Dartmouth GEISEL SCHOOL OF MEDICINE

Dartmouth Health

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Long-term Outcomes of Metabolic Surgery

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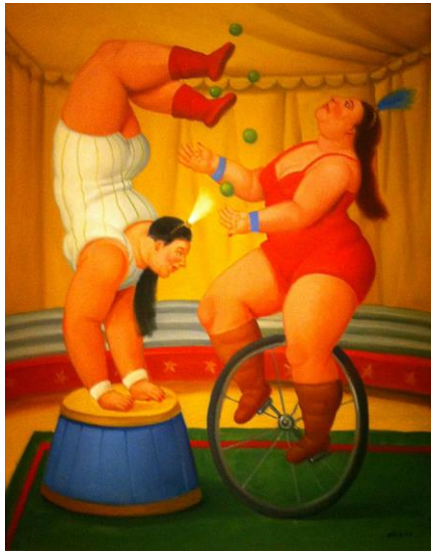
3 September 2024



Fernando Botero, 1932-2023

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Disclosures

I am currently or have recently been a paid consultant to the following companies and organizations:

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Amgen	Eli Lilly & Company
AstraZeneca	Neurogastrx
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Boehringer Ingelheim	Optum Health
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Ethicon	Pfizer
Gelesis	Sidekick Health
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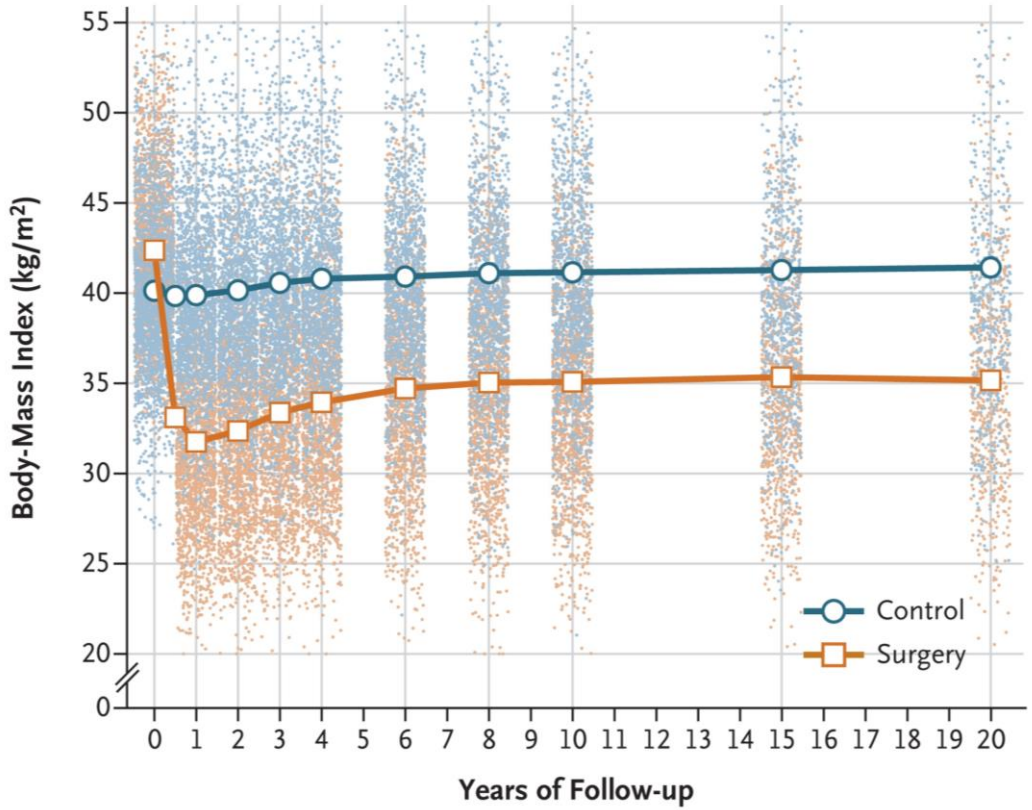
Glyscend	twenty30.health
Intellihealth	Xeno Biosciences
Johnson & Johnson	Zealand

Long-term weight loss after bariatric surgery

Swedish Obesity Subjects Study



N=2010 surgical patients;
2037 matched controls

Operations

Gastric bypass	13%
Banded gastroplasty	**69%**
Gastric banding	18%

Weight Loss

1 year post-op	25%
20 years post-op	18%

Average 28% weight regain

Carlsson LMS *et al*. *NEJM* 2020

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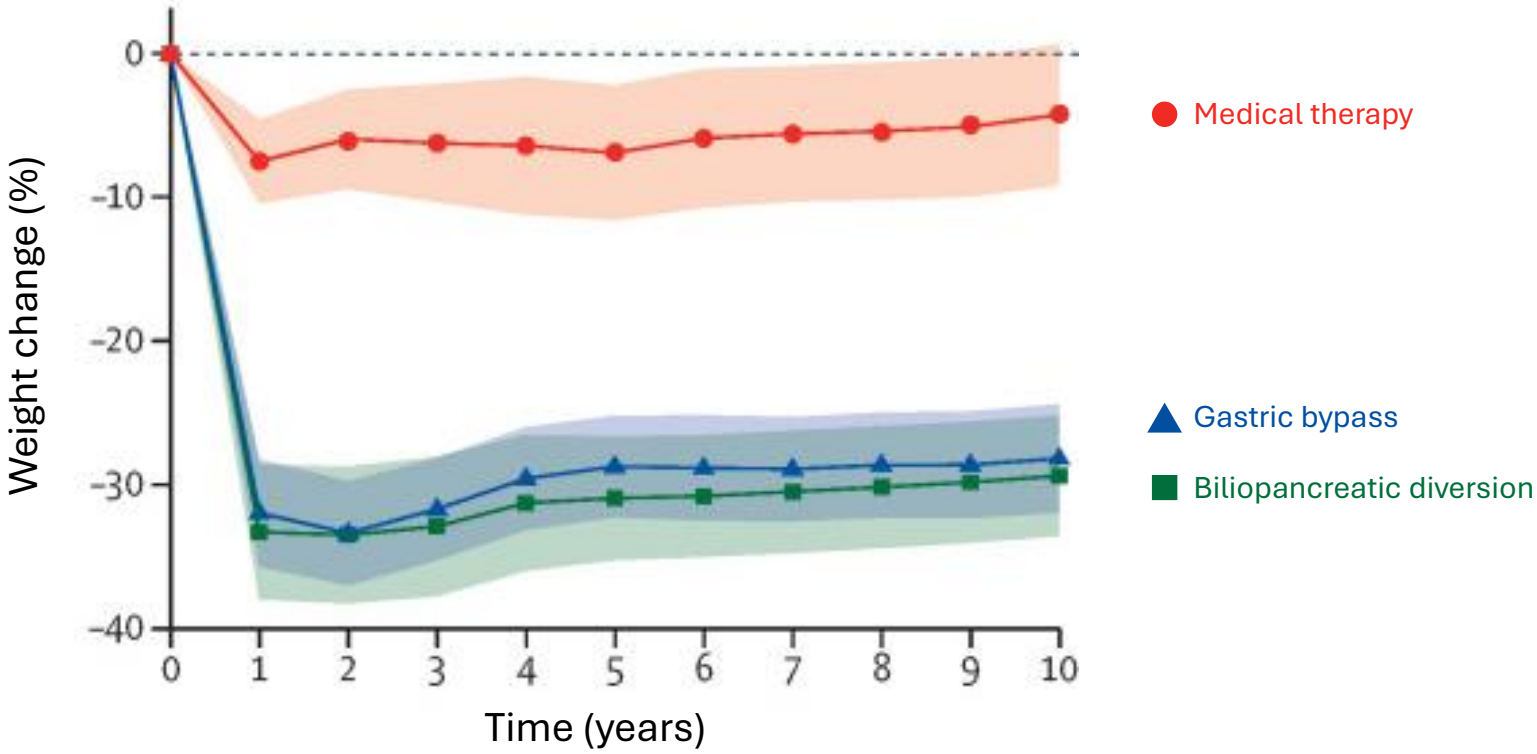
Long-term weight loss after bariatric surgery

