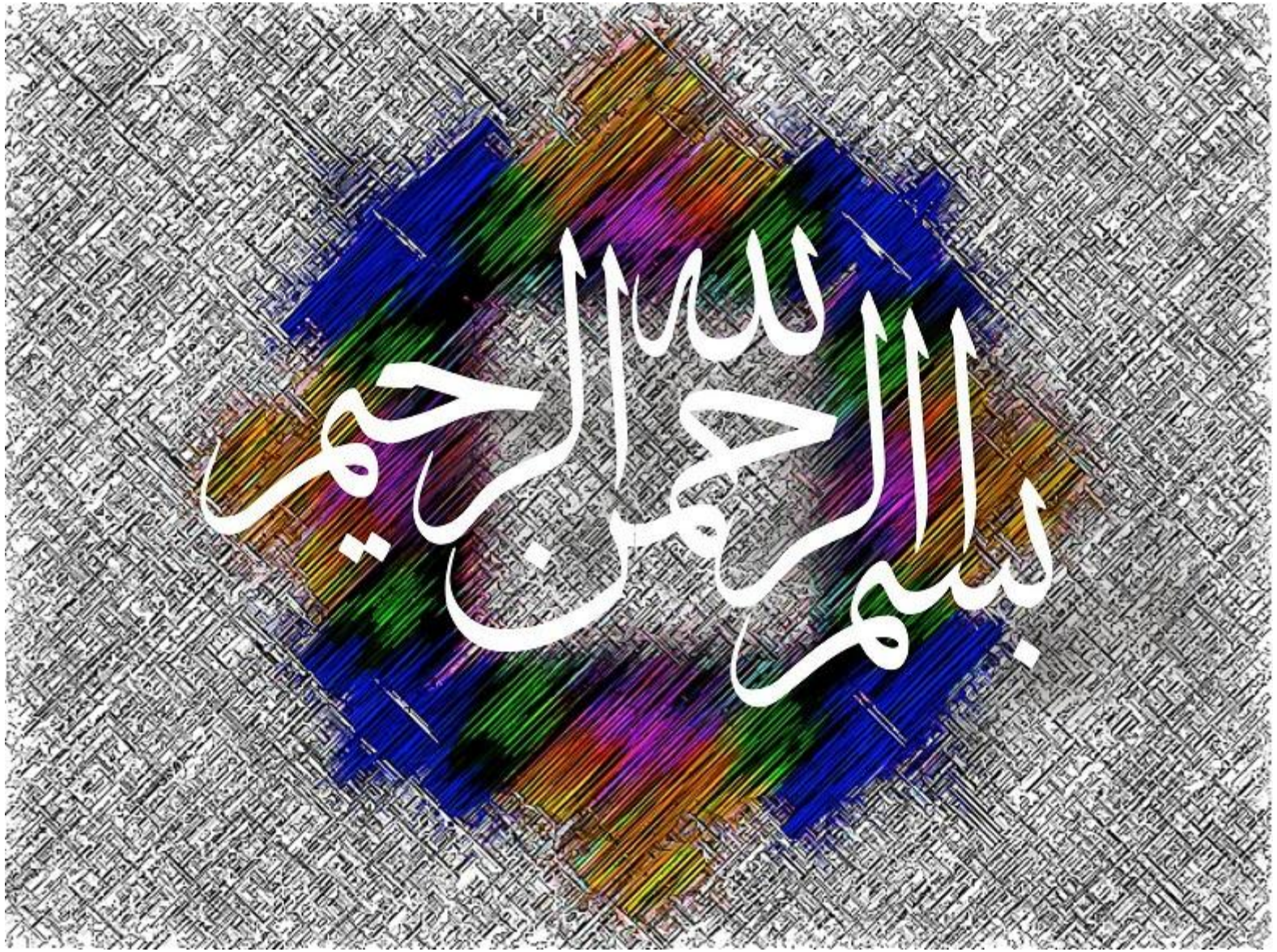
بسم الله الرحمن الرحيم

OBESITY MANAGEMENT IN ADULTS

a REVIEW

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با آرزوی آسمانی آبی وصاف برای شهرزیبای اصفهان

JAMA / REVIEW

IMPORTANCE : Obesity affects # 42% of US adults and is associated with increased rates of type 2 diabetes, hypertension, cardiovascular disease, sleep disorders, osteoarthritis, and premature death.

- Obesity, currently defined as a body mass index (BMI) of ≥ 30 Kg/ m^2 , affects 800 million people worldwide.(1)

- In the United States, approximately 42% of adults have obesity, (2) and obesity-related costs are estimated at $173 billion annually. (3)

ADA - 2024

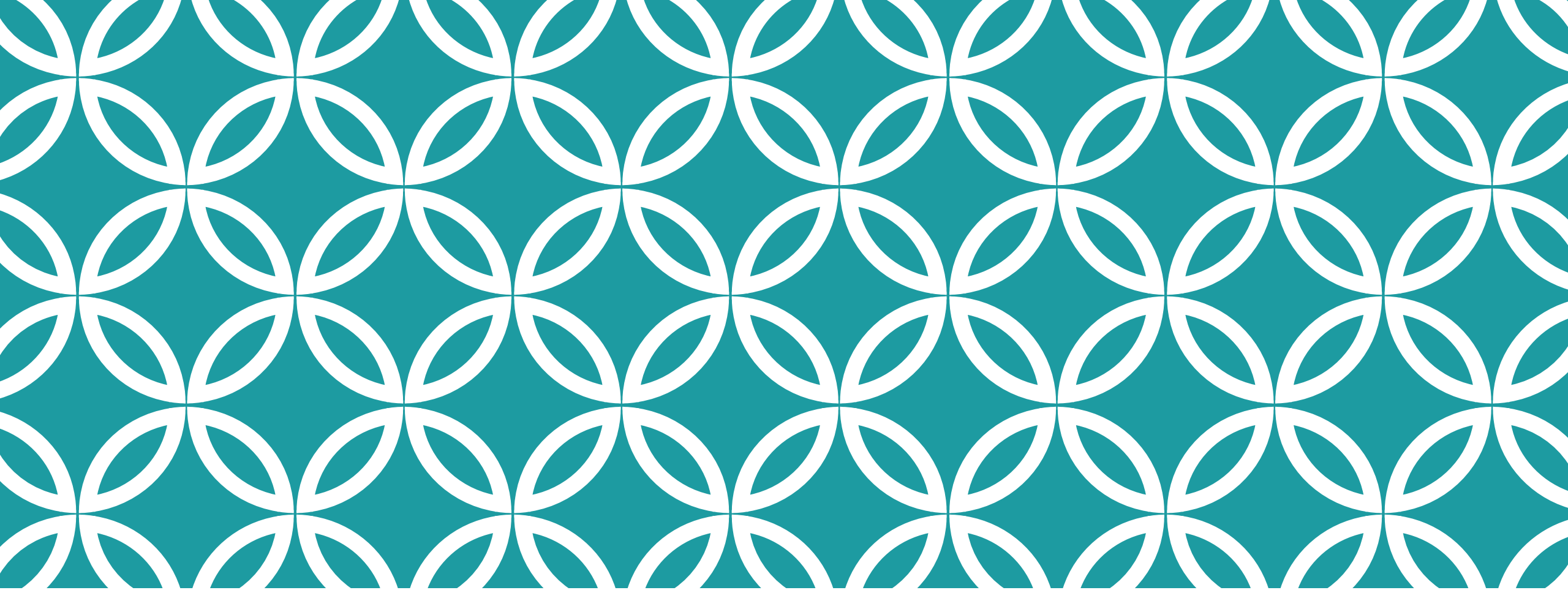
- Obesity is a key pathophysiologic driver of diabetes, other cardiovascular risk factors (e.g., hypertension, hyperlipidemia, nonalcoholic fatty liver disease, and inflammatory state), and ultimately *cardiovascular* and *kidney disease* (30) .

DEFINITION

- Obesity is a chronic disease defined by excess adiposity with structural and functional consequences resulting in increased risk of comorbidities and premature mortality. (4,5)

- Obesity is often associated with stigma, which impairs quality of life and increases morbidity. (6)

- **Weight loss improves glucose, lipids, blood pressure, and obesity-related comorbidities, (4,5,8) and clinicians can offer multiple effective obesity treatments. (9-11)**



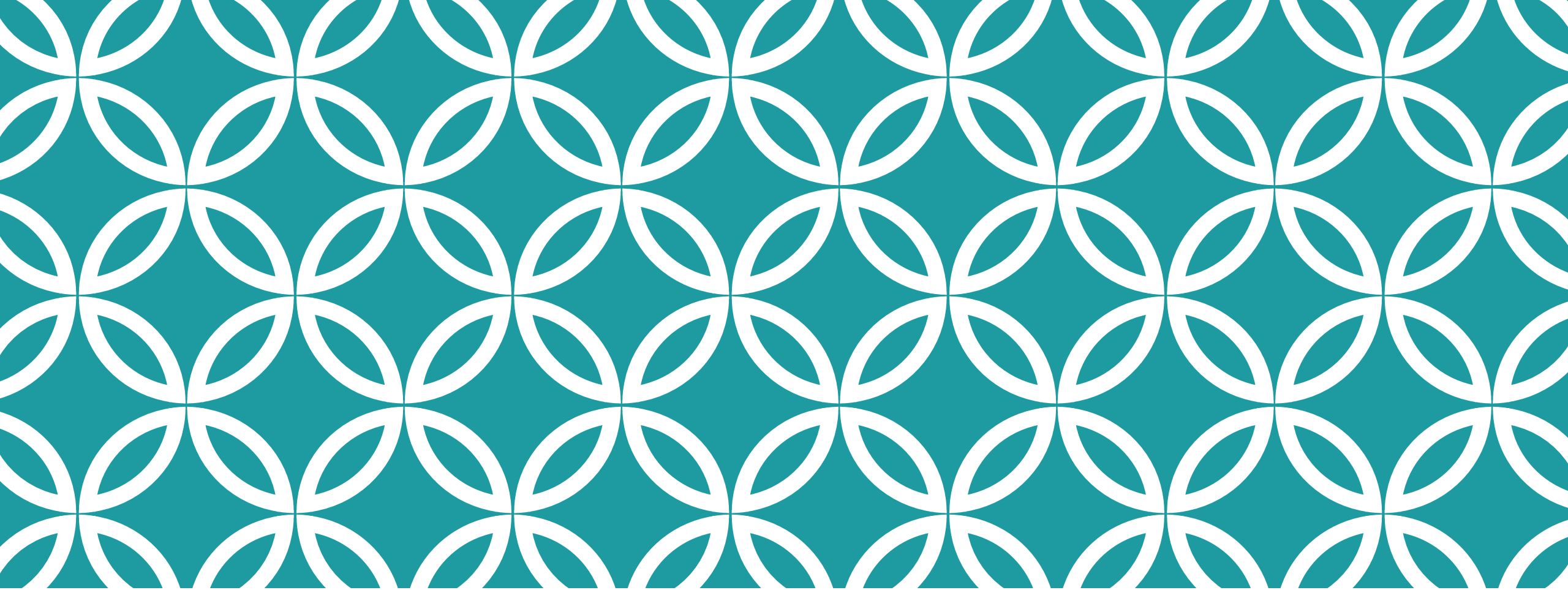
EPIDEMIOLOGY | OBESITY

PREVALENCE

- **The prevalence of obesity worldwide increased between 1975 and 2014 from 3.2% to 10.8% in men and from 6.4% to 14.9% in women. (15)**

- **By 2025, it is anticipated that 18% of men and 21% of women worldwide will have obesity. (15)**

- It is anticipated that by 2030, 48.9% of US adults will have obesity and that racial differences in rates of obesity will increase. (17)



RISK FACTORS | Obesity

- Obesity reflects a chronic energy imbalance , with greater calorie consumption than energy expenditure , (18) and is influenced by multiple factors.

