Understanding the physiology of weight regulation—implications for the medical management of obesity

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Objectives

Learn about the individual's health experience of having obesity.

Why medical management is critical

Learn about the neuroendocrine physiology that regulates weight.

Understand that it is simply not about "will power".

Anti-obesity medications

-What do they do, how do they help?

Individual examples

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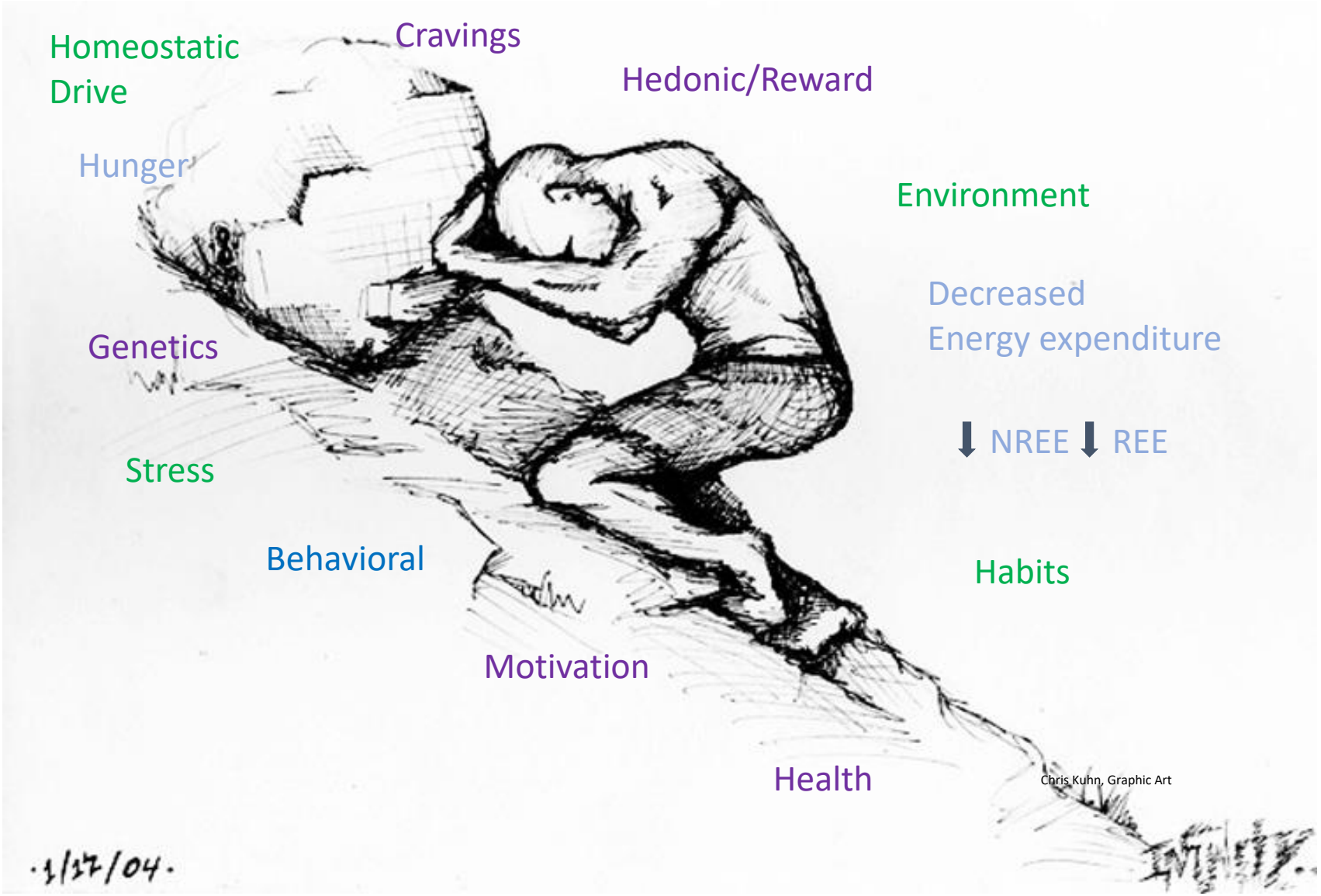
“It’s simple”- standard healthcare advice

“Lose some weight, quit smoking, move around more and eat the carrot.”

Challenge of Weight Loss and Maintenance



Obesity Is Associated With Multiple Comorbidities

Metabolic, mechanical and mental

Metabolic

Mechanical

Mental

Cancers*

Physical functioning

Depression

Anxiety

Sleep apnoea

Asthma

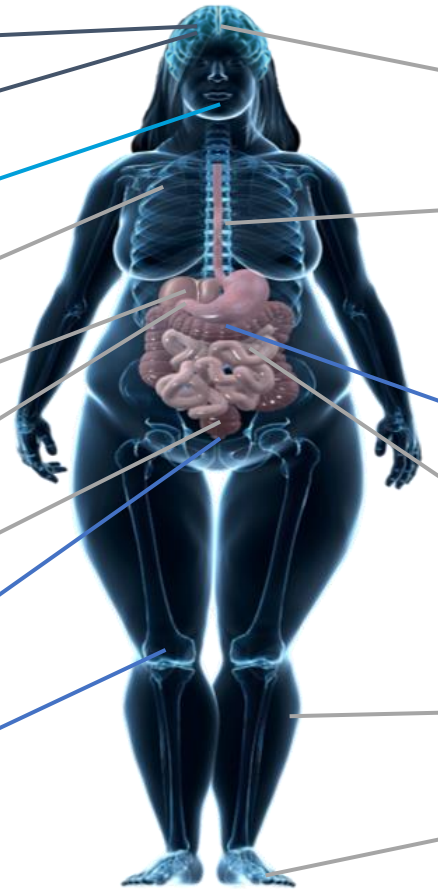
NAFLD

Gallstones

Infertility

Incontinence

Osteoarthritis



CVD and risk factors
- Stroke
- Dyslipidaemia
- Hypertension
- Coronary artery disease
- Congestive heart failure
- Pulmonary embolism

Chronic back pain

Type 2 diabetes
Prediabetes

Thrombosis

Gout

CVD, cardiovascular disease; NAFLD, non-alcoholic fatty liver disease

*Including breast, colorectal, endometrial, esophageal, kidney, ovarian, pancreatic and prostate

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–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

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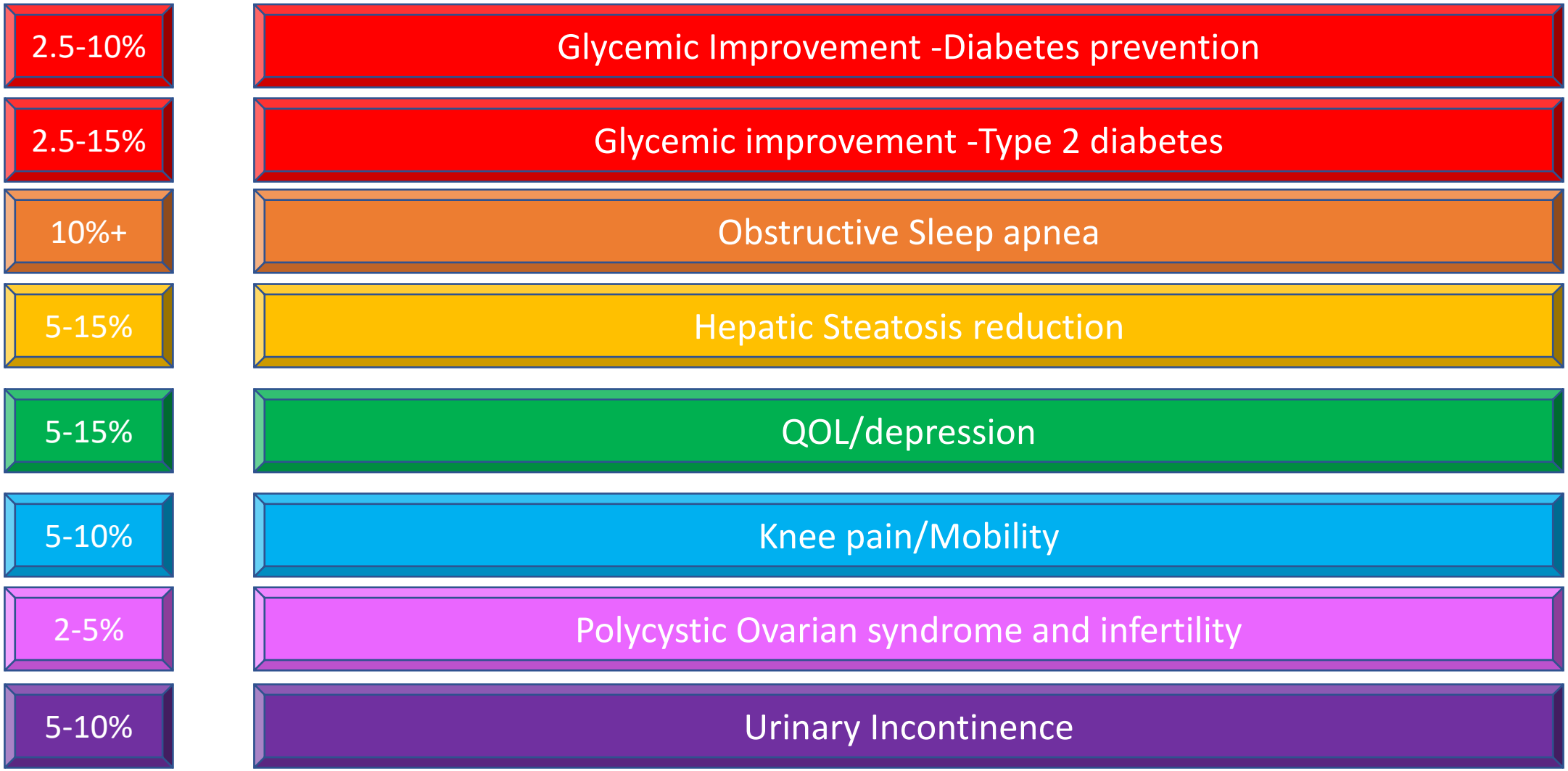
5-15% Weight loss improves comorbidities



Adapted from Ryan DH, Yockey SR. *Curr Obes Rep*. 2017;6(2):187–194. doi:10.1007/s13679-017-0262-y

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Stigma & Shame

“I loathed my body and therefore functioned best when not thinking about it. My body was what was wrong with me.”

