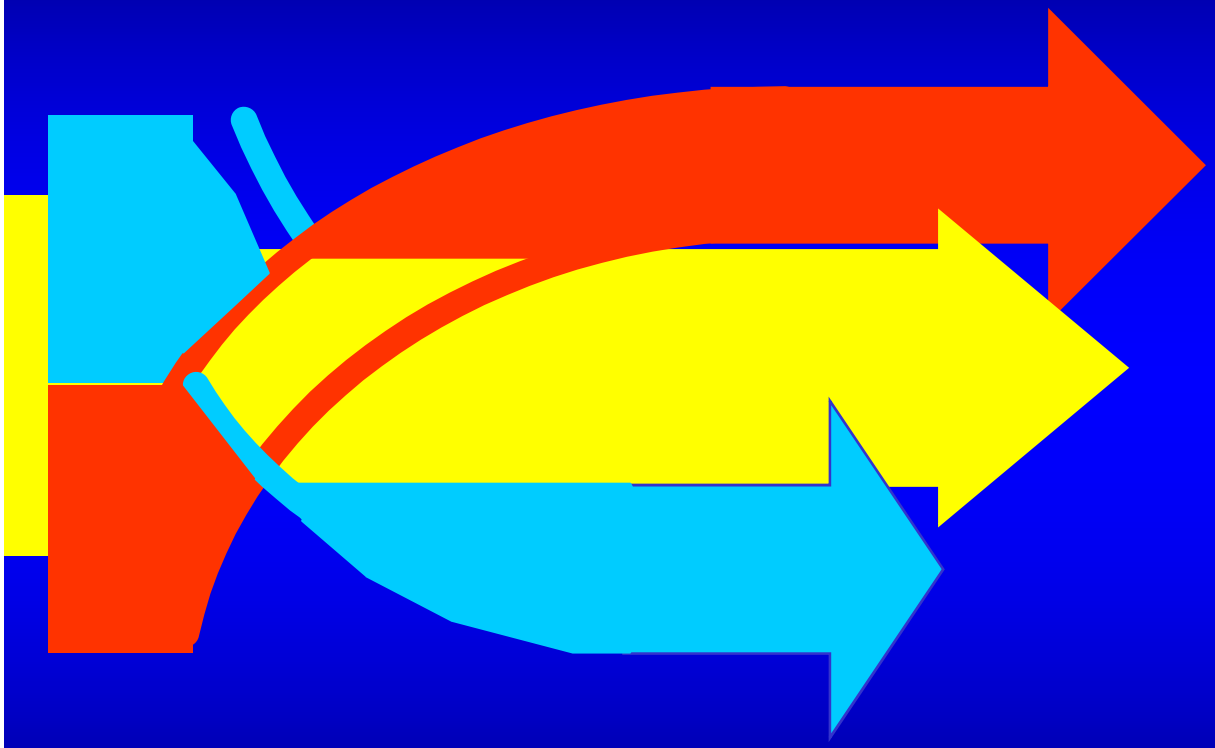
Normal girls: Adrenal Androgens, longitudinal changes



