Pharmacotherapy intervention and the role of Saxenda® in managing Obesity as a chronic disease

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Agenda

Obesity is a chronic disease

Complications related to Obesity

Role of Brain in appetite regulation

Obesity management guidelines

Pharmacotherapy intervention (Efficacy and safety of Saxenda® in managing Obesity)

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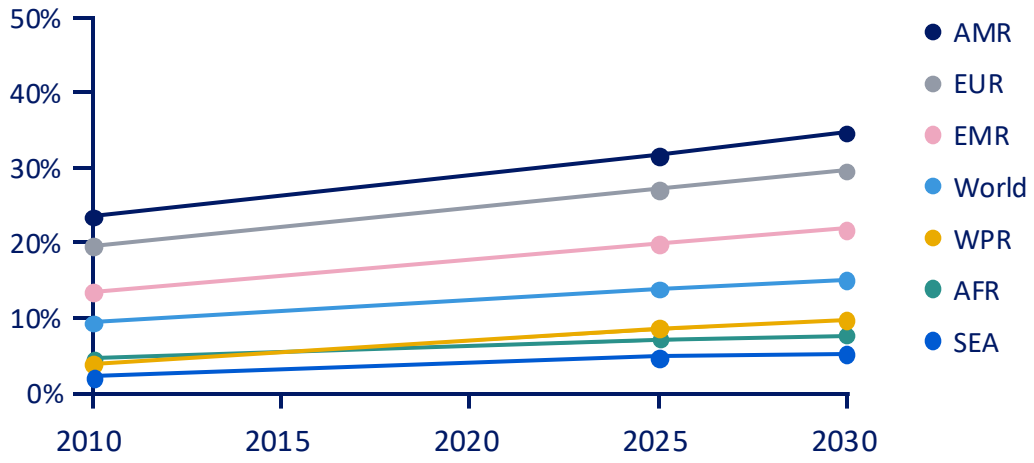
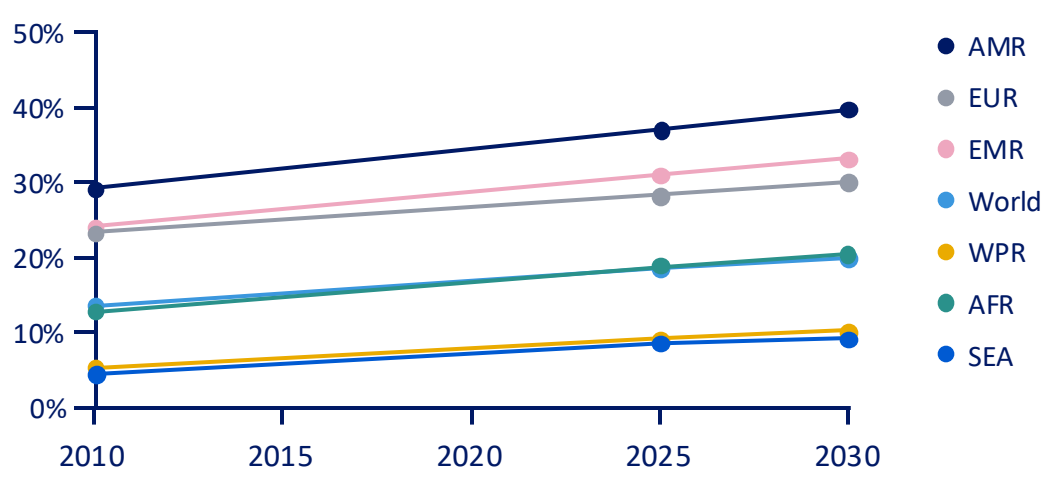
Obesity rates worldwide are increasing

Trends and predictions in the number of adults with obesity by region and by gender

Prevalence of obesity amongst men by regions in 2010–2030



Prevalence of obesity amongst women by regions in 2010–2030



AFR, Africa; AMR, America; EMR, Eastern Mediterranean Region; EUR, Europe; SEA, Southeast Asia; WPR, Western Pacific Region.

1. NCD risk factor collaboration (2017) and World Obesity Federation projections. Available from: https://s3-eu-west-1.amazonaws.com/wof-files/World_Obesity_Atlas_2022.pdf. Accessed October 2022.

Obesity is recognized as a disease and a health issue

"Obesity is a chronic, relapsing, progressive disease process ….need for immediate action for prevention and control of this global epidemic"

World Obesity Federation[1]

"Obesity is a progressive chronic disease, similar to diabetes or high blood pressure, …"

Obesity Canada[3]

"A progressive disease, impacting severely on individuals and society alike,… obesity is the gateway to many other disease areas…"

European Association for the Study of Obesity[4]

"Obesity and overweight as a chronic medical condition (de facto disease state) and urgent public health problem…"

American Medical Association[2]

"It (obesity) is not a lifestyle choice caused by individual greed but a disease caused by health inequalities, genetic influences and social factors.."

Royal College of Physicians UK[5]

"The Treat and Reduce Obesity Act would allow a variety of qualified practitioners, including registered dietitian nutritionists, to more effectively treat this disease, which impacts more than one-third of our nation."

Academy of nutrition and dietetics[6]

"Obesity is a chronic relapsing disease, which in turn acts as a gateway to a range of other non-communicable diseases, such as diabetes, cardiovascular diseases and cancer."[3]

European Commission[7]

"A pathological state (obesity disease) in which a person suffers health problems caused by or related to obesity thus making weight loss clinically desirable …"

Asia Oceania Association for the Study of Obesity[8]

1. Bray et al. Obes Rev 2017;18:715–23; 2. AMA resolutions. June 2012. Available at https://www.ama-assn.org/sites/ama-assn.org/files/corp/media-browser/public/hod/a12-resolutions_0.pdf. Accessed October 2022; 3. Obesity Canada. Available at https://obesitycanada.ca/guidelines/. Accessed October 2022; 4. EASO: 2015 Milan Declaration: A Call to Action on Obesity. Available at https://easo.org/2015-milan-declaration-a-call-to-action-on-obesity/. Accessed October 2022; 5. Royal College of Physicians. Anon. BMJ 2019;364:l45; 6. Raynor et al. J Acad Nutr Diet 2016;116:129–47; 7. European Commission. Obesity prevention. Available from https://knowledge4policy.ec.europa.eu/health-promotion-knowledge-gateway/obesity_en. Accessed October 2022; 8. AOASO position statement, Nagoya Declaration 2015.

Definition and classification of obesity

- Obesity is defined as abnormal or excessive fat accumulation that may impair health
- Body mass index (BMI) provides the most convenient population-level measure of overweight and obesity currently available

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

Classification	BMI (kg/m²)		
	International classification[1]	Asian population[2]	Japanese guidelines[3]
Underweight	<18.5		<18.5
Normal range	≥18.5 and <25	≥18 and <23	≥18.5 - <25
Pre-obesity*	≥25 and <30	≥23 and <25	
Obesity	≥30	>25	
Obesity class I	≥30 and <35		≥25 and <30
Obesity class II	≥35 and <40		≥30 and <35
Obesity class III	≥40		≥35 and <40
Obesity class IV			≥40

*Previously described as overweight according to WHO nomenclature.
BMI, body mass index; JASSO, Japan Society for the Study of Obesity; WHO, World Health Organization.
1. WHO. Obesity: preventing and managing the global epidemic. 2000. Available from https://www.who.int/nutrition/publications/obesity/WHO_TRS_894/en/. Accessed May 2020;
2. Misra A et al. J Assoc Physicians India. 2009;57:163–70; 3. Guidelines for the management of obesity disease 2016 (Japan), issued by JASSO.

Waist circumference as a measure of obesity

- Waist circumference helps to screen health risks of obesity and overweight[1]
- This risk goes up with a waist size that is greater than 88 cm for women or greater than 102 cm for men

Classification	BMI (kg/m²)	Disease risk relative to normal weight†[2]	
		Men ≤40 in (102 cm) Women ≤35 in (88 cm)	Men >40 in (102 cm) Women >35 in (88 cm)
Pre-obesity*	≥25 and <30	Increased	High
Obesity			
Obesity class I	≥30 and <35	High	Very high
Obesity class II	≥35 and <40	Very high	Very high
Obesity class III	≥40	Extremely high	Extremely high

**Previously described as overweight according to WHO nomenclature; †Disease risk for T2D, hypertension and cardiovascular disease.*
BMI, body mass index; in, inches; NIH, National Institutes of Health; T2D, type 2 diabetes; WHO, World Health Organization.
1. WHO. Waist Circumference and Waist-Hip Ratio Report: Expert Consultation, 2008. Available from https://apps.who.int/iris/bitstream/handle/10665/44583/9789241501491_eng.pdf?sequence=1. Accessed March 2021; 2. NIH, National Heart, Lung and Blood Institute. Available from https://www.nhlbi.nih.gov/health/educational/lose_wt/BMI/bmi_dis.htm. Accessed March 2021.

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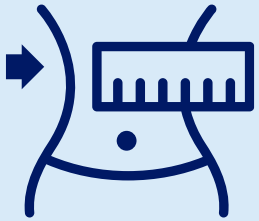
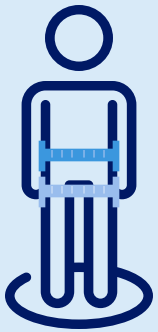
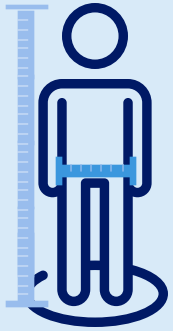
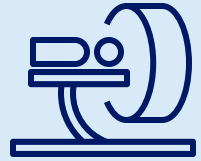
Measuring abdominal obesity

Waist circumference	Waist-to-hip ratio	Waist-to-height ratio	DEXA	CT	MRI
					

WC is the most practical measure[2]

