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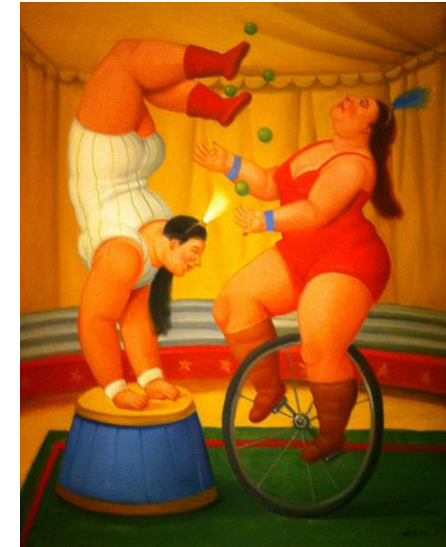
The Pathophysiology of Recurrent Weight Gain After MBS

Lee M. Kaplan, MD, PhD

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Fernando Botero, 1932-2023

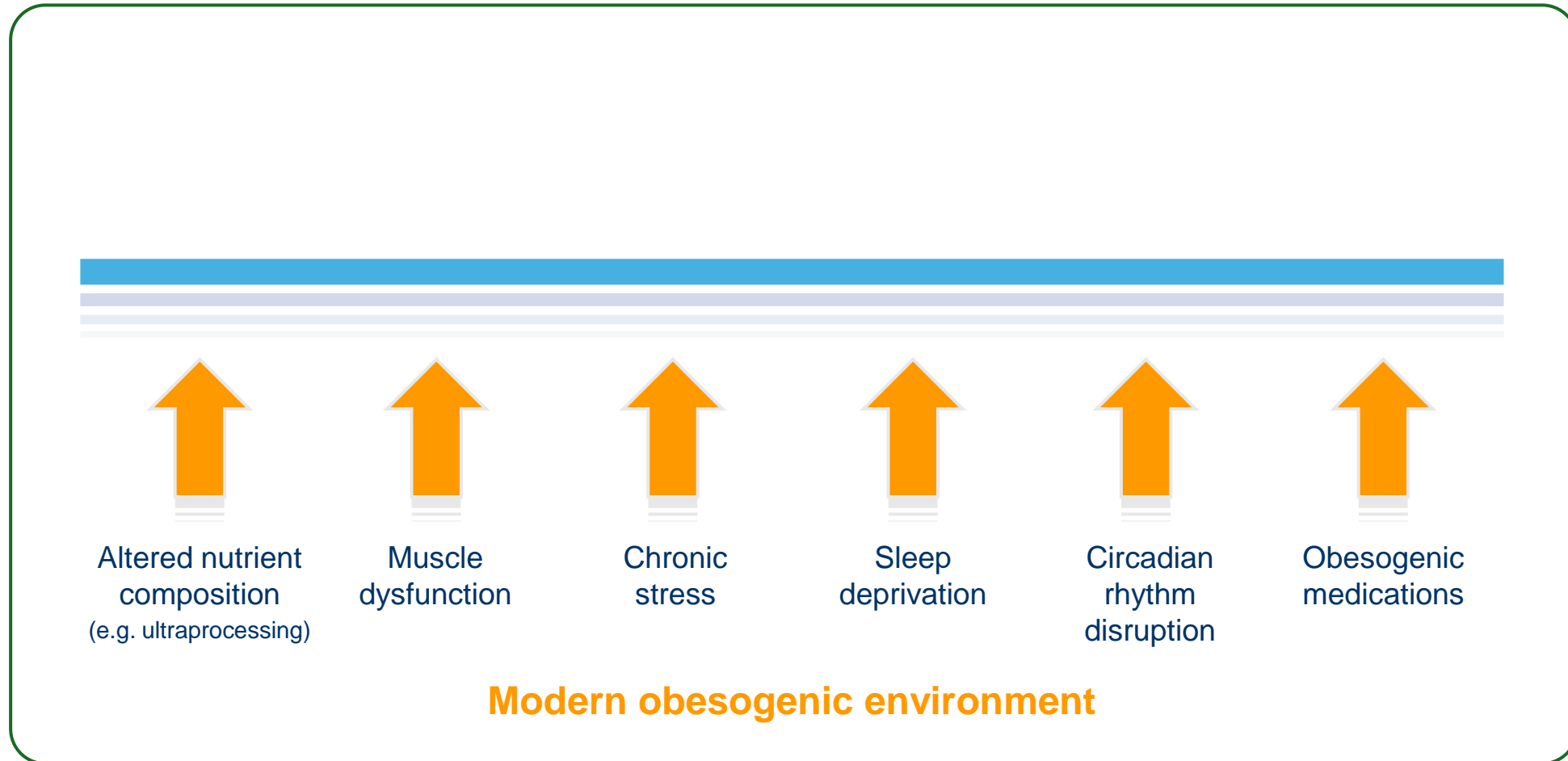
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Disclosures

