Guy's and St Thomas'
NHS Foundation Trust

Obesity update 2024

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Conflicts of interest

Guy's and St Thomas' NHS Foundation Trust

- Advisory work Novonordisk, J&J Ethicon, Lilly
- Educational work: Lilly, Novonordisk, BI, Janssen, MSD, Sanofi, Astra Zeneca
- Institutional Research grant support: Novonordisk
- Shareholder Reset Health and board member

Outline of lecture

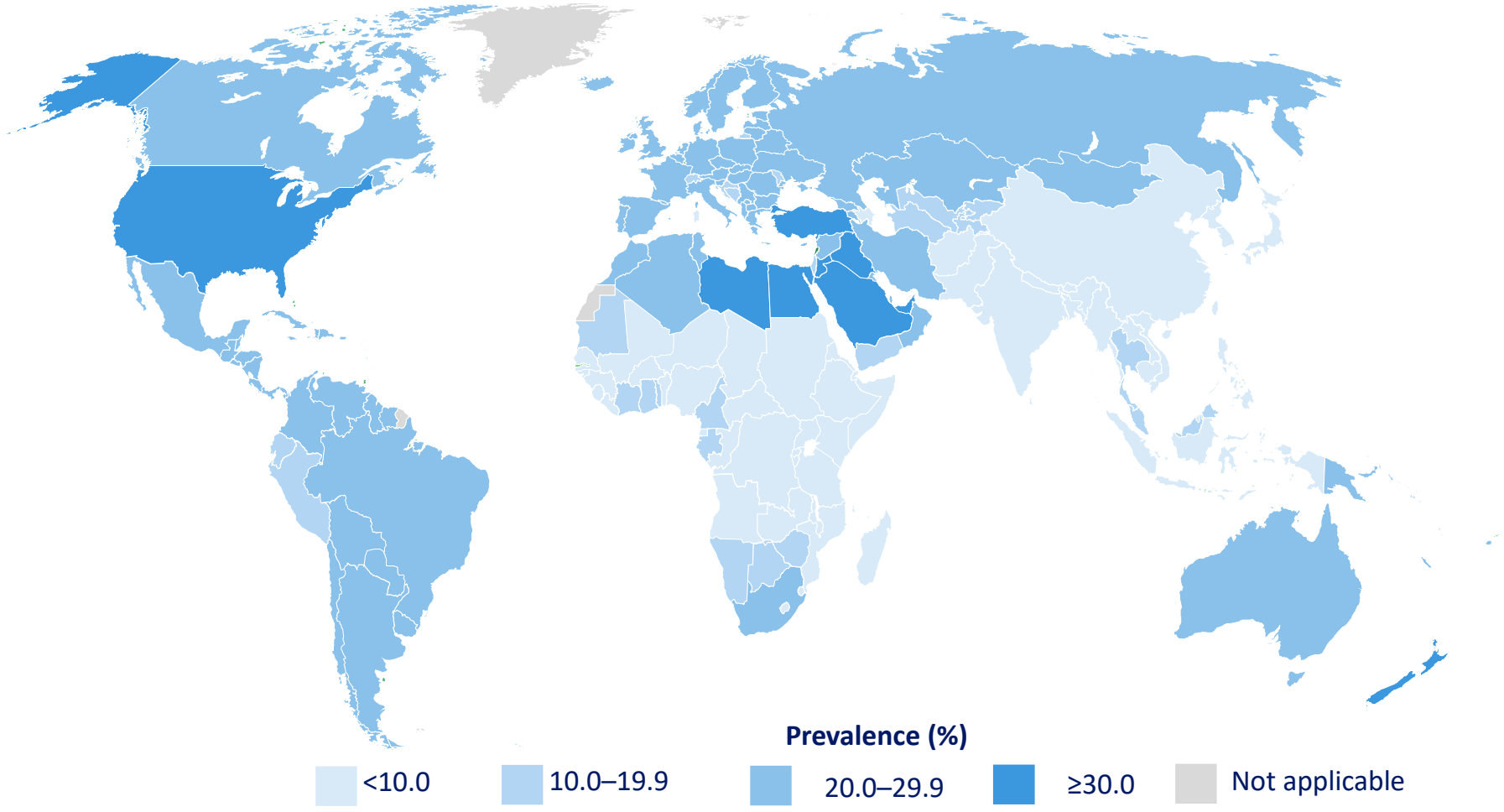
- Introduction to obesity as a chronic disease
- Gut hormone signals and appetite control
- Pharmacotherapy for obesity
- Overview of existing service structures
- Conclusion and learning points

Global prevalence of obesity

Among adults

650

million people
live with obesity



WHO, World Health Organization.
1. WHO. Global Health Observatory (GHO) data. 2017. Prevalence of obesity among adults. Available here. Accessed May 2020;
2. WHO, Obesity & Overweight. 2020. Available here. Accessed May 2020.

Obesity is globally recognised as a disease and health issue

World Health Organization

"Obesity is a chronic disease, prevalent in both developed and developing countries, and affecting children as well as adults."[1]

EMA

"Obesity is recognised as a chronic clinical condition and is considered to be the result of interactions of genetic, metabolic, environmental, and behavioural factors and is associated with increases in both morbidity and mortality."[2]

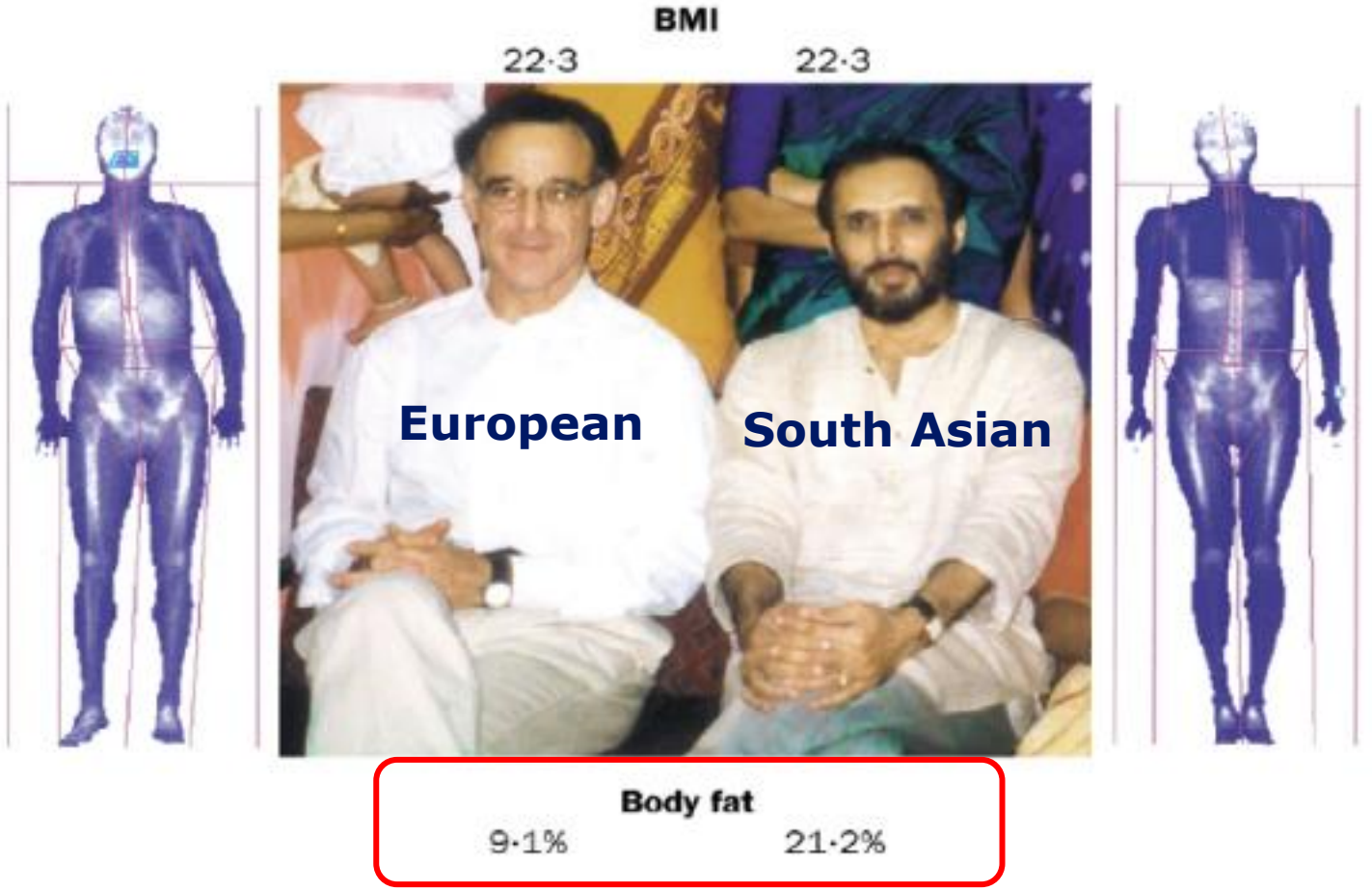
OECD

"Overweight and obese people are a majority today in the OECD area. The obesity epidemic continues to spread, and no OECD country has seen a reversal of trends since the epidemic began."[3]

EMA, European Medicines Agency; OECD, Organisation for Economic Co-operation and Development; WHO, World Health Organization

1. Obesity: preventing and managing a global epidemic. WHO 2000; p1; 2. EMA Draft Guideline on clinical evaluation of medicinal products used in weight control EMA/CHMP/311805/2014, available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/07/WC500170278.pdf;
3. OECD obesity update 2014, available at: http://www.oecd.org/els/health-systems/Obesity-Update-2014.pdf

BMI and body fat



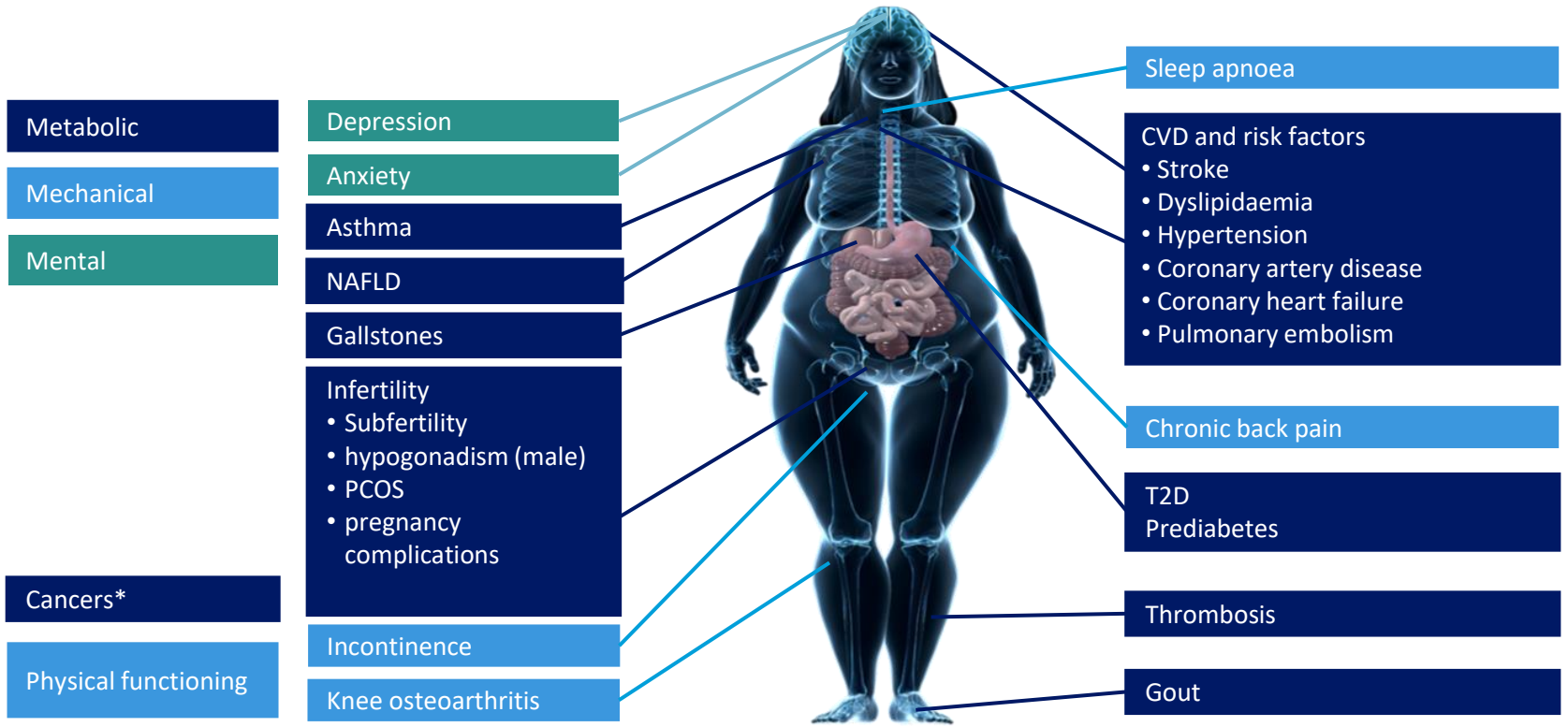
DXA scan of two individuals with the same BMI but markedly different percentage of body fat

BMI, body mass index; DXA, dual energy X-ray absorptiometry

Yajnik CS, Yudkin JS. *Lancet* 2004;363:163.

