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Ohio Cardiovascular and Diabetes Health Collaborative



In partnership with:



The Intersection of Weight Management and Diabetes Care

February 22, 2023



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Ohio Cardiovascular and Diabetes Health Collaborative

Welcome

Shari Bolen, MD, MPH
Co-Principal Investigator, Cardi-OH

Case Western Reserve University School of Medicine

About Cardi-OH

Founded in 2017, the mission of Cardi-OH is to improve cardiovascular and diabetes health outcomes and eliminate disparities in Ohio's Medicaid population.

WHO WE ARE: An initiative of health care professionals across Ohio's seven medical schools.

WHAT WE DO: Identify, produce, and disseminate evidence-based cardiovascular and diabetes best practices to primary care teams.

HOW WE DO IT: Best practices resources are available via an online library at Cardi-OH.org, including monthly newsletters, podcasts, webinars, and virtual clinics using the Project ECHO® virtual training model.

Learn more at Cardi-OH.org



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- The following speakers have no relevant financial interest or affiliation with any organizations that could be perceived as a real or apparent conflict of interest in the context of the subject of their presentation:
 - Shari Bolen, MD, MPH; Benjamin O'Donnell, MD; Amy Zack, MD
- The following members of the planning committee do not have any disclosures or financial relationships from any ineligible companies:
 - Richard Cornachione; Carolyn Henceroth; Gillian Irwin; Michael W. Konstan, MD; Elizabeth Littman; Devin O'Neill; Steven Ostrolencki; Ann Nevar; Claire Rollins; Catherine Sullivan

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Agenda

Topics	Presenter(s)	Timing
Welcome and Overview	Shari Bolen, MD, MPH	5 mins.
The Intersection of Weight Management and Diabetes Care	Benjamin O'Donnell, MD	40 mins.
Audience Question and Answer	Amy Zack, MD (Moderator) Benjamin O'Donnell, MD	10 mins.
Next Steps and Wrap Up	Shari Bolen, MD, MPH	5 mins.



Benjamin O'Donnell, MD
The Ohio State University Wexner
Medical Center



Amy Zack, MD (Moderator)
Case Western Reserve University
School of Medicine



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The Intersection of Weight Management and Diabetes Care

Benjamin O'Donnell, MD

Assistant Professor

Division of Endocrinology, Diabetes, and Metabolism

Medical Director, Medical Weight Management

The Ohio State University Wexner Medical Center

Objectives

- Describe the epidemiology of obesity and its intersection with diabetes.
- Understand the roles of glucagon-like peptide-1 receptor agonists (GLP-1 RA) and sodium-glucose cotransporter-2 inhibitors (SGLT2i) for diabetes and weight loss.
- Prescribe effective and necessary lifestyle modifications as an accompaniment to pharmacological therapy.

Case Presentation - 1

- 65-year-old male presents to discuss options for weight loss. Previously seen in the weight management clinic, last visit in Feb 2020 (had been on lorcaserin, had to stop at that time due to the medication recall). At his initial visit, he described being overweight all of his life, including while in the military and as a child.
- Weight at initial visit June 2019: 443 lbs; Feb 2020: 360 lbs
- Maintained his weight through early part of the pandemic
- Returned April 2022 with weight of 353 lbs, BMI 49.2

Case Presentation - 2

- Past medical history:
 - Type 2 diabetes (T2D), atrial fibrillation, obstructive sleep apnea (OSA), cardiomyopathy but preserved ejection fraction
 - Had COVID in Jan 2022, mod-severe course, required oxygen
 - Minimally mobile, uses a motorized scooter
- Medications:
 - Metformin 1000 mg twice a day, liraglutide 1.8 mg daily
 - Apixaban, Lasix, fluticasone inhaler
- Labs:
 - A1C: 6.5%

