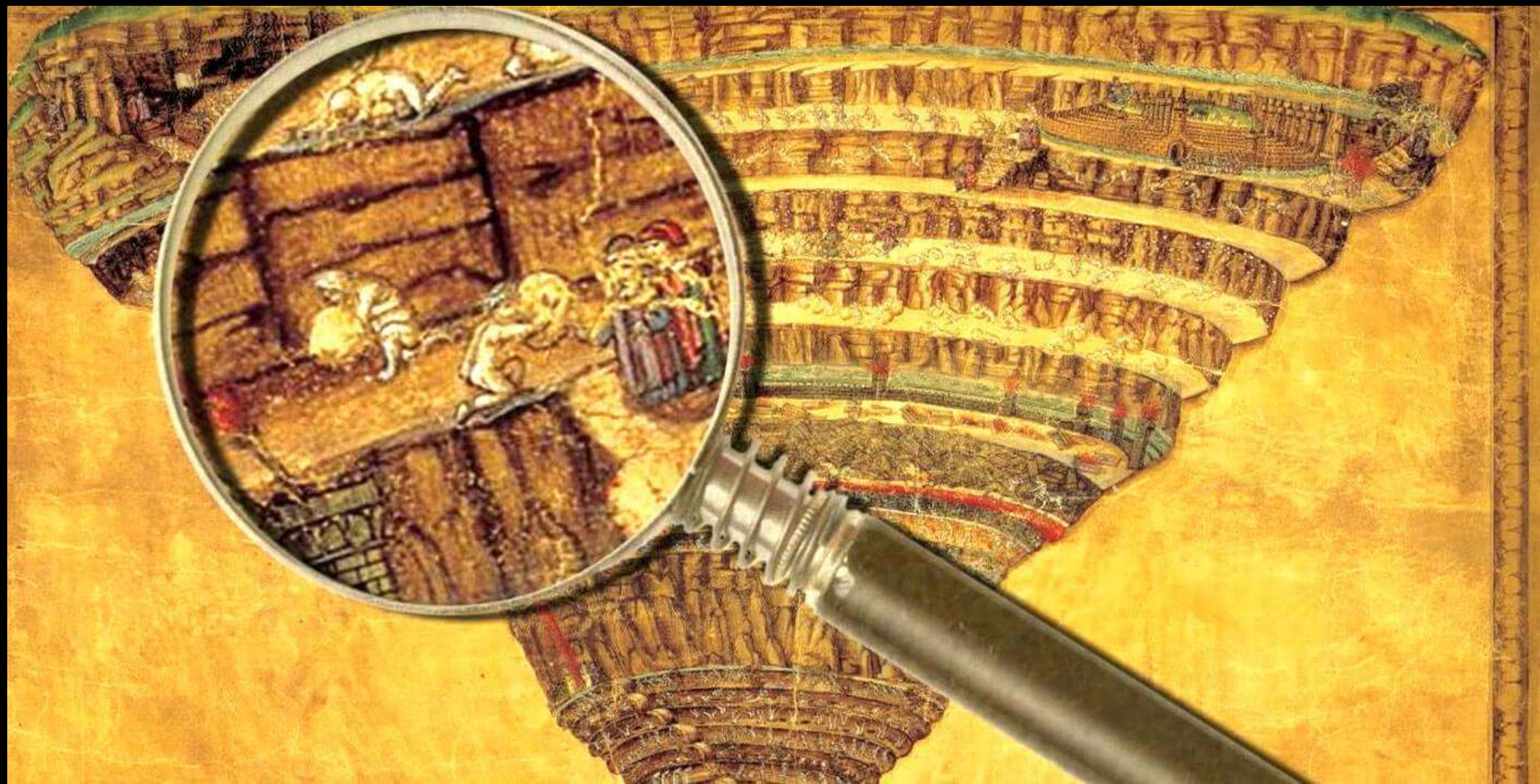
Mechanism of drugs

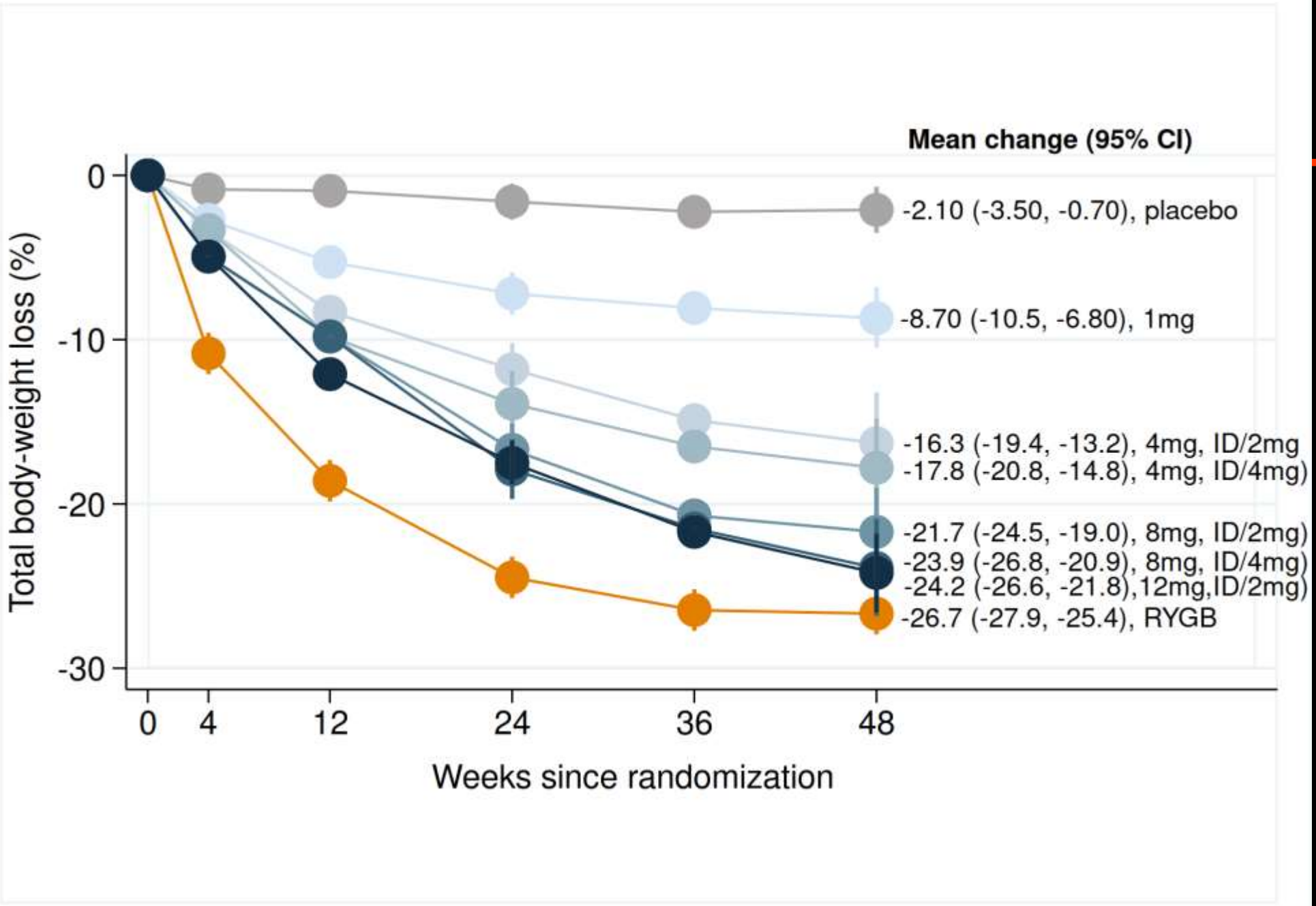
Carel le Roux

University College Dublin
Ulster University
University of Pretoria



Conflicts of interest

- Consilient Health
- Novo Nordisk
- Herbalife
- Johnson & Johnson
- Covidien
- Fractyl
- GI Dynamics
- Lilly
- Boehringer Ingelheim
- Keyron

