



Clinical Benefits of Weight Loss

AAACE Obesity Resource Center

Defining Obesity

- Obesity is a chronic relapsing progressive **disease** defined by abnormal or excessive adiposity that may impair health.^{1,2}
- Multiple pathophysiological aspects¹
 - Genetic
 - Environmental
 - Physiological
 - Psychological
- Abundance of food + low physical activity + genetics/environmental factors → **positive energy balance**
 - Excess energy stored as fat in enlarged/more numerous adipocytes and ectopically^{1,2}
 - Enlarged fat cells/ectopic fat produce/secrete metabolic, hormonal, inflammatory products that damage organs

1. Mechanick JL, et al; AACE. Endocr Pract. 2012 Sept-Oct;18(5):643-648.

2. Bray GA, et al; World Obesity Federation. Obes Rev. 2017 Jul;18(7):715-723.



Evolving Terminology of Obesity

Obesity historically diagnosed as $BMI \geq 30 \text{ kg/m}^2$

BMI not optimally predictive of health

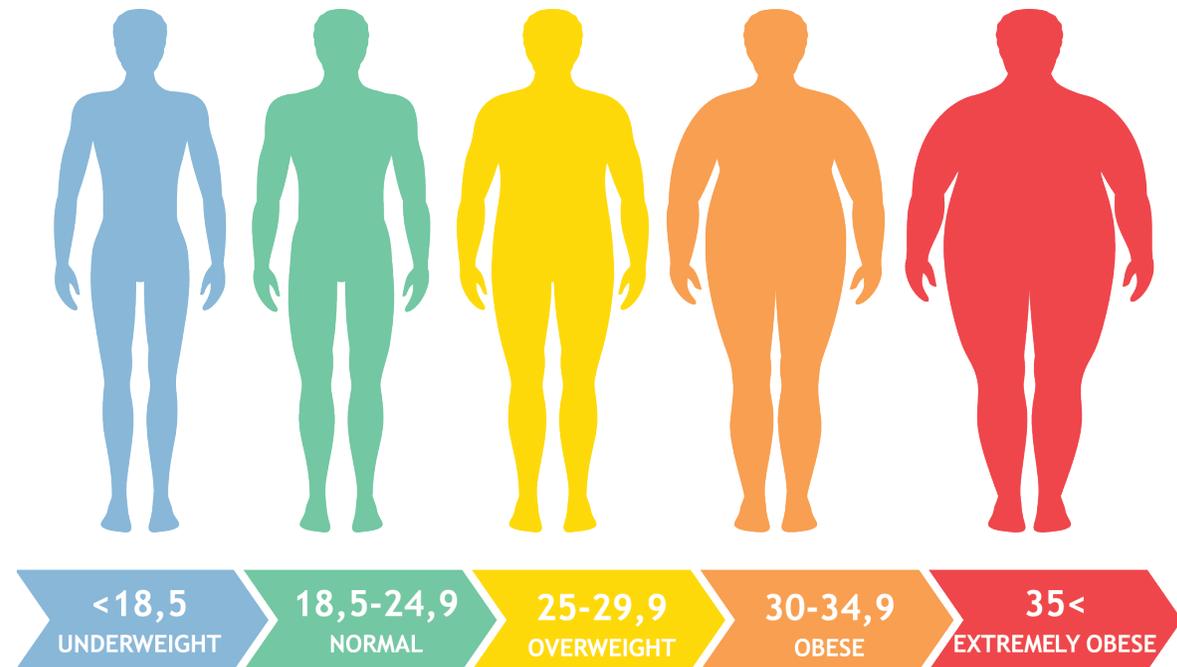
Ethnic differences

Does not recognize cardiometabolic risks associated with waist circumference

Stigmatization of term 'obesity'

"Obesity" does not provide sufficient information of conditions associated with excess adiposity

Body Mass Index

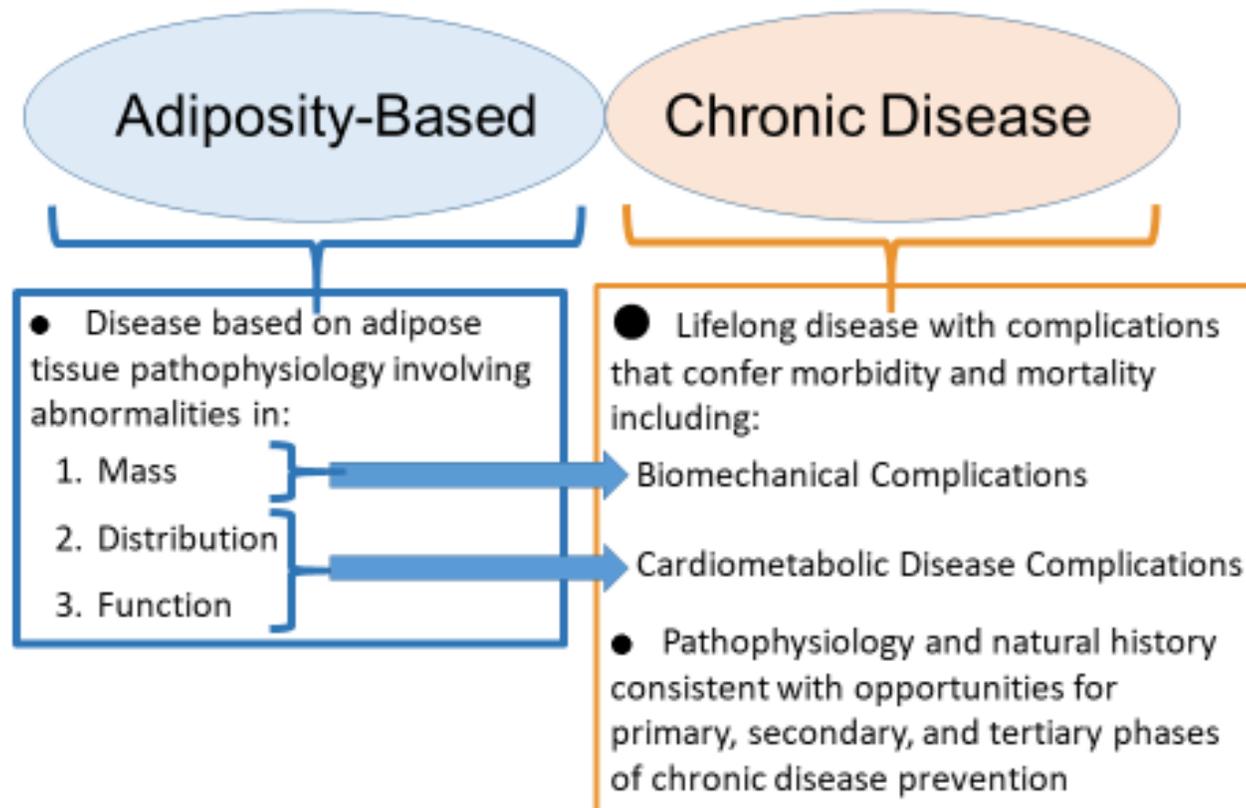


Adiposity-Based Chronic Disease (ABCD): New Diagnostic Term for Obesity

- **ABCD** as the new diagnostic term for obesity by AACE/ACE
- **Adiposity** - obesity (excessive accumulation of fat within the body)
- **Based** – a point at which something can develop
- **Chronic** – persisting over a long period of time
- **Disease** – interruption of the normal function of the body or structure of a body part or system

ABCD: Relevant Diagnostic Term for Obesity

Adiposity-Based Chronic Disease:
A clinically relevant diagnostic term for the disease of obesity

