Basics of Obesity Biology & Weight Loss Physiology

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Disclosure

Advisory Board: Altimmune; Amgen; Astra Zeneca; Biohaven; Boehringer Ingelheim; Calibrate; Carmot/Roche; Cin RX; Currax; Epitomee Medical; Fractyl; Gila Therapeutics; Lilly; Novo Nordisk; Regeneron; Structure Therapeutics; Wondr Health; Zealand Pharma

Consultant: Calibrate; Epitomee Medical; Nestle; Scientific Intake

DSMB: Cin RX

DSMB (Setmelanotide): Rhythm, IQVIA

DSMB (Tirzepatide): Lilly

Speaker's Bureau: Lilly; Novo Nordisk

Stock Options: Calibrate; Epitomee Medical; Roman; Scientific Intake; Xeno Biosciences



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OBJECTIVES: AT THE END OF THE PRESENTATION ATTENDEES WILL BE ABLE TO

1. describe the environmental and genetic factors that interact to produce obesity – its etiology;
2. distinguish the different phenotypic expressions of excess, abnormal and dysfunctional fat storage that drive risk for obesity complications – its pathogenesis; and
3. relate the biologic and physiologic responses to weight reduction that make weight loss difficult and weight regain common – why it's a *chronic* disease.

3

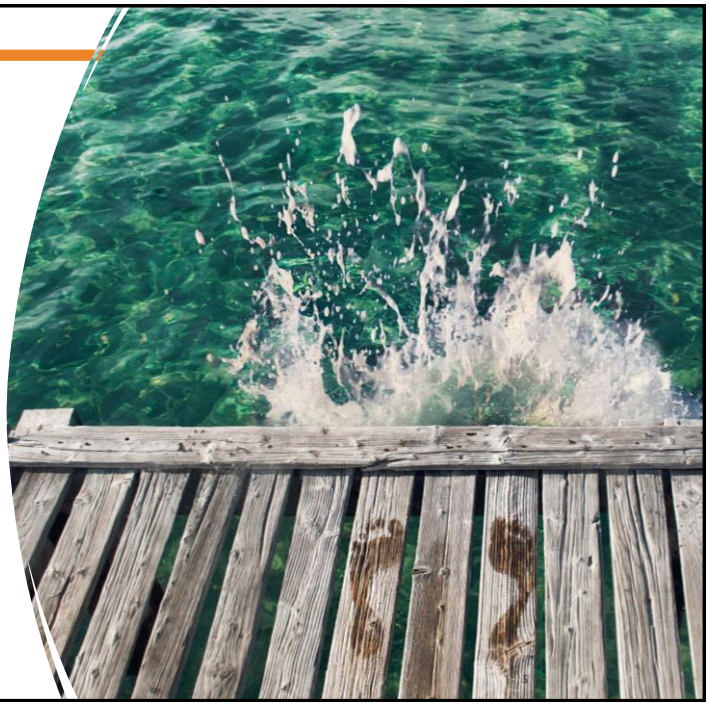
OBJECTIVES: AT THE END OF THE PRESENTATION ATTENDEES WILL BE ABLE TO ANSWER THE FOLLOWING QUESTIONS:

1. Why do some people develop obesity and others don't?
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3. Why do people succeed at weight loss, only to regain?

4

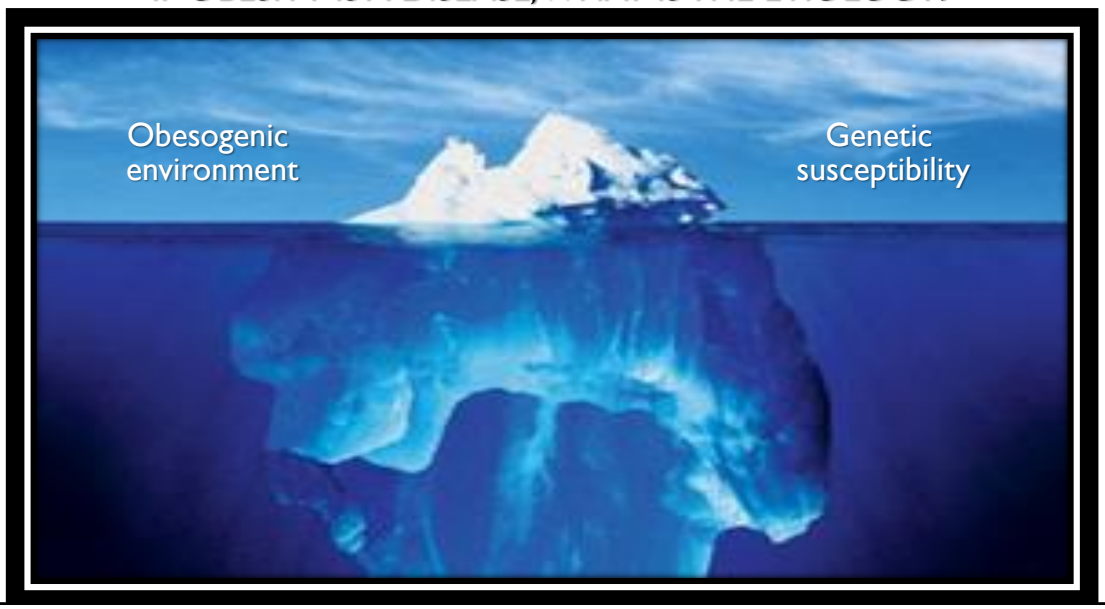
Taking the First Steps to Good Medical Management of Obesity

Understanding the Biologic Basis of Obesity as a Chronic Disease



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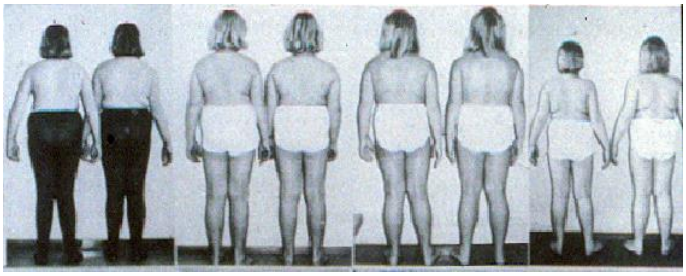
IF OBESITY IS A DISEASE, WHAT IS THE ETIOLOGY?



6

GENETIC CONTRIBUTION TO BODY HABITUS





Borjeson M. *Acta Paediatr Scand*. 1976;65(3):279-287.

7

GENETIC OBESITY RISK

- There are rare single gene (monogenic) variants that greatly increase obesity, especially in childhood, and make it nearly impossible to lose weight
- Approximately 43% of Americans have a high polygenic risk for obesity
  - But this genetic risk does not guarantee obesity
  - 16% - 20% of those with very high polygenic obesity risk scores do not suffer from obesity
  - However, high polygenic obesity risk may make it harder to lose unwanted weight
- Those with the *FTO* gene variant are 67% more likely to develop obesity
  - But they have a 27% greater ability to achieve weight loss with regular exercise
- DNA is **not** destiny

Thaker VV, et al. *Adolesc Med State Art Rev.* 2017;28(2):379-405.

8

IF OBESITY IS A DISEASE, WHAT IS THE ETIOLOGY?



