University of Pittsburgh

Insulin Resistance in Youth vs. Adults: From Physiology to Pathophysiology

Is the Glass Half Empty or Half Full?

Silva Arslanian M.D.
Richard L. Day Professor of Pediatrics

UPMC | CHILDREN'S HOSPITAL OF PITTSBURGH

Swedish Society for Diabetology 2019


Nesli Gungor


Fida Bacha


SoJung Lee


Rola Saad


Julia Warren


Tami Hannon


Hala Tfayli


Ingrid Libman


Sara Michaliszyn
Lindsey George
Javier de La Heras
Elisa Andreatta

NIH (R01, K24, T32, K12, M01, U01), DOD


Nancy Guerra


Kristin Porter


Sally Foster


Resa Stauffer


Steve Burns


Joon Kim

PCTRC Nurses


Kathy Brown


Denise Shearer

Insulin Sensitivity in Man

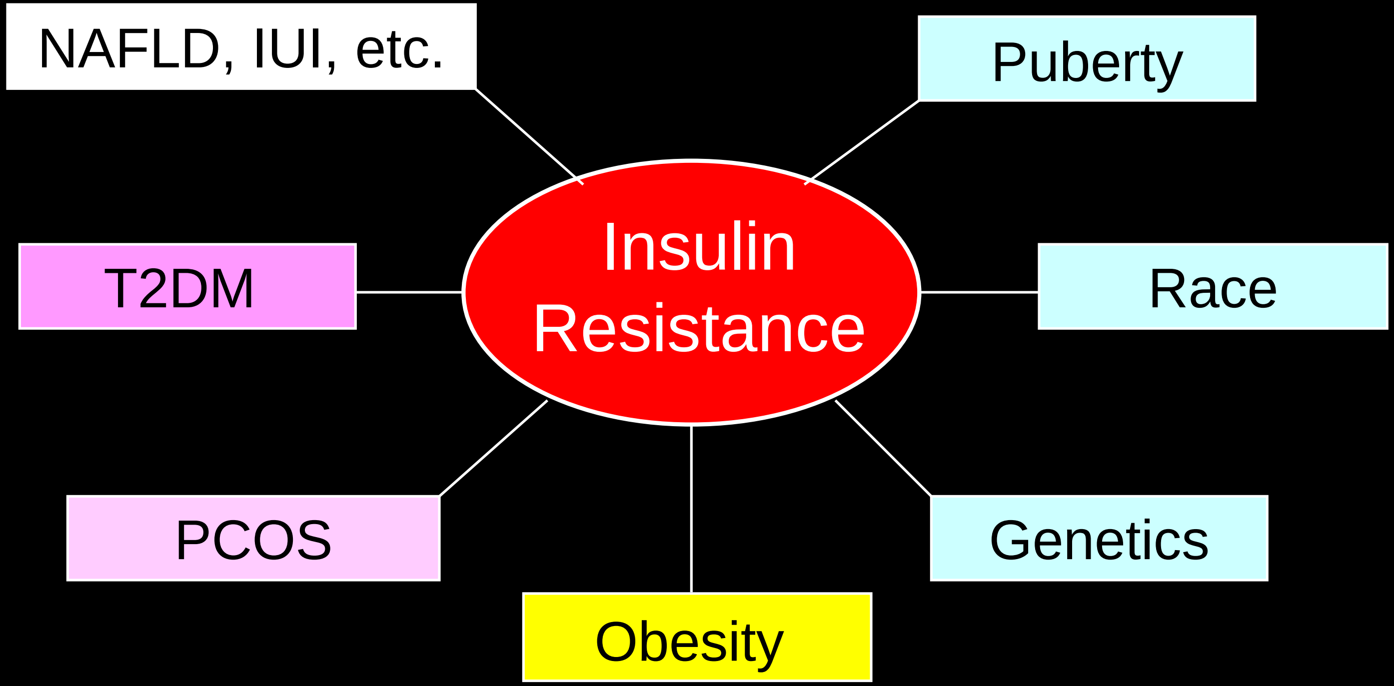
A state in which a given amount of insulin, exogenous or endogenous, produces a subnormal biological response:

- CHO
- Lipid
- Protein

Insulin Resistance in Youth

- Risk factors: Modifiable and Unmodifiable
- Induction of Insulin Resistance
- Alleviation of Insulin Resistance
- Youth-Adult Contrast in Insulin Sensitivity

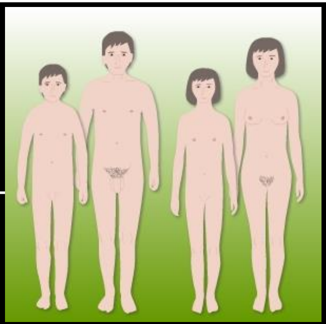
Risk Factors for Insulin Resistance in Youth



Risk Factors for Insulin Resistance in Youth

NAFLD, IUI, etc.

Puberty



T2DM

Insulin Resistance

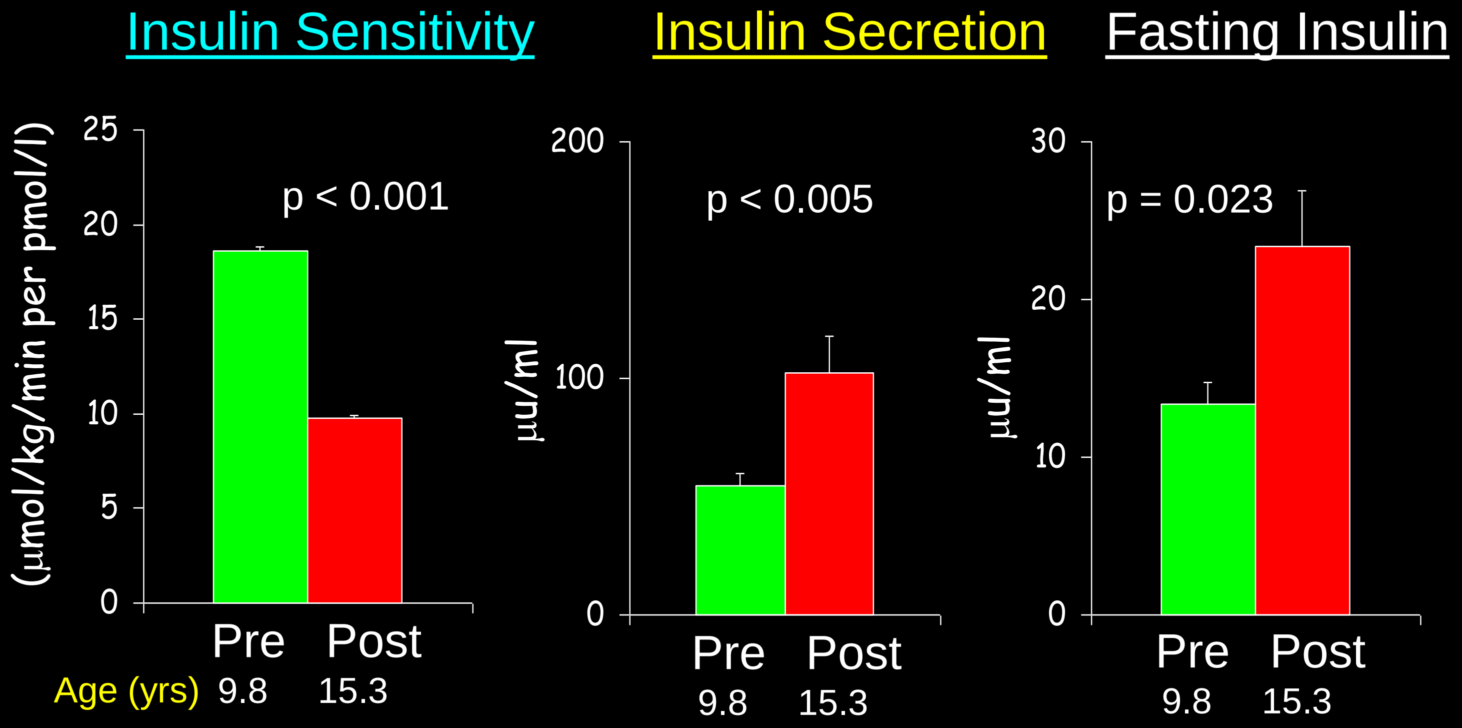
PCOS

Obesity

Genetics

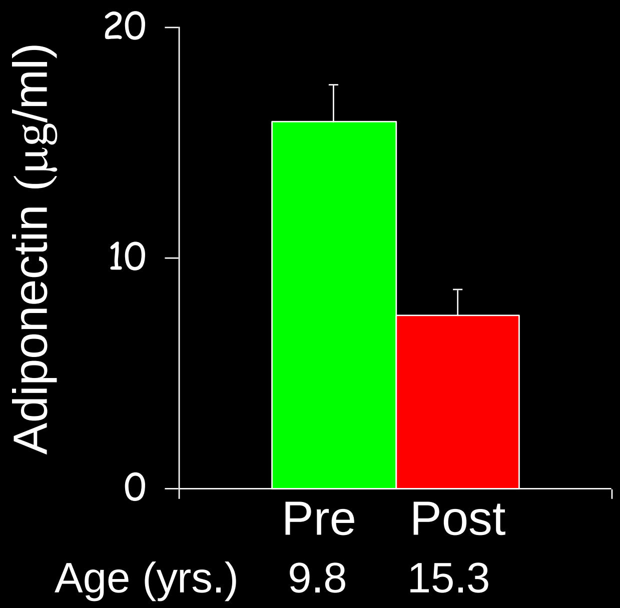
Longitudinal Study of Physiologic Insulin Resistance and Metabolic Changes of Puberty

Pediatr Res 60: 1, 2006



Longitudinal Study of Physiologic Insulin Resistance and Metabolic Changes of Puberty

Pediatr Res 60: 1, 2006



- Insulin sensitivity ↓ by ~ 50%
- Insulin secretion doubled
- The ↓ in insulin sensitivity was independent of changes in % BF
- Adiponectin ↓ by ~50%
- The ratio of Leptin/adiponectin ↑ 5 fold.

Longitudinal Study of Physiologic Insulin Resistance and Metabolic Changes of Puberty

Pediatr Res 60: 1, 2006

- What causes pubertal insulin resistance?
- Does it involve protein and fat metabolism?
- What are the metabolic pathways responsible for it?
- Does pubertal IR have a teleological function?

Protein turnover during puberty in normal children
1996

Correlations Between Fatty Acid and Glucose Metabolism
1994
Potential Explanation of Insulin Resistance of Puberty

Testosterone Treatment in Adolescents with Delayed Puberty: Changes in Body Composition, Protein, Fat, and Glucose Metabolism*
1997

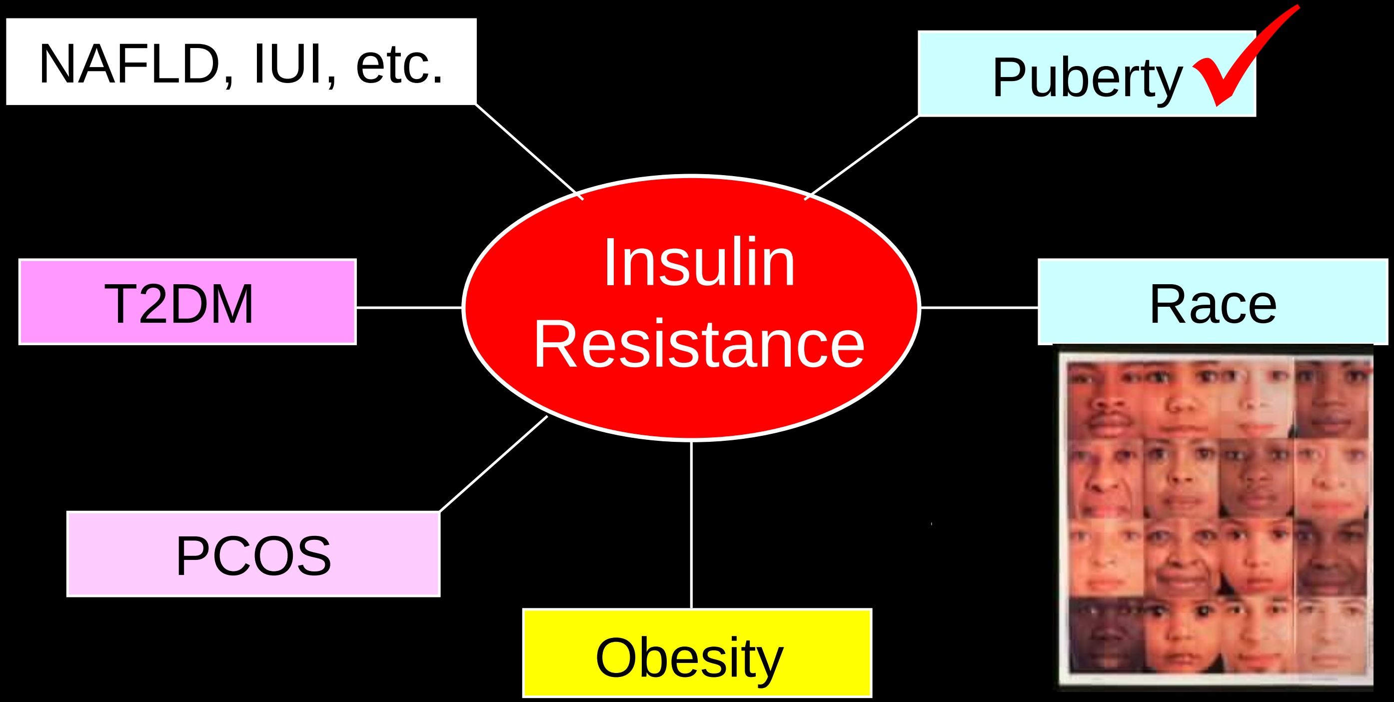
Dihydrotestosterone Treatment in Adolescents with Delayed Puberty: Does it Explain Insulin Resistance of Puberty?
2001

