Detailed Study Notes

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Introduction to this Episode

Obesity increases the risk of a range of chronic diseases and negative health outcomes. And trials where a sufficient amount of weight loss is achieved show health improvements. However, despite the "straightforward" nature of causing weight loss through a hypocaloric diet, it is clear that most people who lose weight will regain some or all of the weight.

This is a result of both the physiologic control of intake and expenditure (i.e. homeostatic regulation by the body to avoid staying at a lower body or fat mass), and environmental factors. Diet-induced weight loss is followed by a number of hormonal changes that encourage weight regain. So how do we tackle this problem?

In this episode, Dr. Priya Sumithran discusses this physiologic control of body mass, in addition to environmental and behavioral factors that make weight loss maintenance difficult. Dr. Sumithran also discusses what this means for setting weight loss targets, choosing the correct intervention, and looking to non-weight-centric approaches for certain individuals. We also discuss the evidence on GLP-1 receptor agonist drugs, such as Semaglutide, as a treatment for obesity.

Connection to Previous Episodes

- Danny and Alan went through the literature on weight loss maintenance in episode 352, titled 'Do Diets Even Work in the Long-term?'. This episode also gets into claims about "all diets fail".
- In episode 395, Danny interviewed renowned obesity researcher Prof. Carel Le Roux, where they discussed misconceptions people have about obesity, what treatment options are available, and what a more inclusive approach looks like.
- Obesity treatments and the issues of weight bias and weight stigma were the subject of conversation in episode 324, where Dr. Fatima Cody Stanford was the guest. This included the practical realities of obesity treatment, and how we can simultaneously accept that weight loss can have significant benefits while also not promoting positions that lead to weight stigma.
- In the current episode with Dr. Sumithran, reference was made to some of Prof. Roy Taylor's research showing weight loss lead to diabetes remission, as well as Taylor's concept of a "personal fat threshold". You can hear Prof. Taylor on the podcast in episode 331.

Body Mass Regulation

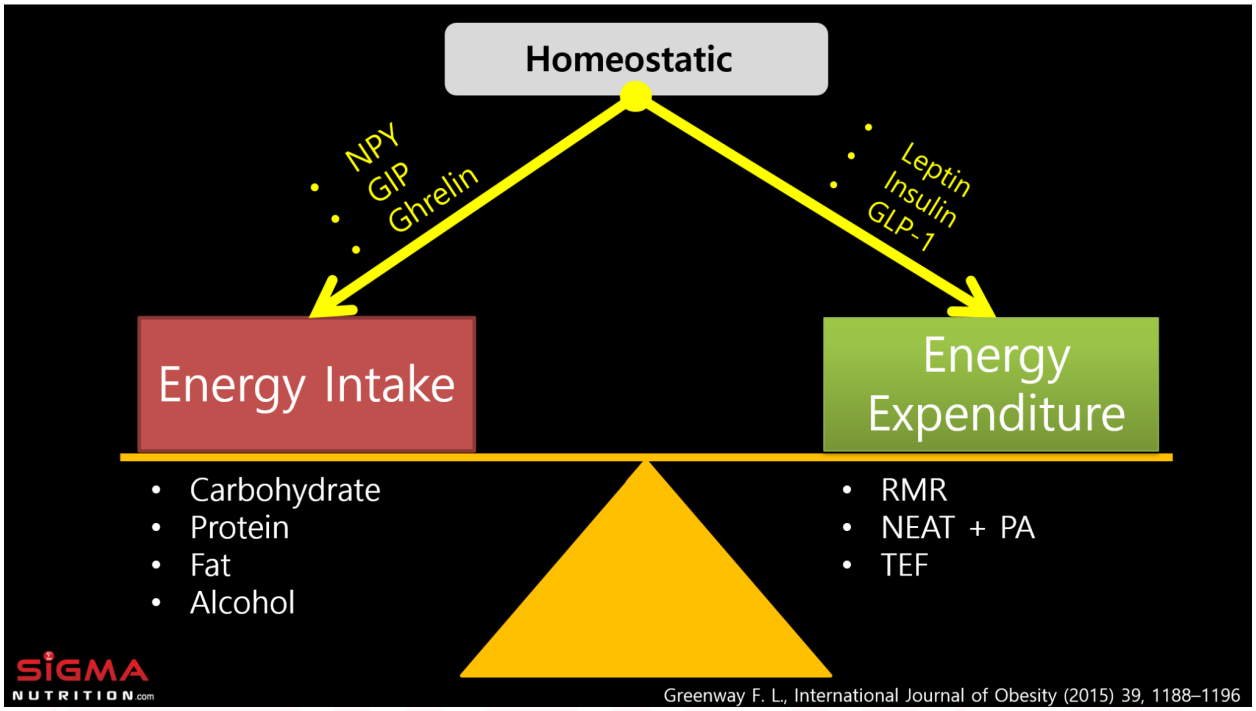
Despite the fact that we have a significant variation in our food intake from day to day, for most adults, body weight can remain remarkably stable over time.

