Understanding Obesity as a Chronic Disease

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Disclosure

Advisory Board: Boehringer-Ingelheim; Eli Lilly; Nestle Healthcare Nutrition; Novo Nordisk; Regeneron; Weight Watchers

Consultant: Amgen; Brightseed; Intuitive Surgical

Grant Recipient: Boehringer-Ingelheim; Eli Lilly; Epitomee; Nestle Healthcare Nutrition; Novo Nordisk; Weight Watchers

Research Grant: KVK Tech; UnitedHealth Group

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Learning Objectives

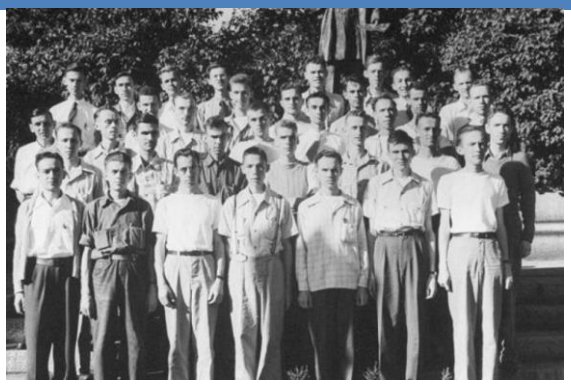
1. Gain an understanding of obesity as a chronic health condition, including its medical definition and physiological mechanisms
2. Learn about the risk factors and causes of obesity
3. Learn about the factors contributing to the heterogeneity of obesity that are considerations for tailoring

Evolution of Thought

"Normal" food intake	"Excess" food intake
+	+
High physical activity	Low physical activity
=	=
↓fat mass	↑fat mass

Evolution of Thought

Obesity is not the extreme converse of starvation



Participants of the Minnesota starvation experiment

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100% Success

Desert Island: Survivor Style

- Survive on what one can forage
- Increased activity is obligatory

Wired Jaw

- Limit the volume consumed by physical barrier

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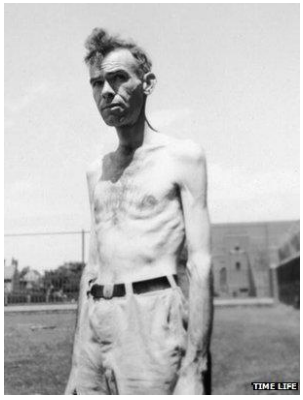
Consequences

- Loss of lean mass
- Increased hunger
- Preoccupation with food
- Malnutrition
- Unsustainable



A participant of the Minnesota starvation experiment

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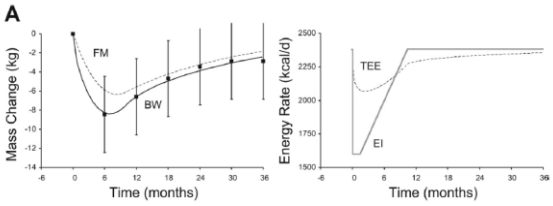
Unsustainable

From a behavioral perspective: "Can I continue this set of behaviors indefinitely?"

- Even if you could, the probability of weight regain remains high and is not of 100% volitional control



AJP-Endocrinol Metab • VOL 298 • MARCH 2010

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Alarms Are Ringing!

Intentional weight loss is perceived as a threat by your brain

- Your brain doesn't know you are doing this on purpose
- Limited calorie intake and resulting loss of mass must be a result of famine or illness
- There is no scenario in the wild where weight loss provides a survival advantage

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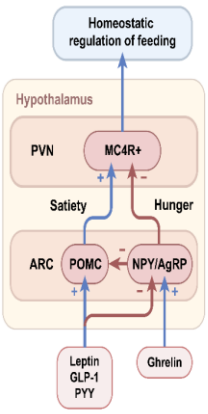
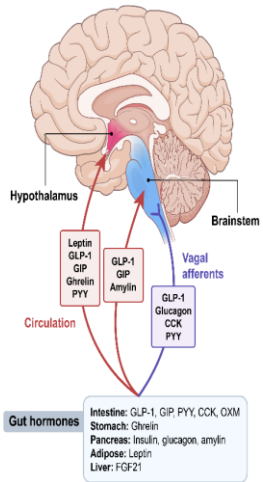
Your Brain Plays Defense

- Loss of mass and sustained reductions in energy intake is a trigger
- Brain shifts hormones to favor
  - INCREASING food intake
  - DECREASING energy expenditure (resting and activity related)





Roh E, Choi KM. Hormonal Gut-Brain Signaling for the Treatment of Obesity. Int J Mol Sci. 2023 Feb 8;24(4):3384.

