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Metabolic Adaptation and Defense of Body Fat Mass: Implications for Obesity Treatment

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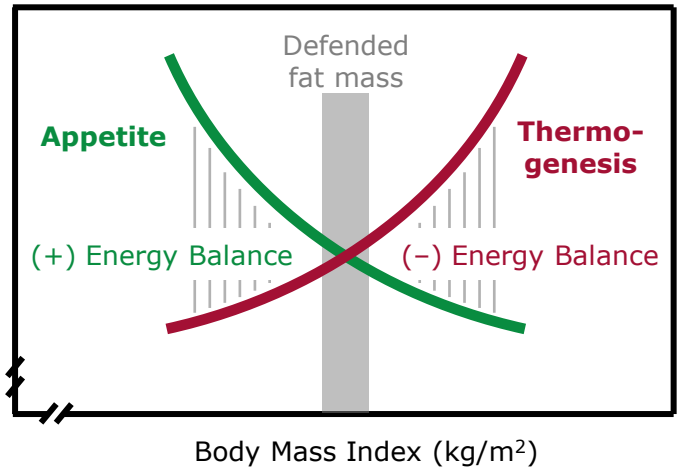


2023 IFSO World Congress

Disclosures

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

Altimmune
Amgen
Boehringer Ingelheim
Gelesis
Gilead Sciences
Eli Lilly & Company
Novo Nordisk
Pfizer
Rhythm Pharmaceuticals
Sidekick Health
The Obesity and Nutrition Institute
twenty30.health
Xeno Biosciences

Competing models of fat mass regulation

Purposeful behavior **drives** the physiology of fat mass regulation

VS.

The physiological regulation of fat mass **drives** behavior

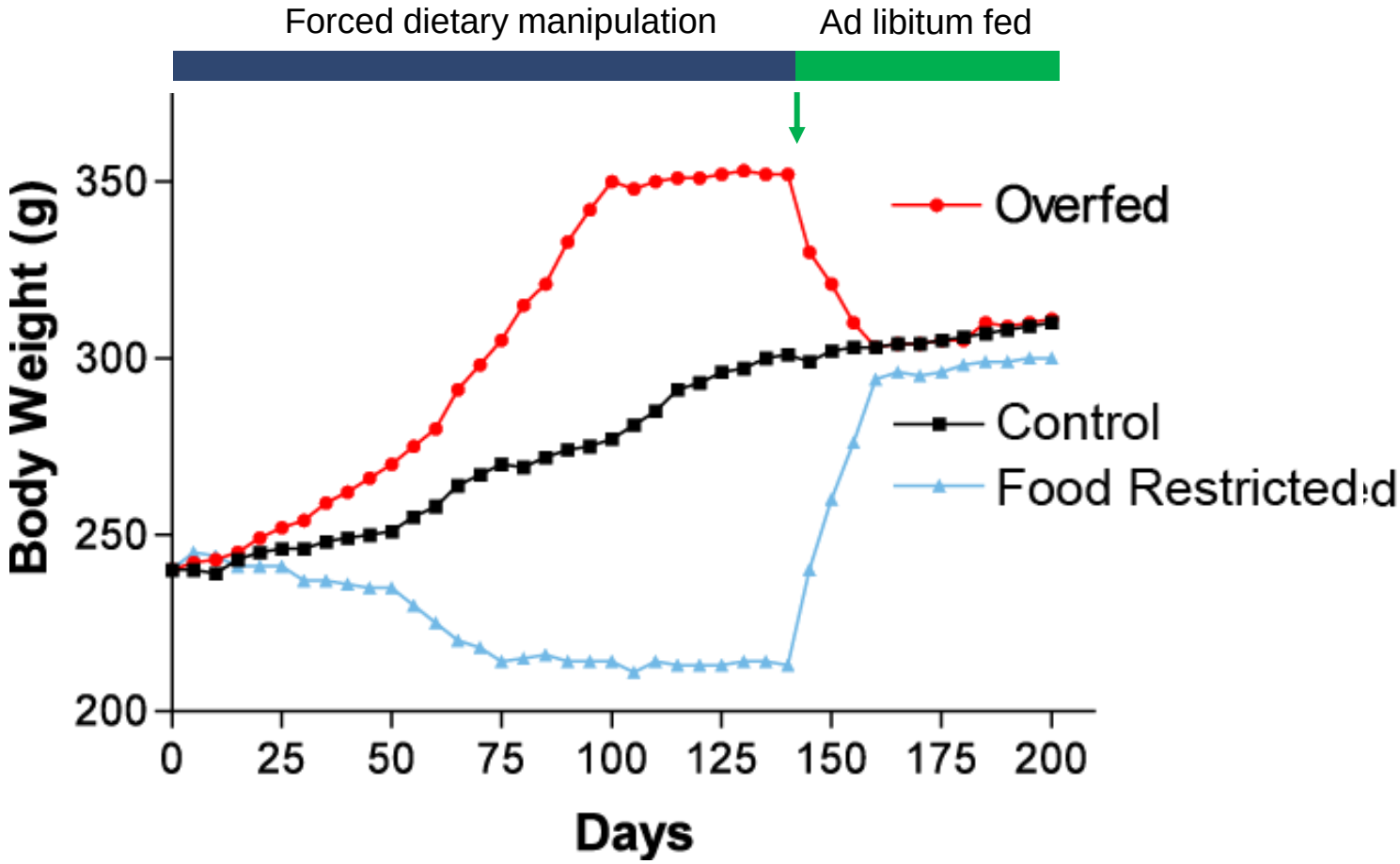
Implications

- Increased caloric intake drives weight gain
- All types of calories have similar effects
- Physical activity causes weight loss directly by burning calories

Implications

- Changes in the modern diet alter energy balance physiology
- The chemical nature of the calories is critical
- Re-regulation of abnormal physiology is essential for success

Defense of a biologically determined body fat mass



Adapted from Woods SC et al., 1989

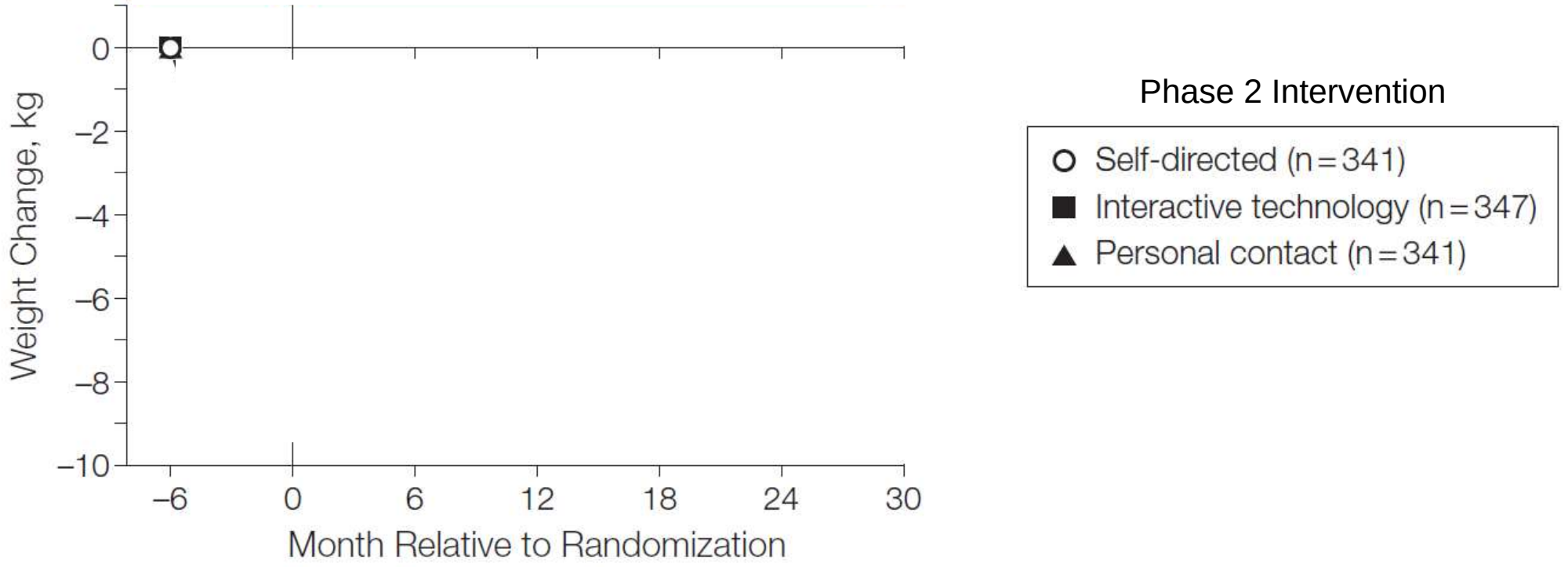
There must be CNS-driven physiological programs …

