

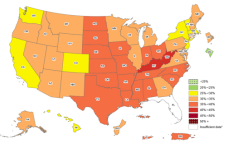
Pathophysiology of Obesity

Melinda V. Gonzalez, PA-C
Martine Altieri, PA-C

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Prevalence

Prevalence of self-reported obesity, 2021¹




- Overweight and obesity affects more than 70% of the US adult population¹
- It is estimated that 93 million Americans are affected by obesity specifically²
- More than 9 million adolescents (children and teens 6 to 19 years old) are affected by excess weight²
- Children who are affected by obesity are 70% more likely to continue being affected into adulthood²

1. Centers for Disease Control and Prevention. Prevalence of Overweight, Obesity, and Severe Obesity among Adults—United States, 2007–2018. *MMWR*. 2021;70(17):3022–3028. <https://www.cdc.gov/mmwr/preview/mmwrhtml/mm7017a3.htm>. Accessed May 23, 2023. <https://www.cdc.gov/obesity/data/adult.html>. Accessed May 23, 2023. <https://www.cdc.gov/obesity/data/adolescent.html>. Accessed May 23, 2023. <https://www.cdc.gov/obesity/data/childhood.html>. Accessed May 23, 2023.

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Definitions

Obesity is defined as a body mass index of 30 or higher and overweight is defined by a BMI of 25 to 29.9.¹



Obesity is a chronic, progressive, relapsing, but treatable multifactorial, neurobehavioral disease, wherein an increase in body fat promotes adipose tissue dysfunction and abnormal fat mass physical forces, resulting in adverse metabolic, biomechanical, and psychosocial health consequences.²

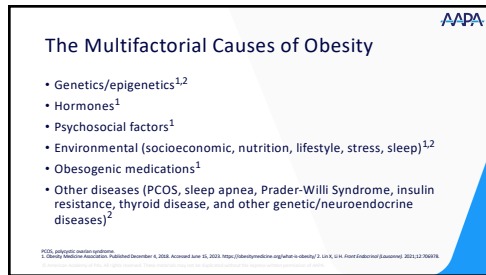
There are intervention strategies and treatment options to manage obesity.

1. World Health Organization. *Obesity: preventing and managing the global epidemic*. Geneva: WHO, 2000. http://www.who.int/dietphysicalactivity/trade_publications.htm. Accessed May 23, 2023. <https://www.cdc.gov/obesity/data/adult.html>. Accessed May 23, 2023. <https://www.cdc.gov/obesity/data/adolescent.html>. Accessed May 23, 2023. <https://www.cdc.gov/obesity/data/childhood.html>. Accessed May 23, 2023.

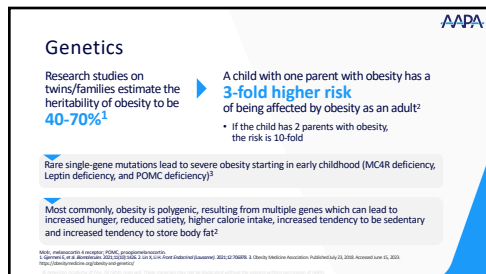
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Epigenetic Factors

Epigenetics is defined as the changes in gene expression or phenotype without changing DNA sequence

- These changes in gene expression are due to environmental experiences and can go as far back as in utero and childhood
- Environmental influences such as lifestyle (nutrition, physical activity, alcohol intake, sleep deprivation), gut microbiota, drugs, obesogenic toxins and intrauterine environment are all factors that can change gene expression without changing DNA gene sequences. This can be passed on to other generations
- Prenatal, postnatal and intrauterine changes like maternal smoking habits, maternal weight, weight gain and blood sugar levels during pregnancy all contribute to offspring with increased obesity risk

L. Hayden et al., Nutrition, 44(2):141-147, 2012; DOI:10.1016/j.nut.2012.02.006. Image from Tong G, Grant PA, Am J Obstet Gynecol. 2013; 208:1198.

