

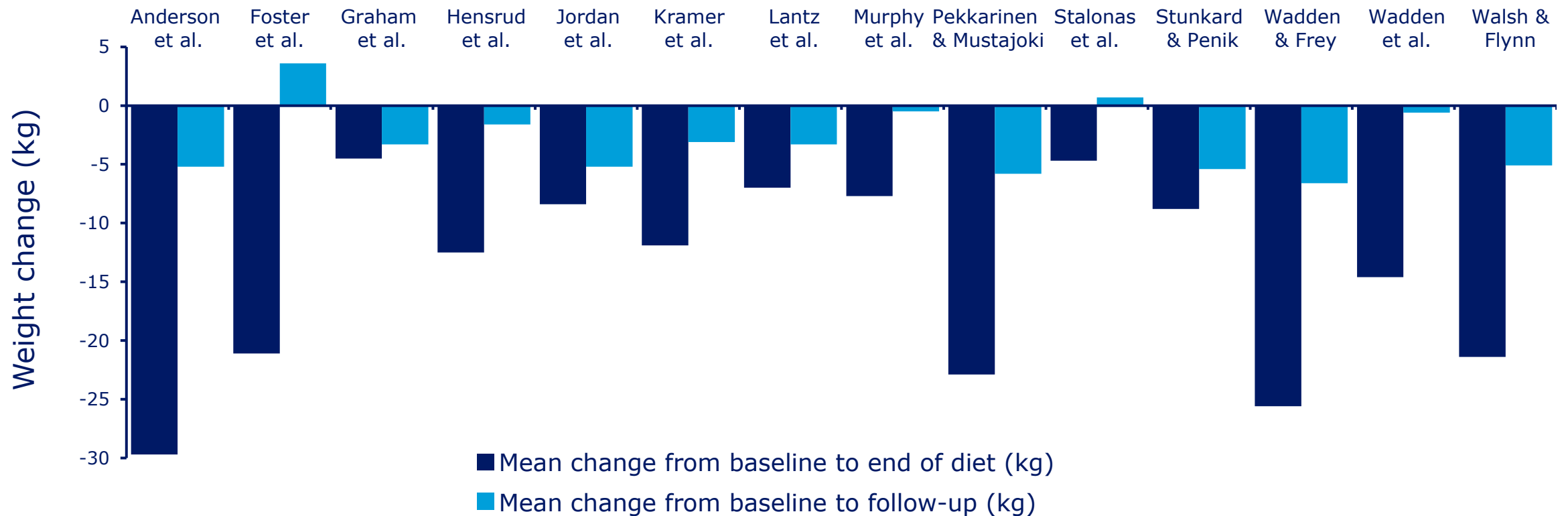
Management of Weight Regain



Gabriella Segal-Lieberman
Head of the Israeli Center for Weight Management
Sheba Medical Center



Maintenance of weight loss is challenging



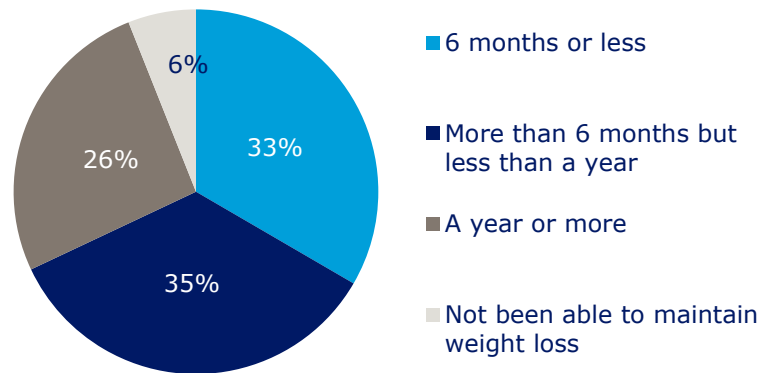
Follow up range from 4 to 7 years



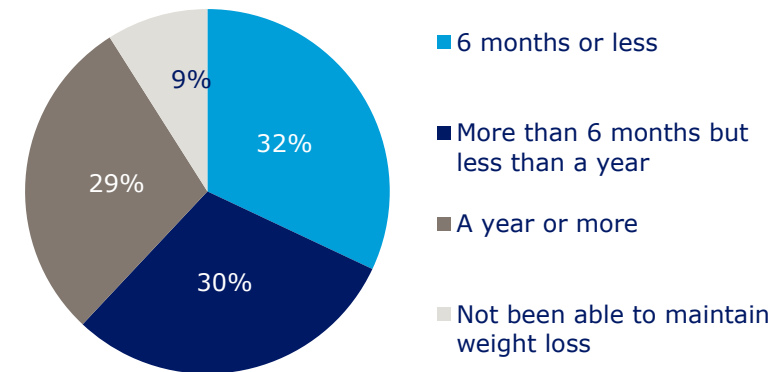
Length of Time Able to Maintain **5%** Weight Loss



Israel PwO, At Least 5% Weight Loss (n=296)



Global PwO, At Least 5% Weight Loss (n=5,506)



% of All PwO with at least 5% weight loss over past 3 years:
% of PwO with at least 5% weight loss able to maintain it for 1 year or more:
% of All PwO able to maintain at least 5% weight loss for 1 year or more:

(Calculated from S21 and S22)

Israel

38%
26%
10%

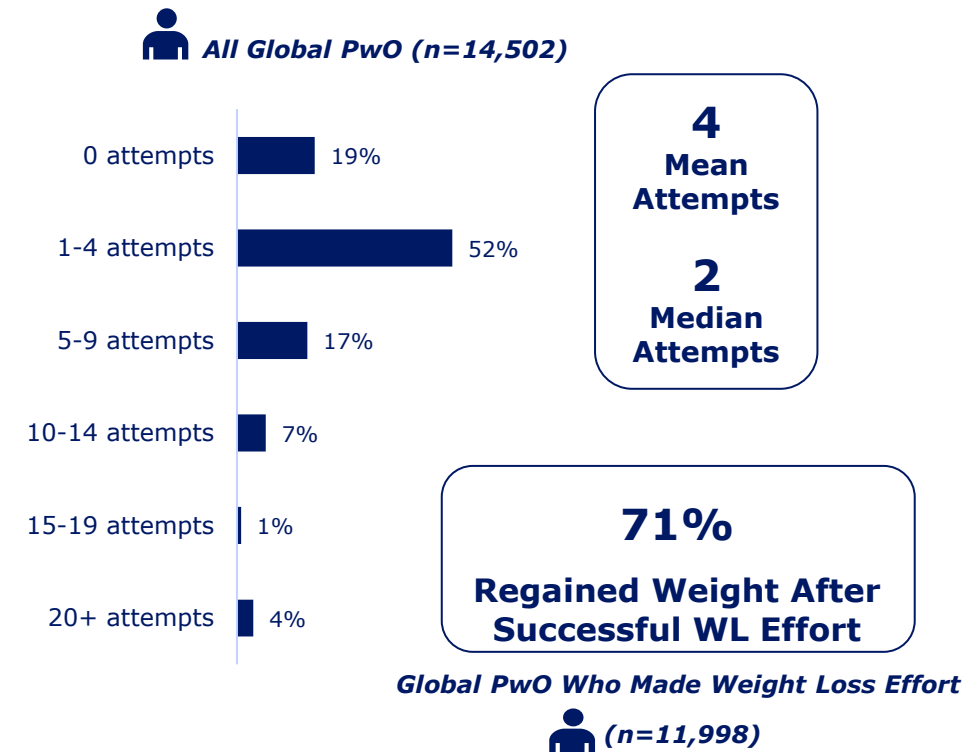
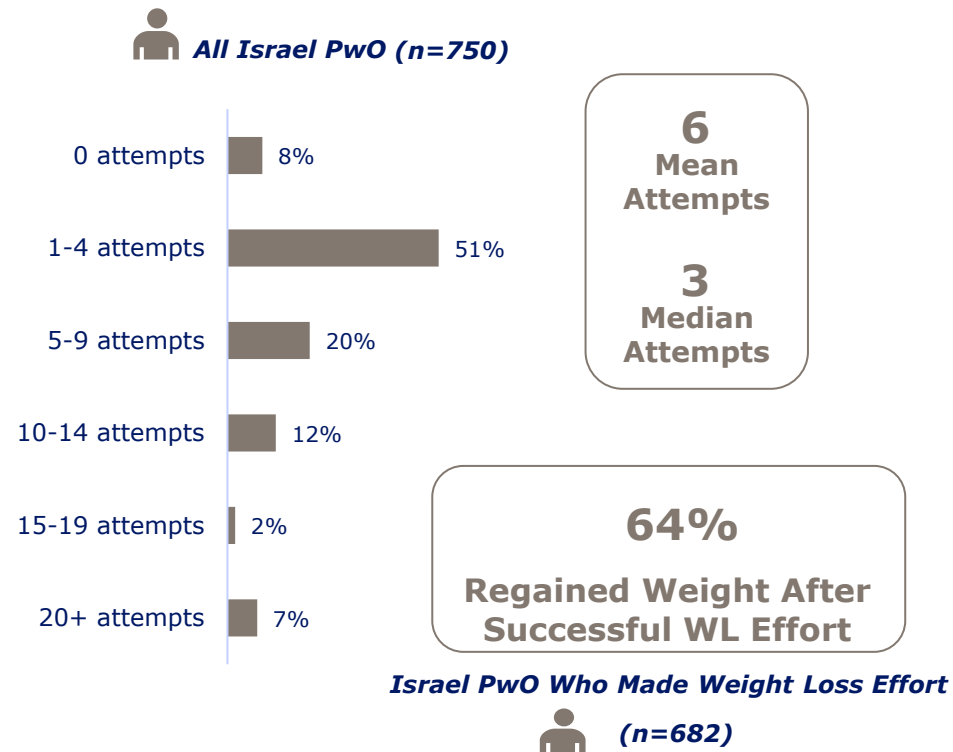
Global

37%
29%
11%

[PwO at Least 5% Weight Loss] S22 You indicated your current weight is less than your maximum weight within the past 3 years. For how long would you say you've been able to maintain your weight loss?



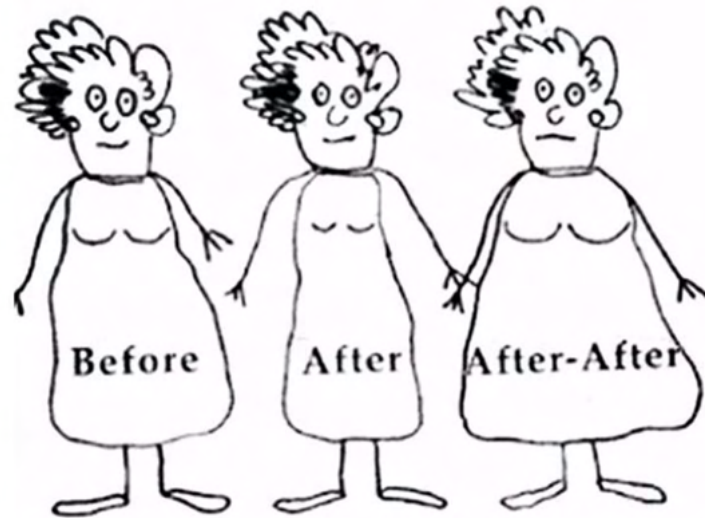
Number of Serious Past Weight Loss Efforts



[All PwO] Q205 How many times in your adult life (after age 18) have you made a serious weight loss effort (e.g., followed a program, set goals, put your mind to it, or worked with a qualified healthcare professional), whether or not you were successful?

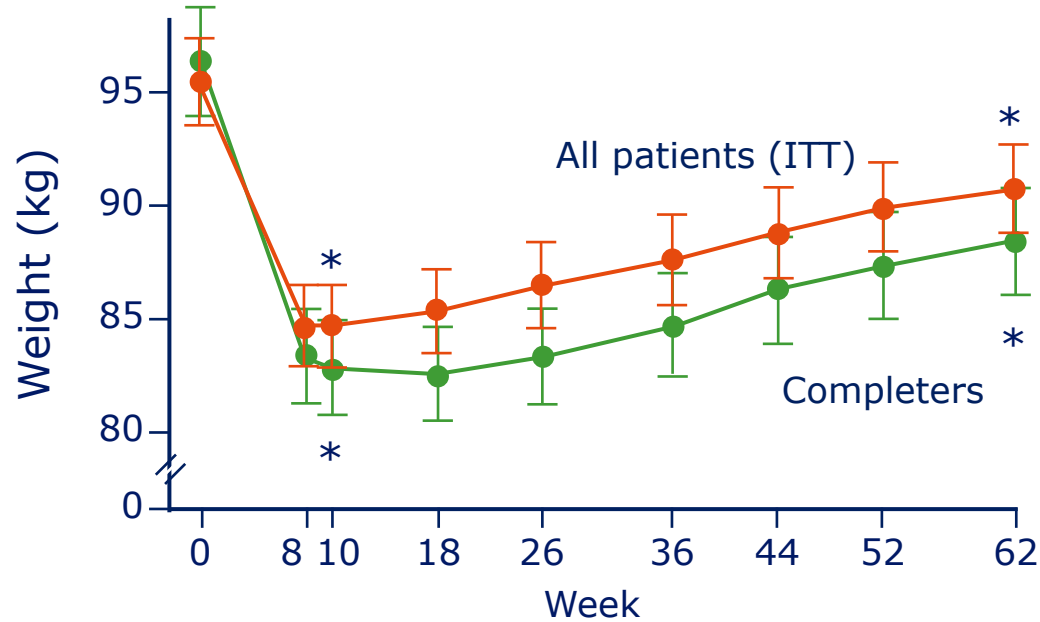
[PwO Made Weight Loss Effort] Q213 Have you ever had what you'd consider a successful weight loss effort, but later regained the weight after keeping it off for at least 6 months?

