TYPE 2 DIABETES MELLITUS: NEW HOPE FOR PREVENTION

Robert Dobbins, M.D. Ph.D.

Learning Objectives

- **Recognize current trends in the prevalence of type 2 diabetes.**

- **Learn differences between type 1 and type 2 diabetes.**

- **List risk factors for type 2 diabetes.**

- **Understand how type 2 diabetes can be prevented or delayed.**

- **Introduce the concept of pre-diabetes.**

Definition

Diabetes mellitus: A chronic disorder characterized by a deficiency of insulin secretion and/or insulin effect, which causes hyperglycemia, disturbances of carbohydrate, fat and protein metabolism, and a constellation of chronic complications .
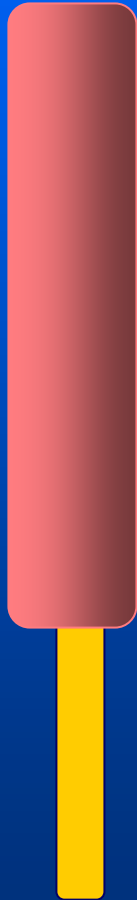
Diagnostic Criteria

	Fasting Glucose	Random	OGTT (2 hr)
Normal	<110 mg/dl (5.5 mM)		<140 mg/dl (7.7 mM)
IFG/IGT	111-125 mg/dl		140-200 mg/dl
Diabetes	≥126 mg/dl (7.0 mM)	>200 mg/dl (11.1 mM)	>200 mg/dl (11.1 mM)

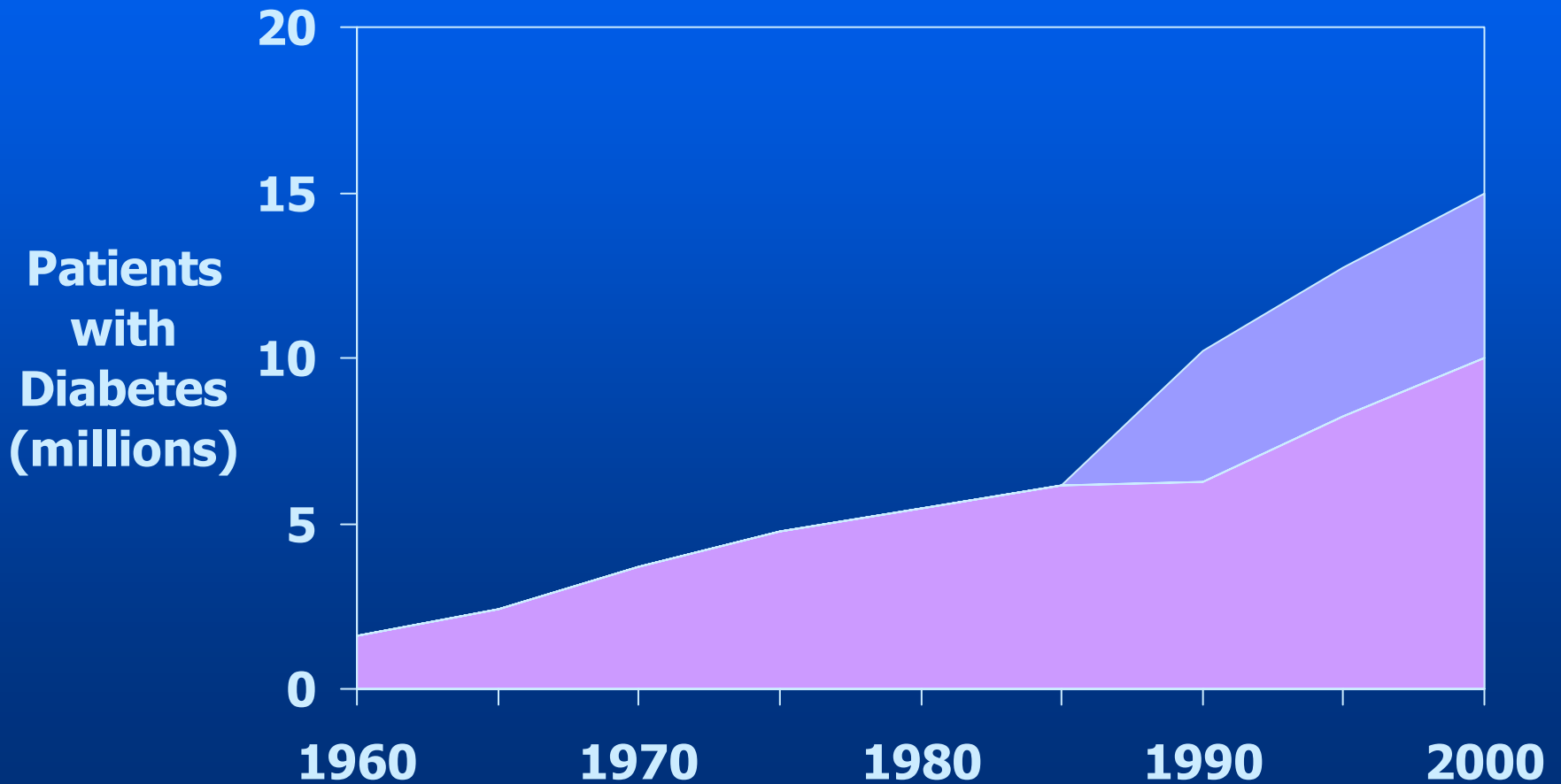*Confirmation on a second day by any of the above methods
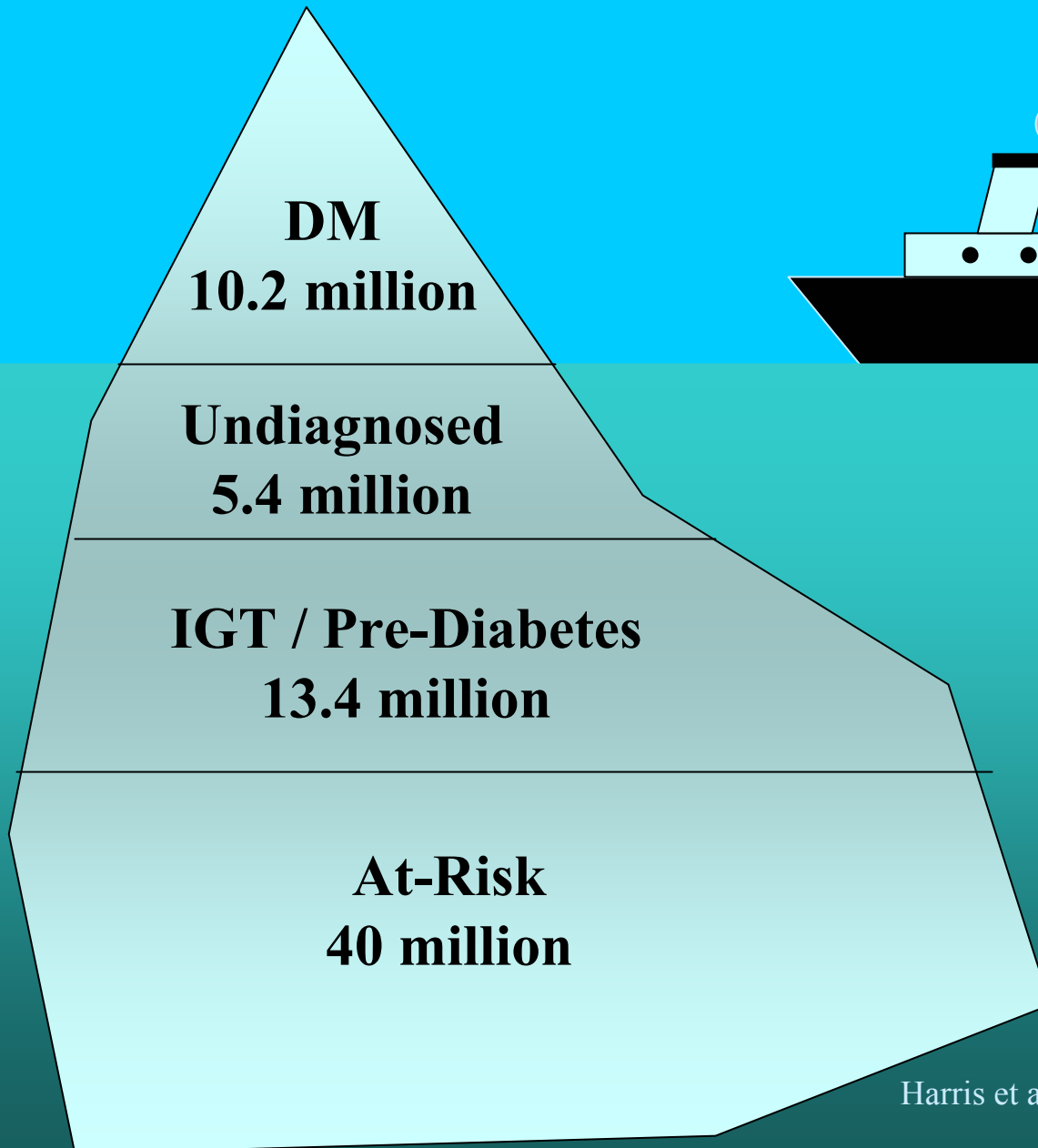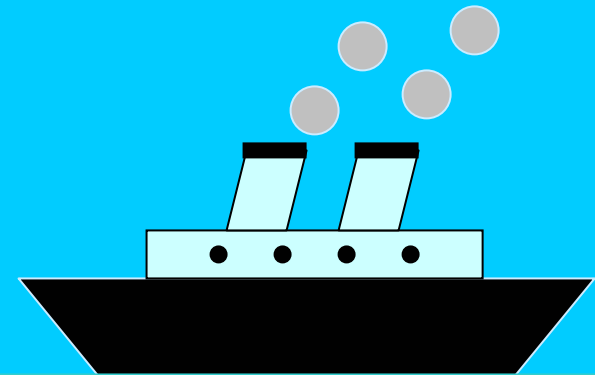
Features of Type 1 Diabetes

