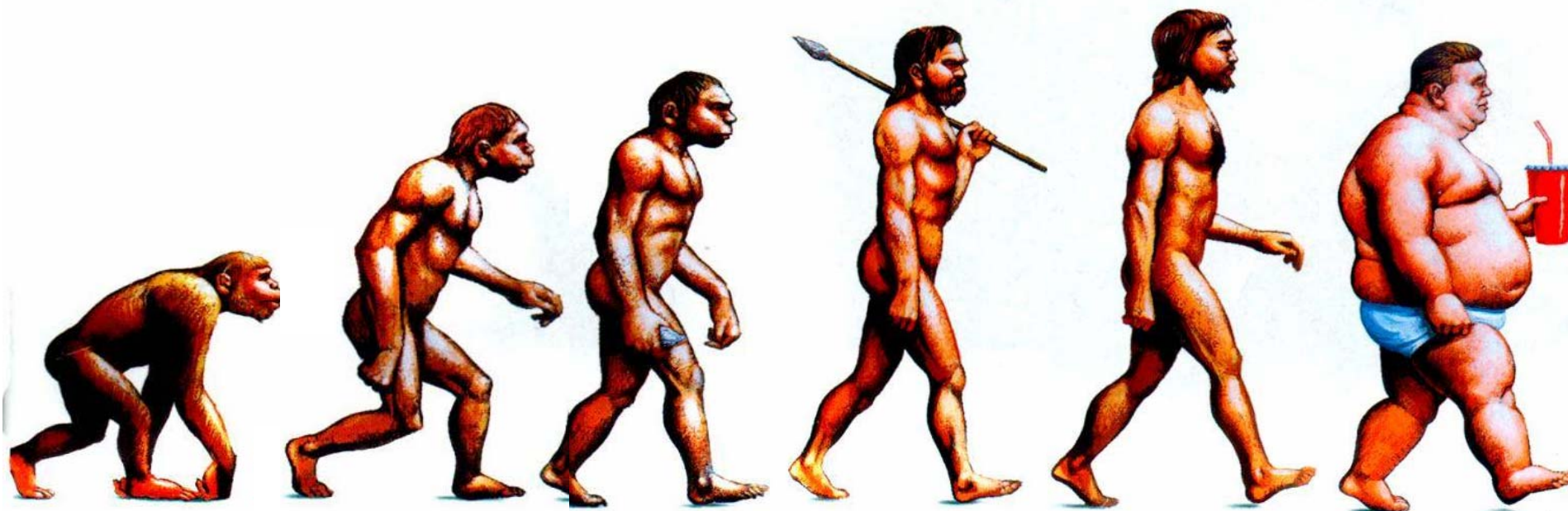




# The Metabolic Syndrome in Children and Adolescents



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Pediatric Clinical Pharmacist



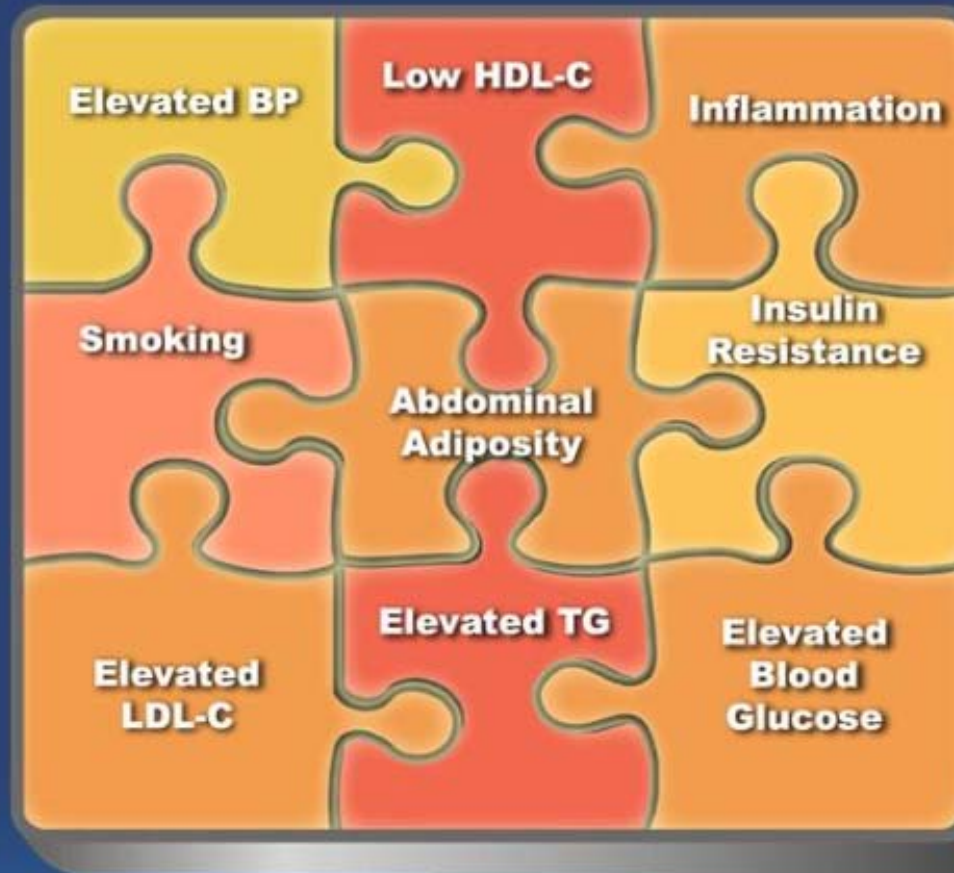
# The Metabolic Syndrome

- Metabolic syndrome: children vs. adults
  - Definition
  - Clinical Implications

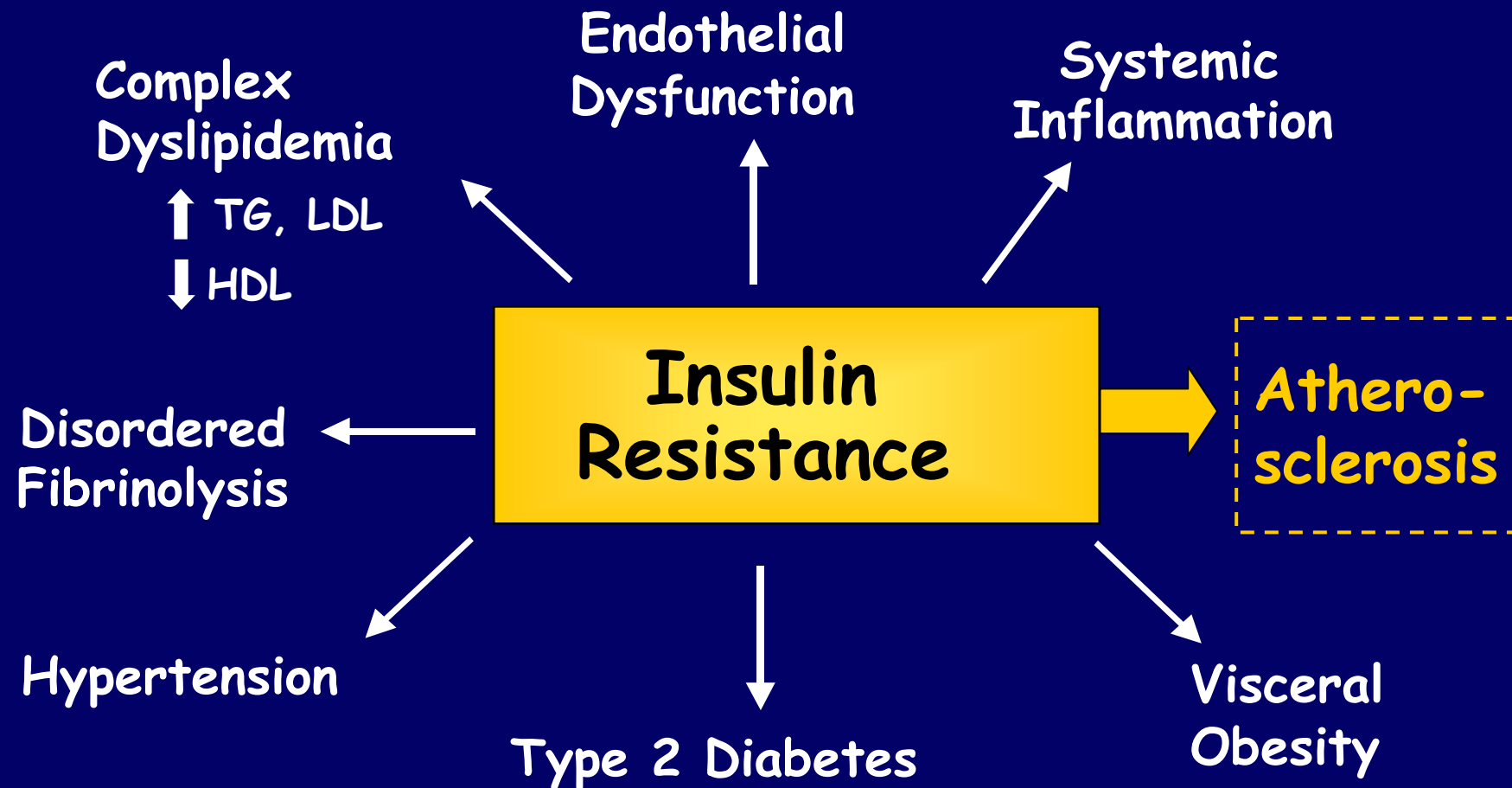
# Cardiometabolic Risk



## Cardiometabolic Risk Factors Tend to Cluster



# The Metabolic Syndrome



Diabetes Care, 1998  
JAMA, 2001



# WHO Criteria for Metabolic Syndrome

In order to make a diagnosis of the metabolic syndrome a patient must present with glucose intolerance, impaired glucose tolerance (IGT) or diabetes and/or insulin resistance, together with two or more of the following components:

- Impaired glucose regulation or diabetes
- Insulin resistance (under hyperinsulinaemic euglycaemic conditions, glucose uptake below lowest quartile for background population under investigation)
- Raised arterial pressure  $\geq 140/90$  mm Hg
- Raised plasma triglycerides ( $\geq 1.7$  mmol/L; 150 mg/dL) and/or low HDL cholesterol ( $< 0.9$  mmol/L, 35 mg/dL men;  $< 1.0$  mmol/L, 39 mg/dL women)
- Central obesity (males: waist to hip ratio  $> 0.90$ ; females: waist to hip ratio  $> 0.85$ ) and/or BMI  $> 30$  kg/m<sup>2</sup>
- Microalbuminuria (urinary albumin excretion rate  $\geq 20$ g/min or albumin:creatinine ratio  $\geq 30$  mg/g)

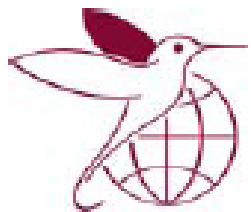
# ATP III Definition of Metabolic Syndrome



Three or more of the following five risk factors:

Risk factor	Defining level
Central obesity <ul style="list-style-type: none"><li>• Men</li><li>• Women</li></ul>	Waist circumference > 102 cm (> 40 in) > 88 cm (> 35 in)
Triglycerides	≥ 150 mg/dL (1.7 mmol/L)
HDL cholesterol <ul style="list-style-type: none"><li>• Men</li><li>• Women</li></ul>	< 40 mg/dL (1.03 mmol/L) < 50 mg/dL (1.29 mmol/L)
Blood pressure	≥ 130/ ≥ 85 mm Hg
Fasting glucose	≥ 110 mg/dL (6.1 mmol/L)

*National Cholesterol Education Program. JAMA, 2001*



# The IDF Definition of Metabolic Syndrome

**Central obesity** (defined as waist circumference  $\geq 94$ cm for European men and  $\geq 80$ cm for European women, with ethnicity specific values for other groups)

plus any two of the following four factors:

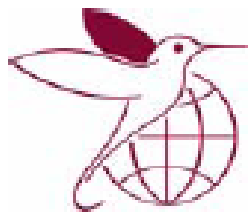
- **raised TG level:**  $\geq 150$  mg/dL (1.7 mmol/L), or **specific treatment for this lipid abnormality**
- **reduced HDL cholesterol:**  $< 40$  mg/dL (1.03 mmol/L\*) in males and  $< 50$  mg/dL (1.29 mmol/L\*) in females, or **specific treatment for this lipid abnormality**
- **raised blood pressure:** systolic BP  $\geq 130$  or diastolic BP  $\geq 85$  mm Hg, or **treatment of previously diagnosed hypertension**
- **raised fasting plasma glucose (FPG)**  $\geq 100$  mg/dL (5.6 mmol/L), or **previously diagnosed type 2 diabetes**  
*If above 5.6 mmol/L or 100 mg/dL, OGTT is strongly recommended but is not necessary to define presence of the syndrome.*



# The Definition of MS in Children

- There was no single definition of the MS in children
- Most definitions were adaptations of the adult:
  - National Cholesterol Education Program
  - WHO World Health Organization
  - European Group for the Study of Insulin Resistance
  - Unique definitions



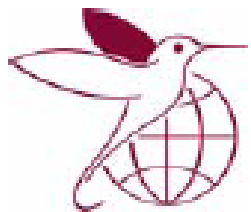


# The IDF Definition of Metabolic Syndrome in Children

## Age 6 to <10 years

- Obesity  $\geq$  90th percentile as assessed by waist circumference
- Metabolic syndrome cannot be diagnosed, but further measurements should be made if family history of metabolic syndrome, type 2 diabetes mellitus, dyslipidaemia, cardiovascular disease, hypertension, or obesity

International Diabetes Federation, Lancet 2007



# The IDF Definition of Metabolic Syndrome in Adolescents

## Age 10 to <16 years

- Obesity  $\geq 90$ th percentile (or adult cutoff if lower) as assessed by waist circumference
- Triglycerides  $\geq 1.7$  mmol/L
- HDL-cholesterol  $< 1.03$  mmol/L
- Blood pressure  $\geq 130$  mm Hg systolic or  $\geq 85$  mm Hg diastolic
- Glucose  $\geq 5.6$  mmol/L (oral glucose tolerance test recommended) or known type 2 diabetes mellitus

## Age $>16$ years

- Use existing IDF criteria for adults<sup>2</sup>

International Diabetes Federation, Lancet 2007



# AHA Scientific Statement

## Progress and Challenges in Metabolic Syndrome in Children and Adolescents

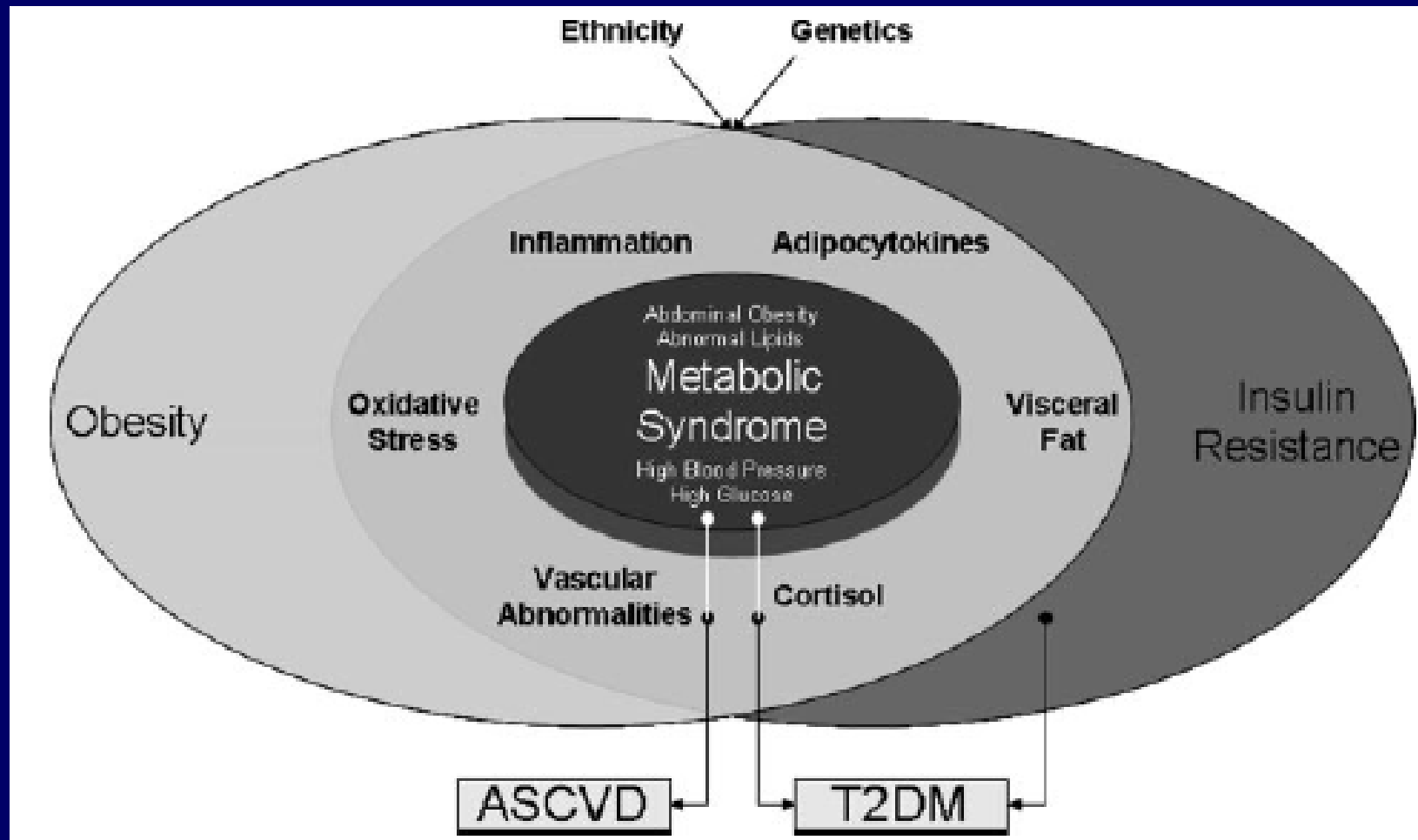
Circulation 2009

# Prevalence of MS in Children



- Third National Health and Nutrition Examination Survey (1988-1994) reported a prevalence of 4%, but the prevalence in overweight children was 30% (*Arch Pediatr Adolesc Med. 2003*)
- A school-based study of North American adolescents found a 4.2% (ATP III) and 8.4% (WHO) prevalence of MS (*J Pediatr. 2004*)
- The prevalence of MS among Canadian children and adolescents was 11.5% (*Int J Obes Relat Metab Disord. 2004*)