- Genetic variants are implicated in its development. (19)

- polygenic risk factors with several variant

- The environment influences the relationship between genetics and obesity risk. (19)

"OBESOGENIC ENVIRONMENTS,"

- For example, greater availability of fast-food restaurants, poor neighborhood walkability , and perceived safety risks can limit physical activity and healthy food options. (20)

- There is a bidirectional association between *depression* and obesity, wherein each diagnosis is associated with increased risk of developing the other. (21)

RISK FACTORS

Additional risks include : *insufficient sleep* and *low socioeconomic status*, in part mediated by chronic stress and food insecurity, which are commonly experienced by racial and ethnic minority populations. (22)

PATHOPHYSIOLOGY OF OBESITY

JAMA -2023

PATHOPHYSIOLOGY OF OBESITY

- Influenced by genetic expression, energy homeostasis is determined by feedback between circulating neuropeptide hormones and the central nervous system. (19,23)

The *gut-brain axis* responds to peripheral signals from the gastrointestinal tract, adipose tissue, and circulating hormones to stimulate or inhibit central neurons based on satiety or hunger. (24)

- *Dysregulation* of this system develops in obesity, often leading to increased hunger and decreased satiety. (18)
- Hormones involved in this process include : **leptin** and **ghrelin**. (18)
- Additionally, hormone response and metabolic adaptation promote weight regain. (18)
- Obesity increases rates of *comorbid conditions* through pathophysiologic and mechanical changes related to excess adiposity and increased weight. (23,24)

Obesity is a complex and multifactorial disease

Energy intake

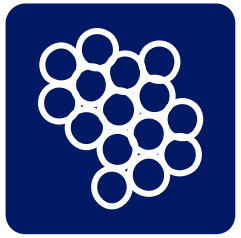
Energy expenditure

Hedonic input

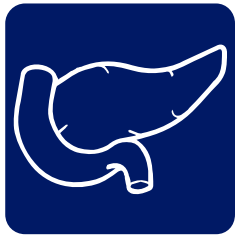
Increased palatability or pleasure

Environment

Inactive lifestyle, smoking cessation, psychosocial factors



Adipose tissue



Pancreas

Gut

Genetics

Medications

1. Badman, Flier. *Science* 2005;307:1909–14; 2. US Department of Health and Human Services, 1998. NIH Publication No. 98-4083

PATHOPHYSIOLOGY OF CVD

- **Related conditions include : asthma, type 2 diabetes, hypertension, obstructive sleep apnea, osteoarthritis, and cardiovascular disease (CVD).** (4,5)

- Weight-related cardiometabolic abnormalities occur due to excess visceral adipose tissue (and possibly an impaired ability to deposit fat into the peripheral adipose tissue such as the gluteofemoral fat compartment), which secretes hormones and proinflammatory cytokines, leading to low-grade systemic inflammation. (23,24,27)

- Lipid deposition into adipose tissue and occurrence of adiposity leads to anatomical changes such as increased pharyngeal soft tissue, contributing to obstructive sleep apnea or mechanical joint load that results in osteoarthritis. (23)

Table 1. Evidence-Based Screening Recommendations for Weight-Related Comorbidities[4,6,14]

Comorbidities[a]	Screening method/diagnostic criteria
Asthma/respiratory disease	History, physical examination; spirometry as indicated
Diabetes	Fasting plasma glucose ≥126 mg/dL; hemoglobin A_{1c} ≥6.5%; 2-h oral glucose tolerance test
Dyslipidemia	Lipid panel that includes triglycerides, HDL-C, LDL-C, total cholesterol, and non-HDL-C
Gastroesophageal reflux disease	History; endoscopy as indicated
Hypertension	Sitting blood pressure ≥130/80 mm Hg
Metabolic syndrome	Three or more of the following: waist circumference ≥88 cm for women, ≥102 cm for men; triglycerides ≥150 mg/dL; fasting plasma glucose ≥100 mg/dL; blood pressure ≥130/85 mm Hg; HDL-C <40 mg/dL in men, <50 mg/dL in women
Nonalcoholic fatty liver disease/nonalcoholic steatohepatitis	Liver function tests; consider calculation of Fibrosis-4 Index; imaging as indicated
Obstructive sleep apnea	Neck circumference, clinical screening questionnaires (eg, STOP-BANG score); polysomnography as indicated
Osteoarthritis	History, physical examination (eg, weight-bearing joints); radiography as indicated
Prediabetes	Fasting plasma glucose 100-125 mg/dL, hemoglobin A_{1c} 5.7%-6.4%, 2-h oral glucose tolerance test

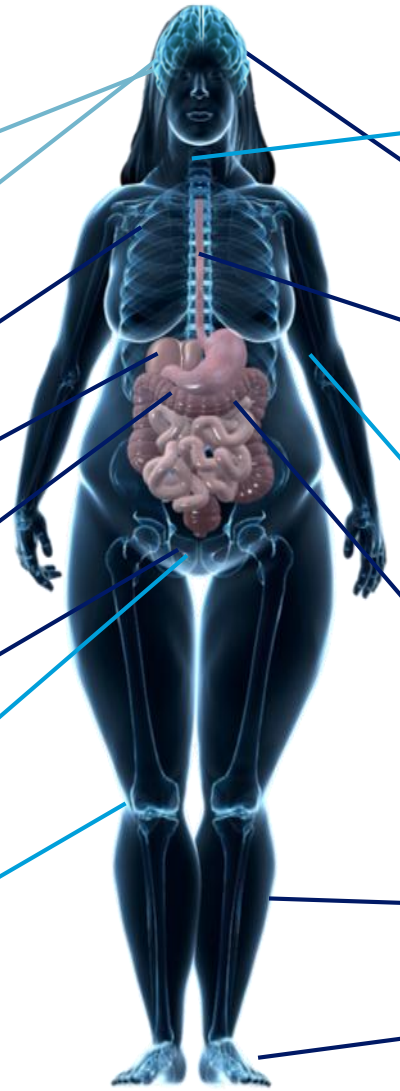
Obesity is associated with multiple comorbidities and complications

Metabolic, mechanical and mental

- Metabolic
- Mechanical
- Mental

- Depression
- Anxiety
- Asthma
- NAFLD
- Gallstones
- Infertility
- Incontinence
- Arthrosis

- Cancers*
- Physical functioning



- Sleep apnoea
- CVD and risk factors
  - Stroke
  - Dyslipidaemia
  - Hypertension
  - Coronary artery disease
  - Congestive heart failure
  - Pulmonary embolism
- Chronic back pain
- Type 2 diabetes
  Prediabetes
- Thrombosis
- Gout

Adapted from Sharma AM. *Obes Rev*. 2010;11:808-9; Guh *et al. BMC Public Health* 2009;9:88; Luppino *et al. Arch Gen Psychiatry* 2010;67:220–9; Simon *et al. Arch Gen Psychiatry* 2006;63:824–30; Church *et al. Gastroenterology* 2006;130:2023–30; Li *et al. Prev Med* 2010;51:18–23; Hosler. *Prev Chronic Dis* 2009;6:A48

DIAGNOSIS AND CLASSIFICATION OF OBESITY

DIAGNOSIS AND CLASSIFICATION OF OBESITY

Body mass index (BMI), calculated as weight in kilograms divided by height in meters squared, is most commonly used to classify obesity on a population level. (28)

The World Health Organization uses BMI to define overweight (25-29.99) , class I obesity (30-34.99) , class II obesity (35-39.99) , and class III obesity (≥40). (28)

BMI

In Asian populations, cardiometabolic diseases occur at lower BMI levels; therefore, some expert guidelines recommend lower BMI thresholds (guidelines differ in thresholds of BMI ≥ 25 and ≥ 27.5 Kg/m² for obesity). (4,9,11)

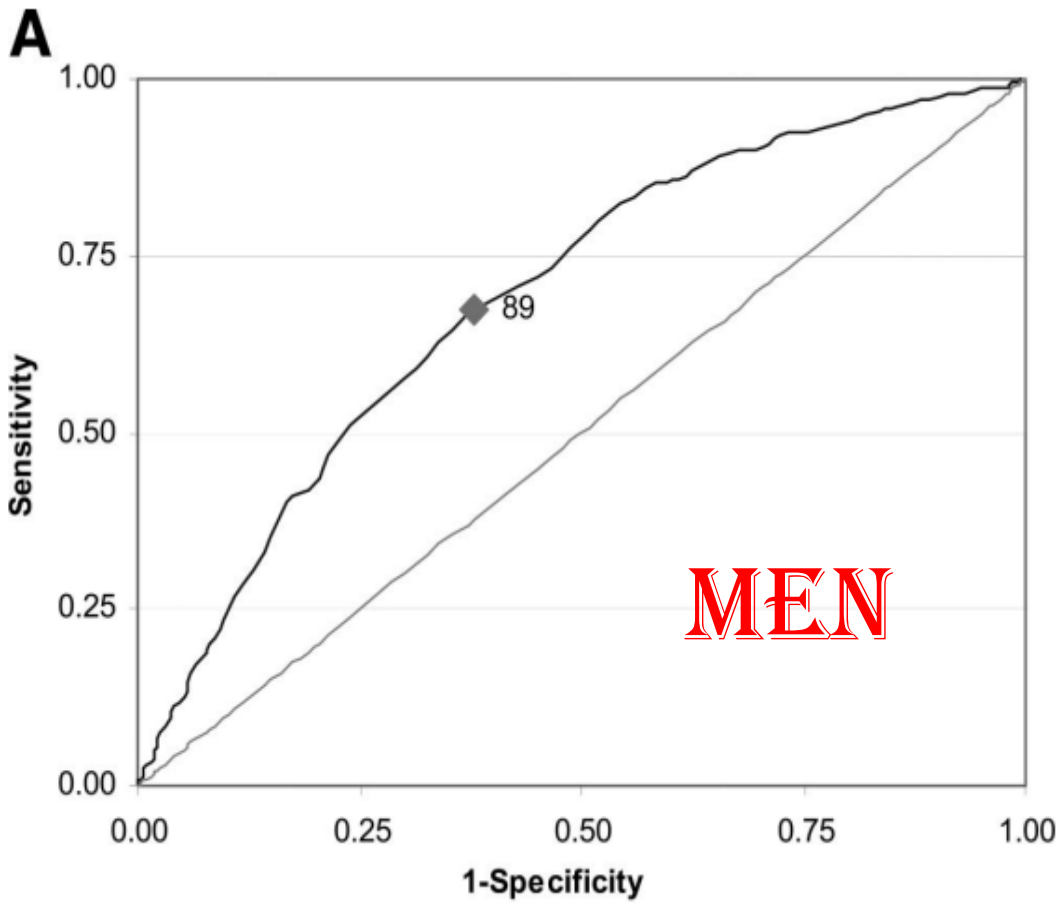
Clinical use of BMI is controversial , / For example : waist circumference is a marker of visceral adiposity associated with increased cardiometabolic risk, (4,5) and guidelines recommend risk stratification based on waist circumference (102 cm for men and 88 cm for women) in patients with a BMI of 25 to 34.9 (4-6)

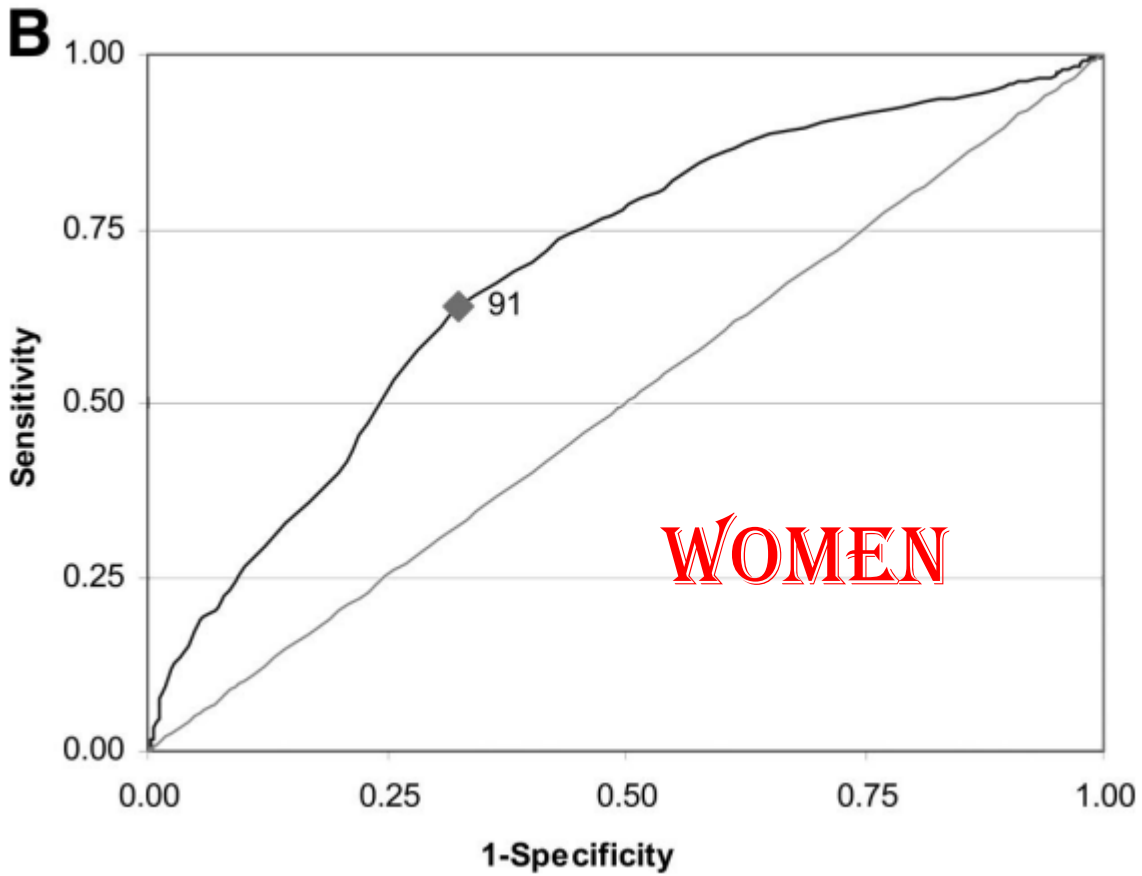
ADA - 2024

- 8.2a To support the diagnosis of obesity, measure height and weight to calculate BMI and perform additional measurements of body fat distribution , like waist circumference , waist to-hip ratio , and/or waist-to-height ratio. / E

