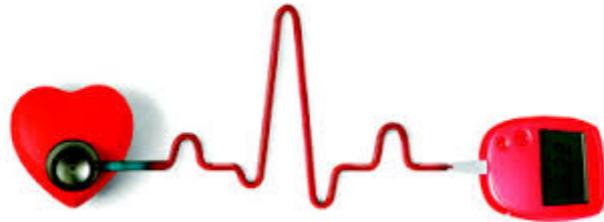


Diabetes and the Heart



Kathleen M. Dungan, MD

Division of Endocrinology, Diabetes &
Metabolism

The Ohio State University



THE OHIO STATE UNIVERSITY
WEXNER MEDICAL CENTER

Disclosures

- I serve on advisory boards or perform consulting activities with Eli Lilly and Tolerion
- As director of our clinical trials unit, I also serve as an investigator for clinical trials sponsored by Eli Lilly, Novo Nordisk, Sanofi Aventis, Viacyte

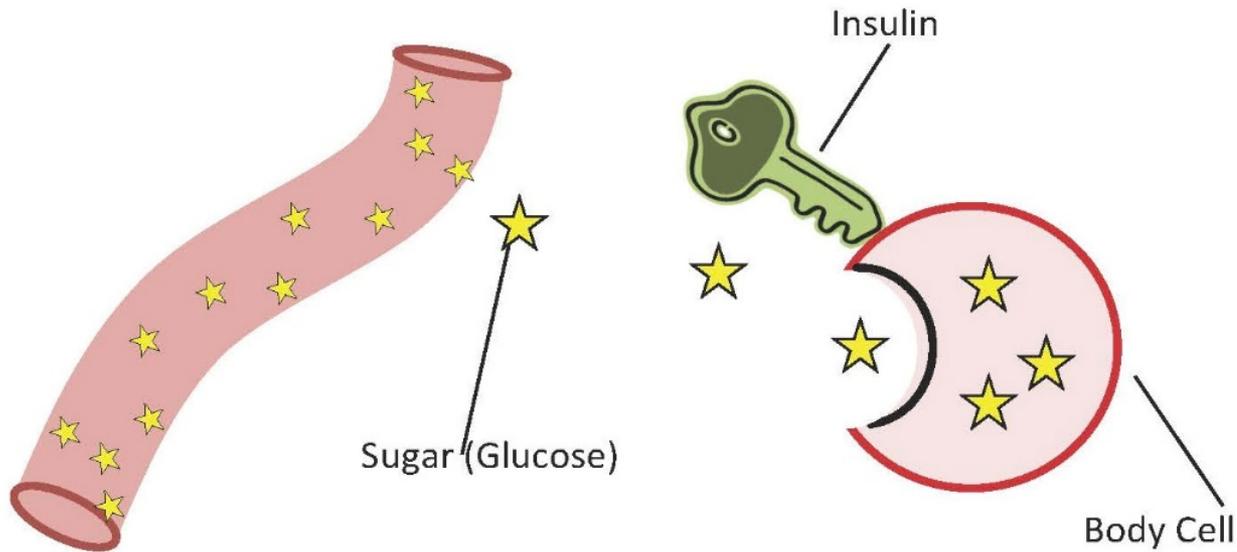


What is Diabetes?

- Diabetes is a group of diseases characterized by high blood glucose levels that result from defects in the body's ability to produce and/or use insulin.



What is Insulin?



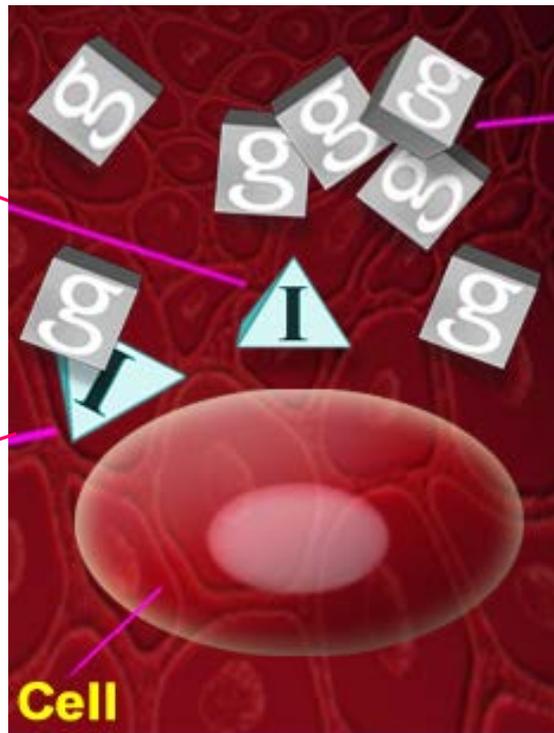
When a cell needs energy, insulin acts as a key to unlock the cell. This opens the cell so sugar can enter and be used for energy.

High Blood Glucose (Hyperglycemia)

In diabetes, blood glucose builds up for several possible reasons...

Too little insulin is made

Cells can't use insulin well



Liver releases too much glucose



Type 2 Diabetes

- Most people with diabetes have type 2
- Most people are over age 40 when diagnosed
- Usually subtle or no symptoms in early stages: 1 in 4 with type 2 aren't aware they have it



Treatment for Type 2 Diabetes May Change Over a Lifetime



Always Includes:

- Education
- Healthy eating
- Blood glucose monitoring
- Physical Activity

May Include:

- Medications, including insulin



Type 1 Diabetes

- 1 in 20 people with diabetes have type 1
- Most people are under age 20 when diagnosed
- Body can no longer make insulin
- Insulin is always needed for treatment

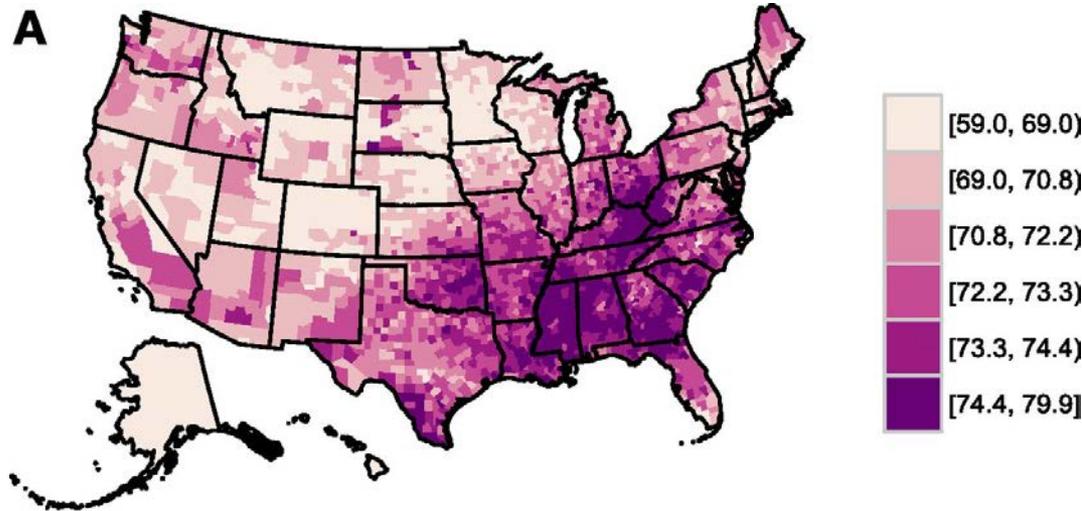
*Eli Lilly and Company Ltd. From
The Discovery of Insulin by Michael Bliss.*



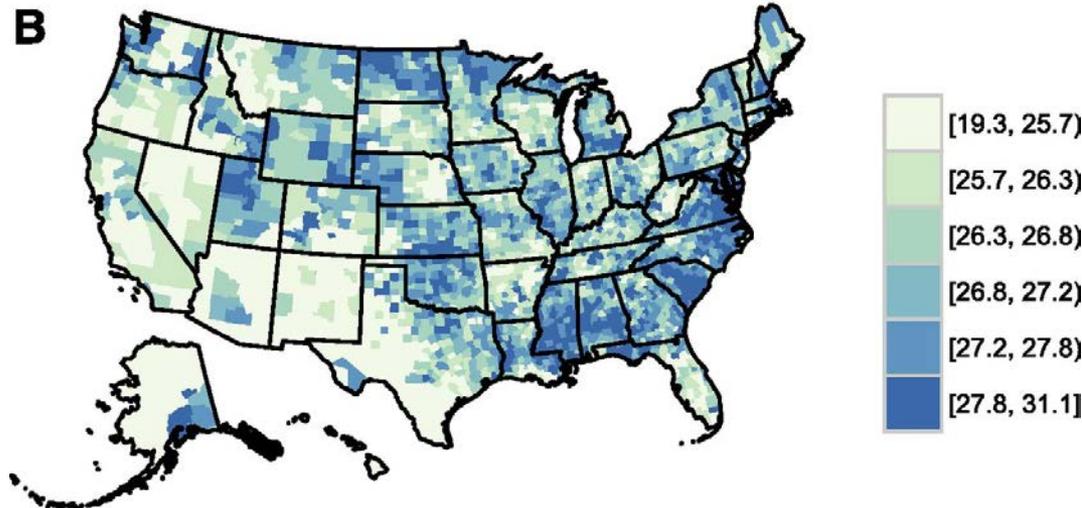
7-year-old child before and 3 months after insulin therapy



Age-standardized diabetes awareness and control by county, 2012.