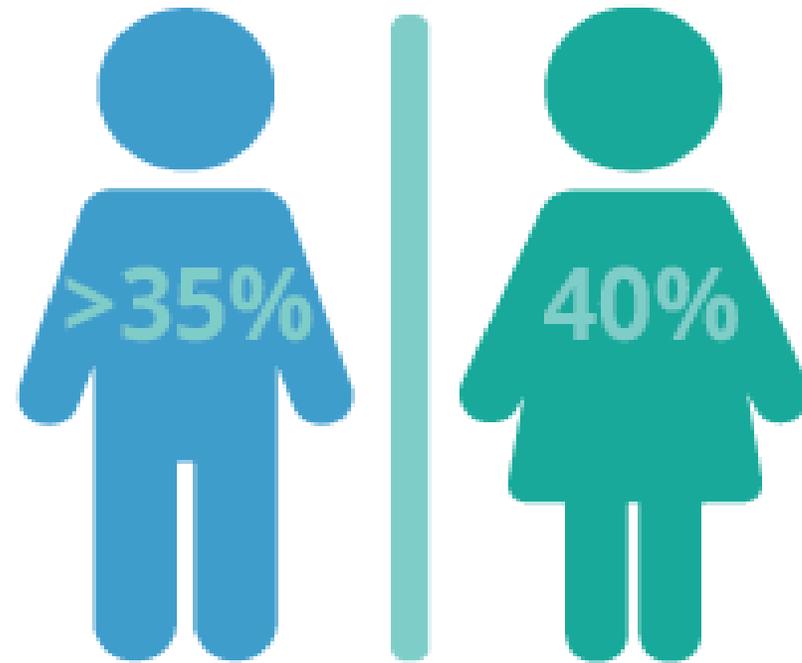


AACE Blueprint for Complications-Centric Approach

- Lifestyle medicine positioned as central pervasive action to promote overall health
- Develop standardized protocols to address weight loss and management of adiposity-based complications
- Contextualize patient care in light of environmental, socioeconomic, ethnic/cultural differences
- Develop evidence-based strategies for implementation, monitoring, and optimization of patient care over time

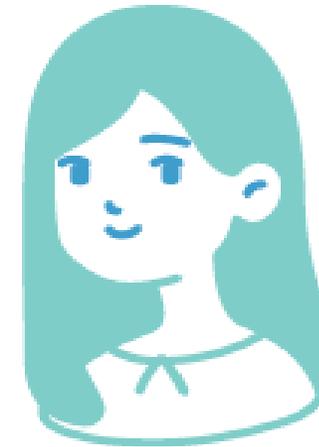
Obesity: Overview

- >35% of men and 40% of US women have obesity
- Obesity is associated with many health problems/morbidity
- Obesity is associated with increased risk for death
 - especially adults <65 years



Childhood and Adolescent Obesity

- Inherited Obesity:
 - For most people, genetics account for small percentage of obesity risk
 - Even if genetics contributes up to 40% of risk, 60% of risk associated with lifestyle factors
 - Rare inherited conditions: Prader-Willi, Bardet-Biedl syndromes, monogenetic obesity
- Childhood/Adolescent Obesity
 - CDC: ~1 in 5 children/adolescents (6-19 yrs) in US has obesity
 - Obese children more likely to grow up to be obese adults; more severe obesity and more extreme obesity-related health problems
 - Factors that contribute to childhood/adolescent obesity
 - Genetics.
 - Metabolism.
 - Eating and physical activity behaviors.
 - Community and neighborhood design and safety.
 - Short sleep duration.
 - Negative childhood events



Peri- and Post-Menopausal Obesity



Obesity prevalence significantly increases in women after age 40:
~65% between 40-59 yrs
~74% in women \geq 60 yrs



Healthy Women Study: average weight gain in perimenopausal women ~5 lbs; 20% women gained \geq 10 pounds



Possible explanations of increased weight with menopause: decreased estrogen levels and decrease in energy expenditure

Estrogen deficiency enhances metabolic dysfunction \rightarrow T2D, MetS, CVD.

Estrogen affects fat storage and distribution.

- Before perimenopause, estrogen deposits fat in your thighs, hips, and buttocks.
- During/after menopause: decreasing estrogen leads to overall increase in total body fat and especially fat around waistline
- Abdominal fat: linked to increase in insulin resistance, diabetes, and inflammatory diseases

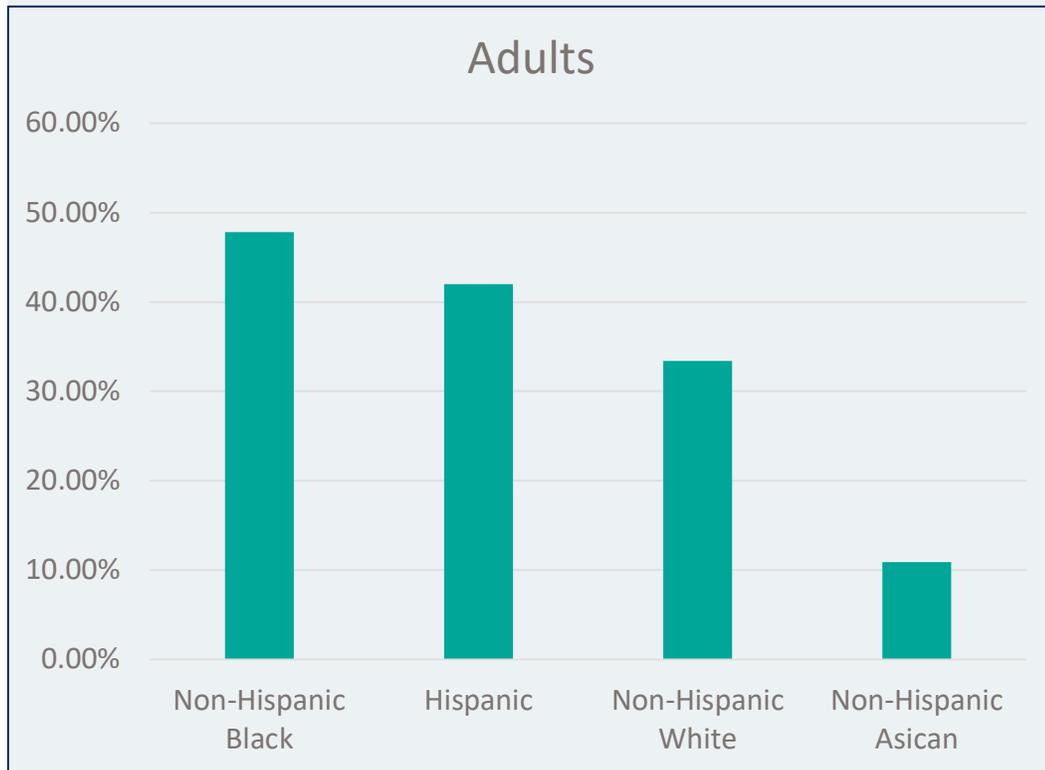
Racial/Ethnic/Socioeconomic Disparities

- Prevalence of obesity in US differs among racial/ethnic groups^{1,2}
- Disparities in health consequences of obesity by race/ethnicity³
- Different average BMIs by ethnicity:^{1,2}
 - US-born Asians:
 - Chinese: 24.9,
 - Asian Indians: 25.8
 - Filipinos: 27.3
 - US-born Hispanics:
 - Cubans: 29.5
 - Puerto Ricans: 30.6
 - Mexicans: 31.1

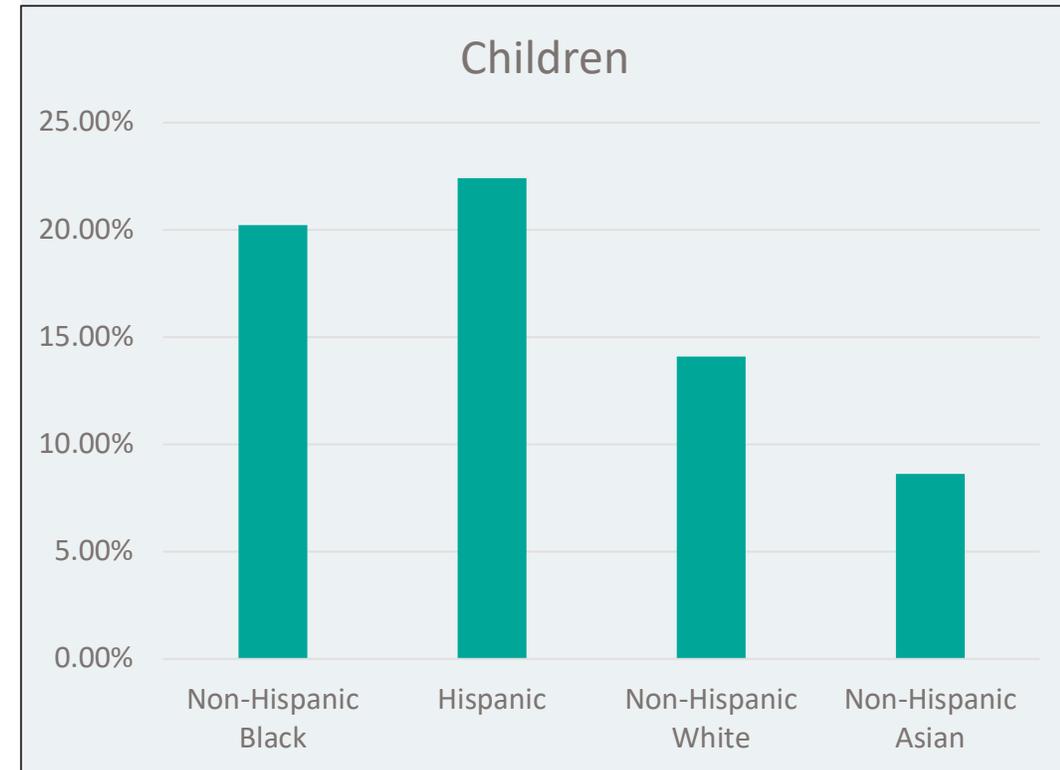


Racial/Ethnic Disparities: Obesity Prevalence

Adults >20 years



Children (2-19 years)



