MUG – Mauritius – April 2009

Weight fluctuations

a risk factor for obesity & metabolic syndrome

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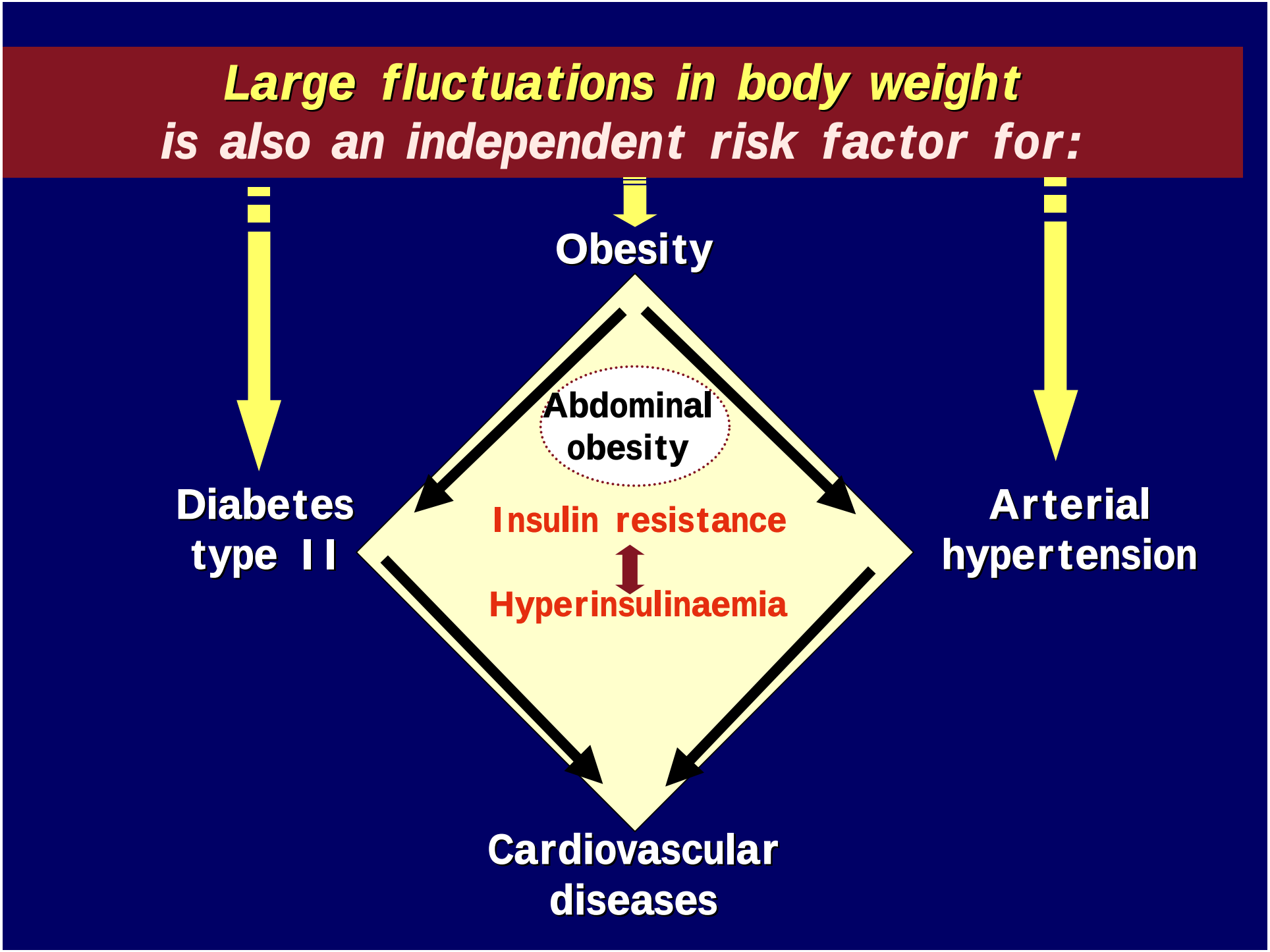
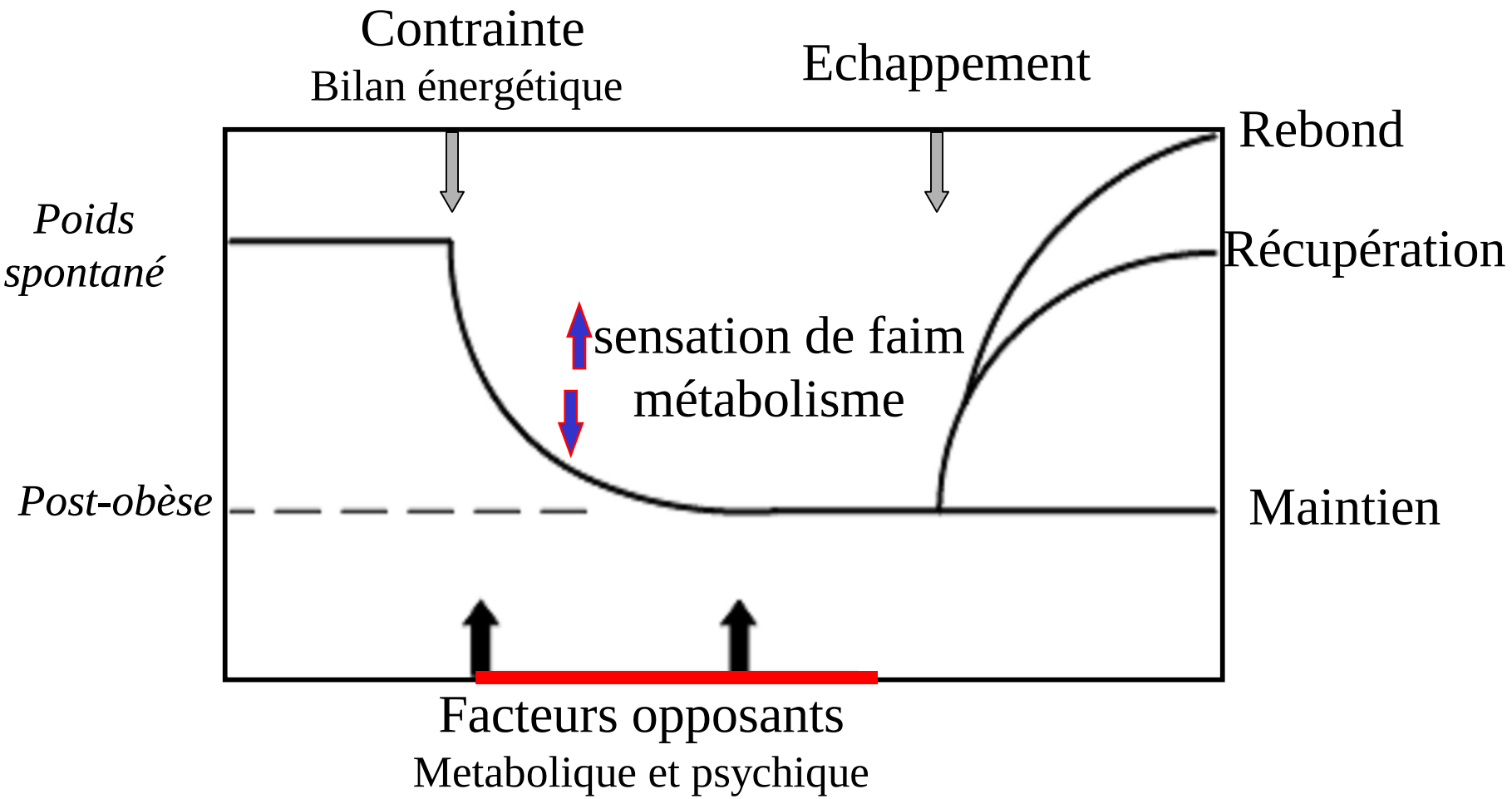

Large fluctuations in body weight
is also an independent risk factor for:
Obesity
Abdominal obesity
Diabetes type II
Insulin resistance
Hyperinsulinaemia
Arterial hypertension
Cardiovascular diseases

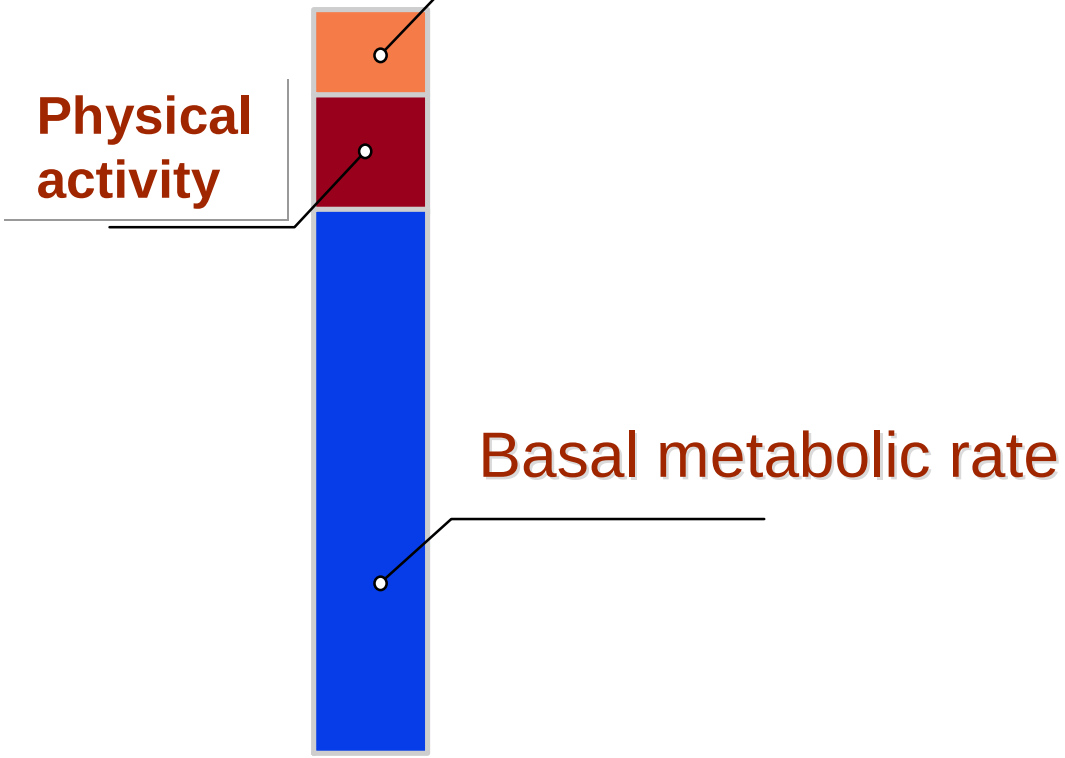
Evolution typique du poids de l'obèse 'traité'



Adapted from Guy-Grand (1980)

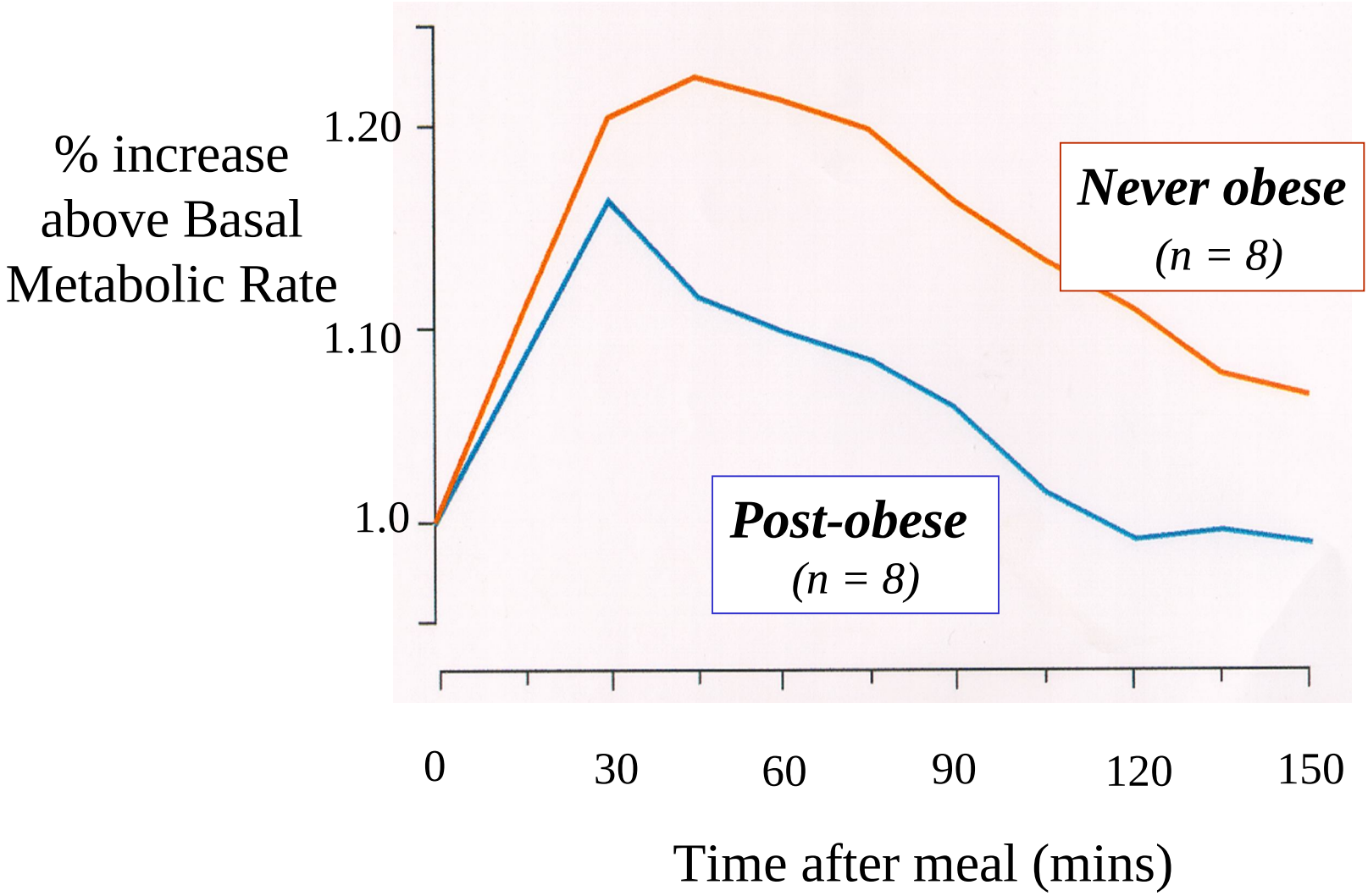
Evaluation of energy expenditure

VO2 and VCO2 measurements – *indirect calorimetry*

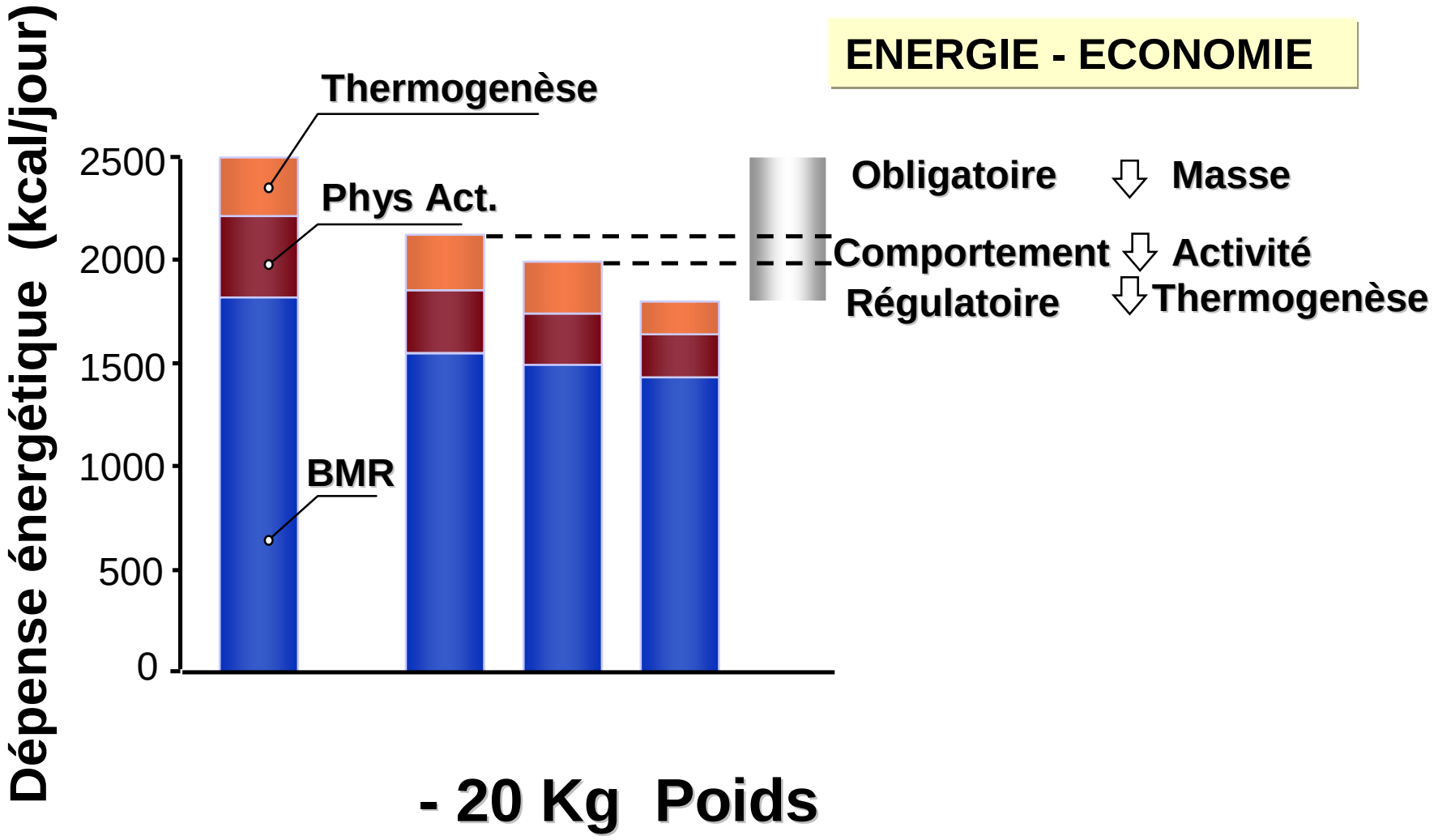


Postprandial thermogenesis in response to a mixed meal (300 kcal)

(Dulloo & Miller *Am J Clin Nutr* 49: 44-50, 1989).