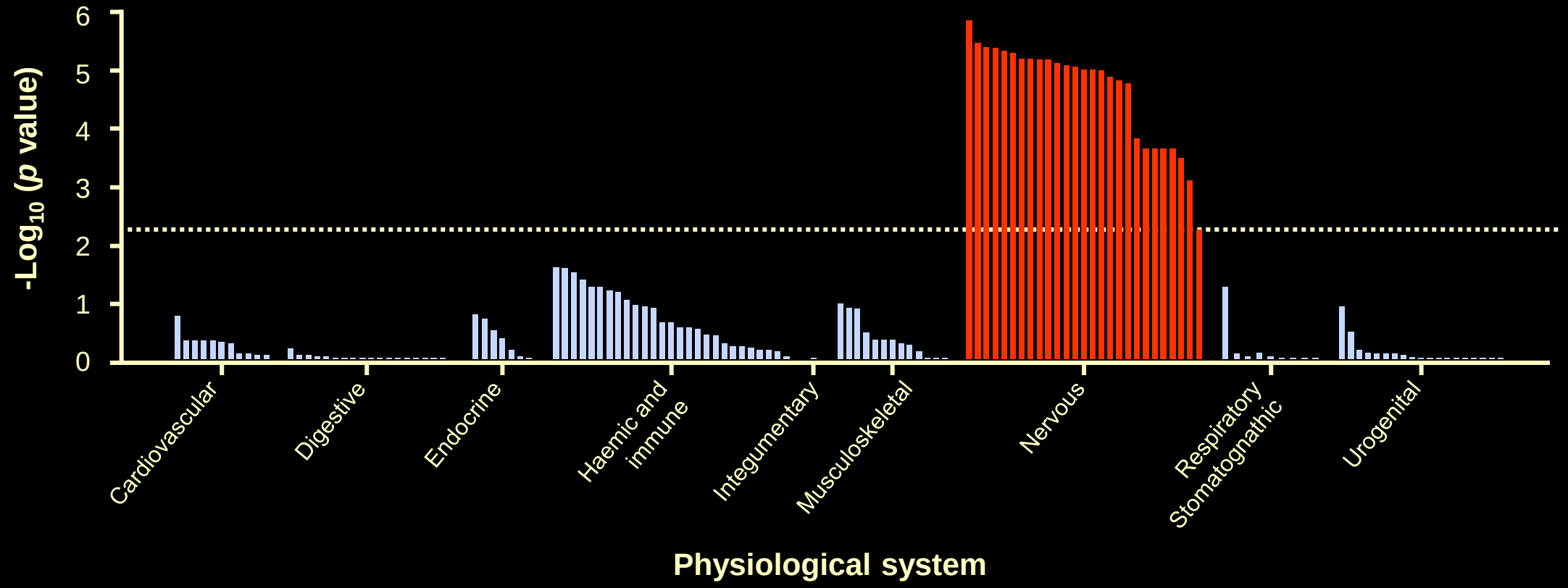


RYGB in MOMS
(JAMA surgery 2020)
vs
retatrutide
(NEJM 2023)
#over 48 weeks

Ricardo Cohen

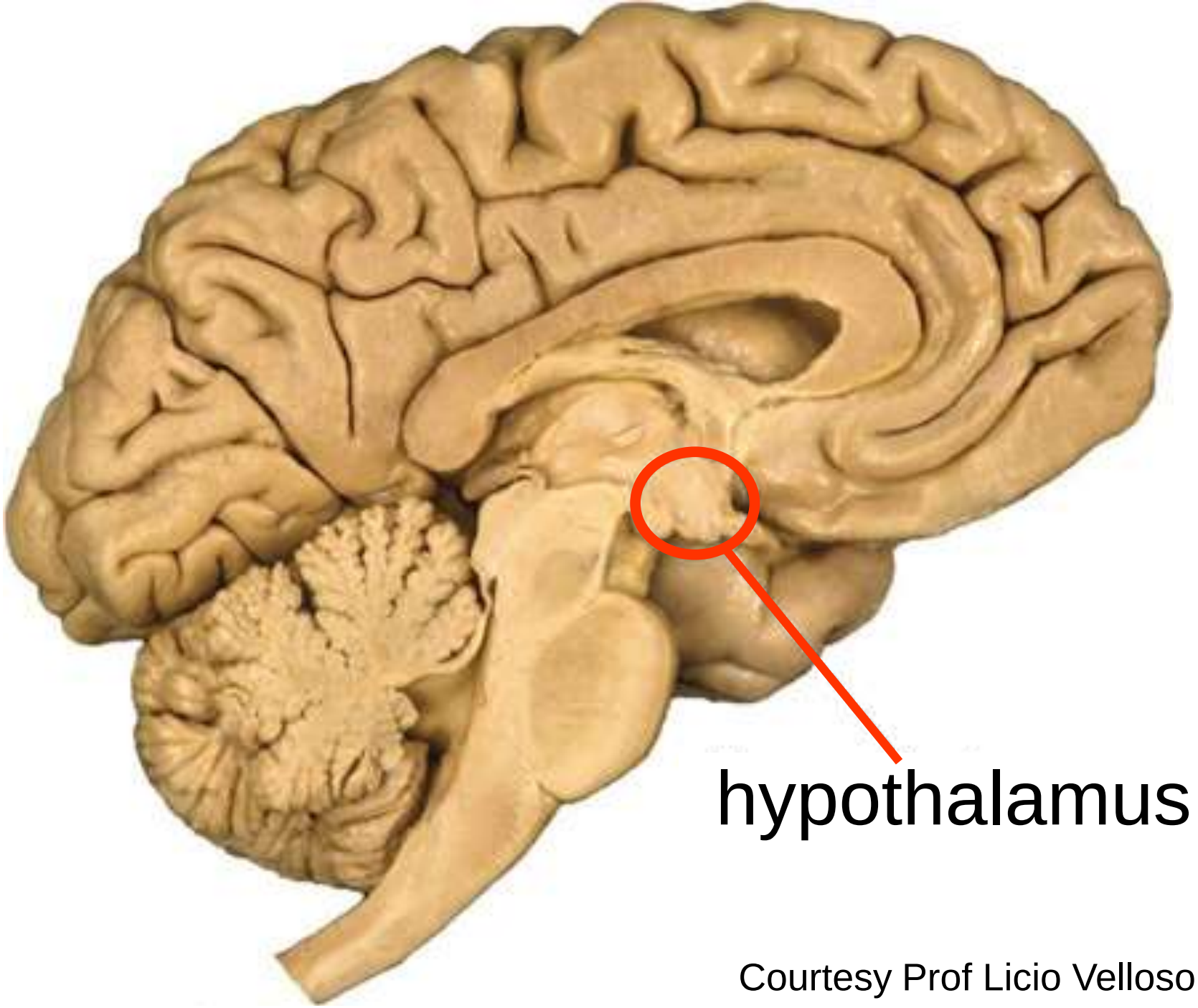
Obesity has genetic determinants: GWAS pathway analyses link CNS genes to obesity

Tissues sorted by physiological system – genes from CNS showed association (in red)



