Obesity and Diabetes in Pregnancy, Risks to Mother and Fetus

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MetroHealth Medical Center,
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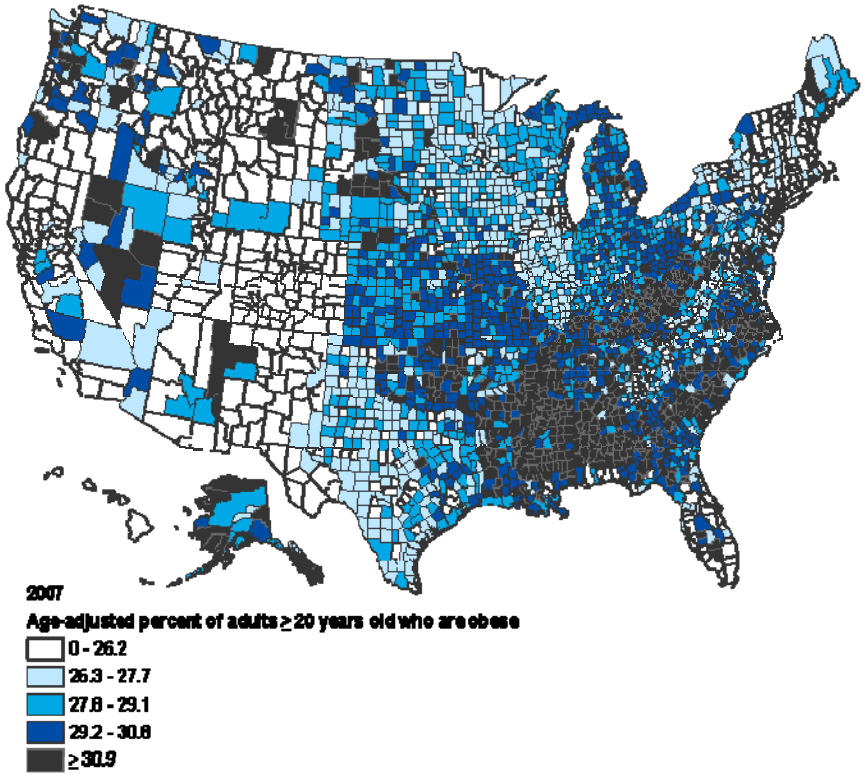
Adult obesity, 2007

0-26.2 >30.9

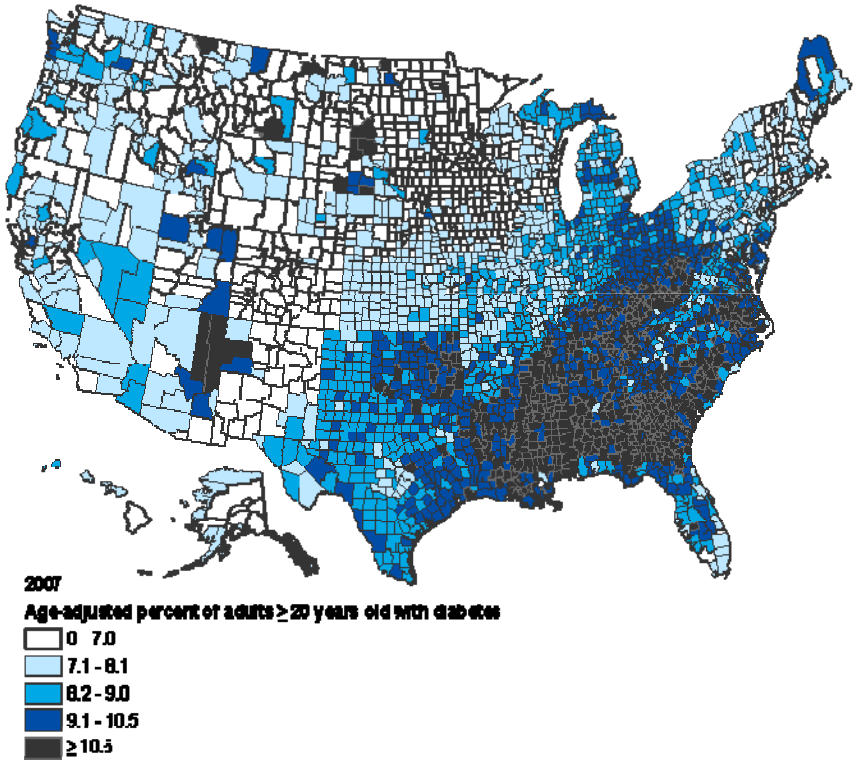
age-adjusted percent



Adult diabetes, 2007

0-7.0 >10.6

age-adjusted percent

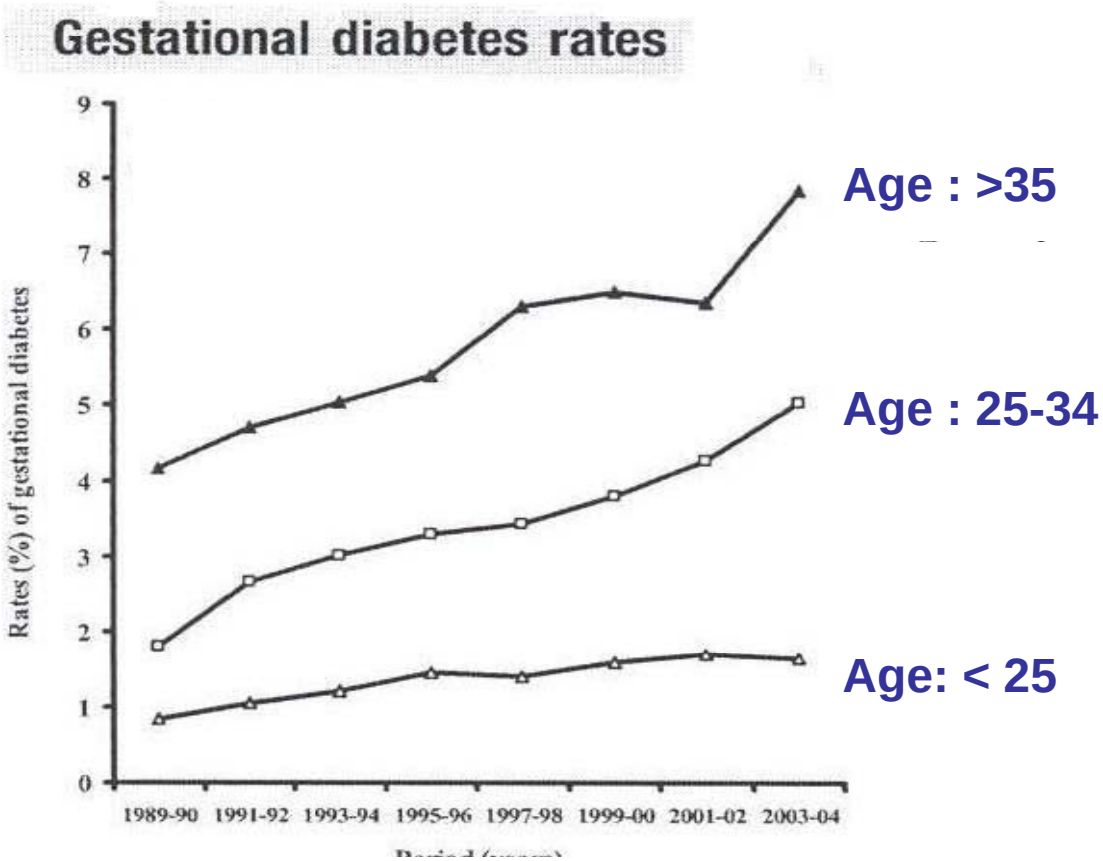


CDC's Division of Diabetes Translation. National Diabetes Surveillance System available at http://www.cdc.gov/diabetes/statistics

MMWR 58; 2009

DIABESITY

Trends in GDM in USA 1989-2004



Getahun; AJOG, 2008

IADPSG recommendations for the Diagnosis of GDM in Pregnancy

GDM = 1 or more values ≥ threshold			
Plasma Glucose	**mg/dl**	**mmol/l**	**≥ threshold (%)**
FPG	**92**	**5.1**	**8.3**
1-hr OGTT-PG	**180**	**10.0**	**14.0**
2-hr OGTT-PG	**153**	**8.5**	**16.1**

IADPSG, Diabetes Care 2010

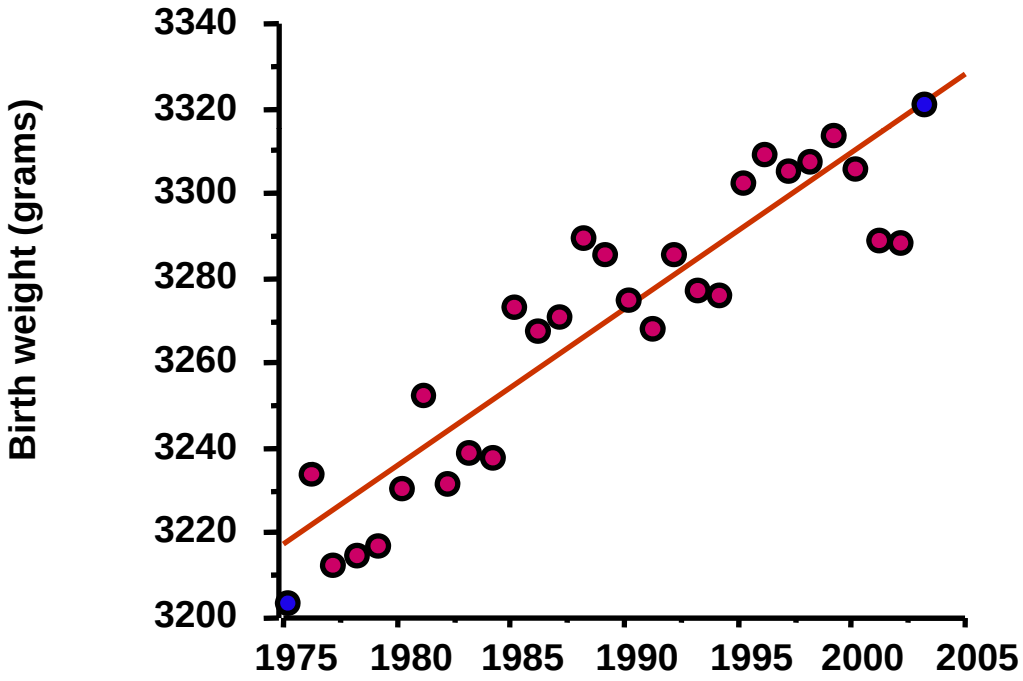
In utero Metabolic Programming of Obesity

Catalano; JCEM, 2003


OCTOBER 4, 2010
Environment Special:
The oceans—why 70%
of our planet is in danger
The Facebook Movie:
The secret history of
social networking
TIME
How the
first nine
months
shape
the rest
of your life
The new science
of fetal origins
BY ANNIE MURPHY PAUL
www.time.com

Increase in Term Birth Weight 1975-2005

MetroHealth (Cleveland, OH)