Hypométabolisme compensatoire



Dulloo AG: Nutrition 9: 366-372 (1993).

Is weight cycling detrimental to health? A review of the literature in humans

Erik Muls et al. IJO, 19 (Suppl 3):S48-50, 1995

Points of controversy

WC makes subsequent weight loss more difficult

WC affects body composition (fat accumulation)

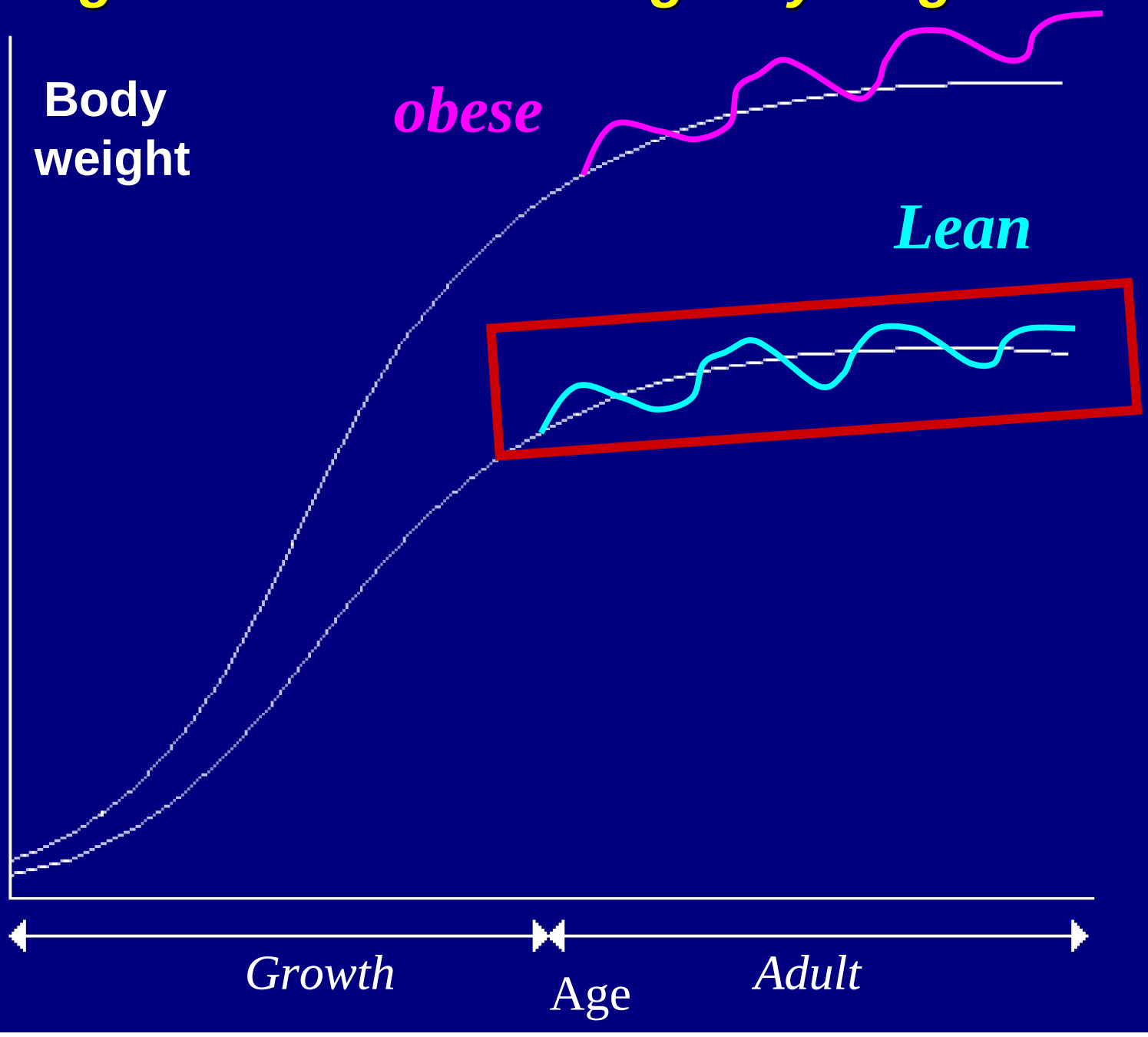
WC decreases resting energy expenditure

WC increases dietary preference for fat

WC promotes cardiovascular diseases

Montani, Viecelli, Prévot, Dulloo. *Int J Obesity* 30: S58-S66 (2006)

Weight fluctuations / weight cycling

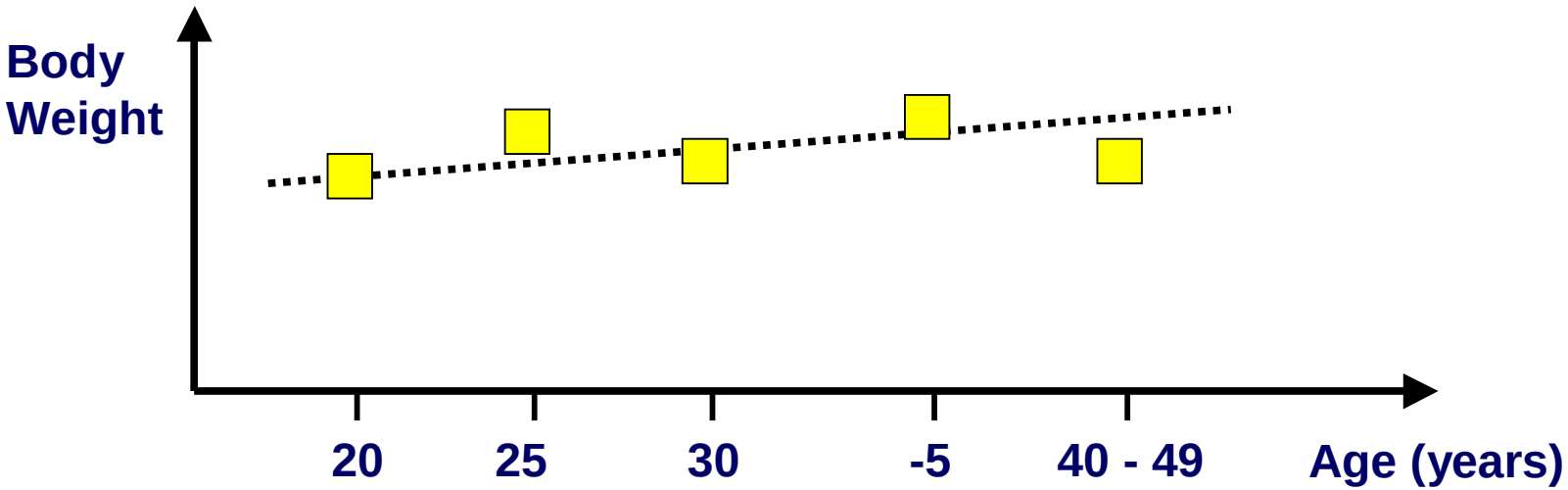


Long-term Weight Cycling and Metabolic Syndrome

Cross-sectional study of 664 Japanese men
BW at age 20, 25, 30, 5y prior and current (40-49)

Simple linear regression model (slope, RMSE)
Classification by quartiles of weight fluctuation
Hypertension, HyperTG, Low HDL-chol, High glucose

Significant association when BMI < 25 kg/m^2
but not when BMI > 25 kg/m^2

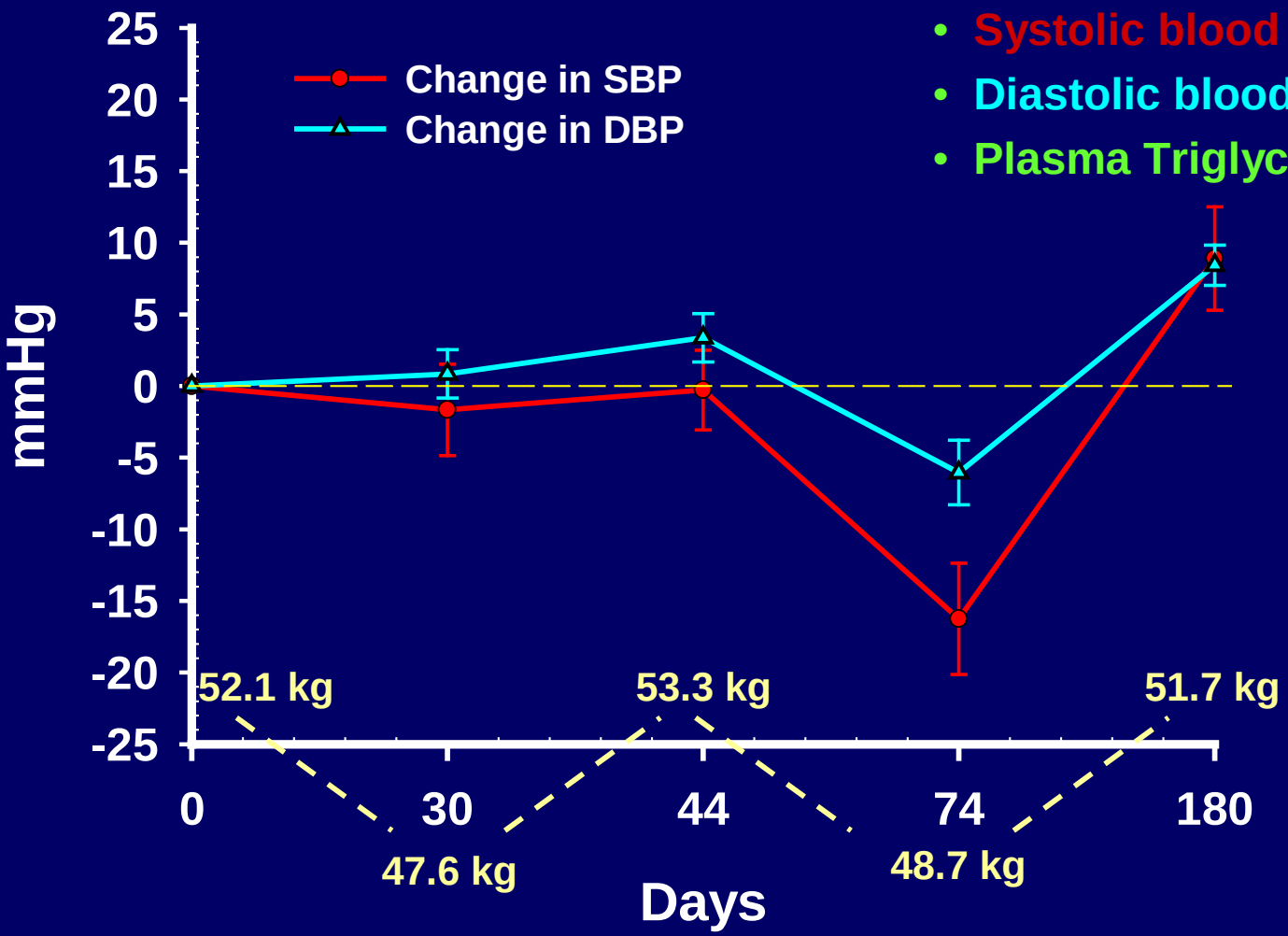


Zhang, Circ J, 2005

Intentional Weight Cycling in Young Lean Japanese Women

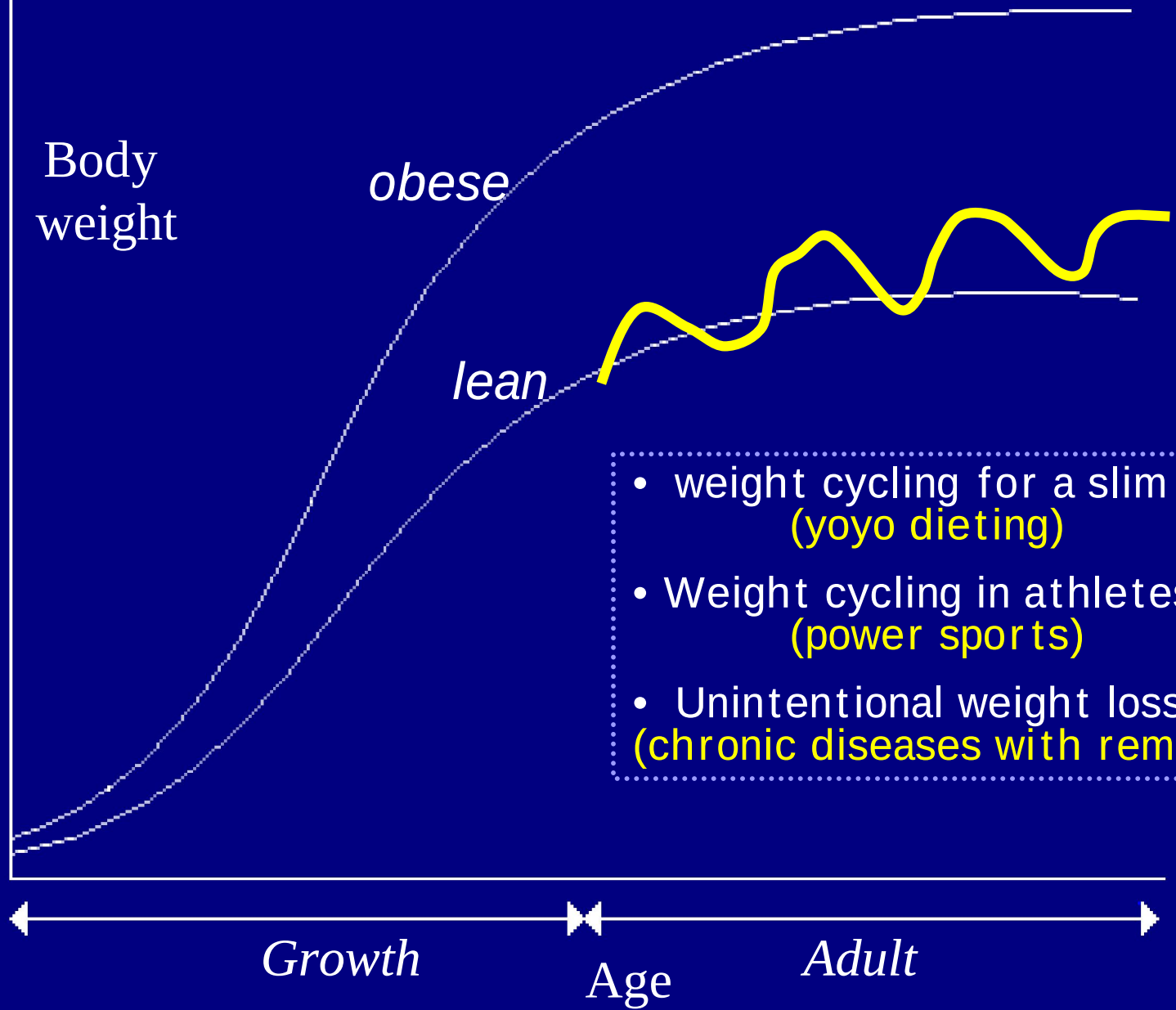
Significant increases in

- **Systolic blood pressure**
- **Diastolic blood pressure**
- **Plasma Triglycerides**



