Pre-diabetes:
The epidemic within the epidemic

… what should we do for these patients?

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Objectives

To understand:

1. Definitions of Pre-diabetes and the Metabolic Syndrome, and their relationship to risk for Type 2 Diabetes, cardiovascular disease, mortality.
2. Evolving treatment paradigms for pre-diabetic patients – evidence and practice.

Today we will be speaking primarily about adult patients with or at-risk for Type 2 diabetes.

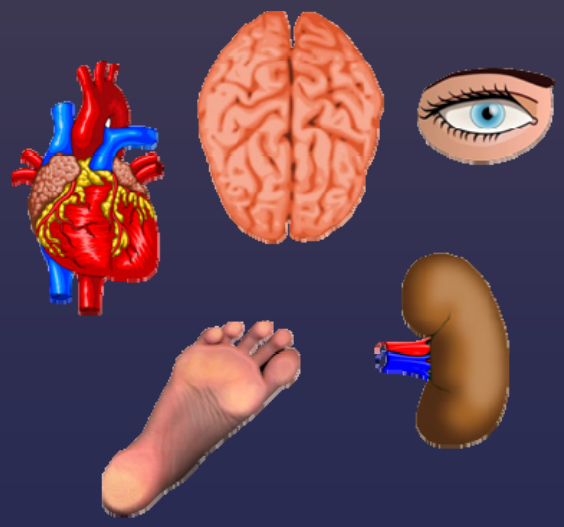
Patients with Type 2 diabetes suffer and die due to vascular "Diabetic Complications"

MACROVASCULAR

- Coronary artery disease, myocardial infarction
- Cerebrovascular disease, stroke
- Peripheral vascular disease, amputation

BOTH

- Congestive heart failure
- Dementia



MICROVASCULAR

- Retinopathy, blindness
- Nephropathy, dialysis
- Neuropathy, foot fractures, amputations
- Periodontal disease

Also: Pregnancy complications

Traditional Model for Diabetes Complications

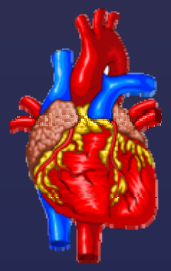
(DCCT – Type 1 diabetes)

Genetics
Lipids
Traditional
CVD Risks

High Blood Glucose
(Diabetes)

Minor
contributions

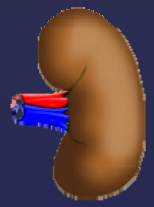
MACROVASCULAR INJURY



CAD/MI

CVD/Stroke

MICROVASCULAR INJURY

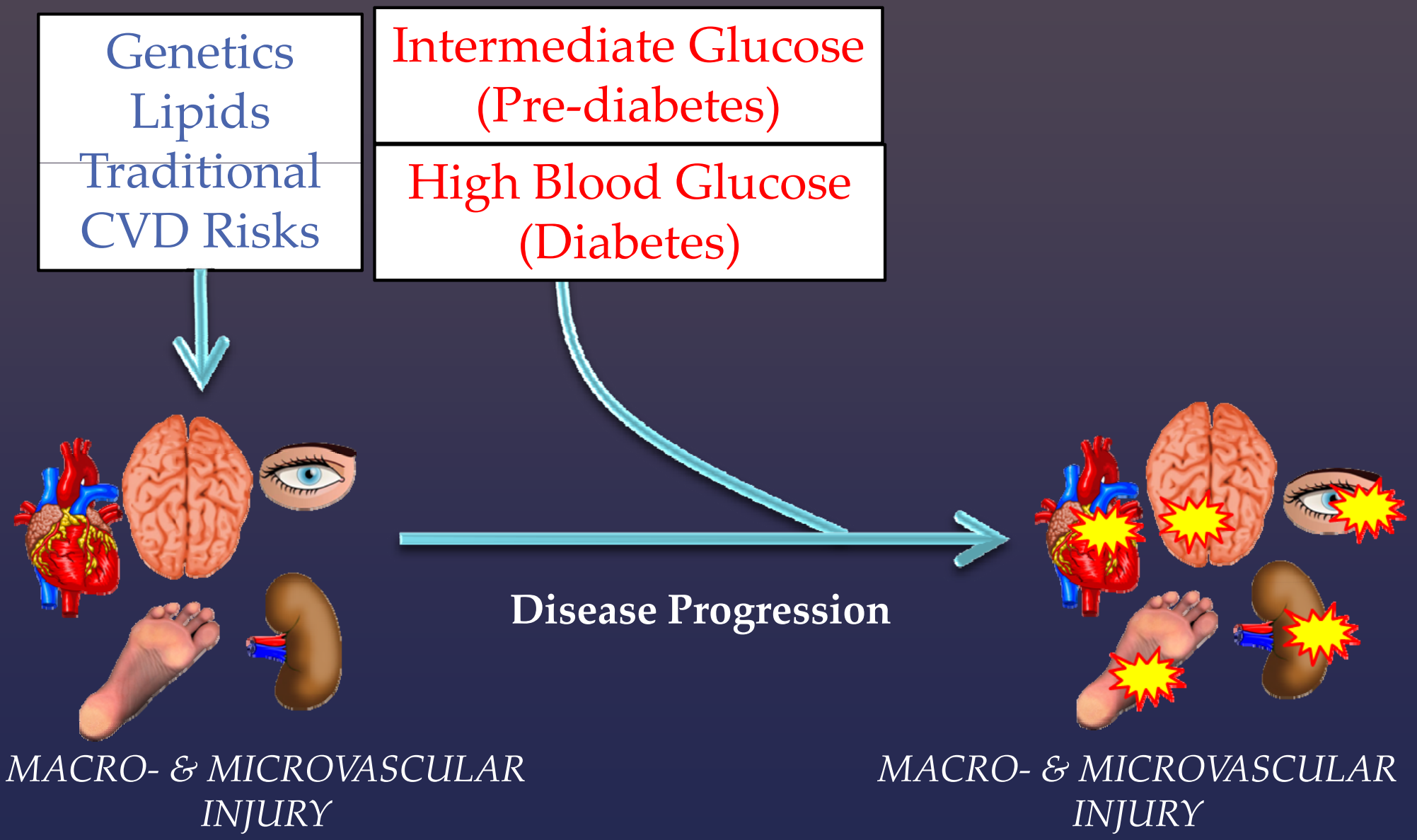


Nephropathy

Neuropathy

Retinopathy

Newer Model for Complications Pathogenesis (UKPDS – Type 2 diabetes)



Defining Pre-Diabetes

Fasting Blood Glucose

- Impaired Fasting Glucose (IFG): 100-125 mg/dL
- Diabetes ≥ 126 mg/dL

75 gm 2 hr oral glucose tolerance test (oGTT)

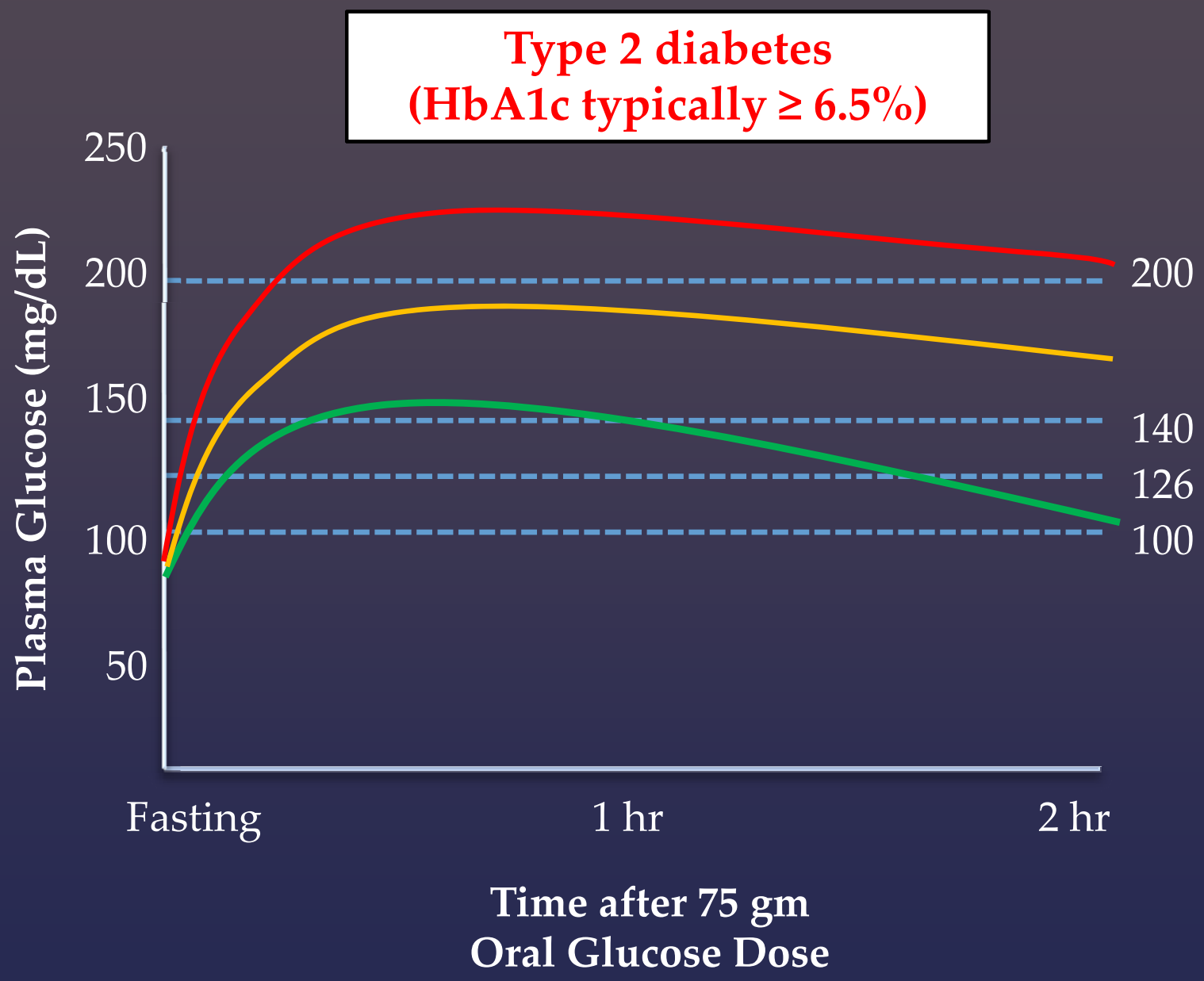
- Impaired Glucose Tolerance (IGTT): 140-199 mg/dL at 2 hrs
- Diabetes: ≥ 200 mg/dL

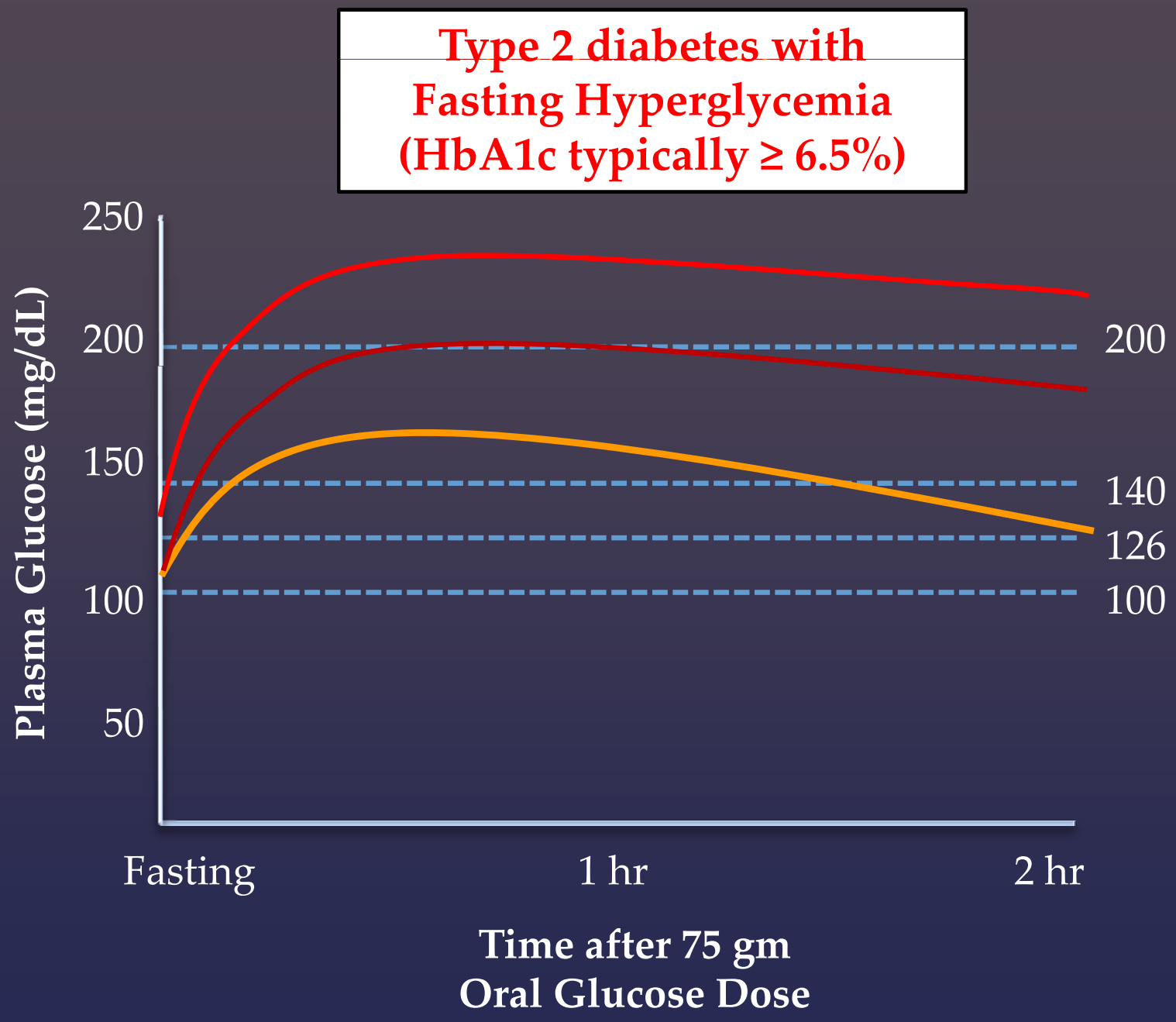
Hemoglobin A1c (HbA1c)