Why is it so difficult to maintain weight loss?

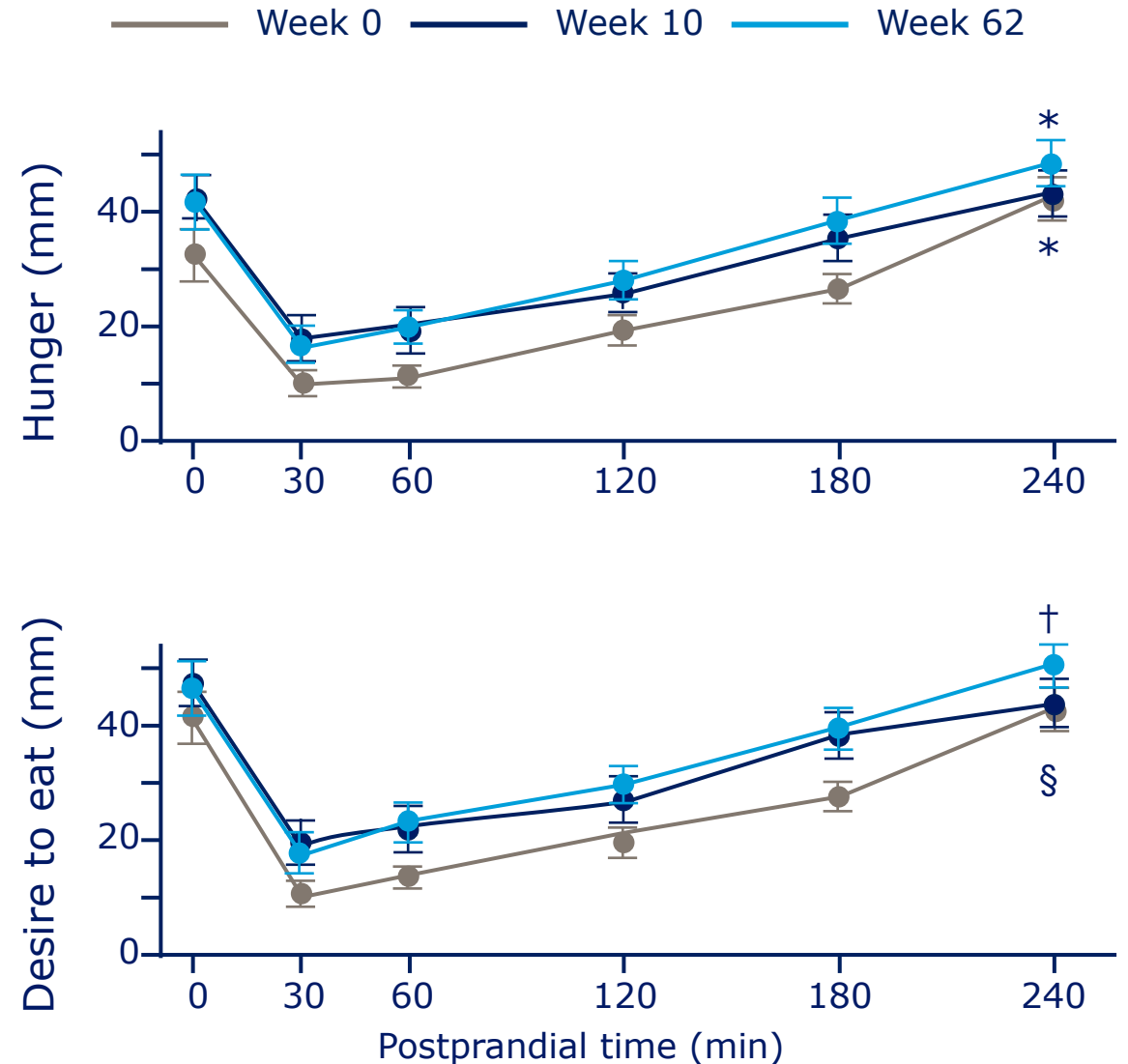


Hunger increases in response to weight loss

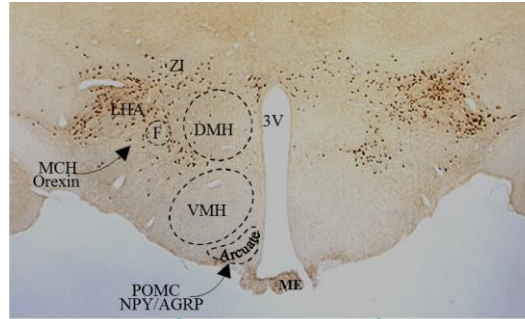
- 50 individuals with overweight/obesity lost weight on a 10-week VLCD
- Appetite was measured using VAS scores at 0, 10 and 62 weeks



* $p < 0.001$, § $p = 0.008$, † $p = 0.09$ vs mean at baseline (week 0)



Hypothalamic Regulation of appetite

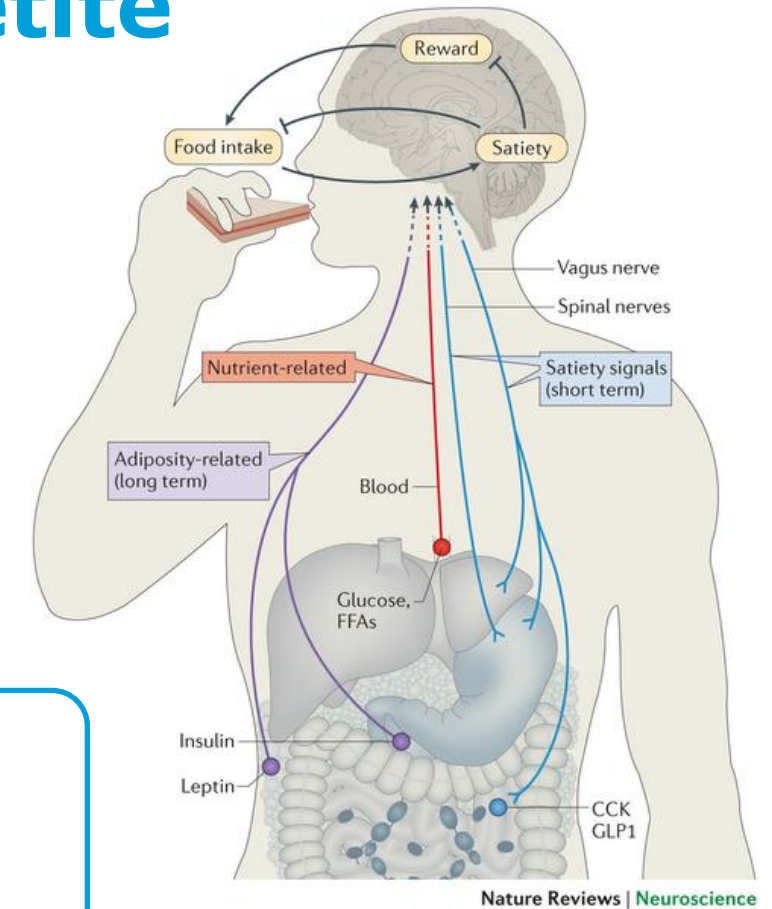


Anorexigenic (Satiety signals)

- POMC
- CART

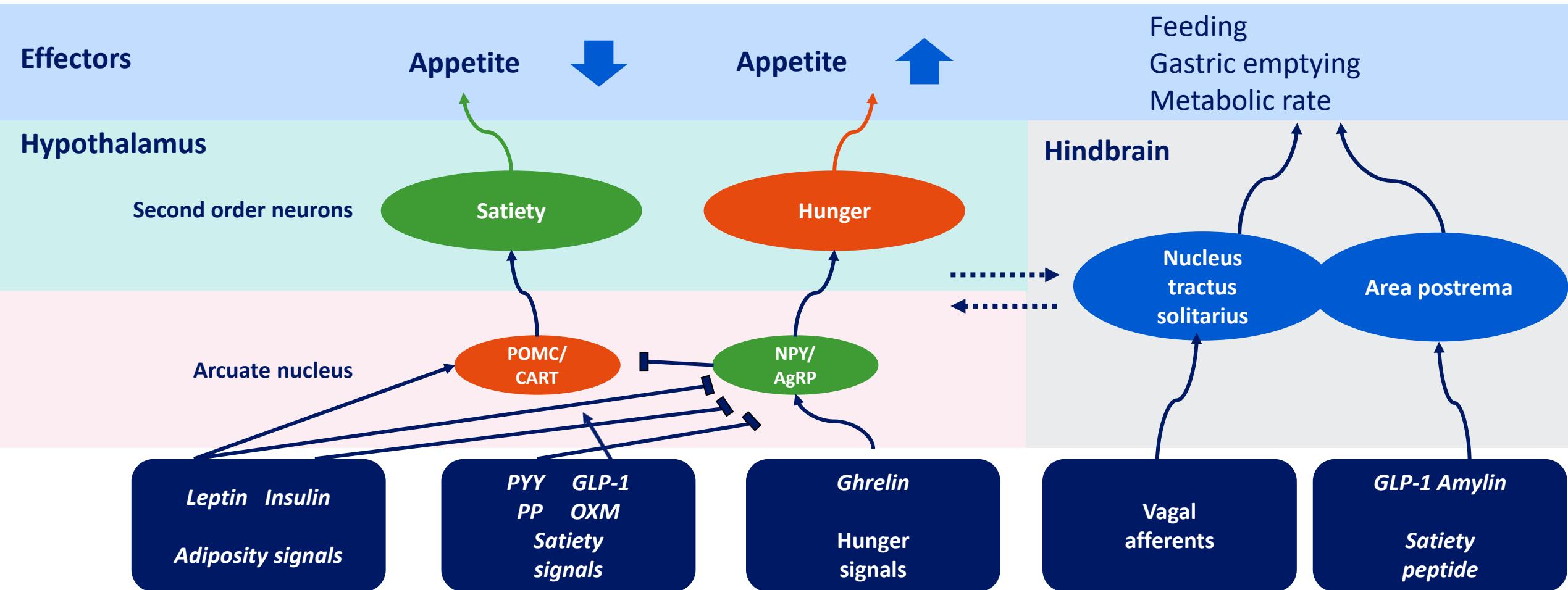
Orexigenic (Hunger signals)

- NPY
- AgRP

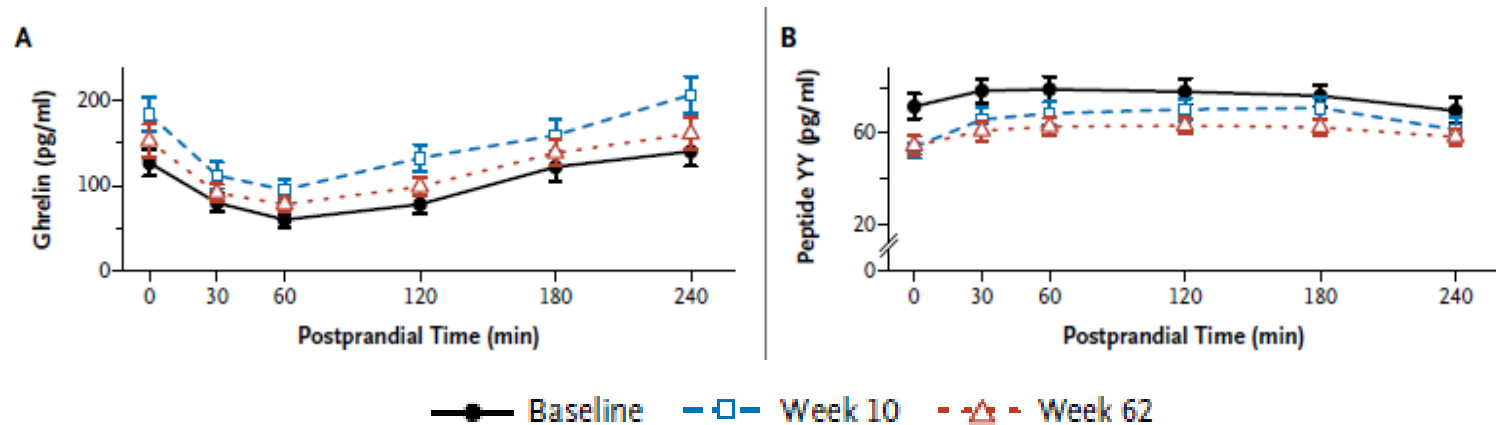
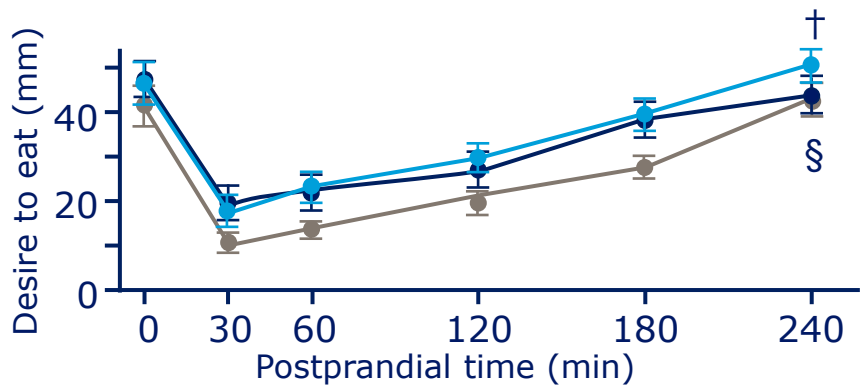
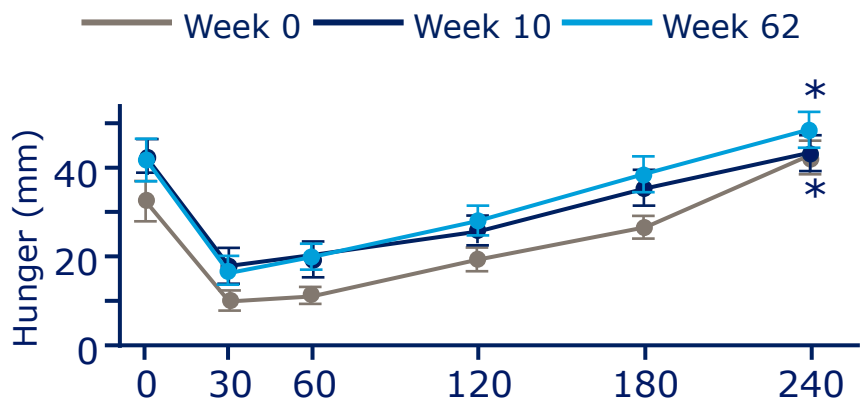