Obesity is associated with multiple complications

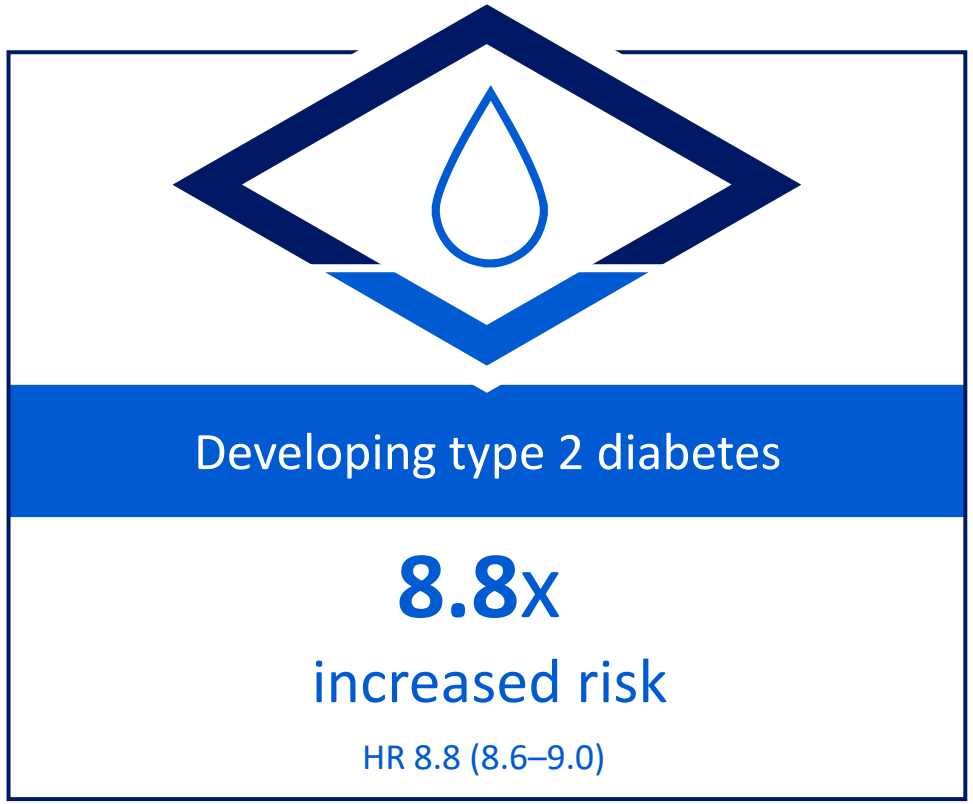
Metabolic, mechanical and mental

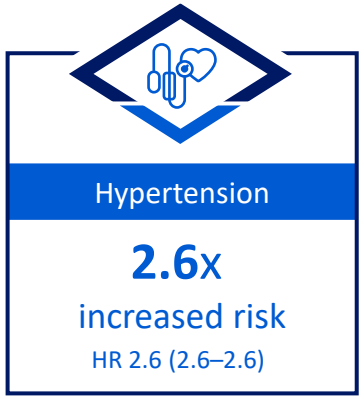


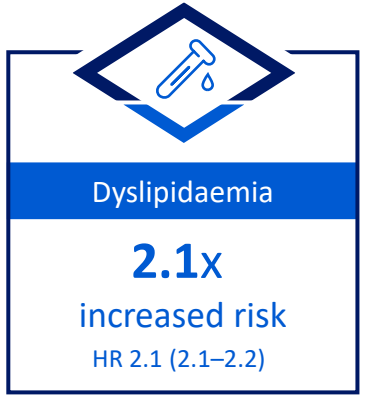
CVD, cardiovascular disease; NAFLD, non-alcoholic fatty liver disease; PCOS, polycystic ovary syndrome
**Including breast, colorectal, endometrial, oesophageal, kidney, ovarian, pancreatic and prostate; T2D, type 2 diabetes*
Adapted from Sharma AM. Obes Rev. 2010;11:808-9; Guh et al. BMC Public Health 2009;9:88; Luppino et al. Arch Gen Psychiatry 2010;67:220–9; Simon et al. Arch Gen Psychiatry 2006;63:824–30; Church et al. Gastroenterology 2006;130:2023–30; Li et al. Prev Med 2010;51:18–23; Hosler. Prev Chronic Dis 2009;6:A48

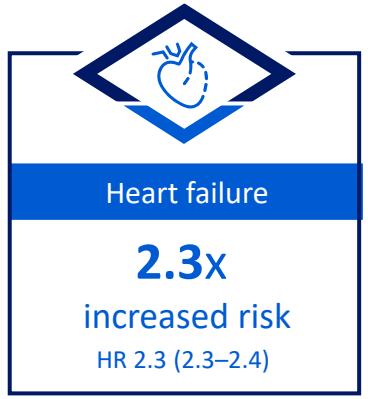
People living with obesity are at higher risk of a number of comorbidities

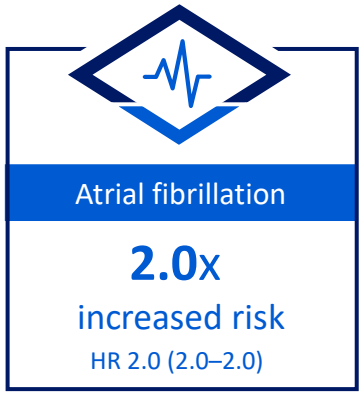
BMI of 35-40 kg/m^2 is associated with risk of serious health outcomes, including:[1*]

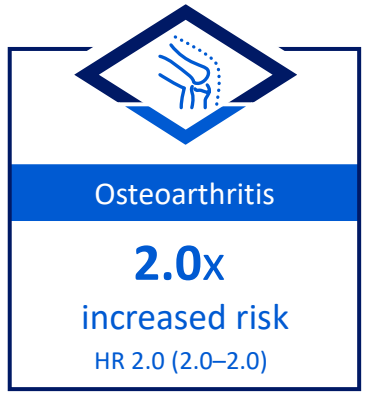








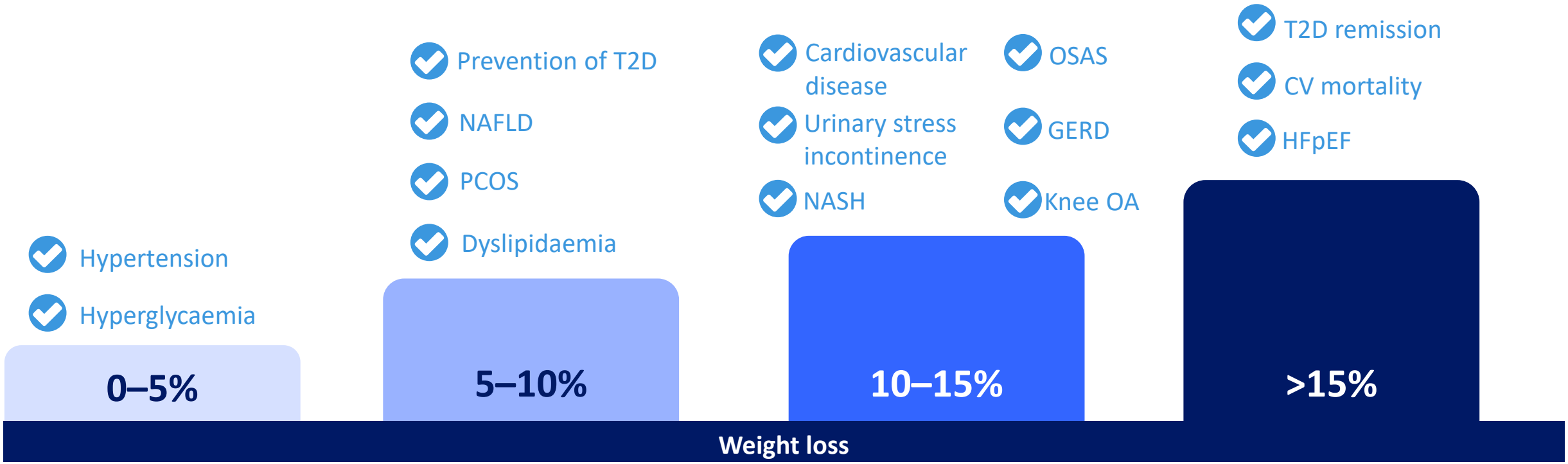




Data from a retrospective cohort study using CPRD GOLD with linked HES data
BMI, body mass index; CPRD, Clinical Practice Research Datalink; HES, Hospital Episode Statistics; HR, hazard ratio 95% confidence interval.
Haase CL et al. Obes Sci Pract 2021;7:137-47.

The effect of weight loss on complications

Towards greater weight loss and overall health improvement



Weight loss of 16% is associated with reduction in all-cause mortality

CV, cardiovascular; GERD, gastro-oesophageal 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; TG, triglycerides.

Garvey WT et al. Endocr Pract 2016;22(Suppl. 3):1–203; Look AHEAD Research Group. Lancet Diabetes Endocrinol 2016;4:913–21; Lean ME et al. Lancet 2018;391:541–51; Benraoune F and Litwin SE. Curr Opin Cardiol 2011;26:555–61; Sundström J et al. Circulation 2017;135:1577–85; Ryan D and Yockey S. Curr Obes Rep 2017;6:187-94.

King's obesity staging score

	Stage 0	Stage 1	Stage 2	Stage 3
	"Normal health"	**"At risk"**	**"Established disease"**	**"Advanced disease"**
Airways	Normal	Snoring	Require CPAP	Cor pulmonale
BMI	<35	35–40	40–60	>60
Cardiovascular	<10% risk	10–20% risk	Heart disease	Heart failure
Diabetes	Normal	IFG	T2DM	Uncontrolled T2DM
Economic	Normal	Expensive travel/clothes	Workplace discrimination	Unemployed due to obesity
Functional	Can manage 3 flights of stairs	Can manage 2 flights of stairs	Requires walking aids or wheel chairs	House bound
Gonadal	Normal	PCOS	Infertility	Sexual dysfunction
Health perceived	Normal	Low mood or QoL	Depression or poor QoL	Severe depression
Body Image	Normal	Dislikes body	Body image dysphoria	Eating disorder

BMI, body mass index; CPAP, continuous positive airway pressure; IFG, impaired fasting glucose; PCOS, polycystic ovary syndrome; QoL, quality of life; T2DM, type 2 diabetes mellitus

