Pharmacologic Treatment for the Prevention of Diabetes

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Disclosed no conflict of interest

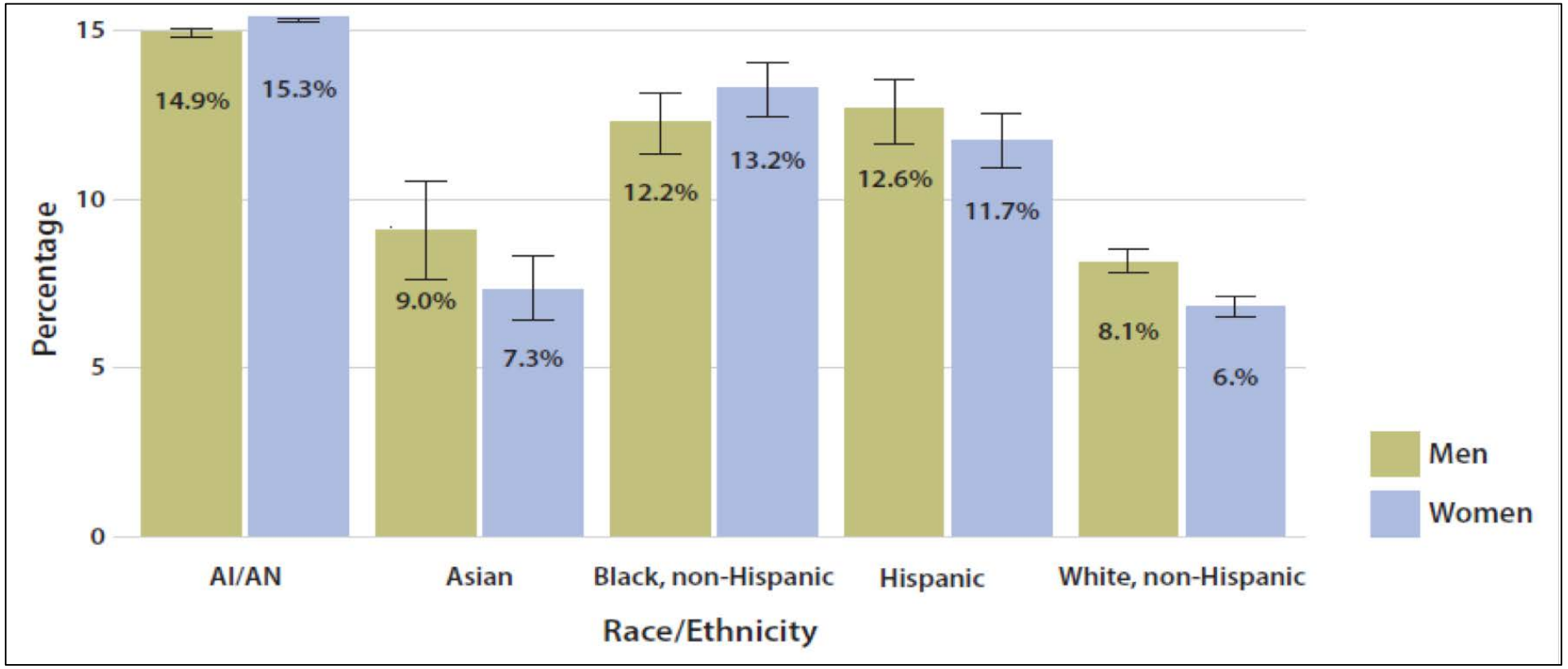
Learning Outcomes/Objectives

- As a result of participating in this activity, participants will be able to:
  - Assess individuals for tailored intervention to prevent and/or delay diabetes.
  - Educate and increase patient awareness on the various risk factors for diabetes development.
  - Evaluate clinical studies of anti-hyperglycemic medications for the prevention of diabetes.

National Diabetes Statistics Report, 2017

- 30.3 million people in the U.S. have diabetes.
  - 7.2 million people with diabetes are undiagnosed.
  - 9.4 % of the U.S. population
- 1.5 million Americans aged 18 years or older were newly diagnosed with diabetes in 2015.
- 84.1 million (33.9%) Americans aged 18 years or older had prediabetes in 2015, based on fasting plasma glucose or A1c levels.
  - More men (36.6%) than women (29.3%)
  - 11.6% of adults with prediabetes reported being told by a health professional of this condition.

National Diabetes Statistics Report, 2017 (2)



Overall, prevalence was higher among American Indians/Alaska Natives (AI/AN, 15.1%), non-Hispanic blacks (12.7%), and people of Hispanic ethnicity (12.1%) than among non-Hispanic whites (7.4%) and Asians (8.0%).

Center for Disease for Control and Prevention. National Diabetes Statistics Report, 2017

Changing the Course of Diabetes: Turning Hope into Reality

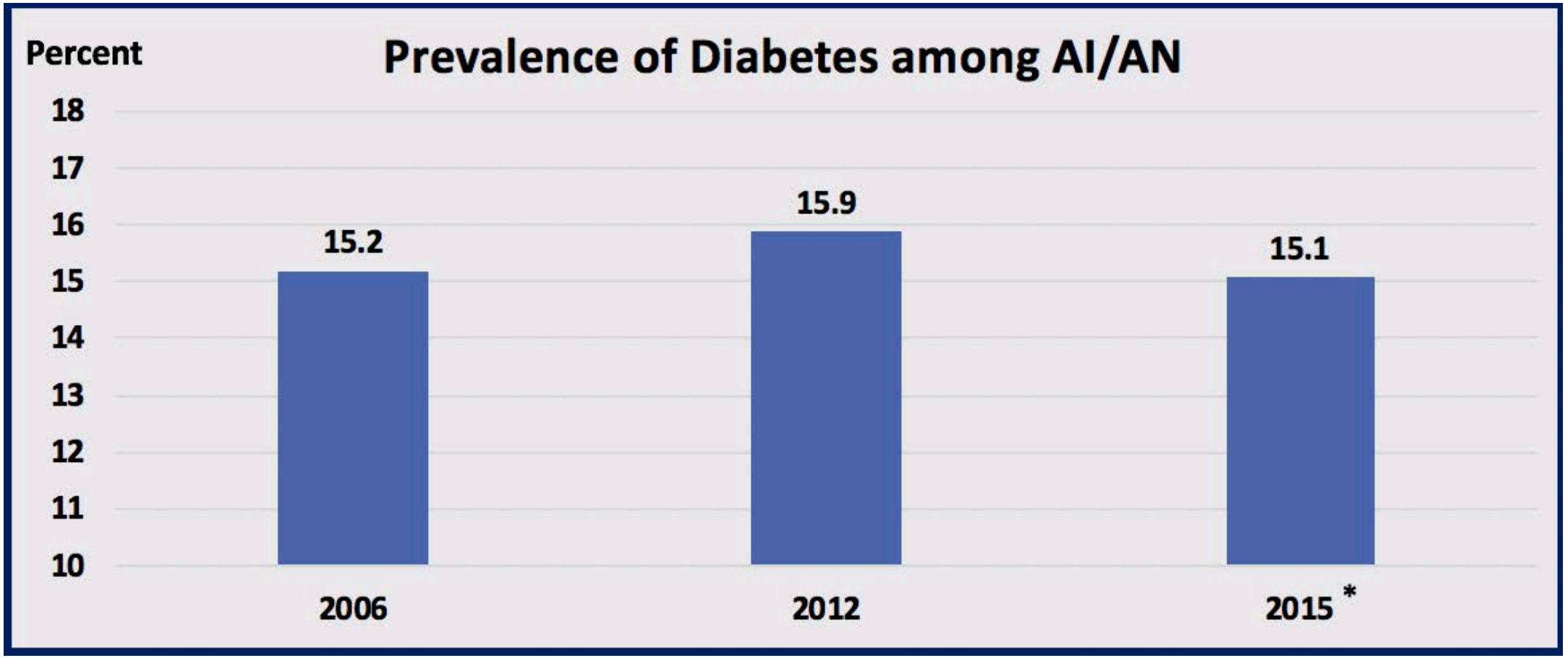
Indian Health Service

Special Diabetes Program for Indians, 2014 Report to Congress

- Recent data show that the rate of increase in diabetes prevalence is slowing in AI/AN adults (aged 20 and older), climbing only from 15.2 percent to 15.9 percent from 2006 through 2012. This trend, plus the continued rise in the U.S. prevalence rate during those years, narrowed the gap in prevalence rates between AI/AN adults (15.9 percent) and U.S. adults (11.7 percent in 2012.

