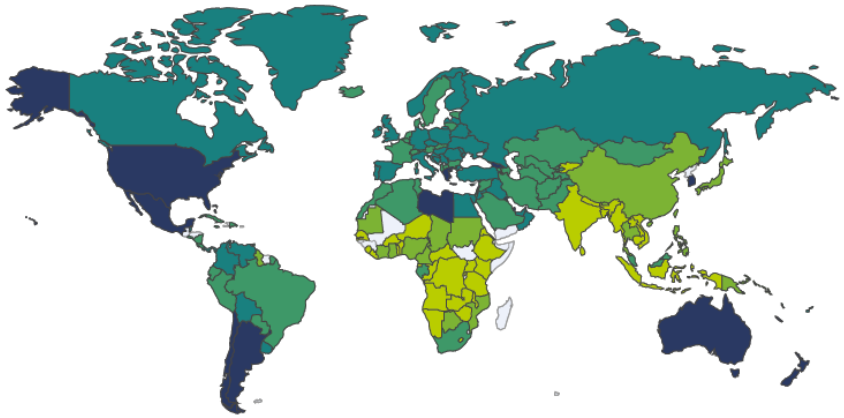
New insights into the treatment of obesity

Summary of key aspects of the livestream
22 March 2023

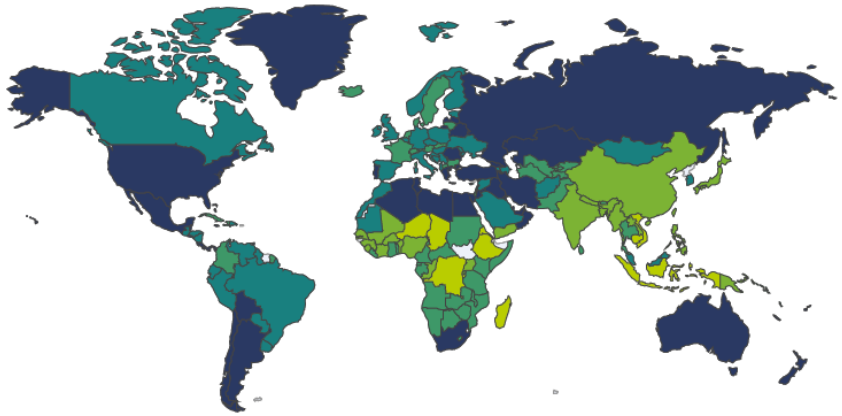
Global prevalence of obesity

World Obesity Federation: World Obesity Atlas 2023

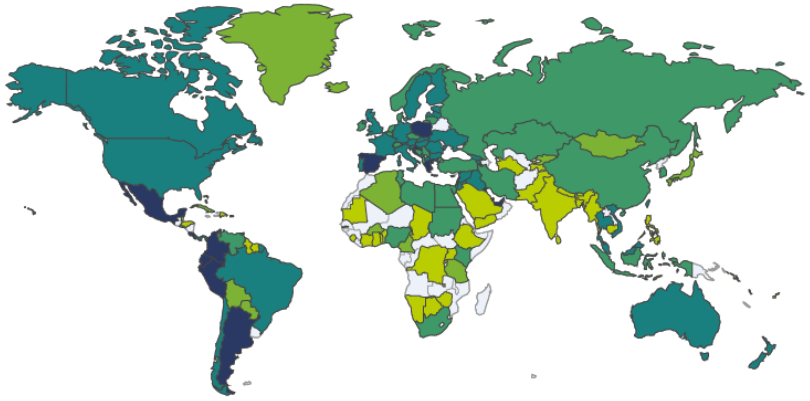
Men living with obesity, Newest available data



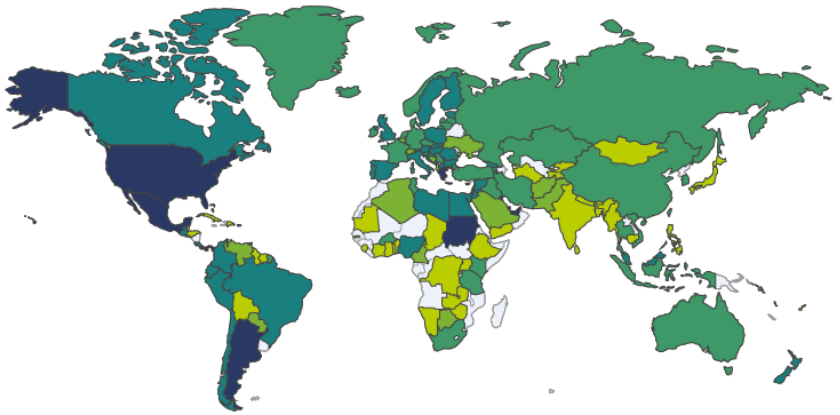
Women living with obesity, Newest available data



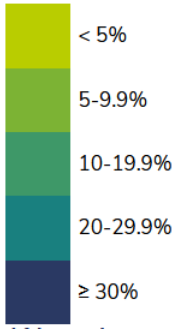
Boys living with either overweight or obesity, Newest available data



Girls living with either overweight or obesity, Newest available data



Prevalence (%)



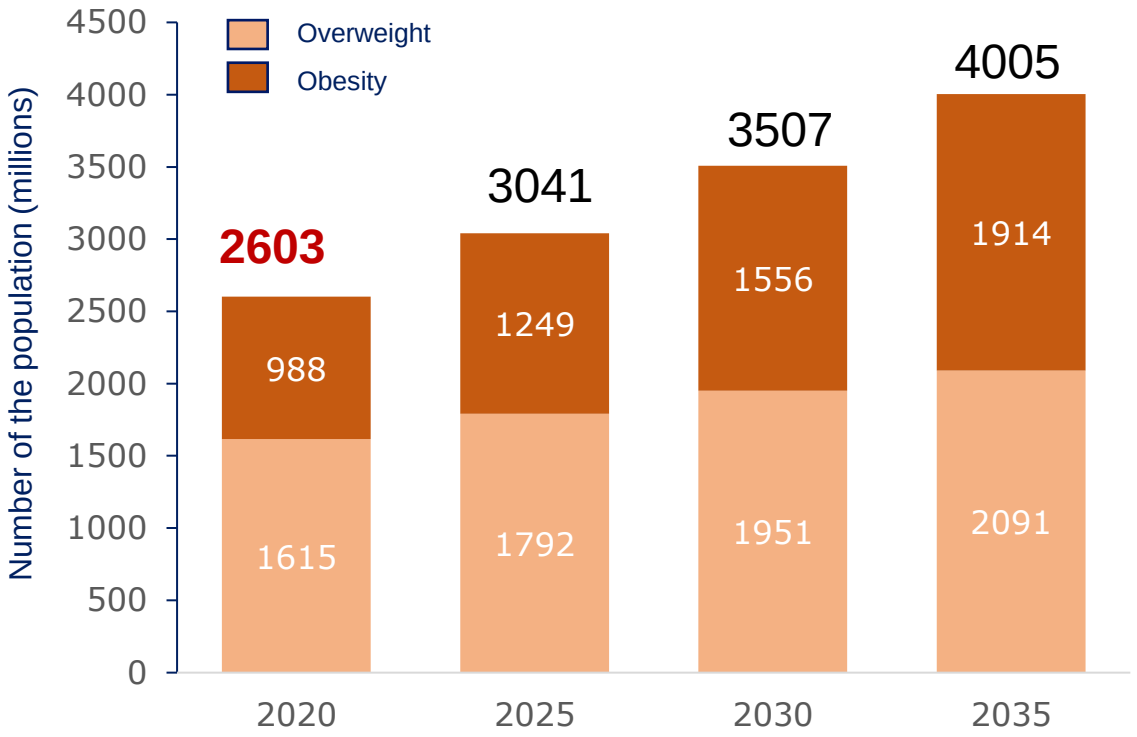
1. World Obesity Federation: Men living with obesity. 2. World Obesity Federation: Women living with obesity. 3. World Obesity Federation: Boys living with obesity. 4. World Obesity Federation: Girls living with obesity Newest available data. Available from: https://data.worldobesity.org/maps/?area=trends&group=M&year=2020. Accessed Mar 2023

