METABOLIC SYNDROME: PREDIABETES, OBESITY AND HYPERLIPIDEMIA

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DISCLOSURE STATEMENT

- No disclosures for either Jessica or Julia

OBJECTIVES:

- Definition of metabolic syndrome and prediabetes
- Prevalence and complications of obesity
- Lifestyle modification
- Pharmacotherapy
- Surgical intervention
- Hyperlipidemia treatment options

THE NATIONAL CHOLESTEROL EDUCATION PROGRAM (NCEP) ADULT TREATMENT PANEL III (ATPIII)

The 2005 ATP III criteria define metabolic syndrome as the presence of any three of the following traits:

- Abdominal obesity, defined as a waist circumference ≥102cm (40in) in males and ≥88cm (35in) in females
- Serum triglycerides ≥150mg/dL or drug treatment for elevated triglycerides
- Serum high-density lipoprotein (HDL) <40 mg/dL in males and < 50 in females or drug treatment for low HDL cholesterol
- Blood pressure ≥130/85 or drug treatment for elevated blood pressure
- Fasting plasma glucose (FPG) ≥100 mg/dL or drug treatment for elevated blood glucose

TABLE 1

Criteria for the diagnosis of prediabetes and diabetes[1,2]

	Prediabetes	Diabetes
A1C	5.7%-6.4%	≥6.5%*
FPG	100-125 mg/dL (5.6-6.9 mmol/L)	≥126 mg/dL (7 mmol/L)*
OGTT	140-199 mg/dL (7.8-11 mmol/L)	≥200 mg/dL (11.1 mmol/L)*
RPG		≥200 mg/dL (11.1 mmol/L)**

FPG, fasting plasma glucose; OGTT, oral glucose tolerance test; RPG, random plasma glucose.

*In the absence of unequivocal hyperglycemia, results should be confirmed by repeating the test.

**Random plasma glucose is diagnostic only in a patient with classic symptoms of hyperglycemia or hyperglycemic crisis.

Diabetologia (2022) 65:275–285
https://doi.org/10.1007/s00125-021-05592-3

ARTICLE

Prediabetes and risk of mortality, diabetes-related complications and comorbidities: umbrella review of meta-analyses of prospective studies

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Received: 26 April 2021 / Accepted: 10 August 2021 / Published online: 31 October 2021

Abstract

Aims/hypothesis The term prediabetes is used for individuals who have impaired glucose metabolism whose glucose or HbA_{1c} levels are not yet high enough to be diagnosed as diabetes. Prediabetes may already be associated with an increased risk of chronic 'diabetes-related' complications. This umbrella review aimed to provide a systematic overview of the available evidence from meta-analyses of prospective observational studies on the associations between prediabetes and incident diabetes-related complications in adults and to evaluate their strength and certainty.

Methods For this umbrella review, systematic reviews with meta-analyses reporting summary risk estimates for the associations between prediabetes (based on fasting or 2 h postload glucose or on HbA_{1c}) and incidence of diabetes-related complications, comorbidities and mortality risk were included. PubMed, Web of Science, the Cochrane Library and Epistemonikos were searched up to 17 June 2021. Summary risk estimates were recalculated using a random effects model. The certainty of evidence was evaluated by applying the GRADE tool. This study is registered with PROSPERO, CRD42020153227.

Results Ninety-five meta-analyses from 16 publications were identified. In the general population, prediabetes was associated with a 6–101% increased risk for all-cause mortality and the incidence of cardiovascular outcomes, CHD, stroke, heart failure, atrial fibrillation and chronic kidney disease, as well as total cancer, total liver cancer, hepatocellular carcinoma, breast cancer and all-cause dementia with moderate certainty of evidence. No associations between prediabetes and incident depressive symptoms and cognitive impairment were observed (with low or very low certainty of evidence). The association with all-cause mortality was stronger for prediabetes defined by impaired glucose tolerance than for prediabetes defined by HbA_{1c}.

Conclusions/interpretation Prediabetes was positively associated with risk of all-cause mortality and the incidence of cardiovascular outcomes, CHD, stroke, chronic kidney disease, cancer and dementia. Further high-quality studies, particularly on HbA_{1c}-defined prediabetes and other relevant health outcomes (e. g. neuropathy) are required to support the evidence.

PREDIABETES

Risk of mortality and comorbidities

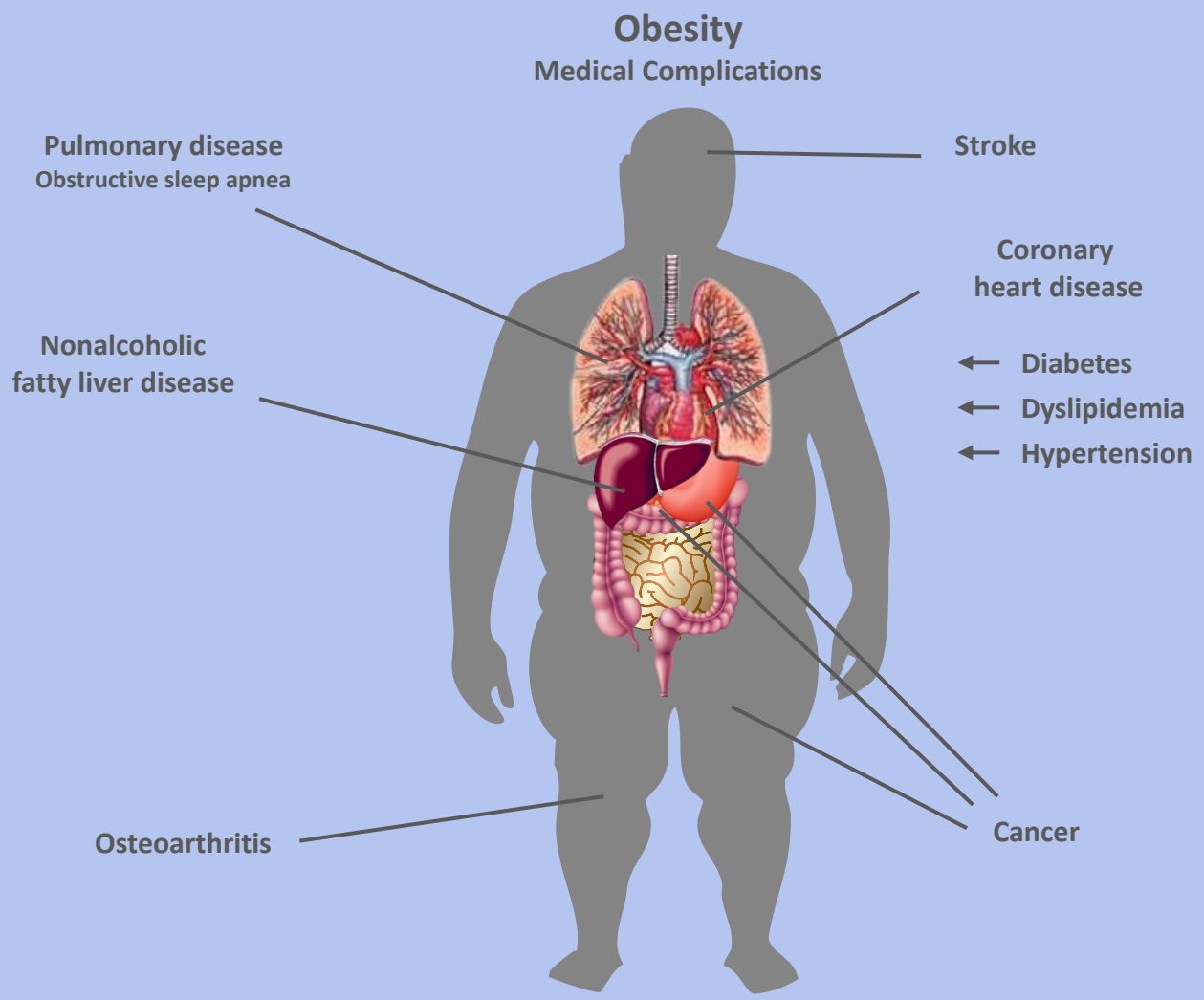
DEFINITION OF OBESITY

The Obesity Medicine Association's Definition of Obesity

"Obesity is defined as a chronic, progressive, relapsing, multi-factorial, neurobehavioral disease, wherein an increase in body fat promotes adipose tissue dysfunction and abnormal fat mass physical forces, resulting in adverse metabolic, biomechanical, and psychosocial health consequences."