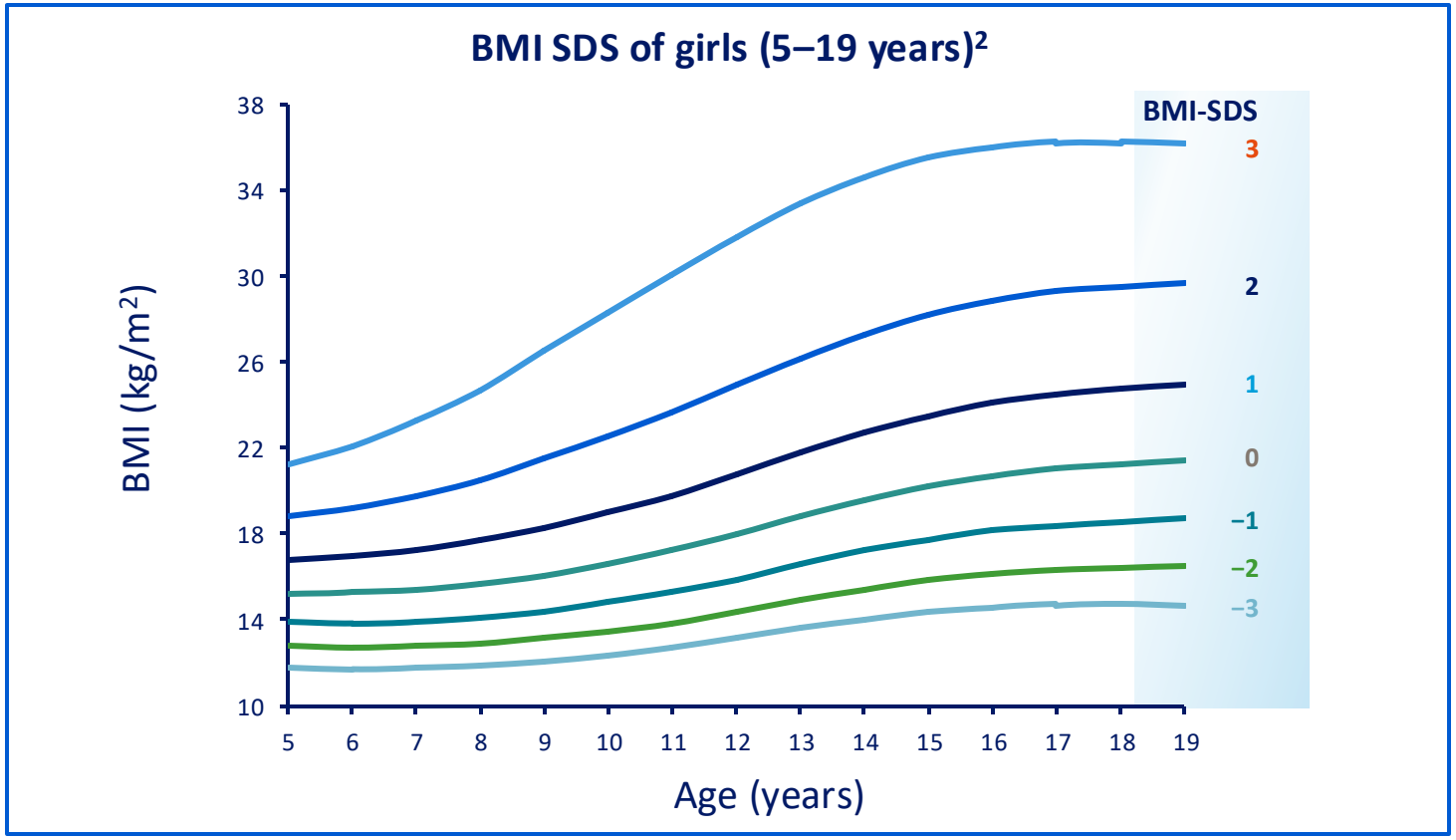
- WC is widely used and waist-to-hip ratio correlates with metabolic risk[1]
- Although traditionally DEXA did not distinguish between abdominal and visceral fat, recent studies have demonstrated that this is possible with high-precision, low X-ray exposure and short scanning time[2]

CT, computed tomography; DEXA, dual-energy X-ray absorptiometry; MRI, magnetic resonance imaging; WC, waist circumference.
1. Cornier et al. Circulation. 2011;124:1996–2019; 2. Kaul et al. Obesity (Silver Spring). 2012;20:1313–18.

Overweight and obesity defined by BMI SDS

BMI SDS:
Indicates standard deviations above/below the average BMI for given age and gender[1]

Positive BMI SDS of 1, 2 or 3 indicates 1, 2 or 3 SDS above the average value[1]



BMI, body mass index; SD, standard deviation; SDS, standard deviation score
1. Must & Anderson. Int J Obesity 2006;30:590–4; 2. WHO BMI-for-age. Available link, accessed Jan 2021

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Obesity is associated with multiple complications

Metabolic

Mechanical

Mental

GERD

Cancers*

Physical functioning

Depression

Anxiety

Asthma

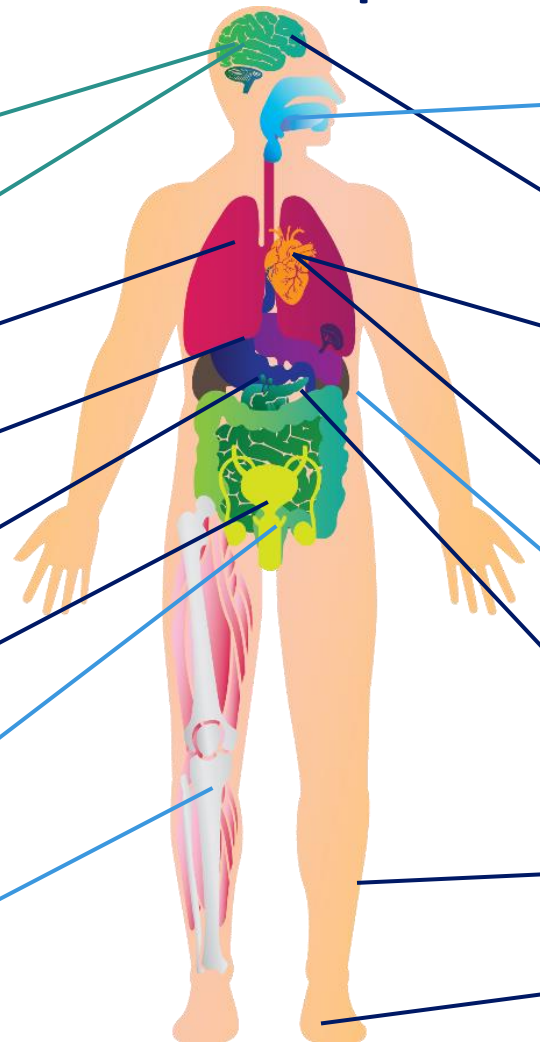
NAFLD

Gallstones

Infertility

Incontinence

Knee osteoarthritis



Sleep Apnoea

Cardiovascular diseases
- Stroke & AF
- Dyslipidaemia
- Hypertension
- Coronary artery disease
- Pulmonary embolism
- HFpEF

Coronary heart failure

Chronic back pain

Type 2 diabetes
Prediabetes

Thrombosis

Gout

Including breast, colorectal, endometrial, oesophageal, kidney, ovarian, pancreatic and prostate.
GERD, gastro-oesophageal reflux disease; HFpEF, heart failure with preserved ejection fraction; NAFLD, non-alcoholic fatty liver disease.
Adapted from Sharma AM. Obes Rev 2010;11:808–9; Guh DP et al. BMC Public Health 2009;9:88; Luppino FS et al. Arch Gen Psychiatry 2010;67:220–9; Simon GE et al. Arch Gen Psychiatry 2006;63:824–30; Church TS et al. Gastroenterology 2006;130:2023–30; Li C et al. Prev Med 2010;51:18–23; Hosler AS. Prev Chronic Dis 2009;6:A48.

How can we improve health and quality of life in people with obesity?

Weight loss leads to overall health improvements in:

Magnitude of weight loss (%)

0–5%
- ✓ Hypertension[1]
- ✓ Hyperglycemia[1]

5–10%
- ✓ PCOS[1]
- ✓ NAFLD[1]
- ✓ Prevention of T2D[1]
- ✓ Dyslipidemia[1]

10–15%
- ✓ OSAS[1]
- ✓ GERD[1]
- ✓ NASH[1]
- ✓ Cardiovascular disease[1]
- ✓ Urinary stress incontinence[2]
- ✓ Knee osteoarthritis[1]

15–20%
- ✓ CV mortality[3]
- ✓ T2D remission[4]
- ✓ Hepatic steatosis[5]

>20%
- ✓ HFpEF[6]
- ✓ Advanced T2D remission[7,8*]
- ✓ Postural instability[9]

Most PwO can achieve significant weight loss, health benefits and improved QoL

Greater sustained weight loss leads to improved health benefits in obesity related complications.

Increased weight loss is associated with improvements in obesity comorbidities[1-5]

Improvements in health must go beyond the scale

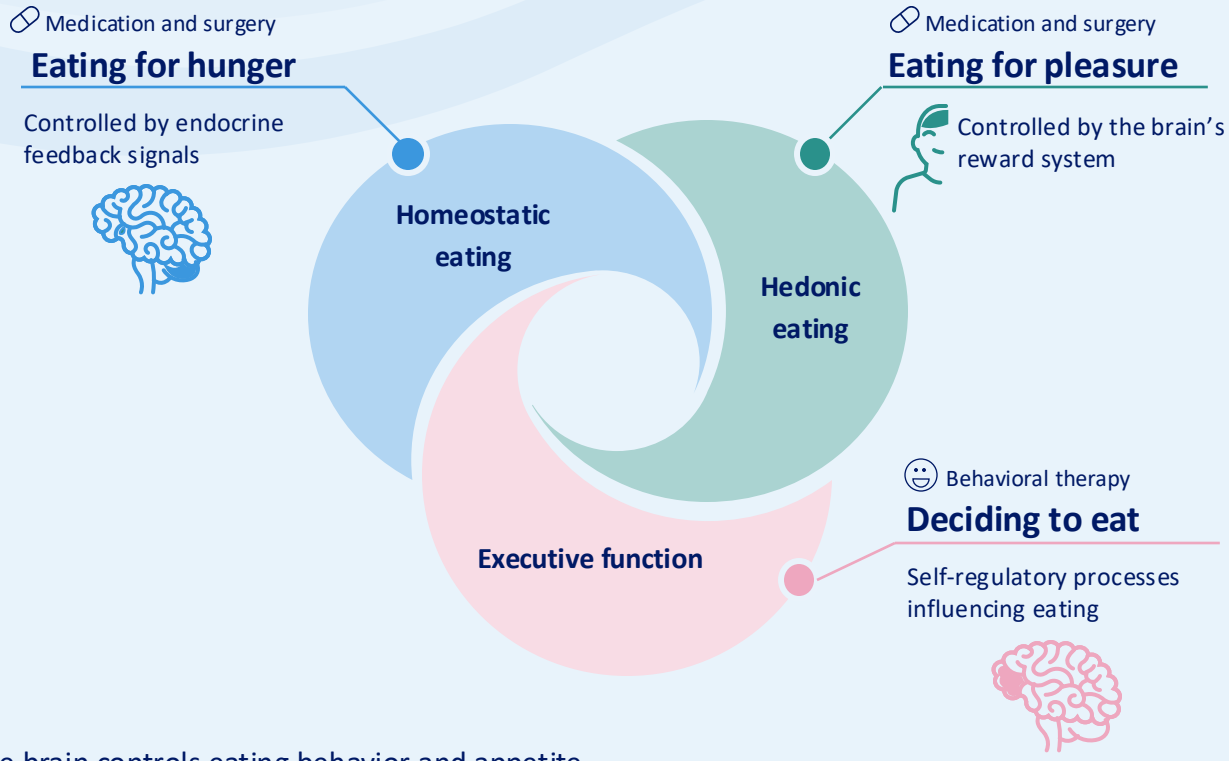
Greater weight loss leads to improved health

**T2D remission rates have been found to plateau at 20-25% total weight loss where 25% total weight loss did not confer additional benefits*

BP, blood pressure; CV, cardiovascular; GERD, gastro-oesophageal reflux disease; HbA1c, glycated hemoglobin; HFpEF, heart failure with preserved ejection fraction; NAFLD; non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; OSAS, obstructive sleep apnoea syndrome; PCOS, polycystic ovary syndrome; T2D, type 2 diabetes; TG, triglycerides.