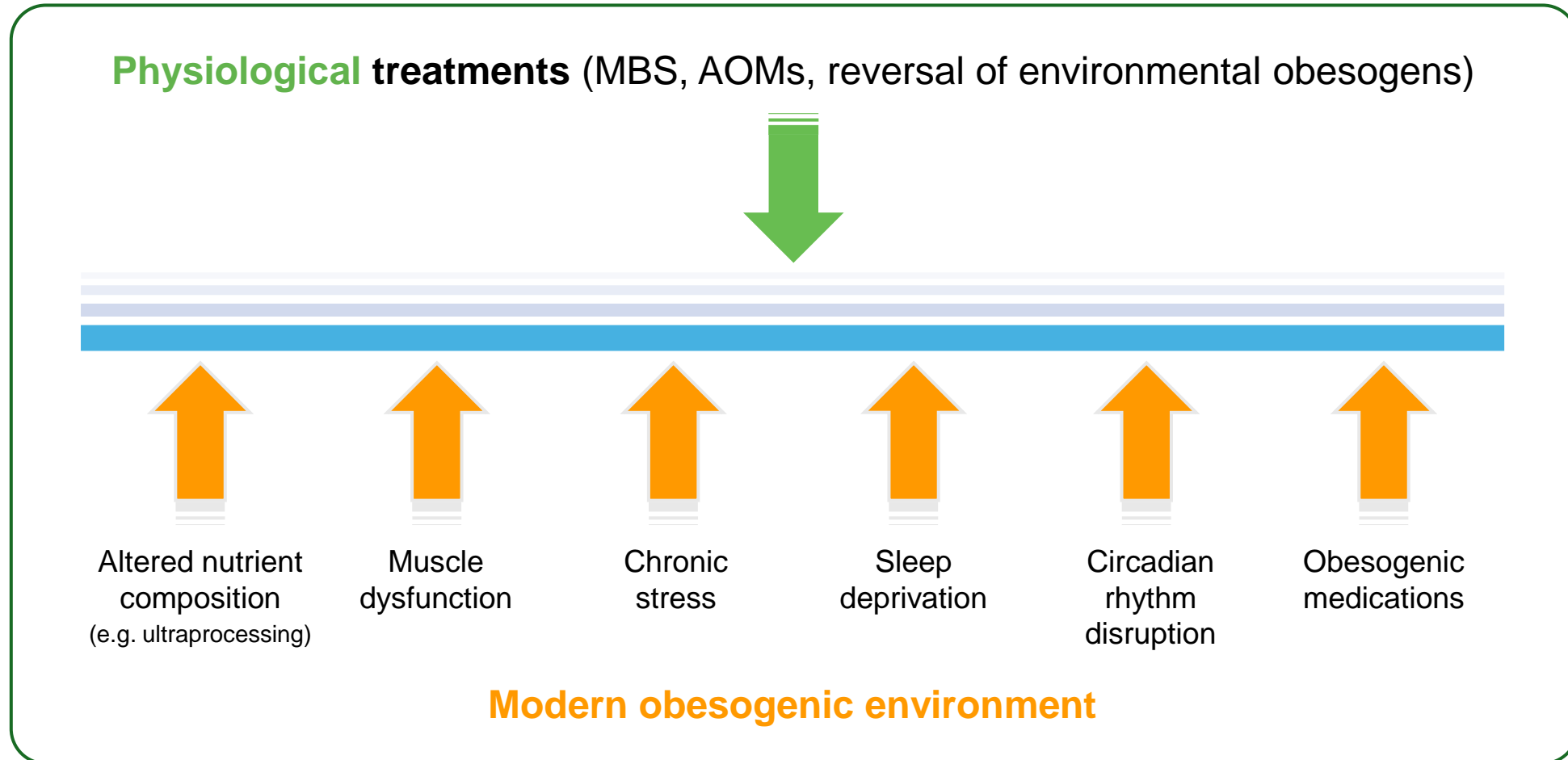
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In obesity, the target fat mass is dysregulated (elevated) from environmental influences on biologically susceptible individuals



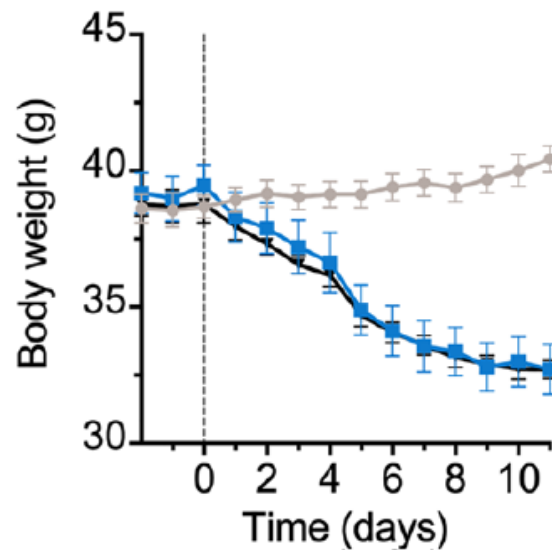
Effective obesity treatments normalize fat mass regulation leading to decreased weight without activating metabolic adaptation