Randomized, controlled trial – medical vs. surgical therapy

Subjects with type 2 diabetes



Mingrone G, *et al.*, *Lancet* 2021

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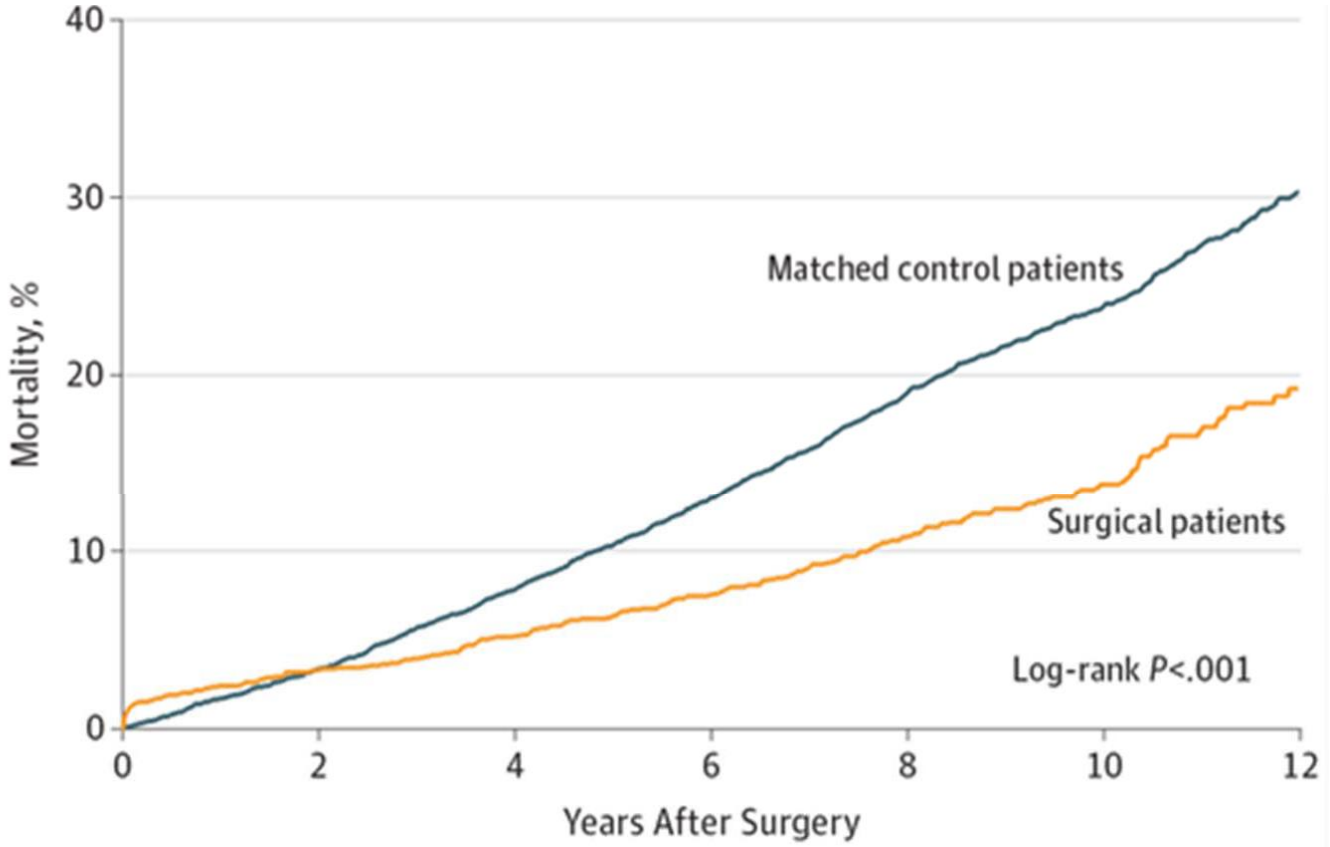
Surgery improves many metabolic and inflammatory complications of obesity

- Type 2 diabetes
- Hypertension
- Hyperlipidemia
- Fatty liver disease
- Chronic kidney disease
- Sleep apnea
- Heart failure with preserved ejection fraction (HFpEF)
- Refractory GERD (primarily gastric bypass)
- Osteoarthritis
- Autoimmune arthritis
- Cognitive dysfunction
- Cancer (at least 18 types)

Bariatric surgery reduces mortality

US Veterans Administration Experience



Arterburn D, *JAMA* 2015

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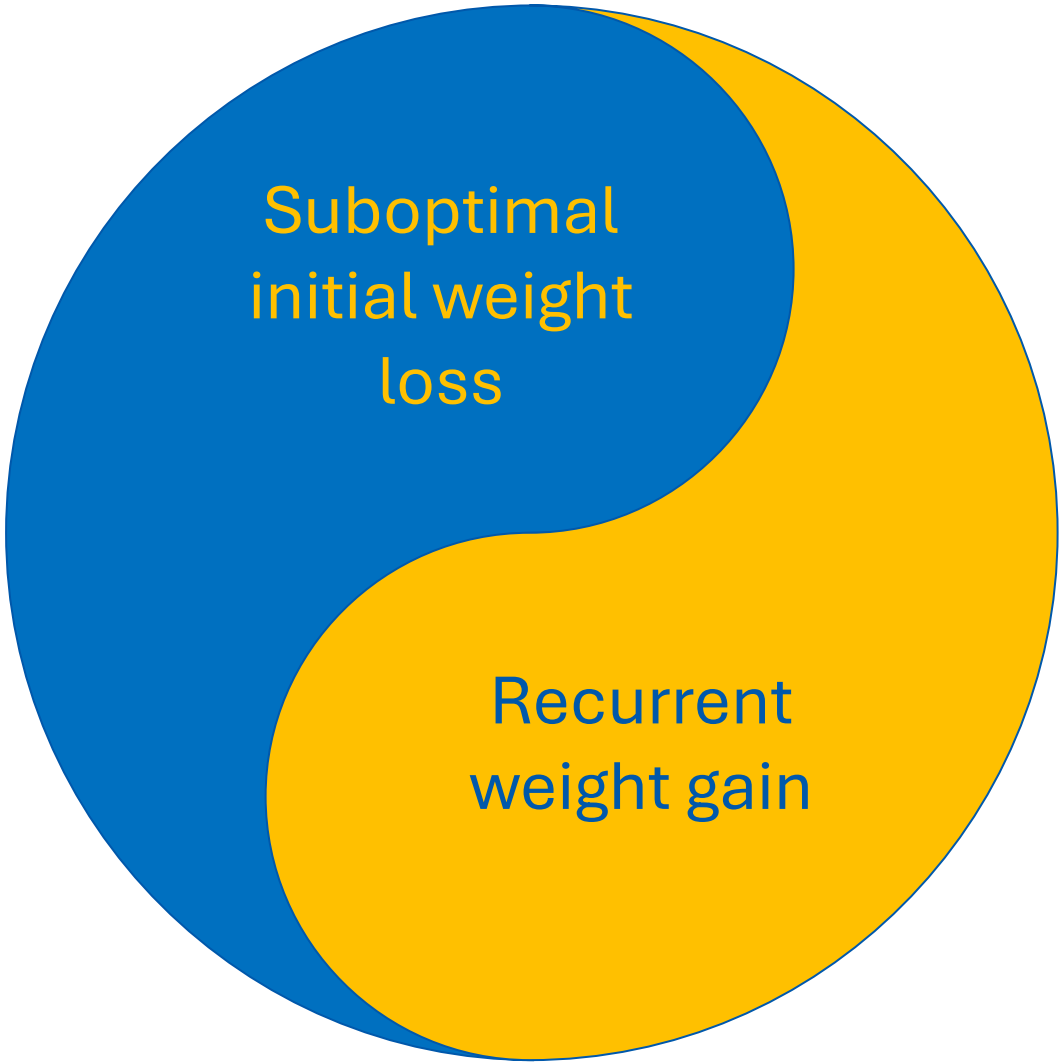
Two major challenges for metabolic/bariatric surgery



Kaplan LM, 2023

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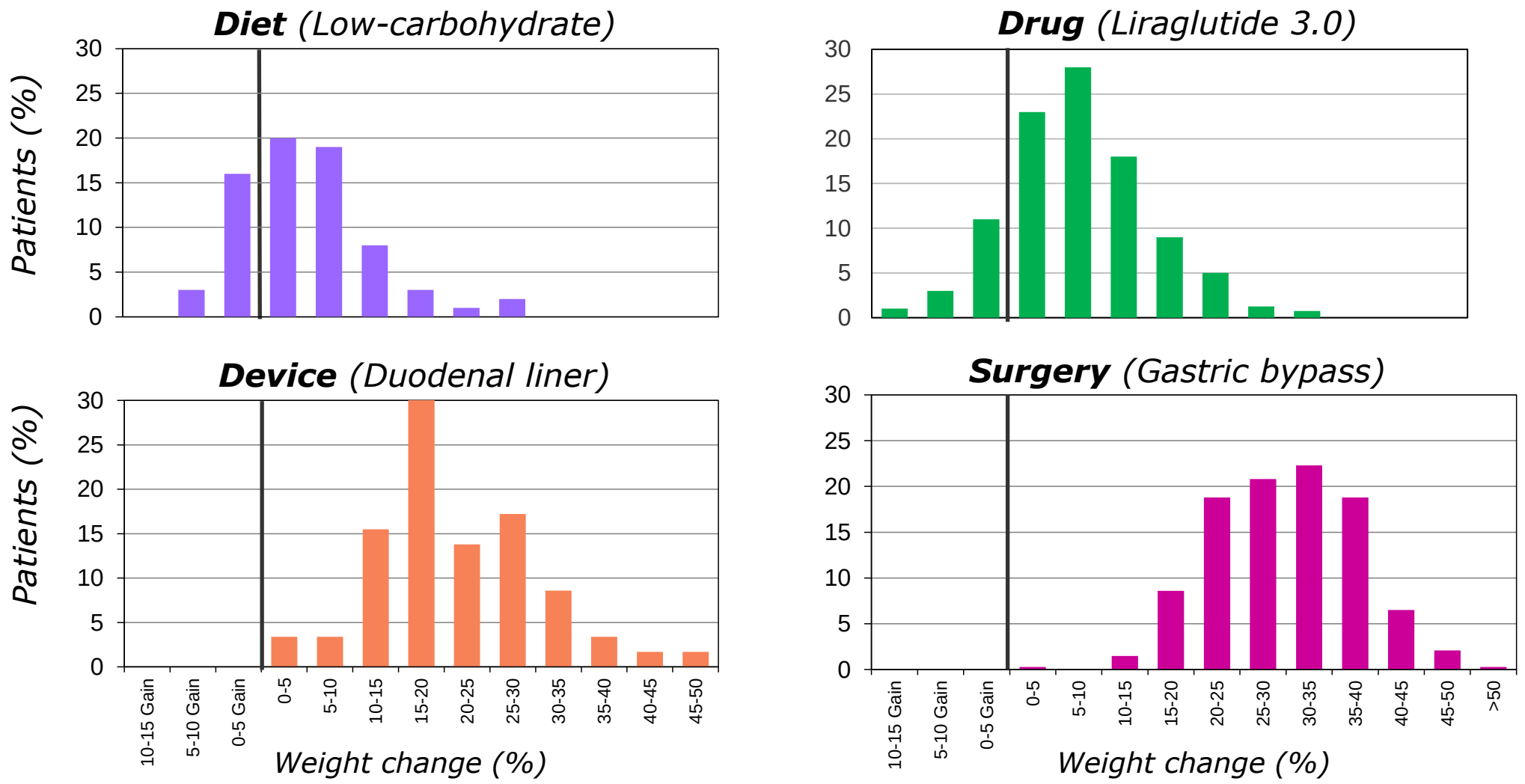
Weight loss varies widely among patients



