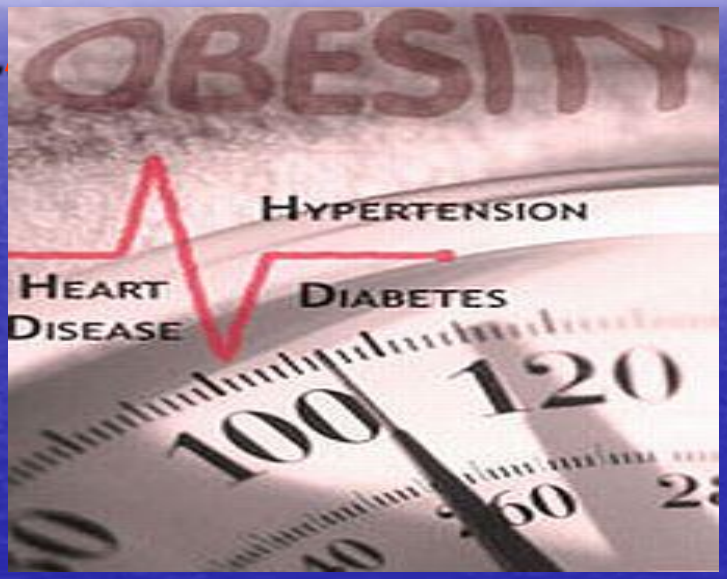
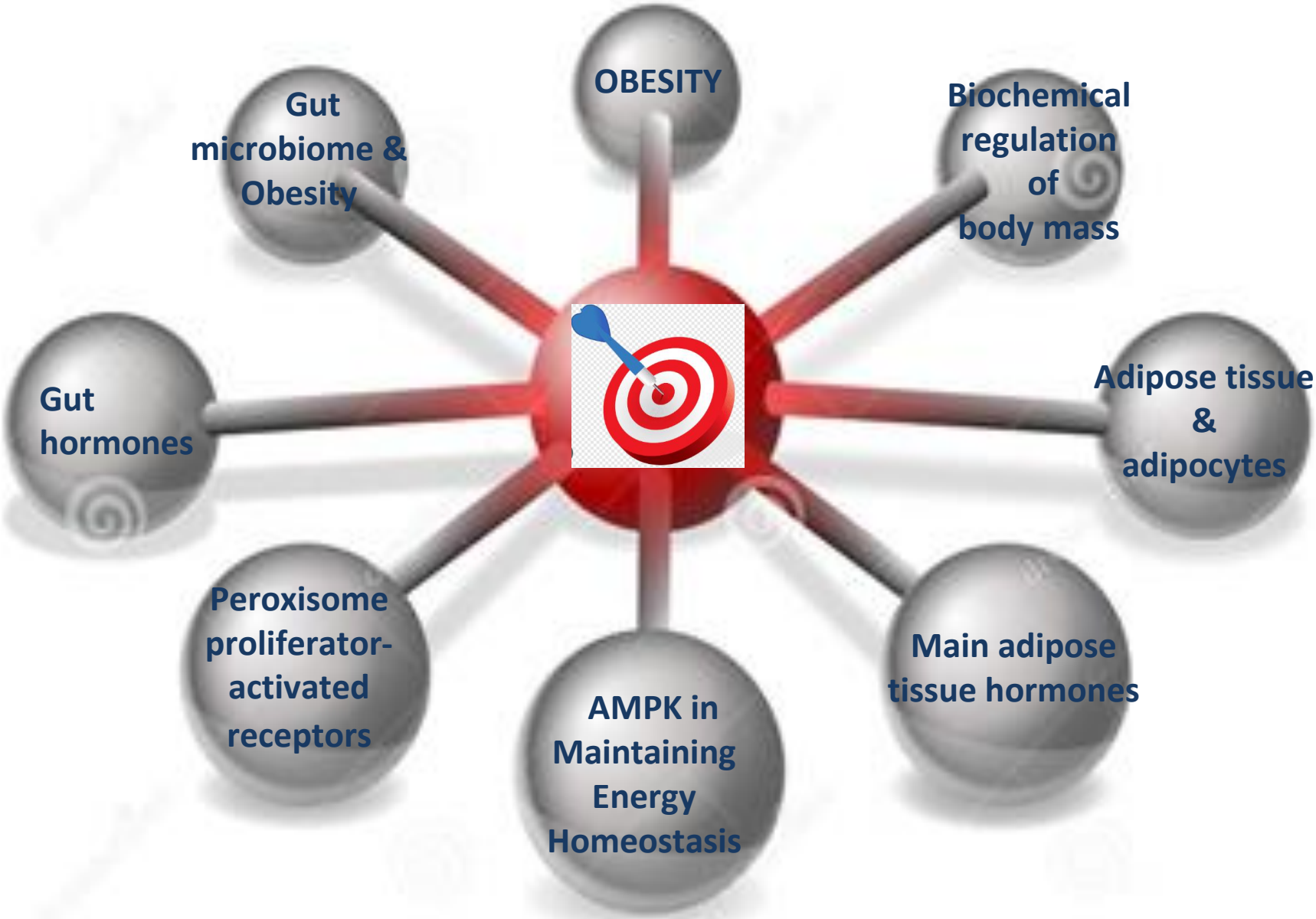
Obesity-Biochemical Regulation of Body Mass-Biochemistry of adipose tissue hormones.



MARIANNA DALAMAGA, MD, MSc, MPH, PhD
Clinical Pathologist-Epidemiologist
PROFESSOR IN BIOLOGICAL CHEMISTRY-CLINICAL BIOCHEMISTRY
MEDICAL SCHOOL, NKUA

EDUCATIONAL AIMS



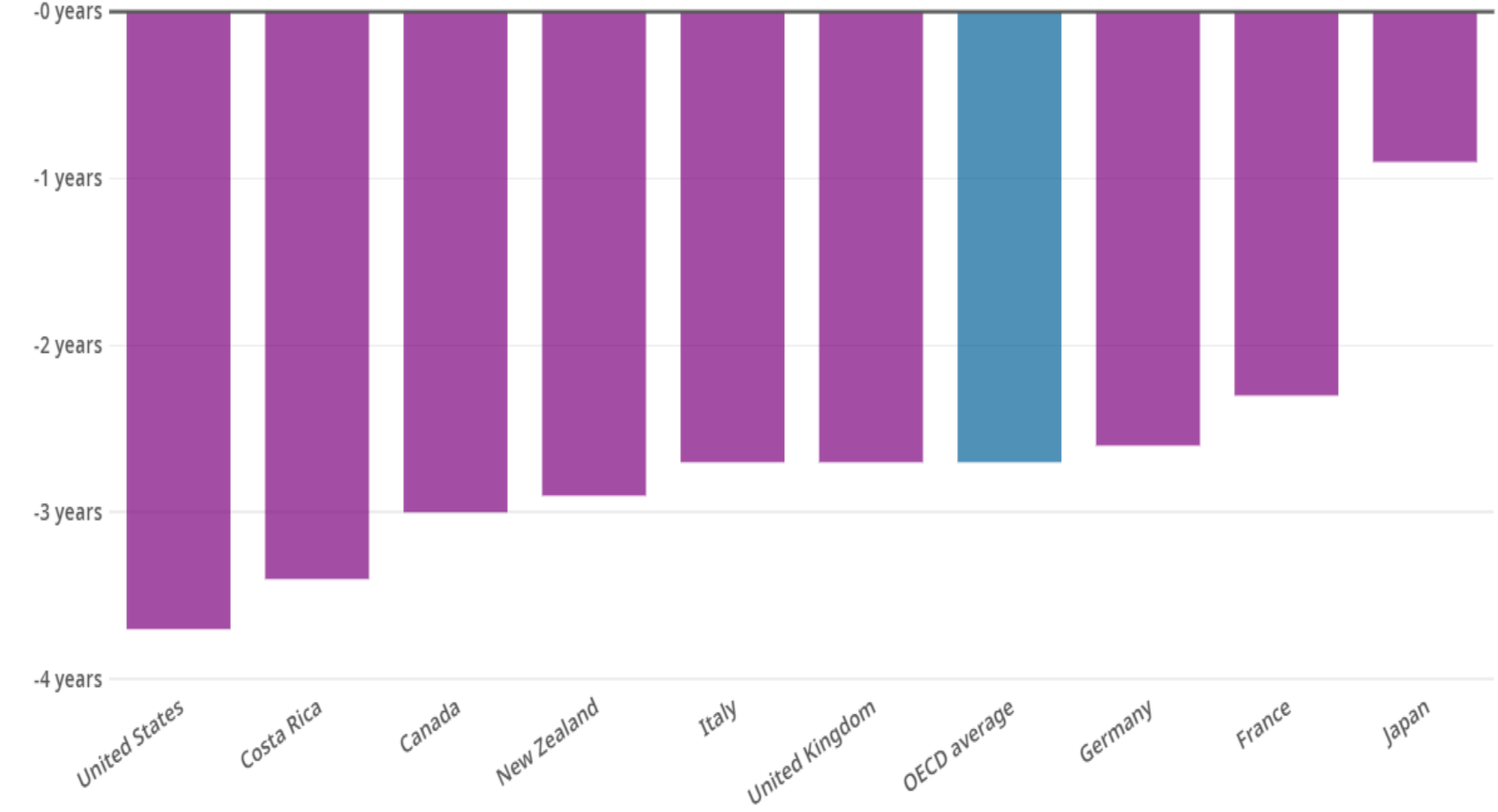
5000 BC-life expectancy
Women 30-33 years
Men: 30-33 years

2020 (EU):
Women: 83.7 years
Men: 78.6 years

The fat lady or the seated lady in a Neolithic settlement on the island of Saliagos around 5,000 BC (Cycladic Art)
Large fat stores gave a survival advantage in the past, but today reduce life expectancy

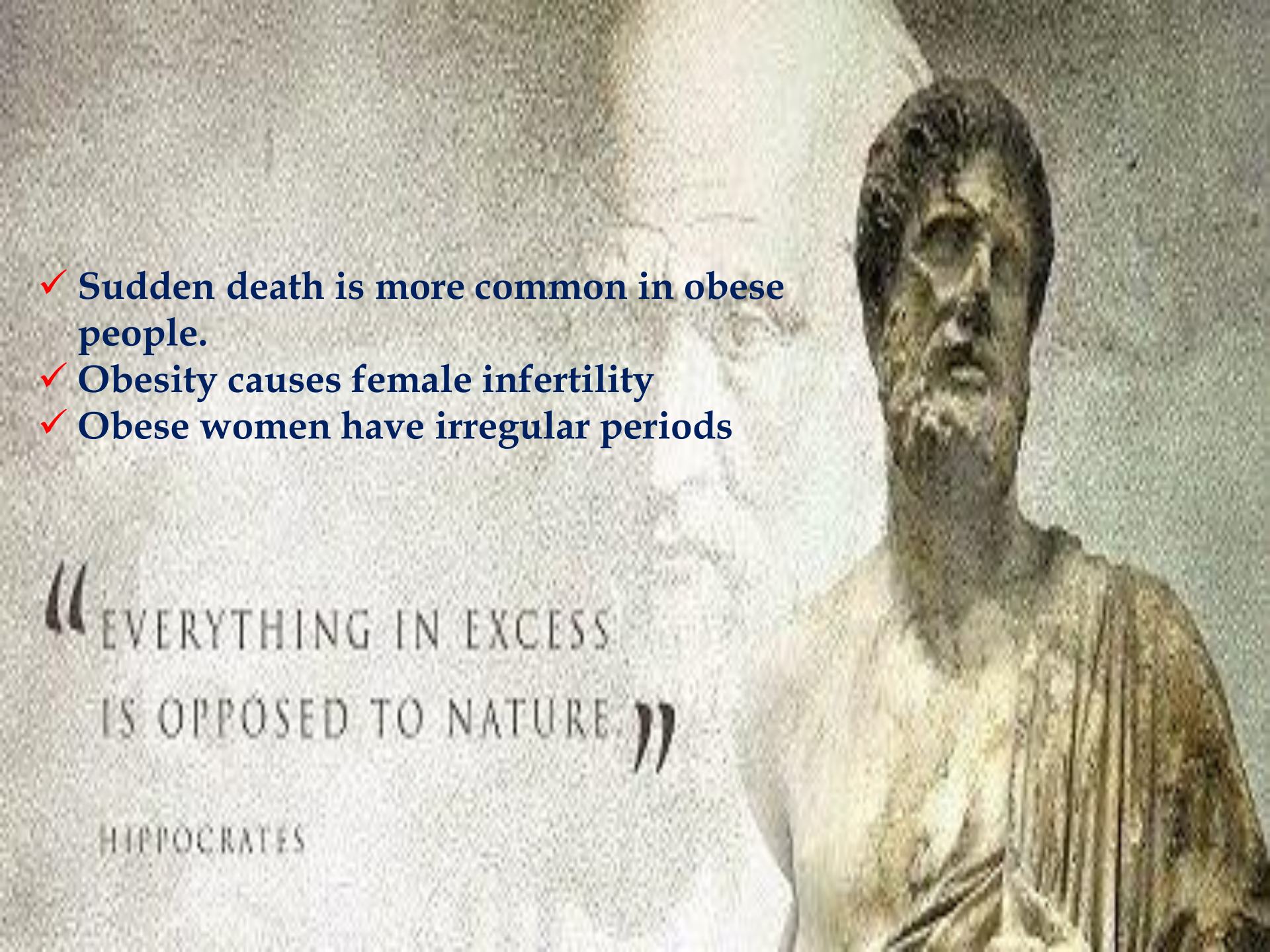
Impact of obesity on life expectancy

years lost, average 2020-2050

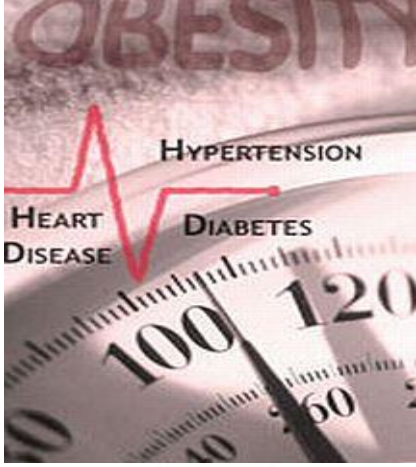


Source: OECD (2022), The Heavy Burden of Obesity.

OECD

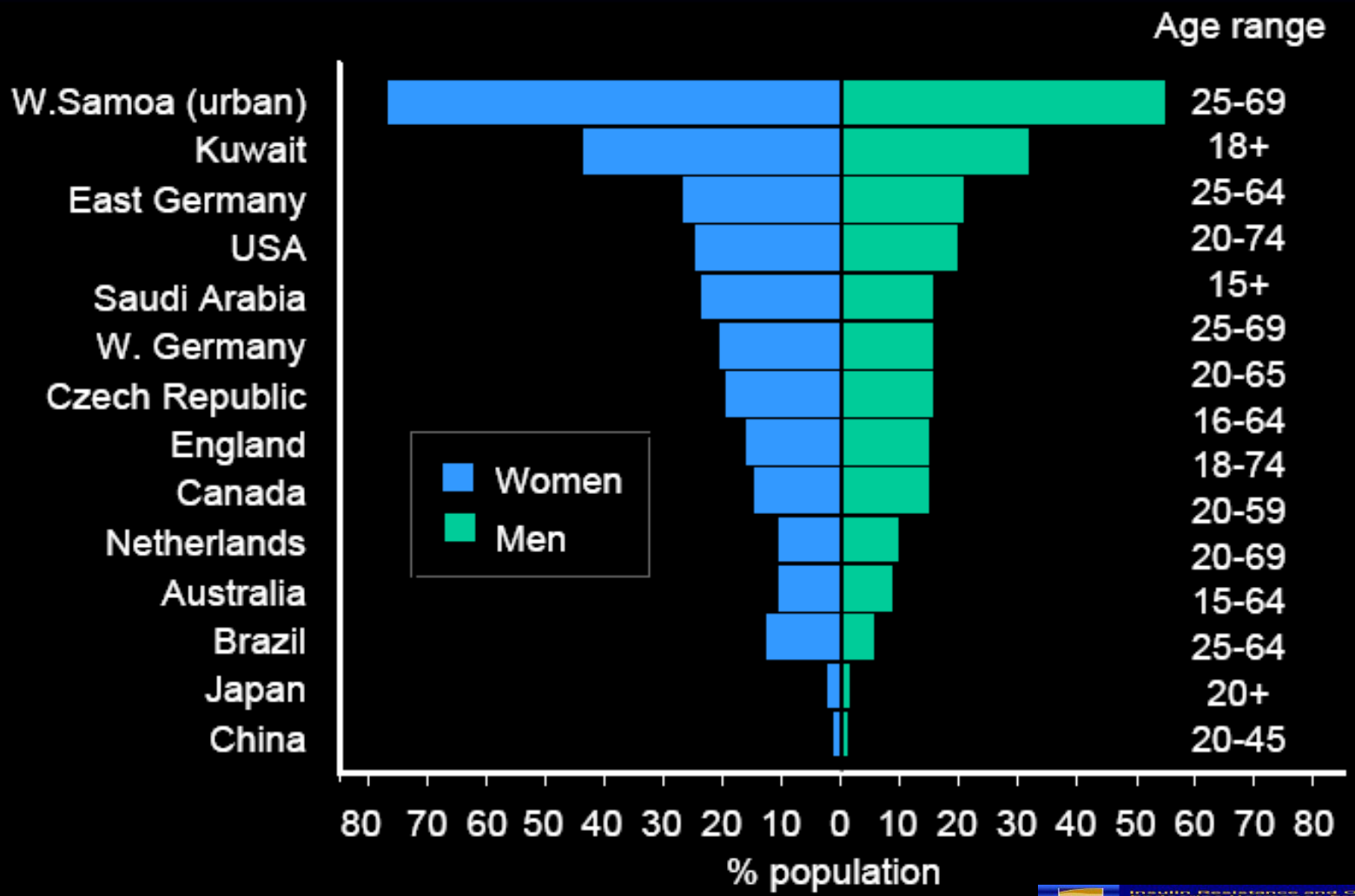

✓ Sudden death is more common in obese people.
✓ Obesity causes female infertility
✓ Obese women have irregular periods
"EVERYTHING IN EXCESS
IS OPPOSED TO NATURE."
HIPPOCRATES

WHO (2016): 1.9 bil adults (39%): excess body weight
NHANES (2018): 42.4% (age-adjusted) of adults are obese
In the U.S. population, 35% of adults are obese and another 35% are overweight, as defined in terms of body mass index (BMI)



Bluher M. Nat Rev Endocrinol 2019; 15(5):288-298

Global Prevalence of Obesity (BMI ≥30)

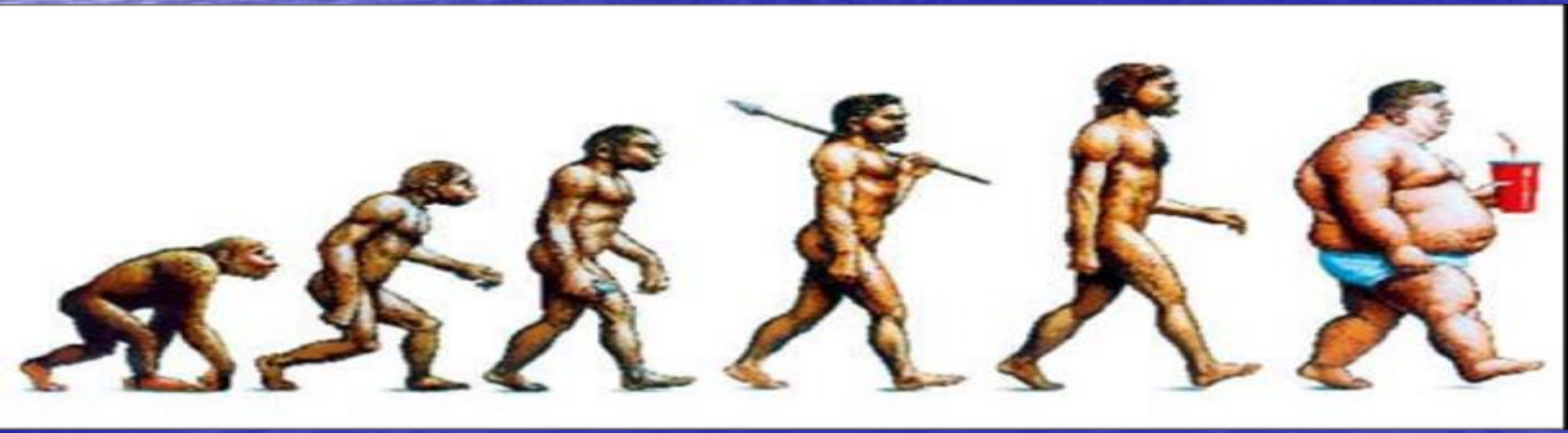


* Most recent available data. S

Unreported World: Obesity in Paradise review – fighting fat on Samoa

Having rejected local food in favour of processed western junk, nine out of 10 people on Samoa are overweight. Sophie Morgan uncovers a quiet epidemic

THE EVOLUTION OF MAN……. TODAY



Eating unhealthy and increasing portions……

1954
Burger King

2.8 oz
202 calories

2004

4.3 oz
310 calories

1955
McDonald's

2.4 oz
210 calories

2004

7 oz
610 calories

1900
Hershey's

2 oz
297 calories

2004

7 oz
1,000 calories

1916
Coca-Cola

6.5 fluid oz
79 calories

2004

16 fluid oz
194 calories

1950s
Movie popcorn

3 cups
174 calories

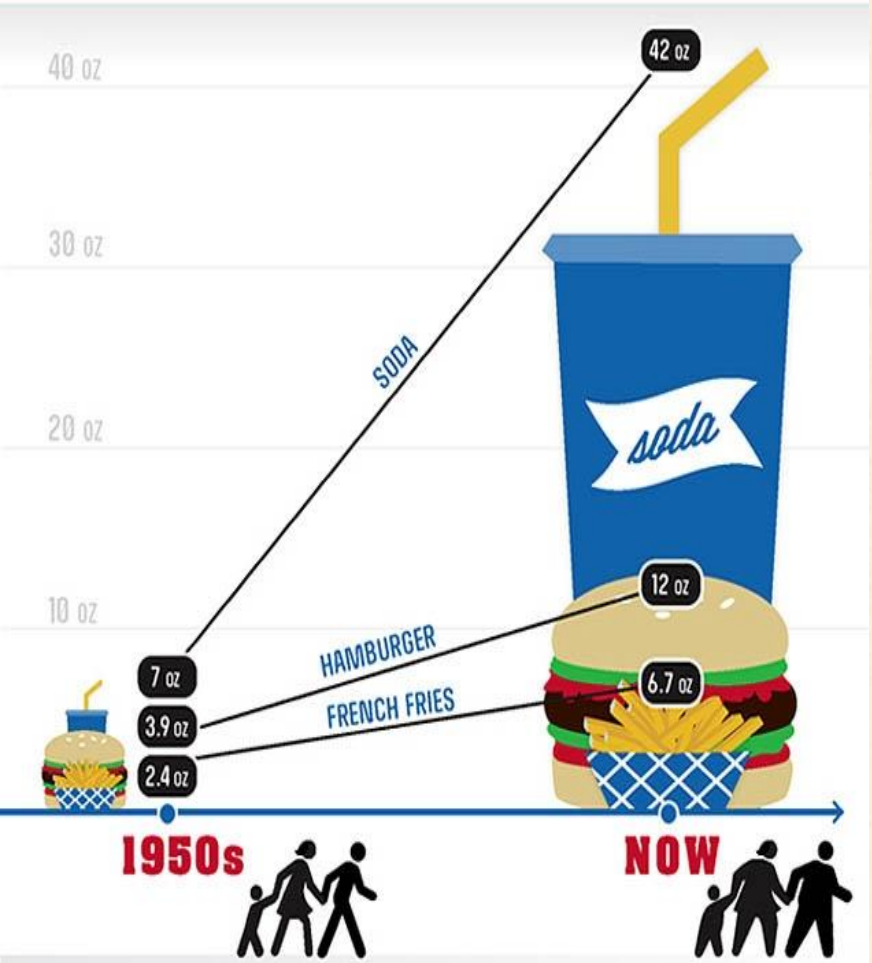
2004

21 cups (buttered)
1,700 calories

Source: National Geographic

THE NEW (AB)NORMAL

Portion sizes have been growing. So have we. The average restaurant meal today is more than four times larger than in the 1950s. And adults are, on average, 26 pounds heavier. If we want to eat healthy, there are things we can do for ourselves and our community: Order the smaller meals on the menu, split a meal with a friend, or, eat half and take the rest home. We can also ask the managers at our favorite restaurants to offer smaller meals.