Kajioka, Metabolism, 2001

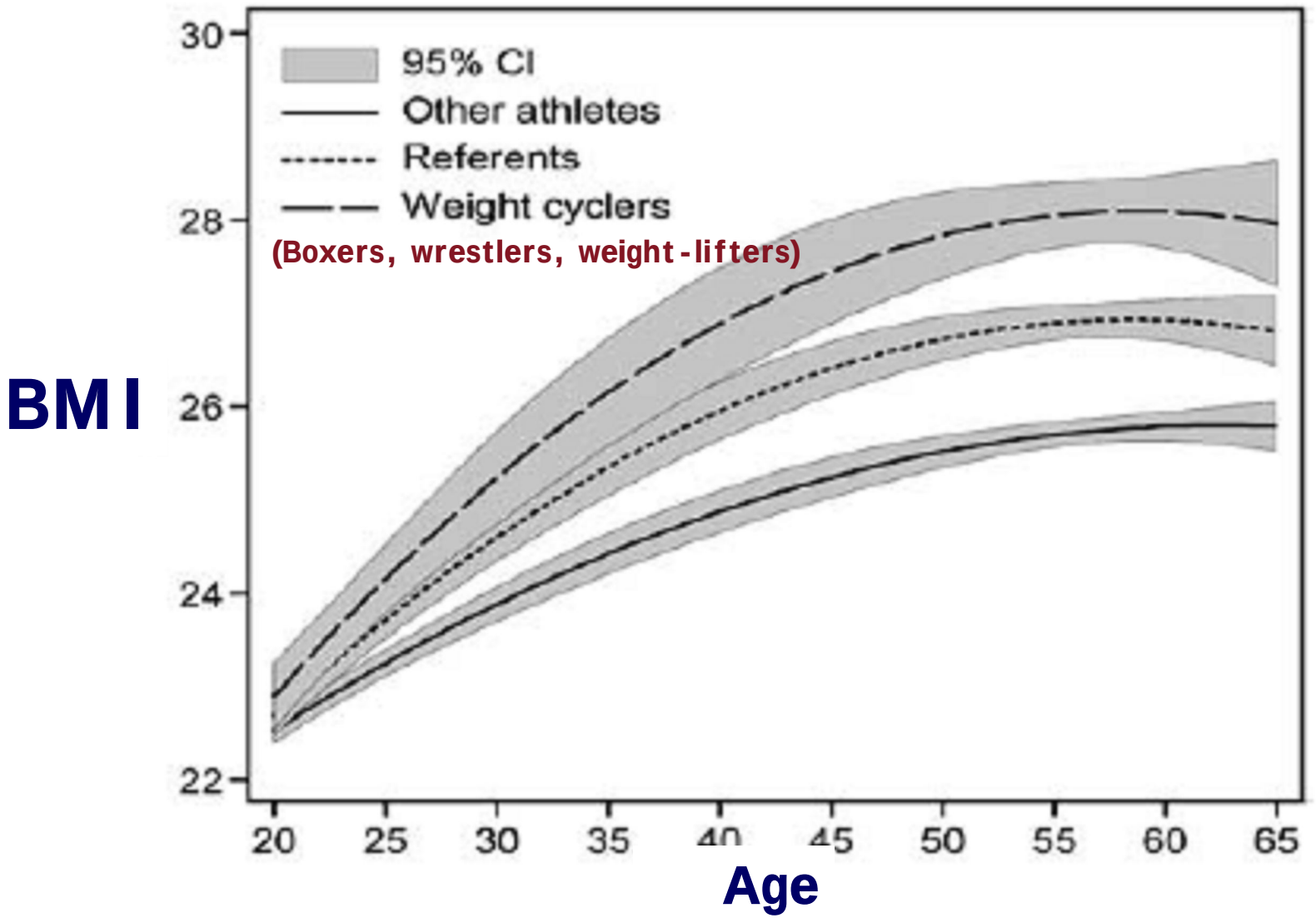
Large weight fluctuations in non-obese adults : an independent risk factor for CV diseases & obesity



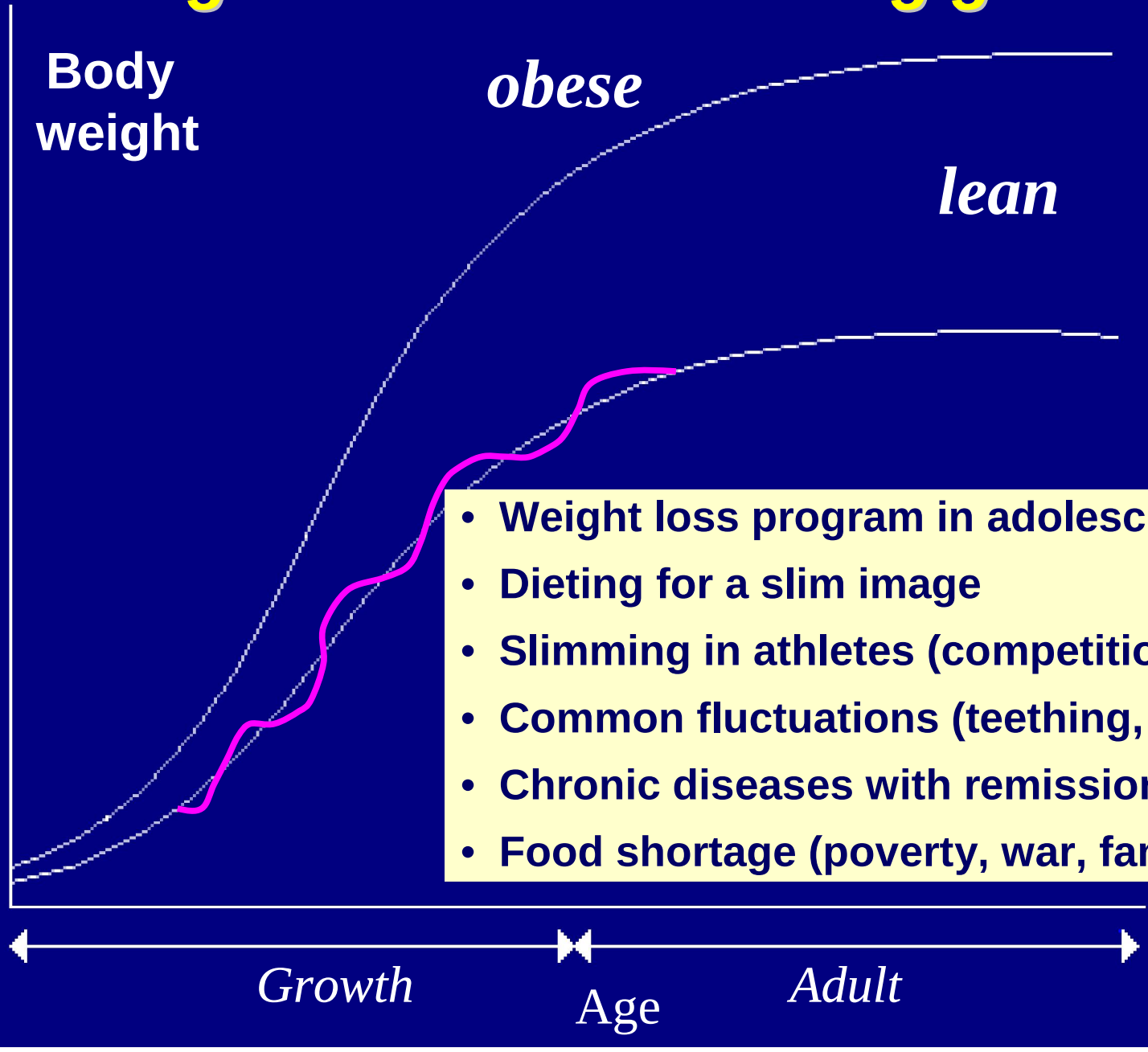
- weight cycling for a slim image (yoyo dieting)
- Weight cycling in athletes (power sports)
- Unintentional weight losses (chronic diseases with remissions)

Weight fluctuations in athletes & subsequent weight gain in middle age

Saarni et al. Int J Obesity (2006) 30: 1639-44



Weight fluctuations during growth ?



- Weight loss program in adolescents
- Dieting for a slim image
- Slimming in athletes (competition)
- Common fluctuations (teething, fever, ...)
- Chronic diseases with remissions
- Food shortage (poverty, war, famine, ...)

Weight fluctuations during early growth?

The strongest predictor of future cardiovascular disease

(and its risk factors)

a combination of

***thinness* at birth and/or early infancy**

followed by

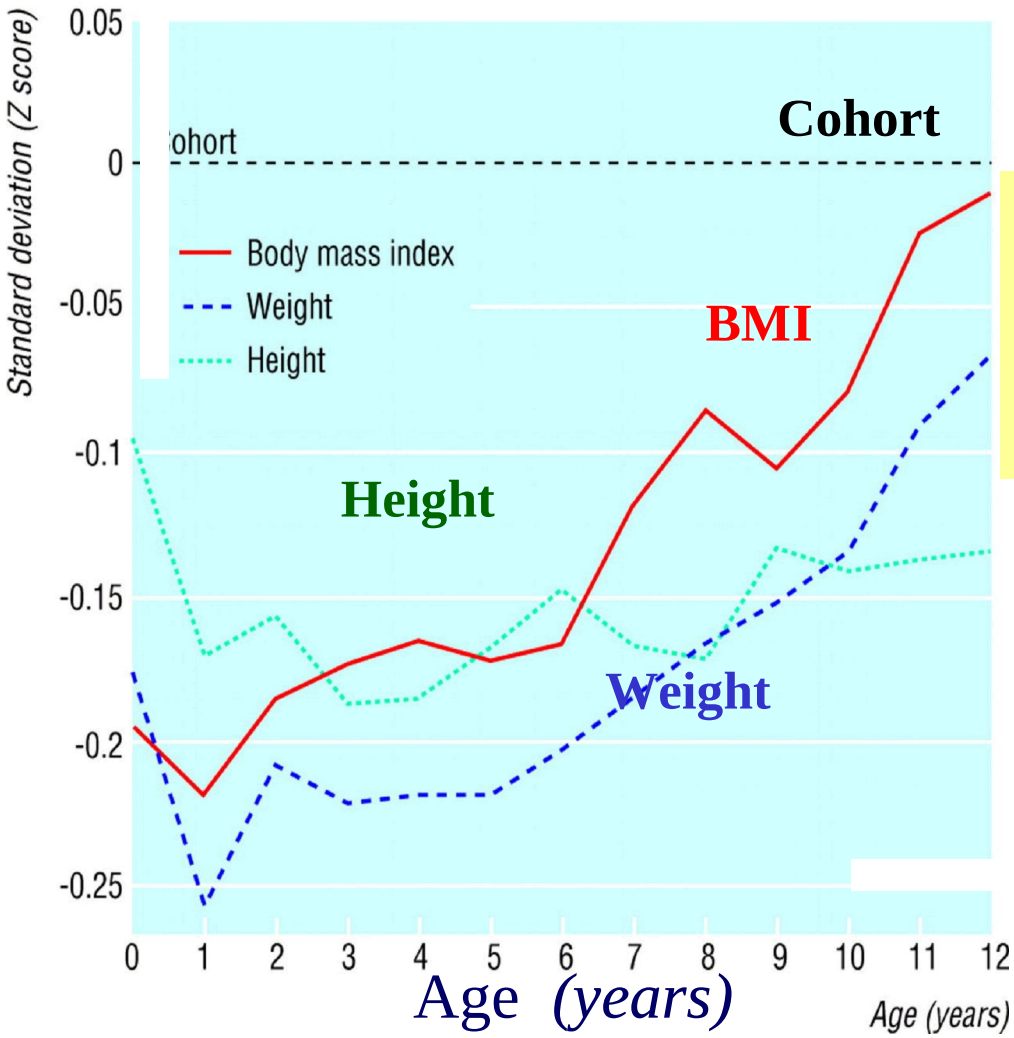
***catch-up growth* during infancy/childhood**

Early growth and later coronary heart disease in later life

*Growth of 357 boys who later developed CHD in a cohort of **4630** boys born in Helsinki*

Eriksson …Barker BMJ 322:949-953 (2001) *Barker… Eriksson NEJM 353:1802-1809 (2005)*

Standard deviation *(Z-score)*

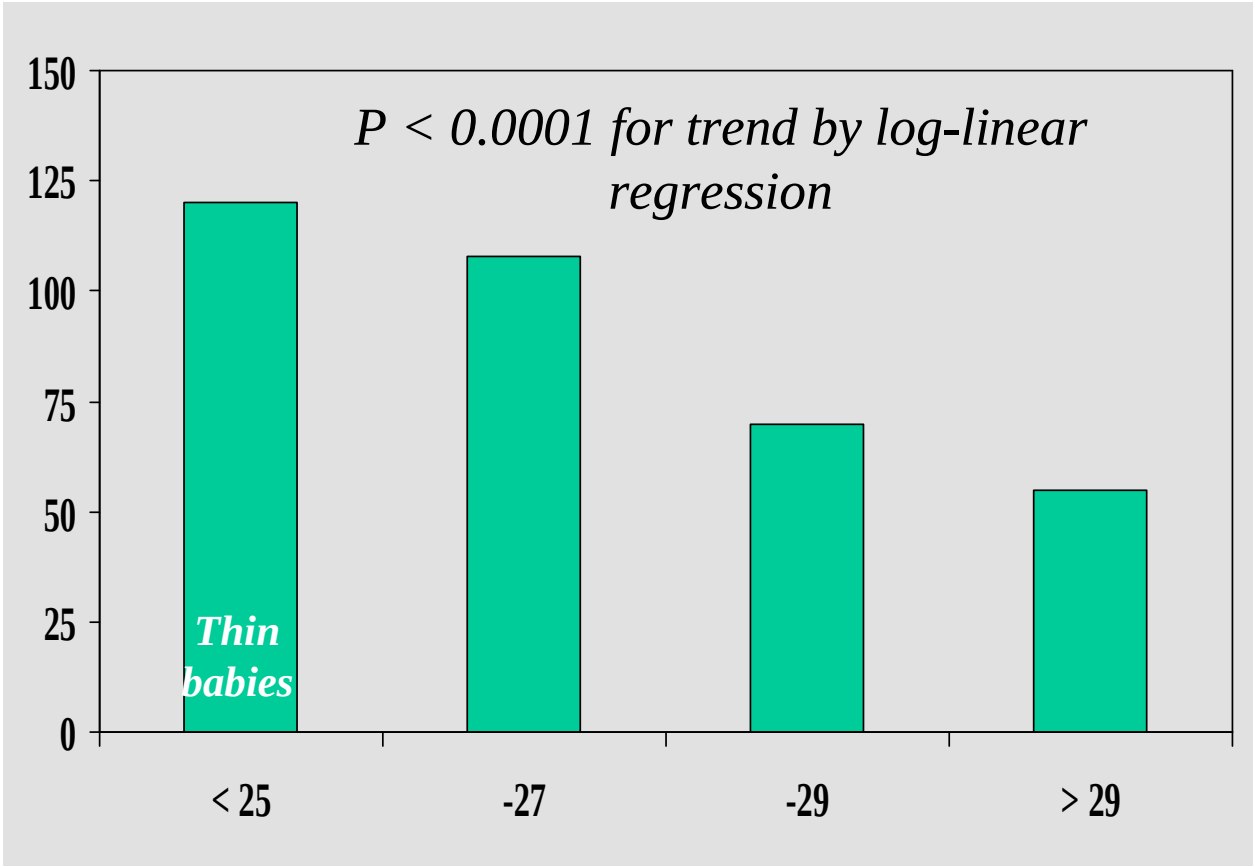


Higher risks for coronary events

was associated with insulin resistance

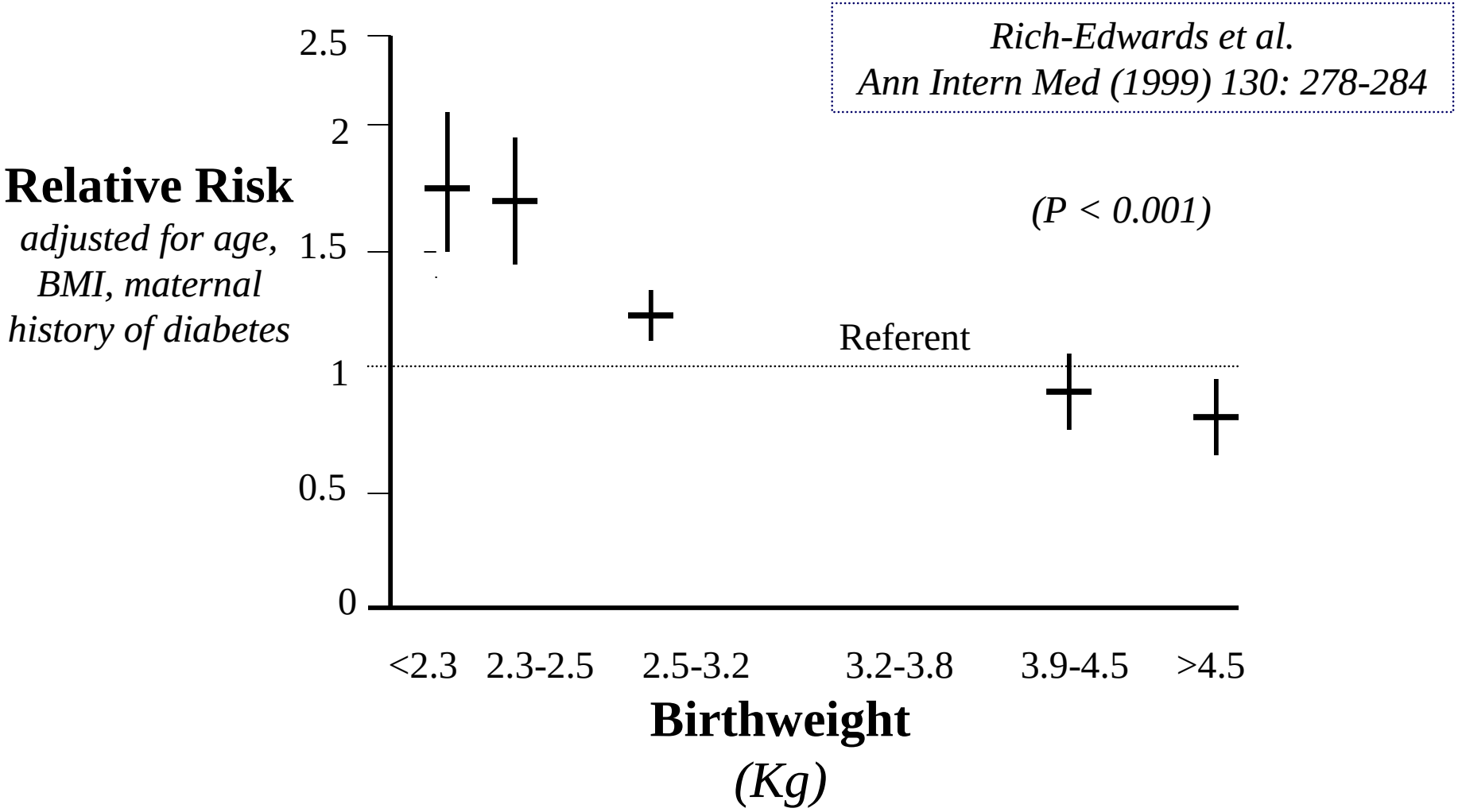
Coronary heart disease death rates in men born in Helsinki during 1924-1933

