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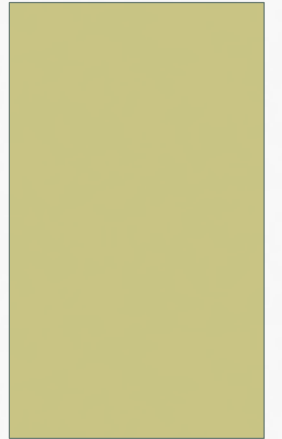
Saturday, August 13, 2016

(Plenary)

9:25 - 9:50 Endocrine and Metabolic Consequences of Being Born
Preterm

PRETERM BIRTH A LIFE-LONG METABOLIC SHADOW?

PAUL HOFMAN 2016



**We are born naked, wet and hungry
Then things get worse.....**

FETAL ORIGINS (THE BARKER) HYPOTHESIS

The origins of adult disease begin in utero.

Fetal malnutrition is proposed as the cause of small birth size and programmed later adult disease.

ADULT DISEASES ASSOCIATED WITH LOW BIRTH WEIGHT

- Obesity
- Ischaemic Heart Disease
- Type 2 diabetes mellitus
- Hypertension
- Metabolic Syndrome

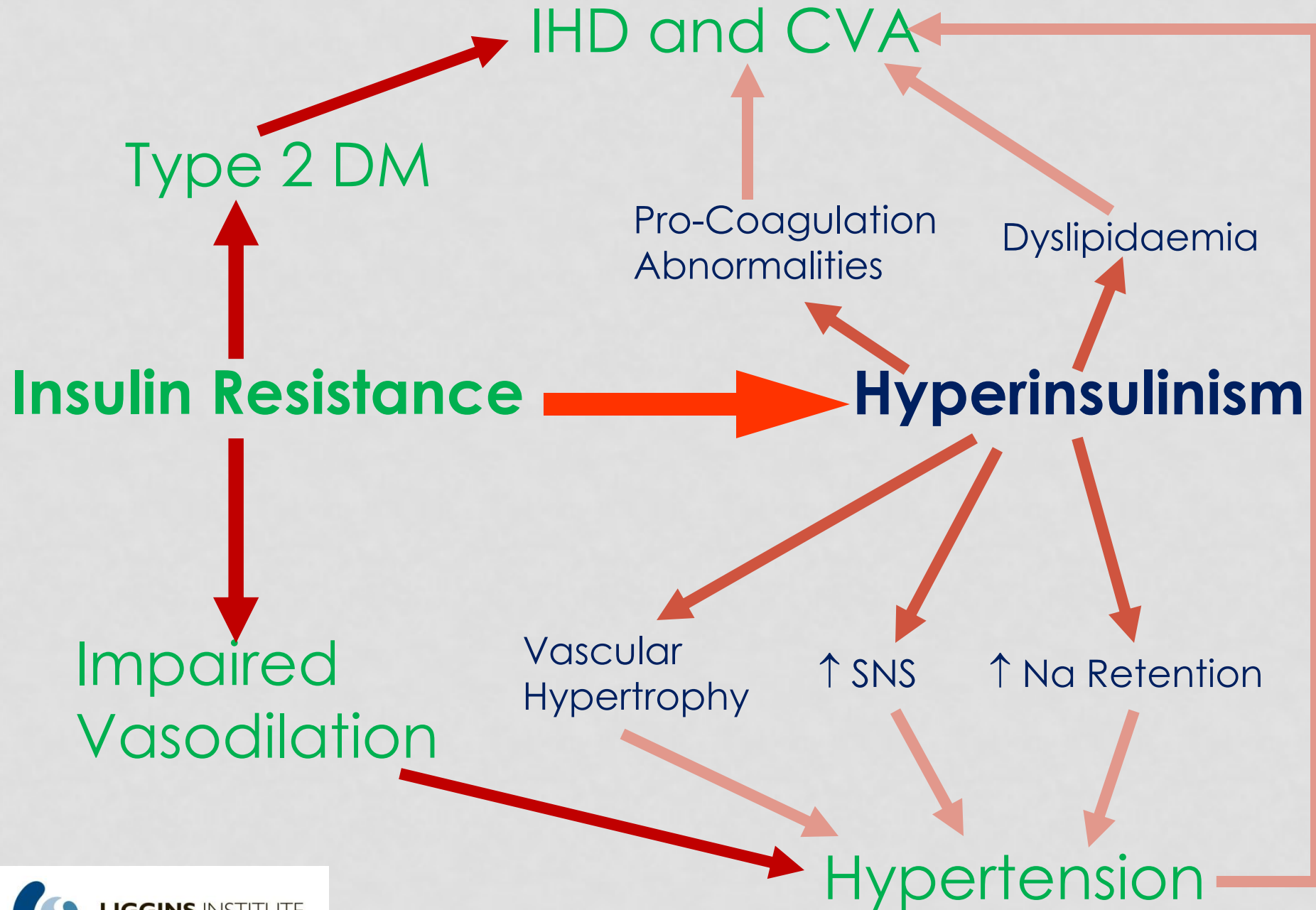
ENDOCRINE CONSEQUENCES OF BEING PRETERM

- Growth
- Altered body composition
- **Insulin resistance**
- Leptin Resistance
- Premature pubarche/ adrenarche
- Polycystic ovarian syndrome
- Early and rapid puberty