Rising prevalence of overweight/obesity

World Obesity Federation: World Obesity Atlas, 2023

988

million people
live with obesity



ANNUAL INCREASE IN ADULT OBESITY 2020-2035

3.0%

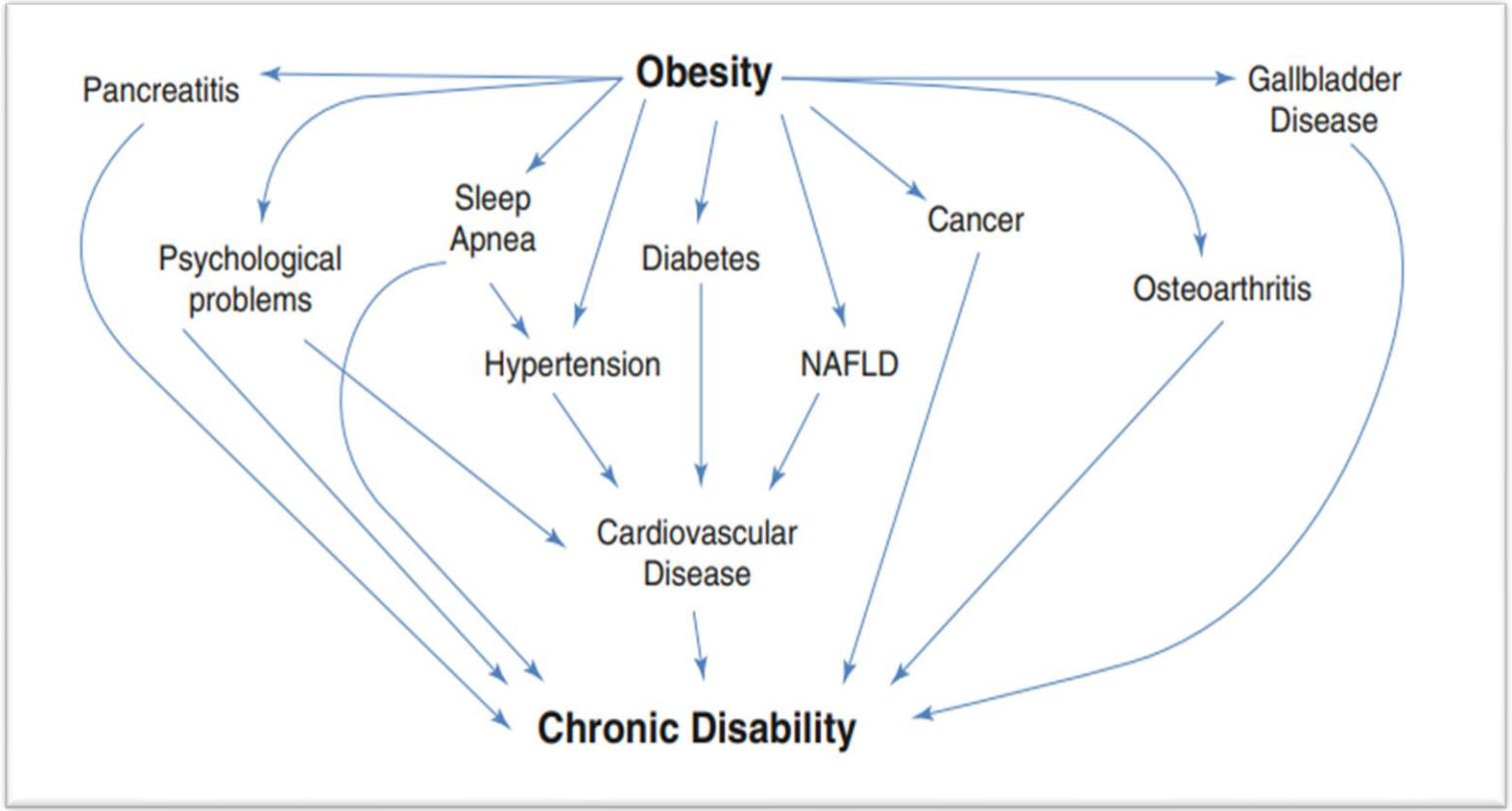
ANNUAL INCREASE IN CHILD OBESITY 2020-2035

5.1%

Figures exclude children under 5 years old.

World Obesity Federation: World Obesity Atlas, 2023. Available from: https://www.worldobesity.org/resources/resource-library/world-obesity-atlas-2023. Accessed Mar 2023.

Obesity strongly associated with many comorbidities and disability



Increased risk of comorbidities

Comorbidity	RR male	RR female
Type 2 diabetes	6.7 [5.6–8.2]	12.4 [9.0–17.1]
Coronary artery disease	1.7 [1.5–2.0]	3.1 [2.8–3.4]
Congestive heart failure	1.8 [1.2–2.6]	1.8 [1.1–3.0]
Hypertension	1.8 [1.5–2.2]	2.4 [1.6–3.7]
Stroke	1.5 [1.3–1.7]	1.5 [1.3–1.7]
Osteoarthritis	4.2 [2.7–6.4]	2.0 [1.9–2.0]
Various cancer types	Type dependent	Type dependent

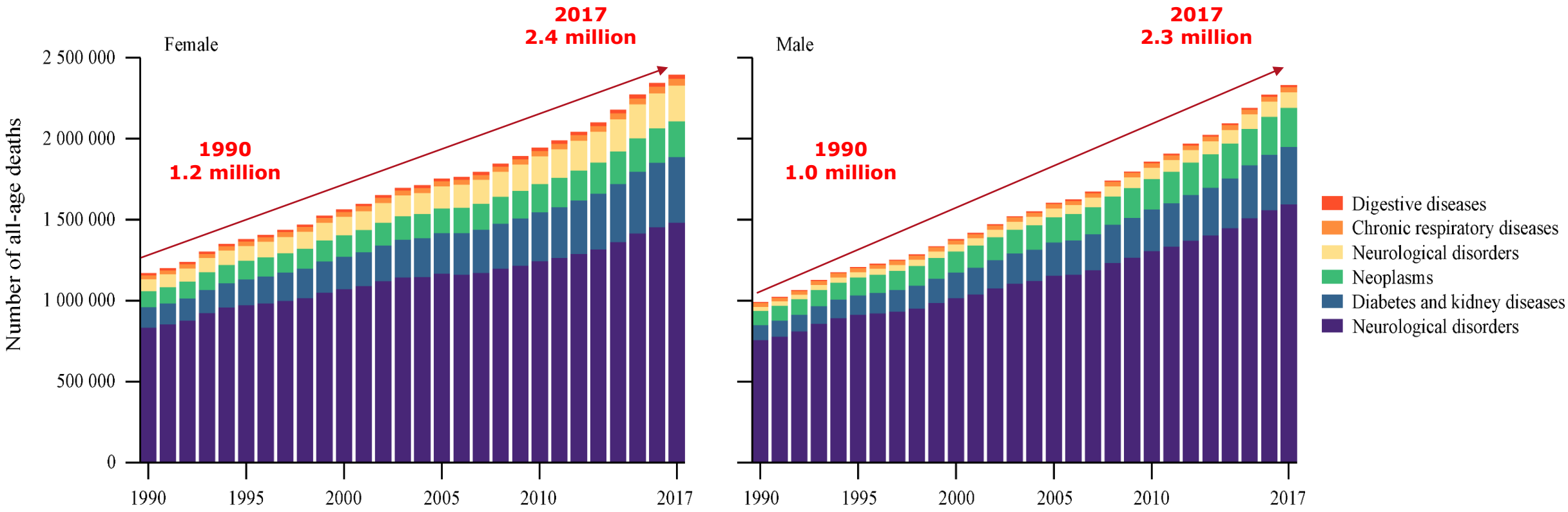
BMI, body mass index; CI, confidence interval; RR, relative risk

Data are meta–analysis [95% CI] for obese (BMI ≥30) versus normal (BMI ≥18.5 to ≤25) weight subjects

Guh DP, et al. BMC Public Health. 2009;9:88.

Emmanuel, J.J., Coppack, S.W. (2016). Health Consequences–Obesity Associated Comorbidities. In: Agrawal, S. (eds) Obesity, Bariatric and Metabolic Surgery. Springer, Cham.

The global deaths attributable to high BMI doubled from 1990 to 2017



Dai H, et al. PLoS Med. 2020 Jul 28;17(7):e1003198.

Weight reductions improve obesity associated co-morbidities

Towards greater weight loss and overall health improvement[1–5]

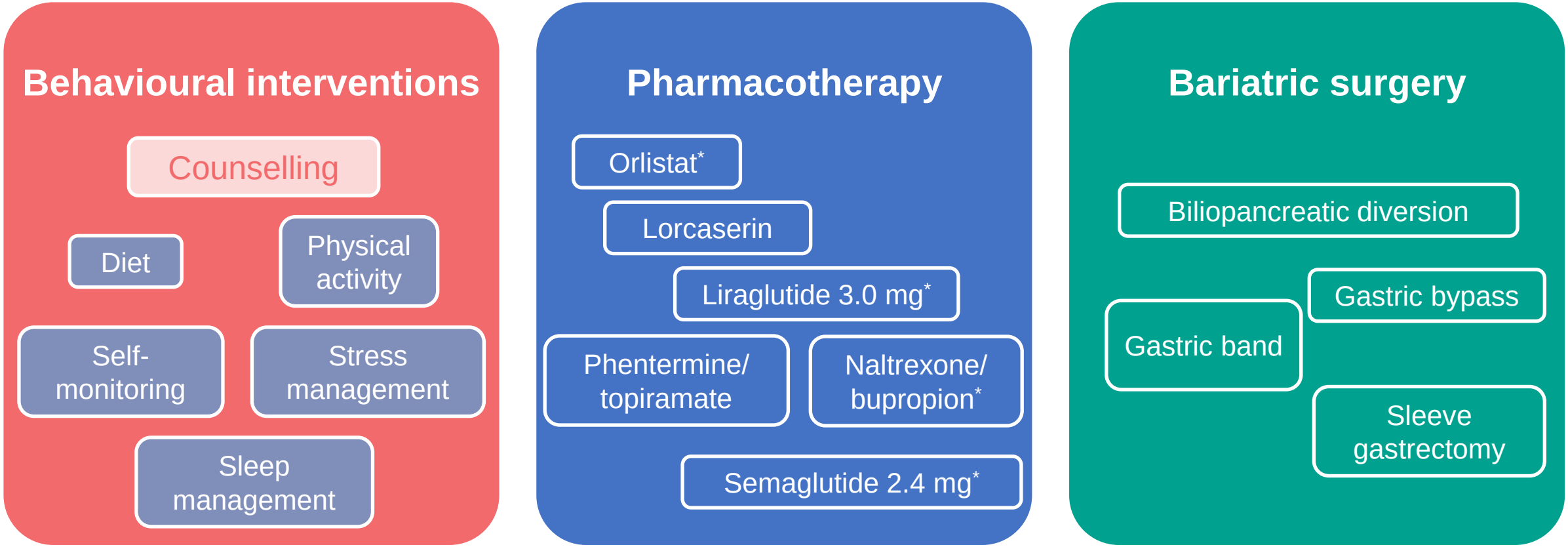
0–5%	5–10%	10–15%	≥15%
Hypertension[1]	Urinary stress incontinence[1]	NASH[1]	Cardiovascular[1] disease
Hyperglycaemia[1]	Prevention of T2D[1]	OSA[1]	NASH[1]
	PCOS[1]	GERD[1]	T2D remission[1,3,5]
	Dyslipidaemia[1]	Knee OA[1]	CV mortality[1,4]
	Asthma/airway disease[1]		HFpEF[1,4,5]
	NAFLD[1]		

Weight loss

CV, cardiovascular; GERD, gastro-esophageal reflux disease; HFpEF, heart failure with preserved ejection fraction; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; OA, osteoarthritis; OSAS, obstructive sleep apnoea syndrome; PCOS, polycystic ovary syndrome; T2D, type 2 diabetes.

