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Breaking the Code: The Science of Weight and How to Use it to Your Advantage

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Disclosure of Conflict of Interest

Robert Kushner, MD Serves on the medical advisory boards for Abbvie, Altimunne, Antag, AstraZeneca, Boehringer Ingelheim, Currax, Eli Lilly, Novo Nordisk, Regeneron, Structure, and Weight Watchers

3 Cutting Edge Topics I am Going to Cover

- ✓Two fundamental biological factors lead to obesity and associated health risks: Appetite dysregulation and lipotoxocity
- ✓The 2025 Lancet Commission recommendations to reframe obesity
- ✓How GLP-1 medications are transforming obesity care

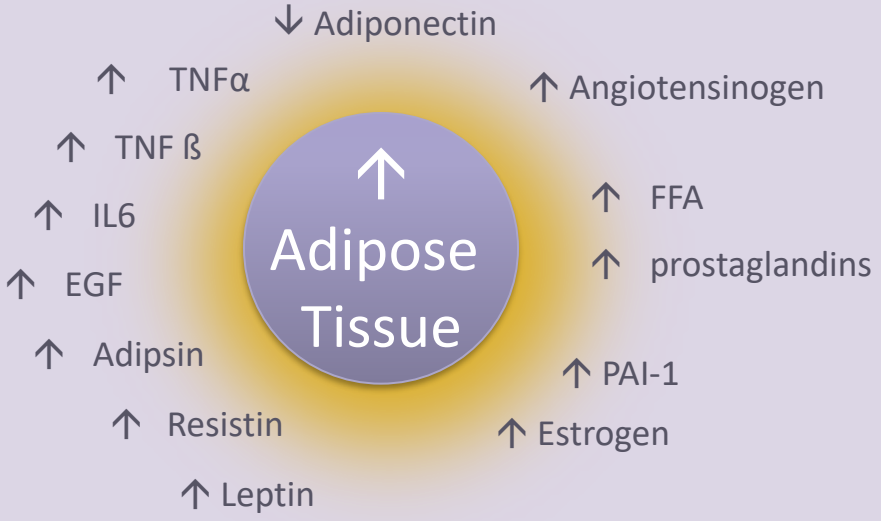
Two Fundamental Biological Factors that lead to Obesity

Appetite Dysregulation

Energy intake

Energy expenditure

Organ System Impairment



LIPOTOXICITY

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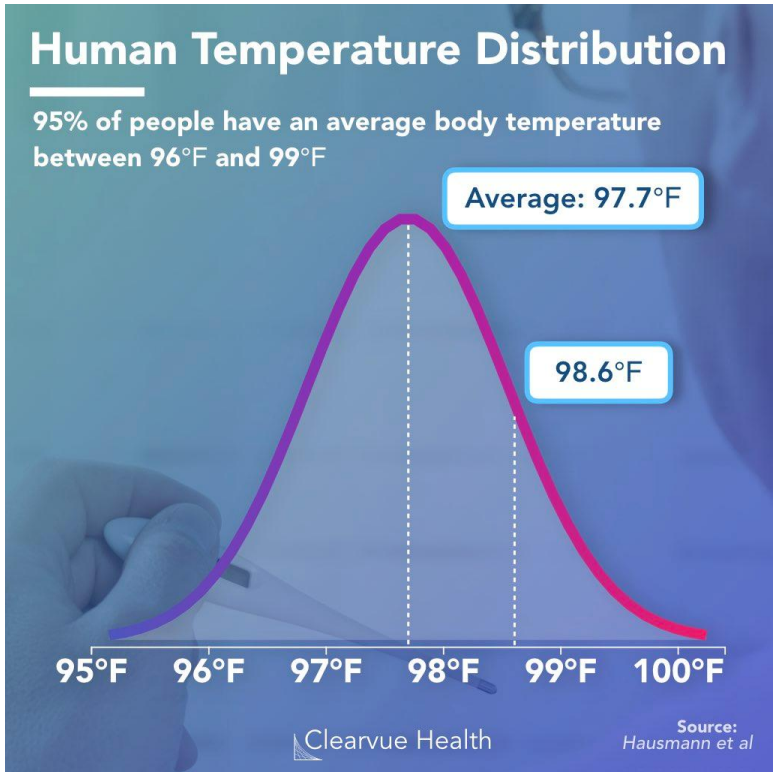
Regulation of Body Functions is Necessary to Maintain Internal Stability and Health



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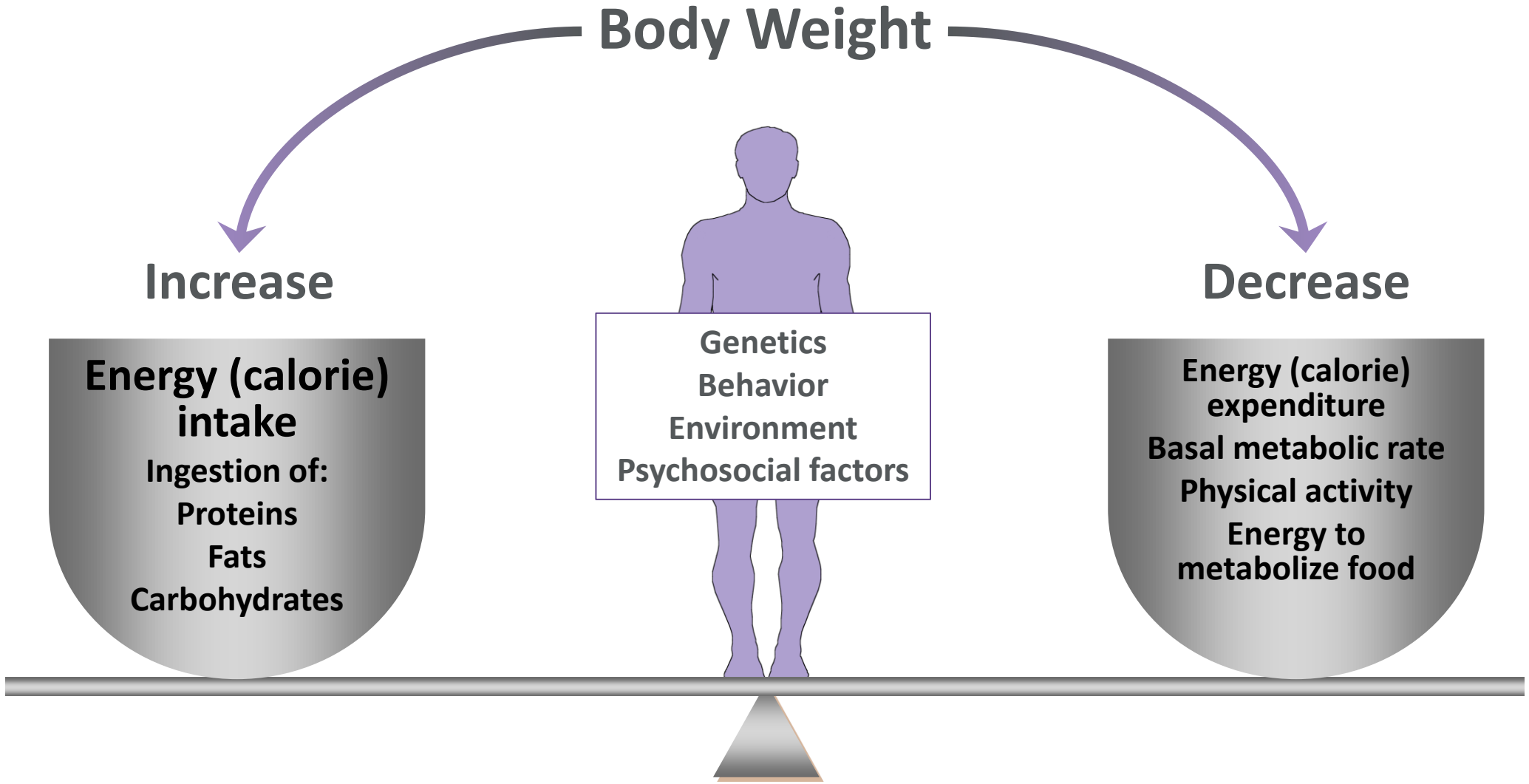
Regulation of Energy Balance