Data from Forsen et. al. BMJ 319: 1403-1407 (1997)

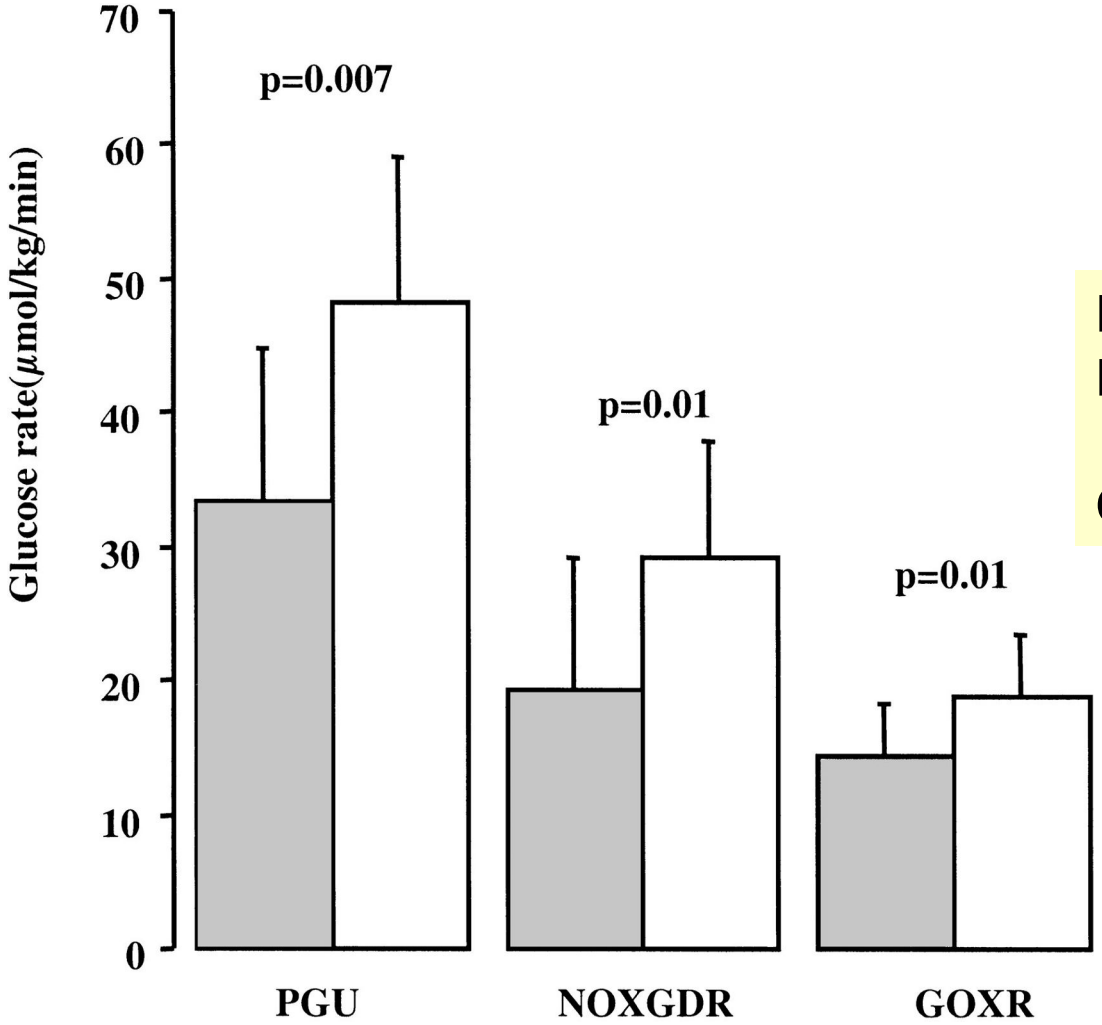


Risk for type 2 diabetes in adult women born between 1921-1946

The Nurses' Health study, USA



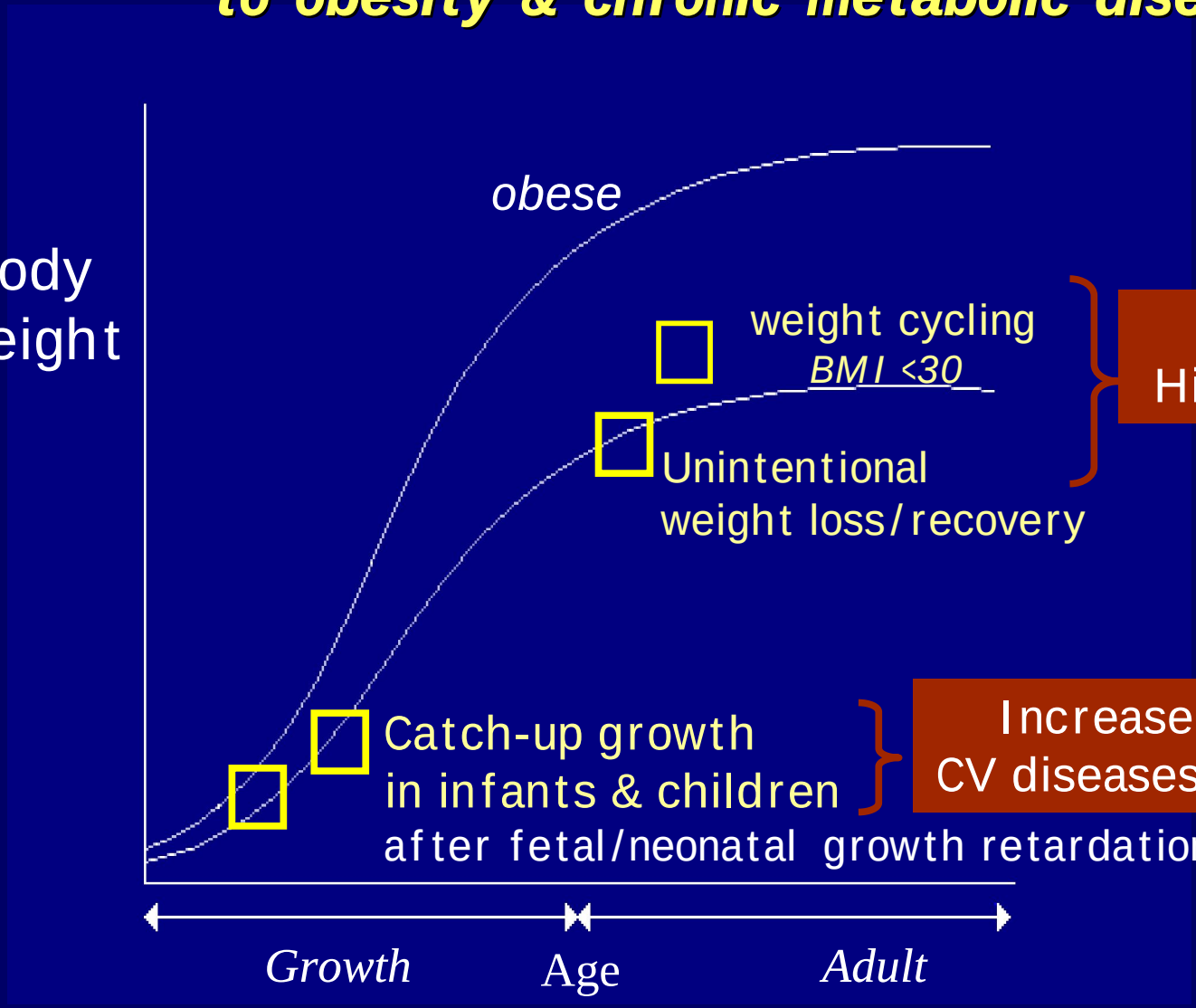
Insulin-mediated glucose disposal in humans born SGA (■) and with normal birth weight (□)



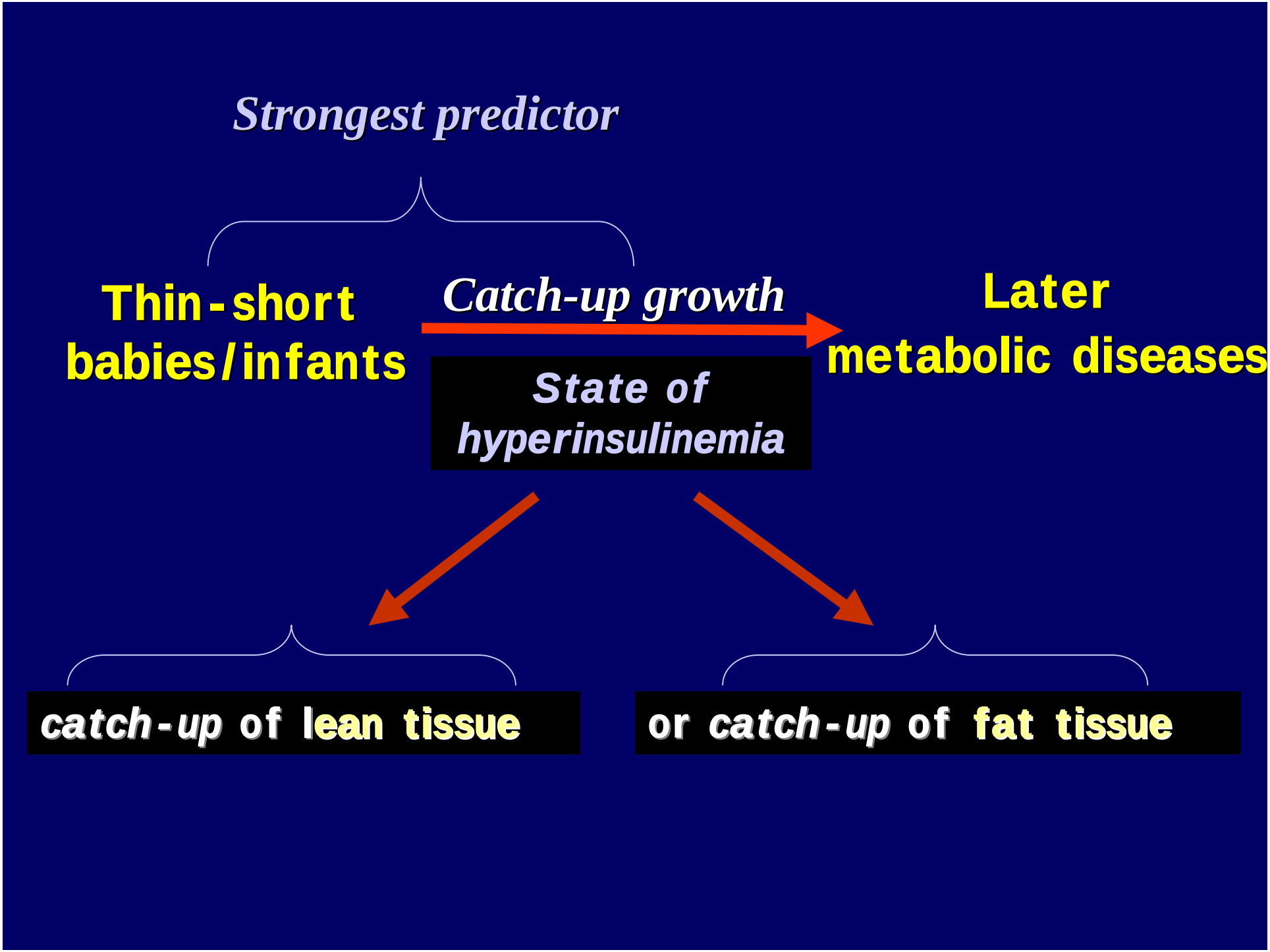
PGU. *plasma glucose uptake*
NOXGDR: *non-oxidative glucose disposal rate*
GOXR: *glucose oxidation rate*

Jaquet, D. et al. J Clin Endocrinol Metab 2001;86:3266-3271

From weight fluctuations to obesity & chronic metabolic diseases



For review: Dulloo et al.: *Int J Obesity* 30 (suppl. 4): S23-S35 (2006)


Strongest predictor
Thin-short babies/infants
Catch-up growth
Later metabolic diseases
State of hyperinsulinemia
catch-up of lean tissue
or catch-up of fat tissue

Preferential catch-up fat after low birth weight / poor neonatal growth

Children born small for gestational age (SGA) have more fat, and less FFM (i.e less lean tissue)

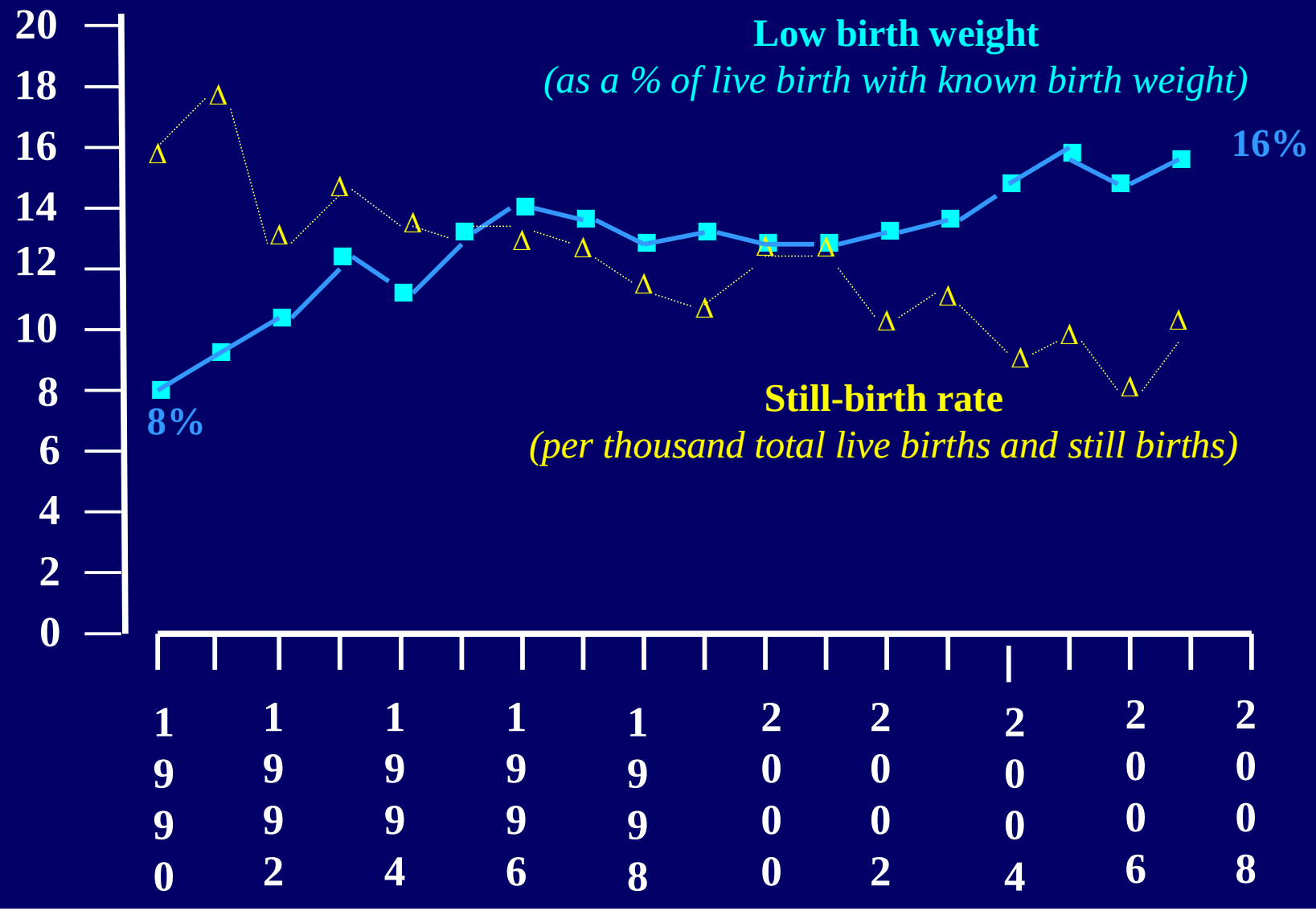
Sas et al. J Clin Endocrinol 85: 3786-3792 (2000)
Martins et al. Br J Nutr 92: 819-825 (2004)
Jornayvaz et al. Metabolism 53: 847-851 (2004)

