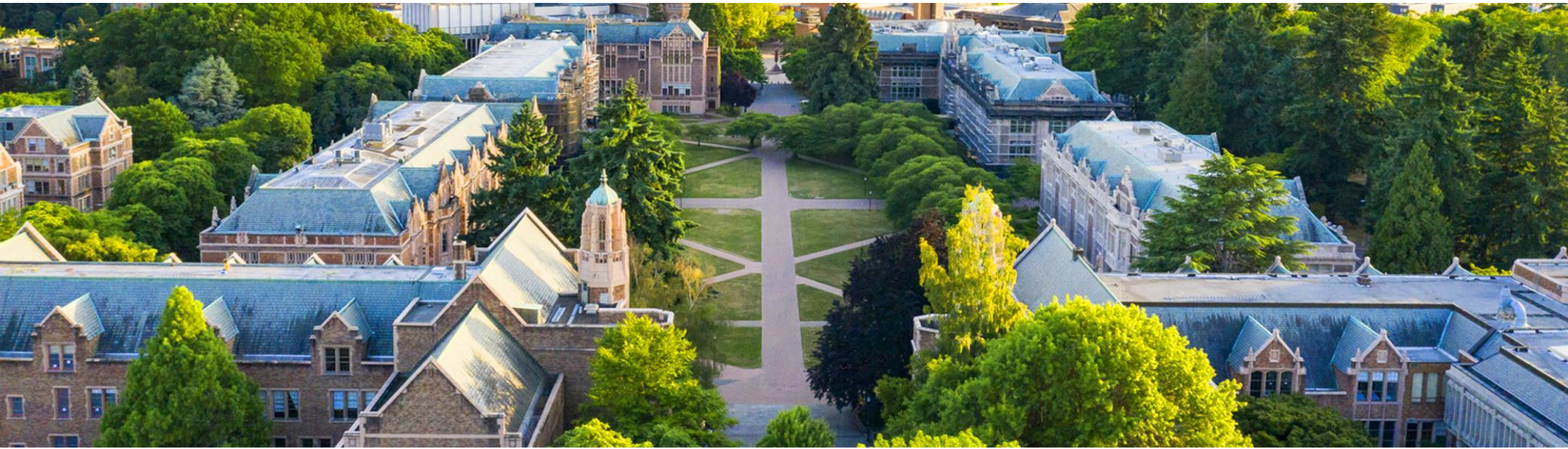




Monotherapy Has Its Place, But Biology Often Demands More

David E. Cummings, MD, FASMBS

**University of Washington
VA Puget Sound Health Care System**

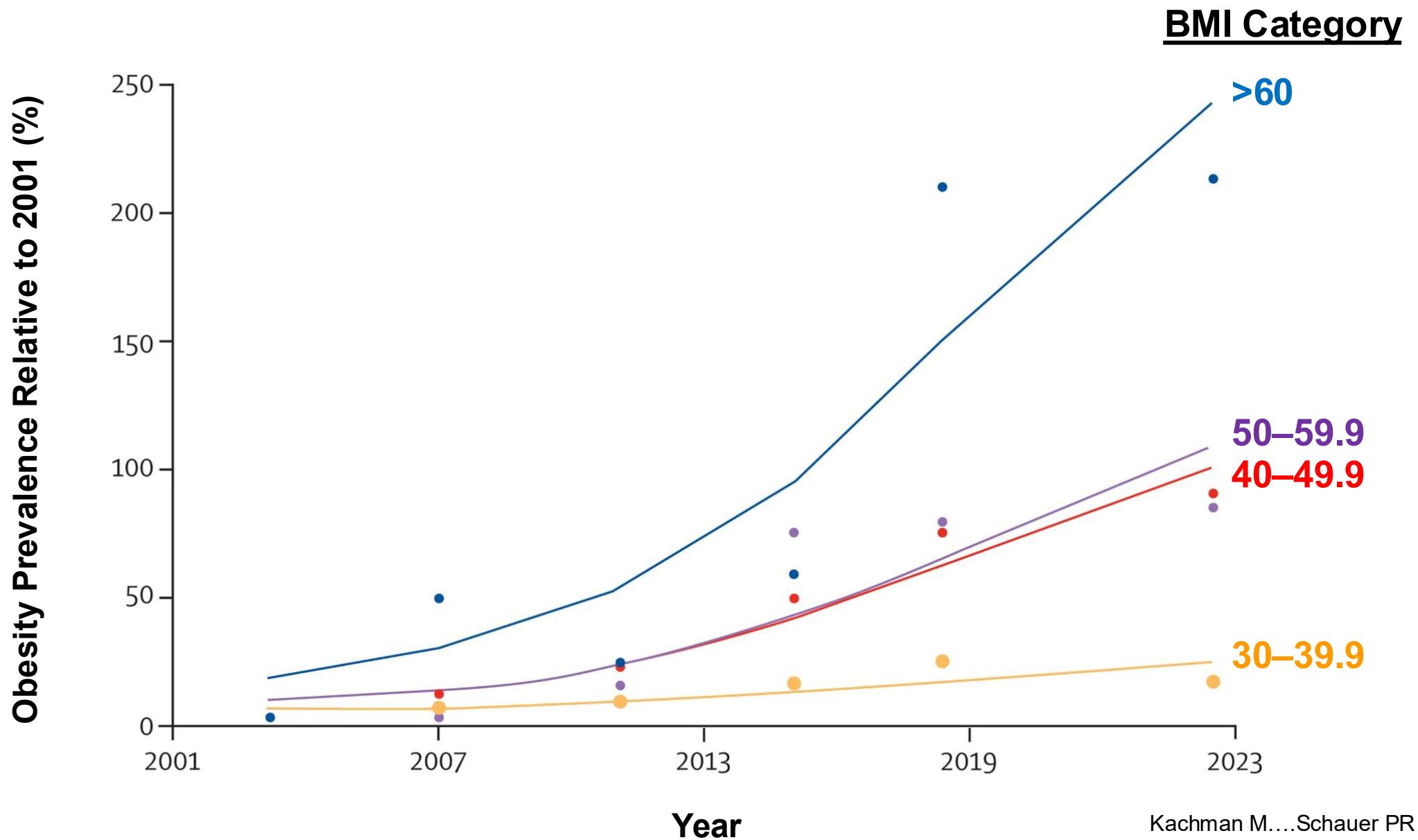


Scientific Advisory Boards

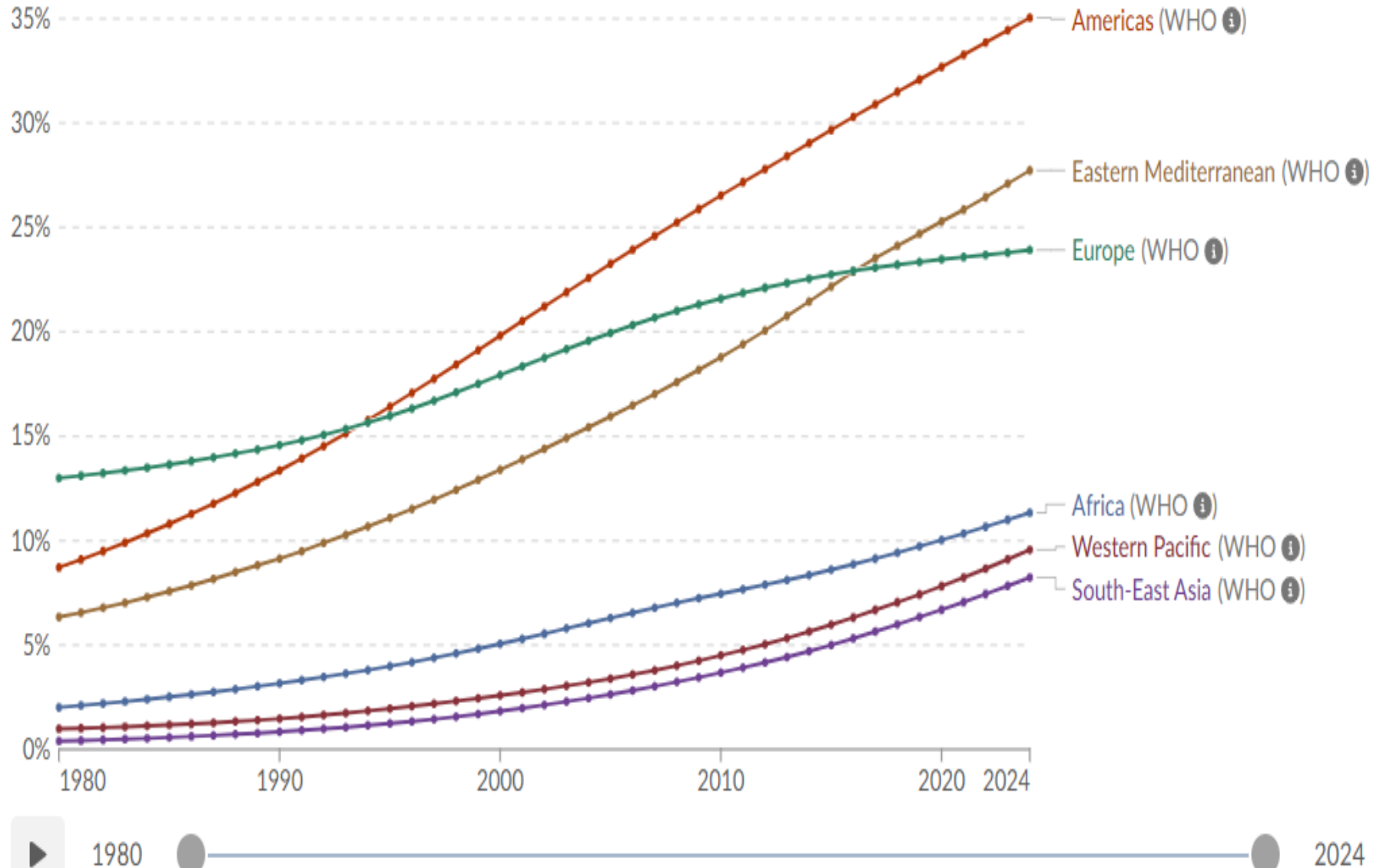
- Lumen Bioscience
- Morphic Medical
- AbbVie
- Endogenex



~250% Increase of Extreme Obesity Prevalance in 20 Years



Obesity Prevalence Continues to Rise Everywhere in the World



THE LANCET

Volume 380 Number 9912 Pages 1023-1260 November 02, 2012 (Friday 8, 2012)

www.thelancet.com

The Global Burden of Disease Study 2010



The Lancet: 4 Entire Volumes, Dec 2012–Jan 2013

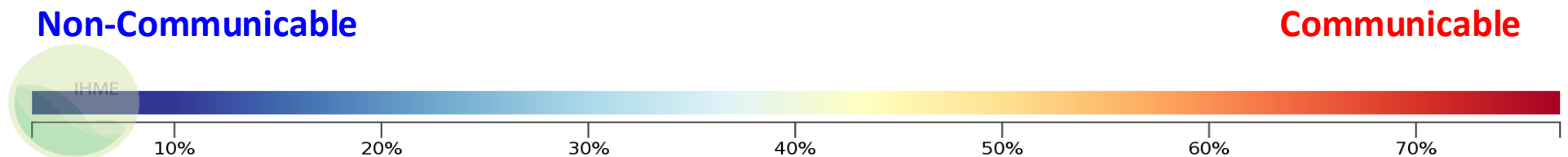
Percent of total DALYs from Communicable,
Maternal, Neonatal & Nutritional Disorders

2010

1990: 2/3 of death & disability were from communicable diseases

2010: 2/3 of death & disability were from non-communicable diseases

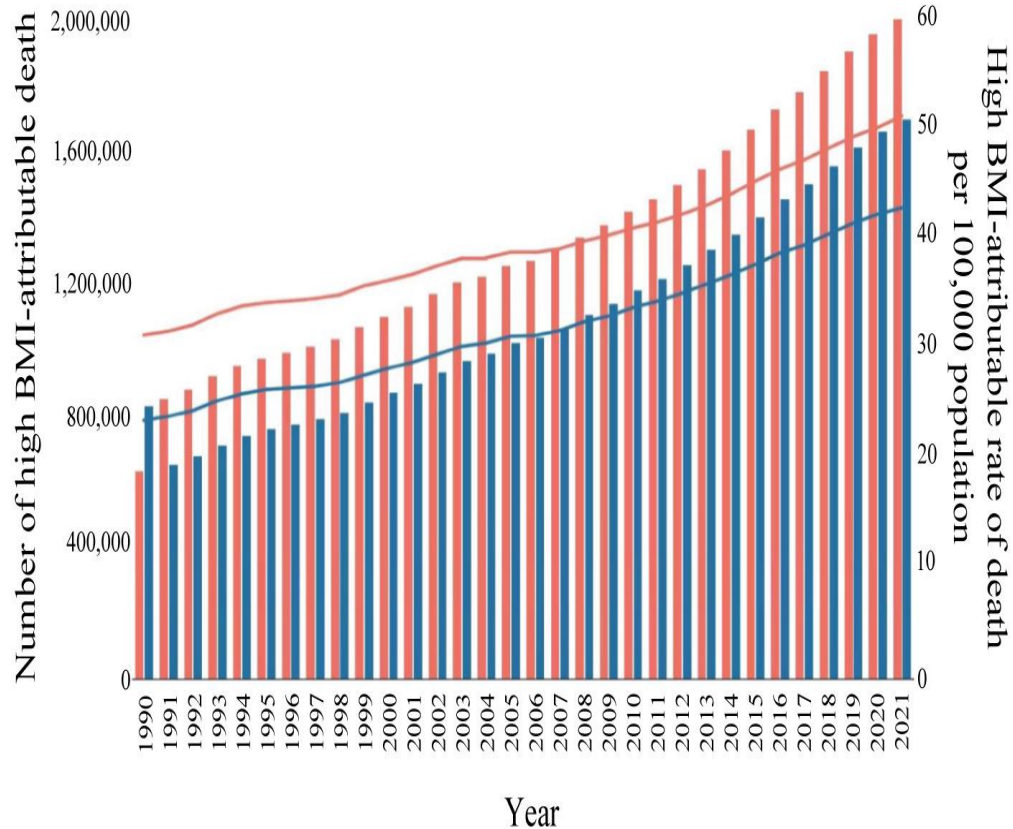
Fastest growing contributors to this: high BMI and high blood glucose



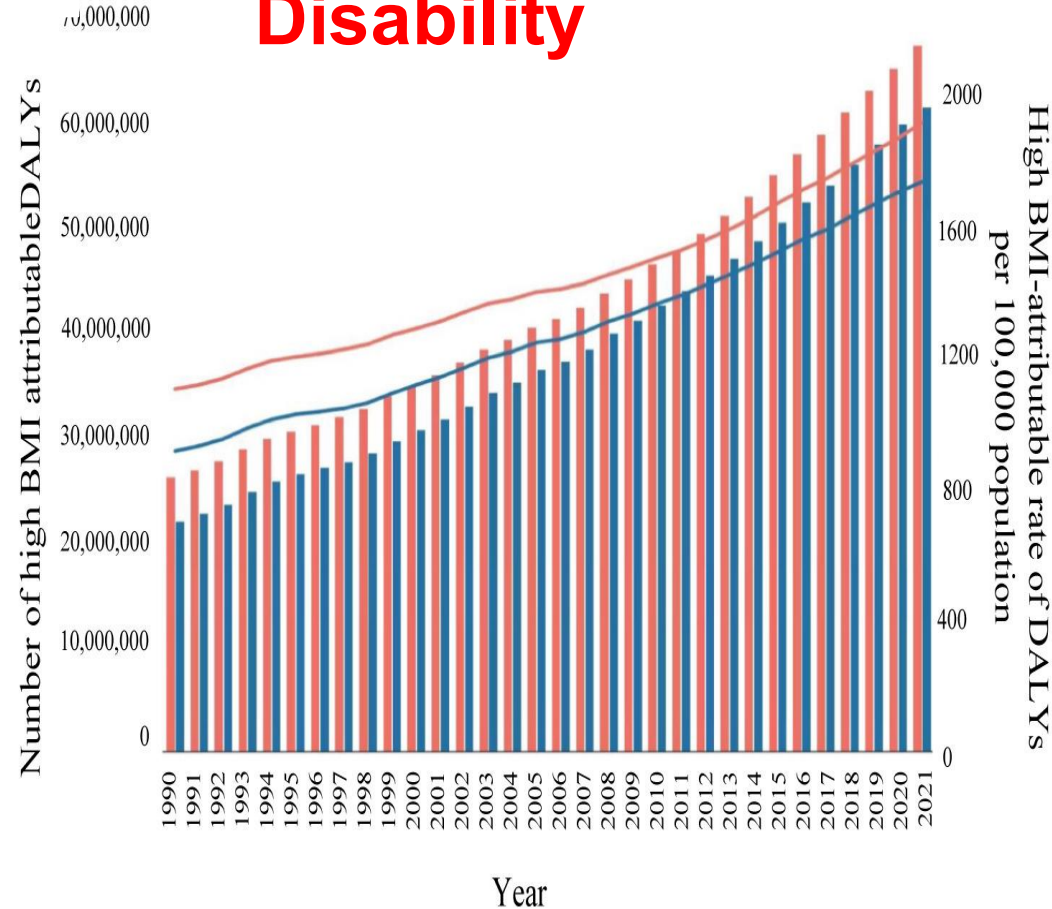
High-BMI Attributable Death & Disability

Continue to Rise Worldwide

Death

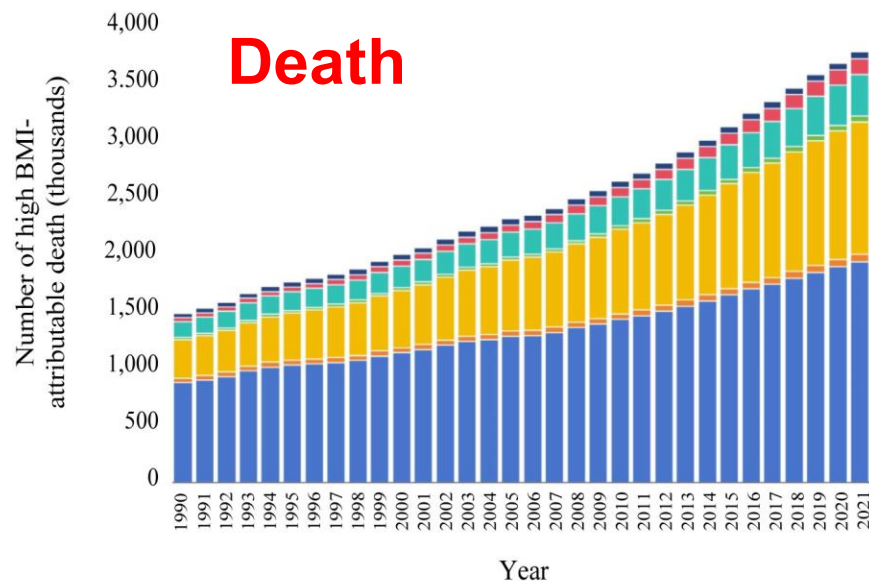


Disability



Global Burden of Disease Group

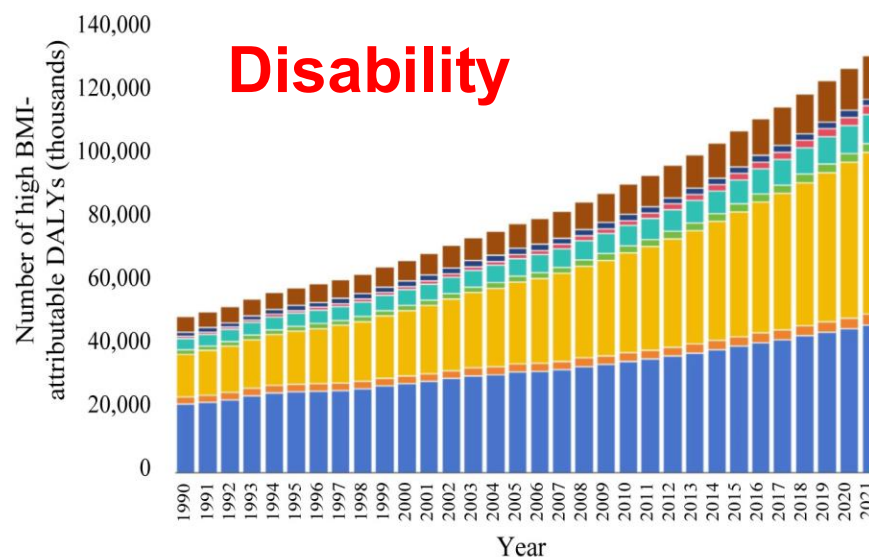
The Lancet 76:1 (2024)



High-BMI Attributable

Death & Disability

Continue to Rise Worldwide

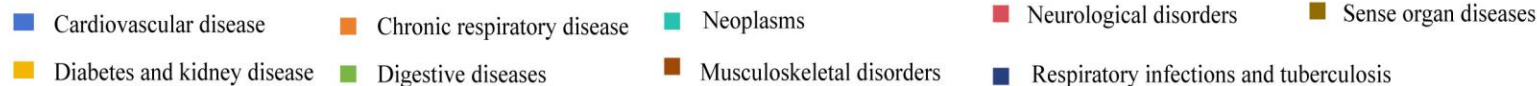


in Every

Category of Disease

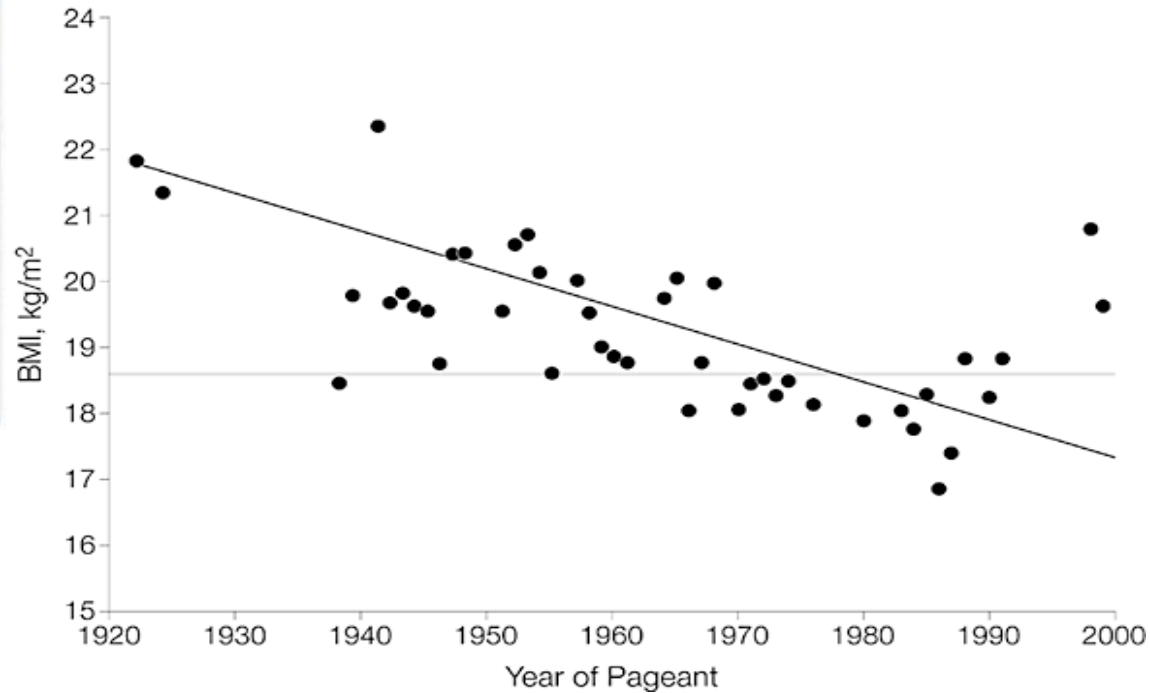
GBD

**Lancet 76:1
(2024)**



Miss America: An Undernourished Role Model?