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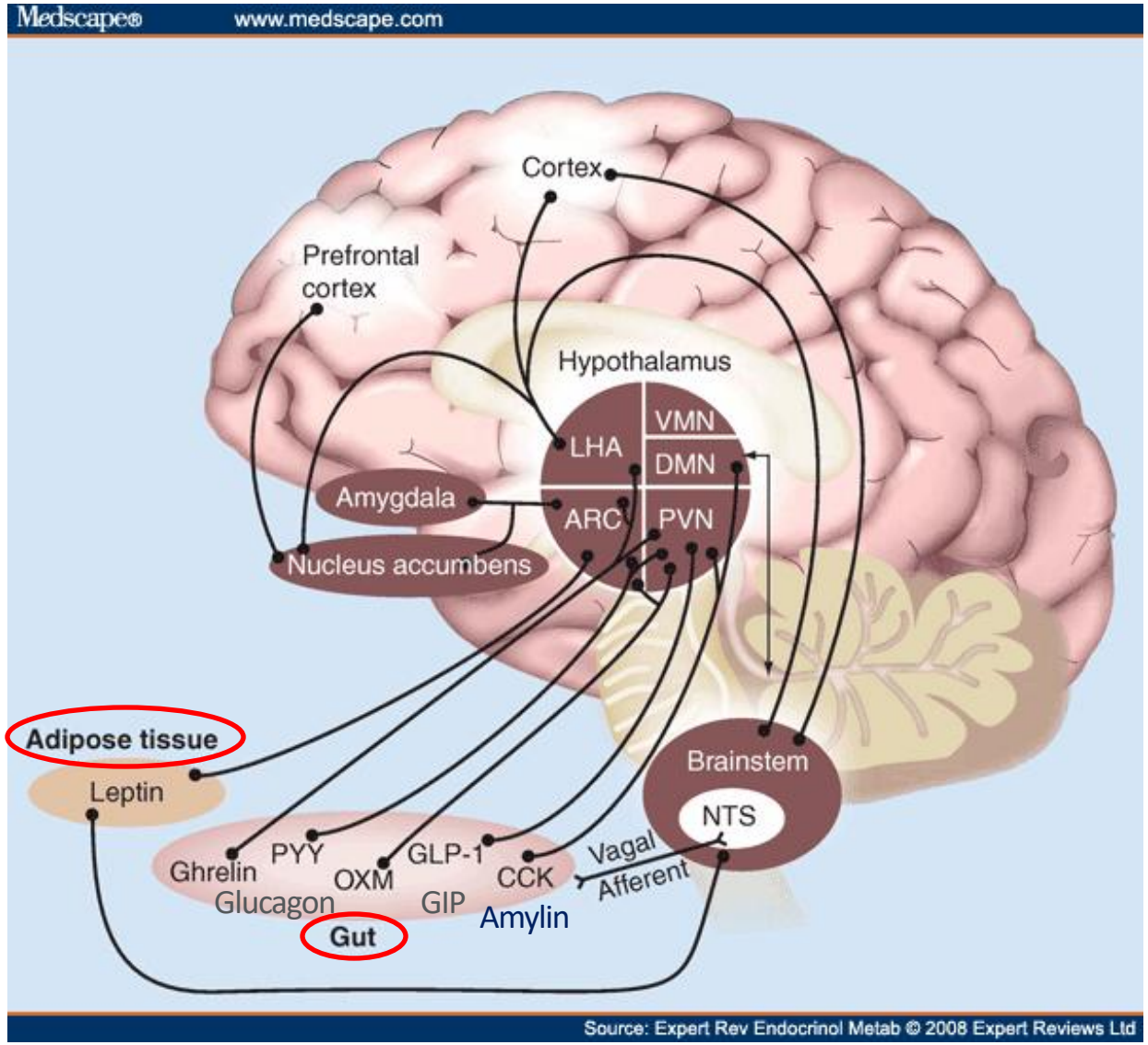
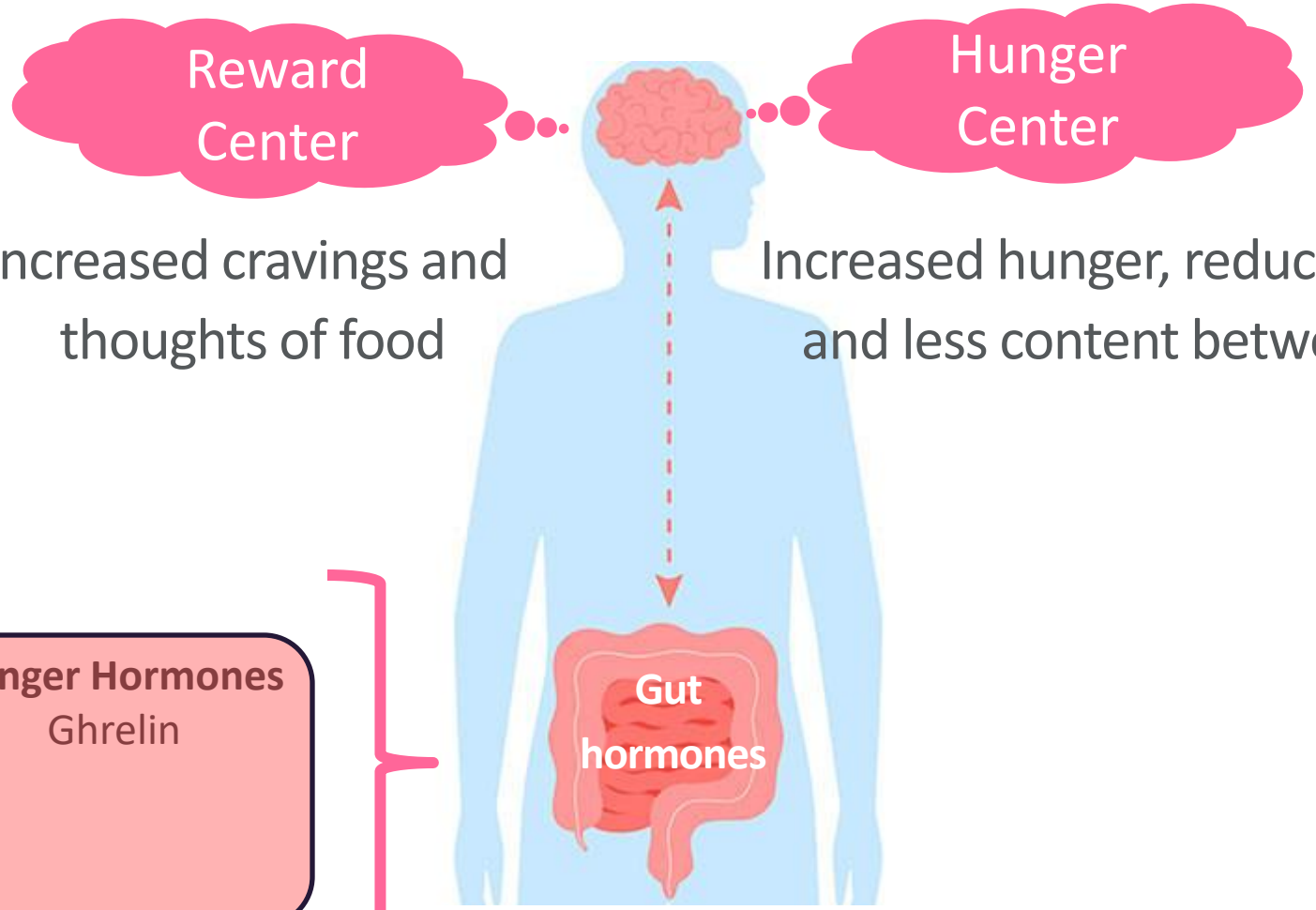
Garvey WT, *Am J Clin Nutr.* 2012;95(2):297-308.

The Gut & Adipose (Fat) Tissue send signals to the Brain to Regulate Appetite and Energy Balance



- In people predisposed to developing obesity, signaling to the brain is dysregulated.
- Appetite cues are enhanced & fullness cues are muted, permitting a sustained positive energy (calorie) balance.
- This leads to expansion of body fat that exceeds a healthy storage capacity.

Dysregulated “Gut Brain Axis”



Satiety Hormones	Hunger Hormones
GLP-1 GIP Amylin Glucagon	Ghrelin

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GLP-1 = glucagon like peptide-1; **GIP** = Glucose-dependent insulinotropic polypeptide

Food Noise

- Persistent, intrusive thoughts about food that are disruptive to daily life and make healthy behaviors difficult

Food Noise Questionnaire
I find myself constantly thinking about food throughout the day
My thoughts about food feel uncomfortable
I spend too much time thinking about food
My thoughts about food have negative effects on me and/or my life
My thoughts about food distract me from what I need to do

5-point Likert-type scale: strongly disagree (scored as 0); disagree (scored as 1); neither agree nor disagree (scored as 2); agree (scored as 3); and strongly agree (scored as 4). A single total score for the questionnaire is calculated by summing responses for the five items, and higher total scores indicate greater levels of food noise.

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Diktas HE, et al. Obesity 2025;33(2):289-297.

A New Way to Think about Obesity

Obesity results from **genetic and environmentally driven dysfunction** of the normal body fat regulatory mechanisms ...
... leading to an **inappropriately elevated** body fat

Overeating does not cause obesity ...
... obesity causes overeating

Undereating does not fix obesity ...
... fixing obesity leads to undereating

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nutrition.org/scientists-claim-that-overeating-is-not-the-primary-cause-of-obesity/. Schwartz. Endocr Rev. 2017;38:267.

Two Fundamental Biological Factors that lead to Obesity

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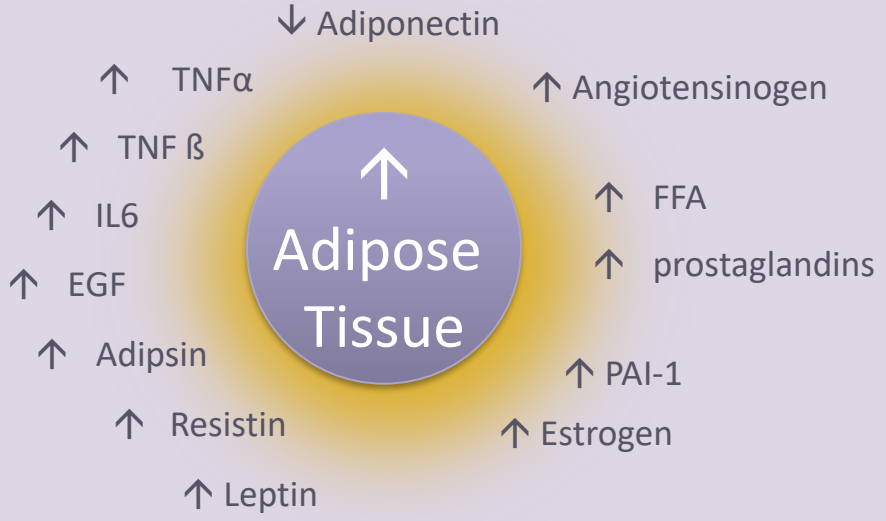
Energy expenditure

