The Impact of Obesity Medications on Chronic Disease Management: From Research to Practice

Robert Kushner, MD

- Former Medical Director, Center for Lifestyle Medicine, Northwestern Medicine
- Professor of Medicine, Northwestern University

Jaime Almandoz, MD

- Medical Director, Weight Wellness Obesity Medicine Program, University of Texas Southwestern Medical Center
- Associate Professor, University of Texas Southwestern Medical Center

Welcome

Today's Moderator

Linda Gigliotti, MS, RDN, CDCES, FAND

- Academy Foundation Board member
- Former Program Director, University of CA Weight Management Program
- Co-editor, Health Professionals Guide to Obesity and Weight Management

Three-Part Webinar Series

Obesity Medications and the RDN: Advance Your Knowledge, Enhance Your Role

Academy of Nutrition and Dietetics Foundation

April 17th
The Impact of Obesity Medications on Chronic Disease Management: From Research to Practice

May 8th
Considerations for Body Composition, Physical Activity and Nutrition with the Use of Obesity Medications

June 4th
Advance and Enhance the Unique Role of the RDN in Today's and Tomorrow's Obesity Care Continuum

This webinar series is made possible through sponsorship from Eli Lilly to the Academy Foundation.
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These webinars do not provide CPE credit.

Planning Committee

Beth Czerwony, MS, RDN, CSOWM, LDN, Weight Management Dietetic Practice Group representative

Linda Gigliotti, MS, RDN, CDCES, FAND, Academy Foundation Board member

Laura Russell, MA, RDN, CDCES, Diabetes Care and Education Dietetic Practice Group representative

Hope Warshaw, MMSc, RD, CDCES, BC-ADM, Academy Foundation Past-chair

2024 Webinar Archives

2024 Webinar Series

Pathophysiology of Obesity and Treatment Using New Anti-Obesity Medications

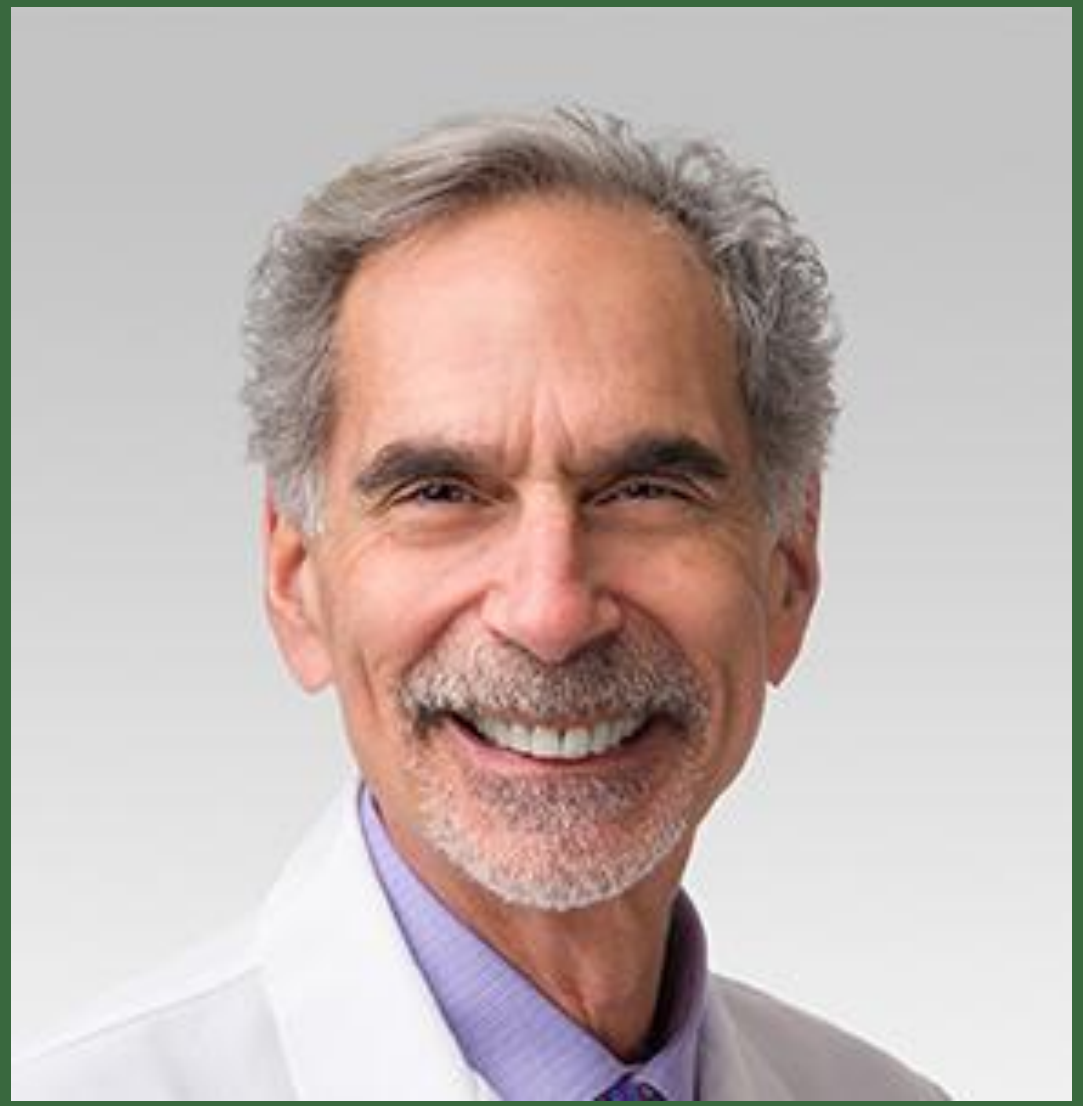
The Role of the RDN to Optimize Short- and Long-term Use of Anti-Obesity Medications

Anti-Obesity Medications: An Interdisciplinary Panel Discusses Cases

Robert Kushner, MD

Affiliations

- Former Medical Director, Center for Lifestyle Medicine, Northwestern Medicine
- Professor of Medicine and Medical Education, Northwestern University Feinberg School of Medicine,
- Past President of The Obesity Society
- Founder of the American Board of Obesity Medicine (ABOM)



Jaime Almandoz, MD, MBA, DABOM, FTOS

Affiliations

- Medical Director, Weight Wellness Obesity Medicine Program at the University of Texas Southwestern Medical Center
- Associate Professor of Internal Medicine, University of Texas Southwestern Medical Center
- Diplomate, American Board of Obesity Medicine (ABOM)
- Board-certified in Endocrinology and Internal Medicine

Disclosures

Robert Kushner, MD

- **Grants/Research Support**: Novo Nordisk
- **Consultant**: Novo Nordisk, Weight Watchers, Eli Lilly, Structure, Boehringer Ingelheim, Altimmune, Regeneron, Antag, Currax, AstraZenica
- **Honorarium**: Novo Nordisk, Weight Watchers, Eli Lilly, Structure, Boehringer Ingelheim, Altimmune, Regeneron, Antag, Currax, AstraZenica

Jaime Almandoz, MD, MBA, MRCPI, FTOS

- **Consultant**: AbbVie, Boehringer Ingelheim, Eli Lilly, Nestle, Novo Nordisk, Wave Life Sciences

Learning Objectives

At the end of the presentation, attendees will be able to:

1. Discuss the proposed new definition and diagnostic criteria for obesity.
2. Describe the basics of pharmaceutical research for FDA approval of a new medication.
3. Explain how obesity management medications (GLP-1 analogs, incretin-based therapies and future categories) impact human physiology to produce weight loss
4. Explain the physiology and research to date on how the above obesity medications impact other chronic conditions.
5. Outline ways that RDNs can inform themselves on the evolving science of obesity management medications and translate the science to their target populations.

New definition and diagnosis recommendations for obesity from the Lancet Commission

Robert Kushner, MD, FTOS, DABOM
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Obesity is a chronic disease

WOF
World Obesity Federation

"The World Obesity Federation takes the position that obesity is a chronic, relapsing, progressive disease process and emphasizes the need for immediate action for prevention and control of this global epidemic"

OC
Obesity Canada

"Obesity is characterized by excess body fat that can threaten or affect your health. Many organizations including the Canadian Obesity Network, now consider obesity to be a chronic disease."

AMA
American Medical Association

"American Medical Association recognizes obesity and overweight as a chronic medical condition (de facto disease state) and urgent public health problem…and work towards the recognition of obesity intervention as an essential medical service…"

EASO
European Association for the Study of Obesity

"A progressive disease, impacting severely on individuals and society alike, it is widely acknowledged that obesity is the gateway to many other disease areas…"

EC
European Commission

"Obesity is a chronic relapsing disease, which in turn acts as a gateway to a range of other non-communicable diseases, such as diabetes, cardiovascular diseases and cancer."

RCP
Royal College of Physicians (UK)

"Obesity is a chronic progressive disease caused by an imbalance between energy intake and energy expended, with a wide range of damaging effects on the body."

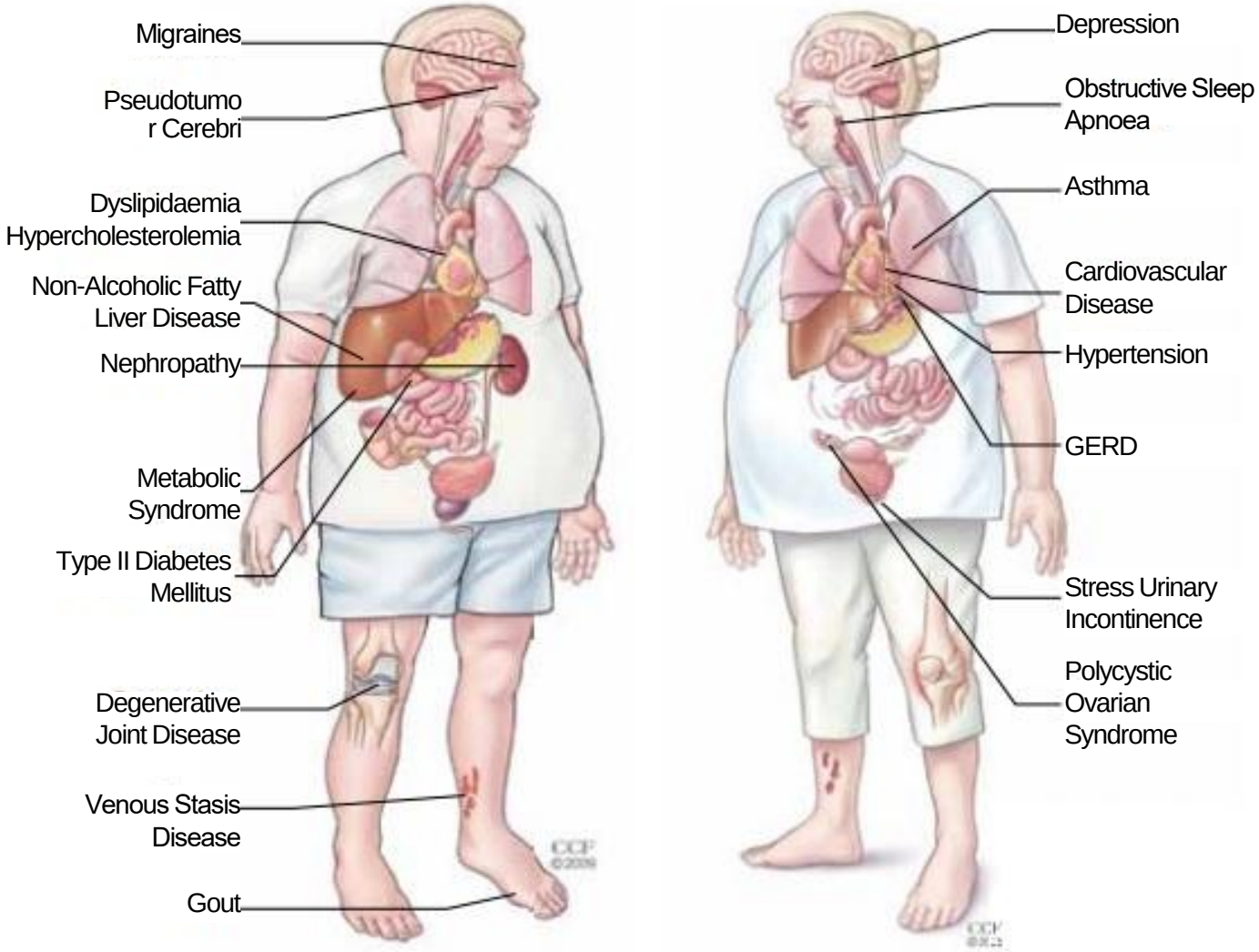
AOASO
Asia Oceania Association for the Study of Obesity

"We hereby propose a concept for international recognition of a pathological state (obesity disease) in which a person suffers health problems caused by or related to obesity thus making weight loss clinically desirable and requiring treatment as a disease entity"

OMA
Obesity Medicine Association (US)

"A chronic, relapsing, multi-factorial, neurobehavioral disease, wherein an increase in body fat promotes adipose tissue dysfunction and abnormal fat mass physical forces, resulting in adverse metabolic, biomechanical, and psychosocial health consequences."

Obesity is Associated with Over 200 complications/comorbidities



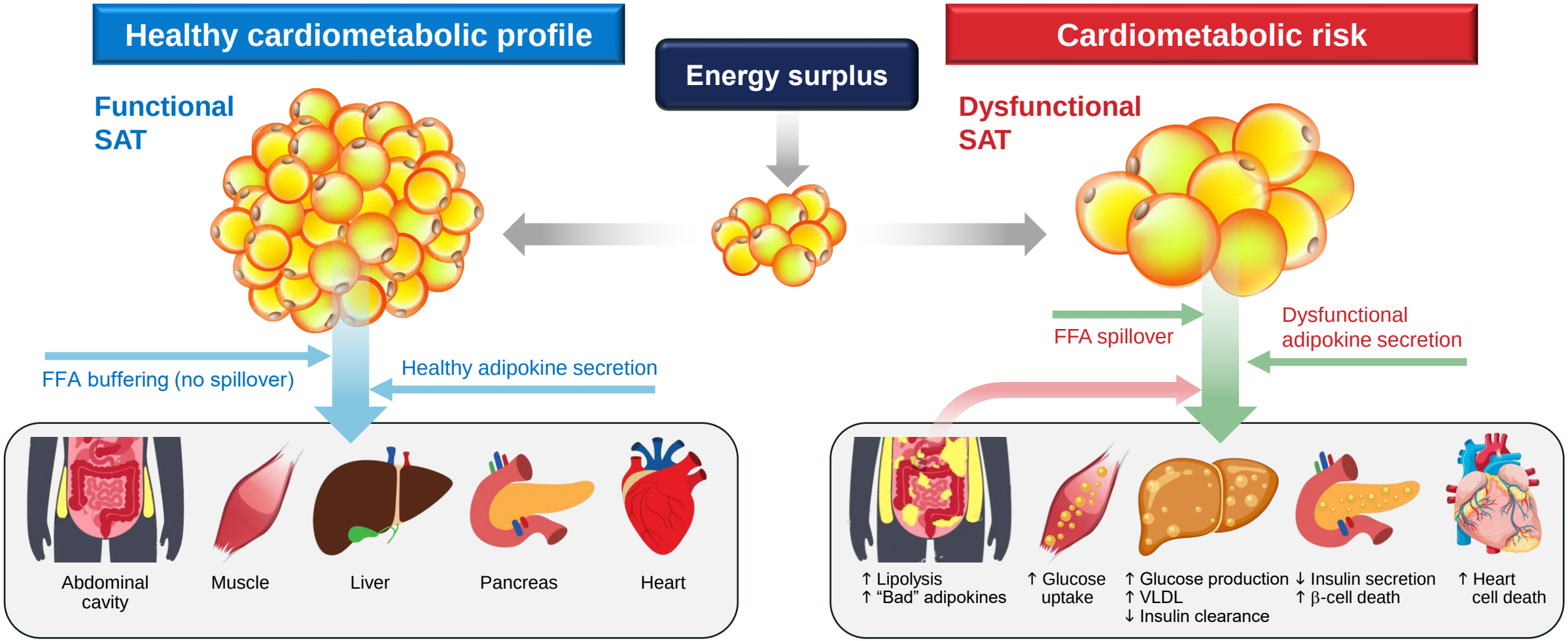
A **disease** is a disorder or abnormal condition affecting the body or mind, characterized by specific signs and symptoms.

Diseases impact an individual's normal physiological or psychological functioning

Yuen MMA. Gastroenterol Clin North Am 2023 Jun;52(2):363-380.

Image courtesy: Adapted from Cleveland clinic (available here)

Consequences of Functional and Dysfunctional Adipose Tissue



FFA: free fatty acid; SAT: subcutaneous adipose tissue; VLDL: very-low-density lipoprotein.

Ross R, et al. *Nat Rev Endocrinology*. 2020;16:177-189.