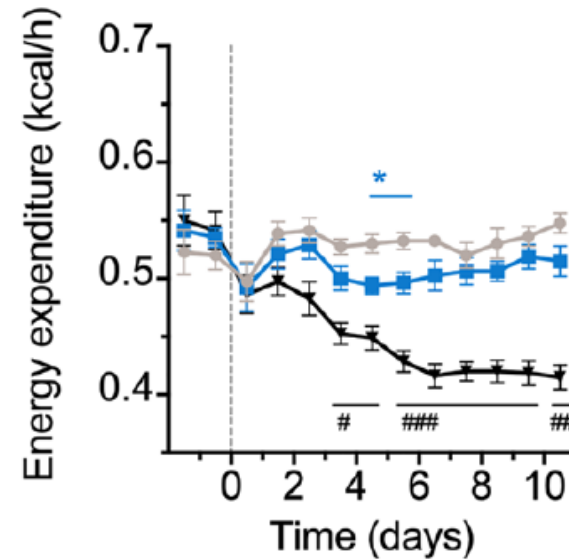
Physiological weight loss is associated with blunting of metabolic adaptation

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

Body weight



Energy expenditure



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	↓	↑

Potential causes of recurrent weight gain

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

Bariatric surgery: defense of a decreased body fat mass

Step 1:

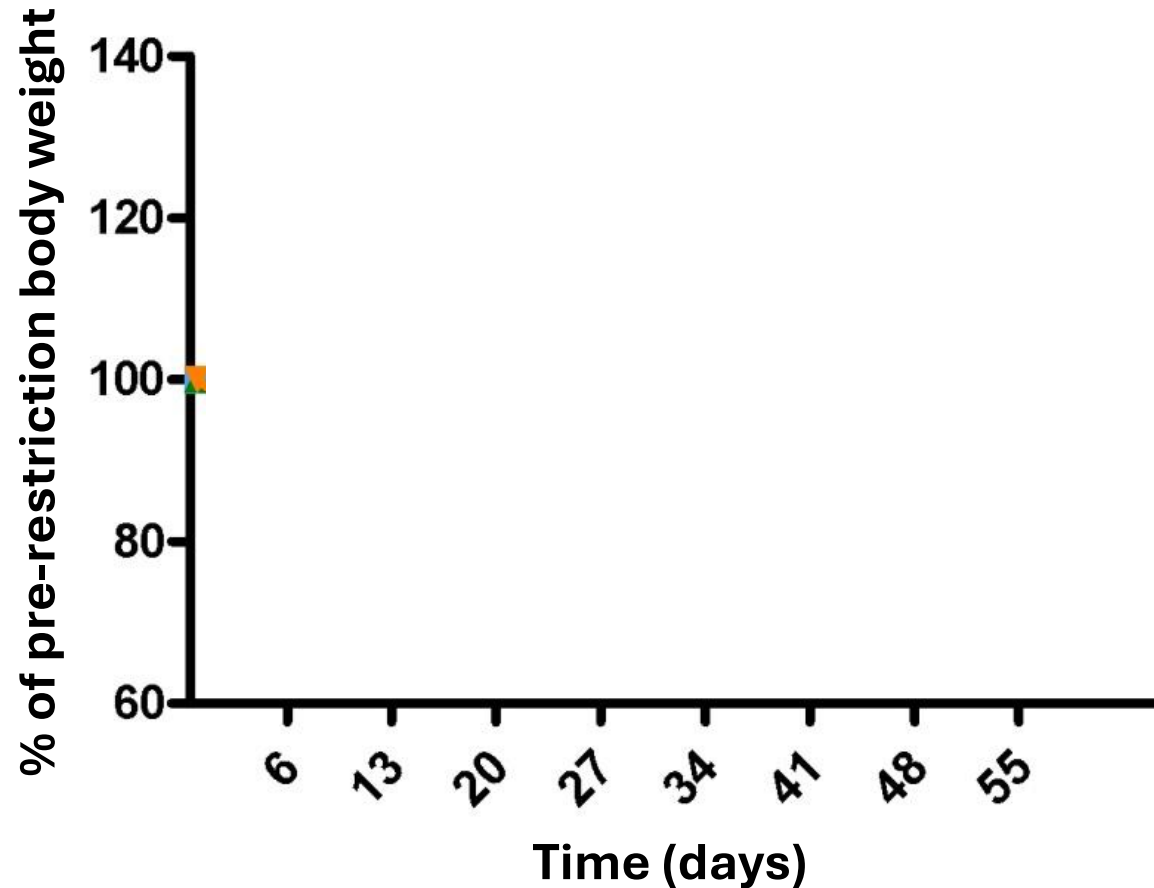
- **Obese**, sham-operated controls (350 gm)
- **Thin**, chow-fed, unoperated (225 gm)
- ▲ **Thin, underfed** to match VSG weight (275 gm)
- ▼ **Thin**, underwent **VSG** (275 gm)

