Obesity Market Review

July 8, 2024

STIFEL | Healthcare

Table of Contents

STIFEL | Healthcare

787 7th Avenue, New York NY 10019, +1 (212) 887-7777
web: www.stifel.com

Executive Summary

This report reviews recent data releases from the American Diabetes Association and recently released abstracts for September's EASD. We then delve into the emerging market for pharmaceutical products for obesity, updating our July 2023 review of the field. If you wish to read other reports in this series, please go to page 3 of our recent report on the oncology field.

Since last July, the obesity drug field has exploded with innovation, interest and activity. We apologize to the impatient reader upfront as this report, ahem, itself suffers from obesity. Here is a summary of key points made in this report:

Likely Winners in Obesity Drug Race Over Next Five to Seven Years Are Becoming Clear:

- While the 2023 ADA and EASD meetings featured a series of practice-changing revelations about the power of triple incretin agonists, orals and small molecules, this year's ADA featured more incremental disclosures. Recently released EASD abstracts are also incremental in nature.
- There is plenty to be excited about but the main outlines of obesity pharmacology through the end of decade largely appear to have been set.
- Novo's CagriSema (amylin/GLP-1 dual agonist) and Lilly's retatrutide (triple agonist) appear likely to replace semaglutide and tirzepatide as the market leaders.
- Amgen's MariTide (GIP antagonist/GLP-1 agonist) has high potential to disrupt this upcoming "King Kong vs. Godzilla" battle of obesity drug titans.
- We are modeling 30% average weight loss in obese persons at one year with MariTide. For a 250-pound person that corresponds to dropping 75 pounds. This result matches the benefit seen with bariatric surgery.
- MariTide has demonstrated the best 12-week efficacy seen in an obesity drug thus far and we await Phase 2 data from Amgen later this year. GIP antagonism has a number of demonstrated benefits including reductions in fat deposits and inflammation.
- There are some other important contenders to take meaningful share of the obesity market in the years ahead. Foremost among these is Viking Therapeutics. Its VK2735 drug has shown outstanding efficacy at 12-weeks treatment and, remarkably, has not yet found its maximum tolerated dose.
- Also, we have seen encouraging data emerging from the GIP/GLP agonist in development by Hercules/Hengrui (HRS-9531) and Gan & Lee's GZR18.
- A key development has involved the recent success of amylin agonists, most notably Zealand's petrelintide. This drug appears to be well tolerated and could be quite commercially impressive given that 30% of GLP-1 users drop off within a month, presumably because they can't tolerate the drugs.

Executive Summary (continued)

- Also of high interest are GIP monotherapy antagonists. The leading contender today is Antag's AT-7687 but others are in the hunt. Preclinical data point to a market very similar than that for amylin agonists. There are obvious combination possibilities such as making an amylin agonist/GIP antagonist to rival GLP-1 monotherapy or triples like retatrutide.
- Another key development involves oral small molecule incretin options such as Lilly's orforglipron or Structure Therapeutics' GSBR-1290. Because these drugs work well and are much less costly to make than peptides it is likely that orals will take meaningful market share in time.
- Further, there are multiple oral small molecule competitors in emerging classes such as CB1 receptor inverse agonists, mitochondrial uncouplers, apelin agonists, NLRP3 inhibitors and MASP inhibitors. Some of these are going to work and could be combined with small molecule GLP-1 agonists to create an even more effective polypill.
- For now, we don't think that small molecule drugs displace the injectables. Their demonstrated efficacy is good but not best-in-class. As in the immunology market, orals will have their place but injectables will reign supreme. In time, of course, this could change, particularly due to the astronomical capital costs associated with the manufacture of today's peptide drugs.

Ongoing Consumerization of the Obesity Market of Profound Importance to U.S. Pharmaceutical Industry

- An important development is the unfolding consumerization of obesity drug buying with the proliferation of online telehealth services selling compounded semaglutide.
- Consumer interest in managing weight is extraordinary and fascination with GLP-1's is off the charts today. Consumers are pulling out their wallets and buying obesity drugs directly. Hundreds of thousands have already done so. Soon, the numbers will be millions.
- Consumerization has profound implications for the future of the pharmaceutical industry as did the shift of the television and record business to online streaming services. Like these businesses, we don't think that this consumerization genie can be put back in the bottle.
- The post-WWII period in the U.S. has involved a gradual shift from a private-pay pharma market to one mediated by payors. With rising co-pays, opaque rebates/refunding and fiscal pressure on governments, it appears likely that more consumers will pay for their obesity medications out of pocket.
- Recent moves by Lilly and Pfizer to offer drugs directly to patients are a good move and commendable. Yet, these services don't come with the type of promotion that obesity DTC marketers like Ro/Hims & Hers are using on services like TikTok.
- We see the consumer obesity market continuing to explode and expect that out-of-pocket spend could eventually exceed $100 billion – far more than is spent today on aesthetic products like Botox®.

Executive Summary (continued)

Lack of Reimbursement for Obesity Drugs Misaligned with Emerging Views of Food Addiction and Benefits to Society of Weight Management

- Conspicuously, the U.S. government doesn't reimburse for obesity drugs at all. Despite overwhelming evidence of obesity harms and patient benefits from incretin drugs, attitudes towards reimbursement among commercial payors in the United States are negative.
- Given fiscal pressures on governments and the U.S. healthcare system we think access to obesity drugs from the payor-mediated market is going to remain heavily titrated for years to come.
- Payor attitudes remind us of days past when drugs for addiction were not widely prescribed or paid for – as addiction, particularly alcoholism, was seen as a moral failing, not a medical condition.
- The evidence that obesity can be thought of as the result of food addiction is surprisingly strong, particularly among children and adolescents.
- The pharmacoeconomics of covering obesity drugs appear quite favorable. USC economists estimate that reimbursing obesity drugs could save over $1 trillion in healthcare costs over the next decade.
- The lack of reimbursement creates obvious pressures and inequities within the entire system as obesity disproportionately impacts the poor.

Political Considerations in the Emerging Obesity Drug Landscape

- An important topic is the political side of the obesity market.
- Today, it is very popular for Democratic politicians to decry the price of GLP-1 agonists. These comments are naïve and fail to recognize the high capital costs that companies like Lilly and Novo are having to bear to meet ongoing demand.
- The strong self-pay consumer market and failure to reimburse obesity drugs creates an obvious imbalance between pharma company / government power dynamics. Payors normally hold the cards and pharma companies do their best to get paid in a world of monopsony. But, without reimbursement Lilly and Novo face a negotiating counterparty with little price leverage.
- Given the extraordinary interest in obesity drugs, there is an obvious opportunity for an enterprising politician to create something like "Operation Warp Speed" (think "Operation SlimFast") to have the government pay for GLP-1's for all citizens in need. Most likely, this would fall outside of Medicaid and Medicare. As with the Pandemic this would need to involve helping to pay for manufacturing capacity and working out a deal with pharma, presumably via some type of tender.
- We think this could be huge vote getter that could appeal to a highly divided nation. Importantly, obesity rates are much higher, on average, in red states, creating an advantage for either party that chooses to seize the opportunity.

Executive Summary (continued)

Future Directions in the Obesity Drug Market (2035 and Beyond)

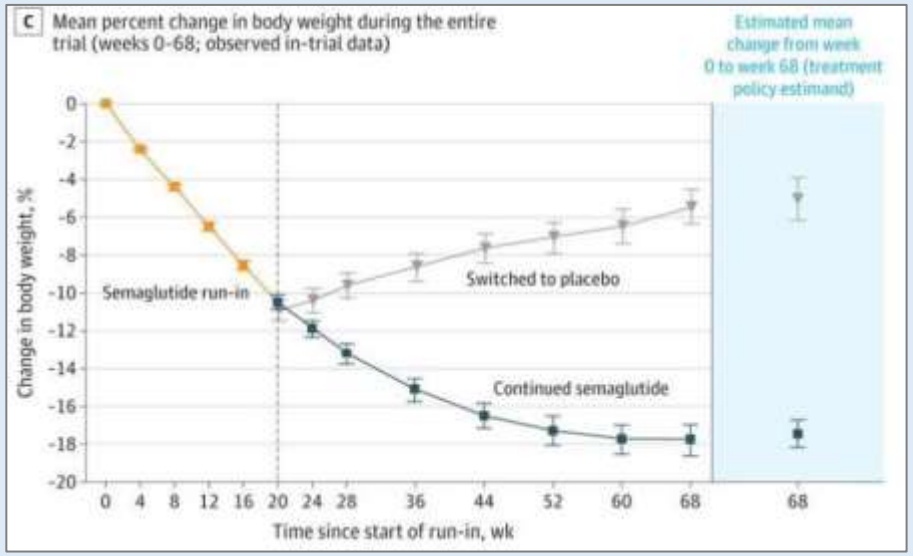
- There are numerous opportunities to improve on current therapeutics including designing drugs that will conserve muscle during weight loss and designing drugs that can be optimized for treatment of comorbid conditions such as fatty liver, heart failure and the like.
- We delve into where the obesity market is going in the decade after next and suggest that the payor-mediated market may see drug developers focus on improving their harm reduction stories.
- Impressive as the data are, for example, from Novo's SELECT study, there is potential to tell a far better story about benefits of obesity drugs by focusing in on why obesity leads to bad outcomes.
- One key factor is insulin resistance. Only about half of obese persons become insulin resistant and the harm from obesity is almost entirely concentrated among these persons.
- Obviously, payors could require that obesity drug reimbursement be limited to persons who are insulin resistant.
- Further, drug companies could develop drugs that are more insulin sensitizing than the current GLP-1 agonists.
- We identify a series of emerging drug classes that could be pursued as joint weight loss / insulin sensitizers.
- Promising emerging players in this area include Adipo Pharma and Juvena.
- A related opportunity is to address the inflammation that results from obesity. Like insulin resistance much of the harm of obesity flows from associated inflammation.
- GLP-1 agonists do a good job of reducing inflammation indirectly but there is the possibility of employing direct anti-inflammation drugs in treating obese patients.
- The etiology of inflammatory obesity is well-known and involves macrophage envelopment of adipocytes through so-called crown-like structures.
- Inflammatory fat is not good for you and, among other things, has been associated with higher risks of cardiovascular disease and cancer.
- In the same sense that obesity causes insulin resistance but not all insulin resistant persons are obese, there is ample evidence that inflammatory fat in persons with "normal" BMI's can cause the same harm as in the obese.
- It appears that our society should invest more in tracking inflammation, especially inflammatory fat deposits, and address it – including with GLP-1 agonists.
- There is obvious potential to expand the obesity market by creating pharmaceuticals that target the specific harms caused by obesity and then marketing these with a precision approach.

Executive Summary (continued)

Weight Rebound After Cessation of GLP-1 Agonists a Top Priority

- We also look at the true "holy grail" of obesity pharmacology – can we prevent weight rebound after cessation of current treatments?
- While not universal, rebound after weight loss is a serious issue and, among other things provides insurers with a reason to not pay for the drugs.
- Consumers are focused on post-GLP1 weight rebound and would be highly interested in strategies to manage it.
- We look at the science and ask whether there might be better approaches to manage weight loss rebound.
- There are multiple potential future scenarios in this regard including drugs that are given infrequently (say once a year), maintenance drugs that are less expensive and have less adverse effects than GLP-1's or, ideally, drugs that can be given only once ("one-and-done" approaches).
- Today, Fractyl is working on a gene therapy that would provide long-term GLP-1 agonism. This is interesting but quite early in its development.
- We think to solve the rebound problem, one needs to consider the root causes of obesity. Ideally, an explanation would for why obesity it has risen so quickly across the world, particularly in the United States. Further, a good explanation should explain the long-term weight loss seen with bariatric surgery.

Weight Regain Rapid After Cessation of Semaglutide



- We look at seven root cause theories: (a) obesity is fixed–it happens and a homeostatic setpoint that will frustrate all efforts at change, (b) obesity is genetic and one would most likely need gene therapy, gene editing or enzyme replacement therapy to change it, (c) obesity has an epigenetic source and is impacted by environment in very specific ways, (d) obesity is caused by fructose addiction, (e) obesity results from dysregulation of dopamine in the brain that doesn't reverse upon weight loss, (f) obesity results from dysregulation of glutamate receptors and can be altered by well-known NMDA drugs or (g) altered lipolysis and oxidation in adipocytes explains much of weight gain and later rebound.
- The glutamate areas, the adipocyte lipolysis/oxidation and addiction areas have the best evidence and will require further scientific work but offer enormous hope to patients and commercial upside to sponsors.

ADA / EASD Clinical Update: Emerging Obesity Data

ADA Presentations / EASD Abstracts

Last year's ADA featured stunning data on Eli Lilly's Retatrutide which showed 22% placebo-adjusted weight loss (58 pounds) at 48 weeks. This was accompanied by similarly impressive data from orforglipron, an oral incretin drug.

This was one of the most exciting professional meetings we had seen. In contrast, this year's ADA was more normal. There was some important news – most importantly the reduction in sleep apnea associated with use of tirzepatide. But there were no practice-changing clinical data on the obesity front.

That is, the clinical data released in the obesity area was for agents that did not beat agents already in development or clinical use in terms of either efficacy or safety.

Altimmune released 48-week data for Pemvidutide, a GLP-1/Glucagon dual receptor agonist, in development for obesity. Four Chinese companies released data at ADA on weight loss associated with incretin drugs. These companies were Hengrui (now Hercules), Gan & Lee, SciWind and Brightgene. Perhaps the most impressive new data released were from Hercules. Their agent, HRS9531, a dual GLP-1/GIP receptor agonist, showed 16.7% weight loss at 24 weeks. These results are better than was shown last year at ADA for Retatrutide in efficacy but not as good as has recently been shown for Roche's CT-388 (GIP/GLP Dual).

Zealand's data for a long-acting amylin agonist, petrelintide were quite important because they was not coupled with a GLP-1 agonist. Nausea was infrequent with this agent.

A number of promising emerging agents were also discussed at ADA including Arrowhead's poster for ARO-INHBE. INHBE knockdown may potentially lead to a suppression in body weight gain, loss of fat mass, and preservation of lean mass. Arrowhead plans to enter the clinic in late 2024 to begin clinical studies of this agent.

A very interesting poster was from OrsoBio which shared a late-breaking poster which showed that TLC-6740, a mitochondrial protonophore, was relatively safe and able to oxidize fat in a Phase 1a study. Also, of interest, was Aldeyra's discussion of recent preclinical data in obesity of a RASP modulator in conjunction with an Investor Roundtable held the day before the ADA conference began. Other interesting presentations and posters were shared by Adocia, Borui, Hanmi, Hansoh, Highfield, Inventage Lab, NeuroBo, Progen, QL, ScholarRock and Sun Pharma.

EASD Abstracts for September were posted online on July 1 but most abstracts haven't appeared yet because it is so early.

QL Pharma of China posted strong data for a GLP-1 agonist showing 11.2% weight loss at max dose at 12-weeks. Innovent showed off mazdutide results at 48-weeks but most of this had been shared before. Lilly is sharing very interesting cardiac biomarker data on what happens with retatrutide in long-run treatment.

ADA Clinical Update

Lilly's Tirzepatide Associated with Reduction in Sleep Apnea

Malhotra A, Grunstein RR, Fietze I, Weaver TE, Redline S, Azarbarzin A, Sands SA, Schwab RJ, Dunn JP, Chakladar S, Bunck MC, Bednarik J; SURMOUNT-OSA Investigators, "Tirzepatide for the Treatment of Obstructive Sleep Apnea and Obesity," *N Engl J Med*, June 21, 2024.

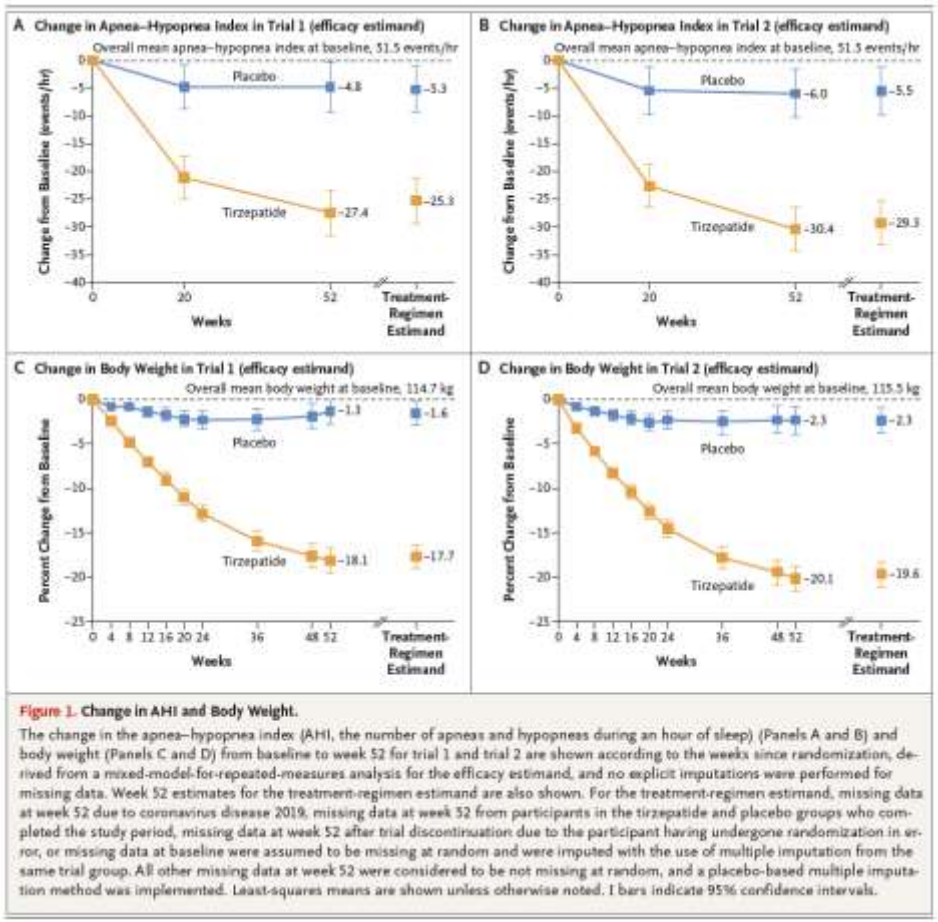


Figure 1. Change in AHI and Body Weight.

The change in the apnea–hypopnea index (AHI, the number of apneas and hypopneas during an hour of sleep) (Panels A and B) and body weight (Panels C and D) from baseline to week 52 for trial 1 and trial 2 are shown according to the weeks since randomization, derived from a mixed-model-for-repeated-measures analysis for the efficacy estimand, and no explicit imputations were performed for missing data. Week 52 estimates for the treatment-regimen estimand are also shown. For the treatment-regimen estimand, missing data at week 52 due to coronavirus disease 2019, missing data at week 52 from participants in the tirzepatide and placebo groups who completed the study period, missing data at week 52 after trial discontinuation due to the participant having undergone randomization in error, or missing data at baseline were assumed to be missing at random and were imputed with the use of multiple imputation from the same trial group. All other missing data at week 52 were considered to be not missing at random, and a placebo-based multiple imputation method was implemented. Least-squares means are shown unless otherwise noted. I bars indicate 95% confidence intervals.

Table 2. Primary and Key Secondary End Points According to Trial Group for the Treatment-Regimen Estimand.*

End Point	Trial 1			Trial 2		
	Tirzepatide N=114	Placebo N=120	Estimated Treatment Difference or Relative Risk (95% CI)†	Tirzepatide N=120	Placebo N=115	Estimated Treatment Difference or Relative Risk (95% CI)†
Primary end point						
Change in AHI (95% CI) — no. of events/hr	−25.3 (−29.3 to −21.2)	−5.3 (−9.4 to −1.1)	−20.0 (−25.8 to −14.2)	−29.3 (−33.2 to −25.4)	−5.5 (−9.9 to −1.2)	−23.8 (−29.6 to −17.9)
Key secondary end points						
Percent change in AHI (95% CI)	−50.7 (−62.3 to −39.1)	−3.0 (−16.9 to 10.9)	−47.7 (−65.8 to −29.6)	−58.7 (−69.1 to −48.4)	−2.5 (−16.2 to 11.2)	−56.2 (−73.7 to −38.7)
Reduction of ≥50% in AHI events at wk 52 — no. (%)	70 (61.2)	23 (19.0)	3.3 (2.1 to 5.1)	86 (72.4)	27 (23.3)	3.1 (2.1 to 4.5)
AHI of <5 or AHI of 5 to 14 with ESS ≤10 at wk 52 — no. (%)	48 (42.2)	19 (15.9)	2.9 (1.8 to 4.8)	60 (50.2)	16 (14.3)	3.3 (2.0 to 5.4)
Percent change in body weight (95% CI)	−17.7 (−19.0 to −16.3)	−1.6 (−2.9 to −0.2)	−16.1 (−18.0 to −14.2)	−19.6 (−21.0 to −18.2)	−2.3 (−3.8 to −0.9)	−17.3 (−19.3 to −15.3)
Change in hsCRP concentration at wk 52 (95% CI) — mg/dl	−1.4 (−1.7 to −1.1)	−0.7 (−1.1 to −0.3)	−0.7 (−1.2 to −0.2)	−1.4 (−1.6 to −1.1)	−0.3 (−0.8 to 0.1)	−1.0 (−1.6 to −0.5)
Change in sleep apnea–specific hypoxic burden at wk 52 (95% CI) — % min/hr	−95.2 (−103.2 to −87.2)	−25.1 (−44.3 to −5.9)	−70.1 (−90.9 to −49.3)	−103.0 (−110.3 to −95.6)	−41.7 (−63.9 to −19.5)	−61.3 (−84.7 to −37.9)
Change in systolic blood pressure at wk 48 (95% CI) — mm Hg	−9.5 (−11.5 to −7.5)	−1.8 (−3.9 to 0.2)	−7.6 (−10.5 to −4.8)	−7.6 (−9.7 to −5.6)	−3.9 (−6.3 to −1.6)	−3.7 (−6.8 to −0.7)
Additional secondary end point‡						
Change in diastolic blood pressure at wk 48 (95% CI) — mm Hg	−4.9 (−6.4 to −3.5)	−2.1 (−3.6 to −0.6)	−2.8 (−5.0 to −0.7)	−3.3 (−4.7 to −1.9)	−2.2 (−3.8 to −0.6)	−1.1 (−3.2 to 1.0)

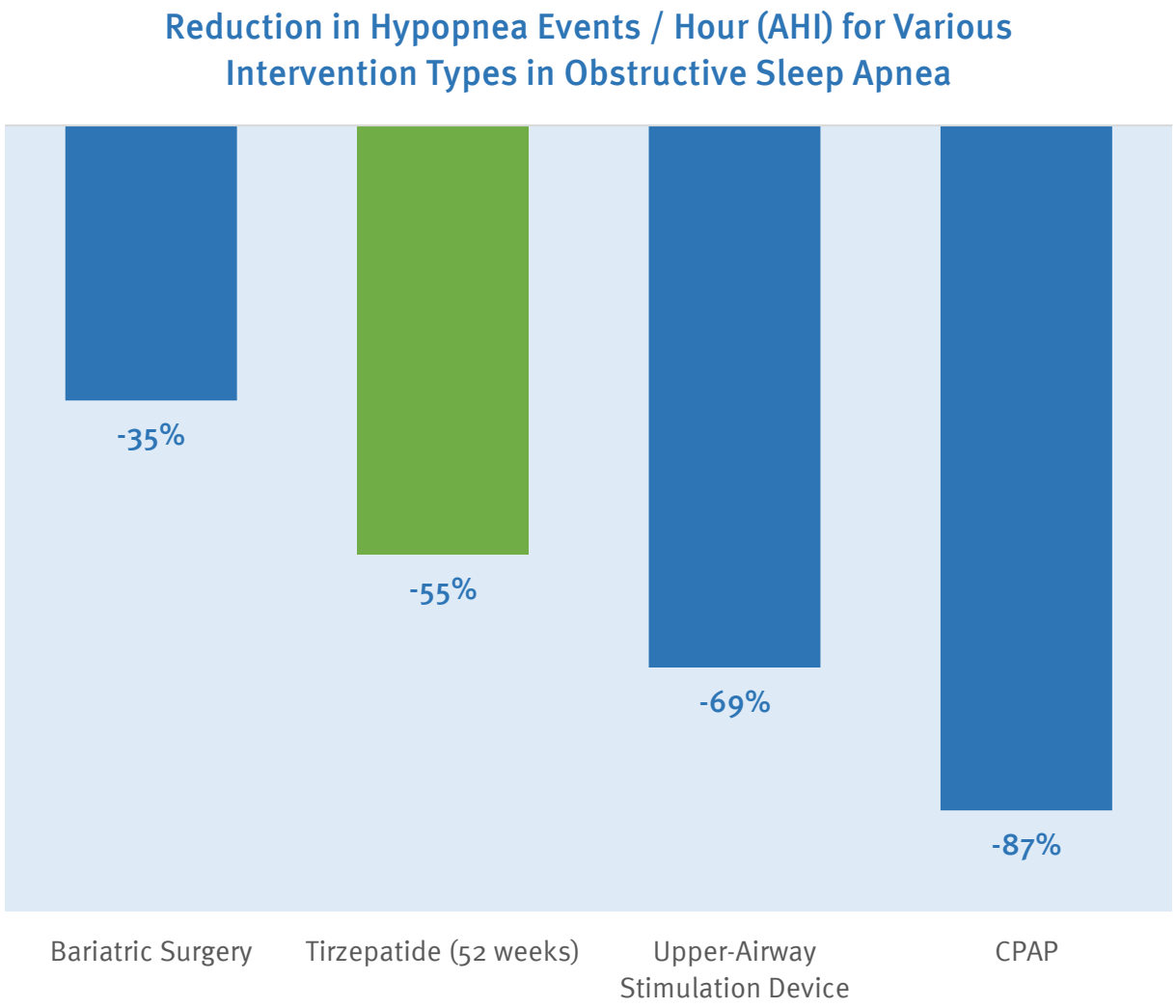
* Data are least-squares means with 95% confidence intervals or numbers and percents of patients, unless otherwise stated. Relative risks are calculated using g-computation methods[24] from logistic regression. P values for categorical end points are based on a logistic regression model. All changes are from baseline to week 52 with the exception of blood pressure, which was change from baseline to week 48 to prevent suspension of PAP therapy in trial 2 from confounding the assessment.

† Differences between the groups are presented as the estimated treatment difference with the exception of the week-52 categories of reduction of ≥50% in AHI events and AHI of <5 or 5 to 14 with ESS ≤10, which are shown as relative risk. Estimated treatment differences for the secondary end points are the differences in the least-squares mean changes. P<0.001 for the primary and key secondary end points with the exceptions of the change in hsCRP concentration at week 52 in trial 1 (P=0.004) and the change in systolic blood pressure at week 48 in trial 2 (P=0.02).

‡ The confidence intervals for this end point have not been adjusted for multiplicity and should not be used to make inferences.

Source: https://www.nejm.org/doi/full/10.1056/NEJMoa2404881

Tirzepatide vs. Alternative Interventions for Sleep Apnea



Lilly shares gained 0.5% on the news that Tirzepatide is associated with less sleep apnea while Resmed (a CPAP pureplay) dropped 14.6% on the news.

The market appears to be assimilating the implications of the NEJM tirzepatide study more or less correctly.

CPAP dramatically reduces the AHI – in almost all cases, to a normal level.

In contrast, tirzepatide reduces the AHI, on average, by 55%. This is meaningful but is no death knell for CPAP manufacturers. In the NEJM paper, 42% of subjects on tirzepatide that were not on CPAP saw resolution of disease.

A good discussion of this trial and its indications appeared this week in Stat+.

Sources: (1) bariatric surgery: https://www.nature.com/articles/s41598-021-84570-6, (2) tirzepatide: https://www.nejm.org/doi/full/10.1056/NEJMoa2404881, (3) upper airway stimulation device: https://www.nejm.org/doi/full/10.1056/NEJMoa1308659 and (4) CPAP: https://www.nejm.org/doi/10.1056/NEJMoa1606599

Hengrui / Hercules Show 16.8% Weight Loss at 24 Weeks

ADA Abstract, "Efficacy and Safety of HRS9531, a Novel Dual GLP-1/GIP Receptor Agonist, in Obese Adults–A Phase 2 Trial"

Author(s): LIN ZHAO, DAN ZHU, DEXUE LIU, TIANRONG PAN, DONGJI WANG, YUAN HUI, HONGWEI LING, HANQIN CAI, MEIFANG ZENG, YUE ZUO, YUQI SUN, YIKE WANG, XIAOYING LI, Beijing, China, Nanyang, China, Hefei, China, Lianyungang, China, Xuzhou, China, Changchun, China, Shanghai, China

Introduction: HRS9531, a novel dual GLP-1 and GIP receptor agonist, has shown prominent efficacy in glycemic control and weight loss in phase 1 trials. This phase 2 study evaluated the efficacy and safety of HRS9531 in obese adults without diabetes.

Methods: In this randomized, double-blind, placebo-controlled phase 2 study, 249 Chinese adults with a BMI of 28-40 kg/m2 were randomized 1:1:1:1:1 to receive once-weekly subcutaneous injections of HRS9531 (1.0 mg, 3.0 mg, 4.5 mg, and 6.0 mg) or placebo for 24 weeks (24W).

Results: **The least-squares mean percentage change in body weight from baseline at W24 was -5.4% (95% CI -7.3% to -3.5%), -13.4% (-15.2% to -11.5%), -14.0% (-15.9% to -12.1%), and -16.8% (-18.8% to -14.9%) in the 1.0 mg, 3.0 mg, 4.5 mg, and 6.0 mg groups, respectively, compared to -0.1% (-2.1% to 1.8%) in the placebo group (P<0.0001 for all comparisons with placebo).** The proportion of participants achieving ≥5% body weight reduction was 52.0%, 88.2%, 92.0%, 91.8%, and 10.2%, respectively. Additionally, HRS9531 outperformed placebo in lowering blood pressure, improving glycemic control, and reducing triglyceride levels. The least-squares mean changes from baseline to W24 in systolic blood pressure ranged from -4.46 to -8.33 mmHg in the HRS9531 groups (placebo: -0.41 mmHg) and in the waist circumference ranged from -5.14 to -12.73 cm in the HRS9531 groups (placebo: -1.82 cm). Most adverse events (AEs) were mild or moderate in severity, and the most common AEs were nausea, diarrhea, decreased appetite, and vomiting, occurring primarily during dose escalation. No serious AEs were treatment-related and no participants discontinued treatment due to treatment-related AEs.

Conclusion: HRS9531 effectively reduced body weight, blood pressure, blood glucose, and triglycerides, with a favorable safety profile. These data support further clinical development of HRS9531 for obesity treatment.

Source: ADA 2024 Website

Gan & Lee Pharmaceuticals Announces Progress on Obesity Treatments at ADA

BEIJING and BRIDGEWATER, N.J., June 22, 2024 /PRNewswire/ -- Gan & Lee Pharmaceuticals (Gan & Lee, Shanghai Stock Exchange: 603087) announced the results of the Phase 1b/2a clinical study of the Company's independently developed glucagon-like peptide-1 (GLP-1) receptor agonist, GZR18 Injection, in an obese/overweight population in China, along with the results of two other innovative insulins' preclinical studies in poster presentations at the American Diabetes Association's （ADA's） 84th Scientific Sessions.

This randomized, double-blind, placebo-controlled, dose-escalation Phase 1b/2a clinical study evaluated the safety, tolerability, pharmacokinetics and efficacy of GZR18 Injection in Chinese subjects with obesity/overweight after multiple administration on a once-weekly (QW) or bi-weekly (Q2W) dosing interval. A total of 36 obese participants were enrolled in the study and randomized in a 3:1 ratio to receive a dose titration of 1.5 mg to 30 mg of GZR18 Injection or a matching placebo for a total of 35 weeks.

The study results demonstrated a superior efficacy of GZR18 Injection than placebo for weight reduction in Chinese obese subjects. **After 35 weeks of treatment, the mean weight change from baseline in the GZR18 QW group was -16.5 kg (95% CI: -19.9 kg, -13.1 kg); the placebo-adjusted mean percent weight change from baseline was -18.6%** (95% CI: -25.5%, -11.6%). Although it was not a head-to-head study, when compared to the published data on weight reduction of similar products currently available on the market, GZR18's weight-reducing ability outperformed Semaglutide and dual-incretin receptor targeted Tirzepatide in similar study duration. Meanwhile, the mean weight change from baseline in the GZR18 Q2W group was -11.3 kg (95% CI: -15.4 kg, -7.2 kg); the placebo-adjusted mean percent weight change from baseline was -13.5% (95% CI: -21.0%, -6.0%).

In terms of safety, GZR18 Injection was well tolerated in obese participants. The most commonly reported adverse events (AE) during treatment were gastrointestinal related AEs, and all were mild to moderate in severity. This is consistent with the incretin-based therapies approved for the treatment of obesity and overweight and occurred mainly in the early dose-escalation period. There were no serious hypoglycemic events in this study and no serious adverse events related to the investigational drug.

Source: https://www.prnewswire.com/news-releases/gan--lee-pharmaceuticals-announces-significant-progress-on-new-diabetes-and-obesity-treatments-at-the-american-diabetes-associations-84th-scientific-sessions-302179565.html

Gan & Lee Show 18.6% Weight Loss at 35 Weeks

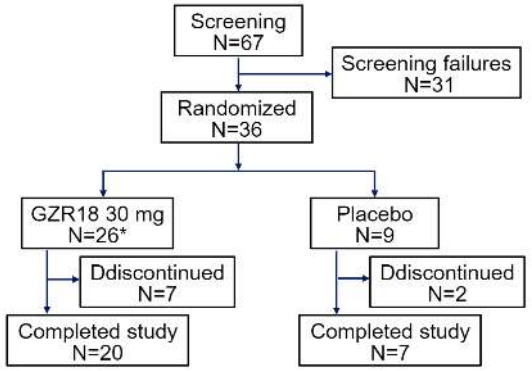
A novel GLP-1 analog, GZR18, induced an 18.6% weight reduction in subjects with obesity in a phase Ib/IIa trial

Linong Ji[1], Wei Chen[2], Ruihua Dong[3], Mingxia Yuan[3], Dong Zhao[4], Shuguang Pang[5], Liyuan Zhao[2], Jing Zhao[2], Zhong-Ru Gan[2]

[1]Peking University People's Hospital, Beijing, China; [2]Gan & Lee Pharmaceuticals, Beijing, China; [3]Beijing Friendship Hospital, Capital Medical University, Beijing, China; [4]Beijing Luhe Hospital, Capital Medical University, Beijing, China; [5]Jinan Central Hospital, Jinan, China.

Results

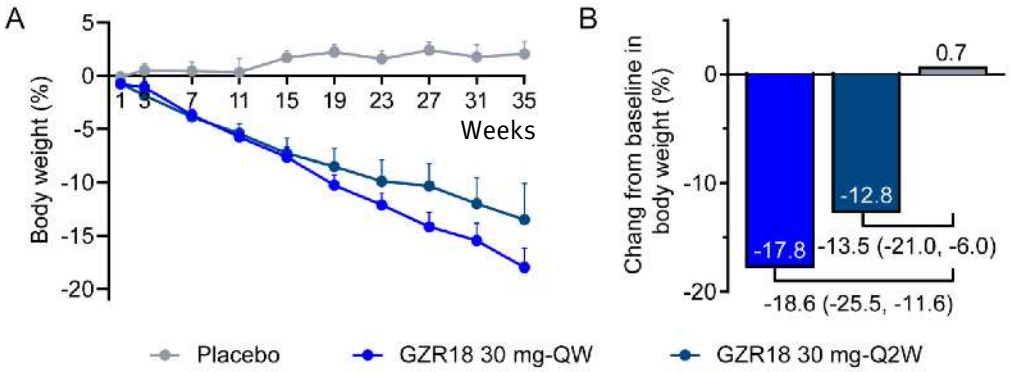
Subject disposition



Demographics and baseline characteristics

Characteristics	GZR18 30mg N=26	Placebo N=9
Male | Female	46.2% | 53.8%	55.6% | 44.4%
Age (years)	35.2 ± 8.79	40.1 ± 9.92
Han# | Other	96.2% | 3.8%	100% | 0
Body weight (kg)	95.07 ± 18.34	94.74 ± 16.50
Height (cm)	167.53 ± 10.52	166.72 ± 7.43
BMI (kg/m^2)	33.63 ± 3.92	33.92 ± 4.29
Waist circumference (cm)	106.83 ± 12.64	104.68 ± 10.50

Results: GZR18 induced an 18.6% weight reduction



Results: Summary of adverse events

- Most AEs were Gastrointestinal related, mild to moderate in severity, mainly occurred in early dose-escalation period.
- One SAE of appendicitis for GZR18 30 mg- QW was reported, not considered IP-related.

AEs, n(%)	GZR18 30 mg- QW, N=16	GZR18 30 mg-Q2W, N=10	Placebo, N=9
TEAE	14 (87.5)	10 (100.0)	7 (77.8)
IP-related TEAE	9 (56.3)	5 (50.0)	3 (33.3)
TEAE leading to discontinuation	3 (18.8)	0 (0)	0 (0)
SAE	1 (6.3)	0 (0)	0 (0)
IP-related SAE	0 (0)	0 (0)	0 (0)
Death	0 (0)	0 (0)	0 (0)
Injection site reaction	0 (0)	0 (0)	0 (0)
Hypoglycemia TEAE	1 (6.3)	1 (10.0)	0 (0)
Gastrointestinal TEAE	9 (56.3)	4 (40.0)	3 (33.3)
Nausea	9 (56.3)	2 (20.0)	1 (11.1)
Diarrhea	7 (43.8)	4 (40.0)	1 (11.1)
Vomiting	4 (25.0)	1 (10.0)	0 (0)
Eructation	4 (25.0)	2 (20.0)	0 (0)
Constipation	0 (0)	2 (20.0)	2 (22.2)

AE= Adverse event, SAE= Serious AE, IP= Investigational product, N= Number of subjects who were randomized and received at least 1 dose of IP, n= Number of subjects per event type, QW= Once a week, Q2W= Once every 2 weeks, TEAE= Treatment-emergent AE

Source: Gan & Lee Poster Presentation, ADA 2024

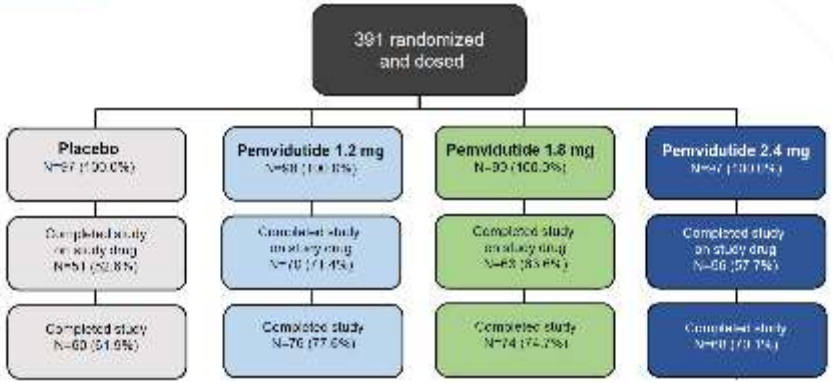
Altimmune's Pemvidutide Shows 15.6% Weight Loss at 48 Wks

PEMVIDUTIDE, A GLP-1/GLUCAGON DUAL RECEPTOR AGONIST, IN SUBJECTS WITH OVERWEIGHT OR OBESITY: A 48-WEEK, PLACEBO-CONTROLLED, PHASE 2 TRIAL (MOMENTUM)

L Aronne[1], M.S. Harris[2], M.S. Roberts[2], J. Buschalk[2], S. Toman[2], J. Kaspar[2], L. He[2], J. Yang[2], J.P. Frias[3], S.K. Browne[3]
[1]Weill Cornell Medicine, New York, NY, USA, [2]Altimmune, Inc, Gaithersburg, MD, USA, [3]Velocity Clinical Research, Los Angeles, CA, USA

altimmune | NASDAQ: ALT

DISPOSITION OF SUBJECTS



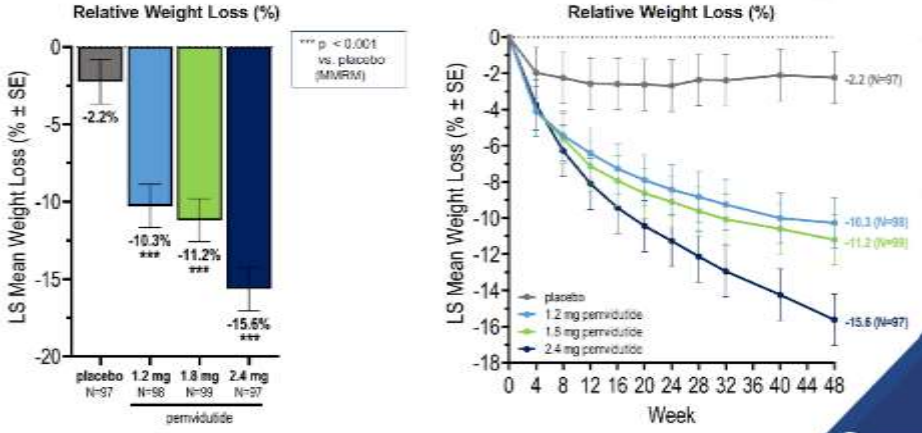
74.1% of subjects receiving pemvidutide completed the study

8

altimmune

Weight Loss of 15.6% Achieved at Week 48 on 2.4 mg

MEAN WEIGHT LOSS OF 32.2 LBS AND MAXIMAL WEIGHT LOSS OF 87.1 LBS



10 MMRM, mixed model for repeated measures

altimmune

OVERVIEW OF ADVERSE EVENTS (AEs)

Characteristic		Treatment			
		Placebo (N=97)	1.2 mg (N=98)	1.8 mg (N=99)	2.4 mg (N=97)
SAEs related to study drug	N (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.0%)
AEs leading to study drug discontinuation					
All AEs leading to discontinuation	N (%)	6 (6.2%)	5 (5.1%)	19 (19.2%)	19 (19.6%)
Drug-related AEs leading to discontinuation	N (%)	2 (2.1%)	4 (4.1%)	16 (16.2%)	15 (15.5%)
Gastrointestinal (GI) AEs—mainly mild to moderate					
Nausea	N (%)	11 (11.3%)	25 (25.5%)	59 (59.6%)	50 (51.5%)
Vomiting	N (%)	3 (3.1%)	6 (6.1%)	27 (27.3%)	27 (27.8%)
Diarrhea	N (%)	5 (5.2%)	8 (8.2%)	10 (10.1%)	18 (18.6%)
Constipation	N (%)	8 (8.2%)	17 (17.3%)	13 (13.1%)	22 (22.7%)
AEs of Special Interest (AESI)	N (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Major Adverse Cardiac Events (MACE)	N (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Cardiac AEs, including arrhythmias	N (%)	4 (4.1%)	3 (3.1%)	4 (4.0%)	3 (3.1%)

- Only 1 drug-related SAE of vomiting
- No AESI or MACE events
- No imbalances in cardiac AEs across treatment groups

18

altimmune

Source: https://ir.altimmune.com/static-files/912ee924-e705-4354-9c7b-fc6a533e62e5

SciWind Data for Oral Ecnoglutide (GLP-1r Agonist)

1871-LB
ADA 2024

Phase 1 topline safety, efficacy, and pharmacokinetics of oral ecnoglutide

Zhiyi Zhu[1], Yao Li[1], Wanjun Guo[1], Qing Zheng[1], Jianhui Deng[1], Eric Adegbite[2], Stephen Ross[2], Libnir Telusca[2], Catherine L. Jones[2], Martijn Fenaux[2], Susan Xu[2], Mohammed K. Junaidi[2]
[1]Hangzhou Sciwind Biosciences, Hangzhou, China [2]Sciwind Biosciences, San Ramon, USA

SCIWIND

BACKGROUND

Ecnoglutide is a cAMP-biased, long-acting GLP-1 receptor agonist being developed for the treatment of type 2 diabetes mellitus and obesity. Oral ecnoglutide (XW004) is formulated with an absorption enhancer, PNAC (T2026).

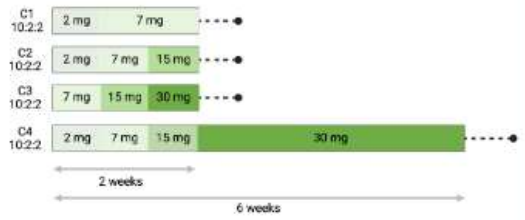
The objective of this study was to evaluate the safety and tolerability, pharmacokinetics, and efficacy of oral ecnoglutide in healthy and overweight/obese adults.

METHODS

We conducted a randomized, double-blind, placebo-controlled Phase 1 study in healthy (Cohorts 1 to 3) and healthy obese (Cohort 4) adults at a single site in Australia. The study enrolled 43 healthy (Cohorts 1-3) and 15 healthy obese (Cohort 4) participants. Participants were randomized to receive placebo, T2026, or oral ecnoglutide as once-daily oral tablets. In Cohorts 1-3, target doses were 7 mg, 15 mg, or 30 mg oral ecnoglutide once daily for 2 weeks (15 days); in Cohort 4 the target dose was 30 mg oral ecnoglutide once daily for 6 weeks (44 days). Treatment periods included gradual dose escalation to the target doses.

Safety, tolerability, pharmacokinetics, and changes in mean body weight from baseline were evaluated. The results of Cohorts 1 to 4 are presented, the study is ongoing to evaluate additional dosing schemes.

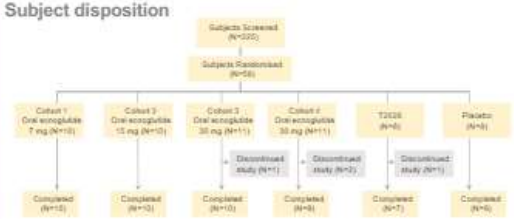
Study design



Study number SCW0503-1011. Randomization of 10:2:2 per cohort indicates planned number of subjects receiving active (n=10), placebo (n=2), and T2026 alone (n=2). Dotted line, follow up.

RESULTS

Subject disposition

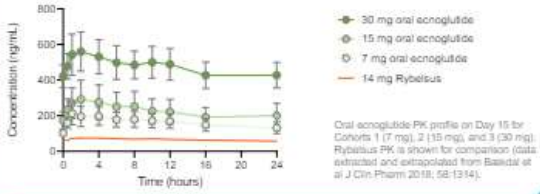


Demographics and baseline characteristics

Parameter*	Oral ecnoglutide Cohort 1 7 mg	Cohort 2 15 mg	Cohort 3 30 mg	Cohort 4 30 mg	T2026	Placebo
	(N=10)	(N=10)	(N=11)	(N=11)	(N=8)	(N=8)
Age (years)	31.5 (13.39)	30.9 (8.28)	33.7 (9.25)	35.5 (8.42)	34.9 (13.29)	31.1 (8.11)
Sex, n (%)						
Male	8 (80)	3 (30)	8 (72.7)	8 (72.7)	4 (50)	5 (62.5)
Female	4 (40)	7 (70)	3 (27.3)	3 (27.3)	4 (50)	3 (37.5)
Ethnicity, n (%)						
Hispanic or Latino	0	1 (10)	3 (27.3)	1 (9.1)	1 (12.5)	2 (25)
Not Hispanic or Latino	9 (90)	9 (90)	7 (63.6)	10 (90.9)	6 (75)	5 (62.5)
Unknown	1 (10)	0	1 (9.1)	0	1 (12.5)	1 (12.5)
Race, n (%)						
White	8 (80)	7 (70)	7 (63.6)	9 (81.8)	7 (87.5)	7 (87.5)
Black or African American	0	0	1 (9.1)	0	0	0
Asian	2 (20)	3 (30)	1 (9.1)	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0	1 (9.1)	1 (12.5)	1 (12.5)
American Indian or Alaska Native	0	0	1 (9.1)	1 (9.1)	0	0
Other	0	0	1 (9.1)	0	0	0
Body weight (kg)	76.43 (7.442)	75.57 (6.586)	77.89 (6.908)	100.07 (6.280)	79.38 (10.804)	86.64 (17.324)
BMI (kg/m²)	25.880 (2.3286)	26.052 (2.0832)	25.783 (2.2104)	32.864 (1.7752)	25.999 (4.3234)	28.729 (4.4369)

*Mean (SD) unless otherwise noted

Pharmacokinetics of oral ecnoglutide at steady state



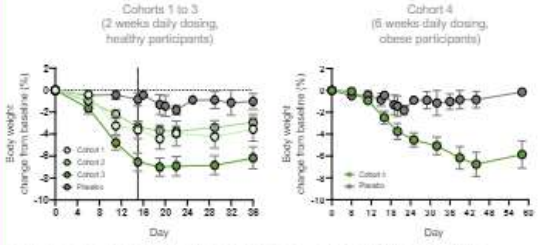
Oral ecnoglutide PK profile on Day 15 for Cohorts 1 (7 mg), 2 (15 mg), and 3 (30 mg). Rybelsus PK is shown for comparison (data extracted and extrapolated from Basedal et al J Clin Pharm 2018; 58:1314).

Body weight change from baseline at Weeks 2 and 6

		Oral ecnoglutide target dose	Body weight change from baseline (%) Week 2	Week 6
Cohorts 1-3				
Placebo	n	N/A	6	N/A
	Mean (SD)		-0.85 (1.458)	
Cohort 1	n	7 mg once daily	10	N/A
	Mean (SD)		-3.63 (2.562)	
Cohort 2	n	15 mg once daily	10	N/A
	Mean (SD)		-3.38 (1.189)	
Cohort 3	n	30 mg once daily	10	N/A
	Mean (SD)		-6.55 (2.605)	
Cohort 4				
Placebo	n	N/A	2	2
	Mean (SD)		-0.45 (0.495)	-0.85 (1.061)
Cohort 4	n	30 mg once daily	9	9
	Mean (SD)		-2.48 (1.742)	-6.76 (3.341)

Week 2 indicates Day 15 for Cohorts 1- 3 and Day 15 for Cohort 4. Week 6 indicates Day 44. Cohorts 1, 2, 3, 4 represent active treatment; placebo is pooled.

Body weight percent change from baseline



Dotted vertical line shows end of dosing. Cohorts 1, 2, 3, 4 represent active treatment; placebo is pooled.

At baseline, participants had a mean BMI of 25.8 to 26.1 kg/m² (Cohorts 1 to 3) and 32.9 kg/m² (Cohort 4). At end of treatment, participants in Cohorts 1 to 3 receiving up to 7, 15, or 30 mg QD oral ecnoglutide for 2 weeks had body weight change from baseline of -3.63%, -3.38%, and -6.55%, respectively vs -0.85% for placebo. Participants in Cohort 4 receiving up to 30 mg QD for 6 weeks had a body weight reduction of -6.76% vs -0.85% for placebo.

