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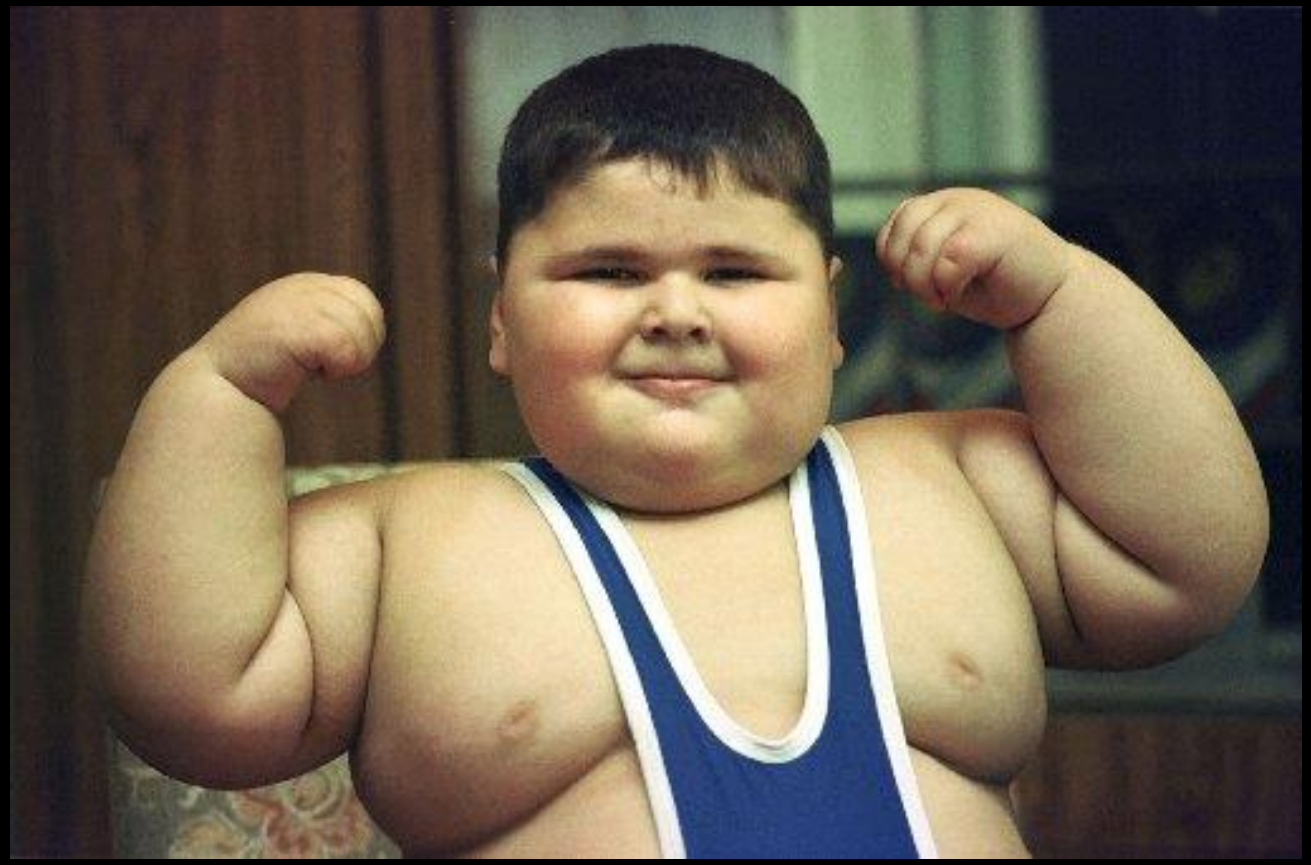
# Obesity



# Obesity

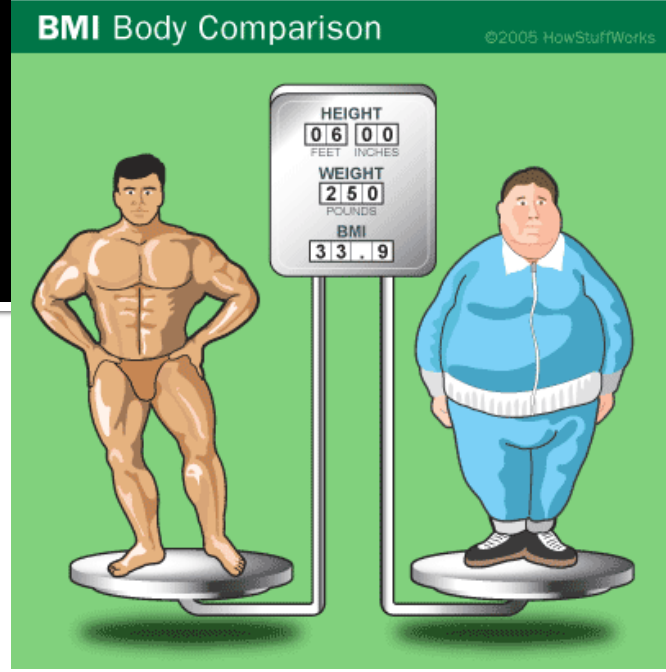
- A disorder affecting body weight regulatory systems
- Characterized by an accumulation of excess body fat
- Primitive societies vs. developed ones! (availability & activity)
- Prevalence increases with age
- Risk of associated diseases (diabetes, hypertension, cardiovascular disease)
- Childhood obesity: three fold increase in prevalence over the last four decades
- In fact, there are more obese than undernourished individuals worldwide

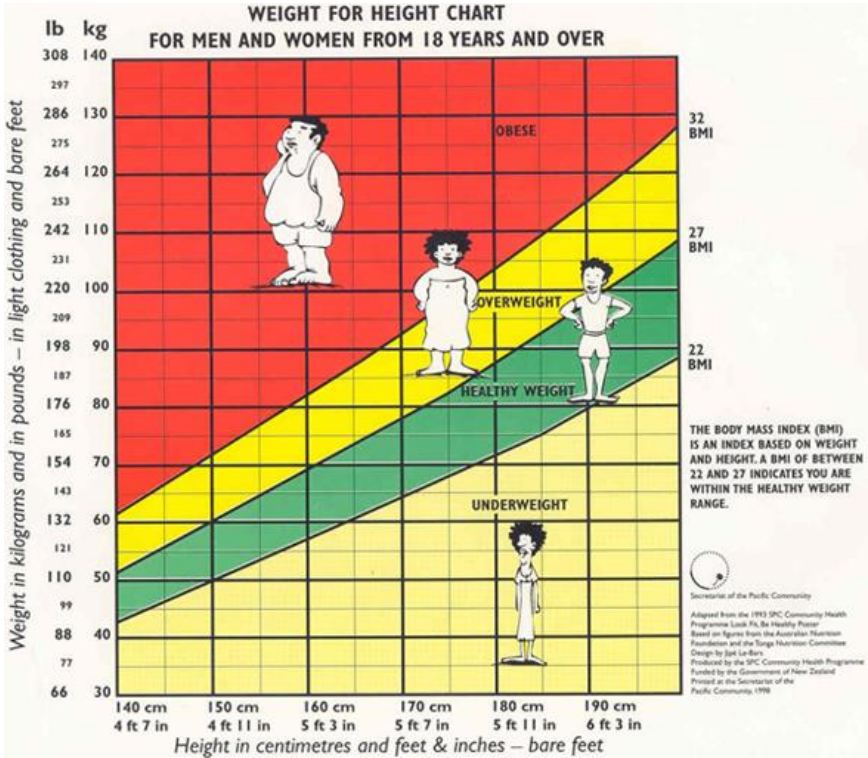
# Statistics

- Approximately 17% of those age 2–19 years are obese
- In USA:
  - Lifetime risk of becoming overweight ~ 50%
  - Lifetime risk of becoming obese is ~ 25%
- Worldwide: 650,000,000 - WHO 2016
- Jordan: 2,800,000 - WHO 2016