Step 2:

Calorie restrict to lose 30% body weight

Step 3:

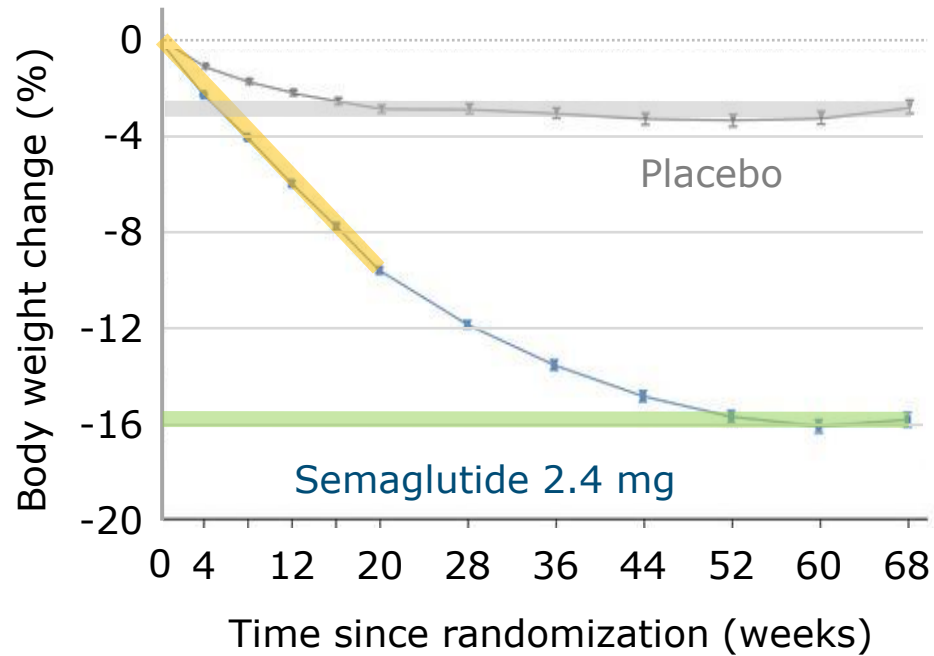
Let them eat what they want



Effect of **calorie restriction** beyond **physiological** weight loss

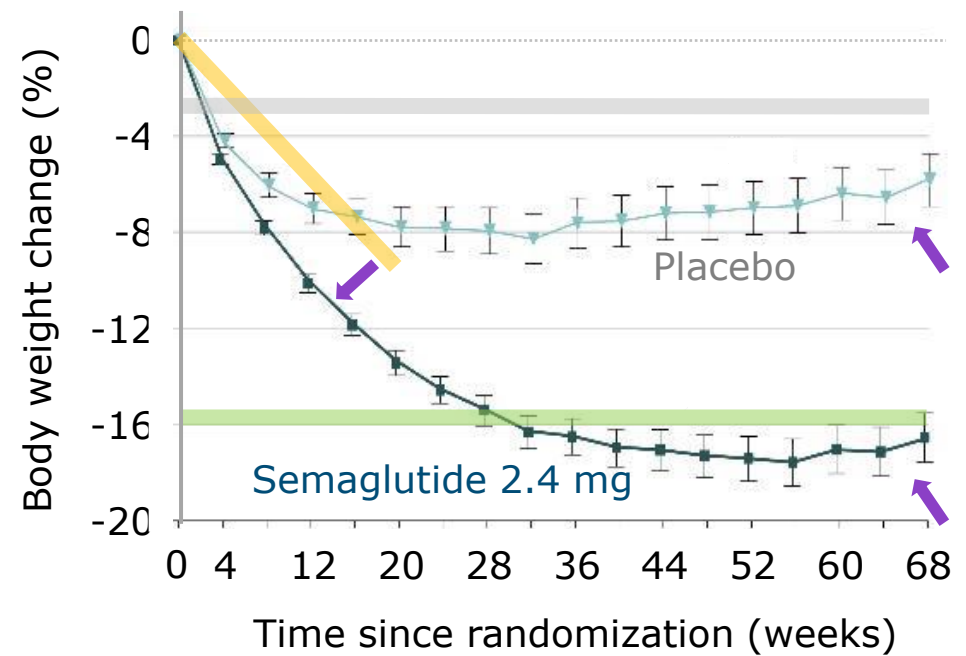
STEP 1 Trial

Subjects without Diabetes
Drug Alone



STEP 3 Trial

Subjects without Diabetes
Drug Plus Calorie Reduction

