IUGR and Macrosomic Phenotypes – How They Develop and How They Change Over Time

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Presented at
Miami Neonatology 2016 – 40th International Conference
November 5th-8th, 2016

This activity is supported by an educational grant from
Mead Johnson Nutrition.

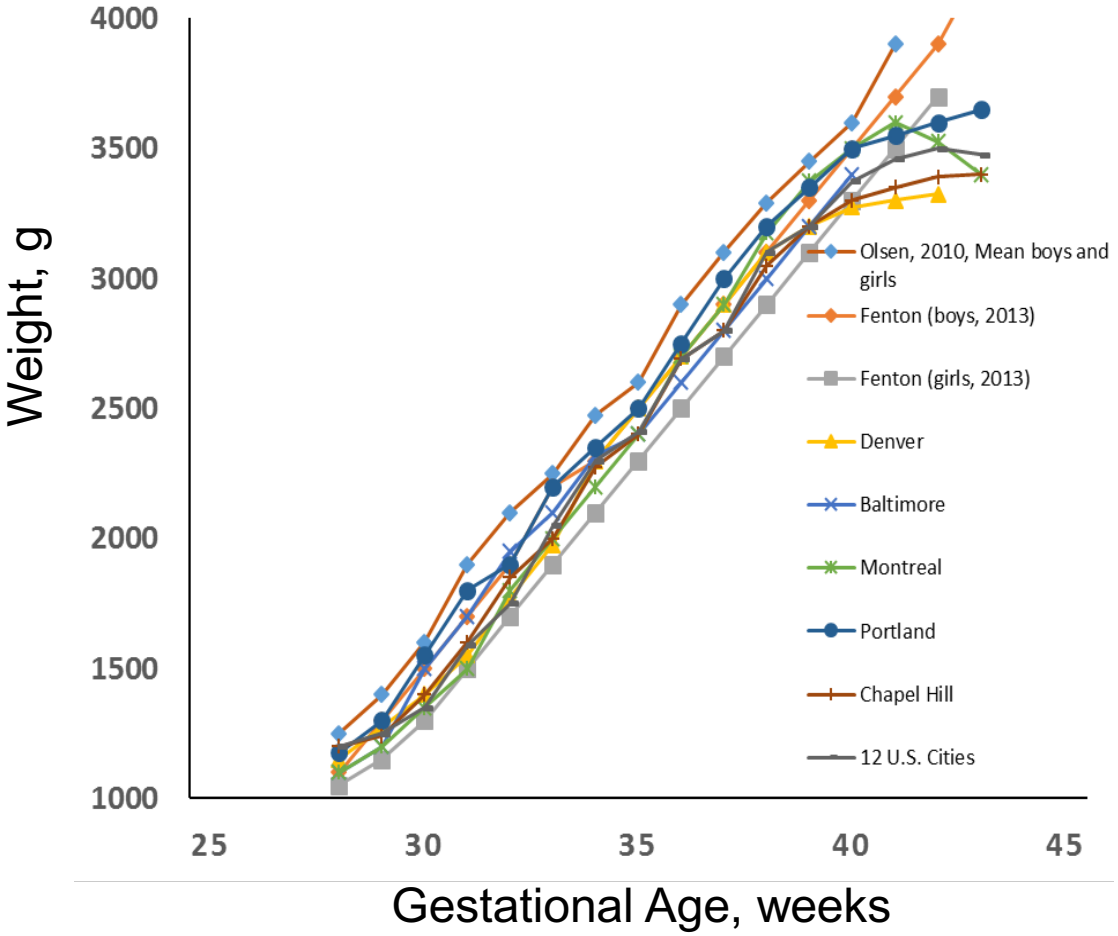
Disclosure

In accordance with the Accreditation Council for Continuing Medical Education Standards, parallel documents from other accrediting bodies, and Annenberg Center for Health Sciences policy, the following disclosure has been made:

William W. Hay, Jr, MD

One time Consultant: Baxter–IV nutrition

Normal human fetuses are supposed to grow (regardless of the growth curve) at an *average* rate of ~17 g/kg/day from 28-40 weeks, with symmetrical growth of head and length.

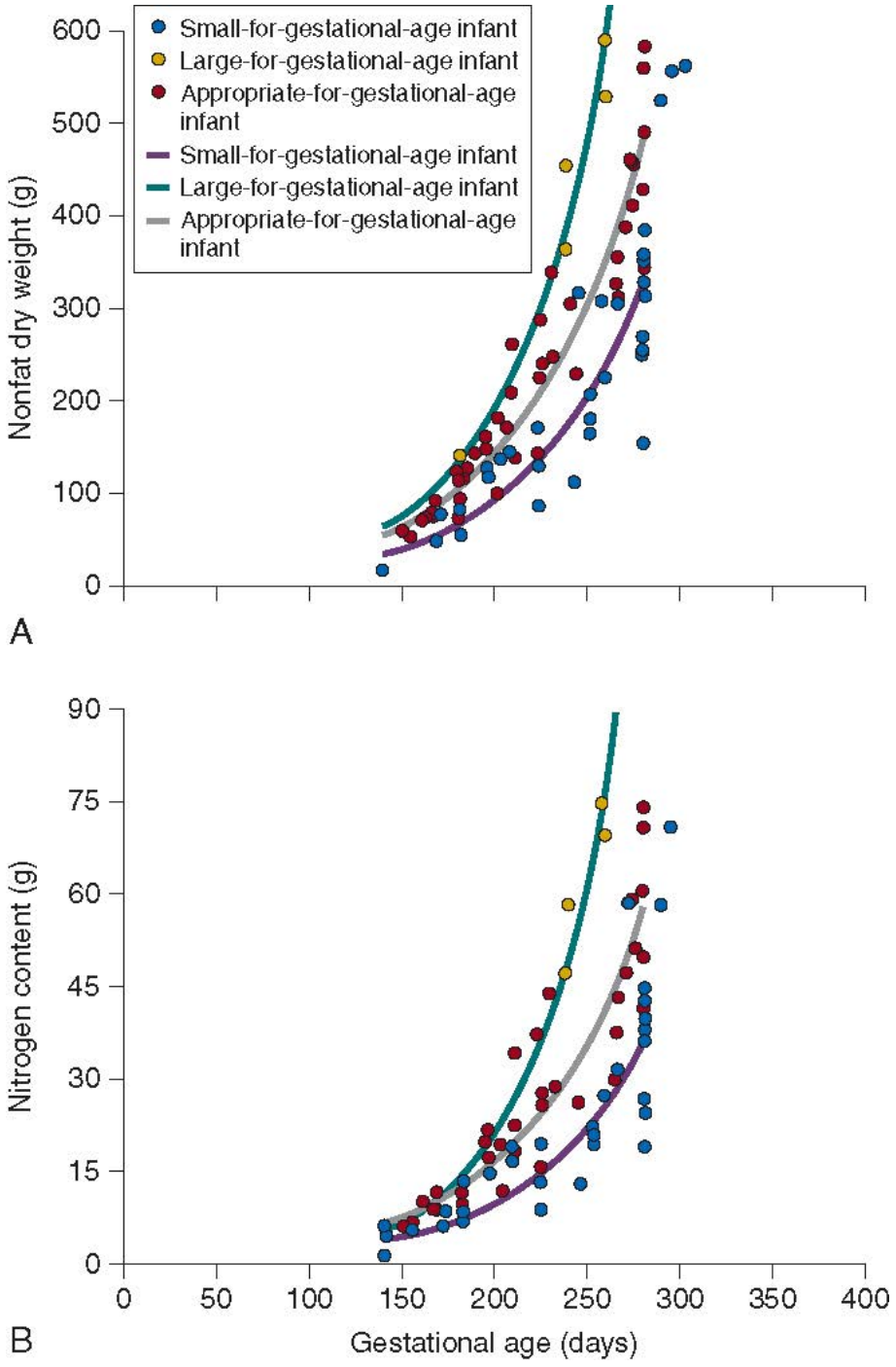


Average 50th %ile birth weights by gestational age

From 6 sources adapted from Naeye R, Dixon J. *Pediatr Res.* 1978;12:987-991 (including "mile high" Denver, CO Lubchenco curve);

Fenton TR, Kim JH. *BMC Pediatr.* 2003;13:59;

Olsen IE, et al. *Pediatrics.* 2010; 125:e214-e224.



17 g/kg/day is the <u>average</u> weight gain of the normal human fetus.

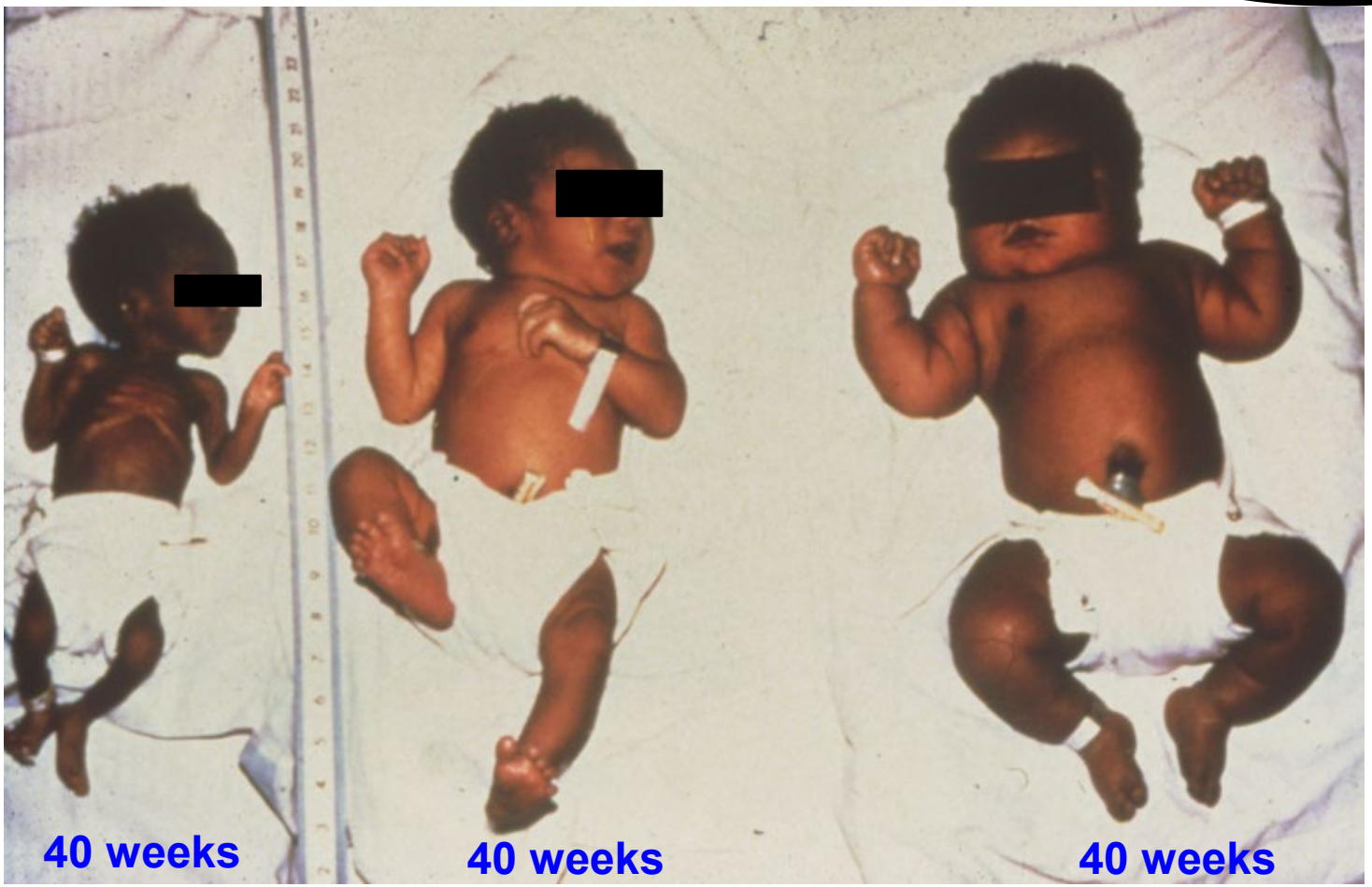
More energy in the maternal diet, fatter fetus, especially the LGA fetus, at risk for later obesity.

Not enough energy in the maternal diet, thinner fetus, at risk for later fat gain.

Original data from Widdowson E. Collated by Sparks JW: Human intrauterine growth and nutrient accretion. *Semin Perinatol.* 8:74, 1984.

Both extremes of fetal growth (SGA/IUGR and LGA/Macrosomia) are associated with similar adult phenotypes of obesity, insulin resistance, diabetes, and cardiovascular disease.

HOW?? And are these the results of similar or different mechanisms?



From National Audiovisual Center, Washington, DC, courtesy of William W. Hay, Jr, MD.

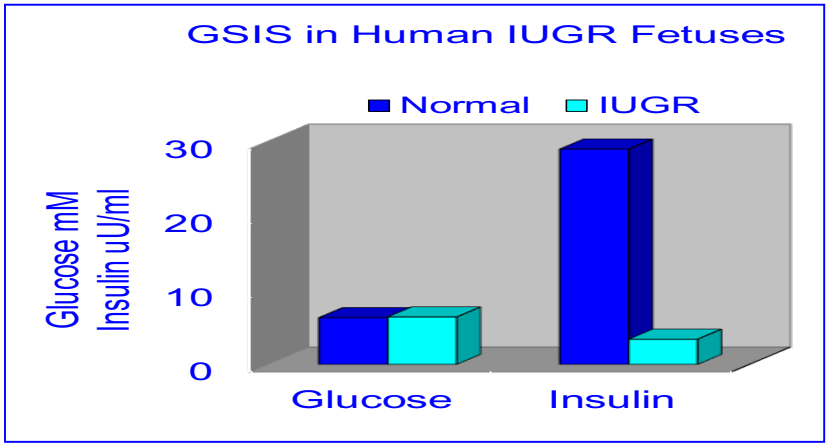
Under Nutrition

IUGR / SGA fetuses and neonates

and consequences of trying to feed them more.

