

# Making Sense of Cardiometabolic Risk in American Indians

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Presented by the Indian Health Service (IHS)  
Division of Diabetes

# Making Sense of Cardiometabolic Risk in American Indians

**Cardiometabolic = Heart Disease + Diabetes**

Prediabetes  
Metabolic Syndrome  
Insulin Resistance



**Decreasing Cardiometabolic Risk**

# Diabetes and Heart Disease in US Adults

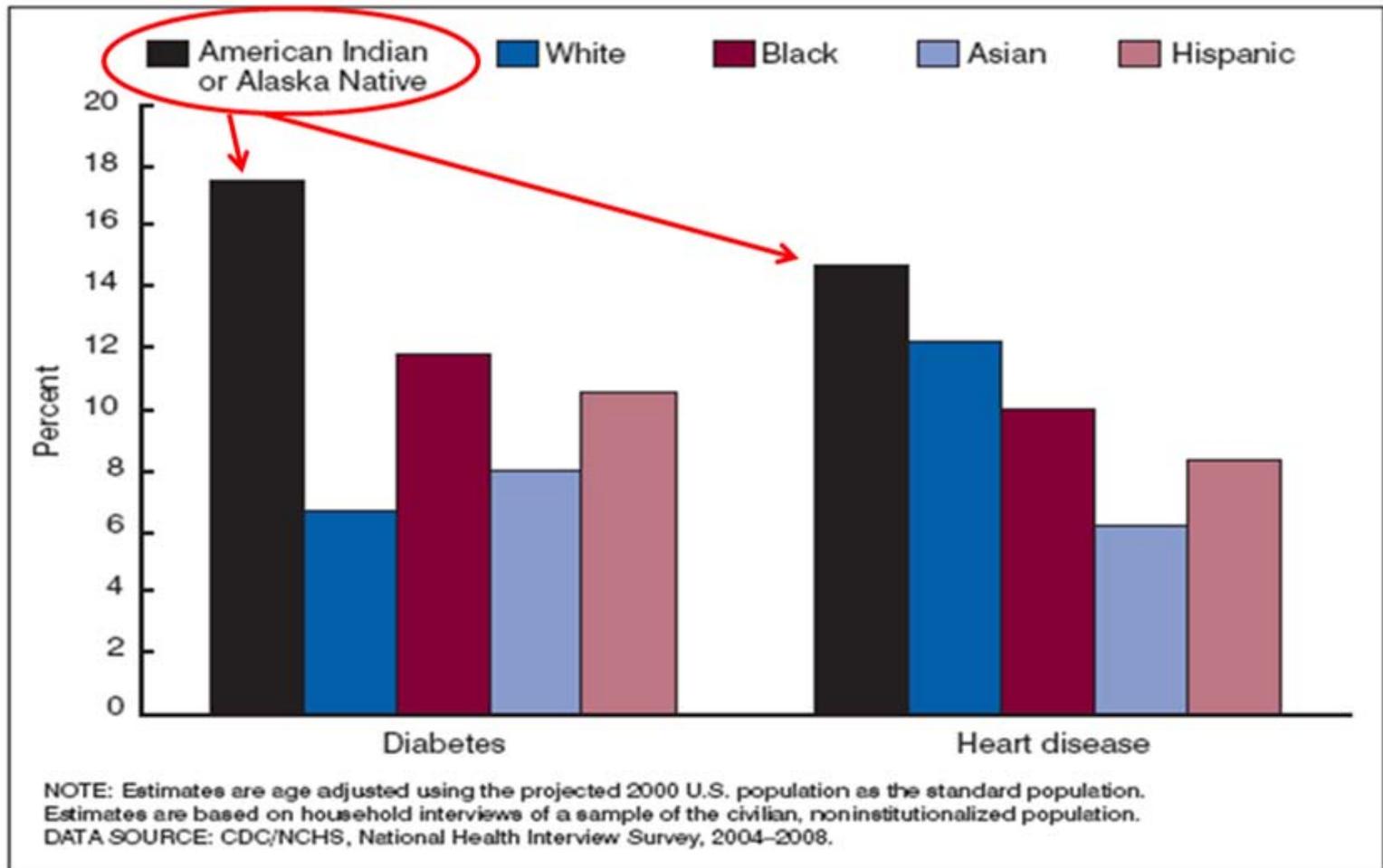
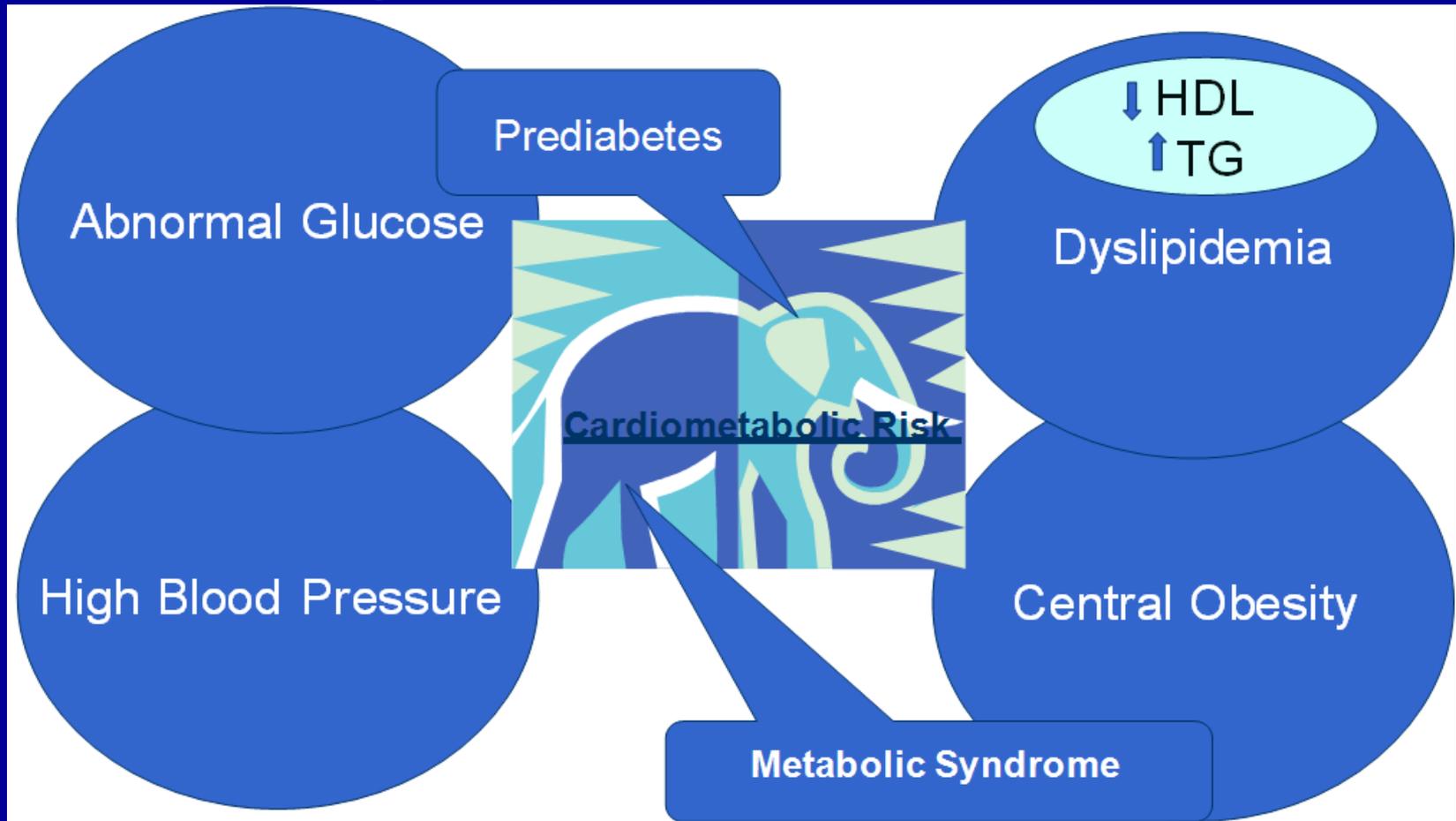


