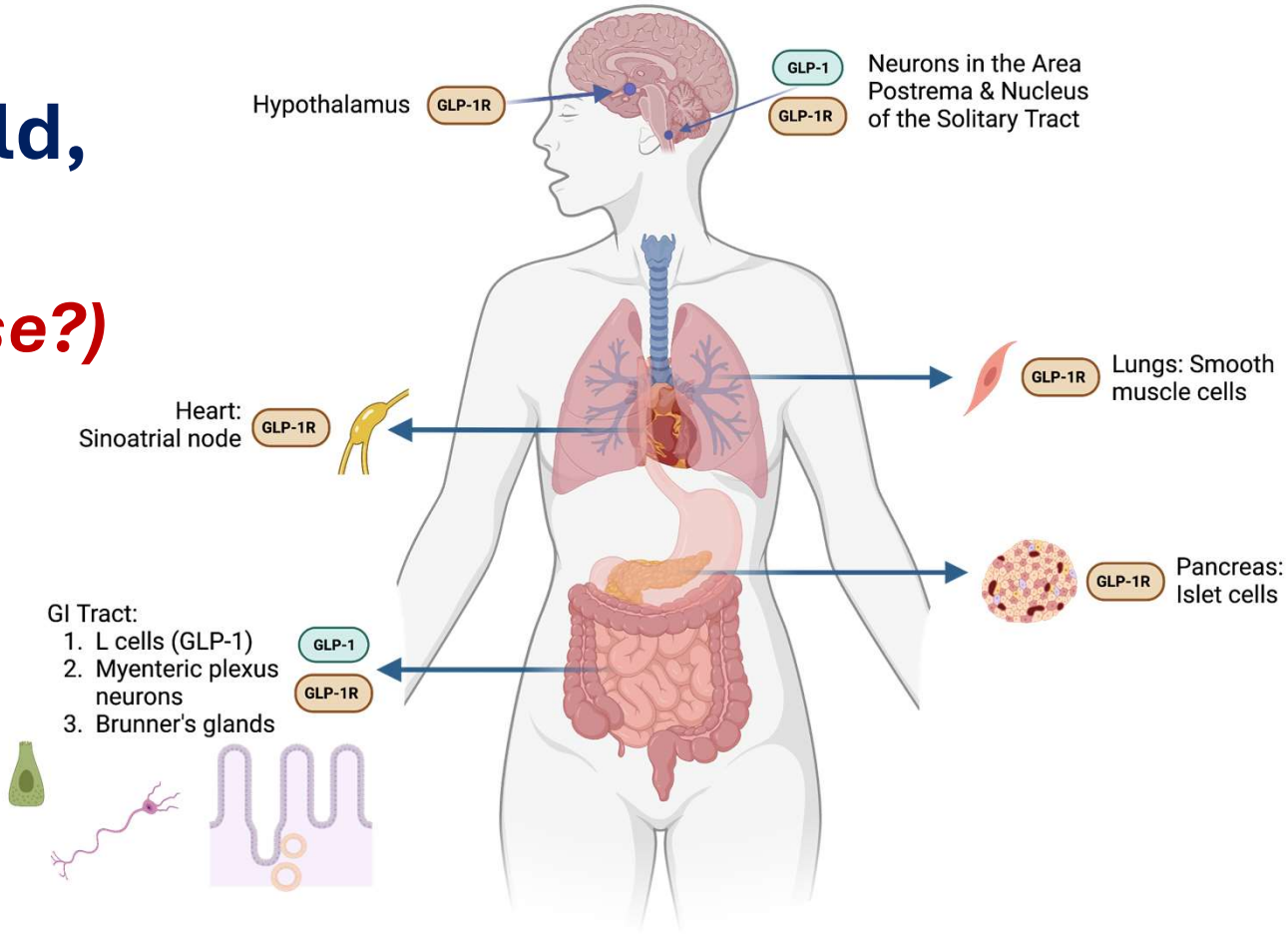
Institute of Metabolic Science

MRC Metabolic Diseases Unit

UNIVERSITY OF CAMBRIDGE

In a ‘post-Ozempic’ world, have we cured obesity?