Hypothalamic regulation of appetite

Peripheral signals modulate appetite and energy expenditure via hypothalamic neurons



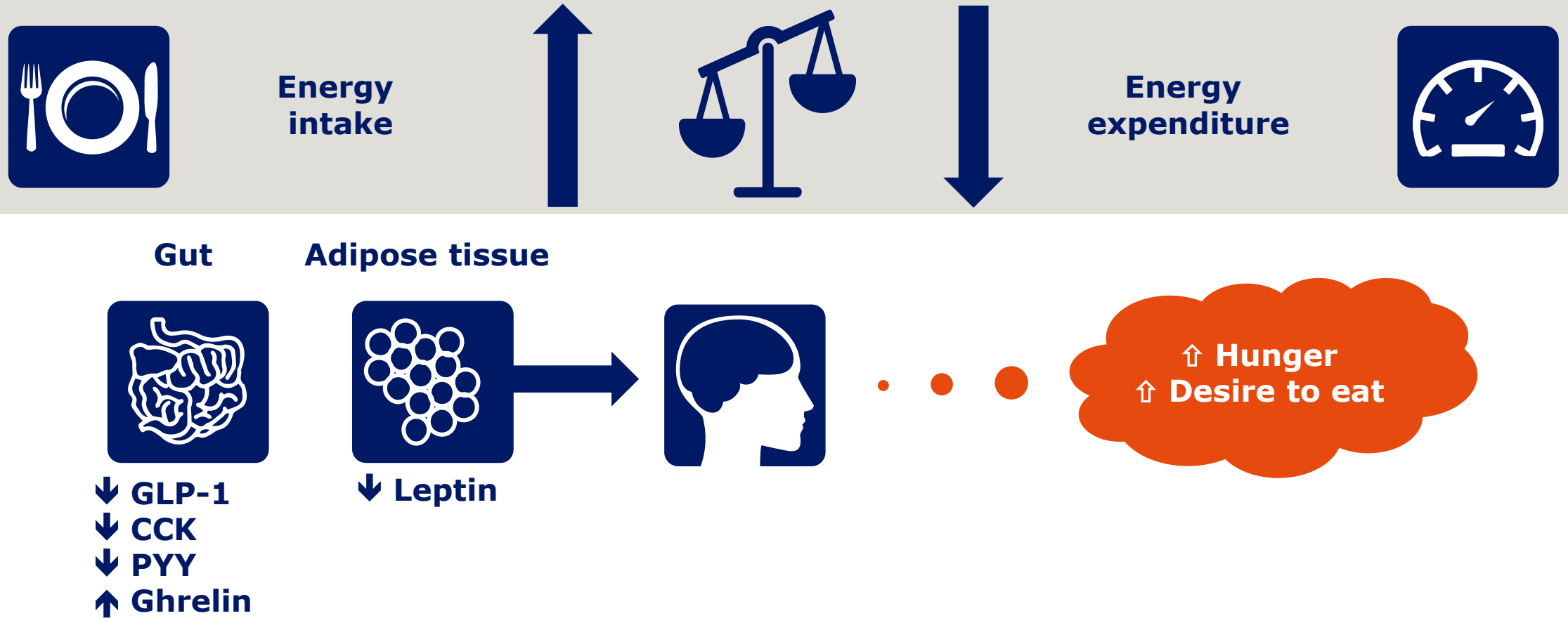
α-MSH, *α*-melanocyte stimulating hormone; AgRP, Agouti-related protein; CART, cocaine and amphetamine regulated transcript; GLP-1, glucagon-like peptide-1; NPY, neuropeptide Y; OXM, oxyntomodulin; POMC, pro-opiomelanocortin; PP, pancreatic polypeptide; PYY, peptide YY



GLP-1 pg/ml

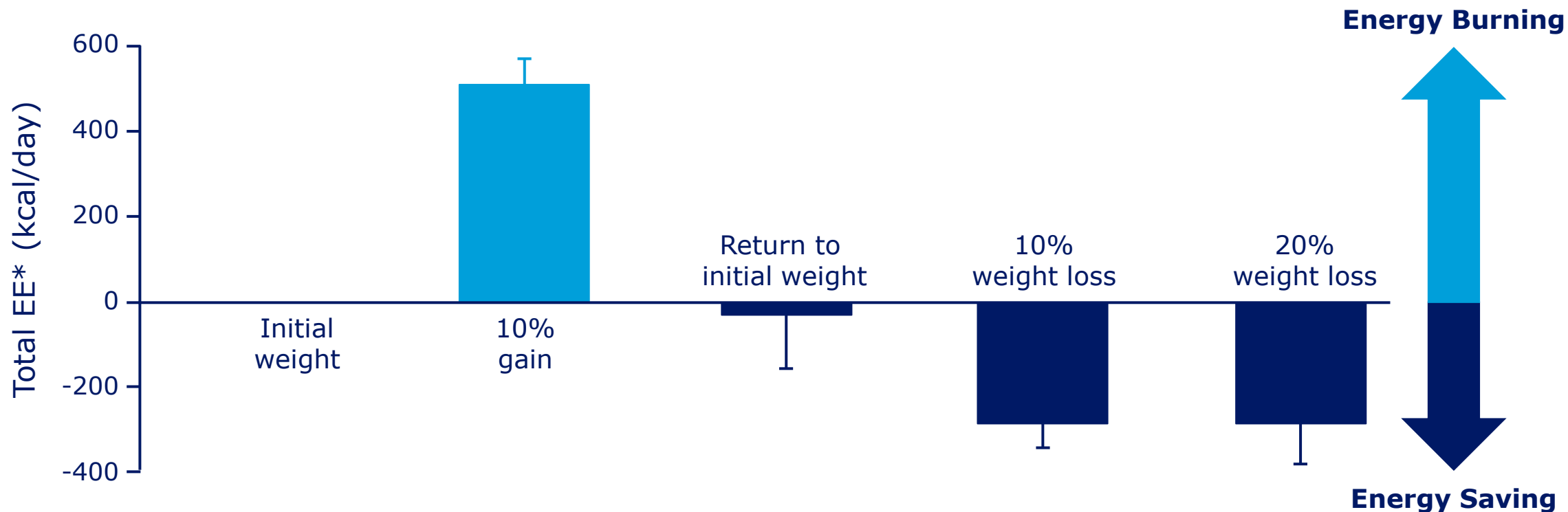
	fasting	Fasting % Δ from week 0	4 h post prandial AUC	AUC Δ from week 0
Week 0	40.8±3.2		48.2±3	
Week 10	34.8±2.7 (p=0.02)	-14.2 (p=0.002)	47.8±3.5 (p=0.26)	-6.9 (p=0.28)
Week 62	37.5±1.9 (p=0.44)	-5.6 (p=0.93)	44.4±2.3 (p=0.31)	-3.9 (p=0.69)

Physiological responses to weight loss favour weight regain^{1,2}



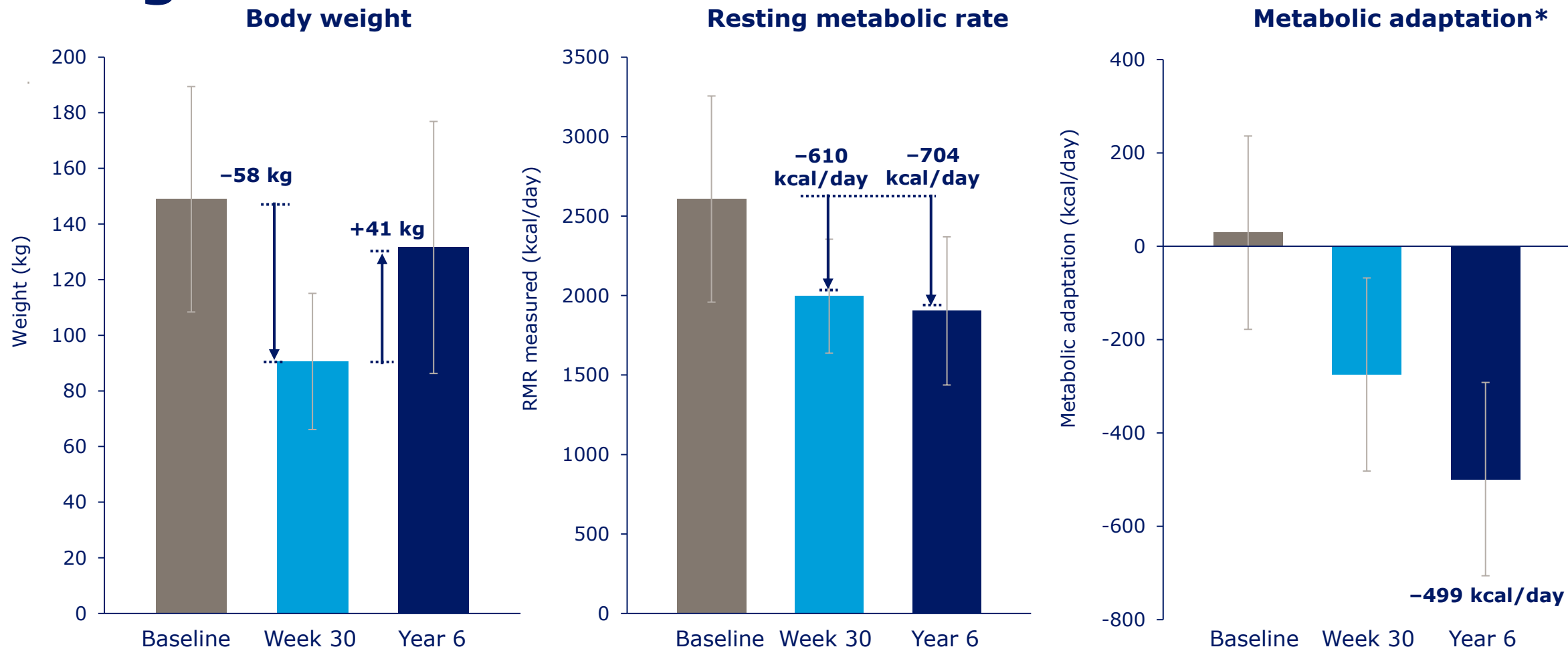
CCK, cholecystokinin; GLP-1, glucagon-like peptide-1; PYY, peptide YY

Weight loss leads to a decrease in energy expenditure



*Observed minus predicted total energy expenditure. EE, energy expenditure

Persistent metabolic adaption following weight loss



Error bars represent standard deviation. Data are for 14/16 participants in the 30-week Biggest Loser weight-loss competition.
*Defined as the residual resting metabolic rate after adjusting for changes in body composition and age.

Why is the metabolism decreased during weight loss?