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Genes Affected by Environmental Epigenetic Factors

Genes are affected by environmental factors through epigenetic mechanisms. Genes are co-coded by methylation. The genes within each section are specific for each factor, and genes placed in the middle space are common between at least two factors.

Tong G, Grant PA, Am J Obstet Gynecol. 2013; 208:1198.

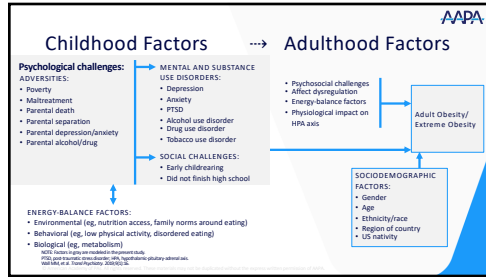
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Psychosocial Factors Attributing to Obesity

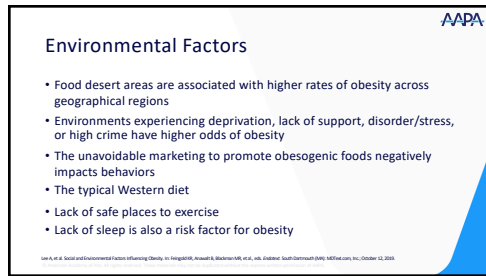
- **Sociodemographic factors**
 - Gender (women > men)
 - Age
 - Ethnicity/race/culture
 - Educational attainment (high school education or less)
- **Mental illness and substance use disorders** (depression, anxiety and eating disorders)
- **Adverse childhood experiences—sexual/physical abuse and neglect**
 - 50% of people with severe obesity reported some form of emotional neglect during childhood

Wahl ME, et al. Transl Psychiatry. 2016;6(2):16.

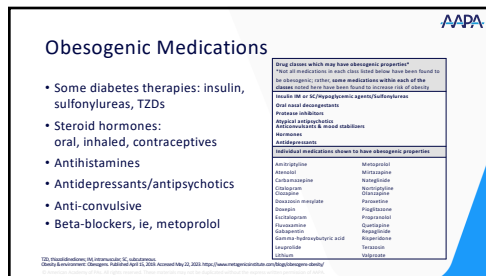
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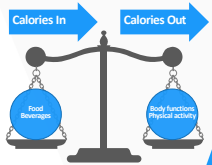
Adipose tissue, inflammation, and dysfunction

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More to the Story than Energy Intake and Expenditure

- Most people have been taught that losing weight is a matter of simple math, like calories in and calories out
- Experts are learning that this decades-old strategy is inaccurate and that, in fact, obesity is a multifactorial disease, with a complex pathophysiology



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Role of Adipose Tissue

- Adipose tissue contains a vast variety of cell types¹
- Excess caloric intake induces cellular remodeling to accommodate demand for triglyceride storage²
- Lack of cellular remodeling can cause cellular stress resulting in inflammation and inability to accommodate increased triglyceride load²
- Result: systemic ectopic lipid deposition (liver, muscle, pancreas) leading to lipotoxicity²

1. Madsen S, et al. Nat Rev Endocrinol. 2014;10(12):721-31. 2. Hebling N, et al. Endocrinol Metab Clin North Am. 2008;13(2):323-342. doi:10.1016/j.encl.2008.03.002

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Role of Energy Balance in Body Weight

Molecules Acting on Long-Term Energy Balance

Body Weight

Energy Intake

Ingestion of:

- Proteins
- Fats
- Carbohydrates

All energy comes from consumed food and drink

Energy Expenditure

- Physical activity
- Diet-induced thermogenesis
- Basal metabolic rate

When energy consumed **exceeds** energy expenditure, 60-80% of energy surplus is stored in fat

1. Madsen et al. *Physiol Rev*. 2013;93(4):1303-1324. 2. Leibel et al. *J Clin Invest*. 1995;95(5):2429-2437. 3. Leibel et al. *J Clin Invest*. 1995;95(5):2429-2437. 4. Leibel et al. *J Clin Invest*. 1995;95(5):2429-2437. 5. Leibel et al. *J Clin Invest*. 1995;95(5):2429-2437.