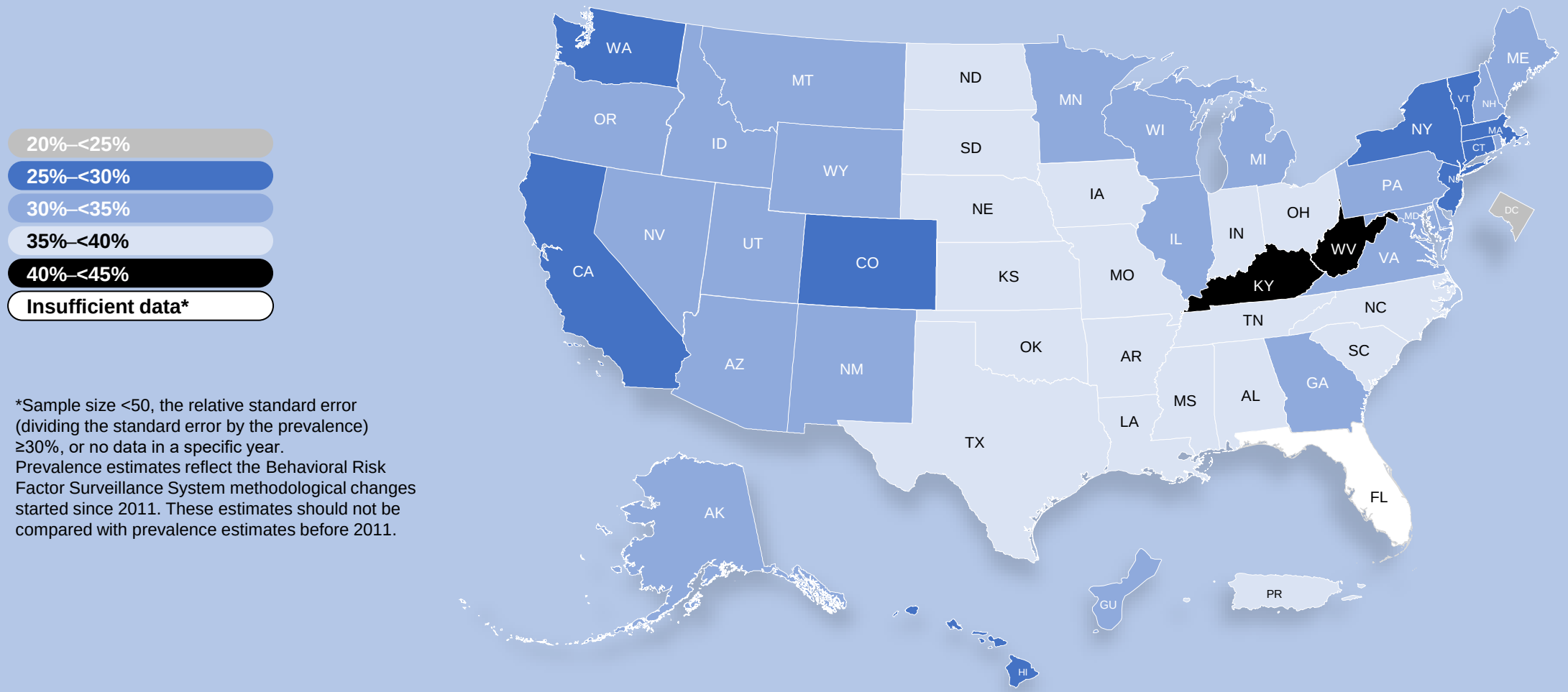
Obesity Medicine Association

OBESITY IMPACTS MULTIPLE COMORBIDITIES



Lopez-Jimenez F, Cortes-Bergoderi M. *Rev Esp Cardiol*. 2011;64(2):140-149.

BMI ≥30 kg/m^2 is prevalent across the U.S., affecting ≥20% of adults in all states



*Sample size <50, the relative standard error (dividing the standard error by the prevalence) ≥30%, or no data in a specific year.
Prevalence estimates reflect the Behavioral Risk Factor Surveillance System methodological changes started since 2011. These estimates should not be compared with prevalence estimates before 2011.

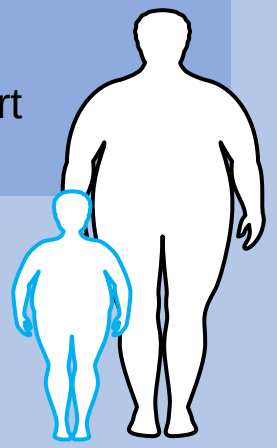
BMI, body mass index; U.S., United States.

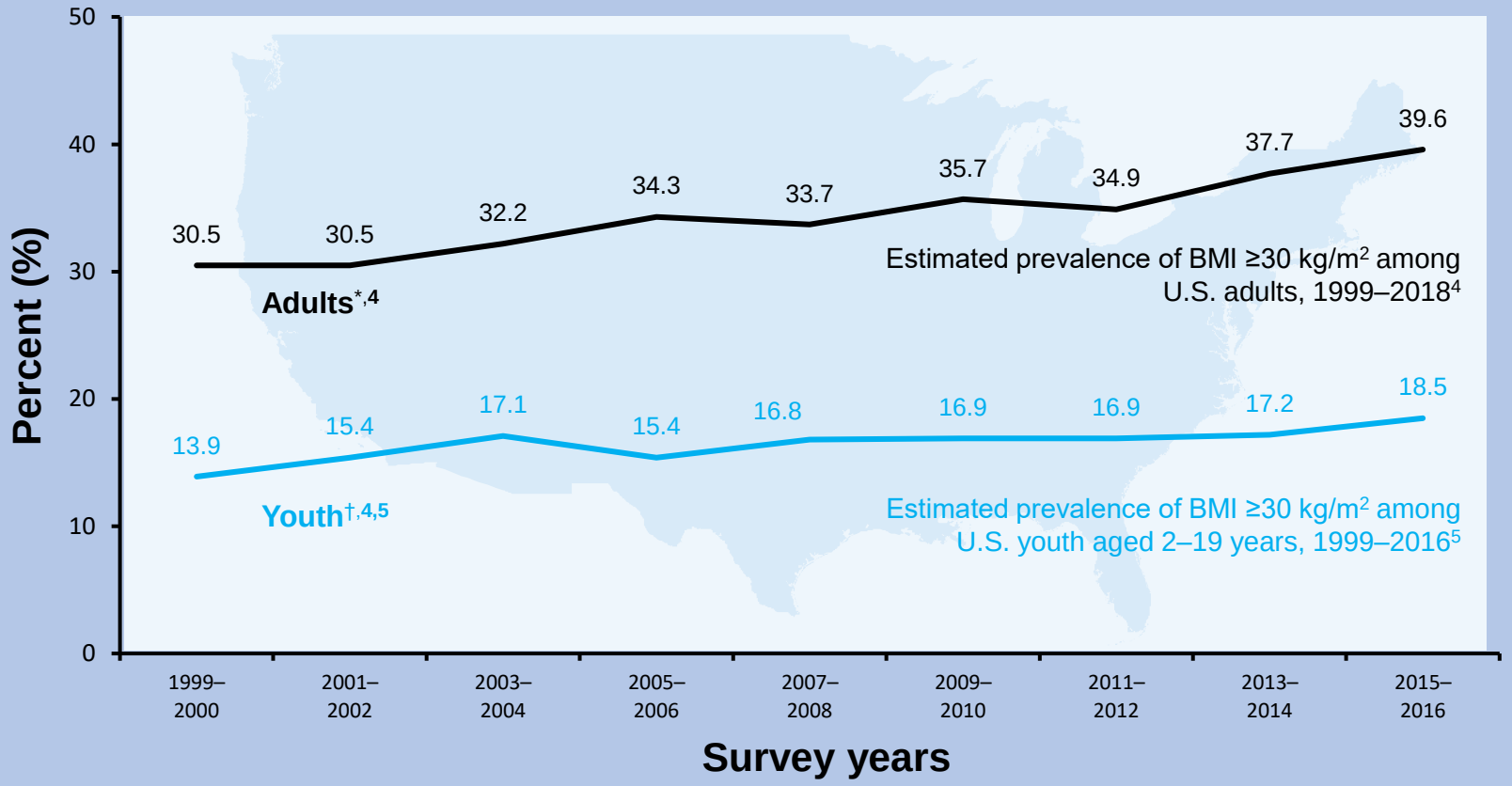
Centers for Disease Control. Adult Obesity Prevalence Maps, 2020. Available at: https://www.cdc.gov/obesity/data/prevalence-maps.html. Accessed May 2023.

Obesity prevalence in U.S. over time

Adults and children

- Pre-obesity and obesity criteria used by the CDC[1]
- Severe obesity classification recommended by the American Heart Association[2,3]





*Significant linear trend. BMI, body mass index; CDC, Centers for Disease Control and Prevention; U.S., United States.
Estimates are age-adjusted by the direct method to the 2000 U.S. census population using the age groups 20–39, 40–59, and 60 and over.
Obesity was defined as BMI ≥95th percentile for age and sex (2000) Centers for Disease Control and Prevention growth charts)2,3

1. CDC Defining Childhood Obesity. Available at: https://www.cdc.gov/obesity/basics/childhood-defining.html?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fobesity%2Fchildhood%2Fdefining.html. Accessed May 2023; 2. Skinner AC et al. JAMA Pediatr. 2014;168:561–566; 3. Kelly AS et al. Circulation 2013;128:1689–1712; 4. Hales CM et al. NCHS Data Brief 2017;288 (National Health and Nutrition Examination Survey). Available at: https://www.cdc.gov/nchs/data/databriefs/db288.pdf Accessed May 2023; 5. Fryar CD et al. Prevalence of Overweight, Obesity, and Severe Obesity Among Children and Adolescents Aged 2–19 Years: United States, 1963–1965 Through 2015–2016 Available at: https://www.cdc.gov/nchs/data/hestat/obesity_child_13_14/obesity_child_13_14.htm Accessed May 2023.

Definition and Classification of Obesity

- **Clinical obesity:** excess adiposity causing negative health outcomes that can be objectively documented by specific signs and symptoms[1]
- Obesity should be treated within a chronic disease framework, **JUST like** other chronic, progressive conditions
- Like other chronic diseases, obesity is a result of multiple environmental and genetic factors[2]

$$\text{BMI} = \frac{\text{weight (kg)}}{\text{height (m}^2\text{)}}$$

The standard measurement of obesity is a BMI ≥30 kg/m^2

Classification	BMI (kg/m^2)	
	International classification[2–4]	Asian population[5]
Underweight	<18.5	
Healthy weight	≥18.5 and <25	≥18 and <23
Pre-obesity*	≥25 and <30	≥23 and <25
Obesity	≥30	>25
Obesity class I	≥30 and <35	
Obesity class II	≥35 and <40	
Obesity class III	≥40	

*Pre-obesity, previously called overweight, medicalizes the term, and like pre-diabetes may assist patients and HCPs in taking their weight more seriously.
BMI, body mass index; WHO, world health organization.

1. Rubino F et al. Lancet Diabetes Endocrinol. 2023;11:226–228; 2. Centers for Disease Control and Prevention (CDC). Defining adult overweight & obesity. Available at: https://www.cdc.gov/obesity/basics/adult-defining.html#:~:text=Obesity%20is%20frequently%20subdivided%20into,BMI%20of%2040%20or%20higher. Accessed June 2023;
3. Obesity playbook. Endocrine Society. 2023. Available at: https://www.endocrine.org/-/media/endocrine/files/obesity/obesity-playbook-final_use.pdf. Accessed May 2023;
4. Bhaskaran K et al. Lancet Diabetes Endocrinol. 2018;6:944–953; 5. Misra A et al. J Assoc Physicians India 2009;57:163–170.