Growth Hormone Treatment in Adolescent Males with Idiopathic Short Stature: Changes in Body Composition, Protein, Fat, and Glucose Metabolism
2007

Insulin Resistance of Puberty

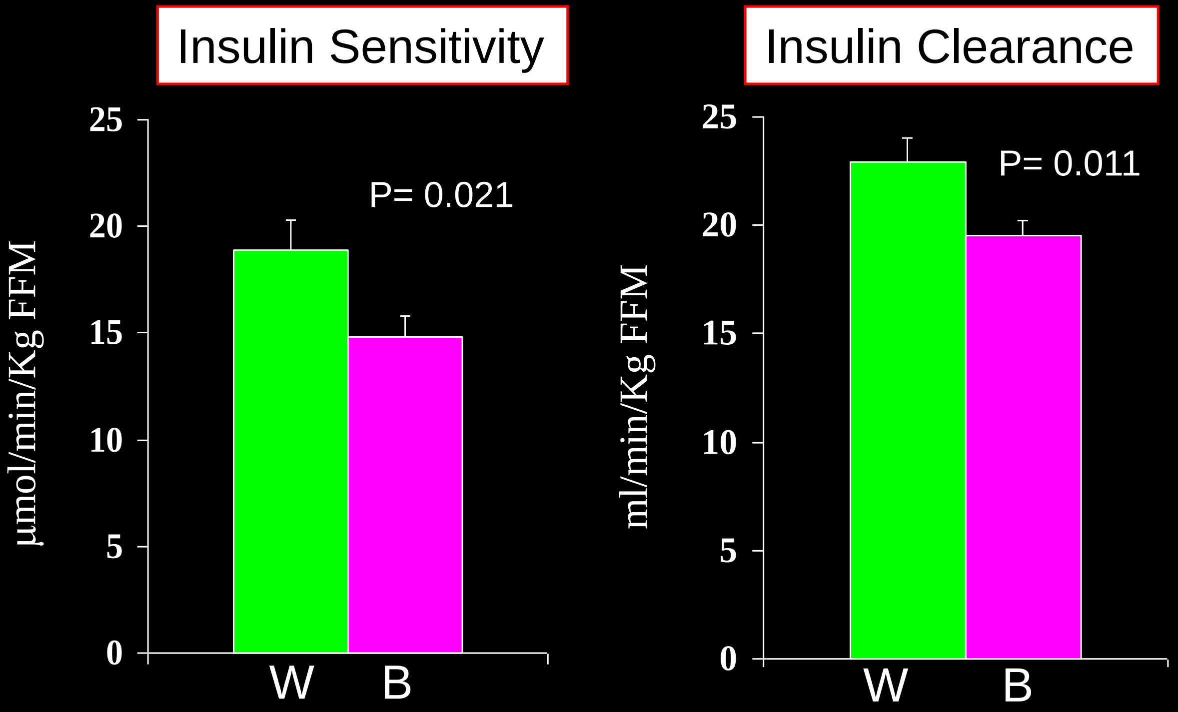
- Pubertal insulin resistance involves protein and fat metabolism.
- Pubertal IR is driven by **GH** and not gonadal sex steroids.
- The ↑ in GH secretion during puberty leads to ↑ lipolysis and ↑ FFA → to insulin resistance through the Randle cycle.
- Pubertal IR and its compensatory hyperinsulinemia may serve to enhance growth and mass accretion.

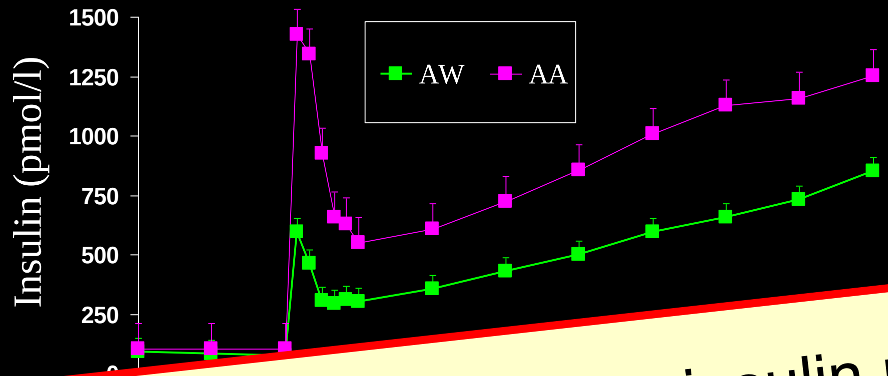
Risk Factors for Insulin Resistance in Youth



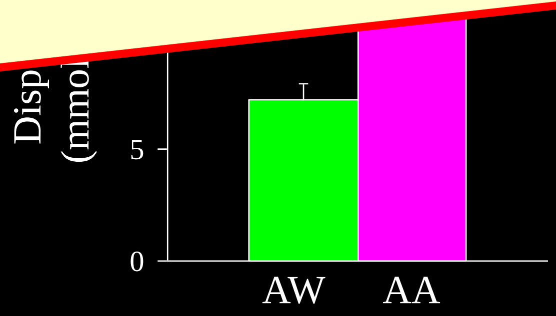
Hyperinsulinemia in African-American Children

Diabetes 51:3014, 2002





Are the black/white differences in insulin resistance and metabolic risks due to **biological differences** or **environmental differences** or **both?**



Arslanian S et al:
Diabetes 51:3014, 2002

Racial Differences in Adiponectin in Youth
Relationship to visceral fat and insulin sensitivity
2006

Ghrelin and Peptide YY in Youth: Are There Race-Related Differences?
2006

Lipolysis in African-American Children: Is It a Metabolic Risk Factor Predisposing to Obesity?*
2001

Fat Oxidation in Black and White Youth: A Metabolic Phenotype Potentially Predisposing Black Girls to Obesity
2008

Obesity, Regional Fat Distribution, and Syndrome X in Obese Black *Versus* White Adolescents: Race Differential in Diabetogenic and Atherogenic Risk Factors
2003

Whole-Body MRI and Ethnic Differences in Adipose Tissue and Skeletal Muscle Distribution in Overweight Black and White Adolescent Boys
2011

Insulin Resistance: Race/Ethnicity

- Adiponectin is ↓ in black youth.
- Ghrelin (hunger hormone) suppression is ↓ in black youth.
- PYY (satiety hormone) is ↓ in black youth.
- Fat oxidation is ↓ in black female youth.
- Visceral fat is ↓ in black youth despite similar BMI or total body fat.
- Fat/CHO intake is ↑ in black youth’s diet, with inverse correlation to IS.
- Diabetogenic risk is worse in black you while atherogenic risk is worse in white youth.

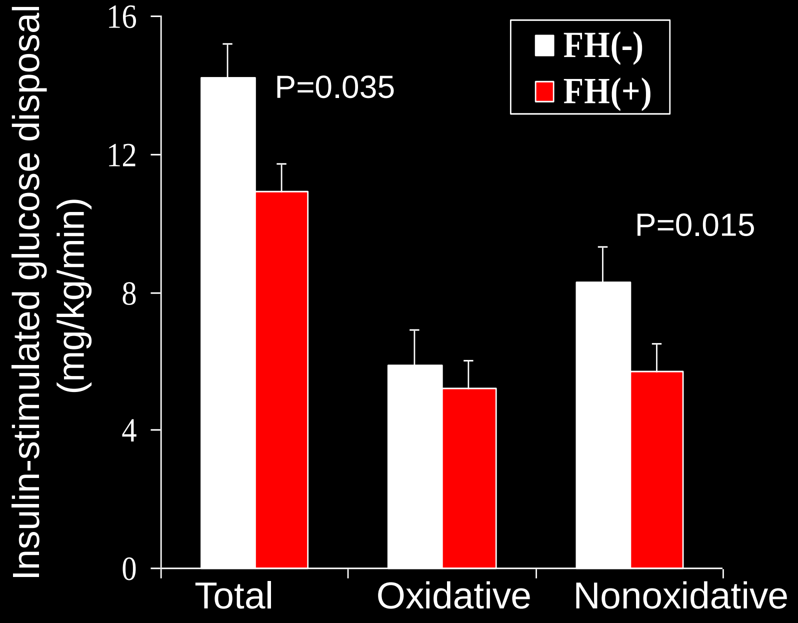
Risk Factors for Insulin Resistance in Youth

Insulin Resistance

- NAFLD, IUI, etc.
- T2DM
- PCOS
- Obesity
- Genetics
- Race ✓
- Puberty ✓

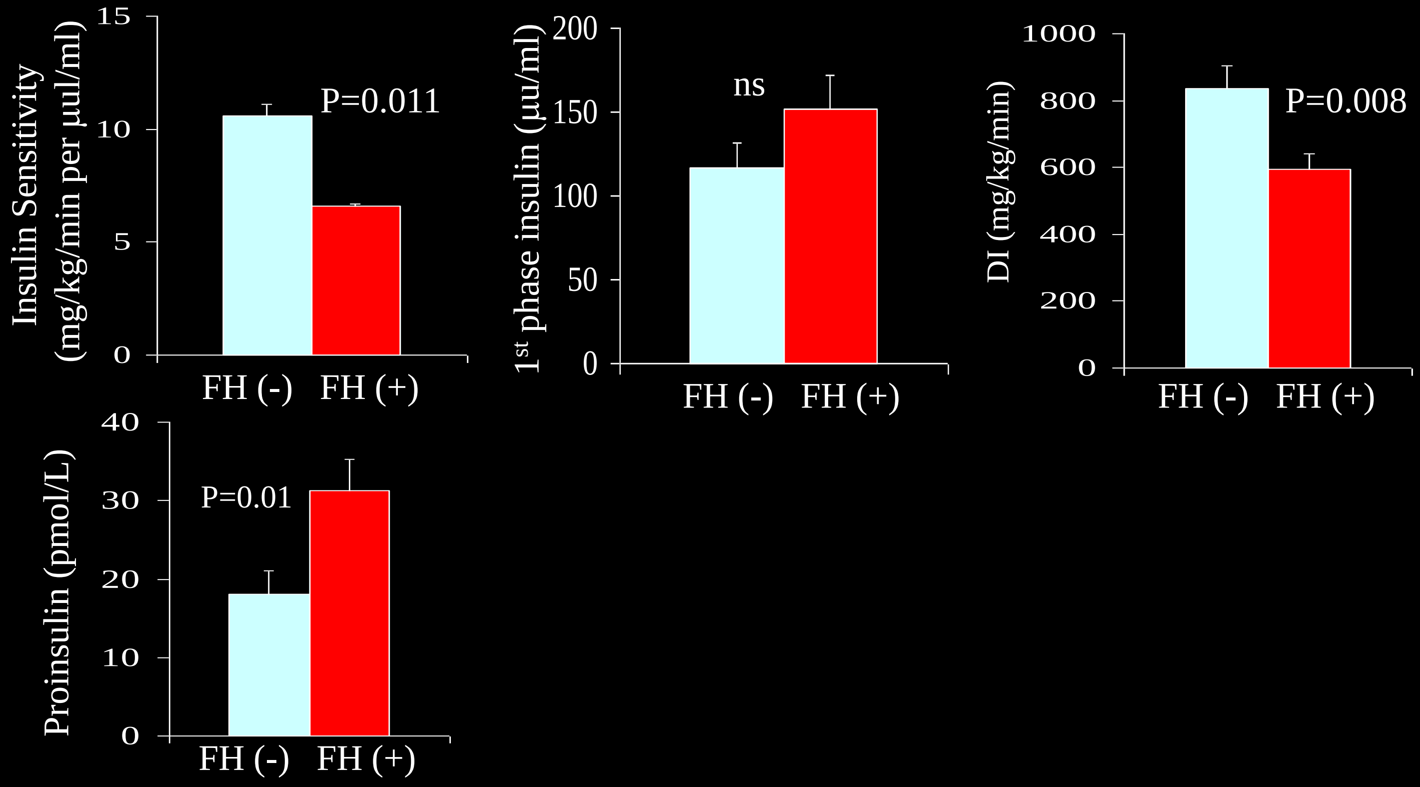
Insulin Sensitivity in African-American Children With and Without Family History of Type 2 Diabetes

1999



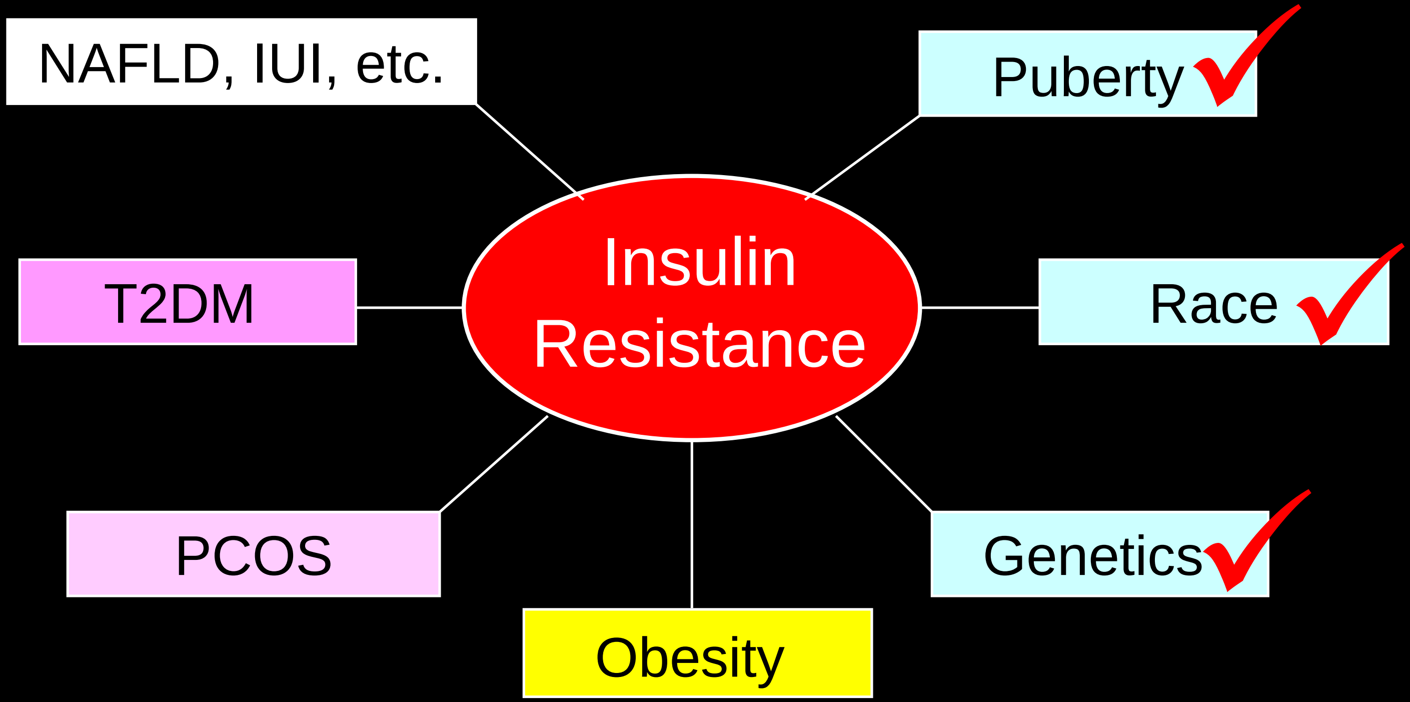
Healthy prepubertal black youth with +FH of T2DM have ~ 20% ↓ insulin sensitivity in the first decade of life.