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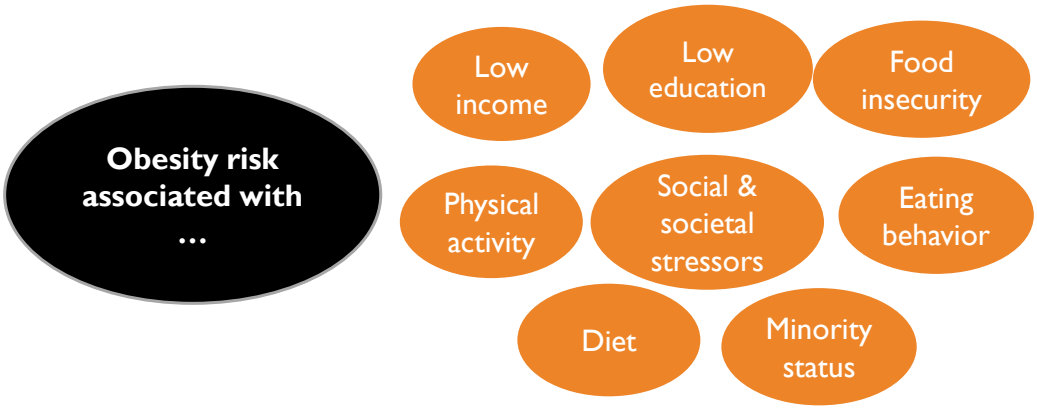
DRUGS THAT CAUSE WEIGHT GAIN

Category	Drugs That May Cause Weight Gain	Possible Alternatives
Neuroleptics	Thioridazine, haloperidol, olanzapine, quetiapine, risperidone, clozapine	Ziprasidone, aripiprazole
Antidiabetic agents	Insulin, sulfonylureas, thiazolidinediones	AGIs, DPP-4is, SGLT2is, GLP-1 RAs, metformin
Steroid hormones	Glucocorticoids, progestational steroids and contraceptives	Barrier methods, NSAIDs
Tricyclic antidepressants	Amitriptyline, nortriptyline, imipramine, doxepin	Protriptyline, bupropion, nefazodone
MAOIs	Phenelzine	
SSRIs	Paroxetine	Fluoxetine, sertraline
Other antidepressants	Mirtazapine, duloxetine	Bupropion
Anticonvulsants	Valproate, carbamazepine, gabapentin, pregabalin, vigabatrin	Topiramate, lamotrigine, zonisamide, felbamate
Antihistamines	Cyproheptadine	Inhalers, decongestants
β- and α-blockers	Propranolol, doxazosin	ACEi, CCBs

(1) Kushner RF, Ryan DH. JAMA. 2014;312:943-952. (2) Apovian CM, et al. J Clin Endocrinol Metab. 2015;100:342-362.

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OBESITY AND SOCIAL DETERMINANTS OF HEALTH

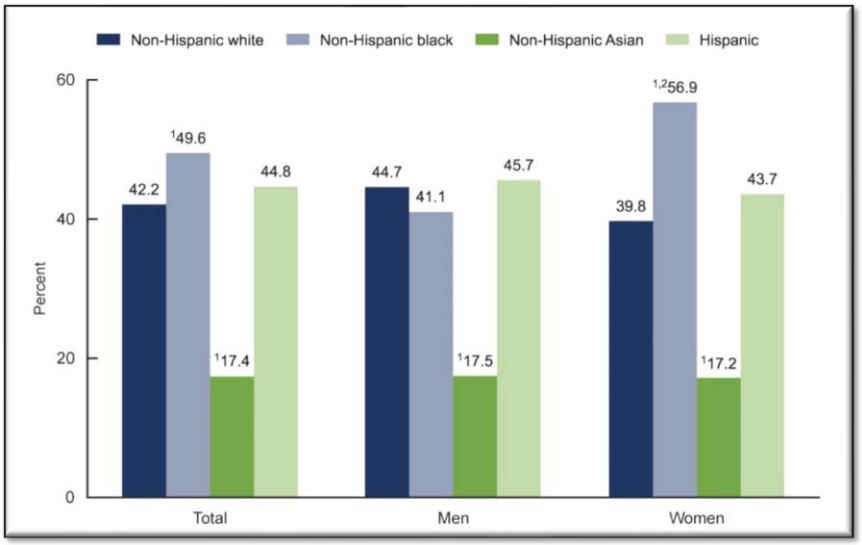


US Centers for Disease Control and Prevention.

11

AGE ADJUSTED PREVALENCE OF OBESITY (BMI ≥30 KG/M^2) BY SEX AND RACE 2017-2018

The highest prevalence of obesity in the US is among black women.



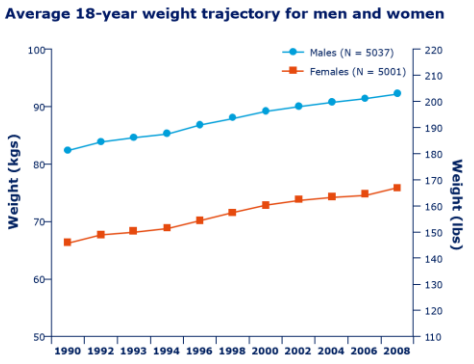
HTTPS://WWW.NIDDK.NIH.GOV/HEALTH-INFORMATION/HEALTH-STATISTICS/OVERWEIGHT-OBESITY

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THE POWER OF THE OBESOGENIC ENVIRONMENT – MOST PEOPLE GAIN WEIGHT OVER EARLY AND MID ADULTHOOD

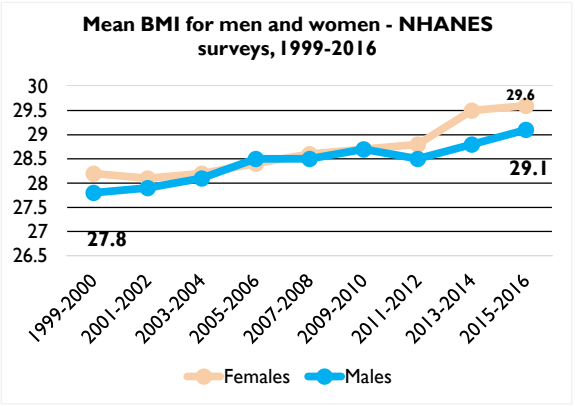
Annual weight gain averaged 0.53 kg (1.17 lb)

>98% of men and >92% of women were on upward-sloping trajectories



Malhotra R, et al. Obesity 2013; 21: 1923-1934

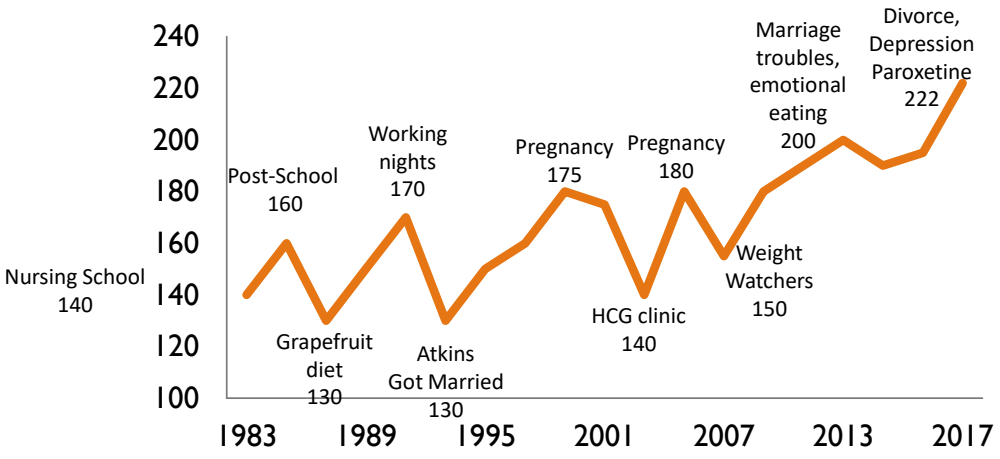
Over 16 years mean BMI increased for men and women by >1 BMI unit



