

Diagnosi Precoce e Prevenzione delle Complicanze in Endocrinologia e Metabolismo

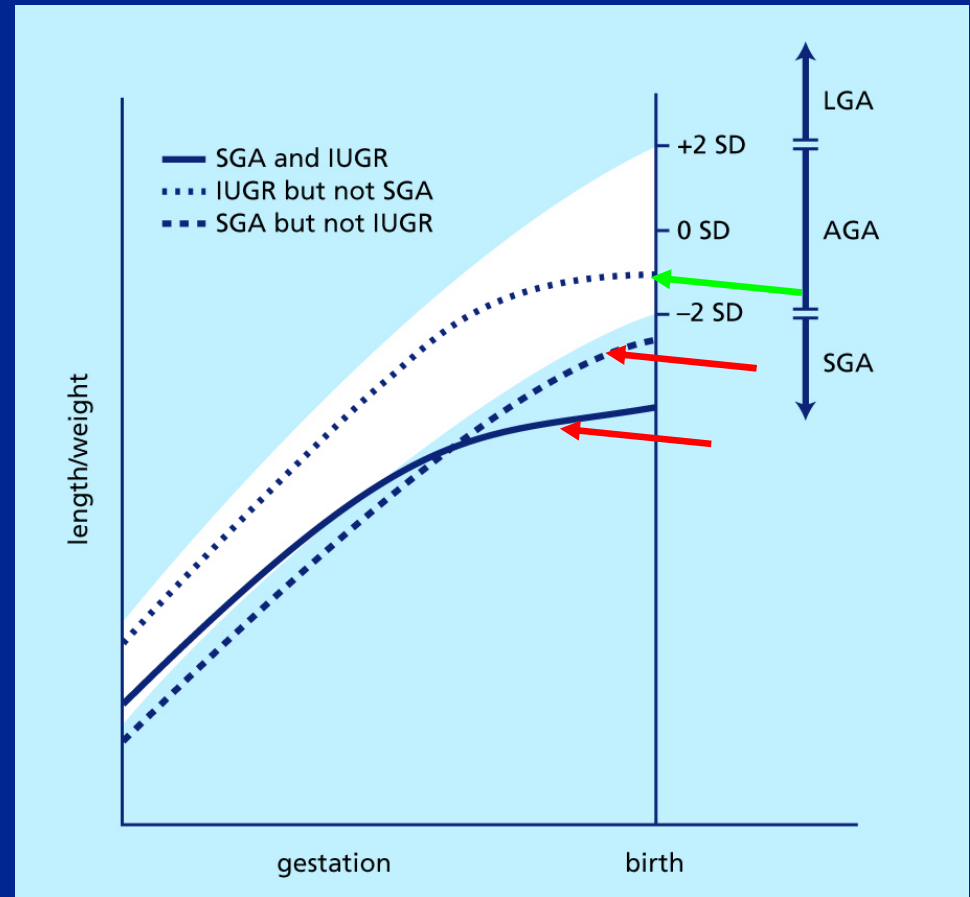
Piccoli per l'Età Gestazionale

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Clinica Pediatrica
Università di Verona

Definizione di Piccolo per l'età gestazionale (SGA)

Peso alla nascita e/o
lunghezza di 2 o più
deviazioni standard (SD) al
di sotto della media per età
gestazionale e sesso

SGA non vuol dire IUGR!



FREQUENZA DI NEONATI SGA PER IL PESO NEL NORD EST
NEGLI ULTIMI ANNI CALCOLATA SU 375182 NATI

	Totale	%
SGA (< 3° cent.)	16592	4,4
SGA (3°-10° cent.)	18455	4,9
AGA	324682	85,7
LGA (> 90° cent.)	15453	4,1

FREQUENZA NEL NORD EST DI NEONATI SGA PER IL PESO
 NEGLI ULTIMI ANNI NEGLI ITALIANI E NEGLI
 EXTRACOMUNITARI CALCOLATA SU 375182 NATI

	Italiani		Extracomunitari	
	Totale	%	Totale	%
SGA (< 3° cent.)	16253	4,4	339	5,3
SGA (3°-10° cent.)	18109	4,9	346	5,4
AGA	319196	86,6	5486	85,9
LGA (> 90° cent.)	15239	4,1	214	3,4

BIRTH-WEIGHT DATA IN ILLINOIS 1980-1995 ACCORDIND TO THE MOTHER'S RACE AND PLACE OF BIRTH

Variable	Subgroup of Mothers			Relative risk (95%CI) In Black mothers	
	US Born	African Born	Us Born	African Born	Us Born
	White	Black	Black		
Raw data					
No of births	44,046	3135	43,322		
Mean birth weight (g)	3,446	3,333	3,089		
Low birth weight (% infants)	4.3	7.1	13.2	1.6 (1.4-1.9)	3.1 (2.9-3.2)
Moderately low	3.6	4.8	10.6	1.3 (1.1-1.6)	3.0 (2.8-3.1)
Very low	0.7	2.3	2.6	3.2 (2.5-4.1)	3.5 (3.1-4.0)
Matched cases					
No of births	2,950	2,950	2,950		
Mean birth weight (g)	3,475	3,341	2,950		
Low birth weight (% infants)	3.6	6.9	8.5	1.9 (1.5-2.4)	2.4 (1.9-2.9)
Moderately low	0.5	2.2	2.4	4.1 (2.4-7.0)	4.5 (2.6-7.7)
Very low					

TABLE 1. Factors Associated With Increased Incidence of Infants Who Are Born SGA

Fetal factors
Karyotypic abnormalities
Trisomy 21 (Down syndrome)
Trisomy 18 (Edward syndrome)
Monosomy X (Turner syndrome)
Trisomy 13 (gonadal dysgenesis)
Other chromosomal abnormalities
Autosomal deletions
Ring chromosomes
Genetic diseases
Achondroplasia
Bloom syndrome
Congenital anomalies
Potter syndrome
Cardiac abnormalities
Maternal factors
Medical conditions
Hypertension
Renal disease
Diabetes (advanced stages) mellitus
Collagen vascular diseases (eg, systemic lupus erythematosus)
Maternal hypoxemia (cyanotic heart disease, chronic anemia, chronic pulmonary disease)
Infection
Toxoplasmosis
Rubella
Cytomegalovirus
Herpesvirus
Malaria
Trypanosomiasis
Human immunodeficiency virus
Nutritional status
Low prepregnancy weight
Low pregnancy weight with poor weight gain during pregnancy
Substance use/abuse
Cigarette smoking
Alcohol
Illicit drugs
Therapeutic drugs (eg, warfarin, anticonvulsants, antineoplastic agents, folic acid antagonists)
Uterine/placental factors
Gross structural placental factors
Single umbilical artery
Velamentous umbilical cord insertion
Bilobate placenta
Placental hemangiomas
Infarcts, focal lesions
Insufficient uteroplacental perfusion
Suboptimal implantation site
Placenta previa
Low-lying placenta
Placental abruption
Demographic factors
Maternal age
Very young age
Older age
Maternal height
Maternal weight
Maternal and paternal race
Parity
Nulliparity
Grand multiparity
Maternal history
Previous delivery of SGA infants
Other
Multiple gestation
Particularly severe in syndromes associated with shared fetal circulation

Adapted from Bernstein and Divon,¹⁸ Pollack and Divon,¹⁹ Wollmann,²⁰ and Keller et al.²¹

Lee PA et al.
Pediatrics 2003; 111: 1253

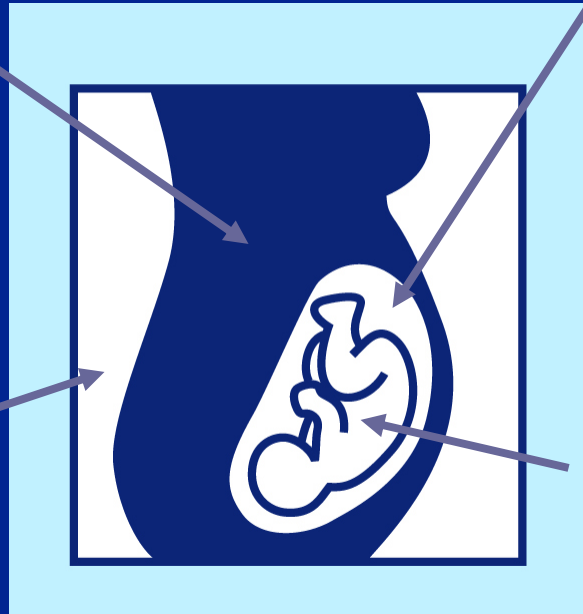
Causes of SGA

Maternal

- Vascular disease
- Environmental factors
- Infection
- Nutrition

Demographic

- Maternal age and height
- Father's size
- Obstetric history
- Race



Placental

- Insufficiency
- Abruption
- Infarction
- Vascular abnormalities

Fetal

- Genetic abnormalities
- Congenital malformations
- Metabolic problems
- Multiple gestations

Table 2. Classification of SGA

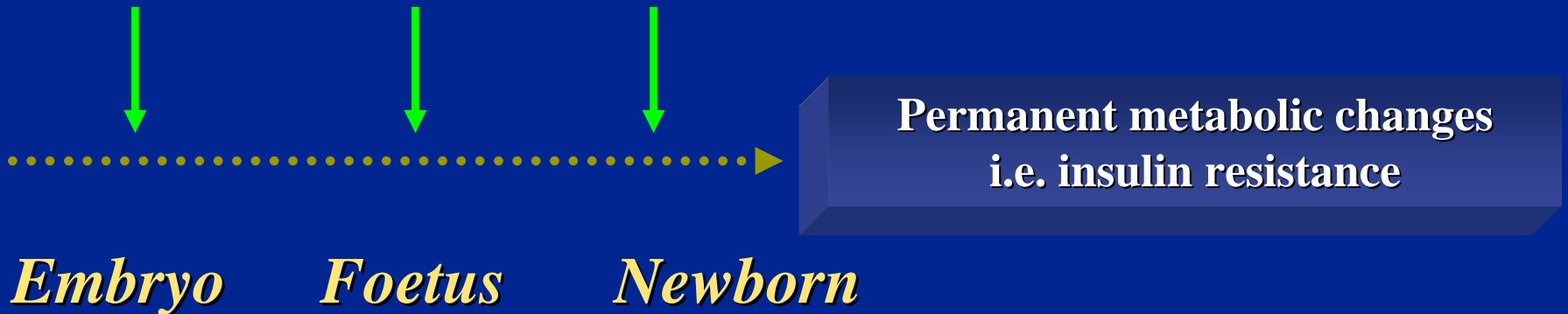
	Type I “symmetrical”	Type II “asymmetrical”
Incidence, %	25	75
Etiopathology	Intrinsic	extrinsic
Cell number	reduced	Normal
Cell size	Normal	Reduced
Head circumference	Reduced	Normal
Ponderal index	Normal	Reduced
Catch-up growth	Rare	Rrequent

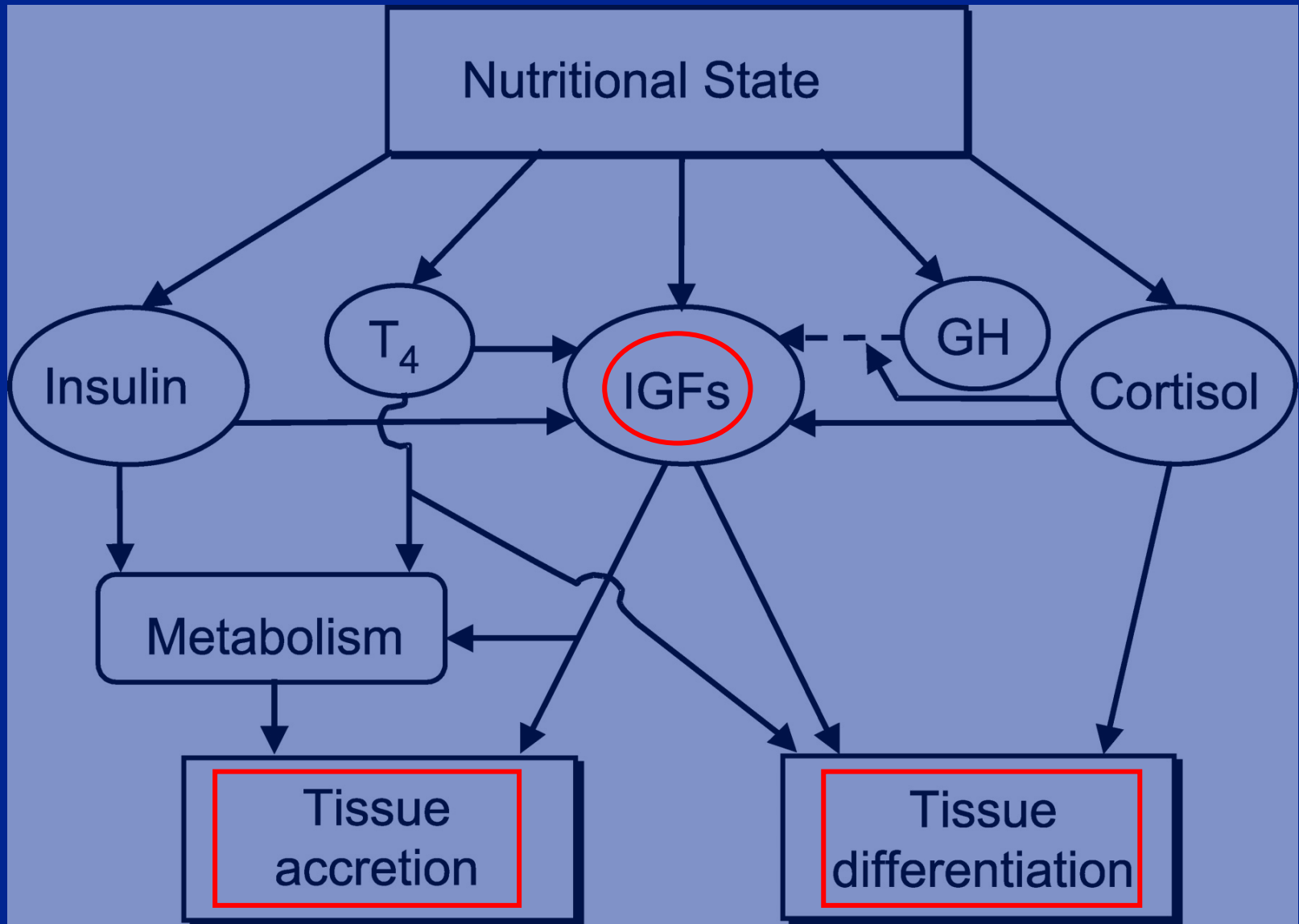
Adapted from Wollman H.A [2]

Reprogramming

Intrauterine Malnutrition

Critical periods





Fowden AL & Forhead AJ. Reproduction 127:515-526,2004

IGF-KO Mice

Gene Mutation

Birth Weight

(% of normal birth weight)

IGF-I

60%

IGF-II

60%

IGF-I + IGF-II

30%

Type I IGF receptor

45%

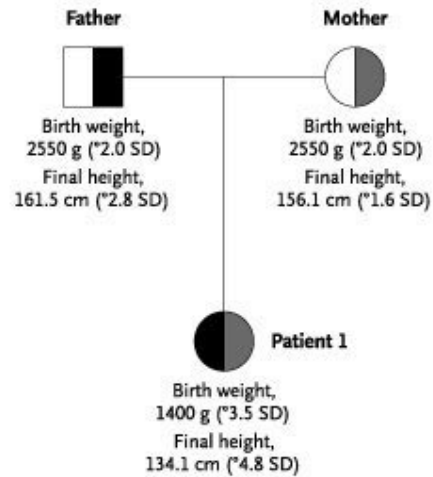
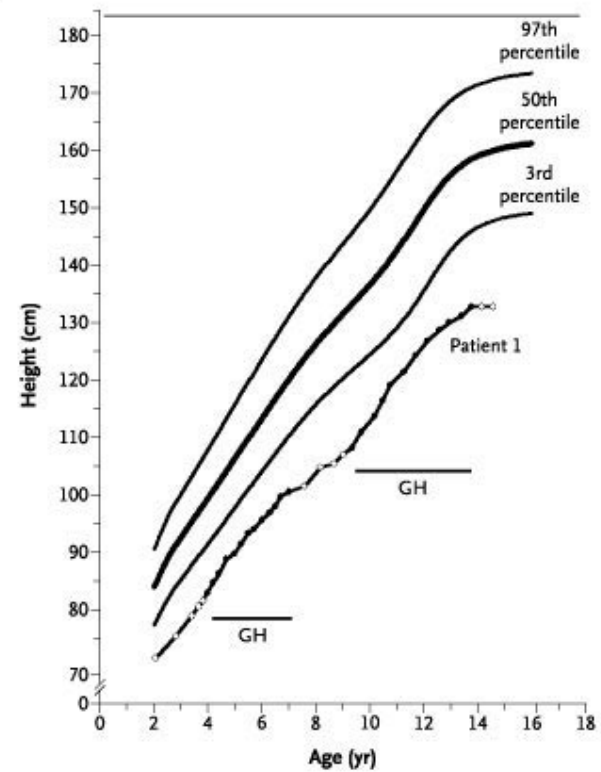