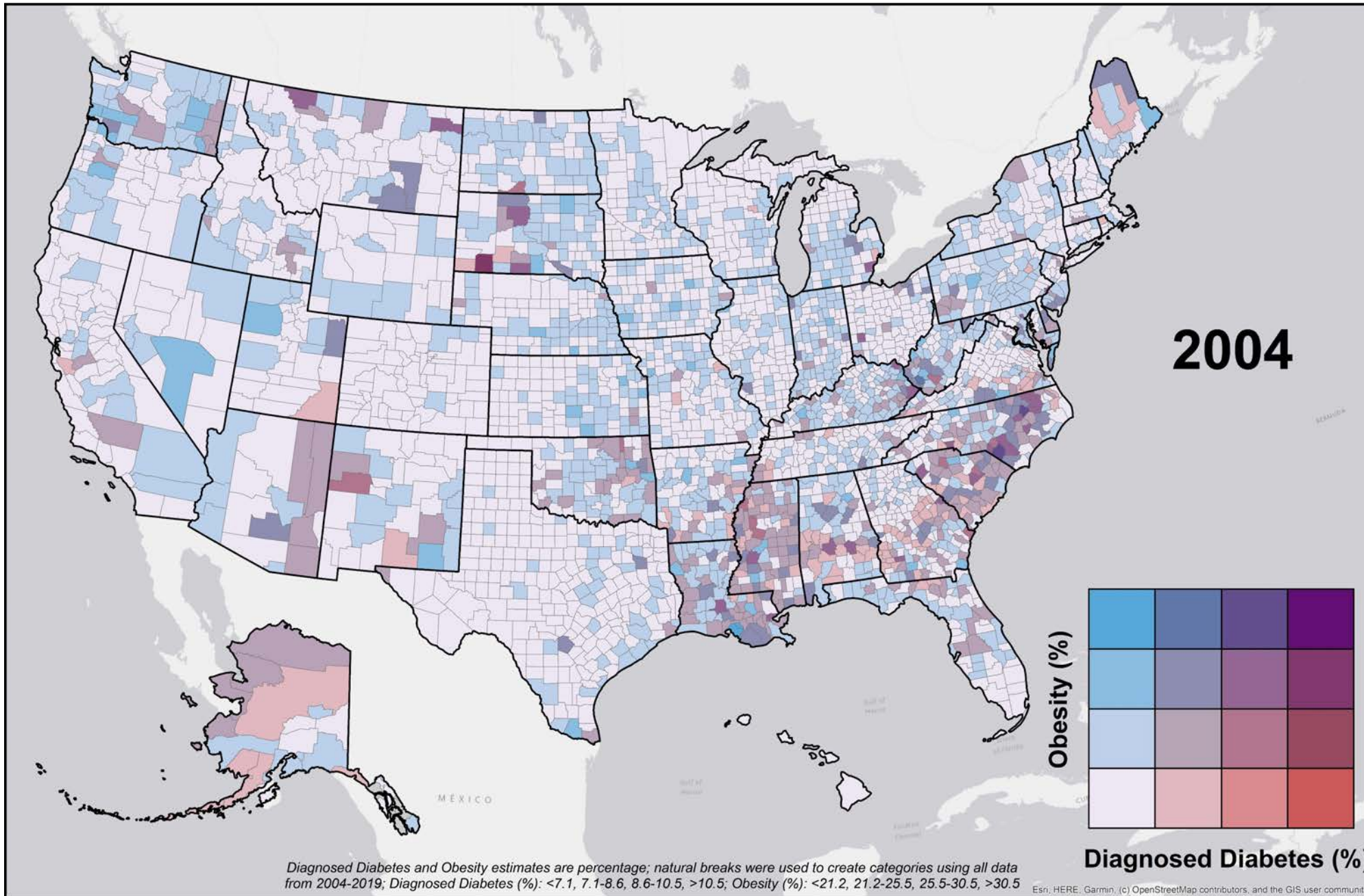


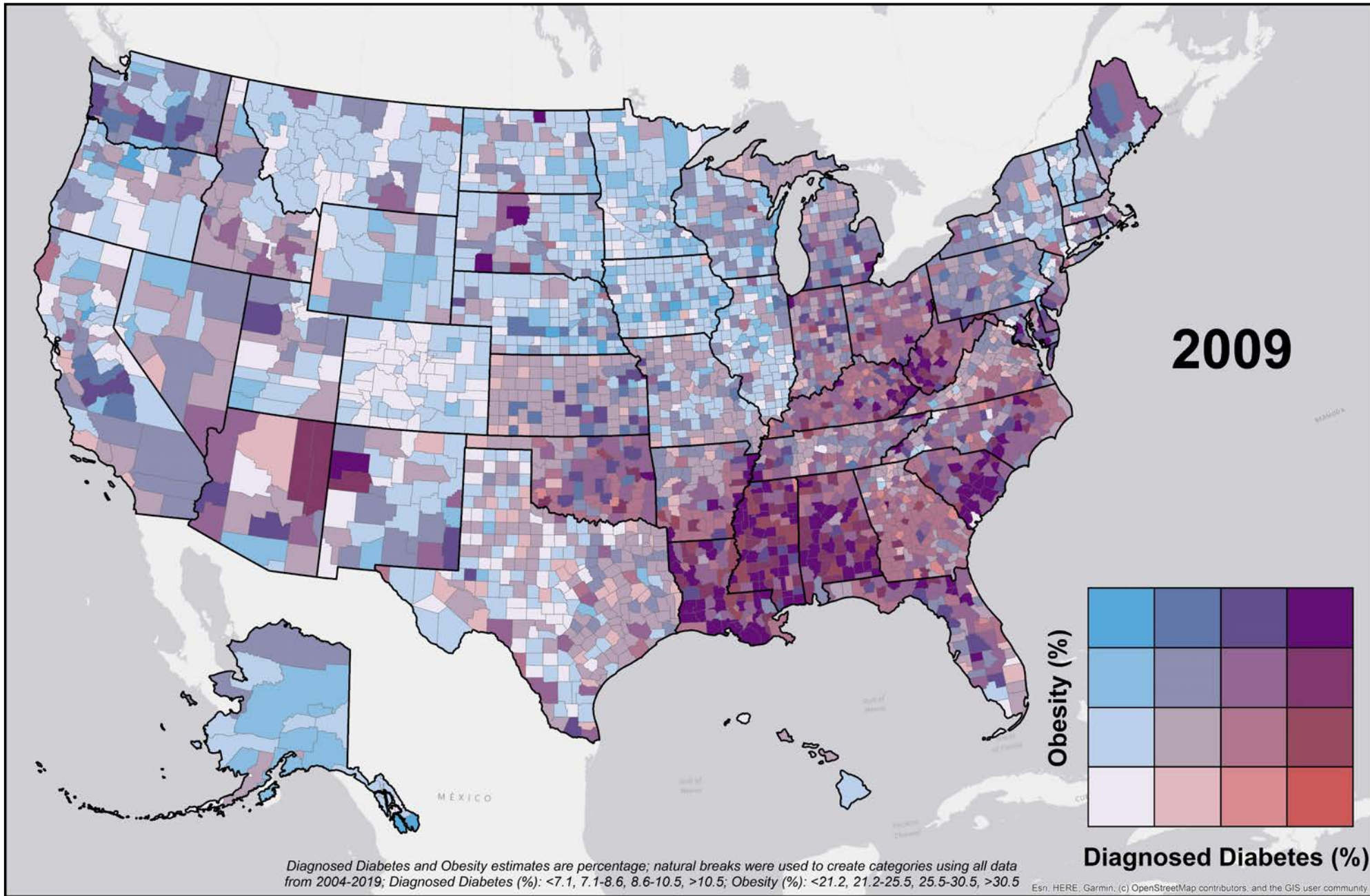
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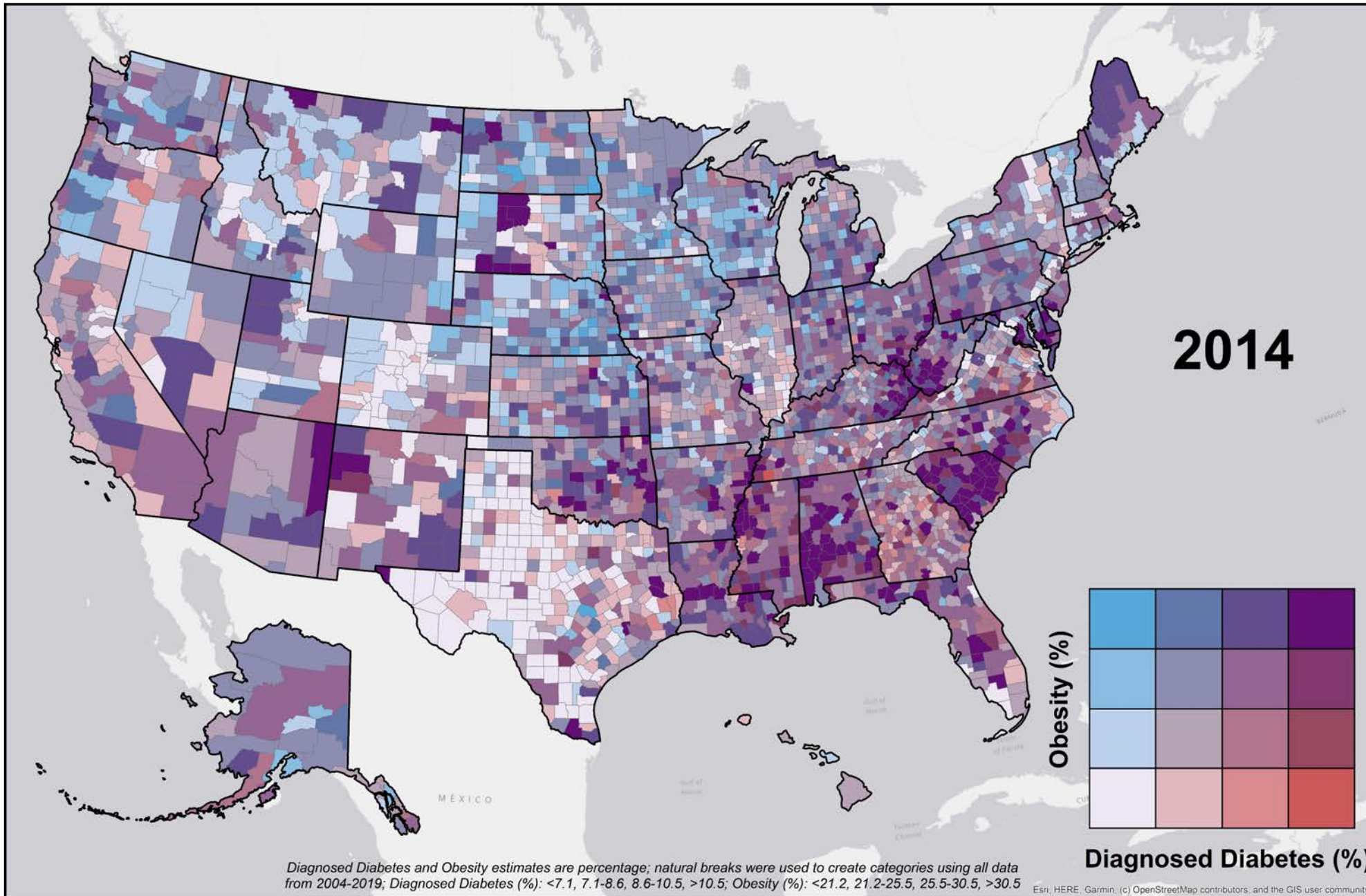
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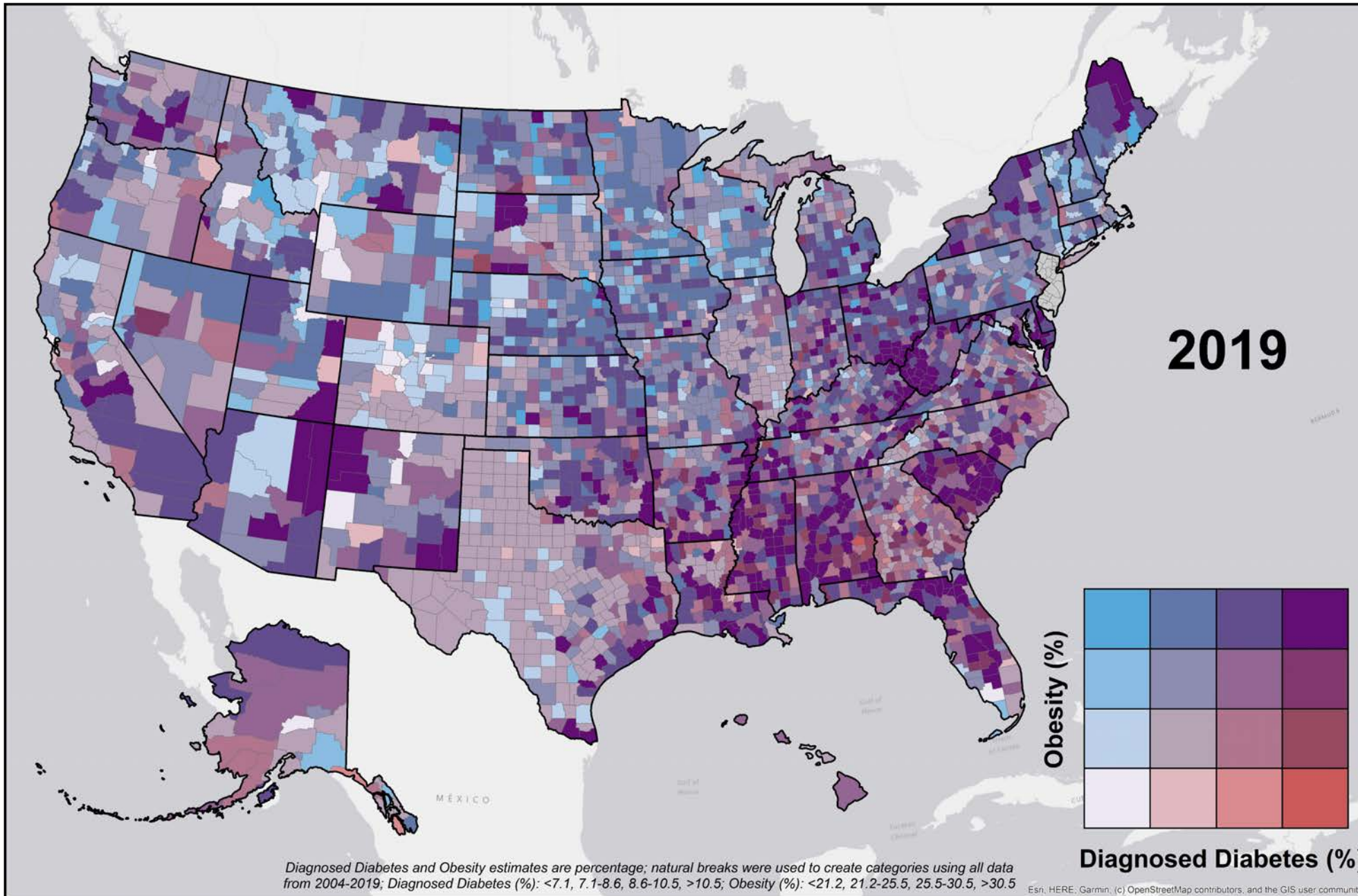
U.S. Adults Diagnosed
with Diabetes vs. Obesity