> *"Energy intake and energy expenditure clearly do not correlate over a short period of time such as a day or two. Equally clearly, however, their correlation over an extended period of time, such as a week to a few months to years, is excellent"*
>
> - *Gropper, Smith & Groff, Advanced Nutrition and Human Metabolism, 6th Ed*.

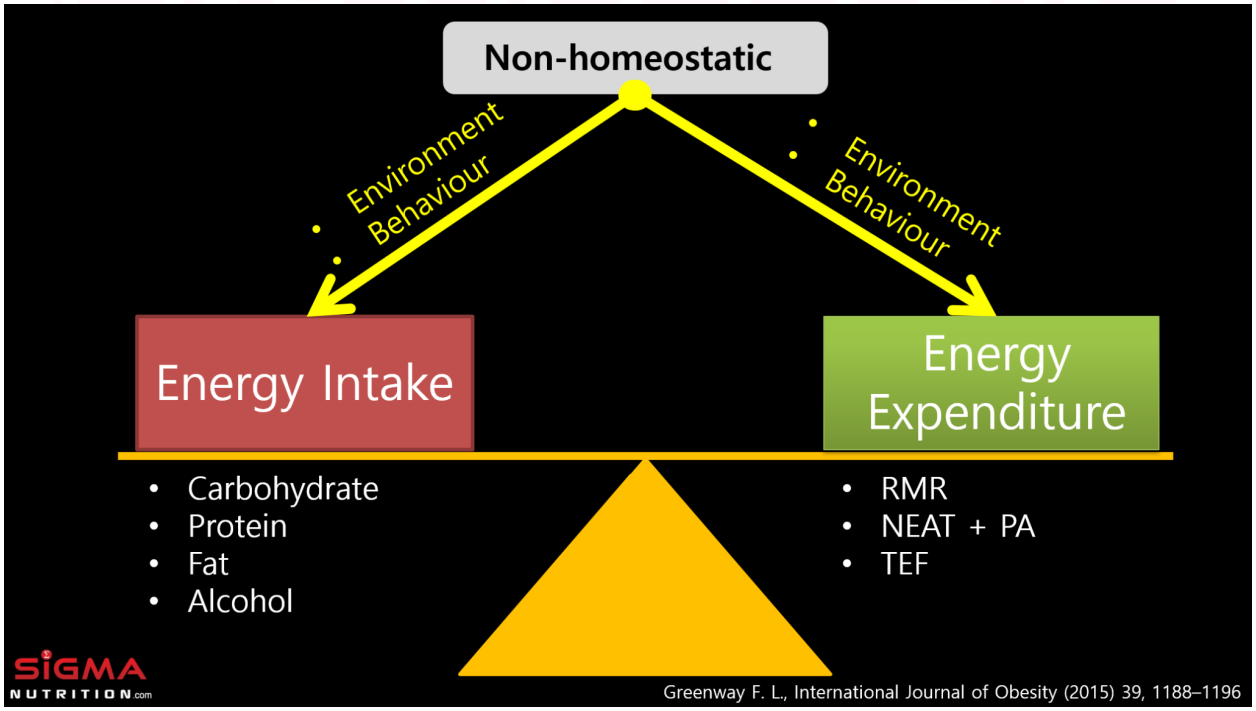
In this episode, Dr. Sumithran gave a really illustrative example of this tight matching up of intake and expenditure in humans:

> *"If you think about the fact that the average adult consumes about 1 million calories per year, and most of us maintain a fairly stable body weight for prolonged periods during our adult lives.*
>
> ***Even if we were to gain 2kg (4.4 lbs) every five years**, that would still indicate that we had matched that intake of a million calories a year with the same expenditure, with a **precision of around 0.2%** over that period of time.*
>
> *And yet, what we are eating and the activity that we are doing varies quite a lot for most of us from day to day. And while there are some people that are really into their fitness and their tracking, it's clear that most of us aren't calculating and matching that carefully, and we don't have to put a lot of effort into maintain stable weight if we are at our usual weight.*
>
> *So that indicates that there is a separate process that we aren't consciously controlling, that is maintaining that sort of stability. "*

This stability is a result of the physiologic regulation of energy intake and energy expenditure. There are many hormones involved in this process of maintaining homeostasis:



However, there are also other factors (the food environment, our behaviors/habits, etc.) than can "override" this homeostatic control, and influence energy intake and expenditure.



Images adapted from: Greenway F. L., International Journal of Obesity (2015) 39, 1188–1196

There are also clearly individual differences in the regulation of expenditure and intake, due to environmental factors, genetic factors, or potentially inflammation at the hypothalamus.

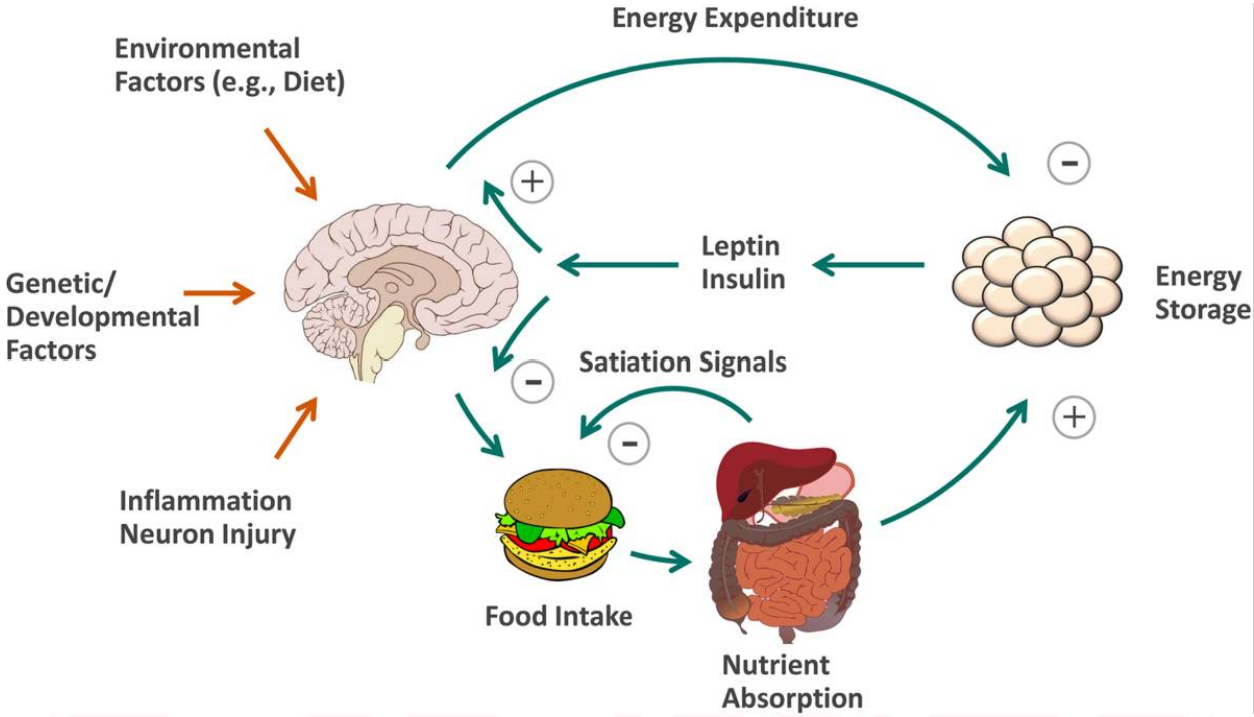


Image from: Guyenet & Schwartz, J Clin Endocrinol Metab. 2012 Mar; 97(3): 745–755

Models of Body Mass Regulation

Dr. Sumithran stated: *"From my interpretation of the bulk of the evidence, bearing in mind that there is a lot of conflicting information, I'm pretty convinced that there is a defense of a minimum amount of fat mass."*

Different models of body mass regulation have been proposed. Three of the most popular include:

1. Set Point Model
2. Settling Point Model
3. Dual Intervention Model

[Note: We did a full episode on these 3 models in episode 391. See this episode for a full detailed breakdown. Below we'll recap some key points]

Set-Point Model

- Lipostatic model- First advanced by Kennedy. - Metaphor of a thermostat - If you go above/below your set point, then processes kick in to bring you back.
- The set-point model is rooted in the idea that a feedback system controlling body weight or fatness requires a “reference level'' to base its response on.