Family History of T2DM: Impaired Insulin Sensitivity & β-cell Dysfunction in White Youth



2005

Risk Factors for Insulin Resistance in Youth



Risk Factors for Insulin Resistance in Youth

Insulin Resistance

NAFLD, IUI, etc.

Puberty

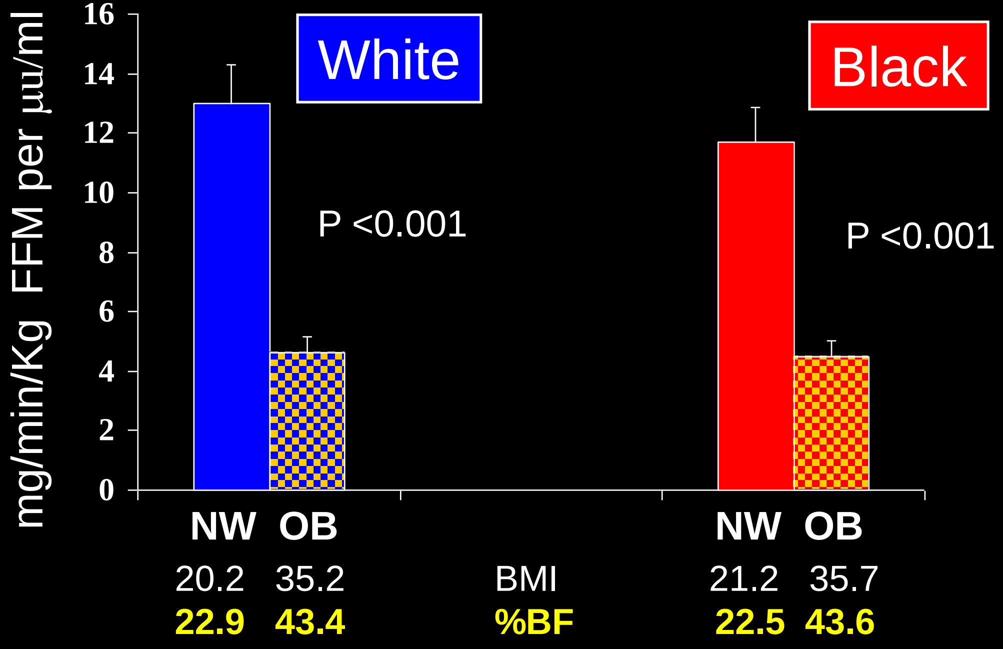
T2DM

Race

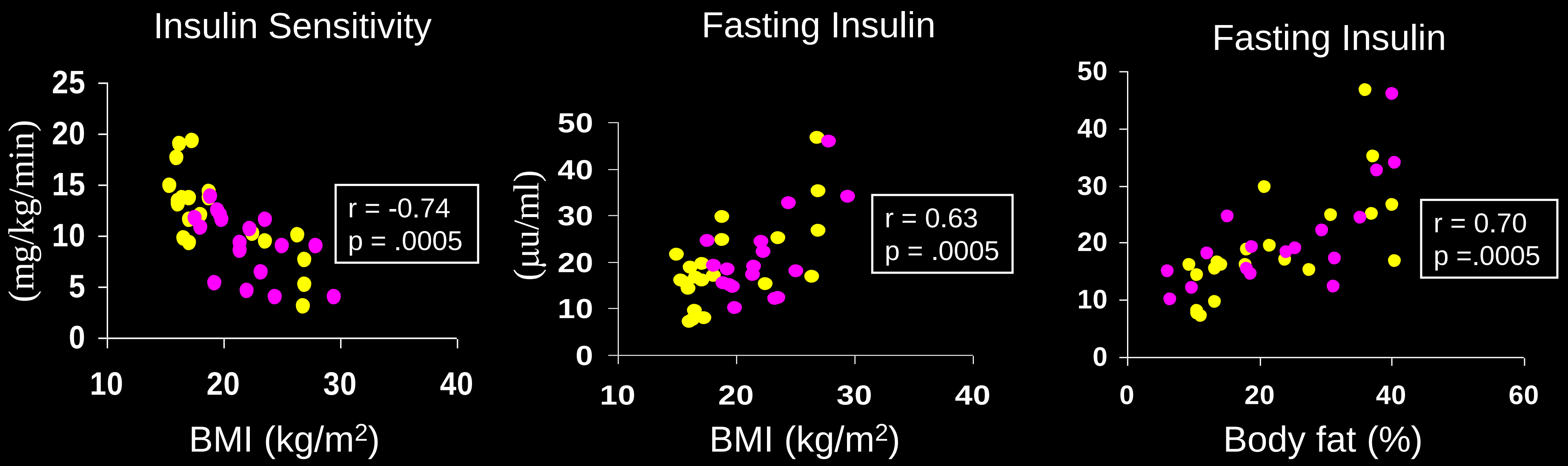
PCOS

Obesity

Insulin Sensitivity in Normal-weight & Obese Adolescents



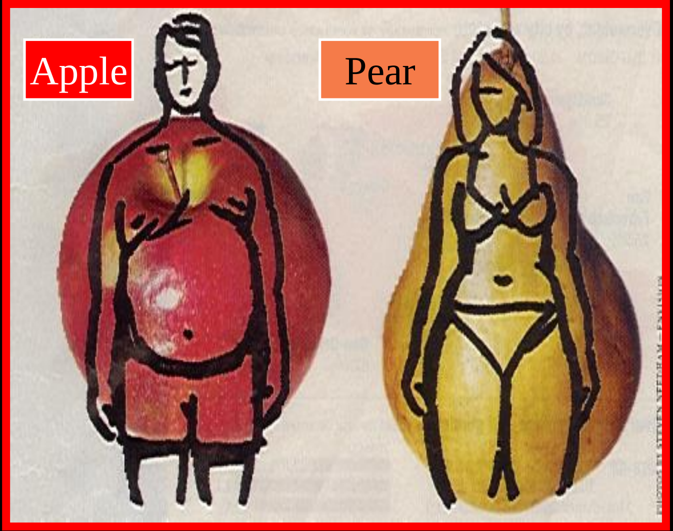
Relationship of BMI and % Body Fat to Insulin Sensitivity & Fasting Insulin

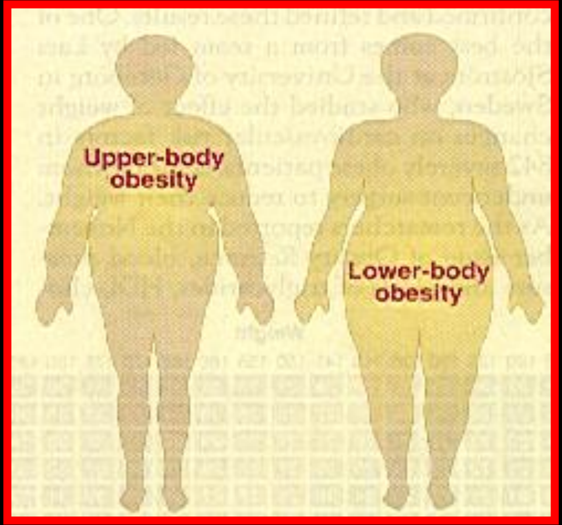


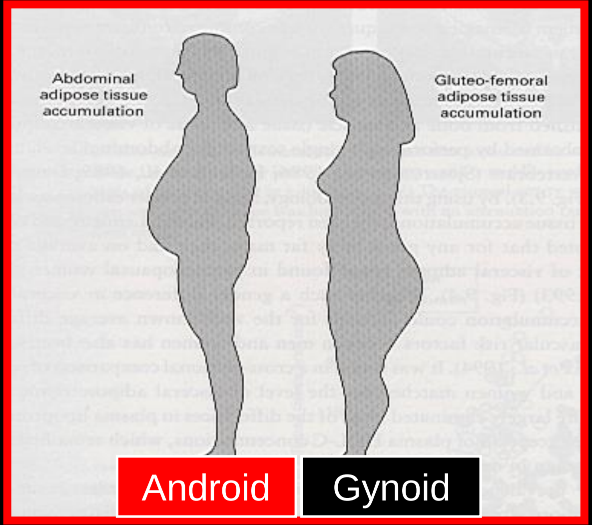
Yellow: *prepubertal*, pink: *pubertal*

Arslanian S, 1998

Do 'Apples' Fare Worse Than 'Pears' in Youth?

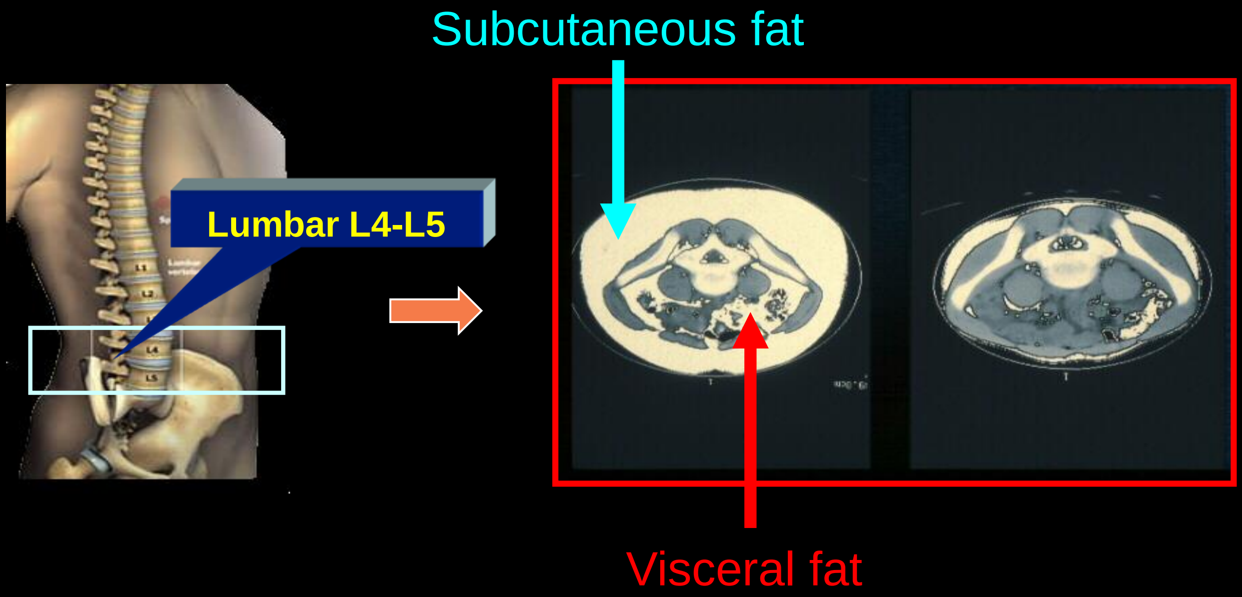




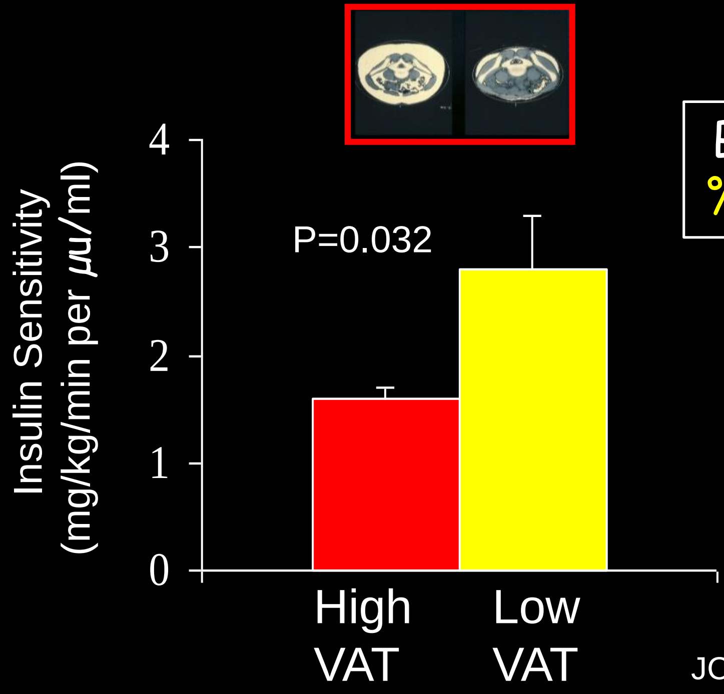


Science 280: 1372, 1998

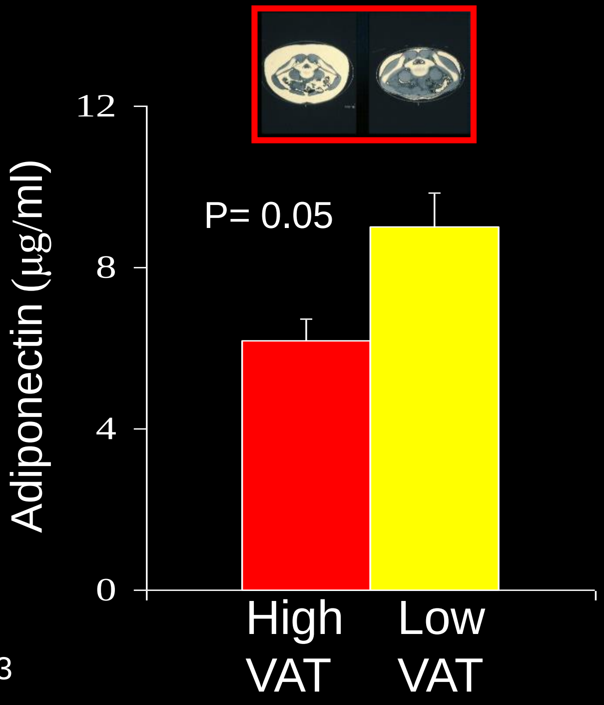
Abdominal Adipose Tissue (CT)