- Abnormal: ≥ 5.7% (5.5%)
- Diabetes: ≥ 6.5%

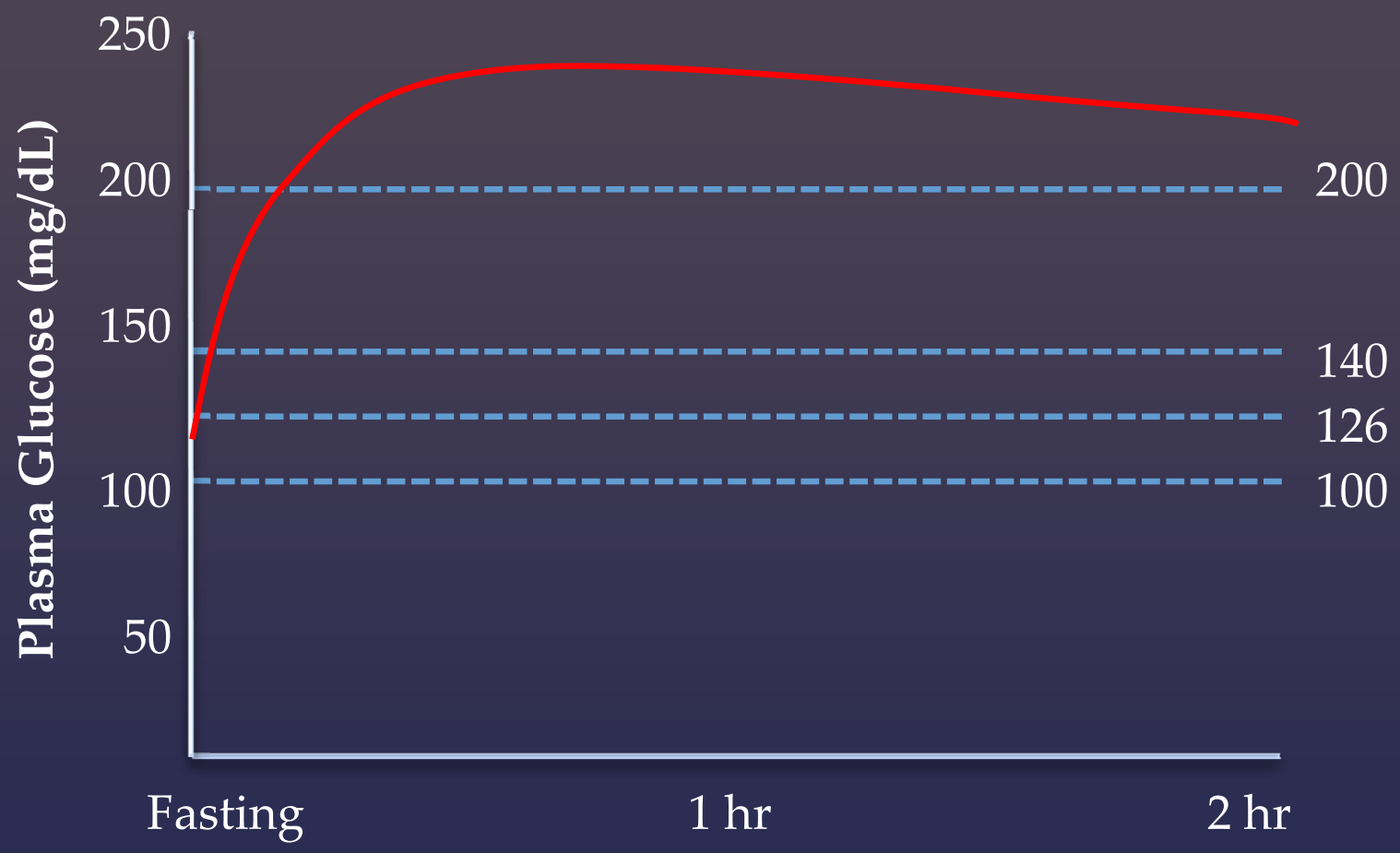
Random Blood Glucose

Diabetes: ≥200 mg/dL on two occasions, or once with symptoms


Type 2 diabetes
(HbA1c typically ≥ 6.5%)
Plasma Glucose (mg/dL)
250
200
150
100
50
200
140
126
100
Fasting
1 hr
2 hr
Time after 75 gm
Oral Glucose Dose


Type 2 diabetes with
Fasting Hyperglycemia
(HbA1c typically ≥ 6.5%)
Plasma Glucose (mg/dL)
250
200
150
100
50
200
140
126
100
Fasting
1 hr
2 hr
Time after 75 gm
Oral Glucose Dose

Type 2 diabetes with
Impaired Fasting Glucose
******33% of patients with IFG******

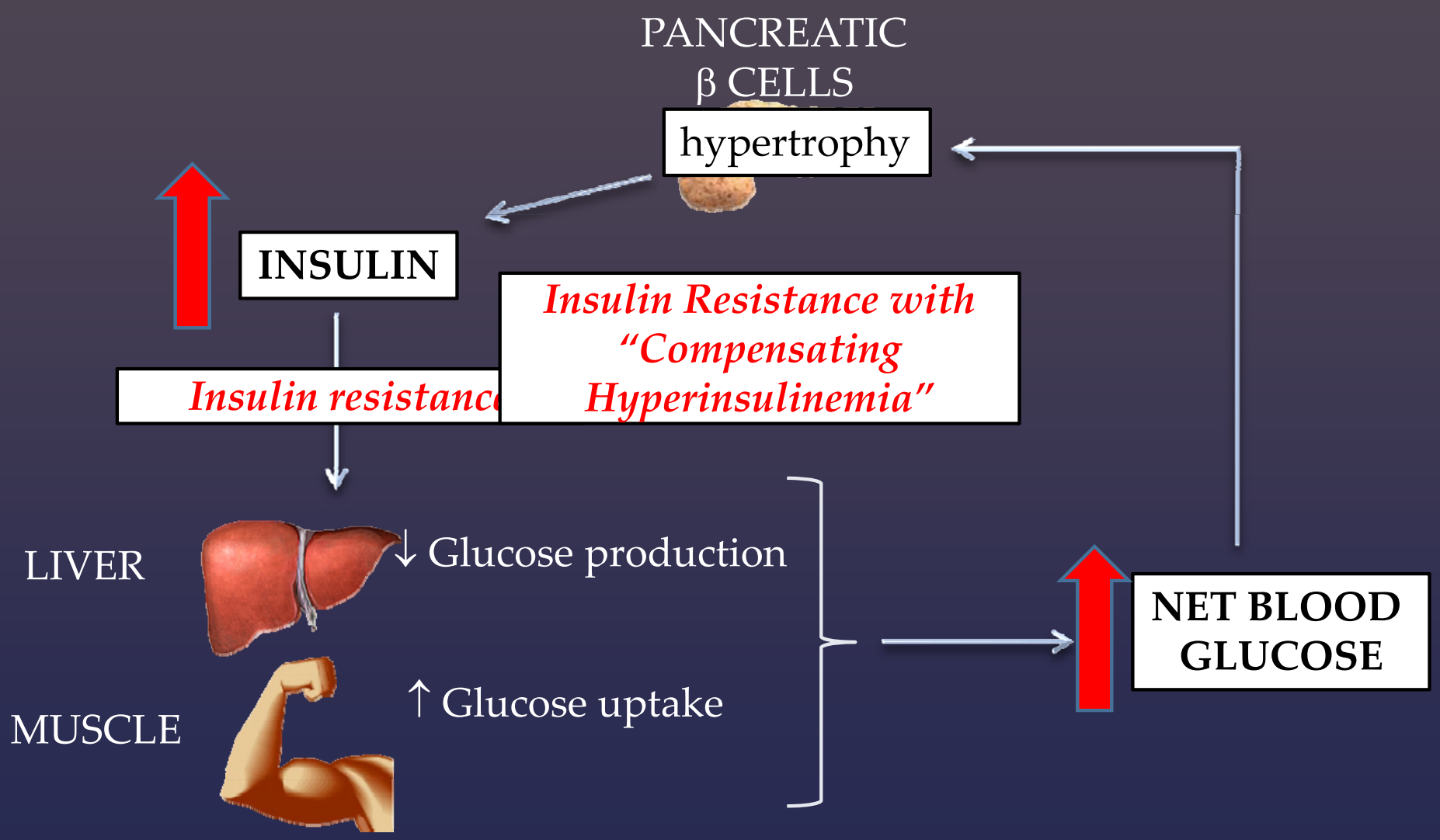


Time after 75 gm
Oral Glucose Dose

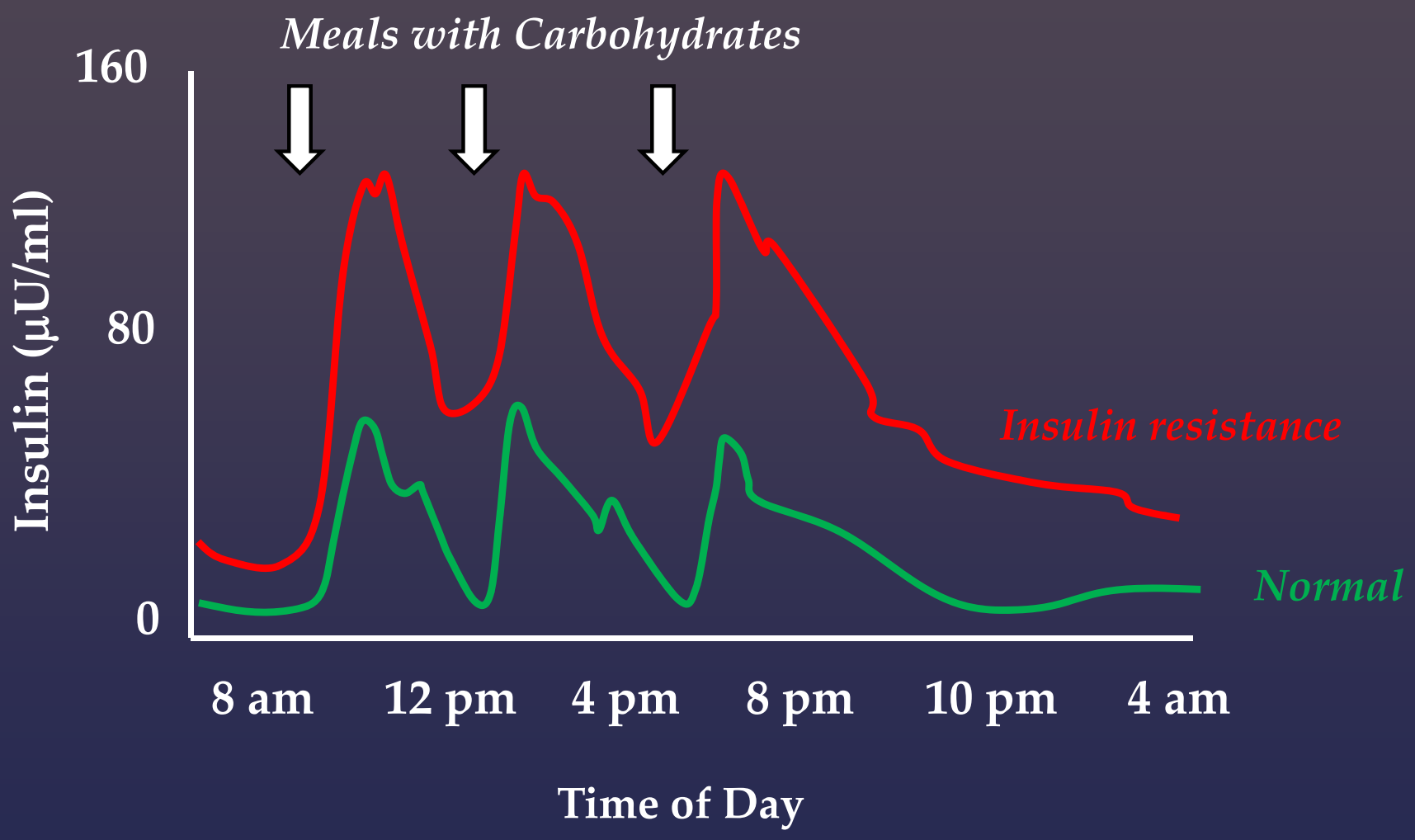
Complications Risk Continuum

IFG < IGT << CGI ~ T2DM

Insulin Resistance – underlying pathology



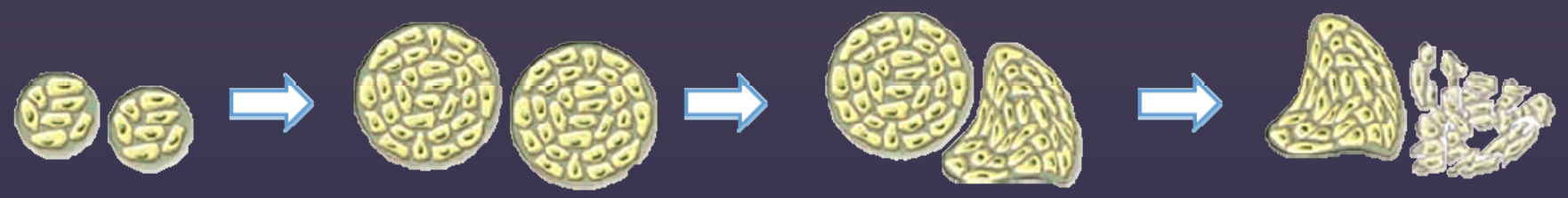
Compensating Hyperinsulinemia



Failure of Pancreatic β Cell compensation: Pre-diabetes and Diabetes

Pancreatic β Cell Health

Normal	Hypertrophy	Dysfunction	Failure

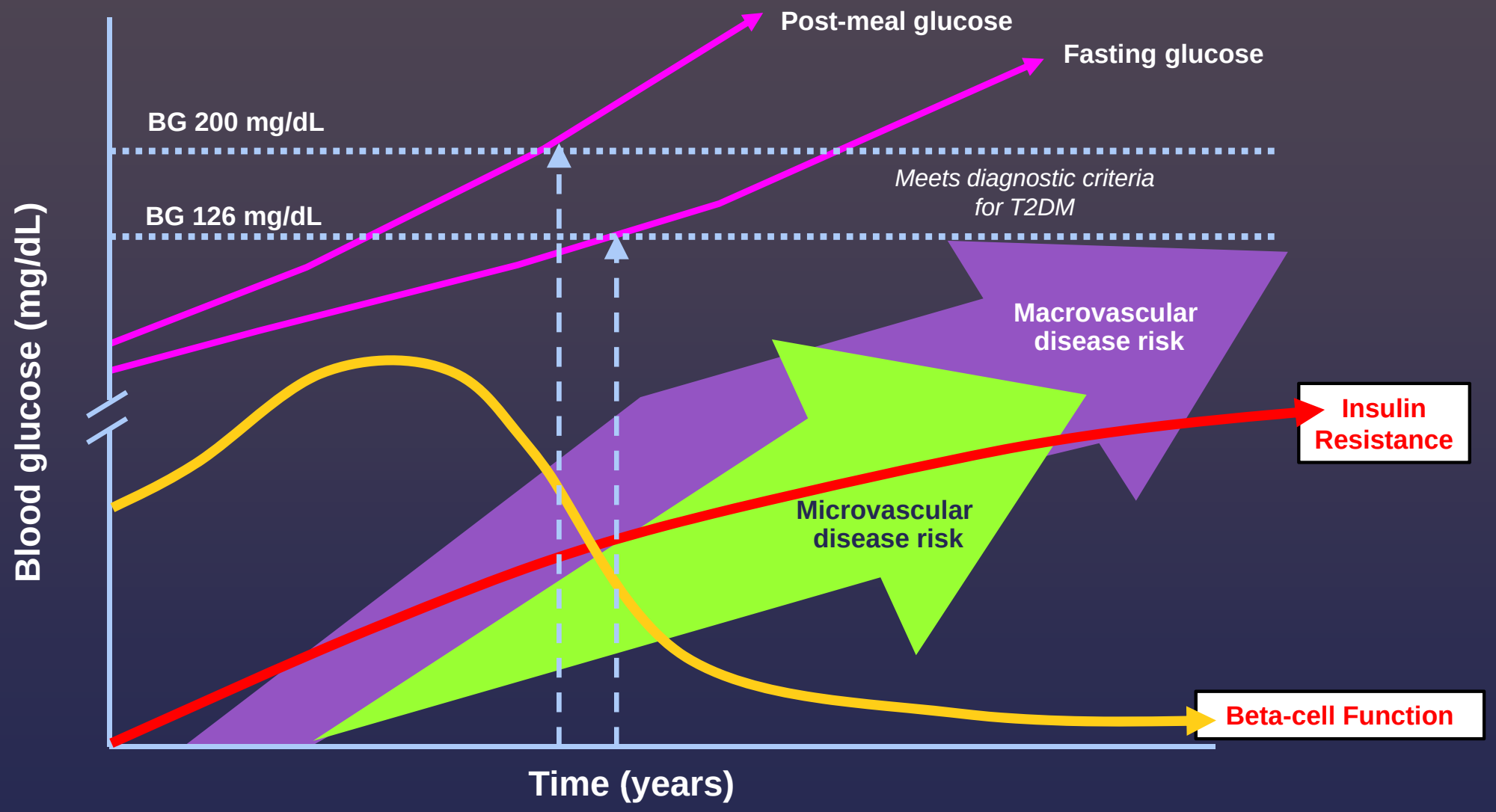


Normal	Hyperinsulinemia (Sufficient)	Hyperinsulinemia (Insufficient)	Variable (Very Insufficient)

Insulin Production Status

Normal Glucose	Pre-diabetes	Diabetes

Insulin Resistance: An early feature of disease



But we don't routinely measure insulin resistance itself in clinical practice….