Obesity staging

- BMI is better suited to describing populations than individuals
- Several obesity staging systems have been developed to assist clinicians in characterizing obesity severity and aid in clinical decision-making

The most well-known staging system is the Edmonton Obesity Staging System (EOSS)

The EOSS is a better predictor of mortality than BMI alone[1]

Complications	Stage 0	Stage 1	Stage 2	Stage 3	Stage 4
Medical	Absent	Preclinical risk factors	Comorbidity	End-organ damage	End stage
Mental		Mild	Moderate	Severe	
Physical Function		Mild	Moderate	Severe	

BMI, body mass index; EOSS, Edmonton Obesity Staging System.

1. Kodsi R et al. Nutrients. 2022;14:967; 2. Sharma AM & Kushner RF. Int J Obes (Lond). 2009;33:289–295.

Obesity meets criteria of a disease

Definition of Health

"a state of complete physical, mental and social **well-being** and **not merely the absence** of disease or infirmity“[1]

AMA Defines a Disease as[2]:

- An impairment of the normal functioning of some aspect of the body
- Characteristic signs or symptoms
- Harm or morbidity

Obesity

- Appetite dysregulation (inappropriate hunger)
- Abnormal energy balance (reduced metabolic rate)
- Endocrine dysfunction

- Increased body fat
- Symptoms associated with increased body fat including:
  - Joint pain
  - Altered metabolism
  - Sleep apnea

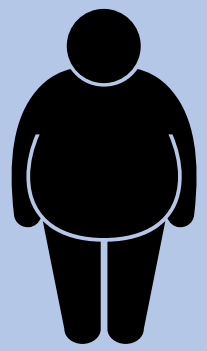
- T2D
- Cardiovascular disease
- Cancer
- Polycystic ovary syndrome
- Infertility
- MASLD
- Dyslipidemia
- Increased mortality

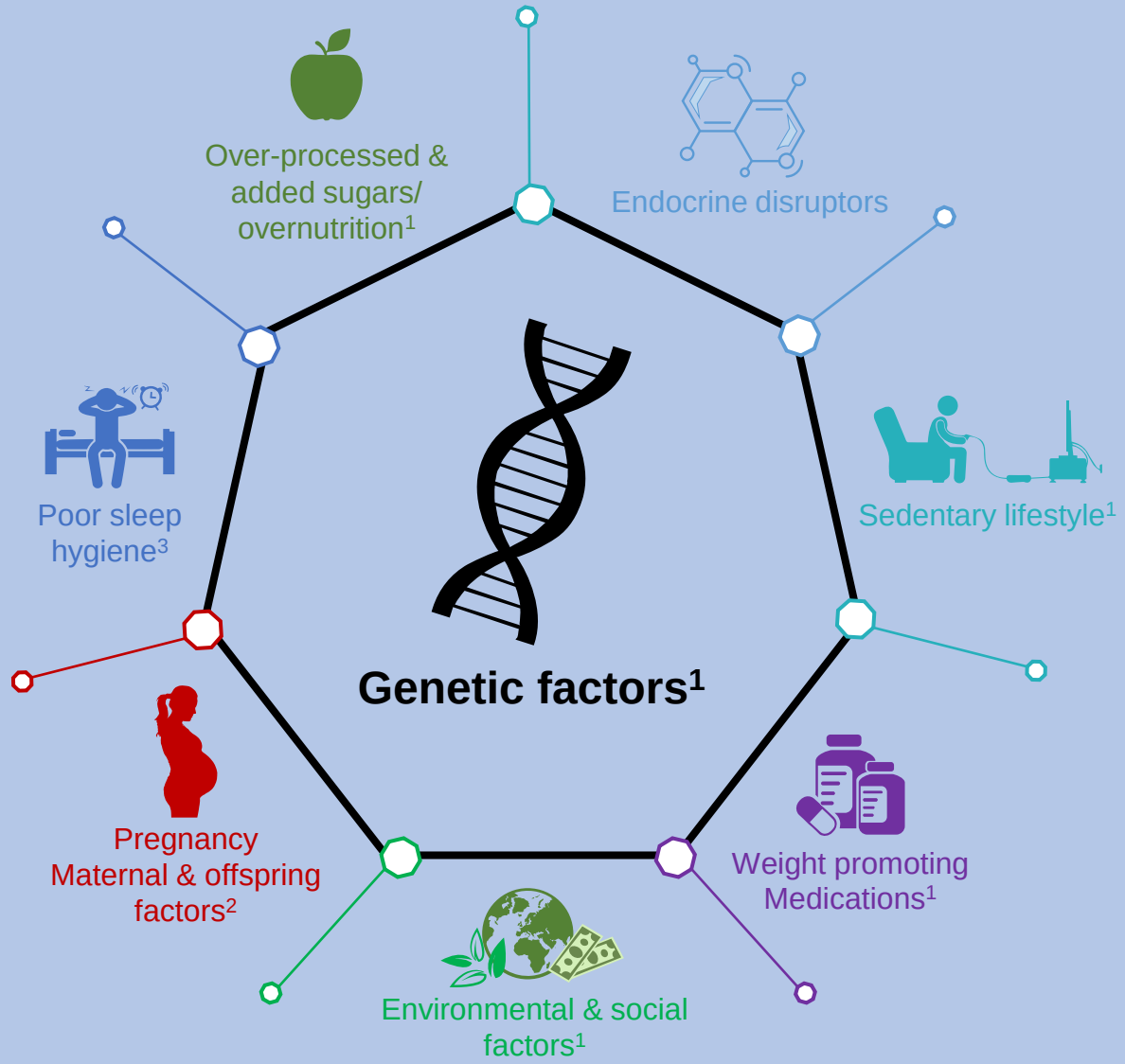
AMA, American Medical Association, MASLD, metabolic dysfunction-associated steatotic liver disease; T2D, type 2 diabetes.

1. World Health Organization. Constitution of the World Health Organization as adopted by the International Health Conference, New York, 19–22 June 1946;
2. Mechanick JI et al. Endocr Pract 2012;18(5):642–648.

Causes of obesity

Several factors interact with the genetic predisposition for caloric retention to cause obesity





1. Gadde KM et al. J Am Coll Cardiol. 2018;71:69–84;2. Kankowski L et al. Front Endocrinol. 2022;13:868441; 3. Papatriantafyllou E et al. Nutrients. 2022;14:1549.

SCREENING AND DIAGNOSES IN OVERWEIGHT/OBESITY

- Annual physical
- Weight-related complications
- Interpretation of BMI (volume status, edema, muscularity)
- Secondary testing when needed (Prediabetes, dyslipidemia, hypertension, cardiovascular disease, OSA, Depression)
- Secondary Hormonal Disorder (Hypothyroidism, hypercortisolism)
- Genetic Syndrome
- Iatrogenic Obesity (medications: substitute for weight-neutral alternative)

WEIGHT EFFECTS OF COMMON MEDICATIONS

Medication	Weight Gain Associated With Use	Alternatives (Weight Reducing in Parentheses)
Diabetes medications	Insulin, sulfonylureas, TZDs, mitiglinide, sitagliptin?[a]	(Metformin, acarbose, miglitol, pramlintide, exenatide, liraglutide, SGLT-2 inhibitors)
Hypertension medications	α-Blocker?, β-blocker?	ACE inhibitors?, calcium channel blockers?, angiotensin-2 RAs
Antidepressants and mood stabilizers	Amytriptyline, doxepin, imipramine, nortriptyline, trimipramine, mirtazapine, fluoxetine?, sertraline?, paroxetine, fluvoxamine	(Bupropion), nefazodone, fluoxetine (short term, sertraline, <1 year)
Oral contraceptives	Depot progesterone	Barrier methods, IUDs

Current approaches to obesity care

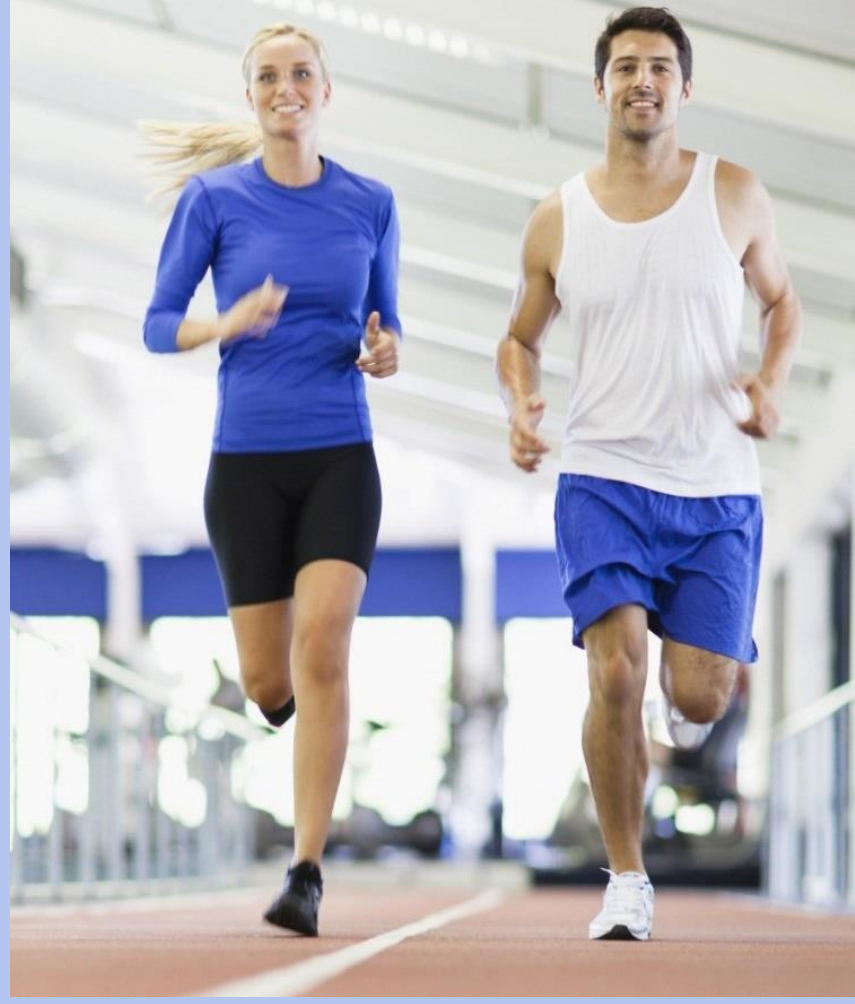
	Physical activity	Diet	Behavioral therapy	AOMs	Surgery
Treatment guidelines	≥150 min prescriptive moderate physical activity/week[1]	Reduced-calorie healthy meal plan*,[1]	High frequency of lifestyle counseling (≥16 sessions in 6 months)†,[2]	BMI ≥30 kg/m^2 OR BMI ≥27 kg/m^2 with significant comorbidity‡,[1,3]	BMI ≥35 kg/m^2 OR BMI ≥30 kg/m^2 and metabolic disease and in "appropriately selected children and adolescents"[4]
HCP adherence	**~50%** recommend guideline levels[5]	**33%** identified correct eating guidelines[5]	**<20%** recommend counseling for people with obesity[5]	**40%** prescribe at the defined BMI threshold[3] **31%** do not prescribe[3] **0.7–2%** of eligible patients receive AOMs[3]	**<33%** refer people with obesity at the defined BMI threshold[3] **11%** do not propose surgery[3]