1. Horn D et al. Postgrad Med. 2022;134:359–75; 2. Garvey WT et al. Endocr Pract. 2016;22(Suppl. 3):1–203; 3. Look AHEAD Research Group, Gregg EW et al. Lancet Diabetes Endocrinol. 2016;4:913–21; 4. Lean ME et al. Lancet. 2018;391:541–51; 5. Sundström J et al. Circulation. 2017;135:1577–85; 6. Benraoune F & Litwin SE. Curr Opin Cardiol. 2011;26:555–61; 7. Meerasa A & Dash S. Diabetes Care 2022;45:28–30; 8. Teasdale, N et al. Int J Obes 2007;31:153–160; 9. Ryan DH and Yockey SR. Curr Obes Rep 2017;6:187–94.

What is the role of the brain in regulating appetite?



The brain controls eating behavior and appetite. Weight is determined and regulated by a unique, three-layer appetite system.

Appetite is normally regulated by a complex interplay of different signals and areas in the brain

Increased understanding of the biology of appetite regulation has led to the development of new generation pharmacotherapy.

Many paths lead to obesity

Obesity is not simply due to an individual's choice or lack of willpower[7]

Appetite is normally regulated by a complex interplay between gut and brain

1. Badman MK & Flier JS. Science. 2005;307:1909–14; 2. van Bloemendaal L et al. Diabetes. 2014;63:4186–96; 3. Klok MD et al. Obes Rev. 2007;8:21–34; 4. Hall K et al. Am J Public Health. 2014;104:1169–75; 5. Berridge KC et al. Brain Res. 2010;1350:43–64; 6. Vallis M. Clin Obes. 2019;9:e12299; 7. Lau D et al. Canadian Adult Obesity Clinical Practice Guidelines: The Science of Obesity. Available from https://obesitycanada.ca/guidelines/science.

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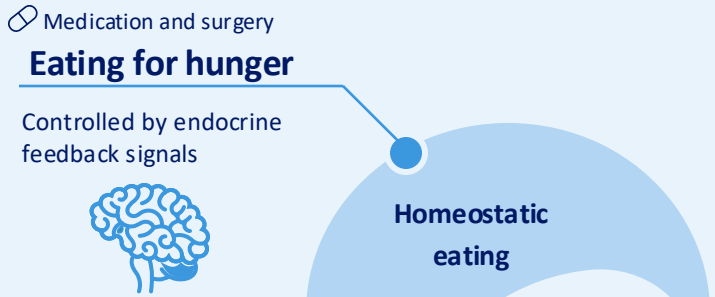
The role of the brain in controlling appetite



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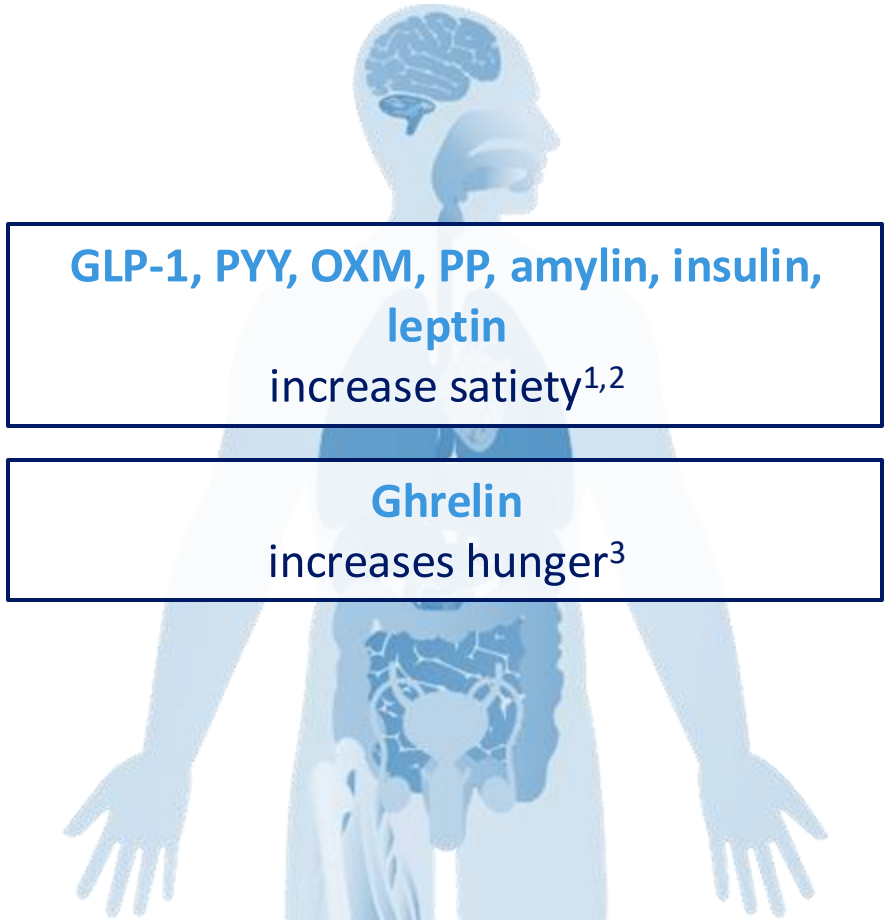

GLP-1, PYY, OXM, PP, amylin, insulin, leptin
increase satiety[1,2]

Ghrelin
increases hunger[3]

GLP-1, glucagon-like peptide-1; POMC, pro-opiomelanocortin; PP, pancreatic polypeptide; PYY, peptide YY; OXM, oxyntomodulin

1. Badman & Flier. Science 2005;307:1909–14; 2. van Bloemendaal et al. Diabetes 2014;63:4186–96; 3. Klok et al. Obes Rev 2007;8:21–34; 4. Hall et al. Am J Public Health 2014;104:1169-75.

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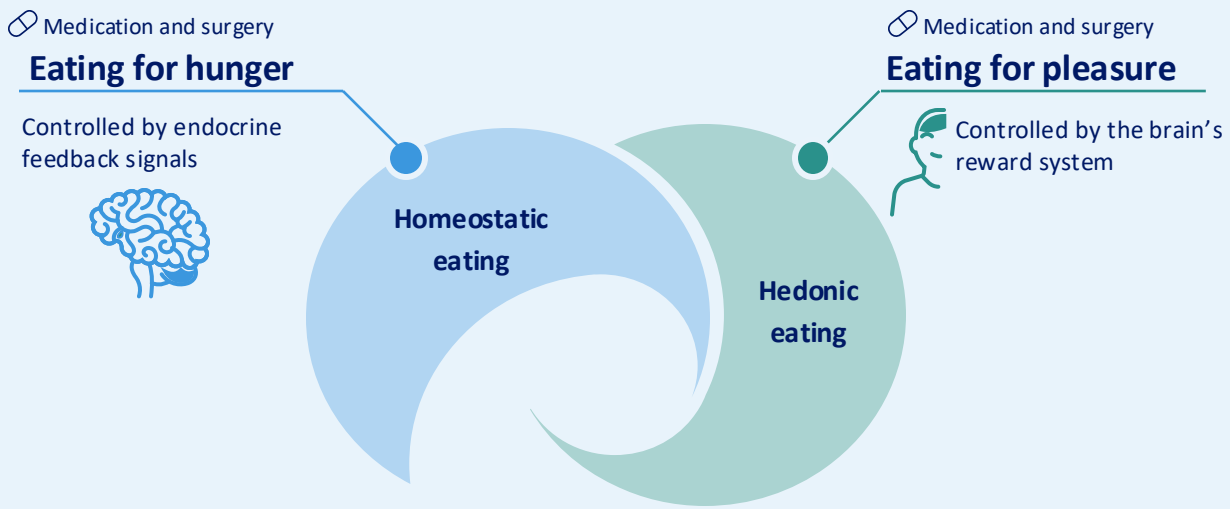

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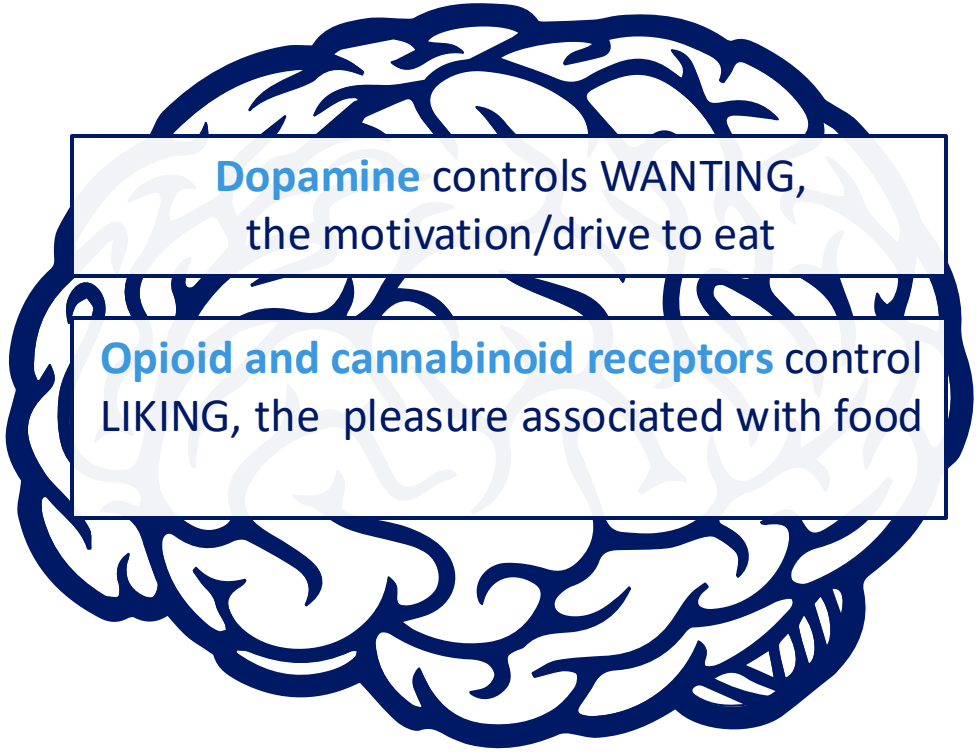

GLP-1, glucagon-like peptide-1; POMC, pro-opiomelanocortin; PP, pancreatic polypeptide; PYY, peptide YY; OXM, oxyntomodulin

1. Badman & Flier. Science 2005;307:1909–14; 2. van Bloemendaal et al. Diabetes 2014;63:4186–96; 3. Klok et al. Obes Rev 2007;8:21–34; 4. Hall et al. Am J Public Health 2014;104:1169-75.