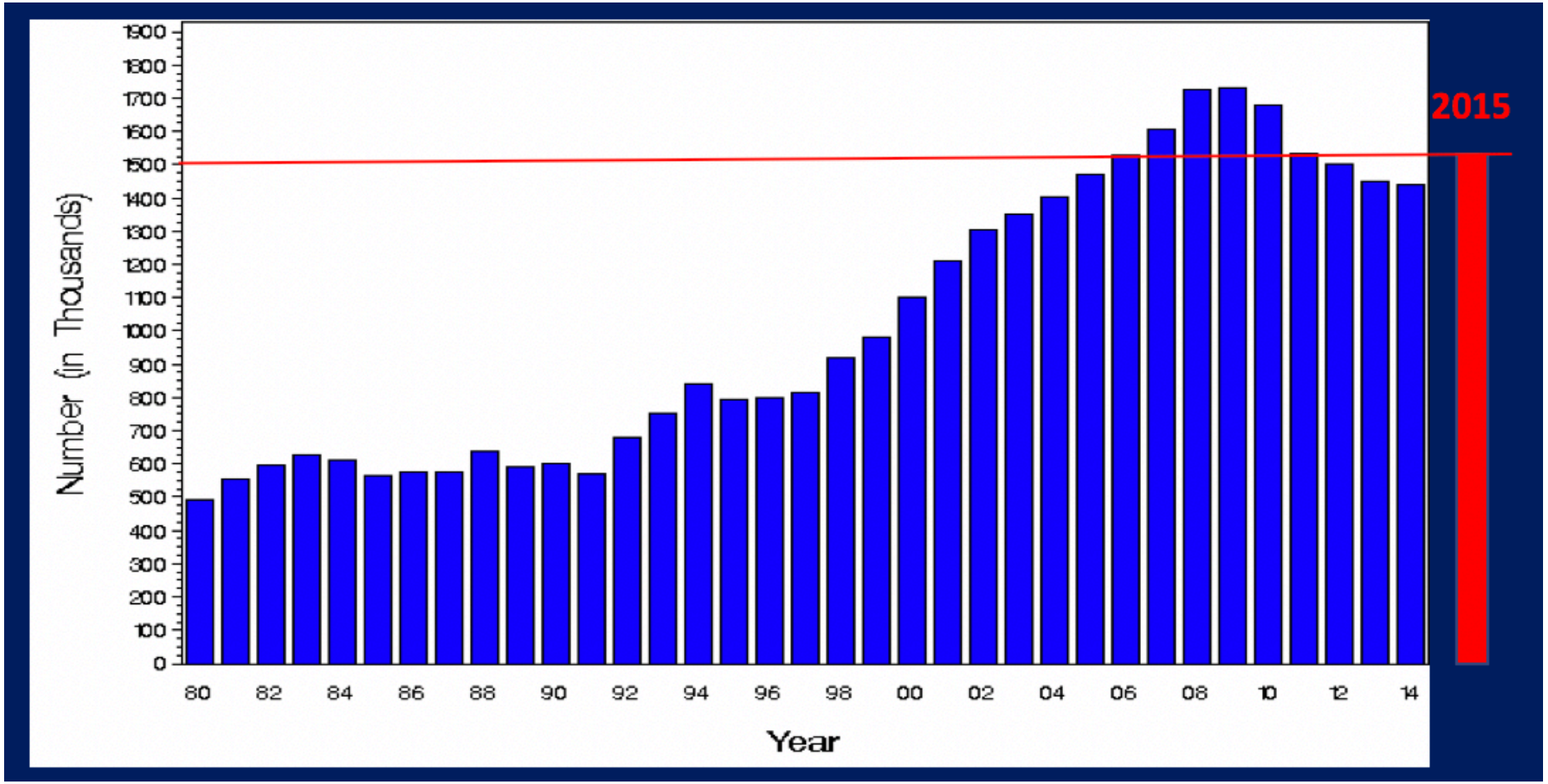
- https://www.cdc.gov/diabetes/pdfs/data/statistics/national-diabetes-statistics-report.pdf
- https://www.ihs.gov/newsroom/includes/themes/responsive2017/display_objects/documents/RepCong_2016/SDPI_2014_Report_to_Congress.pdf

Diabetes Prevalence Trends from National Diabetes Statistics Reports



*The 2015 report includes adults aged 18 years and older; previous years included adults 20 years and older.

Incidence Among Adults



In 2015, an estimated 1.5 million new cases of diabetes (6.7 per 1,000 persons) were diagnosed among U.S. adults aged 18 years or older.

Center for Disease Control and Prevention. National Diabetes Statistics Reports.

National Diabetes Statistics Reports, 2014 and 2017

Prevalence of Prediabetes

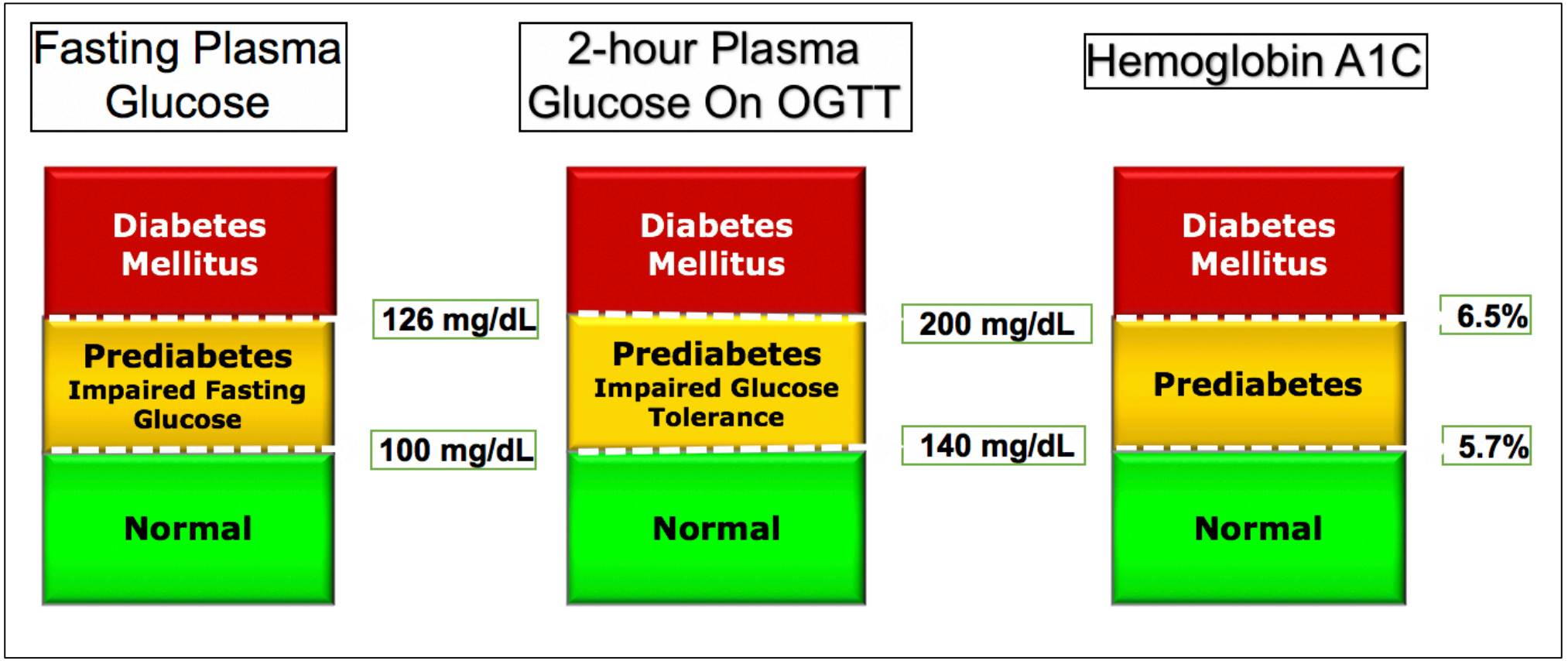
- An estimated 33.9% of U.S. adults aged 18 years or older (84.1 million people) had prediabetes in 2015, based on their fasting glucose or A1C level. Nearly half (48.3%) of adults aged 65 years or older had diabetes.
- Among adults with prediabetes, 11.6% reported being told by a health professional that they had this condition.
- Age-adjusted data for 2011–2014 indicated that more men (33.6%) than women (29.3%) had prediabetes. Prevalence of prediabetes was similar among racial and ethnic groups.

Prediabetes among people aged 20 years or older, United States, 2012

- In 2009–20012, based on fasting glucose or A1C levels, 37% of U.S. adults aged 20 years or older had prediabetes (51% of those aged 65 years or older). Applying this percentage to the entire U.S. population in 2012 yields an estimated 86 million Americans aged 20 year or older with prediabetes.
- On the basis of fasting glucose or A1C levels, and after adjusting for population age differences, the percentage of U.S. adults aged 20 years or older with prediabetes in 2009–2012 was similar for non-Hispanic whites (35%), non-Hispanic blacks (39%), and Hispanics (38%).

