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Futureturns

Will obesity become a curable disease?

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Lucrative drug discoveries can be unpredictable. Take the well-known story of the Pfizer scientists who created a drug called sildenafil citrate as a possible treatment for high blood pressure and angina. While unsuccessful in its intended use, the drug ended up being a very effective solution for erectile dysfunction, which had not been seen as a solvable problem. The accidental discovery was relabeled Viagra and became one of the most profitable drugs of the 1990s.

A similar repurposing of a medicine is happening today, although not because of a failure. An established class of diabetes drugs called GLP-1 (*glucagon-like peptide-1*) is now being tested and used to treat obesity. This reuse of GLP-1 has the potential to be highly lucrative for the companies that produce it, in our view. Moreover, it could reshape the entire healthcare industry.

We explore this development in the Q3 issue of *Futu**returns***, our quarterly report on trends investing in equity markets.

Need to know

- GLP-1 (*glucagon-like peptide-1*) has been used for many years to treat type 2 diabetes. Given it also lowers patients' weight, the drug is now being repurposed as an obesity treatment
- The surge in obesity and excess body weight could cost the global economy more than USD 4 trillion in 2035, or almost 3% of GDP, according to the World Obesity Atlas 2023. Treating obesity as a potentially curable disease could reduce healthcare expenditures substantially over time, in our view
- Novo Nordisk is currently the only pharmaceutical company authorised to distribute GLP-1 as an obesity treatment, but competitors including Eli Lilly are close behind

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Elon and Oprah

Even before the first of the GLP-1s was approved for weight loss, the drugs were being trumpeted on social media. The hashtag #ozempic, referring to the name of one of the diabetes treatments, has over 600 million views on TikTok. In late 2021, Elon Musk revealed on Twitter that he had lost 30 pounds in just two months using the medication. Rumors swirled that reality TV star Kim Kardashian also used the drug to fit into Marilyn Monroe's dress in 2022, which she has denied.

Oprah Winfrey jumped on the bandwagon after the first GLP-1 medication was officially approved in the US for weight loss in June 2022. As a board member and major shareholder of Weight Watchers, she steered the company to buy a doctors telehealth service. This platform should help customers of Weight Watchers gain prescriptions for GLP-1 drugs to supplement the diet.

So, what is happening here? Since when did obesity become classed as a disease and, furthermore, has it really become curable?

I. The problem called obesity

Obesity is typically determined using a ratio of weight to the square of height – known as the body-mass index, or BMI. A BMI over 25 is normally considered overweight; one over 30 is the standard definition of obesity. This means that a man with an average height of 1.8 meters is overweight if he weighs more than 81 kg and obese if he weighs more than 97 kg.

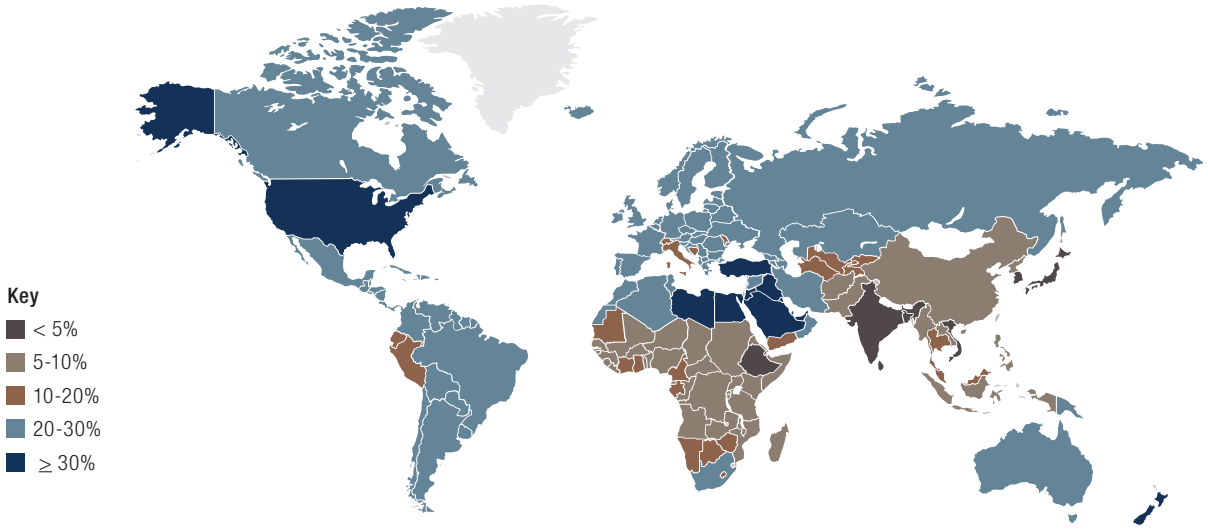
According to the World Health Organization (WHO), worldwide obesity has nearly tripled since 1975. In 2019, 39% of adults were overweight and 13% were obese. Figure 1 shows that the areas with the largest obesity problems are the Middle East, New Zealand and the US, based on 2019 WHO data.