- Then in the early 90s leptin is discovered. Commonly leptin is suggested as the input signal on the system is based, as leptin is secreted by fat cells and therefore leptin production increases with increasing fat mass.
- For people who have a high setpoint and therefore naturally carry a lot of body fat, it can be hard to lose fat because the brain resists weight loss attempts.
- Genes are part of what determines whether someone has a high or low setpoint.
- While there are many usual aspects to the model, some academics say that the set point model simply can’t be a *complete* explanation, given the current prevalence of obesity. And of course this is due to the fact that people’s body mass changes in response to non-biological drives such as lifestyle and behavior.

Settling Point Model

- The “settling point” model of body weight regulation is an explanation that relies solely on energy expenditure adaptations.
- Whereas the set point model assumes that both energy intake and expenditure are functions of body weight, the settling point model assumes that energy expenditure is an increasing function of body weight whereas energy intake is independent of weight
- Idea there is some passive feedback. Not a fixed point, but rather after losing mass and losing lean mass, you will eventually settle at a point where you reach energy balance. But then in cases where there is weight gain, there would be some increase in energy expenditure, and eventually there would be a settling at a level of new energy balance.
- The settling point model suggests that obesity is a result of factors that promote greater energy intake and/or lower energy expenditure (e.g. food environment, TV habits, access to healthy/unhealthy foods).
- When a calorie surplus occurs (intake exceeds expenditure), then fat mass will increase. But there will also be an increase in energy expenditure as weight increases.
- At a certain point, weight will plateau out and maintain as the elevated expenditure matches intake.
- If the settling point model were accurate, we would not expect to see any of the compensatory changes in energy intake/expenditure that occur in order to maintain energy balance – yet such changes are routinely observed.

- A review controlled feeding studies by Hall & Guo (2017) found that responses were more consistent with the set-point model rather than the settling point model.
- "Accurate measurements of energy intake in the laboratory have demonstrated that diet manipulations can lead to short-term compensatory changes in energy intake" … "However, these results cannot be readily extrapolated to the long time scales associated with regulation of human energy balance in the real world." - (see "Feedback Control of Energy Intake" section in this study)

