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GLP-1 at the Two-Year Mark: Lessons, Impact, and What's Next

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Objectives for today

- **Forecasting the future**: How will GLP-1 impact life expectancy?

- **Weight loss without lifestyle change:** What does that mean for long-term risk?

- **Cover dilemmas:** From under disclosure to binge users , how will this reshape claims and underwriting across our products?

- **Surprising use cases**: beyond obesity —what else is emerging?

- **Imagine a world beyond just BMI?** Exploring smarter metrics

- **Clinical environment and lack of F2F health interactions**

GLP-1 Headline News

B B C

Home   News   Sport   Business   Innovation   Health   Culture   Arts   Travel   Earth   Audio   Video

Price of Mounjaro to be discounted in UK pharmacies

GPs can now prescribe weight loss jabs under strict rules

Trump strikes deal with Ozempic and Mounjaro makers to cut prices of obesity injections

'SIGNIFICANT CONCERN' Urgent warning over deadly fake weight loss jabs flooding the UK as crime gangs make dodgy drugs on 'industrial scale'

Weight management drugs are no magic bullets for treating obesity

People need support to keep weight off after treatment

Weight loss jabs affecting Greggs, boss says

Thousands of Ozempic lawsuits cleared to proceed in federal court

Weight-loss drugs draw thousands of lawsuits alleging serious harm

Forecasting the future: How will GLP-1 drugs change outcomes?

Figure 1

Left: Life expectancy in years in the US and UK. **Right:** US general population obesity and morbid obesity
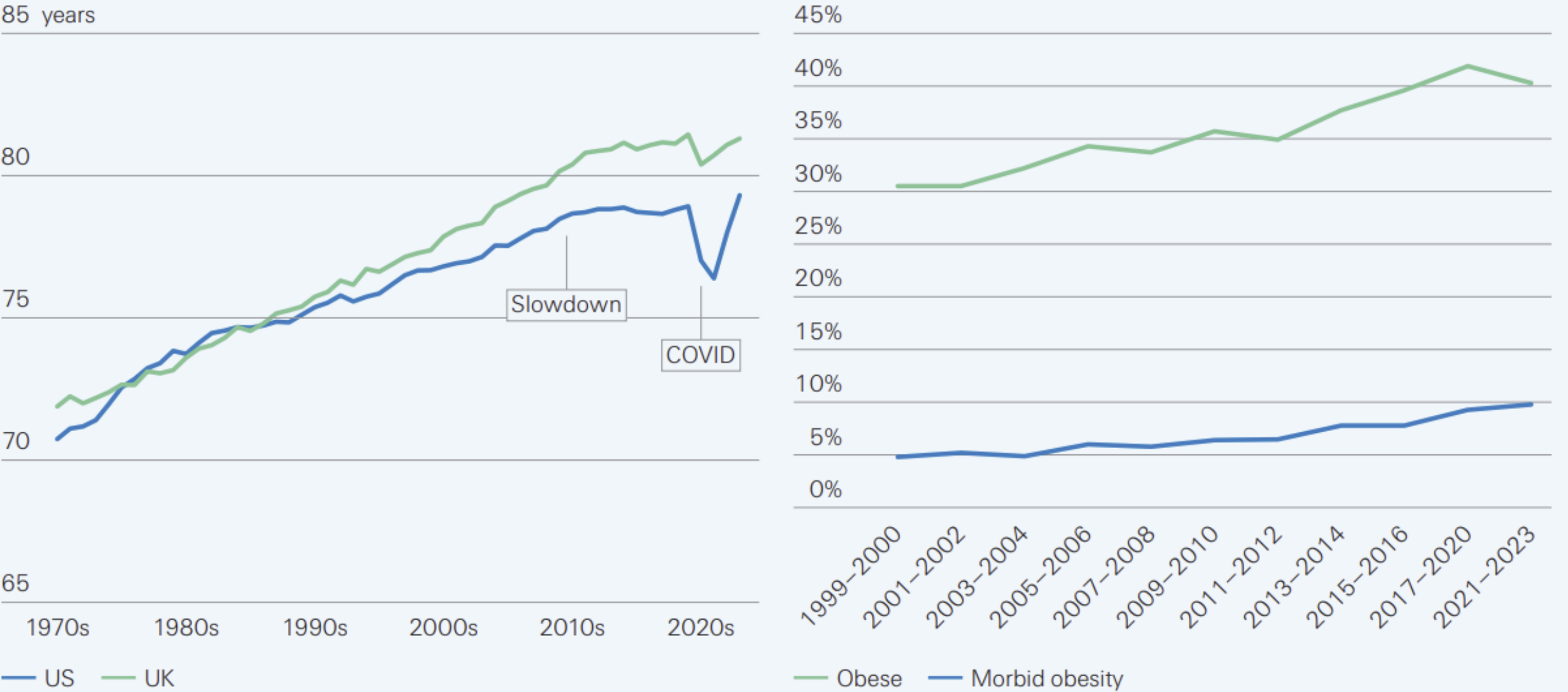
Source: (left) NHANES, (right) Our World in Data

The pathway of metabolic ill health doesn't have to lead to morbidity and mortality
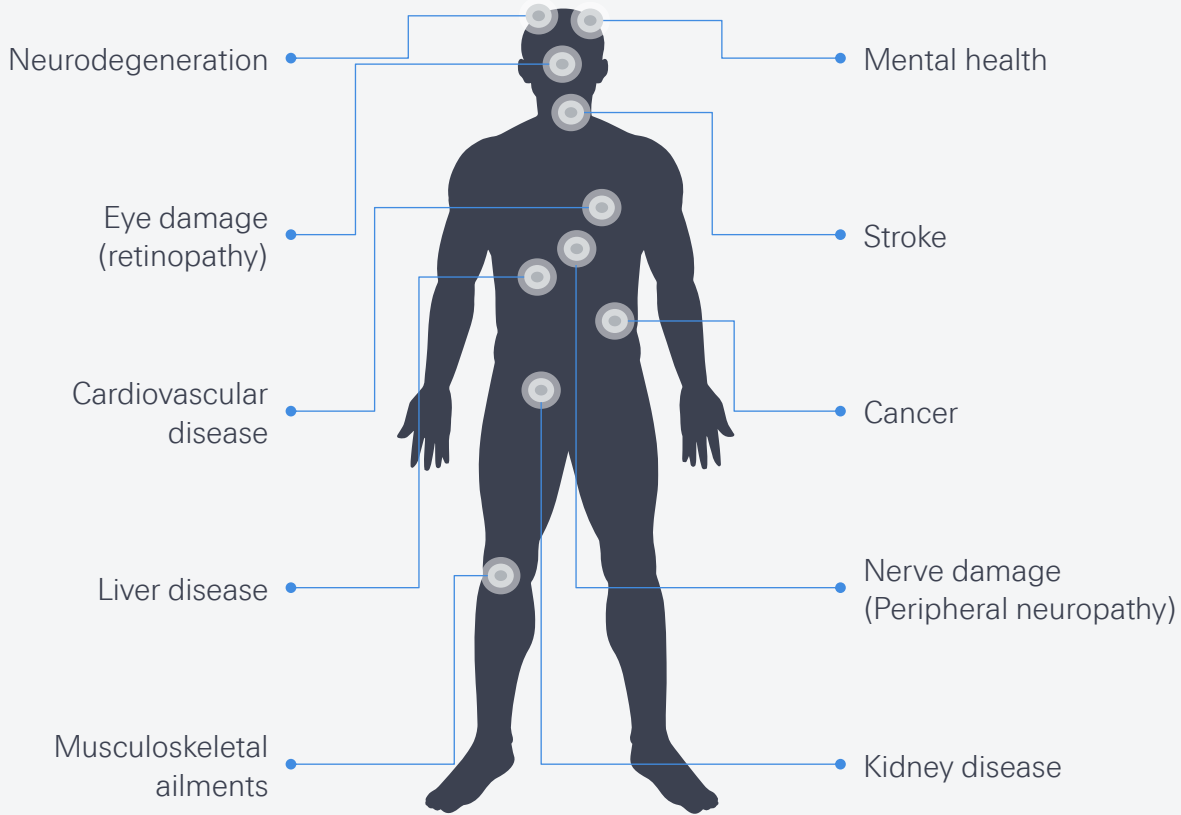
Growing mortality & morbidity risk →

| Unhealthy lifestyle choices | Persistent high blood sugar | Early signs of metabolic disease | Metabolic disease and related major diseases |