# Assessment of Obesity

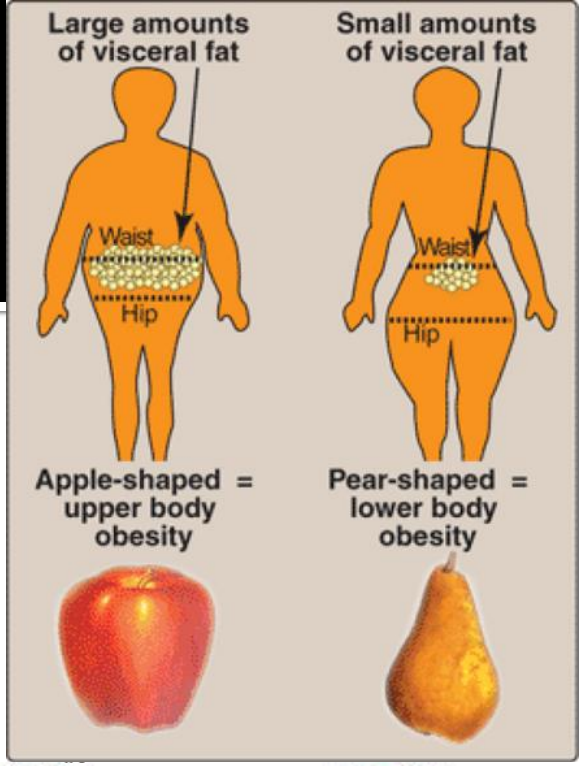
- 1. Body mass index: (exceptions - athletes)
- A measure of relative weight, adjusted for height
- Allows comparisons both within & between populations
- BMI = (weight in kg)/(height in meters)2
- Healthy = 18.5-24.9; Overweight = 25-29.9; Obese = ≥30; morbidly obese >40
- ≈ 2/3 of American adults are overweight & > 36% are obese



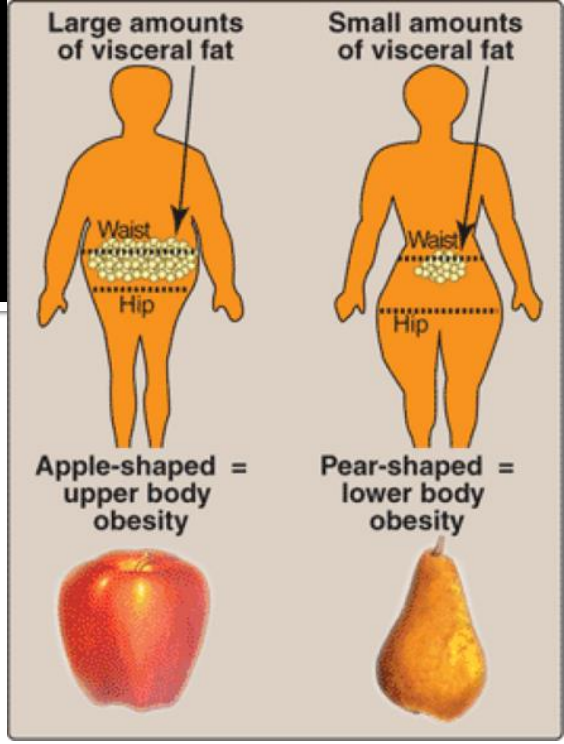
# Assessment of Obesity

- 2. Waist circumference: ≥40 in (2.54cm) (men) and ≥35 in (women)
- 3. Anatomic differences in fat deposition (W/H ratio)
- Android, "apple-shaped," or upper body obesity: excess fat located in the central abdominal area
  - Associated with a greater risk for hypertension, insulin resistance, diabetes, dyslipidemia, & coronary heart disease
  - Waist to hip ratio: >0.8 for women & > 1.0 for me



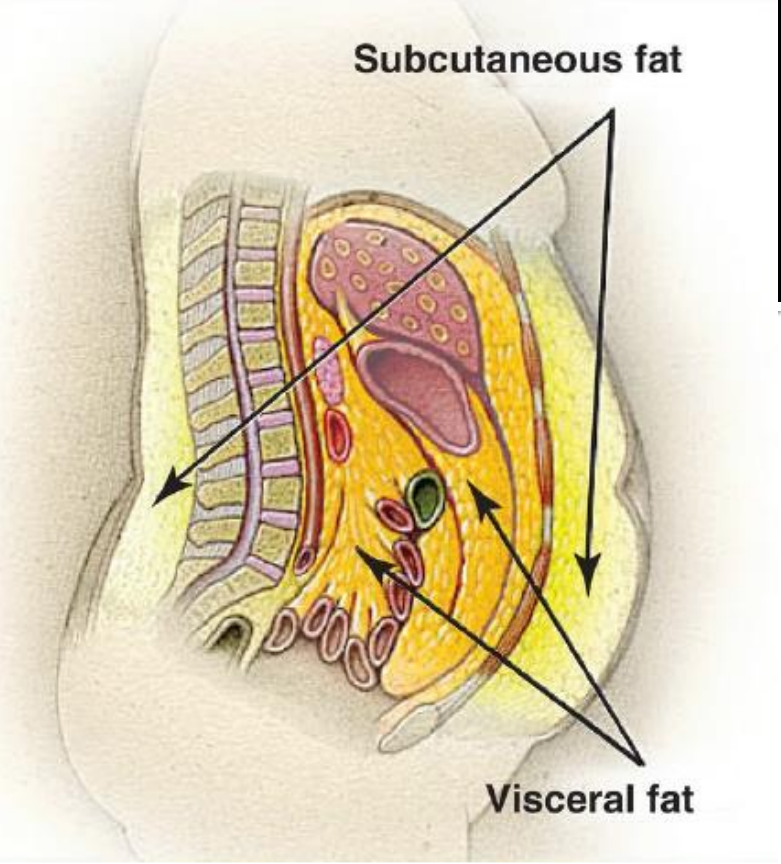

# Assessment of Obesity

- Gynoid, "pear-shaped," or lower body obesity: fat distributed in the lower extremities around the hips or gluteal region
  - Waist to hip ratio: < 0.8 for women & < 1.0 for men
  - Relatively benign health wise
  - Commonly found in females