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The Challenge of more Directly Measuring Body Fat

DXA

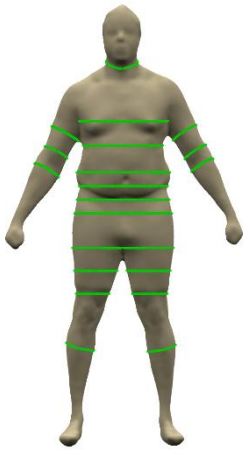
Attenuation of 2 energy level x-ray transmissions (absorbed or scattered). Measures bone and soft tissue

MF-BIA

Uses electrical properties of body to estimate TBW and from that the body fat mass.
Body is modeled as 5

ADP

Assumes two compartment model (fat and lean) with different density. Volume of displaced air determined from changes in air



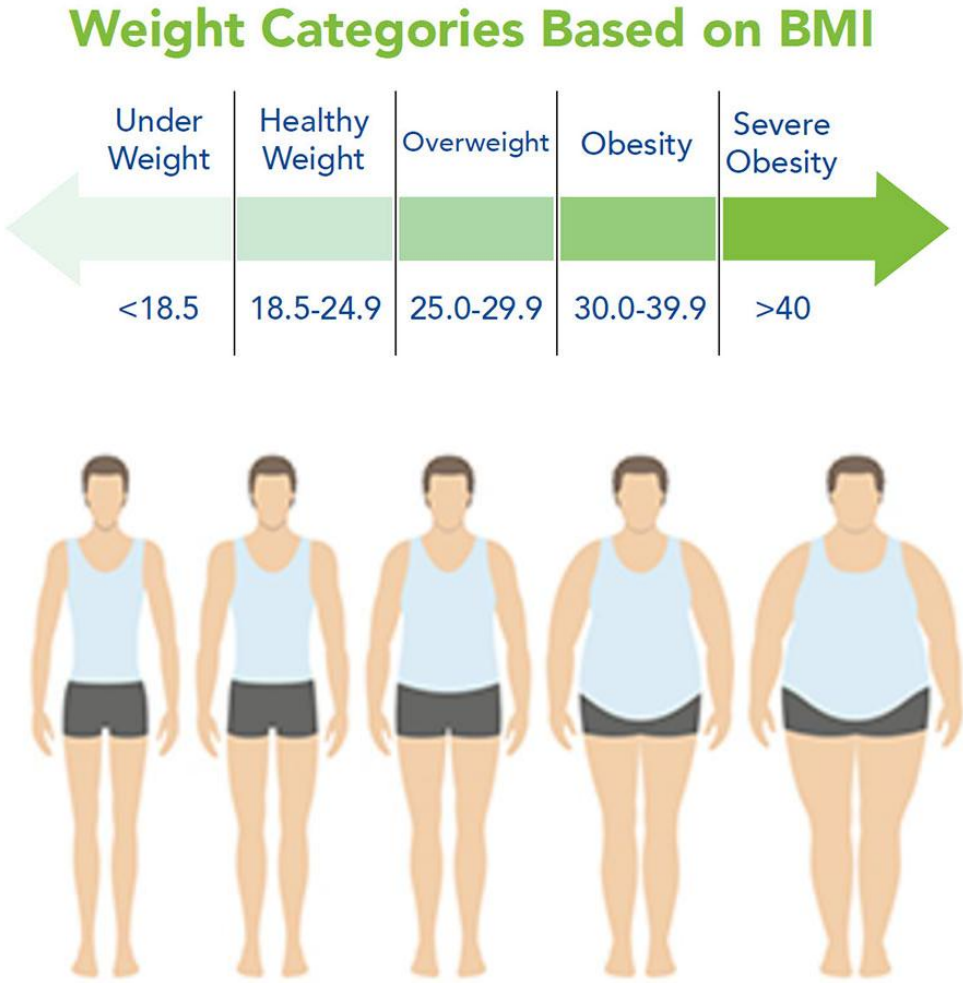
DA

Smartphone app scans and quantifies body anthropometric dimensions and volume, estimates body fat

DXA = Dual X-ray Absorptiometry; MF-BIA = Multiple Frequency Bioimpedance Analysis; ADP = Air Displacement Plethysmography; DA = Digital Anthropometry

Body Mass Index (BMI, kg/m^2)

- **D**efinitions of underweight, healthy weight, overweight and obesity in terms of BMI were established in 1995 by WHO
- **Problems**
- **H**eterogeneity in relative body shape and composition exists across race and ethnic groups, sexes, genders and age-span, and is essential to consider when applying BMI as a measure of adiposity
- **B**MI defines body size with no regard to an individual's health or body composition
- **P**eople are classified as having a disease without ever having received a diagnosis or undergone a medical history or examination



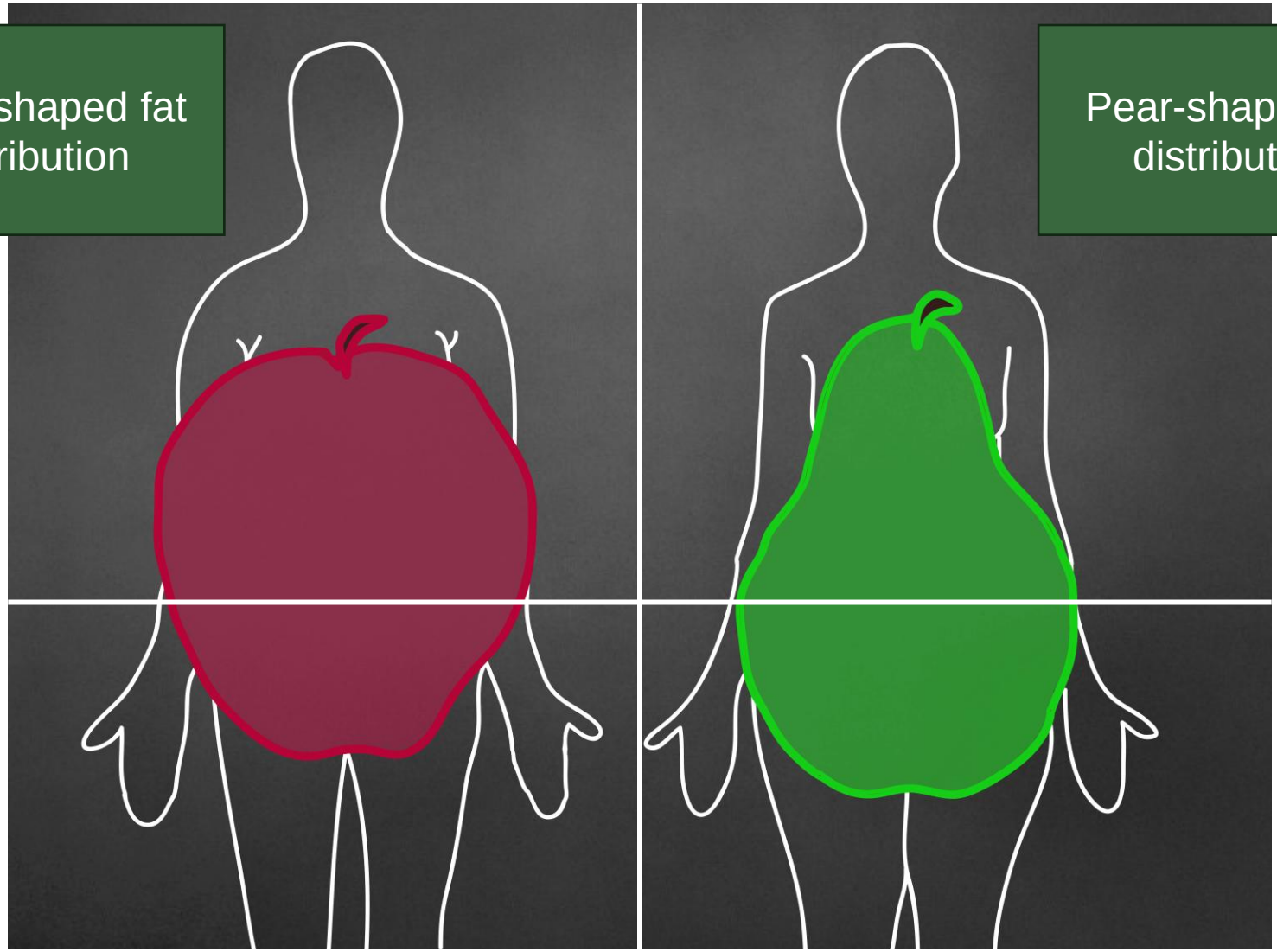
Association of Girth Measurements with Diabetes: TOPS

Apple-shaped fat distribution

Pear-shaped fat distribution

Upper-body fat

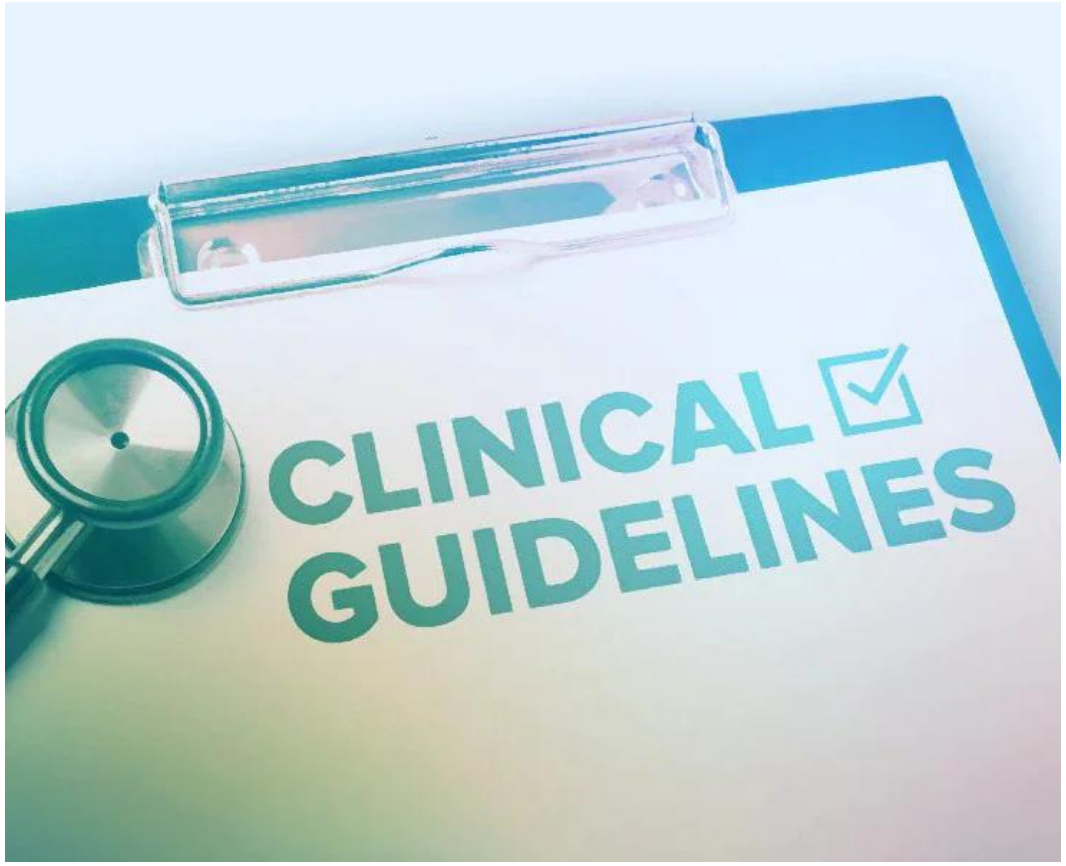
Lower-body fat



Hartz AJ, et al. Am J Epidemiology 1984;119;71-80

Current Practice Guidelines for Assessing Patients with Obesity

- Measure height & weight and calculate BMI annually
- Measure waist circumference for those with a BMI ≤35 kg/m^2
- Assess for weight-related complications



Jensen MD, et al. 2013 AHA/ACC/TOS Guideline for the management of overweight and obesity in adults *J Am Coll Cardiol*. 2014;63(25 Pt B):2985-3023.

Lancet Diabetes & Endocrinology Commission on the Definition and Diagnosis of Clinical Obesity

- 58 commissioners (experts) from around the world used a consensus to arrive at recommendations
- Aim was to reframe the definition of clinical obesity as a condition in which the risk to health associated with excess adiposity be objectively documented by specific signs and symptoms reflecting biological alterations of tissues and organs, which is consistent with existing illness
- Met monthly from June, 2022 – Dec, 2024

Rubino F, et al. Lancet Diabetes Endocrinol 2025 (Published online

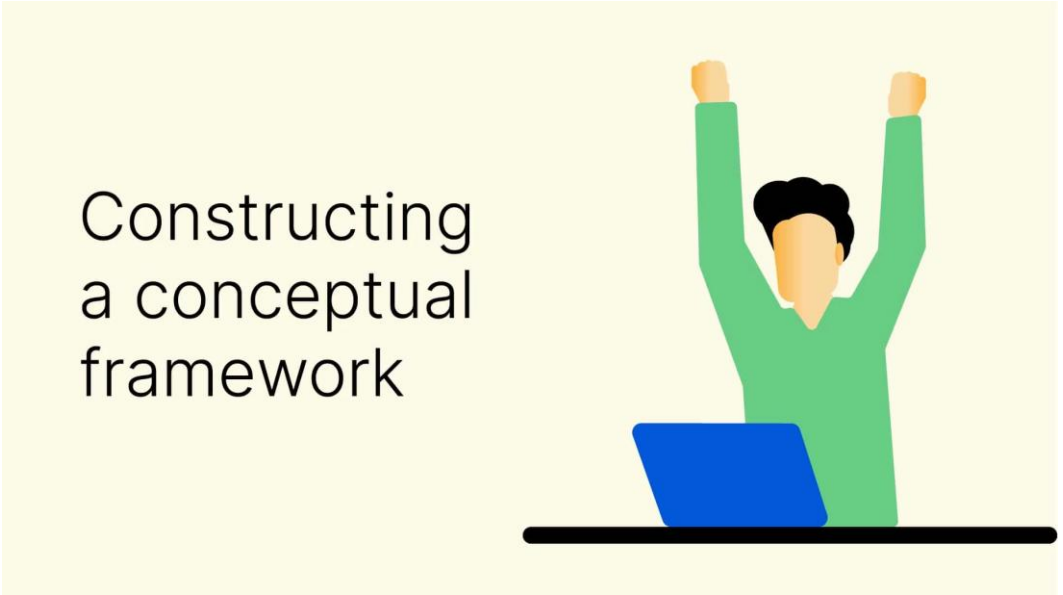
A New Framework for the Diagnosis of Illness due to Obesity

Introduction of 2 new terms: Clinical Obesity and Pre-Clinical Obesity

The commission pragmatically distinguishes clinical obesity from pre-clinical obesity, based on the presence or absence, respectively, of objective clinical manifestations (signs & symptoms) of altered organ function or impairment of an individual's ability to conduct daily activities.

Clinical assessment of obesity should be based on the two following objectives:

1. Confirmation of excess adiposity (obesity status)
2. Diagnosis of clinical or pre-clinical obesity based on objective measures of illness at the individual level

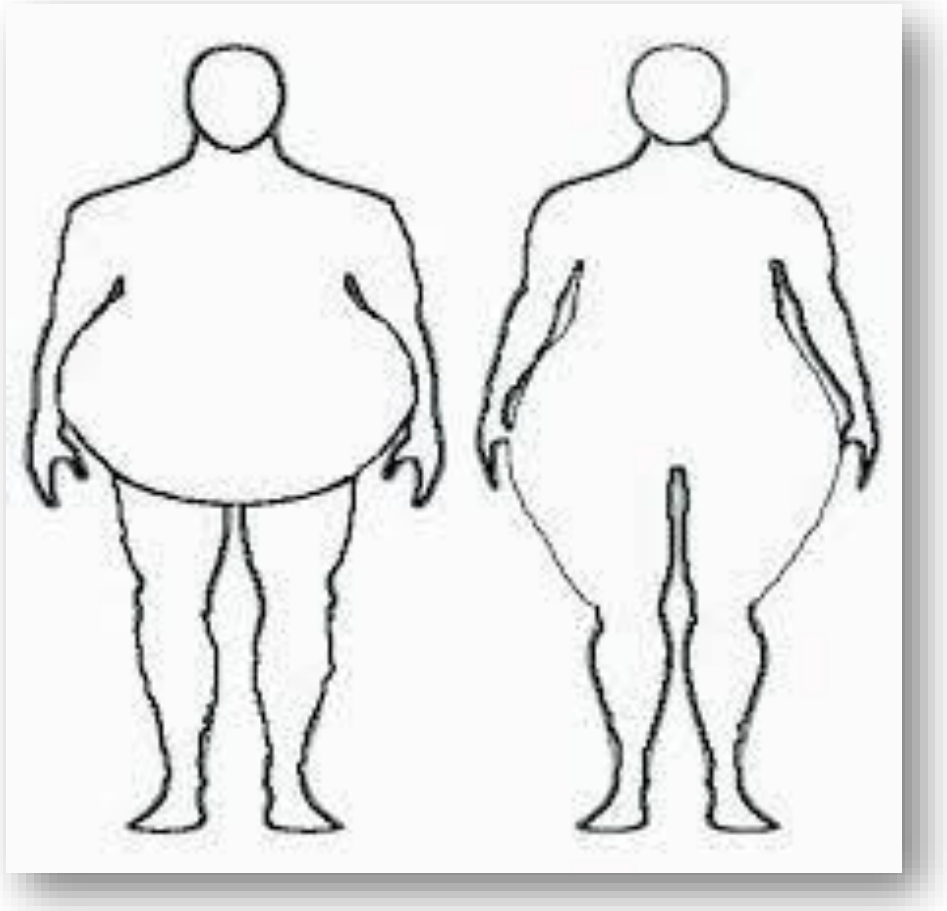


Rubino F, et al. Lancet Diabetes Endocrinol 2025 (Published online January 14)

Defining and Diagnosing Excess Body Fat

Confirmation of Excess Adiposity (obesity status) requires:

- At least <u>one</u> measurement of body size (waist circumference, waist-to-hip ratio or waist-to-height ratio) **in addition to** BMI
- At least <u>two</u> measurements of body size (waist circumference, waist-to-hip ratio or waist-to-height ratio) **regardless of** BMI
- Direct measurements of body fat (e.g., BIA or DEXA scan) can be used when available
- In people with very high BMI (>40 kg/m^2), however, the commission recognizes that it is pragmatically acceptable to assume confirmation of excess adiposity



Obesity is "*a condition characterized by excess adiposity, with or without abnormal distribution or function of adipose tissue*

Rubino F, et al. Lancet Diabetes Endocrinol 2025 (Published online January 14)

Diagnosis of Clinical Obesity

Requires confirmation of obesity status (excess body fat) **Plus** evidence of one or both of the following:

Reduced organ or tissue function specifically due to obesity, including signs and/or symptoms of impaired respiratory, cardiac, renal, musculoskeletal, metabolic, reproduction, hepatic, genito-urinary functions

Trouble with mobility and day-to-day activities such as bathing, eating, continence, etc due to the impact of excess body fat.