- ❖ Decrease in sympathetic tone (40%)
 - ❖ Change in thyroid function (sick euthyroid like)
 - ❖ Increase in muscle efficiency
 - Increase in Myosin Heavy Chain 1 (MHC 1)
 - Increase in Sarco/endoplasmic reticulum Ca²⁺ ATPase (SERCA 2)
- LEPTIN ↓

Reversed by leptin repletion

The decreased EE

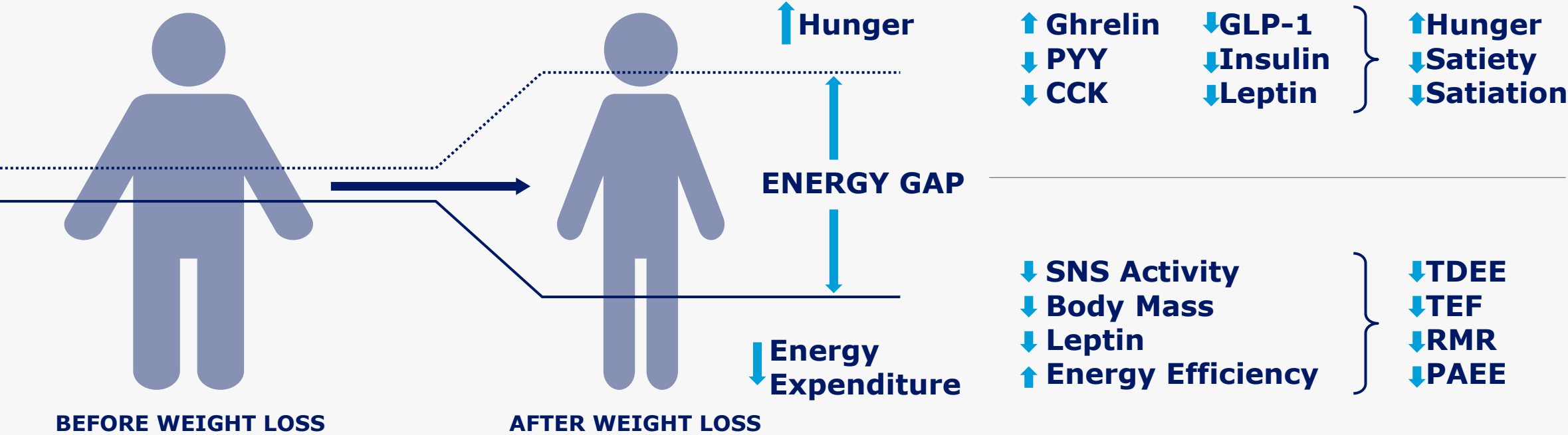
The increased muscle efficiency

Sick euthyroid syndrome

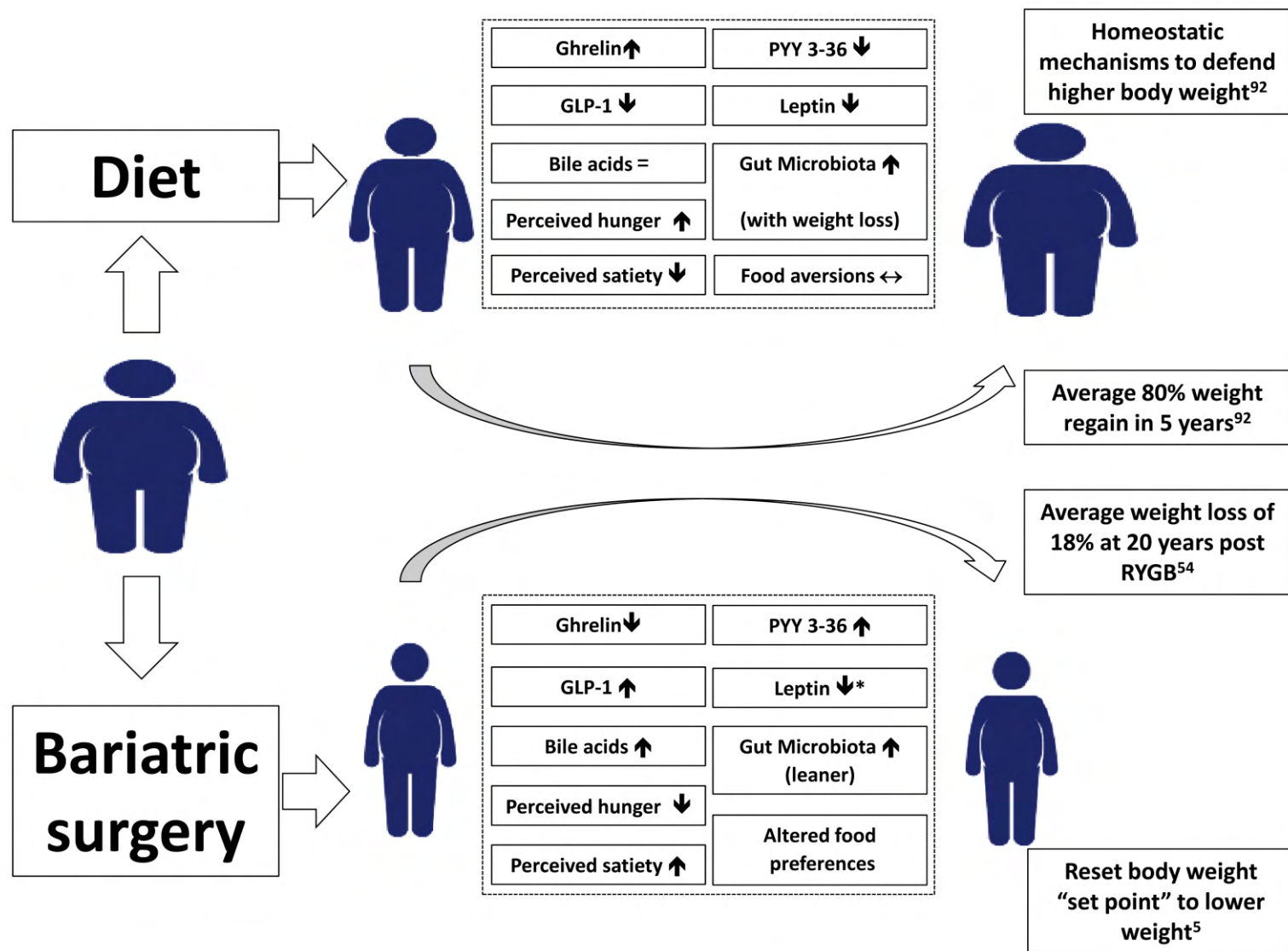
The decreased SNS tone

hyperphagia

Metabolic adaptation to a reduced body weight in obesity

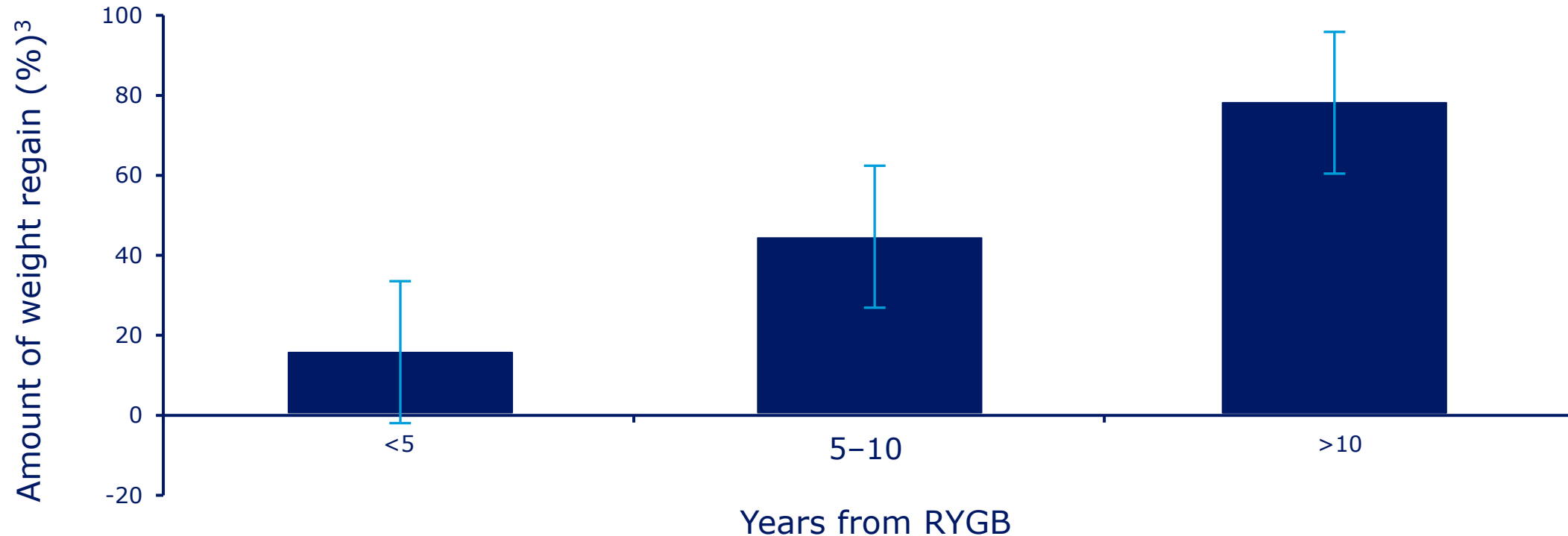


CCK, cholecystokinin; GLP-1, glucagon-like peptide -1; PYY, YY peptide; PAEE, physical activity energy expenditure; RMR, resting metabolic rate; SNS, systemic nervous system; TDEE, total daily energy expenditure; TEF, thermic effect of food



Weight regain after bariatric surgery

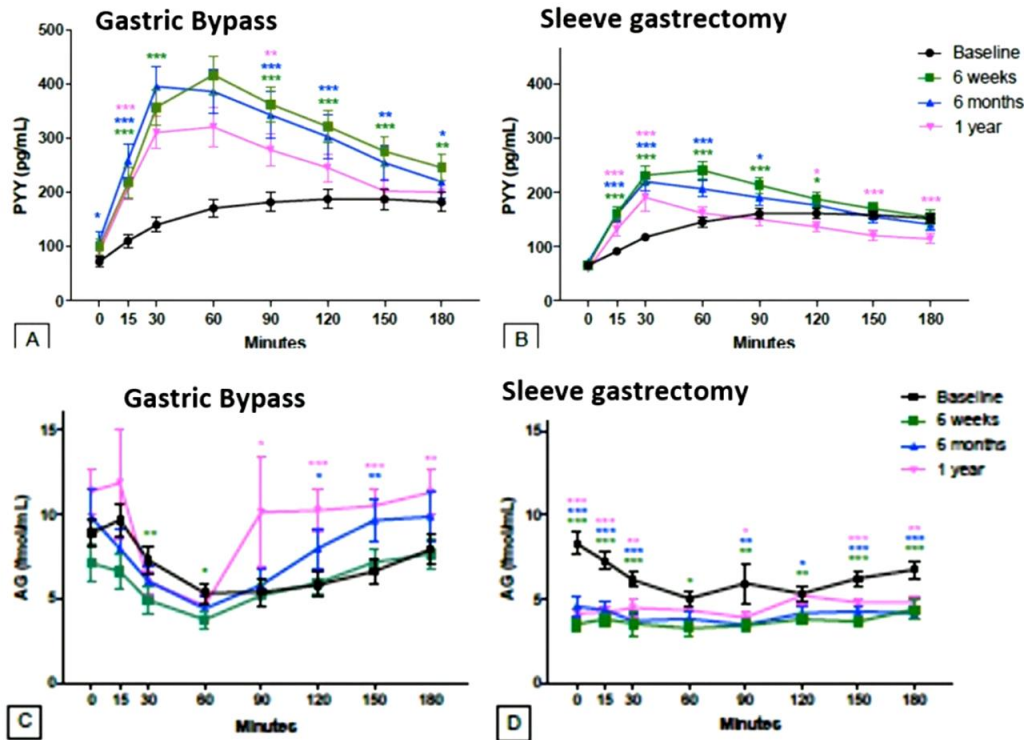
- Significant WR ($\geq 15\%$) occurs in **25–35%** of patients 2–5 years after surgery¹
- However, there is no generally accepted definition for WR. Most are based on kg, BMI units or %EWL²



BMI, body mass index; EWL, excess weight loss; RYGB, Roux-en-Y gastric bypass; WR, weight regain

Do longitudinal changes in gut hormones associate with weight loss?

85 patients (27 GB and 54 SG) longitudinal fasted and meal-stimulated gut hormone assessments
Pre-surgery, 6 weeks, 12 weeks, 26 weeks and 52 weeks

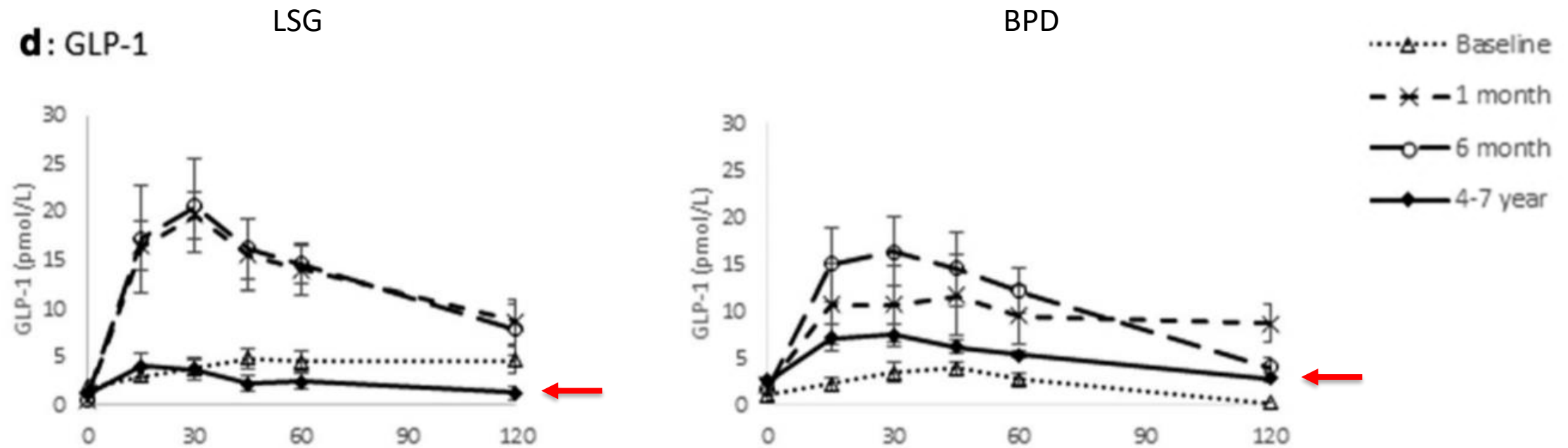


No pre-op predictors of 1-year %weight loss

6-week post-surgery PYY associated with %weight loss

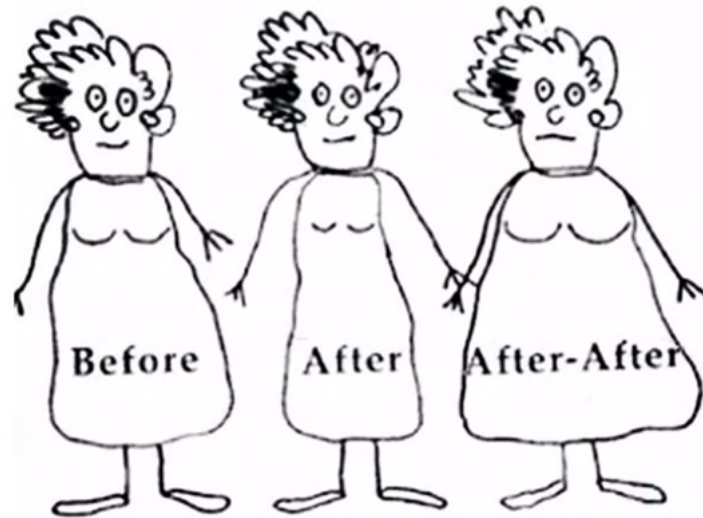
Chaiyasoot K unpublished

Long term follow up post bariatric surgery shows a decrease in OGTT induced GLP-1 levels



Changes in GLP-1 and GIP during the OGTT before and 1 month, 6 months and 4–7 years after LSG and BPD. Value represents mean $\pm$ standard error. GLP1, glucagon-like peptide-1; LSG, laparoscopic sleeve gastrectomy; BPD, biliopancreatic diversion.