by County, 2004 - 2019









Diabetes/Obesity Prevalence and Consequences

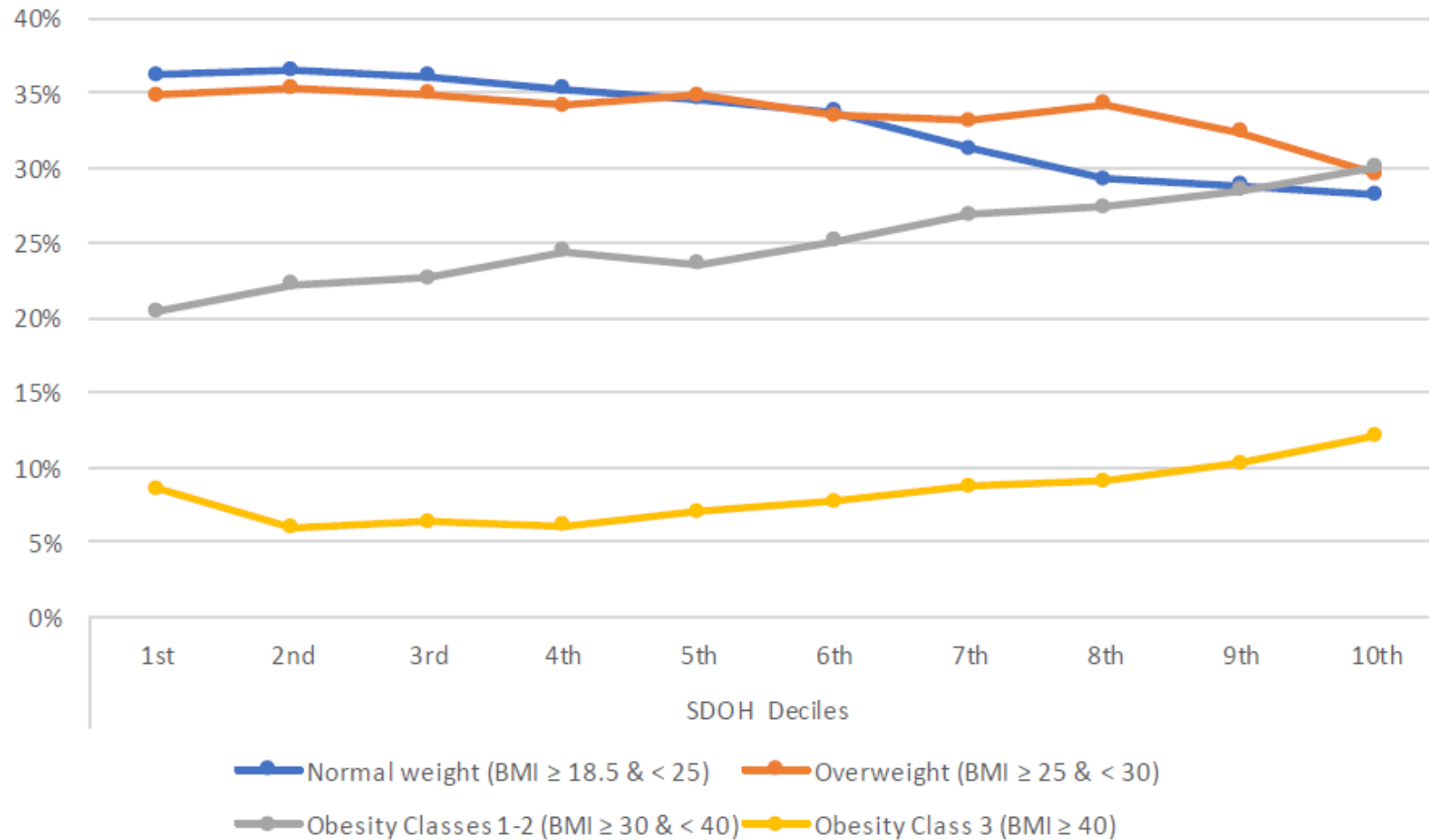


- 37.3 million adults (11.3%) in the U.S. with T2D (2019)
- 96 million adults (1 in 3) with prediabetes (2019)
- 41.9% of adults with obesity (2021)
- Cardiovascular disease (CVD) was the #1 cause of death and diabetes was #7 (2019)
- Estimated annual medical cost of obesity in the U.S. was **\$173 billion** (2019)
 - By comparison, estimated cost of damages from Hurricane Katrina was **~\$170 billion**

Social Determinants of Health and Obesity



Prevalence of BMI Categories, by Social Determinants of Health (SDOH) Deciles



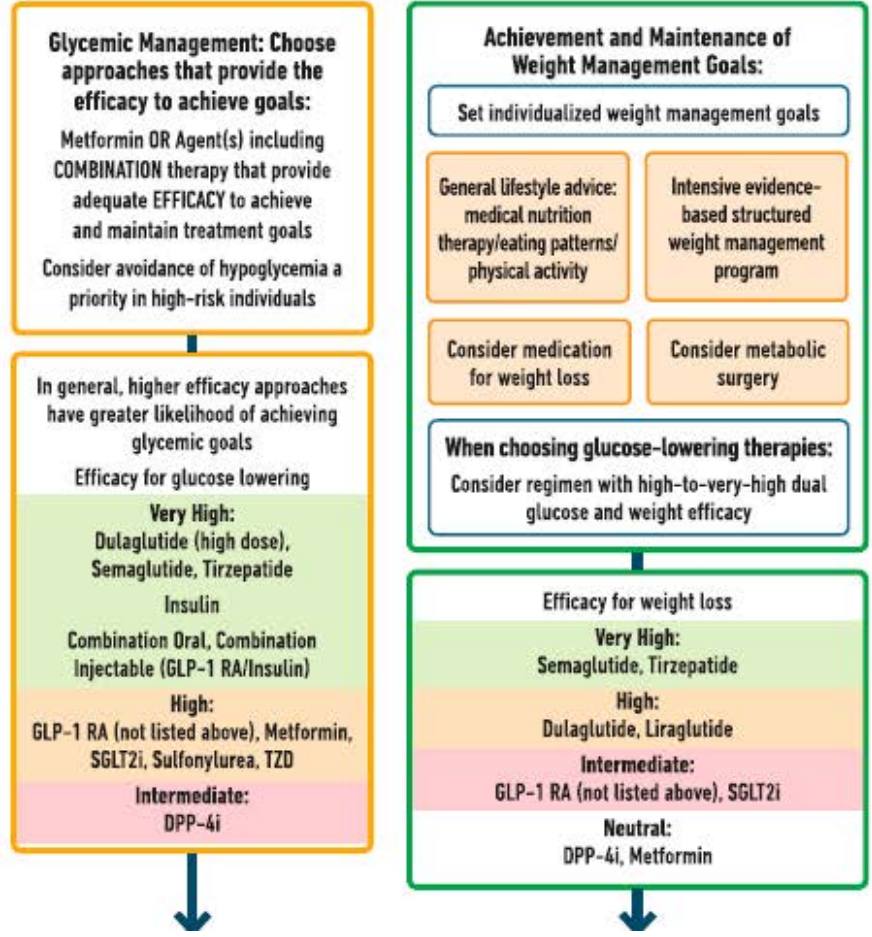
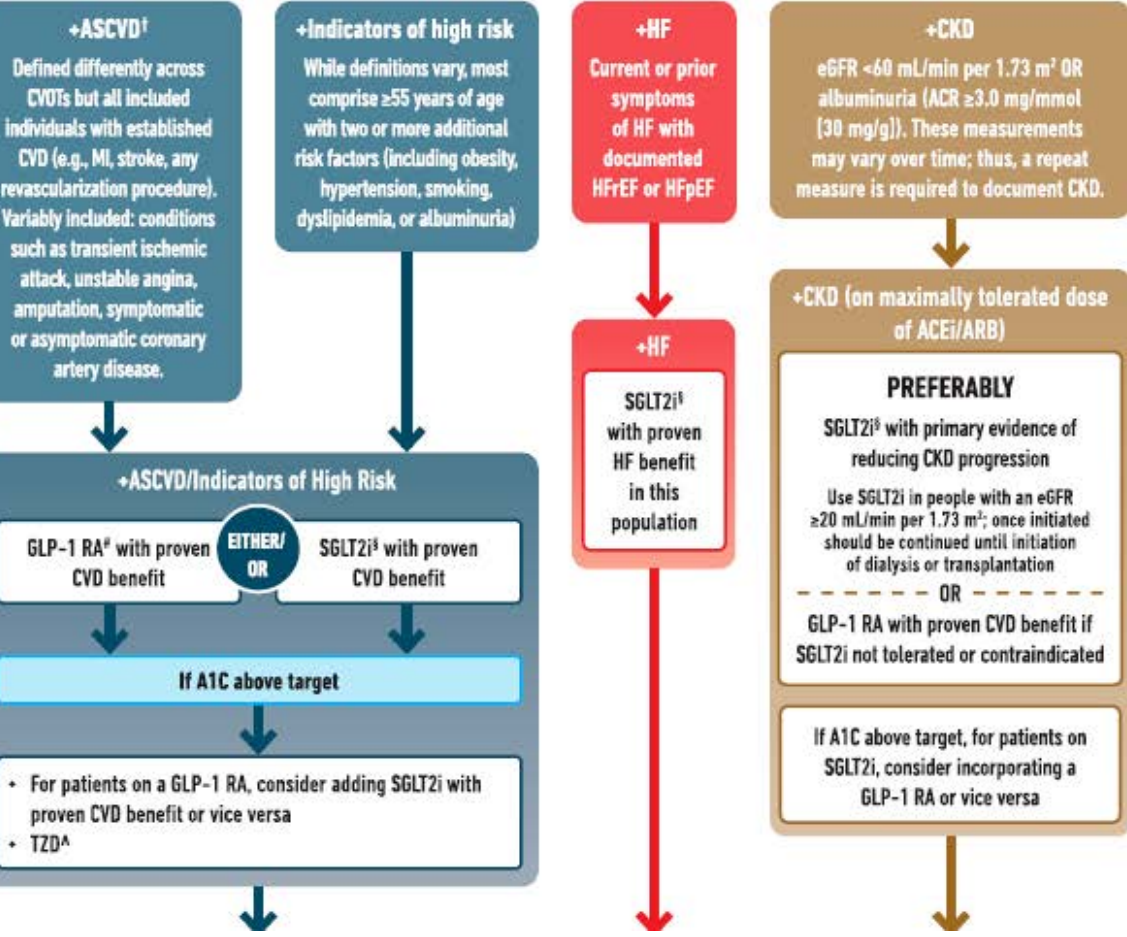
USE OF GLUCOSE-LOWERING MEDICATIONS IN THE MANAGEMENT OF TYPE 2 DIABETES