INSULIN RESISTANCE

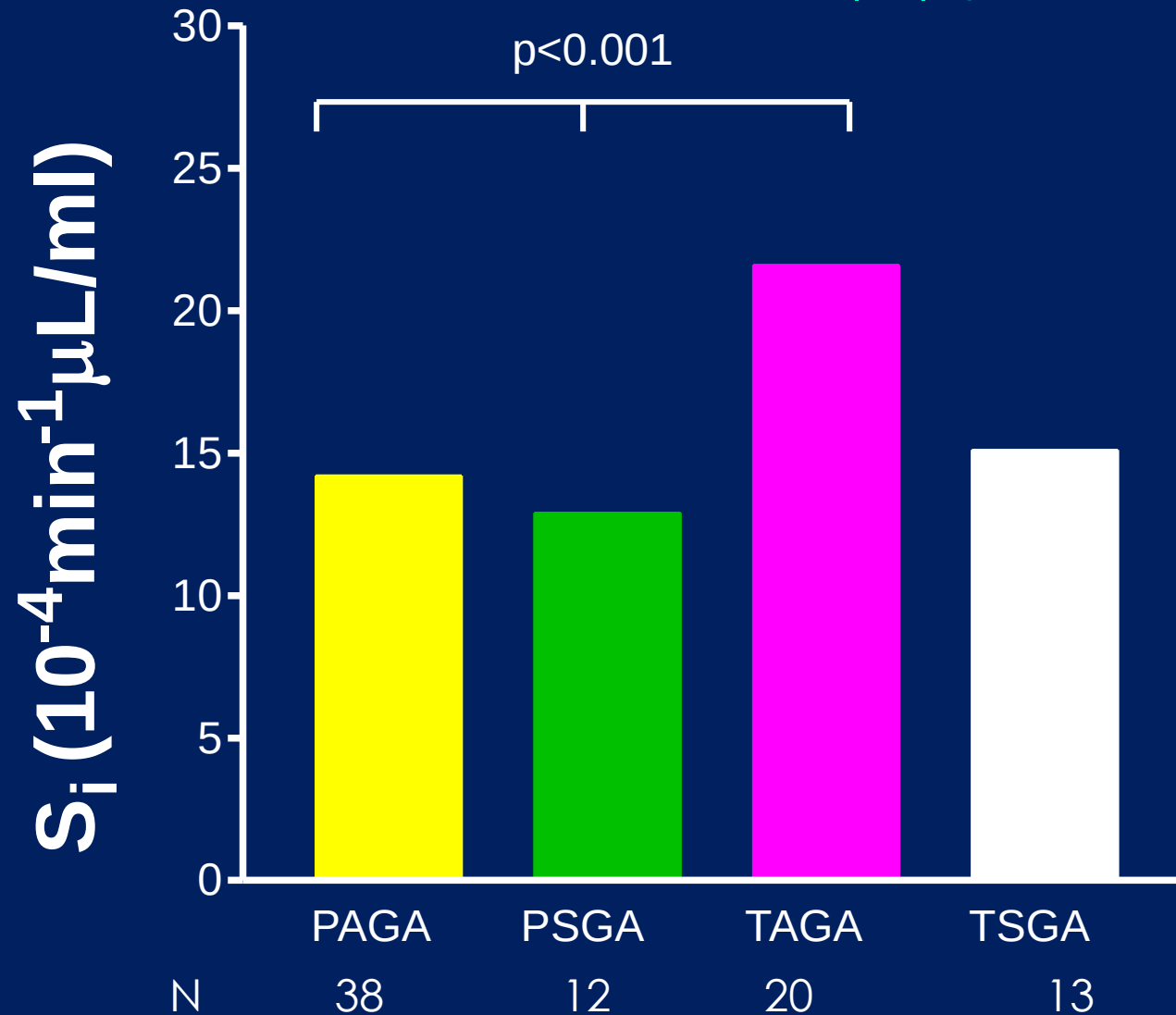
DEFINITION OF INSULIN RESISTANCE

- A reduction in insulin sensitivity to a point where pathological complications are likely.
- Insulin sensitivity is defined by the ability of insulin to regulate serum glucose levels. It does not imply a generalised alteration in tissue insulin sensitivity.

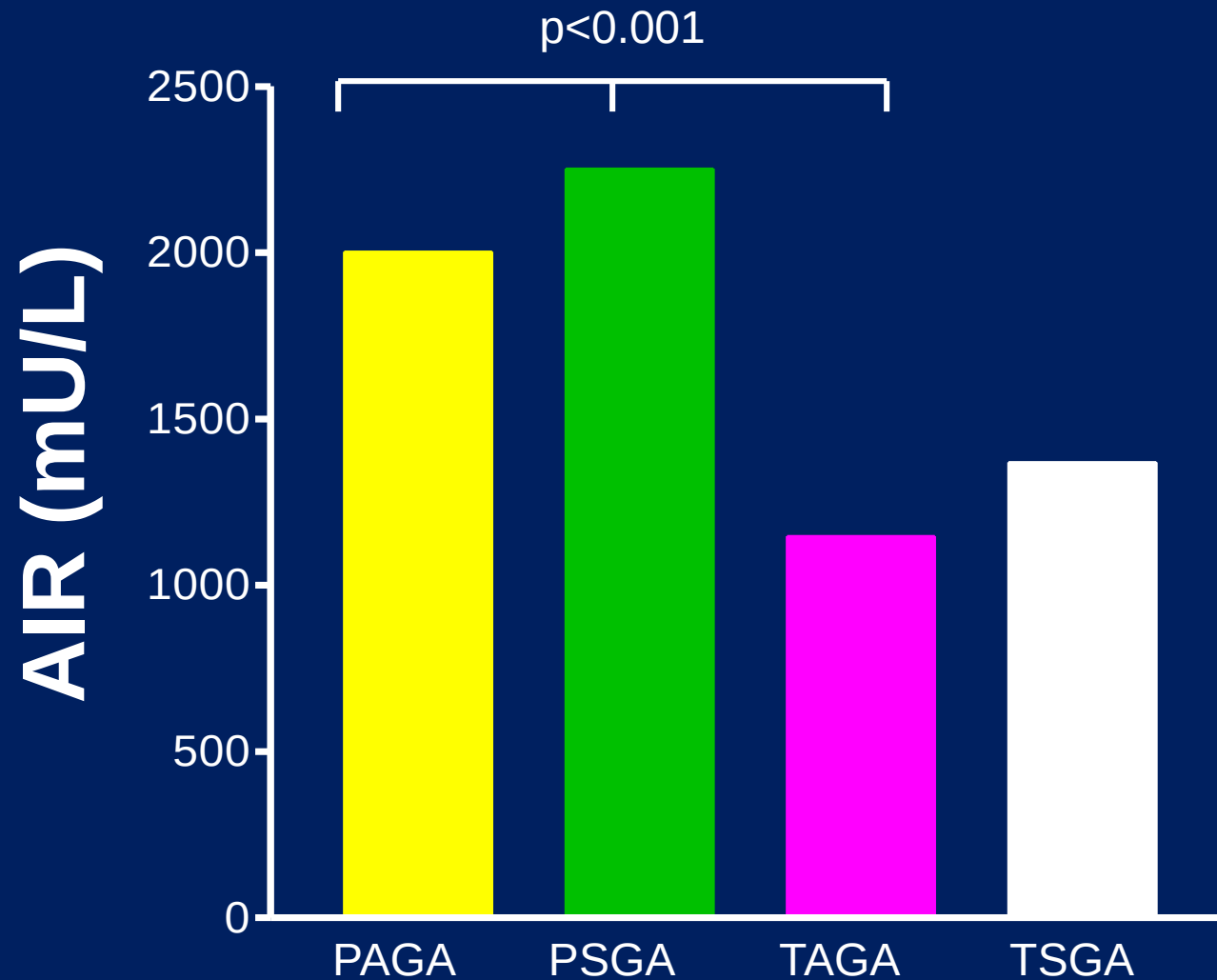


Insulin Sensitivity

Hofman et al. NEJM, 2004. 351(21): p. 2179-86.