Figure 4. Percentage of adults aged 18 years and over who have ever been diagnosed with diabetes, and percentage of adults aged 18 years and over who have ever been diagnosed with heart disease, by race and ethnicity: United States, 2004–2008

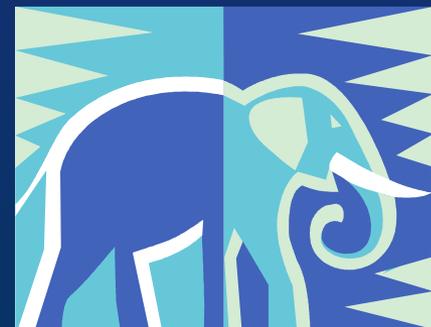
# Type 2 Diabetes and Cardiovascular Disease (CVD) have Many of the Same Risk Factors



# Making Sense of Cardiometabolic Risk in American Indians

## Cardiometabolic = Heart Disease + Diabetes

- Prediabetes = Blood glucose is higher than normal, but not in the range of diabetes.
- Metabolic syndrome
- Insulin resistance



# Prediabetes: Three Questions

1. What does that mean to you ?
2. What characteristics suggest to you that a person is at high risk for soon developing diabetes
3. Does everyone with Prediabetes develop Type 2 Diabetes within a short time frame?

# Prediabetes and the Diabetes Prevention Program (DPP)

## American Diabetes Association (ADA) Definition post-DPP

- Impaired Fasting Glucose (IFG):

FBS  $\geq$  100 mg/dl

**OR**

- Impaired Glucose Tolerance (IGT): 2-hour glucose after Oral Glucose Tolerance Test (OGTT) 140–199 mg/dl

Prediabetes was defined as one of the two...

Q. Why did they define it that way?

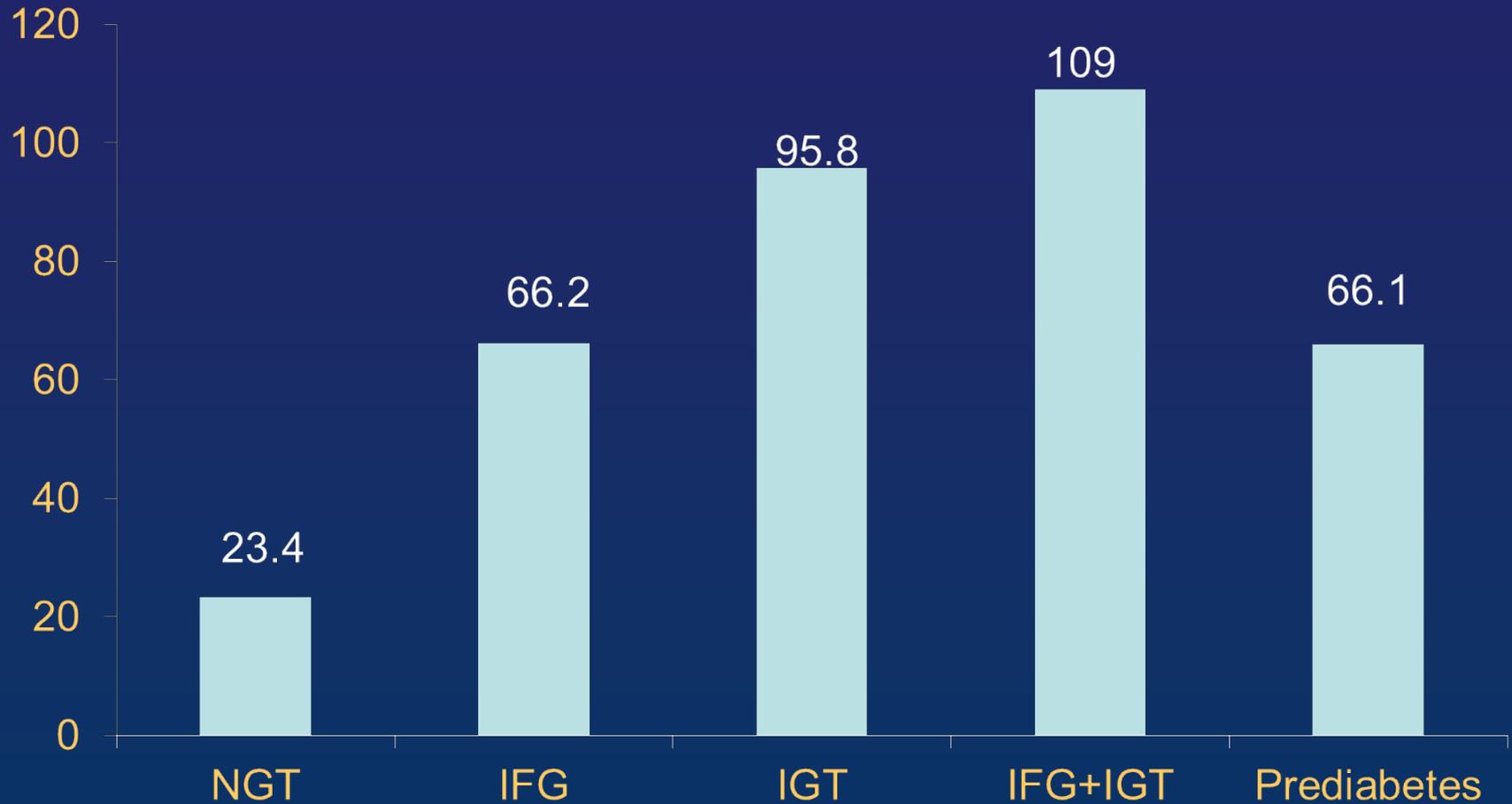
A. To figure out how many people to include in the DPP study.