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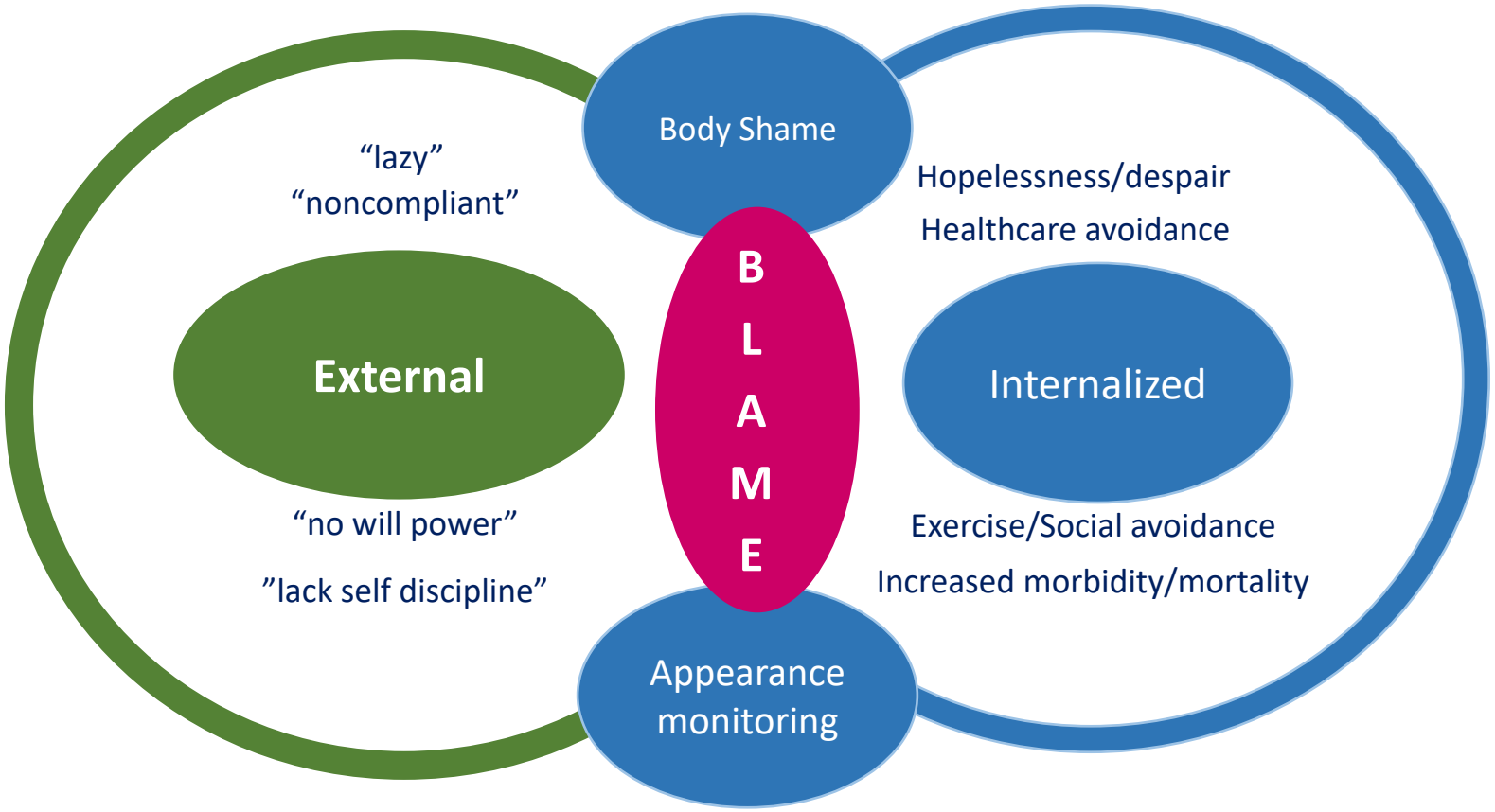
Stigma: An Impediment to Change

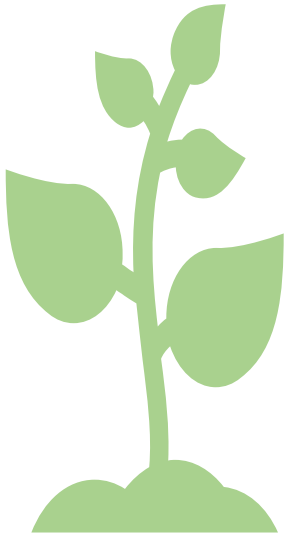


Critical Role of Empathy & Humanity in Health Care

"Be aware of your own biases against weight and recognise that it affects your assessments and action in treating a patient. You may end up hurting someone."

–Individual struggling with weight

First do no harm
-Hippocrates



"Prior to my weight loss, I was afraid of getting through the turn-style at the metro, riding on an airplane, going to the doctor, will there be parking, an elevator -- basic life stuff that just makes you shut down and withdraw."

"This affected my social life, parties, going to restaurants, many events that I just couldn't go to."

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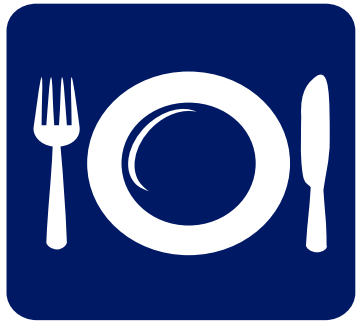
Losing weight is simply a matter of will power-
eat less, exercise more.



Energy Intake

Protein
Carb
Fat

Homeostasis

Genetics

Energy Expenditure

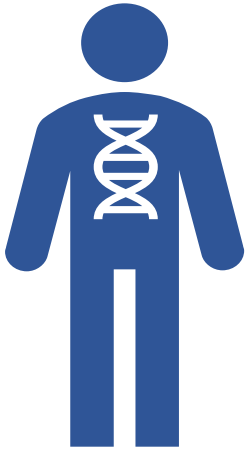
Activity

NEAT

Resting Metabolic Rate

Thermic Effect of Food

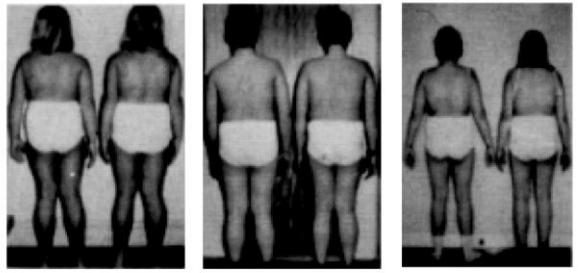
Badman, Flier. *Science* 2005;307:1909–14; US Department of Health and Human Services, 1998. NIH Publication No. 98-4083



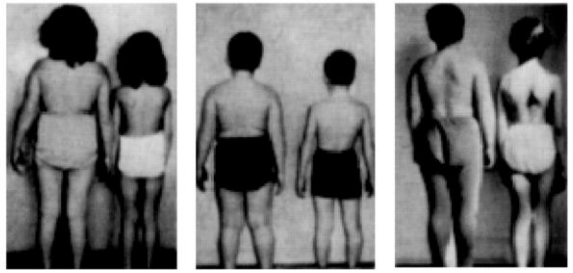
Genetics/Biology

- Polygenic vs. Monogenic
- Twin Studies
- Family History
- Response to intervention

Body Mass in Twins

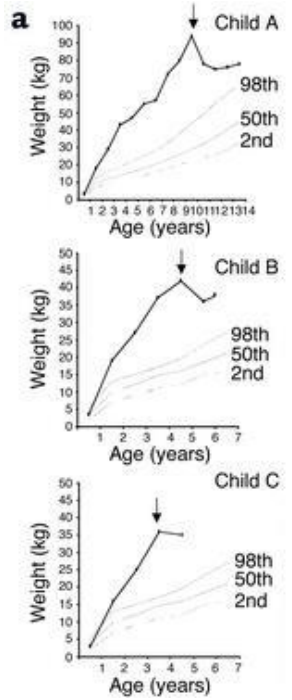


Monozygotic Twins (Intrapair Correlation = 0.66)

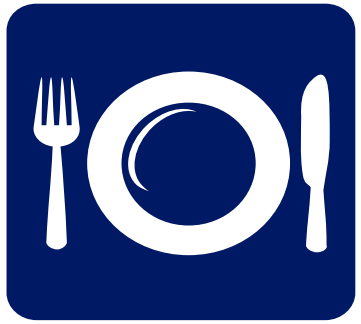


Dizygotic Twins (Intrapair Correlation = 0.26)

Leptin deficiency



Severe hyperphagia
Delayed puberty



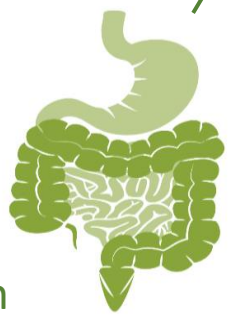
Energy Intake

Protein
Carb
Fat

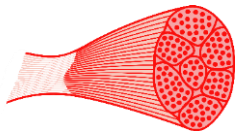
Homeostasis

CCK
PYY
GLP1
amylin

Ghrelin



Leptin +



myokines

Energy Expenditure

Activity

NEAT

Resting Metabolic Rate

Thermic Effect of Food

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

Hedonic input

Increased palatability or pleasure

Wanting

Liking

Reward

Craving

Environment

- Drives acquisition of HF/HC food leading to consumption beyond need

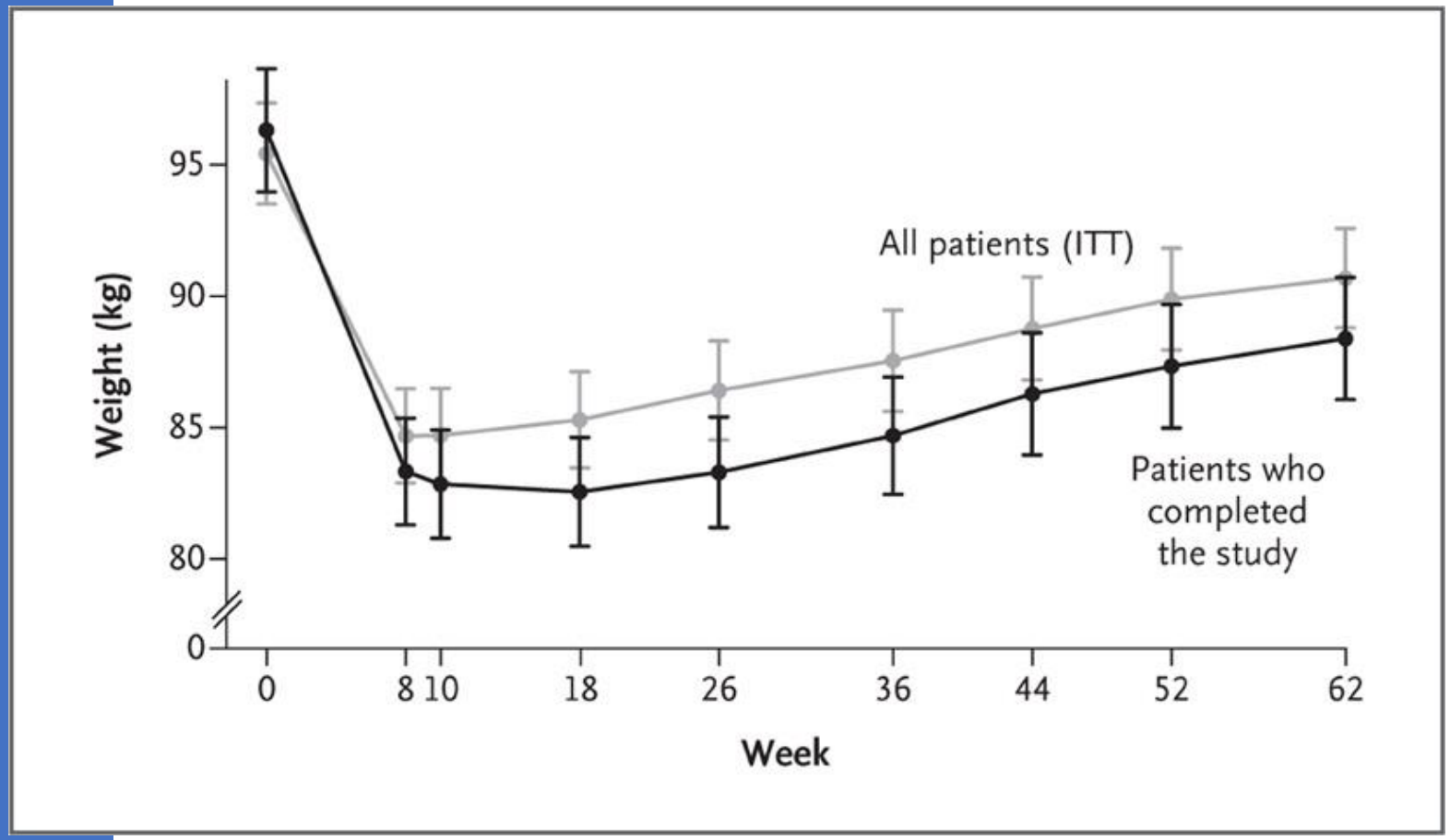
Adapted from Blundell J et al. *Obes Rev.* 2010;11(3):251–270.