[1]Garvey WT, et al. Endocr Pract. 2016;22(Suppl 3):1−203; [2]Look AHEAD Research Group. Lancet Diabetes Endocrinol. 2016;4(11):913−921; [3]Lean ME, et al. Lancet. 2018;391(10120):541−551; [4]Benraoune F, Litwin SE. Curr Opin Cardiol. 2011;26(6):555−561; [5]Sundström J, et al. Circulation. 2017;135(17):1577−1585.

Treatment strategies target distinct phenotypes



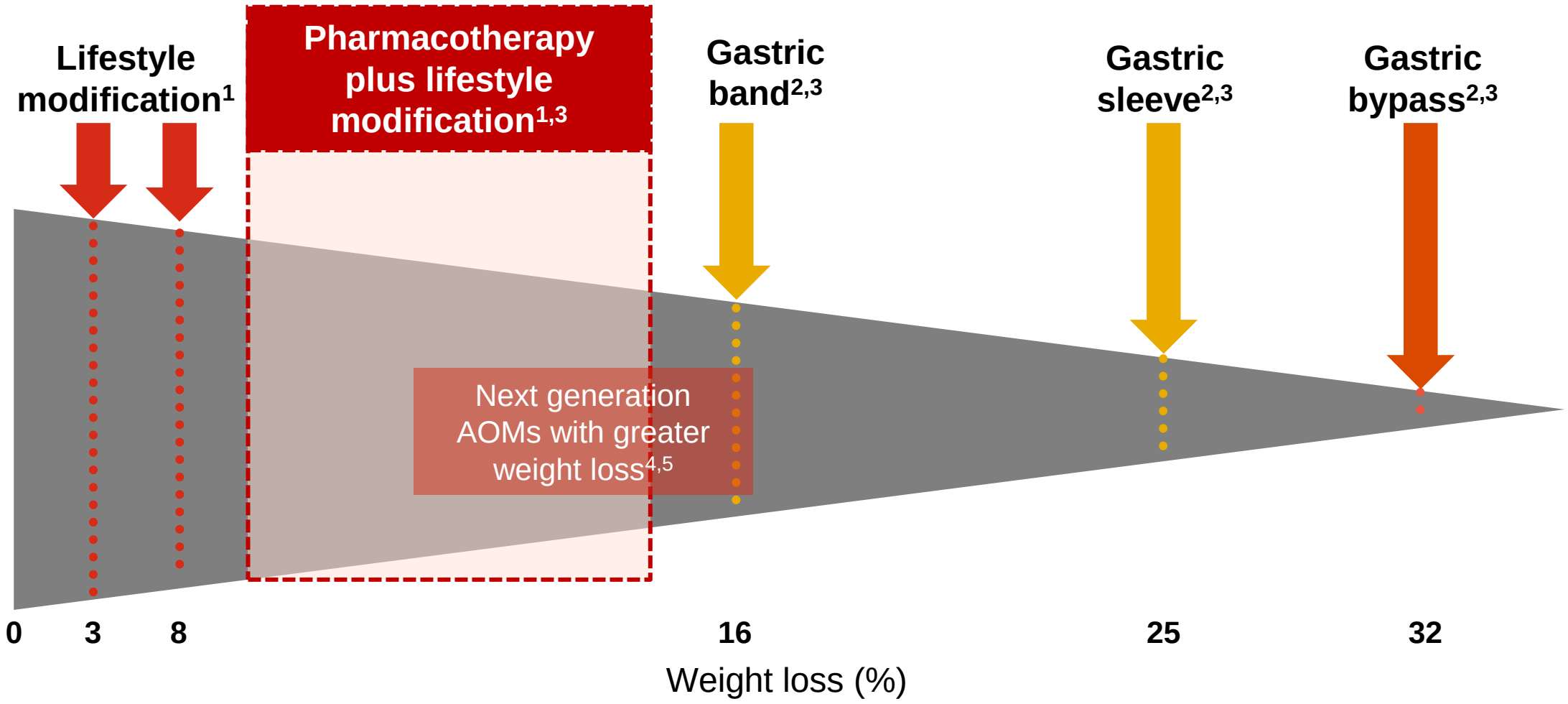
Metabolically healthy obesity
BMI 27 – 33 kg/m²

Obesity with metabolic diseases/risk factors

BMI >40 kg/m²

*May not be approved in all regions for treatment of obesity

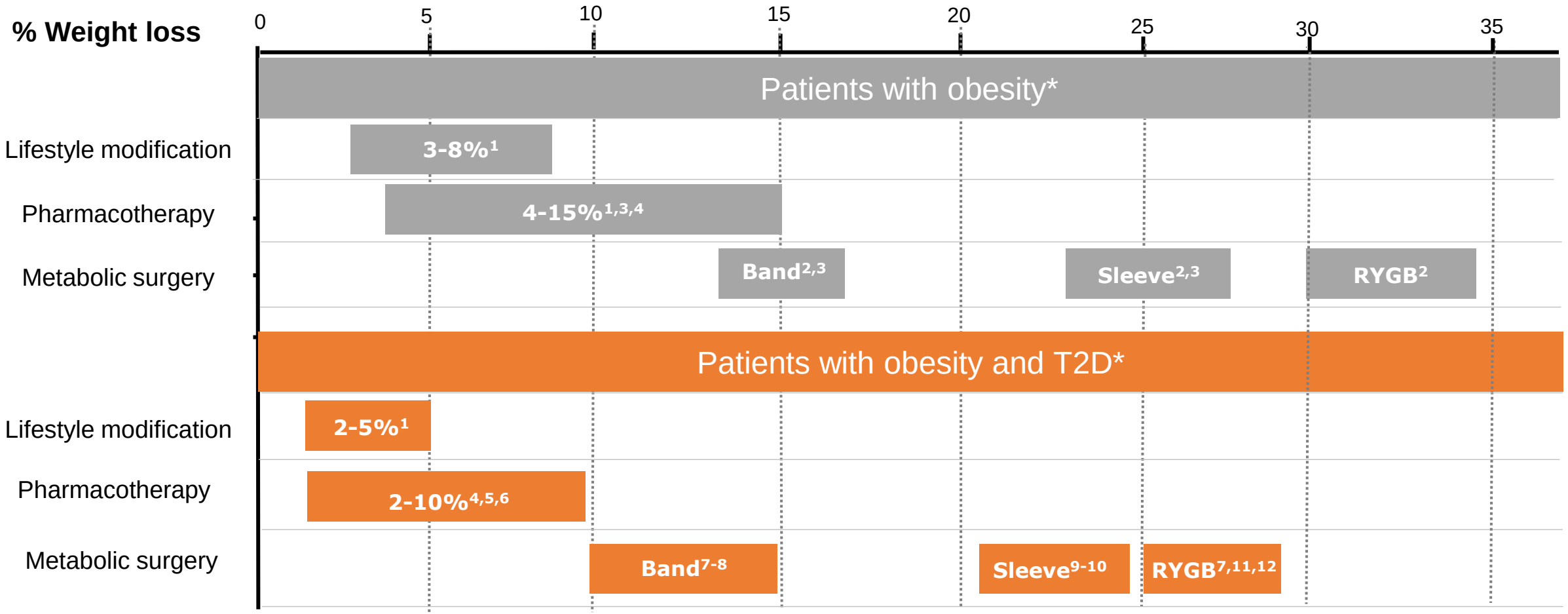
Continuum of weight management in obesity



AOM, anti-obesity medication.

1. Jensen et al. Circulation 2014;129(25 Suppl 2):S102–38; 2. Courcoulas et al. JAMA 2013;310:2416–25; 3. Obesity Drug Outcome Measures: A Consensus Report of Considerations Regarding Pharmacologic Intervention. Available at: http://sphhs.gwu.edu/pdf/releases/obesitydrugmeasures.pdf (accessed Feb 2016);
4. WEGOVY ® Prescribing information Jun 2021; 5. Pilisti E, et al. Metab Clin Exp. 2019;92:170-192.