Pancreatic Growth Failure—with later insulin deficiency (Beta Cell/Islet proliferation and Insulin Secretion—both reduced in the IUGR fetus)

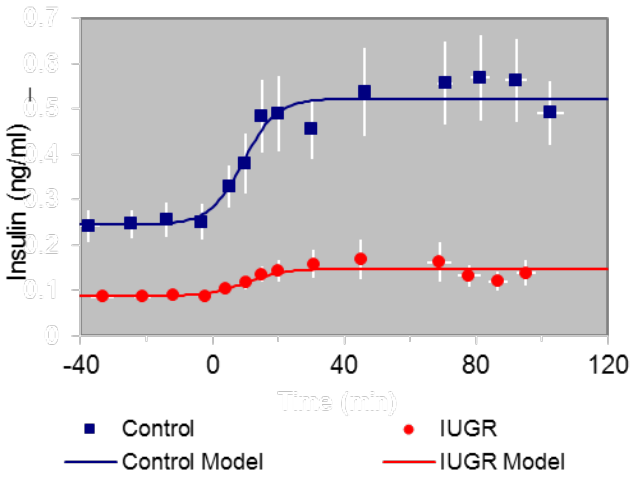
Human IUGR Fetuses: Reduced glucose-stimulated insulin secretion

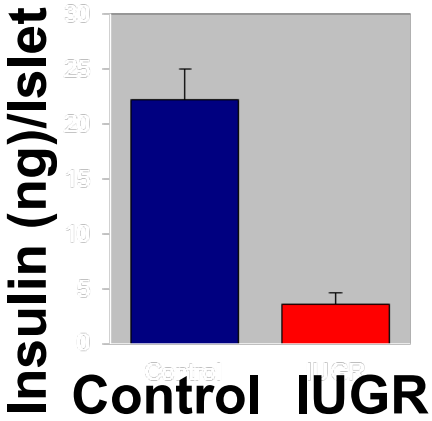


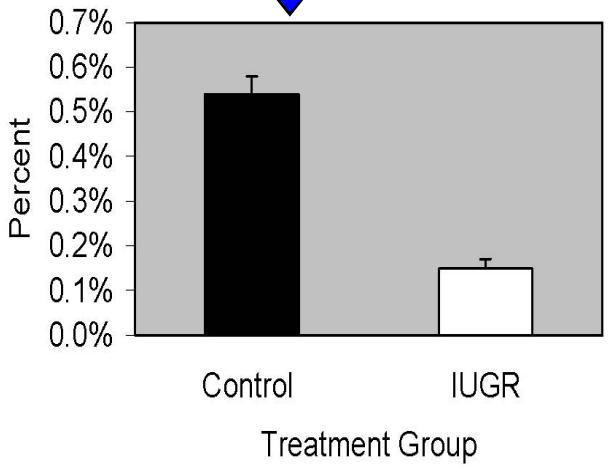
Nicolini et al, 1990

Glucose Stimulated Insulin Secretion (GSIS) is reduced near term) in IUGR fetal sheep, due to

↓ Islet Insulin Content ↻ and ↓ β-cell mitosis

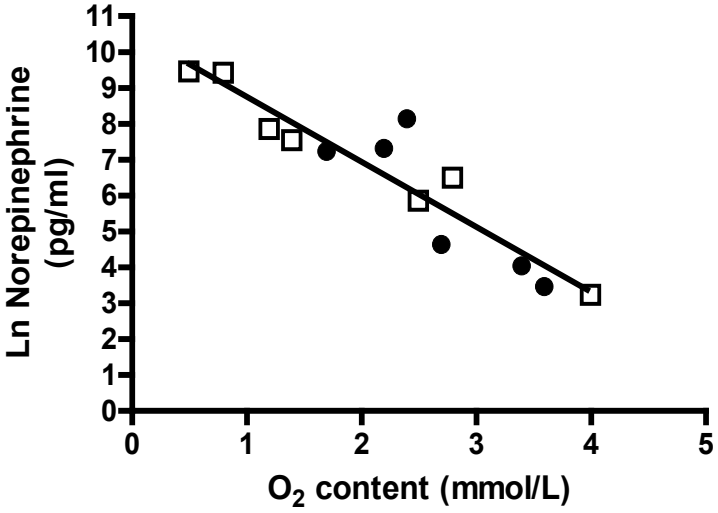


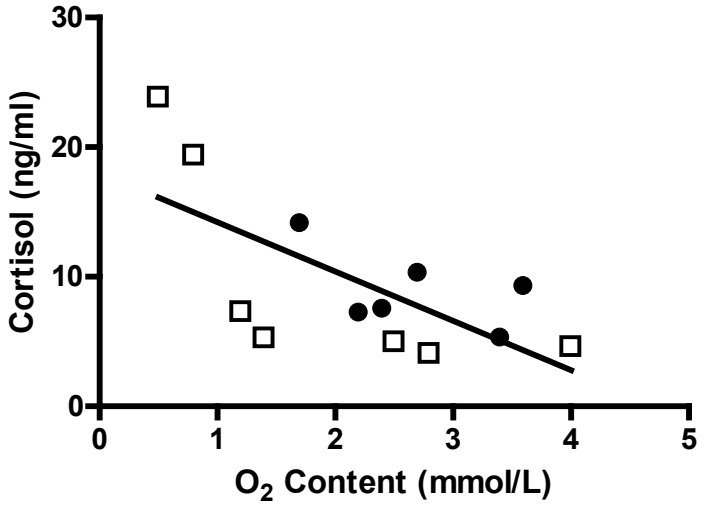




Limesand et al. 2006

Adverse effects of reduced oxygen





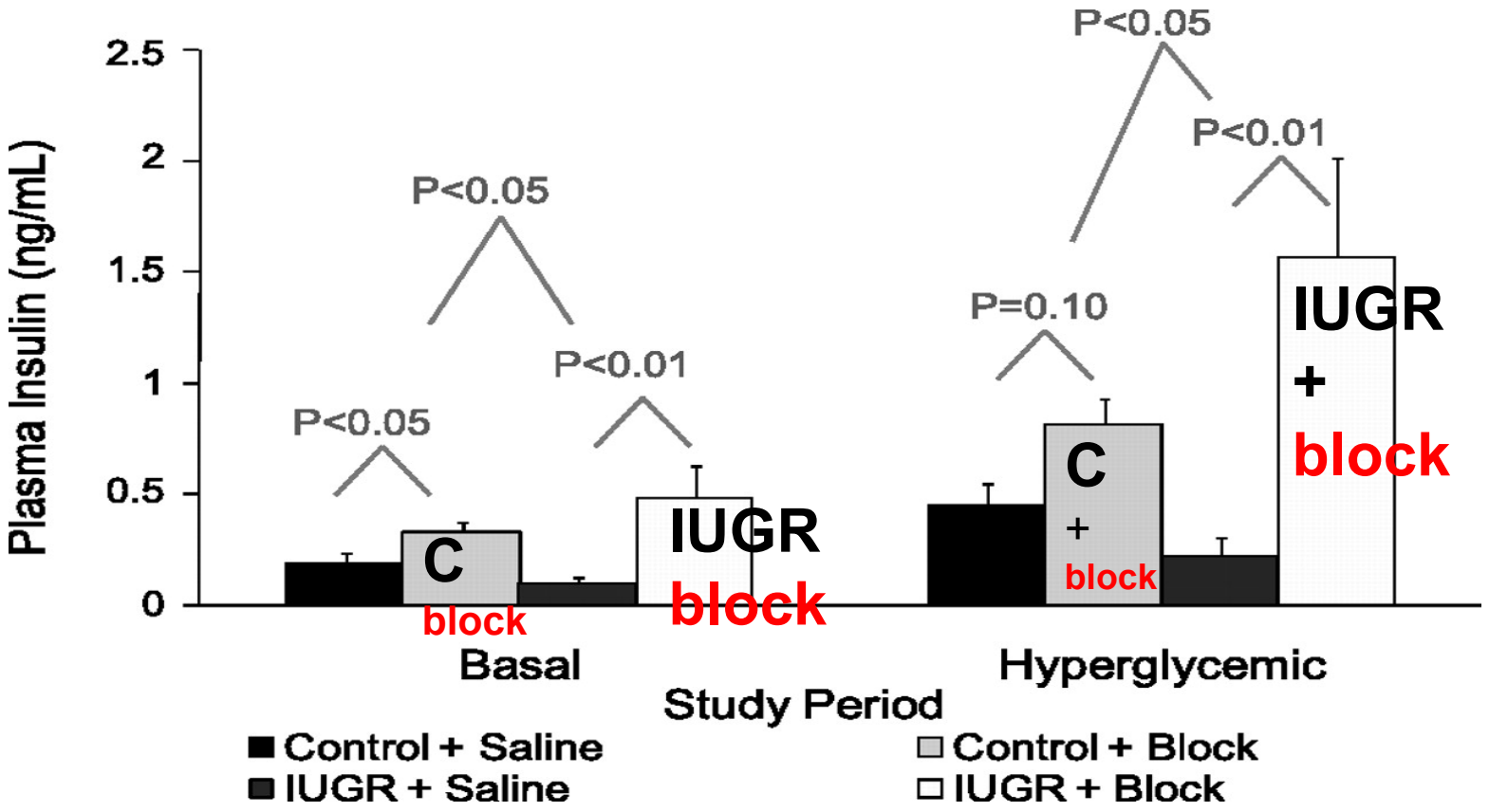
Hypoxia → Increased Catecholamines

Decreased insulin secretion
Decreased insulin action

Hypoxia → Increased Cortisol

Increased gluconeogenesis
Increased protein breakdown

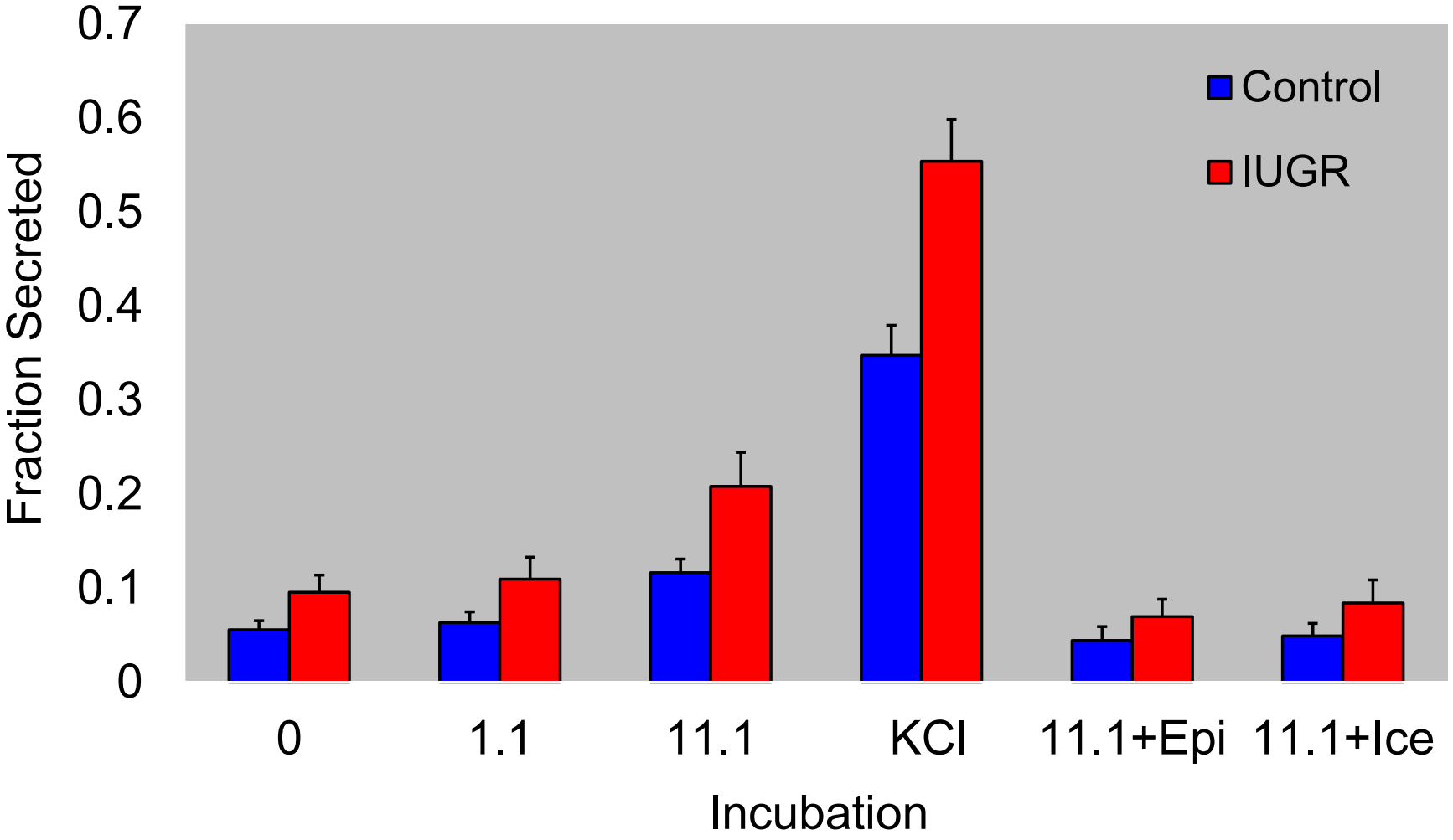
Fetal insulin concentrations increase with blocking of catecholamines, proof that they suppress insulin secretion. Exaggerated in IUGR fetuses! After birth, good care might backfire!



Sean Limesand's studies

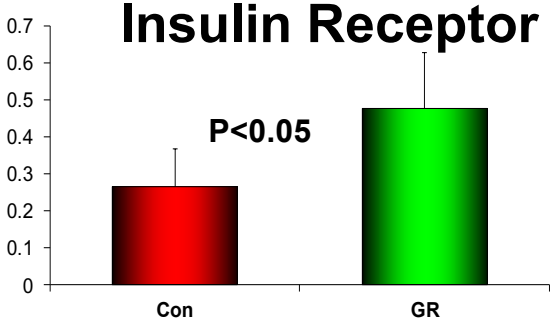
Leos R A et al. *Am J Physiol Endocrinol Metab.* 2010;298:E770-E778. With permission.