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Role of Energy Balance in Body Weight

CONVENTIONAL MODEL

↓ Energy intake

↓ Energy expenditure

↓ Energy balance

↓ Fat storage (energy surplus)

CARBOHYDRATE-INSULIN MODEL

↓ Energy intake

↓ Energy expenditure

↓ Energy balance

↓ Fat storage (energy surplus)

1. Ludwig et al. *N Engl J Med*. 2013;369(12):917-927. 2. Ludwig et al. *N Engl J Med*. 2013;369(12):917-927. 3. Ludwig et al. *N Engl J Med*. 2013;369(12):917-927.

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Role of Resting Metabolic Rate in Energy Balance

- Humans take in energy through the intake of food and drink and expend energy through the resting metabolic rate (RMR)—the thermic effect (TEF) of food and physical activity
- The RMR is the energy expenditure required for maintaining normal body functions and homeostasis. The RMR is proportional to body mass, in particular fat-free mass!
- The components of energy balance influence each other and serve to maintain a constant body mass. For example, when calorie intake is reduced, the body responds by both stimulating hunger and reducing the RMR so that less energy is expended!

1. Madsen et al. *Physiol Rev*. 2013;93(4):1303-1324. 2. Leibel et al. *J Clin Invest*. 1995;95(5):2429-2437. 3. Leibel et al. *J Clin Invest*. 1995;95(5):2429-2437.

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Peripheral and Central Signals Controlling Energy Intake

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Appetite Regulation

The brain is the master regulator of food intake

Appetite is mainly regulated by three systems:

- Agouti-related protein (AGRP) neurons that stimulate food intake
- Neurons in lateral hypothalamus that increase food intake
- Neurons in the parabrachial nucleus that suppress food intake

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The Role of Hormones

Satiety Hormones

AGRP neurons

HUNGER → Homeostatic Eating

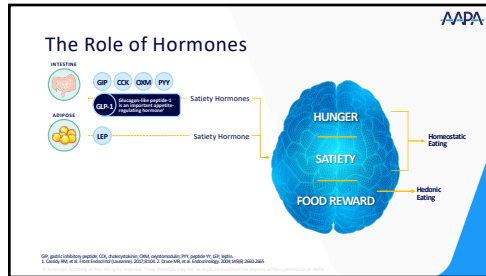
SATIETY → Hedonic Eating

FOOD REWARD → Hedonic Eating

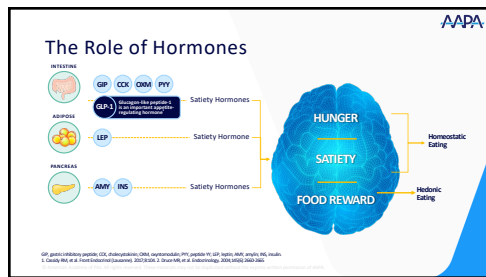
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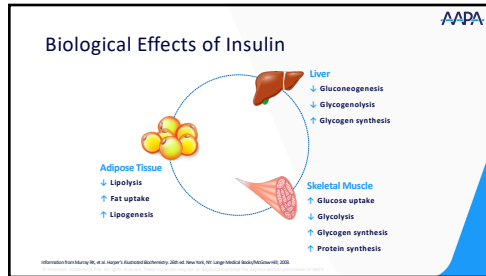


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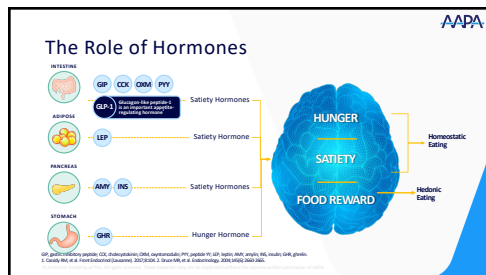
Insulin