← Risk is reversible

Elevated disease risks from obesity

- Neurodegeneration
- Eye damage (retinopathy)
- Cardiovascular disease
- Liver disease
- Musculoskeletal ailments
- Mental health
- Stroke
- Cancer
- Nerve damage (Peripheral neuropathy)
- Kidney disease

Early signs: GLP-1 drugs impact several common risk factors for major causes of morbidity and mortality
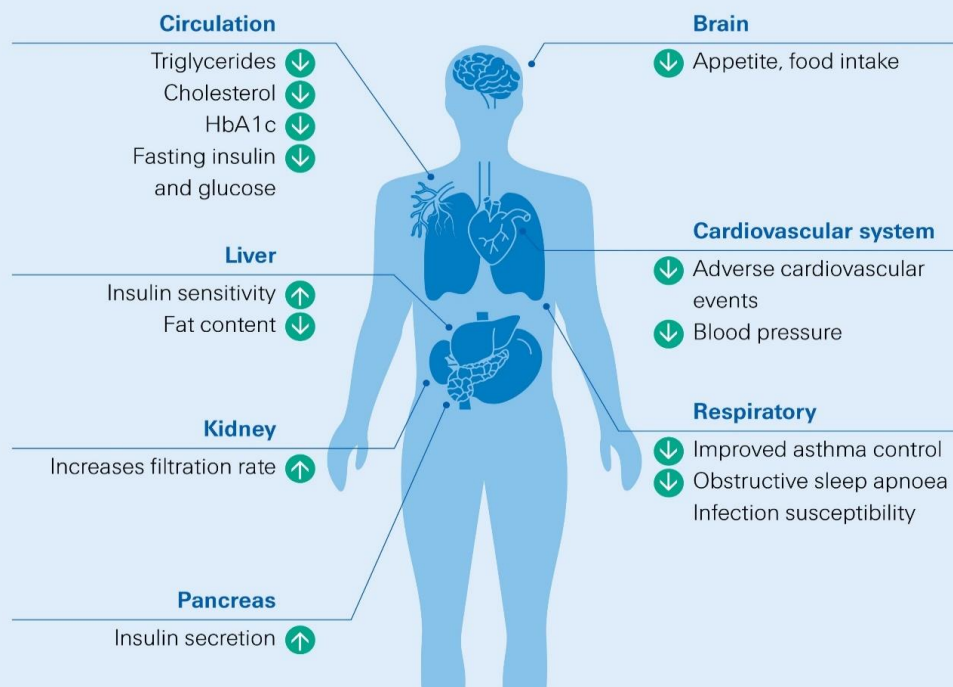

Benefits of GLP-1 drugs for weight loss

Circulation
- Triglycerides ↓
- Cholesterol ↓
- HbA1c ↓
- Fasting insulin and glucose ↓

Liver
- Insulin sensitivity ↑
- Fat content ↓

Kidney
- Increases filtration rate ↑

Pancreas
- Insulin secretion ↑

Brain
- Appetite, food intake ↓

Cardiovascular system
- Adverse cardiovascular events ↓
- Blood pressure ↓

Respiratory
- Improved asthma control ↓
- Obstructive sleep apnoea
- Infection susceptibility

Table 1. Completed cardiovascular (or HF-related) outcome trials with incretin-based therapy.

Trial (Year)	Agent/Dose	Study Population (N)	Primary Outcome (3-Point MACE Unless Stated)	Key CV/HF Findings	Key Ref.
LEADER (2016)	Liraglutide 1.8 mg qd	9340 T2DM + high CV risk	↓ MACE 13% (HR 0.87)	↓ CV death 22%, ↓ all-cause mortality 15%	[6]
SUSTAIN-6 (2016)	Semaglutide 0.5/1 mg qw	3297 T2DM	↓ MACE 26% (HR 0.74)	↓ stroke 39%	[7]
EXSCEL (2017)	Exenatide 2 mg qw	14,752 T2DM	NS 9% MACE↓ (HR 0.91)	↓ all-cause mortality in sub-groups	[17]
HARMONY (2018)	Albiglutide 30–50 mg qw	9463 T2DM + ASCVD	↓ MACE 22% (HR 0.78)	Driven by MI ↓	[18]
REWIND (2019)	Dulaglutide 1.5 mg qw	9901 T2DM (31% ASCVD)	↓ MACE 12% (HR 0.88)	Consistent across MI/stroke	[8]
AMPLITUDE-O (2021)	Efpeglenatide 4–6 mg qw	4076 T2DM	↓ MACE 27% (HR 0.73)	↓ stroke & HF events	[19]
ELIXA (2015)	Lixisenatide 20 μg qd	6068 T2DM + recent ACS	Neutral (HR 1.02)	Heterogeneous class effect	[20]
STEP-HFpEF (2023)	Semaglutide 2.4 mg qw	529 obese HFpEF (±T2DM)	KCCQ +16.6 pts†	↓ HF hospitalisation (HR 0.79)	[11]
SELECT (2023)	Semaglutide 2.4 mg qw	17,604 obese, non-DM + ASCVD	↓ MACE 20% (HR 0.80)	Benefit in primary prevention	[12]
SURPASS-CVOT	Tirzepatide 10/15 mg qw	13,299 T2DM + high CV risk	Non-inferior vs dulaglutide; (HR 0.92)	Secondary analysis → significant-cause death ↓	[21]
SOUL (2025)	Oral semaglutide	9650 T2DM + ASCVD/CKD	↓ MACE 14% (HR 0.86)	Secondary analysis →	[22]

MACE, Major Adverse Cardiovascular Event; CV, Cardiovascular; HF, Heart Failure; T2DM, Type 2 Diabetes Mellitus; ASCVD, Atherosclerotic Cardiovascular Disease; MI, Myocardial Infarction; ACS, Acute Coronary Syndrome; KCCQ, Kansas City Cardiomyopathy Questionnaire; CKD, Chronic Kidney Disease.

GLP-1 Agonists in Cardiovascular Diseases: Mechanisms, Clinical Evidence, and Emerging Therapies

by Han-Mo Yang

Division of Cardiology, Department of Internal Medicine, Seoul National University Hospital, Seoul 03080, Republic of Korea

J. Clin. Med. **2025**, 14(19), 6758; https://doi.org/10.3390/jcm14196758

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AMPLITUDE-O (2021)	Efpeglenatide 4–6 mg qw	40	...troke & HF events	[19]
ELIXA (2015)	Lixisenatide 20 µg qd	60	...terogeneous class effect	[20]
STEP-HFpEF (2023)	Semaglutide 2.4 mg qw	52	...F hospitalisation (HR 0.79)	[11]
SELECT (2023)	Semaglutide 2.4 mg qw	17 ASCVD	↓ MACE 20% (HR 0.80) ... Benefit in primary prevention	[12]
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General population: cumulative all-cause mortality reduction by 2045

US: 4.0% [2.3 − 6.4%]