Race/Ethnic/SES Disparities in Obesity

- Possible mechanisms explaining disparities
 - Health behaviors: knowledge about nutritional food
 - Biological/developmental factors: genetics
 - Social environment
 - Opportunity for physical activity in and after school
 - Access to healthy (vs fast) food
- Socioeconomic status: having a college degree nearly doubles the risk of obesity vs not having a high school diploma
- Cultural norms promoting big-boned, fat/thick adults
- Food as center of community unity

Consequences of Overweight/Obesity

- Physical
 - Increased body fat mass/loss of lean muscle
 - Joint pain/osteoarthritis
 - Impaired mobility/Disability
 - Urinary incontinence
- Medical
 - Metabolic/Altered metabolism
 - Digestive disorders
 - Lung function and Sleep impairments
 - Cancers
 - CVD/Hypertension
 - Hormonal
- Psychiatric/Psychologic
 - Low self-esteem, depression, anxiety, binge-eating disorder





Physical Consequences of Obesity

Increased body fat mass

Joint pain

Impaired mobility, Disability

Urinary Incontinence

Increased Body Fat Mass

- Biologic aging associated with progressive increase in body fat mass, loss of lean body mass¹
 - Intra-abdominal fat increases by over 300% between ages 25-65 years
- Metabolic consequences of reduced muscle mass
 - Low muscle mass strong predictor of morbidity and mortality²
 - Lower physical function
 - Shorter survival
 - Poorer quality of life
- Can interfere with lower extremity physical performance
- Location of body fat distribution: central obesity carries greater risks³

1. Strasser B. Ann NY Acad Sci. 2013;1281:141-159.
2. Prado CM, et al. Ann Med. 2018 Dec;50(8):675-693.
3. Goosens GH. Obes Facts. 2017;10(3):207-215.



Joint Pain and Osteoarthritis

- Obesity accelerates development of hip and knee osteoarthritis (OA)
- Obesity increases risk of hand osteoarthritis¹
- Causes:¹⁻³
 - Biomechanical effects
 - Systemic inflammatory changes
 - Low-grade systemic inflammatory state
 - Production and secretion of adipocytokines involved in OA development
 - Obesity comorbidities (hypertension, impaired glucose and lipid metabolism) –alter joint tissue homeostasis¹

1. Belluzzi E, et al. J Cell Physiol. 2017 Aug;232(8):1971-1978.

2. Santangelo KS, et al. Horm Mol Biol Clin Investig. 2016 May 1;26(2):97-108.

3. Springer BD, et al. Surg Obes Relat Dis. 2017 Jan;13(1):111-118.



Impaired Mobility, Disability

OBESITY:

limits optimal function of cardiopulmonary and metabolic systems → exertion dyspnea and impairments in functional abilities

affects balance and movement control

Is associated with mobility disability: difficulty walking 400 m or climbing stairs¹

interferes with functional mobility and ability to participate in activities of daily living (ADL): standing, bending, walking, climbing, grabbing objects while standing. ²⁻⁴

Affects postural stability.

Impedes motor control, speed

increases risk of fall-related injuries requiring medical treatment – including sprains, strains, dislocations⁴

Implies sedentary lifestyle – impaired exercise tolerance

1. Barbosa JFds et al. J Nutr Health Aging. 2018;22(10):1228-1237.

2. Forhan M, et al. Best Pract Res Clin Endocrinol Metab. 2013;27:129-137.

3. Strasser B. Ann NY Acad Sci. 2013;1281:141-159.

4. Teasdale N, et al. Curr Obes Rep. 2013;2:235-240.



Urinary Incontinence

- Obesity associated with stress urinary incontinence (SUI)¹
 - Increased intra-abdominal pressure
 - Neurogenic and metabolic pathways also contribute
- ACP recommends weight loss and exercise for obese women with UI²
- Overweight associated with 1/3 increased risk of UI, and risk doubled with obesity³

1. Fuselier A, et al. Curr Urol Rep. 2018 Feb 22;19(1):10.

2. Qaseem A/ACP. Ann Intern Med. 2014 Sep 16;161(6):429-440.

3. Lamerton TJ, et al. Obes Rev. 2018 Dec;19(12):1735-1745.





Medical Consequences of Obesity

Metabolic/Altered Metabolism

- Overweight and Obesity are associated with higher risks of prediabetes (HbA1c = 5.7-6.4%) and T2D (HbA1c \geq 6.5%)
 - Insulin resistance¹
- Increasing body weight \rightarrow increased insulin resistance and eventually development of high blood sugar:
 - Prediabetes: Impaired Glucose Tolerance (IGT) or Impaired Fasting Glucose (IFG).
 - Individuals with prediabetes have an increased risk of developing T2D, hypertension and stroke.
 - An estimated 79 million Americans age 20 years or older have prediabetes

Digestive disorders: Obesity and Dyslipidemia

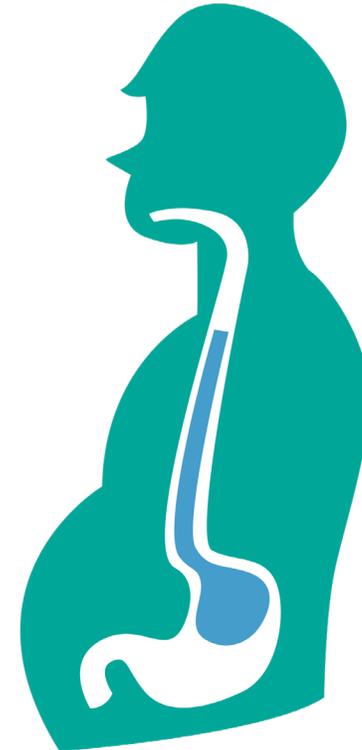
- Increased triglycerides (TG) and free fatty acids (FFA)
- Decreased HDL-C, normal/slightly increased LDL-C
- Increased concentrations of plasma apolipoprotein (apo) B¹
- Elevated fasting and postprandial TG with small dense LDL-C and low HDL-C.
- Increased FFA and obesity-induced inflammation are important in the development of insulin resistance

Digestive disorders: Obesity and Dyslipidemia

- Increased triglycerides (TG) and free fatty acids (FFA), decreased HDL-C with HDL dysfunction, normal or slightly increased LDL-C with increased small dense LDL.
- The concentrations of plasma apolipoprotein (apo) B are often increased, partly the result of hepatic overproduction of apo B containing lipoproteins¹
- The hallmark characteristics = elevated fasting and postprandial TG in combination with the preponderance of small dense LDL and low HDL-C.
- Hypertriglyceridemia may be the major cause of the other lipid abnormalities; leads to delayed clearance of the TG-rich lipoproteins and formation of small dense LDL¹
- Plasma FFA elevated in obese people as result of an increased fatty acid release from adipose tissue and a reduction in plasma FFA clearance.
 - Increased FFA + obesity-induced inflammation play important role in the development of insulin resistance

Digestive disorders: GERD

- Obesity is associated with significant increased risk for gastroesophageal reflux disease (GERD) symptoms and GERD-related complications^{1,2}:
 - Barrett's esophagus
 - Erosive esophagitis
 - Esophageal adenocarcinoma
- Central/abdominal obesity more closely related to GERD vs BMI^{3,4}



Digestive Disorders: Gallbladder Disease

- Obesity is a risk factor for the formation of cholesterol gallstones and gallstone-related complications¹⁻³
- However, rapid weight loss via very low-calorie diets (VLCD) or bariatric surgery increases risk for cholelithiasis in obese patients^{1,2}
 - Risk increases with higher BMI prior to weight loss
 - Prophylactic treatment with oral ursodeoxycholic acid may be recommended¹
- Obesity increases risk of acute pancreatitis^{1,2}

1. Bonfrate L, et al. Best Pract Res Clin Gastroenterol. 2014 Aug;28(4):623-635.
2. Cruz-Monserrate Z, et al. Gastroenterol Clin North Am. 2016 Dec;45(4):625-637.
3. Lammert F, et al. Nat Rev Dis Primers. 2016 Apr 28;2:16024.