Aasheim E, et al *Clinical Obesity* 2011:1;77–84

Obesity is a complex and multifactorial disease

Energy intake

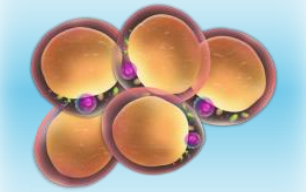
Energy expenditure

Hedonic input

Experienced palatability or pleasure

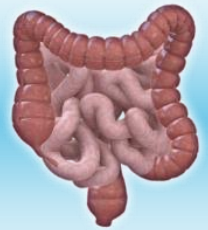
Environment

Inactive lifestyle, smoking cessation, psychosocial factors



Adipose tissue

Pancreas



Gut

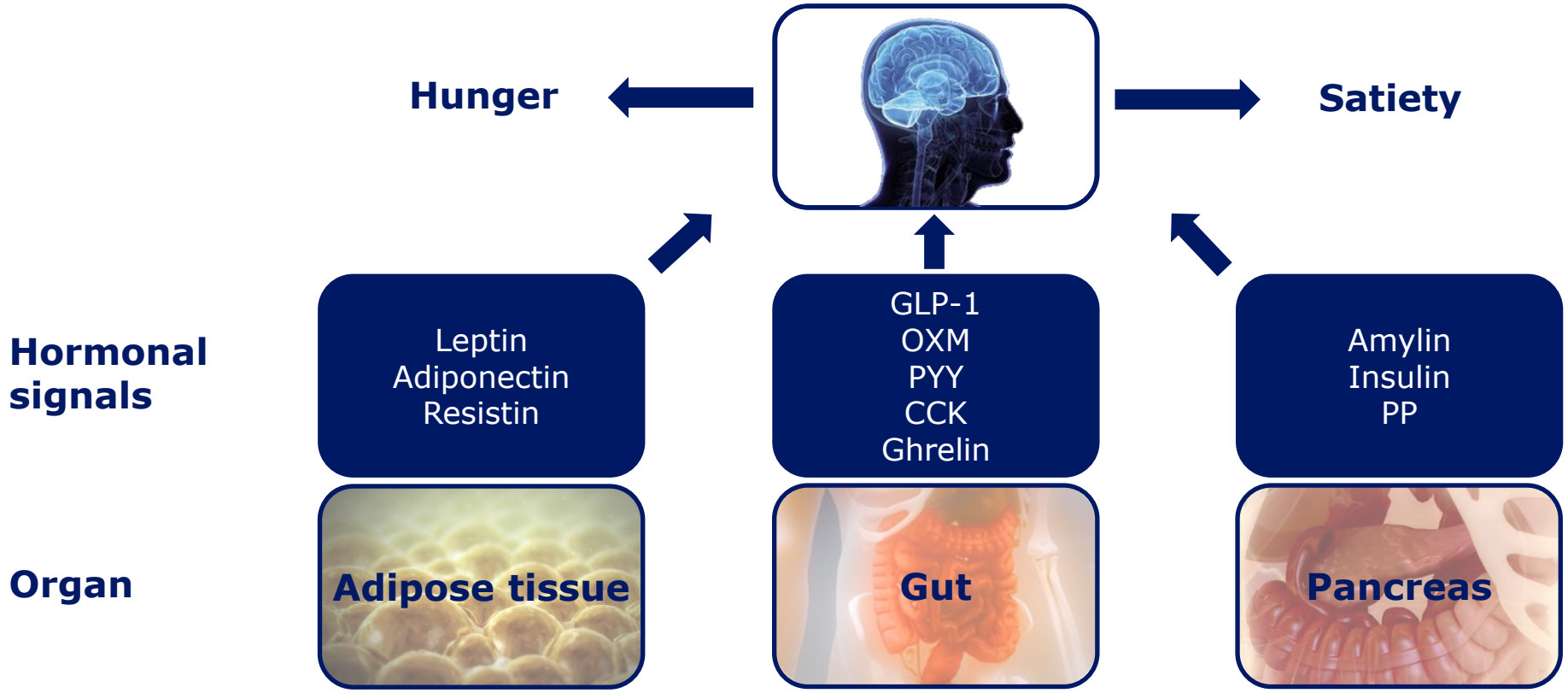
Genetics

Medications

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

Multiple hormonal signals influence appetite

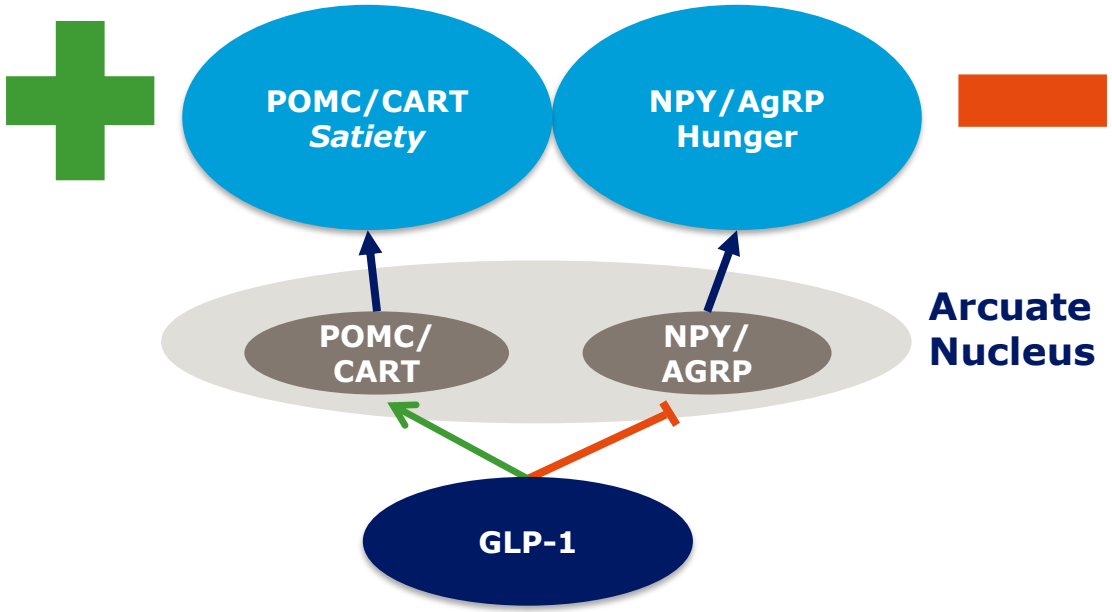
- Multiple endocrine signals influence food intake. These signals are processed by the brain and translated into feelings of satiety or hunger



CCK, cholecystokinin; GLP-1, glucagon-like peptide-1; OXM, oxyntomodulin; PP, pancreatic polypeptide; PYY, peptide-YY

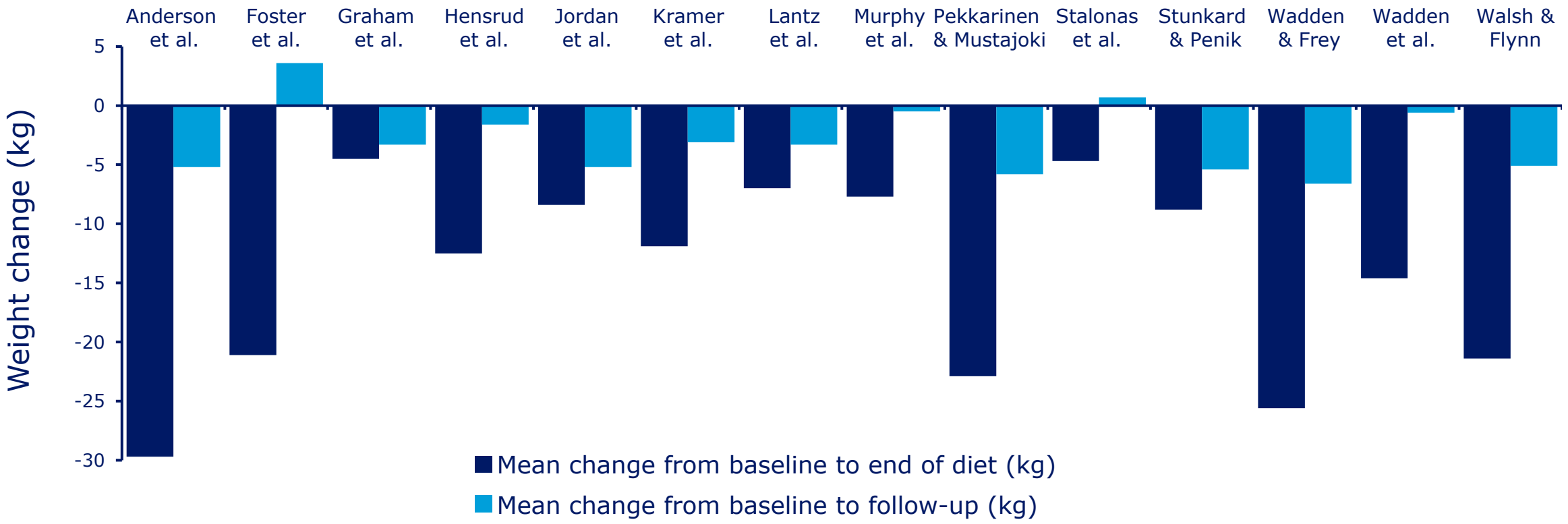
Woods *et al. Int J Obes Relat Metab Disord* 2002;26:S8–10; Badman, Flier. *Science* 2005;307:1909–14

GLP-1 effects on hypothalamic neurons involved in appetite regulation



Secher *et al. J Clin Invest* 2014;124:4473–88

Maintenance of weight loss is challenging



Follow up range from 4 to 7 years

Mann *et al. Am Psychol* 2007;62:220–33

Biological mechanisms act to increase appetite

During and after weight loss

After weight reduction, the brain is stimulated to increase caloric intake by changes in levels of circulating hormones

- ↓ Leptin
- ↑ Ghrelin
- ↓ GLP-1

↓

- ↑ Increased appetite
- ↑ Increased preference for energy-dense foods (high-fat/sugary foods)

GLP-1, glucagon-like peptide-1

Eckel RH. N Engl J Med 2008;358:1941–1950; Murphy KG et al. Nature 2006;444:854–859

Resting energy expenditure is reduced in response to weight loss

Every kg of weight loss

=

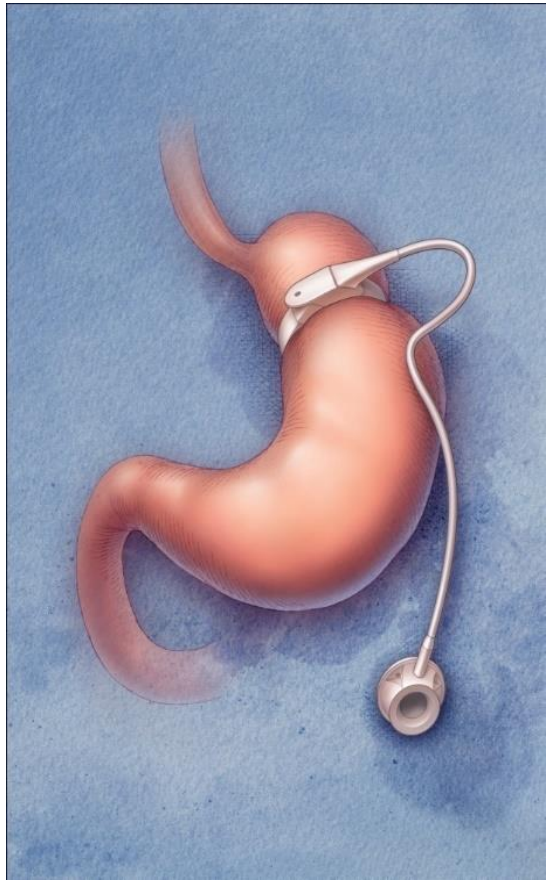
Decrease in 15.4±8.7 kcal/kg resting energy expenditure

Bariatric Surgery in obesity remains the most effective long term weight loss intervention