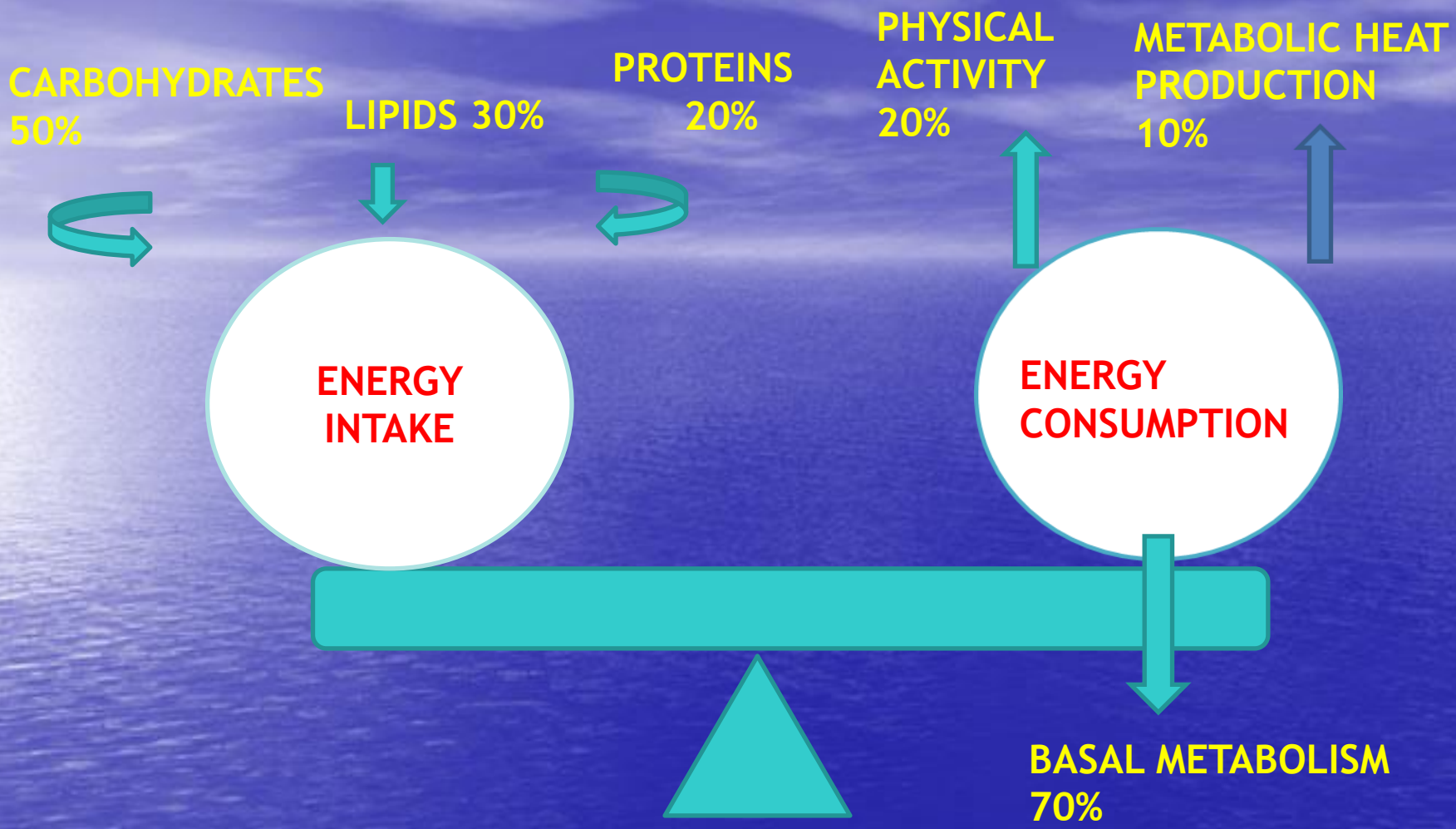


FOR MORE INFORMATION, VISIT MakingHealthEasier.org/NewAbNormal

SUGAR iN DRiNKS

Source: USDA.gov


www.StrangeCosmos.

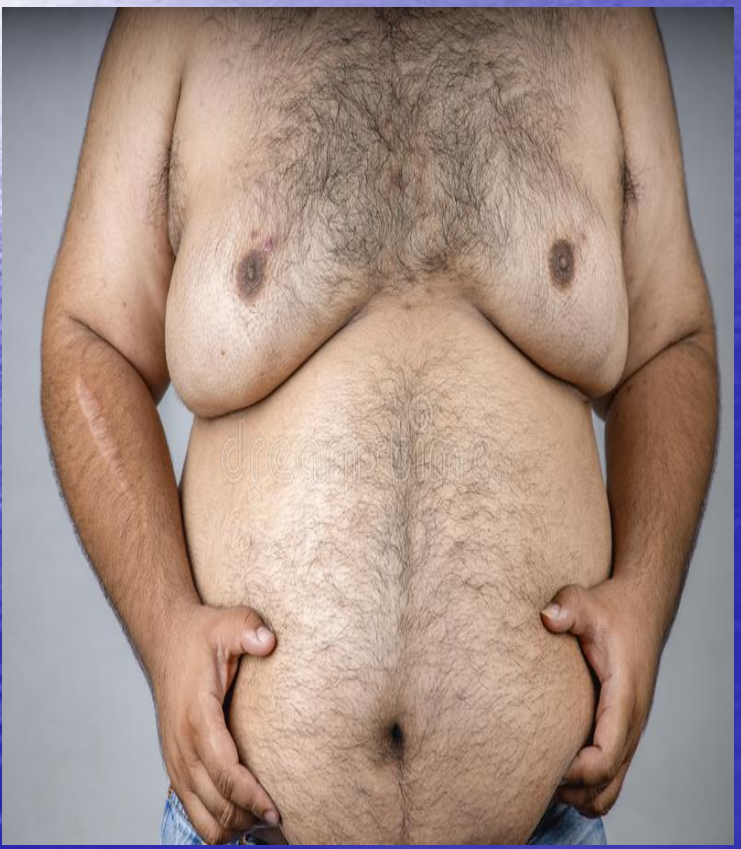


Obesity is a complex, chronic disease representing a chronic energy disturbance. In other words, obesity is the result of taking in more calories in the diet than are expended by the body's fuel-consuming activities

1. WHAT ARE THE CAUSES OF OBESITY?

2. HOW IS OBESITY DEFINED?

Overweight and obesity are defined as abnormal or excessive fat accumulation that presents a risk to health.



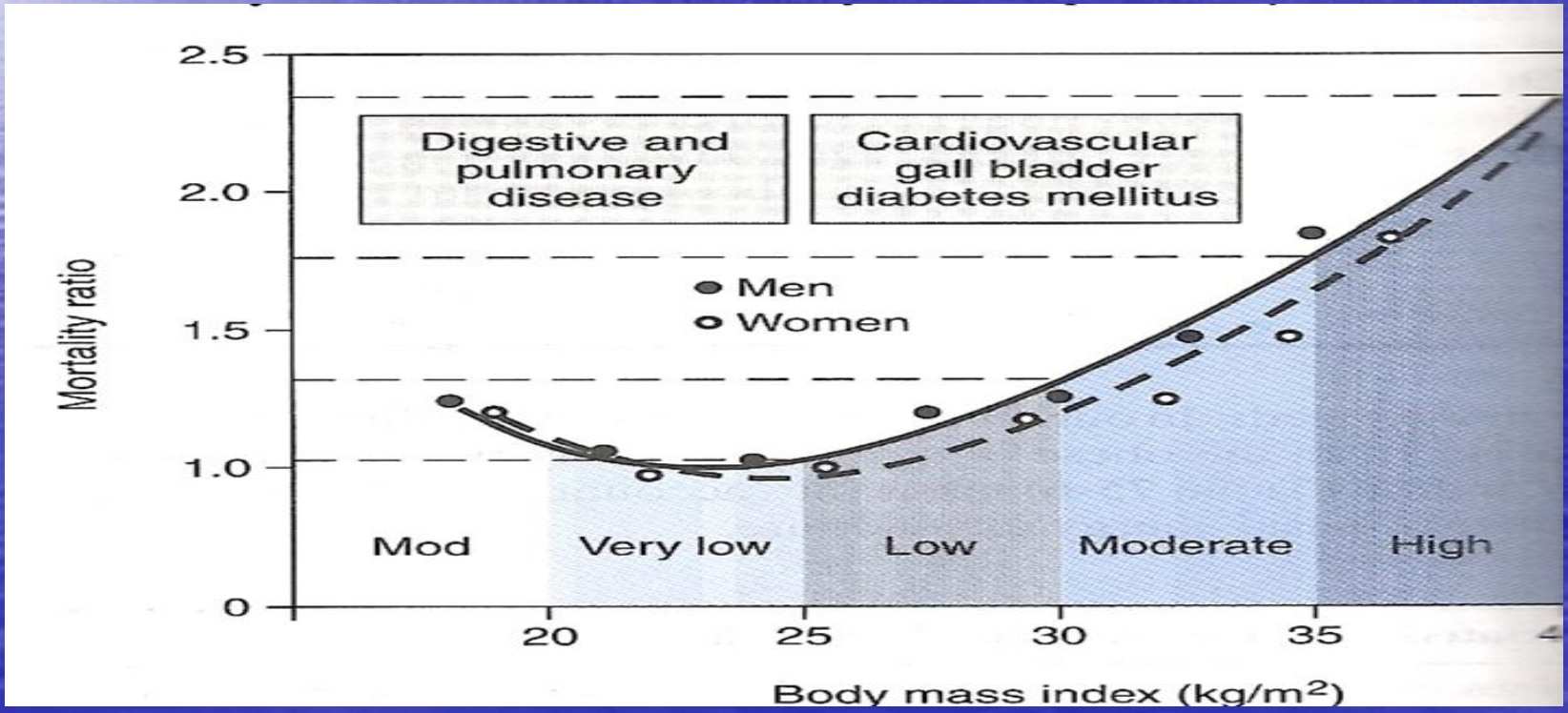
Normal fat percentage in adults

Women: 25-30%

Men: 15-20%

3. HOW IS BODY MASS MEASURED?

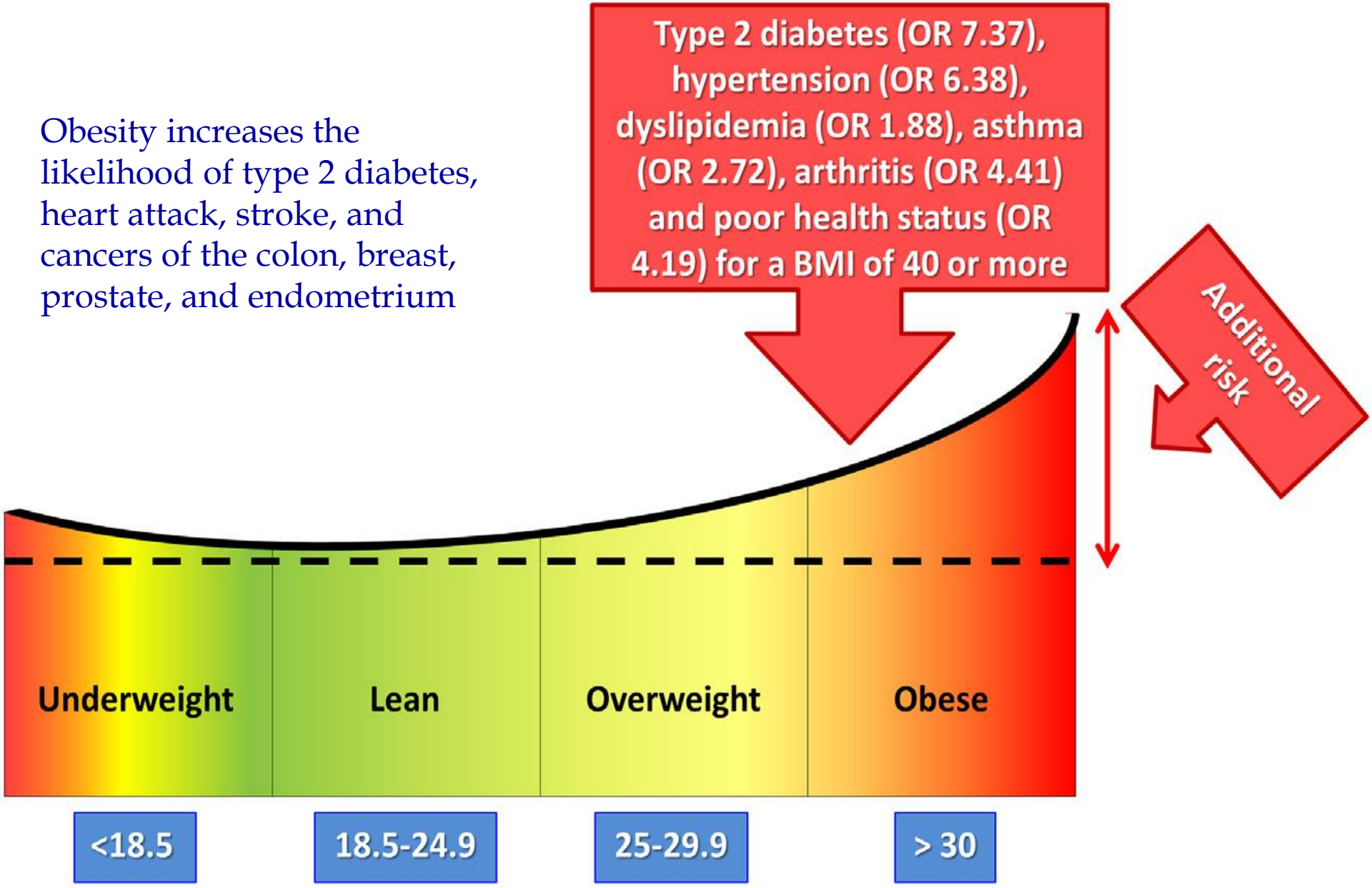
Body Mass Index (BMI) = calculated as $\frac{\text{weight in kg}}{\text{height in m}^2}$



4. HOW WEIGHT STATUS IS CLASSIFIED BASED ON WHO?

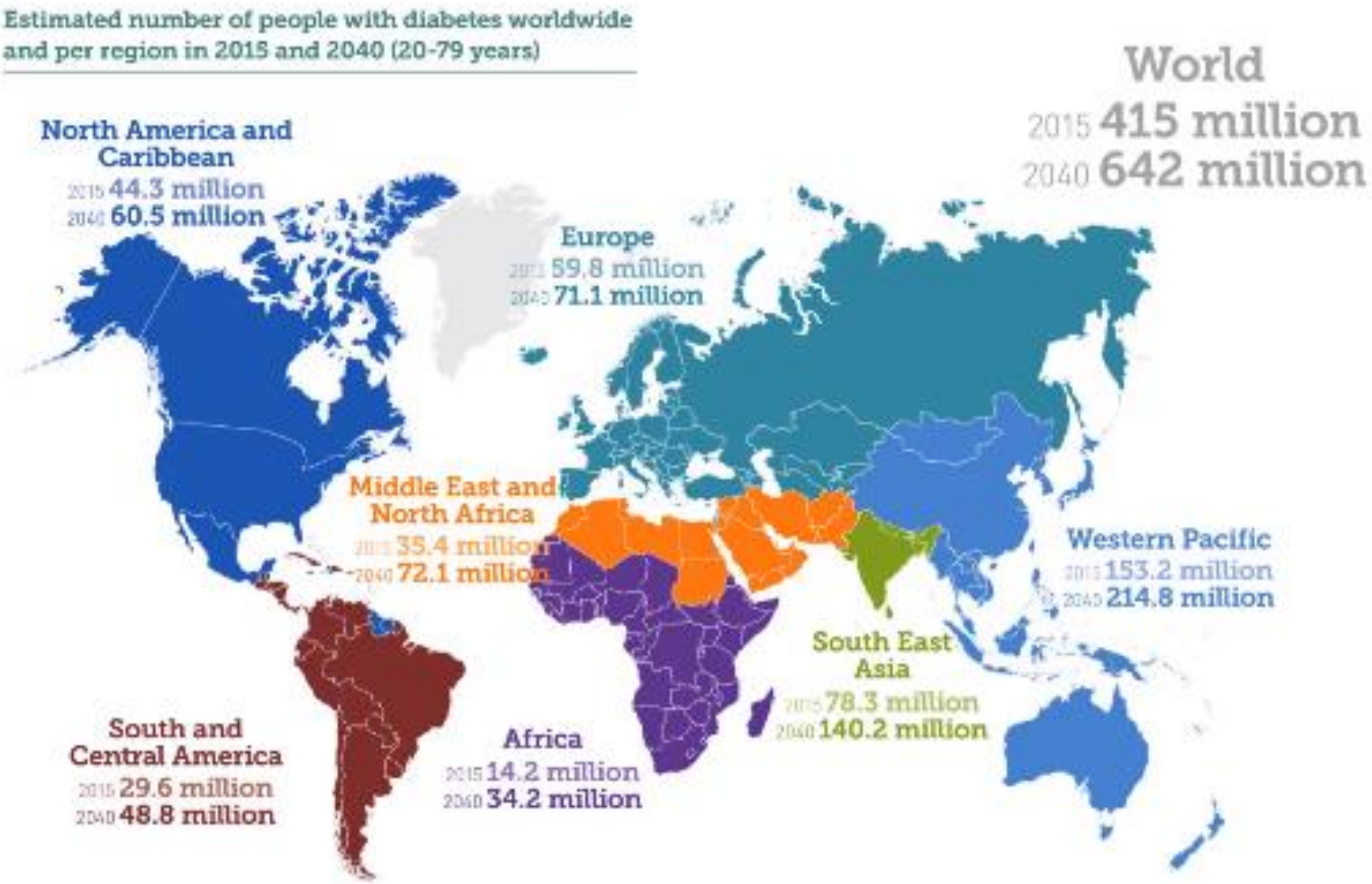
WHO CLASSIFICATION OF WEIGHT STATUS	
WEIGHT STATUS	**BODY MASS INDEX (BMI), kg/m^2**
Underweight	<18.5
Normal range	18.5 – 24.9
Overweight	25.0 – 29.9
Obese	≥ 30
Obese class I	30.0 – 34.9
Obese class II	35.0 – 39.9
Obese class III	≥ 40

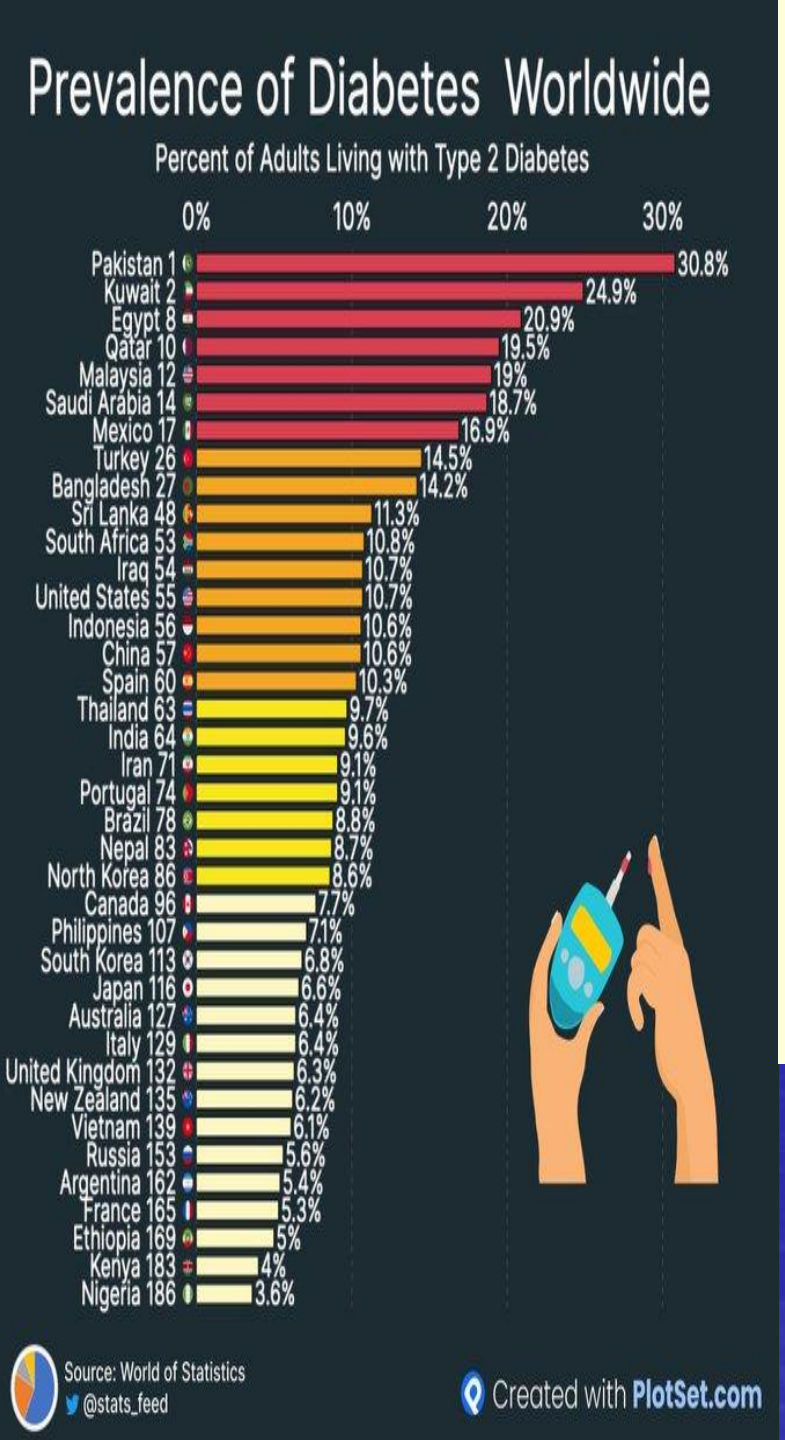
Obesity increases the likelihood of type 2 diabetes, heart attack, stroke, and cancers of the colon, breast, prostate, and endometrium