Rubino F, et al. Lancet Diabetes Endocrinol 2025 (Published online January 14)

Diagnosis of Pre-Clinical Obesity

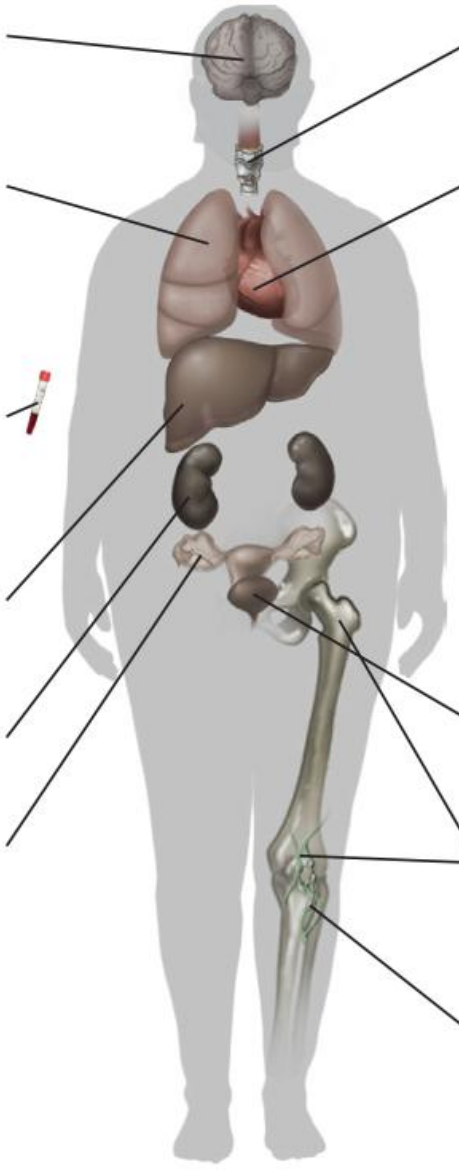
Requires confirmation of obesity status (excess body fat) **But**:

No signs or symptoms suggesting reduced organ or tissue function and an ability to conduct day-to-day activities unhindered.

People with preclinical obesity, however, have a variable but generally increased health risk, including risk of developing clinical obesity and other obesity-related diseases such as cardiovascular disease and some cancers.

Rubino F, et al. Lancet Diabetes Endocrinol 2025 (Published online January 14)

Diagnostic Criteria for Clinical Obesity



CNS
Vision loss, recurrent headaches, or both (due to raised intracranial pressure)

Respiratory system
Hypoventilation, breathlessness, wheezing, or any combination of these (due to reduced lung compliance, diaphragmatic compliance, or both)

Metabolism
The cluster of hyperglycaemia, high triglyceride levels, and low HDL cholesterol

Liver
Metabolic dysfunction-associated steatotic liver disease with fibrosis

Renal
Microalbuminuria with reduced eGFR

Reproductive
Anovulation, oligomenorrhea and polycystic ovary syndrome, male hypogonadism

Limitations of daily activities
Substantial, age-adjusted limitations of daily living

Upper airways
Apnoea or hypopnoea during sleep (due to increased upper airways resistance)

Cardiovascular system
- Heart failure with reduced ejection fraction (due to reduced left ventricular systolic function)
- Chronic fatigue and lower limb oedema (due to impaired diastolic function—heart failure with preserved ejection fraction)
- Chronic or recurrent atrial fibrillation
- Pulmonary artery hypertension
- Recurrent deep-vein thrombosis or pulmonary embolism
- Raised arterial blood pressure

Urinary system
Recurrent or chronic urinary incontinence

Musculoskeletal system
Chronic, severe knee or hip pain (associated with joint stiffness and reduced range of motion)

Lymphatic system
Lower limb lymphoedema (causing chronic pain, reduced range of motion, or both)

Management Recommendations

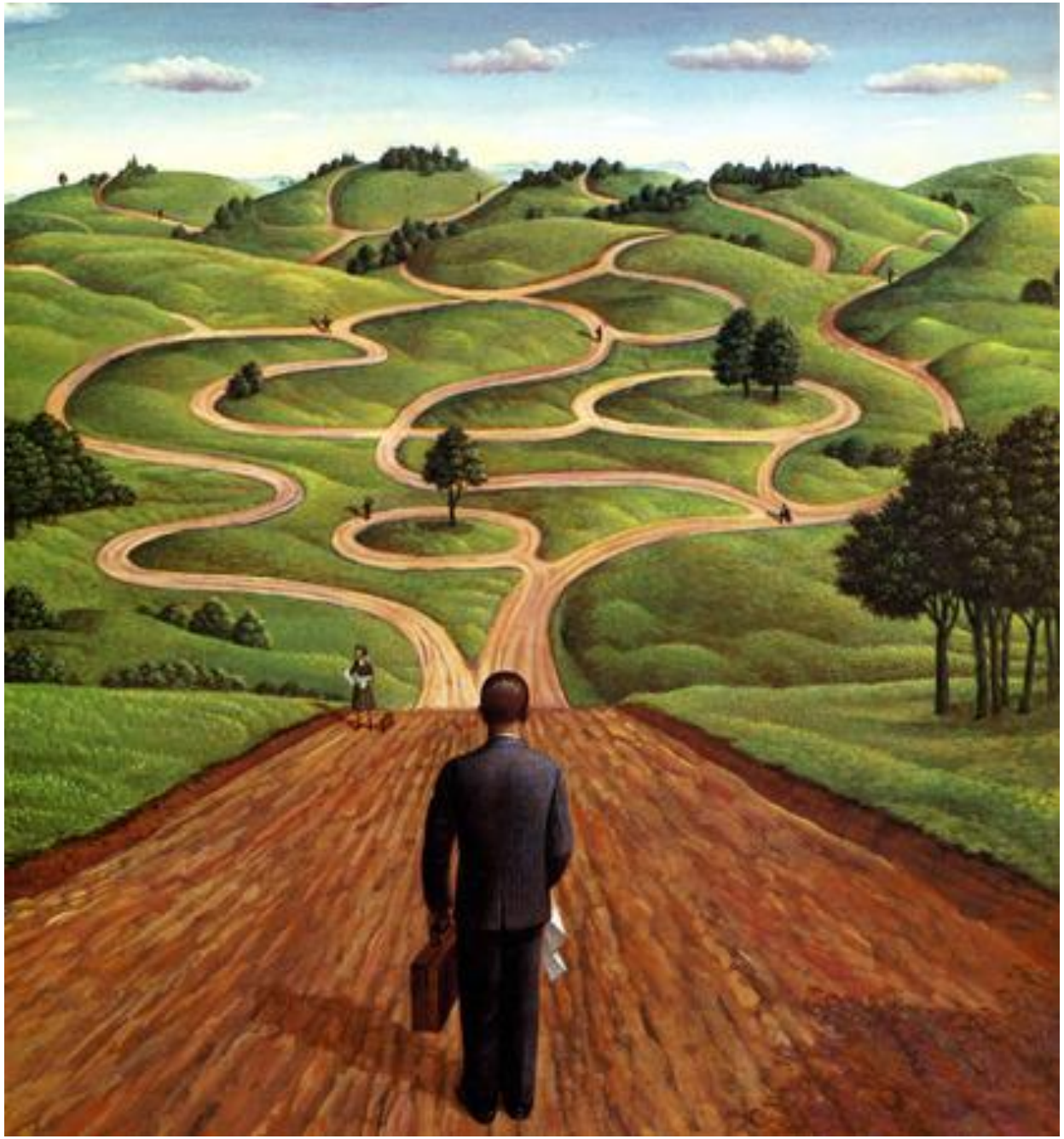
Clinical obesity

- Should receive comprehensive, evidence-based care that is timely and initiated with the aim to fully regain (remission) or improve the function which has been reduced by excess body fat.
- Successful treatment should be assessed by the improvement or resolution of clinical manifestations, rather than measures of weight loss alone.

Pre-clinical obesity

- The approach to care should focus on risk reduction and be based on the individual's specific level of risk
- May only need monitoring over time and health counselling rather than specific obesity treatment if the individual's risk of progression to clinical obesity or other diseases is deemed sufficiently low.

Rubino F, et al. Lancet Diabetes Endocrinol 2025 (Published online January 14)



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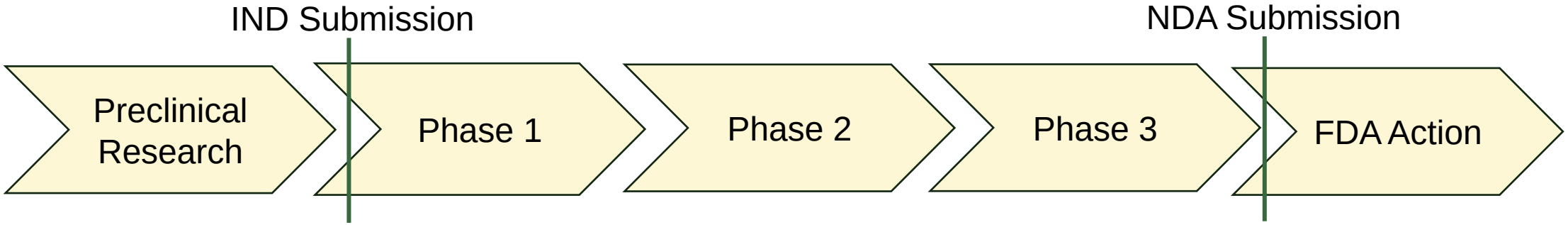
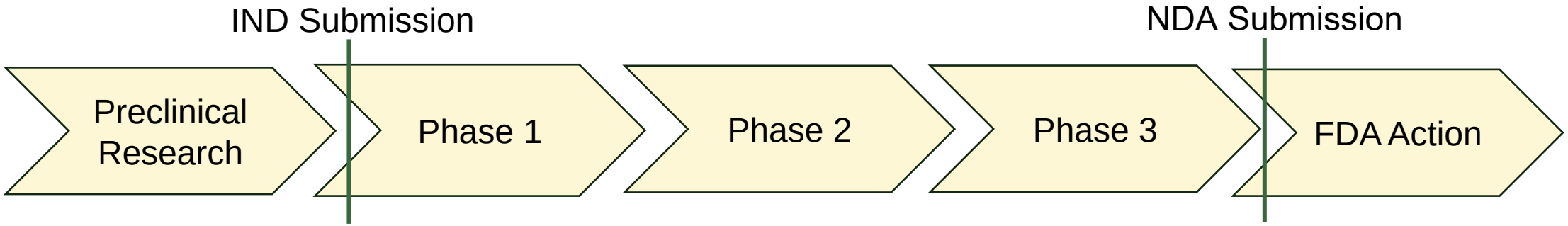
Questions?

FDA Drug Development Process



The Drug Discovery Process:
What Is It
and Its Major Steps

FDA Drug Development Process



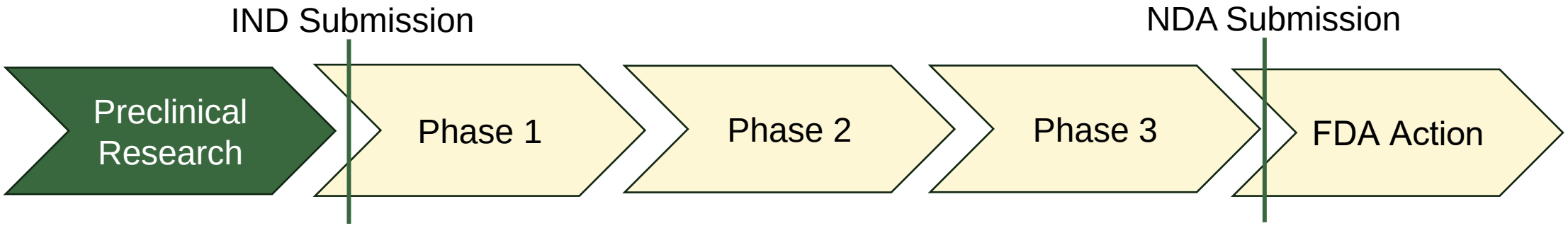
Obesity and Overweight: Developing Drugs and Biological Products for Weight Reduction

Guidance for Industry

January 2025
Clinical/Medical
Revision 2

DRAFT GUIDANCE

FDA Drug Development Process

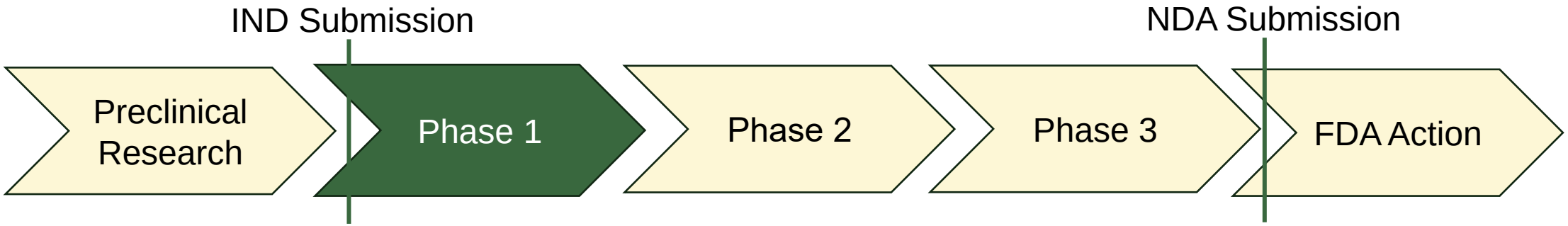


Purpose: To evaluate basic safety and biological effects in non-human subjects. Identify potential toxic effects and determine a safe starting dose for human trial

Tests: Lab and animal studies to assess toxicity, dosing, and mechanisms of action

Outcome: If results are promising, the company files an **Investigational New Drug (IND)** application with the FDA

FDA Drug Development Process



Participants: 20-100 healthy normal weight volunteers

Purpose: To determine safe dosage range, side effects, and how the body processes the drug

- Understand **Pharmacokinetics (PK)** - "What the Body Does to the Drug“ (Absorption, Distribution, Metabolism, Excretion - ADME): How the drug moves through the body
- Understand **Pharmacodynamics (PD)** – "What the Drug Does to the Body“ Mechanism of Action (MoA), Dose-Response Relationship, Therapeutic Window, Efficacy vs. Potency

Duration: Several months

FDA Drug Development Process

Purpose: The test effectiveness and further assess safety and optimal dosing

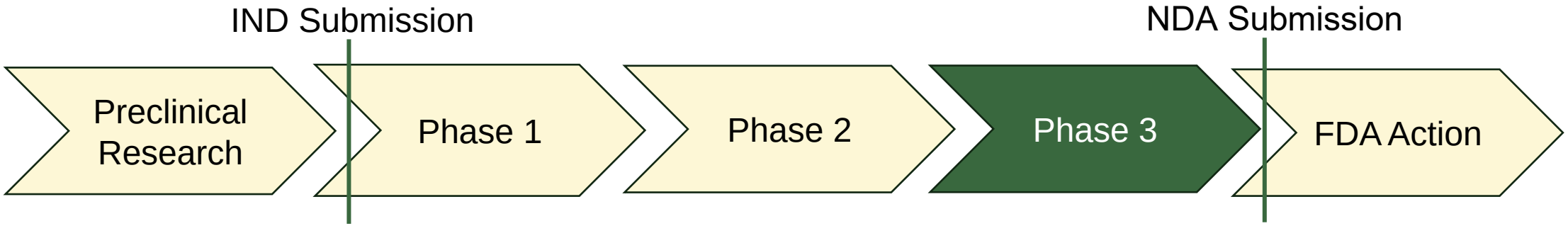
Participants: 100 – 500 adults who have BMI ≥30 or ≥27 if accompanied by at least 1 comorbidity

Study Type: Randomized, placebo-controlled

Primary Efficacy Endpoint: Comparison of the mean percentage change in body weight between drug and control