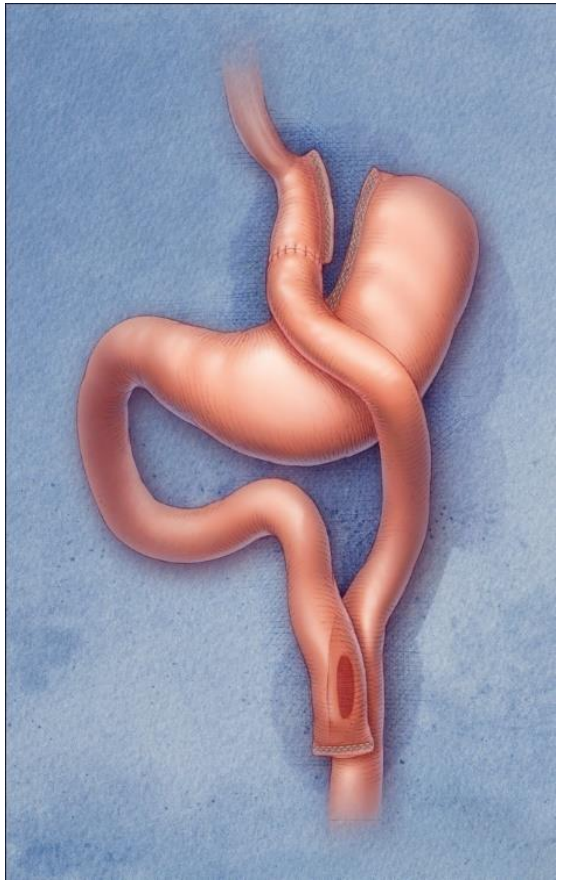
King's College London Founded 1829

NHS Guy's and St Thomas' NHS Foundation Trust

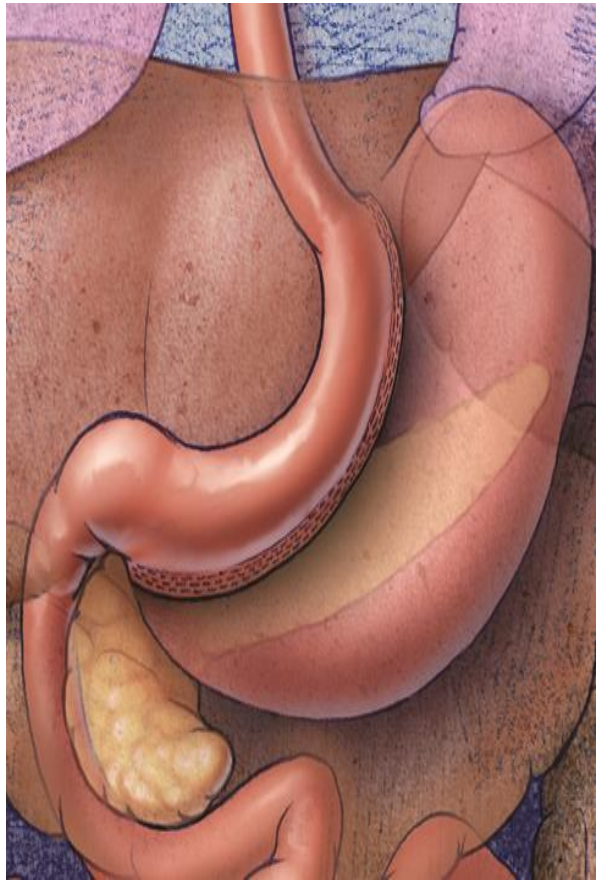
Adjustable Gastric Banding



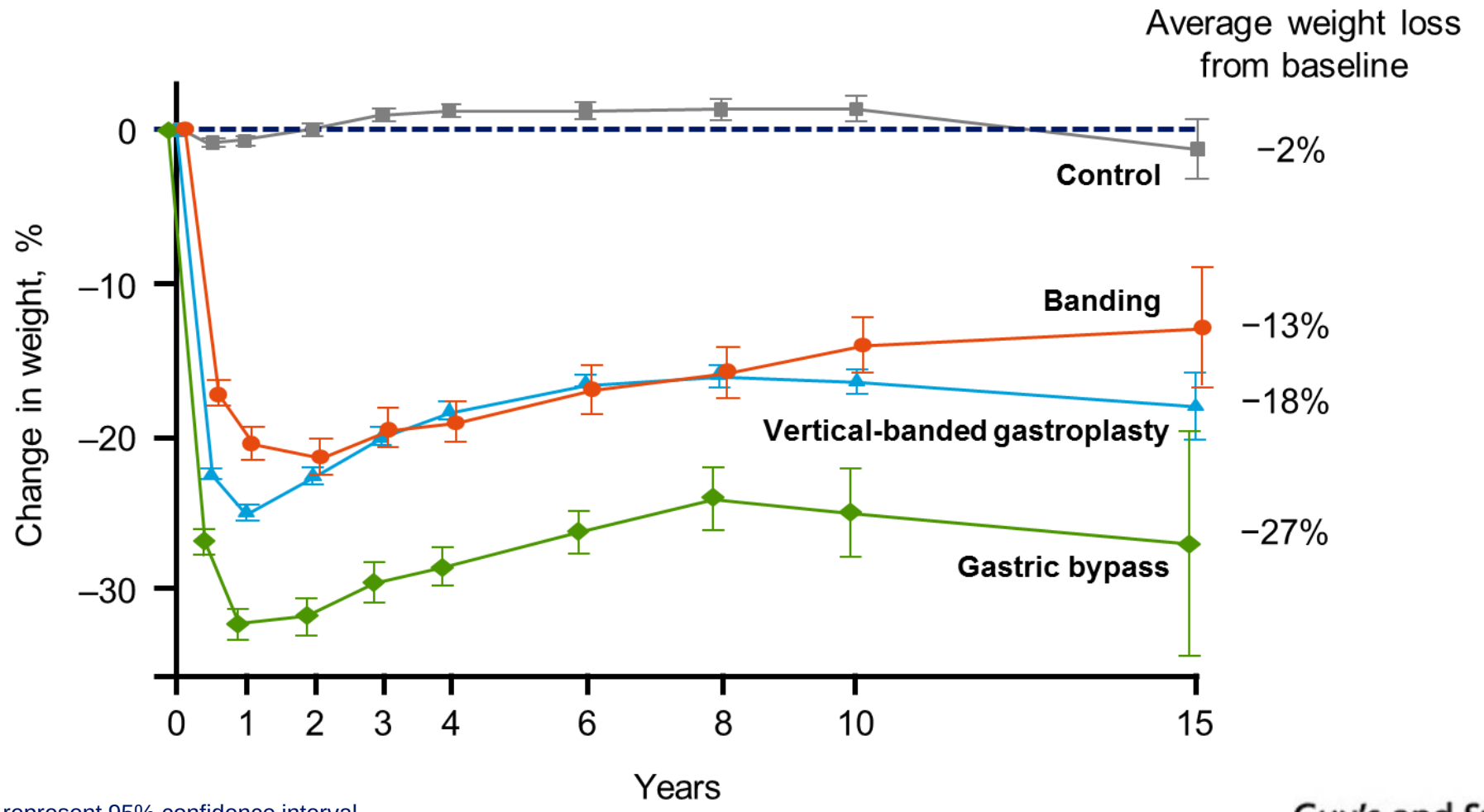
Proximal Gastric Bypass



Sleeve Gastrectomy



Bariatric surgery is associated with maintenance of weight loss



Data are means; bars represent 95% confidence interval.

Sjöström L, et al. N Engl J Med 2007;357:741–52; Martin M, et al. Surg Obes Relat Dis 2010;6:8–15.

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NHS Foundation Trust

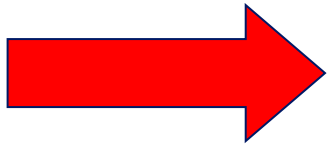
Gastric bypass surgery

↑ GLP-1

↑ PYY3-36

↓ Ghrelin

Improved leptin/
insulin sensitivity

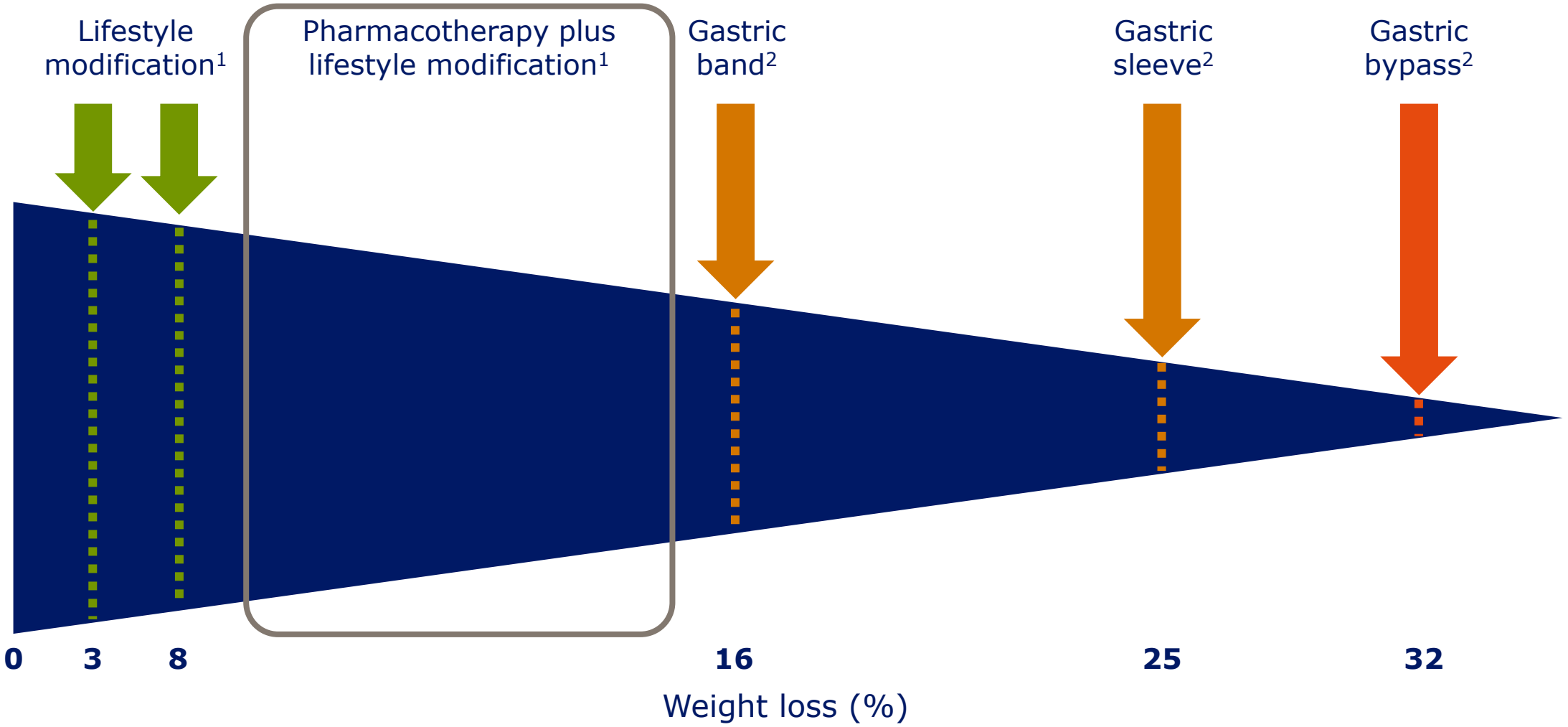


Homeostatic and reward circuitry – reduced hunger and desire to eat

Improved glucose homeostasis
Weight loss

Pharmacotherapy for obesity

Why does everyone want pharmacotherapy for weight loss?



1. Jensen *et al. Circulation* 2014;129(25 Suppl 2):S102–38; 3. 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 15 February 2016)

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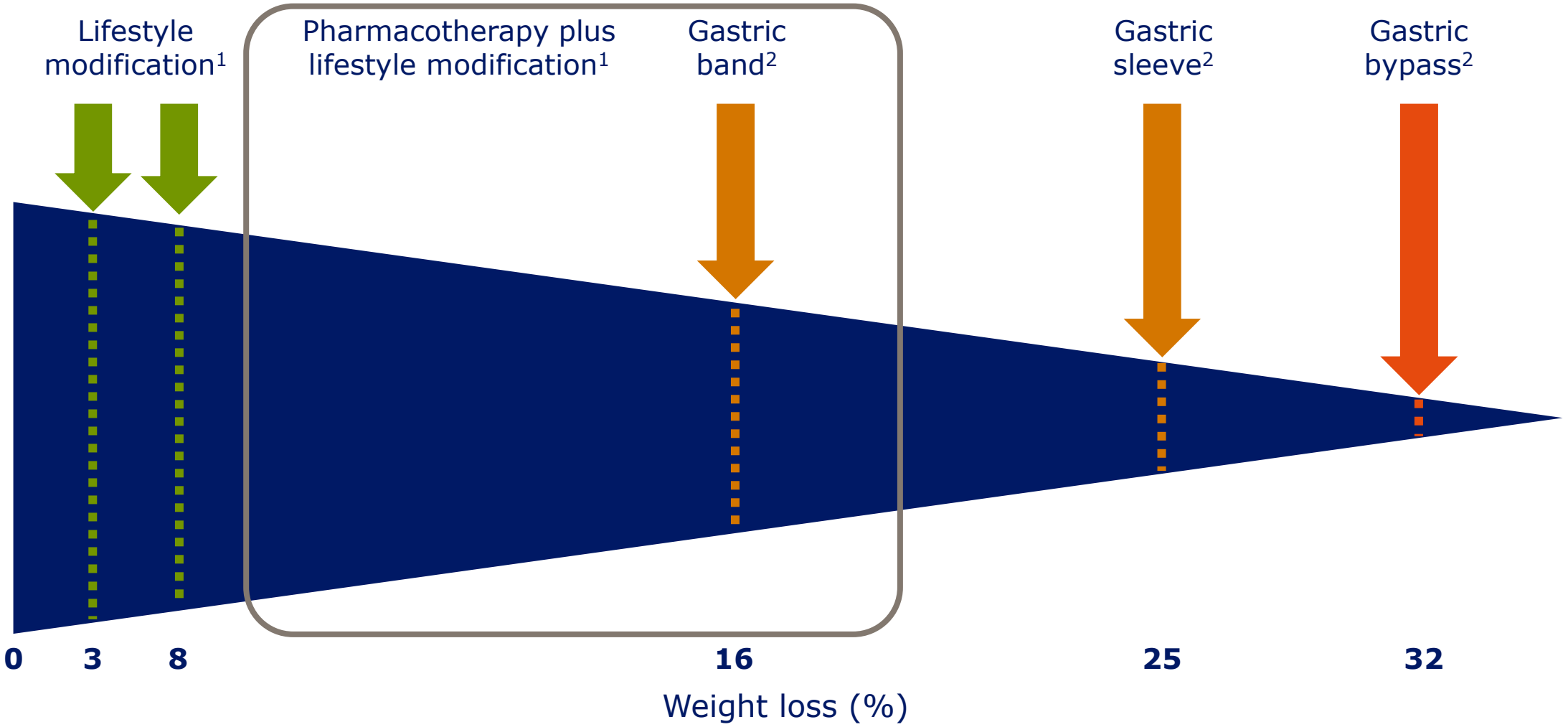

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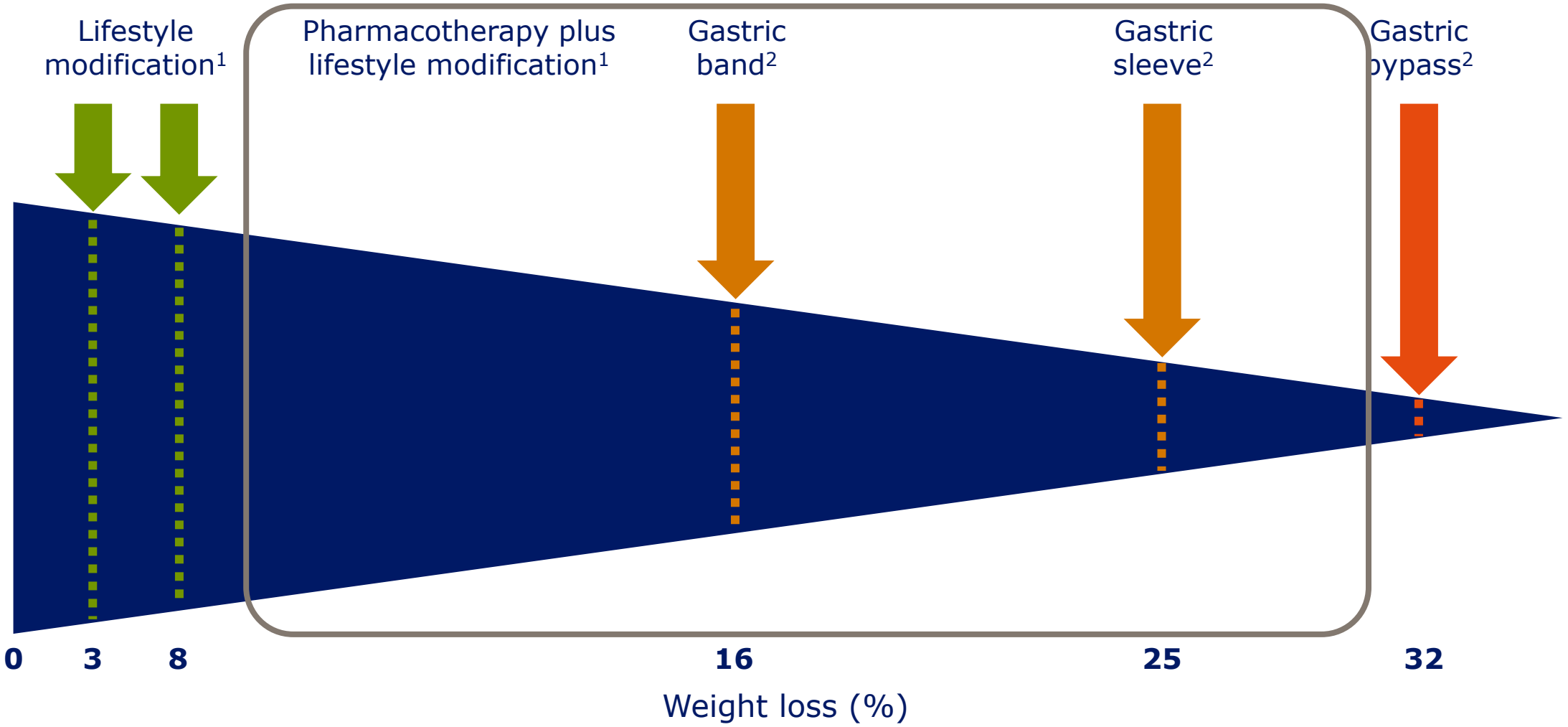