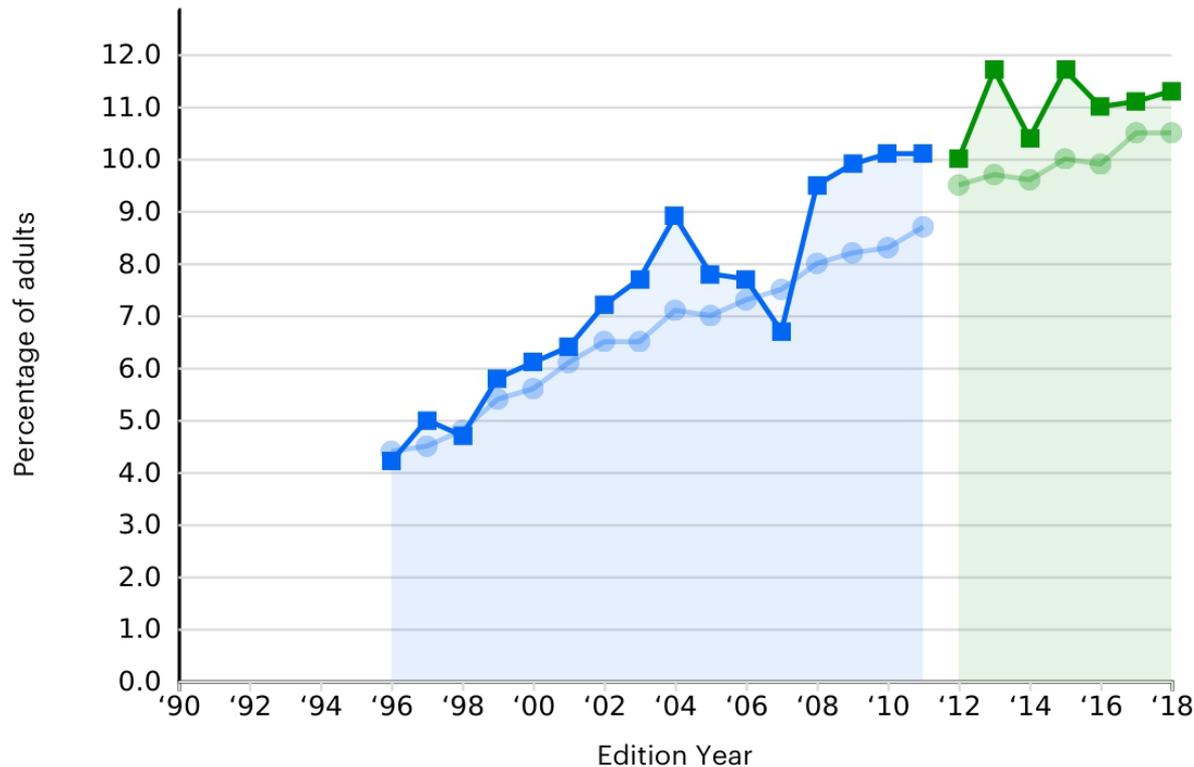


% Aware of
Diagnosis



% under control
FBG <126 mg/dl or
HbA1c <6.5%

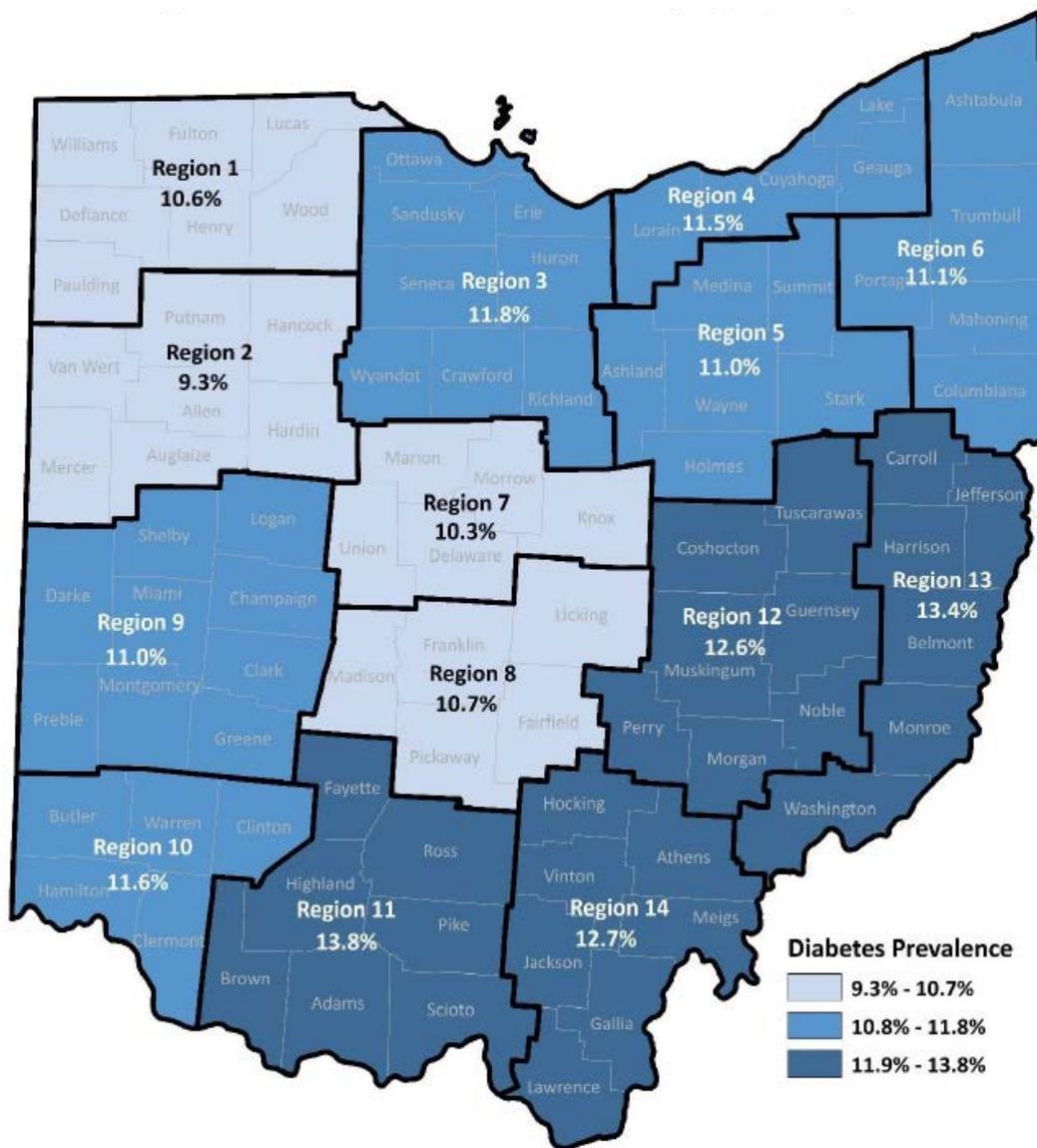
Trends in Diagnosed Diabetes, Ohio vs. US, 2018



- Ohio
- United States

<https://www.americashealthrankings.org/explore/annual/measure/Diabetes/state/OH>

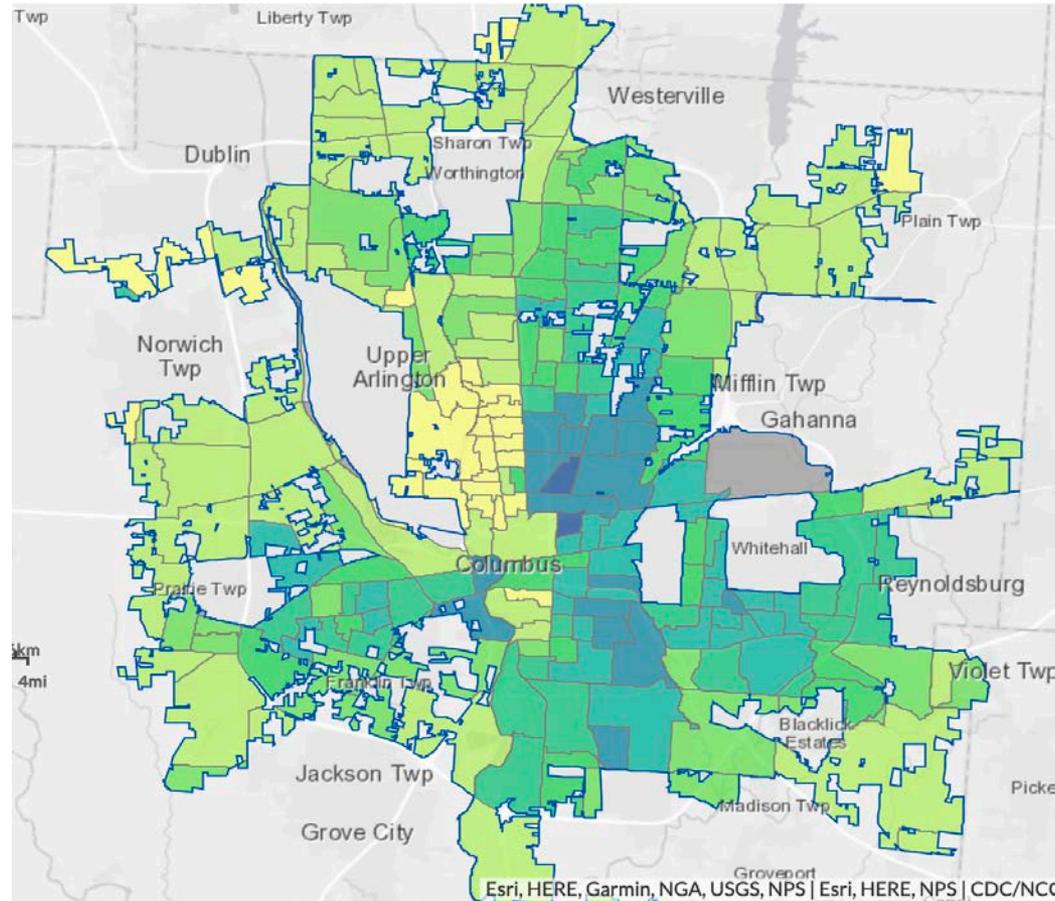
Prevalence of Diabetes by Region*, Ohio 2015



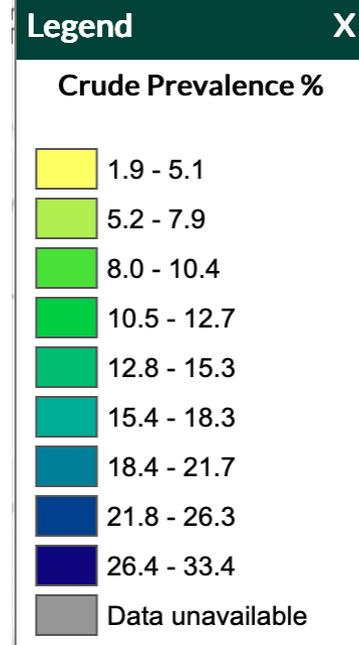
Source: 2015 Ohio Behavioral Risk Factor Surveillance System, Ohio Department of Health, 2017.

*Prevalence estimates are weighted to the 14 regions defined by the Ohio Behavioral Risk Factor Surveillance System.

Columbus: Model-based estimates for diagnosed diabetes among adults aged ≥ 18 years – 2016



Crude Prevalence %: 9.6
 Crude 95% CI: 9.6-9.7
 Age-Adjusted Prevalence %: 11.4
 Age-Adjusted 95% CI: 11.4-11.5
 2010 Census Population: 787,033



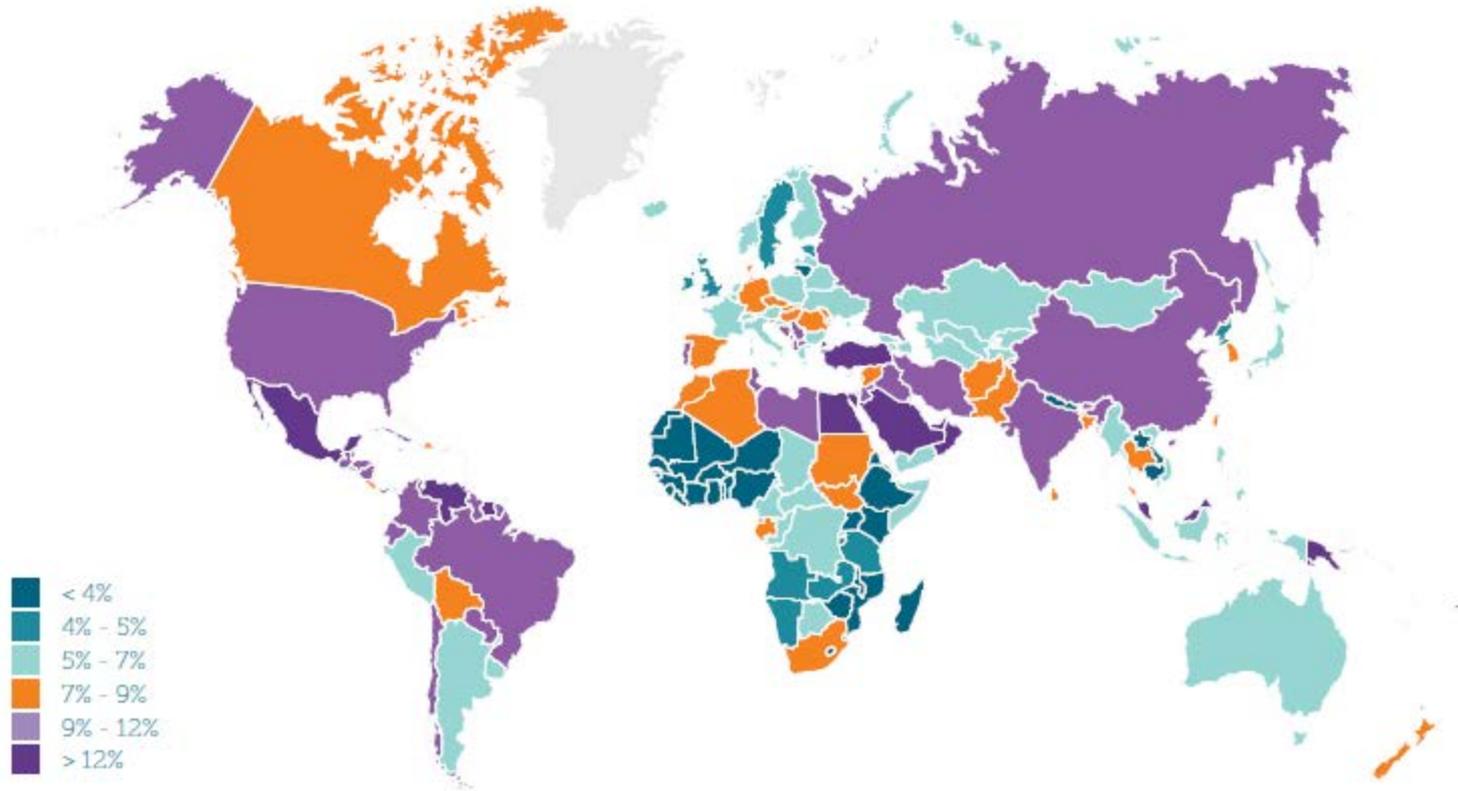
500 Cities Project - https://nccd.cdc.gov/500_Cities/