# Assessment of Obesity

- Biochemical differences in regional fat depots

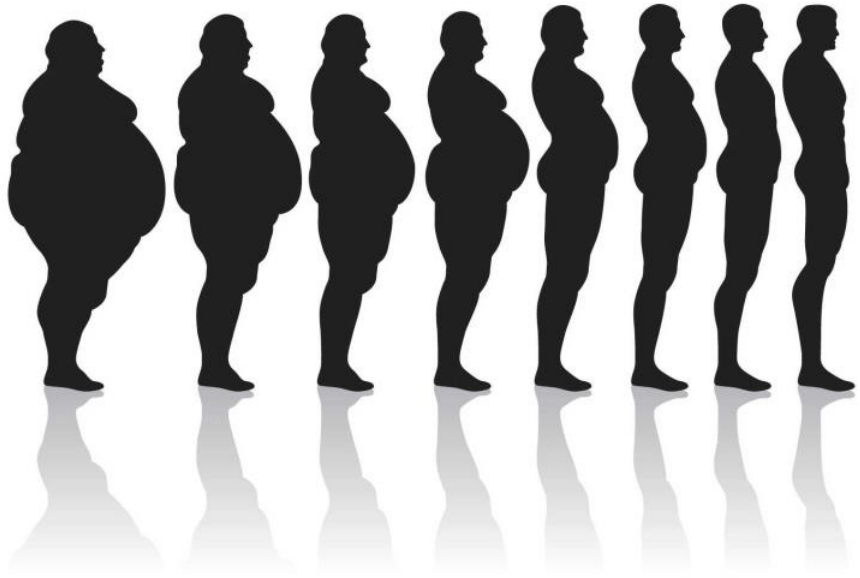



A. Abdominal fat:
  - Cells are much larger
  - Higher rate of fat turnover
  - Hormonally more responsive
  - Readily mobilizable: men lose weight more readily than women
  - Portal vein: fatty acids may lead to insulin resistance & increased synthesis of triacylglycerols, which are released as very-low-density lipoprotein (VLDL)

# Assessment of Obesity

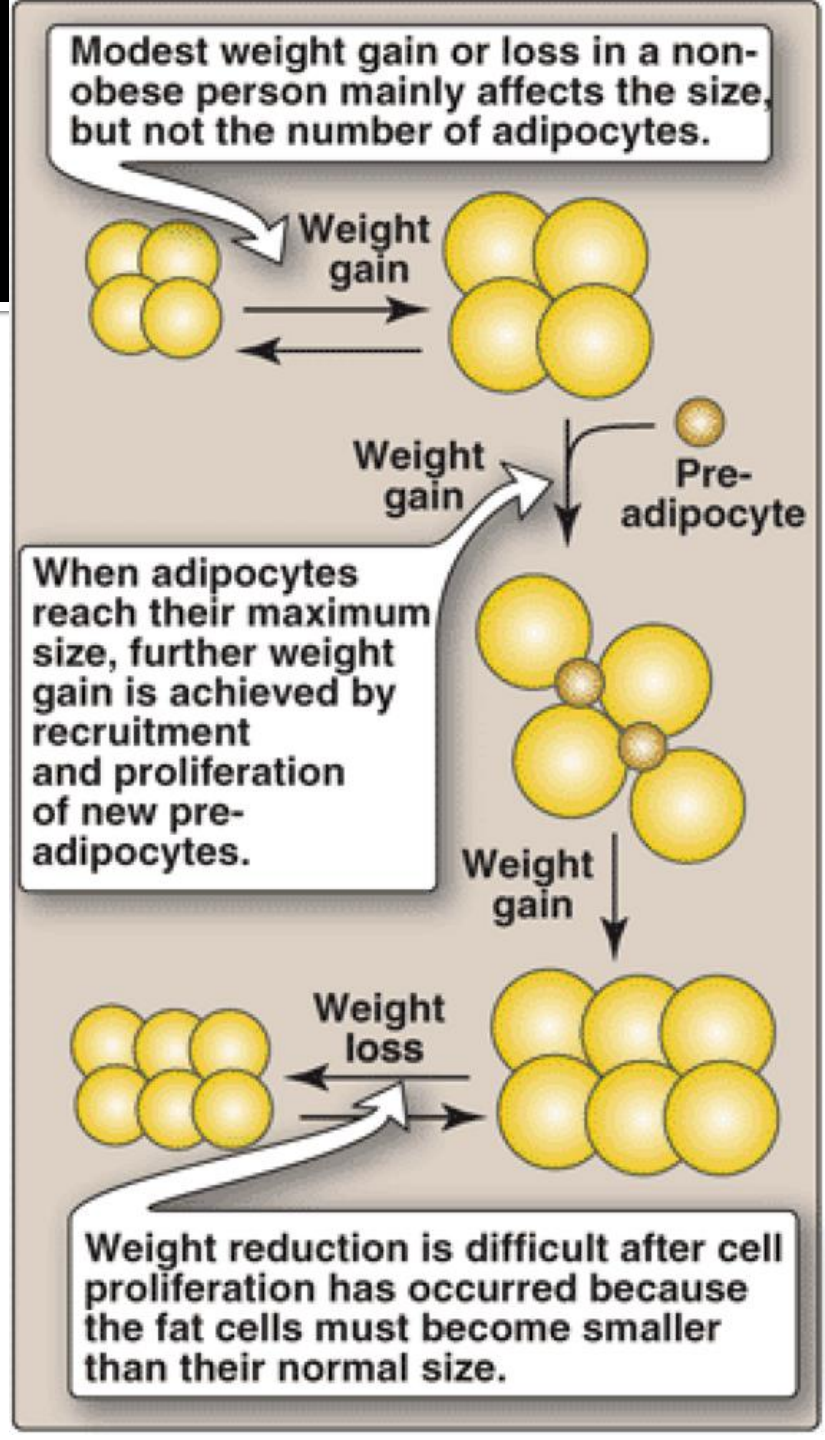
- Biochemical differences in regional fat depots

B. Gluteal fat: fatty acids from gluteal fat enter the general circulation, & have no preferential action on hepatic metabolism