Rubinstein and Caballero *JAMA*. 2000;283:1569-1569



Among people who had lost ≥ 100 lbs with metabolic surgery, rather than be obese again:

- 100% would prefer to be deaf, dyslexic, diabetic, or have heart disease
- 92% would prefer to have a leg amputated
- 89% would prefer to be blind

Gloria! Have you
lost weight?



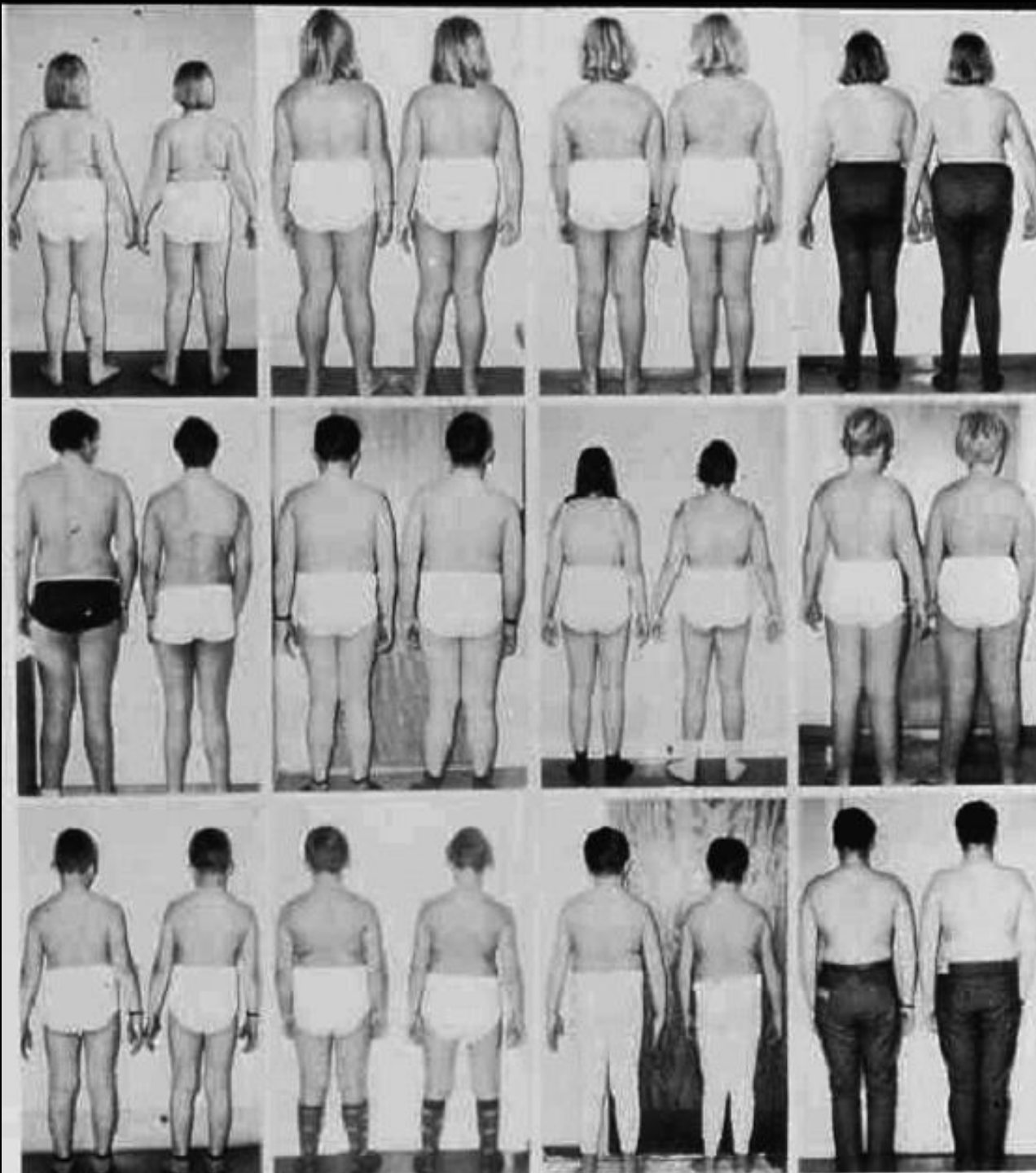
**“Obesity is a
glandular problem:**

Anonymous

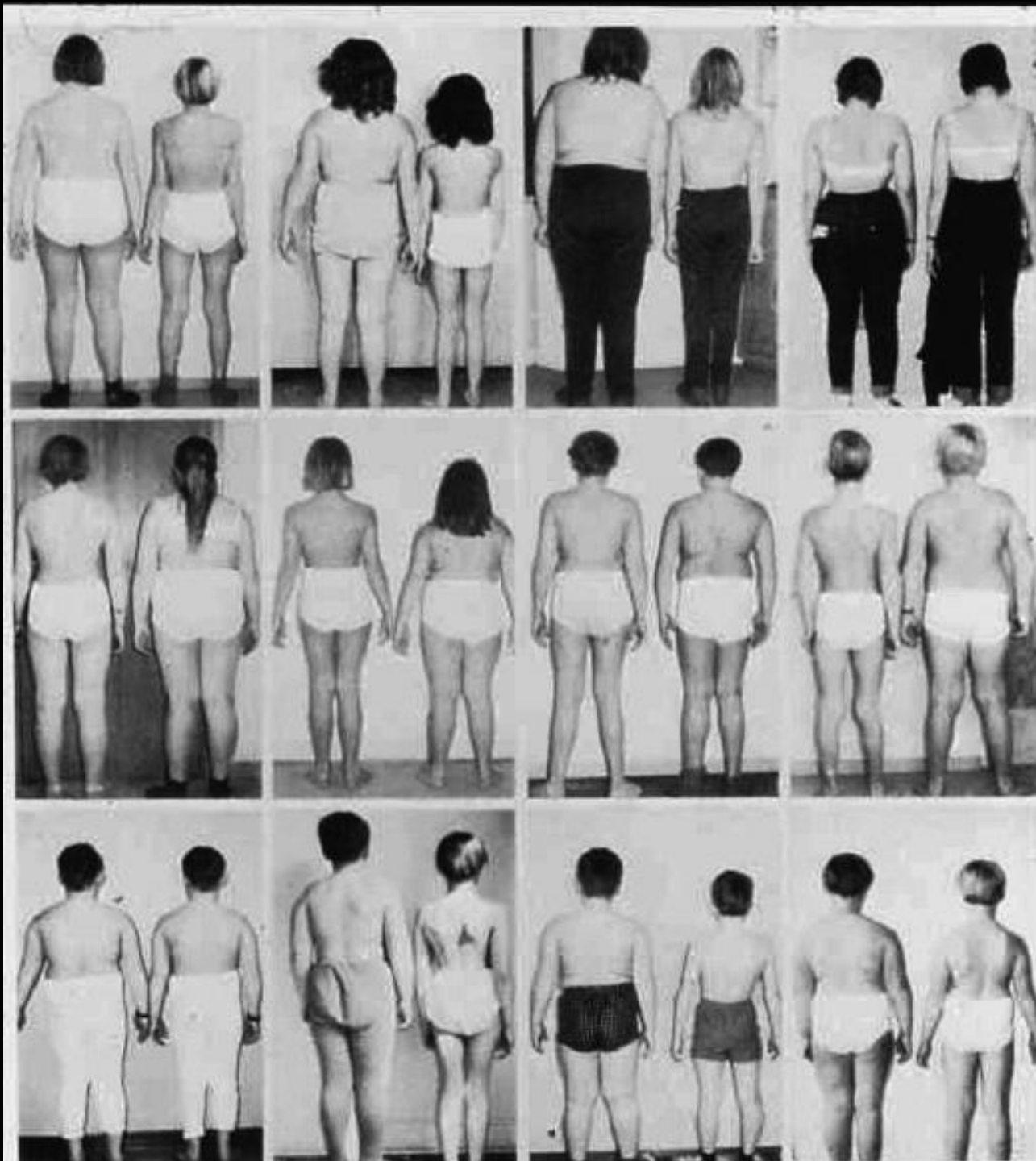
**“Obesity is a
glandular problem:
the salivary gland.”**

Anonymous

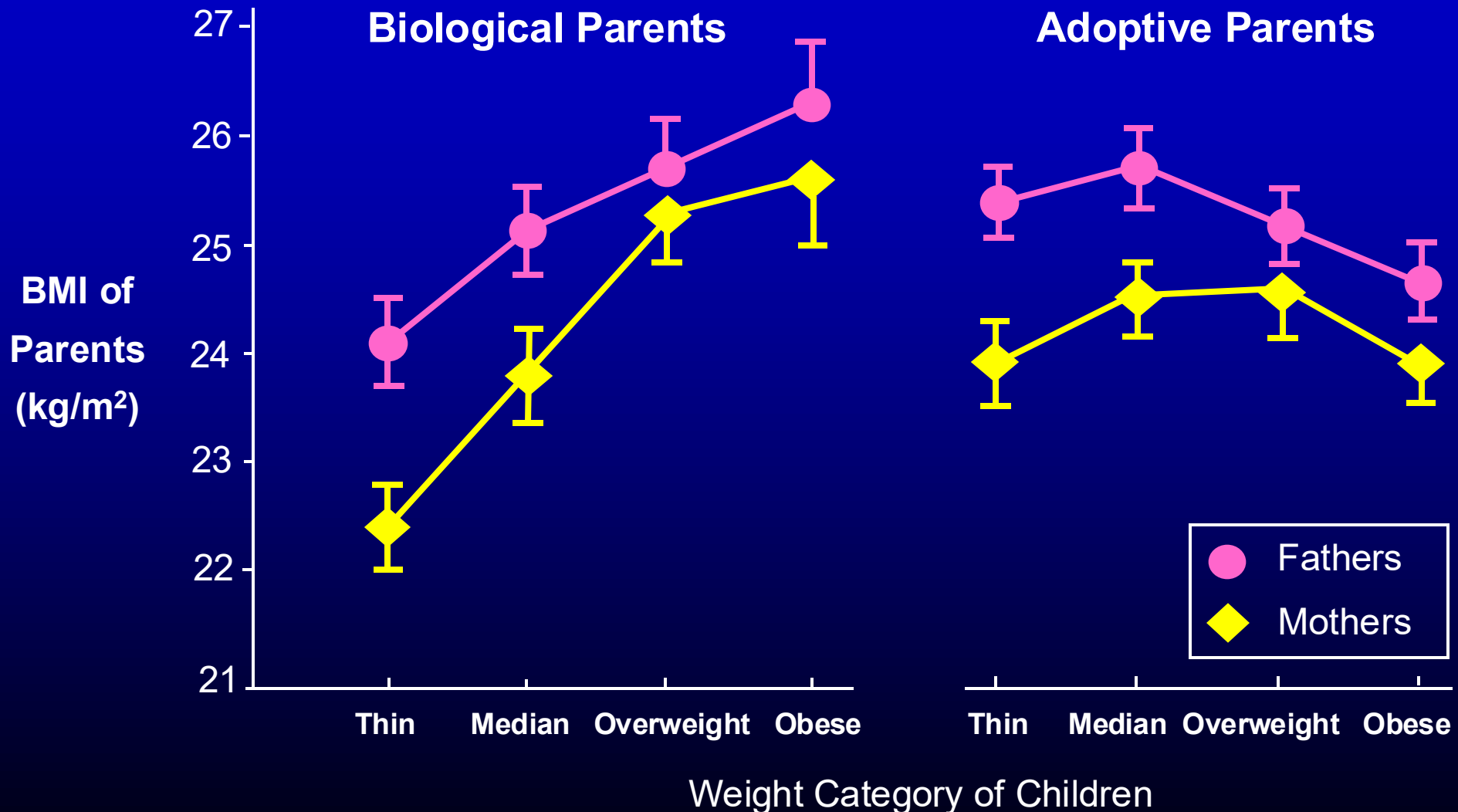
Identical Twins



Fraternal Twins

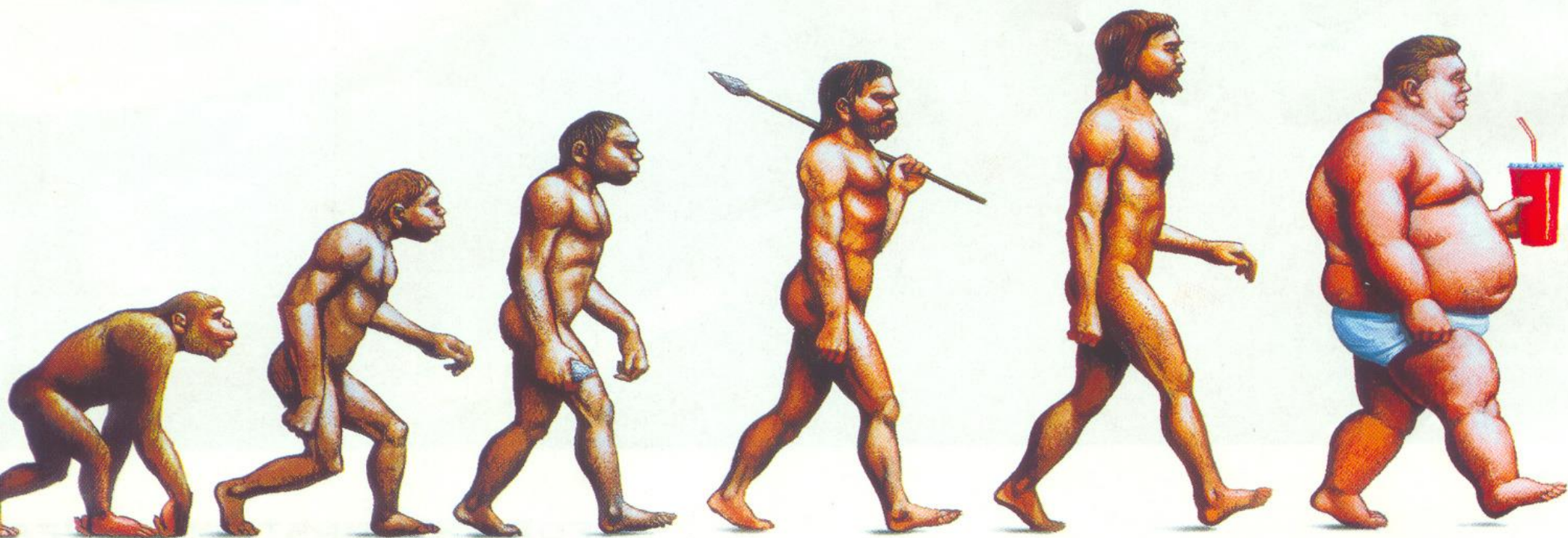


Adopted Children's Weight Correlates With Weight of Their Biological, Not Adoptive, Parents



**In conditions of plenty,
body weight is 60-80%
genetically determined**

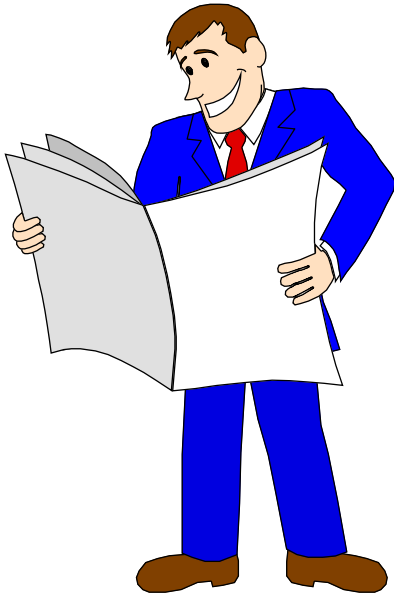




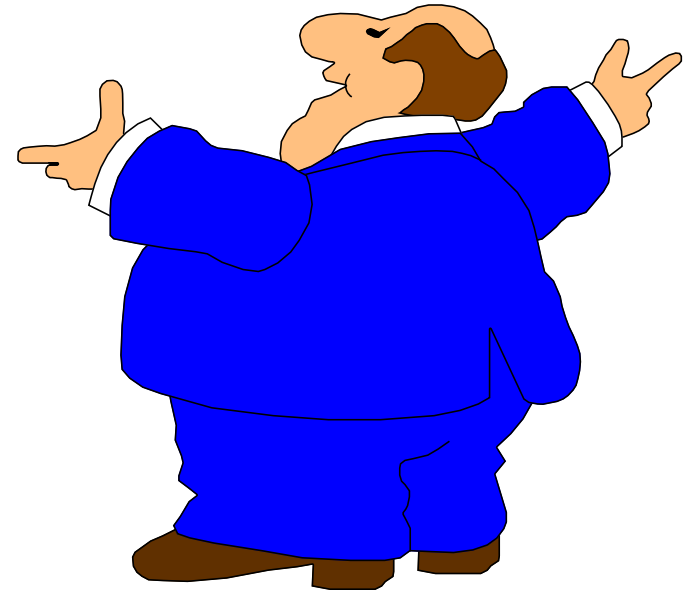




**Body weight is regulated
within a narrow,
individualized range.**



20 year old male
170 lb.



60 year old male
210 lb.

1 lb. per year = 3500 kcal/365 days...or...