Acute Insulin Release

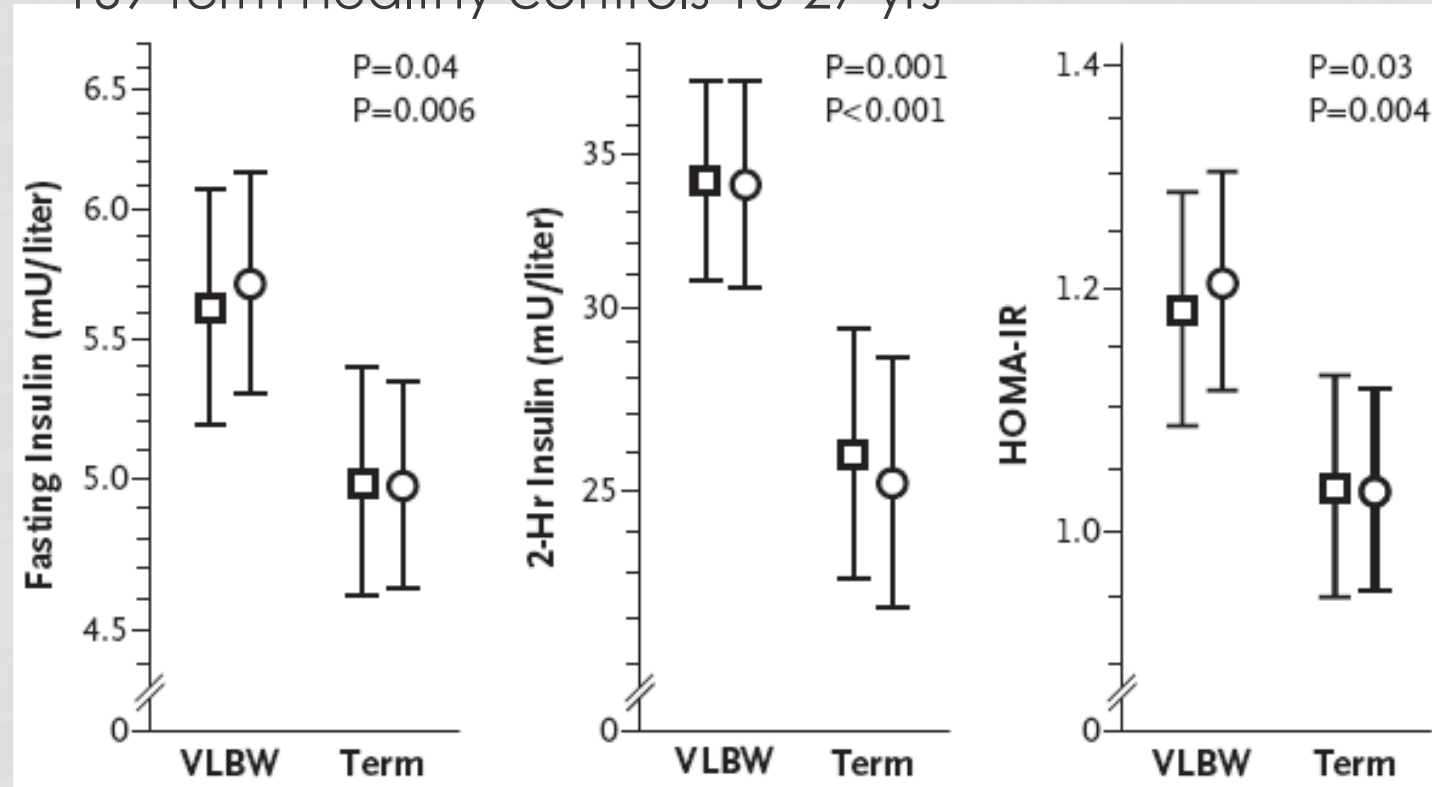


*Hofman NEJM, 2004. **351**(21): p. 2179-86.*

YOUNG PRETERM ADULTS

163 preterm adults 18-27 yrs
169 term healthy controls 18-27 yrs

Oral GTT



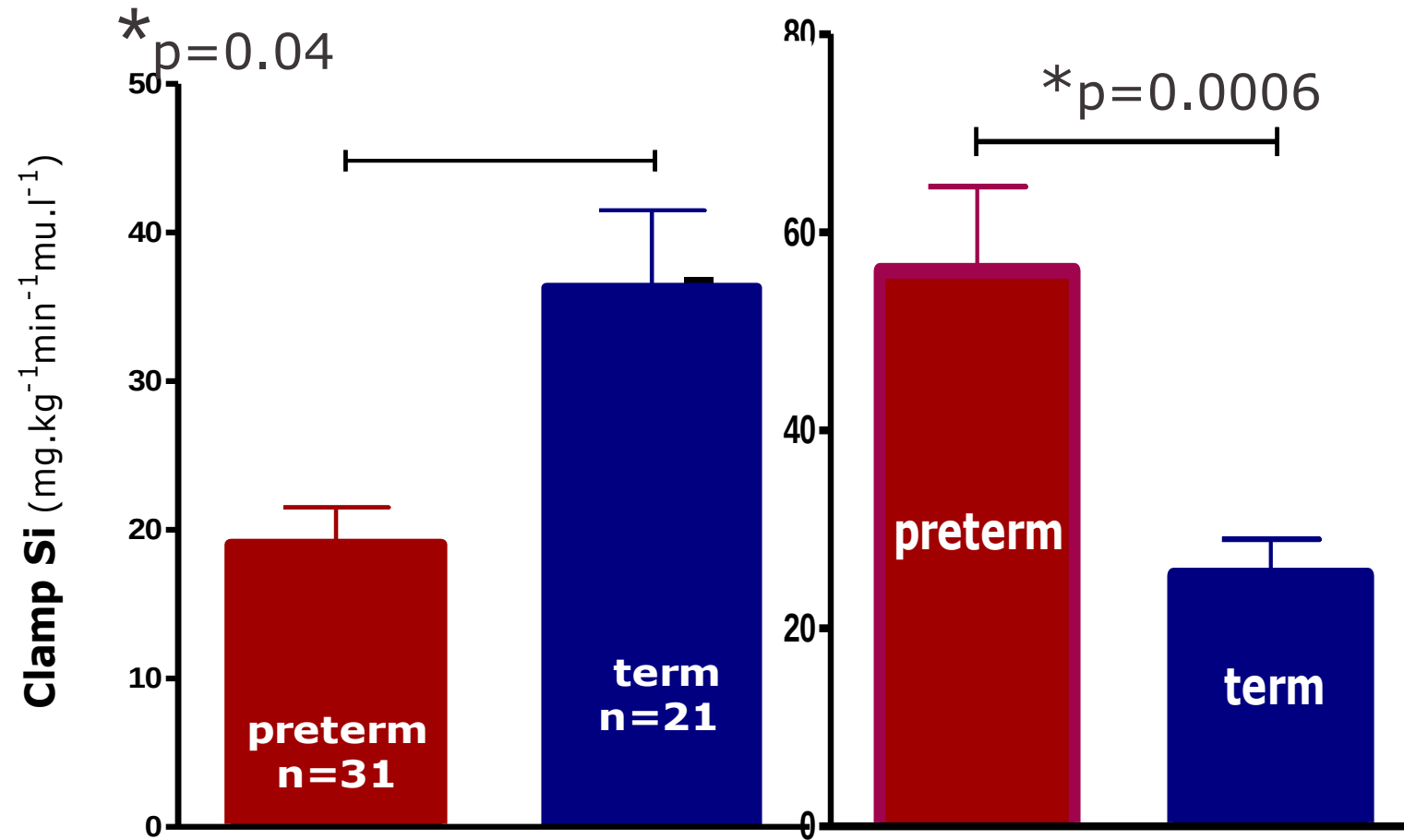
Preterms 5.3-5.9cm shorter
Elevations in systolic BP by a mean 4.6 mmHg

N Engl J Med 2007;356:2053-63.