Nonalcoholic fatty liver disease (NAFLD)

Nonalcoholic steatohepatitis (NASH)

- NAFLD is the most common cause of chronic liver disease; affects >30% adults^{1,2}
- NAFLD: hepatic manifestation of metabolic syndrome
 - Central abdominal obesity common^{1,2}
 - Up to 80% of patients with NAFLD are obese²
 - Obesity associated with initial stages and severity of NAFLD³
 - High prevalence NAFLD if increased visceral adipose tissue (VAT),² insulin resistance, dyslipidemia
- Most patients with NAFLD have simple steatosis (SS); up to 1/3 progress to more severe form of NASH¹

1. Dietrich P, et al. Best Pract Res Clin Gastroenterol. 2014 Aug;28(4):637-653.

2. Milić S, et al. World J Gastroenterol. 2014 Jul 28;20(28):9330-9337.

3. Polyzos SA, et al. Minerva Endocrinol. 2017 Jun;42(2):92-108.



Lung Function and Sleep Impairments

- Obesity interferes with lung function¹
 - Stiffens respiratory system, reduces lung/chest wall compliance
 - Reduced lung volume and vital capacity
 - Increased risk of airway closure and ventilation distribution abnormalities
- Obesity associated with Obstructive Sleep Apnea (OSA)²
 - Excess fat reduces diaphragm mobility, promotes soft tissue edema
 - Obesity reduces lung volume³
 - Increased BMI lowers forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC), functional residual capacity (FRC), and the expiratory reserve volume (ERV)³
 - Poor sleep promotes production of IL-6 and cortisol (stress hormone) which exacerbates insulin resistance

1. Salome CM, et al. J Appl Physiol. 2010;108:206-211.

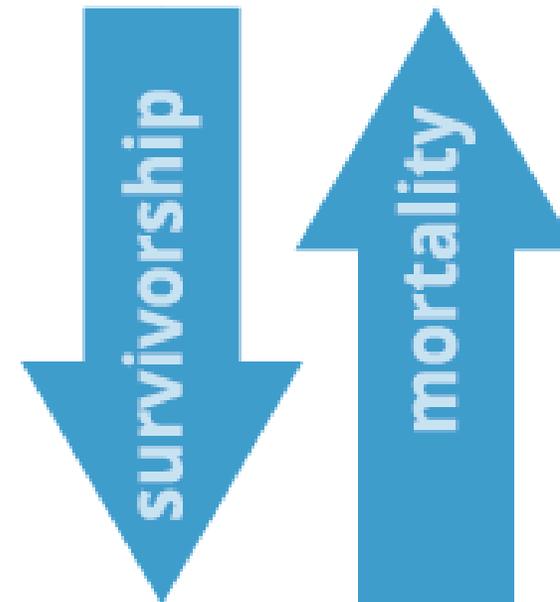
2. Epstein LJ, et al. J Clin Sleep Med. 2009;5:263-276.

3. Zammit C, et al. Internat J Gen Med. 2010;3:335-343.



Obesity and Cancer

- Obesity has been associated with at least 13 different types of cancers:^{1,2}
- In 2012, estimated 28,000 new cases cancer in men (3.5%) and 72,000 new cases in women (9.5%) were due to overweight or obesity¹
- Obesity lowers survivorship/
increases mortality from cancer



1. <https://www.cancer.gov/about-cancer/causes-prevention/risk/obesity/obesity-fact-sheet>

Obesity: Cancer Type and Associated Risk

Type of Cancer	Risk
Endometrial cancer	2-4x risk vs normal weight
Esophageal adenocarcinoma	2x greater risk; morbid obese—4x
Gastric cardia cancer	2x greater risk
Liver cancer	Up to 2x greater risk, especially in men
Kidney cancer	Up to 2x greater risk
Multiple myeloma	Slight increased risk – 10% - 20%
Meningioma	20% increased risk in overweight, 50% increased risk in obese
Pancreatic cancer	1.5x increased risk
Colorectal cancer	Slightly - ~30% increased risk
Gallbladder cancer	~20% increased risk in overweight, ~60% increased risk in obese
Breast cancer in postmenopausal women	20-40% increased risk (also increases breast cancer risk in men)
Ovarian or Thyroid cancer	Slight increased risk (ovarian especially if never used Hormone Therapy), (thyroid - ~10%)

Obesity and Cancer: Possible Mechanisms

- Chronic low-level inflammation
- Fat (adipose) tissue produces excess estrogen – increases risk breast, endometrial, ovarian, other cancers
- Increased blood levels insulin, insulin-like growth factor-1 (IGF-1) = hyperinsulinemia or insulin resistance; predisposes to T2D
 - May increase risk colon, kidney, prostate, endometrial cancers
- Fat cells produce adipokines (hormones that stimulate or inhibit cell growth)
 - Leptin: promotes cell proliferation, level increases with increasing fat
 - Adiponectin: antiproliferative effects, lower level in obese vs normal weight persons
- May directly/indirectly effect other cell growth regulators

Cardiovascular Disease

- Obesity and overweight linked to several factors that increase risk for CVD (coronary artery disease and stroke):
 - High blood lipids, especially high triglycerides, LDL cholesterol, and total cholesterol and low HDL cholesterol
 - High blood pressure
 - Can be challenging to accurately measure blood pressure in obese patient¹
 - Impaired glucose tolerance or type-2 (also called adult onset) diabetes
 - Metabolic syndrome (MetS)
 - Enlarged left ventricle (left ventricular hypertrophy) → increased risk for heart failure.
- AACE recommends weight loss of 5% to 10% to reduce CVD risk

Obesity and Hypertension

- ~50% of hypertensive patients are obese in US
- >1/3 obese patients in US have diagnosis of hypertension (vs <20% normal weight)
- Hypertension in obesity contributes to end organ damage including cardiovascular and chronic kidney disease.
- Very challenging to treat hypertension in obese patient – may require multiple agents

Bidirectional Relationship: Obesity and Blood Pressure

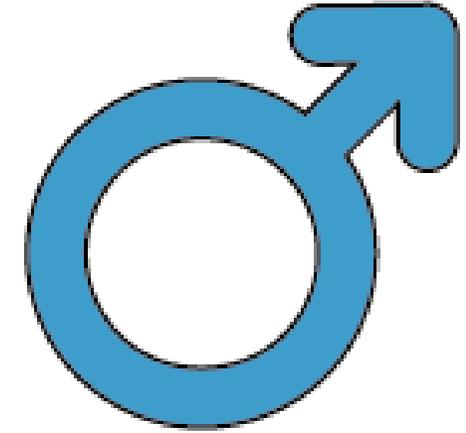
- Obesity is important risk factor for hypertension¹
 - Waist-to-height ratio and waist circumference are most strongly associated with risk of developing hypertension
- Hypertension is major factor in morbidity/mortality associated with obesity²
 - Obesity strongly correlated with treatment-resistant hypertension³
- Mechanisms:
 - Sympathetic nervous system, alteration of renal function , insulin resistance⁴
 - Altered hemodynamics, impaired sodium homeostasis, renal dysfunction, autonomic nervous system imbalance, endocrine alterations, oxidative stress/inflammation, vascular injury⁵

1. Janghorbani M, et al. High Blood Press Cardiovasc Prev. 2017 Jun;24(2):157-166.
2. Landsberg L, et al. J Clin Hypertens (Greenwich). 2013;15(1):14-33.
3. Cohen JB et al. Curr Hypertens Rep. 2019 Feb 12;21(2):16.