CNS, central nervous system; GWAS, Genome-Wide Association Study

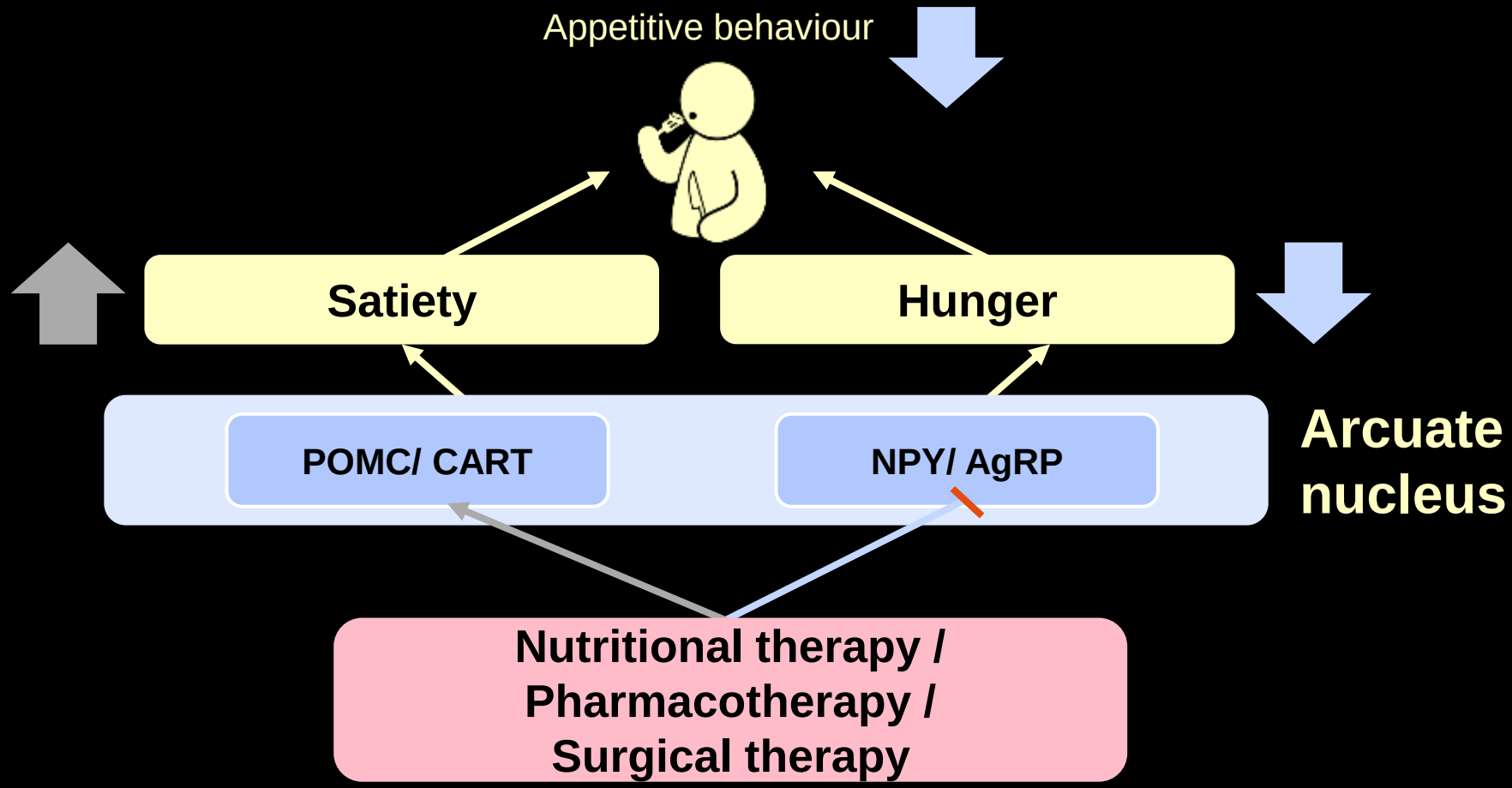
Locke AE, et al. Nature 2015;518:197–206.



Courtesy Prof Licio Velloso

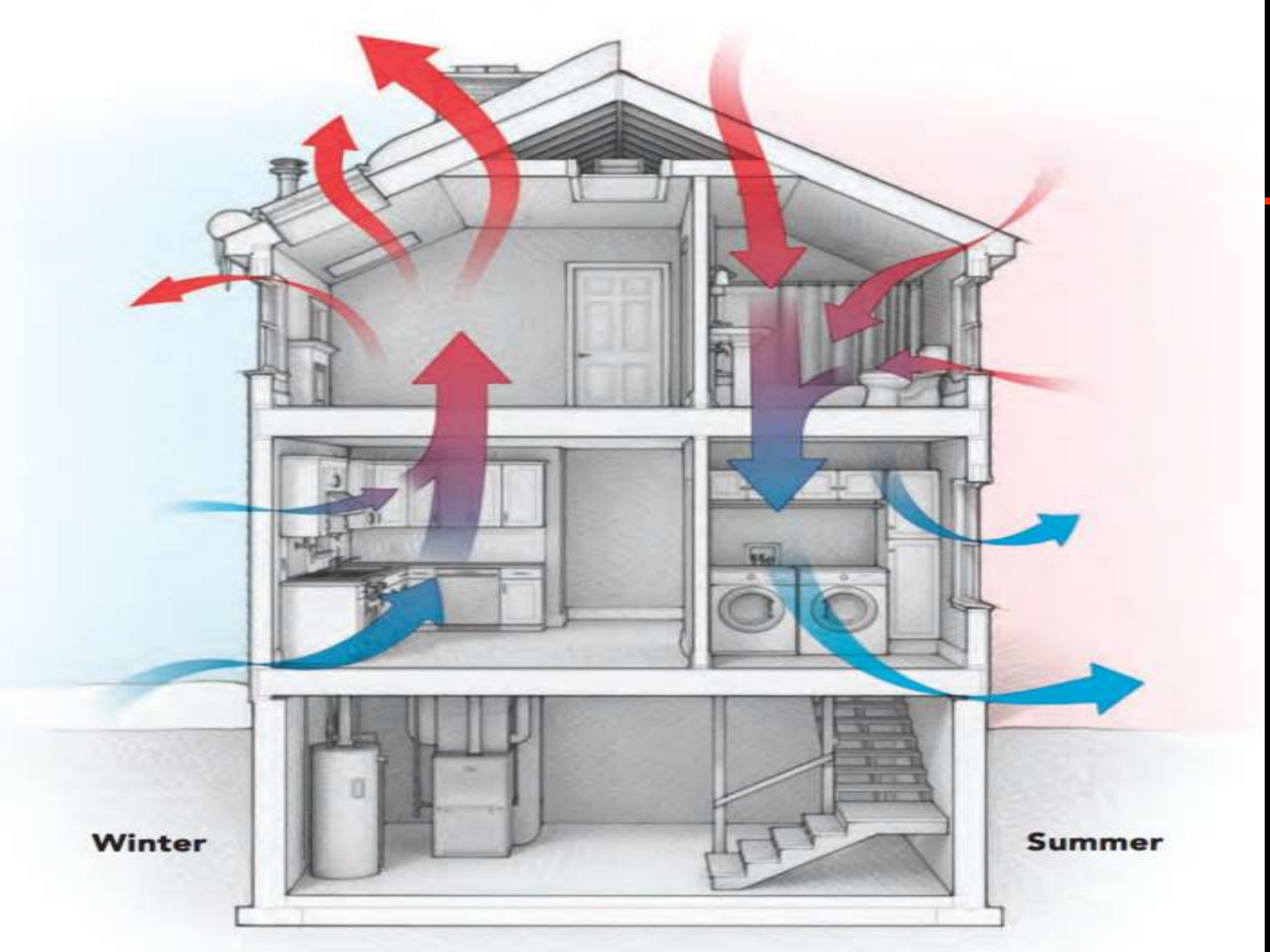
Successful obesity treatments increase satiety and reduce hunger during the weight loss phase

Via neurons in the arcuate nucleus



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.