Organ System Impairment



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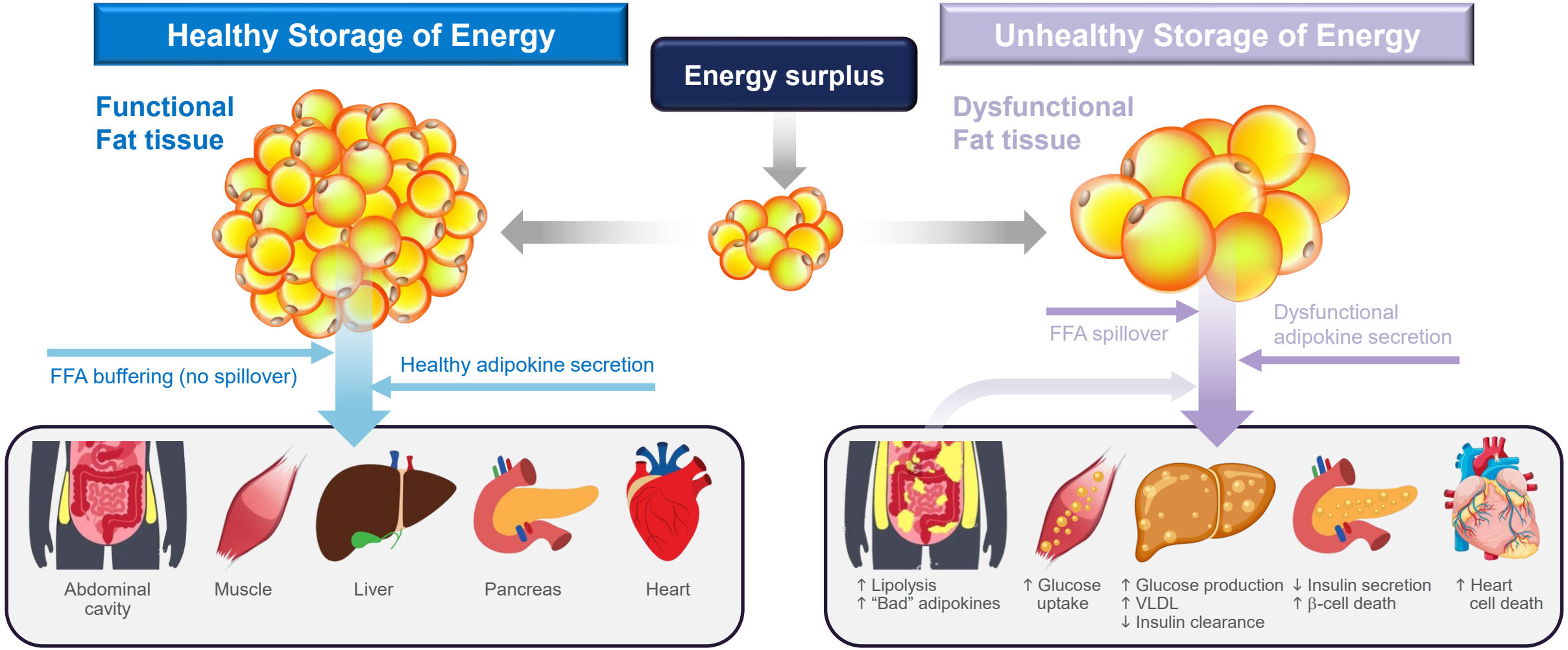
Consequences of Functional and Dysfunctional Adipose (Fat) Tissue



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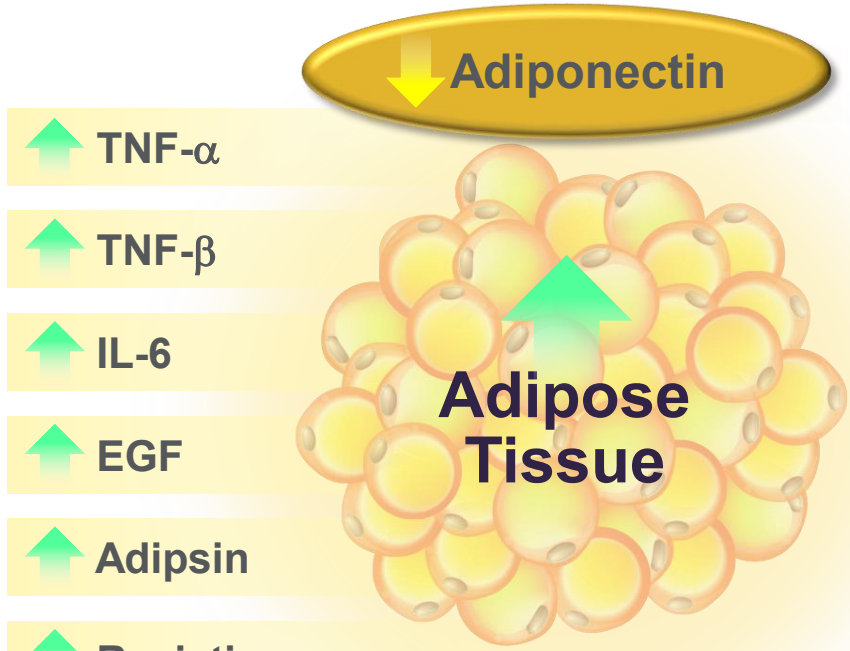
FFA: free fatty acid; SAT: subcutaneous adipose tissue; VLDL: very-low-density lipoprotein.

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

Lipotoxicity: Release of Adipokines and other Products of Fat Tissue

The link between pathophysiology of obesity and associated comorbid conditions

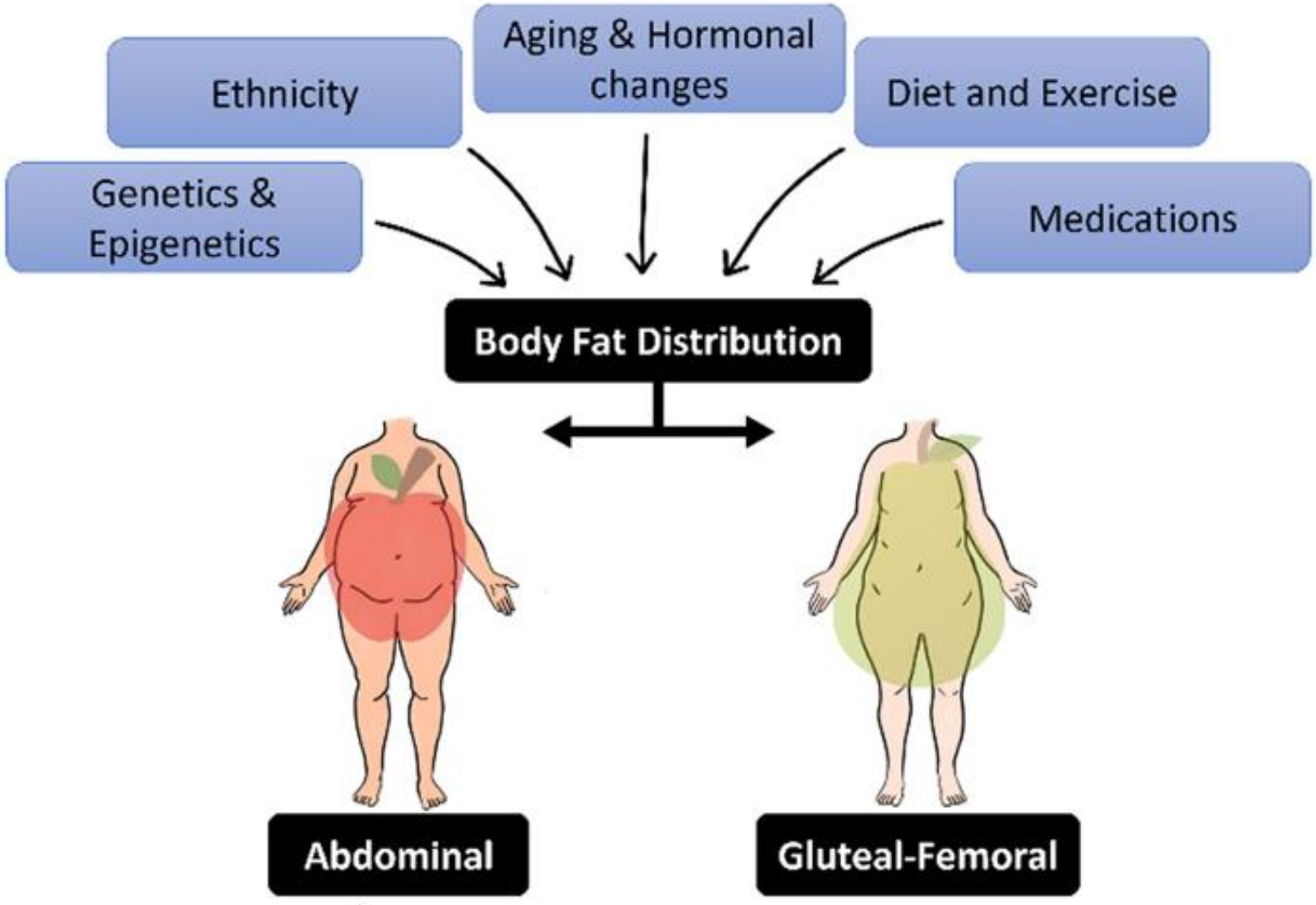


- Inflammation
- Arthritis
- Asthma
- Cancer
- Stroke, heart attack
- PVD

- Hypertension
- Dyslipidemia
- T2D
- Thrombosis

LIPOTOXICITY

What Determines the Distribution and Healthy Capacity of Body Fat?