- To **establish** the current **target fat mass** (current fat mass "set point")
- To **defend** the target fat mass
  - To **store fat** if the body is **below the target**
  - To **mobilize fat** if the body is **above the target**

Obesity develops because of disruption of the first of these programs.

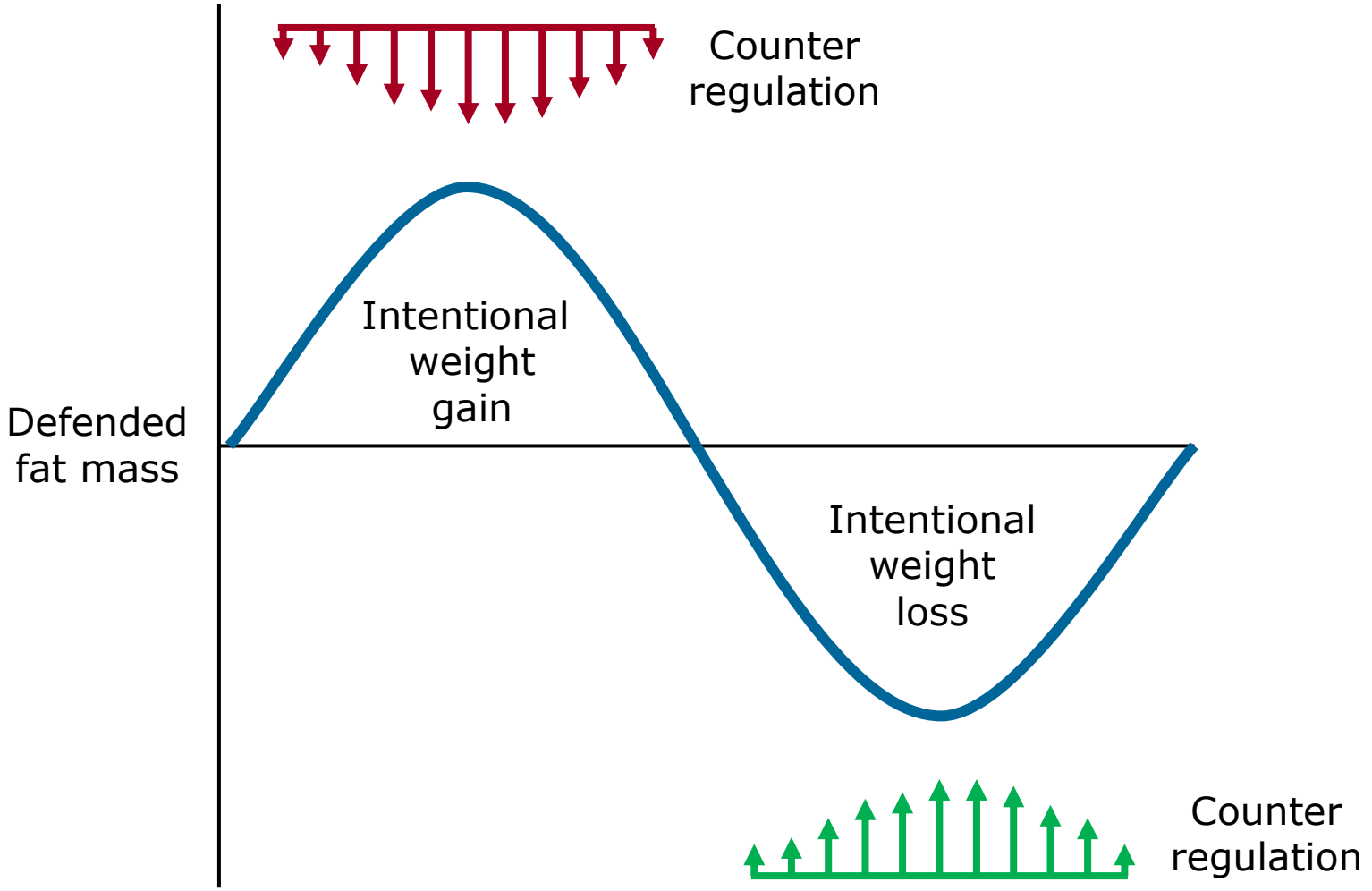
In all common forms of obesity, the second program (defense of the target fat mass) appears unaffected.

Classic weight graph after calorie restriction



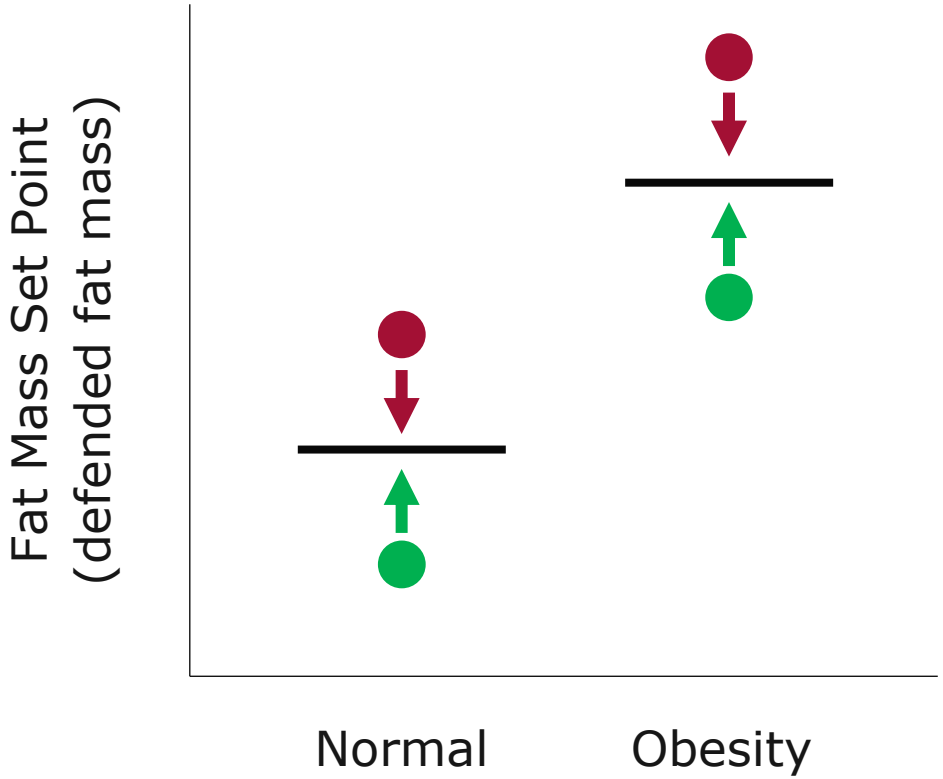
Svetky, et al. *JAMA*. 2008. PMID: 18334689