84% of HCPs failed to identify practices consistent with evidence-based obesity treatment guidelines[4]

*Calorie deficit of 500–1000 calories/day; †Behavioral intervention should be tailored to a patient's ethnic, cultural, socioeconomic and educational background; ‡Whenever possible, minimize medications for comorbid conditions that are associated with weight gain..

AOMs, anti-obesity medications; BMI, body mass index; HCP, healthcare professional.

1. Garvey WT et al. Endocr Pract. 2016;22:1–203; 2. ElSayed NA et al. Diabetes Care. 2023;46:S128–S139; 3. Petrin C et al. Obesity Sci Pract 2016;2:266–271; 4. ASMBS. After 30 years – New guidelines for weight-loss surgery. Available at: https://asmbs.org/articles/after-30-years-new-guidelines-for-weight-loss-surgery. Accessed August 2023; 5. Turner M et al. Obesity. 2018;26:665–671.



EVIDENCE-BASED LIFESTYLE THERAPY

LIFESTYLE / BEHAVIORAL THERAPY

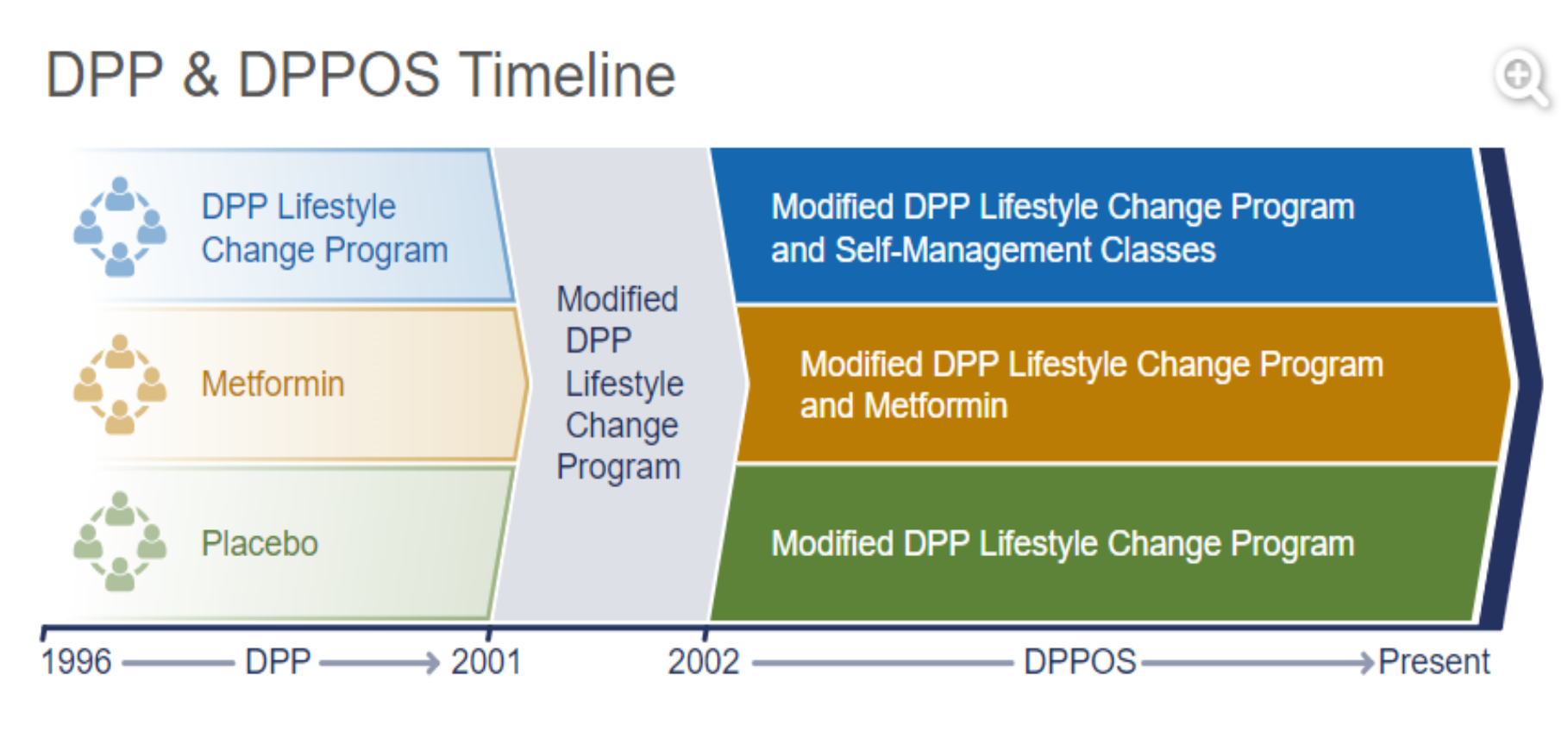
EVIDENCE-BASED LIFESTYLE THERAPY

Meal Planning: Reduced-calorie healthy meal plan (500-750 kcal daily deficit). Individualize based on personal and cultural preferences. Meal plans can include: Mediterranean, Dietary Approaches to Stop Hypertension (DASH), Low-carb, Low-fat, High protein, Vegetarian. Meal replacements. Very low-calorie diet may be an option for select patients and requires medical supervision. Refer to registered dietician or health educator

Physical Activity: Voluntary aerobic physical activity progressing to > 150 minutes/week performed on 3-5 separate days per week. Resistance exercise 2-3 times per week. Reduce sedentary behavior. Individualize program based on preference and physical limitations. Refer to exercise trainer, coach or physical / occupational therapist

Intensive Behavioral Therapy: "Screening for adults using BMI, dietary/nutritional assessment and intensive behavioral counseling to promote sustained weight loss through high intensity interventions on diet and exercise". Self monitoring of food intake, exercise and weight. Goal setting, education, stress reduction, problem solving strategies, motivational interviewing, social support and psychological evaluation, counseling and treatment when needed

NIDDK-SPONSORED DIABETES PREVENTION PROGRAM (DPP) AND ONGOING DPP OUTCOMES STUDY (DPPOS)



WHAT IS THE BEST DIET?

- Mediterranean diet
- Therapeutic lifestyle diet
- DASH (Dietary Approaches to Stop Hypertension)
- Ketogenic diet
- Paleo diet
- Vegetarian diet
- Intermittent fasting
- Commercial diet programs