Kaplan LM, 2016

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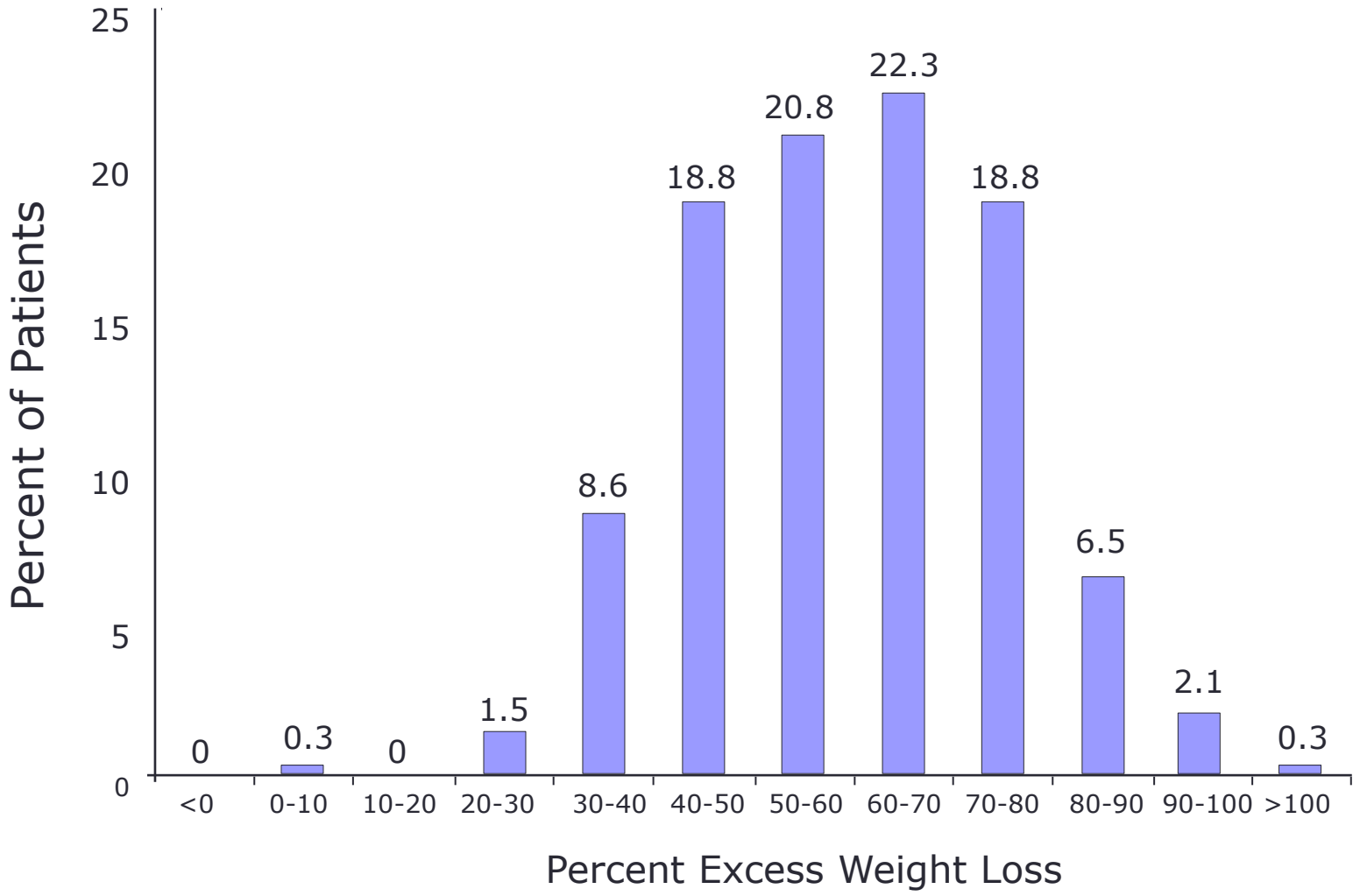
Variable response to surgery is driven by biology



Adapted from Bessler M *et al.*, *Surg Obes Rel Dis* 2008

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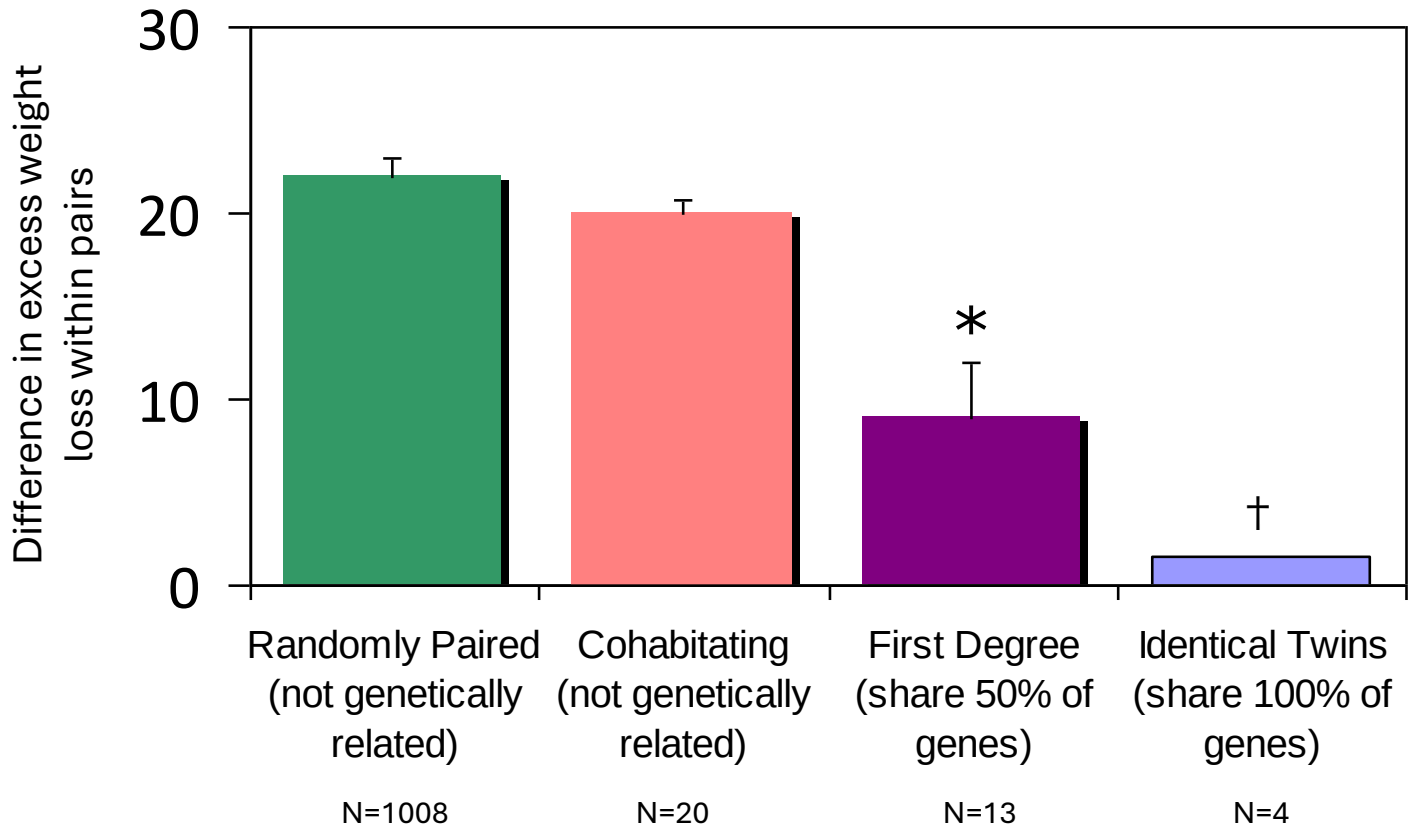
Genetic factors are primary influence over RYGB-induced weight loss