Slide courtesy of Joshua Joseph, MD. The Ohio State University



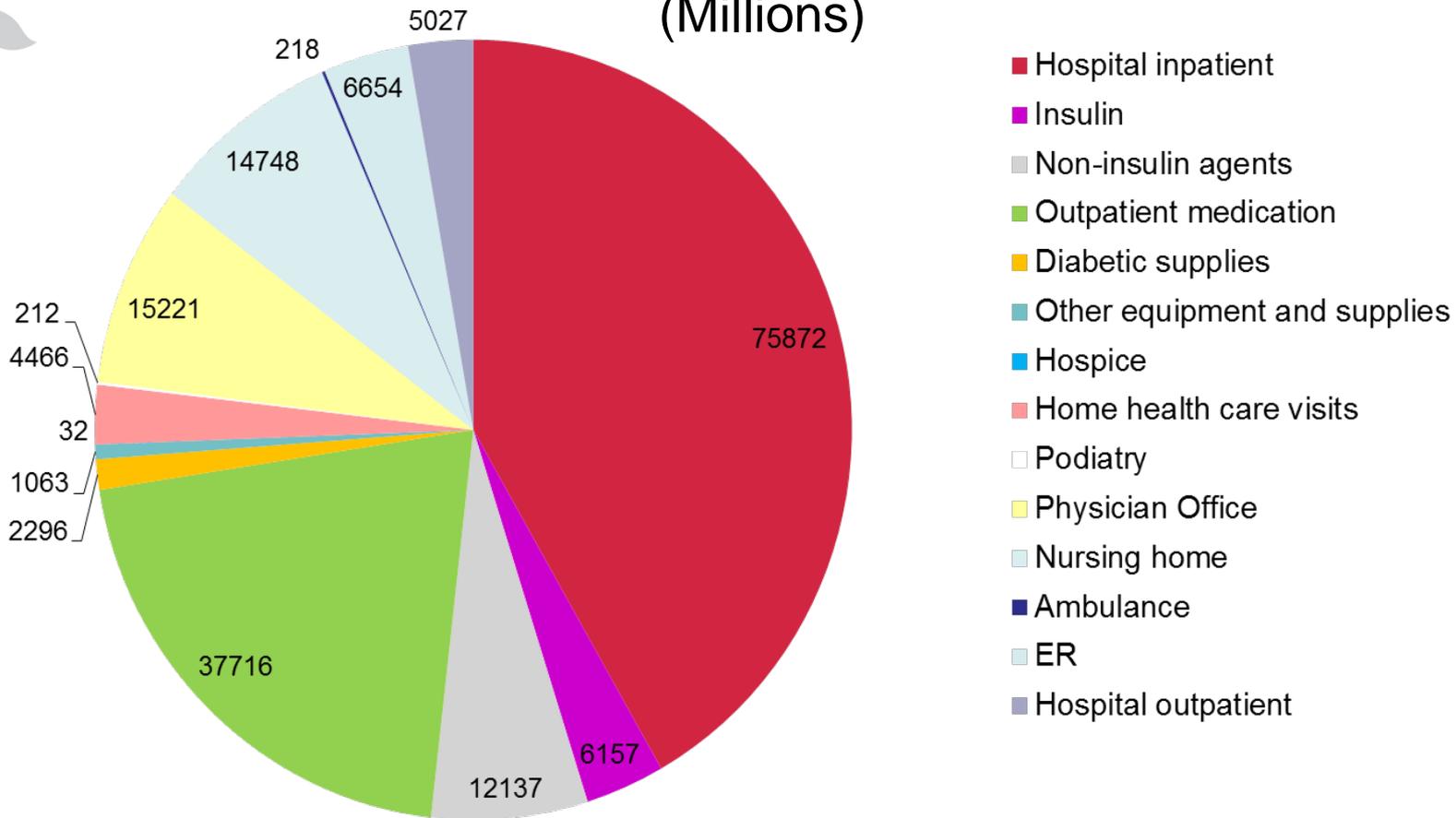
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Map 3.1 Estimated age-adjusted prevalence of diabetes in adults (20-79), 2015



Costs Due to Diabetes in 2012

(Millions)



\$176 billion (direct medical costs)

\$ 69 billion (reduced productivity)

\$245 BILLION (41% increase from 2007)

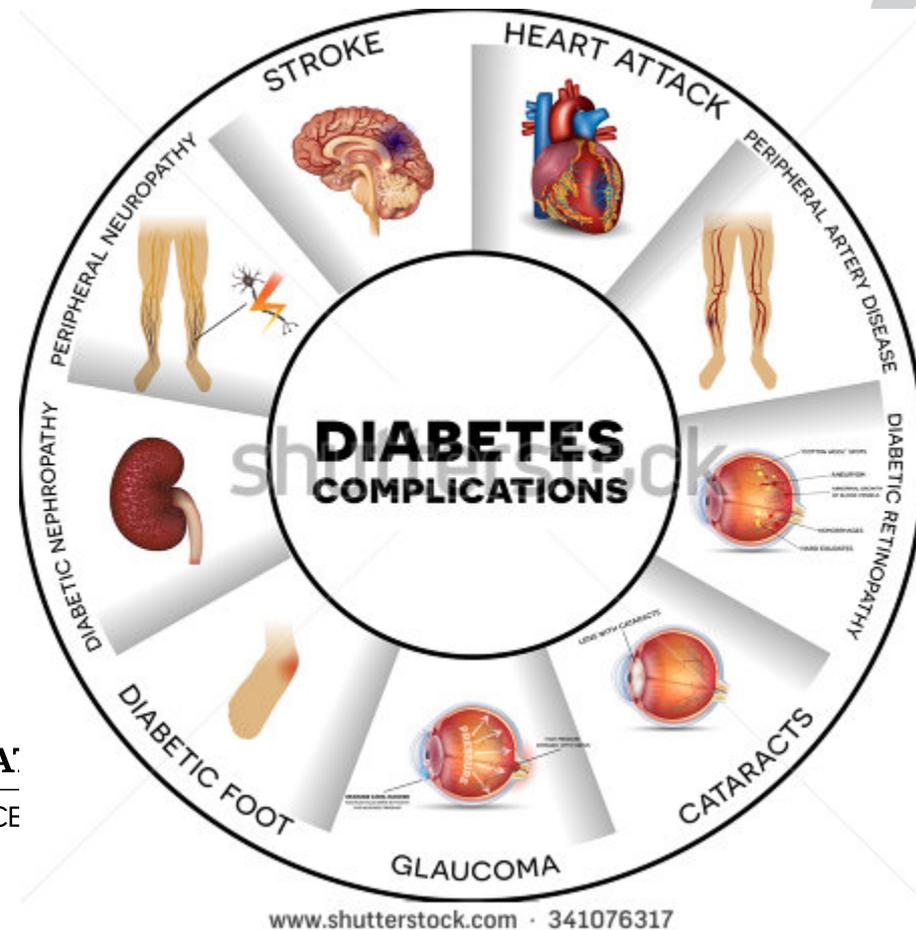
ADA. Diabetes Care 2013; 36:1033



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The Toll of Diabetes

- 7th leading cause of death in the U.S.
 - Heart attack and stroke account for 65% of deaths
- Leading cause of new blindness in adults
- Leading cause of renal failure
- Leading cause of non-traumatic lower limb amputations



TA:
LCE

Know Diabetes by Heart

Simple facts everyone should know.



People living with diabetes are **two times more likely** to develop and die from cardiovascular disease – such as heart disease, heart failure, heart attack and stroke.

:80

In the U.S., **every 80 seconds** an adult with diabetes is hospitalized for heart disease and **every 2 minutes** an adult with diabetes is hospitalized for stroke.

~ 12

For adults at age 60, having type 2 diabetes and cardiovascular disease shortens life expectancy by an average of **12 years**.



In a recent survey* of people age 45 and older with type 2 diabetes **only about half** recognize their risk or have discussed their risk for heart attacks or strokes with their health care providers.

* Conducted online by The Harris Poll

<https://knowdiabetesbyheart.org/>



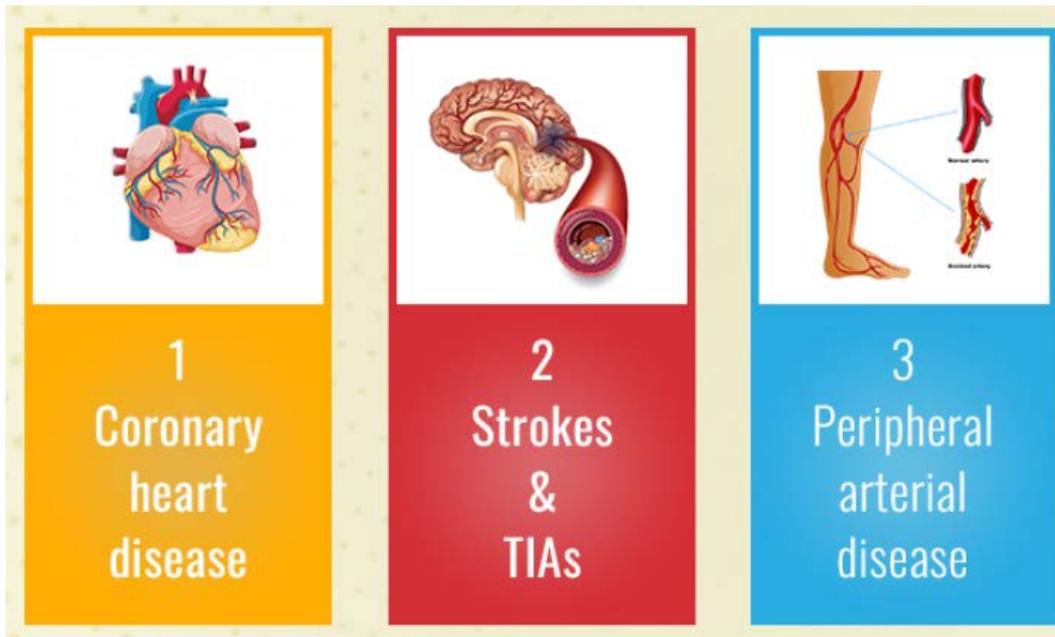
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Types of Heart and Vascular Disease related to Diabetes

Heart

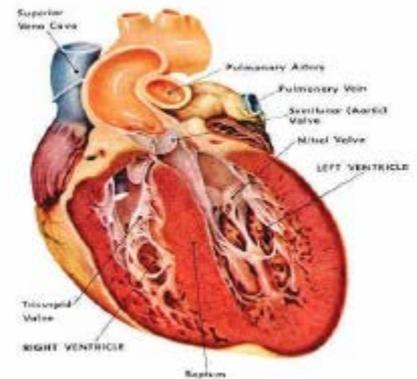
- Coronary artery disease—blood vessels to heart are blocked
- Heart failure—heart does not pump effectively
- Arrhythmia—abnormal heart rhythm

Vascular



Heart Failure

- Chronic condition by which the heart does not pump properly
- Up to 40% have diabetes
- People with diabetes have up to twice the risk of heart failure as other people.
- Caused by coronary artery disease or direct damage from glucose/lipids
- Heart muscle can become weak and dilated (low output), or stiff and thickened
- Symptoms: weakness, short of breath, fatigue, swelling



What Can I do?