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Self-preservation

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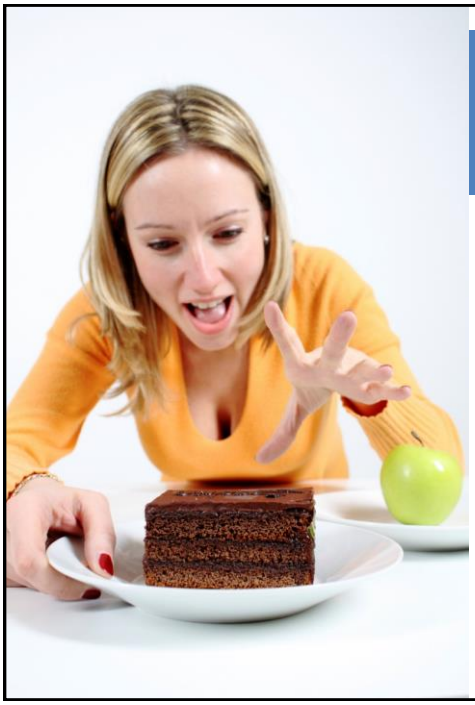

Unsustainable-Physiologically

- What our patients experience as waning will power and diminishing returns is physiology

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Key Points

OUR BRAINS ARE HARDWIRED TO PRESERVE MASS

ENERGY RESTRICTION, PARTICULARLY WHEN EXTENDED, IS PERCEIVED AS A THREAT

HORMONES AND OTHER SIGNALS FROM THE BRAIN WORK TO PREVENT LOSS OF MASS

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What Obesity Isn't

- The result of simple overindulgence
- Fixed with simple changes in calorie intake
- One simple disease
- Simple

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Our "Central" Problem

- Energy regulation is dysfunctional
  - Result is energy imbalance
  - Excess fat accumulation
  - Deposition of fat in various depots
  - Insulin resistance results
  - Metabolic and mechanical abnormalities ensue
- Radiologic evidence
  - Gliosis of the mediobasal hypothalamus
    - Chronic inflammation– results in decreased sensitivity to leptin signaling

Sewaybricker LE, Huang A, Chandrasekaran S, Melhorn SJ, Schur EA. The Significance of Hypothalamic Inflammation and Gliosis for the Pathogenesis of Obesity in Humans. Endocr Rev. 2023 Mar 4;44(2):281-296.

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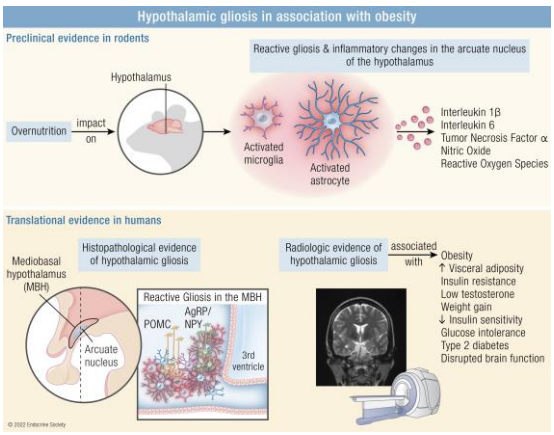
Our "Central" Problem



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Obesity Is a Faulty Thermostat

No fix for the thermostat

- Ambient temperature doesn't change
- Or ambient temperature changes for a limited time
- Worse yet– the thermostat causes the heat to crank up in response to those efforts