Catalano, Obstet Gynecol; 2007

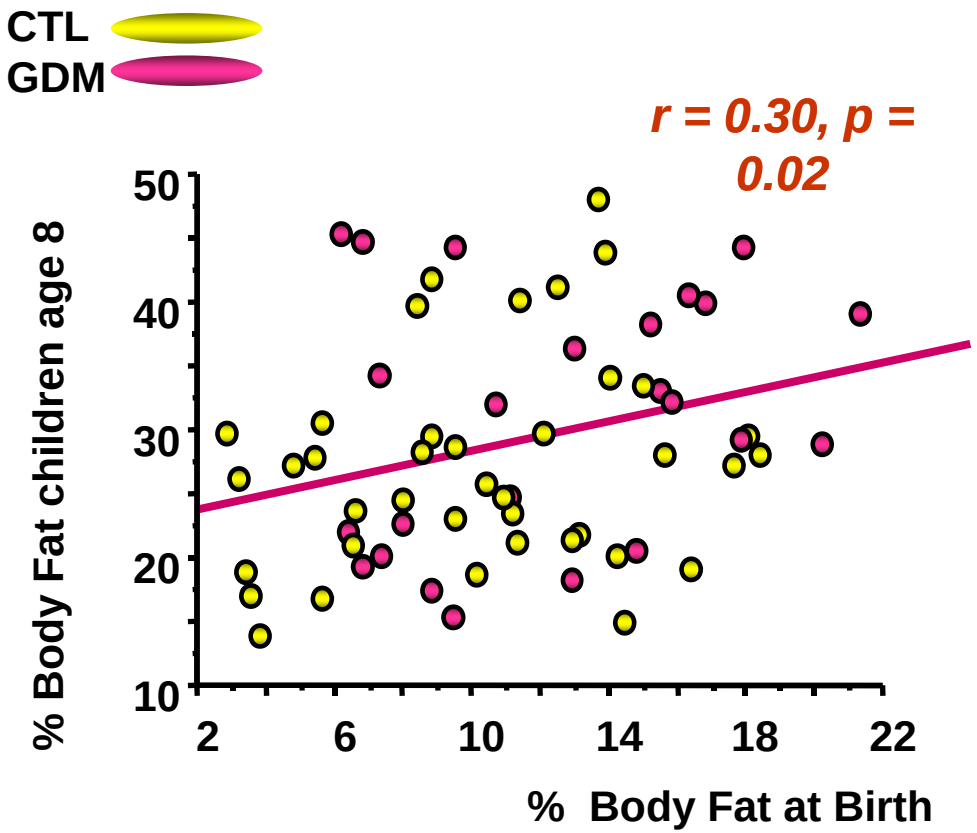
Body Composition in Neonates

	GDM (n = 195)	NGT (n = 220)	*p-value*
Birth Weight (g)	3398 ± 550	3337 ± 549	ns
Lean body mass (g)	2962 ± 405	2975 ± 408	ns
Fat mass (g)	436 ± 206	362 ± 198	0.0002
Body fat (%)	12.4 ± 4.6	10.4 ± 4.6	0.0001

	BMI < 25 (n = 144)	BMI > 25 (n = 76)	
Birth weight (g)	3284 ± 534	3436 ± 567	ns
Lean body mass (g)	2951 ± 406	3023 ± 410	ns
Fat Mass (g)	334 ± 179	416 ± 221	0.008
Body Fat (%)	9.7 ± 4.3	11.6 ± 4.7	0.006

Catalano, AJOG; 2003 Sewell, AJOG; 2006

Adiposity at Birth Predicts Adiposity in Children at Age 8



Catalano; AJCN, 2009

What are the Factors which Facilitate Fetal Fat Accretion ?

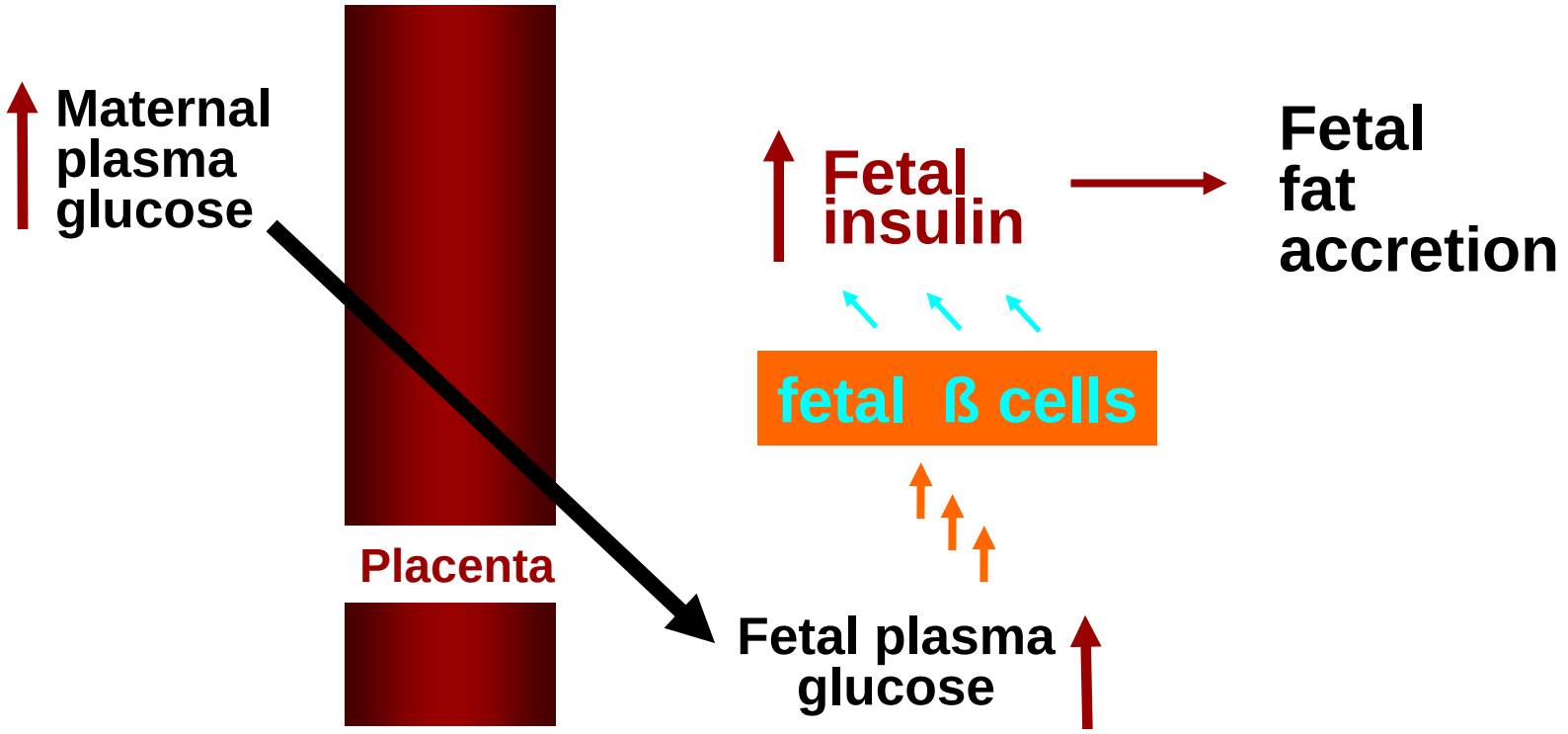
maternal glucose/insulin

maternal lipids

maternal cytokines

Diabetes - Induced Fetal Overgrowth: the Glucose-Insulin Hypothesis

Jorgen Pedersen, 1953



What are the Factors which Facilitate Fetal Fat Accretion ?

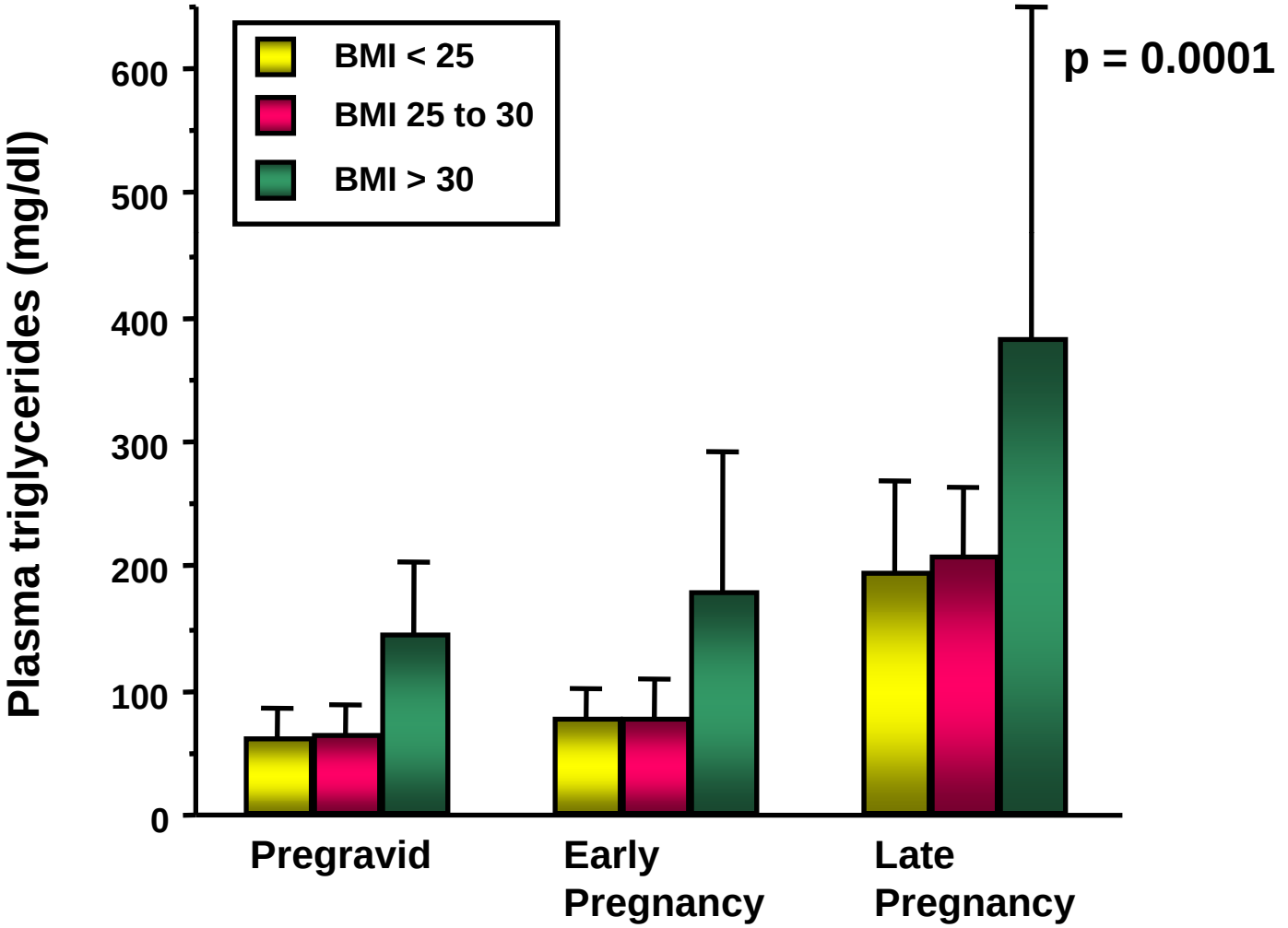
The changes in maternal environment progress from early pregnancy to the end of pregnancy modifying placental function