ORIGINAL ARTICLE

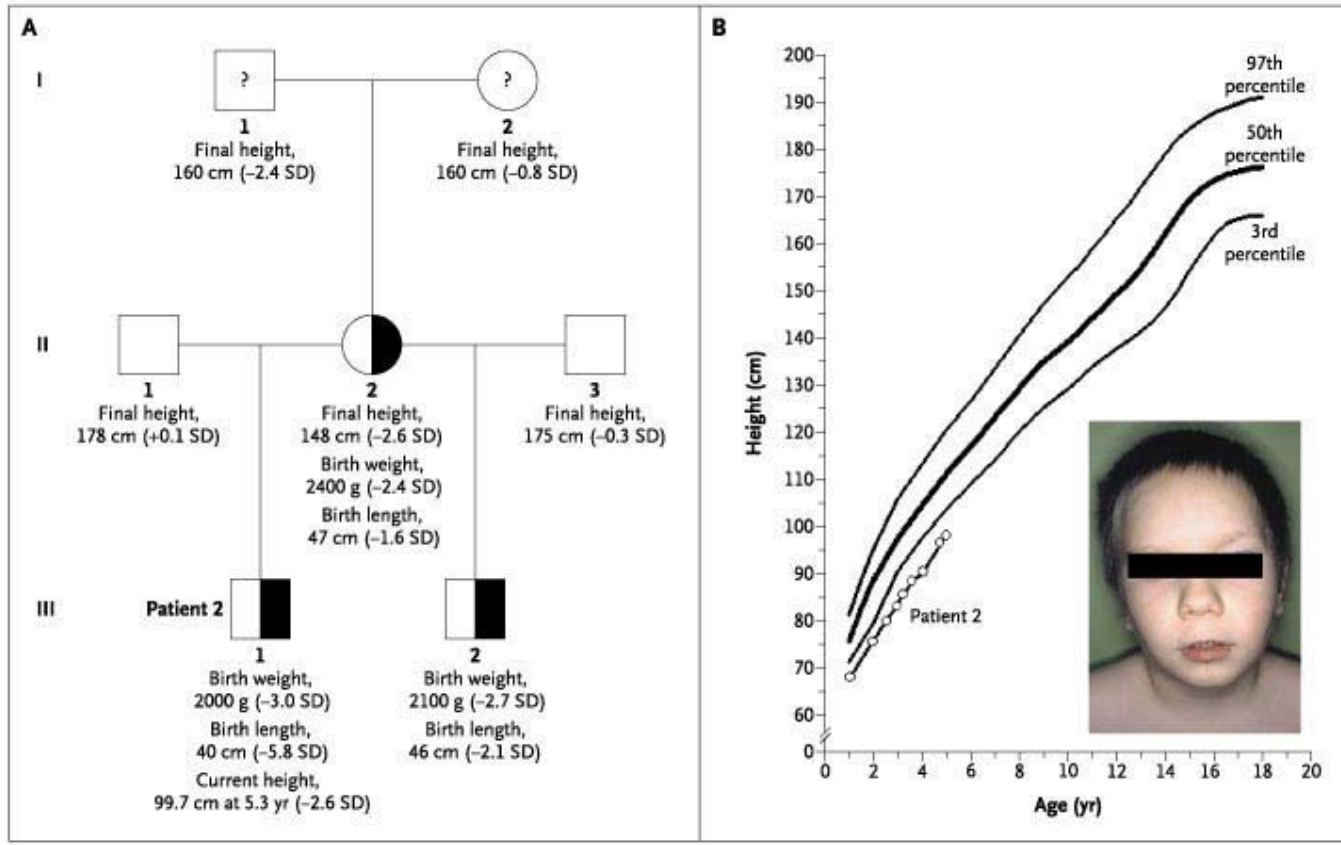
IGF-I Receptor Mutations Resulting in Intrauterine and Postnatal Growth Retardation

M. Jennifer Abuzzahab, M.D., Anke Schneider, M.D., Audrey Goddard, Ph.D., Florin Grigorescu, M.D., Ph.D., Corinne Lautier, Ph.D., Eberhard Keller, M.D., Wieland Kiess, M.D., Jürgen Klammt, Jürgen Kratzsch, Ph.D., Doreen Osgood, Ph.D., Roland Pfäffle, M.D., Klemens Raile, M.D., Berthold Seidel, Ph.D., Robert J. Smith, M.D., and Steven D. Chernausek, M.D., for the Intrauterine Growth Retardation (IUGR) Study Group*

N ENGL J MED 349;23 WWW.NEJM.ORG DECEMBER 4, 2003

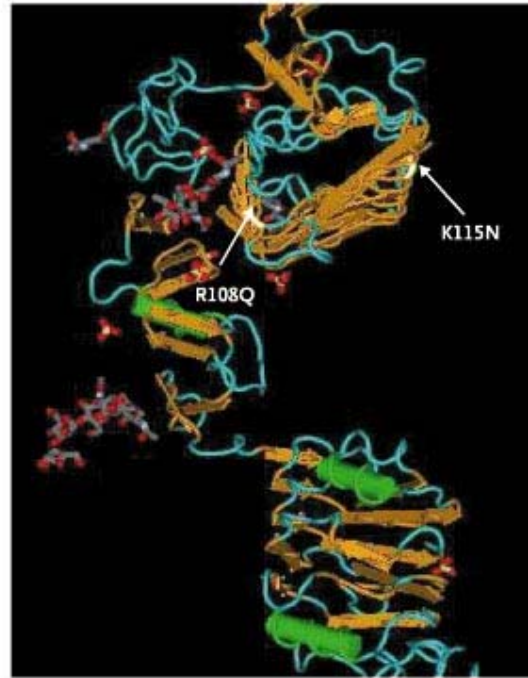
A**B**

Abuzzahab MJ et al NEJM 2003; 349: 2211-22



Abuzzahab MJ et al NEJM 2003; 349: 2211-22

A



B

	100					Q	110			N		120									
Insulin-like growth factor receptor	L	Y	N	L	R	N	I	T	R	G	A	I	R	I	E	K	N	A	D	L	C
Insulin receptor	L	Y	N	L	M	N	I	T	R	G	S	V	R	I	E	K	N	N	E	L	C
							110						M ¹²⁰								

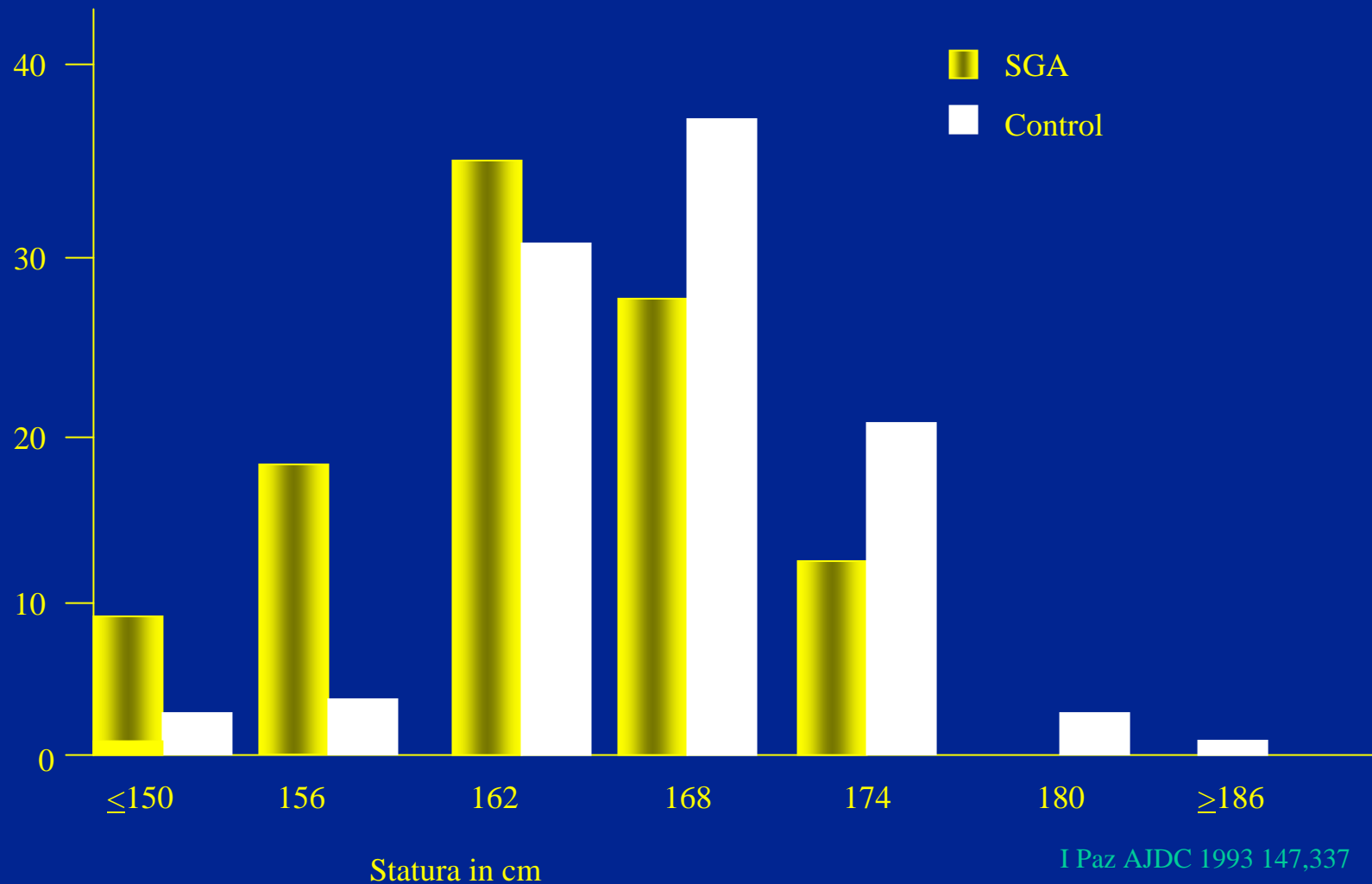
Abuzzahab MJ et al NEJM 2003; 349: 2211-22

PATOLOGIE DELL' ETA' ADULTA E SCARSO ACCRESCIMENTO FETALE

- Bassa statura
- SIDS
- Malattie cardiovascolari
- Diabete tipo 2, ipertensione e iperlipidemia (sindrome x)
- Ipercolesterolemia
- Aumento del fibrinogeno e del fattore VII
- Patologia tiroidea autoimmune