UK: 3.2% [1.8 − 5.1%]
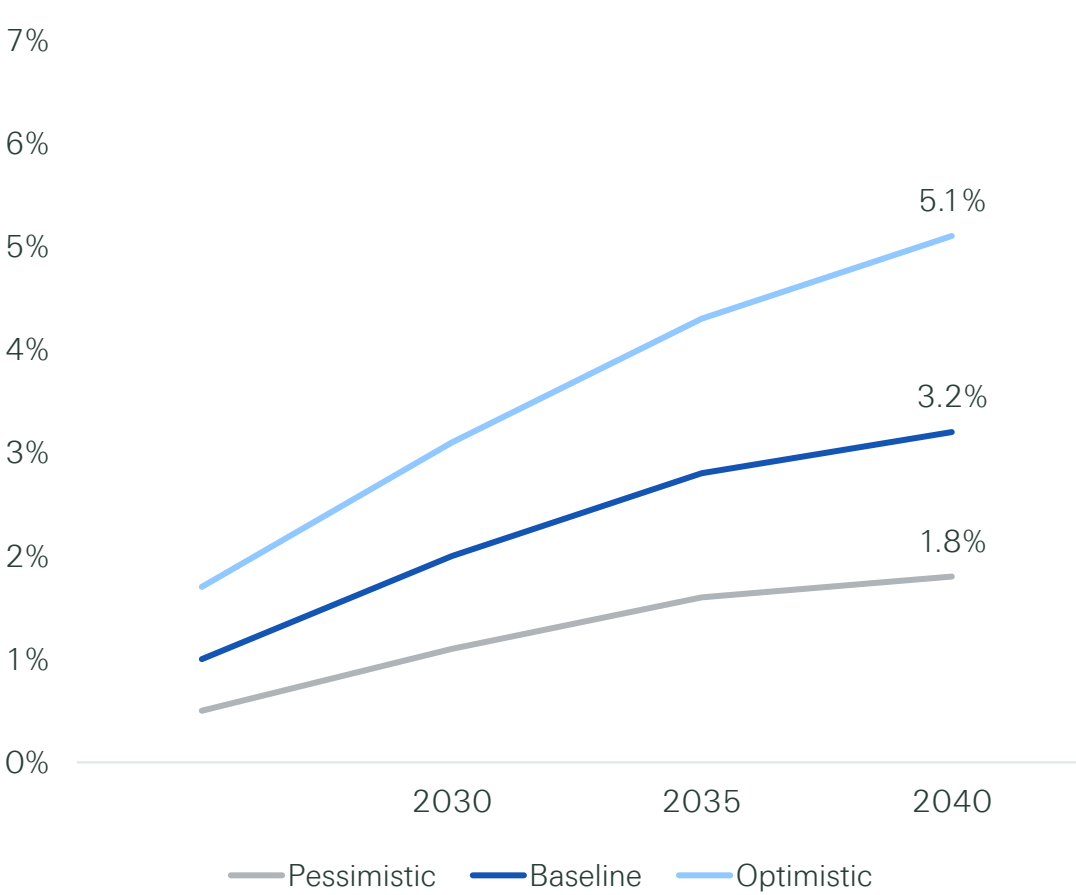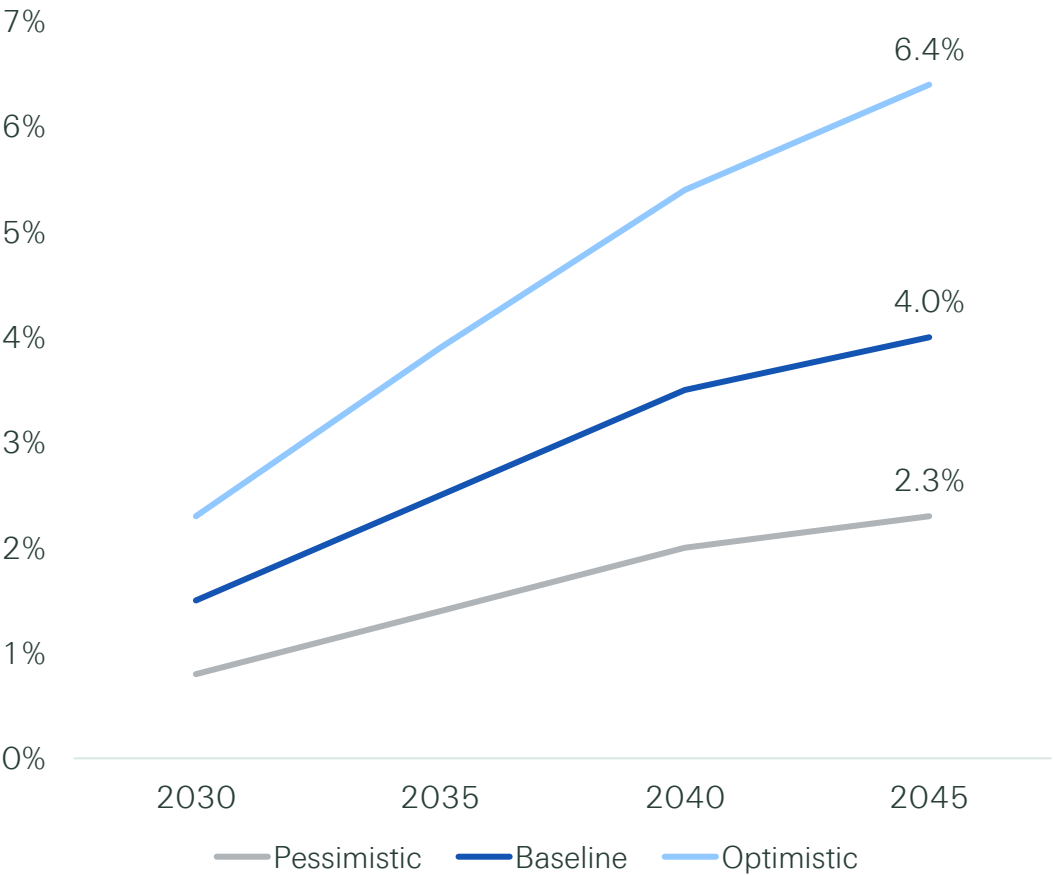
Our metabolic health scenarios examine both GLP-1 and lifestyle improvements

Core forecasting assumptions

Weight loss drugs remain effective

New drugs are released and adopted

Patents expire – drugs more accessible

	Optimistic scenario – the most positive outlook	**Baseline scenario** – the most likely assumption	**Pessimistic scenario** – still positive yet guarded
Drug uptake	**Popular** – with high engagement and population weight loss	Majority use in obese and highly overweight groups.	Mostly **limited use** in treatment-resistant cases
Behaviour change	**Lifestyle changes implemented** support long-term health	Some ongoing lifestyle change expected, with moderate impact.	**Lifestyle changes** remain **underused**, limited impact
Long term outcomes	**Weight loss maintained** in real-world usage	Variable weight loss outcomes with a degree of yo-yo-ing expected.	**High weight regain** is common after stopping medication
Clinical markers	**Strong improvements**	**Moderate improvements** to core markers.	Improvements are **modest** over time
Ongoing usage	Side effects are minimal, long-term drug usage plausible	Side effects are mostly tolerable for short- to medium-term use.	Side effects (eg frailty/muscle loss) and medical caution **limit broader** use

Insurance implications are positive in the short term

Life & Critical Illness	Disability/ Income Protection	Medical/ Health
Sustained results may reduce all mortality including cancer & CVD	Decline in obesity-linked claims over time	>95% use is self-funded UK insurers now offering GLP-1 for in-force management
Obesity contributes to ~30 cancers, heart attacks, strokes	Enhanced MSK condition management Workplace engagement & productivity	More clinician time needed for follow-up Long term reduced need for investigations & procedures

Longer term implications

Pensions, Long Term Care, the *unknown unknowns*

Weight loss without lifestyle change: What does that mean for long-term risk?
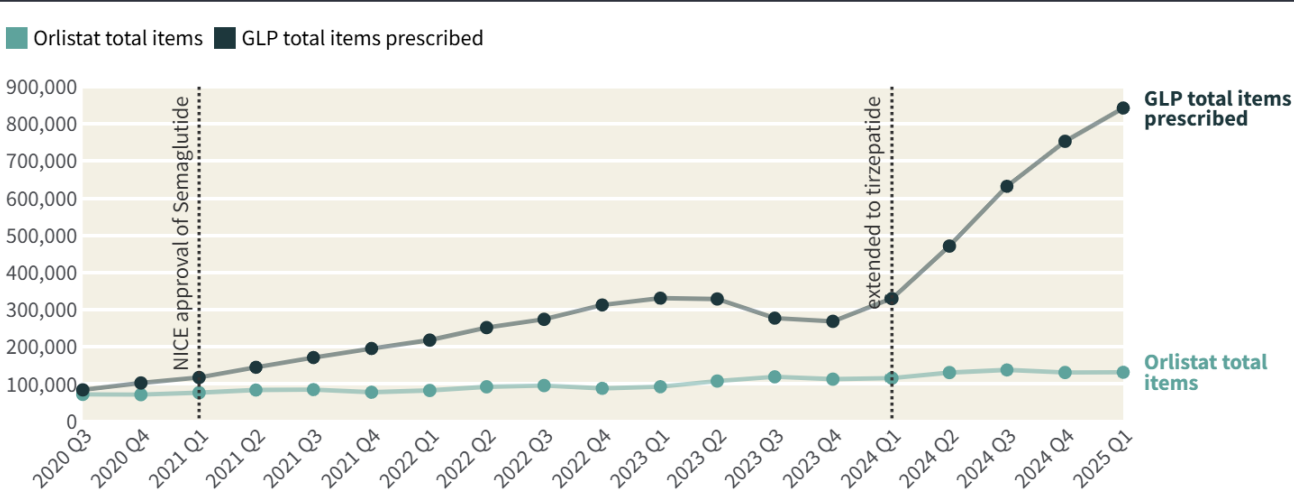
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UK weight loss jab sales increase sevenfold to 2.5 million, new figures show