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Pharmacological options for weight management

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			Mode of action	Indications
Orlistat (Xenical®, Alli®)	✓	✓	Energy wastage	Adjunct to diet for obesity, including weight loss and maintenance
Naltrexone/bupropion (Mysimba®, Contrave®)	✓	✓	Appetite suppression	Adjunct to diet and physical activity for chronic weight management in a) obesity BMI ≥30 kg/m^2 b) overweight BMI ≥27 kg/m^2 with comorbidity
Phentermine/topiramate (Qsymia®)	✗	✓	Appetite suppression	
Liraglutide 3.0 mg (Saxenda®)	✓	✓	Appetite suppression	
Semaglutide 2.4 mg (Wegovy®)	✓	✓	Appetite suppression	
Tirzepatide 5/10/15mg (Mounjaro®)	✓	✓	Appetite suppression	

*Approved for short-term use. FDA Drugs: http://www.fda.gov/Drugs/default.htm; EMA Medicines: http://www.ema.europa.eu/

Licensing Saxenda and Wegovy

- ≥30 kg/m² (obesity), or
- ≥27 kg/m² to <30 kg/m² (overweight) + one weight-related comorbidity

Probably over 50% UK population meets these criteria….

Saxenda and NICE

Guy's and St Thomas' NHS Foundation Trust

- BMI ≥ 35
- Pre-diabetes (6—6.4%)
- Increased cardiovascular risk
- Referral to Tier 3 weight management services
- Needs to be prescribed in hospital
- 2 years only

Only 3000 patients on Saxenda in the NHS!

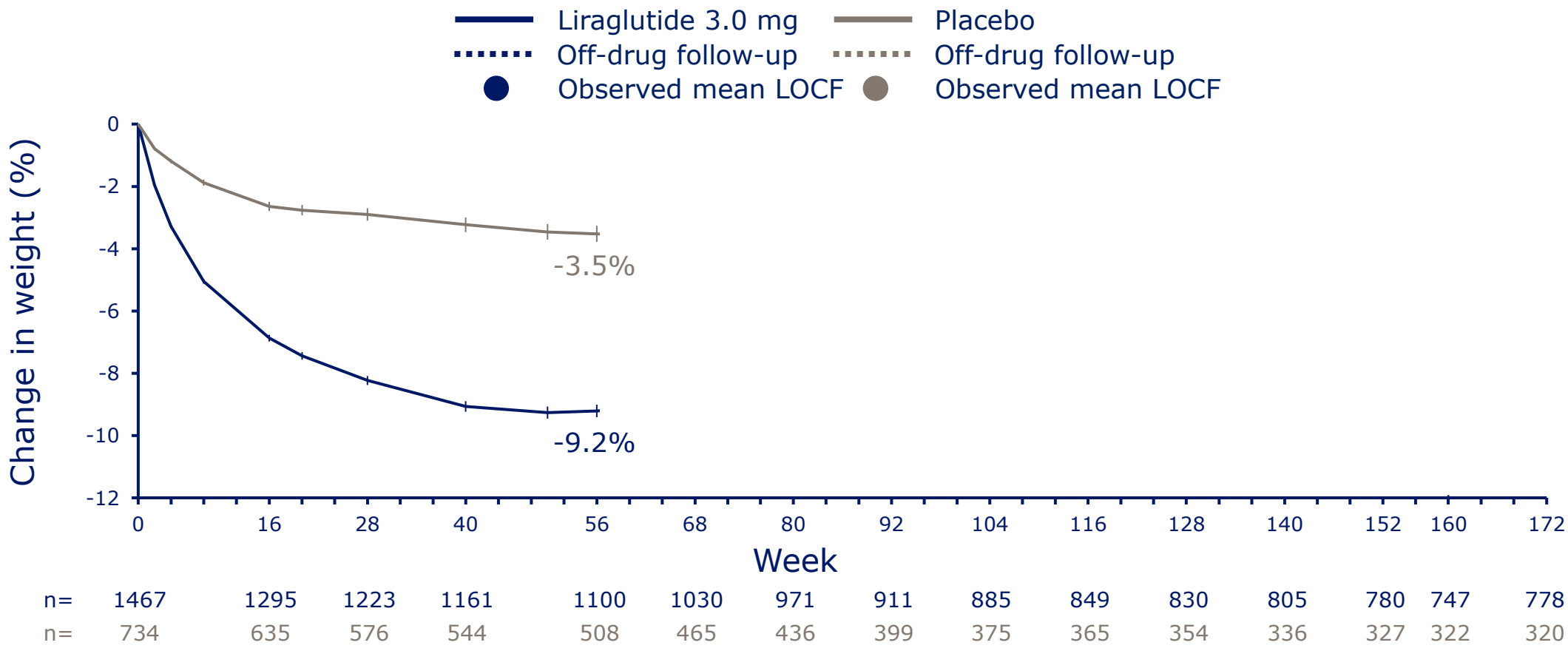
Wegovy and NICE

- BMI ≥ 35 +1 weight –related co-morbidity
- Exceptionally: a BMI of 30.0 kg/m^2 to 34.9 kg/m^2 and meet the criteria for referral to specialist weight management services in NICE's clinical guideline on obesity
- Lower BMI cut-off for certain ethnic populations
- 2 years only

> 4 million people eligible

Liraglutide 3 mg :Change in body weight

SCALE Obesity and Prediabetes: 0–172 weeks



Full analysis set, fasting visit data only. Line graphs are observed means (±SE)
LOCF, last observation carried forward; SE, standard error

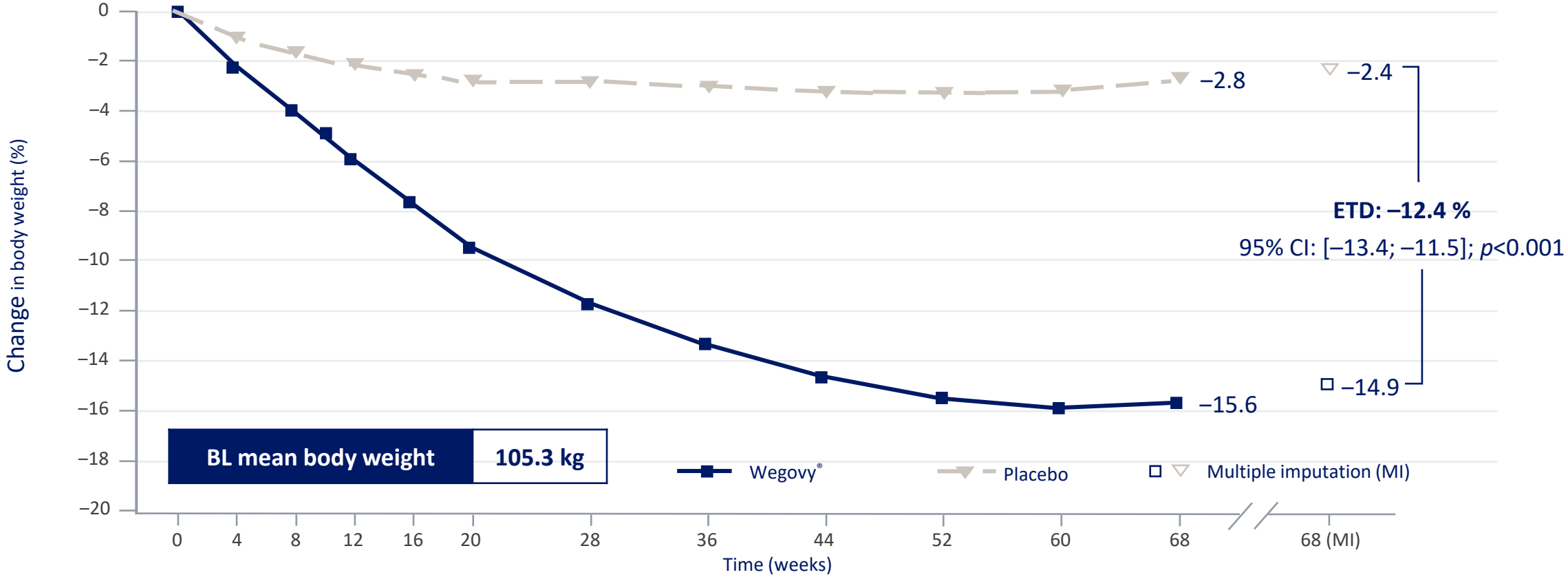
le Roux *et al*. *Lancet* 2017;389:1399–409

Adults with BMI >30 kg/m^2 OR ≥27 kg/m^2 with ≥1 weight-related comorbidity

Semaglutide 2.4 mg: STEP 1

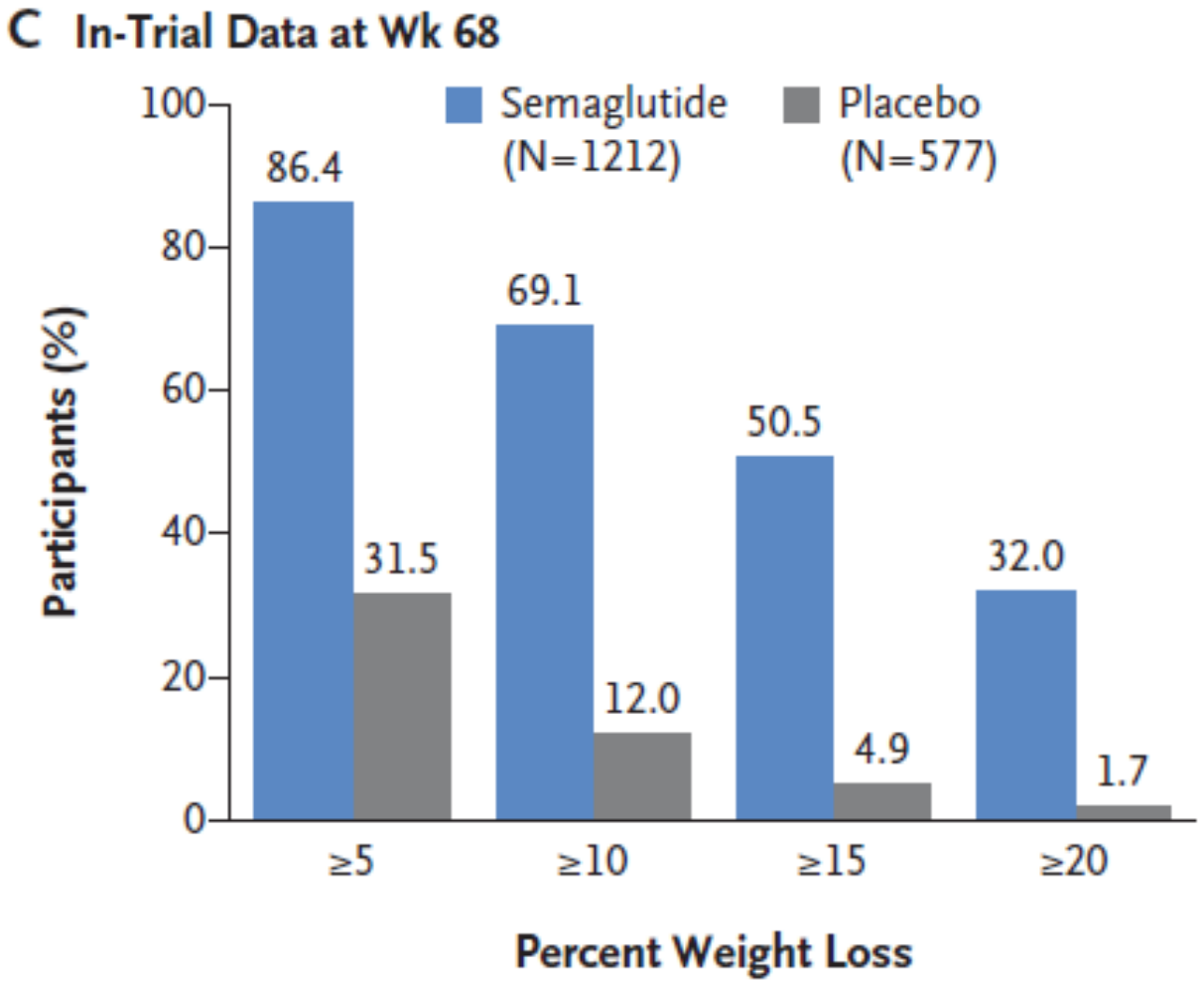
Mean change in body weight (%) from Baseline to Week 68, co-primary endpoint

Adult patients (n=1961) were randomised (2:1) to semaglutide 2.4 mg (n=1306) or placebo (n=655) for a 16-week dose escalation period, followed by a 52-week treatment period, and a 7-week off-treatment follow-up period



Data are from FAS. Observed values for patients completing each scheduled visit and estimates with multiple imputations (MI) from retrieved dropouts.
BL, baseline, ETD, estimated treatment difference; FAS, full analysis set.
Wilding JPH et al. N Engl J Med 2021;384:989–1002.