I have lost weight several times, just can’t maintain it.
In fact, each time I re-gain and I am higher than when I started!

What happens after a 10 week weight loss?

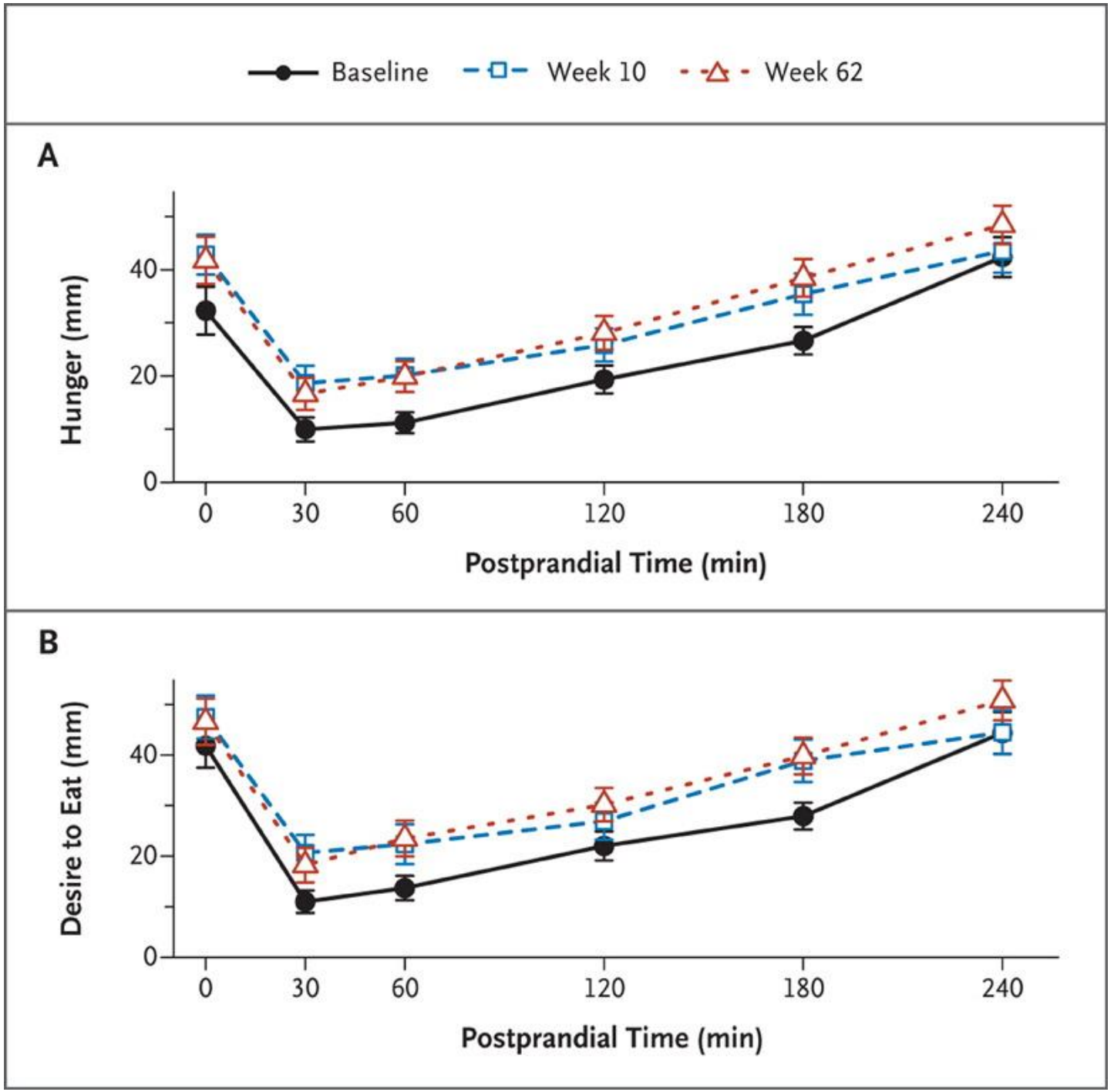
Sumithran, NEJM 2011

Weight Regain

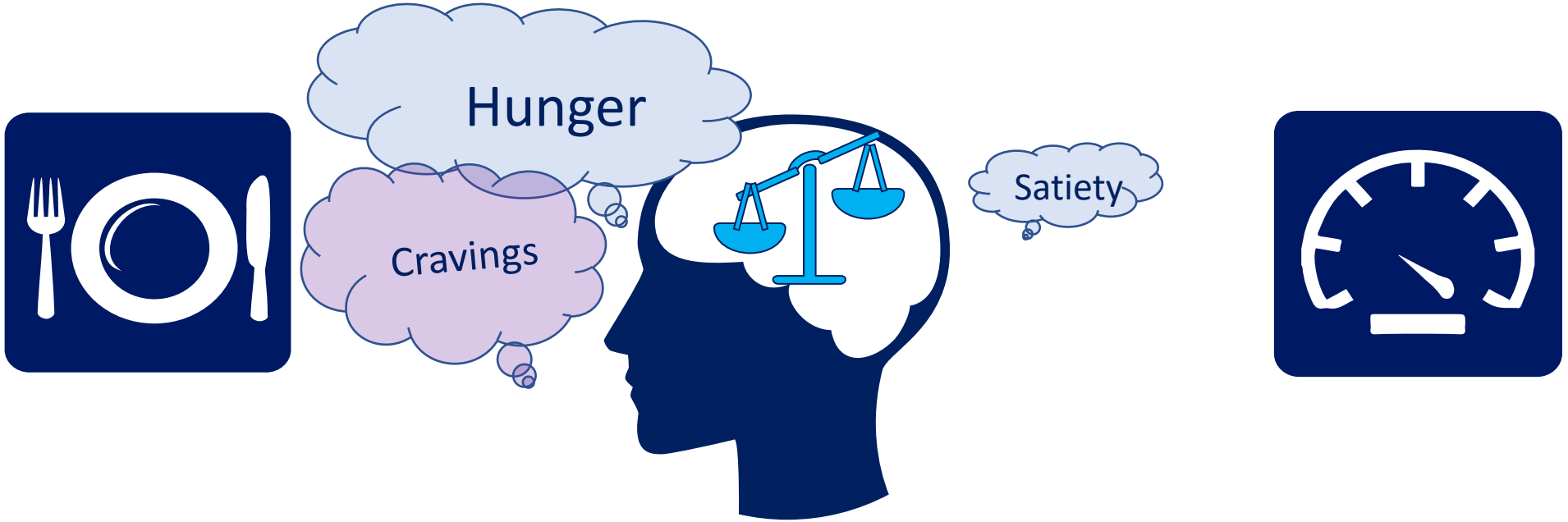


Hunger and desire to eat increase after weight loss -not just immediately after but up to 1 year

Sumithran, NEJM 2011



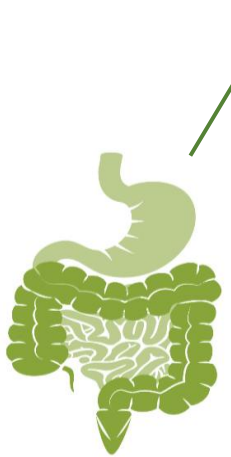
After Weight Loss



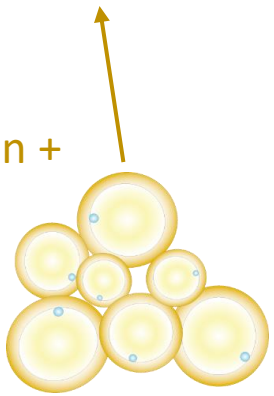
Energy Intake ↑ Homeostatic Hedonic ↓ Energy Expenditure

Protein
Carb
Fat

↓ CCK
PYY
GLP1
Amylin
↑ Ghrelin



↓ Leptin +



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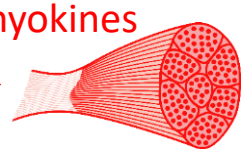
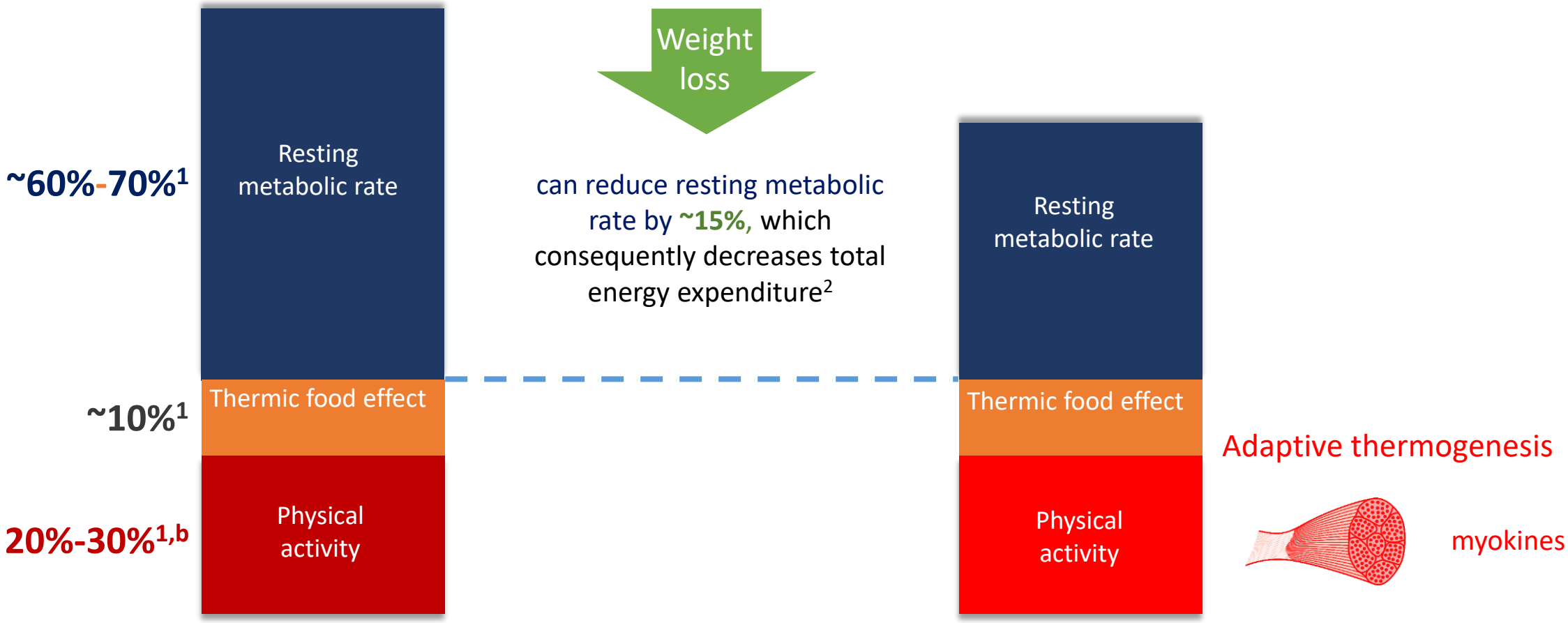


