Pathophysiology and Management of Obesity

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04/04/2025

Disclosures

- None

Objectives

- Obesity impact
- Definition of Obesity
- Pathophysiology
- The Set Point Theory
- Management Options
  - Lifestyle Changes
  - Pharmacotherapy
  - Surgery

Obesity as an Endocrine Epidemic

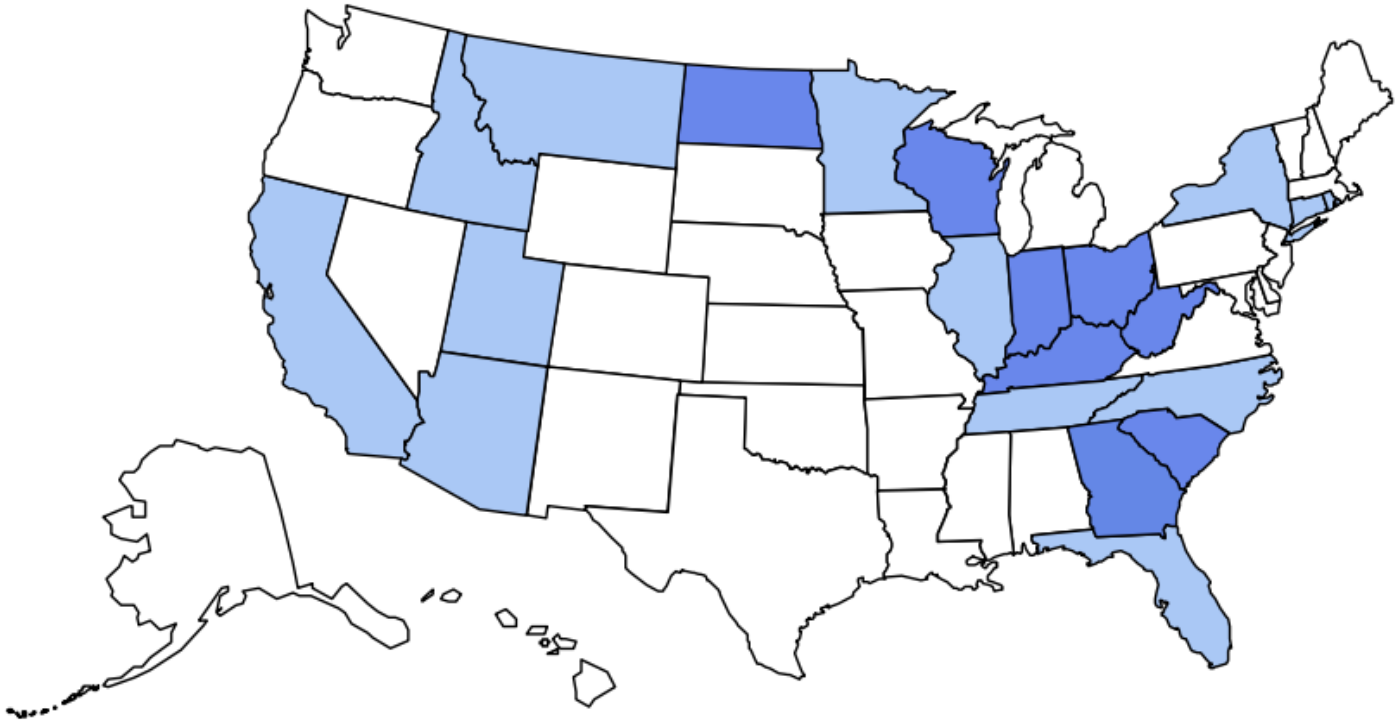
- Global prevalence: ~650 million adults obese.
- U.S. prevalence: 40.3% obese; 73.6% overweight/obese.
- Severe obesity (BMI ≥ 40): 9.4%, up from 7.7% in 2013–2014.
- Endocrine comorbidities:
  - T2DM: 90% of cases linked to obesity; 23% of obese adults affected.
  - PCOS: 50–70% prevalence in obese women.
  - Cushing's syndrome: Excess cortisol mimics obesity phenotype.
- Mortality: 5–20 years reduced lifespan; 3.7 million global deaths tied to obesity.
- Economic burden: $173 billion in U.S. medical costs.

WHO, 2022 and 2016; CDC, NCHS Data Brief 508, 2024; CDC, 2024; Endocr Rev, 2023; JCEM, 2022.

Obesity Trends* Among U.S. Adults

BRFSS, 1985

(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)



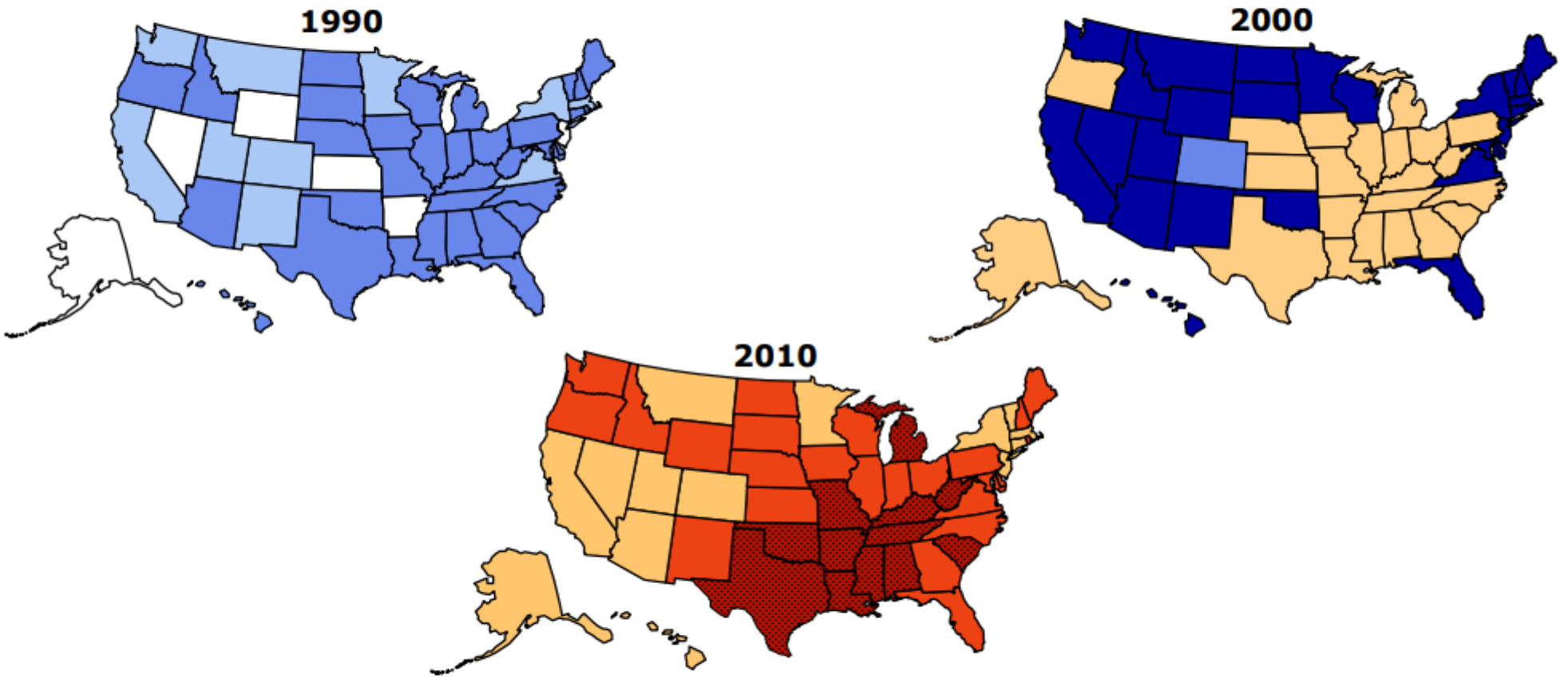
No Data | <10% | 10%–14%

Source: Behavioral Risk Factor Surveillance System, CDC.

Obesity Trends* Among U.S. Adults

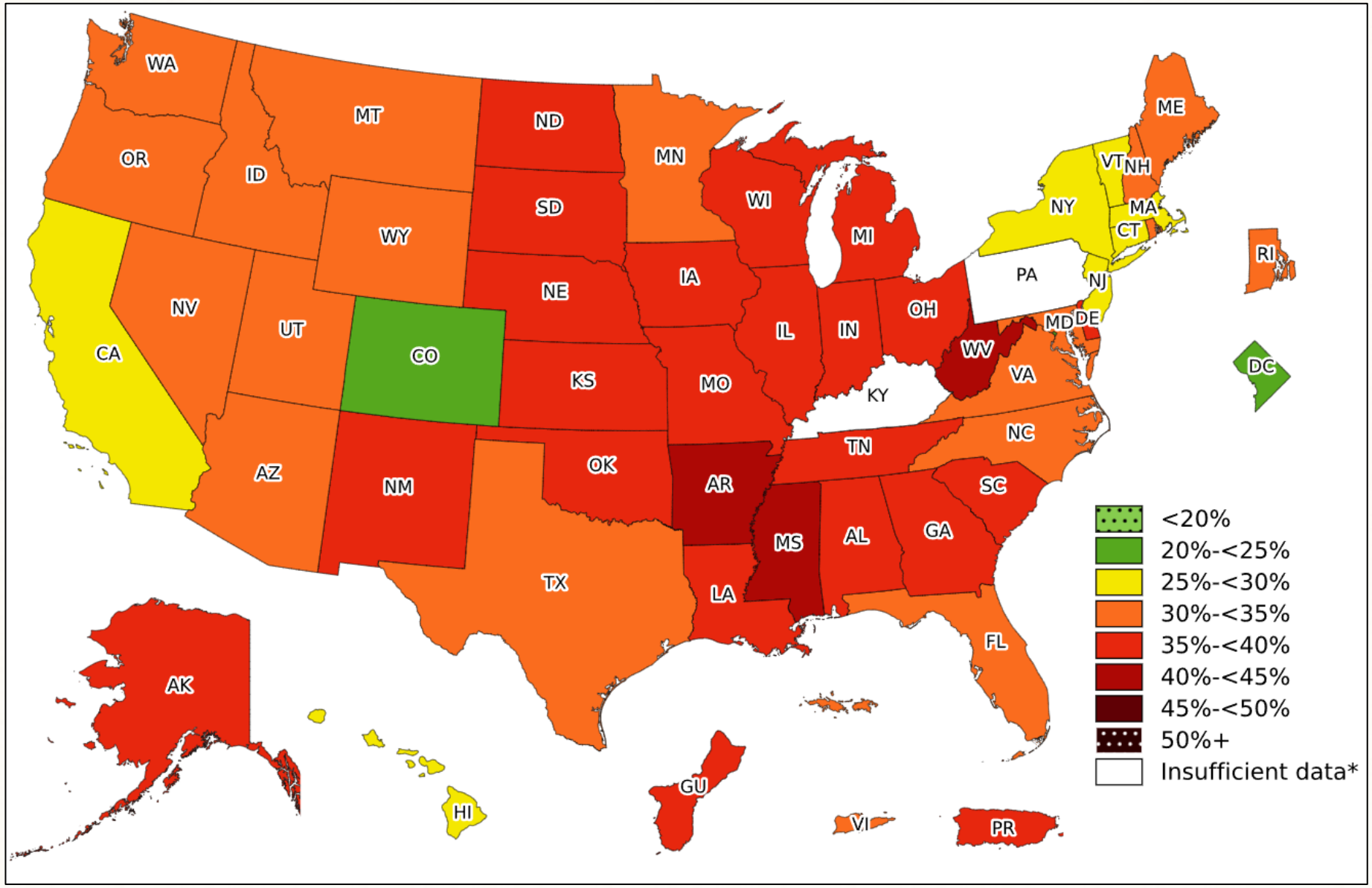
BRFSS, 1990, 2000, 2010

(*BMI ≥30, or about 30 lbs. overweight for 5'4" person)



Source: Behavioral Risk Factor Surveillance System, CDC.

Map of Overall Obesity: 2023



Source: Behavioral Risk Factor Surveillance System

*Sample size <50, the relative standard error (dividing the standard error by the prevalence) ≥30%, or no data in a specific year.

Table: Prevalence of Obesity Based on Self-Reported Weight and Height by State and Territory, BRFSS, 2023

Defining Obesity

METRIC UNITS

$$\text{BMI} = \frac{\text{weight } [\text{kg}]}{\text{height}^2 \ [\text{m}^2]}$$

IMPERIAL UNITS

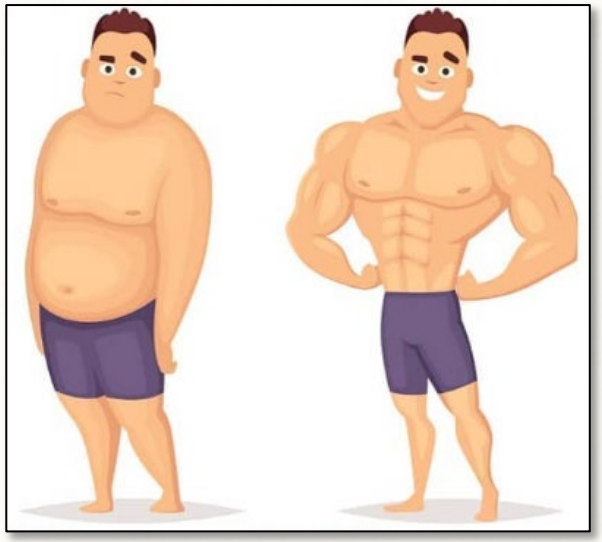
$$\text{BMI} = \frac{\text{weight } [\text{lb}]}{\text{height}^2 \ [\text{in}^2]} \times 703$$

- BMI (Body Mass Index)
  - ≥ 30 kg/m^2 (or ≥ 27 kg/m^2 with endocrine comorbidities).
- Historically used as a quick measure of obesity.
- Limitations:
  - Does not measure body fat directly.
  - Fails to account for muscle mass, bone density, and fat distribution.
  - Same BMI cutoff for all populations – ignores genetic, ethnic, and age-related differences.
  - Cannot differentiate between metabolically healthy and unhealthy obesity.
- Chronic disease: AMA (2013), AACE (2016) and Endo Society (2020)

Rubino F, Cummings DE, Eckel RH, et al. Definition and diagnostic criteria of clinical obesity. *Lancet Diabetes Endocrinol.* 2025;13(3):221-262. doi:10.1016/S2213-8587(24)00316-4.