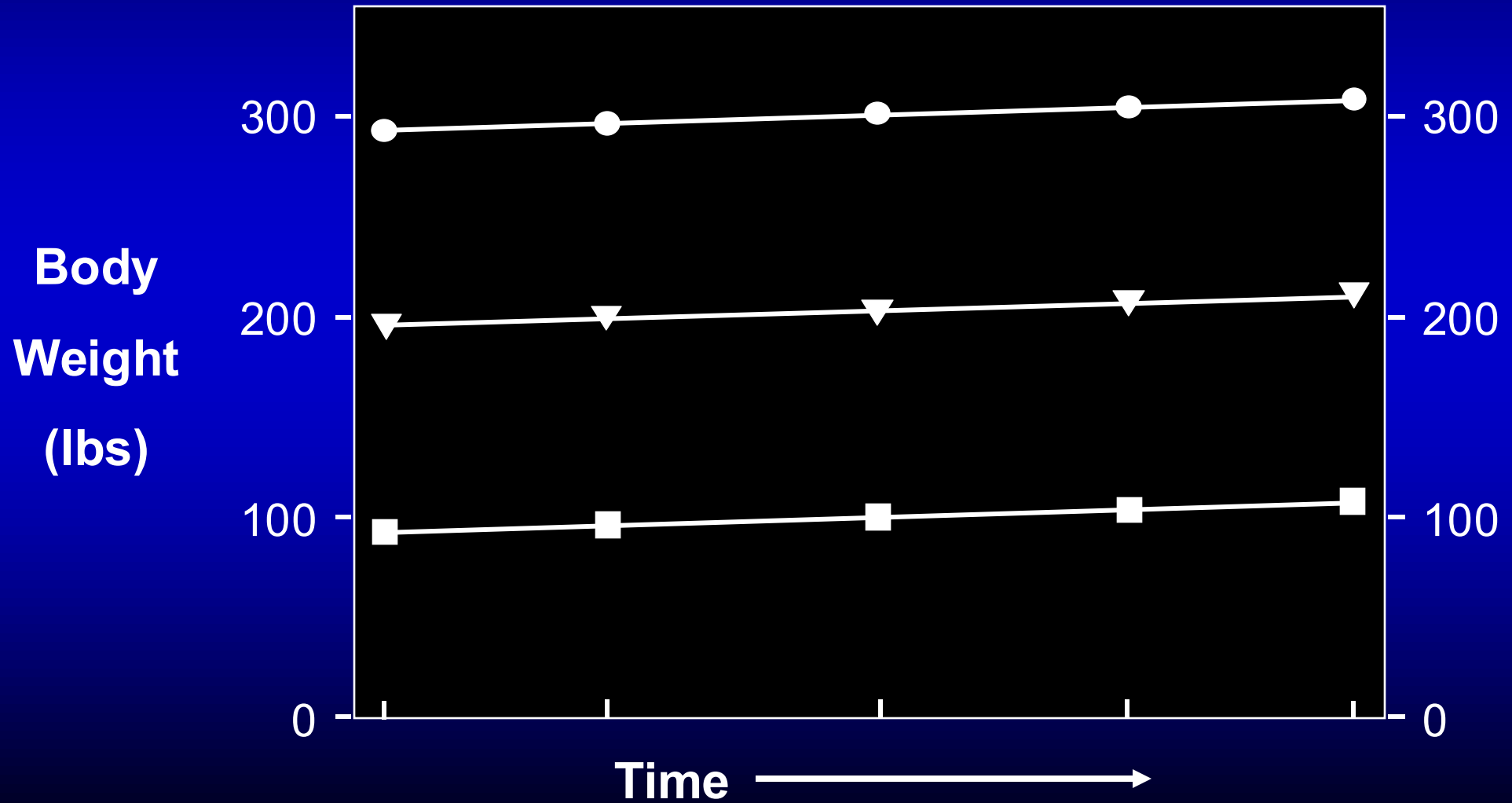
~10 kcal/day



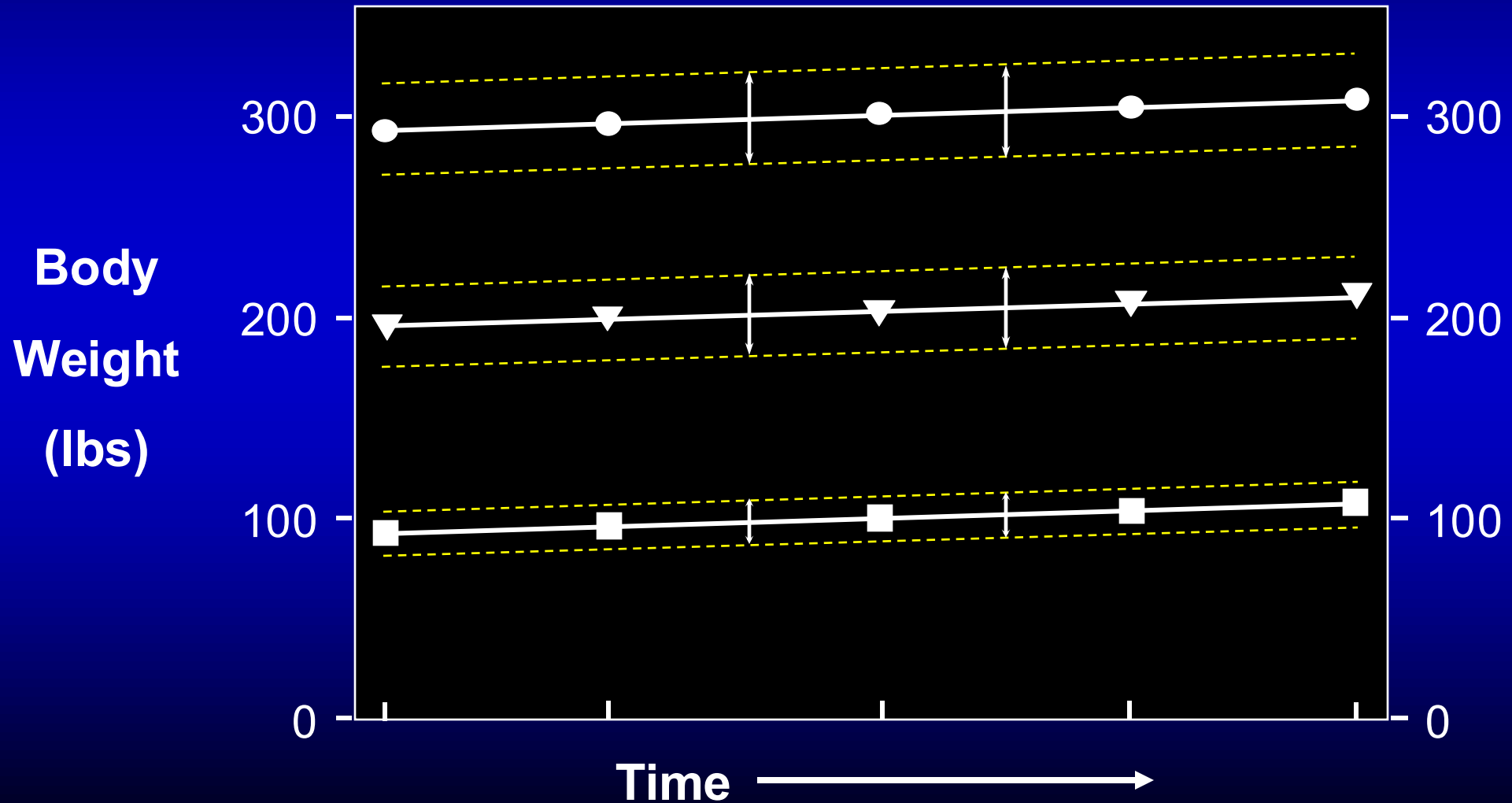
= 18 kcal



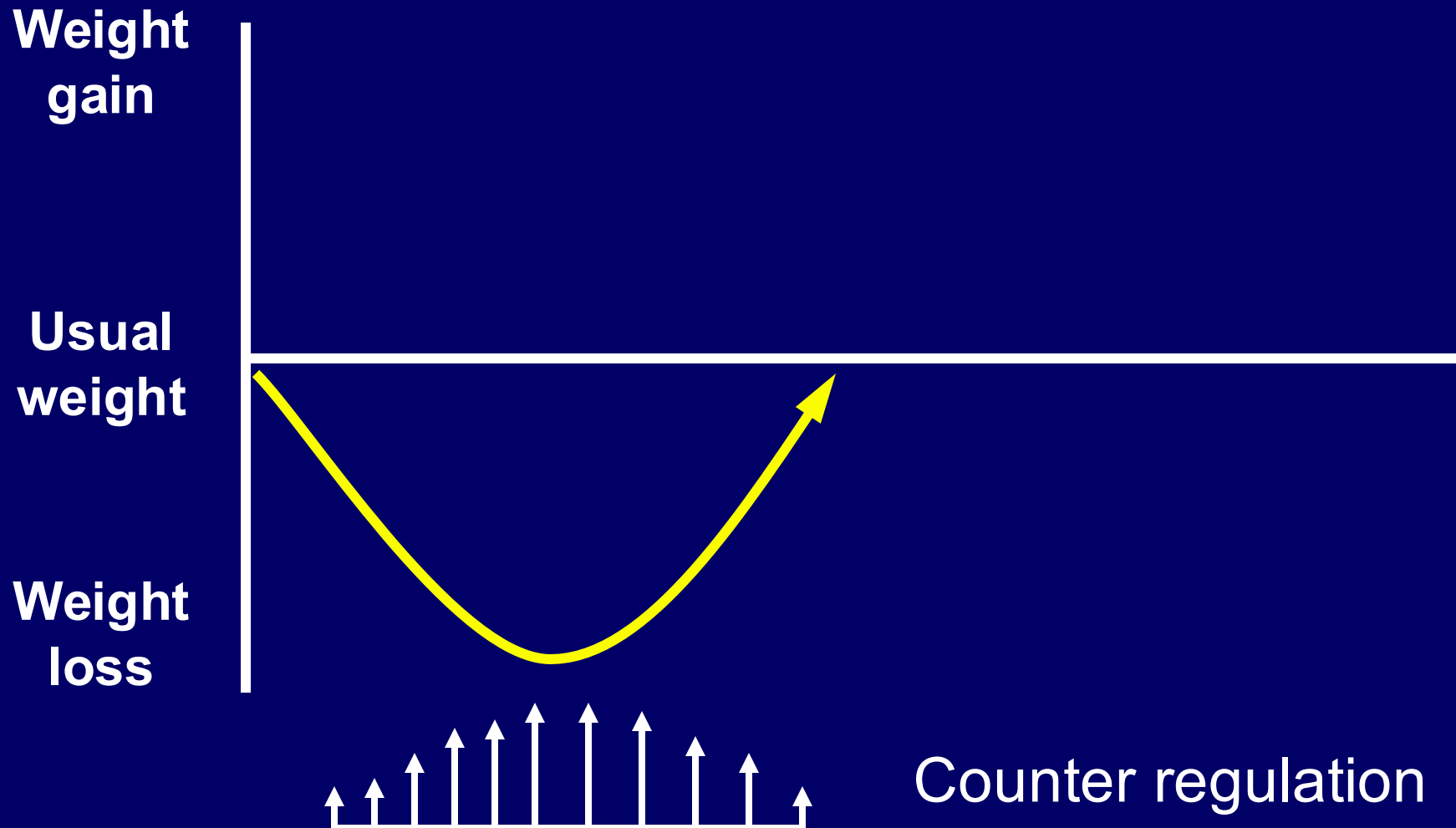
Body Weight Ballpark: 5-10% Volitional Control



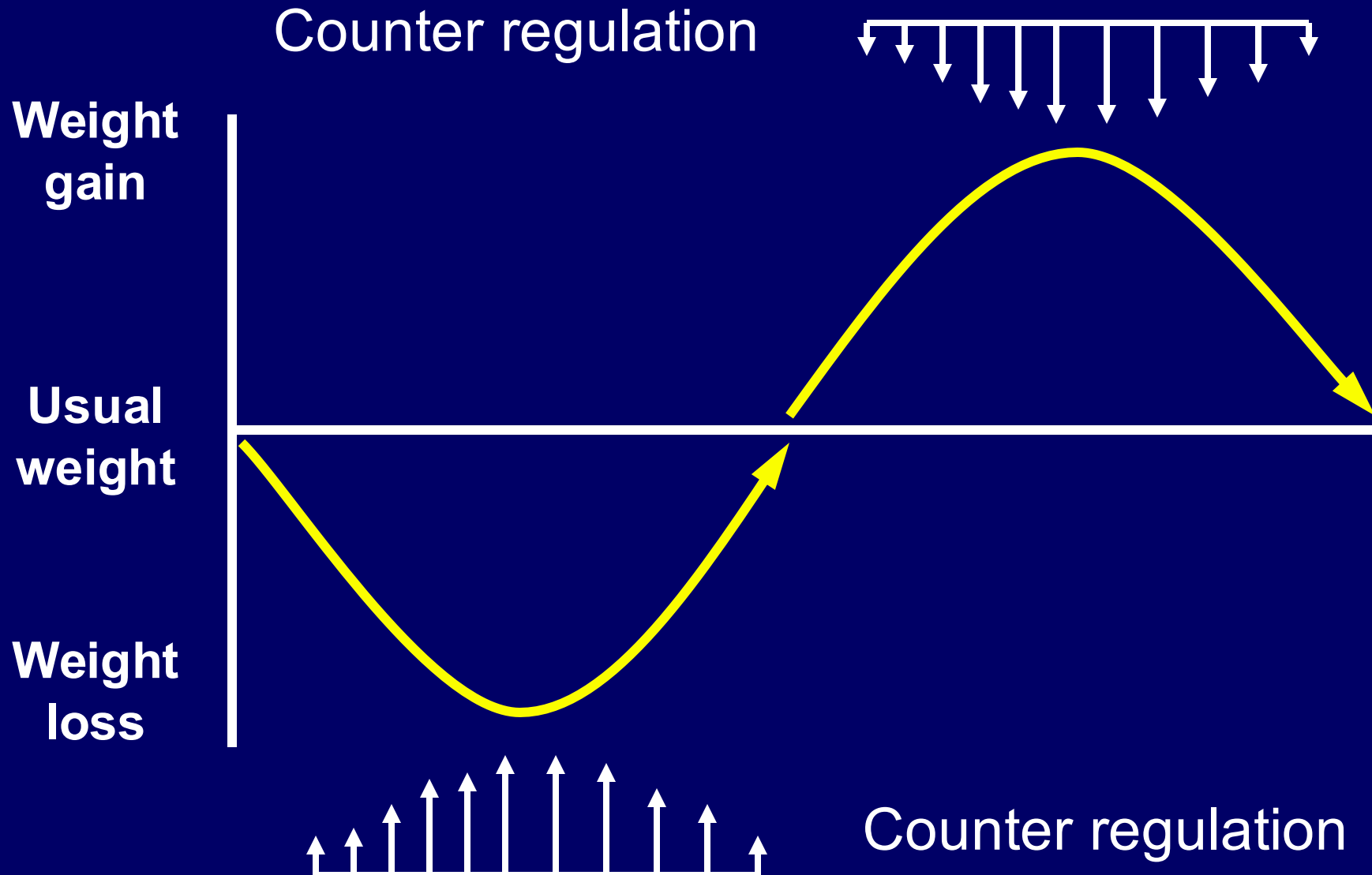
Body Weight Ballpark: 5-10% Volitional Control



“Adipostatic” Body Weight Regulation



“Adipostatic” Body Weight Regulation



POUNDS DROP QUICKLY

With Weight Loss Clinic's P D Q Program... the pounds drop quickly. You can lose from 3 to 5 pounds a week and keep those pounds from coming back!

P D Q is consistent, rapid weight loss, each and every week.

- No foods or gimmicks to buy — no hidden "extras." Proven techniques to keep weight off permanently.

- Weight Loss Clinic offers unequalled one to one counseling.

- Call now. Your first visit is free!

\$79⁺ SPECIAL PROGRAM

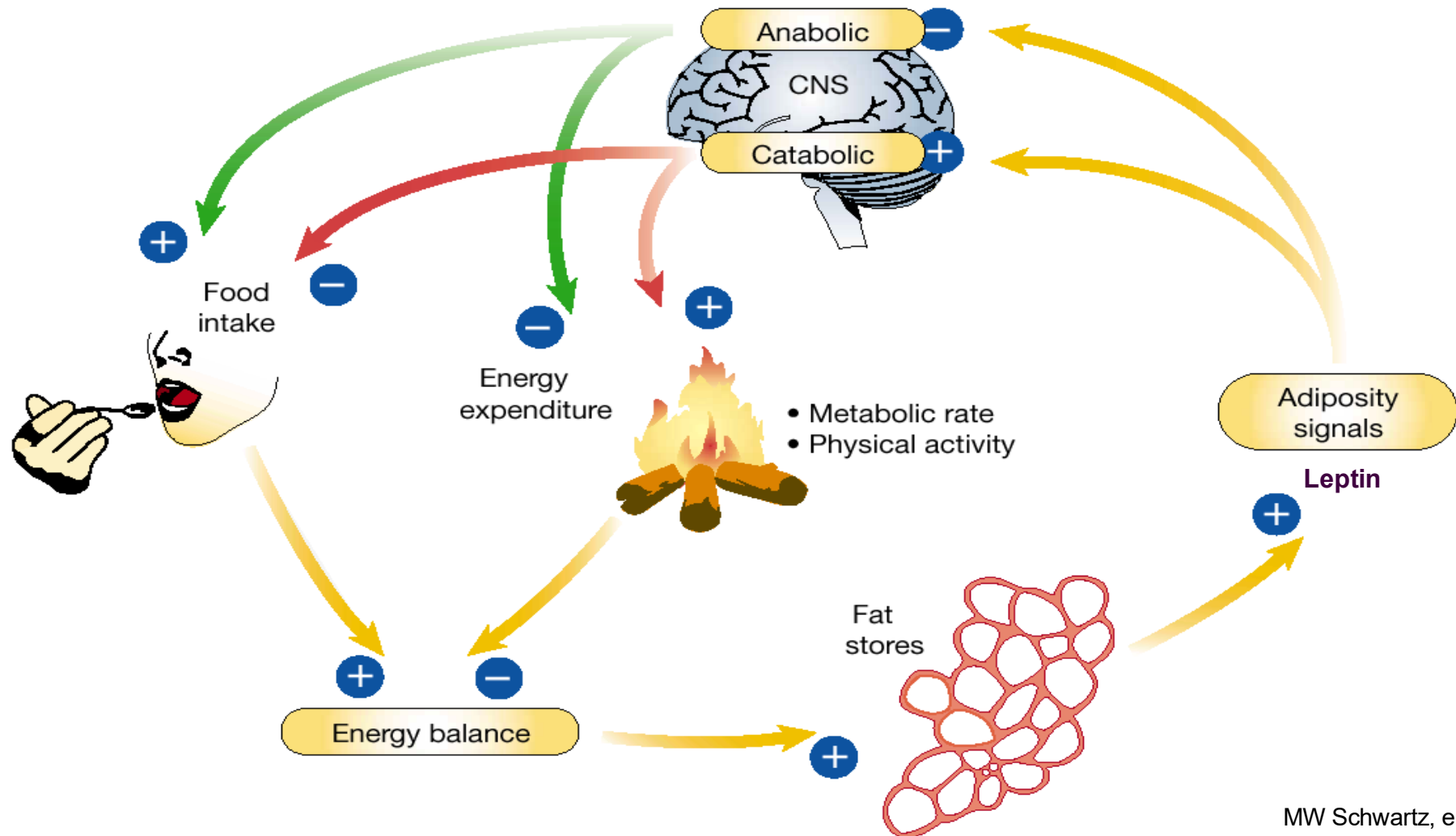
WEIGHT LOSS CLINIC
"Where Lives Change"

*This special program is just \$79 for a limited time. New clients only.

HOURS: 8am to 7pm. Major Credit Cards accepted.