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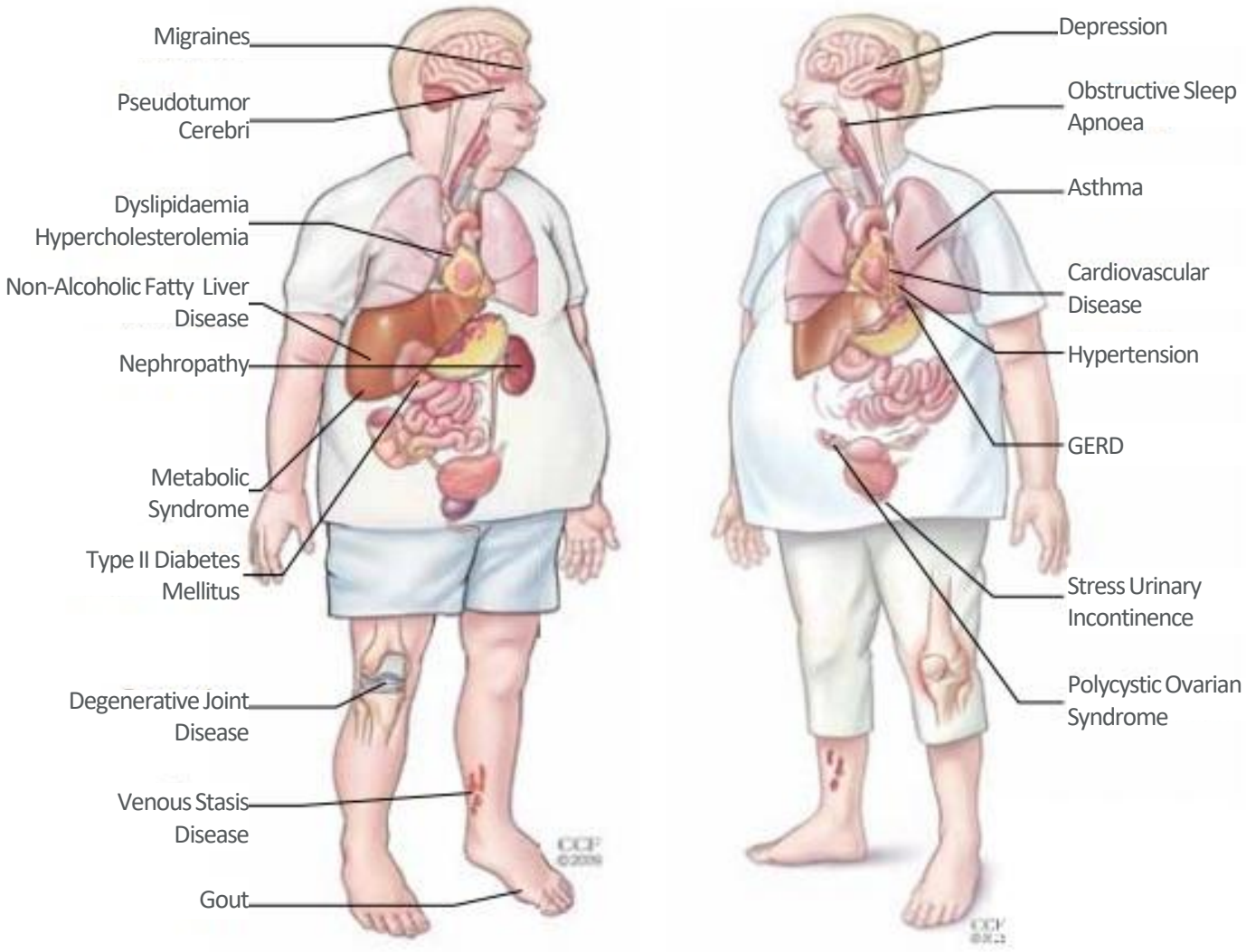
Alser M et al. Frontiers in Nutrition (March) 2024

Obesity is Associated with Over 200 complications/comorbidities



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

Image courtesy: Adapted from Cleveland clinic (available here)

What does all of this mean to you?

Old way of thinking

- "My lifestyle is a personal choice."
- "I just need to work harder to eat less and exercise more."
- "If I struggle, it's my fault."
- "I brought this on myself."
- "Asking for help is the easy way out."

Current way of thinking

- "I have a predisposition to gain weight that is due to abnormal appetite regulation."
- "Stress, mood, medications, and other life events that promote gain."
- "I have a medical condition that would benefit from seeking help."

3 Cutting Edge Topics I am Going to Cover

- ✓Two fundamental biological factors lead to obesity and associated health risks: Appetite dysregulation and lipotoxocity
- ✓The 2025 Lancet Commission recommendations to reframe obesity
- ✓How GLP-1 medications are transforming obesity care

Obesity is a Condition of Excess Body Fat that Causes Harm to Health

But measuring Body Fat in the Primary Care Setting is Challenging

DXA

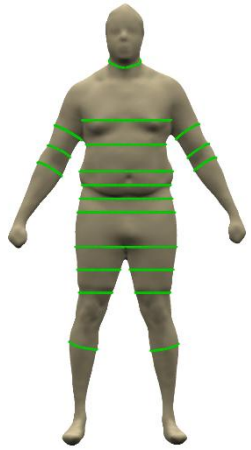
Attenuation of 2 energy level x-ray transmissions (absorbed or scattered). Measures bone and soft tissue

MF-BIA

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

ADP

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



DA

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

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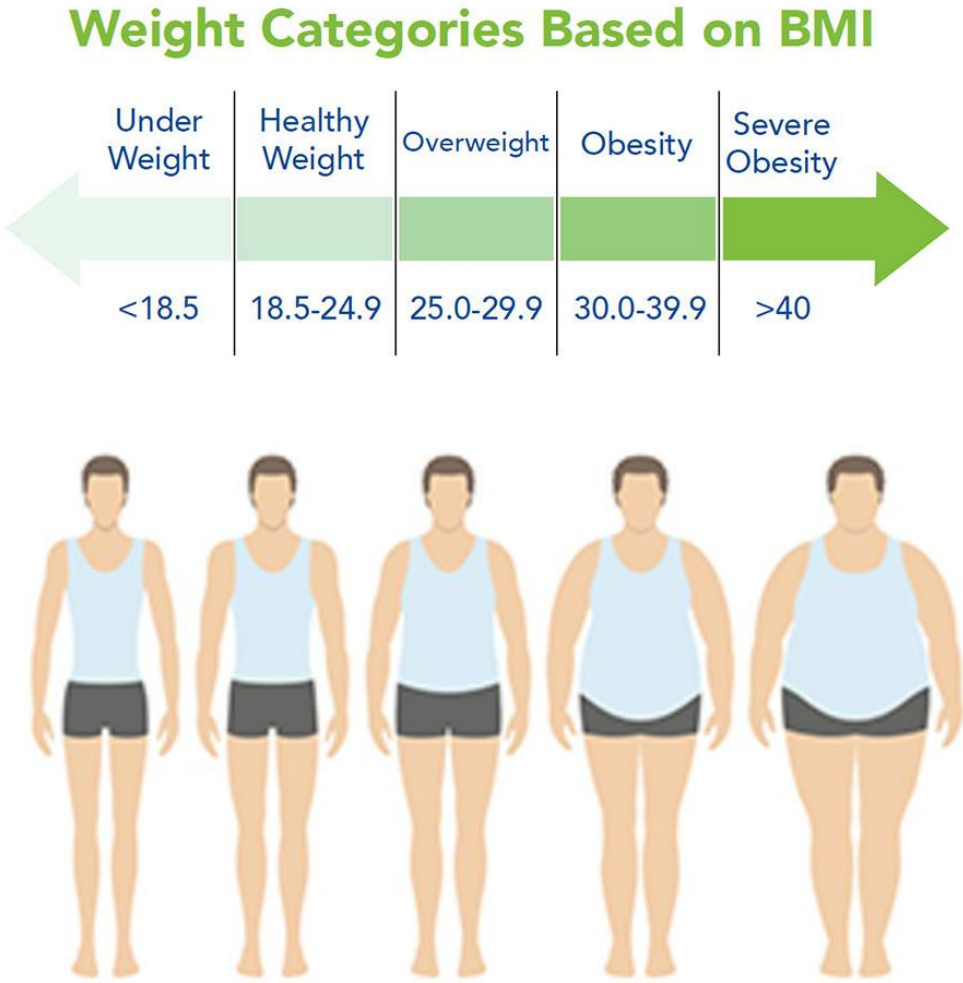
DXA = Dual X-ray Absorptiometry; MF-BIA = Multiple Frequency Bioimpedance Analysis;
ADP = Air Displacement Plethysmography; DA = Digital Anthropometry

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**
- **V**ariability in relative body shape and composition exists across race and ethnic groups, sexes, genders and age-span that 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



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

- 58 commissioners (experts) from around the world used a consensus to tackle 2 unresolved issues in obesity care:
  - To better define how to assess “excess body fat” beyond BMI
  - To better identify when the excess body fat is causing harm to health
- Met monthly from June, 2022 – Dec, 2024

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Rubino F, et al. Lancet Diabetes Endocrinol. 2025 Mar;13(3):221-262.