Center for Disease Control and Prevention. National Diabetes Statistics Report, 2014 and 2017

Diagnostic Criteria for Glucose Intolerance



- Any abnormality must be repeated and confirmed on a separate day.
- The diagnosis of diabetes can also be made based on unequivocal symptoms and a random glucose greater than (>) 200 mg/dL.

- Adapted from: American Diabetes Association. *Diabetes Care.* 2014;37 Suppl 1:S81-90.

Criteria for Screening for Prediabetes/Type 2 Diabetes in Asymptomatic Adult Individuals

Criteria for testing for diabetes or prediabetes in asymptomatic adults

1. Testing should be considered in overweight or obese (BMI ≥ 25 kg/m2 or ≥ 23 kg/m2 in Asian Americans) adults who have one or more of the following risk factors:
   - A1C ≥5.7% (39 mmol/mol), IGT, or IFG on previous testing
   - first-degree relative with diabetes
   - high-risk race/ethnicity (e.g., African American, Latino, Native American, Asian American, Pacific Islander)
   - women who were diagnosed with GDM
   - history of CVD
   - hypertension (≥140/90 mmHg or on therapy for hypertension)
   - HDL cholesterol level <35 mg/dL (0.90 mmol/L) and/or a triglyceride level >250 mg/dL (2.82 mmol/L)
   - women with polycystic ovary syndrome
   - physical inactivity
   - other clinical conditions associated with insulin resistance (e.g., severe obesity, acanthosis nigricans).
2. For all patients, testing should begin at age 45 years.
3. If results are normal, testing should be repeated at a minimum of 3-year intervals, with consideration of more frequent testing depending on initial results, (e.g., those with prediabetes should be test yearly) and risk status.

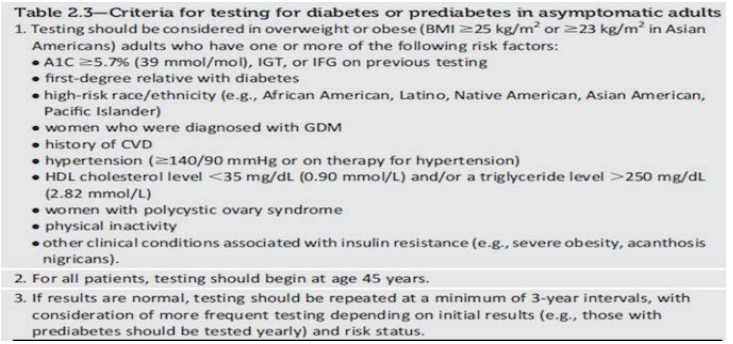


Table 2.3—Criteria for testing for diabetes or prediabetes in asymptomatic adults

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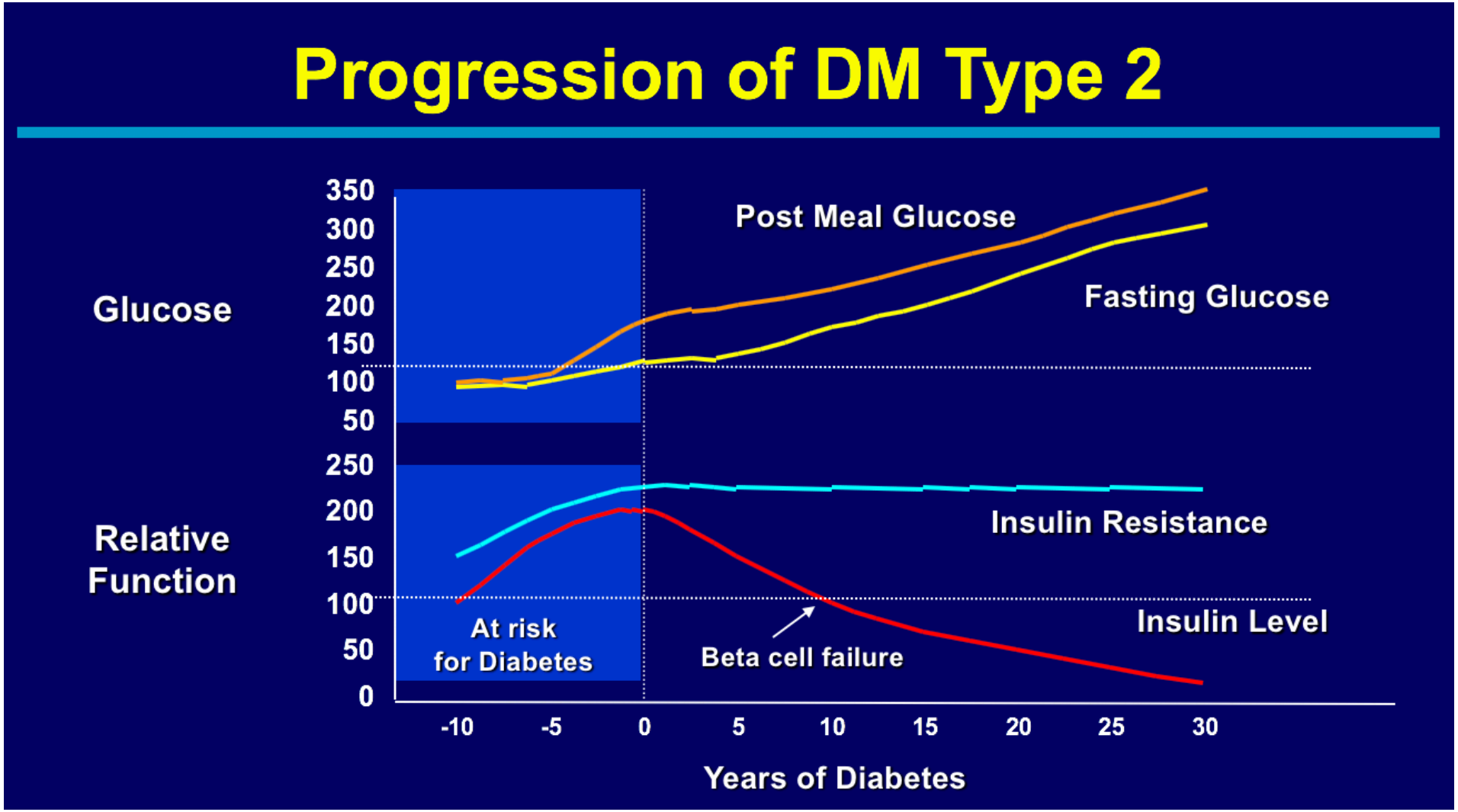
Source: American Diabetes Association, “Classification and Diagnosis of Diabetes.” Diabetes Care 2017.
http://care.diabetesjournals.org/content/40/Supplement_1/S11

Common Medications Associated with Increased Risk for Diabetes

- Anti-Hypertensive Agents – reduce insulin secretion
  - Beta blockers
  - Thiazide diuretics
- Anti-hyperlipidemic agents – increase insulin resistance
  - Nicotinamide (Niacin)
  - Statins
- Steroids – increase weight; increase insulin resistance
- Immunosuppressive agents
- Antibiotics/Anti-retrovirals
- Anti-psychotics – increase weight; increase insulin resistance

Continuum of Dysglycemia



Lifetime Prevalence and Prognosis of Prediabetes without Progression to Diabetes

- Framingham Heart Study – Offspring Cohort participants (18–77 years old)
  - Initial fasting plasma glucose with serial measurements over time
  - Assessed for glycemia progression; CVD and CHD mortality
- Case-control investigation of 4 cohorts: diabetes; prediabetes before age 50 years (Early); prediabetes after 50 years and older; and no diabetes
- Patient characteristics
  - Mean age: 42 years (43% women)
  - Mean age at death: 73 years +/- 10 years
  - Lifetime prevalence of diabetes and prediabetes was 50% (N = 602) and prediabetes but not developing diabetes was 69% (N = 414)

Source: Echouffo-Tcheugui et al, “Lifetime Prevalence and Prognosis of Prediabetes Without Progression to Diabetes.” Diabetes Care 2018. http://care.diabetesjournals.org/content/41/7/e117

Lifetime Prevalence and Prognosis of Prediabetes without Progression to Diabetes (cont.)