4. Seravalle G, et al. Pharmacol Res. 2017 Aug;122:1-7.
5. Susic D, et al. Med Clin North Am. 2017 Jan;101(1):139-157.

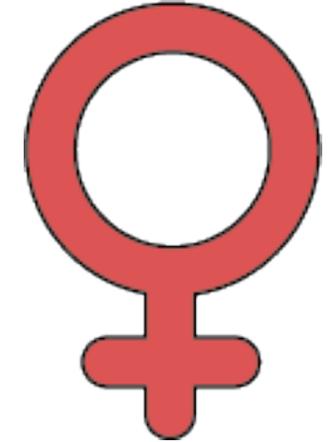


Hormonal Alterations: Males



- Male hypogonadism/Androgen deficiency¹⁻³
 - Total testosterone <280-300 ng/dL and/or free T <5-9 ng/dL
 - Decreased muscle mass, bone mineral density, increased fat mass
 - Weight loss of >5% to 10% needed to significantly increase serum testosterone
 - Testosterone therapy can facilitate weight loss, decrease waist circumference, improve metabolic parameters (for men not seeking fertility)

Hormonal Alterations: Females



- Polycystic ovary syndrome (PCOS)^{1,2}
 - Anovulation, irregular menstrual cycles, may worsen with overweight/obesity
 - Weight loss of $\geq 5\%$ to 15% can improve hyperandrogenism, oligomenorrhea, anovulation, insulin resistance, hyperlipidemia
- Female Infertility^{1,3}
 - Weight loss effective in treating some infertility; target for weight loss goal of $\geq 10\%$ to improve likelihood of conception/live birth
- Obesity as a “modifiable” risk factor for breast cancer risk in postmenopausal women⁴

1. Garvey WT, et al. Endocr Pract. 2016;22(suppl 3):1-205.
2. Cobin RH, et al. Endocr Pract. 2005;11:126-134.

3. Sim KA, et al. Clin Obes. 2014;4:61-68.
4. Kabat GC, et al. [Cancer Epidemiol Biomarkers Prev](#). 2017 Dec;26(12):1730-173



Obesity Medical Consequences Summary

- Altered Metabolism
- Digestive Disorders
 - Obesity and Dyslipidemia
 - GERD
 - Gallbladder Disease
- NAFLD and NASH
- Lung function and sleep impairment

- Cancer
- Cardiovascular disease
- Hypertension
- Hormonal alterations (males and females)



Psychiatric/Psychologic Consequences of Obesity

Obesity and Mood Disorder

- Blame/shame from family, friends and professionals
- Stigma (low self-esteem)
- Bias and Social Isolation
- Depression
- Anxiety



Bidirectional Relationship: Obesity and Depression

- Depression results in weight gain/obesity; overweight/obesity increases likelihood of developing depression¹⁻⁴
- Prevalence of depression in obesity- as high as 2X that in individuals of normal weight¹
- High prevalence mental illness and comorbid obesity⁵
- Study found 43% adults with depression are obese – vs 33% adults without depression⁶
 - As increase severity of depression, increase % of people with obesity.
 - Moderate-to-severe depressive symptoms associated with higher rate obesity – if not taking antidepressant Rx.
 - Highest prevalence of obesity (54.6%) in persons with moderate or severe depressive symptoms on antidepressants.⁶

1. Fuller NR, et al. Clin Obes. 2017 Dec;7(6):354-359.

2. Jantaratnotai N, et al. Obes Res Clin Pract. 2017 Jan-Feb;11(1):1-10.

3. Luppino FS, et al. Arch Gen Psychiatry. 2010 Mar;67(3):220-229.

4. Xiang X, et al. J Psychosom Res. 2015 Mar;78(3):242-248.

5. Avila C, et al. Curr Obes Rep. 2015 Sep;4(3):303-310.

6. Pratt LA, et al. NCHS Data Brief. 2014 Oct;(167):1-8. Dawes AJ, et al. JAMA. 2016 Jan 12;315(2):150-163.



Obesity and Binge Eating Disorder

- Online survey of people with overweight/obesity¹
 - Nearly 1/3 met criteria for binge-eating disorder (BED), food addiction (FA) or BED+FA
 - Disordered eating: greater psychiatric pathology, impulsivity, self-control, depression
- DSM-5 recognizes strong association between obesity and psychiatric syndromes²:
 - Strong association with bipolar spectrum disorders (BSD) and BED.
 - Distinctive pathological eating behaviors may be warning signals in obese patients
- Disordered eating (eg BED) is associated with weight gain over time, increased risk of diabetes and metabolic dysfunction;
 - Patients also have higher risk of psychopathology – mood, anxiety, sleep problems.³

1. Ivezaj V, et al. Obesity (Silver Spring). 2016 Oct;24(10):2064-2069.
2. Segura=Garcia C, et al. J Affect Disord. 2017 Jan 15;208:424-430.
3. McCuen-Wurst C, et al. Ann N Y Acad Sci. 2018 Jan;1411(1):96-105.





Benefits of Weight Loss

Physical

Medical

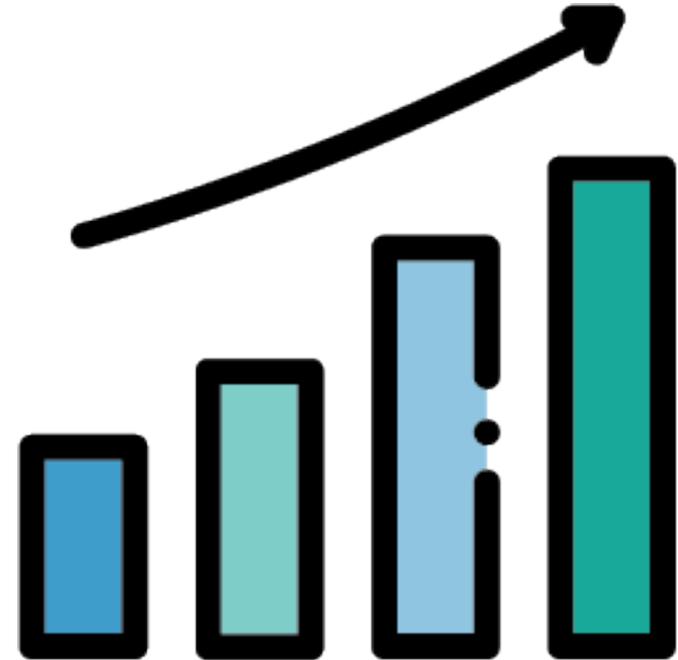
Psychiatric/Psychologic

USPSTF Recommendation Statement

- Adequate evidence that intensive, multicomponent behavioral interventions in adults with obesity can lead to clinically significant improvements in weight status and reduce incidence of T2D among adults with obesity and elevated plasma glucose levels: moderate benefit
- Adequate evidence that behavior-based weight loss maintenance interventions are of moderate benefit
- Adequate evidence that the harms of intensive, multicomponent behavioral interventions (including weight loss maintenance interventions) are small to none
- Adults with BMI ≥ 30 should be referred to intensive, multicomponent behavioral weight loss interventions

Physical Benefits of Weight Loss

- Improved ability to engage in activities of daily living (ADLs)
- Improved mobility
 - Physical activity abdominal fat (around the waist) and total body fat; slows the development of abdominal obesity.
- Easier to engage in physical activity
 - Exercise
 - NEAT (non-exercise activity thermogenesis)
- Reduced symptoms of:
 - Obstructive sleep apnea (OSA)
 - Bladder incontinence
 - Joint pain



Effect of Weight Loss: Asthma

- Weight loss (via caloric restriction) of >7.5% --> improvements in asthma disease factors¹⁻⁴
 - Reduced asthma severity
 - Improved disease control
 - Improved quality of life
 - Improved airway hyperresponsiveness
 - Peak expiratory flow
 - Pulmonary function
 - Markers of oxidative stress, inflammation