*p<0.05 vs. randomly paired or cohabitating; †separate study

Hatoum IJ *et al., J Clin Endo Metab* 2011

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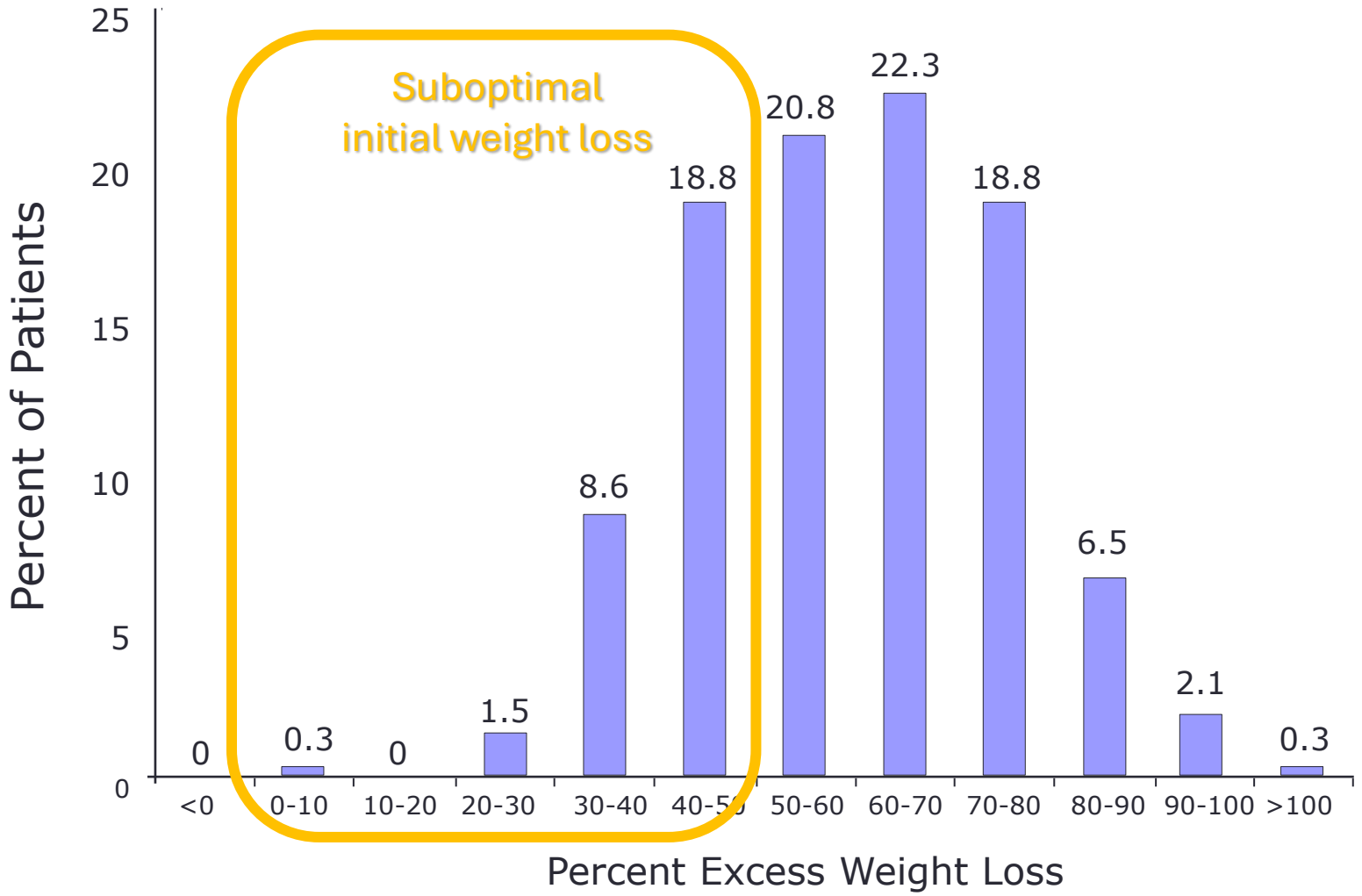
Variable response to surgery is driven by biology



Adapted from Bessler M *et al.*, *Surg Obes Rel Dis* 2008

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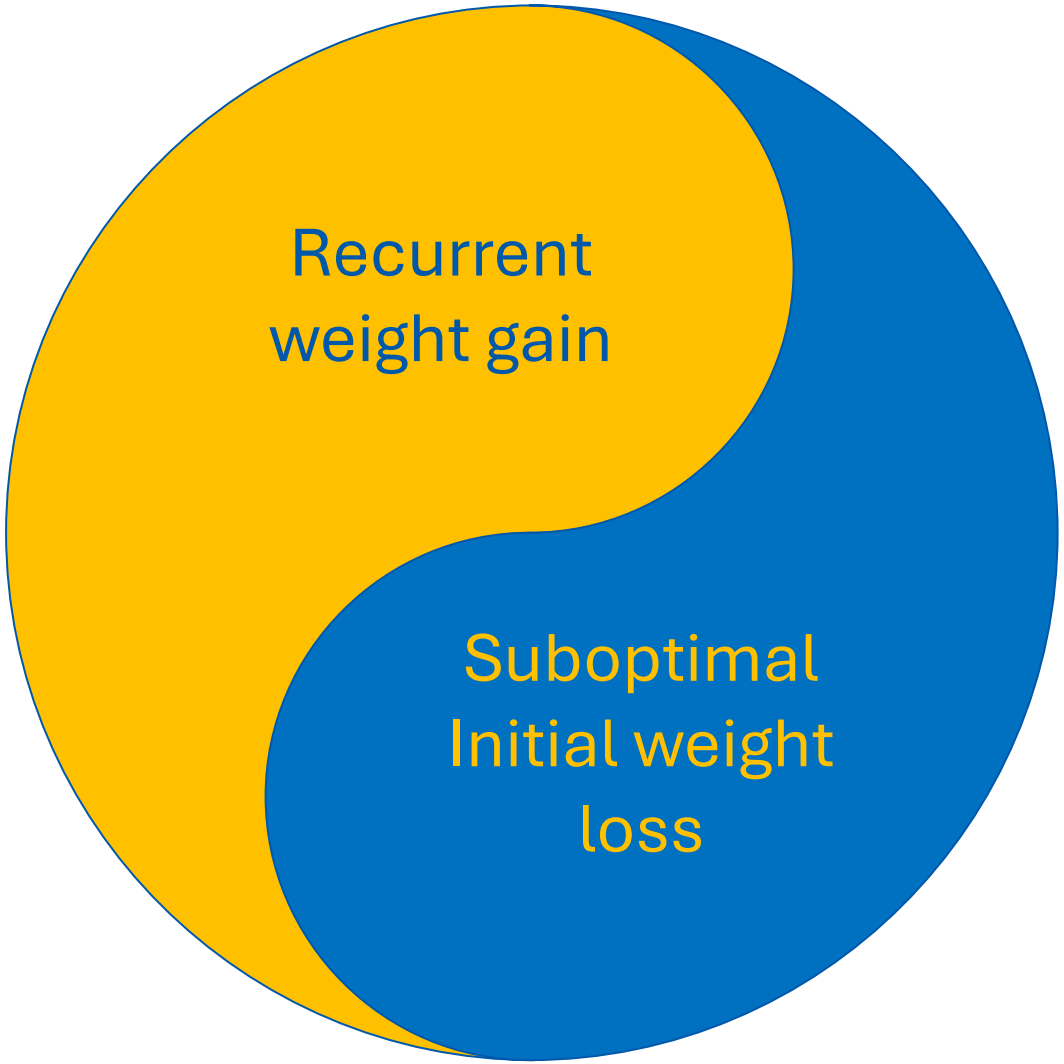
Biological approaches to suboptimal initial weight loss

- Optimize a healthy lifestyle (**without** recommending purposeful calorie reduction)
- **Discontinue or substitute for** weight gain-promoting medications
- **Add a therapy** with a **complementary (additional) mechanism**
  - **Anti-obesity medication**
  - **Surgical conversion** to a procedure with **additional mechanism(s)**
  - **Endoscopic procedure** with a complementary mechanism

Two major challenges for metabolic/bariatric surgery



Kaplan LM, 2023

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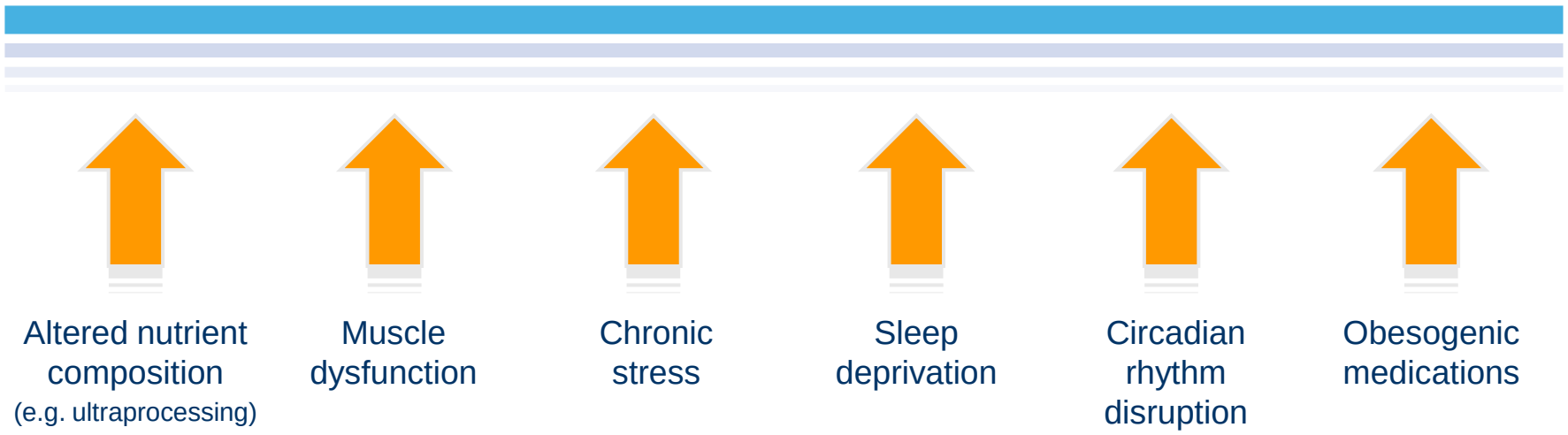
In obesity, the target fat mass is dysregulated (elevated) from environmental influences on biologically susceptible individuals