Insulin Sensitivity & Adiponectin in High vs. Low-VAT Obese Adolescents

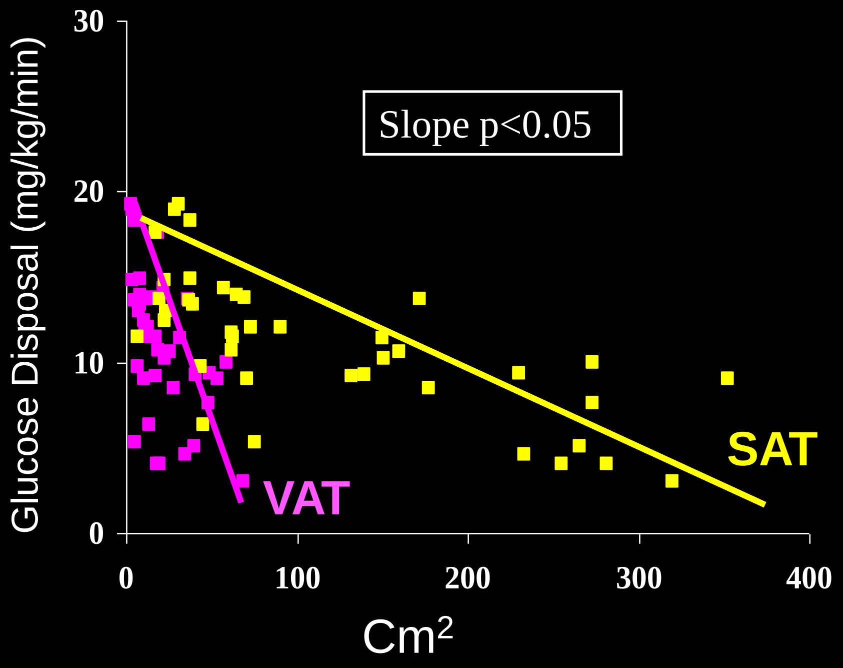


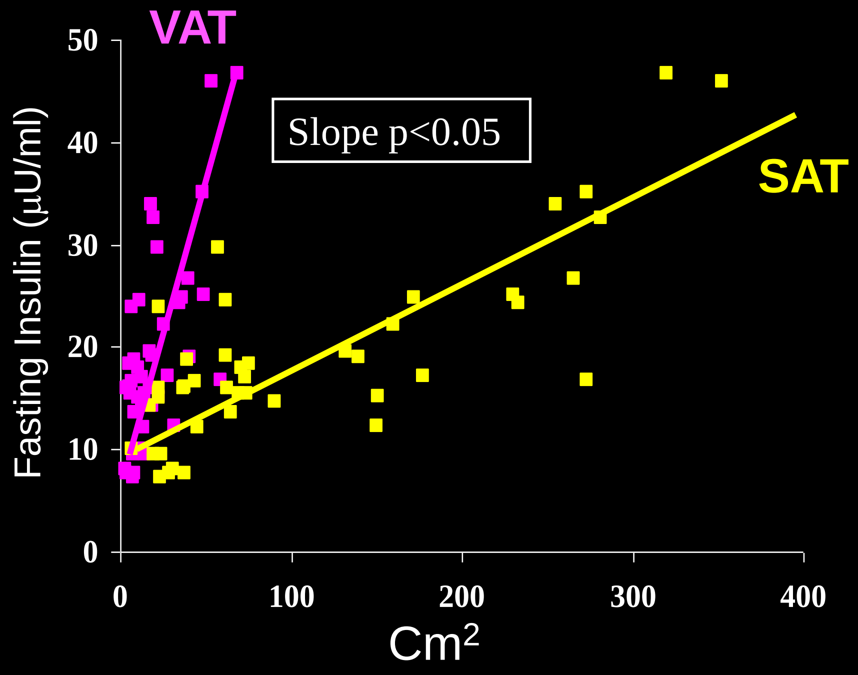
BMI 35.2
% BF 43.4



JCEM 88: 2534, 2003
Diabetes Care 2004

Correlation of VAT & SAT to Insulin Sensitivity & Fasting Insulin

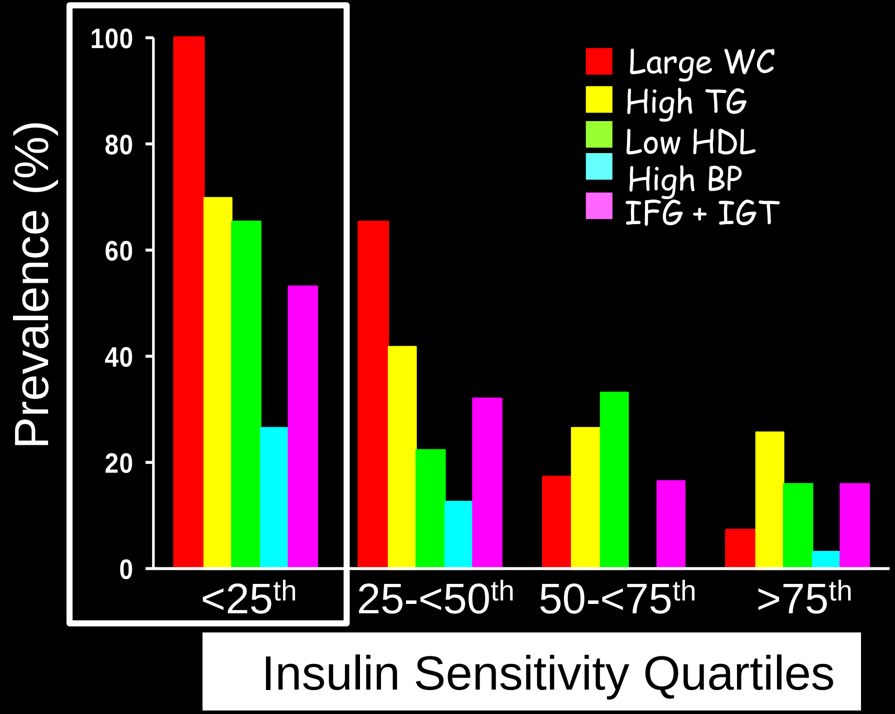


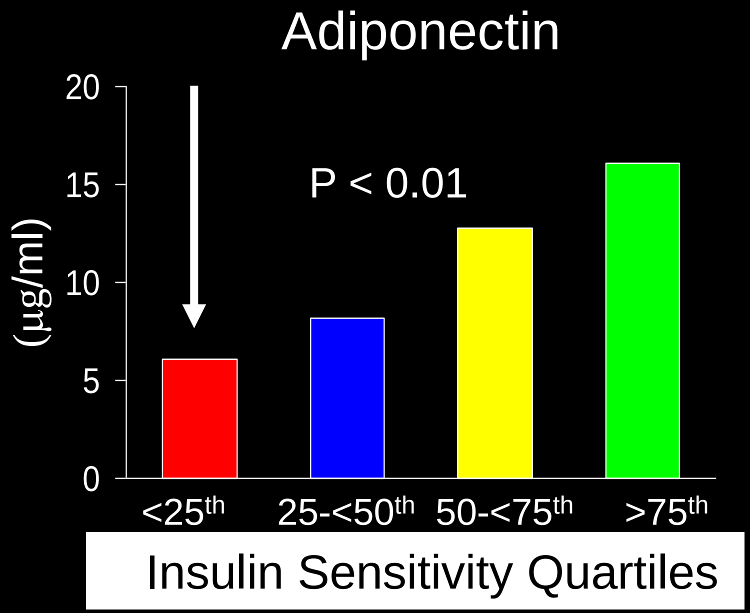


Insulin Resistance

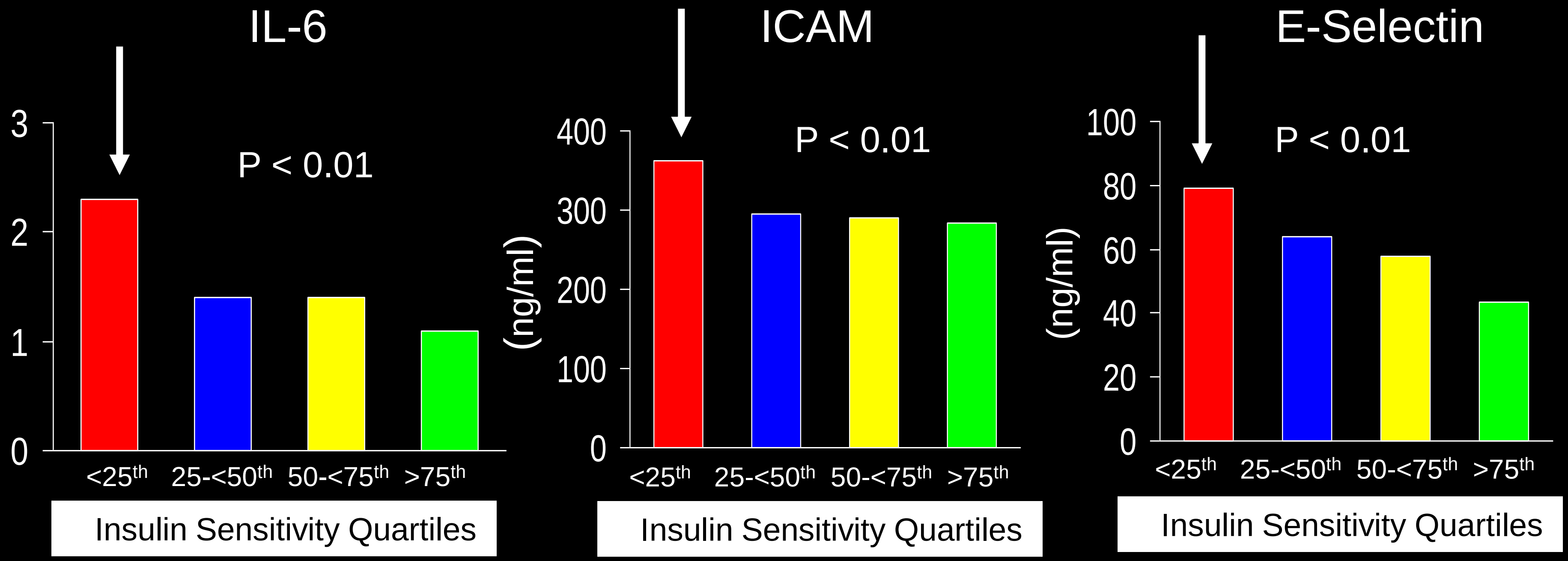
Link to the components of the metabolic syndrome and biomarkers of endothelial dysfunction in youth

Diabetes Care 30: 2091, 2007

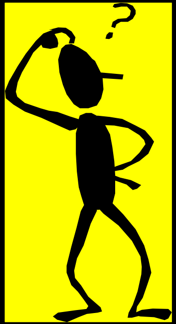




Insulin Sensitivity Quartiles & Biomarkers of Endothelial Dysfunction

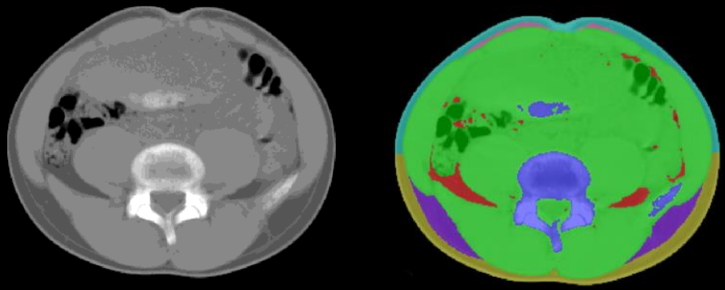


Question



Are all obese youth the same or have similar risk for T2DM or CVD?