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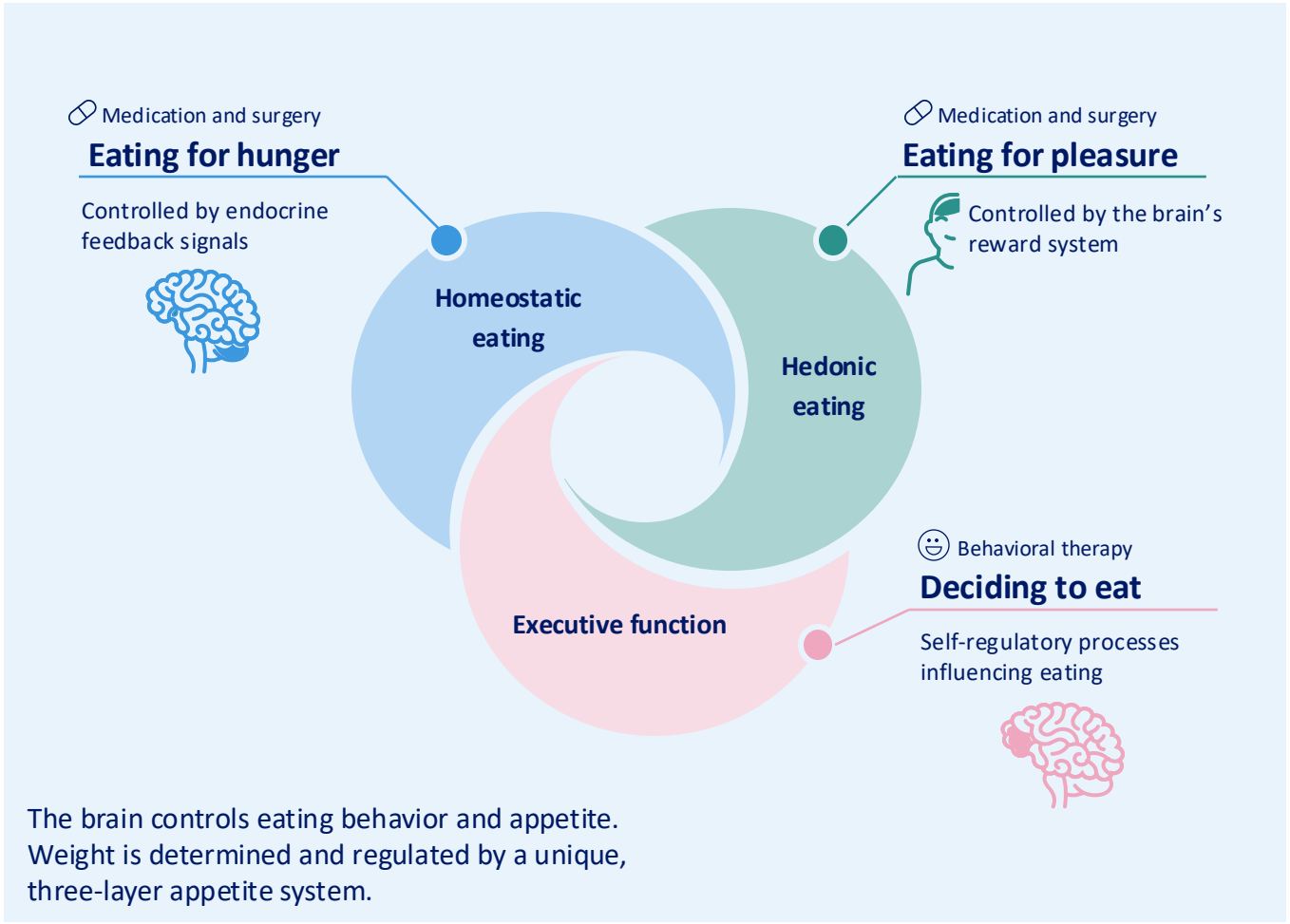
The role of the brain in controlling appetite



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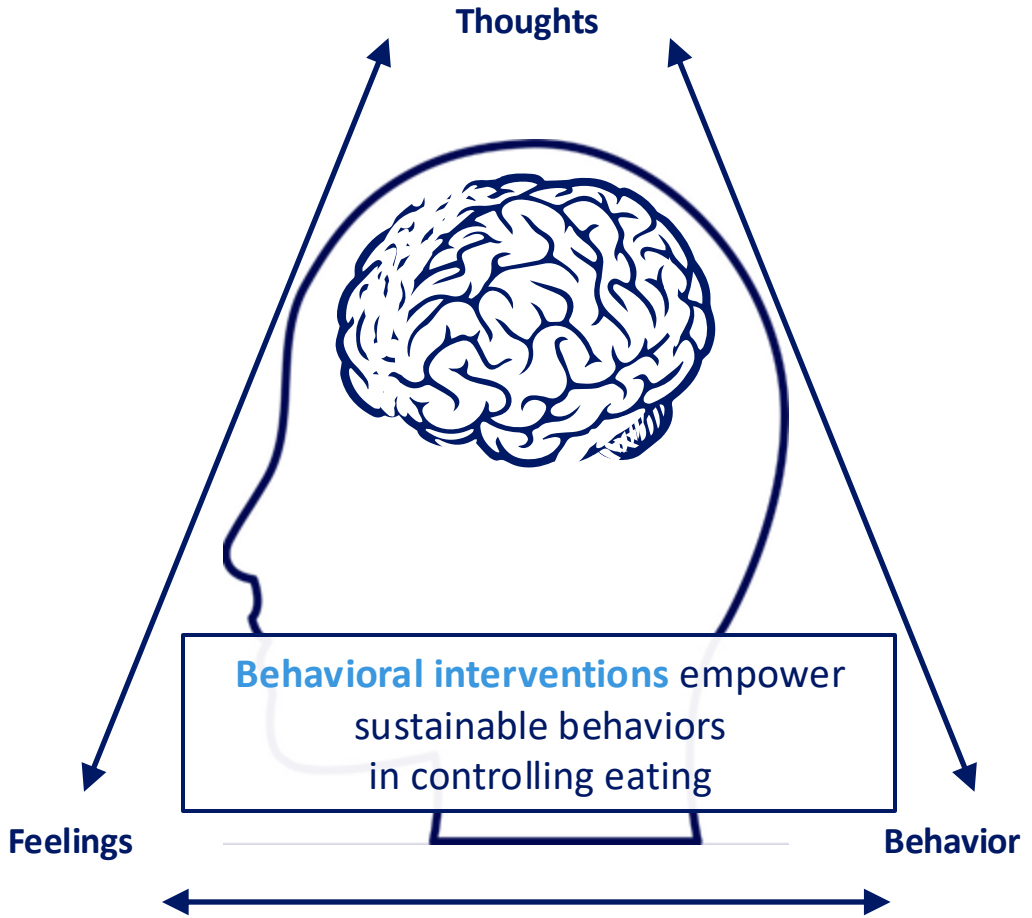

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What are the pillars of obesity management[1]?

Lifestyle recommendations

- Medical nutrition therapy
- Physical activity

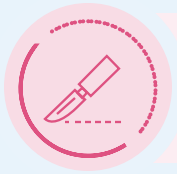
Behavioral interventions: ~5% weight loss

- Behavior modification
- Cognitive behavioral therapy
- Counselling

Pharmacotherapy: ~5–15% weight loss

- Naltrexone/bupropion*†
- Orlistat*†
- Liraglutide 3.0mg*†

Endoscopic / Surgical interventions: ~12–30% weight loss



- Endoscopic procedures: ~12-20% weight loss
- Bariatric surgery: ~20-30% weight loss

The approach to obesity management

Lifestyle changes are a foundation for any chronic disease management.

However, as with other chronic diseases like hypertension or diabetes, pharmacotherapy is needed to address the biology of obesity and is intended as part of a long-term treatment strategy.

Diet & exercise alone
<5% weight loss[2]

New generation pharmacotherapy
15--17% weight loss[3-7]

Three-tiered approach

Adapted from Horn et al. Postgrad Med. 2022;134:359–75. Approved in the EU and US† 1. Horn et al. Postgrad Med. 2022;134:359–75; 2. Wadden TA et al. N Engl J Med. 2005;353:2111–20; 3. Wilding JPH et al. N Engl J Med. 2021;384:989–1002; 4. Torgerson JS et al. Diabetes Care. 2004;27:155–61; 5. Apovian C et al. Obesity. 2013;21:935–43; 6. Pi-Sunyer X et al. N Engl J Med. 2015;373:11–22; 7. Allison D.B et al. Obesity. 2012;20:330–42; 8. Wharton S et al. CMAJ. 2020;192:E875-91.*

How can you change the course of a patient's care?

ASK
for permission to discuss weight

ASSESS
patient history

ADVISE
on treatment options

- Lifestyle recommendations
- Behavioral interventions
- Pharmacotherapy
- Endoscopic / Surgical interventions

AGREE
on treatment plan and goals

ASSIST
with long-term management

Most physicians can effectively manage obesity, as with any other chronic diseases

A structured approach to obesity management is feasible in most clinical settings (solo-practitioners or multi-disciplinary settings), even with time constraints and busy practices[2].