Kaplan LM, 2006

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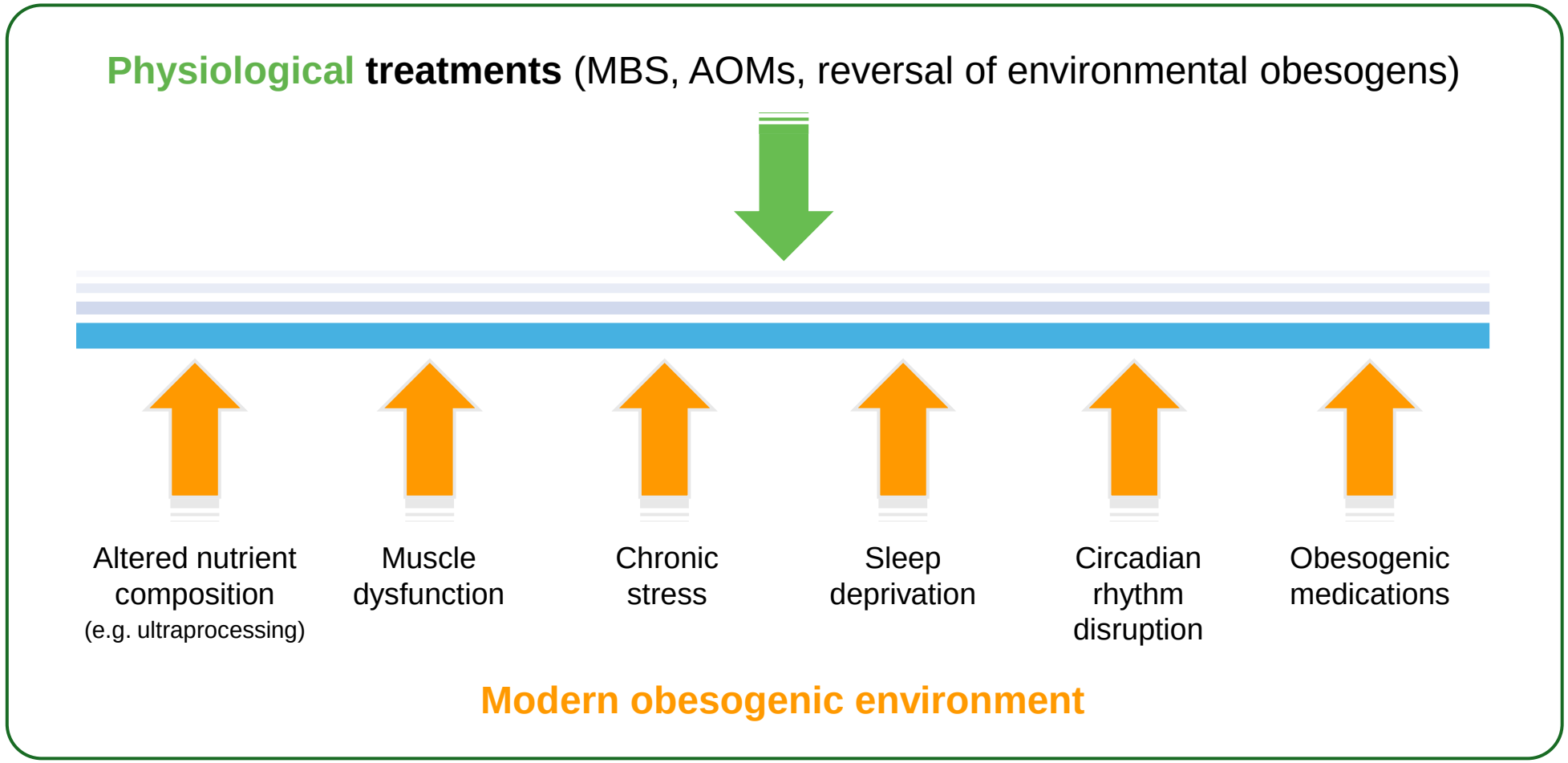
Effective obesity treatments normalize fat mass regulation leading to decreased weight without activating metabolic adaptation



Kaplan LM, 2006

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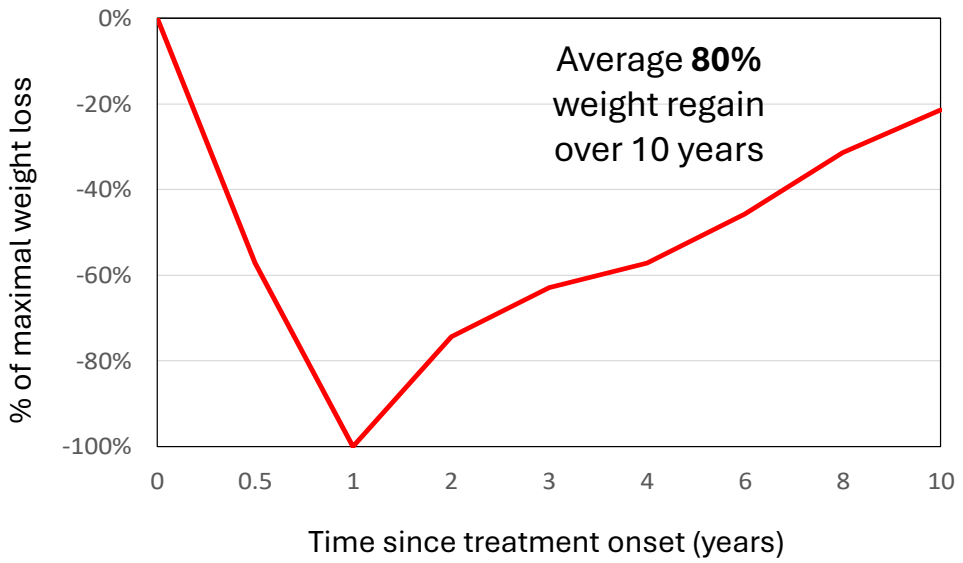
Weight regain with different anti-obesity therapies

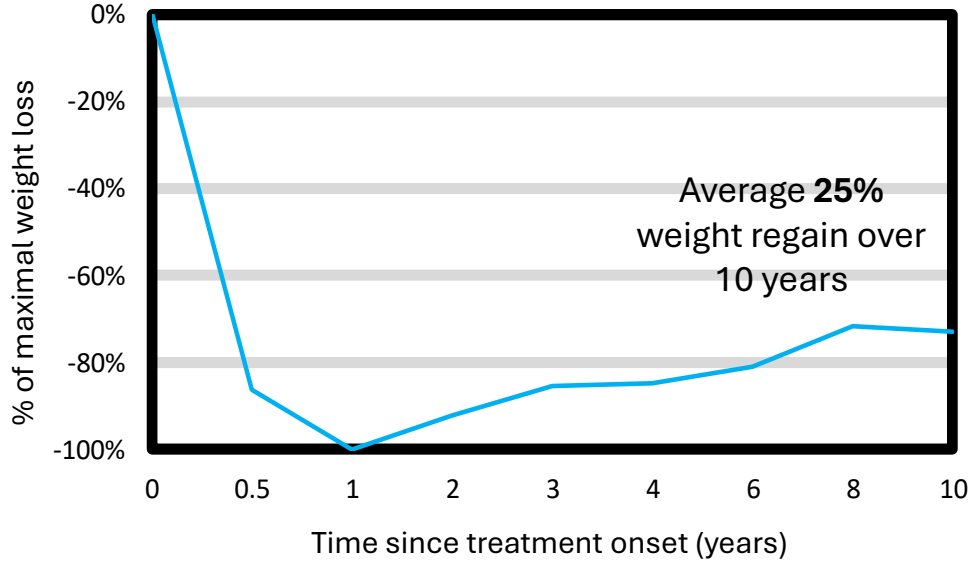
Calorie reduction-based lifestyle therapy

Average maximum weight loss **7-8%**



Metabolic/bariatric surgery

Average maximum weight loss **28-35%**



Adapted from Ryan DH et al., 2019; Kaplan LM, 2019

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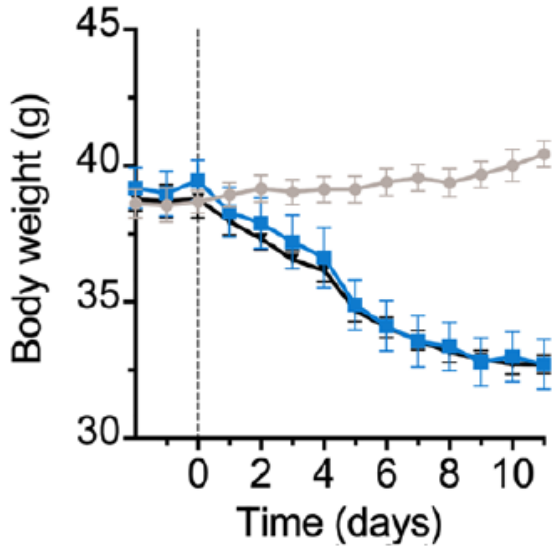
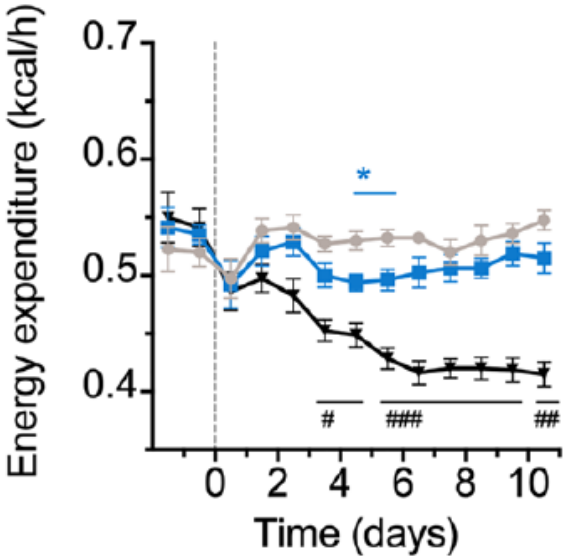
Physiological weight loss is associated with blunting of metabolic adaptation

- Vehicle (placebo)
- Semaglutide, 9.7 nmol/kg/day
- Calorie restricted, weight-matched to semaglutide group

Body weight



Energy expenditure



Adapted from Gavery S *et al*. *JCI Insight* 2020; 5:e133429

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RYGB effects are opposite to those of restrictive dieting

	Calorie restriction (non-physiological)	Metabolic surgery (physiological)
Energy expenditure	↓	↑
Appetite	↑	↓
Hunger	↑	↓
Satiety	↓	↑
Reward-based eating	↑	↓
Stress response	↑	↓
Gut peptides		
Ghrelin	↑	↓
GLP-1, PYY, CCK, amylin	↓	↑