HEALTHY LIFESTYLE BEHAVIORS; DIABETES SELF-MANAGEMENT EDUCATION AND SUPPORT (DSMES); SOCIAL DETERMINANTS OF HEALTH (SDOH)

Goal: Cardiorenal Risk Reduction in High-Risk Patients with Type 2 Diabetes (in addition to comprehensive CV risk management)*

Goal: Achievement and Maintenance of Glycemic and Weight Management Goals



GLP-1 RA and SGLT2i

■ GLP-1 RA

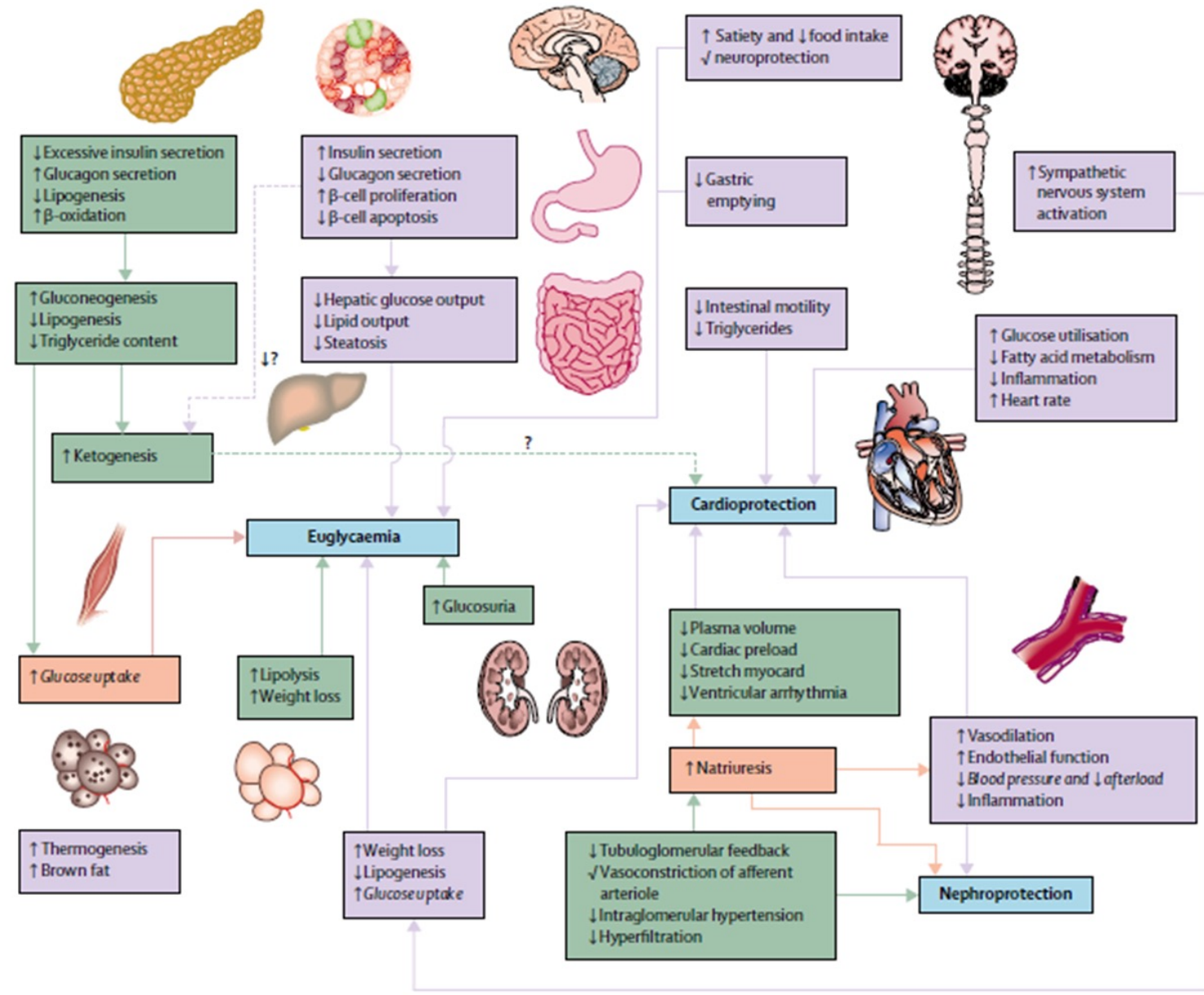
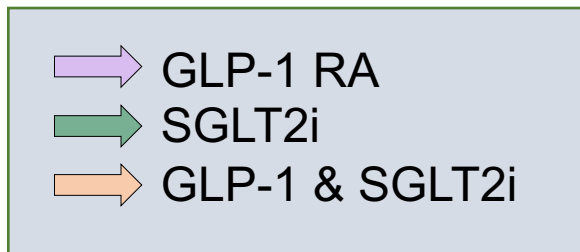
- Enhances glucose-dependent insulin secretion
- Delays gastric emptying
- Reduces intestinal chylomicron production and secretion
- Reduces central appetite

■ SGLT2i

- Inhibits reuptake of glucose through the sodium-glucose cotransporter-2 in the proximal tubule
- Causes glucosuria, and reduces circulating insulin
- Reduces glomerular pressure

Synergistic Effects

- Reductions in:
 - A1C
 - Weight
 - BP
 - Lipid
- No hypoglycemia
- Beneficial cardiovascular and renal outcomes



GLP-1 RA



- Weight loss within comparison studies
- Varying doses and lengths of treatment

Drug	Dose (mg)	Length (wks)	Weight Loss (kg)	Trial Name
Liraglutide (daily)	1.2 mg 1.8 mg	30 weeks 26-52 weeks	-1.9 kg -3.1 to -3.6 kg	SUSTAIN 10, DURATION 6, PIONEER 4, AWARD 6
Exenatide (weekly)	2 mg	24-26 weeks 56 weeks	-2.3 to -2.7kg -1.9 kg	DURATION 5, DURATION 6, SUSTAIN 3
Dulaglutide (weekly)	0.75 mg 1.5 mg	26-40 weeks 26-40 weeks	0.2 to -2.3 kg -1.3 to -3 kg	AWARD 1, AWARD 6, SUSTAIN 7
Semaglutide (weekly)	0.5 mg/1 mg 1 mg 1mg	40 weeks 56 weeks 30 weeks	-4.6kg/-6.5 kg -5.6 kg -5.8 kg	SUSTAIN 7, SUSTAIN 3, SUSTAIN 10
Semaglutide PO (daily)	14 mg	52 weeks	-4.4 kg	PIONEER 4

GLP-1 RA and Cardiovascular Outcome Trials

- GLP-1 RA cardiovascular outcome trials (CVOT) have shown beneficial primary outcomes for liraglutide, semaglutide, and dulaglutide, along with reduced all-cause mortality with exenatide taken once weekly