- 8.3 Accommodations should be made to provide privacy during anthropometric measurements. / E

THE NATIONAL SURVEY OF RISK FACTORS FOR NONCOMMUNICABLE DISEASES OF IRAN -2009





TLGS

Outcome – based cut off point of WC in IRANIAN Peoples (2009) :

≥ 94.5 Cm for men and women , the same

OBESITY IN ADULTS

A clinical practice guideline

BMI IS NOT AN ACCURATE TOOL FOR IDENTIFYING OBESITY-RELATED COMPLICATIONS

Obesity complex disease in which abnormal or excess body fat impairs health

Effects:

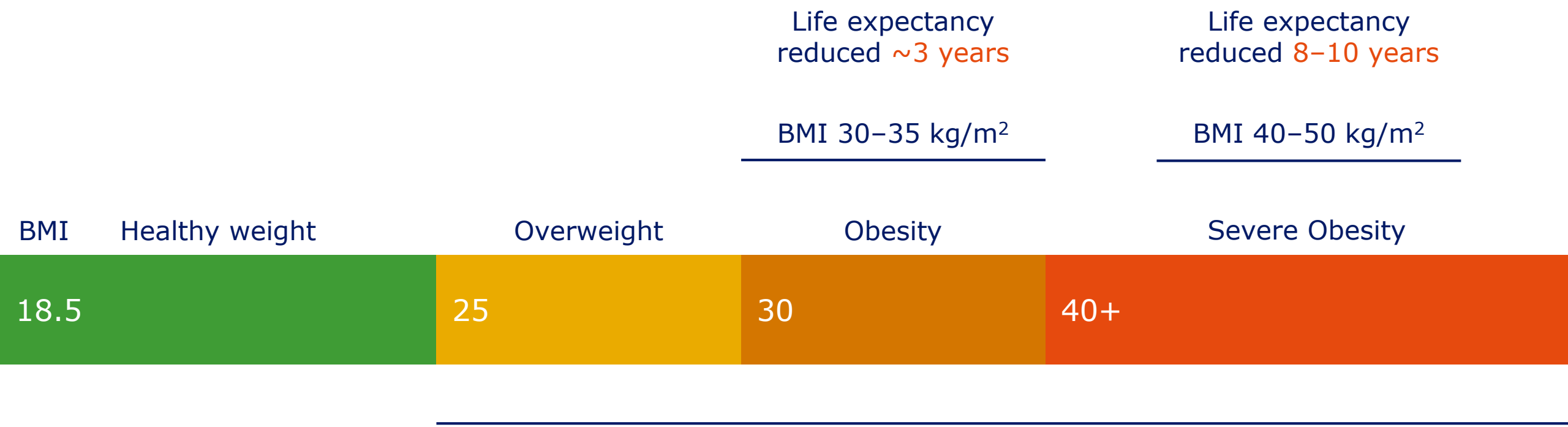
▼ health ▼ quality of life ▼ lifespan

People with obesity experience weight bias and stigma → increased complications and mortality independent of weight or BMI

Weight bias thinking that people with obesity do not have enough willpower or are not cooperative

Stigma acting on weight-biased beliefs

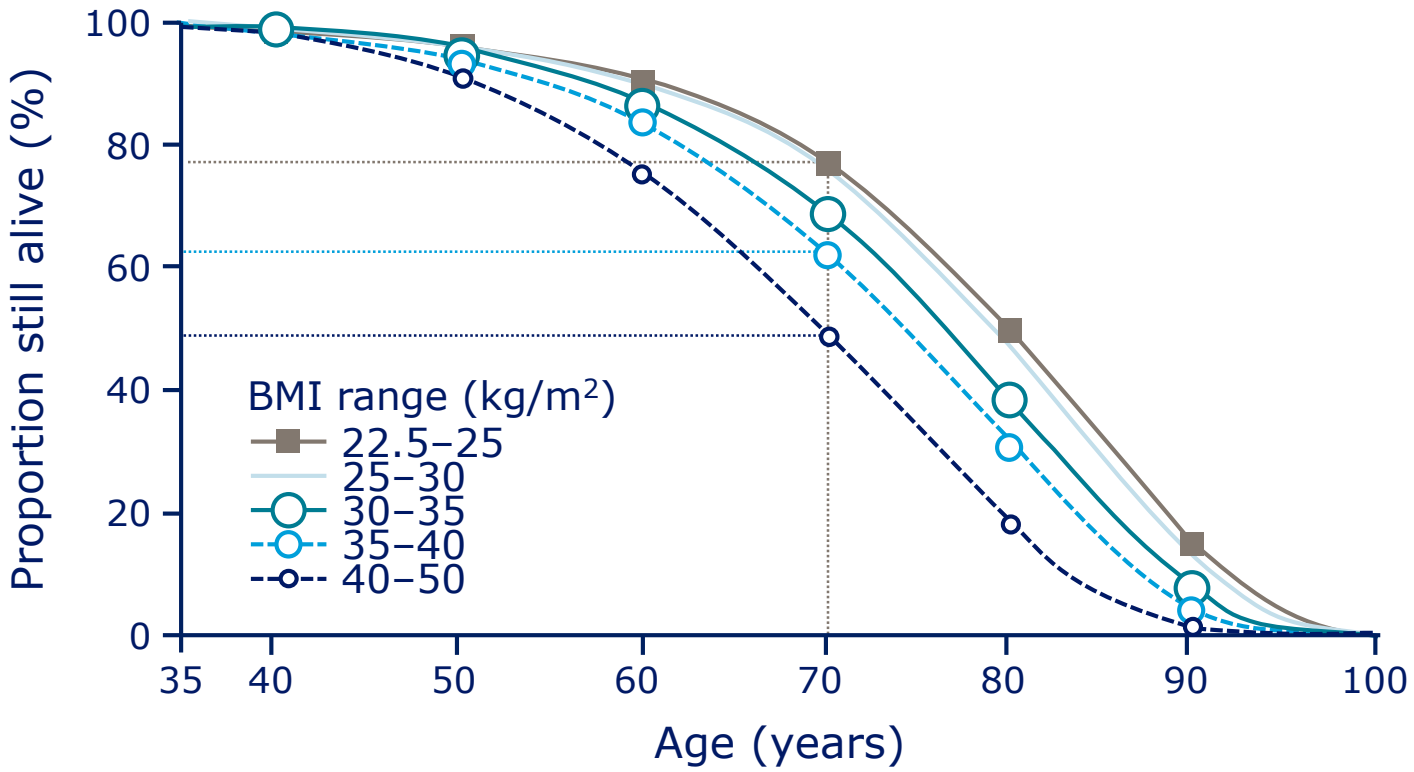
Life expectancy decreases as BMI increases



Based on a meta-analysis of 57 international prospective studies predominantly based in Europe, the United States, Israel and Australia, including BMI information for 894,576 adults. BMI, body mass index.

1. Prospective Studies Collaboration. *Lancet* 2009;373:1083–96.

Life expectancy decreases as BMI increases



Normal BMI = almost 80% chance of reaching age 70

BMI 35–40 = ~60% chance of reaching age 70

BMI 40–50 = ~50% chance of reaching age 70

Data are based on male subjects; n=541,452

Prospective Studies Collaboration. *Lancet* 2009;373:1083–96

The Edmonton Obesity Staging System (EOSS) classifies risk based on several factors independent of BMI (6) ; higher severity scores are associated with increased all-cause mortality (hazard ratio, 2.69; 95% CI, 1.98-3.67) . / **Canadian Guideline - 2020**

- **Screening for *secondary causes* of obesity may be considered based on history and physical examination, including hormonal abnormalities (eg, hypothyroidism, hypercortisolism), psychiatric diagnoses (eg, binge eating disorder), iatrogenic obesity (eg, medications), and genetic syndromes (eg, proopiomelanocortin deficiency).** (4)

Table 2: Edmonton Obesity Staging System (EOSS)

STAGE 0	STAGE 1	STAGE 2	STAGE 3	STAGE 4
▪ **No** sign of obesity-related risk factors ▪ **No** physical symptoms ▪ **No** psychological symptoms ▪ **No** functional limitations	▪ Patient has obesity-related **subclinical** risk factors *(borderline, hypertension, impaired fasting glucose, elevated liver enzymes, etc.)* – or: ▪ **Mild** physical symptoms – patient currently not requiring medical treatment for comorbidities *(dyspnea on moderate exertion, occasional aches/pains, fatigue, etc.)* – or: ▪ **Mild** obesity-related psychological symptoms and/or mild impairment of well-being *(quality of life not impacted)*	▪ Patient has **established** obesity-related comorbidities requiring medical intervention *(HTN, type 2 diabetes, sleep apnea, PCOS, osteoarthritis, reflux disease)* – or: ▪ **Moderate** obesity-related psychological symptoms *(depression, eating disorders, anxiety disorder)* – or ▪ **Moderate** functional limitations in daily activities *(quality of life is beginning to be impacted)*	▪ Patient has **significant** obesity-related end-organ damage *(myocardial infarction, heart failure, diabetic complications, incapacitating osteoarthritis)* – or ▪ **Significant** obesity-related psychological symptoms *(major depression, suicide ideation)* – or: ▪ **Significant** functional limitations *(e.g. unable to work or complete routine activities, reduced mobility)* – or: ▪ **Significant** impairment of well-being *(quality of life is significantly impacted)*	▪ **Severe** *(potential end stage)* disabilities from obesity-related comorbidities – or: ▪ **Severely** disabling psychological symptoms – or: ▪ **Severe** functional limitations

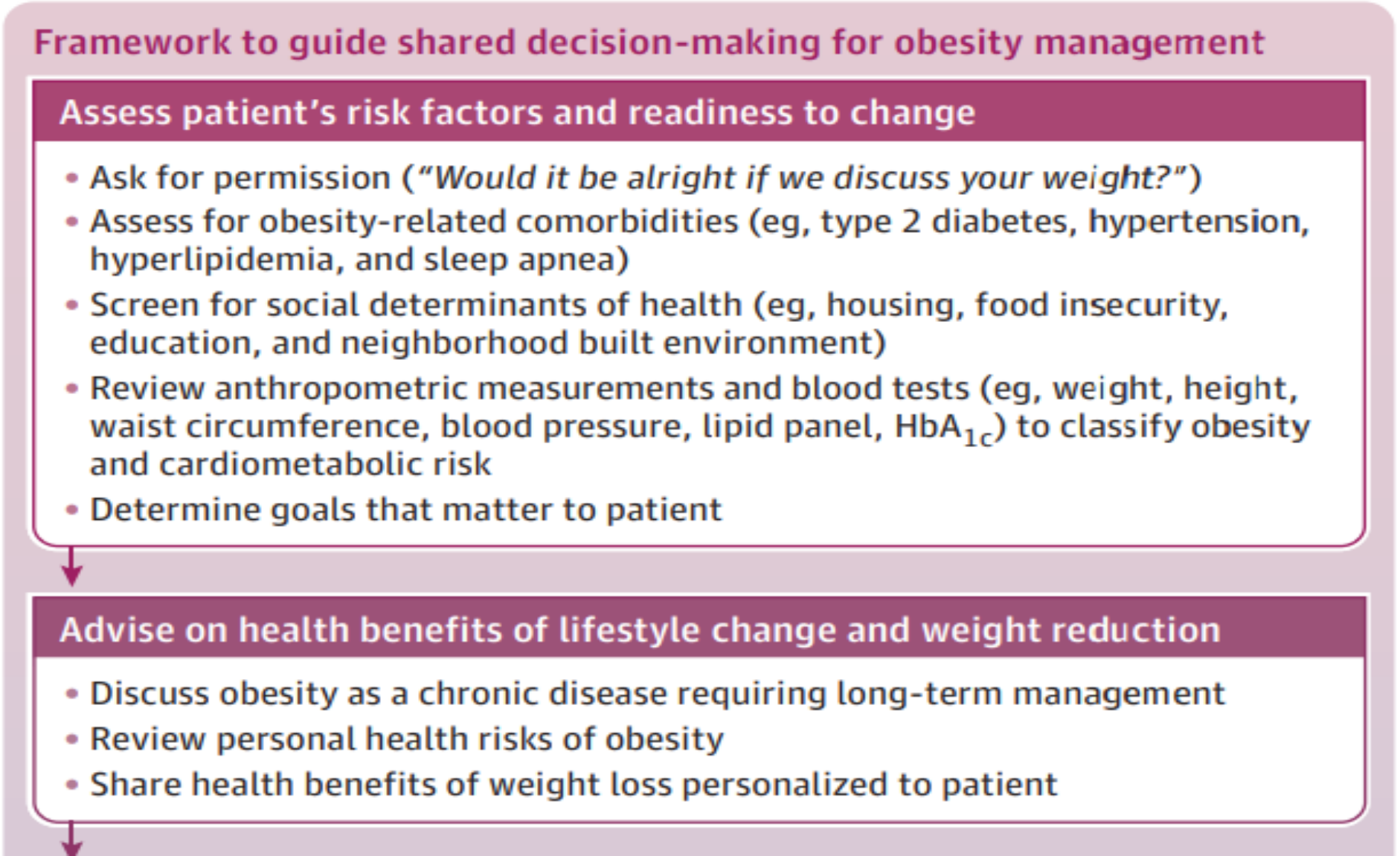
PATIENT-CENTERED APPROACH TO OBESITY CARE

PATIENT-CENTERED APPROACH TO OBESITY CARE

- Patients are also more likely to lose weight when clinicians communicate using a supportive, nonjudgmental approach.