1. Forte GC, et al. Crit Rev Food Sci Nutr. 2018 Jul 24;58(11):1878-1887.

2. Johnson JB, et al. Free Radic Biol Med. 2007;42(5):665-674.

3. Pakhale S, et al. Chest. 2015 Jun;157(6):1582-1590.

4. Ulrik CS. Curr Opin Pulm Med. 2016 Jan;22(1):69-73.



Relationship between Weight Loss and OSA

- Complex interaction between obesity and weight loss¹
 - Weight loss is associated with significant reduction in apnea-hypopnea index (AHI)²
 - Long-term treatment of OSA with CPAP is associated with a small but significant weight gain^{1,2}
 - Weight loss may only benefit a small percentage of patients with sleep apnea¹
 - Screening for OSA before attempting weight loss is recommended³

1. Foster GD, et al. Arch Intern Med. 2009;169:1619-1626.

2. Joosten SA, et al. Chest. 2017 Jul;152(1):194-203.

3. Kline CE, et al. Mayo Clin Proc. 2018 Sep;93(9):1290-1298.



Benefits of Weight Loss

Weight loss reduces symptoms of:¹

- Dyslipidemia
- GERD (symptoms and complications)
- Gallbladder disease
- Nonalcoholic fatty liver disease (NAFLD)
- Nonalcoholic steatohepatitis (NASH)
- Colon cancer

Weight loss and dyslipidemia

- Markedly reduces fasting and non-fasting TG concentrations
- Small reduction in LDL-C
- Weight loss of ~9-22 lbs in obese subjects resulted in a 12% reduction in LDL-C and a 27% increase in LDL receptor mRNA levels
- Modest 5% weight loss leads to substantial reductions in adipose visceral fat tissue (AVT) and adipose subcutaneous tissue (AST) which reduce TG concentrations, cholesterol¹

Weight Loss and Gallbladder Disease

- Weight loss can reduce risk gallbladder disease
- Dietary contribution: Eating foods high in fiber, healthy fats, can reduce risk of gallbladder disease
- Rapid weight loss can cause gallstones



Weight Loss and NAFLD/NASH

- Weight loss is cornerstone for disease prevention and treatment^{1,2}
- Diet and exercise initial steps; often need for pharmacologic and/or surgical intervention
- Importance of reducing visceral (abdominal) fat to reduce risk of progression from simple steatosis (SS)/NAFLD to NASH²
- Mean weight loss of ~12.5 lb via lifestyle intervention led to significant reduction in intrahepatic triglycerides and significantly greater number of patients achieving NAFLD remission vs Control group³

1. Milić S, et al. World J Gastroenterol. 2014 Jul 28;20(28):9330-9337.

2. Polyzos SA, et al. Minerva Endocrinol. 2017 Jun;42(2):92-108.

3. Wong VW, et al. J Hepatol. 2013;59:536-542.



NAFLD/NASH (continued)

- AACE Gx recommend patients with overweight or obesity and NAFLD should be primarily managed with lifestyle interventions
 - Calorie restriction and moderate-to-vigorous physical activity
 - Target 4% to 10% weight loss
- Weight loss as high as 10% to 40% may be required to decrease hepatic inflammation, hepatocellular injury, and fibrosis (Rx, surgery)
- A Mediterranean dietary pattern or meal plan can have a beneficial effect on hepatic steatosis independent of weight loss.

Obesity and Cancer

- People who have lower weight gain in adulthood have lower risk of colon cancer, kidney cancer, and (postmenopausal women) breast, endometrial, ovarian cancers^{1,2}
 - Weight loss may reduce inflammation and protect against cancer
 - Reduced adipose tissue prevents excess amounts of estrogen, reduced risk numerous cancers
- Obese people who undergo bariatric surgery have reduced risk many cancers vs those who do not undergo bariatric surgery¹

1. <https://www.cancer.gov/about-cancer/causes-prevention/risk/obesity/obesity-fact-sheet>

2. GA et al. Clin Chem. 2018;64(1):154-162.



Weight Loss and Hypertension

- ~50% of hypertensive patients are obese in US
- >1/3 obese patients in US have diagnosis of hypertension (vs <20% normal weight)
- Hypertension in obesity contributes to end organ damage including cardiovascular and chronic kidney disease.
- Weight loss is strongly associated with improvements in blood pressure.
- Weight loss medications may not be as beneficial as lifestyle or surgical interventions
 - Unpredictable effects medications



Metabolic Benefits of Weight Loss

- Decreased insulin resistance
- Decreased blood glucose
- Decreased cholesterol
- Decrease in fatty liver

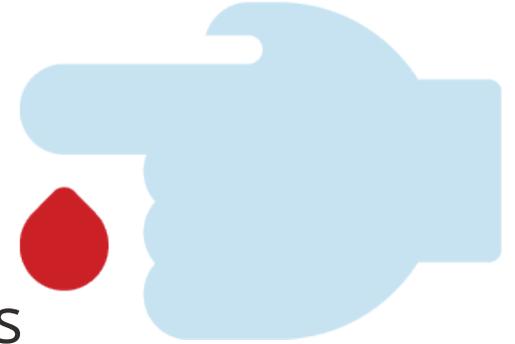
Weight Loss To Prevent Diabetes

- Weight loss is highly effective to prevent, treat T2D¹⁻³
 - ADA recommends loss $\geq 7\%$ of body weight with increased PA ≥ 150 min/week¹
 - Weight loss of $\sim 10\%$ maximally beneficial to prevent future diabetes
 - Weight loss via lifestyle therapy, pharmacotherapy, or bariatric surgery³
- Weight loss in high-risk patients with prediabetes and/or MetS²
 - Prevents progression to T2D
 - Improves insulin resistance
 - Improves CV risk factors
 - Metabolic health benefits – even in absence of classic CV risk factors.
- Weight loss in persons with diabetes³
 - Improves glycemic control in patients with T2D
 - Improves features of NAFLD and NASH

1. Delahanty LM. *Prev Med.* 2017 Nov;104:120-123.
2. Grams J, et al. *Curr Obes Rep.* 2015 Jun;4(2):287-302.
3. Garvey WT, et al. *Endocr Pract.* 2016;22(suppl 3);1-205.



Weight Loss in Patients with T2D



- Benefits of weight loss:¹
 - Improves glycemia
 - Enhances glucose homeostasis via reversing defects in insulin action and secretion from glucose toxicity
 - As increase % weight loss, progressive improvements in glucose homeostasis²
 - Reduces need for conventional glucose lowering medicines
- Metabolic benefits of bariatric surgery generally more pronounced vs lifestyle/medical treatments²
- Hypocaloric feeding via very-low calorie diet or bariatric surgery leads to rapid improvement in insulin sensitivity

1. Delahanty LM. Prev Med. 2017 Nov;104:120-123.

2. Grams J, et al. Curr Obes Rep. 2015 Jun;4(2):287-302.



Effect of Differing Amounts of Weight Loss

5% Weight Loss	≥10% Weight Loss
Improved adipose tissue, liver and muscle insulin sensitivity, β -cell function	Further improvements in β -cell function and insulin sensitivity in muscle
No change in systemic or subcutaneous adipose tissue markers of inflammation	Changes in intrahepatic triglycerides, adipose tissue biological pathways
Simultaneous improvement in metabolic function in multiple organs	Continued improvement in metabolic function in multiple organs

Diabetes Prevention Program (DPP)



- 2 major goals of DPP lifestyle intervention:
 - Minimum 7% weight loss/weight maintenance
 - Minimum of 150 min physical activity similar in intensity to brisk walking.
- Program methods
 - Individual case managers or “lifestyle coaches”
 - Frequent contact with participants
 - Structured 16-session core-curriculum on behavioral self-management strategies
 - Supervised physical activity sessions
 - Flexible maintenance intervention
 - Individualization through a “toolbox” of adherence strategies
 - Tailored materials and strategies to address ethnic diversity
 - Extensive network of training, feedback, and clinical support

Diabetes Prevention Program (DPP)

- DPP program reduced diabetes incidence by 58% after 2.8 years of follow up
 - Sustained improvements in HbA1c, blood pressure, lipid levels.
 - After 15 years follow-up – DPP’s lifestyle intervention sustained a 27% risk reduction in progression to diabetes
- In light of many DPP-like studies that consistently demonstrate weight losses of 7% at 1-year, as of April 2018 Medicare covers CDC-recognized DPP lifestyle programs

Look AHEAD: Lifestyle intervention

- Significantly reduced HbA1c, BP, TG; reduced c-reactive protein (CRP)
- Lowered the amount/costs Rx
- Less self-reported retinopathy
- Reduced risk nephropathy, less sexual dysfunction, decreased incidence UI, decreased incidence fatty liver, remission of sleep apnea, remission of diabetes
- Improved physical functioning, less knee pain, reduced incidence depression, less body image dissatisfaction, improved QoL.