Activity
NEAT
Resting Metabolic Rate
Thermic Effect of Food

Adaptive thermogenesis

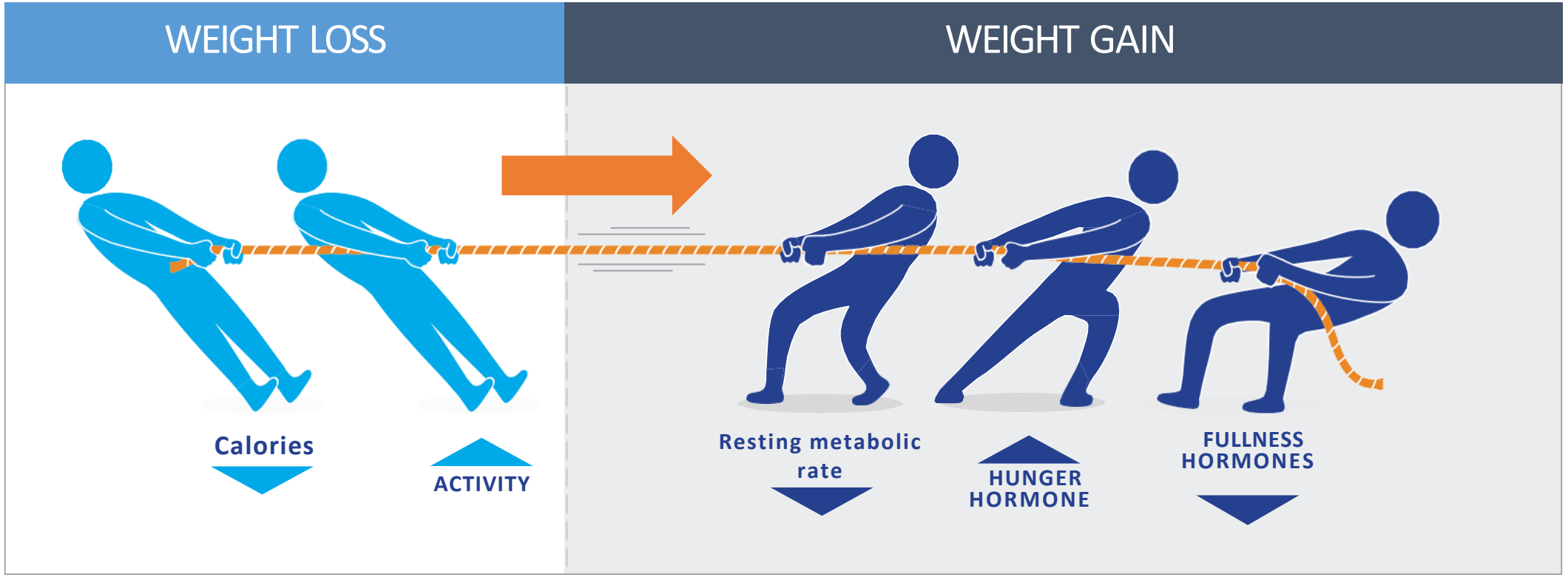
CCK, cholecystokinin; GLP-1, glucagon-like peptide-1; PYY, peptide YY
Adapted from Schwartz *et al. Obes Rev* 2010;11:531–47; Sumithran *et al. N Engl J Med* 2011;365:1597–604

Following weight loss, metabolic adaptation leads to decreases in resting metabolic rate[a] & calories burned



[a]From a review of data from indirect calorimetry to gain insights into the determinants of energy metabolism and its role in weight gain.
[b]The energy expended for physical activity ranges from approximately 15% in very sedentary individuals to up to 50% in highly active individuals.[1]
1. Lam YY, Ravussin E. *Eur J Clin Nutr.* 2017;71(3):318-322. 2. Lam YY, Ravussin E. *Mol Metab.* 2016;5(11):1057-1071.

Metabolic[2,a] and hormonal responses[3] drive regain counteracting an individual's effort to maintain long term weight loss



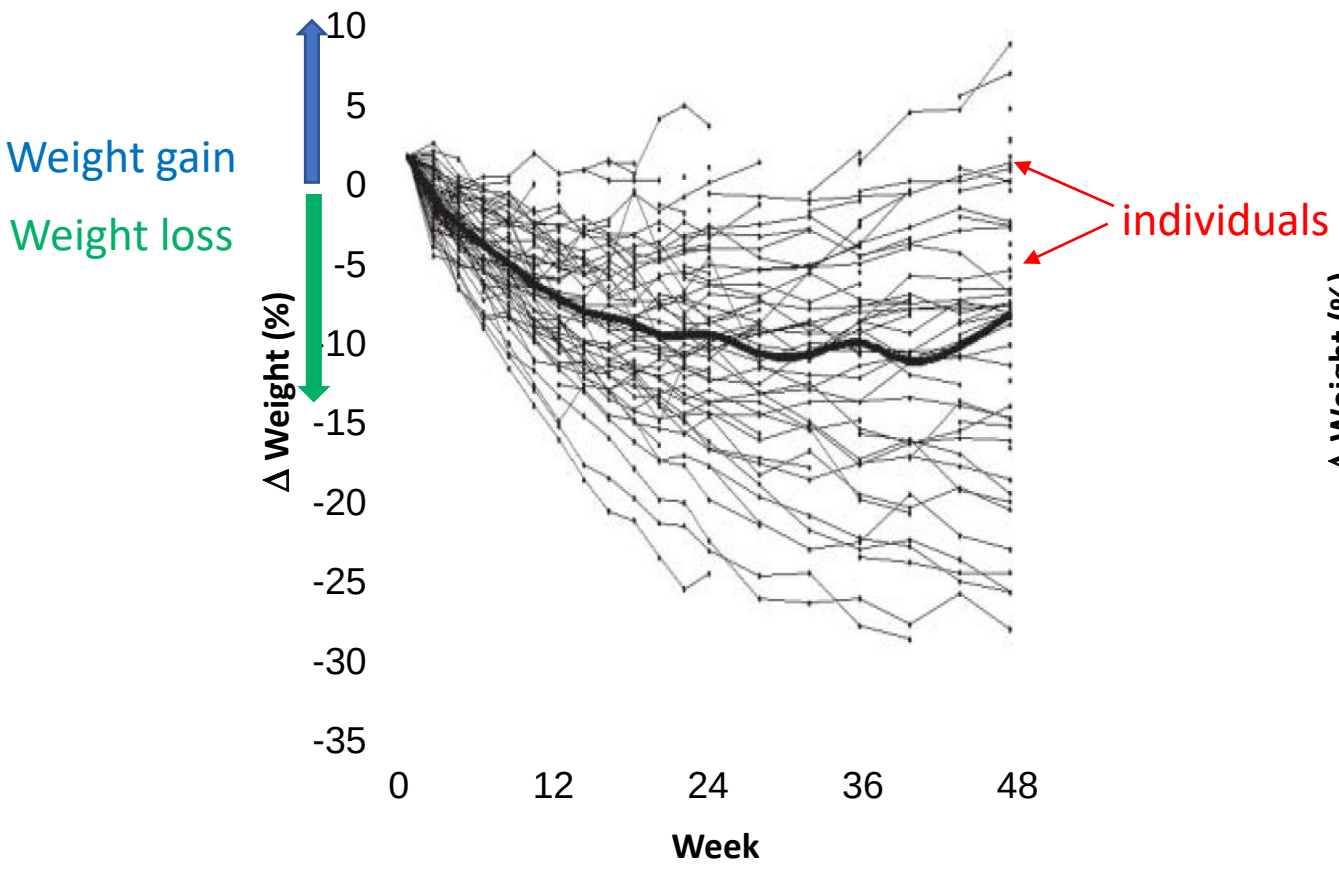
[a]Patients were randomized to calorie restriction (CR), calorie restriction with exercise (CREX), or low-calorie diet (LCD) groups. Mean percentage weight change (SEM) at 6 months by group was –10.4 (0.9)% (CR), –10.0 (0.8)% (CREX), and –13.9 (0.7)% (LCD) of initial body weight.

1. Garvey WT et al. *Endocr Pract.* 2016;22(suppl 3):1-203. 2. Lam YY, Ravussin E. *Mol Metab.* 2016;5(11):1057-1071. 3. Sumithran P et al. *N Engl J Med.* 2011;365(17):1597-1604.

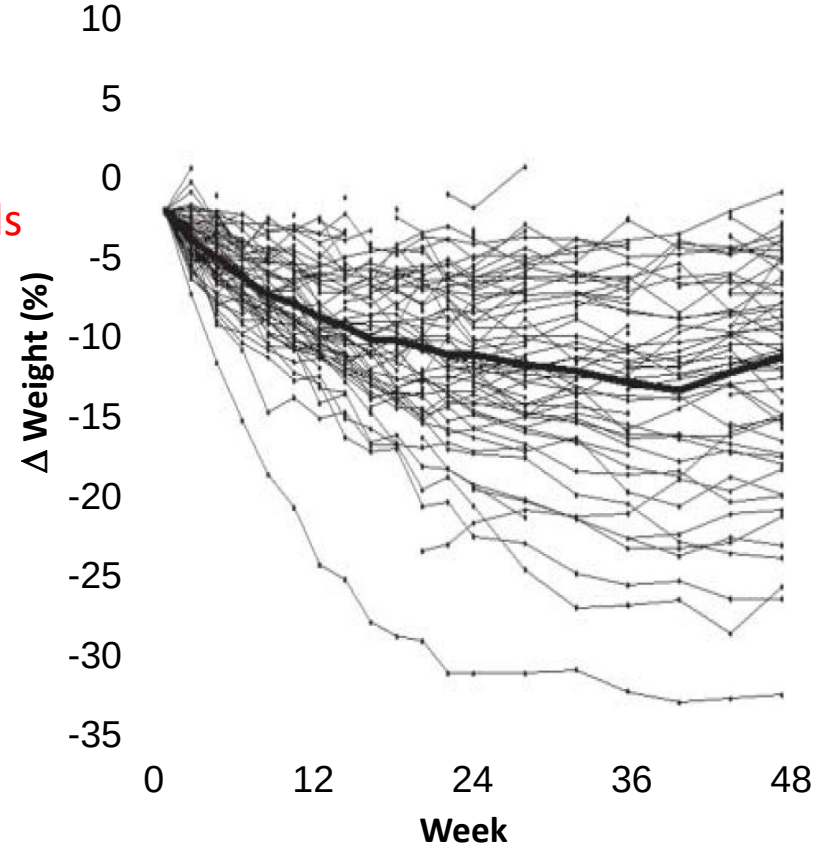
A low carb diet is the only way to lose weight.

What's the Best Diet?

Low-Carbohydrate Ketogenic Diet



Orlistat Plus Low-Fat Diet



Yancy WS, et al. *Arch Intern Med.* 2010;170:136-145.