- Privacy , in wt measurement , BMI

5A FRAMEWORK (ASSESS, ADVISE, AGREE, ASSIST, ARRANGE) FOR OBESITY COUNSELING IN THE OUTPATIENT SETTING (6,31-33)



Agree on quantifiable and achievable goals

- Collaborate to develop specific, measurable, attainable, relevant, and time-based weight loss and behavior change goals that may include changes to diet, physical activity, sleep, and stress management
- Personalize approaches to healthy eating based on patient preferences
- Recommend ≥30 min of moderate physical activity on most days

Assist in selecting treatment using a shared decision-making approach

- Offer intensive behavioral weight management counseling or refer to program
- Include additional treatments as appropriate

  Antiobesity medications if BMI ≥30
  or BMI ≥27 with a weight-related comorbidity

  Metabolic and bariatric surgery if BMI ≥35
  or BMI ≥30 with metabolic disease (eg, type 2 diabetes, steatohepatitis)
  or BMI ≥27.5 in patient of Asian ethnicity

Arrange follow-up to create accountability and enable feedback on progress

- Referral to evidence-based, multicomponent weight-reduction programs, obesity medicine clinic, or metabolic and bariatric surgical clinics as appropriate
- Adjust treatment plan as needed
- Assist the patient in obtaining adequate support and follow-up

BMI indicates body mass index (calculated as weight in kilograms divided by height in meters squared); HbA_{1c}, hemoglobin A_{1c}.

2020 Clinical Practice Guidelines: 5As Framework for Obesity Management in Adults

Obesity is a complex, progressive, and relapsing chronic disease characterized by abnormal and/ or excessive body fat (adiposity) that impairs health.

Please scan code for detailed information.
obesitycanada.ca/guidelines

1 Ask

Weight is a sensitive issue. Do not assume every patient with a larger body has obesity. Ask for permission to discuss body weight. Does the person feel their weight is impairing their medical, functional, or psychosocial health?

"Would it be alright if we discussed your weight?"

If the person is not ready to discuss their weight offer resources about obesity as a chronic disease and an open opportunity to reassess.

2 Assess

Understanding an individual's story and life context is crucial in the management of obesity.

1. The value-based goal that matters to the patient
   e.g. Being able to play at the park with my grandchildren
2. Obesity classification (height, weight, BMI & waist circumference)
3. Adiposity related complications and 'root causes' of weight gain
   *(**4M framework** - Mechanical, Metabolic, Mental and Social Milieu)*
4. Disease severity e.g. Edmonton Obesity Staging System (EOSS)

Primary care assessment
5as Toolkit
obesitycanada.ca/5as-team/

3 Advise On obesity risks. Discuss the health benefits of obesity management.

Medical Nutrition Therapy (MNT)

MNT is used in managing chronic diseases and focuses on nutrition assessment, diagnostics, therapy and counselling. MNT should:

a. be personalized and meet individual values, preferences and treatment goals to promote long term adherence

b. be administered by a registered dietitian to improve weight-related and health outcomes

Physical Activity

30-60 mins of aerobic activity on most days of the week, at moderate to vigorous intensity, can result in:

a. small amount of weight and fat loss

b. improvements in cardiometabolic parameters

c. weight maintenance after weight loss

ⓘ **Remember nutrition and physical activity recommendations are important for all Canadians regardless of body size or composition.**

The Three Pillars of Obesity Management that Support Nutrition and Activity

Psychological Intervention

a. Implement multicomponent behaviour modification

b. Manage sleep, time, and stress

c. Cognitive behavioural therapy and/ or acceptance and commitment therapy should be provided for patients if appropriate

Pharmacological Therapy

a. liraglutide

b. naltrexone/bupropion *(in a combination tablet)*

c. orlistat

CRITERIA

BMI ≥30kg/m² or

BMI ≥27 kg/m² with obesity (adiposity) related complications

Bariatric Surgery

ⓘ Procedure should be decided by surgeon in discussion with the patient.

a. Sleeve gastrectomy

b. Roux-en-Y gastric bypass

c. Biliopancreatic diversion with/without duodenal switch

CRITERIA

BMI ≥40 kg/m² or

BMI ≥35 - 40 kg/m² with an obesity (adiposity) related complication or

BMI ≥30 kg/m² with poorly controlled type 2 diabetes

Treating the root causes of obesity is the foundation of obesity management - refer to the 4M framework - *mechanical, metabolic, mental and social milieu*

4 Agree

Agree on realistic expectations, sustainable behavioural goals, and health outcomes. Agree on a personalized action plan that is practical and sustainable, and addresses the drivers of weight gain.

5 Assist

Assist in identifying and addressing drivers and barriers. Provide education and resources. Refer to appropriate providers or interdisciplinary teams (if available). Arrange for regular, timely follow-up.

obesity canada / obésité canada

L'ASSOCIATION CANADIENNE DES MEDECINS ET CHIRURGIENS BARIATRIQUES
THE CANADIAN ASSOCIATION OF BARIATRIC PHYSICIANS AND SURGEONS

We gratefully acknowledge the Physician Learning Program for their assistance for this Framework design.

Physician Learning Program

Appendix to: Wharton S, Lau DCW, Vallis M, et al. Obesity in adults: a clinical practice guideline

CMAJ 2020. doi:10.1503/cmaj.191707.

THE PATIENT JOURNEY IN OBESITY MANAGEMENT

1 ASK PERMISSION

"Would it be all right if we discussed your weight?"

Asking permission

- Shows compassion and empathy
- Builds patient–provider trust

2 ASSESS THEIR STORY

- Goals that matter to the patient
- Obesity classification (BMI and waist circumference)
- Disease severity (Edmonton Obesity Staging System)

3 ADVISE ON MANAGEMENT

Medical nutrition therapy

- Personalized counselling by a registered dietitian with a focus on healthy food choices and evidence-based nutrition therapy

Exercise

- 30-60 min of moderate to vigorous activity most days

Psychological

- Cognitive approach to behaviour change
- Manage sleep, time and stress
- Psychotherapy if appropriate

Medications

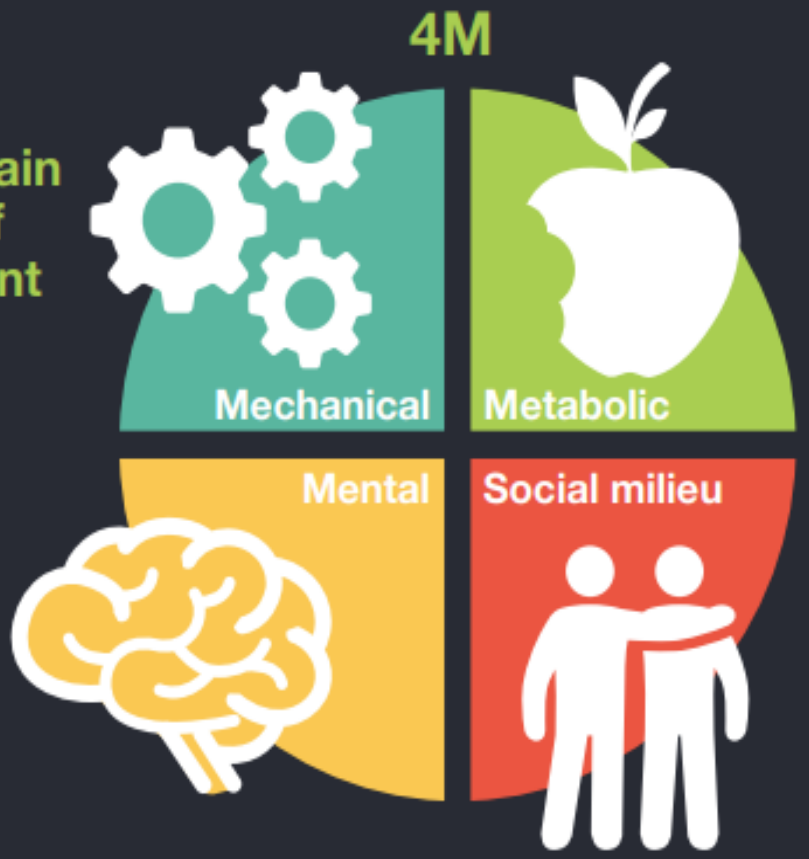
- For weight loss and to help maintain weight loss

Bariatric surgery

- Surgeon–patient discussion

Treating the root causes of weight gain is the foundation of obesity management

Focus on patient-centred health outcomes versus weight loss alone



4 **AGREE** ON GOALS

Collaborate on a personalized, sustainable action plan

5 **ASSIST** WITH DRIVERS AND BARRIERS

Table 2. Components of Comprehensive, Evidence-Based Weight Management for Adults With Obesity[4,5,9,13,14,40-47a]

Approach	Eligible patients[b]	Description or examples	Mean weight loss at 12-24 mo[c]	Other considerations
Multicomponent intensive behavioral lifestyle interventions[13]	• BMI ≥30 • BMI ≥25 with obesity-associated comorbidity[d]	• Evidence-based approaches include goal setting, self-monitoring (eg, food intake, physical activity, daily body weight), dietary change, stimulus control, stress management, cognitive therapy[13,14] • Multicomponent interventions combine these approaches and are delivered by trained facilitators, often referred from a primary care setting[13] • Intensive programs are administered over 1-2 y with ≥12-14 sessions in 6 mo[5] (see Table 3 for examples of programs)	1%-9%[4,5,13]	Higher intensity of weight loss instruction is associated with greater weight loss vs low- and moderate-intensity interventions[4]
Nutritional intervention	• BMI ≥30 • BMI ≥25 with obesity-associated comorbidity[d]	• Restricting/eliminating certain types of foods to create calorie deficit[5] • Generally 1200-1500 kcal/d for women and 1500-1800 kcal/d for men[5]; very low-calorie diets (<800 kcal/d) require specialized medical supervision[5] • Clinicians can provide counseling or refer to dietician • See more details on 3 evidence-based diet patterns in Table 3	3%-8%; 10% with very low-calorie diets[47]	Specific dietary recommendations need to account for patient preference and potential for long-term adherence
Physical activity	All adults regardless of BMI[40]	• ≥150 min/wk moderate-intensity physical activity (30 min 5 times per wk), or 75-150 min/wk vigorous-intensity physical activity[40] • Resistance exercise 2-3 times per wk[4] • >200 min/wk is associated with better maintenance of weight loss[5]	1%-3%[4]	Exercise should be individualized to patients' health and physical limitations and increased as patient is able to tolerate intensity to reach goals[4]

- Behavioral Interventions : education, peer support, coaching, self-monitoring, cognitive restructuring, and goal setting. (4,64)

- Interventions may also address insufficient sleep and chronic stress, which can negatively affect appetite and metabolism. (65)

- Frequent self-weighing improves weight loss and weight loss maintenance. (5,67,68)

NUTRITIONAL APPROACHES

- **#500- to 750-kcal/d deficit**
- portion control, reduction or elimination of ultraprocessed foods (eg, sugar-sweetened beverages), and increased fruit and vegetable intake. (67)
- **DASH (Dietary Approaches to Stop Hypertension), when combined with caloric reduction,**
- time-restricted eating, intermittent fasting , ketogenic diet), (70-72)