# Assessment of Obesity

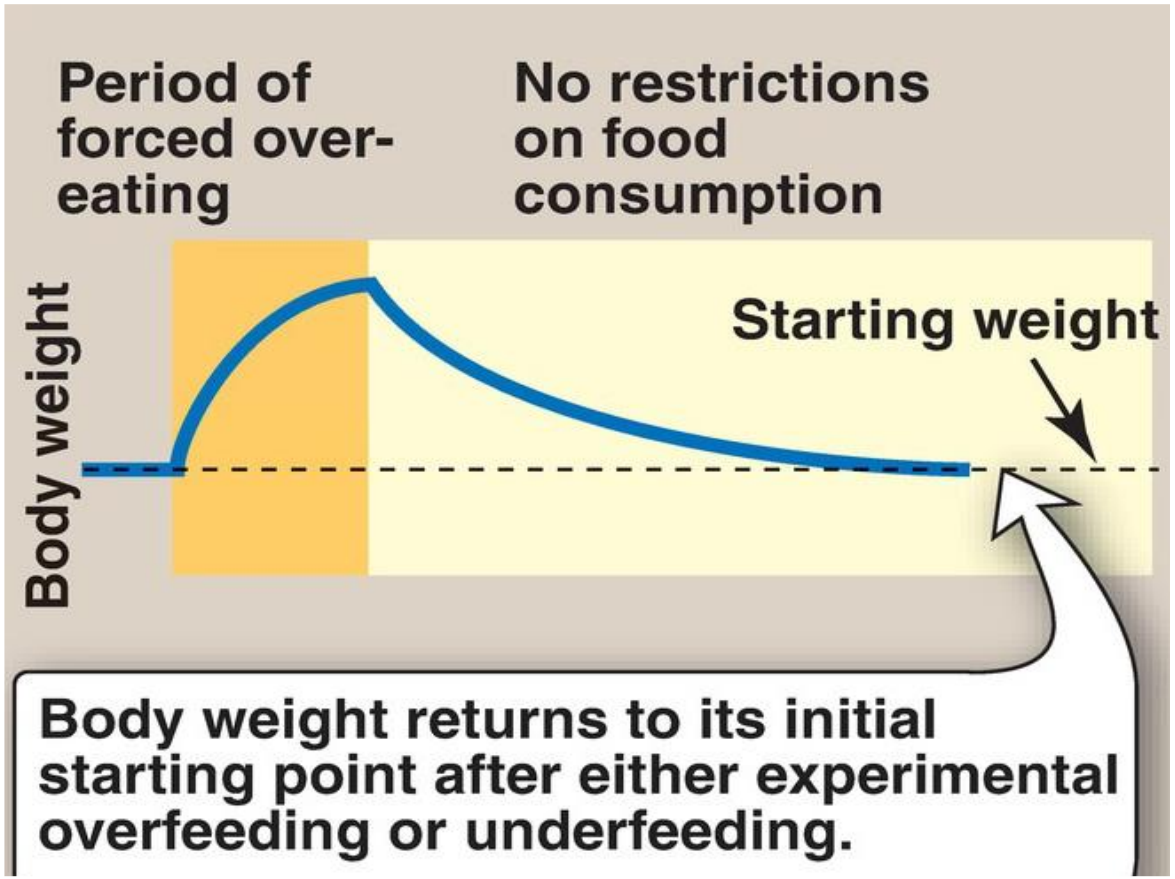
- Number of fat cells
- The ability of a fat cell to expand is limited (2-3 folds)
- Fat cells, once gained, are never lost! (10 years cycle)
- Formerly obese patients have a particularly difficult time maintaining their reduced body weight

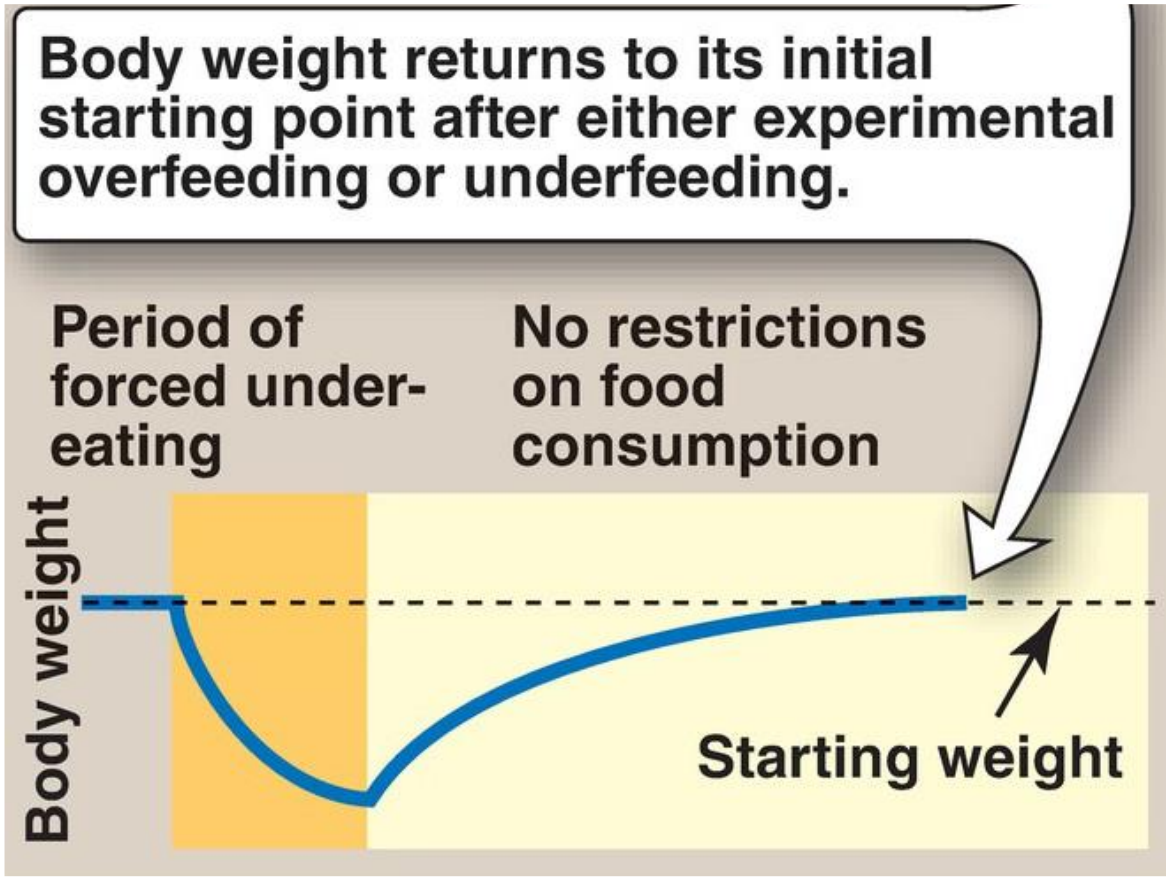


# Body Weight Regulation

***Body weight is stable as long as the behavioral & environmental factors that influence energy balance are constant***

# The concept of a set point! – not a 100%



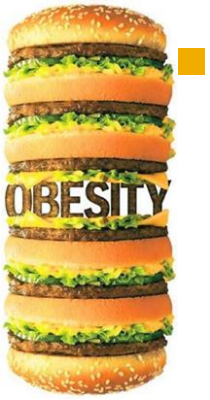



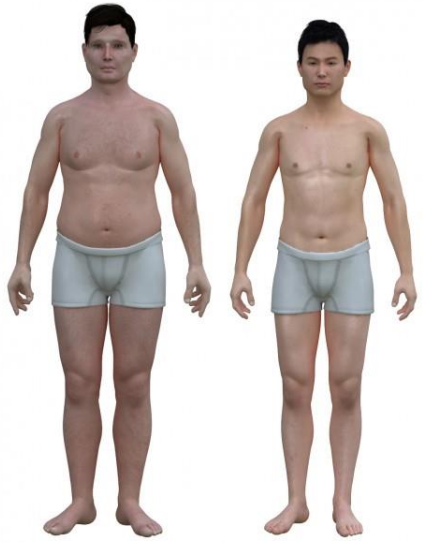
# A. Genetic contributions to obesity

- Uncontrolled, greedy eating behavior
- Genetic mechanisms play a major role in body weight (rather than a lack of willpower)
- Often observed clustered in families
- 80% when parents fat, 9% when parents are lean
- Inheritance is not simple mendelian genetics (a complex polygenic disease)
- Adopted children usually correlates with biologic parents
- Identical twins have very similar BMI

# B. Environmental & behavioral contributions

- The epidemic of obesity occurring over the last four decades! genetic factors are stable on this short time scale