“Adipostat” Model of Body-Weight Regulation



HUNGER

SATIETY

Y5/Y1

Mc4r



NPY



AgRP



α-MSH

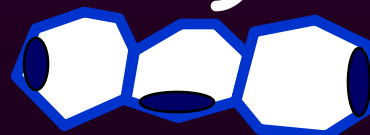
Hypothalamus

NPY
AgRP

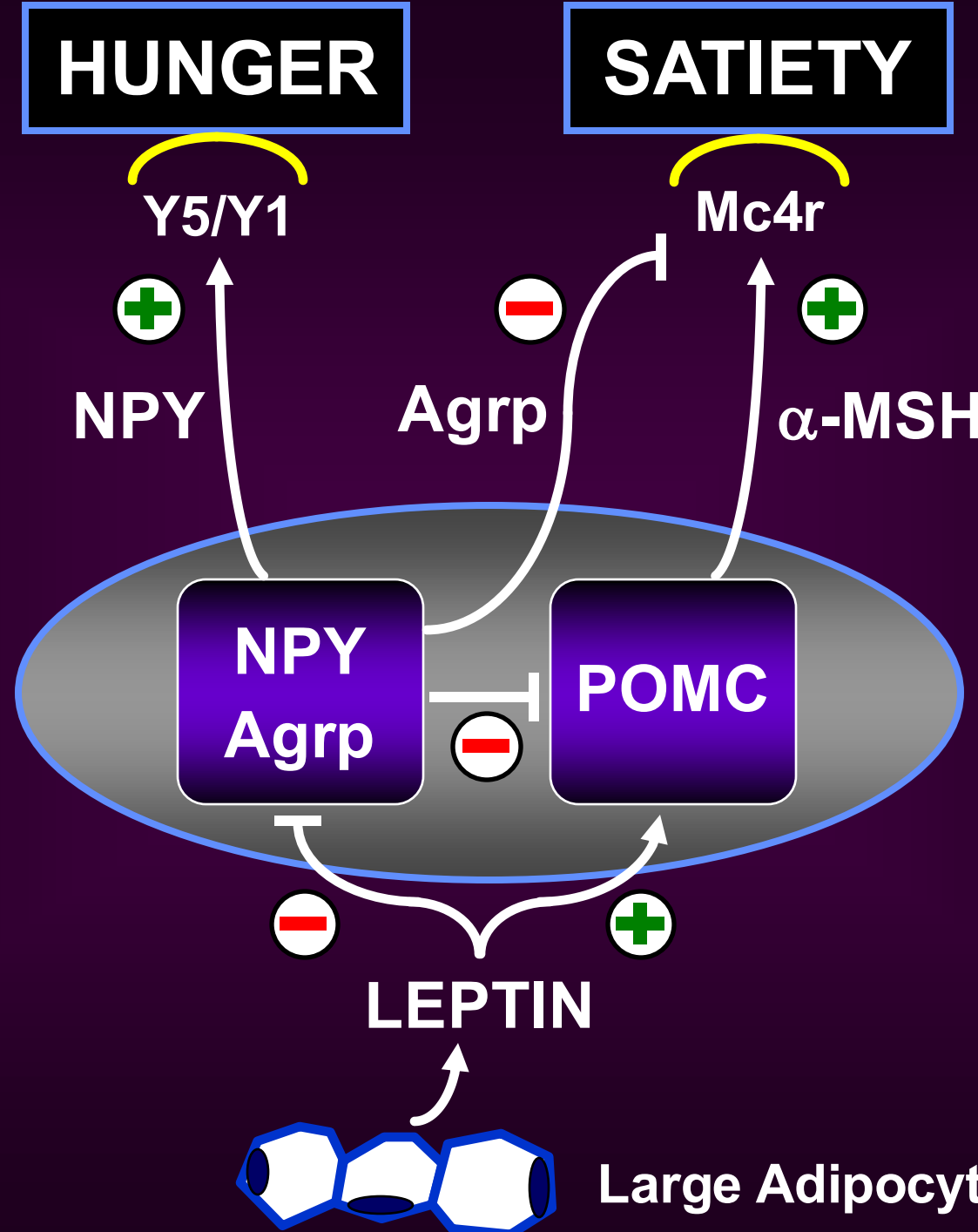
POMC

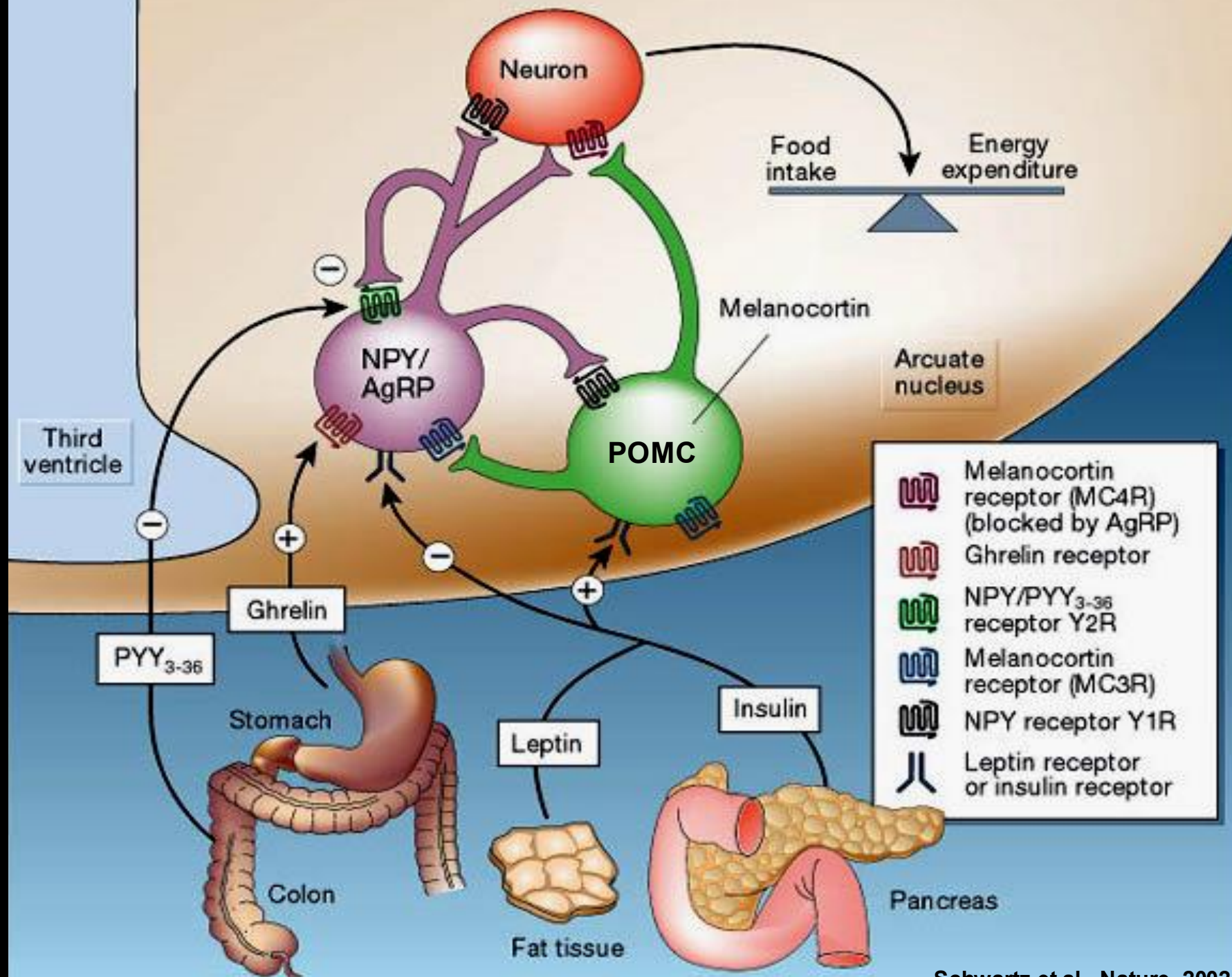
**Arcuate
Nucleus**

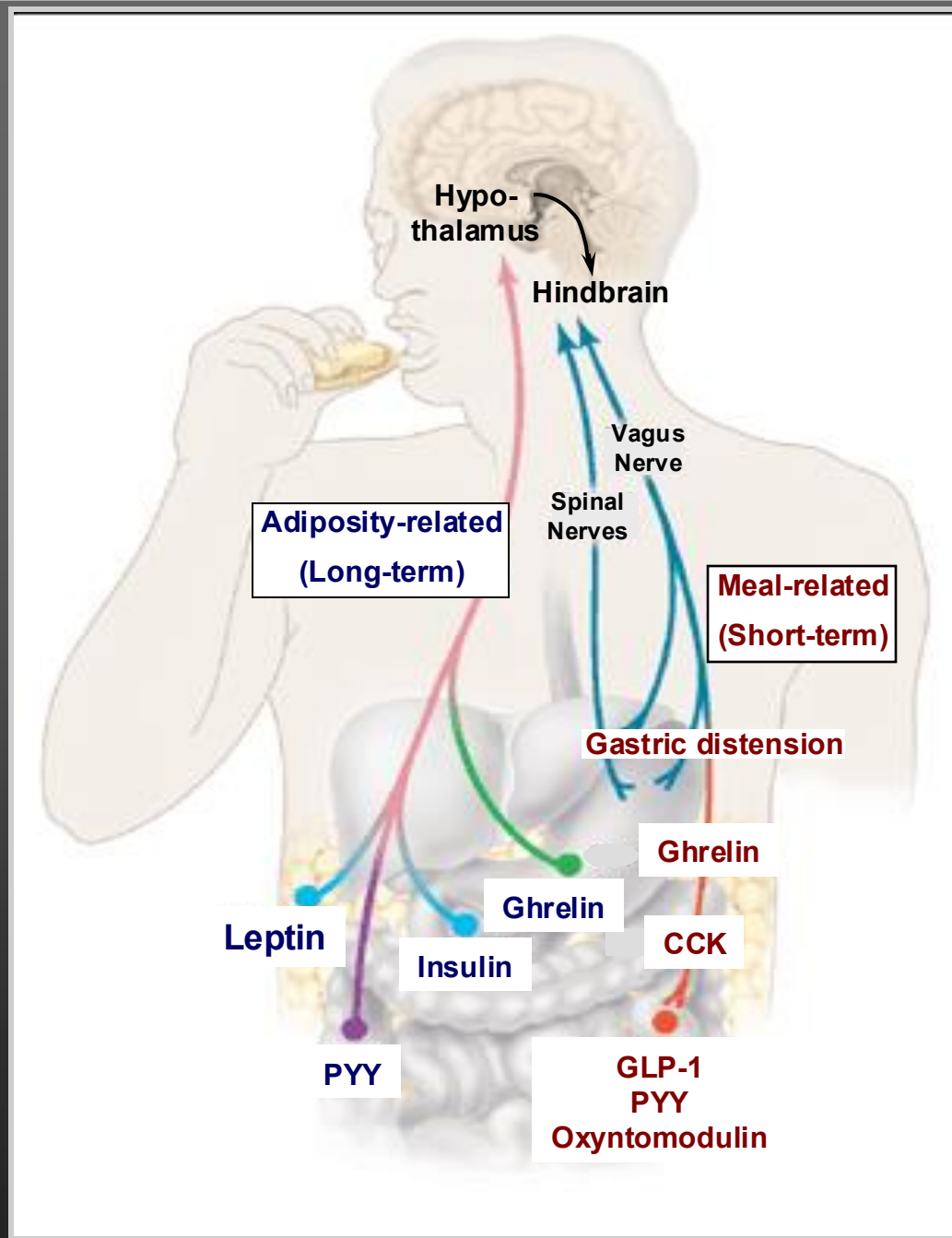
LEPTIN



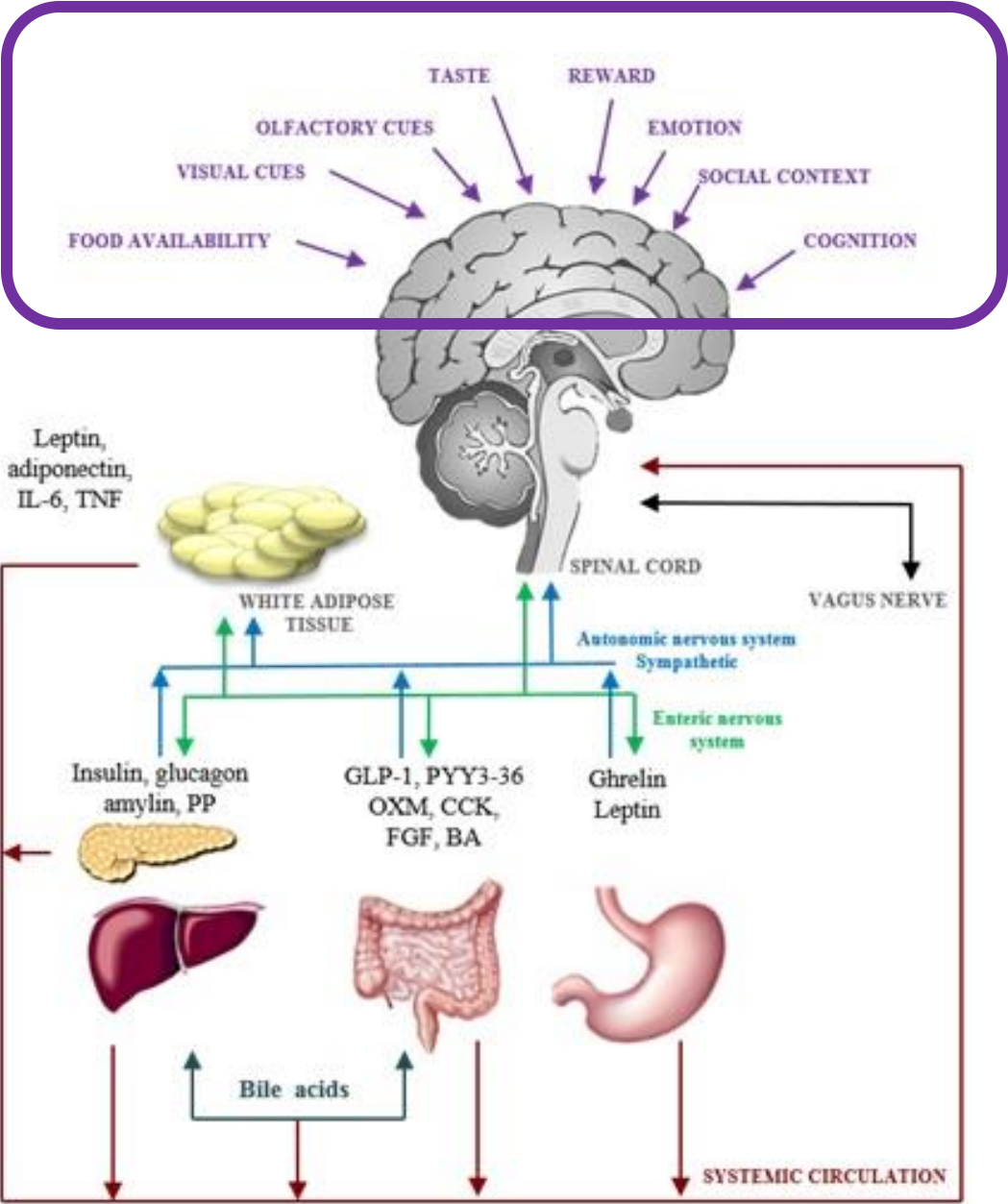
Large Adipocytes



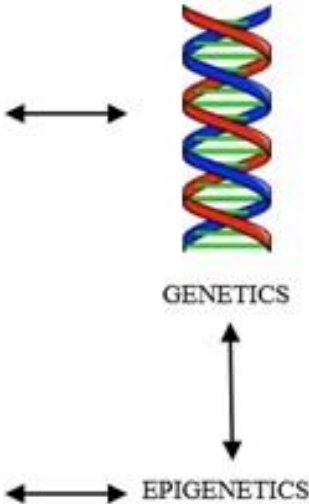




Social, Emotional, & Environmental Factors Interact with Basic Energy Homeostasis



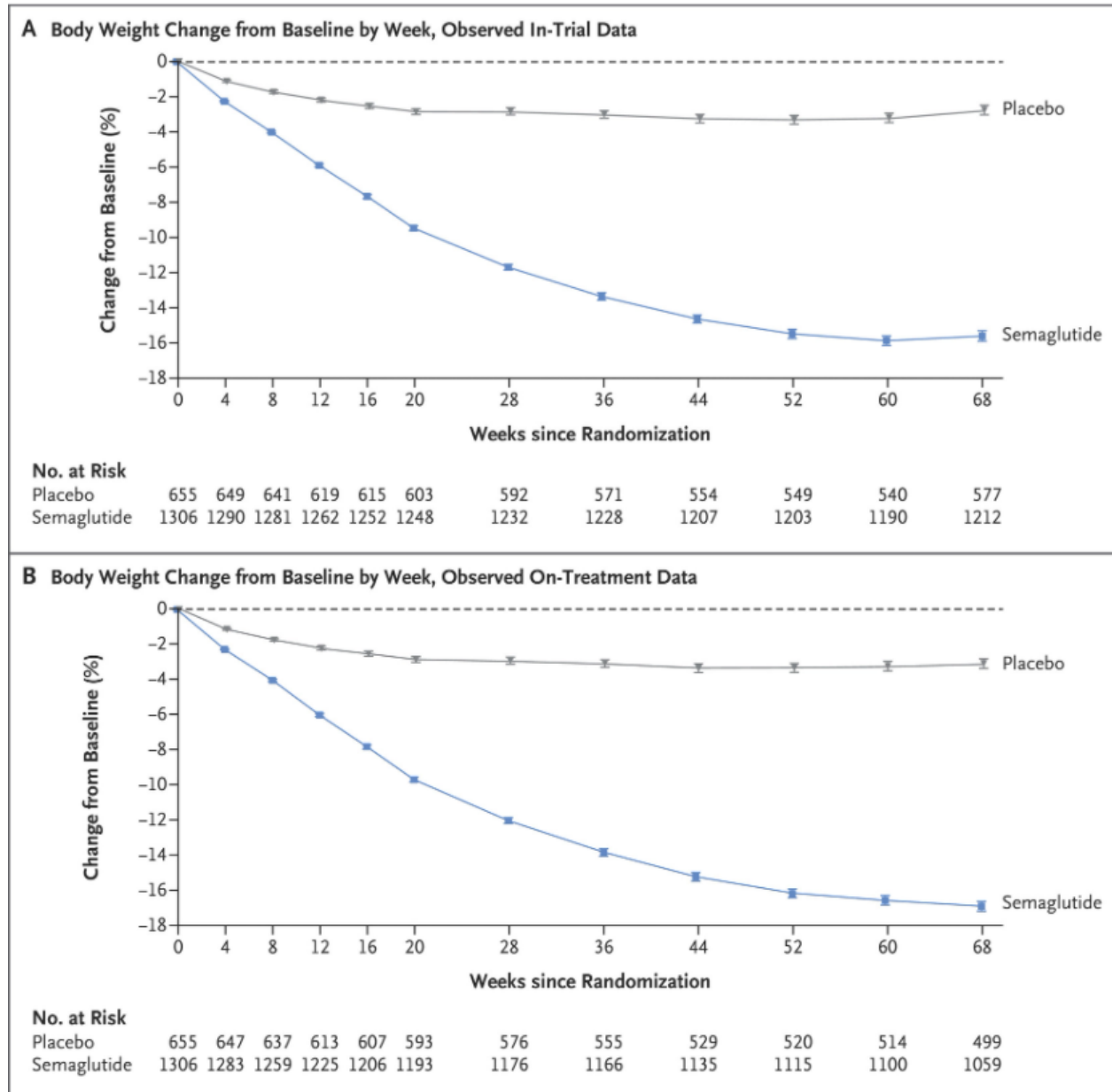
Historically, perturbing any one component of this redundant homeostatic system has not been very effective



STEP 1: Semaglutide vs. Placebo - *No Diabetes*

n=1,961

Body
Weight
Change
(%)



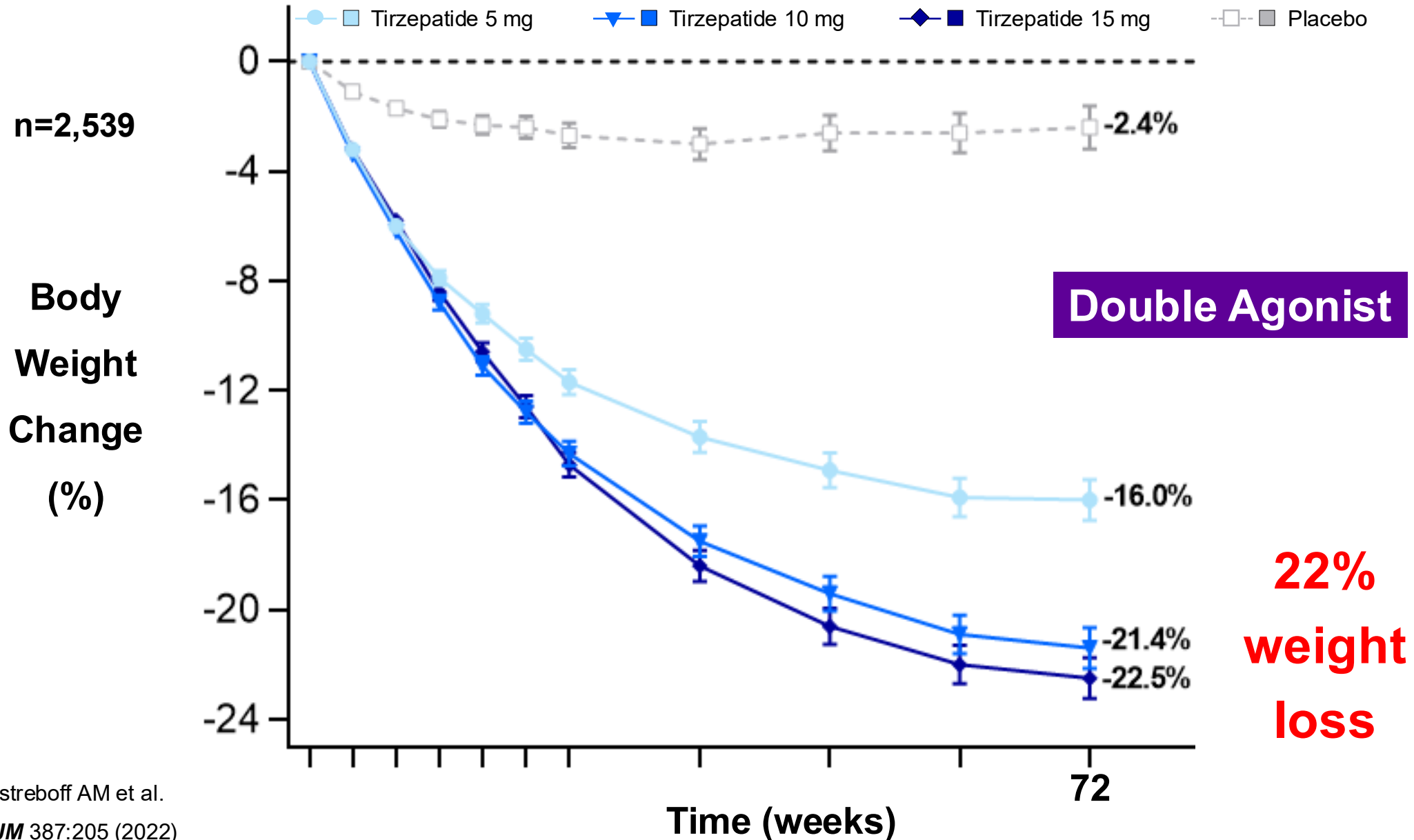
Single Agonist

15%
weight
loss

Wilding, et al.

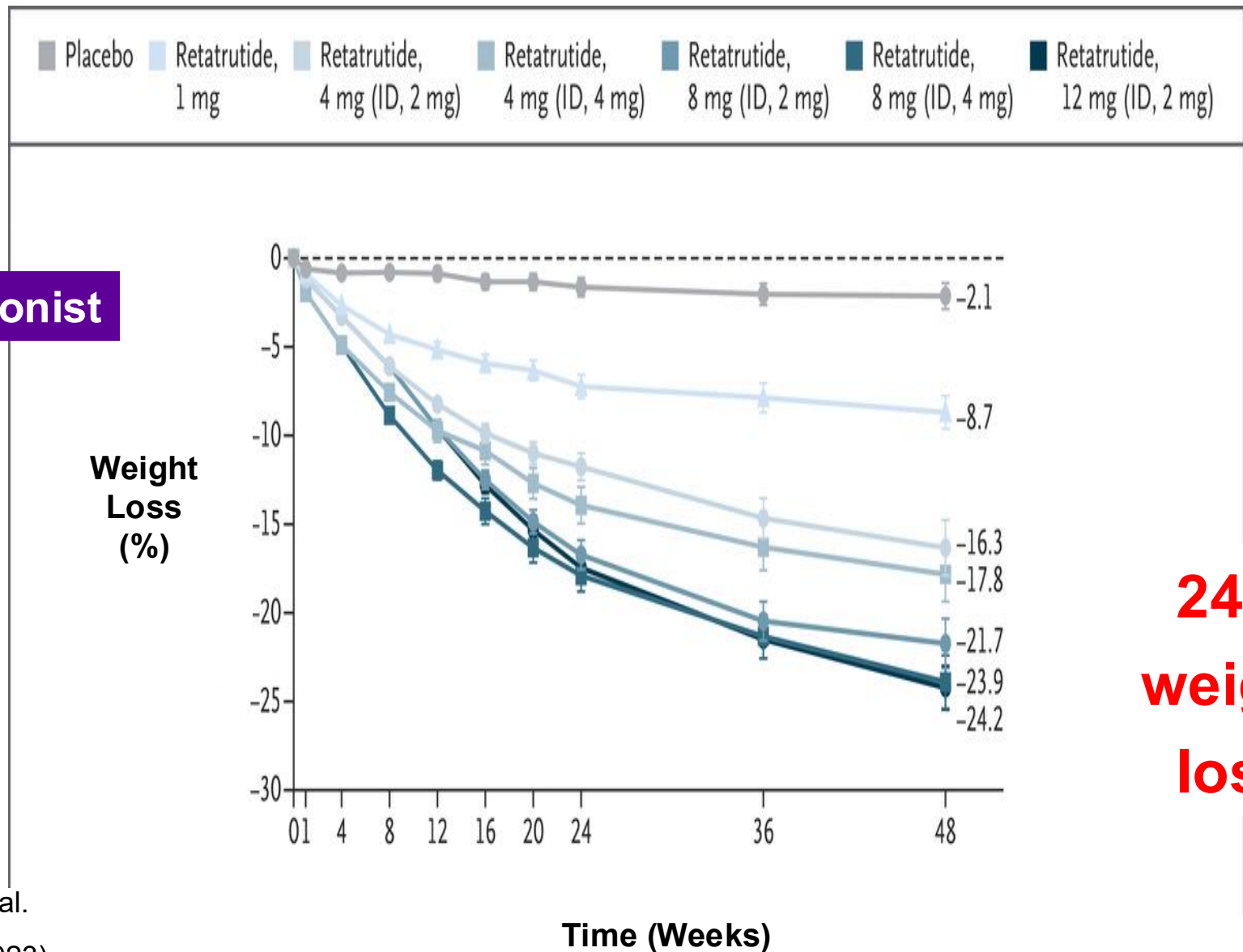
NEJM 384:989 (2021)