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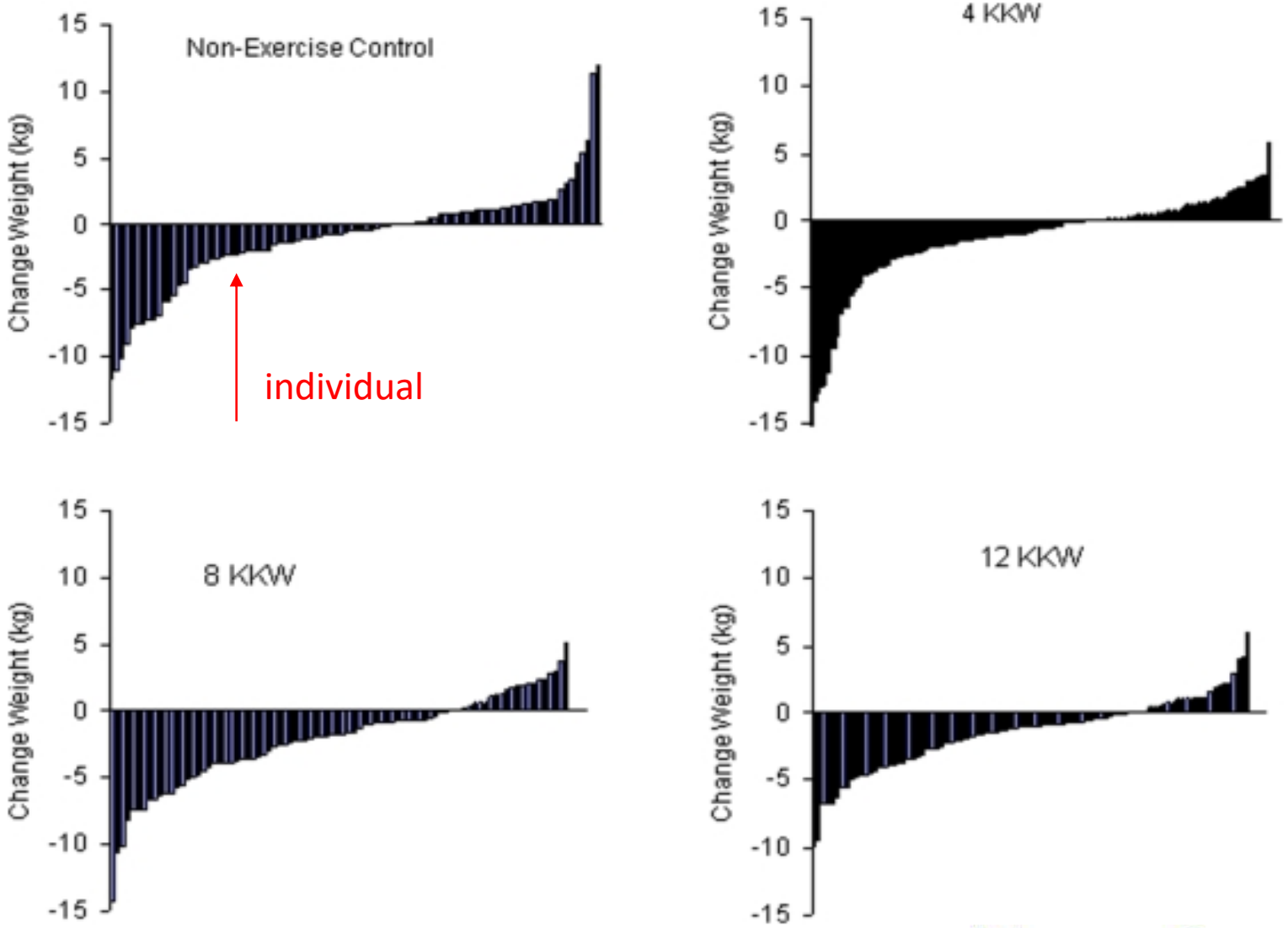
Just Exercise

Weight Change with Exercise - Individual Variation

Weight gain

Weight loss



Church, et al.,PloS One, Feb 2009

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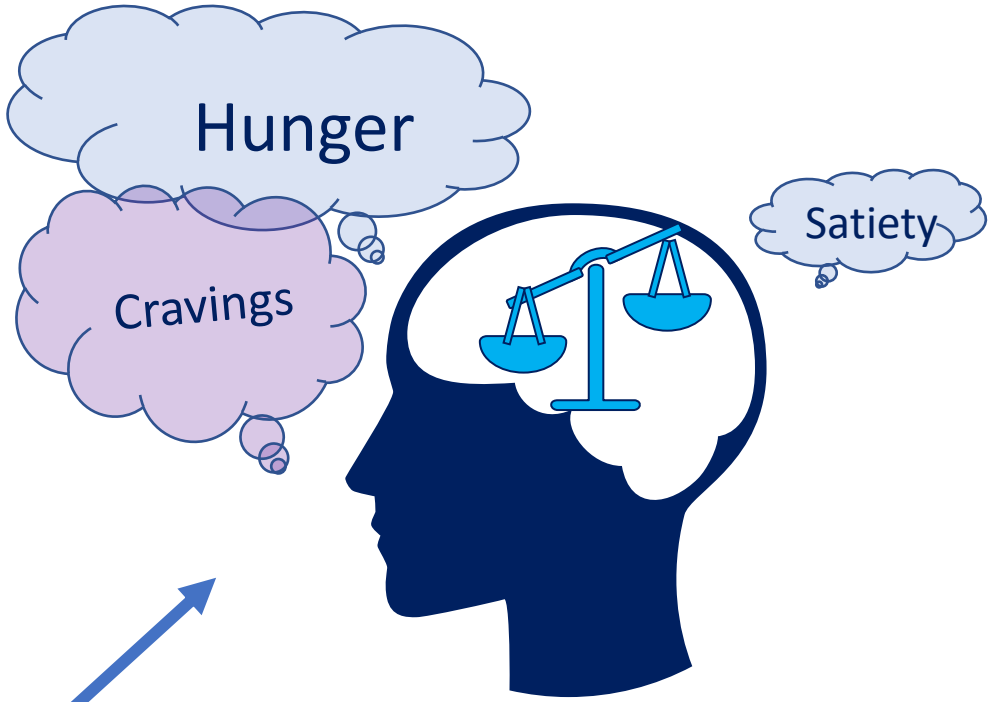
Medications for weight loss don’t work

Anti-Obesity Medications

Indicated as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adults with an initial body mass index (BMI) of: 30 kg/m^2 or greater (obese) or 27 kg/m^2 or greater (overweight) in the presence of at least one weight-related comorbid condition (eg, hypertension, type 2 diabetes mellitus, or dyslipidemia).

After Weight Loss



Hedonic

Homeostatic

Pharmacotherapy targets adaptive physiology, facilitating and sustaining weight loss

Physiology

Pharmacotherapy

↓ Hunger

↑ Satiety

↓ Craving

↓ Preoccupation with food

+

Lifestyle modification

↑ Physical and social activity

↑ Restraint

↓ Dietary cues

↓ Exposure

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

Adapted from Schwartz *et al. Obes Rev* 2010;11:531–47; Sumithran *et al. N Engl J Med* 2011;365:1597–604

Experience of anti-obesity medication

Change in craving

Smaller portions, decreased interest in food and/or drink

Better choices, more mindful, more consistent behavioral change

"My brain is so different"; "I'm able to notice real hunger for the first time"

"I'm less likely to eat sweets even if I'm full"

"I just don't like the taste of it"

"I just don't think about food like I used to—this what normal people must feel"

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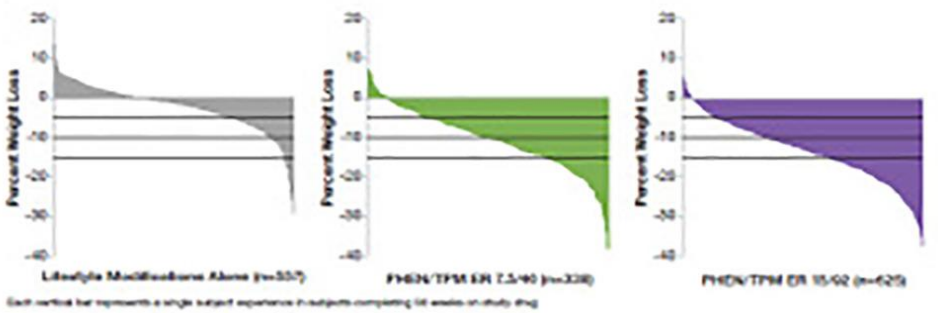
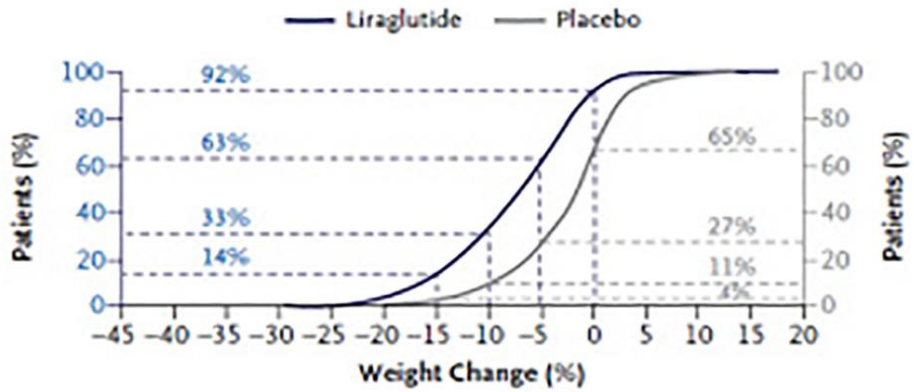
Individualized response to anti-obesity medications-why we need many different options

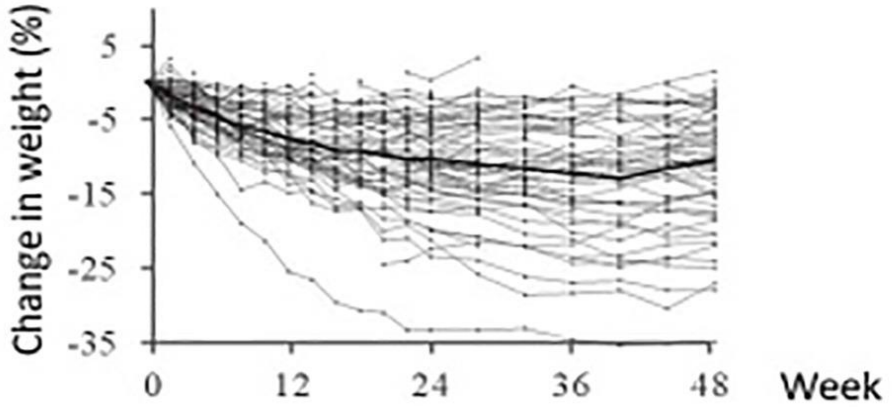


Placebo and Phentermine/Topiramate
McCullough PA, *et al.* Poster AANP 2013.

Naltexone/Bupropion (data shown for those who lost 5% at week 16)
Fujioka K, *et al.* IJO 2016; 40:1369-75



Placebo and Liraglutide 3.0 mg
Pi Sunyer X, *et al.* N Engl J Med 2015; 373:11-22.