Iacobini et al, Metabolism 2019;92:51-60

Diabetes: A global emergency





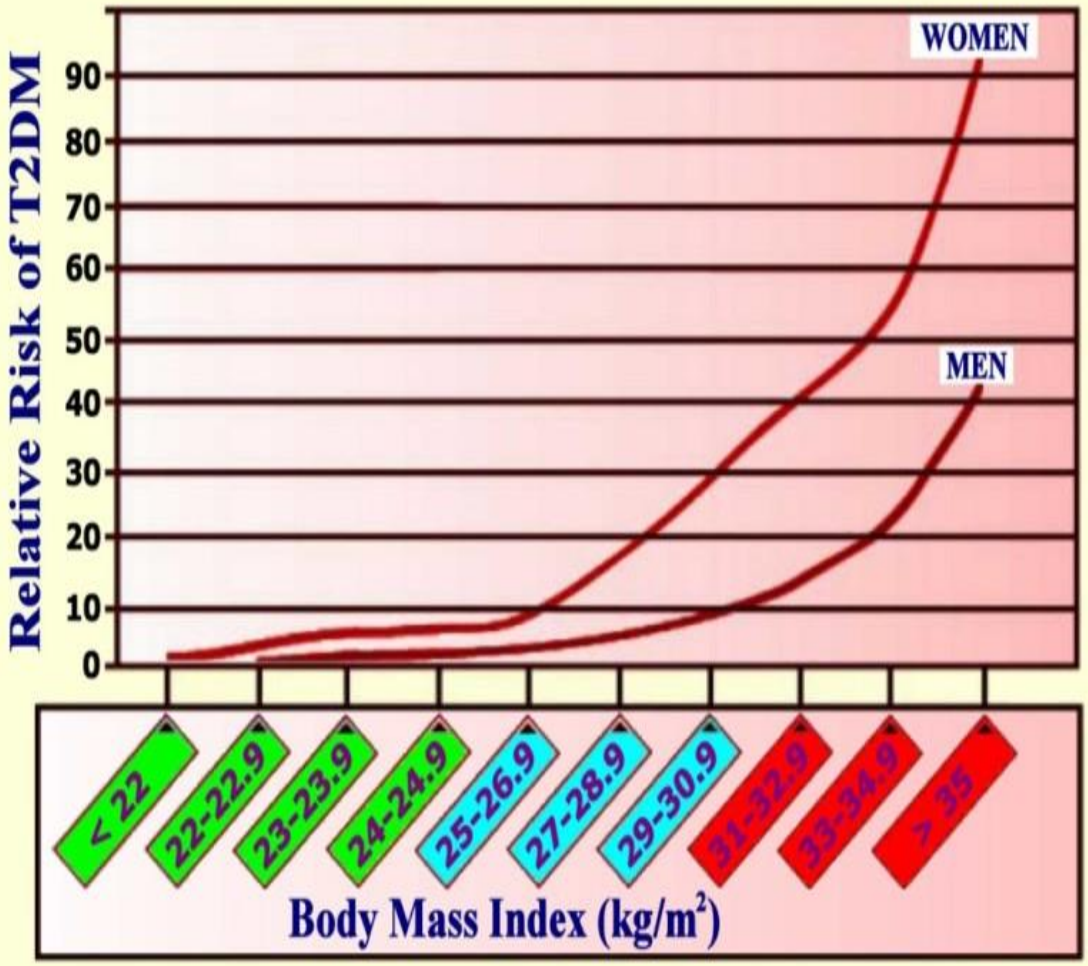
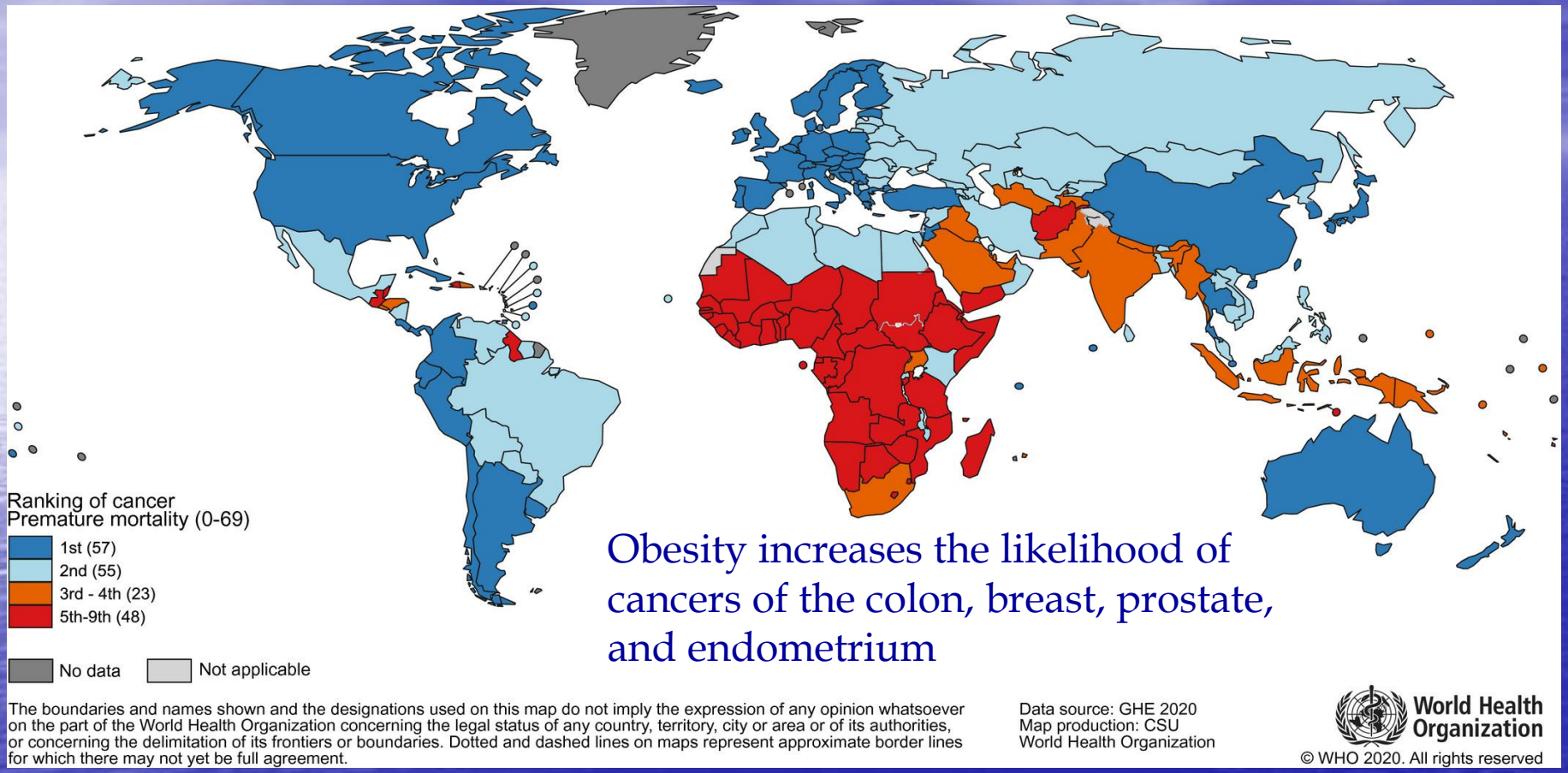


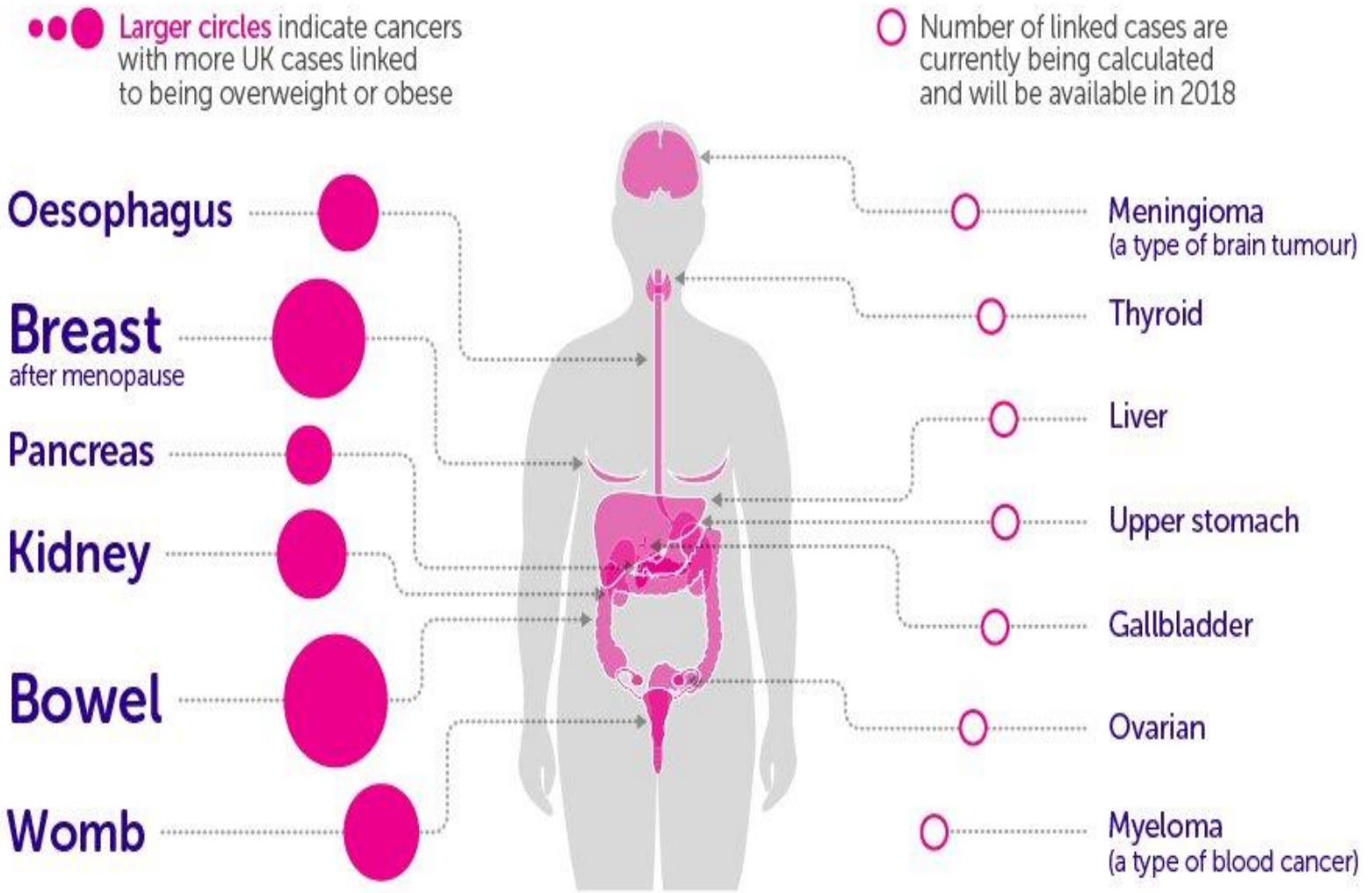
Figure . Body Mass Index (BMI) and Risk of Developing Type 2 Diabetes Mellitus (T2DM) in Male and Female Adults (based on data from Colditz GA *et al*. Ann Intern Med. 1995 (47) and Chan JM *et al*. Diabetes Care 1994 (46)).

Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries



CA: A Cancer Journal for Clinicians, First published: 04 February 2021, DOI: (10.3322/caac.21660)

BEING OVERWEIGHT CAN CAUSE 13 TYPES OF CANCER



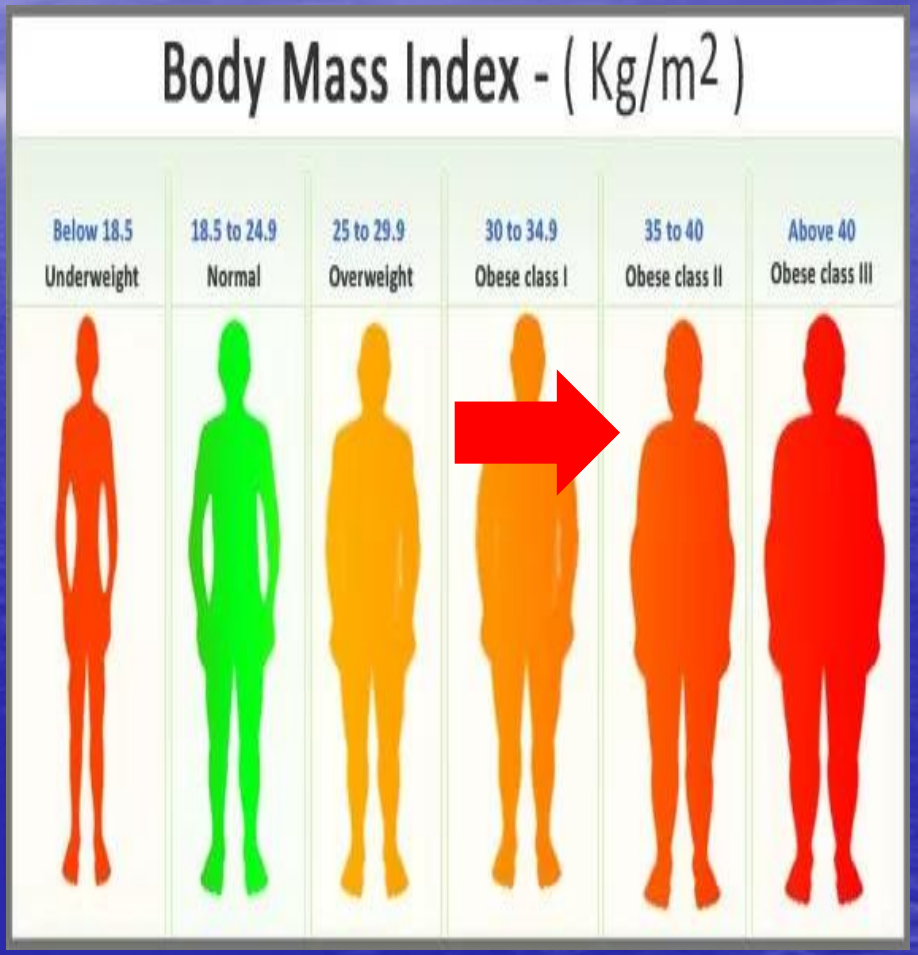
LET'S BEAT CANCER SOONER
cruk.org

CANCER RESEARCH UK

5. IS BMI A PERFECT MEASURE FOR OBESITY?

NO IT ISN'T….

- ✓ Cannot distinguish fat mass from lean, muscle mass
- ✓ Not suitable index for athletes
- ✓ Not suitable indicator for people >65 years old (↑ fat mass)
- ✓ Not suitable indicator for very tall people
- ✓ Very high cut-offs for the Asian race
- ✓ It cannot estimate fat distribution
- ✓ It cannot assess central obesity that may be present even in people with a normal BMI



Pischon et al. *Metabolism 2019; 92: 61-70*
Dalamaga et al. Metabolism *2019; 92: 121-135*

6. OTHER IMPORTANT SOMATOMETRIC INDICATORS OF OBESITY: WAIST CIRCUMFERENCE (WC) & WAIST TO HIP RATIO (WHR)

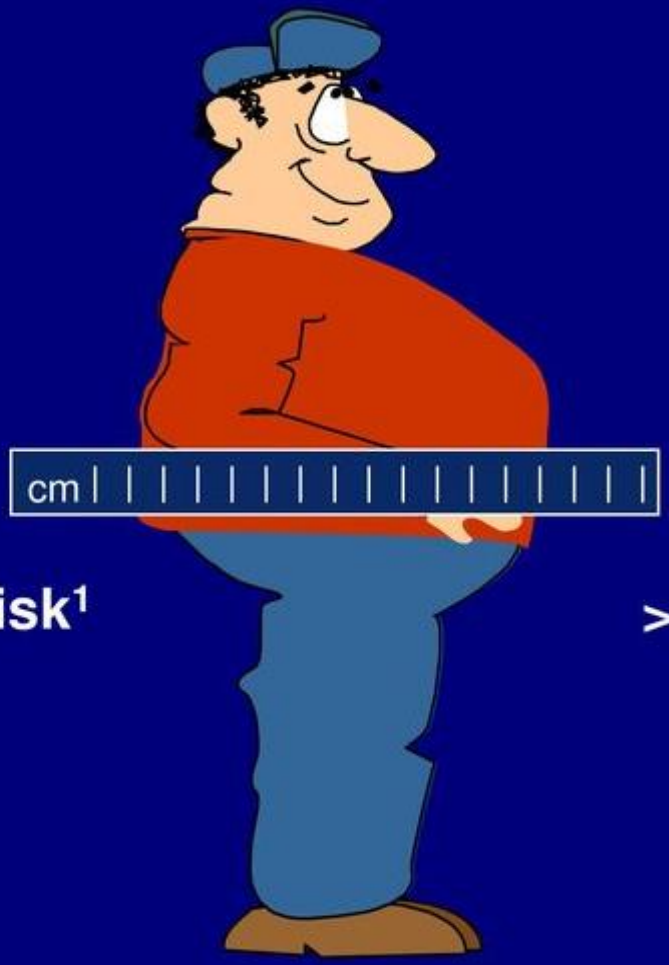
- ✓ Better markers for assessing central obesity
- ✓ Especially for people with BMI: 25-34.9 kg/m2, central obesity is defined as:

  WC: ♂: >102 cm, ♀: >88 cm

  WHR: ♂: >0.95, ♀: >0.80
- ✓ Central obesity is associated with ↑ cardiovascular risk and ↑ risk of cancer
- ✓ Problem in estimating abdominal subcutaneous versus visceral fat
- ✓ Problems measuring WC or WHR due to flatulence especially after a meal

Pischon et al. *Metabolism 2019; 92: 61-70*
Dalamaga et al. Metabolism *2019; 92: 121-135*

REMEMBER: Intra-abdominal fat correlates with waist circumference



Women

>88 cm = Increased risk[1]

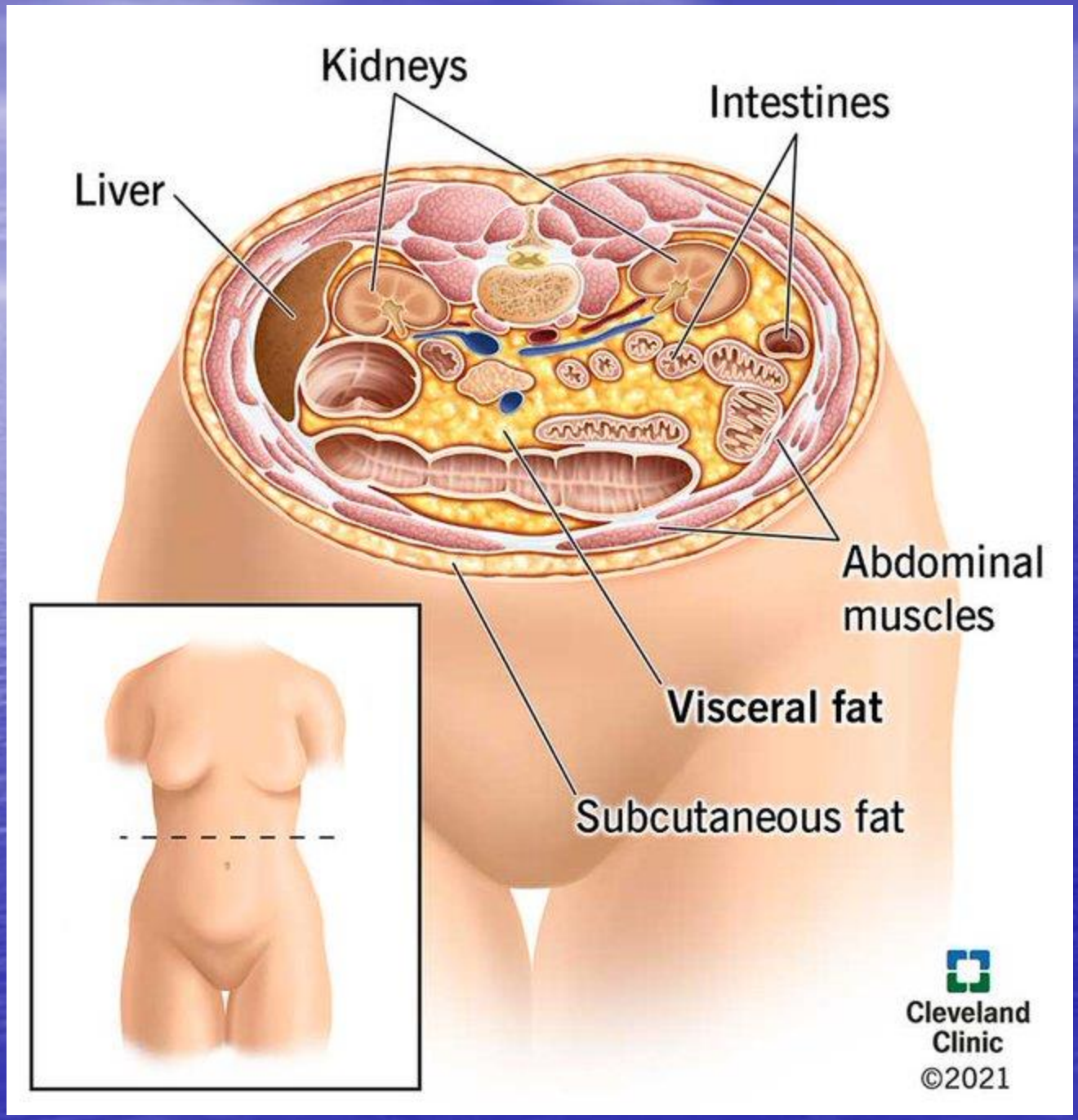
Asian = 80 cm

Men

>102 cm = Increased risk[1]

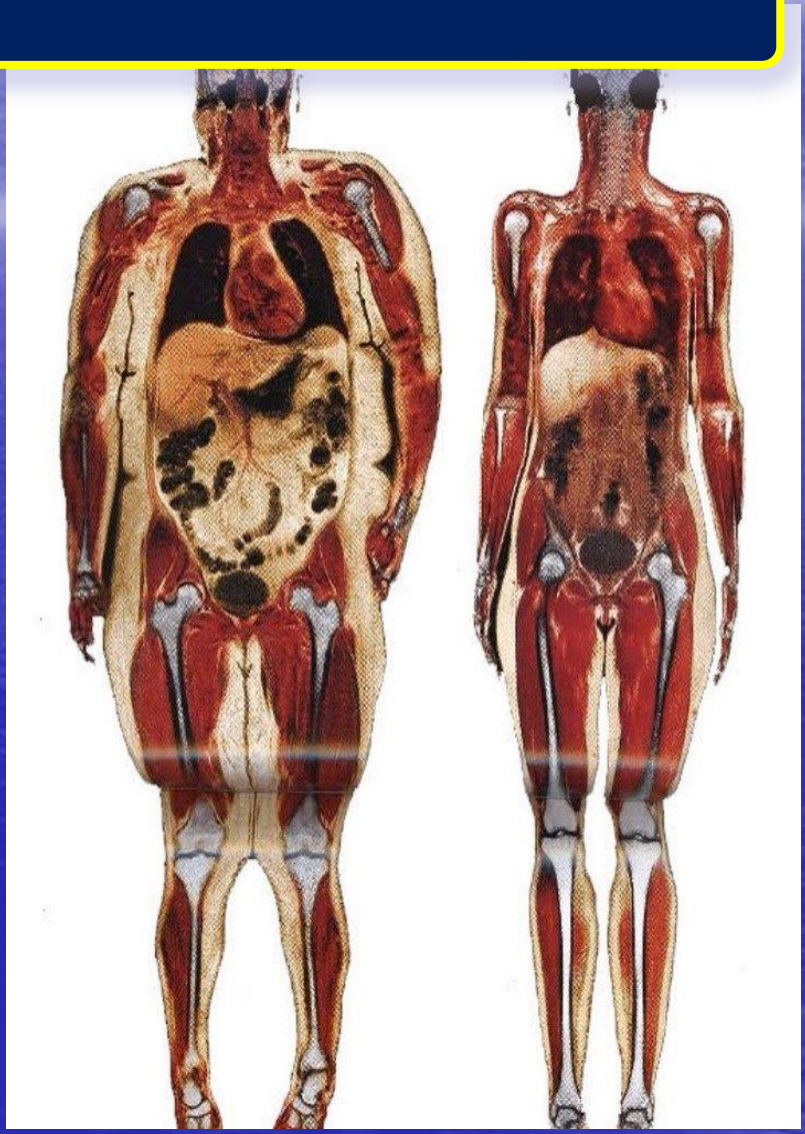
Asian = 90 cm

[1]Lean MEJ, et al. Lancet;1998:351:853–6


Kidneys
Intestines
Liver
Abdominal muscles
Visceral fat
Subcutaneous fat
Cleveland Clinic
©2021

7. OTHER IMAGING TESTS TO ASSESS OBESITY

- Bioelectrical conductance analysis
- Dual Energy X-ray Absorptiometry – (DEXA)
- Ultra Sound of upper abdomen
- Computed tomography (CT)
- Magnetic Resonance Imaging (MRI)
- Measurement of adipose tissue mass and volume (subcutaneous, visceral, epicardial, etc.). Assessment of muscle tissue
- Costly and complex methods
- Impractical methods
- There are no specific cut-offs



Pischon et al. *Metabolism 2019; 92: 61-70*
Dalamaga et al. Metabolism *2019; 92: 121-135*
Borga M et al. J Investig Med 2018;66:887

8. LET'S REMEMBER THE ADIPOSE TISSUE

WHITE ADIPOSE TISSUE

- Adulthood
- Subcutaneous and visceral
- Storage, metabolic and endocrine function
- Fatty acids are released into circulation

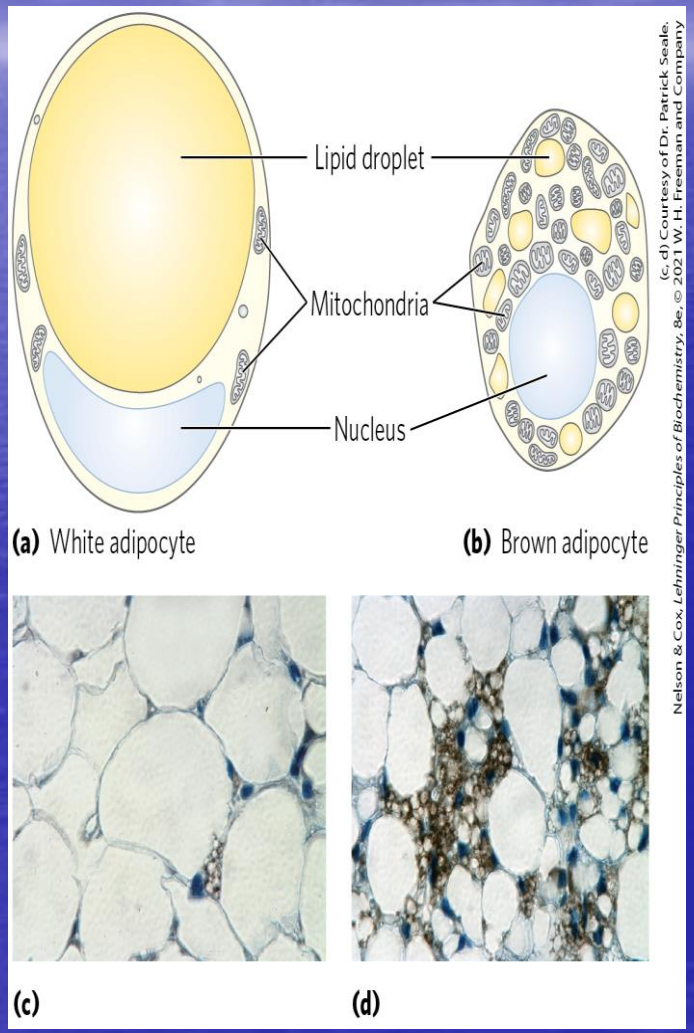
BROWN ADIPOSE TISSUE

- Found predominantly in newborn mammals
- Around the viscera, thoracic cavity, great vessels, parasympathetic ganglia
- Small Adipocytes with a central nucleus, many mitochondria.
- Expression of thermogenin (UCP-1) for non-shivering thermogenesis
- Fatty acids are oxidized directly in the mitochondria to produce heat. It is not used to store energy