Trial	Drug	Population	Primary outcome (MACE)	All-cause death	CV death	MI	Stroke	HHF
LEADER ²⁶³	Liraglutide vs. Placebo	T2DM with high CV risk	0.87 (0.78–0.97)	0.85 (0.74–0.97)	0.78 (0.66–0.93)	0.86 (0.73–1.00)	0.86 (0.71–1.06)	0.87 (0.73–1.05)
SUSTAIN-6 ¹¹⁴	Semaglutide vs. Placebo	T2DM and established CVD or CKD	0.74 (0.58–0.95)	1.05 (0.74–1.50)	0.98 (0.65–1.48)	0.74 ^a (0.51–1.08)	0.61 ^a (0.38–0.99)	1.11 (0.77–1.61)
EXSCEL ¹²⁰	Exenatide vs. Placebo	T2DM	0.91 (0.83–1.00)	0.86 (0.77–0.97)	0.88 (0.76–1.02)	0.97 (0.85–1.10)	0.85 (0.70–1.03)	0.94 (0.78–1.13)
REWIND ¹²⁷	Dulaglutide vs. Placebo	T2DM with high risk of or established CVD	0.88 (0.79–0.99)	0.90 (0.80–1.01)	0.91 (0.78–1.06)	0.96 (0.79–1.15)	0.76 (0.62–0.94)	0.93 (0.77–1.12)

SGLT2i

■ Comparison of weight loss in CVOT

CVOT	Drug	Mean follow-up (years)	Weight reduction (kg)	Outcome
CANVAS n=1000	Canagliflozin	3.6	-1.6	3 Pt MACE - Superior HR 0.86
CREDESCENCE n=4400	Canagliflozin	2.6	-0.8	Combined renal progression and renal/CV death HR 0.7
DECLARE-TIMI n=17,000	Dapagliflozin	4.2	-1.8	CV Death and hHF reduction HR 0.83
EMPA-REG n=7000	Empagliflozin	3	-2	3 Pt MACE - Superior HR 0.86
VERTIS CV n=8200	Ertugliflozin	3.5	-2.4 (5 mg) -2.8 (15 mg)	3 Pt MACE HR 0.97 (CI 0.85–1.11)



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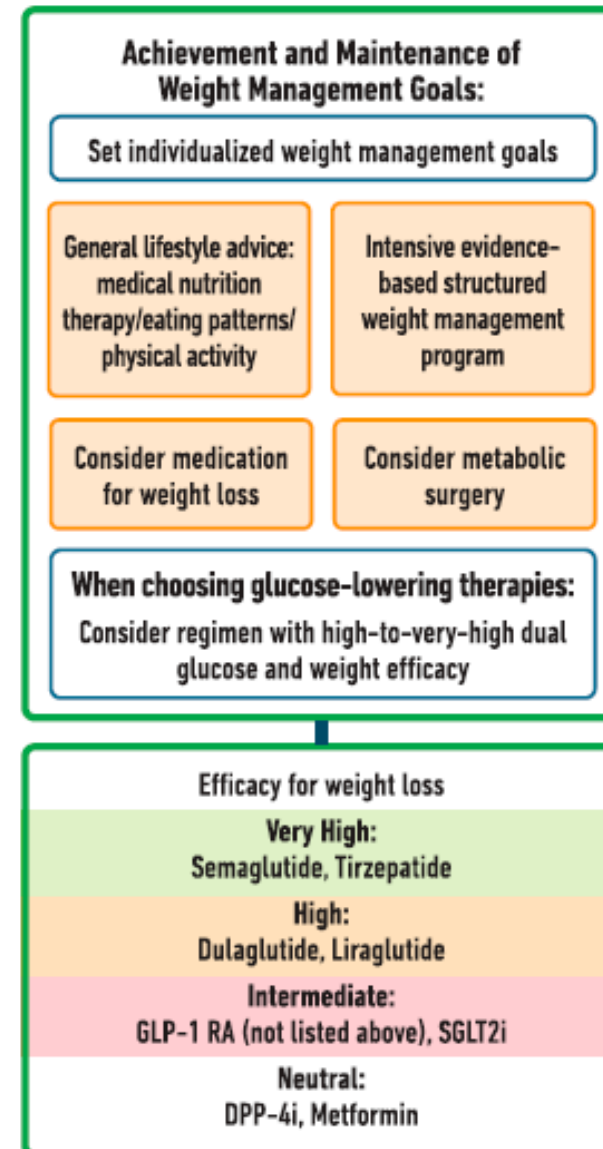
Weight Management Perspective

American Diabetes Association Standards of Care

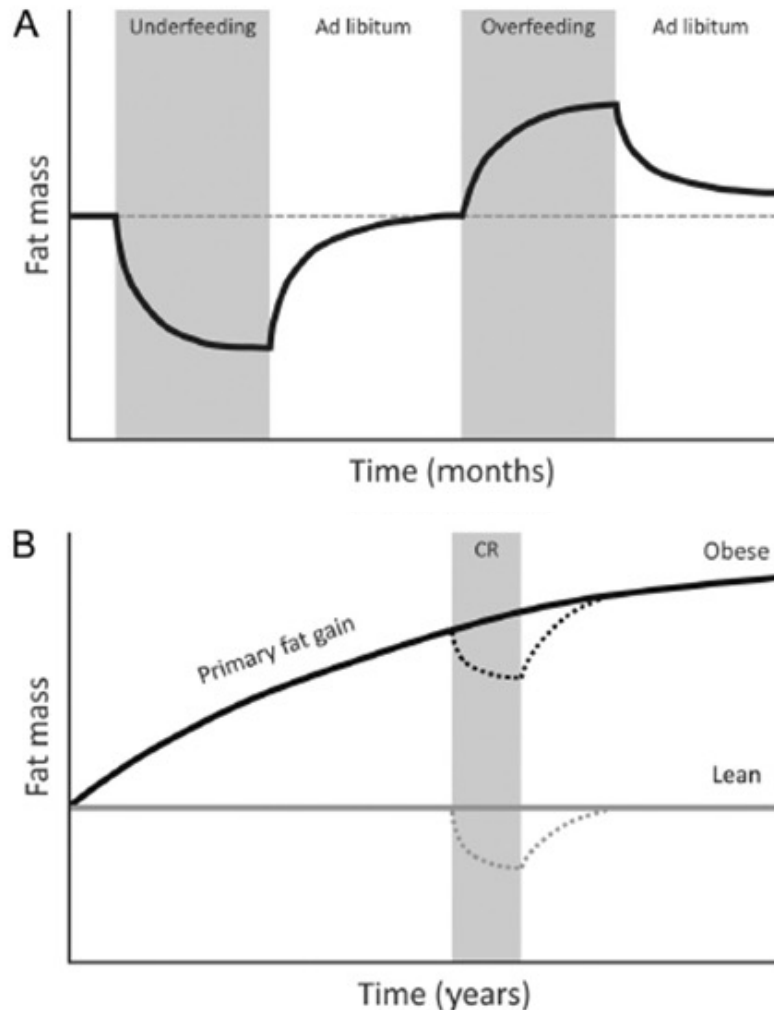
- Focus shifting to high efficacy treatments AND weight management to help provide durable glucose lowering



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Control of Energy Balance



- Total energy expenditure (TEE) = resting metabolic rate + thermic effect of feeding + activity (sedentary + exercise)
 - RMR = 75% of calorie expenditure
- Sedentary level includes most activities of daily living plus NEAT (fidgeting)
- Calorie intake either above needs or below needs affects TEE, with an eventual return to baseline

FIG. 3. Homeostatic regulation of body fat mass. A, Return of fat mass to baseline after short-term underfeeding or overfeeding. B, Gradual increase in the defended level of fat mass with age in an obese individual. The homeostatic response to fat loss induced by calorie restriction (CR) occurs in obese as well as lean individuals, resulting in the recovery of lost fat.

Control of Energy Balance

Putting the formula more simply:

1. Find a way to measure the calories you eat *and drink*.
2. Find a way to measure the calories you burn.
3. Make sure that every day, number one is smaller than number two.

- Tommy Tomlinson



Activity

TABLE IV-5:

DURATION OF VARIOUS ACTIVITIES TO EXPEND 150 KILOCALORIES FOR AN AVERAGE 70 KG (154 LB) ADULT		
Intensity	Activity	Approximate duration in minutes
Moderate	Volleyball, noncompetitive	43
Moderate	Walking, moderate pace (3mph, 20 min/mile)	37
Moderate	Walking, brisk pace (4mph, 15 min/mile)	32
Moderate	Table tennis	32
Moderate	Raking leaves	32
Moderate	Social dancing	29
Moderate	Lawn mowing (powered push mower)	29
Hard	Jogging (5 mph, 12 min/mile)	18
Hard	Field hockey	16
Very Hard	Running (6 mph, 10 min/mile)	13

Source: Surgeon General's Report on Physical Activity and Health

Nutrition



- Low-calorie diet
 - Men 1500-1800 kcal/day
 - Women 1200-1500 kcal/day
- 500 kcal/day deficit should produce roughly 1 lb per week of weight loss
- No one diet is most effective – instead, go with patient preference
- Maintain appropriate balance of nutrients
- Dietary intake should not be lower than 800 kcal per day
- The calorie deficit should produce 1-2 lbs of weight loss per week
- Initial goal of 10% decrease in body weight

Activity

TABLE IV-5:

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Hard	Jogging (5 mph, 12 min/mile)	18
Hard	Field hockey	16
Very Hard	Running (6 mph, 10 min/mile)	13

Source: Surgeon General's Report on Physical Activity and Health



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- Goal is 150 minutes of moderate intensity activity per week
- Multiple studies show **any activity** is better than **none**

Weight Loss Medications: 1959-1997

- **Sympathetic nervous system agonists**

- Phentermine
- Diethylpropion
- Sibutramine

- **Serotonin receptor agonists**

- Fenfluramine
- Dexfenfluramine
- Sibutramine

Weight Loss Medications: 1959-1997

- **Sympathetic nervous system agonists**

- Phentermine
- Diethylpropion
- Sibutramine

Increased CVD risk

- **Serotonin receptor agonists**

- Fenfluramine
- Dexfenfluramine
- Sibutramine

Valvulopathy

Weight Loss Medications: 1999-2020

■ Taking a different approach...