Metabolically Healthy vs. Unhealthy Obese Youth



Fat metabolically **fit** obese youth

AGE: 13.2 yr

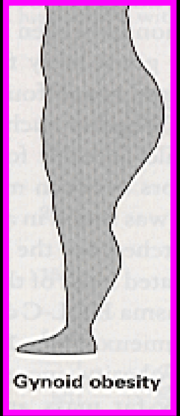
BMI: 32.6 kg/m^2

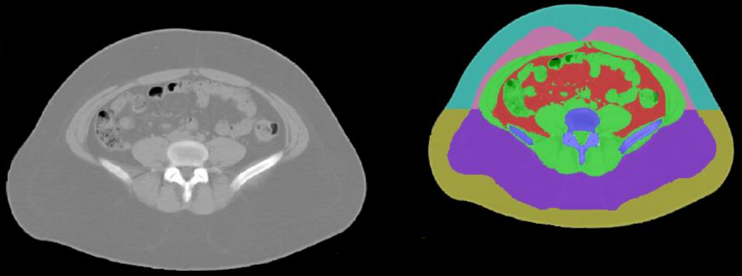
% Body Fat: 42.6%

W/H ratio: 0.86

VAT: 60.0 cm^2

Insulin Sensitivity: 4.5 L





Fat metabolically **unfit** obese youth

AGE: 12.8 yr

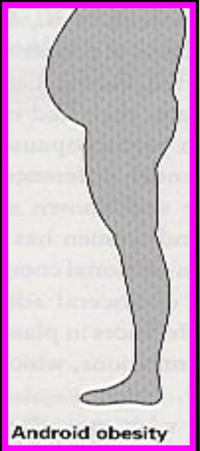
BMI: 33.2 kg/m^2

% Body Fat: 43.8%

W/H ratio: 0.93

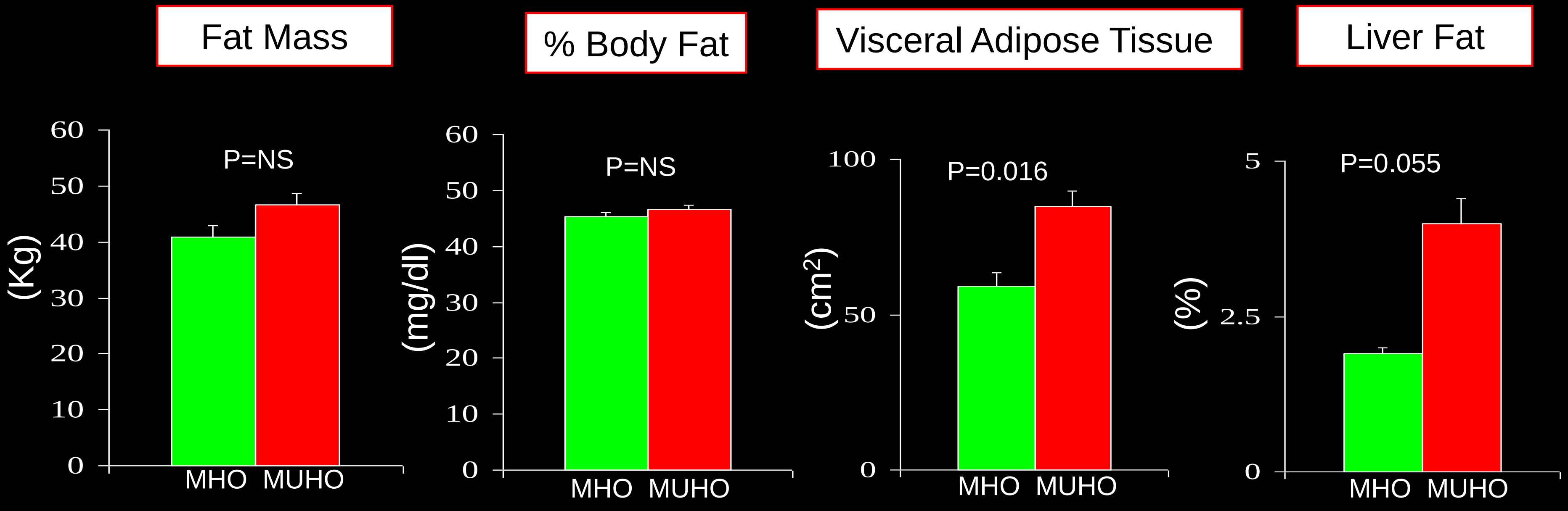
VAT: 93.9 cm^2

Insulin Sensitivity: 1.7

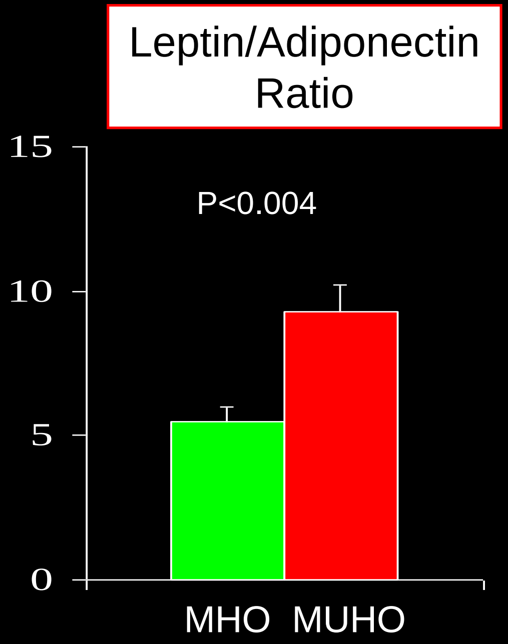


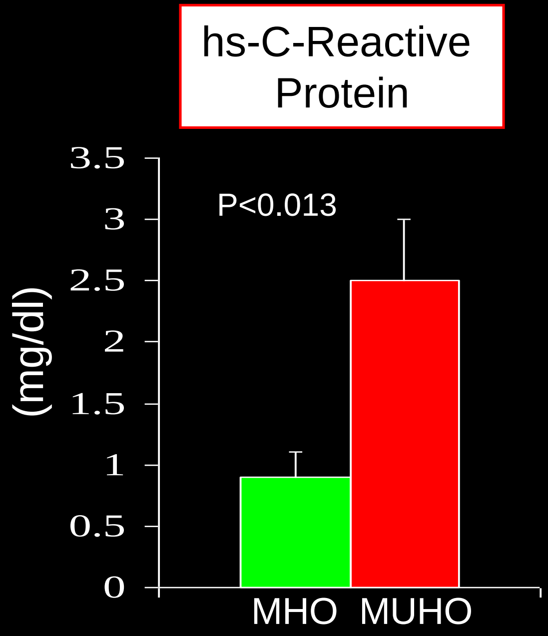
Whole Body, Visceral Adiposity, and Liver Fat in Metabolically Healthy vs. Unhealthy Obese Youth

2006
2016
2019



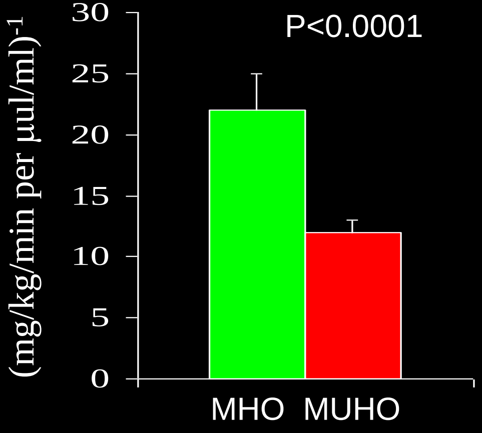
Adipokines & Inflammatory Markers in Metabolically **Healthy** vs. **Unhealthy** Obese Youth



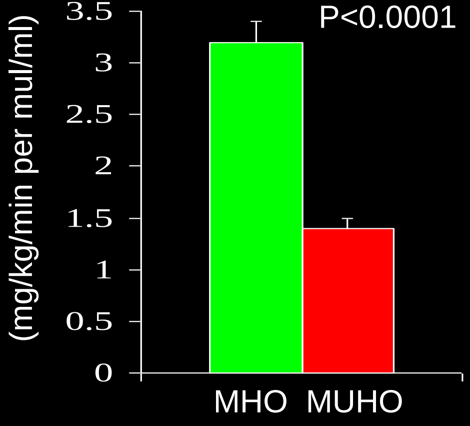


Type 2 Diabetes Risk in Metabolically **Healthy** vs. **Unhealthy** Obese Youth

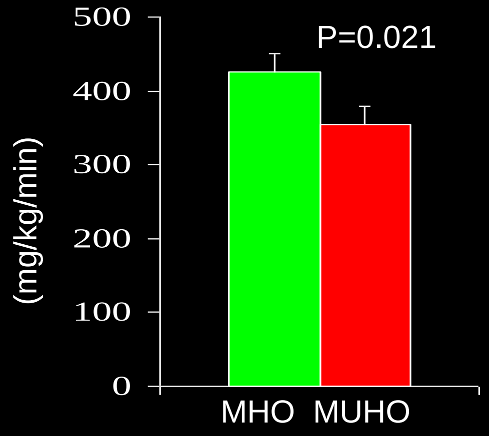
Hepatic
Insulin Sensitivity



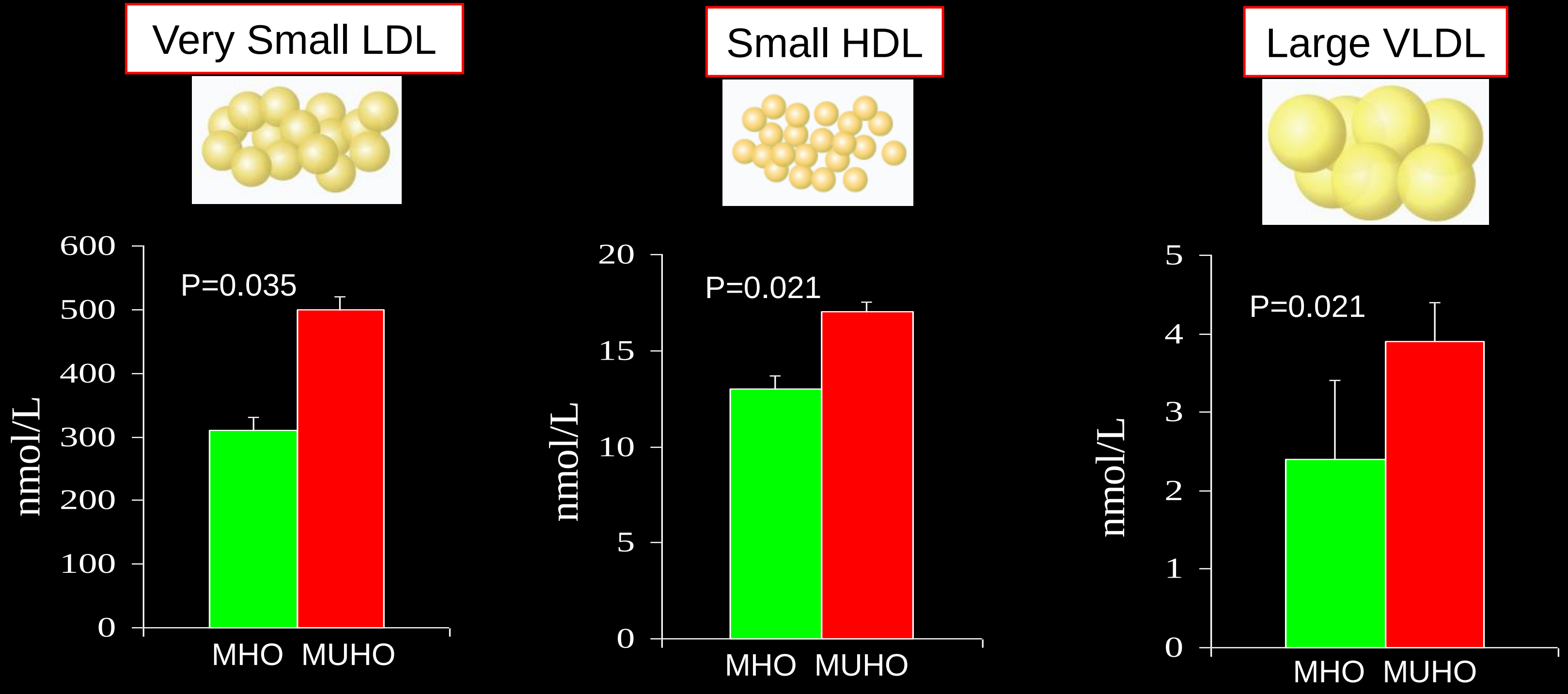
Peripheral
Insulin Sensitivity



β-cell Function
Relative to IS



Atherogenic Lipoprotein Concentrations in Metabolically **Healthy** vs. **Unhealthy** Obese Youth



Take Home Message

Not all obese youth are the same

Metabolically healthy obese youth have more favorable risk profile than metabolically unhealthy youth despite similar BMI and total body fat.

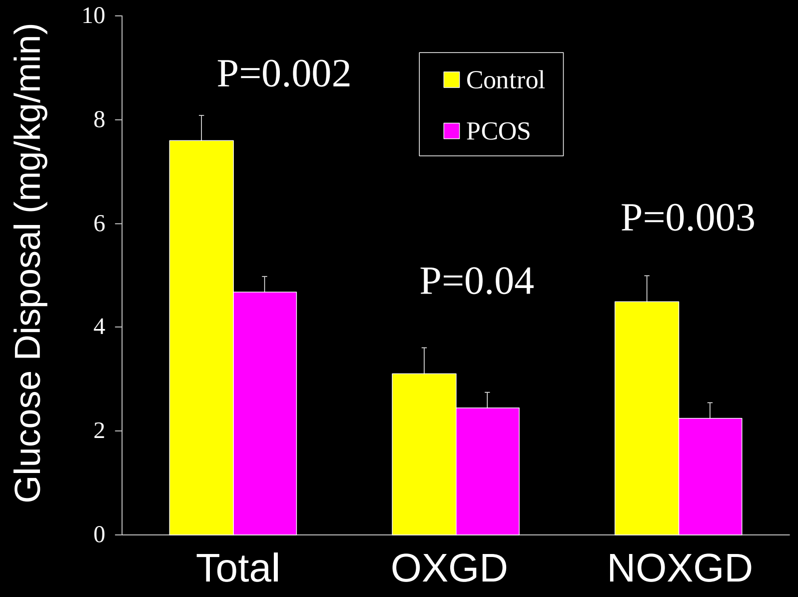
Risk Factors for Insulin Resistance in Youth

Insulin Resistance

- Puberty ✓
- Race ✓
- Genetics ✓
- Obesity ✓
- PCOS
- T2DM
- NAFLD, IUI, etc.