Fryar CD et al. Natl Health Stat Report. 2018 (122):1-16

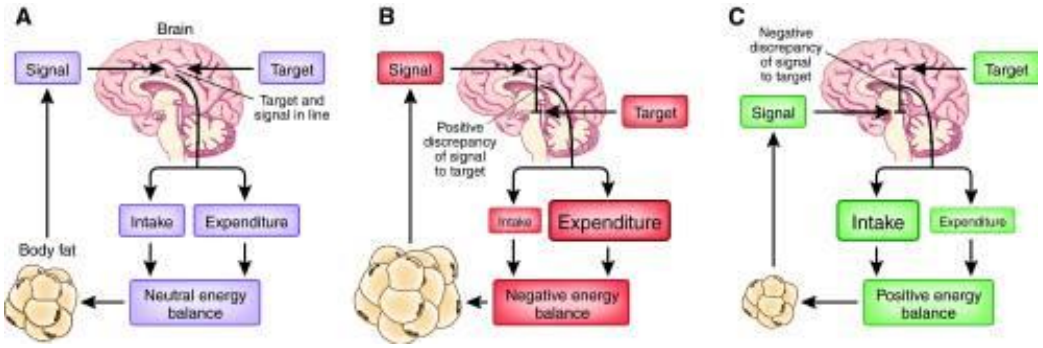
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ON AN INDIVIDUAL BASIS, WEIGHT ACROSS THE LIFESPAN IS OFTEN DRIVEN BY A SERIES OF LIFE EVENTS LIKE THIS…



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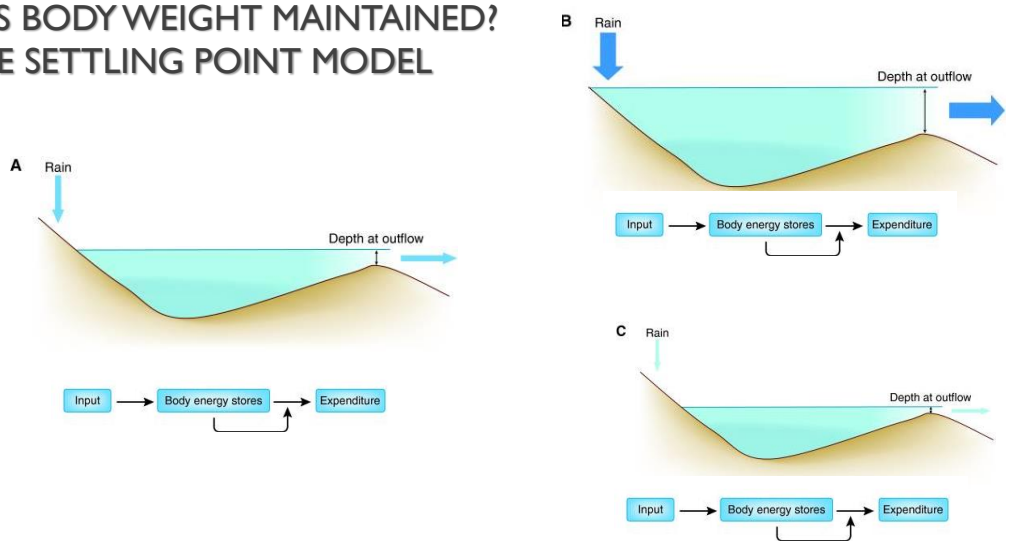
HOW IS BODY WEIGHT MAINTAINED? THE SET POINT MODEL OR LIPOSTATIC MODEL



SPEAKMAN JR, ET AL. SET POINTS, SETTLING POINTS AND SOME ALTERNATIVE MODELS: THEORETICAL OPTIONS TO UNDERSTAND HOW GENES AND ENVIRONMENTS COMBINE TO REGULATE BODY ADIPOSITY. DIS MODEL MECH. 2011 NOV;4(6):733-45..

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HOW IS BODY WEIGHT MAINTAINED? THE SETTLING POINT MODEL

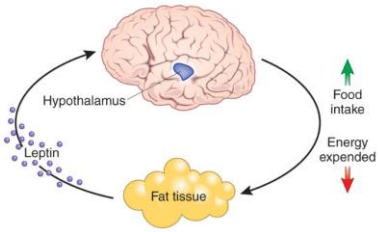


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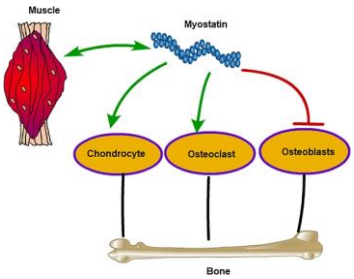
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IMPORTANT PLAYERS IN REGULATION OF BODY WEIGHT, MUSCLE MASS, AND FAT MASS

- Leptin



- Myostatin





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DEFINITION OF OBESITY

- In ICD codes, obesity is defined by the body mass index (BMI)
- Formula: weight (kg) / [height (m)]^2
- For adults age ≥20 years, BMI is interpreted using standard weight status categories. These apply to all body types and ages

Body Mass Index (BMI) Definitions	
BMI	**Weight Status**
Below 18.5	Underweight
18.5-24.9	Normal or Healthy Weight
25.0-29.9	Overweight
30.0 and above	Obesity

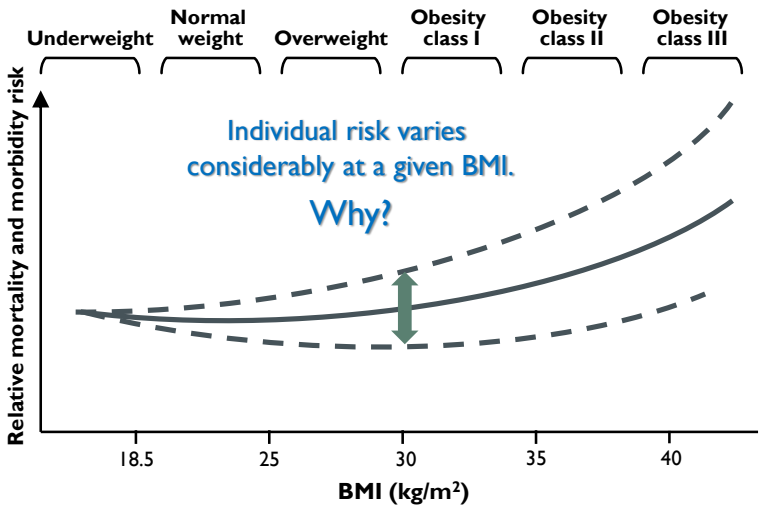
Obesity Classes		
Class	**BMI**	**Severity**
Class I	30.0-34.9	Mild
Class II	35.0-39.9	Moderate
Class III	≥40.0	Severe

Class I, LOE C
Measure height and weight and calculate BMI at least annually

CDC. About adult BMI. https://www.cdc.gov/healthyweight/assessing/bmi/adult_bmi/index.html
Arnett KD, et al. *J Am Coll Cardiol.* 2019;74:1376-1414.