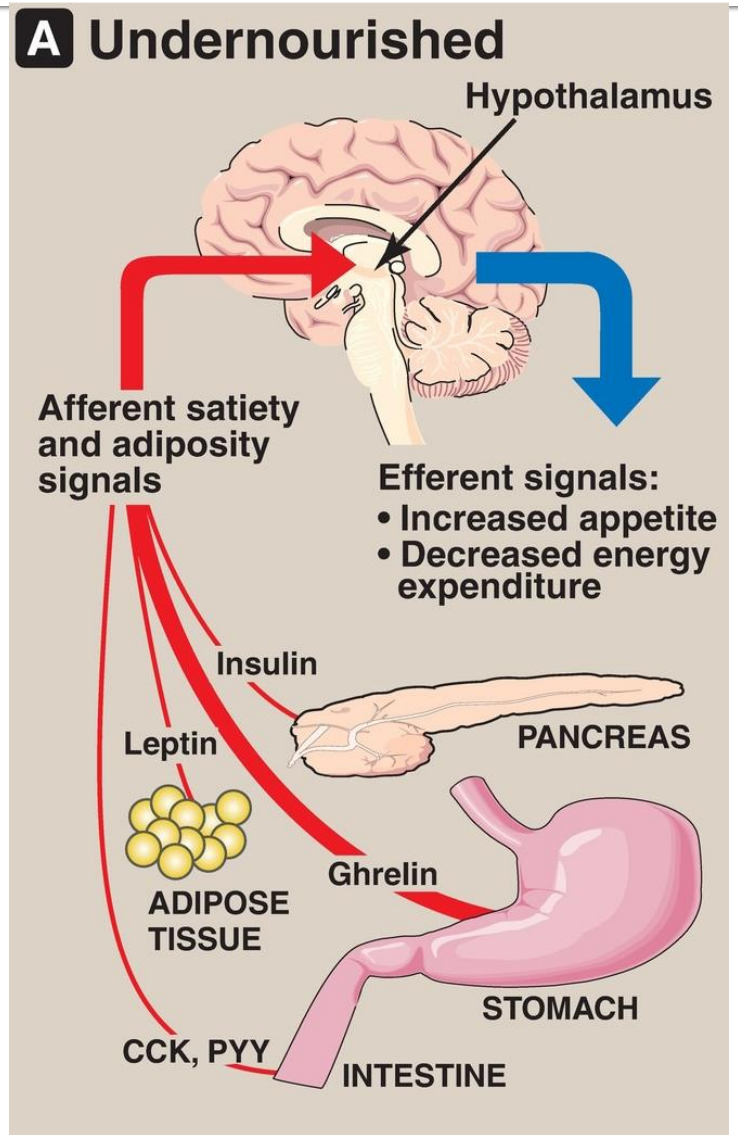
- Environmental & behavioral:
  - Ready available food
  - Energy-dense food
  - Sedentary lifestyles: TV, cars, computer (energy-sparing)
  - Eating behaviors: snacking, portion size, number of people

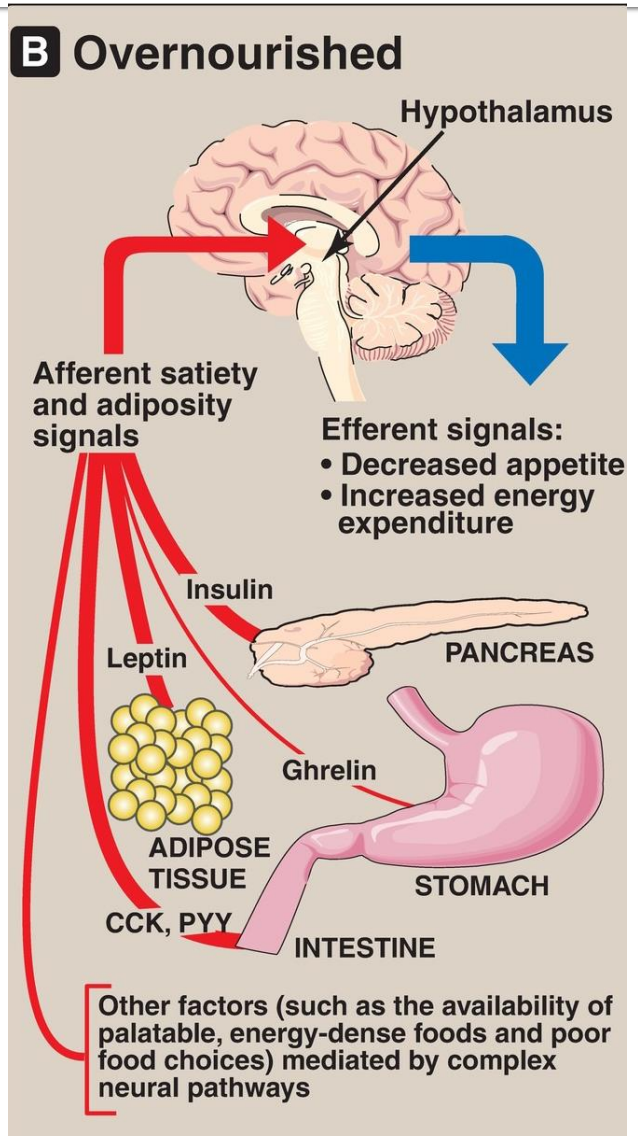
- Men in Japan (aged 46–49 years) are lean (BMI = 20), in California (BMI = 24)