Can pharmacotherapy help maintain weight loss
after a diet?

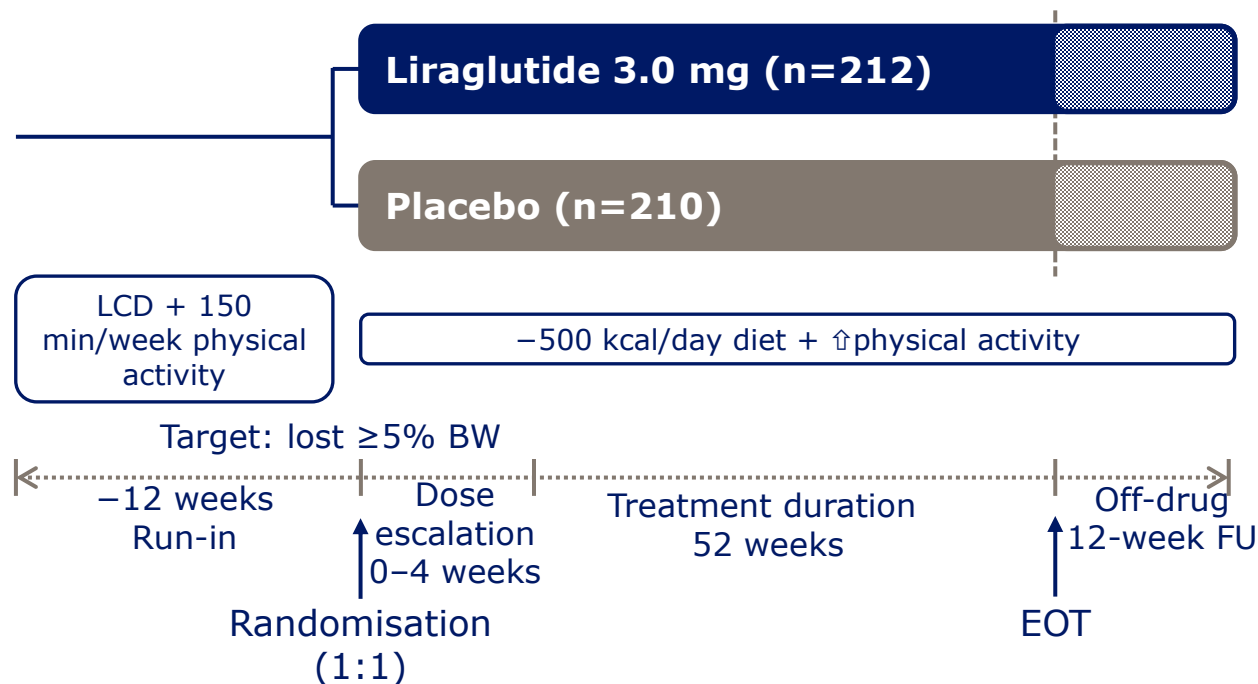


Trial design: SCALE Maintenance

Weight maintenance with liraglutide 3.0 mg after LCD-induced weight loss

551 participants

- ≥ 18 years
- Stable BW
- BMI ≥ 30 kg/m² or ≥ 27 kg/m² + comorbidities



Trial information

- October 2008 to January 2009
- Randomised controlled double-blind study
- 36 sites (US and Canada)

Trial objective

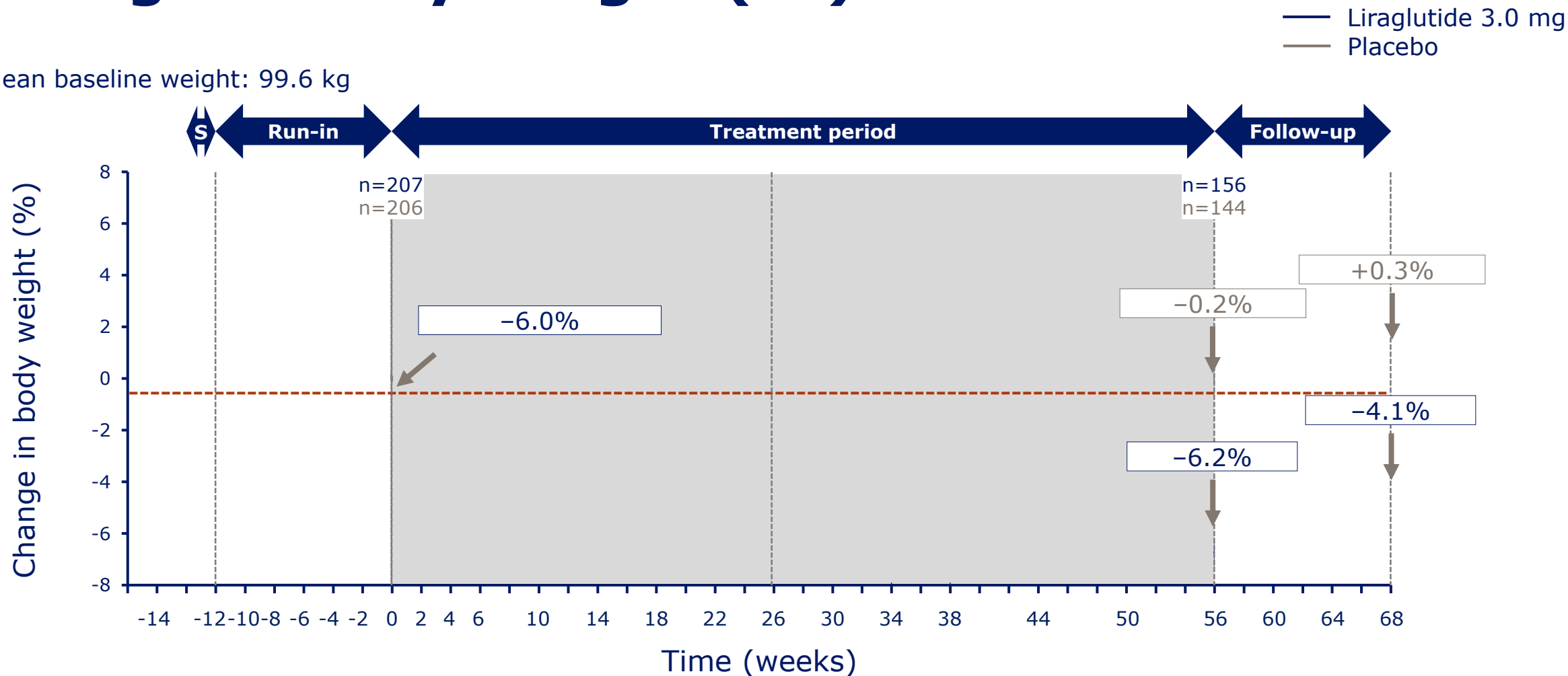
- Efficacy of liraglutide 3.0 mg in maintaining weight loss achieved with a LCD (1200–1400 kcal/diet) and increased physical activity (150 min/week) during run-in

Key endpoints

- Three co-primary: change in BW; maintenance of $\geq 5\%$ WL from LCD run-in; $\geq 5\%$ WL after randomisation
- Secondary: weight change; $>10\%$ WL; maintenance $>50\%$ and $>75\%$ of WL achieved during LCD run-in period

Change in body weight (%)

Mean baseline weight: 99.6 kg

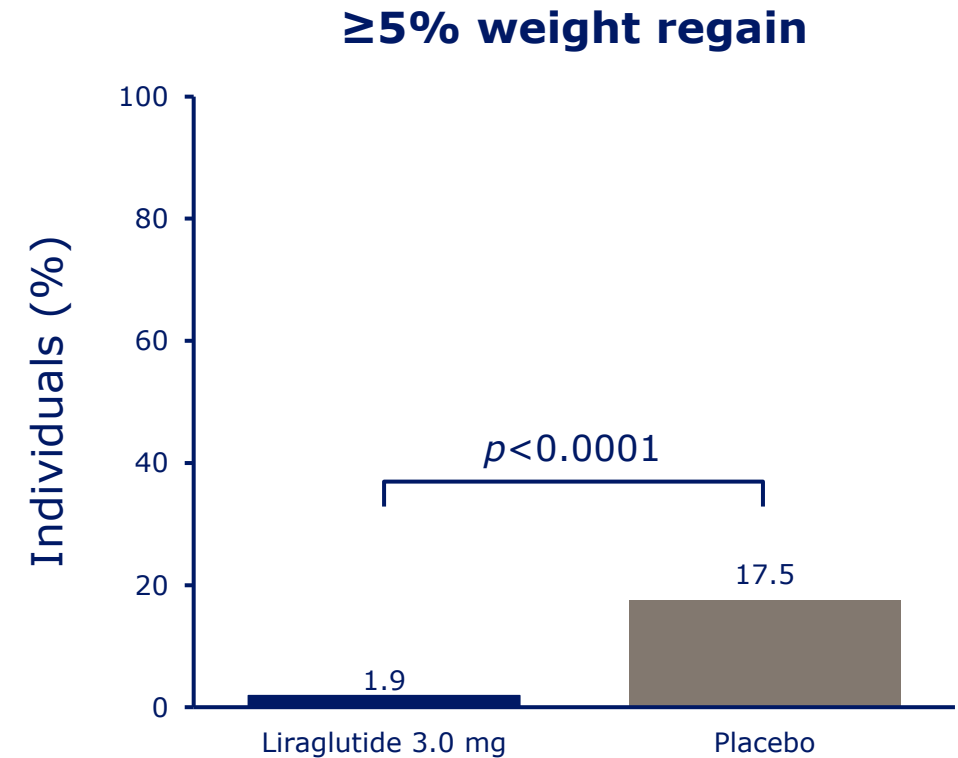
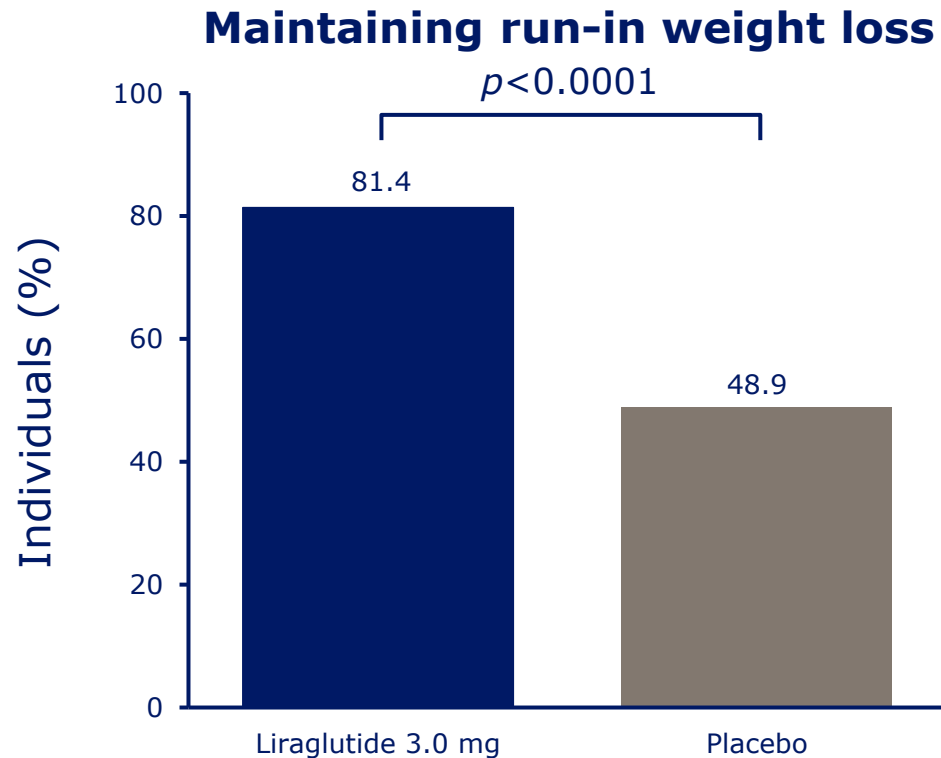