- **80% occur before age 20**
- **May occur at any age**
- **Insulin deficient**
  - autoimmune pathogenesis, HLA linked
  - less commonly non-immune mediated
- **Ketosis prone**
- **Normal insulin sensitivity**

Features of Type 2 Diabetes

- Most common after age 40
- Abdominal obesity present in 90%
- Insulin resistance/hyperinsulinemia
- Ketosis resistant
- Hypertension common
- High VLDL, low HDL cholesterol
- Accelerated atherosclerosis
- High in risk in many ethnic groups

Prevalence of Diagnosed Diabetes Mellitus

DM
10.2 million

Undiagnosed
5.4 million

IGT / Pre-Diabetes
13.4 million

At-Risk
40 million

Harris et al., Diabetes Care, 1998

Risk Factors for Type 2 Diabetes

- Age > 40
- Family history of diabetes
- Ethnicity
- Obesity; abdominal fat distribution
- GDM, or infant > 9 lbs
- Hypertension, hyperlipidemia
- Previous Impaired Glucose Tolerance

Body Mass Index
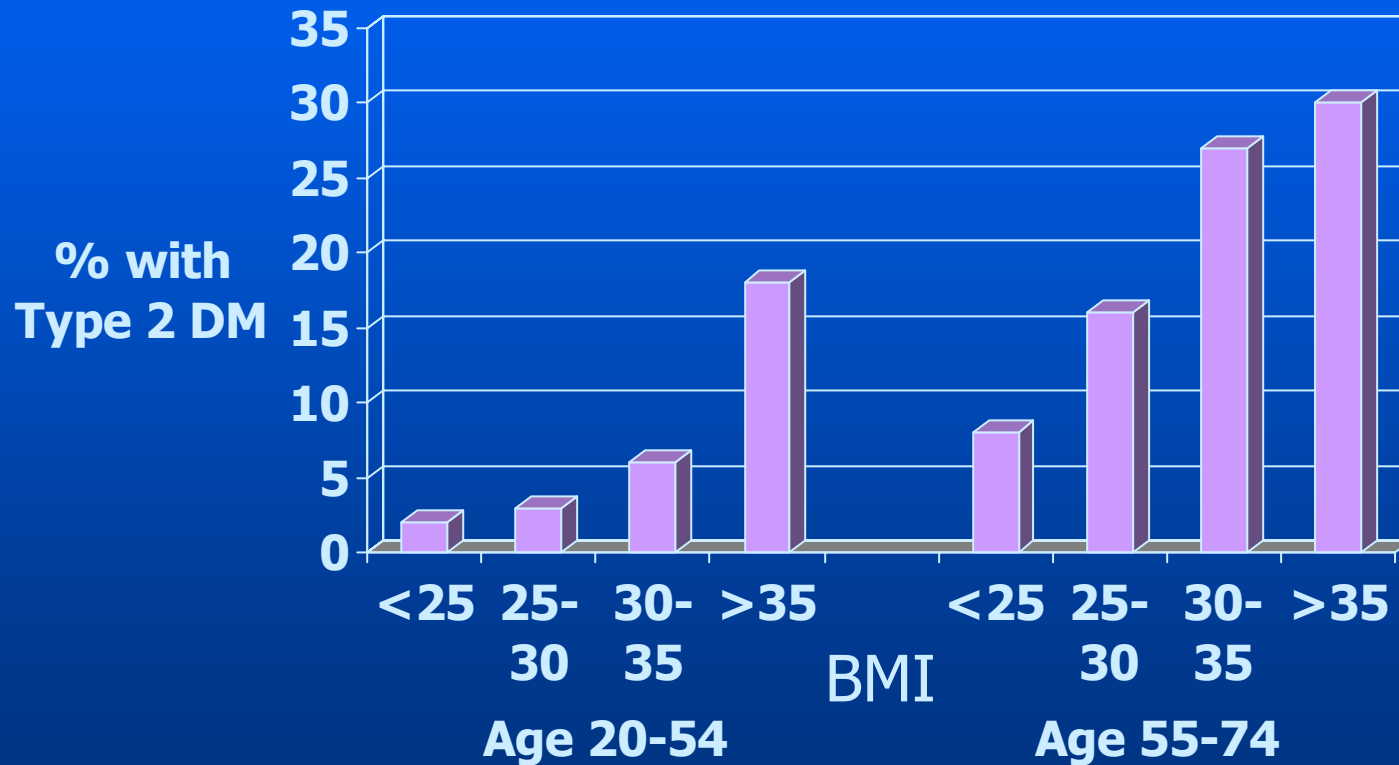
Weight

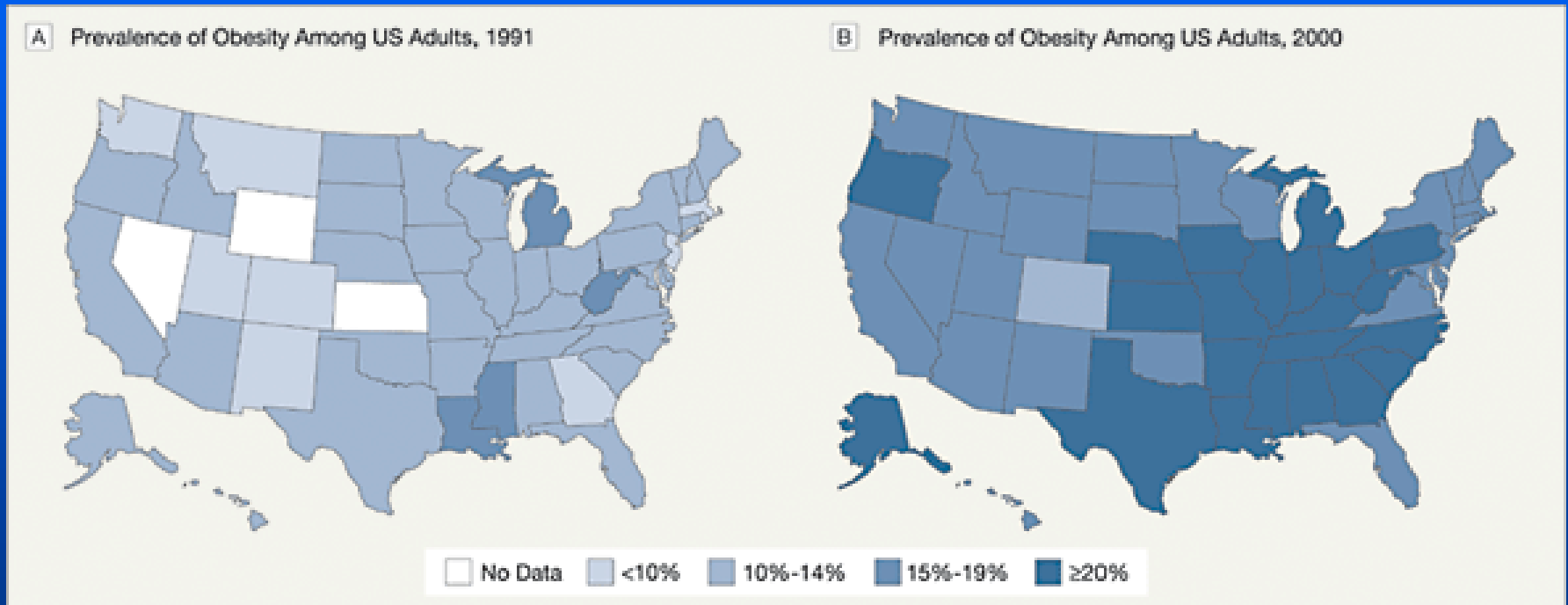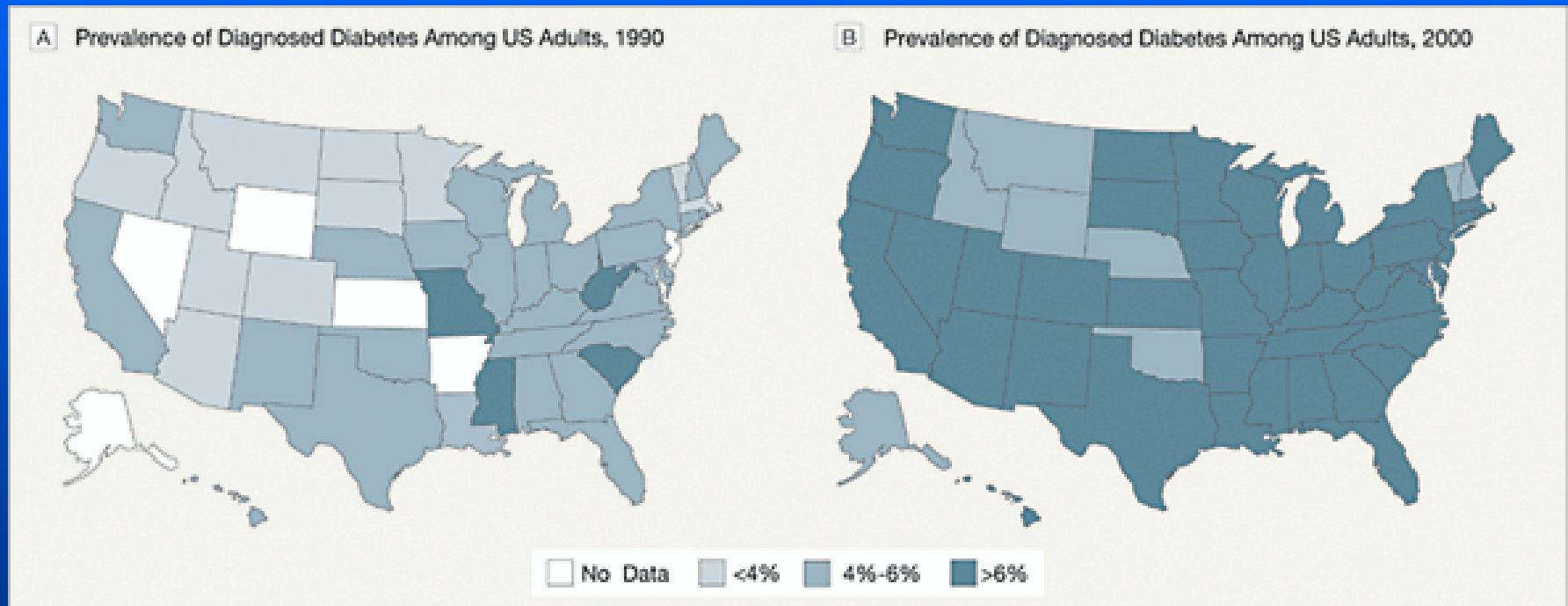| Height	100	105	110	115	120	125	130	135	140	145	150	155	160	165	170	175	180	185	190	195	200	205	210	215	220	225	230	235	240	245	250
5'0"	20	21	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49
5'1"	19	20	21	22	23	24	25	26	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	43	44	45	46	47
5'2"	18	19	20	21	22	23	24	25	26	27	27	28	29	30	31	32	33	34	35	36	37	37	38	39	40	41	42	43	44	45	46