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LIMITATIONS OF BMI



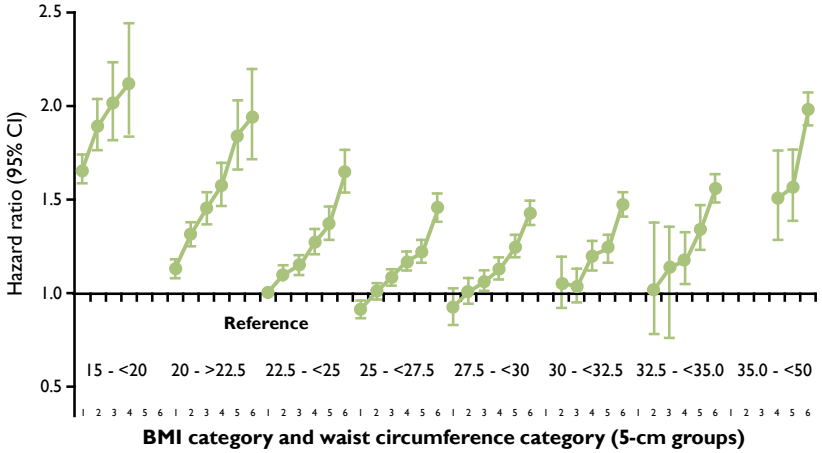
Gonzalez-Muniesa P, et al. *Nat Rev Dis Primers.* 2017;3:17034.

AMA June 14, 2023

Body mass index (BMI) is easy to measure and inexpensive. But BMI is an imperfect measure because it does not directly assess body fat. Furthermore, the BMI originated from historical harm, its has been used for racist exclusion, and BMI is based primarily on data collected from previous generations of non-Hispanic White populations. Due to significant limitations associated with the widespread use of BMI in clinical settings, the AMA suggests that it be used in conjunction with other valid measures of risk such as, but not limited to, measurements of visceral fat, body adiposity index, body composition, relative fat mass, **waist circumference,** and genetic/metabolic factors.

20

HAZARD RATIOS FOR WAIST CIRCUMFERENCE IN 5-CM INCREMENTS AND ALL-CAUSE MORTALITY BY BMI CATEGORY



Adjusted for educational level, marital status, smoking status, alcohol consumption, physical activity, and BMI.
Cerhan JR, et al. *Mayo Clin Proc.* 2014: 89:335-345.

21

VALID CRITICISM OF BMI FOR CLINICAL DIAGNOSIS OF OBESITY: BODY SIZE (BMI) VS EXCESS ABNORMAL BODY FAT





Metabolically Healthy Obesity

- BMI >30 kg/m^2
- Normal waist circumference
- Normal glycemic and cardiovascular risk factors
- Younger; tends to destabilize with aging

Normal Weight Obesity

- BMI <25 kg/m^2
- Increased waist circumference
- Increased visceral and ectopic fat
- Dysglycemia, diabetes, cardiovascular risk factors and disease.

Tsatsoulis A, et al. Curr Obes Rep. 2020 Jun;9(2):109-120.
Oliveros E, et al. Prog Cardiovasc Dis. 2014 Jan-Feb;56(4):426-33.

22

HOW TO MAKE A CLINICAL DIAGNOSIS OF OBESITY

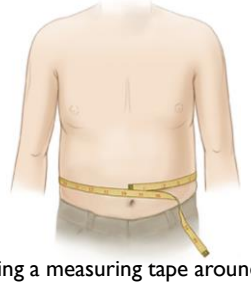
- Obesity is defined by the World Health Organization (WHO) as *excess abnormal body fat, which may impair health*
- Body mass index (BMI) is a good population measure of body fat and an imperfect measure in individuals

For Europids:
Overweight BMI >25 kg/m^2
Obesity BMI >30 kg/m^2
Waist circumference: 35 inches for women & 40 inches for men
Jensen MD, et al. *Obesity.* 2014;22(S2):S1-S410.

For Asians:
Overweight BMI >23 kg/m^2
Obesity BMI >25 kg/m^2
Waist circumference: 31.5 inches for women & 35 inches for men
WHO/IASO/IOTF, 2000.
(http://www.idi.org.au/obesity_report.htm)

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HOW AND WHEN TO MEASURE WAIST CIRCUMFERENCE



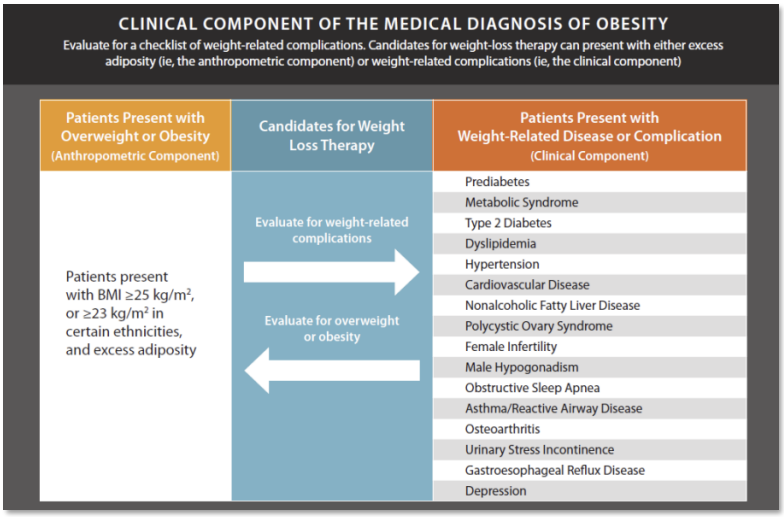
- Waist circumference is measured by placing a measuring tape around the abdomen at the level of the superior border of the iliac crest
- Waist circumference >88 cm (>35 in) for women and >102 cm (>40 in) for men is associated with a higher risk of adverse metabolic consequences of adiposity, regardless of BMI category

Class IIa, LOE B: Measure waist circumference at least annually, or more frequently in adults with overweight and obesity

Jensen MD, et al. *Circulation.* 2013;129(Suppl 2):S102-S138.
Ross R, et al. *Nature Rev Endocrinol.* 2020(3);16:177-189.

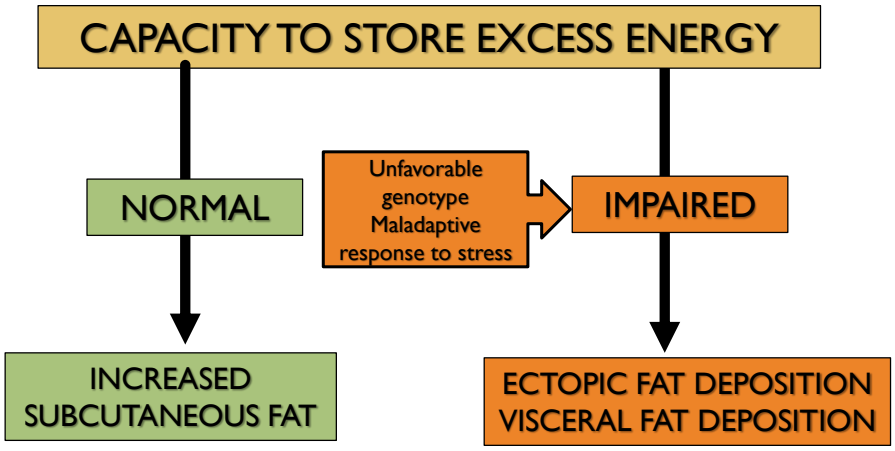
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RETHINKING THE OBESITY DIAGNOSIS: FROM THE AACE CLINICAL GUIDELINES



Garvey WT, et al. *Endocr Pract.* 2016. 22(S3):1-203.