At any adult BMI, those who were smaller at birth have less FFM and more fat
(Δ 4 kg)

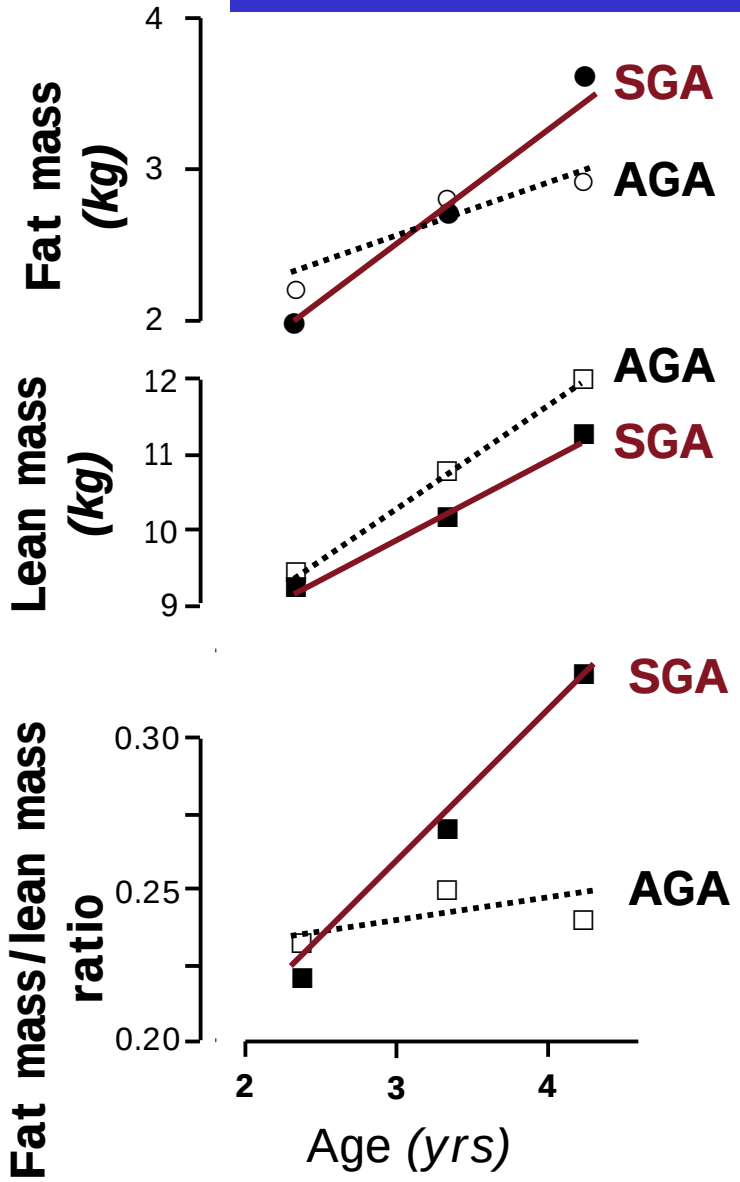
Eriksson et al. Horm Metab Res 34:72-76 (2002)

Low birth weight in Mauritius

Health Statistics Report 2007



The 1st longitudinal study of body composition (by DEXA scanning) in human infants born small for gestational age (SGA)



SGA (Small for gestational age, n=29)

AGA (Appropriate for gestational age, n= 22))

Infants born small show preferential catch-up fat & lower insulin sensitivity (HOMA index)

Figure built from a reanalysis of raw data derived from Ibinez et al. JCEM (2006**)** and published in:

Dulloo et al. *Int J Obesity* 30 (suppl. 4): S23-S35 (2006)

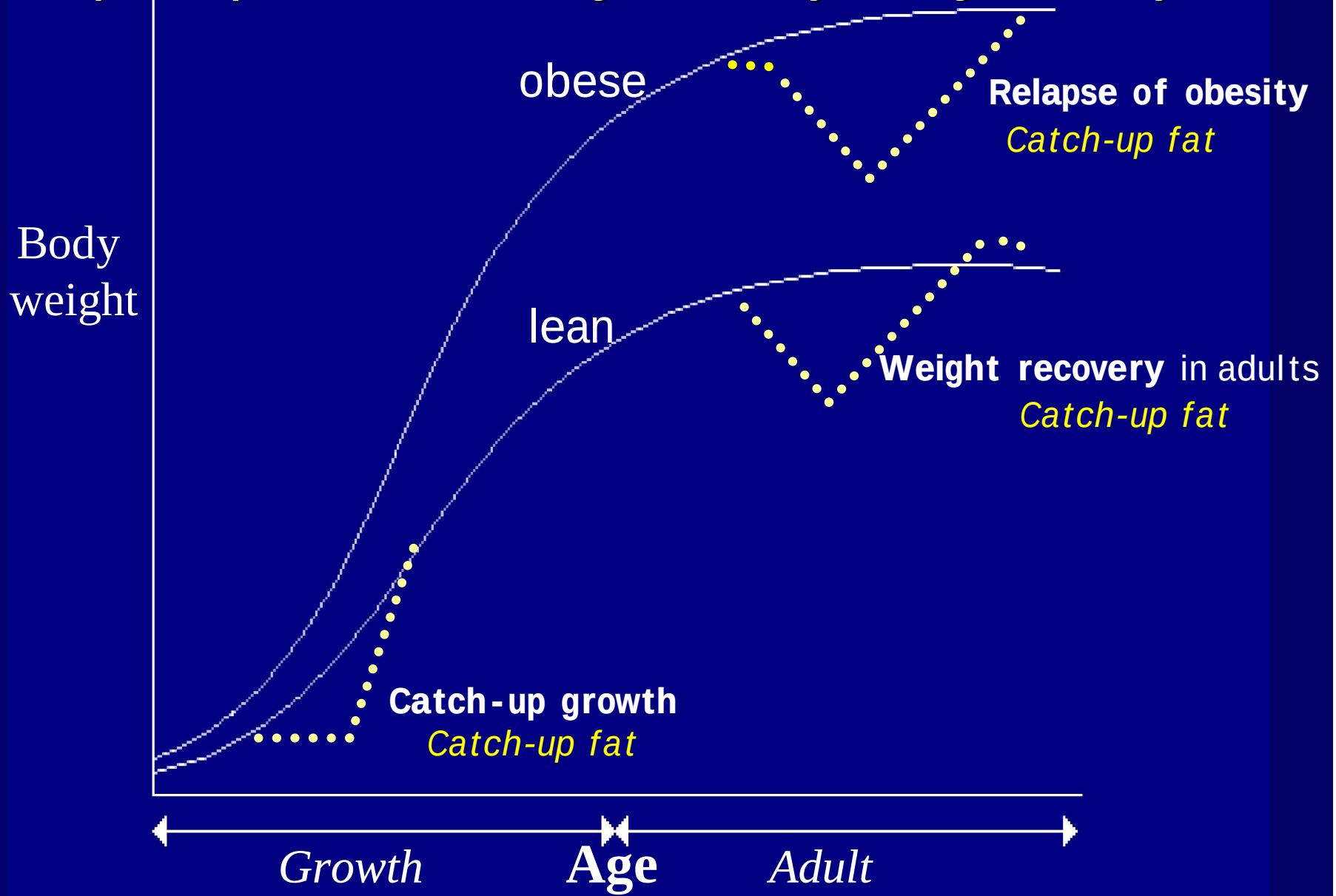
Past reports of "Rapid" fat tissue recovery (catch-up fat) with lean tissue recovery "lagging behind"

Kornfeld & Schuller (1931)	• Emaciated patients in Vienna
Debray *et al.* (1946)	• Prisoners from concentration camps
Keys *et al.* (1950)	• Men after experimental starvation
Ashworth (1969) McLean & Graham (1980) Castilla-Serna et al. (1996)	• Infants / children recovering from protein-energy malnutrition
Barac-Nieto *et al.* (1979) Forbes *et al.* (1984) Mitchell & Truswell (1987)	• Adults after substantial weight loss *(independently of protein level)* • Anorectics regaining weight
Van Eys (1985) Streat *et al.* (1987) Kotler *et al.* (1990)	• Cancer patients • Septic intensive care patients • AIDS patients - parenteral nutrition

Source of references: Dulloo et al. *Int J Obesity* (2002) 26: S46-S57

Preferential catch-up fat:

ubiquitous phenomenon of weight recovery throughout lifecycle



Fundamental questions ?

What are the control systems that regulate fat storage during 'physiological' catch-up fat ?

via increased food intake
(compensatory hyperphagia)

via nutrient partitioning
Shift from lean to fat tissue

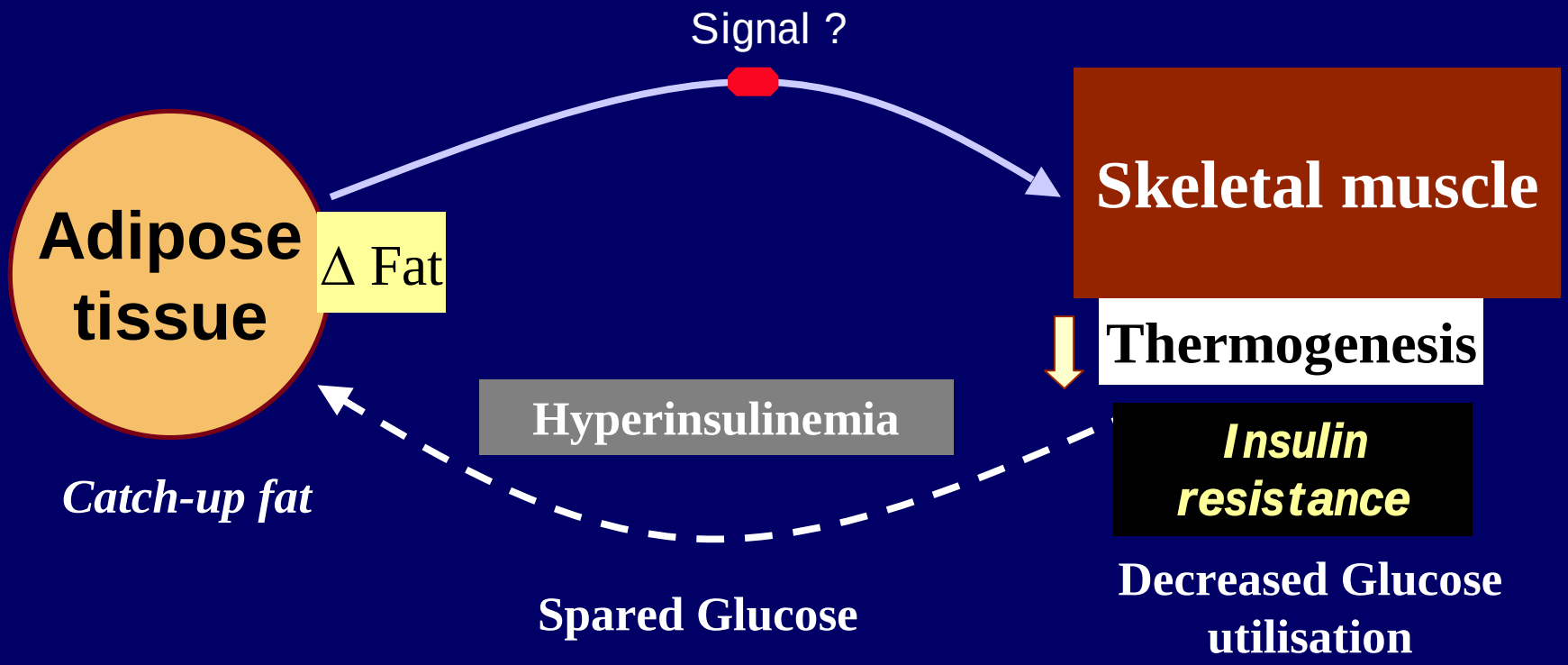
via increased metabolic efficiency
thrifty metabolism - Suppressed thermogenesis

How does 'physiological' catch-up fat turn pathophysiological ?

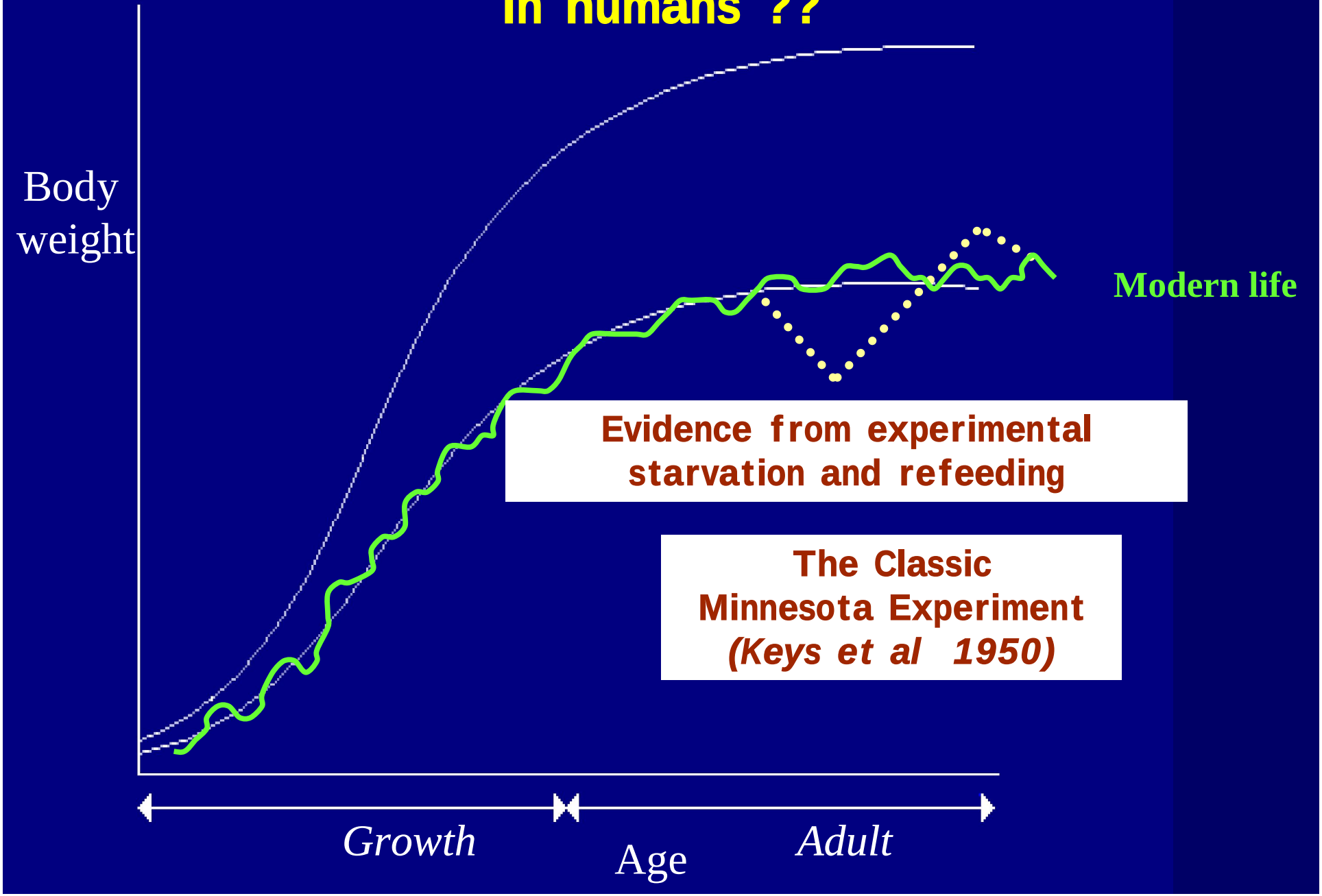
Working hypothesis

Dulloo, Seydoux, Girardier (1990)

Adipose-muscle crosslinks
underlie the thrifty metabolism that drives catch-up fat



‘Thrifty metabolism’ driving catch-up fat in humans ??