Duration: ~ 36 – 48 weeks

FDA Drug Development Process



Purpose: Confirm the drug's efficacy, safety and tolerability

Study Type: Randomized, placebo-controlled, and double-blinded for at least 1 year of treatment of drug vs control as an add-on to standardized recommendations for diet and physical activity in all randomized subjects

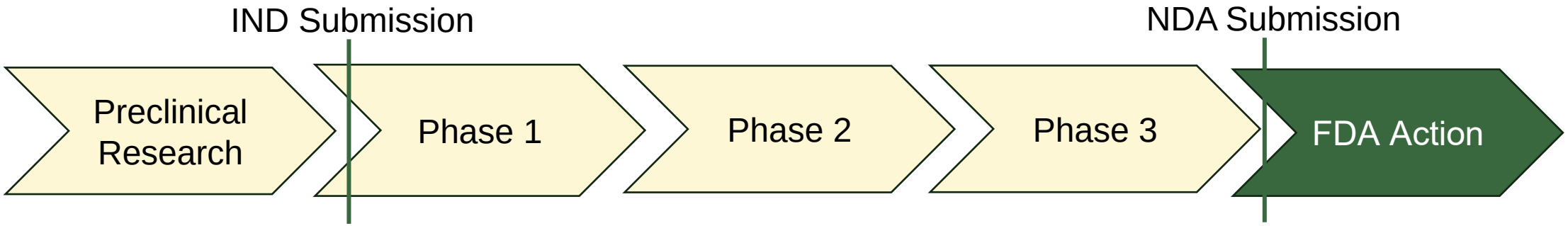
- Lifestyle-modification program should be applicable to patients who would be prescribed the drug and could be implemented in a primary care setting

Population: 3,000 subjects on drug versus at least 1500 on placebo; BMI ≥30 or ≥27 with at least 1 weight-related comorbidity to reflect patient population likely to use the drug

Primary Endpoint: Difference in mean percentage weight reduction between drug and control group of ≥5% and statistically significant

- Conduct ≥1 trial of subjects with type 2 diabetes
- Include other therapeutic targets: cardiometabolic, liver or renal disease
- A representative sample of subjects should have a baseline and follow up measurement of body composition by DXA or a suitable alternative

FDA Drug Development Process



The **NDA submission** is the formal request to the FDA to approve a new pharmaceutical for marketing

Filing & Validation (60 days) – The FDA reviews the submission for completeness

Review Process (6-10 months)

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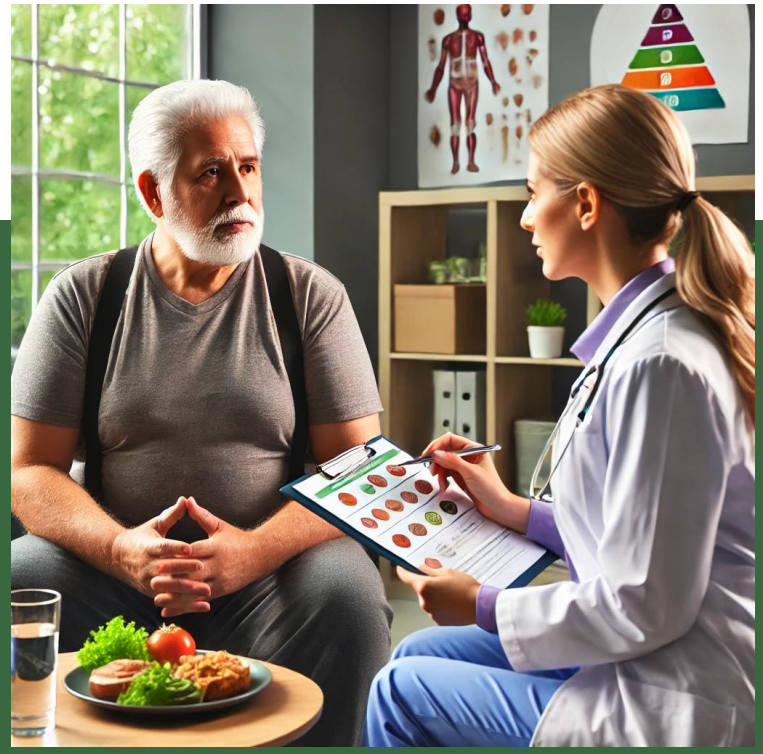
Questions?

UT Southwestern
Weight Wellness

Obesity Medications and the Physiology of Weight Loss



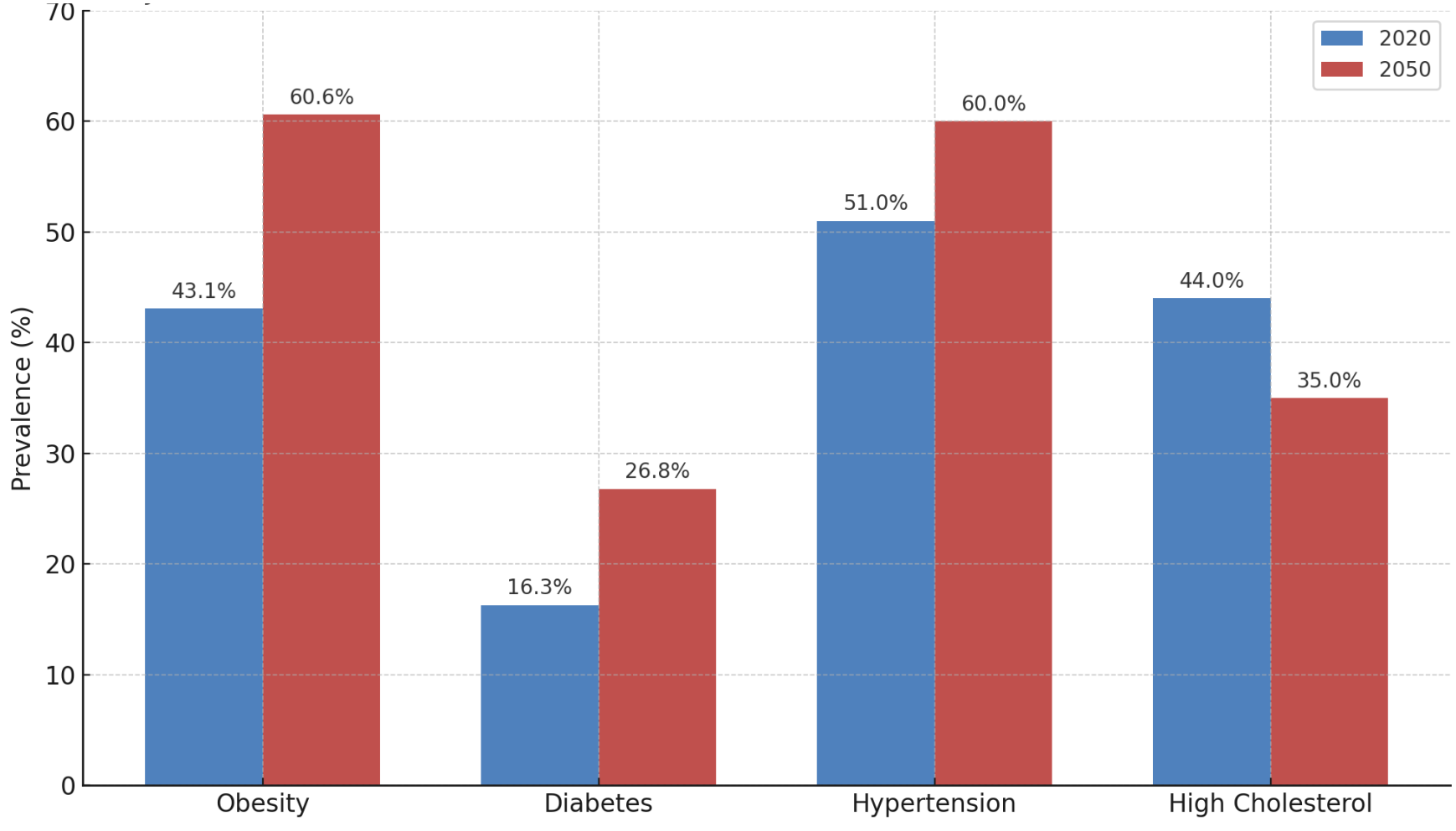
Jaime Almandoz, MD, MBA, DABOM, FTOS
Medical Director, Weight Wellness and Obesity Medicine
Associate Professor of Internal Medicine
Division of Endocrinology and Metabolism
UT Southwestern Medical Center, Dallas, Texas

Objectives

Explain how obesity management medications (GLP-1 analogs, incretin-based therapies, and future categories) impact human physiology to produce weight loss.

Explain the physiology and research to date on how the above obesity medications impact other chronic conditions.

Projected Prevalence of Adverse Cardiovascular Health Factors in US Adults 2020 to 2050

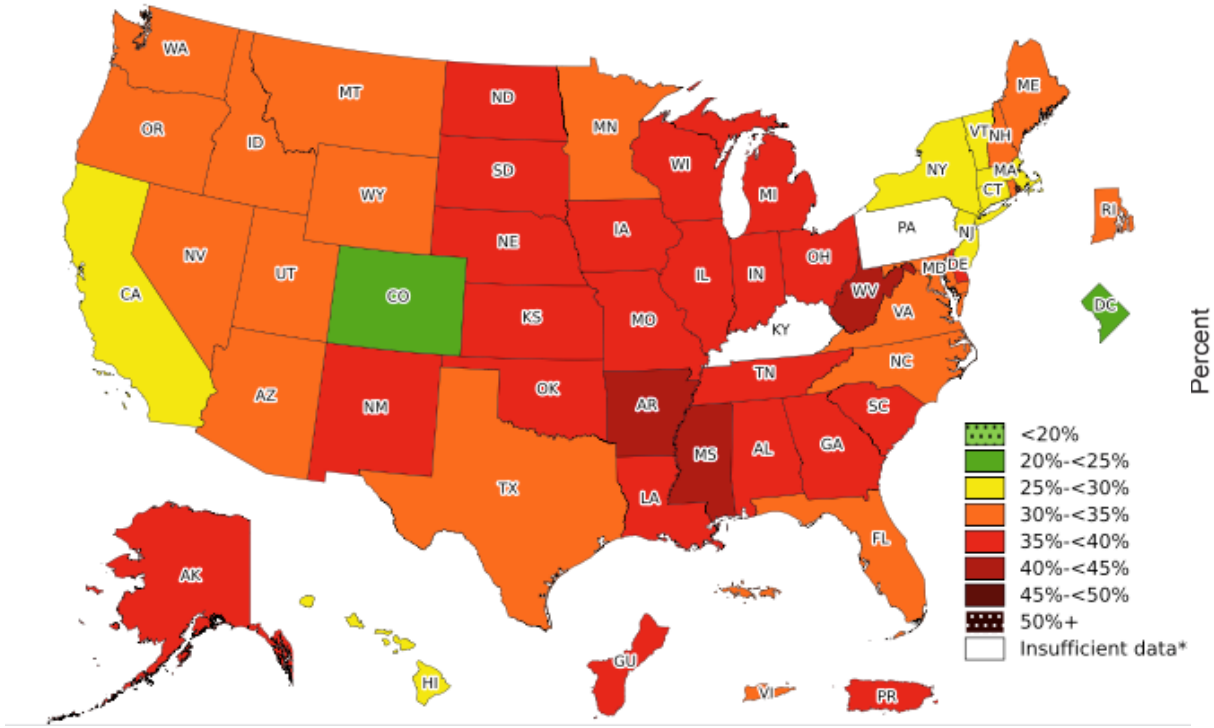


Joynt Maddox et al. Circulation. 2024;149:e00–e00

Prevalence of Obesity and Severity in US

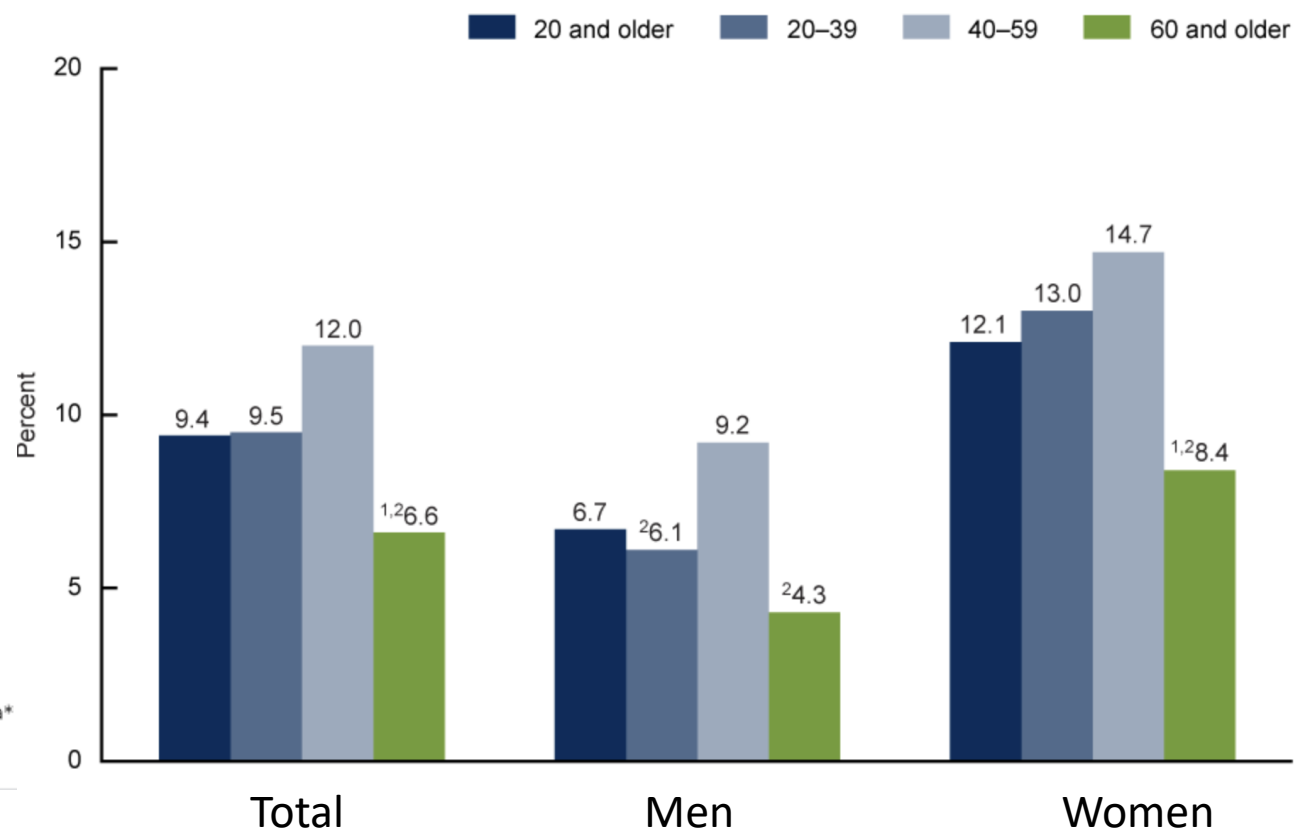
2023 Prevalence of Obesity in US Adults

more than 1 in 5 adults in all U.S. states and territories had obesity.



Centers for Disease Control and Prevention. *Adult Obesity Prevalence Maps*. U.S. Dept of Health and Human Services; 2023.