Summary of adverse events

E, n (%)	Oral ecnoglutide Cohort 1 7 mg (N=10)	Cohort 2 15 mg (N=10)	Cohort 3 30 mg (N=11)	Cohort 4 30 mg (N=11)	T2026 (N=8)	Placebo (N=8)	Total (N=55)
TEAEs	42, 9 (90)	47, 9 (90)	102, 11 (100)	81, 11 (100)	20, 4 (50)	23, 5 (62.5)	315, 49 (84.5)
TEAEs leading to drug withdrawal	0, 0	0, 0	3, 2 (18.2)	0, 0	0, 0	0, 0	3, 2 (3.4)
SAEs	0, 0	0, 0	0, 0	0, 0	0, 0	0, 0	0, 0
AESIs	18, 8 (80)	31, 9 (90)	52, 11 (100)	52, 10 (90.9)	8, 3 (37.5)	10, 4 (50)	169, 45 (77.6)

E, number of events; n, number of subjects

TEAEs > 5% total incidence by preferred term

PT E, n (%)	Oral ecnoglutide (XW004) Cohort 1 7 mg (N=10)	Cohort 2 15 mg (N=10)	Cohort 3 30 mg (N=11)	Cohort 4 30 mg (N=11)	T2026 (N=8)	Placebo (N=8)	Total (N=55)
Overall	42, 9 (90.0)	47, 9 (90.0)	102, 11 (100.0)	81, 11 (100.0)	20, 4 (50.0)	23, 5 (62.5)	315, 49 (84.5)
Nausea	4, 3 (30.0)	10, 7 (70.0)	12, 11 (100.0)	12, 8 (72.7)	0, 0	3, 3 (37.5)	41, 32 (58.2)
Constipation	1, 1 (10.0)	8, 7 (70.0)	6, 6 (54.5)	3, 3 (27.3)	0, 0	1, 1 (12.5)	19, 18 (31.0)
Vomiting	3, 3 (30.0)	0, 0	11, 9 (81.8)	7, 5 (45.5)	0, 0	0, 0	21, 17 (29.3)
Abdominal pain	1, 1 (10.0)	1, 1 (10.0)	5, 5 (45.5)	11, 6 (54.5)	2, 2 (25.0)	1, 1 (12.5)	21, 16 (27.6)
Diarrhea	2, 2 (20.0)	1, 1 (10.0)	5, 5 (45.5)	9, 6 (54.5)	0, 0	3, 2 (25.0)	20, 16 (27.6)
Gastroesophageal reflux disease	3, 3 (30.0)	1, 1 (10.0)	3, 3 (27.3)	4, 4 (36.4)	2, 2 (25.0)	0, 0	13, 13 (22.4)
Abdominal distension	2, 2 (20.0)	3, 3 (30.0)	0, 0	2, 2 (18.2)	0, 0	1, 1 (12.5)	8, 8 (13.8)
Eructation	0, 0	0, 0	3, 2 (18.2)	3, 3 (27.3)	1, 1 (12.5)	0, 0	7, 6 (10.3)
Decreased appetite	7, 7 (70.0)	9, 9 (90.0)	10, 10 (90.9)	9, 8 (81.8)	1, 1 (12.5)	2, 2 (25.0)	38, 36 (65.5)
Headache	6, 4 (40.0)	4, 3 (30.0)	9, 6 (54.5)	5, 4 (36.4)	0, 0	5, 3 (37.5)	29, 20 (34.5)
Dizziness	1, 1 (10.0)	2, 2 (20.0)	5, 5 (45.5)	0, 0	4, 2 (25.0)	0, 0	12, 10 (17.2)
Hypoesthesia	0, 0	0, 0	8, 5 (72.7)	1, 1 (9.1)	0, 0	0, 0	9, 6 (15.5)
Fatigue	1, 1 (10.0)	0, 0	6, 6 (54.5)	3, 3 (27.3)	1, 1 (12.5)	0, 0	11, 11 (19.0)
Catheter site pain	2, 2 (20.0)	0, 0	0, 0	1, 1 (9.1)	0, 0	1, 1 (12.5)	4, 4 (6.9)
Dyspnea	0, 0	0, 0	3, 3 (27.3)	0, 0	0, 0	0, 0	3, 3 (5.2)

PT, preferred term; E, number of events; n, number of subjects

CONCLUSIONS

- Oral ecnoglutide was generally safe and well tolerated and resulted in pronounced weight loss after 6 weeks of dosing
- Higher incidence of AEs in Cohort 3 was attributed to the higher starting dose of 7 mg
- A daily dose of 15 or 30 mg oral ecnoglutide matched or exceeded the exposure of weekly subcutaneous GLP-1 analogs
- Oral ecnoglutide has a potential to be a best-in-class oral GLP-1 receptor agonist

FINANCIAL DISCLOSURES

Z. Zhu, Y. Li, W. Guo, Q. Zheng, J. Deng, E. Adegbite, S. Ross, L. Telusca, C. L. Jones, M. Fenaux, S. Xu, and M. K. Junaidi are employees of Sciwind Biosciences.

Source: ADA 2024 Website

Sun Pharma Data for Utreglutide (GLP-1 Agonist) in Obesity

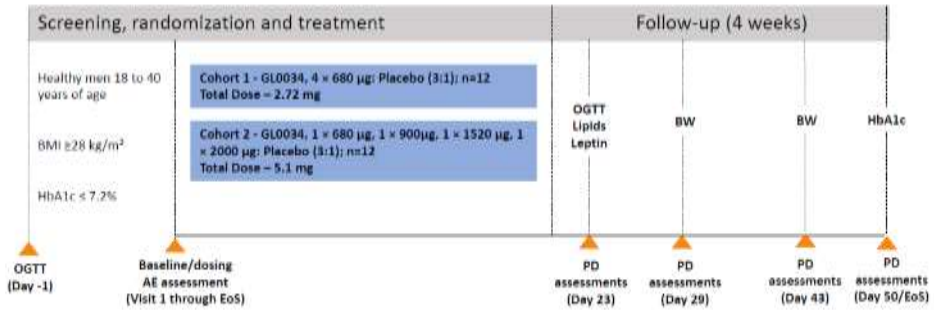
Safety, tolerability, and metabolic effects of once-weekly GL0034 (utreglutide) in individuals with obesity – A multiple ascending dose study

Rajamannar Thennati[1], Vinod Burade[1], Muthukumaran Natarajan[1], Pradeep Shahi[1], Ravishankara Nagaraja[1], Sudeep Agrawal[1], Thierry Duvauchelle[2], Adolfo Garcia-Ocana[3], Guy A. Rutter[4], Richard E. Pratley[5], Bernard Thorens[6], Tina Vilsboll[7]

[1]High Impact Innovations – Sustainable Health Solutions (HISHS), Sun Pharmaceutical Industries Ltd., Vadodara, Gujarat, India; [2]Phastar[1], Le Plessis-Trévise, France; [3] Department of Molecular and Cellular Endocrinology, Arthur Riggs Diabetes and Metabolism Research Institute, City of Hope, Duarte, CA, USA; [4]CR-CHUM, University of Montreal, Quebec, Canada; Section of Cell Biology and Functional Genomics, Division of Diabetes, Endocrinology and Metabolism, Department of Metabolism, Digestion, Reproduction, Imperial College London, London, UK; Lee Kong Chian School of Medicine, Nanyang Technological University, the Republic of Singapore; [5]AdventHealth Translational Research Institute, Orlando, FL, USA; [6]Center for Integrative Genomics, University of Lausanne, Lausanne, Switzerland; [7]Clinical Research, Steno Diabetes Center Copenhagen, Herlev, University of Copenhagen, Copenhagen, Denmark

Study design

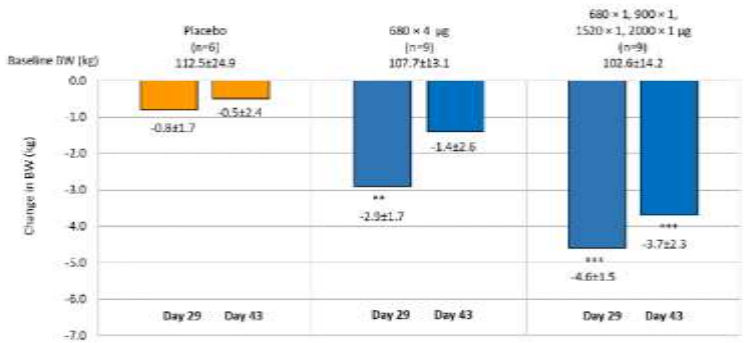
- Randomized, double-blind, single-center, placebo-controlled, Phase 1, multiple ascending-dose study to evaluate the safety, tolerability, PK, and PD of GL0034.
- Healthy males 18 to 40 years of age with a BMI ≥28 kg/m² were eligible.



AE, adverse events; BMI, body mass index; EoS, End of Study; HbA1c, glycated hemoglobin; PD, pharmacodynamics; PK, pharmacokinetics.

Body weight reduction from baseline

Absolute Change in Body Weight on Day 29 & 43



- Participants treated with all doses of GL0034 experienced a significant reduction from baseline in body weight at Day 29 that was sustained through Day 43 in cohort 2
- A reduction of body weight by 1 kg and 0.9 kg per mg dose at four weeks on Day 29,

Change in body weight over time was analyzed using 1-way ANOVA with Dunnett's post test performed using GraphPad Prism 9 (version 9.5.1), LLC, Boston, MA. Missing data were not imputed. Data labels show the mean absolute change ± S.D. from baseline (Day 1). **P <0.01, ***P <0.001 vs respective Day 1 values. ANOVA, analysis of variance; BW, Body weight; SD, standard deviation.

Safety

Summary of AEs	Placebo (n = 6)	GL0034 4 × 680 µg (n=9)	GL0034 1 × 680 µg, 1 × 900 µg, 1 × 1520 µg, 1 × 2000 µg (n=9)
TEAEs	6 (100)	9 (100)	9 (100)
Related to treatment	5 (83.3)	9 (100)	9 (100)
Leading to discontinuation	0 (0)	0 (0)	0 (0)
SAE	0 (0)	0 (0)	1 (11.1)
Related to treatment	0 (0)	0 (0)	1 (11.1)
Leading to discontinuation	0 (0)	0 (0)	0 (0)
Severity (TEAEs)			
Mild	5 (83.3)	8 (88.9)	8 (88.9)
Moderate	2 (33.3)	8 (88.9)	8 (88.9)
Severe	0 (0)	0 (0)	1 (11.1)
Most frequent TEAEs			
Decreased appetite	0 (0)	6 (66.7)	9 (100)
Early satiety	3 (50)	7 (77.8)	9 (100)
Nausea	0 (0)	6 (66.7)	5 (55.6)
Dyspepsia	3 (50)	3 (33.3)	4 (44.4)
Vomiting	1 (16.7)	3 (33.3)	2 (22.2)

Data shown as n (%), where n represents the number of affected patients.

AE, adverse event; BMI, body mass index; PD, pharmacodynamic; SAE, serious adverse event; SD, standard deviation; TEAE, treatment-emergent adverse event.

- The most frequent AEs were gastrointestinal consistent with incretin-class
- One individual with a GI related serious AE of cohort 2, rapidly recovered upon treatment with i. v. rehydration.

Hansoh Data for HS-20094 in T2DM, GLP-1/GIP Agonist

The Phase 2 diabetes data for this GLP1/GIP drug candidate show that HS-20094: (1) was well-tolerated with zero discontinuations or dose adjustments, and no dose correlation for AEs; (2) dose-dependent and statistically significant (incl stat sig against semaglutide) reductions in glucose and body weight (4.8% in Ph2 diabetics at wk4, 7.1% in HV at wk4).

733-P

Safety and Efficacy of HS-20094 in Patients with Type 2 Diabetes: A Randomized, Double-blind, Placebo-controlled, Phase 2 Study

Lin Liu[1], Xiaoxia Shi[2], Zhifeng Cheng[3], Weihong Song[4], Zhongjing Wang[5], Fei He[6], Yimin Cui[1], Junqing Zhang[1]*
[1]Peking University First Hospital, China [2]The first Affiliated Hospital of Nanyang Medical College, China [3]Fourth Affiliated Hospital of Harbin Medical University, China
[4]Chenzhou First People's Hospital, China [5]The Central Hospital of Wuhan, China [6]Taizhou Municipal Hospital, China

Financial Disclosures

- The authors declare no conflict of interest.

Background

- Increasing evidence indicates that a dual Glucagon-like peptide 1 (GLP-1) /glucose-dependent insulinotropic polypeptide (GIP) receptor agonist can achieve synergetic effects on glycemic control and body weight loss by regulating both GLP-1 and GIP receptors [1,2].
- HS-20094, a novel long-acting dual GLP-1/GIP receptor agonist, was found to be well tolerated, with a 4-week weight loss up to 7.12% from baseline at doses up to 15 mg per week in Chinese healthy subjects in a phase 1 study [3].

Objective

- In this phase 2 study, we further explored the safety, pharmacokinetics (PK), and pharmacodynamics (PD) of HS-20094 in patients with type 2 diabetes mellitus (T2DM).

Methods and Material

- This was a randomized, double-blind, placebo-controlled, active referenced trial (NCT06118008).
- Patients with T2DM (HbA1c ≥7.0% to ≤10.0%), poorly controlled with diet and exercise alone or with stable metformin, were enrolled and randomized at 4:1:1 to double-blind HS-20094 (5 mg, 10 mg or 15 mg), placebo and open-label semaglutide (1.0 mg) once-weekly with rapid titration methods (Figure 1).
- The primary endpoint was the safety of HS-20094.

Figure 1. Study Design

Summary or Results

Participants

- Demographic characteristics of 54 randomized patients, including age, FBG, HbA1C, and BMI, were generally balanced among treatment groups.

Safety

- Most (98%) adverse events (AEs) reported were mild or moderate. The most common AEs were gastrointestinal AEs, with no apparent dose-dependency observed (Table 1).
- No drug-related serious AEs, no AEs leading to discontinuation, no death, and no severe hypoglycemia events were reported.

Table 1. Major Gastrointestinal Adverse Events.

	Placebo (pooled)	HS-20094 5 mg	HS-20094 10 mg	HS-20094 15 mg	Semaglutide 1.0 mg (pooled)
N	9	12	12	12	9
Total GI AEs, n (%)	0	3 (25.0)	7 (58.3)	4 (33.3)	4 (44.4)
Abdominal Distension, n (%)	0	2 (16.7)	2 (16.7)	2 (16.7)	3 (33.3)
Nausea, n (%)	0	1 (8.3)	2 (16.7)	1 (8.3)	1 (11.1)
Diarrhea, n (%)	0	1 (8.3)	1 (8.3)	2 (16.7)	2 (22.2)
Vomiting, n (%)	0	1 (8.3)	0	0	1 (11.1)

GI AEs: gastrointestinal adverse events.

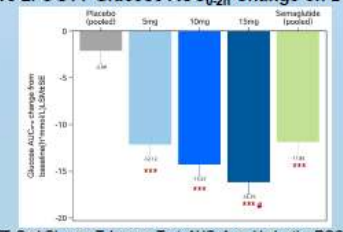
PK Profile

- The median T_{max} was between 16 h and 24 h.
- The geometric mean of $t_{1/2}$ was estimated to be between 142 h and 168 h.
- Exposure (C_{max} and AUC) increased along with the dose within the range of 5–15 mg.

PD (Blood Glucose Lowering)

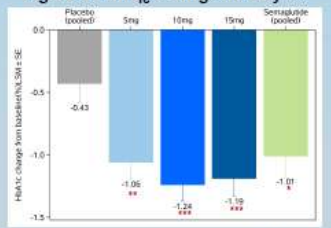
- OGTT Glucose $AUC_{0\text{-}2h}$ on Day 23 was significantly decreased with HS-20094 compared with placebo, in a dose-dependent manner. HS-20094 15 mg showed statistically greater reduction than semaglutide 1.0 mg (Figure 2).
- A significant decrease in HbA1c was observed on Day 29 in all HS-20094 dose groups and semaglutide group compared to placebo (Figure 3).

Figure 2. OGTT Glucose $AUC_{0\text{-}2h}$ Change on Day 23



OGTT: Oral Glucose Tolerance Test; AUC: Area Under the ROC curve

Figure 3. HbA_{1c} Change on Day 29

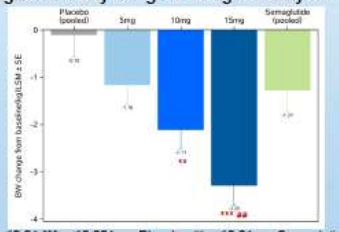


* $p<0.05$; ** $p<0.01$;*** $p<0.001$ *vs.* Placebo. # $p<0.05$ *vs.* Semaglutide.

PD (Weight Loss)

- Mean body weight reduced in a dose-dependent manner in the HS-20094 dose groups, with up to 4.8 % of weight loss in the 15 mg group.
- The change from baseline was statistically greater with HS-20094 15 mg compared with semaglutide 1.0 mg (p=0.0024, Figure 4)

Figure 4. Body Weight Change on Day 29



** $p<0.01$;*** $p<0.001$ *vs.* Placebo. ## $p<0.01$ *vs.* Semaglutide.

Conclusion or Discussion

- HS-20094 was well-tolerated in patients with T2DM.
- HS-20094 had favorable PK profile, and effectively reduced glucose and body weight in a dose-dependent manner.
- These findings support further development of HS-20094 as a potential treatment for T2DM and obesity.

References

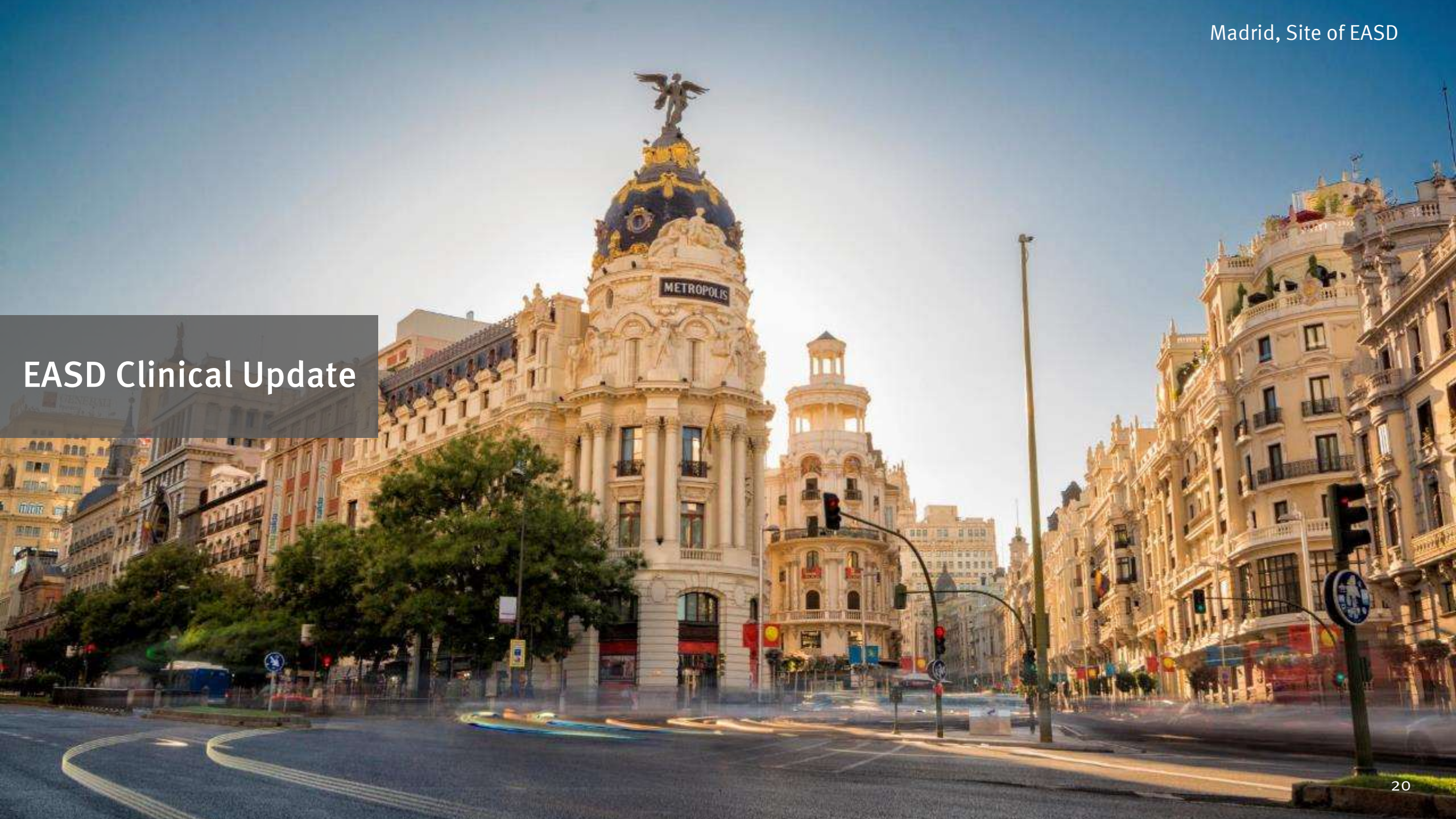
1. Marso, et al. N Engl J Med 2016; 375: 311–22.
2. Tuttle, et al. Lancet Diabetes Endocrinol 2018; 6: 605–17.
3. Xie, et al. The IDF Virtual Congress 2023

Sponsorship

- This study was sponsored by HANSOH PHARMACEUTICAL GROUP Co., Ltd.

Contact details: lfshliulin@163.com

Source: ADA 2024 Website



Madrid, Site of EASD

EASD Clinical Update

QL Pharma Data for ZT002 (GLP-1 Agonist) in Obesity

147. ZT002, a novel ultra long-acting GLP-1 receptor agonist in adults with overweight or obesity: a randomised, placebo-controlled, multiple ascending dose phase 1c study

L. Ji[1], H. Zhou[2], X. Li[2], X. Xu[3], A. Wong[3], Y. Zu[3], X. Song[3], Y. Zhang[3], S. Lin[3], X. Zhang[3], Y. Zhang[3];
[1]Department of Endocrinology and Metabolism, Peking University People's Hospital, Beijing, China, [2]Clinical Trial Research Center, The First Affiliated Hospital of Bengbu Medical University, Benbu, China, [3]Beijing QL Biopharmaceutical Co., Ltd., Beijing, China. 11:15 AM-11:30 AM 15m View abstract

Background and aims: ZT002 is a novel ultra long-acting glucagon-like peptide-1 receptor agonist (GLP-1RA) (t1/2: ~13 days) that is being developed for weight management with monthly subcutaneous administration. We aimed to examine the safety, tolerability, pharmacokinetics, and pharmacodynamics of ZT002 in adults with overweight or obesity.

Materials and methods: A phase 1c, randomized, placebo-controlled, double-blind, multiple ascending dose study was conducted in adults with overweight (24 kg/m2≤ body-mass index [BMI] ‹28 kg/m2) accompanied by at least one co-morbidity or obesity (28 kg/m2≤BMI≤40 kg/m2). This is a 12-14 week multiple ascending dose study comprised of 2 cohorts, and in each cohort, eligible participants were randomly assigned (10:4) to biweekly subcutaneous ZT002 (40 or 80 mg) or matched placebo. In each cohort, the dose of ZT002 was escalated in 2-week intervals to the desired dose over 4-6 weeks, participants were treated at the target dose for 10 weeks, and then followed up for 4 weeks.

Results: Total of 28 participants (N=21 [men]/7 [women]; median age=26 years; median BMI=33.2 kg/m2) were randomly assigned to ZT002 (40 mg group n=10; 80 mg group n=10) or placebo (n=8) and included in the safety and full analysis datasets. Over the 12 or 14-week treatment period, ZT002 was generally well tolerated without any treatment-related discontinuations or drug-related severe adverse events. The most frequent side effects reported were gastrointestinal disorders (nausea, vomiting, diarrhea) and decreased appetite, which were mostly mild to moderate in severity. The exposure at steady state was dose proportional to ZT002 doses. **The mean percent change from baseline to week 12 in body weight was -9.6 % for participants receiving ZT002 in the 40 mg cohort and -0.8% for participants receiving placebo.** The mean percent change from baseline to week 14 in body weight was -13.1% (SE 1.7) for participants receiving ZT002 in the 80 mg cohort and -1.8% (1.3) for participants receiving placebo. Additionally, compared with placebo, ZT002 achieved more profound reductions in waist circumference. Cardiometabolic risk factors improved in all treatment groups.

Source: 60th Annual Meeting, European Association for the Study of Diabetes, Conference Website.

Innovent Mazdutide (GLP-1/GCCR Agonist) Data in Obesity

149. Efficacy and safety of mazdutide in Chinese participants with overweight or obesity (GLORY-1)

L. Ji[1], H. Jiang[2], H. Li[3], J. Tian[4], D. Liu[5], Y. Zhao[6], W. Qiu[7], Y. Bi[8], J. Gu[9], Z. Liu[9], H. Deng[9], Y. Wang[9], L. Li[9], L. Qian[9], The GLORY-1 Investigators;
[1]Peking University People's Hospital, Beijing, China, [2]The First Affiliated Hospital and Clinical Medicine College, Henan University of Science and Technology, Luoyang, China, [3]Zibo Municipal Hospital, Zibo, China, [4]Luoyang Third People's Hospital, Luoyang, China, [5]Nanyang Medical College First Hospital, Nanyang, China, [6]Shenyang Fifth People's Hospital, Shenyang, China, [7]Huzhou Central Hospital, Huzhou, China, [8]Nanjing Drum Tower Hospital, Nanjing, China, [9]Innovent Biologics, Inc, Suzhou, China. 11:45 AM-12:00 PM 15m View abstract

Presentation details

Background and aims: The once-weekly glucagon like peptide-1 and glucagon receptor dual agonist mazdutide showed robust weight reduction and improvement on multiple cardiometabolic risk factors in phase 2 studies. GLORY-1 is a randomized, double-blind, placebo-controlled, 48-week phase 3 trial that evaluated the efficacy and safety of mazdutide in Chinese adults with overweight or obesity.

Materials and methods: We assigned 610 Chinese adults with a BMI ≥28 kg/m2, or ≥24 kg/m2 and at least one weight-related comorbidity, in a 1:1:1 ratio to receive once-weekly, subcutaneous mazdutide 4 mg, mazdutide 6 mg or placebo for 48 weeks.

Results: At baseline, mean body weight was 87.2 kg and mean BMI was 31.1 kg/m2. Percentage change from baseline in weight was significantly greater with mazdutide 4 mg and 6 mg than with placebo at week 32 and 48. Compared with placebo, significantly more participants in mazdutide groups achieved weight reduction ≥5% at week 32, ≥5%, ≥10% and ≥15% at week 48 than those in the placebo group. Change in waist circumference was significantly greater in mazdutide groups than in the placebo group (Table 1). Furthermore, mazdutide (4 mg and 6 mg combined) demonstrated superiority versus placebo on change from baseline to week 48 in systolic blood pressure (estimated treatment difference −6.75 [95%CI: −8.57, −4.94]), triglycerides (−0.52 [−0.66, −0.39]), total cholesterol (−0.45 [−0.57, −0.34]), LDL cholesterol (−0.31 [−0.40, −0.23]), serum uric acid (−50.75 [−61.77, −39.74]) and alanine aminotransferase (−10.00 [−13.19, −6.80]) (P<0.0001 for all comparison). The most frequently reported treatment-emergent adverse events were gastrointestinal, mostly mild to moderate in severity.

Table 1. Body weight and waist circumference endpoints

	Mazdutide 4 mg (N=203)	Mazdutide 6 mg (N=202)	Placebo (N=205)
Percentage change from baseline in weight at week 32, %	−10.97 (0.473)	−13.38 (0.482)	−0.24 (0.469)
Treatment difference versus placebo *	−10.72 (−12.21, −9.23)	−13.14 (−14.64, −11.64)	
Percentage achieving weight reduction ≥5% at week 32, % *†	76.3	84.0	10.9
Percentage change from baseline in body weight at week 48, %	−12.05 (0.572)	−14.84 (0.582)	−0.47 (0.564)
Treatment difference versus placebo *	−11.58 (−13.38, −9.79)	−14.37 (−16.18, −12.56)	
Percentage achieving weight reduction ≥5% at week 48, % *†	73.5	82.8	11.5
Percentage achieving weight reduction ≥10% at week 48, % *†	55.2	67.9	2.9
Percentage achieving weight reduction ≥15% at week 48, % *†	37.0	50.6	2.1
Change from baseline in waist circumference at week 48, cm	−9.48 (0.447)	−10.96 (0.454)	−1.48 (0.440)
Treatment difference versus placebo *	−8.00 (−9.39, −6.61)	−9.48 (−10.88, −8.08)	

Data are least squares mean (SE) for change from baseline and least squares mean (97.5%CI) for treatment difference.
* $P<0.0001$ (2-sided) for superiority comparison versus placebo, controlled for type I error rate.
† The percentage was calculated with the use of Rubin's rules by combining the percentages of participants who met the target in imputed data sets.

Source: 60th Annual Meeting, European Association for the Study of Diabetes, Conference Website.

Cytoki (IL-22) PreClinical Weight Loss Data on Top of GLP-1 Agonist

156. Lipidated interleukin-22 reduces body weight through reduced food intake and increased fecal energy loss in a complementary manner to GLP-1 receptor agonists

M. van de Bunt[1], D. Haß[2], M. Rohm[2], A. Kjølbye[1], R. Jorgensen[1];
[1]Cytoki Pharma, Søborg, Denmark, [2]Helmholtz Center Munich, Neuherberg, Germany. 12:00 PM-12:15 PM 15m View abstract

Background and aims: The atypical cytokine interleukin-22 (IL-22), which acts on epithelial cells, has shown promise as a novel treatment option that would improve long-term outcomes for patients with obesity and diabetes. Here we demonstrate the mode of action underlying the body weight reduction of a long-acting lipidated IL-22 agonist and its combination potential with existing weight loss therapies.

Materials and methods: The effect of lipidated IL-22 on obesity at 2 dose levels was investigated in two diet-induced obese (DIO) models - one at thermoneutrality to characterise the mode of action underlying the weight loss effect, and one at standard conditions to determine the combination potential with a GLP-1 receptor agonist.

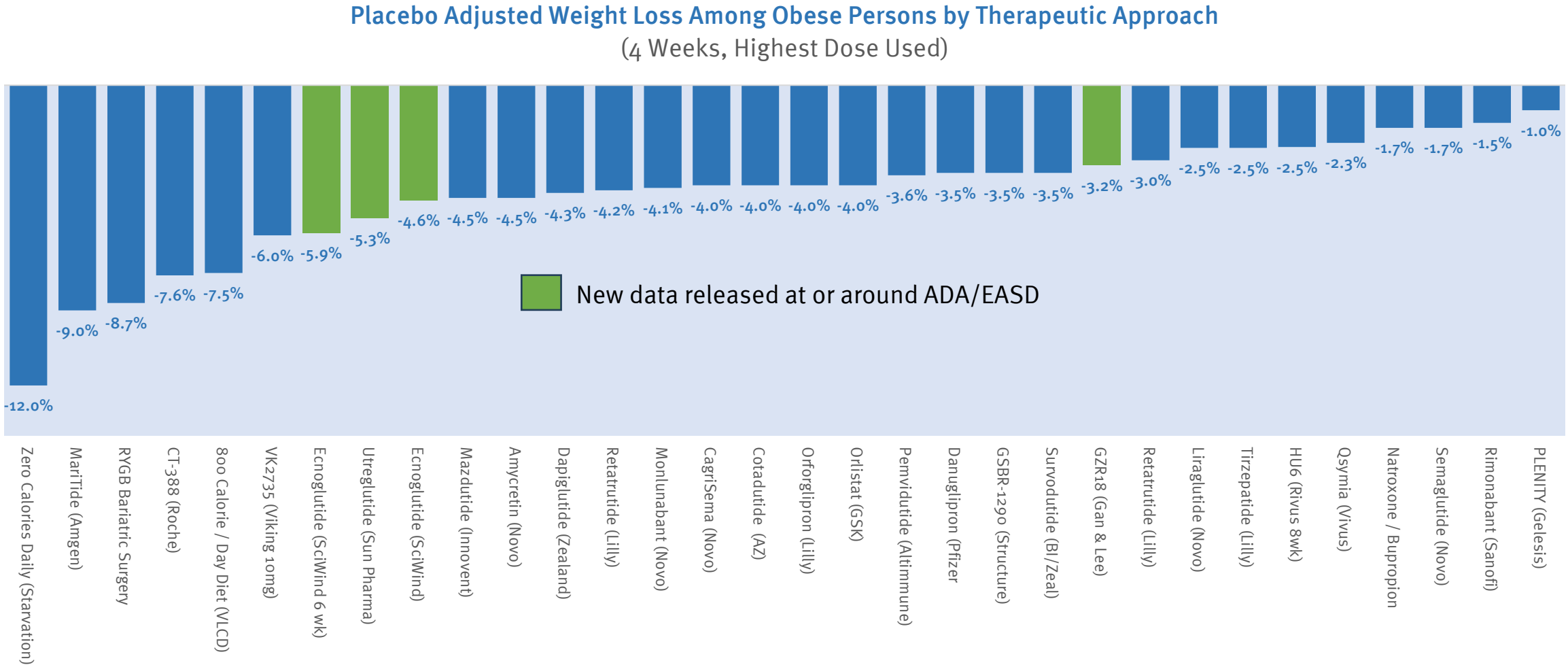
Results: Lipidated IL-22 and 30 nmol/kg semaglutide dosed for 5 weeks in DIO mice led to significantly greater reduction in body weight (-18.9% and -28.5%) compared to vehicle (-3.1%). **Mice treated with a combination of both compounds from study start reduced body weight by -40.4%, demonstrating clear additivity for the two modes of action.** This was further supported by 2 groups that were treated with semaglutide for the first 2 weeks before being switched to either a combination of semaglutide and lipidated IL-22 or lipidated IL-22 alone. The switch combination group showed weight loss (-38.2%) in line with the group that received the combination from study start. The group switched to lipidated IL-22 alone did continue to lose -2.9% weight over the next 3 weeks, albeit at a slower pace than the group receiving semaglutide alone for the entire study duration. To establish how lipidated IL-22 induces weight loss, animals were treated with 2 dose levels of lipidated IL-22 for 4 weeks at thermoneutrality. Lipidated IL-22 led to dose-dependent reductions in food intake, which previous studies with weight-matched control have shown to be insufficient to fully explain the body weight loss. Energy expenditure measurement through indirect calorimetry at weeks 1 and 4 found no increase in energy expenditure for lipidated IL-22. Bomb calorimetry showed a significant dose dependent increase in 24h fecal energy content on day 15 in the lipidated IL-22 groups (17.1 and 18.1 kJ/g) compared to vehicle animals (14.6 kJ/g). Fecal energy loss relative to energy intake through food therefore increased from 6.5% in vehicle animals to 10.0% and 12.8% in the lipidated IL-22 groups. The reduction in body weight in both studies were accompanied by significant dose dependent improvements in fasting plasma insulin, lipids, and liver enzymes.

Source: 60th Annual Meeting, European Association for the Study of Diabetes, Conference Website.

Summarizing New Data

4-Week Weight Loss Leaders After ADA/EASD

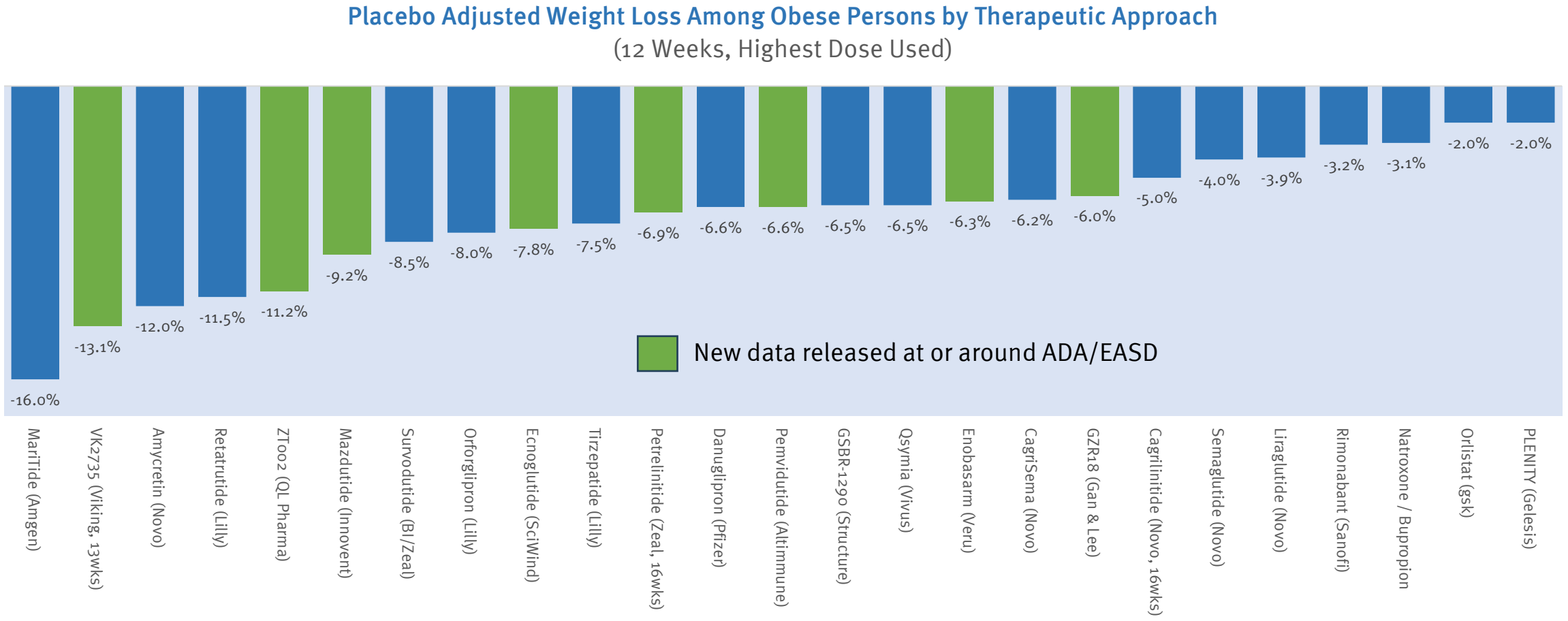
SciWind's Ecnoglutide and Sun's Utreglutide are both competitive at four weeks. Amgen's MariTide and Roche's CT-388 remain the drugs in the efficacy lead at four weeks.



Source: Stifel analysis of various company presentations and press releases. Please note that these are not results from head-to-head studies and would likely be different in such a context. Differences exist in study designs and conditions, and caution should be exercised when comparing data across studies.

12-Week Weight Loss Leaders After ADA/EASD

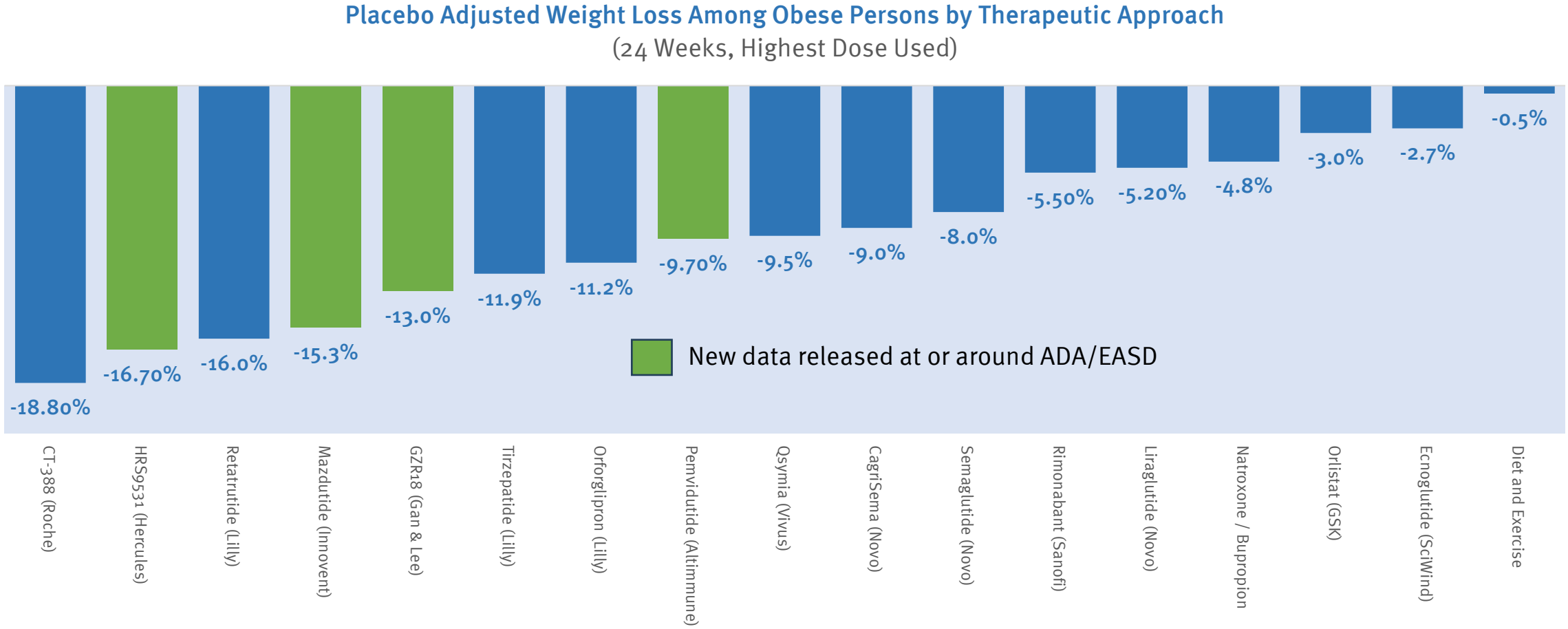
SciWind's Ecnoglutide is somewhat competitive at twelve weeks. Veru released historical data for enobasarm which is associated with 6.3% weight loss and muscle gain at 12 weeks. Enobasarm is one of the few agents to show muscle gain. Zealand's data for a long-acting amylin agonist, petrelintide was important because it was not coupled with a GLP-1 agonist. Nausea was much less common with this agent than with GLP-1s.



Source: Stifel analysis of various company presentations and press releases. Please note that these are not results from head-to-head studies and would likely be different in such a context. Differences exist in study designs and conditions, and caution should be exercised when comparing data across studies.

24-Week Weight Loss Leaders After ADA/EASD

Perhaps the biggest news at ADA was from Hercules/Hengrui which showed 16.7% weight loss for HRS9531, a dual GLP-1/GIP receptor agonist. The efficacy of this drug candidate easily surpassed tirzepatide and, also, outperformed Lilly's "Triple G" retatrutide. Importantly, we have yet to see oral amycretin, MariTide or Viking data at 24 weeks. It is likely that the relative strength of the Hercules molecule will recede as these other contenders release data in the months ahead.



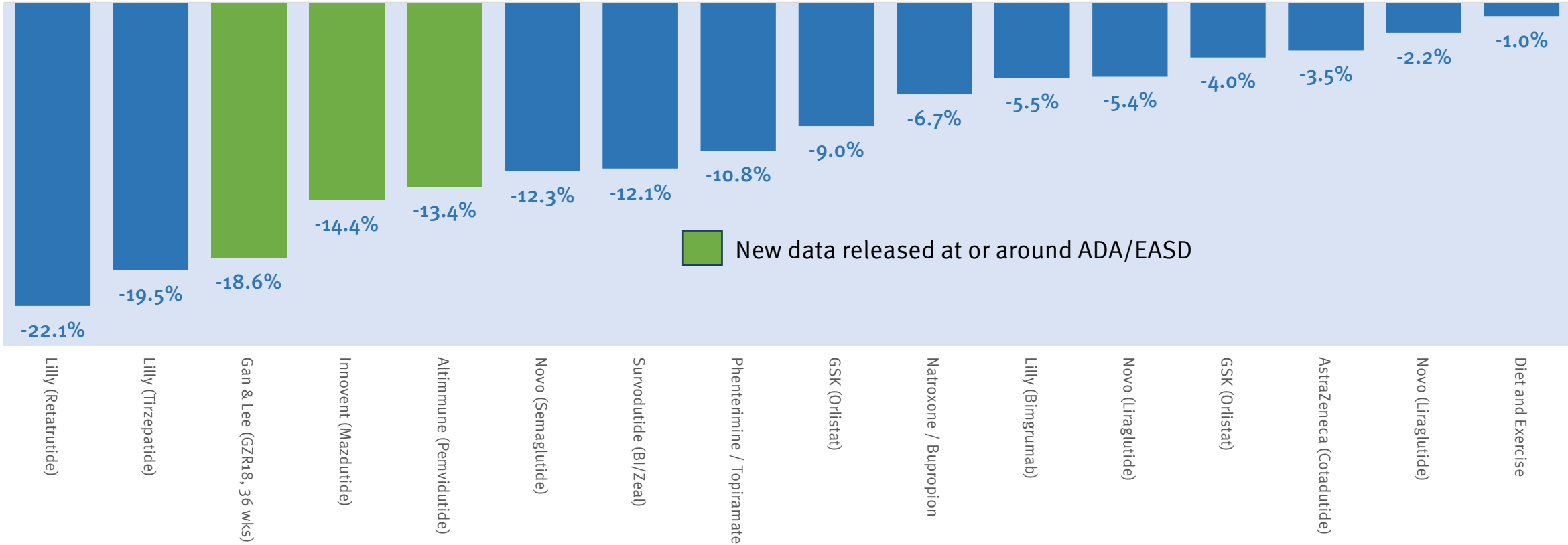
Source: Stifel analysis of various company presentations and press releases. Please note that these are not results from head-to-head studies and would likely be different in such a context.

48-Week Weight Loss Leaders After ADA/EASD

Gan & Lee of China released 36-week data for GZR-18, which look to be competitive against both tirzepatide and retatrutide. Altimmune has the distinction of being the first U.S.-listed biotech to report out 48-week data. These data are less competitive, but the Altimmune molecule had a relatively strong showing on the avoidance of muscle loss relative to other agents.

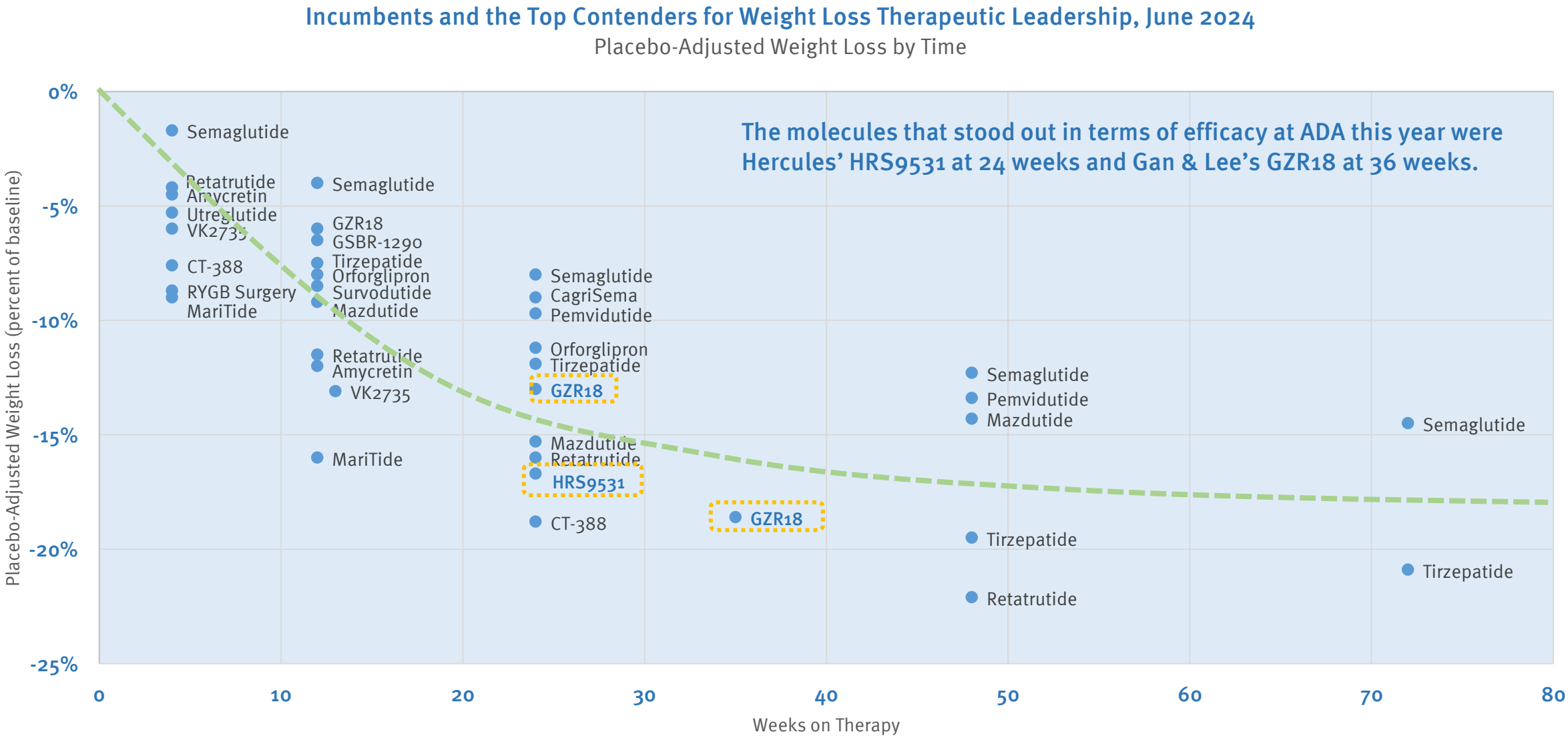
Placebo Adjusted Weight Loss Among Obese Persons by Therapeutic Approach

(48 Weeks, Highest Dose Used)



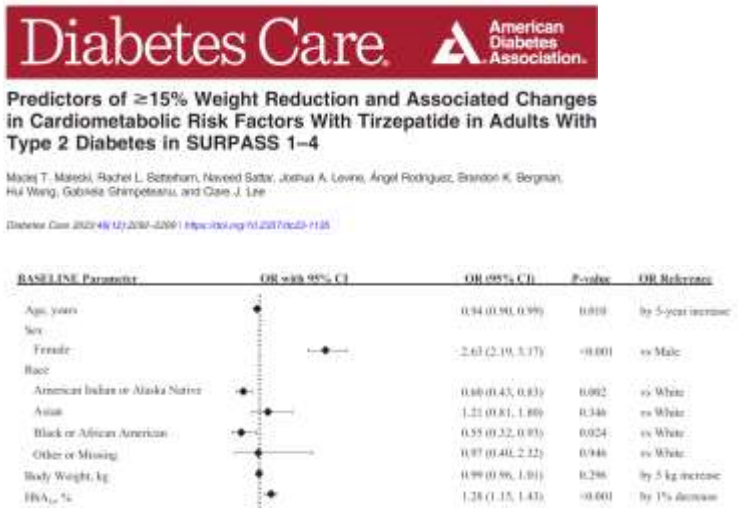
Source: Stifel analysis of various company presentations and press releases. Please note that these are not results from head-to-head studies and would likely be different in such a context.