According to the 2019 Global Burden of Disease report, the number of obese people has outstripped the number suffering from malnutrition since 2010.[1] Increasingly, the medical community is seeing it as more than just a lifestyle issue.

The American Medical Association officially recognized obesity as a disease in 2013. Europe took this step in 2021, with the European Commission calling it a "chronic relapsing disease". According to the National Library of Medicine, obesity is a chronic, non-communicable disease caused by genetic, environmental, physiological, behavioral and sleep factors.[2]

The surge in obesity has had significant repercussions and the situation is likely to worsen. The World Obesity Federation's 2023 atlas predicts that 51% of the world, or more than 4 billion people, will be obese or overweight within the next 12 years.[3] The cost to the global economy is projected to climb in this same period to more than USD 4 trillion, or about 2.9% of worldwide GDP. As shown in Figure 2, healthcare costs for severely or morbidly obese adults in the UK are more than 80% higher than those for adults with lower BMIs.

FIG 1. WORLD MAP OF OBESITY PREVALENCE (BMI> 30 KG/M²)

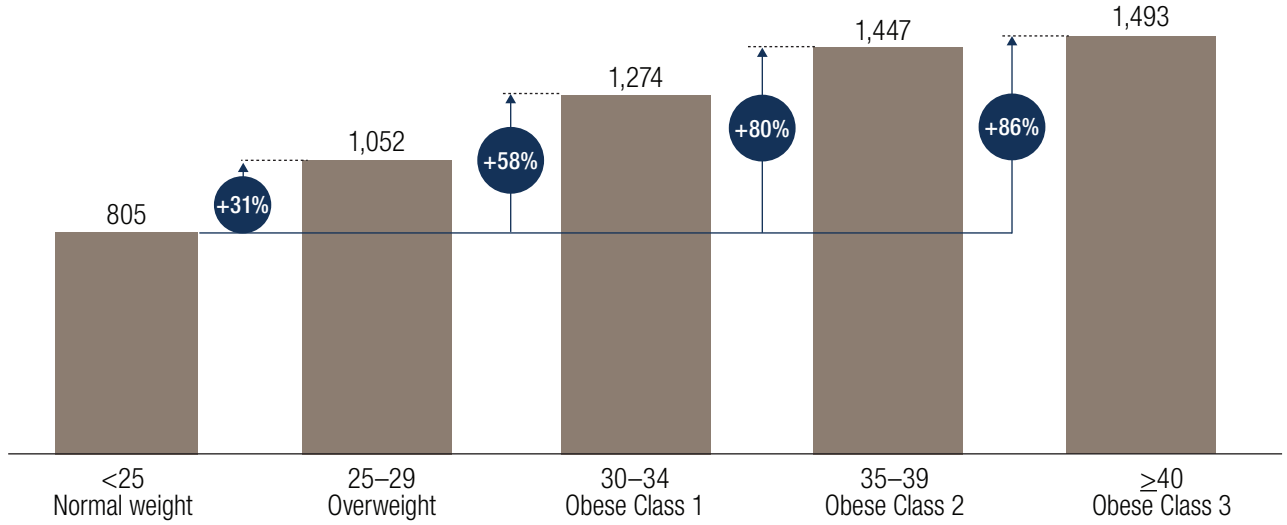


Source: Global Health Observatory Data Repository, see https://apps.who.int/gho/data

[1] https://www.thelancet.com/gbd
[2] https://www.ncbi.nlm.nih.gov/books/NBK279167/
[3] https://www.worldobesity.org/resources/resource-library/world-obesity-atlas-2023

FIG 2. OBESITY AND HEALTHCARE COSTS

Associated medical costs rise as BMI increases
UK medical costs by BMI group, 2012[4] GBP per capita



Source: W.W. Tigbe, A.H. Briggs, and M.E.J. Lean, "A patient-centred approach to estimate total annual healthcare cost by body mass index in the UK Counterweight programme," International Journal of Obesity. August 2013, Federation International de Medecine du Sport and Health Examination Survey, 2012/13. Mckinsey Global Institute analysis.