White Adipose Tissues Store and Supply Fatty Acids

white adipose tissue (WAT) = adipose tissue located under the skin, around deep blood vessels, and in the abdominal cavity

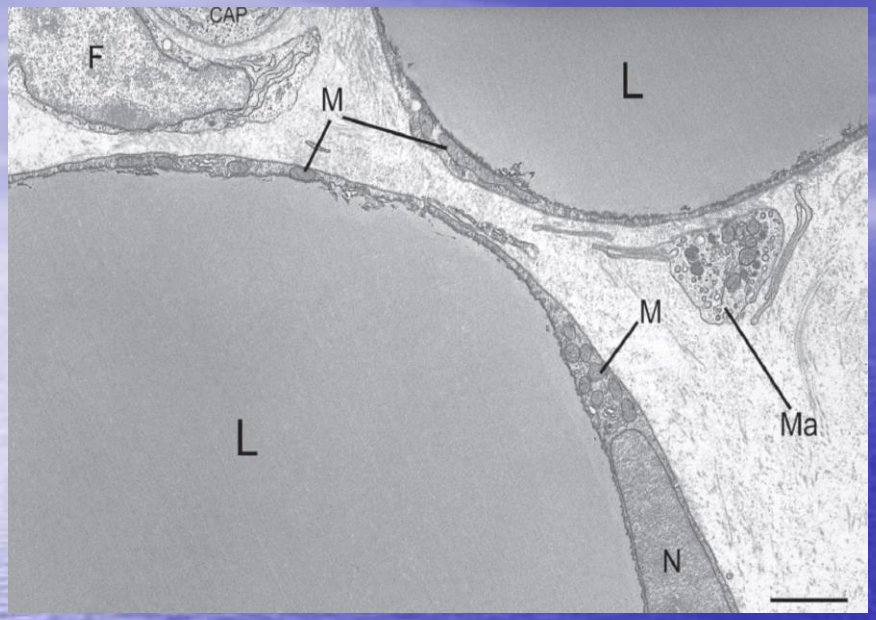
-its **adipocytes** are large, spherical cells filled with a single lipid droplet containing triglycerides (TAGs) and sterol esters



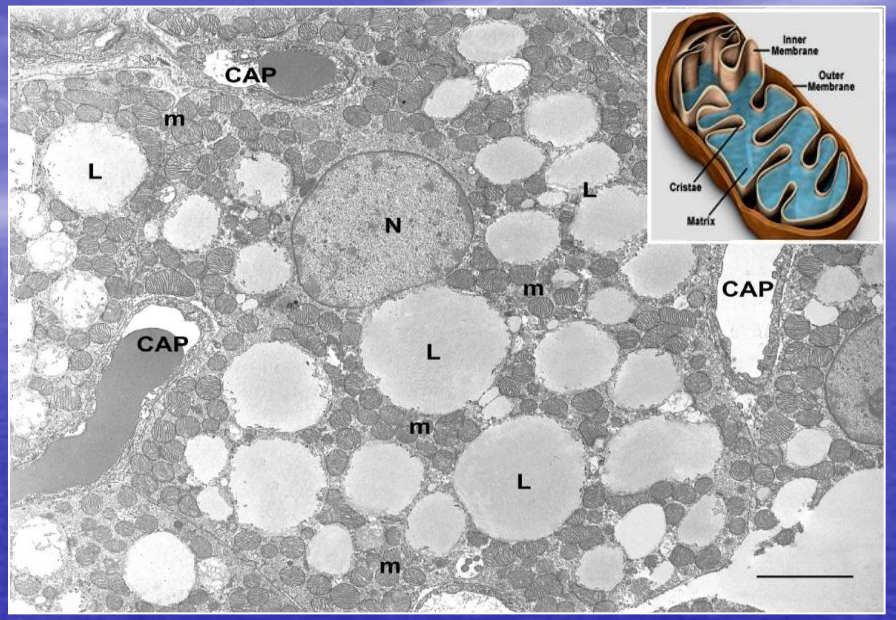
brown adipose tissue (BAT) = adipose tissue specialized for thermogenesis

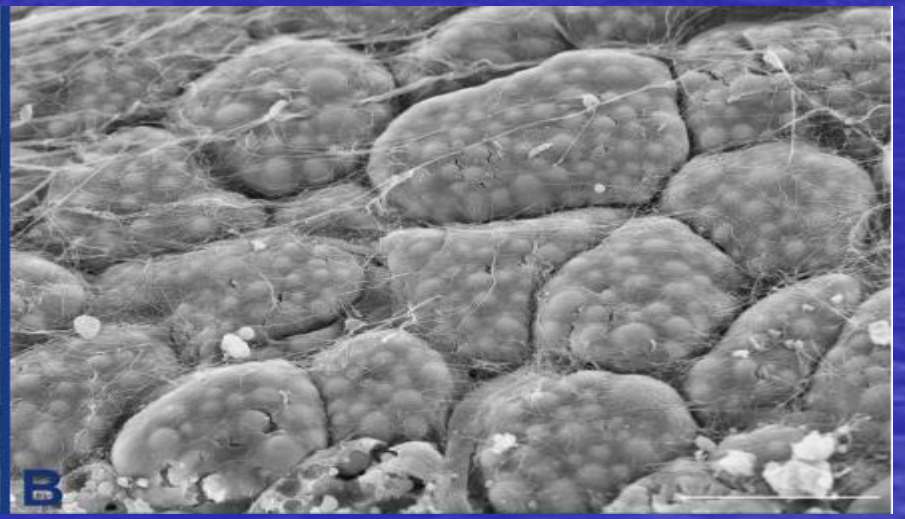
- its **adipocytes** are smaller, polygonal cells filled with multiple smaller lipid droplets,
contain more mitochondria,
contain a richer supply of capillaries and innervation

WHITE adipocyte



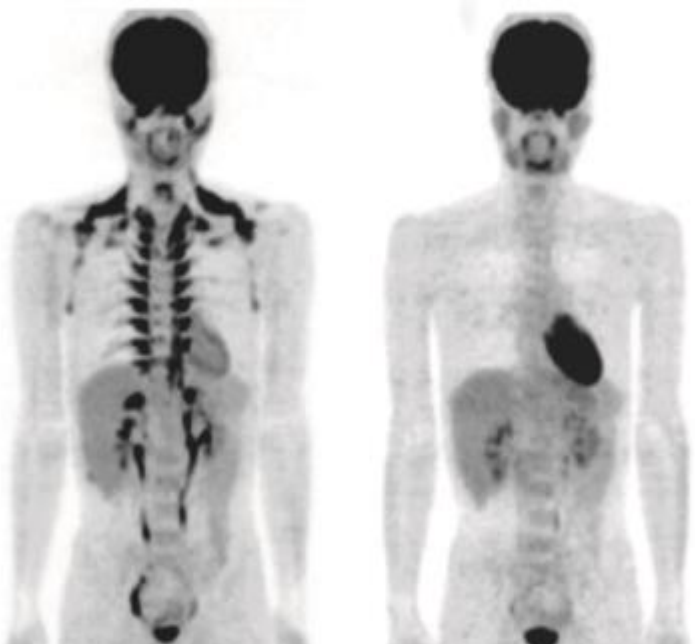
BROWN adipocyte





Distribution of brown adipose tissue

At birth, human infants have brown fat distributed as shown here, to protect the major blood vessels and the internal organs. This brown fat recedes over time, so that an adult has no major reserves of brown adipose tissue



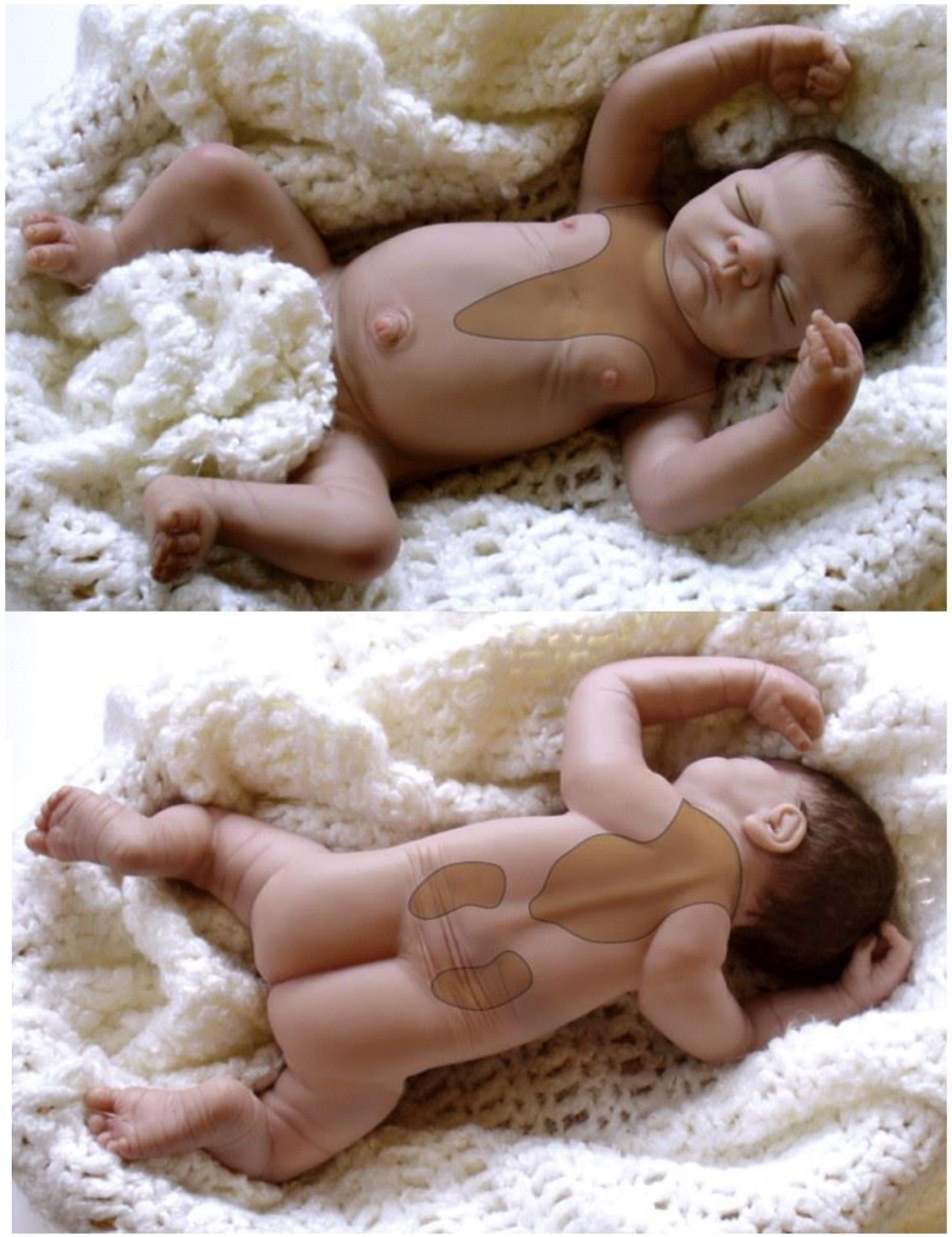
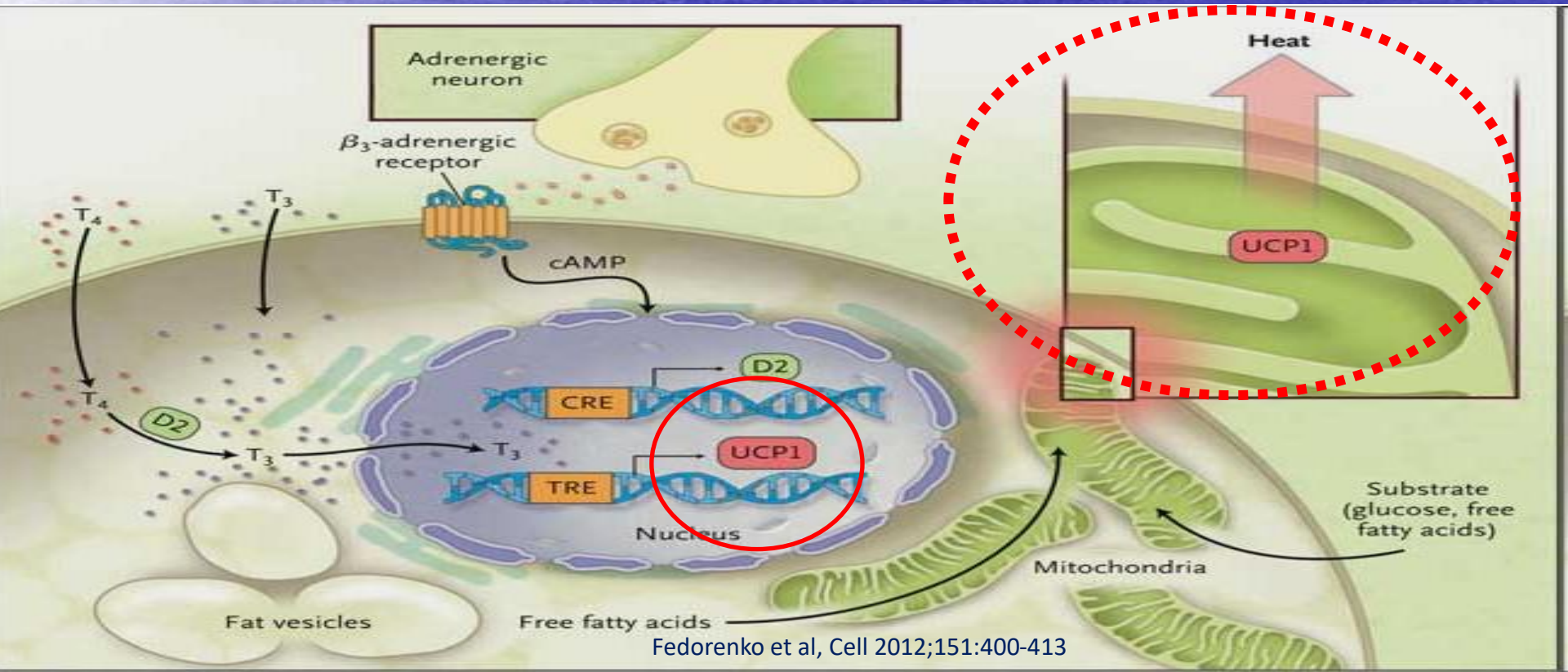


Figure 23-17
.ehninger Principles of Biochemistry, Fifth Edition

Uncoupling Protein 1 in brown adipocytes is Responsible for Thermogenesis

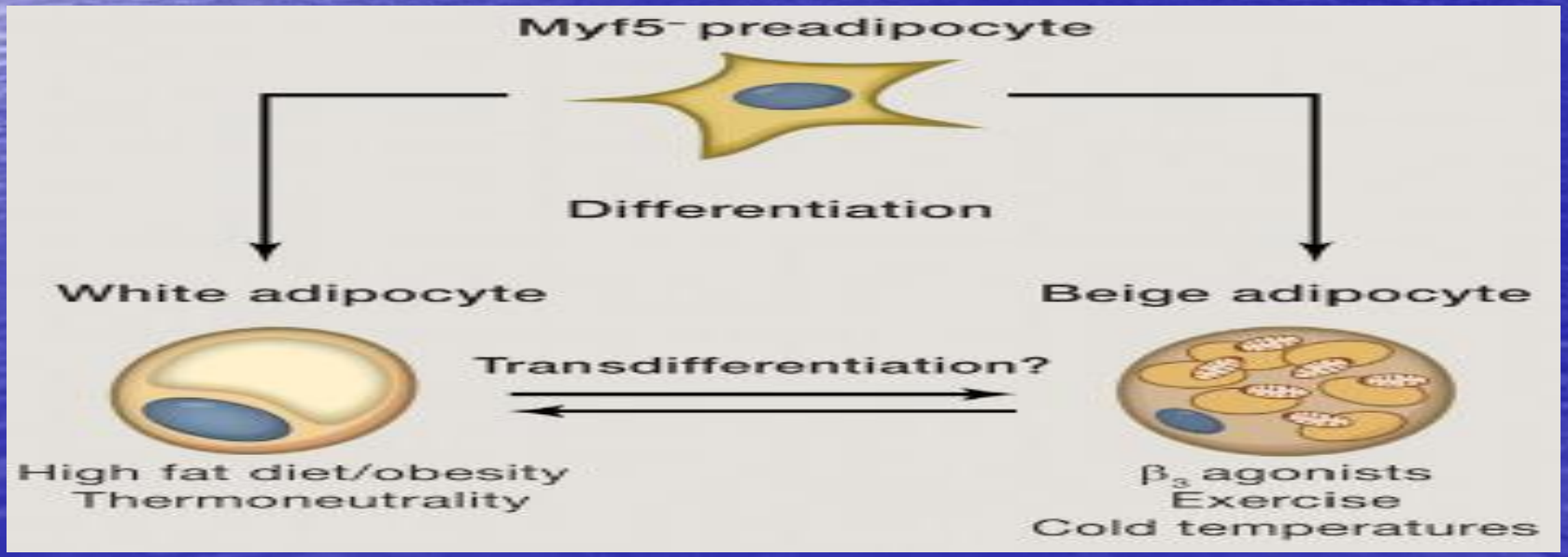
- **uncoupling protein 1 (UCP1)** = protein produced by BAT that allows the H^+ gradient in mitochondria to be dissipated as heat (without shivering) in a process is known as **thermogenesis**
  - keeps organs warm in low temperature environments



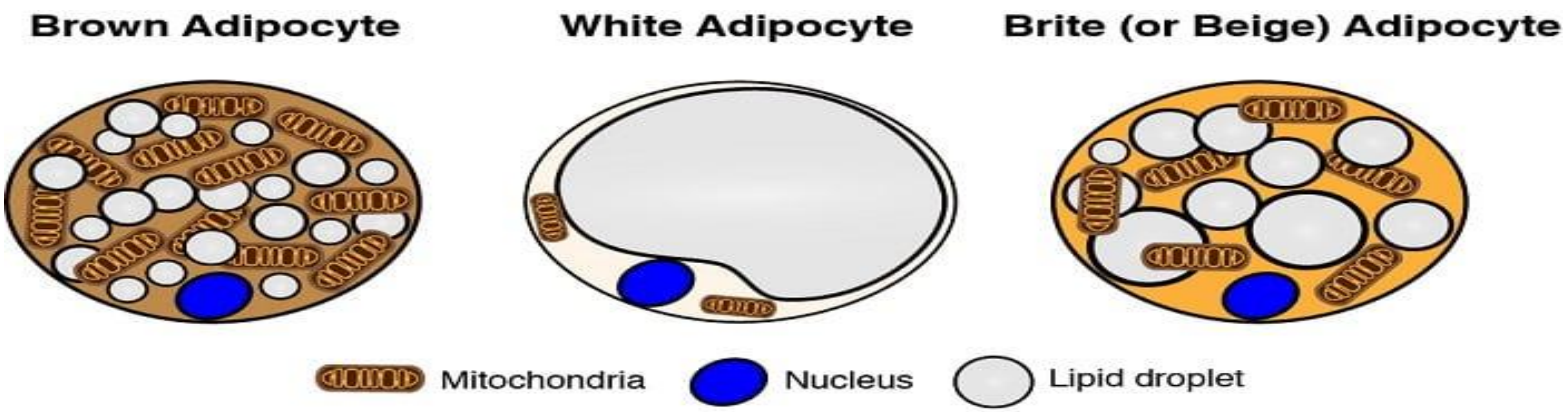
Fedorenko et al, Cell 2012;151:400-413

Another adipocyte category: Beige Adipocytes or Brite (brown in white)

- **beige adipocytes** = adipocytes that can be converted by cold exposure or by β-adrenergic stimulation into cells very similar to brown adipocytes
  - have multiple lipid droplets
  - are richer in mitochondria than white adipocytes
  - produce UCP1



Brown and Beige Adipose Tissues Are Thermogenic



	Brown	*White*	*Brite/beige*
UCP1 Expression	Positive	Negative	Positive
Mitochondrial Density	High	Low	Medium
LD Morphology	Multi-locular	Uni-locular	Multi-locular
Primary Function	Thermogenesis Endocrine	Energy storage Endocrine	Thermogenesis? Endocrine?

https://www.umassmed.edu/guertinlab/research/adipocytes/

Principle

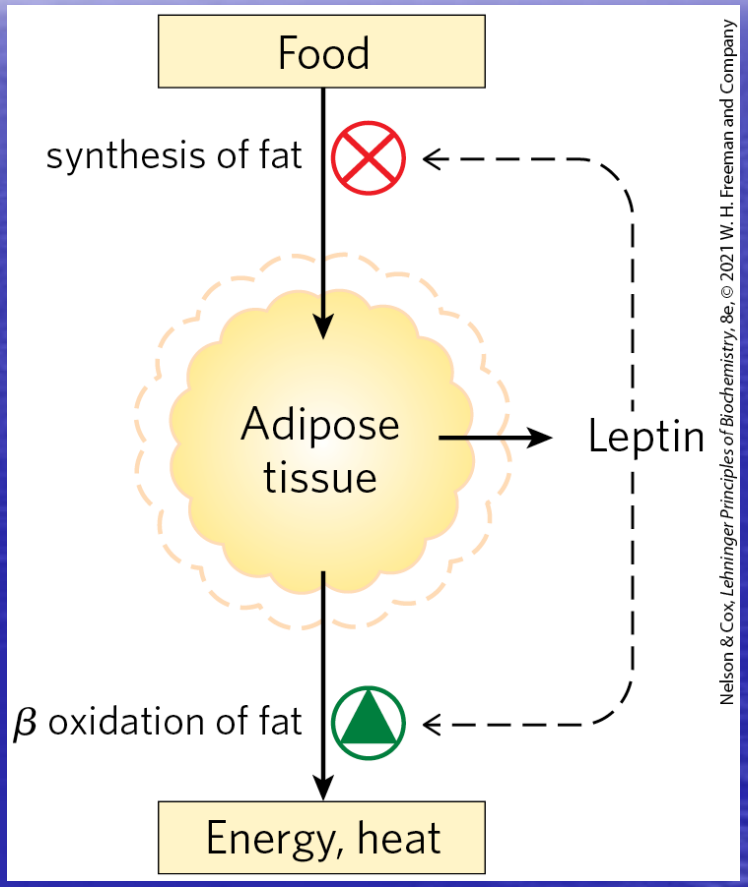
Maintaining an optimal body mass is an important priority in the adult mammal. Body mass is a function of dietary intake, physical activity, and the choice of metabolic fuel, all of which are subject to hormonal regulation. Hormonal signals between the brain, the adipose tissue, and the gastrointestinal tract help to set activity and feeding behavior.