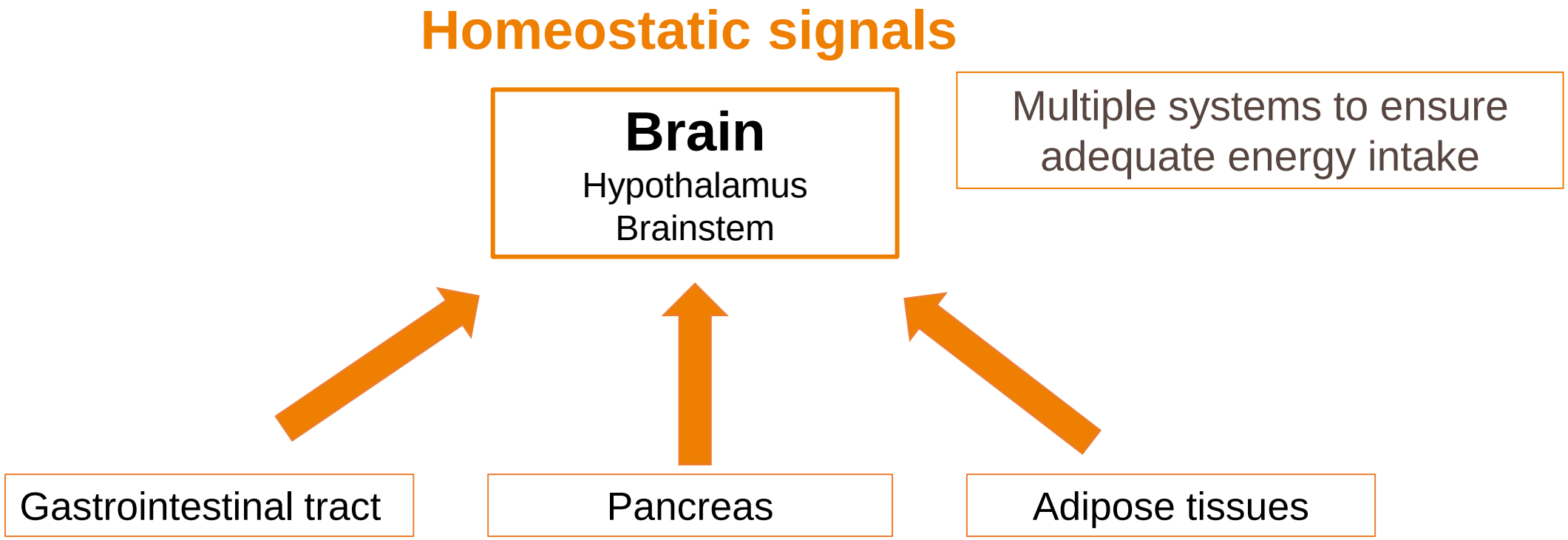
Weight loss in people with obesity impacted by presence of T2D



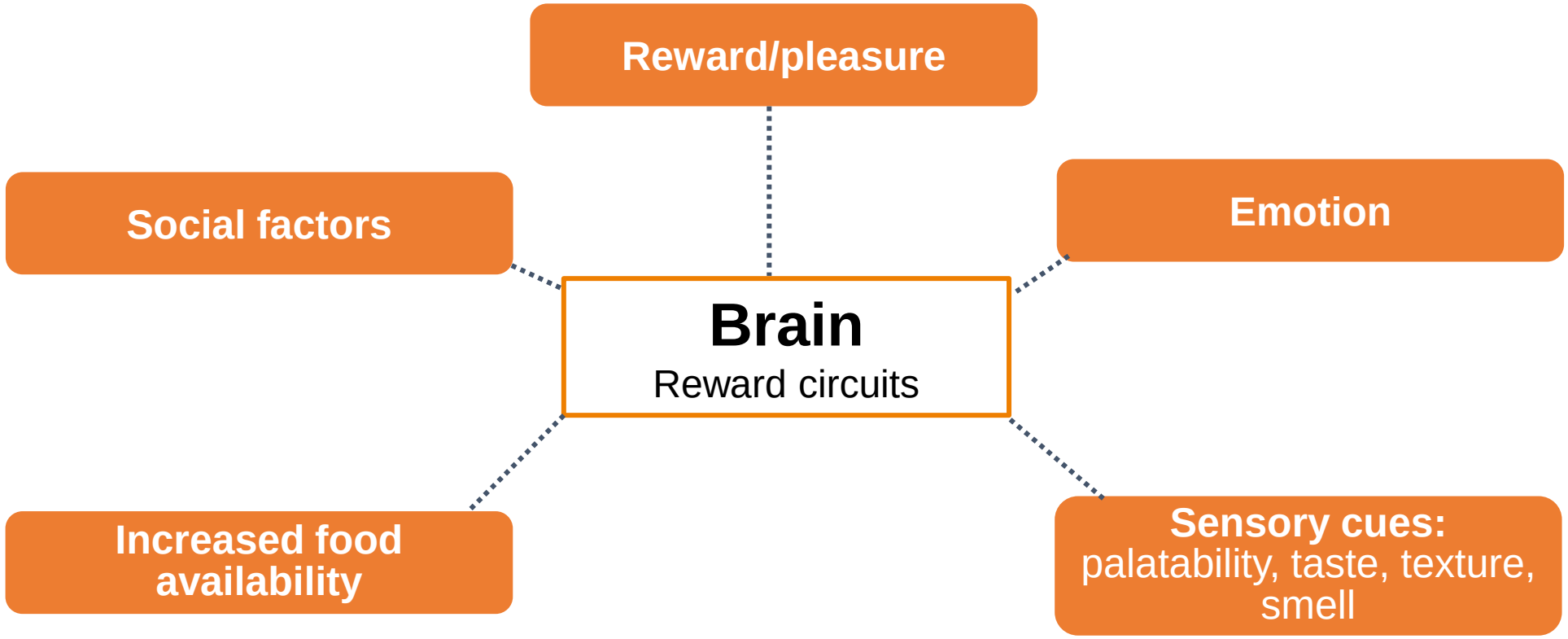
T2D, Type 2 diabetes; RYGB, Roux-en-Y gastric bypass * No head to head trials. Between trial comparisons should be interpreted carefully.

1. Jensen et al. Circulation 2014;129(25 Suppl 2):S102–38; 2. Courcoulas et al. JAMA 2013;310:2416–25; 3. Obesity Drug Outcome Measures: A Consensus Report of Considerations Regarding Pharmacologic Intervention. Available at: http://sphhs.gwu.edu/pdf/releases/obesitydrugmeasures.pdf (accessed Feb 2016); 4. WEGOVY ® Prescribing information Jun 2021 4. Contrave Prescribing Information: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/200063s013lbl.pdf; 5. Qysmia Prescribing Information: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/022580s016lbl.pdf; 6. Wentworth JM, et al. Obes Surg. 2015;25(12):2400-7; 7. Courcoulas AP, et al. JAMA Surg. 2015;150(10):931-40; 8. Abbott S, et al. Surg Obes Relat Dis. 2020 Nov;16(11):1723-1730; 9. Schauer PR, et al. N Engl J Med. 2017;376(7):641-651; 10. Keidar A, et al. Diabetologia. 2013;56(9):1914-8; 12. Hofsø D, et al. Lancet Diabetes Endocrinol. 2019 Dec;7(12):912-924.

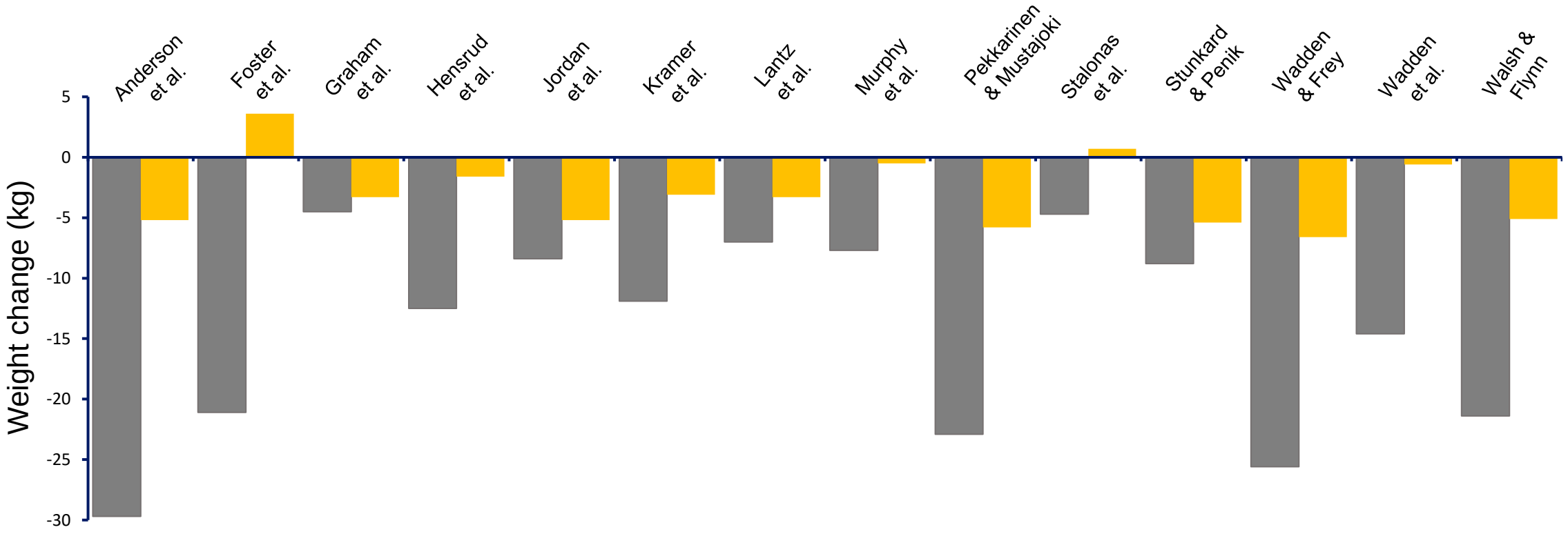
Regulation of energy intake and body weight



Hedonic regulation of energy intake



Lifestyle intervention and weight management



Follow-up range from 4 to 7 years

Mann T, et al. Am Psychol. 2007;62:220–233.