# Molecules that Influence Obesity

Obesity results when energy intake exceeds energy expenditure

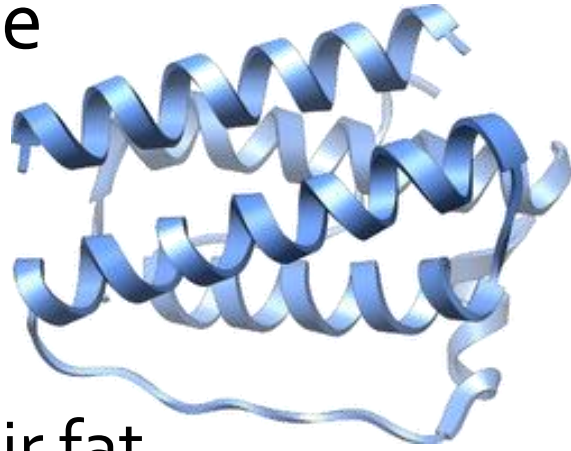
# Molecular influences

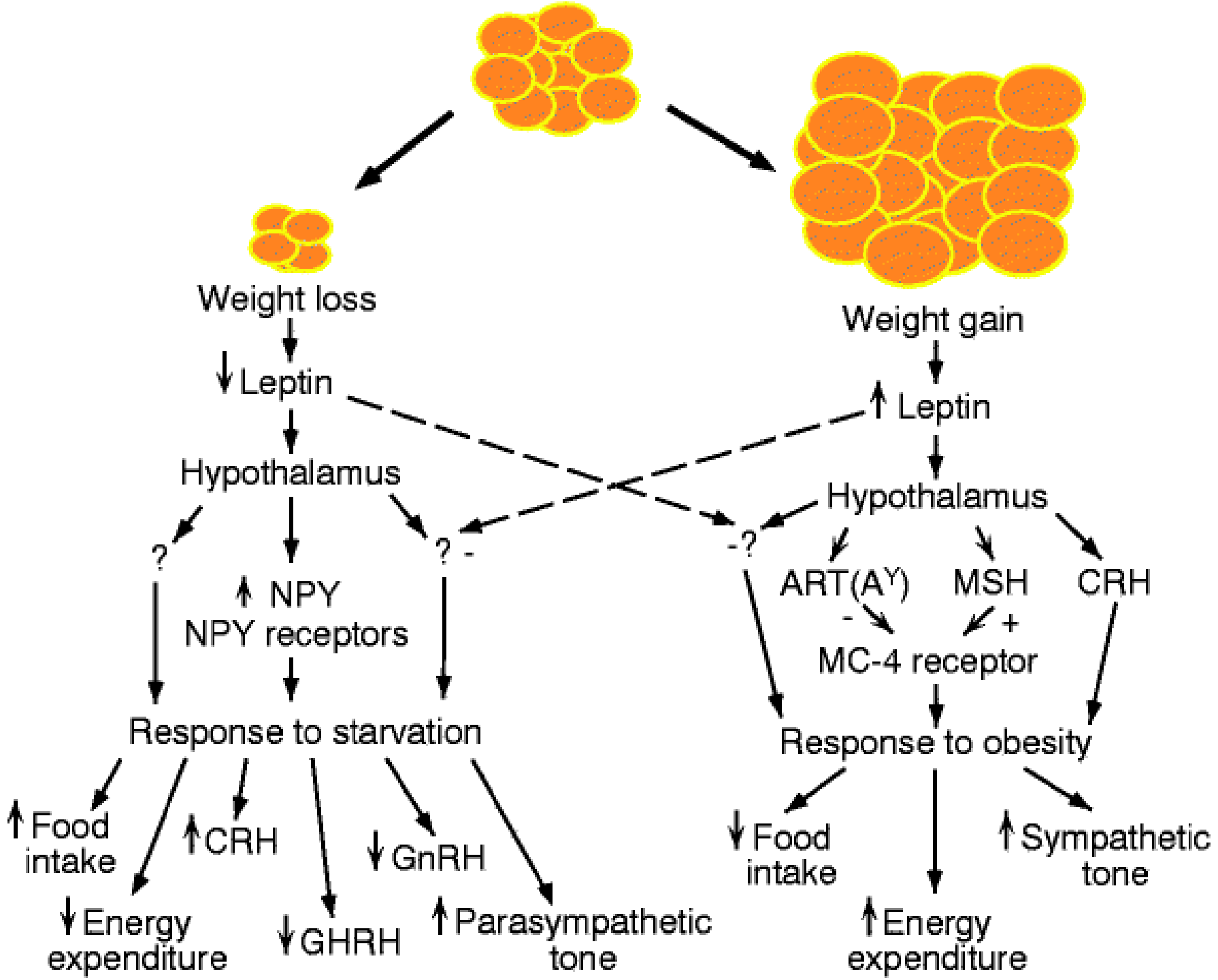


# Long Term Signals

- Reflect the status of fat (TAG) stores
- 1. Leptin: Structure, product of ob gene, Produced proportionally to the adipose mass, Informs the brain of the fat store level, Regulate body fat through the control of appetite & energy expenditure (an anorexigenic effect)
  - Daily injection of leptin in mice
  - Plasma leptin in obese humans is usually normal for their fat mass (resistance to leptin rather than deficiency)




Weight loss
Leptin
Hypothalamus
?
NPY
NPY receptors
? -
Response to starvation
Food intake
Energy expenditure
CRH
GHRH
GnRH
Parasympathetic tone
Weight gain
Leptin
Hypothalamus
-?
ART(AY)
MSH
CRH
-
+
MC-4 receptor
Response to obesity
Food intake
Energy expenditure
Sympathetic tone

# Long Term Signals

- 2. Insulin:
  - Obese individuals are also hyperinsulinemic
  - Like leptin, insulin acts on hypothalamic neurons to decrease appetite
  - Obesity is associated with insulin resistance

# Short Term Signals

- From the GI tract (control hunger and satiety)
- Affect size and number of meals (over minutes to hours)

- In the absence of food intake (between meals)
  - Stomach produces ghrelin – orexigenic (appetite-stimulating)

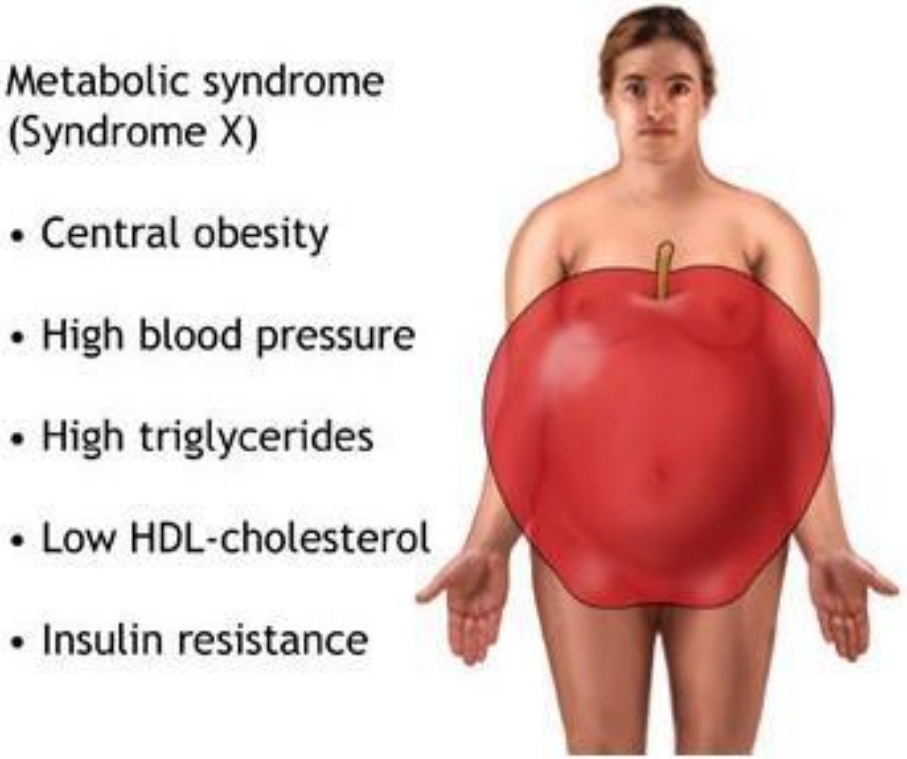
- As food is consumed
  - GI hormones (CCK and peptide YY, …) induce satiety (an anorexigenic effect) → terminating eating

# Short Term Signals

- Within the hypothalamus
  - Neuropeptides (such as orexigenic neuropeptide Y [NPY] and anorexigenic α-MSH and neurotransmitters (such as anorexigenic serotonin and dopamine) are important in regulating hunger and satiety
- Long-term and short-term signals interact
  - Leptin increases secretion of α-MSH and decreases secretion of NPY
  - There are many complex regulatory loops that control the size and number of meals in relationship to the status of body fat stores
- α-MSH (proopiomelanocortin) → ($MC_4R$)
  - Loss-of-function mutations to $MC_4R$ are associated with early-onset obesity