9. WHAT IS THE FATE OF EXCESS DIETARY CALORIES???

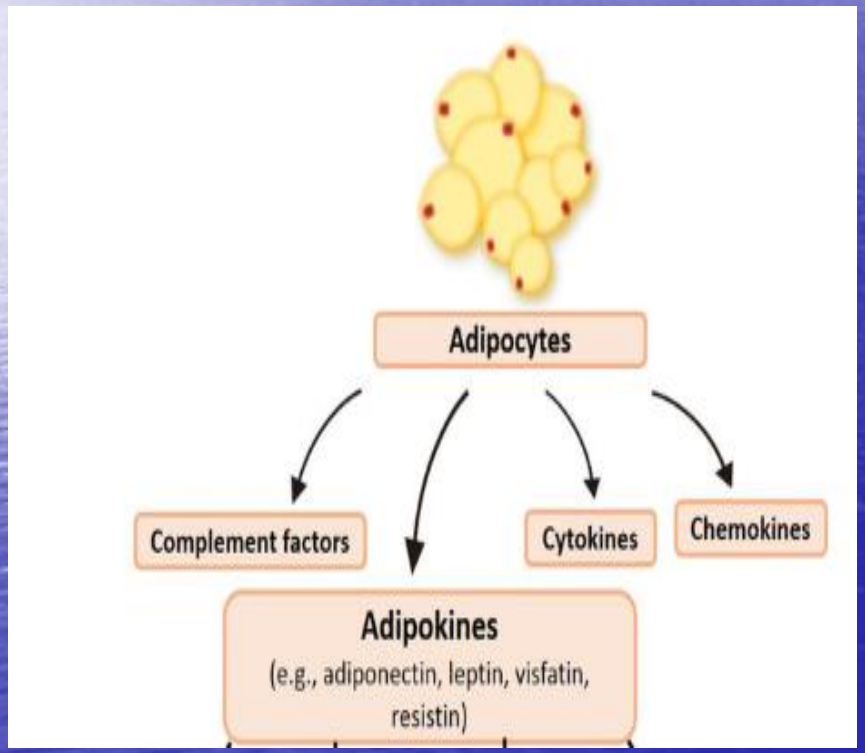
- The body deals with an excess of dietary calories by:
  - converting excess fuel to fat and storing it in adipose tissue
  - burning excess fuel by extra exercise
  - "wasting" fuel by diverting it to heat production (thermogenesis) by uncoupled mitochondria
- In mammals, hormonal and neuronal signals act to keep fuel intake and energy expenditure in balance

Adipose Tissue Has Important Endocrine Functions

There is an "adiposity negative-feedback" model = suggests that eating behavior is inhibited and energy expenditure is increased whenever body weight exceeds a certain "set point" value



10. Adipose Tissue Produces Adipokines



- Adipose tissue is an important **endocrine organ**
- Largest endocrine organ in obese people.
- It **produces adipokines** (peptide hormones) >500 adipokines
- Adipokines may act locally or systemically (endocrine action)
- Adipokines carry information about the adequacy of the energy reserves (TAGs) stored in adipose tissue to other tissues and to the brain

10.1. Leptin is an Adipokine

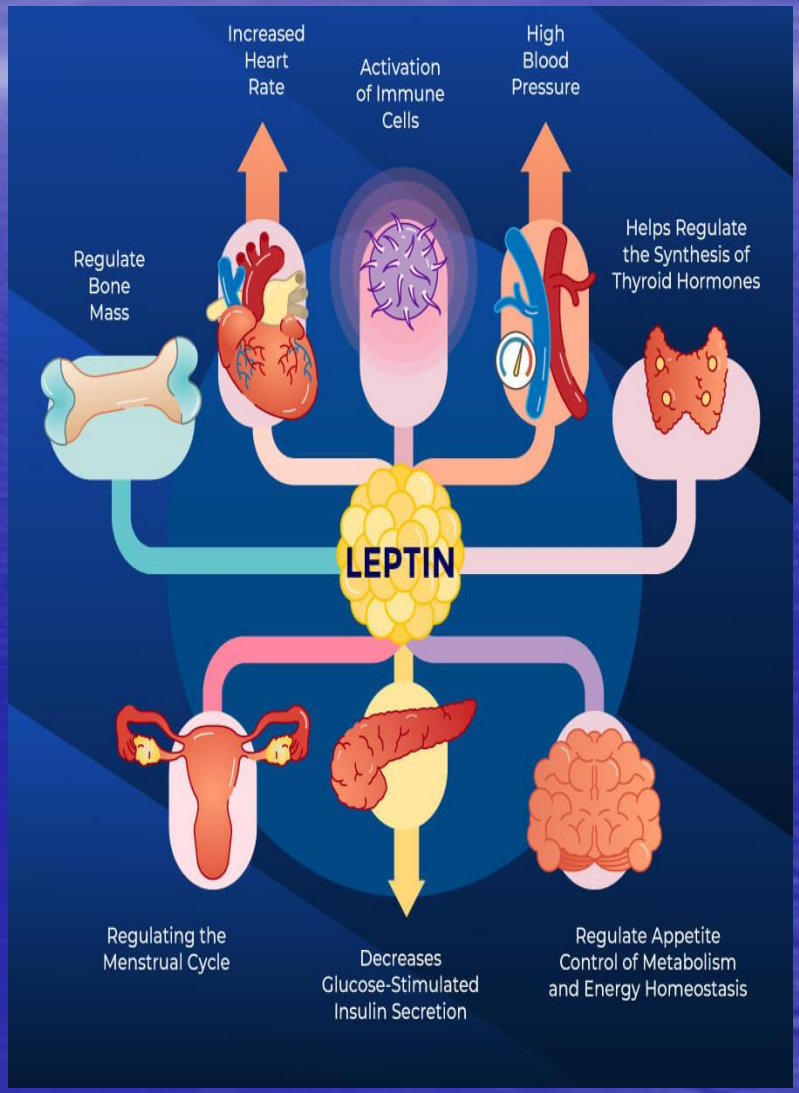
Leptin (from Greek leptos, "thin"). Discovered in 1994

- an adipokine produced by adipose tissue that regulates feeding behavior and energy expenditure to maintain adequate reserves of fat. It acts on receptors in the hypothalamus to curtail appetite.

- Small (167 AA residues) 16-kd protein encoded by the OB (obese) gene in rats or LEP in humans

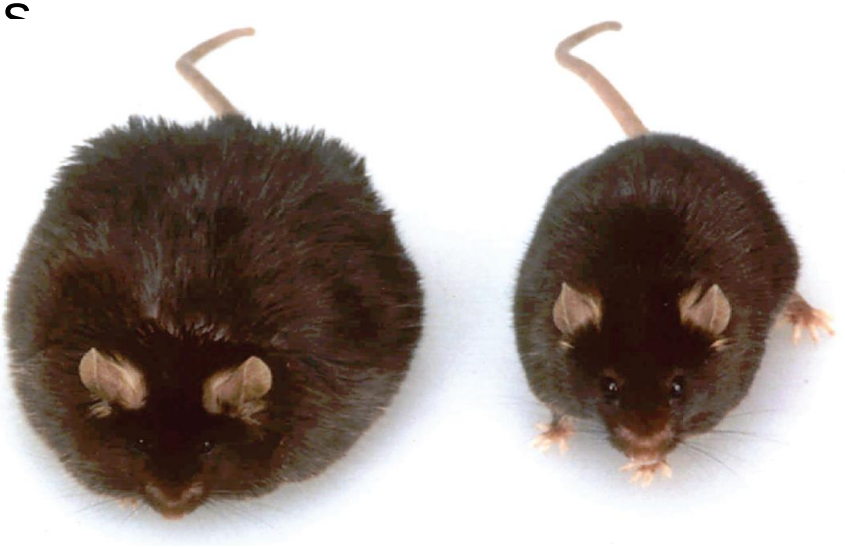
- Its production and release increases with number and size of adipocytes

- Leptin in the blood of women is 2-3X higher than that of men



Obesity Caused by Defective Leptin Production

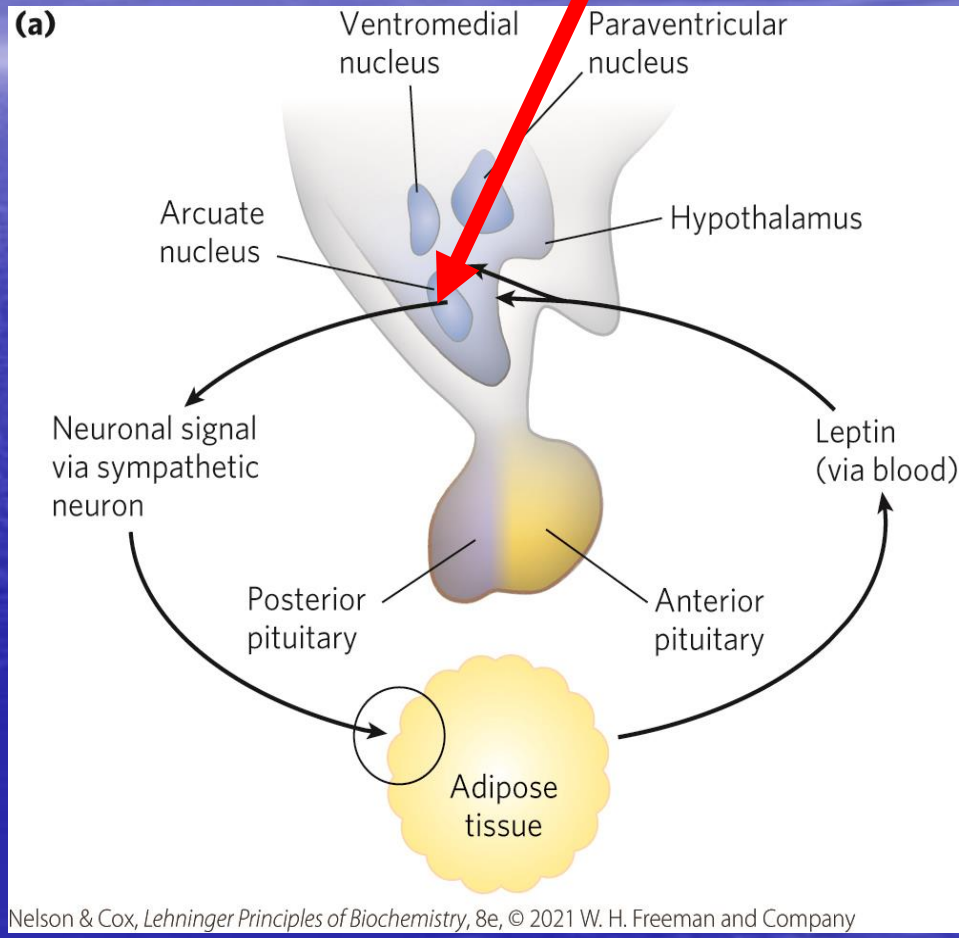
- Mice with two defective copies of the *OB* (obese) gene (*ob*/*ob*) show the behavior and physiology of animals in a constant state of starvation. They exhibit unrestrained appetite are unable to stay warm, grow abnormally large, and do not reproduce.
- Leptin injections into *ob*/*ob* mice cause the mice to:
  - eat less
  - lose weight
  - increase locomotor activity and thermogenesis



The Rockefeller University/AP Photo.

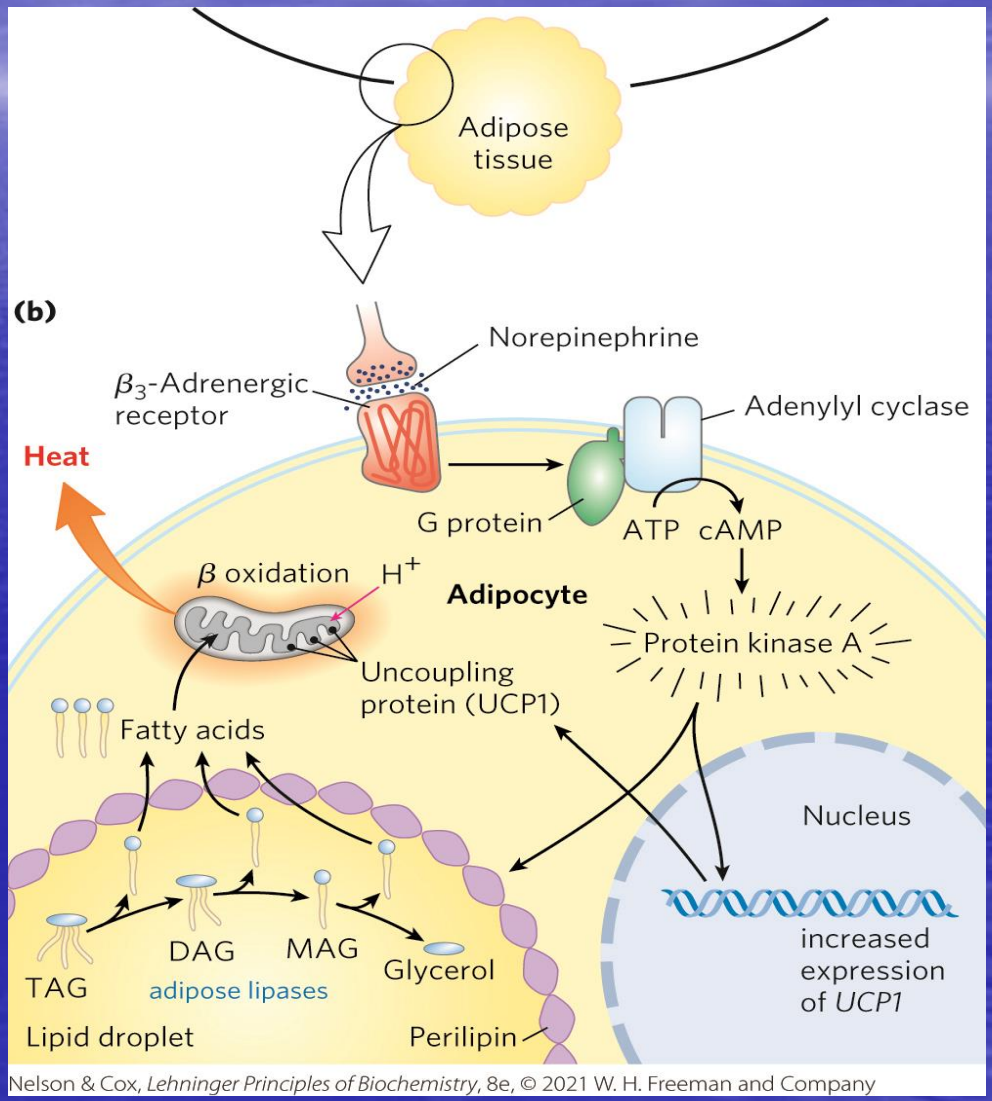
Leptin acts through the Leptin Receptor

- **leptin receptor** = receptor encoded by the *DB* (diabetic) gene that permits signaling by leptin
  - expressed primarily in neurons of the **arcuate nucleus** of the hypothalamus
  - *db*/*db* mice are obese and diabetic



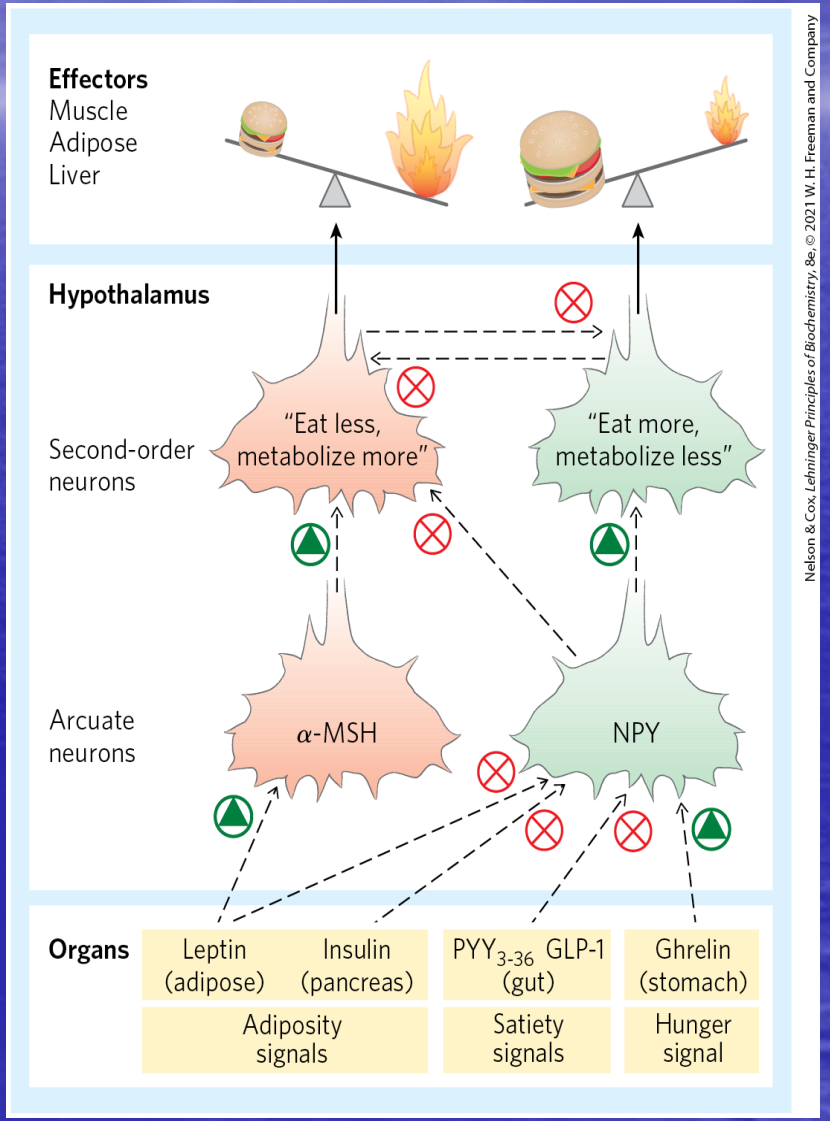
Through leptin, the hypothalamus Regulates: 1) Energy Expenditure & 2) Food intake

- The hypothalamus responds to leptin with norepinephrine signals to adipocytes
- This signal finally activates protein kinase A, which triggers fatty acid mobilization and their uncoupled oxidation in mitochondria, generating heat



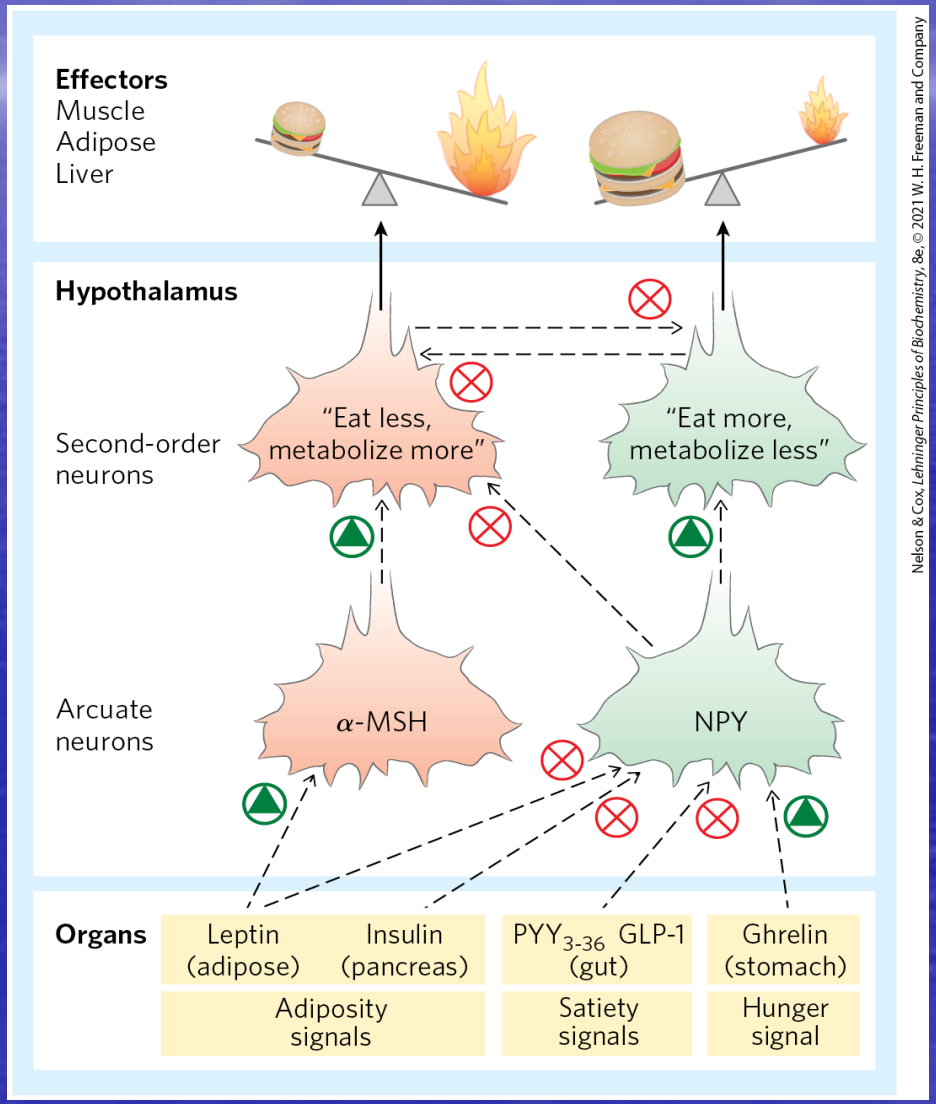
Leptin Stimulates the Production of Anorexigenic Peptide Hormones

- Two types of neurons in the arcuate nucleus control fuel intake and metabolism:
  - **orexigenic** (appetite-stimulating) neurons stimulate eating by producing and releasing **neuropeptide Y (NPY)**
  - **anorexigenic** (appetite-suppressing) neurons produce ***α*-melanocyte-stimulating hormone** (***α*-MSH**) from its polypeptide precursor POMC



Hormones (neuropeptides) That Control Eating

Leptin causes the release of anorexigenic peptides, including **α-MSH,** to inhibit eating



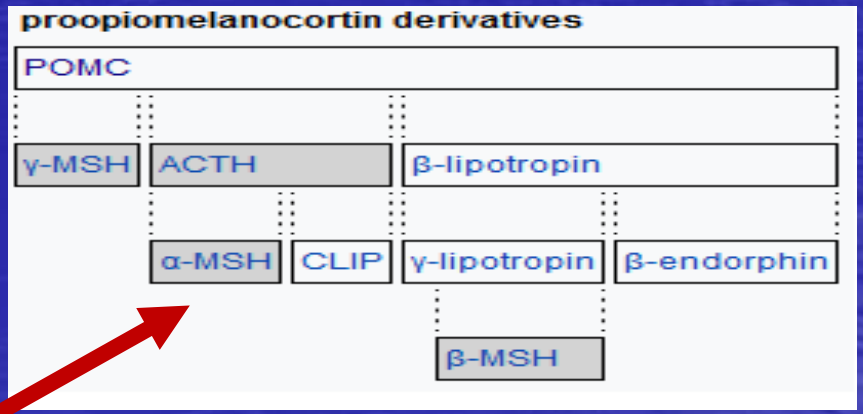
Main neuropeptides that control appetite

- NPY

1) Produced by orexigenic neurons
2) It gives the signal: **Eat!**
3) High concentration of NPY leads to bulimia and obesity

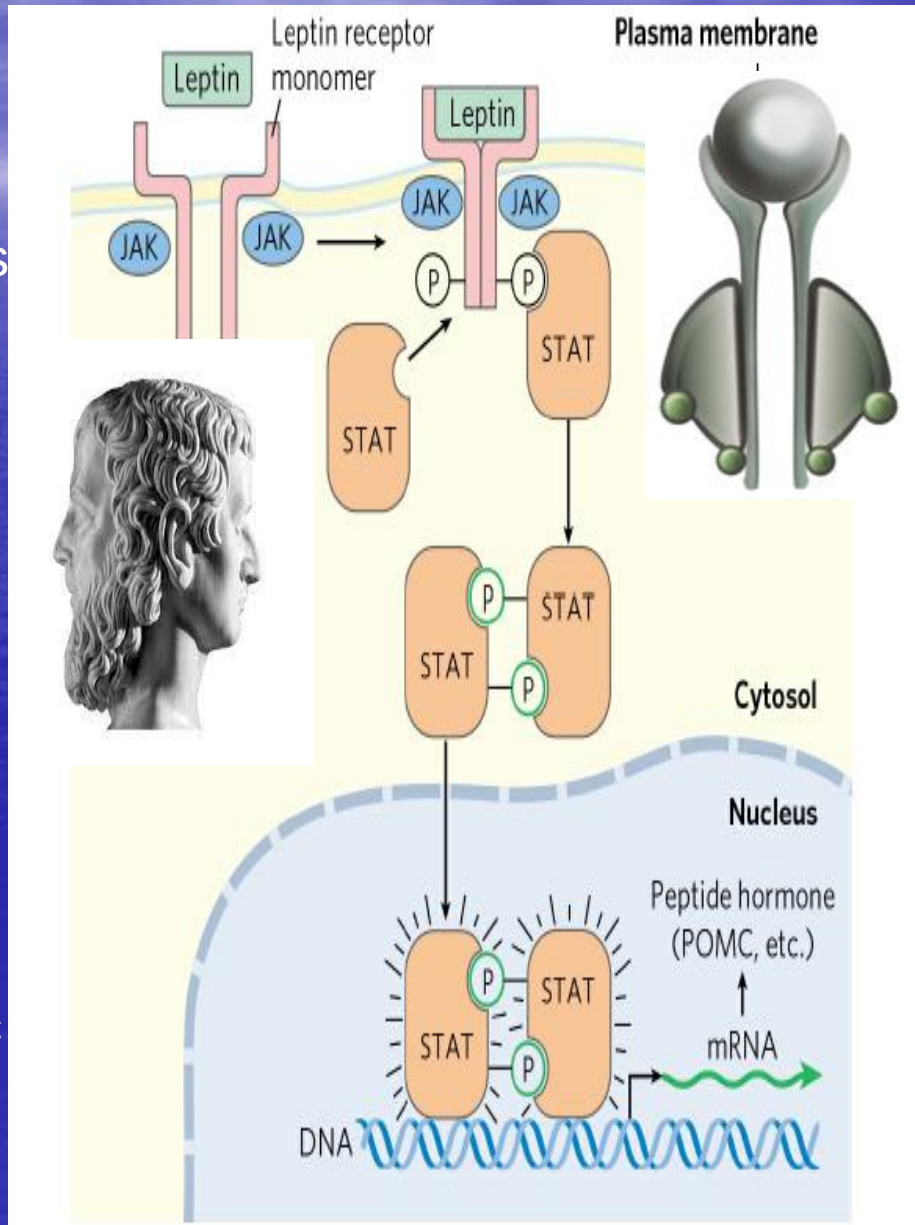
- α-MSH (from POMC)

1) Produced by anorexigenic neurons
2) It gives the signal: **Stop eating!**
3) It is produced from the cleavage of POMC



How does leptin act in the cell???