Check in with your doctor regularly.
Ask about your heart health.



Continue healthy eating habits.
Add fruits and veggies as a start.
Eating better will help you *feel* better.



Keep moving. Alone or with a friend,
it can feel great.



Self-care can be heart care. Lowering your
stress is good for your mind and body.



Quit smoking. For ALL the reasons.



Monitor your blood glucose,
blood pressure, cholesterol and weight.



Take medication(s) as prescribed.

With the
assistance of
your health
care provider



Link between Diabetes, Heart Disease, and Stroke

- Conditions that increase the chance for heart disease or stroke
 - Diabetes
 - Overweight or obese
 - High blood pressure
 - High cholesterol
 - Family history of heart disease
 - Smoking



Who should be tested for diabetes?

>45 years old

Or

RISK FACTORS

(1 or more)

- Obesity/acanthosis
- CVD
- High risk ethnicity
- 1st degree relative with DM
- Gestational DM or baby > 9#
- HTN
- HDL (Good Cholesterol) < 35
- TG > 250 mg/dl
- Polycystic ovarian disease

Repeat screen every 3 years

ARE YOU AT RISK FOR TYPE 2 DIABETES?



Diabetes Risk Test

- 1 How old are you?**
 Less than 40 years (0 points)
 40—49 years (1 point)
 50—59 years (2 points)
 60 years or older (3 points)
- 2 Are you a man or a woman?**
 Man (1 point) Woman (0 points)
- 3 If you are a woman, have you ever been diagnosed with gestational diabetes?**
 Yes (1 point) No (0 points)
- 4 Do you have a mother, father, sister, or brother with diabetes?**
 Yes (1 point) No (0 points)
- 5 Have you ever been diagnosed with high blood pressure?**
 Yes (1 point) No (0 points)
- 6 Are you physically active?**
 Yes (0 points) No (1 point)
- 7 What is your weight status?**
(see chart at right)

Write your score in the box.

↓

Add up your score.

↓

Height	Weight (lbs.)		
4' 10"	119-142	143-190	191+
4' 11"	124-147	148-197	198+
5' 0"	128-152	153-203	204+
5' 1"	132-157	158-210	211+
5' 2"	136-163	164-217	218+
5' 3"	141-168	169-224	225+
5' 4"	145-173	174-231	232+
5' 5"	150-179	180-239	240+
5' 6"	155-185	186-246	247+
5' 7"	159-190	191-254	255+
5' 8"	164-196	197-261	262+
5' 9"	169-202	203-269	270+
5' 10"	174-208	209-277	278+
5' 11"	179-214	215-285	286+
6' 0"	184-220	221-293	294+
6' 1"	189-226	227-301	302+
6' 2"	194-232	233-310	311+
6' 3"	200-239	240-318	319+
6' 4"	205-245	246-327	328+
	(1 Point)	(2 Points)	(3 Points)

You weigh less than the amount in the left column (0 points)

Adapted from Bang et al., Ann Intern Med 151:775-783, 2009.
Original algorithm was validated without gestational diabetes as part of the model.

If you scored 5 or higher:
 You are at increased risk for having type 2 diabetes. However, only your doctor can tell for sure if you do have type 2 diabetes or prediabetes (a condition that precedes type 2 diabetes in which blood glucose levels are higher than normal). Talk to your doctor to see if additional testing is needed.

Type 2 diabetes is more common in African Americans, Hispanics/Latinos, American Indians, and Asian Americans and Pacific Islanders.

For more information, visit us at www.diabetes.org or call 1-800-DIABETES

Visit us on Facebook
[Facebook.com/AmericanDiabetesAssociation](https://www.facebook.com/AmericanDiabetesAssociation)



Lower Your Risk

The good news is that you can manage your risk for type 2 diabetes. Small steps make a big difference and can help you live a longer, healthier life.

If you are at high risk, your first step is to see your doctor to see if additional testing is needed.

Visit diabetes.org or call 1-800-DIABETES for information, tips on getting started, and ideas for simple, small steps you can take to help lower your risk.

<http://www.diabetes.org/diabetes-basics/prevention/diabetes-risk-test/>



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Are my children at risk?

- Type 1 diabetes

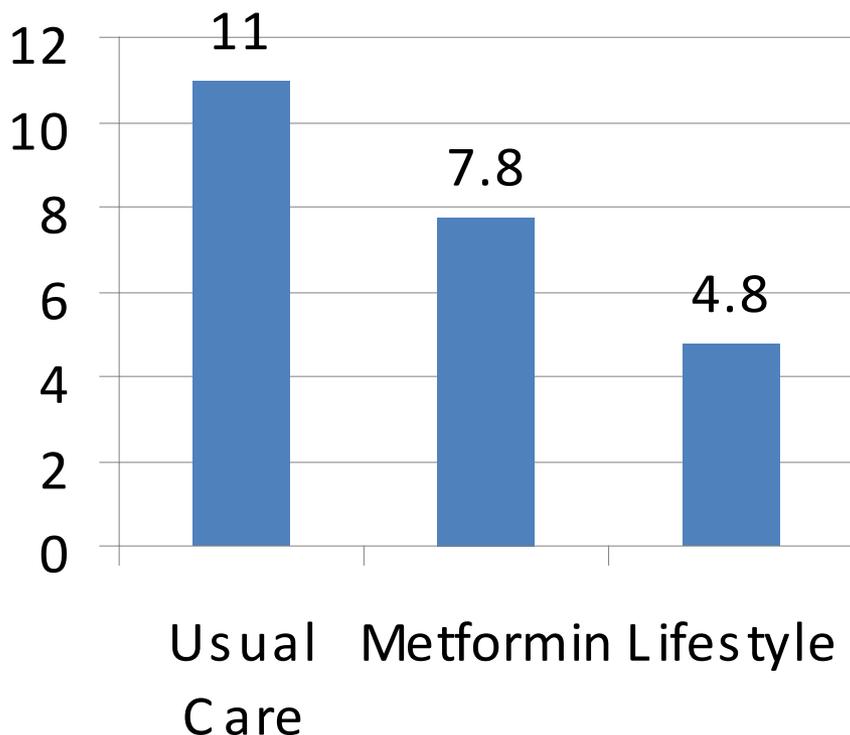
- If you are male the risk is 1 in 17
- If you are female the risk is 1 in 25 if you were diagnosed before age 25, 1 in 100 after age 25

- Type 2 diabetes

- Influenced by environmental factors
- No single gene involved
- Highest risk if
 - Sibling with DM is lean: 2x
 - Sibling + parent have DM: 3x
 - Both parents have DM: 50%, 4x

Diabetes Prevention Program

% of Patients developing Diabetes



3200 Adults with Prediabetes
Follow-up 2.8 years

Intensive lifestyle changes prevent progression from prediabetes to diabetes:

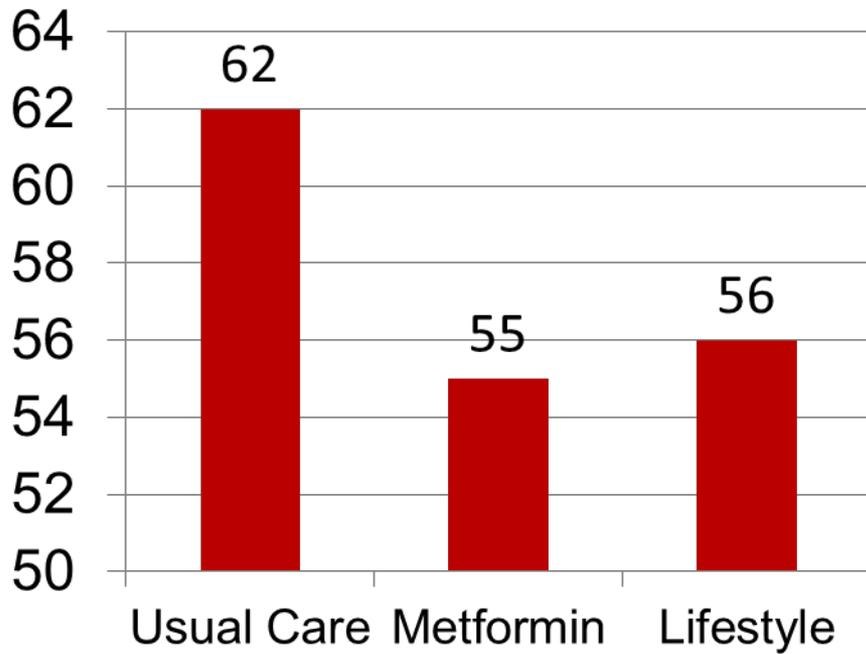
- 7% weight reduction
- Low-calorie, low fat diet
- Exercise 150 min/week
- Frequent contact with educators

N Engl J Med. 2002 Feb 7;346(6):393-403.



Diabetes Prevention Program— *15 Years Later...*

**% of Patients developing
Diabetes**



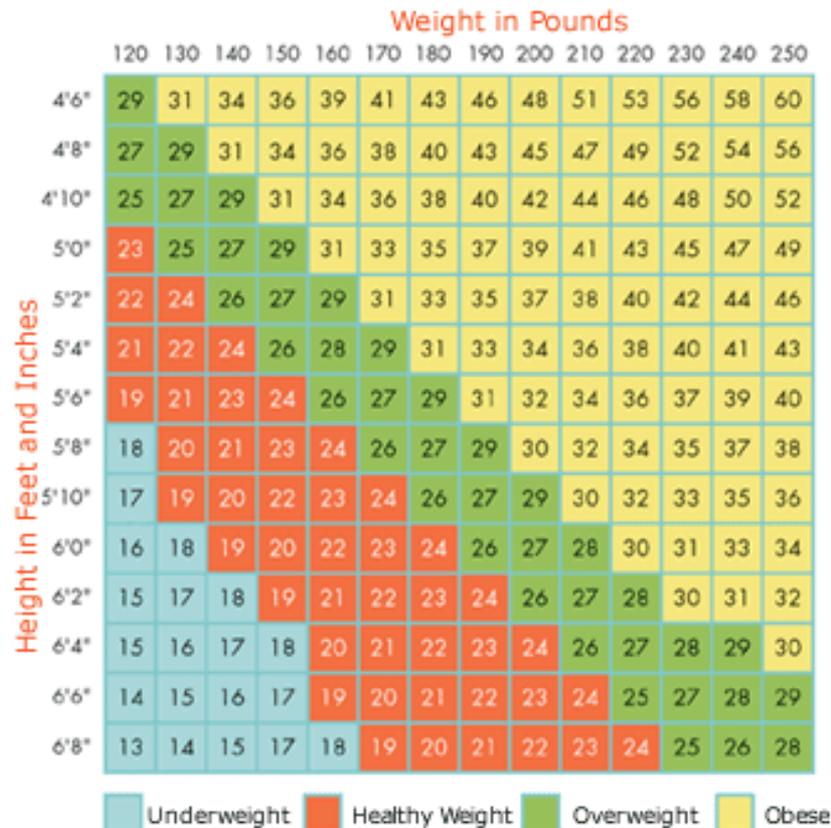
2776 Adults with
Prediabetes

Lifestyle group offered
education twice yearly

Metformin group
continued therapy

Weight loss

- The cornerstone of management for T2DM
- The goal is modest weight loss (7%): improves blood sugars and other risk factors for complications

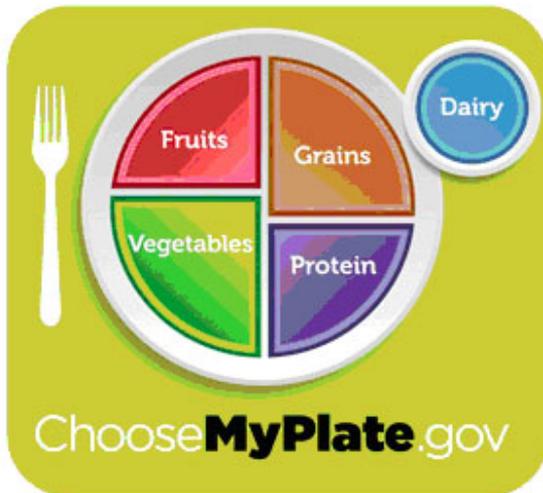


Body mass index calculation



What kind of diet should I follow?