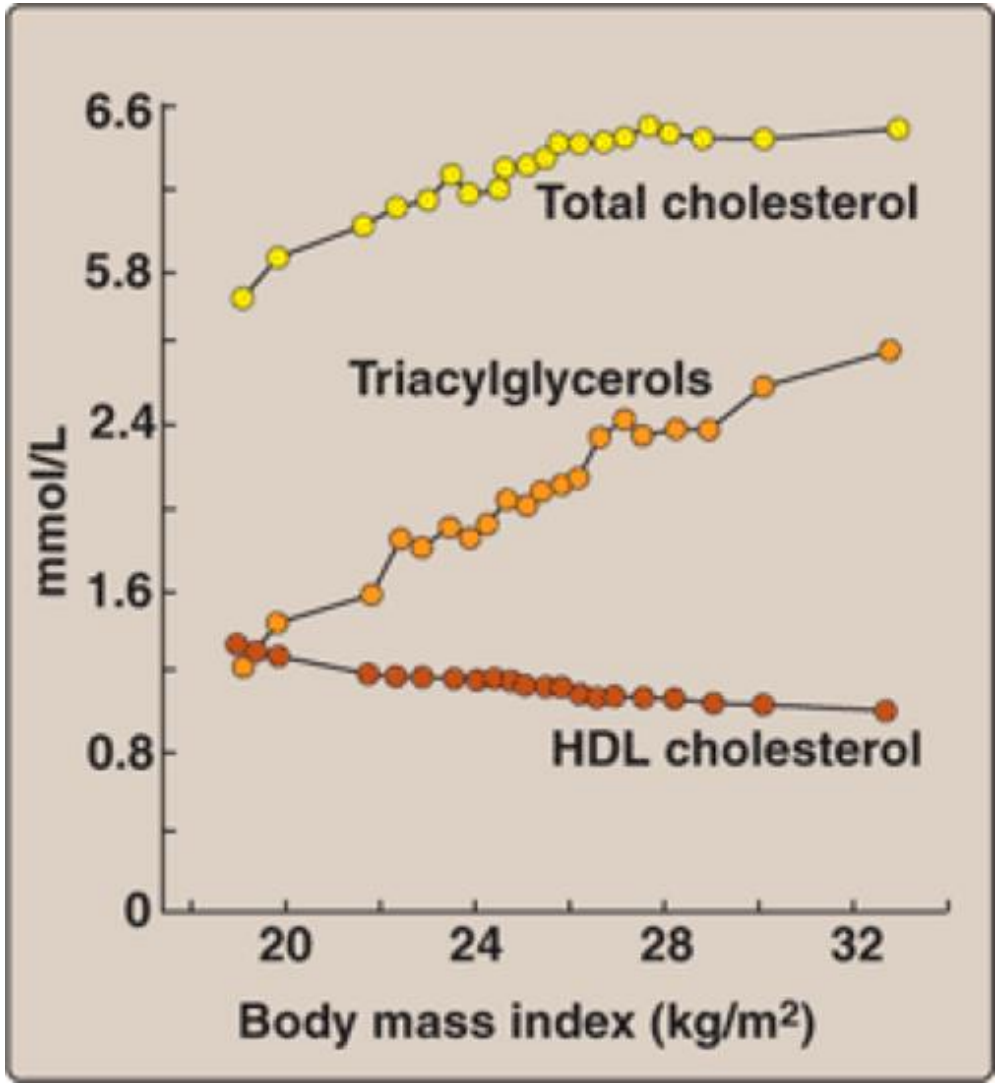
# Metabolic Changes Observed in Obesity

- Metabolic syndrome (insulin resistance syndrome, syndrome X)
  - Glucose intolerance, Insulin resistance, Hyperinsulinemia
  - Dyslipidemia (low HDL & high VLDL)
  - Hypertension
- Increased risk for diabetes mellitus & cardiovascular disorders (men: 4 times higher mortality of cardiovascular disease)
- Dyslipidemia



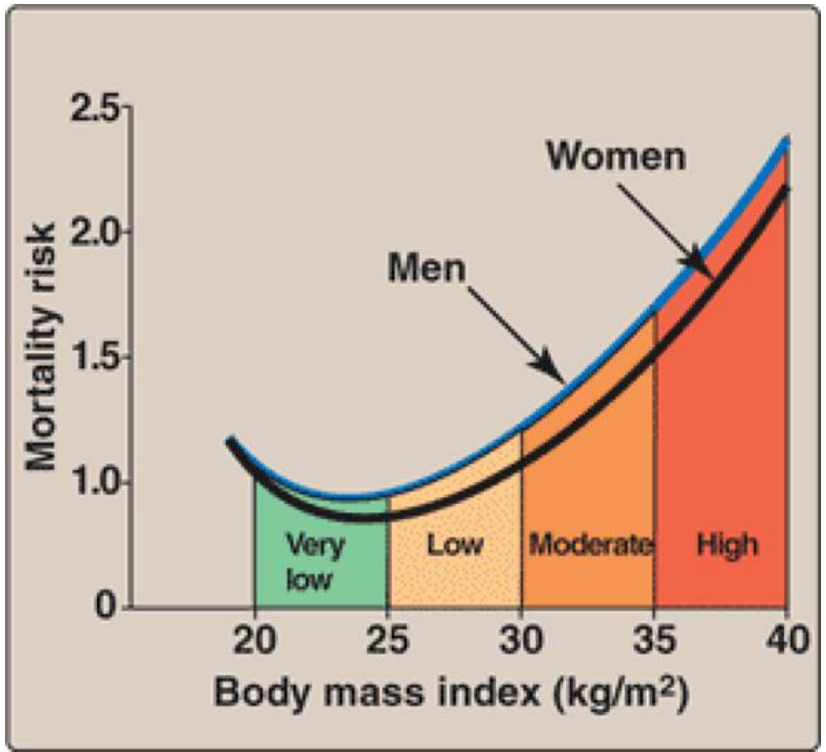
# Metabolic Changes Observed in Obesity

- Insulin resistance causes increased activity of hormone-sensitive lipase, resulting in increased levels of circulating fatty acids
- In liver converted to triacylglycerol & cholesterol
- Released as VLDL, resulting in elevated serum triacylglycerols. Concomitantly, HDL levels are decreased