Health secretary Wes Streeting wants to make the drugs more widely available on the NHS

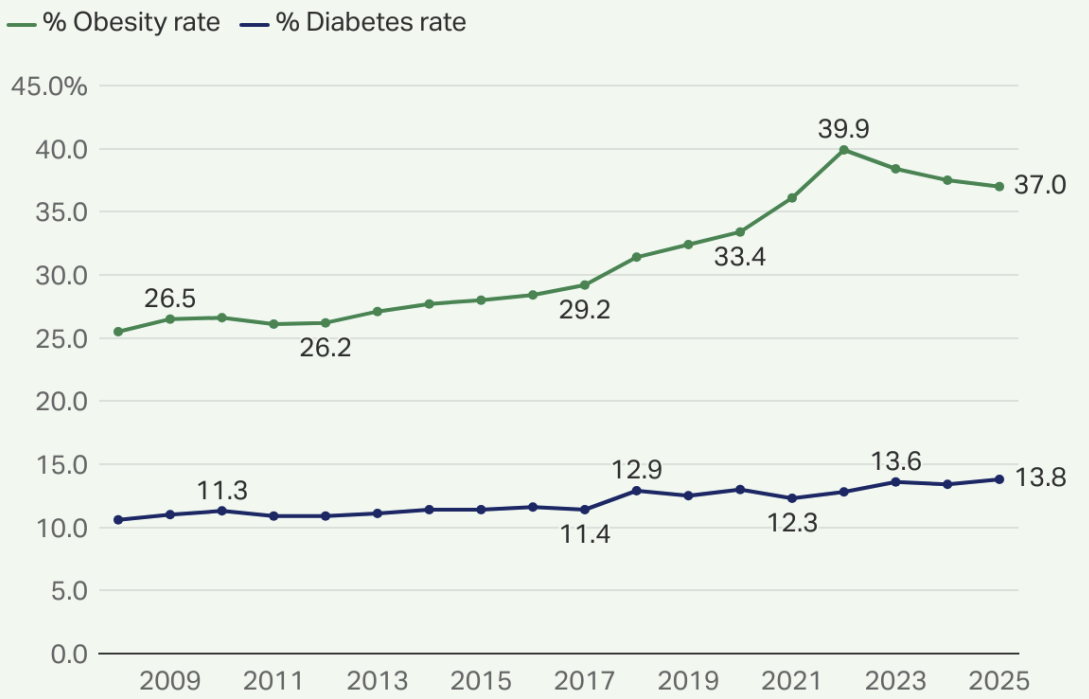**Alex Croft**
Sunday 12 October 2025 19:11 BST

23 Comments

Orlistat total items   GLP total items prescribed

GLP total items prescribed
Orlistat total items

NICE approval of Semaglutide
extended to tirzepatide

900,000
800,000
700,000
600,000
500,000
400,000
300,000
200,000
100,000
0

2020 Q3, 2020 Q4, 2021 Q1, 2021 Q2, 2021 Q3, 2021 Q4, 2022 Q1, 2022 Q2, 2022 Q3, 2022 Q4, 2023 Q1, 2023 Q2, 2023 Q3, 2023 Q4, 2024 Q1, 2024 Q2, 2024 Q3, 2024 Q4, 2025 Q1

Source: OpenPrescribing.net, Bennett Institute for Applied Data Science, University of Oxford, 2025 • This time series shows the surge in NHS England prescriptions for semaglutide and tirzepatide (GLP-1 receptor agonists) since 2020, plotted against prescribing levels of Orlistat, a traditional anti-obesity medication. Following the NICE approval of semaglutide in 2021 and tirzepatide guidance in early 2024, GLP-1 prescribing surpassed Orlistat by a wide margin, growing by over 700% from 2020 to 2025.
Data ranges from May 2020 - June 2025

The King's Fund

Obesity Showing Signs of Decline in U.S.

— % Obesity rate   — % Diabetes rate

45.0%
40.0
35.0
30.0
25.0
20.0
15.0
10.0
5.0
0.0

26.5
26.2
29.2
33.4
39.9
37.0

11.3
11.4
12.9
12.3
13.6
13.8
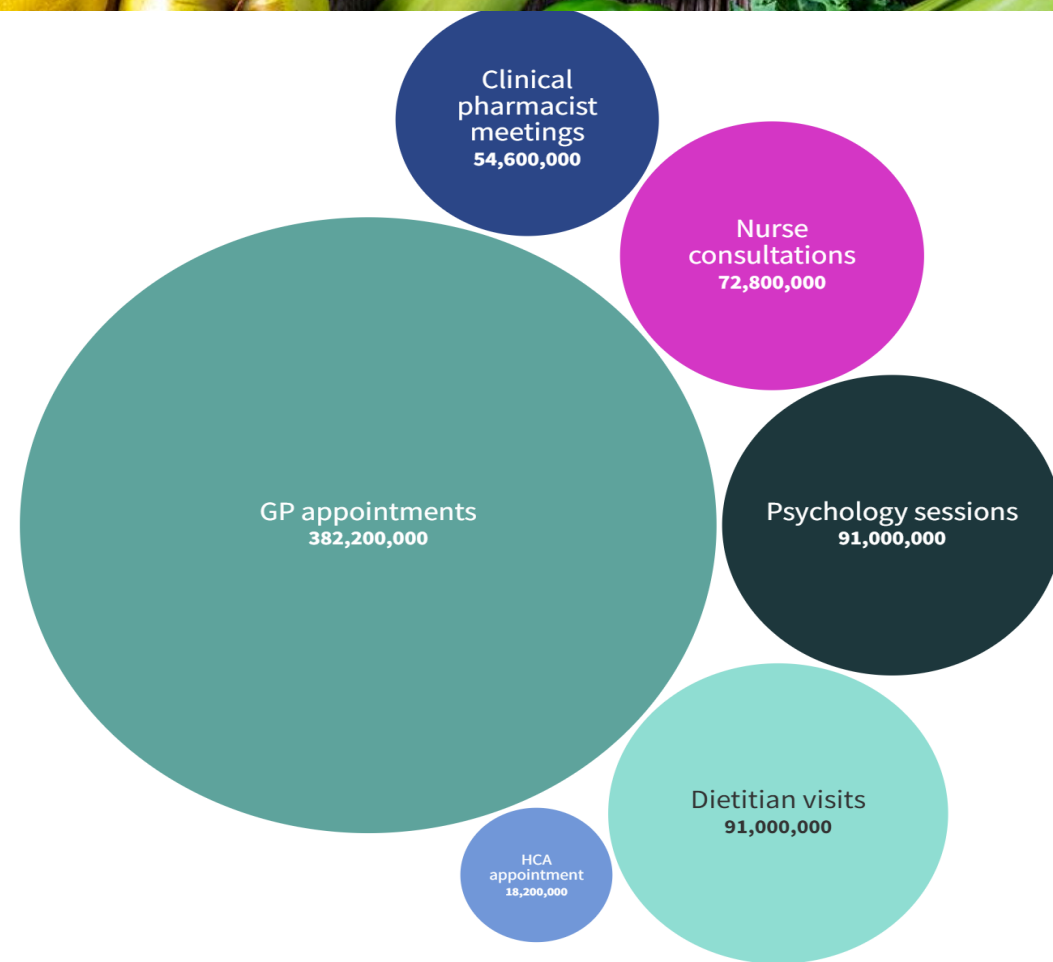
2009 2011 2013 2015 2017 2019 2021 2023 2025

GALLUP

If we aimed for 70% uptake of Tirzepatide in English patients identified as qualifying

- ~ **£3bn** cost of implementation

- Requiring **700 Million appointments**

- Support apps exist but are not automatically linked to GP services/tertiary weight loss clinics

In reality – supply cannot be afforded within the NHS's. ICBs have restricted supply. NHS Scotland have prioritised supply to those with CV risks; T2DM etc, with purely obese patients still needing to wait for Tertiary weight loss clinic appointments

Clinical pharmacist meetings
54,600,000

Nurse consultations
72,800,000

GP appointments
382,200,000

Psychology sessions
91,000,000

Dietitian visits
91,000,000

HCA appointment
18,200,000

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Medications alone – will they save us?