maternal insulin

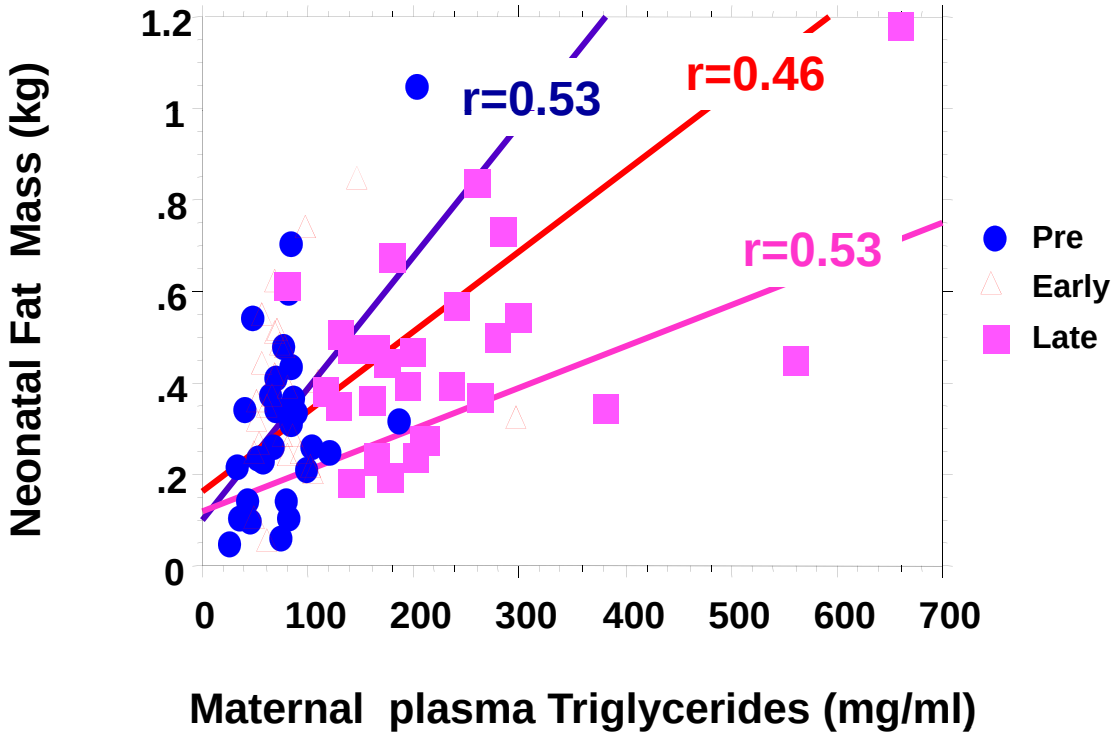
maternal lipids

maternal cytokines

Maternal Triglycerides in Obese



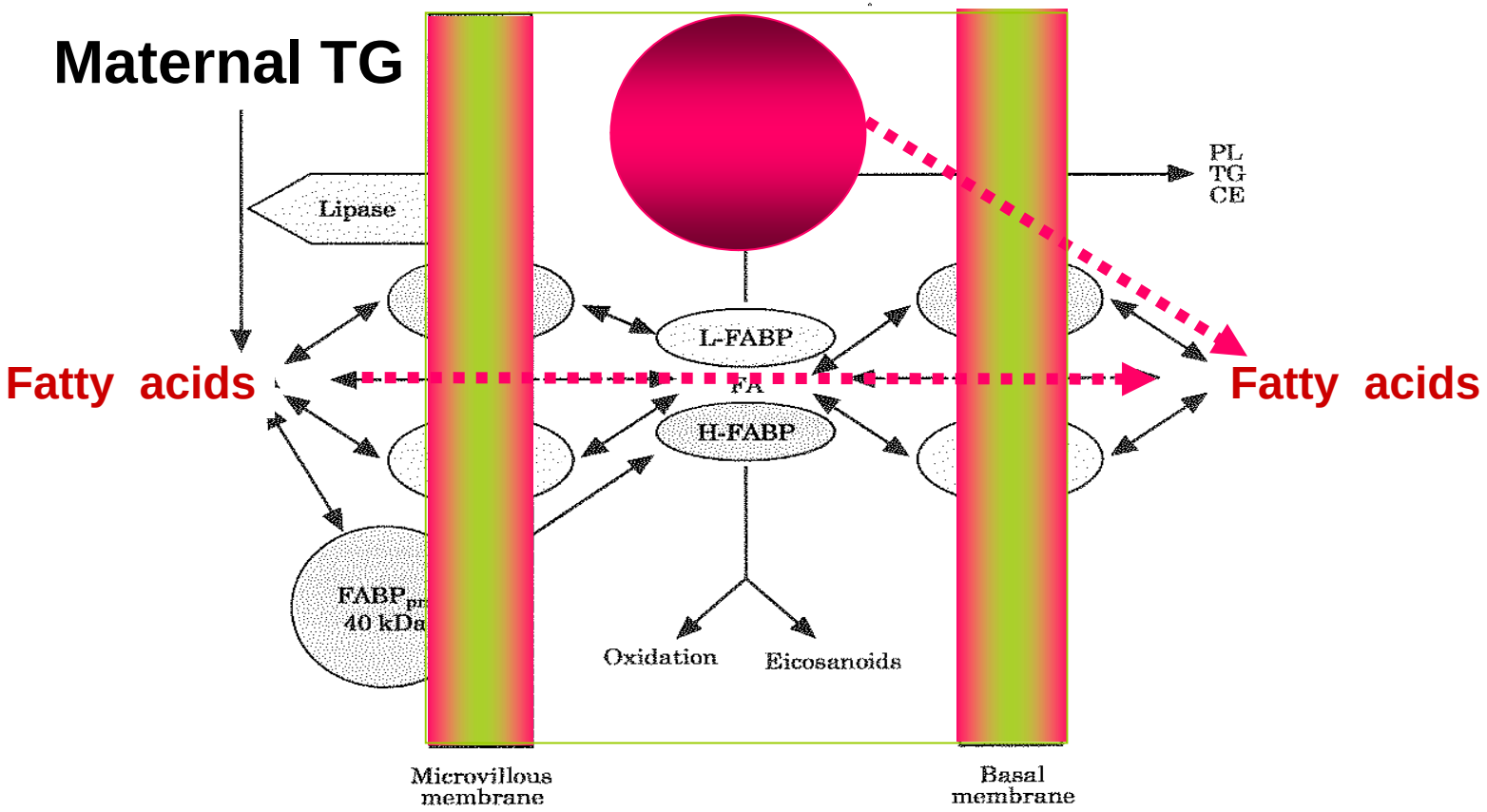
Neonatal Fat Mass and Maternal Triglycerides