Energy balance

adapted from Lee Kaplan

Observational study in participants of the ‘Biggest Loser®’ reality television show

16 participants were included in the follow-up study

Trial information
- Single centre observational study

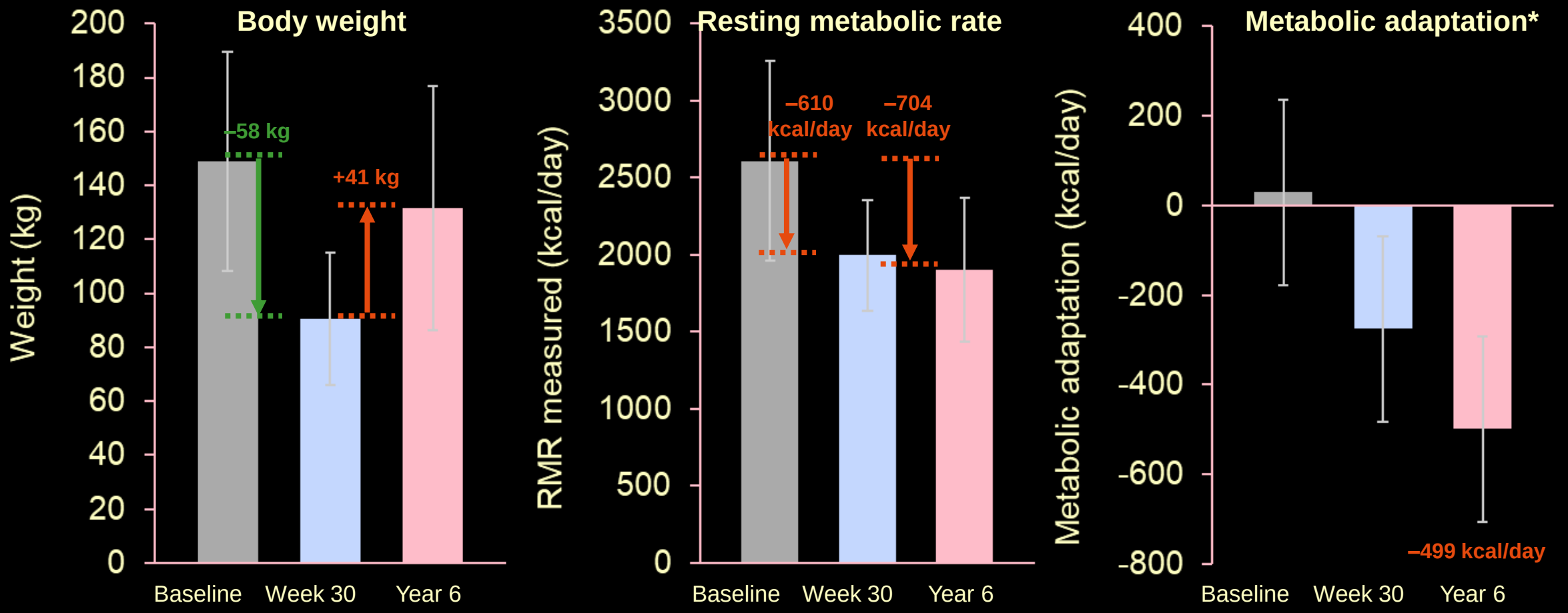
Primary objective
- REE
- Metabolic adaptation calculated as the difference between the measured REE and the REE predicted from linear regression analysis of baseline

Key inclusion criteria
- 16 subjects who previously participated in the Biggest Loser® study

Key exclusion criteria
- Volunteers unwilling or unable to give informed consent.
- Women who are pregnant or breastfeeding
- Subjects with implantable cardio-defibrillator or pacemaker

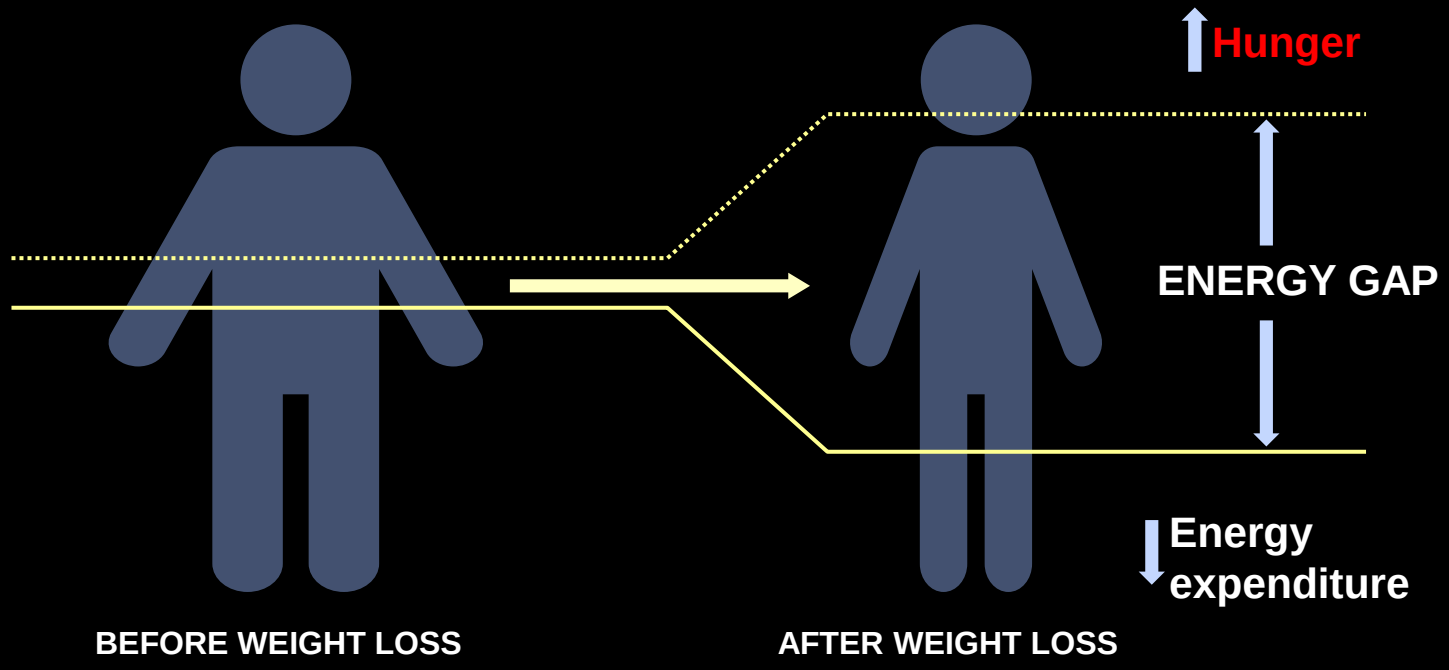
Intervention consisted of: Exercise component consisting of supervised vigorous circuit and/or aerobics training 90 min/d (6 d/wk). Participants were encouraged to exercise up to an additional 3 h/d. Dietary intake was not monitored; however, participants were advised to consume a calorie-restricted diet greater than 70% of their baseline energy requirements as calculated by the following: 21.6 kcal/kg·d × FFM (kilograms) + 370 kcal/d.
FFM, fat-free mass; REE, resting energy expenditure; RMR, resting metabolic rate.
Fothergill E, *et al. Obesity (Silver Spring).* 2016;24:1612–19; Johannsen DL, *et al. J Clin Endocrinol Metab.* 2012;97(7):2489–96.