Fad diets

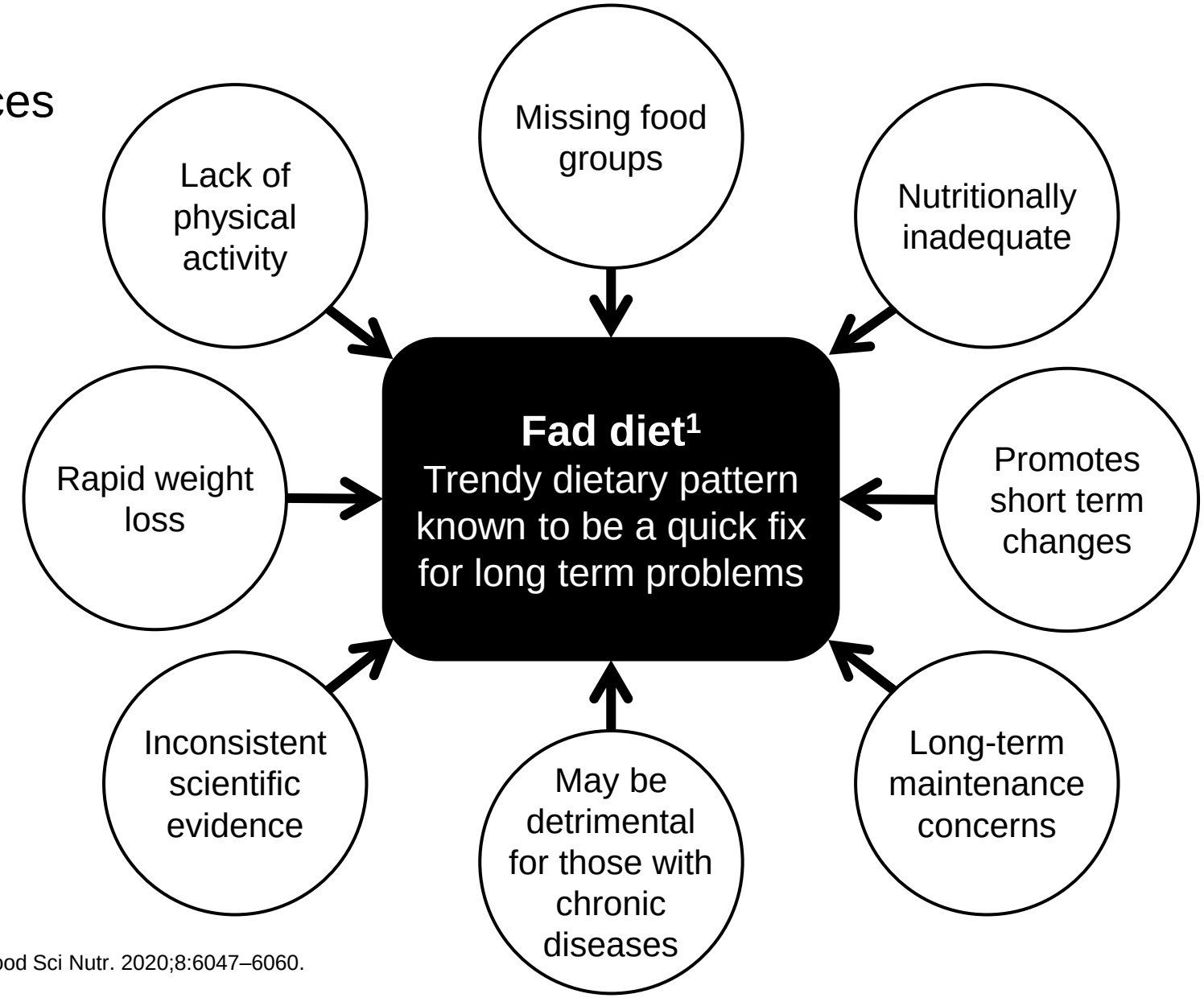
Negative health consequences

Fad diets may temporarily reduce daily caloric intake[1,2]

However

Adverse health outcomes may include inadequate micronutrient intake and increased LDL-c[*,1]

Micronutrient deficiencies may increase the risk of developing comorbidities[†,2]



*Increased LDL-c is associated with the ketogenic diet;
†Comorbidities such as type 2 diabetes, cardiovascular disease, cancer and osteoporosis.
LDL-c, low-density lipoprotein cholesterol.

1. Tahreem A et al. Front Nutr. 2022;9:960922; 2. Malik N et al. Food Sci Nutr. 2020;8:6047–6060.

MEDITERRANEAN DIET

This article has been retracted: N Engl J Med 2018;378(25):2441-2.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 4, 2013 VOL. 368 NO. 14

Primary Prevention of Cardiovascular Disease with a Mediterranean Diet

Ramón Estruch, M.D., Ph.D., Emilio Ros, M.D., Ph.D., Jordi Salas-Salvadó, M.D., Ph.D., Maria-Isabel Covas, D.Pharm., Ph.D., Dolores Corella, D.Pharm., Ph.D., Fernando Arós, M.D., Ph.D., Enrique Gómez-Gracia, M.D., Ph.D., Valentina Ruiz-Gutiérrez, Ph.D., Miquel Fiol, M.D., Ph.D., José Lapetra, M.D., Ph.D., Rosa Maria Lamuela-Raventos, D.Pharm., Ph.D., Lluís Serra-Majem, M.D., Ph.D., Xavier Pintó, M.D., Ph.D., Josep Basora, M.D., Ph.D., Miguel Angel Muñoz, M.D., Ph.D., José V. Sorlí, M.D., Ph.D., José Alfredo Martínez, D.Pharm, M.D., Ph.D., and Miguel Angel Martínez-González, M.D., Ph.D., for the PREDIMED Study Investigators*

Sleep hygiene and stress management

Insufficient sleep is independently associated with a higher risk of obesity, and obesity may lead to reduced sleep quality[1,2]

Sleep deprivation

- ↑ Ghrelin[1*]
- ↓ Leptin[1*]
- ↑ Hedonic signaling
  - ↑ Time and opportunities for eating[1]
- ↓ Physical activity
  - Due to fatigue[1]

Overeating[1]

- ↑ Energy intake
- ↓ Energy expenditure

Sleep extension may mitigate the risk of obesity.[2] How to improve and maintain sleep duration:[3]

- Avoid caffeine and alcohol in the evening; avoid nicotine
- Establish regular bed- and wake-times
- Minimize stress to avoid pre-sleep arousal
  - Engage in relaxing activities
  - Mindfulness** meditation
- Exercise regularly
- Restrict use of electronic devices near bedtime

*Ghrelin: stimulates appetite; leptin: suppresses food intake; **Mindfulness is focused attention on the present moment without judgement.

1. Cooper CB et al. BMJ Open Sport Exerc Med 2018;4:e000392; 2. Tasali E et al. JAMA Intern Med 2022;182:365–374; 3. Irish LA et al. Sleep Med Rev 2015;22:23–36.

Clinical guidelines: Lifestyle intervention is the foundation of obesity treatment

If lifestyle counseling does not yield adequate results, care should be escalated to include pharmacotherapy +/- surgery

Treatment*	BMI category (kg/m^2)				
	≥25	≥27	≥30	≥35	≥40
Diet, physical activity and behavior therapy	With comorbidities	With comorbidities	+	+	+
Pharmacotherapy		With comorbidities	+	+	+
Surgery				+	+

*AHA/ACC/TOS guidelines.
AHA, American Heart Association; ACC, American College of Cardiology; BMI, body mass index; TOS, The Obesity Society.
Jensen MD et al, Circulation 2014;129(25 Suppl 2):S102–S138.

AACE/ACE ALGORITHM FOR THE MEDICAL CARE OF PATIENTS WITH OBESITY

Patient Presentation	Screen positive for overweight or obesity BMI ≥25 kg/m² (≥23 kg/m² in some ethnicities)	Presence of weight-related disease or complication that could be improved by weight-loss therapy

Diagnosis

Evaluation

- Medical history • Physical examination • Clinical laboratory
- Review of systems, emphasizing weight-related complications
- Obesity history: graph weight vs age, lifestyle patterns/preferences, previous interventions

Anthropometric Diagnosis

- Confirm that elevated BMI represents excess adiposity
- Measure waist circumference to evaluate cardiometabolic disease risk

BMI kg/m²

<25 NORMAL WEIGHT <23 in certain ethnicities	25–29.9 OVERWEIGHT | ≥30 OBESITY		
Clinical Diagnosis	**Checklist of Obesity-Related Complications** (staging and risk stratification based on complication-specific criteria)		
Waist circumference below regional/ethnic cutoffs	**None**	**Mild to Moderate**	**Severe**

Diagnostic Categories	**NORMAL WEIGHT (no obesity)**	**STAGE 0**	**STAGE 1**	**STAGE 2**
		No complications	One or more mild-to-moderate complications or may be treated effectively with moderate weight loss	At least one severe complication or requires significant weight loss for effective treatment
		OVERWEIGHT **BMI 25–29.9** OBESITY **BMI ≥30**	**BMI ≥25**	**BMI ≥25**
Phases of Chronic Disease Prevention and Treatment Goals	**PRIMARY** Prevent overweight/obesity	**SECONDARY** Prevent progressive weight gain or achieve weight loss to prevent complications	**TERTIARY** Achieve weight loss sufficient to ameliorate the complications and prevent further deterioration	
Treatment Based on Clinical Judgment	• Healthy meal plan • Physical activity • Health education • Built environment	• Lifestyle/behavioral therapy • Consider pharmacotherapy if lifestyle alone not effective	• Lifestyle/behavioral therapy • Consider pharmacotherapy (BMI ≥27)	• Lifestyle/behavioral therapy • Add pharmacotherapy (BMI ≥27) • Consider bariatric surgery (BMI ≥35)

Follow-Up

- Once the plateau for weight loss has been achieved, re-evaluate the weight-related complications. If the complications have not been ameliorated, weight-loss therapy should be intensified or complication-specific interventions need to be employed.
- Obesity is a chronic disease and the diagnostic categories for obesity may not be static. Therefore, patients require ongoing follow-up, re-evaluation and long-term treatment.