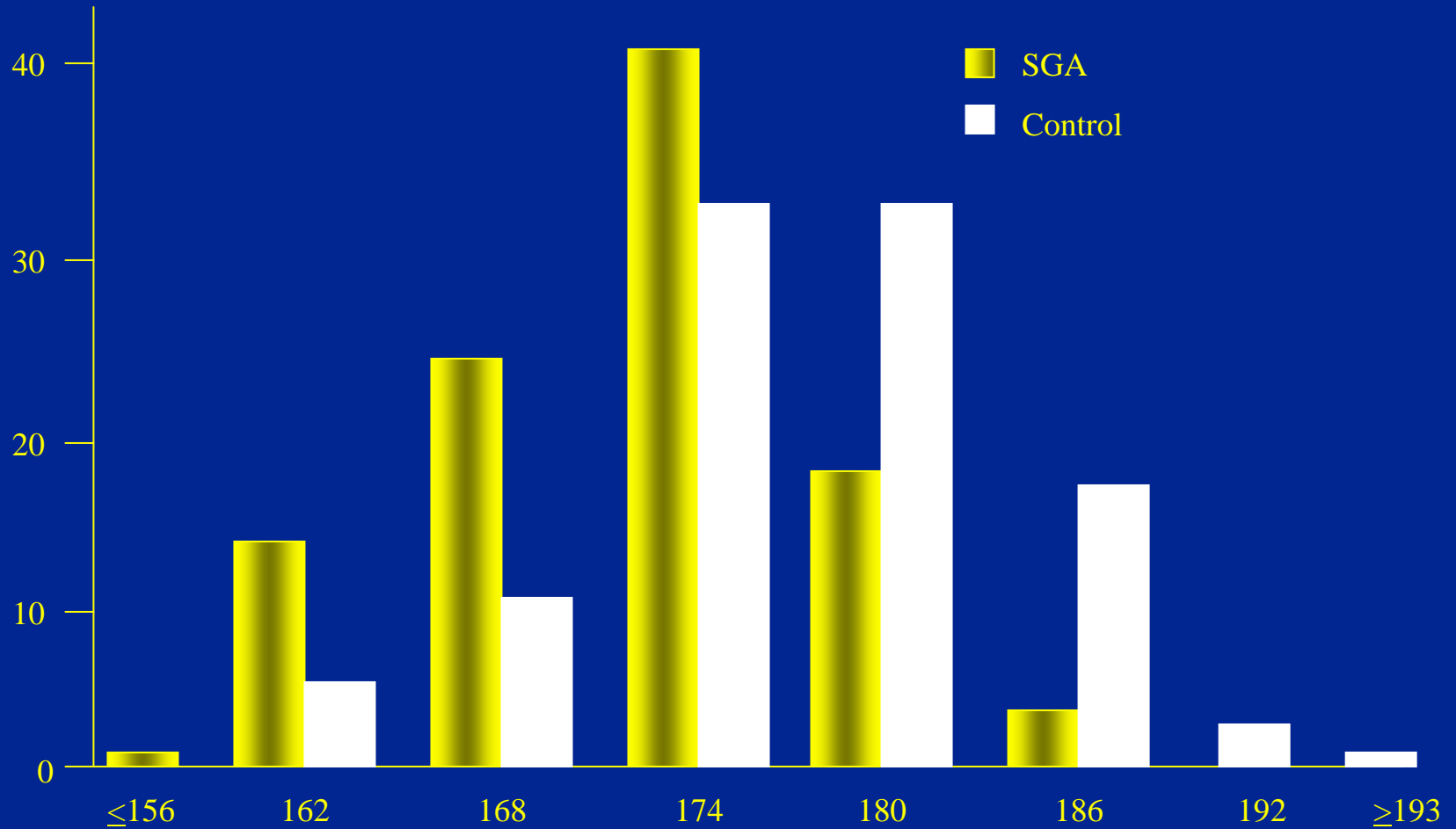
DISTRIBUZIONE STATURALE DELLE FEMMINE NATE SGA A 17 ANNI

% di tutti i soggetti

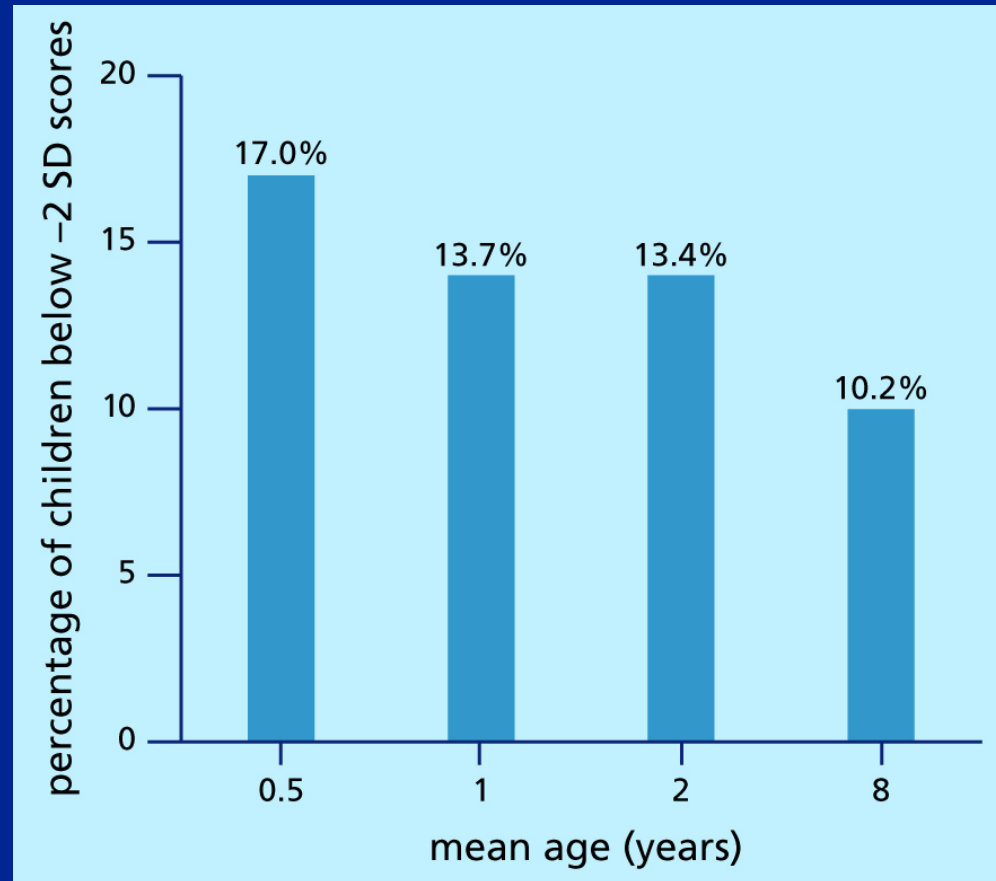


DISTRIBUZIONE STATURALE DEI MASCHI NATI SGA A 17 ANNI

% di tutti i soggetti

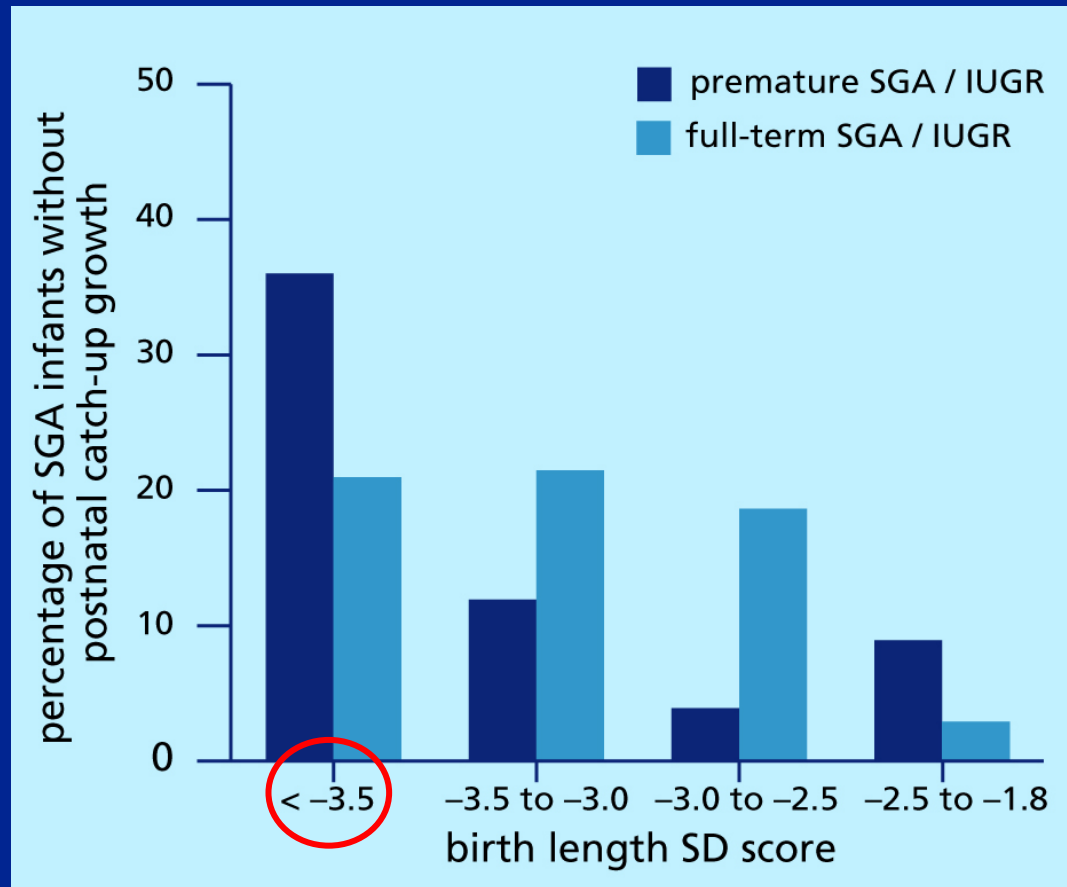


Crescita postnatale di neonati SGA



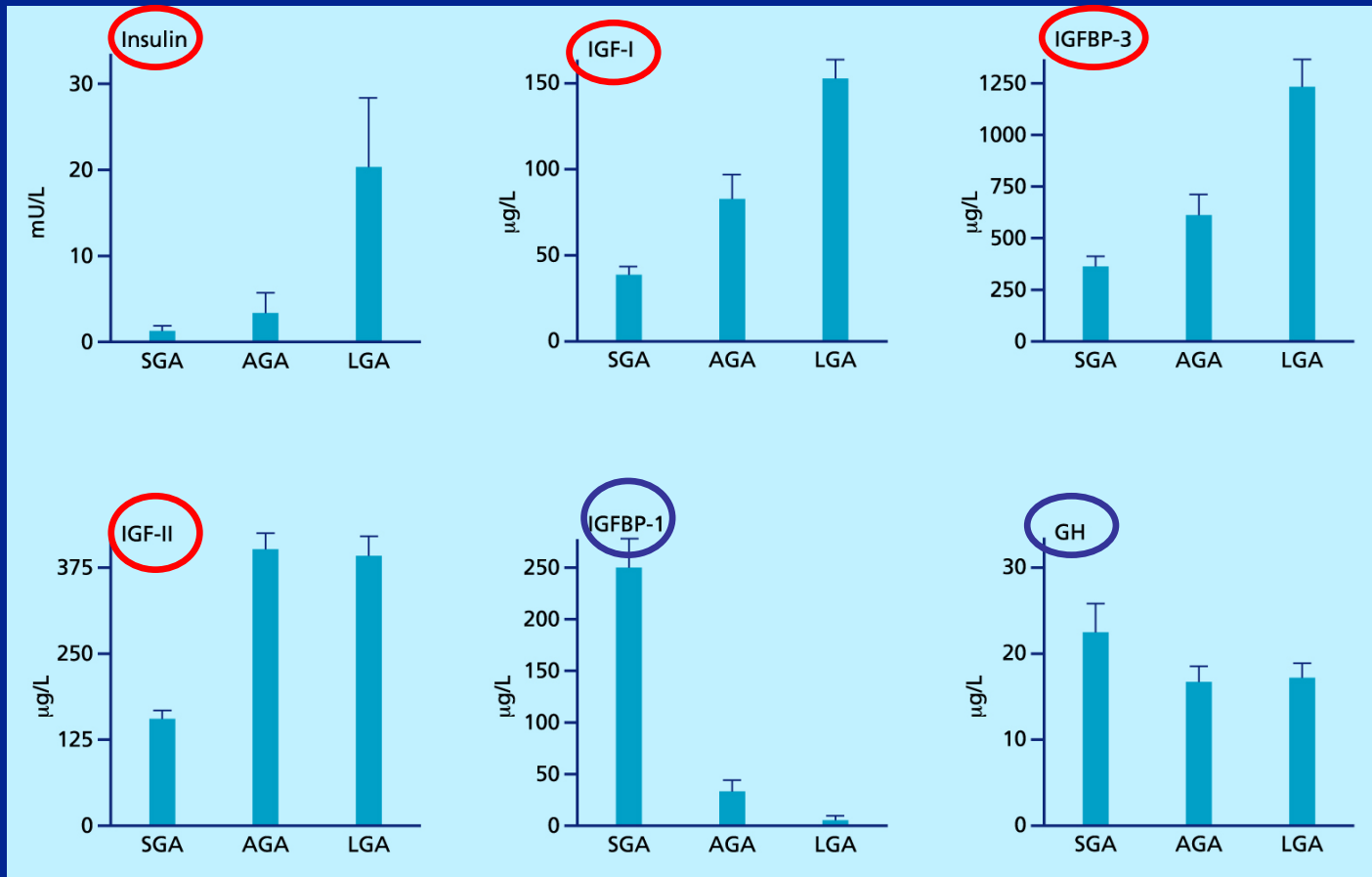
Karlberg J, Albertsson-Wikland K. *Pediatr Res* 1995;38:733-9.

Catch-up growth in bambini nati SGA

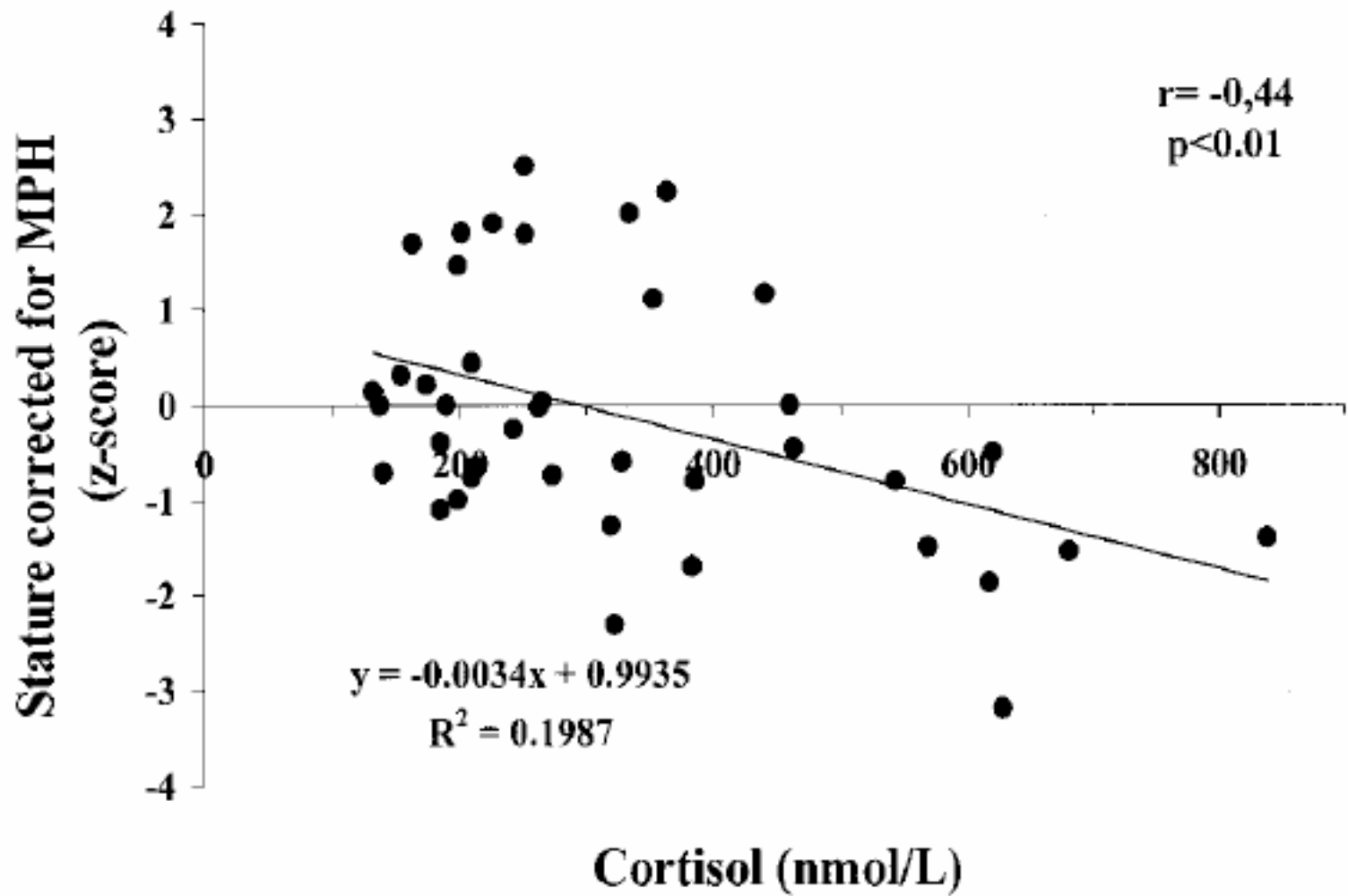


Hokken-Koelega et al. Pediatr Res 1995;38:267-71.

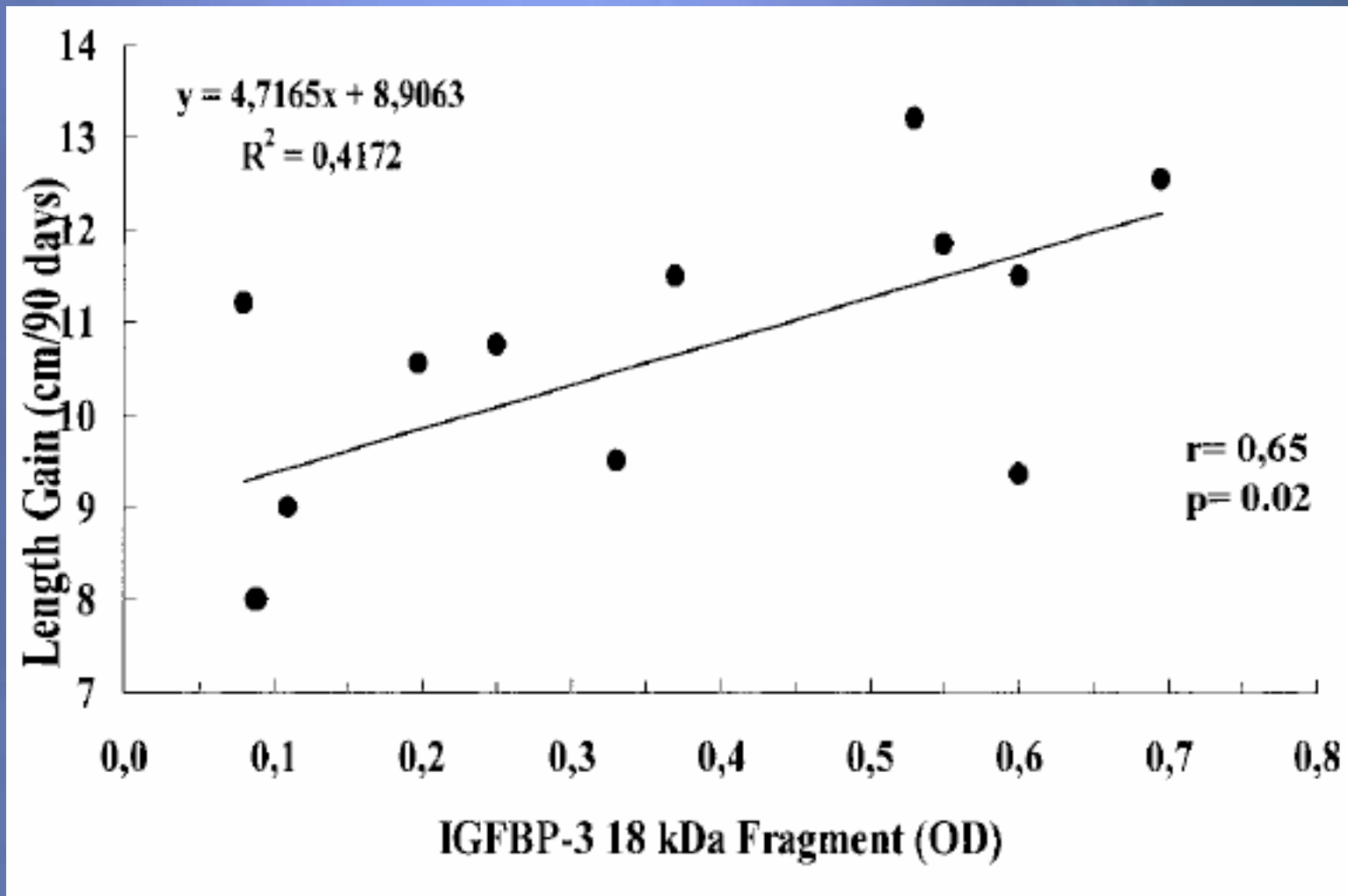
Regolazione ormonale della taglia fetale



de Zegher F et al. J Clin Endocrinol Metab 1997;82:2021-6.

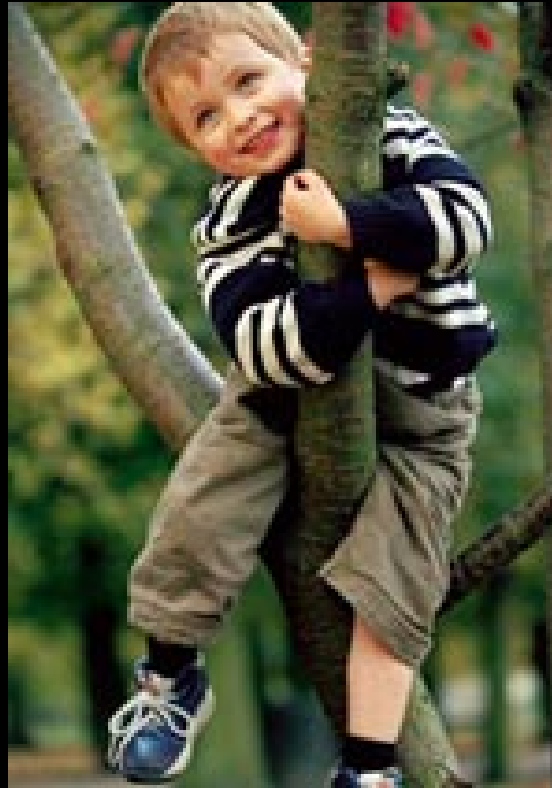


Cianfarani S. et al. Pediatr Res 2002; 51: 94-9

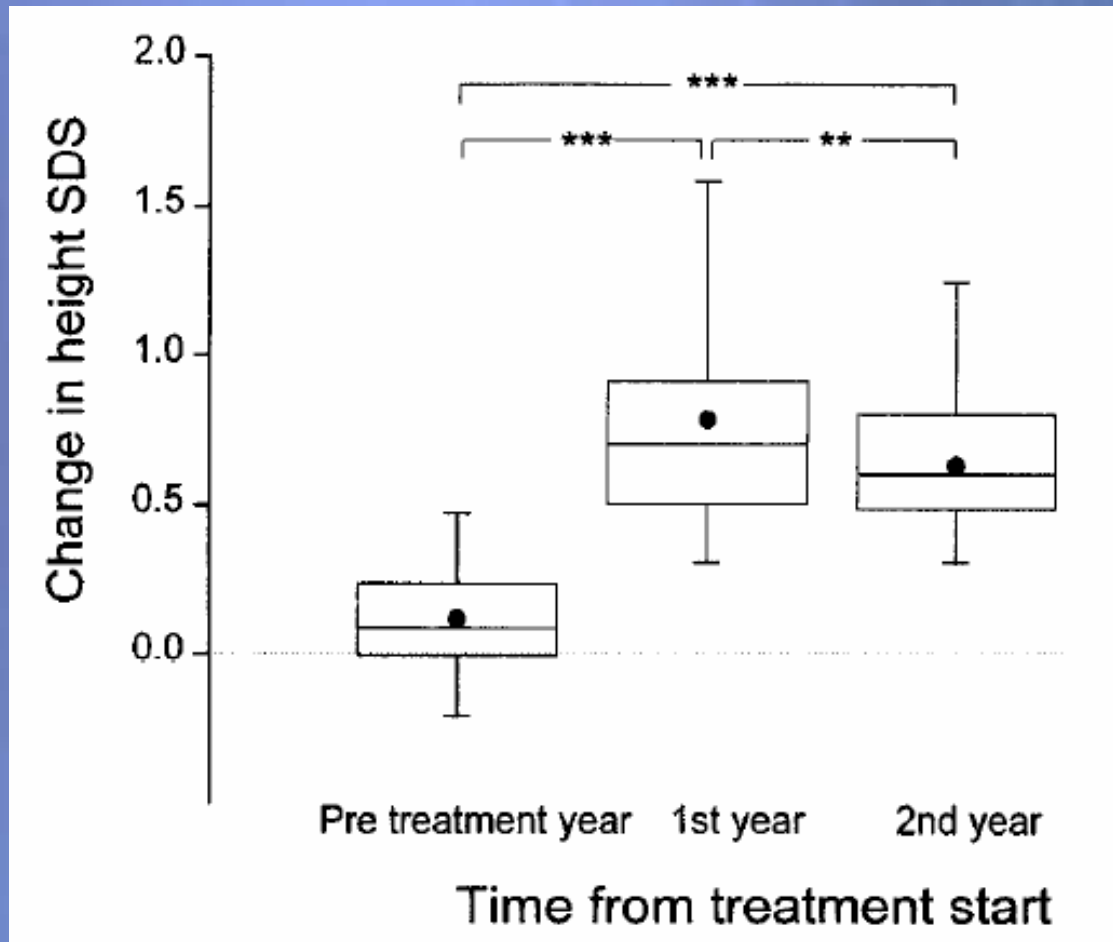


Cianfarani S. et al. *Pediatr Res* 2002; 51: 94-9

“...Voglio crescere!!...”