# Components of Metabolic Syndrome



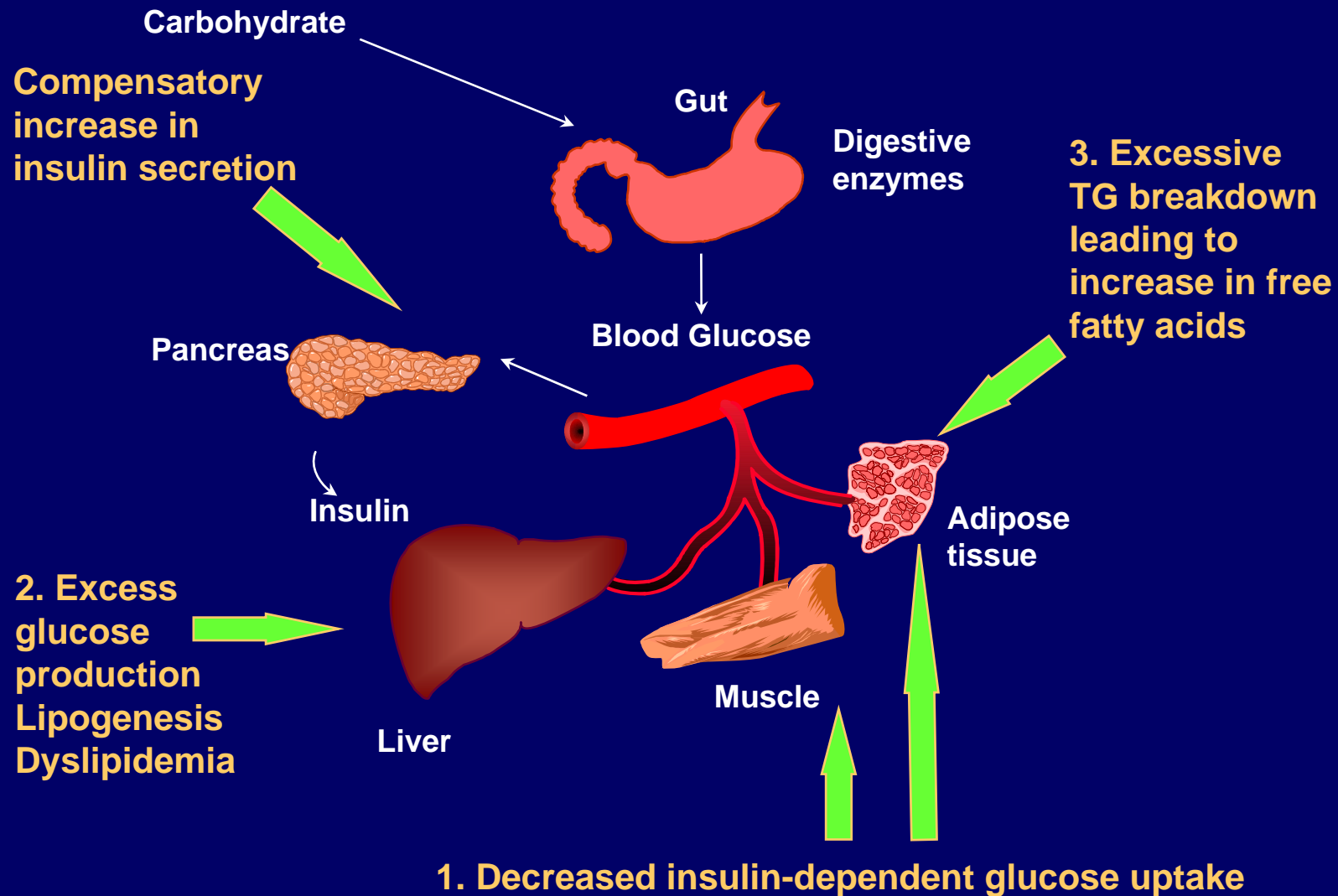


# Insulin Resistance

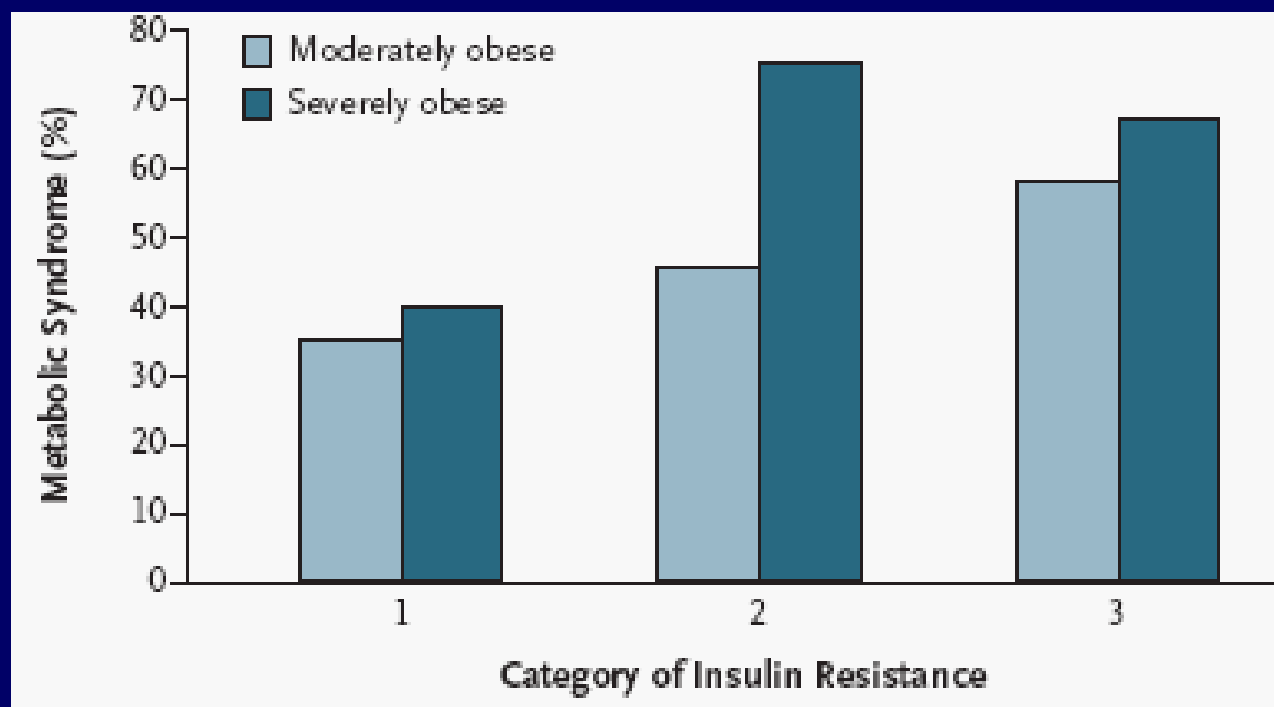
- A core defect in type 2 diabetes
  - A recent study showed that 92% of patients with type 2 diabetes have insulin resistance
- Definition: Impaired response to the physiological effects of insulin (including those on glucose, lipid, and protein metabolism) and the effects on vascular endothelial function

Haffner SM, et al. *Diabetes Care*. 1999;22:562-568.  
Consensus Development Conference of the American Diabetes Association.  
*Diabetes Care*. 1998;21:310-314.

# Insulin resistance



# Insulin Resistance in Obese Children



The prevalence of the MS increased significantly with increasing insulin resistance ( $P < 0.001$ )





# Insulin Resistance and CVD in Children

- Fasting insulin levels in 6-9 -year-old children predicted the children's level of blood pressure at age 9 to 15 years (*Am J Hypertens, 1996*)
- Strong relation over an 8-year period of observation between persistently high fasting insulin levels and the development of cardiovascular risk factors in children and young adults (*Circulation, 1996*)



# Obesity and MS in Children



# Obesity: BMI vs. Waist Circumference

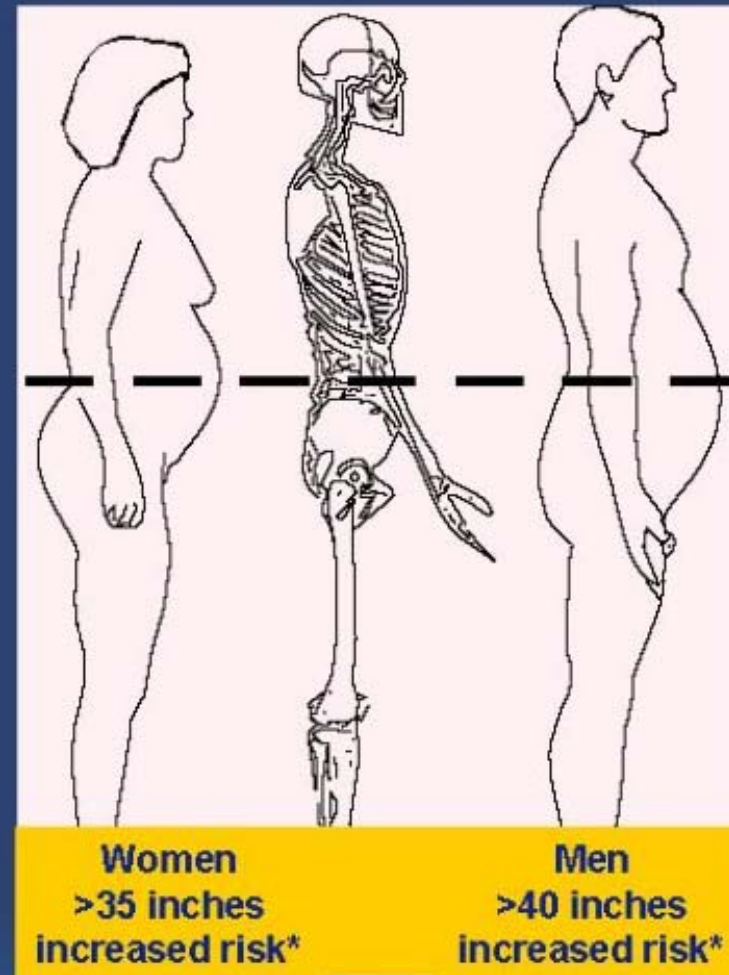
- Waist circumference (WC) is more associated with visceral fat, whereas BMI is more associated with subcutaneous fat  
*(Int J Obes 2006)*
- Visceral fat (MRI), not BMI or waist-hip ratio, was associated with fasting insulin and triglycerides in obese adolescent girls  
*(Am J Clin Nutr 1996)*