Like hypertension or other ongoing chronic conditions, obesity requires long-term treatment

Improvements in health must go beyond the scale

Greater weight loss leads to improved health

1. Horn et al. Postgrad Med. 2022;134:359–75; 2. Braillard O et al. BMC Fam Pract. 2018;19:159.

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Canadian Adult Obesity Clinical Practice Guidelines

1 Ask permission

- Shows compassion and empathy
- Builds patient–provider trust

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

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 behavior change
- Manage sleep, time and stress
- Psychotherapy if appropriate

Medications

- For weight loss and to help maintain weight loss

Bariatric surgery

- Surgeon–patient discussion

4 Agree on goals

Collaborate on a personalized sustainable action plan

Patient at the clinic

5 Assist with drivers and barriers

Wharton et al. CMAJ. 2020;192:E875-91.

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Assessment and diagnosis of people living with obesity: key recommendations for HCPs

1

When screening, assessing and managing PwO, use the 5As framework to initiate the discussion by asking for their permission and assessing their readiness to initiate treatment

2

Measure height, weight and calculate BMI in all adults, and measure waist circumference in individuals with a BMI of 25–35 kg/m^2

3

We suggest a comprehensive history to identify root causes of weight gain as well as complications of obesity and potential barriers to treatment be included in the assessment

4

Measure BP in both arms, fasting glucose or HbA_{1c} and lipid profile to determine cardiometabolic risk and, where appropriate, ALT to screen for NAFLD in PwO

5

Consider using the Edmonton Obesity Staging System to determine the severity of obesity and to guide clinical decision making

ALT, alanine aminotransferase; BMI, body mass index; BP, blood pressure; EOSS, Edmonton Obesity Staging System; HbA1c, glycated hemoglobin; HCP, healthcare professional; NAFLD, nonalcoholic fatty liver disease; PwO, people with obesity.

Rueda-Clausen et al. Canadian Adult Obesity Clinical Practice Guidelines: Assessment of People Living with Obesity. Available from: https://obesitycanada.ca/guidelines/assessment . Accessed October 2022.

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AACE guidelines: staging directs treatment[1]

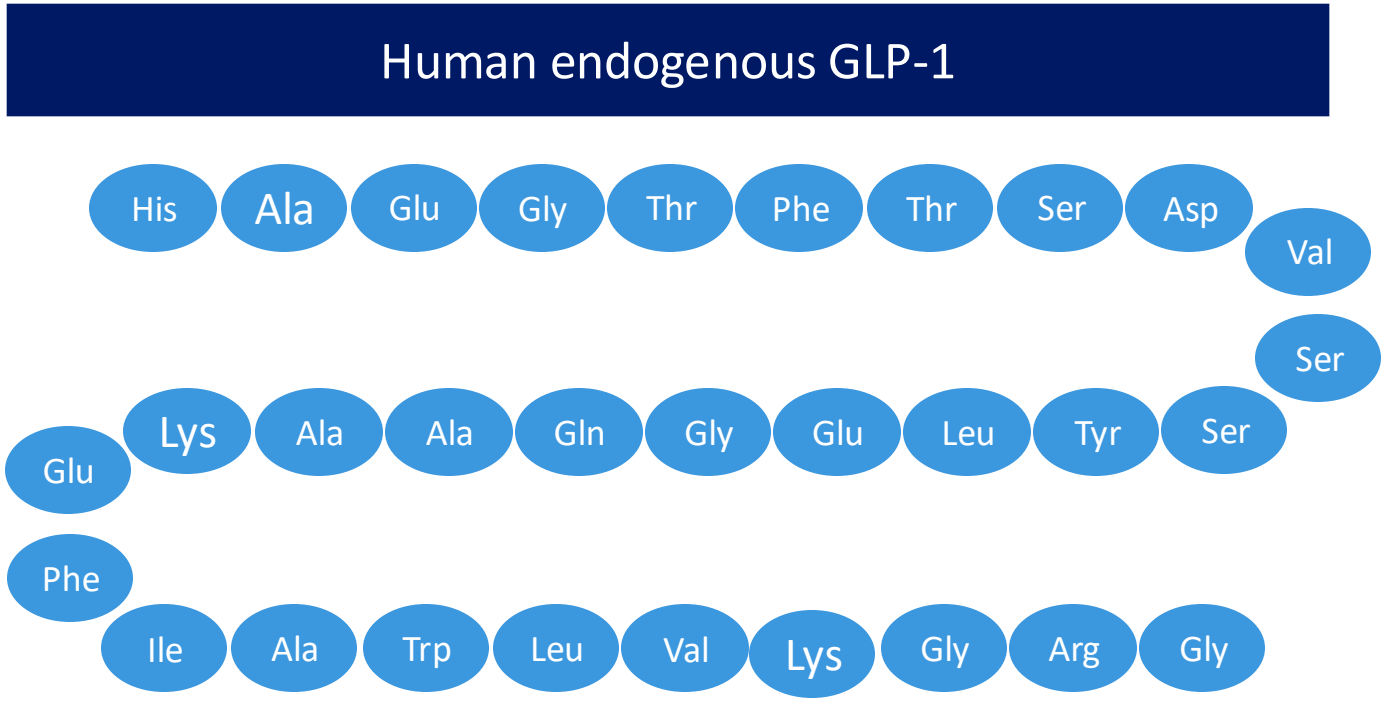
Normal weight (No obesity)	**Stage 0**	**Stage 1**	**Stage 2**
	No complications	One or more mild to moderate complications may be treated effectively with moderate with loss	≥1 Severe complication or requires more aggressive weight loss for effective treatment
	Overweight BMI 25–29.9 kg/m^2 Obesity BMI ≥30 kg/m^2	BMI ≥25 kg/m^2	BMI ≥25 kg/m^2
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 kg/m^2)	Lifestyle/behavioral therapy, add pharmacotherapy (BMI ≥27 kg/m^2), consider bariatric surgery (BMI ≥35 kg/m^2)
Goal: prevent overweight/obesity	**Goal:** prevent progressive weight gain or promote weight loss	**Goal:** achieve weight loss sufficient to ameliorate the complications and prevent further deterioration	

AACE, American association of clinical endocrinologists; ACE, American college of endocrinology; BMI, body mass index.

AACE/ACE algorithm for the medical care of patients with obesity. Available from https://deansomerset.com/wp-content/uploads/2016/06/AACE-ObesityAlgorithm-2016.pdf. Accessed November 2022.

What is GLP-1?

- GLP-1 is a peptide comprised of 31 amino acids
- Member of incretin family
- Secreted predominantly from L-cells in the gut, but also the brain (nucleus tractus solitarius)



Enzymatic degradation by DPP-4

$t_{½}$=1.5–2 min

DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; t½, half-life

Merchenthaler et al. J Comp Neurol 1999;403:261–80; Baggio, Drucker. Gastroenterology 2007;132:2131–57; Ducker, Nauck. Lancet 2006;368:1696–705

GLP-1RAs have multifactorial effects

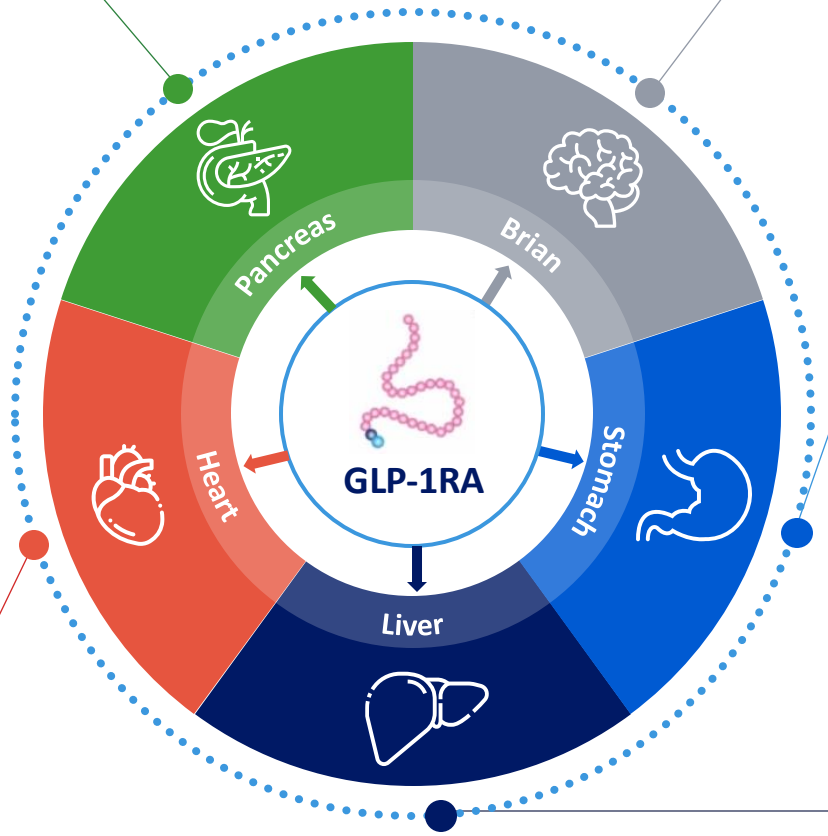
Pharmacological effects

Pancreas

- ↑ Beta-cell function[1]
- ↓ Beta-cell apoptosis[1]
- ↑ Insulin biosynthesis[1]
- ↑ Glucose-dependent insulin secretion[1]
- ↓ Glucose-dependent glucagon secretion[1]

Brain

- ↓ Body weight[5]
- ↓ Food intake[6]
- ↑ Satiety[7,8]



Stomach

- ↓ Gastric emptying[9]

Heart

- ↓ Cardiovascular risk[2]
- ↓ Fatty acid metabolism[3]
- ↑ Cardiac function[3]
- ↓ Systolic blood pressure[3]
- ↓ Inflammation[4]

Liver

- ↓ Endogenous glucose production[10]
- ↑ Hepatic insulin sensitivity[10]
- ↓ *De novo* lipogenesis[10]
- ↓ Lipotoxicity[10]
- ↓ Steatosis[11]

GLP-1RA, glucagon-like peptide-1 receptor agonist

Adapted from Campbell & Drucker. Cell Metab 2013;17:819–37; Pratley & Gilbert. Rev Diabet Stud 2008;5:73–94. Full reference list in slide notes; Mehta et al. Obes Sci Pract. 2017;3(1):3-14

Liraglutide is a once-daily, human GLP-1 analogue

Human endogenous GLP-1

$t_{½}$ = ~2 mins

C-16 fatty acid (palmitoyl)