ADULT RESULTS

Insulin sensitivity

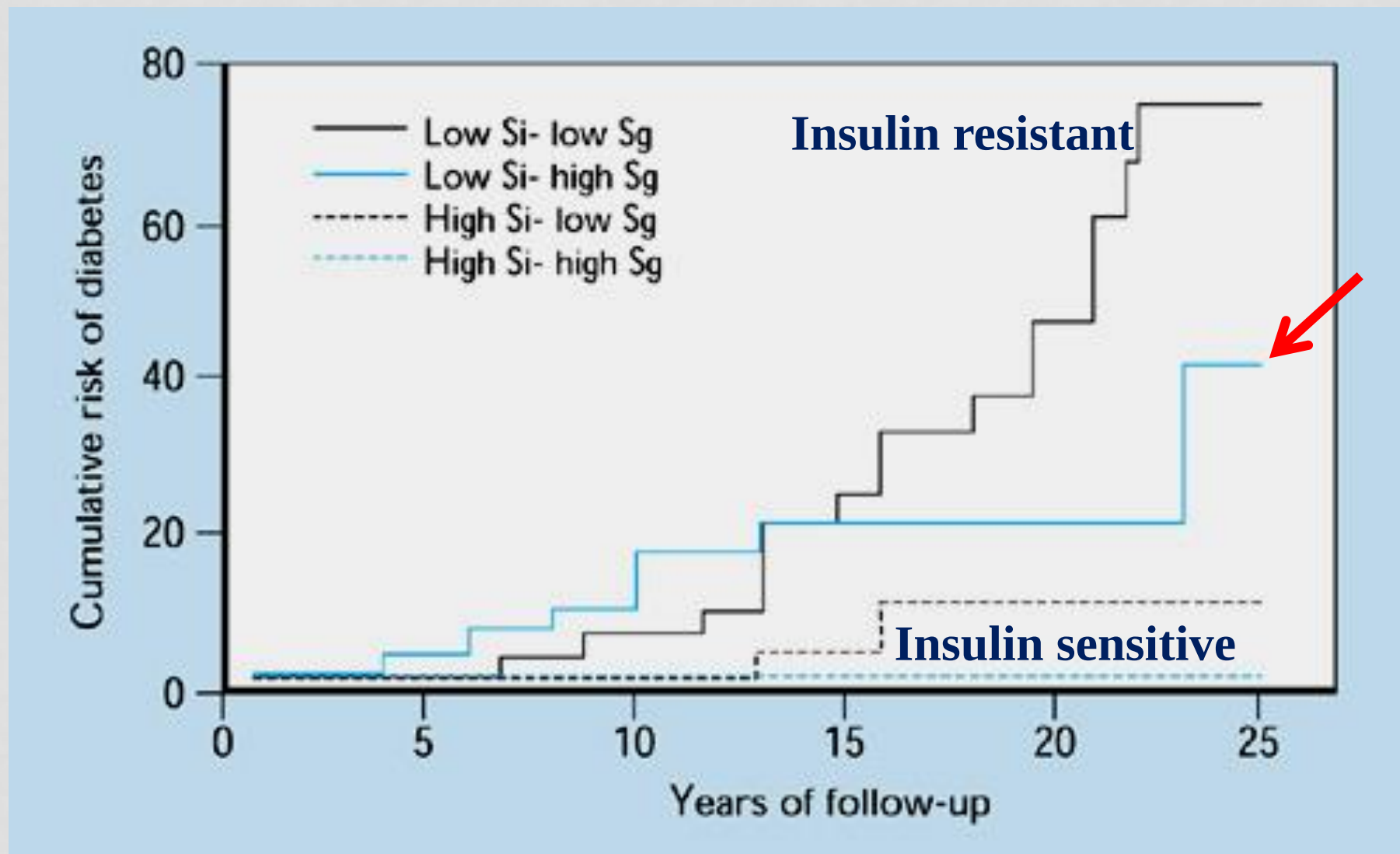
Insulin secretion



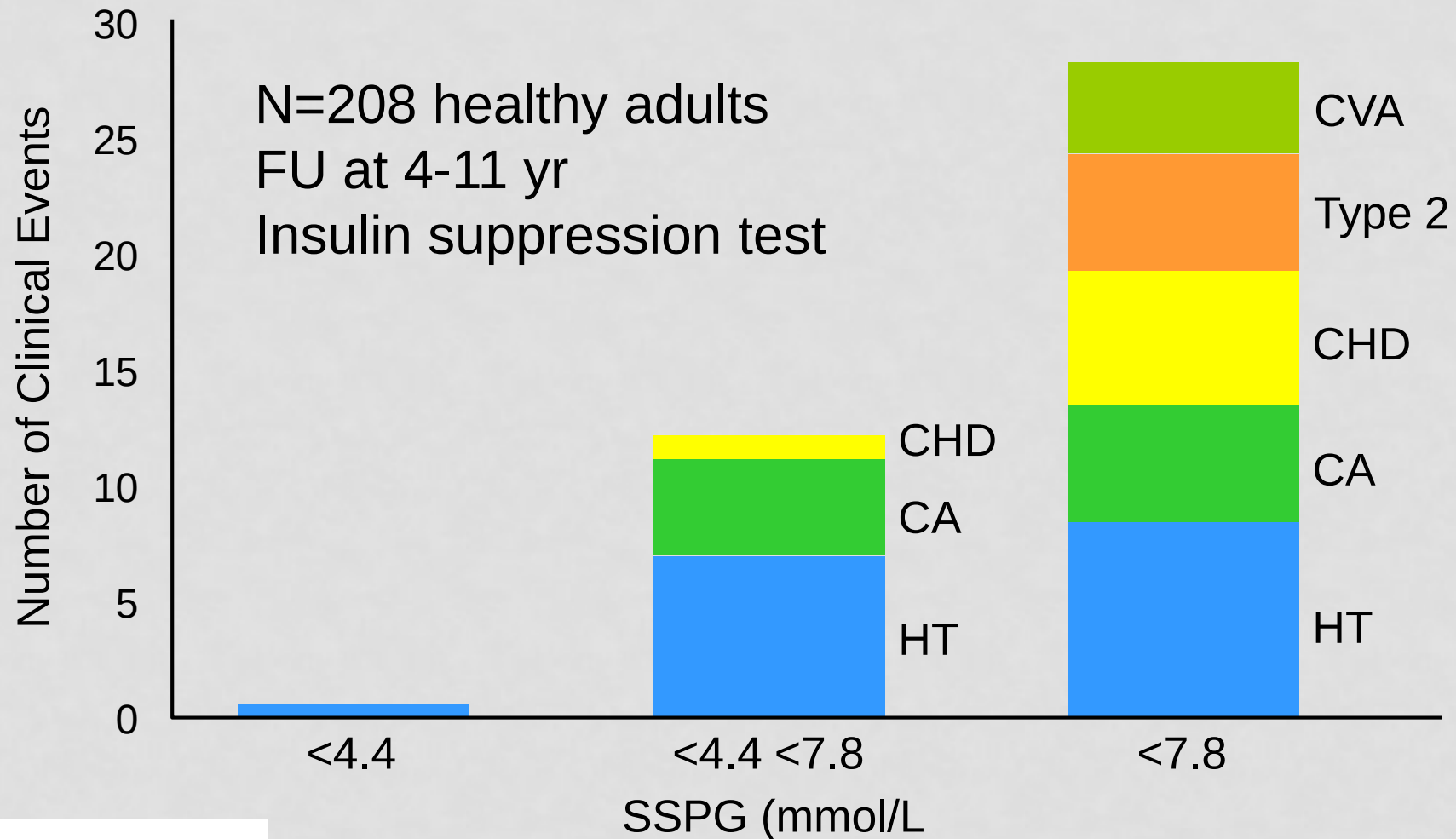
Does insulin sensitivity track over time?

Is reduced insulin sensitivity associated with later disease and reduced longevity?