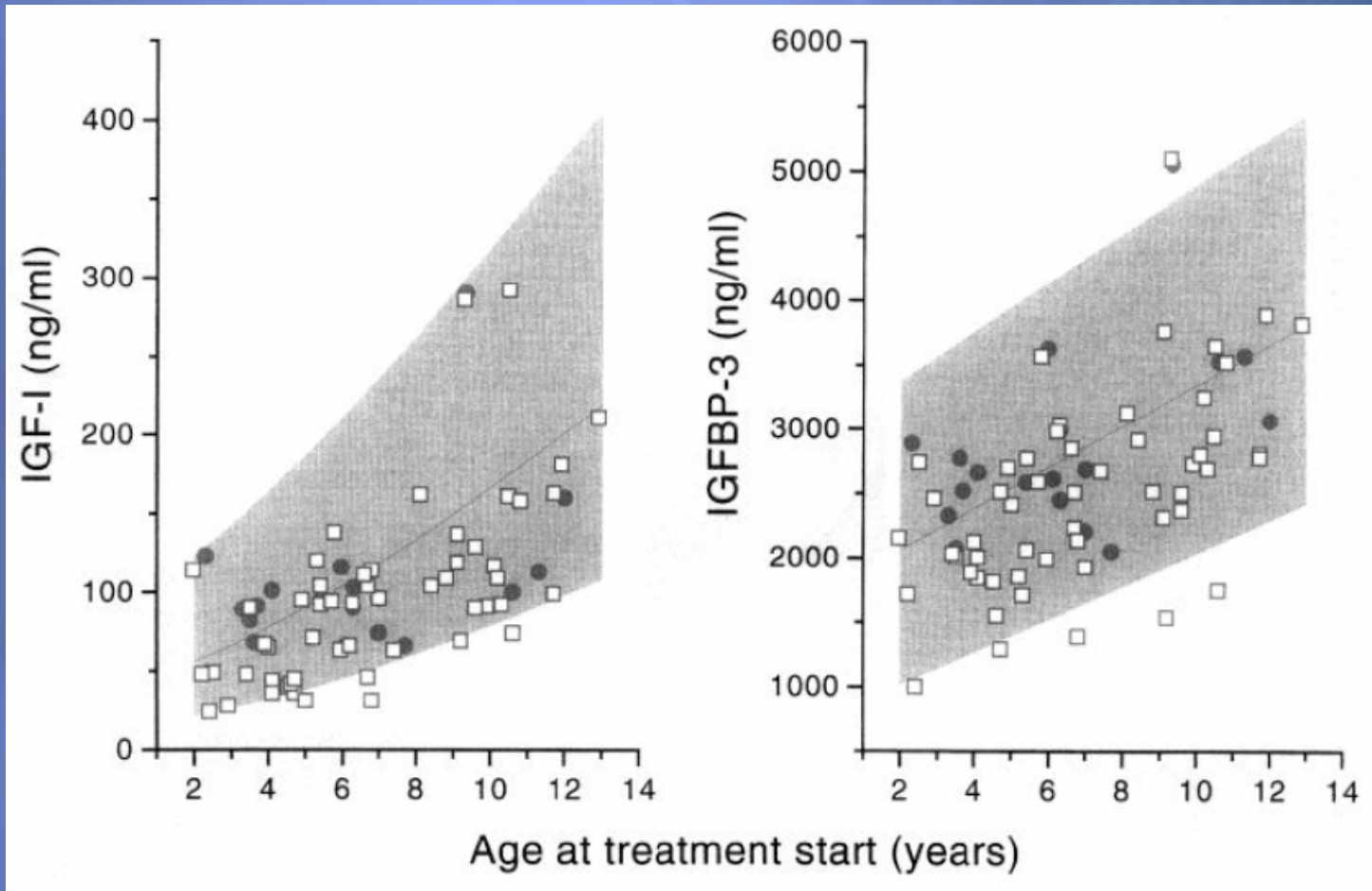


Growth in SGA children



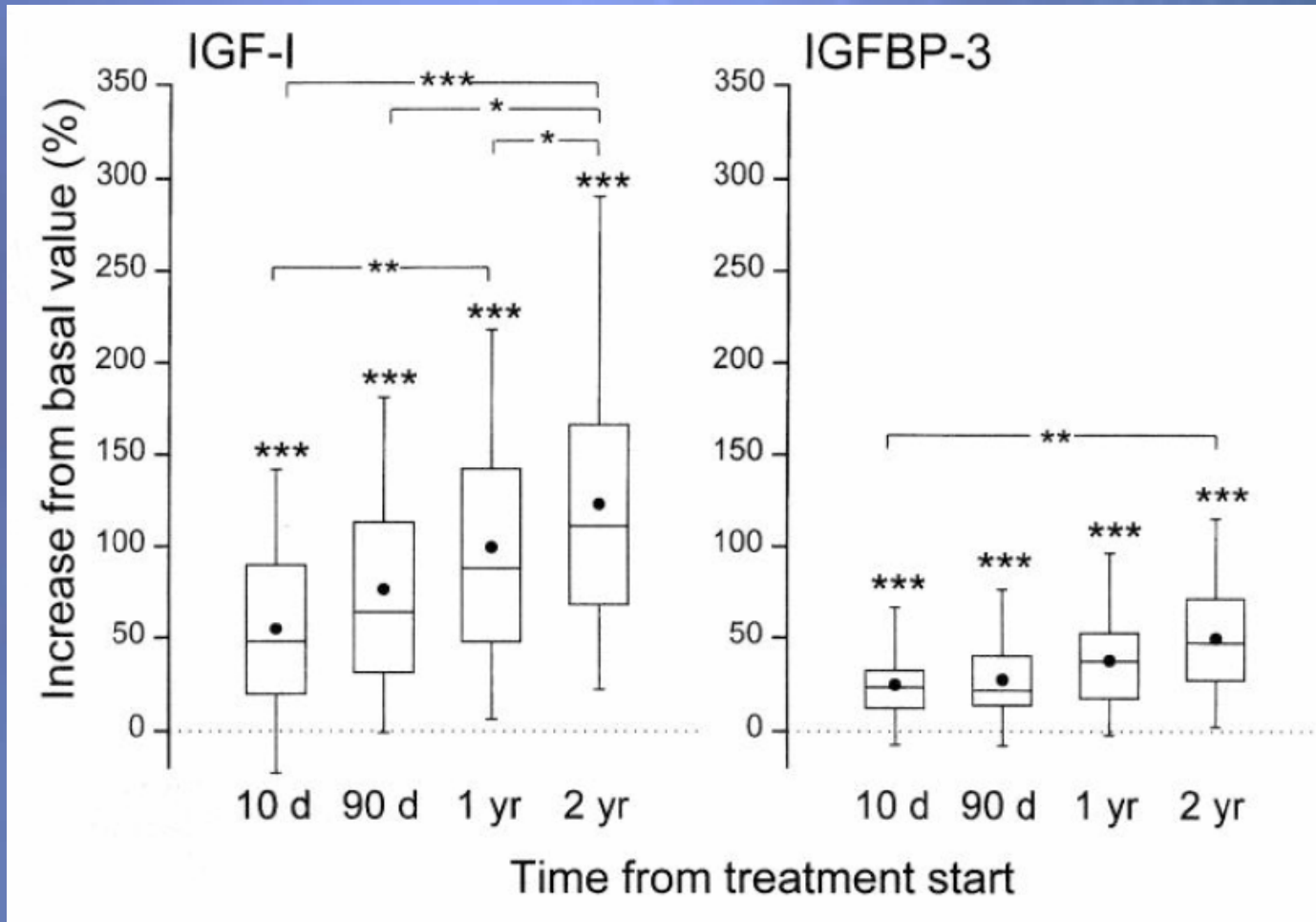
Boguszewski M et al. *JCE&M* 1996; 81: 3902-8

IGF-I and IGFBP-3 in SGA children



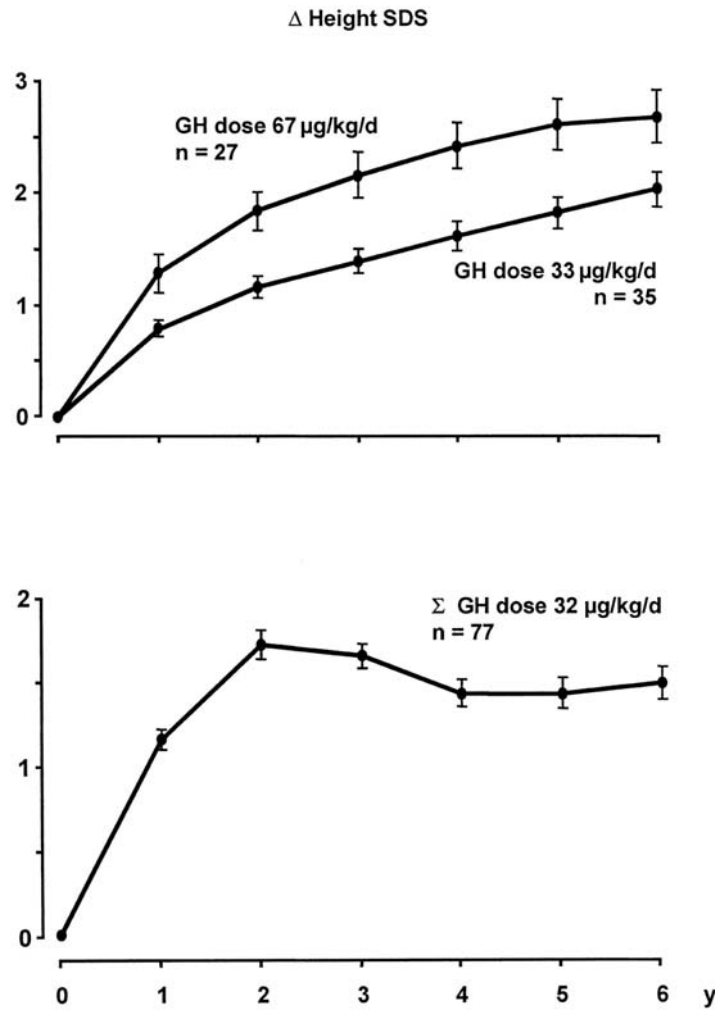
Boguszewski M et al. *JCE&M* 1996; 81: 3902-8

Increase in IGF-I and IGFBP3 levels during GH treatment in SGA children



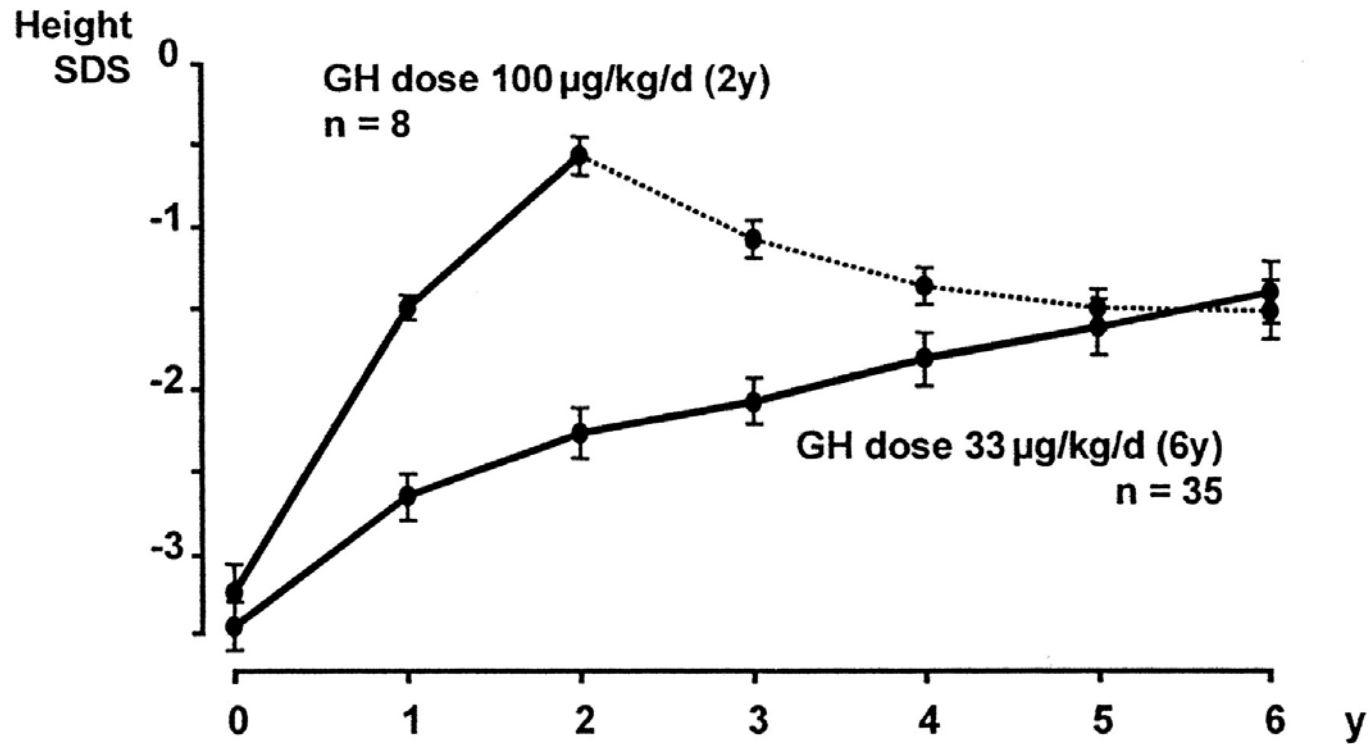
Boguszewski M et al. *JCE&M* 1996; 81: 3902-8

Crescita negli SGA trattati con GH a vario dosaggio



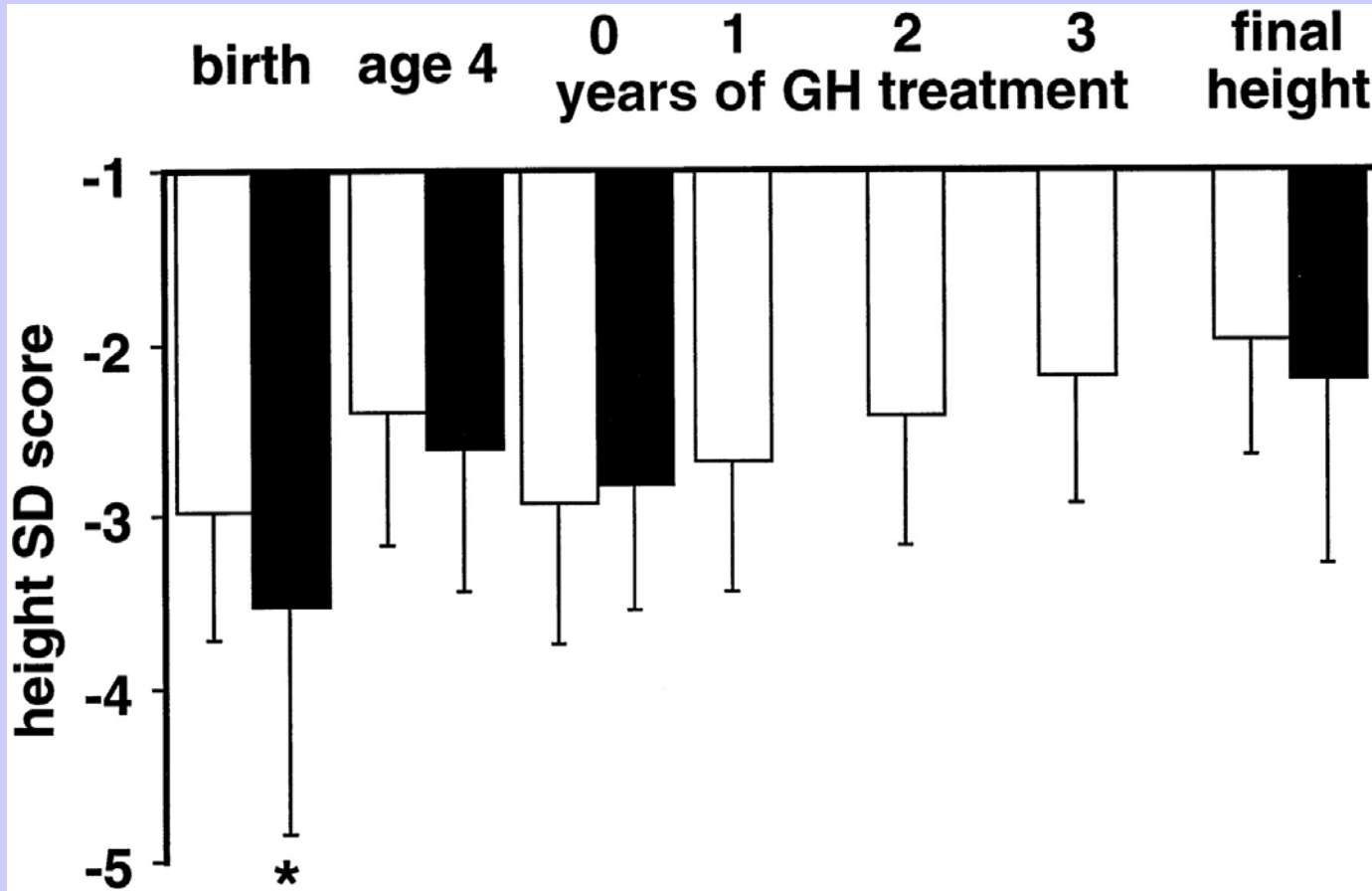
de Zegher, F. et al. J Clin Endocrinol Metab 2000;85:2816-2821