FDA-APPROVED ANTI-OBESITY MEDICATIONS FOR CHRONIC WEIGHT MANAGEMENT

CLINICAL GUIDELINES

FDA APPROVED MEDICATIONS

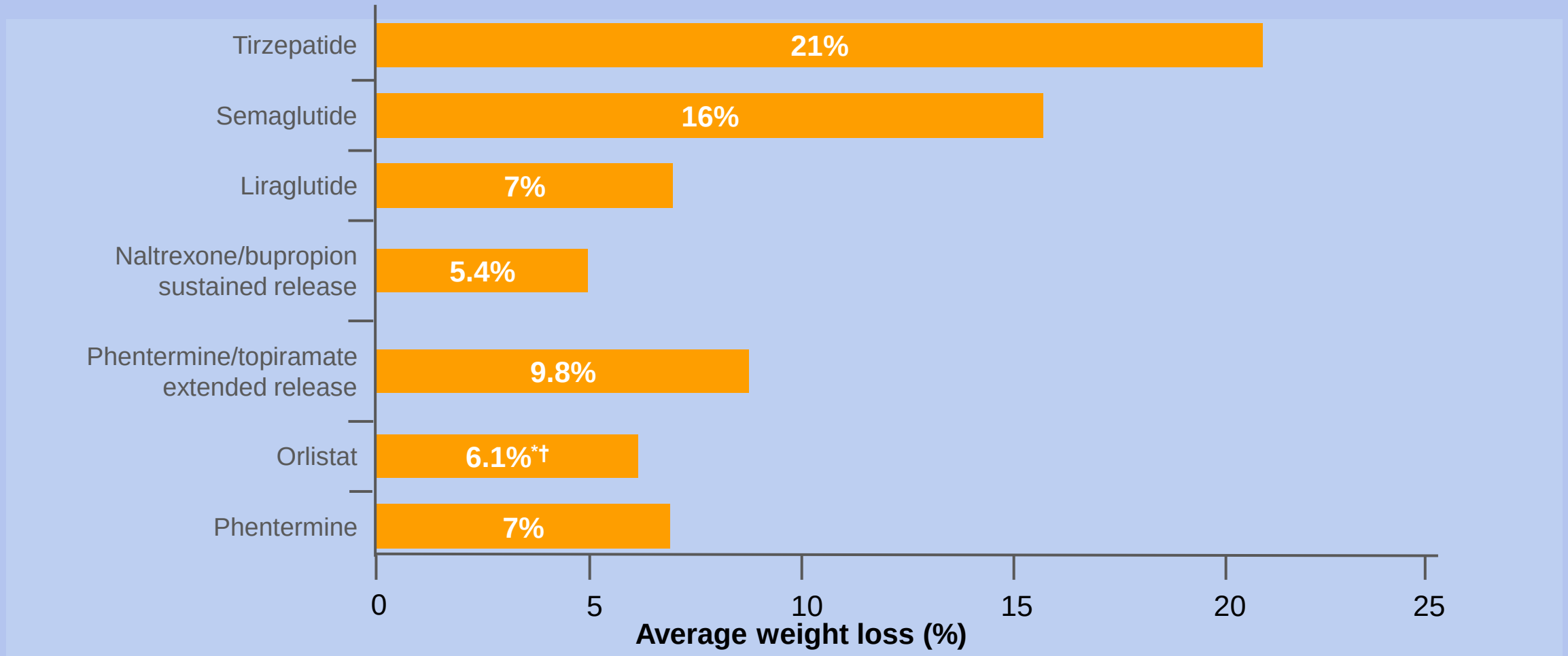
Name	Class	Dosage form
Tirzepatide	Dual GIP/GLP-1 receptor co-agonist*	Subcutaneous; 5 mg, 10 mg or 15 mg once weekly
Semaglutide	GLP-1 receptor agonist	Subcutaneous; 1.7 or 2.4 mg once weekly
Liraglutide	GLP-1 receptor agonist†	Subcutaneous; 3.0 mg once daily
Naltrexone/bupropion	Opioid receptor antagonist; dopamine and norepinephrine reuptake inhibitor†	Oral; 32 mg/360 mg daily
Phentermine/topiramate	Sympathomimetic + anticonvulsant (GABA receptor modulation, carbonic anhydrase inhibition, glutamine antagonism)†	Oral; 7.5–15 mg/46–92 mg daily
Phentermine‡	Sympathomimetic	Oral; 15–30 mg once daily
Orlistat	Pancreatic lipase inhibitor	Oral; 120 mg three times daily

Approved for pediatric/adolescent use#

*The exact mechanisms of action for weight management are not fully understood. Information from U.S. product labels, except where noted; †The FDA identifies Gelesis100 oral superabsorbent hydrogel as a device similar to ingestible balloons that are delivered in the form of a "pill"; ‡Not approved for long-term use; # Phentermine is reserved for short-course therapy for adolescents ≥16 years old, phentermine and topiramate extended-release capsules are approved for patients aged ≥12 with a BMI in the 95th percentile or greater when standardized for age and sex.
The data supporting these tables are derived from the Prescribing Information labelling approved by the US Food and Drug Administration.
GABA, gamma-aminobutyric acid; GLP-1, glucagon-like peptide-1; SR, sustained-release.
1. Bray GA et al. Lancet 2016;387:1947–1956; 2. Grunvald E et al. Gastroenterology. 2022;163:1198–1225; 3. Tirzepatide company announcement. Available at: https://investor.lilly.com/node/47701/pdf. Accessed September 2023; 4. Samms RJ et al. Trends Endocrinol Metab. 2020;31:410–421. Additional references in slide notes.

Update in progress

CURRENT PHARMACOTHERAPY: OVERVIEW



The data supporting these tables are derived from the Prescribing Information labeling approved by the U.S. Food and Drug Administration.
*Data from randomized controlled trials >52 weeks in duration; †Assuming the average patient in the orlistat and placebo groups weighed 100 kg at baseline.
Adapted from Bray GA et al. Lancet 2016;387:1947–56. Additional references in slide notes.

Semaglutide: safety and benefits

Adverse events: Most common adverse events (incidence ≥5%)

- Nausea
- Vomiting
- Diarrhea
- Constipation
- Injection site reactions
- Headache
- Hypoglycemia in patients with T2D

- Lowers BP
- Improves cholesterol
- Improves blood sugar
- Prevents further MACE events in those with established CV disease
- Can use in adults and children 12 and older

T2D, type 2 diabetes.
Wegovy™ (Semaglutide 2.4 mg) Prescribing Information. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/215256s000lbl.pdf. Accessed August 2022.

Tirzepatide: GIP/GLP-1; safety and benefit

Adverse events: Most common adverse events (incidence ≥5%)

- Nausea
- Vomiting
- Diarrhea
- Constipation
- Abdominal pain

- Injection site reactions
- Fatigue
- Dyspepsia

- Improves cholesterol
- Improves BP
- Improves Blood glucose
- *Reminder: contraception*

Prescribing Information. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/215256s000lbl.pdf.

WARNING: RISK OF THYROID C-CELL TUMORS

In rats, GLP-1/GLP medications caused dose-dependent and treatment-duration-dependent thyroid C-cell tumors at clinically relevant exposures. It is unknown whether these medications cause thyroid C-cell tumors, including medullary thyroid carcinoma (MTC) in humans.

Contraindicated in patients with a personal or family history of MTC or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2).

BLACK BOX WARNING

SURGICAL INTERVENTIONS

CANDIDATES FOR BARIATRIC SURGERY

Indications to undergo bariatric surgery:[1]

Not responding to past nonsurgical weight loss attempts

BMI is ≥35 kg/m^2 regardless of the presence, absence or severity of comorbidities*

OR

- BMI of 30–34.9 kg/m^2 for individuals with metabolic disease
- BMI ≥27.5 kg/m^2 in the Asian population
- Appropriately selected children and adolescents with class II or III obesity

Relative contraindications for bariatric surgery:[2,3]

- Severe heart failure
- Unstable coronary artery disease
- End-stage lung disease
- Active cancer treatment
- Portal hypertension
- Drug/alcohol dependency
- Decompensated cirrhosis

Given the complexity of the disease of obesity, candidates for bariatric and metabolic surgery should be evaluated by a multidisciplinary team with access to medical, surgical, psychiatric and nutritional expertise[1,4]

*Per the 2022 American Society for Metabolic and Bariatric Surgery (ASMBS) and International Federation for the Surgery of Obesity and Metabolic Disorders (IFSO).
BMI, body mass index; GI, gastrointestinal; OA, osteoarthritis; T2D, type 2 diabetes.

1. Eisenberg D et al. Surg Obes Relat Dis. 2022;18:1–12; 2. Stahl JM and Malhotra S. Obesity surgery indications and contraindications. Available at: https://www.ncbi.nlm.nih.gov/books/NBK513285/, Accessed May 2023; 3. Rinella ME et al. Hepatology. 2023;77:1797–1835; 4. ElSayed NA et al. Diabetes Care. 2023;46:S128–S139.

METABOLIC SURGERY IS THE MOST EFFECTIVE INTERVENTION FOR SEVERE OBESITY

After metabolic surgery, patients may achieve:

- Reduction in overall mortality[1–3]
- Decreased CVD risk factors and incidence of CVD[1,3]
- Remission of albuminuria and early-stage CKD[4]
- Significant and durable weight loss[1,2] (>15% weight loss for ≥10 years)[2]
  with individual variability in weight loss response[5]
- Delay/prevention of type 2 diabetes and reduced need for antihyperglycemic medicine[1,3,6]
- Decreased risk of hormone-related cancer development.
  (in women, 42% decrease in overall cancers and a 50% decrease in endometrial cancers)[3,7]

Among patients with MASH and obesity, bariatric surgery, compared with nonsurgical management, was associated with a significantly lower risk of incident major adverse liver outcomes and MACE*[8]

Comparatively, patients lost more weight with RYGB than with SG and AGB. However, RYGB has the highest 30-day rate of major adverse events[9]

*MACE encompasses all-cause mortality, coronary artery events, cerebrovascular events, heart failure, nephropathy and atrial fibrillation.
AGB, adjustable gastric band; CKD, chronic kidney disease; CVD, cardiovascular disease; MACE, major adverse cardiovascular events; MASH, metabolic dysfunction-associated steatohepatitis; RYBG, Roux-en-Y gastric bypass; SG, sleeve gastrectomy.

1. ElSayed NA et al. Diabetes Care. 2023;46:S128–S139; 2. El Ansari W and Elhag W. Obes Surg. 2021;31(4):1755–1766; 3. Sjöström L. J Int Med. 2013;273(3):219–234; 4. Cohen RV et al. JAMA Surg. 2020;155:e200420; 5. Courcoulas AP et al. JAMA Surg. 2018;153:427–434; 6. Schauer PR et al. N Engl J Med. 2017;376:641–651; 7. Bruno DS and Berger NA. Ann Transl Med. 2020;8:S13; 8. Aminian A et al. JAMA. 2021;326:2031–2042; 9. Arterburn D et al. Ann Intern Med. 2018; 169:741–750.

VERTICAL SLEEVE GASTRECTOMY (VSG)

A laparoscopic longitudinal resection of 75–80% of the stomach to an ideal size of 150 mL (permanent)[1]
Ideal postoperative size preserves the stomach vagal innervation[1]
Reduces food and calorie intake[1,2]
Favorable changes in gut hormones involved in hunger, satiety and blood glucose control[2]
Evidence suggests improvement in type 2 diabetes even independently of weight loss[2]
Leads to 15–30% weight loss[3]
GERD is a large factor in determining if VSG or RYGB is best for a patient
Patients with GERD are known to be poor candidates[2]

GERD, gastroesophageal reflux disease; RYBG, Roux-en-Y gastric bypass; VSG, vertical sleeve gastrectomy.

1. Piché MÈ et al. Can J Cardiol. 2015;31:153–166; 2. ASMBS Bariatric Surgery Procedures 2014. Available here, Accessed May 2023; 3. Lager CJ et al. Obes Surg. 2017;27:154–161.