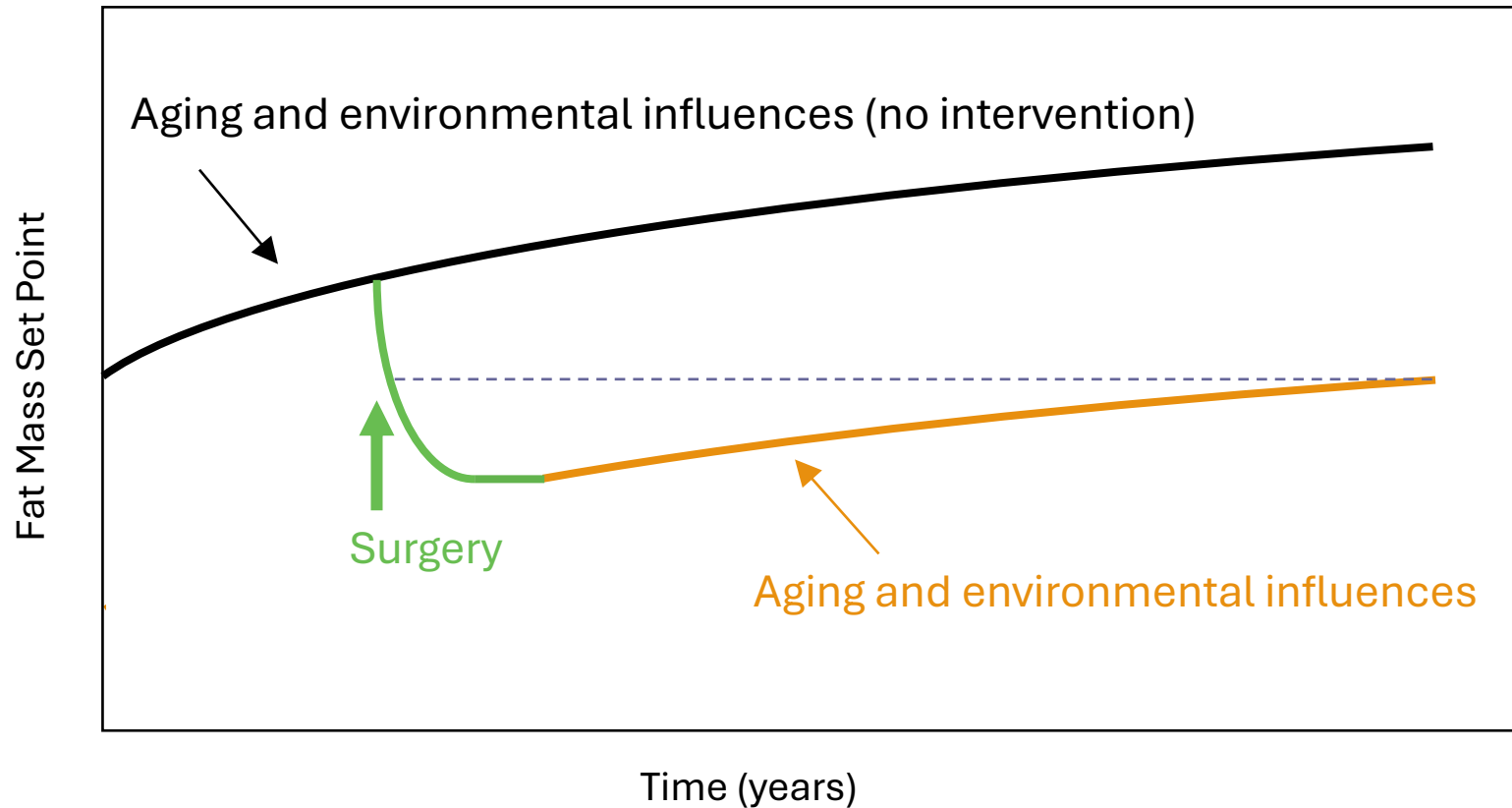


Potential causes of recurrent weight gain

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

Most recurrent weight gain is NOT from surgical or patient failure

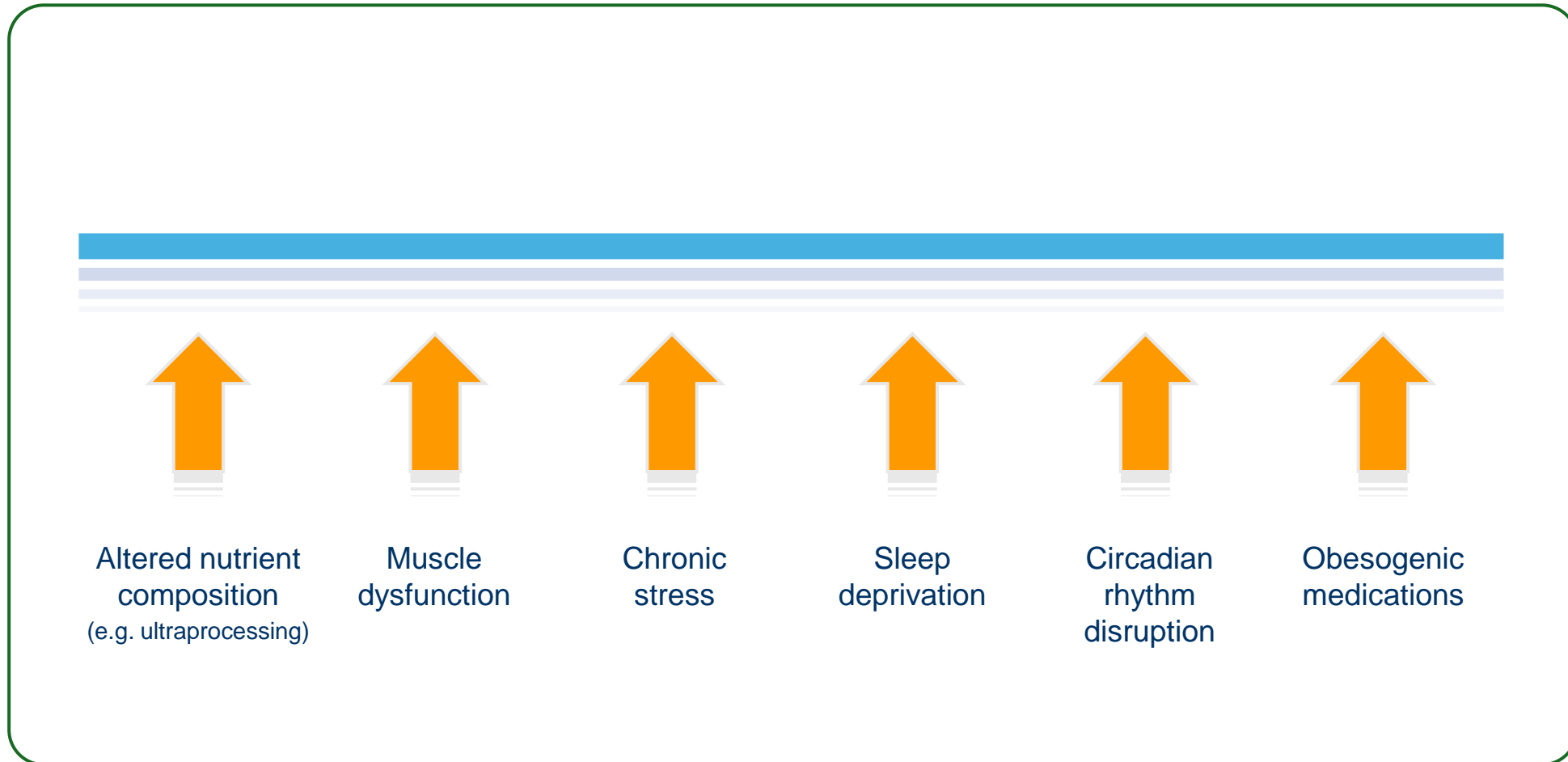
Long-term Progression of Obesity



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

Environmental influences raise the defended fat mass