The Metabolic Syndrome – MetSyn

"Clinical Insulin Resistance"

Must have 3 of the following 5 criteria:

- IFG, IGT, or Type 2 diabetes*
- Blood pressure* ≥ 130/85 mm Hg
- Triglycerides* ≥150 mg/dL
- HDL-C* < 40 mg/dL* in men or < 50 mg/dL in women
- Waist circumference ≥ 40" in men or ≥ 35" in women**

***or prior treatment for these conditions.**
****U.S. Caucasians; cut-offs for other ethnicities are established**

NCEP/ATPIII recommendations

Other Conditions with MetSyn Features

- Obstructive sleep apnea
- Polycystic ovarian syndrome
- Gestational diabetes and history of high birth weight (≥ 9 lbs) infants
- Chronic inflammatory conditions: rheumatoid arthritis, psoriasis, inflammatory bowel disease
- Hypothyroidism (including subclinical)
- Cushing's syndrome/disease
- Atypical antipsychotics therapy
- Accutane (Isotretinoin) therapy
- HIV protease inhibitor therapy

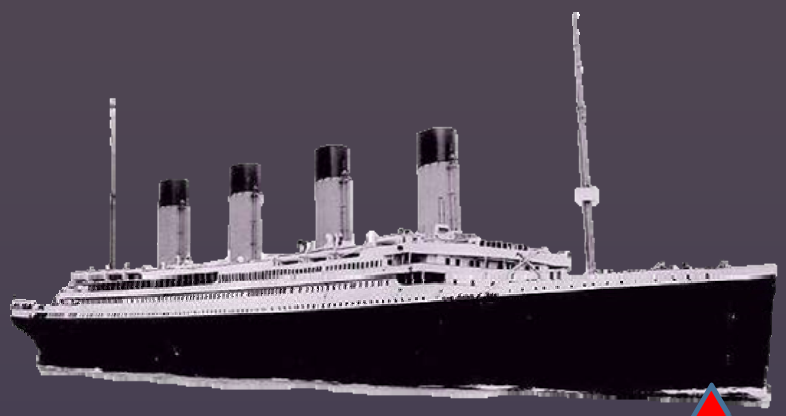
Metabolic Syndrome (MetSyn): Essentially a Pre-diabetic State

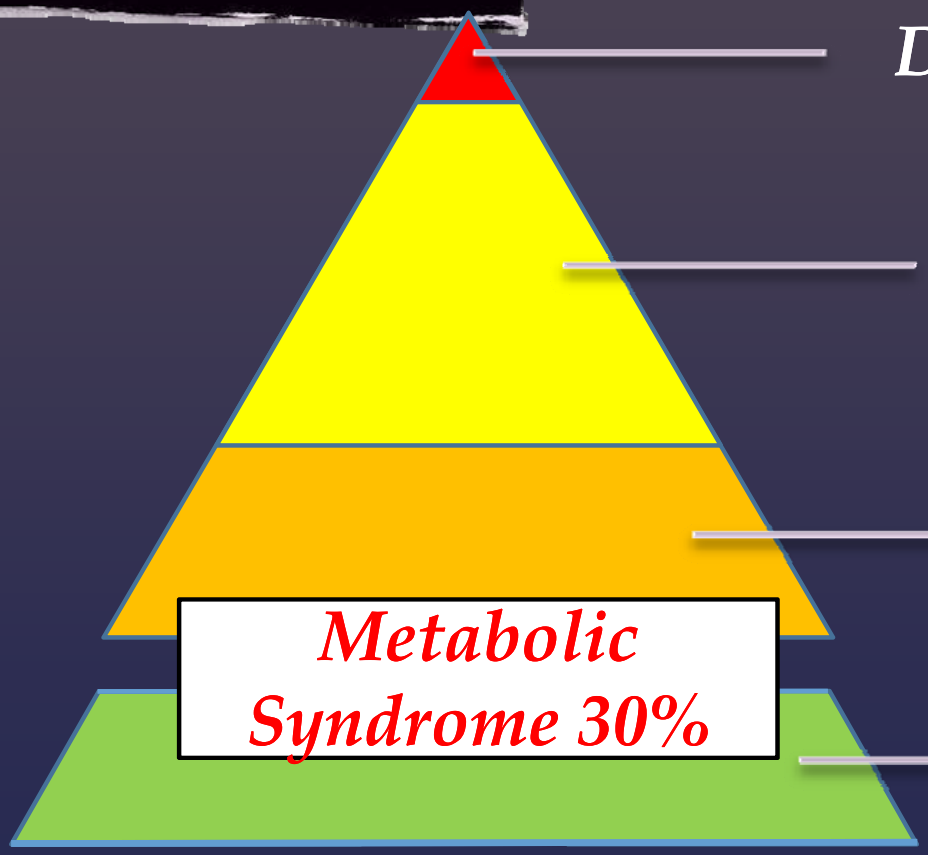
- **MetSyn *without IFG or IGT*: 5-fold increase in diabetes risk**
- **MetSyn with IFG or IGT: 5- to 7-fold increase in diabetes risk**
- **MetSyn: 75% prevalence in IFG+IGT**

Because these conditions are so co-prevalent, it is difficult, perhaps impossible, to completely determine their separate contributions to cardiovascular and microvascular risk for any given patient we see.

Grundy, SM; J. Am. Coll. Cardiology (2006) 47:1093

Top of the Pyramid or Tip of the Iceberg?





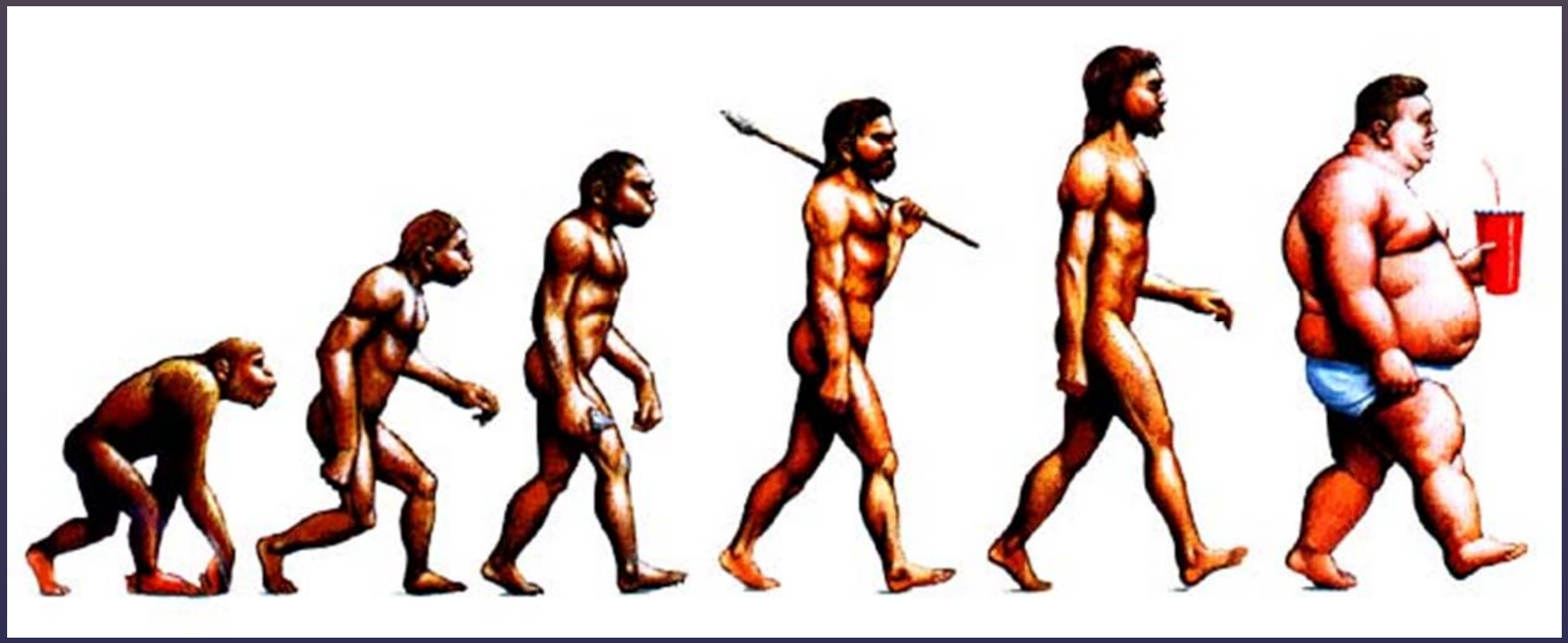
Diabetes (9%)

Pre-diabetes (40%)

Obesity and Overweight (70%)

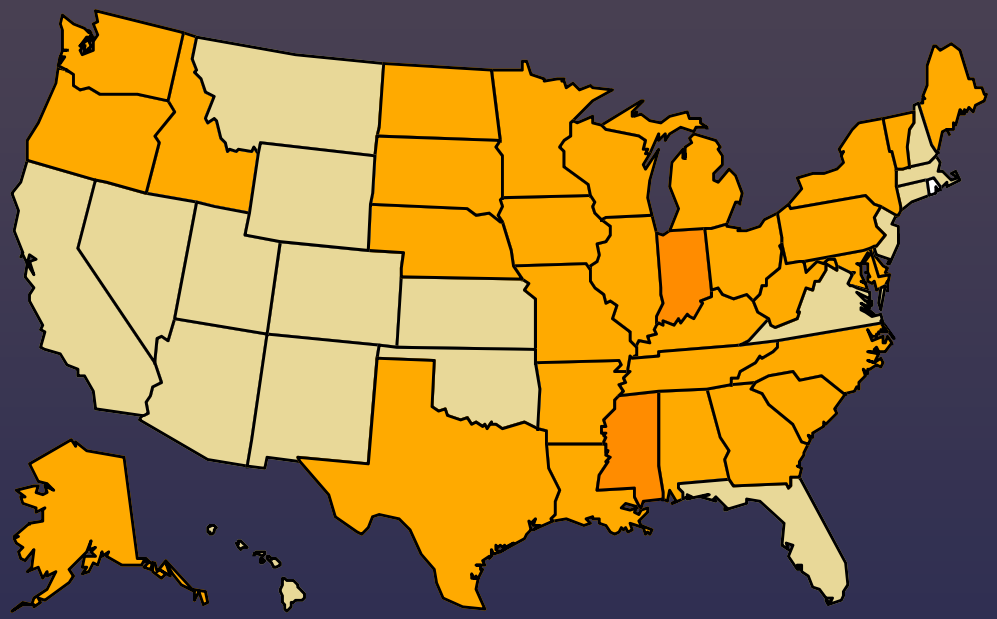
Metabolically normal?

What's going on?