2023 Prevalence of Severe Obesity in US Adults



2000-2023: Class III obesity increased 4.7% to 9.4%

Emmerich SD et al. NCHS Data Brief, no 508. Sept. 2024

Magnitude of Weight Reduction and Health Improvements

- Blood glucose
- Triglycerides

3%

- HDL-Cholesterol[1]
- Systolic and diastolic blood pressure
- Hepatic steatosis measured by MRS[2]
- Patient Reported Outcome Measures
  - Symptoms of urinary stress incontinence[3]
  - Measures of sexual function[4,5]
  - Quality of life measures (IWQOL)[6]

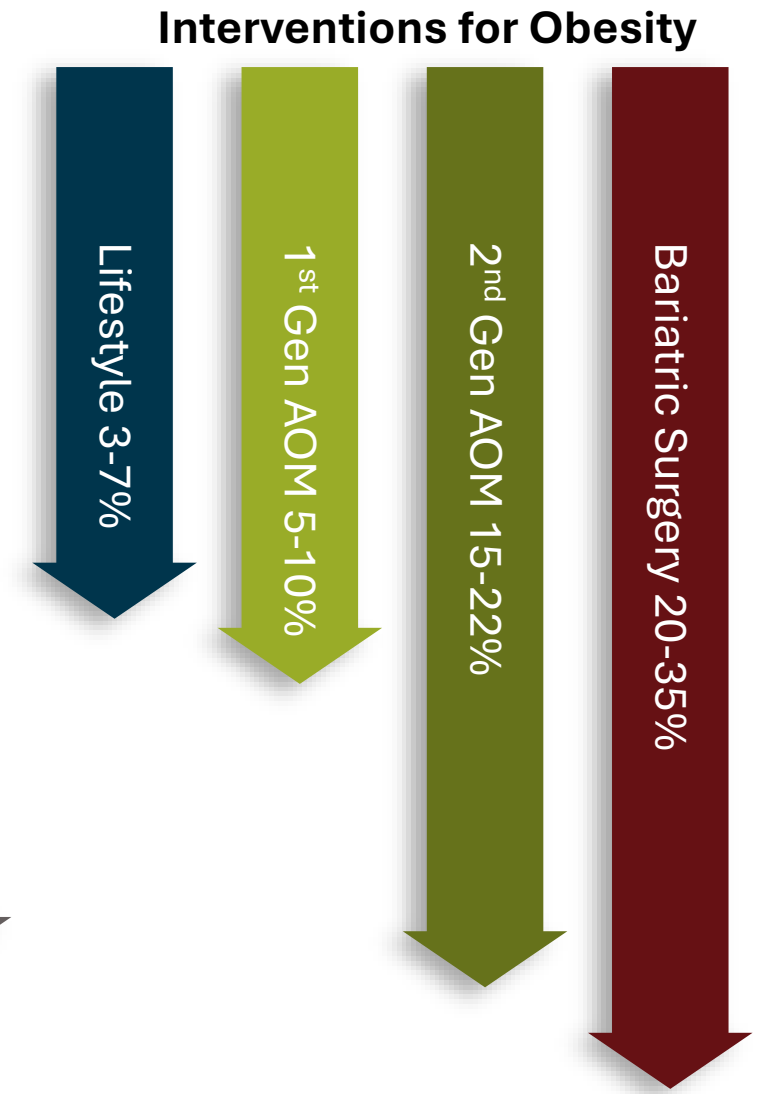
5%

- NASH (MASLD/MASH) Activity Score on biopsy[7]
- OSA Apnea-Hypopnea Index[8]

10%

- Remission of T2D, reduction in CV events, mortality

≥15%

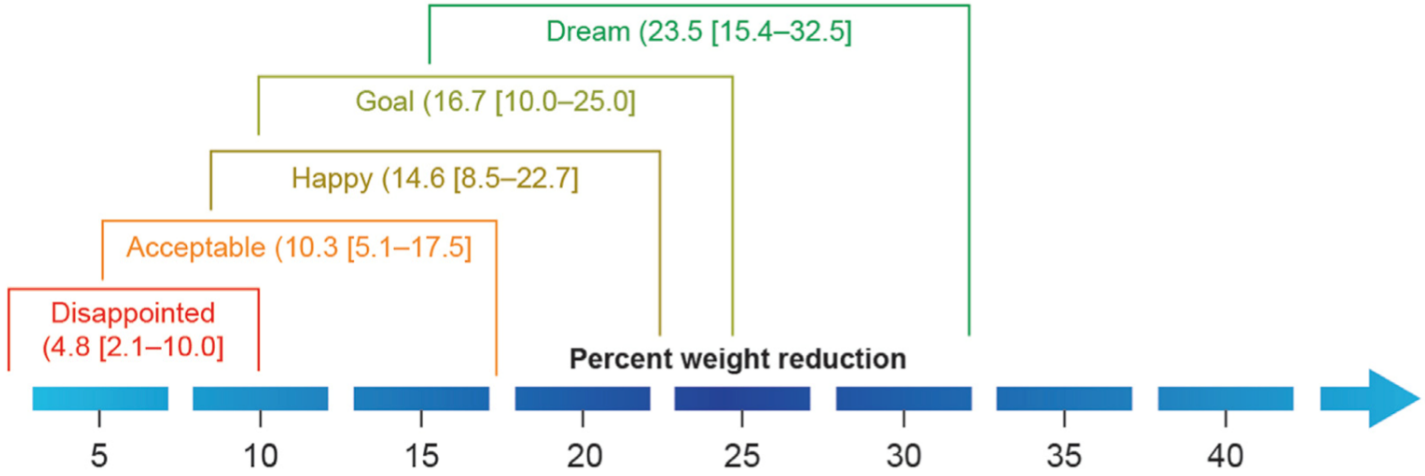


1. Wing RR et al. *Diabetes Care*. 2011;34:1481-1486. 2. Lazo M et al. *Diabetes Care*. 2010;33:2156-2163. 3. Phelan S et al. *J Urol*. 2012;187:939-944.
4. Wing RR et al. *Diabetes Care*. 2013;36:2937-2944. 5. Wing RR et al. *J Sex Med*. 2010;7:156-165. 6. Engel SG et al. *Obes Res*. 2003;11:1207-1213.
7. Promrat K et al. *Hepatology*. 2010;51:121-129. 8. Foster GD et al. *Arch Intern Med*. 2009;169:1619-1626. 9. Després JP et al. *BMJ*. 2001;322:716-720.

Patient Preferences for Weight Loss: OBSERVE Study Insights

Weight Loss Preferences Among People with Obesity (OBSERVE Study)

- **Median preferred weight reductions**:
  - Dream: **23.5%**
  - Goal: **16.7%**
  - Happy: **14.6%**
  - Acceptable: **10.3%**
  - Disappointed: **4.8%**



Individual Differences in Preferences

- **Women preferred greater weight loss** than men
- **Higher BMI** and **weight self-stigma** were associated with higher weight loss goals
- **Hispanic participants** had significantly higher preferred reductions than White participants
  - Especially among **Hispanic women**

Gudzune et al. Endocrine Practice. 2024 Jun 18

Patient Preferences for Weight Loss: OBSERVE Study Insights

Preferences better align with newer AOMs or surgery:
Lifestyle changes or older medications unlikely to meet patient goals—supporting use of **highly effective OM therapies** or **bariatric interventions**.

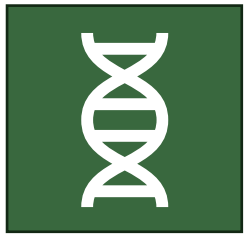
Shared decision-making is crucial:
Tailoring care to **patient preferences** may improve satisfaction, adherence, and outcomes in obesity treatment.

Weight stigma influences goals:
Patients with greater internalized stigma reported more extreme weight-reduction desires—underscoring the need for holistic care approaches.

Gudzune et al. Endocrine Practice. 2024 Jun 18

Limitations of Diet and Exercise for Long-Term Weight Loss

Most individuals regain lost weight
Only ~15–25% of people can maintain ≥10% weight loss through lifestyle interventions alone.



Highly individual response:
Genetic and environmental factors cause wide variability in weight loss and recurrence outcomes.

Short-lived effects of diet and exercise:
Most lifestyle interventions show weight loss plateau after 6–9 months, often followed by gradual regain.

Behavioral fatigue and lack of reinforcement often undermine long-term adherence to diet and exercise.

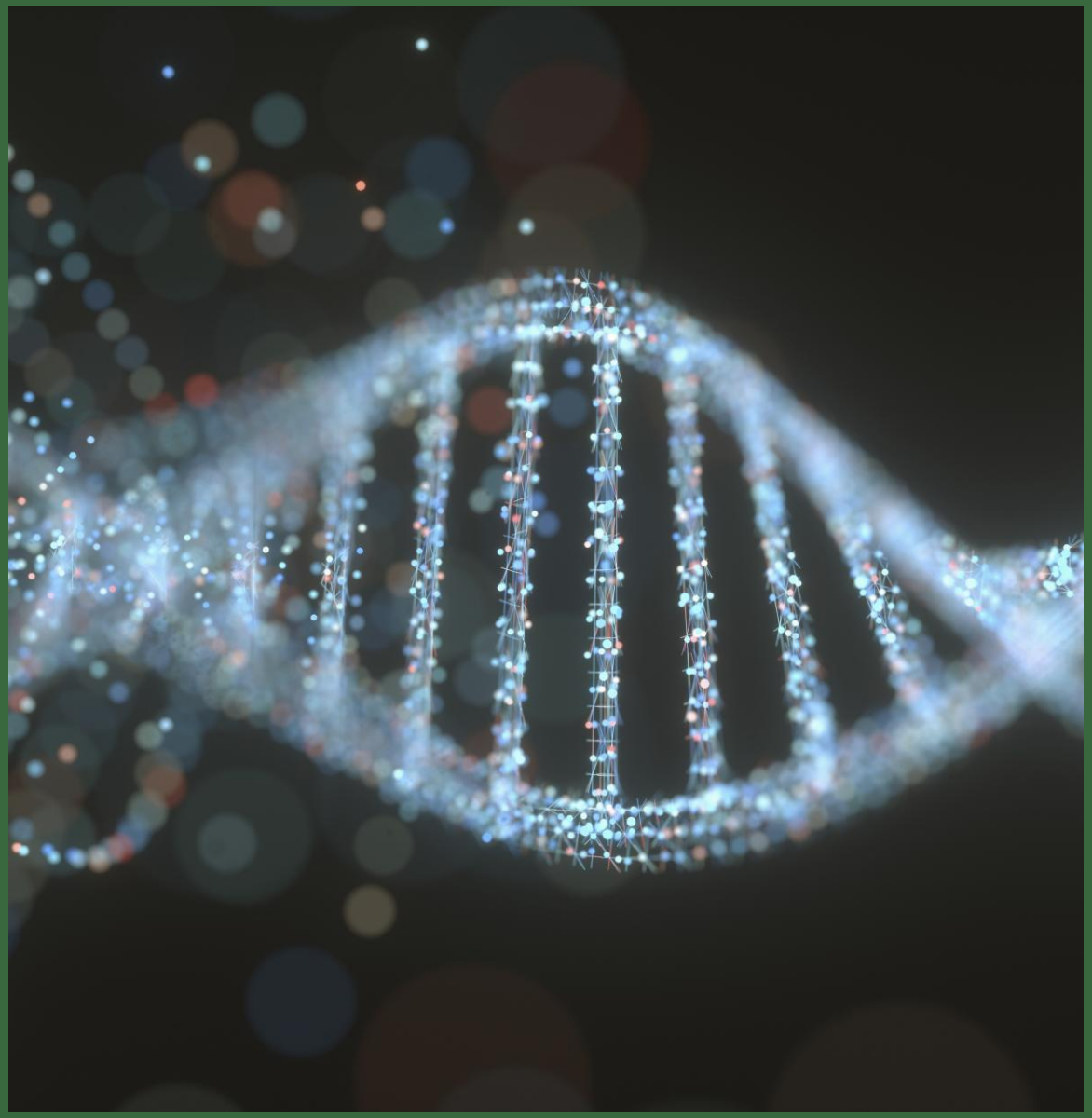
Rosenbaum M, Foster G. Nat Metab. 2023 Aug;5(8):1266-1274

Limitations of Diet and Exercise for Long-Term Weight Loss

Biological resistance to weight loss: Weight loss triggers metabolic and neuroendocrine adaptations that favor weight regain, including:

- ↓ Resting energy expenditure
- ↑ Muscle efficiency (lower caloric burn for same activity)
- ↑ Hunger, ↓ Satiety

CNS-mediated regulation: Evolutionarily conserved systems strongly defend body fat stores via hormonal and neuronal signals.



Rosenbaum M, Foster G. Nat Metab. 2023 Aug;5(8):1266-1274

Homeostatic Hunger – A Physiologic Survival Mechanism

- Triggered by **acute caloric deprivation** to maintain energy balance
- Governed by the **hypothalamus–gut axis** and **neuroendocrine signaling**
- Initiated by:
  - **Empty stomach → Ghrelin release**
  - **Low blood sugar → Hypothalamic activation**
  - **Motilin-driven gut contractions**
- Signals via **vagus nerve, dopamine**, and **AgRP neurons in the hypothalamus**
- Suppressed by:
  - **Gastric distention** → vagal mechanoreceptors
  - **Nutrients** (amino acids, fats) → **GLP-1, PYY, CCK release**
  - **Increased insulin and glucose levels, and satiety hormones**
- Leads to **progressive satiety**: early (mechanical), medium (hormonal), late (metabolic).

Fasano N Engl J Med 2025;392:372-81

Hedonic Hunger – Pleasure Over Necessity

Driven by **reward and emotional stimuli**, not energy need

Dominates in **food-rich environments**, bypassing metabolic regulation

Triggered by:
- **Sensory cues** (sight, smell, ads)
- **Emotions** (stress, sadness, joy)

Linked to:
- **Dopamine reward pathways**, **endocannabinoids**, **orexin**, **opioids**
- **Cravings for sugar, fat, and salt**

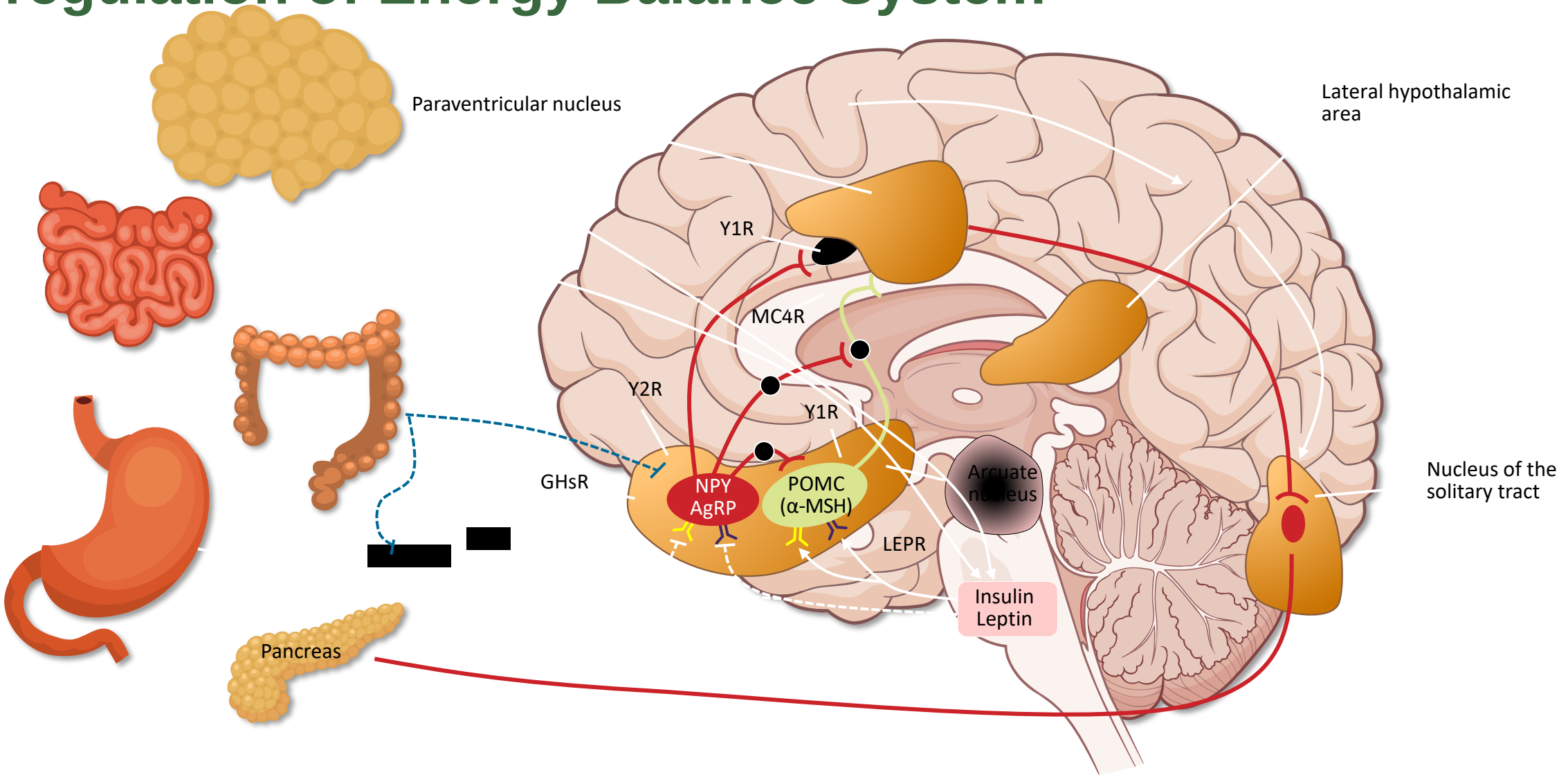
Measured by the **Power of Food Scale (PFS)**

Often **unrelated to BMI**, but may lead to **impulse-driven eating**

Requires **individualized strategies** to address effectively

Fasano N Engl J Med 2025;392:372-81

Dysregulation of Energy Balance System



FDA-Approved Obesity Medications

UT Southwestern Weight Wellness

Bupropion/ Naltrexone

Bupropion blocks reuptake of dopamine and norepinephrine in various brain regions, including the mesolimbic reward pathway, prefrontal cortex, and hypothalamus. Naltrexone inhibits opioids in the mesolimbic dopamine system.

↑ DA/NE

DA/MOP-R

Phentermine-Topiramate

↑ NE/DA/5-HT

GABA-R and CAI

Affects various brain regions involved in mood regulation, including the cortex, hippocampus, and amygdala

GLP-1 RA and dual GIP/GLP-1 RA

Liraglutide
Semaglutide

GLP-1 RA

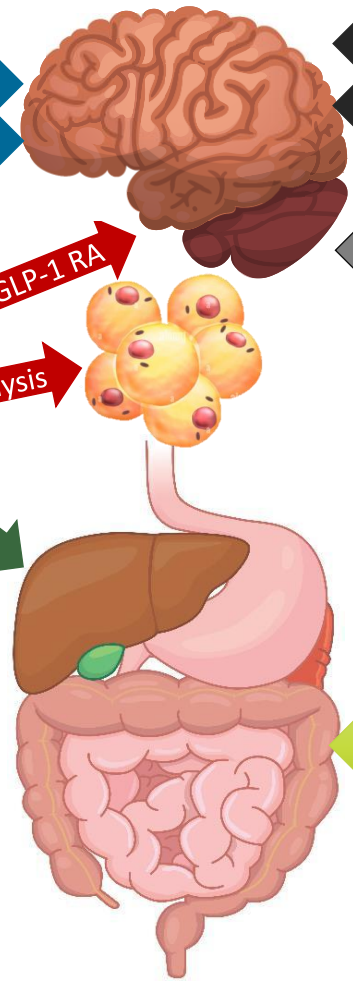
Tirzepatide

GIP/GLP-1 RA

↓↑ Lipolysis

↓ GASTRIC EMPTYING

↓ GASTRIC EMPTYING



Phentermine

↑ NE/DA/5-HT

Increases the release of norepinephrine, dopamine and serotonin in the hypothalamus.