Dieting activates powerful compensatory biological mechanisms that favour weight regain

Reduced energy intake (diet = famine)

- ↑ circulating levels of the appetite-stimulating hormone ghrelin
- ↓ in satiety hormones (GLP-1 and PYY)
- ↑ brain response to food cues in homeostatic and reward regions
- ↓ energy expenditure

Weight regain

Sumithran P, Proietto J. Clin Sci (Lond). 2013;124:231–241.

Bariatric surgery leads to favourable changes in GI signals

- ↓ circulating levels of ghrelin
- ↑ in satiety hormones (GLP-1 and PYY)
- ↓ brain response to food cues in homeostatic and reward regions

Marked sustained weight loss

Sumithran P, Proietto J. Clin Sci (Lond). 2013;124:231–241.

Challenges in obesity treatment

- Better phenotyping for etiology-based (tailored) obesity treatment
- Behaviour interventions are frequently not successful in the long term
- Bariatric surgery is not suitable for many patients
- Effective and safe pharmacotherapies are required as scalable therapy

Emerging pharmacotherapy for weight loss and obesity-related metabolic abnormalities

Gut Hormones

- Long-acting high-dose GLP-1RA
- Dual GLP-1/glucagon coagonist
- Dual GLP-1/GIP coagonist
- Triple GLP-1/glucagon/GIP coagonist
- Oxyntomodulin
- PYY analog
- Amylin mimetics
- Dual amylin/calcitonin coagonist
- Anti-ghrelin vaccine

Nutrient sensor/anorectics

- Leptin analog
- GDF15 mimetics
- GPR55 and GPR 40 receptor (GPCR) agonists

CNS

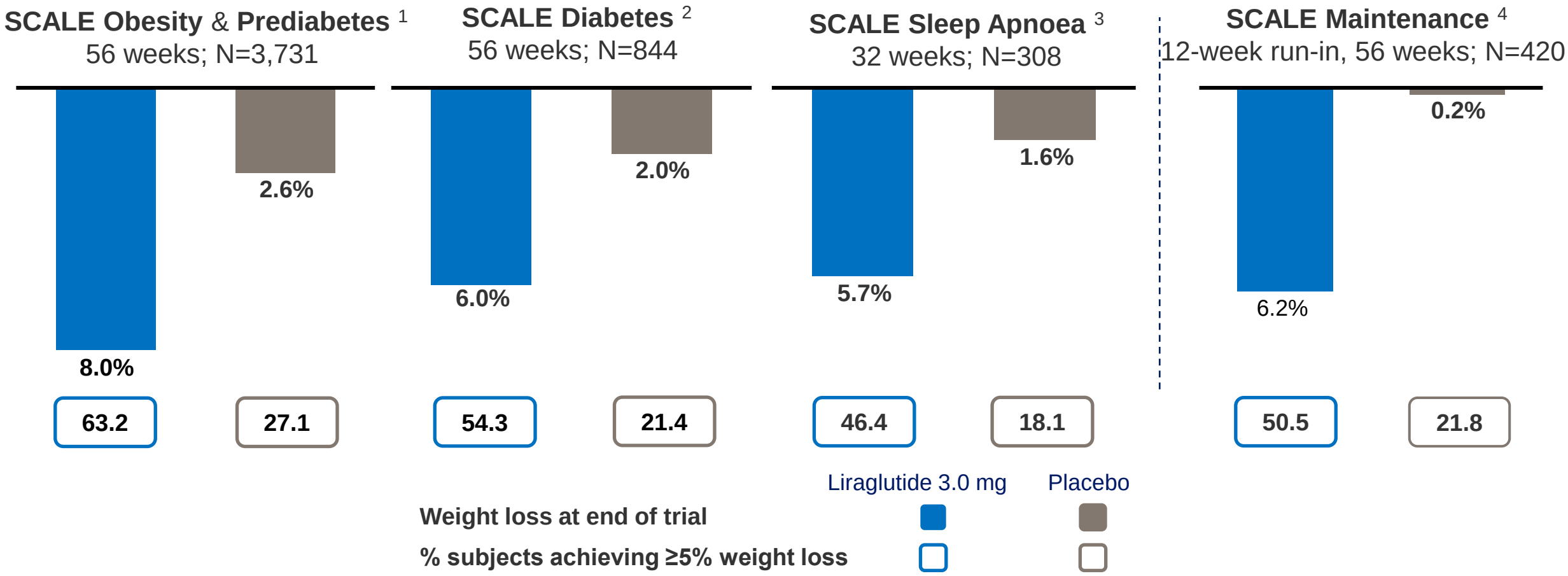
- MC4R agonist
- Y5 receptor inhibitor
- Zonisamide/bupropion
- Triple monamine reuptake inhibitor (dopamine/NE/serotonine)
- Cannabinoid 1 receptor blocker

Energy metabolism

- Methionine aminopeptidase 2 inhibitor
- Farnesold X receptor agonist
- FGF21 receptor agonist
- FGF4 inhibitor
- AMPK activators

O'Neil P., et al. Lancet 2018; Ambery P et al., Lancet. 2018; Frias JP et al., Lancet. 2018; Jall S et al., Mol Metab. 2017; Behary P et al., Diabetes Care. 2019; Le Foll C et al. Diabetes. 2015; Hjuler ST et al., Obesity (Silver Spring). 2016; Altabas V et al., Immunotargets Ther. 2015; Clément K et al. Nat Med. 2018; Mullican SE et al. Nat Med. 2017; Bouyakdan K et al., J Clin Invest. 2019; Collet TH et al, Mol Metab. 2017; Mashiko S et al. Mol Pharmacol. 2007; Gadde KM et al, J Clin Psychiatry. 2007; Sjödin A, Int J Obes (Lond). 2010; Boon MR et al, FASEB J. 2014; Inagaki T, Front Endocrinol (Lausanne). 2015; Summermatter S et al, Int J Obes (Lond). 2012.

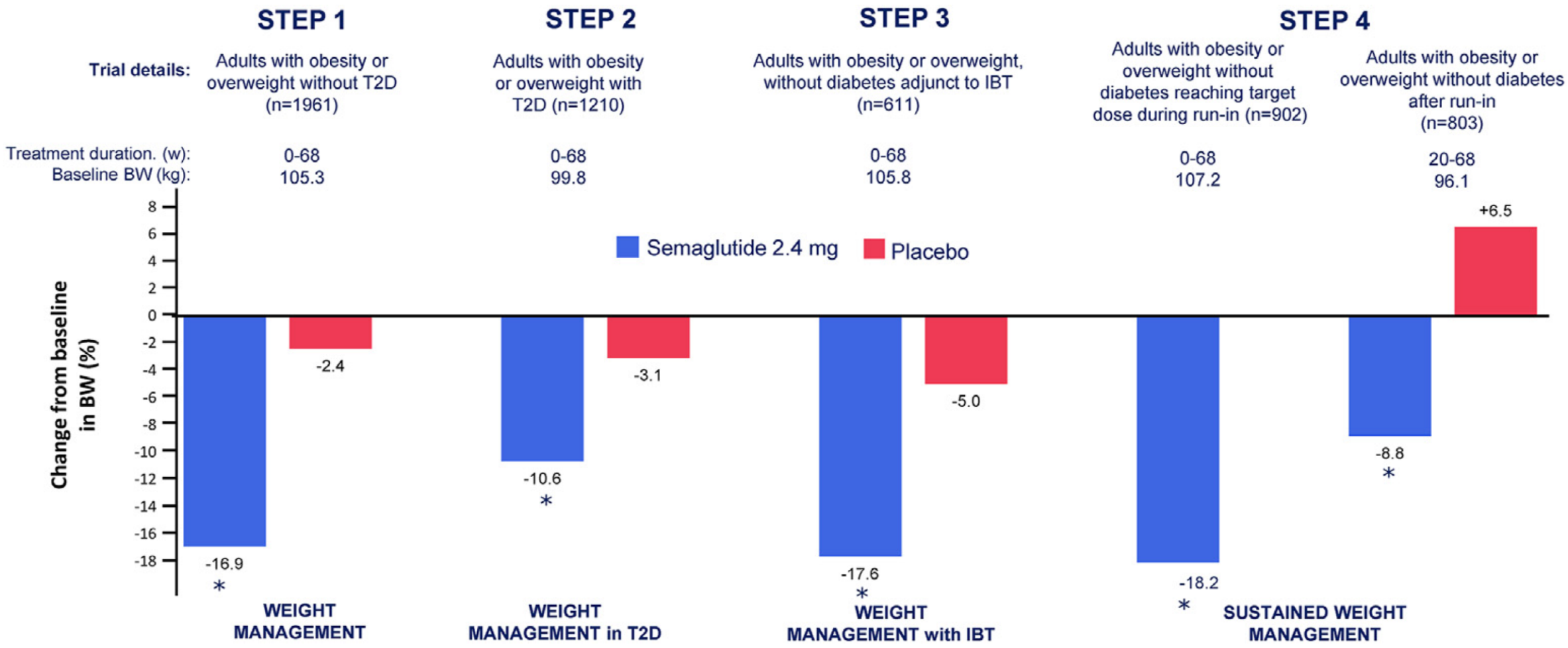
Weight loss across SCALE trials with liraglutide



Data are observed means; LOCF at end of trial; N, number of individuals contributing to the analysis.