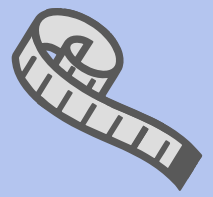
ROUX-EN-Y GASTRIC BYPASS (RYGB)

Favorable changes in gut hormones and neuroendocrine signaling involved in hunger, satiety and induction of type 2 diabetes[1] is responsible for the weight reduction[1,2]
Reduces the stomach to a small pouch size of ~30 mL and connects it directly to a more distal section of the small intestine (permanent)[1]
Reduces food and calorie intake[1]
Bypasses a section of the small intestine, inhibiting absorption[1,3]
Requires biochemical surveillance of nutritional status and bariatric surgery follow-up every 3 or 6 months (during first 2 years post surgery)[2]
Roux-en-Y gastric bypass leads to weight loss of 30–35% and has been shown to be more effective than VSG[4]
Resolves GERD in patients with known GERD prior to surgery[1]

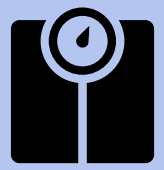
GERD, gastroesophageal reflux disease; RYBG, Roux-en-Y gastric bypass; VSG, vertical sleeve gastrectomy.

1. ASMBS Bariatric Surgery Procedures 2014. Available here, Accessed May 2023; 2. Celiker H. Med Hypotheses. 2017;107:81–89; 3. Piché MÈ et al. Can J Cardiol. 2015;31:153–166;
4. Lager CJ et al. Obes Surg. 2017;27:154–161.

PHARMACOTHERAPY FOR OBESITY AS AN ADJUNCT TO BARIATRIC SURGERY



SG patients given phentermine/topiramate 3 months preoperatively and 2 years postoperatively had greater weight loss at 2 years than SG patients given no weight loss medications.[1,2]



Preliminary studies in postoperative bariatric surgery patients suggest that GLP-1 RAs reduce postprandial hypoglycemic episodes and improve glycemic variability.[3] They also facilitate substantial reversal of post-bariatric surgery weight regain.[4]

GLP-1, glucagon-like peptide 1; RA, receptor agonist; SG, sleeve gastrectomy.

1. Vivus, Inc. Available here. Accessed May 2023; 2. Clinicaltrials.gov. Available here. Accessed May 2023; 3. Llewellyn DC et al. Obesity 2023; 31:20-30;
4. Jensen AB et al. Obes Surg 2023;33:1017-25.

THERE IS NO EASY FIX!!

HYPERLIPIDEMIA MANAGEMENT

LIFESTYLE, AND PHARMACOLOGICAL APPROACHES

WHY DO LIPIDS MATTER?

"These risk factors are associated with insulin resistance, which is related to coronary heart disease and diabetes. Cardiovascular risk factors often seen in conjunction with the metabolic syndrome include hypertension, atherogenic dyslipidemia, a prothrombotic state, and in many patients, glucose intolerance. Two predisposing conditions, obesity and physical inactivity, both of which are recognized as CVD risk factors, often accompany the metabolic syndrome."

Diabetes Mellitus: A Major Risk Factor for Cardiovascular DiseaseA Joint Editorial Statement by the American Diabetes Association; the National Heart, Lung, and Blood Institute; the Juvenile Diabetes Foundation International; the National Institute of Diabetes and Digestive and Kidney Diseases; and the American Heart Association**Originally published**7 Sep 1999https://doi.org/10.1161/01.CIR.100.10.1132Circulation. 1999;100:1132–1133

DEFINITION OF PRIMARY VS SECONDARY PREVENTION

- **Primary Prevention**: lowering LDL to reduce atherosclerotic cardiovascular disease (ASCVD) risk in those without established cardiovascular disease
- **Secondary Prevention**: Lowering LDL to reduce ASCVD risk in those **with** established cardiovascular disease to prevent a subsequent events. Divided into: at very high-risk groups and at low-risk group.

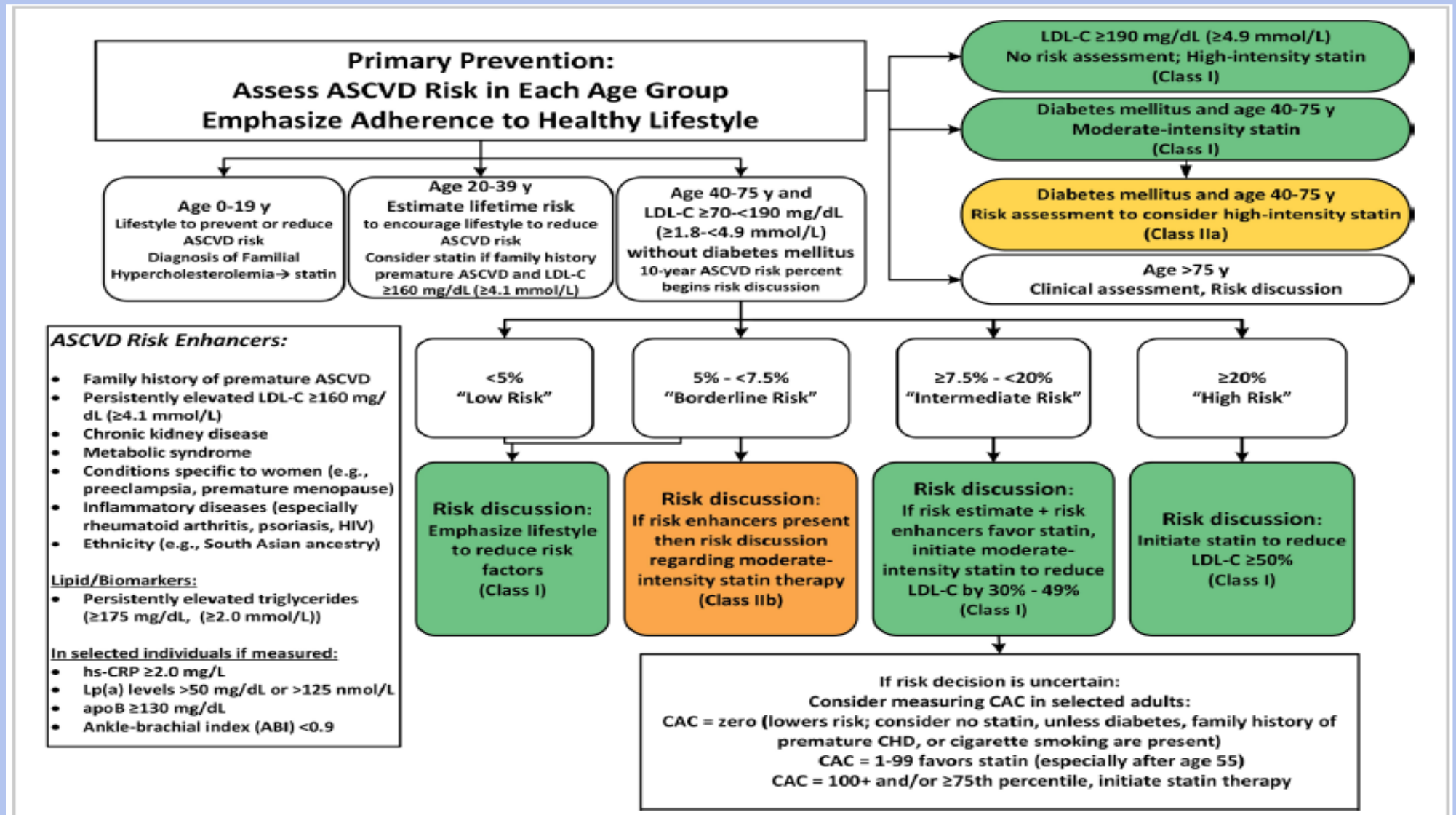


Figure 2. Primary Prevention

apoB indicates apolipoprotein B; ASCVD, atherosclerotic cardiovascular disease; CAC, coronary artery calcium; hsCRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; and Lp(a), lipoprotein (a).