Summary: Difference Makers at the ADA/EASD Conferences



Source: Stifel analysis of various company presentations and press releases. Please note that these are not results from head-to-head studies and would likely be different in such a context.

Technical Factors: Does Selection of Trial Participants Gender Matter?


Diabetes Care

American Diabetes Association.

Predictors of ≥15% Weight Reduction and Associated Changes in Cardiometabolic Risk Factors With Tirzepatide in Adults With Type 2 Diabetes in SURPASS 1–4

Maciej T. Malecki, Rachel L. Batterham, Naveed Sattar, Joshua A. Levine, Angel Rodriguez, Brandon K. Bergman, Hui Wang, Gabriela Ghimpeteanu, and Clare J. Lee

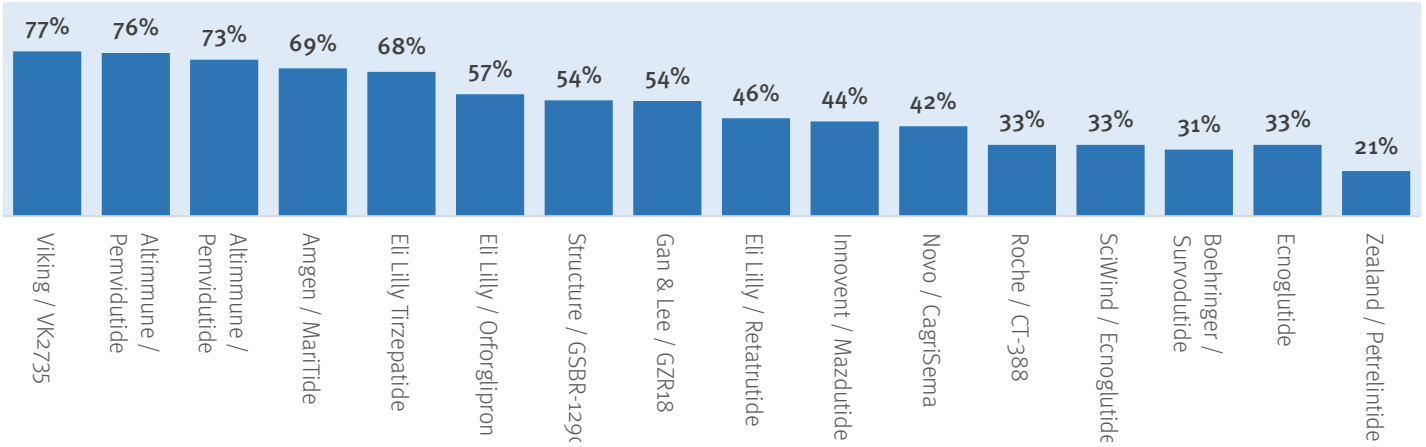
BASELINE Parameter	OR with 95% CI	OR (95% CI)	P-value	OR Reference
Age, years		0.94 (0.90, 0.99)	0.010	by 5-year increase
Sex				
Female		2.63 (2.19, 3.17)	<0.001	vs Male
Race				
American Indian or Alaska Native		0.60 (0.43, 0.83)	0.002	vs White
Asian		1.21 (0.81, 1.80)	0.346	vs White
Black or African American		0.55 (0.32, 0.93)	0.024	vs White
Other or Missing		0.97 (0.40, 2.32)	0.946	vs White
Body Weight, kg		0.99 (0.99, 1.01)	0.298	by 5 kg increase
HbA_{1c}, %		1.28 (1.15, 1.43)	<0.001	by 1% decrease

Women lose 2.4% more of their BW on average on GLP-1's at 52 weeks than men.* This means that one could bias a trial by including a disproportionate number of female subjects.

One can see in the chart (above right) that there are large differences in gender composition in studies so it might make a difference in results.

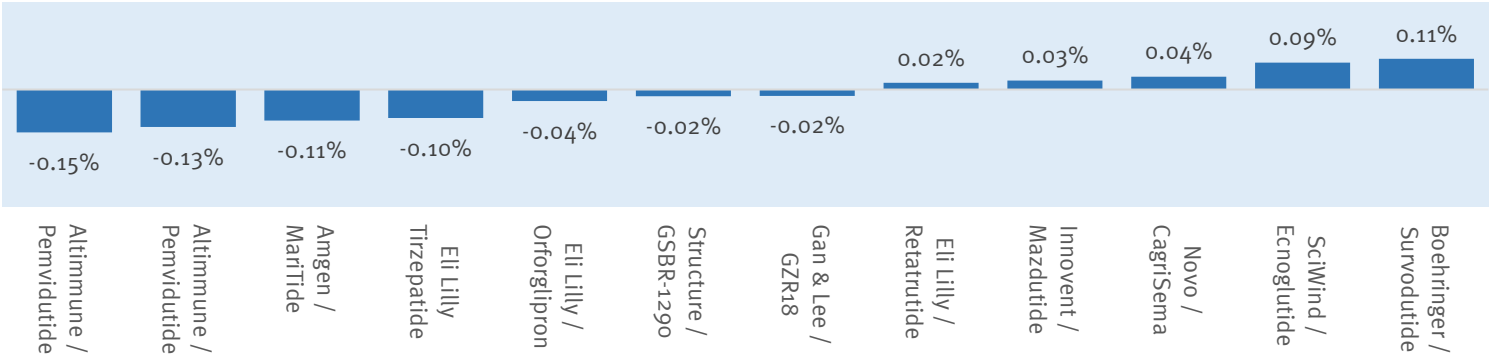
The chart at right looks at whether it matters. The answer is that gender-biasing subject mix makes very little difference. We found no cases where an agent would have been ranked differently due to gender composition of a sample.

Percent Female in Clinical Study



Difference in Implied Percent Weight Loss From Adjusting Gender Mix to 50/50 at 12 Weeks for Various Agents

(assumes straight line gender differential in BW loss %)



* https://www.acc.org/About-ACC/Press-Releases/2024/06/24/18/36/Semaglutide-Leads-to-Greater-Weight-Loss-in-Women-then-Men-with-HF-Improves-HF-Symptoms-in-Both-Sexes

Source: Stifel analysis of various company presentations and press releases. Please note that these are not results from head-to-head studies and would likely be different in such a context.

Technical Factors: What Impacts Nausea and Discontinuation Rates?

It's not uncommon to hear industry participants say to each other something like "sure, XYZ agent has great weight loss, but have you seen their tolerability results?"

We agree, tolerability matters and is a big deal.

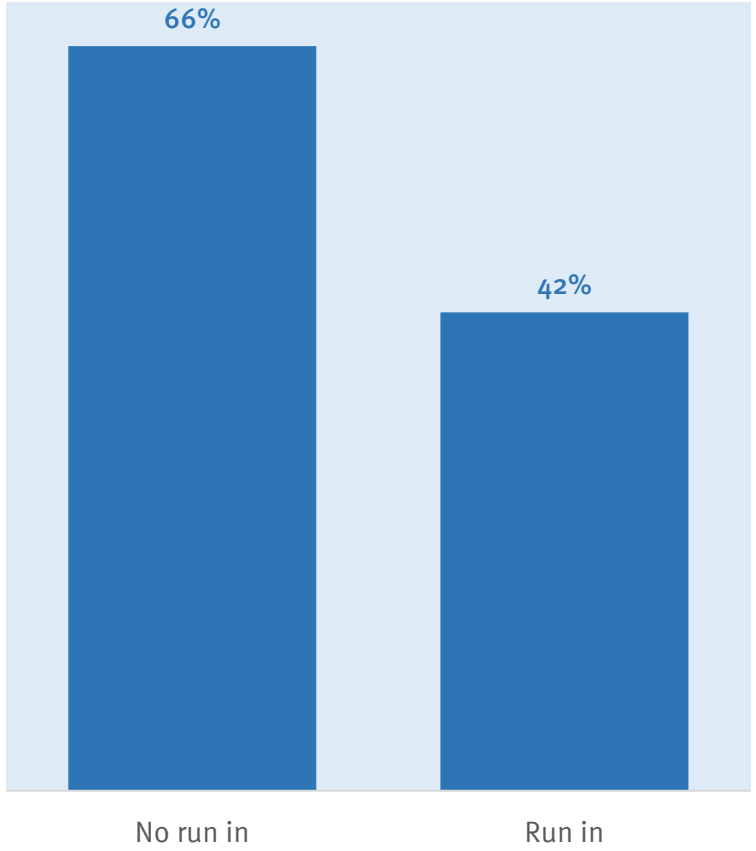
We wish to note, however, that one needs to look at whether the study used a dose escalation run in when comparing tolerability of agents.

Nausea is much less likely if there is not a dose escalation period for an agent.

Also, there is nausea and there's nausea. Net discontinuation rates (discontinuation in active arm vs. placebo) can tell you a lot if the nausea was bad enough to drop out. Run-in dose escalation makes a big difference in net discontinuation rates.

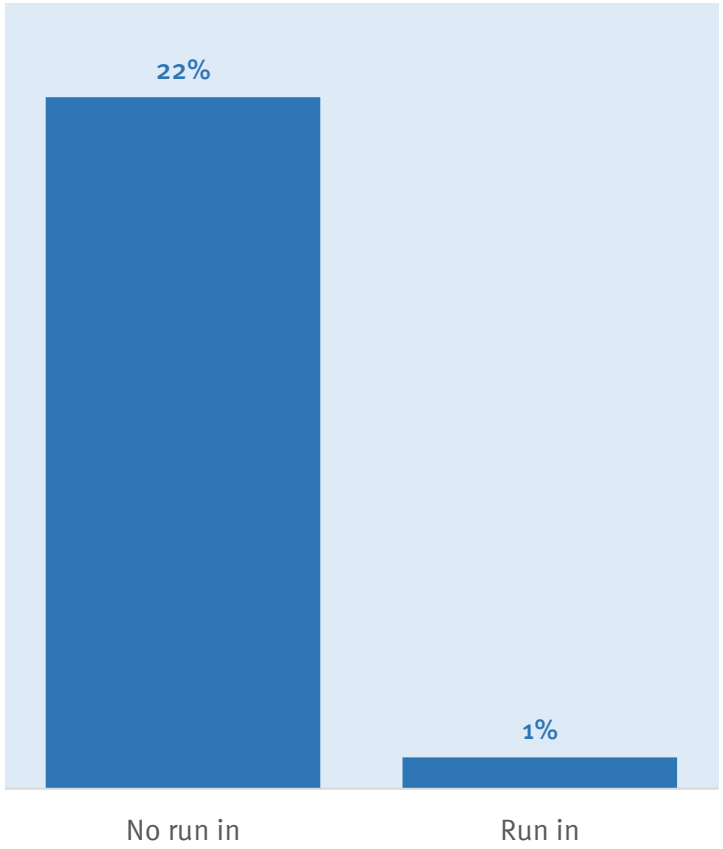
Average Nausea Rate at High Dose in Incretin Clinical Trials by Whether a Dose Escalation Run-in Was Used

(11 agents used dose escalation and 3 did not)



Average Trial Discontinuation Rate vs. Placebo in Incretin Clinical Trials by Whether a Dose Escalation Run-in was used

(12 agents used dose escalation and 4 did not)



Source: Stifel analysis of various company presentations and press releases. Please note that these are not results from head-to-head studies and would likely be different in such a context.

The Global Obesity Epidemic

The Facts on Obesity Prevalence in the United States

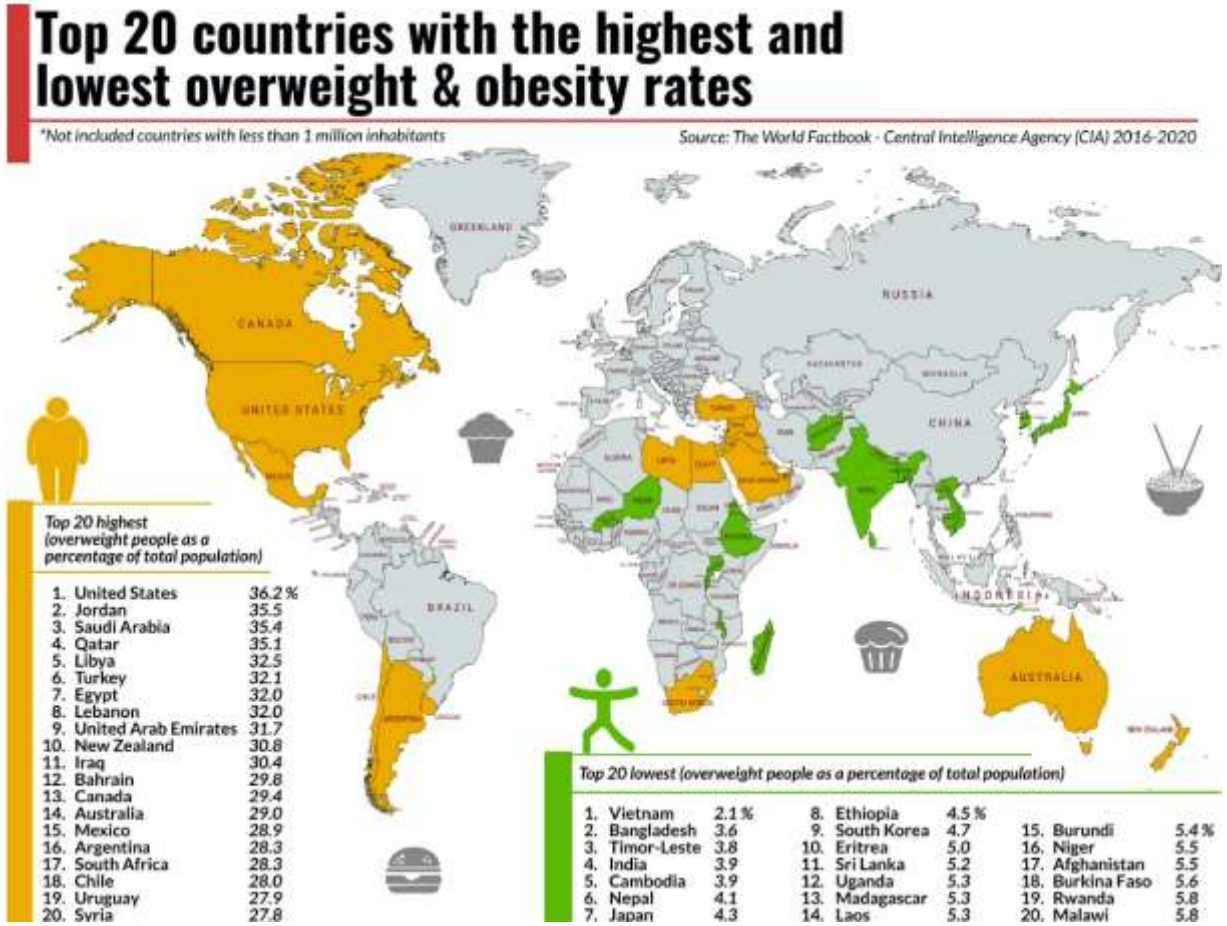
The recent explosion of interest in obesity drugs marks what appears to be the most important chapter in the history of the pharmaceutical industry.

One would normally think of the advent of anesthesia, antibiotics, blood pressure medications, pain drugs or statins as the seminal contributions of the pharma industry.

But the reality is that life expectancy in the United States is well below where it should be and it's clear enough that progress in this area is linked to the high rate of chronic diseases such as heart disease, kidney disease and liver disease. It's also increasingly clear that controlling the obesity epidemic will make a big difference in managing these chronic diseases.

Obesity is a massive scourge on Western civilization and appears to be the central public health issue in the United States.

In 2022, the adult obesity rate in the U.S. was 36.2%. The U.S. obesity rate is almost double that of other OECD countries.



Source: FactMaps, The World Factbook (Central Intelligence Agency).

A Quarter of the World's Population Will be Obese by 2035

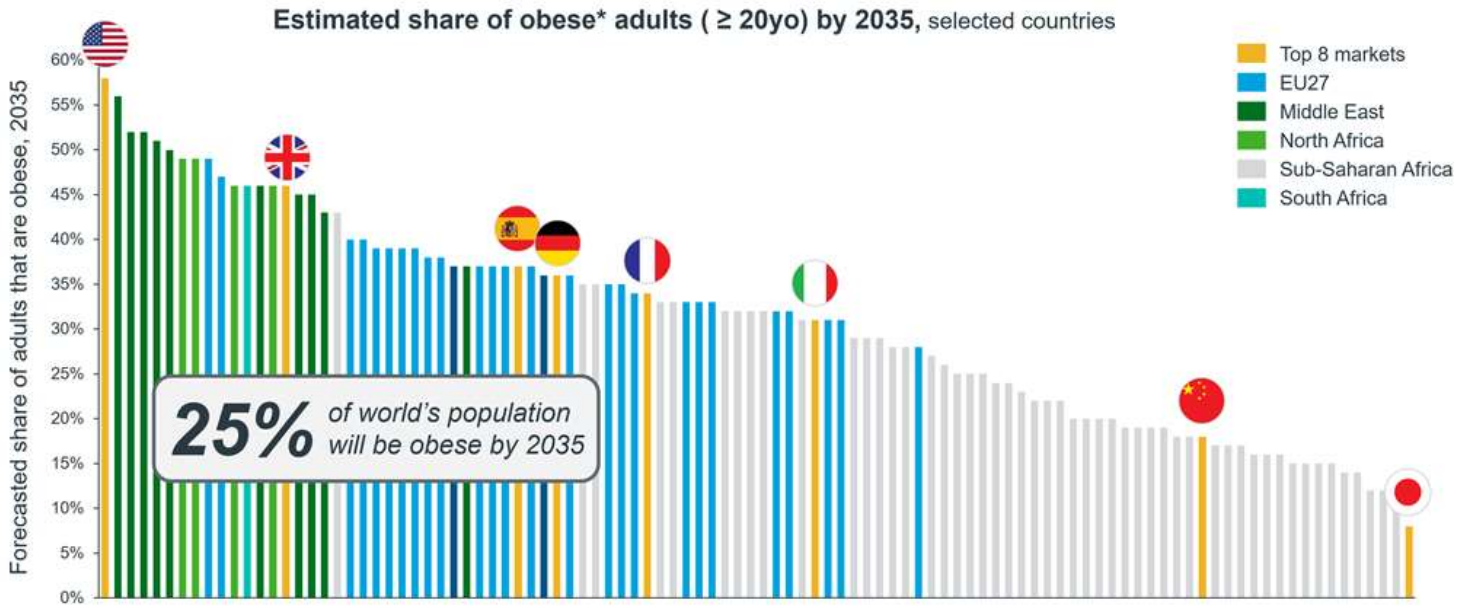
Perhaps more concerning is where obesity is going – both in the U.S. and elsewhere. IQVIA recently published the chart at right using data from the World Obesity Federation.

IQVIA notes that "the global prevalence of obesity, defined as having a body mass index (BMI) equal to or greater than 30 kg/m2, is expected to rise from 14% of the world's population in 2020 to 25% by 2035, or 1.9 billion people."[1]

Another estimate sees over 4 billion obese persons on the planet by 2035.[2]

Obesity increases all cause mortality due to increased risks of cardiovascular disease, cancer and diabetes in affected individuals. It is now understood that many major disease states are linked to obesity and it's becoming increasingly clear that control of obesity offers a major opportunity to extend lifespans and reduce medical costs.[3]

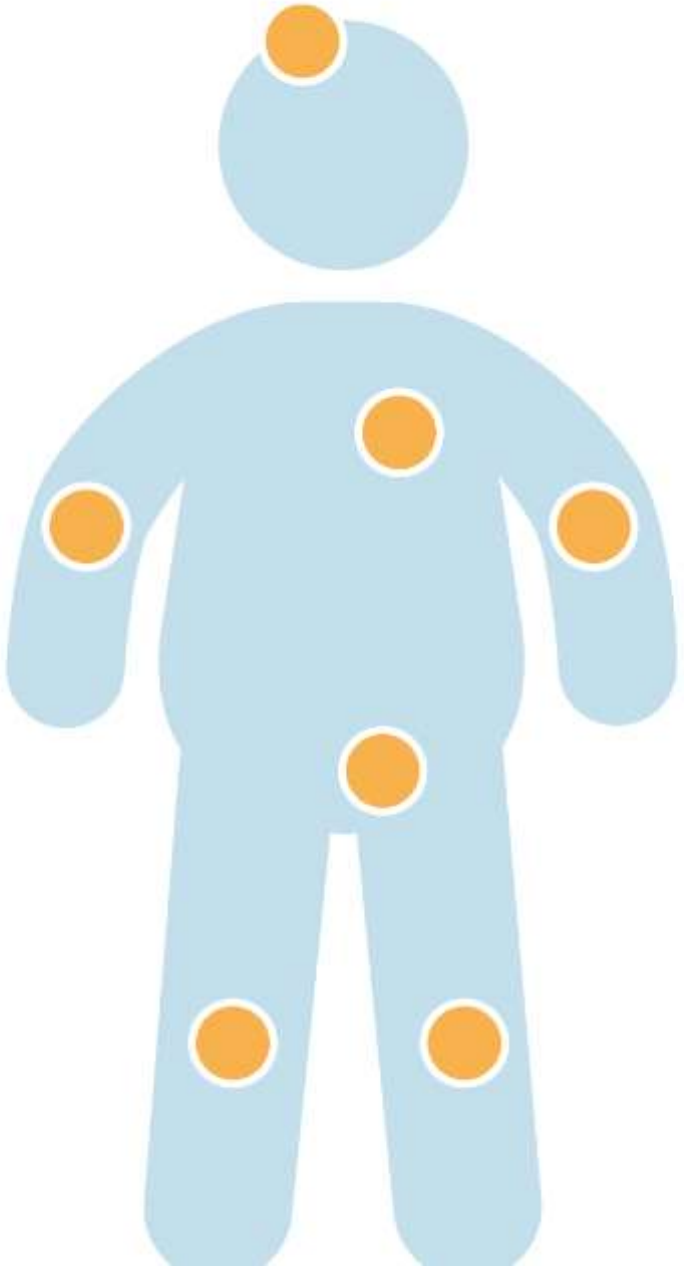
Figure 1: The global prevalence of obesity



1 Gores and Rickwood, "2024: The obesity market's inflection point?," Blog posting, Feb 22, 2024

2 Okunogbe, A, et al. *BMJ Glob Health* 2022; 7(9):p.e009773. 3

3 Di Angelantonio, E, et al. *Lancet*. 2016;388(10046):776-86; Afshin, A, et al. *N Engl J Med*. 2017;377(1):13-27; Powell-Wiley TM, et al. *Circulation*. 2021;143(21):e984-e1010; Khan SS, et al. *JAMACardiol*. 2018;3(4):280-7; Nguyen NT, et al. *ObesSurg*. 2011;21(3):351-5; JastreboffAM, and Kushner RF, *Ann Rev Med*.2023; 74:125-39.



200+ complications are associated with obesity including:

- Type 2 diabetes
- Heart or cardiovascular disease
- Cancer
- Arthritis
- Urinary incontinence
- Infertility
- Depression
- Anxiety

Source: Yuen MM et al. A Systematic Review and Evaluation of Current Evidence Reveals 195 Obesity-Associated Disorders (OBAD). Presented at: Obesity Week 2016; October 31–November 4, 2016; New Orleans, LA. Poster T-P-3166.

Obesity Has A Giant Effect on Human Mortality

The results in this Oxford study suggest that Americans are losing *410 million* life years due to obesity. A large-scale reduction in obesity would substantially improve lifespan in many Western countries.

Prospective Studies Collaboration; Whitlock G, Lewington S, Sherliker P, Clarke R, Emberson J, Halsey J, Qizilbash N, Collins R, Peto R., "Body-mass index and cause-specific mortality in 900 000 adults: collaborative analyses of 57 prospective studies," *Lancet*, Mar 28, 2009, pp. 1083-96.

Collaborative analyses were undertaken of baseline BMI versus mortality in 57 prospective studies with 894 576 participants, mostly in western Europe and North America (61% [n=541 452] male, mean recruitment age 46 years, median recruitment year 1979, mean BMI 25 kg/m^2). In both sexes, mortality was lowest at about 22.5-25 kg/m^2. Above this range, positive associations were recorded for several specific causes and inverse associations for none, the absolute excess risks for higher BMI and smoking were roughly additive, and each 5 kg/m^2 higher BMI was on average associated with about 30% higher overall mortality (hazard ratio per 5 kg/m^2 1.29): 40% for vascular mortality (HR 1.41); 60-120% for diabetic, renal, and hepatic mortality (HRs 2.16, 1.59, and 1.82, respectively); 10% for neoplastic mortality (HR 1.10); and 20% for respiratory and for all other mortality (HRs 1.20 and 1.20, respectively).

This Oxford University research paper found that moderate obesity (BMI of 30 to 35), which is now common, reduces life expectancy by about 3 years, and that severe obesity (BMI › 40), which is still uncommon, can shorten a person's life by 10 years. This 10 year loss is equal to the effects of lifelong smoking.

Among the 900,000 men and women in the study, mortality was lowest in those who had a BMI of 23 to 24. This means that if a person were 1.70m (5 feet 7 inches) tall, for example, his or her optimum weight would be about 70kg (154 pounds).

Source: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(09)60318-4/fulltext

Obesity Associated with Hallmarks of Cellular Aging

Kivimäki et.al., "Obesity and risk of diseases associated with hallmarks of cellular ageing: a multicohort study," *Lancet Healthy Longevity*, July 5, 2024, pp. e454-e463.

We analysed longitudinal data from participants aged 38–72 years in the UK Biobank study and examined reproducibility of our findings in two community-based cohorts from Finland. **Our study presents reproducible and robust population-level evidence that individuals with obesity (BMI ≥30·0 kg/m2), compared with those with healthy weight (BMI 18·5–24·9 kg/m2), are 1·4–2·4 times more likely to develop one or multiple diseases previously shown to be linked to hallmarks of cellular ageing.** The associations between other risk factors and co-occurrence of multiple hallmark-related diseases, such as low education, unhealthy diet, smoking, high alcohol consumption, physical inactivity, and depression, were not as strong as those with obesity. Half of the excess mortality in people with obesity was attributable to hallmark-related diseases.

	Participants	Cases	Basic model* HR (95% CI)	Multivariable adjusted† HR (95% CI)
UK Biobank				
First disease				
Healthy weight	137 235	47 642	1 (ref)	1 (ref)
Overweight	171 628	69 998	1·13 (1·11–1·14)	1·11 (1·10–1·13)
Obesity	91 737	43 413	1·44 (1·43–1·46)	1·40 (1·38–1·41)
Second disease				
Healthy weight	137 235	16 593	1 (ref)	1 (ref)
Overweight	171 628	26 946	1·16 (1·14–1·18)	1·14 (1·12–1·16)
Obesity	91 737	18 617	1·65 (1·62–1·69)	1·56 (1·53–1·60)
Third disease				
Healthy weight	137 235	5916	1 (ref)	1 (ref)
Overweight	171 628	10 308	1·19 (1·15–1·22)	1·16 (1·12–1·20)
Obesity	91 737	7743	1·84 (1·78–1·90)	1·70 (1·65–1·77)
Finnish cohorts				
First disease				
Healthy weight	38 335	8258	1 (ref)	1 (ref)
Overweight	26 719	7703	1·27 (1·23–1·31)	1·25 (1·21–1·29)
Obesity	10 586	3654	1·72 (1·66–1·79)	1·66 (1·60–1·73)
Second disease				
Healthy weight	38 335	2131	1 (ref)	1 (ref)
Overweight	26 719	2220	1·29 (1·21–1·37)	1·26 (1·19–1·34)
Obesity	10 586	1174	1·93 (1·79–2·07)	1·83 (1·70–1·97)
Third disease				
Healthy weight	38 335	572	1 (ref)	1 (ref)
Overweight	26 719	688	1·40 (1·25–1·57)	1·35 (1·21–1·51)
Obesity	10 586	446	2·59 (2·29–2·94)	2·37 (2·08–2·69)

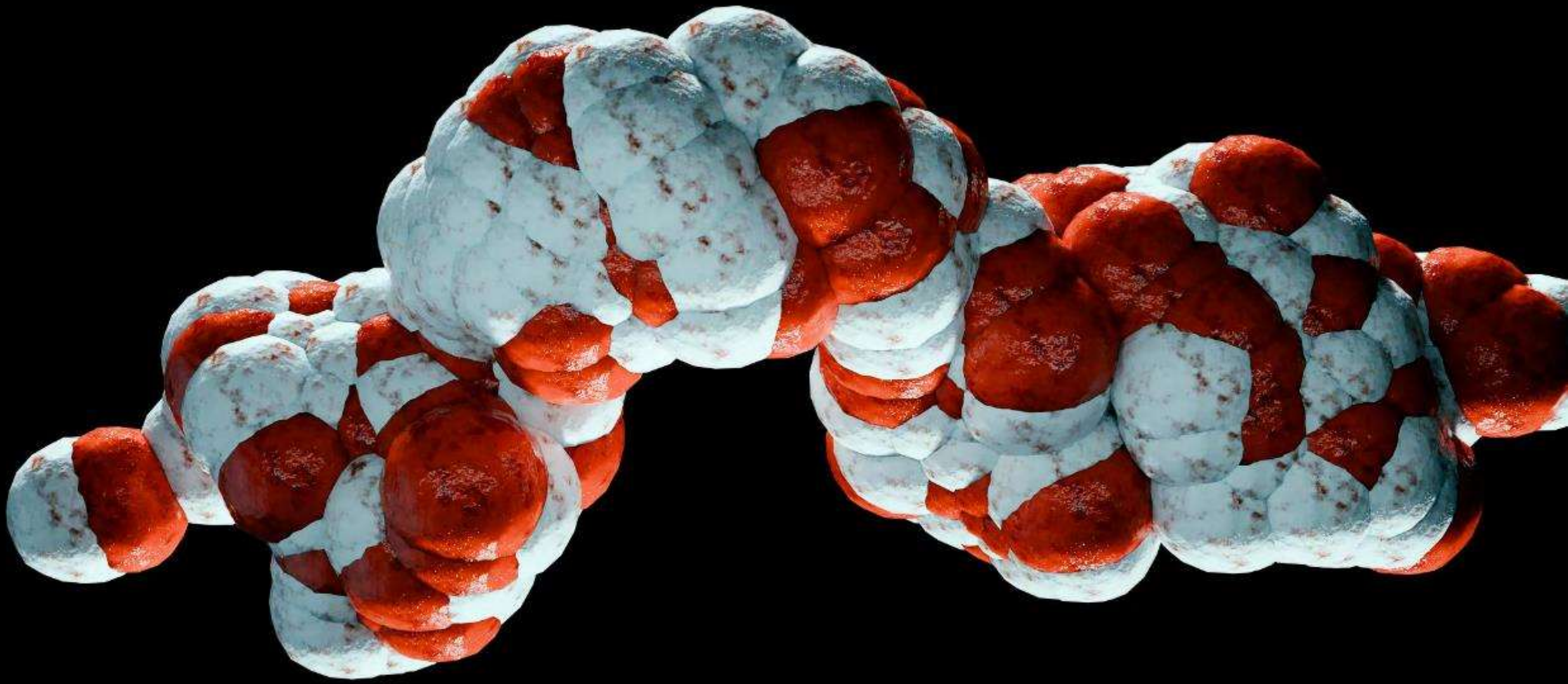
A healthy weight was defined as a BMI of 18·5–24·9 kg/m², overweight was defined as a BMI of 25·0–29·9 kg/m², and obesity was defined as a BMI of 30·0 kg/m² or higher. HR=hazard ratio. *Adjusted for age, sex, and ethnicity (UK Biobank) or cohort (Finnish cohorts). †Adjusted for age, sex, ethnicity (UK Biobank), cohort (Finnish cohorts), education, dietary factors (UK Biobank), smoking, physical activity, alcohol consumption, and depression.

Table 2: **Associations of obesity with any hallmark-related diseases and disease co-occurrence**

Source: https://www.thelancet.com/journals/lanhl/article/PIIS2666-7568(24)00087-4/

Alexandria Center for Life Sciences, South San Francisco, CA. Source: Stifel

Obesity Pharmaceutical Market Review



Glucagon-like peptide 1

Drugs Making a Big Difference in Obesity Epidemic

The advent of semaglutide and tirzepatide has been transformative for the U.S. market in many respects:

1. We are seeing profound weight loss and changes in diet that is starting to impact consumer product industries
2. We are seeing the highest valuations in the history of the industry (Lilly / Novo shares)
3. We are seeing the highest revenue forecasts in the history of the industry tied to these drugs
4. We are seeing the highest consumer interest in pharmaceuticals linked to these drugs
5. We are seeing unprecedented competition emerge as interest in these drugs continues to rise across society

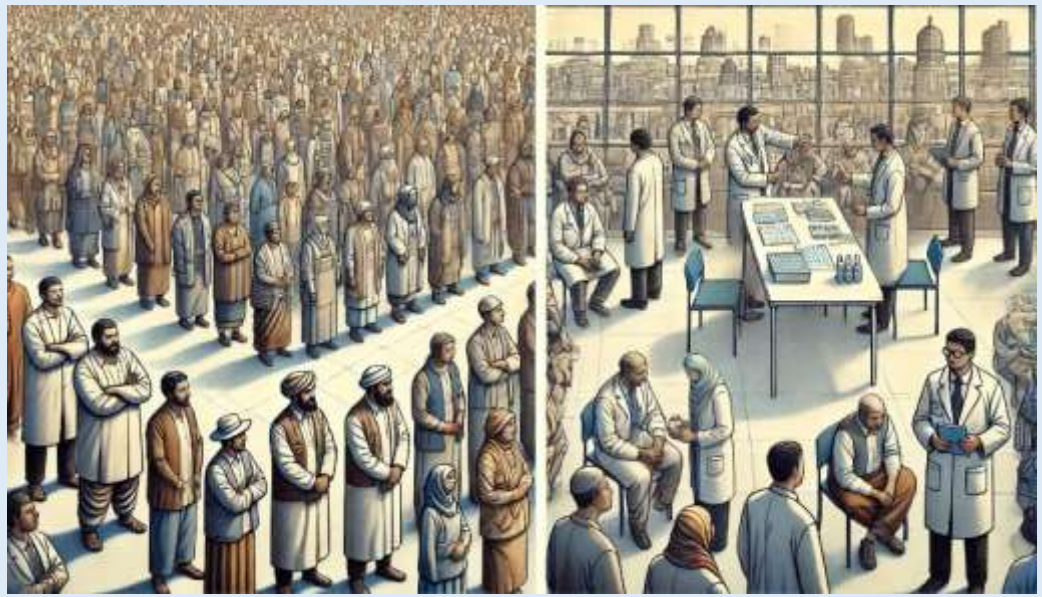
Novo Nordisk's semaglutide, a second generation GLP-1 agonist, was the first obesity drug to capture the world's imagination as an attractive option for weight loss. Lilly's tirzepatide, a GLP-1 / GIP agonist has posted even more impressive weight loss statistics.

Major Unmet Needs Remain in the Market

For all the excitement, there is still much unmet need to control obesity via novel therapies:

1. Payor coverage of GLP-1's for obesity remains sparse
2. Access to drugs is limited due to price and poor insurance coverage. Medicare / Medicaid do not cover GLP-1's for obesity.
3. The cost of the drugs is out of reach of the patients who need them the most – the poor.
4. The drugs involve enormous spend on manufacturing capacity.
5. The drugs need to be used chronically or people gain weight back when they stop using them
6. The drugs can be associated with muscle loss

It's not at all obvious that we are going to solve these problems easily. Small molecule approaches, for example, would be transformative as the economics of manufacture are far more favorable but it is far from clear today that small molecules are going to be competitive against peptide-based incretins.



The number of persons getting access to GLP-1 drugs is far smaller than those who wish to use the drugs. Access is a huge issue.

This report will delve into these issues. We will discuss the evolution of the market starting with where we've been and ending with where we are going and where the market needs to go.

First Generation: Small Molecules with Modest Efficacy and Frequent Safety Problems

The recent history of obesity drugs began with small molecules that for various reasons was less than satisfactory. Phen/Phen and rimonabant had safety issues. There is a longer history of obesity drugs that is not particularly pleasant starting with the use of thyroid extract in the 1800s.[4]

Orexigen's Contrave® was somewhat effective but not enough to motivate consumers. Eisai's attempt with lorcaserin was not effective and was associated with an imbalance of cancer cases.

Perhaps the best historical results came from Vivus' Qsymia® which remains an attractive and competitive alternative to today's incretins and emerging small molecule alternatives.

We saw the first GLP-1's approved in the mid-2000s. Byetta was approved in 2005 and involved a twice-daily injection. Twenty-four-week weight loss was around 3% with this drug. Similar levels of weight loss have been observed with Victoza (liraglutide) which was approved as daily injection in 2010.

Vivus' Qsymia remains a highly competitive small molecule treatment option for obesity today. This drug was the best of the pre-incretin obesity drug era.

4 For details see https://www.reuters.com/article/business/healthcare-pharmaceuticals/factbox-a-troubled-history-for-weight-loss-drugs-idUSTRE71063Y/

Numerous Early Obesity Drugs Off the Market

Müller TD, Blüher M, Tschöp MH, DiMarchi RD, "Anti-obesity drug discovery: advances and challenges," *Nature Reviews Drug Discovery*, Mar 2022.

Pharmacotherapy of obesity has a long and chequered history that is constituted by promising drugs that were withdrawn due to safety concerns. In the last century, the pharmacological management of obesity has included amphetamines, thyroid hormones, dinitrophenol and various drug combinations (rainbow pills) that were withdrawn shortly after regulatory approval due to serious adverse effects (Table 1). Several centrally acting sympathomimetics such as phentermine, cathine and diethylpropion continue in short-term use. Medicines that have been investigated in obesity include agents as diverse as mitochondrial uncouplers, sympathomimetics, serotonergic agonists, lipase inhibitors, cannabinoid receptor antagonists and a growing family of gastrointestinal-derived peptides chemically optimized for pharmaceutical use. A sobering realization across most of these approaches is the common inability to achieve placebo-adjusted mean weight loss greater than 10% of initial body weight when chronically administered at tolerable doses. As greater weight loss is achieved, it is typically accompanied by various serious acute or chronic adverse effects. (Table 1).

Source: https://www.nature.com/articles/s41573-021-00337-8

Table 1 | History of weight loss drugs

	Drug (full dose and administration)	Company	Approval	Weight loss (placebo/drug)	Side effects	Refs
Withdrawn	*Mitochondrial uncoupler*					
	DNP	Stanford University	1933–1938 (USA)	No data for controlled treatment ≥52 weeks	Hyperthermia, tachycardia, fever, tachypnoea, death	
	Sympathicomimetic					
	Diethylpropion/afepramone	Merrell National Drug	1959–present (EU)	No controlled treatment ≥52 weeks	Nausea, constipation, insomnia, headache, tension and irritation, seizures	
Withdrawn	Methamphetamine	Abbott Laboratories	1947–1979 (USA)		Nigh risk for abusiveness and addiction	
	Phenmetrazine	Ciba-Geigy Corp	1956–present (USA)		Nausea, diarrhoea, dry mouth	
	Phendimetrazine	Carnick Laboratories	1959–present (USA)		Nausea, diarrhoea, dry mouth	
Withdrawn	Phenylpropanolamine	Thompson Medical	1960–2000 (USA)		Haemorrhagic stroke	
Withdrawn	Fenfluramine and dexfenfluramine	Wyeth Ayerst	1973–1997 (USA)	−2.8%/−5.4%	Cardiac valvular insufficiency and pulmonary hypertension	
	Cathine (nor-pseudoephedrine) (53.3 mg, OD, oral)	Riemser Pharma	1975–present (EU, only for short-term use)	−2.4%/−6.6% to 9.9% (dose-dependent, short-term use only)	Tachycardia, increase in blood pressure, restlessness, sleep disorder, depression	
Withdrawn	Sibutramine (10 mg, OD)	Abbott Laboratories	1997–2010 (USA, EU)	+0.7%/−1.7%	Non-fatal myocardial infarction and stroke (in individuals with pre-existing CVD)	
	Phentermine (15–30 mg, OD, oral)	Teva Pharmaceuticals	1959–present (USA, only for short-term use)	−1.7%/−6.6% to −7.4% (dose-dependent)	Palpitations, elevated blood pressure	
	Polypharmacy					
Withdrawn	Rainbow pills	Clark & Clark and others	1961–1968 (USA)	No controlled treatment ≥52 weeks	Insomnia, palpitations, anxiety, increase in heart rate and blood pressure, death	
	CB1 receptor blocker					
Withdrawn	Rimonabant (20 mg, OD)	Sanofi SA	2006–2009 (EU)	−1.6%/−6.4%	Depression, suicidal ideation	
	Pancreatic lipase inhibitor					
	Orlistat (120 mg TID, oral)	Roche Pharmaceuticals	1999–present (USA, EU)	−6.1%/−10.2%	Liver injury, gastrointestinal symptoms	
	5-HT$_{2C}$ serotonin agonist					
Withdrawn	Lorcaserin (10 mg, BID, oral)	Arena Pharmaceuticals, Eisai	2012–2020 (USA)	−2.2%/−5.8%	Depression, suicidal ideation, palpitations, gastrointestinal symptoms, increased cancer risk	
	Sympathomimetic/anticonvulsant					
	Phentermine/topiramate ER (with titration) (15 mg/92 mg, OD, oral)	Vivus	2012–present (USA)	−1.2%/−7.8% to 9.3% (dose-dependent)	Depression, suicidal ideation, cardiovascular events, memory loss, birth defects	
	Opioid receptor antagonist/dopamine and noradrenaline reuptake inhibitor					
	Naltrexone SR/bupropion SR (with titration) (32 mg/360 mg, BID, oral)	Orexigen Therapeutics Inc.	2014–present (USA, EU)	−1.3%/−5.0% to −6.1% (dose-dependent)	Seizures, palpitations, transient blood pressure elevations	
	GLP1R agonists					
	Liraglutide (with titration) (3.0 mg, OD, subcutaneous injection)	Novo Nordisk	2014–present (USA, EU)	−2.6%/−8%	Nausea/vomiting, diarrhoea, constipation, pancreatitis, gallstones	
	Semaglutide (2.4 mg, once weekly, subcutaneous injection)	Novo Nordisk	2021 (USA)	−2.4%/−14.9%	Nausea/vomiting, diarrhoea, constipation	

BID, twice daily; CB1, cannabinoid receptor 1; CVD, cardiovascular disease; DNP, 2,4-dinitrophenol; ER, extended release; GLP1R, glucagon-like peptide 1 receptor; SR, sustained release; TID, three times daily; OD, once daily.

Second Generation: GLP-1's Deliver Serious Weight Loss

Semaglutide Approval to Agents on the Market Through 2027

Google Search Term Frequency for Term "Ozempic" vs "Viagra", Jan 2018 to Jul 2024

The approval of Ozempic (semaglutide) in 2017 changed everything. With 12% weight loss at six months, a tipping of sorts was reached. Word started to spread among consumers about weight loss achieved with Ozempic®. Use of the drug started to take off.

However, as is clear from the chart above showing Google search term relative frequency this did not happen right away.

Interest in Ozempic really picked up as the Pandemic was coming to an end, surpassing search frequency for the consumer's previous favorite lifestyle drug (Viagra®) and has hit an all-time high this summer. Today, the term "Ozempic" is Googled eight times more often than "Viagra".

Source: Google Trends

Two Medical Studies Electrify the Market

A key event that triggered the current wave of interest in obesity drugs was publication of results from the STEP 1 trial in March 2021. This trial documented 14% placebo-adjusted weight loss in 68 weeks from going on Novo's semaglutide.

At the time this was huge news and pointed to a way to meaningfully reduce weight that had not yet been possible.

Not to be outdone, Eli Lilly sped up the approval of tirzepatide to replace Trulicity (dulaglutide). The long-standing rivalry between Novo Nordisk and Eli Lilly has helped to fuel market interest and to create quite the sensation in the marketplace.

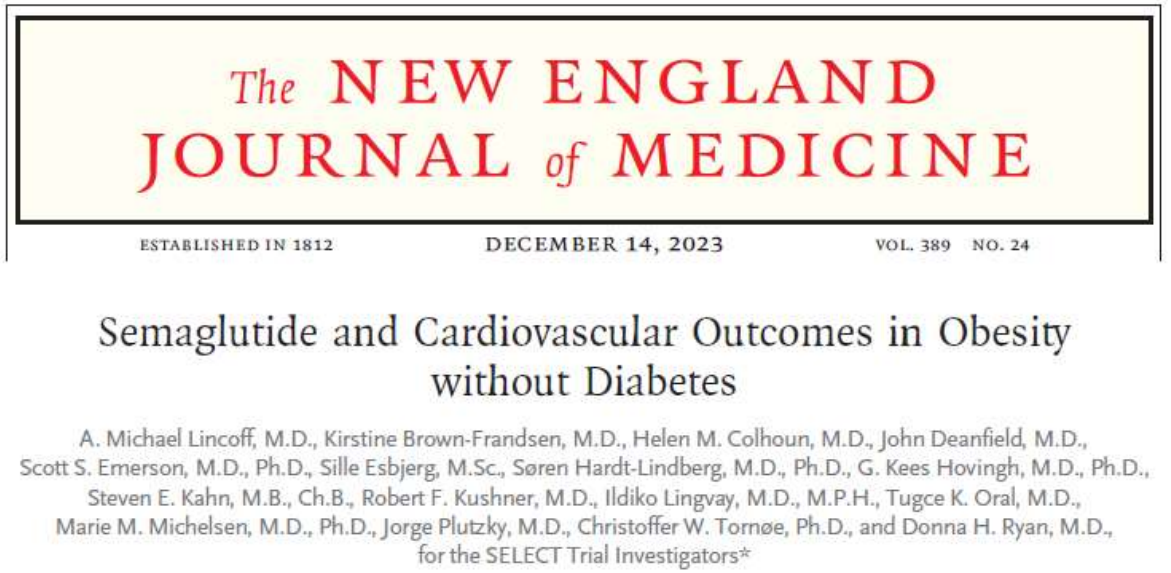
It's hard to put one's finger on any one thing but it would be hard to overemphasize the importance of Novo's SELECT data that has shown many benefits from losing weight.

We are now reaching a point where the obesity "pipeline in a product" phenomenon looks to overshadow what came before in immunology with drugs like Humira and Dupixent.*

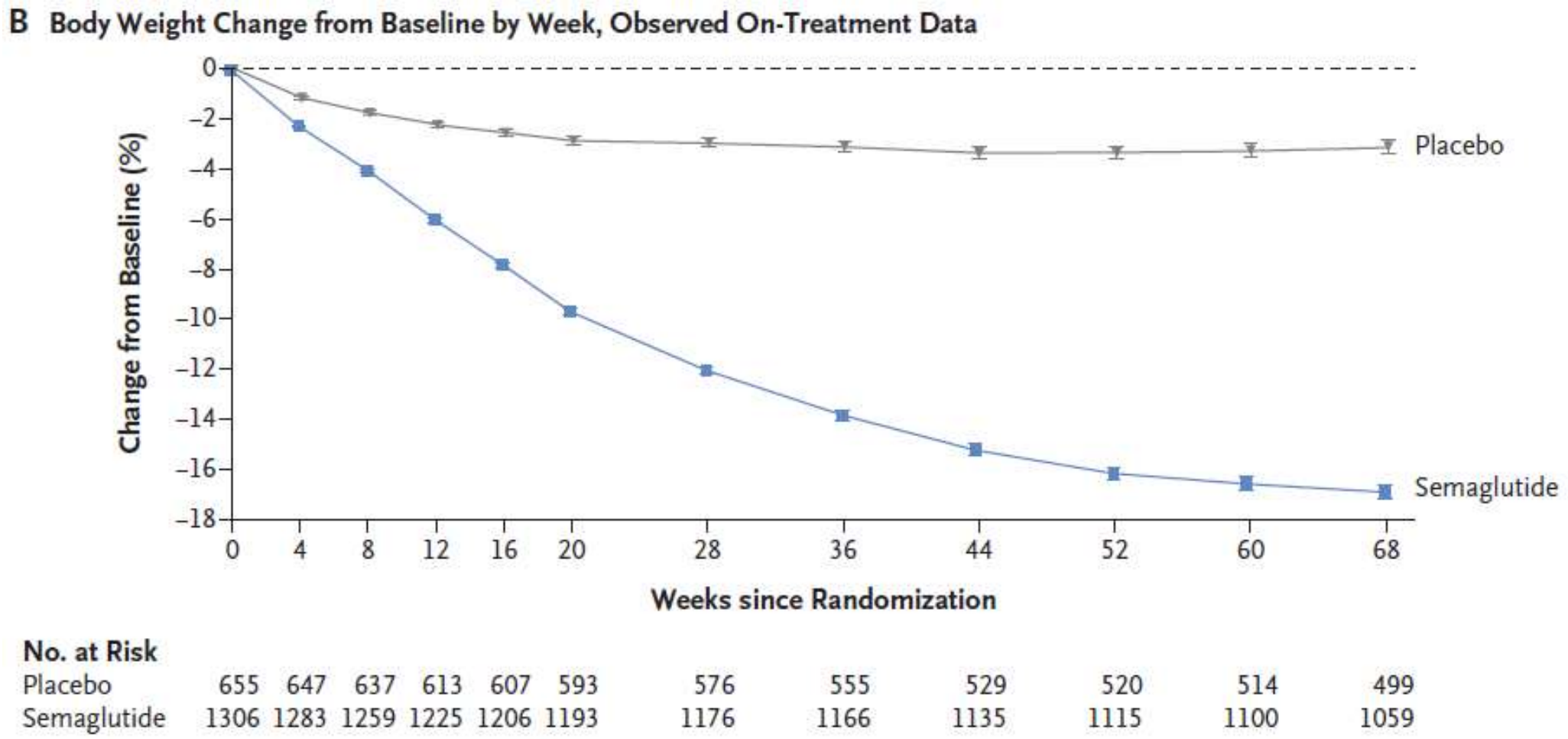
* See Dani Blum, "The Promise of Weight-Loss Drugs," *New York Times*, June 24, 2024.