Approach	Mean 12-mo weight loss (95% CI) vs control, kg	Overview	Other benefits and considerations	Dietary Guidelines for Americans recommended[4]
Nutritional approaches				
Low-fat vegan- or vegetarian-style diet[57]	6.6 (3.4-9.8)[50]	• 10%-25% of calories from fat • Eliminate meat and fish; may include eggs/dairy • Often low in saturated fats, high in fiber	• Increase in insulin sensitivity[57] • Potential reduced environmental impact[58]	Yes
Low-carbohydrate diet[59]	6.4 (3.9-8.9)[50]	<40% of calories from carbohydrates	• Decrease in SBP, DBP, glucose, insulin resistance, and triglycerides[59,60] • Increase in HDL-C[59,60]	No
Mediterranean diet[4]	2.5 (1.9-3.1)[61]	• Focus on dark green vegetables, fruits, nuts, and legumes • Moderate to high intake of fish and seafood • Low intake of red meat and dairy fat • Use of extra virgin olive oil as main source of dietary fat	• Decrease in SBP, DBP, LDL-C,[59] hemoglobin A_{1c}, and triglycerides[61] • Increase in HDL-C[61] • Potential reduced environmental impact[58]	Yes

WT STOP

- Weight loss typically plateaus after 6 months due to metabolic adaption and hormonal changes contributing to decreased adherence, but metabolic adaptation usually slows after 12 months. (18,67)

Weight-Gain Effect of Common Medications

Medication classes promoting weight gain include antihyperglycemics (eg , glyburide, insulin), antidepressants (eg , amitriptyline, mirtazapine), antipsychotics (eg , olanzapine, quetiapine), antiepileptics (eg , gabapentin, carbamazepine) , β-blockers , progesterone - based contraceptives , corticosteroids , and antiretroviral therapy (eg , protease inhibitors). (12,77)

COUNTERACT

Metformin (1000 mg total daily dose) and topiramate (100 mg/d) counteract the effects of some weight gain–promoting agents, particularly antipsychotics and can be considered as adjunctive therapy (topiramate: mean difference, −3.76 kg ; 95% CI, −4.92 kg to −2.69 kg ; metformin : mean difference, −3.27 kg ; 95% CI, −4.66 kg to −1.89 kg). (79,80)

ANTIOBESITY MEDICATIONS

ANTI – OBESITY MEDICATIONS

- Use of weight-loss supplements, such as green tea extract or herbs, is not recommended. (6,97)

- Among individuals with inadequate response to lifestyle modifications, guidelines recommend initiating an antiobesity medication in nonpregnant patients with obesity or with overweight (BM≥27) and weight-related complications (Table4) . (4,10,11)

ADA - 2024

- 8.13 - Nutritional supplements have not been shown to be effective for weight loss and are not recommended. / A

GLP-1 RECEPTOR AGONISTS - (*SEMAGLUTIDE & LIRAGLUTIDE*)

GLP-1 receptor agonists mimic the effects of GLP-1.

After eating ,*GLP-1 acts* on : the hypothalamus to suppress appetite , delay gastric emptying , increase glucose-dependent insulin release , decrease glucagon secretion , and increase pancreatic β-cell growth. (98)

THE STEP TRIALS

- Subcutaneous *semaglutide (Ozempic)* was FDA approved to treat obesity in 2021 and is dosed once weekly. (10)

- The STEP trials examined the efficacy of semaglutide.

- The STEP 1 and STEP 3 trials included individuals with obesity without diabetes (mean BMI # 38 Kg/m²). (81,99)

- In these clinical trials, mean weight loss at 68 weeks was **14.9%** (placebo 2.4%; difference 12.4%; 95% CI 11.5%-13.4%) and **16.0%**

THE STEP TRIALS

- **In STEP 1, participants were encouraged to follow a reduced-calorie diet and participate in 150 min/wk of physical activity.** (81)

- **In STEP 3, participants started with low-calorie meal replacements for 8 weeks followed by a reduced-calorie diet, a goal of 200 min/wk of physical activity, and 30 individual visits with a dietitian.** (99)

- **After cessation of semaglutide, participants *regained* significant amounts of weight.** (96,100)

- After 52 wks mean weight *regain* was *11.6%* of lost weight. (100)

THE STEP 4 TRIAL

- In the STEP 4 trial, participants completed 20 weeks of semaglutide treatment and were transitioned to placebo for an additional 48 weeks. (96)

- Mean weight regain was 6.9% of lost weight during the placebo administration. (96)

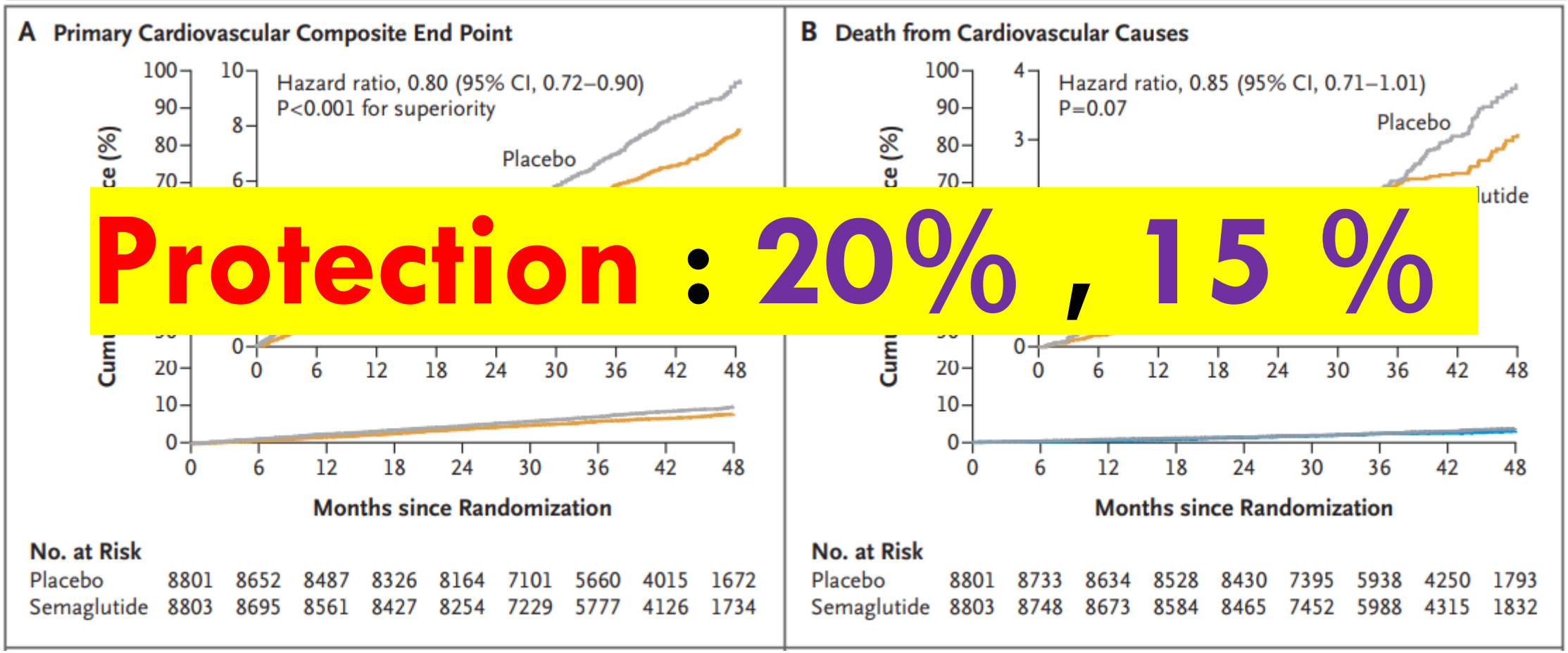
- *These results suggest that long-term use is necessary.* (96,100)

ORAL SEMAGLUTIDE (RYBELSUS)

- In a clinical trial that randomized 667 adults with obesity without diabetes to either semaglutide or placebo for 68 weeks, mean weight loss with 50 mg/d oral semaglutide was 15.1% vs 2.4% for placebo . (89)

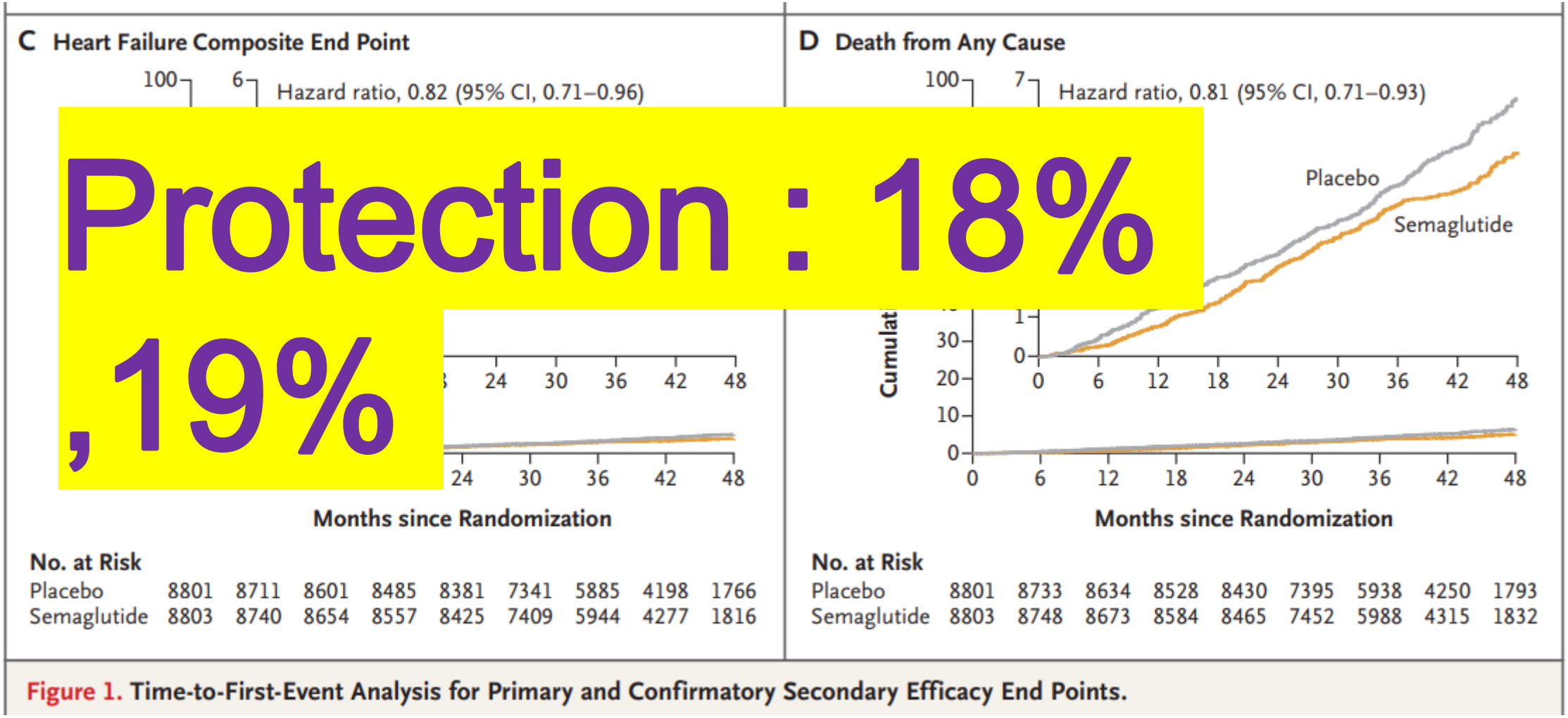
- Oral semaglutide (Rybelsus) is not yet FDA approved for obesity alone. (89)

SEMAGLUTIDE & CVOT IN OBESITY WITHOUT DIABETES



Protection : 20% , 15 %

SEMAGLUTIDE AND CARDIOVASCULAR OUTCOMES IN OBESITY WITHOUT DIABETES



Protection : 18% ,19%

Figure 1. Time-to-First-Event Analysis for Primary and Confirmatory Secondary Efficacy End Points.

SUBCUTANEOUS LIRAGLUTIDE (VICTOZA)

- Subcutaneous liraglutide was FDA approved to treat obesity in 2014. (10)
- In an RCT of 3731 individuals with obesity, compared with placebo, liraglutide (Victoza) achieved a mean weight loss of 8.0% at 56 weeks (difference, 5.4%; 95% CI, 5.8%-5.0%). (85)
- Although it is dosed daily, it is widely used and preferred for some patients due to cost and availability.