- The most effective diet is the one that *you* can continue long-term
- Carbs:
 - The total amount is important
 - Avoid refined sugars



Fat Matters, Carbs Count, but Calories are King!

(Allan Borushek)

What about Very low carb/Keto?

- Improved sugars
- But may also increase LDL cholesterol (the bad stuff)
- High protein not recommended for people with kidney disease
- Use caution if you are taking an SGLT2 inhibitor, have type 1 diabetes or have had ketoacidosis

**CURE DIABETES
170 HOURS**



**CURE DIABETES
WITH SUGAR & RICE**



JOHN McDOUGALL MD

**KEY TO CURE
DIABETES**



CURE DIABETES



**100%
WORKS**

NATURAL

Learn to Read Nutrition Labels

1. Start here

2. Check the total calories per serving

3. Limit these nutrients

4. Get enough of these nutrients

Nutrition Facts	
Serving Size 2/3 cup (55g) Servings Per Container About 8	
Amount Per Serving	
Calories 230	Calories from Fat 72
	% Daily Value*
Total Fat 8g	12%
Saturated Fat 1g	5%
Trans Fat 0g	
Cholesterol 0mg	0%
Sodium 160mg	7%
Total Carbohydrate 37g	12%
Dietary Fiber 4g	16%
Sugars 1g	
Protein 3g	
Vitamin A	10%
Vitamin C	8%
Calcium	20%
Iron	45%
* Percent Daily Values are based on a 2,000 calorie diet. Your daily value may be higher or lower depending on your calorie needs.	
	Calories: 2,000 2,500
Total Fat	Less than 65g 80g
Sat Fat	Less than 20g 25g
Cholesterol	Less than 300mg 300mg
Sodium	Less than 2,400mg 2,400mg
Total Carbohydrate	300g 375g
Dietary Fiber	25g 30g

5. Quick Guide for % Daily Value:
5% or less is low and 20% or more is high

1. Eat plenty of fruits and vegetables.
2. Choose whole-grain foods
3. Eat fish, especially oily fish (like salmon, trout, herring).
4. Limit saturated and *trans* fats.
5. Limit red meat, choose lean meats and skinless poultry.
6. Choose low-fat dairy products, such as skim milk or low-fat yogurt.
7. Limit beverages and foods with added sugars.
8. Learn about sodium content in foods.

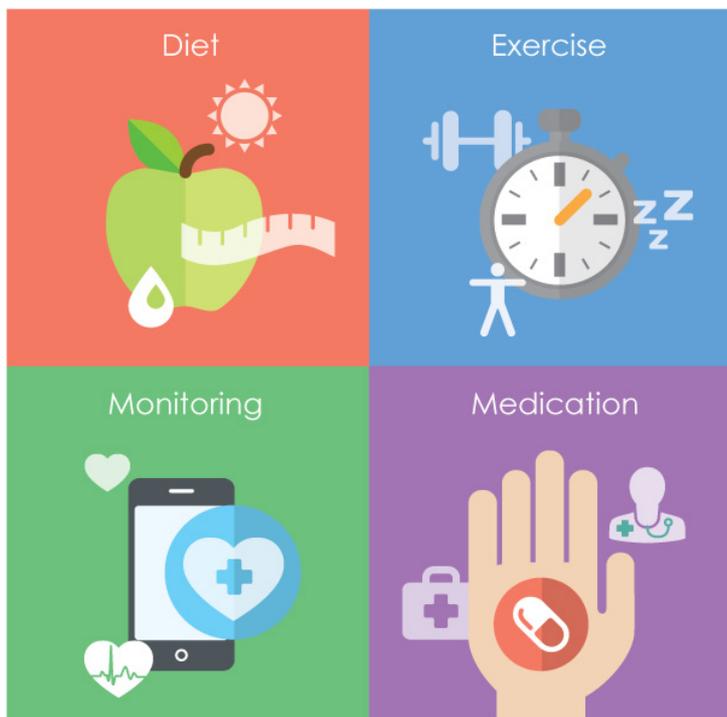
Does this mean I can't eat treats?

- If you *must* splurge
 - Portion control
 - Substitute one carb for another
 - Take an extra walk
 - Learn to count carbs and adjust your medication



But I already know what I need to do...

Learn how to take control of your diabetes with diabetes self-management education



- Is this a good sugar?
- What do I do if I'm high?
- What do I do if I'm low?
- What should I do if I'm sick?
- Should I eat that?
- How do I take this medicine?
- What kind of exercise can I do?
- How can I prevent complications?
- And many more...



Exercise

- 150 min. of moderate to vigorous aerobic activity/week
- Resistance exercise 2-3x/week
- Flexibility and balance training 2-3x/week for older adults (including yoga/tai chi)
- Important for keeping weight off
- Benefit in reducing sugars



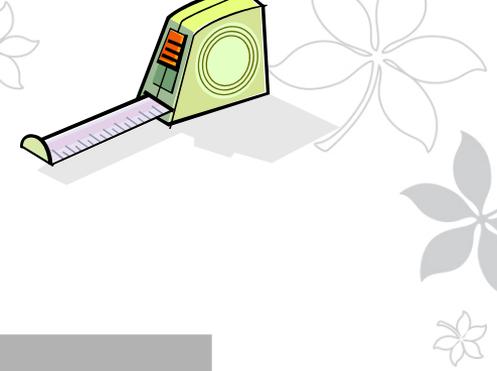
So you want to start an exercise program...

- Talk to your doctor to make sure it is safe
- You may need an exercise stress test
- See your doctor if you experience chest pain or discomfort, shortness of breath or racing heart



Where should my sugars be?

Measuring Success



	ADA ¹
A1C	<7%
Fasting/premeal glucose	90-130
Postmeal glucose	<180 (peak)

Goals should be individualized

What does my A1c mean?

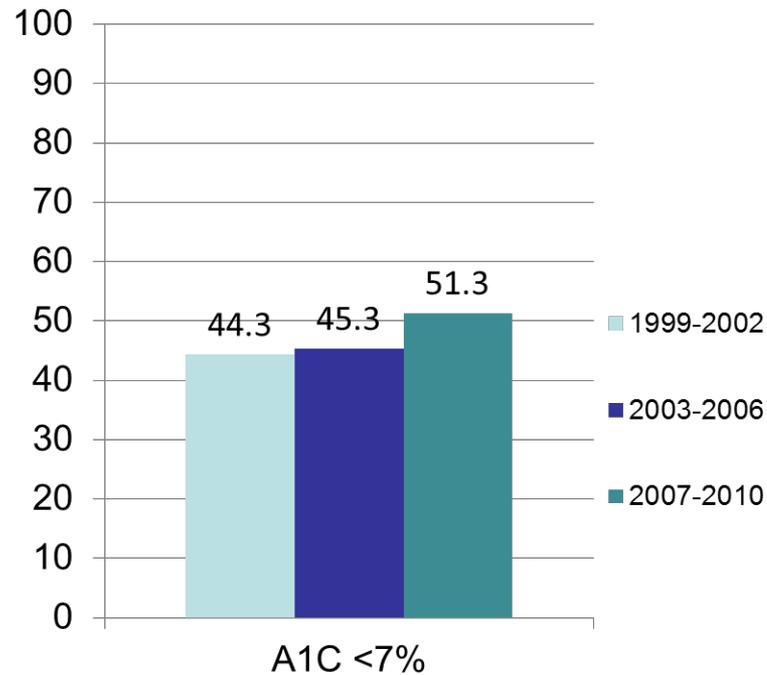
A1c %	3 Month Average Blood sugar
4.0	65
4.5	83
5.0	100
5.5	118
6.0	135
6.5	153
7.0	170
7.5	187
8.0	204
8.5	222
9.0	240
9.5	258
10.0	275
10.5	293
11.0	310
11.5	328
12.0	345

DIABETES CARE, VOLUME 25, NUMBER 2, FEBRUARY 2002



HbA1c <7% among people with diabetes in the US

NHANES Data



How often should I check?

- Depends upon medications used
 - Insulin: 3+ times/day
 - Oral Hypoglycemics: 1+ time/day

But it only improves glucose control if you use the information!



Can you find the pattern?

9/1/15	8:00	114
	12:00	214
9/2/15	7:00	85
	6:30	174
	9:00	210
9/3/15	6:30	121
	11:30	229
	7:00	72
9/4/15	7:00	112
	5:30	181
	9:00	145
9/5/15	12:00	281
	7:00	142
9/6/15	7:00	89
	11:30	210
9/7/15	6:30	121

Day	Breakfast			Lunch			Dinner			Bedtime		Night
	before	insulin	after	before	insulin	after	before	insulin	after	insulin		
Mon 11-15	82	10	128	109	12	172	15	198	209	22	21	
Tue 16	92	10	160	13	170	15	206	21	21			
Wed 17	122	10	132	13	165	15	161	22	22			
Thu 18	89	10	94	12	189	15	72	22	22			
Fri 19	118	11	95	12	212	16	188	22	22	69		
Sat 20	139	16	148	13	134	15	200	22	22	31		
Sun 21	102	10	96	12	210	16	200	22	22	31		



Connecting and Downloading



My fitness pal

Apps

Summary

831 CALORIES REMAINING

Goal	Food	Exercise	Net
1200	+ 369	- 0	369

Carbs: 40% / 55%
 Fat: 53% / 30%
 Protein: 7% / 15%

Recent News:

- Gifilein completed her food and exercise diary for 03/14/2012 and was under her calorie goal (14 hours ago)
- Gifilein burned 155 calories doing 60 minutes of "Walking, 3.0 mph, mod. pace, walking dog"

Calorie King

Categories

- Alcoholic Drinks
- Ales & Beers
- Ciders, Wines
- Coolers, Cocktails, Shooters
- Liqueurs, Liquors & Spirits
- Bars, Breakfast Cereals
- Beverages (Sports, Energy & Meal Shakes, Soda, Coffee, Tea)
- Coffee & Iced Coffee
- Energy/Nutritional Drinks & Mixes, Water
- Fruit/Vegetable Juices
- Malt, Cocoa & Hot Chocolate
- Milk & Flavored Milk
- Non Dairy Drinks: Soy, Rice, Nut, Cereal
- Soft Drinks, Soda
- Tea & Iced Tea