- -The leptin signal is transduced by the JAK-STAT system, also used by growth factors.
- -The leptin receptor dimerizes when leptin binds to the extracellular domains of two monomers.
- -It undergoes phosphorylation on several Tyr residues by a Janus kinase (JAK).
- -The Ⓟ-Tyr residues become docking sites for proteins that are signal transducers and activators of
- transcription (STATs)
- -The docked STATs are then phosphorylated, dimerized and
- move to the nucleus, binding to specific DNA sequences and stimulating the expression of target genes.



Leptin Triggers a Signaling Cascade That Regulates Gene Expression

- Leptin receptor monomers dimerize and undergo phosphorylation on several Tyr residues
  - initiates a chain of events that ends with the increased synthesis of the POMC gene (and production of α-MSH)

- Leptin also:
  - increases synthesis of the mitochondria in brown and beige adipocytes
  - stimulates UCP1 synthesis

Leptin and Human Obesity:

- Could human obesity be the result of insufficient leptin production and therefore be treatable by the injection of leptin?

Unfortunately, blood levels of leptin are usually much higher in obese animals than in animals of normal body mass

- Leptin injections are not effective at reducing weight in individuals that do not have a defective leptin gene (*OB*)
  - indicates some downstream element in the leptin response system is defective in obese individuals (leptin resistance)
- Most cases of human obesity involve one or more factors (multifactorial) in addition to leptin

Leptin injection is useful in cases of:

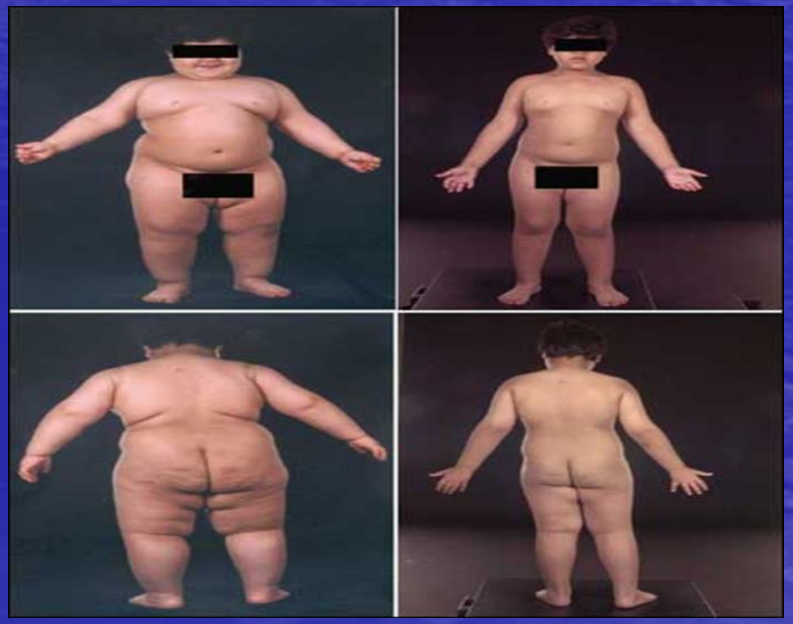
- In states of leptin deficiency (for example congenital)
- In conditions characterized by lipodystrophy

Published: 08 April 2014

Leptin therapy gains FDA approval

Gunjan Sinha

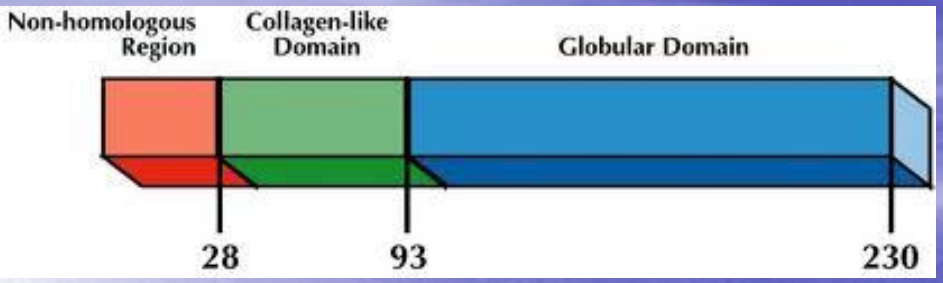
Nature Biotechnology **32**, 300–301(2014) | Cite this article

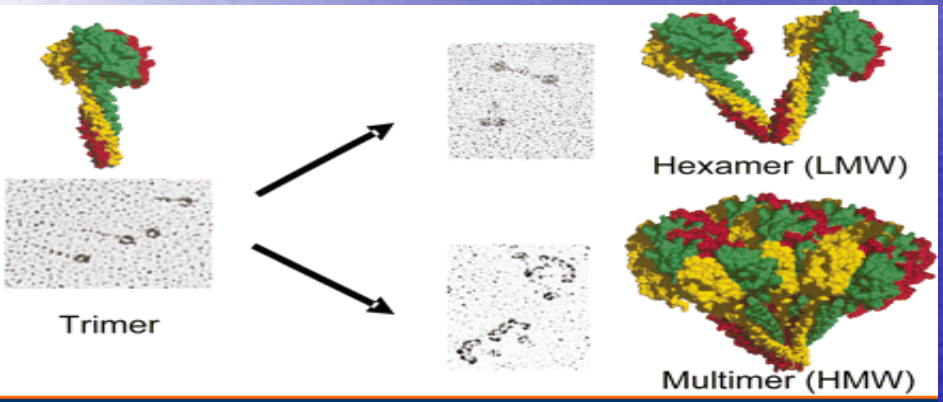


10.2. Adiponectin is another Adipokine

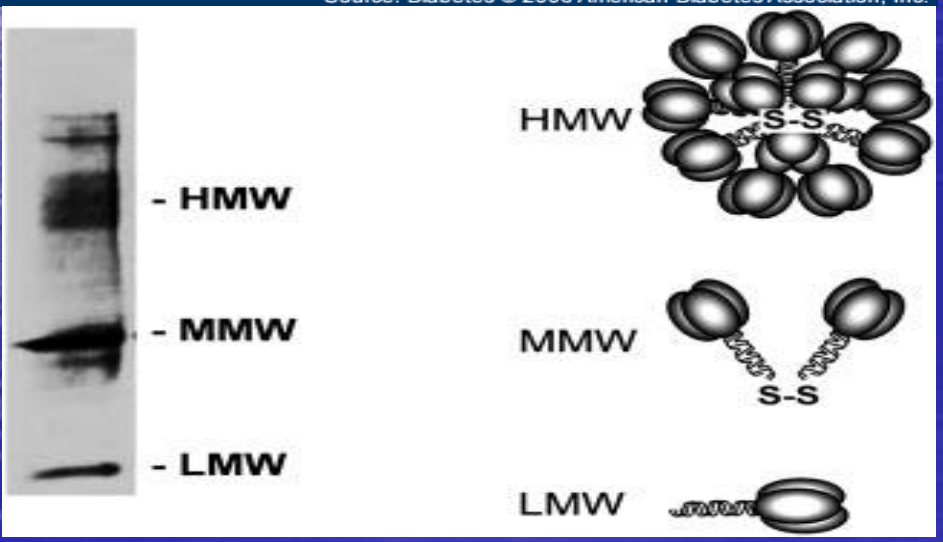
- **Adiponectin = an adipokine produced in adipose tissue**
- **Peptide hormone (244-amino-acid-long polypeptide)**
- **Discovered during 1995-2000 by 4 research groups** (Scherer et al, 1995; Hu et al, 1996; Nakano et al, 1996; and Maeda et al, 1996).
- **In humans, it is encoded by the ADIPOQ gene and is produced primarily in adipose tissue, but also in muscle and even in the brain**
- **It is involved in regulating glucose levels and fatty acid breakdown**
- **It accounts for about 0.01% of all plasma protein at around 5-10 µg/mL**
- **Plasma levels of adiponectin are lower in obese subjects than in lean subjects !!!**

Adiponectin structure and forms





Source: Diabetes © 2006 American Diabetes Association, Inc.



- Adiponectin automatically self-associates into larger structures. Initially, three adiponectin molecules bind together to form a homotrimer
- The trimers continue to self-associate and form hexamers or dodecamers
- Recent studies showed that the high-molecular-weight form may be the most biologically active form regarding glucose homeostasis

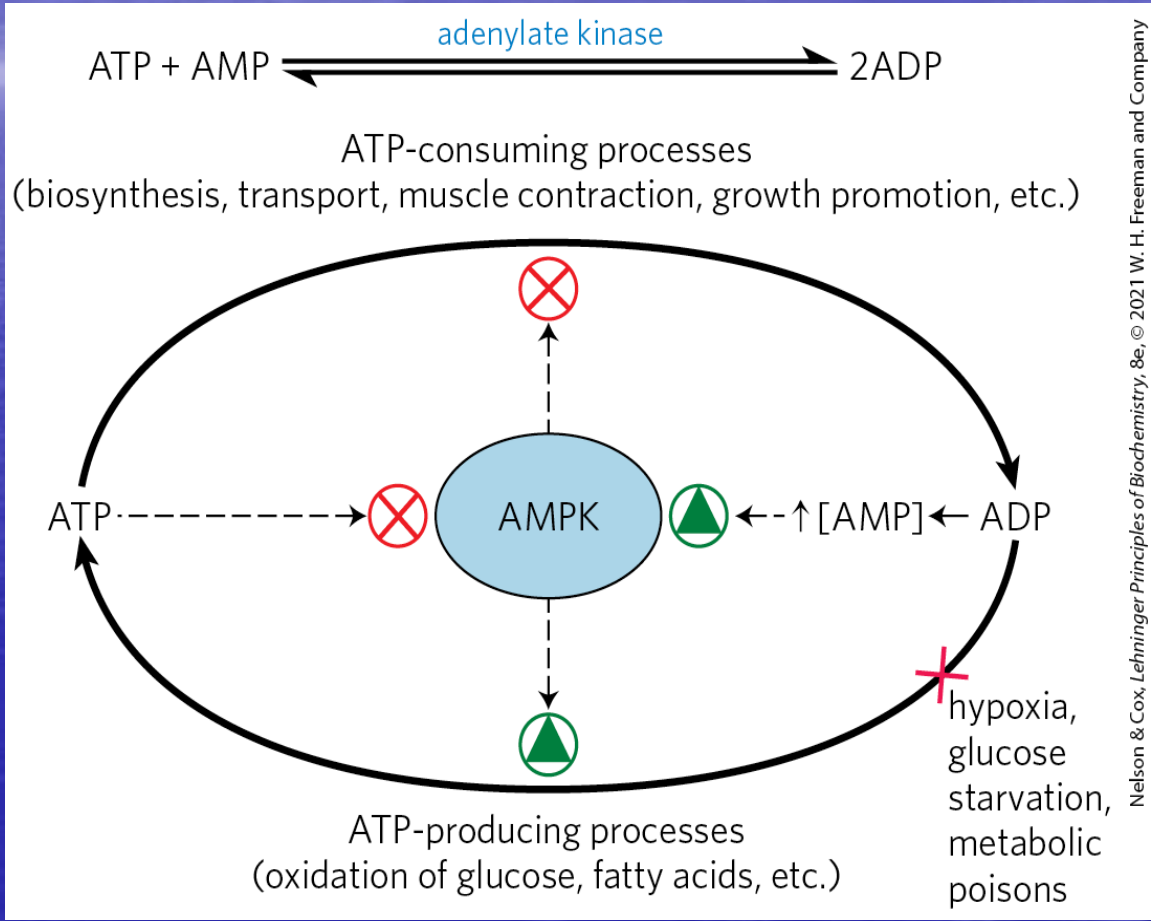
Adiponectin Acts through AMPK to Increase Insulin Sensitivity

- **adiponectin** = an adipokine produced in adipose tissue
  - stimulates fatty acid uptake and oxidation
  - inhibits fatty acid synthesis
  - sensitizes muscle and liver to insulin

- **AMP-activated protein kinase (AMPK)** = mediates many effects of adiponectin

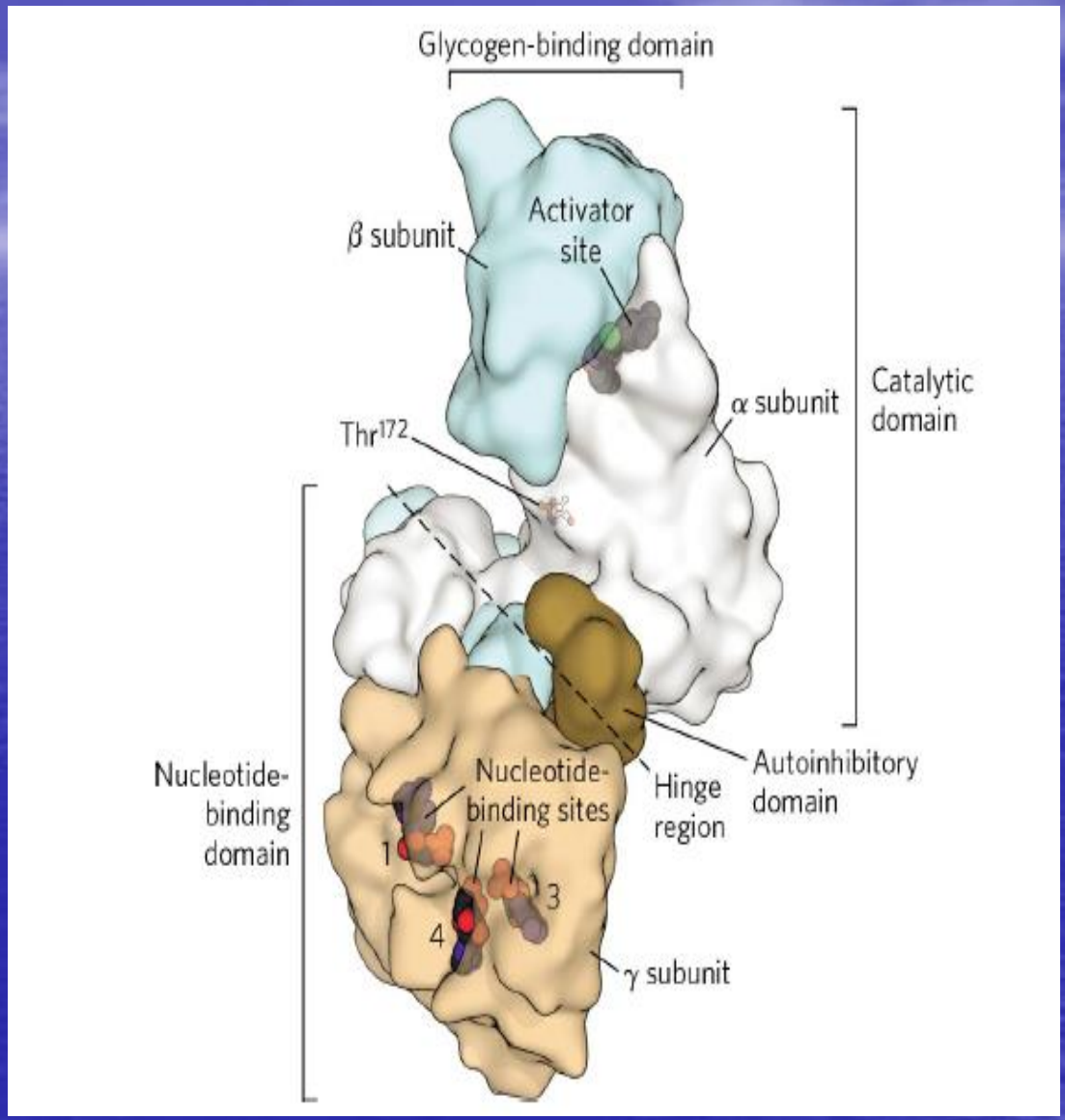
The Role of AMPK in Maintaining Energy Homeostasis

- Adiponectin triggers phosphorylation and activation of AMPK
- **AMPK is activated by factors that signal the need to shift metabolism toward energy generation (↑ ATP) and away from energy-requiring biosynthesis**
- AMPK is activated by AMP

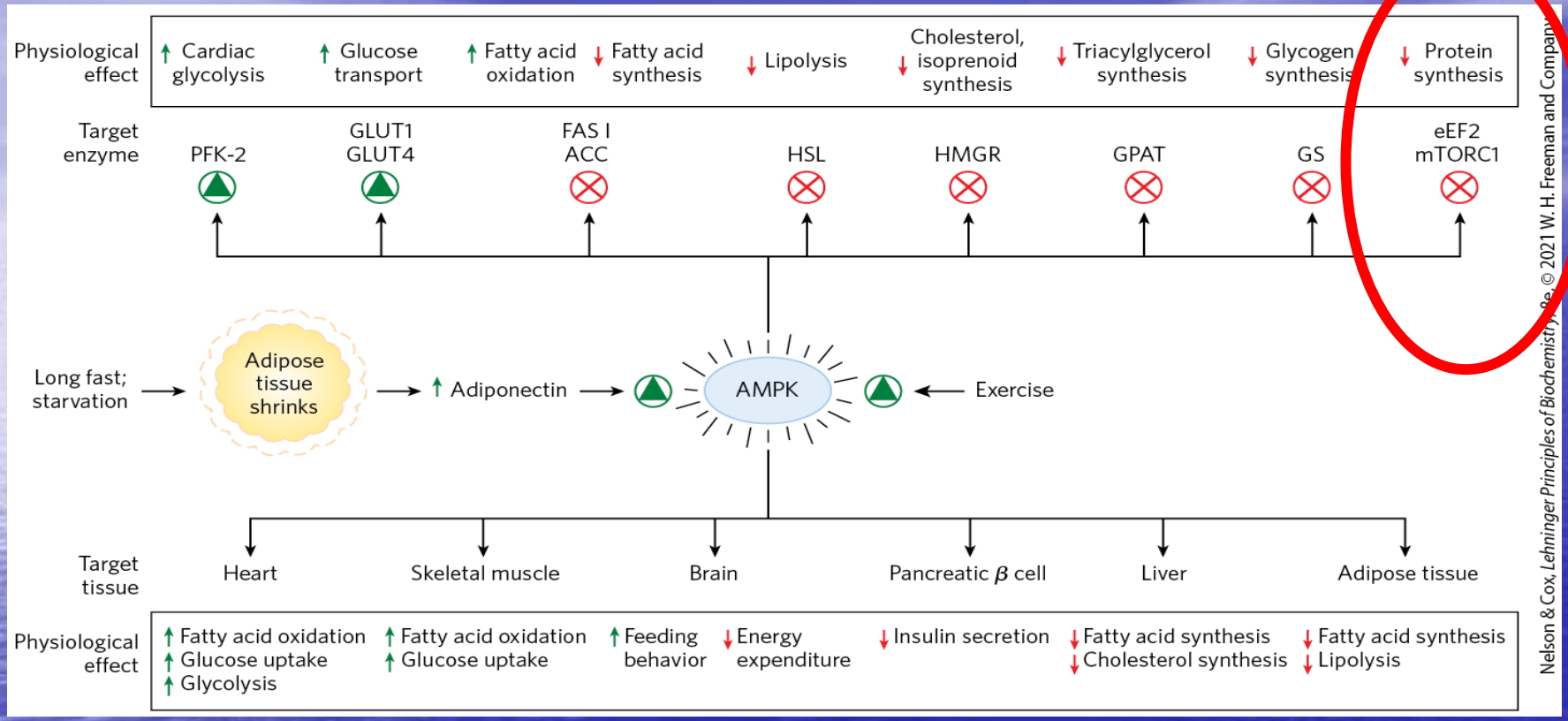


Structure of AMPK

- The enzyme is a **heterotrimer** (3 subunits) with two distinct halves: a catalytic module and a nucleotide-binding module with four nucleotide-binding sites
- The hinge region that connects these two modules contains an
- autoinhibitory domain, which, in the absence of bound AMP, occupies the substrate-binding site and inactivates the enzyme
- Thr172, which, when phosphorylated, activates
- the enzyme 100-fold
- A glycogen-binding domain in
- the catalytic module presumably mediates AMPK binding to glycogen particles, where the enzyme acts to balance
- glycogen synthesis and breakdown.

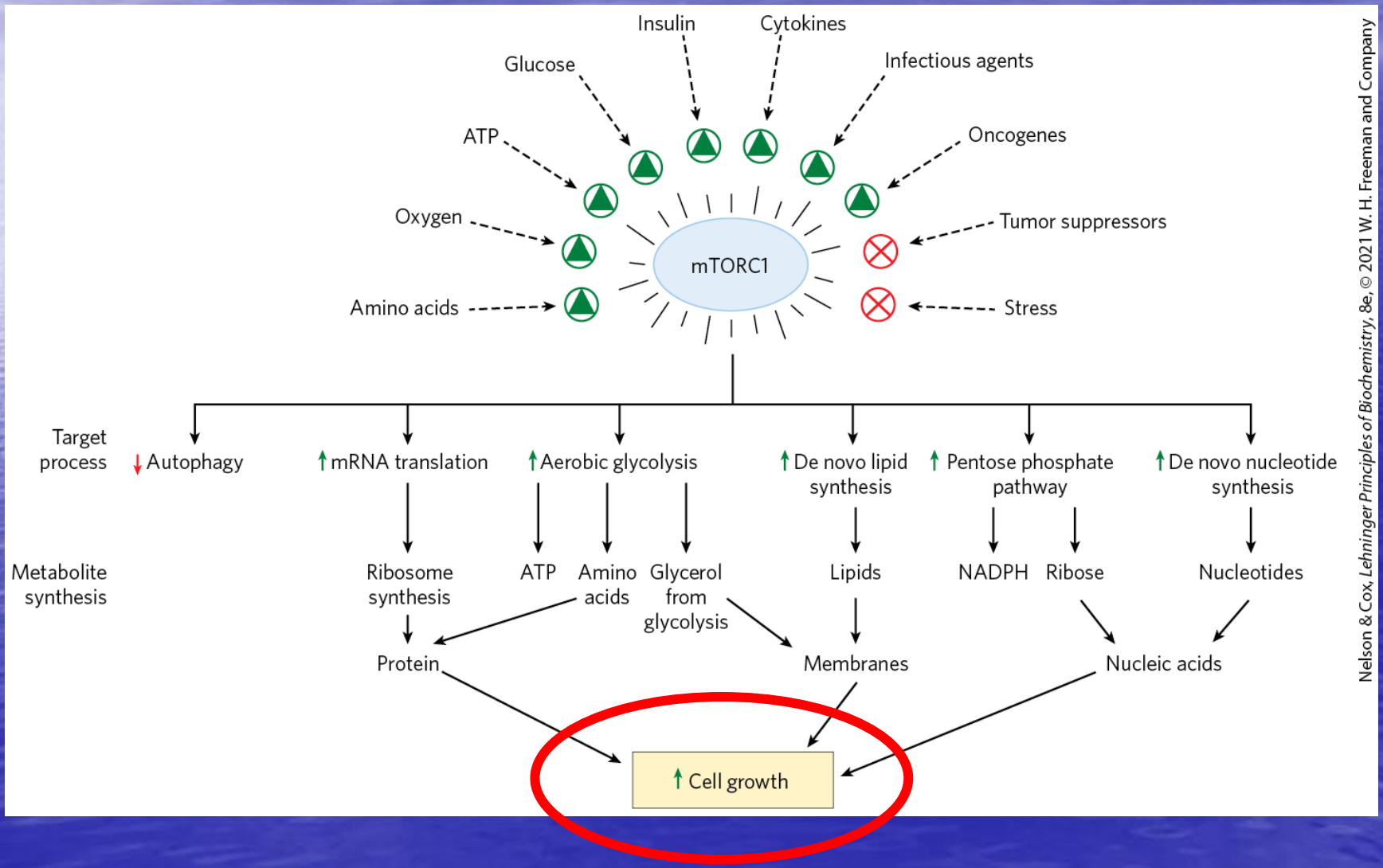


AMPK Coordinates Catabolism and Anabolism in Response to Metabolic Stress



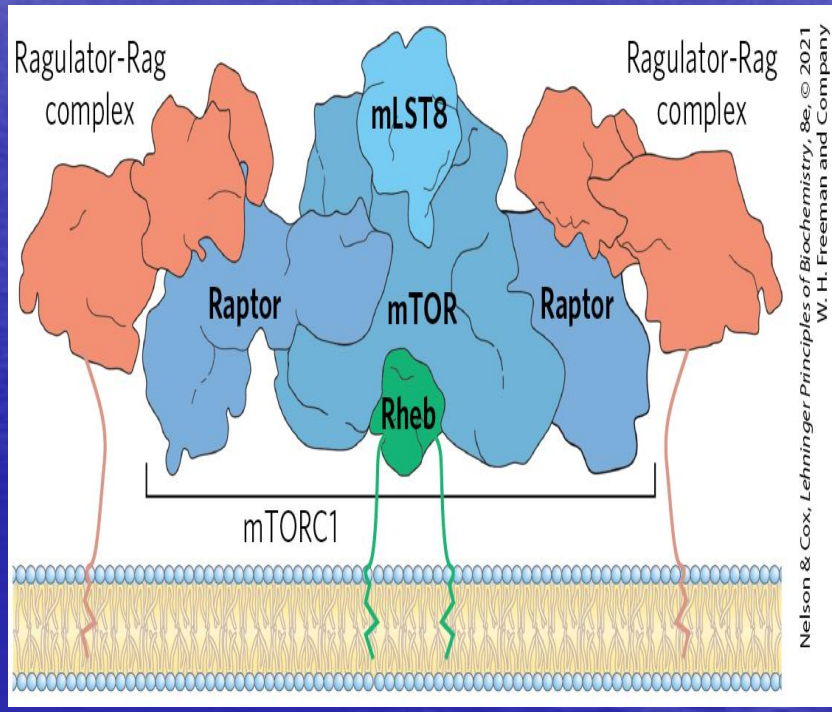
It inhibits energy-consuming processes and stimulate energy-producing processes (to generate ATP). At the cytoplasmic surface of lysosomes, AMPK interacts with a second central regulator of cellular activity, the **protein kinase mTORC1**. This complex enzyme gauges whether sufficient nutrients and low molecular weight substrates are available to support cell growth and proliferation. Together, the two protein kinases control major aspects of a cell's activity and fate.