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.
RMR, resting metabolic rate. Fothergill E, *et al. Obesity (Silver Spring).* 2016;24:1612–19.

Weight loss triggers compensatory biological pathways



↑ Ghrelin
↓ PYY
↓ CCK
↓ Thyroxin
↓ GLP-1
↓ Insulin
↓ Leptin

→ ↑ Hunger
→ ↓ Satiety
→ ↓ Satiation

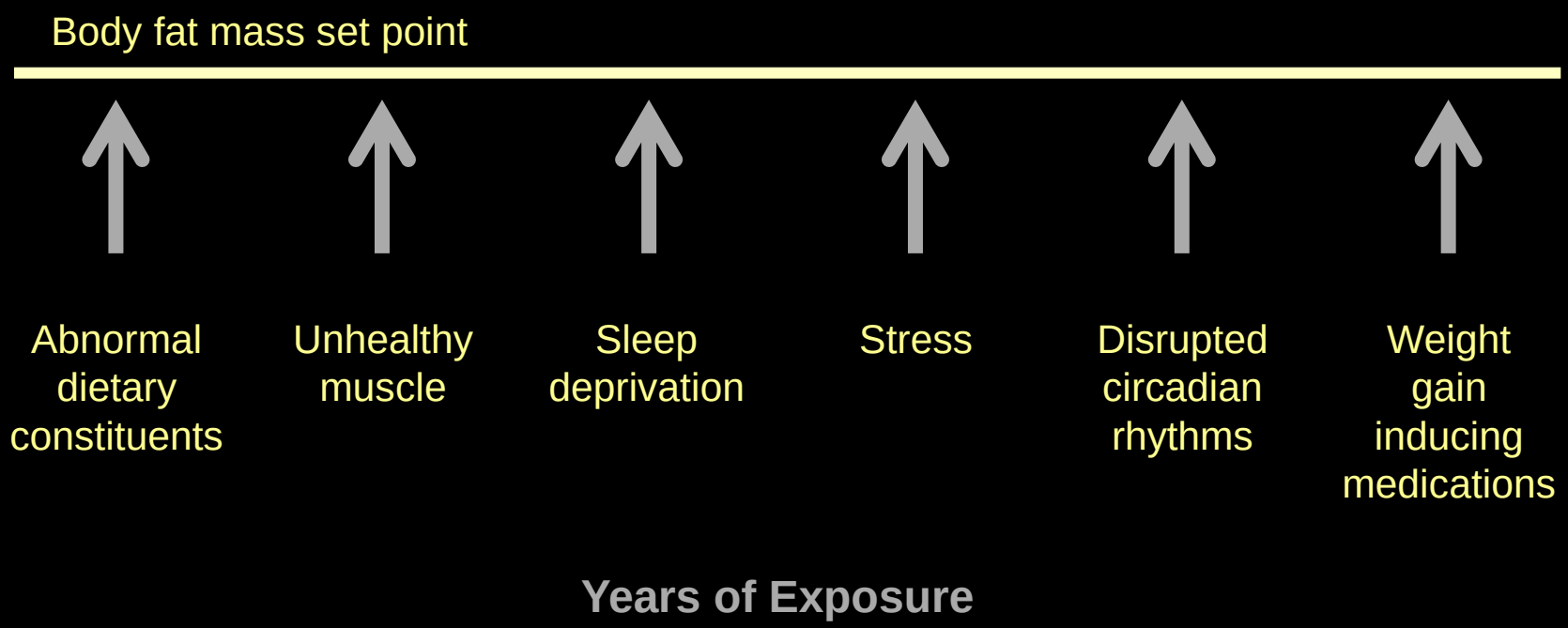
↓ SNS activity
↓ Body mass
↓ Leptin
↑ Energy efficiency

→ ↓ TDEE
→ ↓ TEF
→ ↓ RMR
→ ↓ PAEE

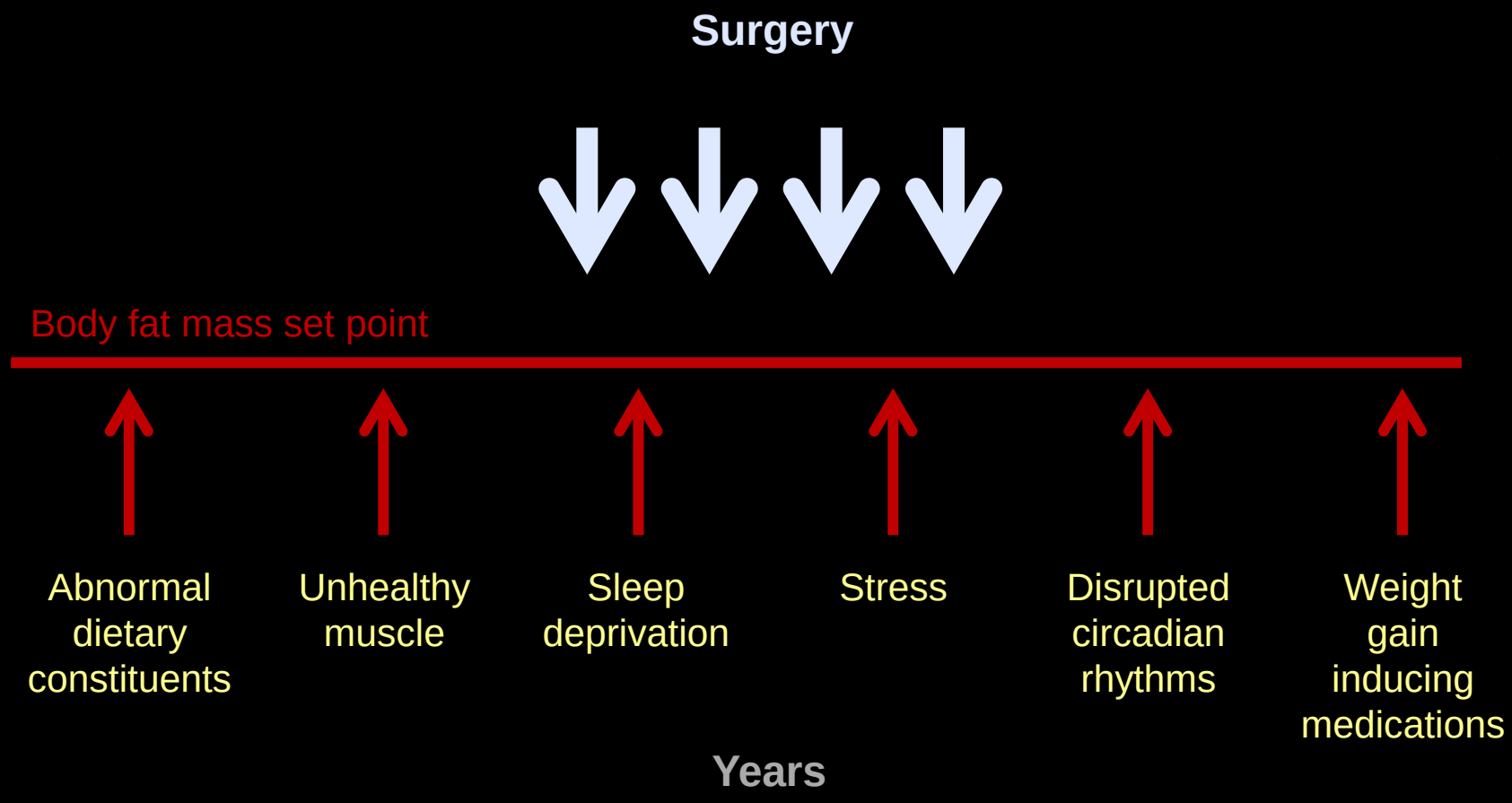
CCK, cholecystokinin; GLP-1, glucagon-like peptide 1; PYY, peptide tyrosine tyrosine; PAEE, physical activity energy expenditure; RMR, resting metabolic rate; SNS, sympathetic nervous system; TDEE, total daily energy expenditure; TEF, thermic effect of food.