25

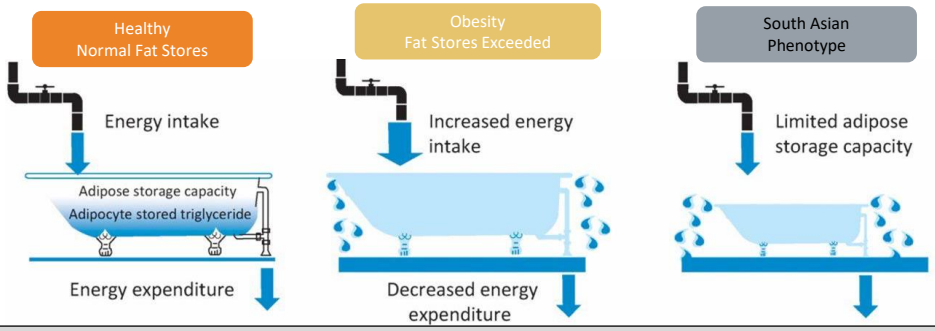


Ibrahim MM. Subcutaneous and visceral adipose tissue: structural and functional differences. Obesity Reviews. 2010 Jan;11(1):11-8.

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THE SOGGY BATHROOM CARPET MODEL OF OVER-NUTRITION–RELATED METABOLIC DISEASE

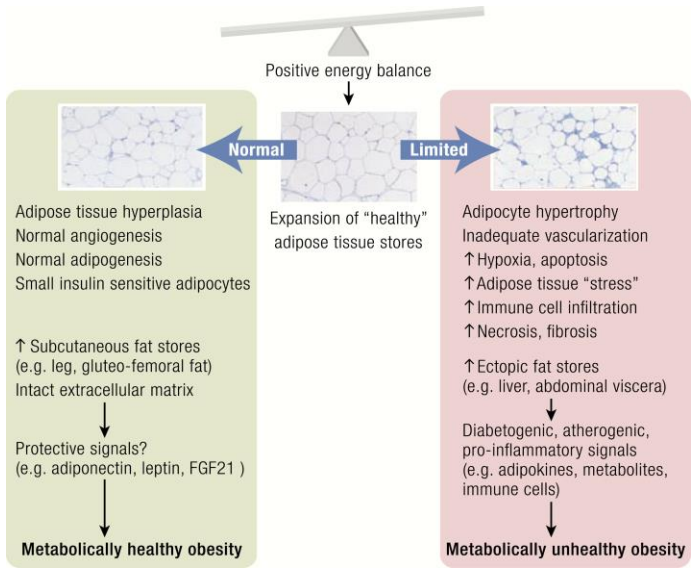
The "soggy carpet" is a metaphor for ectopic adipose tissue.



- When the ability to store healthy fat is exceeded by a continuous positive energy balance, ectopic and abnormal fat stores give rise to metabolic disease
- The ability to store fat in healthy depots is determined by genetics, hormones, and other factors
- Some individuals, such as those of South Asian descent, have little capacity to store excess fat in healthy depots and develop ectopic and abnormal fat stores at lower BMI levels

O'Rahilly S. Diabetes. 2021;70:29-38.

27



Blüher M. Endocr Rev. 2020;41:405-420.

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HOW DOES OBESITY DRIVE OTHER DISEASES?

- Burden of excess fat – biomechanical effects
  - Knee arthritis
  - Obstructive sleep apnea
  - GERD
  - Urinary incontinence
  - Others

- Products of excess abnormal fat
  - Prothrombotic effects
  - Proinflammatory effects
  - Immune function effects
  - Promote blood pressure elevation
  - Promote insulin resistance
  - Promote angiogenesis promoting
  - Others

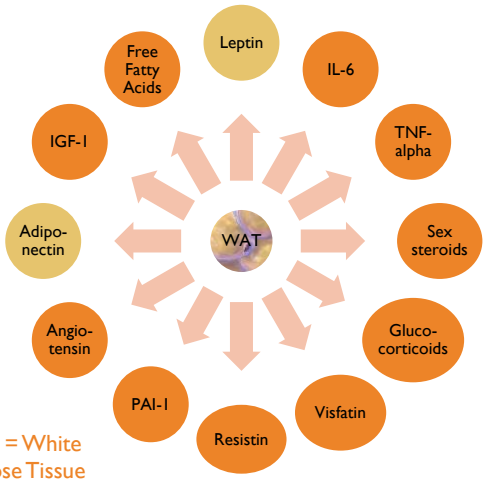
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IMPORTANT SECRETORY PRODUCTS OF WHITE ADIPOSE TISSUE

- Visceral and ectopic white adipose tissue has a more UNFAVORABLE physiologic profile, produces more pro-inflammatory and pro-thrombotic cytokines.

LOCATION, LOCATION, LOCATION:

- Ectopic and visceral fat can have important local and regional effects.



WAT = White Adipose Tissue

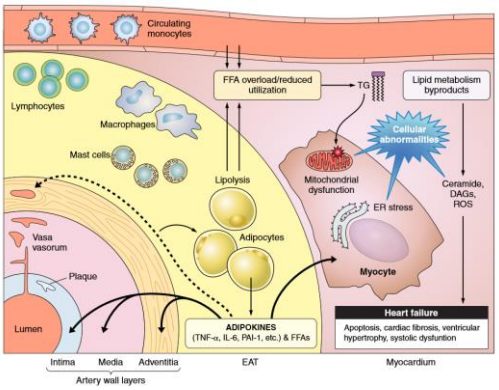
Coelho M, Oliveira T, Fernandes R. Biochemistry of adipose tissue: an endocrine organ. Arch Med Sci. 2013;9(2):191-200.

30

LOCATION, LOCATION, LOCATION

- Visceral and ectopic (muscle, liver, pancreas, epicardial) adipose tissue produces more pro-inflammatory and pro-thrombotic cytokines.
- Visceral and ectopic fat are mobilized first with weight loss.

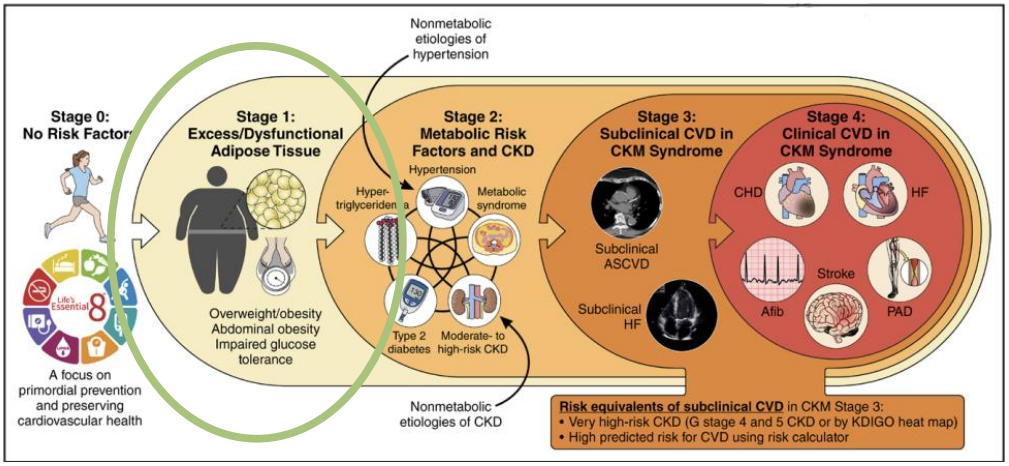
Role of epicardial adipose tissue in cardiovascular risk



Cherian S et al. Am J Physiol Endocrinol Metab. 2012;303:E937-E949.