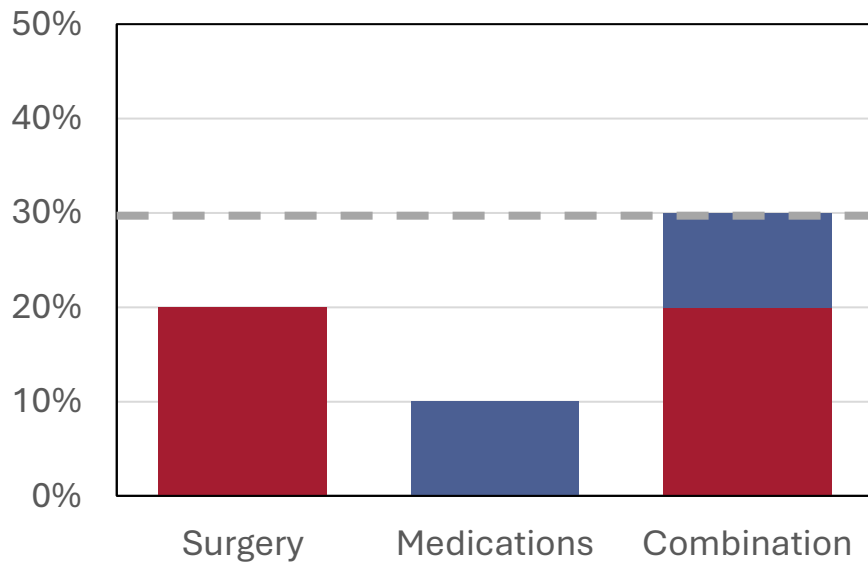
Potential causes of recurrent weight gain

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 - Continued exposure to obesogenic environment
 - Environmental toxins
 - Chronic stress (e.g., emotional, sleep deprivation, PTSD)
 - Obesogenic diet
 - Obesogenic medications
- **Biological factors**
 - Genetic predisposition?