Apple Cinnamon Breakfast Cereals, dry
 1 cup (1.4 oz)
 Calories 160

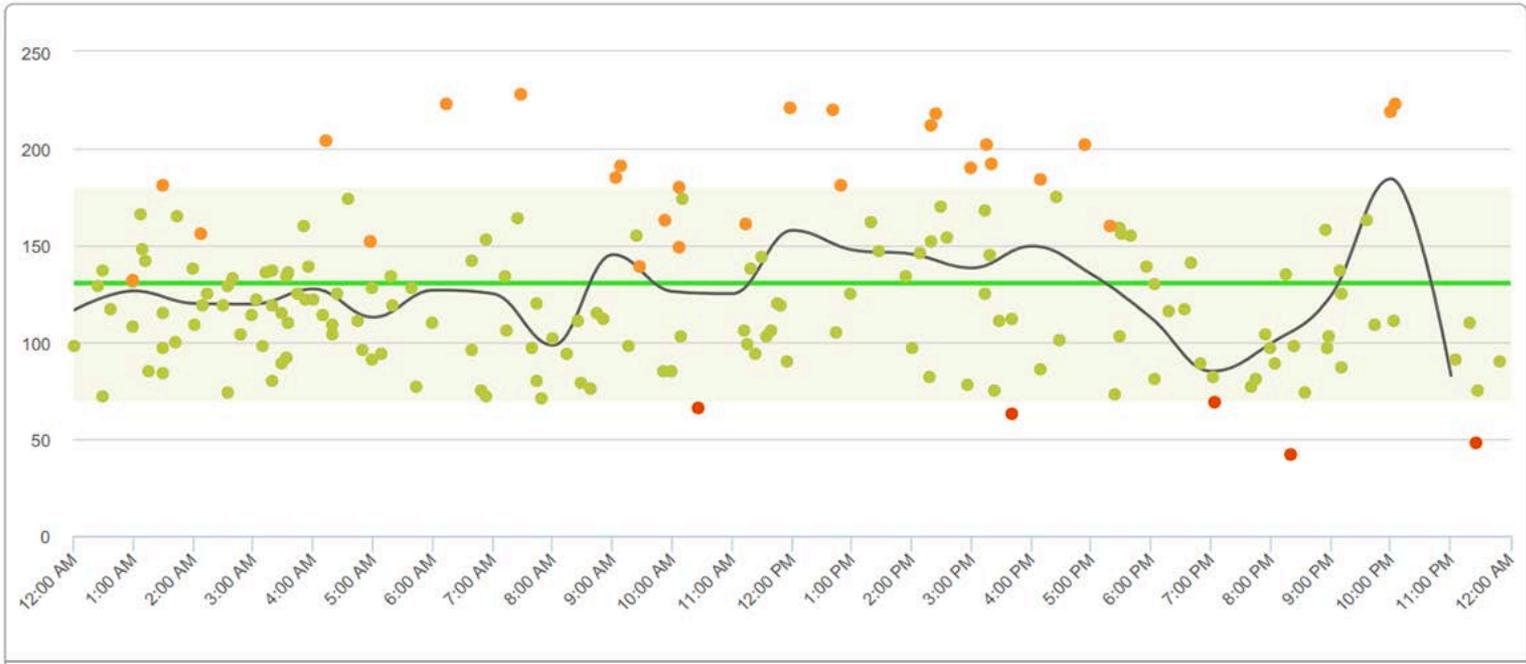
		% Daily Value
Total Fat	2g	3%
Sat. Fat	0g	0%
Trans Fat	0g	
Cholesterol	0mg	0%
Sodium	153mg	6%
Total Carbs.	32g	11%
Dietary Fiber	2.7g	11%
Sugars	13.3g	
Protein	2.7g	
Calcium	133.3mg	
Potassium	86.7mg	

Mysugr

Features:

- Your synced BGs
- Your estimated A1c
- Your CGM data
- Calculate your bolus (EU only)
- Your personal diabetes coaching (US only)

BG - Time of Day



BY TIME	ALL	MORNING	AFTERNOON	EVENING	NIGHT
		5 am - 10 am	10 am - 3 pm	3 pm - 9 pm	9 pm - 5 am
# of Readings	180	35	34	42	69
Average (mg/dL)	124	122	137	120	122
Standard Dev	39	41	43	42	33
Low (mg/dL)	42	71	66	42	48
High (mg/dL)	228	228	221	202	223

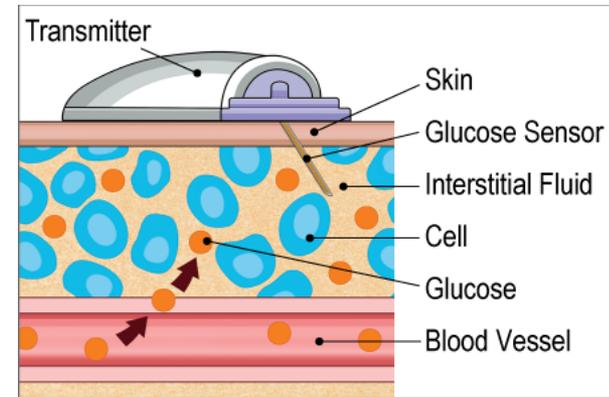
— Before Meal Upper Limit: 130
 Target Range: 70-180
 ● Below
 ● In Range
 ● Above
 — Average line

CGM: continuous glucose monitoring

- Eras of glucose measurement



- Tiny filament just under the skin samples glucose levels every 5 minutes
- **Replace** frequent glucose checks!



CGM Components



The diagram shows three components of the Eversense CGM system: a small rectangular sensor, a black square smart transmitter, and a smartphone displaying a mobile app. The app screen shows a large number '109 mg/dL' and a line graph. A Bluetooth symbol is positioned between the transmitter and the app.

Sensor Smart Transmitter Mobile App

Eversense



The image shows the Freestyle Libre CGM system. It includes a handheld receiver device with a screen displaying '112 mg/dL', a circular sensor, and a smartphone displaying a mobile app with a screen showing '112 mg/dL'. A black double-headed arrow indicates the connection between the receiver and the smartphone.

Sensor

Freestyle Libre



The image shows the Dexcom CGM system. On the left, a close-up of the transmitter and sensor is shown with arrows pointing to each. In the center, a person's abdomen has a sensor patch applied. On the right, a smartphone displays the Dexcom mobile app with a screen showing '110 mg/dL' and a line graph. The word 'Receivers' is written above the smartphone.

Transmitter

Sensor

Receivers

Dexcom



The image shows the Medtronic CGM system. It includes a handheld receiver device with a screen displaying '110 mg/dL', a circular sensor, and a smartphone displaying the Medtronic mobile app with a screen showing 'Blood Sugar' and a line graph. Labels 'Recorder', 'Sensor', and 'Server' are placed near the receiver device.

Server

Recorder

Sensor

Medtronic

So many drugs...

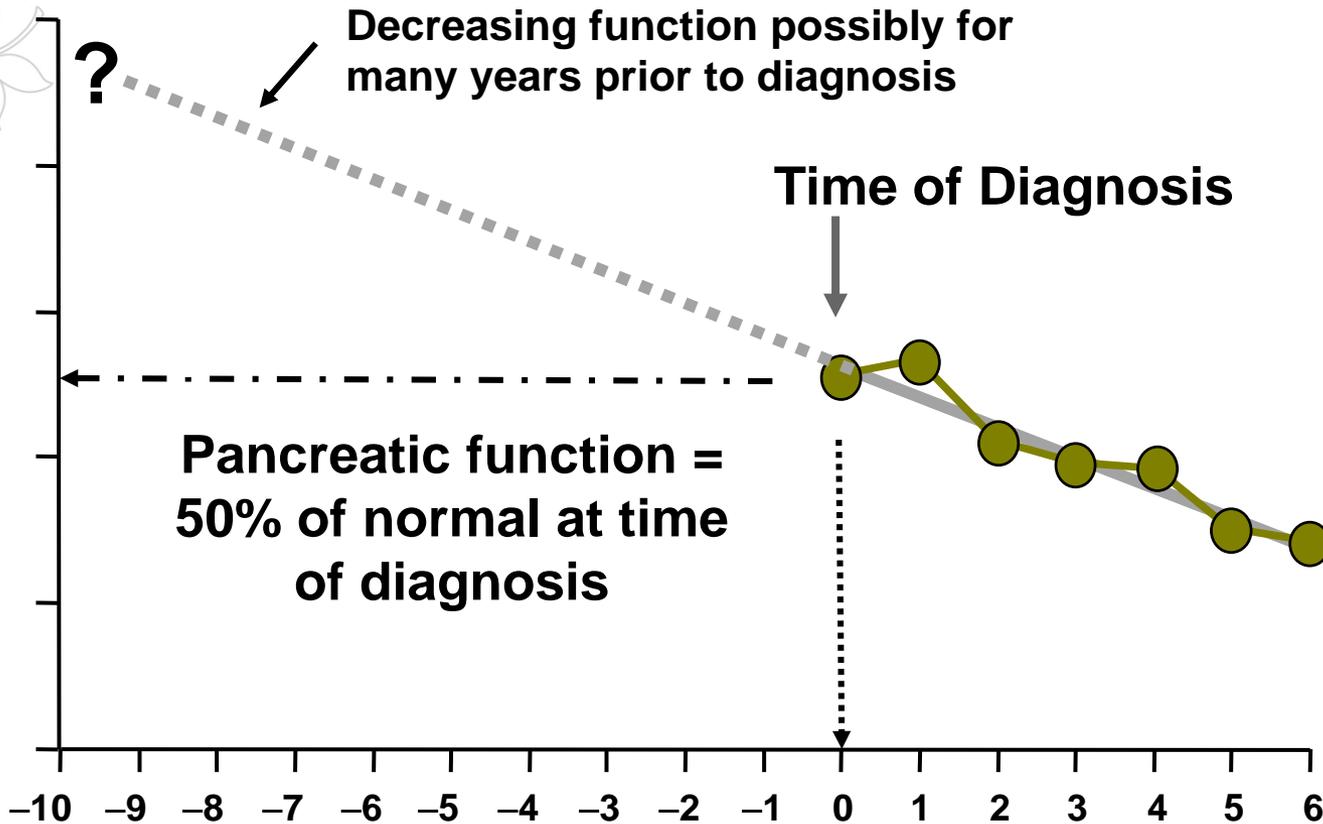
In general, treatment has to be tailored to fit you

- Effectiveness
- Safety
- Hypoglycemia
- Cost
- Weight gain



But it worked for me before!

Declining Pancreas Function in T2DM



Adapted from Holman RR. *Diabetes Res Clin Pract.* 1998;40(suppl):S21-S25.

UKPDS Group. *Diabetes.* 1995;44:1249-1258. Reproduced with permission from Elsevier.



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Long-term safety

- The FDA requires all new diabetes drugs to demonstrate long-term safety to the heart
 - Requires very large trials ~10,000 patients
 - Patients usually have known vascular disease
 - Typically 3-5 years



The first diabetes drug to demonstrate reduced cardiac events

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

“...significantly lower rates of **death from cardiovascular causes** (3.7%, vs. 5.9% in the placebo group; 38% relative risk reduction), **hospitalization for heart failure** (2.7% and 4.1%, respectively; 35% relative risk reduction), and **death from any cause** (5.7% and 8.3%, respectively; 32% relative risk reduction).”