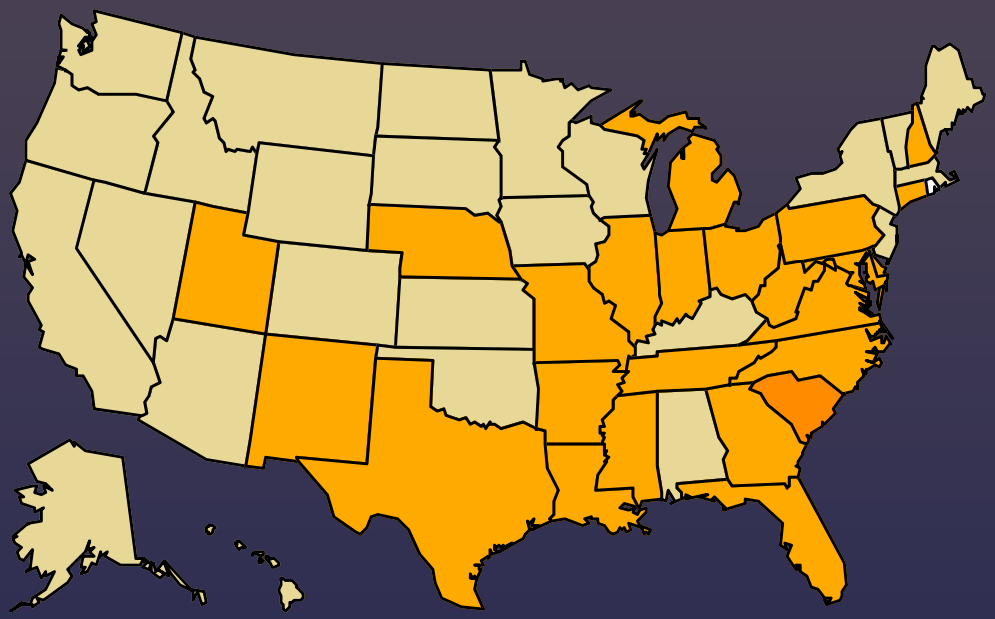
1994

Obesity



- ≤14%
- 14-17.9%
- 22-25.9%
- 22-25.9%
- ≥26%

Type 2 diabetes

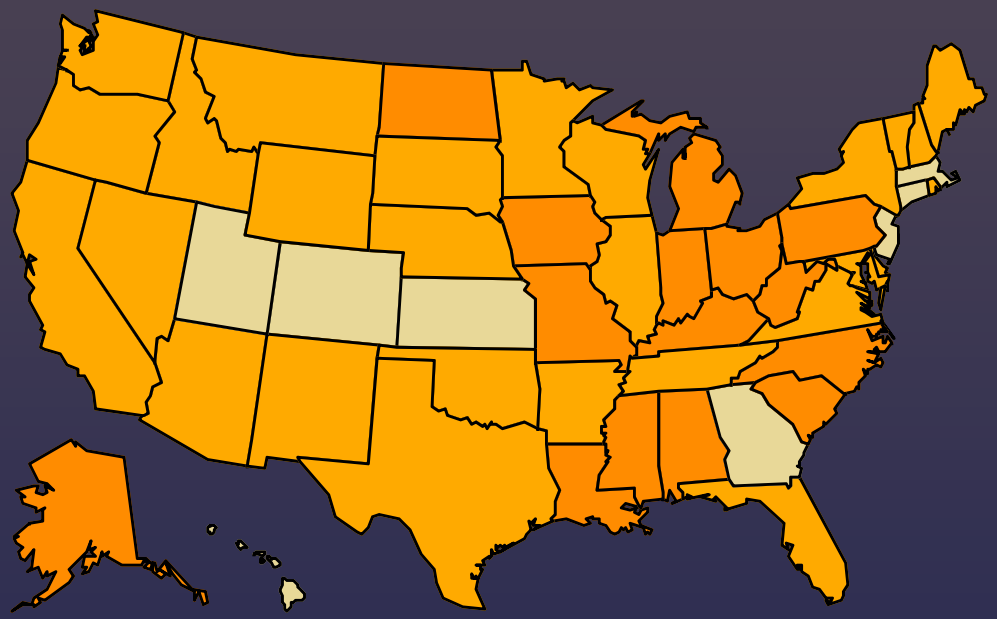


- ≤4.5%
- 4.5-5.9%
- 6.0-7.4%
- 27.5-8.9%
- ≥9%

CDCs Division of Diabetes Translation National Diabetes Surveillance

1996

Obesity



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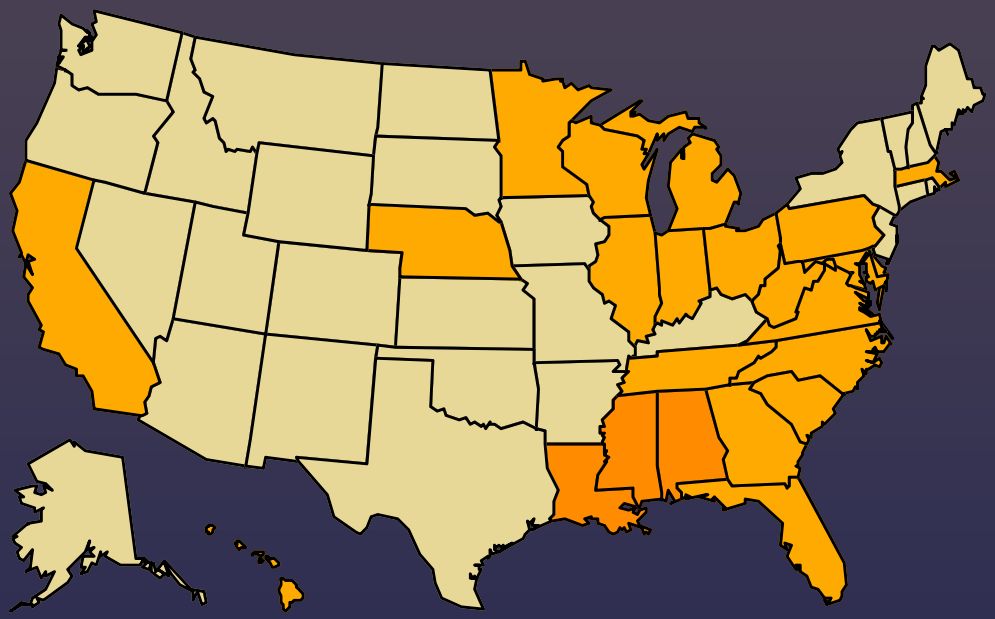

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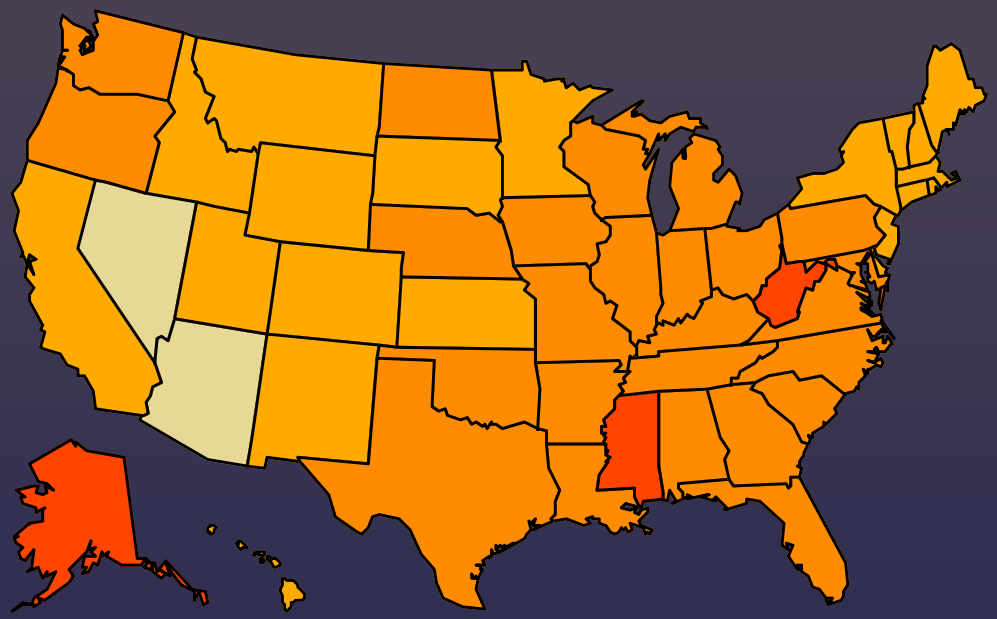
1998

Obesity



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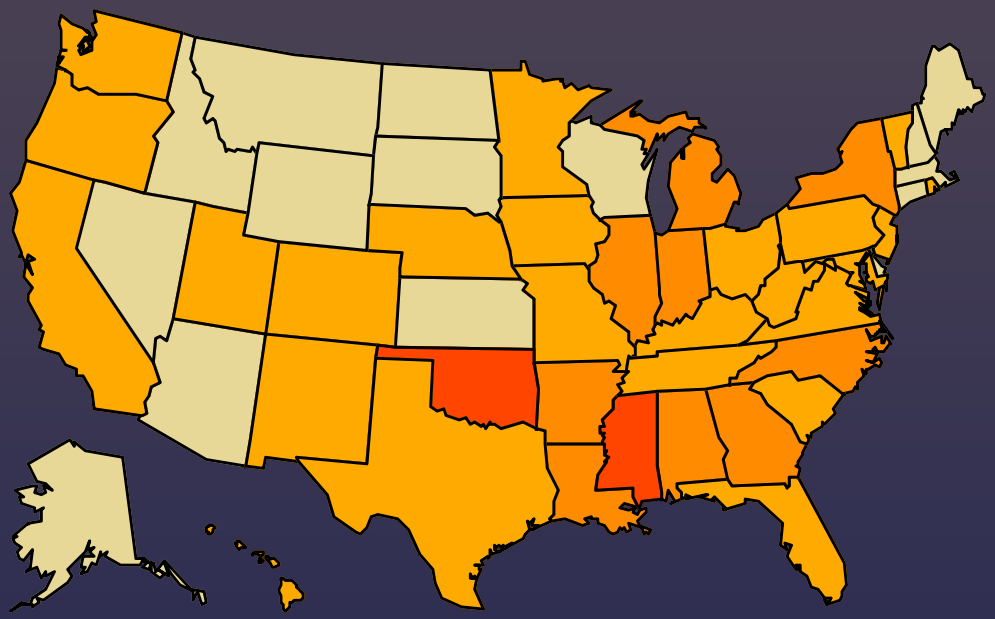
Type 2 diabetes



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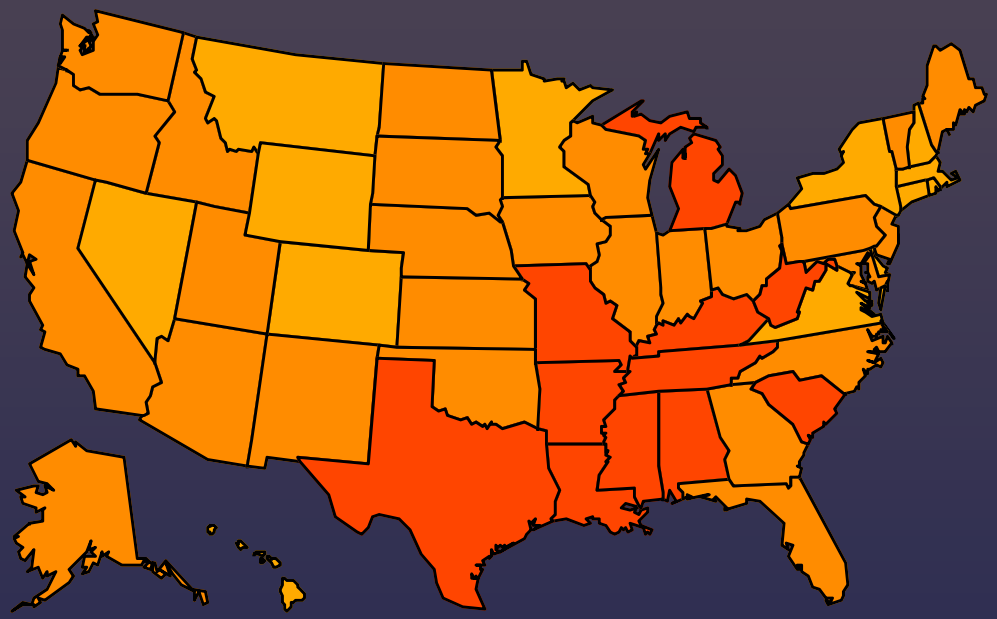
2000

Obesity



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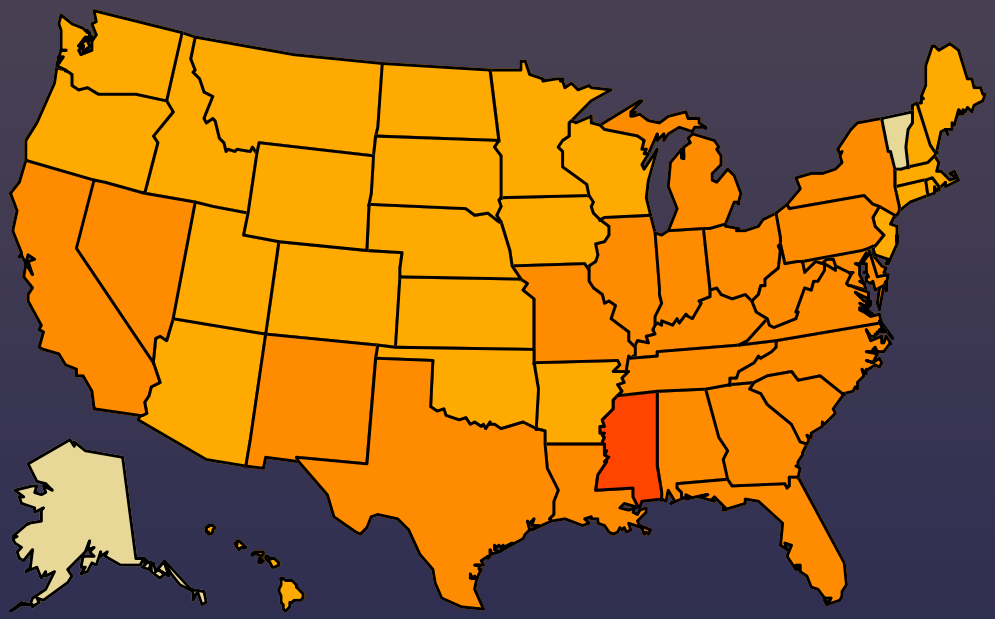
Type 2 diabetes



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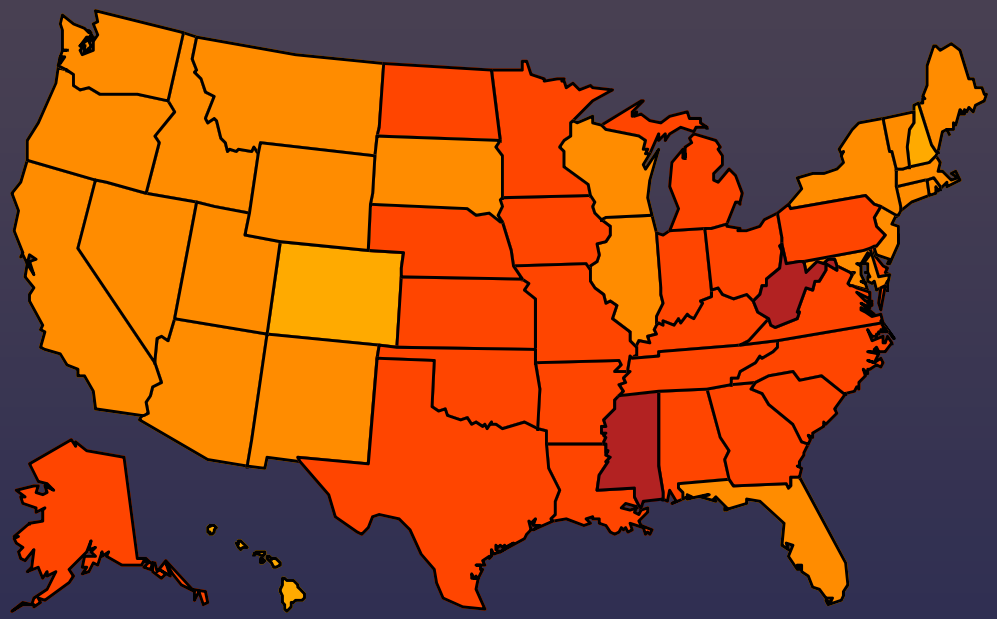
2002

Obesity



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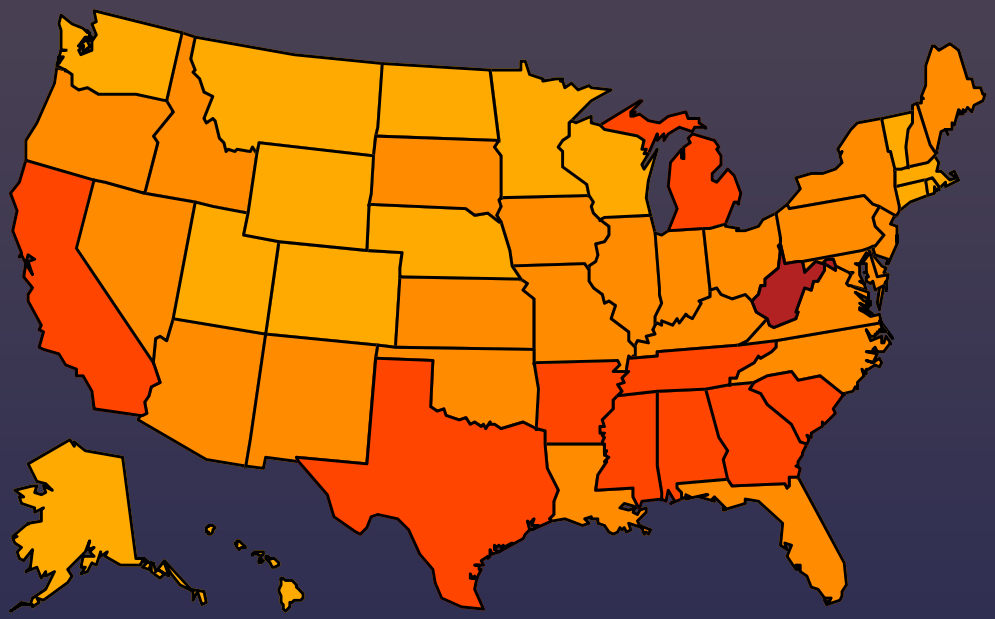
Type 2 diabetes