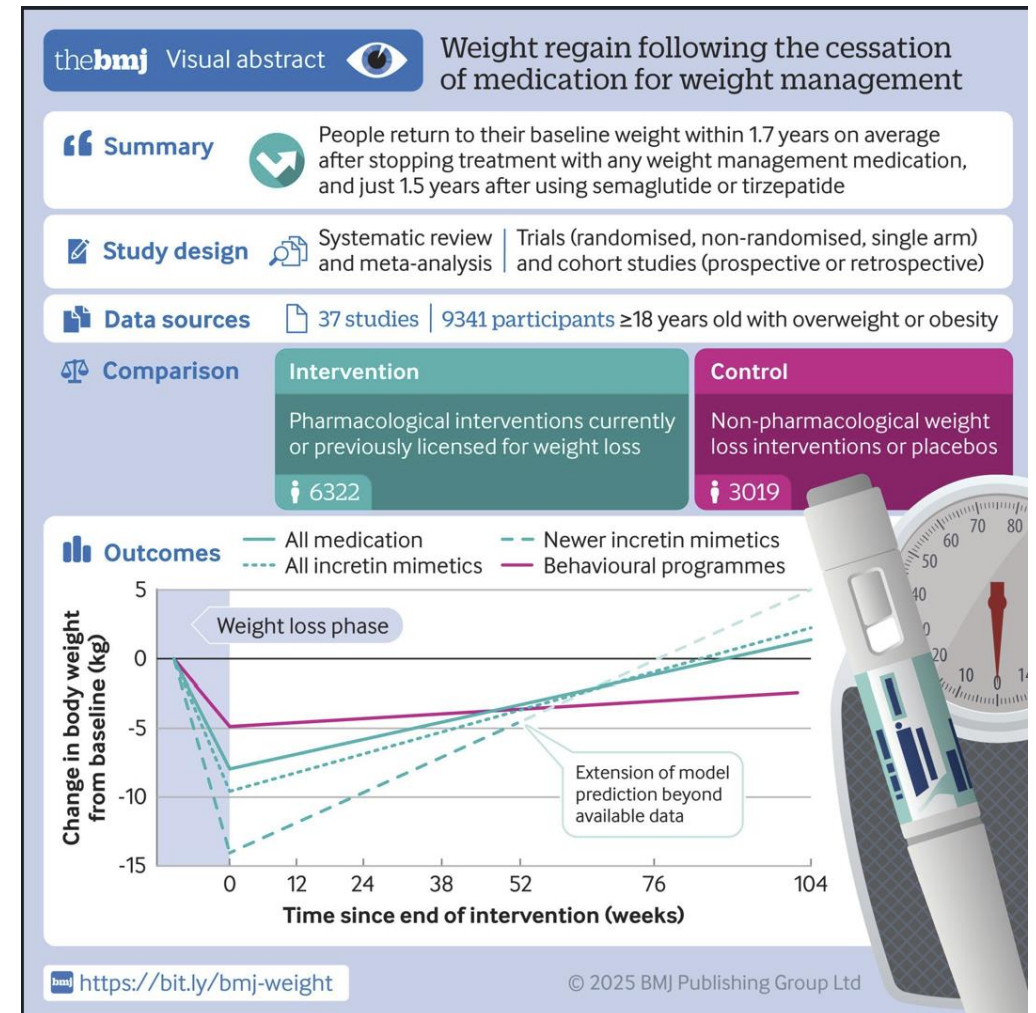1. You **stop the medication once target weight reached**

- Meta-analysis showed a return to baseline weight by 1.7 years of stopping, and a return to abnormal risk profile by 1.4.

- Faster and greater weight loss resulted in faster return to pre-medicated levels

- The CV risk markers follow the weight trend

- Expect to see cycling of weight

2. **Continued "maintenance dose"** for life/microdosing

- expensive, oral agents should be cheaper
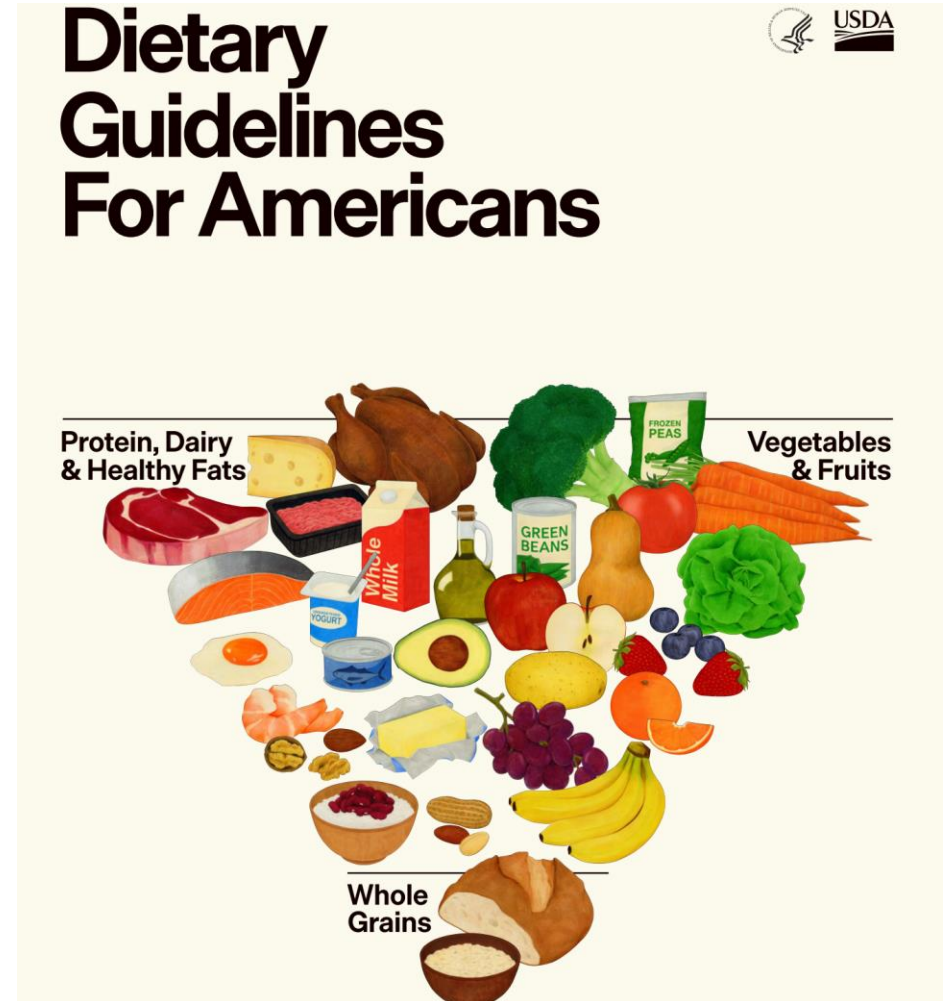
- lack of evidence as to long term health implications

Is treating the symptom enough?