5'3"	18	19	19	20	21	22	23	24	25	26	27	27	28	29	30	31	32	33	34	35	35	36	37	38	39	40	41	42	43	43	44
5'4"	17	18	19	20	21	21	22	23	24	25	26	27	27	28	29	30	31	32	33	33	34	35	36	37	38	39	39	40	41	42	43
5'5"	17	17	18	19	20	21	22	22	23	24	25	26	27	27	28	29	30	31	32	32	33	34	35	36	37	37	38	39	40	41	42
5'6"	16	17	18	19	19	20	21	22	23	23	24	25	26	27	27	28	29	30	31	31	32	33	34	35	36	36	37	38	39	40	40
5'7"	16	16	17	18	19	20	20	21	22	23	23	24	25	26	27	27	28	29	30	31	31	32	33	34	34	35	36	37	38	38	39
5'8"	15	16	17	17	18	19	20	21	21	22	23	24	24	25	26	27	27	28	29	30	30	31	32	33	33	34	35	36	36	37	38
5'9"	15	16	16	17	18	18	19	20	21	21	22	23	24	24	25	26	27	27	28	29	30	30	31	32	32	33	34	35	35	36	37
5'10"	14	15	16	17	17	18	19	19	20	21	22	22	23	24	24	25	26	27	27	28	29	29	30	31	32	32	33	34	34	35	36
5'11"	14	15	15	16	17	17	18	19	20	20	21	22	22	23	24	24	25	26	26	27	28	29	29	30	31	31	32	33	33	34	35
6'0"	14	14	15	16	16	17	18	18	19	20	20	21	22	23	23	24	24	25	26	26	27	28	29	29	30	31	31	32	33	34	34
6'1"	13	14	15	15	16	16	17	18	18	19	20	20	21	22	22	23	24	24	25	26	26	27	28	28	29	30	30	31	32	32	33
6'2"	13	13	14	15	15	16	17	17	18	19	19	20	21	21	22	22	23	24	24	25	26	26	27	28	28	29	30	30	31	31	32
6'3"	12	13	14	14	15	16	16	17	17	18	19	19	20	21	21	22	22	23	24	24	25	26	26	27	27	28	29	29	30	31	31
6'4"	12	13	13	14	15	15	16	16	17	18	18	19	19	20	21	21	22	23	23	24	24	25	26	26	27	27	28	29	29	30	30

Height

Correlation BMI and Fat Mass
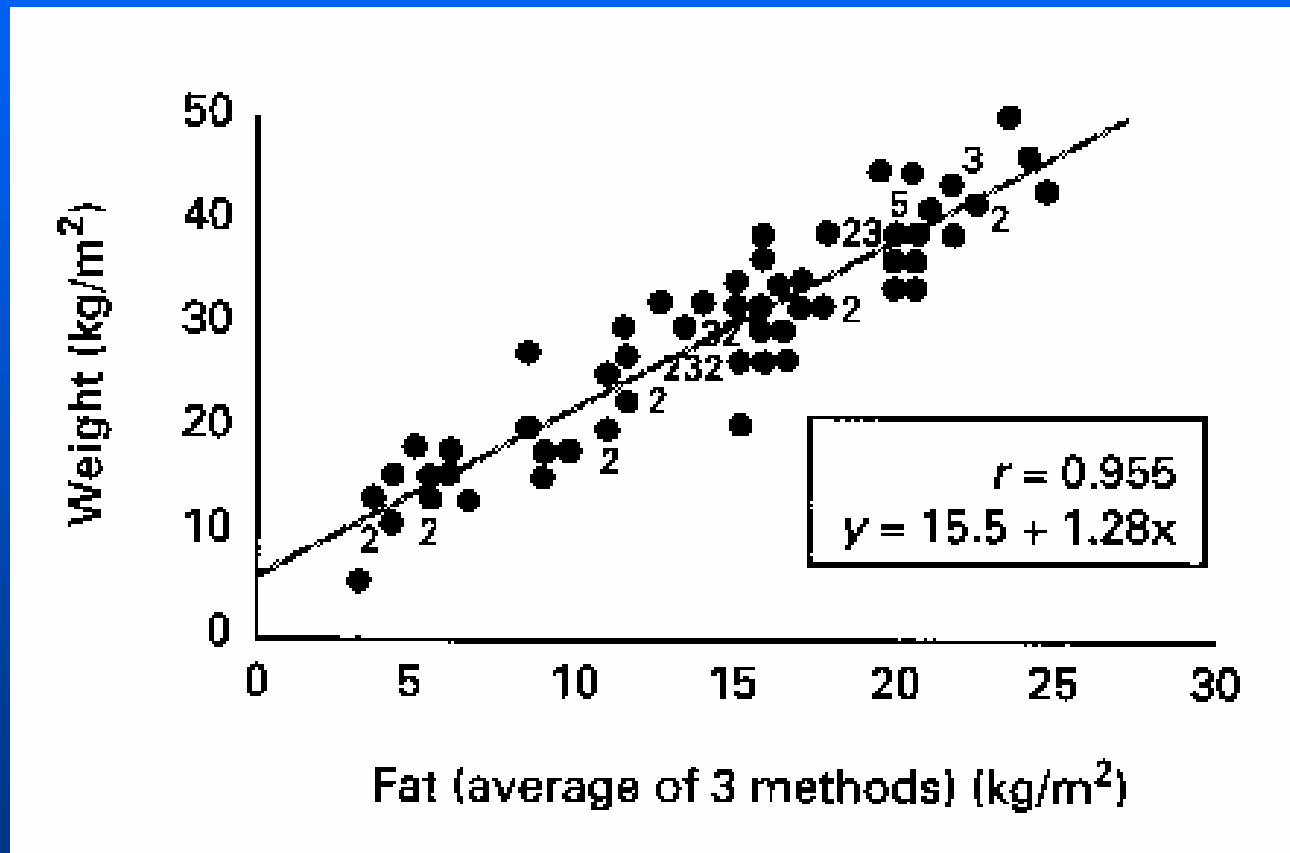
Prevalence of Type 2 DM by Body Mass Index