Crescita negli SGA trattati con GH a vario dosaggio



de Zegher, F. et al. J Clin Endocrinol Metab 2000;85:2816-2821

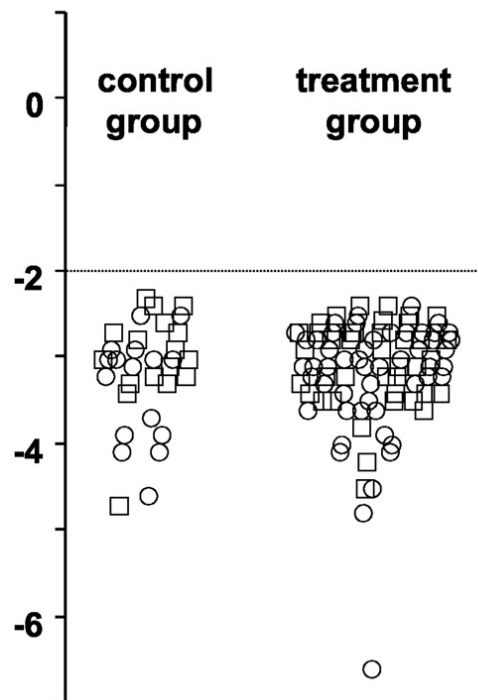
GH Treatment in IUGR



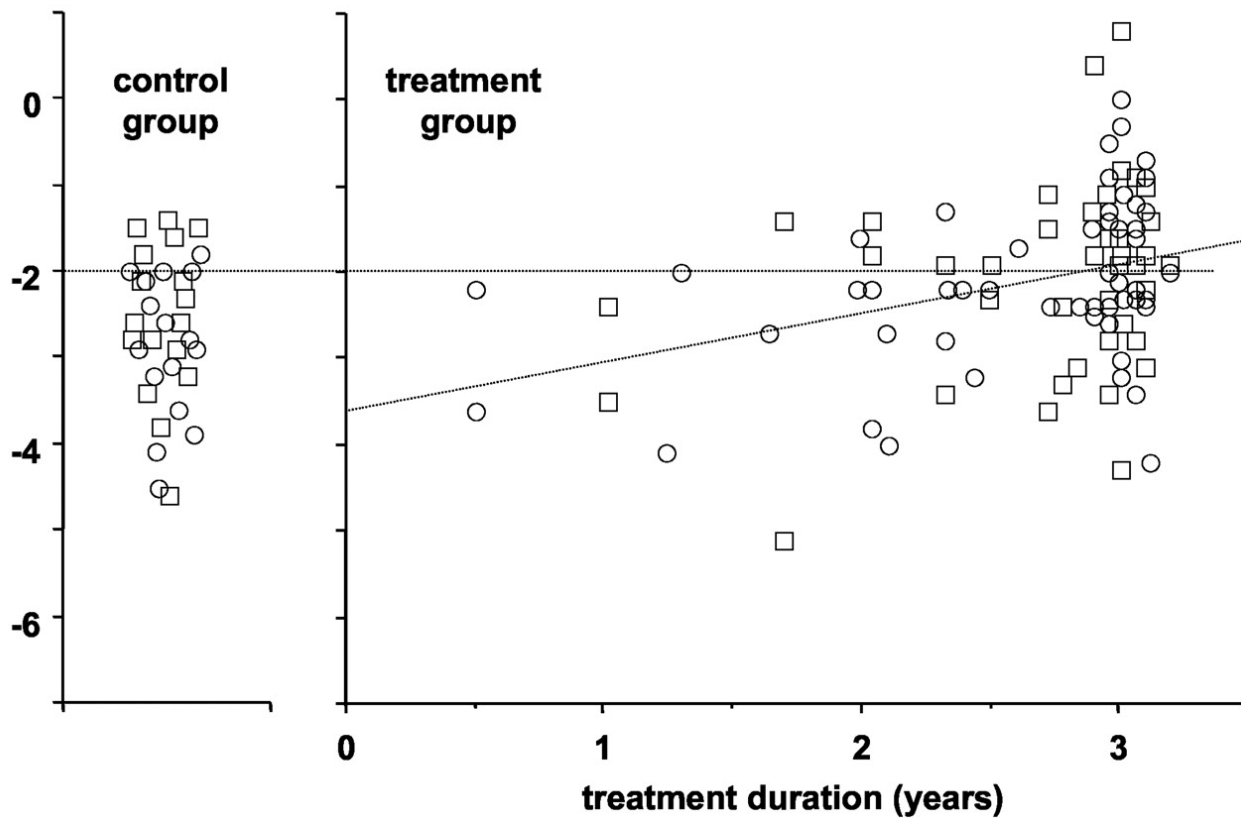
Coutant, R. et al. J Clin Endocrinol Metab 1998;83:1070-1074

No Caption Found

A Height SDS at baseline



B Adult height SDS



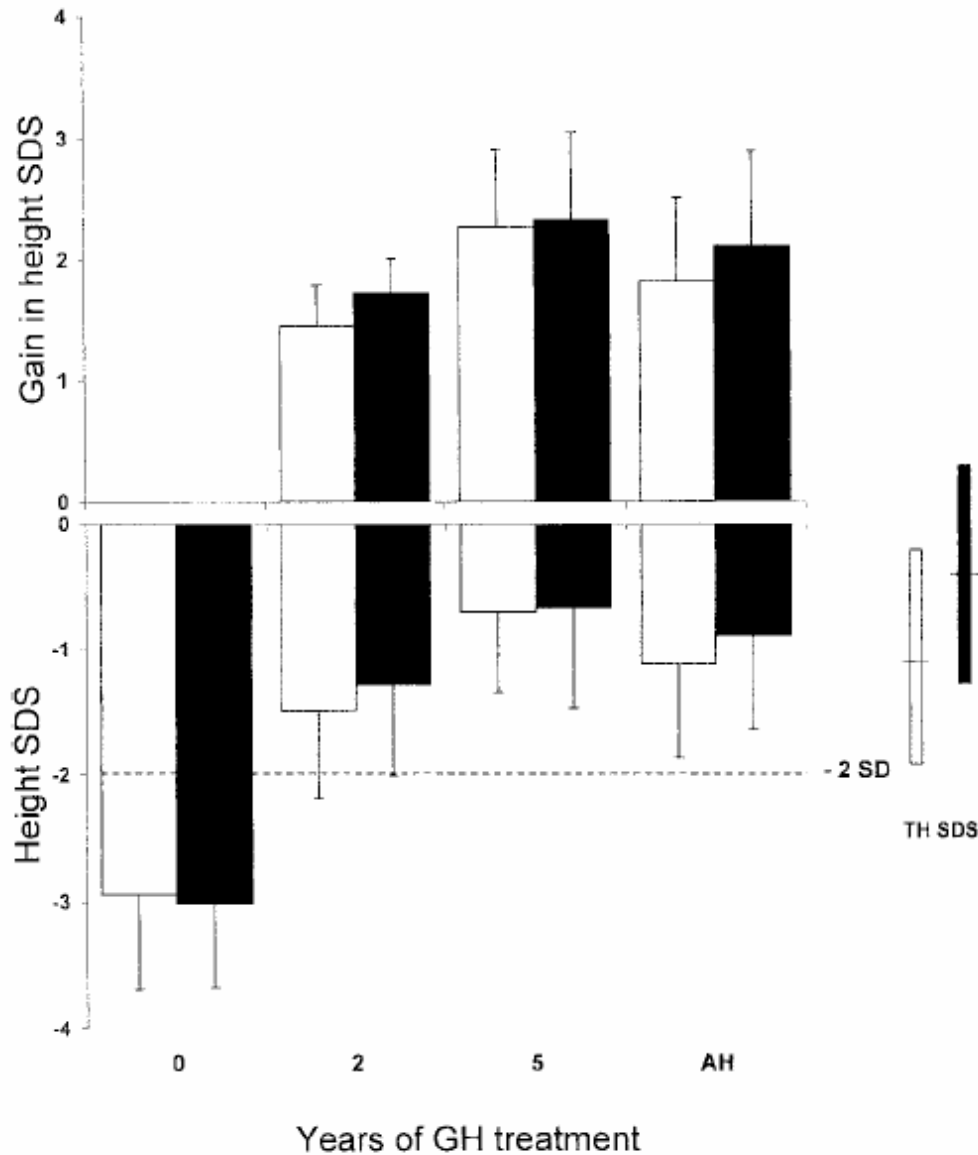
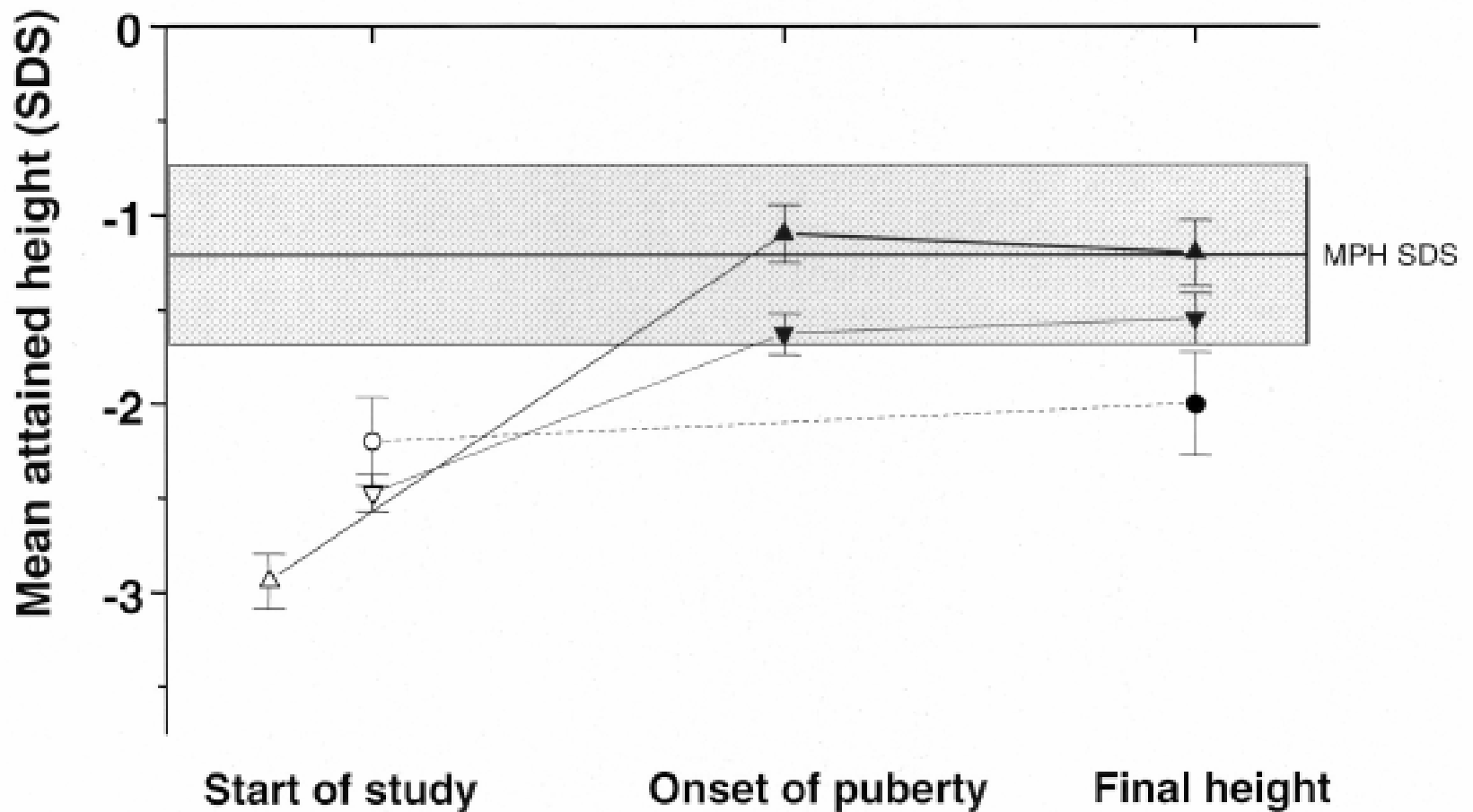


FIG. 1. *Bottom panel*, Height SDS (\pm SD) during GH treatment and at AH in relation to TH. *Top panel*, Gain in height SDS (\pm SD) from the start until 2 yr of GH treatment, until 5 yr of GH treatment, and until AH. □, Group A; ■, group B.

Van Pareren Y et al
JCE&M 2003; 88: 3584-3590,



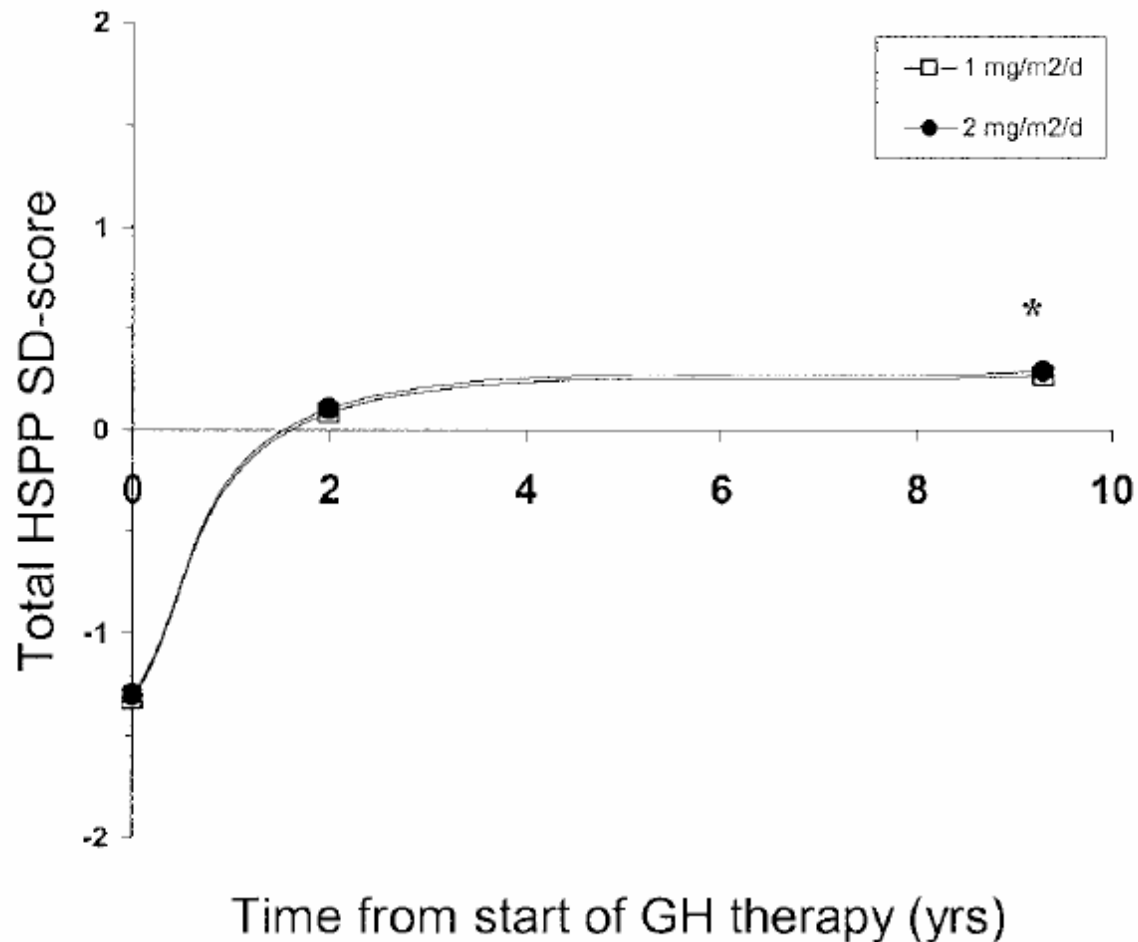


FIG. 7. Self-perception total HSPP SD score for both GH groups during GH treatment, corrected for gender and age at start. Significant increase from start: *, $P < 0.001$.