(& what is the role of cheese?)



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Biotechnology and Biological Sciences Research Council

The NEW ENGLAND JOURNAL of MEDICINE

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Once-Weekly Semaglutide in Adults with Overweight or Obesity

John P.H. Wilding, D.M., Rachel L. Batterham, M.B., B.S., Ph.D., Salvatore Calanna, Ph.D., Melanie Davies, M.D., Luc F. Van Gaal, M.D., Ph.D., Ildiko Lingvay, M.D., M.P.H., M.S.C.S., Barbara M. McGowan, M.D., Ph.D., Julio Rosenstock, M.D., Marie T.D. Tran, M.D., Ph.D., Thomas A. Wadden, Ph.D., Sean Wharton, M.D., Pharm.D., Koutaro Yokote, M.D., Ph.D., Niels Zeuthen, M.Sc., and Robert F. Kushner, M.D., for the STEP 1 Study Group*

Received: 9 September 2022 | Revised: 9 November 2022 | Accepted: 16 November 2022

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Obesity A Research Journal | THE OBESITY SOCIETY | WILEY

ORIGINAL ARTICLE

Clinical Trials and Investigations

Two-year effect of semaglutide 2.4 mg on control of eating in adults with overweight/obesity: STEP 5

Sean Wharton[1] | Rachel L. Batterham[2,3,4] | Meena Bhatta[5] | Silvio Buscemi[6,7] | Louise N. Christensen[5] | Juan P. Frias[8] | Esteban Jódar[9,10] | Kristian Kandler[5] | Georgia Rigas[11] | Thomas A. Wadden[12] | W. Timothy Garvey[13]

Some vital statistics:

There are 1 billion people in the world with obesity

~ 1 in 8 Americans are on GLP1 medications

~ 1.5 – 2.5 million people in the UK are on GLP1 medications

In the UK (with an NHS), 95% of people are taking it privately

Whenever I speak about these weight loss drugs,
I am consistently asked 3 questions:

1. **Should we be treating obesity with drugs?**

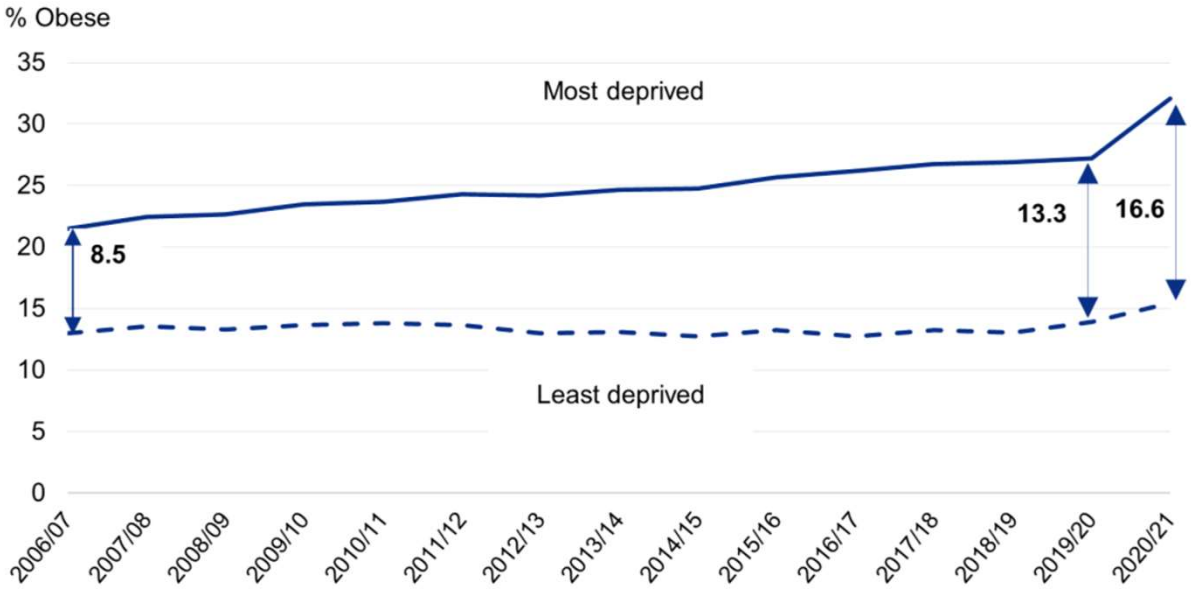
2. **Aren't these drugs a *short-cut* that don't tackle the *root cause* of obesity?**