The STEP 1 Semaglutide Trial Results

The SELECT Study Results



The STEP 1 Study Results in 2021 Showed Deep Weight Loss with Semaglutide



Source: https://www.nejm.org/doi/10.1056/NEJMoa2032183

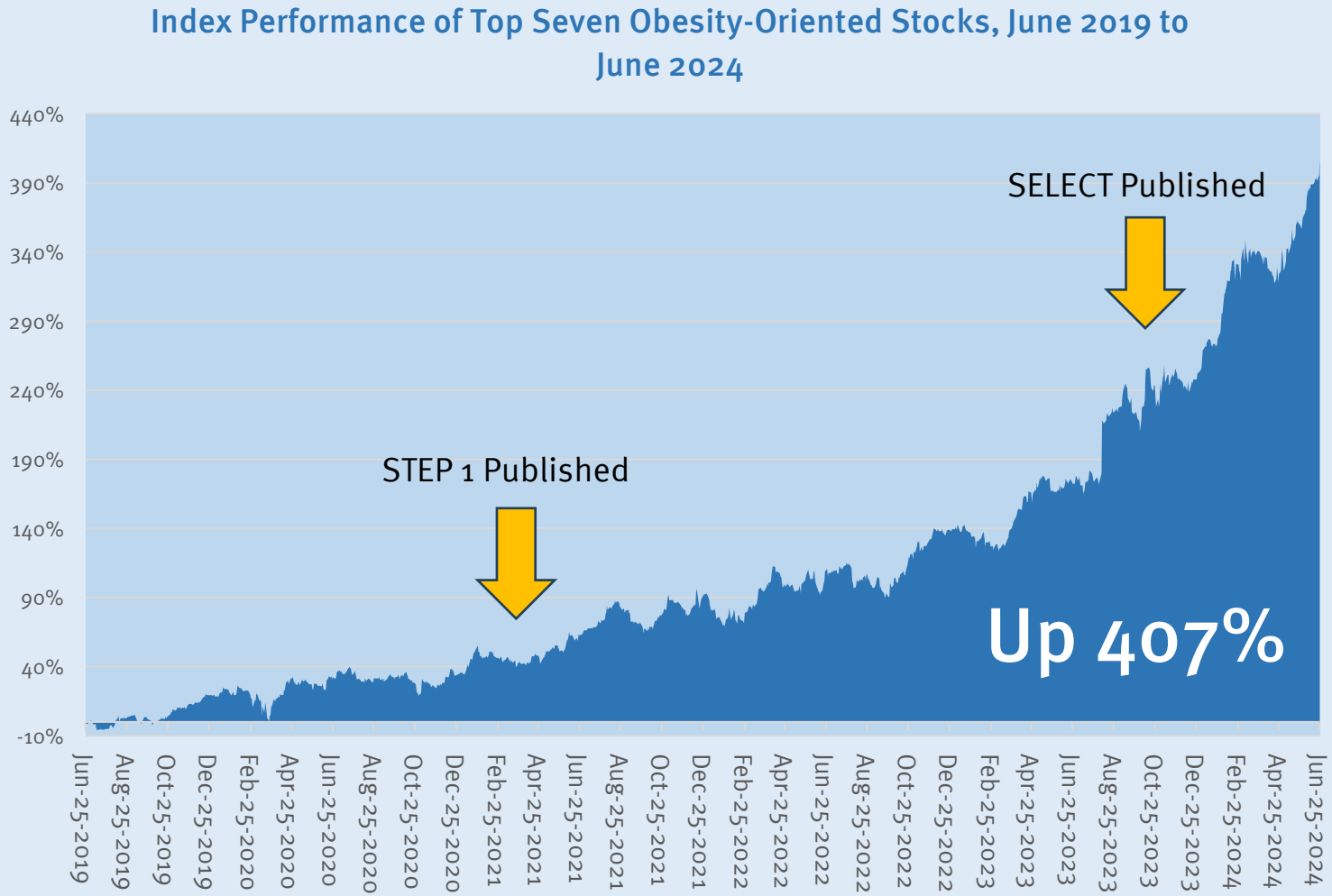
Obesity-Oriented Stocks Take Off After STEP 1 Results and SELECT Results

We think of the STEP 1 Study as ground zero for the current wave of interest in obesity.

This has been accompanied by an explosion in valuations of companies pursuing obesity drugs.

We are not aware of any past development in the pharma industry where a group of companies added this much value so quickly.

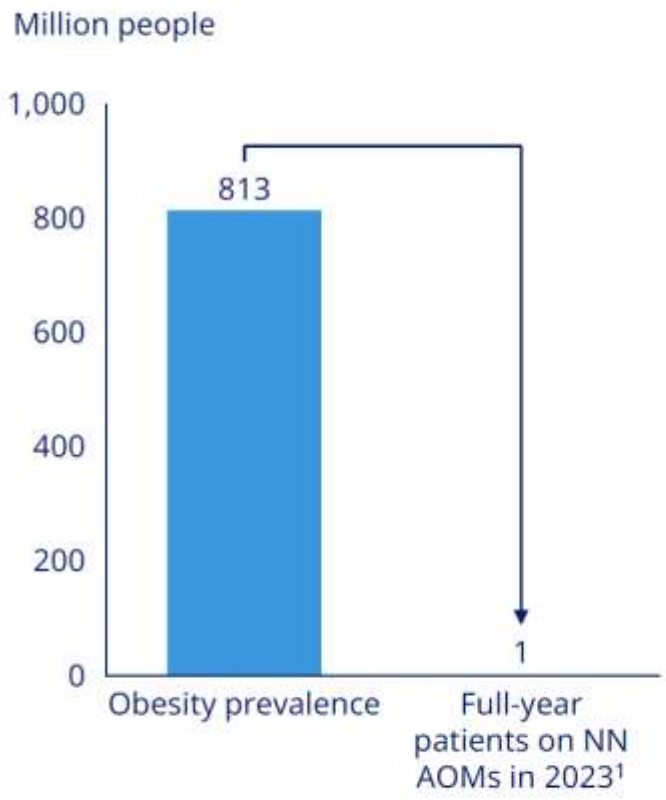
The chart above shows that a value-weighted index of seven obesity-oriented stocks (Lilly, Novo, Amgen, Zealand, Altimmune, Viking and Skye) rose 407% over the last five years (339% on an equal weighted basis). The XBI, by contrast, rose 10% in the same period.



Source: S&P CapitalIQ

Despite Success of Semaglutide, Patients are Not Getting Access to GLP-1s. Large Unmet Need Remains.

Few people are treated for obesity today



Key market changes since the Wegovy® launch in 2021

	Patients	Prescribers	Payers
Before	Needs to be activated	Consider treating obesity	NAO: Limited willingness to cover AOMs
	Low adherence eg due to tolerability, affordability and treatment expectations	Sporadic local guidelines	IO: Mostly out-of-pocket
After	Decision-maker with consumer like behaviour	Treat obesity	NAO: Good coverage (excluding Medicare Part D)
	Increasing adherence as barriers are addressed, but still not chronic care	Sporadic local guidelines	IO: Mostly out of pocket, but open to selected reimbursement

[1]The number represents the estimated full-year patients reached with Novo Nordisk products as outlined in the 2023 Annual Report
AOM: Anti-obesity medications; IO: International Operations; NAO: North America Operations; NN: Novo Nordisk
Source: World Obesity Atlas 2023, Novo Nordisk Annual Report 2023

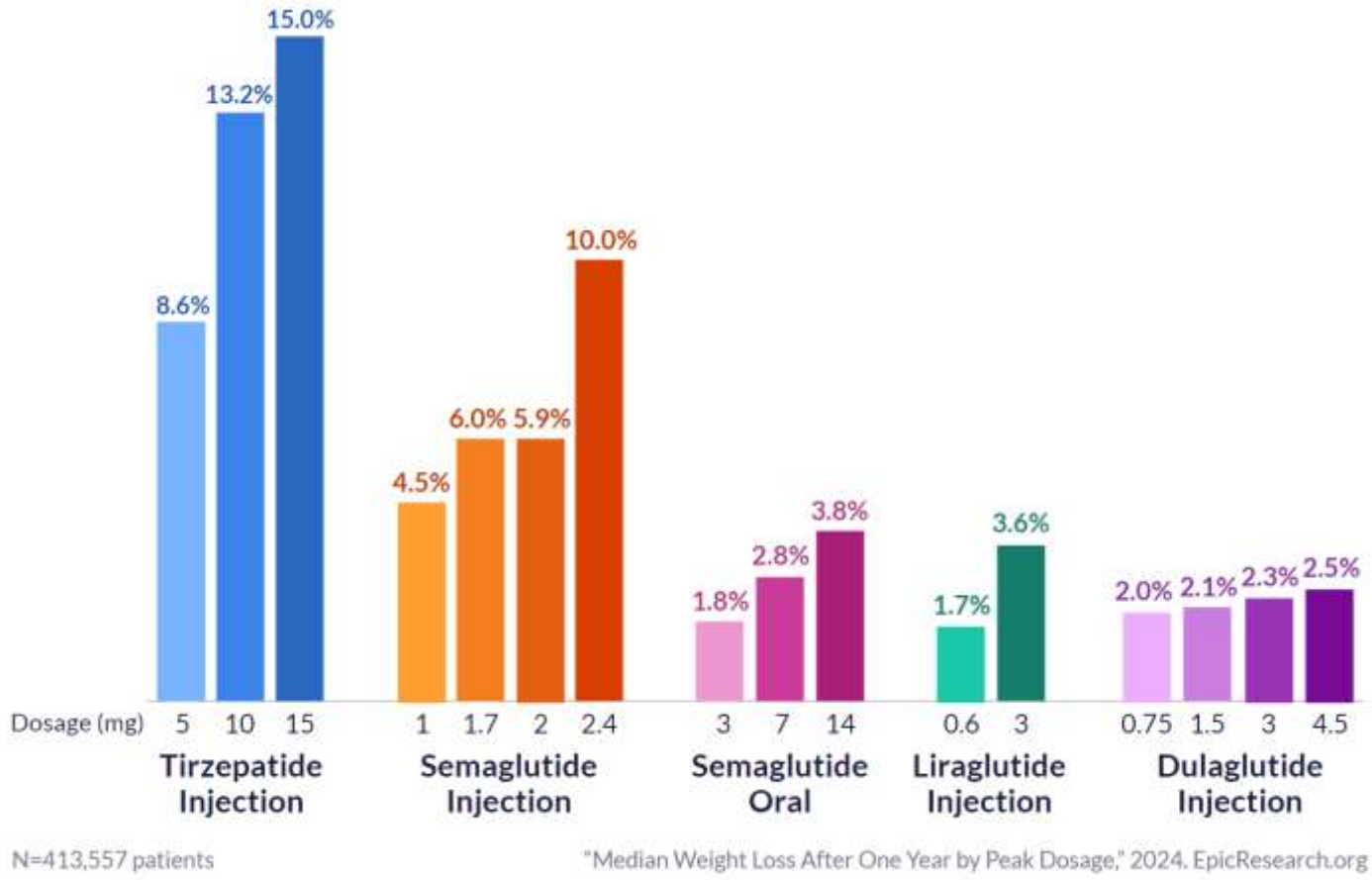
CMD24 CAPITAL MARKETS DAY

Source: https://www.novonordisk.com/content/dam/nncorp/global/en/investors/irmaterial/cmd/2024/P5-Obesity-Care.pdf

Real World Data: Patients on Tirzepatide / Semaglutide Injection Losing Substantial Weight

Deal Team Study, Epic Research, March 14, 2024

To better understand how different GLP-1 medications, routes, and dosages might influence weight change, we studied 413,557 patients who were prescribed tirzepatide, liraglutide, dulaglutide, or injectable or oral semaglutide for a minimum of 180 days. We stratified patients by the peak dosage of the medication prescribed within the year of GLP-1 treatment to determine how dosage might influence the amount of weight loss experienced. We found that higher dosages of all GLP-1 medications studied were associated with greater median weight loss a year after starting the medication, as seen in Figure 1. Patients on tirzepatide experienced greater weight loss than those on liraglutide, dulaglutide, oral semaglutide, and all but the highest dose of injectable semaglutide. Patients on injectable semaglutide achieved greater median weight loss than patients prescribed oral semaglutide.



Source: https://www.epicresearch.org/articles/tirzepatide-and-injectable-semaglutide-correlated-with-greatest-weight-loss-among-glp-1-medications

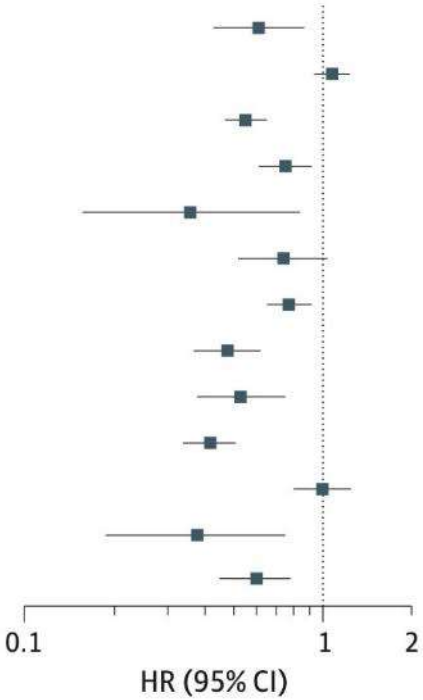
Real World Data: Patients on GLP-1's Getting Less Cancer

Wang et.al., JAMA, July 5, 2024

Thirteen human malignant neoplasms have been identified as obesity-associated cancers (OACs), ie, the presence of excess body fat is associated with increased risk of developing cancer and worse prognosis in patients with these specific tumors. The glucagon-like peptide receptor agonist (GLP-1RA) class of pharmaceuticals are effective agents for the treatment of type 2 diabetes (T2D) and for achieving weight loss, but the association of GLP-1RAs with the incident risk of 13 OACs is unclear. In this study of patients with T2D who were cancer free at baseline, taking GLP-1RAs compared with insulin was associated with a lower risk of 10 of 13 OACs. The potential cancer-preventative effects of OACs by GLP-1RAs warrant further long-term studies as well as studies of individual newer and possibly more effective antidiabetic and weight loss agents as well as those with multihormone agonist activities.

Figure 2. Risk of 13 Obesity-Associated Cancers Among Patients Receiving Glucagon-Like Peptide 1 Receptor Agonists (GLP-1RAs) vs Those Receiving Insulins

Outcome (N = 1 651 452)	Group prescribed GLP-IRAs but not insulin, No (%) (n = 48 983)	Group prescribed insulin but not GLP-IRAs, No (%) (n = 1 044 745)	HR (95% CI)
Esophageal cancer (n = 48 437)	49 (0.10)	77 (0.16)	0.60 (0.42-0.86)
Breast cancer (n = 13 768)	427 (3.08)	379 (2.94)	1.07 (0.93-1.23)
Colorectal cancer (n = 48 443)	223 (0.46)	391 (0.81)	0.54 (0.46-0.64)
Endometrial cancer (n = 25 750)	160 (0.62)	210 (0.82)	0.74 (0.60-0.91)
Gallbladder cancer (n = 48 587)	<10 (<0.02)	19 (0.04)	0.35 (0.15-0.83)
Stomach cancer (n = 48 449)	56 (0.12)	75 (0.16)	0.73 (0.51-1.03)
Kidney cancer (n = 48 322)	223 (0.46)	284 (0.59)	0.76 (0.64-0.91)
Hepatocellular carcinoma (n = 48 397)	79 (0.16)	167 (0.35)	0.47 (0.36-0.61)
Ovarian cancer (n = 25 739)	51 (0.20)	94 (0.37)	0.52 (0.37-0.74)
Pancreatic cancer (n = 48 490)	123 (0.25)	290 (0.60)	0.41 (0.33-0.50)
Thyroid cancer (n = 48 527)	154 (0.32)	149 (0.31)	0.99 (0.79-1.24)
Meningioma (n = 48 518)	11 (0.02)	29 (0.06)	0.37 (0.18-0.74)
Multiple myeloma (n = 48 527)	80 (0.17)	131 (0.27)	0.59 (0.44-0.77)

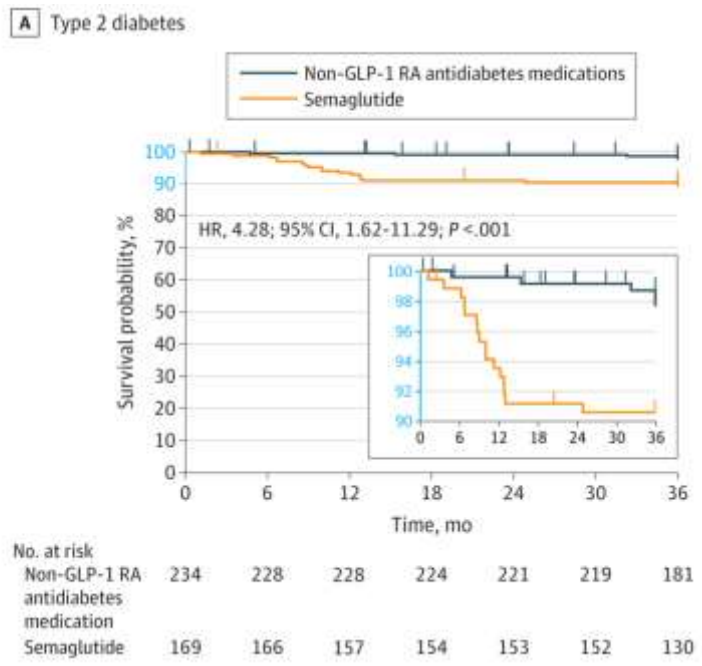


Source: https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2820833

Real World Data: Some Recent Concern over NAION

Hathaway JT et.al., "Risk of Nonarteritic Anterior Ischemic Optic Neuropathy (NAION) in Patients Prescribed Semaglutide," *JAMA Ophthalmology*, Jul 3, 2024: p. e242296.

In a retrospective matched cohort study using data from a centralized data registry of patien evaluated by neuro-ophthalmologists at 1 academic institution from December 1, 2017, through November 30, 2023, a search for International Statistical Classification of Disea and Related Health Problems, Tenth Revision code H47.01 (ischemic optic neuropathy) and search yielded 16 827 patients with no history NAION. Propensity matching was used to asse whether prescribed semaglutide was associat with NAION in patients with type 2 diabetes (T or overweight/obesity, in each case accountin for covarying factors (sex, age, systemic hypertension, T2D, obstructive sleep apnea, obesity, hyperlipidemia, and coronary artery disease) and contraindications for use of semaglutide. The cumulative incidence of NAION was determined with the Kaplan-Meier method and a Cox proportional hazards regression model adjusted for potential confounding comorbidities. Data were analyzed from December 1, 2017, through November 30, 2023.



Source: https://pubmed.ncbi.nlm.nih.gov/38958939/

Notes

1 See https://www.fda.gov/drugs/questions-and-answers-fdas-adverse-event-reporting-system-faers/fda-adverse-event-reporting-system-faers-public-dashboard.

2 Three cases were reported, for example, in Q1 2024.

3 Adverse drug reactions are systematically underreported to adverse event databases. The expected reporting rate of actual is around 6%.

4 See https://pubmed.ncbi.nlm.nih.gov/16689555/.

5 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3659384/

It's important to note that this is a single center retrospective study and that there have been no reports of NAION and semaglutide in the literature before. NAION is not a fatal disease, and the risk of permanent blindness is very low. Further, the frequency of the condition seen in the study is low and that is for patients visiting an eye hospital (Mass Eye and Ear).

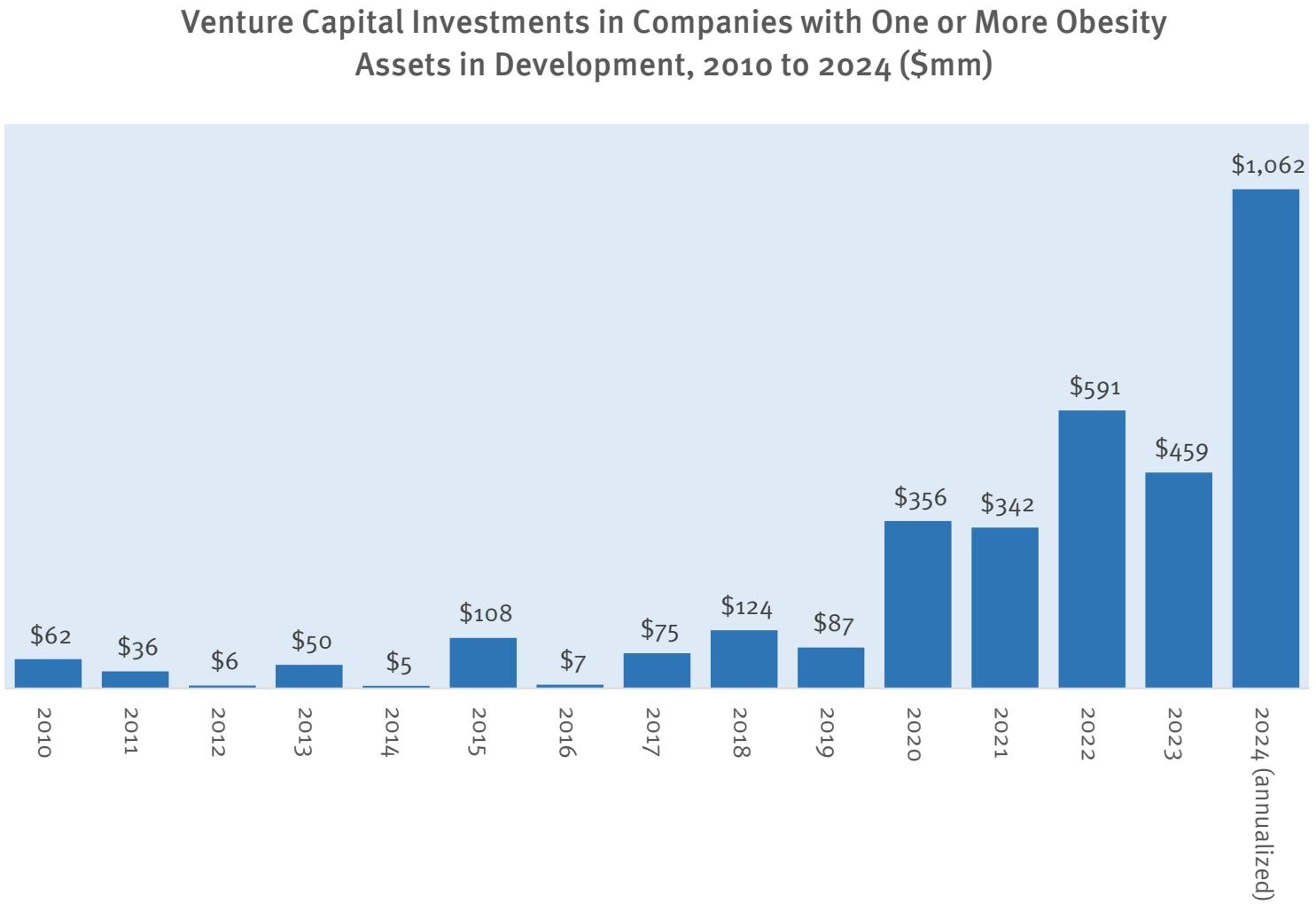
Since 2006, there have been a total of 29,525 adverse reactions for semaglutide according to FDA's adverse event reporting system (mainly GI events).[1] Of these, 8 were for NAION (all recent – presumably mainly from Mass Eye and Ear).[2] Assuming 94% underreporting, one would infer 133 cases ever in the U.S. of NAION on semaglutide.[3]

According to Novo Nordisk's last investor presentation, there were approximately 4 million Americans on semaglutide in Q1 2024. While not all adverse events get reported to FAERS, the risk of NAION with semaglutide would seem to be incredibly low. Around one in twenty thousand (extrapolating 2024 data). This is not materially different than the background disease prevalence rate.[4]

Interestingly, the #1 risk factor for NAION is obstructive sleep apnea (OSA).[5] Over 80% of NAION patients have it. As noted elsewhere, GLP-1 agonists are helpful for this condition. Hathaway et.al. controlled for sleep apnea with their case control study using a Cox model and argue that NAION is still more likely in those on semaglutide. But they did not disclose how many of the patients on emaglutide with NAION had OSA. That would be helpful information in evaluating whether or not there is a third factor accounting for the association of NAION with semaglutide use.

Venture Dollars Pour Into the Obesity Field

A key metric of interest is the volume of venture dollars flowing into companies in a given therapeutic area. The chart shows that investment is up tenfold between 2024 and 2019 and that investments over the last years are up quite substantially from prior years.



Source: DealForma. Investments through June 28, 2024 annualized to derive 2024 estimate.

Top Venture Rounds in Obesity, 2022 to 2024

Hercules CM NewCo	$400mm May 2024
Metsera	$290mm Apr 2024
KALLYOPE	$236mm Feb 2022
CARMOT THERAPEUTICS	$160mm Feb 2022
CARMOT THERAPEUTICS	$150mm May 2023

Growth in Size of Obesity Drug Pipeline

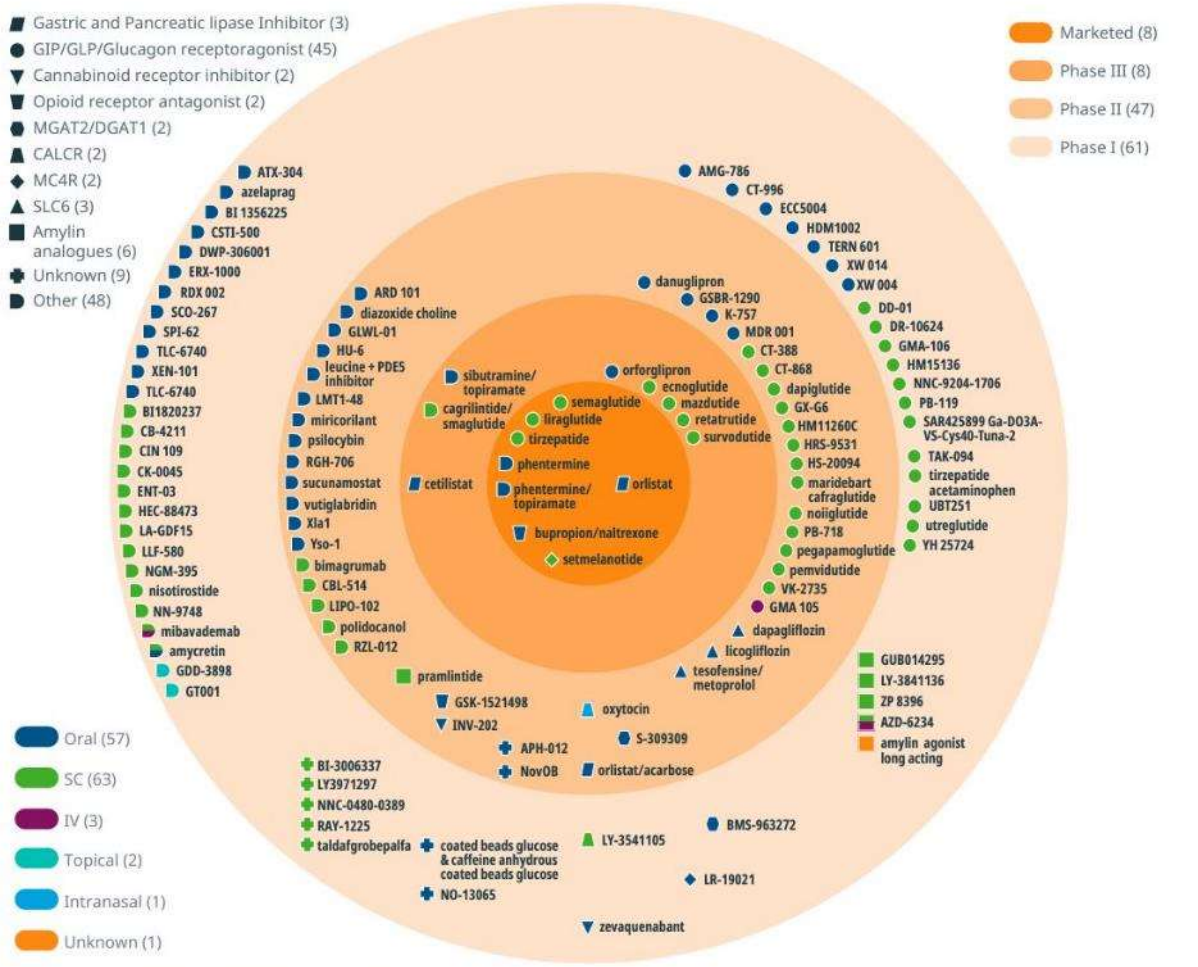
As we contemplate the market in June 2024, one cannot help but note the explosion in the sheer number of anti-obesity agents on the market or under investigation.

In our review of the market in June 2023, we counted a total of 51 obesity agents under investigation or approved. Soon thereafter, we visited with several funds and found that we had missed at least 15 agents so, perhaps, the real number was something like 75 agents on the market or in investigation. Obviously, a huge number for any market.[5]

We were quite surprised to see a report by IQVIA in January 2024 noting that 124 obesity agents were on the market or in development.

The chart at right shows the shape of the pipeline and the emerging diversity of MOA's under investigation.

Exhibit 20: Obesity pipeline by phase, target and route of administration



Source: Citeline Trialtrove, IQVIA Institute, Jan 2024.

5 See https://www.iqvia.com/insights/the-iqvia-institute/reports-and-publications/reports/global-trends-in-r-and-d-2024-activity-productivity-and-enablers

Obesity Pipeline Has Tripled in Size Over The Last Year

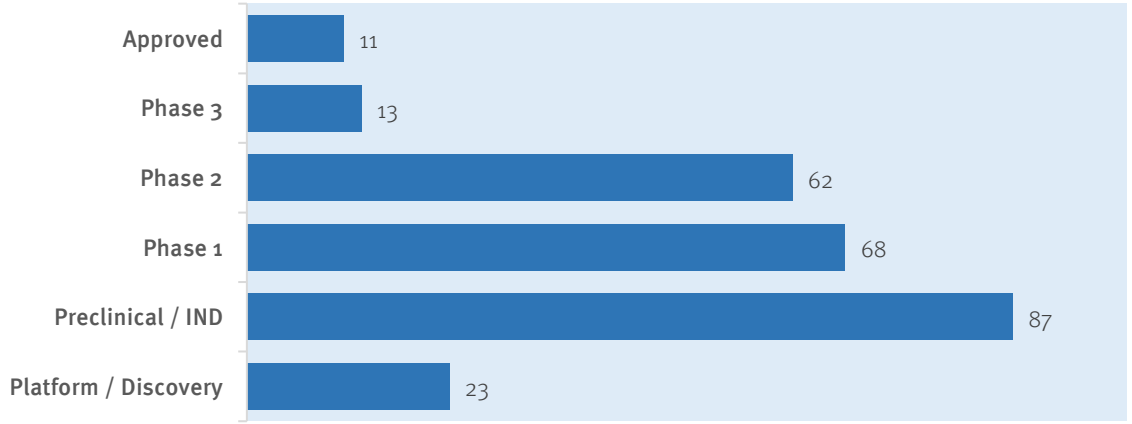
Determined this year to do our best to get the numbers right, we reviewed numerous SEC filings, private placement documents, partnering conference sites, Google search results and market reviews to document the extent of the obesity drugs pipeline.

We excluded agents from companies like Camurus, Rhythm and Soleno that are developing drugs for rare obesity disorders. We also excluded undescribed programs. Many companies indicate that they have undeclared early-stage programs (think recent comments from Amgen and Pfizer). Presumably, there are dozens if not hundreds of additional undeclared discovery-stage and preclinical programs in development for obesity at the moment.

As of June 2024, we count **264 agents** for obesity that are either approved or in development.

The pipeline has more than **tripled** in size in a single year!

Number of Drugs in Obesity Pipeline by Stage of Development, June 2024



As noted in the chart above, we count 154 agents that are in clinical development or approved.

To state the obvious, it seems quite unlikely that the FDA is going to approve more than a few dozen additional obesity drugs in the next decade. Thus, overwhelmingly, most drug candidates in development will not be able to reach the market.

Chart source: Stifel analysis of internal database of obesity drugs in active development. Dataset compiled from multiple sources.

Obesity Drug Gold Rush Underway

The explosion in interest reminds of two prior “gold rushes” to hit the pharma field: immuno-oncology and Covid drugs. Like the Step 1 Wegovy® trial, the publication of the KEYNOTE-001 study in May 2015 showing how well Keytruda® worked in non-small cell lung cancer set off a massive gold rush which, ultimately, led to over 1,000 attempts to develop immune stimulation drugs to combat cancer.

Today, while there are a number of approved therapies, interest in the field has died down as relatively few conventional therapies (orals and antibodies) have managed to outperform Keytruda

Similarly, the pipeline of drugs for combatting Covid-19 grew to over 500 agents in development by September 2022 – only eighteen months after the Pandemic began.[6]

The success of first generation GLP-1 drugs has set off a mad rush to develop novel drugs for obesity. The pace of capital inflow and new pipeline reminds one of the California Gold Rush.

6 See https://www.canada.ca/en/patented-medicine-prices-review/services/npduis/analytical-studies/posters/future-covid19.html.

The Obesity Drug Market's Evolution to 2027

A star is born: Lilly's retatrutide to beat current agents on the market.

We would include drugs that are currently in Phase 3 development in the second-generation obesity drug group. These will be drugs that have generated 48-week data and include retatrutide, a triple incretin agonist.

At present, retatrutide looks highly likely to be approved by the FDA and was featured in an article in the *New England Journal of Medicine* last year.[7]

To quote Ania Jastreboff, MD, Ph.D., Associate Professor of Medicine & Pediatrics, Endocrinology & Metabolism, at Yale School of Medicine:

> "Participants treated with the highest dose of retatrutide achieved a mean weight reduction of 24.2% [see chart at right]; this translates to an average absolute weight reduction of about **58 pounds over 11 months** of the study. Given that participants had not yet reached a weight plateau at the time the study ended, it appears that full weight reduction efficacy was not attained."

Retatrutide is a worthy alternative to bariatric surgery and is positioned to be approved by the FDA in either 2026 or 2027.

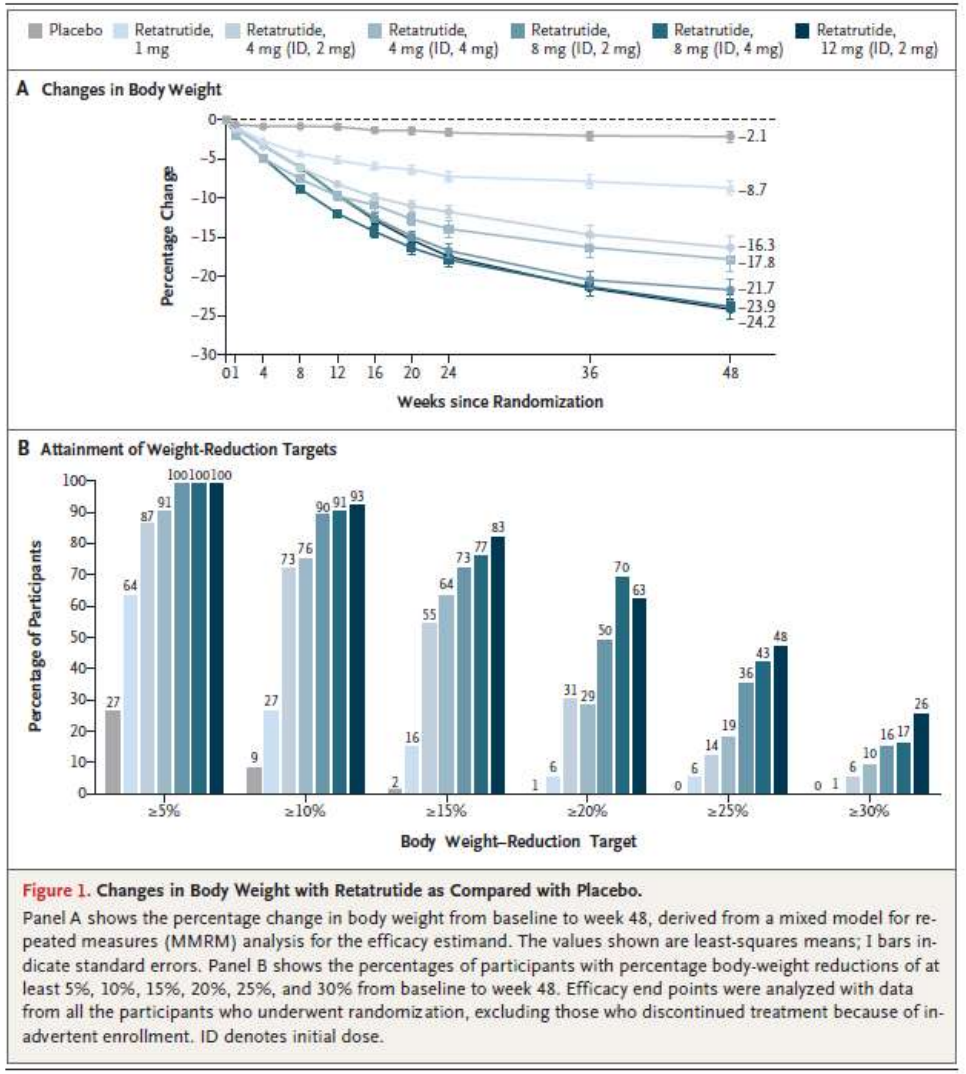


Figure 1. Changes in Body Weight with Retatrutide as Compared with Placebo.

Panel A shows the percentage change in body weight from baseline to week 48, derived from a mixed model for repeated measures (MMRM) analysis for the efficacy estimand. The values shown are least-squares means; I bars indicate standard errors. Panel B shows the percentages of participants with percentage body-weight reductions of at least 5%, 10%, 15%, 20%, 25%, and 30% from baseline to week 48. Efficacy end points were analyzed with data from all the participants who underwent randomization, excluding those who discontinued treatment because of inadvertent enrollment. ID denotes initial dose.

7 See https://www.nejm.org/doi/full/10.1056/NEJMoa2301972

The Obesity Drug Market's Evolution to 2027 (continued)

Patients are going to have at least six modern incretins available to them by 2027. The market will end up quite crowded with options.

Altimmune's pemvidutide is also well positioned to be approved by 2027. This drug achieved 13.4% weight loss at 48 weeks. Obviously, not nearly as good as retatrutide. Pemvidutide is a long-acting "balanced" dual agonist of both glucagon-like peptide 1 (GLP-1) and glucagon that is in development for the treatment of obesity and nonalcoholic steatohepatitis (NASH).

Pemvidutide's effect on glucagon positions the drug poorly for treating diabetes but makes it an excellent candidate for treatment of obese persons with liver disease. Glucagon agonism can have direct effects on energy expenditure in the liver in addition to decreasing appetite.

To quote Rajna Golubic, PhD, of the Oxford Centre for Diabetes, Endocrinology and Metabolism:

> "balanced for greater affinity for the GLP-1 receptor vs glucagon, so that the beneficial effects outweigh the effect for glucose but it still harnesses the benefits of glucagon on liver with a decrease in liver fat, with positive effects on heart, positive effects on kidneys, and other beneficial metabolic effects."

BI and Zealand's survodutide is also positioned to be on the market by 2027. This is another balanced GLP-1 / glucagon agonist, although the drug saw a 27% treatment discontinuation rate in a Phase 2 study. Compare this to a 16% discontinuation rate at the highest dose for retatrutide.

By 2027 we should see supply constraints impacting access to semaglutide and tirzepatide fall off – allowing Lilly and Novo to both achieve sales of their drugs at well over $20 billion each.

We expect to see something like **six approved incretin options** with good to great weight loss and side effect profiles by 2027.

The Benefits of Competition

Berkeley Lovelace Jr., CNBC, June 23, 2024

The next wave of obesity drugs is coming soon.

Drug companies are racing to develop GLP-1 drugs following the blockbuster success of Novo Nordisk's Ozempic and Wegovy and Eli Lilly's Mounjaro and Zepbound.

Some of the experimental drugs may go beyond diabetes and weight loss, improving liver and heart function while reducing side effects such as muscle loss common to the existing medications. At the 2024 American Diabetes Association conference in Orlando, Florida, researchers are expected to present data on 27 GLP-1 drugs in development.

"We've heard about Ozempic and Mounjaro and so on, but now we're seeing lots and lots of different drug candidates in the pipeline, from very early-stage preclinical all the way through late-stage clinical," said Dr. Marlon Pragnell, ADA's vice president of research and science. "It's very exciting to see so much right now."

Approval by the Food and Drug Administration is likely years away for most. Some of the drugs showcased could be available for prescription in the U.S. within the next few years.

Source: https://www.nbcnews.com/health/health-news/beyond-ozempic-glp-1-drugs-promise-weight-loss-health-benefits-rcna157525

"We've witnessed an unprecedented acceleration in the development of GLP drugs," said Dr. Christopher McGowan, a gastroenterologist who runs a weight loss clinic in Cary, North Carolina. "We are now firmly entrenched in the era of the GLP."

While the existing drugs are highly effective, new drugs that are more affordable and have fewer side effects are needed, McGowan added.

Expanding the number of weight loss drugs available is important for several reasons, experts say.

More options could also help alleviate the shortages seen in the U.S. with Novo Nordisk's and Lilly's weight loss drugs.

Increased competition could drive down the high cost of the drugs over time. A month's supply of Wegovy or Zepbound can cost more than $1,000, often financially untenable for many patients, experts say.

Patients can also respond differently to treatments, said Dr. Fatima Cody Stanford, an associate professor of medicine and pediatrics at Harvard Medical School. In fact, some have found the existing GLP-1 options ineffective.

"Different GLP-1 drugs may have varying levels of efficacy and potency," she said. "Some patients may respond better to one drug over another, depending on how their body metabolizes and responds to the medication."

Consensus Forecast for 2027: It Remains a Semaglutide / Tirzepatide World

Analysts foresee relatively little progress from new agents in the market by 2028 and give most of the credit to today's incumbents. CagriSema and Survodutide (BI456906) are seen as relatively small contributors. MariTide (AMG133) gets virtually no credit.

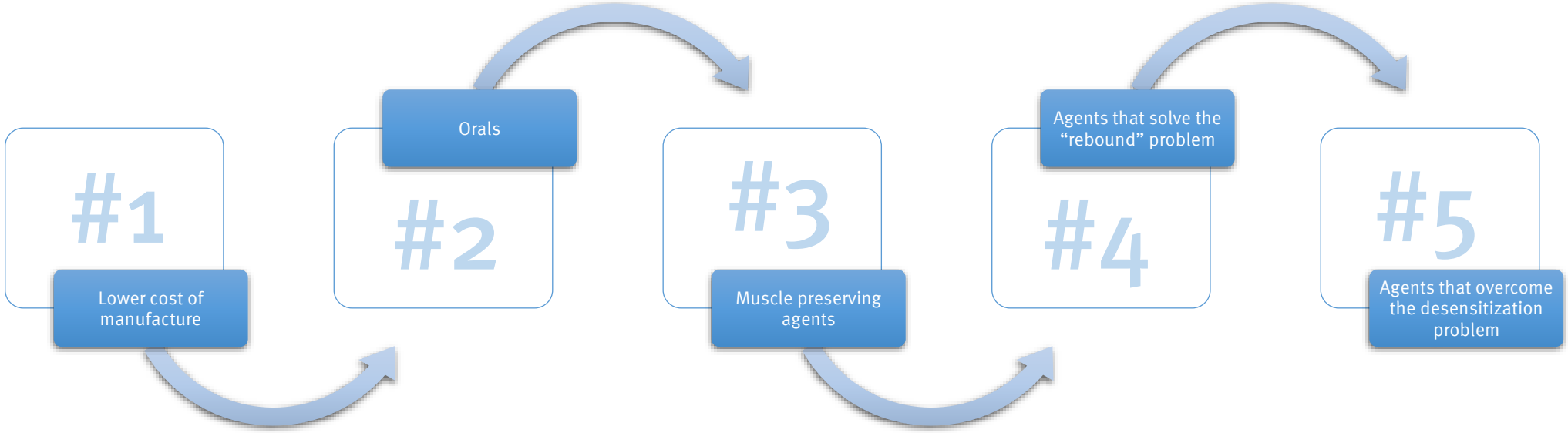
Source: PharmaSights

Third Generation Obesity Drugs
Outlook on Approvals in 2028 to 2034 Period

Third Generation Drugs: The Obesity Drug Market: 2028 to 2034

We count drug candidates that are currently in preclinical development, Phase 1 or Phase 2 as candidates to become approved third generation obesity drugs. These drug candidates could reasonably be expected to hit the market between 2028 and 2034.

Despite the obvious crowding that is set to take place in the incretin class, there will still be ample room for competition, particularly for drugs that solve major unmet needs in the incretin market:



There are so many good ideas being developed today. An obvious opportunity is to find agents that would be additive in some mechanistic way to retatrutide or tirzepatide and then to develop the drug on top of that agent.

Alternatively, one could sidestep these agents with a lower cost frontline option or develop an agent for the patients who do not achieve satisfactory weight loss.

Gut-Brain Regulation of Appetite a Central Feature of Current Efforts to Manage Weight

Müller TD, Blüher M, Tschöp MH, DiMarchi RD, "Anti-obesity drug discovery: advances and challenges," *Nature Reviews Drug Discovery*, Mar 2022.

Various peripherally derived endocrine factors regulate food intake by jointly acting on defined neurocircuits in the hypothalamus and other brain regions (Fig. 2). Although this tightly controlled system is pivotal for survival, it has emerged as a major obstacle to achieving sizeable body weight reduction, as it progressively defends against negative energy balance and undernutrition. One of the likely relevant underlying mechanisms is a decrease in peripheral adiposity signals (leptin, insulin) following weight loss, and prolonged fasting leads to increased expression and sensitization to orexigenic neuropeptides in the hypothalamus and the hindbrain. Simultaneously, the expression of and sensitivity to anorexigenic neuropeptides decrease in these same areas to constitute a double-barrelled defence of body weight. Concurrently, the density and strength of the orexigenic agouti-related peptide (AgRP)/neuropeptide Y (NPY) fibres that project from the arcuate nucleus (ARC) to the paraventricular hypothalamic nuclei increase in response to prolonged fasting. This remodelling of the ARCAgRP/NPY projections correlates with increased activation of paraventricular hypothalamic nuclei neurons with the goal to restore food intake. Another obstacle in weight loss pharmacology is that persistent elevation of adiposity signals such as leptin and insulin results in desensitization, leading to an impaired responsiveness of this homeostatic system. A striking finding supporting this perspective is that leptin supplementation shows remarkable efficacy in lowering body weight in individuals with congenital leptin deficiency, but is largely ineffective in more common polygenetic forms of obesity.

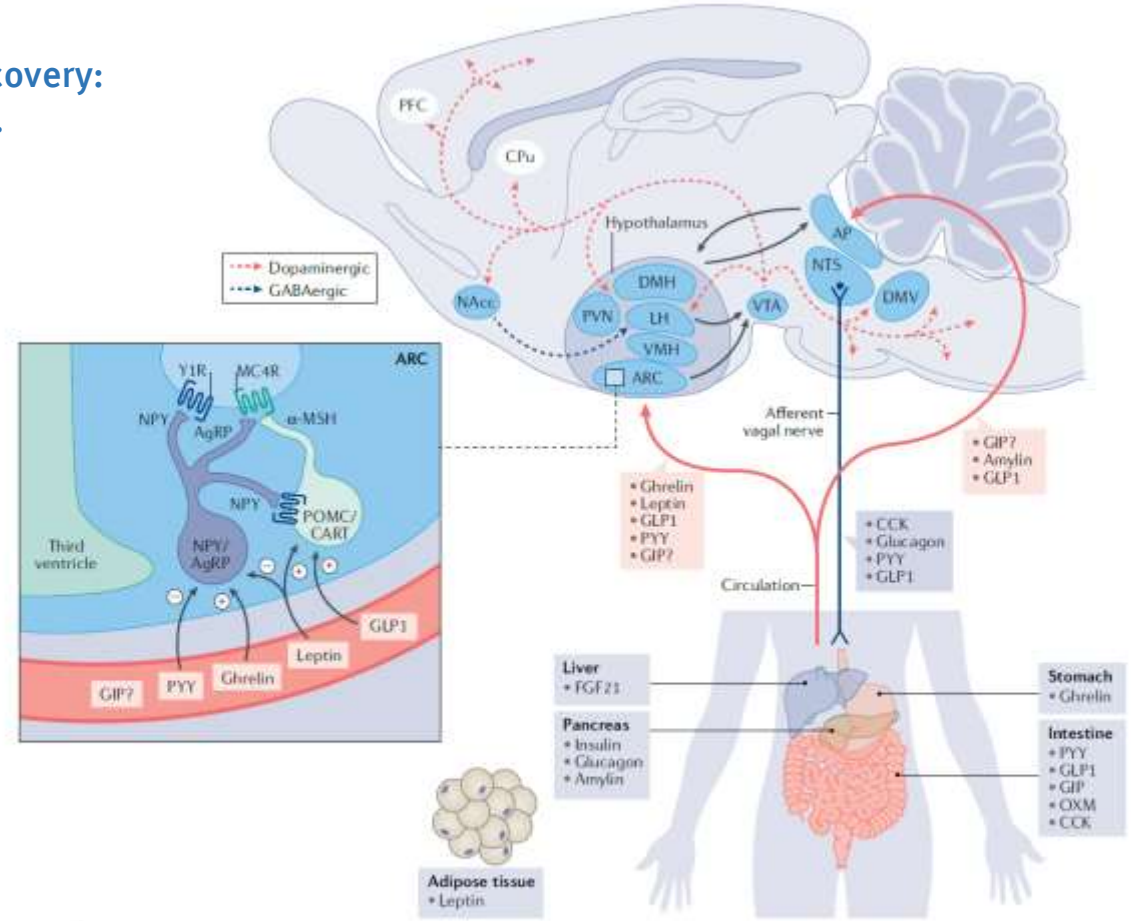


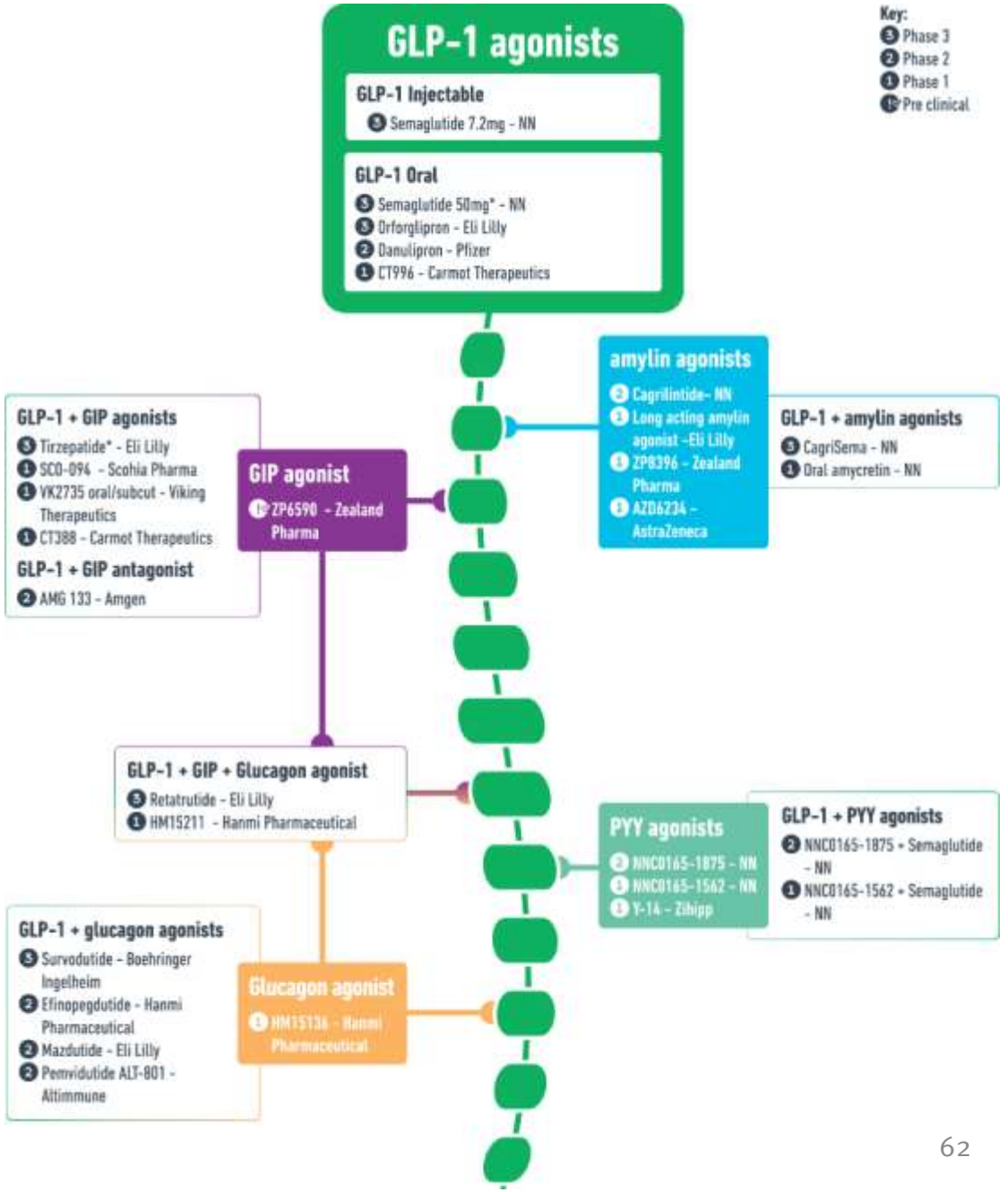
Fig. 2 | **Gut–brain regulation of food intake.** Peripheral hormones integrate in central control of homeostatic and hedonic eating behaviour. α-MSH, α-melanocyte-stimulating hormone; AgRP, agouti-related peptide; AP, area postrema; ARC, arcuate nucleus; CART, cocaine- and amphetamine-regulated transcript; CCK, cholescystokinin; CPu, caudate putamen; DMH, dorsomedial hypothalamus; DMV, dorsal motor nucleus of the vagus; FGF21, fibroblast growth factor 21; GIP, glucose-dependent insulinotropic polypeptide; GLP1, glucagon-like peptide 1; LH, lateral hypothalamus; MC4R, melanocortin 4 receptor; NAcc, nucleus accumbens; NPY, neuropeptide Y; NTS, nucleus tractus solitarius; OXM, oxyntomodulin; PFC, prefrontal cortex; POMC, pro-opiomelanocortin; PVN, paraventricular nucleus; PYY, peptide tyrosine tyrosine; VMH, ventromedial hypothalamus; VTA, ventral tegmental area; Y1R, neuropeptide Y receptor type 1.