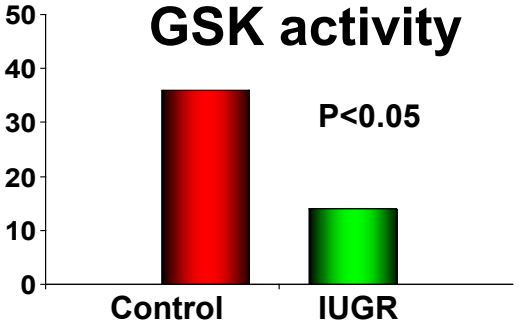
IUGR islets also have
increased Fractional Islet Insulin Secretion!
(in culture, without or with catecholamines)

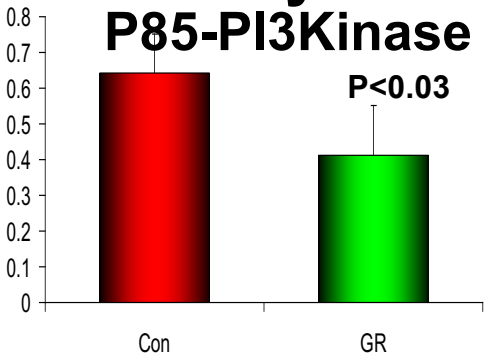


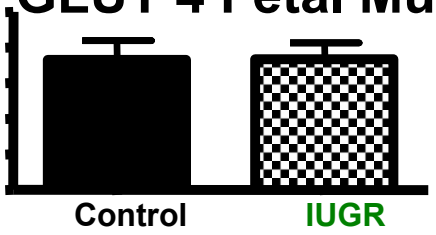
Adapted from Limesand, et al. *Endocrinology.* 2006 147(3):1488-1497.

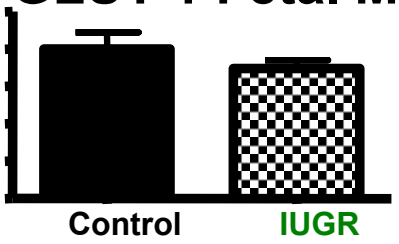
Positive adaptation to "chronic" reductions in fetal glucose, increasing Glucose and Insulin Sensitivity—with risk of later life development of increased fat storage and obesity.

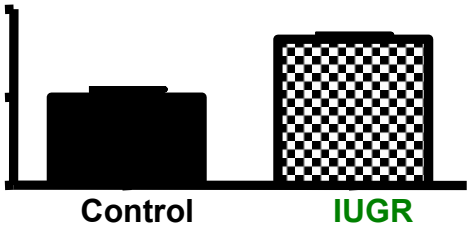








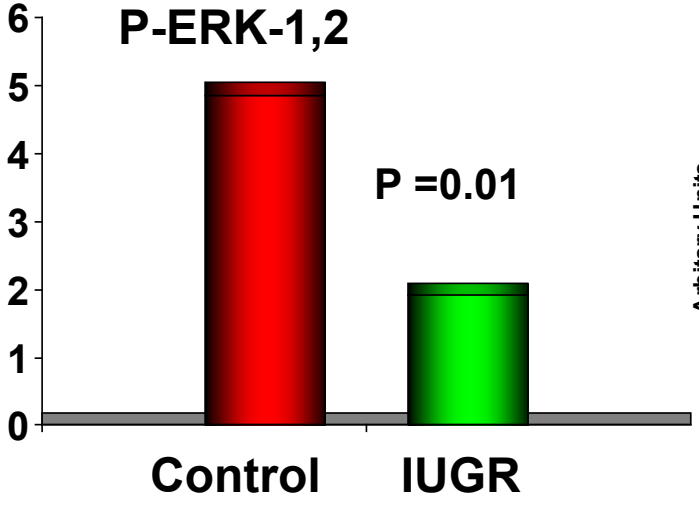


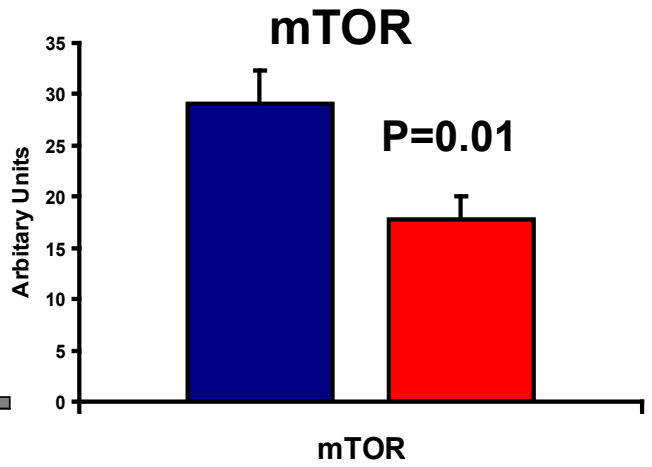


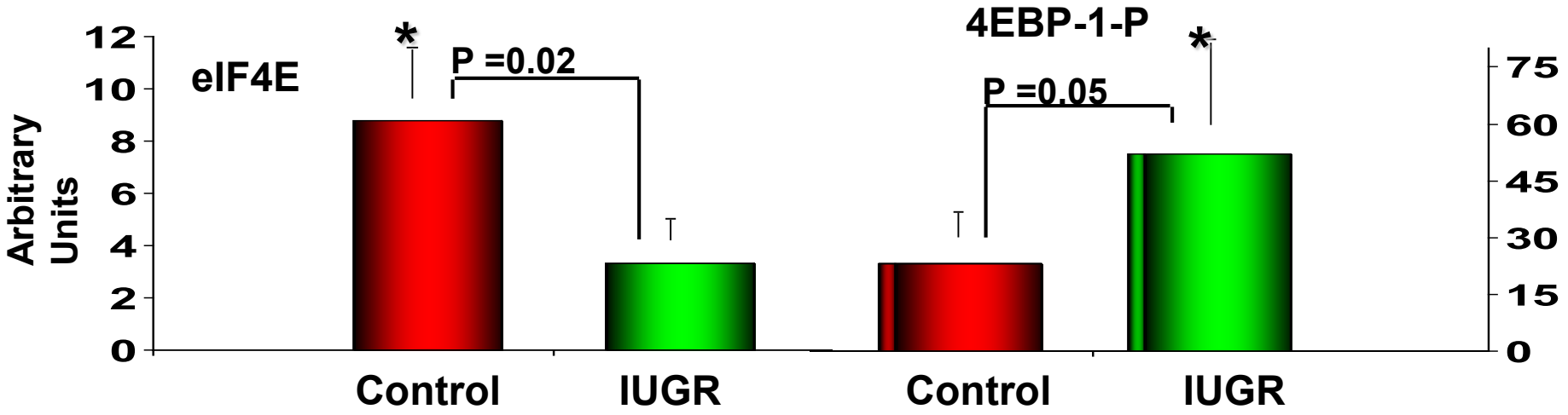
These changes maintain glucose utilization and insulin sensitivity---ie, GUR/kg is normal at less than normal [Glu] and [Ins].

	Control		IUGR
GUR	5 mg/kg/min	=	5 mg/kg/min
[G]	20 mg/dL	→	10 mg/dL
[I]	12 µU/mL	→	5 µU/mL

Adapted from Limesand, et al. *Endocrinology.* 2006 147(3):1488-1497. Wallace JM, et al. *Am J Physiol Endocrinol Metab*. 2007;293:E1233-41.



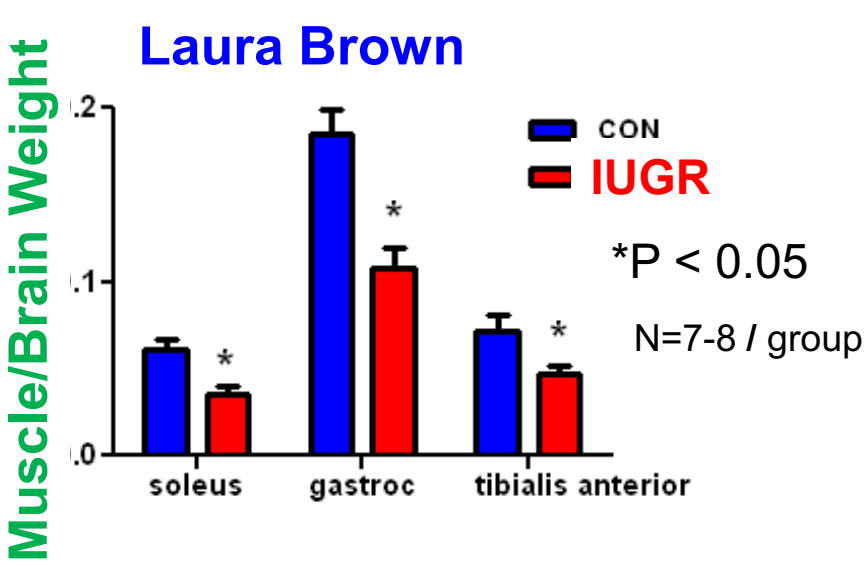


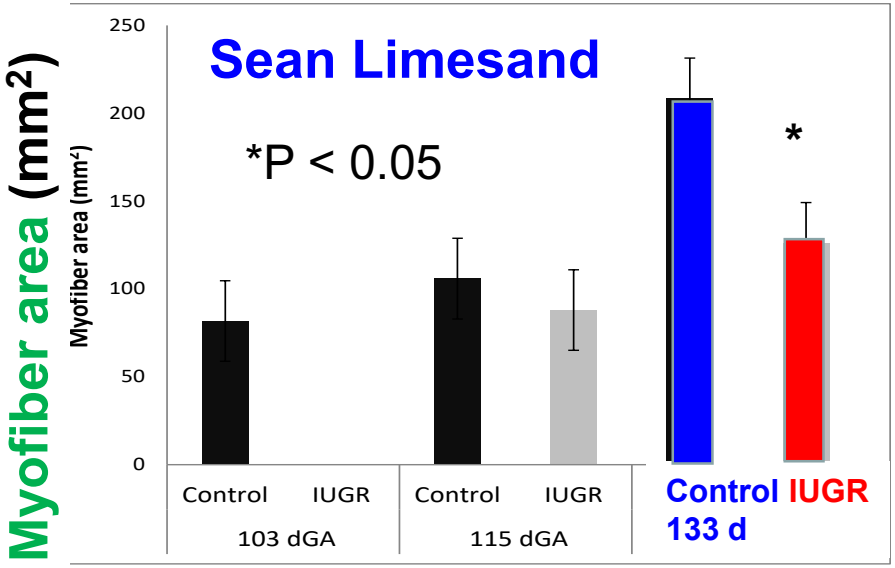


Fetuses with chronic IUGR show reduced P-ERK-1,2, mTOR, and eIF4E, plus an increase in total/phosphorylated binding protein, 4EBP-1-P, indicating decreased capacity for synthesis of amino acids into protein and IGF-1 stimulated cell proliferation. A result? A potential cause? Or both?

Courtesy of Jed Friedman, PhD, University of Colorado School of Medicine, Aurora, CO.

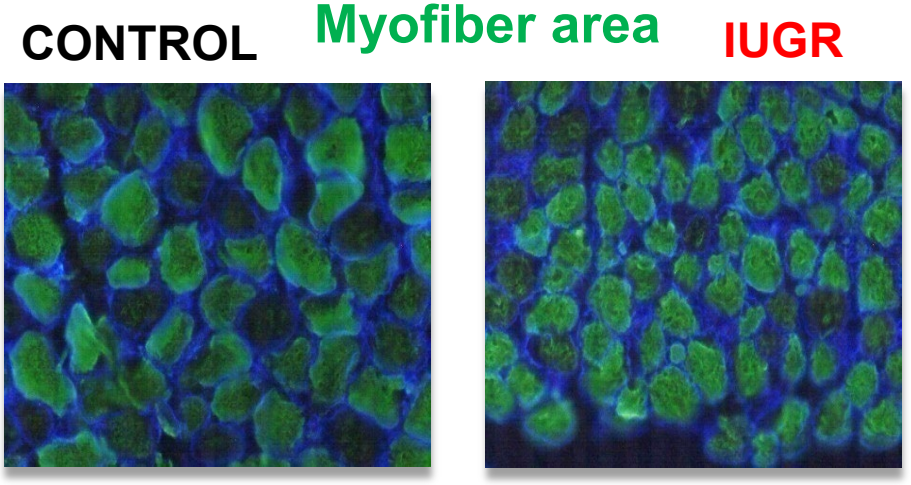
Decreased fetal muscle mass in Placental Insufficiency IUGR model



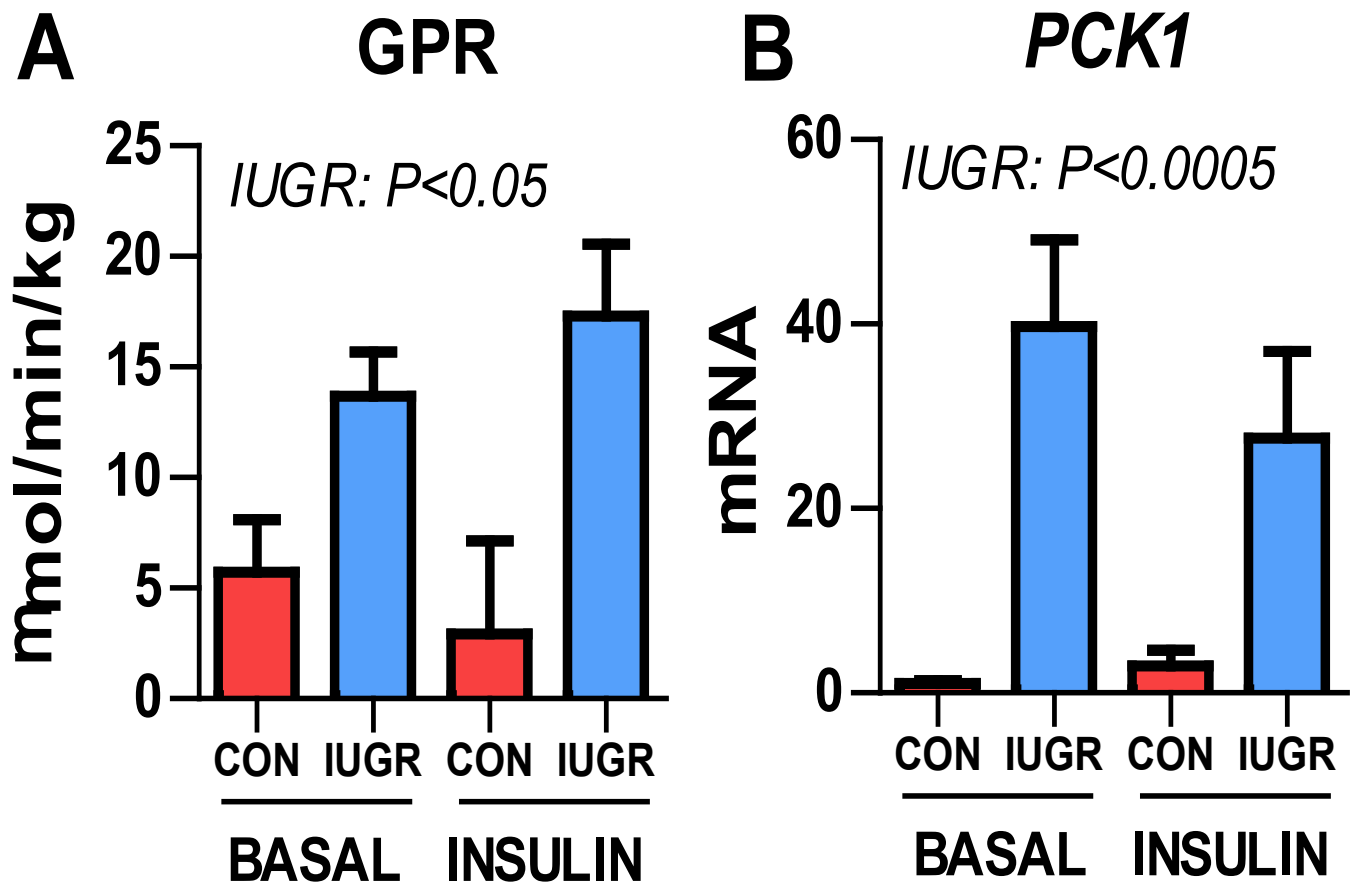


Chronically restricted fetal AA supply, energy, insulin, and IGFs in IUGR fetuses (*and preterm infants*) decreases muscle growth (mass and myofiber area).