Q. What are the problems with the definition?

A. Lots of other things can tell us someone is at high risk for diabetes.

B. People don't always have both, or they may have one test positive but not the other.

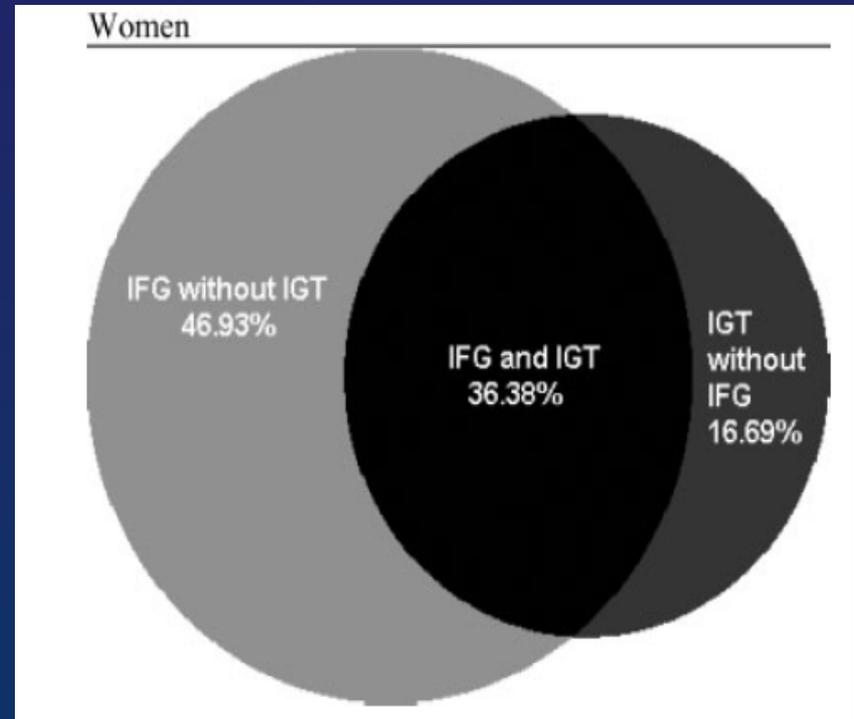
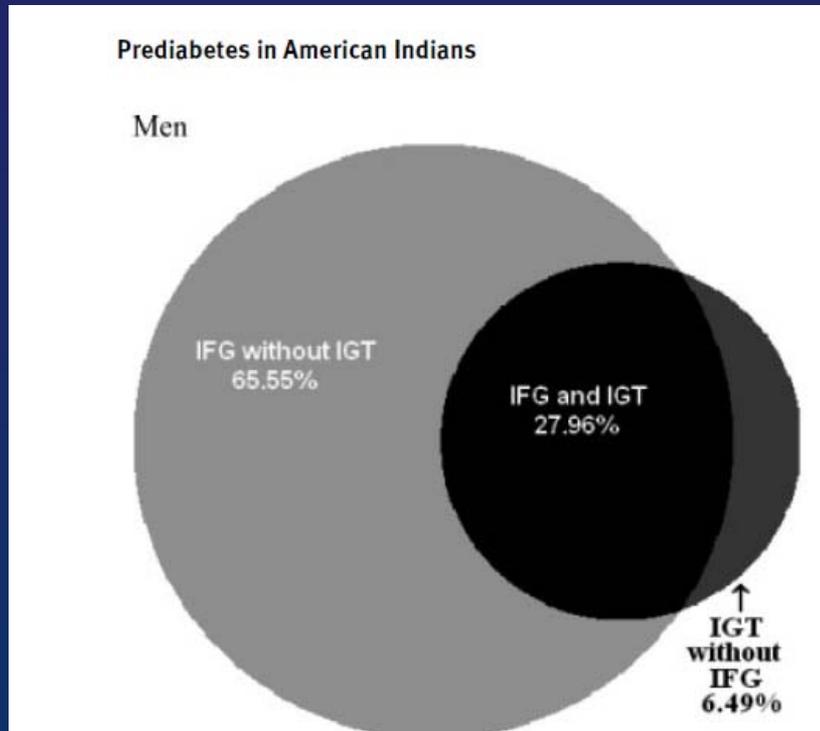
# Incidence\* of Diabetes in American Indians by Prediabetes Status: Strong Heart Study



\* Per 1000 person-years

Wang Diabetes Metab Res Rev 2010

# Proportions of IFG alone, IGT Alone, and Both IFG+IGT in American Indians with Prediabetes: Strong Heart Study 45–74 Years Old



Prediabetes was identified by Fasting Blood Glucose (FBG) in 87.5%.

# Prediabetes 2010

## ADA Definition

IFG: FBS  $\geq$  100 mg/dl

**OR**

IGT: 2-hour glucose after OGTT < 200 mg/dl

Prediabetes was defined as one of the two...

And now in 2010:

**A1c 5.7-6.4%**

Q. Do we have data from American Indians that A1c can be used to define Prediabetes?

A. We have the best data that anyone has for any population regarding Prediabetes parameters.

# So What is Prediabetes?

- A special category defined by the ADA from laboratory measures of glucose/A1c which indicate that someone does not have normal insulin secretion to control blood sugar to normal.
- A1c definition for Diabetes and Prediabetes has come from research done on American Indians.
- A way (not the only one way) of identifying a person's risk of developing Type 2 diabetes within a few years.
- “Prediabetes” (IFG and IGT) was necessary to do the DPP. Then A1c was added.

# Cardiometabolic Risk

- Prediabetes = Blood glucose/A1c higher than normal, but not as high as diabetes
- Metabolic Syndrome = a cluster of risk factors frequently found in people who develop type 2 diabetes and cardiovascular disease
- Insulin Resistance



## Rationale for *The Metabolic Syndrome*: NCEP:ATP-III, 2001

- Risk partner to elevated LDL cholesterol
- Represents risk factors that cluster and often accompany obesity
- ↑ risk for ASCVD
- ↑ risk for type 2 diabetes
- Not designed as a risk engine

Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. *JAMA*. 2001;285:2486-2497.

# Clinical Criteria for Metabolic Syndrome

Measure (any 3 of the following)	Categorical Cutpoints
Elevated waist circumference	≥102 cm men (40 inches ) ≥88 cm women (35 inches)
Elevated triglycerides	≥150 mg/dL or on Rx for elevated TG
Reduced HDL-C	<40 mg/dL men <50 mg/dL women or on Rx for reduced HDL-C
Elevated blood pressure	≥130 mm Hg systolic or ≥85 mm Hg diastolic or on antihypertensive Rx with history of hypertension
Elevated fasting glucose	≥100 mg/dL or on Rx for elevated glucose

# Prevalence\* of Metabolic Syndrome in Northern Plains and Southwest American Indians

	<b>Total</b>	<b>Men</b>	<b>Women</b>
All	50%	45%	53%
No Diabetes Mellitus (DM)	42%	37%	46%
DM	87%	84%	88%