# Cardiometabolic Risk



## How to Measure Waist Circumference

- Locate upper hip bone and top of right iliac crest
- Place measuring tape in horizontal plane around abdomen at iliac crest
- Ensure tape is snug, but does not compress the skin
- Tape should be parallel to floor
- Record measurement at the end of a normal expiration

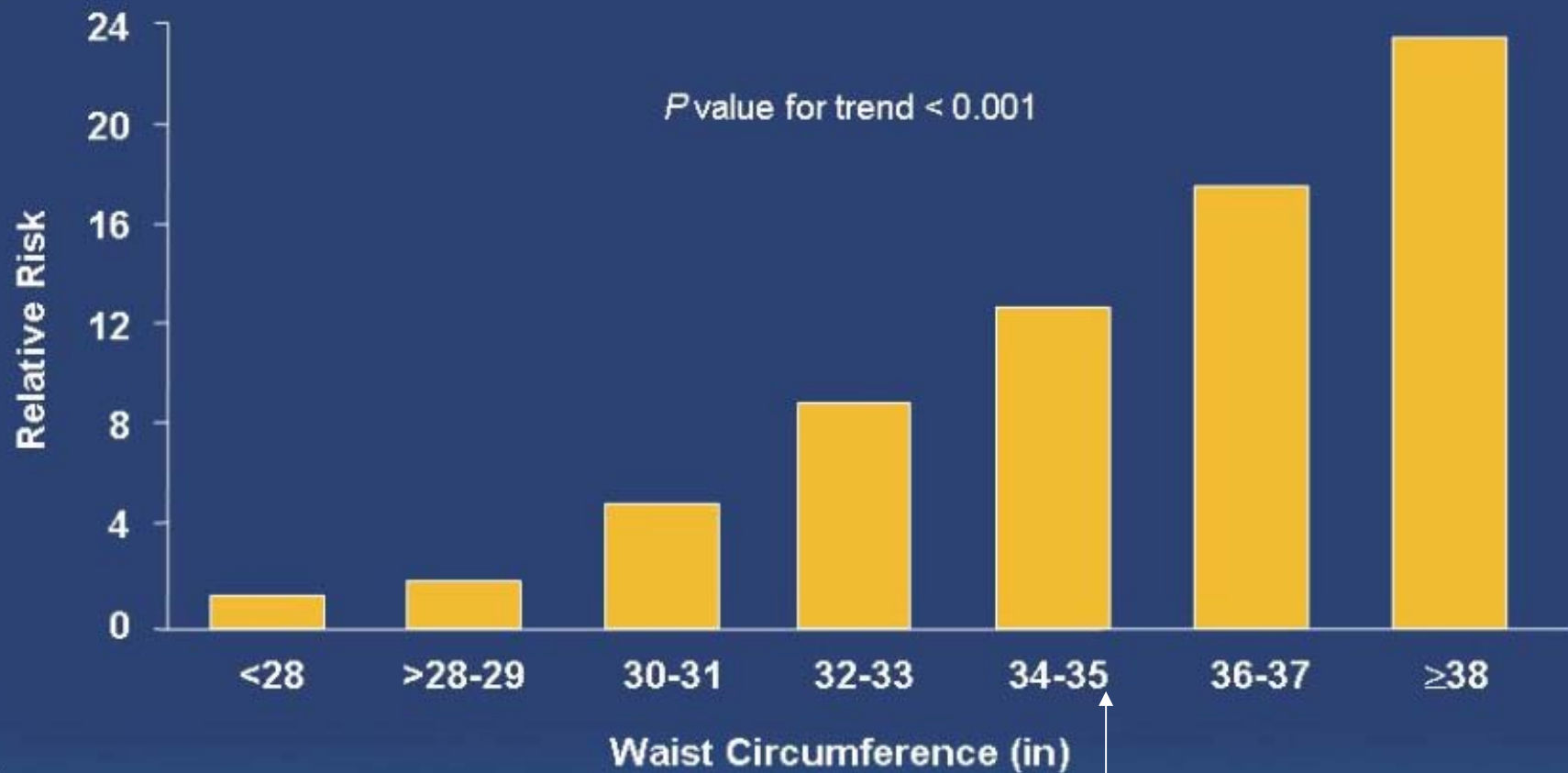


\*Ethnic/age-related differences in body fat distribution may affect validity of waist circumference as surrogate for abdominal fat

## Cardiometabolic Risk



### Abdominal Adiposity Is Associated With Increased Risk of Diabetes

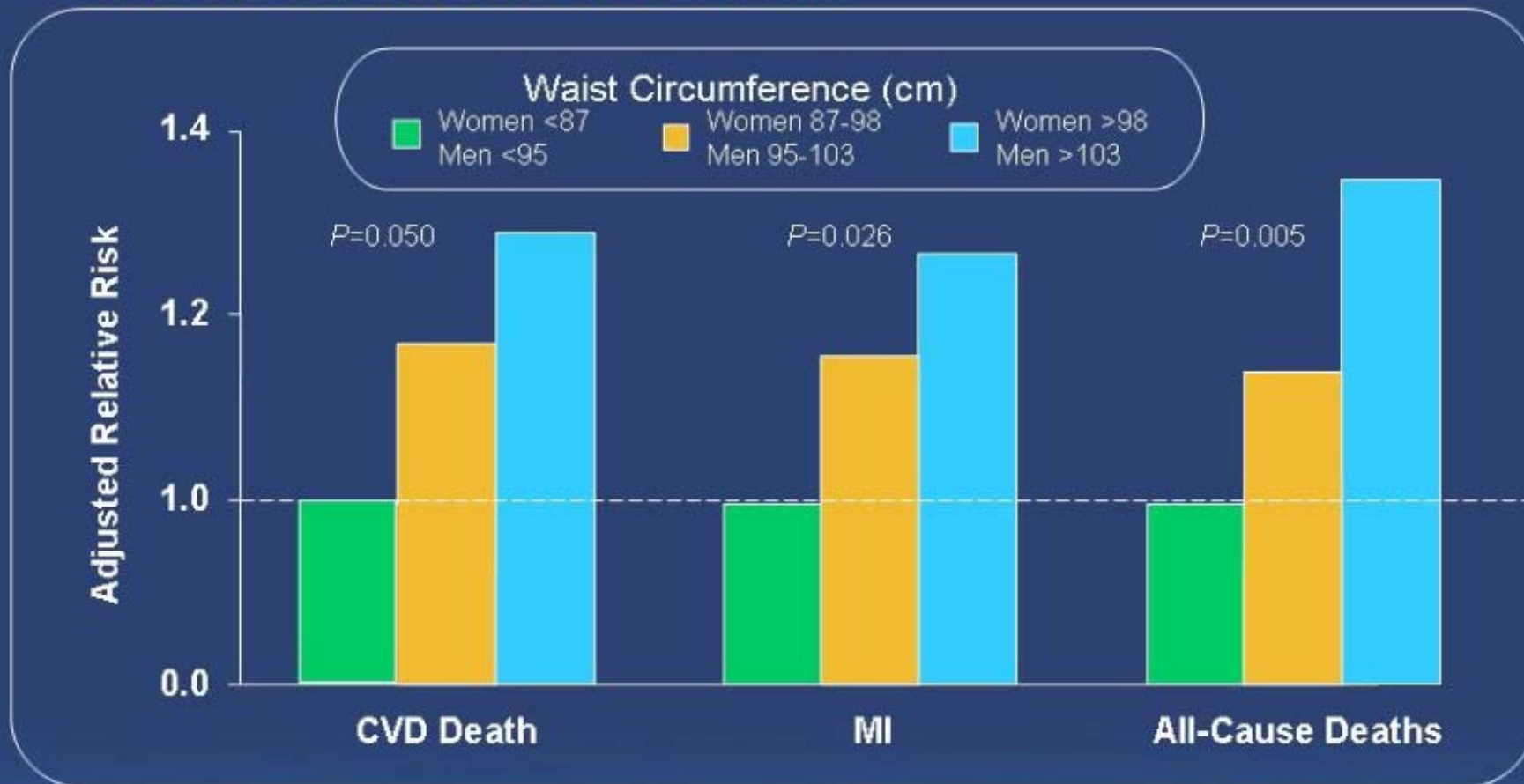


Carey VJ, et al. *Am J Epidemiol.* 1997;145:614-619.