Increasing Prevalence of Obesity in the United States

A. Prevalence of Obesity Among US Adults, 1991

B. Prevalence of Obesity Among US Adults, 2000

No Data <10% 10%-14% 15%-19% ≥20%

Mokdad et al., JAMA, 2001

Increasing Prevalence of Type 2 DM in the United States

A Prevalence of Diagnosed Diabetes Among US Adults, 1990

B Prevalence of Diagnosed Diabetes Among US Adults, 2000

No Data   <4%   4%-6%   >6%

5.1% = 10.2 million people   7.3% = 15 million people

Mokdad et al., JAMA, 2001

Dallas
Heart Disease
Prevention Project

SOUTHWESTERN

R DONALD W. REYNOLDS FOUNDATION

Risk Factors for Type 2 Diabetes

Percent of Nondiabetic Individuals

Number of Risk Factors
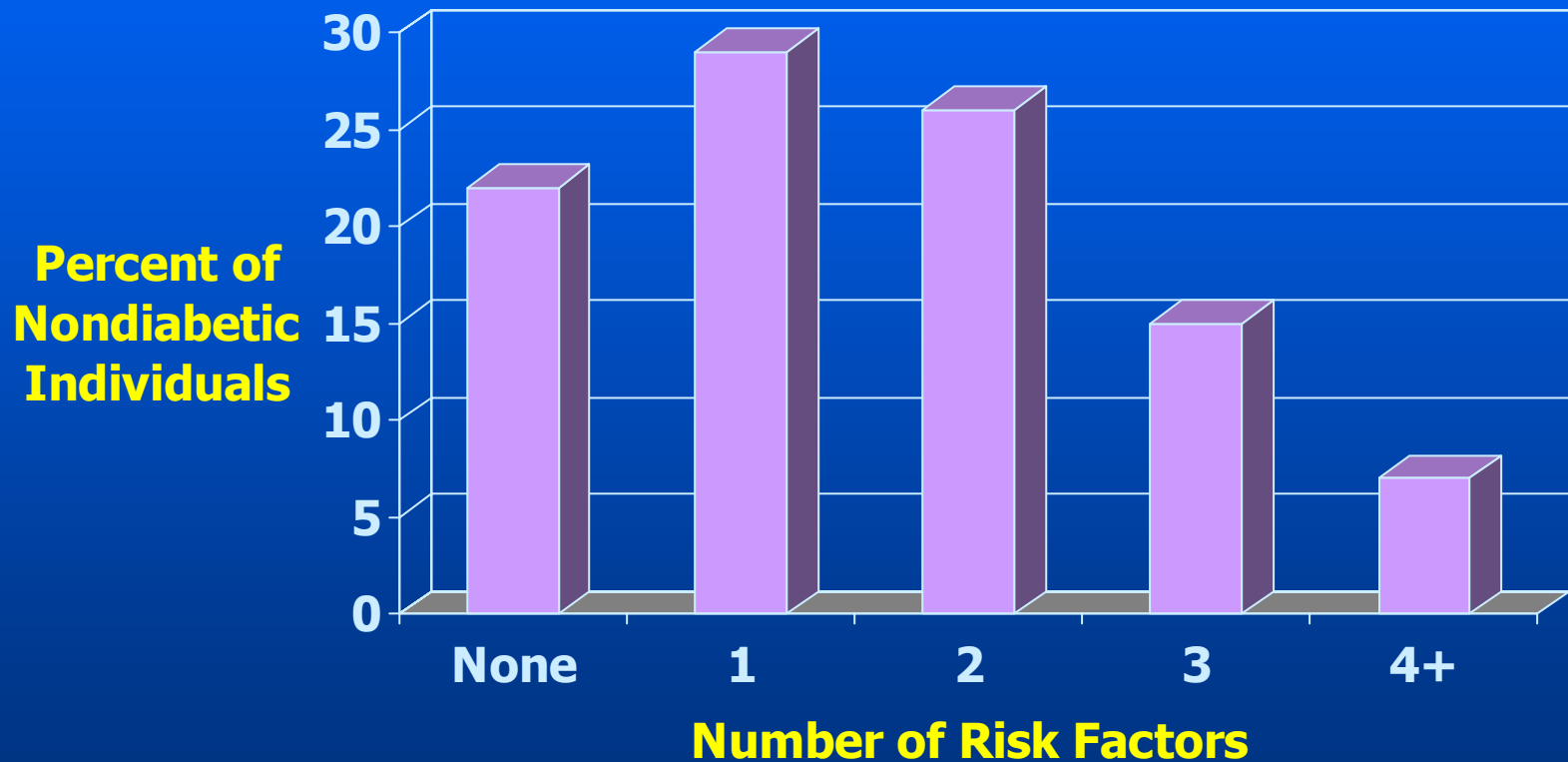
Microvascular Complications

- **Diabetic retinopathy**
  - background retinopathy
  - macular edema
  - proliferative retinopathy
- **Diabetic nephropathy**
- **Diabetic neuropathy**
  - distal symmetrical polyneuropathy
  - mononeuropathy (peripheral, cranial nerves)
  - autonomic neuropathy

Diabetic Retinopathy

Macrovascular Complications

Complications

- Coronary Heart Disease
- Cerebrovascular Disease
- Peripheral Vascular Disease

Risk Factors

- Dyslipidemia
- Hypertension
- Smoking
- Family history
- Hyperglycemia

Complications of Diabetes
Magnitude of the Problem

- **Diabetic retinopathy: most common cause of blindness before age 65**

- **Nephropathy: most common cause of ESRD**

- **Neuropathy: most common cause of non-traumatic amputations**

- **2-3 fold increase in cardiovascular disease**

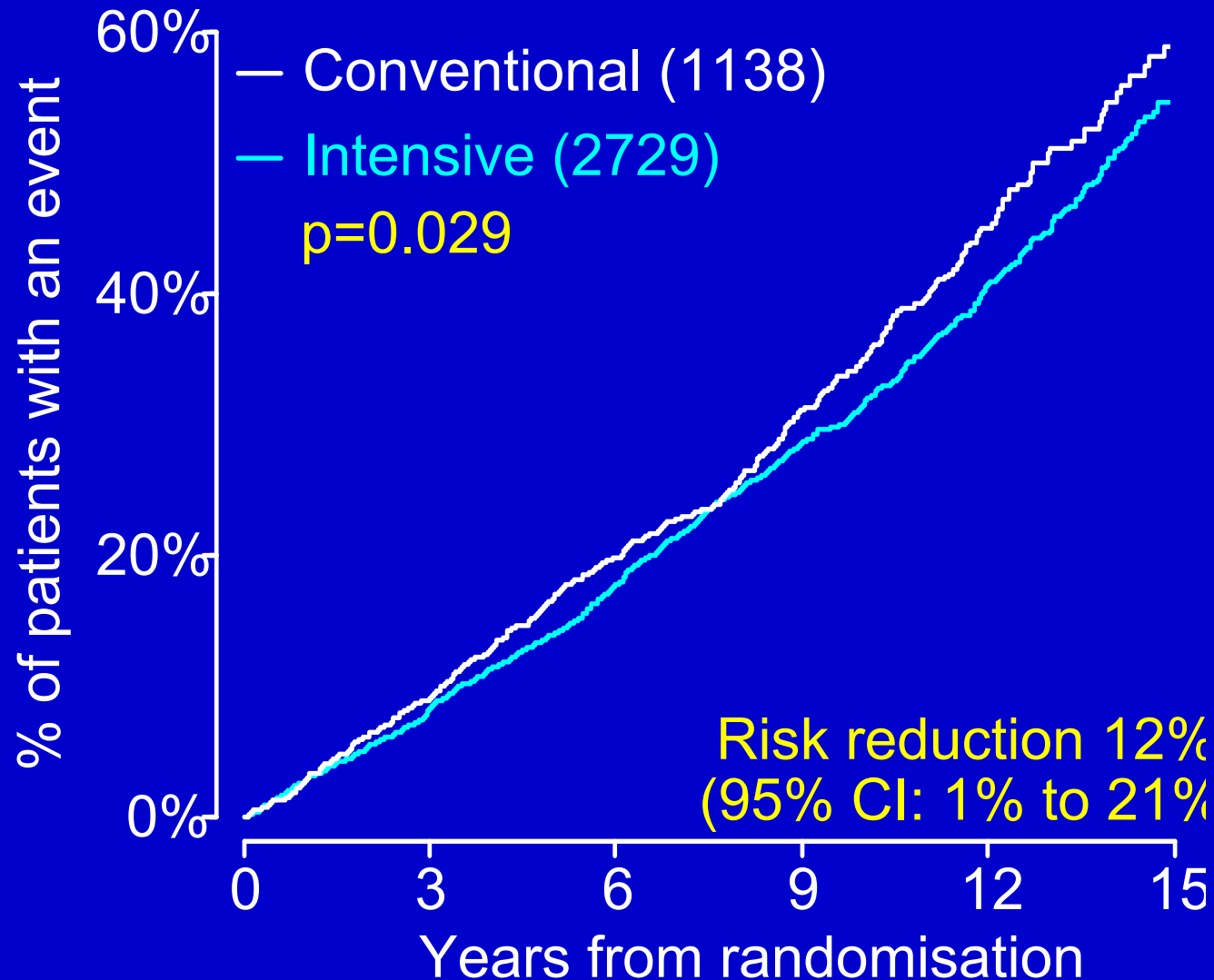# Mortality Due to Diabetes Mellitus is Steadily Increasing