Long term diabetes risk of insulin resistance



LONG TERM RISKS OF INSULIN RESISTANCE

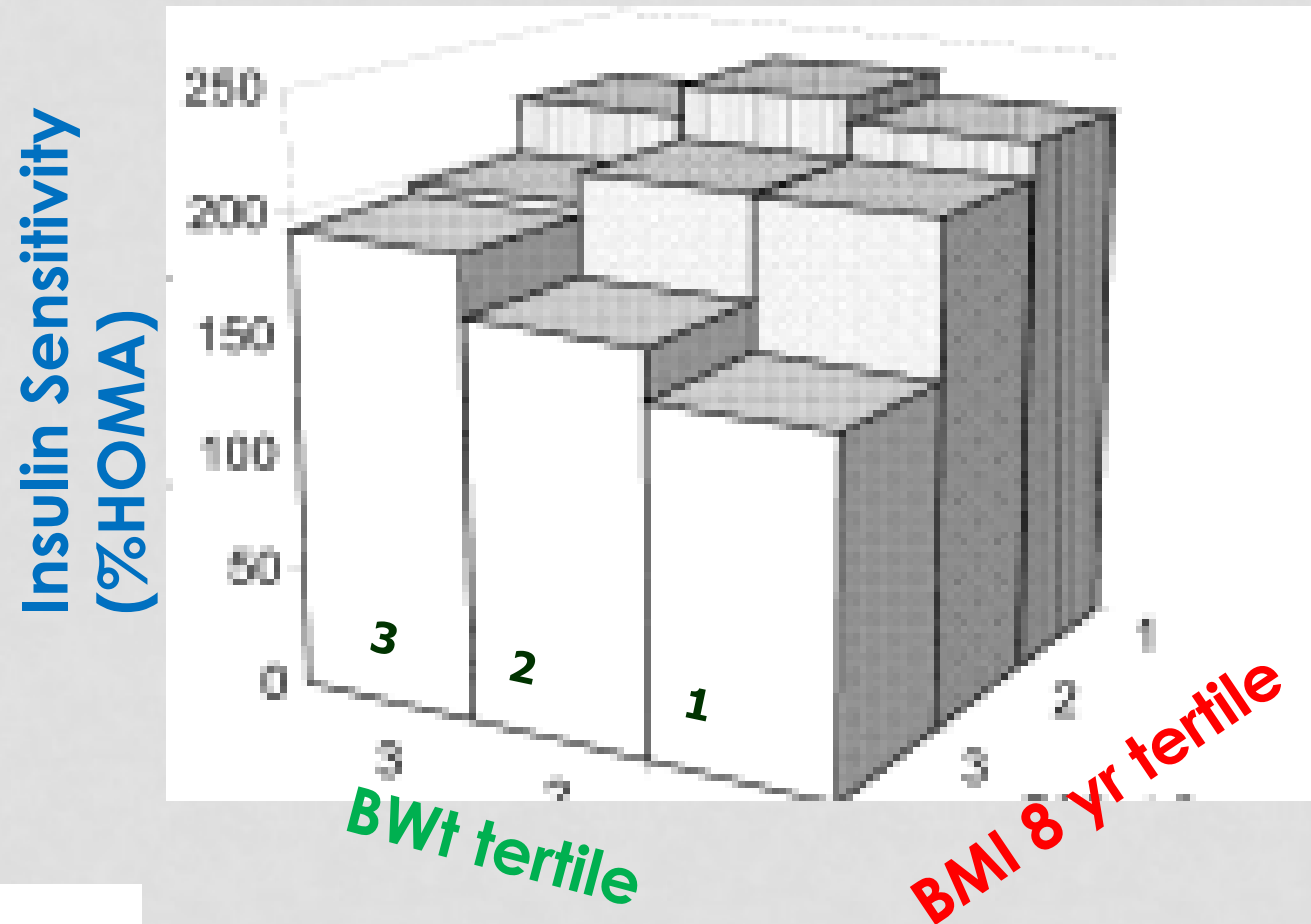


TYPE 2 DIABETES RISK IS INCREASED IN PRETERM DANISH ADULTS

- Random sample of 6,784 subjects aged 30-60 year old.
- 443 preterm (<37 weeks; 6.5%)
- T2D present in
 - 6.9% Preterm
 - 6.5% Term SGA
 - 4.2% Term AGA ($p < 0.001$)
- Reduced insulin sensitivity seen in preterm while both reduced insulin sensitivity and beta cell function seen in SGA

BODY COMPOSITION

BIRTH WEIGHT, BMI AND INSULIN SENSITIVITY



EARLY INFANCY

- Atkinson *et al.*, using DEXA, found that preterm children, at 40 weeks corrected gestation, had elevated fat mass and reduced lean mass compared to healthy term equivalents[48]
- Modi *et al.* demonstrated preterm infants at the equivalent of 40 weeks' gestation had increased visceral and reduced subcutaneous fat

Ann NY Acad Sci, 2000. 904: p. 393-9

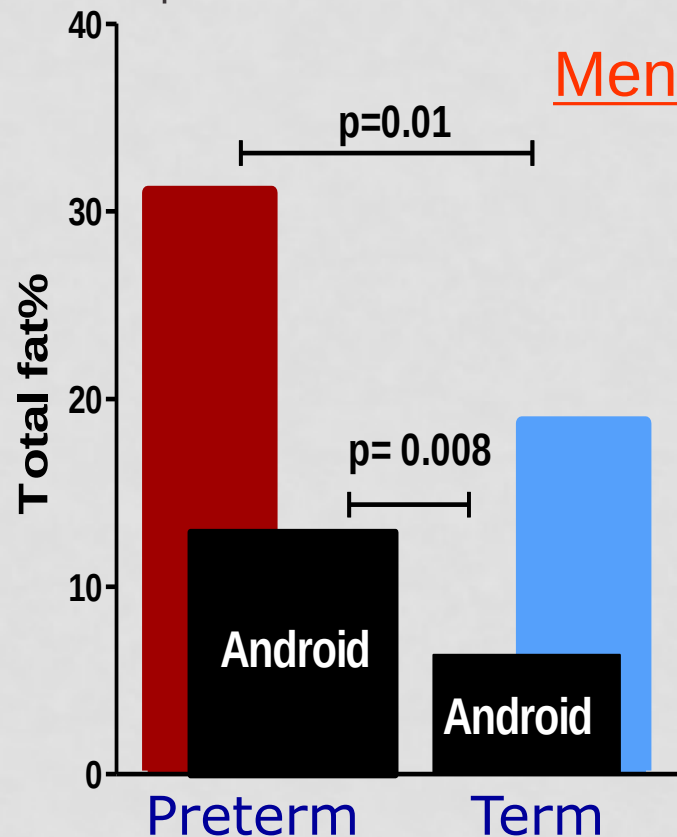
Pediatr Research, 2005. 57(2): p. 211-5

EARLY ADULTHOOD

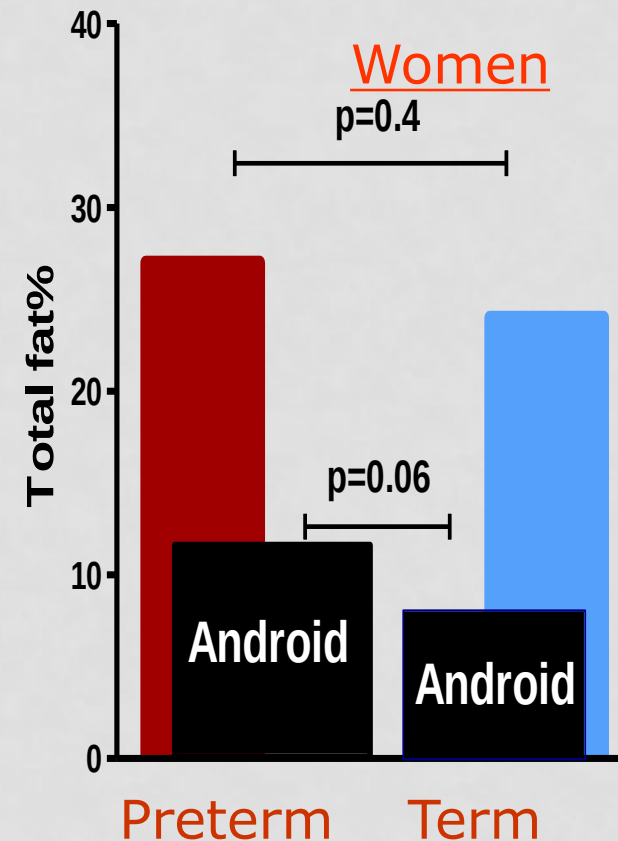
- Euser *et al.* found that early postnatal weight gain in preterm children was associated with a higher percentage of body fat, more abdominal fat and higher BMI at 19 years