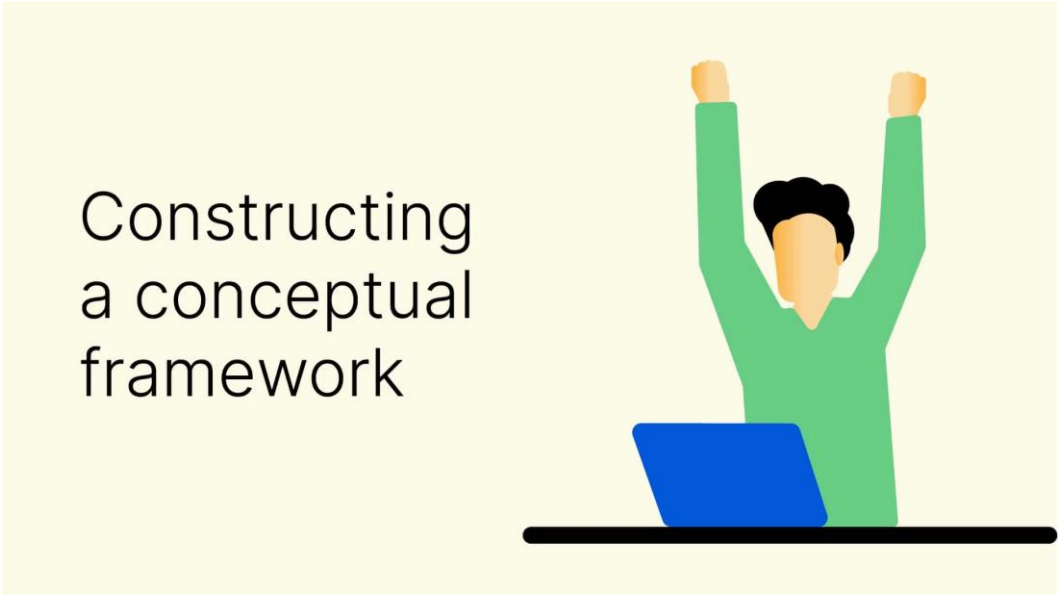
A New Framework for the Diagnosis of Illness due to Obesity

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



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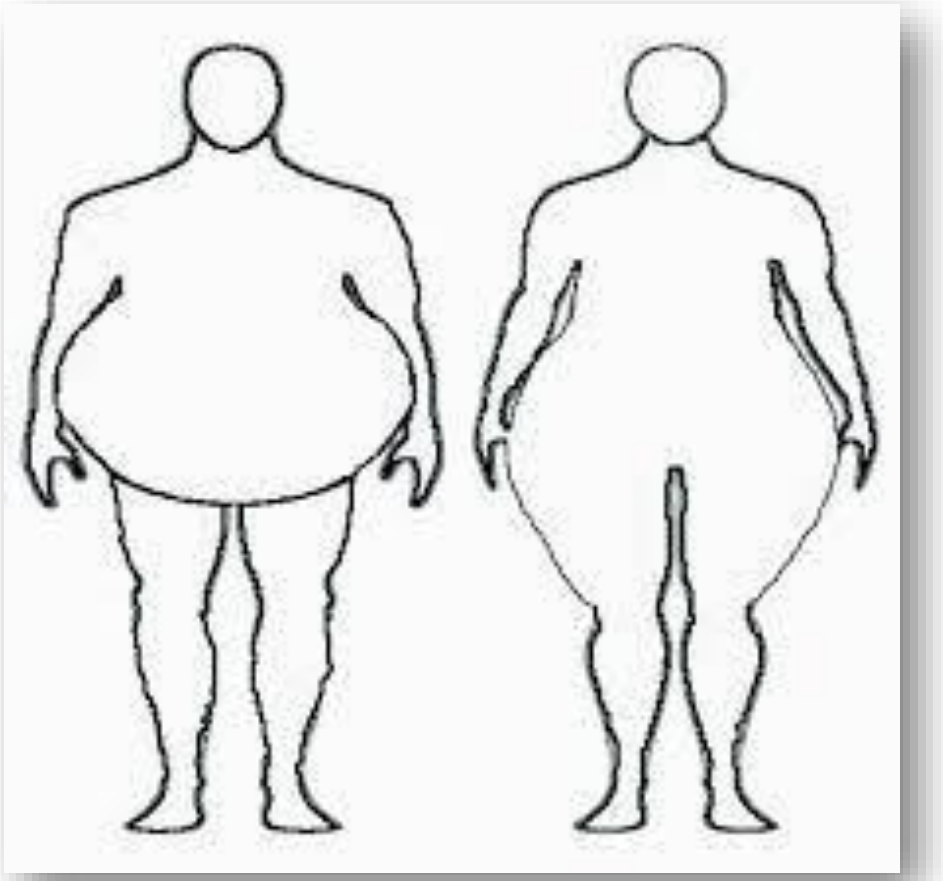
Rubino F, et al. Lancet Diabetes Endocrinol. 2025 Mar;13(3):221-262.

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, 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*



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Rubino F, et al. Lancet Diabetes Endocrinol. 2025 Mar;13(3):221-262.

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 Mar;13(3):221-262.

Diagnosis of Pre-Clinical Obesity

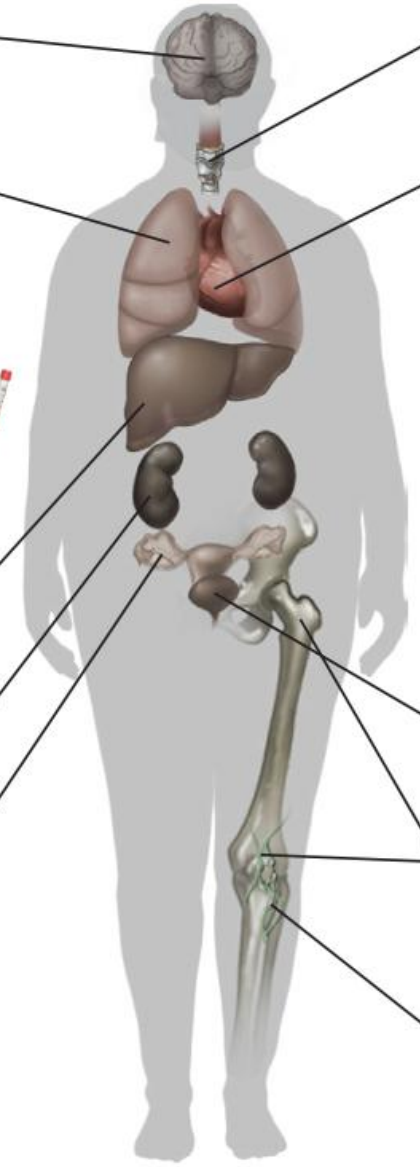
Requires confirmation of obesity status (excess body fat) **But**:

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 Mar;13(3):221-262.

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)

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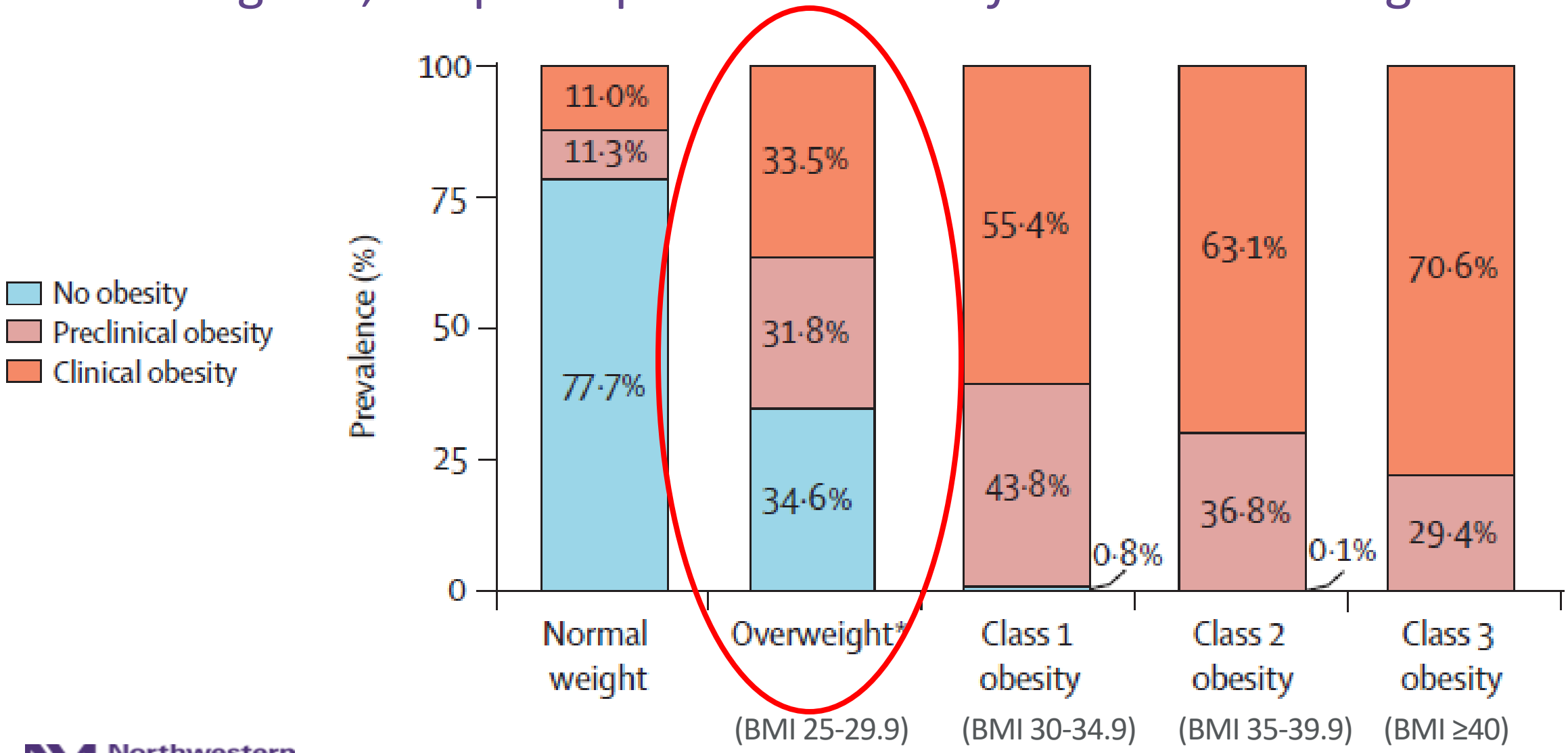
Prevalence of Obesity, Preclinical obesity, and Clinical Obesity among 250,000 participants in the *All of Us* Research Program



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Yao Z, et al. Lancet. Published online June 16, 2025

What does the Commerssion Report mean to you?

- If your BMI is between ~23 to 30 kg/m^2, it is useful to have another body measurement taken (waist circumference) to confirm or refute that you have excess body fat.
- You can have obesity (excess body fat) without any signs, symptoms or blood tests or reduced daily limitations that show harm to your health. The commission calls this Pre-clinical obesity.
  - However, you are at increased risk for development of harm to your body. You can focus on healthy lifestyle behaviors or further treatment if indicated.
- If you have obesity with any signs, symptoms or blood tests or reduced daily limitations, the commission calls this Clinical obesity.
  - You should seek treatment for obesity and any existing medical problems, considering any modality that is beneficial to you (lifestyle changes, medications, bariatric surgery.