\* Age-adjusted

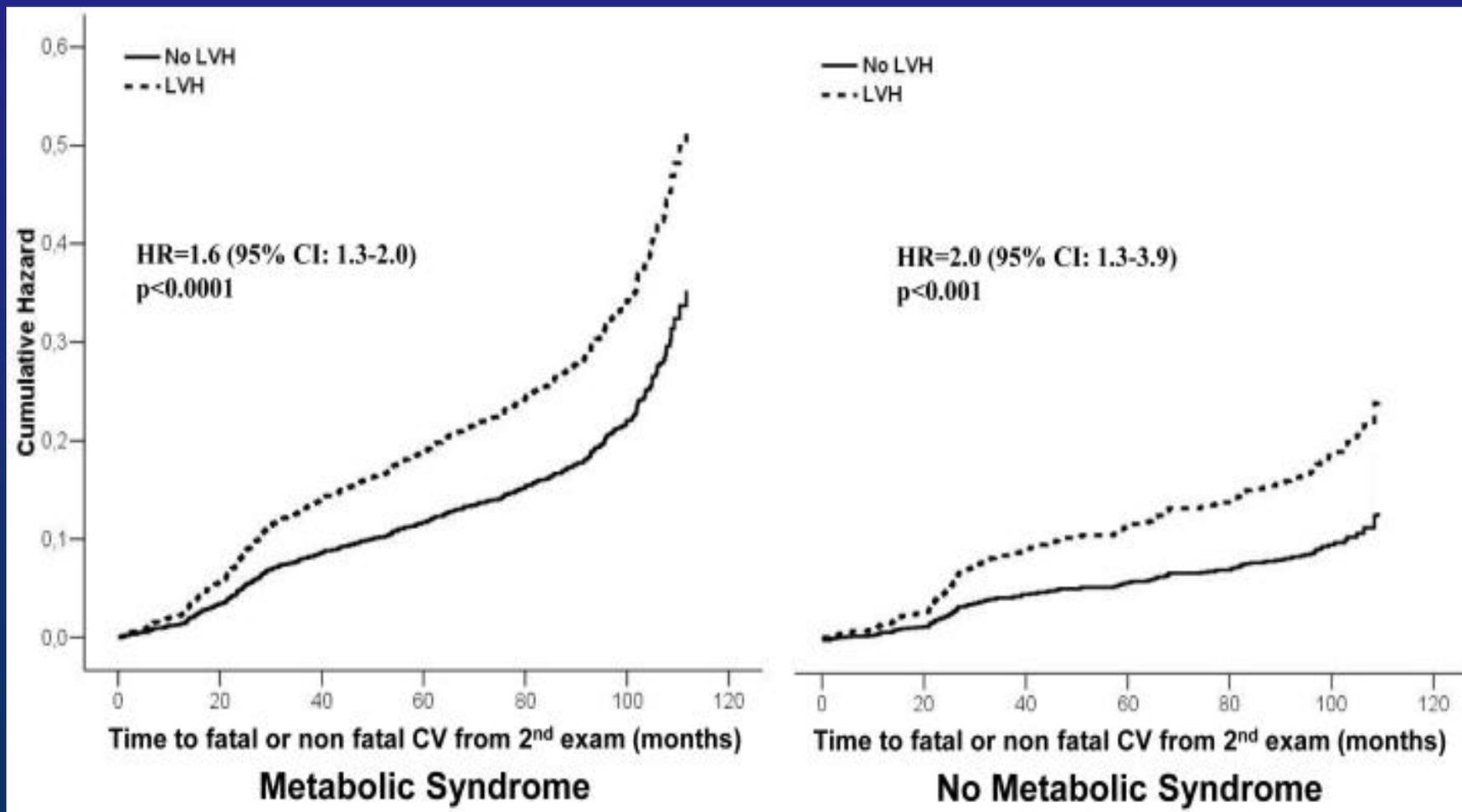
Sinclair Diabetes Care 2011

# Metabolic Syndrome and Diabetes Risk in American Indians

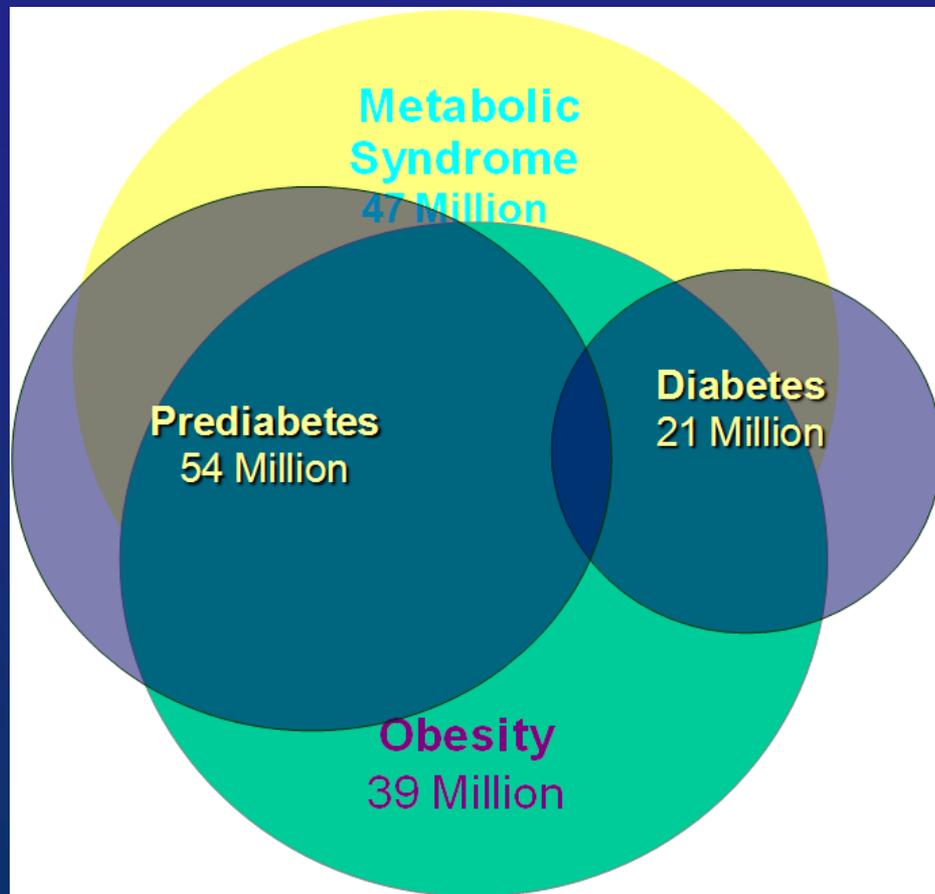
- Strong Heart Study:  
Diabetes risk doubled in American Indians with Metabolic Syndrome.
- Pima Indian Studies:  
Components of Metabolic Syndrome affected risk of diabetes differently.  
Body size and lipids predicted diabetes.  
Blood pressure did not.  
High insulin levels and obesity are the really strong DM risk factors.

Resnick Diabetes Care 2003  
Hanson Diabetes 2002

# Risk of CV Event with and without Metabolic Syndrome and Left Ventricular Hypertrophy Strong Heart Study



# Cardiometabolic Risk: The Challenge



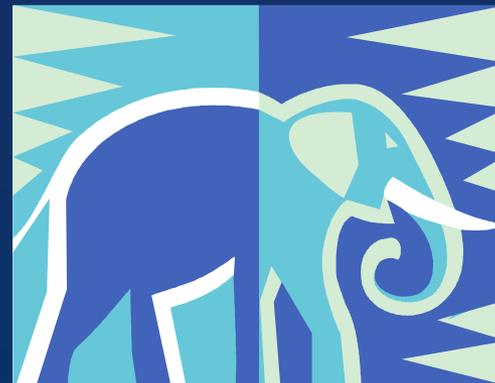
- (1) "Prevalence of the Metabolic Syndrome among US Adults", JAMA, January 16, 2002 – Vol. 287, No. 3;
- (2) "The Continuing Epidemic of Obesity and Diabetes in the United States, JAMA, September 12, 2001 – Vol. 286, No. 10.

# Metabolic Syndrome in American Indians

- *“Although the underlying cause of the metabolic syndrome (MS) is not entirely clear, it is thought that MS results from central obesity and insulin resistance (IR).*
- *IR has long been known to be a predictor of type 2 diabetes in many populations, including American Indians, the group with a rising prevalence of obesity and the highest rate of diabetes in the United States.*
- *In addition to being a predictor of diabetes, MS has now been shown to be associated with higher risk of cardiovascular disease, independent of diabetes, in American Indians as well as in other ethnic groups.*
- *Furthermore, MS may carry a risk beyond that of single risk factors.*
- *Identifying MS in American Indians and treating the factors that comprise it may reduce risk of both diabetes and cardiovascular disease in this population.”*

# Cardiometabolic Risk

- Prediabetes = Blood glucose/A1c higher than normal but not as high as diabetes
- Metabolic Syndrome = a cluster of risk factors frequently found in people who develop Type 2 diabetes and cardiovascular disease
- Insulin Resistance