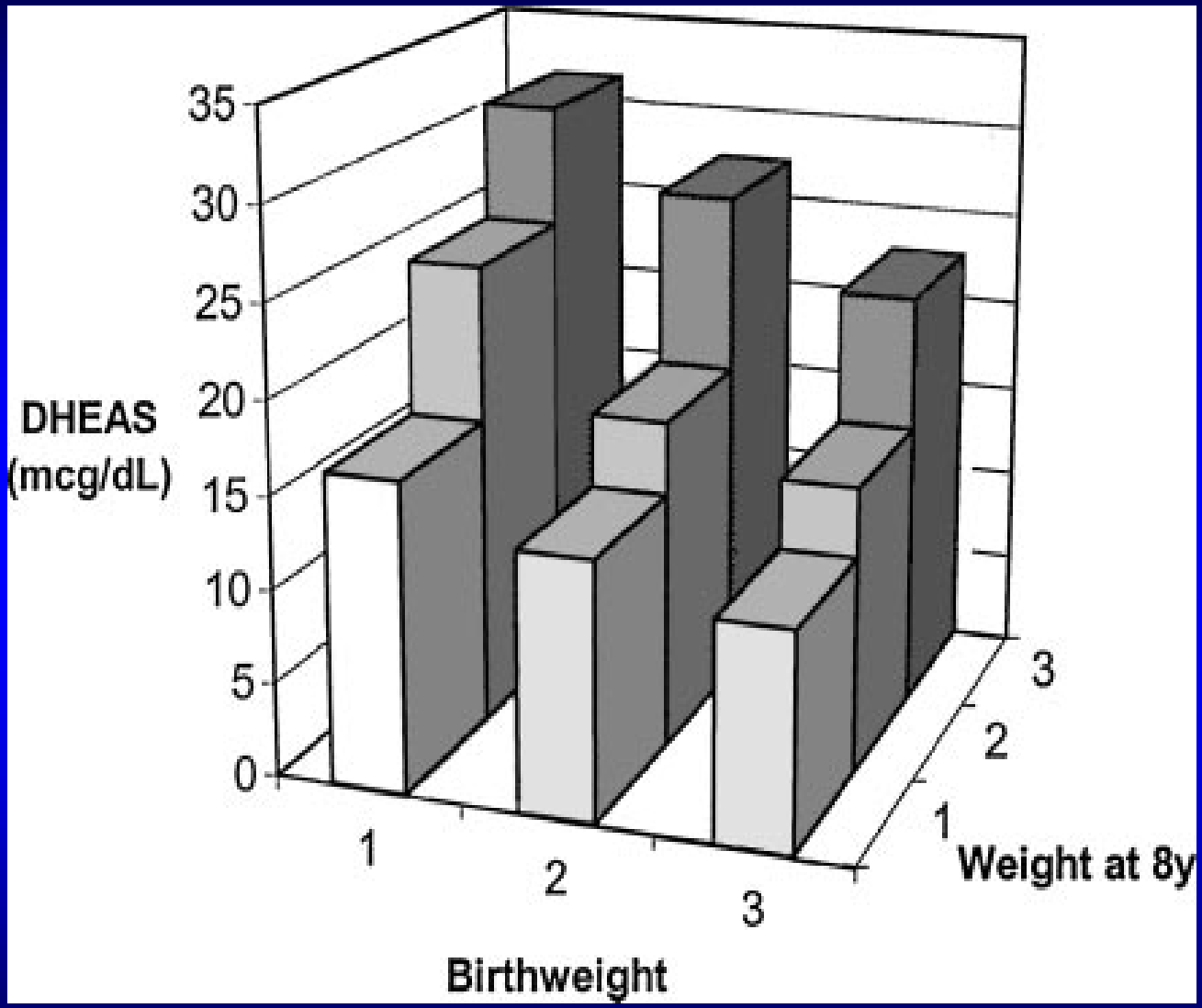


Postnatal catch-up growth



Obesity
Insulin resistance
Thelarche
Adrenarche

Birth *2 years* *5 to 8 years*



Ong et al. J Clin Endocrinol Metab 2004;89:2647--2651

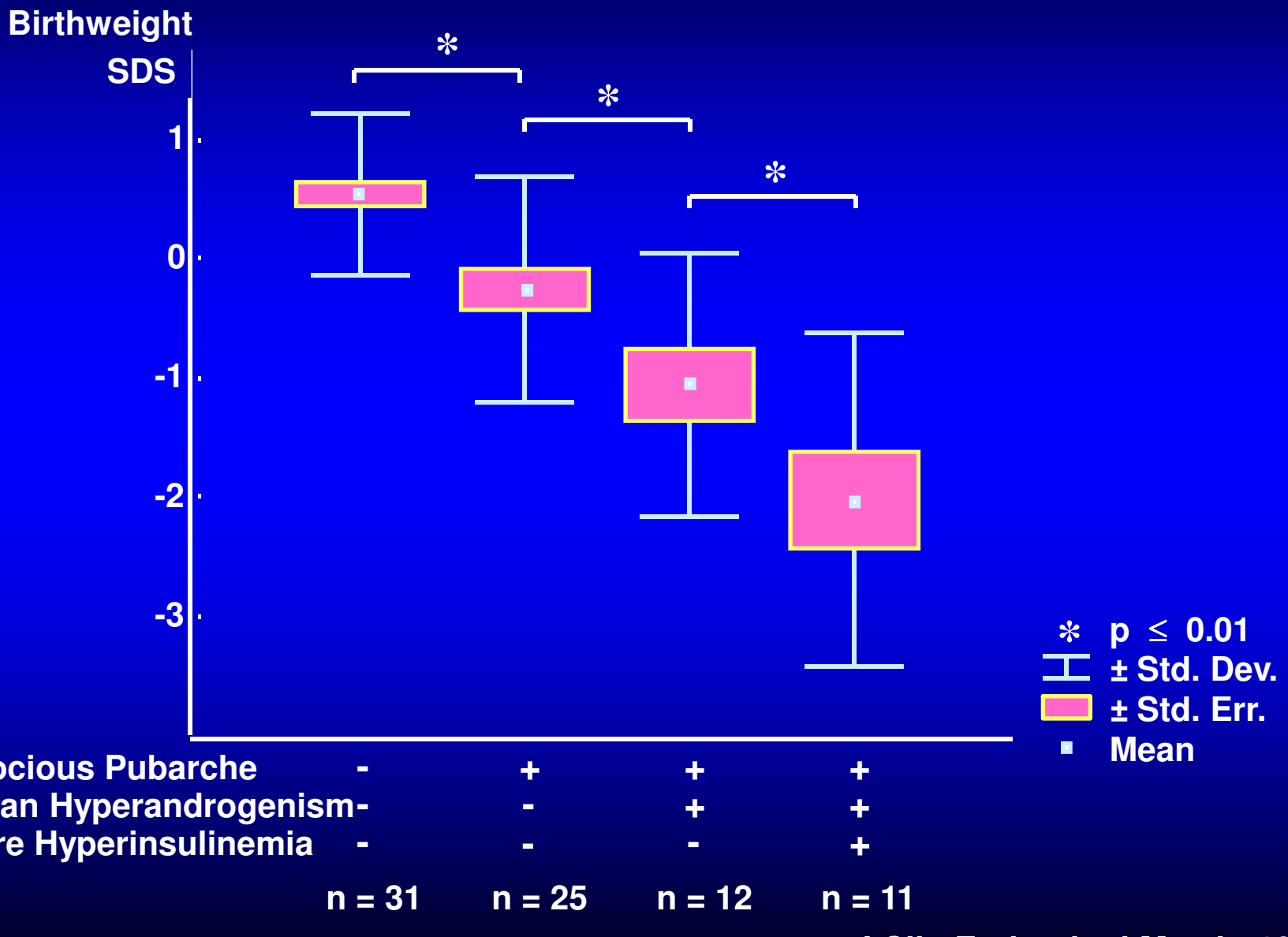
Precocious Adrenarche / Pubarche

- Onset of pubic hair < 8yrs (girls)
- Bone Age advance
- Raised DHEA and DHEAS
- Final height not compromised

Increased risks in low birth weight populations for:

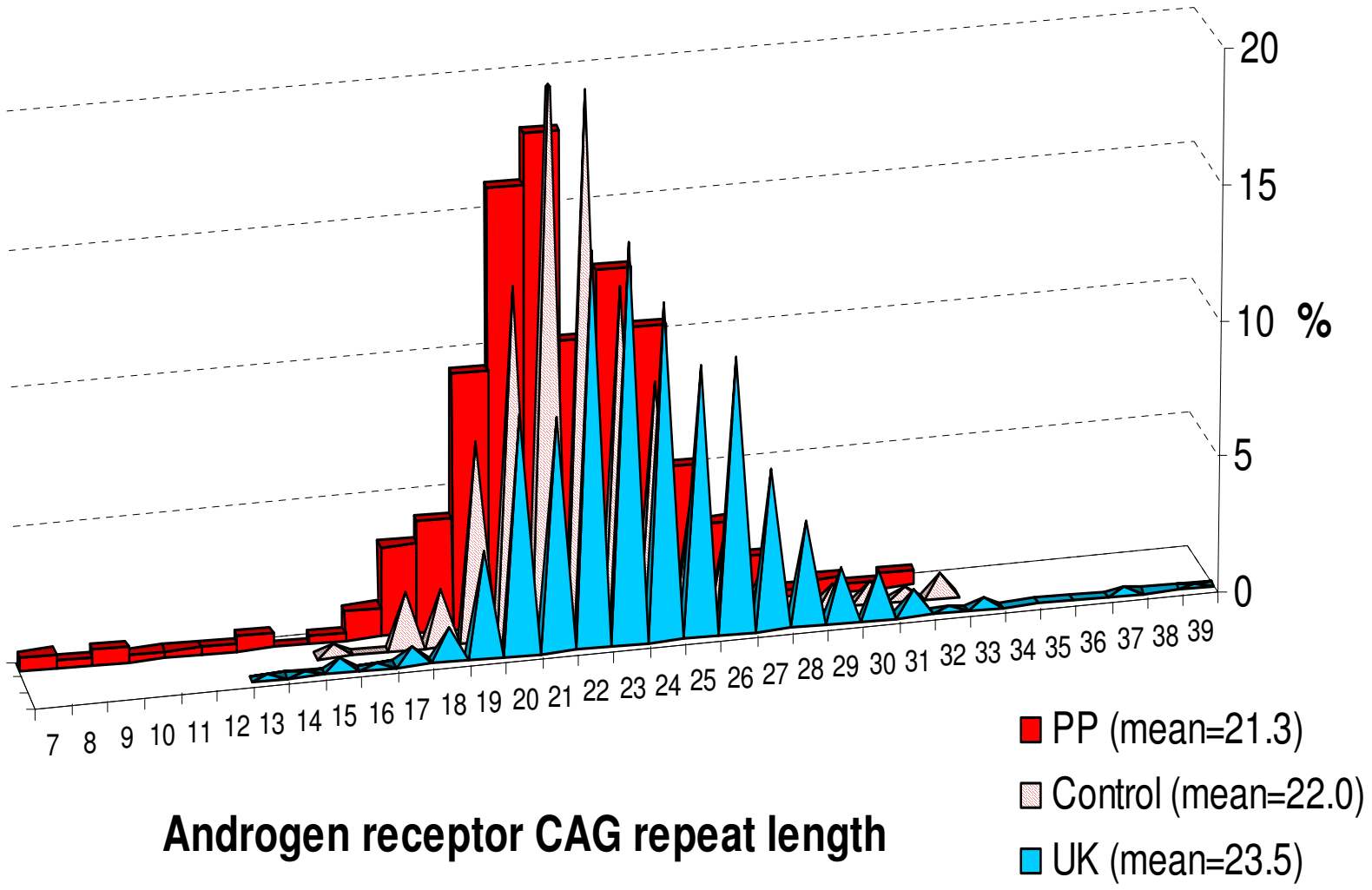
- Functional ovarian hyperandrogenism
- PCOS
- Syndrome X