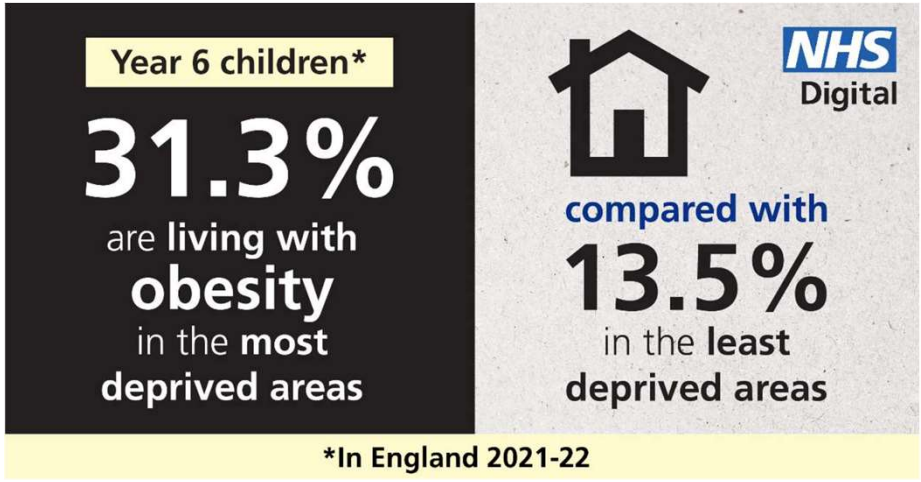
3. **Won't the weight come back on when you stop taking the drug?**

1. Should we be treating obesity with drugs?

Inherent in this question is the assumption
that there is a ‘morality’ to obesity;
that it is a choice.

Obesity rates in English children 10-11y





https://digital.nhs.uk/data-and-information/publications/statistical/national-child-measurement-programme

What has driven up rates of obesity?

Changes in environment

Changes in behaviour

Built environment

Food environment

Why is there a huge variation in body-weight?

Differences in genes & biology

(heritability of body-weight 40% - 70%)

Genetics of body-weight =

Biology of brain influencing feeding behaviour

Obesity is a consequence of those with susceptible genes meeting a permissive (risky? Unhealthy?) environment

The lower down the socio-economic ladder, the more permissive the environment

Thus prevalence of obesity is nearly twice as prevalent in the poorest in society.

Are we medicalizing obesity?

What is the definition obesity?

Carrying too much fat that it begins to influence your health.

Should we treat obesity?