Glicemia e insulinemia dopo stop trattamento con GH

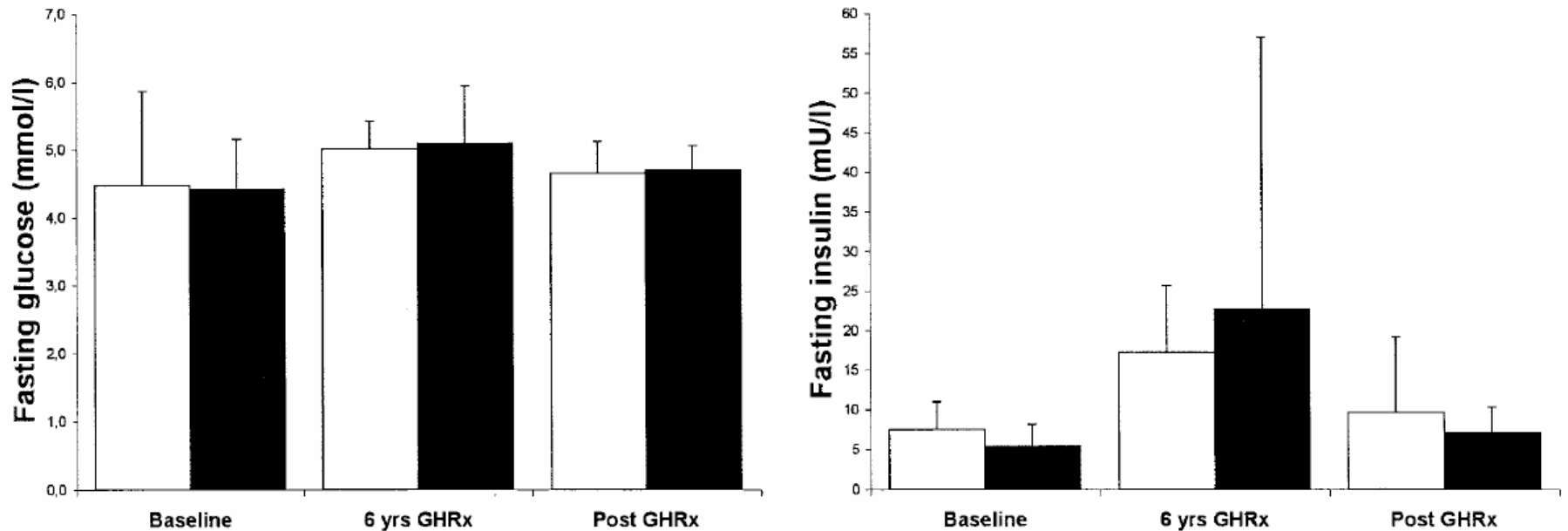


FIG. 1. Mean (+SD) fasting glucose levels (*left*) and fasting insulin levels (*right*) before treatment, at 6 yr of GH treatment, and at 6 months after discontinuation of treatment for group A (□) and B (■), respectively.

Van Pareren Y et al. JCE&M, 2003, 88:347-353

Pressione arteriosa

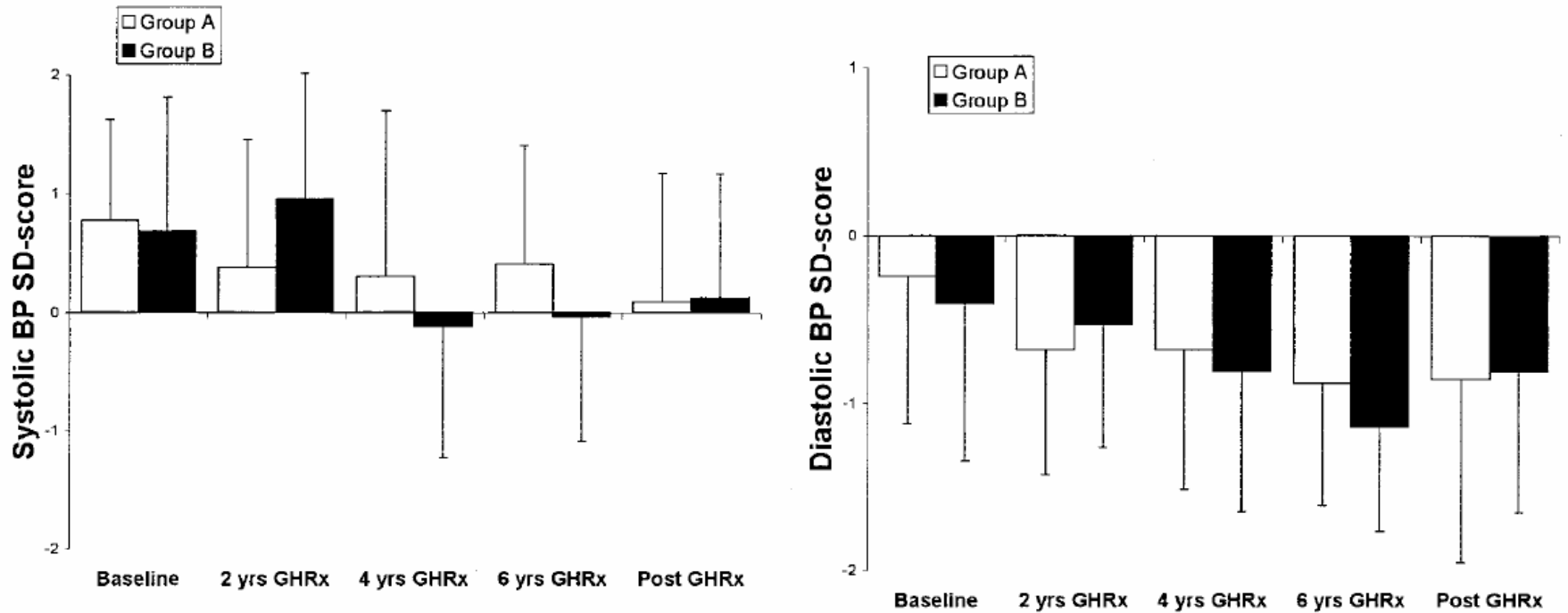
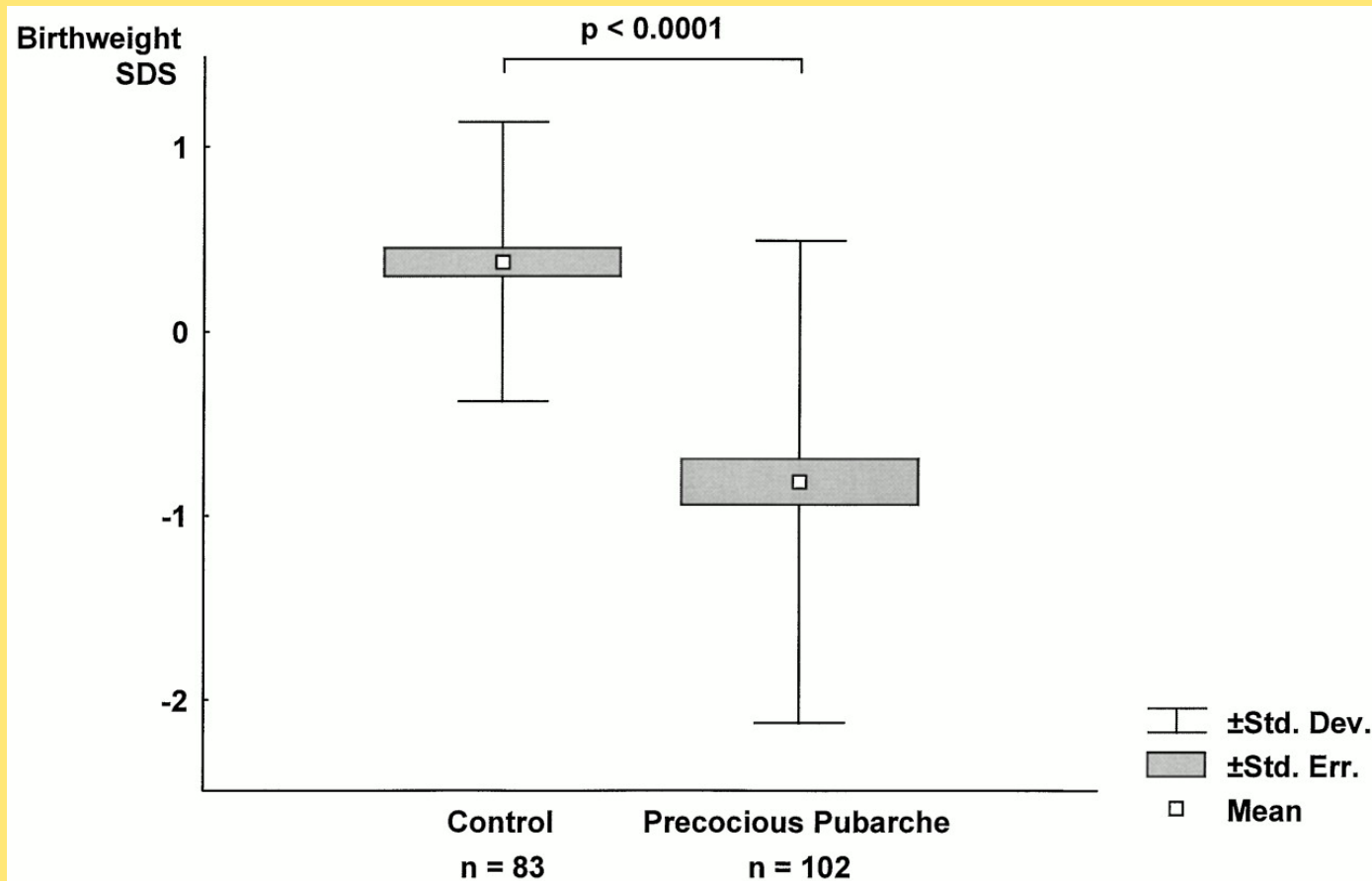


FIG. 4. Mean (SD) systolic BP SD score (*left*) and diastolic BP SD score (*right*) using age-matched reference values before GH treatment, at 6 yr of GH treatment, and at 6 months after discontinuation of treatment for group A (□) and group B (■).

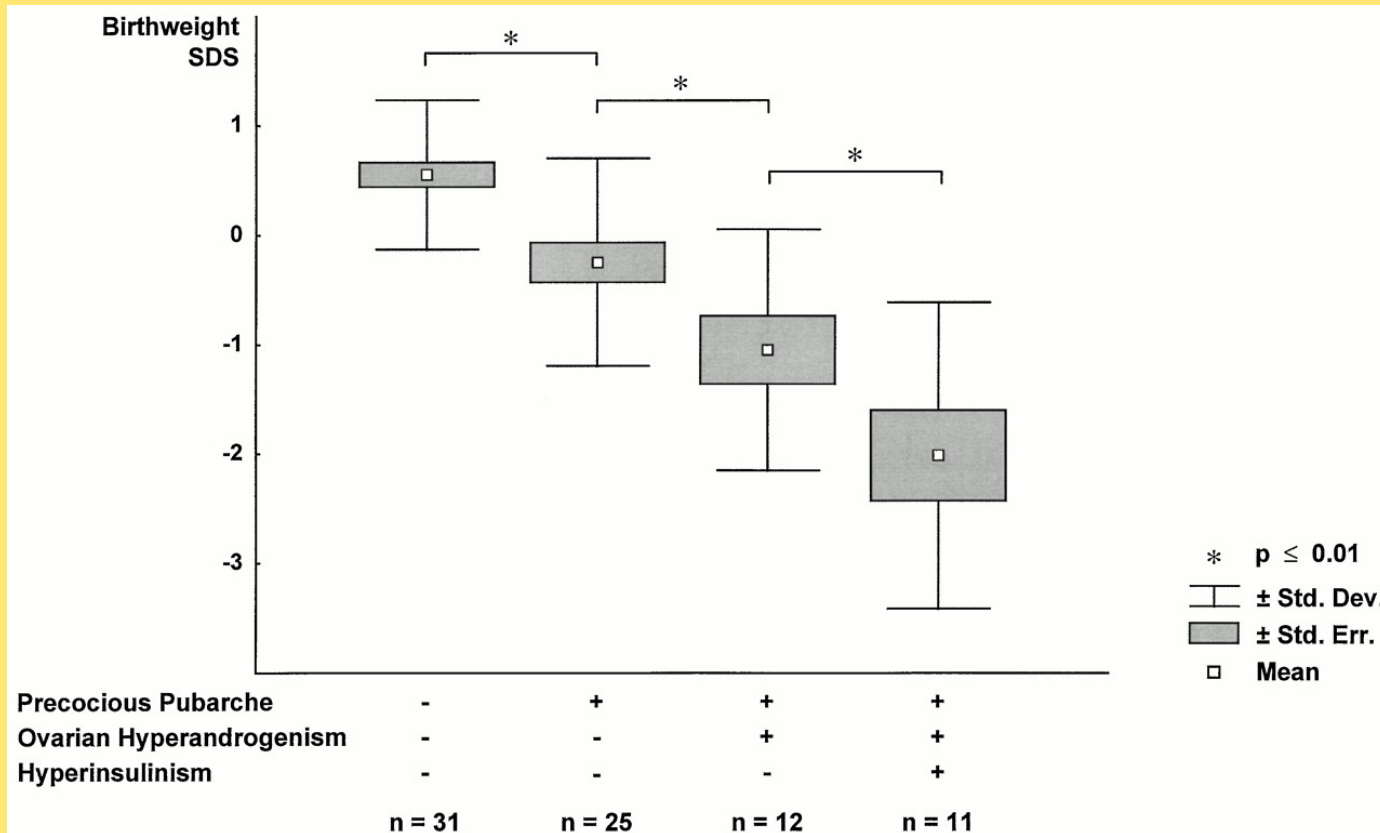
Van Pareren Y et al. JCE&M, 2003, 88:347-353

Birth Weight in Patients with Premature Pubarche



Ibanez, L. et al. J Clin Endocrinol Metab 1998;83:3558-3562

Birth Weight in Patients with Premature Pubarche, Hyperandrogenism and Hyperinsulinism

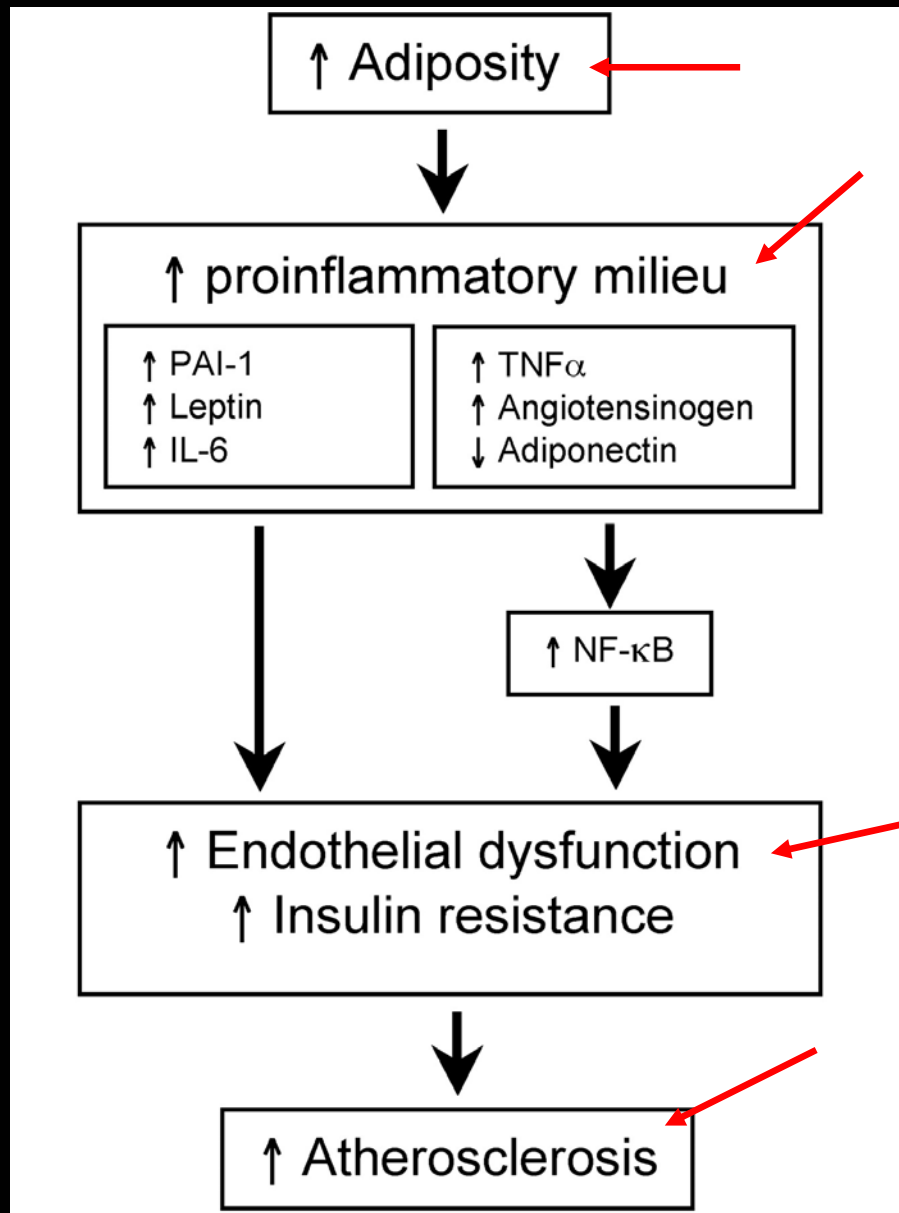


Ibanez, L. et al. J Clin Endocrinol Metab 1998;83:3558-3562

Adiponectin Levels Are Reduced in Children Born Small for Gestational Age and Are Inversely Related to Postnatal Catch-Up Growth