mTORC1 Activation Signals and the Cellular Process it Activates



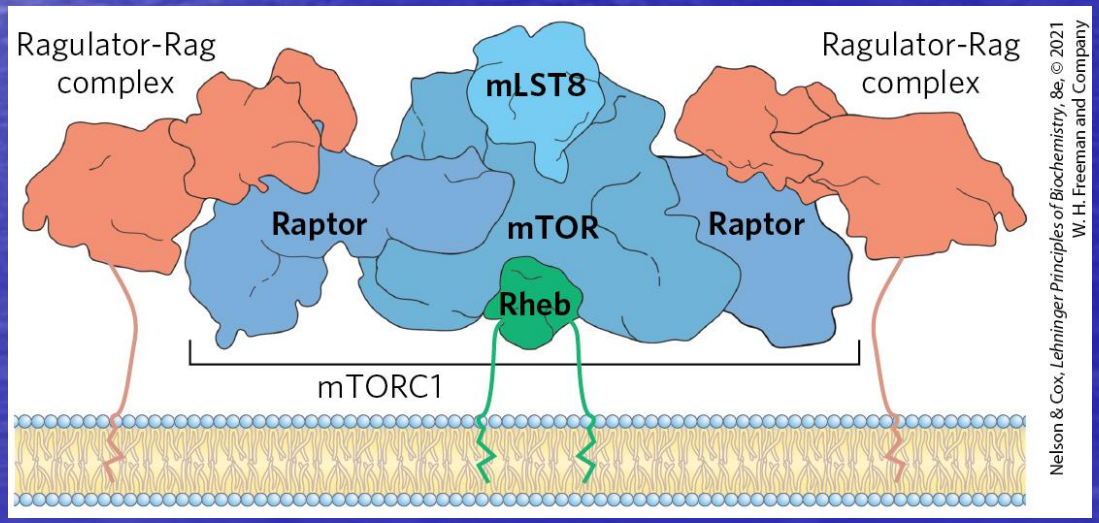
The mTORC1 Pathway Coordinates Cell Growth with the Supply of Nutrients and Energy

- **mTOR** = a highly conserved Ser/Thr kinase
  - forms a complex, **mTORC1**, with a scaffold protein, raptor, and other regulatory proteins
- mTORC is recruited to the cytosolic surface of the lysosome through raptor by the Ragulator-Rag complex
- **Rheb** = G protein that activates the protein kinase activity of mTOR

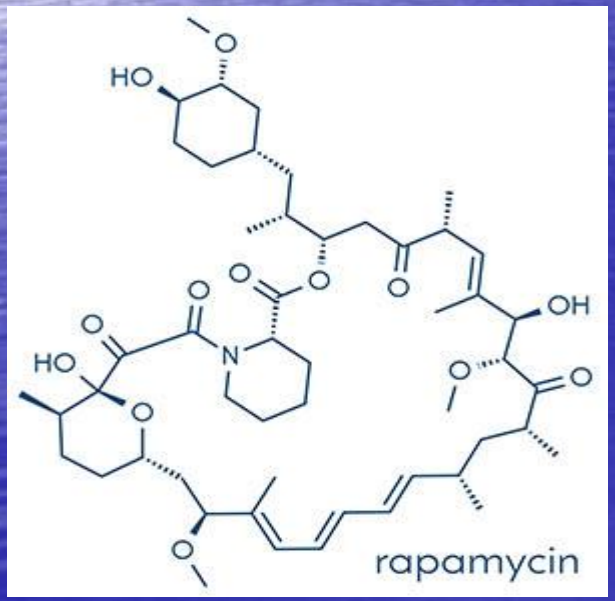


The mTORC-Ragulator-Rag Complex on the Lysosomal Surface

- the complex integrates signals from inside and outside of the lysosome about:
  - the energy status of the cell
  - the availability of critical amino acids needed for protein synthesis
  - the presence of growth factors



mTORC1:The HisTORy behind the Discovery of Rapamycin



Dr Sehgal

Rapamycin, a specific inhibitor of mTOR, has been shown to be useful in the treatment of certain diseases (cancer, diabetes, etc). Rapamycin was initially discovered as an antifungal metabolite produced by Streptomyces hygroscopicus from a soil sample of Easter Island (also known as Rapa Nui).

What else in the metabolic puzzle?

GI TRACT HORMONES

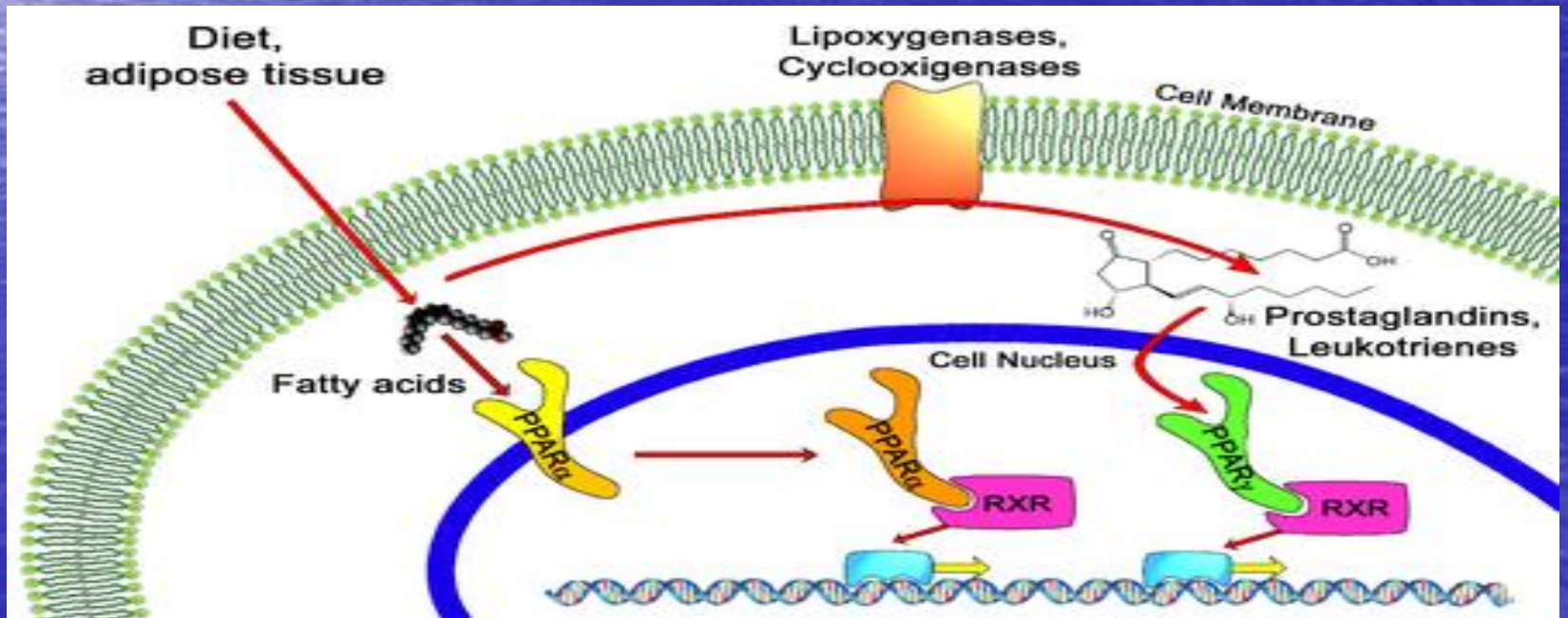
ADIPOKINES

GUT MICROBIOME

ENZYMES & TRANSCRIPTION FACTORS

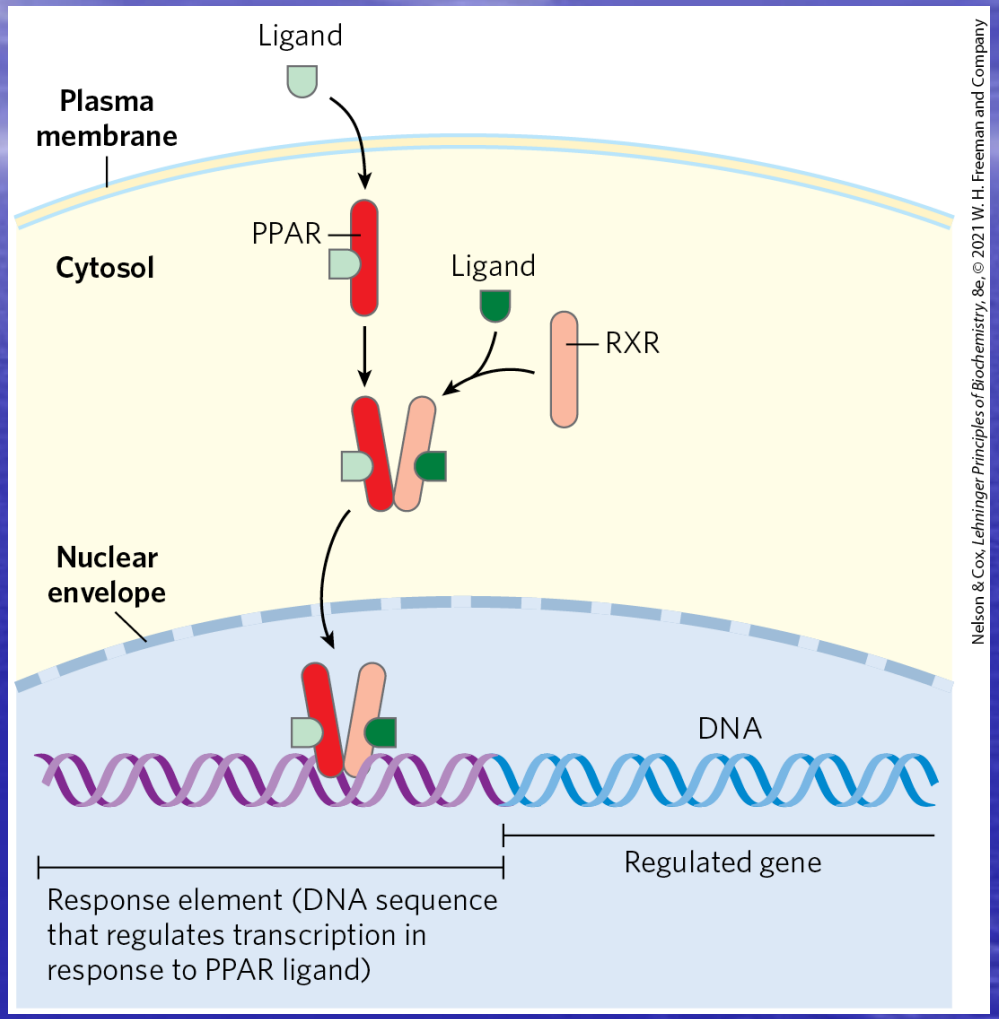
11. How does diet Regulate the Expression of Genes Central to Maintaining Body Mass?

- **Through peroxisome proliferator-activated receptors (PPARs) =** family of ligand-activated transcription factors
  - respond to changes in dietary lipid by altering the expression of genes involved in fat and carbohydrate metabolism



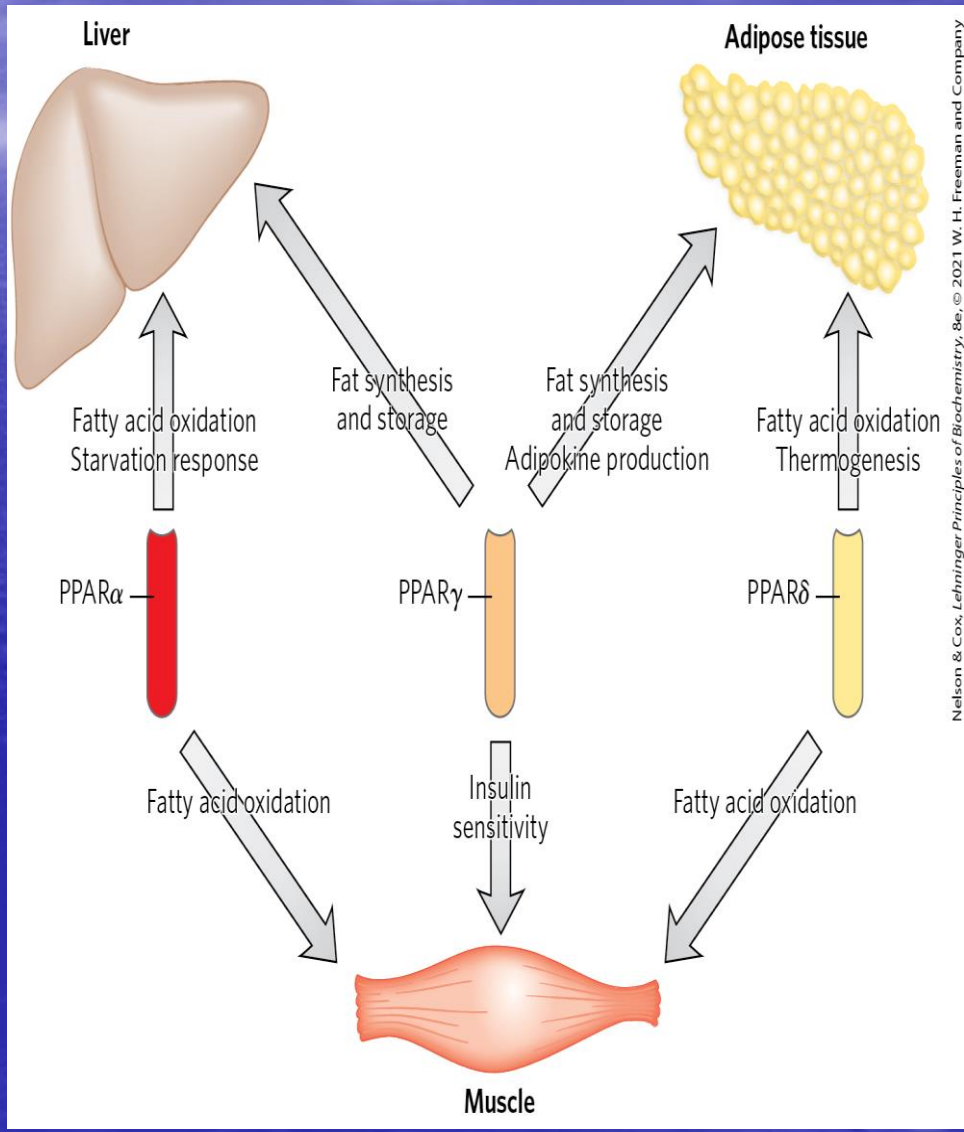
Mode of Action of PPARs

- Ligands are fatty acids or fatty acid derivatives
- PPARs form heterodimers in the nucleus with RXR
- the heterodimers bind to regulatory regions of DNA



The Three PPAR Isoforms Regulate Lipid and Glucose Homeostasis

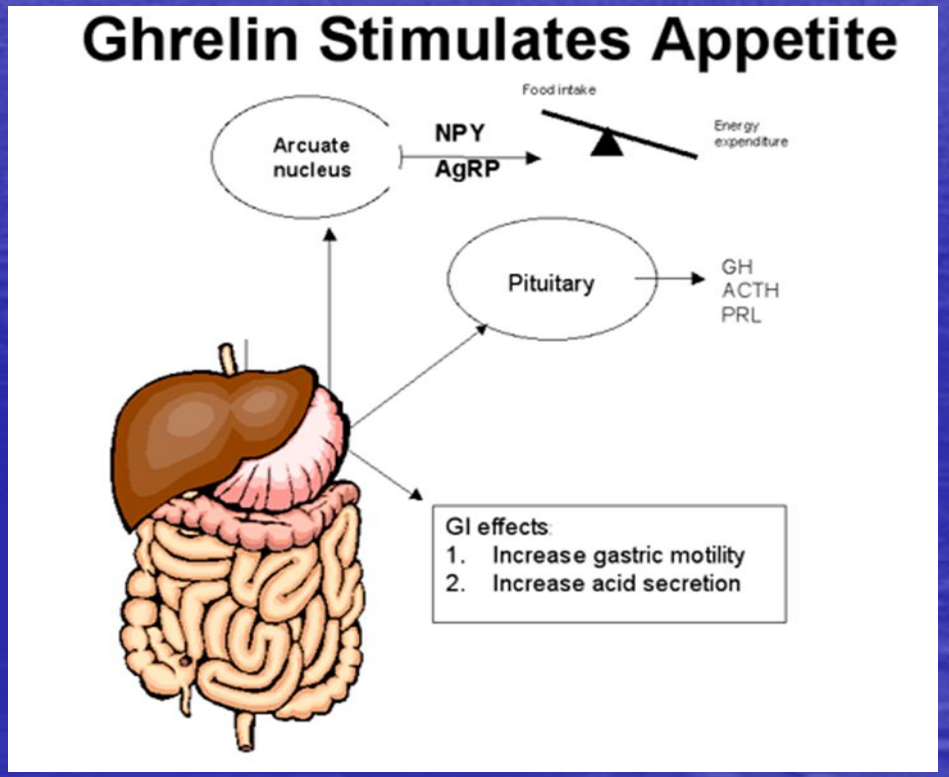
- **PPARγ** = regulates the differentiation of fibroblasts into adipocytes and lipid synthesis and storage in adipocytes
- **PPARα** = regulates the uptake and β oxidation of fatty acids and the formation of ketone bodies during fasting
  - expressed in liver, kidney, heart, skeletal muscle, and brown adipose tissue
- **PPARδ** = regulates β oxidation and energy dissipation through uncoupling of mitochondria
  - acts in the adipose tissue and muscle



12. How is short-term Eating Behavior influenced?

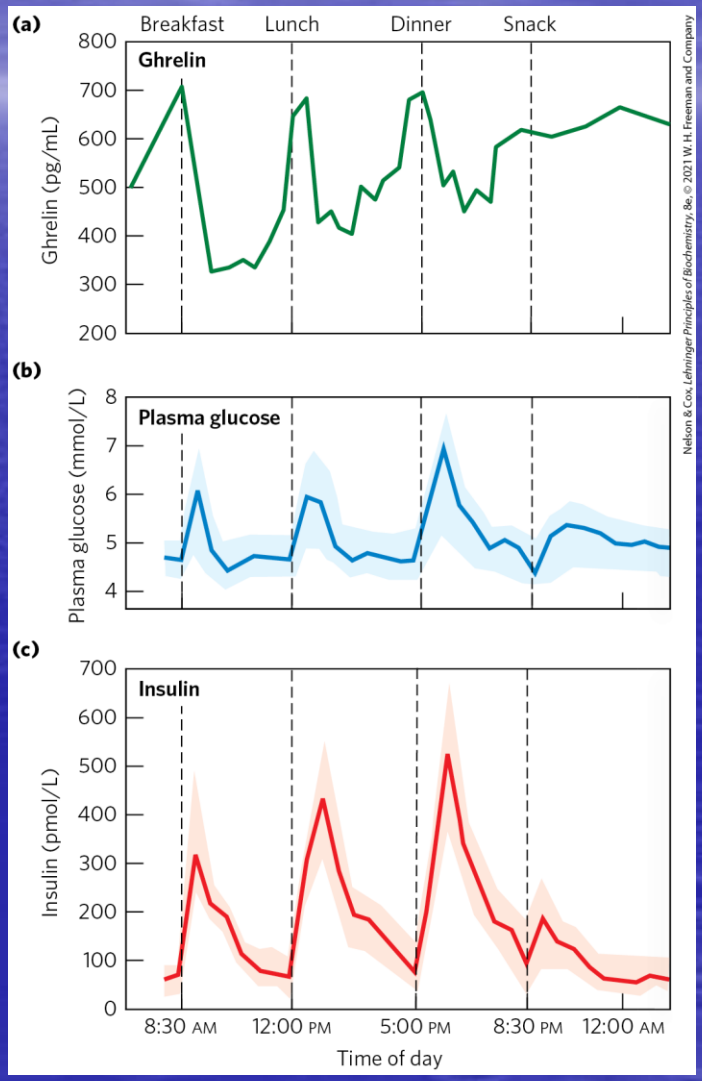
Short-Term Eating Behavior Is Influenced by gastrointestinal hormones: Ghrelin and PYY_{3-36}, as well as Cannabinoids

- **ghrelin** = a peptide hormone produced in cells lining the stomach
  - acts on orexigenic (appetite-stimulating) neurons in the arcuate nucleus to activate hunger
  - works on a shorter time scale than leptin and insulin
  - acts through a GPCR



Variations in Blood Concentrations of Glucose, Ghrelin, and Insulin

- Ghrelin concentration in the blood peaks just before a meal
- Injection of ghrelin into humans produces immediate sensations of intense hunger
- Individuals with Prader-Willi syndrome, whose blood levels of ghrelin are exceptionally high, have an uncontrollable appetite, leading to extreme obesity that often results in death before the age of 30.