PCOS after Precocious Pubarche: Relation to Reduced Fetal Growth



J Clin Endocrinol Metab, 1998

Excess shorter AR CAG alleles (≤ 20 repeats) in Spanish PP women (37%) vs. Spanish controls (25%, *p=0.002*)



All Spanish women vs. UK control women (*p<0.0005*)

Barcelona Precocious Pubarche Cohort

Aromatase Haplotypes

Haplotype	Controls	Precocious Pubarche	Odds Ratio
AAGG**	26 (9%)	58 (16%)	2.5 (1.4~4.4)
AGGG*	78 (26%)	69 (18%)	1.0
AGGT	45 (15%)	50 (13%)	1.3 (0.8~2.1)
GAGG	116 (39%)	150 (40%)	1.5 (1.0~2.2)
others	35 (12%)	47 (13%)	~

Overall $p<0.0001$; *$p<0.05$, **$p<0.01$

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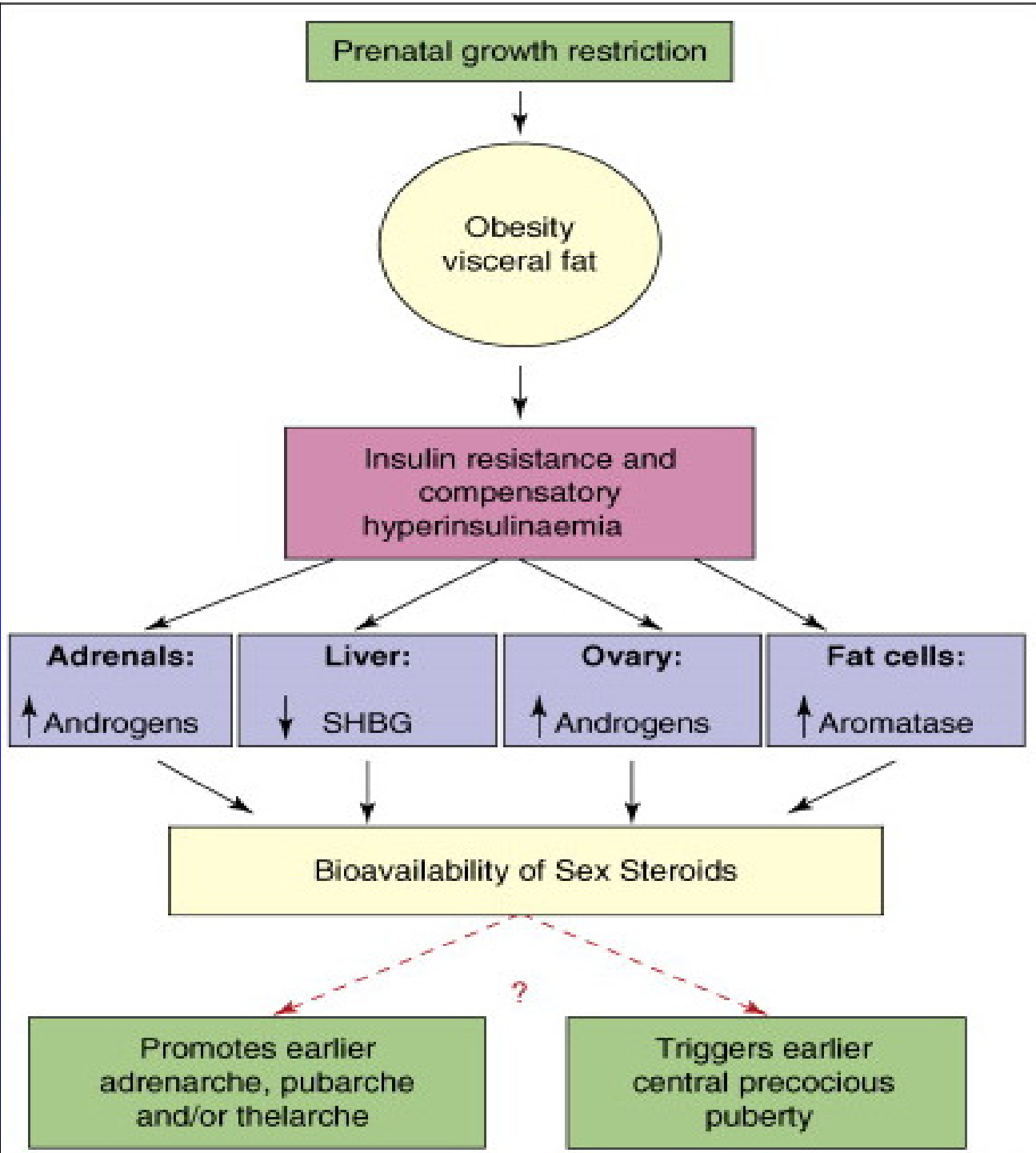
Age of Pubertal Onset and Menarche in White Girls		Breast stage 2		Menarche	
Studies:	N	mean	sd	mean	sd
Reynolds and Wines 1948	49	10.8	1.1	12.9	1.4
Marshall and Tanner 1969	192	11.15	1.10	13.47	
Roche et al 1995	67	11.2	0.7		
Herman-Giddens 1997	15,439	9.96	1.82	12.88	1.20
Whincup 2001	1068			12.9	12.8-13.1
Sun et al 2002, NHANES III:	594				
Median age at entry into stage 2		10.38	10.1-10.65		
Mean age for being in stage 2		11.05	0.18 (se)		
Freedman et al 2002, Bogalusa:					
1973/1974	1398	10.4		12.7	12.6-12.9
1992-1994	1230			12.5	12.4-12.8
Chumlea et al 2003, NHANES III:		10.4	10.1-10.7	12.55	12.31-12.79
Anderson et al 2003					
1963-70, NHES II, III	1454			12.8	12.73-12.87
1988-1994, NHANES III	452			12.6	12.48-12.71



Ahmed et al 2009
Trends in
Endocrinology &
Metabolism
20:237-242

Adverse outcomes of early puberty:

- Increased adolescent risk-taking behaviour
- Shorter adult stature
- Increased adult BMI, waist circumference and adiposity
- Increased risk of adult-onset diabetes (owing to elevated BMI)
- Increased cardiovascular disease risk markers (including insulin resistance, blood pressure and metabolic syndrome)
- Increased risk of premenopausal breast cancer
- Increased all-cause mortality

Ahmed et al 2009 Trends in Endocrinology & Metabolism 20:237-242

Determinants of normal puberty

- Role of weight gain/insulin
- First genes related to menarche identified
- Developmental determinants of adult disease
- Sexual dimorphism
- Timing of puberty and adult physiology

Acknowledgements

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- Ken Ong

UNIVERSITAT DE BARCELONA

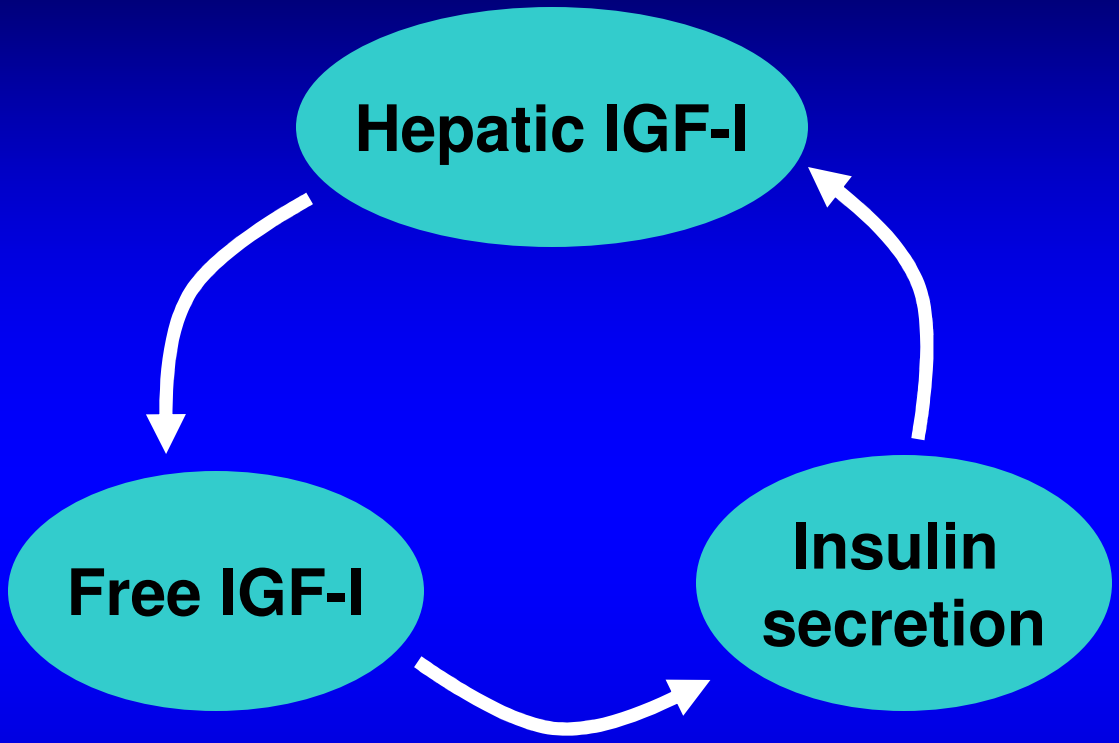
- Lourdes Ibáñez

- Francis de Zegher

ALSPAC
AVON LONGITUDINAL STUDY OF PARENTS AND CHILDREN

- Marcus Pembrey
- Jean Golding

GH/IGF-I axis and beta cell function



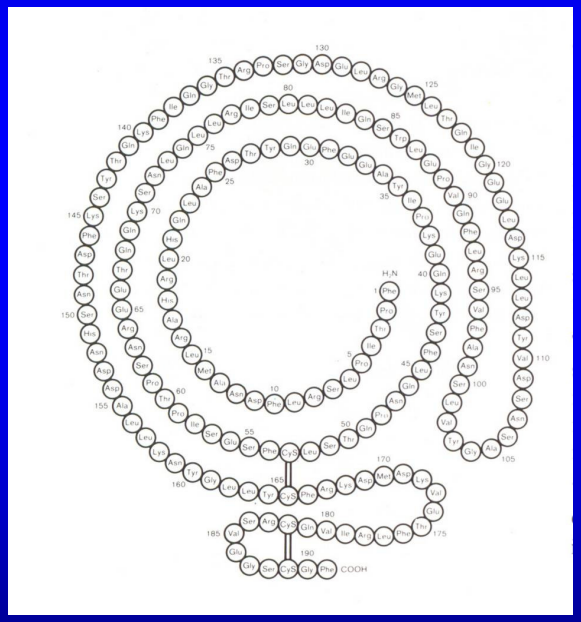
- IGF-I and beta cell function
- Beta cell mass
- Growth hormone

GH – IGF-I axis

Growth Hormone

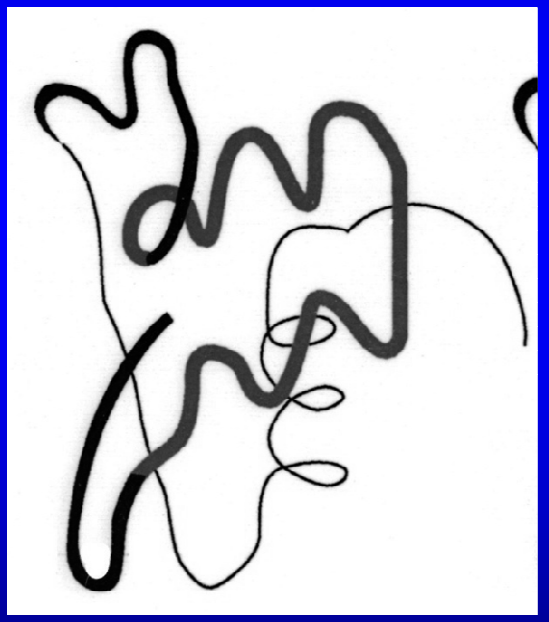
IGF-I

Growth Hormone



- Insulin antagonist
- Beta cell mass?