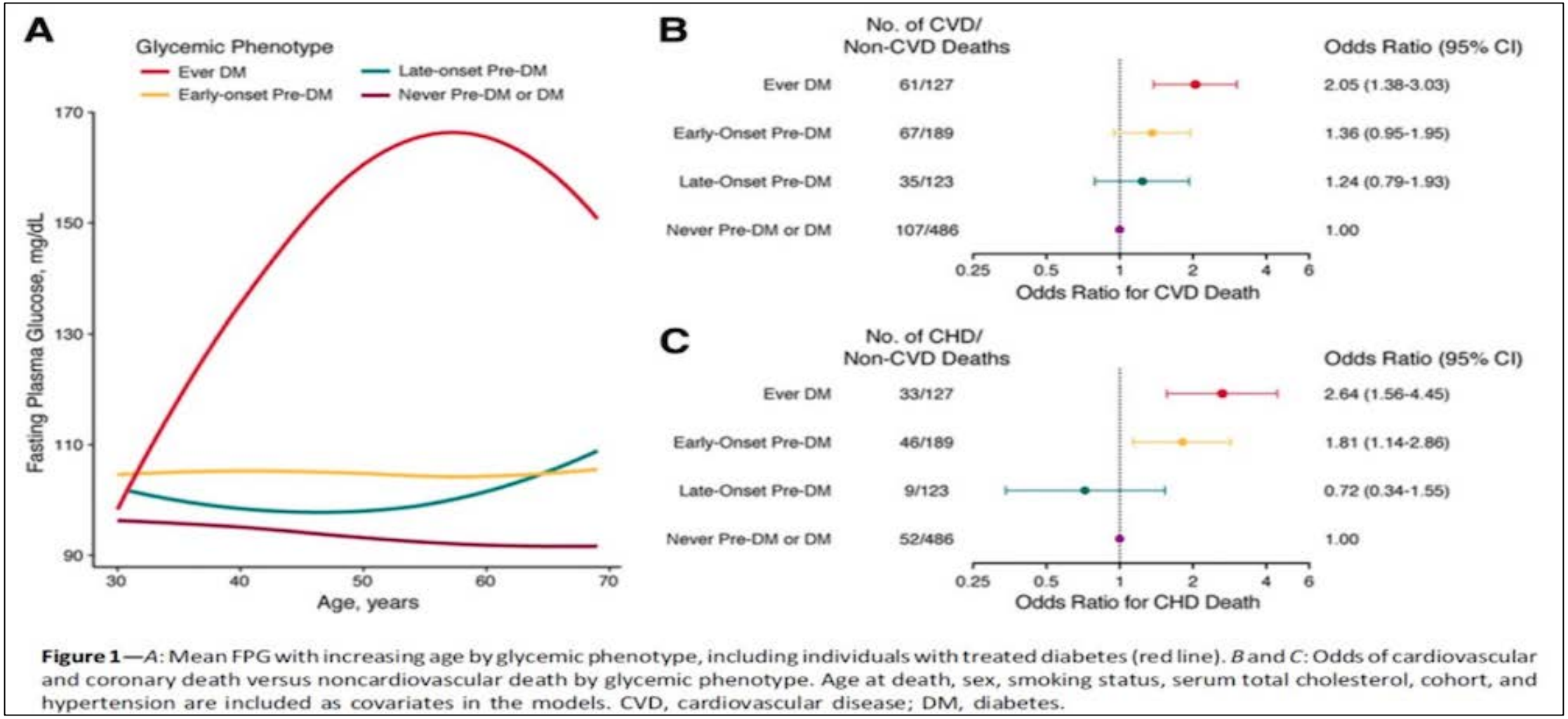


Figure 1—*A*: Mean FPG with increasing age by glycemic phenotype, including individuals with treated diabetes (red line). *B* and *C*: Odds of cardiovascular and coronary death versus noncardiovascular death by glycemic phenotype. Age at death, sex, smoking status, serum total cholesterol, cohort, and hypertension are included as covariates in the models. CVD, cardiovascular disease; DM, diabetes.

Source: Echouffo-Tcheugui et al, "Lifetime Prevalence and Prognosis of Prediabetes Without Progression to Diabetes." Diabetes Care 2018. http://care.diabetesjournals.org/content/41/7/e117

Prevention or Delay of Type 2 Diabetes: Standards of Medical Care in Diabetes – 2018

Recommendations

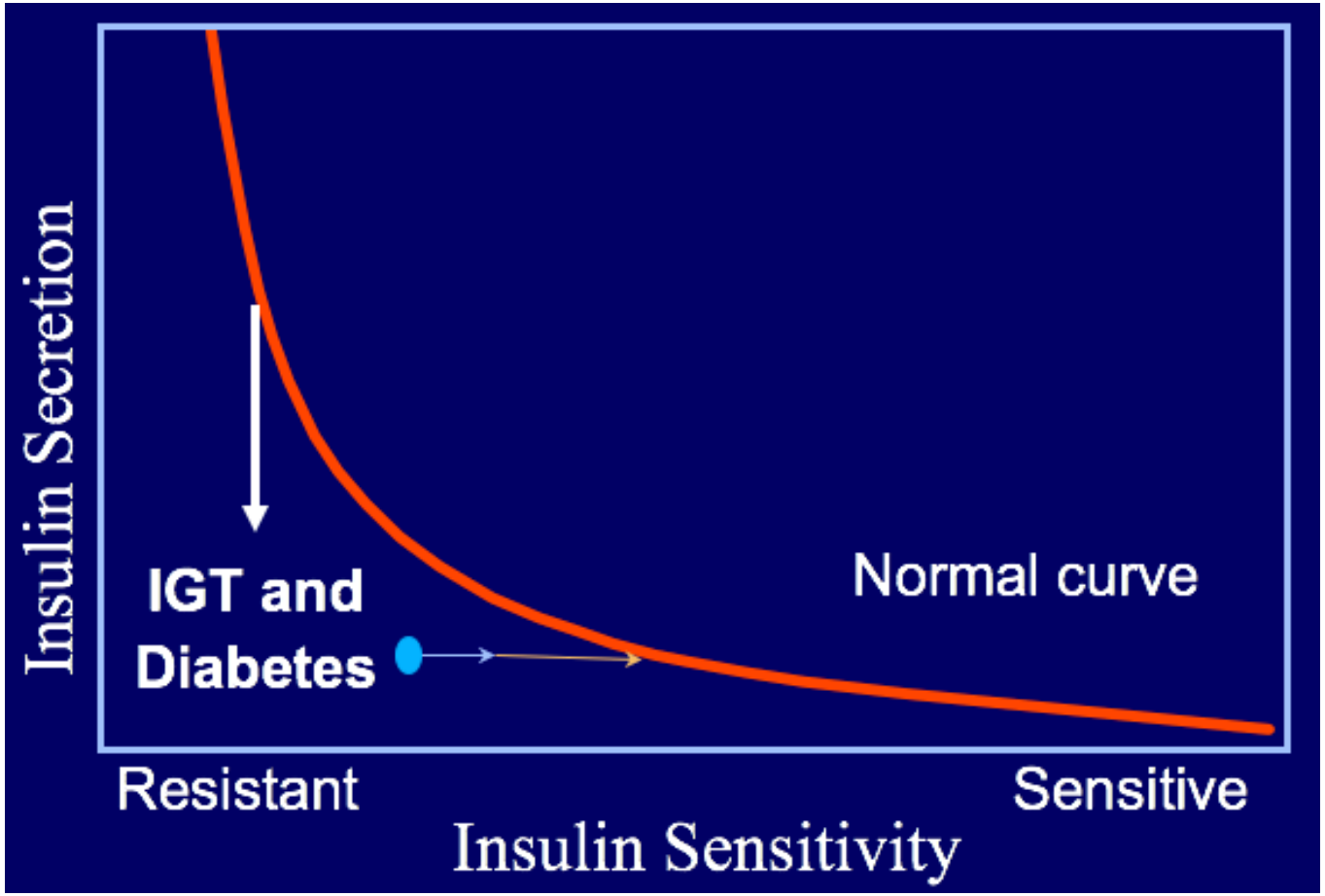
- At least annual monitoring for the development of diabetes in those with prediabetes is suggested.
- Patients with prediabetes should be referred to an intensive behavioral lifestyle intervention program modeled on the Diabetes Prevention Program to achieve and maintain 7% loss of initial body weight and increase moderate-intensity physical activity (such as brisk walking) to at least 150 min/week.
- Technology-assisted tools including Internet-based social networks, distance learning, and mobile applications that incorporate bidirectional communication may be useful elements of effective lifestyle modification to prevent diabetes.
- Given the cost-effectiveness of diabetes prevention, such intervention programs should be covered by third-party payers.

Pharmacologic Interventions: Recommendations

- Metformin therapy for prevention of type 2 diabetes should be considered in those with prediabetes, especially for those with BMI ≥35 kg/m2, those aged <60 years, and women with prior gestational diabetes mellitus.
- Long-term use of metformin may be associated with biochemical vitamin B12 deficiency, and periodic measurement of vitamin B12 levels should be considered in metformin-treated patients, especially in those with anemia or peripheral neuropathy.