Catalano et al. unpublished

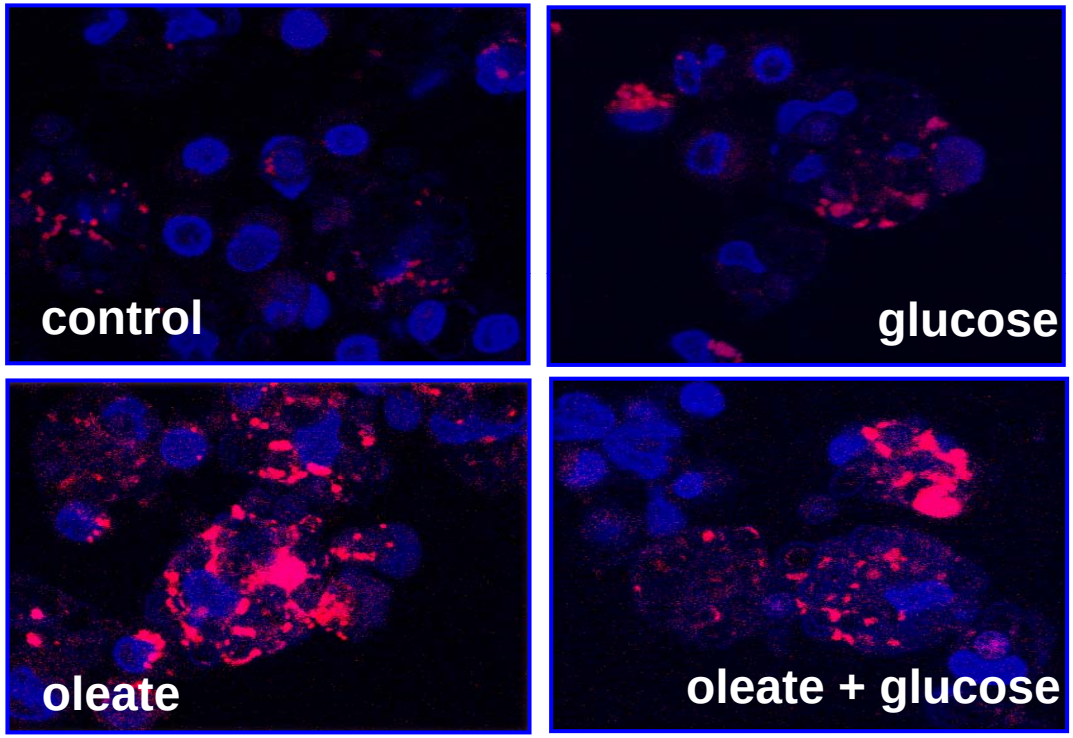
Placental Pathways for Lipid Transfer

S30



Haggarty, *Trophoblast Research,2002*

Substrates for Lipid Synthesis in Primary Trophoblast Cells

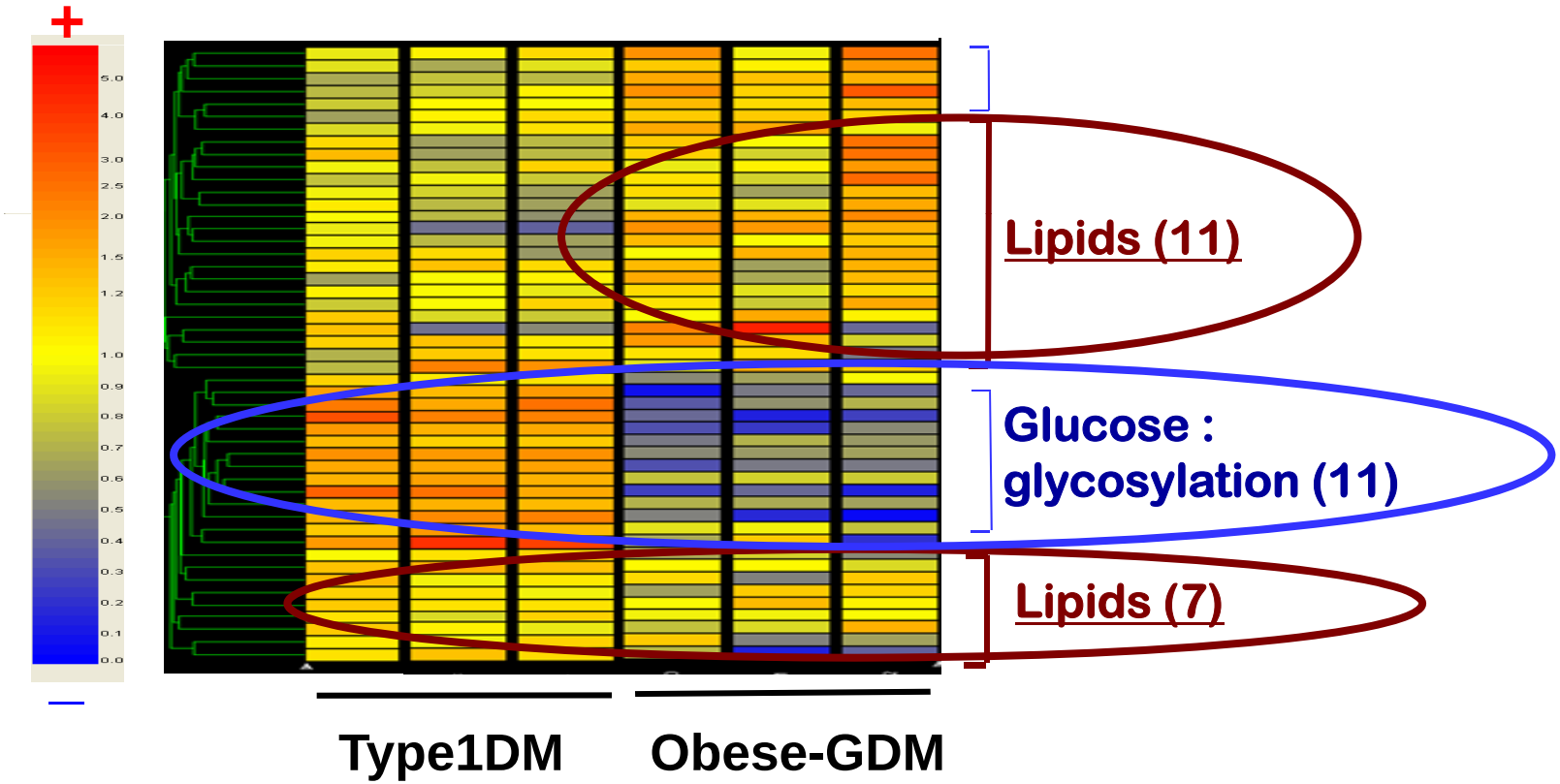


X 4 X 3.8

lipid accumulation (relative fold change vs. control)

Radaelli, AJOG; 2009

Changes in Metabolic Genes in Term Human Placenta



Radaelli, AJOG; 2009

What are the Factors which Facilitate Fetal Fat Accretion ?

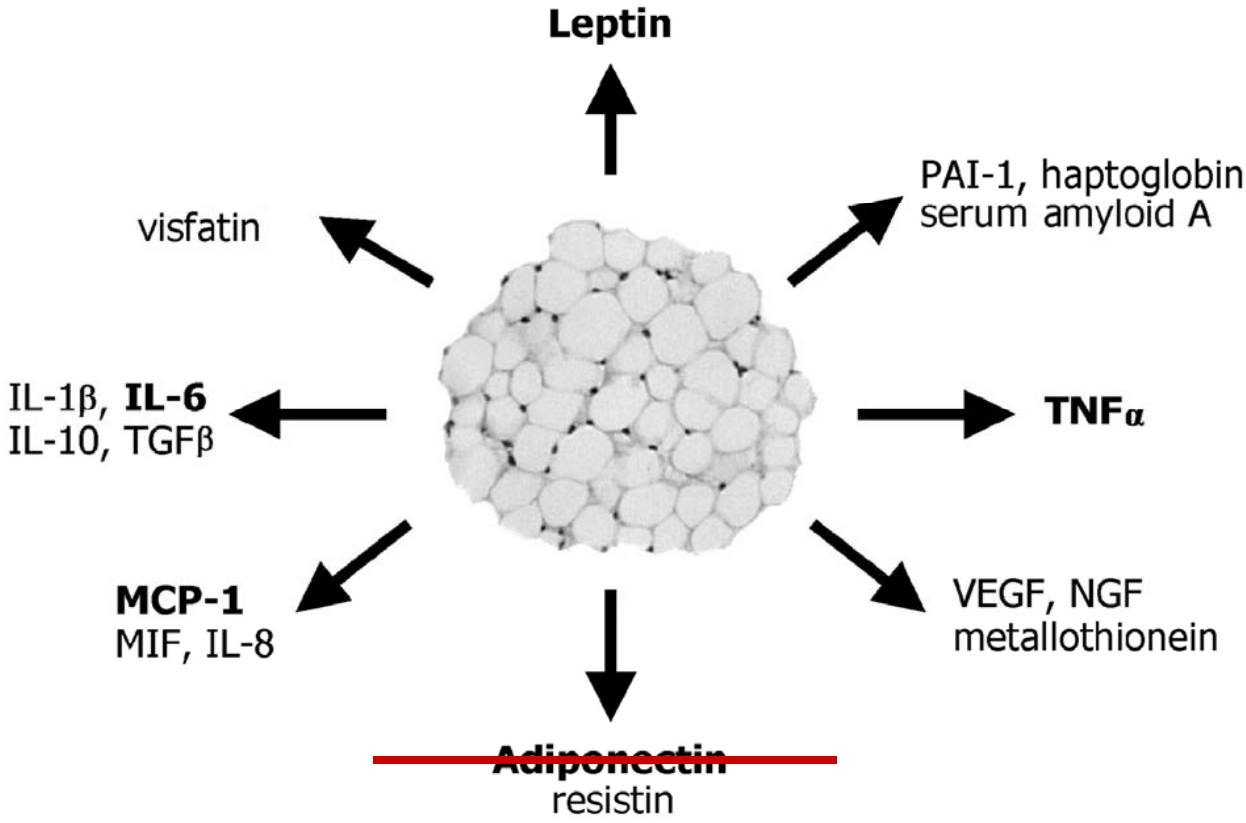
The changes in maternal environment progress from early pregnancy to the end of pregnancy modifying placental function

maternal insulin

maternal lipids

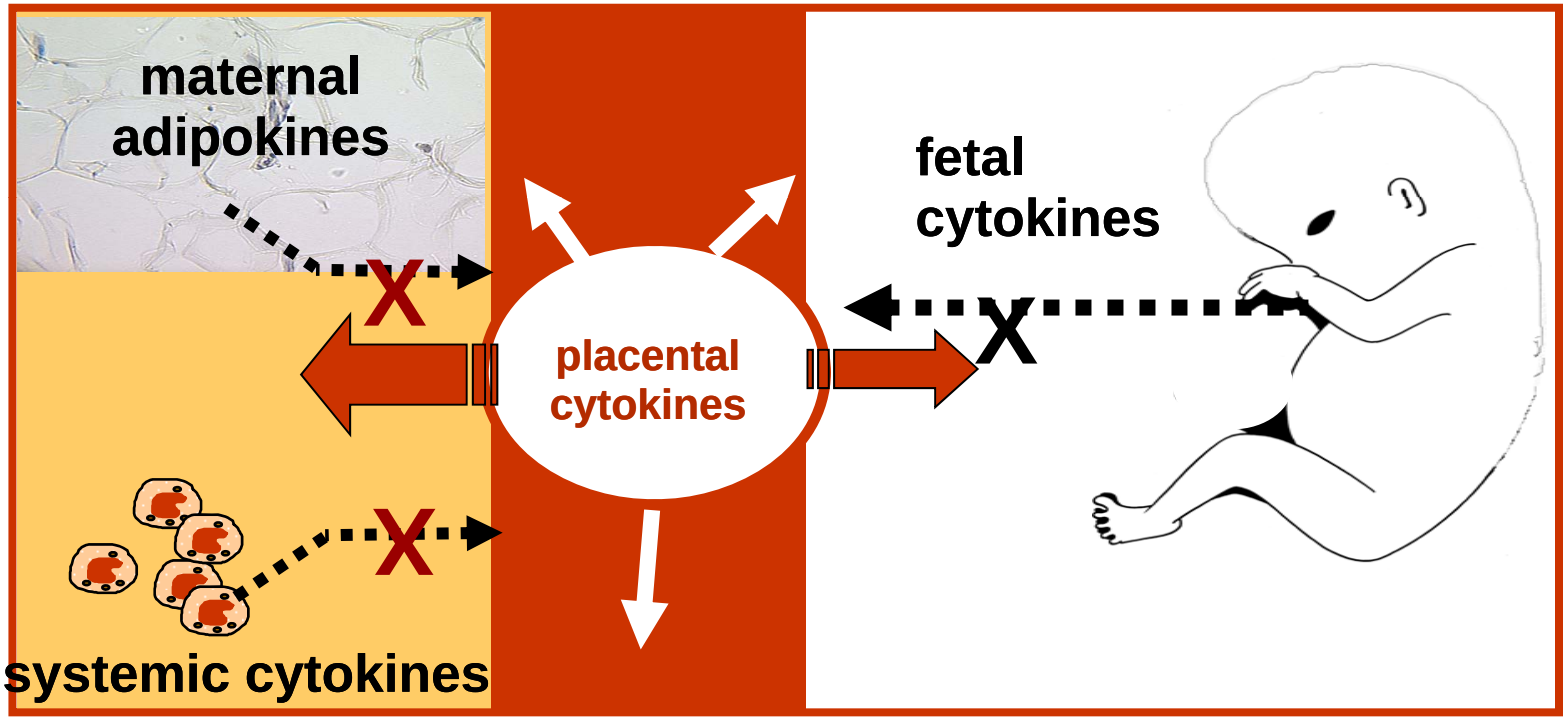
maternal cytokines

Placenta and Adipose Tissue have Similar Cytokine Profile



Trayhurn, J. Nutr. 2006

Adipo-Cytokines in Pregnancy

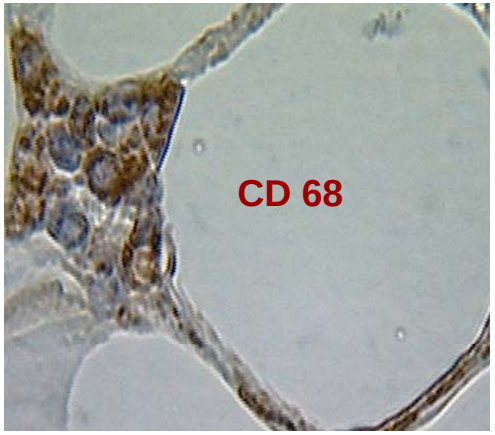


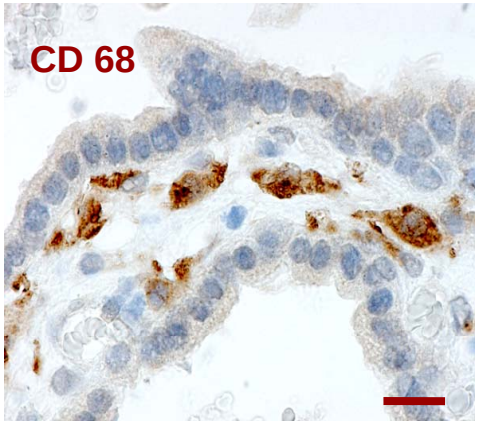
Maternal Systemic Inflammation

	Lean n = 53	Obese n = 68	*p value*
Pre-gravid BMI	**22.0 ± 1.9**	**38.4 ±6.3**	
Gestational age	**38.8 ± 0.5**	**38.8 ± 0.6**	***ns***
Plasma insulin (μU/ml)	**11.8 ± 5.6**	**26.0 ± 14.6**	**0.0001**
Plasma glucose (mg/dl)	**74 ± 7**	**79 ± 11**	**0.006**
Adiponectin (μg/ml)	**10.7 ± 4.6**	**9.7 ± 4.0**	***ns***
Leptin (ng/ml)	**31.9 ± 20**	**72.1 ± 34.7**	**0.0001**
IL-6 (ng/ml)	**2.4 ± 1.4**	**4.6 ± 3.4**	**0.0001**
TNF–alpha (pg/ml)	**1.4 ± 0.9**	**1.3 ± 0.5**	***ns***
CRP (ng/ml)	**8074 ± 6467**	**12433 ± 7918**	**0.004**