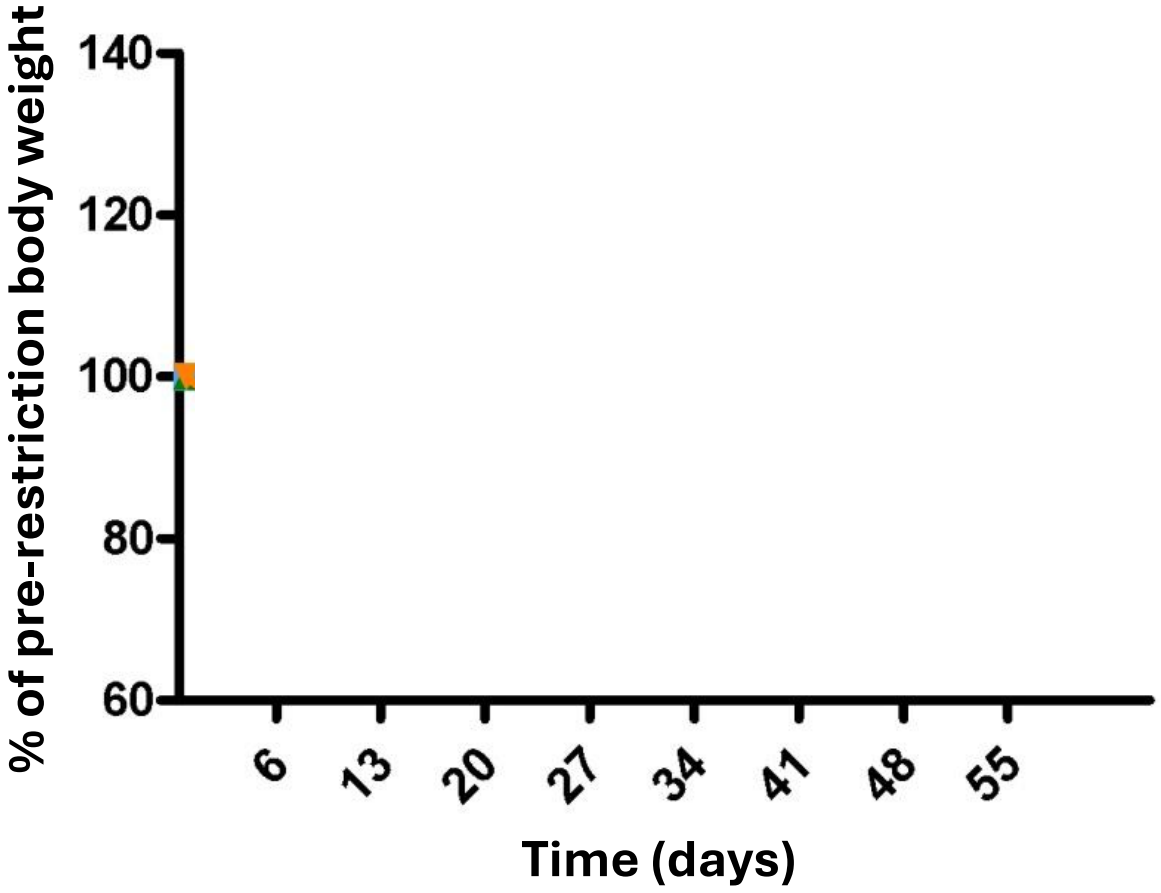
Kaplan LM, 2016

Potential causes of recurrent weight gain

- **Promotion of non-physiological weight loss**
  - Restrictive dieting

Kaplan LM, 2024

Bariatric surgery: defense of a decreased body fat mass



Step 1:

- **Obese**, sham-operated controls (350 gm)
- **Thin**, chow-fed, unoperated (225 gm)
- **Thin**, **underfed** to match VSG weight (275 gm)
- **Thin**, underwent **VSG** (275 gm)

Step 2:

Calorie restrict to lose 30% body weight

Step 3:

Let them eat what they want

Stefater MA et al. *Gastroenterology* 2010

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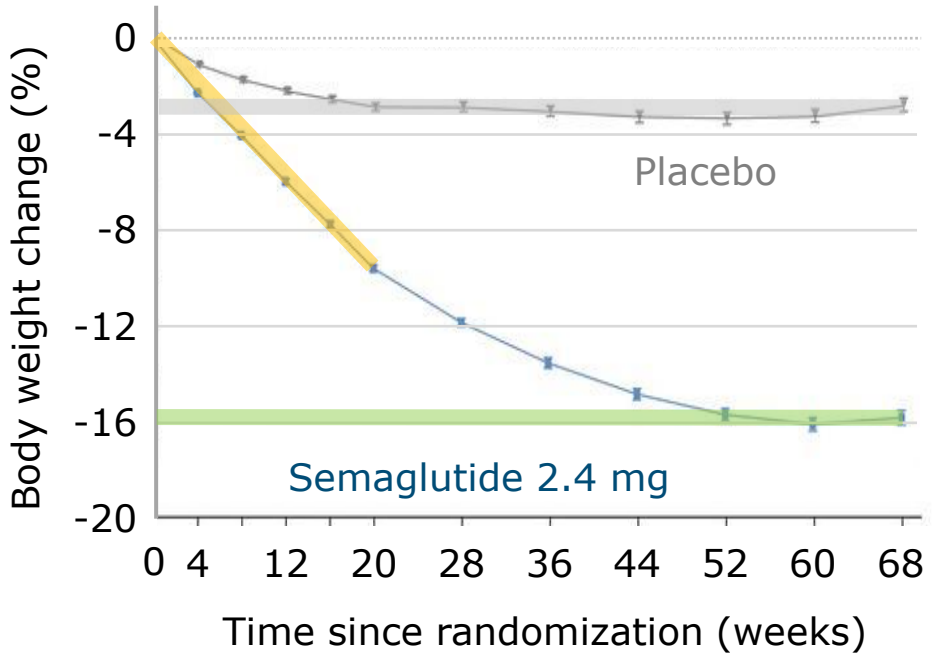
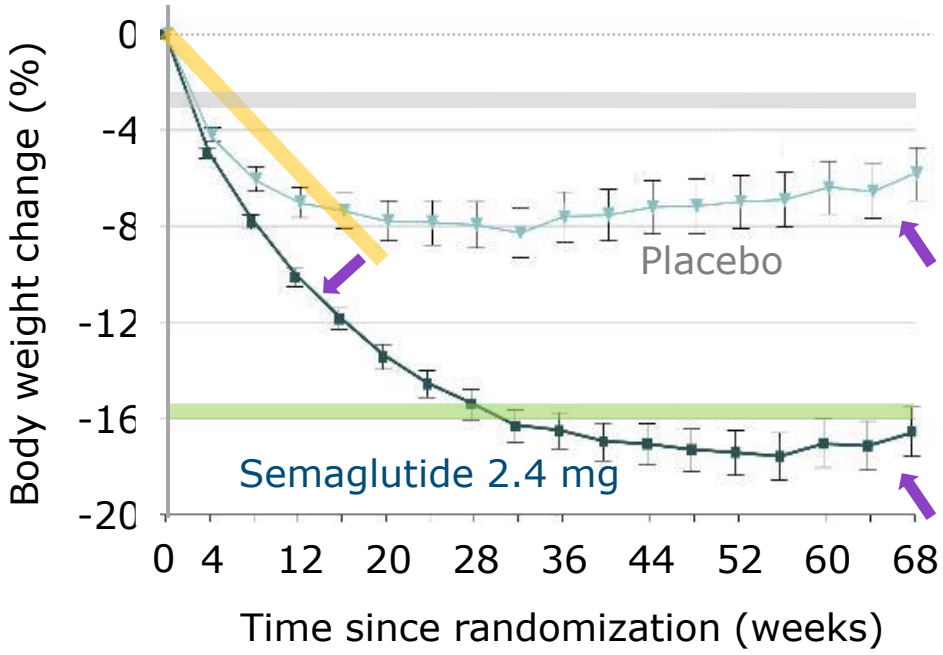
Effect of calorie restriction beyond physiological weight loss

STEP 1 Trial
Subjects without Diabetes
Drug Alone



STEP 3 Trial
Subjects without Diabetes
Drug Plus Calorie Reduction



Adapted from Wilding JPH *et al.*, *NEJM* 2021 and Wadden TA *et al.*, *JAMA* 2021

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Potential causes of recurrent weight gain

- Promotion of non-physiological weight loss
  - Restrictive dieting
- **Progression of disease**