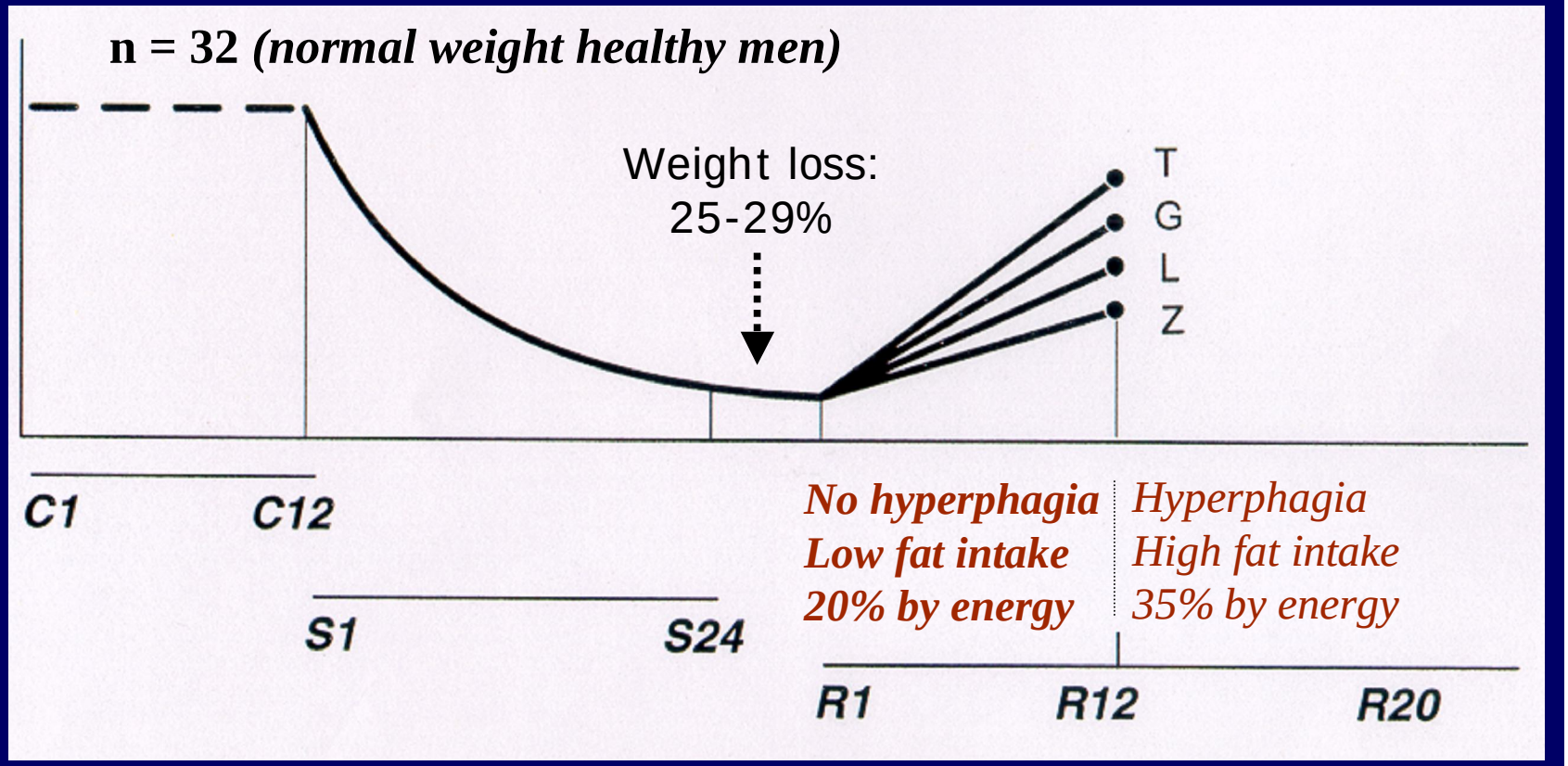


Evidence from experimental starvation and refeeding

The Classic Minnesota Experiment *(Keys et al 1950)*

Design of the Minnesota Experiment

(Keys et al. 1950)



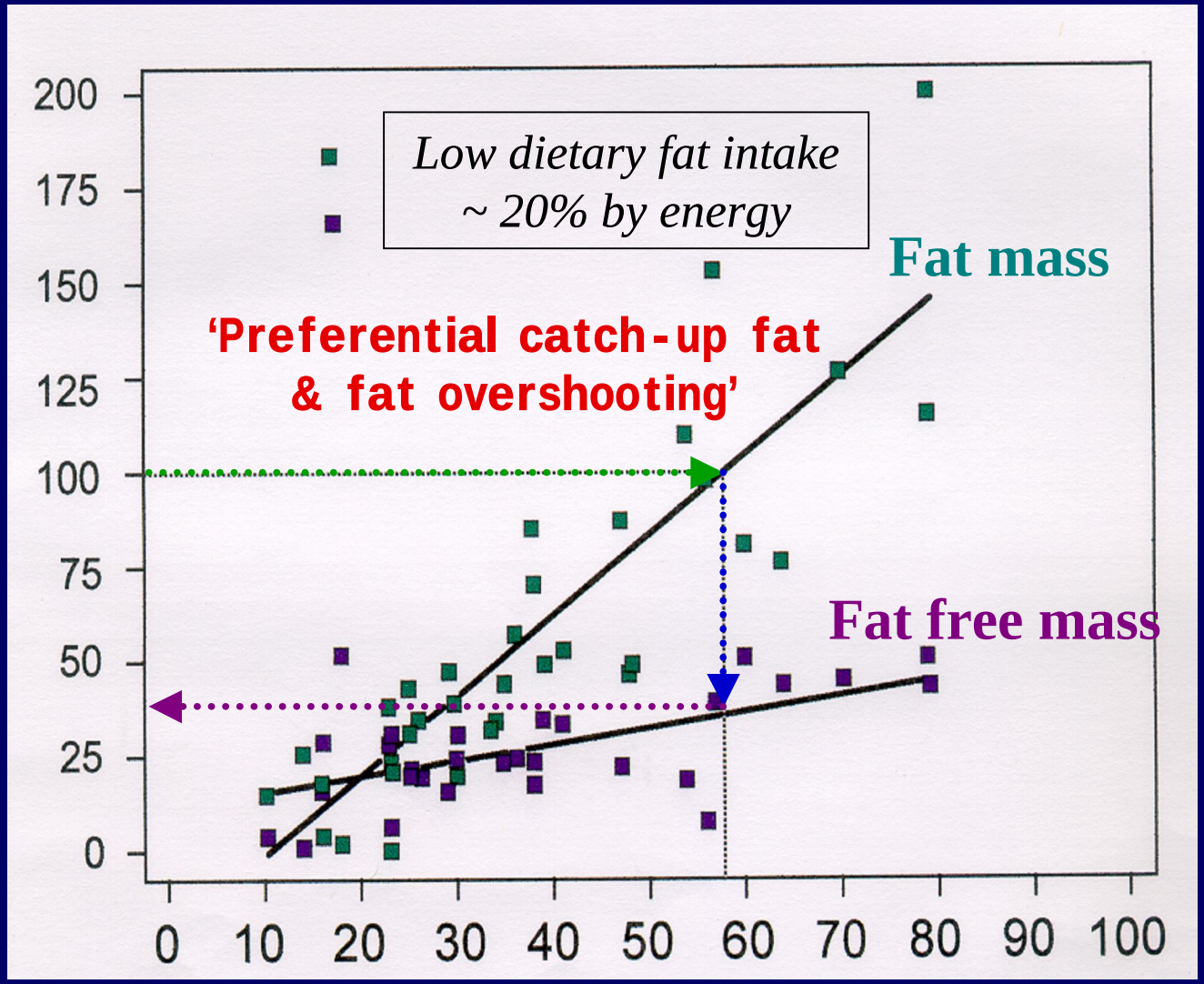
	Control period	Semistarvation			Refeeding *restricted*		Refeeding *ad libitum*	
Food intake	+	+	+	+	+	+	+	+
BMR	+	+	+	+	+	+	+	+
Body composition	+		+	+	+		+	

The men volunteers in the 'Minnesota Experiment': after nearly 6 months of experimental semistarvation

Keys et al. 1950 : The Biology of Human Starvation

Minnesota Experiment (Keys et al. 1950)

Recovery of Fat and FFM *(% loss)*

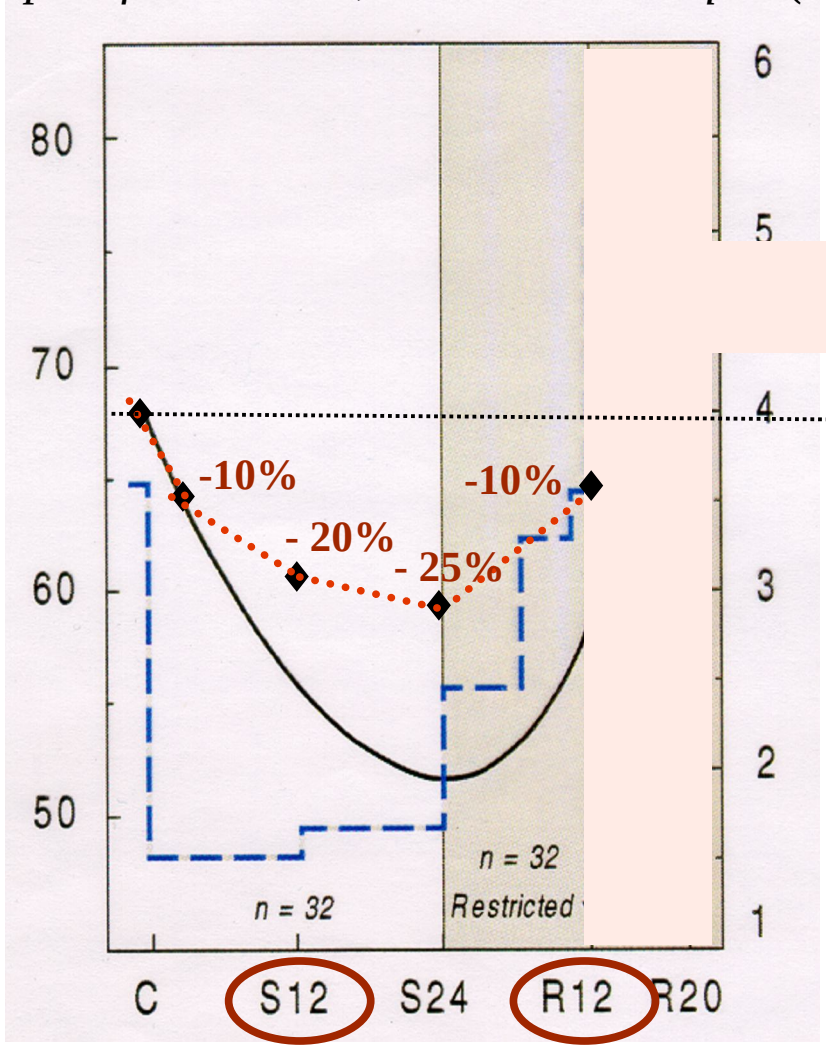


Recovery of weight *(% loss)*

After 12 weeks of restricted refeeding (n=32)

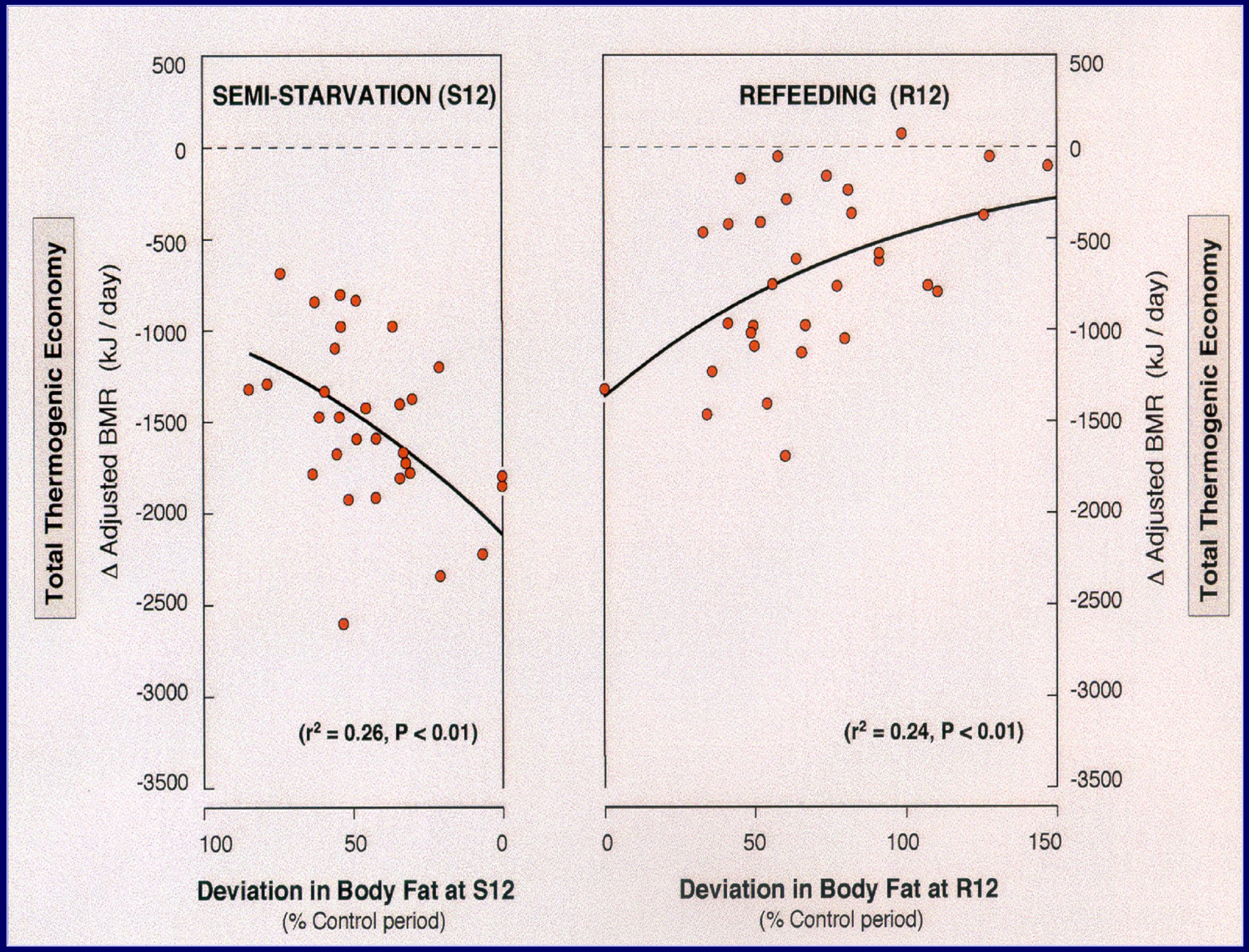
'Minnesota Experiment' Revisited

Adapted from Dulloo, Girardier & Jacquet (1996, 1998)