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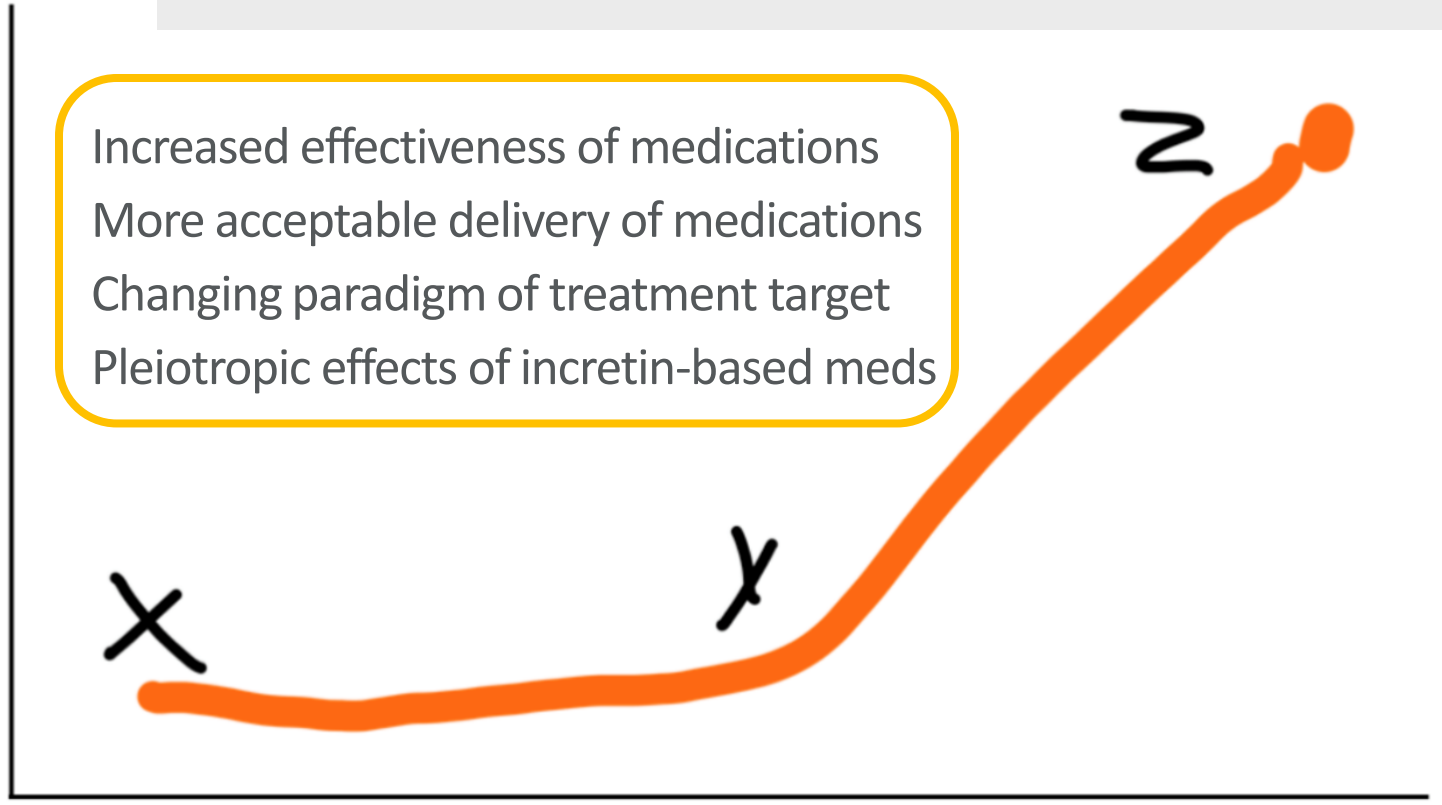
Inflection Point

DECEMBER 19, 2023 | 5 MIN READ

The Biggest Health and Medicine Stories of 2023

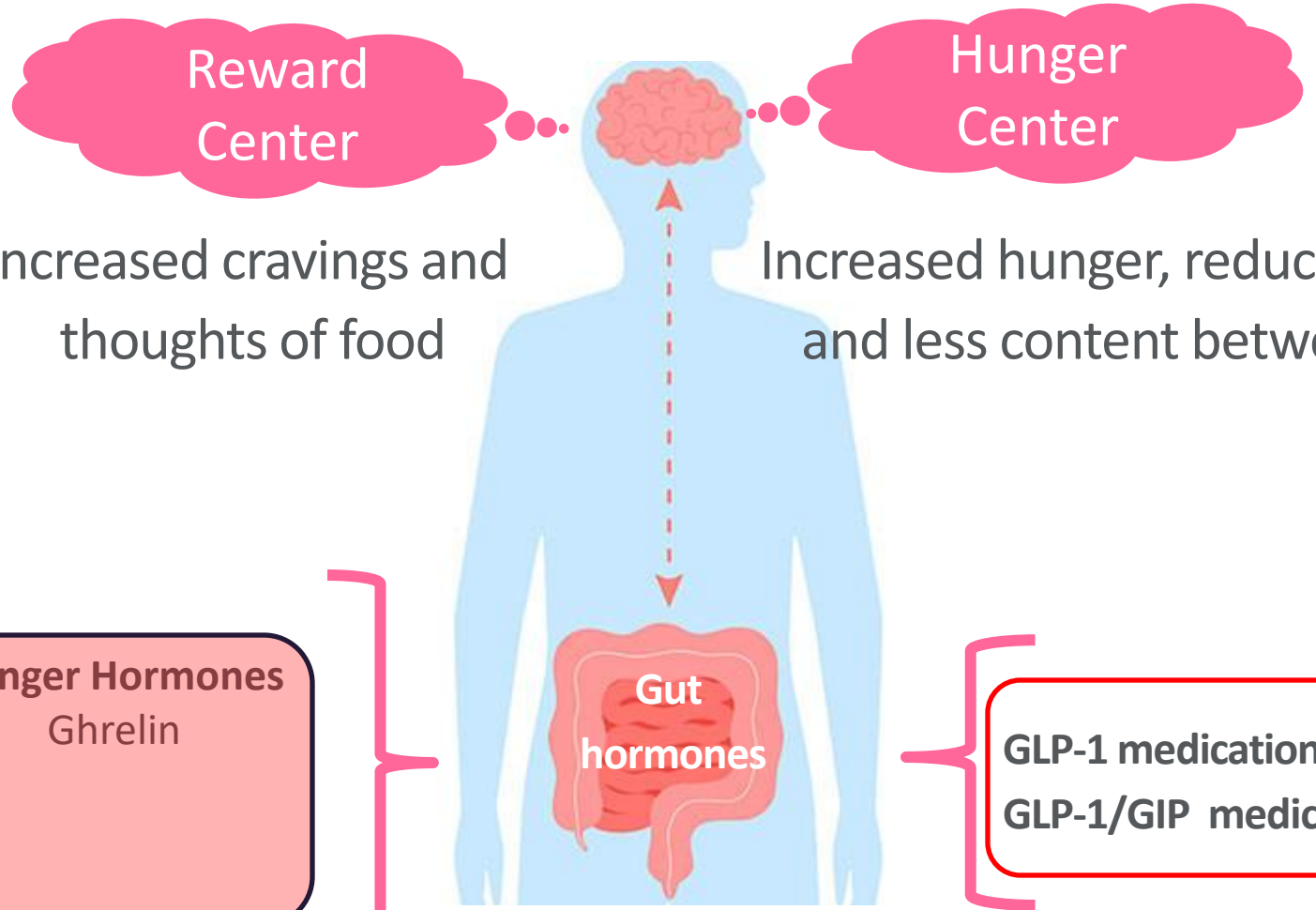
From new uses for weight-loss drugs to the first CRISPR gene editing therapy, these were some of the most impactful health stories of the year

Increased effectiveness of medications
More acceptable delivery of medications
Changing paradigm of treatment target
Pleiotropic effects of incretin-based meds



https://www.scientificamerican.com/article/the-biggest-health-and-medicine-stories-of-2023/

Dysregulated "Gut Brain Axis" Treated with Hormone-Based Meds



Satiety Hormones	Hunger Hormones
GLP-1 GIP Amylin Glucagon	Ghrelin

GLP-1 medication (Semaglutide)
GLP-1/GIP medication (Tirzepatide)

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GLP-1 = glucagon like peptide-1; **GIP** = Glucose-dependent insulinotropic polypeptide