Increasing Deaths Due to Diabetes

Source: U.S. National Center for Health Statistics
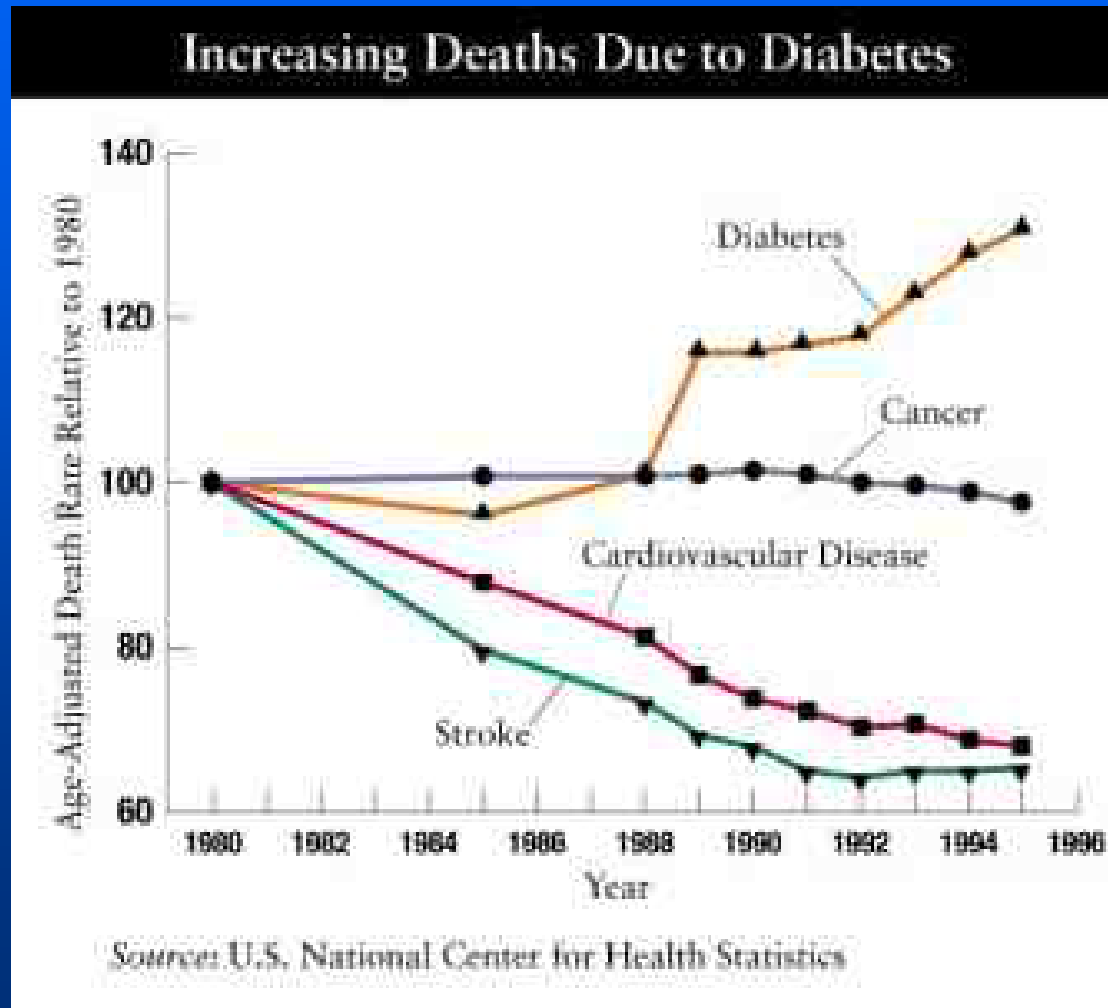
Prevention of Diabetic Complications

- **Weight reduction**
- **Exercise**
- **Control glycemia**
- **Improve lipid profile**
- **Smoking cessation**
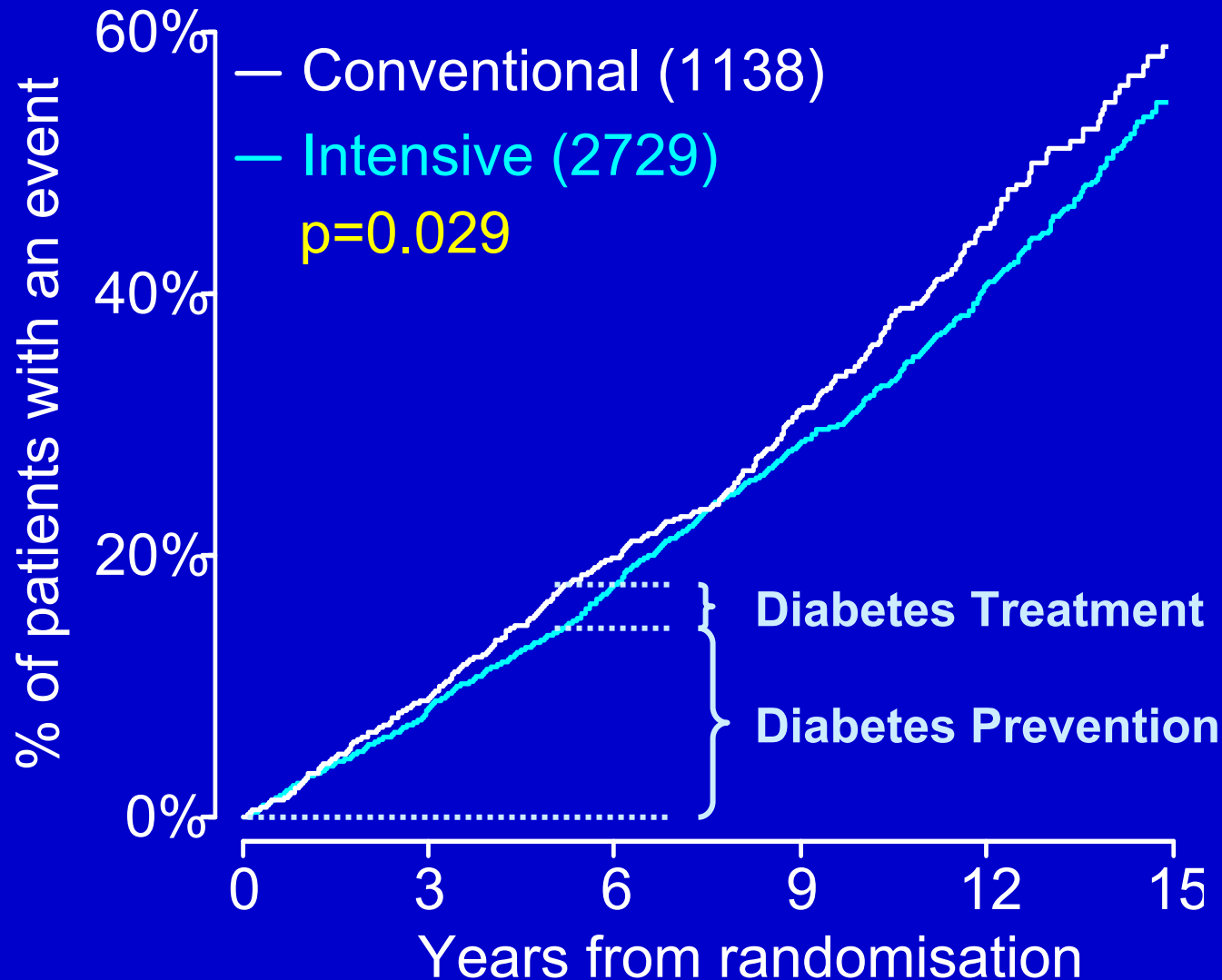- **Treat Hypertension**
- **Daily aspirin therapy**