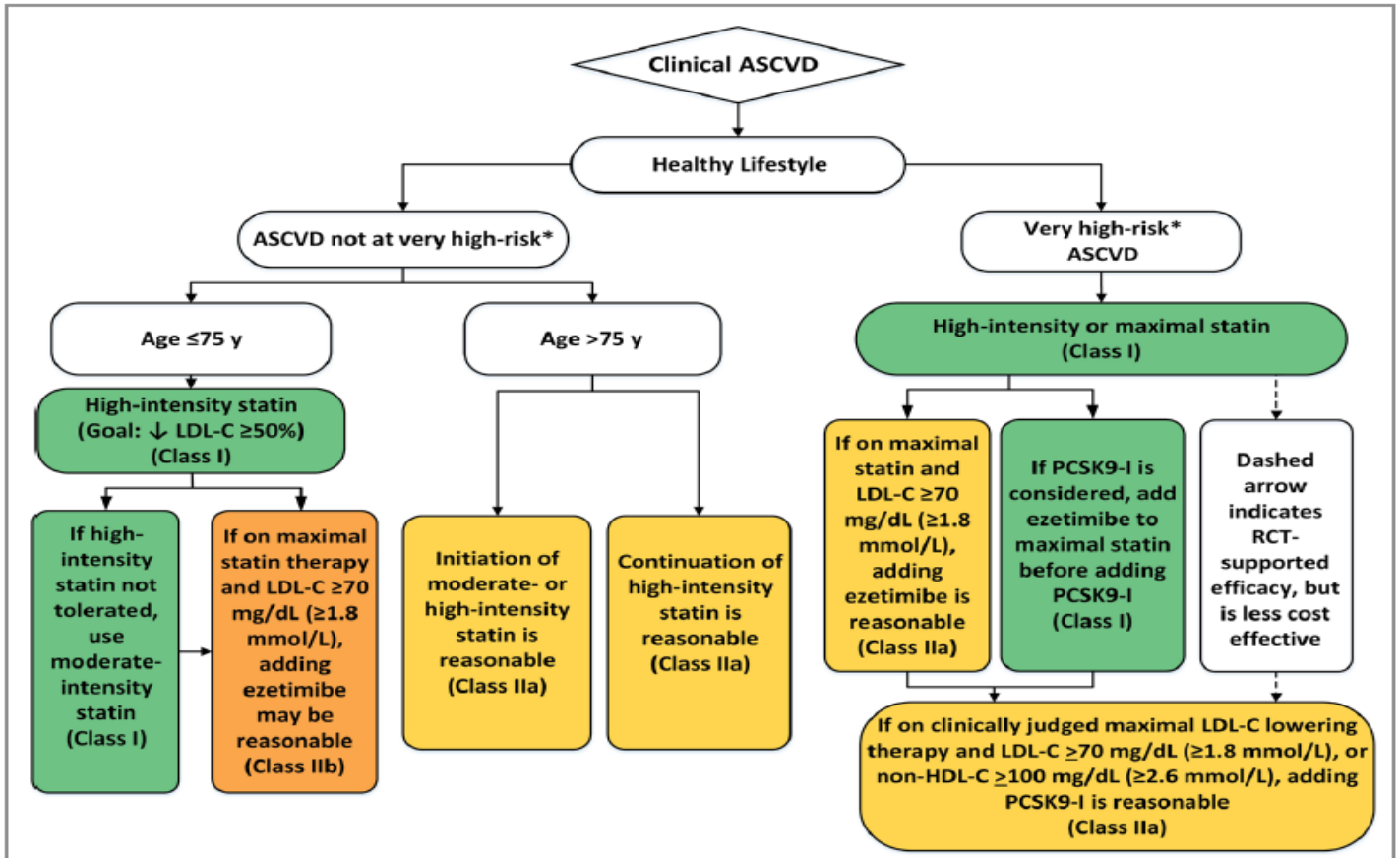


Figure 1. Secondary Prevention

ACS indicates acute coronary syndrome; ASCVD, atherosclerotic cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; and PCSK9i, PCSK9 inhibitor. *Very high risk includes a history of multiple major ASCVD events or 1 major ASCVD event and multiple high-risk conditions.

Definition of Very High Risk ASCVD

>1 Major ASCVD Event

- Recent ACS (within past 12 months)
- History of MI (other than recent ACS above)
- History of ischemic stroke
- Symptomatic PAD (claudication with ABI < 0.85 or previous revascularization or amputation)

Or

1 Major Event + >1 High Risk Conditions

- Age ≥ 65 years
- Familial hypercholesterolemia
- Prior CABG or PCI outside of the major ASCVD event
- Diabetes mellitus
- Hypertension
- CKD (eGFR 30-59 ml/min/1.73 m2)
- Current smoking
- Persistently elevated LDL-C ≥100 mg/dl (≥2.6 mmol/L) despite maximally tolerated statin therapy and ezetimibe
- History of congestive HF

V. Lifestyle Recommendations

Intensity Stratified by Degree of CV Risk, Type of Dyslipidemia, and Related Complications

	General recommendations	Initial considerations	Implementation
Nutrition	Whole-food, plant-based, Mediterranean, and DASH diets recommended	Nuts, seeds, and avocado OK if no adiposity. If animal products consumed, order of preference: fish (especially fatty fish); lean meat and skinless poultry; limit processed foods	Focus on whole grains, legumes, vegetables, and fruits Avoid added sugars, salt, and fat Limit low-fiber grains and potatoes ("white starches"), fried foods, fast foods, and alcohol (especially if high triglycerides) Limit calories for 5-10% weight reduction[a] (if overweight/obesity)
Physical activity	Physical activity ≥3 times/week Reduce/break up prolonged sitting	Start with low duration and intensity of activity and increase slowly until activity goals are met	150-300 minutes/week of moderate-intensity or 75-150 minutes/week of high-intensity activity Resistance training ≥2 times/week
Sleep	Sleep duration 6-8 hours/night	Screen for and treat sleep apnea	Lifestyle modification with weight loss as needed Avoid sleeping pills
Mental health	Assess for depression, anxiety, and substance abuse	Lifestyle modification Address substance abuse Refer to mental health professionals as needed	Encourage community involvement (community centers, charitable organizations, schools, houses of worship, etc) and use of support services
Smoking	No tobacco or nicotine related products	Avoid passive exposure to tobacco smoke	Nicotine in any formulation is associated with atherosclerosis

[a] See AACE/ACE Comprehensive Clinical Practice Guidelines for Medical Care of Patients with Obesity and AACE/ACE Treatment Algorithm for the Medical Care of Patients With Obesity.

Abbreviations: CV = cardiovascular; DASH = Dietary Approaches to Stop Hypertension.

HMG-COA Reductase Inhibitors

Otherwise known as “statins”

Mechanism of Action	Dose	Common side effects	Safety Concerns	Monitoring
• Inhibits 3-hydroxy-3-methlglutaryl-coenzyme A reductase • Inhibiting cholesterol synthesis in the liver • Leads to upregulation of hepatic LDL receptors • **21-55% reduction in LDL** • **6-30% Triglyceride reduction** • **2-10% increase in HDL**	• 5-80mg depending on drug • Simvastatin dose 40mg or less. • **Simvastatin 20mg or less if on Nifedipine or ranolazine.**	• Myalgias • Arthralgia • weakness • Headache • Abdominal pain • Hyperglycemia • Nausea • Constipation • **ALT/AST elevation**	• **Rhabdomyolysis <5% - check CK elevation.** • Drug interactions with CYP450 inhibitors • May need adjustment for renal issues depending on drug choice. • Do not use with acute hepatic failure or decompensated cirrhosis.	• Check liver function before initiation of therapy • Monitor myopathies. • New-onset diabetes

CHOLESTEROL ABSORPTION INHIBITORS

Ezetimibe

Mechanism of Action	Dose	Common side effects	Safety Concerns	Monitoring
• Inhibits intestinal absorption of cholesterol • Decreases delivery of cholesterol to the liver • Decreases **Apolipoprotein B 11-16%** • **In combination with statins reduces LDL up to 25%.**	• 10mg	• Diarrhea • Arthralgia • Myalgia • fatigue	• Rhabdomyolysis rare but more common when co-administered with statins or fenofibrate. • No renal or hepatic adjustments needed.	• No extra monitoring needed.

ADENOSINE TRIPHOSPHATE-CITRATE LYASE INHIBITORS

bempedoic acid

Mechanism of Action	Dose	Common side effects	Safety Concerns	Monitoring
• Inhibits adenosine triphosphate-citrate lyase protein • Increases LDL-C clearance. • ACL inhibition activated in the liver and to a small amount the kidneys but not in skeletal or adipose tissue • **Lower LDL-c by 21%** • **Up to 38% lowering with Ezetimibe**	• 180mg daily • Started after max tolerated statin • **New indication for primary and secondary prevention of cardiac events in patients unable to take statins** • **Second indication for LDL lowering**	• URI • Muscle spasms • Hyperuricemia • Gout • Back and extremity pain	• Tendon rupture • **Don't start in those with history of tendon disorder** • **Caution in renal failure or history of gout.** • Cholelithiasis.	• **Monitor uric acid levels** • eGFR > 30 • Cirrhosis Child-Pugh Class A-B no dose adjustment needed. • Monitor LFT's

PCSK9 INHIBITORS (PROPOTEIN CONVERTASE SUBTILISKIN/KEXIN TYPE 9)

alirocumab, evolocumab

Mechanism of Action	Dose	Common side effects	Safety Concerns	Monitoring
• Inhibits PCSK9 binding with LDLRs • Increasing the number of LDLR available to clear LDL helping to lower LDL-Calc levels. • **Lowers LDL-Calc by 48-71%** • **Increases HDL by 49-58%** • **Lowers Apo B by 42-55%**	• Dose every 2 weeks or every month Subcutaneous. • Used after max tolerated dose of statin for **high-risk ASCVD after 1 previous event.**	• Nasopharyngitis • URI • UTI • Myalgia • Backpain • angioedema	• Site reactions • Must keep it refrigerated. • Latex sensitivity with evolocumab	• No extra monitoring needed.

PCSK9 SMALL INTERFERING RIBONUCLEIC ACIDS

inclisiran

Mechanism of Action	Dose	Common side effects	Safety Concerns	Monitoring
• SiRNA direct catalytic breakdown of mRNA for PCSK9 synthesis binding to LDL receptors. • Increases LDL receptor recycling and decreasing circulating LDL. • **Lowers LDL by at least 50% (with statin)**	• 284mg SC every 3 months twice then every 6 months. • To be given with statins. • No renal or hepatic adjustments	• Inj. site reactions • Arthralgia • bronchitis	• No serious reactions or concerns reported	• No extra monitoring needed.

FIBRIC ACID DERIVATIVES

gemfibrozil, fenofibrate, fenofibric acid

Mechanism of Action	Dose	Common side effects	Safety Concerns	Monitoring
• Inhibits peripheral lipolysis • Lowers VLDL-C and LDL-C • Transforming into less atherogenic forms of LDL. • **Decreases TG 20-35%** • **Increases HDL 6-18%**	• Gem: 600 twice daily. • Fen: 40-160mg daily • Fen acid: 35-105mg daily • ER dose 135mg daily. • Renal dosing for GFR 35-59 • Stop if GFR< 30 • **Do not use if hepatic disease**	• GI symptoms • Abdominal pain • Elevated liver enzymes • Myalgia with statins • Elevated ck levels • Fibrates can increase serum creatinine levels	• Renal or hepatic impairment • Caution: if on anticoagulants- increase bleeding	• Baseline creatinine and liver function • **Period monitoring of renal and liver function.** • **CBC every 12 months**. • HDL-C 2 months after start.

OMEGA-3 FATTY ACIDS

Icosapent ethyl

Mechanism of Action	Dose	Common side effects	Safety Concerns	Monitoring
• Reduce hepatic VLDL lipoprotein triglyceride synthesis and increasing triglyceride clearance from circulating VLDL. • **Decreases Trig 27-45%, VLDL-C 20-42%, Apo B 4%.** • Other ethyl esters may increase LDL-C 45%	• 2gm twice daily • No renal or hepatic adjustment	• arthralgia • Increase bleeding • Constipation • Nausea • Taste perversion	• Increased bleeding risk or prolonged bleeding times. • Caution in those with fish/shellfish sensitivities • Increase frequency of symptomatic afib/flutter with ethyl esters in 1st 2-3 months after initiation.	• Periodic ALT/AST monitoring

THANK YOU