Source: https://www.nature.com/articles/s41573-021-00337-8

Gen 3 Innovators Typically Use GLP-1 Agonism as the Backbone of the Pipeline for Gut Hormone-Based Obesity Treatments

Melson, E., Ashraf, U., Papamargaritis, D. et al. What is the pipeline for future medications for obesity?. *Int J Obesity*, Feb 1, 2024

Additionally, a large pipeline of entero-pancreatic hormone-based pharmacotherapies is under development, with the aim to enhance and/or complement the efficacy and mechanisms of action of GLP-1 RA. Tirzepatide is the first combination of entero-pancreatic hormones [dual GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) RA] that has been approved for T2D management based on the findings from the phase 3 SURPASS programme. The marked WL achieved with tirzepatide in the SURPASS trials led to the phase 3 SURMOUNT programme, assessing tirzepatide as treatment for obesity.



Source: https://www.nature.com/articles/s41366-024-01473-y

Third Generation Pipeline: Obesity Drugs in Development for the Next Decade

The Third Generation Drug Pipeline is Rich and Diverse

There are three ways to reduce weight of a human: (1) cause the human to eat less (appetite suppression), (2) fail to store energy in food as fat or (3) cause the stored energy to be used less efficiently. A final approach to obesity involves no change in weight but instead looks to preserve muscle mass. We count 66 separate drug mechanisms that fall into one of these categories.

Appetite Suppressants (138 Agents)

Cannabinoid Agonist
DAT Antagonist
Duodenum Masker
GDF15 analogue
Ghrelin Inverse Agonist
GLP-1 Receptor Agonist
GLP-2 Receptor Agonist
Glucagon Receptor Agonist
Incretin: Amylin Analogue
5-HT2A receptor agonist
GPR40 receptor antagonist
Gut Blocker
IGF-1 Agonist
IRS2 modulator
Leptin sensitizer
MAS/Angiotensin System
Melanocortin 4 Agonist
Mucin Enhancer
NPYR2 Agonist
Nutrient receptor agonists
PTP1B inhibitor
Psychedelic
PYY Agonist
Serotonin 6 Antagonist
Serotonin-2c Agonist
Taste Receptor: TASR2

Energy Storage Blockers (24 agents)

Acarbose
Delta-5-Desaturase
GIP inhibitor
HDAC11 inhibitor
INHBE Modulator
Lipase Inhibitors
LPL Activator
MGAT2
Microbiome modulators
mir-515-5p modulator
Mots-c Modulator
RASP Modulator
SLC13A5 protein inhibitors
SPTBN1
VEGF Inhibitor

Energy Usage Efficiency (40 agents)

Adenosine A3 Agonist
Adipocyte Biology: IL-22
Adipogenesis: GPR75
AMPK activator
Apelin Receptor Agonist
FGF21 agonist
Glucagon RA
Inflammation: NLRP3
IP6K Modulator
Lipolysis Agonists
MAP/ERK modulator
mir-22-3p modulator
Mitochondrial Uncoupler
Nuclear Rec: ERR Agonist
SCD-1 Inhibitor
SHIP1 agonist
Sirt1 Activator
THRB Agonist

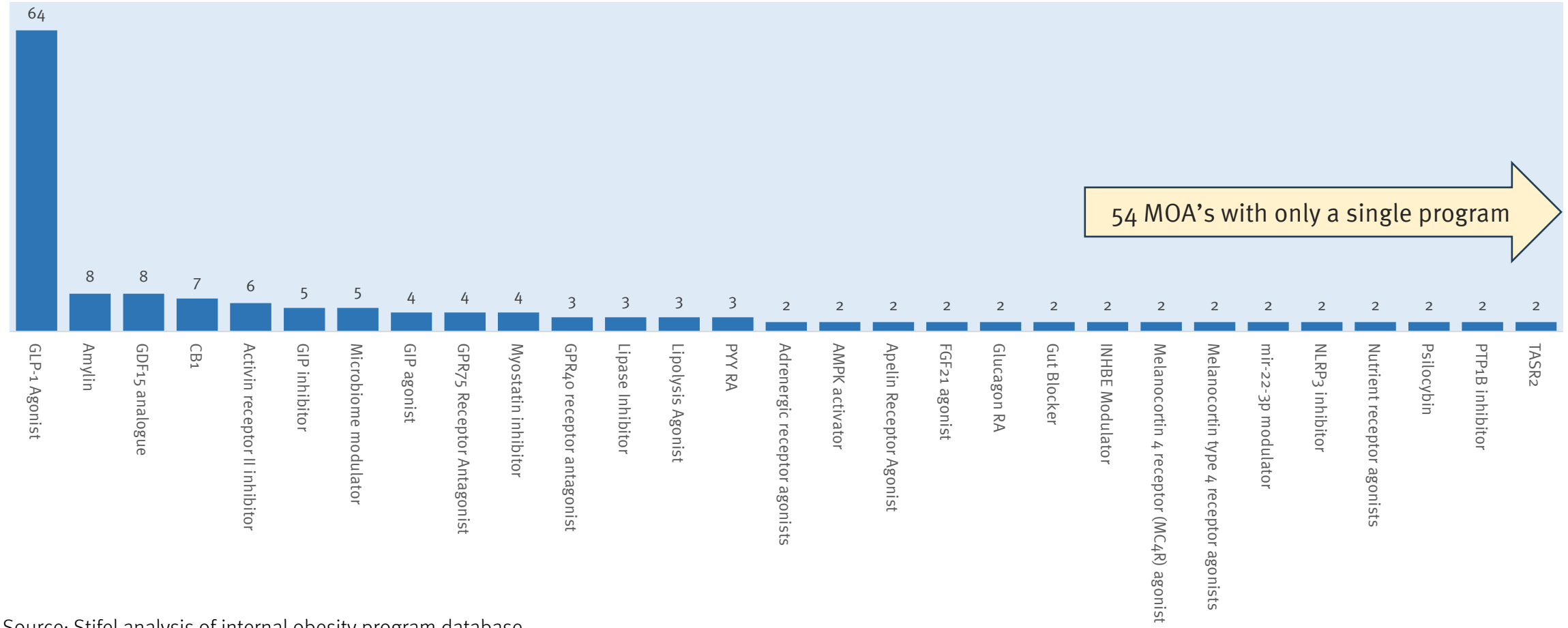
Muscle Preservants (16 agents)

Activin receptor II inhibitor
IGF-2 Fusion Protein
Myostatin inhibitor
SARM
Testosterone Replacement

MOA Crowding Analysis

The GLP-1 agonist space is very crowded. Other MOA's with more than three or more programs in development include amylin, GDF15, CB1, Activin receptors, GIP inhibitors, microbiome modulators, GIP agonists, GPR75, and myostatin inhibitors. Compared to other fields like immuno-oncology and immunology, the obesity drug development area is relatively uncrowded – except in the GLP-1 space.

Number of Obesity Programs by MOA (Pipeline or Approved, June 2024, 2 or more programs only included)

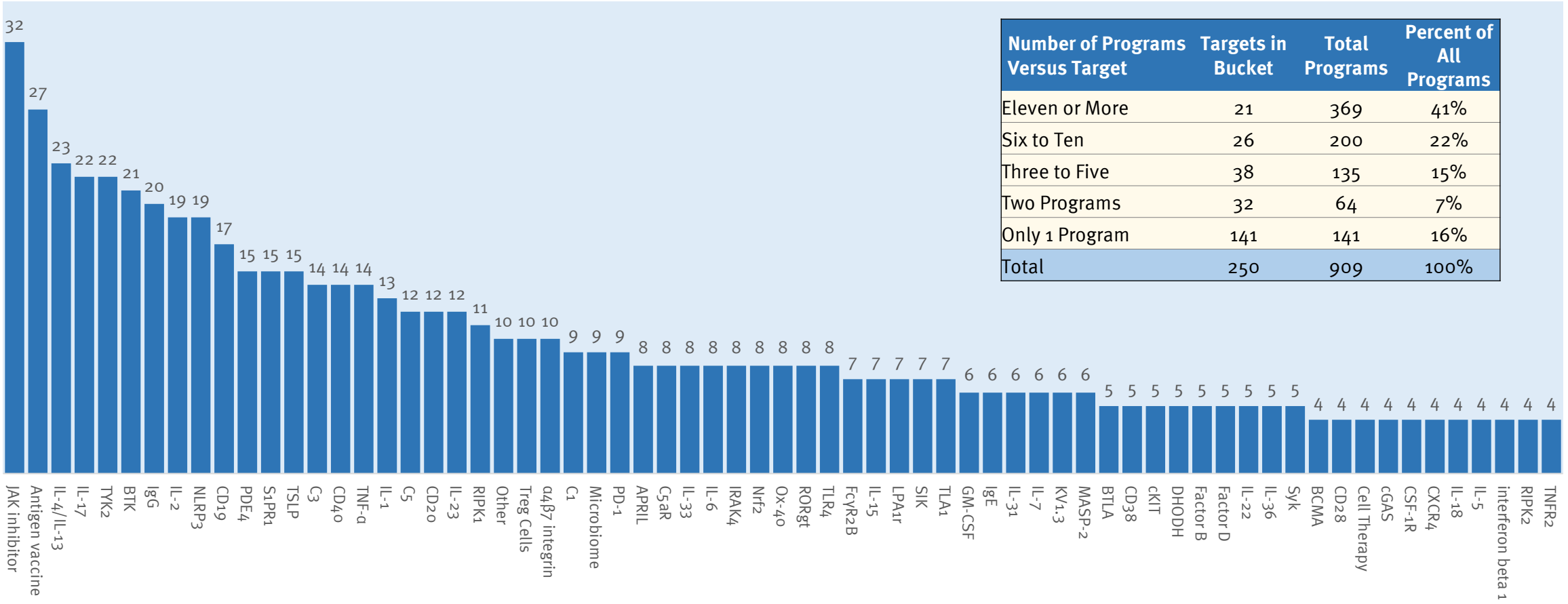


Source: Stifel analysis of internal obesity program database.

Comparison to the Immunology Drug Field

We track over 900 pipeline programs in the Stifel immunology database. Strikingly, over 60% of programs are in fields with six or more programs in development. The field is highly crowded in comparison to the obesity drug field.

Count of Immunology Programs by Target (4 or More Programs in Development, June 2024)



Number of Programs Versus Target	Targets in Bucket	Total Programs	Percent of All Programs
Eleven or More	21	369	41%
Six to Ten	26	200	22%
Three to Five	38	135	15%
Two Programs	32	64	7%
Only 1 Program	141	141	16%
Total	250	909	100%

Source: Analysis of Stifel database of autoimmune and immunology pipeline programs, June 2024. The Stifel database was compiled from Google searches, search of EvaluatePharma, search of DealForma, search of partnering websites, internal Stifel documents and Wall Street research.

Selected Third Generation Approaches to Obesity in Development

These are just a few of the promising novel approaches in develop to improved obesity pharmacology by 2034.

Amylin Agonists

Amylin affects glucose by slowing gastric emptying through reduced glucagon secretion after eating, and by appetite suppression. Recent positive data from Novo Nordisk on its oral amycretin and CagriSema and Zealand Pharma's Petrelintide clearly show that amylin agonists can be additive to GLP-1 agonists. Amylin agonism is here to stay in the long-run.

Apelin Receptor Agonists

Apelin agonists, like BioAge's azelaprag, can control obesity by improving metabolism when combined with incretin drugs. Azelaprag is an oral small molecule that mimics apelin, a peptide hormone that's released during exercise. In preclinical trials, azelaprag has shown the potential to increase weight loss and restore muscle.

Biased GLP-1 Agonists

A major issue with GLP-1 agonists is that weight loss tails off over time. Many users report that the drugs initially work for them but become less effective in time. This is likely due to receptor internalization. Biased agonists from Roche, Metsera, SciWind, Structure and others may beat internalization. Early results with CT-388 look highly promising.

CB1 Blockers

CB1 receptor inhibition helps with obesity by reducing appetite and increasing energy expenditure. Sanofi's rimonabant was an approved CB1 receptor antagonist but was pulled due to impact on CNS conditions. More recently, Novo acquired Inversago which has a peripheral only CB1 blocker. This drug and a competing mAb from Skye are in Phase 2 studies.

GIP Inhibitors

GIP antagonists hold promise by reducing insulin secretion, enhancing fat breakdown, improving insulin sensitivity, regulating appetite, and increasing energy expenditure. Amgen's MariTide contains a GIP inhibitor which shows powerful weight loss. Other companies developing drugs in this class include Antag, GMAX and Orion.

Glucagon Agonism

Glucagon agonism can help with weight loss through stimulation of lipolysis and increasing energy expenditure. Glucagon is a hormone produced by the pancreas that primarily works to increase blood glucose levels in the liver. Strong weight loss seen with pemvidutide, survodutide and mazdutide illustrates the potential of glucagon drugs.

GPR75 Antagonism

Genetic studies show that individuals with loss-of-function mutations in GPR75 have a reduced risk of obesity. GPR75 and its ligand 20-Hete are involved in appetite regulation, thermogenesis and improvement of glucose use. The pipeline of drugs in this area from Confometrx, Orion and Regeneron is early but highly promising.

Gut Modulators

Bariatric surgery (esp. roux-en-y) can reduce weight in several ways: (1) food bypasses nutrient absorption sites and (2) food gets to lower intestine where it can stimulate nutrient sensing cells. There are many approaches to gut modulation including lipase inhibitors, alpha-glucosidase inhibitors, glucose beads and mucin enhancers. Data to date has been limited.

Muscle Preservers

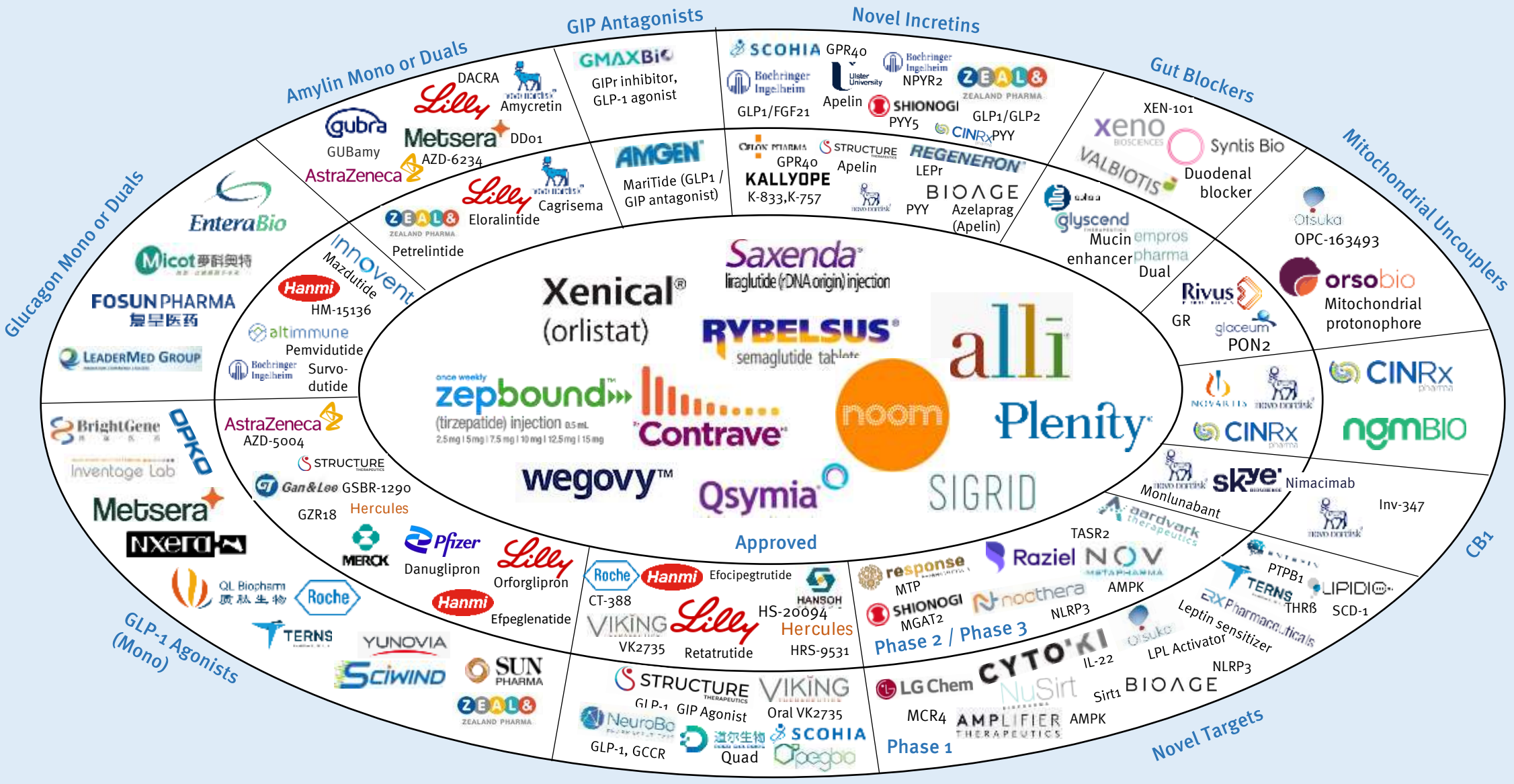
Myostatin is a growth factor that negatively regulates muscle growth. It signals through the Activin receptor type II (ActRIIB). Blockers of myostatin or ActRIIB can increase muscle mass, an important need in obesity management. A related approach, SARMS, promotes muscle protein synthesis. Data to date in this area from Versanis (Lilly), Veru and others is promising.

Nuclear Receptor Modulators

Nuclear receptor modulators such as ER, GR, LXR, FXR and PPAR control obesity by targeting receptors involved in the regulation of metabolism, energy expenditure, and adipogenesis. Compounds in development by companies such as Pelagos improve insulin sensitivity, reduce lipid accumulation, enhance fatty acid oxidation, and regulate appetite. Early and exciting area.

Source: Stifel analysis of internal obesity program database.

Clinical Stage Obesity Drug Pipeline



Source: Stifel investment banking analysis

Pre-Clinical Obesity Drug Pipeline

20-Hete Blocker

ORION biotechnology

Amylin Analogue

ALGORAE PHARMACEUTICALS

STRUCTURE THERAPEUTICS

Apelin RA

VASA THERAPEUTICS

Brown Fat Cells

biorestorative therapies

CB1 Antagonists

AGENTIX

AMGEN

BIONANOSIM

CORBUS PHARMACEUTICALS

DAT Antagonist

Reviva PHARMACEUTICALS

ERR Agonist

PELAGOS PHARMACEUTICALS

FAM13A

AMGEN

FGF21 agonist

REJUVENATE BIO

YUHAN

Ghrelin

HELSINN

GIP Inhibitor

ANTAG THERAPEUTICS

Helicore Biopharma

Incregen Therapeutics

ORION biotechnology

GLP-1 Agonists

Adocia
AprilBio
Crinetics
EnteraBio
Fractyl Health
Hepagene
Highfield Bio
LG Chem
Metsera
Vivani Medical

GLP-1 Dual/Triple/Quad

CinFina Pharma
Deep Apple Therapeutics
Metsera
Micot
NeuroBo Pharma
Pep2Tango Therapeutics
Progen
SciWind

Glucagon Analogue

Hanmi

GPR75

ConfometRx

ORION biotechnology

REGENERON science to medicine

Gut Nonsystemic Drug

LUMEN BIOSCIENCE

HDAC11 inhibitor

Myracle THERAPEUTICS

IGF-2

Juvena THERAPEUTICS

INHBE Modulator

Alnylam PHARMACEUTICALS

arrowhead pharmaceuticals

WAVE LIFE SCIENCES

IP6K Modulator

THE UNIVERSITY of NORTH CAROLINA at CHAPEL HILL

IRS2 modulator

HOUSEY PHARMA

Lipolysis Agonist

Medytox

Long-Acting ANP

Lilly

Melanocortin Agonists

deep apple

Endevica Bio

LG Chem

PALATIN

MGAT2

Bristol Myers Squibb

Mir-22 / Mitochondria

APTAMIR

Pesalis THERAPEUTICS

Microbiome modulators

APTORUM

Emmyon Metabolic Health

KOBIOLABS

YSOPIA bioscience

MicroRNA Targets

APTAMIR

Mitochondrial Uncouplers

Equator Therapeutics

MITO BIOPHARMA

Mots-c Modulator

CohBar INC

Neural Targets

eracal therapeutics

NLRP3 Inhibitor

nodthera

ventyx BIOSCIENCES

RASP Modulator

aldeyra

SHIP1 agonist

UPSTATE MEDICAL UNIVERSITY

SLC13A5 inhibitor

Eternygen

SPTBN1

BULLFROGAI

TASR2

Kindex Pharmaceuticals

Source: Stifel analysis

Third Generation Pipeline:
Body Composition / Muscle Enhancement Strategies

Muscle Preservation Pipeline

A year ago, just one or two assets on this page were in active development. Development activity in weight loss muscle preservation has exploded.

Current Phase of Development	Drug Category: Activin receptor II inhibitor	Myostatin agonist	SARMs/Testosterone	Apelin	Other Approaches
Phase 2 / Phase 3	Lilly Bimagrumab	REGENERON Trevogrumab ScholarRock Apitegromab	LIPOCINE Testosterone veru Enobasarm	BIOAGE Azelaprag, Oral STRUCTURE THERAPEUTICS ANPA-0073, Oral	biophytis BIO101 (MAS receptor activator)
Phase 1	ELEVAI Probiotic that expresses ActRIIA and Myostatin LOKNA REGENERON Garetosmab	KEROS THERAPEUTICS KER-065			
Pre-Clinical	biohaven Aldefgrobep alfa 35 Pharma, iBIO SIXPEAKS BIO	biohaven Taldefgrobep iBIO, PeptiDream ScholarRock SRK-439		VASA THERAPEUTICS VS-367, SubQ* Ulster University, APIE THERAPEUTICS NXera	Immunis Juvena THERAPEUTICS, Emmyon Metabolic Health IGF-2 Fusion Protein

Source: Stifel Investment Banking Research and DealForma

* Well positioned for co-formulation with SubQ incretin drugs

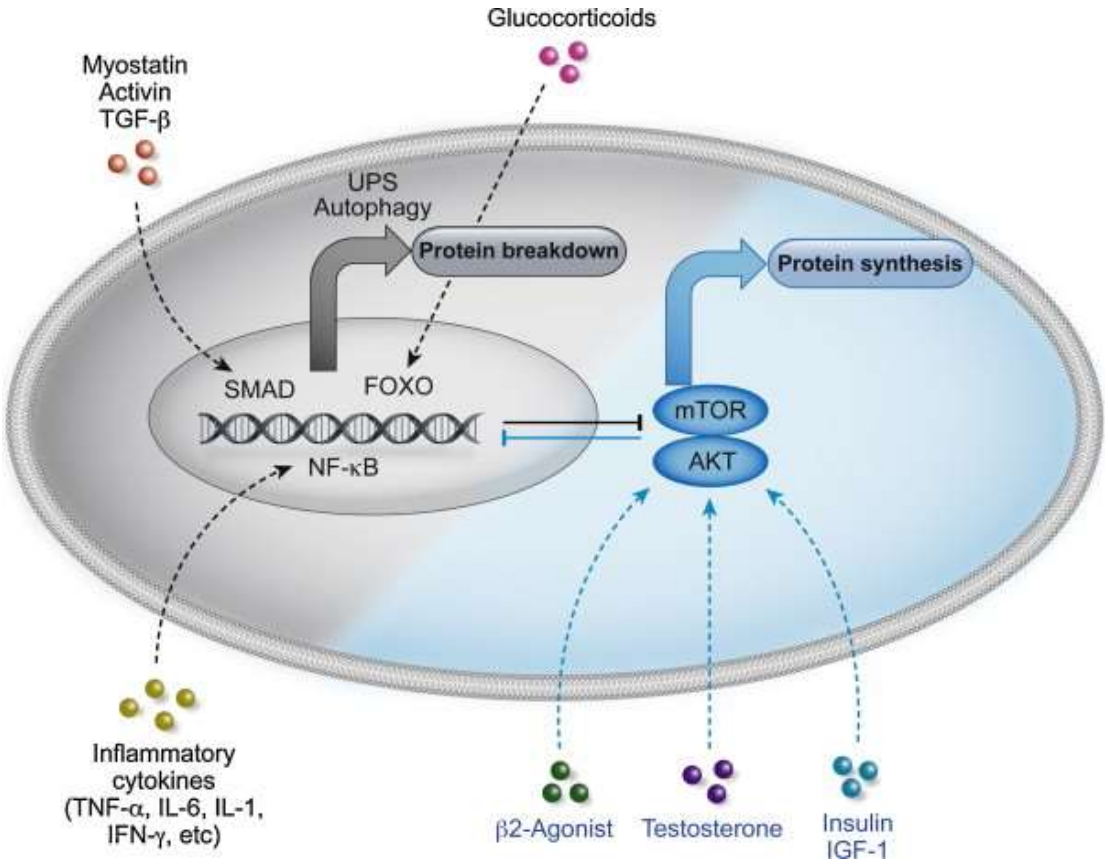
Biological Pathways at Work with Muscle Enhancers

Han HQ, Zhou X, Mitch WE, Goldberg AL, "Myostatin/activin pathway antagonism: molecular basis and therapeutic potential," *Int J Biochem Cell Biol.* Oct 2013, pp. 2333-47.

Myostatin, also referred to as growth differentiation factor-8 (GDF-8), belongs to the transforming growth factor-beta (TGF-β) family of secreted factors. It is predominantly expressed in skeletal muscle, although cardiac muscle and adipose tissue also express it at low levels. Myostatin is secreted from muscle cells and acts in a paracrine/autocrine fashion by binding to its muscle surface receptor complex, triggering a downstream signaling cascade.

Myostatin/activin signaling blockade can be achieved by several types of proteins that interfere with ligand–receptor interactions. Examples of these large molecule inhibitors include antagonistic peptibody, antibody, decoy receptor and native binding protein, which prevent ligand binding to the transmembrane receptor complex on the muscle cell surface. A number of such agents have been shown to be efficacious in preclinical disease models.

The dramatic growth of interest in pharmacological use of myostatin/activin antagonists has now established several clear conclusions. Although several signaling pathways regulate muscle homeostasis, the myostatin/activin-ActRIIB signaling pathway is a dominant pathway whose inhibition can override the influence of other pathways and lead to a prevention or reversal of muscle loss in diverse disease states.



Veru's Enobasarm Shows Over 10% Net Lean Mass Gain

Potential to Optimize Weight Loss with Enobosarm: Meta-analysis of Body Composition from Three Randomized Clinical Trials Support the Ability of Enobosarm to Preserve Muscle while Reducing Fat

C. PRADO[1], J. CRAWFORD[2], A. DOBS[3], W. EVANS[4], D. RODRIGUEZ[5], I. SHALEV[5], G. BARNETTE[5], M. STEINER[5]

1-Ag, Food & Nutri Sci Dept, University of Alberta, Edmonton, AB, Canada; 2-Dept of Medicine, Duke Cancer Center, Durham, NC, USA; 3-The Johns Hopkins Hospital, Baltimore, MD, USA; 4-Duke University School of Medicine, Durham, NC, USA; 5-Department of Research and Development, Veru Inc., Miami, Florida, USA

Financial Disclosures

Conducted by GTx, Inc. and exclusive global license for enobosarm by Veru Inc.

Background

Enobosarm is a novel oral selective androgen receptor modulator shown to increase lean mass and decrease fat mass. Enobosarm may benefit patients on GLP-1 RA for weight loss by preserving muscle while augmenting fat loss.

Objective

A meta-analysis was conducted of three randomized clinical studies of enobosarm involving older men, postmenopausal women, and older patients who have muscle loss due to advanced cancer, to evaluate the ability of enobosarm to preserve muscle while reducing fat.

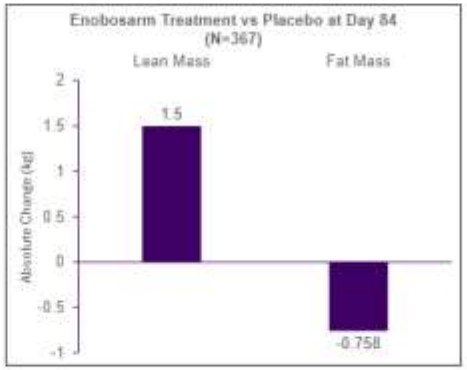
Methods and Material

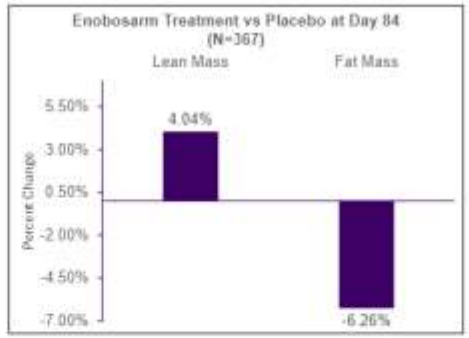
Meta-analysis was conducted of 3 randomized clinical trials evaluating enobosarm 3mg q day versus placebo and who had a Day 84 DXA scan to assess body composition: Phase 2 501 study in older males (>60 yo) and postmenopausal women (n= 24 placebo and 24 enobosarm), Phase 2 502 study in patients with muscle wasting because of advanced cancer (n=30 placebo and 31 enobosarm), and Phase 3 504 study in patients with advanced lung cancer (n=135 placebo and 124 enobosarm).

Results

At Day 84, DXA scan showed an absolute increase in lean mass of 1.5 kg in enobosarm treated vs placebo (p=0.00004), and % change in lean mass of a 4.04 % in enobosarm vs placebo (p=0.00007). Absolute decrease in fat mass was 0.758 kg in enobosarm treated vs placebo (p=0.015), and % change in fat mass was a loss -6.26 % in enobosarm vs placebo (p=0.006). Enobosarm was generally well tolerated with no increase in frequency of gastrointestinal side effects compared to placebo.

Results





Conclusion or Discussion

In meta-analysis of 367 older men, postmenopausal women, and older patients with muscle loss from advanced cancer, enobosarm therapy resulted in reductions in fat mass while preserving lean mass. This meta-analysis supports the potential of enobosarm when combined with a GLP-1 RA to preserve muscle, while preferentially reducing fat to potentially result in a higher quality weight loss in overweight and obese patients. A Phase 2b randomized controlled trial is currently underway to evaluate the safety and efficacy of enobosarm in preserving muscle mass and augmenting fat loss in older patients receiving a GLP-1 RA for weight loss.

References

1- Narayanan R et al. Mol Cell Endocrinol 2017)
2- Dalton JT et al. Curr Opin Support Palliat Care 7:345-351, 2013
3- Kamrakova M et al Calcif Tissue Int 106:147-157,2020
4- Hoffman DB et al. J Bone Metab 37:243-255, 2019
5- Kearbey JD et al Pharm Res 26:2471-2477, 2009
6- Dobs AS et al. Lancet Oncol 14:335-45, 2013
7- Dalton JT et al. J Cachexia Sarcopenia Muscle 2:153-161, 2011
8- Leciejewska N et al. J Phys and Pharma 70:525-533, 2019

Source: ADA Website, June 2024

Regeneron Running a Giant Muscle Preservation Study

A Study to Test if Trevogrumab or Trevogrumab With Garetosmab When Taken With Semaglutide is Safe and How Well They Work in Adult Patients With Obesity for Weight Loss and Fat Loss (COURAGE)

Study Overview

Brief Summary

This study is researching experimental drugs called trevogrumab and garetosmab (called "study drugs") in combination with another drug, semaglutide (Wegovy®). Part A of the study, the sponsor is only researching trevogrumab. Part B of the study the sponsor is researching trevogrumab, garetosmab, and Wegovy either alone or in different combinations with each other. Part A of the study is focused on healthy participants. Part B of the study is focused on participants with obesity. The aim of Part A of the study is to see how safe and tolerable the study drug is in healthy participants. The aim of Part B of the study is to see how safe and effective the study drug is when combined with Wegovy.

Parts A and B of the study are looking at several other research questions, including:

- What side effects may happen from taking the study drug
- How much study drug is in the blood at different times
- Whether the body makes antibodies against the study drug (which could make the drug less effective or could lead to side effects)

Show less

Detailed Description

Part A Healthy Volunteers

Part B (starts after treatment for Part A has completed) Participants with Obesity

Study Start (Actual)
2024-03-13

Primary Completion (Estimated)
2026-06-24

Study Completion (Estimated)
2026-06-24

Enrollment (Estimated)
624

Study Type
Interventional

Phase
Phase 2

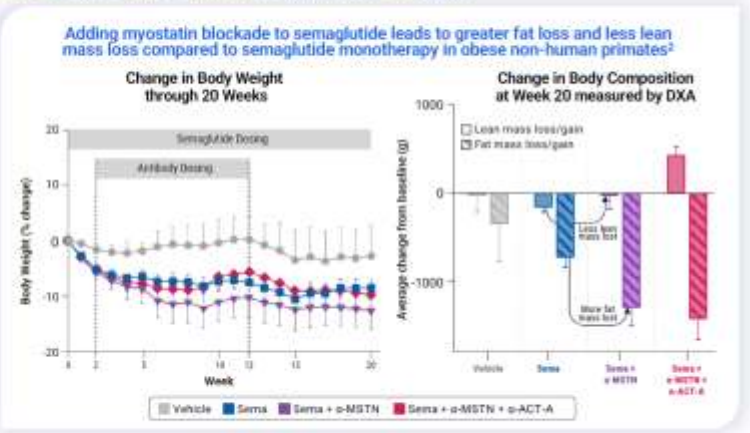
Obesity combinations aim to improve quality of weight loss; exciting early data supporting potential unimolecular solutions

GLP-1 based therapies, such as semaglutide (sema) and tirzepatide, are emerging as standards of care for weight loss; However, up to 40% of weight loss from these agents is due to decreases in lean muscle mass[1]

Novel approaches for obesity

	Rationale	Program status
GLP-1/GIP-based therapy + α-MSTN + α-ACT-A	Improving quality of weight loss by preserving lean muscle during weight loss	Mid-2024: Start Phase 2 study of semaglutide with trevogrumab (anti-myostatin) ± garetosmab (anti-activin A)
GLP-1/GIP-based therapy + LEPR	Improving maintenance of weight loss following incretin discontinuations	Phase 2 study now underway testing combinations of tirzepatide ± mibavademab
GPR75	GPR75 gene mutations are associated with protection against obesity	siRNA, small molecule, and antibody candidate identification and screening underway

Adding myostatin blockade to semaglutide leads to greater fat loss and less lean mass loss compared to semaglutide monotherapy in obese non-human primates[2]



17 [1]Wilding, Diabetes Obes Metab, 2022, PMID: 35441478. [2]from Mastaitis J, et al. Manuscript in preparation and ADA 2023 presentation, n=10 per arm, DXA: dual-energy X-ray absorptiometry measurement

This slide contains investigational drug candidates that have not been approved by any regulatory authority.

REGENERON

Source: Clinicaltrials.gov and Regeneron 2024 annual meeting presentation to shareholders.

Regeneron Phase 1 Data for Trevogrumab at ADA

OR: CLINICAL THERAPEUTICS—OTHER THERAPEUTIC AGENTS | JUNE 14 2024

34-OR: The Effect of Combined Activin A and Myostatin Blockade on Body Composition—A Phase 1 Trial FREE

DINKO GONZALEZ TROTTER; STEPHEN DONAHUE; CHRIS WYNNE; SHAZIA ALI; PRODROMOS PARASOGLOU; ANITA BOYAPATI; KUSHA MOHAMMADI; BRET J. MUSSER; PRETTY MEIER; JASON MASTAITIS; EVELYN GASPARINO; JESUS TREJOS; JOHN D. DAVIS; GARY A. HERMAN; ROBERT PORDY

REGENERON®

Introduction: Preclinical data suggest myostatin and activin A are important negative regulators of muscle mass. Trevogrumab (a monoclonal antibody [mAb]) binds and blocks myostatin signalling, while garetosmab (a mAb) binds and blocks activin A, AB and AC signalling. Here, the effects of administering trevogrumab and garetosmab, alone or in combination, on body composition in healthy participants was assessed.

Methods: This Phase 1, double-blind, placebo-controlled study randomized healthy males and postmenopausal females to single-dose or multiple-dose parts of the study. For single-dose, females received: trevogrumab 6 mg/kg (n=6); garetosmab 10 mg/kg (n=6); combination trevogrumab 6 mg/kg and garetosmab (1 mg/kg, n=6; 3 mg/kg, n=6; 10 mg/kg, n=12); or placebo (PBO; n=12). For multiple-dose, females received: garetosmab 10 mg/kg every 4 weeks (Q4W; n=6) or PBO (n=2); combination trevogrumab 6 mg/kg and garetosmab 10 mg/kg every 2 weeks (n=6) or PBO (n=4). In the multiple dose part, males received garetosmab 10 mg/kg Q4W (n=8) or PBO (n=8).

Results: **Thigh muscle volume (TMV) increased from baseline 7.7% with trevogrumab 6 mg/kg + garetosmab 10 mg/kg (nominal P<0.001 vs PBO) and 4.6% with trevogrumab 6 mg/kg (nominal P<0.05 vs PBO) 8 weeks after single-dose. Total fat mass and android fat mass (AFM) decreased from baseline with trevogrumab 6 mg/kg + garetosmab 10 mg/kg (-4.6% and -6.7%; both nominal P<0.05 vs PBO).** After multiple-dose, TMV initially increased after 3 doses of trevogrumab 6 mg/kg + garetosmab 10 mg/kg but decreased to similar levels as PBO at Week 28; AFM and visceral fat mass decreased from baseline by 14.3% and 20.1%, respectively (both nominal P<0.05 vs PBO). No safety concerns were identified in any active treatment groups.

Strong data!

Source: ADA 2024 Website, https://diabetesjournals.org/diabetes/article/73/Supplement_1/34-OR/154774/34-OR-The-Effect-of-Combined-Activin-A-and

Regeneron's Competitive Positioning in Obesity/Muscle

Ryan Crowe, VP Investor Relations, Regeneron, June 11, 2024

Regeneron looks at obesity a little differently than a lot of the other companies out there. We believe that the solution to obesity is not starvation or food aversion but rather muscle and metabolism. And we have two antibodies that we think can help preserve muscle during the weight loss phase of patients taking these GLP-1s and GIP agonists or antagonists. And by preserving muscle over time, your metabolic rate will be conserved, and therefore, you should be able to hopefully maintain the weight that you do lose from preserving the muscle and your metabolic rate.

So, what we presented last month was a single ascending dose study of both trevogrumab, our GDF8 or myostatin antibody; and garetosmab, our activin A antibody, and we were very encouraged by that data, limited read through since it's a single dose, but we did see muscle growth from these patients in terms of thigh muscle volume. And we also saw a reduction in fat. So, both of those things are exactly what we would want to see from these antibodies.

And we also saw very good tolerability, particularly for trevogrumab, which we dosed in over 400 patients and has a very benign profile, which, of course, is very important in a broad population that we would hope to serve for obesity.

Yes. So bimagrumab is probably the one in the lead here, and that's a product that Lilly acquired from a company called Versanis, and I believe they're approaching the end of their study at this point. Bimagrumab blocks the activin type 2 receptor. And there's around three dozen different growth factors and BMPs that bind to this receptor, including myostatin and activin A. So they've kind of gone at the approach of block the receptors so nothing binds to it.

We've decided on a different approach, where we're only going to selectively target GDF8 and activin A, two different antibodies. So we're able to separate and parse out what we think the true negative regulators of muscle growth are. And by doing that, we believe we'll be able to potentially have a better side effect profile since we know exactly what we're blocking and what its downstream effects on the body are. And as I've mentioned, we have a lot of data on trevogrumab's tolerability and safety profile that looks very, very clean.

And so we believe that will be sufficient to at least preserve body composition. And with activin A, at least in nonhuman primates, we were able to see some muscle growth and additional fat loss. So we're very encouraged. We hope the data from the nonhuman primates that we presented last year at ADA can translate to humans. That's what the Phase 2 study we're currently running is intending to do. And as I mentioned, we hope to have data sometime next year from at least the first 26 weeks of that study to read out.

Source: https://investor.regeneron.com/static-files/170984d5-2a68-4c4b-bc6c-22bea8c710ba

Scholar Rock Preclinical Data for SRK-439 Impressive

CAMBRIDGE, Mass.--(BUSINESS WIRE)--Jun. 24, 2024-- Scholar Rock (NASDAQ: SRRK), a late-stage biopharmaceutical company focused on advancing innovative treatments for spinal muscular atrophy (SMA), cardiometabolic disorders, and other serious diseases where protein growth factors play a fundamental role, today announced that the first participants were dosed in the Phase 2 EMBRAZE proof-of-concept trial, designed to assess the safety and efficacy of apitegromab, an investigational, highly selective myostatin inhibitor, to preserve lean muscle mass in individuals living with obesity and on background therapy of a GLP-1 receptor agonist (GLP-1 RA). The trial will also evaluate the effects of apitegromab on the durability of weight loss upon withdrawal of GLP-1 RA therapy. The results from this trial will inform the development of SRK-439, a novel investigational selective myostatin inhibitor optimized for the treatment of cardiometabolic disorders, including obesity.

The Company also presented new preclinical data that support the potential of SRK-439 to increase lean mass and contribute to a favorable body composition following withdrawal from GLP-1 RA treatment. These data were presented by Melissa Fulham, PhD, of Scholar Rock, at the American Diabetes Association's 84th Scientific Sessions on June 23rd in Orlando, Florida.

"We are happy to share the exciting news that we've dosed the first participants in our EMBRAZE clinical trial ahead of schedule and to have new preclinical data with SRK-439, our highly selective anti-myostatin, featured at the American Diabetes Association Scientific Sessions," said Jay Backstrom, M.D., MPH, President and Chief Executive Officer at Scholar Rock. "SRK-439 preclinical data to date have demonstrated preservation of lean mass with GLP-1 RA-induced weight loss, attenuation of fat mass regain following GLP-1 RA withdrawal, and greater potency compared to an anti-ACTRII antibody. Together, these data continue to support a best-in-class potential for healthy weight loss management and could be transformative for the management of weight loss. We are looking forward to providing additional updates on our cardiometabolic program as we advance SRK-439, as well as the EMBRAZE trial."

Shown below are results for body composition at baseline (6 days before semaglutide treatment), the end of semaglutide treatment (at 4 weeks), and at the end of the semaglutide withdrawal period (at 8 weeks):

Endpoint (units)	IgG control + semaglutide	SRK-439 + semaglutide	P value
Absolute lean mass (g) at baseline	24.8	25.5	n.s.
Absolute lean mass (g) at 4 weeks	22.3	26.4	P<0.001
Absolute lean mass (g) at 8 weeks	25.1	29.4	P<0.0001
Absolute fat mass (g) at baseline	11.8	10.3	n.s.
Absolute fat mass (g) at 4 weeks	5.9	3.8	n.s.
Absolute fat mass (g) at 8 weeks	12.7	8.3	n.s.
Relative lean mass (%) at 8 weeks	57.1%	65.8%	P<0.001
Relative fat mass (%) at 8 weeks	28.7%	18.0%	P<0.01

"These new preclinical data provide compelling evidence that SRK-439 contributed to lean muscle preservation during GLP-1 RA-induced weight loss and attenuated fat mass rebound following discontinuation of semaglutide," said Mo Qatanani, PhD, Chief Scientific Officer at Scholar Rock. "Mice receiving SRK-439 treatment had significantly more lean mass at the end of the semaglutide withdrawal period. These exciting data continue to support the differentiated profile of SRK-439 and its potential to contribute to healthier weight management and long-term metabolic benefits during and after GLP-1 RA treatment."

Source: https://investors.scholarrock.com/news-releases/news-release-details/scholar-rock-announces-new-srk-439-preclinical-data-showing

Key Question for Muscle Preservation Drugs: Do They Matter?

Yes. GLP-1 agonists cause concerning and clinically meaningful loss of muscle mass.

Peter Attia, Blog Posting, Feb 2023

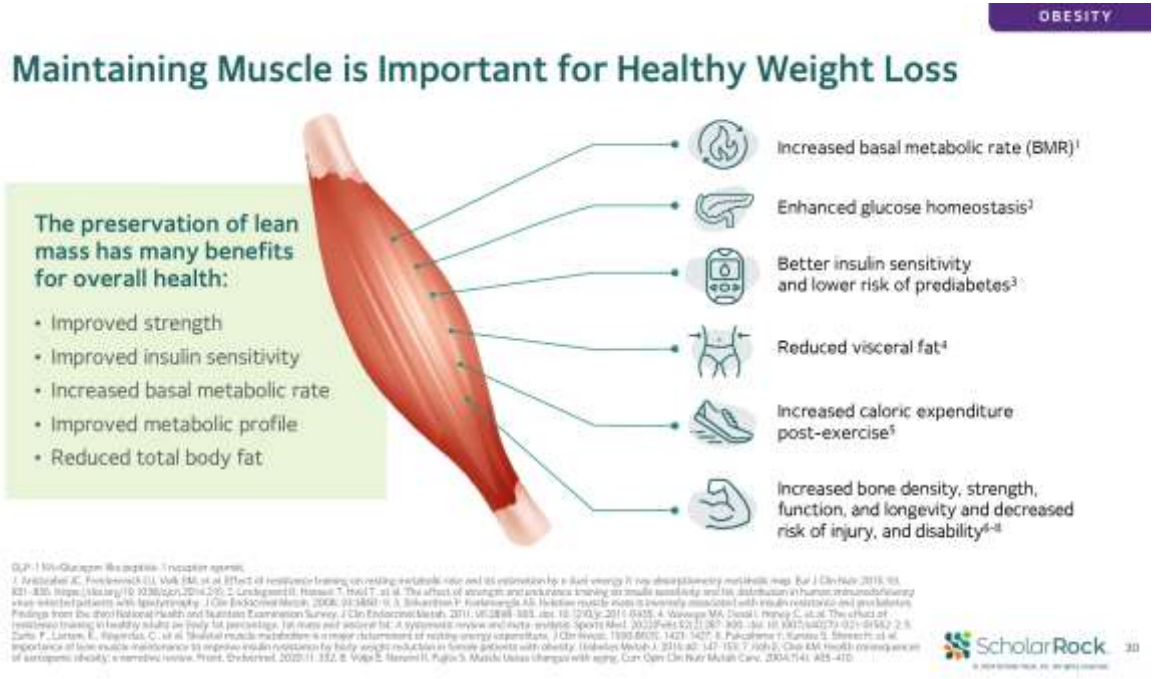
… from the information we can scrape together based on sub-cohort data, these "miracle drugs" start to look a bit less miraculous. In 2021's STEP 1 trial – the first trial demonstrating the efficacy of semaglutide as a treatment for adult obesity – a subset of 140 patients underwent DEXA scans for body composition analysis. Among these patients, lean mass accounted for approximately 39% of total weight loss – substantially higher than ideal. In a substudy of 178 patients from the SUSTAIN 8 trial on semaglutide as a diabetes treatment, the average proportion of lean mass loss was nearly identical at 40%, despite lower doses and less total weight loss than in the STEP 1 trial.

It's important to note that both of these trials were conducted in adults with overweight or obesity, and higher lean mass loss among such individuals can still be an acceptable cost for dramatic weight reduction as long as overall body composition is improving. Indeed, despite the high lean mass losses, the proportion of lean mass to total body mass still increased in STEP 1 patients by an average of roughly 3% and in SUSTAIN 8 patients by an average of just over 1%.