Defining Obesity

- Diagnosis should consider:
  - Body composition (fat vs. muscle).
  - Metabolic health markers (insulin resistance, inflammation, etc.).
  - Functional health impacts (mobility, fatigue, sleep apnea).
  - Waist circumference and visceral fat more predictive of health risk than BMI alone.
- Multifactorial Approach:
  - Imaging (DEXA, MRI)
  - Biomarkers (e.g., insulin resistance)
  - Clinical presentation



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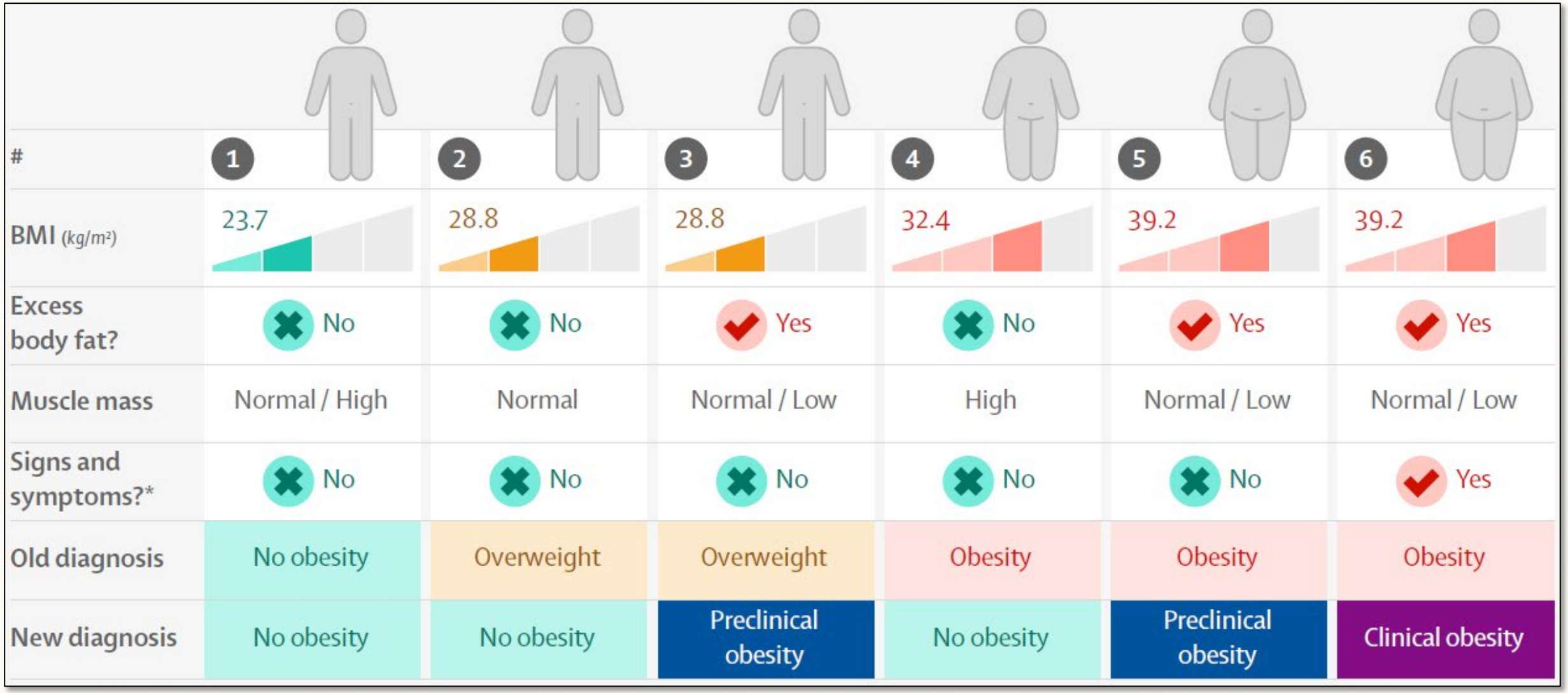
https://www.abc.net.au/news/2022-01-02/the-problem-with-the-body-mass-index-bmi/100728416

Pre/Clinical Obesity



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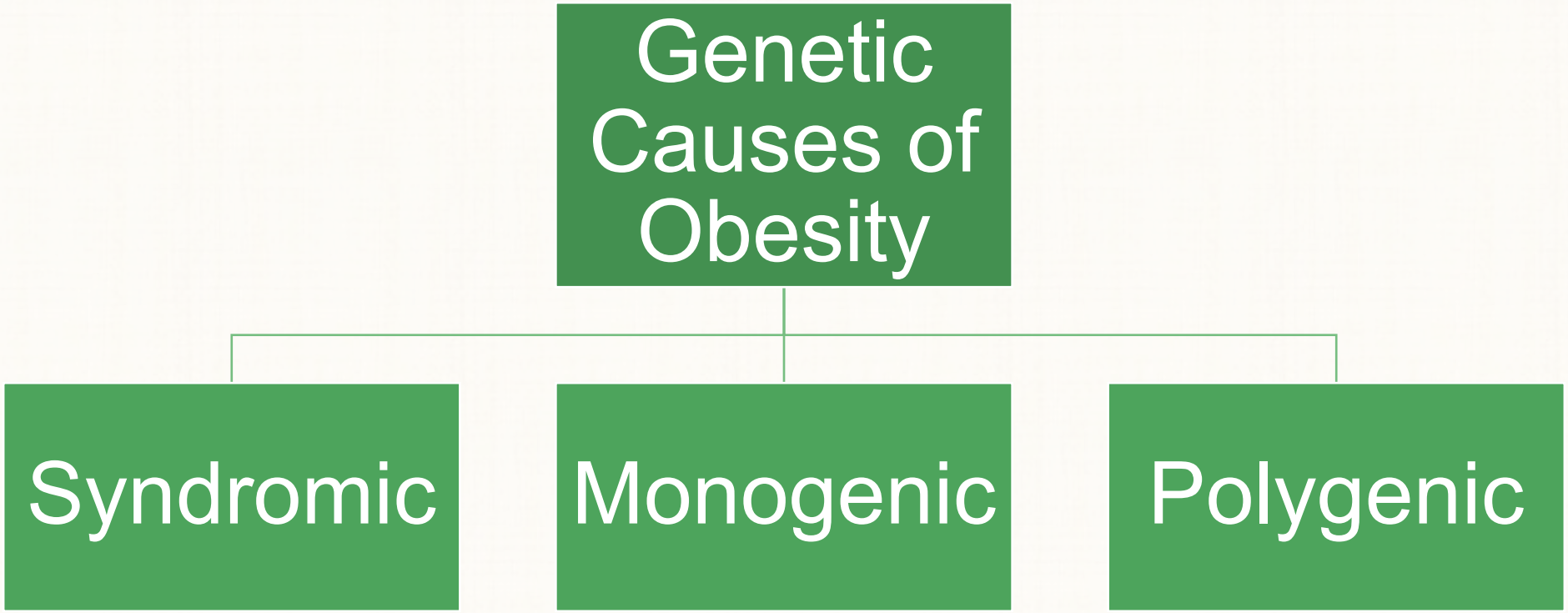
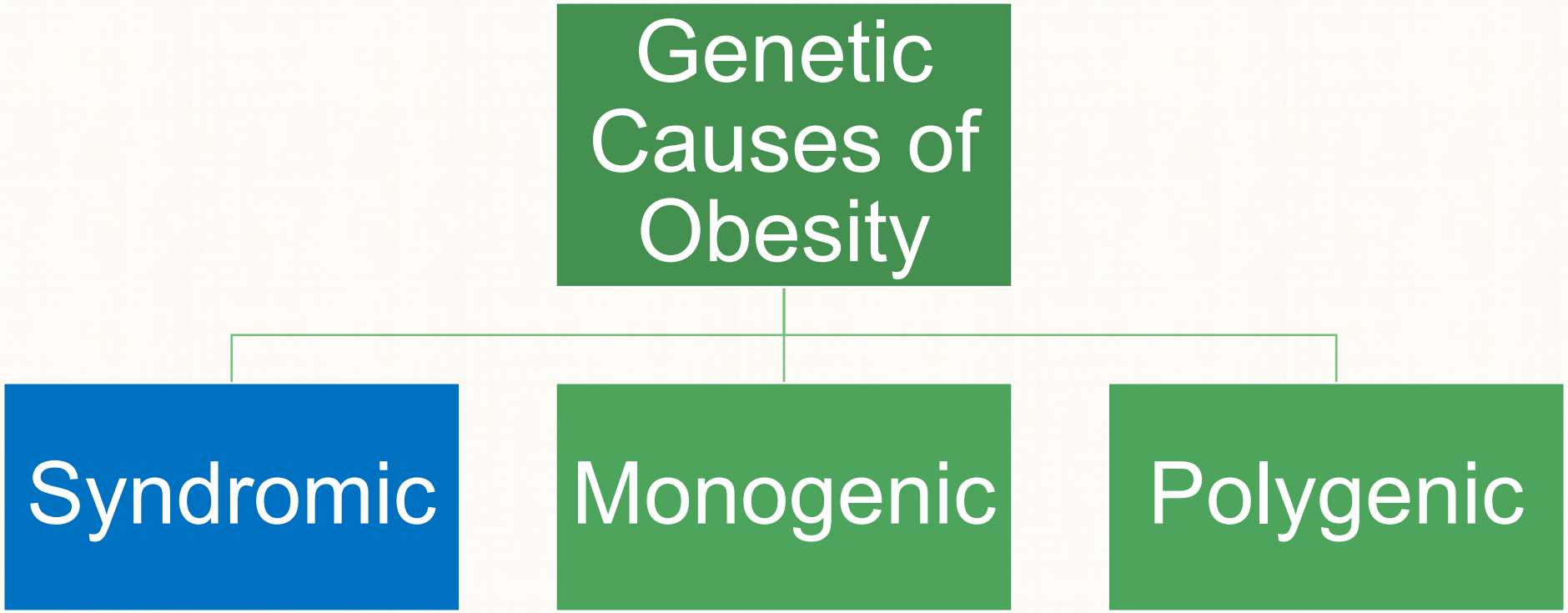
Pathophysiology

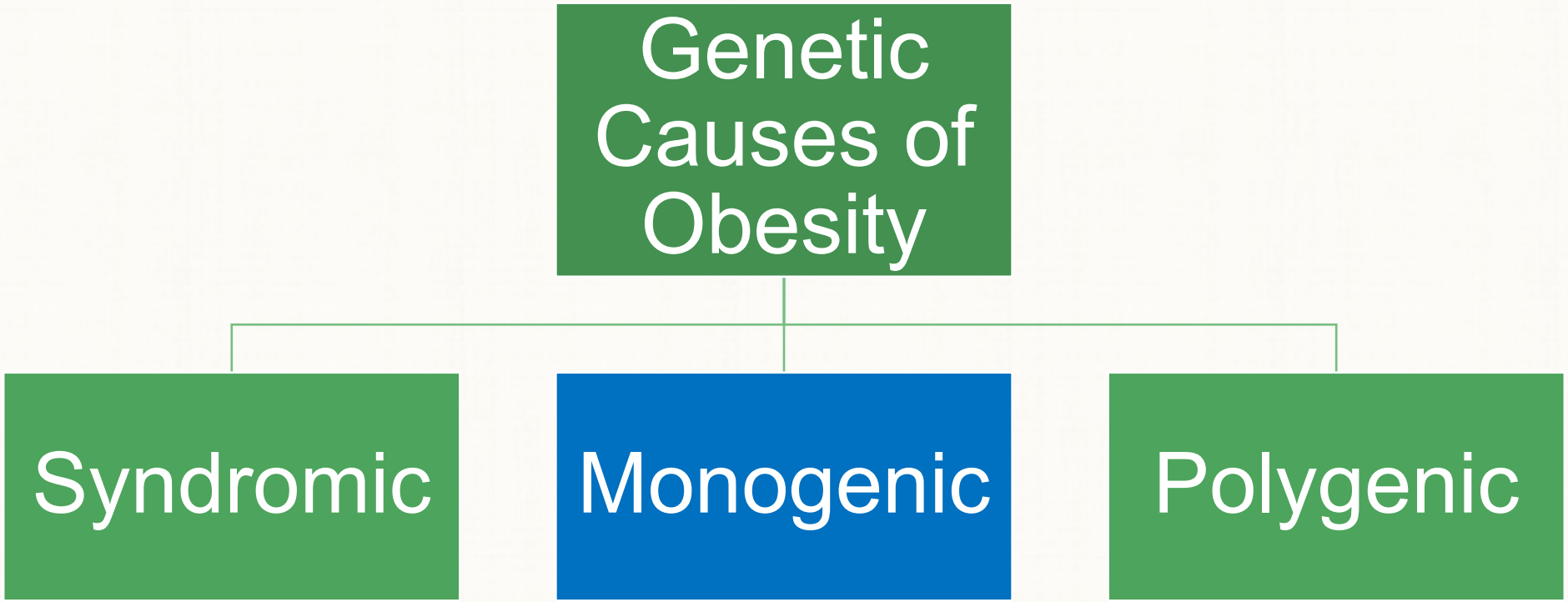
- Energy imbalance: Intake > expenditure, modulated by endocrine signals.
- Key players: Hypothalamus, gut hormones, adipose tissue.
- Genetic predisposition: 40–70% heritability
- Environmental triggers: Ultra-processed foods, sedentary lifestyle.