SURMOUNT-1: Tirzepatide vs. Placebo – *No Diabetes*



Retatrutide vs. Placebo – No Diabetes

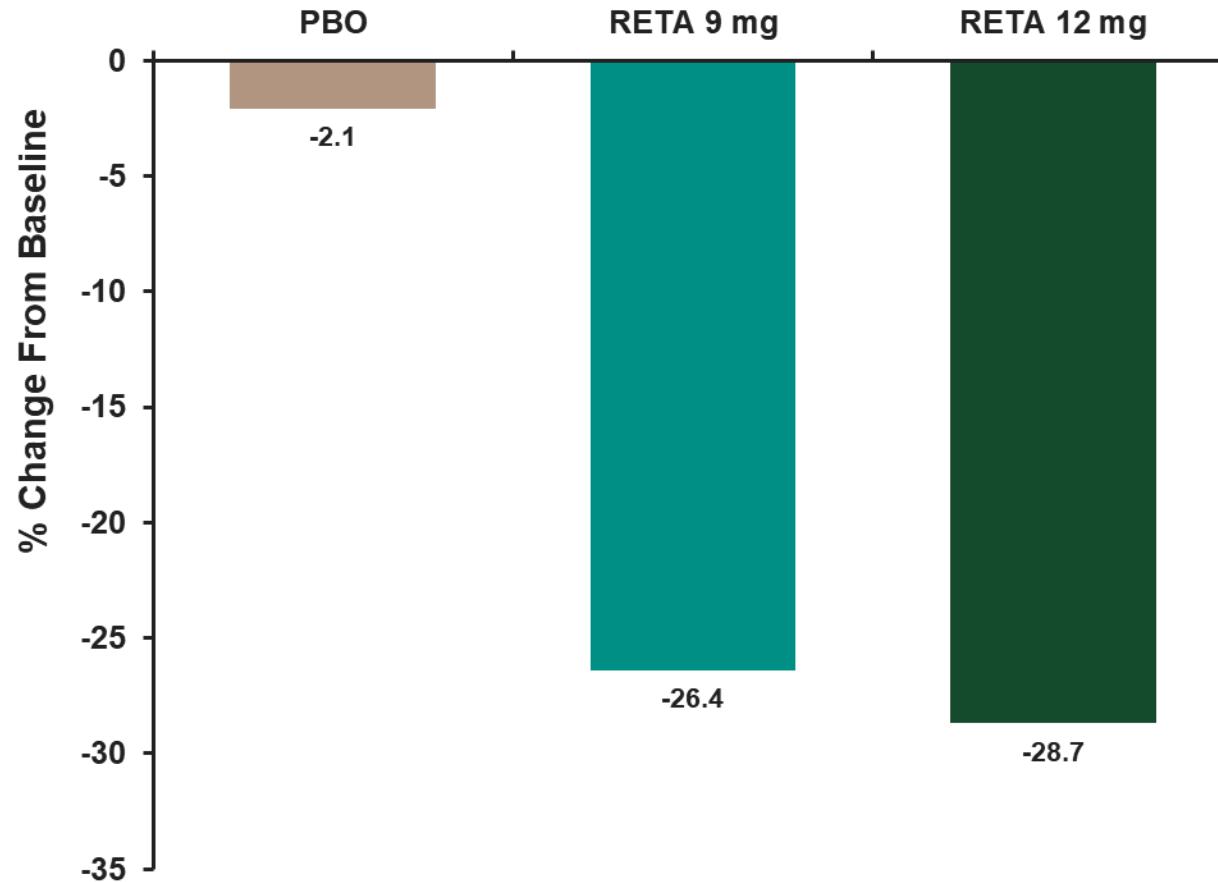
Triple Agonist



24%
weight
loss

Retatrutide: TRIUMPH-4 Results

Efficacy Estimand

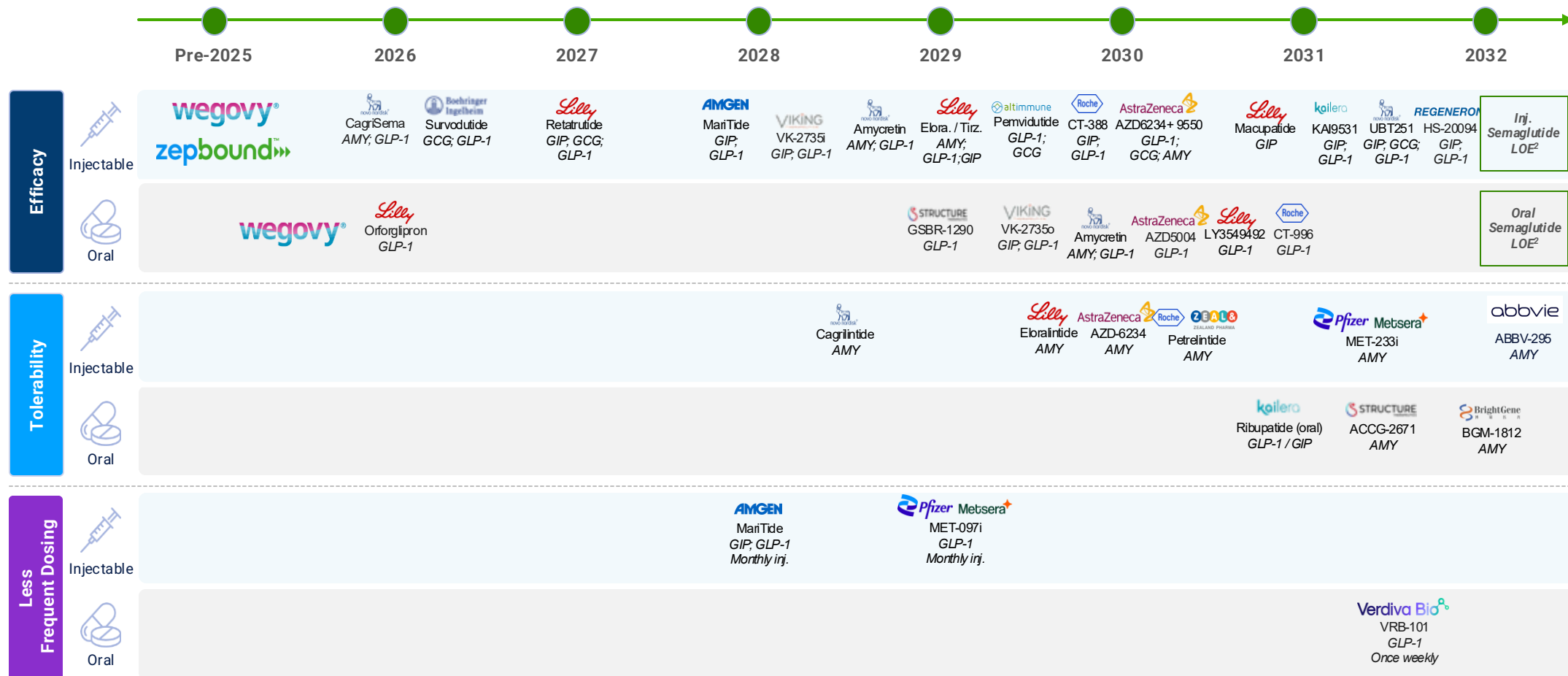


Baseline BW=112.7 kg

**29%
weight
loss**

Triple Agonist

Emerging Obesity Management Medications Through 2032

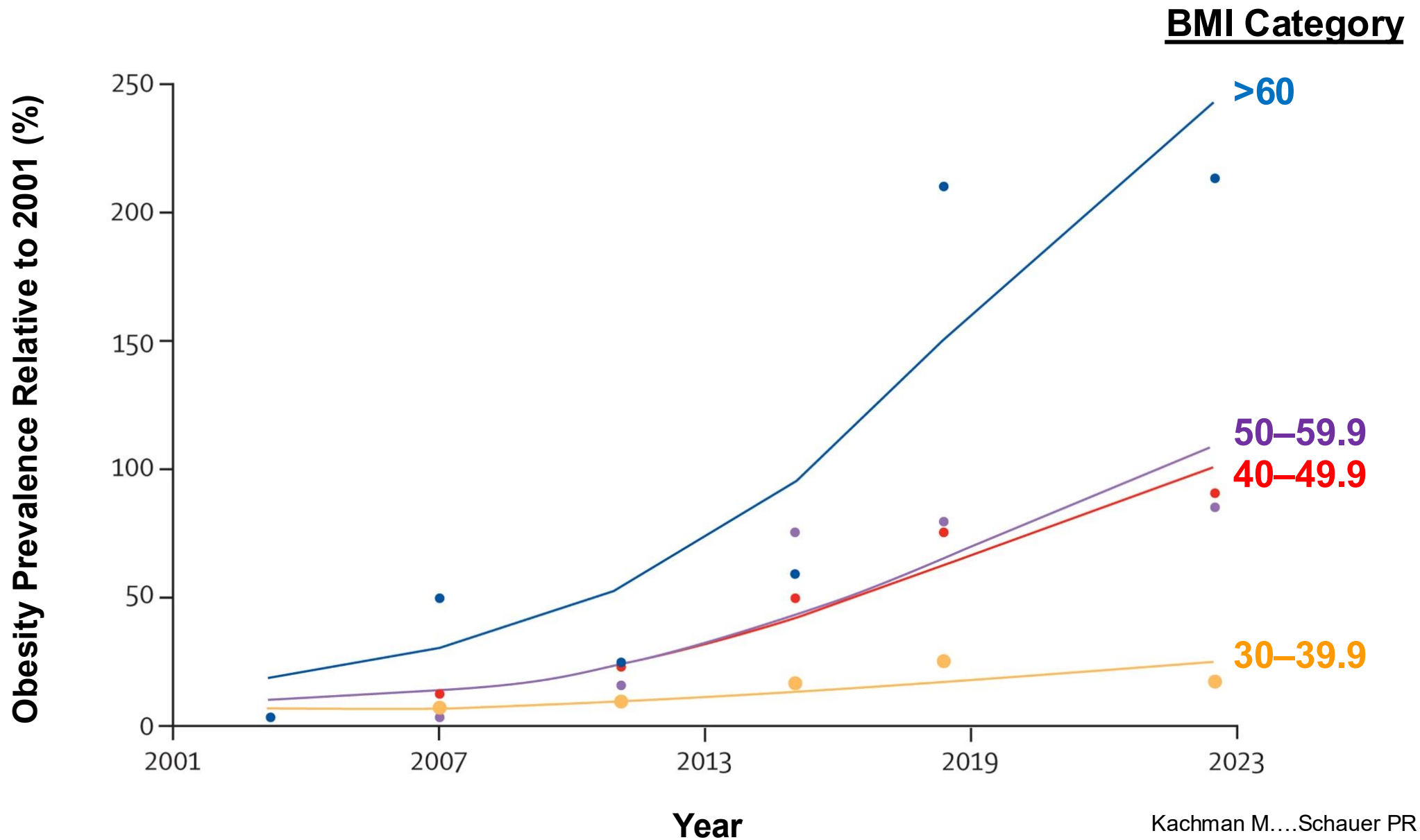


AMY = amylin receptor agonist; GCG = glucagon receptor agonist; GIP = glucose-dependent insulinotropic polypeptide receptor agonist; GLP-1 = glucagon-like-peptide-1 receptor agonist

Investigational product launch timelines are estimates only based on publicly available information¹

- Source: clinicaltrials.gov, company publications
- US Semaglutide Loss of Exclusivity (LOE) is 2032. EU LOE is 2031. China, Canada, India, and Brazil LOE is 2026.

~250% Increase of Extreme Obesity Prevalance in 20 Years



**Obesity meds augment
the benefits of
metabolic surgery &
metabolic endoscopy**

Obesity Management Meds

Augment Benefits of Metabolic Surgery

Study	Bariatric Procedure	Medication	Number of Participants	Duration	Additional Weight Loss (kg)	Additional Weight Loss TWBL vs EBWL
Schwartz et al, ³⁰ 2016	RYGB or LABG	Phentermine Phentermine-topiramate	52 13	90 d	6.35 3.81	12.8%EBWL 12.9% EBWL
Zoss et al, ³³ 2002	LABG	Orlistat 120 mg TID	38	8 mn	8	
Wharton et al, ⁴⁴ 2019	RYGB, LABG, LSG	Liraglutide 3 mg	117			5.5% TBWL
Suliman et al, ⁴⁶ 2019	Any bariatric surgery	Liraglutide	188			6.1% TBWL
Pajecki et al, ⁴⁷ 2013	Any Bariatric surgery	Liraglutide	15			
Gazda et al, ⁴⁹ 2021	Any bariatric surgery	Any GLP-1	207	9 mn		6.9% TBWL
Jensen et al, ⁵⁰ 2023	Any bariatric surgery	Liraglutide Semaglutide				
Lautenbach et al, ⁴⁸ 2022	RYGB or LSG	Semaglutide	44	6 mn		10.3% TBWL
Mosli et al, ⁴⁰ 2017	IGB	Liraglutide	108	12 mn	8 kg ^a	
Mehta et al, ⁵¹ 2023	IGB	Any anti-obesity medication (AOM)	102	12		2.9% TBWL
Badurdeen et al, ¹³ 2021	ESG	Liraglutide	52	12 mn		4% TBWL
Gala et al, ⁴² 2024	ESG	Any AOM Tirzepatide	1506	24 mn		No difference

GRAVITAS RCT

BARI-OPTIMIZE RCT

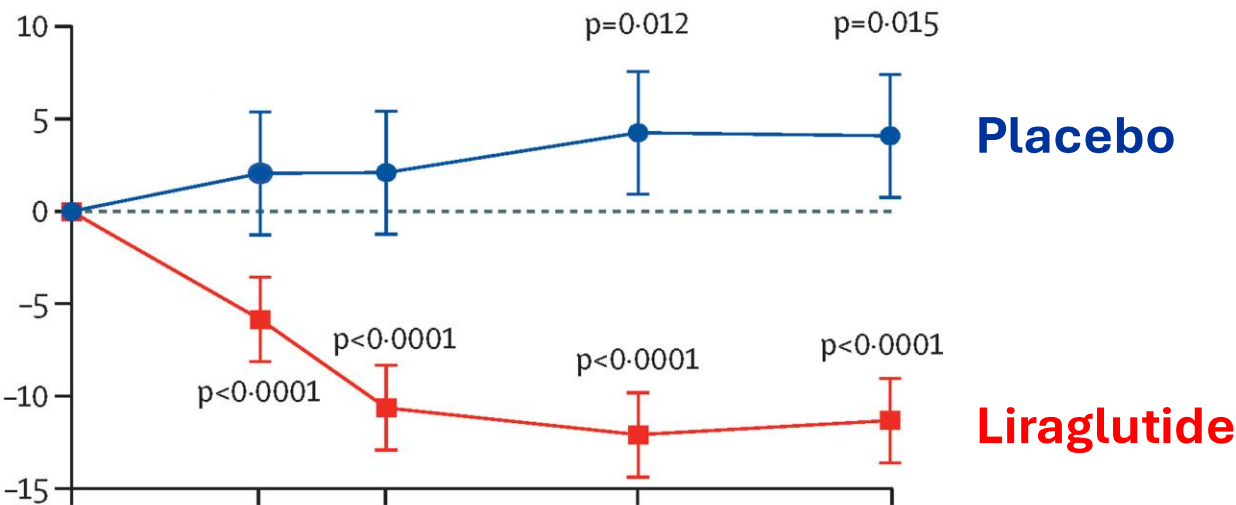
Brown et al, JAMA Net Open 2025 RCT

BARI-STEP RCT

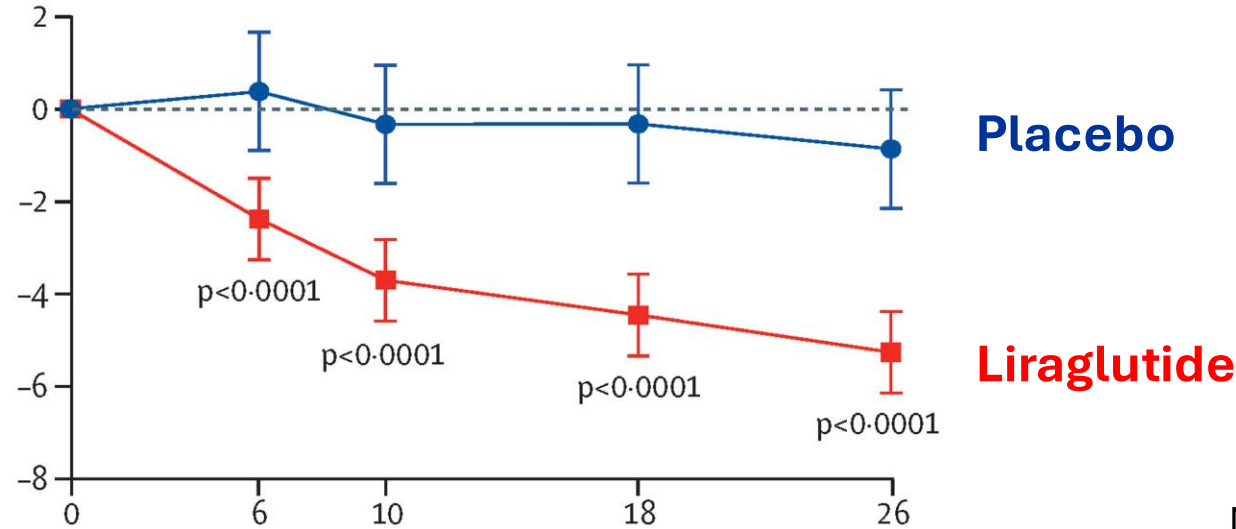
Everyone had undergone RYGB or SG

GRAVITAS RCT

A1c
Change
(mmol/mol)

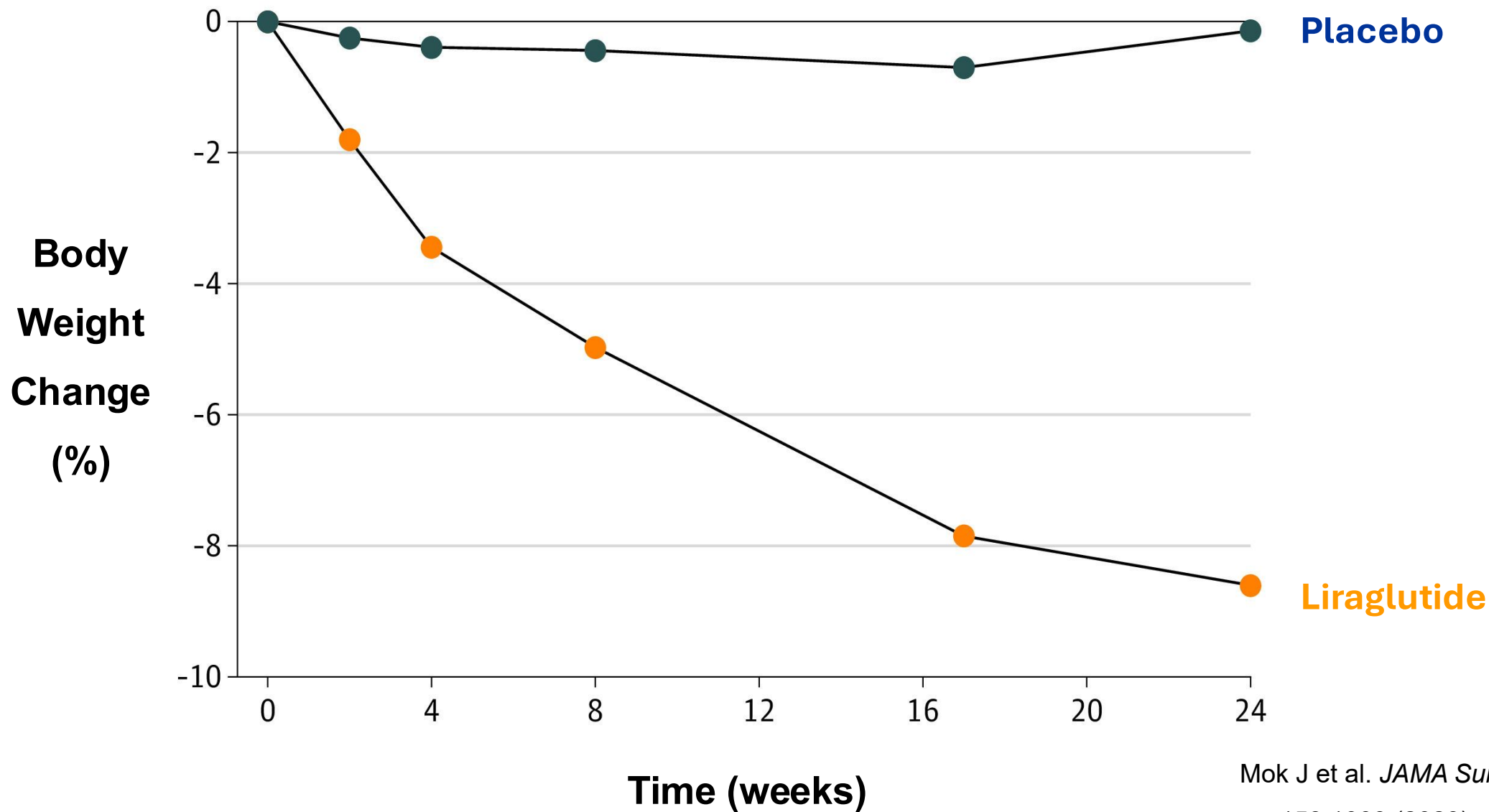


Body
Weight
Change
(kg)



Everyone had
undergone
RYGB or SG

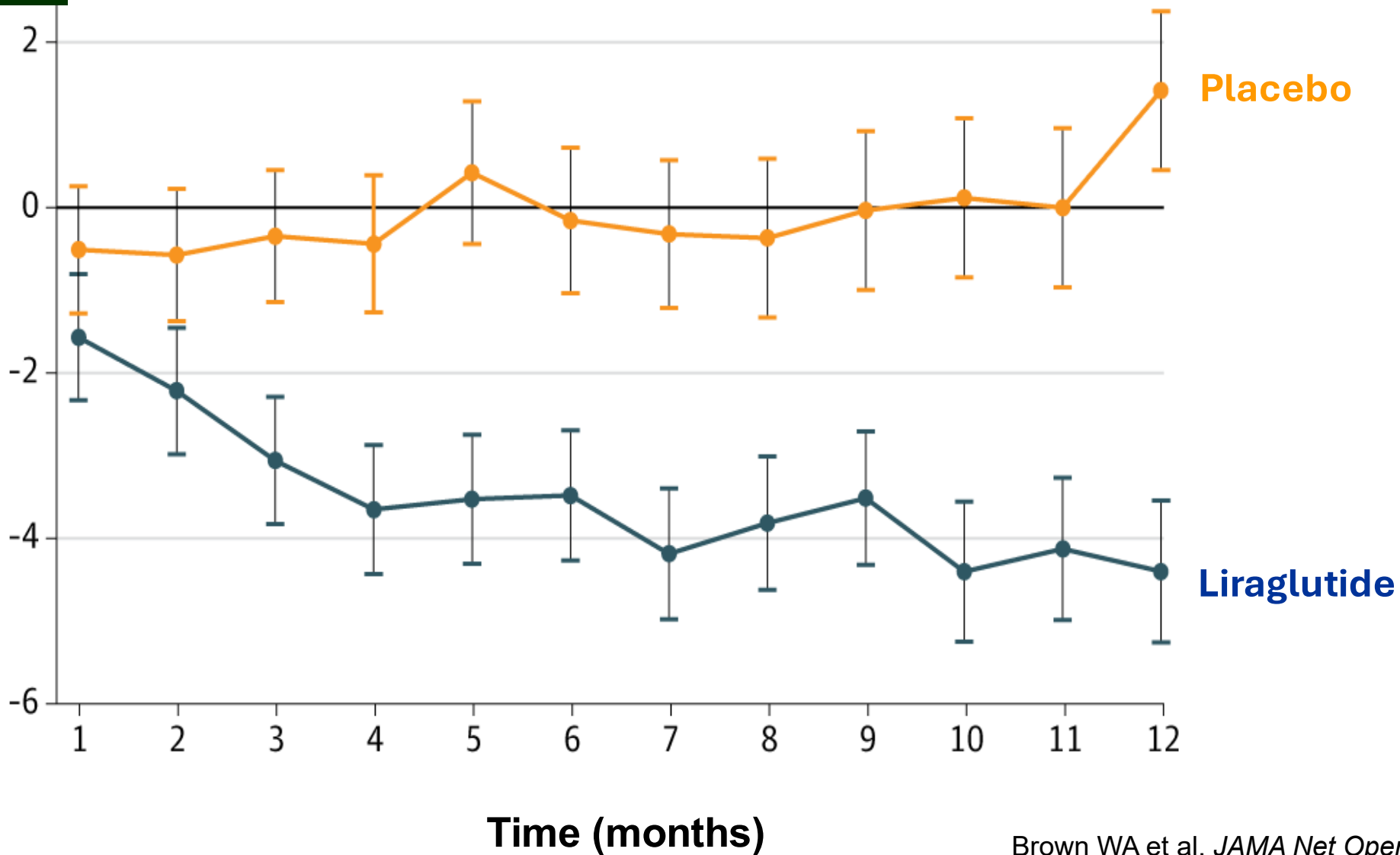
BARI-OPTIMIZE RCT



Everyone had
undergone
RYGB, SG,
OAGB, or LABG

Brown et al RCT

Body
Weight
Change
(%)

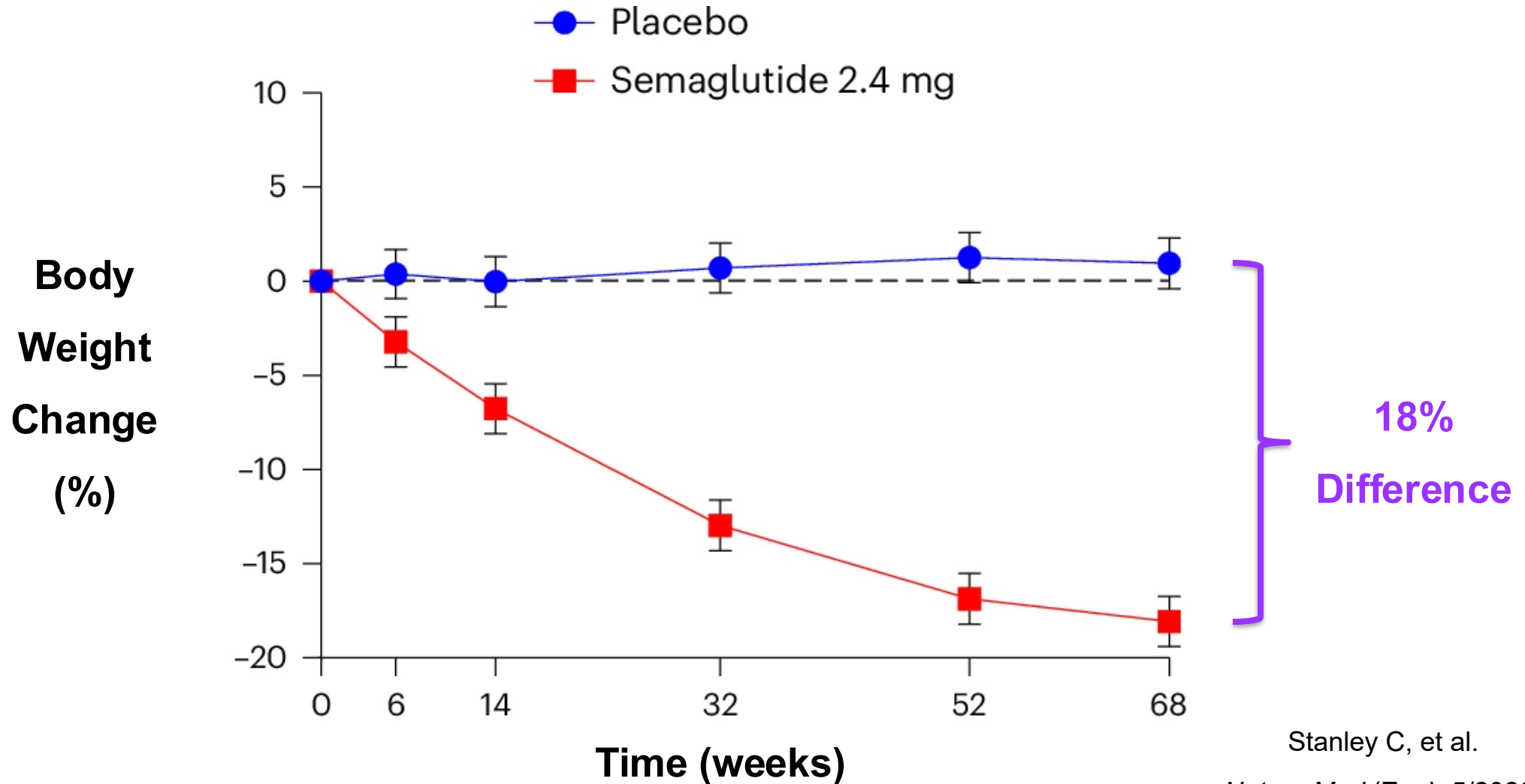


Brown WA et al. *JAMA Net Open*

8(10)e2539848 (2025)

BARI-STEP RCT

Semaglutide vs Placebo for Poor Weight Loss After RYGB or VSG



Stanley C, et al.