Mean ($\pm$ SD); Full analysis set. S, screening period; SD, standard deviation
Wadden et al. *Int J Obes (Lond)* 2013;37:1443-51

Individuals maintaining or regaining weight loss

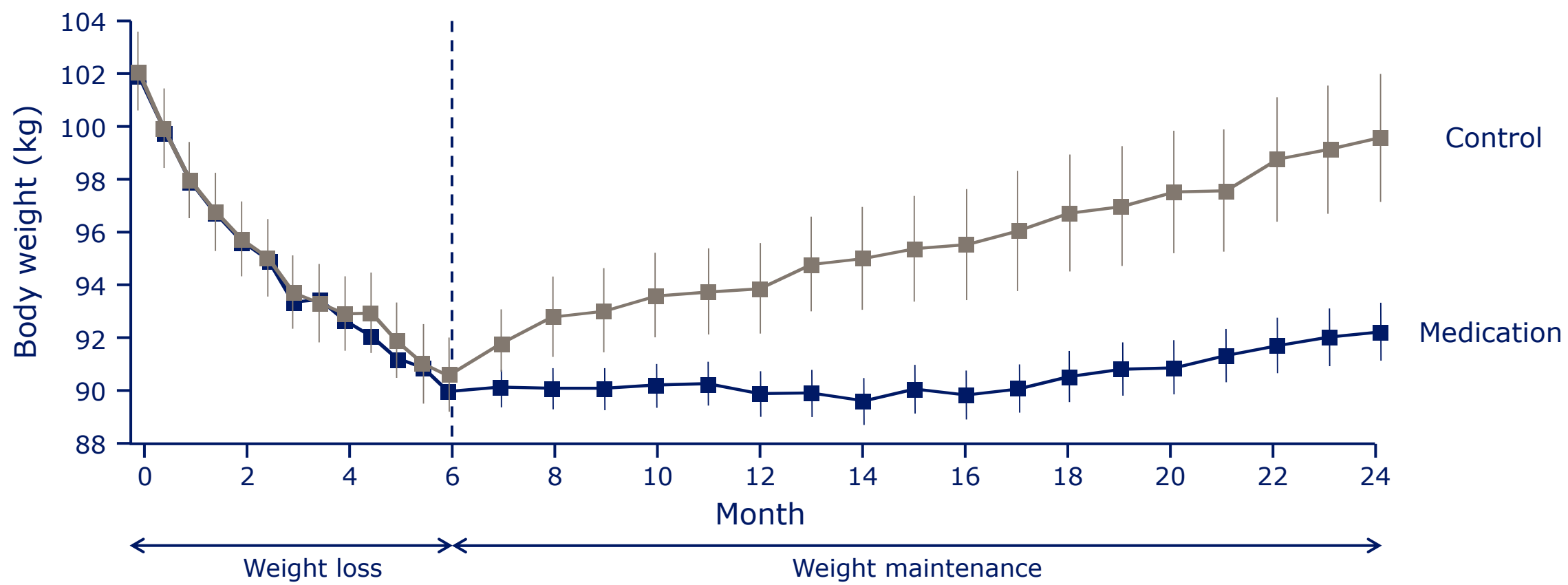
At week 56

Mean baseline weight: 99.6 kg



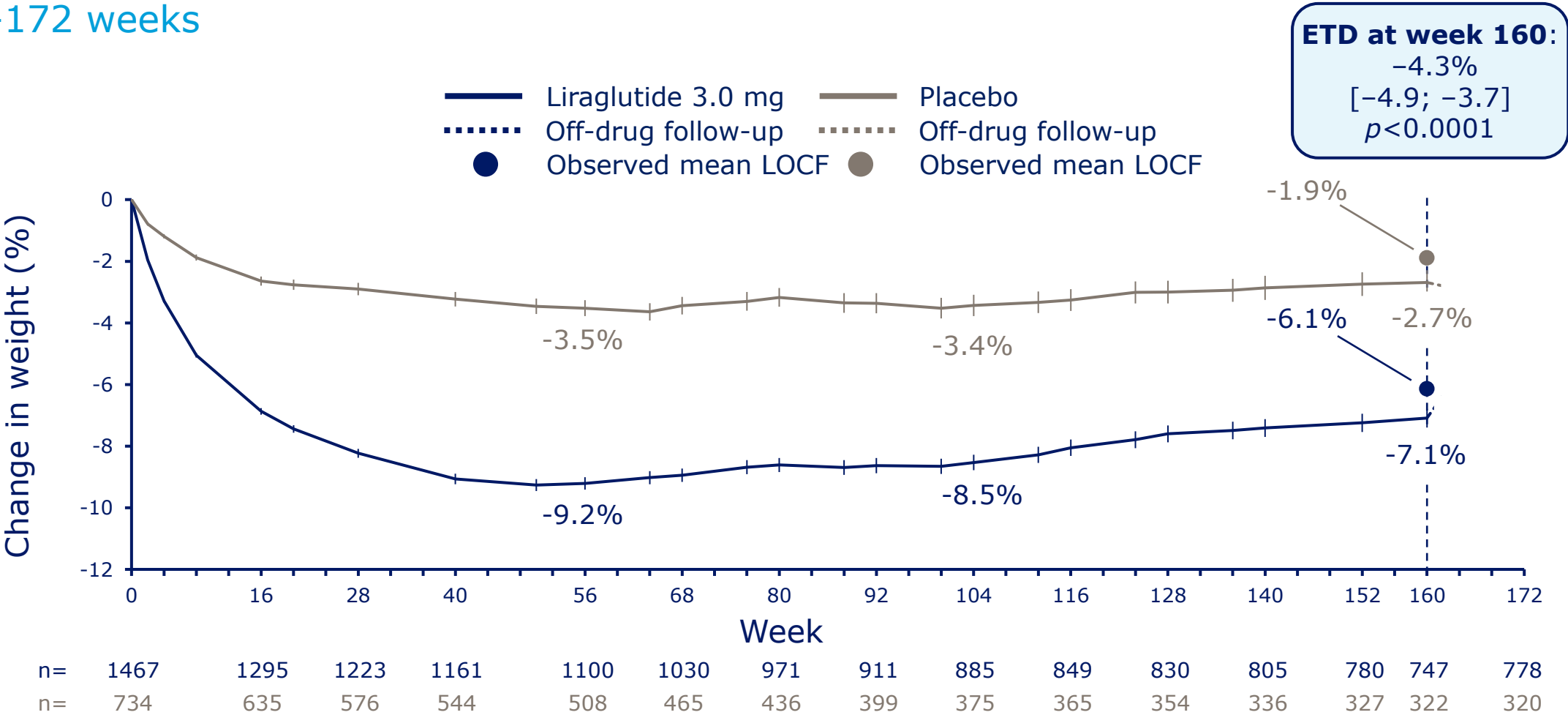
Full analysis set; LOCF at week 56. LOCF, last observation carried forward
Wadden et al. *Int J Obes (Lond)* 2013;37:1443–51

Continuing medication prevents weight regain



Change in body weight (%)

0–172 weeks

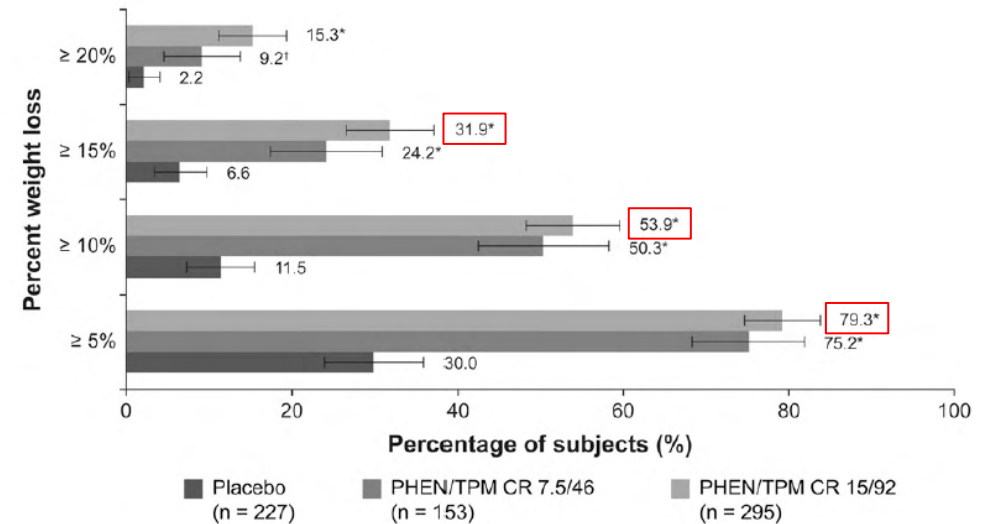
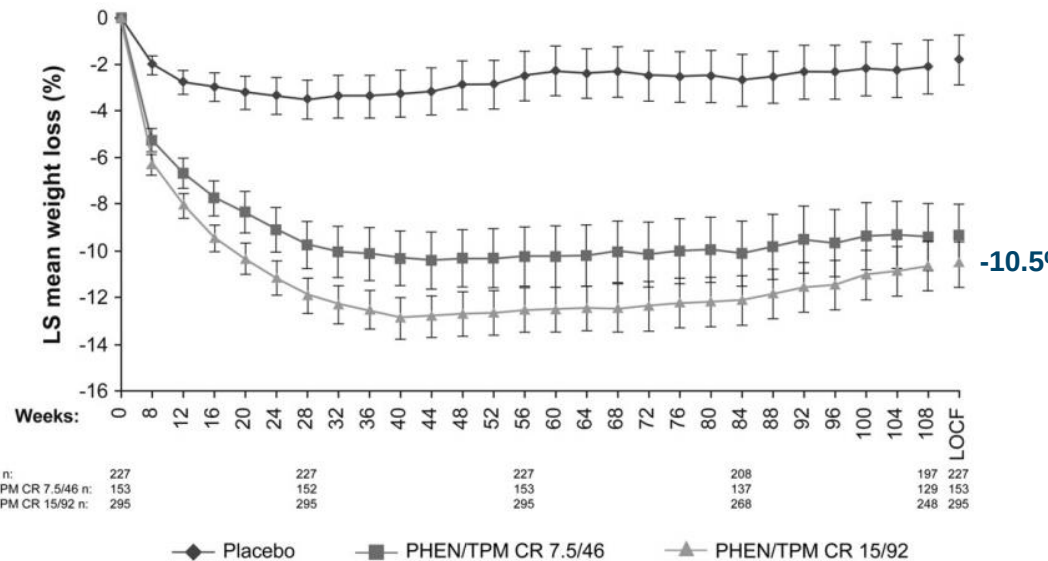
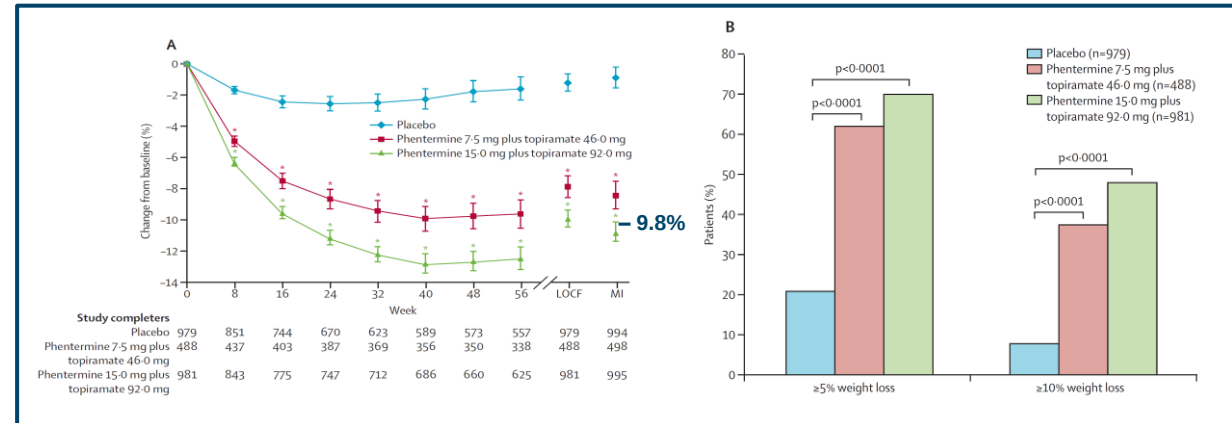


Full analysis set, fasting visit data only. Line graphs are observed means ($\pm$ SE)
LOCF, last observation carried forward; SE, standard error