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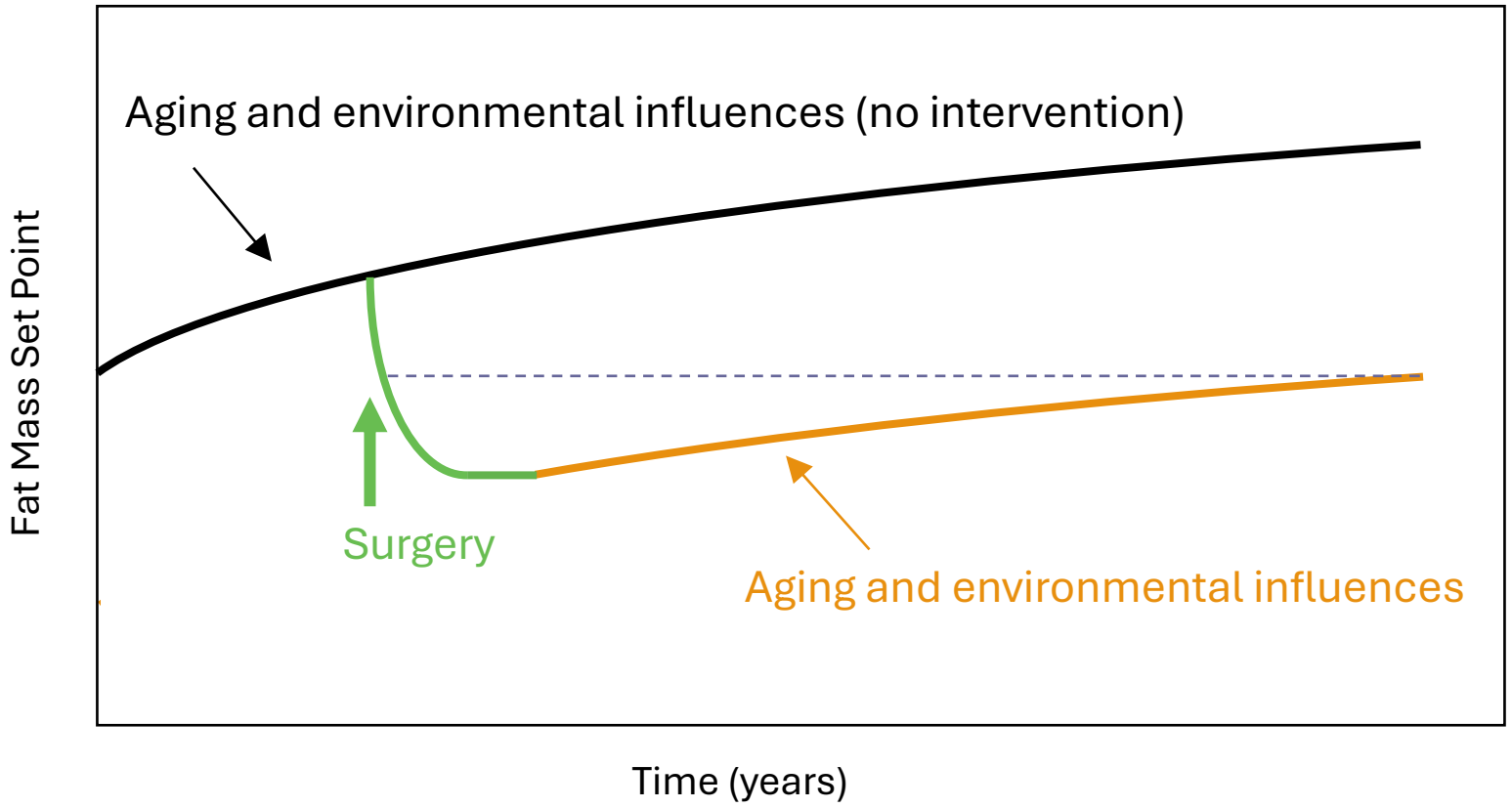
Most recurrent weight gain is NOT from surgical or patient failure

Long-term Progression of Obesity



Kaplan LM, 2016

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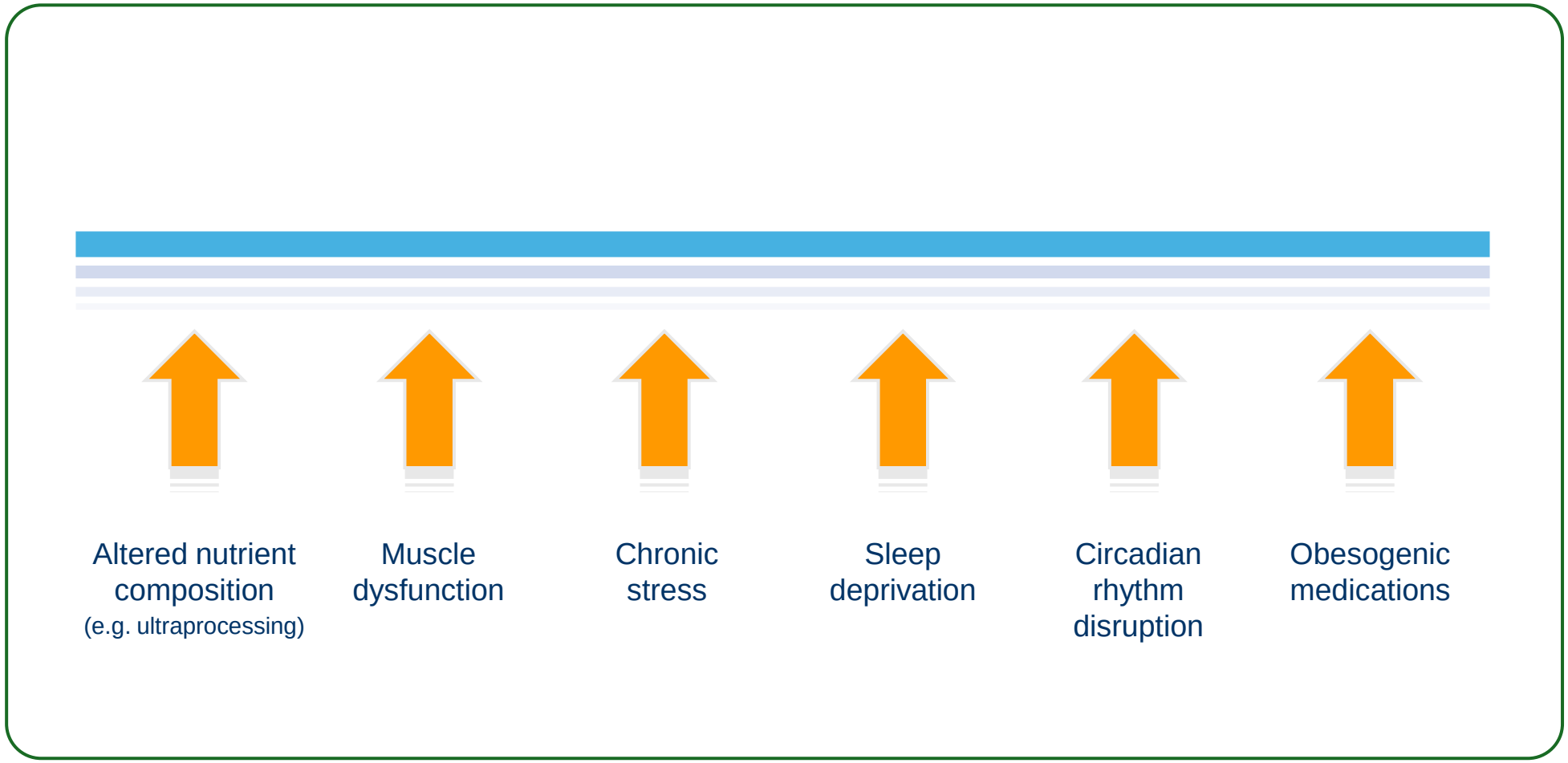
Potential causes of recurrent weight gain

- Promotion of non-physiological weight loss
  - Restrictive dieting
- Progression of disease
- **Environmental factors**
  - Continued exposure to obesogenic environment
  - Environmental toxins
  - Chronic stress (e.g., emotional, sleep deprivation, PTSD)
  - Obesogenic diet
  - Obesogenic medications

Kaplan LM, 2024

Environmental influences raise the defended fat mass



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Potential causes of recurrent weight gain

- **Promotion of non-physiological weight loss**
  - Restrictive dieting
- **Progression of disease**
- **Environmental factors**
  - **Continued exposure to obesogenic environment**
  - Environmental toxins
  - Chronic stress (e.g., emotional, sleep deprivation, PTSD)
  - Obesogenic diet
  - Obesogenic medications
- **Biological factors**
  - Genetic predisposition?
    Not as clear as for suboptimal initial weight loss

Kaplan LM, 2020

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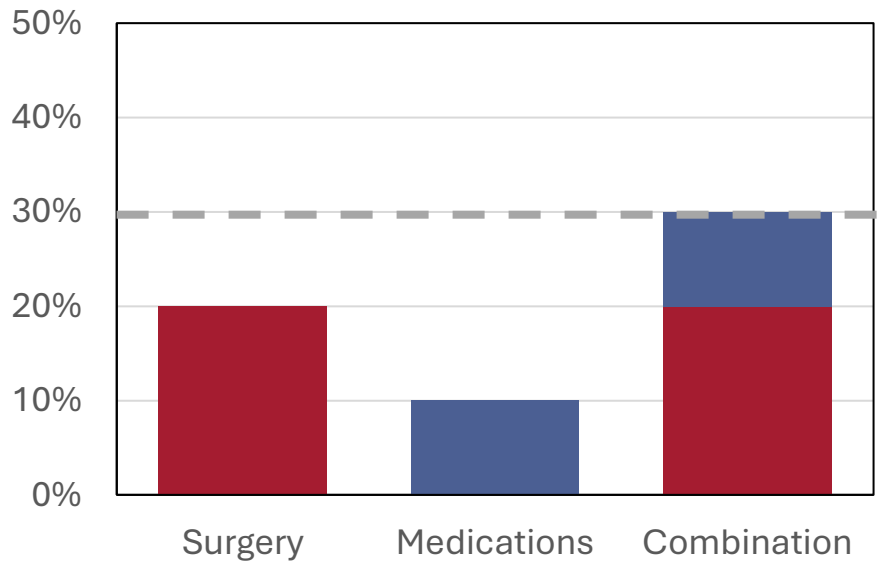
Medical therapy for suboptimal weight loss or recurrent weight regain

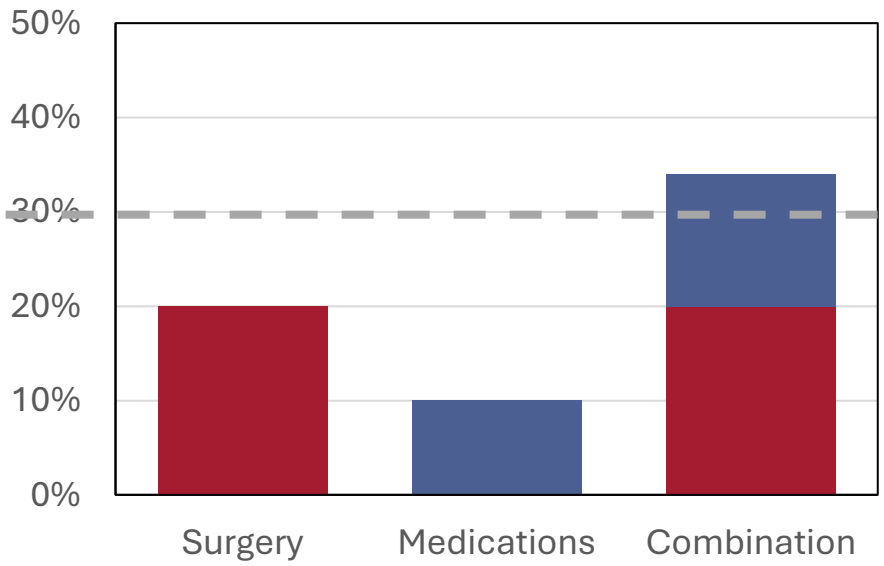
If surgery worked mechanically (restriction or malabsorption) ...