GENDER DIFFERENCES IN BODY COMPOSITION & S_I IN ADULTS

Despite similar height, preterm men were 18 kg heavier than term men ($p=0.04$) and had lower S_I ($p=0.01$) as compared to term men



Preterm & term women had similar weight ($p=0.98$) and slightly lower S_I ($p=0.06$)



PREMATURE PUBARCHE

PREMATURE PUBARCHE

- Pubarche is usually caused by adrenarche - the normal maturation of the zona reticularis in both boys and girls, resulting in the development of pubic hair, axillary hair, and adult apocrine body odour.
- Due to increased activity of the P450C17 increasing DHEA (mainly) and androstenedione levels.
- Serine phosphorylation associated with this change and similar serine phosphorylation of the insulin receptor observed in insulin resistance.
- Thus, there is a biochemical association between early adrenarche and insulin resistance states

Miller et.al. Proc. Natl. Acad. Sci. USA 92 (1995)

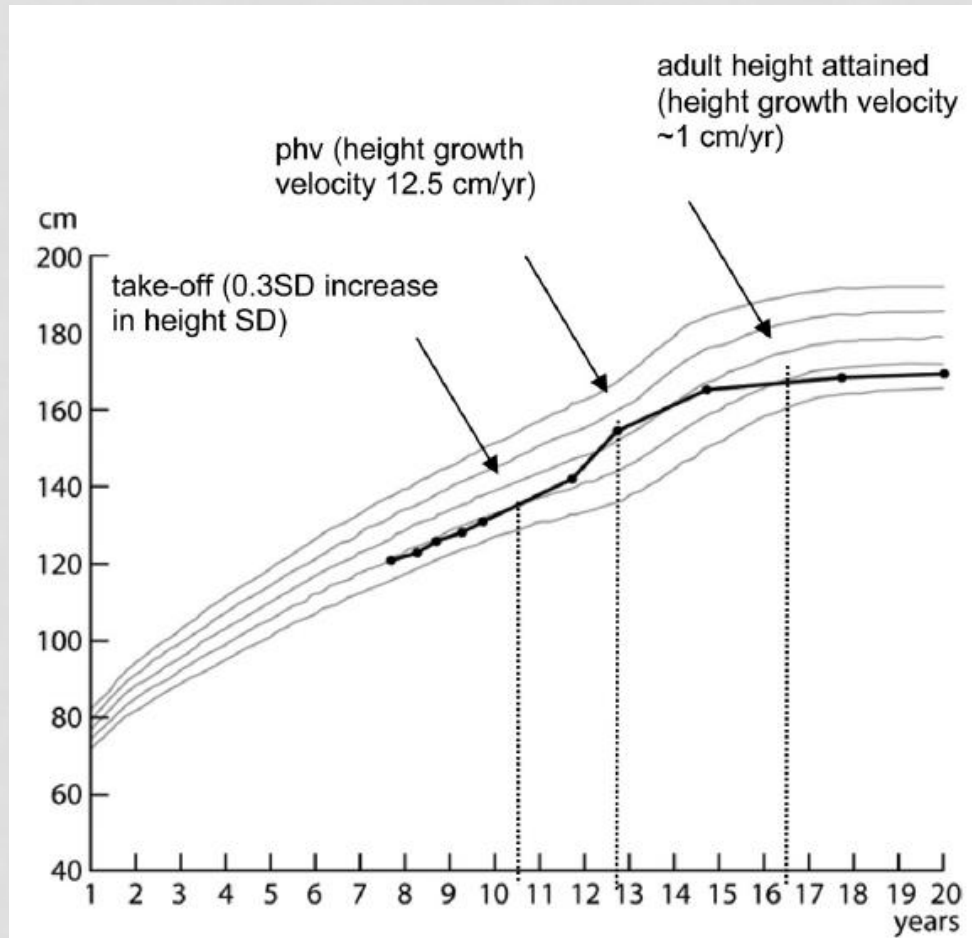
PREMATURE PUBARCHE (PP) AND INSULIN RESISTANT STATES

- Defined as pubic hair <8 years in girls and 9 years in boys.
- Observed much more commonly in known childhood insulin resistant states (esp. SGA, **preterm birth** and obesity)
- In one Australian study 35% of 89 children with PP had SGA and 25% were preterm. 65% were overweight

Neville et al , Arch Dis Child 2005

PUBERTAL TIMING AND PCOS

EARLIER ONSET OF PUBERTY IN PRETERM AND SGA



128 VLBW

147 term-born control subjects.

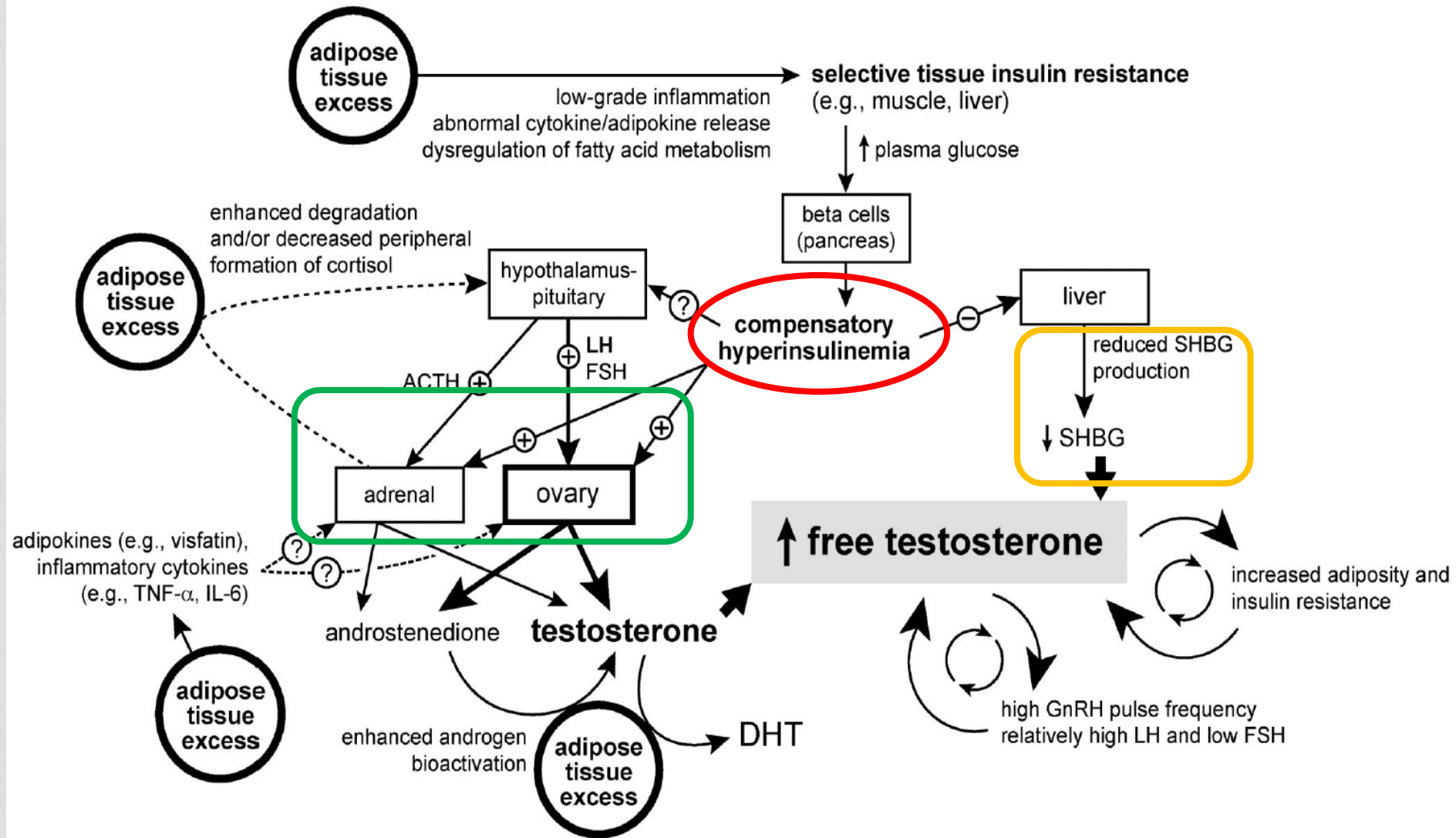
Age at take-off was 0.8 yr earlier in VLBW and 0.9 yr earlier () in those born SGA.