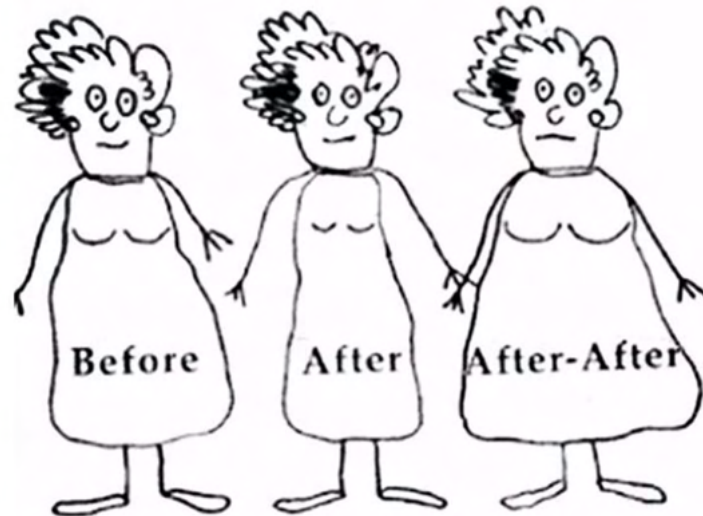
Phentermine + topiramate (Qsymia)

N=2487
 BMI: 27–45
 56 weeks

- Placebo
- P-7.5 mg, T-46.0 mg
- P-15.0 mg, T-92.0 mg



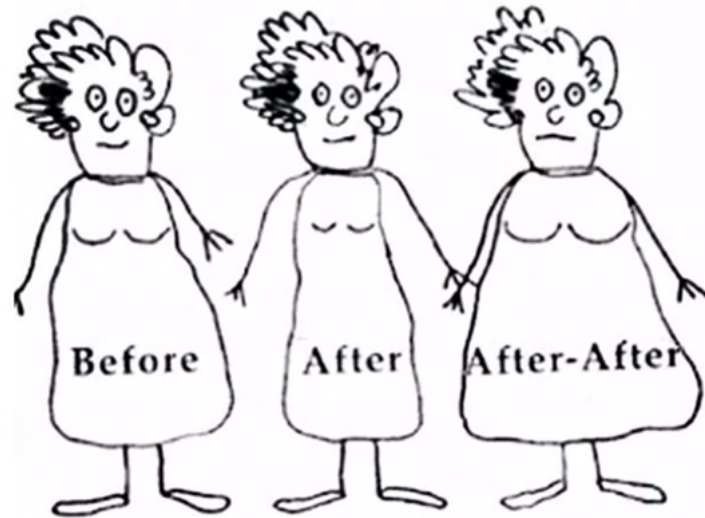
Can pharmacotherapy help maintain weight loss after a diet?



yes

- As long as the drug is taken
- At least for a few years

Can pharmacotherapy be used for weight regain
after bariatric surgery?



Liraglutide 3.0 mg after bariatric surgery

	Creange	Rigas	Talbot	Shehadeh	Muratori	Abrahamsson	Wharton	Rye	Suliman
Study type	retrospective	retrospective	retrospective	retrospective	retrospective	retrospective	retrospective	retrospective	prospective
Number of participans	25	48	32	25	20	13	117	20	76
Type of surgery	LAGB\ RYGB\LSG\LA GB & RYGB	LAGB\ LSG\ GBP	Bariatric surgery	sleeve gastrectomy\ gastric banding\ gastric bypass\ Last both	LSG\RYGB\LA GB	GBS	RYGB\ AGB\ Gastric sleeve	RYGB \ LSG\ VBG\ AGB	SG\ RYGB\ Other
Time from surgery to saxenda tx	-	-	1.1 years	-	4.5 years	At least 2 years	7.8 years	6.3 years	4 years
Duration of Saxenda tx	24 weeks	7 months	9 months	3 months	10.9 months	15-20 months	7.6 months	28 weeks	213 days
Weight loss under saxenda	-9.45%	-13.4%	-7.2%	-10%	-5.2 kg\m2	-10.4%	-5.5%	-9.7%	-6.1% -12.2%

Rye P, Modi R, Cawsey S, et al. Efficacy of High-Dose liraglutide as an adjunct for weight loss in patients with prior bariatric surgery. OBES SURG. 2018;28(11):3553–3558 \ M Suliman, Buckley A, Al Tikriti A, Tan T, le Roux CW, Lessan N, et al. Routine clinical use of liraglutide 3 mg for the treatment of obesity: outcomes in non-surgical and bariatric surgery patients. Diabetes Obes Metab. 2019;21(6):1498–501. \ Wharton S et al : Liraglutide 3.0 mg for the management of insufficient weight loss or excessive weight regain post-bariatric surgery. Clinical obesity Clinical Obesity. 2019;9:e12323\ Rigas G, Talbot ML, Tam C. The role of adjuvant pharmacotherapy in the management of patients with a partial response to bariatric metabolic surgery-the first Australian experience. Obes Facts. 2018;11(suppl 1):1-358 \ Talbot L LK, Tam C, Rigas T. Liraglutide use in patients who have regained weight after bariatric surgery: the first Australian experience. Abstract 0.078 presented at the 22nd World Congress of the International Federation for the Surgery of Obesity Metabolic Disorders, August 29-September 2, 2017, London, UK. 2017, \ Shehadeh N ZW, Zuckerman Levin N, Said W, Zolotov S, Elemetry A. Liraglutide treatment in post-bariatric surgery patients who failed to maintain weight reduction. Surg Obes Relat Dis. 2017;13:S144. A5173. \ Muratori F DSG, Pellegrino D, Vignati F. Effectiveness of liraglutide 3.0 mg treatment on weight regain after bariatric surgery in severely obese patients. Obes Facts. 2018;11(Suppl 1):280. T4P117. Abrahamsson N HA. GLP-1 analog treatment in the failed gastric bypass patient. Poster 2233-P presented at: 75th Annual Meeting and Scientific Sessions of the ADA; June 2015; Boston, MA.\ Creange C, Lin E, Ren-Fielding C, et al. Use of liraglutide for weight loss in patients with prior bariatric surgery. Surg Obes Relat Dis. 2016;12(7):S157.

A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL USING LIRAGLUTIDE FOR WEIGHT REGAIN AFTER ROUX-EN-Y GASTRIC BYPASS

Presented at Obesity Week 2021, ID: oral 001

Holly F Lofton MD

Clinical associate professor of surgery and medicine

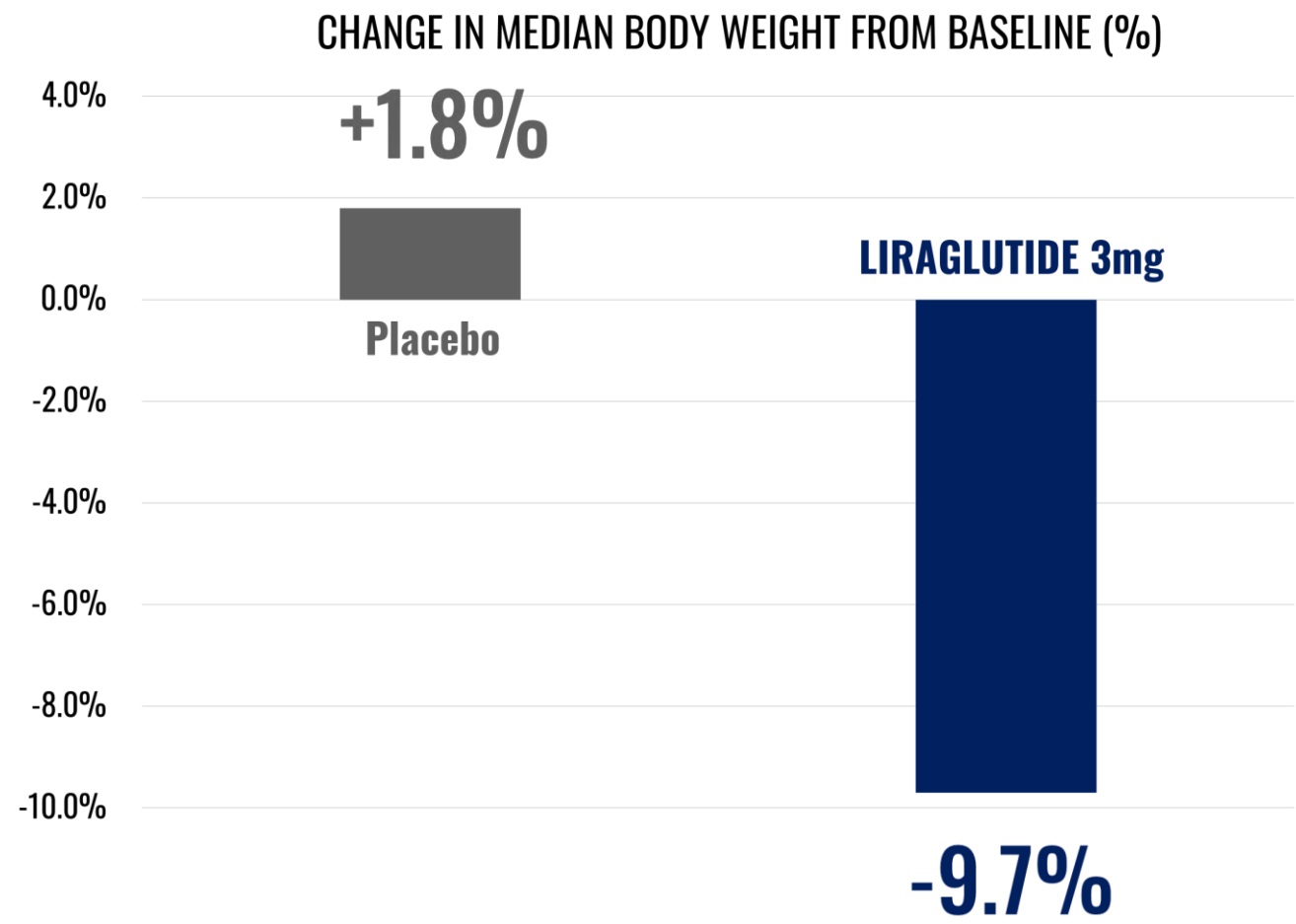
Director, medical weight management program

Division of Bariatric Surgery and Internal Medicine, NYU Langone Health

PATIENT SELECTION

- This **56 weeks**, double-bind, placebo-controlled study was conducted in **132 patients** who achieved $\geq 25\%$ Total body weight loss (TBWL) post RYGB.
- Patients also had to regain $\geq 10\%$ TBWL after reaching nadir weight.
- Patients were 18-120 months post-RYGB and met criteria for weight management pharmacotherapy.
- **2:1 randomization to receive Liraglutide 3.0 mg or placebo**
- Primary endpoint: proportion of patients losing $\geq 5\%$ of baseline body weight

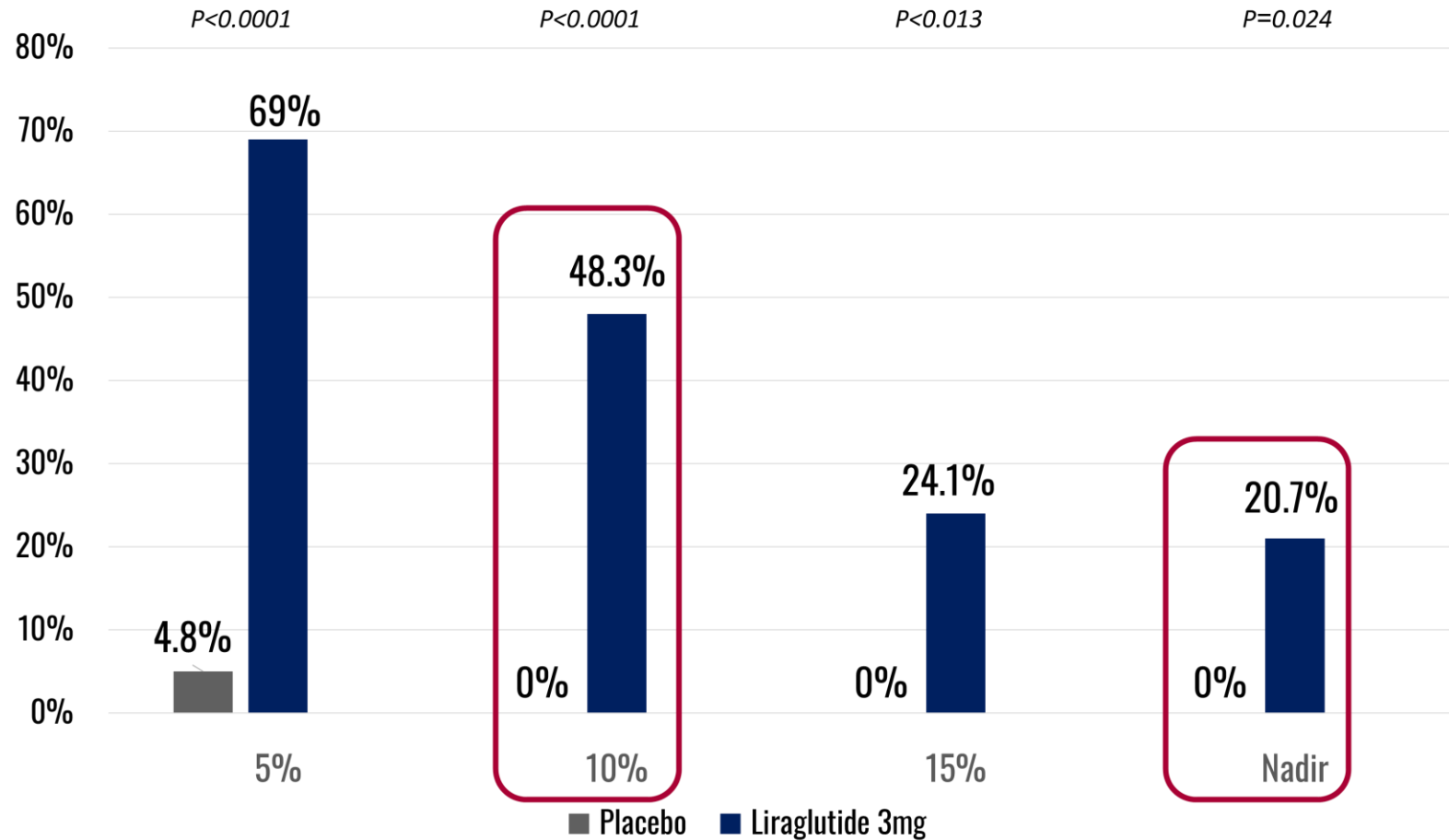
SIGNIFICANT DIFFERENCE IN MEDIAN BODY WEIGHT BETWEEN SAXENDA OR PLACEBO TREATED PATIENTS AT 12 MONTHS