Weight Loss and Women

- Academy of Nutrition and Dietetics: Counsel all women of reproductive age regarding risks of pre-pregnancy obesity, excessive gestational weight gain, postpartum weight retention¹
 - Weight loss before pregnancy improves fertility, decreases risk of poor maternal/fetal outcomes¹
 - Maternal pre-pregnancy obesity increases risk preterm birth; varies by age and race/ethnicity²
- PCOS:^{3,4}
 - Low dose OCs and lifestyle interventions → weight loss and significant improvements in psychosocial parameters;
 - Changes in serum testosterone, FG and body weight had greatest benefits³
 - Combining OC + lifestyle interventions had greatest benefit to HRQoL³
 - Weight loss of even 2% to 5% improves ovulation and spontaneous pregnancy⁴

1. Stang J, et al. J Acad Nutr Diet. 2016 Apr;116(4):677-691.

2. Liu B, et al. [Lancet Diabetes Endocrinol](#). 2019 Aug 5.

3. Dokras A, et al. J Clin Endocrinol Metab. 2016 Aug;101(8):2966-2974.

4. Ryan DH et al. Curr Obes Rep. 2017 June;6(2):187-194



Weight Loss Effects: Postmenopausal Women

- Women's Health Initiative (WHI) observational study and follow-up: 61,335 postmenopausal women had their weight change determined over a 3-year period with subsequent follow-up.
 - Breast cancer:
 - Women with weight loss $\geq 5\%$ had significantly lower breast cancer incidence vs women with stable weight¹
 - WHI Dietary Modification randomized clinical trial (n=48,835 postmenopausal women): following low-fat eating pattern significantly reduced deaths after breast cancer
 - Moderation regarding dietary composition and body weight maintenance can reduce a postmenopausal woman's risk of being diagnosed with breast cancer and of dying after breast cancer¹
 - Mortality:
 - Normal-weight central obesity associated with excess risk of mortality (~same as women with BMI-defined obesity with central obesity)
 - Importance of prevention and control of central obesity even if normal BMI²
 - Cardiovascular disease (2683 postmenopausal women with normal BMI (18.5 to $<25 \text{ kg/m}^2$) with no known CVD at baseline³
 - Median 18 years of follow-up: postmenopausal women with normal BMI: elevated trunk fat and reduced leg fat associated with increased risk of CVD
- Menopausal hormone therapies (MHT) may prevent T2D⁴

1. Pan K, et al. [Oncotarget](#). 2019 May 3;10(33):3088-3092.
2. Sun Y, et al. [JAMA Netw Open](#). 2019 Jul 3;2(7):e197337.

3. Chen GC, et al. [Eur Heart J](#). 2019 Jun 30.
4. Lovre D, et al. [J Endocr Soc](#). 2019 Jun 6;3(8):1583-1594.



Hormonal Benefits: Testosterone

- Testosterone therapy in men with testosterone deficiency and obesity:¹
 - Increases lean body mass, decreases fat mass, improves overall body composition
- Long-term testosterone therapy in men with testosterone deficiency:
 - Significant/sustained weight loss, marked reduction in waist circumference and BMI, improvement in body composition^{1,2}
 - T therapy more effective for weight loss vs bariatric surgery
 - Ameliorates components of the metabolic syndrome

1. Traish AM. [Curr Opin Endocrinol Diabetes Obes](#). 2014 Oct;21(5):313-322.

2. Salman M, et al. [Aging Male](#). 2017 Mar;20(1):45-58.



Psychiatric/Psychologic Benefits of Weight Loss

- Improved mood, decrease in anxiety and depressive symptoms
- Improved mental clarity, focus and attention
- Weight loss decreases depression symptoms (if non-clinically depressed)¹
- Treatment of one comorbidity (obesity/depression) improves the course of the other condition²
- Among patients going for bariatric surgery – high prevalence of depression (19%) and binge eating disorder (17%).
 - Bariatric surgery consistently associated with postop decreases in prevalence of depression (8-74% decrease) and severity of depression symptoms (40-70% decrease)³

1. Fuller NR, et al. Clin Obes. 2017 Dec;7(6):354-359.

2. Jantaratnotai N, et al. Obes Res Clin Pract. 2017 Jan-Feb;11(1):1-10.

3. Dawes AJ, et al. JAMA. 2016 Jan 12;315(2):150-163.



Racial and Ethnic Differences

- Majority of obesity studies predominantly involve White participants¹
 - Results of studies may not be generalizable to non-Whites
- Effect of food insecurity, lack of physical activity, type of foods eaten (sugar/sugar sweetened) can increase risk childhood/adolescent obesity risks²
- Need to address infrastructure and access to physical activity and nutritious food

1. Haughton CF, et al. Prev Med Rep. 2018 Feb 2;9:131-137.

2. Au LE. [J.Nutr.](#) 2019 Jun 7



Weight loss approaches

- Diet/lifestyle intervention/exercise
 - Importance of weight training and other exercises with diet-induced weight loss – to minimize risk of losing muscle strength¹
- Pharmacotherapy
- Bariatric surgery



Role of NEAT

- Physical activity (PA) is either exercise-related thermogenesis (EAT) or non-exercise activity thermogenesis (NEAT)¹
- Most individuals get very little formal exercise²
- Energy is expended with spontaneous NEAT¹
- NEAT is major component of daily activity-related thermogenesis
 - Examples: leisure time activity, sitting, standing, ambulation, toe-tapping, shoveling snow, playing piano, dancing, washing, cooking, fidgeting, etc.¹

1. Von Loeffelholz C, et al. Endotext (Internet). MDText.com, Inc. 2014.

2. <https://www.ncbi.nlm.nih.gov/books/NBK279077>. Kotz CM, et al. Minn Med. 2005 Sep;88(9):54-57.



Weight-Loss Medications

- Overall, weight loss medications are associated with:
 - Modest decrease in fasting blood glucose (FBG) and waist circumference (WC)
 - No clinically meaningful changes in systolic/diastolic BP or cholesterol profile vs PBO.
- NO drug improves all cardiometabolic risk factors.

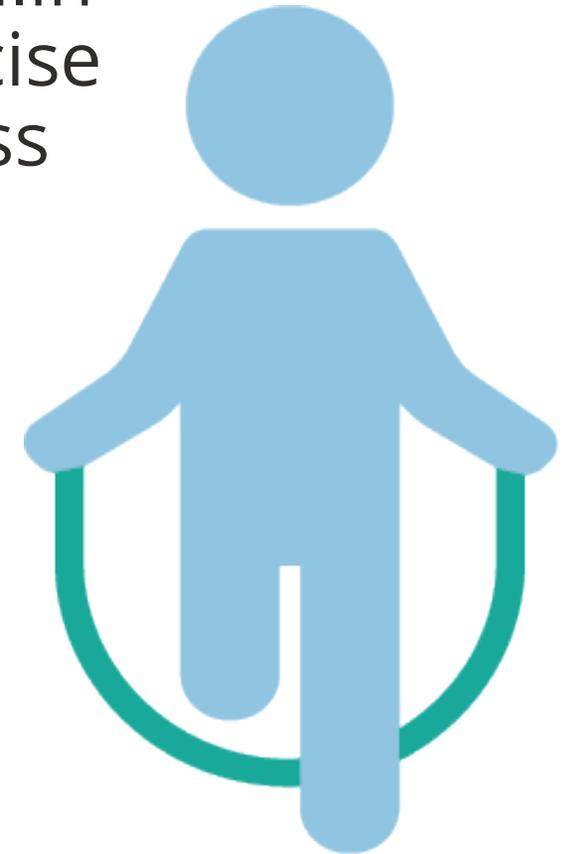


Weight Loss Medications

Medication	Benefits	Other
Phentermine-topiramate	Substantial decrease WC Modest decrease in FBG, HbA1c, BP	Minimal effect on cholesterol
Liraglutide	Substantial decrease FBG, HbA1c, WC	Minimal effect on blood pressure, cholesterol
Naltrexone-bupropion	Moderate increase HDL-C	Minimal effect FBG, WC
Orlistat	Decrease in LDL-C	Decrease in HDL-C