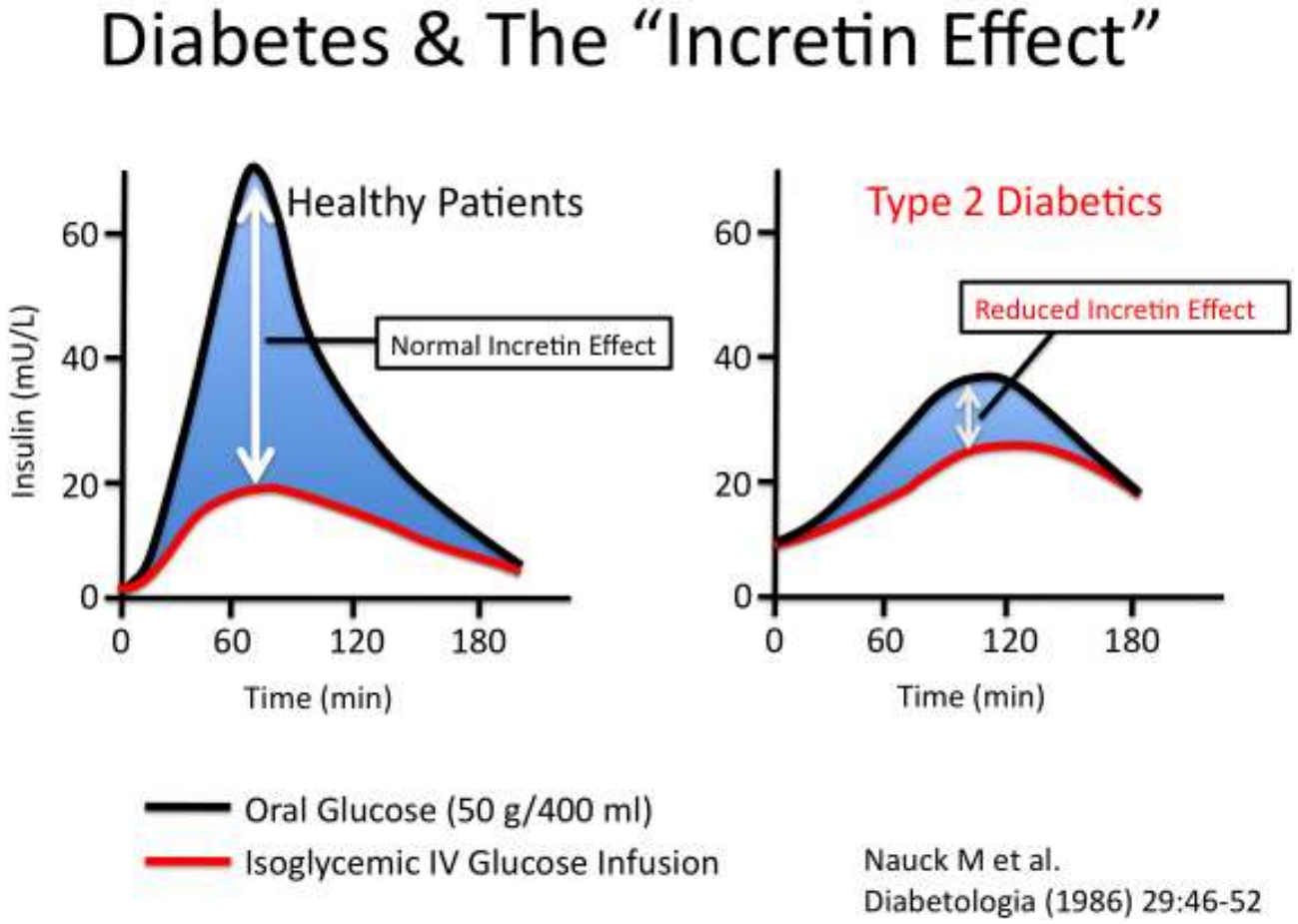
Do we ask this about literally any other disease?

High blood pressure? Arthritis? Cancer?

Obesity is a disease and should be treated like any other

2. Aren’t these drugs a *short-cut* that don’t tackle the *root cause* of obesity?

Glucose-dependent insulinotropic polypeptide (GIP) & glucagon-like peptide-1 (GLP-1).



The saliva of the Gila monster contains exendin-4, a structural analogue of human GLP-1, but with a much longer half-life.

Semaglutide
GLP-1R monoagonist
Ozempic/Wegovy
(Novo Nordisk)

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Tirzepatide - GLP1R/GIPR dual agonist

Mounjaro/Zepbound *(Eli Lilly)*

The NEW ENGLAND JOURNAL of MEDICINE

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Tirzepatide Once Weekly for the Treatment of Obesity

Ania M. Jastreboff, M.D., Ph.D., Louis J. Aronne, M.D., Nadia N. Ahmad, M.D., M.P.H., Sean Wharton, M.D., Pharm.D., Lisa Connery, M.D., Breno Alves, M.D., Arihiro Kiyosue, M.D., Ph.D., Shuyu Zhang, M.S., Bing Liu, Ph.D., Mathijs C. Bunck, M.D., Ph.D., and Adam Stefanski, M.D., Ph.D., for the SURMOUNT-1 Investigators*

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Health

Highly effective weight-loss drug Zepbound approved in the US and UK

A drug called tirzepatide and sold under the name Zepbound has been approved in the US and the UK for use as a weight-loss medication

By Grace Wade

9 November 2023

These drugs mimic natural hormones

In fact, you might consider some people with obesity to be deficient in these hormones

So I don’t think they are a short-cut

How about these drugs not tackling the ROOT cause of obesity?