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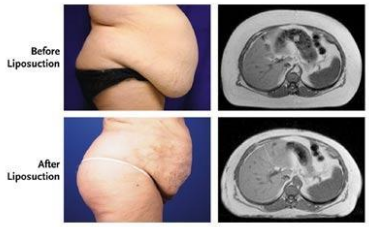
EXCESS/DYSFUNCTIONAL ADIPOSE TISSUE IS A DRIVER OF CARDIOVASCULAR DISEASE, MEDIATED THROUGH CKM SYNDROME



Ndumele CE, et al. Circulation. Circulation. 2023;148:1606–1635.

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LARGE VOLUME LIPOSUCTION: NO EFFECTS ON INSULIN SENSITIVITY OR CVD RISK FACTORS



- 15 women with obesity
- subcutaneous adipose tissue volume reduced with liposuction by 44% (-9.1 kg) in normoglycemic patients and 28% (-10.5 kg) in those with diabetes
- Measures at 12-16 weeks

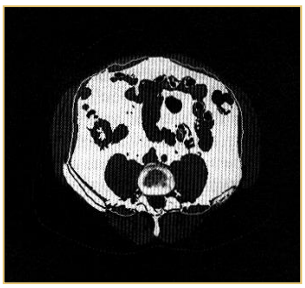
No significant difference in either group for

- insulin sensitivity of muscle, liver, or adipose tissue
- C-reactive protein, interleukin-6, tumor necrosis factor alpha, and adiponectin
- blood pressure
- plasma glucose & insulin
- lipids

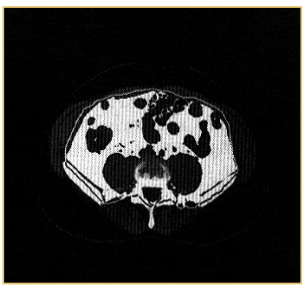
Klein S, et al. Absence of an effect of liposuction on insulin action and risk factors for coronary heart disease. N Engl J Med. 2004 Jun 17;350(25):2549-57.

33

WEIGHT LOSS SEEMS TO REDUCE VISCERAL ADIPOSE TISSUE PREFERENTIALLY



Before weight loss
(95 kg, BMI 32)

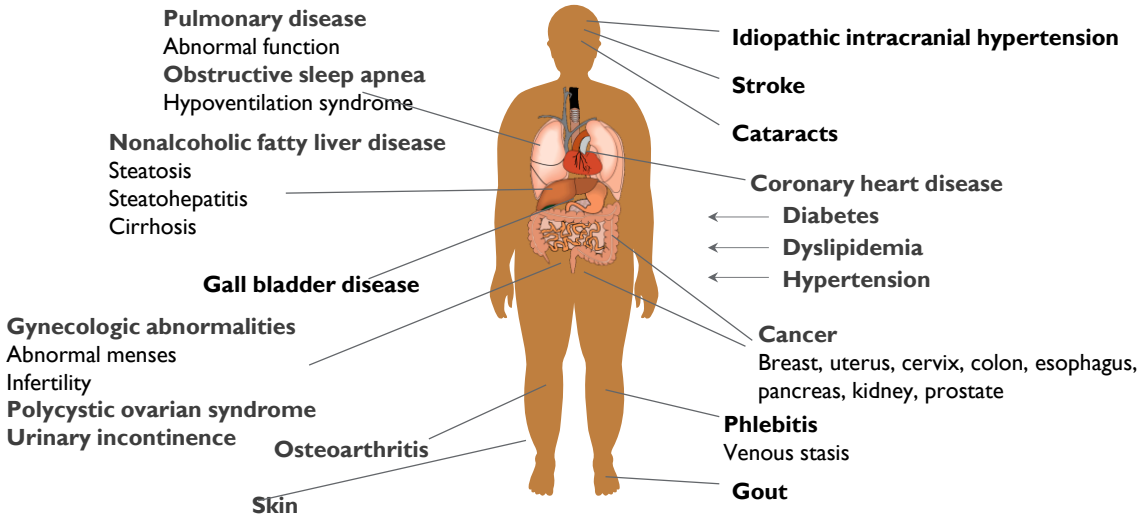


After 10-kg–weight loss
(85 kg, BMI 29)

Després J-P. *Baillière's Clin Endocrinol*. 1994;8:629.

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COMORBIDITIES ASSOCIATED WITH OBESITY



Coelho M, Oliveira T, Fernandes R. Biochemistry of adipose tissue: an endocrine organ. *Arch Med Sci.* 2013;9(2):191-200.

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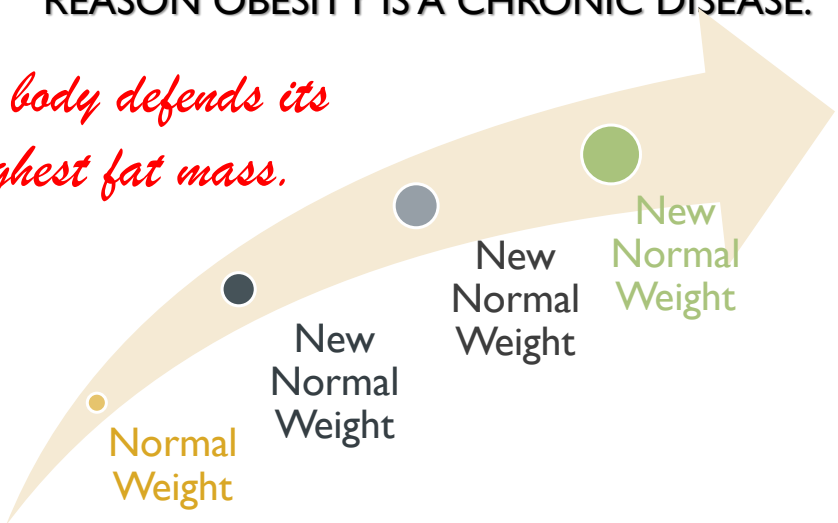
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THE BODY WEIGHT SET POINT / SETTLING POINT IS THE REASON OBESITY IS A CHRONIC DISEASE.

The body defends its highest fat mass.