GLP-1 agonists have also grown in popularity as a weight loss drug among those without obesity, a trend I find somewhat disconcerting. While those with obesity stand to reap considerable health benefits from fat loss, the potential benefits of fat loss among healthy-weight individuals are minimal and are unlikely to offset the sizable health risks associated with reduced lean mass. Even among patients with obesity, not all can afford to lose significant lean mass. Sarcopenic obesity, which is especially common in older populations, is characterized by the dual hazards of excess fat mass and low levels of skeletal muscle.

Source: https://jamanetwork.com/journals/jama/article-abstract/2819410

Keeping muscle while losing fat is fundamentally healthy:



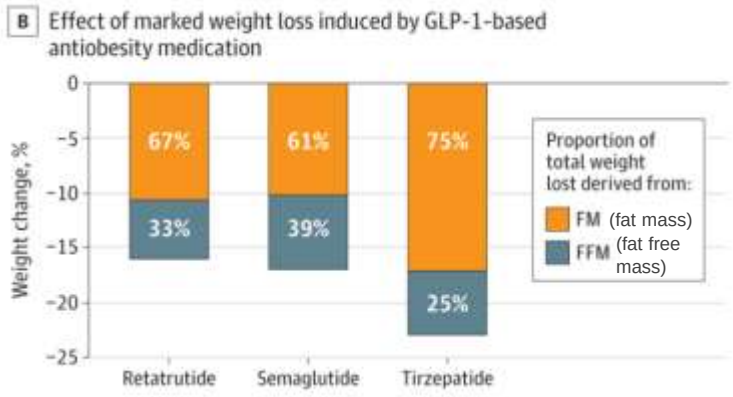
Key Question for Muscle Preservation Drugs: Do They Matter?

No. When you weigh less you need less muscle. Losing some muscle mass is not clinically relevant.

From: Conte C, Hall KD, Klein S. Is Weight Loss-Induced Muscle Mass Loss Clinically Relevant? *JAMA*. Jun 3, 2024

The loss of fat free mass (FFM) is not clinically relevant and is normal. Weight loss helps muscle function and there is little evidence that Activin II receptor blockage matters.

"The marked weight loss induced by GLP-1–based antiobesity medications and the results from several trials that found 25% to 40% of the weight lost was composed of FFM/lean body mass (Figure, B) have led to concerns regarding adverse effects of GLP-1–based antiobesity medications on physical function… However, none of these studies reported the effects of weight loss on SMM (skeletal muscle mass) or objective measures of physical function. It is unlikely that the decline in SMM that occurs with even large amounts of weight loss impairs physical function. People with obesity generally have greater amounts of FFM (fat-free mass) and SMM than lean people, so the decrease in SMM induced by weight loss represents a small fraction of total body SMM. Moreover, even though the decrease in SMM can sometimes cause a decrease in muscle strength, it does not necessarily have an adverse effect on physical function. Intentional weight loss causes a greater relative decrease in body fat than FFM or SMM, so the ratio of FFM/SMM to fat mass increases. Accordingly, physical function and mobility improve after weight loss despite the decrease in FFM/SMM, even in older adults with decreased FFM and SMM at baseline. In addition, weight loss improves the "quality" of remaining muscle



by decreasing intramyocellular and intermuscular triglycerides and increasing muscle insulin sensitivity. Nonetheless, the effect of GLP-1–based antiobesity medications on FFM has led to an interest in developing concomitant pharmacotherapy to mitigate the decrease in FFM/SMM. A 2024 study in mice found that stimulating muscle growth by blocking the activin II receptor prevented the decrease in FFM during weight loss induced by GLP-1 agonism, but did not result in greater benefits in exercise performance or glucose homeostasis than weight loss induced by GLP-1 agonism alone."

The stories told about having worse body composition after weight rebound are not accurate.

"It has been proposed that weight loss and subsequent regain in people with obesity could have detrimental effects on body composition, based on short-term studies that found a greater relative increase in fat mass than FFM in regained weight than in lost weight, suggesting repeated cycles of weight loss and regain will increase whole-body adiposity. However, these studies involved refeeding following experimental weight loss in lean individuals (eg, the Minnesota Starvation Experiment) or illness-induced cachexia (eg, tuberculosis, cancer). Such data do not accurately reflect weight regain after intentional weight loss in people with obesity, where the composition of weight regained is nearly identical to the composition of weight lost. GLP-1–based pharmacotherapy and bariatric surgery can achieve marked weight loss in people with obesity. Even though the absolute decrease in FFM/SMM is related to total weight loss, the decrease in FFM/SMM in relation to baseline is usually small and the relative reduction in FFM/SMM is less than the relative reduction in fat mass, resulting in an improvement in physical function.

Source: https://jamanetwork.com/journals/jama/article-abstract/2819410

The Phrase "Body Composition" May be in Your Future

At home scales like the InBody Dial H30 are affordable and allow for reasonably reliable measurement of muscle mass and fat mass.*

BMI Analysis Can be Highly Misleading

Quail and Dannenberg, *Nature Reviews Endocrinology*, 2019

Box 1 | **Weighing the value of BMI**

High BMI has been associated with reduced mortality following certain health events, including heart failure, heart attack and some cancers[173]. This observation is known as the obesity paradox, and is debated widely owing to its clinical implications. Several competing explanations for the obesity paradox have been proposed.

Weight and the metabolic syndrome do not always correlate

BMI is used as a readily available cost-effective surrogate for predicting obesity comorbidities. Although this assumption is reasonable for population studies, ~25% of individuals who are obese are metabolically healthy[174] and ~20% of individuals who are lean are metabolically obese[175] (metabolically obese normal-weight; that is, they have qualitatively similar health risks as people who are obese despite having a healthy-range BMI).

BMI categories are not one-size-fits-all

BMI does not consider age or sex; therefore, certain demographics are frequently misclassified (for example, postmenopausal women)[176]. Additionally, BMI categories are based on morbidity and mortality statistics from white European populations, and do not universally predict adverse health conditions. For example, a high number of Asian Indians with a healthy-range BMI have type 2 diabetes mellitus. Therefore, BMI categories need to be adjusted between populations[177].

BMI is not static

For some cancers, weight loss is the first symptom that prompts a medical evaluation. Although illness-induced weight loss is unlikely to push an individual into an entirely new BMI category, even modest weight loss can have biological consequences. For example, 10% acute weight loss in women who are morbidly obese leads to an improvement in some systemic markers of the metabolic syndrome and inflammation[156], and reduced systemic predictors of metastasis based on preclinical models[124].

Body fat is a killer.**

Britton et.al., *JACC*, Jul 2013.

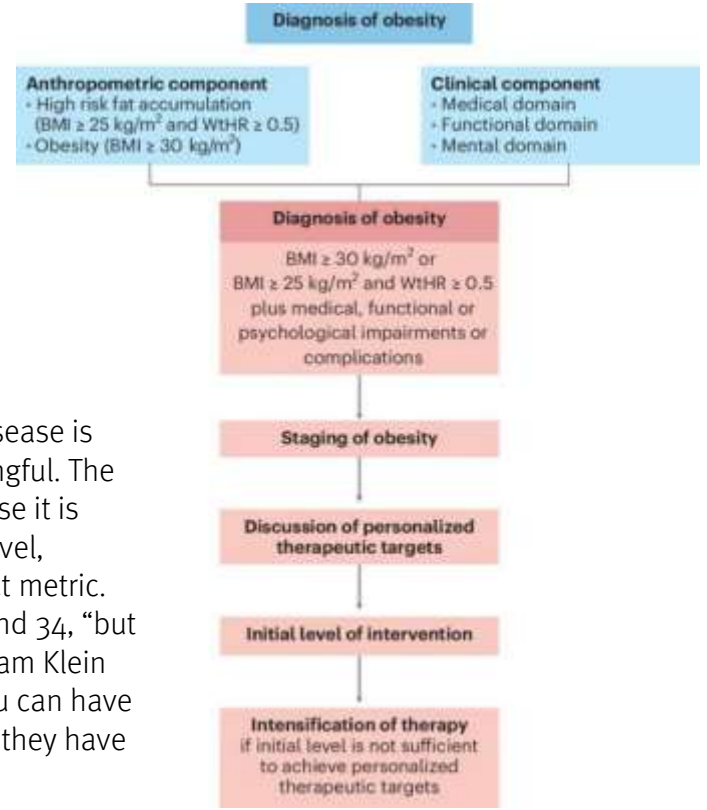
Participants from the Framingham Heart Study (n = 3,086) underwent assessment of fat depots using multidetector computed tomography and were followed up longitudinally for a median of 5.0 years. After multivariable adjustment, visceral adipose tissue was associated with cardiovascular disease (hazard ratio: 1.44; p = 0.01) and cancer (hazard ratio: 1.43; p = 0.005).

High BMI Not Always a Sign of Ill Health

C. Aschwanden, *Scientific American*, Jun 2024

One major objection raised to declaring obesity a disease is that its basic diagnostic measure may not be meaningful. The standard for measuring obesity is BMI, in part because it is easy to gauge, is inexpensive and, at a population level, correlates well to body fat levels. But it's an imperfect metric. Actor Dwayne "The Rock" Johnson has a BMI of around 34, "but he's not obese—he's a very muscular kind of guy," Sam Klein says. On the other end of the spectrum, he says, "you can have people with a normal BMI who are very doughy, and they have a high body fat percentage."

New EASO Guidelines Include Body Composition for Obesity Management***



* See https://inbodyusa.com/studies/.
** See https://www.nbcnews.com/health/health-news/fat-more-important-weight-alone-health-study-n535041., *** See https://acrobat.adobe.com/id/urn:aaid:sc:EU:ec471819-3fa8-4927-a73f-d2fd6797ac88
# See https://www.scientificamerican.com/article/people-who-are-fat-and-healthy-may-hold-keys-to-understanding-obesity/
Sources: https://www.nature.com/articles/s41574-018-0126-x, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4142485/, https://pubmed.ncbi.nlm.nih.gov/35717418/.

What Will Muscle Enhancing Drugs Mean for Society?

We are sitting up and paying attention to the muscle enhancement drug category after seeing Regeneron's data for its combo of a myostatin inhibitor with an Activin receptor II inhibitor.

Whether clinically relevant or not for obesity management, the type of data showed by Regeneron are jaw-dropping. Or perhaps we should say arm-pumping.

Muscle up 8% and fat mass down 7% in *eight* weeks. Wow.

And the drugs are subQ which means they could be administered at home. BioAge's apelin agonist is IV as is Lilly's bimagrumab. Those will be used for severe patients.

One quickly gets into the same conversations that we are having about GLP-1 agonists:

1. How much will these drugs cost?
2. What will the label look like with respect to safety?
3. Can you keep the muscle on long-term even if you stop taking the drugs?

This area is interesting but there are questions with the activins (e.g., repro tox / black box). A key next step will be trials involving combos of these drugs with incretins and working out the safety in larger, longer trials.

Importantly, there are some orthogonal MOA's here.* Veru's enobasarm works through a different pathway than the myostatin inhibitors as does the apelin class. Immunis and Juvena are working on yet other approaches. This means that one can tune up these drugs for efficacy.

Not that it will be so needed. As is illustrated at right in the case of Liam Hokstra, congenital myostatin deficiency works well but does not lead to health issues.

We don't think we are taking a big leap to say that sales of drugs in this class could easily go in the tens of billions.

The market will include those losing weight on GLP-1's, the sarcopenic (see a discussion on previous page re: persons with normal BMI who have excess fat – the "skinny fat"), and consumers who wish to augment their muscle – both for aesthetic and health reasons. The phrase "body composition" will be uttered much more a decade from now than today, particularly because it be easily measured with readily available in-home equipment.

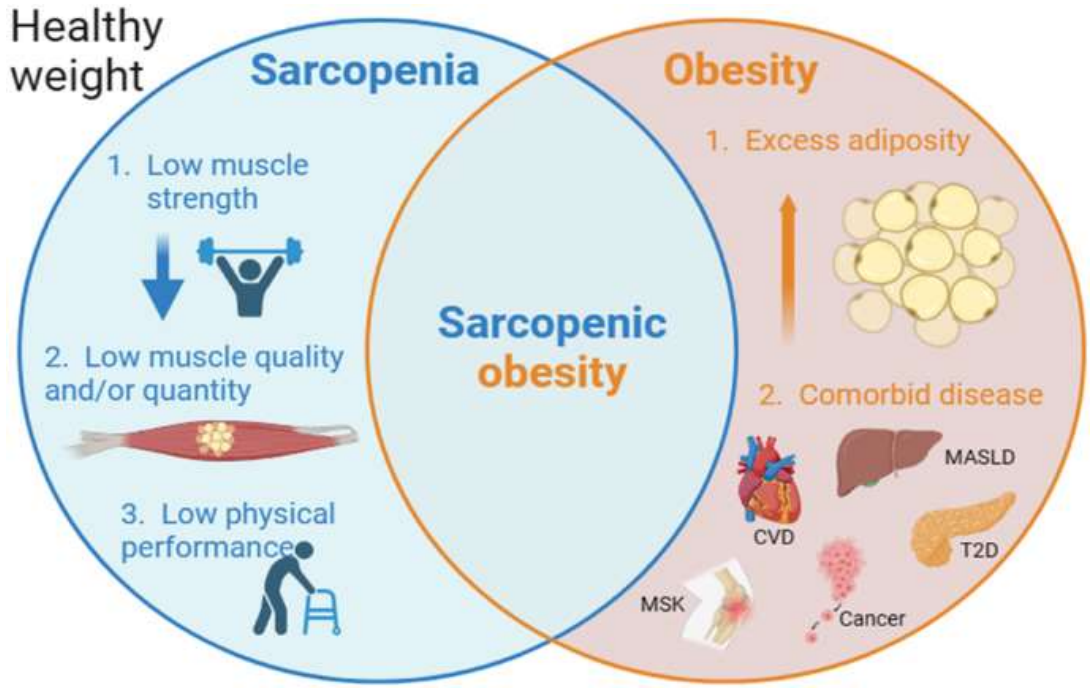
While perhaps not as important as obesity drugs, the new class of muscle enhancers will be very important for society – offering a major option for loss of muscle – one of the most important causes of death in the elderly and those with advanced disease.

The German boy Liam Hokstra was born with mutations causing congenital myostatin deficiency. He waved around five-pound dumbells like stuffed animals as a three-year old.

* See Carrie Arnold, "After obesity drugs' success, companies rush to preserve skeletal muscle," *Nature Biotechnology*, March 2024

(https://www.nature.com/articles/s41587-024-02176-5).

Sarcopenic Obesity a Major Killer of the Elderly



Benz E, Sarcopenia and Sarcopenic Obesity and Mortality Among Older People. *JAMA Netw Open*. Mar 4, 2024, p. e243604.

This large-scale, population-based cohort study assessed participants from the Rotterdam Study from March 1, 2009, to June 1, 2014. Associations of sarcopenia and sarcopenic obesity (SO) with all-cause mortality were studied using Kaplan-Meier curves, Cox proportional hazards regression, and accelerated failure time models fitted for sex, age, and body mass index (BMI). Data analysis was performed from January 1 to April 1, 2023.

In the total population of 5888 participants (mean [SD] age, 69.5 [9.1] years; mean [SD] BMI, 27.5 [4.3]; 3343 [56.8%] female), 653 (11.1%; 95% CI, 10.3%-11.9%) had probable sarcopenia and 127 (2.2%; 95% CI, 1.8%-2.6%) had confirmed sarcopenia. Sarcopenic obesity with 1 altered component of BC was present in 295 participants (5.0%; 95% CI, 4.4%-5.6%) and with 2 altered components in 44 participants (0.8%; 95% CI, 0.6%-1.0%). An increased risk of all-cause mortality was observed in participants with probable sarcopenia (hazard ratio [HR], 1.29; 95% CI, 1.14-1.47) and confirmed sarcopenia (HR, 1.93; 95% CI, 1.53-2.43). Participants with SO plus 1 altered component of BC (HR, 1.94; 95% CI, 1.60-2.33]) or 2 altered components of BC (HR, 2.84; 95% CI, 1.97-4.11) had a higher risk of mortality than those without SO. Similar results for SO were obtained for participants with a BMI of 27 or greater.

In this study, sarcopenia and sarcopenic obesity were found to be prevalent phenotypes in older people and were associated with all-cause mortality. Additional alterations of BC amplified this risk independently of age, sex, and BMI. The use of low muscle strength as a first step of both diagnoses may allow for early identification of individuals at risk for premature mortality.

Sources: https://www.nature.com/articles/s41366-024-01529-z, https://pubmed.ncbi.nlm.nih.gov/38526491/

Third Generation Pipeline:
Key Upcoming Clinical Catalysts

Ten Important Catalysts for Third Generation Obesity Drugs

1. MariTide Phase 2 Data
2. Retatrutide Phase 3 Data
3. Small molecule GLP-1's
4. Lilly's SURMOUNT-MMO data
5. Viking's VK2735 Phase 3 Start
6. Novo's CB1 Data
7. Antag's GIP1 Antagonist
8. Amylins / Novo's Cagrisema
9. RNAi from Arrowhead
10. GPR75's

1 Upcoming MariTide Phase 2 Data Will Define the Market

Bob Bradway, Amgen Earnings Call, May 2024

"Now let me just add one other important update. Whereas we don't normally comment on interim data, especially for our Phase II trial, we recognize there is significant interest in obesity in MariTide, so we'll provide additional commentary today. **The interim Phase II analysis for this study is complete, and we are very encouraged with the results that we've seen thus far** and with the conduct of the trial. Following the interim analysis, I would say we're confident in MariTide's differentiated profile and believe it will address important unmet medical needs.

We are actively planning a broad Phase III program including obesity, obesity-related conditions and diabetes. Obviously, we expect to carefully complete our ongoing Phase II trial before then moving as swiftly as appropriate to establish the safety and efficacy of this potential medicine in Phase III trials. We've initiated activities as well to further expand manufacturing capacity with both clinical and commercial supply in mind."

Bob Bradway
Chief Executive Officer
Amgen

Source: https://www.gurufocus.com/news/2426629/q1-2024-amgen-inc-earnings-call-transcript

Jay Bradner Comments on Amgen May 2024 Earnings Call

Thank you, Bob, and good afternoon, everyone. Let me start with MariTide. Reiterating Bob's comments, we are very pleased with the results seen with MariTide thus far. And we're very pleased with the overall conduct of the ongoing Phase II trial. **All arms remain active, patient dropout has not been an issue, and we're fully on track for top line 52-week data from this 11-arm Phase II study in late 2024.**

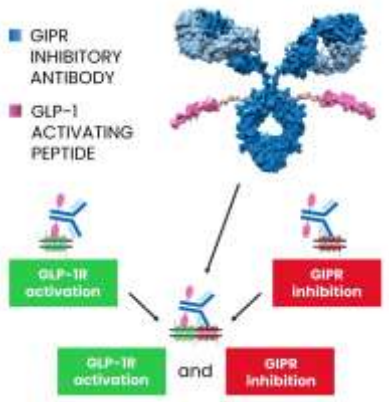
We're seeing a differentiated profile of MariTide and are confident that it will address important unmet medical needs, obesity, obesity-related conditions and diabetes. We look forward to completing the ongoing Phase II study and working with regulators to move rapidly to the broad Phase III program. Later this year, we plan to initiate an additional dedicated Phase II trial investigating MariTide for the treatment of diabetes in patients with and without obesity. This new trial is not a gating step for our Phase III program in patients with obesity.

Jay Bradner
Chief Scientific Officer
Amgen

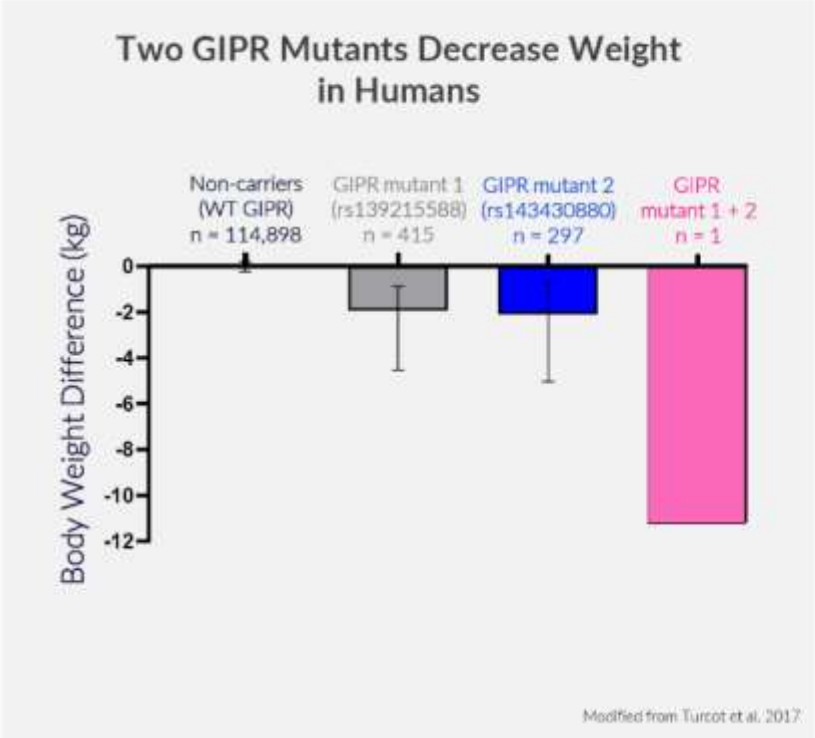
Source: https://www.gurufocus.com/news/2426629/q1-2024-amgen-inc-earnings-call-transcript

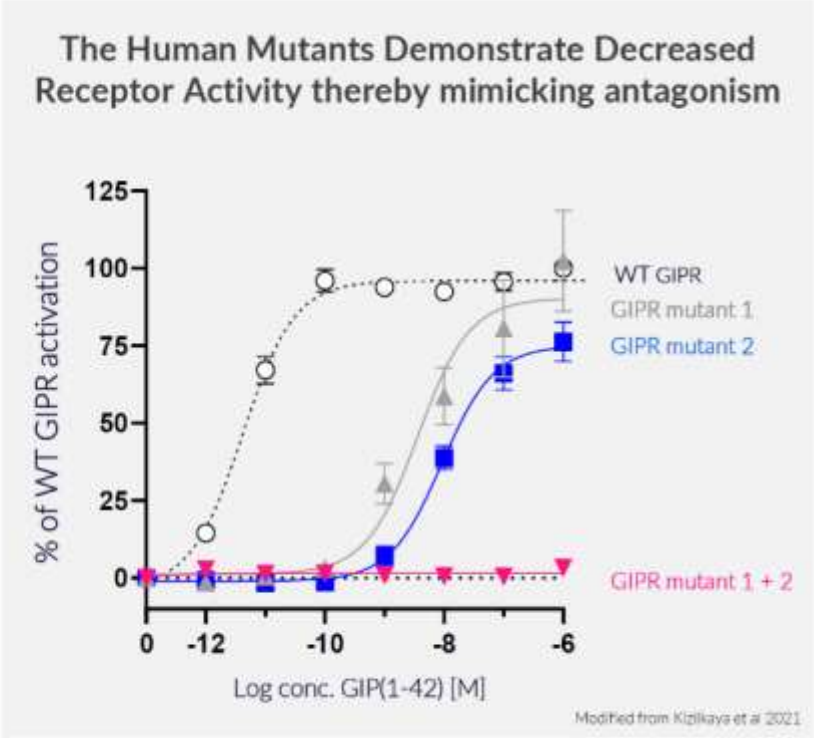
MariTide Motivated by Fact That GIP Receptor Mutations Are Associated With Lower Weight

MariTide: GLP-1r activation + GIPr inhibition.



Rationale



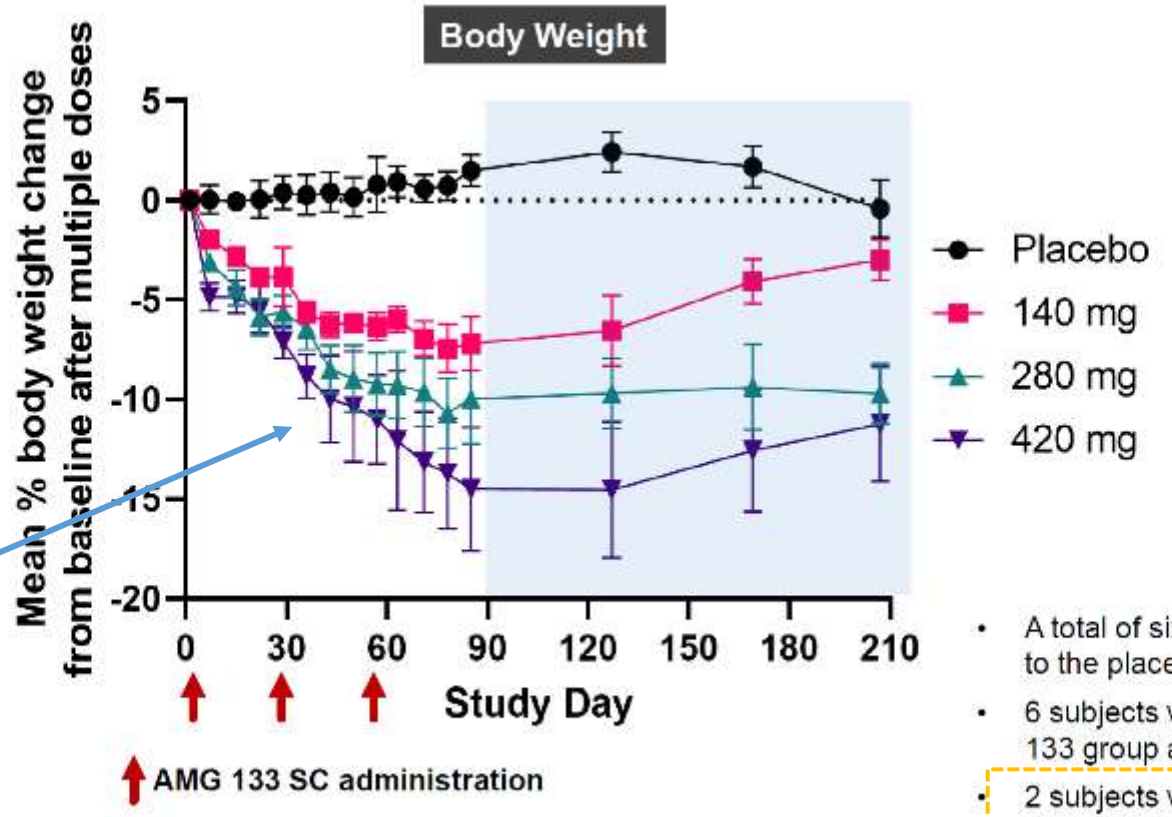


See https://www.nature.com/articles/s41588-017-0011-x, https://www.frontiersin.org/journals/cell-and-developmental-biology/articles/10.3389/fcell.2021.749607/full, https://www.nature.com/articles/s41588-018-0334-2, https://diabetesjournals.org/diabetes/article/70/9/1929/137729/The-Role-of-GIP-Receptor-in-the-CNS-for-the,

The Scale of Weight Loss Seen with MariTide (AMG133) Has Never Been Seen Before with a Pharmacological Agent

The observed weight loss with a GLP1 agonist and GIPr antagonist corresponds to going from 250 pounds to 215 pounds in three months.

The weight loss slope at the 420mg dose is extreme. Patients lost 1% of their body weight *every six* days.



- A total of six subjects were randomized to the placebo group across cohorts
- 6 subjects were randomized to the AMG 133 group at each dose level
- 2 subjects were replaced in the 420 mg dose group

SC = subcutaneous; mg = milligram.

12

Note that two subjects dropped out of the Phase 1b at the high dose. This discontinuation rate is not unusual for the GLP-1 class, however.

Understanding GIP: When Glucose Goes Through the Gut Something Happens: GIPr is Agonized

A landmark study performed in humans was published in 1964 in Lancet.[8]

The study showed that blood insulin levels were about three times greater after humans consumed glucose compared to when it was given intravenously (IV), while blood glucose levels were similar.

Thus, something in the intestine was responsible for 2/3 of the effect; a yet to be identified incretin hormone.

The principal incretin hormone proved to be gastric inhibitory polypeptide (GIP)[9].

Explanation: IV glucose bypasses the gut which avoids agonism of GIP, in turn resulting in less insulin signaling.


insight review articles

Insulin signalling and the regulation of glucose and lipid metabolism

Saltiel and Kahn identified GIP as the main explanation of why insulin production largely requires that glucose pass through the gut.

8 McIntyre N et al. *Lancet* 1964; 2:20-21
9 Saltiel AR and Kahn CR. *Nature* 2001; 414:799-806

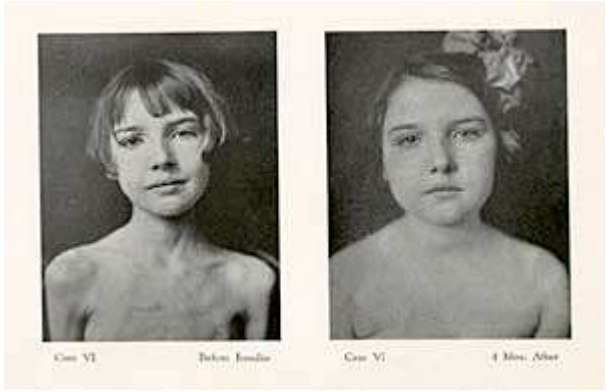
Understanding GIP: Hypoinsulinism Leads to Starvation

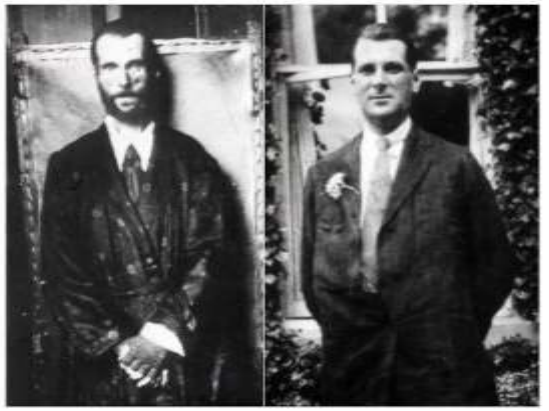
By partial reduction of insulin, a GIP antagonist can induce a state of weight loss. In the extreme, full ablation of insulin in Type 1 diabetes leads to starvation because insulin is required to absorb nutrients into cells.

"Type I diabetes has been described as 'starvation in the midst of plenty.' Despite hyperphagia and high levels of circulating fuels, insulin deficiency prevents effective use of fuels by many tissues, hence 'starving' them of nutrition."[10]

Prior to the invention of insulin, children with Type 1 diabetes starved to death. Below are remarkable photos of persons whose lives happened to overlap with the discovery and availability of insulin from Eli Lilly.

Before and after pictures of persons treated with insulin in the 1920s

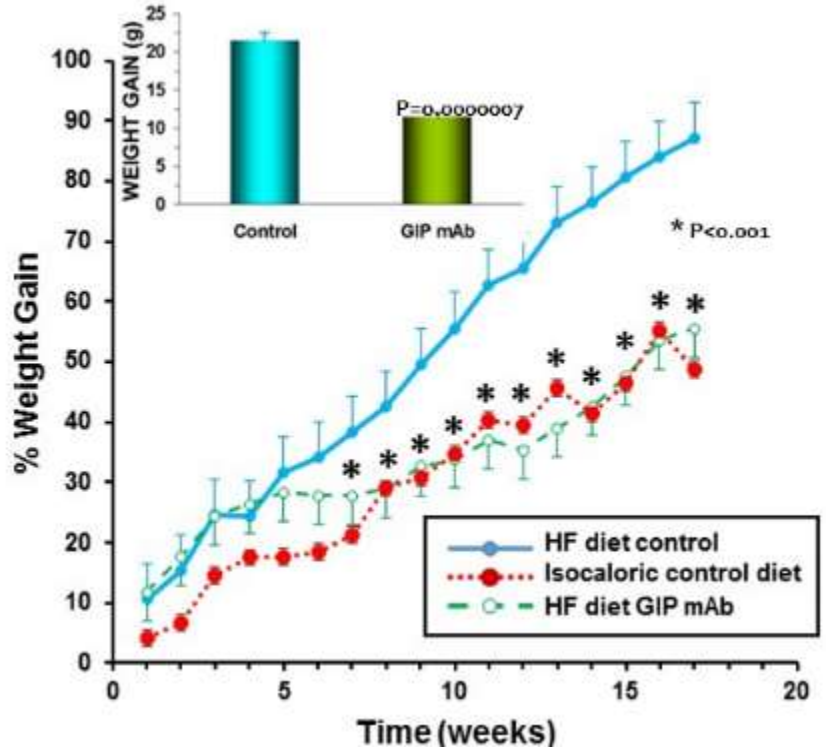




9 *Endocr Rev*, Volume 40, Issue 1, February 2019, Pages 1–16

Boylan and Wolfe Explained Rationale for GIP Antagonism in a 2015 Paper

GIP is the principal incretin responsible for stimulating insulin release. This, in turn, causes circulating glucose to be stored as fat.

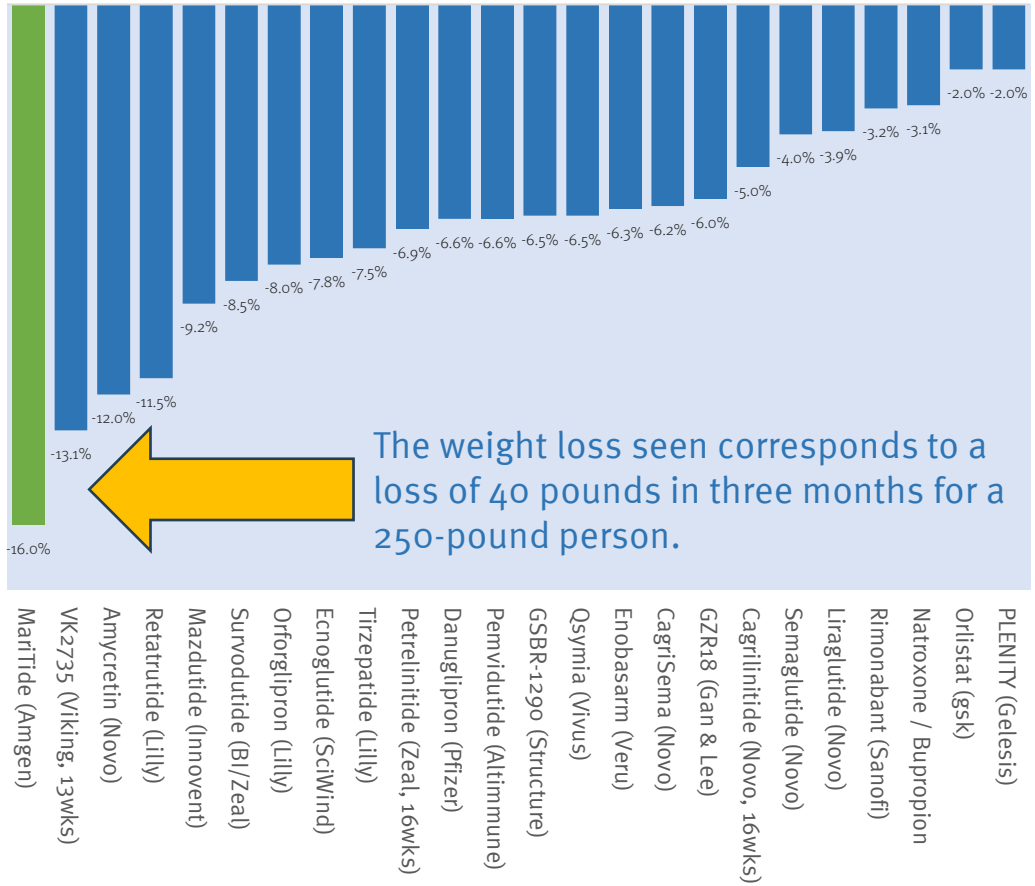


- Mike Wolfe and Mike Boylan conducted a series of pathbreaking experiments at Case Western in which they explored whether GIP blockade might be a good strategy for weight loss.[10]
- This work was independent of Amgen's genetic work but led to very similar insights.
- In this seminal study done in C57BL/6 mice, a **GIP antibody attenuated the insulin response to oral glucose by 2/3** (similar to the 1964 human study in *Lancet*)[11] and eliminated the insulin response to co-administered intraperitoneal glucose.
- The effect of the anti-GIP mAb on weight was dramatic; weight gain *decreased by 46.5%* and was equivalent to the low-fat diet control mice.
- There were *no differences* in the amount of food consumed among the treatment groups.
- An intriguing possibility with GIP blockage is that the nausea and potential muscle loss side effects of GLP-1's could be avoided. You eat the same amount of food but just fail to store it as fat because you are making less insulin.

10. Boylan MO et al. Am J Physiol 2015; 309:E1008-E1018.
11. McIntyre N et al. Lancet 1964; 2:20-21

Amgen's MariTide Has Set a 3-Month Record for Weight Loss

Placebo Adjusted Weight Loss Among Obese Persons by Therapeutic Approach
(12 Weeks, Highest Dose Used)



Source: Stifel analysis.

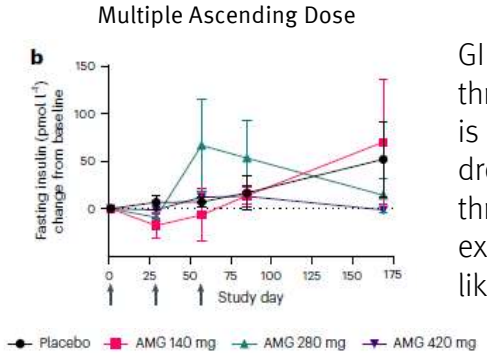
Amgen's Phase 1b weight loss record is sort of like Bob Beamon's famous, as yet unmatched, long-jump world record in the 1968 Olympics. No other agent has ever come close.

Will MariTide Emerge as the Strongest Agent Yet?

There are a number of considerations that deserve attention in handicapping MariTide's prospects based on currently disclosed data. The highest dose of the MAD study saw four of eight participants drop out after tolerability issues. However, Amgen did not do a dose-escalation run-in. Thus, there is a very good chance that observed tolerability in Phase 2 will be much improved. On the other hand, the spectacular weight loss seen in the high dose arm could reflect severe nausea caused by the lack of a run-in. Another factor is that the two highest doses in MAD study were heavily enrolled with females (11/16 or 69%). This would tend to bias the results versus other agents that have gender balanced designs.

Negatives

1 Didn't See Deep Drops in Insulin in Humans



GIPR antagonism can reduce weight through multiple mechanisms. A key MOA is reduction of GIP expression and resulting drop in insulin. This was not seen in two of three doses. On the other hand, the study excluded diabetes which are most the most likely candidates for this pharmacology.

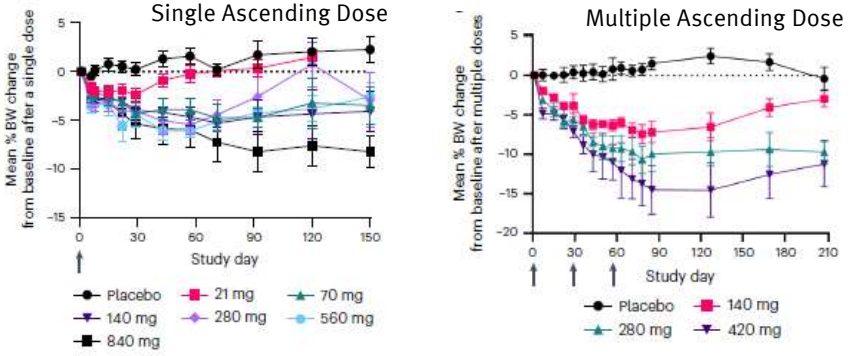
2 Very Small Sample Sizes for MAD Dosing Arms. While Drop in Weight Was Huge Hard to Generalize

Véniant et.al., *Nature Metabolism*, Feb 2024

"The main limitation of this FIH study was the small sample size. Cautious interpretation of PD effects, including metabolic parameters is thus required. Furthermore, the participants had neither diabetes nor high triglyceride and cholesterol levels, which further limits the generalizability of the metabolic parameter findings."

Positives

1 Very little rebound – even with a single dose.



2 Didn't dose escalate – which means that tolerability issues are likely manageable in Phase 2 with a dose run-in.

Véniant et.al., *Nature Metabolism*, Feb 2024

"At the highest MAD dose of 420 mg, four participants withdrew from the study before receiving the second dose after reporting mild GI-related adverse events; therefore, intra-patient dose-escalation-based regimens may offer a future advantage in decreasing the first-dose effect seen with AMG 133."

Source: https://www.nature.com/articles/s42255-023-00966-w

What We Will Learn from Amgen's Phase 2 Readout?

What we can expect to see from Amgen at year end 2024.

ACTIVE, NOT RECRUITING

Dose-ranging Study to Evaluate the Efficacy, Safety, and Tolerability of AMG 133 in Adult Subjects With Overweight or Obesity, With or Without Type 2 Diabetes Mellitus

Study Overview

Brief Summary

The study aims to compare and assess the dose response of 3 selected doses of AMG 133 compared with placebo, on inducing and maintaining weight loss from baseline at Week 52 in participants with overweight or obesity without diabetes mellitus (Cohort A) and in participants with overweight or obesity with Type 2 diabetes mellitus (Cohort B).

Official Title

A Phase 2 Randomized, Placebo-controlled, Double-blind, Dose-ranging Study to Evaluate the Efficacy, Safety, and Tolerability of AMG 133 in Adult Subjects With Overweight or Obesity, With or Without Type 2 Diabetes Mellitus

Conditions

Obesity | Overweight | Type 2 Diabetes Mellitus

Intervention / Treatment

- Biological: AMG 133
- Drug: Placebo

Study Start (Actual)

2023-01-18

Primary Completion (Estimated)

2024-10-04

Study Completion (Estimated)

2026-01-02

Enrollment (Actual)

592

Study Type

Interventional

Phase

Phase 2

We will see performance of MariTide for weight loss all the way through 52 weeks for up to 592 subjects.

The study is being conducted at 82 centers.

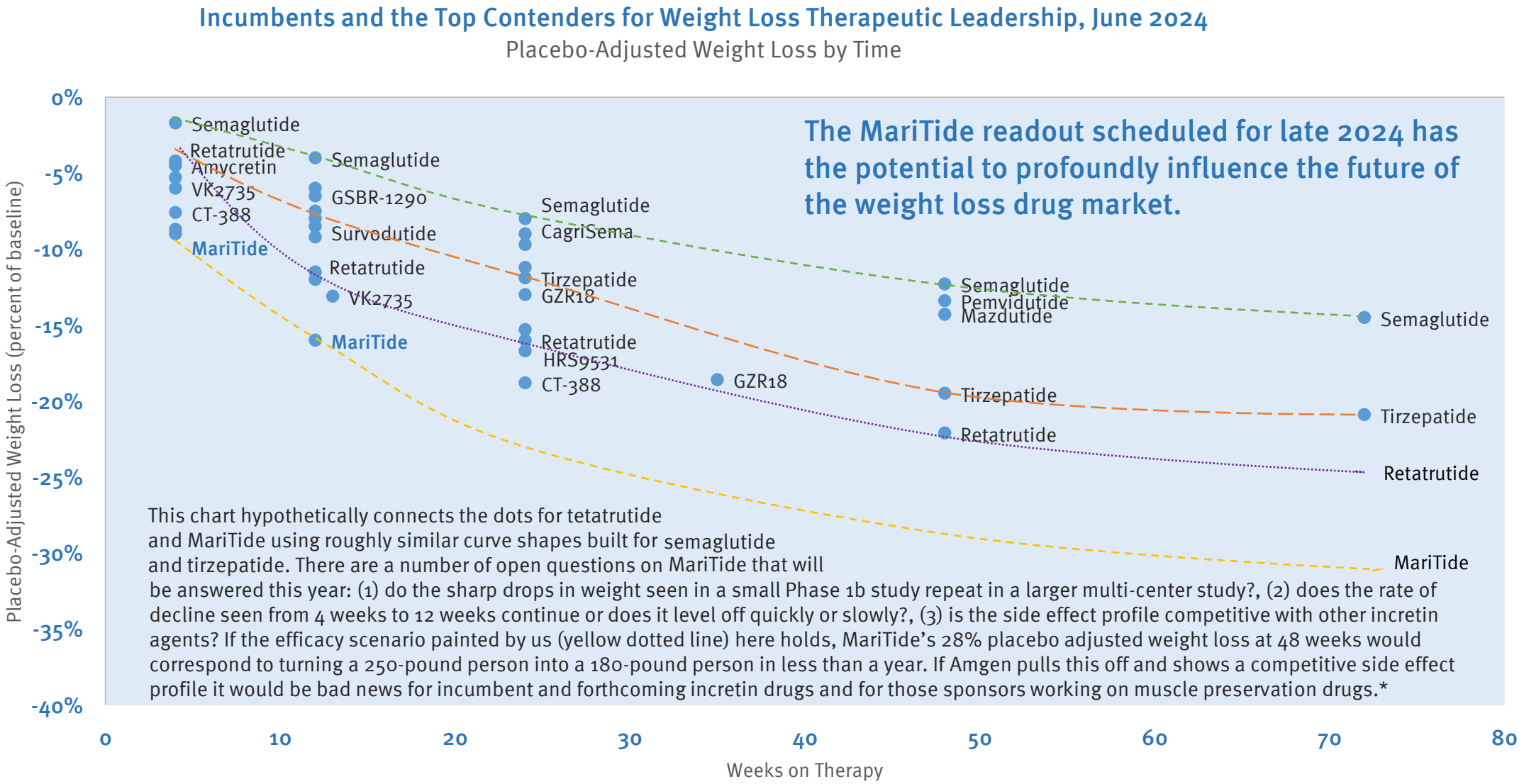
Subjects are divided into placebo and active arms. The active includes diabetes and non-diabetic obese persons.

We will see data on discontinuation rates, side effects and dose response that goes well beyond what has been disclosed thus far. Amgen is also collecting beta cell function measures, insulin resistance measures and body composition.

This may prove to be one of the most important clinical readouts in the history of the pharmaceutical industry.

Source: Clinicaltrials.gov

Why Amgen's MariTide Readout in Late 2024 is so Important

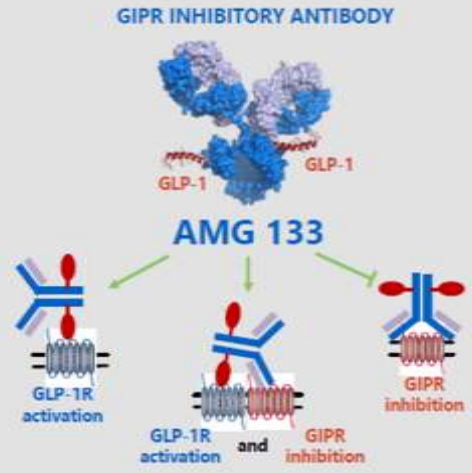


* The weight loss on bariatric surgery at one year is quite similar to what we are modelling here. See, for example: https://www.endocrinepractice.org/article/S1530-891X(20)35977-2/.

Source: Stifel analysis of various company presentations and press releases. Please note that these are not results from head-to-head studies and would likely be different in such a context.

Hypothetical MariTide Timeline

By our estimate, MariTide (AMG133) could be available to be launched into the U.S. market in a little less than four years from now. This assumes, of course, that Amgen is able to generate positive Phase 3 clinical studies.



When launched, MariTide has the potential to offer a major new option for patients including unprecedented weight loss. Key advantages will involve monthly dosing, combined appetite suppression, muscle preservation and slower rebound after treatment cessation. From an Amgen shareholder perspective: (1) monthly dosing implies that Amgen needs to make much less material than its competitors; (2) MariTide can use Amgen's enormous recombinant protein manufacturing capacity in places like Juncos PR, Rhode Island and Ohio and (3) MariTide is a biologic resulting in much better treatment under IRA – interestingly, semaglutide & tirzepatide are not technically biologics (< 40 amino acids). Negatives of the molecule include (1) need to be careful of not inducing hypoinsulinemia in persons who have severely impaired beta-cell function and (2) larger needle size required than with peptide products – would be similar to a Repatha® injection.

May 2024
Interim look at Phase 2 data. Study is fully enrolled.

Q4 2024
Report on topline Phase 2 data including 52-week results

Q2 2025
Phase 2 study open label extension underway.

Enrollment in two Phase 3 studies is well underway.

Q4 2025
Amgen starts additional marketing studies to show long-term health effects.

Phase 1b study in Chinese individuals in HK completes.

Phase 3 study enrollment is completed.

Q4 2026
Phase 3 studies read out.

3-year data is available on OLE patients.

Data on rebound for those who ceased treatment is also available.

Q2 2027
Amgen files a BLA with the FDA, using a PRV to accelerate review.

Q1 2028
Amgen launches MariTide in the United States market.

Q1 2029
MariTide launches in China, Japan and Europe.

Q4 2029
Results of marketing studies on the health effects of MariTide released.

2 Upcoming Retatrutide Phase 3 Data

While Amgen's MariTide has amazing 12-week weight loss data, the molecule still has a lot to prove. Can it replicate the pace of weight loss at 48 weeks with reasonable tolerability and side effects? Time will tell but there is another great option with advanced data.

The best performing molecule to date with 48-week data is Eli Lilly's **retatrutide**. Patients on the drug lost 22% of their body weight on a placebo-adjusted basis.

While not quite the 28% we envision for MariTide, it's a whole lot of weight loss. Are patients going to care that much about the difference?

The key thing we are watching for this molecule is the emergence of Phase 3 Retatrutide data. As shown on the next page, Lilly has at least three Phase 3 studies underway with Retatrutide (TRIUMPH-1, TRIUMPH-2 and TRIUMPH-3). TRIUMPH-1 is slated to report topline results by February 2026. Those data will be very important in the history of the obesity drug sector. Interestingly, Lilly is running a head-to-head study of retatrutide against semaglutide. We think retatrutide could launch in Q1 2027 (less than three years from now) and a full year before MariTide.

There is a very good reason scientists are calling Retatrutide the "Godzilla of weight loss".