Source: American Diabetes Association, “Prevention or Delay of Type 2 Diabetes: Standards of Medical Care in Diabetes—2018.” *Diabetes Care 2018*.
http://care.diabetesjournals.org/content/41/Supplement_1/S51.article-info

Diabetes Prevention Rationale



- Insulin Resistance
  - Weight Loss
  - Increase Activity
  - Metformin
  - Thiazolidinediones

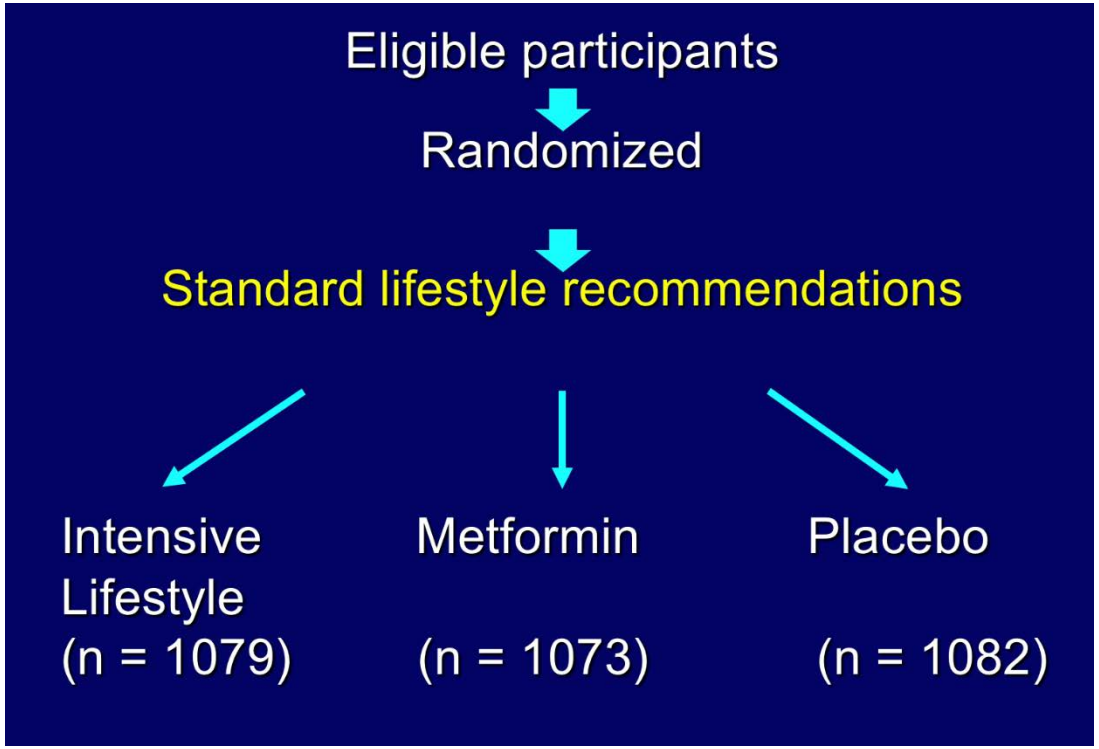
The Diabetes Prevention Program

A Randomized Clinical Trial to Prevent Type 2 Diabetes in Persons at High Risk

- N Engl J Med 346:393-403, 2002

Study Interventions

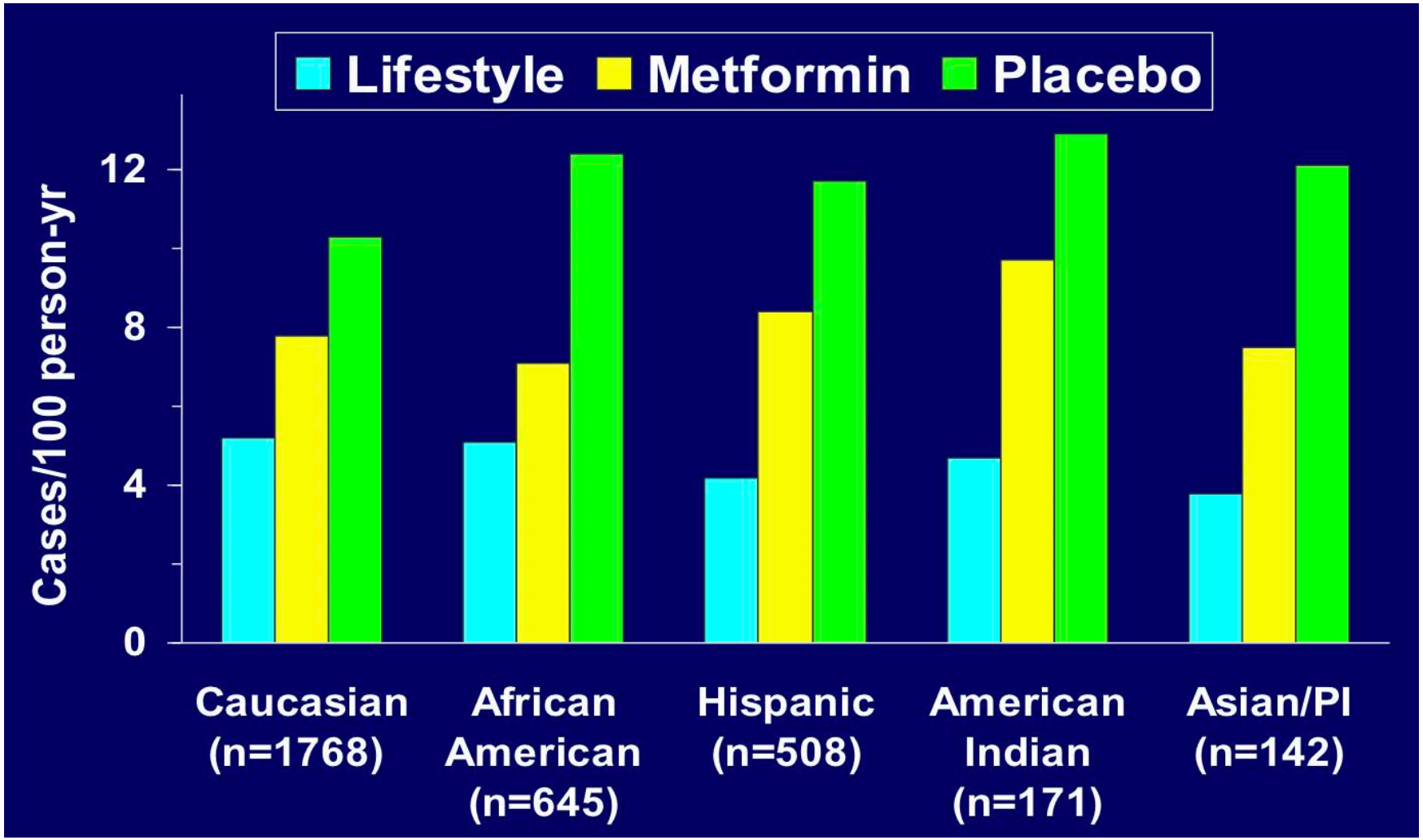
- Eligible participants were randomized into one of three standard lifestyle recommendations:
  - Intensive Lifestyle (n = 1079)
  - Metformin (n = 1073)
  - Placebo (n = 1082)