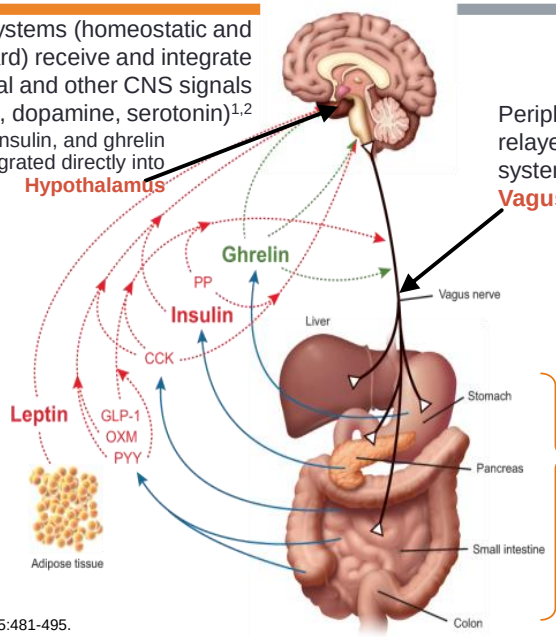
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COMPLEX PERIPHERAL SIGNALS ARE INTEGRATED INTO CNS SYSTEMS TO REGULATE BODY WEIGHT

Brain systems (homeostatic and reward) receive and integrate peripheral and other CNS signals (eg, dopamine, serotonin)[1,2]

Leptin, insulin, and ghrelin are integrated directly into **Hypothalamus**

Peripheral signals are relayed to brain systems via blood and **Vagus Nerve** [1,2]



Peripheral signals are released by pancreas, gastrointestinal system, and adipose tissue[1,2]

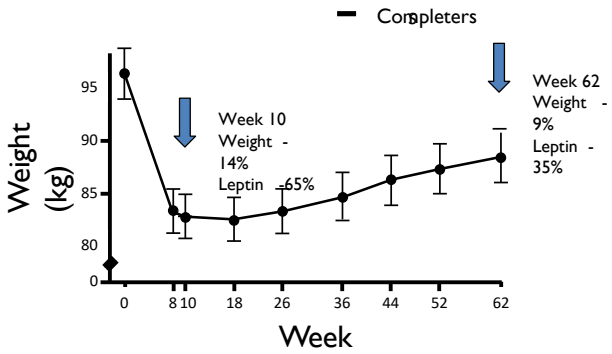
CNS, central nervous system
PfC, prefrontal cortex
NAc, nucleus accumbens
VTA, ventral tegmental area
PP, pancreatic polypeptide
CCK, cholecystokinin;
GLP-1, glucagon-like peptide 1
OXM, oxyntomodulin
PYY, peptide YY.
Primarily based on data from animal studies.

Appetite Stimulating
Appetite Suppressing

1. Yu JH et al. *Diabetes Metab J.* 2012;36(6):391-398.
2. Mendieta-Zerón H et al. *Gen Comp Endocrinol.* 2008;155:481-495.

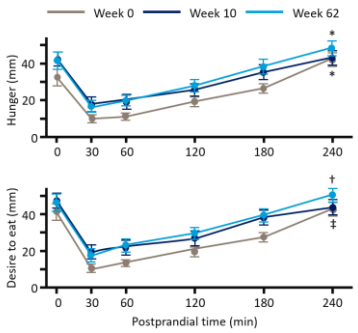
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BIOLOGIC RESPONSES TO WEIGHT LOSS – ENERGY INTAKE



Average Weight and Leptin changes baseline to week 62.

The inpatient weight loss program was started at week 0 and completed at week 10; outpatient counseling continued until week 62.



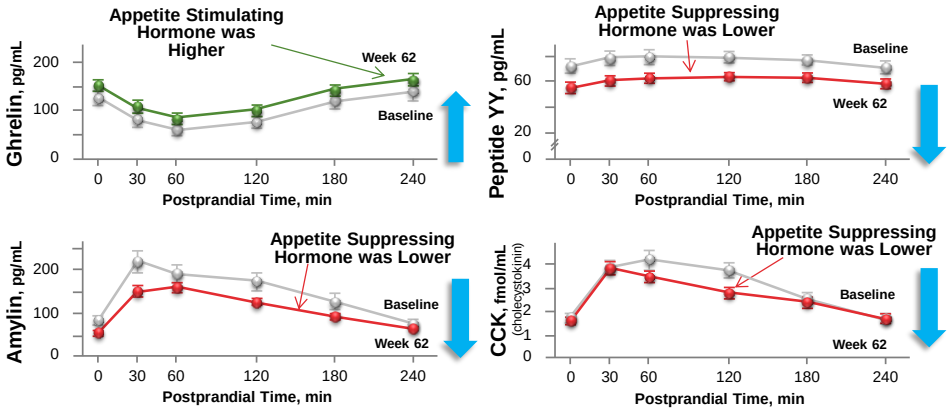
Gut Hormone changes:
- Ghrelin
- PYY, CCK, GLP-1, insulin, amylin

Sumithran P, et al. *N Engl J Med.* 2011;365:1597-1604.

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CHANGES IN APPETITE SIGNALS AFTER WEIGHT REDUCTION

Mean fasting and postprandial levels of some peripheral signals at baseline and 62 weeks



10-week, lifestyle-based weight loss intervention in healthy overweight and obese adults (n=34) led to sustained elevations in appetite stimulating hormone(s) and decreases in appetite suppressing hormones

Sumithran P, et al. *N Engl J Med.* 2011;365:1597-1604.

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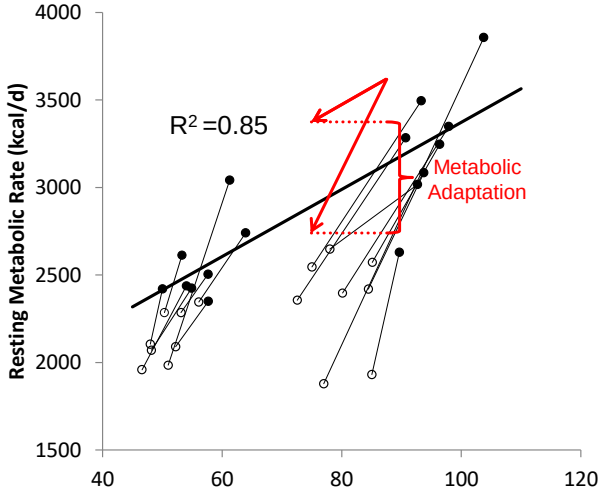
DANNY, WINNER OF THE BIGGEST LOSER CONTEST



Johannsen et al. JCEM (2012)

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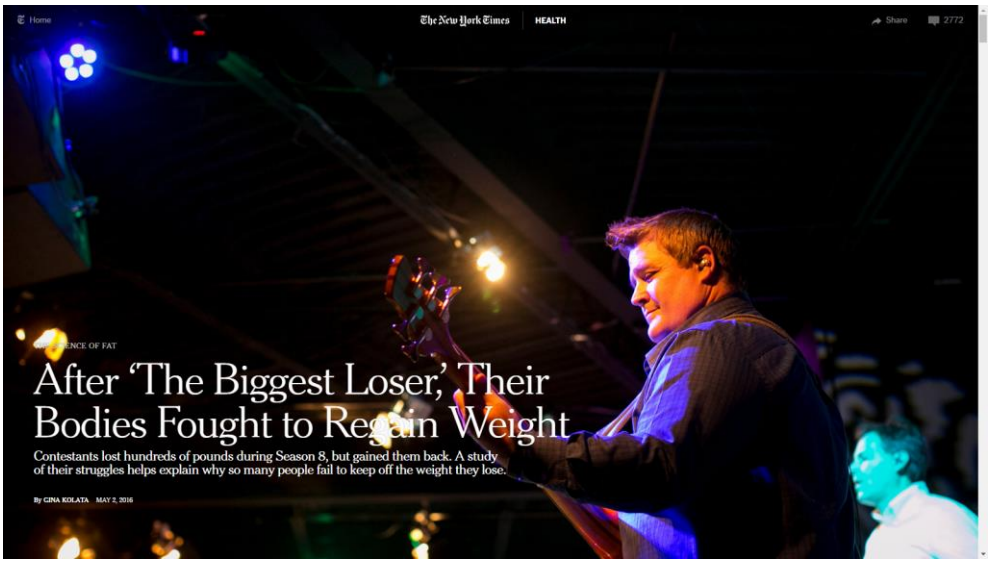
DISPROPORTIONATE REDUCTION IN METABOLIC RATE BEFORE AND AFTER WEIGHT LOSS