the **bmj** Visual abstract — Weight regain following the cessation of medication for weight management

Summary — People return to their baseline weight within 1.7 years on average after stopping treatment with any weight management medication, and just 1.5 years after using semaglutide or tirzepatide

Study design — Systematic review and meta-analysis | Trials (randomised, non-randomised, single arm) and cohort studies (prospective or retrospective)

Data sources — 37 studies | 9341 participants ≥18 years old with overweight or obesity

Comparison

Intervention	Control
Pharmacological interventions currently or previously licensed for weight loss	Non-pharmacological weight loss interventions or placebos
6322	3019

Outcomes — All medication / All incretin mimetics / Newer incretin mimetics / Behavioural programmes

Change in body weight from baseline (kg) vs Time since end of intervention (weeks)

Weight loss phase

Extension of model prediction beyond available data

bmj https://bit.ly/bmj-weight

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GLP-1's and dietary measures are similar

- Both GLP1 agonists OR low carb diets slow the transit of food through the GI tract = levelling out of glucose

- Latest USDA guidance targets the underlying cause;

  - eat real, nutrient dense food

  - eat the right amount for your size and activity level

  - hydrate adequately

  - prioritise protein

  - include full fat dairy

  - support gut health with fibre and fermented foods

  - limit % of daily intake to <10% from saturated fats

  - watch out for and limit highly processed foods, added sugars (also in meats) and refined carbohydrates

  - Avoid sugary or energy drinks

Added sugars may appear on ingredient labels under many different names, including high-fructose corn syrup, agave syrup, corn syrup, rice syrup, fructose, glucose, dextrose, sucrose, cane sugar, beet sugar, turbinado sugar, maltose, lactose, fruit juice concentrate, honey, and molasses. Examples of non-nutritive sweeteners include aspartame, sucralose, saccharin, xylitol, and acesulfame K.

Dietary Guidelines For Americans

USDA

Protein, Dairy & Healthy Fats

Vegetables & Fruits

Whole Grains

Not without controversy!

From under disclosure to binge users , what's the impact on risk and experience?

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Why this matters

2.5 billion people are overweight

Obesity stigma is a reality and so....

830 million living with diabetes

Key driver of our rated portfolio

Continues to be hidden in claims

Can Underwriting continue to rely on BMI?

- Up to 20% people under disclose their BMI currently

- GLP-1 drugs break the BMI−risk link

- Static measures ignore metabolic biomarkers

- Does not account for age, sex, or ethnicity adequately

- Not the best predictor of metabolic risk

Early pilot indications: When holistic claims management include metabolic health

5 out of 14 completed referrals have successfully RTW

Average clinical improvement across the 14 claimants:

		Average	Range
Weight lost (kg)	↓	7.2	1.6 – 24.4
Weight loss (%)	↓	5.6	1.6 – 12.3
Waist circumference (cm)	↓	4.4	-3 – 10
BMI points	↓	2.9	-1.4 – 9.3

Measurements were recorded at an average of 3 months following completion of programme with additional improvements in blood pressure and HbA1c readings, with some further ceasing diabetes and migraine medication.

5 claimants have RTW:

£790,550 savings
Total Reserve Released

£32,500 cost
Total Cost of Programmes
(6 Residential, 7 Virtual, 1 Dietician-only)

86% engagement
18 of 21 claimants accepted the offer

Claims team has demonstrated excellent handling of referral discussion and subsequent case management.

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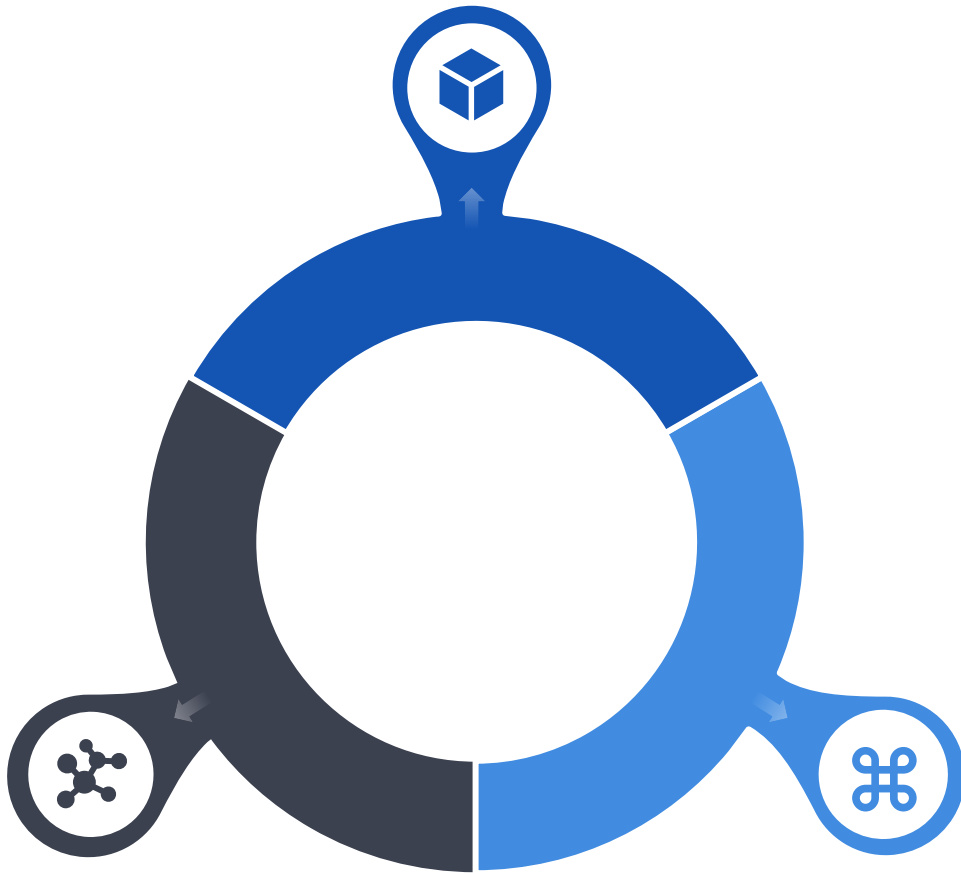
Experience impact
- Mortality assumptions assume stability that may not occur in the long term
- Worse than expected mortality in healthy cohorts
- If their uptake and effectiveness continue, these medications will raise questions around current pricing, reserving and valuation assumption

Underwriting Impact
- Anti-selection: Improved labs/BMI mask underlying poor metabolic health
- GLP-1 usage remains masked in underwriting
- Is single point BMI underwriting out of touch with reality?

Claims
- Early-duration claims deterioration
- How do we assess GLP-1 misrep if masked in underwriting?
- Does holistic claims management hold the key?

Challenges and unknowns associated with GLP-1 drugs suggest caution

Managing drug use

Discontinuation due to Side Effects: 1/3 of patients after a month, 1/2 within 3 months, long before any benefits appear.

Muscle and bone: more than just fat is lost, perhaps 1/3 of weight lost is bone density and muscle – frailty concerns. New drugs seek to address this.

Lifestyle essentials: both exercise and diet are essential if we want to minimise reversal and regain. Currently little motivation to make these changes.

Ongoing considerations

Weight regain: numbers vary, regains of 33% – 50% seem average. **Some studies show net weight regain.** Weight regain would be fat.

Yo-yo use: will patients resume drug use after time? What does this mean over time? If weight returns, how much risk reduction will persist?

Accessibility: on-patent costs are very high which limits widespread access.

Surprising use cases: Beyond diabetes and obesity—what else is emerging?

Figure.