Catalano, Diabetes Care; 2009

Placenta and WAT Resident Macrophages in Pregnancy with Obesity



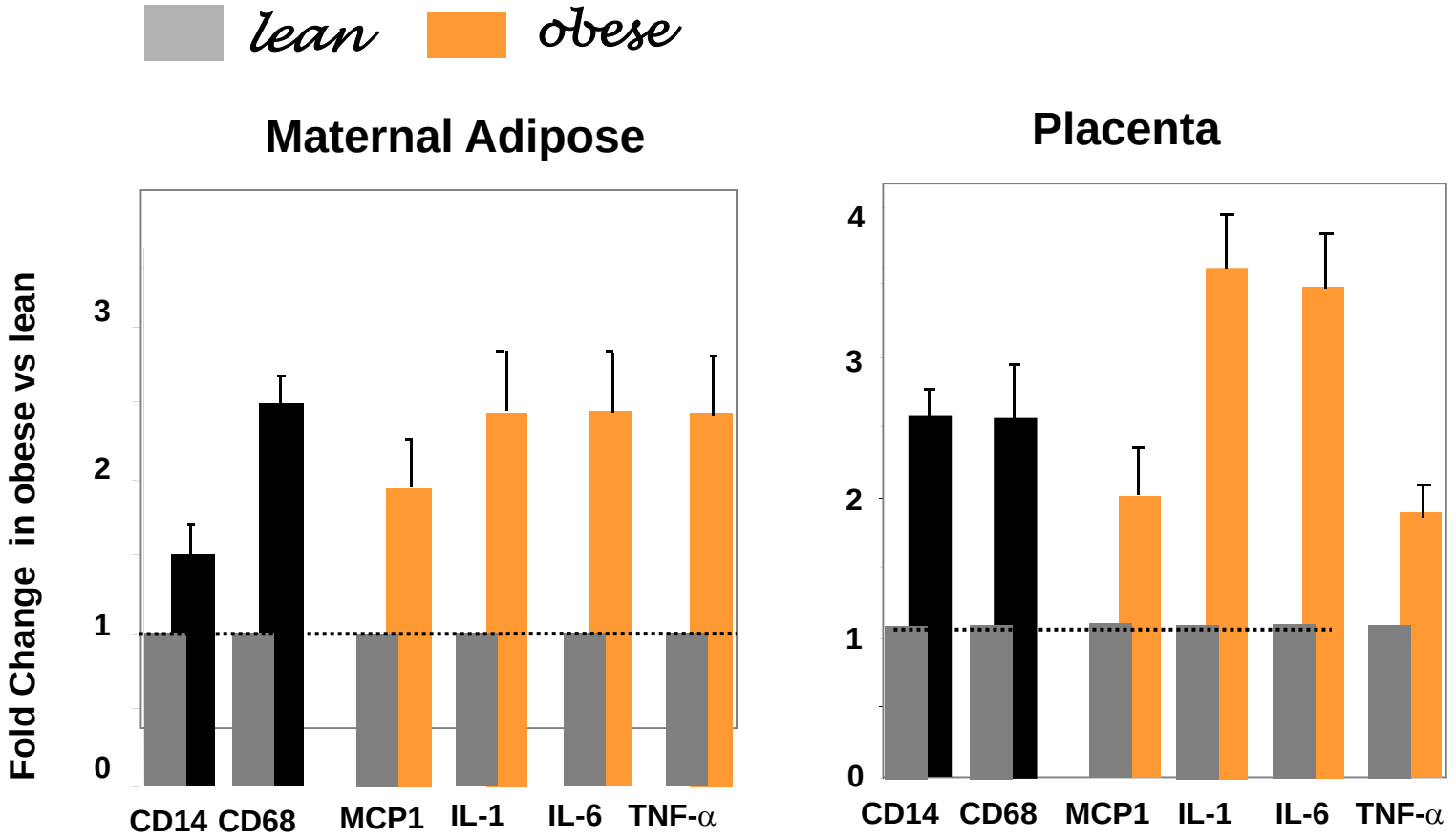


Originate from activated maternal monocytes

Localize in tissue stromal compartment

Have similar functional phenotype

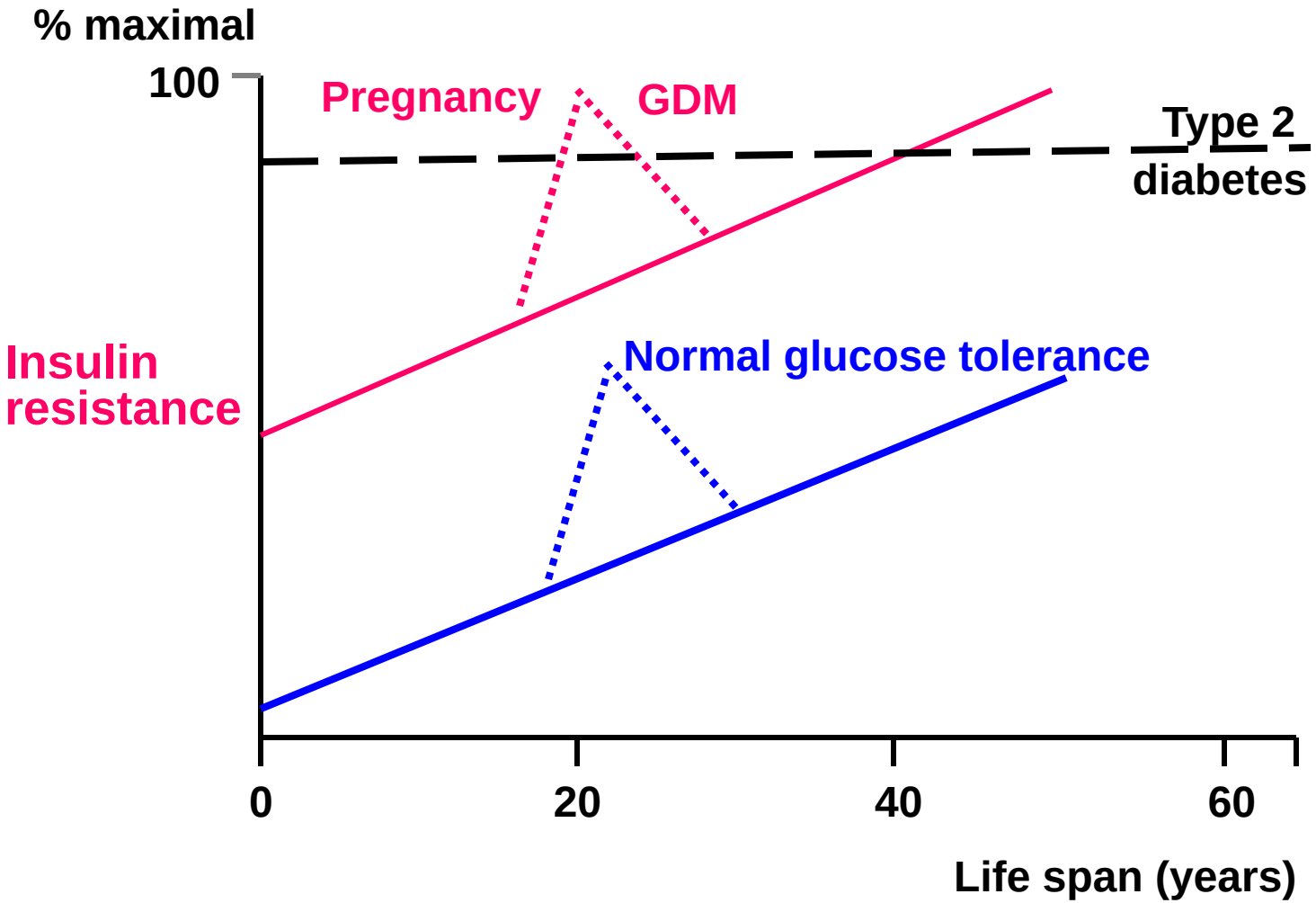
Inflammatory Markers in Placenta and Adipose Tissue of Obese Women