Completely TRUE

With the exception of vaccines,
most drugs are not designed to PREVENT disease.

Obesity is a consequence of those with susceptible genes
meeting a permissive (risky? Unhealthy?) environment

The lower down the socio-economic ladder, the more permissive the environment
Thus prevalence of obesity is nearly twice as prevalent in the poorest in society.

You need the right tool for the job.

Drugs to treat obesity,
Public health measures, legislation, education
to PREVENT obesity

3. Won’t the weight come back on when you stop taking the drug?

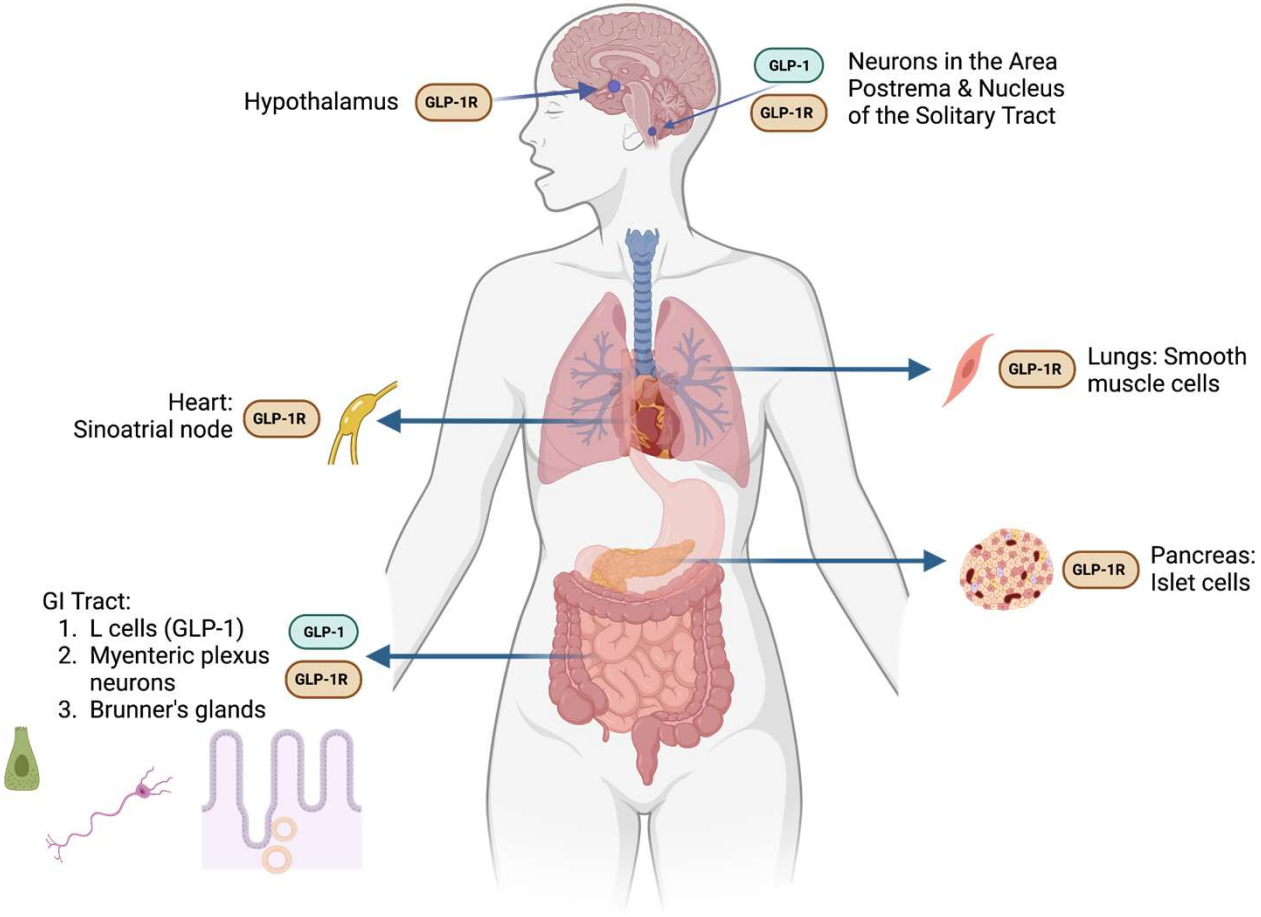
YES!.....