Defense of fat mass and body weight – in both directions



Adapted from Jonathan Purnell

Relationship to set point drives fat mass protective response



● = **Hyper**adiposity state

↓ Response to hyperadiposity:
Decreased appetitive drive
Increased thermogenesis

● = **Hypo**adiposity state

↑ Response to hypoadiposity:
Increased appetitive drive
Decreased thermogenesis

Hypoadiposity

Definition: the state of having **less than the body's target amount of fat**

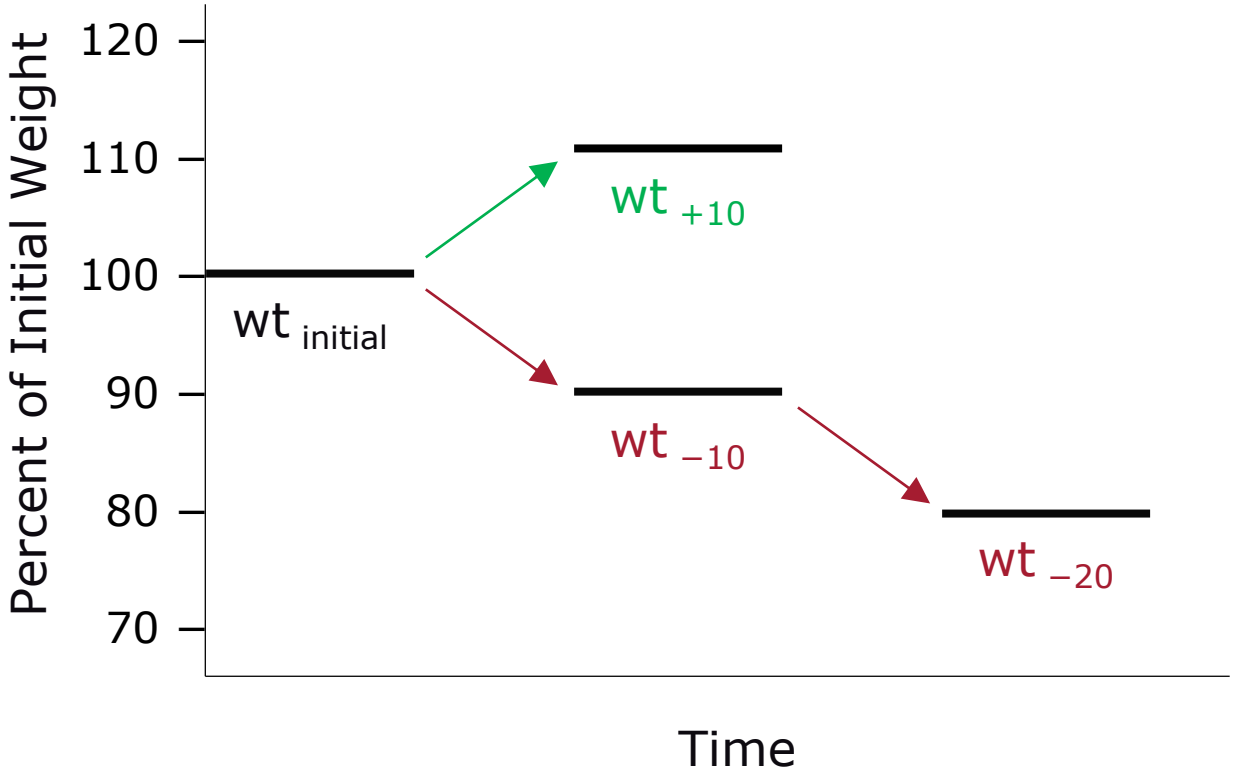
- NOT weight loss
- NOT diminished body fat
- Can occur in people of all sizes
- Similar to what has been called the "weight-reduced state"
- But not all types of weight loss lead to the "weight-reduced state"
- Hypoadiposity does not need to have resulted from weight loss
- It could result from an influence that raises the target fat mass

Human weight perturbation protocol

Dietary restriction / overfeeding

(demonstrated no change in fat mass set point)

Normal weight individuals *and* people with obesity



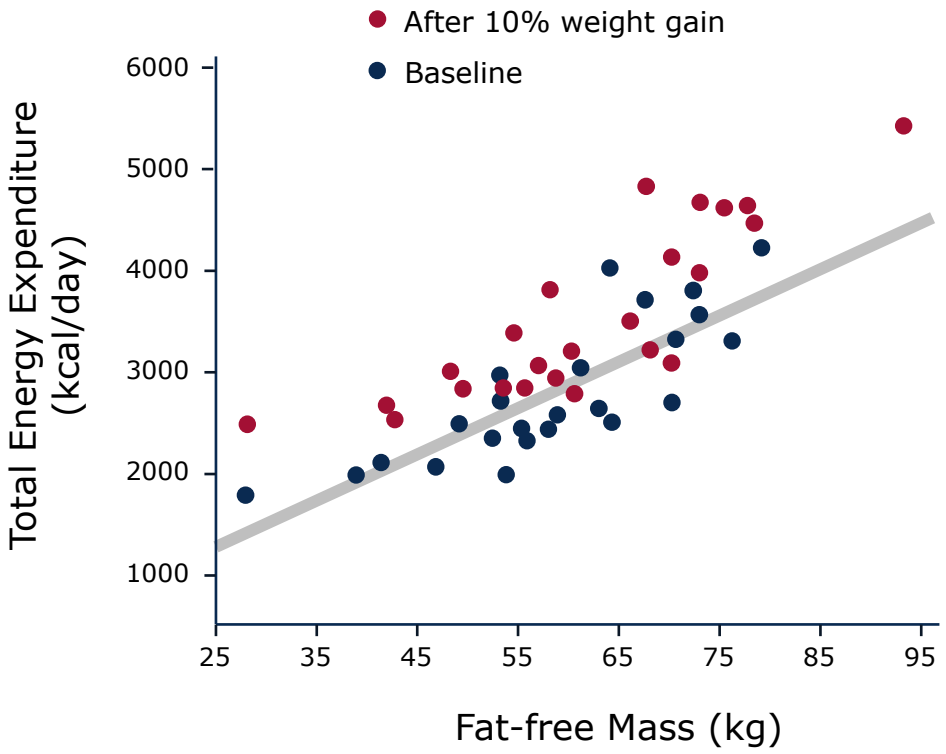
Studies

Energy expenditure
Energy intake
Neuroendocrine axes
Autonomic physiology
Muscle physiology
Brain imaging