Non-diabetes indications for GLP11-Ras
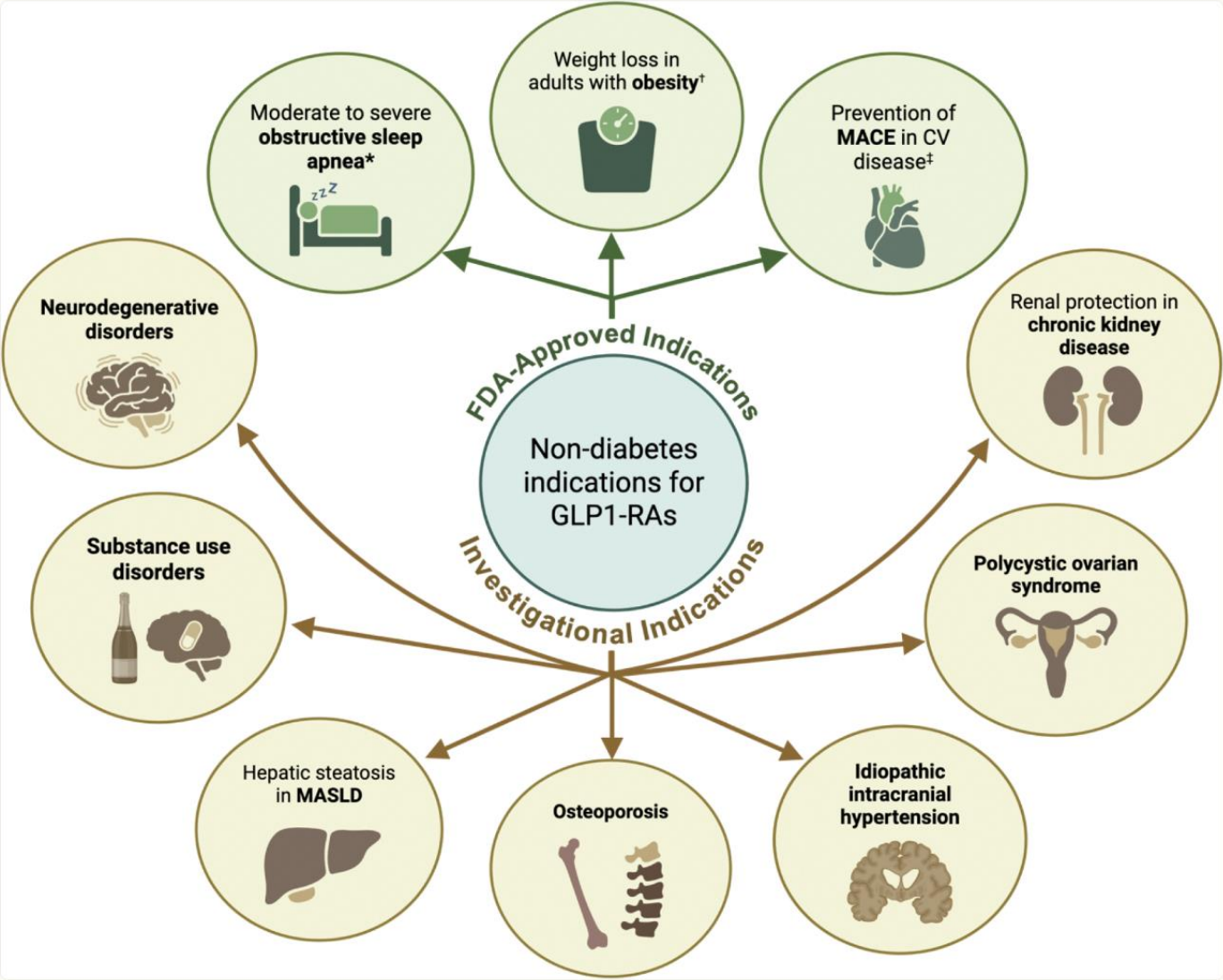
The expanding scope of GLP-1 receptor agonists: Six uses beyond diabetes - PMC

Emerging uses in clinical medicine

Connects to Metabolic Health weight loss benefit in all except neurodegenerative

Claims scenario's seen;

- prior to MSK surgery

- adjunct in high dose steroid treatments

What (might be) coming along?

E-PAPER   DECODED   OPINIO

Home / Health / Gene therapy for weight loss: Can one shot replace lifelong GLP-1 drugs?

Gene therapy for weight loss: Can one shot replace lifelong GLP-1 drugs?

US biotech firm Fractyl Health is developing Rejuva, an experimental gene therapy that aims to trigger long-term weight loss by programming the pancreas to produce more GLP-1 hormone

Mouse study only
Self limiting impact

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Imagine a world beyond just BMI? Exploring smarter metrics for risk

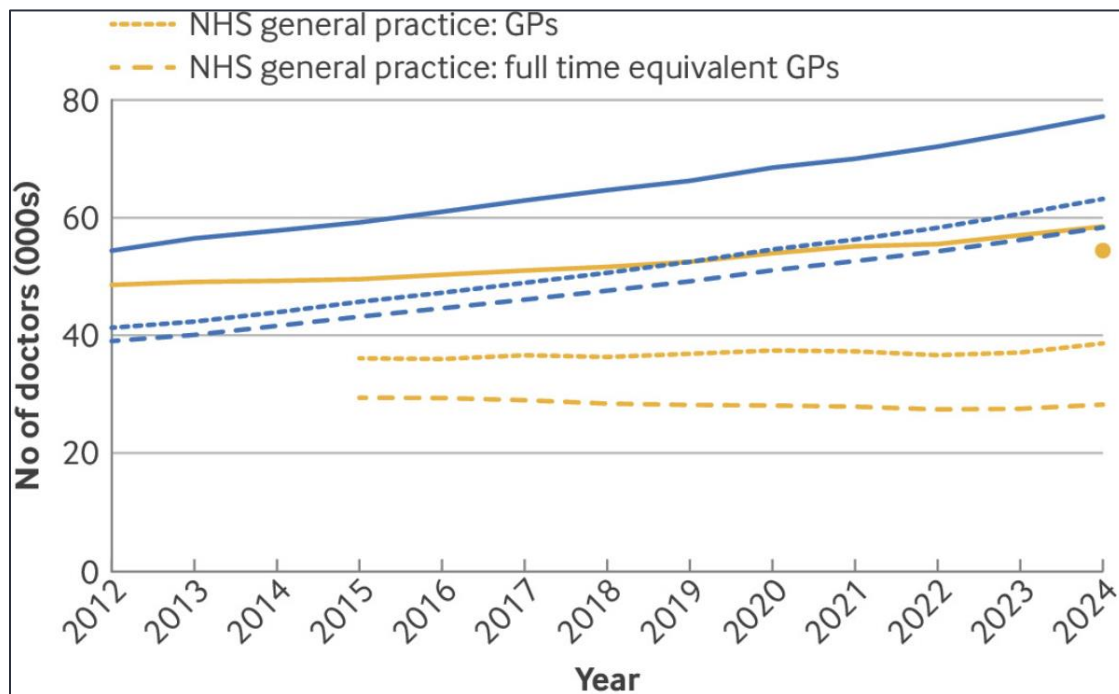# Swiss Re's definition of metabolic health