Börjeson M. The aetiology of obesity in children. A study of 101 twin pairs. Acta Paediatr Scand. 1976 May;65(3):279-87. doi: 10.1111/j.1651-2227.1976.tb04887.x. PMID: 944990.


Genetic Causes of Obesity
Syndromic
Monogenic
Polygenic

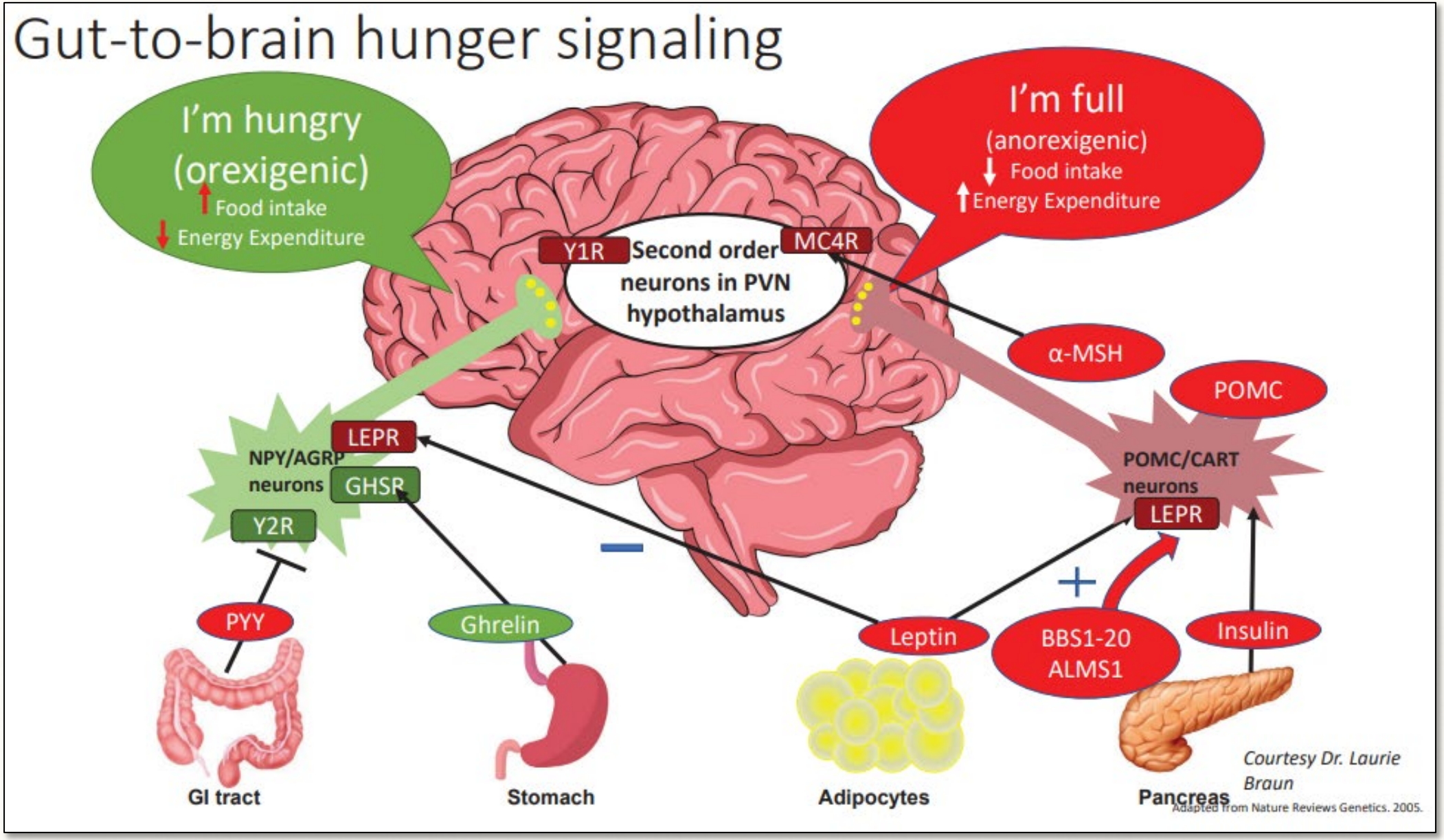


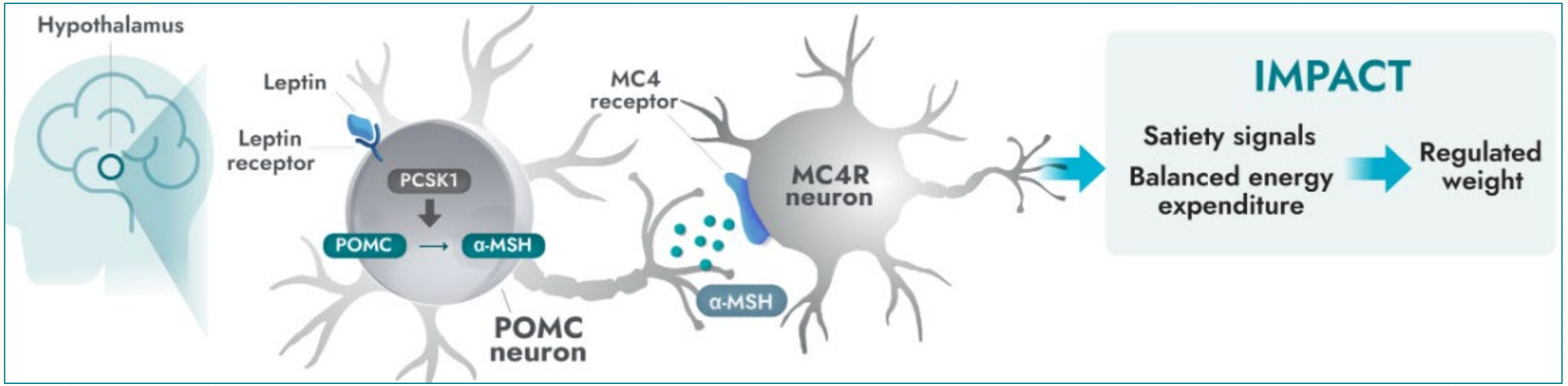
Prader-Will (1/25,000), Bardet-Biedl (1/125,000), Albright Hereditary Osteodystrophy (1/1,000,000) Fragile X (1/2,500) and Beckwith-Widemann (1/10,000).

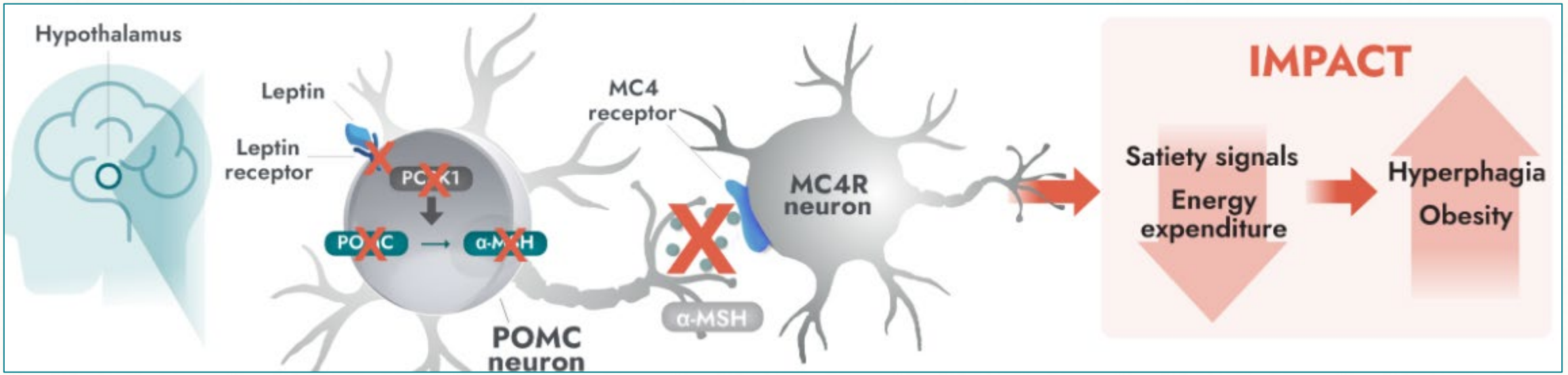


Congenital leptin deficiency as an example. Found in mice and later humans as a factor in hypothalamus signaling for triggering when the brain feels full. One of many in these orexigenic and anorexigenic pathways