VLBW subjects were more likely to have a pubertal growth spurt that was at least 2 yr earlier than population average [odds ratio 3.8)]

PCOS AND PRETERM WOMEN

- Insulin resistance from any cause can cause PCOS
 - SGA
 - **Preterm**
 - Type 1 diabetes mellitus
 - Obesity
 - Cortisol excess
- The combination of two causes (usually obesity plus one other) increases the risk of PCOS developing, probably by increasing the insulin resistance and the hyperinsulinism.

PCOS AND SGA – PROPOSED AETIOLOGY



PCOS IS INCREASED IN PRETERM WOMEN

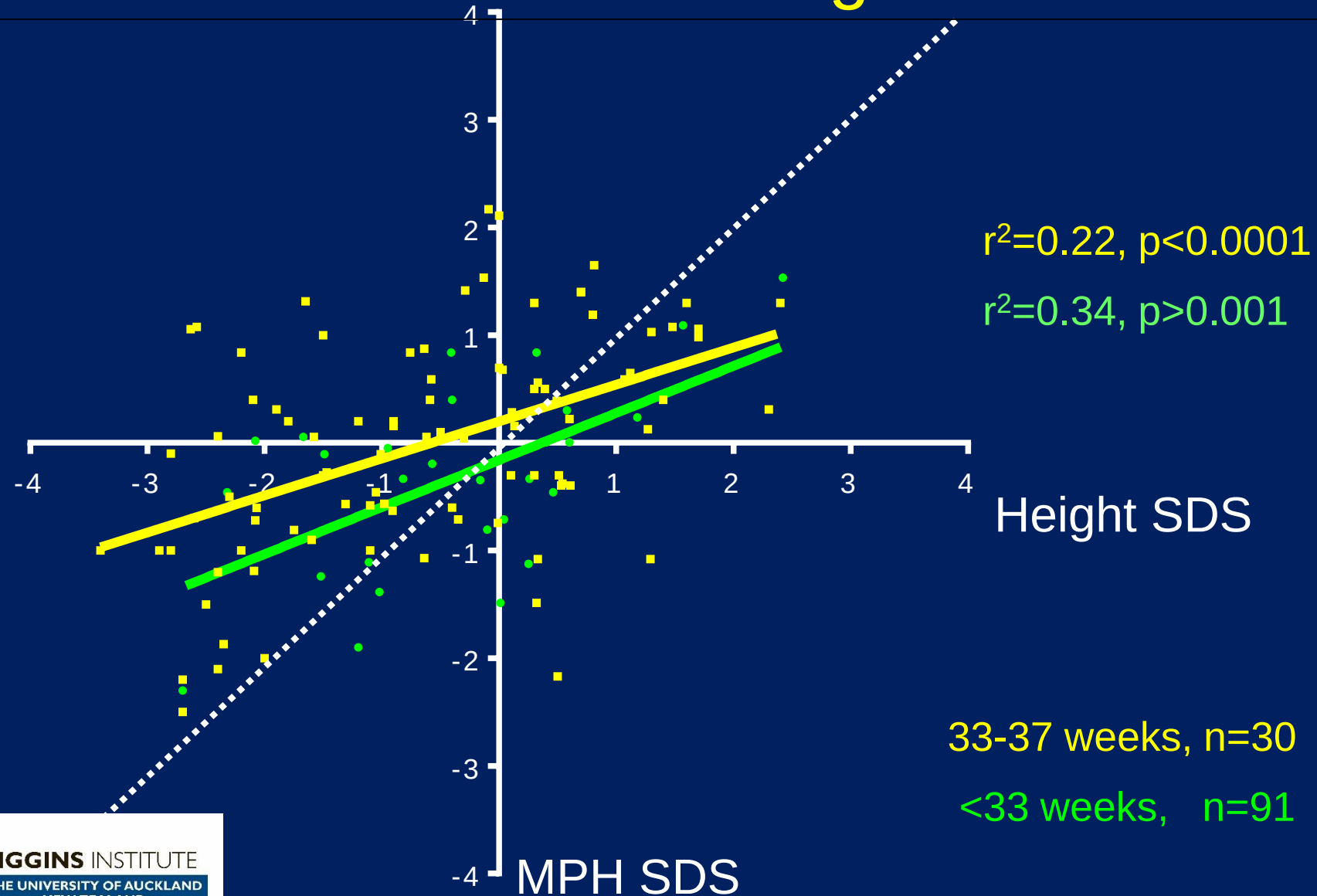
Pandolfi et al. Metabolism Clinical and Experimental 57 (2008) 999–1004

	LBW (35)	Term AGA (35)	<i>P</i> value
Age (y)	21.8 ± 1.4	22.0 ± 1.5	NS
Birth weight (g)	2093 ± 414	3259 ± 311	<.0001
Gestational age (wk)	35.8 ± 3	39.5 ± 1.5	<.0001
WHR	0.75 ± 0.08	0.73 ± 0.13	NS
BMI (kg/m ²)	21.9 ± 3.5	21.9 ± 2.8	NS
Clinical features of PCOS in LBW and control group			

	LBW	Term AGA	<i>P</i> value ^a
Irregular menses	14/35 (40%)	2/35 (5.7%)	.0006
Acne	11/35 (31.4%)	8/35 (22.8%)	NS
Hirsutism	12/35 (34.3%)	6/35 (17.1%)	NS
Polycystic ovaries	10/31 (32.2%)	5/32 (15.6%)	NS