..... like most other drugs

High blood pressure medications

These are drugs, not cosmetic tools.

As with all drugs, there are side effects.



Incretin specific side-effects

Nausea

Diarrhoea

Constipation

Reduced alcohol/smoking??

Side-effects due to rapid weight loss

Loss of lean-mass

Pancreatitis/Gall stones

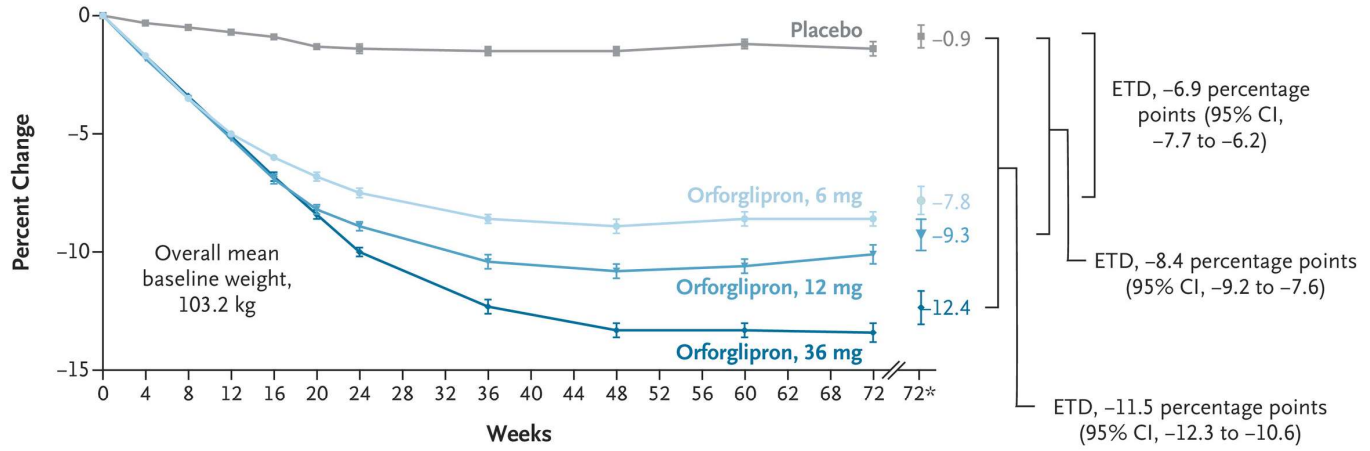
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Orforglipron, an Oral Small-Molecule GLP-1 Receptor Agonist for Obesity Treatment

Sean Wharton, M.D.,[1-3] Louis J. Aronne, M.D.,[4] Adam Stefanski, M.D., Ph.D.,[5] Nasreen F. Alfaris, M.D., M.P.H.,[6] Andreea Ciudin, M.D., Ph.D.,[7-11] Koutaro Yokote, M.D., Ph.D.,[12] Bruno Halpern, M.D., Ph.D.,[13] Alpana P. Shukla, M.D.,[4] Chunmei Zhou, M.S.,[5] Lisa Macpherson, M.S.P.H.,[5] Sheryl E. Allen, M.D.,[5] Nadia N. Ahmad, M.D., M.P.H.,[5] and Suzanne R. Klise, B.S.,[5] for the ATTAIN-1 Trial Investigators*