Gut-to-brain hunger signaling

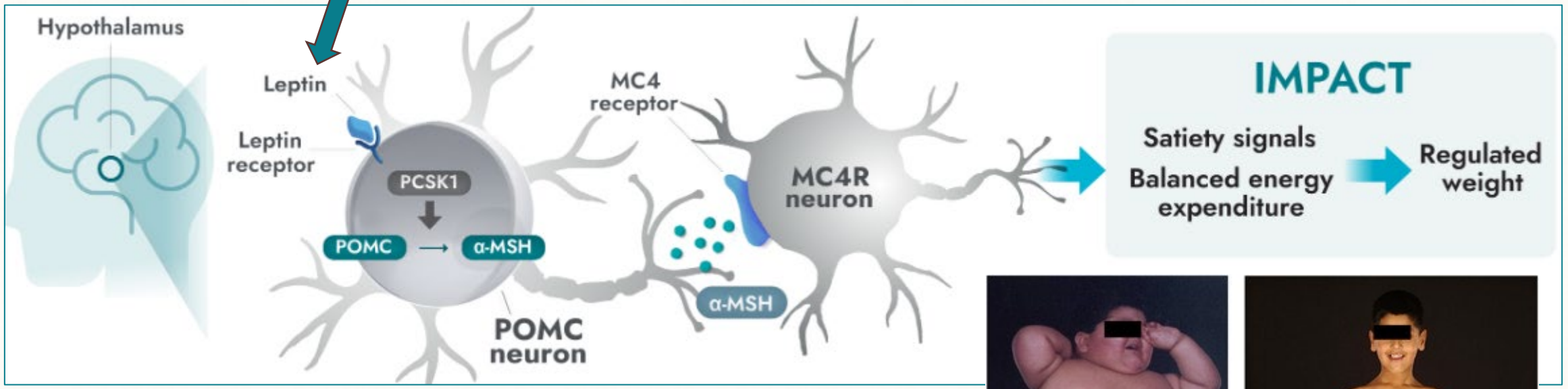






https://www.imcivree.com/hcp/ppl/moa/

Metreleptin



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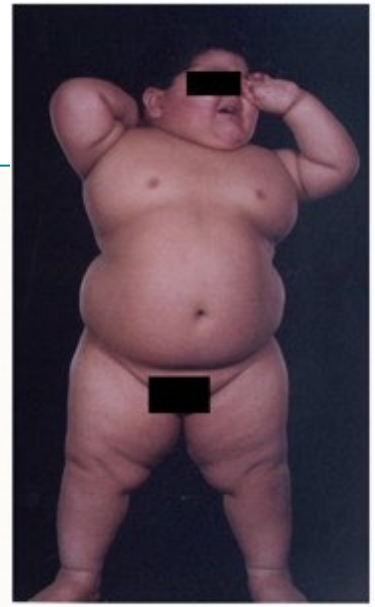
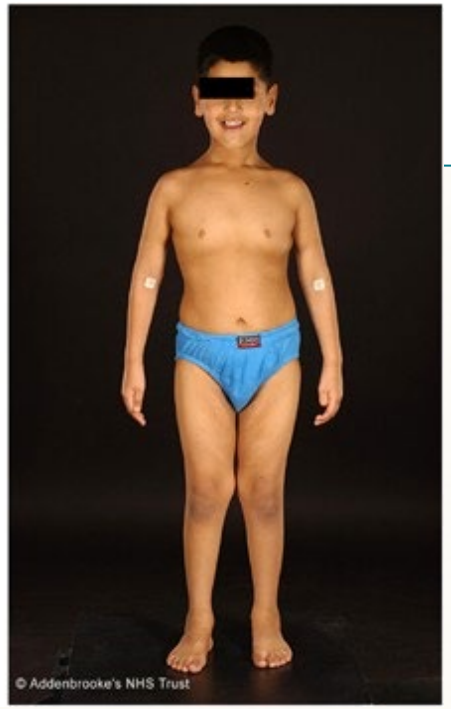
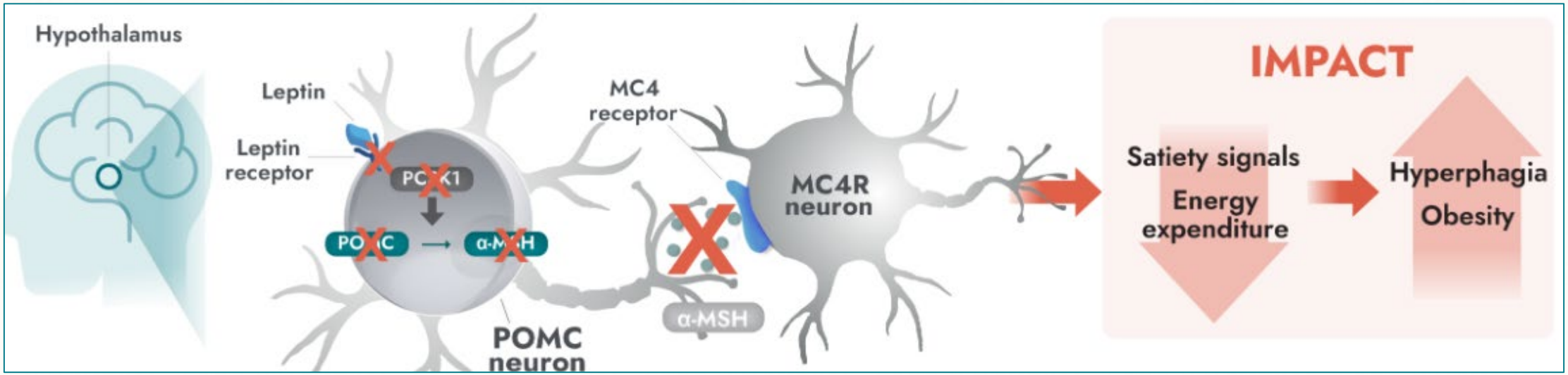
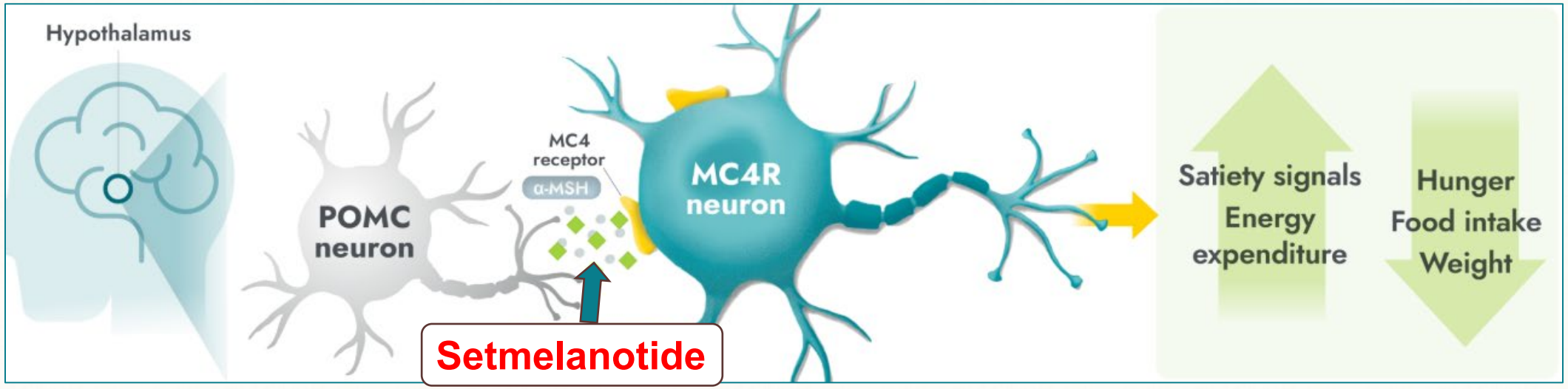
Congenital Leptin Deficiency





Farooqi IS, O'Rahilly S. 20 years of leptin: human disorders of leptin action. J Endocrinol. 2014 Oct





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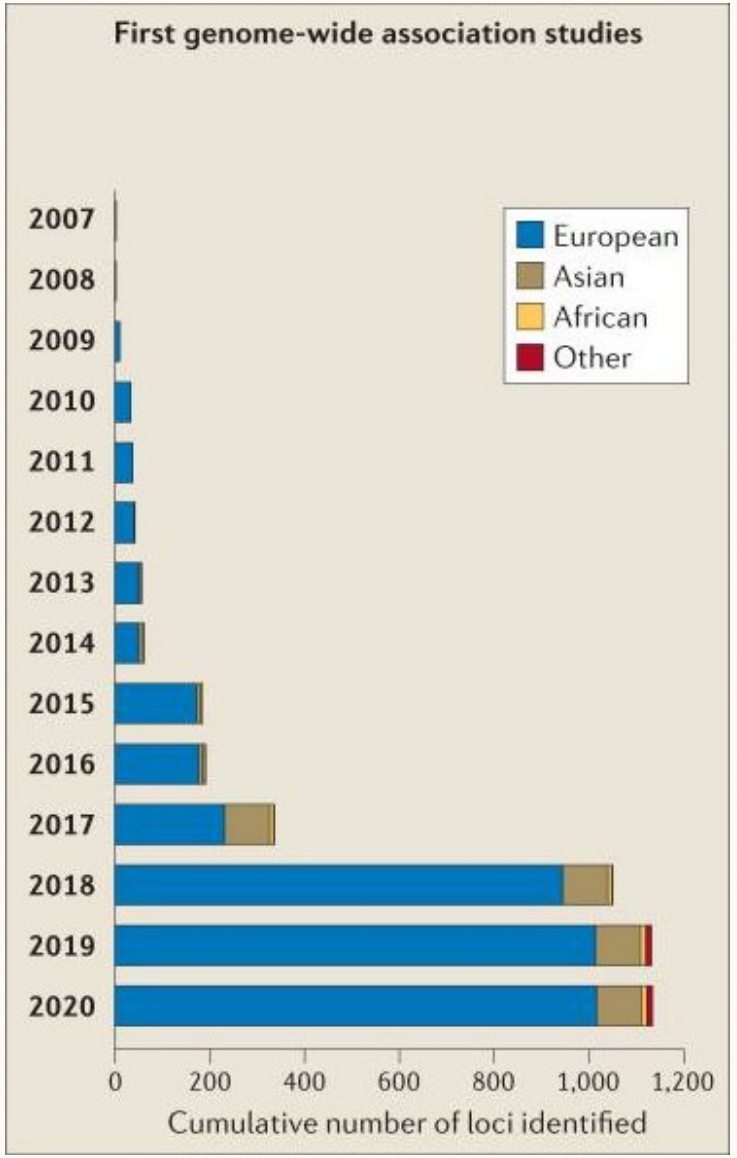
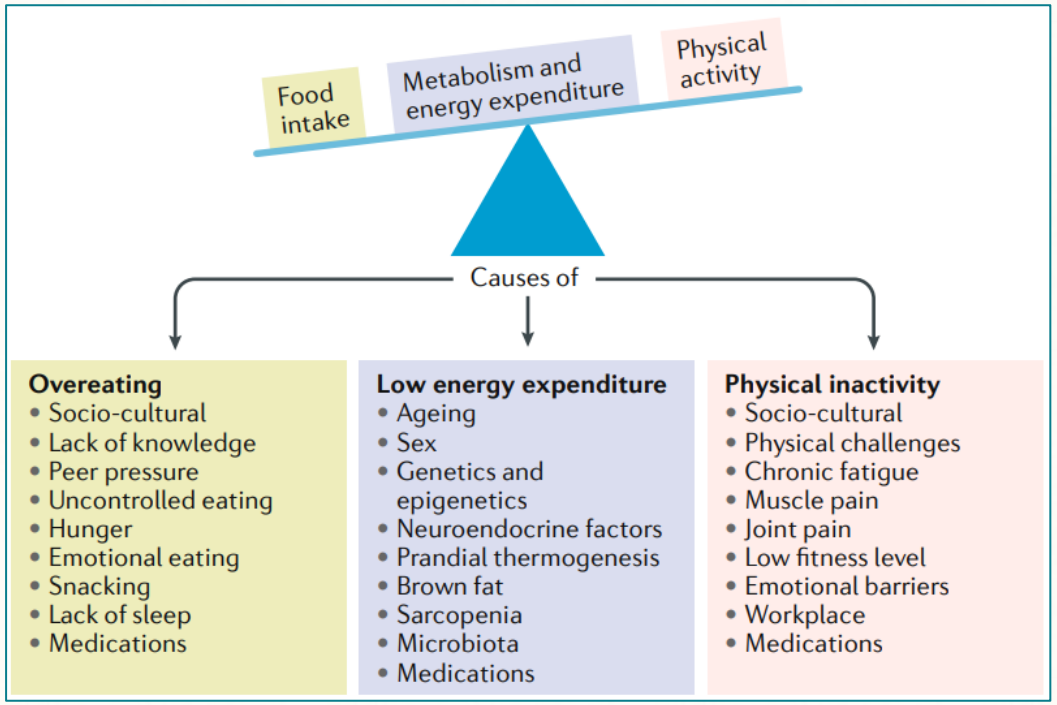
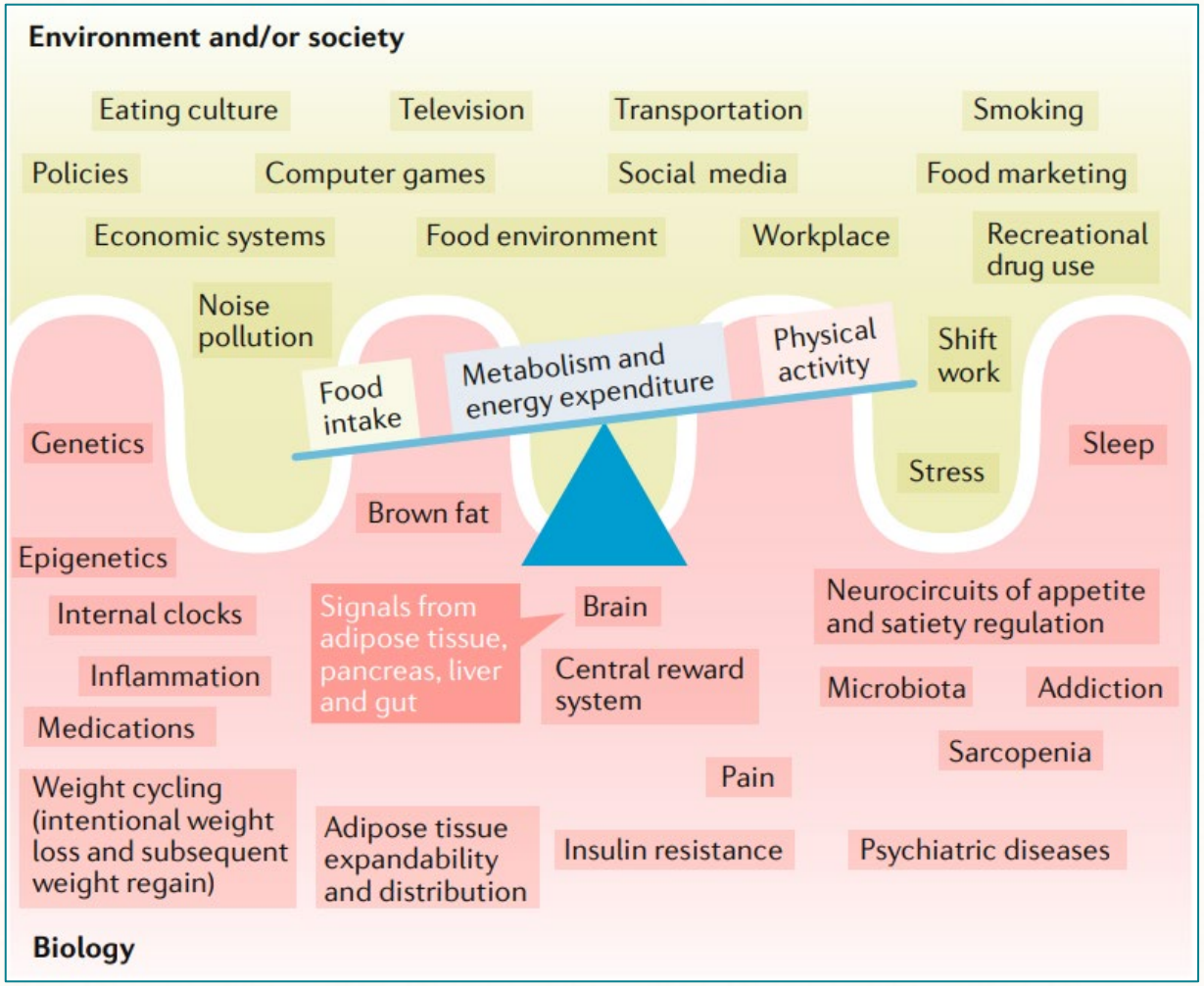
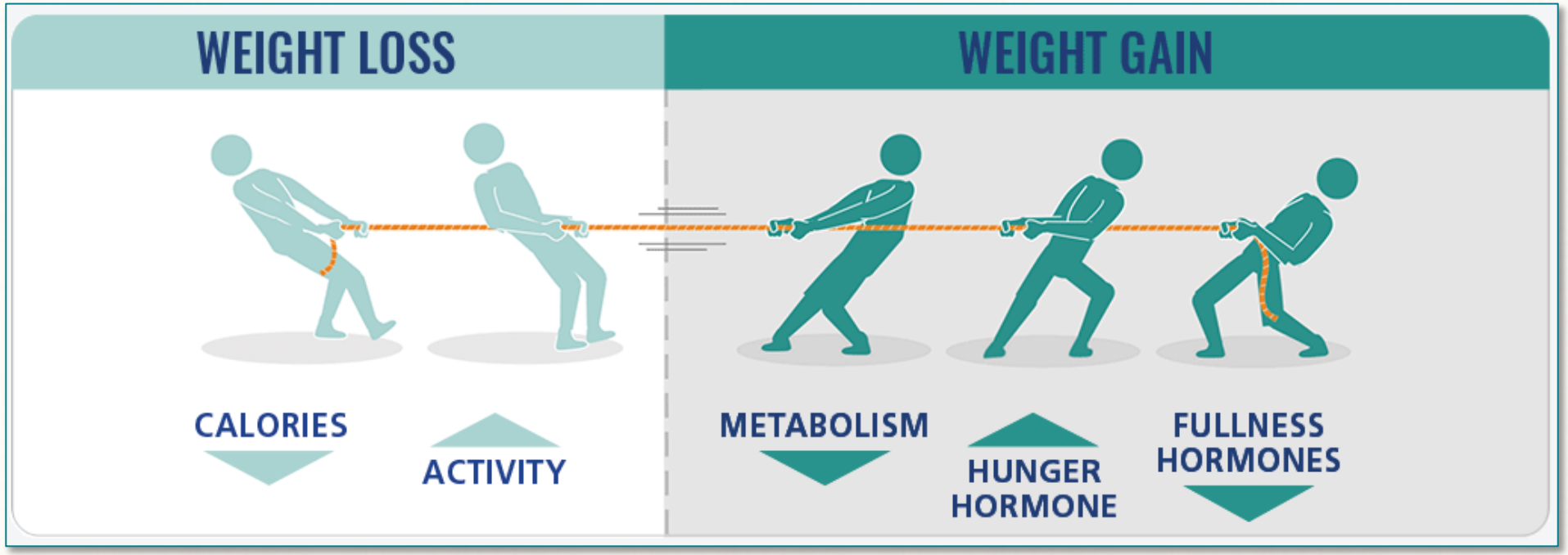