Liraglutide

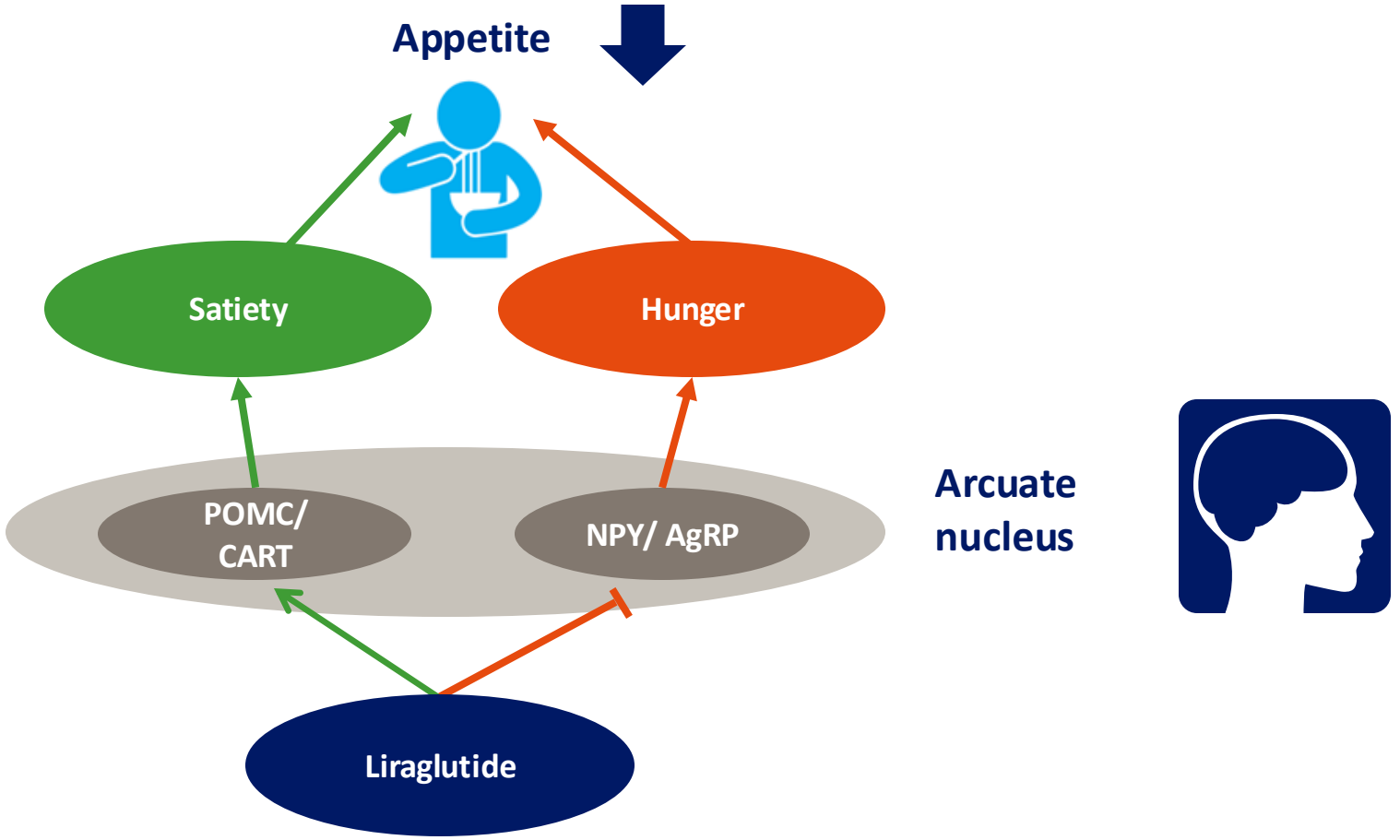
97% amino acid homology to human GLP-1; improved PK: albumin binding through acylation; heptamer formation

↓

Slow absorption from subcutis
Resistant to DPP-4
Long plasma half-life
($t_{½}$ = 13 h)

DPP-4, dipeptidyl peptidase-4;
GLP-1, glucagon-like peptide-1; PK, pharmacokinetics
Knudsen et al. J Med Chem 2000;43:1664–1669; Degn et al. Diabetes 2004;53:1187–1194

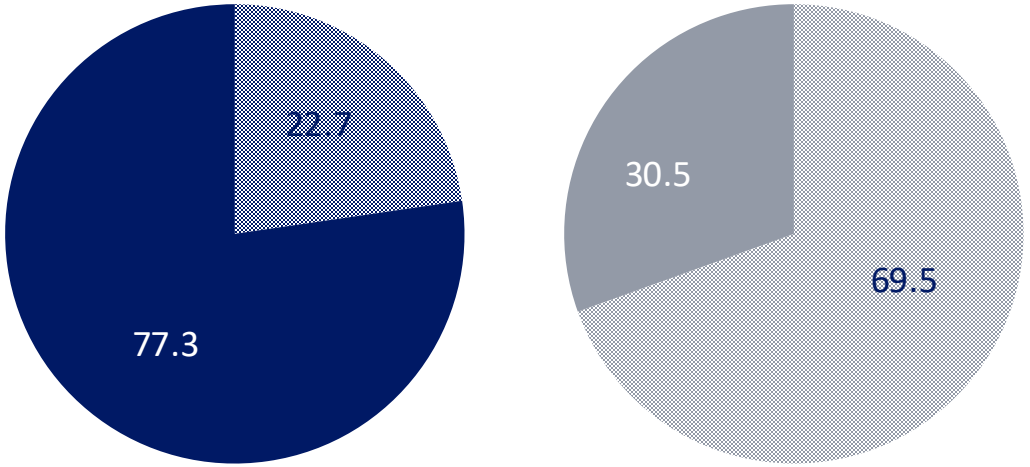
Liraglutide increases satiety and reduces hunger



AgRP, Agouti-related peptide; CART, cocaine- and amphetamine-regulated transcript; NPY, neuropeptide Y; POMC, pro-opiomelanocortin
Secher et al. J Clin Invest 2014;124:4473–88; van Can et al. Int J Obes (Lond) 2014;38:784–93

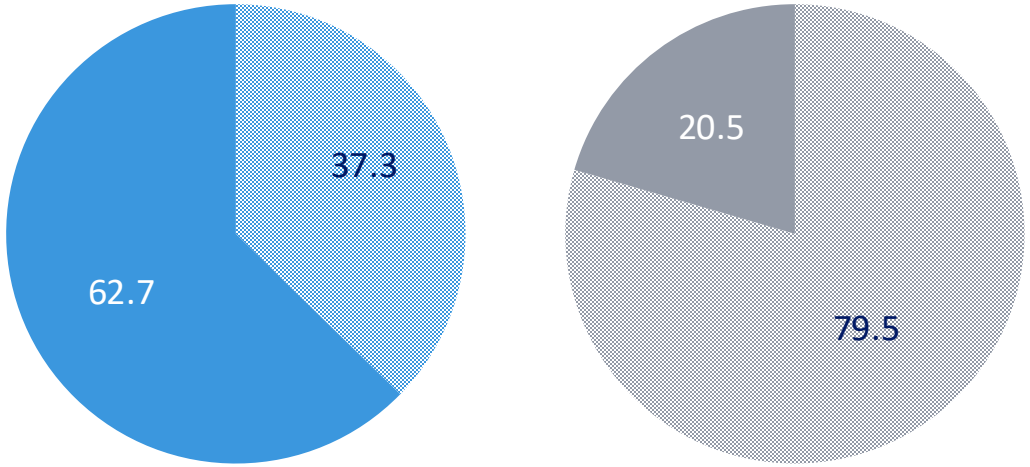
Proportion of early responders

SCALE Obesity and Prediabetes, %



Liraglutide 3.0 mg | Placebo

SCALE Diabetes, %



Liraglutide 3.0 mg | Placebo

Early responders

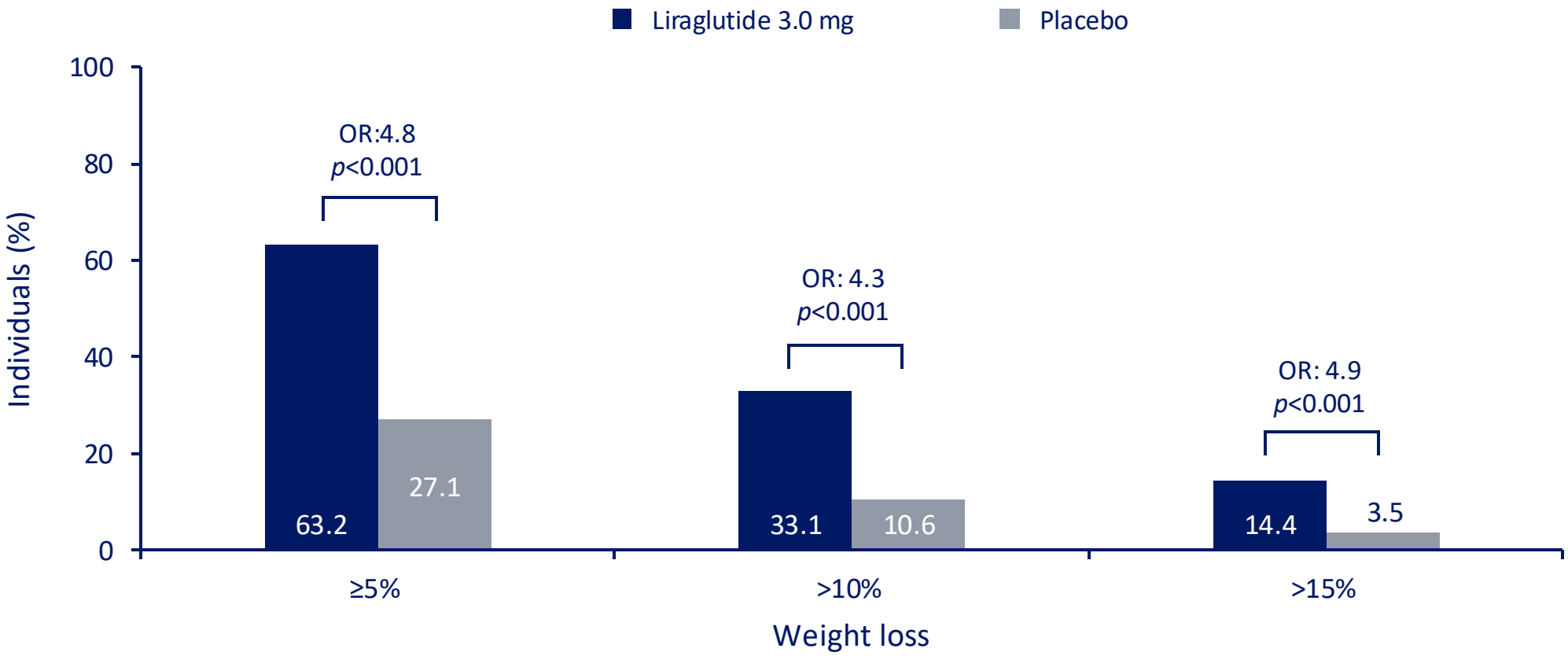
Early non-responders

Data are those individuals with body weight data available at week 16. Early responders, individuals who achieved ≥4% weight loss from baseline at 16 weeks; early non-responders; individuals who achieved <4% weight loss from baseline at 16 weeks.
Fujioka et al. Obesity (Silver Spring) 2016;24:2278–88