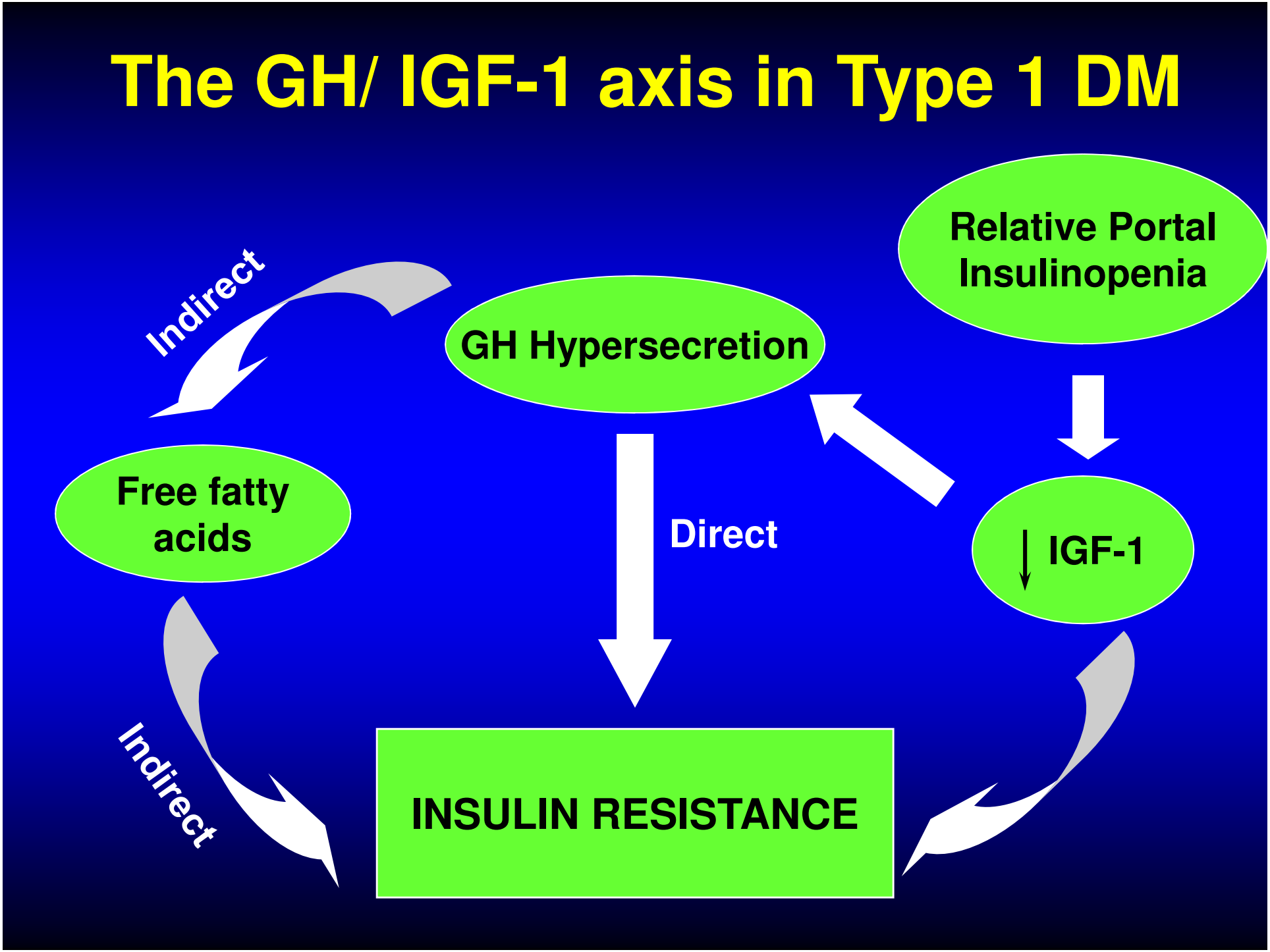
IGF-I



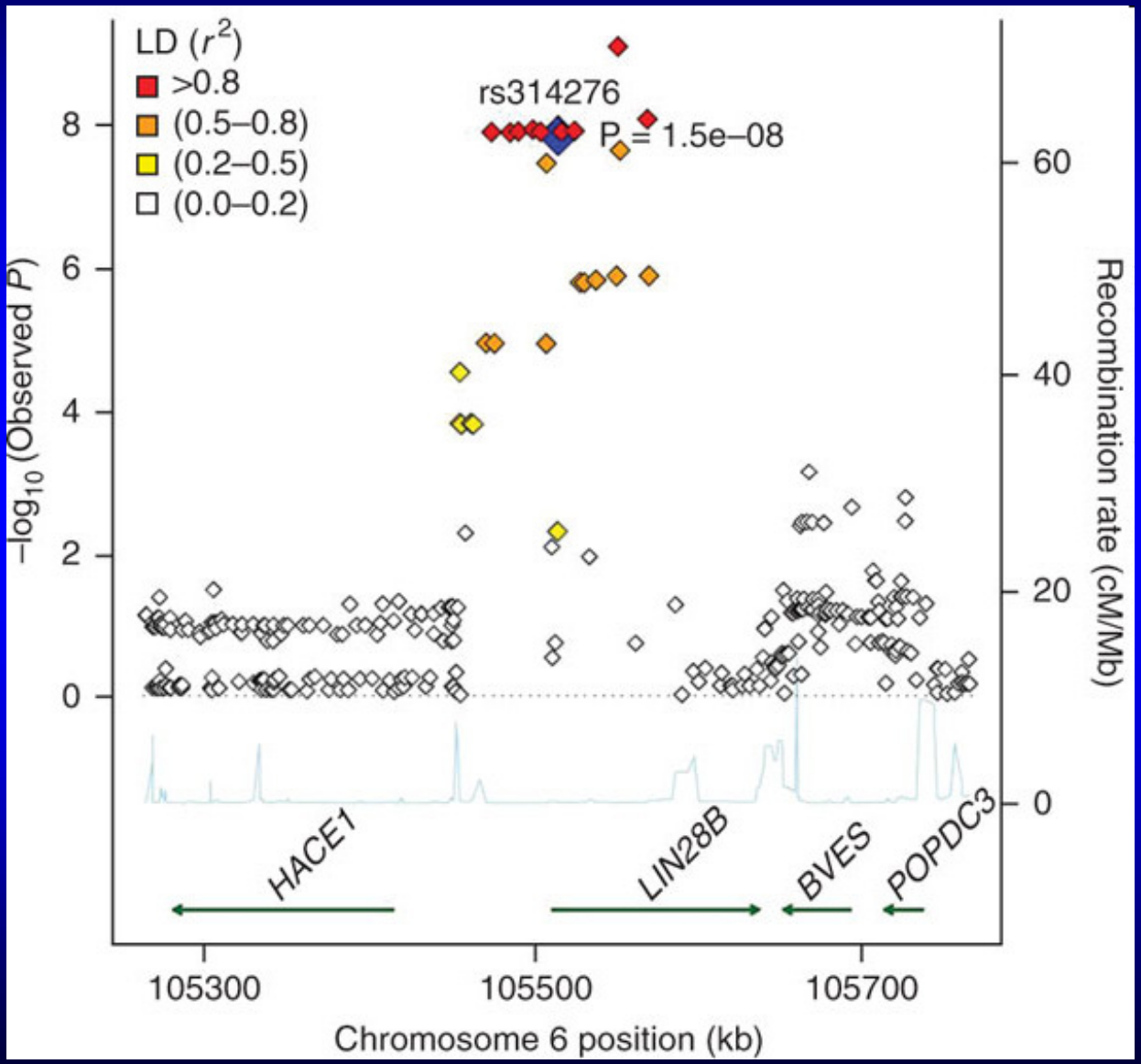
- Insulin sensitisor
- Beta cell function?