At week 56, the median weight lost from BWL-B was 9.7% (IQR=2.4–15.0) and -1.8% (IQR=-4.2–0.7) in the Liraglutide and placebo arms, respectively (p<0.00001)

Holly F Lofton et al, A Randomized, Double-Blind, Placebo-Controlled Trial Using Liraglutide for Weight Regain after RYGB. Oral presentation, Obesity Week 2021

Proportion of Patients who lost 5%, 10%, 15% or Met/Exceeded Nadir at 12M



Evaluate whether poor post-surgery weight loss can be improved by tailored pharmacotherapy



Multi-disciplinary Team Assessment

↓ Glucagon-like peptide-1 (GLP-1)

Exogenous GLP-1 receptor agonist

↑ Acyl-Ghrelin

GOAT inhibitor

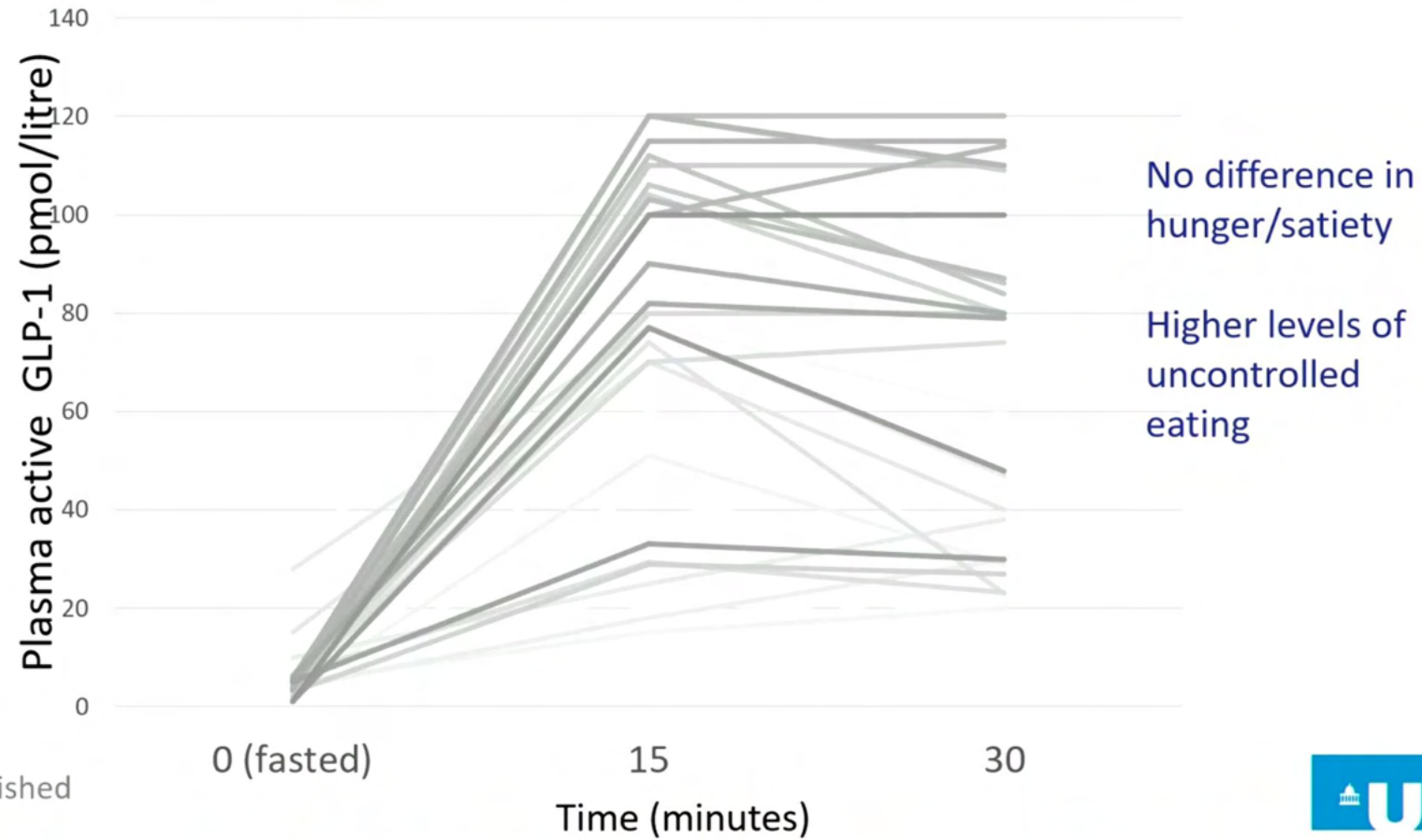
uclh

BARI  **OPTIMISE**



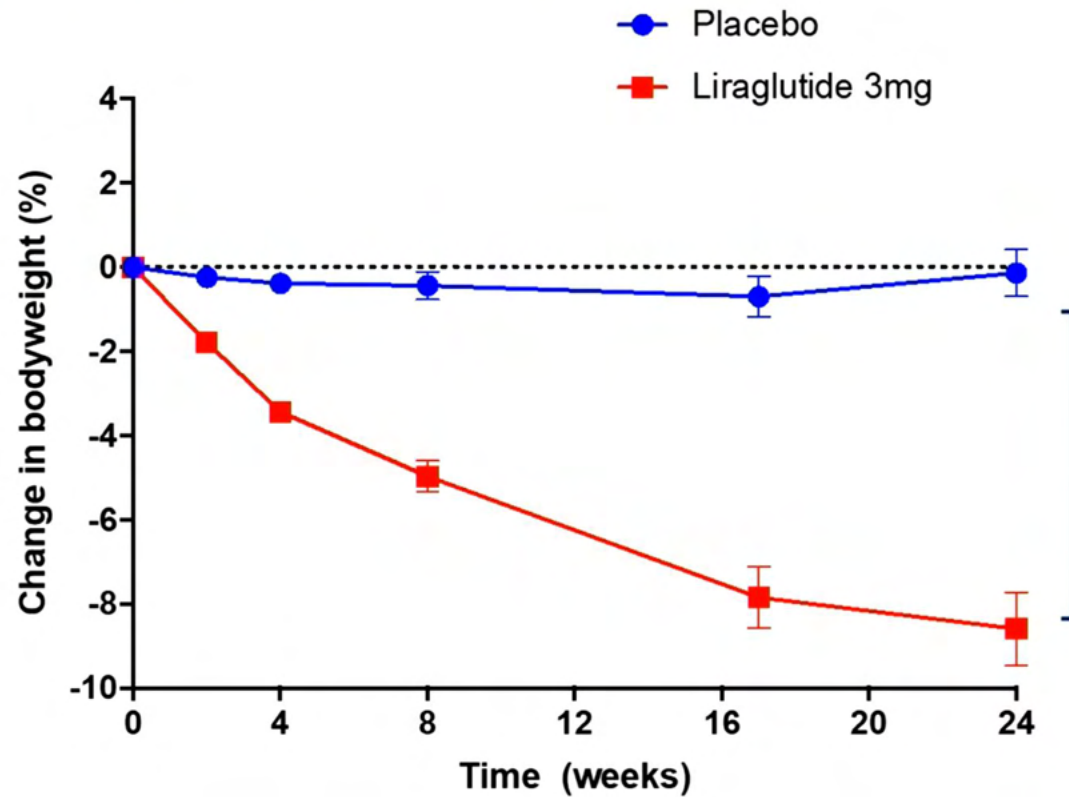
UCL

Marked variability in nutrient-stimulated active GLP-1



Change in bodyweight (%)

0-24 weeks



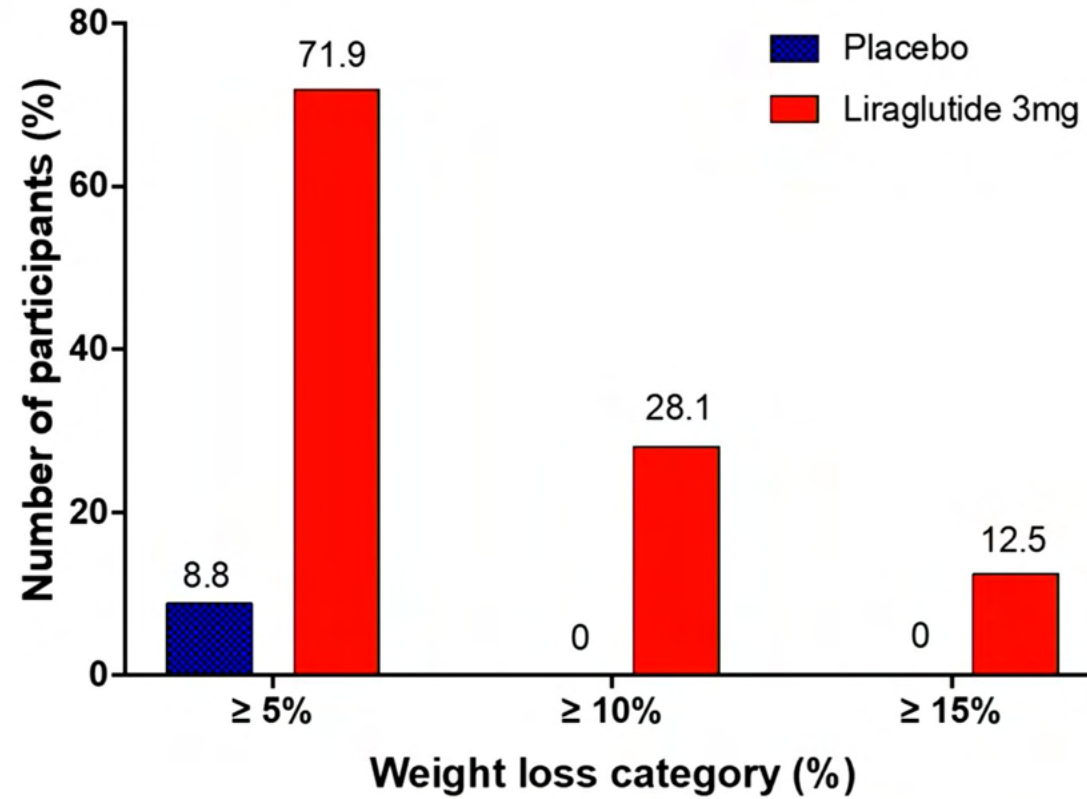
ETD = -8.29 (-10.42 to -6.16)

$p < 0.001$

Categorical weight loss

0-24 weeks

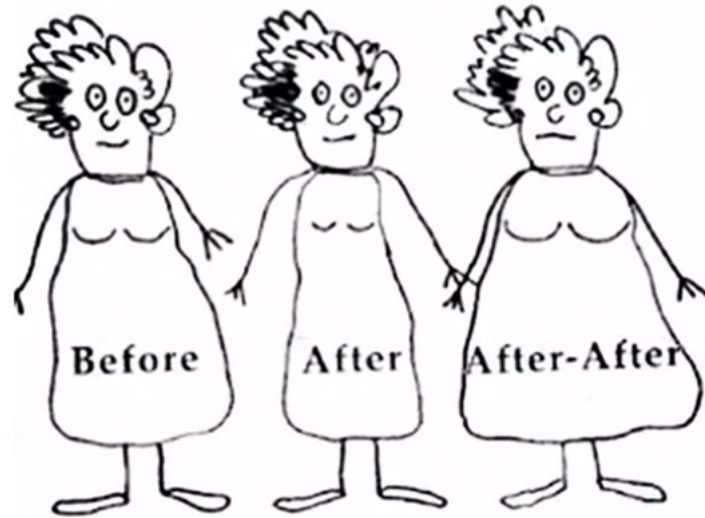
BARI  OPTIMISE



uclh

 UCL

Can pharmacotherapy be used for weight regain after bariatric surgery?



yes

- As good as without surgery

In summary

Weight loss leads to a decrease in metabolic rate and an increase in the desire to eat, both lasting for a prolonged period of time, challenging the ability to maintain weight loss

The decrease in metabolic rate accompanying weight loss is explained by a decrease in sympathetic tone, a decrease in the thyroid axis and an increase in muscle efficiency, and these factors improve by leptin supplementation. The performance of physical activity, including resistance training should be encouraged.

In order to maintain the achievement of weight loss, in parallel with a continuous program and behavioral framework, medications can be used to overcome the increased appetite.

GLP-1 analogs were shown to be effective for maintaining weight loss achievement after a diet as well as after bariatric surgeries