GLP-1 RA

Act centrally in the brainstem, hypothalamus, and reward centers of the brain to increase glucose-dependent insulin secretion, inhibit glucagon secretion, and delay gastric emptying.

GIP/GLP-1 dual RA

Augment the central acting effect on appetite suppression.

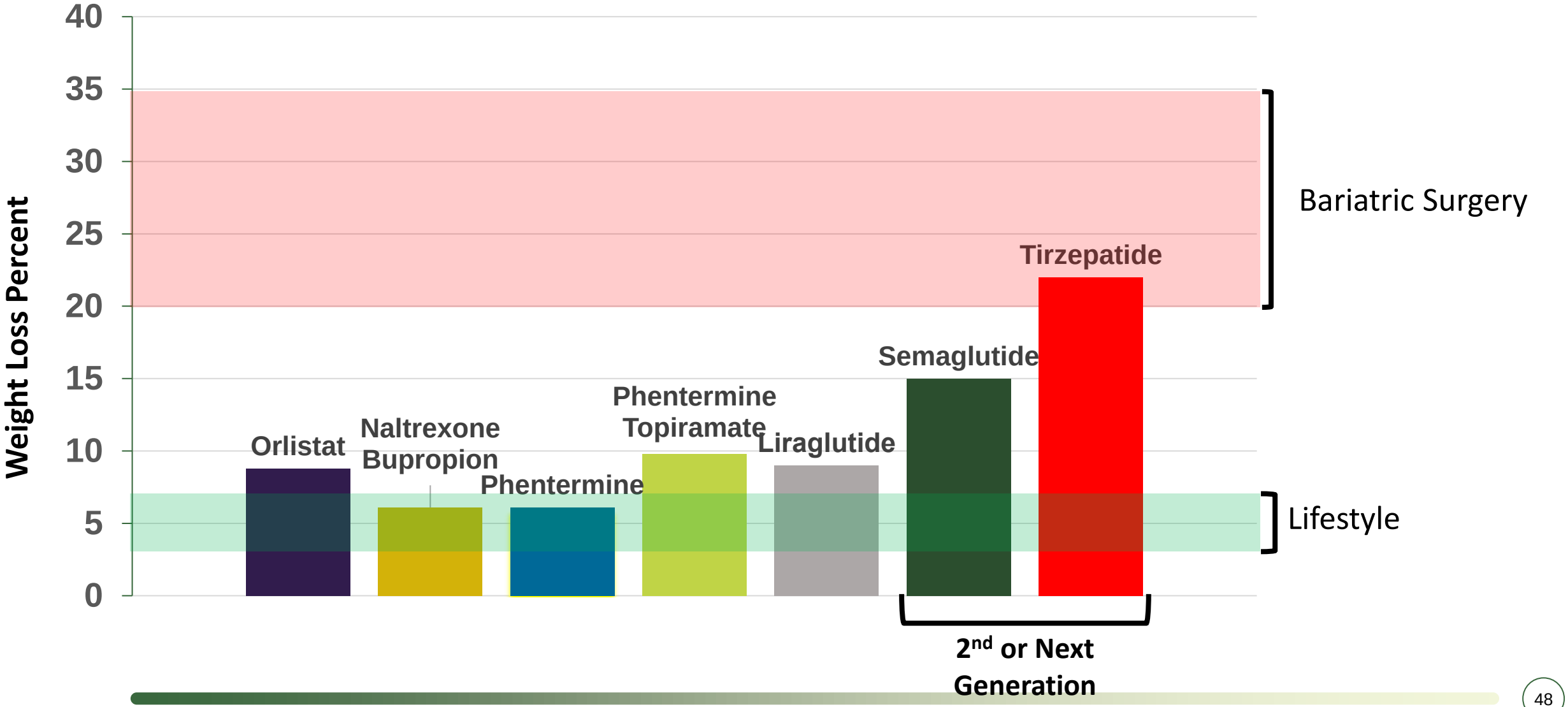
Orlistat

LIPASE INHIBITION

Deactivates pancreatic and gastric lipases that facilitate fat absorption in the small intestine.

Gudzune K, Kushner R, JAMA. 2024;332(7):571-584

Effectiveness of Obesity Medications vs. Lifestyle and Bariatric Surgery for Treating Obesity



1. Chakthoura M et al. *eClinicalMedicine*. 2023;58:101882. 2. Peterli R et al. *JAMA*. 2018;319:255-265.

Significant Sustained Weight Loss With Non-GLP-1RA

Average weight loss 10.4% with a mean follow-up of 4.4 years

At Final Visit

- Mean OMs at final visit: 2.1
- 65.0% taking ≥2 OM
- Mean number of OM trialed: 4.3

Patients who Maintained ≥10% WL

- 92 unique OM combinations
- 13% metformin monotherapy
- 9% metformin, phentermine, topiramate

Key Predictors of ≥10% Weight Loss

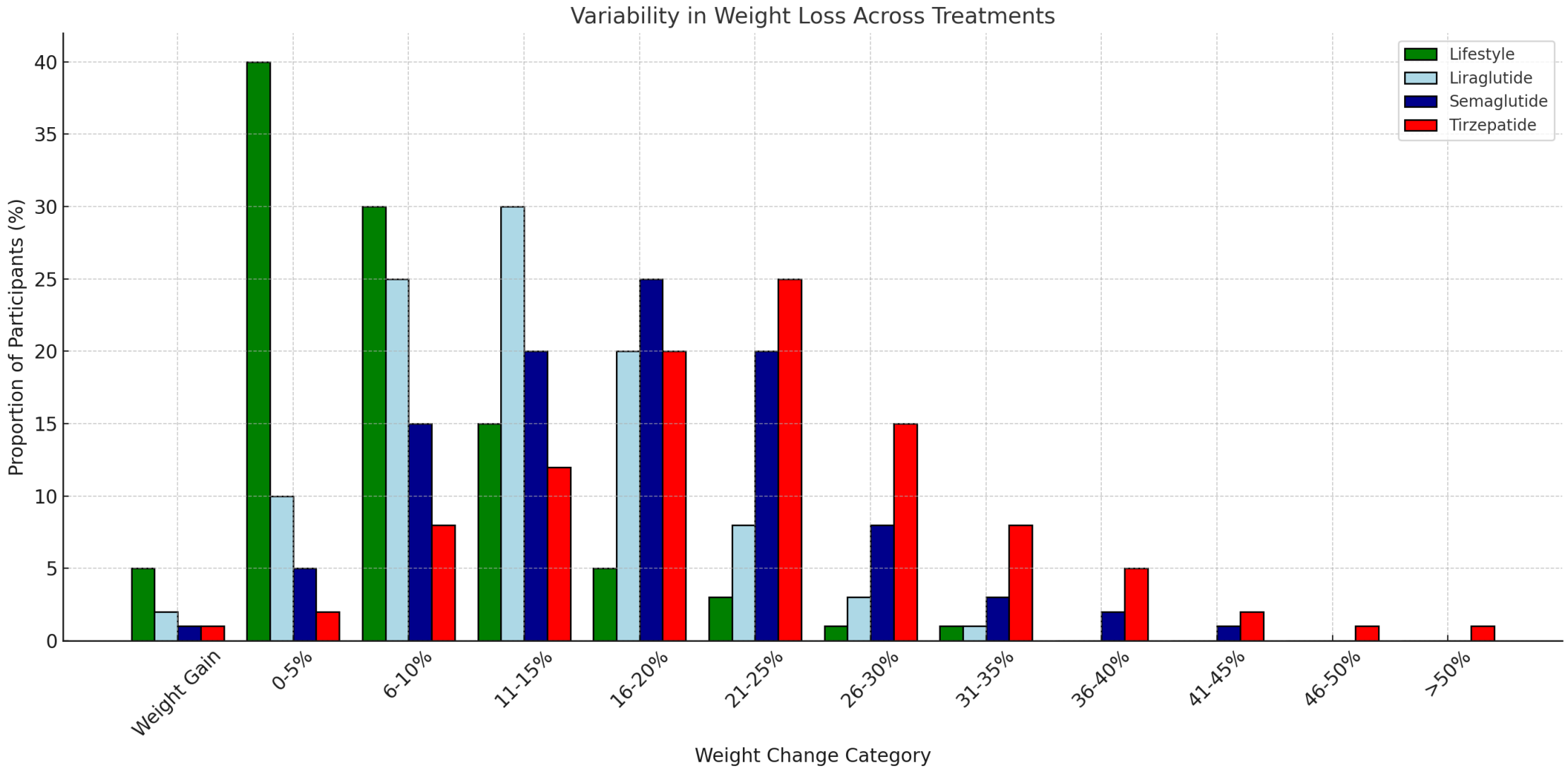
- More clinic visits OR 1.04, *P* = .002
- Metformin OR 1.91, *P* = .009
- Topiramate OR 2.50, *P* < .001
- Bupropion OR 2.06, *P* = .013

Clinical Implications

- Long-term AOM use can yield **clinically meaningful, durable weight loss**
- **Polypharmacotherapy** mirrors management of other chronic diseases
- Real-world evidence supports need for **personalized, sustained therapy**

Weintraub et al. JCEM, 2023, 108, e832–e841

Weight Loss Varies with GLP-1 and GIP/GLP-1 RA



Perdomo et al. Lancet. 2023;401:1116.

Weight Recurrence After GLP-1/GIP Therapy Cessation

STEP 1 Extension (Semaglutide 2.4 mg)

•Participants lost **17.3% of body weight** over 68 weeks on semaglutide + lifestyle

•After stopping treatment and lifestyle support:

- Regained **~11.6 percentage points** of lost weight
- Net loss at 1-year post-cessation: **only –5.6%**

•**~2/3 of weight lost was regained** within 1 year

•Cardiometabolic benefits (e.g., HbA1c, BP, lipids) also **reverted toward baseline**

•Findings underscore **need for long-term treatment** in chronic obesity care

SURMOUNT-4 (Tirzepatide)

•During initial 36-week lead-in, mean weight loss: **–20.9%**

•After switching to placebo:

- Participants regained **~14% of body weight**
- Net loss from baseline: **–9.9%**

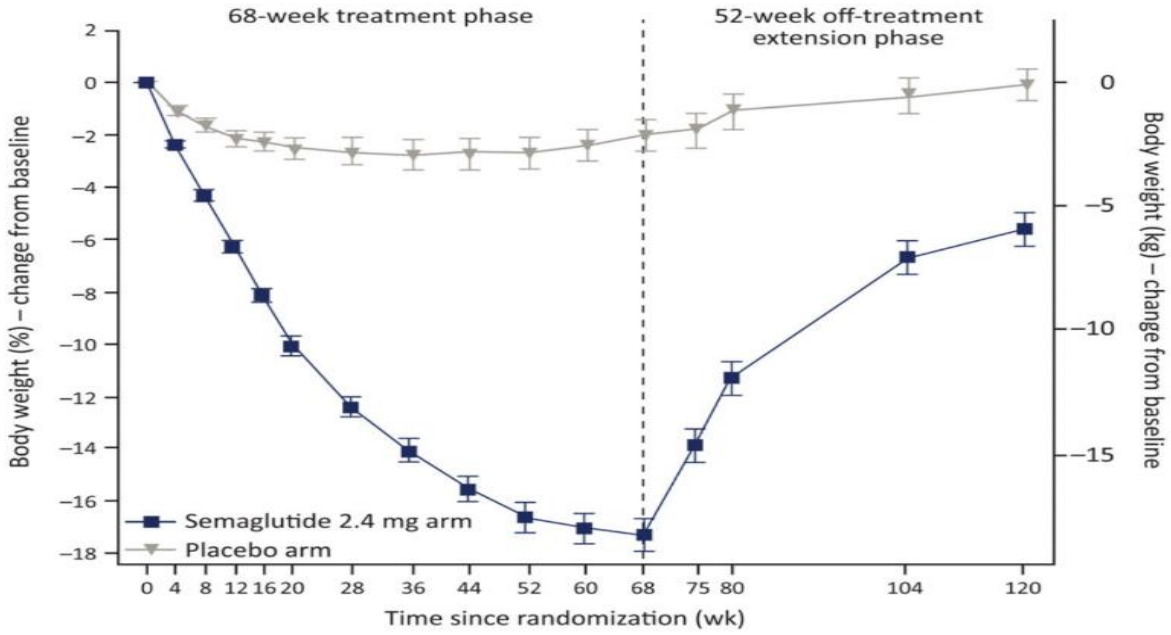
•Those who continued tirzepatide lost an **additional 5.5%** → total **–25.3%**

•Only **16.6%** of those switched to placebo **maintained ≥80% of weight loss**

- vs **89.5%** on continued tirzepatide

•Continued therapy prevented recurrence and maintained improvements

STEP-1 Extension Semaglutide



Wilding et al. Diabetes Obes Metab. 2022;24:1553–1564; Aronne et al. JAMA. 2024;331(1):38-48

Persistence with Obesity Medications

Study Overview

- Retrospective cohort of **1,911 adults** with obesity in Ohio and Florida (2015–2022)
- Evaluated persistence with AOM at **3, 6, and 12 months** after initial prescription fill
- Median BMI: 38 kg/m²; 75% female; 84% privately insured

Persistence Rates

- 3-month: **44%**
- 6-month: **33%**
- 12-month: **19%**

Medication-Specific 12-Month Persistence

- Semaglutide: **40%**
- Liraglutide: **17%**
- Phentermine-topiramate: **13%**
- Naltrexone-bupropion: **10%**
- Orlistat: 0%

Key Predictors of 1-Year Persistence

- Semaglutide: **AOR 4.26** (95% CI: 3.04–6.05) vs phentermine-topiramate
- Naltrexone-bupropion: **AOR 0.68** (CI: 0.46–1.00)
- Each 1% weight loss at 6 months → **6% ↑ odds** of 12-month persistence

Gasoyan et al. Obesity. 2024 Mar;32(3):486-493

Factors Associated with GLP-1 Discontinuation

- **30% of patients discontinued** within the **first 4 weeks**, before reaching therapeutic dose
- **Age 18–34** was the group **most likely** to discontinue early
- **High social vulnerability** (e.g., financial hardship, access barriers) linked to **lower persistence**
- Prescriptions from **non-specialists (e.g., PCPs, OB/GYNs)** associated with **lower treatment duration**
- **Fewer provider visits** during the first 12 weeks predicted early discontinuation
- **Higher out-of-pocket costs** (esp. $60–99/month) reduced persistence vs lower costs improved
- **Southern U.S. regions** and **rural areas** had lower rates of persistence
- **GI side effects** (nausea, vomiting) during dose titration frequently led to drop-out
- Patients with **fewer comorbidities** were more likely to discontinue early

Loss of Employer Sponsored Coverage

THE WALL STREET JOURNAL.