By simultaneously targeting three pathways (GIP, GLP, Glucagon), retatrutide aims to provide more effective management of obesity and type 2 diabetes than existing treatment

Source: https://www.prnewswire.com/news-releases/lillys-phase-2-retatrutide-results-published-in-the-new-england-journal-of-medicine-show-the-investigational-molecule-achieved-up-to-17-5-mean-weight-reduction-at-24-weeks-in-adults-with-obesity-and-overweight-301863690.html

Select Trials – Retatrutide

Study	Indication*	Title	Phase	Patients	Primary Outcome**	Primary Completion	Completion
NCT05882045	Obesity	A Study of Retatrutide (LY3437943) in Participants With Obesity and Cardiovascular Disease (TRIUMPH-3)	3	1800	Percent Change from Baseline in Body Weight	Jan 2026	Feb 2026
NCT05931367	Obesity	A Study of Retatrutide (LY3437943) Once Weekly in Participants Who Have Obesity or Overweight and Osteoarthritis of the Knee (TRIUMPH-4)	3	405	Percent Change from Baseline in Body Weight and Change from Baseline in the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) Pain Subscale Score	Feb 2026	Mar 2026
NCT05929066	Obesity	A Study of Retatrutide (LY3437943) in Participants Who Have Obesity or Overweight (TRIUMPH-1)	3	2100	Percent Change From Baseline in Body Weight	Apr 2026	May 2026
NCT05929079	Obesity	A Study of Retatrutide (LY3437943) in Participants With Type 2 Diabetes Mellitus Who Have Obesity or Overweight (TRIUMPH-2)	3	1000	Percent Change from Baseline in Body Weight	May 2026	May 2026
NCT06354660	Type 2 Diabetes	Effect of Retatrutide Compared With Placebo in Adult Participants With Type 2 Diabetes and Inadequate Glycemic Control With Diet and Exercise Alone (TRANSCEND-T2D-1)	3	480	Change from Baseline in Hemoglobin A1c (HbA1c)	Jun 2026	Jul 2026
NCT06297603	Type 2 Diabetes	Effect of Retatrutide Compared With Placebo in Participants With Type 2 Diabetes and Moderate or Severe Renal Impairment, With Inadequate Glycemic Control on Basal Insulin, With or Without Metformin and/or SGLT2 Inhibitor (TRANSCEND-T2D-3)	3	320	Change from Baseline in Hemoglobin A1c (HbA1c)	Sep 2026	Oct 2026
NCT06260722	Type 2 Diabetes	Effect of Retatrutide Compared With Semaglutide in Adult Participants With Type 2 Diabetes and Inadequate Glycemic Control With Metformin With or Without SGLT2 Inhibitor (TRANSCEND-T2D-2)	3	1250	Change from Baseline in Hemoglobin A1c (HbA1c)	Dec 2026	Mar 2027

Source: Eli Lilly Q1 2024 Earnings Presentation, pages 41-42.

3 Small Molecule GLP-1's Important to Watch

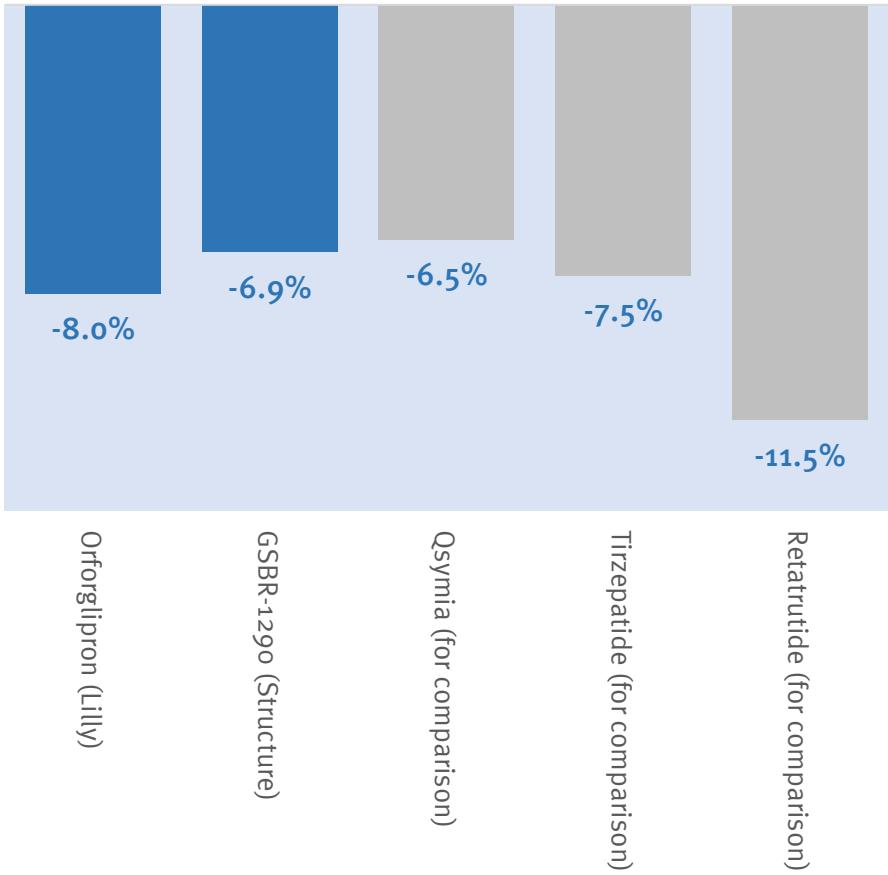
GLP-1 peptide agonists such as Semaglutide have clearly changed the obesity market forever. A once-a-day oral GLP-1 would have some obvious advantages.

First, an oral would be more attractive to some patients. While Wegovy® and Zepbound involve just a weekly pinprick to patients, many would prefer an oral over an injectable.

We are aware of twelve small molecule GLP-1 agonists that are advancing in clinical development. These are from Pfizer, Structure, Lilly, Hengrui/Hercules, Biolexis, Gilead, Mindrank AI, Regor, Roche, SciWind, Terns, Yunovia and AstraZeneca. These small molecules have important advantages over peptidic oral medications such as Rybelsus and Amycretin: (1) no fasting requirement before usage in the morning, (2) much lower cost of manufacture and (3) ease of co-formulation with small molecules from other mechanism classes. On the other hand, oral amycretin data are superior to what has been seen with small molecules.

Weight loss estimates at 12-weeks are available for orforglipron from Lilly and GSBR-1290 from Structure at right. Both Structure and Lilly look good versus tirzepatide but are not competitive against retatrutide.[12] On the other hand, the cost of these oral drugs should be far more attractive for patients.

Placebo Adjusted Weight Loss Among Obese Persons with Small Molecule Orals
(12 Weeks, Highest Dose Used)



12. We do not show data for Pfizer's danuglipron. It's a twice-daily drug that has been paused for reformulation after a high rate of nausea side effects in a Phase 2 study. Further, average weight loss at 12-weeks shown in non-diabetic obese individuals on ClinicialTrials.gov is not competitive (https://clinicaltrials.gov/study/NCT04617275). Further, neither Astrazeneca/Eccogene nor Regor have yet to report out human weight loss data. Also not shown TTP273 from VTV Therapeutics. This agent saw a significant AE burden in a 2017 ADA presentation and has not been developed further since then.

Many Patients Prefer an Oral Obesity Drug Option

Data on patient preferences for oral versus injectable obesity medications can be found in various studies, surveys, and clinical trials. Here are some key points from the available research:

Patient Surveys and Preferences: A study published in the journal *Diabetes, Obesity and Metabolism* (2021) conducted a survey among patients with obesity to assess their preferences for oral versus injectable GLP-1 receptor agonists.[12] The study found that a significant proportion of patients preferred oral medications due to convenience, fear of needles, and ease of use. In a survey of patients with type 2 diabetes (many of whom also struggle with obesity), preferences indicated a strong inclination towards oral medications if they were perceived to be as effective as injectable options.

Clinical Trials and Real-World Data: Clinical trials have been conducted to compare the efficacy and patient satisfaction between oral and injectable GLP-1 receptor agonists. For instance, the PIONEER 6 trial evaluated the safety and efficacy of oral semaglutide and included patient-reported outcomes on satisfaction and preference. Many participants reported higher satisfaction with the oral formulation.[13] Real-world data from healthcare providers also suggest that patient adherence to obesity treatment regimens is higher with oral medications compared to injectables, primarily due to the ease of administration.

Efficacy and Safety Perception: While many patients express a preference for oral medications, some are willing to use injectables if they perceive them to be more effective. A study in *Obesity Reviews* (2018) highlighted that patients' willingness to accept injectable treatments increased when they were educated about the superior efficacy of injectables.

12. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7839441/
13. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7887531/

Not all orals are created equal

Patients prefer orals to injectables. But the pinprick from today's pen presentations of Wegovy® and Zepbound® bother very few patients anymore.

The critical benefit of orals is on the manufacturing side. We estimate that Lilly and Novo are having to spend $20 to $40 billion each to get the manufacturing capacity built to support the rollout of current and future peptide incretin therapies.

Small molecule therapies involve a miniscule fraction of this spend on the manufacturing side.

The simpler the small molecule synthesis, the better. The higher the bioavailability of the small molecule therapy the better.

There are certain "oral" incretin drugs that involve delivery of peptides using permeation enhancers. Think Rybelsus® or oral amycretin.

While clinically effective these drugs can make the manufacturing cost problem worse because of poor bioavailability. Rybelsus, for example, has less than one percent bioavailability (https://pubmed.ncbi.nlm.nih.gov/33969456/).

Leading Small Molecule Oral GLP-1 Agonists in Development

Danuglipron (PF-06882961)

Description: Danuglipron is an oral GLP-1 receptor agonist being developed for obesity and type 2 diabetes.

Clinical Status: It is in late-stage development, with over 1,400 participants enrolled in its Phase 2b study. While the drug has shown substantial weight loss it is being reformulated given AE's and twice-daily dosing.

Adverse Events: Common side effects include nausea, vomiting, and diarrhea, which are consistent with the GLP-1 receptor agonist class. AE rates have been high.

GSBR-1290

Description: GSBR-1290 is an oral GLP-1 receptor agonist targeting obesity and type 2 diabetes.

Clinical Status: Structure has shown positive results in Phase 1 trials, demonstrating dose-dependent efficacy and a favorable safety profile. Phase 2a studies are ongoing, with Phase 2b studies planned soon.

Adverse Events: Adverse event rates were on the high side and were GI related. However, Structure has not yet optimized its dose escalation and should be able to reduce these AEs.

Orforglipron

Description: Orforglipron is an orally administered GLP-1 receptor agonist being evaluated for weight management and glycemic control.

Clinical Status: In a recent Phase 2 study, orforglipron demonstrated substantial weight loss ranging from 8.6% to 12.6% over 26 weeks, compared to a 2.0% weight loss in the placebo group.

Adverse Events: Similar to other GLP-1 receptor agonists, mainly during dose escalation. Favorable discontinuation rates versus other oral agents.

AZD5004 / ECC5004

Description: AZD5004 is an orally administered GLP-1 receptor agonist being evaluated for weight management and glycemic control.

Clinical Status: In a recent Phase 1 study, AZD5004 showed good weight loss and tolerability.

Adverse Events: No data available yet.

Lilly Delivering the Goods on Orfo

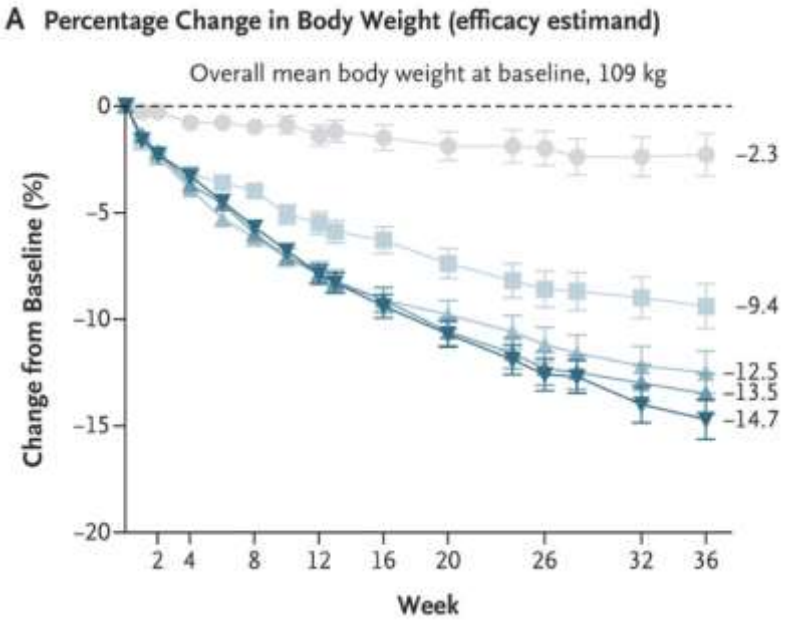
Daily Oral GLP-1 Receptor Agonist Orforglipron for Adults with Obesity

Sean Wharton, M.D., Thomas Blevins, M.D., Lisa Connery, M.D., Julio Rosenstock, M.D., Sohini Raha, Ph.D., Rong Liu, Ph.D., Xiaosu Ma, Ph.D., Kieren J. Mather, M.D., Axel Haupt, M.D., Deborah Robins, M.S., Edward Pratt, M.D., Christof Kazda, M.D., et al., for the GZGI Investigators*

***New England Journal of Medicine*, June 23, 2023**

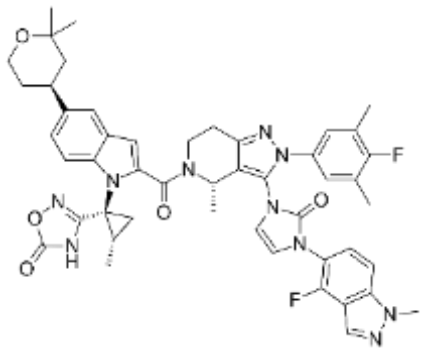
In this phase 2, randomized, double-blind trial, we enrolled adults with obesity, or with overweight plus at least one weight-related coexisting condition, and without diabetes. Participants were randomly assigned to receive orforglipron at one of four doses (12, 24, 36, or 45 mg) or placebo once daily for 36 weeks. The percentage change from baseline in body weight was assessed at week 26 (primary end point) and at week 36 (secondary end point).

A total of 272 participants underwent randomization. At baseline, the mean body weight was 108.7 kg, and the mean body-mass index (the weight in kilograms divided by the square of the height in meters) was 37.9. At week 26, the mean change from baseline in body weight ranged from −8.6% to −12.6% across the orforglipron dose cohorts and was −2.0% in the placebo group. At week 36, the mean change ranged from −9.4% to −14.7% with orforglipron and was −2.3% with placebo. A weight reduction of at least 10% by week 36 occurred in 46 to 75% of the participants who received orforglipron, as compared with 9% who received placebo. The use of orforglipron led to improvement in all prespecified weight-related and cardiometabolic measures. The most common adverse events reported with orforglipron were gastrointestinal events, which were mild to moderate, occurred primarily during dose escalation, and led to discontinuation of orforglipron in 10 to 17% of participants across dose cohorts. The safety profile of orforglipron was consistent with that of the GLP-1 receptor agonist class.

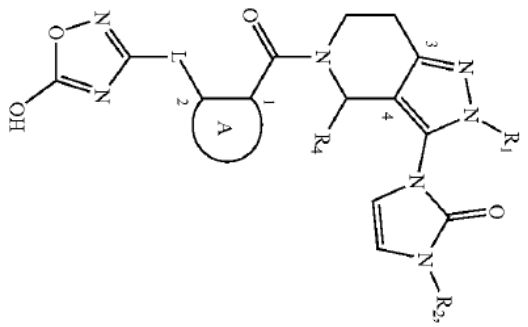


Source: https://www.nejm.org/doi/full/10.1056/NEJMoa2302392

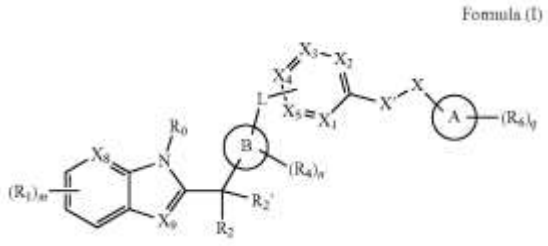
Chemical Structures of Selected Small Molecule GLP-1 Agonists



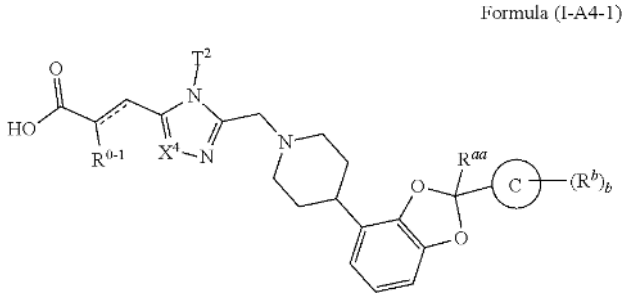
Lilly/Chugai - Orforglipron



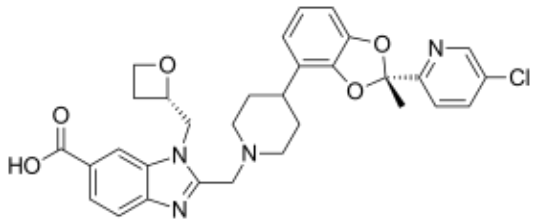
Eccogene/AZ - AZD-5004



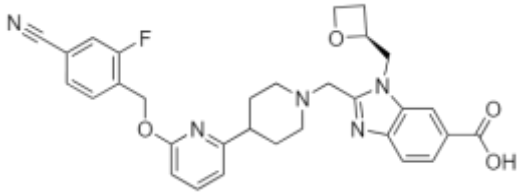
Mindrank - MDR-001



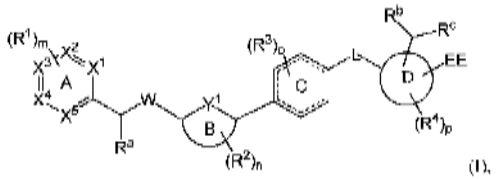
Structure - GSBR1290



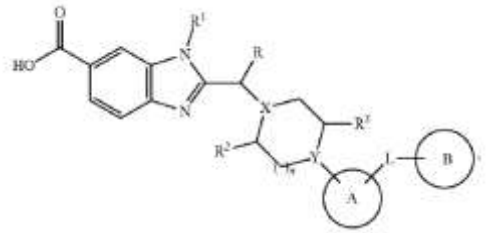
Pfizer - Lotiglipron



Pfizer - Danuglipron



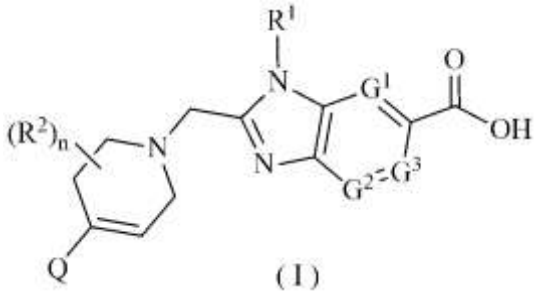
Regor - RGT-075



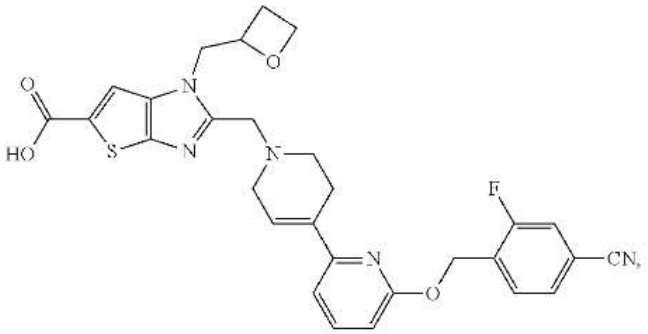
Terns - RGT-075

Sources: Orforglipron: https://patents.google.com/patent/US20230382912A1; GSBR1290: https://patents.google.com/patent/US11897851B2; RGT-075: https://patents.google.com/patent/US20220024901A1; Lotiglipron: https://en.wikipedia.org/wiki/Lotiglipron; Danuglipron: https://en.wikipedia.org/wiki/Danuglipron; Eccogene: https://patents.google.com/patent/US11584751B1 (first compound referenced); Mindrank AI (https://patents.google.com/patent/US20240067630A1) and Terns (https://patents.google.com/patent/US20230150998A1) first compound referenced.

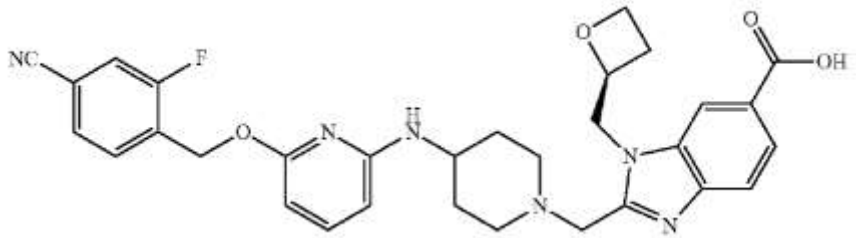
Chemical Structures of Small Molecule GLP-1 Agonists (cont.)



Hengrui – HRS7535



SciWind – XW014 (example)



Yunovia / Ildong – ID110521156 (example)

Pfizer's lotiglipron was terminated due to liver transaminase elevations. The lotiglipron scaffold has been taken forward, more or less, by Danuglipron, Hengrui/Hercules, Regor, SciWind, Terns and Yunovia/Ildong.

In contrast, the chemotypes used by Lilly/Chugai, Eccogene/AZ, Mindrank AI and Structure are differentiated and are less likely to incur the type of liver issue seen with lotiglipron.

Sources: Hercules/Hengrui: https://patents.google.com/patent/JP2023520003A/; Yunovia (https://patents.google.com/patent/US20230002348A1).

Orforglipron in Nine Phase 3 Studies with 2026 Registration Possible

Study	Indication*	Title	Phase	Patients	Primary Outcome**	Primary Completion	Completion
NCT05971940	Type 2 Diabetes	A Study of Orforglipron (LY3502970) in Adult Participants With Type 2 Diabetes and Inadequate Glycemic Control With Diet and Exercise (ACHIEVE-1)	3	520	Change from Baseline in Hemoglobin A1c (HbA1c)	Apr 2025	Apr 2025
NCT05803421	Type 2 Diabetes	A Study of Daily Oral Orforglipron (LY3502970) Compared With Insulin Glargine in Participants With Type 2 Diabetes and Obesity or Overweight at Increased Cardiovascular Risk (ACHIEVE-4)	3	2620	Time to First Occurrence of Any Major Adverse Cardiovascular Event (MACE-4) [Myocardial Infarction (MI), Stroke, Hospitalization for Unstable Angina, or Cardiovascular (CV) Death]	Apr 2025	Dec 2025
NCT06109311	Type 2 Diabetes	A Study of Orforglipron (LY3502970) in Participants With Type 2 Diabetes and Inadequate Glycemic Control With Insulin Glargine, With or Without Metformin and/or SGLT-2 Inhibitor (ACHIEVE-5)	3	520	Change from Baseline in Hemoglobin A1c (HbA1c) Compared to Placebo	Jun 2025	Jun 2025
NCT06010004	Type 2 Diabetes	A Long-term Safety Study of Orforglipron (LY3502970) in Participants With Type 2 Diabetes (ACHIEVE-J)	3	399	Number of Participants with Treatment Emergent Adverse Events (TEAEs)	Jun 2025	Jun 2025
NCT06045221	Type 2 Diabetes	A Study of Orforglipron (LY3502970) Compared With Semaglutide in Participants With Type 2 Diabetes Inadequately Controlled With Metformin (ACHIEVE-3)	3	1576	Change from Baseline in Hemoglobin A1c (HbA1c)	Jul 2025	Jul 2025
NCT06192108	Type 2 Diabetes	A Study of Orforglipron (LY3502970) Compared With Dapagliflozin in Adult Participants With Type 2 Diabetes and Inadequate Glycemic Control With Metformin (ACHIEVE-2)	3	888	Change from Baseline in Hemoglobin A1c (HbA1c)	Oct 2025	Oct 2025
NCT05872620	Obesity	A Study of Orforglipron in Adult Participants With Obesity or Overweight and Type 2 Diabetes (ATTAIN-2)	3	1500	Mean Percent Change from Baseline in Body Weight	Jun 2025	Jun 2025
NCT05931380	Obesity	A Study of Once-Daily Oral Orforglipron (LY3502970) in Japanese Adult Participants With Obesity Disease (ATTAIN-J)	3	236	Mean Percent Change in Body Weight	Jun 2025	Jul 2025
NCT05869903	Obesity	A Study of Orforglipron (LY3502970) in Adult Participants With Obesity or Overweight With Weight-Related Comorbidities (ATTAIN-1)	3	3000	Mean Percent Change from Baseline in Body Weight	Sep 2025	Sep 2027

Source: Eli Lilly Q1 2024 Earnings Presentation, pages 37.38.

Other Complementary Oral Obesity Drug Classes in Development

In the same sense that we are seeing incretin protein companies developing duals and triple combos, it should be possible to combine multiple active agents to create a particularly effective oral anti-obesity medication. For example, both Vivus' Qsymia® and Currax's Contrave® combine known active agents.

CB1 Inverse Agonists

Novo Nordisk showed impressive Phase 1 obesity data with a CB1 inverse agonist at ADA. Novo is now indicating that it has modeled the weight loss achieved in Phase 1 and expects to see 15%+ weight loss with single agent Monlunabant at a mature time point.

With Phase 2 results expected in the second half of 2024 the peripherally CB1 class is indeed an exciting one.

Importantly, the CB1 class is orthogonal in MOA to GLP-1 agonism suggesting that one could combine the two.

Companies developing oral CB1's that are near the clinic include Corbus Discovery. BioNanoSim, Tetra and Agentix. Both Skye and Amgen are developing biologics.

We are watching developments in the peripheral CB1 inverse agonist space with high interest.

Apelin Agonists

Apelin agonists control weight by interacting with the apelin receptor (APJ), which is involved in various physiological processes, including the regulation of energy metabolism, appetite, and insulin sensitivity. Apelin can increase energy expenditure by enhancing the activity of brown adipose tissue (BAT), which is responsible for thermogenesis (heat production). This process burns calories and helps in reducing body fat. Further, Apelin can reduce appetite and promote the breakdown of fats while reducing the synthesis of new fats. This helps in lowering fat accumulation in the body while not impacting muscle. BioAge's Azelaprag, an apelin agonist, prevented muscle atrophy and promoted muscle protein synthesis in older adults under bed rest in a Phase 1 study. Excitement was high regarding this "exercise in a pill" molecule at ADA this year. Also promising is Structure's apelin agonist.

Mitochondrial Uncouplers

Small molecule mitochondrial protonophore uncouplers result in increased nutrient oxidation to produce a given amount of ATP. The mitochondrial uncoupler 2,4-dinitrophenol (DNP) generates dramatic and reliable weight-loss effects in humans without changes in food intake but is not considered safe.

This MOA is also orthogonal to GLP-1s, Apelins and CB1s.

Rivus is in Phase 2 studies for obesity with HU6, a mitochondrial uncoupler. Initial data are promising but need to be confirmed.

OrsoBio has just entered the clinic in this area with TLC-6740. Recent data from TLC-6740 presented at ADA were promising showing some effect on weight with a lack of show-stopping adverse events.

4 Lilly's SURMOUNT-MMO Data for Tirzepatide

A Study of Tirzepatide (LY3298176) on the Reduction on Morbidity and Mortality in Adults With Obesity (SURMOUNT-MMO)

Brief Summary

This study will investigate the effect of tirzepatide on the reduction of morbidity and mortality in adults living with obesity and provide additional evidence for the potential clinical benefits of tirzepatide in this population.

Official Title

A Phase 3, Randomized, Double-blind, Placebo-Controlled Study to Investigate the Effect of Tirzepatide on the Reduction of Morbidity and Mortality in Adults With Obesity

Conditions

Obesity | Overweight

Intervention / Treatment

- Drug: Tirzepatide
- Drug: Placebo

Other Study ID Numbers

Study Start (Actual)

2022-10-11

Primary Completion (Estimated)

2027-10-07

Study Completion (Estimated)

2027-10-07

Enrollment (Actual)

15374

Study Type

Interventional

Phase

Phase 3

Novo Nordisk's SELECT study followed over 17,600 people from 41 countries between 2018 and 2021 to see if semaglutide reduced the risk of heart attack, or heart-related death in the obese and overweight.

The SELECT study showed a 15% reduction in the risk of death from cardiac cause and a 20% reduction of risk of death from any cause.

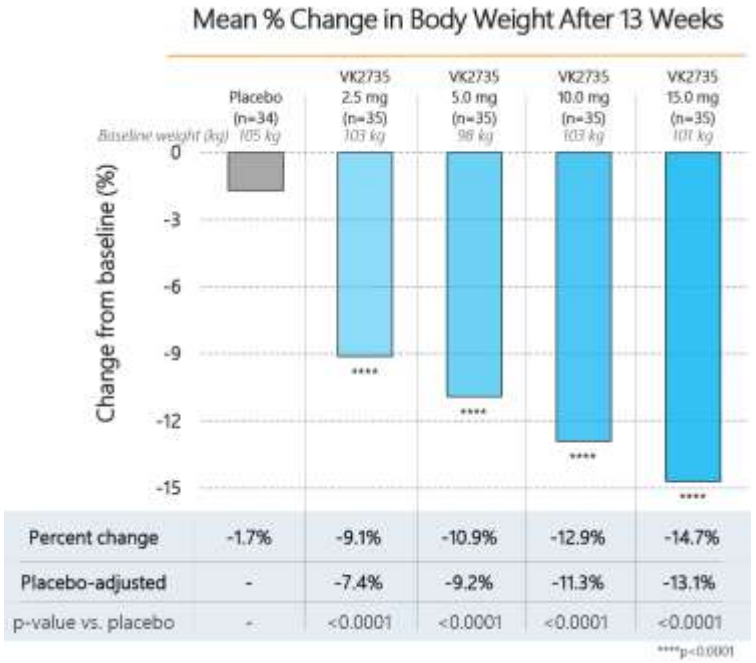
As seen at left, Lilly has fully enrolled the SURMOUNT-MMO study with 15,374 subjects.

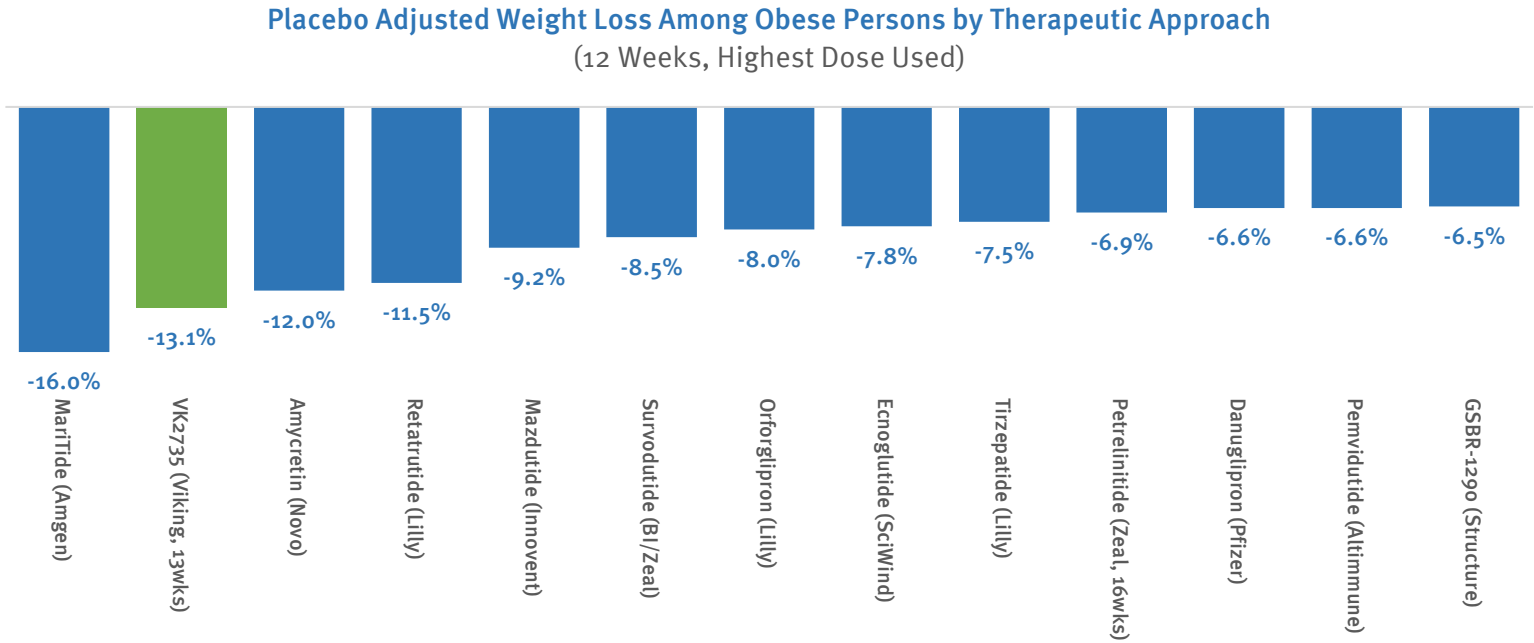
Because tirzepatide leads to deeper weight loss than Semaglutide the results of this study should be stunning in illustrating benefits from weight loss across a number of diseases.

These data will help to impact reimbursement for tirzepatide and future weight loss agents to come.

Source: https://clinicaltrials.gov/study/NCT05556512

5 Viking's VK2735 Long-Term Potential





Viking's VK2735 is a dual SubQ GLP-1 / GIP agonist that has recently reported Phase 2a data. These data (shown at above left) indicate that patients on VK2735 were able to drop 13.1% of their body weight at just 12 weeks on the drug. These result beat semaglutide, tirzepatide and retatrutide. The only agent to do better, thus far, has been Amgen's MariTide (see chart at above right). Study discontinuations on the highest dose of VK2735 were barely higher than what was seen on placebo, making this an attractive all-around candidate for patients. Study discontinuations with MariTide were substantially higher. Viking is now talking to FDA about whether to do a Phase 2b study or, instead, go straight to Phase 3. A key point is that the company has not yet found a maximal tolerated dose and has not gone beyond 13 weeks dosing in its previous study. **Extraordinarily, there is still room to take dose up which implies that VK2735 might be able to give MariTide a run for its money as the king of weight loss.** The company has nearly $1bn in cash on hand to fund these. Viking should be in a position to register VK2735 for FDA approval some time in 2028 or 2029.

Source of chart on left: Viking corporate presentation, June 2024. Chart at right is from Stifel analysis.

6 Novo's Phase 2 Monlunabant: Topline Data in Late 2024

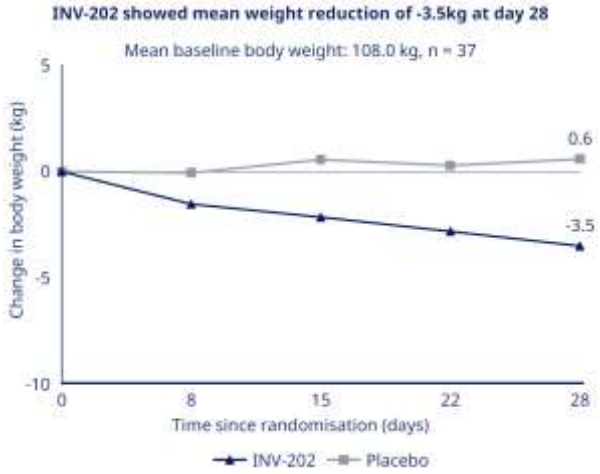
Martin Lange, Novo Nordisk
Q1 2024 Investor Call, May 2024

"...we're quite excited about Monlunabant and the potential because we've seen potential for substantial weight loss with a scalable oral, and that is of course very exciting. However, we have to rule out potential safety issues. The ongoing phase 2 trial will give us a good readout on the efficacy, and it will also give us a reasonable readout of the safety profile of Monlunabant.

However, to fully de-risk this, we intend to investigate this, as we already announced, in a somewhat larger study to secure that obviously our efficacy, and also our safety assessment of this is right. So, you'll get a good first readout from the ongoing phase 2 trial, but you'll see even more for -- from the next."

Martin Lange, Novo Nordisk
Capital Markets Day, Mar 2024

"Right now, we are currently investigating Monlunabant in a typical fashion. These are four-week data. We can always disclose how convincing a placebo-controlled trial is focused on weight loss. You have to consider this is out to 28 days. **When we put that into our model, we expect around 15% weight loss. And that is in a tablet form.** And, if we can rule out neuropsychiatric disorders it also appears to be very safe and tolerable. Really, really big upside."



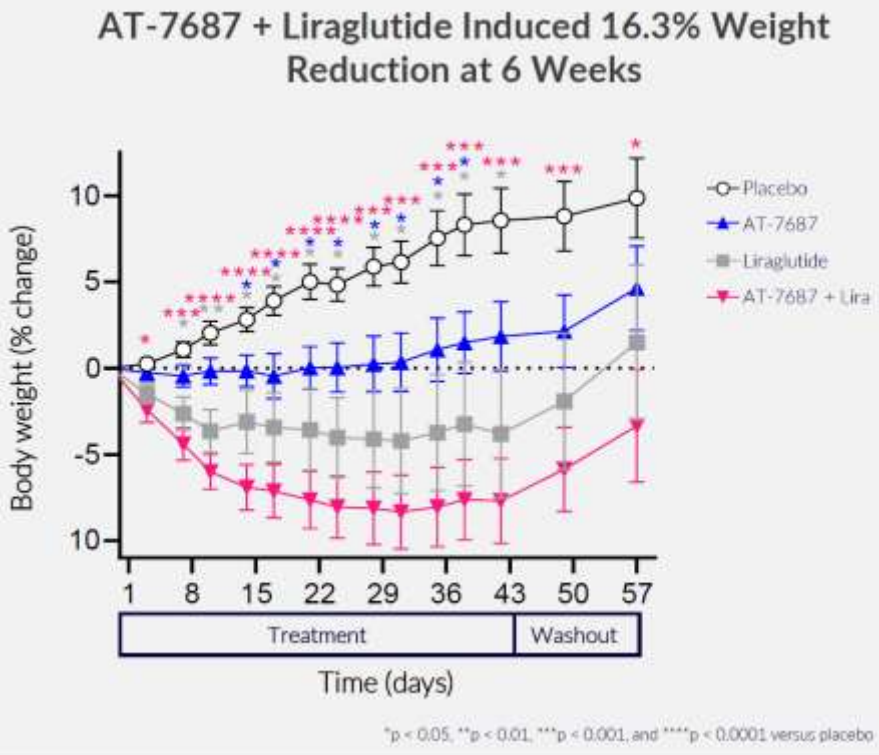
Martin Lange, Executive Vice President, Head of Development, Novo Nordisk

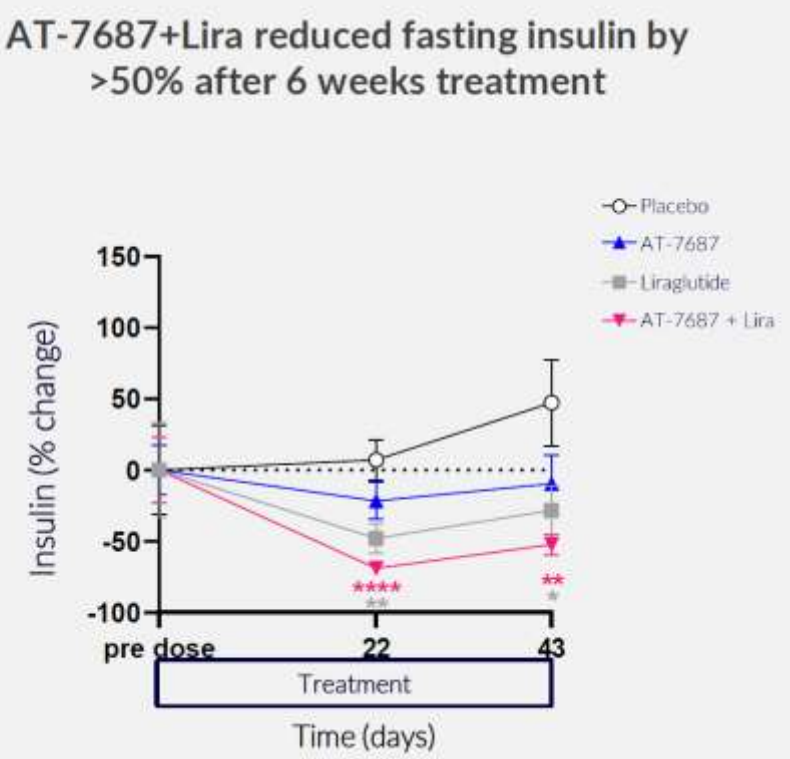
Source: Q1 Investor call transcript and Capital Markets Day video and slides (https://www.novonordisk.com/investors/capital-markets-day-2024.html).

7 Antag's GIP Blocker: Potential Alternative to GLP-1's

Like MariTide, Antag's AT-7687 is a potent peptide GIP receptor antagonist. However, unlike MariTide, Antag's molecule does not agonize GLP-1. The result is that a patient can choose whether to take a GLP-1 agonist alone or to instead go with GIP receptor antagonist alone or to combine with another incretin agonist (e.g., amylin). This would allow patients to avoid the nausea inducing effect of GLP-1's if they prefer. Given that 30% of GLP-1 users terminate use due to tolerability, the market for a monotherapy GIP agonist could be very large. Antag's upcoming Phase 1 data will be definitive for this emerging drug class.

Studies in non-human primates put on fatty diets show that Antag's GIP antagonist lowers insulin and results in much less weight gain:

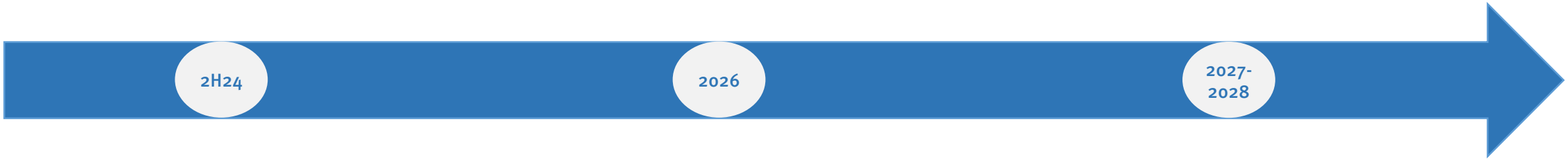




Charts are from Antag.

Antag to Have First GIP Blocker Monotherapy Data in 2026

Phase 1 Studies to Begin Within Six Months	Phase 1b PoC Data in 2026	Phase 2 Data in 2027/28
✓ AT-7687 has completed GLP tox studies ✓ IND submission for AT-7687 in obesity is planned for 2H 2024 ✓ First-patient-first-visit for Phase 1a in obesity expected 1H25	✓ Phase 1 studies designed to enable early proof-of-concepts in obesity ✓ Phase 1a/1b will provide initial safety, tolerability, and pharmacokinetics data ✓ Both trials are designed as double-blind, randomized, placebo-controlled ✓ Obesity trial plans to enroll 25 patients in each arm ✓ Phase 1b expected to begin in 2H 2025, with data in 2026	✓ Phase 2 studies preliminarily expected to begin in late 2026 ✓ Phases 2 study in obesity expected to enroll ~300 patients ✓ Both Phase 2 studies will be designed to set up pivotal Phase 3 trials in ~2028



Other Monotherapy GIP Molecules in Development (all pre-clinical):

Helicore Biopharma

Incregen Therapeutics

novo nordisk

ORION biotechnology

STRUCTURE THERAPEUTICS

TERNS PHARMACEUTICALS

GIP Levels are an Independent Mortality Risk Factor

Diabetologia (2020) 63:1043–1054
https://doi.org/10.1007/s00125-020-05093-9

ARTICLE

Glucose-dependent insulinotropic peptide and risk of cardiovascular events and mortality: a prospective study

Amra Jujić[1,2] · Naeimeh Atabaki-Pasdar[3] · Peter M. Nilsson[3] · Peter Almgren[3,4] · Liisa Hakaste[5,6,7,8] · Tiinamaija Tuomi[5,6,7,8] · Lisa M. Berglund[3,4] · Paul W. Franks[3,9,10] · Jens J. Holst[11,12] · Rashmi B. Prasad[3,4] · Signe S. Torekov[11,12] · Susana Ravassa[13,14,15] · Javier Diez[13,14,15,16,17] · Margaretha Persson[3] · Olle Melander[3] · Maria F. Gomez[3,4] · Leif Groop[3,4,7] · Emma Ahlqvist[3,4] · Martin Magnusson[1,2,18]

Received: 24 July 2019 / Accepted: 18 December 2019 / Published online: 23 January 2020

In meta-analyses, higher fasting levels of GIP were associated with risk of higher total mortality (HR = 1.22; p = 4.5 × 10−5) and death from CVD (HR1.30; p = 0.001). In accordance, 2SMR analysis revealed that increasing GIP concentrations were associated with CAD and myocardial infarction, ar an additional reverse 2SMR revealed no significant effect of CAD on GIP levels, thus confirming a possible effect solely of GIP on CAD.

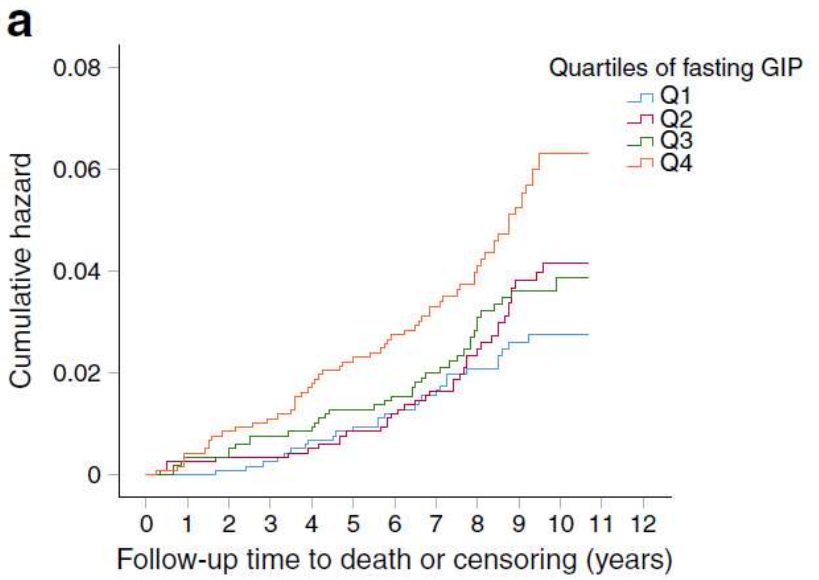


Fig. 1 Total mortality risk in quartiles of fasting GIP. (**a**) Cumulative hazard for total mortality over a mean follow-up of 8.8 years for fasting GIP quartiles in PPP-Botnia ($p = 0.001$). (**b**) Cumulative hazard for total

Source: https://link.springer.com/article/10.1007/s00125-020-05093-9

Evidence Indicates that Both GIP Agonism and Antagonism Can Work

Review

MOLECULAR METABOLISM

Targeting the GIPR for obesity: To agonize or antagonize? Potential mechanisms

Jonathan E. Campbell [1,2,3,*]

ABSTRACT

Background: Glucose-dependent insulinotropic peptide (GIP) is one of two incretin hormones that communicate nutrient intake with systemic metabolism. Although GIP was the first incretin hormone to be discovered, the understanding of GIP's biology was quickly outpaced by research focusing on the other incretin hormone, glucagon-like peptide 1 (GLP-1). Early work on GIP produced the theory that GIP is obesogenic, limiting interest in developing GIPR agonists to treat type 2 diabetes. A resurgence of GIP research has occurred in the last five years, reinvigorating interest in this peptide. Two independent approaches have emerged for treating obesity, one promoting GIPR agonism and the other antagonism. In this report, evidence supporting both cases is discussed and hypotheses are presented to reconcile this apparent paradox.

Scope of the review: This review presents evidence to support targeting GIPR to reduce obesity. Most of the focus is on the effect of singly targeting the GIPR using both a gain- and loss-of-function approach, with additional sections that discuss co-targeting of the GIPR and GLP-1R.

Major conclusions: There is substantial evidence to support that GIPR agonism and antagonism can positively impact body weight. The long-standing theory that GIP drives weight gain is exclusively derived from loss-of-function studies, with no evidence to support that GIPR agonisms increases adiposity or body weight. There is insufficient evidence to reconcile the paradoxical observations that both GIPR agonism and antagonism can reduce body weight; however, two independent hypotheses centered on GIPR antagonism are presented based on new data in an effort to address this question. The first discusses the compensatory relationship between incretin receptors and how antagonism of the GIPR may enhance GLP-1R activity. The second discusses how chronic GIPR agonism may produce desensitization and ultimately loss of GIPR activity that mimics antagonism. Overall, it is clear that a deeper understanding of GIP biology is required to understand how modulating this system impacts metabolic homeostasis.

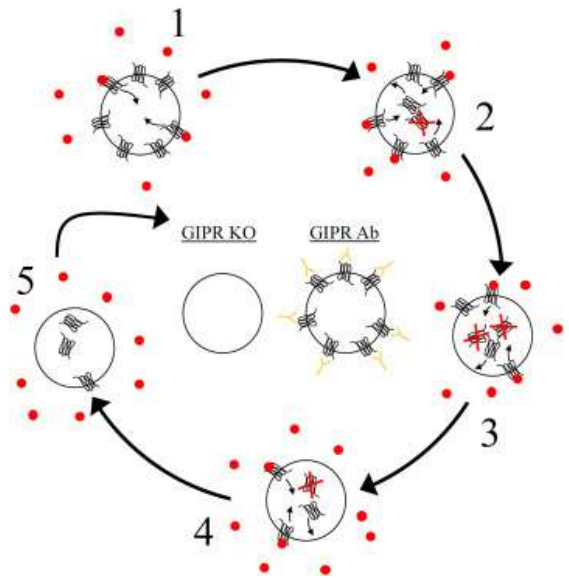


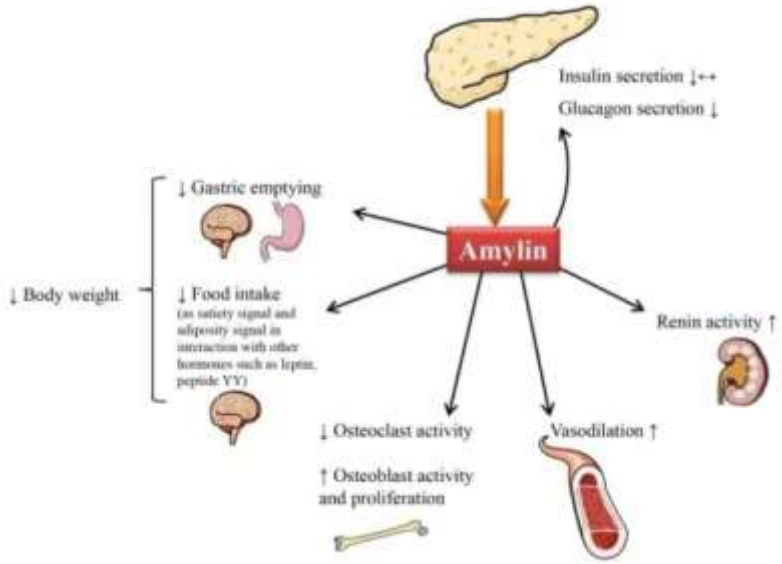
Figure 2. Chronic Agonism Equals Antagonism: A Hypothesis. 1) Agonism of the GIPR leads to internalization of the number of receptors that is proportional to the concentrations of agonists. 2) Some receptors will recycle back to the membrane, while others will degrade. 3–5) Chronic agonism eventually decreases the number of receptors present on the membrane to effectively resemble loss of function caused by either Gipr knockout or GIPR antagonism (GIPR Ab).