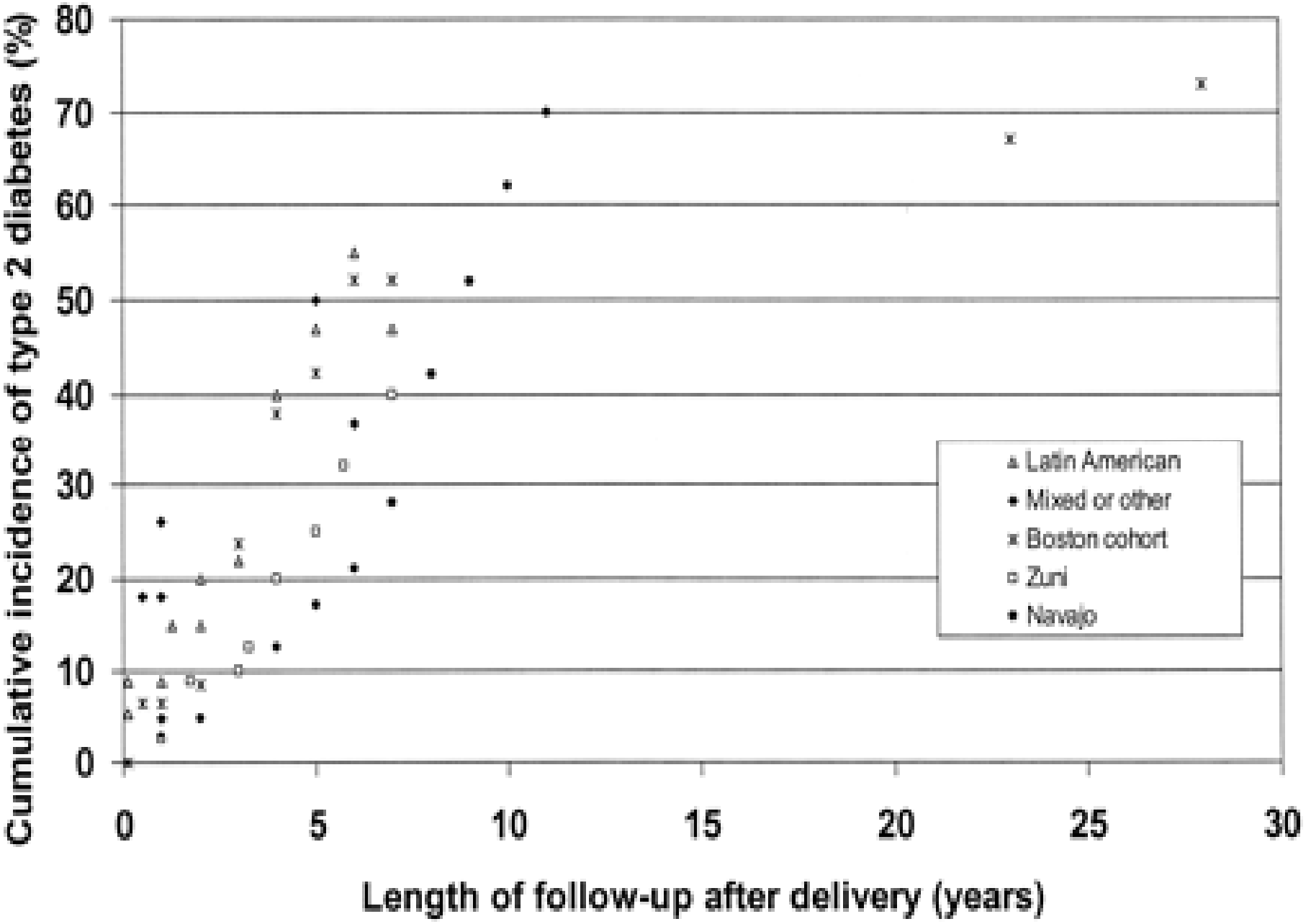


Basu, Obesity. 2010

Long Term Maternal Risks of GDM and Obesity During Pregnancy

Pregnancy as a Stress Test for Future Metabolic Disorders





Kim, Diabetes Care; 2002

The Journal of Clinical Endocrinology & Metabolism 87(7):3227–3235

Insulin Resistance Syndrome in Women with Prior History of Gestational Diabetes Mellitus

ANILA VERMA, CHARLOTTE M. BONEY, RICHARD TUCKER, AND BETTY R. VOHR

Department of Community Health (A.V.), Brown Medical School, Providence, Rhode Island 02912; Department of Pediatrics (C.M.B.), Division of Endocrinology and Metabolism, Rhode Island Hospital, Brown Medical School, Providence, Rhode Island 02903; and Department of Pediatrics (R.T., B.R.V.), Women and Infants' Hospital, Brown Medical School, Providence, Rhode Island 02905

Prevalence of the Metabolic Syndrome

- **GDM - 27.2%**
- **Control - 8.2%**

- **Hazard of developing metabolic syndrome 5.6 times (95% CI 2.6 – 12.3) among pre-gravid obese (BMI > 27.3 kg/m^2) vs. non-obese women.**

Verma, JCE&M; 2002

The Journal of Clinical Endocrinology & Metabolism 90(7):4004–4010

doi: 10.1210/jc.2004-1713

The Prevalence of the Metabolic Syndrome in a Danish Population of Women with Previous Gestational Diabetes Mellitus Is Three-Fold Higher than in the General Population

Jeannet Lauenborg, Elisabeth Mathiesen, Torben Hansen, Charlotte Glümer, Torben Jørgensen, Knut Borch-Johnsen, Peter Hornnes, Oluf Pedersen, and Peter Damm

Departments of Obstetrics (J.L., P.H., P.D.) and Endocrinology (E.M.), Rigshospitalet, Copenhagen University Hospital, 2100 Copenhagen, Denmark; Steno Diabetes Center (T.H., C.G., K.B.-J., O.P.), 2820 Gentofte, Denmark; and Research Center for Prevention and Health (T.J.), Glostrup University Hospital, 2600 Glostrup, Denmark

Prevalence of Metabolic Syndrome

GDM – 38.4%

Control – 13.4%

Obese women (BMI > 30 kg/m^2) with previous diet treated GDM had a 7-fold increase risk of the metabolic syndrome compared with normal-weight women.

Lauenborg, JCE&M; 2005

Which Factors Could be Modified in Obese/Diabetic Pregnant Women to Limit Fetal Adiposity ?