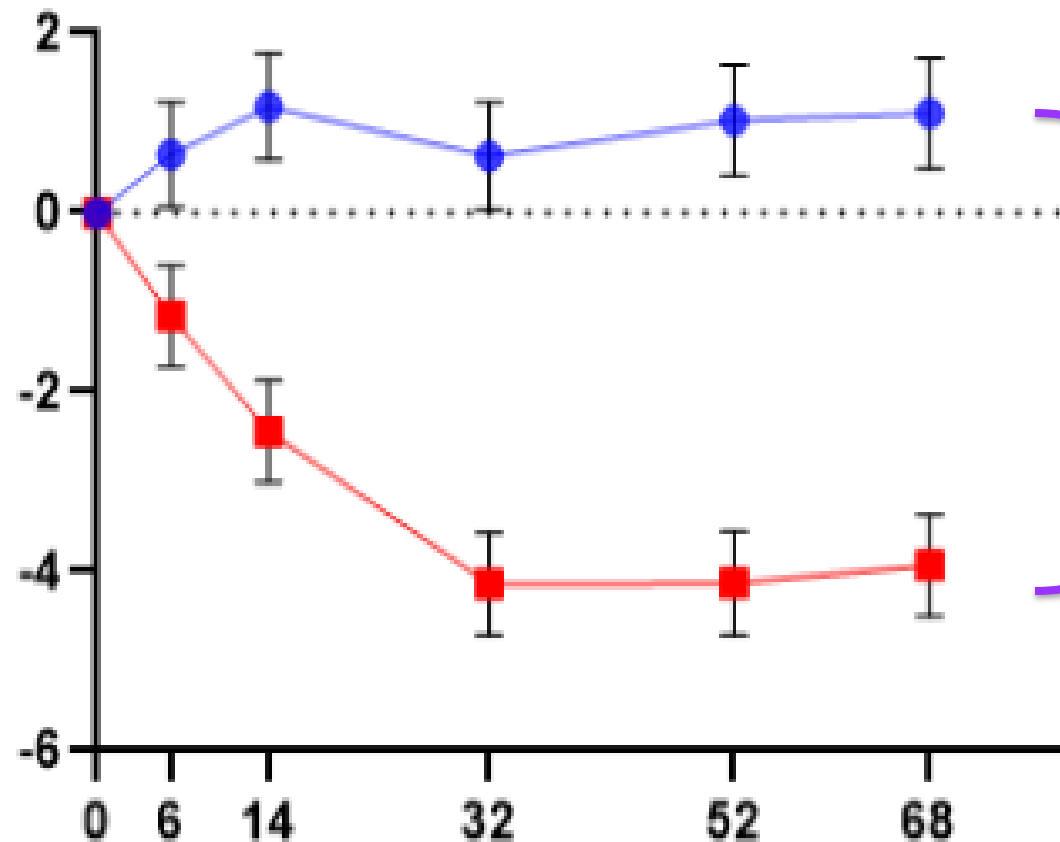
Nature Med (Epub 5/2026)

BARI-STEP RCT

Semaglutide vs Placebo for Poor Weight Loss After RYGB or VSG

Patients with
Pre-Diabetes

HbA1c
Change
(mmol/mol)

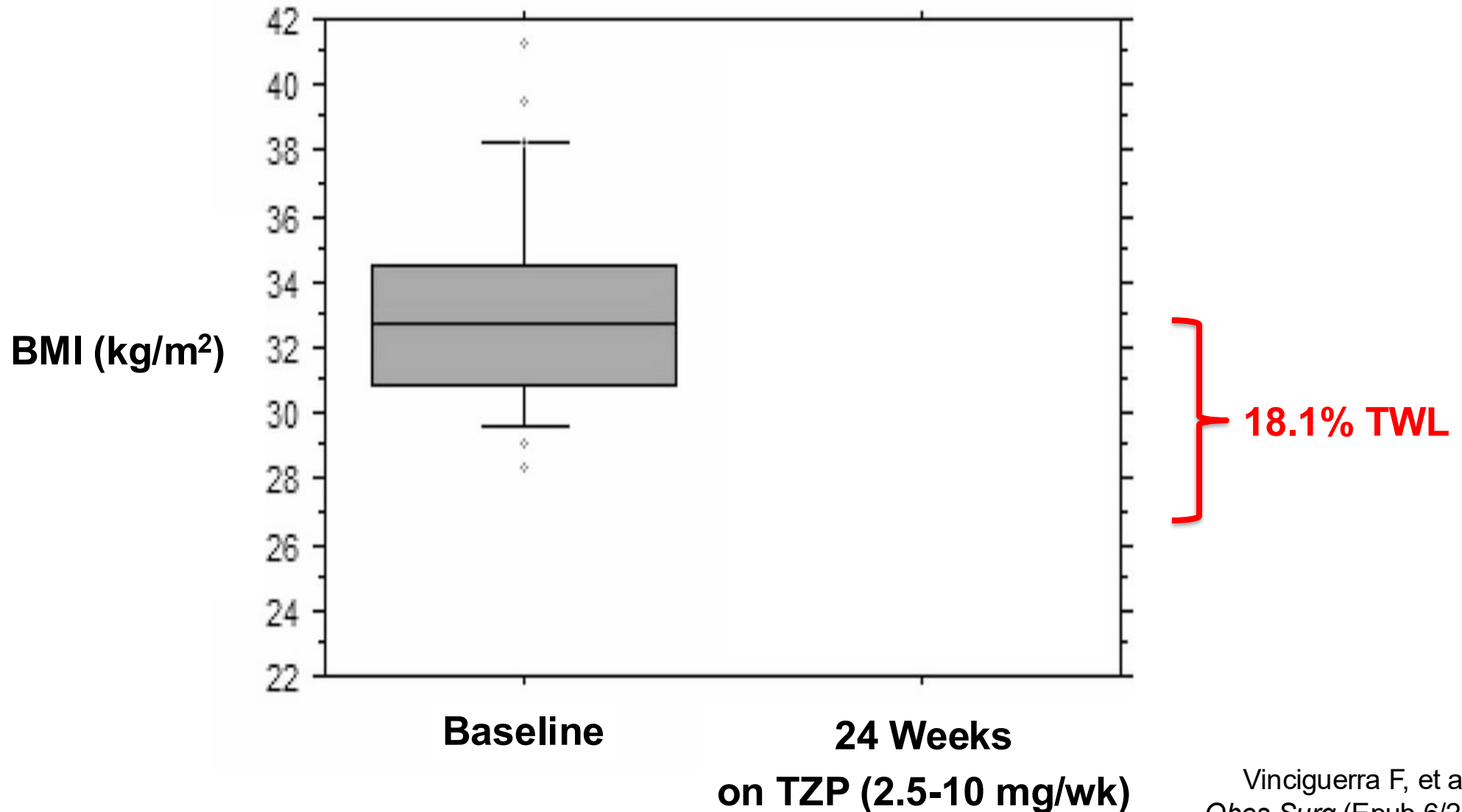


2.9% A1c
Difference

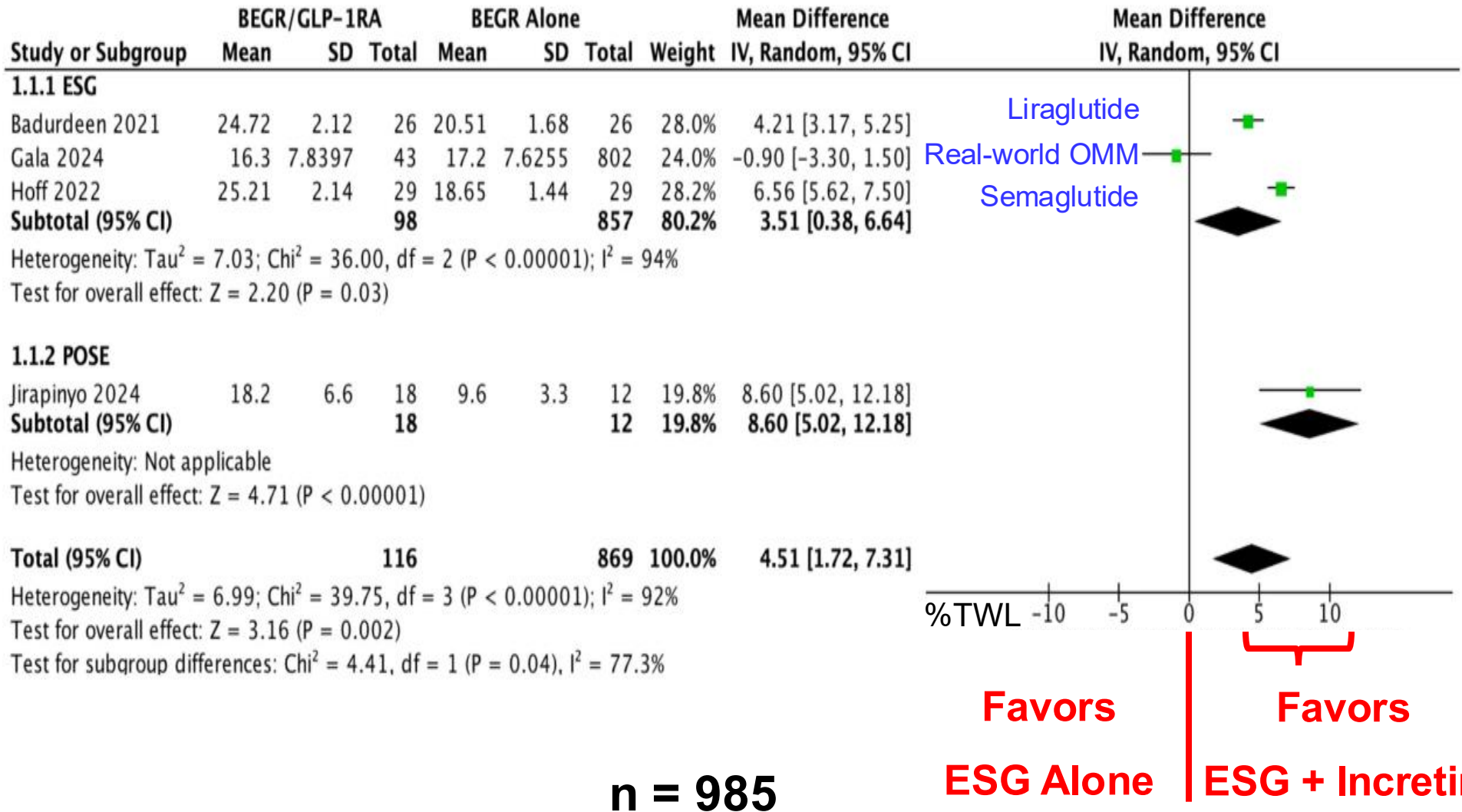
Stanley C, et al.

Nature Med (Epub 5/2026)

Tirzepatide Promotes >18% Total Weight Loss at 24 Weeks After Recurrent Weight Gain Following Metabolic Surgery or Endoscopy



Weight Loss with ESG +/- Incretin Meds



**Metabolic/bariatric surgery
is still more effective
than any medicine!**

Incidence of Hard Adverse Outcomes with Metabolic Surgery vs. Incretin Meds

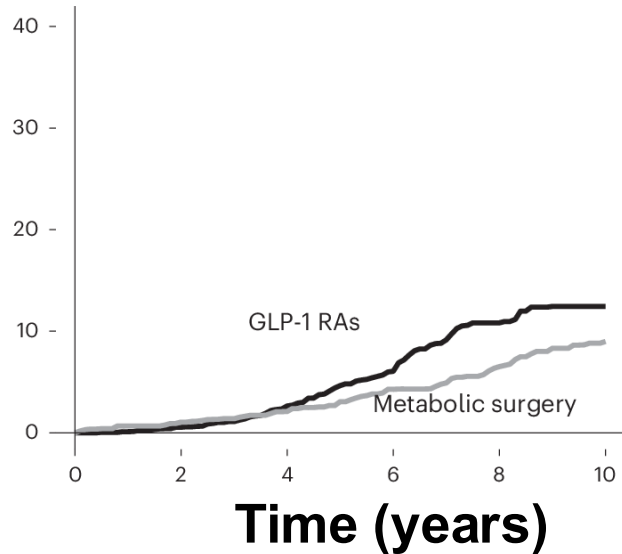
M6 Study

Death

↓ **32%**

With MBS

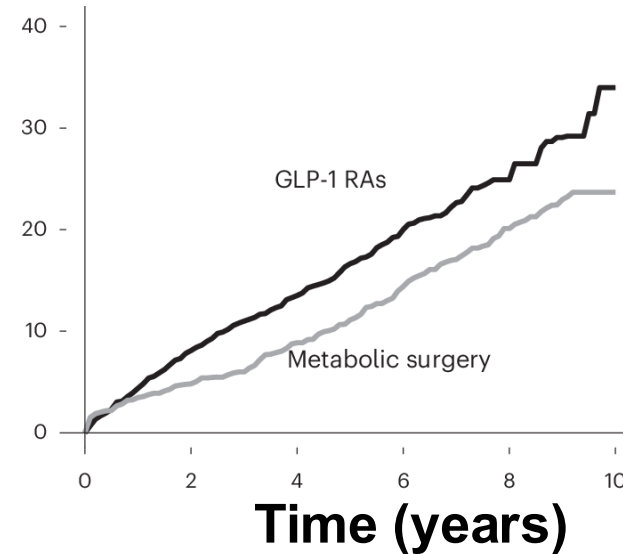
n = 3932



MACE

↓ **35%**

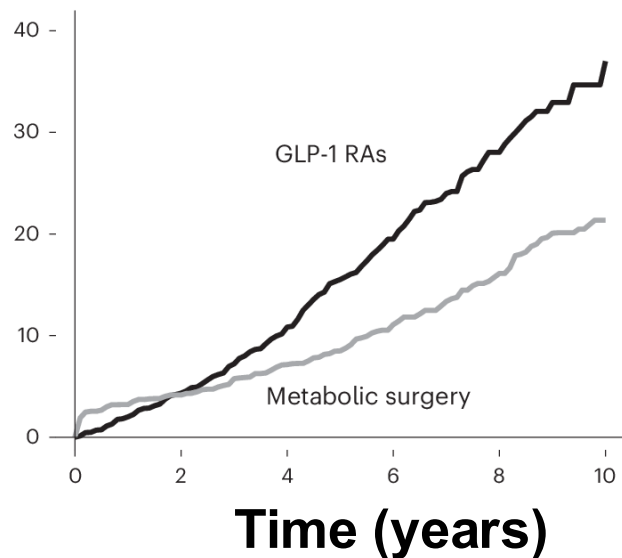
With MBS



Nephropathy

↓ **47%**

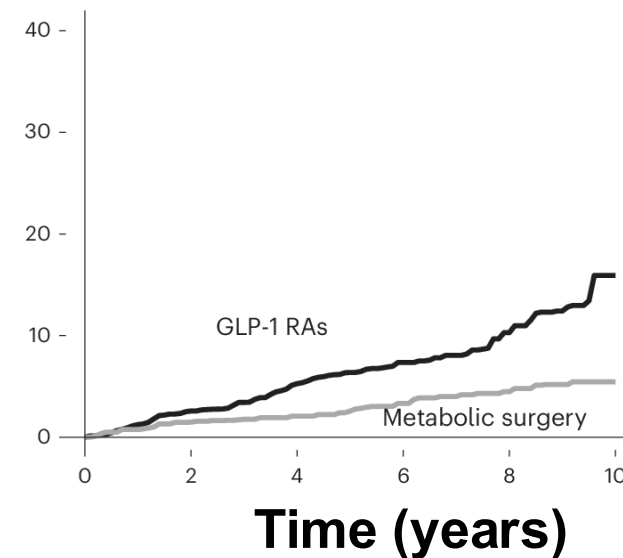
With MBS



Retinopathy

↓ **54%**

With MBS





XXVIII IFSO World Congress

9-12 September 2025 | Santiago, Chile

“Combined Therapies: The Dawn of a New Era”



XXX IFSO WORLD CONGRESS

"Advancing Multimodal Obesity Care"