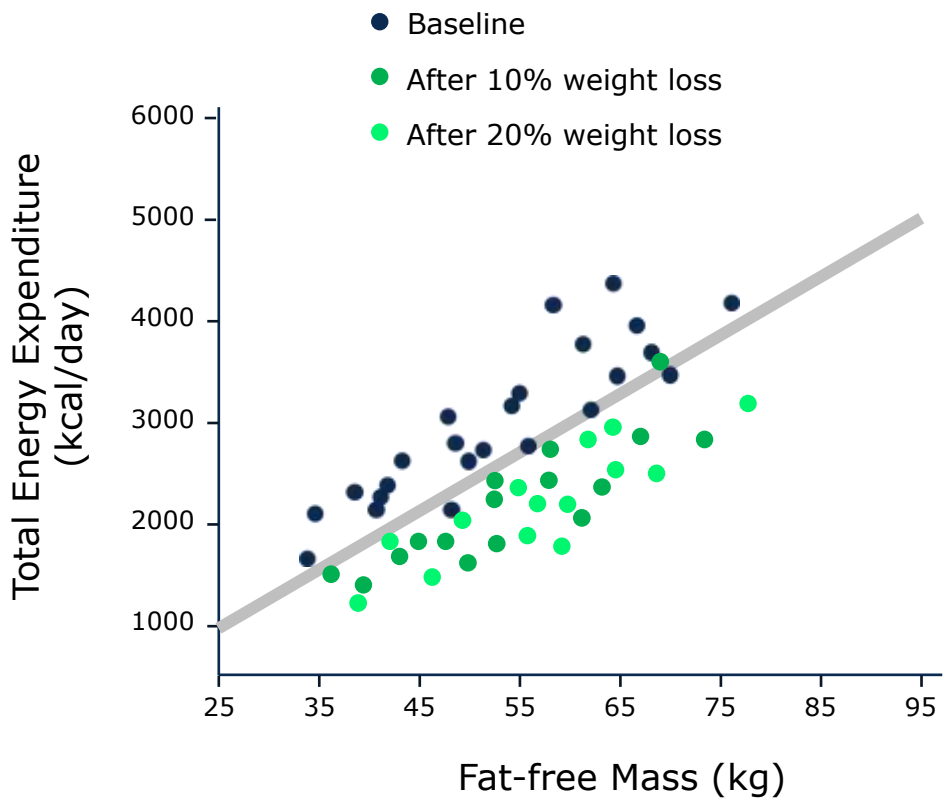
Leibel RL *et al.*, *NEJM* 1995;335:521

Physiology of the weight-altered state

Hyperadiposity

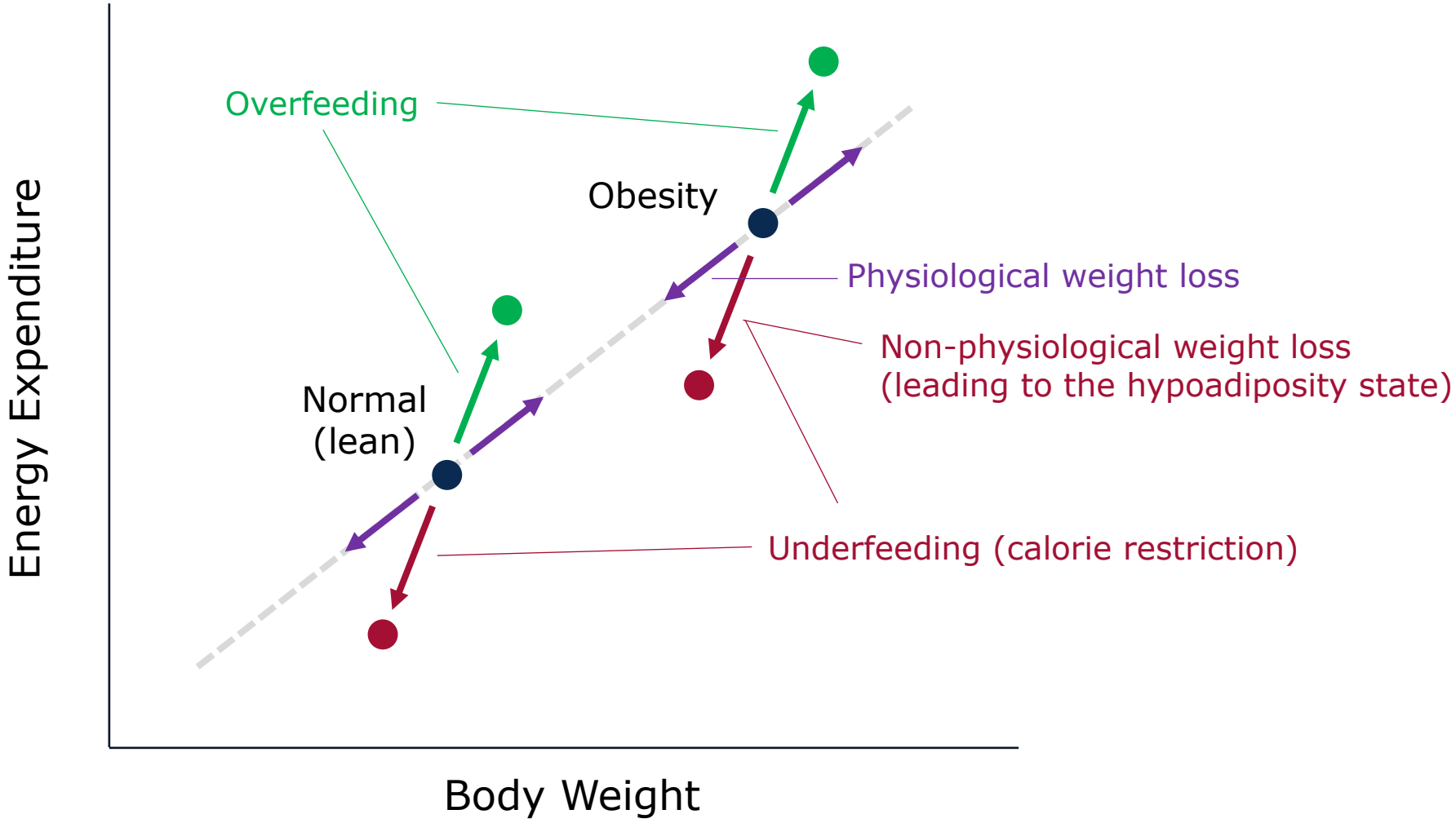


Hypoadiposity

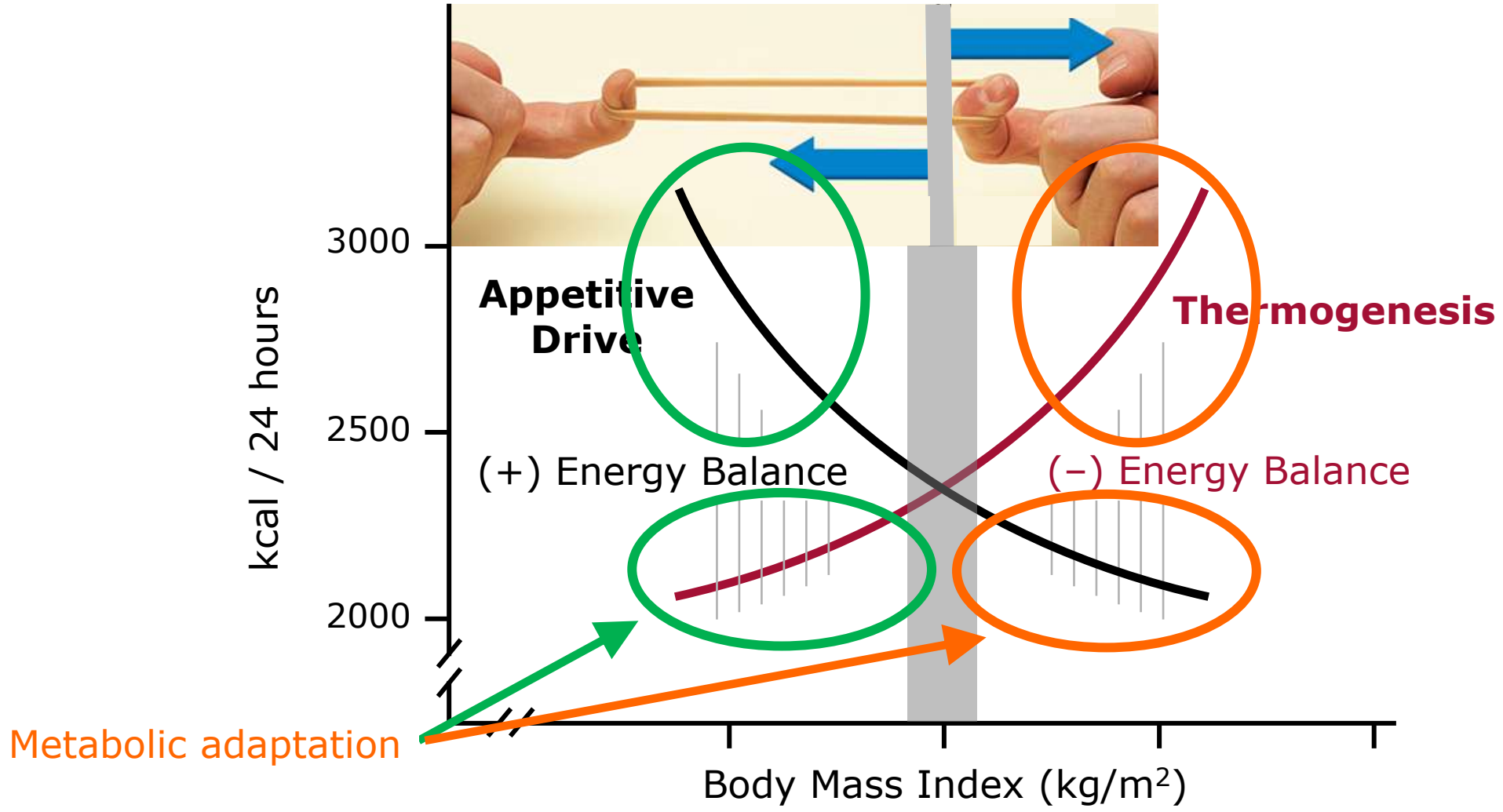