# Cardiometabolic Risk



## Abdominal Adiposity Is Associated With Increased Risk of CV Events

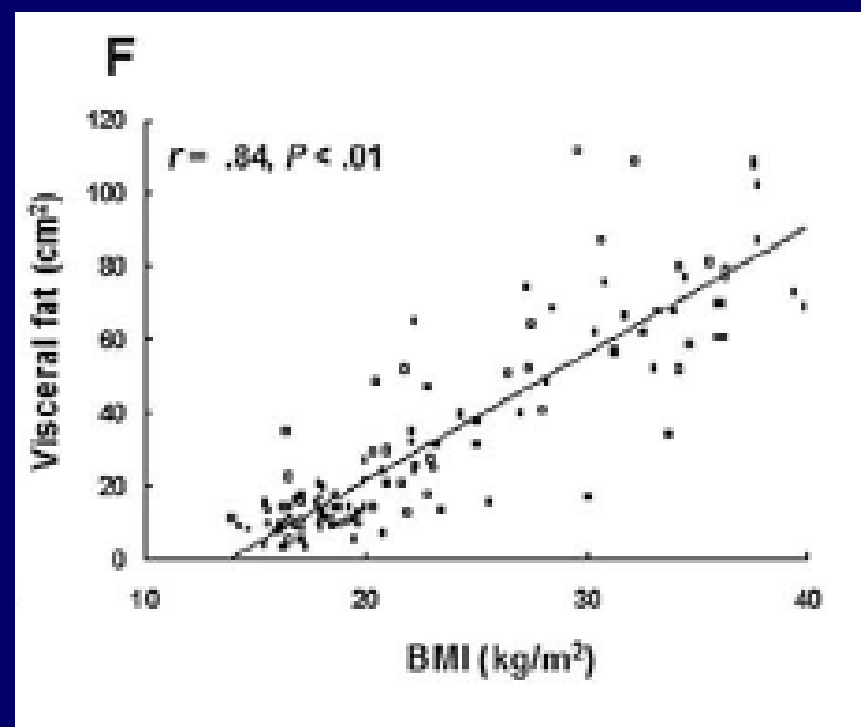
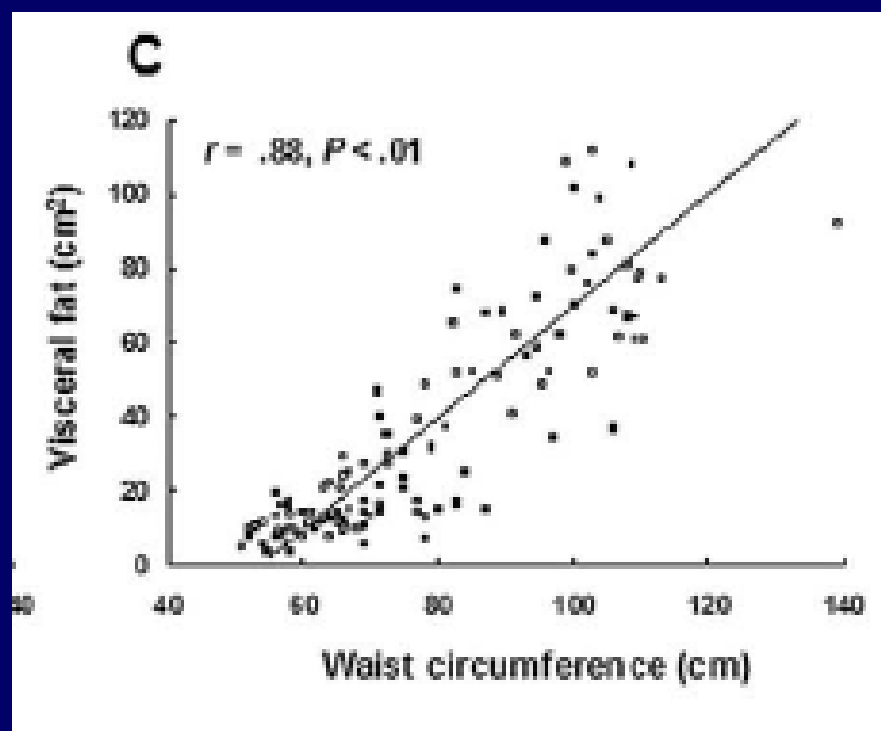




# Obesity in Children

- >20% of all children and adolescents in the US are overweight
- Childhood adiposity is a strong predictor of obesity, insulin resistance and abnormal lipids in adulthood (*J Pediatr* 2001, *Metabolism* 1996)
- The rate of increase in adiposity during childhood was significantly related to the development of cardiovascular risk in young adults (*Circulation* 1999)

# Obesity in Children: WC vs. BMI



WC were significantly associated with measures of abdominal fat and insulin resistance





# Obesity and MS in Children and Adolescents

- The % of subjects with impaired glucose tolerance increased directly with the severity of obesity
- The prevalence of the MS was 38.7% in moderately obese subjects and 49.7% in severely obese subjects

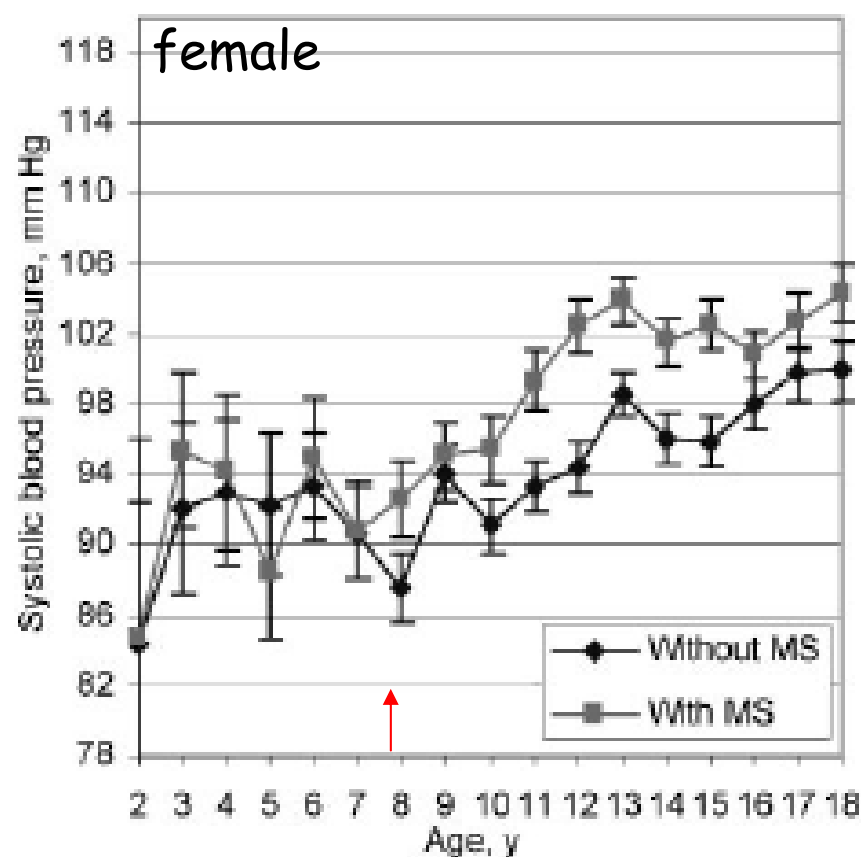
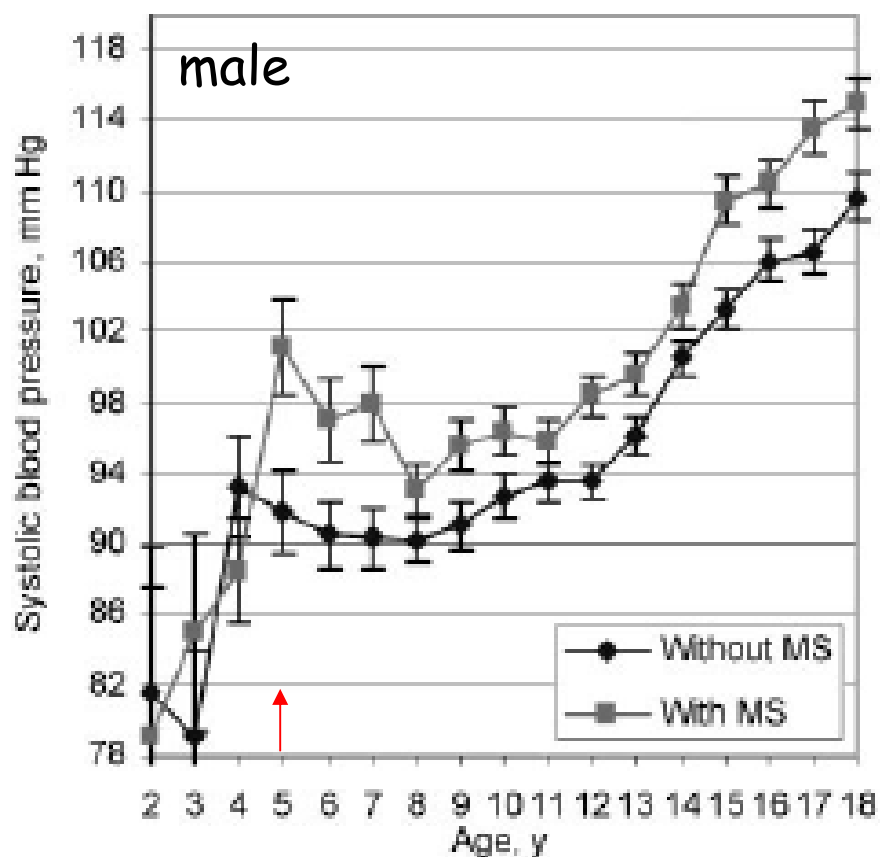
NEJM, 2004