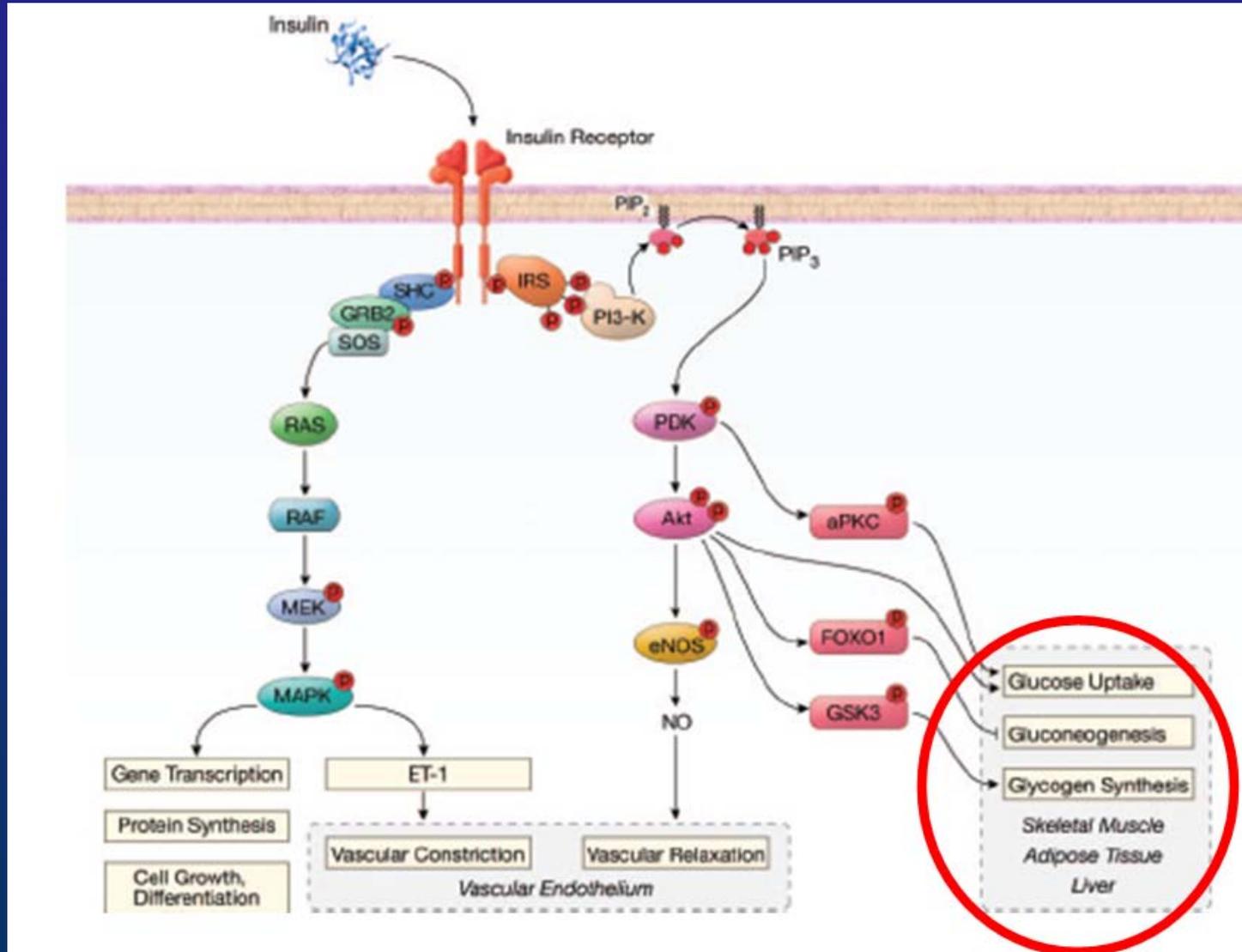
# Insulin Resistance (IR)

- A reduced sensitivity in the tissues of the body to the action of insulin to lower blood glucose
- A given insulin concentration causes less of an effect on glucose metabolism than normal

Adapted from Reaven GM. *Diabetes/Metabol Rev.* 1993;9(Suppl 1):5S-12S.



# Insulin Signaling Pathway in Cells



# Insulin Resistance is Selective

High insulin levels



**OTHER SIGNALING  
PATHWAYS**

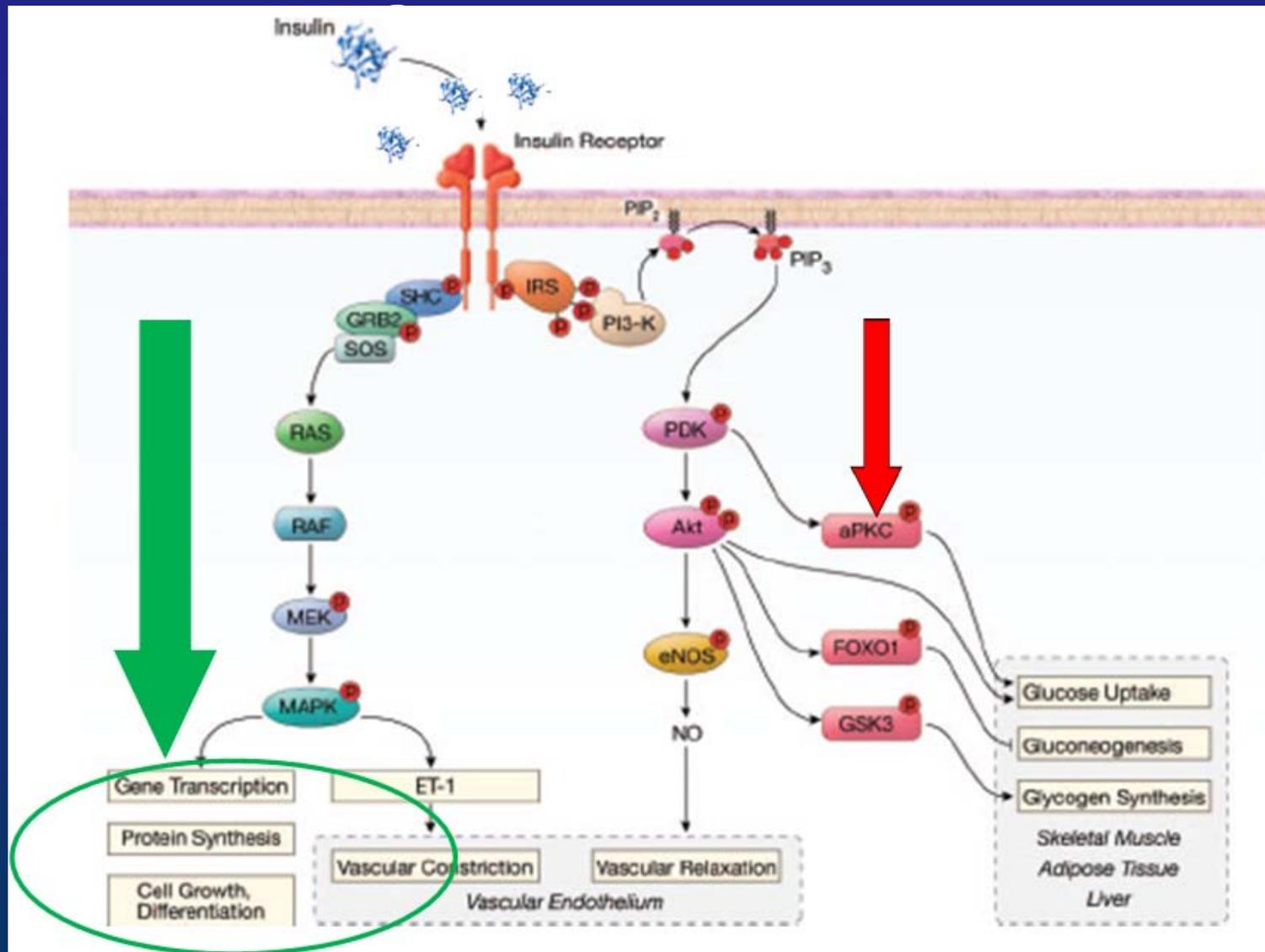


**RESISTANCE**



**GLUCOSE CONTROL**

# Insulin Increases to Overcome “resistance”



# What Causes Insulin Resistance ?

## Long Answer

Genes

Aging

Obesity

High-fat foods

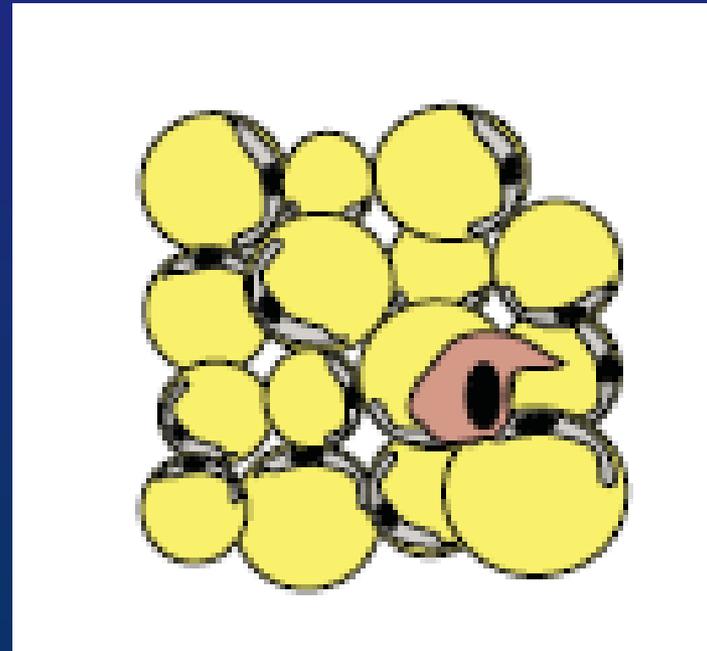
Cytokines like Resistin

Inflammatory cytokines

Low physical activity ....