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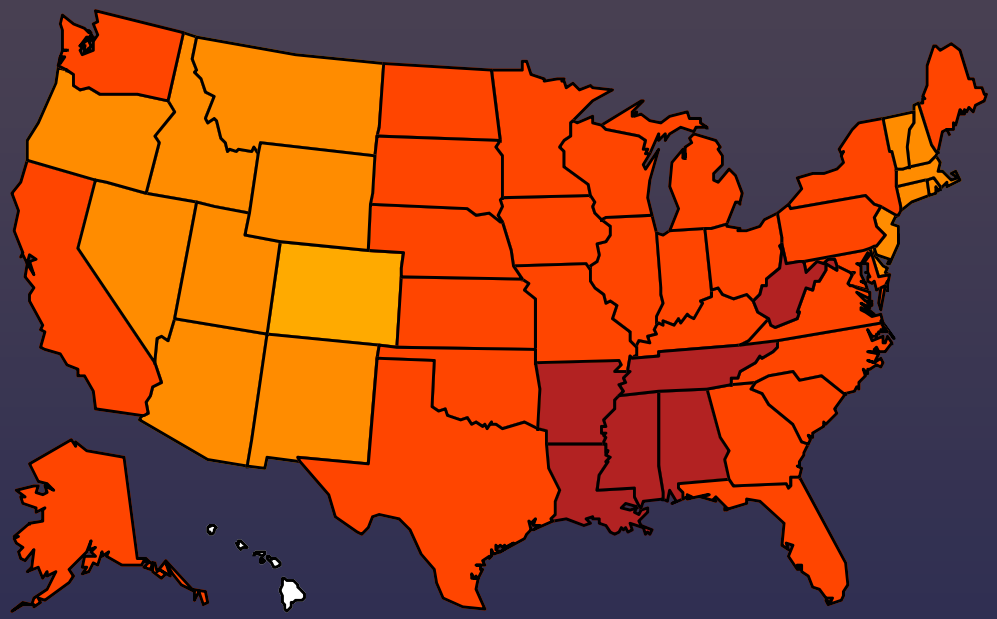
CDCs Division of Diabetes Translation National Diabetes Surveillance

2004

Obesity



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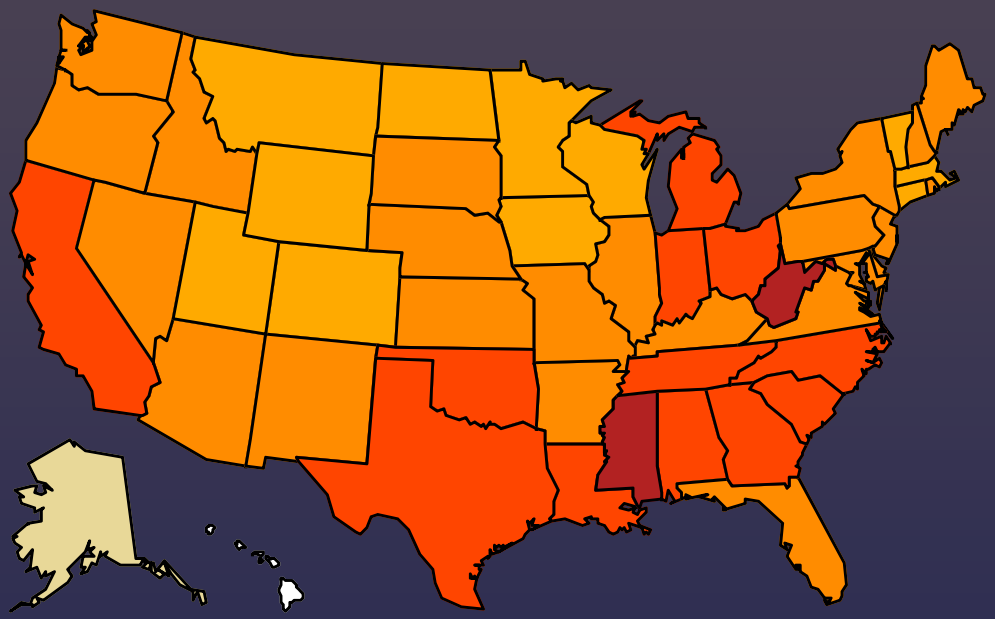
Type 2 diabetes



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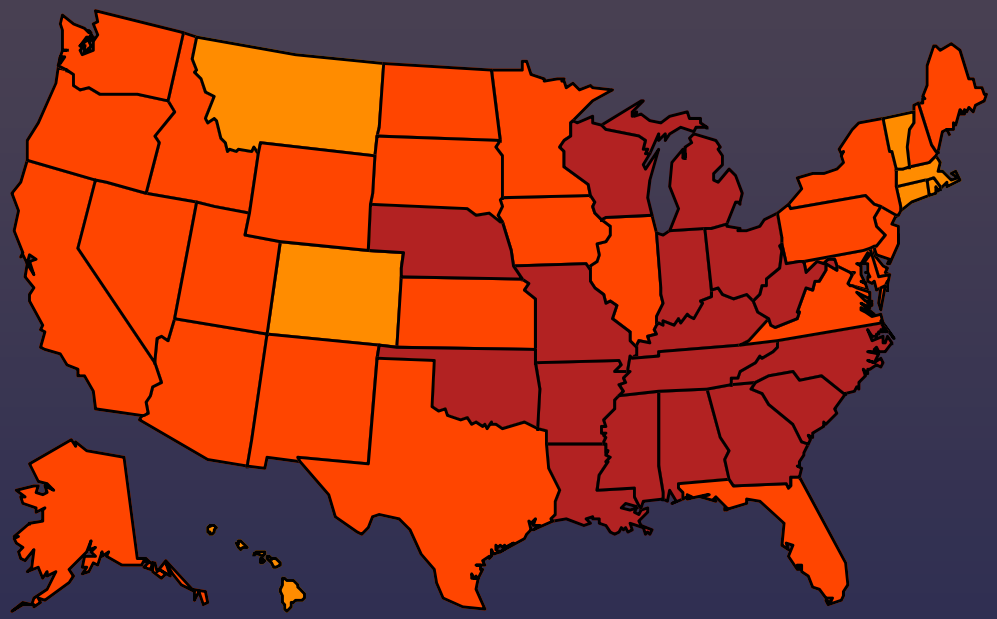
2006

Obesity



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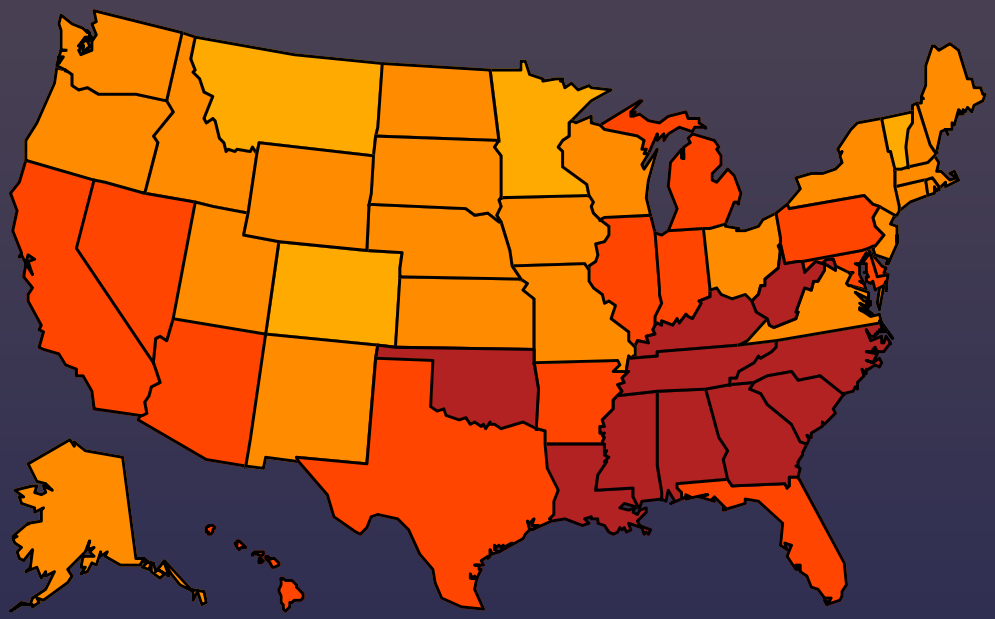
Type 2 diabetes



- ≤4.5%
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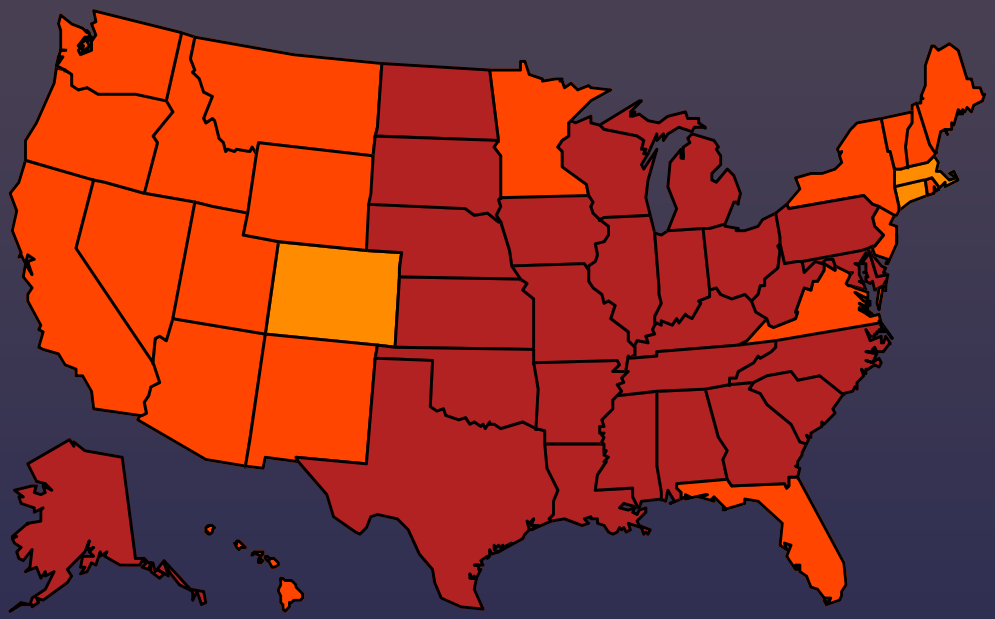
2008

Obesity



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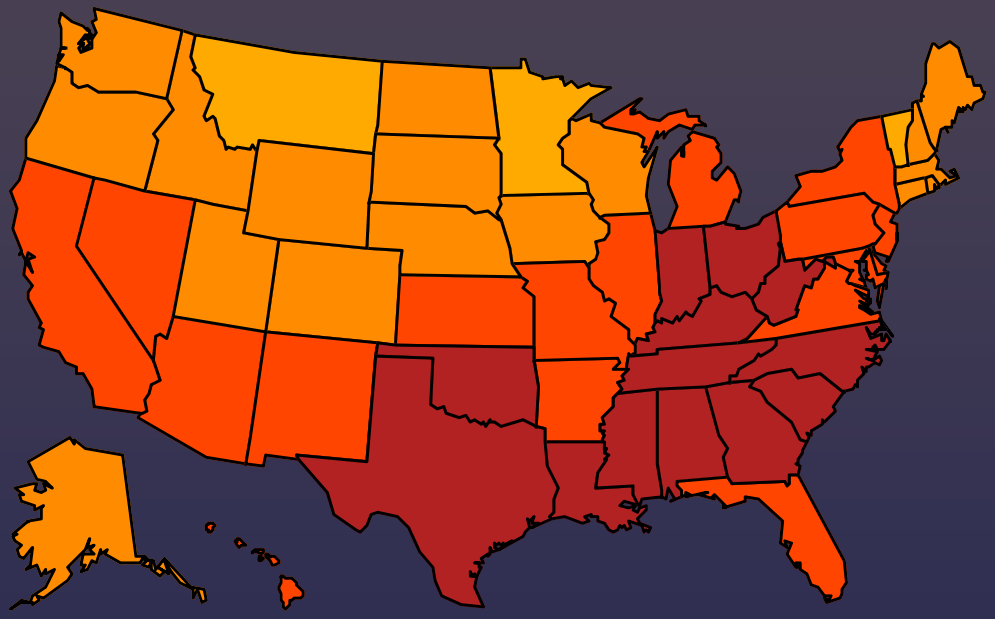
Type 2 diabetes



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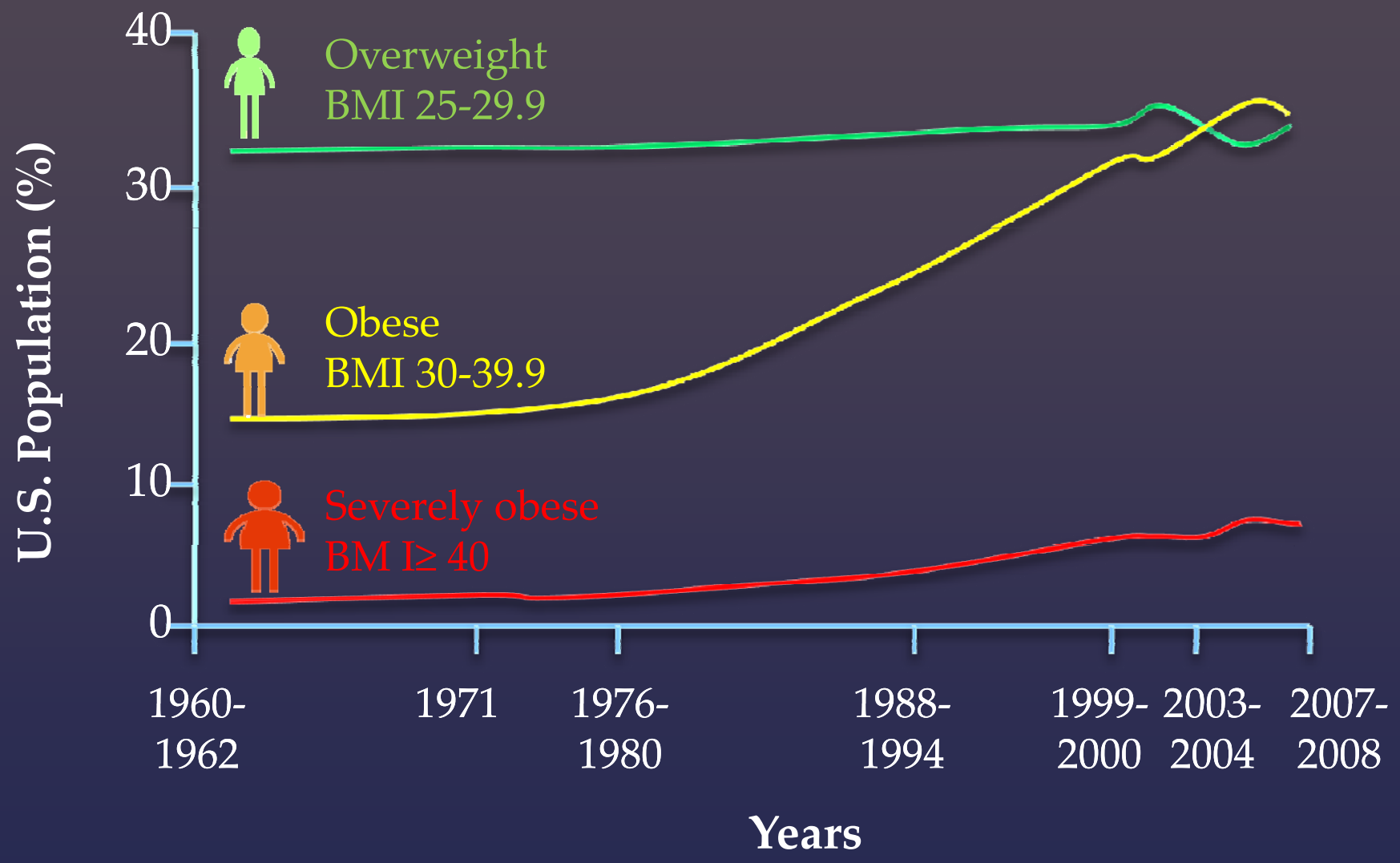
CDCs Division of Diabetes Translation National Diabetes Surveillance

Obesity Outstripping Overweight in U.S.