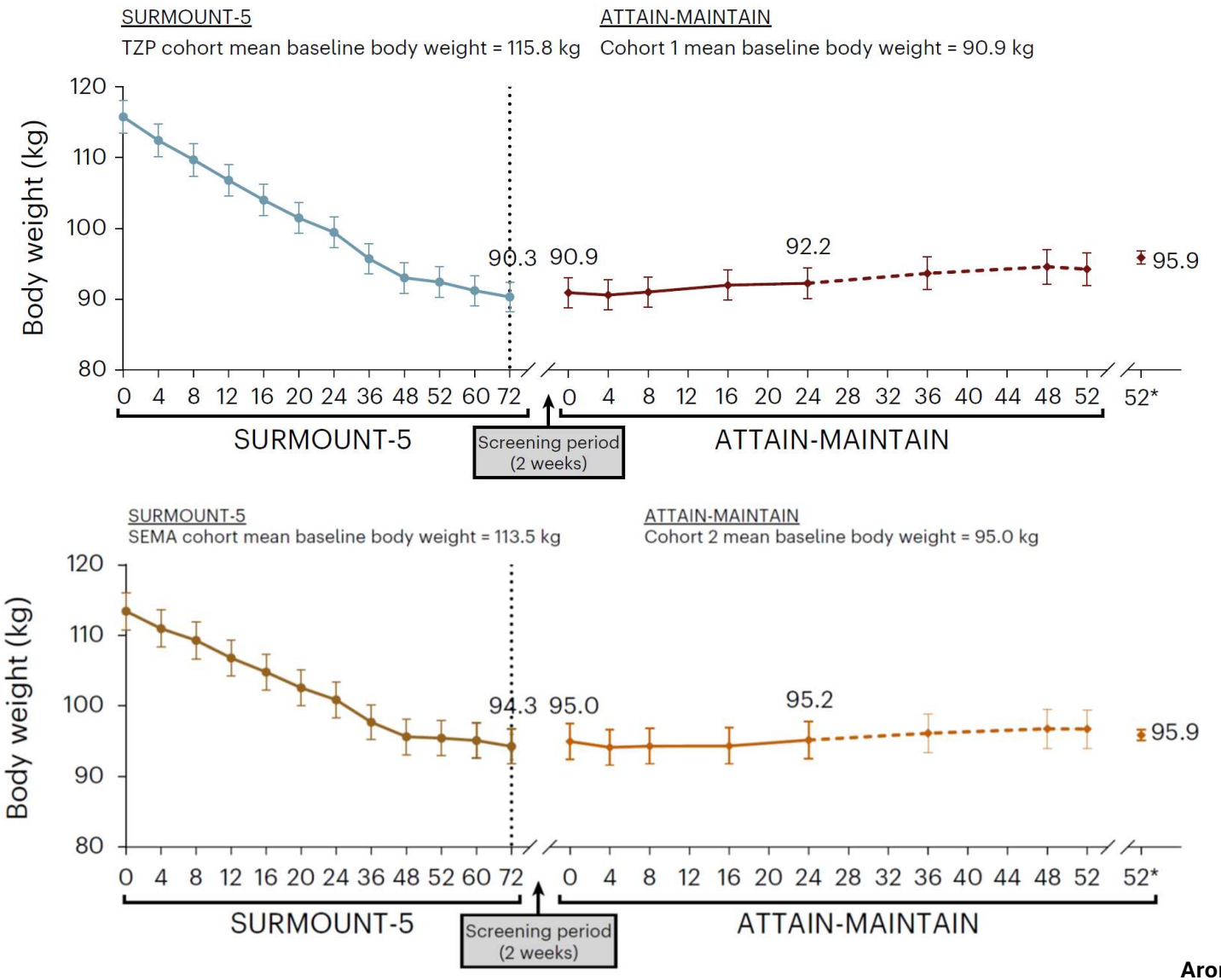
B **Change in Body Weight from Baseline to Week 72 (efficacy estimand)**



No. of Patients

Placebo	949	937	923	910	875	847	817	766	716	688	654	949
Orforglipron, 6 mg	723	713	702	690	675	664	652	630	601	578	559	723
Orforglipron, 12 mg	725	719	695	687	672	652	648	624	602	582	559	725
Orforglipron, 36 mg	730	715	704	689	670	662	644	617	583	573	549	730