Dual-intervention Point Model

- So as we observe metabolic adaptations to both undereating and overeating (or increasing/decreasing activity) but also observe that environmental and behavioral factors impact body mass, we need a model that accounts for both.
- One that has been suggested is the dual-intervention point model.
- This suggests that rather than there being a single set point, there are two "intervention points"; an upper and lower intervention point (see in graphic).
- These points have a "zone of indifference" between them, within which fat mass can change due to environmental factors. And only when fat mass passes beyond one of the intervention points, does the physiological feedback mechanisms cause body fat levels to come back into the zone of indifference.
- John Speakman has proposed the "drifty gene" hypothesis to explain the inter-individual variation in the upper intervention point.
- Some individuals have an elevated upper intervention point, caused by the change in evolutionary pressure, where humans no longer face a predation risk. This allowed the upper intervention point to "drift" upwards independently of the lower intervention point.
- Such individuals fail to compensate for positive energy balance in the same way as others as their upper intervention points are much higher than others.
- Others do respond appropriately (physiologically speaking) to weight gain via feedback mechanisms that cap their intake.

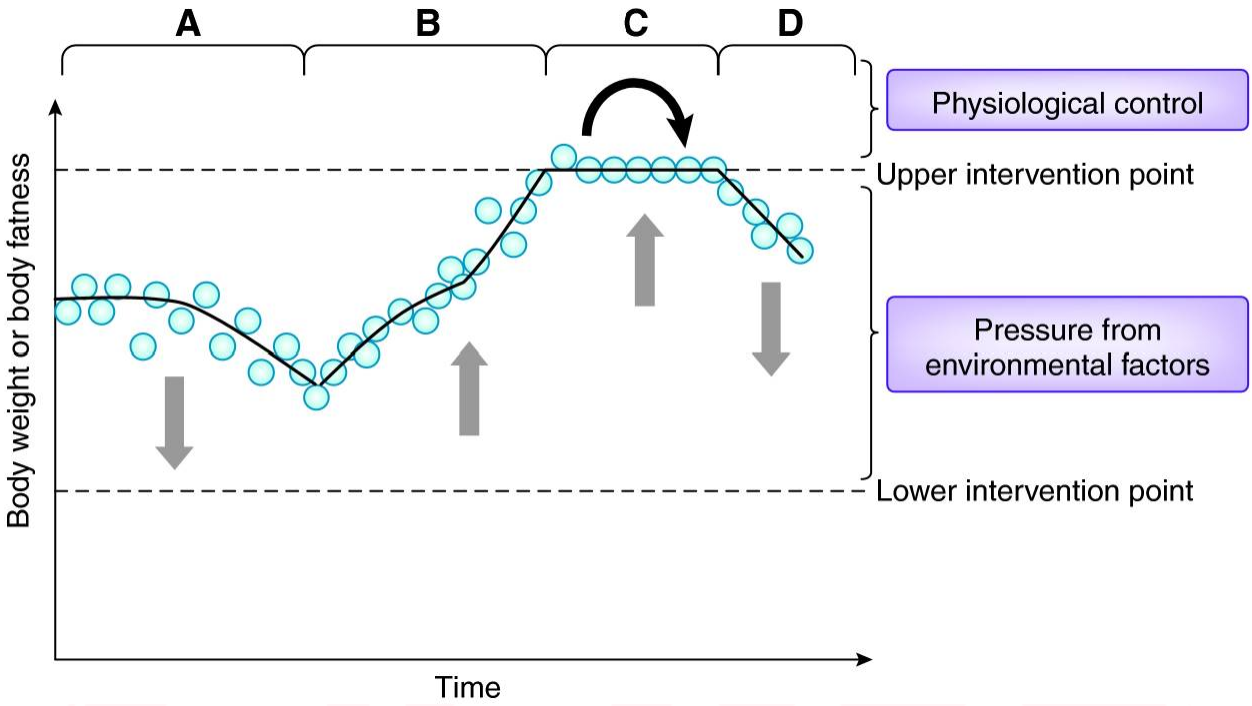


Image from: Speakman et al., Dis Model Mech. 2011 Nov;4(6):733-45.