# Hypertension and MS in Children

- Fasting insulin is significantly correlated with blood pressure in children and adolescents (*Hypertension 1997*)
- There is a strong association between childhood hypertension and adult MS (*Pediatrics 2007*)

# Systolic Blood Pressure and MS

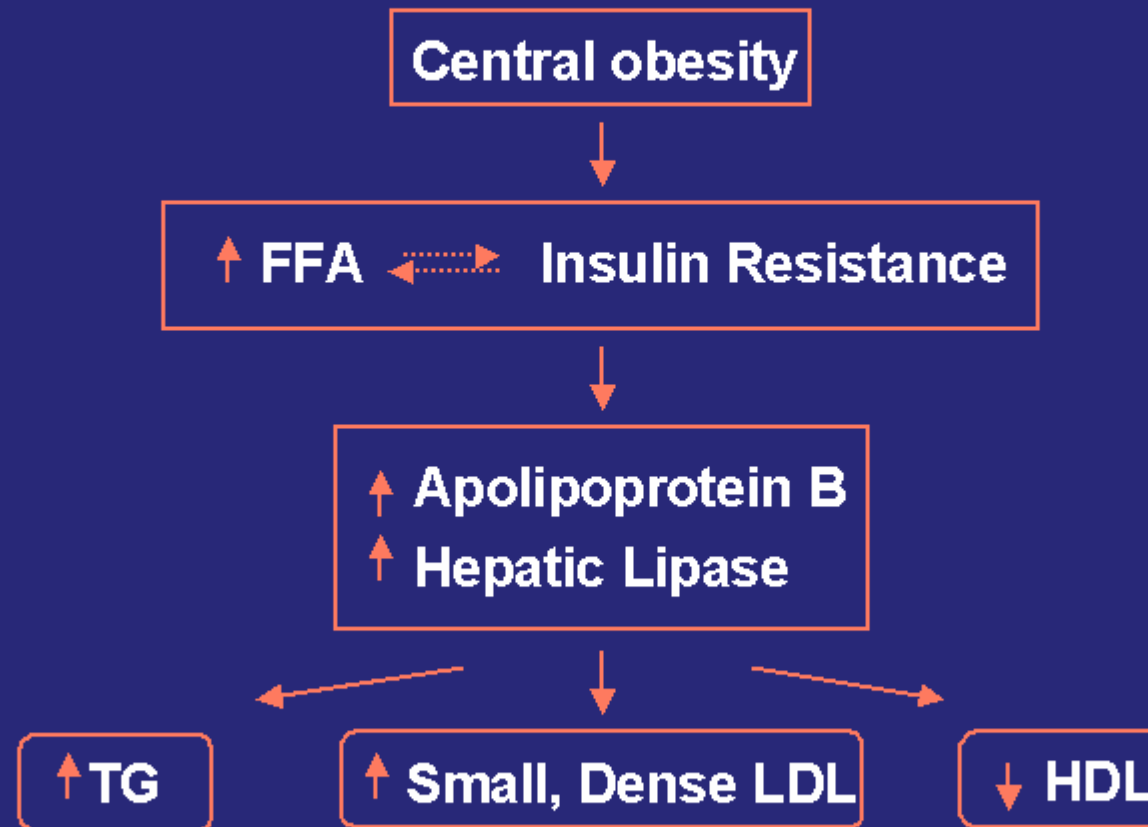




## Lipid Abnormalities and MS

- Overweight children have significantly higher levels of total cholesterol, LDL cholesterol, and triglycerides and lower HDL-C levels than normal-weight children (Am J Clin Nutr 2006)

# Relationship Between Obesity and Insulin Resistance and Dyslipidemia



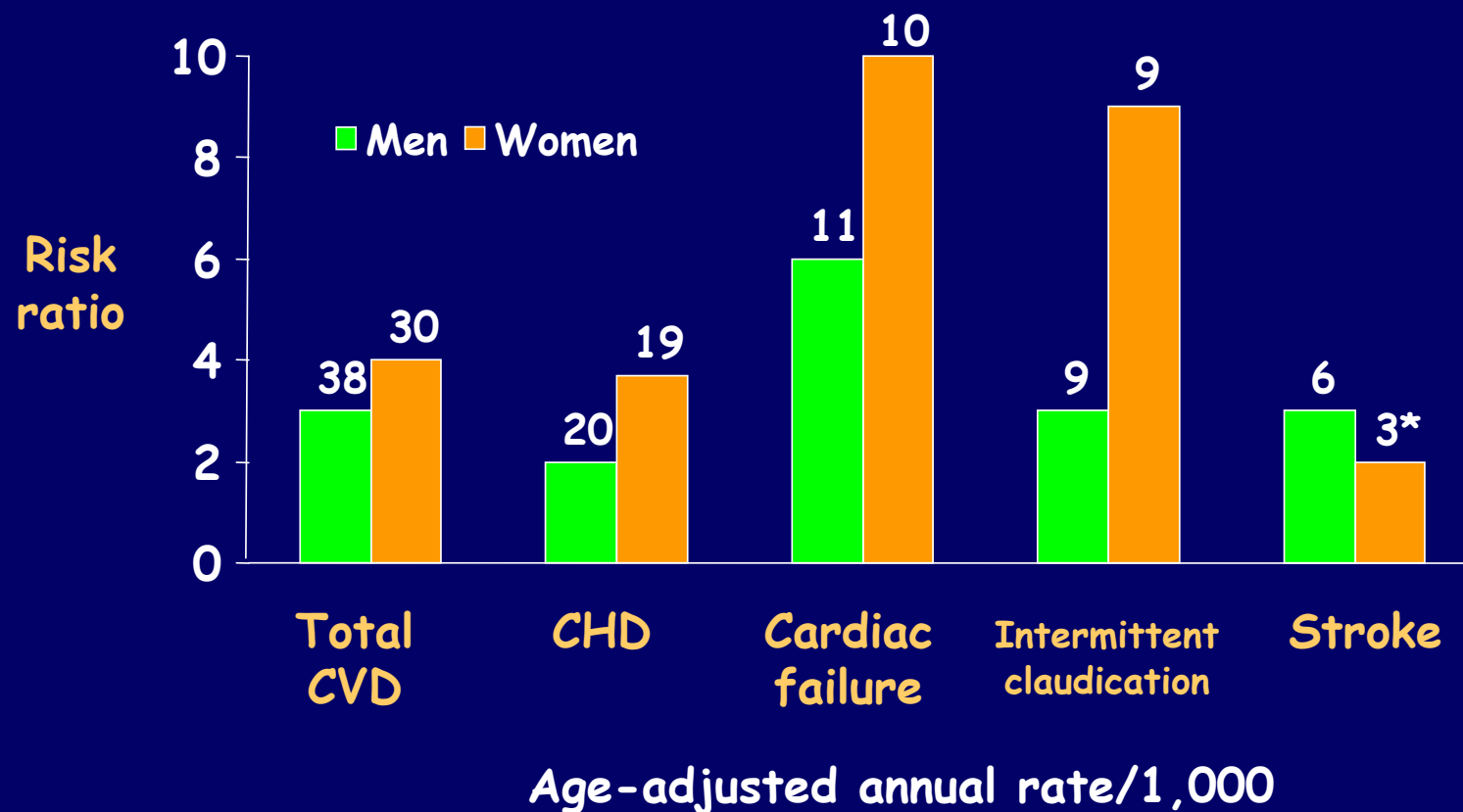


## T2DM and Metabolic Syndrome

- If diabetes is not already present, the metabolic syndrome is a strong predictor for its development
- The risk for type 2 diabetes being five times more likely in individuals with the syndrome

*Diabetes Care 2004;27(11):2676-81*

# Framingham Heart Study 30-Year Follow-Up: CVD Events in Patients With Diabetes



$P < 0.001$  for all values except \* $P < 0.05$ . (Ages 35-64)

Wilson PWF, Kannel WB. In: *Hyperglycemia, Diabetes and Vascular Disease*. Ruderman N et al, eds. Oxford; 1992.