HEALTH | HEALTHCARE

Employers Cut Off Access to Weight-Loss Drugs for Workers

As costs mount for popular drugs such as Wegovy, a cousin of Ozempic, health plans are restricting coverage to save money

By Peter Loftus Follow

Aug. 2, 2023 at 5:30 am ET

The University of Texas System said it would end coverage of Novo Nordisk's Wegovy and Saxenda for its employees and others covered by its healthcare plans. PHOTO: BILL MCCULLOUGH FOR THE WALL STREET JOURNAL

Wall Street Journal, August 2, 2023

Variable Global Pricing for GLP-1 Obesity Meds

Global Pricing of Semaglutide for Obesity (S/C)

Prices vary drastically across countries for the **same medication**

- **Highest price**: $804 per 30-day course in the **United States**
- **Lowest price**: $95 in **Turkey**

Estimated minimum price (EMP): $40

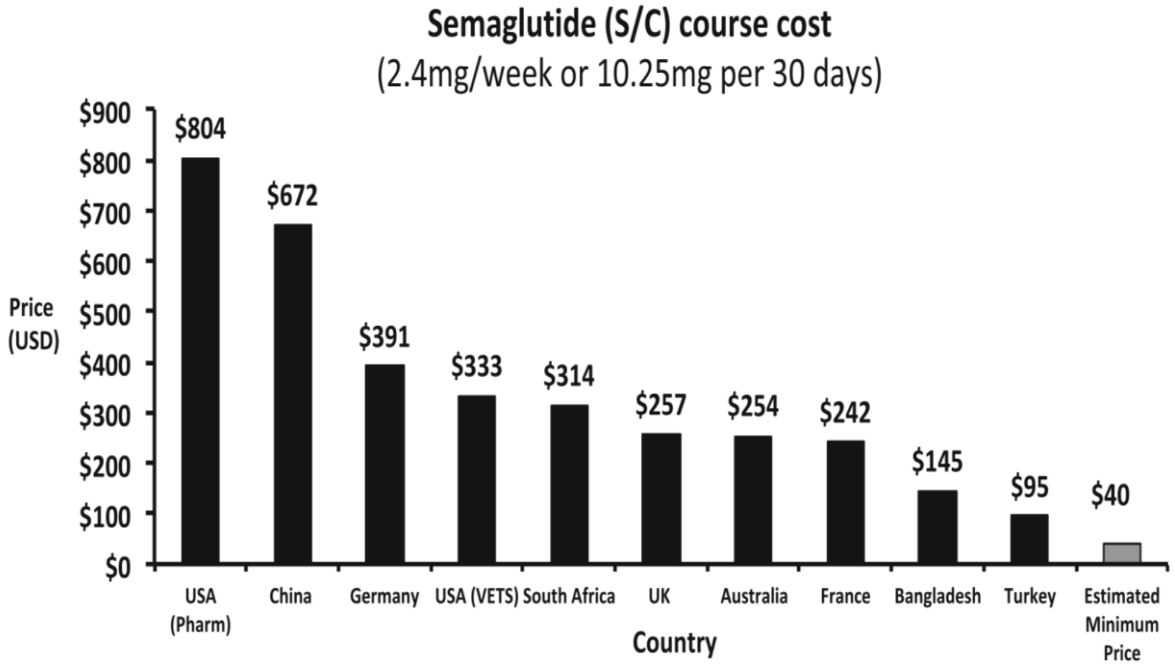
- Based on manufacturing costs + formulation + packaging + 10% profit

Despite similar cost to produce, **U.S. price is ~20× higher than EMP**

Oral semaglutide (14 mg daily):

- US $578 vs IN $65

Cost of GLP-1 therapy remains a major barrier to global access and equitable care



Levi et al. *Obesity (Silver Spring). 2023;31:1270–1279*

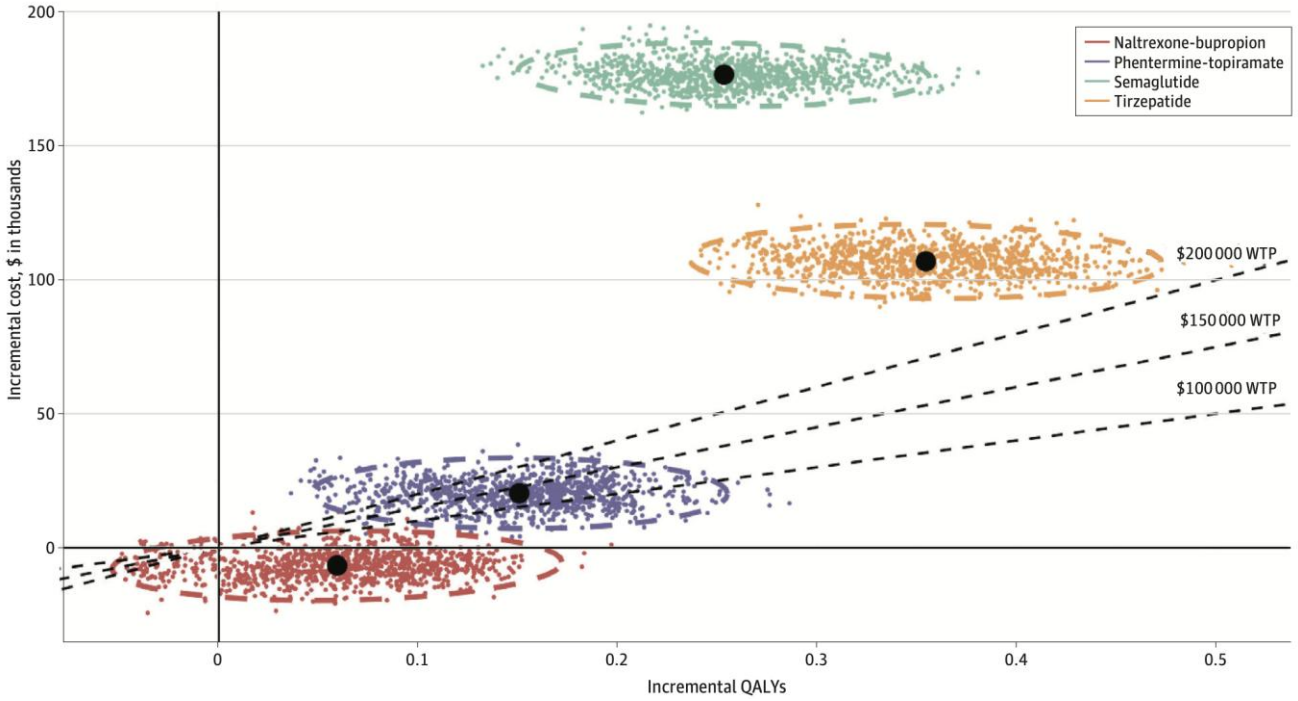
Cost-Effectiveness of the Obesity Medications vs Lifestyle Modification Over a Lifetime

Health Benefits (per 100,000 eligible individuals)

- **Obesity cases averted**:
  - Tirzepatide: **45,609**
  - Semaglutide: **32,087**

- **Diabetes cases averted**:
  - Tirzepatide: **20,854**
  - Semaglutide: **19,211**

- **Cardiovascular cases averted**:
  - Tirzepatide: **10,655**
  - Semaglutide: **8,263**



- Both meds produced the **greatest gains in life-years and QALYs**

Hwang et al. *JAMA Health Forum.* 2025;6(3):e245586

Cost-Effectiveness of the Obesity Medications vs Lifestyle Modification Over a Lifetime

Cost-Effectiveness (ICER per QALY gained)

- **Tirzepatide**: $197,023/QALY
- **Semaglutide**: $467,676/QALY
- Not cost-effective at current net prices ($100K/QALY benchmark)

Required Discounts to Meet $100K/QALY

- Tirzepatide: **–30.5%** from net price
- Semaglutide: **–81.9%** from net price

Key Implications

- Both drugs deliver **substantial lifetime health gains**
- But are not **economically sustainable** at current prices
- **Policy changes and price negotiations** are needed for equitable access
- **Naltrexone-bupropion** was cost-saving; **phentermine-topiramate** cost-effective only in select groups

Hwang et al. *JAMA Health Forum.* 2025;6(3):e245586

Semaglutide 2.4 mg for Weight Loss in People with Obesity Without Diabetes (SELECT Trial)

17,604 participants with overweight/obesity and preexisting cardiovascular disease

- Once-weekly **semaglutide 2.4 mg vs placebo** over **208 weeks**

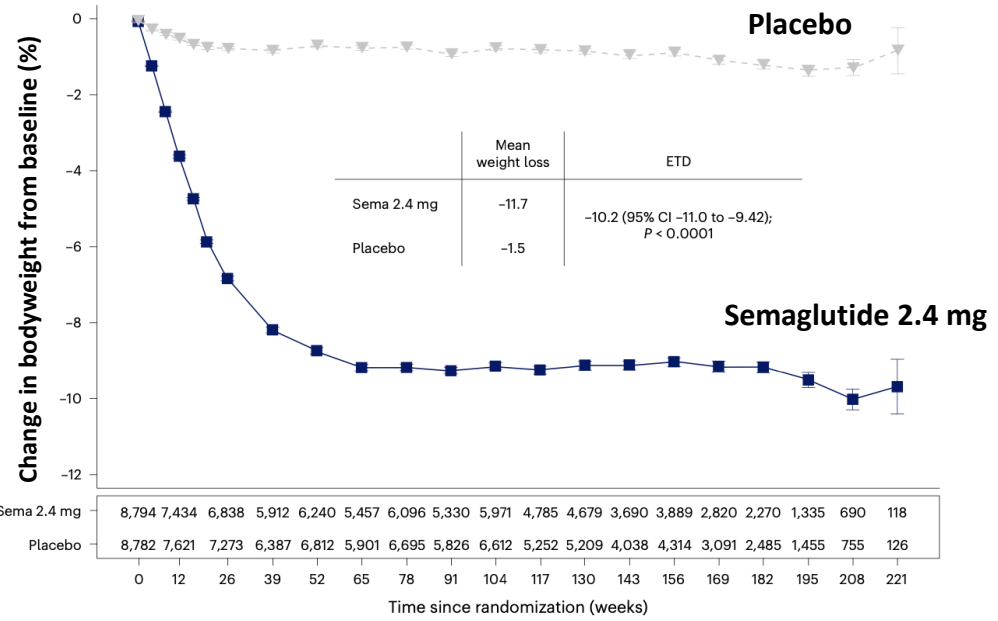
Clinically Meaningful Weight Loss Achieved

Mean weight loss: Semaglutide: **−10.2%** vs. placebo: **−1.5%**

- ≥5% loss: **67.8% (sema)** vs 21.3% (placebo)
- ≥10% loss: **44.2% (sema)** vs 6.9%
- ≥20% loss: **11.0%**

Anthropometric Improvements

- **Waist circumference**: −7.7 cm vs −1.3 cm (P < 0.0001)
- **BMI category improvement**:
  - **52.4% sema** vs 15.7% placebo
  - 12% reached **BMI <25 kg/m²** (vs 1.2% placebo)



Ryan et al. Nat Med. 2024 Jul;30(7):2049-2057

Tirzepatide for Obesity and T2D Prevention SURMOUNT-1 Trial

3-year data on weight change and T2D Prevention

Up to 20% weight loss sustained over 176 weeks

- Mean loss:
  - 12.3% (5 mg)
  - 18.7% (10 mg)
  - 19.7% (15 mg)
- Compared to just **−1.3% with placebo**

Marked reduction in progression to type 2 diabetes

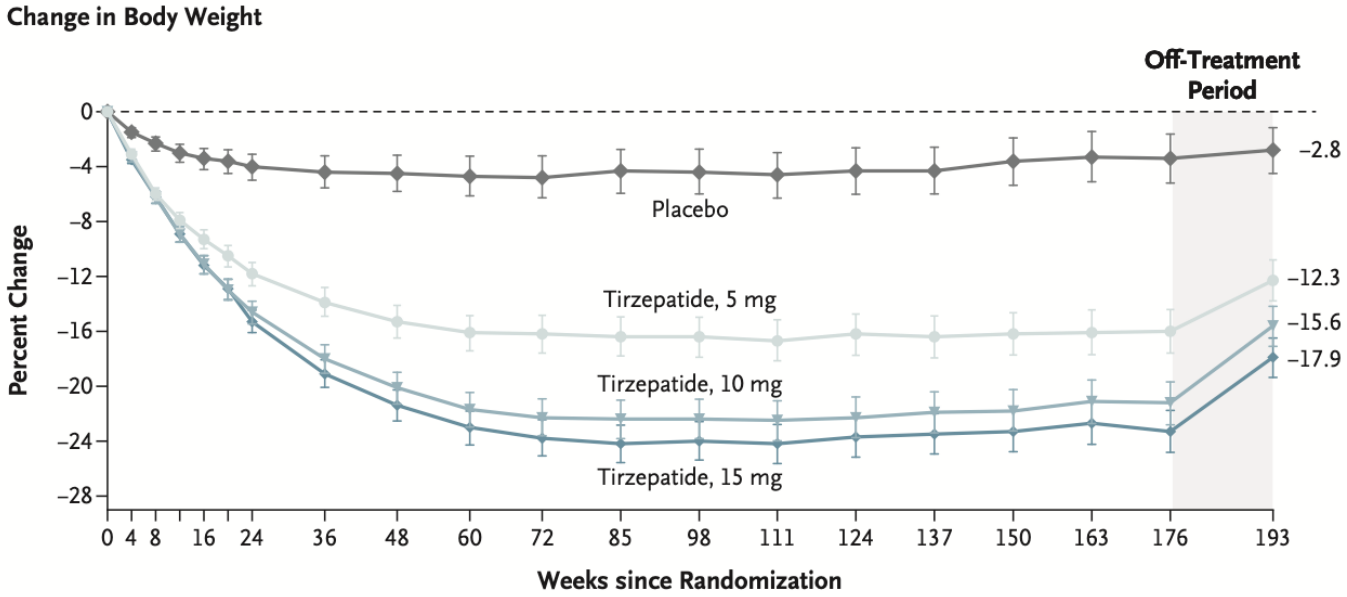
- Type 2 diabetes incidence:
  - Tirzepatide: **1.3%**
  - Placebo: **13.3%**
  - Hazard ratio: **0.07** (P < 0.001)

High rates of reversion to normoglycemia

- Up to **93.3%** on tirzepatide vs. 58.9% with placebo

Glycemic benefit seen even with <5% weight loss, suggesting **direct effects** on β-cell function and insulin sensitivity

Also improved cardiometabolic risk factors and **quality of life**



Jastreboff et al. NEJM N Engl J Med 2025;392:958-71.

Oral Semaglutide for Obesity

OASIS-1 Trial – 68wk phase 3 trial in PwO without T2D – oral semaglutide 50 mg

Mean weight loss: –15.1% vs –2.4% with placebo

- Estimated treatment difference: **–12.7 percentage points** ($p < 0.0001$)

Proportion of participants achieving:

- ≥5% loss: **85% vs 26%**
- ≥20% loss: **34% vs 3%**

Cardiometabolic benefits:

- ↓ Waist circumference: –13.0 cm
- ↓ HbA1c: –0.3%
- ↓ Systolic BP: –6.3 mmHg
- ↓ CRP: –50.4%
- ↑ HDL cholesterol: +4.8%

Glycemic improvement in prediabetes subgroup:

- 88% reached **normoglycemia (HbA1c <5.7%)** vs 49% with placebo

Clinical Implications

Administered **once daily in oral tablet form**

- Provides an alternative to injectable GLP-1 therapies

Knopp et al. Lancet. 2023 Aug 26;402(10403):705-719

Orforglipron for Obesity

Phase 2 Trial – 36wk trial in PwO without T2D – oral orforglipron (GLP-1RA)

Dose-dependent weight loss at 36 weeks:

- –9.4% (12 mg)
- –12.5% (24 mg)
- –13.5% (36 mg)
- –14.7% (45 mg)
- Placebo: –2.3%

Categorical responder rates at 36 weeks:

- ≥10% weight loss: up to **75%**
- ≥15% weight loss: up to **48%**
- Placebo: 9% and 1%, respectively

Metabolic and anthropometric improvements:

- ↓ BMI and waist circumference
- ↓ Systolic blood pressure by up to **–10.5 mmHg**
- Improved **lipid profiles**

Clinical Implications:

- First **non-injectable small molecule GLP-1RA** to demonstrate efficacy approaching injectable agents
- Potential to **increase accessibility and adherence** for obesity treatment

Wharton et al. N Engl J Med 2023;389:877-888

Survodutide for Obesity

Phase 2 Trial – 46wk trial in PwO without T2D – Survodutide (GCG/GLP1-RA)

Dose-dependent weight loss at 46 weeks

- –6.2% (0.6 mg) → –14.9% (4.8 mg) with planned treatment
- –6.8% → –18.7% with actual treatment
- Placebo: –2.8%

High responder rates with 4.8 mg dose (actual treatment):

- ≥5%: 98%
- ≥10%: 82%
- ≥15%: 67%
- ≥20%: 38%

Cardiometabolic improvements:

- ↓ Waist circumference: –16.6 cm
- ↓ SBP: –8.3 mmHg | ↓ DBP: –4.7 mmHg
- ↓ Triglycerides, ALT, HbA1c

Mechanism: Combines appetite suppression (GLP-1) with glucagon receptor activation

Implications: Potentially greater efficacy than GLP-1 monotherapy; supports further phase 3 studies

leRoux et al. Lancet Diabetes Endocrinol 2024;12:162–73

Retatrutide for Obesity

Phase 2 Trial – 48wk trial in PwO without T2D – Retatrutide (GIP/GCG/GLP1-RA)

Weight loss at 48 weeks

- –8.7% (1 mg) | –17.1% (4 mg) | –22.8% (8 mg) | –24.2% (12 mg)
- Placebo: –2.1%

High responder rates (12 mg dose):

- ≥5% loss: **100%**
- ≥10%: **93%**
- ≥15%: **83%**
- ≥20%: **48%**
- ≥30%: **26%**

Metabolic & cardiovascular benefits

- ↓ Waist circumference: up to –19.6 cm
- ↓ HbA1c, fasting glucose, insulin, triglycerides
- ↓ SBP: –7.8 mmHg | ↓ DBP: –3.7 mmHg
- 72% of those with prediabetes reverted to **normoglycemia**

Implications: Among the most effective obesity medications to date, supporting continued development in phase 3 trials

Jastreboff et al. N Engl J Med 2023;389:514-526

CagriSema for Obesity or Overweight

Phase 3 Trial – 68wk trial in PwO without T2D – CagriSema (Amylin/GLP1-RA)

Weight Loss Outcomes (Trial Product Estimand)

- **–22.7%** with CagriSema
  - vs –11.8% (cagrilintide), –16.1% (semaglutide), and –2.3% (placebo)
- **40.4% of patients lost ≥25% of body weight**
  - vs 6.0% (cagrilintide), 16.2% (semaglutide), 0.9% (placebo)

Dosing Patterns

- Only **57.3%** of patients on CagriSema reached the **highest dose**
  - Compared to 82.5% (cagrilintide) and 70.2% (semaglutide)