**STEFANO CIANFARANI, CHIARA MARTINEZ, ARIANNA MAIORANA, GIUSEPPE SCIRÈ,
GIAN LUIGI SPADONI, AND SERGIO BOEMI**

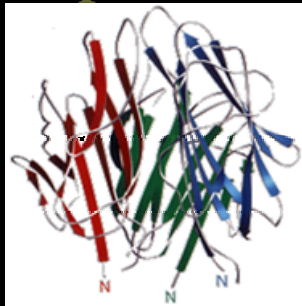
Rina Balducci Center of Pediatric Endocrinology, Department of Public Health, Tor Vergata University (S.C., C.M., A.M., G.S., G.L.S.), 00133 Rome, Italy; and Division of Nuclear Medicine, S. Eugenio Hospital (S.B.), 00144 Rome, Italy



Many adipokines whose expressions are altered during obesity promote inflammation and can promote insulin resistance, endothelial dysfunction, and, ultimately, atherosclerosis

Adiponectin

- Exclusively secreted by adipocytes
- Paradoxically, adiponectin levels are reduced in obese subjects
- Insulin-sensitizing properties
- Decreased concentrations of adiponectin precede the onset of type 2 diabetes
- Replenishment of adiponectin reverses insulin

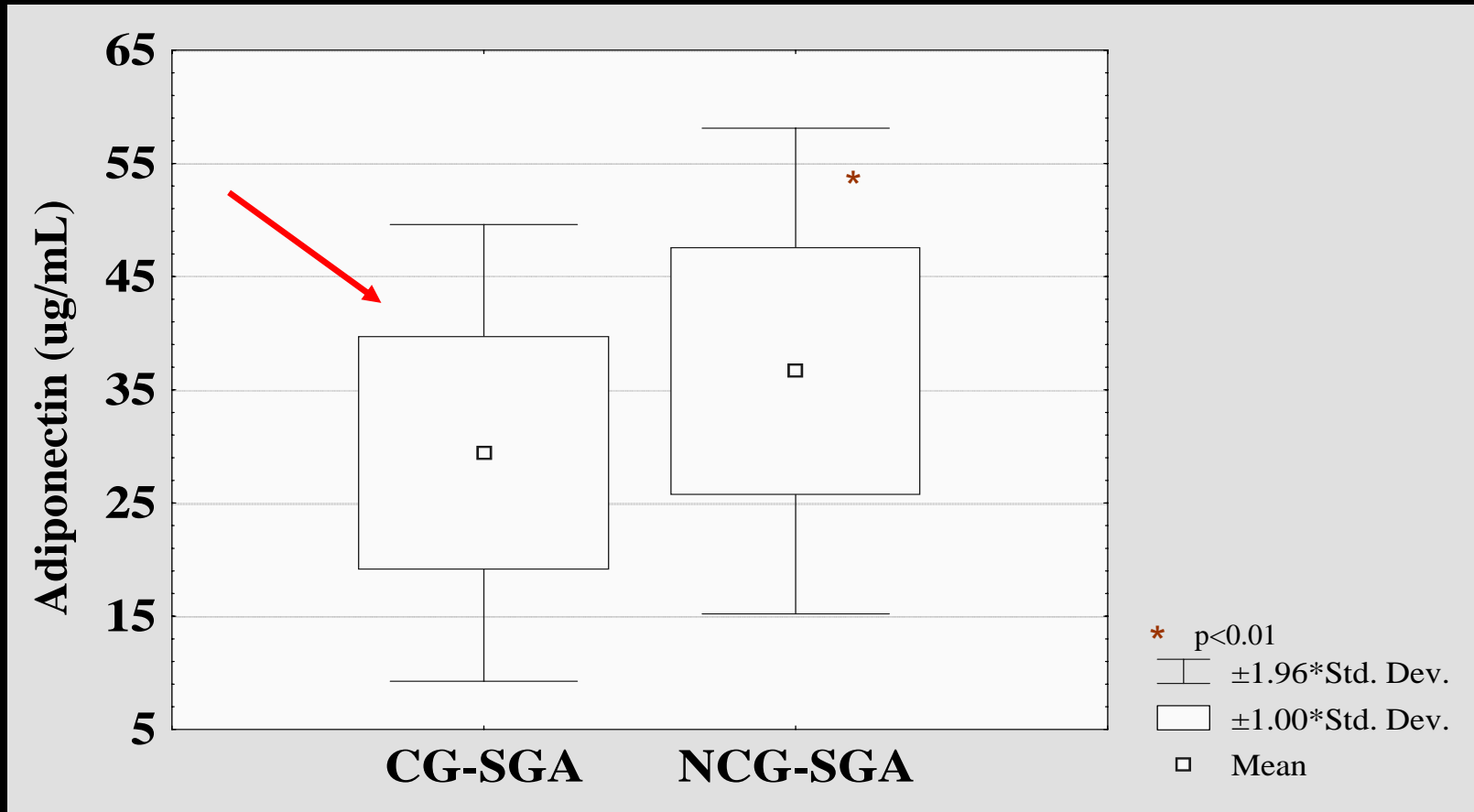


- resistance in diabetic mice
- Anti-inflammatory properties
- Anti-atherogenic properties

Adiponectin levels in SGA children

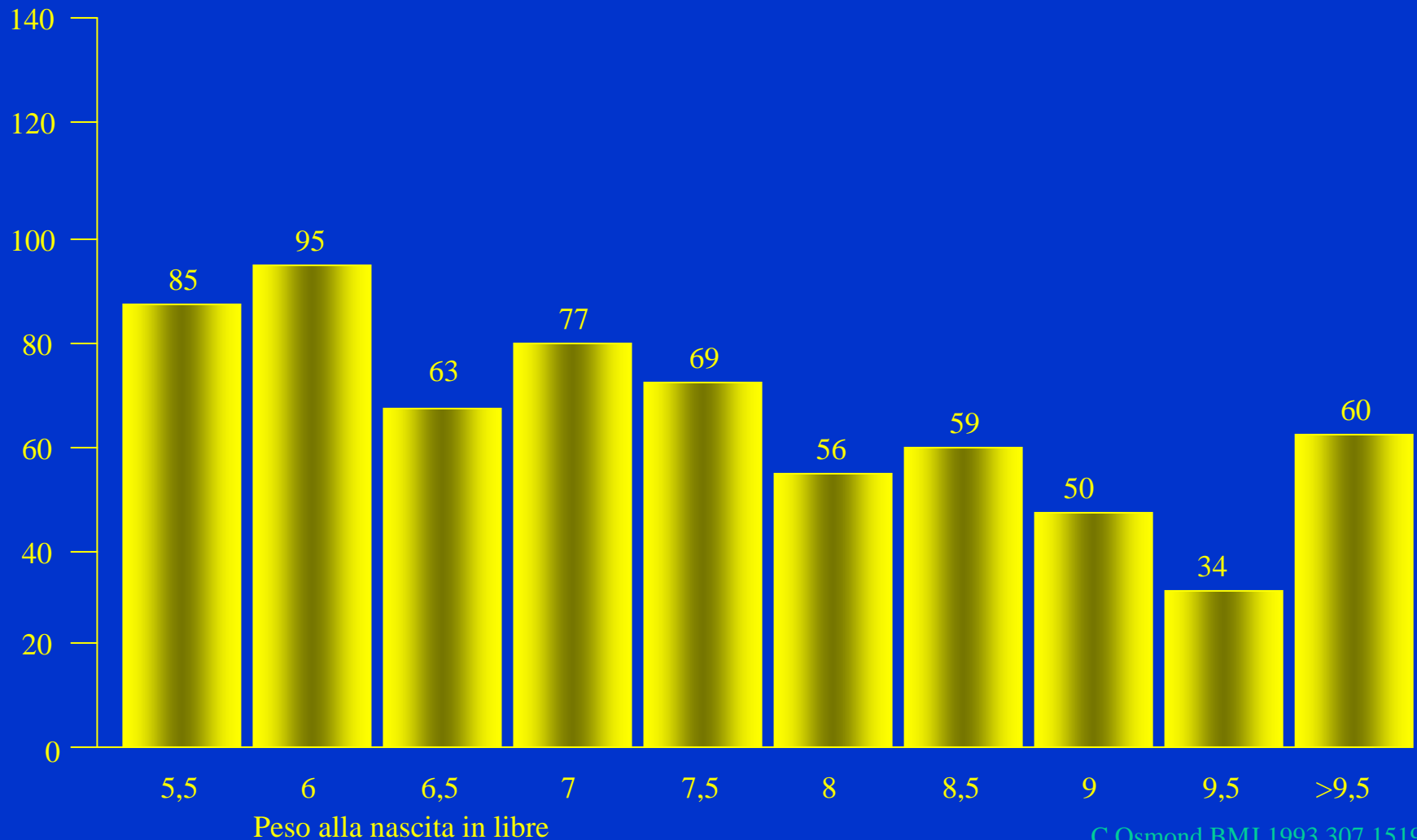


Adiponectin levels in CG-SGA and NCG-SGA children



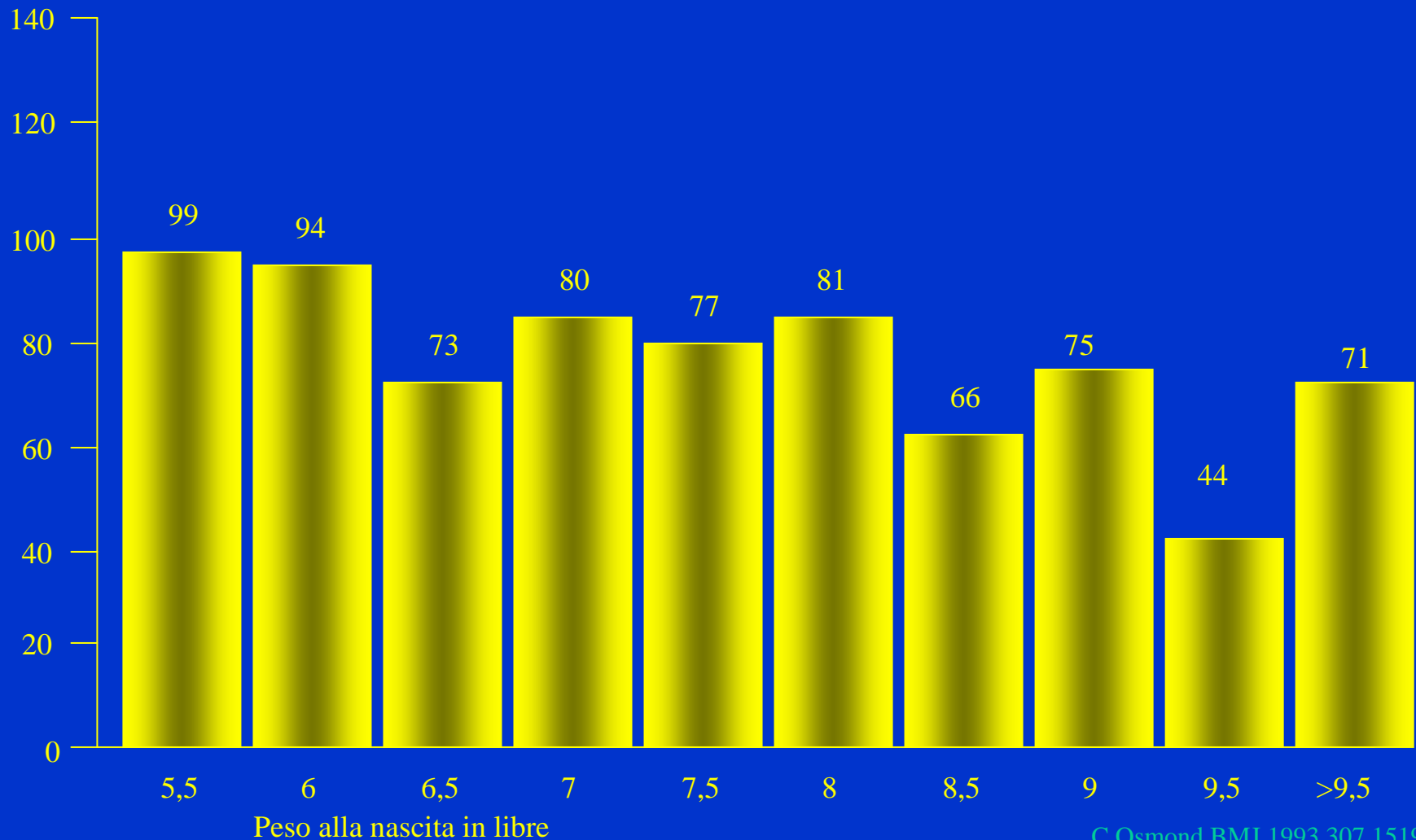
RATIO STANDARDIZATA DI MORTE PER MALATTIE CARDIOVASCOLARI NELLE DONNE □ DI 65 ANNI

Ratio di mortalità standardizzata



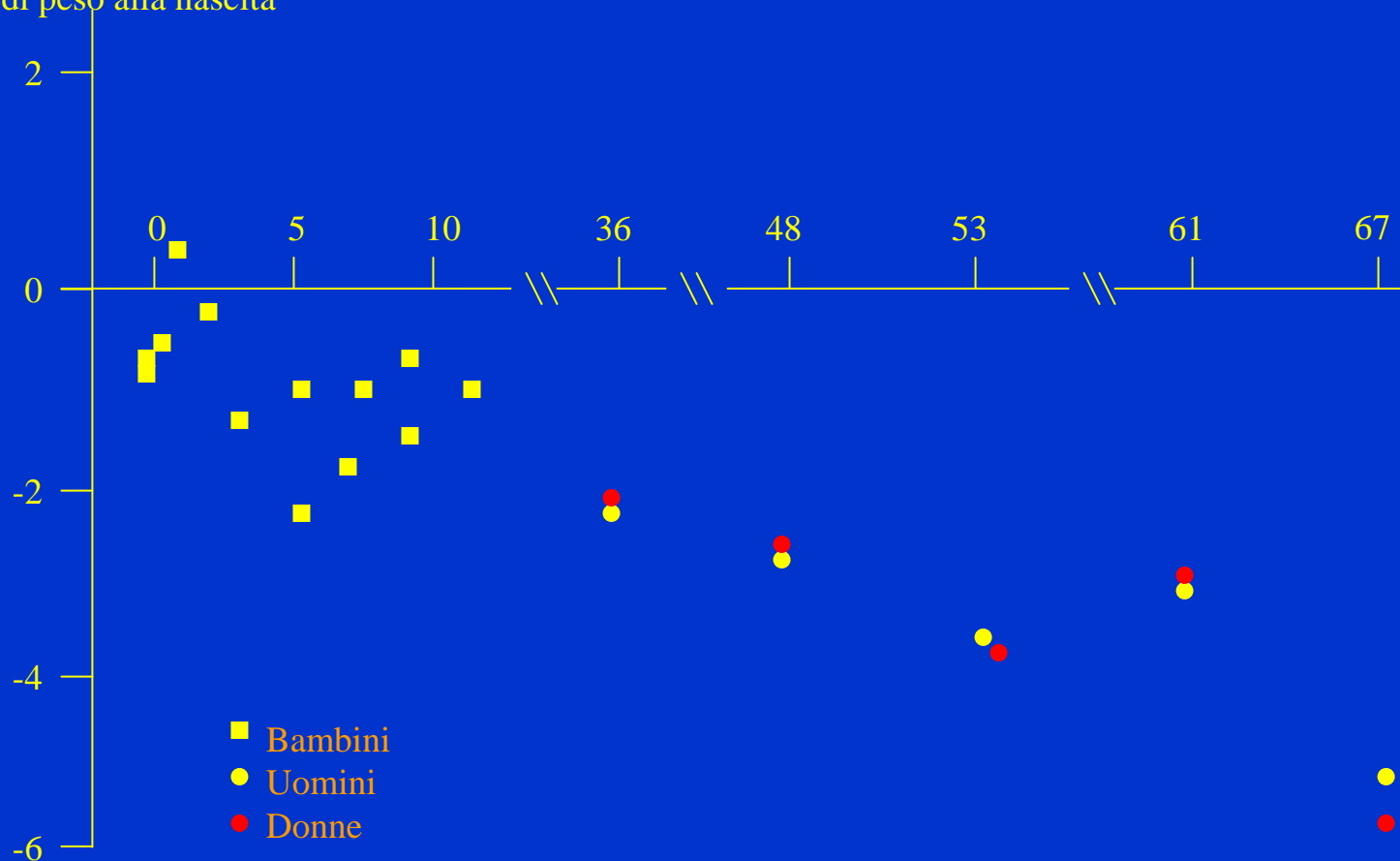
RATIO STANDARDIZATA DI MORTE PER MALATTIE CARDIOVASCOLARI NEI MASCHI □ DI 65 ANNI