Insulin Sensitivity in Adolescents with PCOS

J Pediatr 138: 38, 2001



	PCOS	Control
Age (yrs)	12.0 ± 0.7	12.1 ± 0.6
Free T. (pg/ml)	7.2 ± 1.4	3.4 ± 1.0
BMI (kg/m^2)	33.1 ± 1.8	31.4 ±1.3
% Body Fat	43.2 ± 1.4	45.6 ± 1.1
FM (kg)	34.8 ±2.9	34.0 ± 2.2
TAF (cm^2)	546 ± 49	484 ± 44

Risk Factors for Insulin Resistance in Youth

NAFLD, IUI, etc.

Puberty ✓

T2DM

Insulin Resistance

Race ✓

✓ PCOS

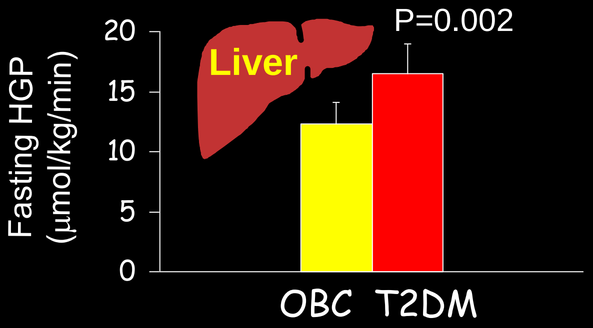
Genetics ✓

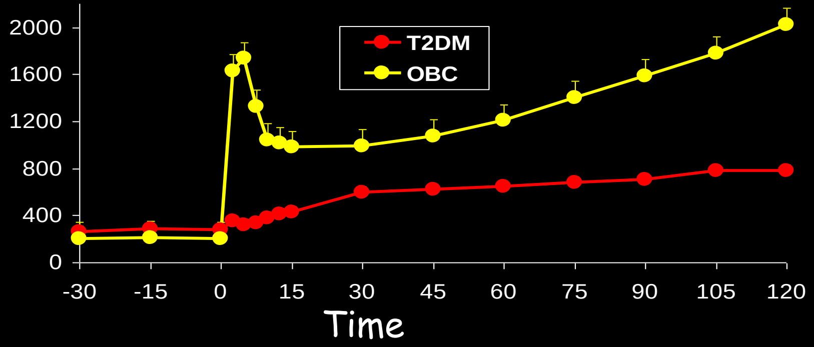
Obesity ✓

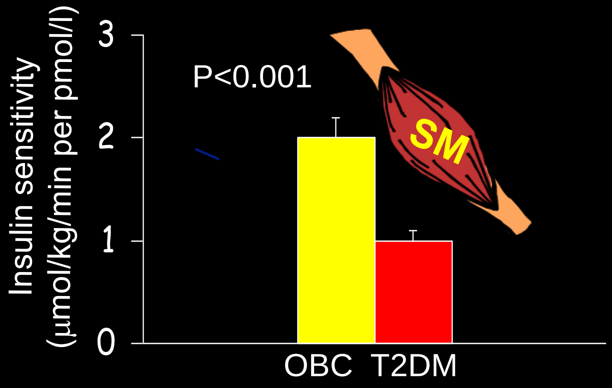
Diabetes Care 28: 638, 2005

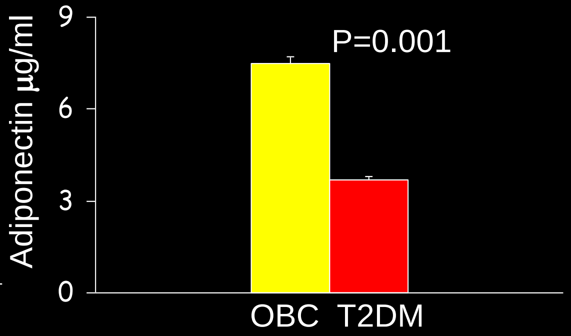
Youth Type 2 Diabetes

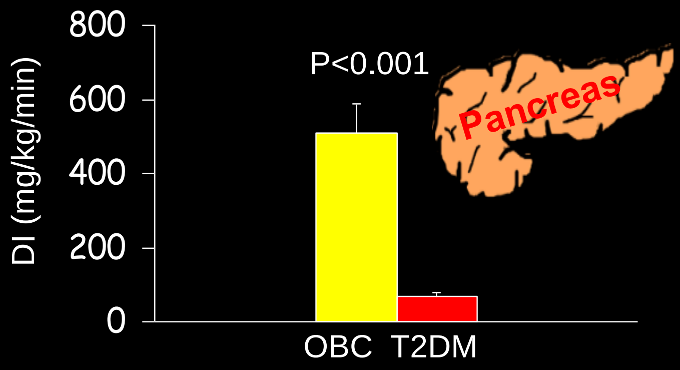
Insulin resistance, β-cell failure, or both?





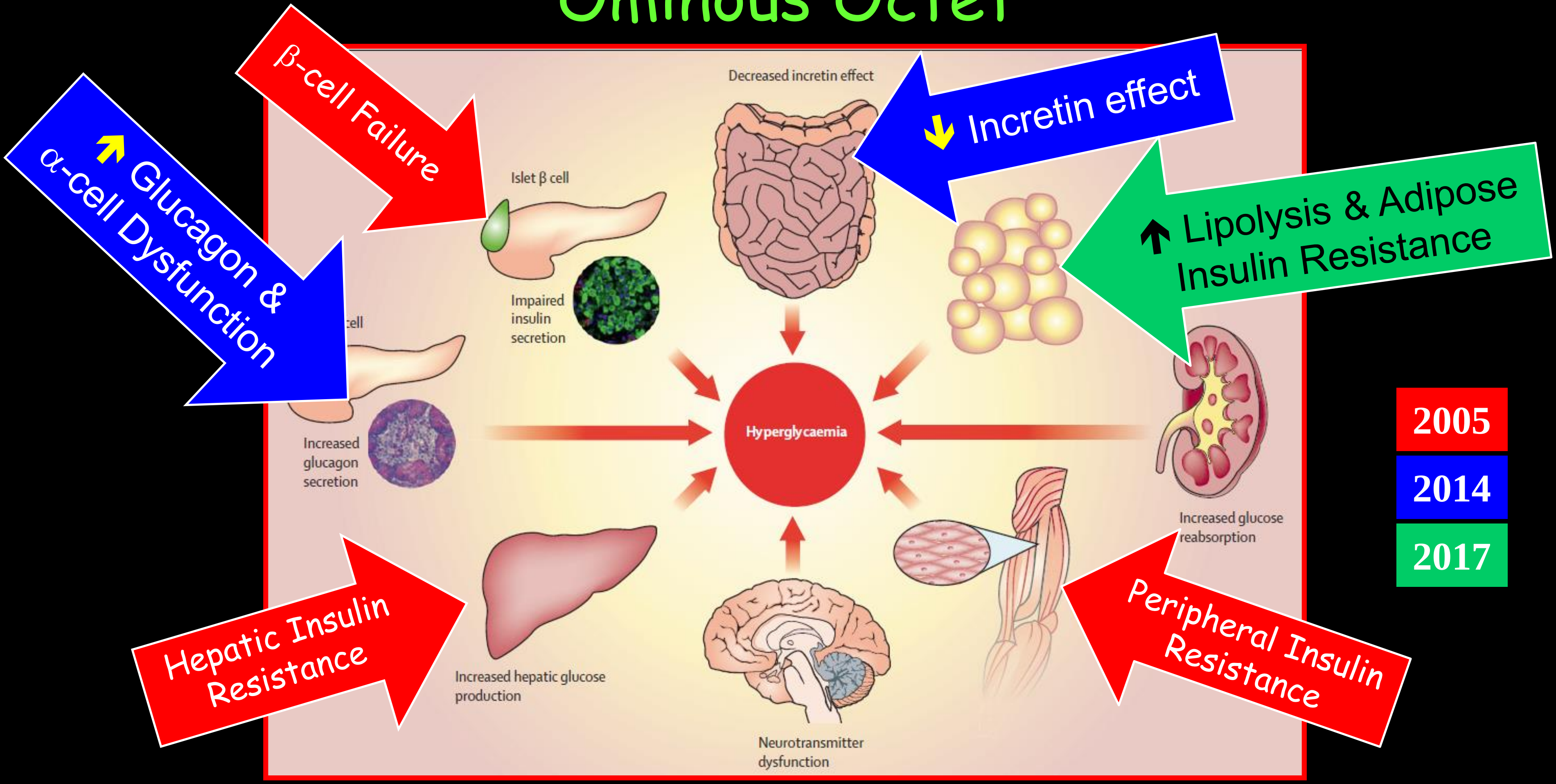






Diabetes 58: 773, 2009

Ominous Octet



2005

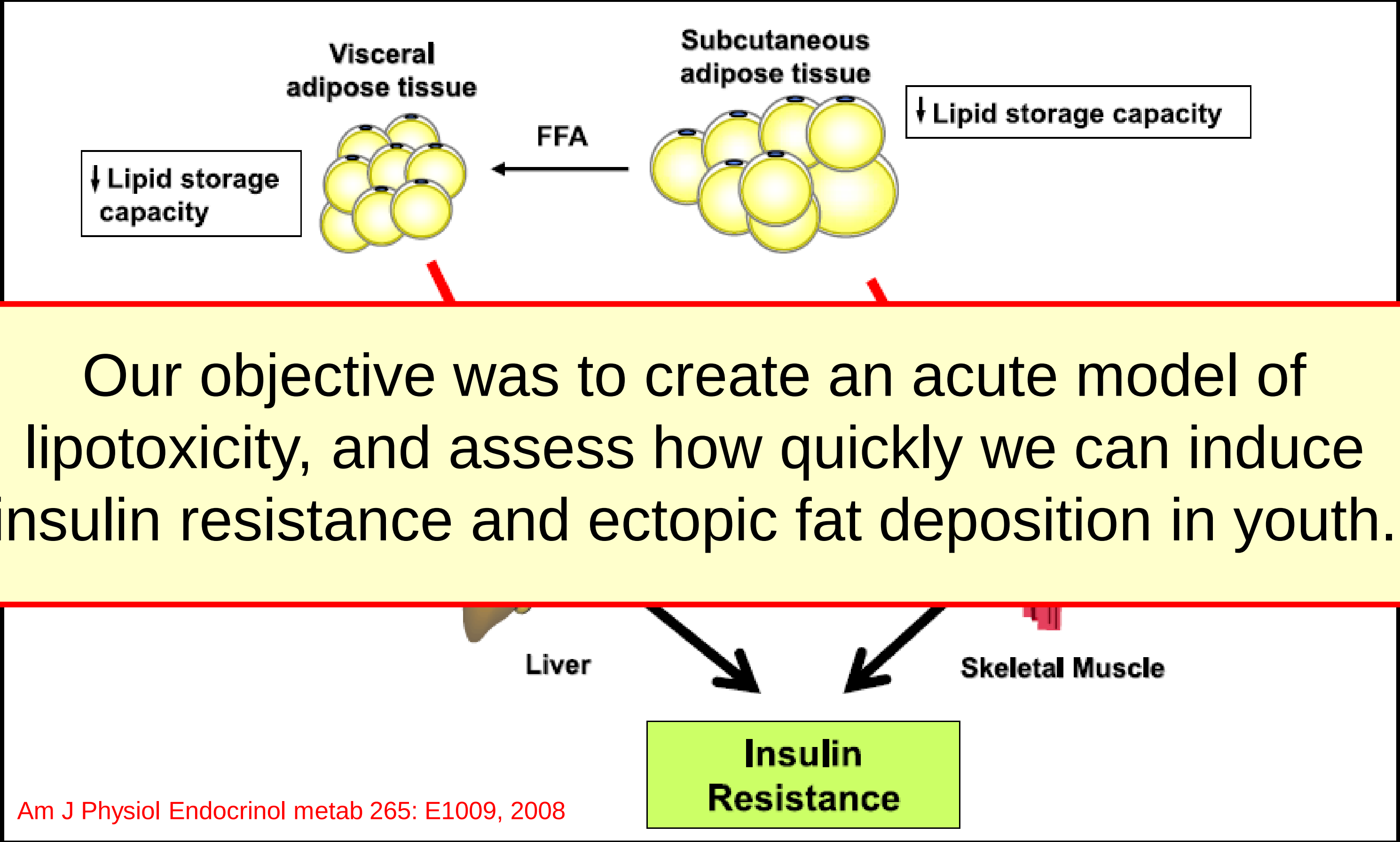
2014

2017

Insulin Resistance in Youth

- Risk factors: Modifiable and Unmodifiable
- Induction of Insulin Resistance
- Alleviation of Insulin Resistance
- Youth-Adult Contrast in Insulin Sensitivity

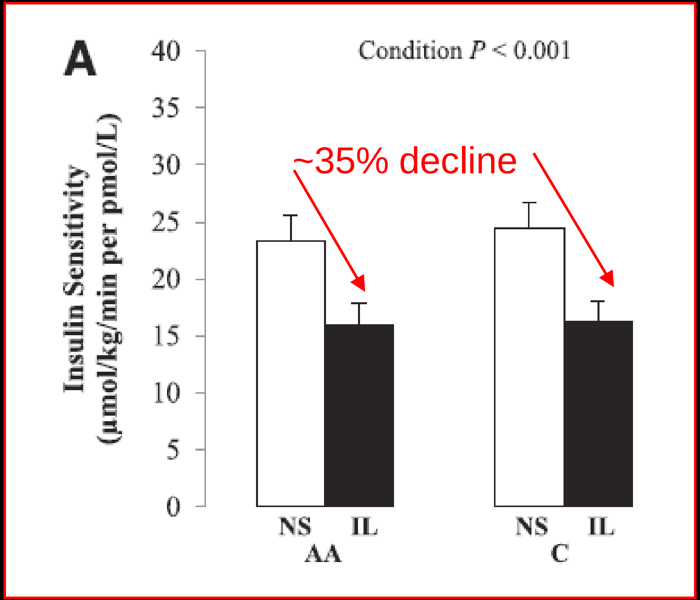
Fat Induced Insulin Resistance Model



Our objective was to create an acute model of lipotoxicity, and assess how quickly we can induce insulin resistance and ectopic fat deposition in youth.