Average weight at base-line and ATTAIN-MAINTAIN results



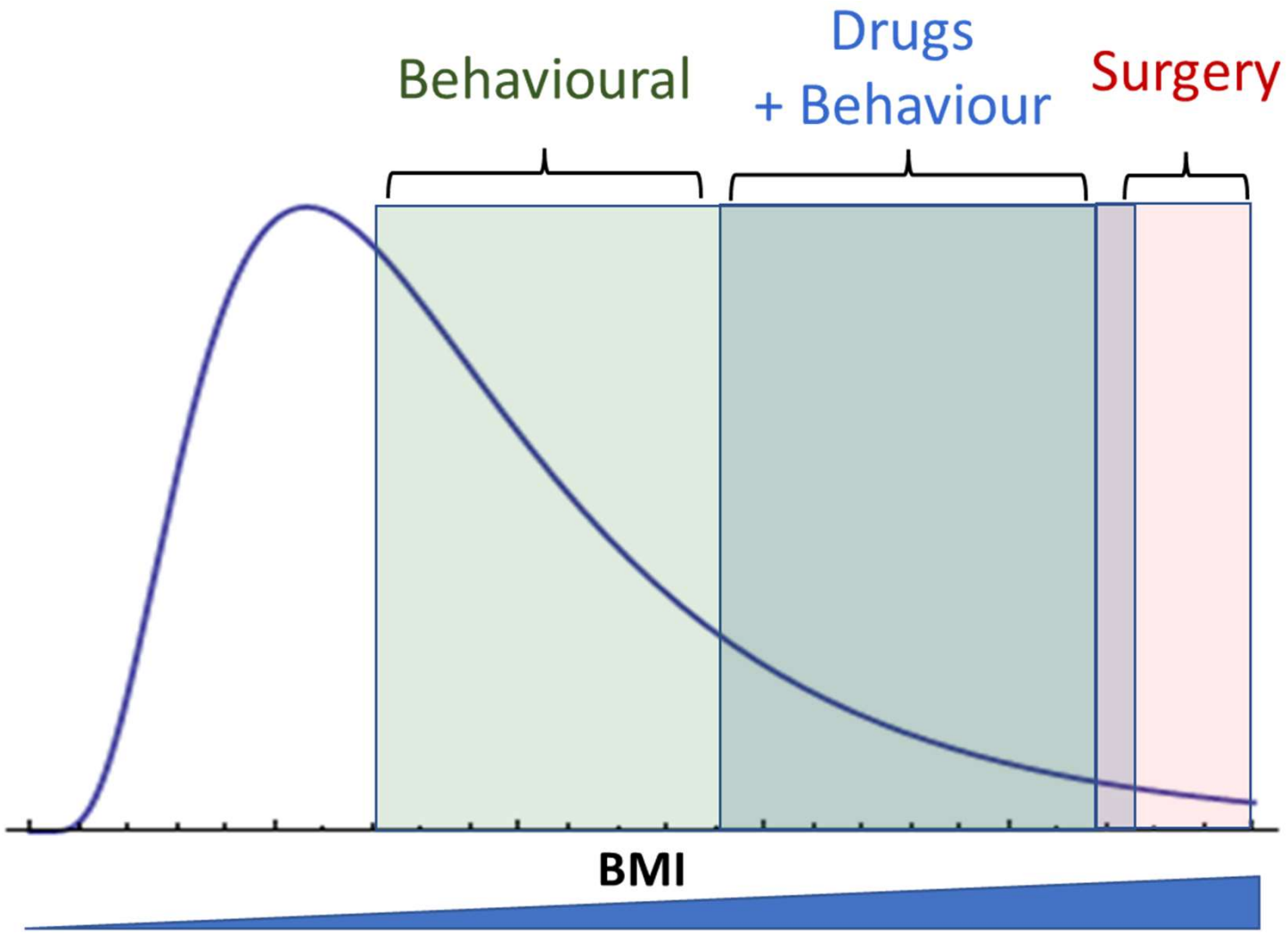
Aronne et al, Nature Medicine 2026

Have we cured obesity?

No.

What is the role of cheese in a post Ozempic world?

Have we cured obesity?



Dowsett and Yeo, Trends in Mol Med

In summary:

1. **Should we be treating obesity with drugs?**

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3. **Won't the weight come back on when you stop taking the drug?**

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Questions?

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