Mechanisms?



Chronic placental insufficiency induced IUGR leads to hepatic insulin resistance and development of persistent glucose production.



Hepatic insulin resistance in PI-IUGR fetal sheep. (A) *In vivo* glucose production rates and (B) liver *PCK1* mRNA are increased in PI-IUGR fetuses (basal) and not suppressed in insulin-clamp (n=6-8 each).

Courtesy Stephanie Wesolowski, PhD, University of Colorado, Denver, CO.

Mixed Hyper- and Hypo-glycemia in IUGR infants. More complicated than what you thought!

(*a clinical problem explained by basic science research*)

1. **Hyperglycemia**

- Reduced pancreatic β-cell number and insulin production.
- Hypoxia and catecholamine suppression of insulin secretion and insulin action.
- Hepatic insulin resistance (hypoxia and high catecholamines) and increased glucose production (increased cortisol).

2. **Hypoglycemia**

- Greater head/brain to body/liver ratio, thus greater body weight-specific glucose utilization rate.
- Increased peripheral tissue glucose uptake capacity, from increased or at least maintained glucose transporters.
- Increased fractional insulin secretion (particularly after reduction in catecholamine concentrations) and greater susceptibility to metabolic stimulation of insulin secretion.

Other mixed outcomes

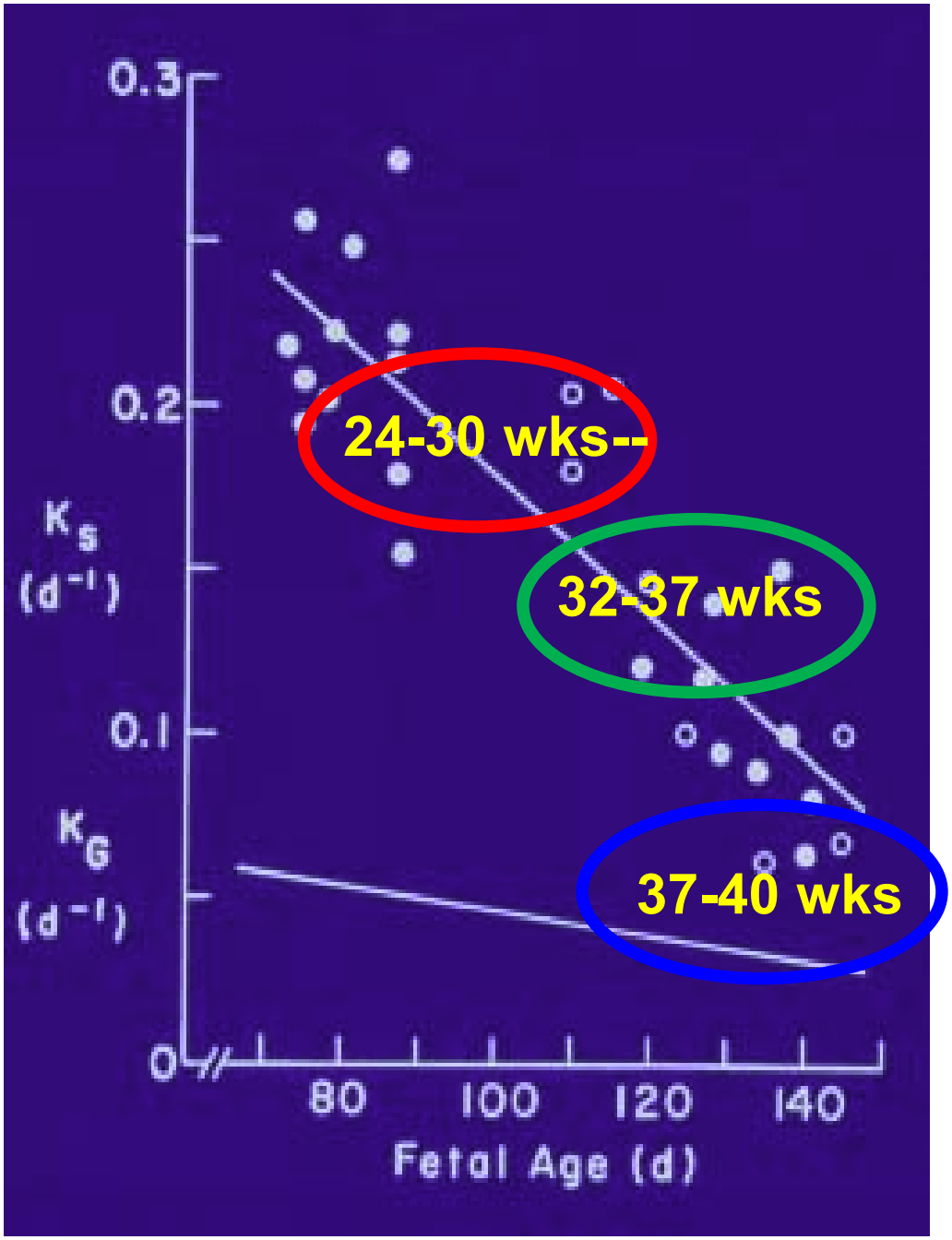
Catch-up Growth in Exclusively Breast Fed SGA Infants

- Growth occurs in sequence
- Normalization of lean mass occurs by 4 months of age
- Normalization of bone mineral content occurs by 12 months
- Fat mass still reduced at 12 months of age

Catch-up Growth in Formula Fed SGA Infants

- **Early catch up of fat mass**, and then production of **obesity**
- Associated with **elevated levels of IGF-1** and **low levels of adiponectin** (adipocyte-secreted hormone that enhances insulin sensitivity and glucose metabolism), **risk** factors **for later development of obesity and insulin resistance.**

de Zegher F, et al.*J Clin Endocrinol Metab*. 2013.



"Normal" fetuses and preterm infants of the same gestational age need more protein to grow. The key is the right amount at the right time!

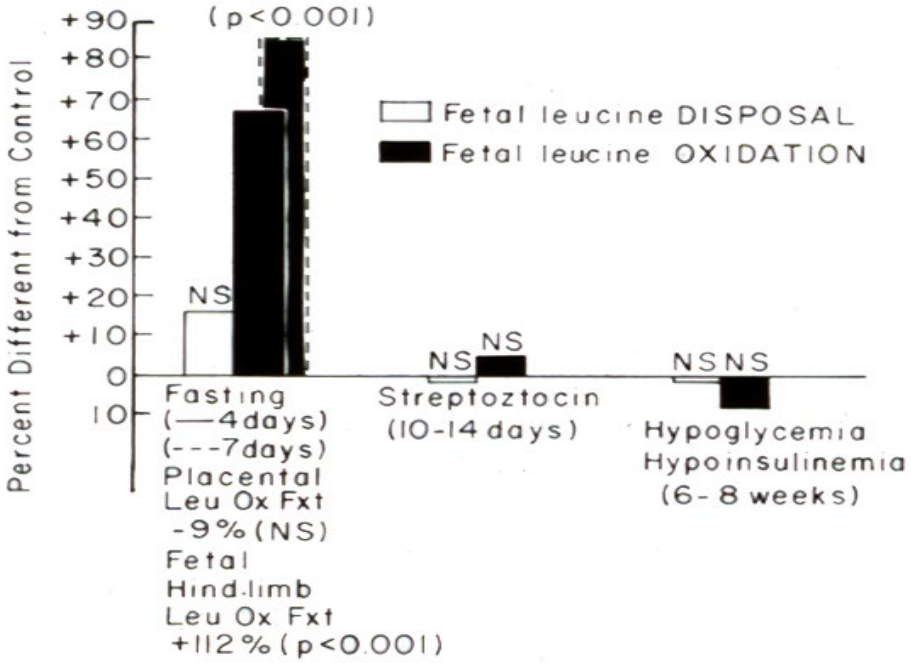
Between 24 and 30 weeks, amino acid requirements = 3.6-4.8 g/day.

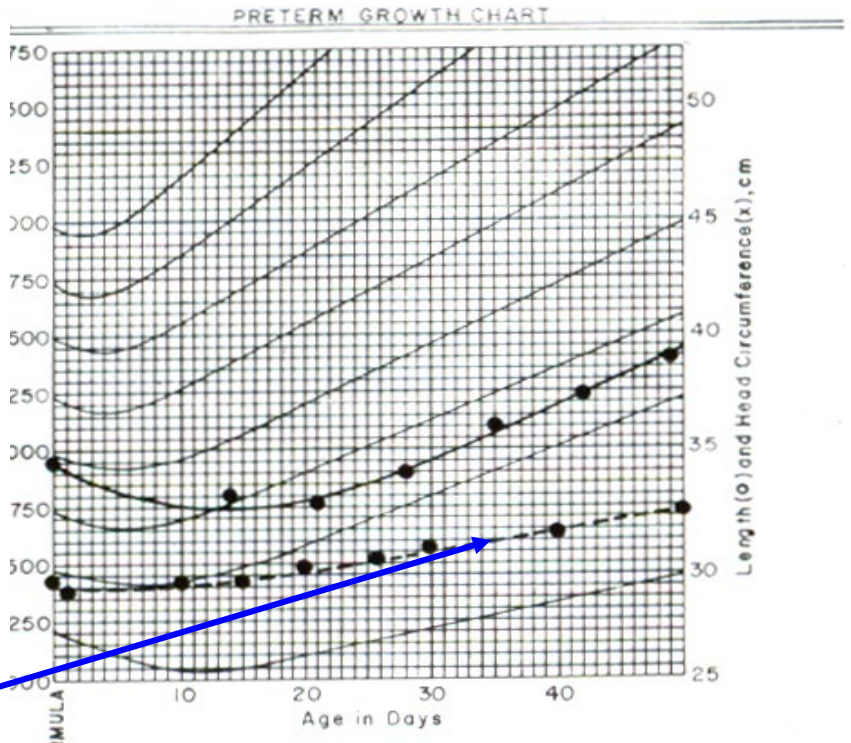
Between 32 and 37 weeks, fractional growth rate decreases, as does the protein requirement for growth, to *2.5-3.5 g/kg/day*.

At term, protein requirements decrease to those of the normal breast fed infant, or 1.5-2.0 g/kg/day.

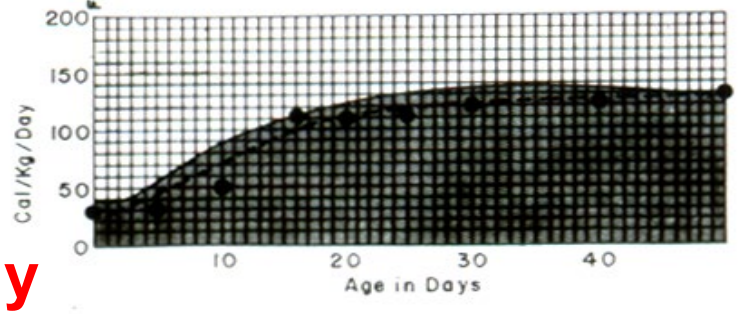
Hay Jr WW, et al. Fetal requirements and placental transfer of nitrogenous compounds. In: Polin RA, Fox WW, Abman SH, eds. *Fetal and Neonatal Physiology*. 4th ed. Philadelphia, PA: Saunders; 2011:585-614.

Caution—Long-term adaptation to energy and protein deficiency in IUGR fetuses.





Reduced rate of growth,
but return to normal cellular energy/oxidative metabolism.



Higher protein diets in chronically IUGR infants might not work as well.

Promotion of faster weight gain in infants born SGA: Is there and adverse effect on later blood pressure?

- Infants e37weeks gestation from 5 hospitals in the UK
- Birth weight <10 percentile
- Randomized: standard infant formula (n=147; n=83 age 6-8 years) or nutrient enriched formula until 9 months of age (n=152;n=70 age 6-8)

	Standard (n=83)	Nutrient Enriched (n=70)	P value
Diastolic	61.3	64.8	**0.01**
MAP	76.9	79.9	**0.03**
Systolic	100.5	102.5	0.2

Adjusted for age, sex, socioeconomic status, z score for weight and height

- Faster early weight gain programmed higher later blood pressure in both groups of SGA infants.

Singhal A, et al. *Circulation.* 2007;115:213-220.

Given the growth restriction phenotype, growth restriction appears to be a "set up".