Any Diabetes Related Endpoint (cumulative)
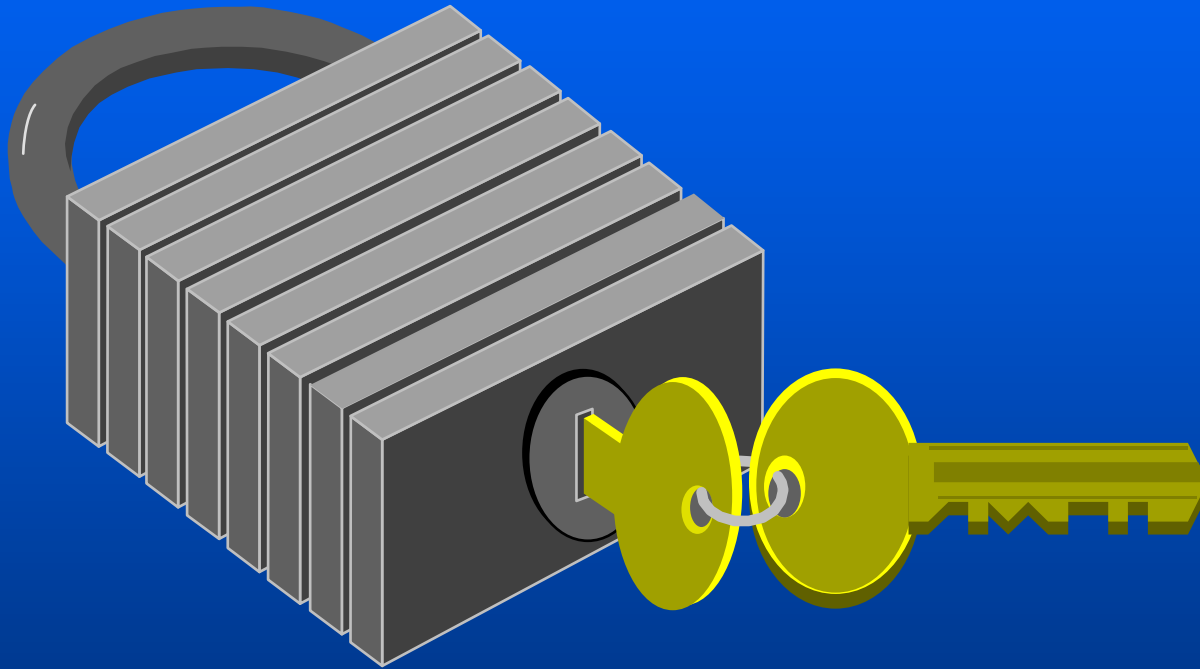
1401 of 3867 patients (36%)

— Conventional (1138)
— Intensive (2729)
p=0.029

Risk reduction 12%
(95% CI: 1% to 21%

% of patients with an event

Years from randomisation

ukpds

Any Diabetes Related Endpoint (cumulative)

1401 of 3867 patients (36%)

— Conventional (1138)
— Intensive (2729)
p=0.029

Diabetes Treatment

Diabetes Prevention

% of patients with an event

Years from randomisation

ukpds

Prevention is the Key

Come and get it!

Exercise
Every Little Bit Helps

Prevention of Type 2 Diabetes
Finnish Diabetes Prevention Study Group

- **522 subjects**
- **2:1 female:male ratio**
- **Age - 40-65 years**
- **Weight - BMI > 25**
- **Impaired glucose tolerance with plasma glucose of 140-200 mg/dl 2h after ingesting 75 gm of oral glucose**
- **Exclusions - diabetes, chronic illness, psychological or physical disabilities**

Design of Interventions
Finnish Diabetes Prevention Study Group

- **Randomized to two study groups**
- **Control Group**
  - 2-page leaflet on diet and exercise
  - nutritionist reviewed a 3-day food diary
- **Intervention Group**
  - individualized, detailed diet/exercise advice
  - nutrition appointments every 2-3 months
  - 3-day food diary completed every 3 months
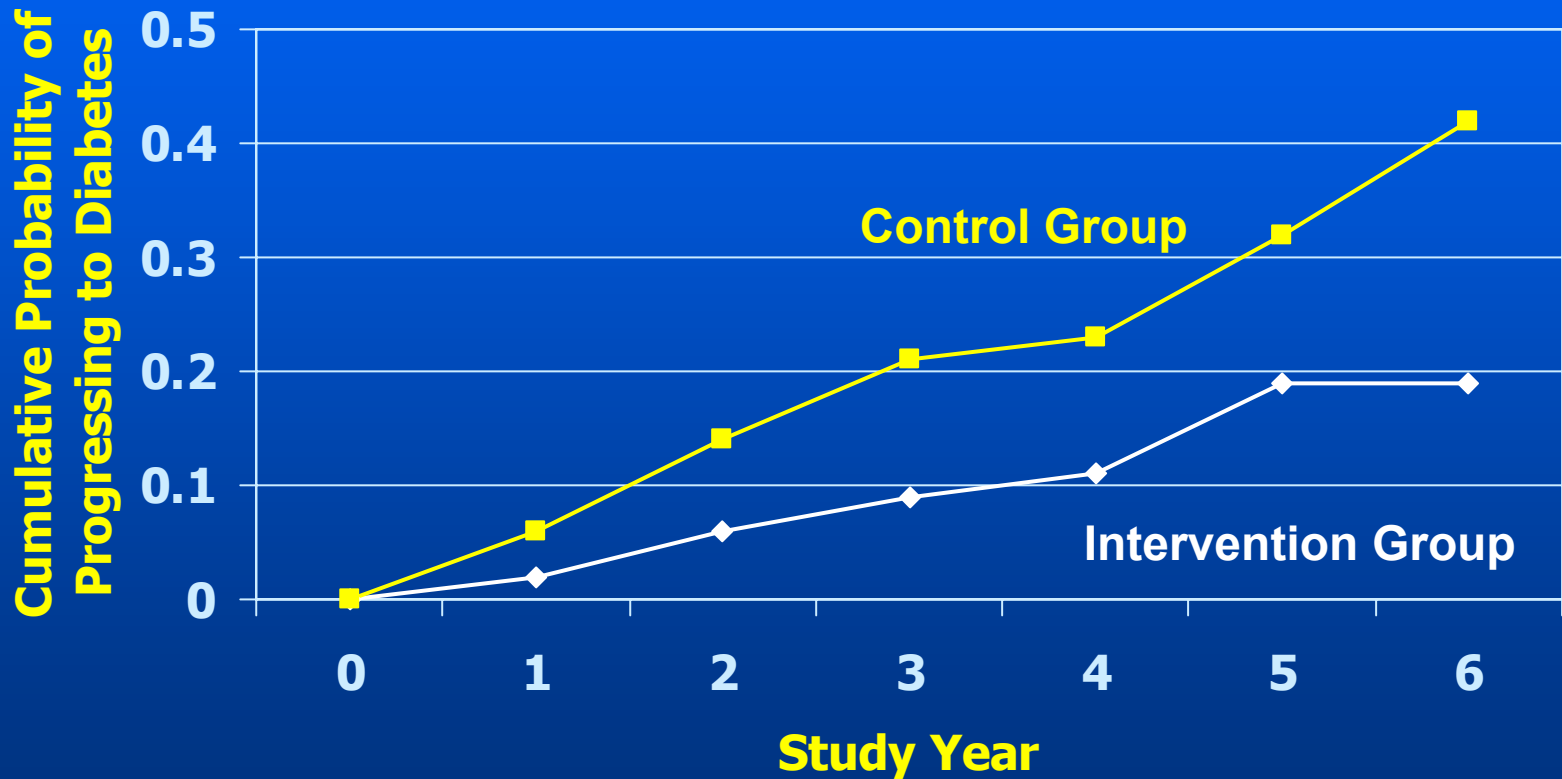 - Supervised, progressive, individually-tailored physical training sessions