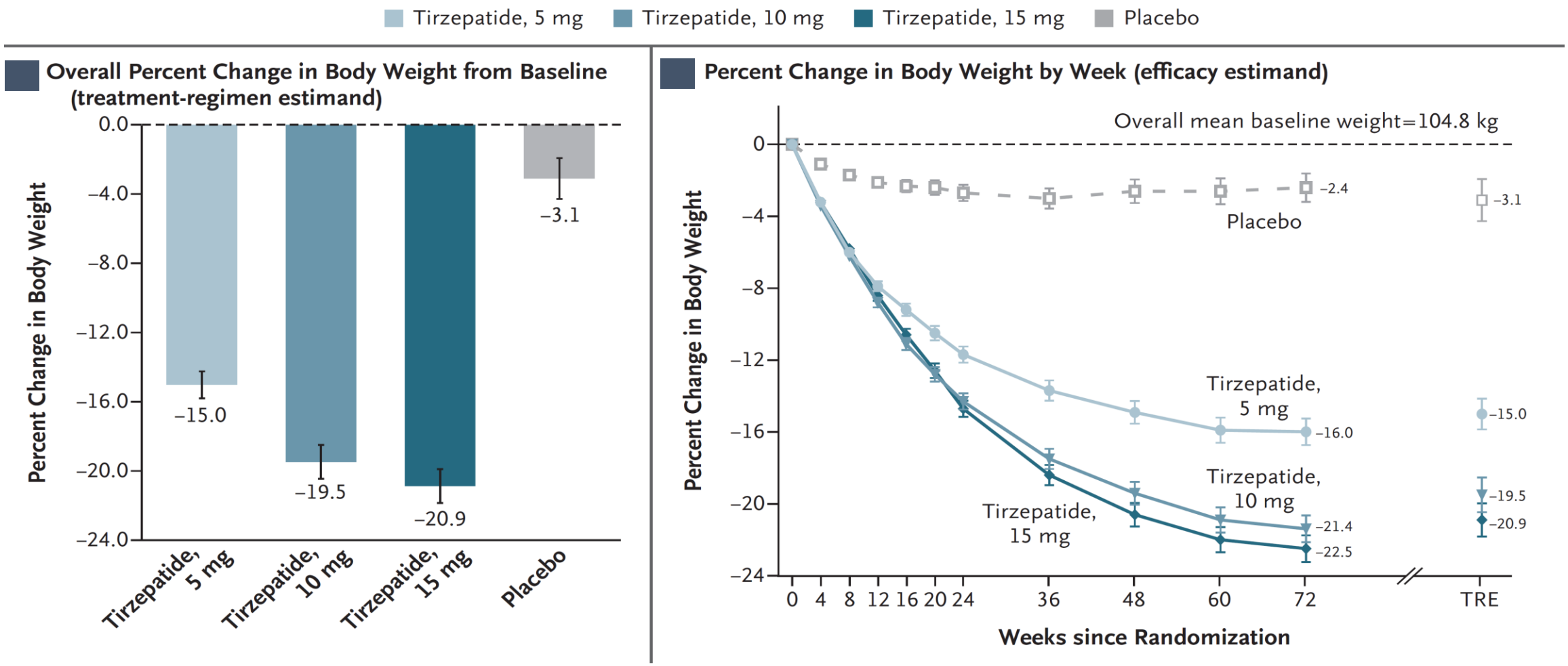
1. Pi-Sunyer X, et al. N Engl J Med. 2015;373:11-22; 2. Davies MJ, et al. JAMA. 2015;314:687-99;
3. Wadden TA, et al. Int J Obes. 2013;37:1443-51, 4. Blackman A, et al. Int J Obes. 2016;40:1310-9.

Weight loss in the STEP trials with semaglutide



Drucker DJ, Mol Metab. 2022;57:101351.

SURMOUNT-1: effects of tirzepatide on body weight in obesity

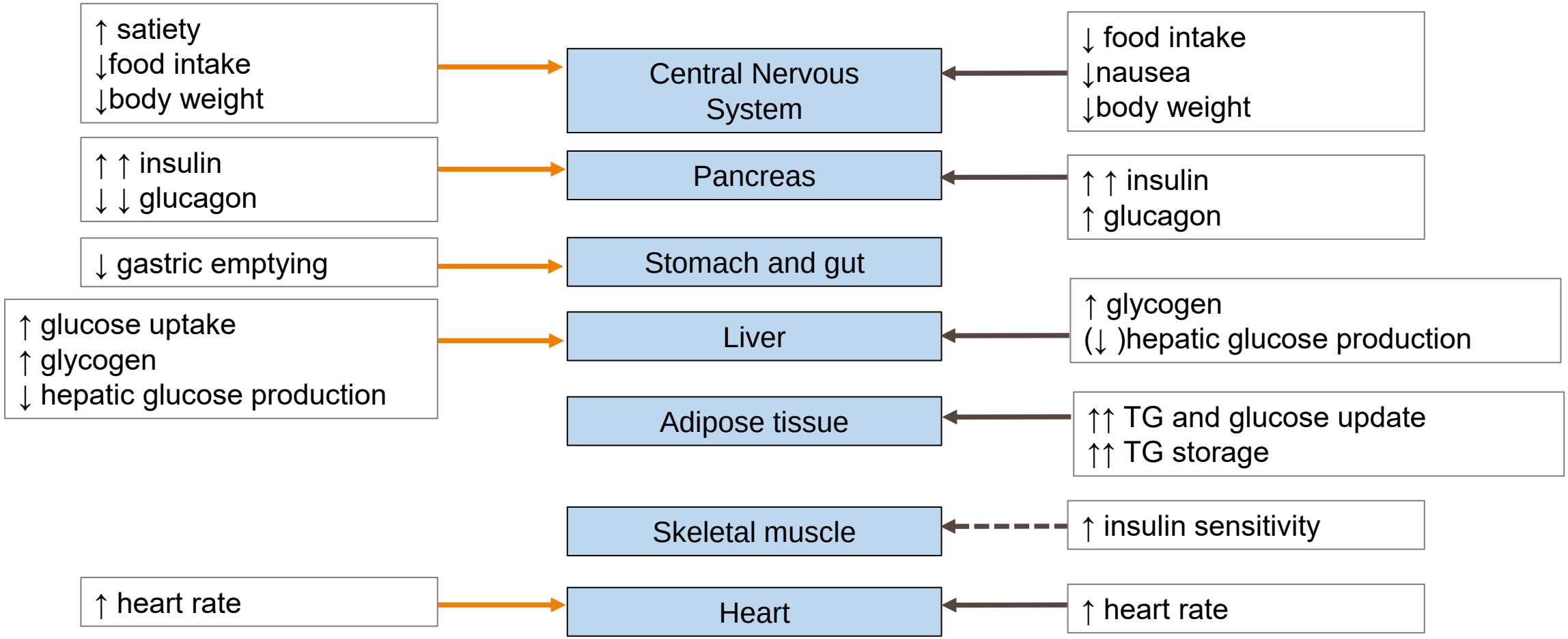


Tirzepatide is not approved for obesity

Jastreboff AM, et al, N Engl J Med. 2022;387(3):205-216.

Glucagon-like receptor-1 agonism

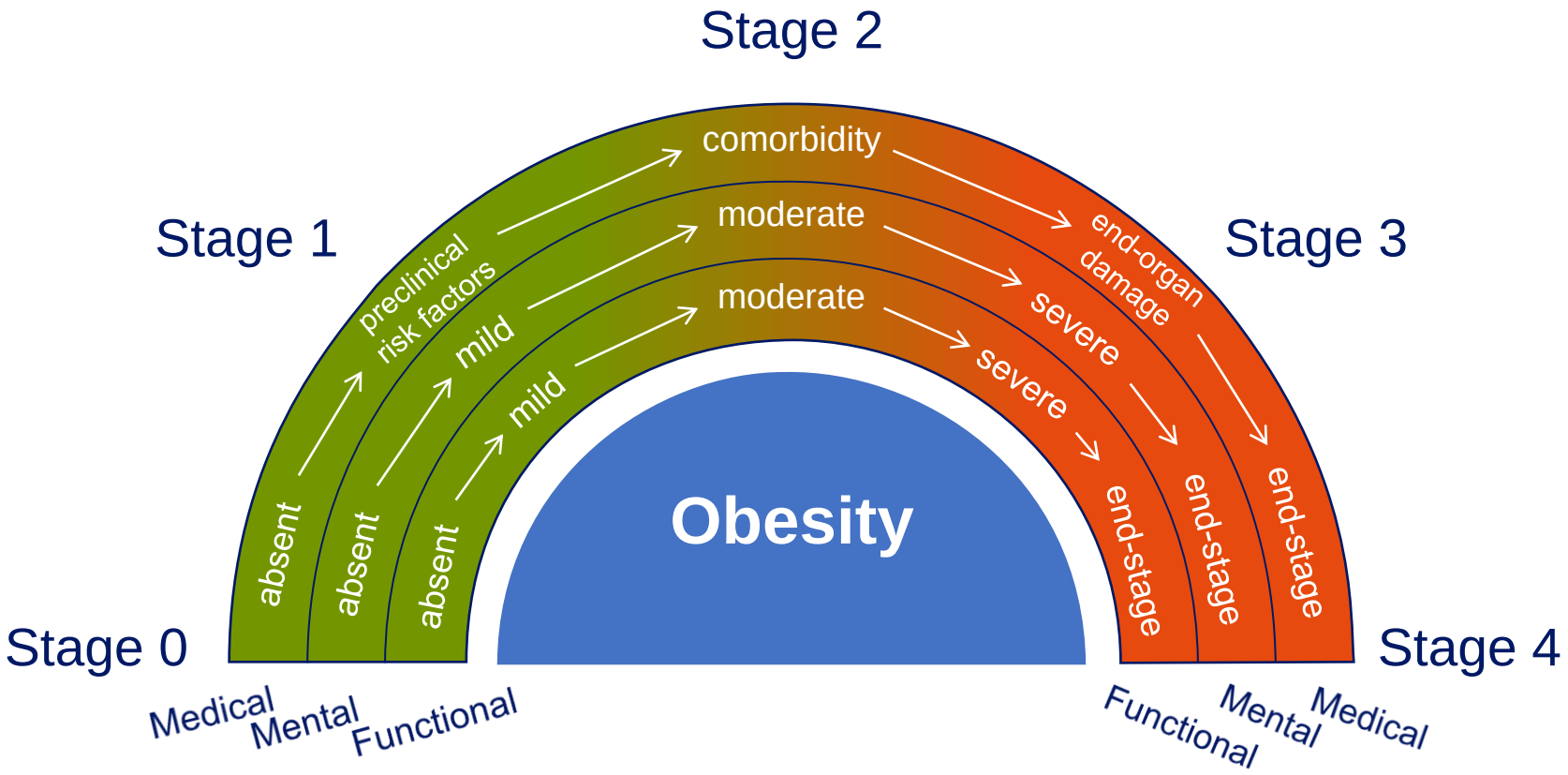
Glucose-dependent insulinotropic polypeptide receptor agonism



Gallwitz B. Front Endocrinol. 2019;10:389,
Samms R, et al. Trends Endocrinol Metab. 2020;31:420-421.