Adaptations to under nutrition, when presented with different later life conditions (eg, high calorie diet, limited exercise), lead to several specific adult disorders—

- **Decreased pancreatic growth, development, and insulin secretion**
  Type 2 Diabetes
- **Increased insulin and glucose sensitivity for glucose uptake**
  Obesity
- **Decreased amino acid synthesis into protein and for cell growth**
  Short stature, poor neurodevelopment and cognitive capacity
- **Development of hepatic insulin resistance and glucose production**
  Hyperglycemia, Type 2 diabetes
- **Increased development of later obesity**
  Inflammation, cardiovascular disease (hypertension, stroke, MIs)

Later life metabolic and nutritional problems of the IUGR infant

Developmental programming of excess fat production, aggravated by fat/high glycemic index diets to develop—

- more obesity
- insulin resistance
- glucose intolerance
- type 2 diabetes
- systemic inflammation
- cardiovascular disease

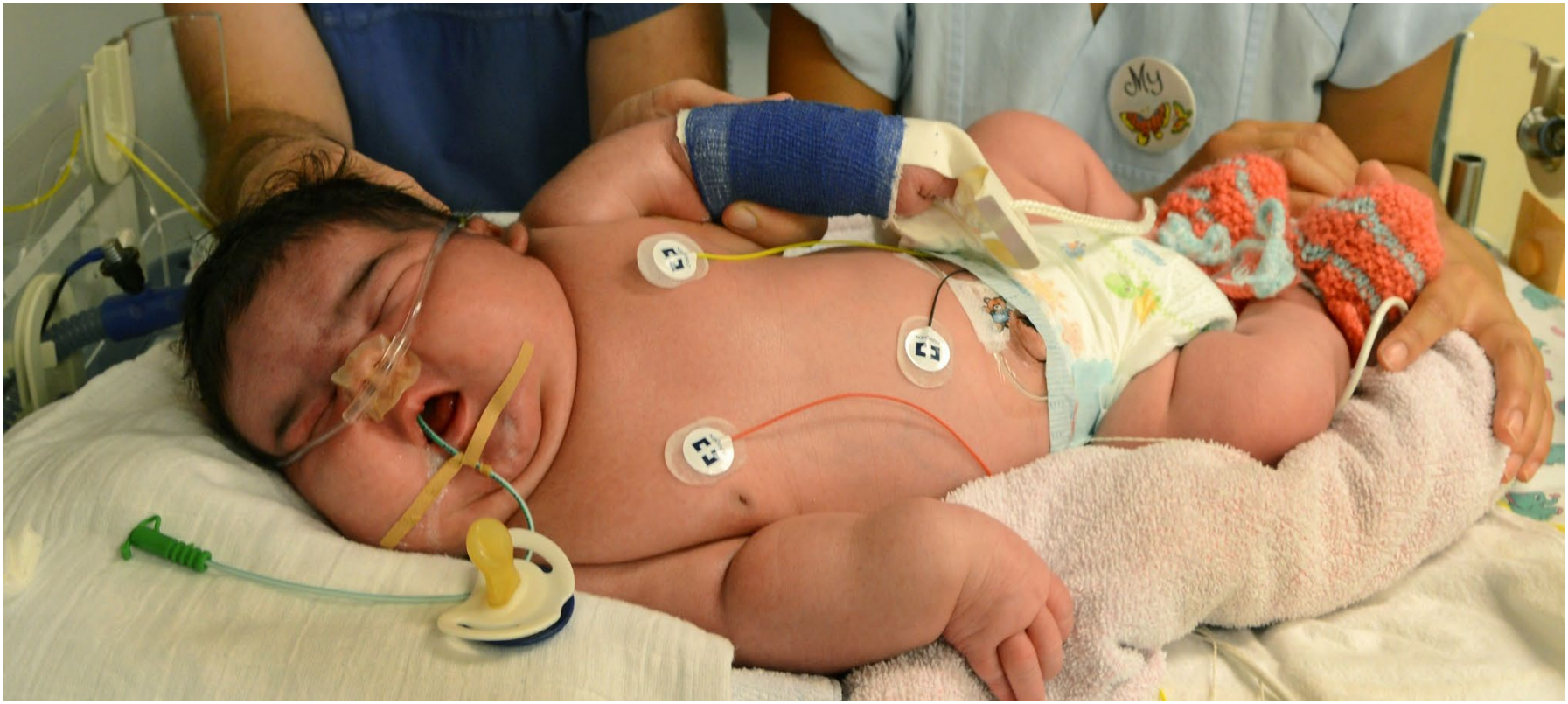
Metabolic Syndrome

Over Nutrition

LGA-MACROSOMIC INFANTS

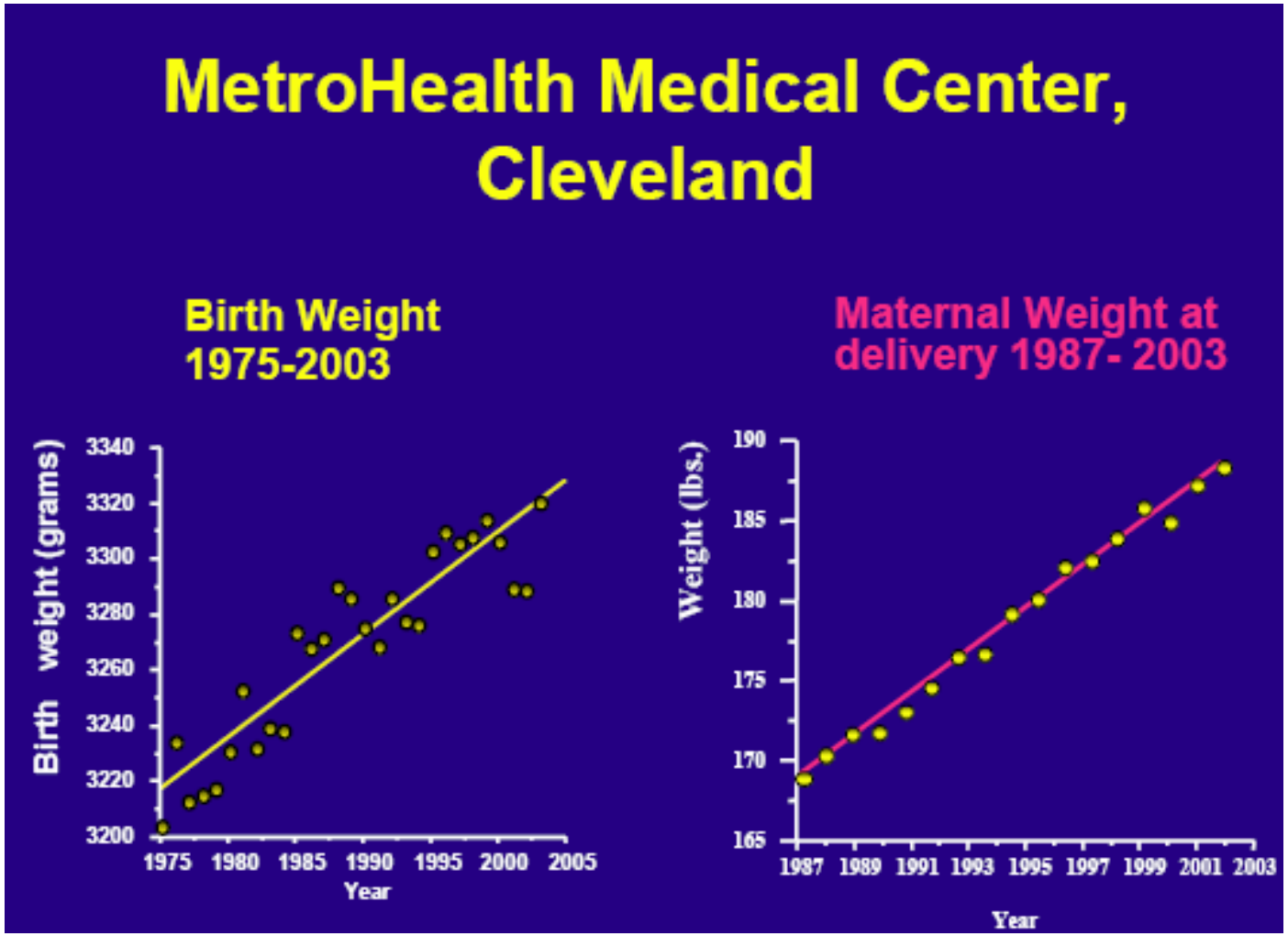
and consequences of trying to feed them more.

First off, they don’t look like they need more food.



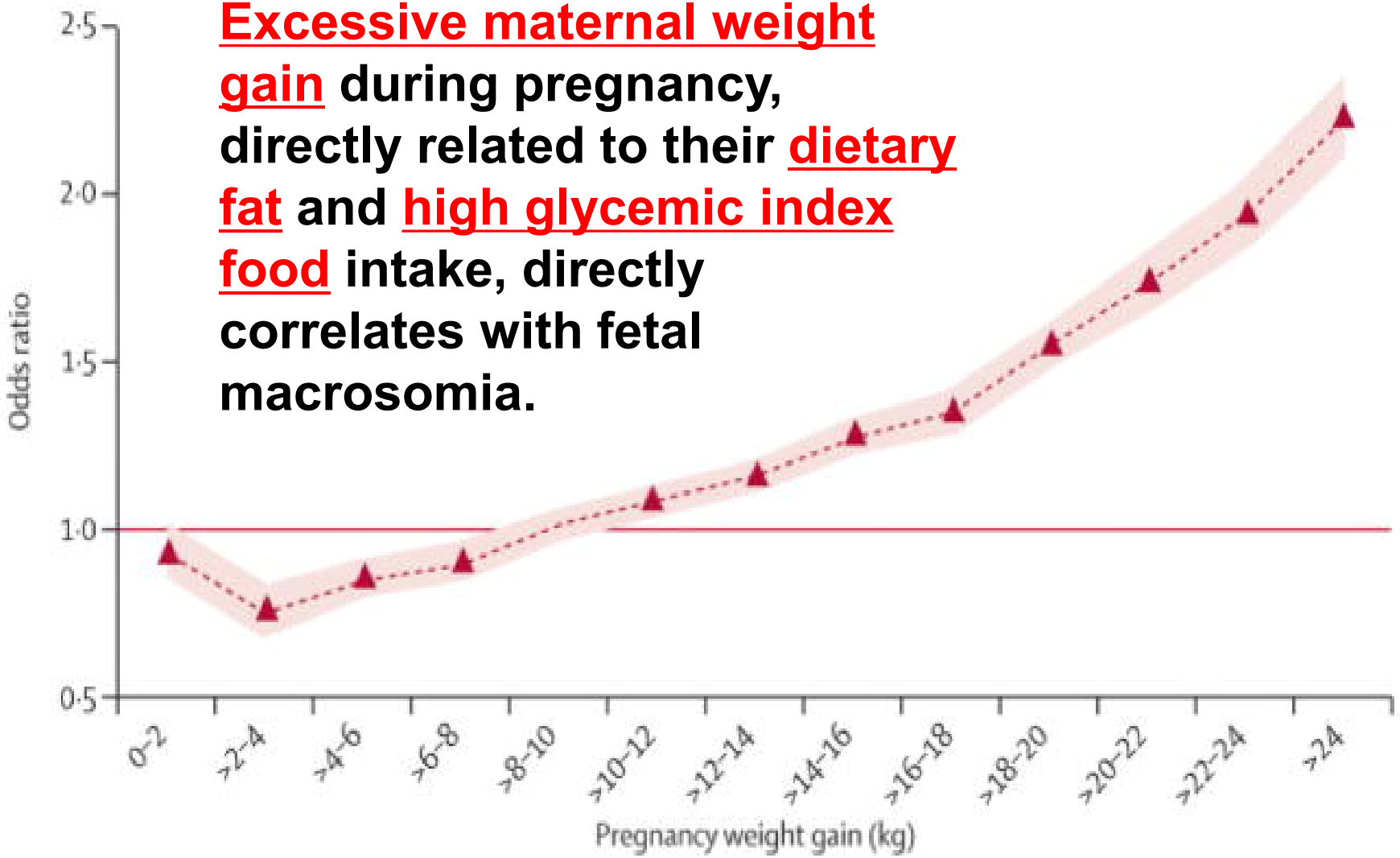
Waltraud Grubitzsch/picture-alliance/dpa/AP Images

And not just IDMs—many infants are fatter and fatter these days as maternal obesity grows and grows.



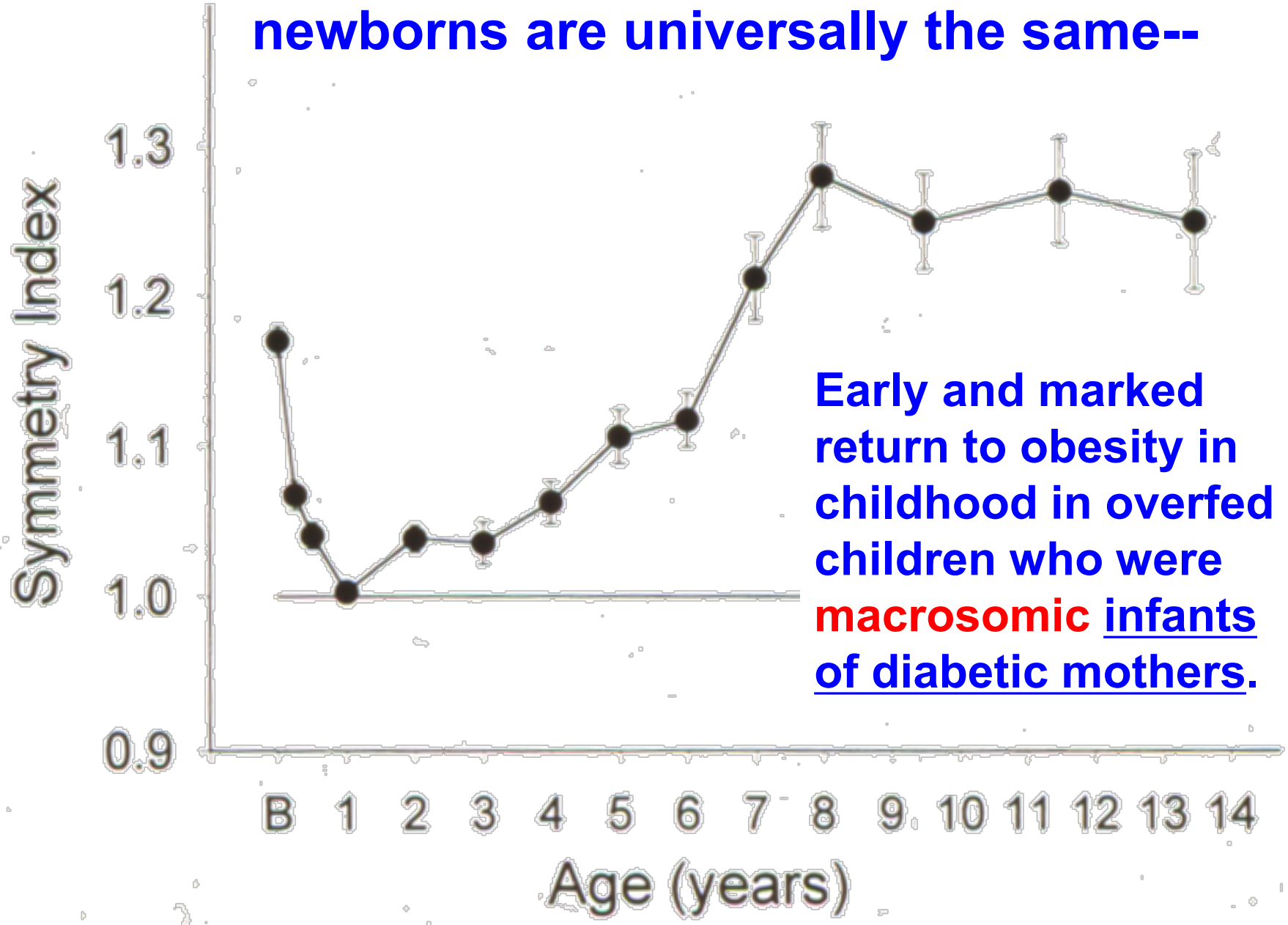
Courtesy Patrick Catalano, MD, The MetroHealth System, Cleveland, OH

Excessive maternal weight gain during pregnancy, directly related to their dietary fat and high glycemic index food intake, directly correlates with fetal macrosomia.