Leibel R et al. *N Engl J Med* 1995

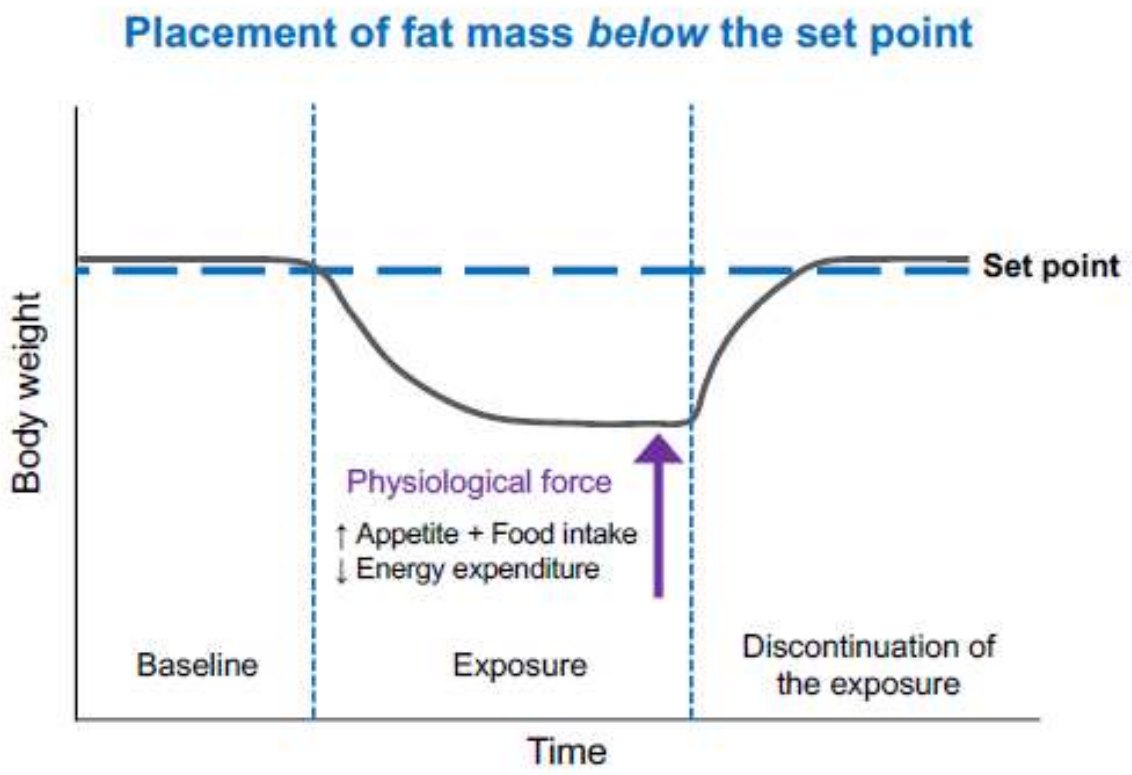
Body size, weight changes and energy expenditure



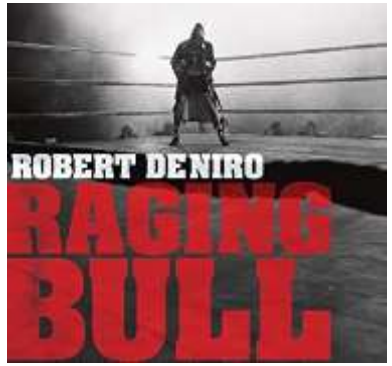
The body defends a fat mass "set point" by metabolic adaptation