Ratio di mortalità standardizzata



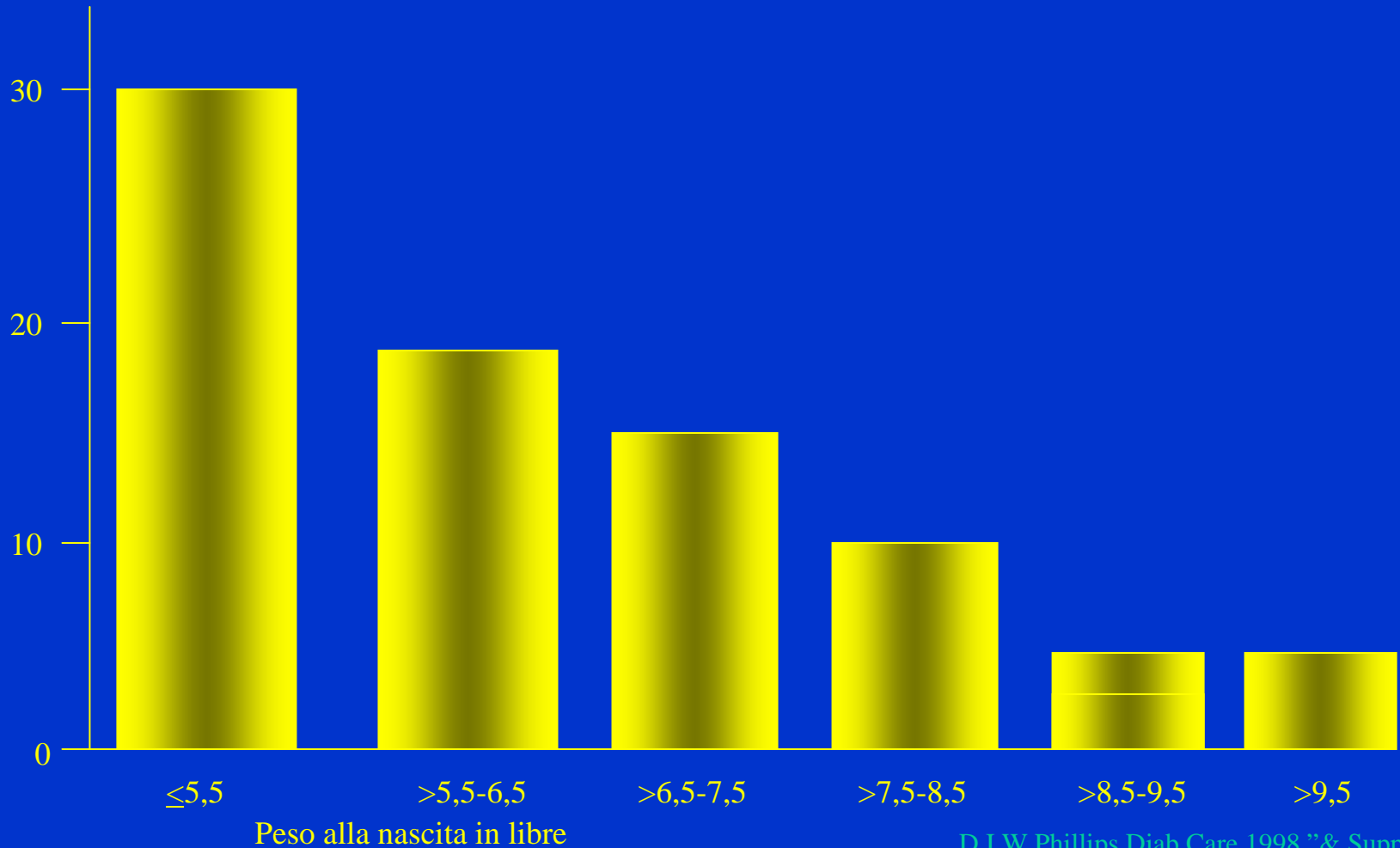
RELAZIONE TRA PRESSIONE SISTOLICA E PESO ALLA NASCITA ALLE DIFFERENTI ETA'

Differenza nella pressione sistolica
Per Kg di peso alla nascita



PREVALENZA DELLA SINDROME DA INSULINORESISTENZA IN SOGGETTI DI 64 ANNI

% di tutti i soggetti



Aortic wall thickness in newborns with intrauterine growth restriction

Lancet 2005; 365: 1484–86

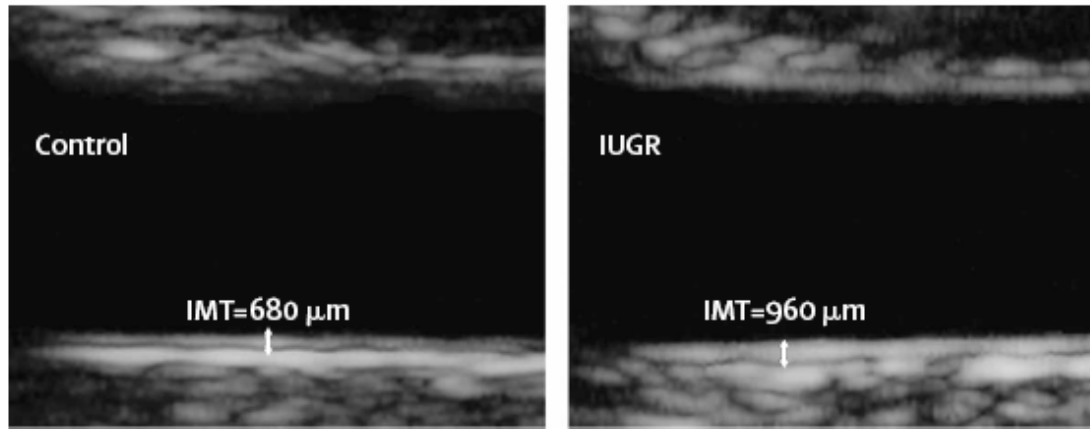
Michael R Skilton, Nick Evans, Kaye A Griffiths, Jason A Harmer, David S Celermajer

See [Comment](#) page 1444

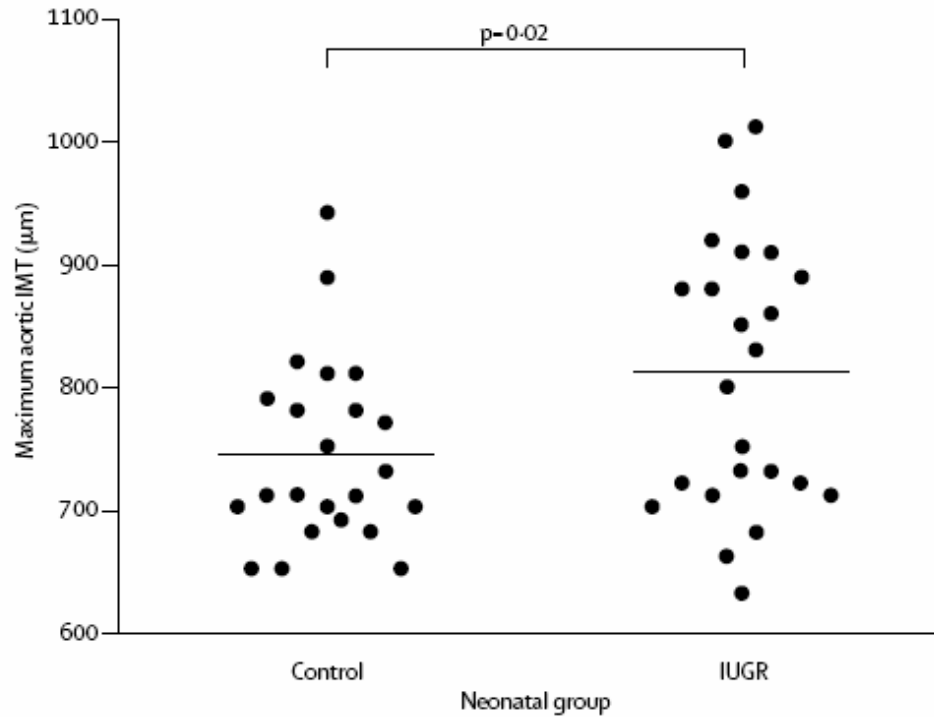
Much epidemiological evidence has linked low birthweight with late cardiovascular risk. We measured aortic wall thickness (a marker of early atherosclerosis) by ultrasonography in 25 newborn babies with intrauterine growth restriction and 25 with normal birthweight. Maximum aortic thicknesses were significantly higher in the babies with intrauterine growth restriction (810 μm [SD 113]) than in those without (743 μm [76], $p=0\cdot02$), more so after adjustment for birthweight (300 $\mu\text{m}/\text{kg}$ [45] vs 199 $\mu\text{m}/\text{kg}$ [29], $p<0\cdot0001$). Newborn babies with growth restriction have significant aortic thickening, suggesting that prenatal events might predispose to later cardiovascular risk.

Department of Medicine,
University of Sydney, Sydney,
Australia (M R Skilton BSc,
N Evans DM, K A Griffiths DMU,
Prof D S Celermajer PhD),
Departments of Newborn Care
(N Evans), and Cardiology
(J A Harmer BSc,
Prof D S Celermajer), Royal
Prince Alfred Hospital, Sydney,

A



B

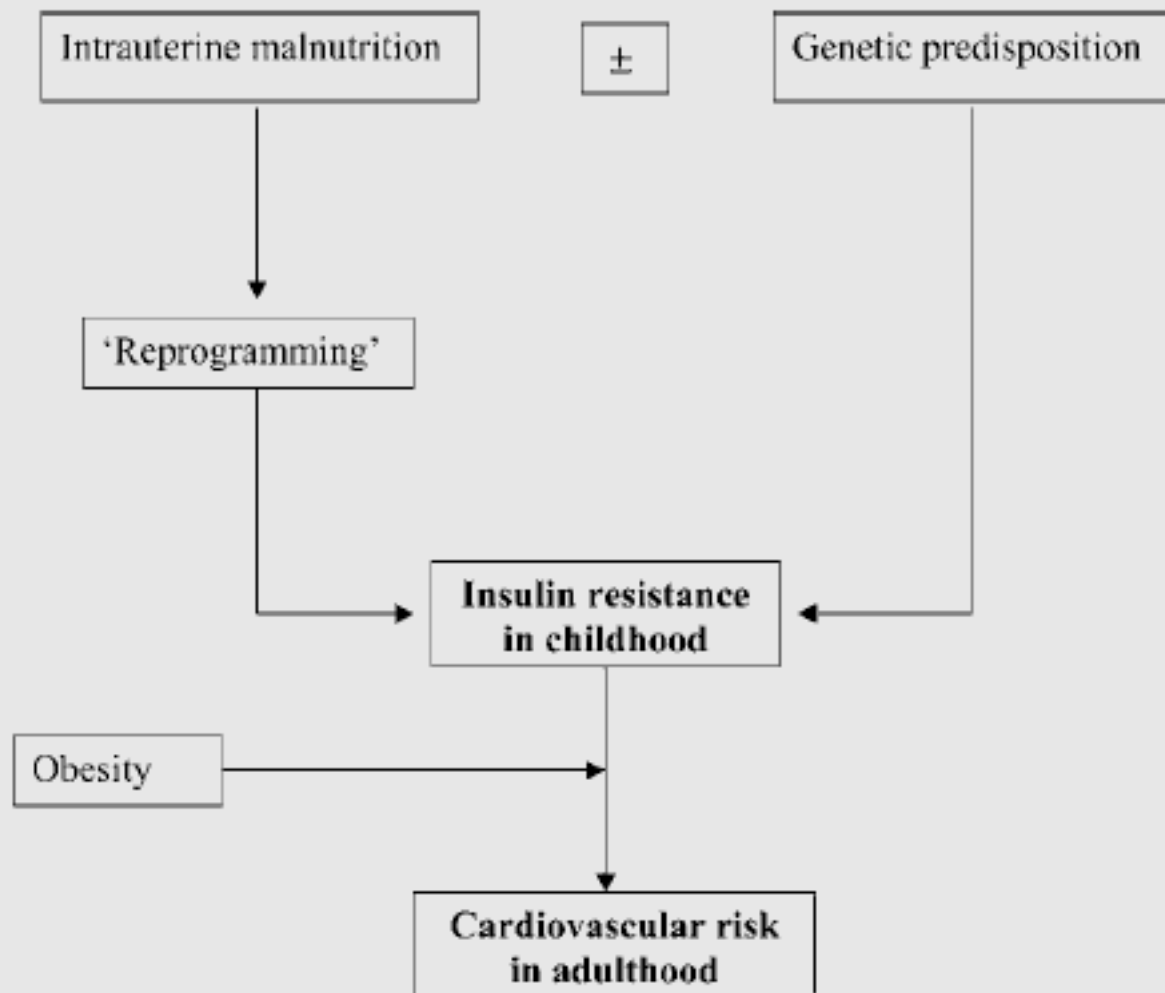


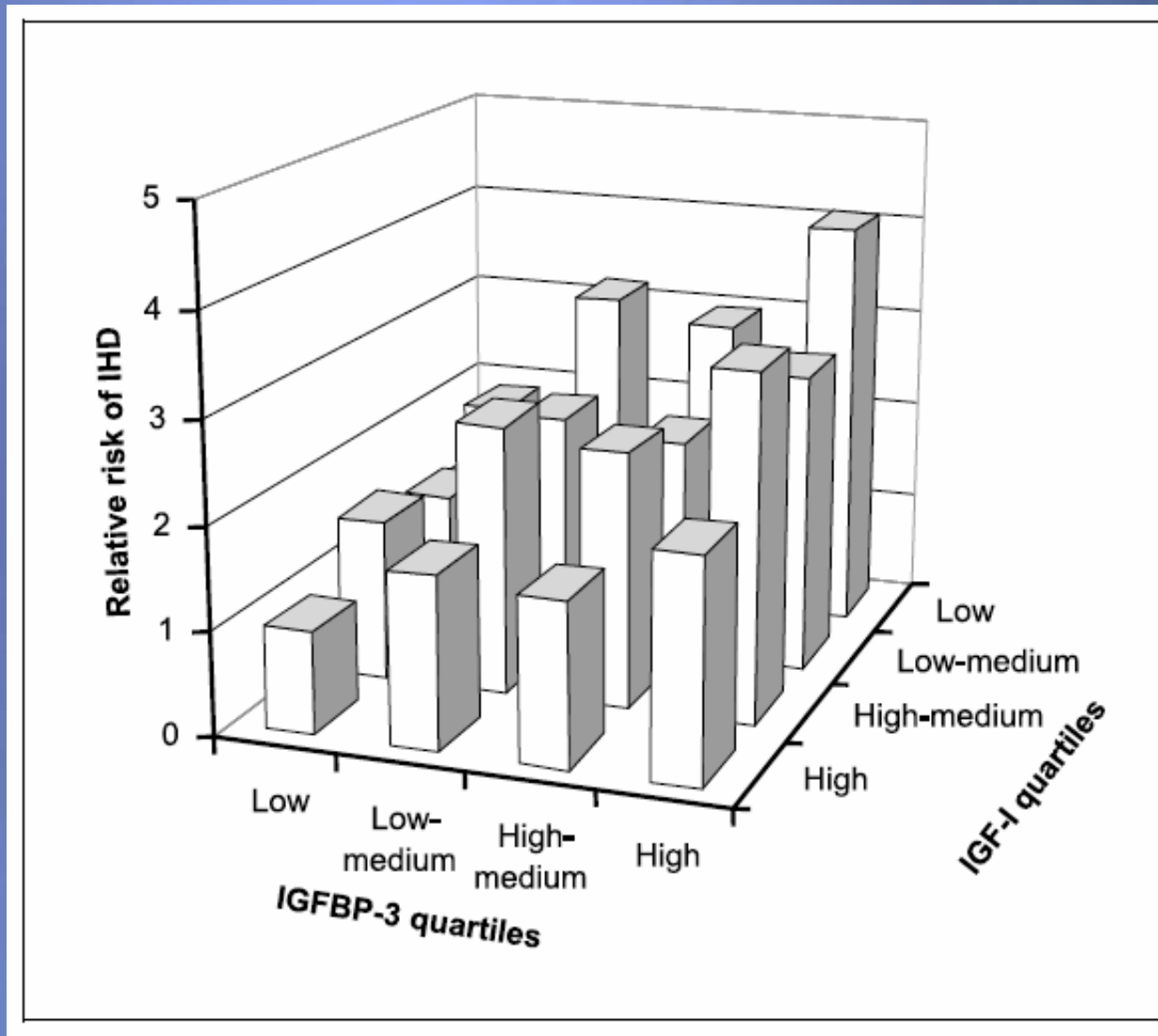
Skilton MR et al. Lancet 2005; 365: 1484-6

	Controls (n=23)	IUGR (n=24)	p
Number (%) male	14 (61%)	9 (38%)	0.15
Gestational age (completed weeks)	40 (1)	39 (1)	0.48
Birthweight (g)	3762 (306)	2713 (221)	<0.0001
Length (cm)	51.3 (2.1)	47.1 (2.5)	<0.0001
Head circumference (cm)	35.2 (1.3)	33.5 (1.0)	<0.0001
Ponderal index	28 (2)	25 (2)	0.0005
Postnatal age (days at study)	2 (1)	2 (1)	0.82
Maternal age (years)	33 (5)	31 (7)	0.36
Maternal smoking (%)	3 (13%)	9 (38%)	0.08

Data are mean (SD), or number (%) where indicated.

Table: Demographic data for control and intrauterine growth restricted (IUGR) neonates





Jensen RBB et al. Horm Res 2003; 60 (Suppl 3): 136-48

Conclusioni

- ✦ L'IGF-I è un fattore determinante della crescita prenatale e postnatale precoce.
- ✦ I neonati SGA mostrano transitorie alterazioni dell'asse GH/IGF-I e del sistema delle IGF.
- ✦ Lunghezza alla nascita, target height e BMI sono i fattori predittivi più importanti per la statura dei bambini.
- ✦ Non vi è evidenza di un reprogramming dell'asse GH/IGF-I, HPAAs e tiroideo nell'infanzia.
- ✦ La terapia con GH migliora la statura finale nei soggetti SGA.
- ✦ La terapia con GH può influenzare l'aterogenesi (?) nei soggetti SGA.