Medical therapy for suboptimal weight loss or recurrent weight regain

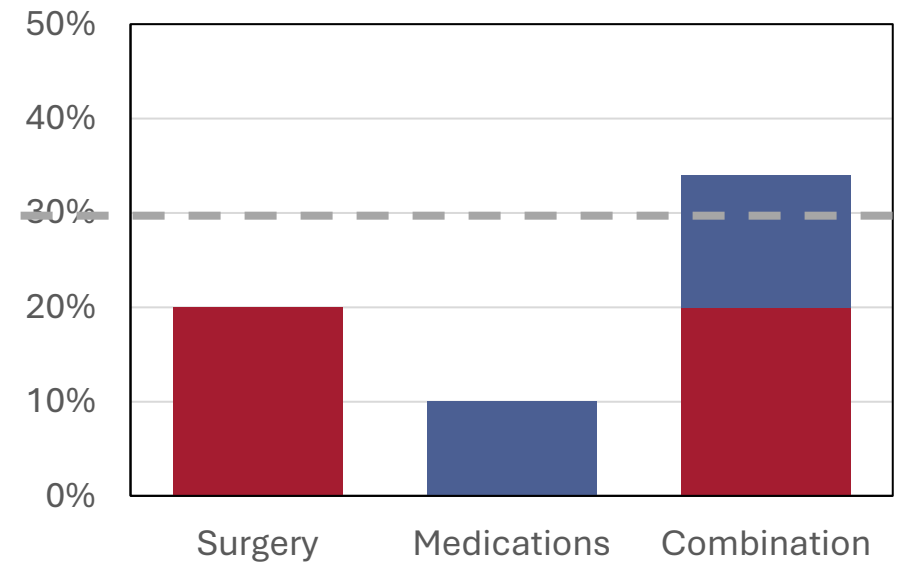
If surgery worked mechanically (restriction or malabsorption) ...

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



Since surgery works physiologically ...

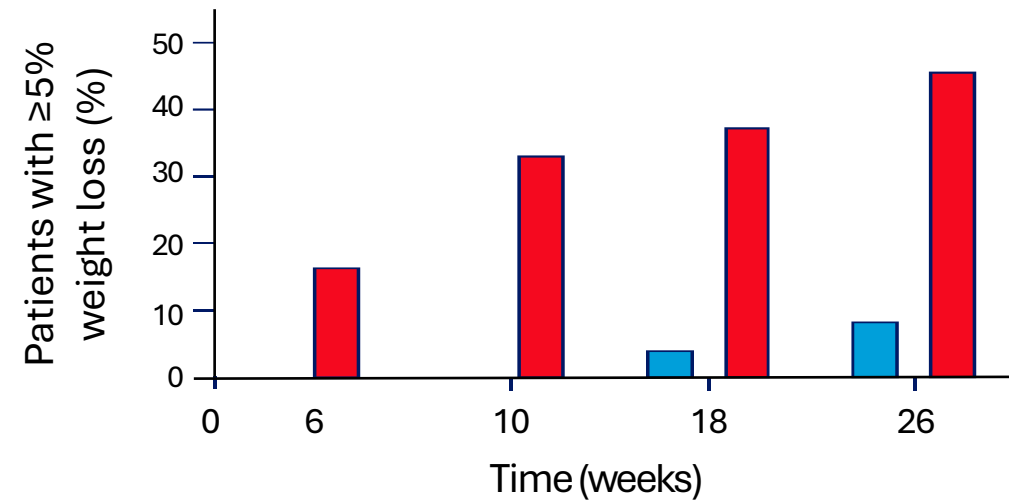
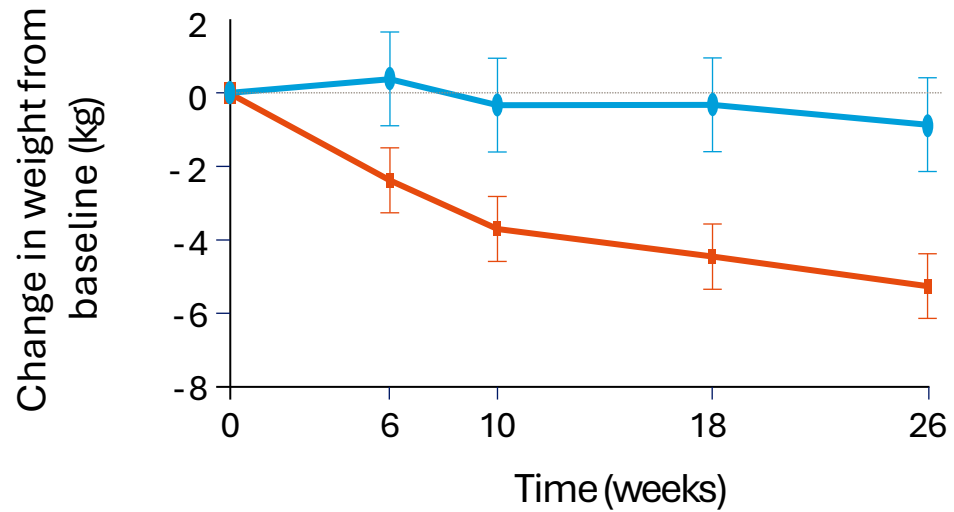
... complementary mechanisms allow for **synergy**