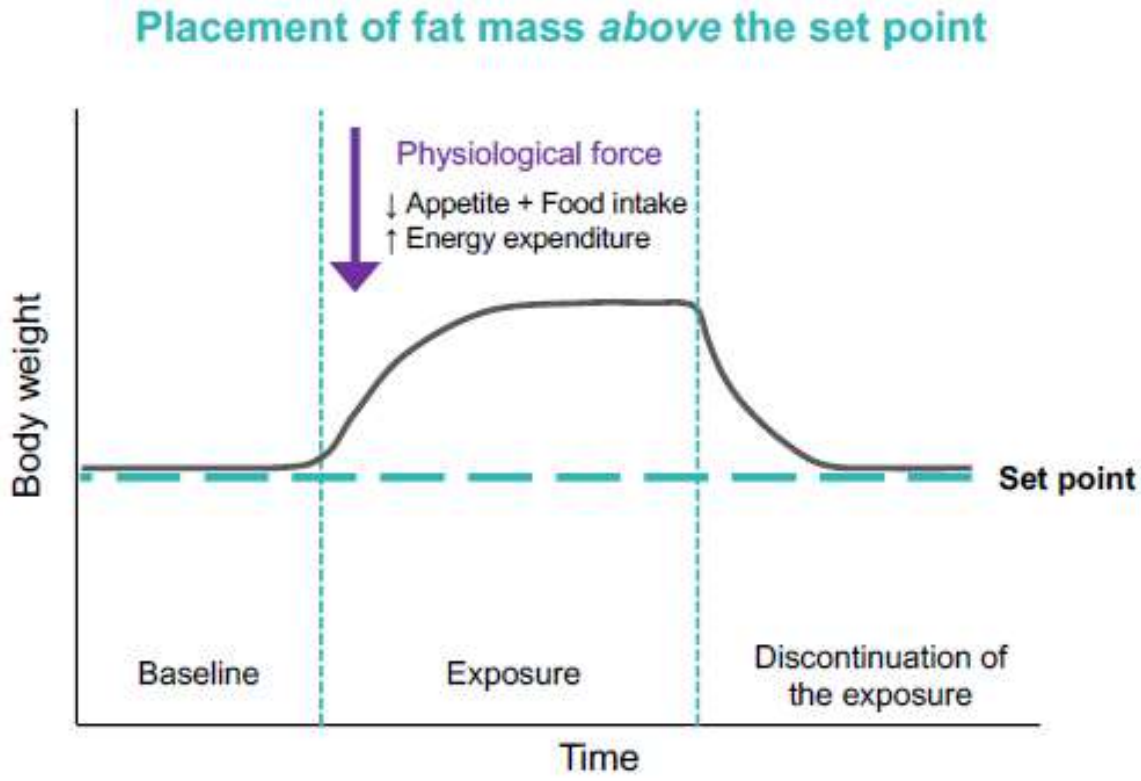


Brute force reduction in body fat mass

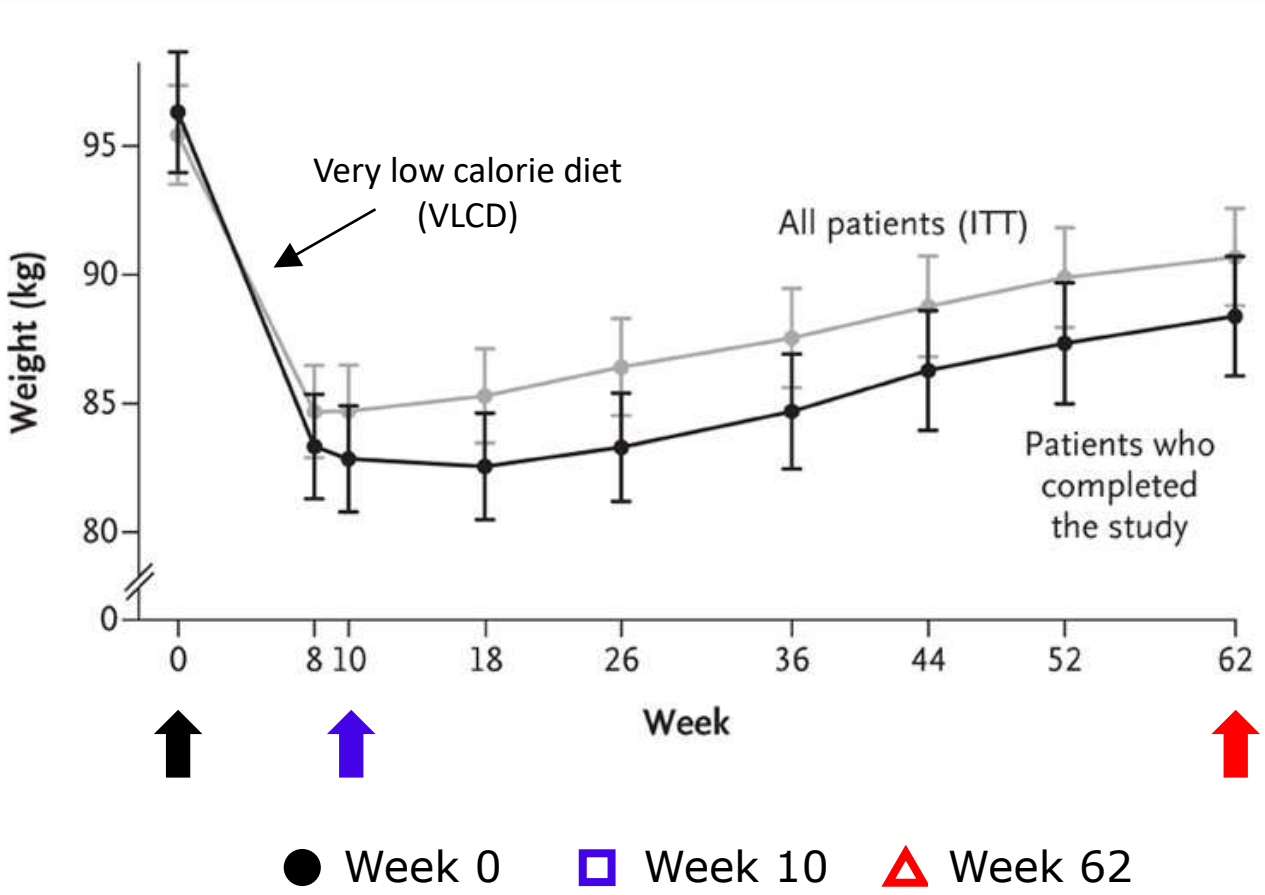


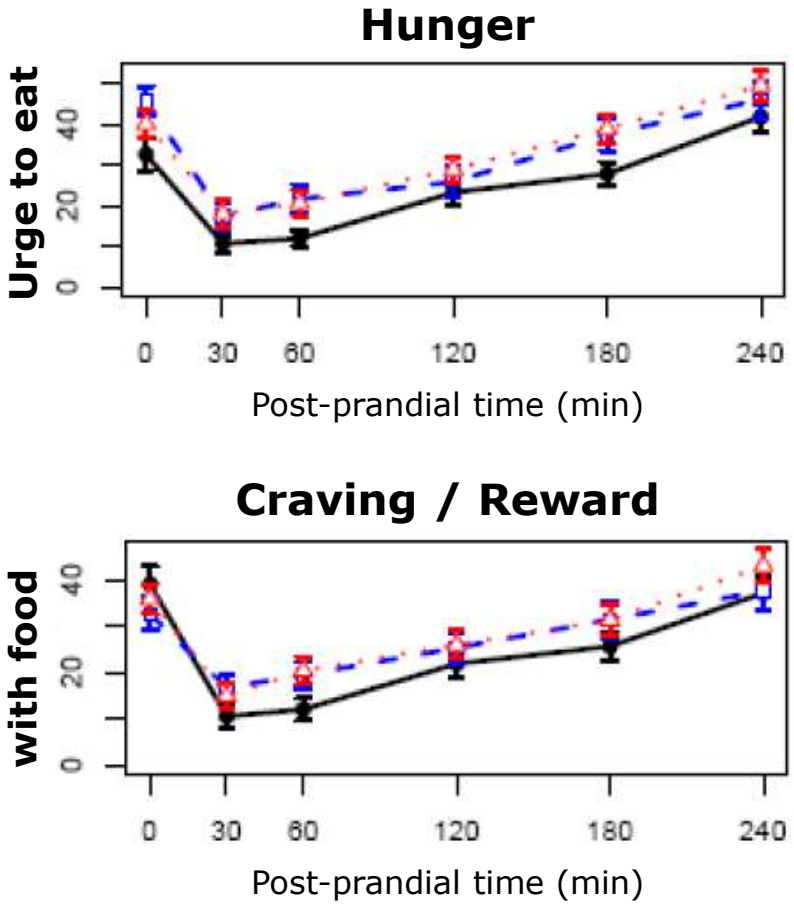
Brute force increase in body fat mass





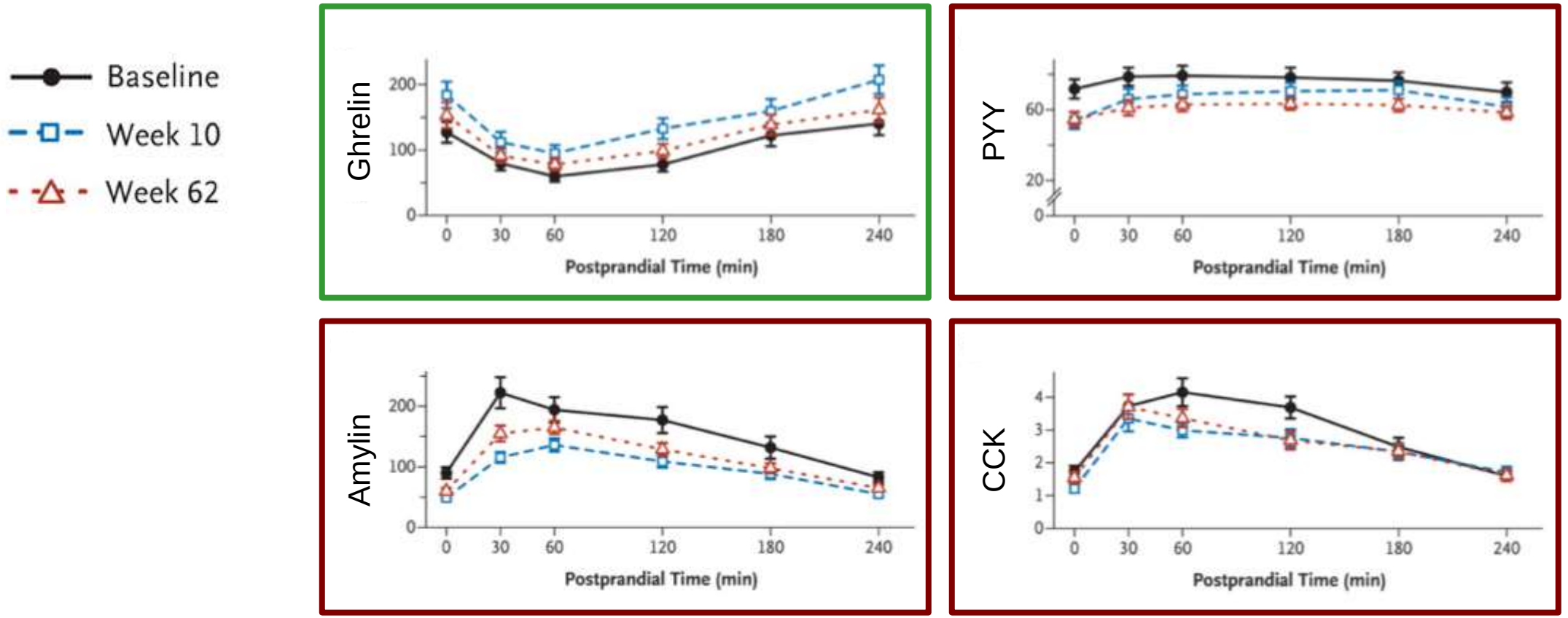
How does the body defend its fat mass?