Categorical weight loss

SCALE Obesity and Prediabetes: At week 56

Mean baseline weight: 106.2 kg

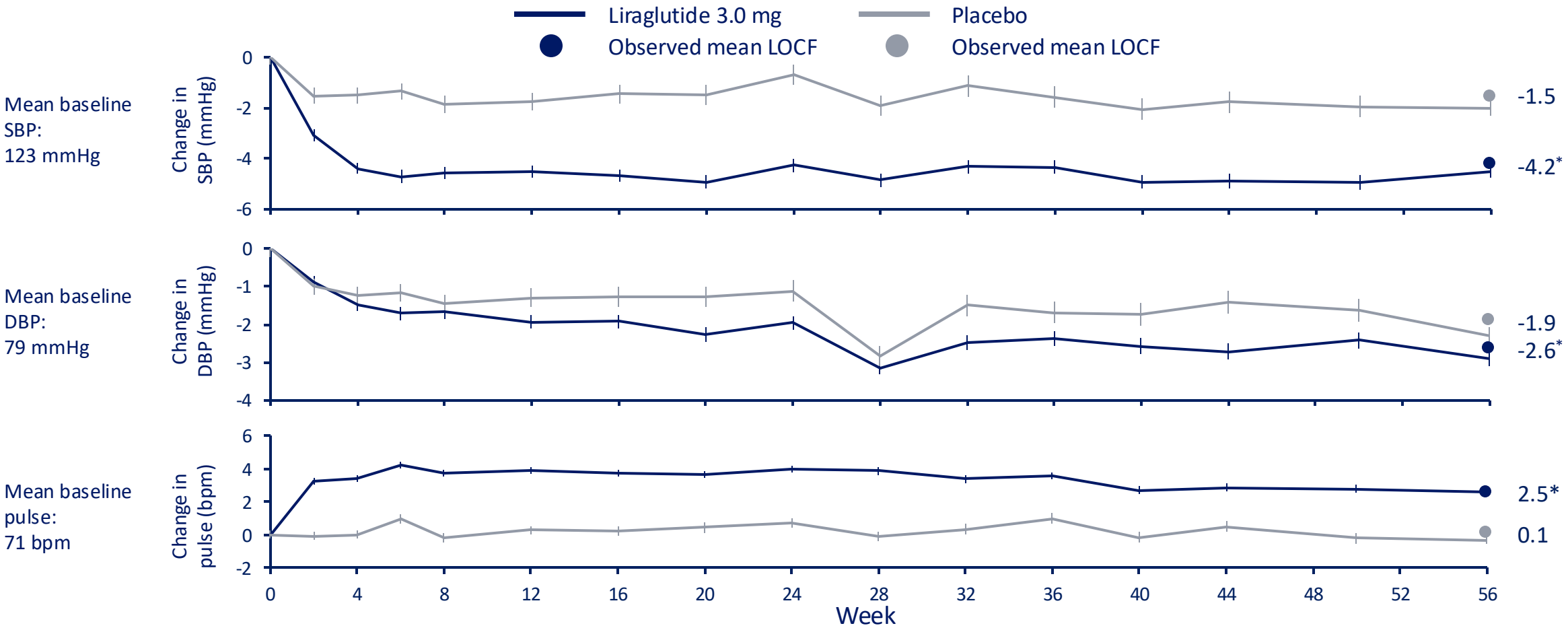


Data are observed means for the full analysis set (with LOCF) and the odds ratios (OR) shown are from a logistic regression analysis (the analysis for achieving 15% weight loss was performed post hoc). LOCF, last observation carried forward; OR, odds ratio

Pi-Sunyer et al. N Engl J Med 2015;373:11–22

Changes in blood pressure and pulse

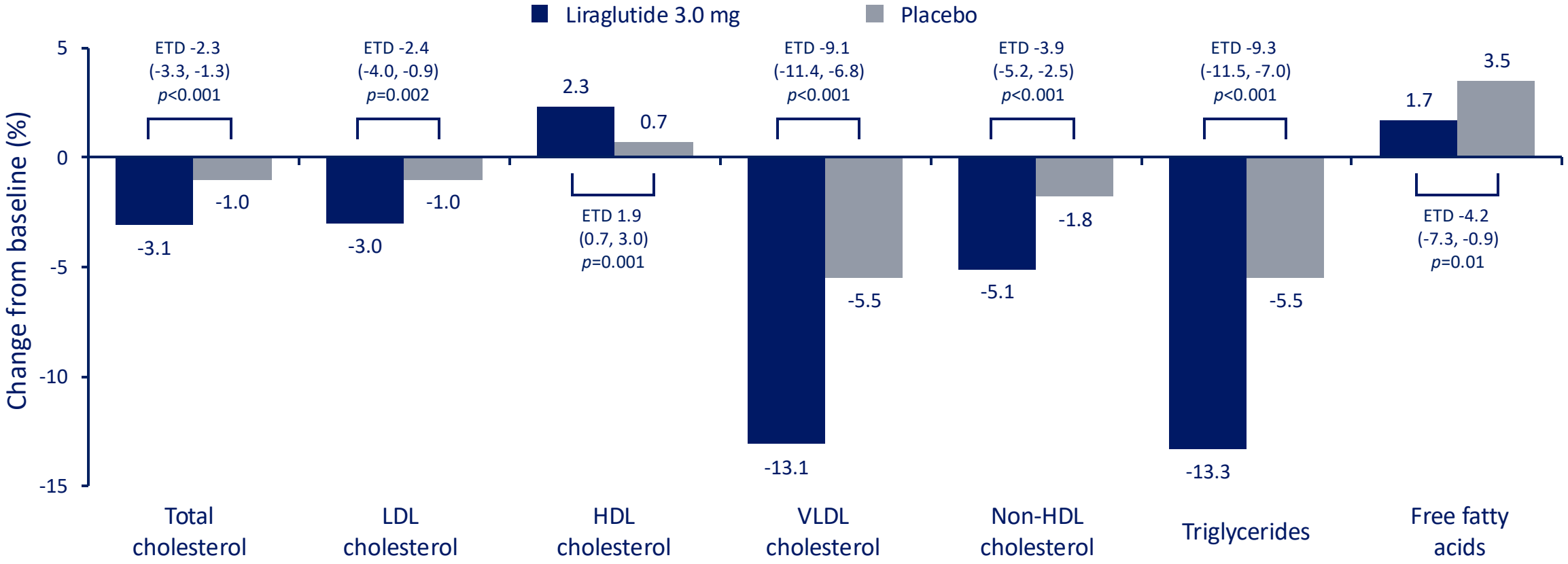
SCALE Obesity and Prediabetes: 0-56 weeks



*FAS, LOCF (blood pressure); SAS, LOCF (pulse). Data are observed means (±SE) of all participants attending each visit. Statistical analyses are ANCOVA. *p<0.001.*
ANCOVA, analysis of covariance; bpm, beats per minute; DBP, diastolic blood pressure; FAS, full analysis set; LOCF, last observation carried forward;
SAS, safety analysis set; SBP, systolic blood pressure; SE, standard error
Pi-Sunyer et al. N Engl J Med 2015;373:11–22

Change in fasting lipids

SCALE Obesity and Prediabetes: 0-56 weeks



FAS, LOCF. Data are based on observed geometric means. Statistical analysis is ANCOVA. ETD, estimated treatment difference (95% CI); FAS, full analysis set; LOCF, last observation carried forward

Pi-Sunyer et al. N Engl J Med 2015;373:11–22

Trial design: Intensive Behavioural Therapy for Obesity

52 week, single centre, open-label, parallel-group-design, randomised controlled trial

150 participants

- BMI ≥30–≤55 kg/m²
- Age ≥21–≤70 years
- Stable BW
- FPG <7.0 mmol/L
- BP <160/100 mmHg

Trial information

- September 2016 to December 2018
- Single centre, open-labelled, parallel-group-design randomised controlled trial
- Duration: 52 weeks

Trial objective

- To test the efficacy of IBT and assess whether the addition to IBT of liraglutide 3.0 mg would significantly increase weight loss.