Tuomilehto et al., NEJM, 2001

Success Achieving Treatment Goals
Finnish Diabetes Prevention Study Group

Goal of Intervention	Intervention Group	Control Group
	% of subjects	
Weight Reduction (>5% of body weight)	43	13
Fat Intake (<30% of energy intake)	47	26
Saturated Fat Intake (<10% of energy intake)	26	11
Fiber Intake >15 g / 1000 kcal	25	12
Exercise >4 hours / week	86	71

Tuomilehto et al., NEJM, 2001

Prevention of Type 2 Diabetes
Finnish Diabetes Prevention Study Group

Cumulative Probability of Progressing to Diabetes

Control Group

Intervention Group

Study Year

Tuomilehto et al., NEJM, 2001

Prevention of Type 2 Diabetes
Finnish Diabetes Prevention Study Group

Tuomilehto et al., NEJM, 2001
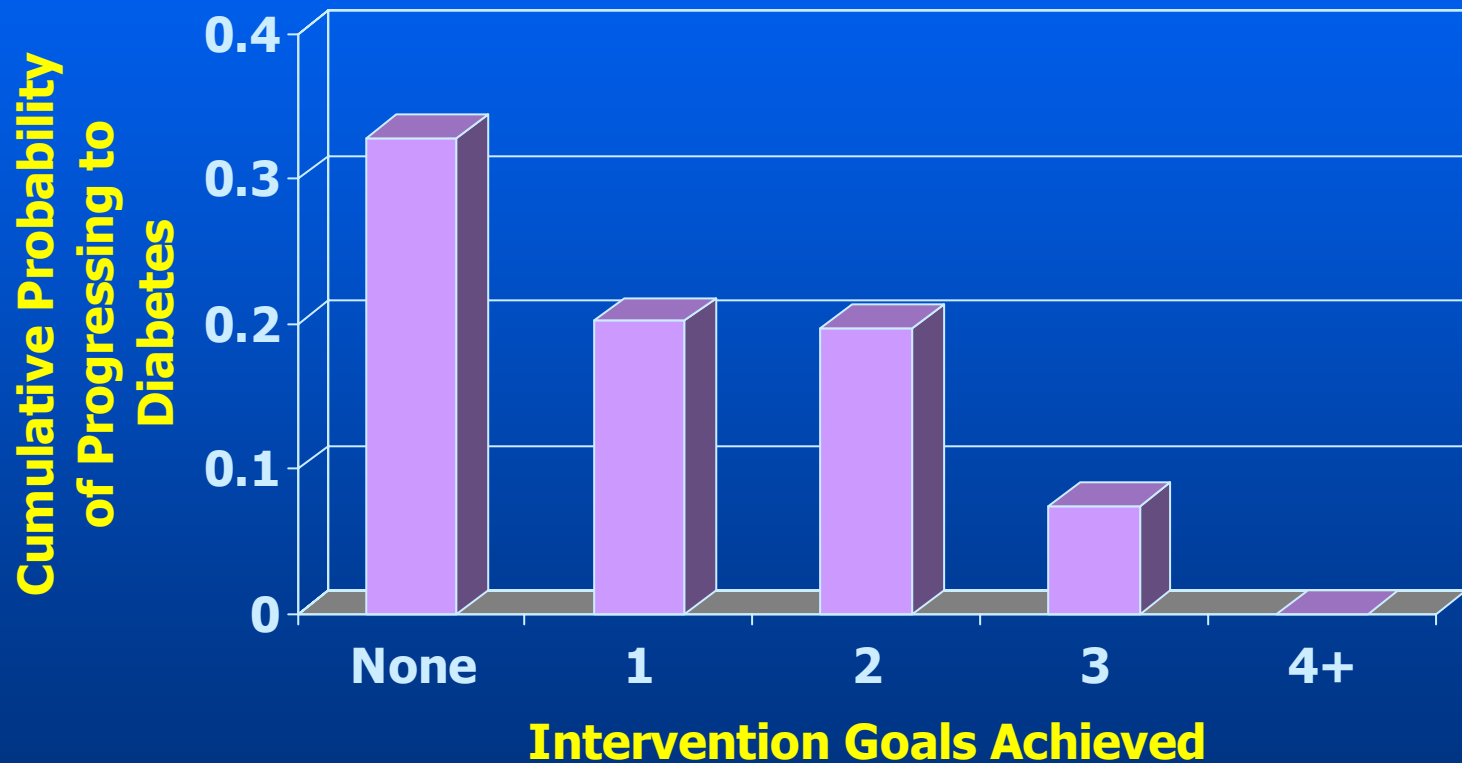
Prevention of Type 2 Diabetes
Diabetes Prevention Program Research Group

- **3234 subjects**
- **2:1 female:male ratio**
- **Age - >25 years**
- **Weight - BMI > 24**
- **Impaired glucose tolerance on an OGTT or impaired fasting glucose**
- **Exclusions - diabetes, chronic illness, taking medications altering insulin sensitivity**

DPPRG, NEJM, 2002

Design of Interventions
Diabetes Prevention Program Research Group

- **Randomized to three study groups**
- **Control Group**
  - standard lifestyle recommendations with an annual dietitian visit and placebo medication
- **Drug Treatment Group**
  - standard lifestyle recommendations
  - Metformin or Rosiglitazone
- **Intensive Lifestyle Modification Group**
  - diet/exercise/behavior modification curriculum
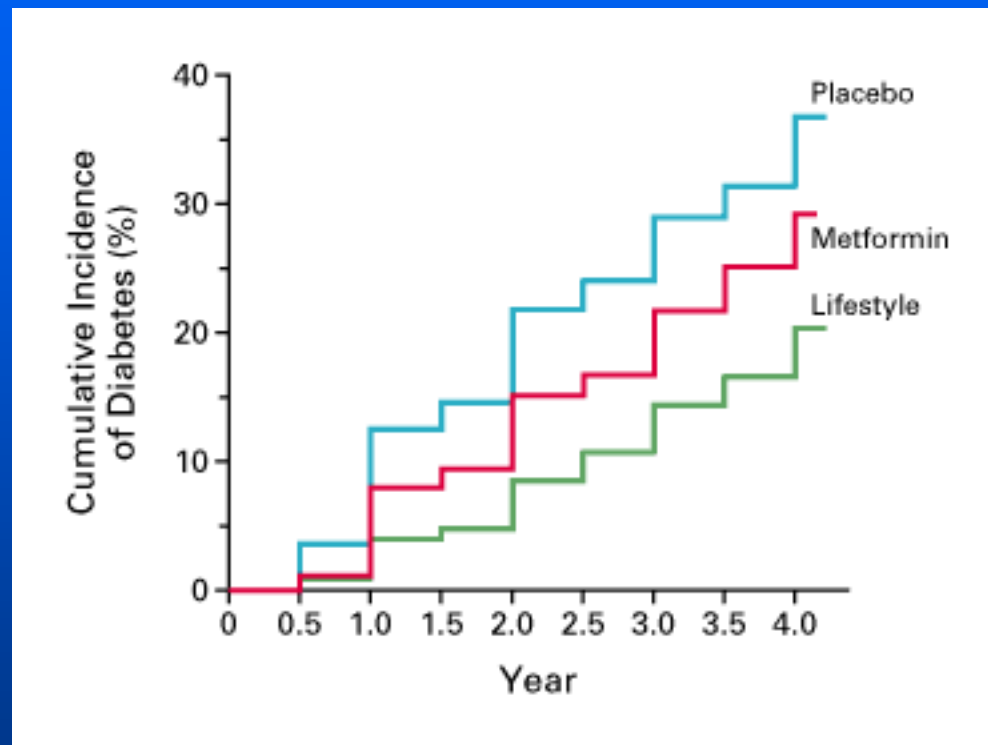 - monthly case-manager visits and group sessions