Melby CL, *et al. Nutrients.* 2017;9:468.

Obesity and Its Care: A Battle of Forces that Influence the Fat Mass Set Point



Obesity and Its Care: A Battle of Forces that Influence the Fat Mass Set Point



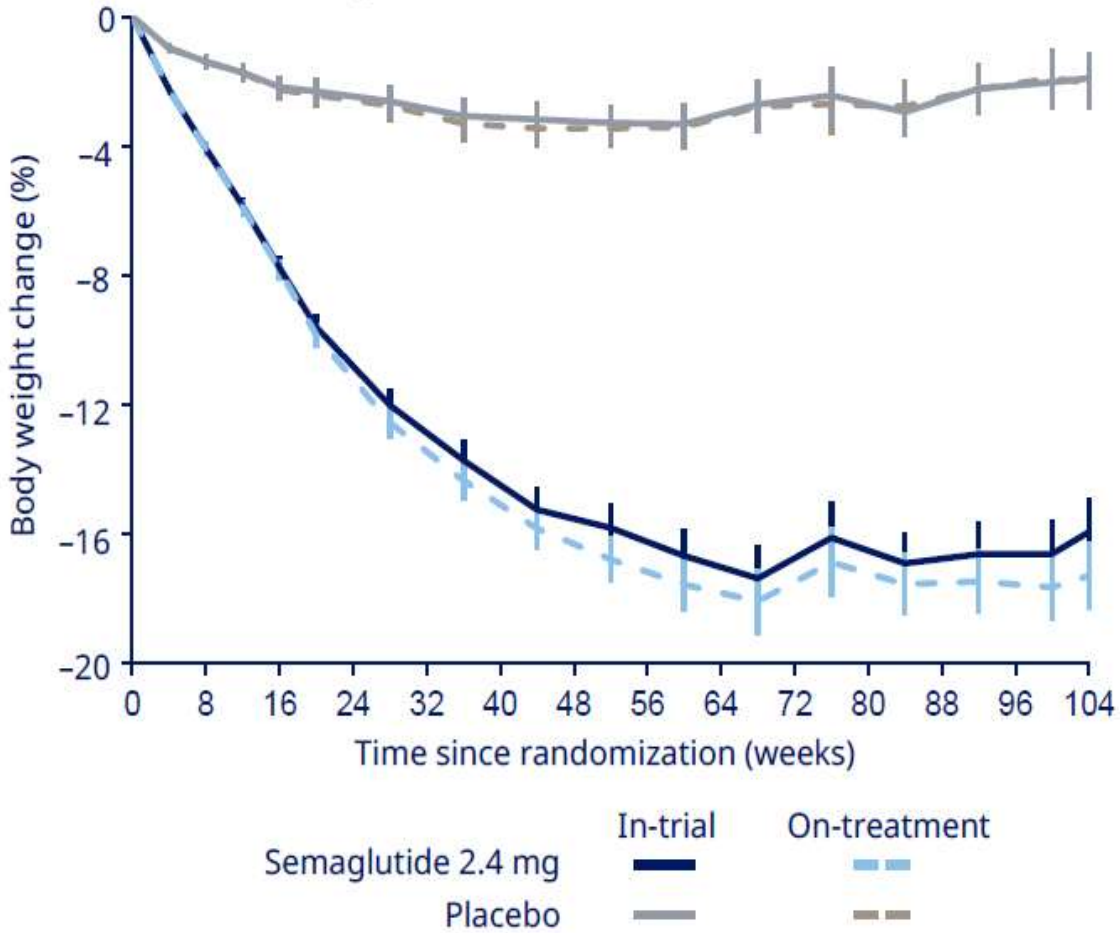
STEP 5: semaglutide 2.4mg for 104 weeks

Garvey et al. Nature Medicine 2022

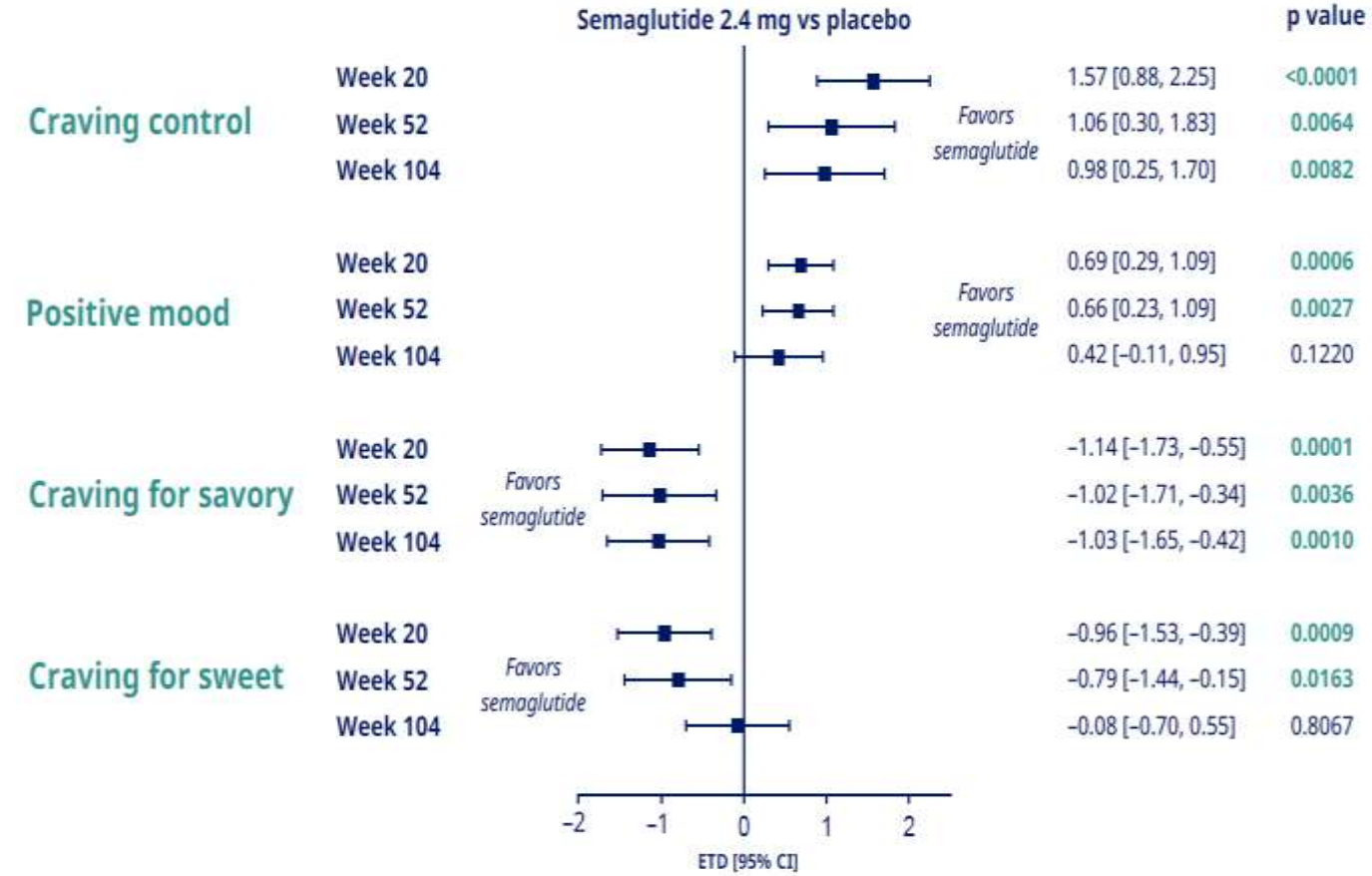
STEP 5 overall population

Observed mean change over time

Mean at baseline: 106.0 kg



Change in CoEQ domain scores

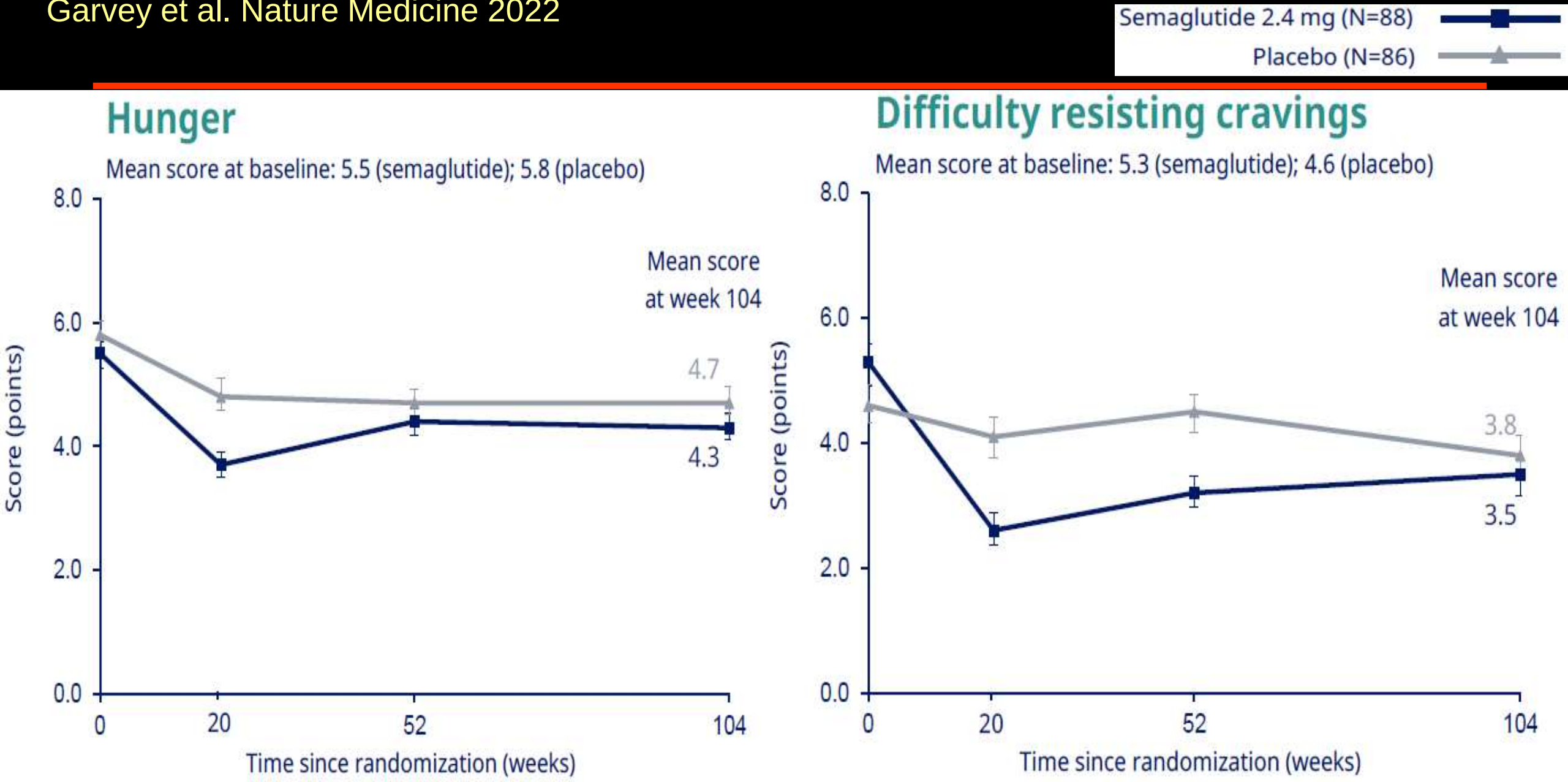