SEMAGLUTIDE > LIRAGLUTIDE

- Systematic reviews and meta-analyses of GLP-1 receptor agonists reported that subcutaneous semaglutide reduced weight and improved weight-related comorbidities significantly ***more than*** liraglutide and was associated with lower rates of gastrointestinal adverse events. (101,102)

TIRZEPATIDE

- Mounjaro is a synthetic peptide with dual-hormone agonistic activity at the GLP-1 receptor, like semaglutide, and additionally at the glucose-dependent insulinotropic polypeptide (GIP) receptor.
- Tirzepatide is dosed subcutaneously once weekly. (42)

TIRZEPATIDE

- An RCT of 2539 adults with obesity and without diabetes randomized participants to 1 of 4 groups: 15 mg, 10 mg, or 5 mg of tirzepatide or placebo; all participants received lifestyle counseling sessions,a reduced-calorie diet, and physical activity for 72 weeks. (42)
- At 72-week follow-up, mean weight loss for tirzepatide was 20.9% for 15mg of tirzepatide, 19.5% for 10 mg of tirzepatide, 15.0% for 5 mg of tirzepatide, and 3.1% for placebo. (42)
- Tirzepatide was FDA approved for treatment of obesity in November 2023

TIRZEPATIDE > SEMAGLUTIDE > LIRAGLUTIDE

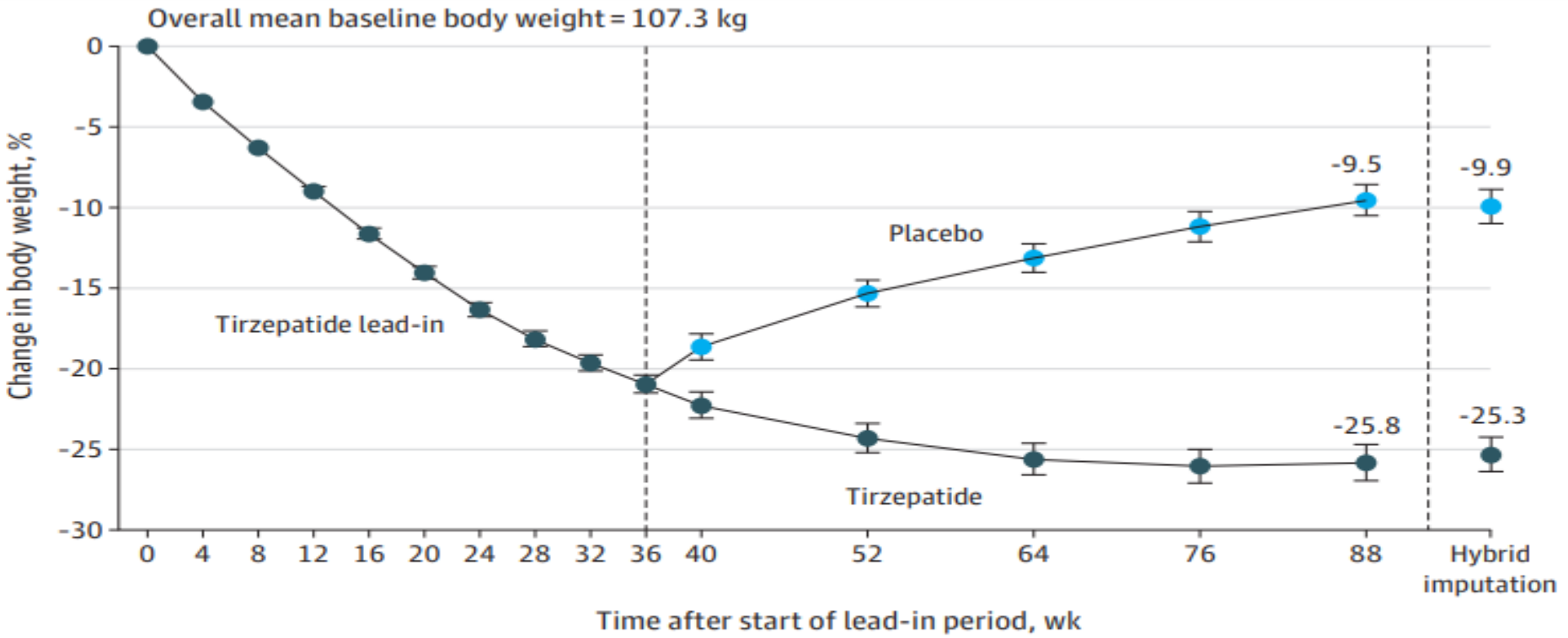
(15 MG/WK) (2.4 MG/WK) (3 MG/D)

- A recent meta-analysis of RCTs that included 12 371 adults with overweight or obesity without diabetes reported that 15 mg weekly of tirzepatide was associated with greater weight loss compared with 2.4 mg weekly of subcutaneous semaglutide (mean difference, 5.1%; 95% CI, 0.6%-9.8%) and 3 mg daily of subcutaneous liraglutide (mean difference, 13.0%; 95% CI, 8.8%-17.4%). (105)

THE SURMOUNT-4 RANDOMIZED CLINICAL TRIAL

Figure 2. Effect of Tirzepatide vs Placebo on Body Weight and Waist Circumference

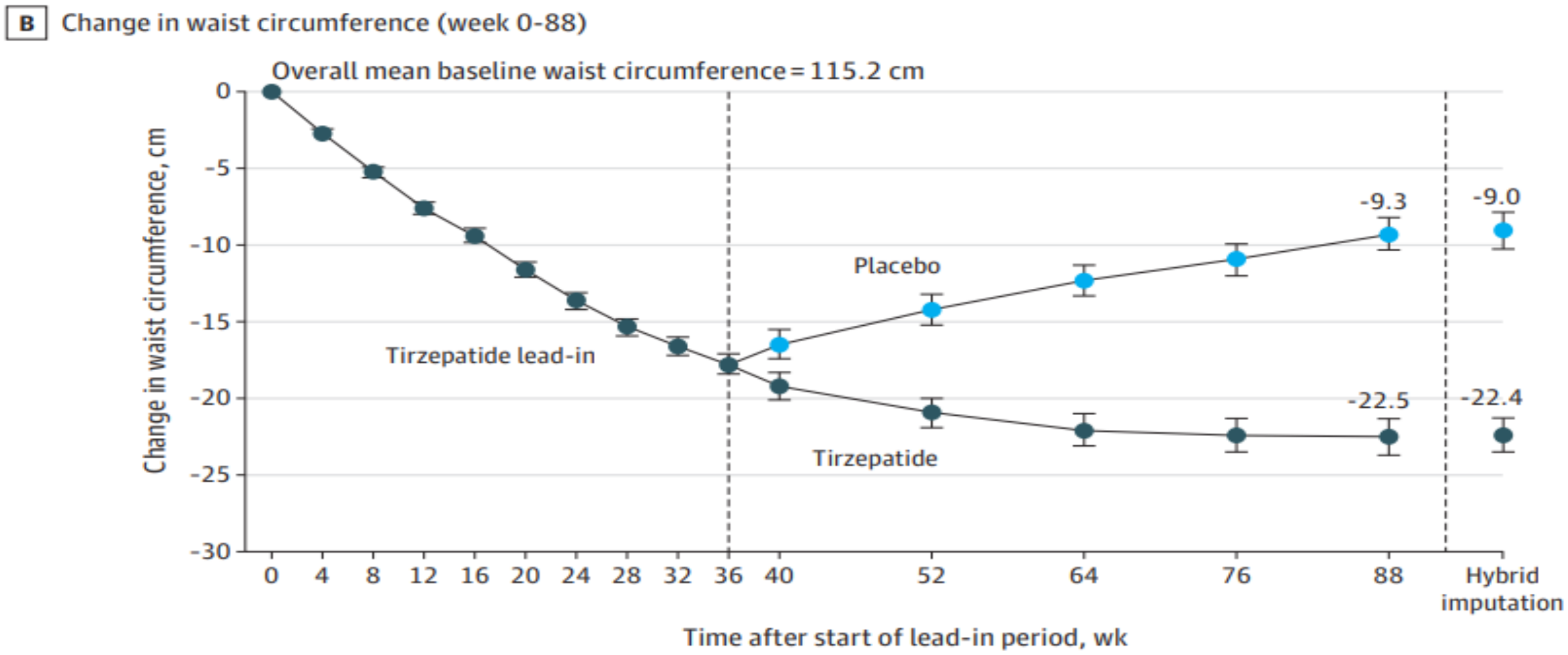
A Percent change in body weight (week 0-88)



No. at risk

Tirzepatide lead-in	670	666	669	668	667	667	669	663	659	670				
Tirzepatide										335	333	328	317	310	310	335
Placebo										335	330	317	303	292	289	335

THE SURMOUNT-4 RANDOMIZED CLINICAL TRIAL



PHENTERMINE-TOPIRAMATE

- Combined oral phentermine-topiramate was FDA approved in 2012 for obesity. (10)
- Topiramate's exact weight-loss mechanism is unknown but is thought to alter appetite and decrease energy intake. (106)

- In systematic reviews, phentermine-topiramate was associated with greater weight loss compared with orlistat and naltrexone-bupropion. (108,109)

NALTREXONE-BUPROPION

- The combination of oral naltrexone-bupropion was FDA approved for obesity in 2014. (10)

- Bupropion stimulates hypothalamic proopiomelanocortin neurons while naltrexone simultaneously blocks opioid-mediated proopiomelanocortin autoinhibition, which reduces reactivity to food cues and improves dysregulation of eating control in mesolimbic pathways. (41)

ORLISTAT

- Orlistat is a pancreatic lipase inhibitor oral medication that prevents triglycerides from being hydrolyzed, thus deceasing the absorption of free fatty acids.
- Orlistat was FDA approved for obesity in 1999. (10)
- Mean weight loss with orlistat is 2.8% to 4.8%, and gastrointestinal adverse effects are frequent, including : flatulence, steatorrhea, and diarrhea. (10,109)
- Orlistat may cause malabsorption of fat-soluble vitamins; thus, patients should take a multivitamin containing vitamins A, D, E, and K , 2 hours apart from orlistat daily. (10)

GELESIS 100

- **Gelesis100 is a nonsurgical device that was FDA approved in 2019 to treat obesity.**
- **It is a superabsorbent orally administered hydrogel capsule that releases cellulose)and citric acid particles, thereby increasing bulk in the stomach and creating a sensation of satiety.** (10)
- An RCT of 436 participants showed a mean weight loss of 2.1% more with Gelesis100 compared with placebo (P < .001) , and 59% of those receiving Gelesis100 attained 5% or greater weight loss compared with 42% of those receiving placebo (P < .001). (112)

ANTIOBESITY MEDICATIONS APPROVED BY THE FDA FOR SHORT-TERM USE (12 WEEKS)

- Four sympathomimetic oral amines : *phentermine* , *diethylpropion* , *benzphetamine* , and *phendimetrazine* are currently FDA approved for short-term use (12 weeks). (10,113,114)

- **These agents increase norepinephrine, leading to appetite suppression.** [113]

METFORMIN

- Metformin In RCTs and prospective studies, oral metformin was associated with **# 3%** weight loss, and **# 25% to 50%** of participants achieve at least 5% weight loss. (94)

- **Doses of metformin greater than 1500 mg are associated with the greatest weight loss.** (93,94)
- **Metformin's pleiotropic effects include : decreased inflammation , increased insulin and leptin sensitivity , and decreased hunger and ghrelin levels, especially with twice-daily dosing.** (94)

Table 4. Antiobesity Medication Management, Ordered by Greatest Difference in Percentage Weight Loss