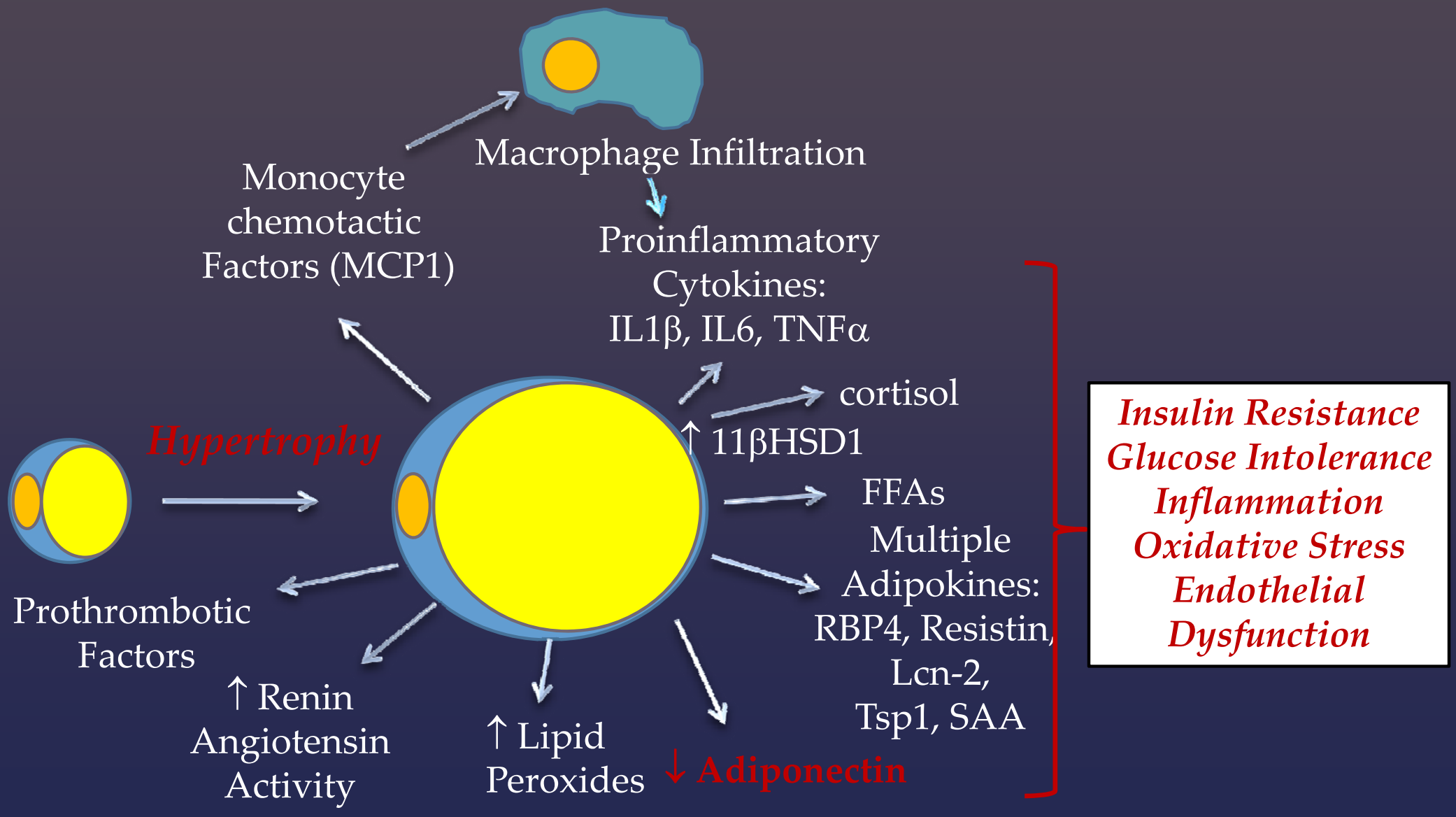


CDC/NCHS, National Health Examination Surveys 1960-2008

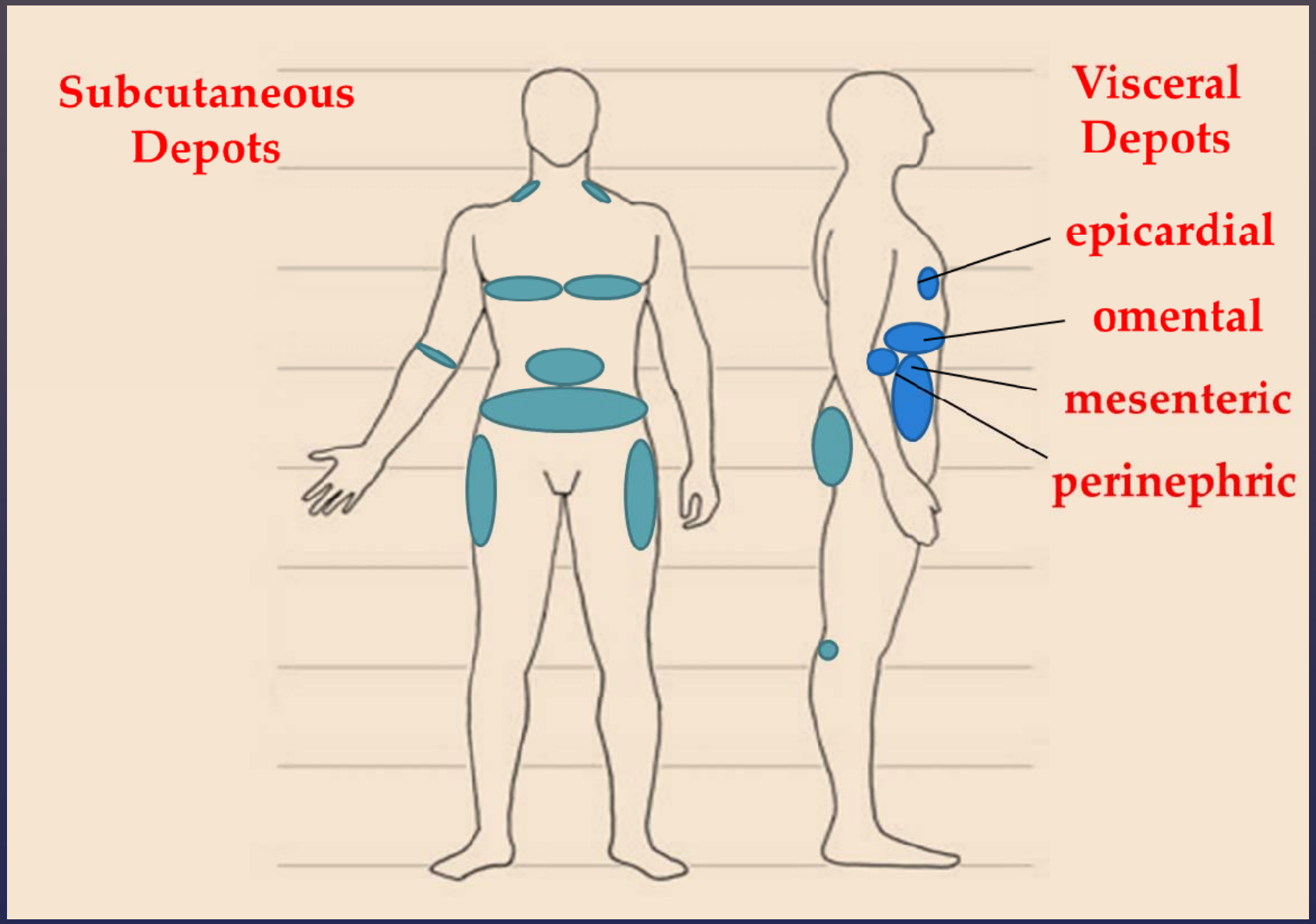
Normal Functions of Healthy Adipose Tissue

1. **Nutrient storage – short term and long term**
2. **Mechanical cushioning/connective tissue function/insulation**
3. **Non-shivering Thermogenesis (Brown Fat)**
4. **Endocrine (Secretory) Function:**
   - **Food intake/satiety**
   - **Immune function**
   - **Reproduction**

When Good Fat Goes Bad: Enlargement of Adipocytes in Obesity

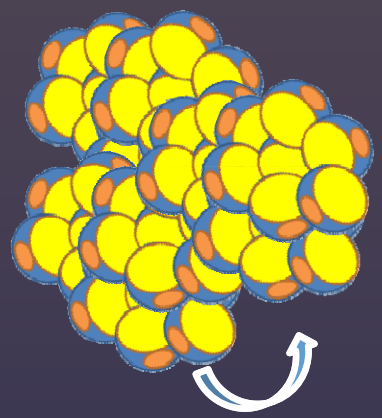


The Adipose Organ(s)

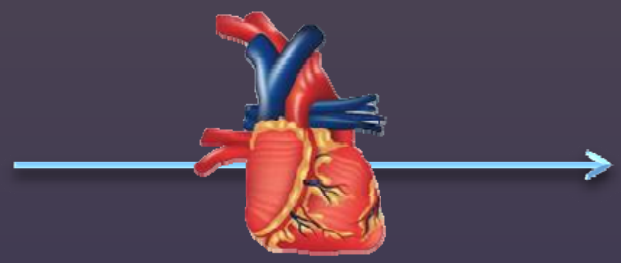


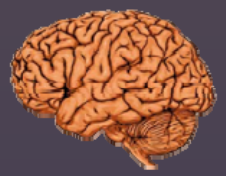
Fat Depots Differ in Biological Functions

Subcutaneous Fat



Systemic Effects via General Circulation



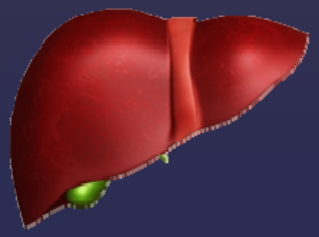


CNS

Skeletal Muscle

Autocrine/Paracrine Effects

Hepatic & β cell Effects via Portal Circulation

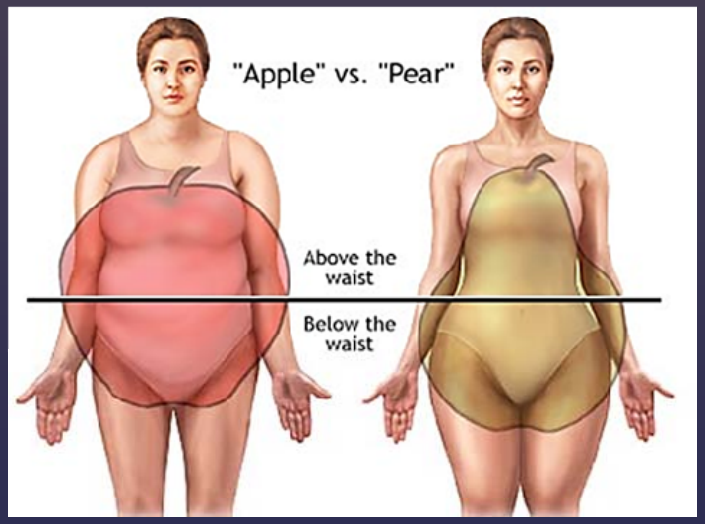


Liver

Visceral Fat

Fat Distribution Predicts Disease

"Central obesity" is one of the principal risk factors for MetSyn, Pre-diabetes, and Type 2 diabetes.



Noteworthy Exceptions to Obesity = Bad Fat

1. *Lean Family Members of Type 2 Diabetics (genetics)*
   - Increased features of metabolic syndrome and risk for future diabetes.
   - BMI is normal but visceral adipose tissue (bad fat) is relatively increased for body size

2. *Metabolically "Healthy" Obese*
   - Normoglycemic, non-hyperinsulinemic
   - No dyslipidmia
   - No hypertension
   - Even with BMI > 40 kg/m^2 (!)

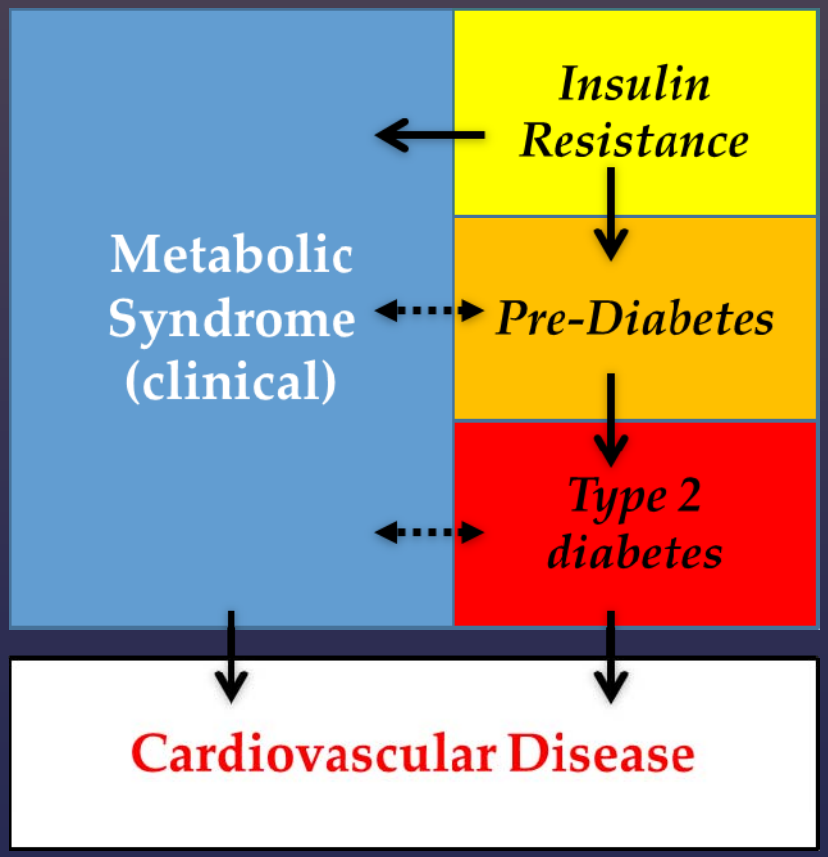
Why treat Pre-diabetes?