- Insulin is secreted by pancreatic β -cells. Its levels are also positively correlated with body weight and adipose mass, and they provide a negative feedback signal to the central nervous system¹
- Like leptin, high levels of insulin result in reduced food intake; obesity is characterized by insulin resistance and hyperglycemia²
- According to some studies, increased insulin secretion contributes to obesity pathogenesis by stimulating the adipocyte uptake of fatty acids and glucose and the caloric storage in form of fat, while concomitantly inhibiting lipolysis³

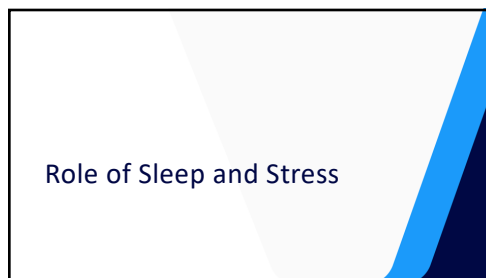
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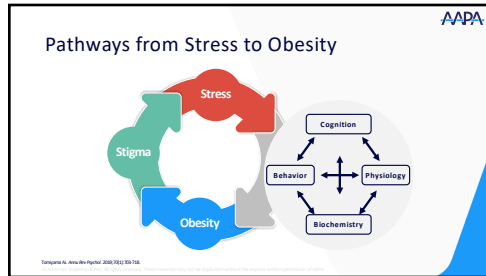
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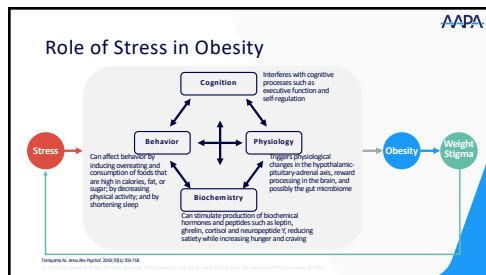
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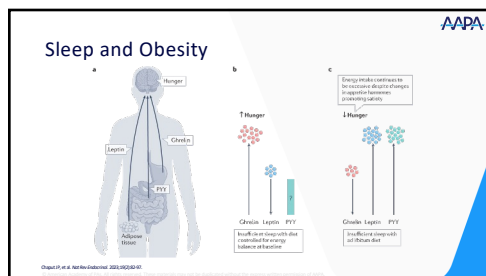
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Short Sleep Can Negatively Impact Weight Homeostasis

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- Multiple pathways are likely to mediate the adverse effect of sleep loss on the risk of obesity. Several of these pathways interact with one another!
- Another important mechanism is brain glucose utilization, which appears to be reduced after sleep deprivation?

```

    graph TD
      A[INSUFFICIENT SLEEP] --> B["↓ Ghrelin  
↓ Leptin"]
      B --> C["↑ Appetite"]
      C --> D["↑ Energy intake  
(especially after dinner)"]
      D --> E[Positive energy balance]
      E --> F["↑ 24h energy expenditure"]
  
```

*When energy intake is controlled, opposite effects when energy intake is allowed.
 †Chaput et al. Nat Rev Endocrinol. 2015;11(12):739-749. doi:10.1038/nrendo.2015.104

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How Does Lack of Sleep Affect the Human Body?

AAPA

Insufficient sleep and circadian misalignment are important metabolic stressors and are associated with weight gain and obesity.

```

    graph TD
      A[Brief Sleep] --> B["Disturbed feeling of hunger  
and satiety"]
      A --> C["↓ secretion of ghrelin  
↓ Leptin secretion"]
      A --> D["↓ sensitivity of the tissue to insulin"]
      A --> E["↑ appetite for sweets"]
      B --> F["↑ food intake  
↑ calorie content of the diet"]
      C --> F
      D --> F
      E --> F
      F --> G[Overweight/obesity]
      A --> H["Delayed and reduced REM  
phase"]
      A --> I[night craves]
      A --> J["Reduced sleep performance"]
      A --> K["Decreased quality of sleep"]
      A --> L["Increased number of  
awakenings"]
  
```

Chaput et al. Nat Rev Endocrinol. 2015;11(12):739-749. doi:10.1038/nrendo.2015.104

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Metabolic Adaptation

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Metabolic Adaptation

- The physiology of weight loss creates a tug of war in the brain and body



- Metabolic adaptation is the body's biological drive to regain the body mass that was lost
- The body reacts by slowing metabolism and altering appetite-regulating hormones

Phenology of Weight Loss, Published Online 2012. Accessed May 21, 2023. <http://www.iftkitchen.com/metabolic-adaptation/>

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Why Does This Happen?