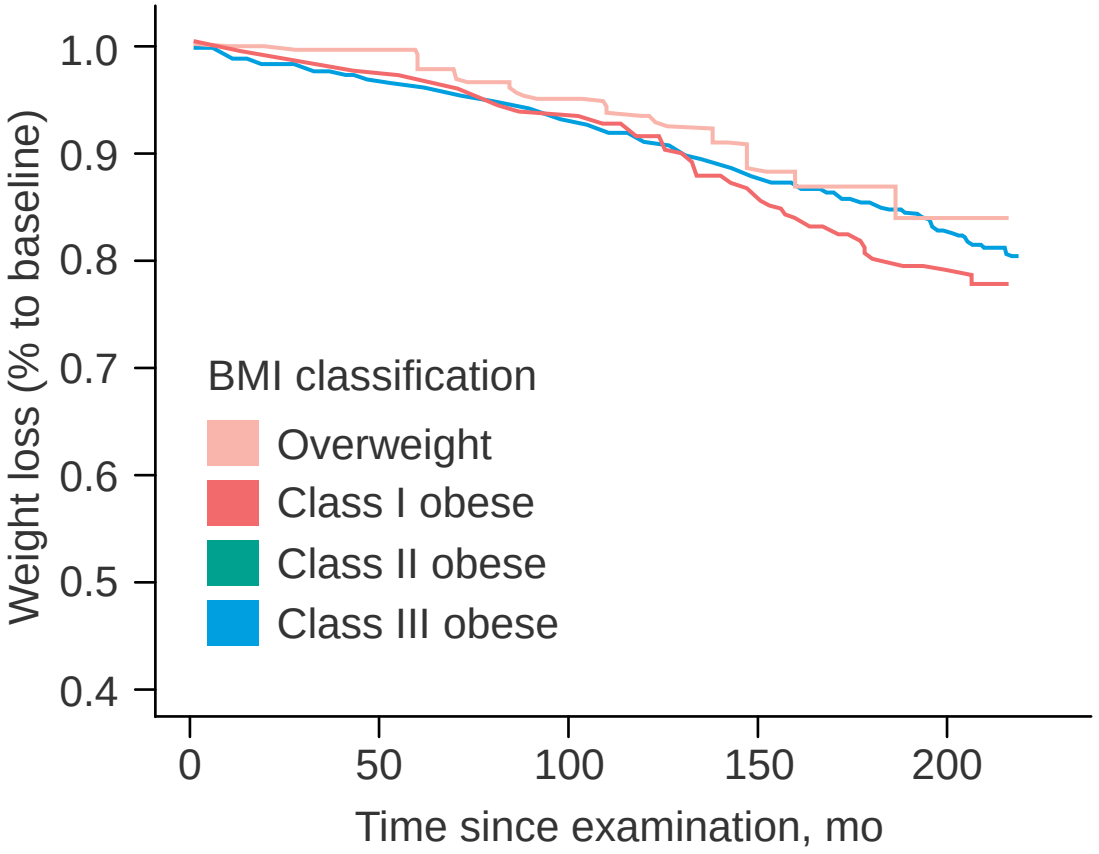
Treatment decisions based on comorbidities?

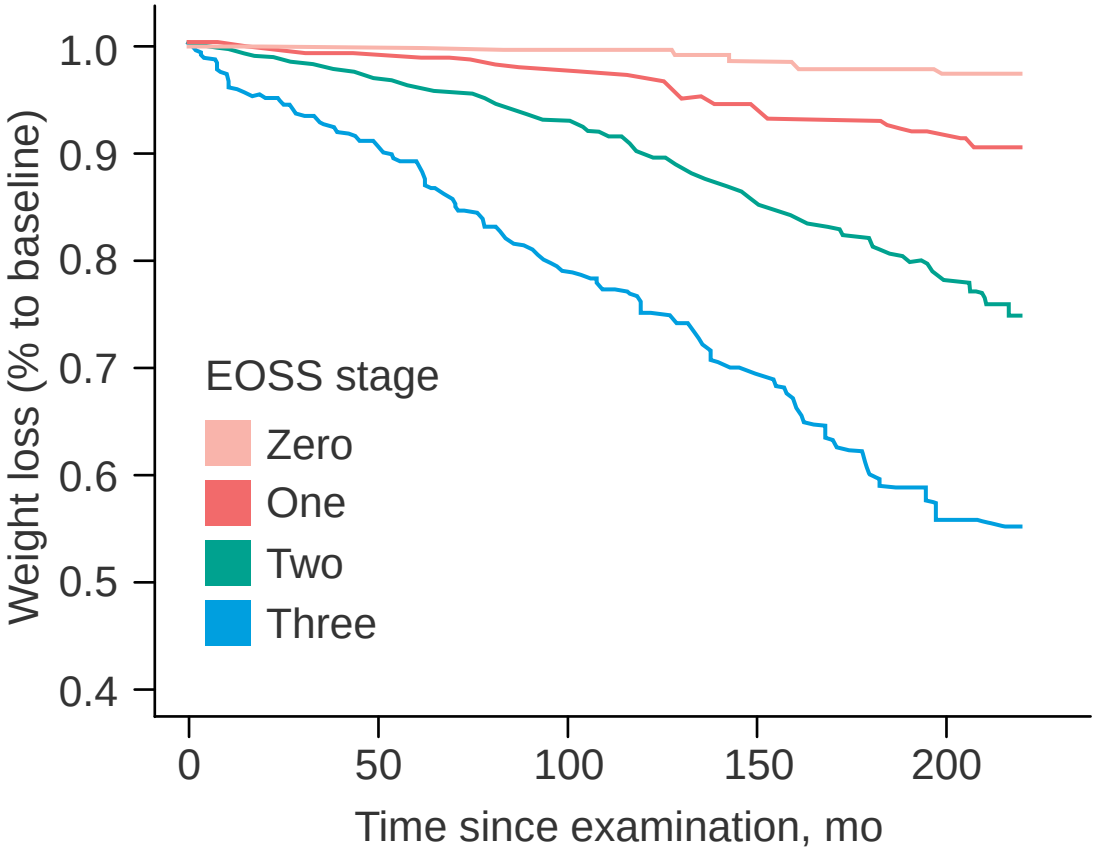
EOSS, Edmonton Obesity Staging System



Sharma, Kushner. Int J Obes (Lond) 2009;33:289–295.

EOSS stage predicts obesity-related mortality better than BMI





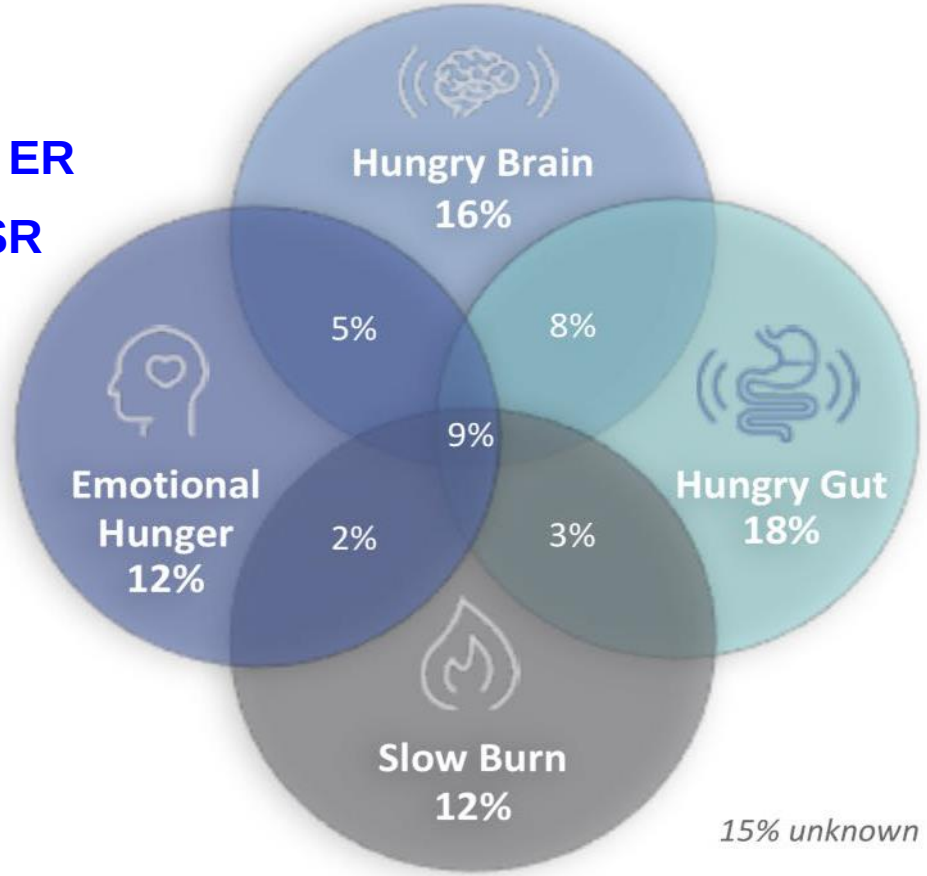
BMI, body mass index; EOSS, Edmonton Obesity Staging System.