According to the WHO, obesity is directly responsible for at least 5% of deaths worldwide.[5] It is associated with illnesses including diabetes, strokes and heart disease. Obesity increases the risk of 13 types of cancer, including those of the breast, bowel and womb. It was also found to raise the odds of a patient dying from Covid-19. In short, obesity is an epidemic, causing an explosion in healthcare costs across the globe.

II. Treating obesity

Historically, obesity could be treated with lifestyle interventions, medications, and metabolic and bariatric surgery – clinical terms for halving the size of your stomach through surgery. So far, none of these options has proved bulletproof.

Altering lifestyles though diet and exercise is challenging for many, especially with the proliferation of processed foods that feed lifelong sugar addictions. Additionally, in response to restrictive diets, a human body slows its metabolism to hang on to nutrients for as long as possible. This explains why stopping a diet usually results in regaining the lost weight – and sometimes more.

Bariatric surgery is also not without problems. Combined with lifestyle intervention, it has been effective for most patients. However, the internal scar tissues are known to cause nasty side effects like internal leakage and obstruction of the stomach.

There are also risks of infection and anesthesia-related risks, as with any surgery. This procedure is only recommended for patients with morbid obesity, or BMIs above 40. It can result in weight loss of 50%, but a smaller stomach means the patient must measure food intake to ensure they get the necessary vitamins and minerals. What's more, slipping back into old eating habits can undo the surgery by stretching the stomach again.

Historical obesity medicines have had minimal efficacy and were plagued by safety issues – including fen-phen, once touted as the wonder drug of the '90s but later withdrawn because of its association with heart disease. This has contributed to limited coverage from insurers. However, experts say this is all poised to change, or is already changing, with the arrival of the more efficacious GLP-1 drugs.

The first GLP-1 officially approved for obesity treatment in the US and EU is marketed under the brand Wegovy. The Danish company Novo Nordisk produces Wegovy, which has the same active ingredient, semaglutide, as Novo's diabetes drug Ozempic. Wegovy is said to lower a patient's weight by 15% through weekly injection. US rival Eli Lilly also has a GLP-1 treatment on the market for type 2 diabetes, called Mounjaro, which is expected to be approved for obesity by the end of 2023 or start of 2024. This drug has been shown to lower weight by up to 15-20%, also via weekly injection.

[4] Includes primary care, general practitioner prescriptions, hospitilisation, accident and emergency and outpatient care. 2003 values taken from Tigbe et al. (2013) adjusted using 2012/13 Federation Internationale de Medecine du Sport and Health Examination Survey data on per capita UK costs in each category.

[5] https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight

Insurance reimbursement

Most health insurance plans do not cover obesity treatment with GLP-1 drugs yet; however they do reimburse their use for diabetes and most also cover bariatric surgery. We expect GLP-1 obesity reimbursements to increase once some long-term studies by both Novo and Lilly can demonstrate a positive health result. These studies are designed to show the long-term effects of lowering body weight on cardiovascular issues like strokes, heart attacks and clogged arteries. They are also investigating the effects on hips, knees and other joints, and on metabolic diseases including obstructive sleep apnea. The outcome of the first study is expected in the summer of 2023.

Experts predict that the reimbursement of GLP-1s will start slowly, depending on the outcome of the studies. They may at first be limited to obese patients with previous cardiovascular problems or heart issues.

Despite the high price of Wegovy today (USD 16,000 per year), a rollout to all obese patients would, in theory, lower overall costs for the healthcare system in the long run by reducing strokes, hip replacements and the need for apnea machines. However, providing GLP-1s at the current price to all of the 100 million obese people in the US today would bankrupt the entire healthcare system and the US government, as we are talking about an annual USD 1.5 trillion increase in healthcare spending. The savings it would bring would only come in the years and the decades ahead.

On top of that, the largest insurance scheme in the US – the Medicare program for the elderly, funded mostly by the federal government — is prohibited by law from covering prescriptions for weight loss.

Sold out

Demand for Wegovy is already enormous, despite its recent launch and lack of insurance coverage. Novo Nordisk scaled up production massively, but teething troubles at an outsourcing partner and a shortage of injection pens have caused demand to outstrip supply. In the meantime, Novo Nordisk has lowered the dosage of Wegovy and postponed the European launch. This shows that US patients have truly embraced the treatment and, if they can, are willing to spend more than USD 10,000 per year on it. Only an estimated 3 million US patients are being treated for obesity with Wegovy today. So far, it remains a treatment for the rich.