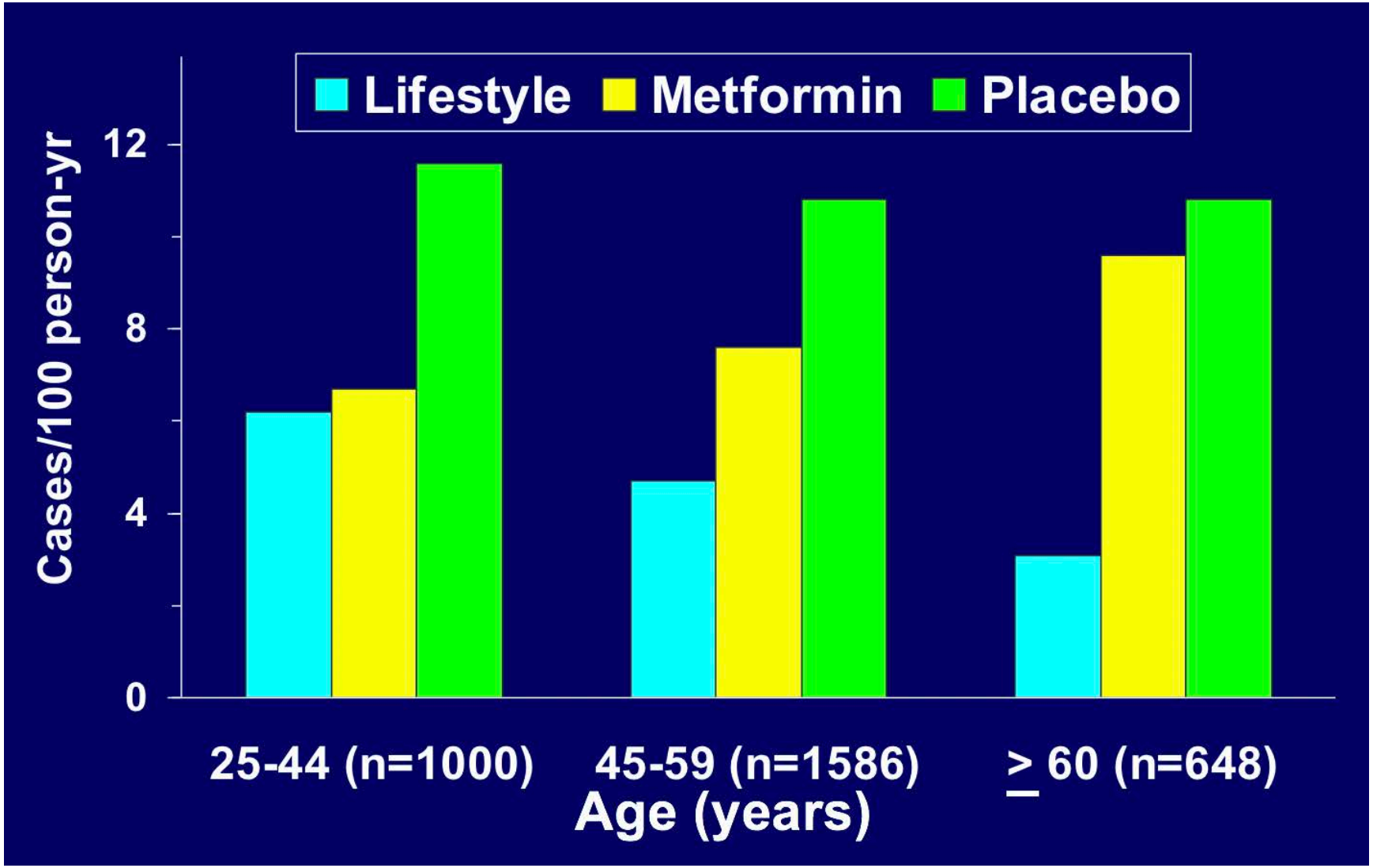
Self-reported Characteristics of DPP Cohort

- 68% women; 20% > 60 years old
- Mean BMI: 35 for women; 32 for men — except Asian/Pacific Islanders
- 2/3 with family history of DM
- 1/3 with hypercholesterolemia — except American Indians
- 30% with HTN
- Glycemia: FBG — 106; 2 Hr PP — 165; HbA1c — 5.9% (nearly 30% of cohort with HbA1c > 6.1%)