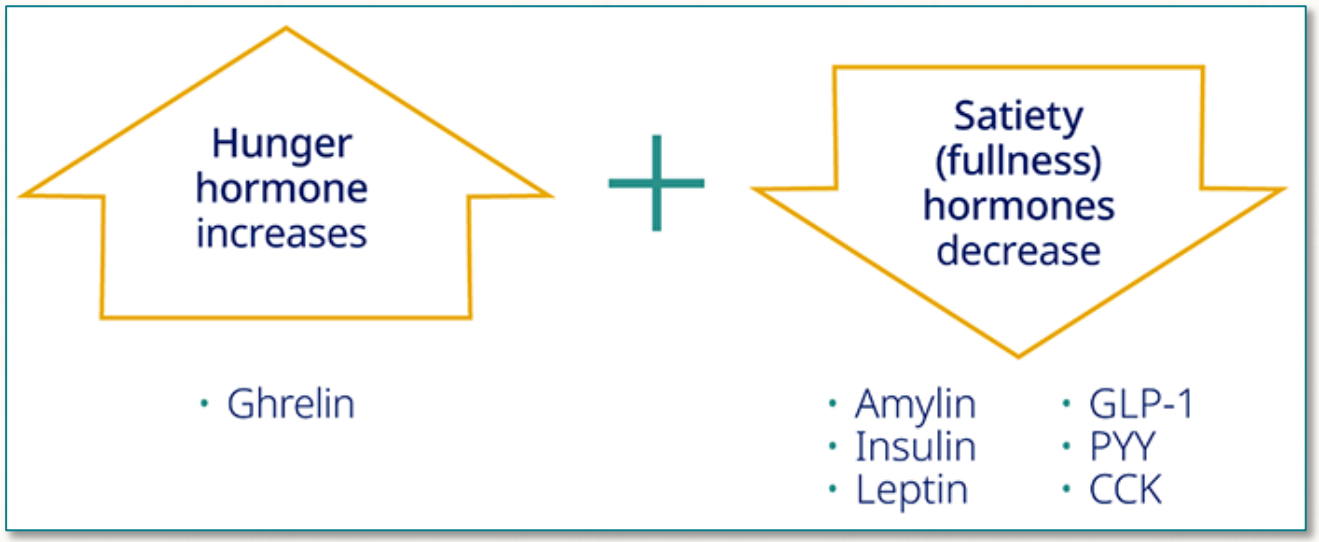
Loos RJF, Yeo GSH. The genetics of obesity: from discovery to biology. Nat Rev Genet. 2022 Feb;23(2):120-133. doi: 10.1038/s41576-021-00414-z. Epub 2021 Sep 23. PMID: 34556834; PMCID: PMC8459824.





Blüher M. Obesity: global epidemiology and pathogenesis. Nat Rev Endocrinol. 2019 May;15(5):288-298. doi: 10.1038/s41574-019-0176-8. PMID: 30814686.





https://www.rethinkobesity.com/metabolic-adaptation.html

The Set Point Theory and Long-Term Hormonal Adaptations

- Weight loss triggers a 'set point' defense mechanism
- NEJM Study (2011): Long-term hormonal changes persist post-weight loss
- Key hormones: Increased ghrelin, amylin, PYY, CCK
- Implications: Appetite increases, energy expenditure drops, challenging sustained weight loss.

Sumithran P, et al. "Long-Term Persistence of Hormonal Adaptations to Weight Loss." NEJM, 2011.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Long-Term Persistence of Hormonal Adaptations to Weight Loss

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ABSTRACT

BACKGROUND

After weight loss, changes in the circulating levels of several peripher involved in the homeostatic regulation of body weight occur. Whether th are transient or persist over time may be important for an understanding of behind the high rate of weight regain after diet-induced weight loss.

METHODS

We enrolled 50 overweight or obese patients without diabetes in a 10-week program for which a very-low-energy diet was prescribed. At baseline (be

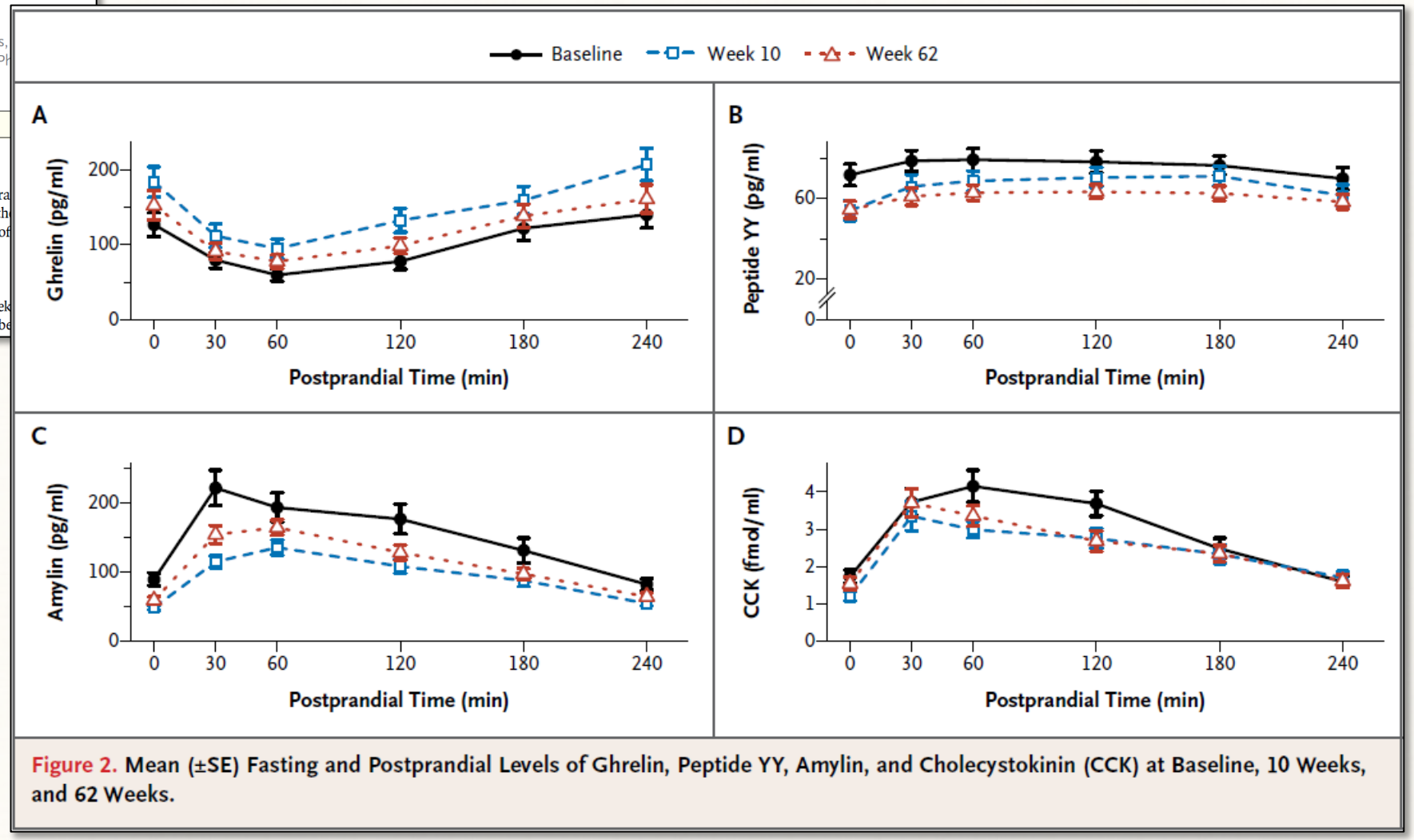

Figure 2. Mean (±SE) Fasting and Postprandial Levels of Ghrelin, Peptide YY, Amylin, and Cholecystokinin (CCK) at Baseline, 10 Weeks, and 62 Weeks.

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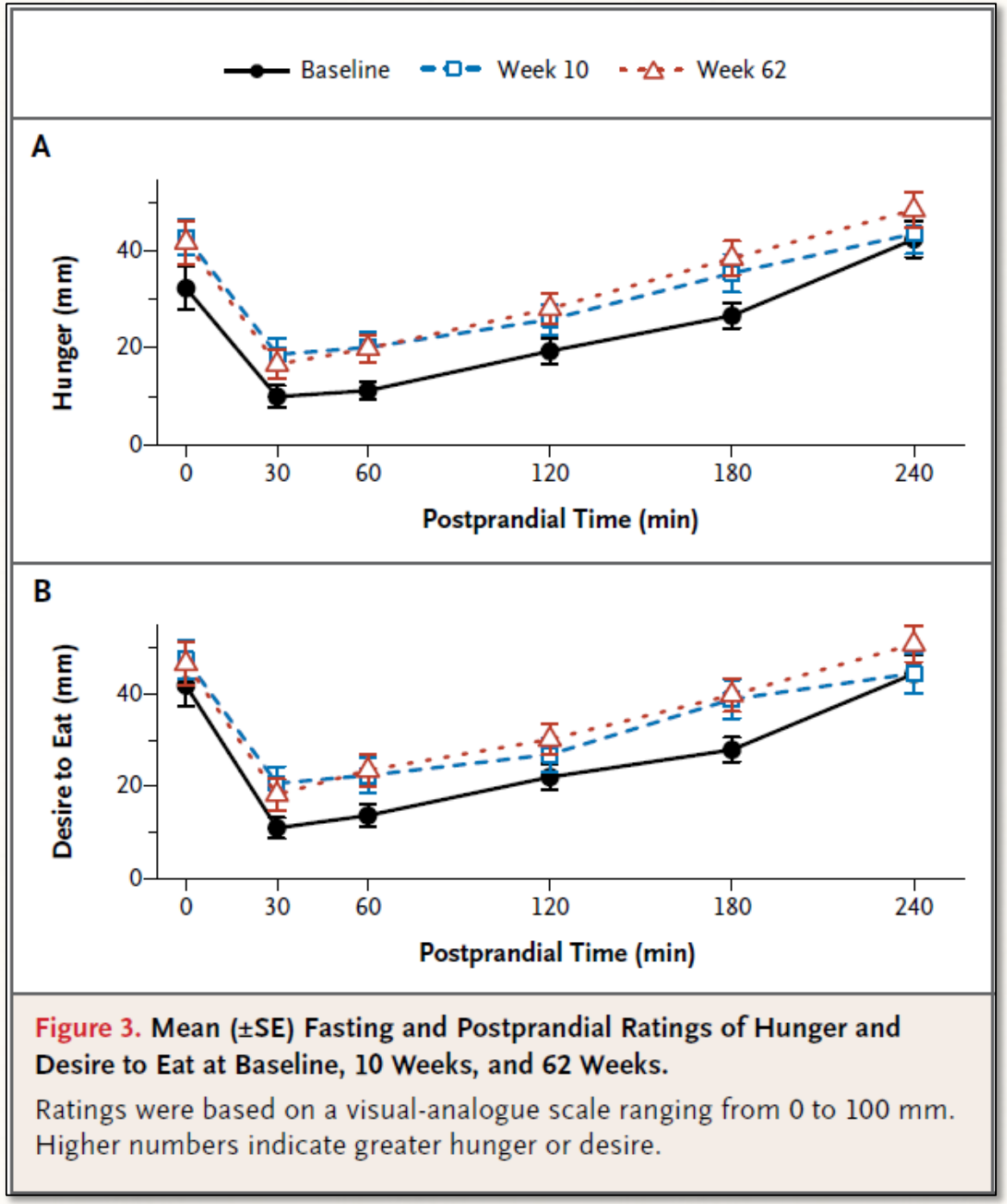


Figure 3. Mean (±SE) Fasting and Postprandial Ratings of Hunger and Desire to Eat at Baseline, 10 Weeks, and 62 Weeks.