Weight Loss in Obesity: Threshold of Benefits

- The benefits of weight loss on weight related complications start with really small amounts of weight loss.
- So even 3 - 5% weight loss (on average) shows benefits on:
    - Prevention of diabetes (in people who don't have diabetes)
    - Reduction in elevated triglycerides
    - Reduction in blood pressure
    - Improvements in blood glucose control in people who have diabetes.
- But progressive weight loss has progressive benefits, at least within the range of between ~5% to 25% weight loss.
    - As people lose more weight within that range, on average, there are greater benefits.
- So for example, things like preventing/treating non-alcoholic fatty liver disease (NAFLD), sleep apnea, etc. require about 10% weight loss or more.
- Similarly, remission of diabetes in people who have early diabetes takes at least 10 to 15% weight loss on average.

- Quality of life improves even with 5% to 10% weight loss, but on average QoL improves more with greater weight loss.
- In the episode, I (Danny) reference a review by Tahrani & Morton (2022) titled *'Benefits of weight loss of 10% or more in patients with overweight or obesity: A review'.*

Targets for Weight Loss: Potential Issues

- Having targets or goals can be an important part of clinical practice, especially when a certain health outcome due to weight loss is being targeted.
- But there a number of important questions about the ethics and implications of setting certain targets.
    - Are targets being set unrealistic?
    - What are the ethics of setting weight loss targets?
- Dr. Sumithran mentioned a recent debate on this topic at the 2022 International Congress of Obesity.
- In the episode Dr. Sumithran said she thought that a weight loss target can never be the only goal because it's far more important to understand the *why*; i.e. asking "Why are you needing to lose weight? Why do you want to lose weight? What will you be wanting to achieve out of the weight?"
    - These are important questions to ask because those things might be achievable even without a weight target.
- So it's important not to just set a goal for the sake of getting to a particular number.
- When people hear that a BMI of 20 - 25 is the "healthy" range, this can have the unintended consequence of them then thinking that: a) in order to be healthy, one must have a BMI in this range, and/or b) having a BMI in this means you are healthy. And neither of these things is completely true at an individual level.
- So setting a goal of getting to a BMI under 25 may be both unnecessary or even problematic, given the difficulty for many in achieving and maintaining that. So instead it's likely better to focus on outcomes that they should care about (blood pressure, blood glucose, LDL-C, etc.).

BMI vs. Health Outcomes: Disconnect at Individual Level

- As an example of where BMI doesn't always align with a health outcome on an individual, we mentioned some of Roy Taylor's work on weight loss and diabetes remission.
- The image below shows three individuals, demonstrating their relative positions within the population BMI distribution:
    - One is living with obesity
    - One is overweight
    - One is of "normal"weight
- Each individual lost 15kg of body weight (indicated by the blue arrow, showing their BMI move from the original red dot to the lower BMI of the blue dot).
- This weight loss lead to their glucose tolerance normalising, which was the goal health outcome.
- However, if we look at their BMIs, after weight loss they are each still within the same BMI group they started in (e.g. participant on the right is still in the obesity category).