# T2DM in Children

- The prevalence of T1DM in adolescents is 1.7/1000, whereas the prevalence of T2DM is 4.1/1000.
- This increase coincides with increasing rates of overweight and physical inactivity in children

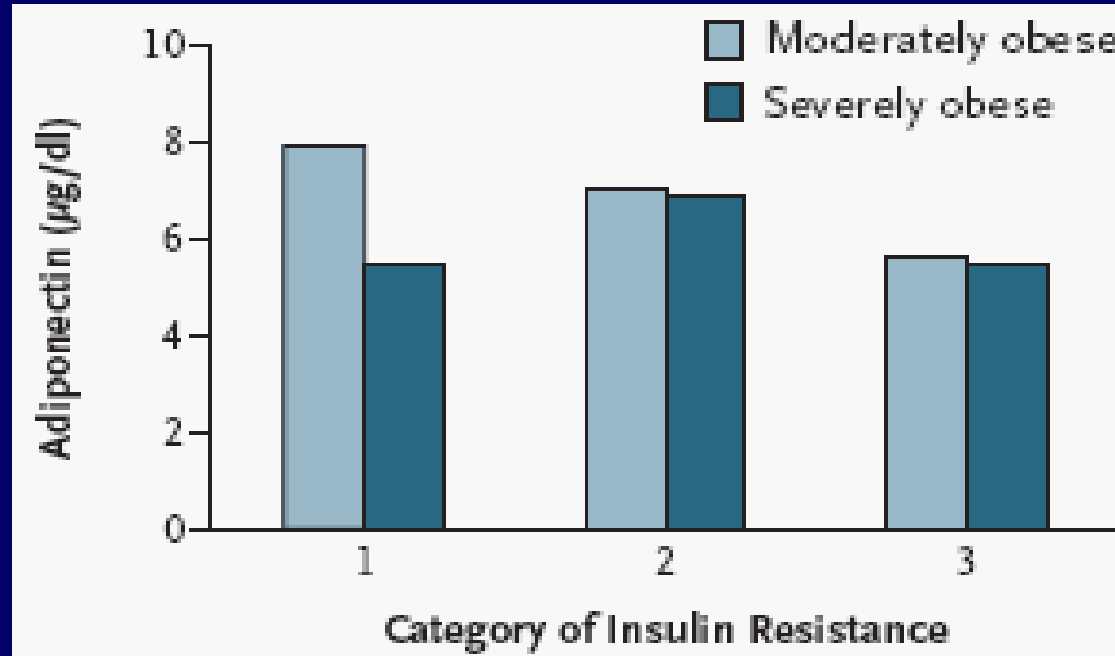




# Markers of Metabolic Syndrome

- Proinflammatory cytokines (IL-6, TNF-) and adipocytokines (adiponectin and leptin) are associated with obesity and insulin resistance (*Eur J Clin Invest 2002*)
- CRP was associated with insulin resistance and components of the MS in adolescents (*Diabetes Care 2005*)
- Endothelial dysfunction: carotid artery intima-media thickness (c-IMT)

# Adiponectin in Obese Children



- $p=0.04$  for the association with the obesity group
- $p=0.005$  for the association with the insulin-resistance



# CRP levels in Obese Children

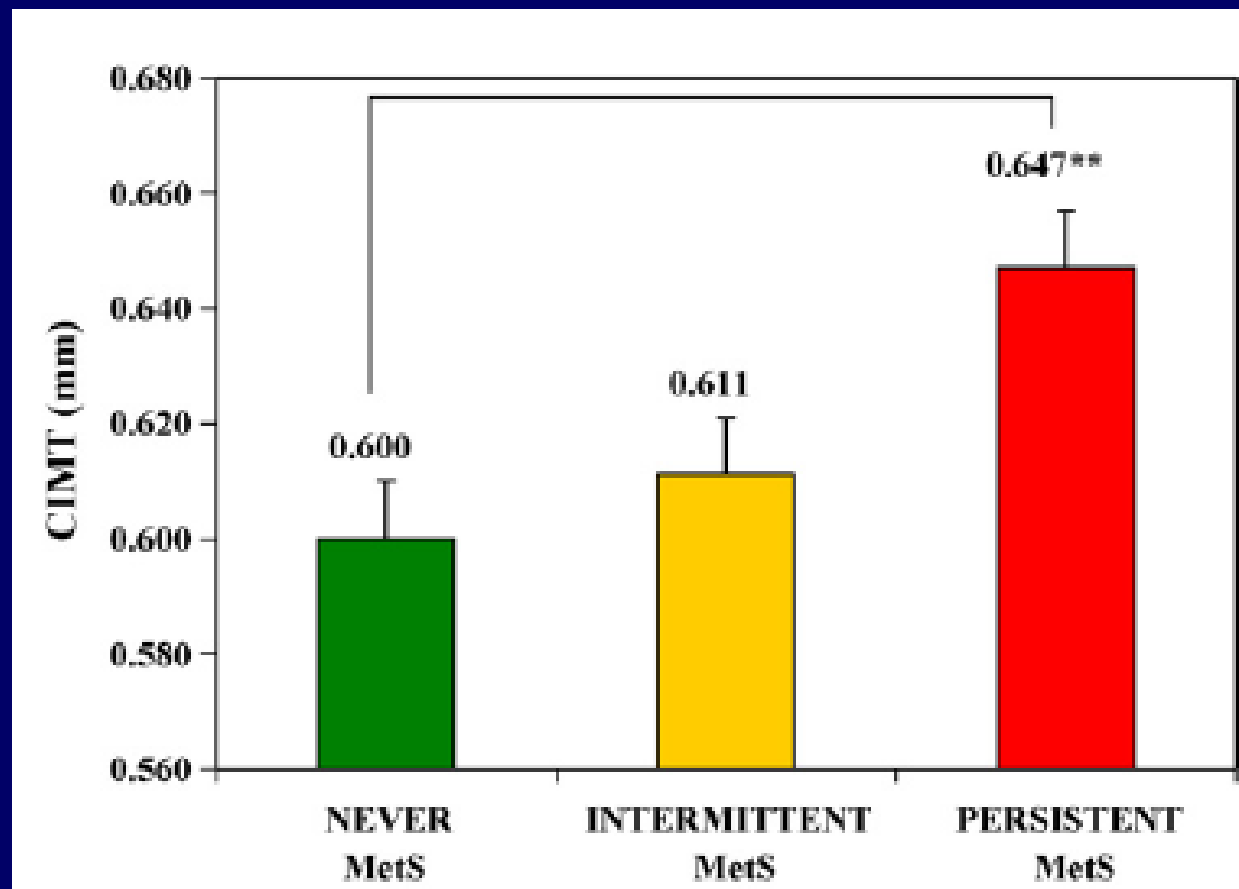


NEJM, 2004

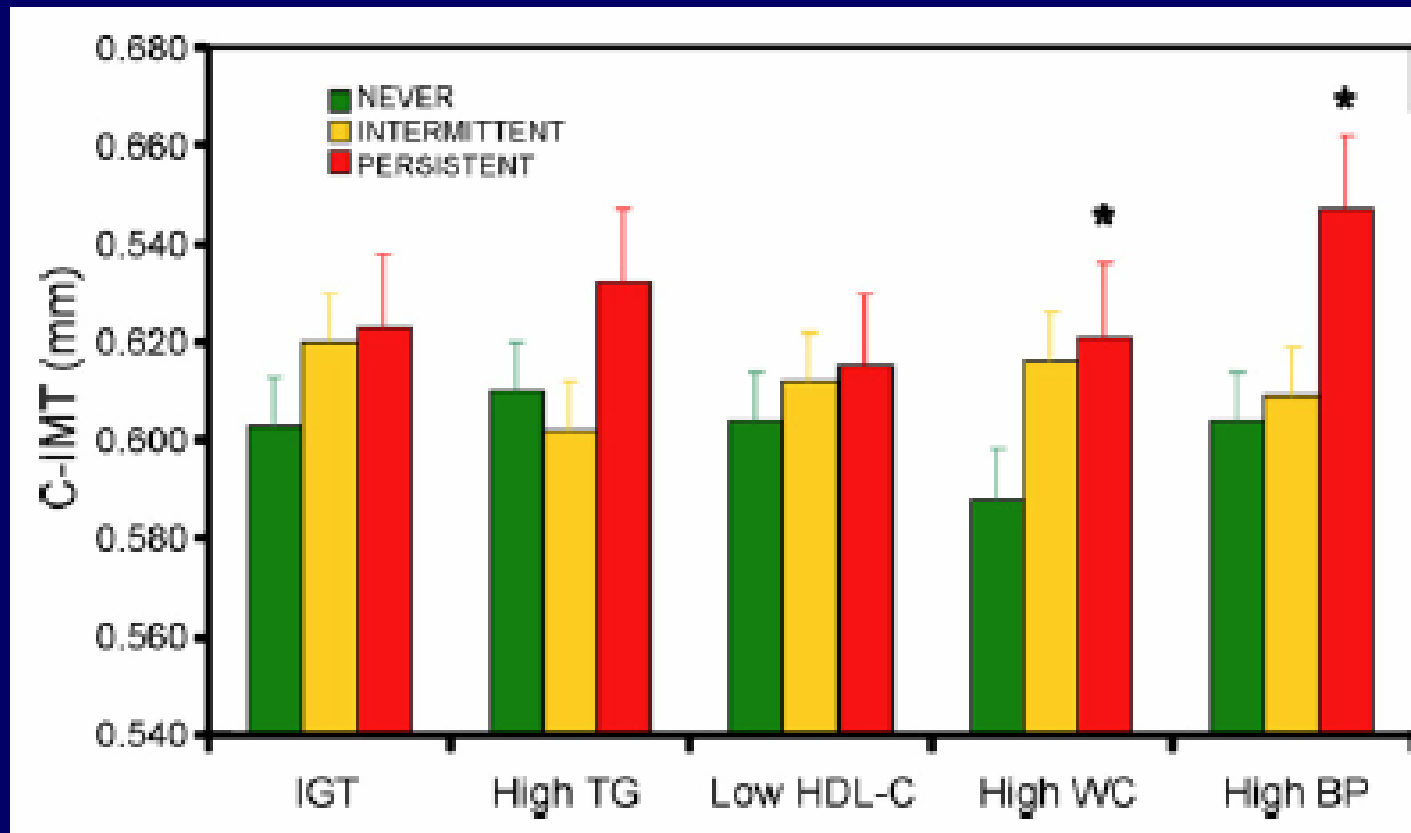
- CRP levels were significantly related to the degree of obesity ( $P < 0.001$ ), but not to the level of insulin resistance ( $P = 0.12$ ).
- The levels tended to rise with the number of components of the MS