Improve Maternal Insulin Resistance

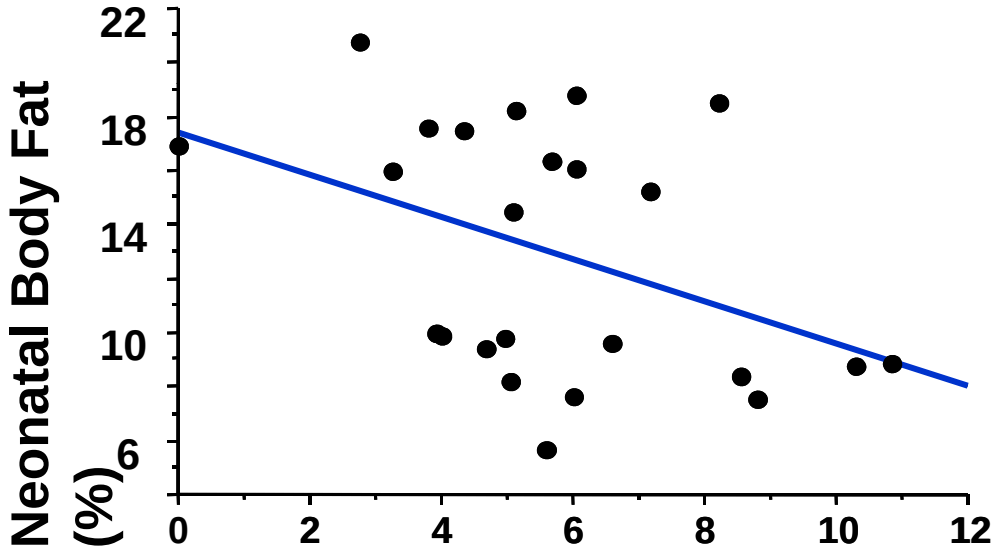
Insulin sensitizers: metformin/TZDs

? Concern with placental transfer

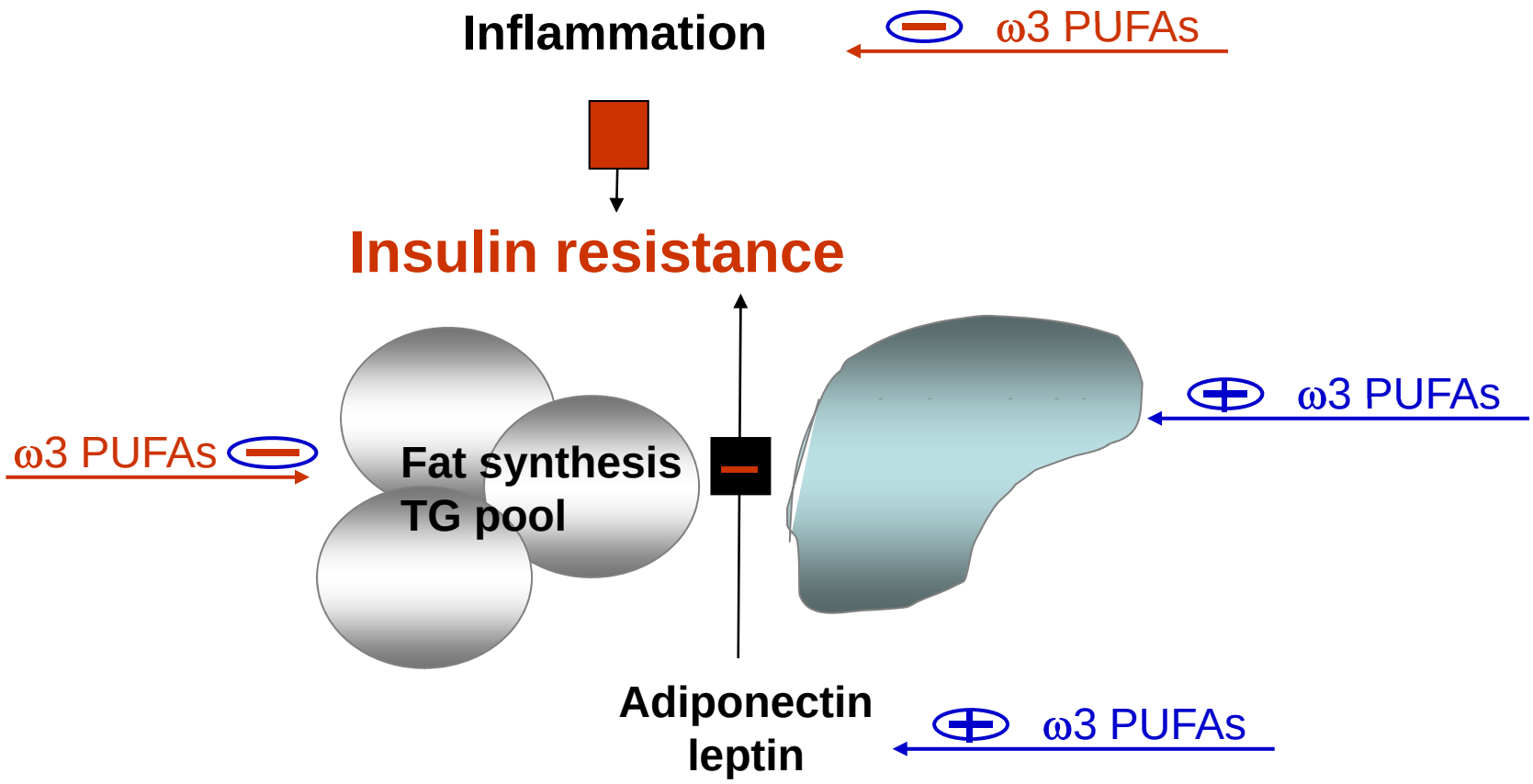
Nutrient supplements

omega 3 and 6 PUFAs

Omega-3 and Neonatal % Body Fat



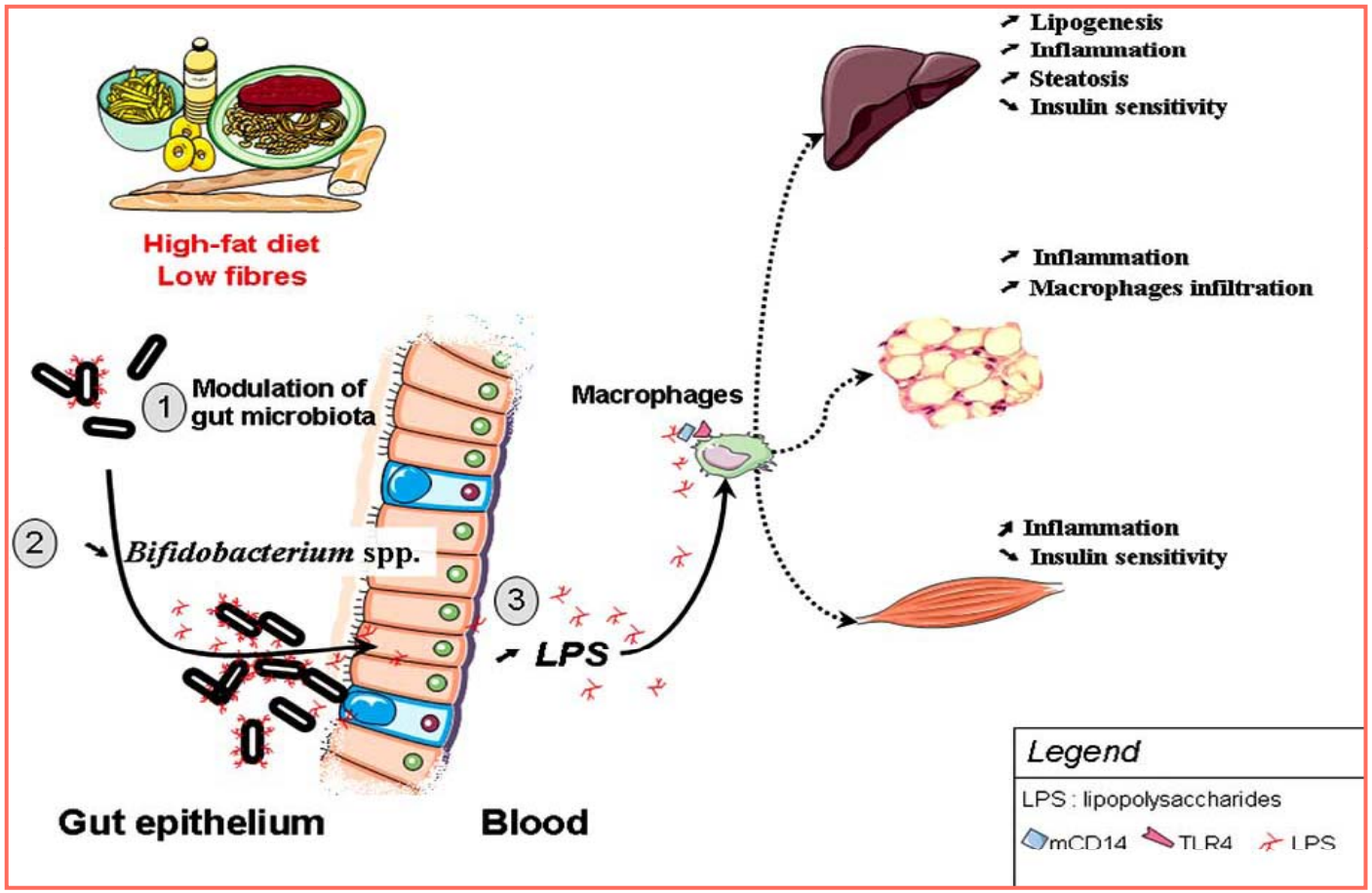
Molecular Mechanisms of ω-3 PUFAs



Potential Modifications of Maternal Diet

>>>> Microbiota

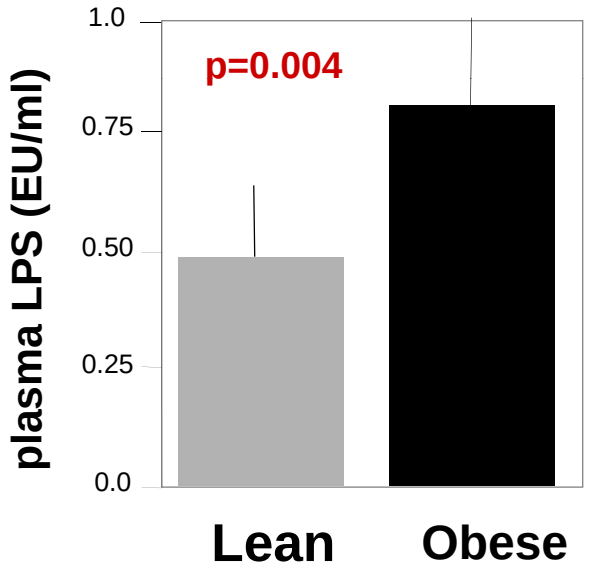
Role of the Gut Microbiota in Energy Metabolism and Metabolic Disease



Current Pharmaceutical Design, 2009, P. Cani & N. Delzenne

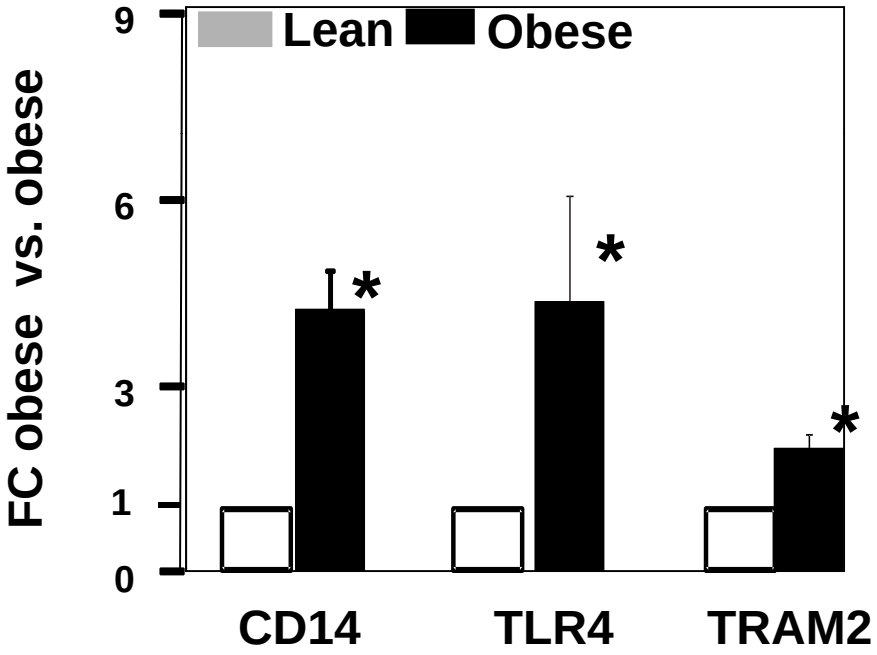
Role of LPS in Human Pregnancy

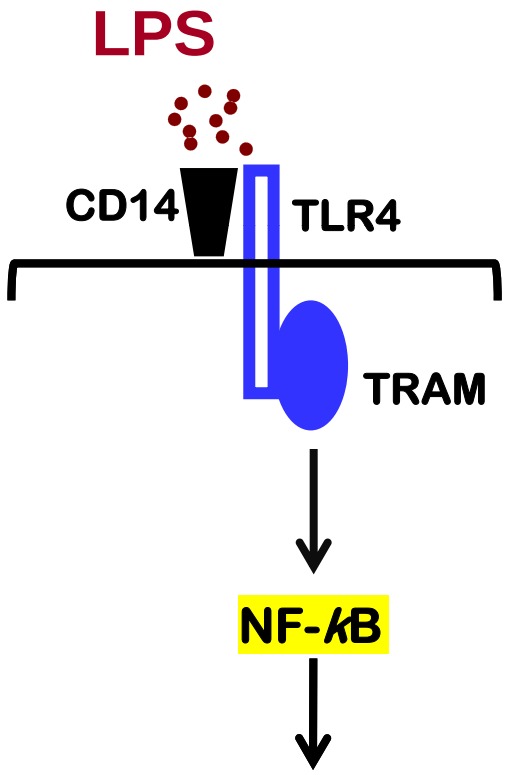
Maternal Plasma term pregnancy



Basu, 2010; Obesity

Expression of Adipose Tissue Genes Related to LPS-sensing

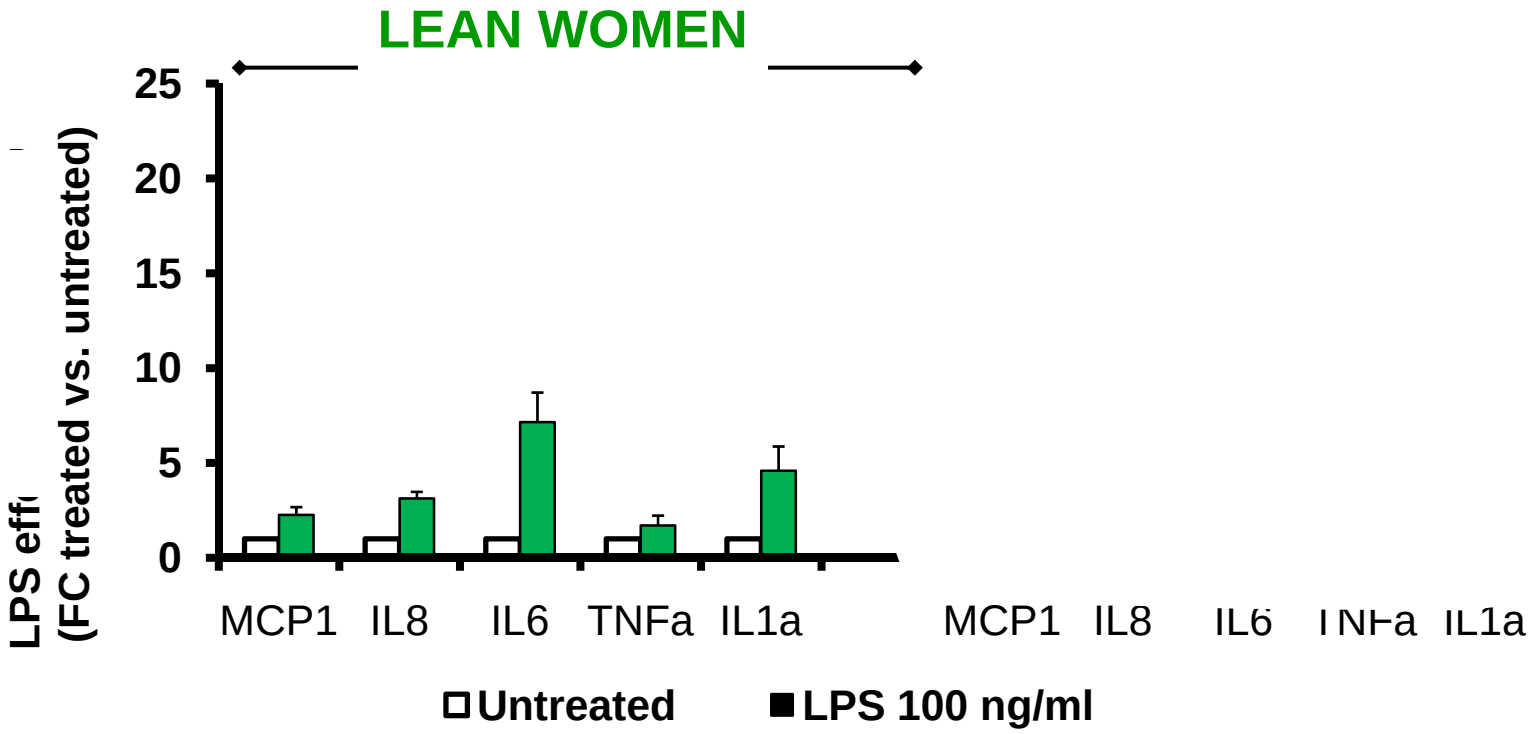




Immune response genes (e.g. cytokines)

Basu, 2010; Obesity

Effect of LPS on Cultured Adipose Cells (term pregnancy)



Basu, 2010; Obesity

British Journal of Nutrition (2009), **101**, 1679–1687
doi:10.1017/S0007114508111461

Probiotics and dietary counselling contribute to glucose regulation during and after pregnancy: a randomised controlled trial