Medications (trial)	Mechanism of action	Mean weight loss from baseline[a]	Dosing[b]	Additional benefits	Most common adverse effects (placebo, treatment)[c,d]	Monitoring[d]	Contraindications[d]	Mean 30-d retail cost, $ (dose)[e]
FDA approved for long-term use[10]								
Tirzepatide (SURMOUNT-1[42])	Dual-hormone agonistic activity at GLP-1 and glucose-dependent insulinotropic polypeptide receptors, regulating energy balance by signals in CNS and adipose tissue[42]	Treatment: 20.9%; placebo: 3.1%; difference, 17.8% with 15 mg at 72 wk	• Starting dose: 2.5 mg/wk subcutaneously • Titration speed: not faster than every 4 wk • Titration: by 2.5 mg • Maximum dose: 15 mg/wk subcutaneously	• Improved: waist circumference, blood pressure, hemoglobin A_{1c}, lipid profile[42] • Consider use in patients with impaired glucose tolerance	Nausea (10%, 31%), diarrhea (7%, 23%), vomiting (2%, 12%), constipation (6%, 12%), alopecia (1%, 6%), abdominal pain (3%, 5%)	• Glucose if taking insulin or sulfonylurea • Hydration if gastrointestinal adverse effects • Signs/symptoms of pancreatitis or gallbladder disorders • Anticipatory guidance about symptoms of thyroid mass	• Personal or family history of medullary thyroid carcinoma • MEN type 2	1022-1221 (15 mg)
Semaglutide, subcutaneous (STEP 1[81])	Activates GLP-1 receptor, with metabolic effects on glucose-dependent stimulation of insulin secretion, delayed gastric emptying[10]	Treatment: 14.9%; placebo: 2.4%; difference, 12.5% with 2.4 mg at 68 wk	• Starting dose: 0.25 mg/wk subcutaneously • Titration speed: not faster than every 4 wk • Doses: 0.25, 0.5, 1.0, 1.7 mg/wk • Maximum dose: 2.4 mg/wk subcutaneously	• Improved: waist circumference, blood pressure, hemoglobin A_{1c}, CVD events, lipid profile[81,82] • Consider use in patients with impaired glucose tolerance	Nausea (17%, 44%), diarrhea (16%, 32%), constipation (10%, 23%), dyspepsia (4%, 10%), vomiting (7%, 25%)	• Glucose if taking insulin or sulfonylurea • Hydration if gastrointestinal adverse effects • Signs/symptoms of pancreatitis or gallbladder disorders • Diabetic retinopathy	• Personal or family history of medullary thyroid carcinoma • MEN type 2 • History of pancreatitis is a precaution but not a contraindication	1333-1648 (2.4 mg)

Table 4. Antiobesity Medication Management, Ordered by Greatest Difference in Percentage Weight Loss

Medications (trial)	Mechanism of action	Mean weight loss from baseline[a]	Dosing[b]	Additional benefits	Most common adverse effects (placebo, treatment)[c,d]	Monitoring[d]	Contraindications[d]	Mean 30-d retail cost, $ (dose)[e]
Phentermine-topiramate ER (EQUATE[83])	Phentermine increases norepinephrine in CNS, topiramate modulates GABA receptors in the CNS[10,12]	Treatment: 9.2%; placebo: 1.7%; difference, 7.5% with 15 mg/92 mg at 28 wk	• Starting dose: 3.75 mg/23 mg daily • Next dose: 7.5 mg/46 mg daily for 12 wk • Titration speed: not faster than every 2 wk • Titration amount: by 3.75 mg/23 mg • Maximum dose: 15 mg/92 mg daily	• Improved: waist circumference, systolic blood pressure, hemoglobin A_{1c}, lipid profile[83,84] • Consider use in patients with comorbid migraines[10]	Paresthesia (4%, 23%), dry mouth (0%, 19%), constipation (8%, 16%), headache (13%, 16%), insomnia (5%, 10%), dizziness (2%, 8%)	• Heart rate, blood pressure • Serum bicarbonate • Symptoms of acute metabolic acidosis, nephrolithiasis, suicidality, or angle-closure glaucoma • Potassium if taking potassium-sparing diuretic • Dermatologic reactions	• CVD • Uncontrolled hypertension • Untreated hyperthyroidism • History of glaucoma, calcium-phosphate nephrolithiasis • Within 14 d of MAOI use	98-214 (15 mg/92 mg)
Liraglutide (SCALE[85])	Activates GLP-1 receptor, with metabolic effects on glucose-dependent stimulation of insulin secretion, delayed gastric emptying[10]	Treatment: 8.0%; placebo: 2.6%; difference, 5.4% with 3 mg at 56 wk	• Starting dose: 0.6 mg/d subcutaneously • Titration speed: not faster than weekly • Titration: by 0.6 mg • Maximum dose: 3 mg/d subcutaneously	• Improved: waist circumference, blood pressure, hemoglobin A_{1c}, CVD events, lipid profile[82,85] • Consider use in patients with impaired glucose tolerance	Nausea (15%, 40%), diarrhea (9%, 21%), constipation (9%, 20%), dyspepsia (5, 10%), vomiting (4%, 16%)	• Glucose if taking insulin or sulfonylurea • Signs/symptoms of pancreatitis or gallbladder disorders • Worsening depression, suicidal thoughts, behavior change • Heart rate	• Personal or family history of medullary thyroid cancer • MEN type 2 • Pancreatitis is a precaution but not a contraindication	1333-1498 (3 mg)
Naltrexone-bupropion ER (COR-II[41])[f]	Bupropion activates proopiomelanocortin neurons in the hypothalamus, naltrexone blocks opioid-mediated proopiomelanocortin autoinhibition	Treatment: 5.6%; placebo: 1.2%; difference, 4.4% with 32 mg/360 mg at 56 wk	• Starting dose: 8 mg/90 mg daily • Titration speed: not faster than weekly • Titration amount: by 8 mg/90 mg • Maximum dose: 32 mg/360 mg daily (dosed as 16 mg/180 mg twice daily)	• Improved: waist circumference, hemoglobin A_{1c} in type 2 diabetes, lipid profile[41] • Consider use in patients interested in reducing tobacco or alcohol use[10,86]	Nausea (7%, 33%), constipation (7%, 19%), headache (10%, 18%), vomiting (3%, 11%), dizziness (3%, 10%), insomnia (6%, 9%), dry mouth (2%, 8%), diarrhea (5%, 7%)	• Heart rate, blood pressure • Kidney and liver function • Depression, suicidal ideation, anxiety, mania, panic attacks	• Uncontrolled hypertension • History of seizures • At risk of alcohol withdrawal • Bulimia or anorexia nervosa • Within 14 d of MAOI use • Long-term opioid use	99-698 (8 mg/90 mg; 4 tablets/d)

(continue

Table 4. Antiobesity Medication Management, Ordered by Greatest Difference in Percentage Weight Loss (continued)

Medications (trial)	Mechanism of action	Mean weight loss from baseline[a]	Dosing[b]	Additional benefits	Most common adverse effects (placebo, treatment)[c,d]	Monitoring[d]	Contraindications[d]	Mean 30-d retail cost, $ (dose)[e]
Orlistat (European Multicenter Orlistat Study[87])	Gastric and pancreatic lipase inhibitor with decreased absorption of triglycerides[10]	Treatment: 10.2%; placebo: 6.1%; difference, 4.1% with 120 mg 3 times daily at 52 wk	• 60 mg 3 times daily • 120 mg 3 times daily	• Improved: blood pressure, glucose, lipid profile[87] • Consider if patient has chronic constipation[9]	Steatorrhea (5%, 31%), increased defecation (7%, 20%), oily spotting (1%, 18%), liquid stool (10%, 13%), fecal urgency (3%, 10%), flatus with discharge (0%, 7%), fecal incontinence (0%, 7%)	• Fat-soluble vitamin levels (A, D, E, K) • Liver function if symptoms of hepatic impairment • Administer multivitamin 2 h apart from orlistat	• Deficiency in fat-soluble vitamins • Calcium oxalate nephrolithiasis • Chronic malabsorption • Cholestasis	• 49-67 (Over the counter) • 280-597 (Prescription)
FDA approved for short-term use (12 wk)[10]								
Diethylpropion[88]	Increases norepinephrine release in CNS[10]	Treatment: 9.8%; placebo: 3.2%; difference, 6.6% with 50 mg twice daily at 24 wk	• IR: 25 mg 3 times daily before meals • ER: 75 mg/d	Waist circumference improved[88]	• Dry mouth (41%, 69%), insomnia (22%, 53%), constipation (14%, 39%), headache (25%, 33%), dizziness (9%, 14%) • Incidence of all adverse effects decreased at 3-6 mo	• Can cause direct cardiac myocyte toxicity • Heart rate, blood pressure • Mood	• Sedative use • Susceptibility to amphetamines • CVD • Avoid use with ethanol • Use within 1 y of another anorectic medication	19-60 (Generic; 75 mg ER)
Phentermine (EQUATE[83])	Increases norepinephrine release in CNS[10]	Treatment: 6.1%; placebo: 1.7%; difference, 4.4% with 15 mg at 28 wk	• Starting dose: 8 mg/d (tablet) or 15 mg/d (capsule) • Titration speed: not faster than every 2 wk • Titration: can combine 8 mg + 15 mg as 23 mg or increase from 15 mg to 30 mg • Maximum dose: 37.5 mg/d	Nonsignificant reduction in systolic and diastolic blood pressure and waistline vs placebo for 7.5 mg and 15 mg phentermine[83]	Paresthesia (4%, 5%), dry mouth (0%, 12%), headache (13%, 10%), constipation (8%, 8%), insomnia (6%, 11%), dizziness (2%, 3%)	Heart rate, blood pressure	• CVD • Uncontrolled hypertension • Untreated hyperthyroidism • Within 14 d of MAOI use	• 12-17 (Generic; 37.5 mg) • 15-27 (Brand name; 8 mg)

Table 4. Antiobesity Medication Management, Ordered by Greatest Difference in Percentage Weight Loss (continued)

Medications (trial)	Mechanism of action	Mean weight loss from baseline[a]	Dosing[b]	Additional benefits	Most common adverse effects (placebo, treatment)[c,d]	Monitoring[d]	Contraindications[d]	Mean 30-d retail cost, $ (dose)[e]
Commonly used off label								
Semaglutide, 50 mg oral (OASIS 1[89])	Activates GLP-1 receptor, with metabolic effects on glucose-dependent stimulation of insulin secretion, delayed gastric emptying[10]	Treatment: 15.1%; placebo: 2.4%; difference, 12.7% with 50 mg at 68 wk	• Starting dose: 3 mg/d • Titration speed: not faster than every 4 wk • Titration: 7 mg, 14 mg, 25 mg, 50 mg • Maximum dose: 50 mg/d	• Improved: waist circumference, blood pressure, hemoglobin A_{1c}, lipid profile[89] • Consider use in patients with impaired glucose tolerance	Nausea (15%, 52%), constipation (15%, 28%), diarrhea (17%, 27%), vomiting (4%, 24%)	Not reported	Not reported	926-1041 (7 mg)
Topiramate (EQUATE[83])	Topiramate modulates GABA receptors in CNS[10]	Treatment: 6.4%; placebo: 1.7%; difference, 4.7% with 92 mg at 28 wk	• Starting dose (IR): 12.5 mg/d to 25 mg/d • Titration speed: not faster than weekly • Titration amount: by 25 mg • Maximum dose (IR): 200 mg twice daily	Consider use in patients with migraines, antipsychotic-induced weight gain, binge eating disorder, alcohol use disorder[10,79,86]	Paresthesia (4%, 22%), dry mouth (0%, 7%), constipation (8%, 6%), insomnia (6%, 5%), dizziness (2%, 4%)	• Symptoms of acute angle-closure glaucoma • Acute metabolic acidosis • Nephrolithiasis • Depression, anxiety, suicidal ideation	Use with care if history of glaucoma, metabolic acidosis, calcium phosphate kidney stones	9-37 (Generic)
Semaglutide (SUSTAIN 1[67,90])[h]	Activates GLP-1 receptor, with metabolic effects on glucose-dependent stimulation of insulin secretion, delayed gastric emptying[10]	Treatment: 4.7%; placebo: 1.1%; difference, 3.6% with 1.0 mg at 30 wk in patients with type 2 diabetes	• Starting dose: 0.25 mg/wk subcutaneously • Titration speed: not faster than every 4 wk • Doses: 0.25, 0.5, 1.0, 2.0 mg/wk • Maximum dose: 2 mg/wk subcutaneously	• Improved: waist circumference, blood pressure, hemoglobin A_{1c}, CVD events, lipid profile[90] • Consider use in patients with impaired glucose tolerance	Nausea (8%, 24%), diarrhea (2%, 11%), constipation (1%, 4%), vomiting (2%, 7%)	• Glucose if taking insulin or sulfonylurea • Signs/symptoms of pancreatitis or gallbladder disorders • Diabetic retinopathy	• Personal or family history of medullary thyroid carcinoma • MEN type 2 • Pancreatitis is a precaution but not a contraindication	926-1041 (2 mg)

(continu

Table 4. Antiobesity Medication Management, Ordered by Greatest Difference in Percentage Weight Loss (continued)