III. Curing obesity

The first generation of GLP-1 treatments (Wegovy and the obesity version of Mounjaro, called Tirzepatide) are injectables. They work in two different ways:

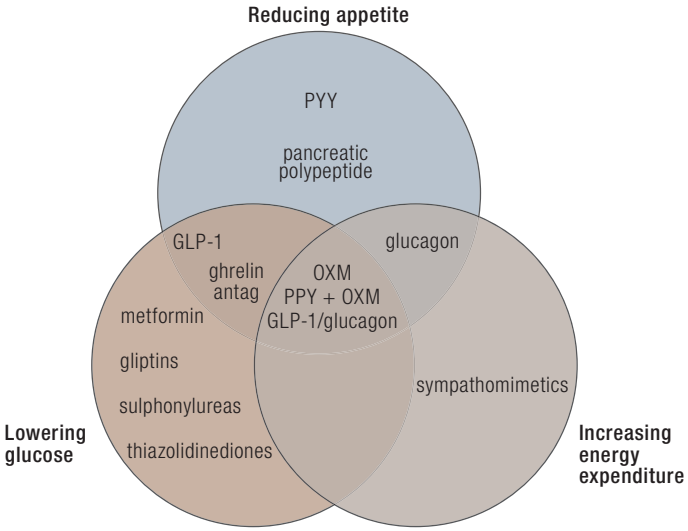
- By reducing the amount of glucose (or sugar) in your blood
- By making the brain give out the signal that you are satiated

Tirzepatide also slows digestion, which might explain the slightly higher weight loss from that treatment shown in the studies. The second generation will be oral versions with similar effects, according to the studies done so far.[6] These are one to two years away from launching and are undergoing phase 3 tests.

The third-generation treatments will combine GLP-1s with another ingredient, glucagon, which should increase energy expenditure of the body and boost the weight loss to 20-25% - at least according to the early-stage test results, which are not always a reliable indicator for final efficacy or approval.

Both Novo Nordisk and Eli Lilly are working on second- and third-generation products and are clearly in the lead. Other pharmaceutical companies, including Pfizer, Zealand Pharma and Gilead, are trying to break up the obesity duopoly by researching their own treatments; however, none has reached the last phase of the required clinical trials yet.

FIG 3. POTENTIAL MECHANISM OF ACTION FOR OBESITY DRUGS



Lifetime treatment

Although weight loss of as much as 25% seems a real game changer, there is a serious caveat: this is a lifetime treatment. Based on what we know today, stopping use of GLP-1s will result in regaining at least two-thirds of the lost weight within a year.[7] Why? It has to do with the so-called set point theory: your body has a set weight that it will want to return to after a strong diet. Weight gains are normally gradual, and your weight set point also increases gradually. However, when calories are suddenly restricted because of war, famine or diet, lost weight is typically regained quickly.[8]

[6] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9302409

[7] See Diabetes, obesity and metabolism, a journal of pharmacology and metabolism: Weight regain and cardiometabolic effects after withdrawal of semaglutide: The STEP 1 trial extension. https://dom-pubs.onlinelibrary.wiley.com

[8] See National library of medicine: Is there evidence for a set point that regulates human body weight? https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2990627/

Unfortunately, GLP-1 medications haven't been around long enough to know what the long-term outlook is for people with obesity and whether there is an optimum length of time to use them for the body to lower its weight set point.

So, does this make the current GLP-1s a cure for obesity? No, not really; it makes the drug more of a chronic treatment, comparable to the way hypertension has been treated since the 1980s. Today, there are few people above age 60 in the western world who are not on hypertension drugs.

IV. GLP-1s: the next smartphones?

Wall Street has a reputation for being enthusiastic about exponential growth opportunities, and this new class of obesity treatments seems to fall into that category. Just do the maths: sales of anti-obesity drugs have already reached USD 2 billion for an estimated 3 million patients, even with limited supplies. With 100 million obese people in the US alone and projections for 4 billion worldwide in the years to come, a USD 60 billion sales target by the end of this decade seems realistic.