- Orlistat (1999) – pancreatic lipase inhibitor
- Rimonabant (2006 EU only) – CB1 receptor antagonist

■ Retracing our steps...

- Phentermine-Topiramate (2012)
- Lorcaserin (2012)
- Naltrexone-Bupropion (2014)
- Liraglutide (2014)

Weight Loss Medications: 1999-2020

■ Taking a different approach...

- Orlistat (1999) – pancreatic lipase inhibitor
- Rimonabant (2006 EU only) – CB1 receptor antagonist

Increased risk of suicide

Increased risk of cancers (lung, colon, pancreas)

■ Retracing our steps...

- Phentermine-Topiramate (2012)
- Lorcaserin (2012)
- Naltrexone-Bupropion (2014)
- Liraglutide (2014)

Weight Loss Medications

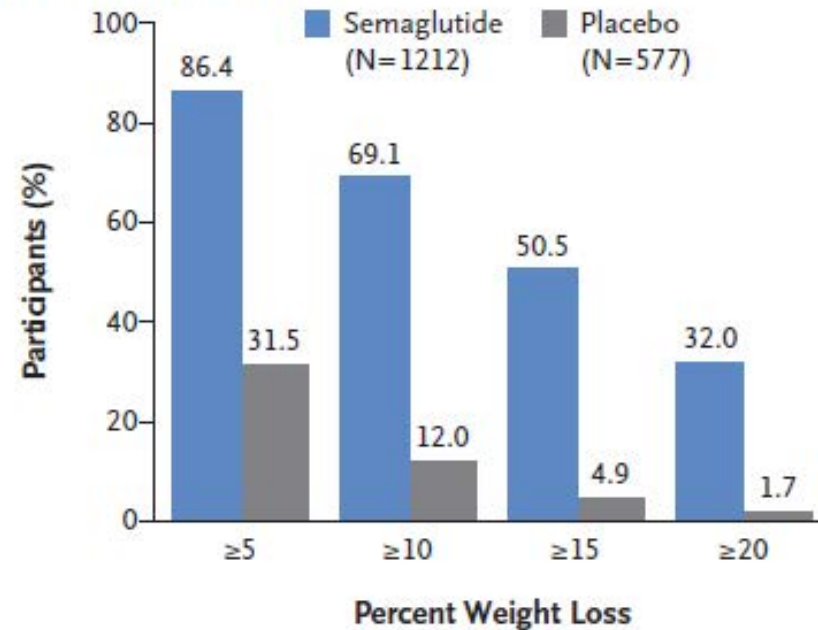
- Approved medications prior to 2020
- Most medications provide reliable results of 5-10% weight loss

Drug	Weight Loss Above Placebo	Pluses	Minuses
Phentermine	3.6 kg (7.9 lbs) in 2-24 weeks	Inexpensive, greater weight loss	No long-term data, side effects
Orlistat	2.9-3.4% (6.5-7.5 lbs) - 1 year	Non-systemic, long-term data, inexpensive OTC	Side effects, less weight loss
Phentermine + Topiramate	14.5 lbs (low dose) 18.9 lbs (high dose) – 1 year	Robust weight loss, long term data	Teratogenic, cost \$\$
Buproion + Naltrexone	6.3kg (~13 lbs) – 1 year	Greater weight loss, food addiction(?)	Side effect profile, cost = \$\$
Liraglutide 3.0mg	5.6kg (12.3 lbs) – 1 year	Side effect profile, long term data, CVOT data	Injectable, cost \$\$\$\$

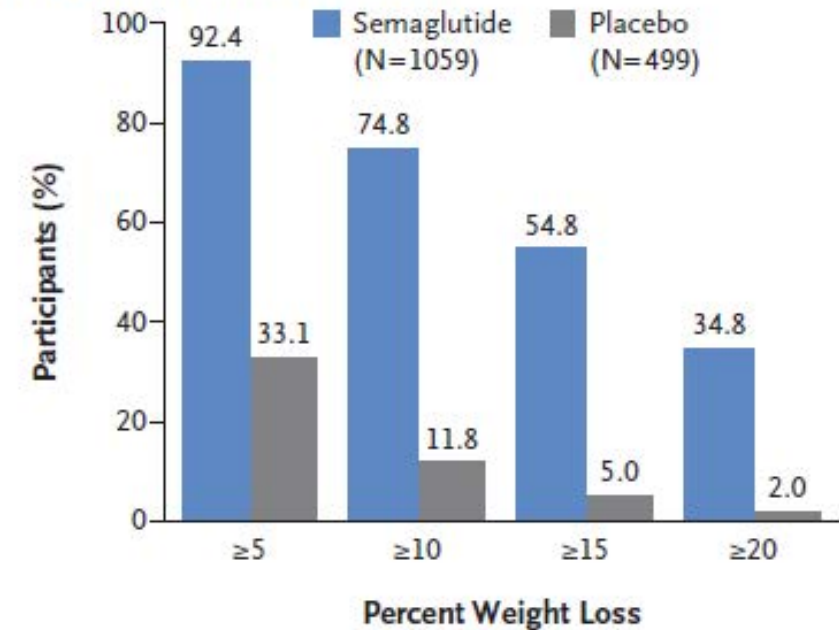
Semaglutide 2.4 mg

- 68 weeks, 2:1 randomized to sema 2.4 mg vs. placebo
- 500 kcal deficit and 150 minutes moderate activity
- -12.4%, -12.7 kg vs. placebo

C In-Trial Data at Wk 68



D On-Treatment Data at Wk 68





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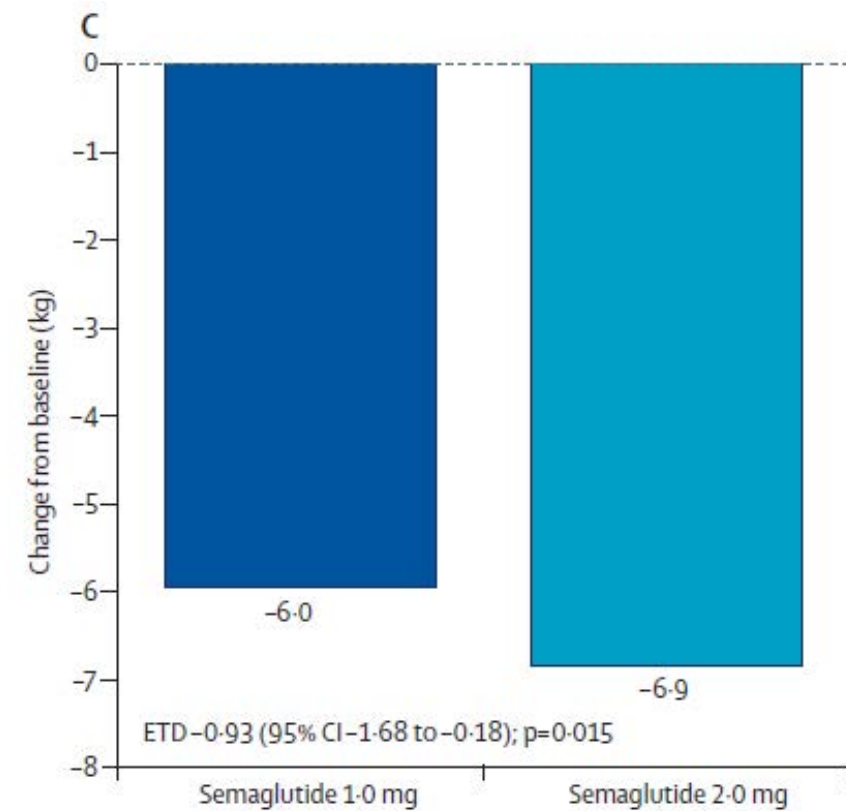
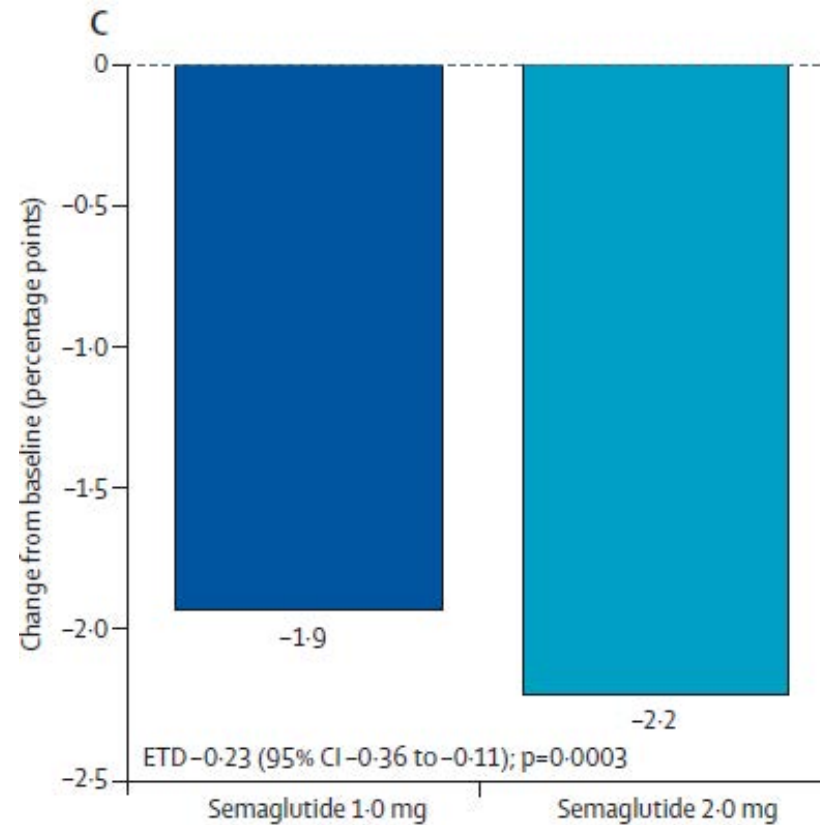
T2D Treatment with Weight Management Perspective