Odds Ratio for High Birth Weight (> 4000 g).
(mean and 95% confidence intervals)

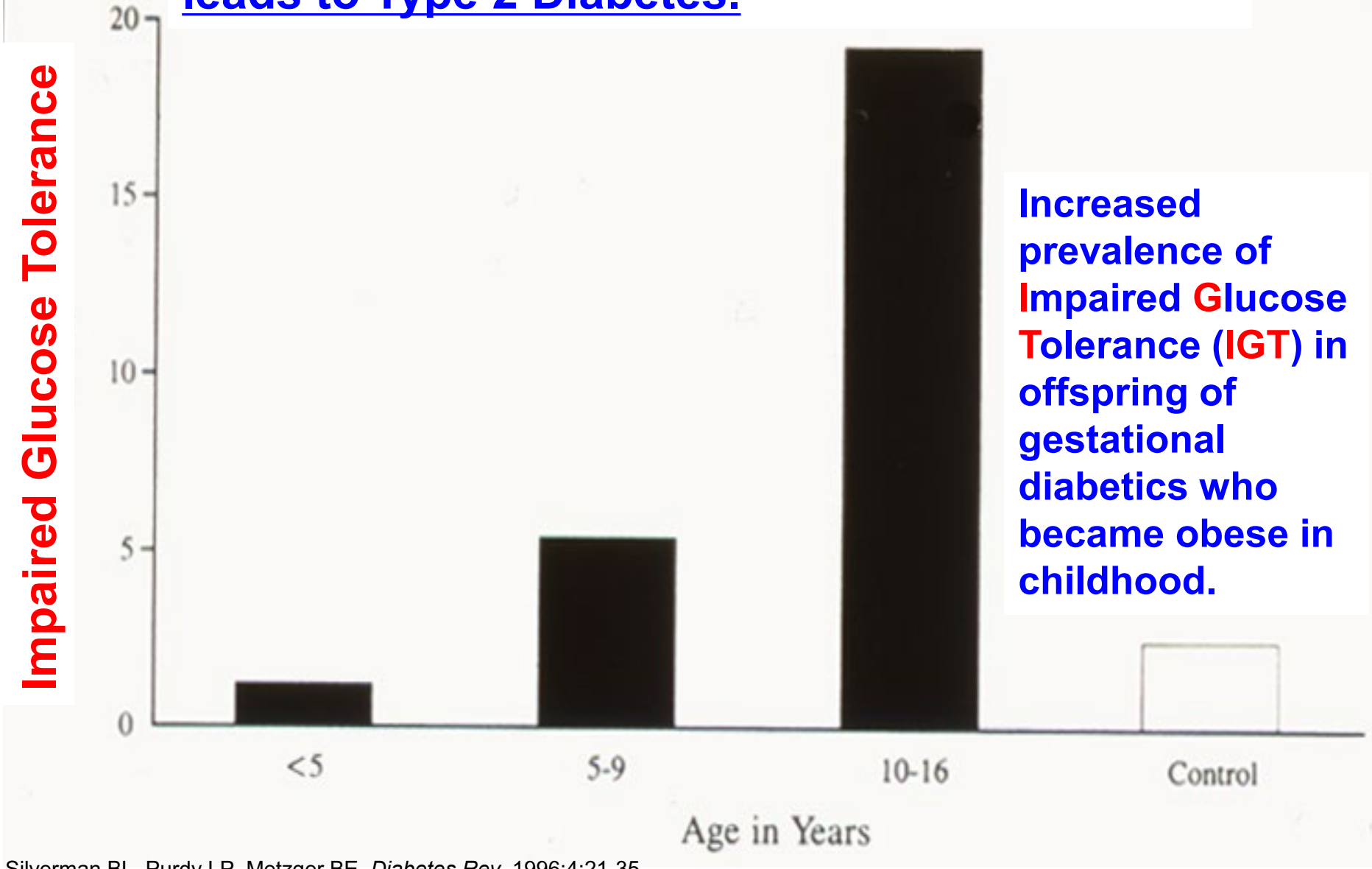
The consequences in LGA, Macrosomic newborns are universally the same--



Early and marked return to obesity in childhood in overfed children who were macrosomic infants of diabetic mothers.

Silverman BL, Purdy LP, Metzger BE. *Diabetes Rev.* 1996;4:21-35.

And the obesity that is produced and regenerated in macrosomic IDM offspring leads to Type 2 Diabetes.

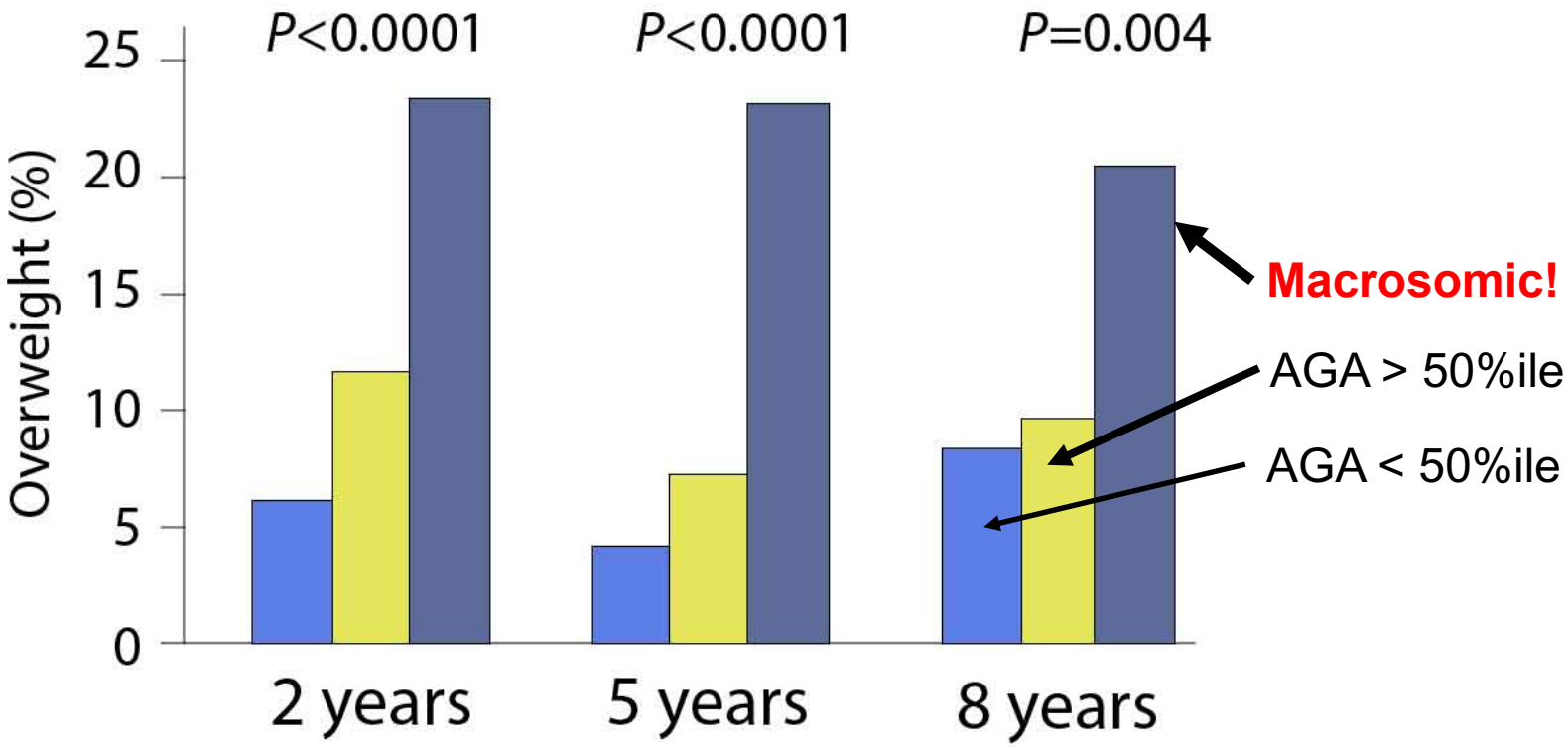


Increased prevalence of Impaired Glucose Tolerance (IGT) in offspring of gestational diabetics who became obese in childhood.

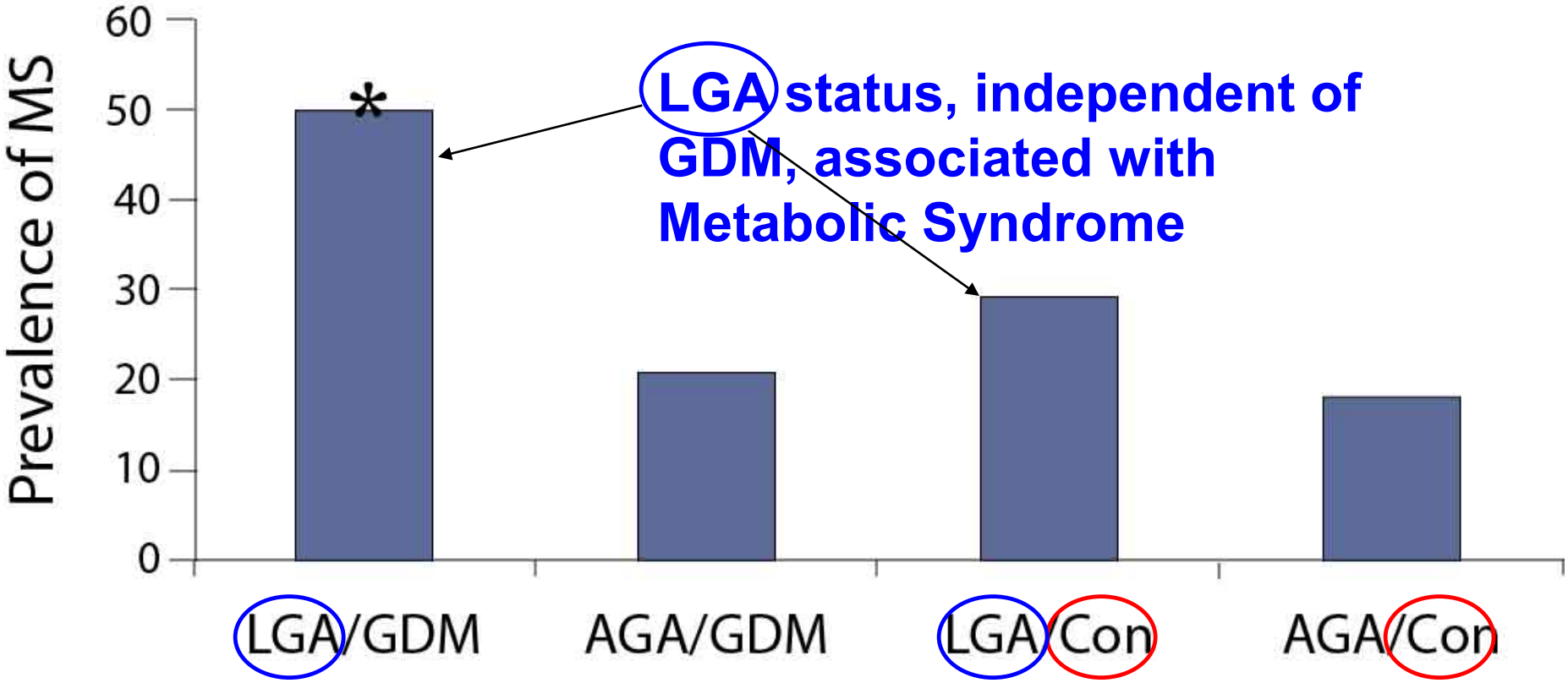
Silverman BL, Purdy LP, Metzger BE. *Diabetes Rev.* 1996;4:21-35.

And not just in IDMs

Prevalence of overweight at 2, 5, and 8 years of age in children in relation to birth size (**non-IDMs**)



Prevalence of METABOLIC SYNDROME at any age among children grouped according to birth weight and maternal diabetes.

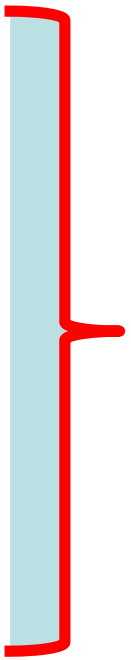


Adapted from Charlotte M. Boney et al. *Pediatrics.* 2005;115:e290-e296.

Metabolic and nutritional problems of the macrosomic infant

Already programmed with excess fat from maternal obesity and high fat/high glycemic index diet to further develop obesity and its consequences—

- more obesity
- insulin resistance
- glucose intolerance
- diabetes
- systemic inflammation
- cardiovascular disease



Metabolic Syndrome

What could we do to prevent such rapid gains in weight and the inevitable consequences?