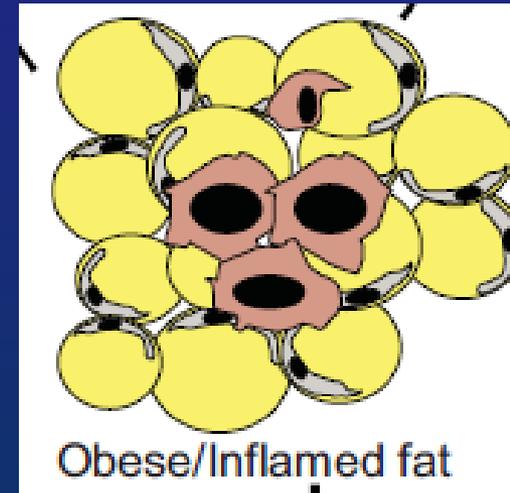
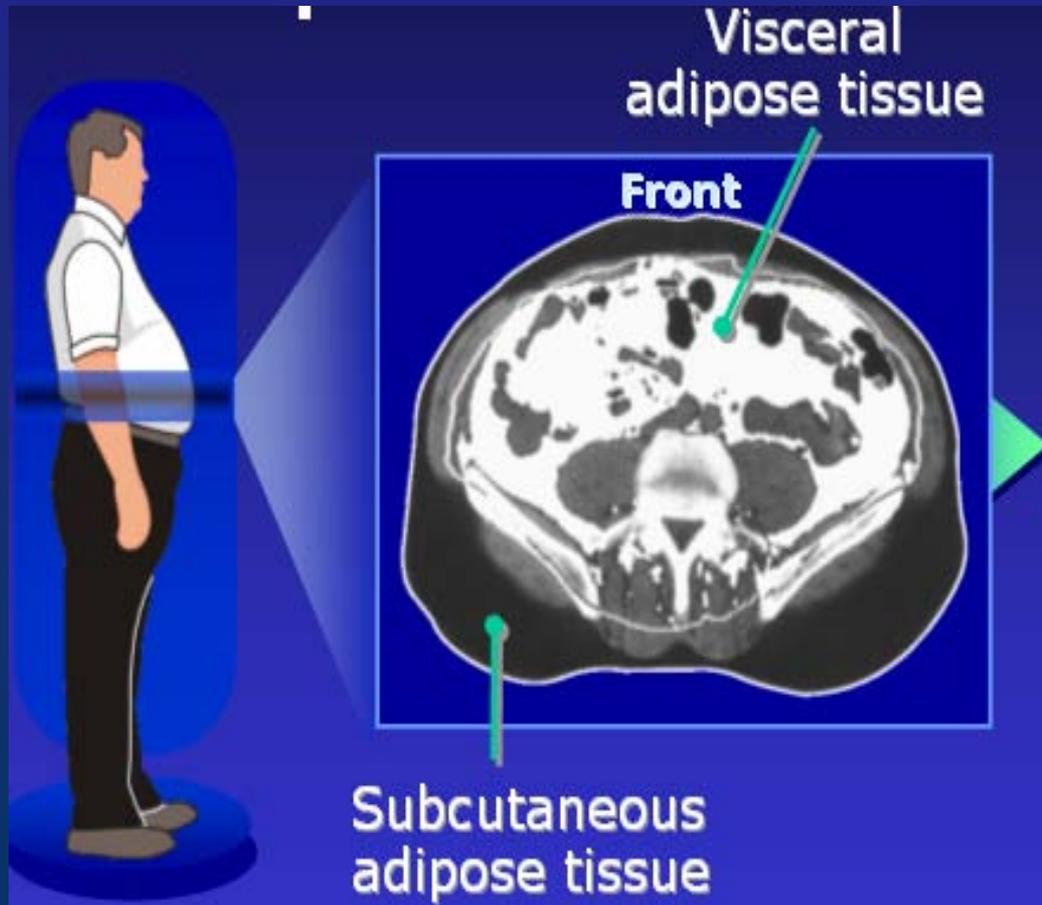
## Short Answer

Fat



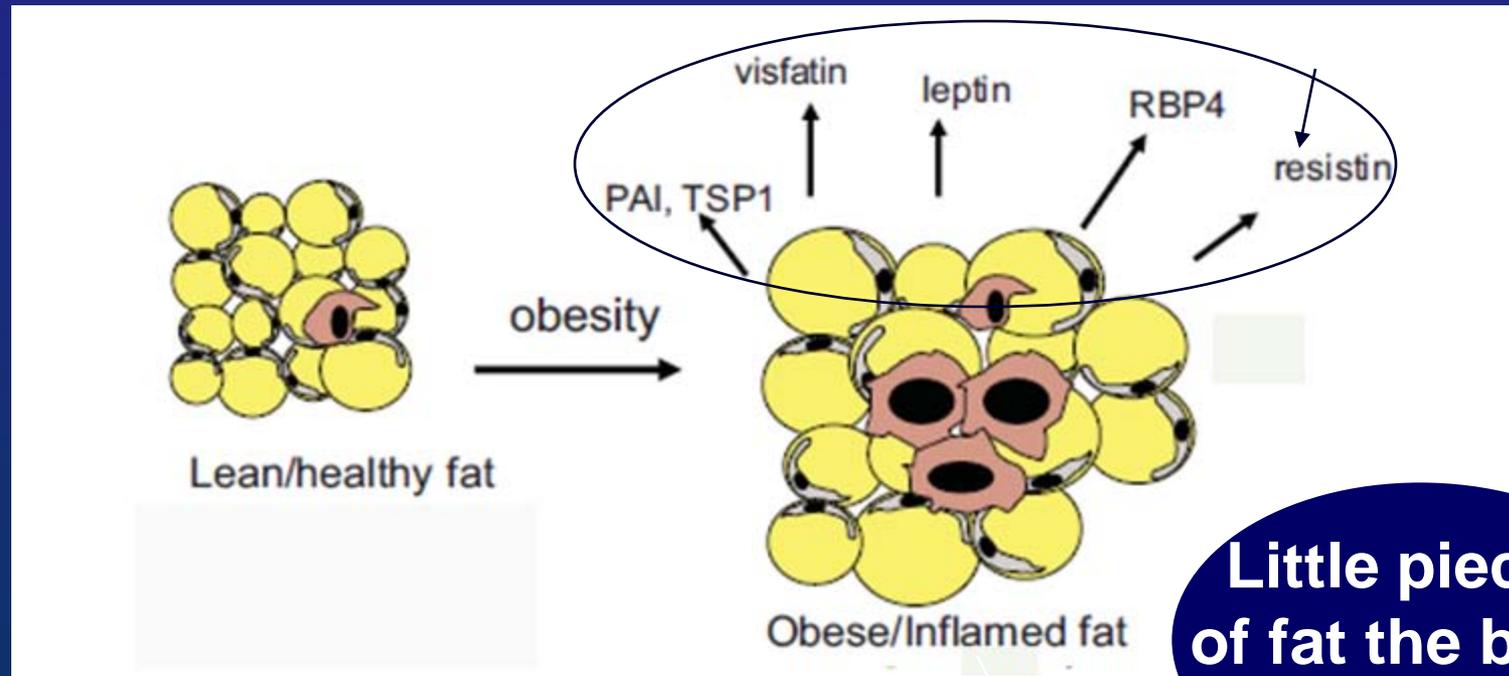
Fat cells in abdomen

# Insulin Resistance: Not Just Any Old Fat Fat in the Abdomen



# Fat Releases Cytokines and Free Fatty Acids

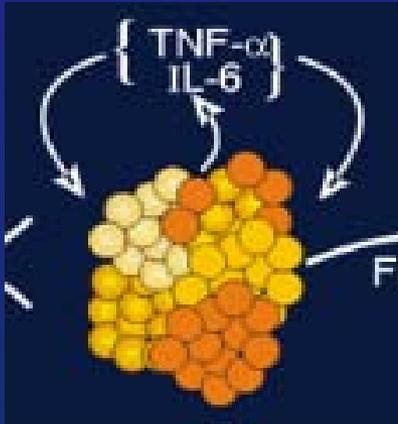
**Cytokines = Messages to Other parts of the body**