Case Presentation - 3

- 65-year-old male with T2D, OSA, previously on lorcaserin, currently on metformin and liraglutide
- Changed liraglutide to semaglutide 1 mg with modest impact on appetite
- 1 month later, no change in weight, increased to semaglutide 2 mg
- Better appetite effect, he reported better glucose control as well
- Current weight: 323 lbs (-30 lbs in 5 months), A1C: 6.5% (8/2022)

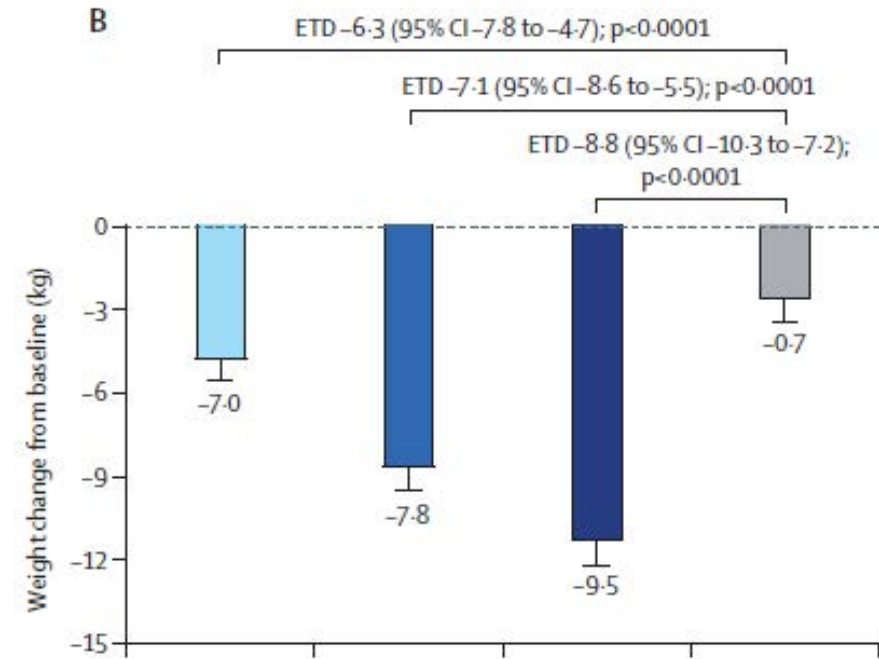
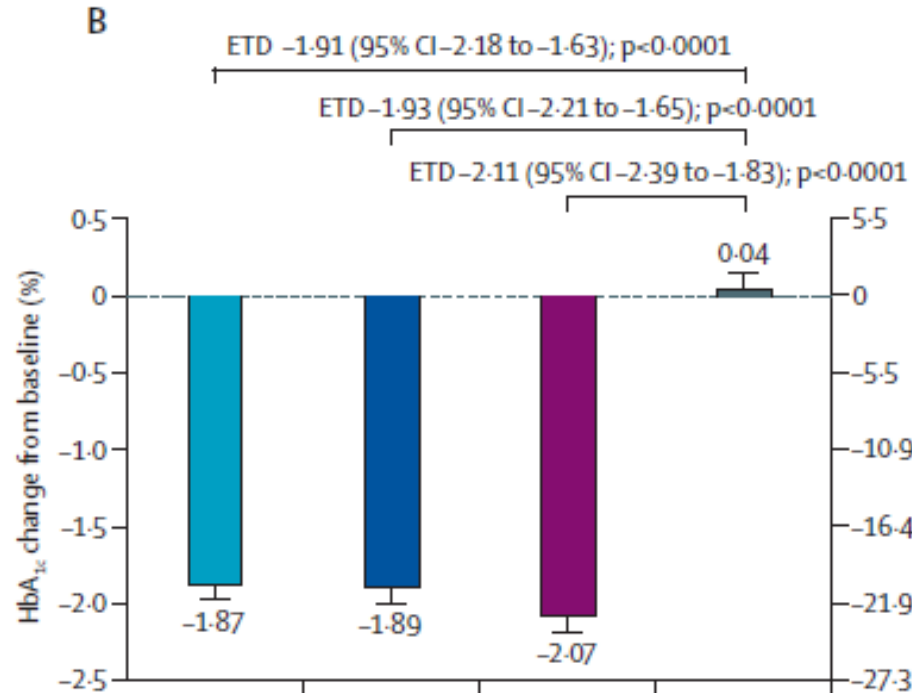
Semaglutide 1.0 and 2.0 mg

- Higher dose provides better A1C lowering and potential better weight loss in patients with T2D



Tirzepatide – SURPASS 1

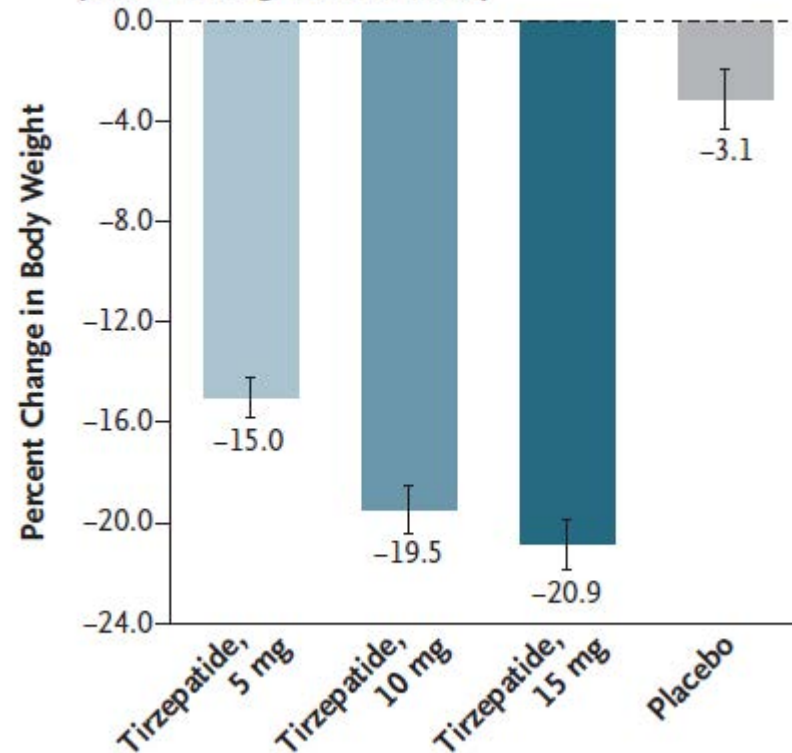
- GLP-1/GIP RA once weekly, 5, 10, and 15 mg doses
- 40 weeks
- 45% with prior oral agent use



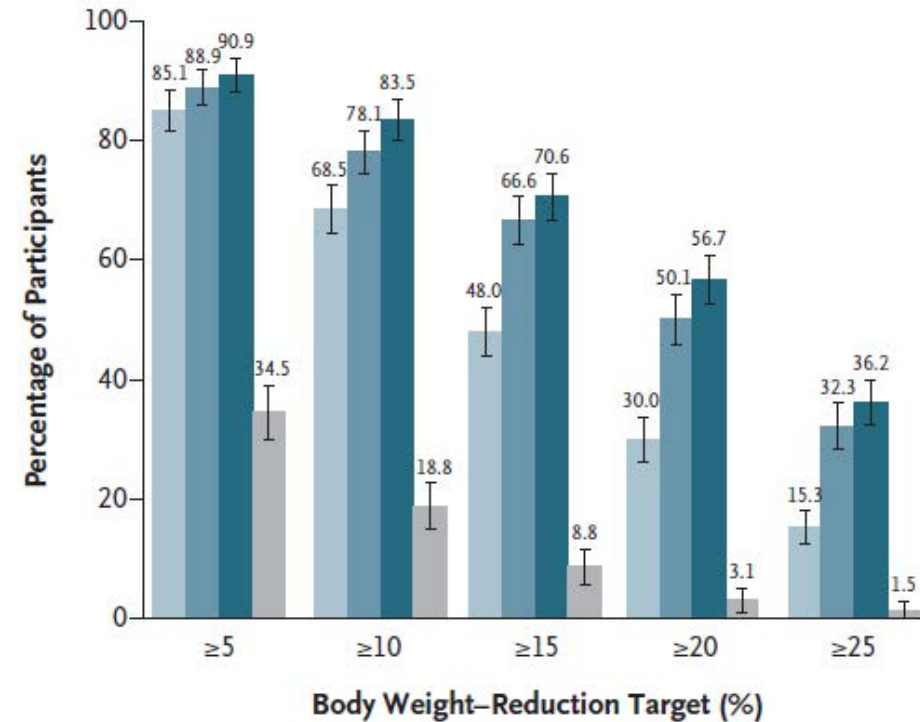
Tirzepatide – SURMOUNT - 1

- Same 5, 10, 15 mg doses vs. placebo
- 72 weeks
- 500 kcal deficit
- 150 minutes of moderate activity per week