Growth

The GH/ IGF-1 axis in Type 1 DM

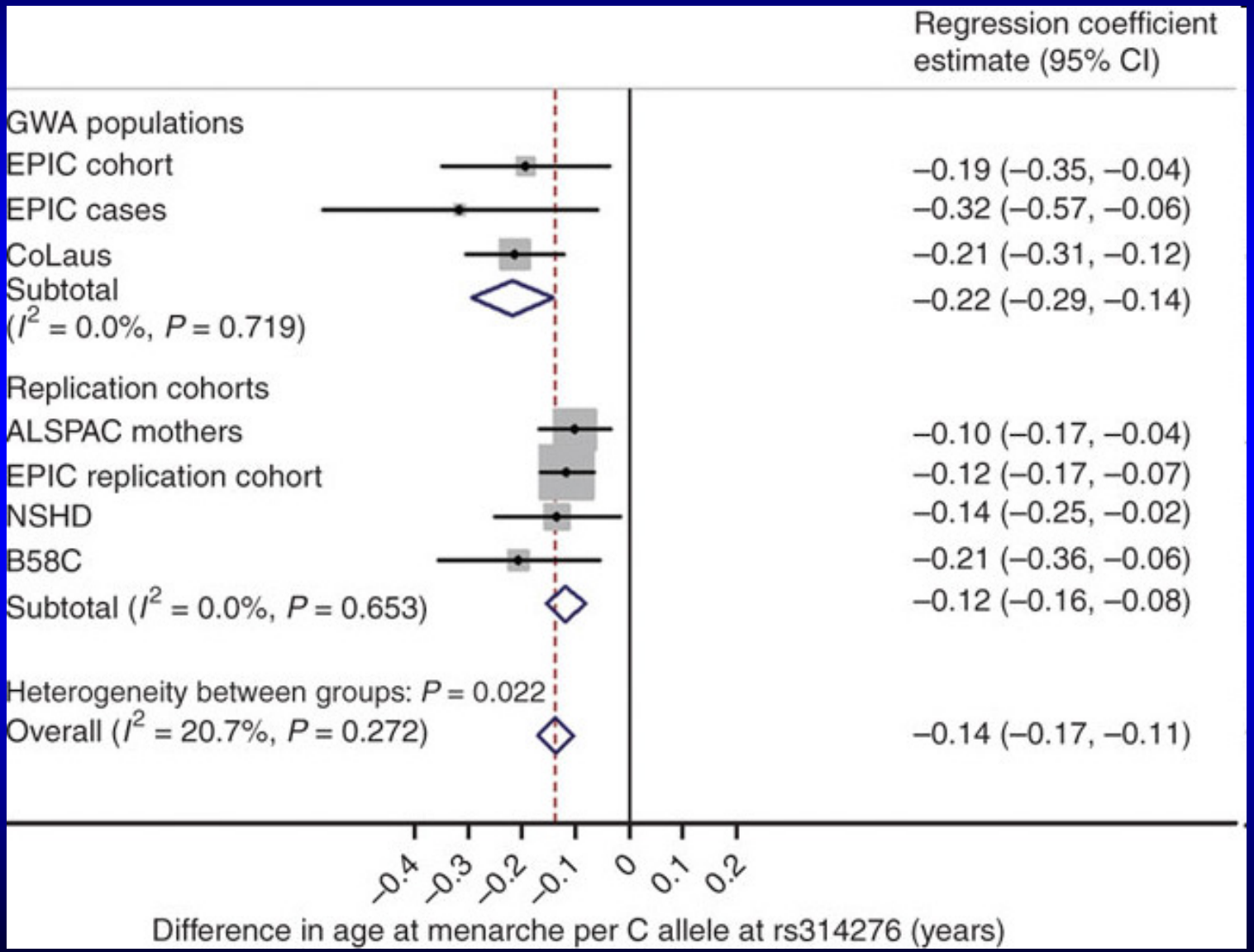


Regional plot of the locus around *LIN28B* associated with age at menarche



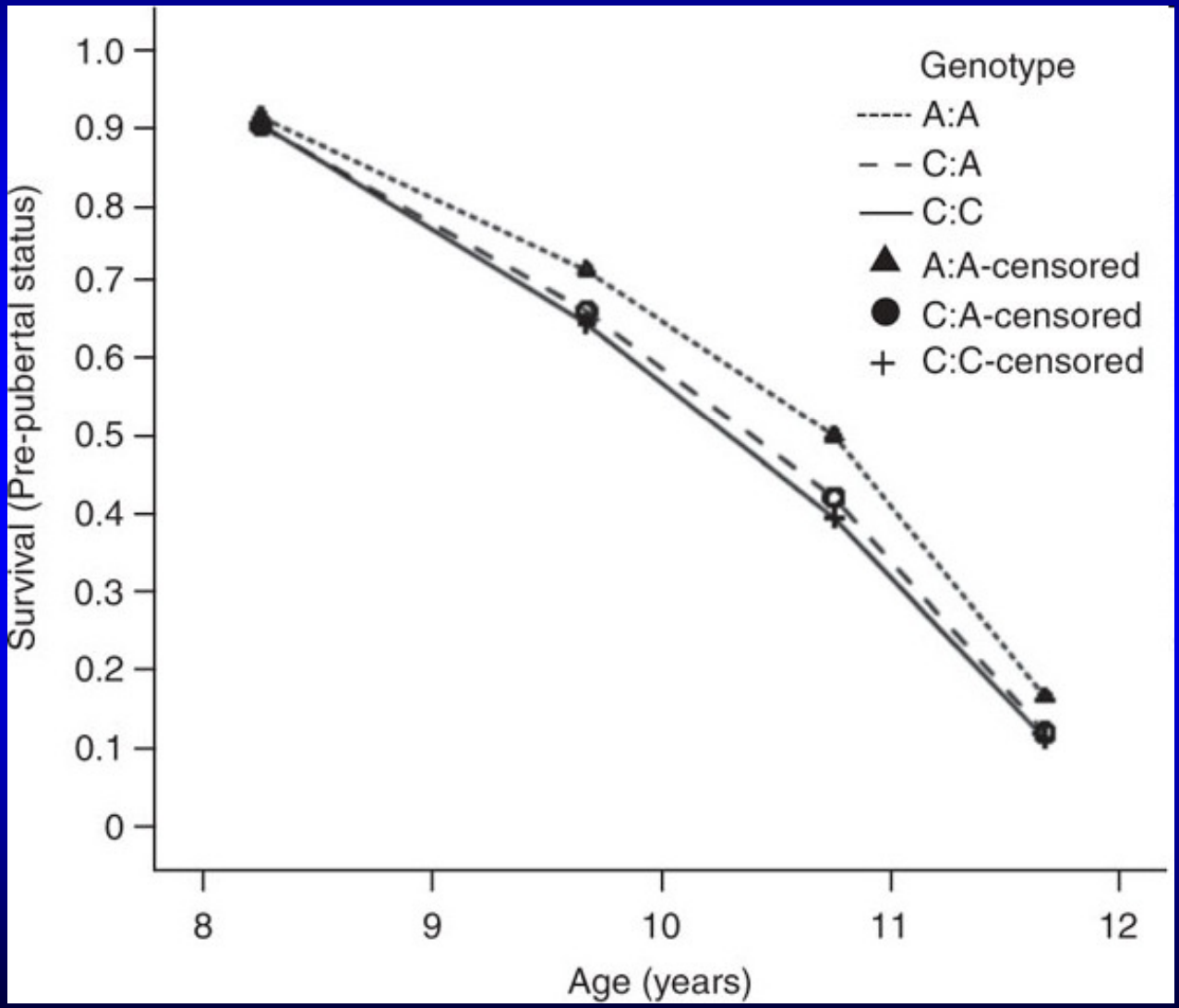
Ong et al 2009 Nature Genetics 41:729-733