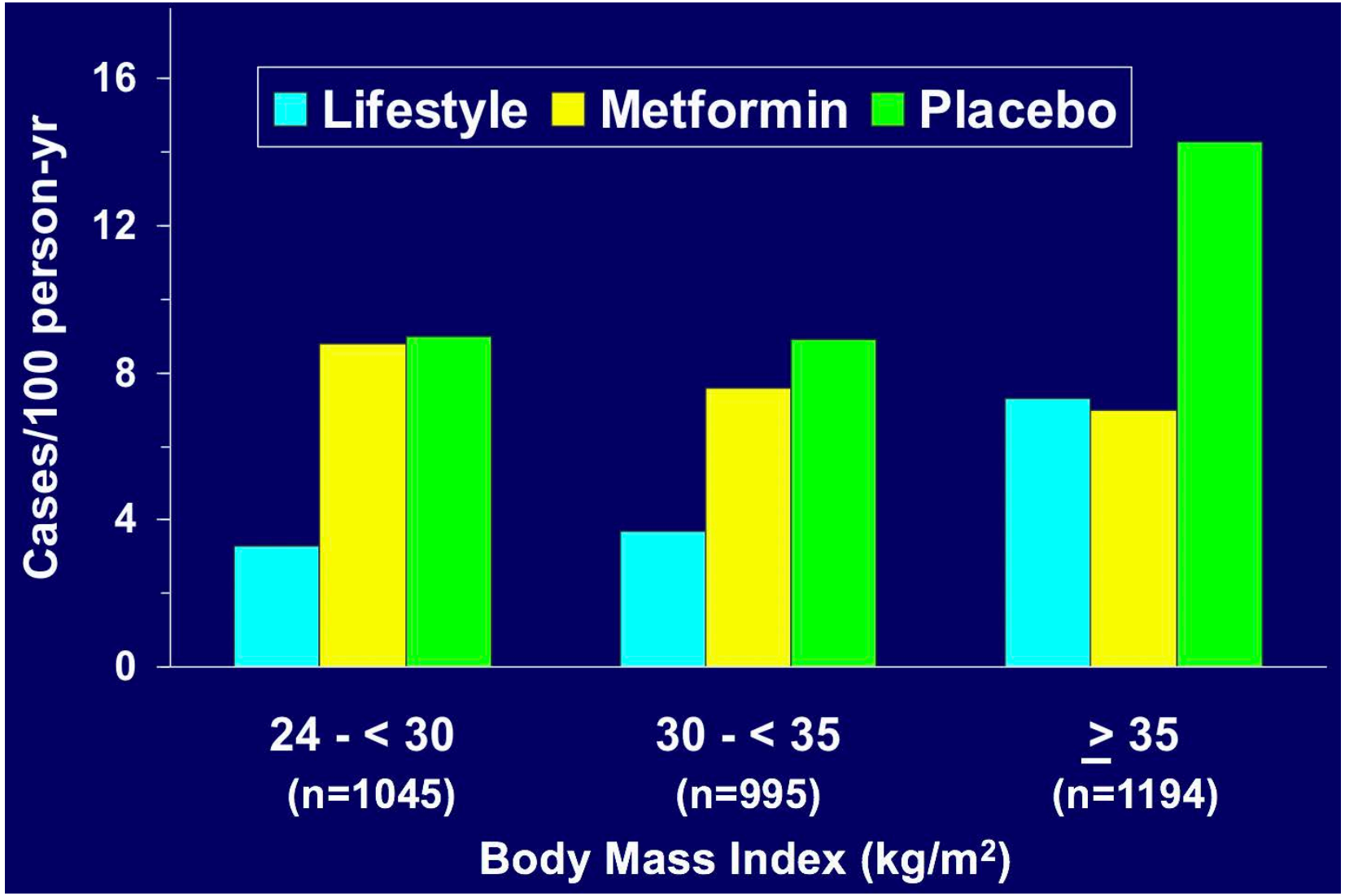
Diabetes Incidence Rates by Ethnicity



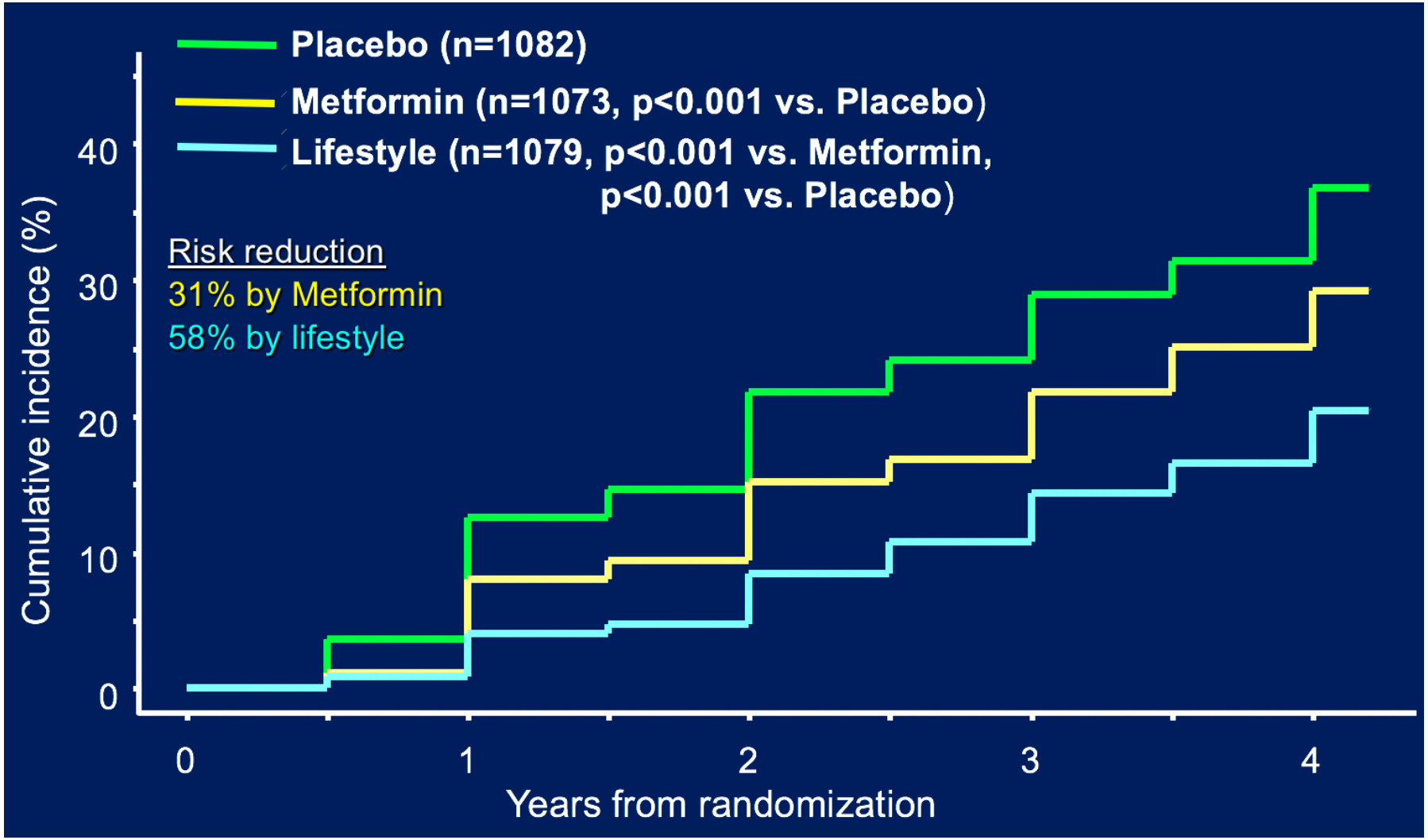
Diabetes Incidence Rates by Age



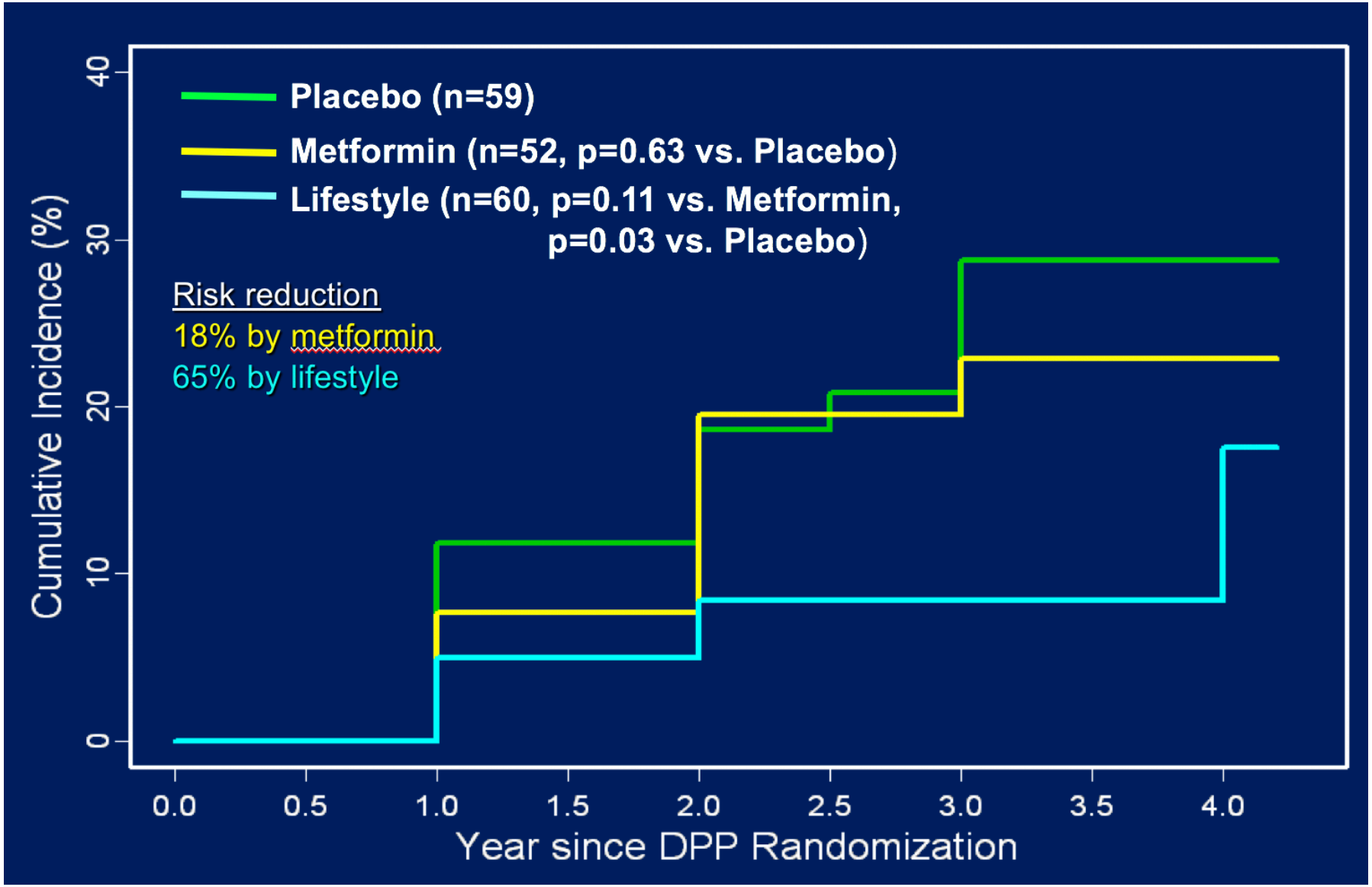
Diabetes Incidence Rates by BMI



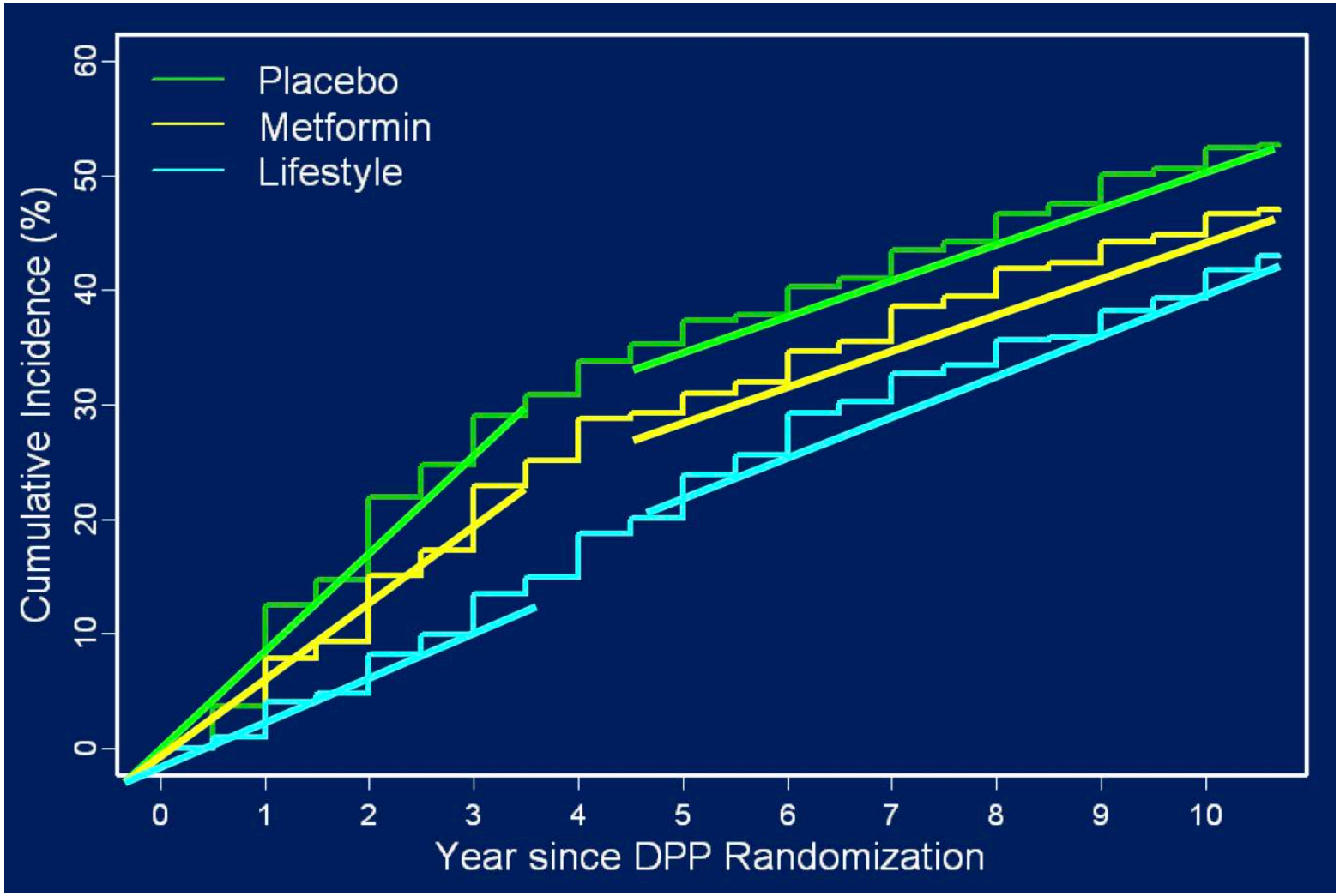
DPP Incidence of Diabetes



AI DPP Incidence of Diabetes

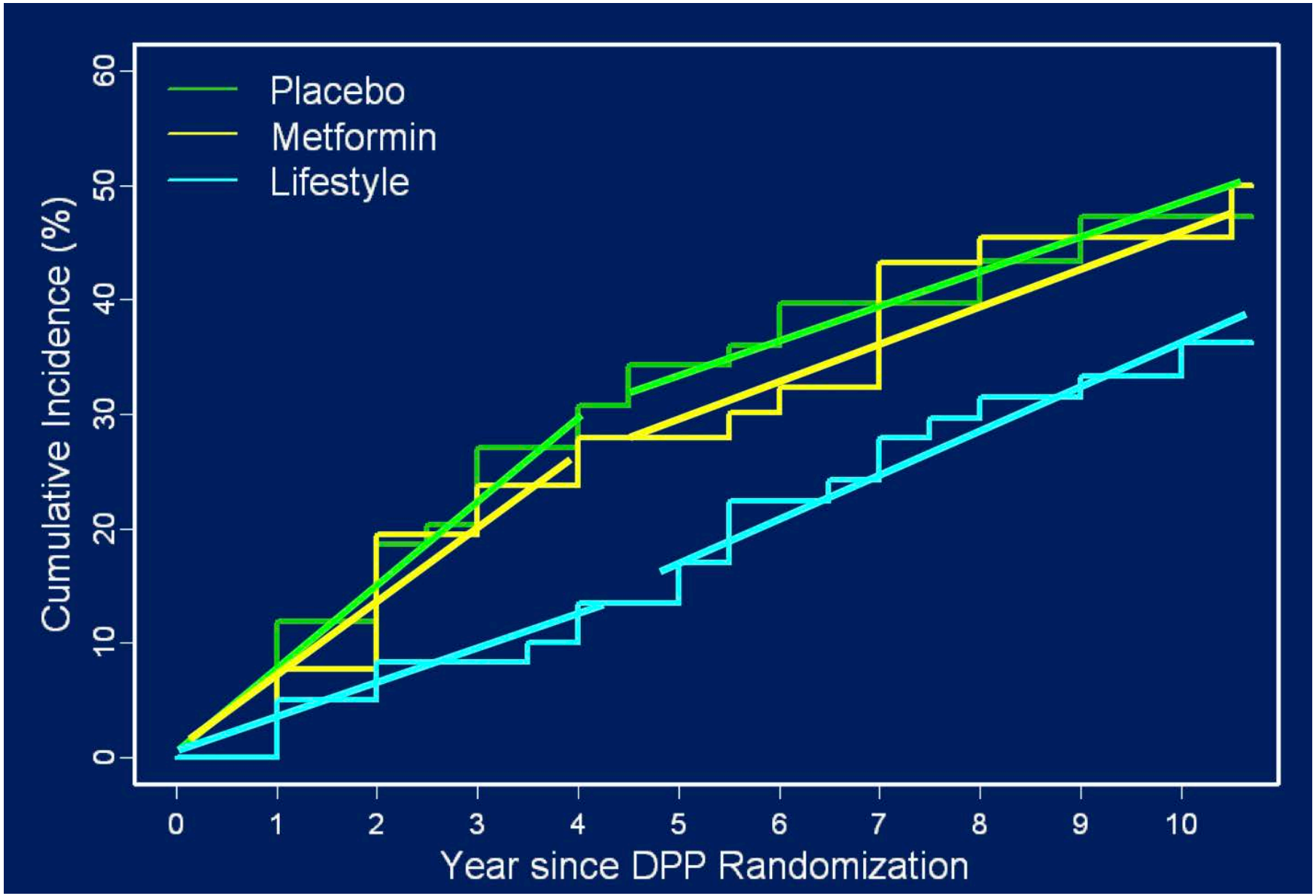


Incidence of Diabetes – Overall



Source: Knowler et al. “10-year follow-up of diabetes incidence and weight loss in the Diabetes Prevention Program Outcomes Study.” Lancet. 2009; 374:1677-1686 (Figure 3)
https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(09)61457-4/fulltext

AI Incidence of Diabetes – Overall



Pharmacologic Intervention Trials in Prediabetes

Medication	Number of Patients	Duration of Treatment	Cumulative Rates of DM: Controls	Cumulative Rates of DM: Medication	Risk Reduction
Rosiglitazone 8 mg daily	2,365 2,634 placebo	3.0 years	25.0%	10.6%	62%
Pioglitazone 45 mg daily	303 299 placebo	2.4 years	16.7%	5.0%	72%
Acarbose 100 mg TID	714 714, placebo	3.2 years	42%	31.5%	25%
Glargine, 0.4 u/kg/day	737 719 placebo	6.2 years	31%	25%	28%

No clear evidence that secretagogues or DPP-4 inhibitors reduce the development of diabetes

Resource – *JAMA Internal Medicine*

"Long-term Sustainability of Diabetes Prevention Approaches –
A Systematic Review and Meta-analysis of Randomized Clinical Trials"

- J. Sonya Haw, MD; Karla I. Galaviz, PhD; Audrey N. Straus, MSN; et al.
- *JAMA Internal Medicine*. 2017;177(12):1808-1817.
- https://jamanetwork.com/journals/jamainternalmedicine/article-abstract/2661704

- "Findings: In this meta-analysis of randomized clinical trials including 49,029 participants, lifestyle modification and medications promoting weight loss or insulin sensitization were associated with reduced diabetes risk by 36% to 39%. Effects of medications were not sustained after they were discontinued; effects of lifestyle modification, however, were sustained after intervention was stopped, although the effects waned over time."