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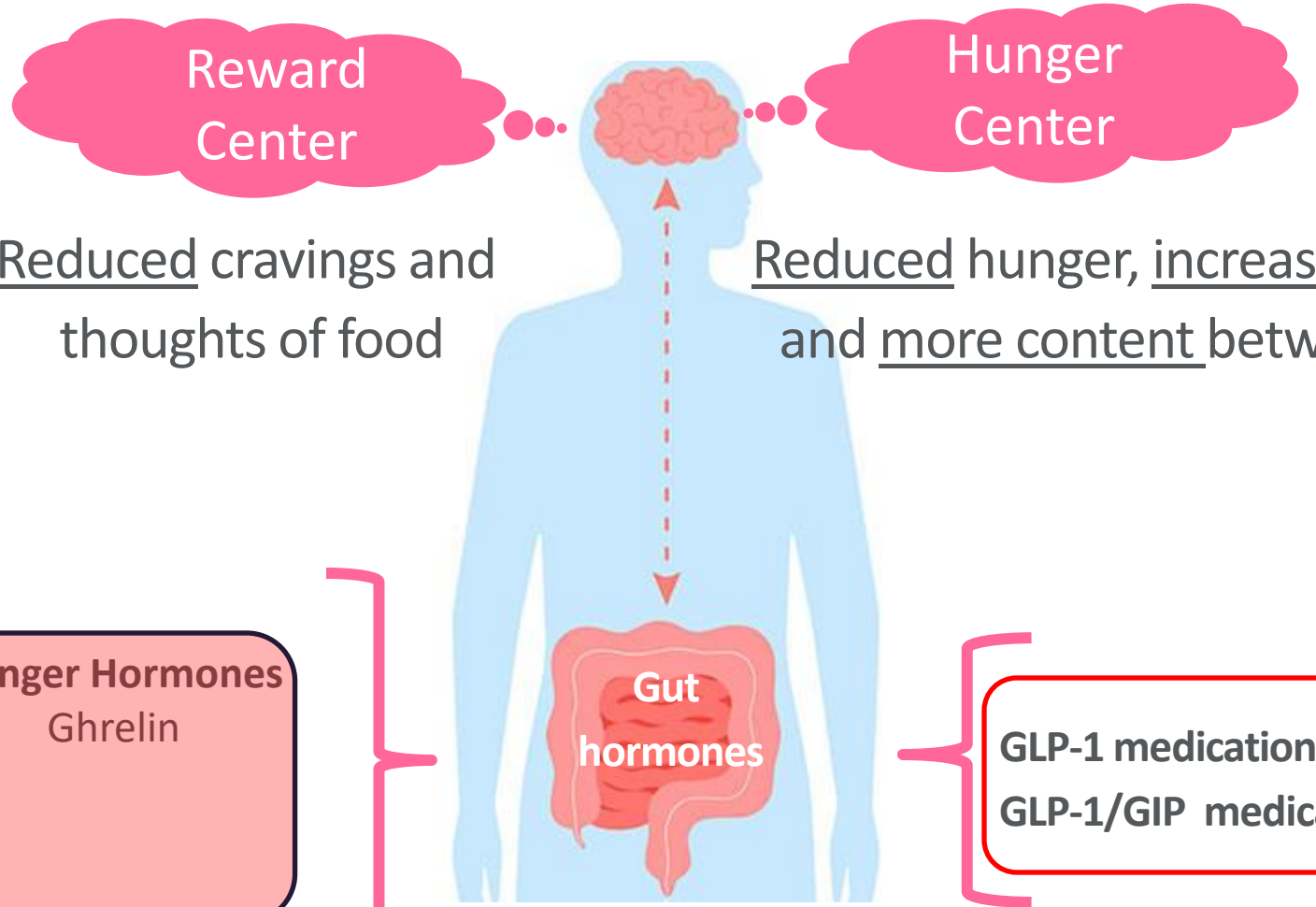

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GLP-1 medication (Semaglutide)
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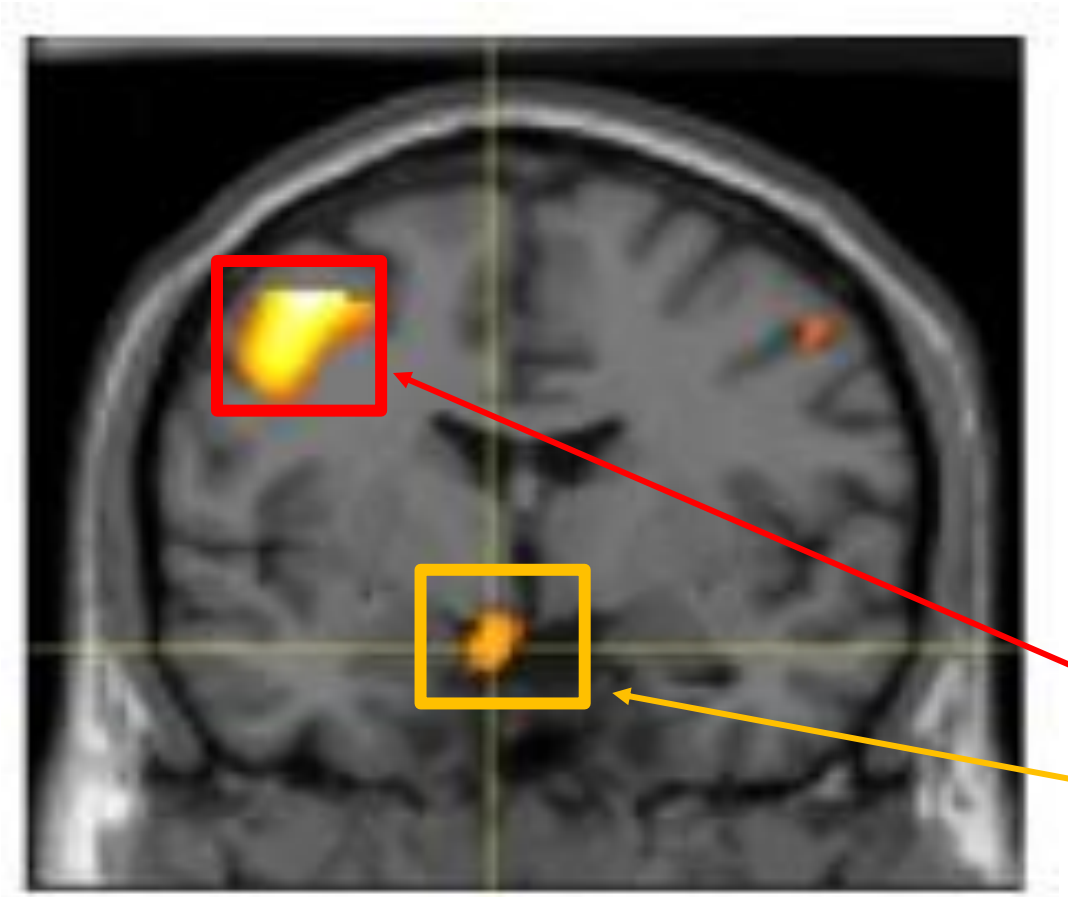
GLP-1 = glucagon like peptide-1; **GIP** = Glucose-dependent insulinotropic polypeptide

GLP-1 activates areas of brain involved in appetite regulation



- GLP-1 is associated with activation of areas of the brain implicated in regulation of appetite and food intake
- Peak increases in blood GLP-1 concentrations are correlated with increases in regional cerebral blood flow in the left dorsolateral prefrontal cortex (reward center) and the hypothalamus (hunger center)

GLP-1, glucagon-like peptide-1; PET, positron emission tomography

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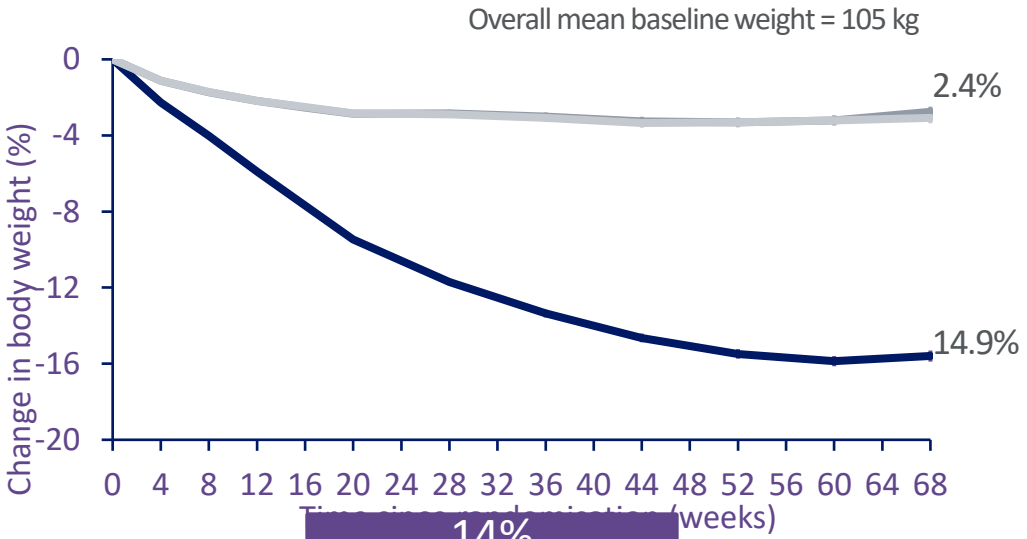
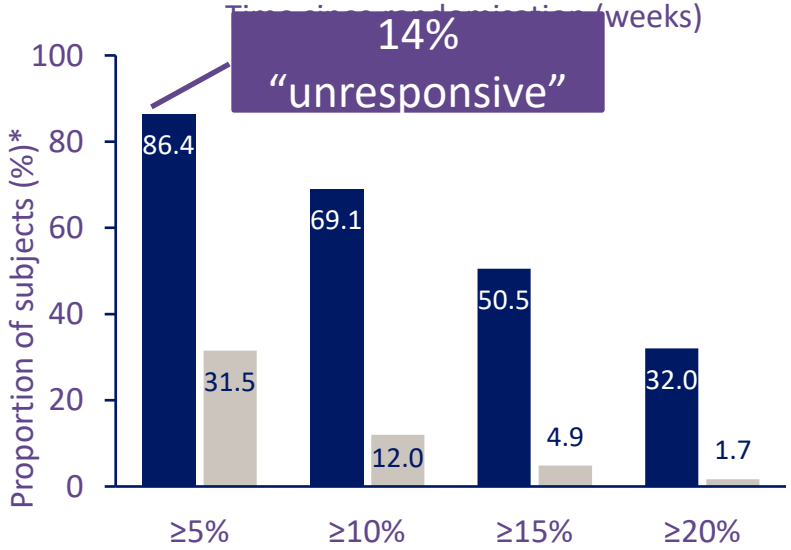
Pannacciulli *et al. Neuroimage* 2007;35:511–17