Meta-analysis of the effect of each C allele at rs314276 in LIN28B on earlier age at menarche



Ong et al 2009 Nature Genetics 41:729-733

Survival in pre-pubertal status (Tanner breast stage 1) by age and *LIN28B* rs314276 genotype in ALSPAC girls (*N* = 3,233)



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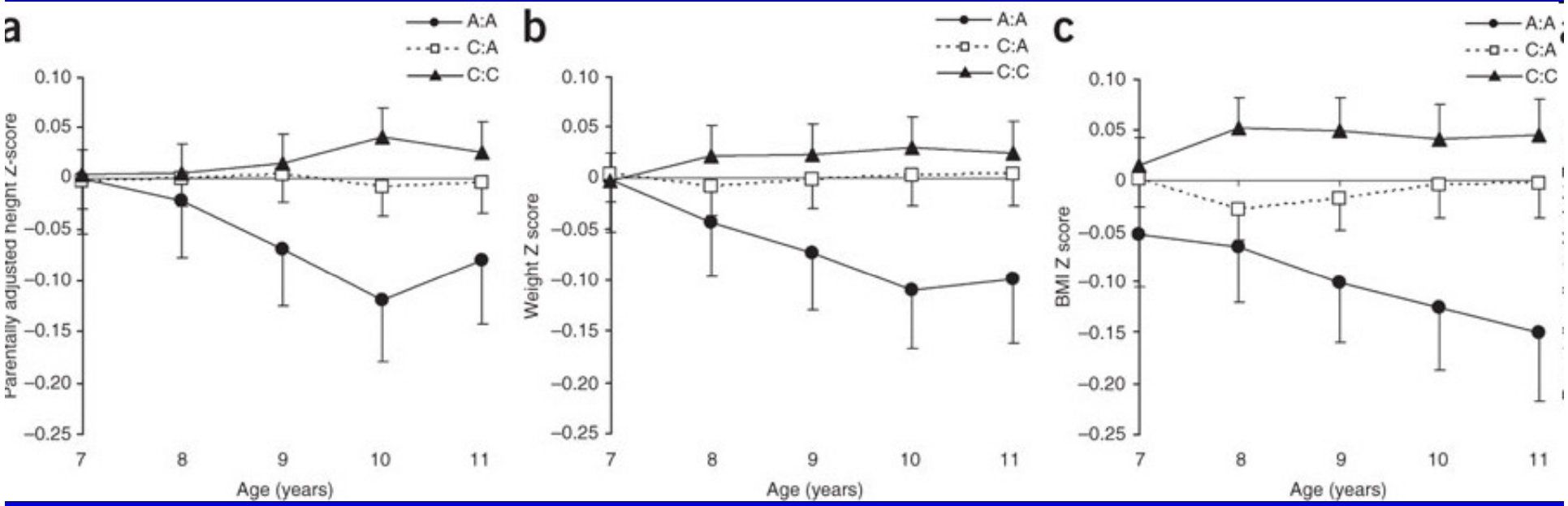
Adolescent growth in ALSPAC girls by *LIN28B* rs314276 genotype



Height **Weight** **BMI**

Ong et al 2009 Nature Genetics 41:729-733

Non Obese Adolescents with HA

with and without ovarian PCO

	Total	Non-PCO	PCO	*P*
N	86	53	33	
Age at PCO assessment (yr)	17 ± 0.2 *	17 ± 0.3	18 ± 0.4	*NS*
Age at menarche (yr)	11.8 ± 0.1	11.8 ± 0.1	11.7 ± 0.2	*NS*
Testosterone (ng/dL)	84 ± 4	85 ± 5	84 ± 5	*NS*
DHEAS (μg/dL)	251 ± 10	246 ± 14	259 ± 16	*NS*
FSH (IU/L)	5.1 ± 0.2	5.1 ± 0.2	5.1 ± 0.4	*NS*
LH (IU/L)	8.4 ± 0.6	7.6 ± 0.7	9.8 ± 1.2	*NS*
Birthweight (Kg)	3.0 ± 0.1	2.9 ± 0.1	3.3 ± 0.1	*< 0.0005*
Body Mass Index (Kg/m^2)	22.9 ± 0.3 *	22.3 ± 0.4	23.9 ± 0.5	*< 0.01*
HOMA-IR	3.0 ± 0.2	2.7 ± 0.2	3.5 ± 0.3	*< 0.01*
Androstenedione (ng/dL)	353 ± 14	332 ± 17	389 ± 22	*< 0.05*
SHBG (μg/dL)	1.0 ± 0.1	1.1 ± 0.1	0.8 ± 0.1	*< 0.05*