Longest Study to Date

Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial



Hertzel C Gerstein, Helen M Colhoun, Gilles R Dagenais, Rafael Diaz, Mark Lakshmanan, Prem Pais, Jeffrey Probstfield, Jeffrey S Riesmeyer, Matthew C Riddle, Lars Rydén, Denis Xavier, Charles Messan Atisso, Leanne Dyal, Stephanie Hall, Purnima Rao-Melacini, Gloria Wong, Alvaro Avezum, Jan Basile, Namsik Chung, Ignacio Conget, William C Cushman, Edward Franek, Nicolae Hancu, Markolf Hanefeld, Shaun Holt, Petr Jansky, Matyas Keltai, Fernando Lanas, Lawrence A Leiter, Patricio Lopez-Jaramillo, Ernesto German Cardona Munoz, Valdis Pirags, Nana Pogossova, Peter J Raubenheimer, Jonathan E Shaw, Wayne H-H Sheu, Theodora Temelkova-Kurktschiev, for the REWIND Investigators*

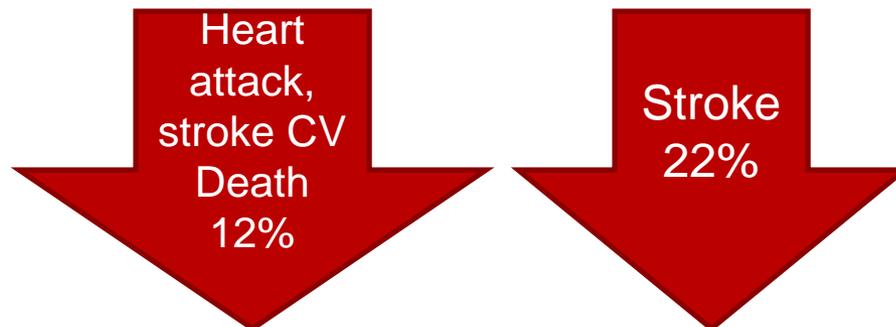
Summary

Background Three different glucagon-like peptide-1 (GLP-1) receptor agonists reduce cardiovascular outcomes in *Lancet* 2019; 394: 121-30

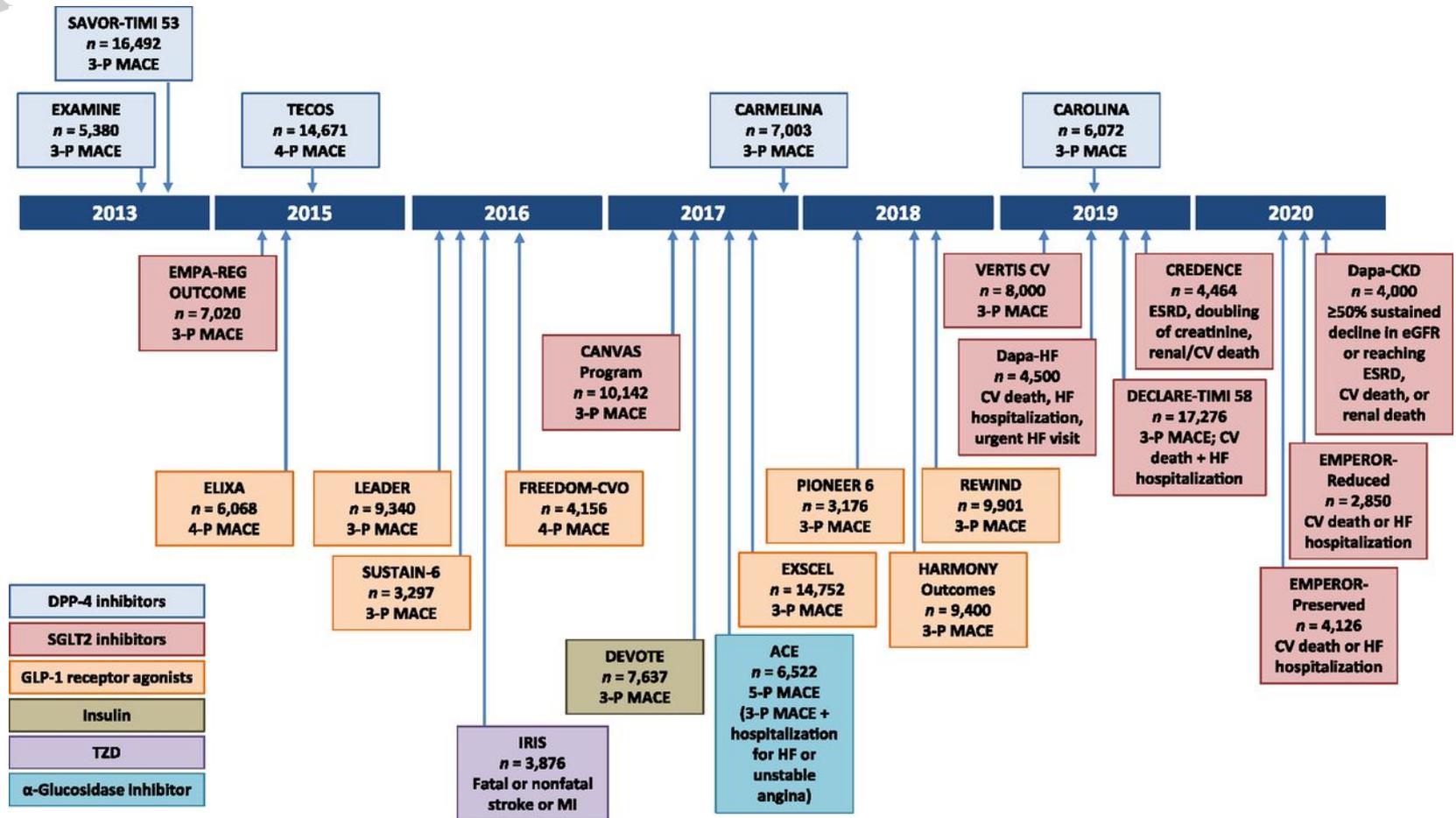
9901 participants

5.4 years

Previous cardiovascular disease at baseline: 31%

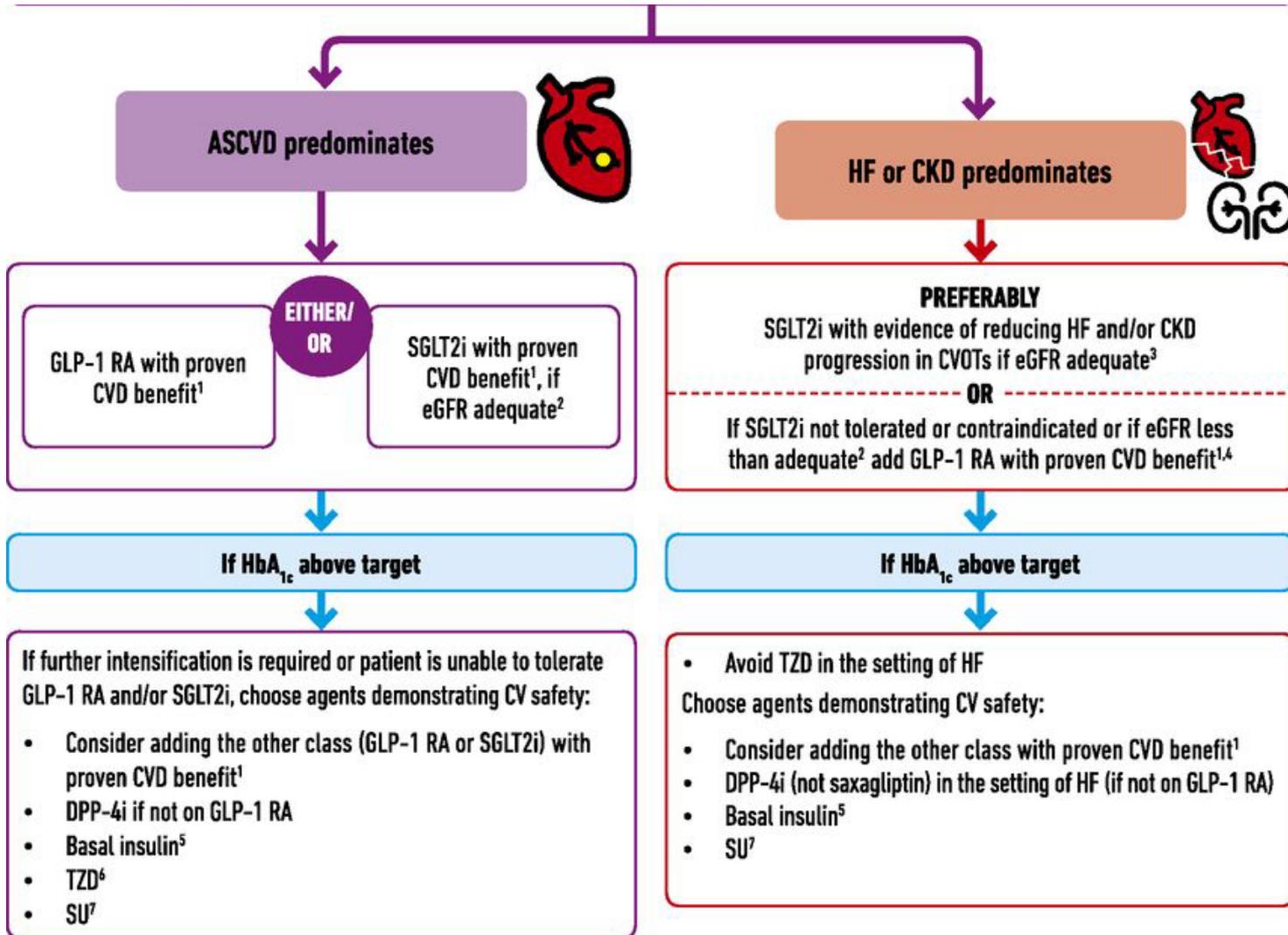


Completed and ongoing CVOTs



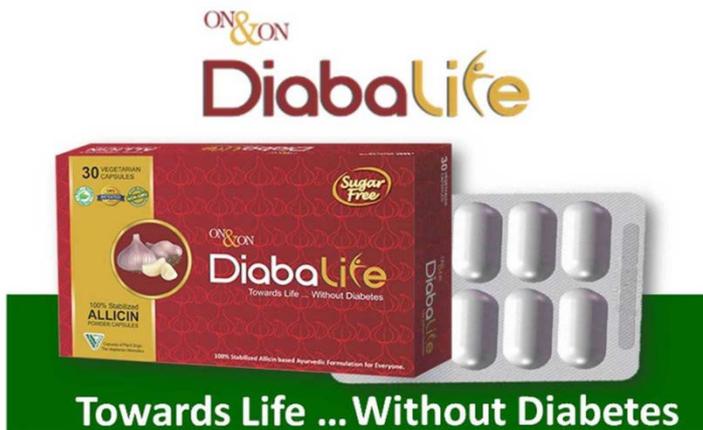
3-P, 3-point; 4-P, 4-point; 5-P, 5-point.
William T. Cefalu et al. Dia Care 2018;41:14-31

Choosing glucose-lowering medication in established Cardiovascular disease (ASCVD), heart failure (HF) or chronic kidney disease (CKD)



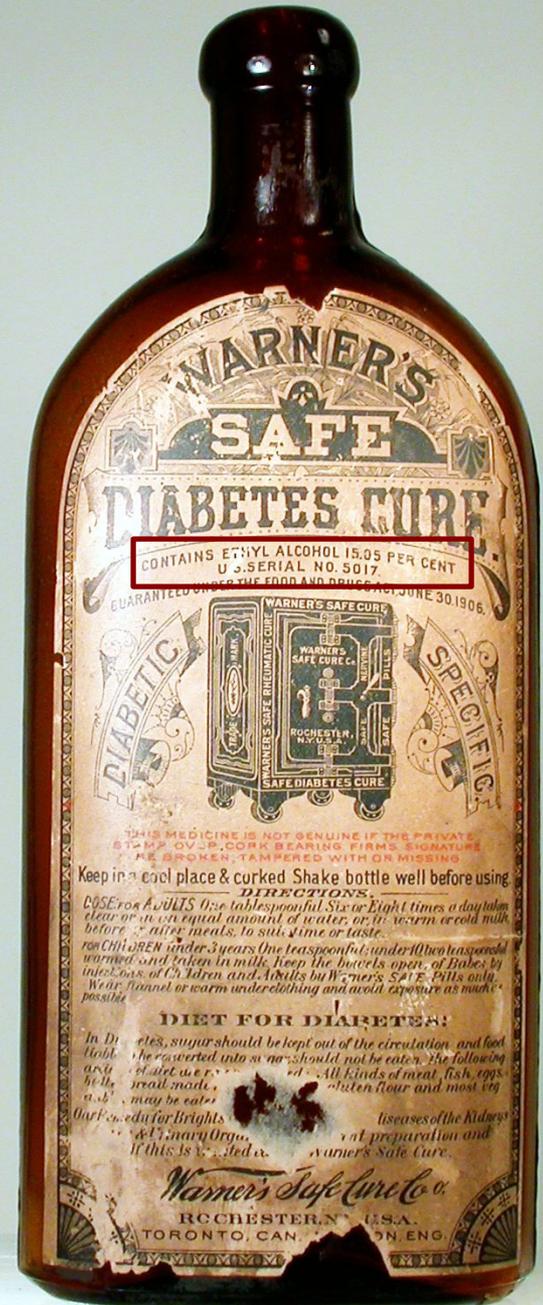
Should I take this supplement?