● Markers ●●● Factors

- Nutrition
- Physical activity
- Sleep

Lifestyle behaviours

- BMI
- Others[1]
- HbA1c
- Hypertension

Clinical markers

Psycho-social factors

- Mental health
- Societal factors
- Behavioural change

Medical advancements

- GLP-1 drugs
- Medications[2]
- Wearables[3]
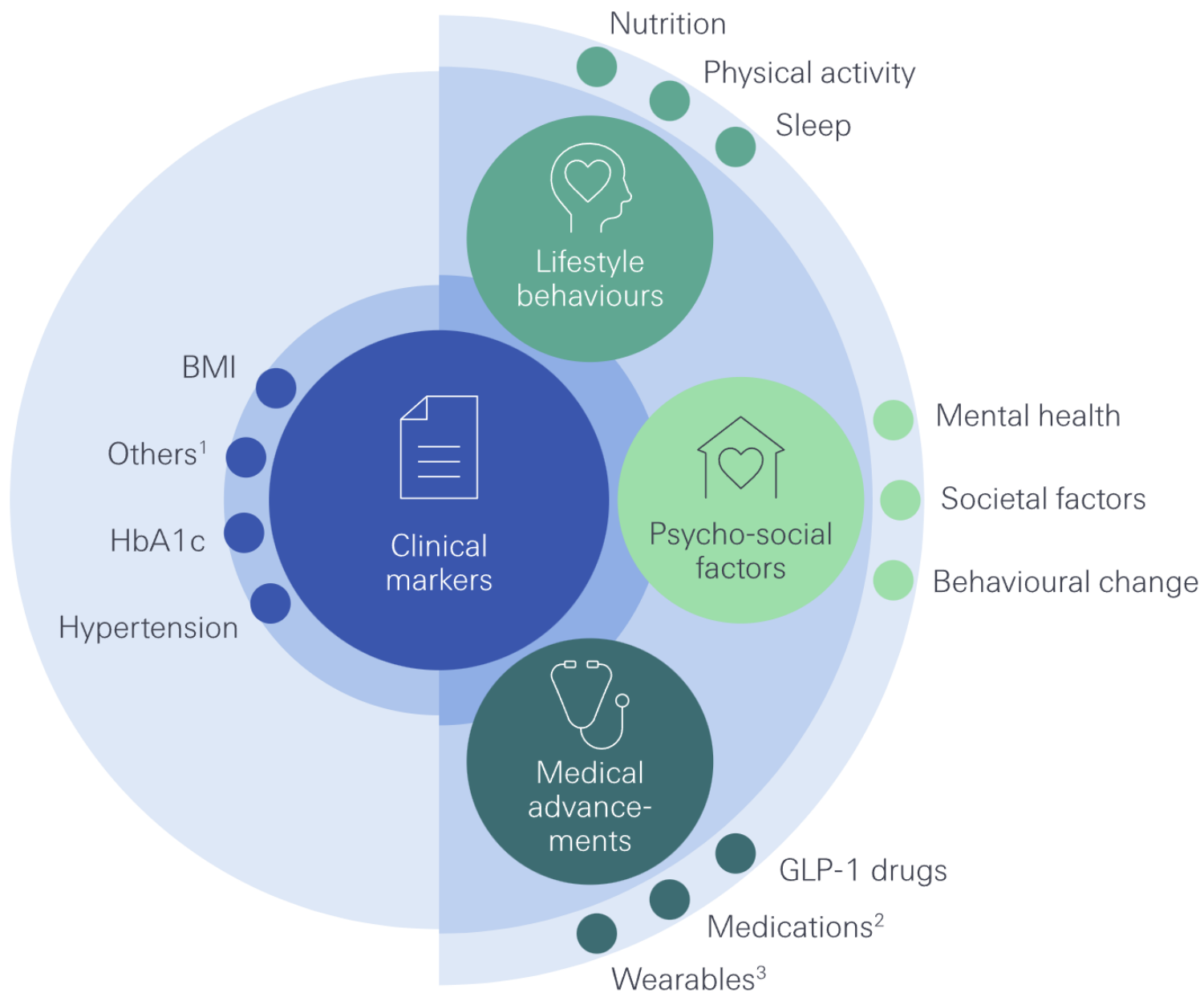
Redefining metabolic health

- ❖ GLP-1's are not the only solution to poor metabolic health
- ❖ valuable tool in a holistic approach to obesity treatment that supports positive lifestyle changes
- ❖ The future of underwriting is BMI + metabolic context, not BMI alone

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Introducing ChatGPT Health

Every day, millions of people ask ChatGPT for support with their health

Researchers report 'astounding' obesity surge in U.S. — Harvard Gazette
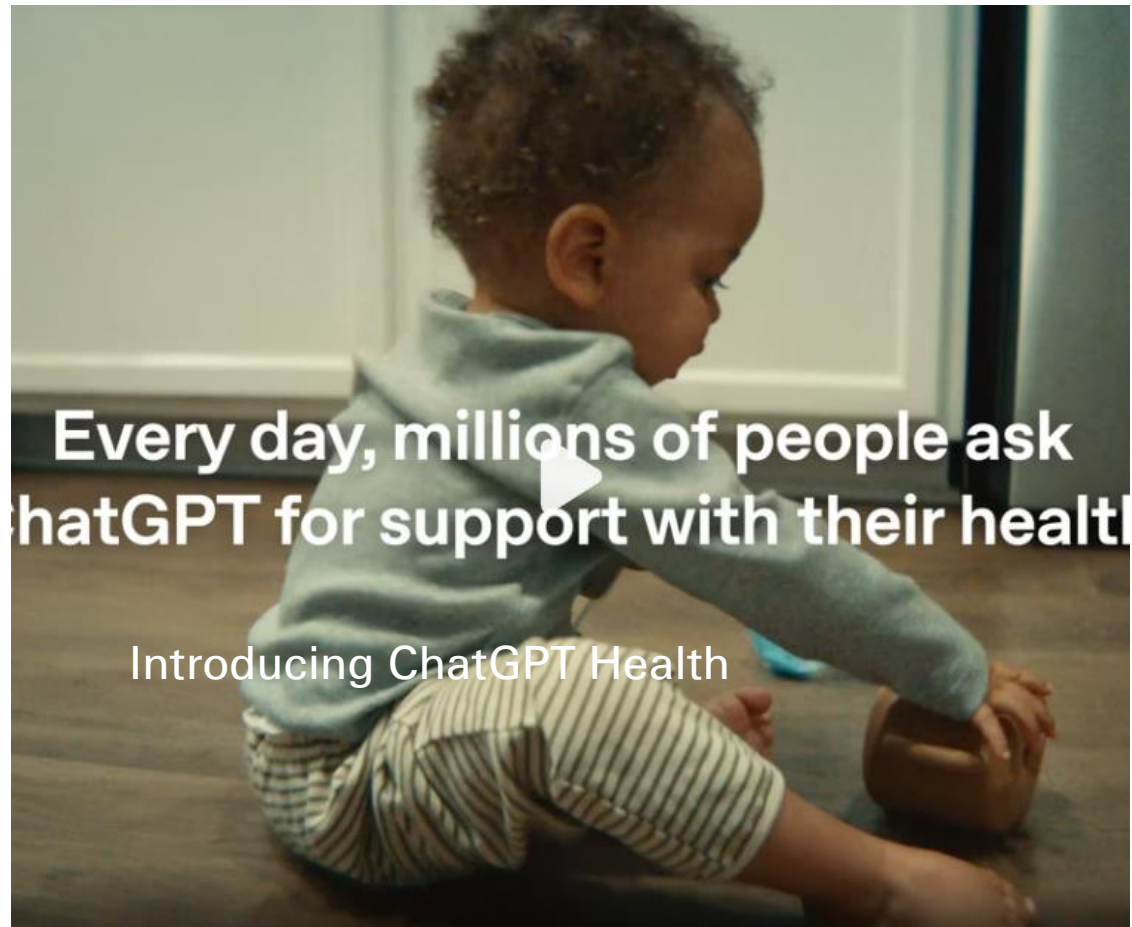
GLP1's in the context of the Clinical environment and underwriting

Pressure on clinical services

Could WMM's help detect disease more promptly?

- 1.3 Million undiagnosed T2 diabetics in UK

- 4.2 Million undiagnosed hypertensives (under 55) in UK

- CV disease improvements in the under 60's have stalled

- NHS Healthchecks under utilised (5 yearly, ages 40-74)
  - March '24 Scotland reported 5% completion rate of eligible patients
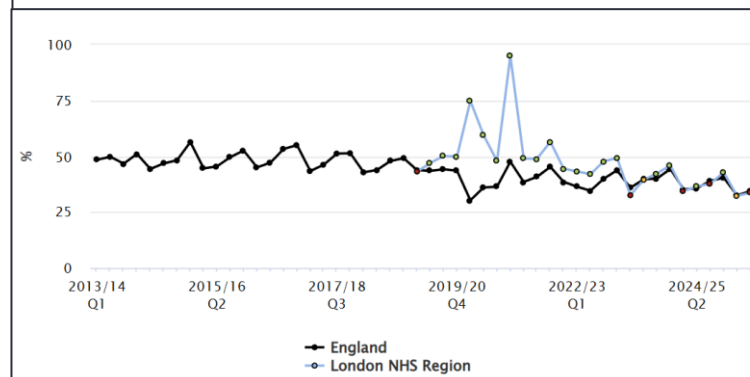
Haggis, neeps and tatties

Any questions?

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Thank you!

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