STEP-1: Semaglutide 2.4 mg s/c once a week vs placebo for weight loss

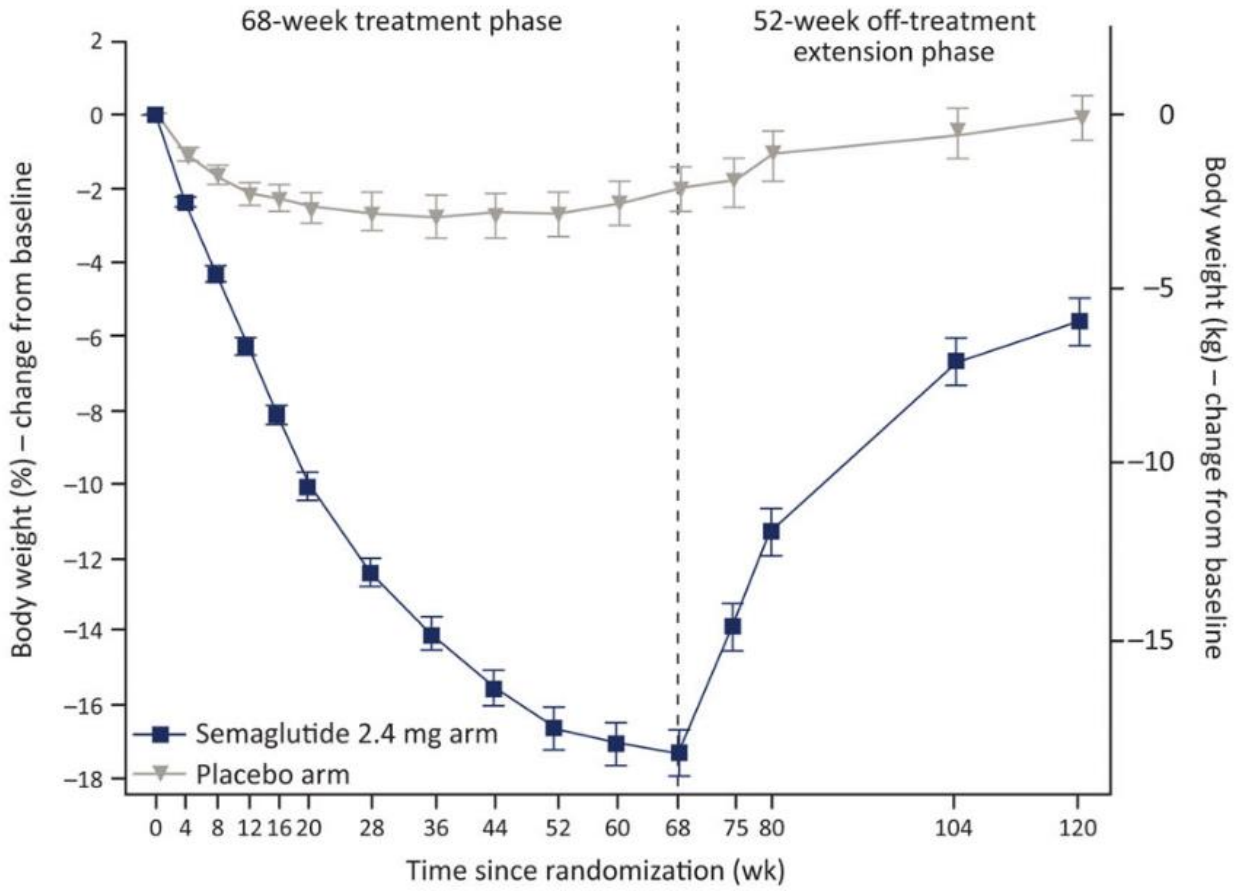


Wilding JPH et al. N Engl J Med 2021;384:989–1002.

Semaglutide 2.4 mg: The STEP 1 trial extension

GLP-1R

Weight Loss %



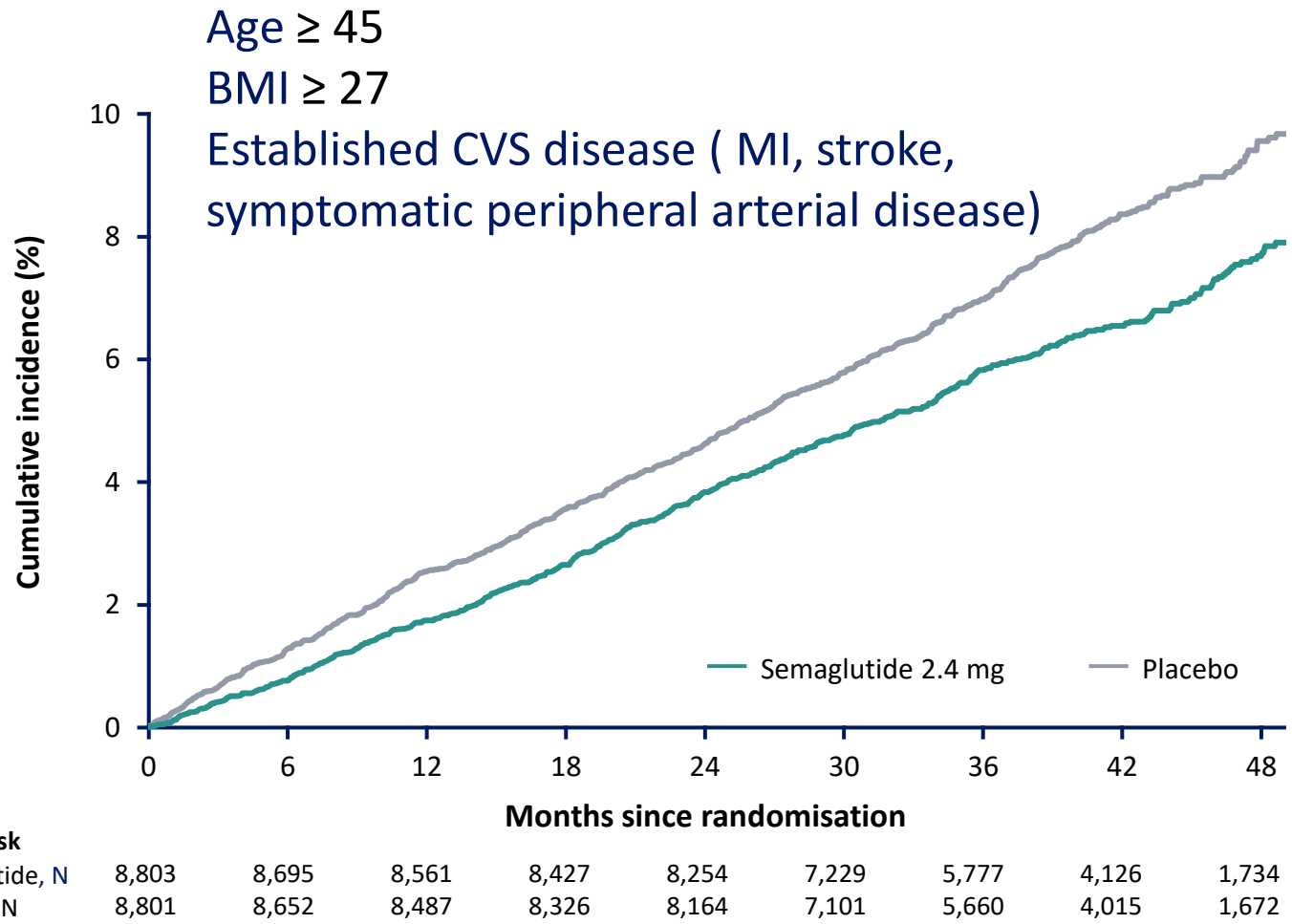
Wilding JPH, et al. Diabetes Obes Metab. 2022;24:1553-1564.

SELECT: cardiovascular benefits of semaglutide 2.4 mg

The NEW ENGLAND JOURNAL of MEDICINE

December 2023

Primary cardiovascular composite end point (n=16,604)



No. at risk

Semaglutide, N	8,803	8,695	8,561	8,427	8,254	7,229	5,777	4,126	1,734
Placebo, N	8,801	8,652	8,487	8,326	8,164	7,101	5,660	4,015	1,672

20% relative risk reduction

1.5% absolute risk reduction

Compared with placebo in people with obesity and established CVD, without T2D

All three components (death from CV causes, non-fatal MI and non-fatal stroke) contributed to MACE risk reduction

Mean follow-up time: 39.8 months

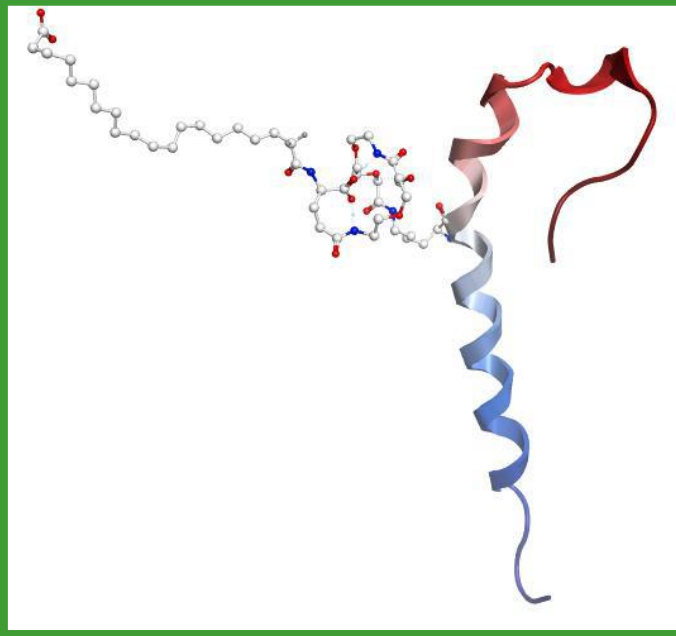
Efficacy end point	Semaglutide 2.4 mg	Placebo
No. of patients reaching end point (%)	569 (6.5%)	701 (8.0%)
HR (95% CI); *P*	0.80 (0.72 to 0.90); <0.001 for superiority	

**MACE was defined as death from CV causes, non-fatal myocardial infarction, or non-fatal stroke. Cumulative incidence (using the Aalen–Johansen method) of the composite MACE primary end point. The HR was estimated using a Cox proportional hazards regression model. The x axis is truncated at 48 months due to the limited number of patients in the trial after 48 months. CI, confidence interval; HR, hazard ratio; CVD, cardiovascular disease; MACE, major adverse cardiovascular events; MI, myocardial infarction; T2D, type 2 diabetes.*

Lincoff AM, et al. *N Engl J Med* 2023;doi:10.1056/NEJMoa2307563.

Tirzepatide

- Tirzepatide is a dual GIP and GLP-1 receptor agonist[1,2]
  - Tirzepatide has greater affinity for the GIP receptor than for the GLP-1 receptor[2]
- It is a small molecule with a molecular weight of 4.8 kDa, for once-weekly subcutaneous administration[1,2]



Tirzepatide
39-amino acid linear peptide conjugated to a C20 fatty diacid moiety via a linker connected to the lysine residue at position 20

GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1; T2D, type 2 diabetes..

1. Willard FS et al. JCI Insight 2020;5:e140532; 2. Coskun T et al. Mol. Metab 2018;18:3–14; 3. Frias JP et al. Lancet 2018;392:2180–93.