Breastfeeding, considered dichotomously (yes or no), and the Odds Ratio for Later Obesity

- Obesity in the US affects 35%, of adults (~17% of youth aged 2-19).
- Women that were OW/OB prior to conception carried 60% of all US pregnancies (2013).
- Children born to obese mothers have increased likelihood of childhood obesity.
- **Exclusive breastfeeding is protective against elevated obesity risk.**

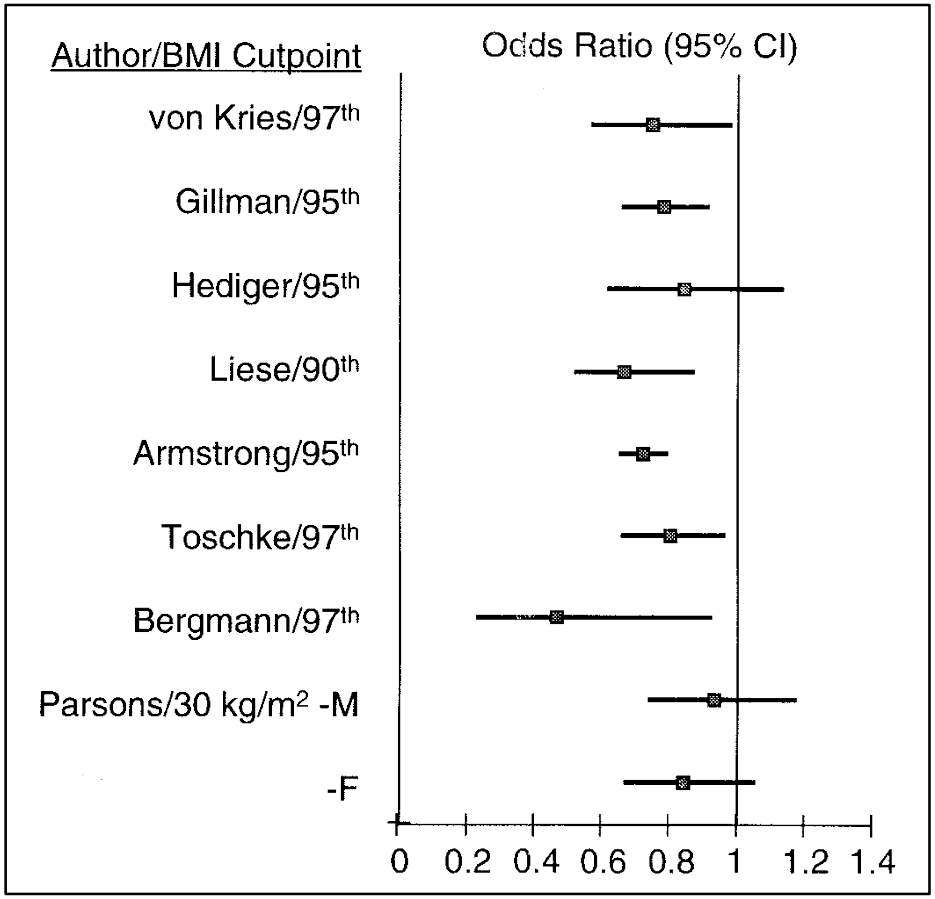
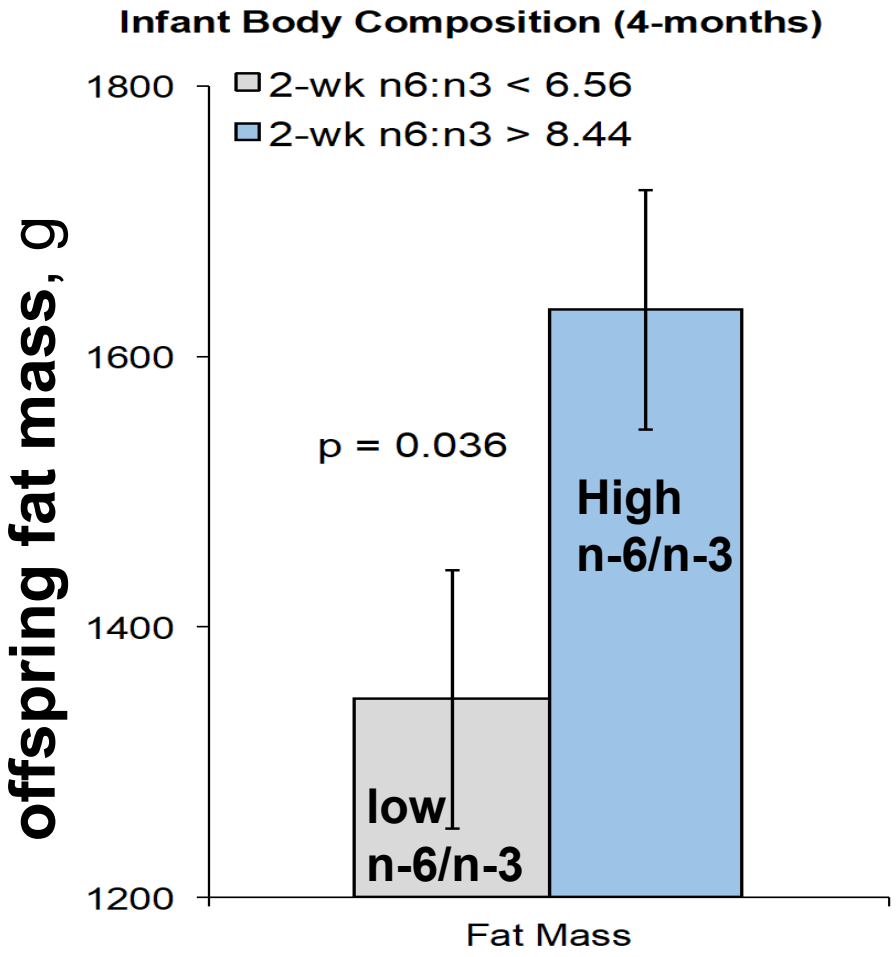
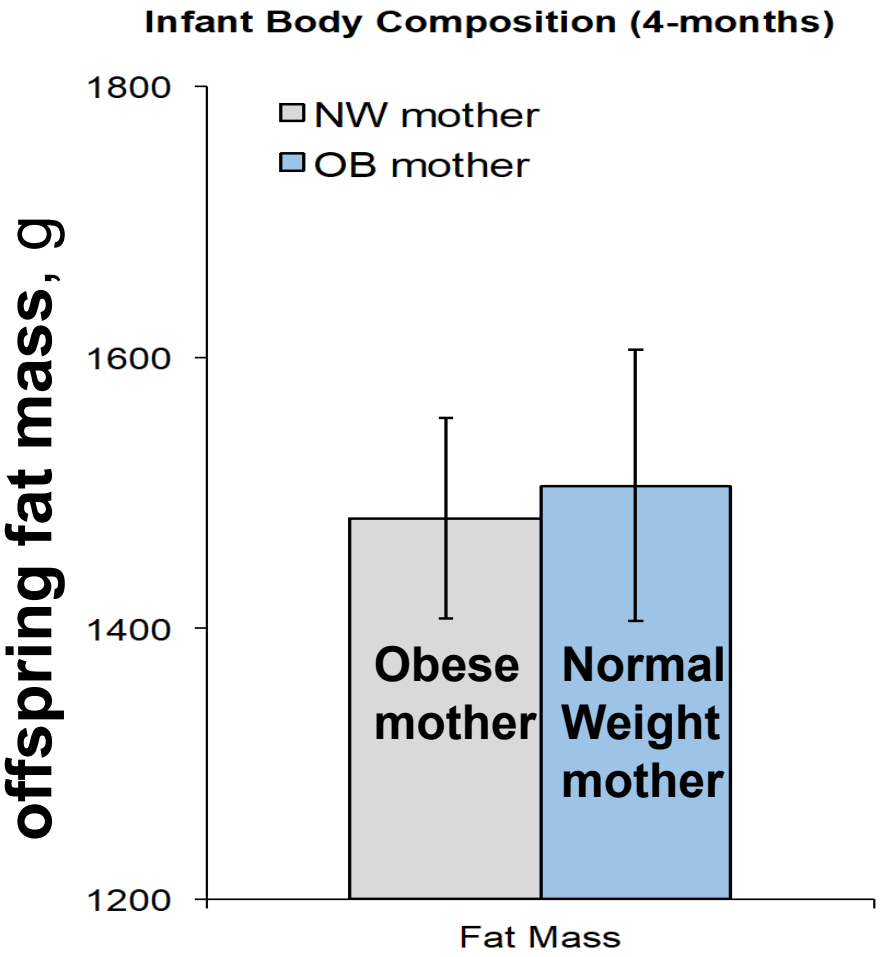


Fig 6. Breastfeeding, considered dichotomously (yes or no), and the OR for later obesity.

But—milk has to be "healthy" too.

Possible that the **milk n-6/n-3 ratio** is more important than maternal BMI and fat gain in producing offspring fat mass?



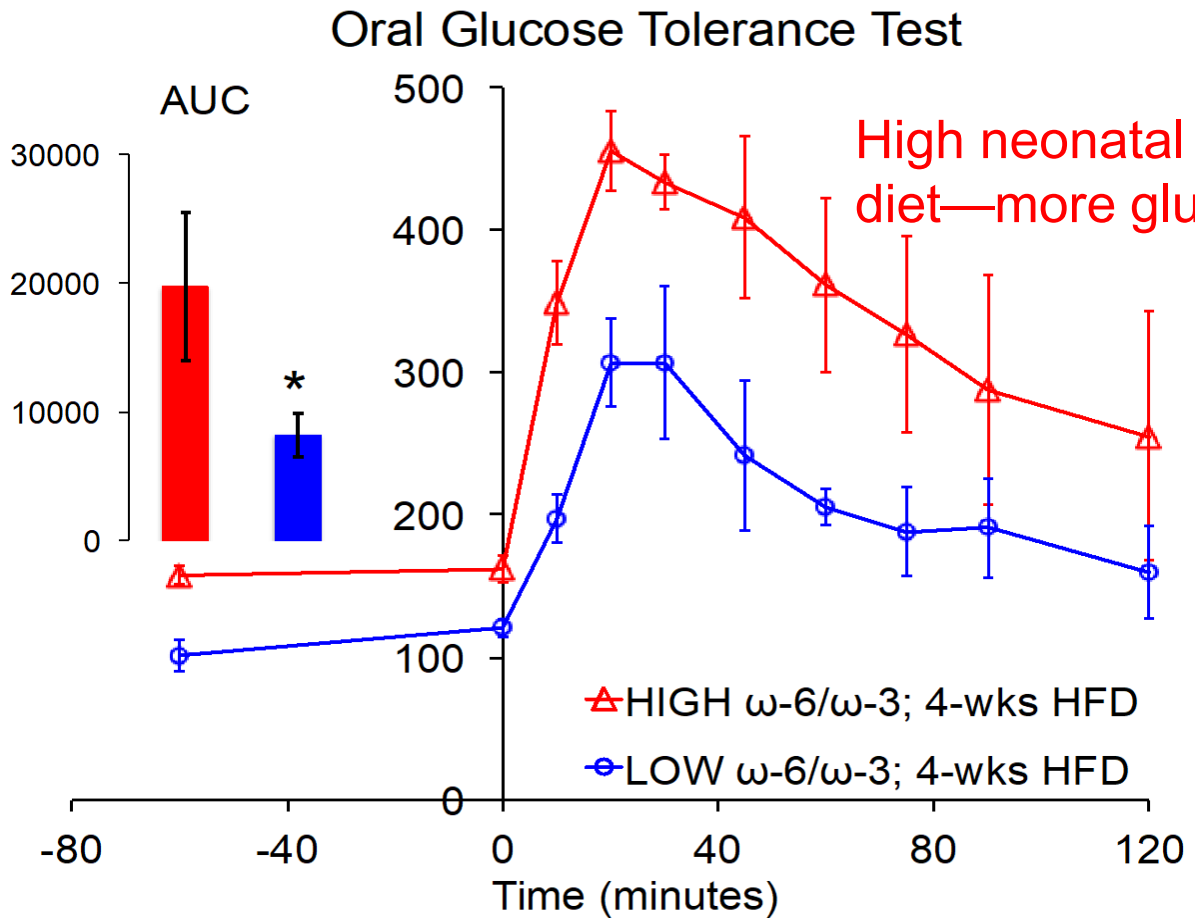


➢ **Each 1-unit increase n-6/n-3 = 0.6–1.4 g fat mass/day.**

Young BE, et al. *Adv Nutr.* 2012;3:675-686. With permission.

The benefit might be very long lasting—

Adult **mice** who received a LOW n-6/n-3 fatty acid ratio diet as neonates had better glucose tolerance post 4-weeks of High Fat/High Sucrose diet: Eating well might be beneficial!