Sumithran P, *et al*., *NEJM* 2011;365:1597

Gut hormones mediate compensatory metabolic adaptation

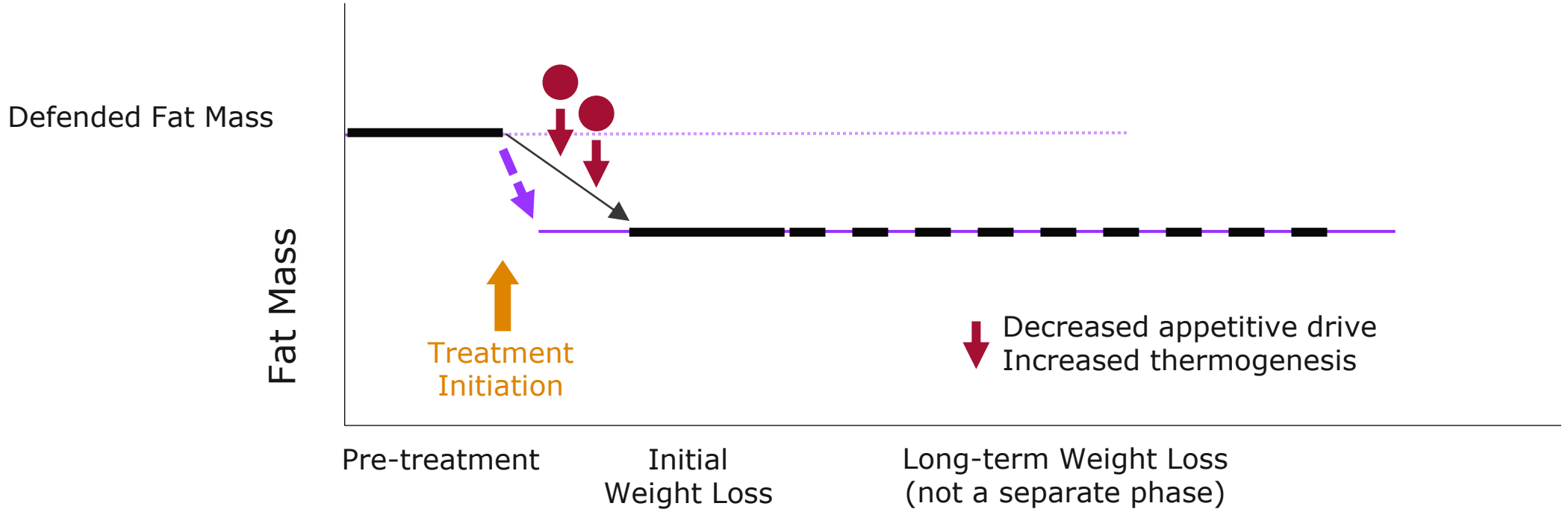


Sumithran P, *et al.*, *NEJM* 2011;365:1597

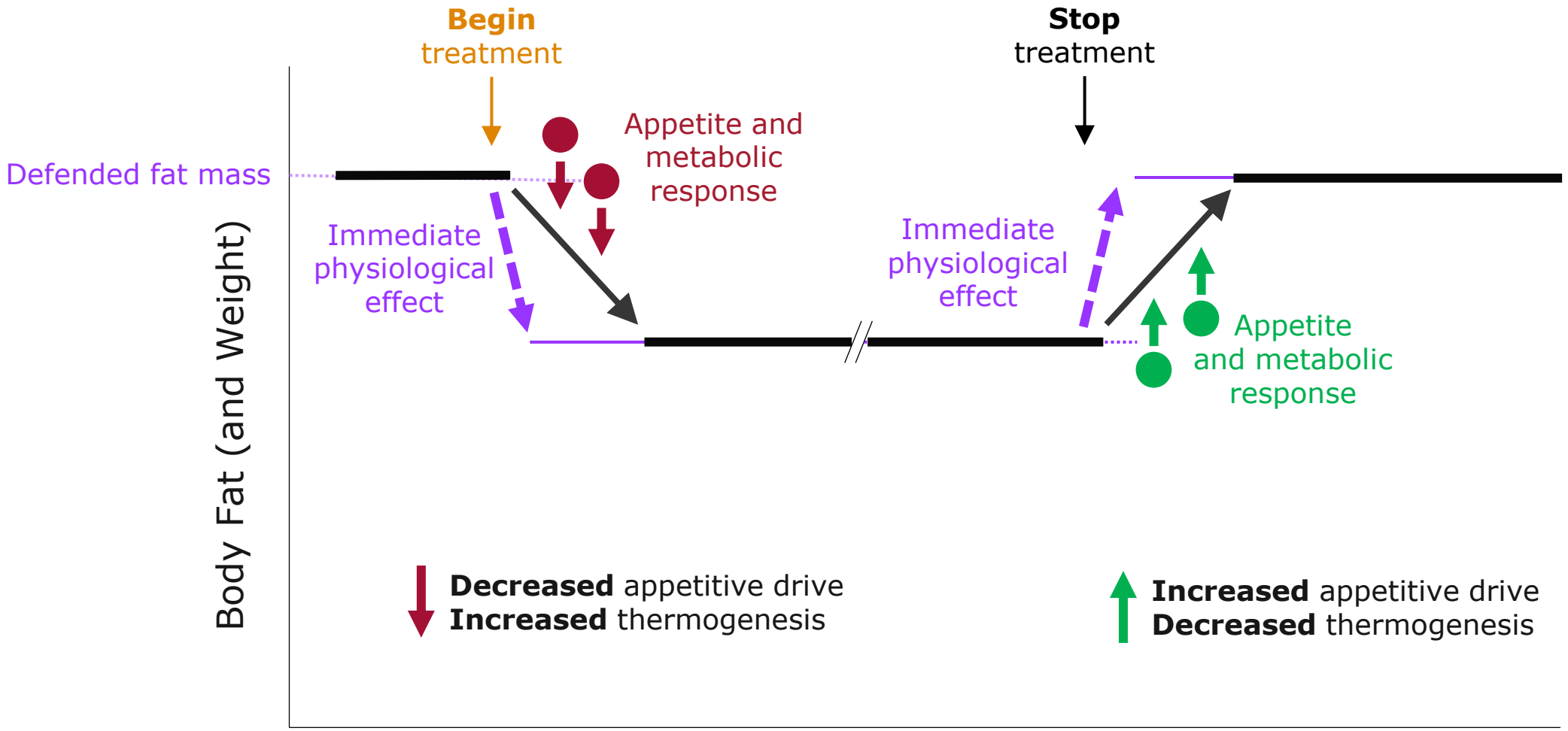
Bariatric surgery is an example of physiological weight loss