Padwal et al. CMAJ. 2011;183:E1059-1066.

Selection of antiobesity medications based on phenotypes enhances weight loss: A pragmatic trial in an obesity clinic

Stratification of obesity into **four phenotypes**:

- Hungry brain (abnormal satiation) → **phentermine-topiramate ER**
- Emotional hunger (hedonic eating) → **bupropion-naltrexone SR**
- Hungry gut (abnormal satiety) → **liraglutide**
- Slow burn (decreased metabolic rate) → **low-dose phentermine plus resistance training**

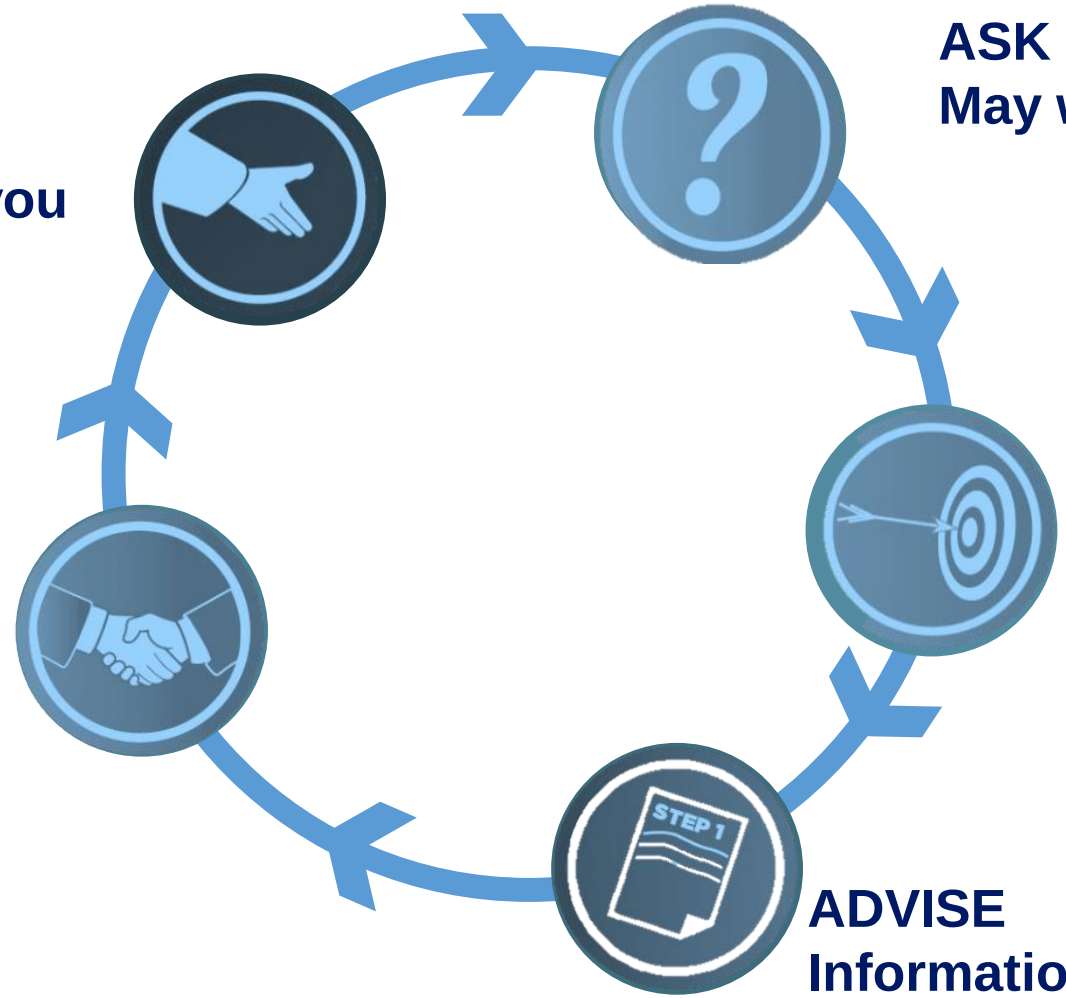


The phenotype-guided approach was associated with 1.75-fold greater weight loss after 1 year.

The proportion of patients who lost >10% at 1 year was 79% compared with 34% with non-phenotype-guided treatment.

Acosta A, et al. Obesity (Silver Spring). 2021;29:662-671.

“5A” Concept of Obesity Management



ASK
May we talk about your weight?

ASSESS
Clinical investigation

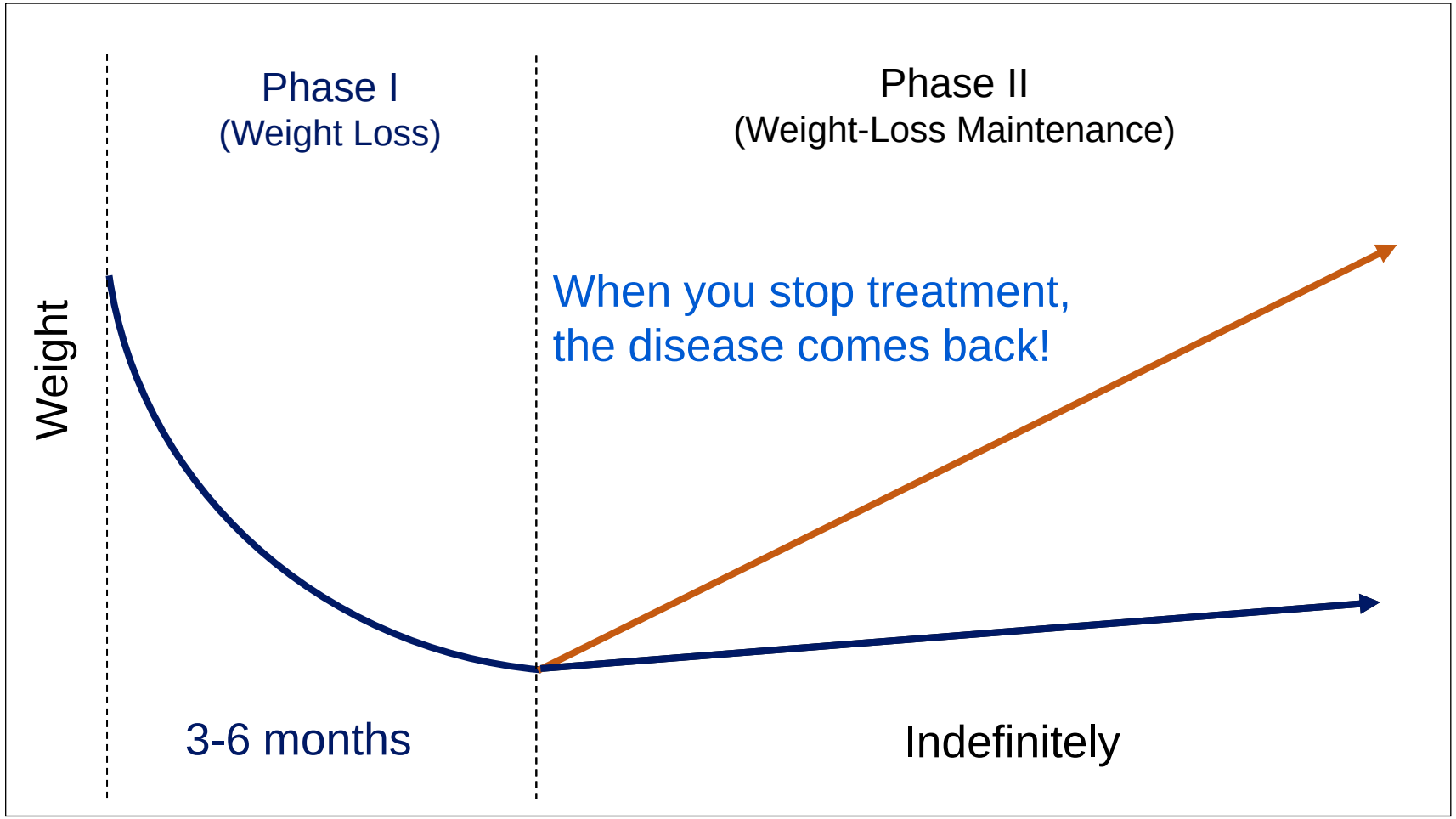
ADVISE
Information about treatment options

AGREE
Define treatment goals

ASSIST
I can help you

5As of Obesity Management. Canadian Obesity Network. 2011. https://obesitycanada.ca/resources/5as/

Obesity is a chronic progressive condition



Summary

- Obesity is a chronic progressive medical condition/disease that leads to multiple co-morbidities and premature mortality
- Compensatory mechanisms defend against weight loss and often lead to weight regain
- Obesity treatment is an escalating life-long management
- Treatment goals should be shifted from weight loss only to improved health despite obesity
- New pharmacological treatments are based upon increased understanding of body weight regulation and are more efficacious
- Combination treatment targeting different pathways that regulate body weight and using polymodal therapies lead to greater weight reduction