Pfizer's CEO, Albert Bourla, said at the J.P. Morgan Healthcare Conference in January 2023 that he saw the combined global market for GLP-1 drugs for obesity and diabetes growing to USD 90 billion. He expects the arrival of oral GLP-1 drugs to make them much more accessible to patients. (Note that Pfizer is developing its own oral GLP-1 treatment, though it is years behind the offerings from Novo Nordisk and Eli Lilly.)

Comparisons with Viagra and hypertension drugs are obvious. Some optimists have even compared Wegovy to the introduction of the iPhone. The launch of the iPhone in the last decade represented a technological leap forward, and smartphones are now ubiquitous. Furthermore, the iOS and Android operating systems have preserved their duopoly amongst operating systems, comparable to Novo Nordisk and Eli Lilly's head start in the obesity market.

Blockbuster sales of USD 60 billion would make GLP-1s the best-selling drugs in the world, beating the current record of Comirnaty – the Covid-vaccine from Pfizer and BioNTech that had sales of USD 56 billion in 2022. Furthermore, for GLP-1s this would be yearly recurring sales, versus the two or three shots needed of Comirnaty.

Obstacles to overcome

As always, such exponential growth is not a sure thing. In this case, the production needs to be expanded massively, especially as oral drugs need more active ingredients than injectables. Supply issues need to be resolved, and the next generations of GLP-1s need to be approved according to plan and with better weight loss outcomes and no negative side effects.

In addition, the price of the treatment needs to fall dramatically to make reimbursement possible for more health insurance programs. Staff shortages could also slow growth – and not just medical staff. An advisory body serving the UK's National Health Service recently recommended Wegovy for certain patients with obesity who have other medical conditions, but only in combination with lifestyle changes. This raises the question: who will coach these patients to a better lifestyle, the already overloaded NHS general practitioners?

More people reaching healthy weights would bring enormous health benefits, thus reducing pressure on the medical system and, in the long run, lowering healthcare costs for society. Though the outlook remains uncertain for the reasons mentioned, GLP-1s seem to provide an excellent shot at that goal, the best we ever had. Even so, we would not compare GLP-1s to smartphones – at least not yet.

V. Investing to solve obesity

Treating obesity could boost quality of life for millions, while delivering quality earnings growth for companies and investors. Since Wegovy received the first FDA approval in June 2022, shares of Novo Nordisk and Eli Lilly have delivered index-beating returns of more than 45%. In that time, Novo increased it growth outlook for 2023 from 13-19% for both sales and operating profit to 24-30% for sales and 28-34% for operating profit, citing robust growth for the GLP-1 franchise to treat obesity and diabetes.

Lilly's latest research showed statistically significant weight loss of up to 15.7% after 72 weeks of using Tirzepatide. The company hopes to get FDA approval in the fourth quarter of 2023. Although obesity and diabetes are a smaller part of Lilly's business than Novo's, investors seem to treat both companies the same when it comes to GLP-1 news flow.

As part of LOIM's trends investing range, the Golden Age strategy offers a strong link to the new obesity treatments. Both Novo Nordisk and Eli Lilly are some of the key investment holdings[9] in the sub-trend Healthy Aging. Even after the recent rallies, the potential for GLP-1s to grow into a USD 60 billion market is not properly discounted in today's share prices, in our view.[10]

[9] Holdings and/or allocations are subject to change.

[10] Novo Nordisk trades at Price-to-Earnings ratio (PE) for 2024 of 27 and a dividend yield of 1.5%, while Eli Lilly trades at a PE of 37 and a 1% dividend yield.

Ancillary benefits

The suppliers to both companies could also offer attractive investment opportunities. Thermo Fisher Scientific, for instance, is an external manufacturer that helps Novo keep up with the growing demand for Wegovy. For them, producing GLP-1 drugs is the next leg of growth after the Covid vaccines.

Dexcom and Abbott Labs, with their devices for measuring glucose in the blood, also benefit from the GLP-1 revolution. The devices have mainly been sold to type 1 diabetes patients so far, but they are likely to be in increasing demand among type 2 diabetes and obese patients undergoing GLP-1 treatment who want to monitor their blood sugar levels – thus creating a much larger market. Both Dexcom and Thermo Fisher Scientific are part of the sub-trend eHealth within the Golden Age strategy.

Sometimes the link to obesity is even less obvious for the strategy. During a recent press conference, the Israeli company InMode mentioned a growing demand for its skin-tightening machines due to GLP-1-related weight loss in the US. This suggests that other industries could be impacted by the trend. Apparently losing weight is just the first step, tightening the loosened skin the second, and perhaps a new wardrobe is the third?

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