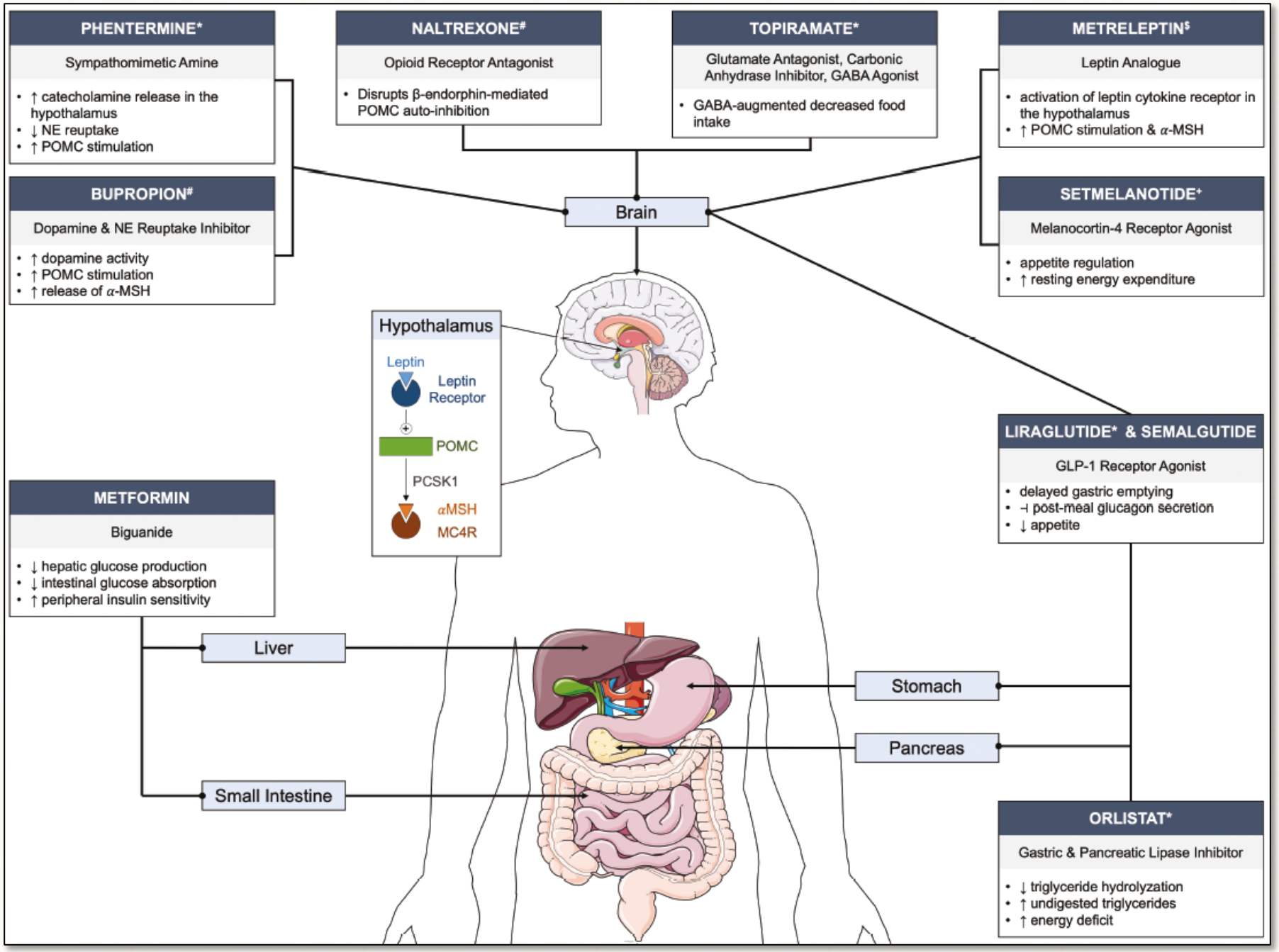
Ratings were based on a visual-analogue scale ranging from 0 to 100 mm. Higher numbers indicate greater hunger or desire.

Lifestyle Interventions: The Old Foundation

- Diet: Caloric deficit (500–750 kcal/day), individualized plans.
- Exercise: 150–300 min/week moderate activity.
- Behavioral therapy: Self-monitoring, goal setting.
- Evidence: 5–10% sustained loss possible (Hamdy et al., 2023).

	Weight gain	Weight neutral	Weight loss
Diabetes	Insulin Sulfonylureas TZDs	DPP4 inhibitor	Metformin GLP-1 agonist SGLT2 inhibitor
Anti-depressants	Mirtazapine, Amitriptyline, Paroxetine, Nortriptyline, Citalopram	Fluoxetine, Sertraline, Imipramine, Escitalopram, Duloxetine	Bupropion
Anti-seizure	Carbamazepine, Gabapentin, Oxcarbazepine, Pregabalin, Valproate	Lacosamide, Phenytoin, Clonazepam, Lamotrigine, Levetiracetam	Topiramate Zonisamide
Anti-histamine	Diphenhydramine, Hydroxyzine	Desloratadine, Fexofenadine, Levocetirizine	
Antipsychotics	Olanzapine, Clozapine, Quetiapine	Haldol, Ziprasidone, Aripiprazole	

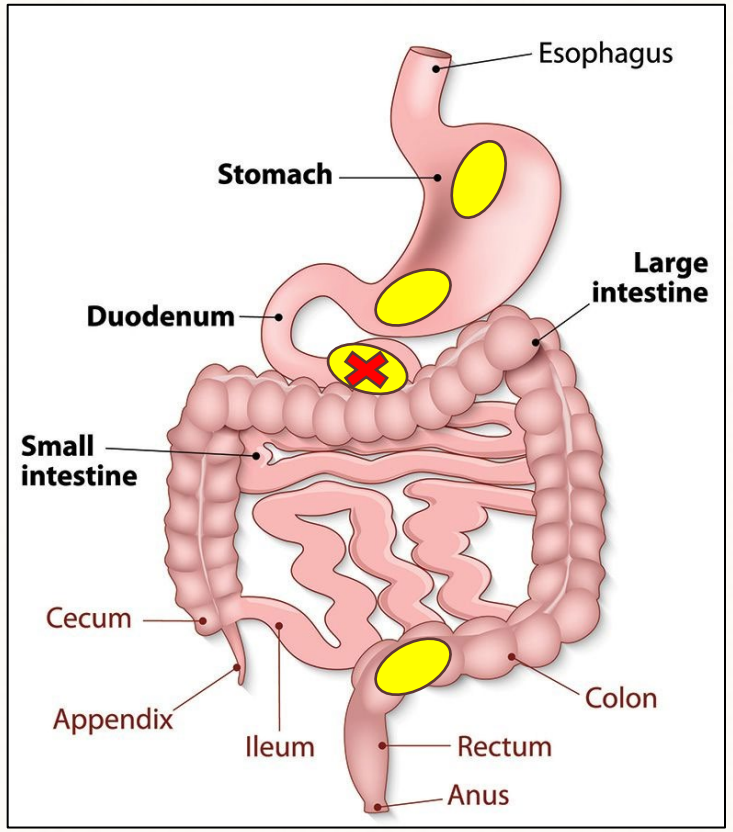
Weintraub MA, Ameer B Drug-associated weight gain and clinical alternatives, *Handbook of Obesity*


PHENTERMINE*
Sympathomimetic Amine
• ↑ catecholamine release in the hypothalamus
• ↓ NE reuptake
• ↑ POMC stimulation
BUPROPION#
Dopamine & NE Reuptake Inhibitor
• ↑ dopamine activity
• ↑ POMC stimulation
• ↑ release of α-MSH
NALTREXONE#
Opioid Receptor Antagonist
• Disrupts β-endorphin-mediated POMC auto-inhibition
TOPIRAMATE*
Glutamate Antagonist, Carbonic Anhydrase Inhibitor, GABA Agonist
• GABA-augmented decreased food intake
METRELEPTIN§
Leptin Analogue
• activation of leptin cytokine receptor in the hypothalamus
• ↑ POMC stimulation & α-MSH
SETMELANOTIDE+
Melanocortin-4 Receptor Agonist
• appetite regulation
• ↑ resting energy expenditure
Brain
Hypothalamus
Leptin
Leptin Receptor
POMC
PCSK1
αMSH
MC4R
LIRAGLUTIDE* & SEMALGUTIDE
GLP-1 Receptor Agonist
• delayed gastric emptying
• ⊣ post-meal glucagon secretion
• ↓ appetite
METFORMIN
Biguanide
• ↓ hepatic glucose production
• ↓ intestinal glucose absorption
• ↑ peripheral insulin sensitivity
Liver
Small Intestine
Stomach
Pancreas
ORLISTAT*
Gastric & Pancreatic Lipase Inhibitor
• ↓ triglyceride hydrolyzation
• ↑ undigested triglycerides
• ↑ energy deficit

Orlistat - Peripheral

- Fat Absorption Blocker (Rx Xenical, OTC Alli)
  - Mechanism: Pancreatic lipase inhibitor
  - Effect: Reduces fat absorption by ~30%
  - Weight loss: 3-5% over placebo
  - Side effects: GI (steatorrhea, flatulence).

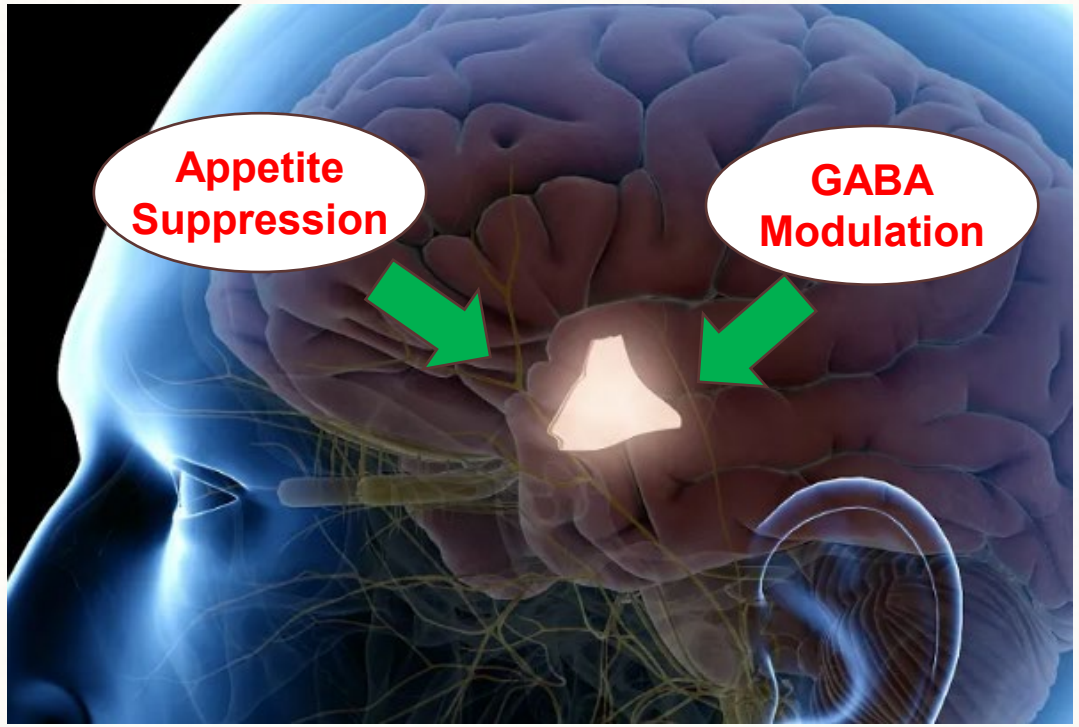
https://www.mentalfloss.com/article/619261/olestra-fat-free-snack-controversy-1990s



Phentermine – Sympathomimetic

- Phentermine: Appetite Suppression via CNS
  - Mechanism: Norepinephrine release in hypothalamus
  - Effect: Reduces hunger
  - Weight loss: 5-7% short-term
  - Limitation: Short-term use (3 months)

Phentermine/Topiramate – Combo Power



- Phentermine/Topiramate: Dual Action (Qsymia)
  - Mechanism: Appetite suppression + GABA modulation
  - Effect: Synergistic weight loss (8-10%)
  - Brain target: Hypothalamic hunger circuits
  - Consideration: Teratogenicity risk

Naltrexone/Bupropion – Reward System Focus

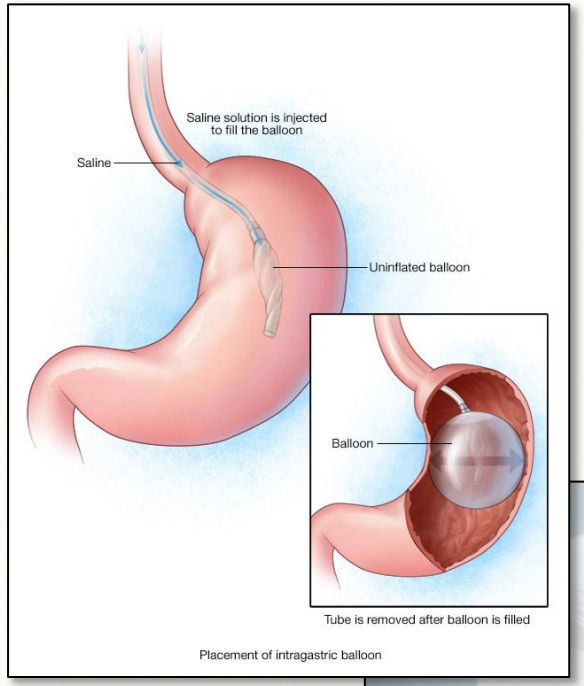
- Naltrexone/Bupropion: Craving Control (Contrave)
  - Mechanism: Opioid antagonism + dopamine/norepinephrine boost
  - Effect: Reduces food reward, 5-6% loss
  - Brain target: Mesolimbic reward pathway
  - Note: Psychiatric monitoring