The Thermostat is Broken

01	02	03
Take off your clothes	Open the windows	Turn on the ceiling fan

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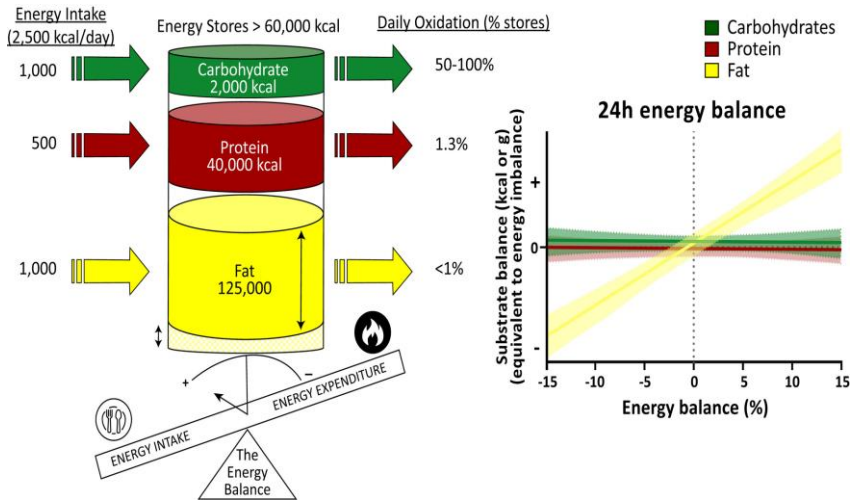
Beyond appetite regulation: Targeting energy expenditure, fat oxidation, and lean mass preservation for sustainable weight loss



Obesity, Volume: 30, Issue: 4, Pages: 841-857, First published: 25 March 2022, DOI: (10.1002/oby.23374)

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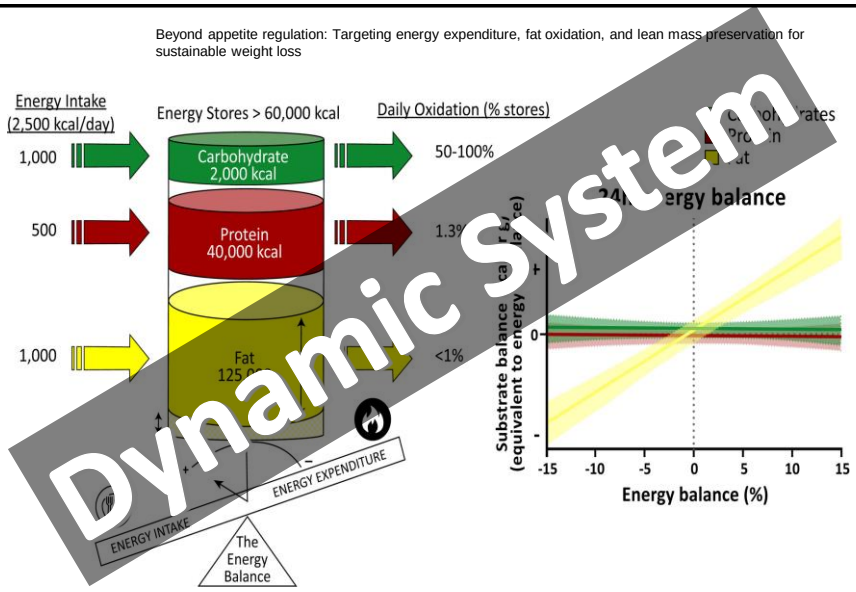

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Obesity vs. Weight Gain

- Obesity is
  - A result of central dysregulation of energy balance
  - Results in excess fat mass
  - Adaptive counter regulatory response that makes weight loss difficult
- Weight gain is
  - Change in body weight (not necessarily limited to fat mass)
  - May result from excess energy intake (but not always)
  - Physiologic response that restores energy balance

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Physiologic Determinants of Weight Gain

In the setting of energy restriction

- Metabolically Thrifty
  - Low resting energy expenditure
  - Low fat oxidation (limited metabolic flexibility)
  - Reduced sympathetic activity
- Metabolically Spendthrift
  - Limited decrease in resting energy expenditure
  - ++ Metabolic flexibility
  - Maintained sympathetic activity