Am J Physiol Endocrinol metab 265: E1009, 2008

Insulin Sensitivity in Response to FFA Elevation in Prepubertal Youth



Diabetes 62: 2917, 2012

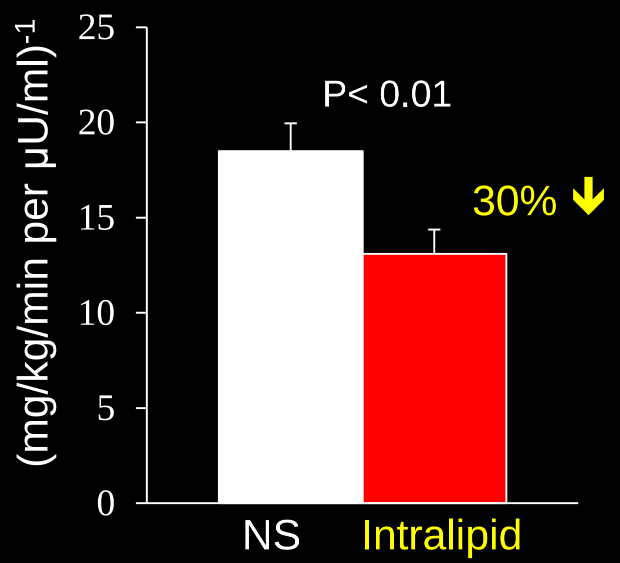
Paired experiments of NS vs. **20% IL** infusion for 3 hrs. followed by a 2hr. hyerglycemic clamp

FFA: ↑ from ~ 0.21 to 0.61 mmol/L

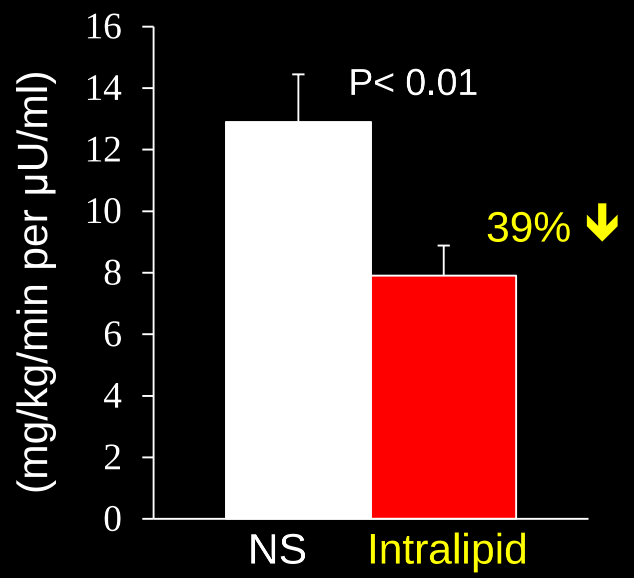
Effect of Intralipid Infusion on Hepatic & Peripheral Insulin Sensitivity in Healthy Normal-Weight Adolescents

(2013)

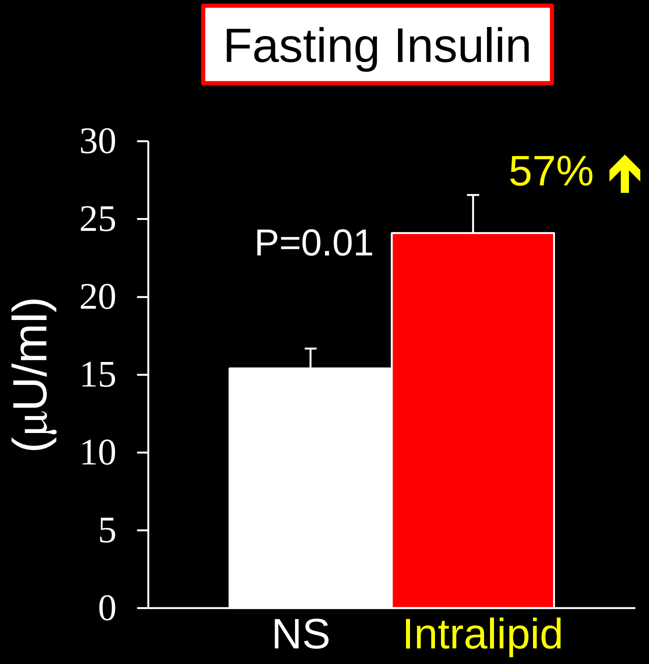
Hepatic Insulin Sensitivity

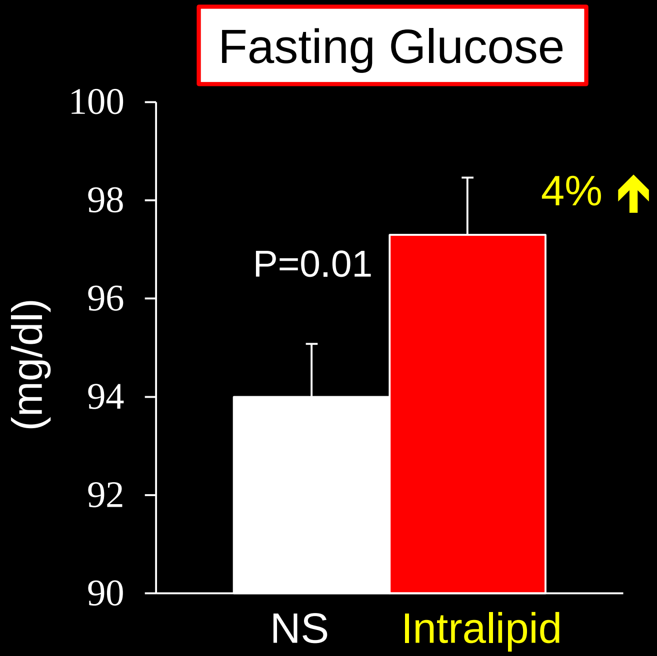


Peripheral Insulin Sensitivity

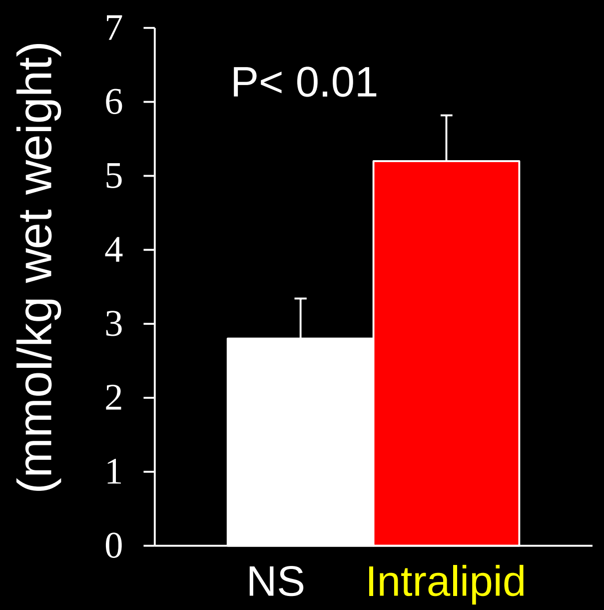


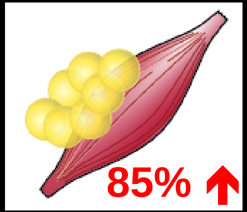
Effect of Intralipid Infusion on Fasting Glucose & Insulin in Healthy Normal-Weight Adolescents





Effect of Intralipid Infusion on Intramyocellular Lipid (IMCL) in Healthy Normal-Weight Adolescents

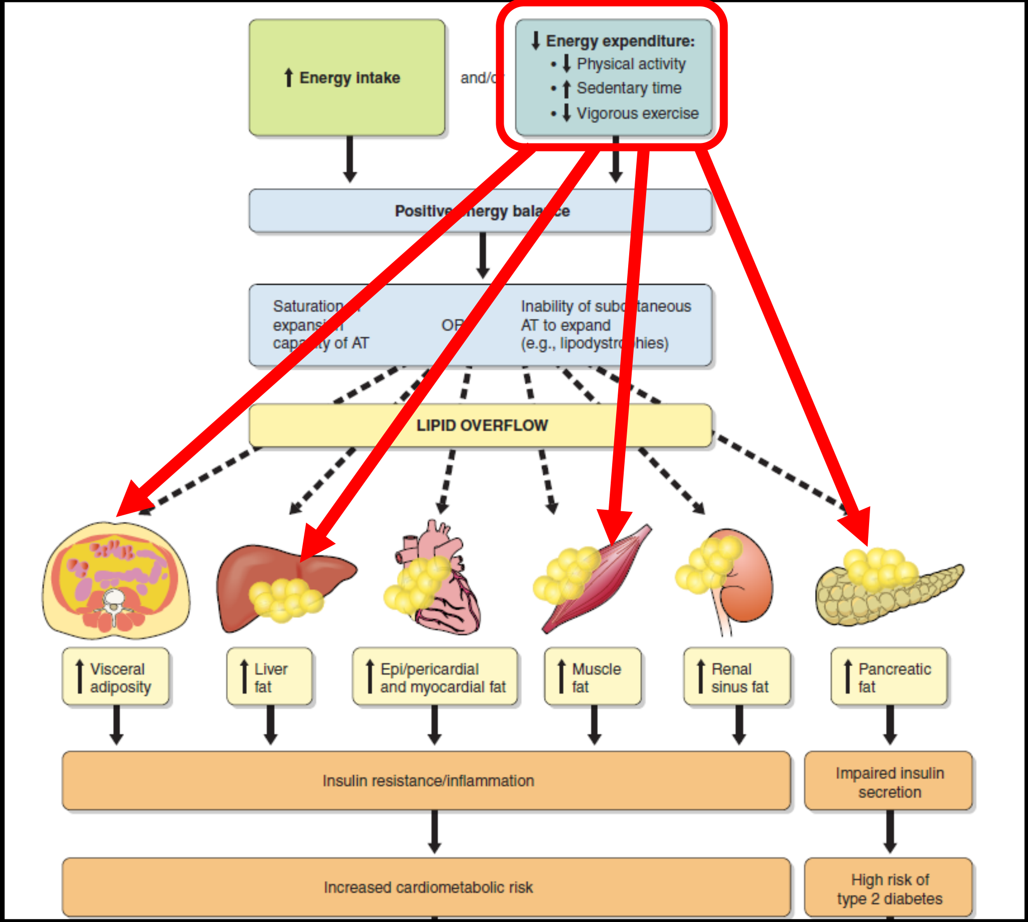




Insulin Resistance in Youth

- Risk factors: Modifiable and Unmodifiable
- Induction of Insulin Resistance
- Alleviation of Insulin Resistance
- Youth-Adult Contrast in Insulin Sensitivity

Lipid Overflow Theory

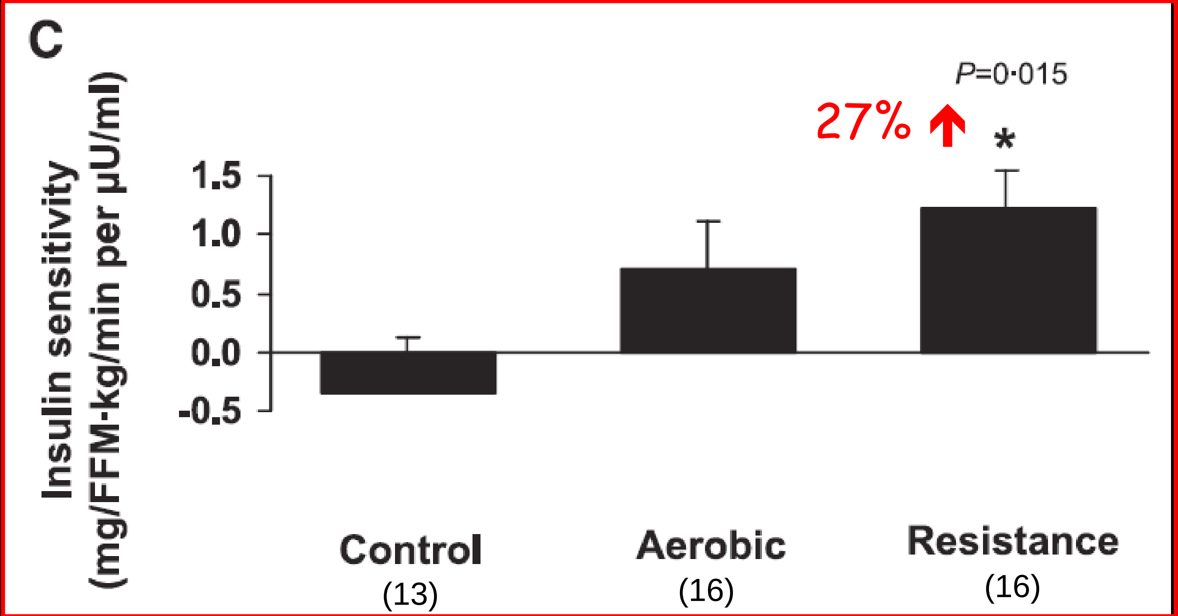


Physiol Rev 93: 359, 2013

Effects of Aerobic Versus Resistance Exercise Without Caloric Restriction on Abdominal Fat, Intrahepatic Lipid, and Insulin Sensitivity in Obese Adolescent Boys