- Type 2 diabetes develops at 10-15% per year
- CVD mortality increases continuously with blood glucose levels
- 2.5-fold increase in CVD mortality over 5 years, even after adjustments for age, sex, and other traditional CV risk factors (IFG).
- 62% increase in adjusted *all-cause mortality* over 5 years (IGT)
- Increased rates of microvascular disease (retinopathy, nephropathy, neuropathy)

DPP Study Group
Barr et. al, Circulation. 2007; 116: 151-157

Arguments for Even Earlier Intervention

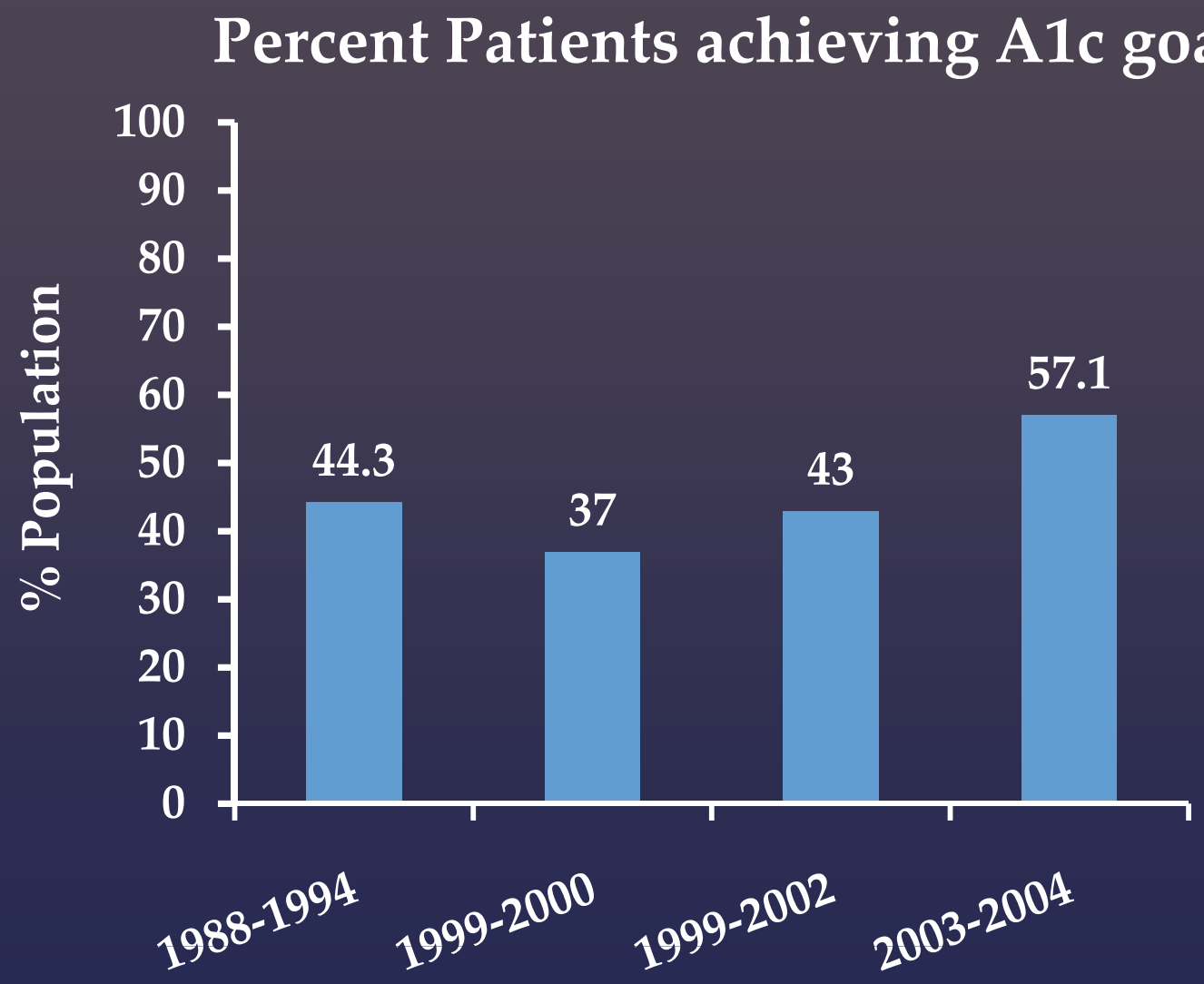
1. *MetSyn is a major CV risk factor <u>even without IFG/IGT</u>*



- **MetSyn conveys risk greater than the sum of its individual parts**
- **≥2-fold increase in risk of MI or stroke (women > men); *i.e.*, the risk equivalent of tobacco in some populations**
- **Strong predictor of future diabetes**

Ninomiya et al., *Circulation*. Jan 6 2004;109(1):42-46.

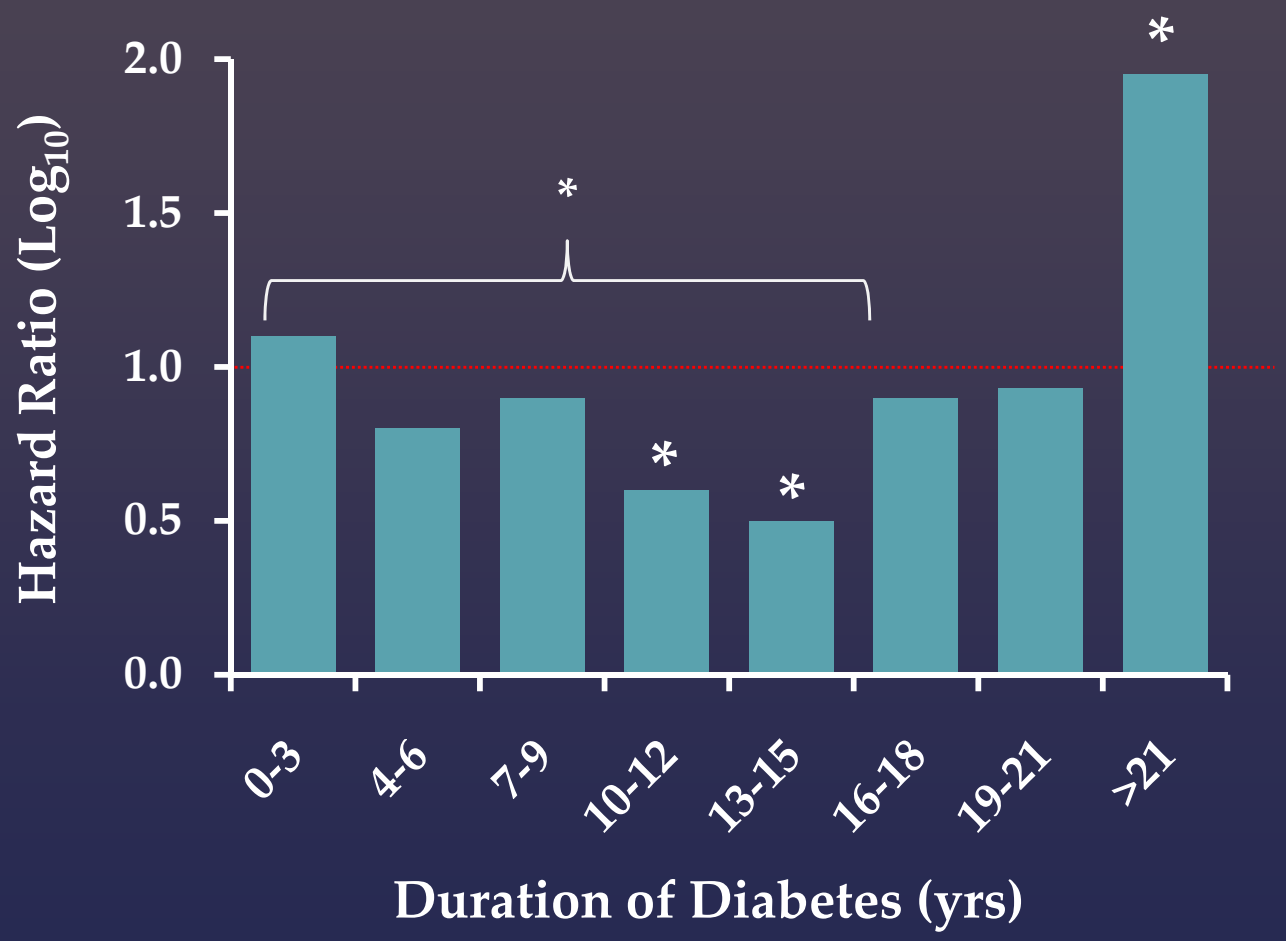
2. *Secondary prevention by insulin treatment of Type 2 diabetes is problematic at best*



NHANES data from Vouri et al., J Manag Care Pharm (2011) 17:304

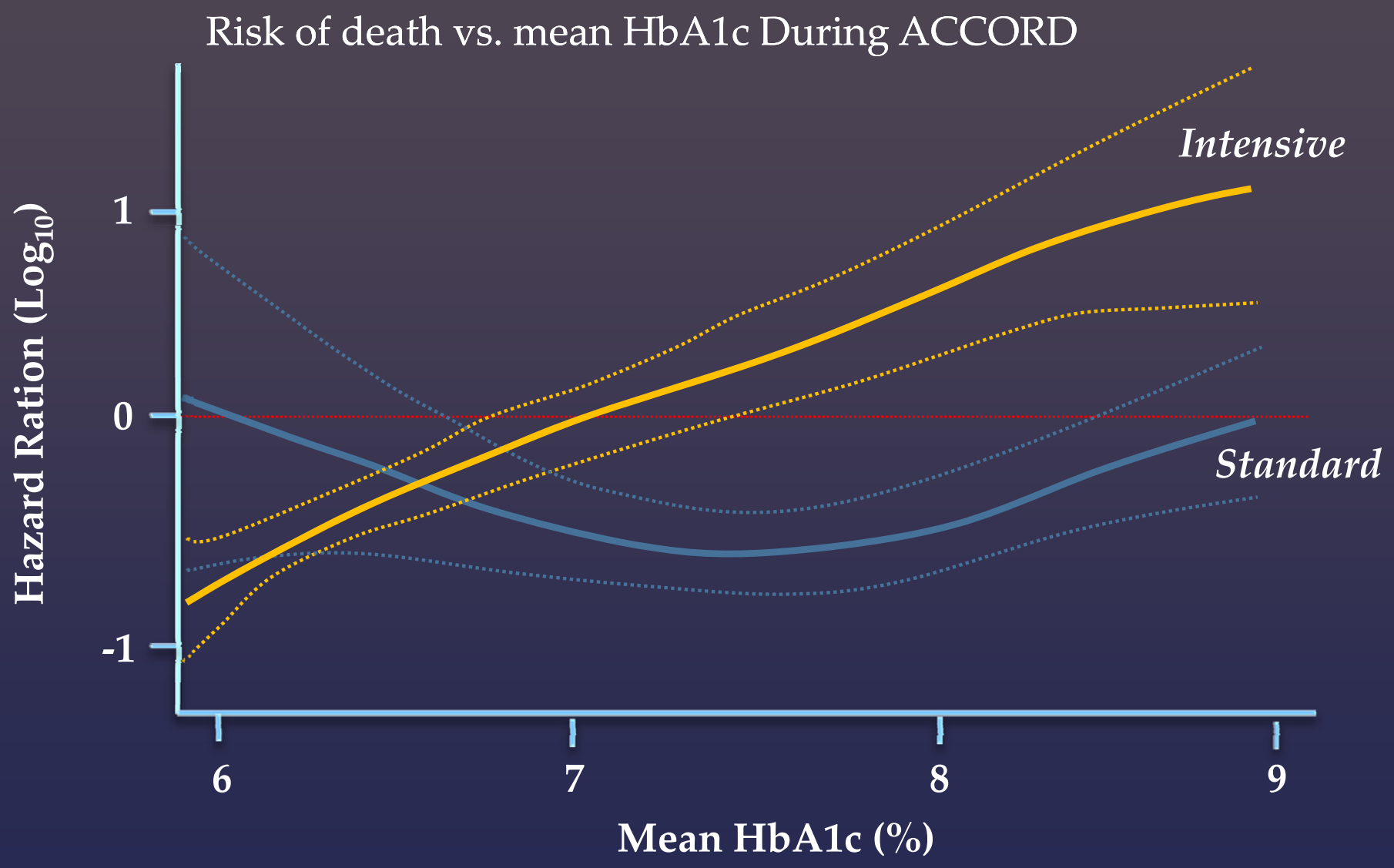
Does achieving HbA1c goals = success?

Risk of CV Events with Intensive Insulin Therapy in the ACCORD trial



*$p < 0.05$ for risk reduction or increase

Increased Risk of Death with Intensive Therapy



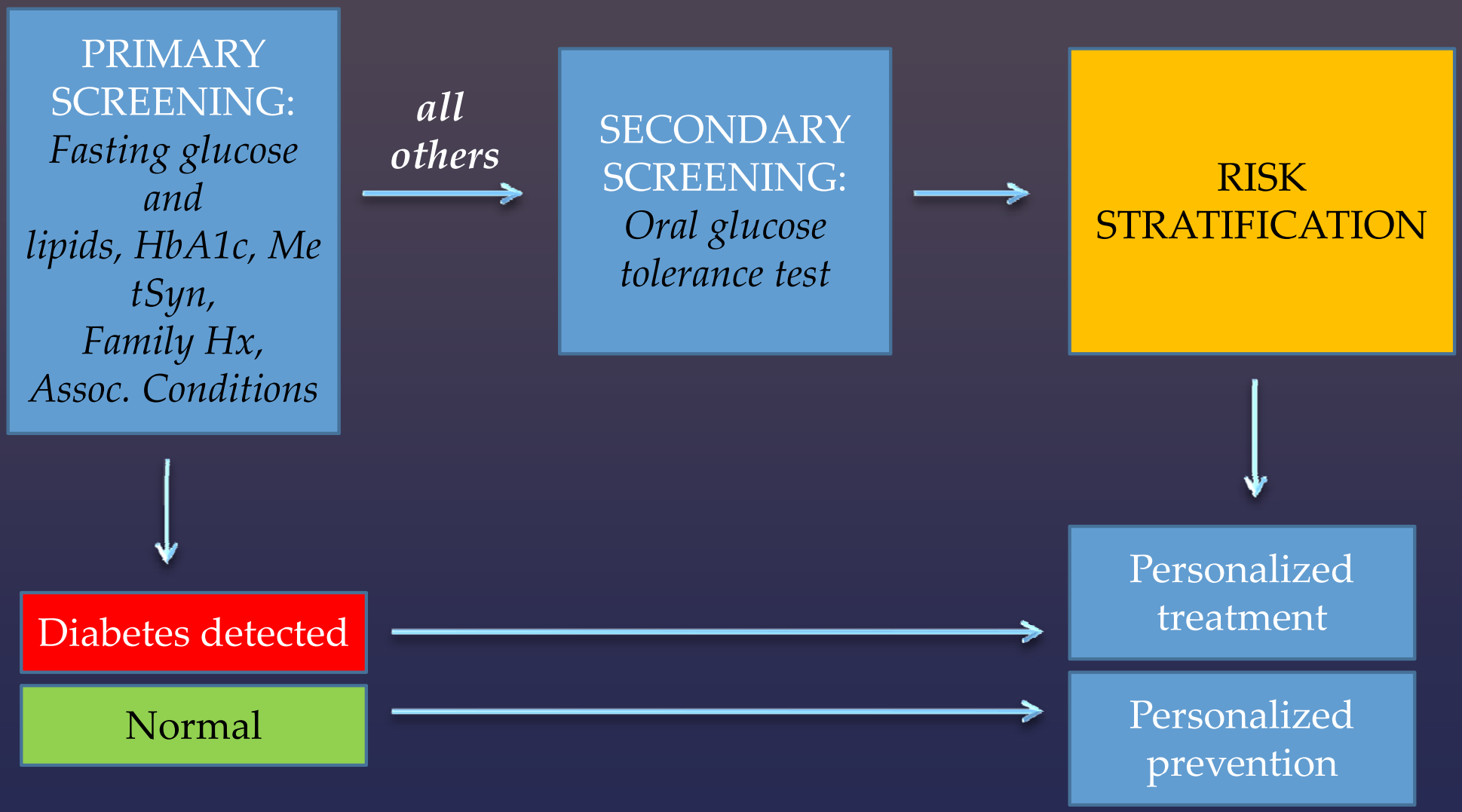
Riddle MC et al. Diabetes Care. 2010;33(5):983

Insulin therapy is necessary, appropriate, and beneficial for treatment of Type 2 diabetes… but when we get to that point, our options are more limited, and our patients' responses are not always ideal.