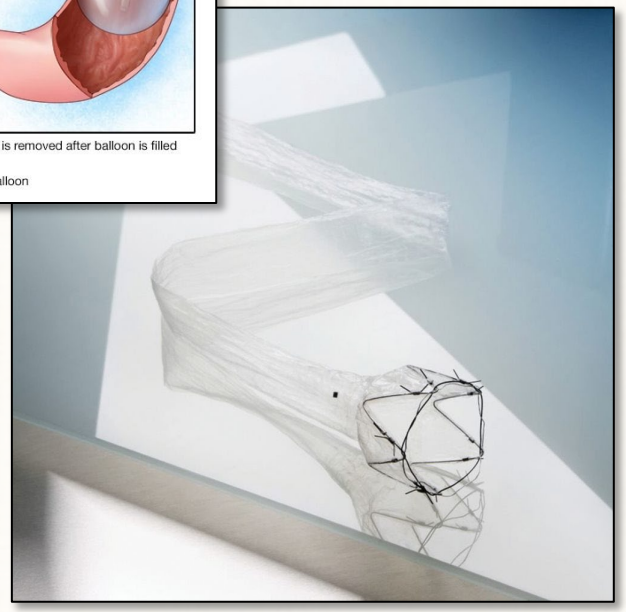
Incretin Based Therapies

- Liraglutide (Saxenda) – 3 mg
  - First GLP-1 receptor agonist for obesity
  - Mimics GLP-1: slows gastric emptying, signals satiety via hypothalamus
  - Achieves 5-8% weight loss
- Semaglutide (Wegovy) – 2.4 mg
  - Potent GLP-1 agonist, suppresses appetite via hypothalamus/rewards centers
  - STEP trials: >15% weight loss, nearing surgical outcomes
  - Injectable, oral forms in development
- Tirzepatide (Zepbound)
  - Dual GIP/GLP-1 agonist
  - SURMOUNT trials: >20% weight loss
  - Also indicated for OSA

Non-Surgical, Non-Drug Treatments

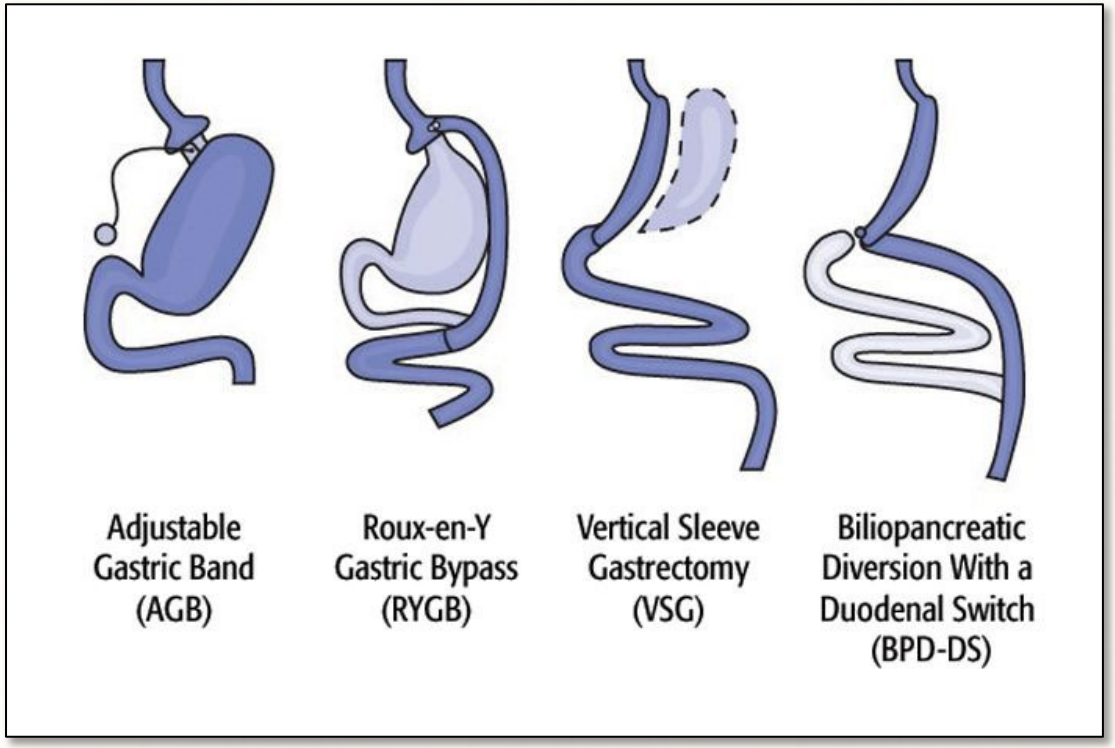
- Intragastric Ballons (e.g. Orbera)
  - Temporary device occupies stomach space for 6-12 months
  - Drives 10-15% weight loss via restriction
  - Leverages anatomy
- Swallowed Hydrogel (Plenity)
  - Hydrogel particle capsules taken before meals with water
  - Mimics food volume, yields 6% weight loss on avg
  - Better for lower BMIs, excreted in stool
- Duodenal Liner (EndoBarrier)
  - Sleeve lines the first 60 cm of small intestines
  - Inserted via endoscopy, meant to mimic Roux-En-Y changes
  - 10-15% early weight loss, not U.S. approved yet (safety concerns)





Bariatric Surgery: Lasting Impact

- Types: Sleeve gastrectomy, Roux-en-Y, bypass
- Mechanism: Restriction, malabsorption, hormonal shifts
- Effect: 20-30% sustained weight loss
- Indications: BMI ≥35 or ≥30 with comorbidities (changed 2022).



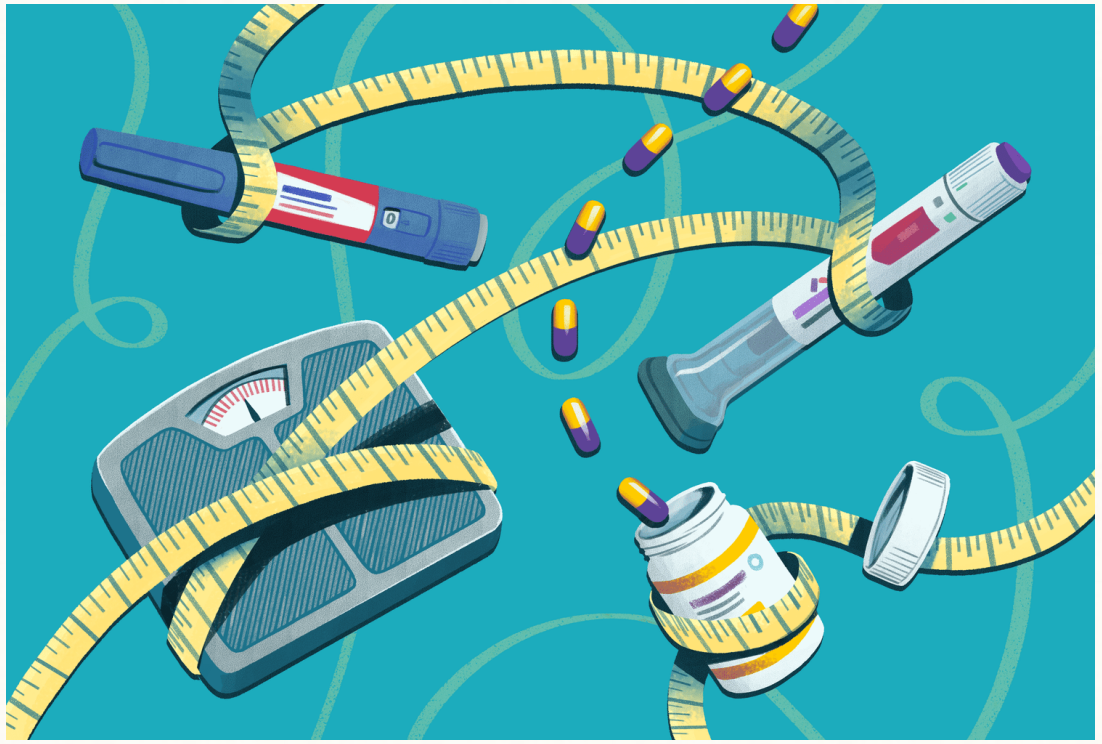
Medical vs Surgical Weight Loss

- **Medical (Pharmacotherapy):** GLP-1 agonists (e.g., semaglutide 2.4 mg) achieve ~15-17% weight loss at 68 weeks (STEP trials), while tirzepatide (Zepbound) reaches ~21-23% (SURMOUNT-1, 2023). CagriSema (Phase 3, 2024) shows 22.7% loss in non-diabetics (REDEFINE 1).
- **Surgical (Bariatric):** Roux-en-Y gastric bypass (RYGB) and sleeve gastrectomy (SG) yield 20-25% loss at 5-10 years (NIDDK, 2021; updated 2024 meta-analysis). RYGB outperforms SG long-term (22% vs. 16% at 5 years).
- **Comparison:** Surgery offers greater durability (10-year data) and higher diabetes remission (70-80% vs. 20-50% with meds). Meds close the gap short-term but require ongoing use.

Closs, L., et al. "Surgery is associated with better long-term outcomes than pharmacological treatment for obesity: a systematic review and meta-analysis." Scientific Reports, 2024

Combining Forces: Multimodal Care

- Lifestyle + meds + surgery = synergy
- Example: Meds post-surgery for regain
- Personalization key: Genetics, preferences
- Goal: Sustainable health gains



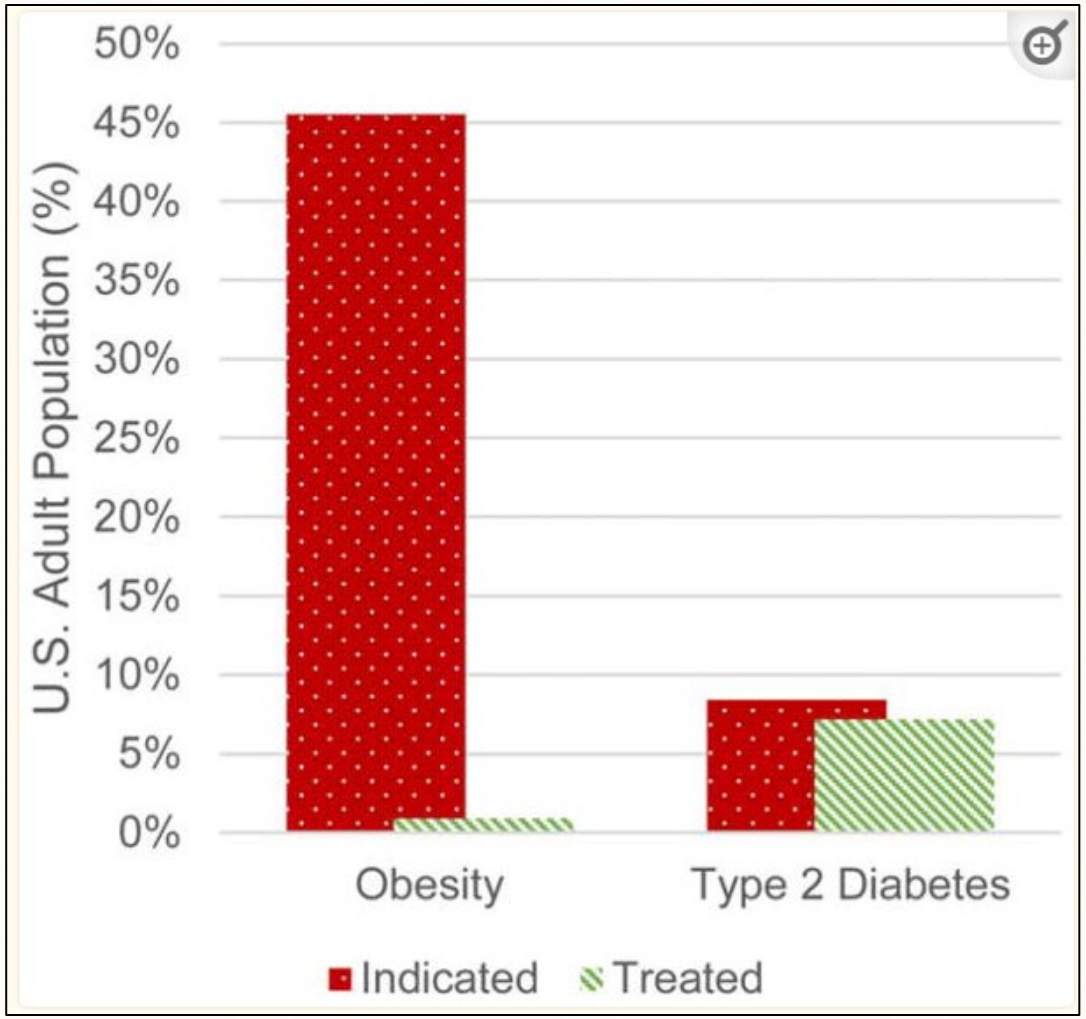
Diagnosis	Weight loss target, %	Expected outcome
Metabolic syndrome	10	Prevention of type 2 diabetes
Type 2 diabetes	5–15	Reduction in glycated haemoglobin; reduction in diabetes medication; diabetes remission if short duration
Dyslipidaemia	5–15	Lower triglycerides; increase HDL, decrease LDL
Hypertension	5–15	Lower blood pressure; decrease in medication
NAFLD	10 40	Reduction in intrahepatocellular lipids and inflammation
Polycystic ovary syndrome	5–15	Ovulation; reduction of hirsutism; decrease in androgen levels; increase insulin sensitivity
Sleep apnoea	7–11	Decrease apnoea/hypopnoea index
Asthma	7–8	Improvement of forced expiratory volume at 1 s (FEV1)
Gastro-oesophageal reflux disease	10 or more	Reduced symptoms

Note that weight loss will depend upon the nature of comorbidity.