Success Achieving Treatment Goals
Diabetes Prevention Program Research Group
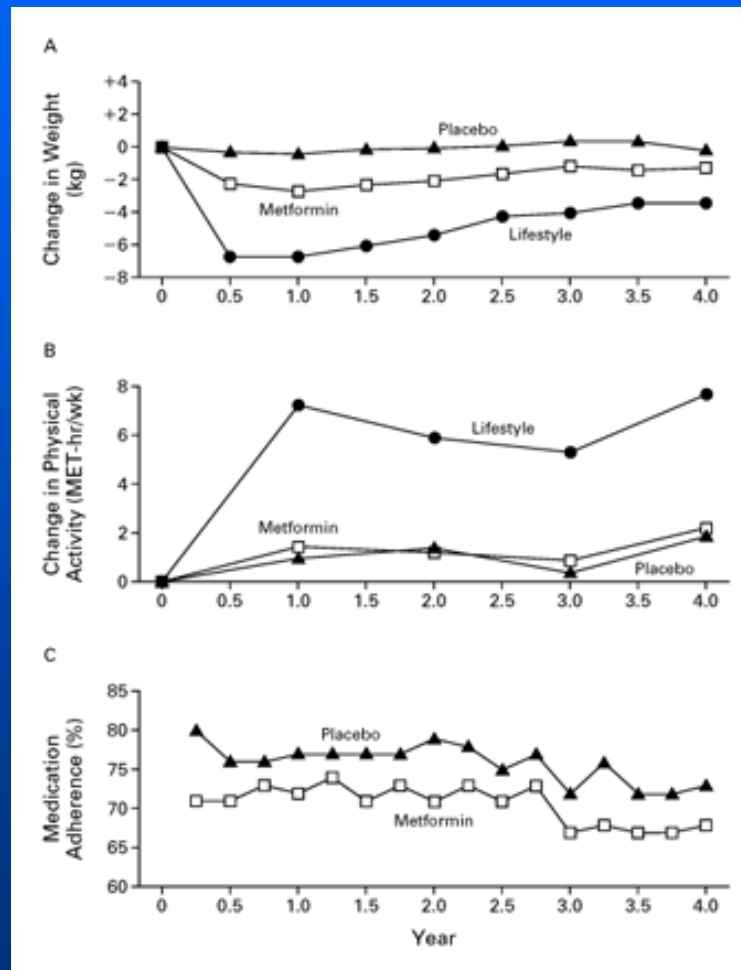
Prevention of Type 2 Diabetes
Diabetes Prevention Program Research Group

Prevention of Type 2 Diabetes
Summation of Clinical Trials

- **Goals**
  - Lose weight - 10-20 pounds is enough
  - increase activity to walking 30 min/day or going to a gym 3 days/week
- **Results**
  - One case of diabetes is prevented for every 7-8 people who participate in an intensive lifestyle intervention program for 3 years
  - Achieving all diet and exercise goals virtually stalls the progression to diabetes

Definition

Pre-diabetes: A serious, treatable medical condition in which blood glucose levels are higher than normal but not yet high enough to be diagnosed as diabetes. Without intervention, nearly one-half of these individuals progress to clinical diabetes in five years.

For info see http://www.diabetes.org/main/info/pre-diabetes.jsp

Type 2 Diabetes Screening Program
## Conditions that must be met

- **Disease represents a significant burden**
- **Natural history of the disease is understood**
- **The disease can be recognized at a preclinical (asymptomatic) stage**
- **Sensitive and specific screening tests are available**
- **Early detection and treatment improve outcomes**
- **Testing and treatment are cost-effective**
- **Systematic procedures can be adopted**
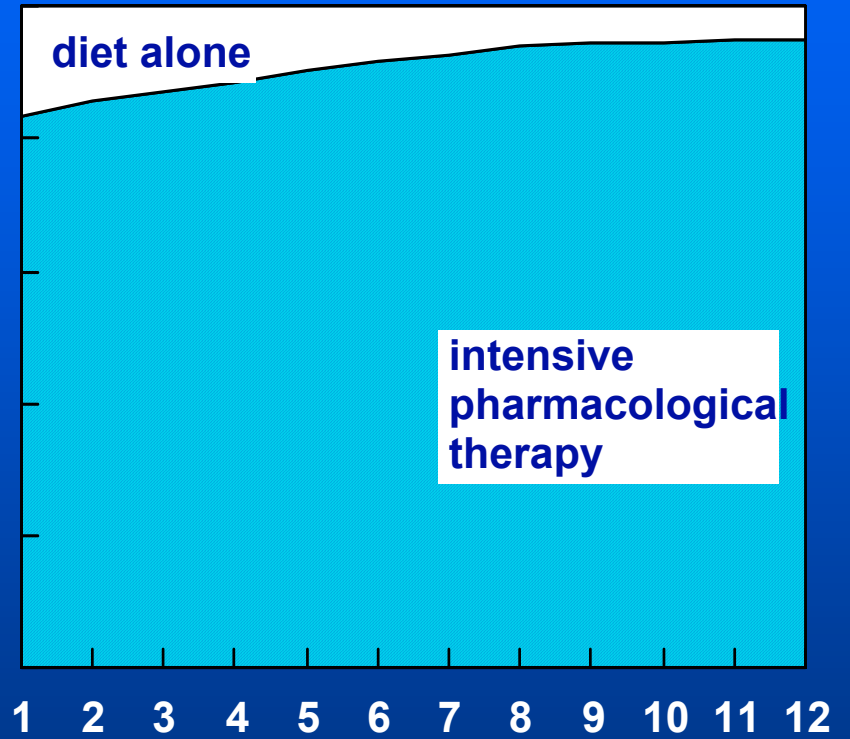
Socioeconomic Costs of Diabetes Mellitus

- **Diabetes costs the U.S. economy $105 billion annually**

- **One out of every ten U.S. healthcare dollars is spent for diabetes**

- **One of four Medicare dollars pays for care in individuals suffering from diabetes**
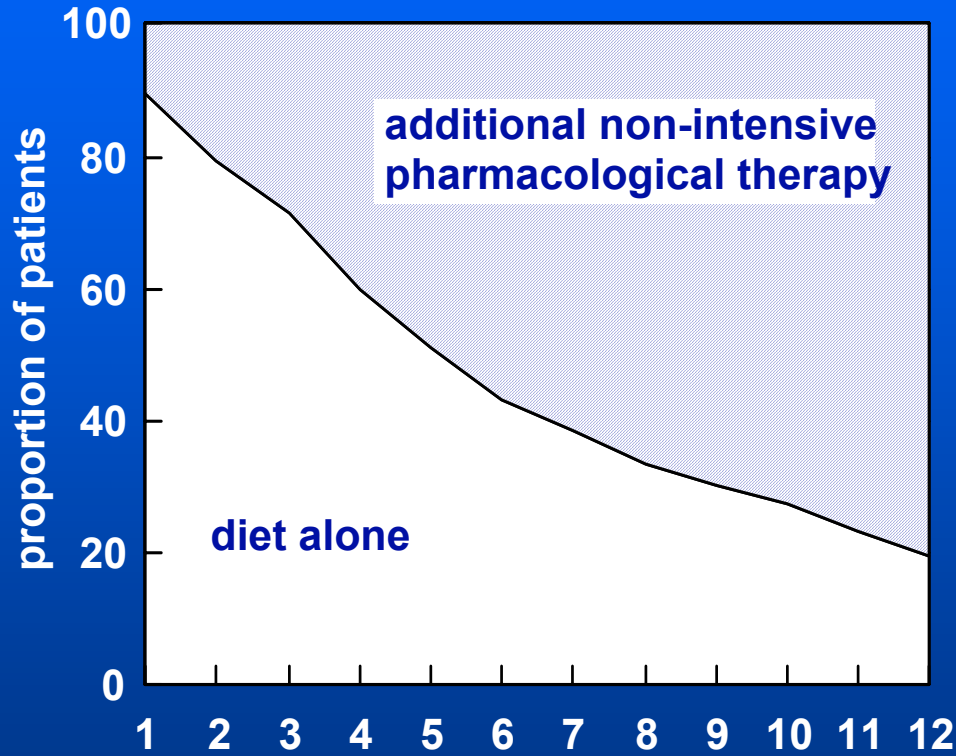
Pathophysiology-based Therapy for Type 2 Diabetes

- **Defect in insulin sensitivity**
  - exercise
  - weight reduction
  - thiazolidinediones
  - metformin
- **Defect in insulin secretion**
  - sulfonylureas (mild defect)
  - insulin (severe defect)

Pathophysiology-based Therapy for Type 2 Diabetes

- **Increased hepatic glucose output**
  - metformin > thiazolidinediiones
  - insulin (sulfonylurea)
- **Carbohydrate absorption (post-prandial hyperglycemia)**
  - acarbose

Prevention of Diabetic Complications

- Optimize glycemic control
- Control hypertension < 135/85 mm Hg
- Screen at diagnosis, then annually for microalbuminuria
- Use angiotensin converting-enzyme inhibitor when microalbuminuria is reproducible

Prevention of Diabetic Complications

- **Ophthalmoscopic exam of the eye every 3-6 months with a formal exam annually**

- **Determine the fasting lipid profile each year and treat to LDL <100**

- **Prescribe 325 mg aspirin to be taken daily**

Diagnostic Criteria for Diabetes

- **Symptoms of diabetes +**

  casual glucose > 200 mg/dl (11.1 mmol/l)

- **FPG $\geq$ 126 mg/dl (7.0 mmol/l)**

- **2h PG > 200 mg/dl (11.1 mmol/l) during OGTT**

*Confirmation on a second day by any of the above methods