In short…

The horse is already out of the barn.

New Approach: Early Diagnosis and Treatment



U. of Utah
Care Met Clinic

A Risk Stratification Approach for Pre-diabetes

Moderate Risk

- IFG alone
- Normal glucose + MetSyn
- Normal glucose + Assoc. Condition

High Risk

- IFG + MetSyn
- IGT alone

Very High Risk

- IFG + IGT
- IGT + MetSyn
- IGT + Assoc. Condition

U. of Utah
Care Met Clinic

Can we treat Pre-diabetes and MetSyn?

Goals are two-fold:

- Prevent Diabetes
- Prevent Vascular Complications

Diabetes Prevention Program Trial (DPP) - 2002

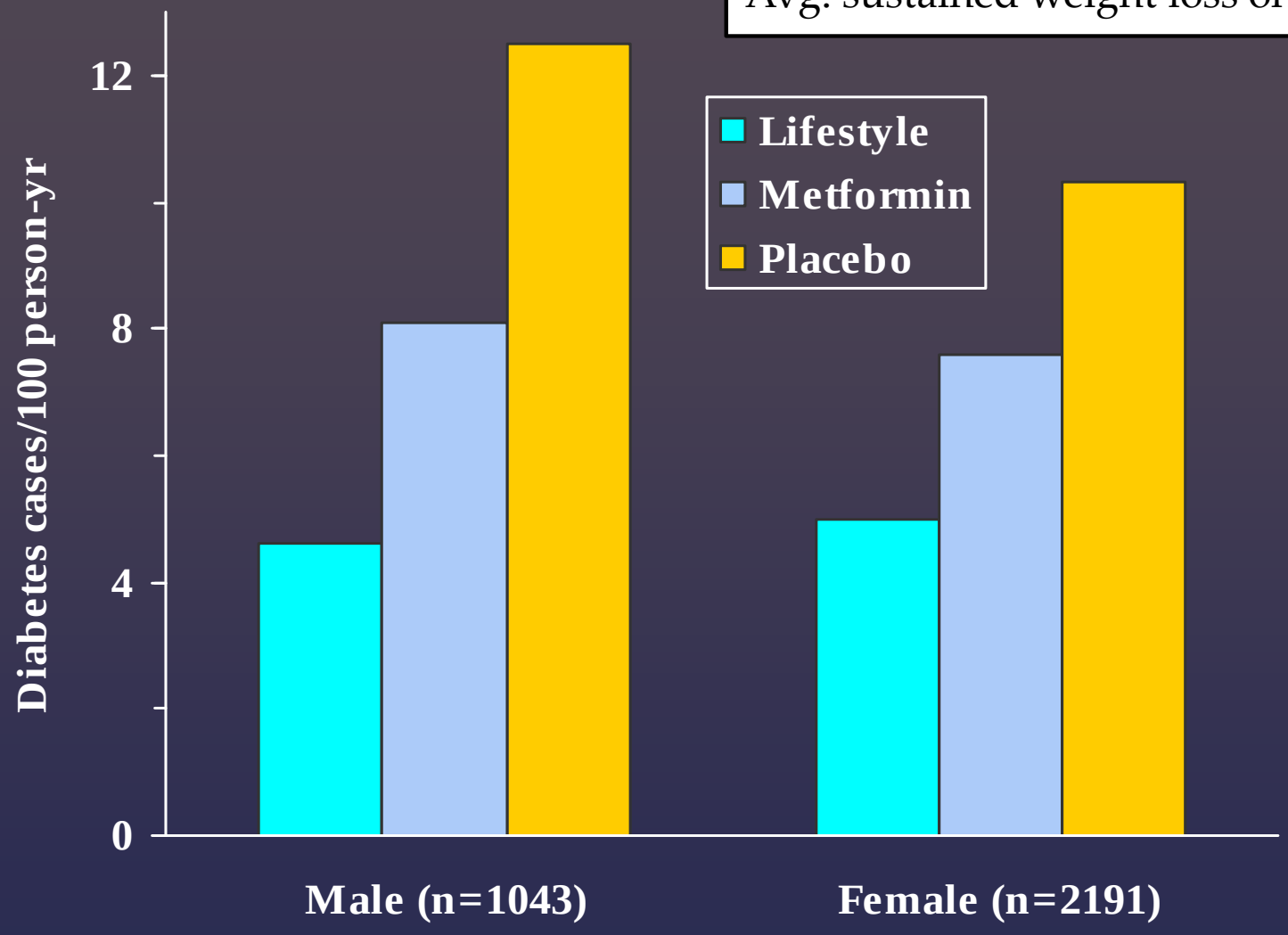
27 center intervention trial, 3200 adult participants with IGT, BMI ≥ 24
Highly ethnically, age, and gender diverse

Randomized to:

- Intensive lifestyle modification (healthy diet, increased physical activity)
- Standard care plus Metformin (an insulin sensitizer)
- Standard care plus placebo

Primary outcome: Diabetes incidence

Metformin – 31% Risk Reduction
Lifestyle – 58% Risk Reduction
Avg. sustained weight loss only 7-8 lbs

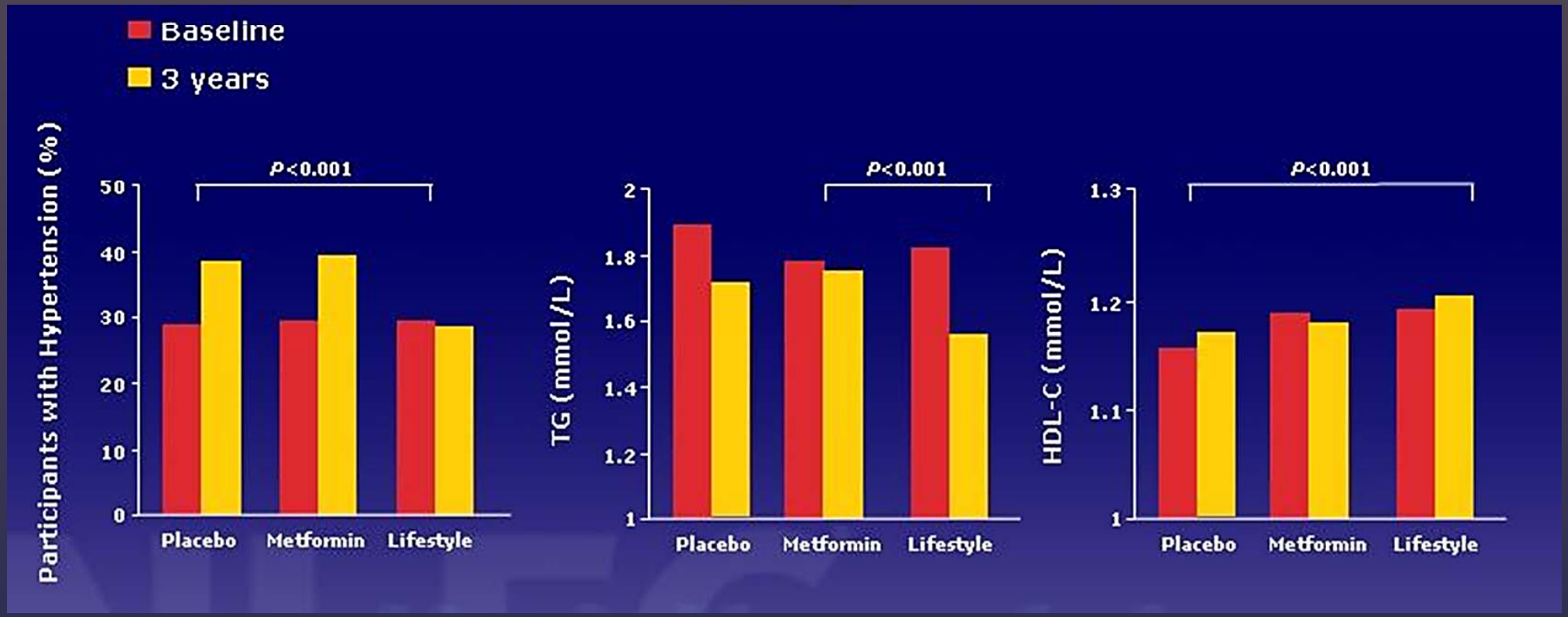


A similar 58% Reduced Risk for Diabetes reported for Lifestyle Intervention in the Finish Diabetes Prevention Study (2003)

The DPP Research Group, *NEJM 346*:393-403, 2002

What about CVD Risk Modification?

US DPP Secondary Outcomes Analysis



Finish DPS Secondary Outcomes Analysis

- 38% reduced prevalence of MetSyn
- 52% reduced prevalence of abdominal obesity

Diabetes Prevention Program Research Group. Diabetes Care. 2005;28:888-894

Pharmacological Interventions Also Work

Metformin

- U.S. DPP
- Indian DPP

Thiazolidinediones (Pio-, Rosi-, Troglitazone)

- DREAM
- U.S. DPP (troglitazone arm)
- ACT NOW
- TRIPOD
- PIPOD

Acarbose

- STOP-NIDDM

All showed significant risk reductions for Diabetes in range of 25-30%

Sulfonylureas and other secretagogues: show no sustained risk reduction!

Pillars of Future Pharmacological Therapy for Pre-diabetes and MetSyn

Drugs that enhance β cell function, prevent β cell failure

- GLP1 agonists (*e.g.*, exenatide)
- DPP-IV inhibitors (*e.g.*, sitagliptin)

Insulin sensitizers

- Metformin
- Pioglitzone
- Future PPAR agonists and fat-targeted therapies

Weight loss – appetite and energy expenditure

- Many new drugs in pipeline

Recent Use of a "Rational" Treatment Strategy

105 patients with IGT and/or IFG were treated for 9 months with:

- Insulin sensitizers alone (pioglitazone + metformin); n=40
- Insulin sensitizers plus a GLP1 agonist (pioglitazone + metformin + exenatide; n=47
- Lifestyle intervention (light) only; n=18
- Measured changes in oral glucose tolerance test as well as specific effects on insulin sensitivity and pancreatic β cell function

Insulin sensitizers alone →

insulin sensitivity: ↑ 42%
β-cell function: ↑ 50%
12% of patients with IGT reverted to normal glucose tolerance

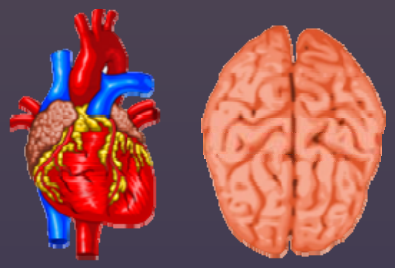
Insulin Sensitizers + GLP1 agonist →

insulin sensitivity: ↑ 52%
β-cell function: ↑ 109%
***59%** of patients with IGT reverted to normal glucose tolerance*

Amato et. al., Endocr Pract. (2012) 18:342-50.

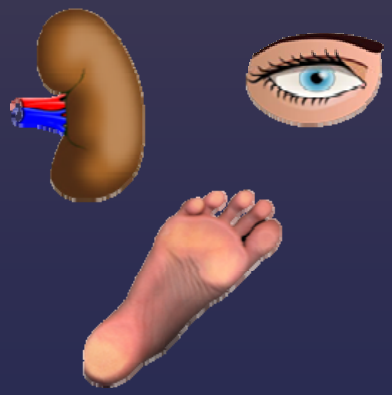
Desperately seeking "hard" outcomes data…

Macrovascular Disease – CV Event Reduction



- Myocardial infarction
- Stroke
- Rate of revascularization procedures
- Survival after first event

Microvascular Disease



- Blindness
- Dialysis
- Amputation

…and related mortality for all of the above.

Bariatric surgery for all?

- Gastric bypass and sleeve gastrectomy (not gastric banding)
- 67% diabetes remission one year after surgery; *96%* remission when in patient's with better pancreatic β cell function at time of surgery
- 66% of patients no longer require diabetes medications.
- Weight loss does not impact remission rates.
- Cardiovascular risk factors improve in parallel.
- Cost-benefit analyses support it.

2012 ASBMB, PL-110: Predictors for Remissions of Type 2 Diabetes Mellitus Following Roux En Y Gastric Bypass Perugini et al.

Future of Personalized Medicine: Fine-tuning risk stratification

Glycemia

- GlycoMark
- Fructosamine
- Fructosamine-HbA1c Glycation Gap

Inflammation

- hs-CRP
- Fibrinogen
- Lp-associated PLA2
- Cytokines

Lipid-related

- Lipid NMR – particle counts, small dense LDL
- Apo A and Apo B measurements
- HDL2
- Lp(a)

Oxidative stress

- Urinary F2-isoprostanes
- ox-LDL

Adipokines

- Adiponectin
- Leptin
- RBP4

Genetics

- ApoE
- Prothrombin
- Factor V Leiden
- GWAS genes
- Whole genome sequencing (soon)

CONCLUSIONS

- *Type 2 diabetes is only the end-point of a long process of metabolic deterioration that starts with insulin resistance.*
- *Pre-diabetes (IFG, IGT, and elevated A1c) and MetSyn are already signs of established disease for most patients.*
- *Earlier detection and intervention are needed on a patient-by-patient basis.*
- *Lifestyle modification interventions are extremely effective.*
- *However, a combination of lifestyle modification with pharmacological and surgical therapies will be needed in order to make a significant impact on this epidemic.*

Thank you.

Questions?