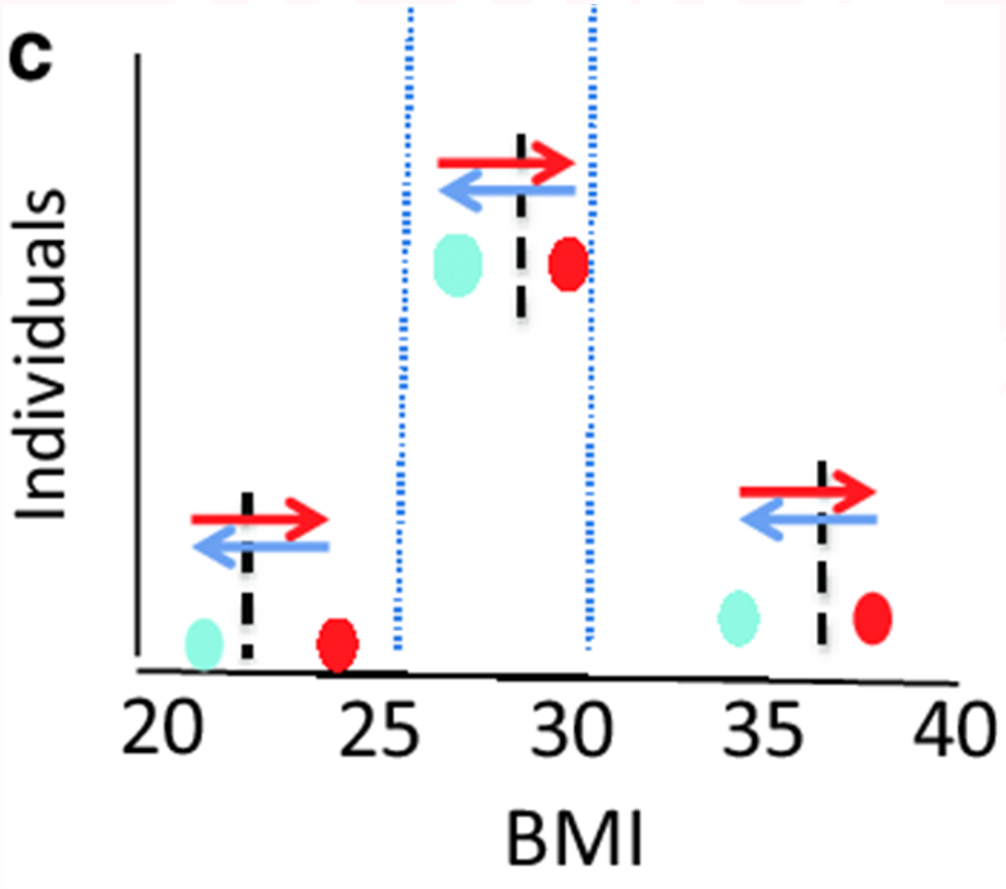


Image from: Zhyzhneuskaya & Taylor, Obesity and Type 2 Diabetes, In: Obesity, pg 195-226.

GLP-1 Receptor Agonist Drugs

- GLP-1 is a hormone that our gut normally produces that increases satiety, slows down gastric emptying, and stimulates the pancreas to produce some extra insulin if our blood glucose levels are getting elevated.
- There are a large number of these gut hormones: GLP-1, GIP, amylin (a pancreatic hormone).
- Recent drug developments that show great promise for obesity treatment are based on these gut hormones.
- The GLP-1 receptor agonists have been on the market for around 20 years, primarily as a diabetes drug.
- Several GLP-1 receptor agonists are approved for use in type 2 diabetes: exenatide, liraglutide, lixisenatide, dulaglutide, and semaglutide.
- All are administered as subcutaneous injections, although oral semaglutide is available. We started off with ones that you had to take twice a day and then once a day and now once a week.
- Semaglutide is the most recent GLP-1 receptor agonist that has been marketed for treatment of obesity or long term weight management (in people without diabetes).
- So when they're tested for the management of weight in people without diabetes a medication like Semaglutide at the dose that's used for weight management would result on average in about 12 to 15% weight loss.
- As an example, a phase 3 trial called STEP 1 (Wilding et al., 2021) evaluated the use of once per week semaglutide (2.4 mg subcutaneously) in adults with obesity or overweight, who did not have diabetes.
    - The mean reduction in body weight after 68 weeks was 14.9% in the semaglutide group versus 2.4% with placebo.
        - The estimated treatment difference was 12.4% (95% CI 11.5–13.4) or 12.7 kg (95% CI 11.7–13.7).
- There are responders and non-responders, but on average the weight loss is around two to three times greater mean weight loss compared with the medications we've had to date.
- Currently, it seems likely that this treatment would need to be continued long-term in order to maintain the weight loss.