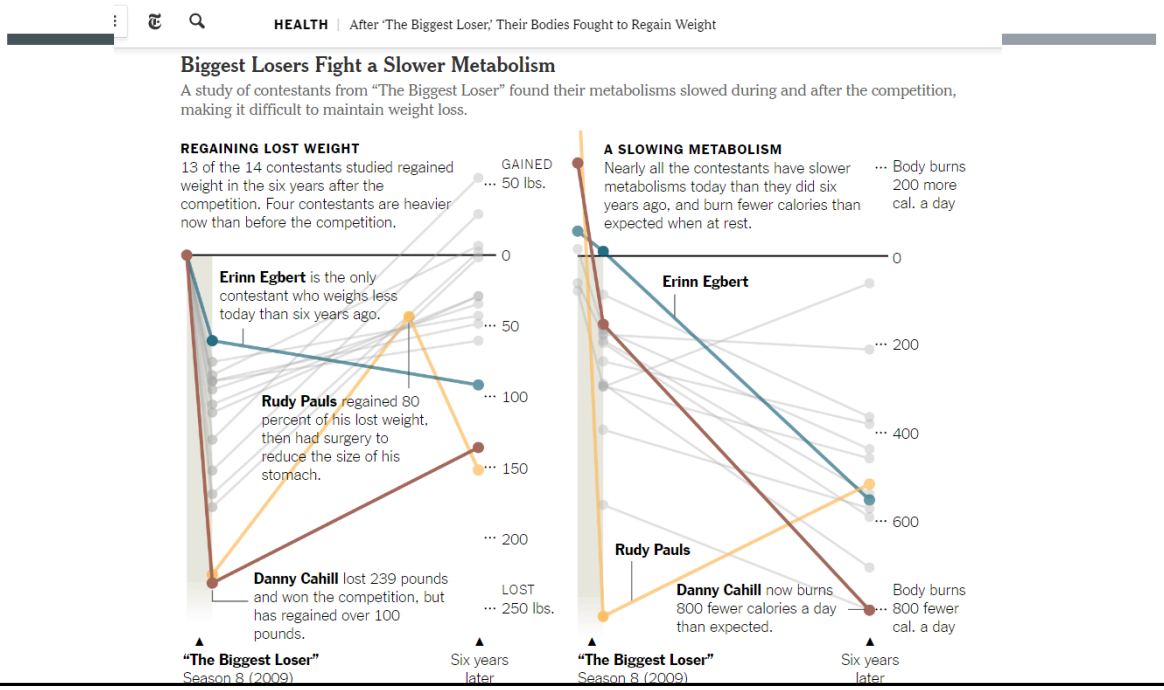
DL Johannsen et al. JCEM 97(7):2489–2496 (2012)

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THE BIGGEST LOSER 6 YEARS LATER



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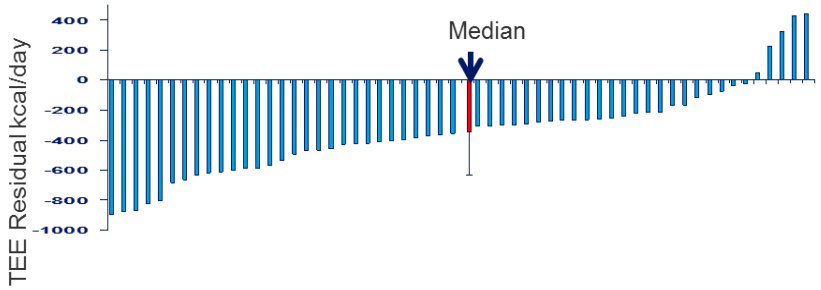
METABOLIC ADAPTATION TO REDUCED OBESITY

- Reduction in resting metabolic rate greater than that predicted with weight loss alone
- Associated with degree of reduction in leptin levels
- Greater weight loss = greater metabolic adaptation
- Subject to individual variability
- Metabolic adaptation after weight loss has been demonstrated for up to 6 years.

Ravussin, E. and Ryan, D. H. Obesity, 2016. 24: 1607-1608.

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VARIABILITY IN METABOLIC CHANGES AFTER WEIGHT LOSS



Mean (SD) = -345 (293) kcal/day

Rosenbaum et al, AJCN 2008; 88:906.

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BIOLOGIC AND PHYSIOLOGIC ADAPTATIONS TO THE WEIGHT REDUCED STATE

- Alterations in appetite regulation[1]
  - ↑ Ghrelin (hunger hormone) and ↓ GLP-1, GIP, CCK, PYY, insulin, and amylin (satiety hormones)

- Alterations in energy expenditure[2,3]
  - ↓ Resting energy expenditure
  - ↑ Muscle efficiency
  - Related to ↓ leptin levels

1. Sumithran P et al. *N Engl J Med*. 2011;365:1597-1604. 2. Johannsen DL et al. *J Clin Endocrinol Metab*. 2012;97:2489-2496.
3. Ravussin E et al. *Obesity*. 2016;24:1607-1608.

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CHANGING OUR WAY OF THINKING: OBESITY IS LESS ABOUT WILL POWER AND MORE ABOUT STRONG BIOLOGIC FORCES MAKING WEIGHT LOSS DIFFICULT AND REGAIN EASY





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ACTION NEEDED: DISCUSS THE BIOLOGY OF WEIGHT REGULATION WITH YOUR PATIENTS

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TAKE HOME POINTS

1. Clinical obesity is defined as excess abnormal body fat which impairs health.
2. Obesity etiology is complex! Genetic susceptibility and environmental drivers determine risk. Social determinants of health play a role.
3. Long term weight loss is difficult because metabolic and biologic adaptations provide physiologic defense of the body's highest fat mass.
4. The brain is the central regulator of food intake and body weight regulation.

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OBJECTIVES: AT THE END OF THE PRESENTATION ATTENDEES WILL BE ABLE TO

1. describe the environmental and genetic factors that interact to produce obesity – its etiology;
2. distinguish the different phenotypic expressions of excess, abnormal and dysfunctional fat storage that drive risk for obesity complications – its pathogenesis; and
3. relate the biologic and physiologic responses to weight reduction that make weight loss difficult and weight regain common – why it's a *chronic* disease.

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OBJECTIVES: AT THE END OF THE PRESENTATION ATTENDEES WILL BE ABLE TO ANSWER THE FOLLOWING QUESTIONS:

1. Why do some people develop obesity and others don't?
2. Why do some people get obesity complications and others don't?
3. Why do people succeed at weight loss, only to regain?

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NOW FOR PART 2…



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