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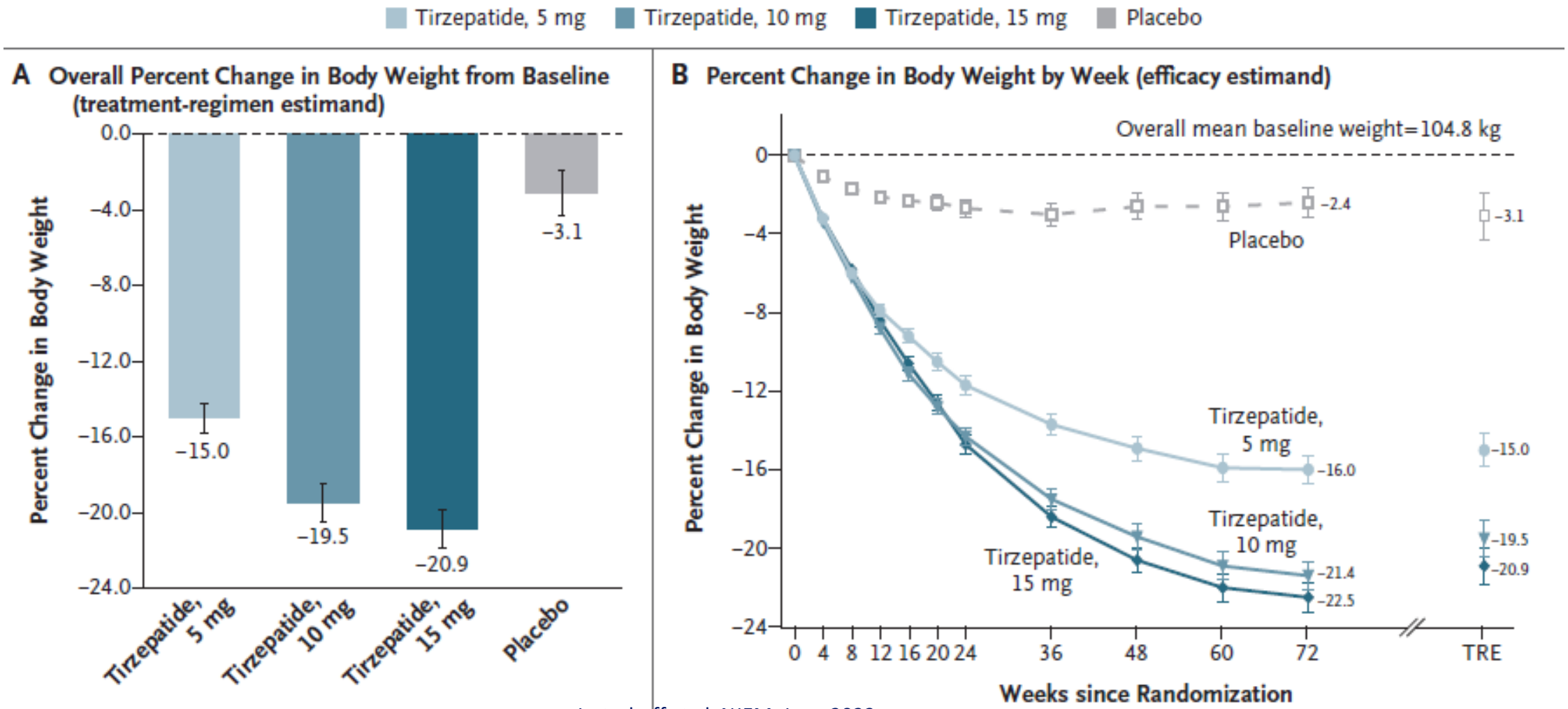
ORIGINAL ARTICLE

Tirzepatide Once Weekly for the Treatment of Obesity



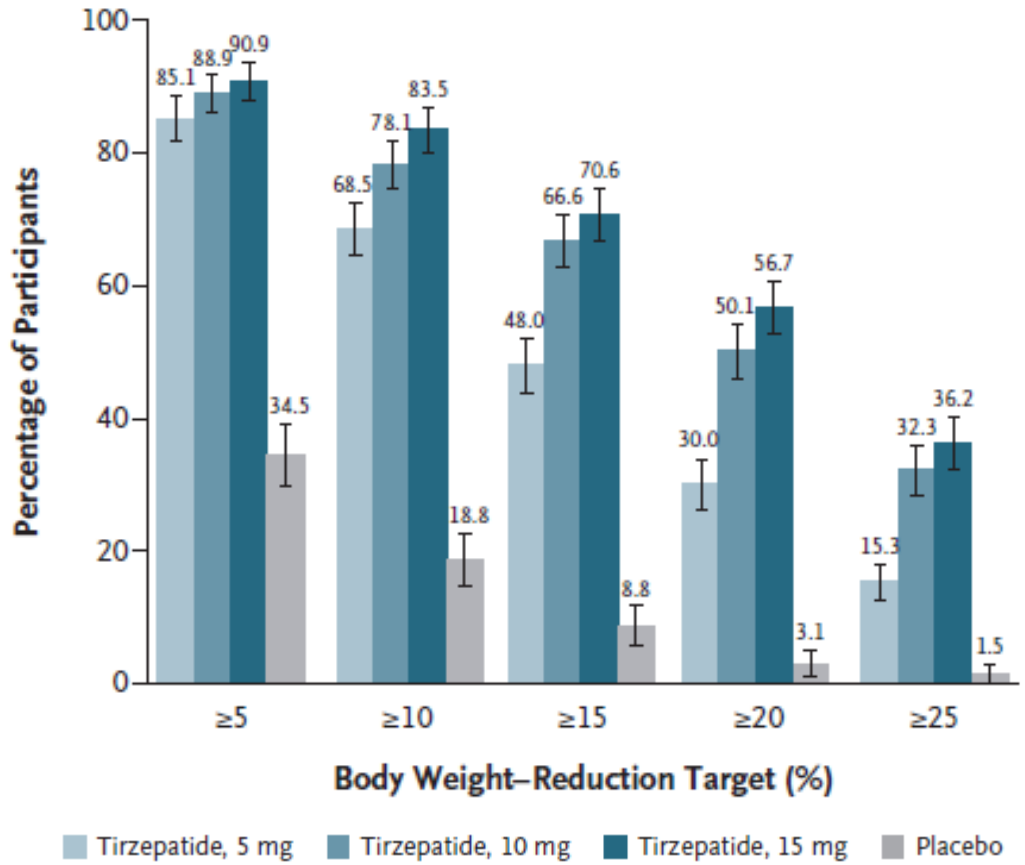
Jastreboff et al, NJEM, June 2022

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Tirzepatide Once Weekly for the Treatment of Obesity

C Participants Who Met Weight-Reduction Targets (treatment-regimen estimand)



Jastreboff et al, NJEM, June 2022

GLP-1shortages nationally and globally

…shortages to last until 2024

Future therapies for weight loss +/- DM control: exciting times!

	Class	Name	Phase	Indication
GLP1-RA	SQ	Semaglutide 7.2mg (similar to STEP-UP DM study)	3	Obesity
	Oral	Semaglutide 25 and 50mg	3	Obesity & T2DM
	Oral	Orforglipron	2	Obesity & T2DM
	SQ	Semaglutide 8mg and 16mg	2	T2DM
	Oral	Danuglipron	2	Obesity
	Oral	Lotiglipron	2	Obesity & T2DM
Dual/Triple incretin agonists	GLP1+GRA	Mazdutide 9mg	2	Obesity
	GLP1+GRA	Pemvidutide	2	Obesity
	GLP1+GRA	B1456906	2	Obesity
	GLP1+GIP	CT-388	2	Obesity & T2DM
	Triple agonist GLP1+GIP+GRA	Retatrutide	2	Obesity & T2DM
	GLP1+Amylin	Semaglutide+cagrilinitide (Redifine 2 like study)	3/2	Obesity & T2DM
Other	GLP1 agonist+GIP antagonist	AMG-133	2	Obesity
	TAS2R agonist	ARD-101	2	Obesity
	Type II-B activin rec. modulator	Bimagrumab	2	Obesity
	PYY agonist	PYY 1875	2	Obesity

National Patient Safety Alert

Department of Health & Social Care

NHS England

Shortage of GLP-1 receptor agonists

Date of issue:	18-Jul-23	Reference no:	NatPSA/2023/008/DHSC

This alert is for action by: All organisations involved in prescribing and dispensing GLP1-RA medicines

This is a safety critical and complex National Patient Safety Alert. Implementation should be co-ordinated by an executive lead (or equivalent role in organisations without executive boards) and supported by clinical leaders in diabetes , GP practices, pharmacy services in all sectors , weight loss clinics, private healthcare providers, those working in the Health and Justice Sector.

Explanation of identified safety issue:

There are very limited, intermittent supplies of all glucagon-like peptide-1 receptor agonists (GLP-1 RAs) [NOTE A].

Supplies are not expected to stabilise to meet full market demand until at least mid-2024.

The supply issues have been caused by an increase in demand for these products for

Actions required

Actions to be completed as soon as possible, and not later than 18/10/2023

Actions for clinicians and prescribers of GLP-1 RAs until supply issues have resolved.

1. Only prescribe GLP-1 RAs for their licensed indications.
2. Do not initiate new patients on GLP-1 RAs for the duration of the shortage.

Will pharmacotherapy be available in the NHS?

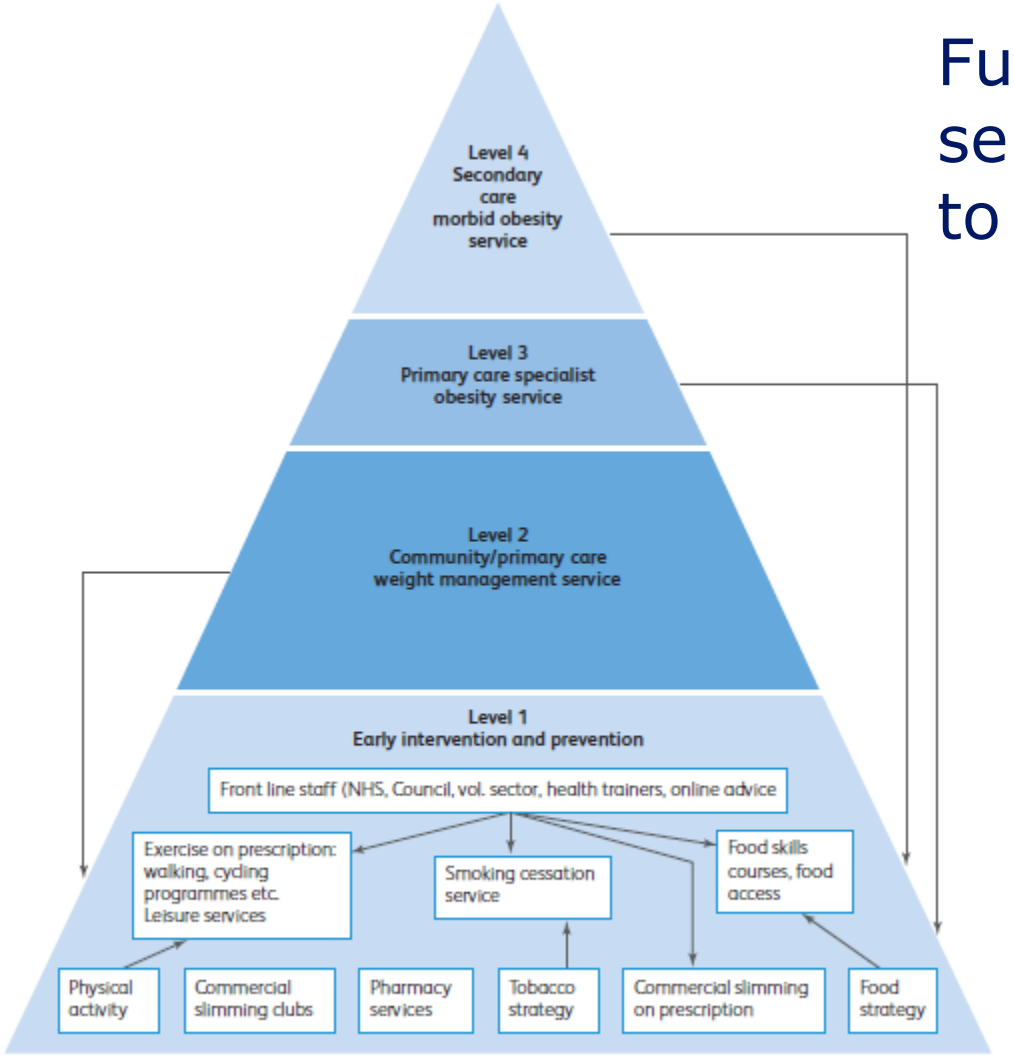
- Availability for pharmacotherapy likely to be limited
- NHS England considering whether prescribing should take place in primary practice
- No real financial plans on who is going to pay for this
- 50% of the country remains without Tier 3/4 services
- Long waiting times to access Tier 3
- Very limited metabolic surgery in the UK- very long waiting lists

Wegovy phasing

Cohort	Indicative timeline	Eligible patients
Group 1	Dec 2023	• **Active malignancy** requiring weight loss for planned treatment • Weight loss required for **organ transplantation** • **IIH** requiring frequent lumbar punctures and/or visual compromise • BMI 35-45 requiring weight loss ahead of a planned **time-sensitive surgery** • **Assisted conception** over the age of 35 following review by a fertility service • **Severe OHS**
Group 2	TBC	• History of ischaemic heart disease, stroke, heart failure (NYHA class III-IV) or NASH • BMI >35 kg/m^2 (or 32.5 kg/m^2 depending on ethnicity) and **3 or more weight related co-morbidities**, including; CKD (stages 3 or 4), dyslipidaemia, hypertension, NAFLD, PCOS, pre-diabetes/T2DM, OSA/CPAP
Group 3	TBC	• BMI >35 kg/m^2 (or 32.5 kg/m^2 depending on ethnicity) and **2 weight related co-morbidities** • Patients eligible for or already receiving a GLP-1 analogue as obesity therapy, or part of their treatment for T2DM • Patients with pre-diabetes who need to be switched to Wegovy from Saxenda due to supply chain interruption
Group 4	TBC	• All other eligible patients as defined in NICE TA 875

Overview of existing service structures

Tiers of Weight Management Services



Example of an obesity care pyramid for adults (Birmingham and Solihull Weight Management Service (Adult) care pathway). Note: The term 'severe and complex obesity' is now preferred to 'morbid' obesity.