Case Study

- 44-year-old woman with long-standing hypothyroidism prescribed levothyroxine 200 mcg daily for over five years. However, she has had difficulty in maintaining adherence and has gained 20 pounds over the past year with the symptom of mild fatigue.
- Her TSH level was 33 mIU/L (NL 0.358 – 3.74) with a free-T4 level of 0.86 ng/dL (NL 0.76 – 1.46), and a random blood glucose level was 175 mg/dL.
- She has a family history of diabetes—mother with type 2 diabetes.
- She has history of sleep apnea and vitamin D deficiency; other medications include cholecalciferol at 1000 units daily. She does not smoke.
- She is concerned about her risk of diabetes and her obesity.
- Physical examination only revealed her obesity and Acanthosis nigricans.

Case Study (continued)

- Thyroid replacement was adjusted over a few months and her TSH level was normalized.
- She did not lose a significant amount of weight with thyroid replacement.
- Her prediabetes status was confirmed and she was started on phentermine in January 2017. After three months she lost 17 pounds, and her glycemia dramatically improved.

Measure	**Value**	**Value**	**Value**	**Value**	**Value**
Visit Date (Month Year)	January 2016	July 2016	September 2016	December 2016	April 2017
A1c level (%)	-	6.7	5.9	6.0	5.3
Weight (pounds)	253	248	249	252	235
BMI	43.4	42.5	42.6	43.3	40.3

Pharmacologic Intervention Trials in Prediabetes: Weight-Loss Medications

Medication	Number of Patients	Duration of Treatment	Average Weight Loss (Kg)	Cumulative Rates of Diabetes	Risk Reduction
Orlistat 120 mg TID	1,640 1,637 placebo	4.0 years	6.9 4.1	18.8 % 28.8 %	45%
Liraglutide 3.0 mg daily	1,472 738 placebo	3.0 years	6.1 1.9	2.0 % 6.0 %	67%
Phentermine/topiramat, 7.5/46 mg or 15/92 mg	159, 15/92 mg 114, 7.5/46 mg 159, placebo	2.0 years	12.4 11.0 2.5	1.3 % 1.8 % 6.1 %	78.7% 70.5%
Lorcaserin 10 mg BID	Post hoc analysis of 6,136	1.0 years	(> 5% weight loss) 40% 16%	3.2 % 5.0 %	36%

Thank you for your attention

Any Questions?