Aerobic training: with/without weight loss

- Study found greater improvement in insulin sensitivity in adults who performed exercise training with at least moderate weight loss ($\geq 3\%$) vs exercise training alone.
 - Benefits to acute insulin response, triglycerides, non-HDL cholesterol concentration, low density lipoprotein (LDL) particle size, high density lipoprotein (HDL) particle size.
 - Modest weight loss needed with exercise for improved cardiovascular benefits



Amount of Weight Loss Needed for Benefit

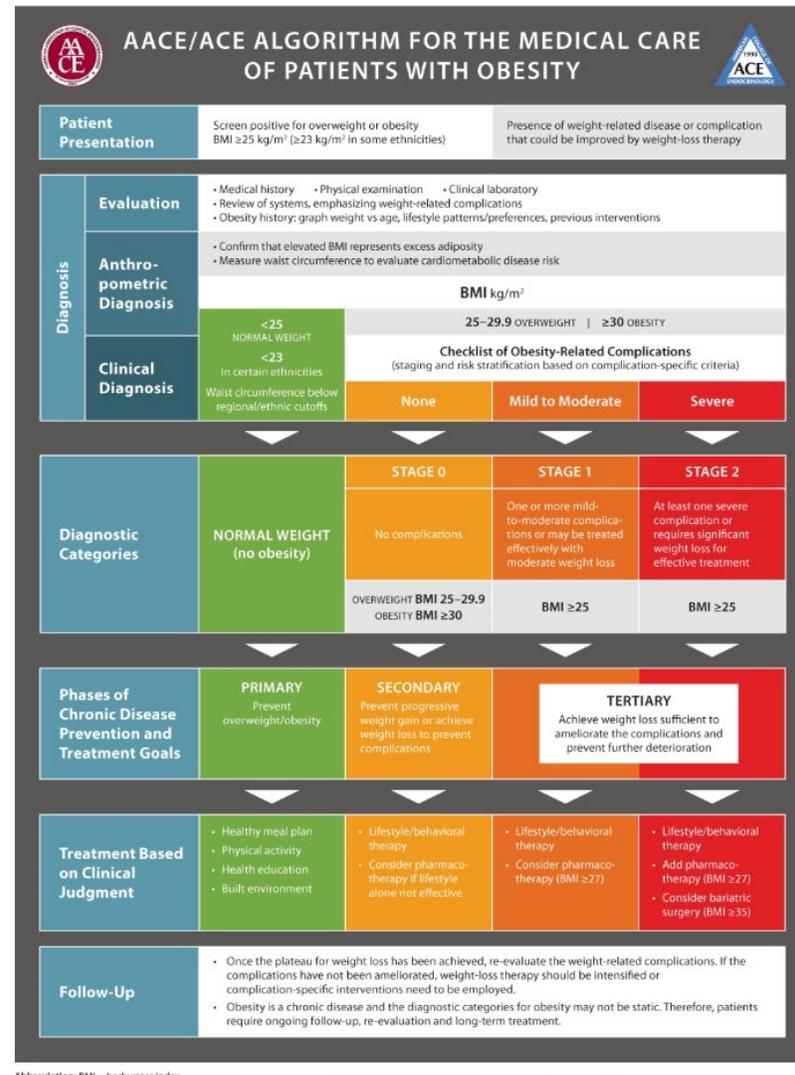
- Even small amounts weight loss have benefit to glycemic measures, TG
 - PCOS: 2% to 5% can improve menstrual irregularities, infertility
 - For 1kg (2.2 lb) weight loss: 16% reduction in risk for T2D
 - No clear benefit for weight loss >10kg (22lb) regarding T2D prevention
- Clinically meaningful weight loss: at least 5%
- Modest weight loss (5% to 10%):
 - Associated with improved systolic and diastolic BP, HDL-C
 - Improvements in QoL, depression, mobility, sexual dysfunction, urinary stress incontinence
- Additional weight loss (>10% to 15%) needed for improvements to OSA, NASH
 - Reduction in mortality



AACE/ACE ALGORITHM

Medical Care of Patients with Obesity

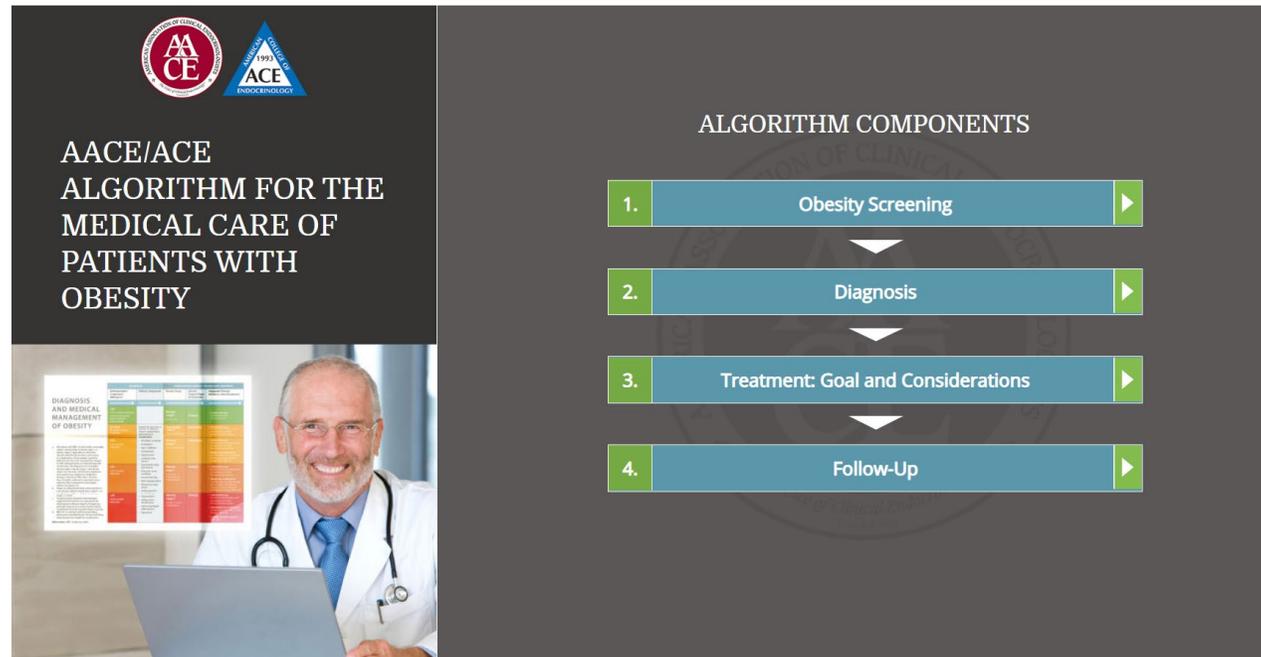
Algorithm for Medical Care of Patients with Obesity



Algorithm Components

Access the interactive AACE/ACE Obesity Algorithm

<https://www.aace.com/disease-state-resources/nutrition-and-obesity/treatment-algorithms/obesity-algorithm#/components>



The screenshot displays the AACE/ACE Obesity Algorithm interface. On the left, there is a dark grey header with the AACE and ACE logos, followed by the text "AACE/ACE ALGORITHM FOR THE MEDICAL CARE OF PATIENTS WITH OBESITY". Below this is a photograph of a smiling male doctor in a white coat and stethoscope, looking at a laptop. To the left of the doctor is a small thumbnail of the algorithm document. On the right, a dark grey panel titled "ALGORITHM COMPONENTS" lists four steps in a vertical sequence, each in a teal bar with a green arrow on the right and a white downward arrow between steps:

1. Obesity Screening
2. Diagnosis
3. Treatment: Goal and Considerations
4. Follow-Up

Summary

- Benefits of weight loss are extensive, extend over multiple areas of physiology
- No magic bullets that can mimic or replace weight loss
- Ideal body weight does NOT need to be achieved to experience benefits
 - Weight loss of at least 5% or 10% can have substantial health benefits
- Weight loss without exercise is STILL important
 - Exercise is NOT required
 - NEAT: Non-exercise activity thermogenesis