Two Hypotheses:

- 1 Thrifty Gene Hypothesis:**

Several thousand years ago, environmental pressures and natural selection would favor those who could survive long periods of famine when food was scarce.
- 2 Hypothalamic Feeding Center – Adipostat:**

There's an axis between all our organs and CNS that would tightly control food intake in the long term.

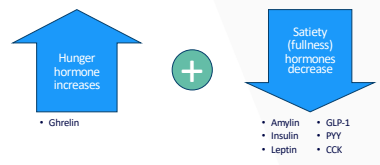
 - The system receives afferent signals arising from hormones (leptin, ghrelin, insulin, etc.) to the gut or adipose tissue that would establish a "set point" of energy reserves primarily in the form of adipose tissue and organ glycogen storage thresholds.

ONE, several thousand years ago. Nutrition Science 142, March 2014. Metabolic adaptation to weight loss: A brief review. J Strength Cond Res. 2012;26(10):2848-2854. doi:10.1519/JSC.0b013e3182444444

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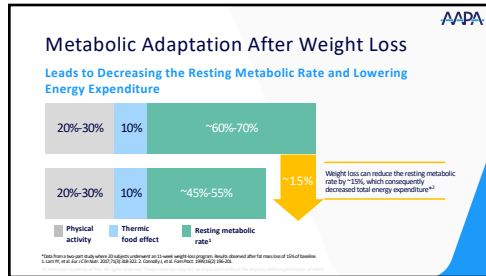
As the Body Loses Weight, Metabolic Adaptation Occurs by Affecting Hormonal Changes



- Ghrelin
- Amylin
- Insulin
- Leptin
- GLP-1
- PYY
- CCK

GLP-1, ghrelin, insulin, PYY, amylin, CCK, cholecystikinin. Phenology of Weight Loss, Published Online 2012. Accessed May 21, 2023. <http://www.iftkitchen.com/metabolic-adaptation/>

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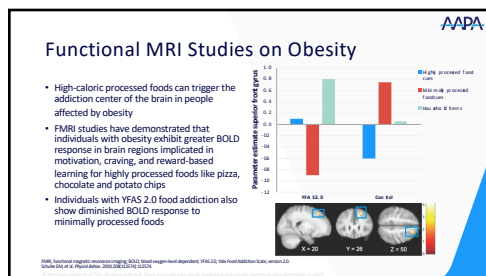
Difficulties of Long-Term Management

Metabolic Adaptation / Set Point Observation

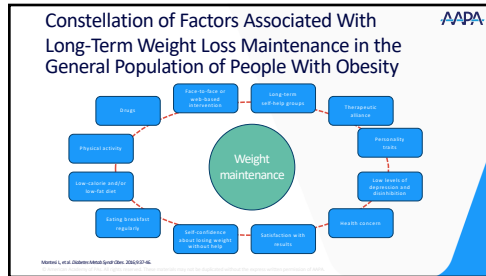
- Dopamine modulates motivation and reward thus dopamine deficiency perpetuates pathological eating to compensate for decreased activation of dopamine!
- The action of GLP-1 is impaired in people with obesity even in those with normal glucose tolerance, resulting in increased gastric emptying and decreased satiety signaling?
- Thus, people with obesity have decreased dopamine receptors and decreased GLP-1 action and are therefore less satisfied by food, have fewer feelings of satiety, and are prone to eat highly caloric food to compensate?

GLP-1 (glucagon-like peptide 1)
1. Wang, et al. Nature 2003;393(6692):681-687. 2. Madsbad, et al. Diabetologia 2004;47(12):2129-2135.

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Conclusions

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THANK YOU

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