A Randomized, Controlled Trial

Diabetes 61: 1-9, 2012

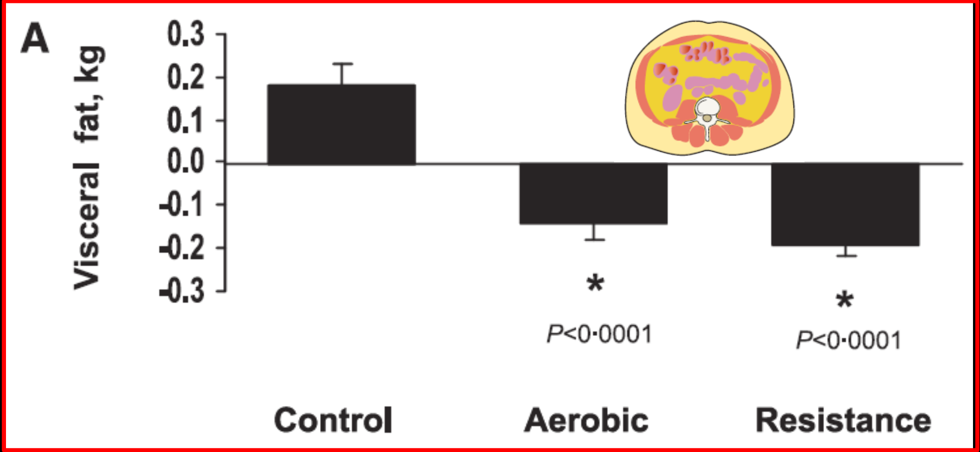


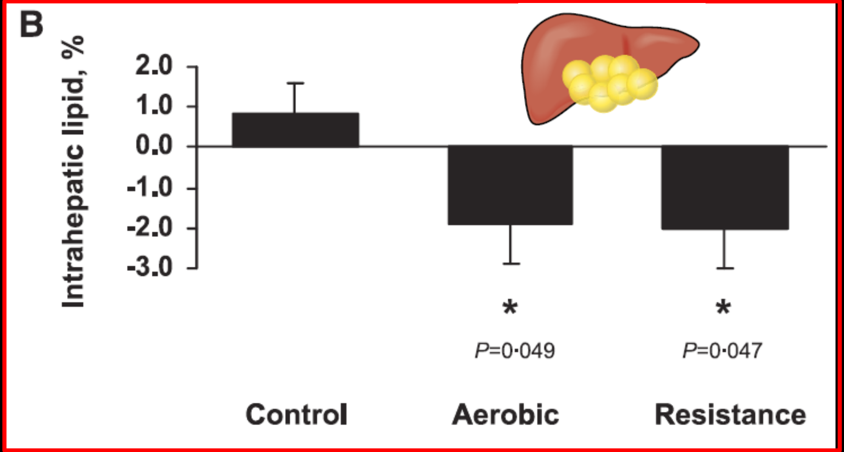
3 m. exercise training
3x/week, 60 min/session
no calorie restriction
Average Wt. 100 Kg

Effects of Aerobic Versus Resistance Exercise Without Caloric Restriction on Abdominal Fat, Intrahepatic Lipid, and Insulin Sensitivity in Obese Adolescent Boys

A Randomized, Controlled Trial

Diabetes 61: 1-9, 2012





Insulin Resistance in Youth

- Risk factors: Modifiable and Unmodifiable
- Induction of Insulin Resistance
- Alleviation of Insulin Resistance
- Youth-Adult Contrast in Insulin Sensitivity

Treatment Options for type 2 Diabetes in Adolescents and Youth

Overall Failure rate 45.6%

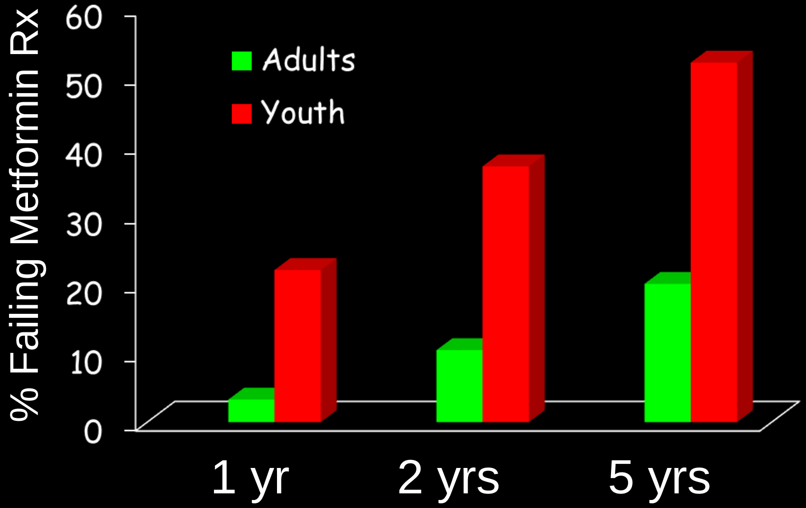
Metformin Failure rate 51.7%

Met + Rosi Failure rate 38.6%

Designed in 2002, ended 2/2011, results April 2012

Metformin failure Rate in T2DM

Adults vs. Youth

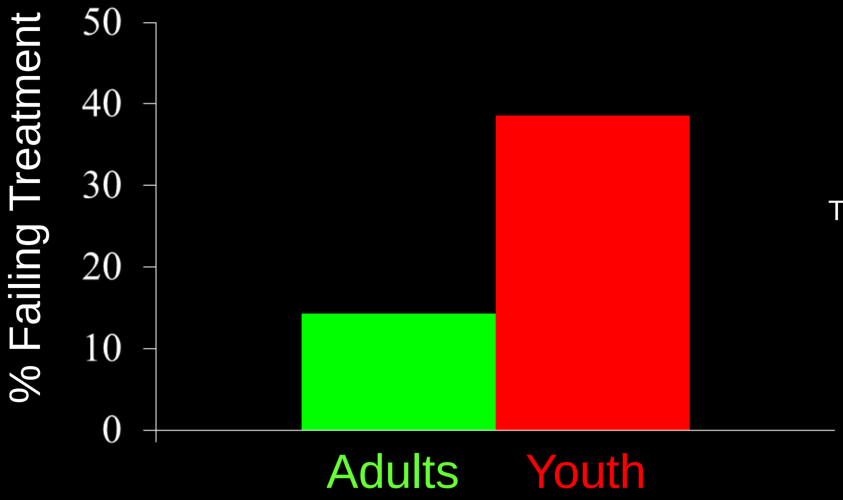


Failure Definition
TODAY: HbA1c >8% x 6m
ADOPT : FG > 180 mg/dl x 2.

Kahn et al for ADOPT study, NEJM 2006
Zeitler et al for TODAY study, NEJM 2012

Metformin + Rosi Failure Rate in T2DM

Adults vs. Youth



Failure Definition
TODAY: HbA1c >8% x 6m
DOD: Start of Insulin

Rascati et al Diabetes, Obesity & Metabolism 2013
Zeitler et al for TODAY study, NEJM 2012

Natural History of Type 2 Diabetes

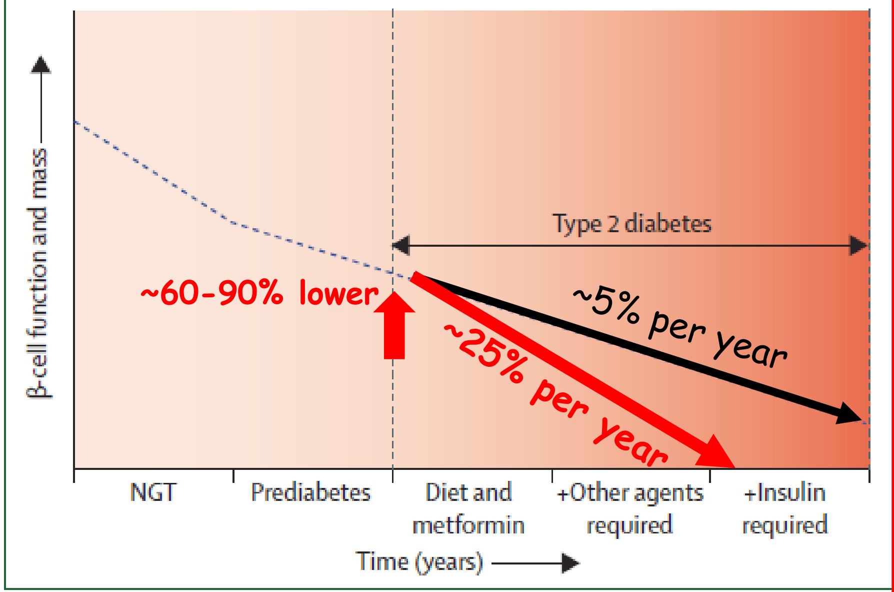


Figure 6: Natural history of type 2 diabetes and possible inadequacies of the standard therapeutic approach

Lancet June 25, 2011

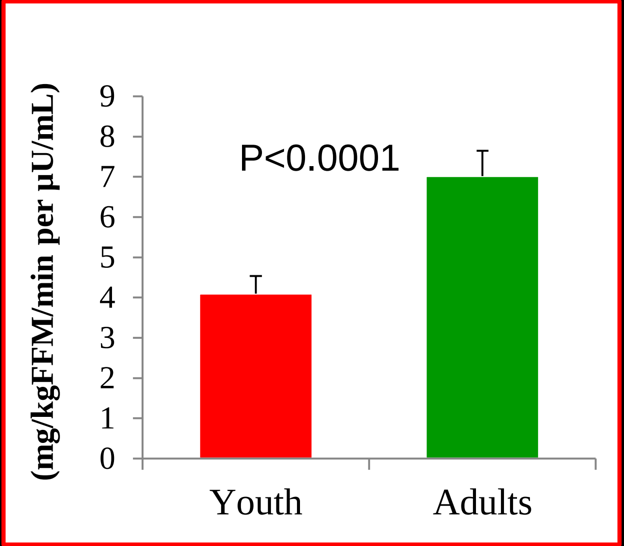
Youth Type 2 Diabetes

One or more of the pathophysiological mechanisms of type 2 diabetes is worse in youth compared with adults.

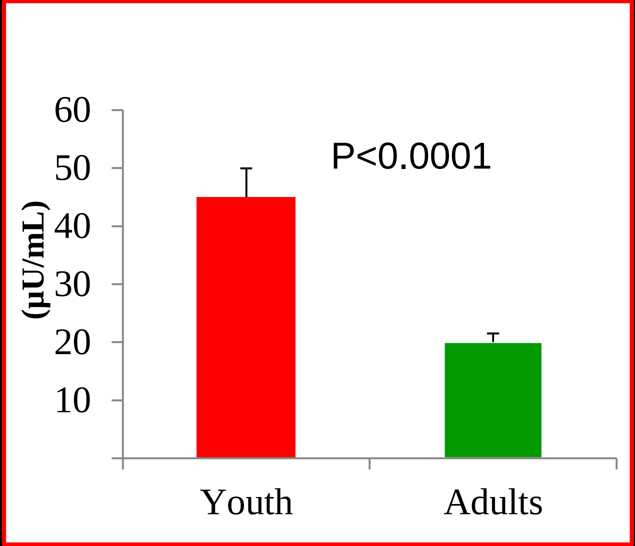
Insulin sensitivity across the lifespan from obese adolescents to obese adults with impaired glucose tolerance: Who is worse off?

Pediatric Diabetes 2017

Insulin Sensitivity



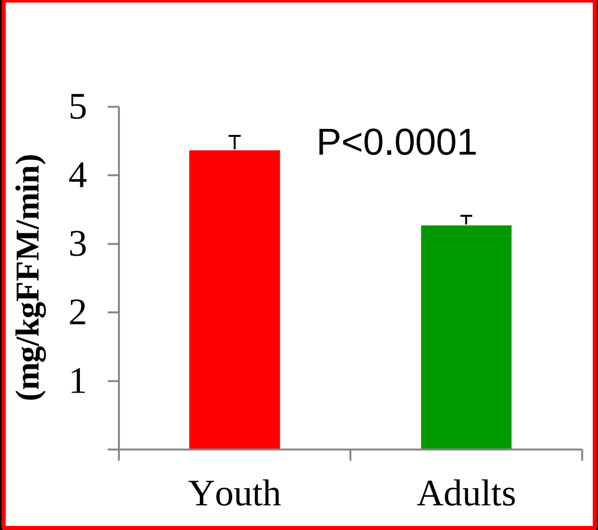
Fasting Insulin



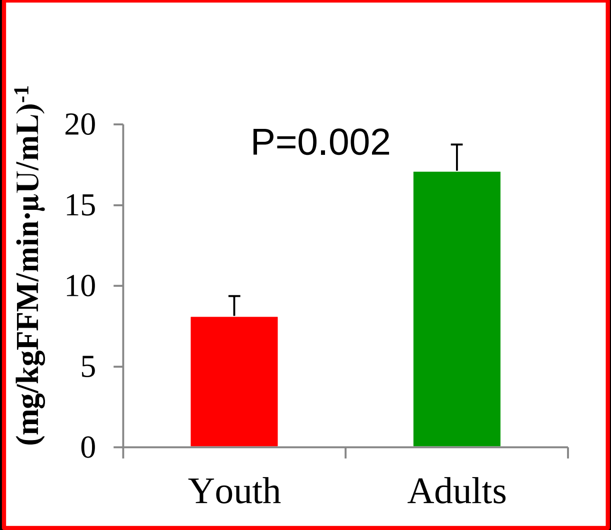
Insulin sensitivity across the lifespan from obese adolescents to obese adults with impaired glucose tolerance: Who is worse off?

Pediatric Diabetes 2017

Hepatic Glucose Production



Hepatic Insulin Sensitivity



University of Pittsburgh

Tack


Pittsburgh