GROWTH

Premature Childhood Height (at 5-10 yrs) vs Parental Height



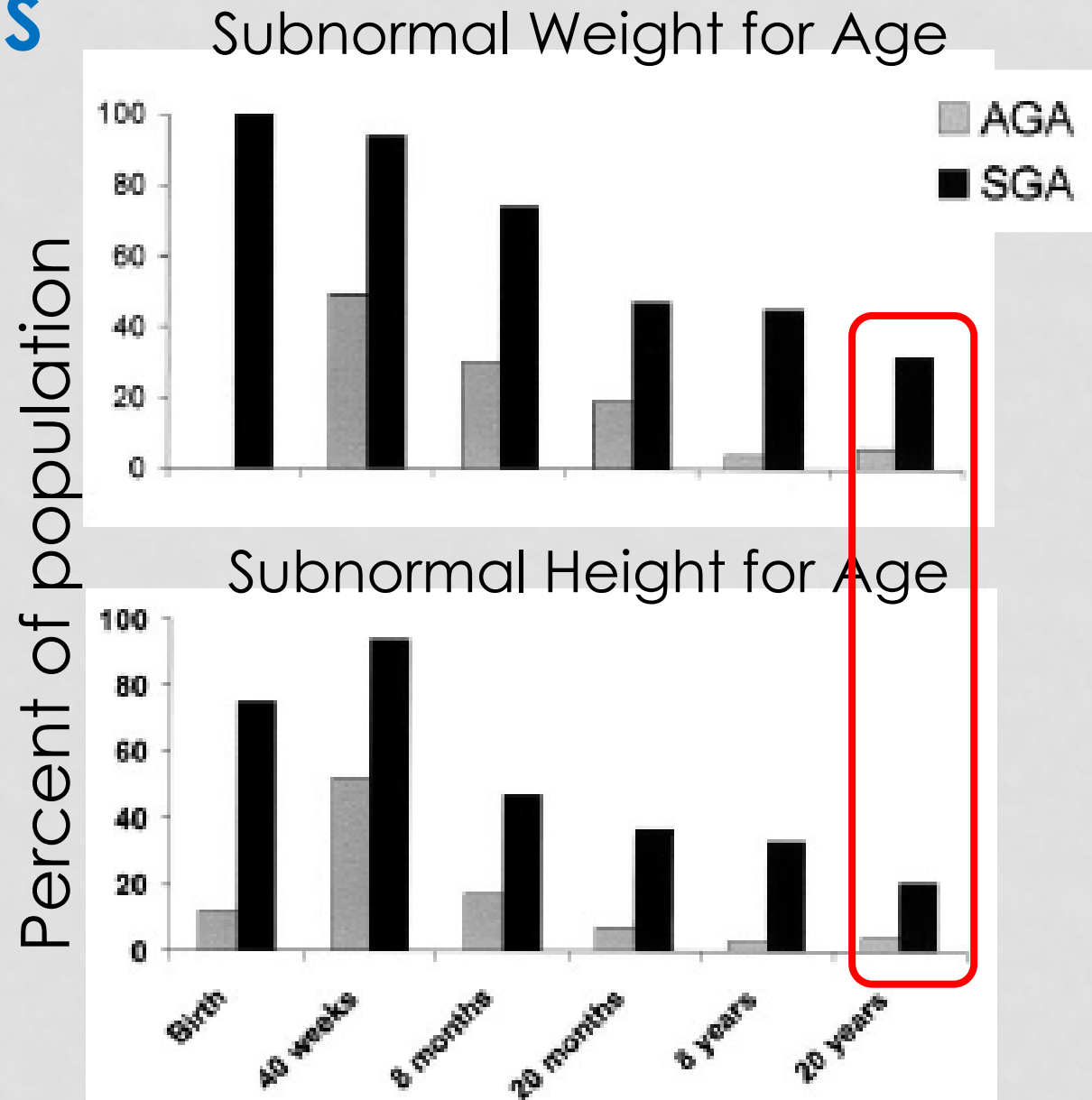
VLBW INFANTS AT 20 YRS OF AGE

- Born 1977-9, <1500 gm.
- 103M, 92 F. 1189 gm, 30 wks.
- 101 M and 107 F controls chosen at 8 years age

• Ht SDS	8 yrs	20 yrs
• Males	-0.5	-0.4*
• Male controls		+0.03*
• Females	-0.2	-0.3
• BMI matched controls.		

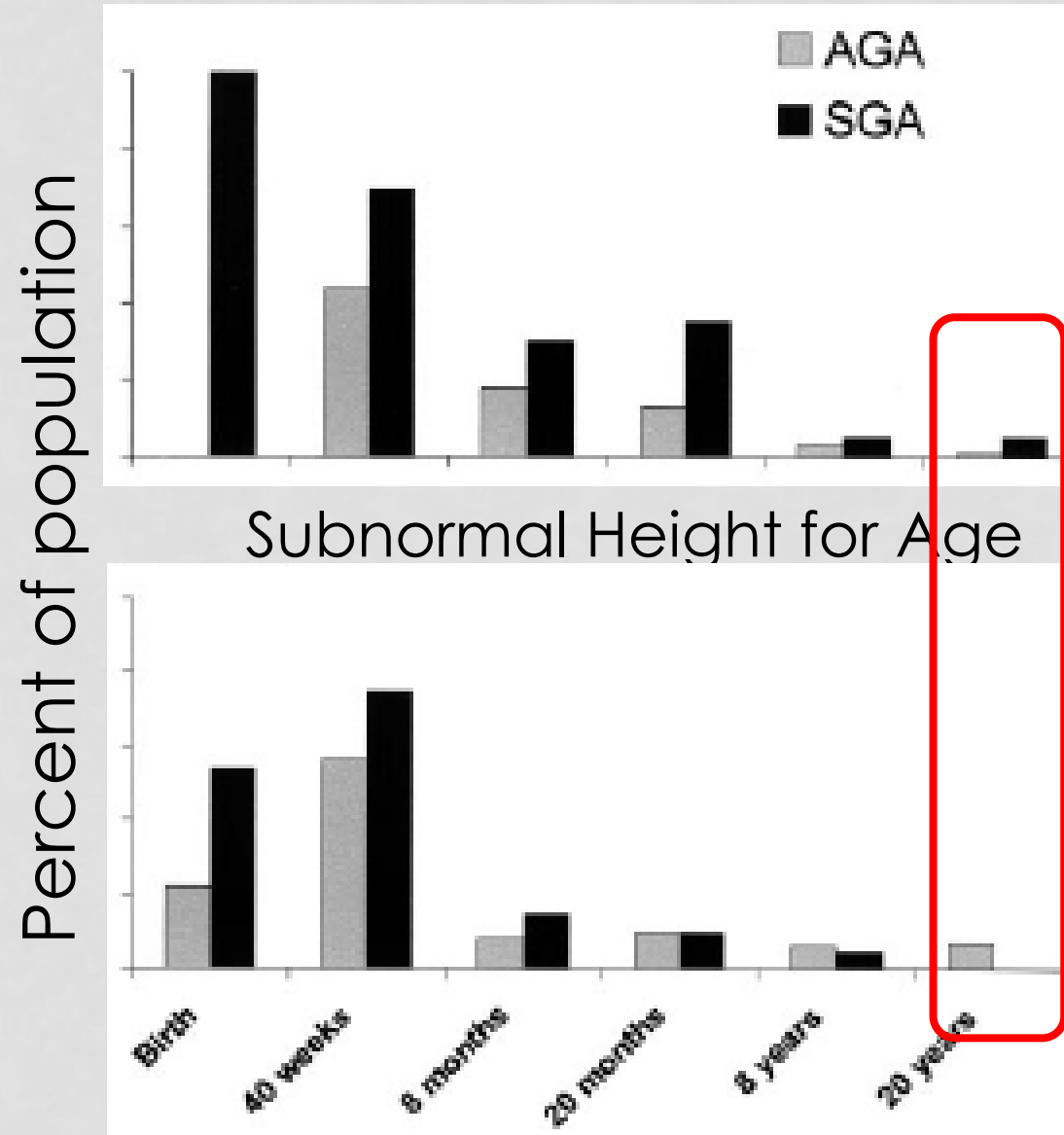
*p <0.05

BOYS



Girls

Subnormal Weight for Age



Hack et al. Pediatrics 2003; 112, e30-8.

FACTORS PREDICTIVE OF SHORT STATURE IN VLBW INFANTS AT 20 YRS OF AGE

- Shorter mother
- Lower birth weight SDS
- Longer duration of neonatal hospital stay

Hack et al. Pediatrics 2003; 112, e30-8

SUMMARY

- Preterm birth is associated with a risk of multiple long term metabolic and endocrine sequelae
- Reduced insulin sensitivity/insulin resistance and secondary hyperinsulinism appear to be a primary underlying metabolic abnormality.
- Most sequelae require an associated increase in fat mass/ adiposity to become apparent – probably causing a greater reduction in insulin sensitivity
- Lifestyle changes in childhood and weight restriction can prevent most sequelae occurring.

THANK YOU!