Minnesota Experiment Revisited

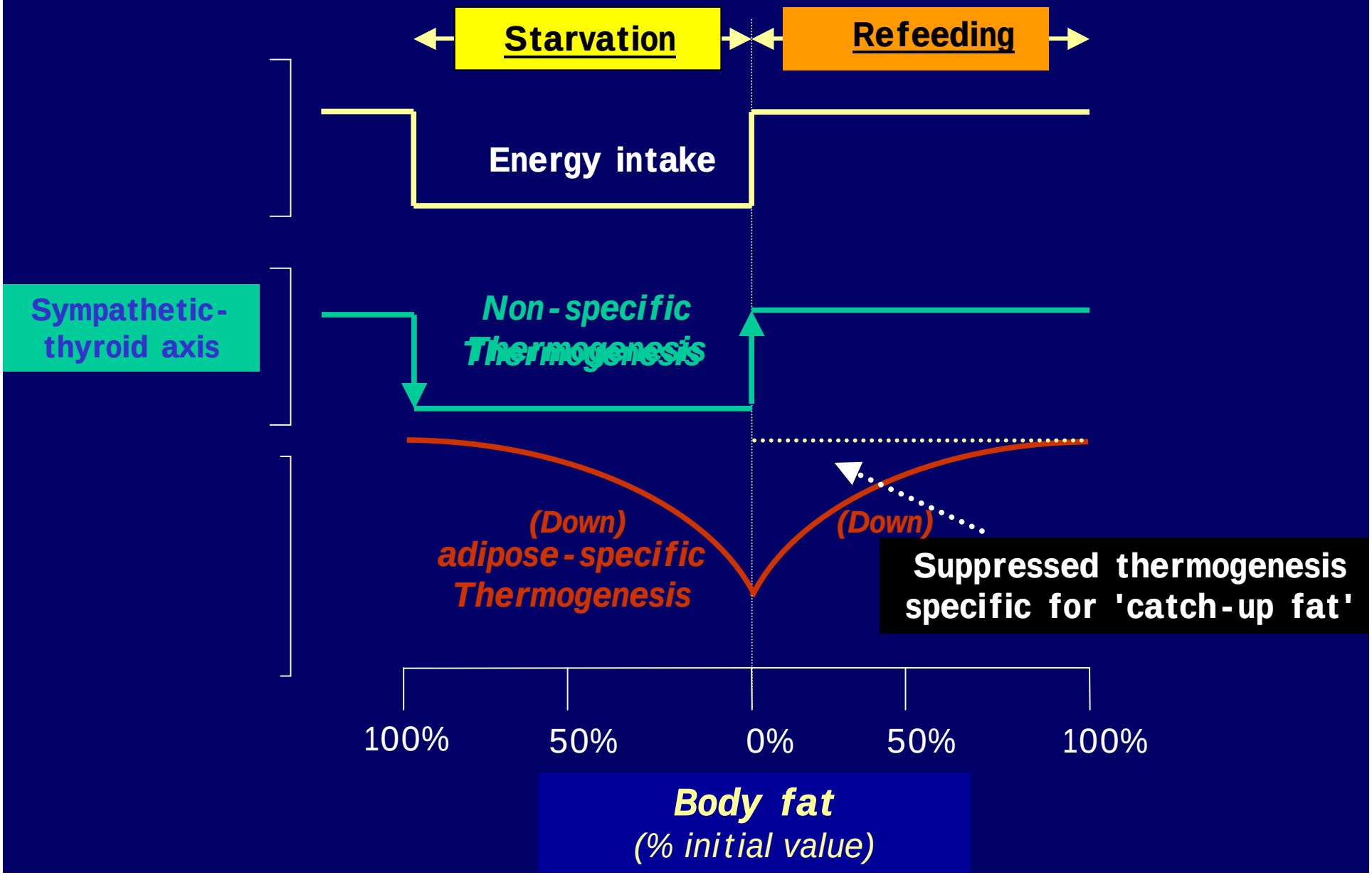
Dulloo et al. Am J Clin Nutr 1998;68:599-606



Feedback control system between fat stores & thermogenesis

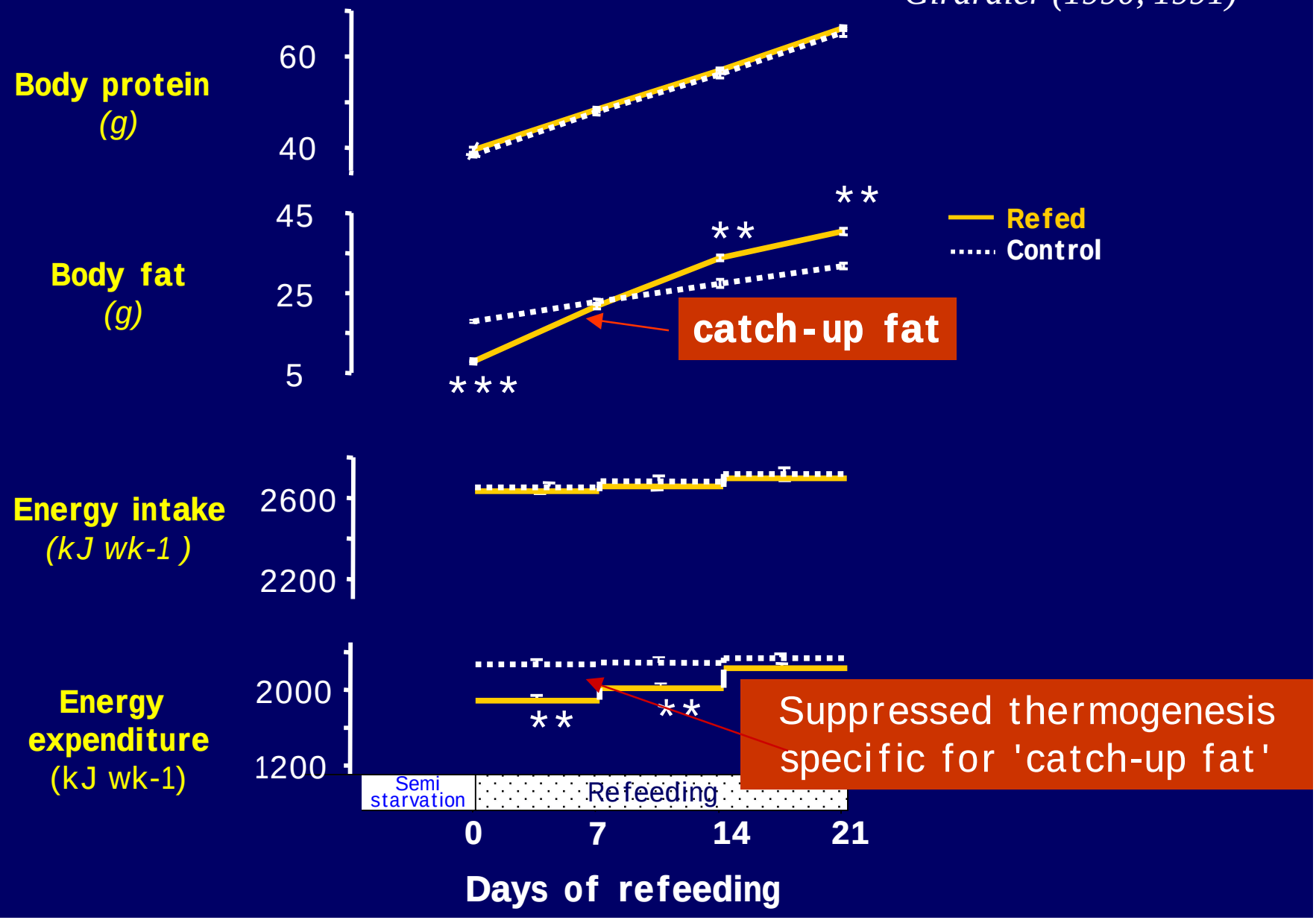
Concept of dual-adaptive thermogenesis

Dulloo et al. *Int J Obesity* **25** (Suppl. 5):S22-S29. (2001)

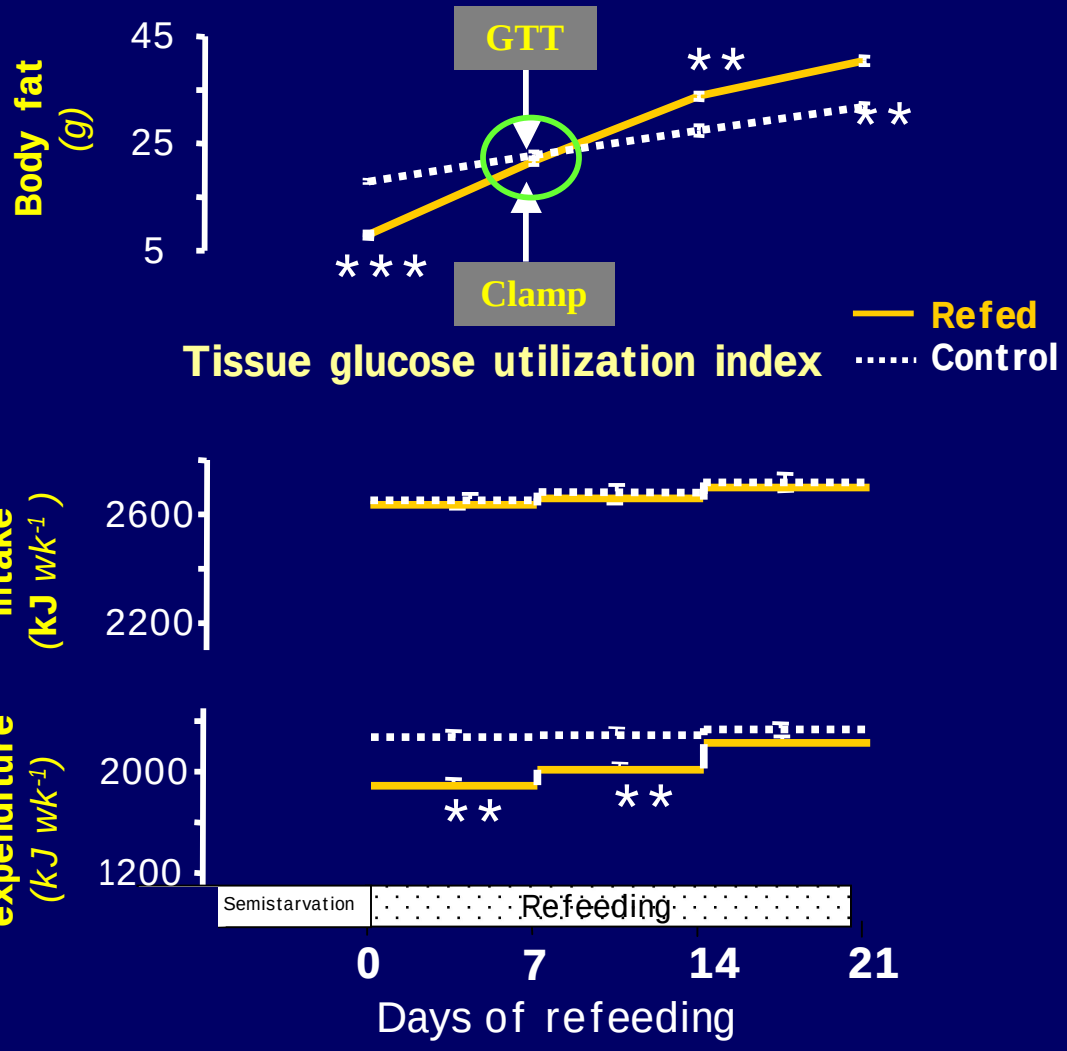


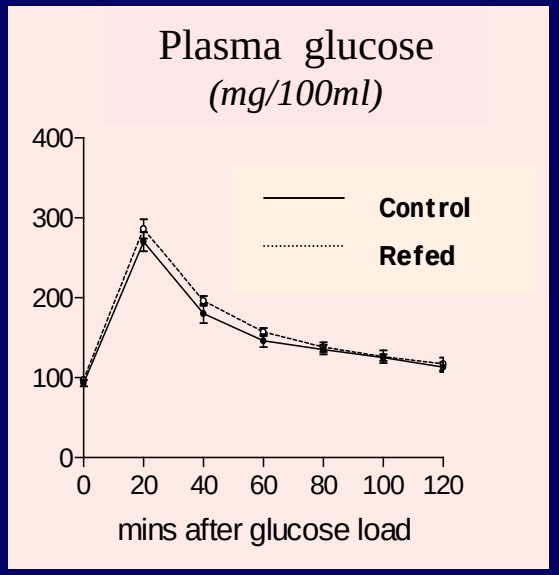
Catch-up fat resulting only from suppressed thermogenesis: *a rat model*

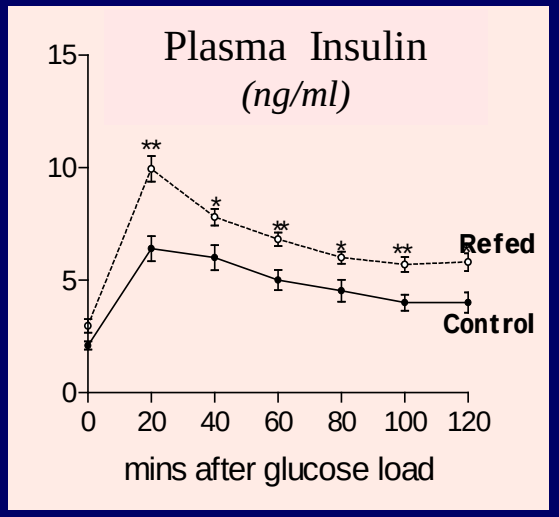
Adapted from Dulloo, Seydoux & Girardier (1990, 1991)



Suppressed thermogenesis favouring catch-up fat: a state of hyperinsulinemia / Insulin resistance



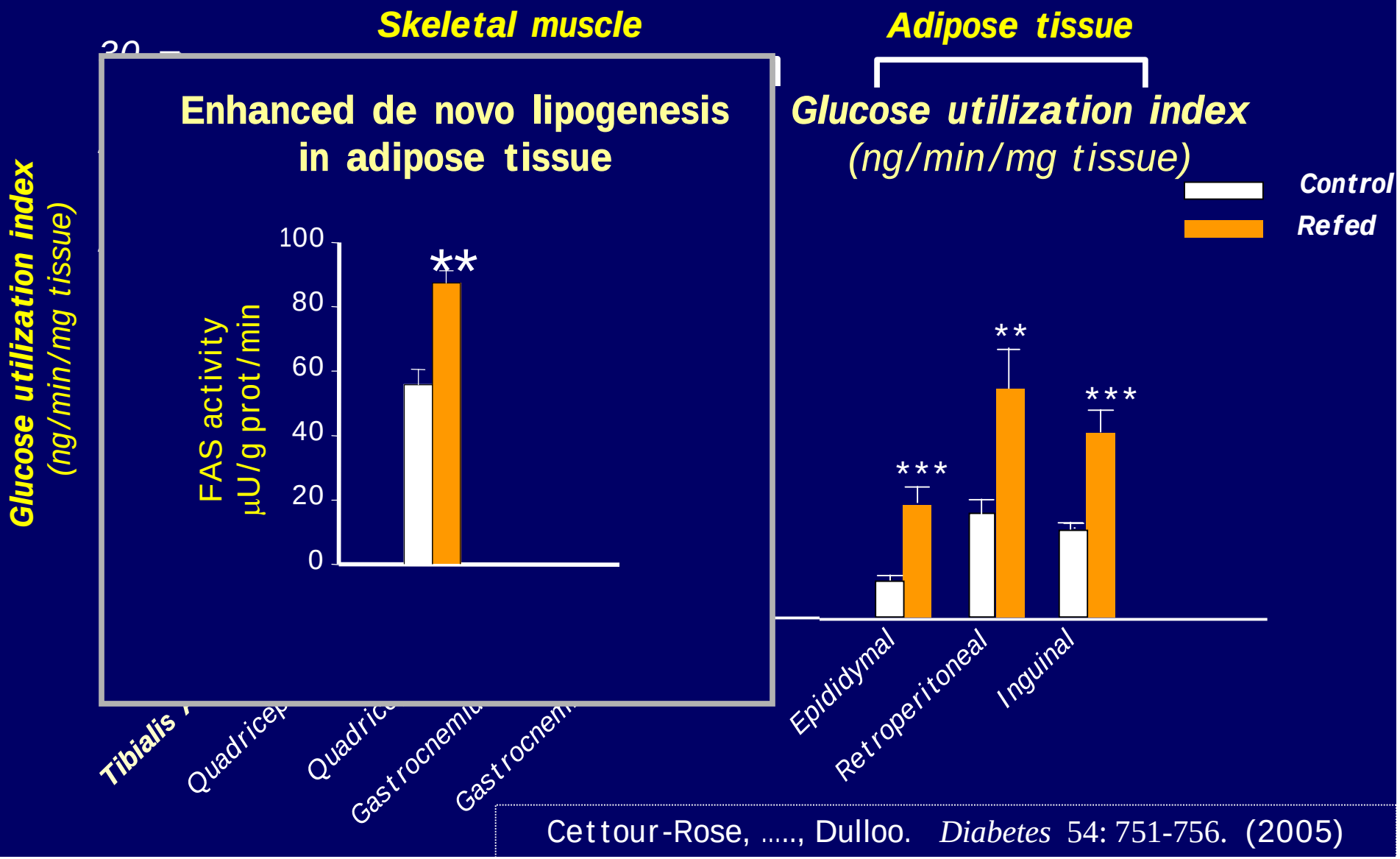




Crescenzo, ……, Dulloo .: *Diabetes 52: 1090-1097. (2003)*

Suppressed thermogenesis favouring catch-up fat:

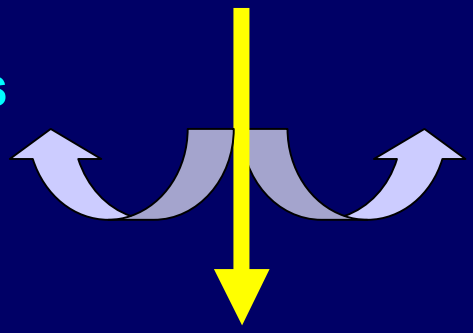
Glucose redistribution from skeletal muscle to adipose tissue



Cettour-Rose, ..., Dulloo. *Diabetes* 54: 751-756. (2005)