... combination with medications would be additive *at most*



Since surgery works physiologically ...

... complementary mechanisms allow for *synergy*



Kaplan LM, 2020

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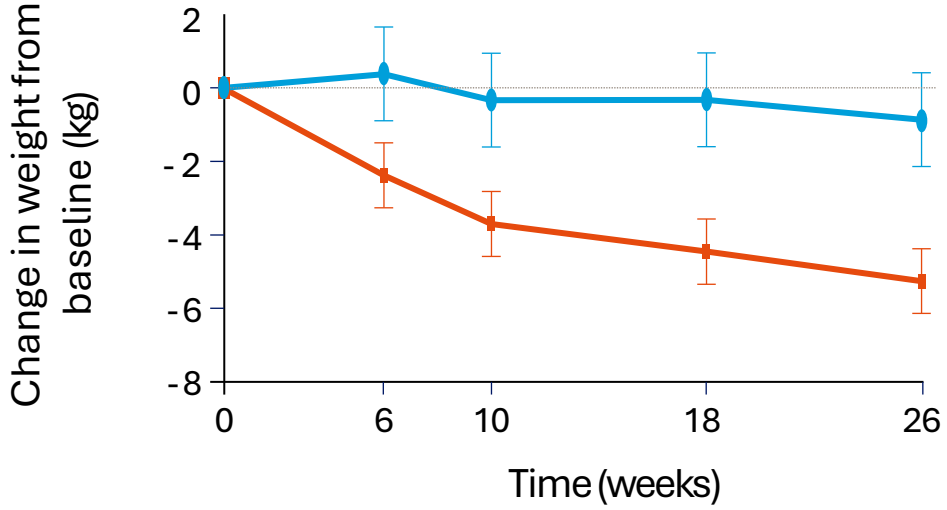
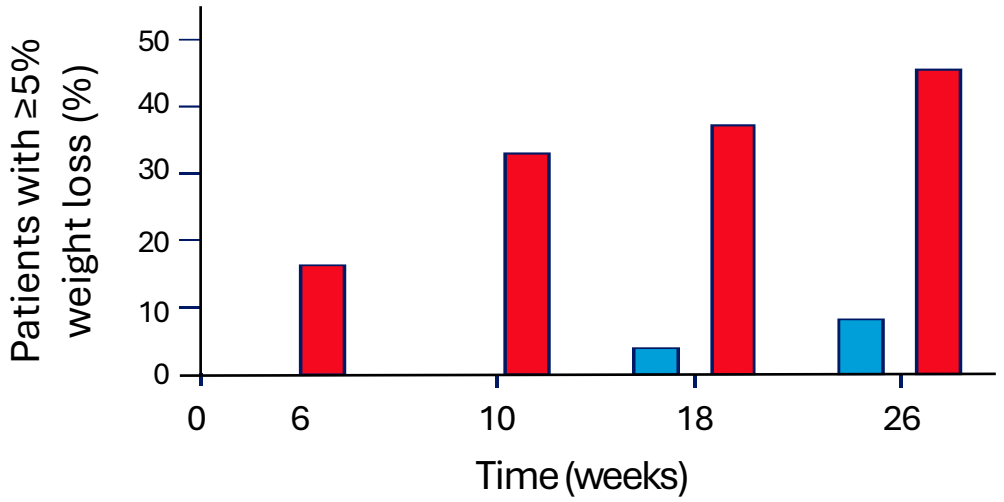
Postoperative pharmacotherapy augments surgical weight loss

GRAVITAS Study

Liraglutide 1.8 mg vs. Placebo after Gastric Bypass

Patients with Type 2 Diabetes





Placebo

Liraglutide

Miras AD *et al.*, *Lancet Diabetes Endocrinol* 2019

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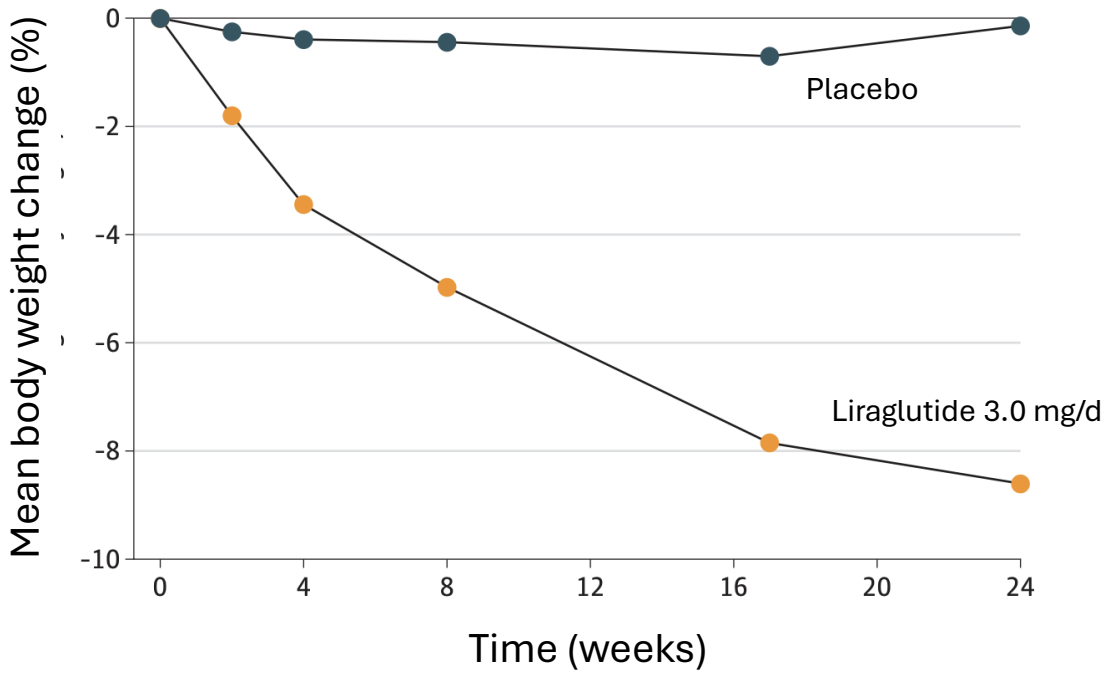
Liraglutide 3.0 mg augments weight loss after metabolic surgery

BARI-OPTIMISE Trial

Subjects with suboptimal (<20%) initial weight loss after metabolic surgery

Liraglutide 3.0 mg/day vs. placebo

(N=70)



Mok J *et al.*, *JAMA Surg* 2023

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Potential means of addressing recurrent weight gain

Cause of weight gain	Potential solution
Promotion of non-physiological weight loss (purposeful calorie restriction beyond what surgery naturally provides)	**Avoid recommending purposeful calorie reduction – let the surgery do its job!**
Progression of disease	Add an **additional therapeutic mechanism** • Start or add an **anti-obesity medication** • **Convert to a different MBS** operation • Add a **complementary endoscopic** treatment
Environmental factors	**Address the environmental factors** or add an **additional therapeutic mechanism**
Surgical complication	Correct the **surgical anatomy**
Intrinsic biological or genetic factors	Add an **additional therapeutic mechanism**

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Strategies for using medical-surgical combinations - 1

Pre- and peri-operative medical therapy

- **Stepped care** (medical **followed by** surgical care)
  - Particularly appropriate for **lifestyle-based** medical treatment
  - Previous anti-obesity medications generally **stopped** at the time of surgery
- **Preoperative weight loss** – primary benefit is liver fat mobilization
  - Short-term calorie reduction or meal replacement
  - Anti-obesity medications
- **Simultaneous initiation of combination therapy**
  - Creates problem of **not knowing which drug will work best** in a particular patient
  - Because of synergy between surgery and medications, **preoperative medication response may not predict postoperative medication response**

Kaplan LM, 2023

Strategies for using medical-surgical combinations - 2

Postoperative medical therapy

- **Enhancement** of **suboptimal post-operative weight loss**
- **Rescue** of **recurrent post-operative weight regain**
- **Allows personalized approach** to account for patient-to-patient variability in response to medications
- **Amenable to standard sequential "trial-and-error" approach** to using anti-obesity medications

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Practical use of combination medical-surgical therapy

- Pharmacological treatment **after completion of surgical weight loss** is the most promising strategy
- Pharmacological treatment **works best for suboptimal initial weight loss**
  - There is also **benefit for recurrent weight gain**, but this use is less well studied
- Pursue a **step-wise treatment strategy** after surgery as you would before surgery
- Add new therapies after stable response to previous therapies (i.e., after reaching plateau)
- There are currently **no good predictors** for choosing the "right" medication for an individual patient
- **Drugs can be effective in combination with surgery that are ineffective alone**
- **Anticipate life-long use** of **successful** approaches

Kaplan LM, 2023

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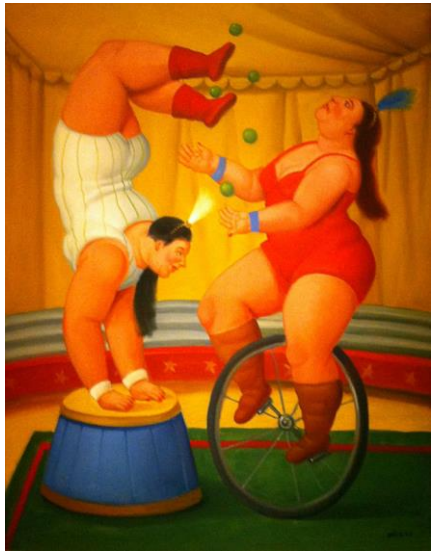

Fernando Botero, 1932-2023

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