CoEQ was assessed in 88 participants in the semaglutide group and 86 in the placebo group. P values are not adjusted for multiplicity. CI, confidence interval; CoEQ, control of eating questionnaire; ETD, estimated t
Data are based on the treatment policy estimand (assesses treatment effect regardless of treatment discontinuation or rescue intervention).

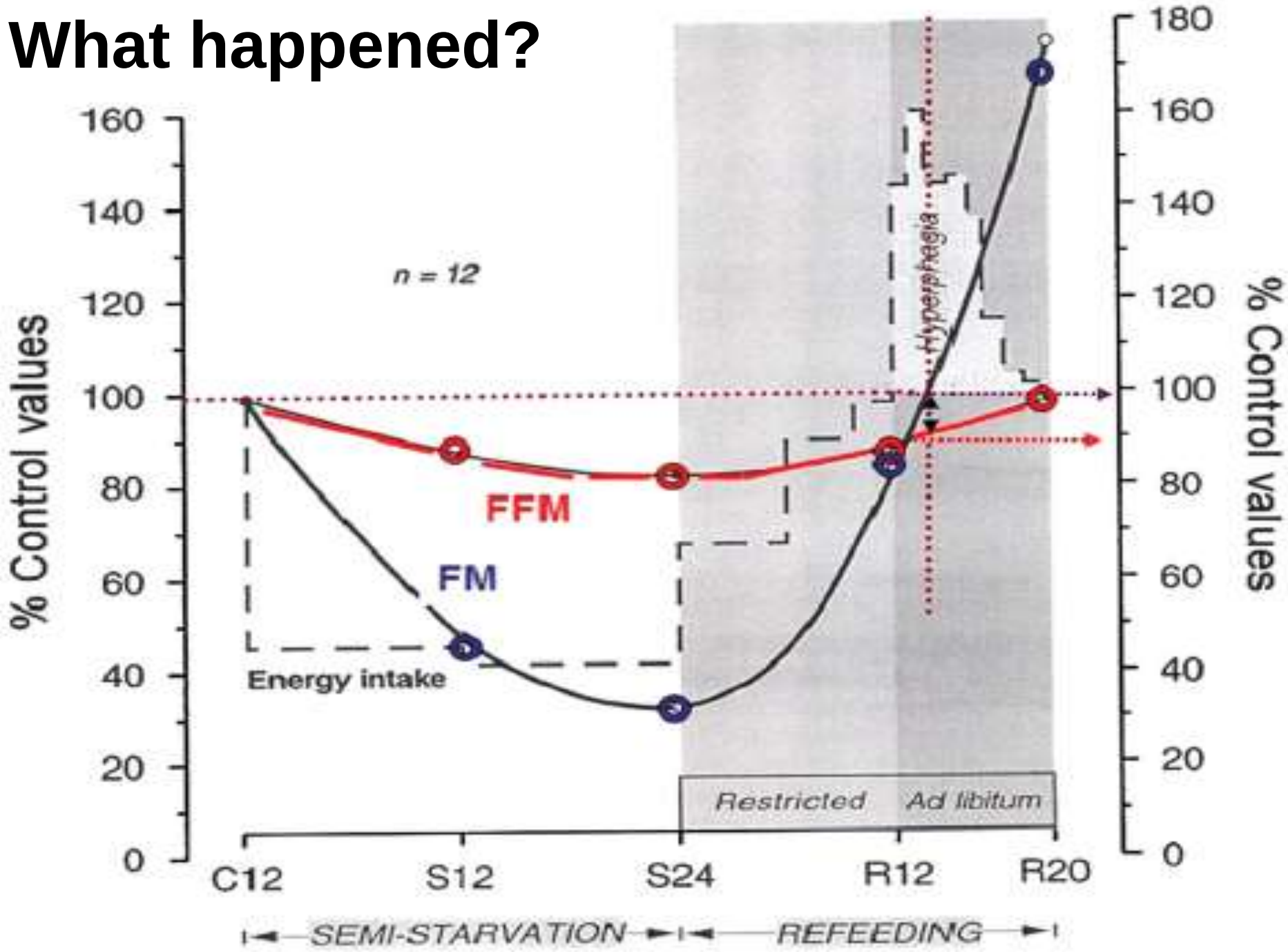
Wharton S, et al. Presented at the 39th Annual Meeting of The Obesity Society (TOS) held at ObesityWeek®, virtual meeting, November 1–5, 2021.