Physiological weight loss

(e.g., **targeted lifestyle change**, **effective medications**, **bariatric surgery**)

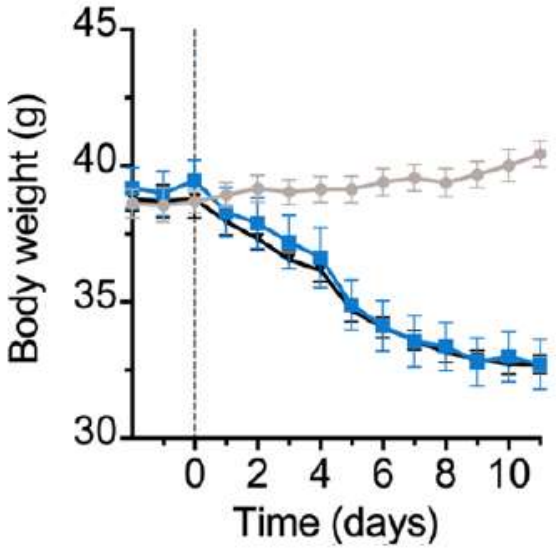


Removal of effective therapy returns the set point to baseline

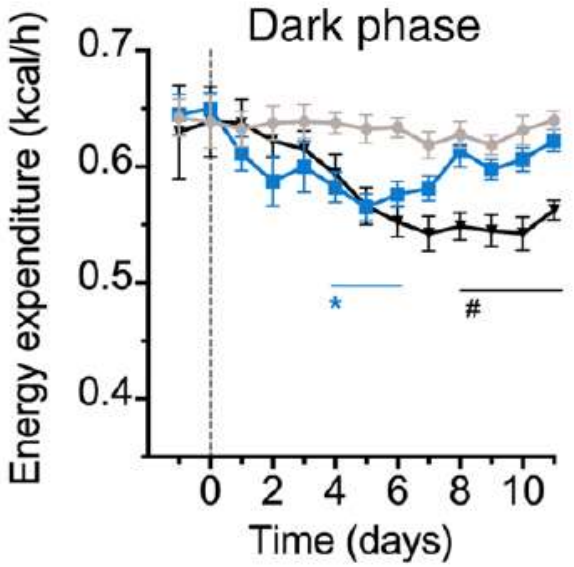


Semaglutide-induced weight loss is associated with blunting of metabolic adaptation

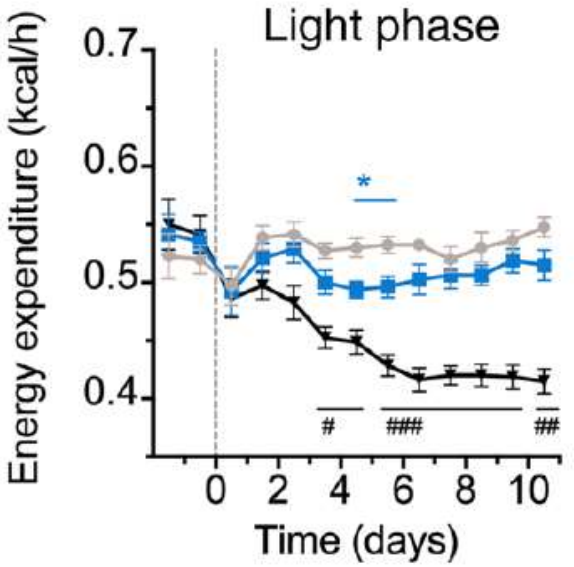
Body weight

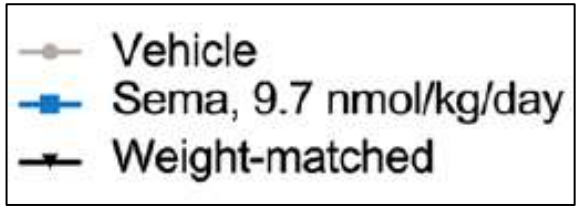


Energy expenditure



Energy expenditure





Gavery S *et al*. *JCI Insight* 2020; 5:e133429; doi.org/10.1172/jci.insight.133429

Conclusions

- **"Hypoadiposity" is the physiological state of the body having less fat than it currently wants**
- **It generates counter-regulatory forces that seek to defend the pre-treatment fat mass** and return the patient with obesity to his/her original elevated set point
  - These counter-regulatory forces are also called "**metabolic adaptation**"
  - However, they influence both **energy expenditure and appetitive drives**
  - **They work in both directions** – weight gain from overfeeding induces a compensatory "hyperadiposity"
  - They account for the limited effectiveness of non-physiological weight loss strategies
- **Bariatric surgery** and **effective anti-obesity medications** suppress these metabolic adaptations, lowering weight without inducing hypoadiposity
- Clinical evidence (decreased appetite, durability of response) suggests that **physiologically-mediated lifestyle changes similarly reduce weight without inducing hypoadiposity**

Implications

Understanding the physiology of the hypoadiposity state and how physiological obesity treatment limits metabolic adaptation can strongly enhance our ability to manage individual patients with obesity

Discovery of the cellular and molecular components of the programs that set and defend the body’s fat mass will likely reveal new markers and targets for effective obesity prevention and treatment

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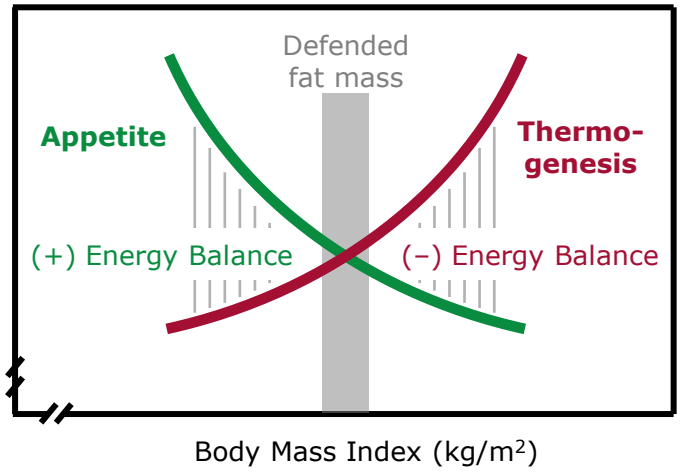

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