Postoperative pharmacotherapy augments surgical weight loss

GRAVITAS Study

Liraglutide 1.8 mg vs. Placebo after Gastric Bypass
Patients with Type 2 Diabetes



- Placebo
- Liraglutide

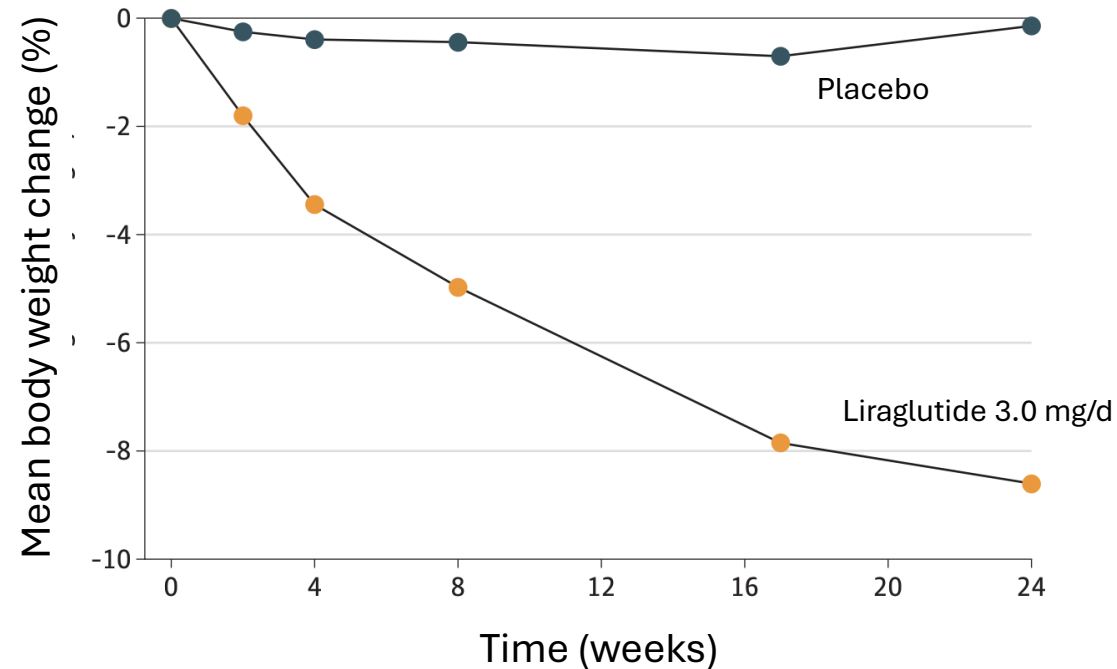
Liraglutide 3.0 mg augments weight loss after metabolic surgery

BARI-OPTIMISE Trial

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

Liraglutide 3.0 mg/day vs. placebo

(N=70)



Potential means of addressing recurrent weight gain

Cause of weight gain

Promotion of non-physiological weight loss
(purposeful calorie restriction beyond what surgery naturally provides)

Progression of disease

Environmental factors

Surgical complication

Intrinsic biological or genetic factors

Potential solution

Avoid recommending purposeful calorie reduction – let the surgery do its job!

Add an **additional therapeutic mechanism**

- Start or add an **anti-obesity medication**
- **Convert to a different MBS** operation
- Add a **complementary endoscopic** treatment

Address the environmental factors or
add an **additional therapeutic mechanism**

Correct the **surgical anatomy**

Add an **additional therapeutic mechanism**



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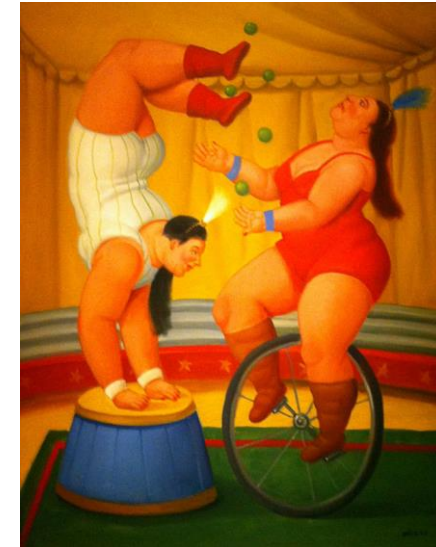
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