Orlistat plus low-fat, reduced-calorie diet

Yancy et al. *Arch Intern Med* 2010;170:136–45

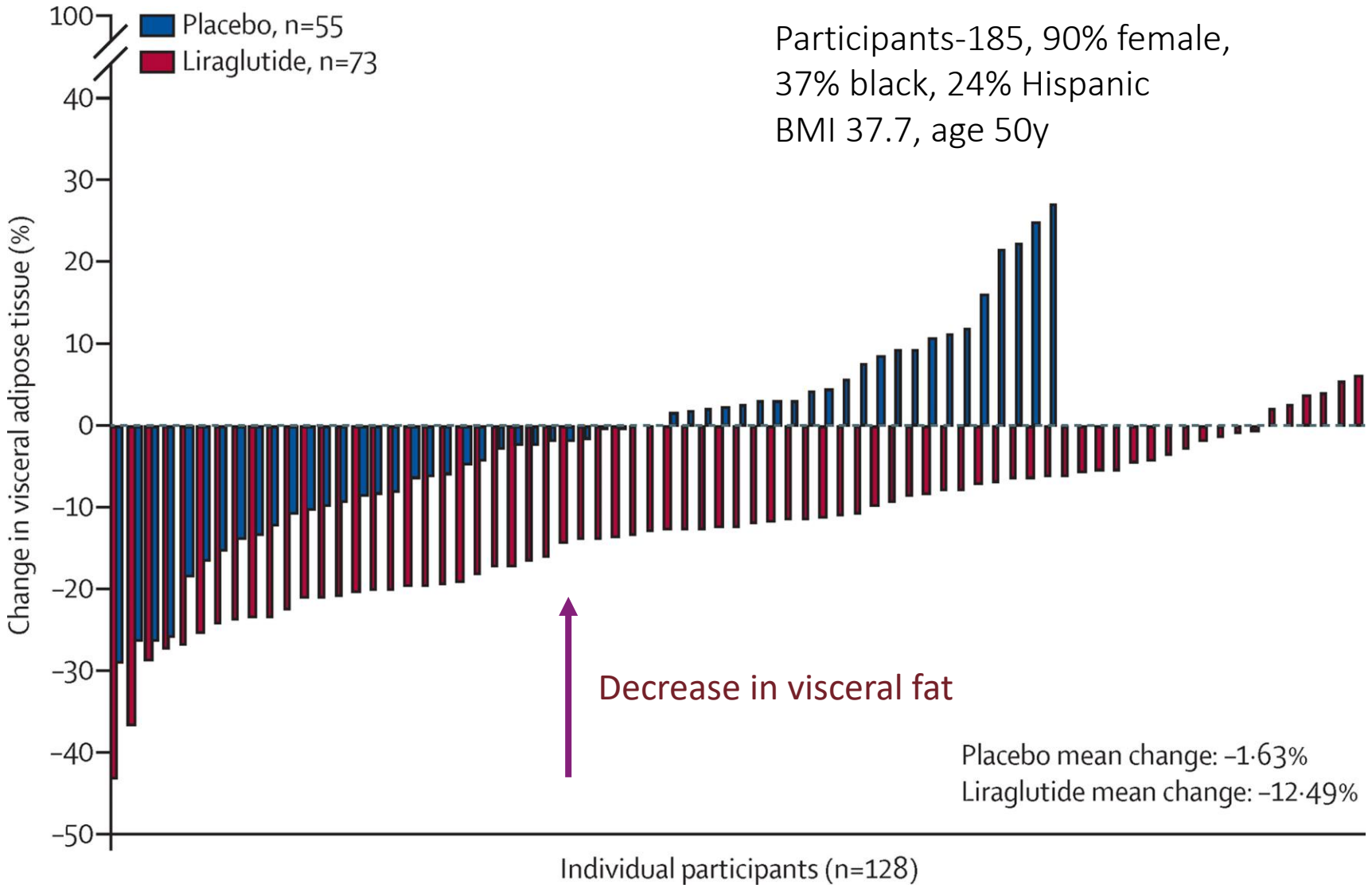
Diabetes, Obesity and Metabolism, Volume: 23, Issue: S1, Pages: 50-62, First published: 23 September 2020, DOI: (10.1111/dom.14200)

It’s not just about the pounds

Decrease in visceral fat leads to decrease in inflammation

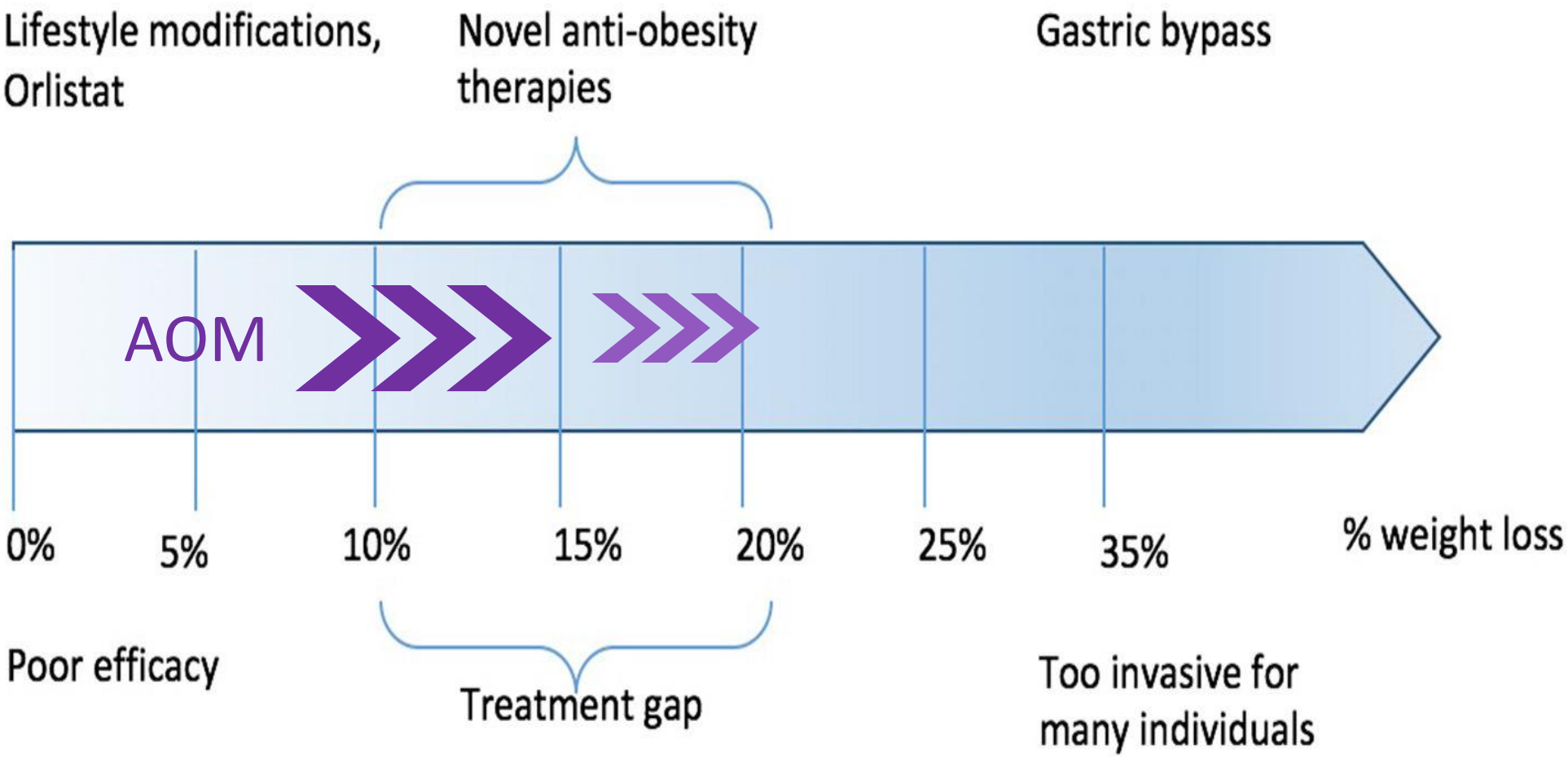
May be the reason for improved cardiovascular risks

Decrease in visceral fat with liraglutide 3.0 mg vs placebo over 40 weeks



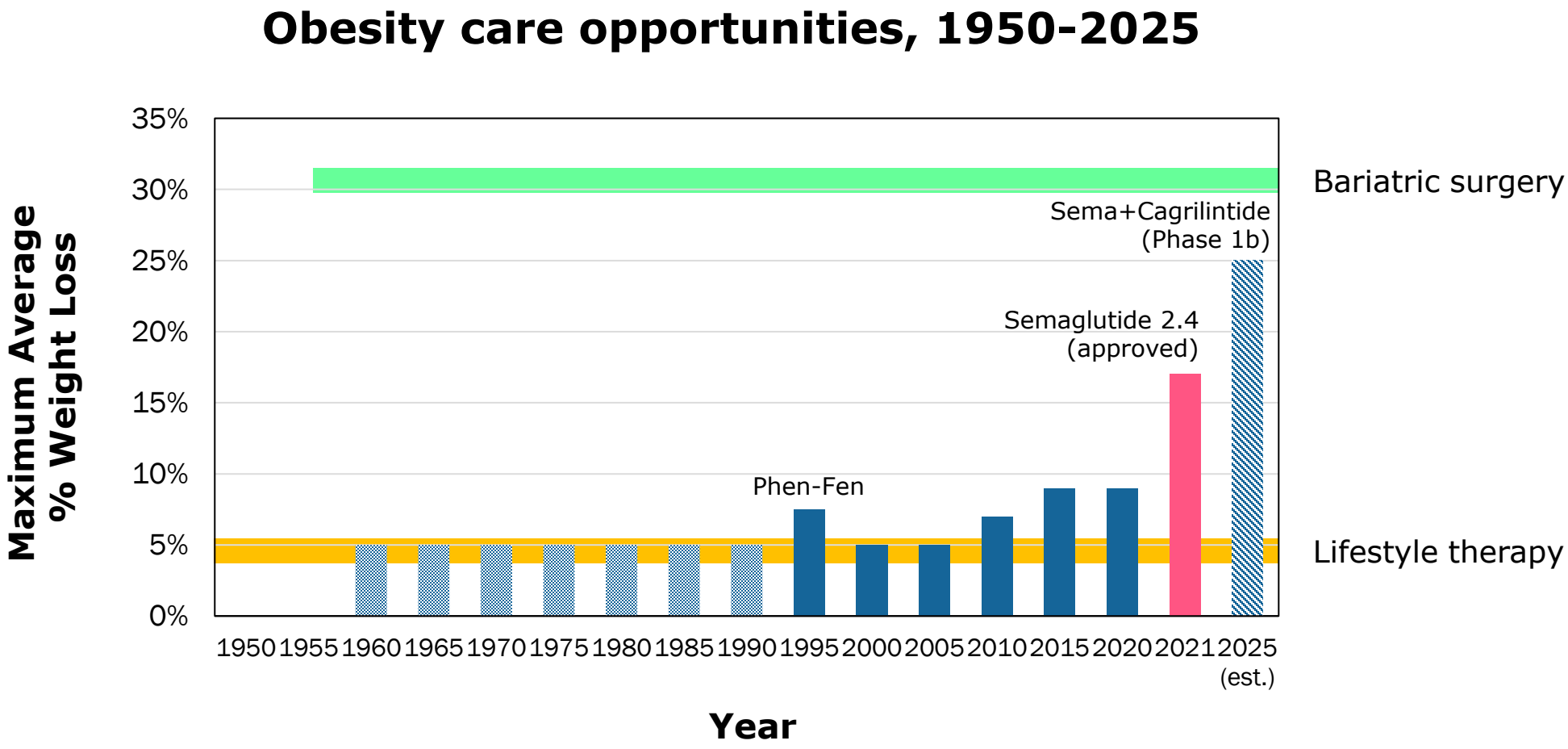
Neeland, I et al. The Lancet 9(9): 595-605, Sept 2021