Values are mean ± SEM

Ibanez L et al JCEM in press 2007

Developmental Origins of PCO and PCOS

Differential developmental pathways

- Low BW — In development of PCOS
- High BW — With and without PCO

- Parallels U-shaped risk for T2D

Implications for definition of PCOS and treatment

PCOS Criteria

In Adults: Rotterdam 2003

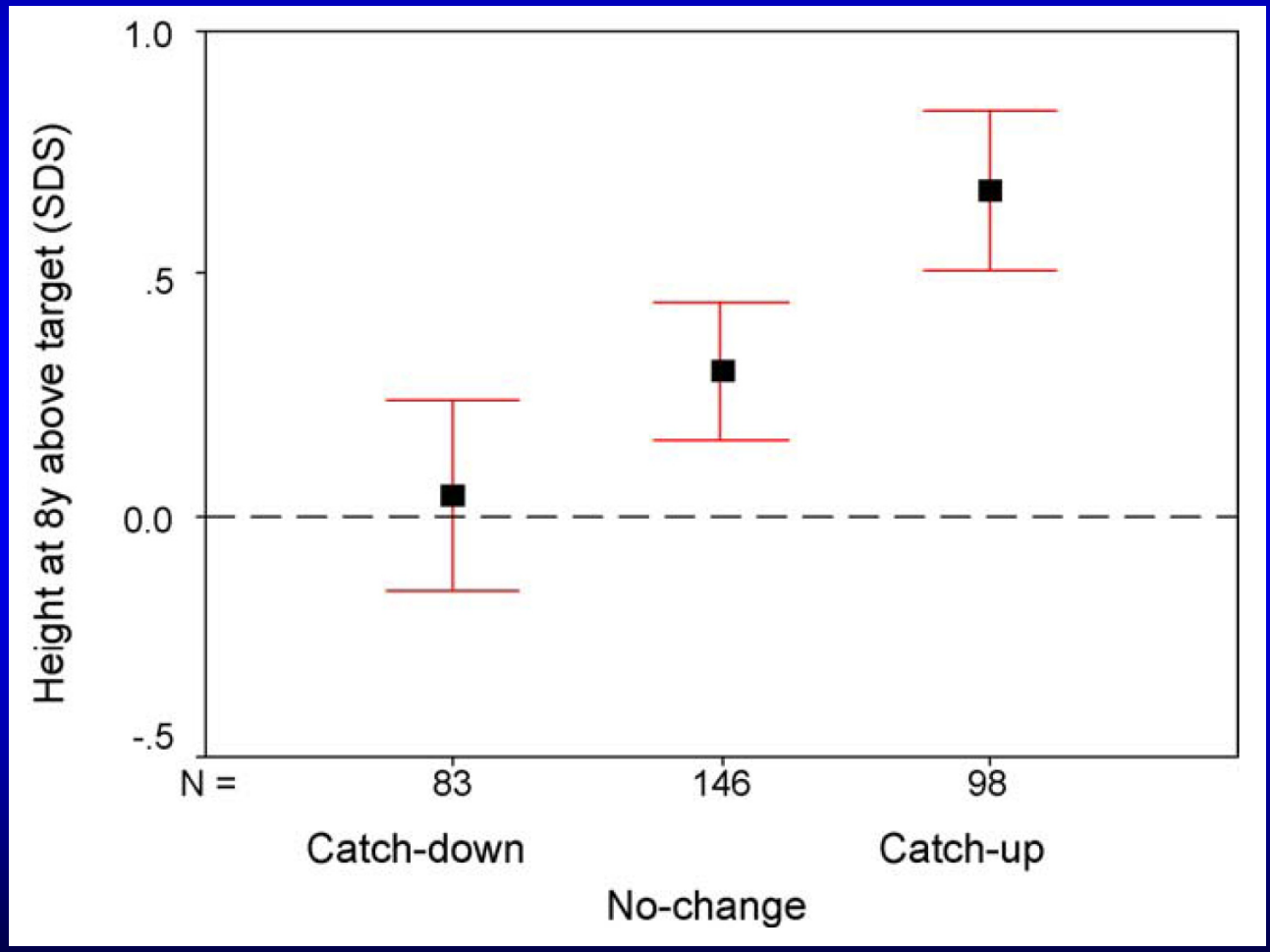
- Oligo/anovulation *and/or*
- Clinical and/or biochemical signs of HA
- Polycystic ovaries by u/s

In Adolescents: No established diagnostic criteria

- Anovulation is common for 2 years post menarche, so difficult to differentiate if PCOS
- Multifollicular ovaries common in adolescence
- Transvaginal u/s not appropriate, difficult to image in obese adolescents
- Difficult to define androgen excess due to lack of normative data
- Normal insulin resistance of puberty

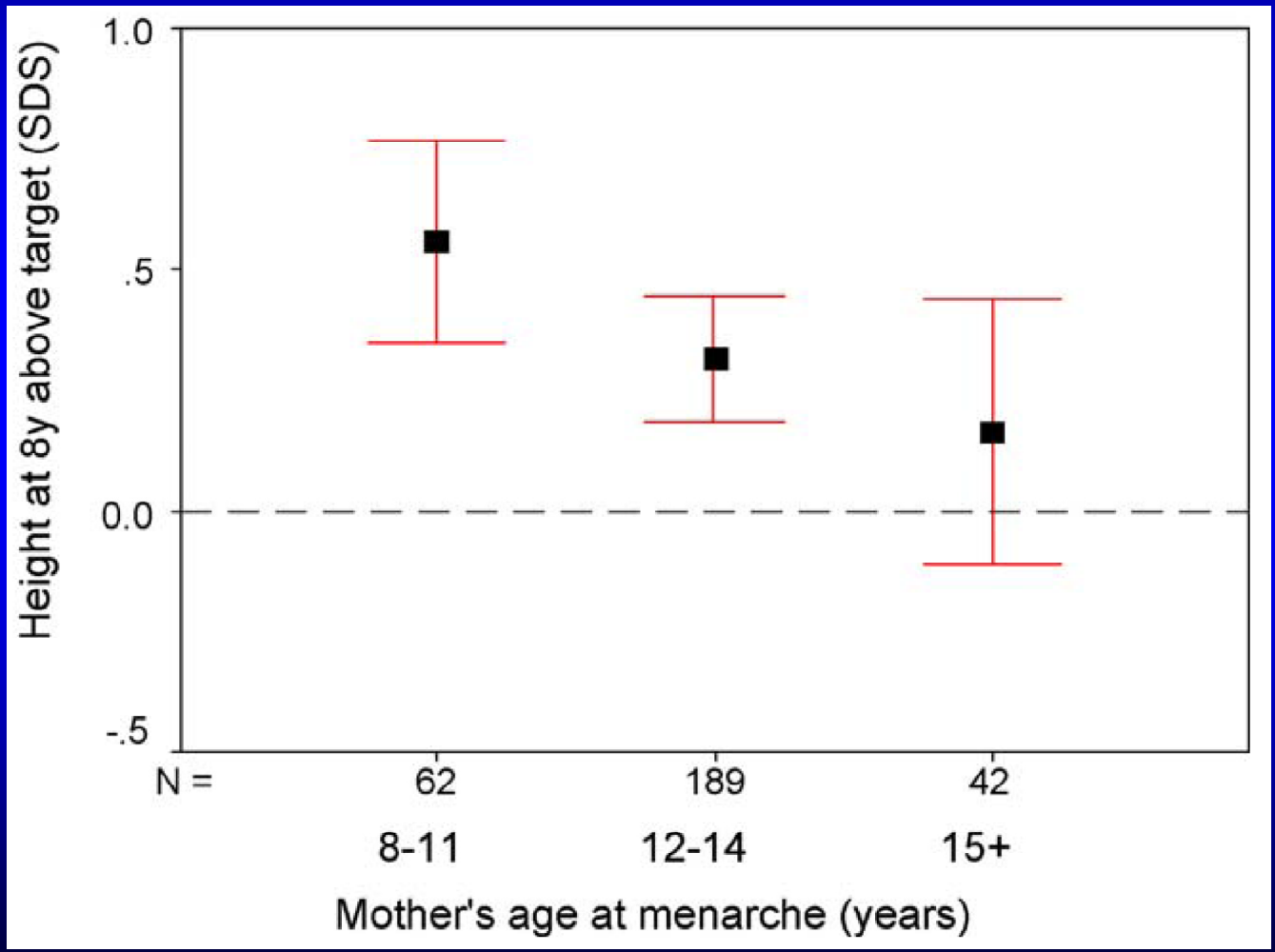
Khan U 2007, J Pediatr Adolesc Gynecol

Childhood height relative to mid-parental height, by pattern of infant weight gain



Dunger et al 2006 Molecular & Cellular Endocrinology 254-255:140-145

Childhood height relative to mid-parental height, by mother's age at menarche



Dunger et al 2006 Molecular & Cellular Endocrinology 254-255:140-145