24-27 August 2027

ifso2027.org



IFSO
PARIS 2027

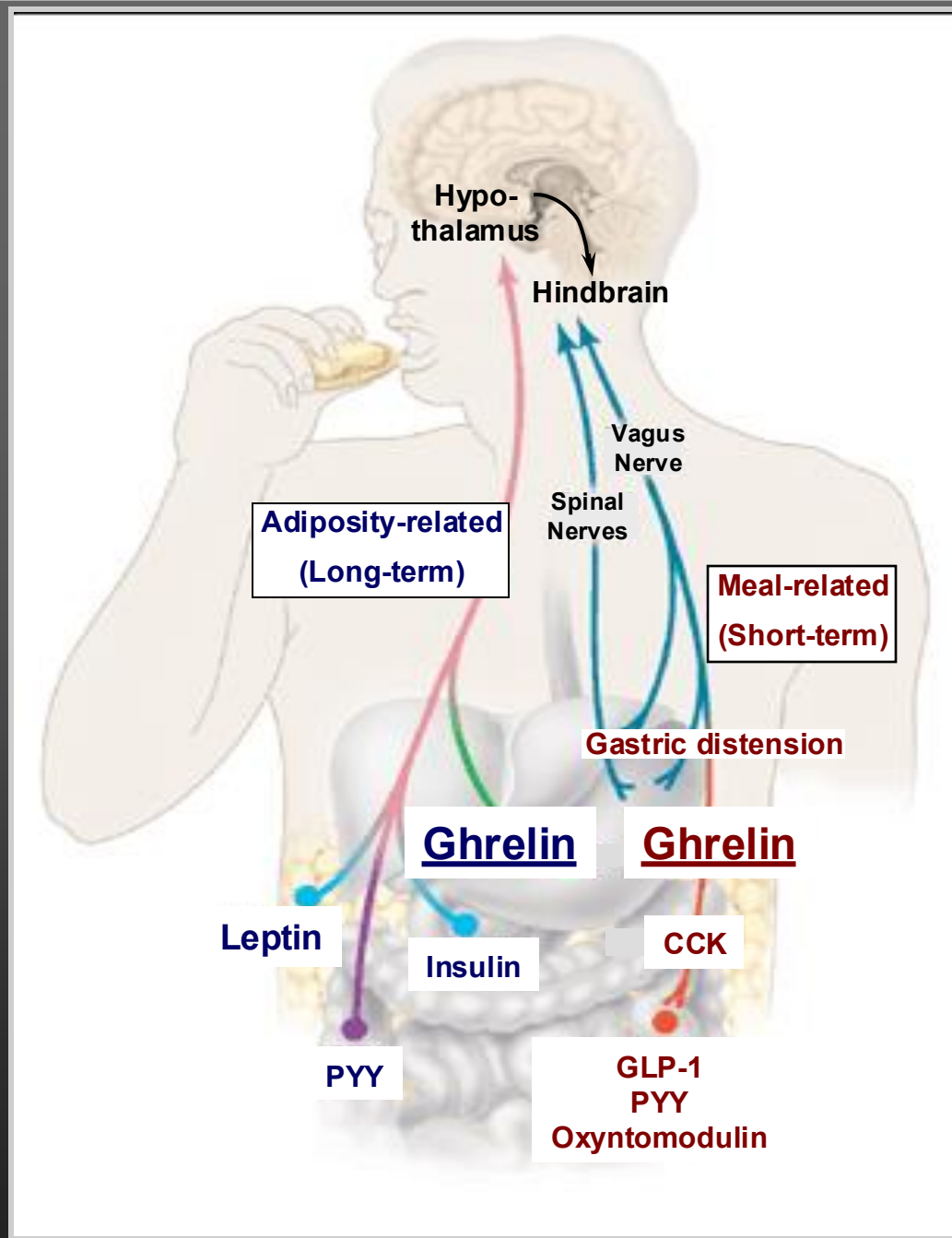
See you in

PARIS





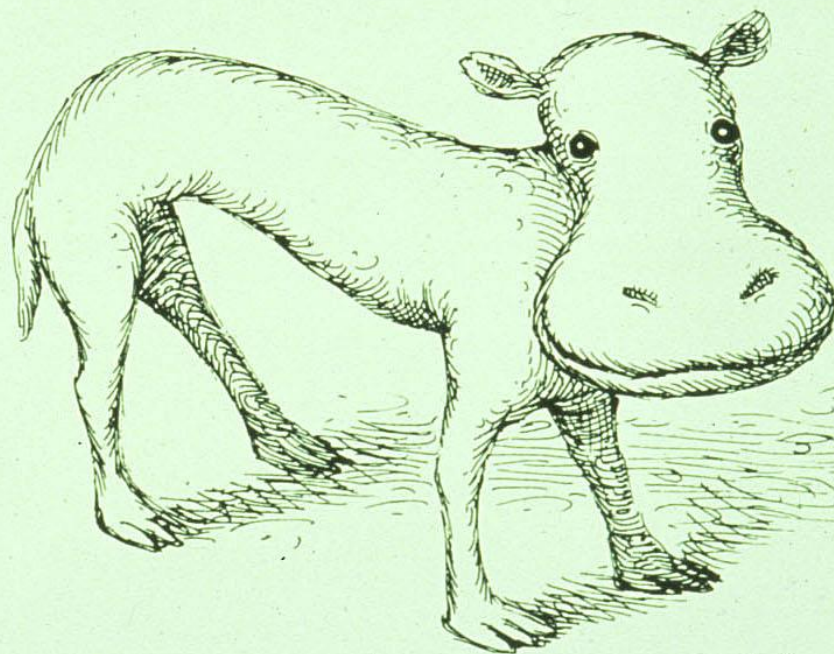
Thank you



HIPPOSUCTION

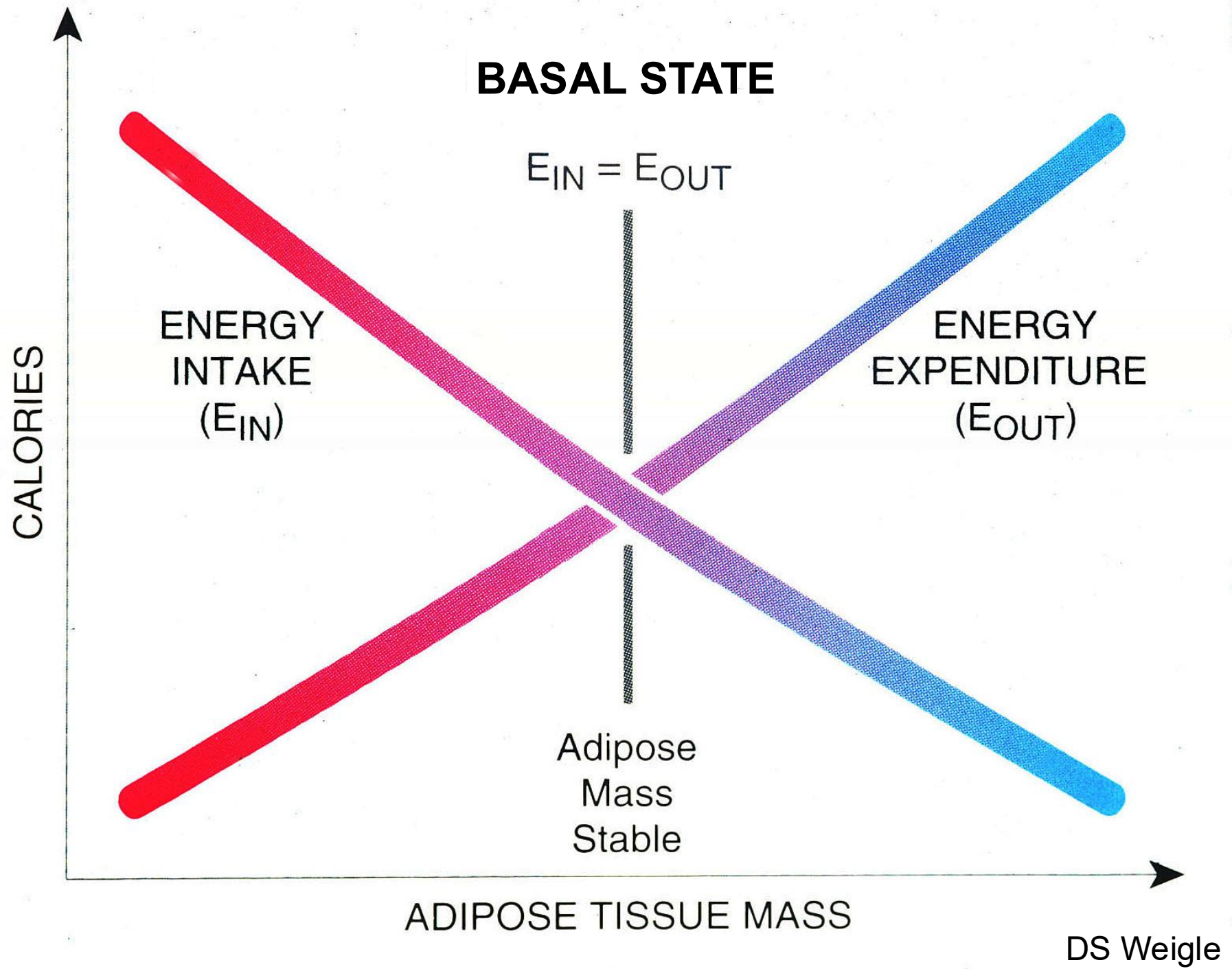


BEFORE

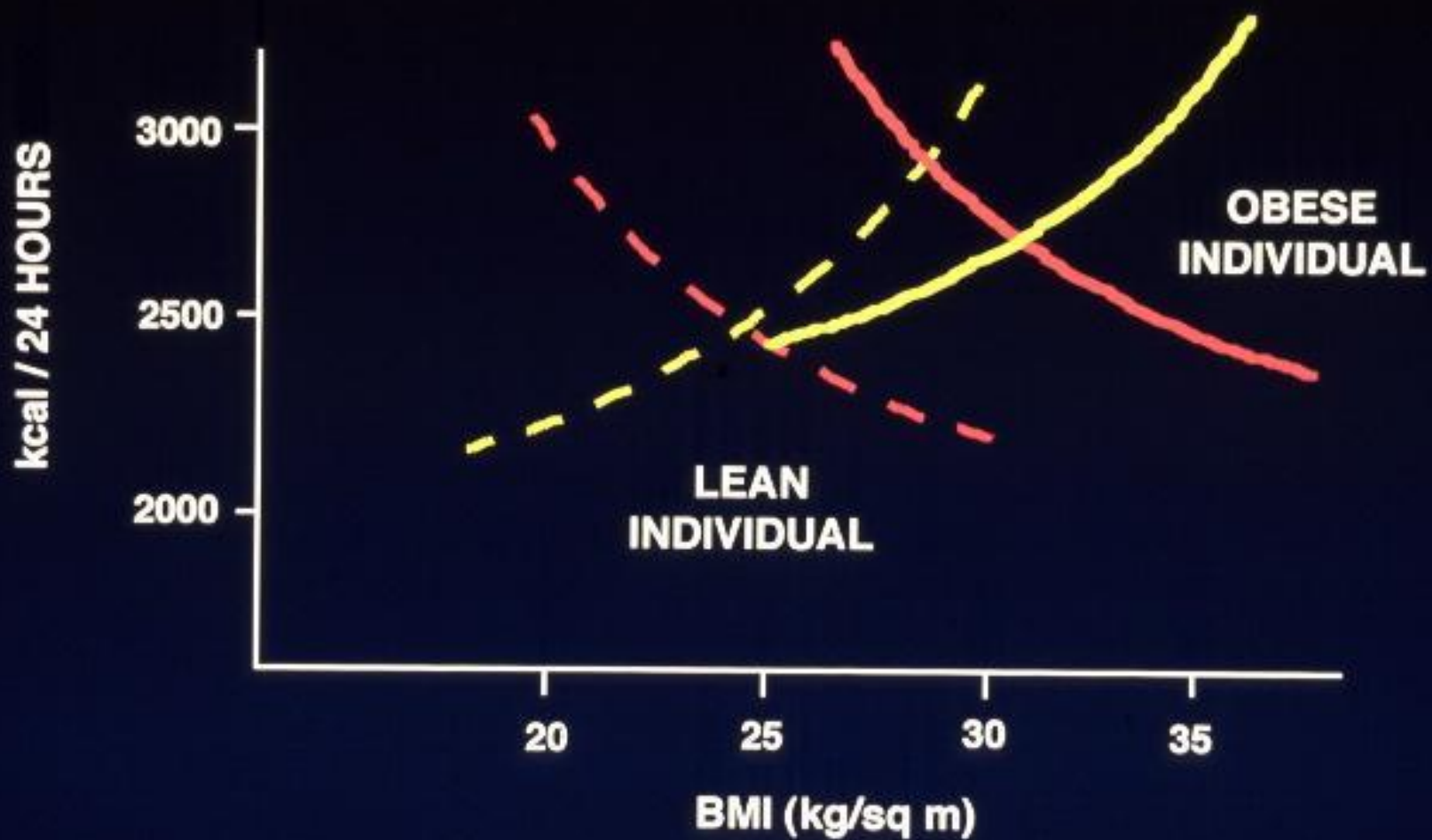


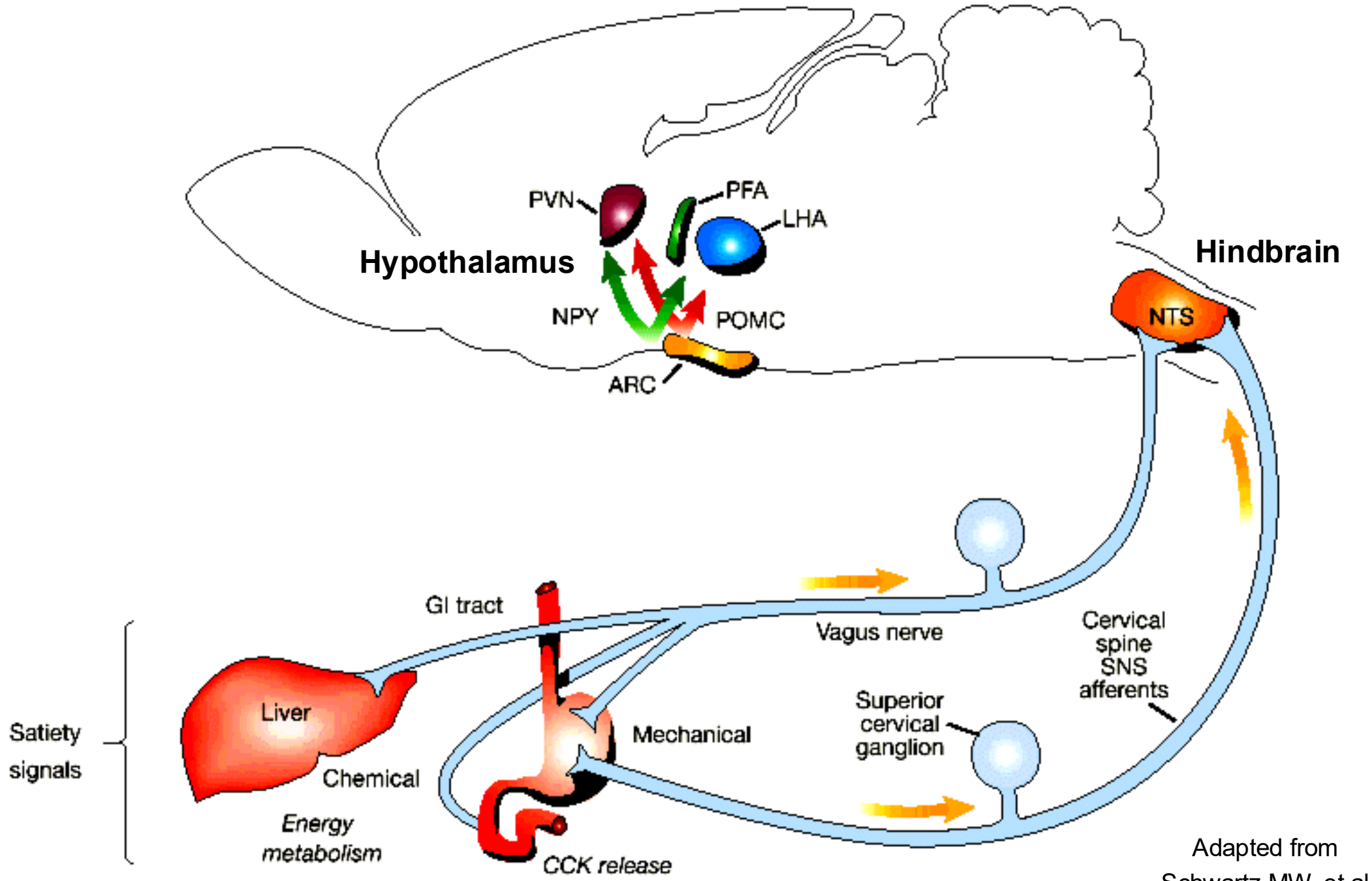
AFTER

John Brian



REGULATION OF BODY COMPOSITION





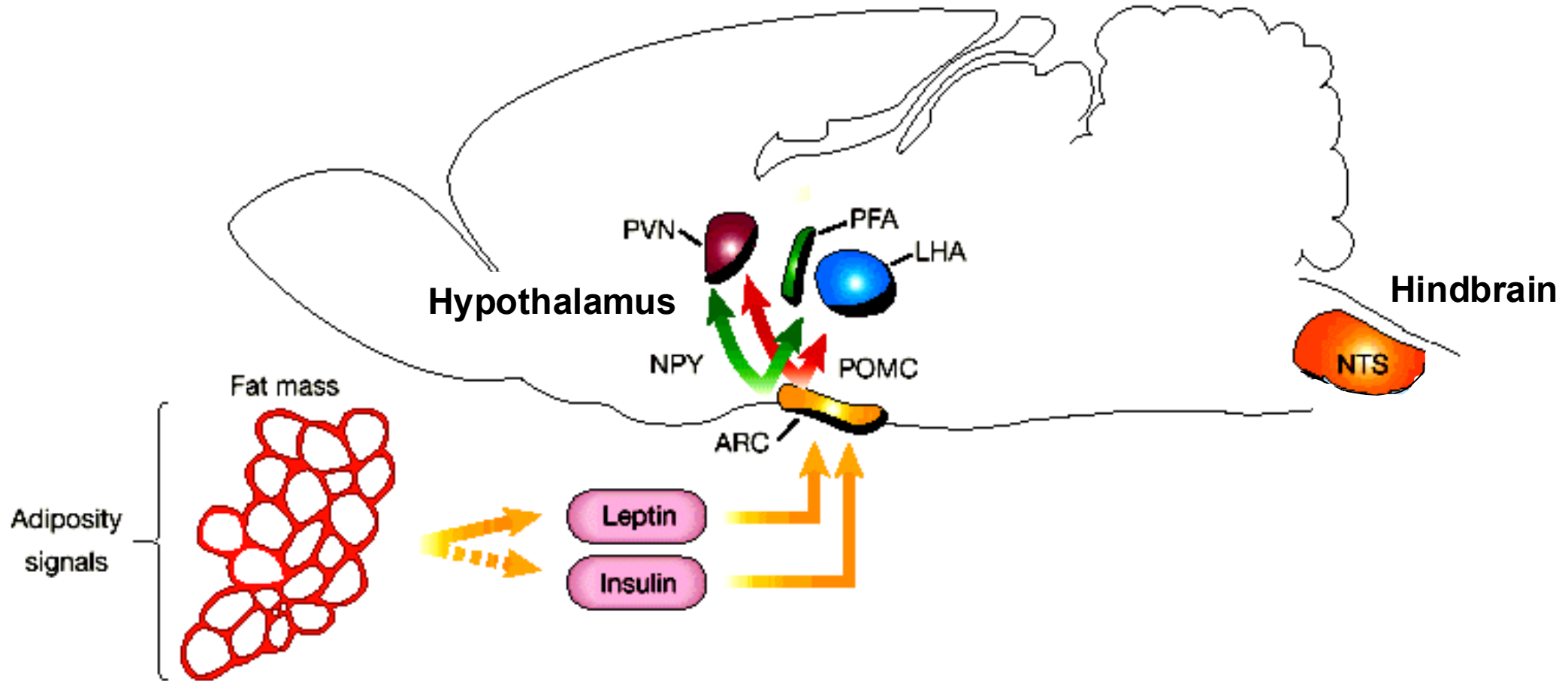
Adapted from
Schwartz MW, et al
Nature 404:661

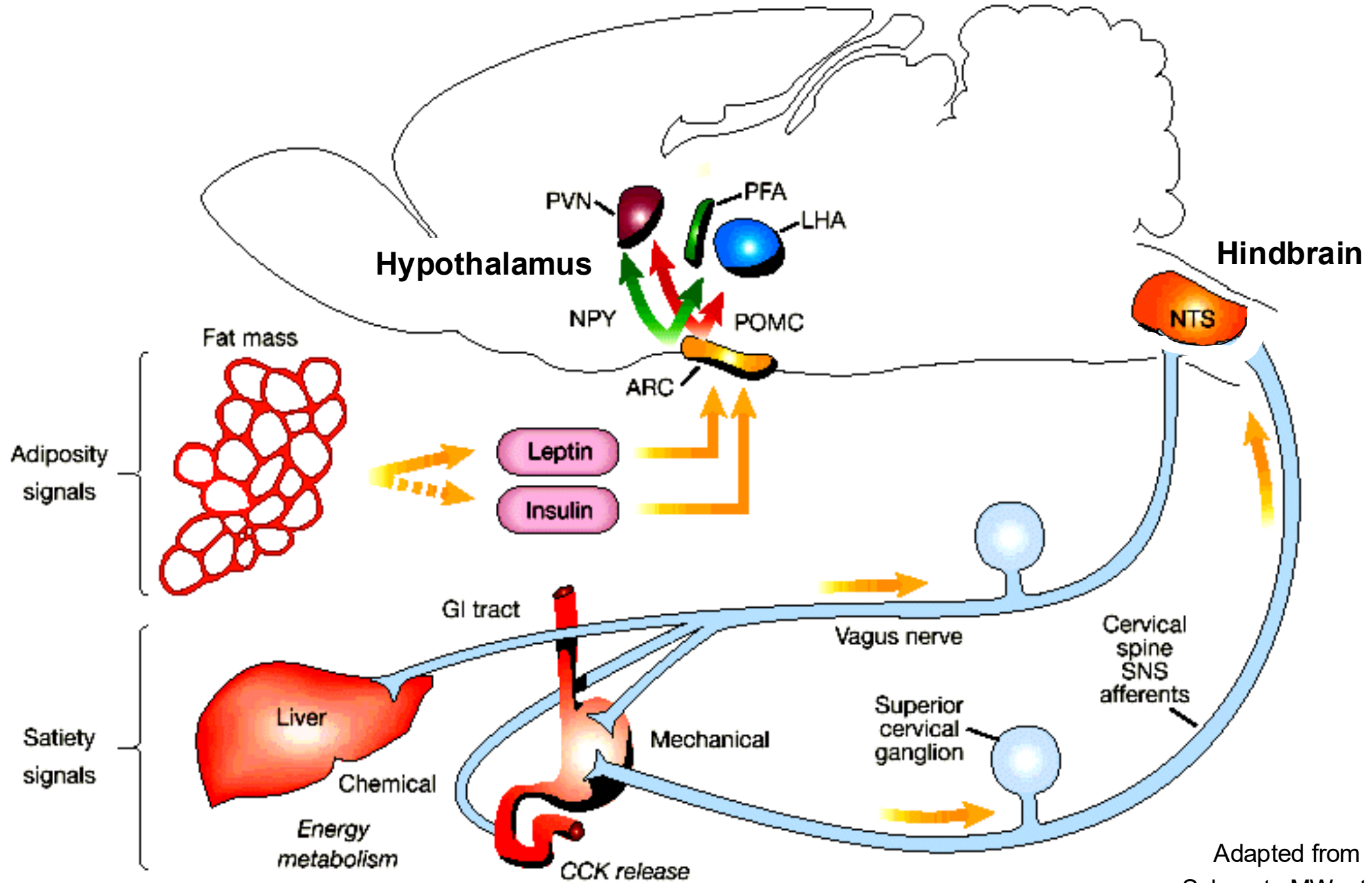
Table 1

Selected GI and pancreatic peptides that regulate food intake

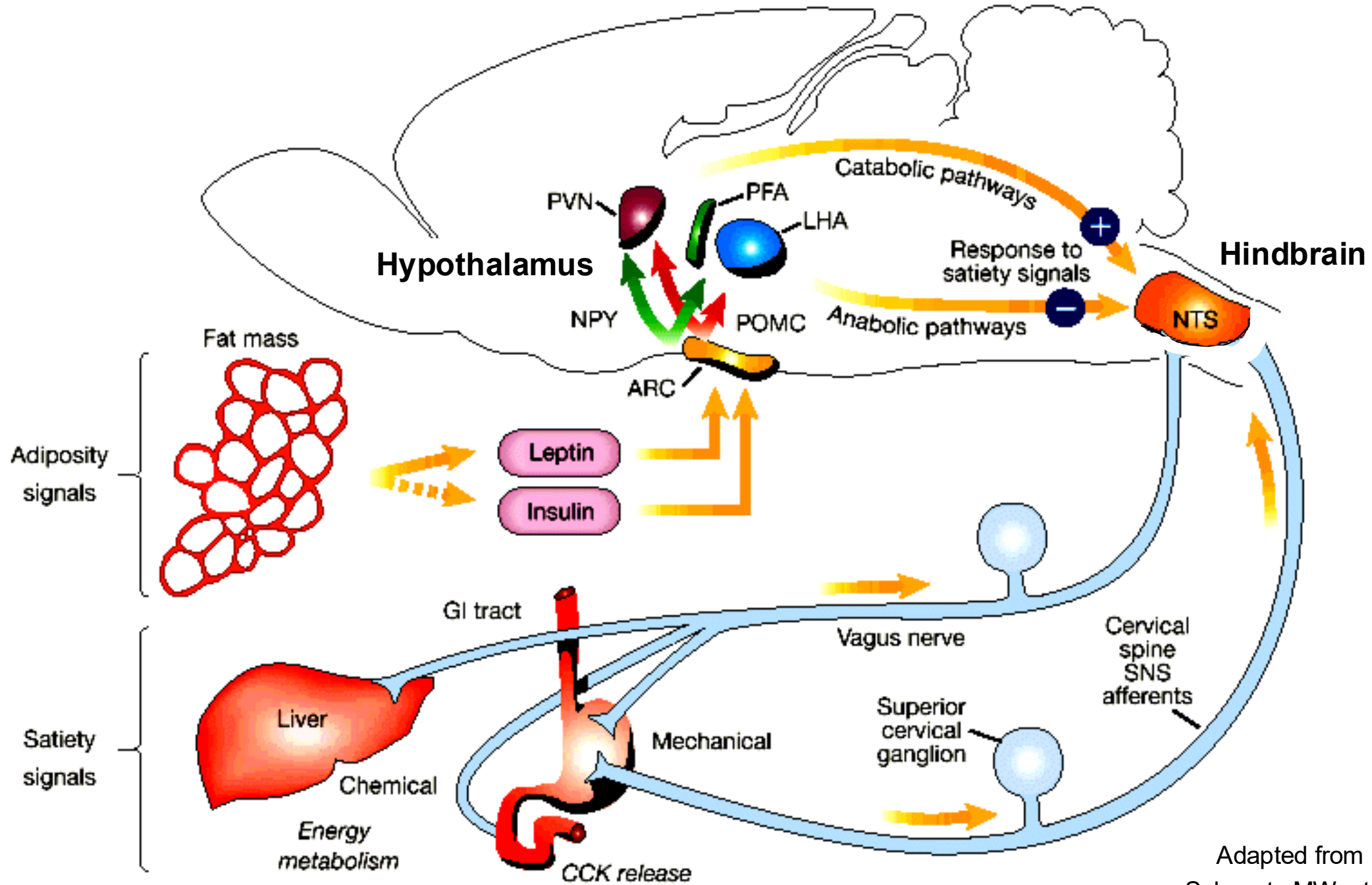
Peptide	Main site of synthesis	Receptors mediating feeding effects	Sites of action of peripheral peptides germane to feeding			Effect on food intake ^A
			Hypothalamus	Hindbrain	Vagus nerve	
CCK	Proximal intestinal I cells	CCK1R	X	X	X	↓
GLP1	Distal-intestinal L cells	GLP1R	X?	X?	X	↓
Oxyntomodulin	Distal-intestinal L cells	GLP1R and other	X			↓
PYY ₃₋₃₆	Distal-intestinal L cells	Y2R	X		X	↓
Enterostatin	Exocrine pancreas	F1-ATPase β subunit			X	↓
APO AIV	Intestinal epithelial cells	Unknown	X		X	↓
PP	Pancreatic F cells	Y4R, Y5R		X	X	↓
Amylin	Pancreatic β cells	CTRs, RAMPs	X	X		↓
GRP and NMB	Gastric myenteric neurons	GRPR		X	X	↓
Gastric leptin	Gastric chief and P cells	Leptin receptor	?	?	X	↓
Ghrelin	Gastric X/A-like cells	Ghrelin receptor	X	X	X	↑

CTRs, calcitonin receptors; RAMPs, receptor activity-modifying proteins; GRP, gastrin-releasing peptide; NMB, neuromedin B; GRPR, GRP receptor. X? indicates that it is unclear whether physiologically relevant quantities of GLP1 from the gut evade DPP4-mediated degradation in blood to activate GLP1 receptors in the brain, although these receptors might interact with CNS GLP1 to regulate food intake. ? indicates that it seems very unlikely that gastric leptin interacts in a physiologically meaningful way with leptin receptors in the hypothalamus or hindbrain, which are important targets of leptin secreted from adipocytes. ^AEffect of peripheral peptides on food intake. In some cases, central administration yields opposite results.