STEP 5: semaglutide 2.4mg for 104 weeks

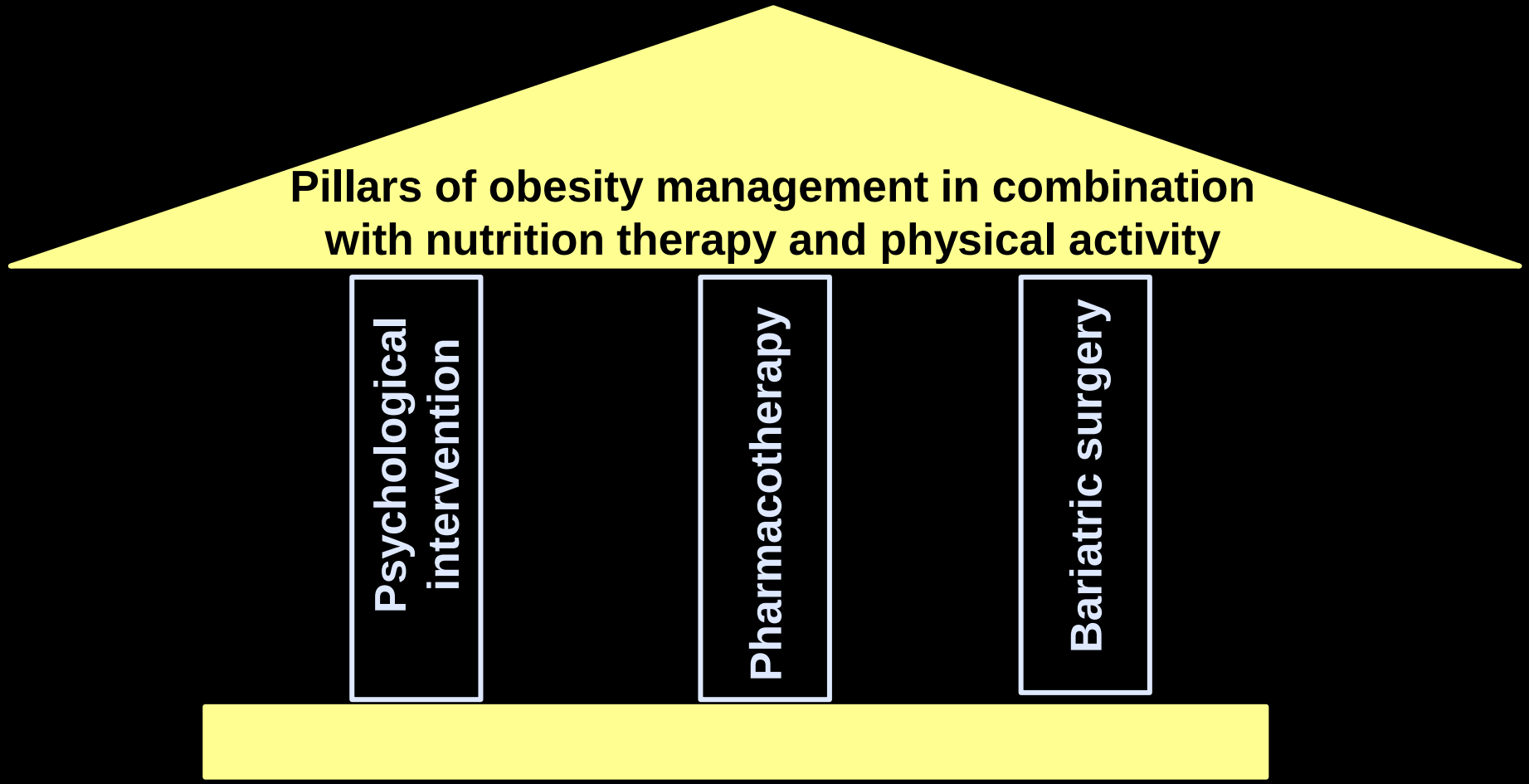
Garvey et al. Nature Medicine 2022



What happened?



Framework for obesity management



Wharton S et al. CMAJ 2020;192:e875-e891 (supplement).

Conclusions

- Anti-obesity medications
  - Treat the complex and chronic set of diseases of obesity
  - Reduces excess adipose tissue and improves health
  - Chronic treatment is required for a chronic disease


METABOLIC
MEDICINE
HEROES

Acknowledgements

Funding: Science Foundation Ireland, Vetenskapsrådet, Wellcome Trust, Moulton Foundation, NIHR, EKF Diagnostics, AnaBio

Metabolic Medicine group University College Dublin

- Neil Docherty, Loai Shakerdi, Meera Nair, Natasha Kapoor, Werd Al-Najim

University College Dublin

- Catherine Godson, Donal O'Shea, Ronan O'Connell, Ronan Cahill, Donal Brennan, John Garvey, Helen Heneghan

Trinity College Dublin

- John Reynolds, Conor Murphy, Jessie Elliott

Sweden

- Torsten Olbers, Anders Thorell, Lars Fandriks, Almantas Maleckas, Lena Carlsson, Per-Arne Svensson

Imperial College London

- Steve Bloom, Mohammad Ghatei, Alex Miras, Andrew Frankel, Julian Teare

King's College London

- Francesco Rubino, Stephanie Amiel, Simon Aylwin, Ameet Patel, Cynthia Borg, Royce Vincent

University of Zurich

- Thomas Lutz, Marco Bueter

Musgrove Hospital, Taunton

- Richard Welbourn, Rob Andrews, Dimitri Pournaras, Alan Osborn

Florida State University

- Alan Spector

Oswaldo Hospital, São Paulo

- Ricardo Cohen

Catholic University of Chile

- Camilo Boza

Saudi Arabia

- Al-Qahtani, Ghalia Abdeen