Obesity, Volume: 27, Issue: 5, Pages: 691-699: 23 April 2019

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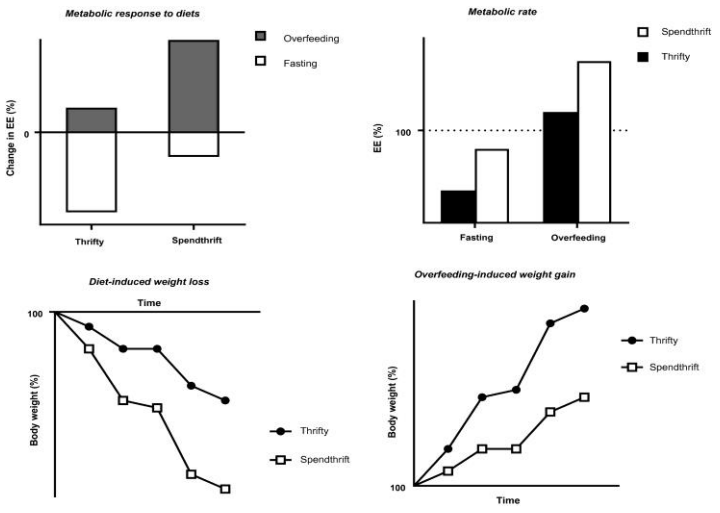

Metabolic Determinants of Weight Gain in Humans

Obesity, Volume: 27, Issue: 5, Pages: 691-699, 23 April 2019

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Key Points

- Obesity is different from simple weight gain
- Obesity involves central dysregulation of energy balance
- That dysregulation is further influenced by genetic determinants of responses to availability to energy

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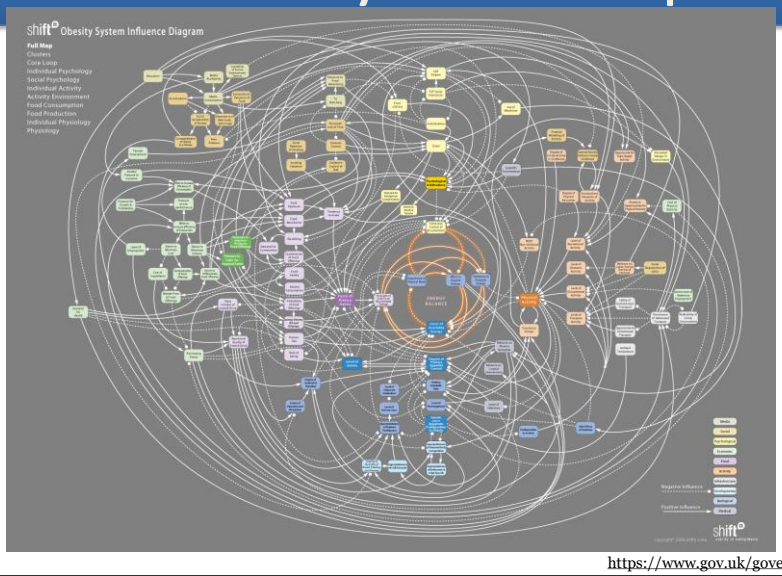
Obesity Is a Complex Disease



https://www.gov.uk/government/publications/reducing-obesity-obesity-system-map

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Heterogeneity of Disease

- Interplay between physiologic, genetic, and environmental factors
- This helps to explain the heterogeneity of the disease
- Also explains why it is chronic in nature