Goal of Medical Therapy for the Treatment of Obesity-targeting physiology



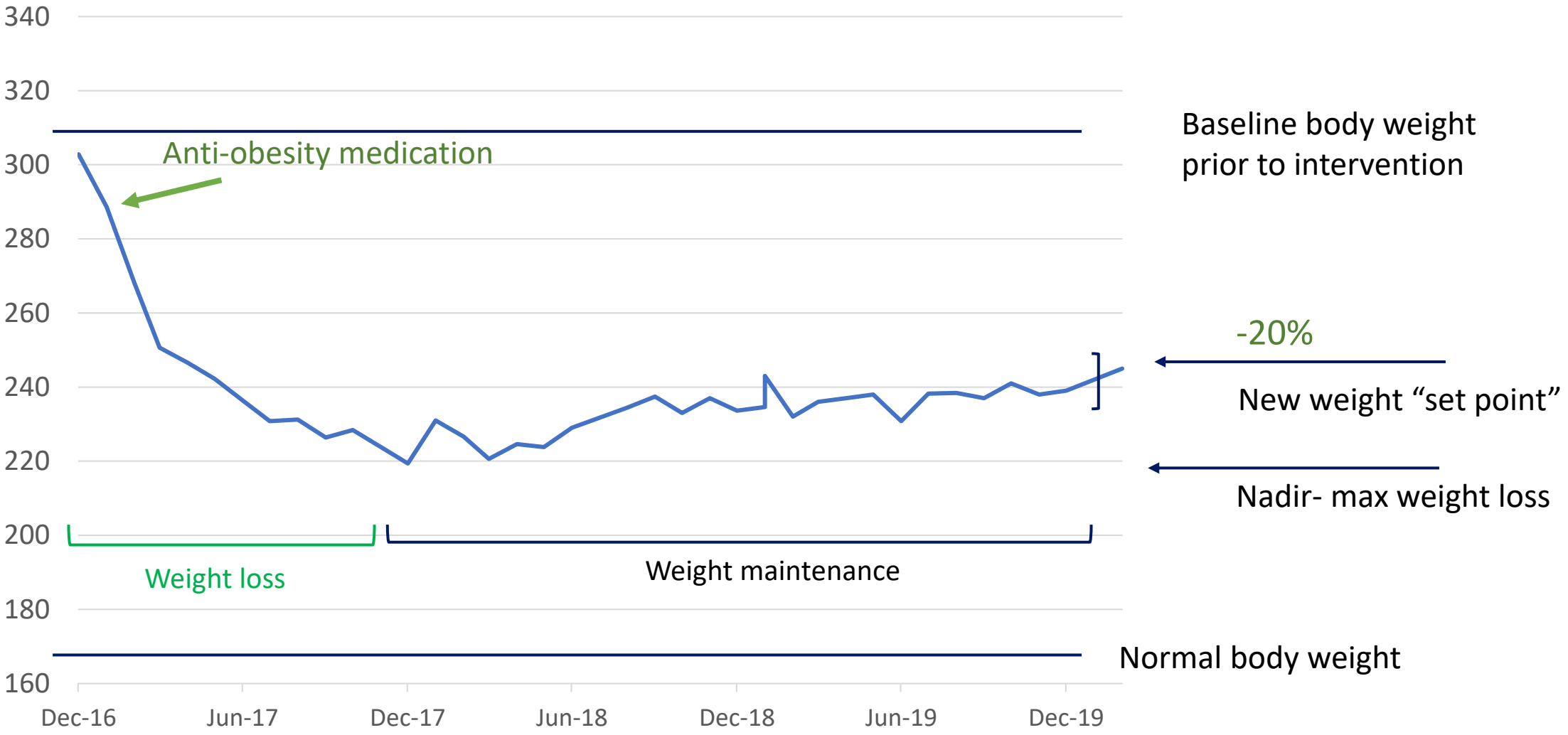
Adapted from: Hope D, Tan T, Bloom S. Front. Endocrinol., 15 August 2018 | https://doi.org/10.3389/fendo.2018.00442

Improving efficacy of anti-obesity medications-targeting new pathways

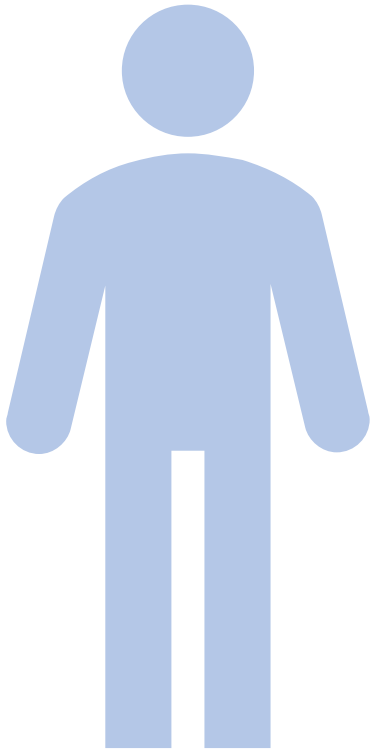


Courtesy of Lee Kaplan, MD

20% Weight Loss & Management with chronic use of AOM



Clinical case- John

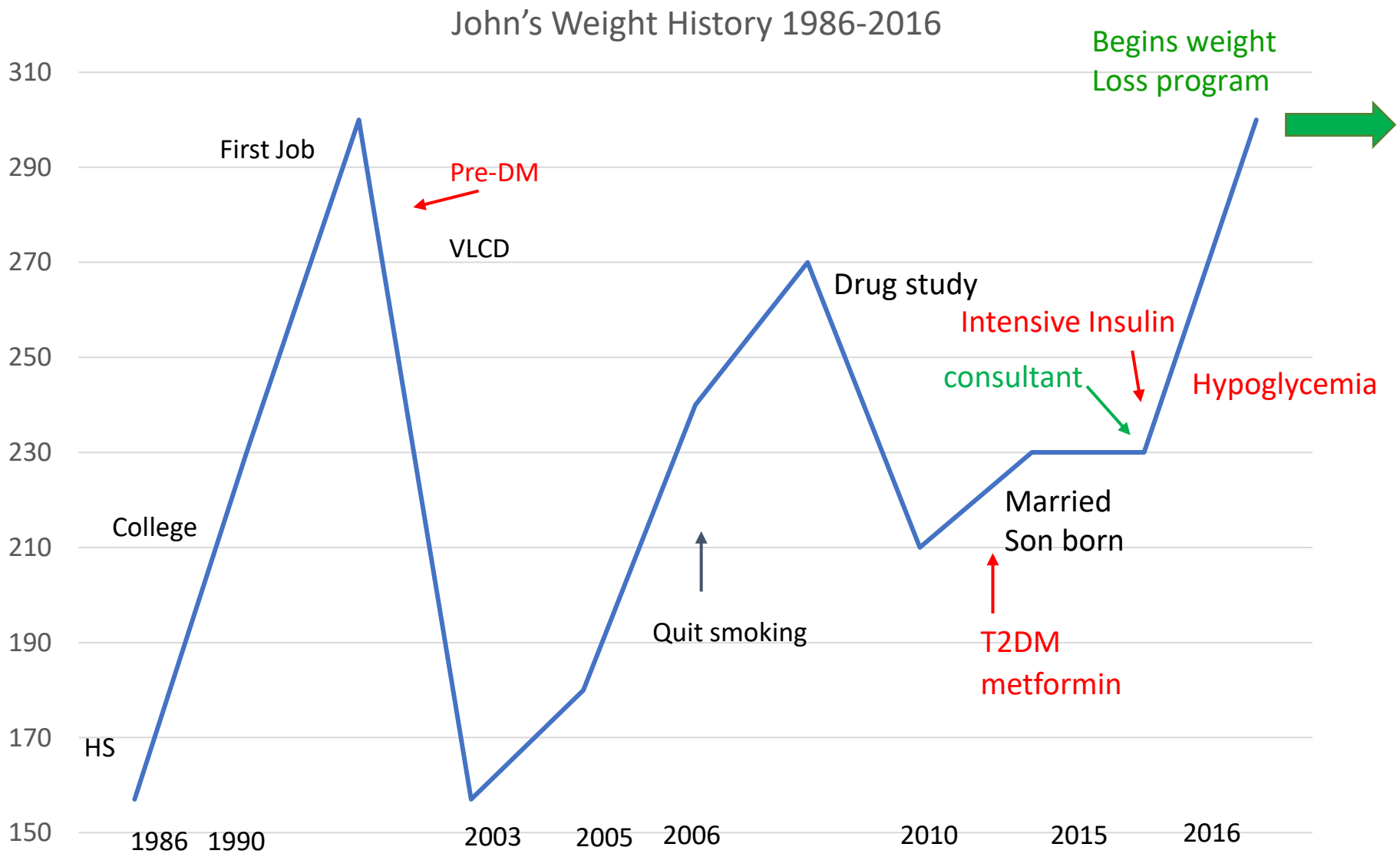


Name:	Sex:	Race:
John	Male	Caucasian
Age:	**BMI:**	**HbA_{1c}:**
49 years	43 kg/m^2	9.0

Notes- intensive insulin therapy x 6 months resulted in weight gain of 70 pounds

- Comorbidities: Type 2 diabetes x 5 years, hypertension, hyperlipidemia, hypogonadism, asthma, osteoarthritis pain esp knee, anxiety, insomnia/night-time waking, GERD, NAFLD
- Weight History: see chart Current Wt: 305 lb Ht: 5' 9" Edmonton Stage 3
- Medication: **Insulin degludec 320 units daily, insulin aspart at meals (15-20u+/meal),** metformin 2 gm a day; beta blocker for HTN and anxiety, clonazepam for anxiety (3 mg + day)
- Activity: sedentary, anxiety prevents him from going to studio (artist), IT consultant

What can we learn from a weight history?



Reference

Management-John

2016-2020

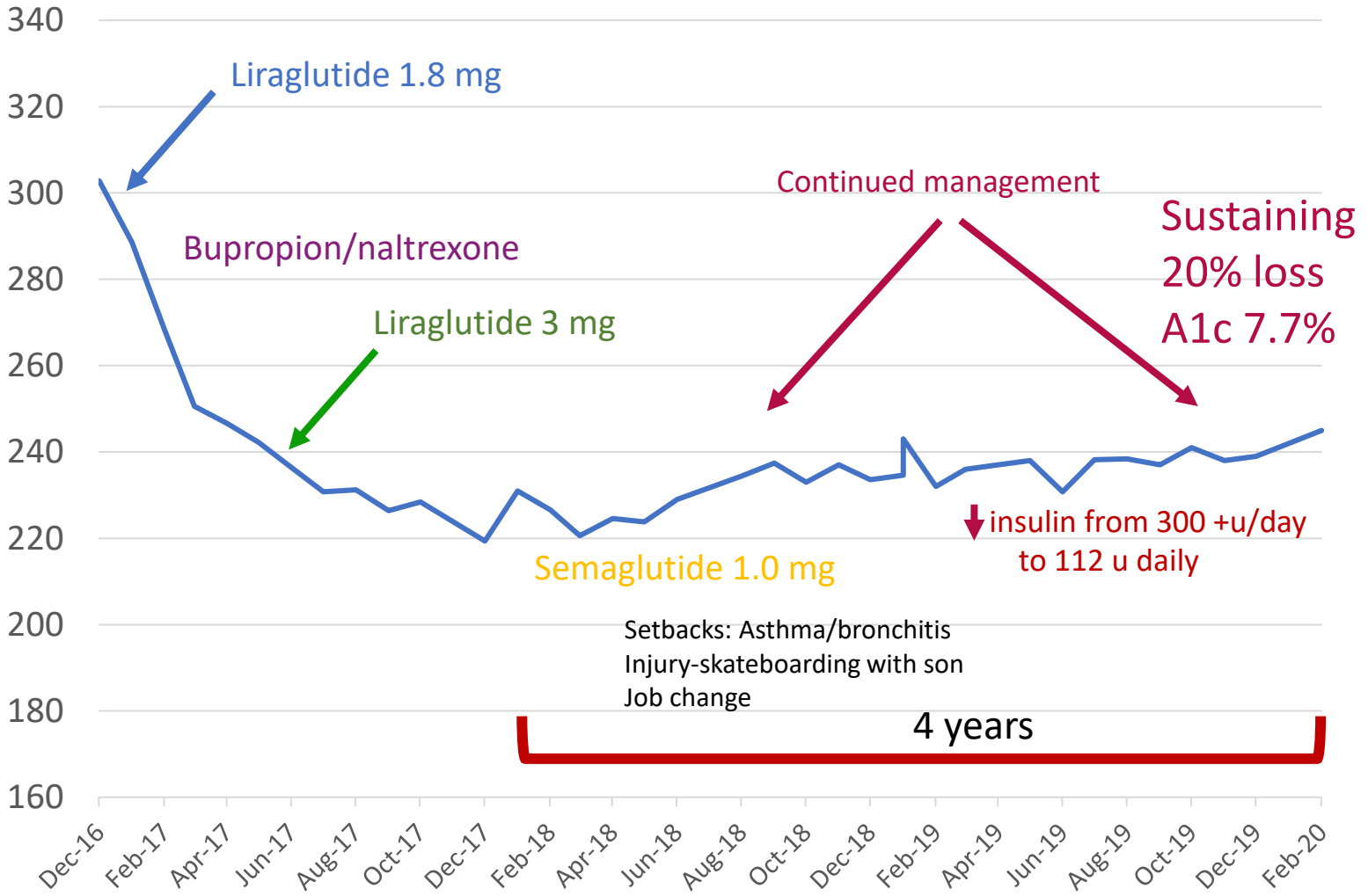
Goals:

- optimize blood glucose
- decrease total insulin load
- weight loss
- improve mobility /pain management/rx asthma
- Improve NAFLD
- manage anxiety

Anti-obesity medication to facilitate weight loss with lifestyle intervention

Pedometer/ physical therapy/activity

Anxiety/stress management



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Andrea, Clinical case

Name: Andrea

Sex: Female

Race: Black

Age: 47 years

BMI: 46 kg/m^2

HbA$_{1c}$: 5.9%

Notes

- Medical conditions: **Hypertension, prediabetes, chronic knee pain, insomnia, anxiety, back pain, peripheral neuropathy**
- Weight Hx: Not below 240 lbs since birth of son (1993), lost 30 pounds with WW and kept off for a year and regained
- Hates exercise; no exercise growing up
- Litigator, reports average stress
- Minimal meal planning, eats out, recognizes reward eating at the end of the day, cravings

Andrea- Management

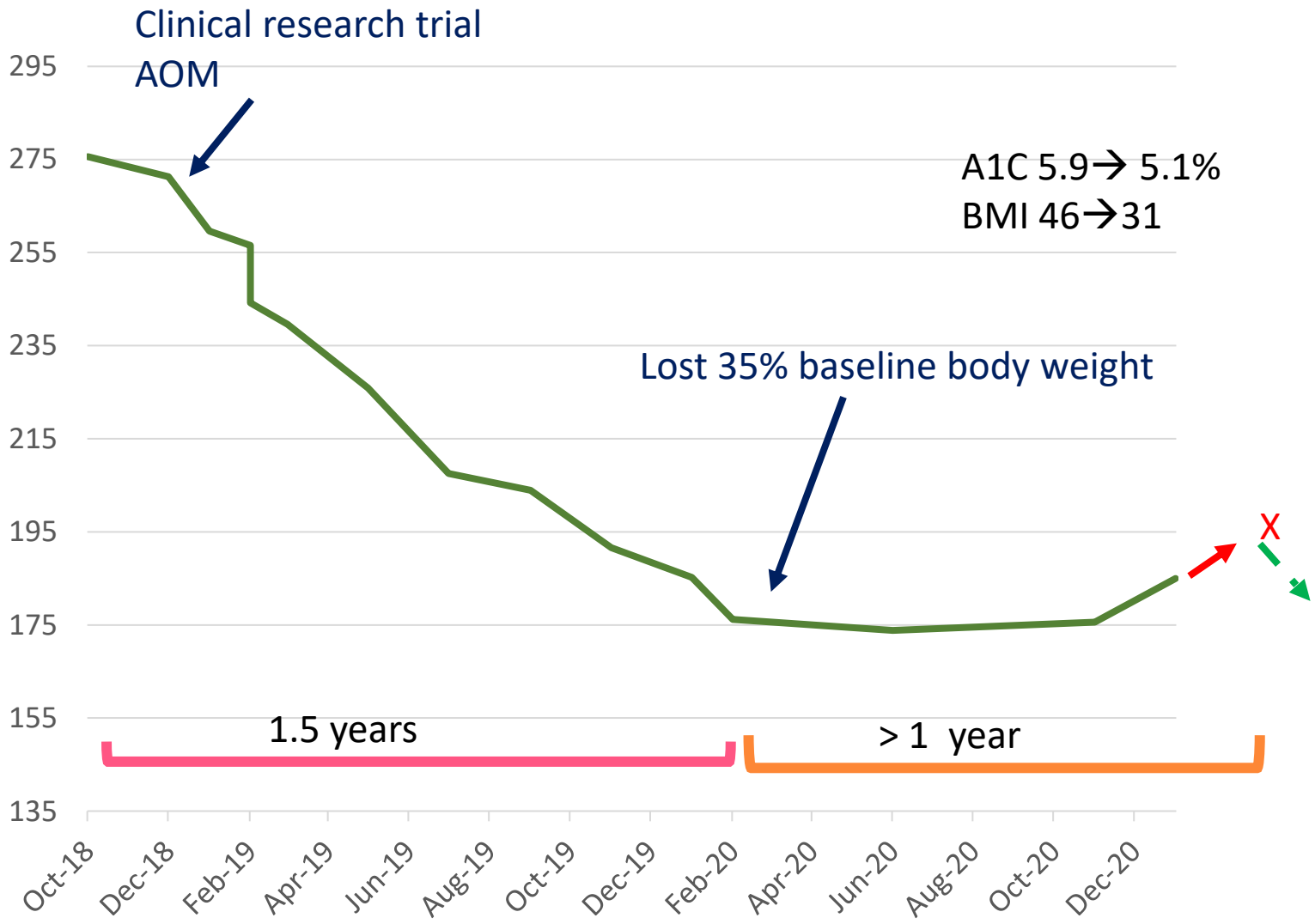
Goals:

- Weight loss
- Improve mobility / knee pain
- Normalize glucose (pre-diabetes→ normal)
- Help food management
- Manage cravings for sweets
- Improve BP

Knee pain improved, overall mobility improved, started at gym

X Off trial, started to regain weight, about 25 pounds

Started AOM, weight coming back down

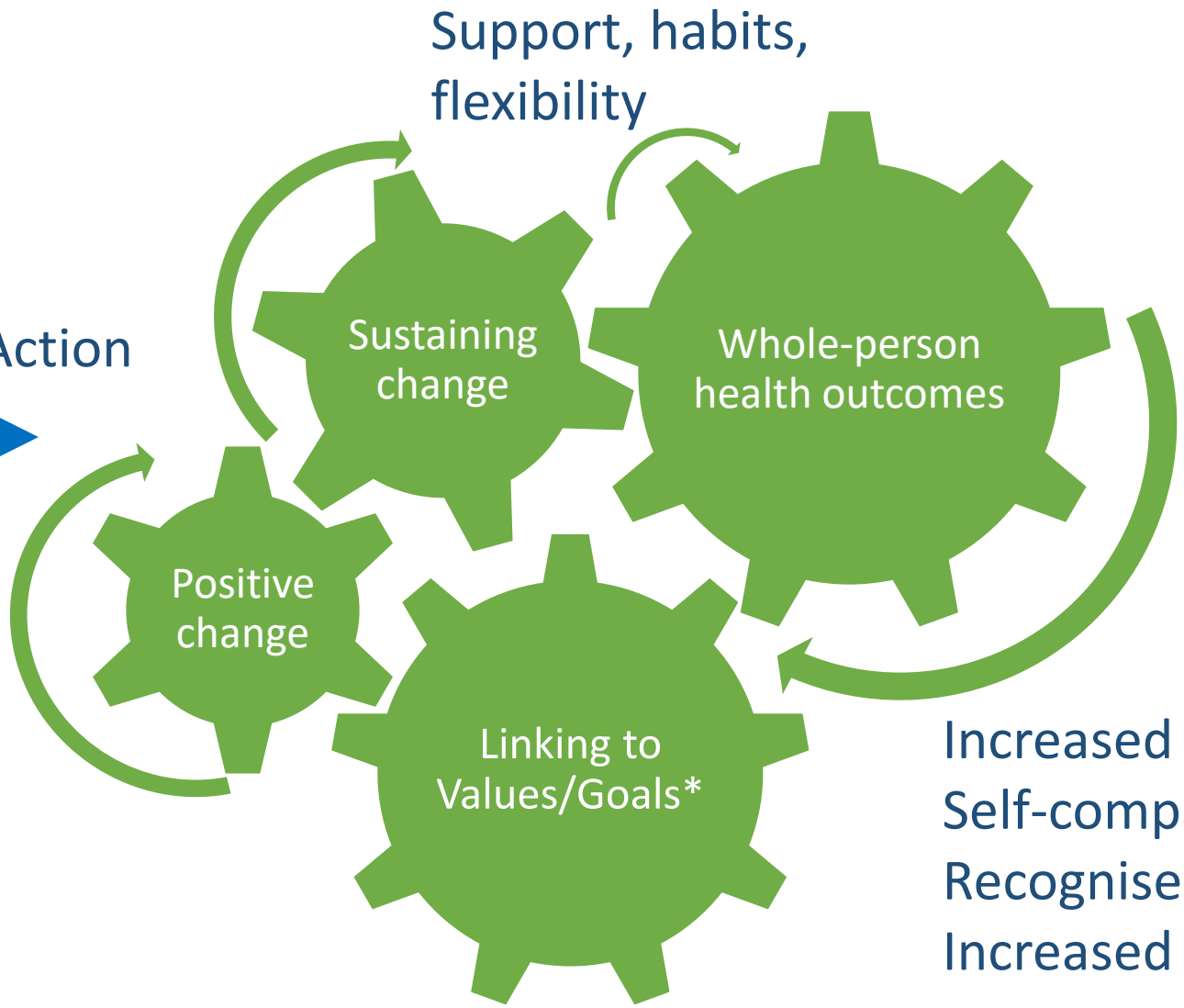


HOPE: A Critical Factor to Change

Anti-Obesity Medication

Action

Increase in activity, physical, social, action, new habits



Increased internal resources
Self-compassion/acceptance
Recognise own strengths
Increased emotional well-being

*Adapted from Luig T et al. *Clin Obes.* 2018;8:411–423.

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Conclusions

- Complex neurobiology protecting weight-driving hunger, appetite, decreasing satiety.
- Adaptations to metabolism, lowered resting metabolic rate and decrease calories burned for activity.
- Anti-obesity medication facilitates lifestyle changes by targeting neuroendocrine regulatory pathways moderating appetite, satiety, etc., it shifts physiologic “set point”.
- Heterogeneous, individual responses to all interventions for weight loss -need a variety of treatments

Questions?

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