A Overall Percent Change in Body Weight from Baseline (treatment-regimen estimand)



C Participants Who Met Weight-Reduction Targets (treatment-regimen estimand)

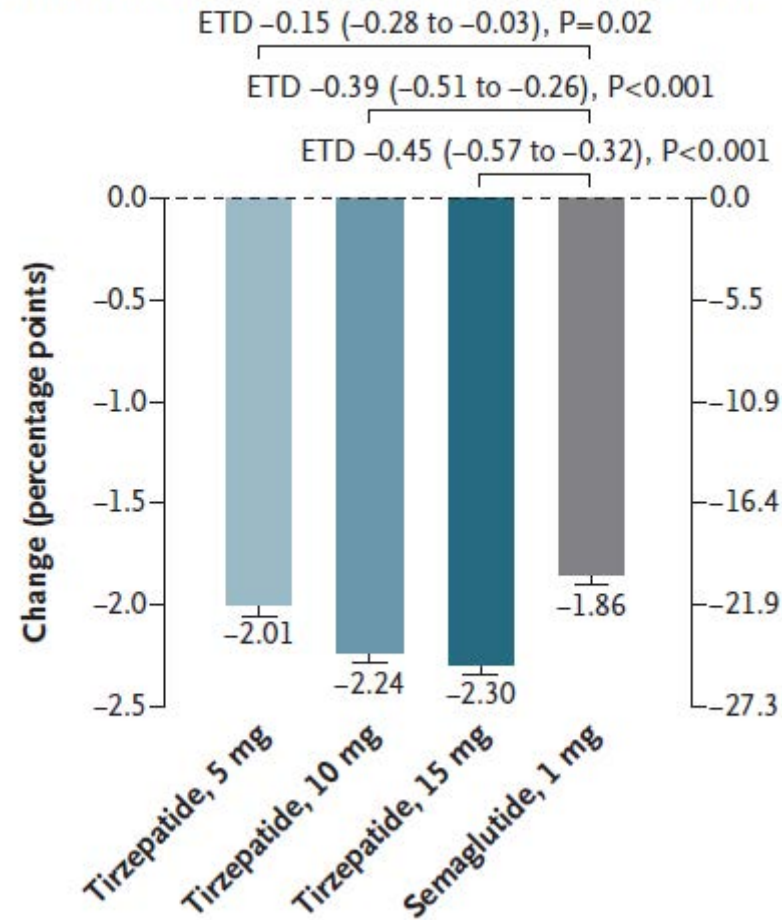


Semaglutide vs. Tirzepatide SURPASS2

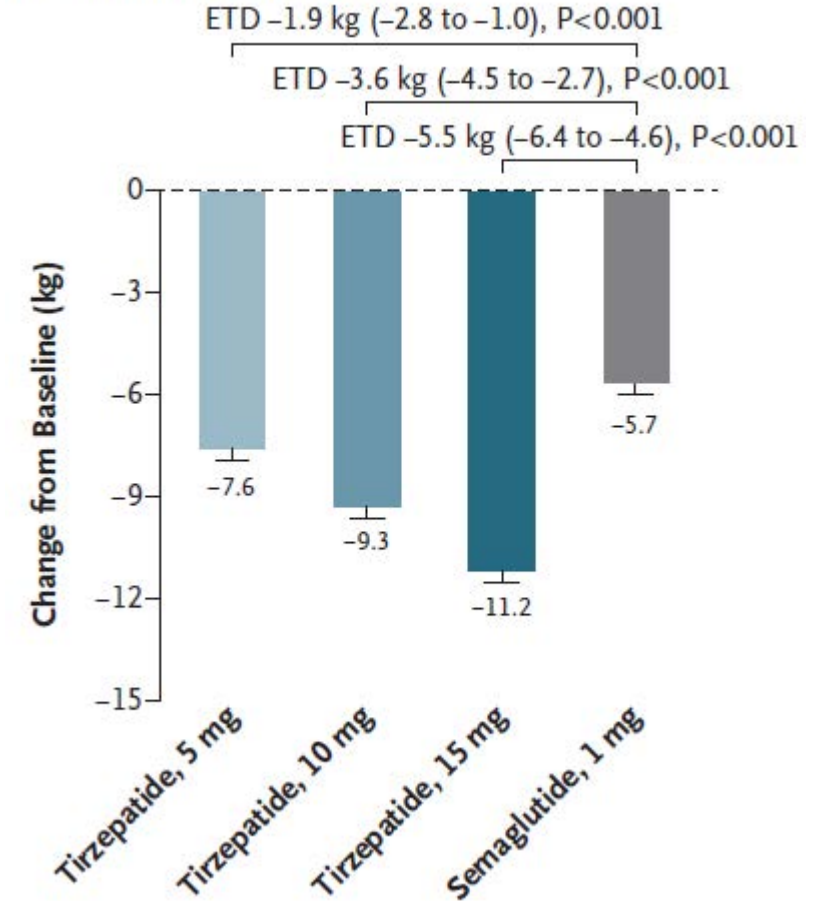


- 5, 10, and 15 mg doses of tirzepatide vs. 1 mg semaglutide
- 40 weeks
- Baseline 100% use of metformin

A Change in Glycated Hemoglobin Levels from Baseline



A Change in Body Weight



Closing Thoughts

- Lifestyle modification, including weight management, is part of the foundation of diabetes management
- Several options in diabetes management to assist with weight loss
- SGLT2i provide more modest weight loss but with many other beneficial effects
- GLP-1 RA with very good A1C and weight loss effects plus CVOT data
- GLP-1/GIP with best A1C and weight loss effect thus far
- Multidrug regimens provide an additional effect

Resources



- Centers for Disease Control: Preventing Type 2 Diabetes (for patients)
 - cdc.gov/diabetes/prevent-type-2/guide-prevent-type2-diabetes.html
- National Diabetes Prevention Program
 - cdc.gov/diabetes/prevention/index.html
- Metabolic Rate Calculators
 - Mifflin St. Jeor Calculator: calculator.net/bmr-calculator.html
 - Harris-Benedict Calculator: inchcalculator.com/harris-benedict-calculator/



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Audience Question and Answer

Amy Zack, MD

Case Western Reserve University School of Medicine

Speakers

REMINDER:
Submit questions using the 'Q&A' feature



Benjamin O'Donnell, MD
The Ohio State University Wexner Medical Center



Amy Zack, MD (Moderator)
Case Western Reserve University School of Medicine



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Next Steps and Wrap Up

Shari Bolen, MD, MPH

Case Western Reserve University School of Medicine

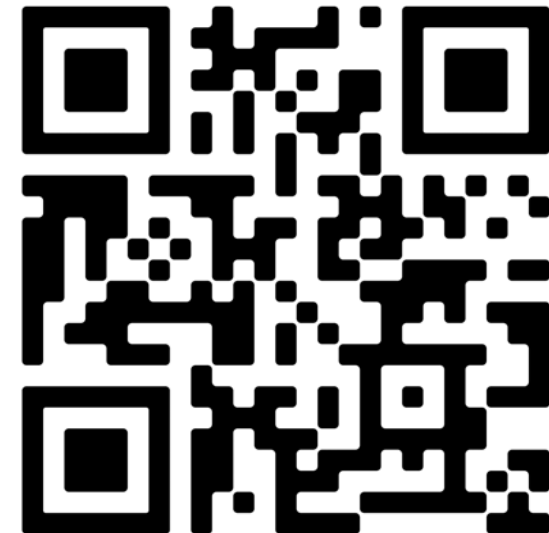
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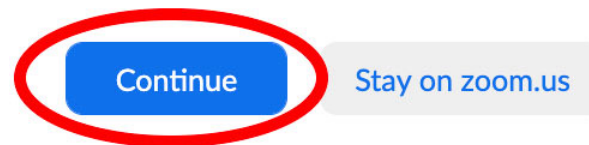


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Wednesday, May 24, 2023 | 12-1 p.m. ET



WEBINAR TOPIC

Sleep Disorders and Cardiovascular Risk

KEYNOTE SPEAKER

Jennifer Molano, MD

Associate Professor of Neurology
University of Cincinnati



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Registration information coming soon.

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