Funding for Tier1-4 services is inadequate to meet demands

Tier 3 services: Results: Service providers

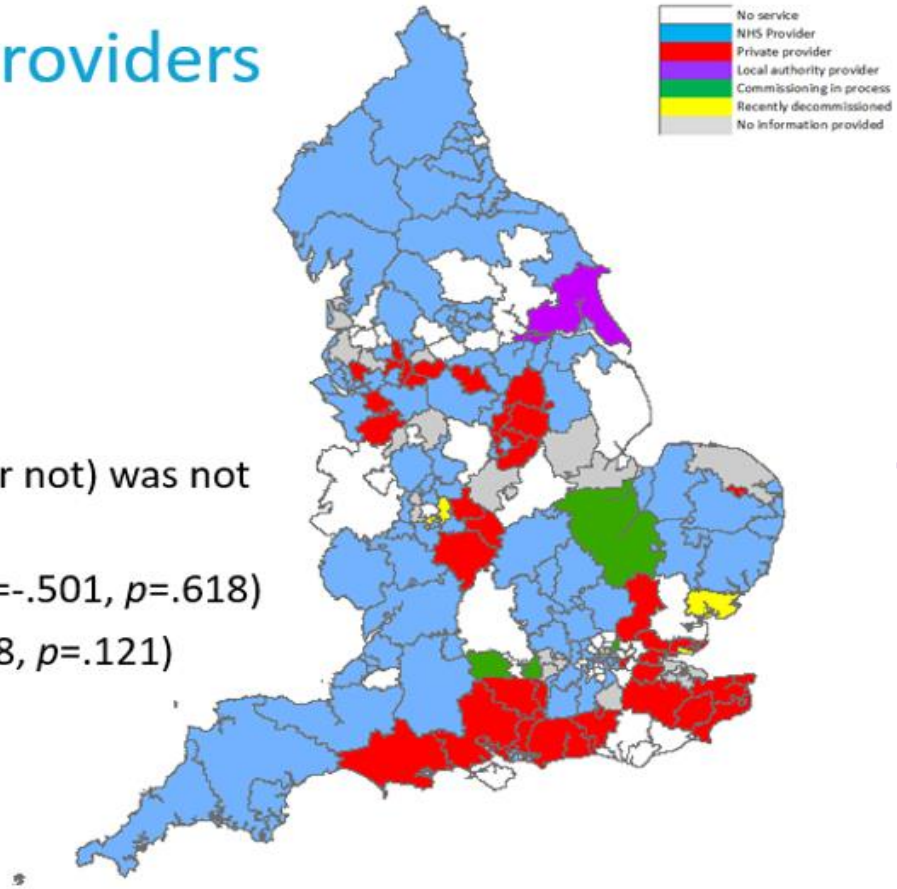
NHS provider 97 CCGs

Private provider 37 CCGs

Local authority 1 CCG

Commissioning of a service (or not) was not related to:

- size of CCG population [5] (t=-.501, p=.618)
- local obesity rate [6] (t=1.558, p=.121)

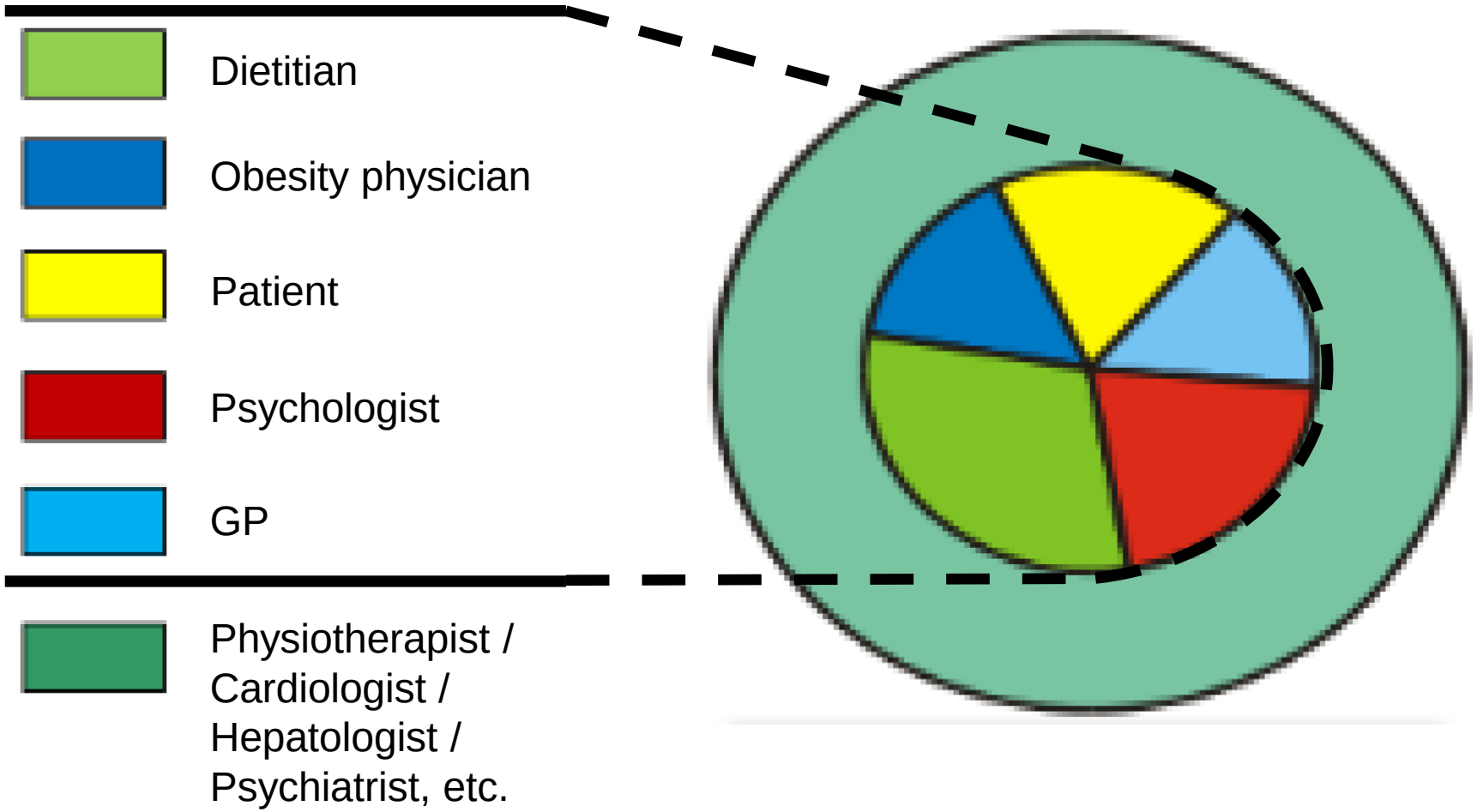


Set-up services cater for very small number of patients

- 135 CCGs (68.2%) commissioned a tier 3 service,
- 6 CCGs (3.0%) were in the process of setting up a service,
- 39 CCGs (19.7%) reported having no service,
- 3 CCGs (1.5%) were decommissioning their service, 11 CCGs did not answer or reported the information as unavailable

Lighter life survey, 2016

Multidisciplinary Team working in Tier 3



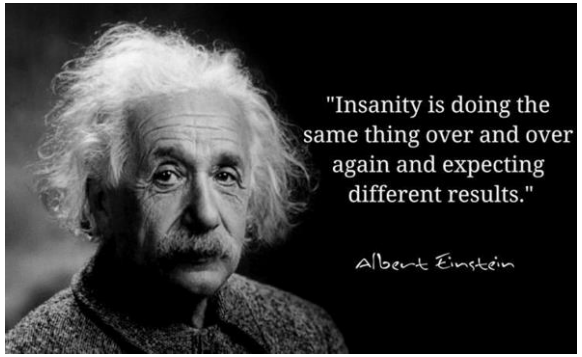
The potential for digital weight management services

In UK, > 4 m eligible for pharmacotherapy
Only 0.3% have access to services

Insights from the pandemic revealed, compared to F2F services, digital delivery:

Increased reach, particularly to patients in rural areas and those who don't traditionally engage

Reduced time and environmental impact from not having to travel to appointments



Potential to expand services rapidly without the extra provision of capital expenditure

Supported tailoring of services to individuals

Source: Public Health England. Supporting weight management services during Covid-19: Phase 1 Insights (2020)

NICE Approved to Support Obesity Pharmacotherapy

Roczen was Successful in the Early Valuation Assessment of Digital Weight Management Technologies

NICE National Institute for Health and Care Excellence

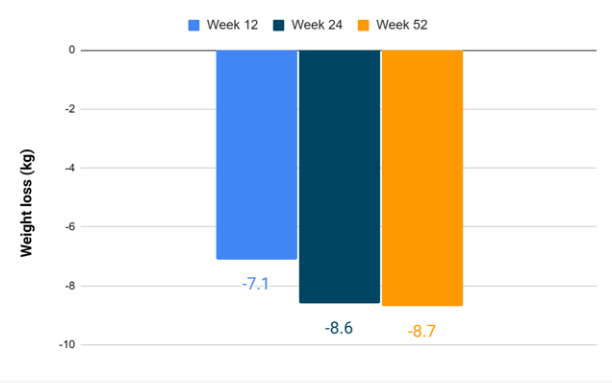
roczen

At 1 year, participants lost just under 9 kg
69% maintained ≧ 5% body weight

Digital services to enable easier access to weight management support

Four digital programmes can be used to help the NHS deliver specialist weight management services to support the use of medication in England, NICE has said in draft guidance.

15 August 2023



	Week 12	Week 24	Week 52
Mean weight (kg) ±SD	89.9±17.9	88.7±18.4	90.0±20.2
Mean weight loss ±SD	7.1±4.7 kg	8.6±6.0 kg	8.7±6.9 kg
Completers	450	305	127

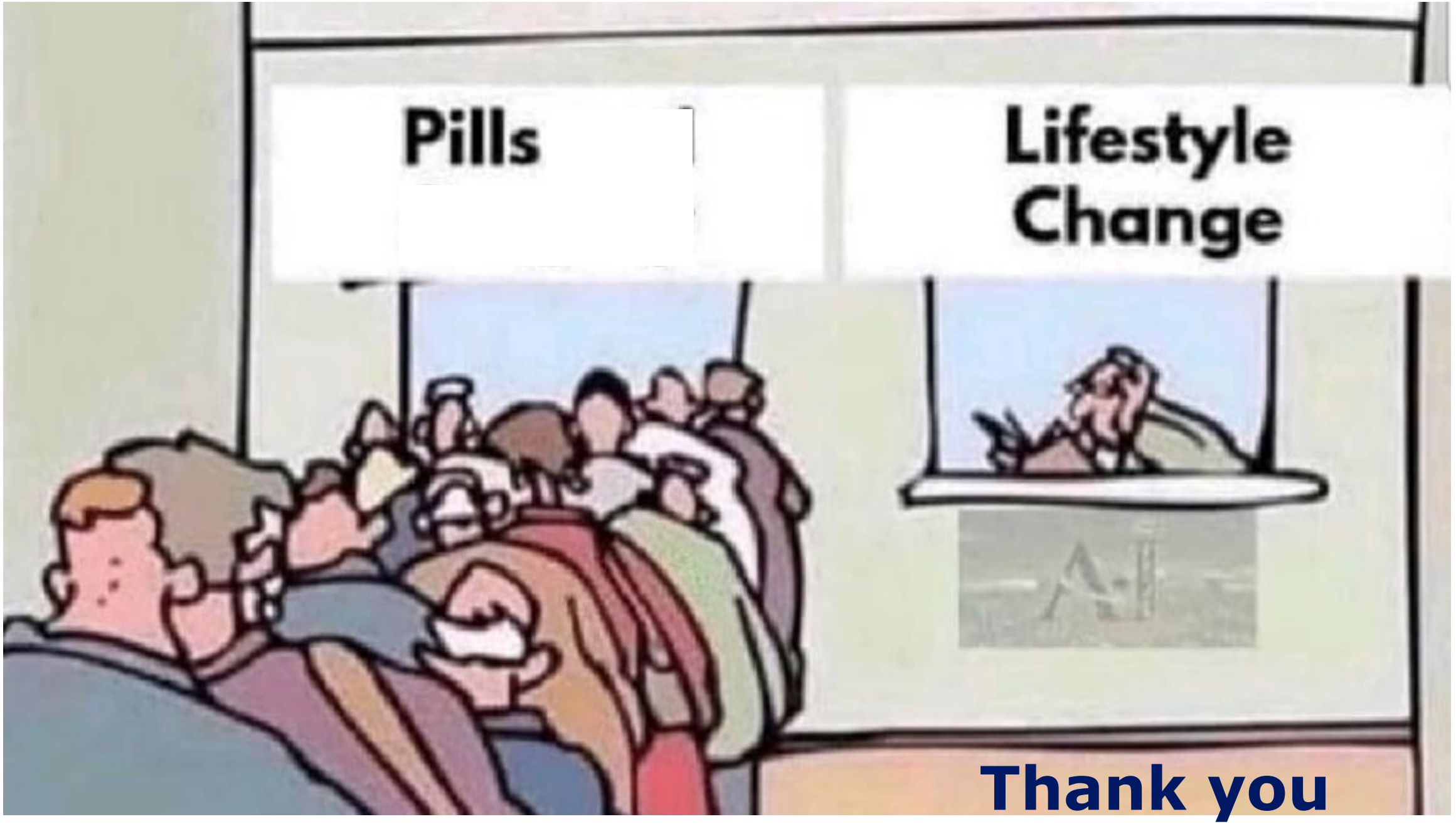
roczen Oviva liva SECOND NATURE

NHS Foundation Trust

Obesity science and practice, Feb 2024

Summary

- Obesity is a chronic and multifactorial chronic disease
- The regulation of body weight is complex – gut hormones play an important role
- Assessment of complications is important- use risk scores eg King's obesity staging criteria
- We have effective pharmacotherapy for the treatment of obesity
- Cost and supply will limit use of these medications in the NHS
- Multidisciplinary working is an essential part in the management of obesity



Thank you