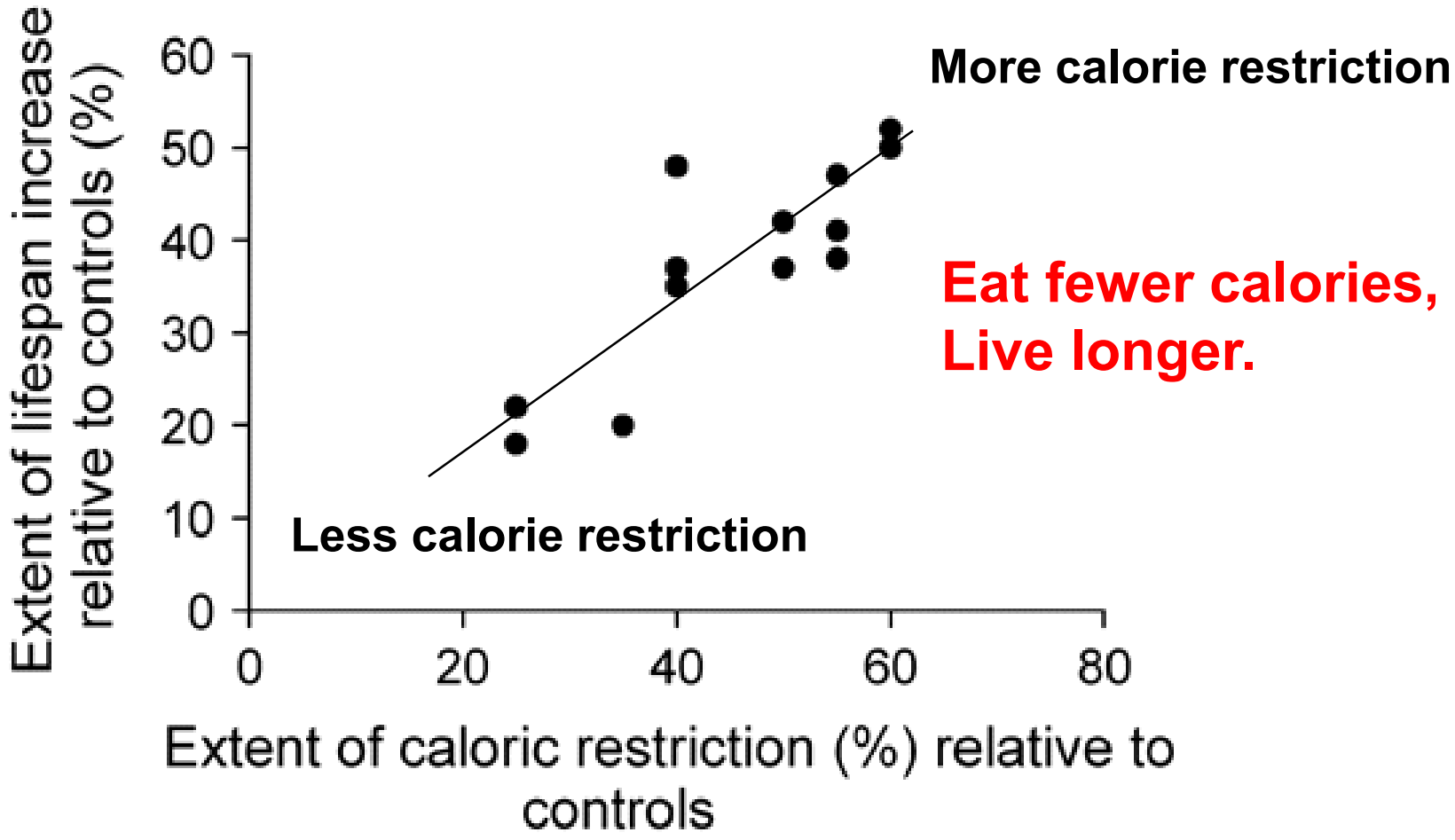


High neonatal n-6/n-3 fatty acid ratio diet—more glucose intolerant

Low neonatal n-6/n-3 fatty acid ratio diet—more glucose tolerant

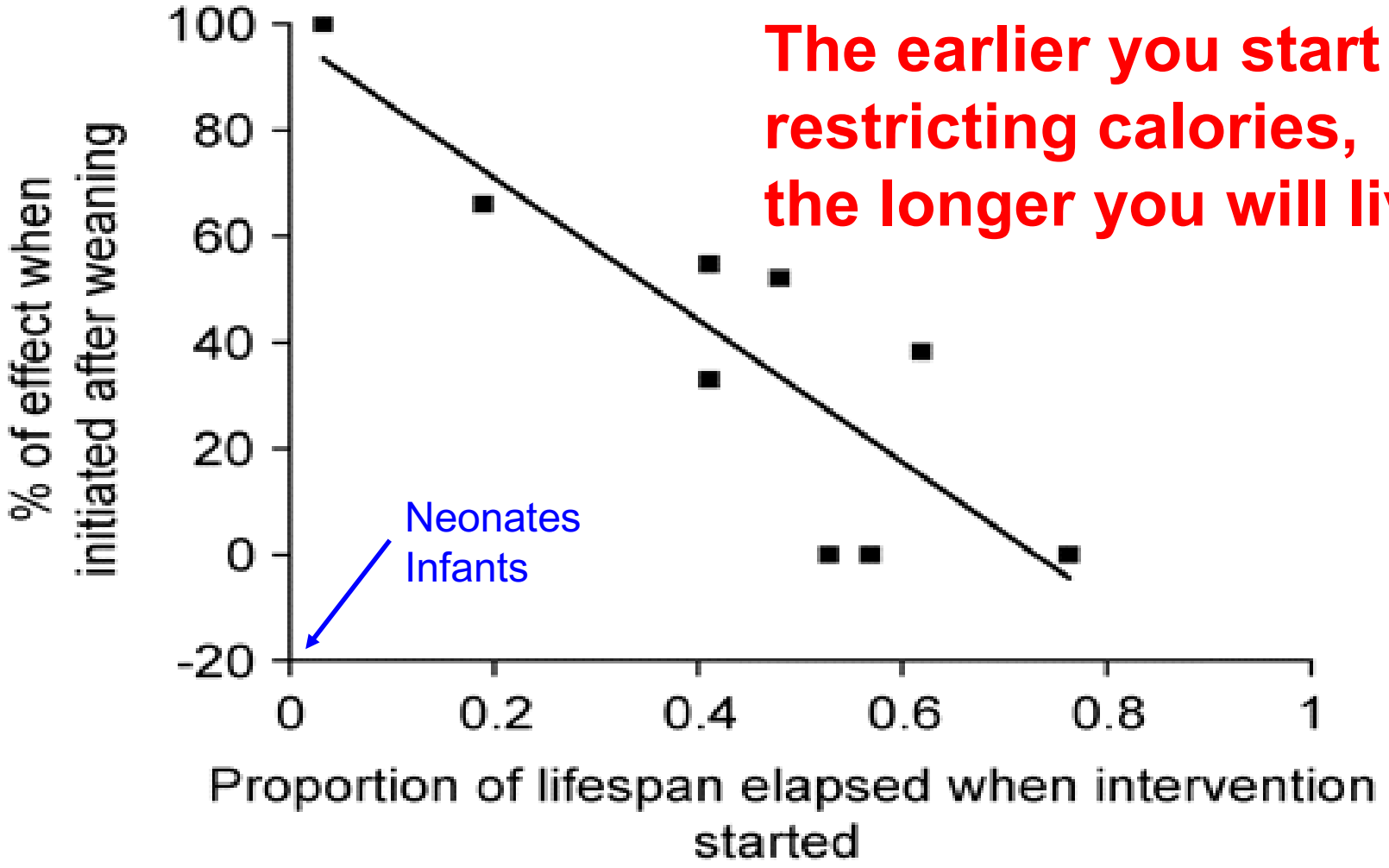
Unpublished data courtesy Michael Rudolph, PhD, University of Colorado School of Medicine, Denver, CO. 2015

The benefits of Calorie Restriction (*percentage increase in lifespan over controls*) in relation to the extent of restriction (*percentage decrease in intake relative to controls*); studies of both rats and mice.



Speakman JR, Hambly C. *J Nutr.* 137:1078-86, 2007. With permission.

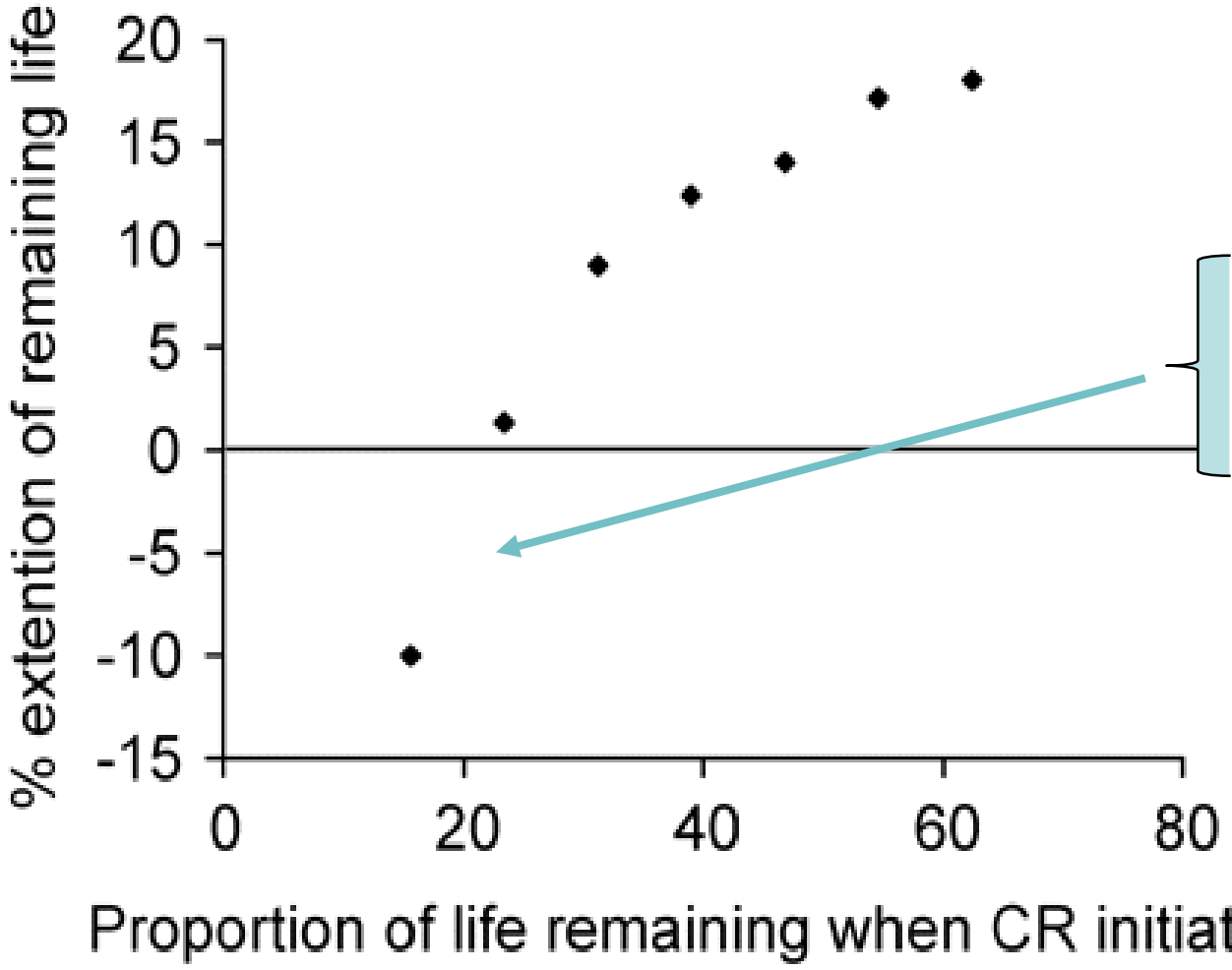
The effect of Calorie Restriction expressed relative to the same effect when initiated at weaning as a function of the proportion of expected lifespan that had elapsed when restriction was initiated. Several studies of rodents (mice and rats).



The earlier you start restricting calories, the longer you will live.

Speakman JR, Hambly C. *J Nutr.* 137:1078-86, 2007. With permission.

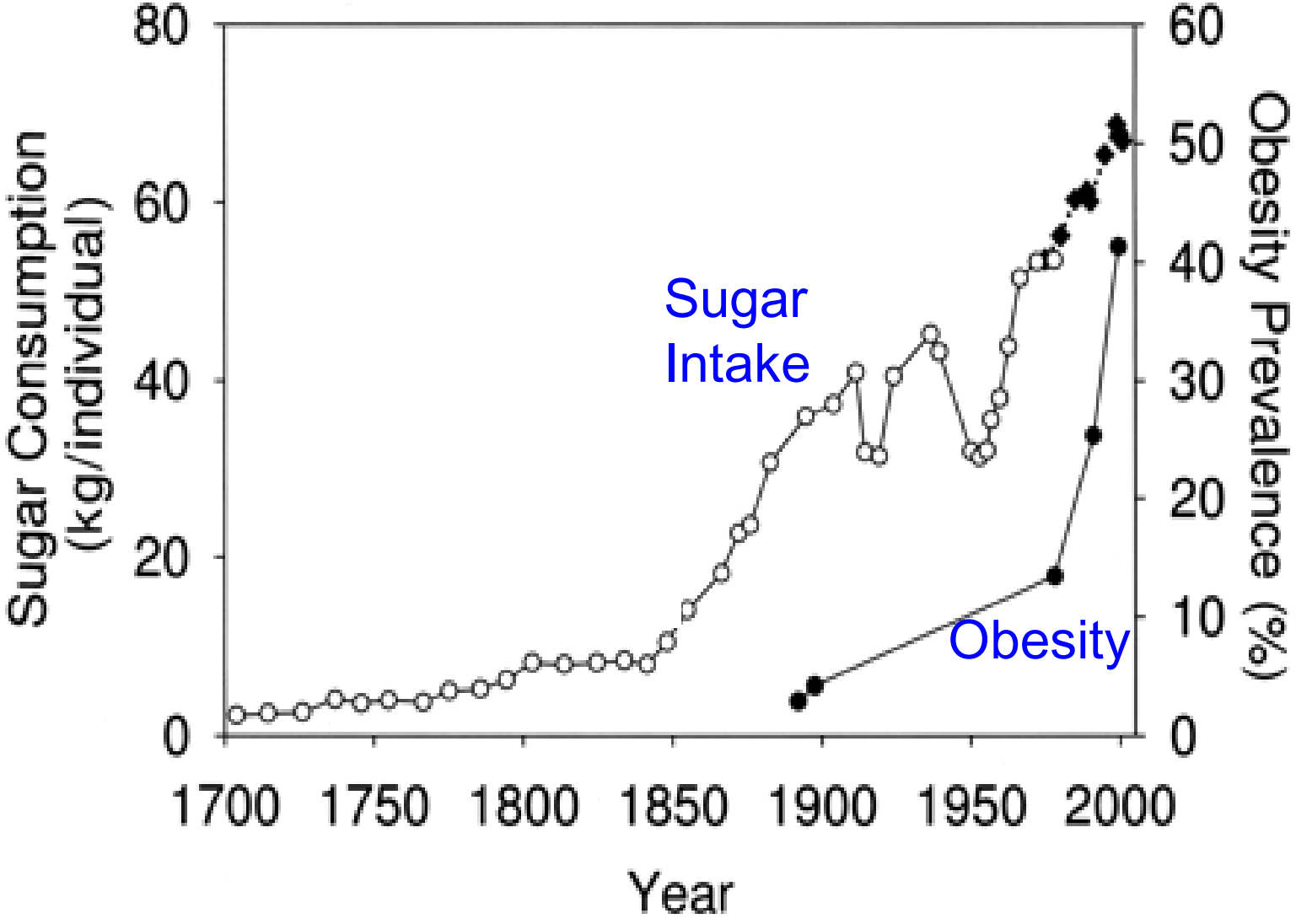
Modeled benefits of Calorie Restriction (*percentage extension of remaining life*) in relation to the proportion of expected life remaining when restriction was initiated. Even when expressed relative to the remaining lifespan, the benefits decline as age of onset increases.



If you're over 60, LIVE IT UP !! as there is little further increase in life span in response to calorie restriction.

Speakman JR, Hambly C. *J Nutr.* 137:1078-86, 2007. With permission.

Although maybe YOU should be careful of too much dessert.



Courtesy Richard Johnston, MD, PhD.

Summary

1. Growth patterns, from small to large, are a continuum, and represent more or less nutrition.

2. Nutrition does matter, and the mechanisms—programming via epigenetic phenomena in the context of developmental plasticity—are clearly well established and fundamental.

3. Over feeding energy for any infant (preterm, IUGR, SGA, LGA, IDM) has only produced more fat gain, which persists, contributing measurably to obesity and the metabolic syndrome in later life.

4. Individual fatty acids, particularly the n-3 long chain PUFAs, may be more important than the amount of lipid fed to infants.

5. While human milk appears to be best, mother has to eat well to optimize it. Healthy mothers produce healthy offspring!

6. Establish healthy eating early, continue it for life.

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- Paul Rozance, MD
- Laura Brown, MD
- Stephanie Wesolowski, PhD
- Patti Thureen, MD (deceased)
- Kendra Hendrickson, RD (UCH)
- Many wonderful fellows and lab personnel

Funding

- NICHD K12 and T32 training grants (Hay, PI and PD)
- NCATS CTSA (Hay, Director, Child and Maternal Health Pilot Grant Program and the Early Life Exposures Program)
- NIH grants for collaborators: K08/R01 (Rozance), K12/R01 (Brown), K01/R01 (Wesolowski)