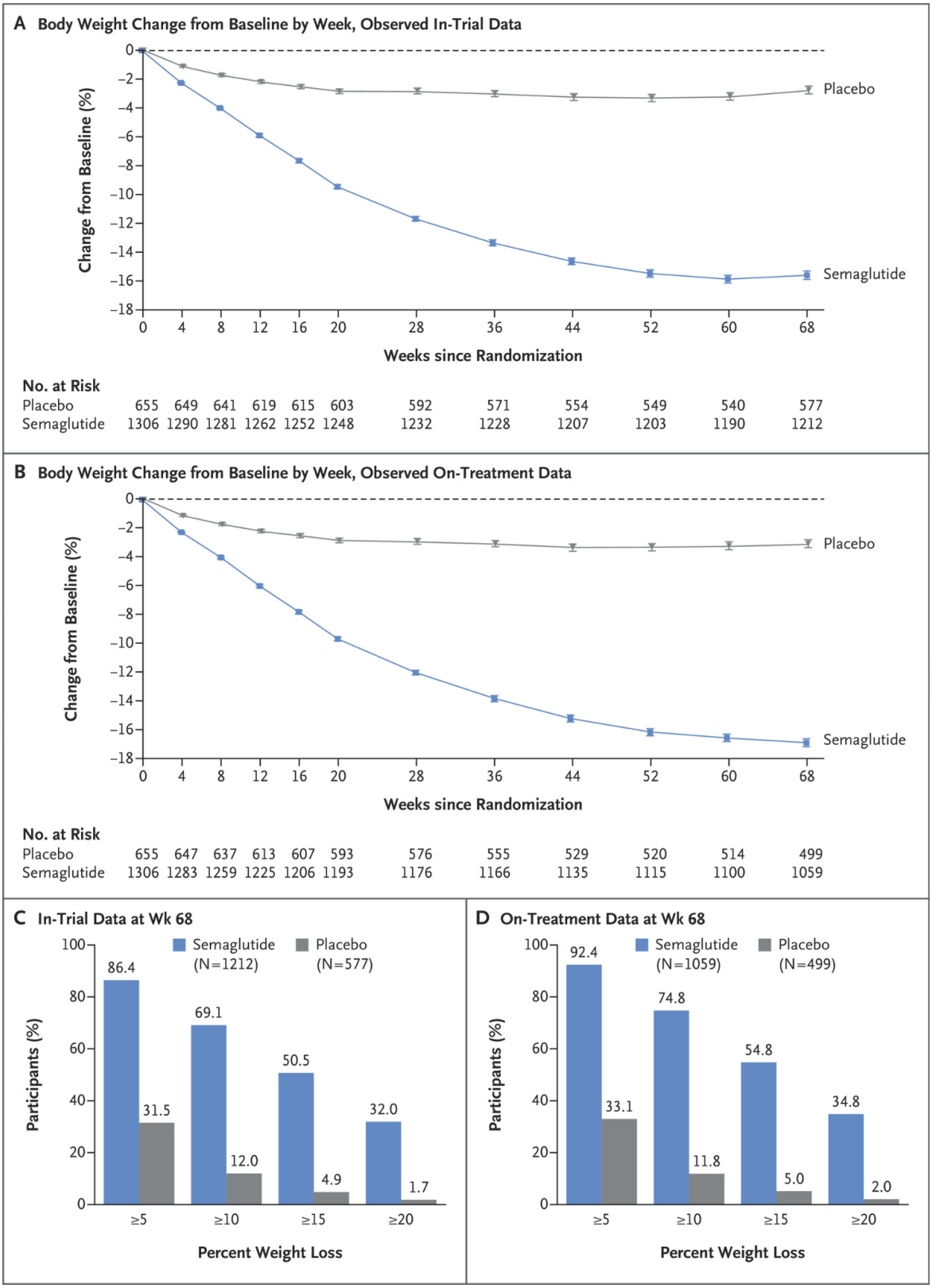


Image from: [Wilding et al., N Engl J Med. 2021 Mar 18;384(11):989-1002.]