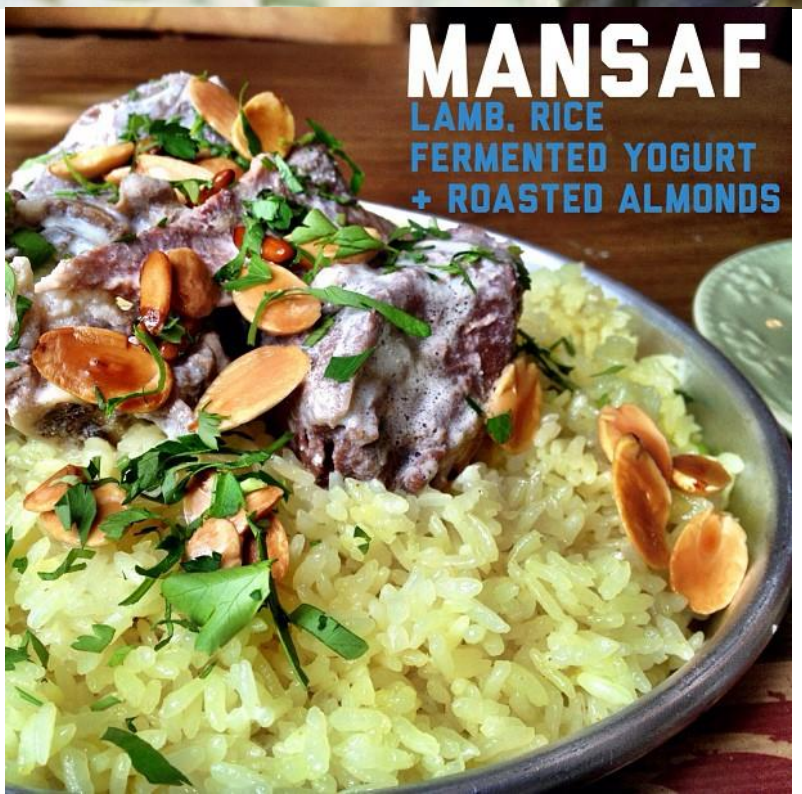
# Obesity and Health

- Correlated with increased risk of death
- Risk factor for:
  - Adult onset diabetes; Hypercholesterolemia; High plasma TAGs; Hypertension; Heart disease; Some cancers; Gallstones; Arthritis; Gout
- The relationship is stronger for <55 yrs
- After age 74, there is no association between increased BMI & mortality



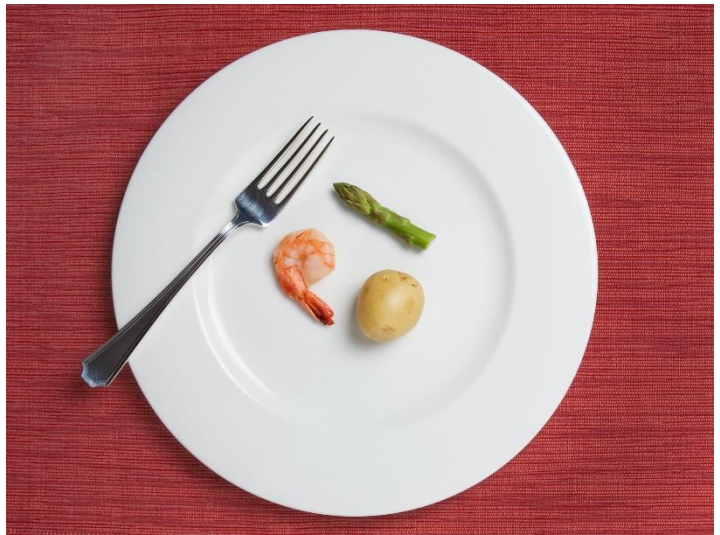
# Weight Reduction

- Physical activity
- Create an energy deficit
- Increases cardiorespiratory fitness
- Combine caloric restriction & exercise with behavioral treatment may lose about 5–10% of body weight over a period of 4–6 months



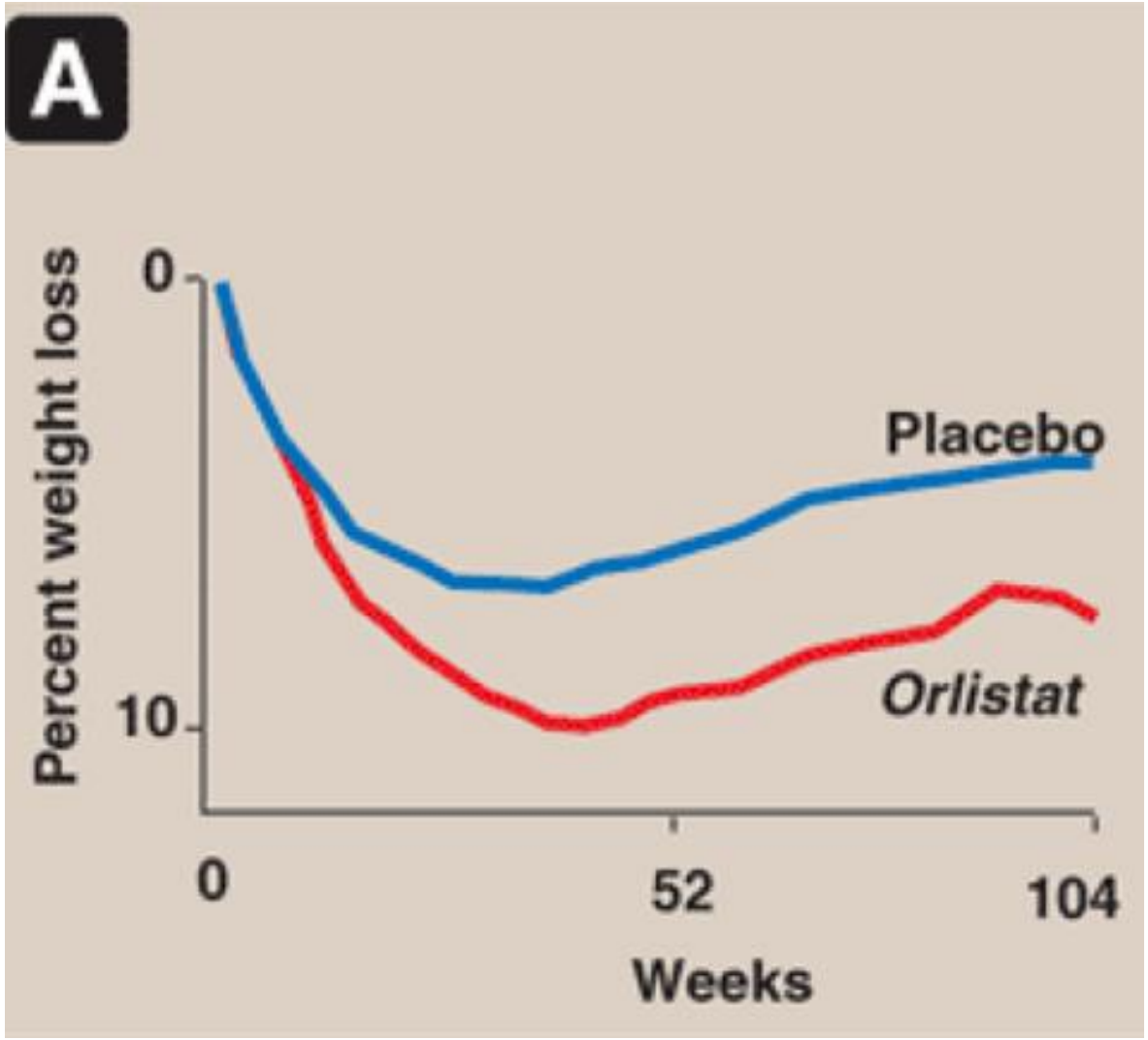
# Weight Reduction

- Caloric restriction
- The most common approach
- 1 pound (454 gm) of adipose tissue corresponds to approximately 3,500 kcal
- Ineffective over the long term for many individuals



# Weight Reduction

- Pharmacologic & surgical treatment
- Two medications (BMI ≥ 30):
  - Sibutramine: appetite suppressant that inhibits the reuptake of both serotonin & norepinephrine
  - Orlistat: lipase inhibitor that inhibits gastric and pancreatic lipases



# Weight Reduction

- Surgical procedures are an option for the severely obese patients
- Surgery produces greater & more sustained weight loss than dietary or pharmacologic therapy, but has substantial risks for complications