# c-IMT and MS in Overweight Children



# c-IMT and MS Component in Overweight Children





# Risk Factors for the MS

- Heredity
- Ethnic Differences
- Lifestyle Behaviors
  - *Television-Watching Habits*
  - *Physical Activity*
  - *Dietary Intake*



# MS and Physical Activity

- Prevention of overweight and obesity in adults and children
- Lower levels of inflammatory cytokines and markers of oxidative stress
- Positively correlated with insulin sensitivity in adolescents (*Int J Obes Relat Metab Disord*, 2002)
- Associated with improved endothelial function and HDL-C, even in the absence of weight loss (*Metabolism*, 2005)



## MS: Treatment

- Comprehensive behavioral modification in overweight children reduces body weight, improves body composition, and positively modifies many of the components of the MS within 3 months, and these effects are maintained at 1 year (*Pediatrics, 2005*)
- Combined dietary and exercise interventions improve endothelial dysfunction in overweight children (*Circulation, 2004*)

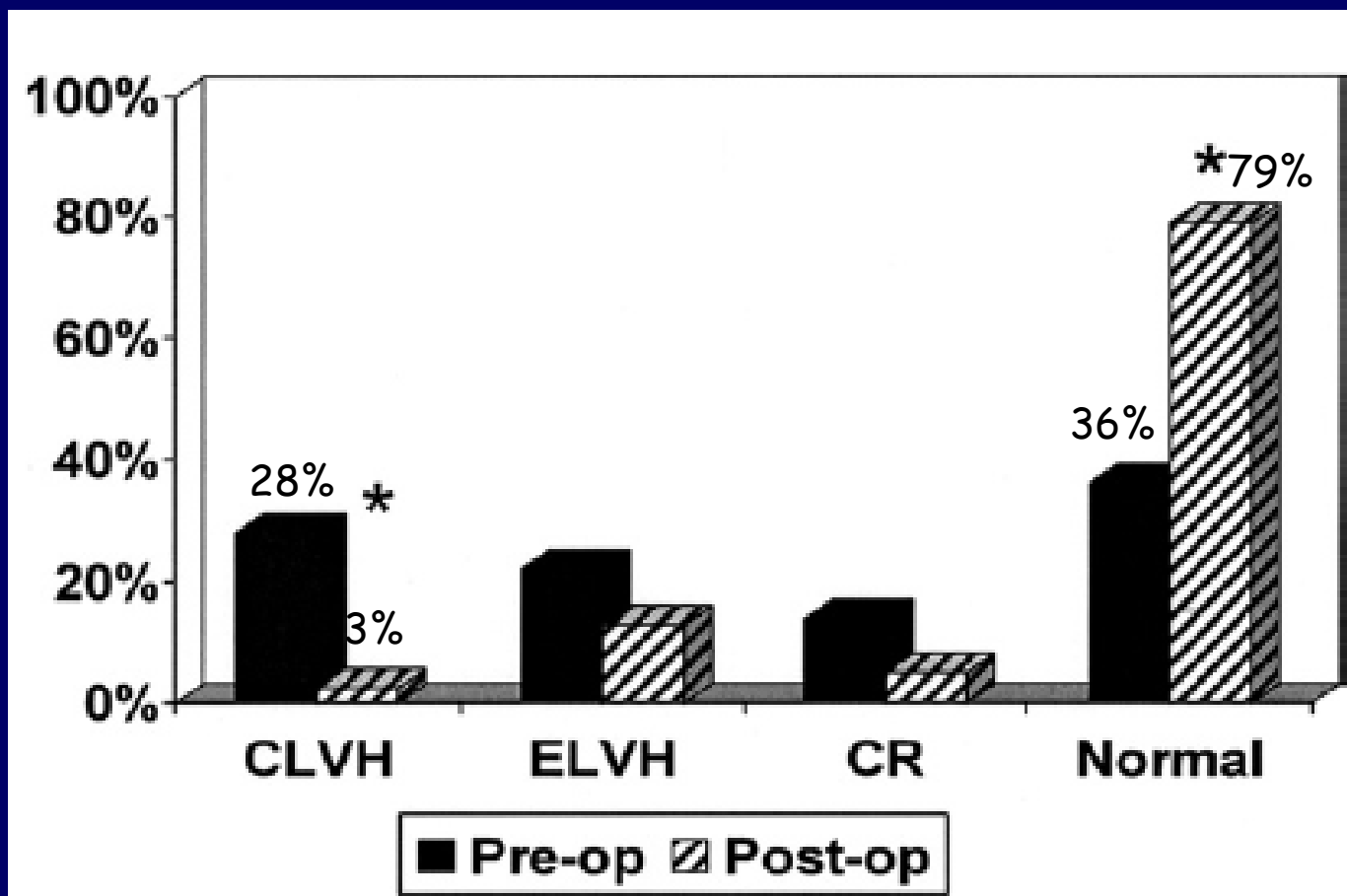




# Reversibility of Cardiac Abnormalities

- Change in LV mass index ( $54 \pm 13$  to  $42 \pm 10$  g/m<sup>2.7</sup>, p 0.0001) correlated with weight loss (r=0.41, p<0.0001).
- Diastolic function improved (mitral E/Ea lateral  $7.7 \pm 2.3$  at pre-operative vs.  $6.3 \pm 1.6$  at post-operative, p<0.003).

# Effects of Weight Loss on LV Geometry Patterns

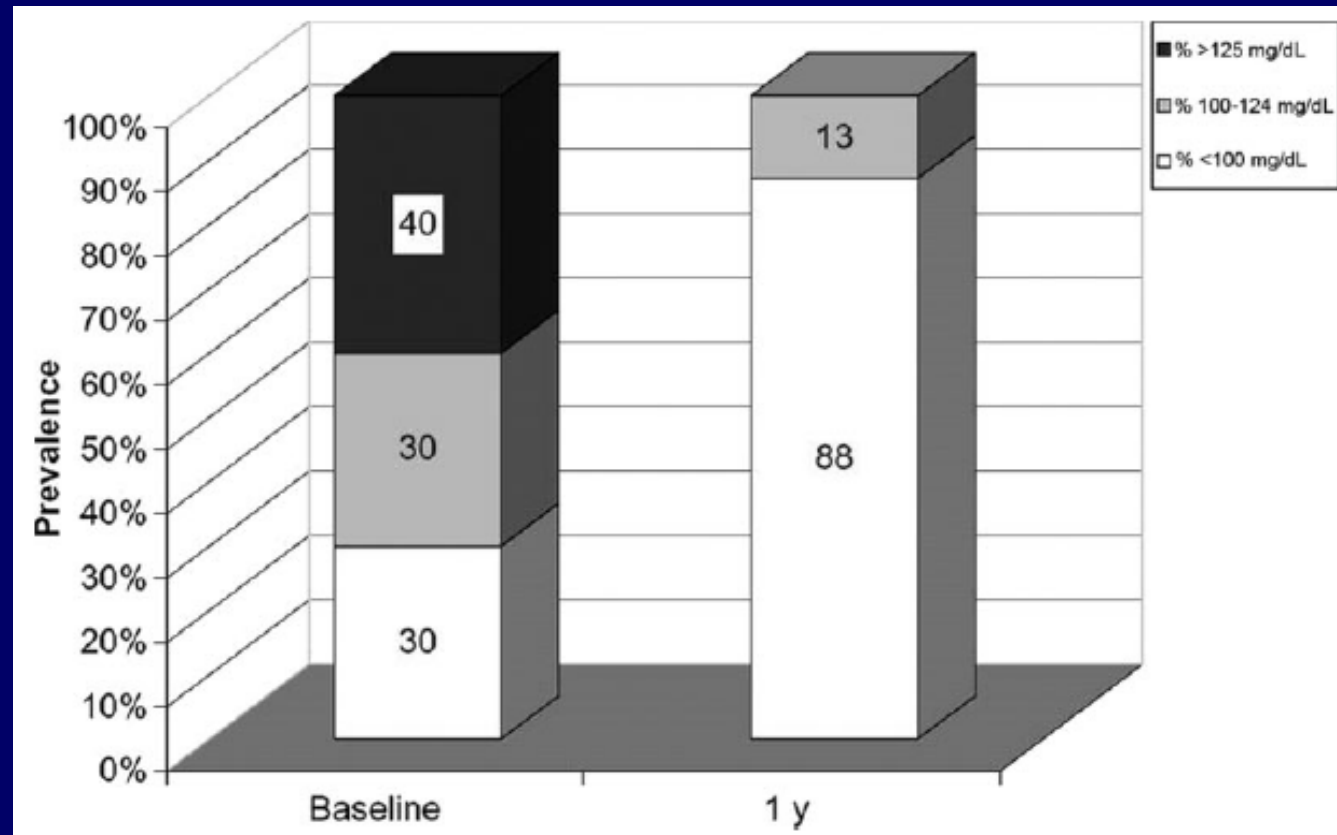




## Improvement in T2DM and in CV Risk

- 11 adolescents who underwent Roux-en-Y gastric bypass (BMI  $50 \pm 5.9$  kg/m<sup>2</sup>)
- After surgery there was significant improvements in BMI (34%), fasting blood glucose (41%), fasting insulin conc. (81%), hemoglobin A1c levels (7.3%-5.6%)
- There were improvements in serum lipid levels and blood pressure

# Change in Glucose Homeostasis



After surgery there was evidence of remission of type 2 diabetes mellitus in all but 1 patient