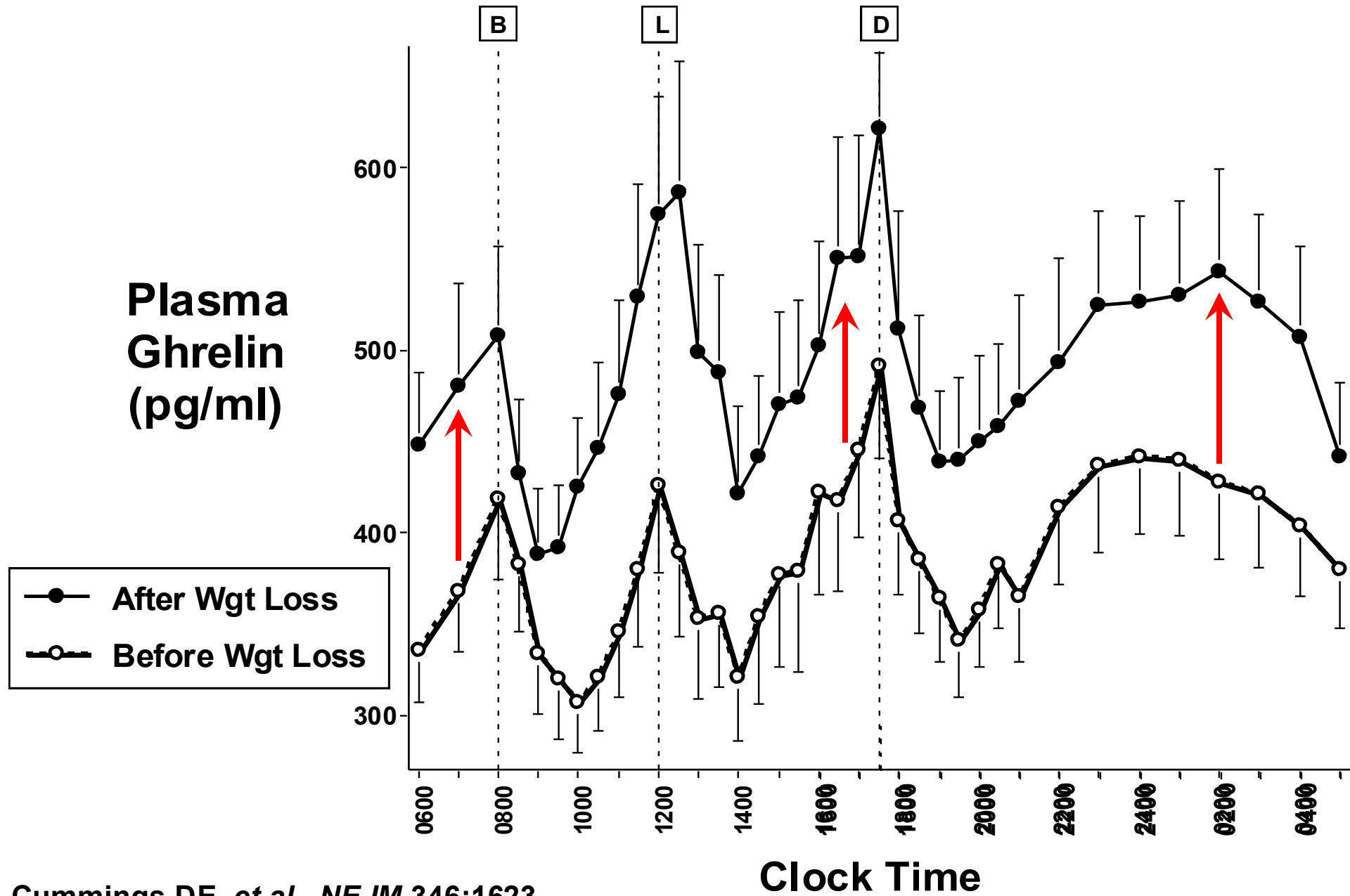
Adapted from
Schwartz MW, et al
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Adapted from
Schwartz MW, et al
Nature 404:661

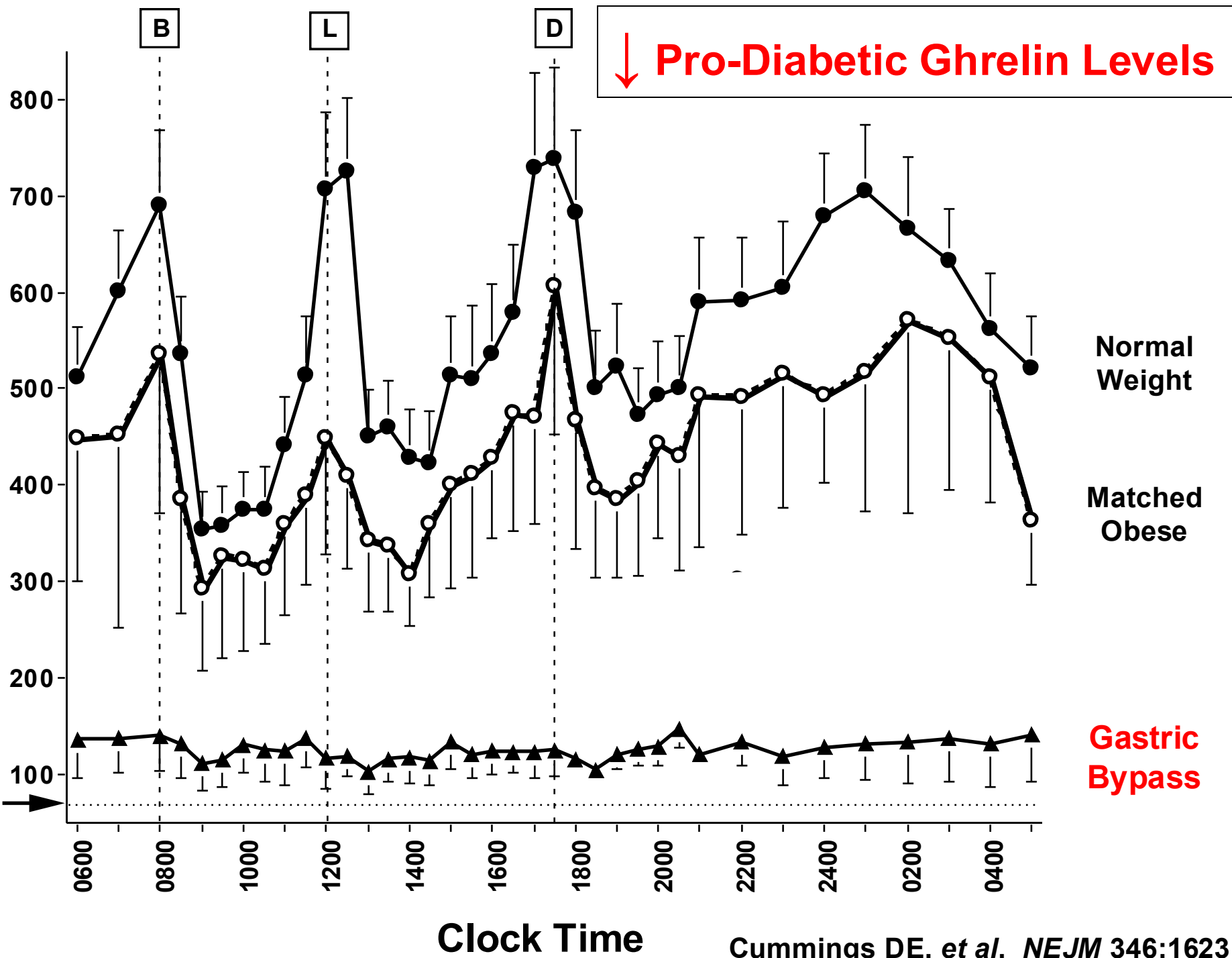
Plasma Ghrelin Increases After Diet-Induced Weight Loss

Plasma
Ghrelin
(pg/ml)



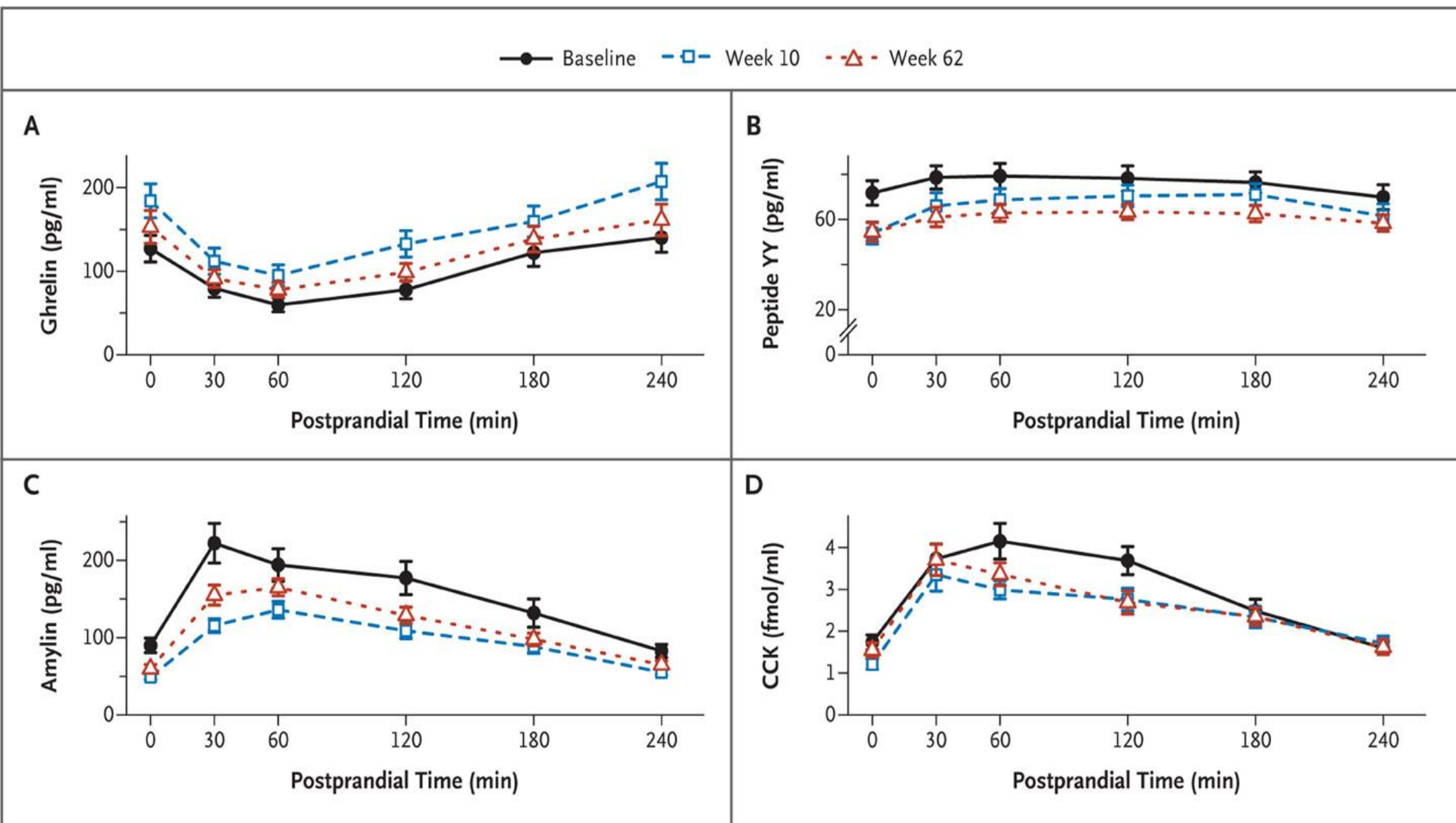
Plasma
Ghrelin
(pg/ml)

Detection
Limit



**Do compensatory
hormonal responses
to weight loss
wane over time?**

Persistent Compensatory Hormonal Adaptations to Sustained Weight Loss



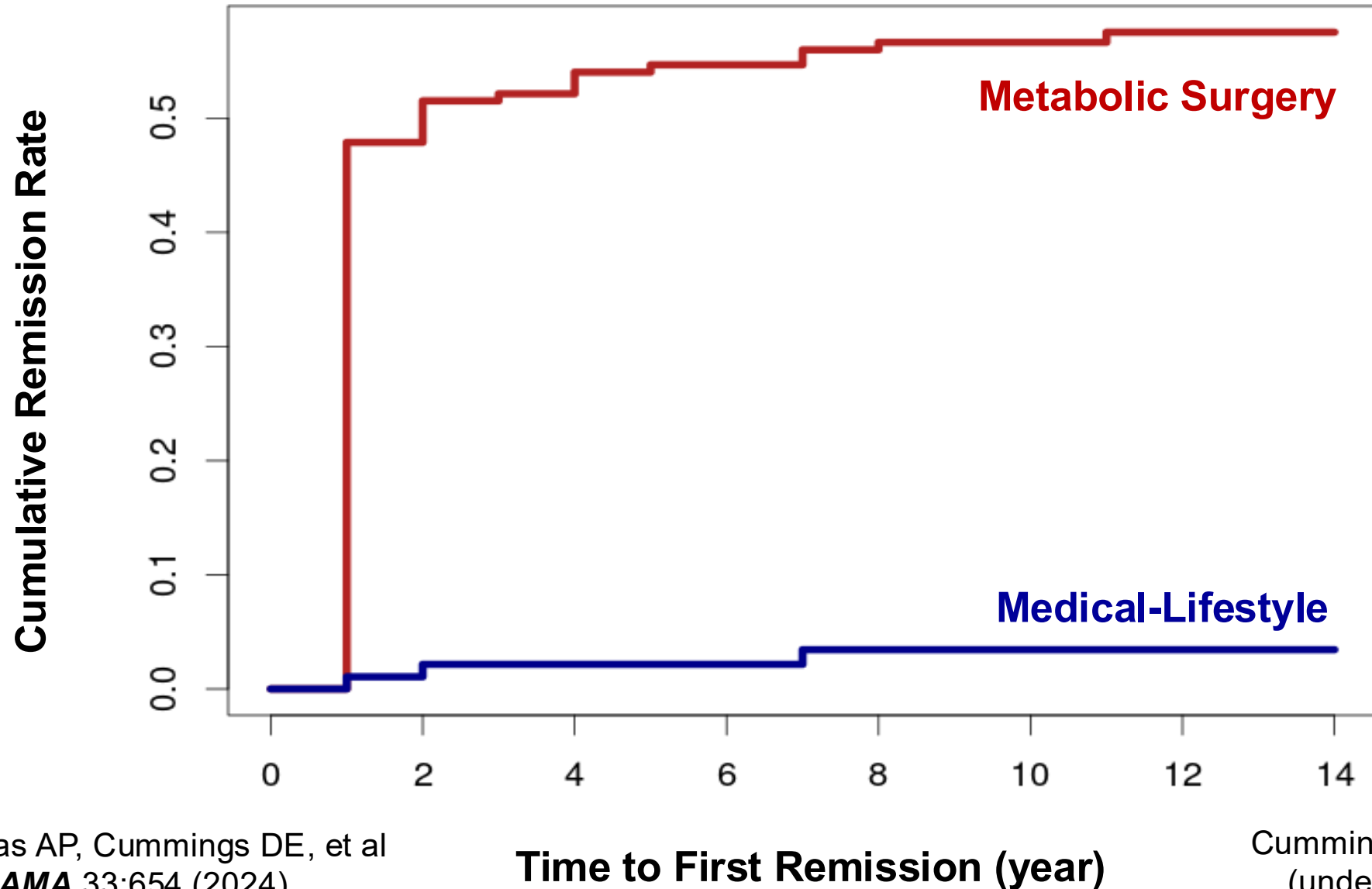
Benefits on Hard Outcomes with Incretin Meds in RCTs

- **Weight loss & diabetes improvement**
 - Improved lipids & bp
- **↓ Major adverse kidney events**
 - Perkovic V, *NEJM* 2024 (FLOW)
- **↓ Major adverse liver events**
 - Kanwal F, *JAMA IM* 2024
- **↓ Sleep apnea (↓ AHI by 50%)**
 - Malhotra A, *NEJM* 2024 (SURMOUNT-OSA)
- **Osteoarthritis improvement**
 - Bliddal H, *NEJM* 2024
- **↓ CHF**
 - STEP-HFpEF & SUMMIT
- **↓ Major adverse cardiovascular events**
 - SELECT, SUSTAIN 6, SURPASS-CVOT

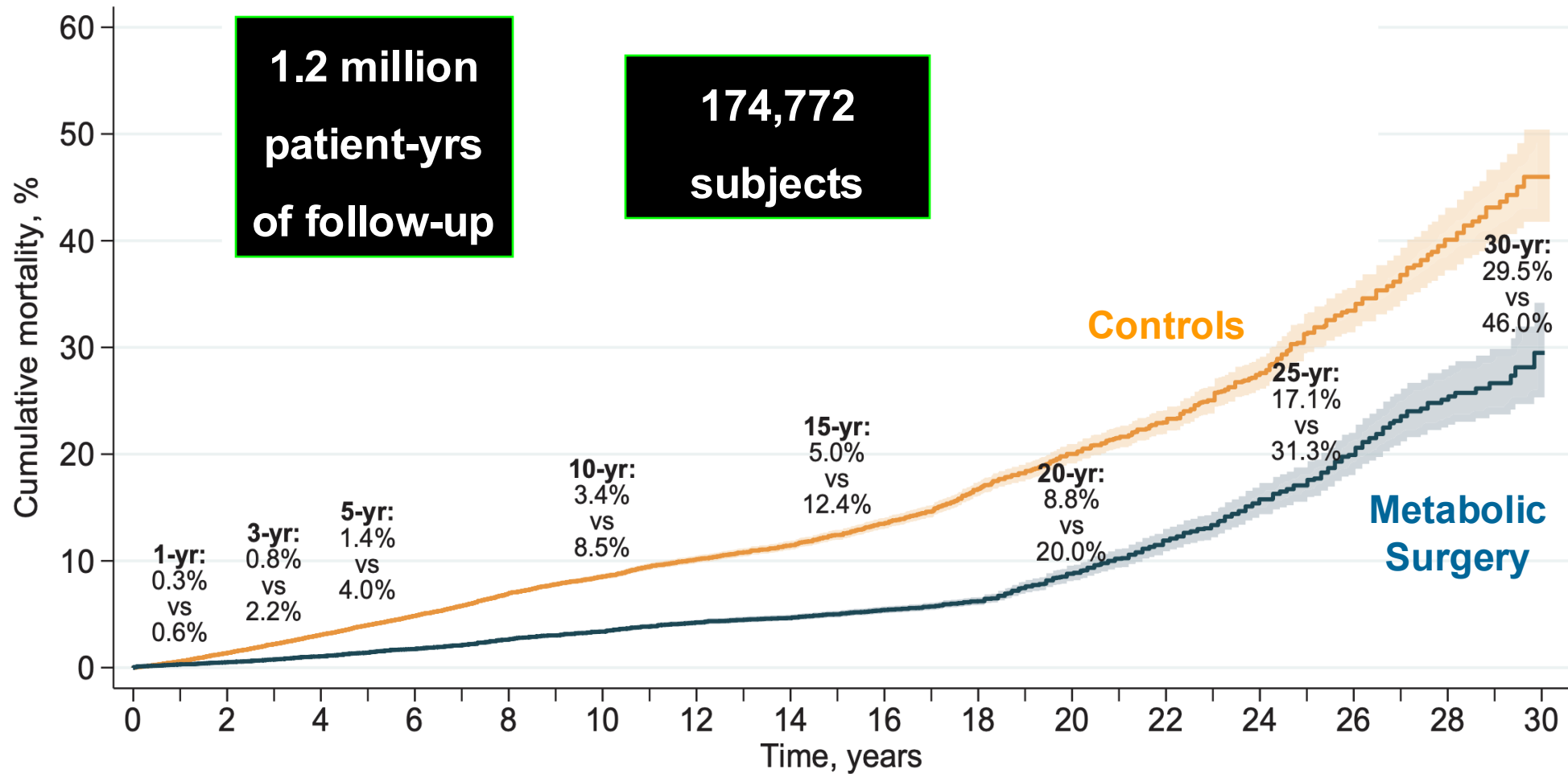
Cost to Save One Life

- **GLP-1 Meds:** **\$3,000,000**
- **Metabolic Surgery:** **\$300,000**

Diabetes Remission Over 14 Years in ARMMS Study



Cumulative All-Cause Mortality



Number at risk

Non-surgical	108987	96181	70908	46202	19899	12878	9230	7399	6019	2756	2101	1566	813	413	206	26
Metabolic surgery	65785	61183	48240	34847	16482	13098	11605	10483	9811	6844	1997	1456	878	474	239	34