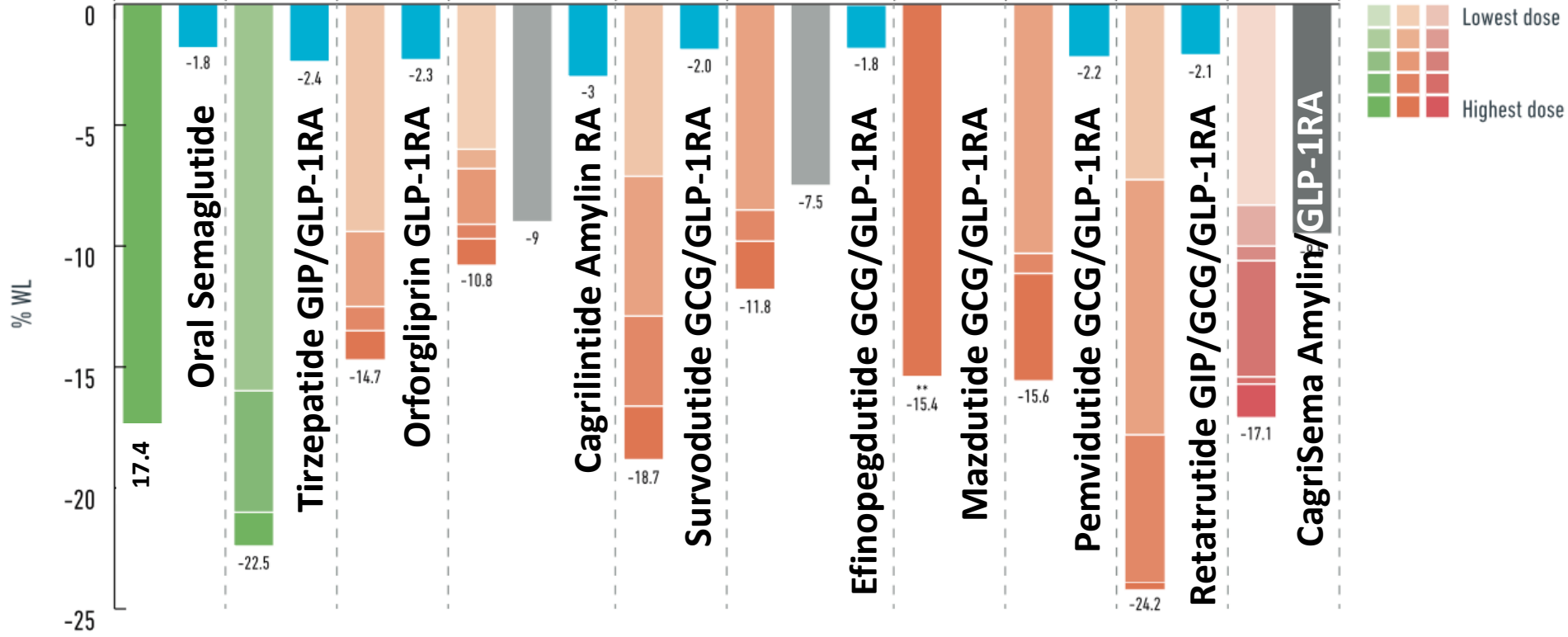
Implications: CagriSema combines two complementary pathways:

- **Semaglutide (GLP-1 receptor agonist)**: reduces appetite, slows gastric emptying, improves glycemic control
- **Cagrilintide (amylin analogue)**: enhances satiety, suppresses food intake, and delays gastric emptying

Novo Nordisk. REDEFINE 1 Press Release. Dec 20, 2024. www.novonordisk.com

Obesity Medication Pipeline Weight Loss Outcomes

	Oral Semaglutide[A]	Tirzepatide[A]	Orfoglipron[A]	Cagrilintide[A]	Survodutide[A*]	Efinopegdutide[B]	Mazdutide[C*]	Pemvidutide[A*]	Retatrutide[A]	CagriSema[B]
Dose and frequency	50mg OD	5/10/15mg OW	12/24/36/45mg OD	0.3/0.6/1.2/2.4/4.5mg OW	0.6/2.4/3.6 4.8mg OW	5/7.4/10mg OW	9mg OW	1.2/1.8/2.4mg OW	1/4/8/12mg OW	0.16/0.3/0.6/ 1.2/2.4/4.5 +SEMA 2.4mg OW
Route	PO	SC	PO	SC	SC	SC	SC	SC	SC	SC
Mechanism of action	GLP-1	GLP-1 + GIP	GLP-1	Amylin	GLP-1 + GCG	GLP-1 + GCG	GLP-1 + GCG	GLP-1 + GCG	GLP-1 + GIP + GCG	GLP-1 + Amylin
Number of participants	667	2539	272	706	387	474	80	391	338	95
Timepoint (weeks)	68	72	36	26	46	26	24	48	48	20
Baseline weight (kg)	105.4	104.8	108.7	107.4	105.7	113.3	96.9	104	107.7	95.7 - 99.6
Comparator	PBO	PBO	PBO	LIRA 3.0mg / PBO	PBO	LIRA 3.0mg / PBO	PBO	PBO	PBO	PBO+SEMA 2.4mg



Melson E, et al. Int J Obes (Lond). 1 February 2024 DOI: 10.1038/s41366-024-01473-y

Established and Emerging Evidence for Obesity Meds

❤️ **Cardiovascular disease**
- ↓ MACE (e.g., in SELECT, SURMOUNT-MMO, REDEFINE-CV)
- CV benefit trials ongoing for **CagriSema**, planned for **Survodutide** & **Retatrutide**

🧠 **Neurodegenerative diseases**
- GLP-1RAs under investigation in **Alzheimer's** and **Parkinson's disease**
- Potential neuroprotective effects via CNS mechanisms

🫁 **Obstructive sleep apnea (OSA)**
- Tirzepatide showed efficacy in **SURMOUNT-OSA**
- Weight loss and possibly direct airway effects may play a role

🩺 **Metabolic-associated steatotic liver disease (MASLD/MASH)**
- Agents like **semaglutide**, **retatrutide**, and **survodutide** being tested in trials
- Focus on reducing hepatic fat, inflammation, and fibrosis

♀️ **Polycystic ovary syndrome (PCOS)**
- GLP-1RAs improve **insulin resistance, weight**, and **menstrual function**
- Focus on metabolic and reproductive outcomes

🍷 **Addiction and reward-related conditions**
- Exploring roles in **alcohol use disorder**, **nicotine dependence**, and **impulsive eating**

💪 **Sarcopenic obesity**
- Trials combining **GLP-1RAs** with **bimagrumab (ActRII antagonist)** to preserve lean mass

Modified from Drucker. *Diabetes Care. 2024 Nov 1;47(11):1873-1888*

Tirzepatide for Obesity in PwT2D

SURMOUNT-2 Phase 3 Trial in PwO with T2D – Mean weight loss 14.7% in TZP 15 mg vs. 3.2% PBO

Weight Loss at 72 Weeks
–13.4% (10 mg) | –15.7% (15 mg) vs –3.3% with placebo

Glycemic Control

- **HbA1c reduction**:
  - –2.07% (10 mg) | –2.08% (15 mg) vs –0.51% with placebo
  - Treatment difference: ~–1.6% ($p < 0.0001$)

- **HbA1c target achievement** at week 72:
  - <7.0%: 87% (10 mg), 84% (15 mg), vs 36% (placebo)
  - ≤6.5%: 80% (10 mg), 79% (15 mg), vs 20%
  - <5.7% (normoglycemia): 46–49% vs 4%

- **Diabetes treatment simplification**:
  - More patients managed with **no or fewer glucose-lowering meds**

Garvey et al. Lancet 2023; 402: 613–26

Tirzepatide for Moderate to Severe OSA

SURMOUNT-OSA Trial – Phase 3

Two phase 3 trials in patients with moderate-to-severe OSA and obesity

- Trial 1: patients **not using PAP therapy**
- Trial 2: patients **on stable PAP therapy**

Significant weight loss

- –17.7% to –19.6% total body weight loss at 52 weeks
- Compared to –1.6% to –2.3% with placebo

Improved cardiometabolic risk markers

- ↓ Systolic BP: up to –9.5 mmHg
- ↓ hsCRP

Tirzepatide for Moderate to Severe OSA

SURMOUNT-OSA Trial – Phase 3

Marked reductions in apnea–hypopnea index (AHI)

- Trial 1: ↓ 25.3 events/hr with tirzepatide vs ↓ 5.3 with placebo
- Trial 2: ↓ 29.3 events/hr with tirzepatide vs ↓ 5.5 with placebo
- ~60–70% achieved ≥50% AHI reduction

Better patient-reported sleep outcomes

- ↓ Sleep disturbance and sleep-related impairment (PROMIS scores)

~43–51% no longer met criteria for moderate-to-severe OSA

- Based on **AHI falling below diagnostic threshold** after tirzepatide treatment
- Suggests potential for **OSA remission** in a substantial proportion of patients

Malhotra et al. N Engl J Med 2024;391:1193-1205

Proposed Mechanisms: How Tirzepatide Improves OSA

- **Substantial weight loss** reduces pharyngeal fat deposition and upper airway collapsibility—key contributors to OSA
- **Decreased central adiposity** improves thoracic compliance and respiratory mechanics during sleep
- **Enhanced insulin sensitivity** may reduce ventilatory instability and intermittent hypoxia
- **Improved leptin and ghrelin signaling** may enhance ventilatory control and reduce arousal threshold
- **Reduced systemic inflammation** and sympathetic activity may support better upper airway neuromuscular tone

Malhotra et al. N Engl J Med 2024;391:1193-1205

Semaglutide 2.4mg for CV Risk Reduction

SELECT Trial – 20% Reduction in MACE with semaglutide 2.4 mg vs. placebo

SELECT Trial: Semaglutide in Obesity Without Diabetes

- **17,604 adults** with overweight/obesity (BMI ≥27) and **established CVD**, but **no diabetes**
- Weekly **semaglutide 2.4 mg** vs placebo for ~34 months

Primary Cardiovascular Outcome

- 20% relative risk reduction in MACE:
  - 6.5% (semaglutide) vs 8.0% (placebo)
  - HR: **0.80** (95% CI: 0.72–0.90, **p<0.001**)
- Driven by lower risk of **nonfatal MI**: HR 0.72 (CI: 0.61–0.85)

Other Cardiometabolic Effects

- Mean weight loss: **–9.4%** vs –0.9% (placebo)
- Waist circumference ↓ –7.6 cm
- HbA1c ↓ –0.32%, CRP ↓ –38%, SBP ↓ –3.8 mmHg
- 66% of patients with prediabetes reverted to normoglycemia

Malhotra et al. N Engl J Med 2024;391:1193-1205

Semaglutide 2.4mg for MASH F2-3

ESSENCE Trial – Phase 3 interim results from first 800 patients completing 72 weeks of treatment

ESSENCE Trial: Semaglutide 2.4 mg for MASH (F2–3)

- **800 participants** with biopsy-proven MASH and stage F2–F3 fibrosis
  - Phase 3, 240-week trial; interim analysis at **72 weeks**

Primary Histologic Endpoints (72 weeks)

- **62.9%** of semaglutide-treated patients achieved **MASH resolution without fibrosis worsening**
  - vs **34.1%** with placebo (EDP: **28.9 percentage points**, **p < 0.0001**)
- **37.0%** had **fibrosis improvement without worsening of MASH**
  - vs **22.5%** with placebo (EDP: **14.4 percentage points**, **p < 0.0001**)

Body Weight and Metabolic Outcomes

- Mean weight loss: **–10.5%** with semaglutide vs **–2.0%** with placebo
  - Estimated difference: **–8.5%** ($p < 0.0001$)
- Improvements in inflammation, liver enzymes, and metabolic parameters (detailed data pending)

Malhotra et al. N Engl J Med 2024;391:1193-1205

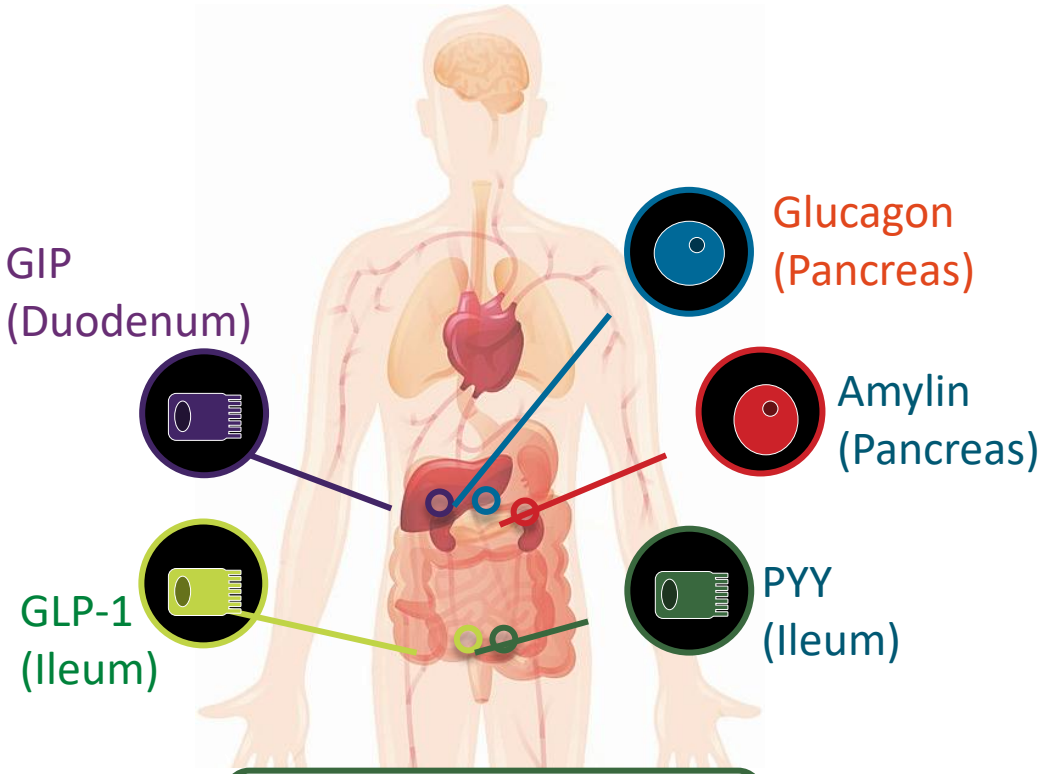
Secretion and Proposed Actions of Nutrient Stimulated Hormones in Pipeline for Treating Obesity

GIP

- ↓ appetite ↓ nausea
- ↑ insulin ↑ glucagon
- ↓ gastric acid secretion
- ↑ lipid deposition
  ↑ lipogenesis
- ↓ bone resorption

GLP-1

- ↓ appetite ↑ nausea
  ↓ food intake
- ↑ insulin ↓ glucagon
- ↓ gastric emptying
- ↑ lipolysis
- ↑ cardioprotection
  ↓ heart rate



PYY

- ↓ appetite ↑ nausea
  ↓ food intake
- ↓ gastric emptying
- ↑ energy expenditure

Glucagon

- ↓ appetite ↑ nausea
  ↓ food intake
- ↑ insulin
- ↑ hepatic glucose production
  ↑ lipid oxidation
  ↓ hepatic lipid synthesis
- ↓ gastric emptying
- ↑ energy expenditure
- ↑ heart rate

Amylin

- ↓ appetite ↓ food intake
- ↓ glucagon
- ↑ energy expenditure
- ↓ gastric emptying
- ↓ osteoclast activity
  ↑ osteoblast activity

Melson. Int J Obes (Lond). 2024 Feb 1:1-9

Take Home Message

UT Southwestern
Weight Wellness

Obesity medications work by restoring balance to the biological systems that regulate appetite and satiety—counteracting powerful physiologic defenses against weight loss.

Sustained treatment is essential: Discontinuation commonly results in significant weight recurrence, emphasizing the chronic and relapsing nature of obesity.

New obesity medications offer health benefits beyond weight loss, including improvements in glycemic control, cardiovascular risk, sleep apnea, liver health, and inflammation.

Emerging therapies are targeting multiple pathways simultaneously, offering new opportunities for durable weight loss and broader metabolic improvements.

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Questions?

How do we stay informed?
How do we translate science to our intended audience?

Professional engagement

- Professional organizations
  - Academy of Nutrition and Dietetics Dietetic Practice Groups (WMDPG, DDPG)
  - The Obesity Society
  - American Society of Metabolic and Bariatric Surgery (ASMBS)
  - Association of Diabetes Care & Education Specialists (ADCES)
  - American Diabetes Association (ADA)

Journals and newsletters

Practice guidelines, standards of care and/or recommendations

Continuing education and formal training

- Conferences and meetings
- Trainings
  - CDR Certificate in Obesity for Pediatrics and Adults
- Specialized certifications
  - CDR Certified Specialist in Obesity and Weight Management (CSOWM)
  - CDCES and BC-ADM

Online resources

- Online communities (i.e. LinkedIn)
- Webcasts and podcasts

Mentorship

- Network
- Ask for feedback
- E-mailing lists/discussion boards (WMDPG & DDPG)

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Questions?

Save the Date!

May 8th
Considerations for Body Composition, Physical Activity and Nutrition with the Use of Obesity Medications
Registration now open!

June 4th
Advance and Enhance the Unique Role of the RDN in Today's and Tomorrow's Obesity Care Continuum
Registration coming soon!

All webinars will be recorded and archived for free on-demand viewing.

Academy of Nutrition and Dietetics Foundation

Thank you!