**So who cares?**

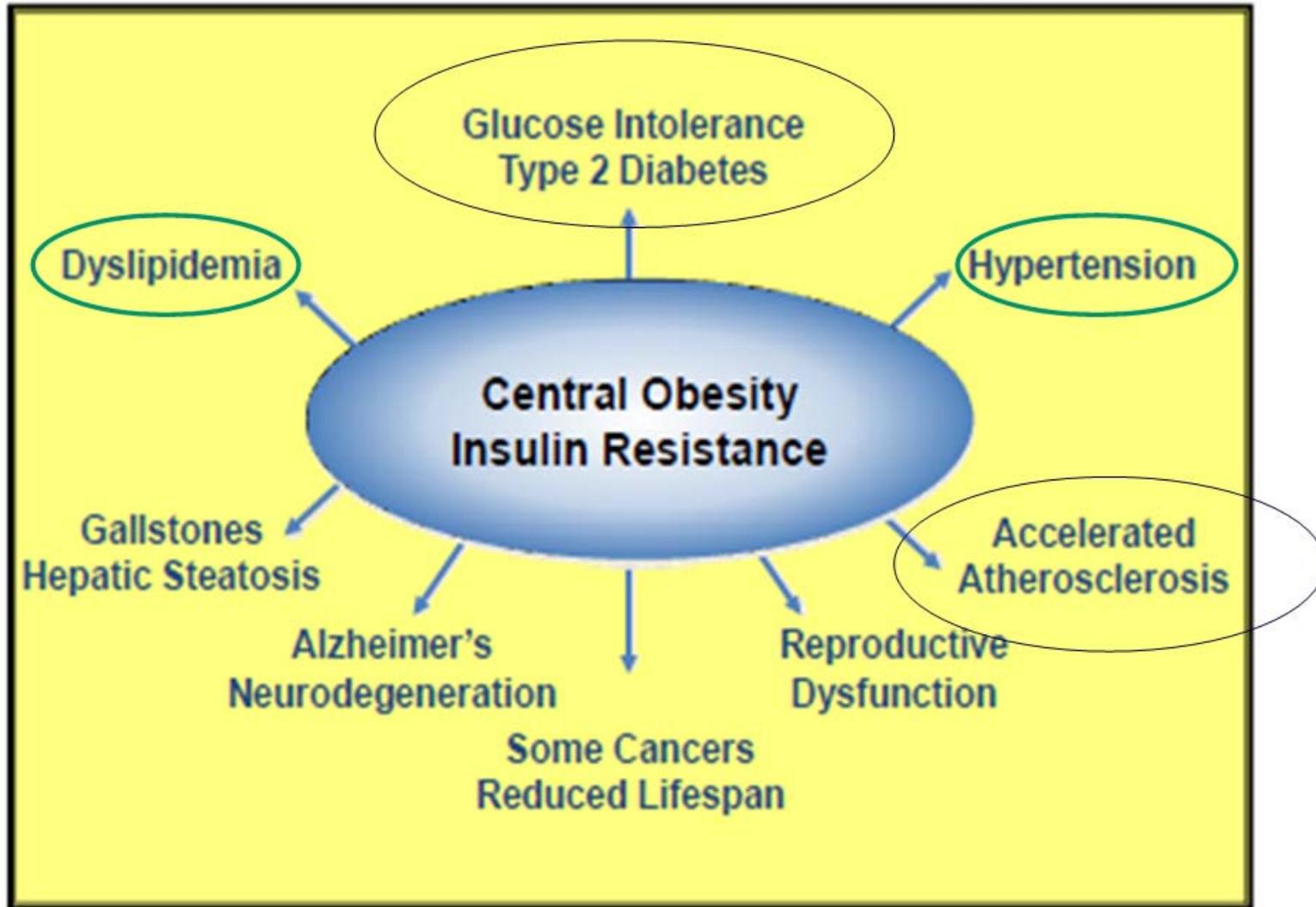
**Free Fatty Acids**

# Free Fatty Acids + Cytokines Affect Blood Vessels, Lipid Levels, and Insulin Resistance and Secretion



**Hypertension**  
**Insulin Resistance**  
**Low HDL and High Triglycerides**  
**Cytokine Toxicity to Beta Cells**

# Insulin Resistance and the Metabolic Syndrome



# Insulin Resistance underlies Cardiometabolic Risk

- Insulin resistance is the best predictor for the development of Type 2 diabetes in American Indians.
- Insulin resistance is related to many other factors such as age, diet, and exercise.

Q. So why not just measure insulin levels to find insulin resistance?

A. Test is not reliable from laboratory to laboratory.

B. Normal values are a problem.

# Intensive Lifestyle Management First Line Therapy for Cardiometabolic Risk

“The preferred treatment approach for pre-diabetes is intensive lifestyle management .... given its safety and the strong evidence of efficacy in improving glycemia and reducing cardiovascular risk factors.”

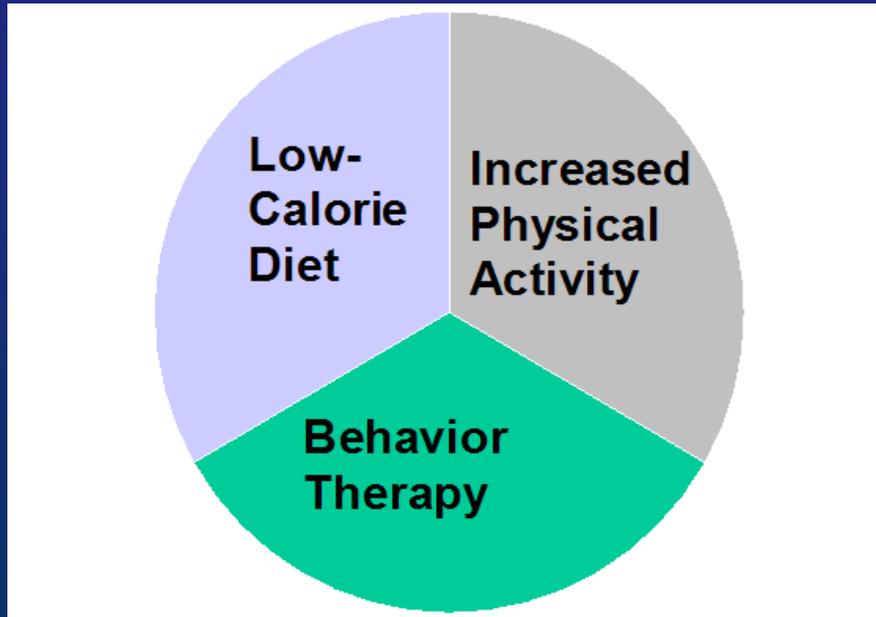
ACE 2008

“There is strong overlap between cardiovascular risk factors and pre-diabetes.... ‘metabolic risk’  
... ”

We recommend that lifestyle management be considered first-line therapy for patients at increased metabolic risk.”