- Supplements not regulated by FDA
 - Not required to demonstrate safety or effectiveness
 - Contents may not be consistent with the label
- “Natural” does not necessarily mean “safe”

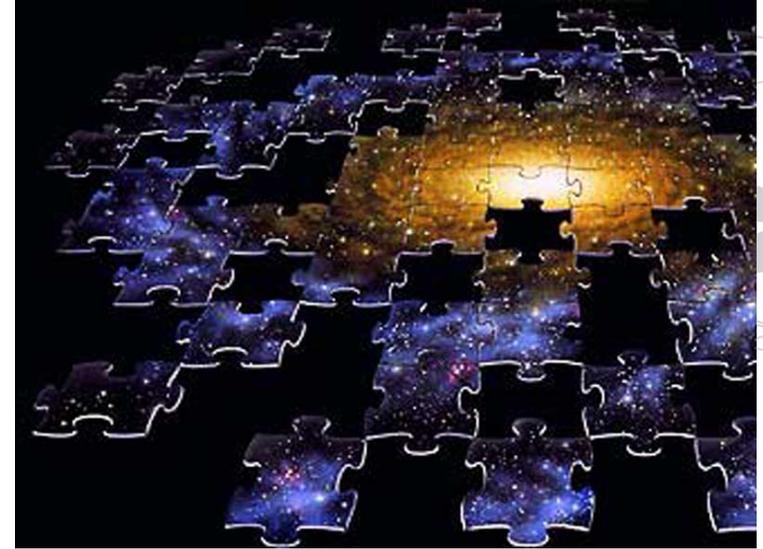


- (1) A medicine which is CURING diabetes 100%.....
- (2) Its going to work on both types of diabetes.....
- (3) Let us make India free from diabetes.....
- (4) Contact me for purchase the product...

(M)8128746329



Global Treatment of T2DM



- **Glucose control is only one of the pieces of the puzzle for diabetes**
- **Aggressive therapy is necessary for**
 - Blood pressure
 - Cholesterol
- **Aggressive multiple risk factor interventions prevent complications**

KEY TESTS/EXAMS

Hemoglobin A1c

**Quarterly if treatment change
Twice yearly if stable**

Dilated eye exam

Yearly

Foot exam

Yearly (at risk more often)

Lipid profile

1-2 years

Urine Microalbumin

Yearly

Blood pressure

Each visit

Weight

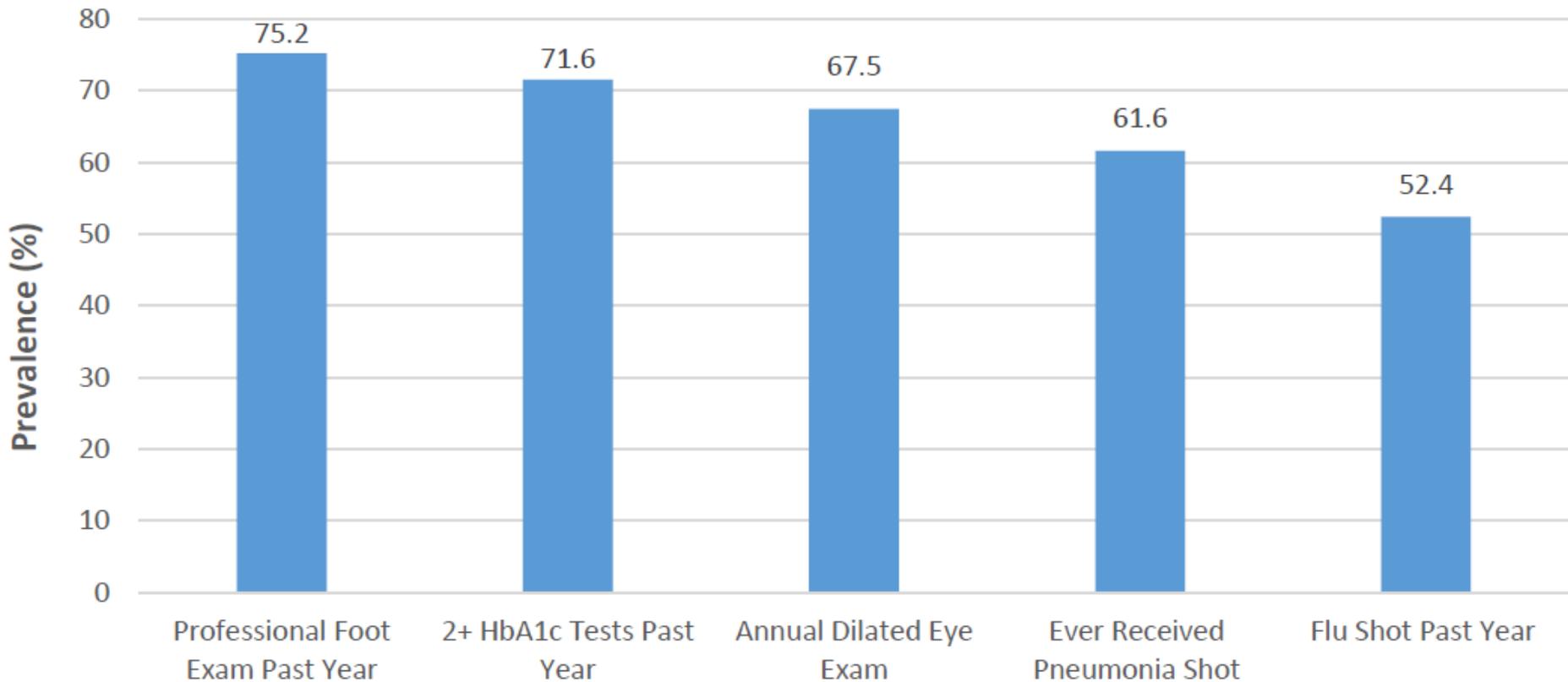
Each visit

GYN/family planning

Each visit



Prevalence of Professional Diabetes Care Measures, Ohio 2014

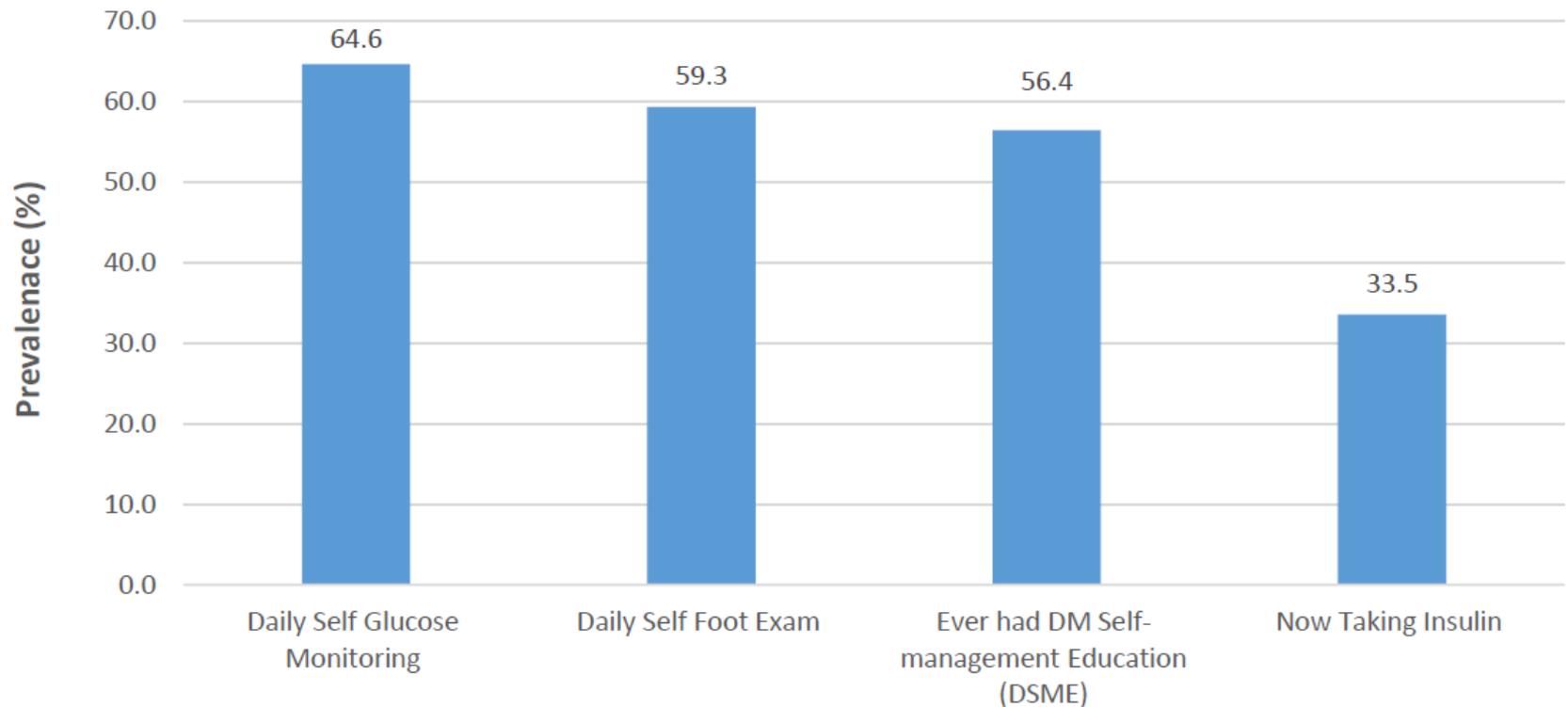


Source: 2014 Ohio Behavioral Risk Factor Surveillance System, Ohio Department of Health, 2017.

*Diabetes care measures were not collected in 2015.



Prevalence of Self Diabetes Care Measures, Ohio 2014



Source: 2014 Ohio Behavioral Risk Factor Surveillance System, Ohio Department of Health, 2017.

*Diabetes care measures were not collected in 2015.



Common Diabetes Myths

- There is no diabetes in my family, so I don't have to worry
- I have seen the effects of diabetes on my family so there is nothing I can do about it
- I developed diabetes because I eat too much sugar
- If I get diabetes I can never eat any sugar
- I can tell my sugar is high so I don't need to check it
- I don't have to worry because my doctor said I have "borderline diabetes"
- Metformin causes kidney damage
- Insulin causes complications
- I don't need to do anything about my diabetes because I plan to lose weight.



When to see a specialist

- There are 25 million people with diabetes and only 3000 Endocrinologists!
- Many primary care providers have dedicated programs or teams
- Diabetes self-management education programs
- Reasons for referral:
 - Uncontrolled despite working closely with your team
 - Special devices (insulin pumps)
 - Severe hypoglycemia



Conclusions

- Diabetes places a substantial clinical and economic burden on the U.S.
- Lifestyle changes, as part of a multi-pronged approach, can prevent or delay DM and prevent complications
- Glucose lowering therapy should be individualized and goal-directed