Exclusion

- History of MTC; T1D/T2D; renal, hepatic, CV disease; hypertension; psychiatric disorders; bariatric surgery

Key endpoints

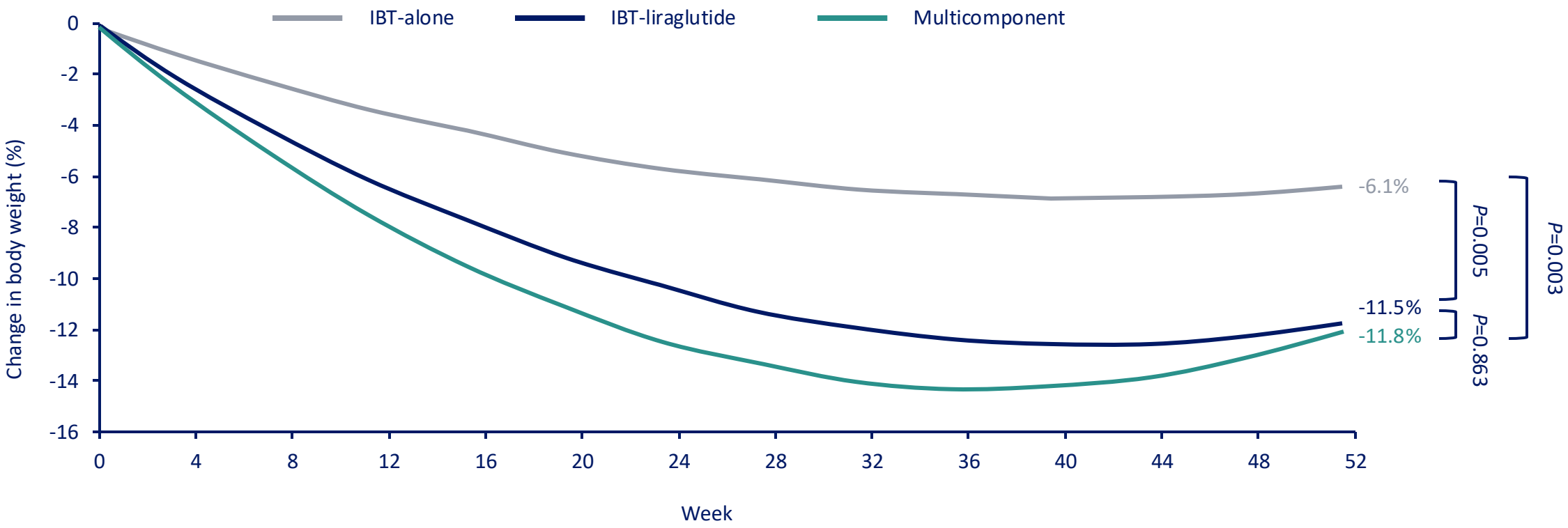
- Primary[1]: Change in weight (%) from baseline to week 52
- Secondary2: ≥5%, ≥10%, and ≥15% weight loss (week 24 and week 52), change in weight (%) from baseline to week 24, CVD risk factors, glycaemic control, mood, quality of life, eating behaviour, appetite, sleep, and satisfaction with weight loss.

IBT consists of lifestyle counselling as currently recommended by the Centers for Medicare and Medicaid Services. Subjects assigned IBT will have 14 brief lifestyle counselling visits the first 24 weeks, followed by monthly visits in weeks 25-52. Multicomponent intervention consists of IBT, liraglutide 3.0 mg and a 1000–1200 kcal/day portion controlled diet. Safety endpoints include physical examination, adverse events (AEs), standard laboratory tests, and mental health assessed by the Columbia Suicidality Severity Rating Scale (C-SSRS) and Patient Health Questionnaire (PHQ-9). BP, blood pressure; BW, body weight; CV, cardiovascular; FPG, fasting plasma glucose; IBT, intensive behaviour therapy; MTC, medullary thyroid carcinoma, T1/2D, type 1/2 diabetes

1.; Wadden et al. Obesity (Silver Spring) 2019; 27(1): 75-86; 2. ClinicalTrials.gov: NCT02911818. Accessed November 2018. Available here

Mean change in body weight over time (%)

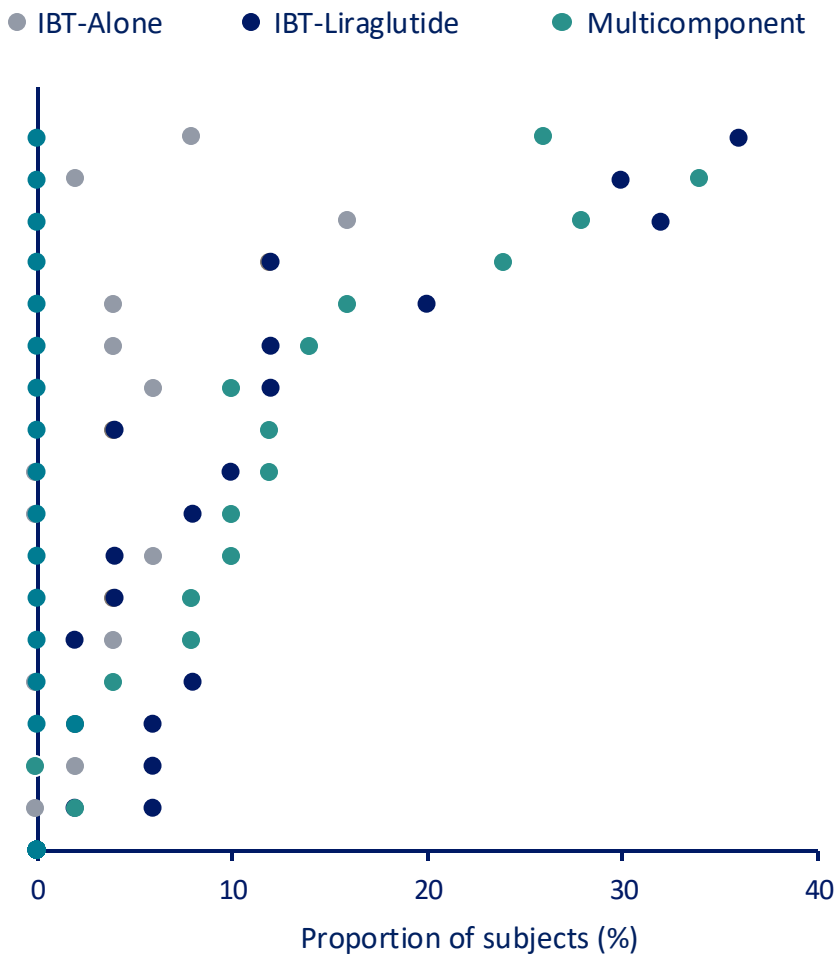
0–52 weeks



Data are estimated mean percentage reduction in the ITT population. ITT, intention to treat
Wadden et al. Obesity (Silver Spring) 2019; 27(1): 75-86

Adverse events with incidence of ≥5%

	IBT-Alone %	IBT-Liraglutide %	Multicomponent %
Nausea	8	36	26
Constipation	2	30	34
Upper respiratory tract infection	16	32	28
Musculoskeletal injury	12	12	24
Gastroenteritis	4	20	16
Diarrhoea	4	12	14
Vomiting	6	12	10
GERD	4	4	12
Injection site irritation	0	10	12
Fatigue	0	8	10
Sinusitis	6	4	10
Knee pain	4	4	8
Lower back pain	4	2	8
Abdominal pain	0	8	4
Headache	2	6	2
Tonsillopharyngitis	2	6	0
Depressed mood	0	6	2



Data are number of participants who had an event (%)
Wadden et al. Obesity (Silver Spring) 2019; 27(1): 75-86

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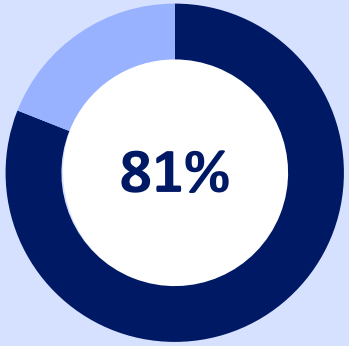
Achieving and maintaining weight loss

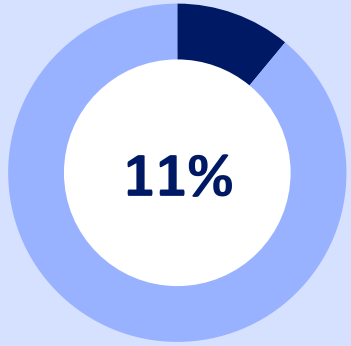
Results from the ACTION IO study

Proportion of PwOs

Global PwO (n=14,502)



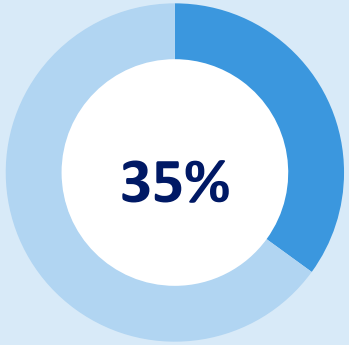
PwOs who made at least one serious attempt at weight loss



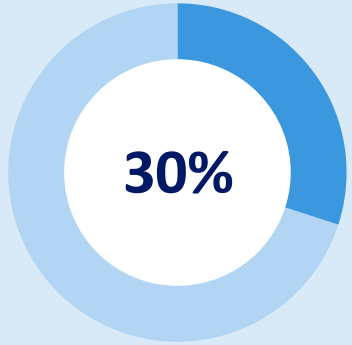
maintained ≥5% weight loss for a year or more

HCP perception

All Global HCPs (n=2,785)



HCPs perceive that only 35% PwO made a serious weight loss effort

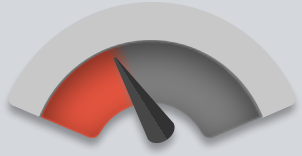


were successful with their WL effort

HCP, healthcare professional; PwO, people with obesity; WL, weight loss.
Caterson et al. Diabetes Obes Metab 2019; 21:1914-24 .

Why is it so difficult to maintain weight loss in the long-term once obesity is established?

Weight loss



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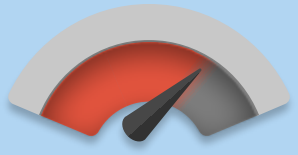
Adaptations that resist weight loss[1]

Hormone levels
↓ satiety hormones
↑ hunger hormones

Metabolism
↓ energy expenditure

↓

Weight regain



Adaptive biological responses lead to persistence of obesity

Once obesity is established, the body demonstrates a variety of adaptations to weight loss that promote weight regain.

Chronic weight management requires interventions that address these metabolic adaptations.

Following weight loss, changes in hormones and resting metabolic rate minimize energy deficit[1,2]

Further weight loss and sustained long-term weight loss is difficult due to metabolic adaptations[1,2]

Metabolic adaptations

1. Fothergill et al. Obesity (Silver Spring). 2016;24:1612–19; 2. Sumithran et al. N Engl J Med. 2011;365:1597–604.

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Summary

1 Many paths can lead to obesity	2 Adaptive biological responses lead to persistence of obesity as a chronic disease	3 Long-term pharmacotherapy should be an integral part of standard of care for obesity management	4 Most PwO can achieve sustained weight loss, health benefits and improved QoL with proper obesity care	5 Most healthcare practitioners in most clinical settings can manage obesity as any other chronic disease
Obesity is caused by a complex interplay of several factors, both genetic and environmental. It is not simply due to an individual's choice or lack of willpower	Weight loss following lifestyle interventions is not sustainable in the long-term due to adaptive biological responses	As with other chronic diseases, pharmacotherapy is needed to address the biology of obesity, in addition to healthy lifestyle choices	Greater sustained weight loss leads to health benefits in obesity related complications and improved quality of life	A structured approach to obesity management is feasible in most clinical settings and leads to wide-ranging benefits for people with obesity

Pharmacotherapy intervention and managing Obesity as a chronic disease

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