Kirsi Laitinen[1,2]*, Tuija Poussa[3], Erika Isolauri[4,5] and the Nutrition, Allergy, Mucosal Immunology and Intestinal Microbiota Group

[1]*Department of Biochemistry and Food Chemistry, University of Turku, 20014 Turku, Finland*
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[3]*Stat-Consulting, 33230 Tampere, Finland*
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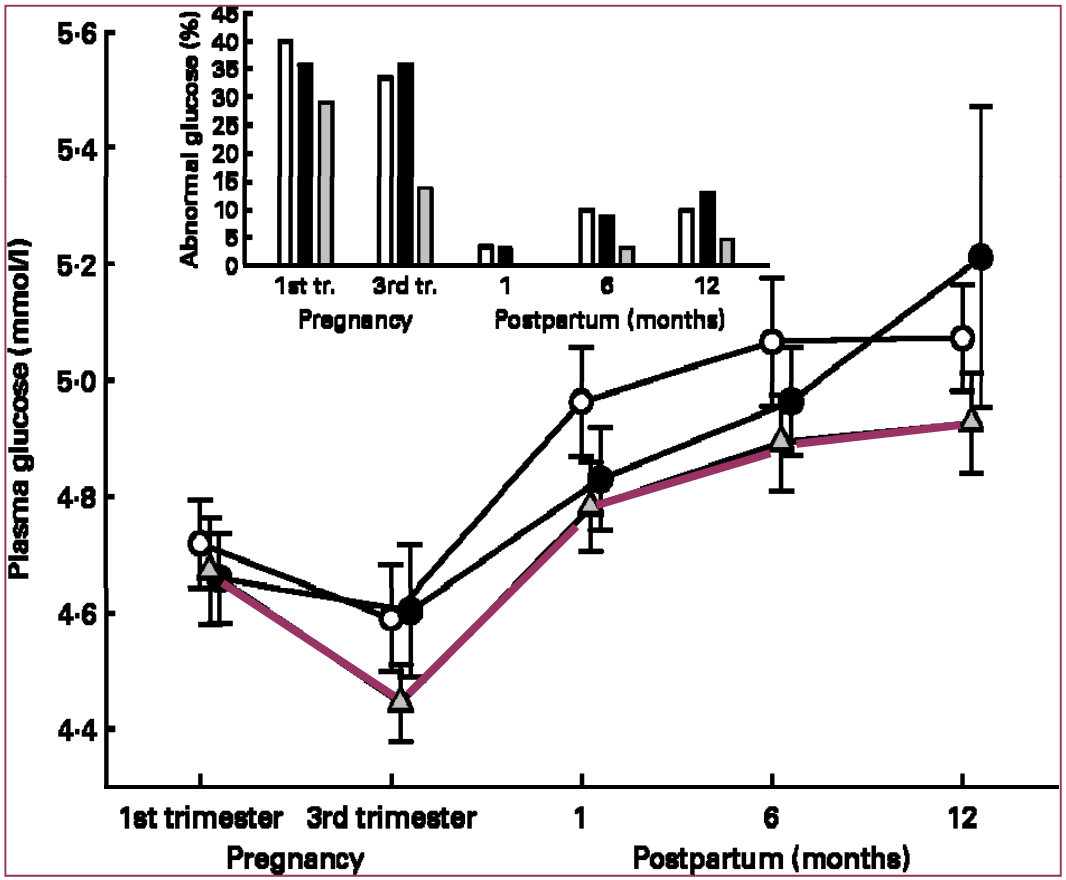
Maternal Plasma Glucose on Probiotic Diet



Laitinen, Br J Nutr; 2009

NICHD HD-22965, PO-50-11089, GCRC-MO-1 RR-80, ADA and

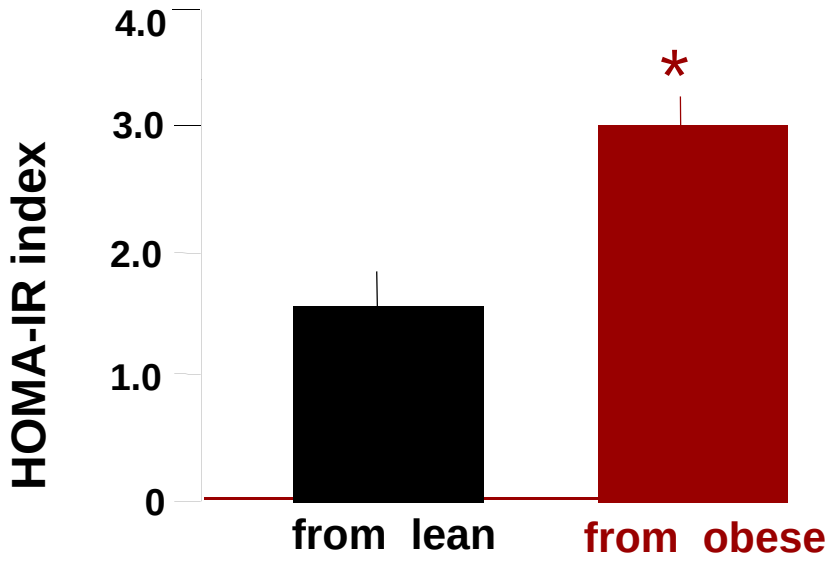
Diabetes Association of Greater Cleveland

Metabolic Profile of Neonates of Obese Women

	Neonates of lean mothers n = 53	Neonates of Obese Mothers n = 68	*p value*
Gestational age	38.8 ± 0.5	38.8 ± 0.6	ns
Birth weight (g)	3217 ± 452	3320 ± 460	*ns*
Neonatal body fat %	11.6 ± 2.9	13.1 ± 3.4	0.001
Placental weight (g)	614 ± 152	693 ± 184	0.01
Adiponectin (μg/ml)	30.8 ± 10.0	30.6 ± 9.7	*ns*
Leptin (ng/ml)	8.2 ± 4.7	14.7 ± 13.6	0.0001
IL-6 (ng/ml)	2.4 ± 1.4	3.5 ± 2.3	0.01
TNF–alpha (pg/ml)	1.7 ± 0.6	1.7 ± 0.3	*ns*
CRP (ng/ml)	121 ± 97	202 ± 286	*ns*
Cord plasma insulin (μU/ml)	7.0 ± 3.8	9.2 ± 4.7	0.02
Cord plasma glucose (mg/dl)	60 ± 13	66 ± 14	0.07

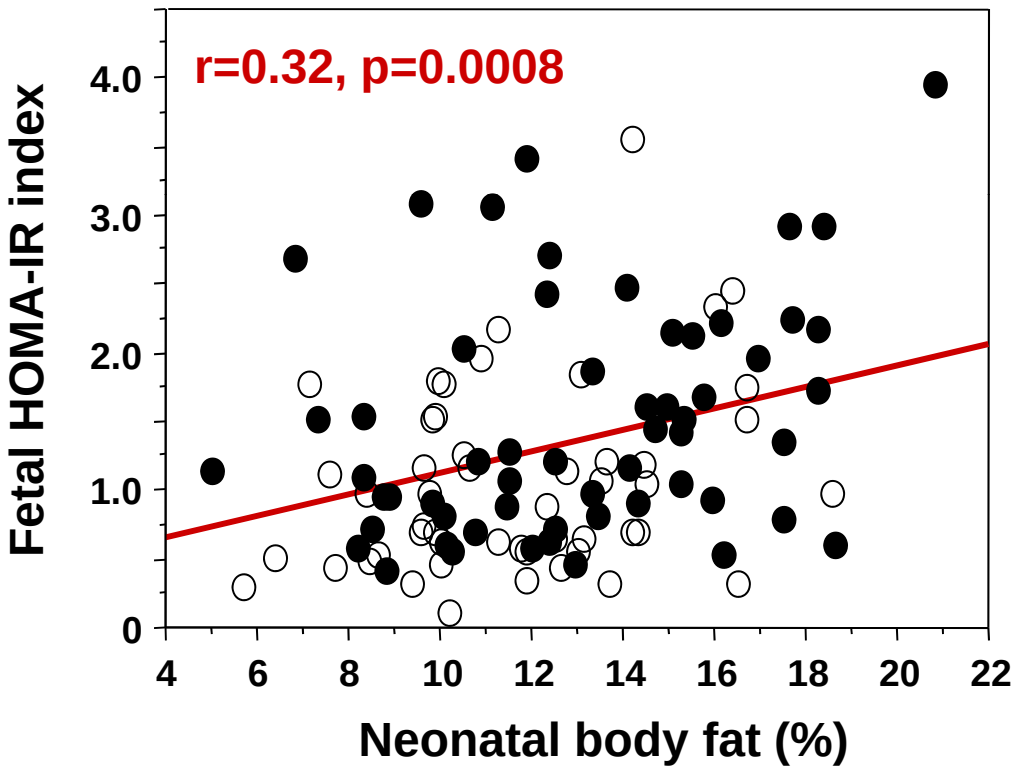
Catalano, Diabetes Care; 2009

Estimates of Neonatal Insulin Resistance at Birth



Catalano, Diabetes Care; 2009

Insulin Resistance and Adiposity at Birth



Catalano, Diabetes Care; 2009

Maternal Anthropometrics in Relation to % Body Fat in Children at Age 8

	Tertile 1 (n=21)	Tertile 2 (n=21)	Tertile 3 (n=21)	*p value*
% Body fat (DXA)	19.7±2.6	28.2±2.6	39.3±4.3	0.0001
CDC weight percentile	39.8±27.5	66.0±19.1	88.0±11.4	0.0001
Maternal				
Age at delivery (yr)	30.7±3.8	29.8±5.2	31.6±4.6	ns
Height (cm)	167±6	166±7	166±9	ns
Pre-gravid Weight (kg)	64.8±15	66.2±13	84.4±26	0.002
Pre-gravid BMI (kg/m^2)	23.5±6.1	23.9±4.0	30.8±9.3	0.0001
Weight Gain (kg)	14.2±6.9	14.3±5.7	11.6±7.6	ns

Catalano; AJCN, 2009

Metabolic Dysregulation in Children at Age 8

	Tertile 1 (n=21)	Tertile 2 (n=21)	Tertile 3 (n=21)	*p value*
Child body fat by DXA (%)	19.7±2.6	28.2±2.6	39.3±4.3	*0.0001*
Waist circumference (cm)	55.3±5.0	62.0±6.8	72.0±8.0	*0.0001*
Systolic BP (mm Hg)	105±8	109±5	114±13	*0.01*
HOMA-IR	1.5±0.5	2.2±1.1	3.4±1.7	*0.002*
Triglyceride (mmol/L)	0.62±0.3	0.72±0.32	1.23±0.77	*0.009*
Leptin (ng/mL)	2.5±0.6	7.6±4.7	15.9±7.0	*0.0001*

Catalano; AJCN, 2009

Maternal Pre-gravid Obesity as a Predictor of Neonatal and Childhood Obesity

@ Birth:

Maternal obesity

is the strongest predictor of fetal adiposity : accounts for 7% of the variance

Childhood:

Pre-gravid BMI > 30 O.R. 5.45 (95% CI 1.62 – 18.4)

Maternal obesity

accounts for 17.6% of the variance in childhood obesity

Treated GDM appears to be less of a risk factor for childhood obesity as compared to maternal pregravid obesity