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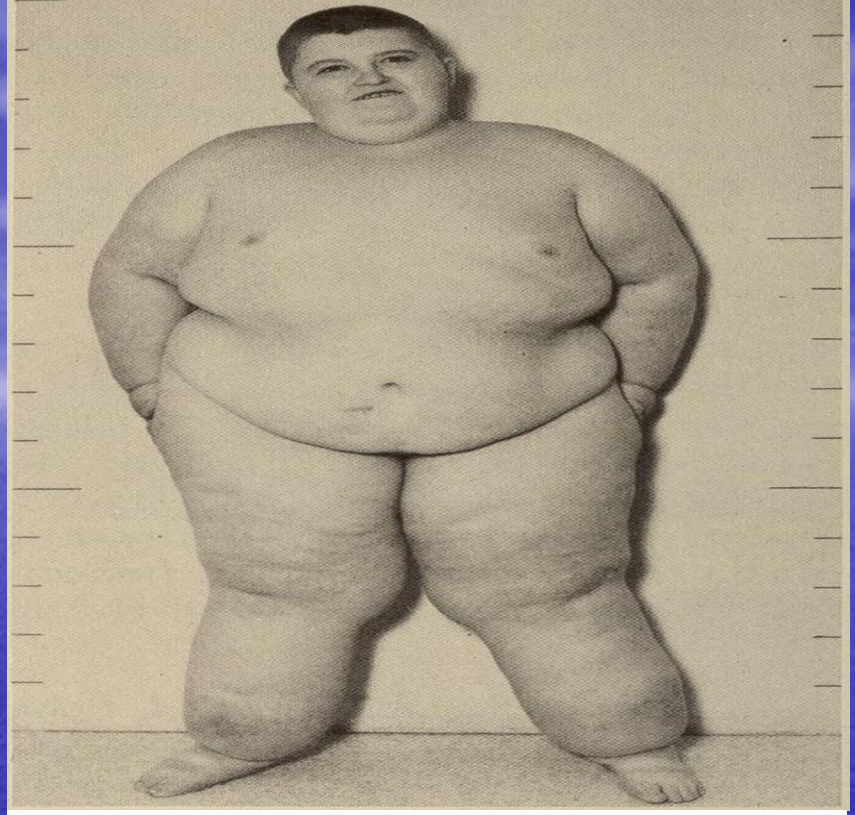
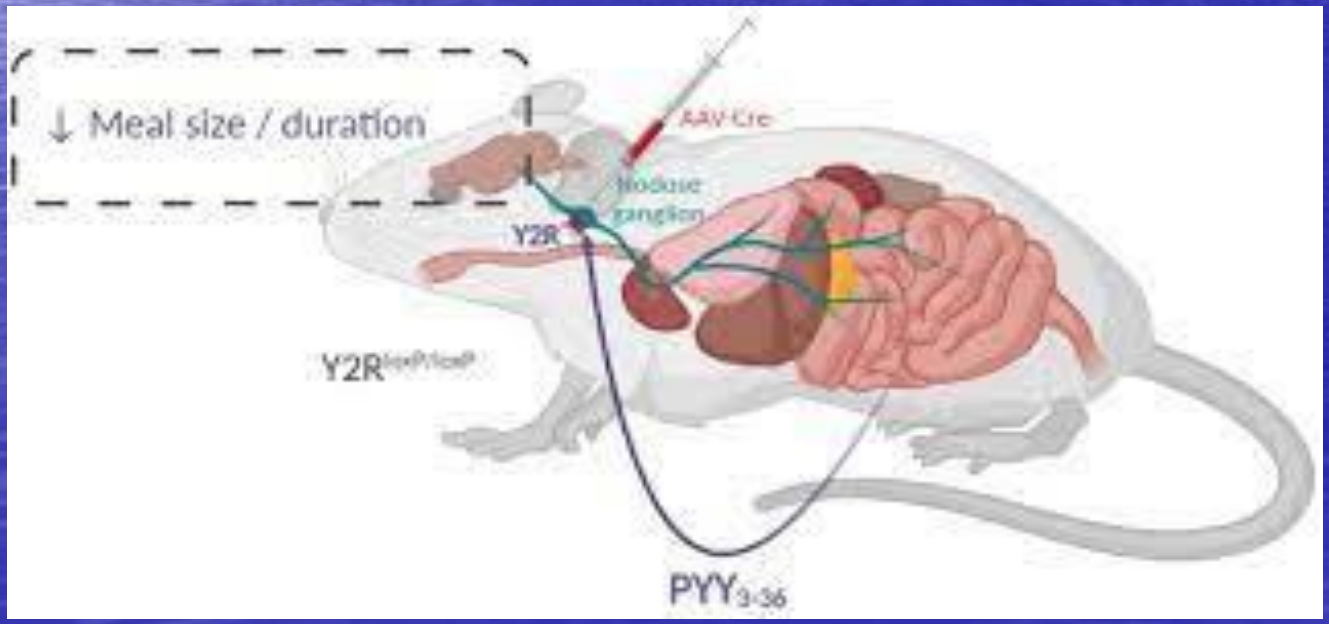


Another gut hormone: PYY_{3-36} Acts to Lessen Hunger After a Meal

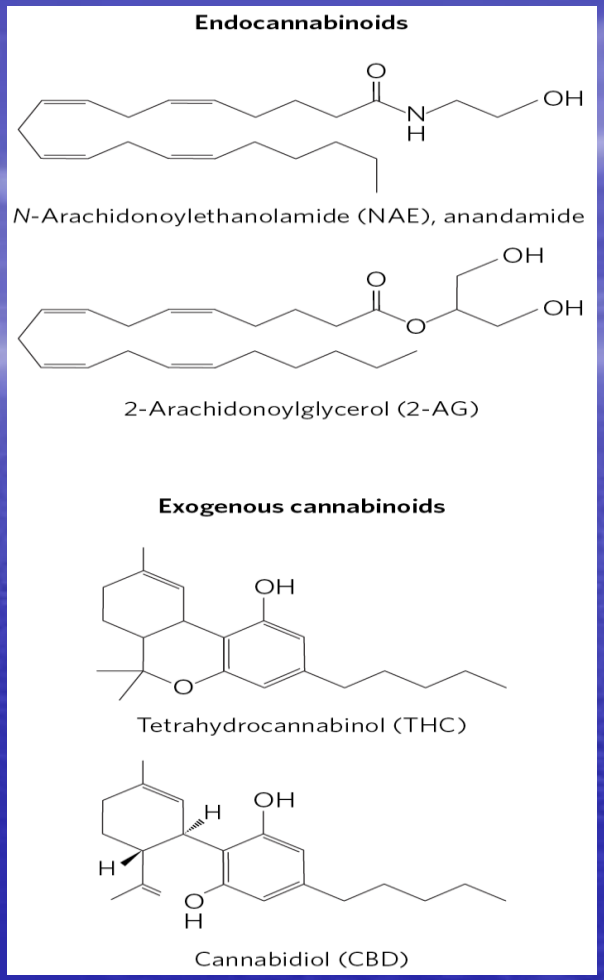
- **PYY_{3-36}** = a peptide hormone secreted by endocrine cells in the small intestine and colon in response to food entering from the stomach
  - acts on orexigenic neurons in the arcuate nucleus to inhibit NPY release and reduce hunger



Cannabinoids

- **endocannabinoids** = eicosanoid lipid messengers that signal the availability of sweet or fatty food and stimulate its consumption
  - act through specific GPCRs in the brain and PNS that control ion channels

- cannabinoid receptors also mediate the psychoactive effects of Δ^9-tetrahydrocannabinol (the main active ingredient in marijuana)



12. Gut microbiome and obesity

Vol 444|21/28 December 2006

NEWS & VIEWS

PHYSIOLOGY

Obesity and gut flora

Matej Bajzer and Randy J. Seeley

The intestinal bacteria in obese humans and mice differ from those in lean individuals. Are these bacteria involved in how we regulate body weight, and are they a factor in the obesity epidemic?

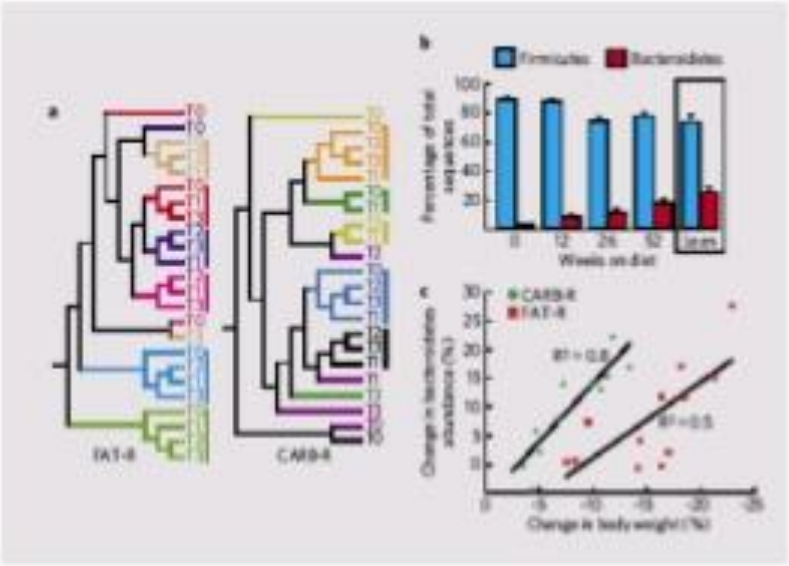
MICROBIAL ECOLOGY

Human gut microbes associated with obesity

Two groups of beneficial bacteria are dominant in the human gut, the Bacteroidetes and the Firmicutes. Here we show that the relative proportion of Bacteroidetes is decreased in obese people compared to lean people, and that this proportion increases with weight loss on two types of low-calorie diets. Our findings suggest that obesity has a microbial component, which might have potential therapeutic implications.

Trillions of microbes live in the human gut, helping to break down otherwise indigestible foods[1]. Transplanting the gut microbiota from normal mice into germ-free recipients increases their body fat without any increase in food consumption[2], raising the possibility that the composition of the microbial community in the gut affects the amount of energy extracted from the diet[3].

The relative abundance of the two predominant bacterial divisions (deep evolutionary lineages or superkingdoms) in mice differs between lean and obese animals: mice that are genetically obese (*ob/ob*) have 50% fewer Bacteroidetes, and correspondingly more



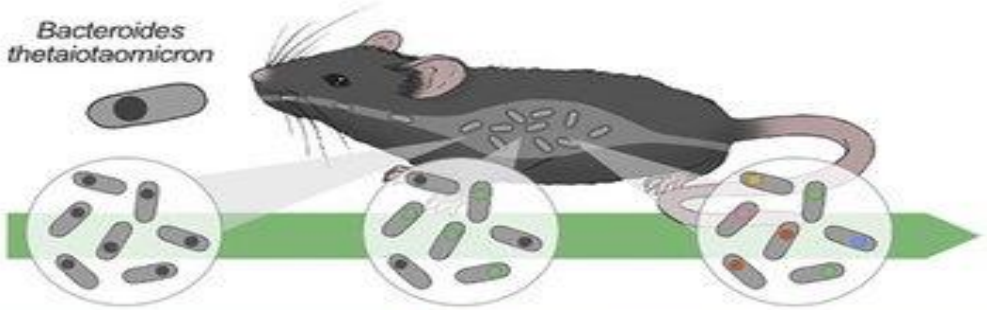
- Diets designed for reduced energy intake/slimming, with either reduced fat or reduced carbohydrate
- Microbiota approaches lean profile with weight loss – no info on diets (nutrient substitution)

Ley et al., Nature (2006)

Gut microbiome

- Adult humans are hosts to ~10^{14} gut microbes.
- 10- 100 X more the number of human cells
- Characterized by abundance and diversity
- Endocrine system that produces several metabolites influencing metabolism
- Gut microbiome establishes a powerful symbiosis with our body

The effect of host diet on bacterial evolution



Standard Diet

Metabolite Abundance

Simple Sugars

Short-Chain Fatty Acids

Genetic Diversity

Low

Mutations Promote Fiber Degradation

Western Diet

Metabolite Abundance

Simple Sugars

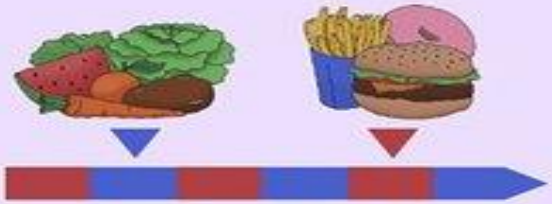
Short-Chain Fatty Acids

Genetic Diversity

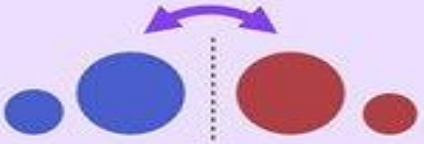
Low

Mutations Promote Mucus Degradation

Alternating Diet



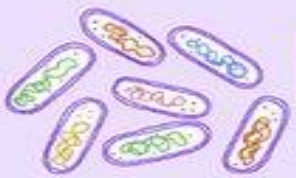
Metabolite Abundance



Alternates With Diet

Genetic Diversity

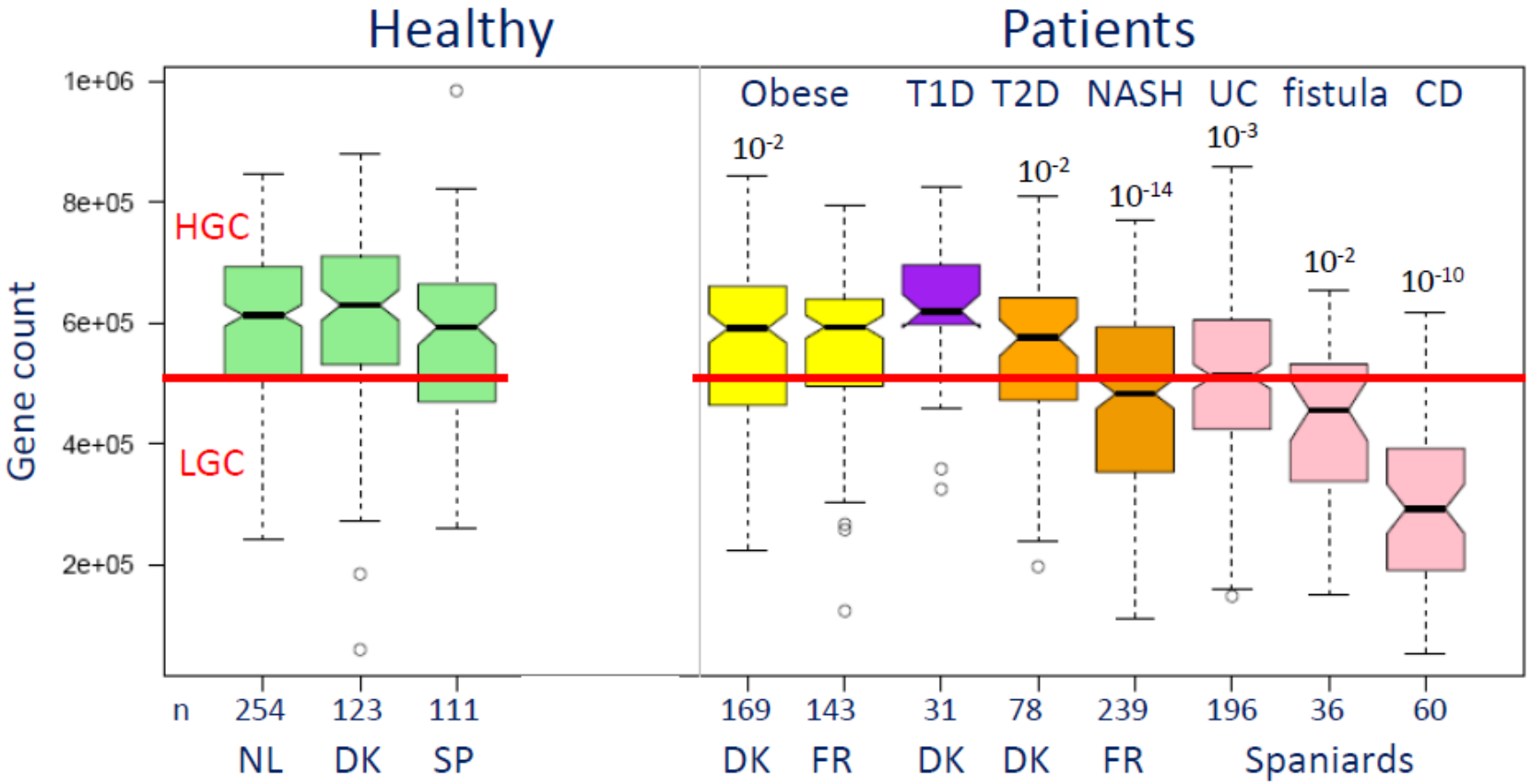
High



Fluctuating Selection

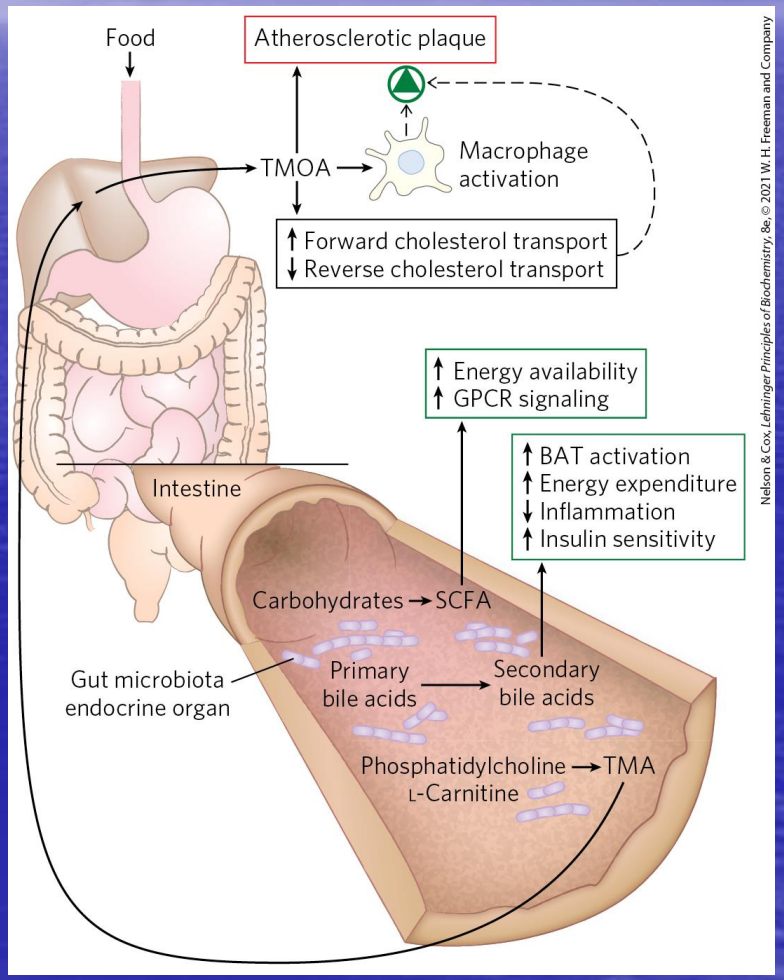
Unique Genetic Signature

A common alteration is loss of microbial richness



Gut microbes in the Gut Influence Energy Metabolism and Adipogenesis

- Lean and obese individuals harbor different combinations of microbial symbionts in the gut
- Gut microbes release: 1) fermentation products—the short-chain fatty acids acetate, propionate, butyrate, and lactate—that enter the bloodstream and trigger metabolic changes in adipose tissue, and 2) secondary bile acids.
  - influence release of gut hormones that regulate body mass



Endocrine Cell Interactions with Gut Microbes May Affect Gut Hormones Release

- endocrine cells in the intestinal tract secrete peptides that modulate food intake and energy expenditure:
  - the anorexigenic $PYY_{3–36}$ (and GLP-1)
  - the orexigenic ghrelin

- peptide release may be affected by the interaction of endocrine cells with specific microbes in the gut or with their fermentation products

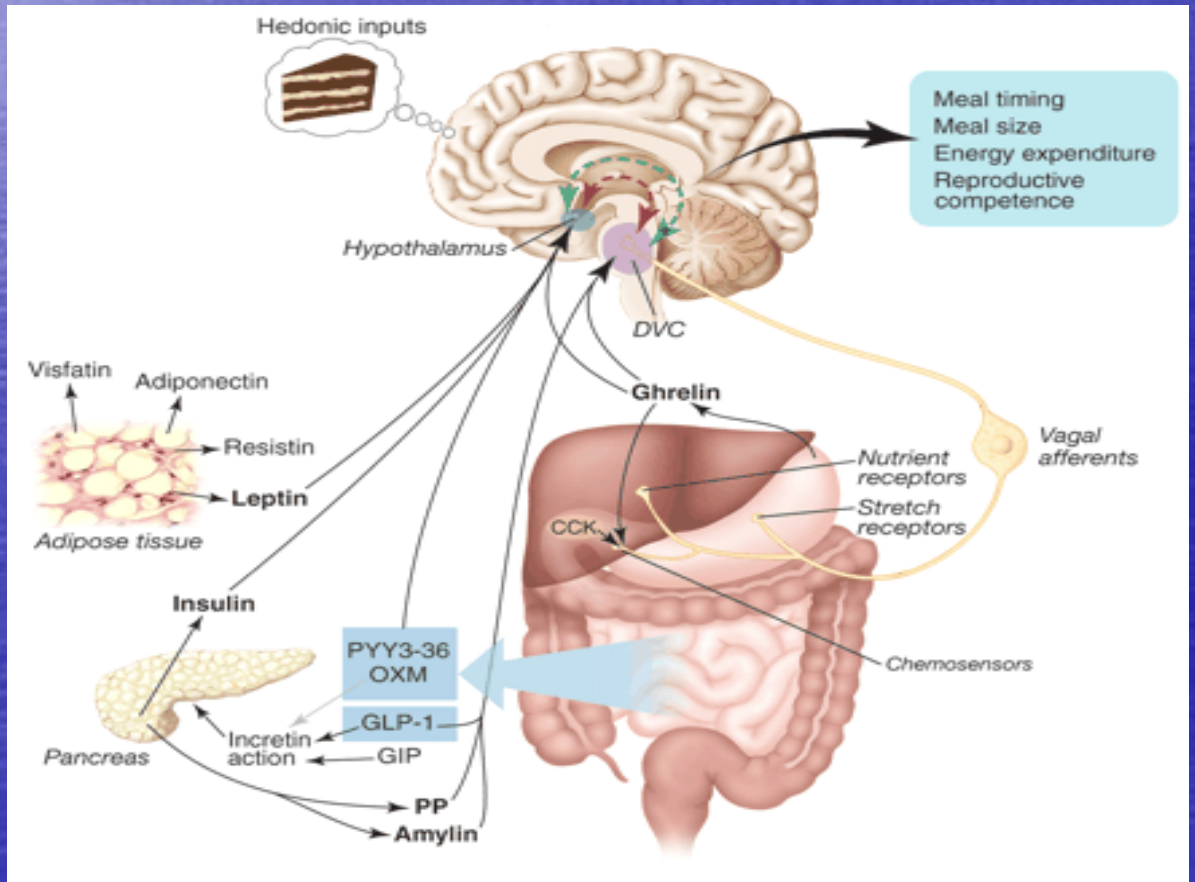

Microbiota transfer from twins discordant for obesity
Are gut microbiome changes the cause or the effect of obesity????
Genetically identical germ-free mice
Slim
Obese

How can we alter gut microbiome and promote weight reduction?

- Healthy diet
- Weight reduction might be accomplished by adding to the gut either:
  - **probiotics** (microbial species e.g. *Bifidobacterium spp* that disfavor adipogenesis)
  - **prebiotics** (nutrients that favor the dominance of probiotic microbes): fructans, polymers of fructose that are indigestible by animals, favor a specific microbial community
  - Synbiotics (probiotics+prebiotics)
  - Fecal transplantation?

CONCLUSION

There is a complex neuroendocrine system that controls food intake and metabolism presumably evolved to protect against starvation and to eliminate counterproductive accumulation of fat (extreme obesity). The difficulty most people face in trying to lose weight testifies to the remarkable effectiveness of these controls.



SUMMARY

- ✓ Obesity is increasingly common in all countries predisposing people to several chronic, life-threatening conditions, including cardiovascular disease, type 2 diabetes and cancer. BMI is a practical index of obesity
- ✓ Adipose tissue produces leptin, a hormone that regulates feeding behavior and energy expenditure. Leptin production and release increase with the number and size of adipocytes.
- ✓ Leptin acts on brain receptors causing the release of appetite-suppressing peptides, including α-MSH, that act in the brain to inhibit eating.
- ✓ Adiponectin stimulates fatty acid uptake and oxidation and inhibits fatty acid synthesis. It also sensitizes muscle and liver to insulin. The actions of adiponectin are partly mediated by AMPK, which is also activated by low [AMP] and exercise.

- ✓ Protein kinase mTORC1 triggers cell growth if all nutrients are available. AMPK and mTORC1 determine the energetic status of a cell.
- ✓ PPARs are transcription factors that determine the synthesis of many enzymes involved in lipid metabolism and adipocyte differentiation.
- ✓ Ghrelin, a hormone produced in the stomach, acts on appetite-stimulating neurons to increase hunger before a meal. PYY_{3-36}, a peptide hormone of the intestine, acts at the same site to lessen hunger after a meal. Endocannabinoids signal the availability of sweet or fatty food and stimulate its consumption.
- ✓ Gut microbes produce fermentation products and secondary bile acids influencing the release of gut hormones that regulate body mass.

LEARNING OBJECTIVES-Students should be able to answer the following questions OR to:

- Recognize the obesity pandemic. • What are the causes of obesity?
- How is obesity defined? • How is body mass measured?
- How is weight status classified based on WHO?
- What are the health risks associated with obesity?
- Is BMI a perfect measure for obesity?
- Are there other measures/indices of body mass?
- Explain the role of white and brown adipose tissue.
- Describe the structure and function of white, brown and beige adipocytes.
- What is the fate of excess dietary calories?
- Which hormones are produced by the adipose tissue?
- Explain the metabolic role of leptin and its molecular mechanism of action (receptor and signaling).
- Which are the main neuropeptides that control appetite?
- Explain the metabolic role of adiponectin and its molecular mechanism of action.
- What is the role of AMPK in maintaining energy homeostasis?

LEARNING OBJECTIVES-Students should be able to answer the following questions OR to:

- Explain how the mTORC1 Pathway Coordinates Cell Growth with the Supply of Nutrients and Energy.
- How do PPAR Isoforms Regulate Lipid and Glucose Homeostasis?
- What is the molecular mode of action of PPARs?
- How is short-term eating behavior influenced? Which are the main gut hormones in short-term eating behavior? Explain their function.
- What is the gut microbiome and its role?
- How do gut microbes influence Energy Metabolism and Adipogenesis?
- How can we alter gut microbiome and promote weight reduction?

Multiple choice questions-SAMPLE

1. **Which is FALSE about neuropeptide Y (NPY)?**

A. It is produced by orexigenic neurons

B. It gives the signal: Eat!

C. High concentration of NPY leads to bulimia and obesity

D. It is produced by anorexigenic neurons

2. Which of the following hormones and neuropeptides are orexigenic?

A. Ghrelin

B. PYY 3-36

C. Ghrelin and NPY

D. α-MSH

E. α-MSH and PYY3-36

Study material

- 1) slides
- 2) Nelson DL, Cox MM. Lehninger Principles of Biochemistry. 8th edition. NY 2021: chapter 23.4: pages: 867-875

Thank you very much for your attention!!!