Durrer Schutz D. European Practical and Patient-Centred Guidelines for Adult Obesity Management in Primary Care. Obes Facts. 2019;12(1):40-66.

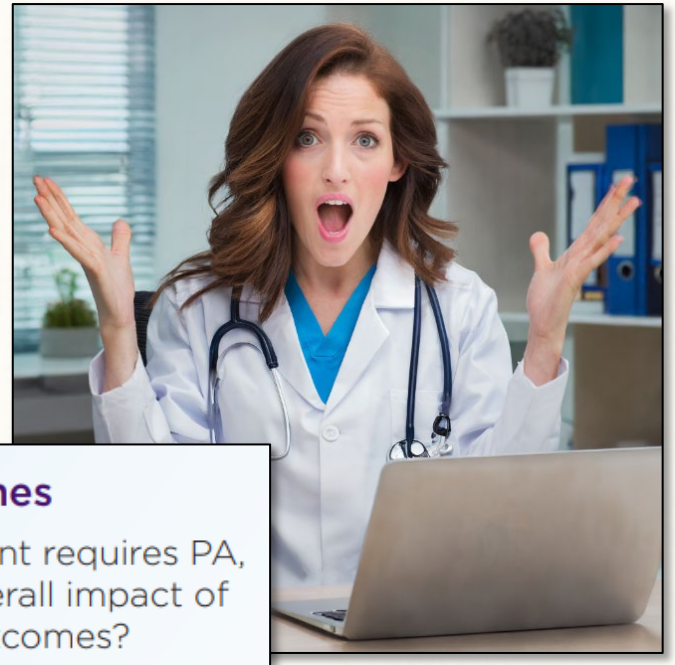
Low Treatment Rate of Obesity

- Anti-obesity pharmacotherapy is indicated as an adjunct to reduced-calorie diet and increased physical activity in adults with a body mass index ≥30 or ≥27 kg/m^2 with hypertension, type 2 diabetes, or dyslipidemia.
- Just under half (**46%**) of adults in the United States **fit the criteria for use of anti-obesity pharmacotherapy**, but **only 2%** of those receive such treatment.
- This is in sharp contrast to the **8.4% of adults in the United States diagnosed with diabetes**, with **86%** of those receiving anti-diabetes pharmacotherapy.



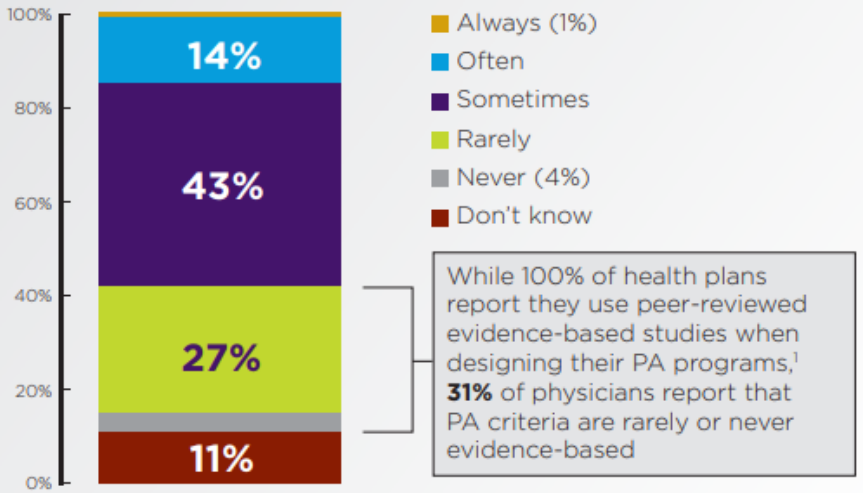
Thomas CE, Mauer EA, Shukla AP, Rathi S, Aronne LJ. Low adoption of weight loss medications: A comparison of prescribing patterns of antiobesity pharmacotherapies and SGLT2s. Obesity (Silver Spring). 2016 Sep;24(9):1955-61

Barrier to Treatment: Prior Authorizations



Clinical validity of PA programs

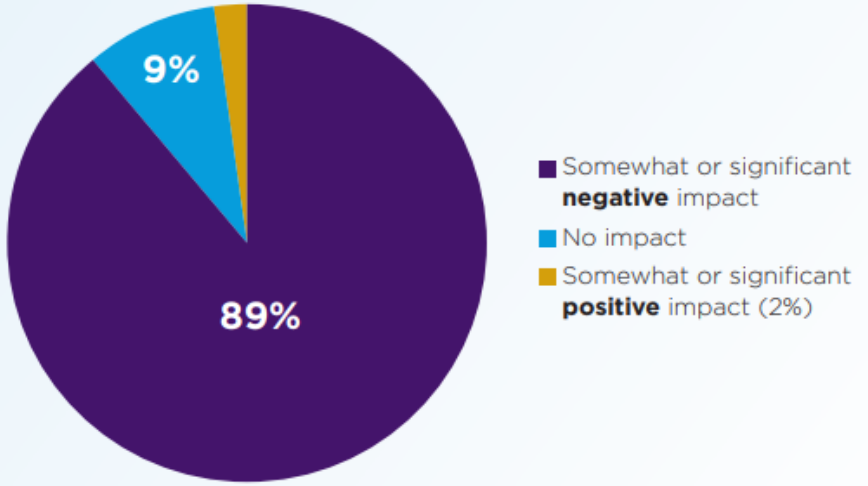
Q: How often are health plans' PA criteria based on evidence-based medicine and/or guidelines from national medical specialty societies?



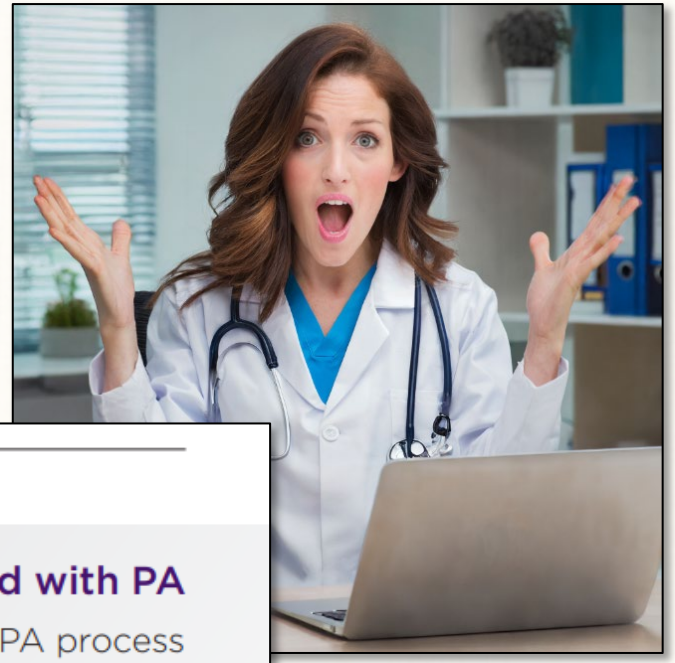
While 100% of health plans report they use peer-reviewed evidence-based studies when designing their PA programs,[1] **31%** of physicians report that PA criteria are rarely or never evidence-based

Impact of PA on clinical outcomes

Q: For those patients whose treatment requires PA, what is your perception of the overall impact of this process on patient clinical outcomes?



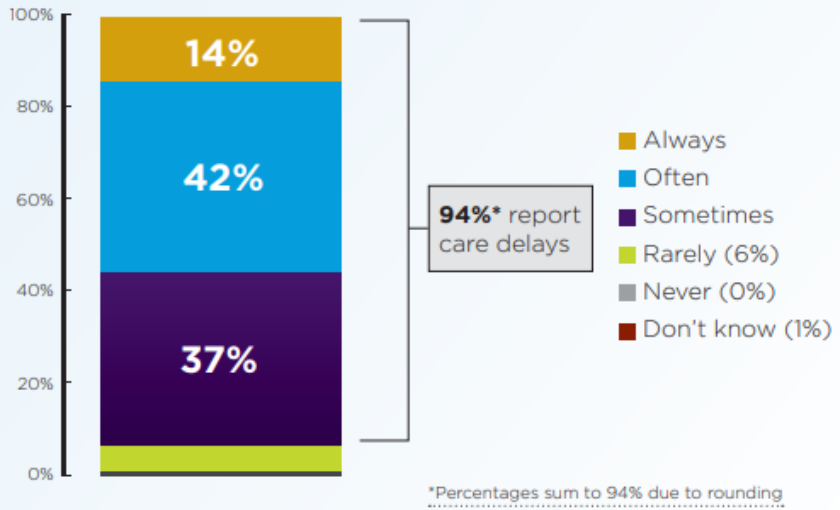
Barrier to Treatment: Prior Authorizations



Patient impact

Care delays associated with PA

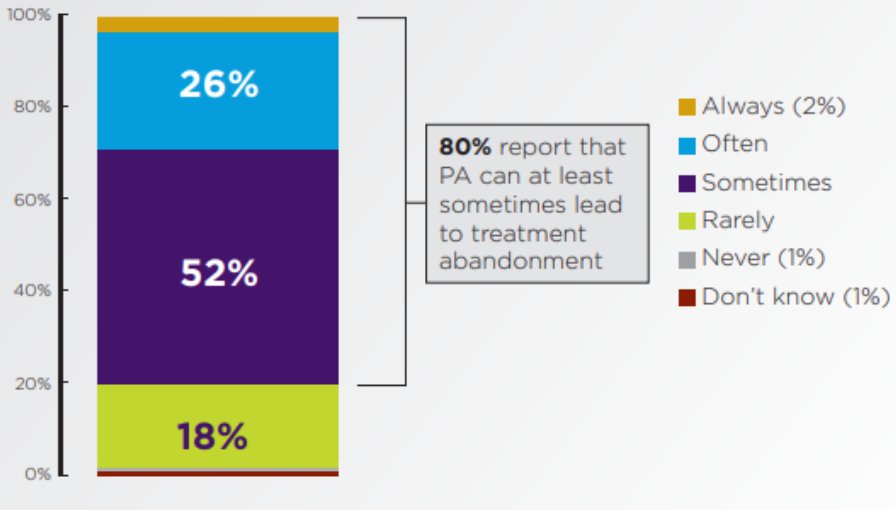
Q: For those patients whose treatment requires PA, how often does this process delay access to necessary care?



*Percentages sum to 94% due to rounding

Abandoned treatment associated with PA

Q: How often do issues related to the PA process lead to patients abandoning their recommended course of treatment?



Upcoming Hormonal Drug Targets

- Glucagon (e.g., Retatrutide, UBT251)
  - Increases energy expenditure by stimulating thermogenesis and fat oxidation in liver and adipose tissue.
  - Synergizes with GLP-1/GIP to balance satiety with metabolic rate, reducing fat storage.
- Amylin (e.g., CagriSema, Amycretin)
  - Acts on hindbrain (area postrema) to enhance satiety, reduce food intake.
  - Slows gastric emptying further, complementing GLP-1 for sustained fullness.
- Activin/Myostatin (e.g., Bimagrumab)
  - Inhibits ActRIIA/B receptors, reducing fat mass while preserving lean muscle.
  - May influence amygdala to curb emotional eating, addressing behavioral drivers

Multi-Hormone Combinations in Development

- CagriSema (Novo Nordisk) – GLP-1/Amylin
  - REDEFINE-1 (Phase 3, 2024): 22.7% weight loss (68 weeks, non-diabetics).
  - REDEFINE-2 (Phase 3, 2025): 15.7% weight loss (type 2 diabetes).
  - Mechanism: Amylin + GLP-1 for prolonged satiety.
- Retatrutide (Eli Lilly) – GLP-1/GIP/Glucagon
  - Phase 2 (2023): 24.2% weight loss (48 weeks).
  - Phase 3 TRIUMPH ongoing: Obesity, osteoarthritis, OSA.
  - Mechanism: Glucagon increases energy expenditure.
- UBT251 (Novo Nordisk) – GLP-1/GIP/Glucagon
  - Phase 1: 15.1% weight loss (12 weeks).
  - Mechanism: Triple action boosts thermogenesis.

Oral Therapies and Novel Mechanisms

- Orforglipron (Eli Lilly) – Oral GLP-1 Agonist
  - Phase 2 (2023): 14.7% weight loss (36 weeks).
  - Phase 3 ATTAIN ongoing: Easy oral administration.
- Oral Amycretin (Novo Nordisk) – GLP-1/Amylin
  - Phase 1 (2024): 13.1% weight loss (12 weeks).
  - Mechanism: Amylin reduces food intake.
- Mazdutide (Eli Lilly) – GLP-1/Glucagon
  - Phase 2 (2023): 15.4% weight loss (24 weeks).
  - Mechanism: Glucagon boosts energy expenditure.
- Bimagrumab (Eli Lilly) – Activin/Myostatin Inhibitor
  - Phase 2 (2024): 20.5% fat loss, 3.6% lean mass gain.
  - Mechanism: Reduces fat, may target emotional eating.

Expanding Horizons in Obesity Treatment

- Tirzepatide (Eli Lilly) – GLP-1/GIP
  - Testing 20-25 mg doses for >21-23% weight loss.
  - SURPASS-CVOT (2025): Cardiovascular outcomes in T2DM.
- Semaglutide (Novo Nordisk) – GLP-1 Agonist
  - Phase 3: 7.2 mg dose for obesity.
  - Non-obesity Phase 3: Alzheimer’s, MASH.
- Multi-Hormone Future
  - Survodutide (GLP-1/glucagon, Phase 3): 18-20% weight loss.
  - Eloralintide + tirzepatide (Phase 2, 2025): Amylin-based combo.

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