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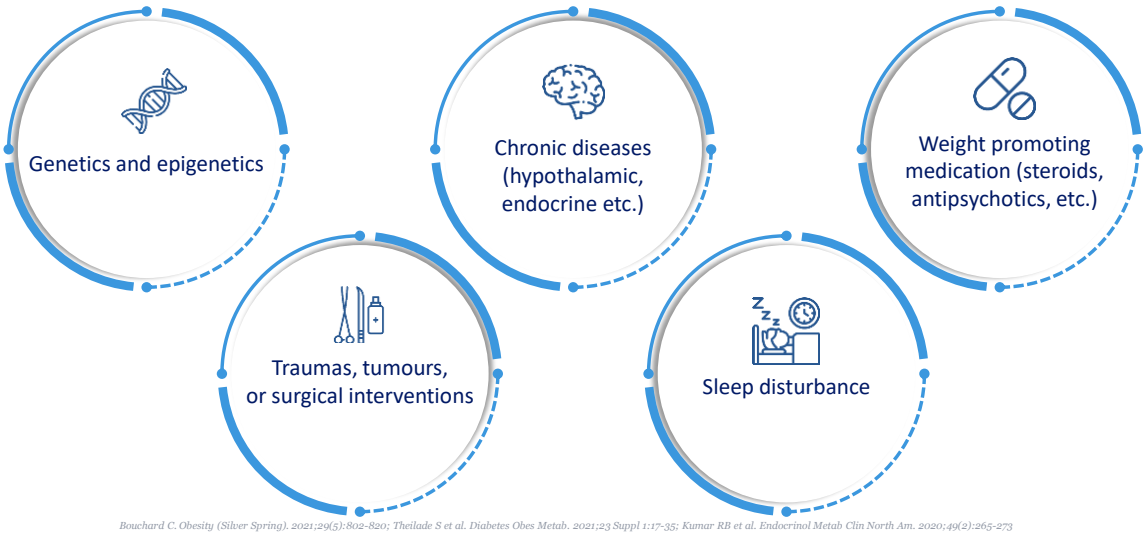
Contributors to Obesity – Biological



Bouchard C. Obesity (Silver Spring). 2021;29(5):802-820; Theilade S et al. Diabetes Obes Metab. 2021;23 Suppl 1:17-35; Kumar RB et al. Endocrinol Metab Clin North Am. 2020;49(2):265-273

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Contributors to Obesity – Life Stages

Individual life experiences (injury, more sedentary job)

Life stages (menopause, aging)

Transitions or events associated with weight gain (pregnancy, stressful life events)

Smith LH et al. Scand J Public Health. 2011;39(4):396-402; Lewis KH et al. *Curr Obes Rep.* 2016;5(2):282-290; *Rueda-Clausen CF et al. Canadian Adult Obesity Clinical Practice Guidelines: Assessment of People Living with Obesity. Available from: https://obesitycanada.ca/guidelines/assessment*

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Contributors to Obesity – Psychosocial

Social

- Sociocultural practices and beliefs
- Social determinants of health
- Built environment

Psychological

- Mood and anxiety
- Binge-eating disorder
- Attention-deficit hyperactivity disorder
- Self-worth and identity

Lewis KH et al. *Curr Obes Rep.* 2016;5(2):282-290; *Rueda-Clausen CF et al. Canadian Adult Obesity Clinical Practice Guidelines: Assessment of People Living with Obesity. Available from: https://obesitycanada.ca/guidelines/assessment*

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Our Obesogenic Environment

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Challenges of the Obesogenic Environment

- Easy to maintain positive energy balance
  - Access to food
  - Mechanization
  - High energy dense food
- Takes significant effort to maintain body weight
  - Dietary restraint
  - Voluntary energy expenditure

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Obesity Mirrors Other Chronic Diseases

Which of these diseases is affected by environment, genetics, and behavior?

Disease	Environment	Genes	Behavior
Hypertension	X	X	X
Diabetes	X	X	X
Obesity	X	X	X

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Key Points

- Obesity is complex in etiology and presentation
- There is heterogeneity in obesity
- Environmental factors are key in presentation and chronicity
- Obesity is like other chronic diseases we treat

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Summary

- Obesity is a dysregulation of energy balance that results in excess fat mass
- Hard-wired mechanisms that were evolutionarily protective are ill-equipped to deal with our current obesogenic environments
- Like other chronic diseases, there are genetic, environmental, and behavioral contributors to obesity phenotypes

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(True/False)Weight Loss, Particularly by Restriction of Calories, Is Perceived as a Threat by Your Brain.

A. True
B. False

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In the Setting of Energy Restriction, People Who Are "Metabolically Thrifty" Tend to Respond

A. By burning more calories at rest and increasing the amount of fat they burn
B. By increasing sympathetic activity at rest to maintain body temperature
C. By reducing resting energy expenditure and minimizing the amount of fat they burn

You See a Patient with Persistent Weight Gain Who Now Has a BMI= 37 kg/m2. What Factors May Be Contributing to the Cause of the Obesity?

A. Working a 3rd shift job for the past 2 years
B. Depression that is not well controlled
C. Living in a low-resource neighborhood that lacks non-fast food options
D. All of the above