Medications (trial)	Mechanism of action	Mean weight loss from baseline[a]	Dosing[b]	Additional benefits	Most common adverse effects (placebo, treatment)[c,d]	Monitoring[d]	Contraindications[d]	Mean 30-d retail cost, $ (dose)[e]
Liraglutide (LEAD-3[91])[h]	Activates GLP-1 receptor, with metabolic effects on glucose-dependent stimulation of insulin secretion, delayed gastric emptying[10]	Treatment (1.8 mg): 2.6%; control (glimepiride, 8 mg): +1.2%; difference, 3.8% at 52 wk in patients with type 2 diabetes	• Starting dose: 0.6 mg/d subcutaneously • Titration speed: not faster than weekly • Titration: by 0.6 mg • Maximum dose: 1.8 mg/d subcutaneously	• Improved: waist circumference, blood pressure, hemoglobin A_{1c}[91] • Consider use in patients with impaired glucose tolerance	Nausea (8%, 29%), diarrhea (9%, 19%), constipation (5%, 11%), vomiting (4%, 9%) (glimepiride; no placebo in this study)	• Glucose if taking insulin or sulfonylurea • Signs/symptoms of pancreatitis or gallbladder disorders • Worsening depression, suicidal thoughts, behavior change • Heart rate	Pancreatitis is a precaution but not a contraindication	1104-1340 (3 mg)
Bupropion[92]	Bupropion activates proopiomelanocortin neurons in the hypothalamus[41]	Treatment: 4.9% (up to 12.9% with gradual increase to 200 mg twice daily at 24 wk); placebo: 1.3%; difference, 3.6% with 200 mg SR twice daily at 8 wk (n = 50)	• Starting dose (SR): 100 mg/d • Titration speed: not faster than every 2 wk • Maximum dose: 200 mg twice daily • Starting dose (ER): 150 mg/d • Titration speed: every 1 to 2 wk • Maximum dose: 450 mg/d	Consider use in patients with depression, seasonal affective disorder, anxiety, attention-deficit/ hyperactivity disorder, dysthymia if indicated	Insomnia (4%, 20%), dry mouth (20%, 52%), rash (0%, 8%), nervousness (4%, 16%)	• Blood pressure • Depression, suicidal ideation, anxiety, mania, panic attacks • Because bupropion lowers seizure threshold, it should be weaned slowly	• Uncontrolled hypertension • Seizure disorder • Bulimia or anorexia nervosa • Within 14 d of MAOI use	5-27 (Generic; 300 mg ER)

Metformin (Diabetes Prevention Program Outcomes Study[93])	Increased insulin and leptin sensitivity, decreased hunger and ghrelin levels[94]	Treatment: 6.2%; placebo, 2.8%; difference, 3.5% with 1500 mg at 15 y	• Both IR and ER can be taken once or twice daily
			• For IR and ER:
			  • Starting dose: 500 mg/d
			  • Titration speed: not faster than weekly
			  • Titration amount: by 500 mg
			  • Dose: 2500 mg/d
				• Hemoglobin A_{1c} improved[94]
				• Consider use in patients with polycystic ovary syndrome, antipsychotic-induced weight gain, impaired glucose tolerance, or chronic constipation[94g]
					• Gastrointestinal adverse effects in 10%-20% (treatment group)
					• Some patients tolerate one formulation but not the other
					• Taking at the end of a meal can reduce risk of adverse effects
						• Glucose if taking insulin or sulfonylurea
						• Vitamin B_{12} after long-term use
						• Reassess dose if glomerular filtration rate decreases to <45 mL/min
							• Advanced cirrhosis (class C)
							• Glomerular filtration rate <30 mL/min
							• Heart failure with poor perfusion
								• 3-13 (Generic
								• IR is less expensive than ER

Pharmacotherapy[e]	• BMI ≥30 • BMI ≥27 with obesity-associated comorbidity[5] • Consider with inadequate response to lifestyle therapy and/or presence of mild to moderate obesity complications[4]	Medications vary in terms of administration and dosage (minimum-maximum dose): • FDA approved for long-term use • Semaglutide (0.25-2.4 mg/wk subcutaneously) • Phentermine-topiramate ER (3.75/23 mg/d to 15/92 mg/d orally) • Liraglutide (0.6-3 mg/d subcutaneously) • Naltrexone-bupropion ER (8 mg/90 mg daily to 16 mg/180 mg twice daily orally) • Orlistat (60-120 mg 3 times daily orally) • FDA approved for short-term use • Diethylpropion (IR: 25 mg 3 times daily; ER: 75 mg/d orally) • Phentermine (8 mg/d to 8 mg 3 times daily or 15-37.5 mg/d orally) • Commonly used off label • Tirzepatide (2.5-15 mg/wk subcutaneously) • Semaglutide (3-50 mg/d orally) (50-mg/d oral dose not yet available) • Topiramate (12.5-200 mg/d in 1 to 2 divided doses) • Semaglutide (0.25-2.0 mg/wk subcutaneously) • Liraglutide (0.6-1.8 mg/d subcutaneously) • Bupropion (SR: 100-200 mg twice daily orally; ER: 150-450 mg/d orally) • Metformin (500-2500 mg/d orally)	5% (naltrexone-bupropion, 32 mg/360 mg daily)[41] to 21% (tirzepatide, 15 mg once weekly)[42f]	• See Table 4; adverse effects can often be avoided with slow dose titration or reducing dose to last tolerated dose • Administer concurrent with lifestyle interventions

BARIATRIC ENDOSCOPIC PROCEDURES

BARIATRIC ENDOSCOPIC PROCEDURES

- Currently, 2 bariatric endoscopic procedures are FDA approved : intragastric balloons and endoscopic sleeve gastroplasty.

- Intragastric balloons occupy space in the stomach, delay gastric emptying, and increasing satiety. (117) -- 10.2% (range, 9.6%-29.2%)

- Patients with a BMI of 30 to 40 are eligible and typically require an upper endoscopy to place the balloon and fill it with saline.
- The devices are removed via endoscopy after 6 to 8 months.

ENDOSCOPIC SLEEVE GASTROPLASTY

- **Endoscopic sleeve gastroplasty is an organ-sparing, transoral endoscopic procedure designed to reduce stomach volume.**

- Endoscopic sleeve gastroplasty achieved 13.6% weight loss compared with 0.8% with lifestyle modifications alone. (119)

- **Procedural contraindications (eg, hiatal hernia, gastric ulcers),**

METABOLIC AND BARIATRIC SURGERY

METABOLIC AND BARIATRIC SURGERY

- Recent guidelines recommend that metabolic and bariatric surgery should be considered for patients with a BMI of 35 or greater and patients with a BMI of 30 to 34.9 who have concurrent metabolic disease.

- Lower weight thresholds should be applied to Asian populations. (9)

METABOLIC AND BARIATRIC SURGERY

- Two metabolic and bariatric procedures comprise more than 90% of all surgeries:

  (1) laparoscopic sleeve gastrectomy (LSG), in which approximately 85% of the stomach is removed by separation along the greater curvature, and

  (2) Roux-en-Y gastric bypass (RYGB) surgery, in which a small gastric pouch is connected directly to the jejunum. (43)

- Both are typically performed laparoscopically.

METABOLIC AND BARIATRIC SURGERY

- **Expected 12-month weight loss is approximately 25% after LSG and approximately 30% after RYGB, with sustained weight loss at 5 years.** (44,120)

- Early *complications* include : anastomotic leaks (LSG: 1%-7%; RYGB: 0.6%-4.4%) , stenosis (LSG: 1%-9%; RYGB: 8%- 19%), postoperative bleeding (11%) , and venous thromboembolic events (incidence not reported) ; late *complications* include : internal hernia and marginal ulceration (RYGB: 2.5%-5%). (121)

METABOLIC AND BARIATRIC SURGERY

- Pre– and post–metabolic and bariatric surgery screening and supplementation for micronutrients (thiamin, vitamin B_{12}, folate, iron, vitamin D, calcium, vitamin A, vitamin E, vitamin K, zinc, and copper) is recommended ; typical doses vary based on surgical procedure. (45)

Metabolic and bariatric surgery	• BMI ≥35 • BMI ≥30 with obesity-associated comorbidity[9] • Consider with inadequate response to lifestyle therapy and/or presence of severe obesity complications[4]	• Laparoscopic sleeve gastrectomy: approximately 85% of stomach removed by separation along greater curvature[43] • Roux-en-Y gastric bypass: small gastric pouch connected directly to jejunum[43]	25%-35%[5,44]	• Major complications <5%[44,45] • Long-term monitoring necessary for risks related to nutritional deficiency and bone health[45] • Administer concurrent with lifestyle interventions

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); ER, extended release; FDA, US Food and Drug Administration; IR, immediate release; SR, sustained release.

[a] Interventions should be used simultaneously or serially with long-term follow-up. Randomized trials cannot fully replicate clinical care, in which clinicians see patients over long periods and add or adjust weight-loss approaches for individual patients. All patients undergoing weight-loss interventions should engage in nutrition, physical activity, and/or behavioral interventions.

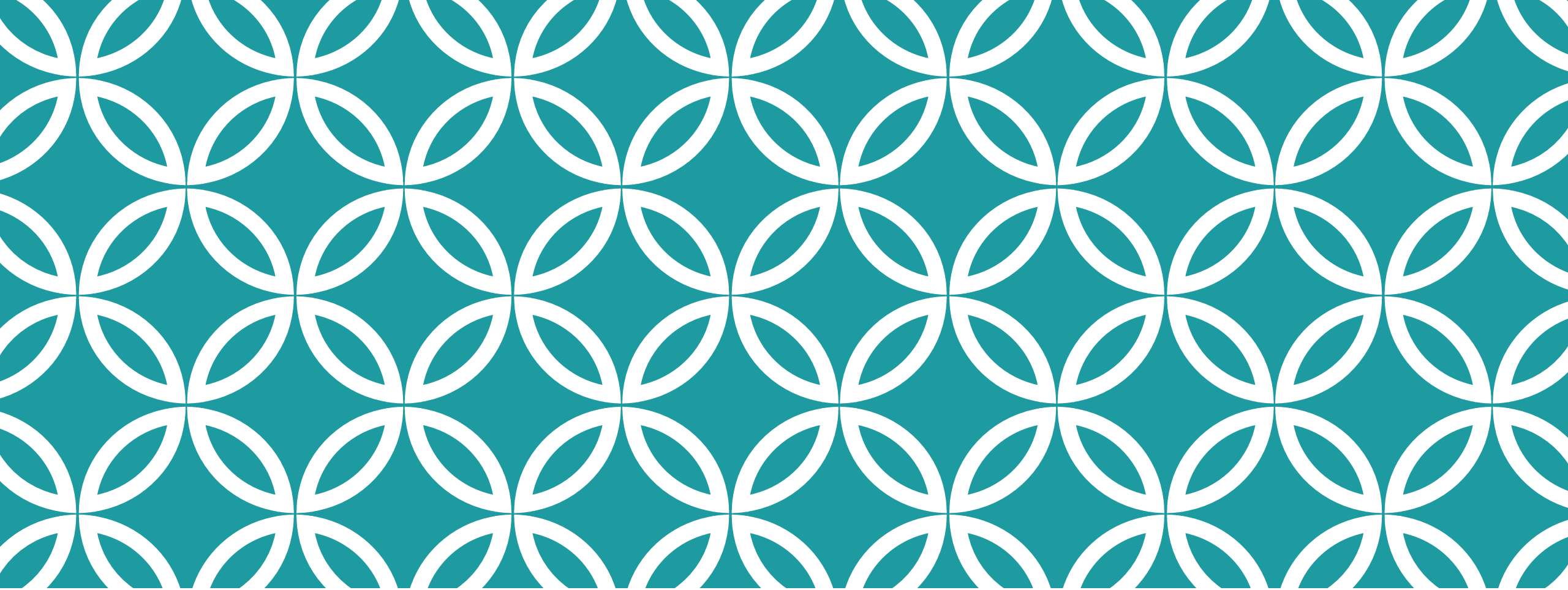
[b] Lower thresholds in Asian populations.

[c] Expected ranges are approximate based on meta-analysis and clinical guidelines, generally in a 12- to 24-mont time frame.

[d] Obesity-related comorbidity is defined based on the presence of at least 1 risk factor, including abnormal bloo glucose levels, hypertension, and dyslipidemia.

[e] See Table 4 for detailed information.

[f] Range is listed for antiobesity medications FDA approved for long-term use.



WEIGHT-LOSS MAINTENANCE AND LONG-TERM OBESITY MANAGEMENT

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- **Maintaining weight loss is difficult and may be supported by continued clinical intervention.** (123)

- **In longitudinal observational studies, people who successfully maintain weight often use *behavioral strategies*, such as : physical activity, regular self-weighing ,** (67) **a reduced-calorie diet , and a consistent eating pattern.** (124,125)

- **Patients may need to increase their physical activity (>200 min/wk is often required).** (5) / regular physical activity (200–300 min/week). A

In summary:

- Obesity is a complex, chronic, multifactorial disease
- Following weight loss, a number of counter-regulatory responses occur that favour weight regain
- Obesity, like any other chronic disease, requires long term treatment

ازتوجه وصبوری شمابی نهایت سپاسگزارم