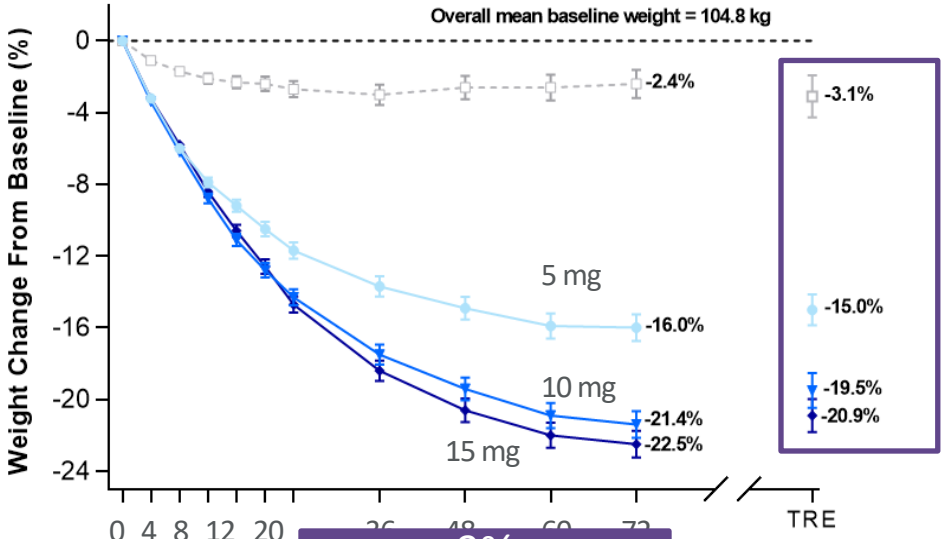
Looking at the Data from the Semaglutide and Tirzepatide Pivotal Trials

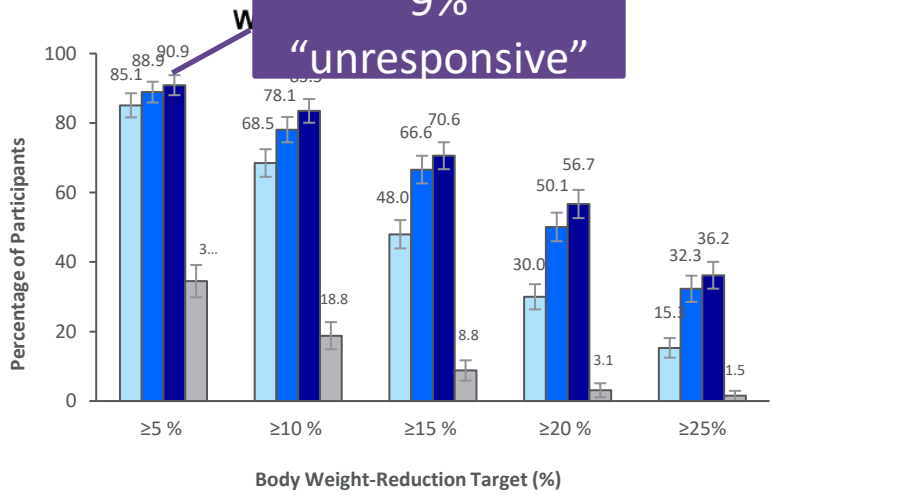
Semaglutide





Tirzepatide





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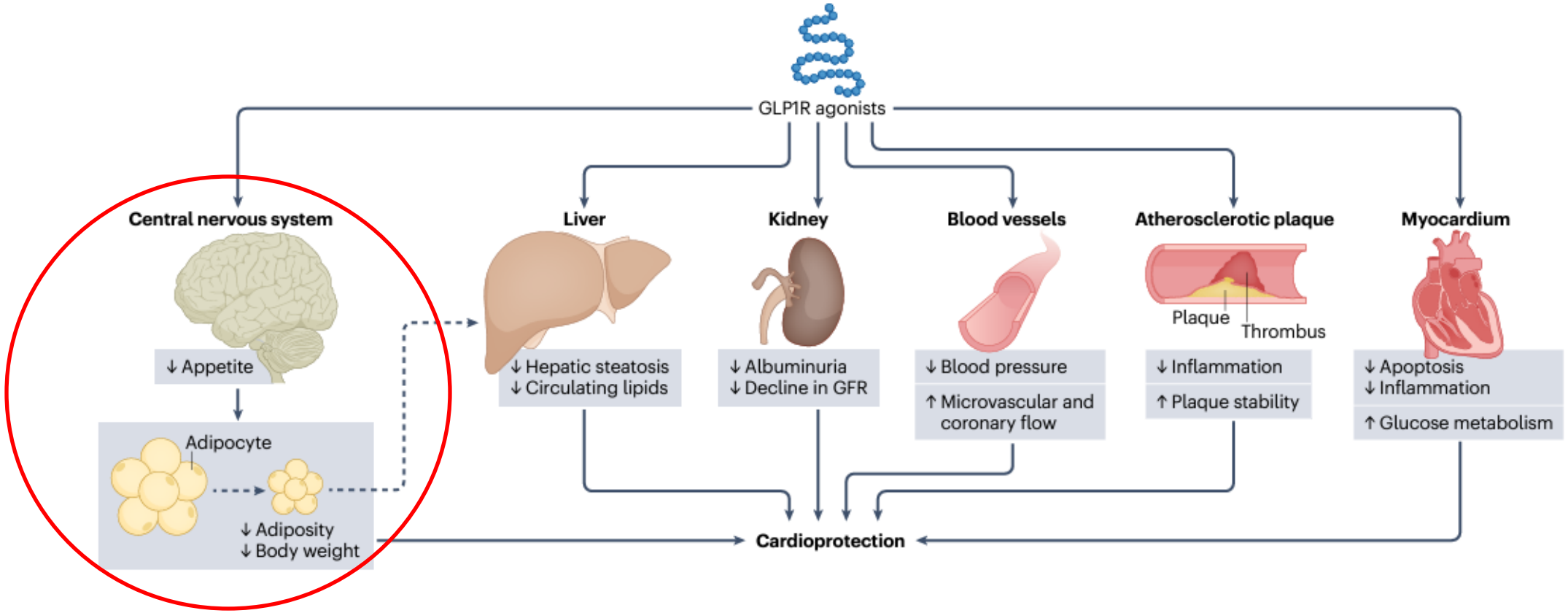
TRE – treatment-regimen estimand

Wilding JPH, et al. N Engl J Med 2021;384:989-100;Jastreboff AM, et al N Engl J Med 2022;387:205-216

GLP-1 has benefits beyond weight loss



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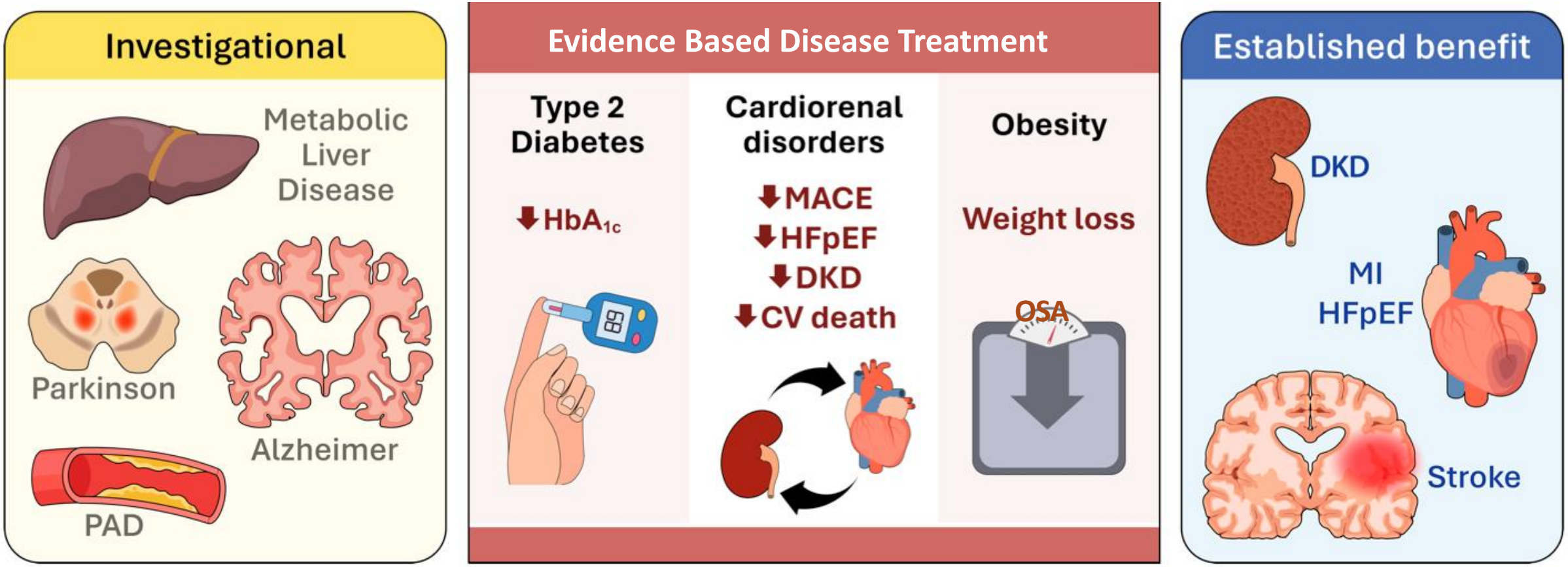
Ussher JR and Drucker DJ. Nature Rev Cardiol 2023;20:463-474

Established and Emerging Benefits from GLP-1 Meds



MACE-major adverse cardiovascular events; DKD-diabetic kidney disease; MI-myocardial infarction; HFpEF-heart failure with preserved ejection fraction; peripheral arterial disease; CV-cardiovascular disease; OSA-obstructive sleep apnea

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

What does this mean for you?

- The development of GLP-1 medications has been transformative in the treatment of obesity.
- GLP-1 medications address the underlying biology of appetite dysregulation we talked about in the first section of my talk.
- Average weight loss is 15% for semaglutide and 21% for tirzepatide, with 1/3 of people losing ≥20%-25%
- If you feel that obesity medications may help control your weight, talk to your healthcare professional to see if you are a candidate for use.

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