Endocrine Society 2008

# Diabetes Prevention Program: Lifestyle Intervention Decreases Cardiometabolic Risk



**Q. What does Lifestyle Intervention do to prevent diabetes and decrease CV risk?**

**A. Reduces Insulin Resistance**

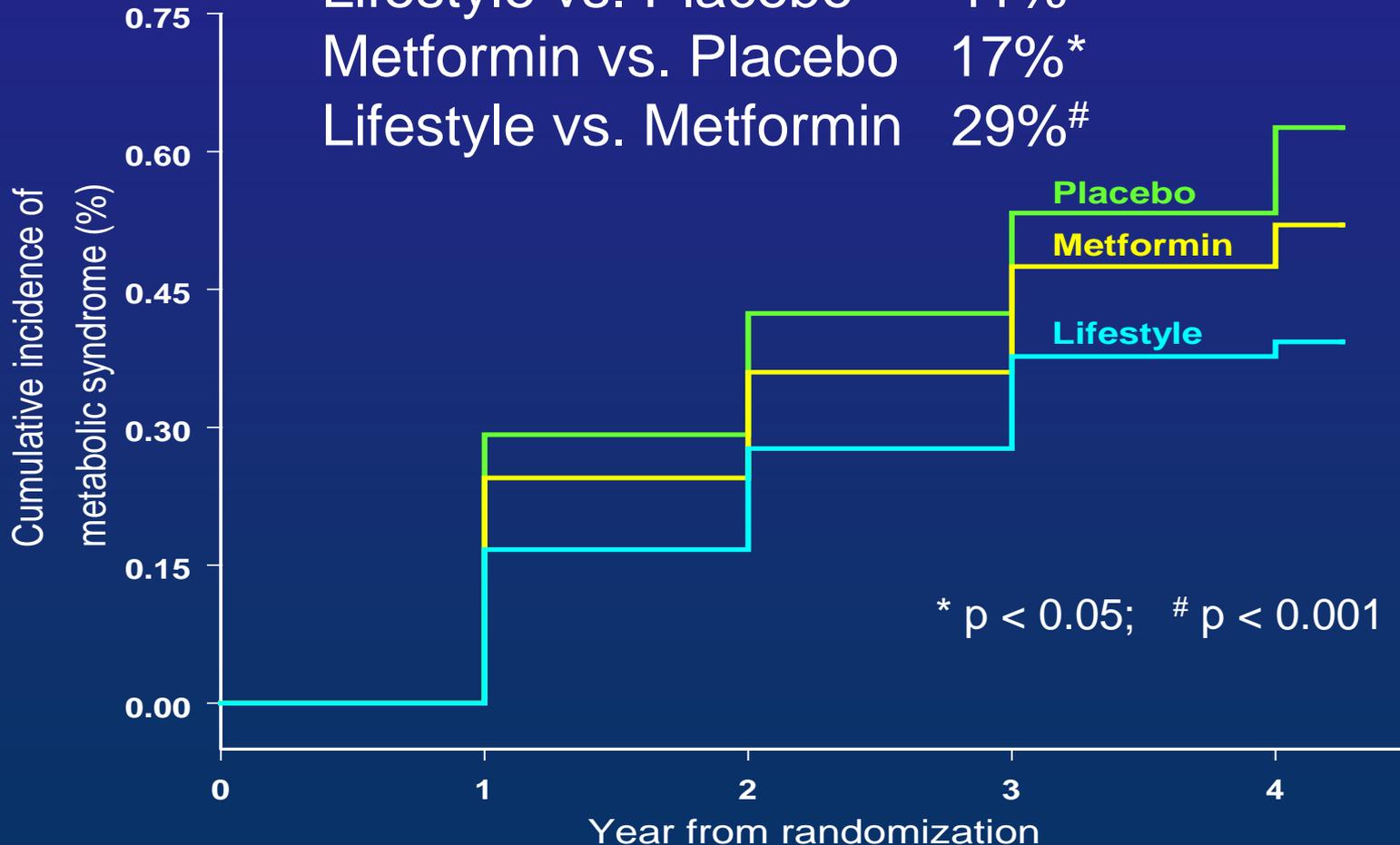
# Incidence of the Metabolic Syndrome

## Risk reduction:

Lifestyle vs. Placebo 41%#

Metformin vs. Placebo 17%\*

Lifestyle vs. Metformin 29%#



## Some Key Findings

- HTN was present in 30% of subjects at baseline; over 3 years it **increased** in the placebo and metformin groups, but significantly **decreased** in the ILS group
- TG **decreased** in all groups, but fell significantly more in ILS group
- ILS significantly **increased** HDL-C and **decreased** LDL Phenotype B
- After 3 yrs the use of medications to achieve targets for HTN was **27-28% less** and for dyslipidemia was **25% less** in the ILS group

Diabetes Care 28:888-894, 2005

# New from the Strong Heart Study: Risk Calculator for Four-Year Risk of Diabetes in American Indians ages 35 Years and Older



.....incorporates prediabetes, metabolic syndrome traits, and other factors that likely stem from insulin resistance.

<http://strongheart.ouhsc.edu/DMcalculator/calculator.html>

# Strong Heart Diabetes Risk Calculator

**Predicting risk of developing incident diabetes (DM) defined by either fasting plasma glucose (FPG) or hemoglobin A1c (HbA1c) (denoted as FPG/A1C-DM), or by HbA1c only (denoted as A1C-DM), or by FPG only (denoted as FPG-DM) in the next 4 years for a person who does not currently have FPG/A1C-DM, or A1C-DM, or FPG-DM, respectively (select one).**

FPG/A1C-DM  A1C-DM  FPG-DM

**Gender**  Male  Female

**Age (year)**

**Waist circumference (cm)**

**Taking hypertension medications for high blood pressure?**  No  Yes

**Systolic blood pressure (SBP) (mmHg)**

**Diastolic blood pressure (DBP) (mmHg)**

**Do you have any of sisters or brothers who had diabetes?**  No  Yes

**Fasting plasma glucose (FPG) (mg/dL)**

**Hemoglobin A1c (HbA1c) (%)**

**Triglycerides (TG) (mg/dL)**

**Urinary albumin and creatinine ratio (UACR) (mg/g)**

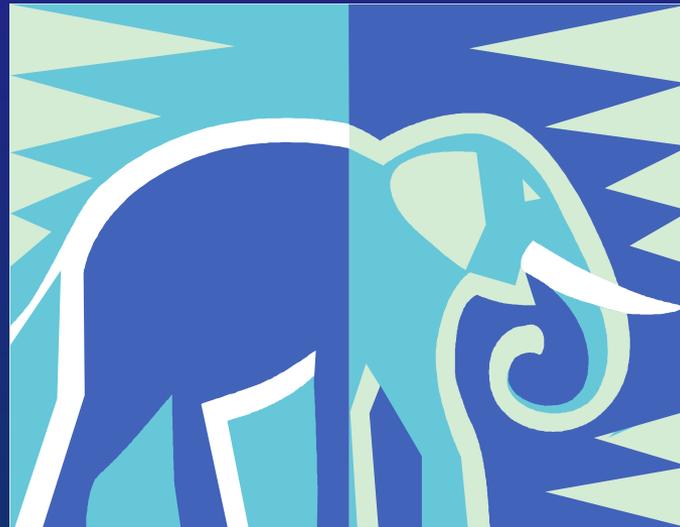
**Your Estimated Risk:**  %

# Making Sense of Cardiometabolic Risk

- **Prediabetes**

- **Metabolic Syndrome**

Cardiometabolic Risk



- **Insulin Resistance**

**How do we get him out of the living room?  
Lifestyle Intervention**

# Resources to Reduce Cardiometabolic Risk

<https://www.hncp.org/wst/hpdp/NLB/default.aspx>

<http://www.diabetesprevention.pitt.edu/glb/materials.aspx>



Native Lifestyle Balance  
DPP Curriculum modified  
by Carol Percy /Shiprock

“The GLB program is designed for overweight individuals age 18 and older who have prediabetes and/or the metabolic syndrome.”

# Making Sense of Cardiometabolic Risk in American Indians

## **Cardiometabolic = Heart Disease + Diabetes**

1. Names and definitions for CMR work in Indians.
2. Talking about CMR helps broaden the focus to many risk factors associated with Insulin Resistance.
3. Lifestyle Intervention reduces the risk factors.
4. There are several ways to find people at increased CMR, but the important issue is having effective programs to reduce CMR.