Suppressed thermogenesis

Adipose tissue insulin hyperresponsiveness



Skeletal muscle insulin resistance

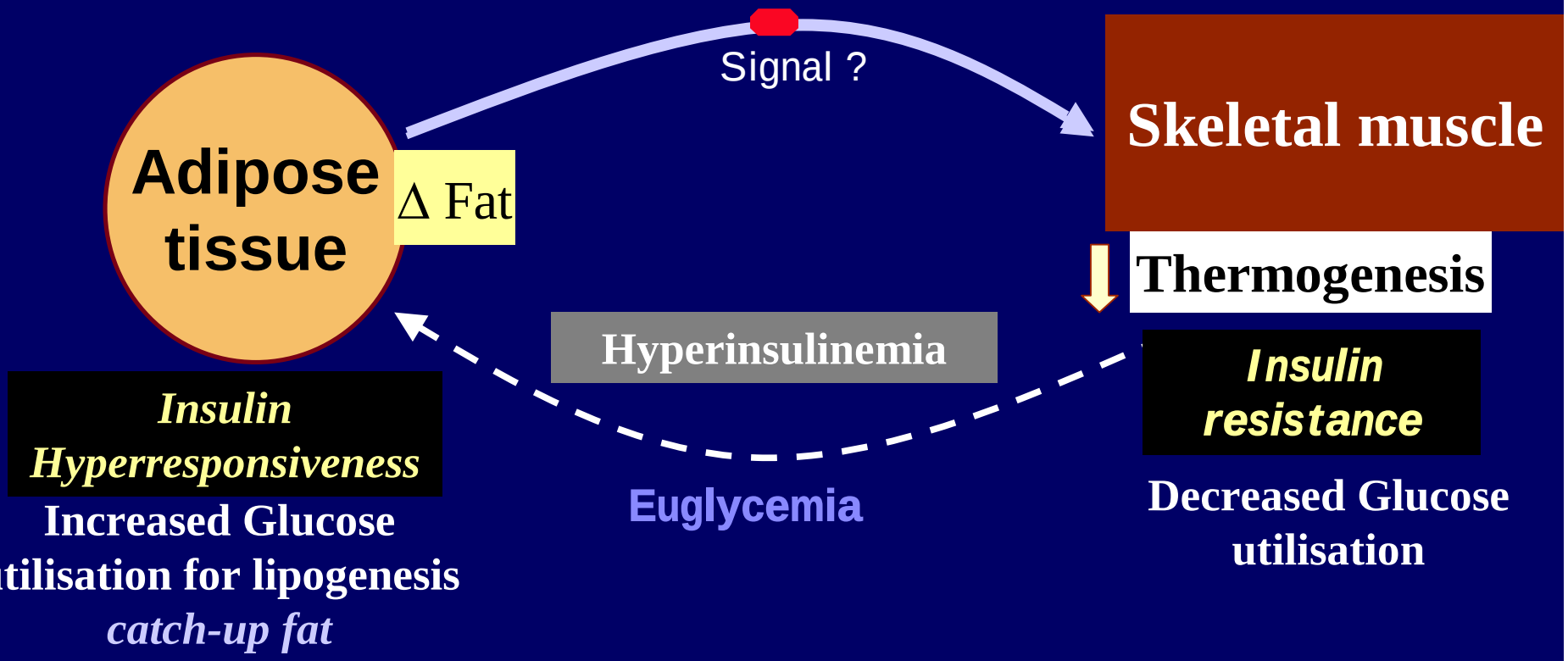
Hyperinsulinemia

Catch-up fat

Excess adiposity

Skeletal muscle insulin resistance and hyperinsulinemia precede the development of excess adiposity

Suppressed thermogenesis favouring catch-up fat (on a low-fat diet): Glucose redistribution

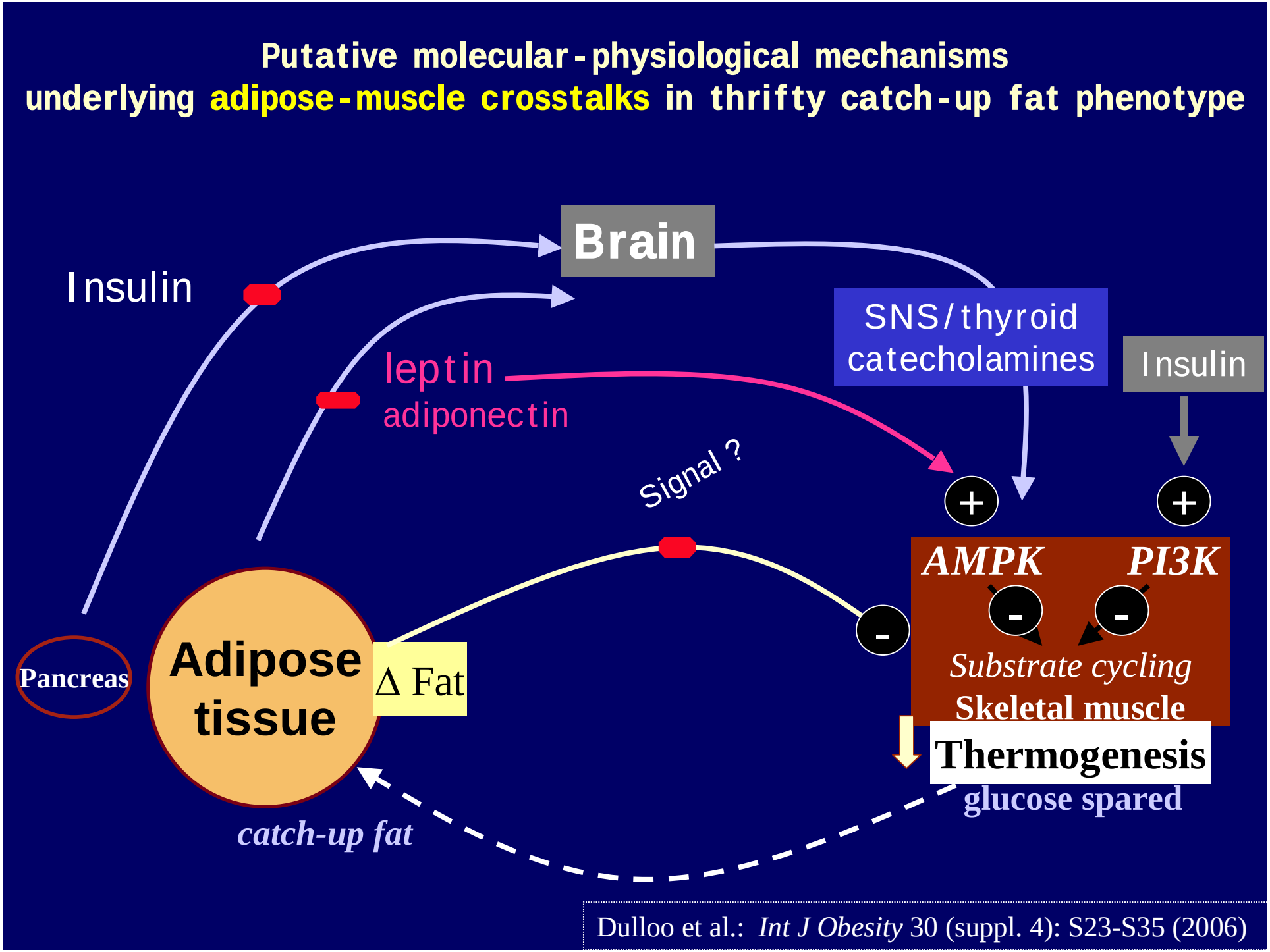


Will an increase in dietary fat compromise this homeostatic system ?

Role of suppressed thermogenesis in susceptibility to insulin resistance & glucose intolerance

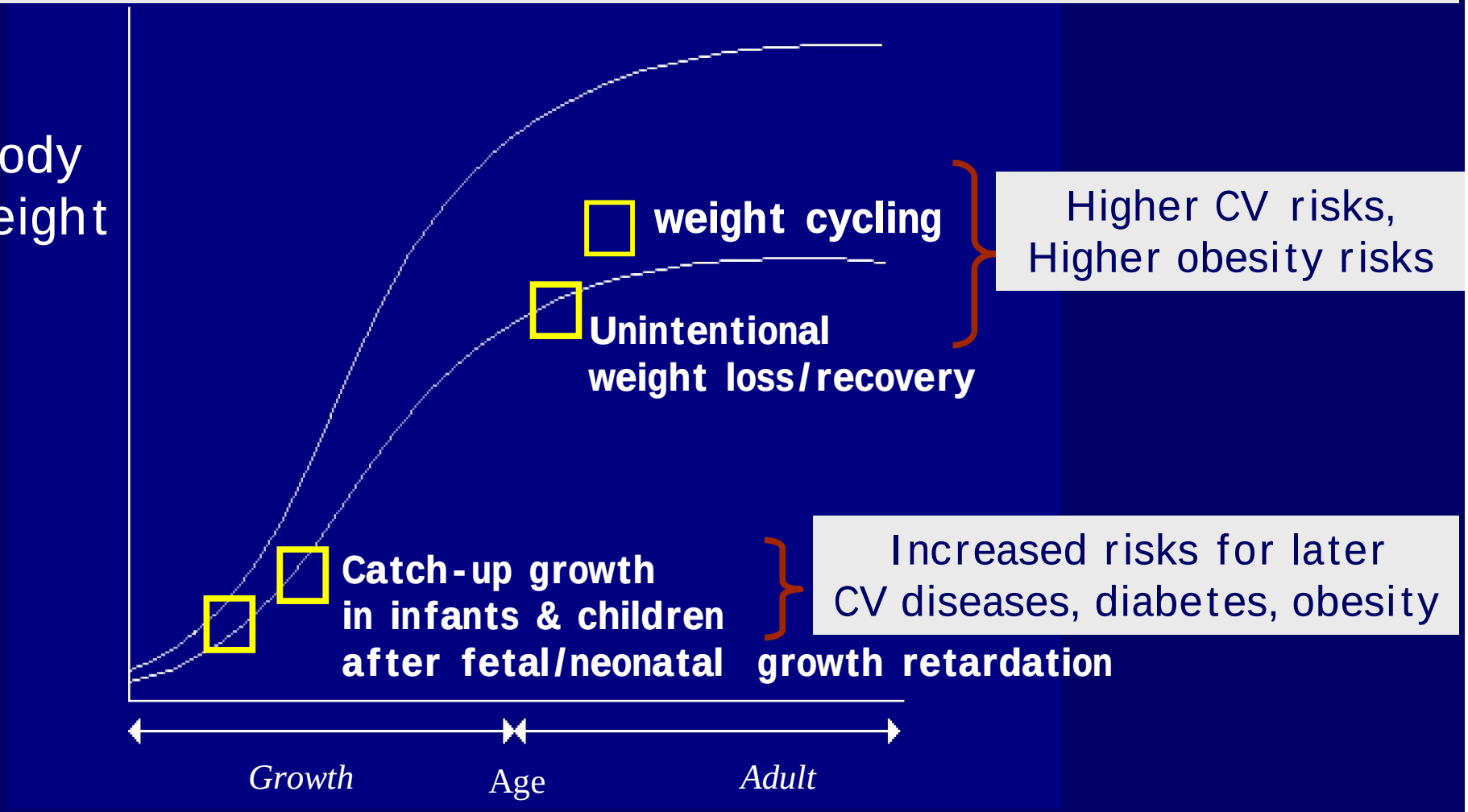
	Adaptive Catch-up fat on low-fat diet	maladaptive Catch-up fat on high-fat diet
Thermogenesis	↓	↓↓
Insulin	↑	↑↑
Glucose tolerance	–	↓
Muscle *PI3K*	↓	↓↓
Muscle *AMPK*	–	↓

Summarized from: Summermatter, ….., Dulloo. FASEB J 22: 774-785 (2008)


Putative molecular-physiological mechanisms
underlying adipose-muscle crosstalks in thrifty catch-up fat phenotype
Brain
Insulin
leptin
adiponectin
SNS/thyroid
catecholamines
Insulin
Signal ?
+
+
AMPK
PI3K
-
-
-
Substrate cycling
Skeletal muscle
Thermogenesis
glucose spared
Pancreas
Adipose
tissue
Δ Fat
catch-up fat
Dulloo et al.: Int J Obesity 30 (suppl. 4): S23-S35 (2006)

Take home message

A role for a '*thrifty catch-up fat phenotype*'
in pathways to insulin-resistance syndrome



For review: Dulloo et al.: *Int J Obesity* 30 (suppl. 4): S23-S35 (2006)

Take home message I

Genes/reprogramming/lifestyle Interactions

Thin-short babies/infants

Adults (normal/overweight)

Catch-up growth

Weight recovery

Later insulin-related chronic diseases

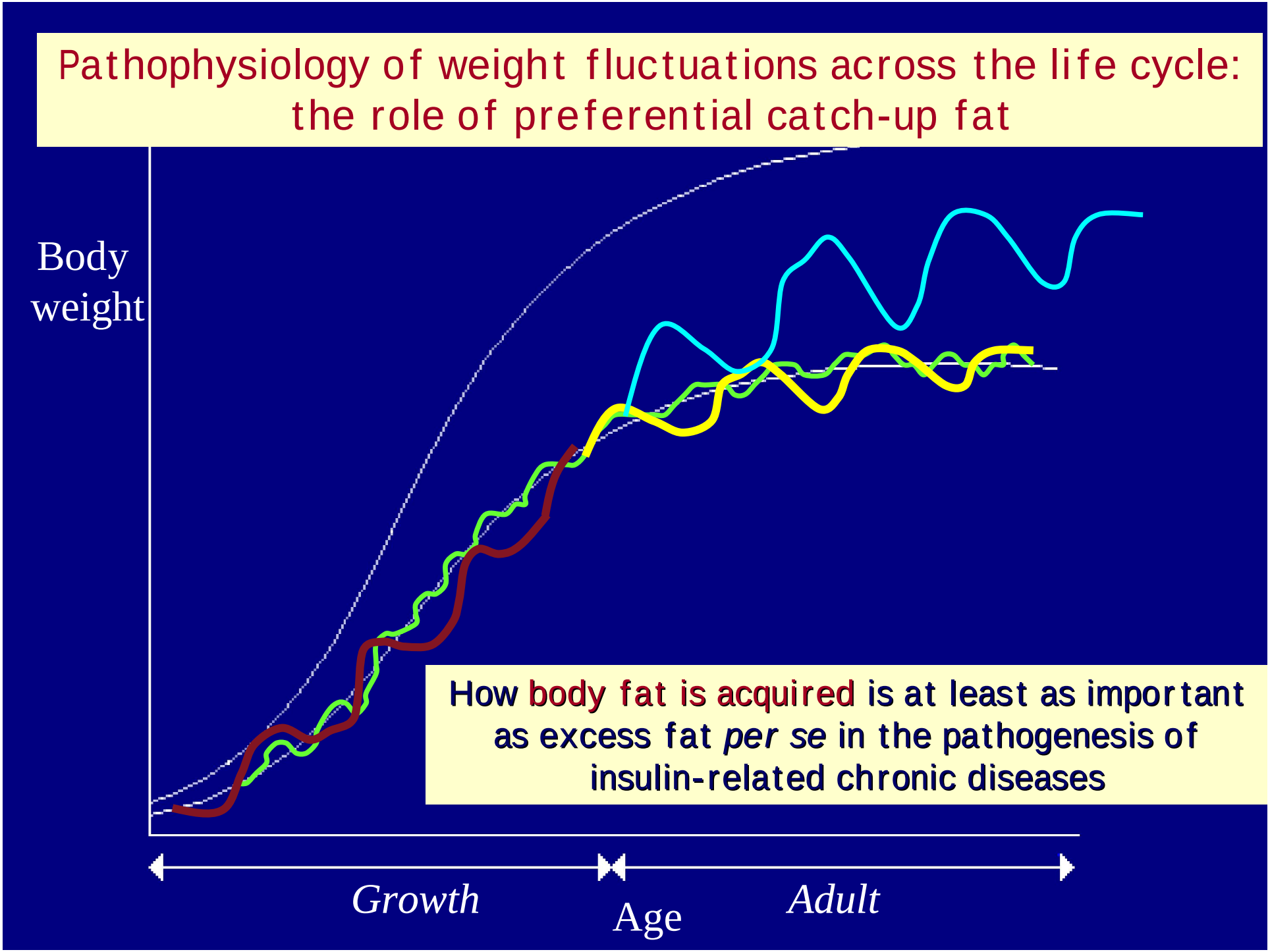
Obesity, diabetes, CV diseases

state of catch-up fat

Regulation of fat storage via <u>suppressed thermogenesis</u>

(energy conservation for the purpose of catch-up fat)

Pathophysiology of weight fluctuations across the life cycle: the role of preferential catch-up fat



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Philippe Cettour-rose

Françoise Assimacopoulos-Jeannet

University of Frederico II
Naples

Raffaella Crescenzo
Susanna Iossa

Hippocrates *400 BC*

‘‘ Do not allow the body to attain extreme thinness,
for that, too, is treacherous,

but bring it only to a condition
that will naturally continue unchanged,
whatever that may be ’’