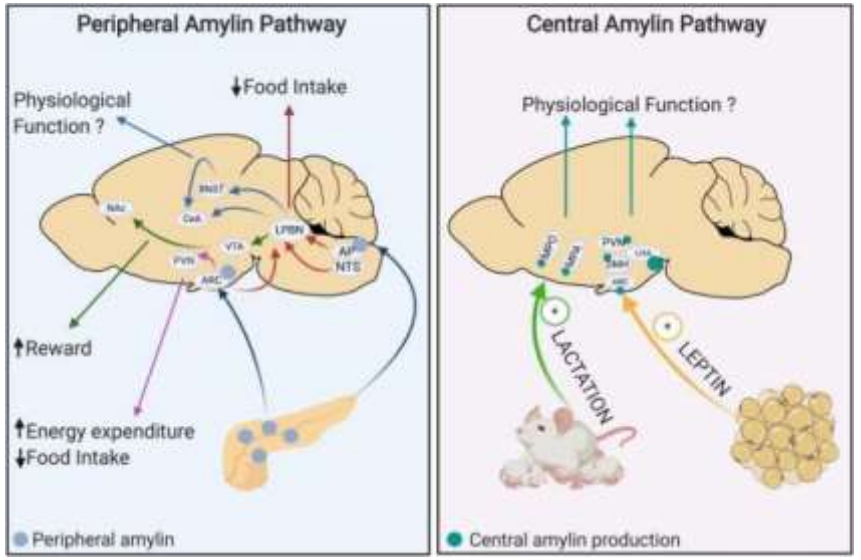
Source: https://www.sciencedirect.com/science/article/pii/S2212877820302131

8 Future Results from Novo's CagriSema and Amylin Analogues Will be Key Drivers of Direction of Obesity Drug Landscape

Amylin, co-secreted with insulin from pancreatic beta cells, exerts its satiating effects by acting on both the homeostatic and hedonic regions of the brain. Semaglutide, a GLP-1 receptor agonist, reduces appetite by targeting GLP-1 receptors in the hypothalamus, enhancing insulin production, decreasing glucagon secretion, and delaying gastric emptying. The distinct but complementary mechanisms of amylin analogs and GLP-1 receptor agonists create an additive effect on appetite suppression. Considering the diverse and intricate nature of obesity's pathogenesis, combination therapy targeting multiple pathophysiological pathways is a rational approach to enhancing weight loss outcomes through pharmacotherapy. Clinical trials have shown promising weight loss results with cagrilintide alone and in combination with semaglutide, supporting the further development of this therapy for sustained weight management.

Amylin functions as an appetite suppressant by inhibiting gastrointestinal motility and delaying gastric emptying post-meals, leading to reduced appetite. The metabolic regulatory effects of amylin are mediated through amylin receptors (AMYRs), highlighting these receptors as significant pharmaceutical targets for diabetes and obesity treatment.



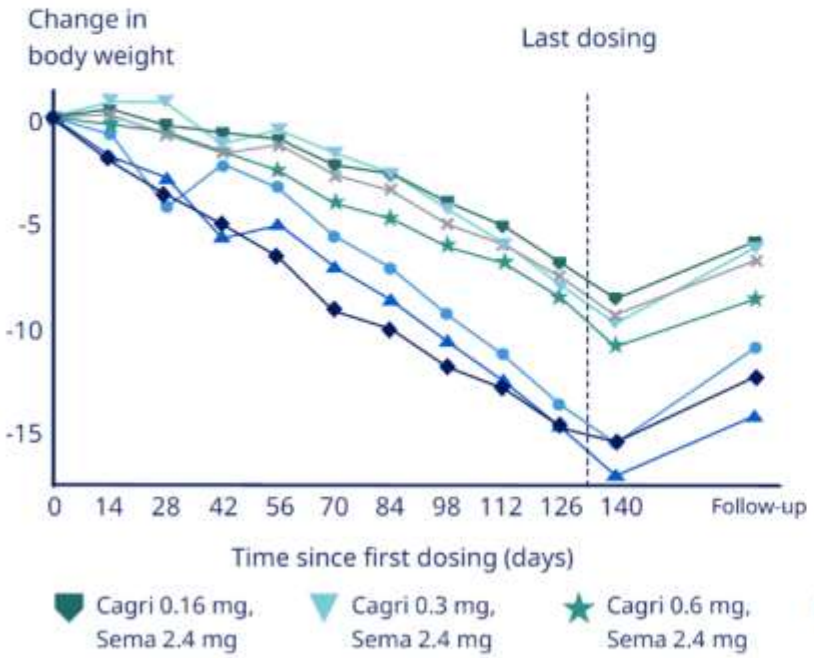


Source of chart on lower right: https://www.sciencedirect.com/science/article/pii/S0196978120301157. chart on upper right: https://synapse.patsnap.com/blog/targeting-the-amylin-receptor-for-obesity-weight-reduction

CagriSema Delivered Strong Results in a Phase 1 Trial

In a 20-week phase 1 trial, CagriSema showed weight loss of 17% and appeared to have a safe and well tolerated profile

Weight loss for different doses of CagriSema in phase 1



The GI profile appeared similar to semaglutide 2.4 monotherapy

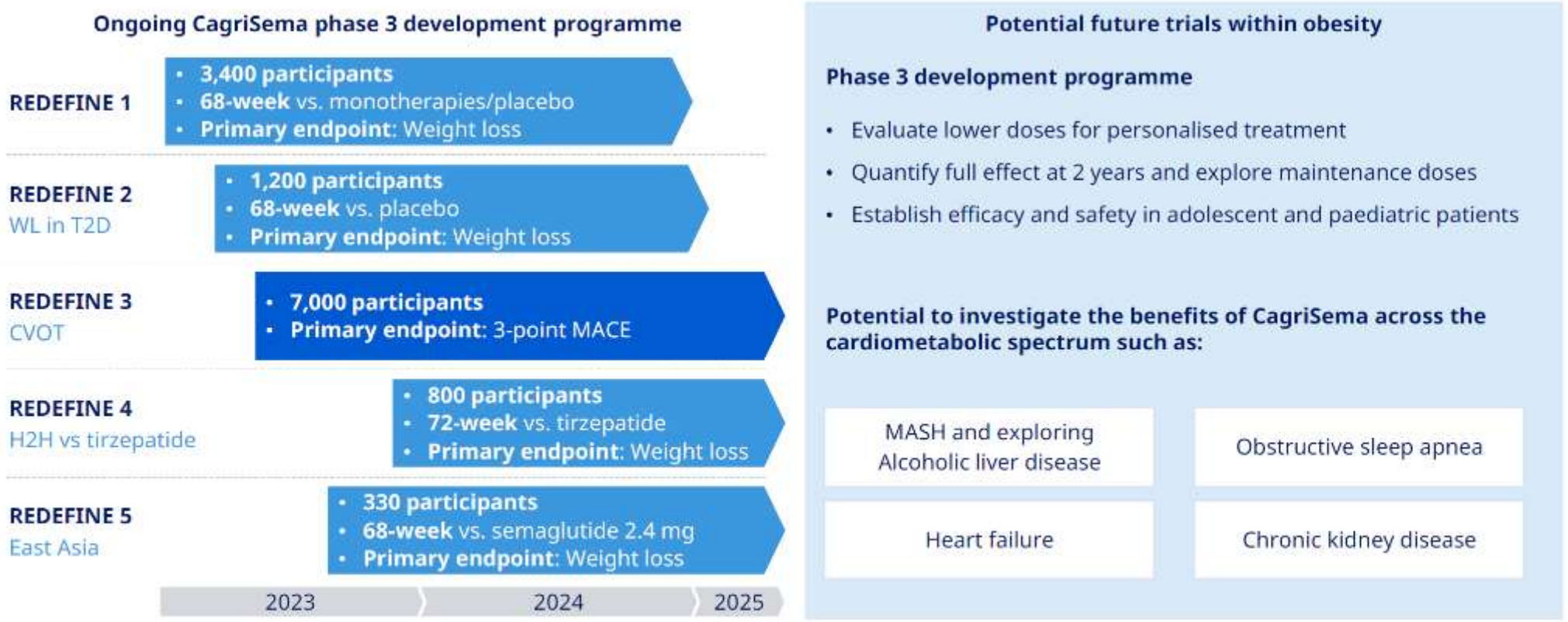
	n=12	n=12	n=12	n=12	n=12	n=11	n=24
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
AEs	11 (92)	12 (100)	11 (92)	12 (100)	12 (100)	11 (100)	23 (96)
SAEs[1]	0	0	0	1 (8)	0	0	0
AEs leading to withdrawal	1 (8)	0	0	1 (8)	0	0	0
GI disorders	7 (58)	10 (83)	7 (58)	10 (83)	11 (92)	9 (82)	19 (79)

[1] The serious adverse event was meningitis
CagriSema: Cagrilintide in combination with semaglutide; Cagri: Cagrilintide; Sema: semaglutide; SAE: Serious adverse events; GI: Gastro-intestinal; Change in body weight is analysed using a mixed model for repeated measurements, where all changes from baseline in body weight measurements enter as the dependent variables and treatment, visit and baseline body weight enter as fixed effects. Treatment and baseline body weight are nested within visit.
Source: Adapted from Enebo et al. Lancet. 2021 May 8;397(10286):1736-1748.

Source: https://www.novonordisk.com/content/dam/nncorp/global/en/investors/irmaterial/cmd/2024/P5-Obesity-Care.pdf

Novo Planning a Comprehensive Phase 3 Program for CagriSema That Will Enroll 13,000 Subjects

Novo indicated at its Capital Markets Day that we will see a Phase 3 CagriSema REDEFINE1 readout later in 2024

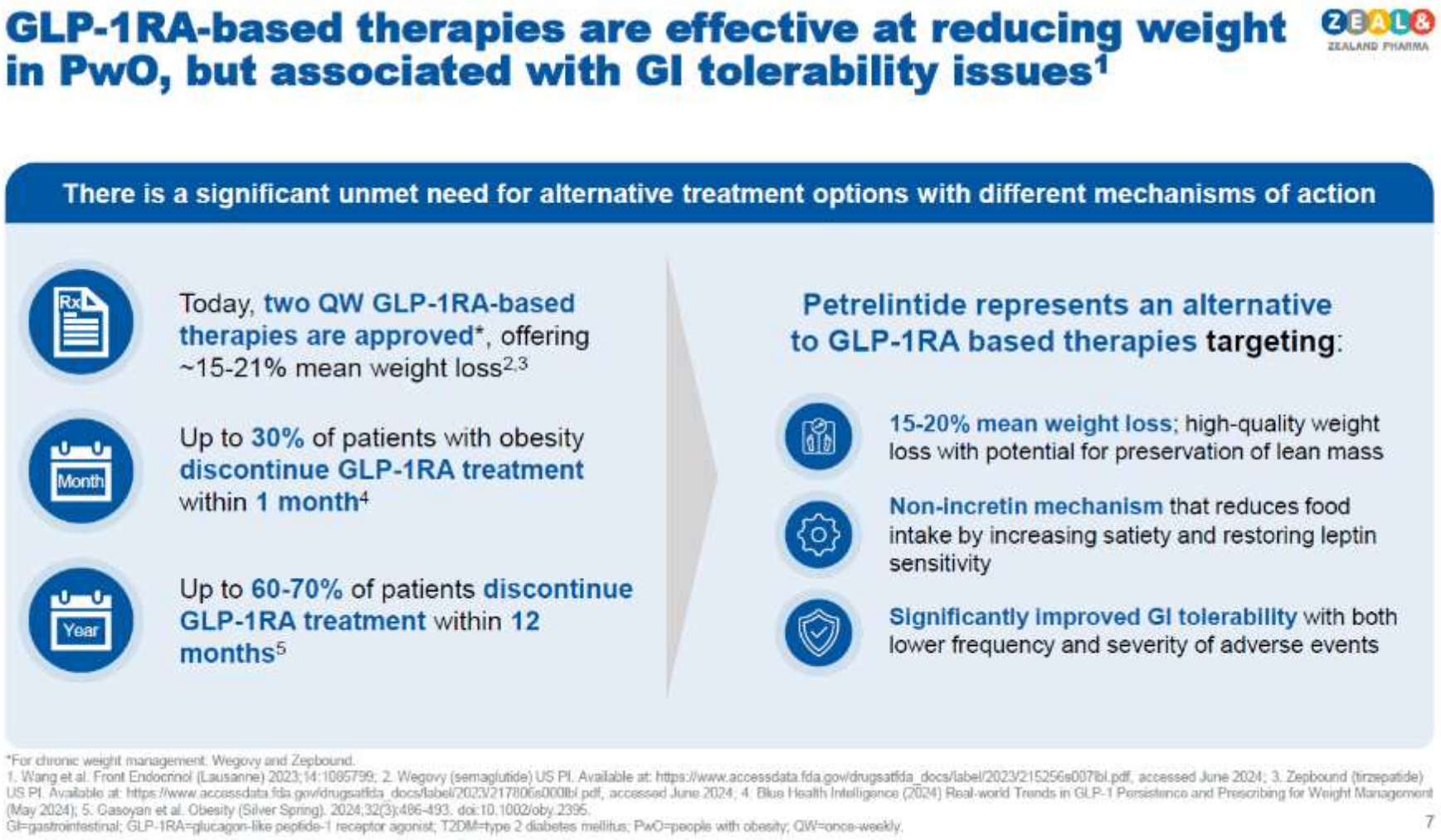


Note: The 44-week REDEFINE 6 trial in China is also ongoing with 300 participants
CVOT: Cardiovascular Outcomes Trial; H2H: Head-to-Head; MACE: Major adverse cardiovascular event; MASH: Metabolic dysfunction-associated steatohepatitis; WL: Weight Loss; ORC: Obesity-related comorbidity

CMD24 CAPITAL MARKETS DAY

Source: https://www.novonordisk.com/content/dam/nncorp/global/en/investors/irmaterial/cmd/2024/P5-Obesity-Care.pdf

Zealand Pharma Notes Issues with GLP-1's



Amylin agonism is considered a possibly gentler approach to weight loss than GLP-1 agonism.

There is high excitement in our industry at present about the potential of amylin agonists to augment the incretin armamentarium for obesity management.

Among other things, amylin improves leptin resistance.

Given that 30% of GLP-1 users discontinue within a month due to tolerability issues, there is an obvious large opportunity for an amylin agonist such as Zealand's petrelinitide.

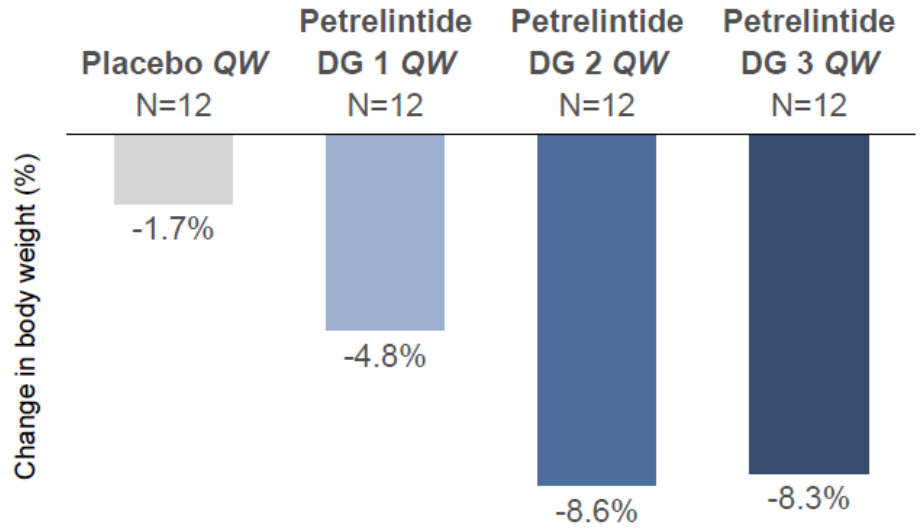
There is a challenging history of side effects with past amylin presentations (e.g., pramlintide), including diarrhea.

But the recent Zealand data looks quite promising. Time will tell if this drug delivers.

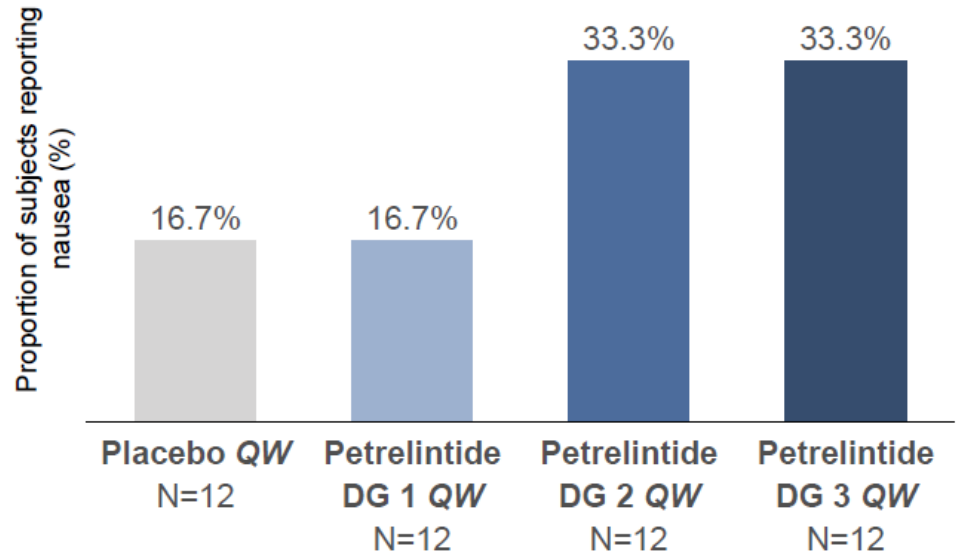
Zealand's Petrelintide Treatment (Amylin Agonist) was Effective and Well-Tolerated at All Dose Levels in the 16-Week Trial

The nausea reported in the active arms of the trial was mild in all but one of thirty-six cases.

Change in body weight from baseline at week 16



Proportion of subjects reporting nausea in the 16-week trial



Source: https://www.zealandpharma.com/media/kiioen11/zealand-pharma_petrelintide-part-2-mad-16-week-trial_conference-call-20-june-2024.pdf

9 RNAi from Arrowhead, Alnylam and Wave

Strong effect of INHBE KO on obesity. Potential for longer run obesity control with RNAi

Liver-specific silencing of INHBE with ARO-INHBE, an siRNA therapeutic, for metabolic diseases

Arrowhead ADA Poster, June 2024

Michelle Ngai, Feng Liu, Puhui Li, Xiaokai Li, Cole Christy, Holly Hamilton, Maria Afrazi, Pierce Sullivan, Tao Pei, James Hamilton, Zhi-Ming Ding
Arrowhead Pharmaceuticals Inc., Madison, WI, USA

INTRODUCTION

- Incretin-based therapies are powerful and effective for obesity and metabolic outcomes, but significant loss of lean mass and adverse GI events at high dose levels has prompted the identification of a novel mechanism of action
- Large-scale human genetic studies support an association between pLOF INHBE variants and 1) reduced WHRadjBMI, 2) improved metabolic profile including lower TG, higher HDL, and reduced fasting glucose levels
- Activin E signaling regulates adipose lipid storage and mobilization
- Activin E levels are elevated in individuals with obesity, insulin resistance, and NAFLD
- siRNA targeting hepatic INHBE has potential to be a novel therapeutic for metabolic diseases

AIM

- Evaluate the potential therapeutic benefits of INHBE silencing in obese and diabetic mouse models with a mouse surrogate of ARO-INHBE
- Evaluate the pharmacodynamic effects of ARO-INHBE in cynomolgus monkeys

METHODS

Rodent studies

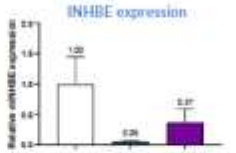
- Diet-induced obese (DIO) and db/db mouse models
- Dosing regimen: weekly 9 mpk subcutaneous (SC) dosing of mouse surrogate ARO-INHBE; daily 0.48 mpk tirzepatide as benchmark; co-treatment of weekly INHBE (9 mpk) and daily tirzepatide (0.48 mpk)
- Body weight, body composition (lean versus fat mass) via Dual X-ray Absorptiometry (DEXA) scans, glucose homeostasis (fasting glucose, insulin, HOMA-IR, oGTT), lipid metabolism (non-esterified fatty acids, beta-hydroxybutyrate) assessed at various points over the course of the studies

Non-human primate study

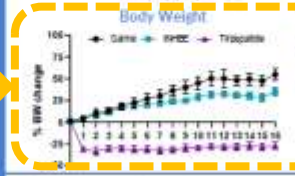
- Cynomolgus monkeys (n=3) received 2 SC doses (D1 and D29) of ARO-INHBE at 3 mpk
- Liver biopsies were collected for INHBE mRNA expression via qRT-PCR

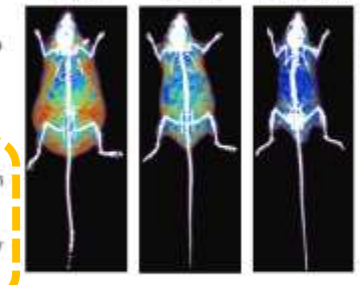
PHARMACOLOGICAL STUDIES OF INHBE siRNA IN RODENT MODELS

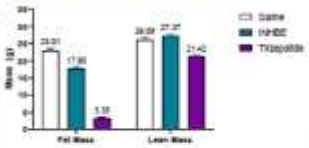
Knockdown of hepatic INHBE mRNA expression with surrogate RNAi-trigger results in an improved body composition with 1) BW suppression, 2) fat mass loss, 3) lean mass retention



- DIO mice were administered with saline (weekly), mouse surrogate ARO-INHBE (9 mpk, weekly), or tirzepatide (0.48 mpk, daily)
- n=10 for each treatment group
- INHBE mRNA expression reduced by ~95%
- INHBE silencing led to a 19% suppression of body weight compared to saline controls

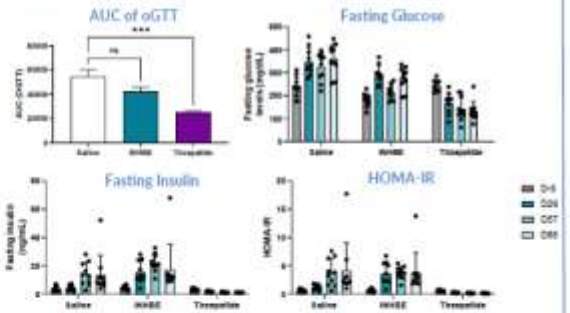






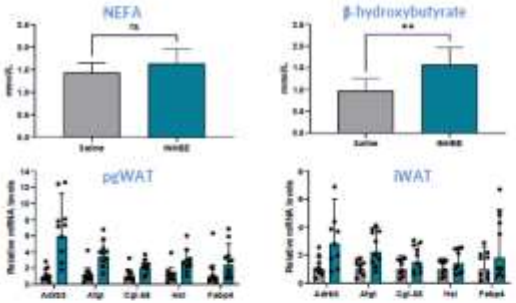
- Body composition analysis through DEXA imaging indicates a 26% loss of fat mass and preservation of lean mass with INHBE silencing

Impact on glycemic control is mild based on oGTT, fasting glucose, fasting insulin, and HOMA-IR indicators



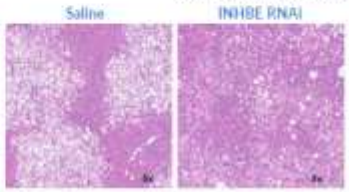
- Animals were fasted for 6 hours prior to glucose homeostasis analysis

INHBE KD improves catecholamine sensitivity, increasing lipid mobilization and oxidation



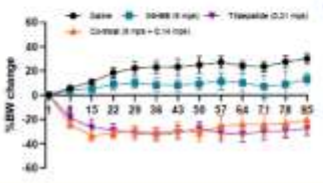
- INHBE KD animals treated with CL316,243 (1 mpk, IP) had increased circulating ketone levels and expression of lipolytic genes relative to control group

Increased lipid mobilization with INHBE silencing does not lead to liver steatosis



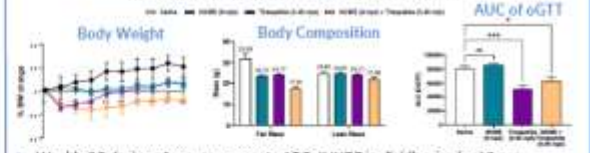
- H&E staining of the liver indicate there is less fat accumulation in DIO mice treated with INHBE RNAi

Co-treatment of tirzepatide with INHBE siRNA allows use of lower tirzepatide dose for similar therapeutic effect in DIO mice



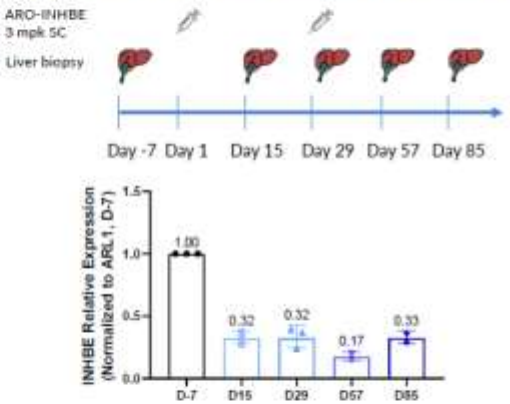
- Co-treated DIO mice (n=10 per treatment group) were administered 9 mpk mouse surrogate ARO-INHBE weekly and 0.14 mpk tirzepatide daily
- Co-treated mice showed similar levels of %BW change as mice treated with a higher dose level of tirzepatide

INHBE silencing in the db/db mouse model results in an improvement in body composition



- Weekly SC dosing of mouse surrogate ARO-INHBE in db/db mice (n=10 per treatment group) resulted in: 1) 15% suppression in BW compared to the saline group, 2) 26% loss of fat mass, 3) lean mass retention, 4) lack of improvement in oGTT

PHARMACODYNAMIC STUDY OF ARO-INHBE IN CYNOMOLGUS MONKEYS



- After a single 3 mpk SC dose, hepatic INHBE mRNA expression was reduced by ~70% (n=3; n=2 on D57 and D85)
- Knockdown was maintained through D85 with a second dose on D29

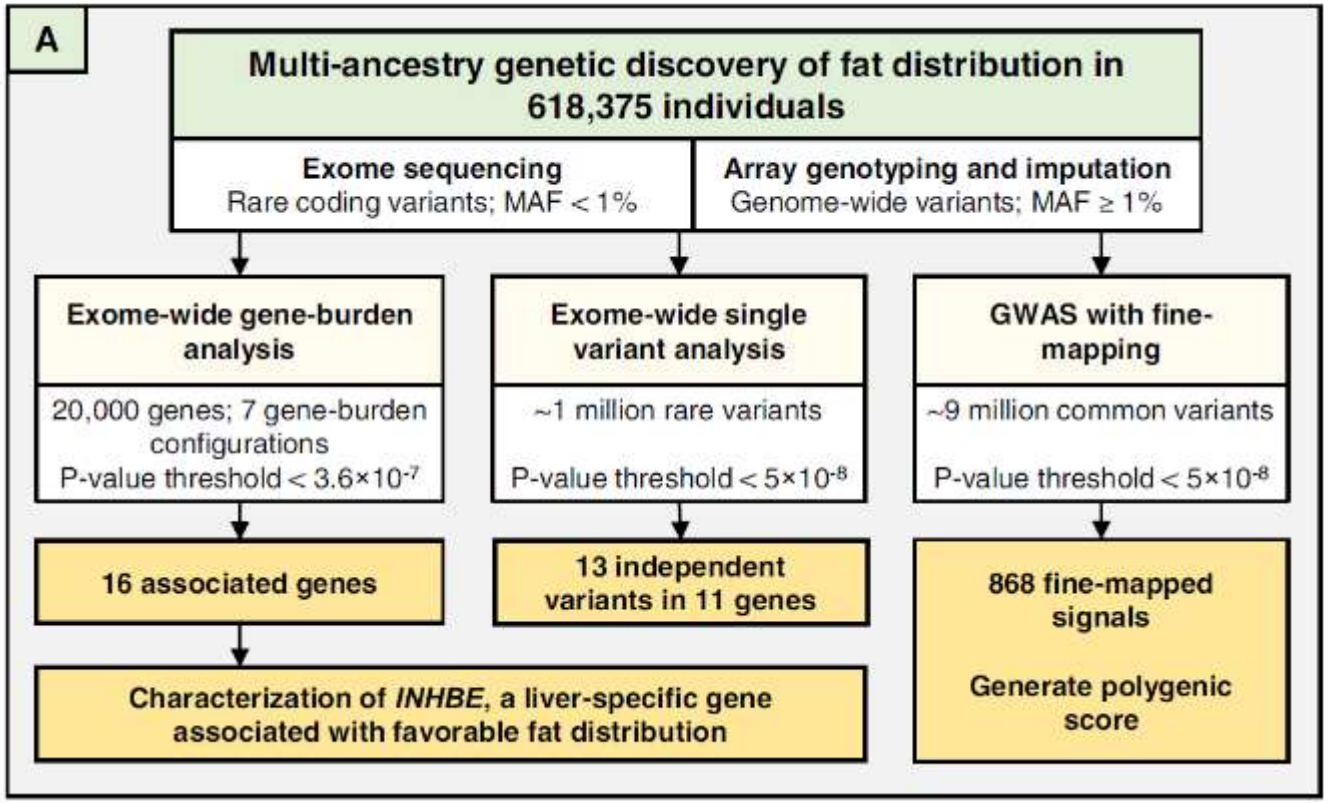
CONCLUSIONS

- ARO-INHBE is a potent RNAi therapeutic capable of silencing hepatic INHBE mRNA expression
- Pre-clinical studies with a mouse surrogate of ARO-INHBE in DIO and db/db models indicate that INHBE KD potentially leads to a suppression in body weight gain, loss of fat mass, and preservation of lean mass likely due to the increased lipolysis
- Co-treatment of tirzepatide with INHBE RNAi has the potential to allow for the use of a lower tirzepatide dose without compromising the therapeutic effect

INHBE Influences Belly Fat

Multiancestry exome sequencing reveals *INHBE* mutations associated with favorable fat distribution and protection from diabetes

Akbari et. al., *Nature Communications*, Aug 23, 2022



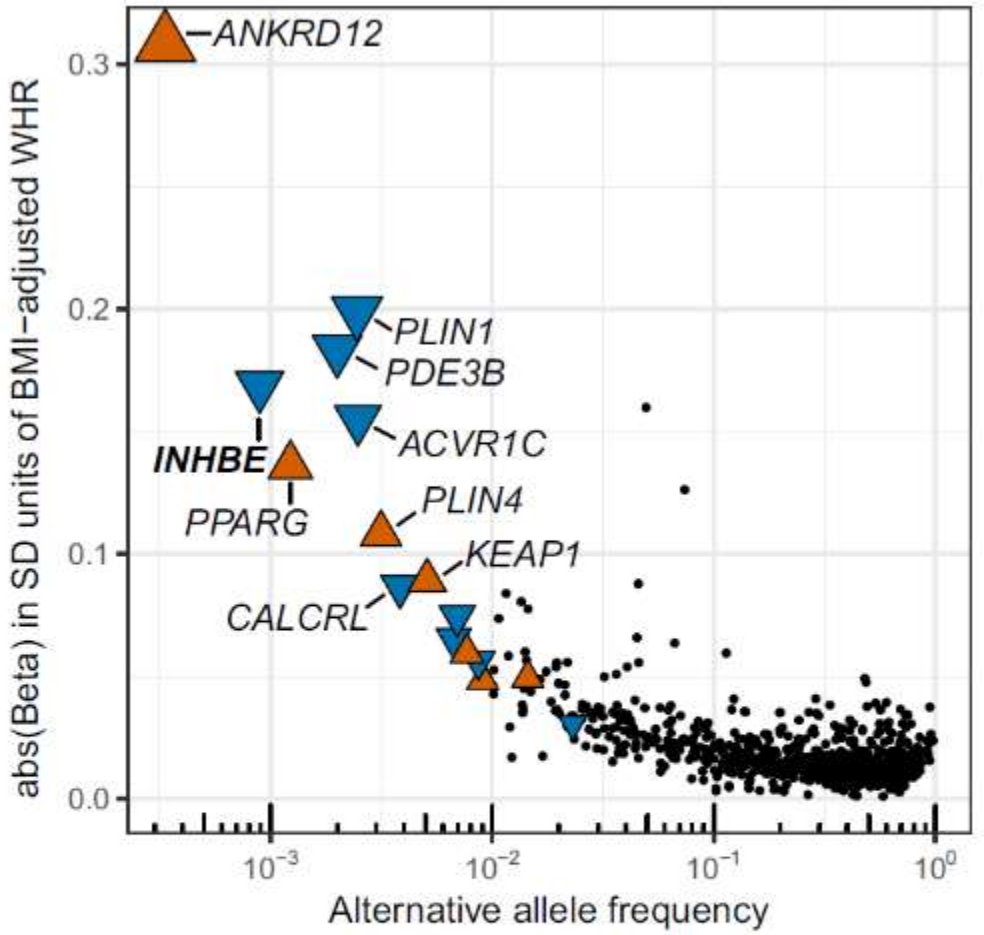


Fig. 2 | Associations with BMI-adjusted WHR for common and rare alleles in the multi-ancestry analysis. The 16 genes with exome-wide significant gene-burden associations are shown as colored triangles, with the triangles pointing upwards (orange) or downwards (blue) indicating associations with higher and lower BMI-adjusted WHR, respectively. The 868 fine-mapped common variants are indicated as black dots. The alternative allele frequency for each variant or gene-burden genotype is indicated on the *x*-axis. SD standard deviation, WHR waist to hip ratio, BMI body mass index.

Source: https://www.nature.com/articles/s41467-022-32398-7

Source: https://investors.alnylam.com/press-release?id=26816

Biotechs Turn to Gene Silencing for Obesity Drugs that Can Last Longer than Wegovy®

Allison DeAngelis and Elaine Chen, *Stat+*, May 23, 2024

Enticed by the immense market opened by GLP-1 weight loss drugs Wegovy and Zepbound, a handful of biotech companies are trying to develop next-generation, longer-lasting therapies based on a very different approach: RNA interference.

Scientists at Regeneron and Alnylam are aiming to silence a gene expressed in the brain called GPR75, what Regeneron Chief Scientific Officer George Yancopoulos calls the “laziness gene.”

Alnylam has also homed in on the INHBE gene, expressed in the liver. Scientists found that people with mutations in the gene have a lower waist-to-hip ratio — a surrogate for abdominal fat, the type of fat that’s especially harmful and is linked to cardiovascular problems. Other companies like Wave Life Sciences and Arrowhead Pharmaceuticals have caught on and are also pursuing RNAi therapies aimed at blocking INHBE.

Even Novo Nordisk, the company behind Ozempic and Wegovy, is heavily investing in this approach to obesity.

The RNAi drug developers say that blocking INHBE can still compete with the current GLP-1 drugs on overall body weight reduction, though. In early tests, Wave’s INHBE candidates have shown similar weight loss as Wegovy, according to CEO Paul Bolno. Meanwhile, Arrowhead’s experimental therapy reduced weight gain by 20% in mouse studies, compared to controls.

The INHBE therapies Alnylam, Arrowhead, and Wave are developing all travel to the liver. But behind the scenes, they are each also exploring whether they can directly target the cells that store fat, known as adipocytes. These cells are particularly sensitive to the type of RNA used in gene-silencing therapies, Hamilton said, though the scientific community doesn’t have a clear answer why. Adipocytes don’t die off and replenish as quickly as other cell types, which helps the therapy last longer in patients’ bodies, he added.

Source: https://www.statnews.com/2024/05/23/weight-loss-drugs-rna-interference-gene-silencing-regeneron/

Emerging Interest in microRNA Therapies for Obesity

Molecular Therapy: Nucleic Acids Vol. 26 December 2021

miR-21 mimic blocks obesity in mice: A novel therapeutic option

Said Lhamyani,[1,13] Adriana-Mariel Gentile,[1,13] Rosa M. Giráldez-Pérez,[2] Mónica Feijóo-Cuaresma,[3] Silvana Yanina Romero-Zerbo,[1,4] Mercedes Clemente-Postigo,[5] Hatem Zayed,[6] Wilfredo Oliva-Olivera,[7] Francisco Javier Bermúdez-Silva,[1,4] Julián Salas,[8] Carlos López Gómez,[9] Abdelkrim Hmadcha,[4,10] Nabil Hajji,[11] Gabriel Olveira,[1,4] Francisco J. Tinahones,[7] and Rajaa El Bekay[1,12]

Interestingly, in vivo treatment with the miR-21 mimic blocked weight gain induced by a high-fat diet in obese mice, without modifying food intake or physical activity. This was associated with metabolic enhancement, WAT browning, and brown adipose tissue (AT) thermogenic programming through vascular endothelial growth factor A (VEGF-A), p53, and transforming growth factor β1 (TGF-β1) signaling pathways. Our findings suggest that miR-21 mimic-based therapy may provide a new opportunity to therapeutically manage obesity and consequently, its associated alterations.

Companies Working on microRNA's Targets for Obesity

APTAMIR

Resalis THERAPEUTICS

The clinical potential of circulating microRNAs in obesity

Chenbo Ji[1]* *and Xirong Guo*[1,2]*

Abstract | Obesity is a complex condition that is characterized by excessive fat accumulation, which can lead to the development of metabolic disorders, such as type 2 diabetes mellitus, nonalcoholic fatty liver disease and cardiovascular diseases. Evidence is accumulating that circulating microRNAs (miRNAs) act as a new class of endocrine factor. These miRNAs are released by many types of tissue, including adipose tissues. miRNAs might serve as endocrine and paracrine messengers that facilitate communication between donor cells and tissues with receptor cells or target tissues, thereby potentially having important roles in metabolic organ crosstalk. Moreover, many miRNAs are closely associated with the differentiation of adipocytes and are dysregulated in obesity. As such, circulating miRNAs are attractive potential biomarkers and hold promise for the development of miRNA-based therapeutics (such as miRNA mimetics, anti-miRNA oligonucleotides and exosomes loaded with miRNA) for obesity and related disorders. Here we review the latest research progress on the roles of circulating miRNAs in metabolic organ crosstalk. In addition, we discuss the clinical potential of circulating miRNAs as feasible biomarkers for the assessment of future risk of metabolic disorders and as therapeutic targets in obesity and related diseases.

Exosomes
Homogenous extracellular vesicles (40–100 nm) that originate from the endocytic recycling pathway, with specific markers such as CD9, CD63, ALIX, flotillin 1 and TSG101.

Microvesicles
Heterogeneous extracellular vesicles (50–1,000 nm) that are produced directly through the outward budding and fission of membrane vesicles from the plasma membrane with no definite markers.

[1]*Maternity and Child Health Care Institute, Women's Hospital of Nanjing Medical University (Nanjing Maternity and Child Health Care Hospital), Nanjing, China.*
[2]*Present address: Tongren Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China.*
**e-mail: chenboji@njmu.edu.cn; xrguo@njmu.edu.cn*
https://doi.org/10.1038/s41574-019-0260-0

Obesity is a major global health issue that contributes to the occurrence of metabolic disorders, such as type 2 diabetes mellitus (T2DM) and non-alcoholic fatty liver disease (NAFLD)[1,2]. The mechanisms that connect obesity with metabolic disorders are complicated, however, the dysregulation of adipose tissue-derived molecules is probably an important factor[3–5]. Many studies have focused on the role of hormones (such as leptin and adiponectin) and circulating lipids (such as free fatty acids) with well-defined target tissues and signalling pathways in the development of obesity-associated disorders[3].

Evidence is accumulating that microRNAs (miRNAs) act as a new class of endocrine factor[6,7]. Defined as single-stranded non-coding RNAs containing 19–22 nucleotides, miRNAs are found in all eukaryotic cells and some viruses, and act to negatively regulate gene expression on a post-transcriptional level via binding complementarily to the target mRNA[8–11]. Mature miRNAs are formed inside the cell and exert their function in the cytoplasm as well as being released into the circulation and various body fluids in animals (for example, urine, saliva and lymphatic fluid)[11,12] (BOX 1). Of note, miRNAs can be packaged within structures called extracellular vesicles[13,14]. These vesicles, which include exosomes and microvesicles, are cell-derived membranous structures which contain numerous miRNAs and transfer between cells, thereby establishing intercellular communication as well as travelling between distant organs to foster interorgan crosstalk[13,15]. In addition, miRNAs are protected from RNase degradation within extracellular vesicles by forming complexes with RNA- binding proteins and by the lipid bilayer that surrounds the vesicle. Extracellular vesicles facilitate miRNA trafficking to distal organs and/or cells via receptor-mediated endocytosis, phagocytosis or direct fusion with the plasma membrane of target cells[13].

Importantly, distinct circulating miRNA profiles are reported between patients with metabolic disorders (for example, obesity and T2DM) and healthy individuals[16–19]. As such, circulating miRNAs have potential as biomarkers for obesity and related metabolic disorders. The specific circulating miRNAs that are associated with metabolic effects and their tissue and cellular sources have attracted considerable attention among researchers. In addition, miRNAs are carried within extracellular vesicles, which can effect various functions of neighbouring and distal cells[20,21] (FIG. 1). The potential roles of miRNAs in metabolic organ crosstalk provide a new angle for us to understand the mechanisms of obesity-related complications in various organs and lead to new and improved treatments.

In this Review, we summarize findings on the roles of obesity-related and adipose tissue-derived or adipose tissue-enriched circulating miRNAs in metabolic

Source: https://www.nature.com/articles/s41574-019-0260-0

10 GPR75 Data Over Next 24 Months Likely to Impact Obesity Drug Market

GWAS study by Regeneron discovers GPR75 as target for obesity management. Loss of function variants of the G-protein coupled receptor, GPR75, are associated with 12lbs lower bodyweight and 55% lower odds of obesity.

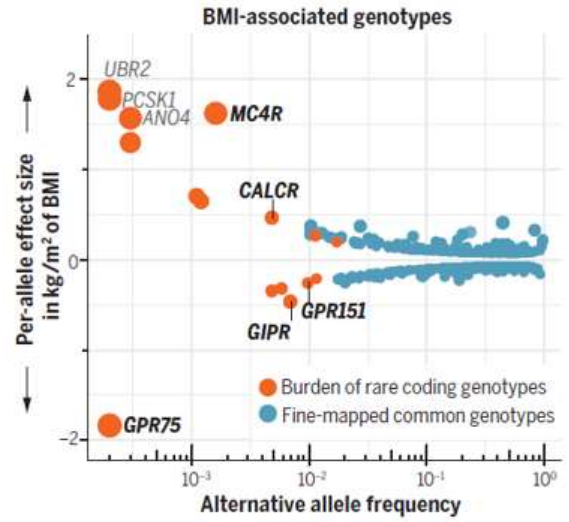
Akbari *et al.*, *Science* **373**, 73 (2021) 2 July 2021

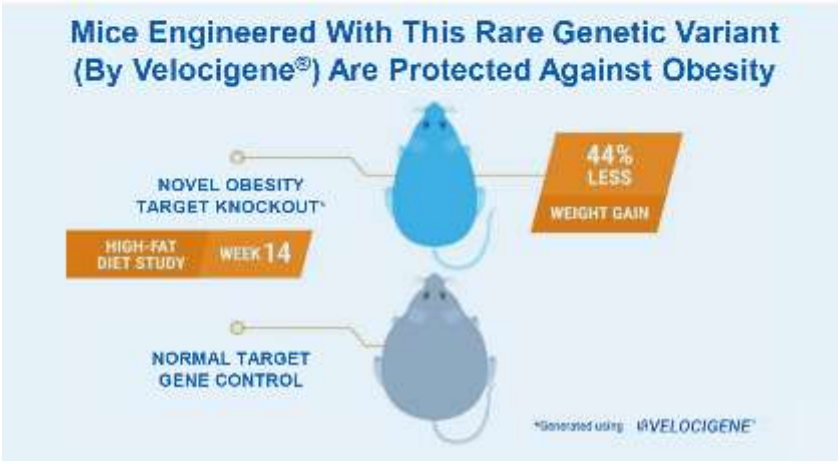
RESEARCH ARTICLE SUMMARY

HUMAN GENOMICS

Sequencing of 640,000 exomes identifies *GPR75* variants associated with protection from obesity

Parsa Akbari†, Ankit Gilani†, Olukayode Sosina†, Jack A. Kosmicki, Lori Khrimian, Yi-Ya Fang, Trikaldarshi Persaud, Victor Garcia, Dylan Sun, Alexander Li, Joelle Mbatchou, Adam E. Locke, Christian Benner, Niek Verweij, Nan Lin, Sakib Hossain, Kevin Agostinucci, Jonathan V. Pascale, Ercument Dirice, Michael Dunn, Regeneron Genetics Center, DiscovEHR Collaboration, William E. Kraus, Svati H. Shah, Yii-Der I. Chen, Jerome I. Rotter, Daniel J. Rader, Olle Melander, Christopher D. Still, Tooraj Mirshahi, David J. Carey, Jaime Berumen-Campos, Pablo Kuri-Morales, Jesus Alegre-Diaz, Jason M. Torres, Jonathan R. Emberson, Rory Collins, Suganthi Balasubramanian, Alicia Hawes, Marcus Jones, Brian Zambrowicz, Andrew J. Murphy, Charles Paulding, Giovanni Coppola, John D. Overton, Jeffrey G. Reid, Alan R. Shuldiner, Michael Cantor, Hyun M. Kang, Goncalo R. Abecasis, Katia Karalis, Aris N. Economides, Jonathan Marchini, George D. Yancopoulos, Mark W. Sleeman, Judith Altarejos, Giusy Della Gatta, Roberto Tapia-Conyer‡, Michal L. Schwartzman‡, Aris Baras‡*, Manuel A. R. Ferreira‡, Luca A. Lotta‡*





Murtaza et.al., *Biochimie*, April 2022:

The metabolic syndrome is a plethora of related disorders that are frequently associated with morbidity and mortality in addition to economic burden. While various treatment options are available, the need to understand the pathology and find new targets still remains.

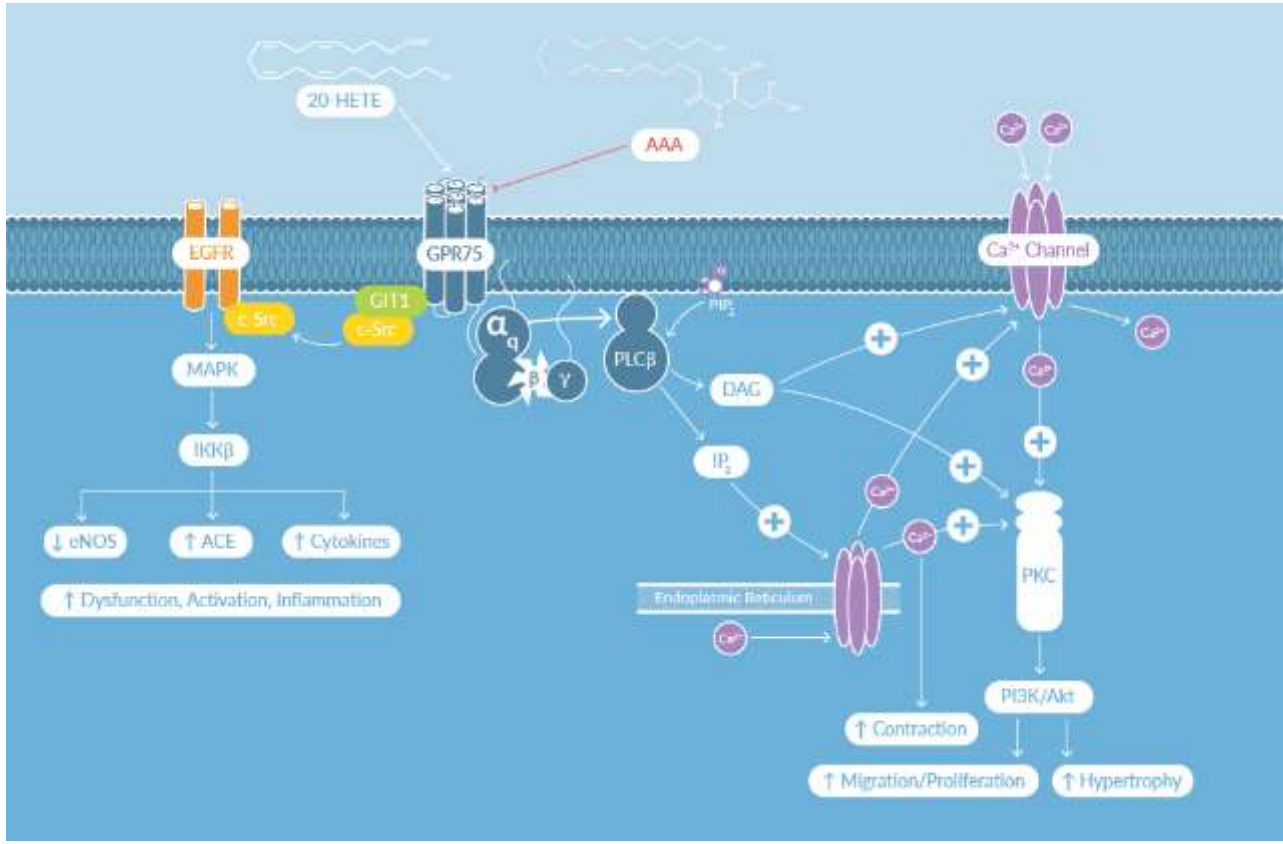
Recent data have suggested GPR75 as one such exciting target that has shown to have highly druggable potential. In this review, we have discussed the recent findings on GPR75 in terms of its expression and signaling and the way it could be a novel target in diseases associated with metabolic syndrome including obesity, dyslipidemia, diabetes, cardiovascular disease, and cerebrovascular disease. In addition, the opportunities and challenges related with the druggable potential of GPR75 have also been highlighted in this review.

Sources: https://www.science.org/doi/10.1126/science.abf8683, https://newsroom.regeneron.com/news-releases/news-release-details/regeneron-genetics-center-discovers-gpr75-gene-mutations-protect, https://www.sciencedirect.com/science/article/abs/pii/S0300908422000141

GPR75 Binds to 20-HETE and CCL5/RANTES

Fan F, Roman RJ. GPR75 Identified as the First 20-HETE Receptor: A Chemokine Receptor Adopted by a New Family. *Circ Res*., May 26, 2017, pp. 1696-1698.

G protein-coupled receptor 75 (GPR75) has been identified as a 20-HETE receptor. It signals through Gq/phospholipase C (PLC)/protein kinase C (PKC) and c-Src/EGFR pathways (fig below). Previously GPR75 was deorphanized as an inflammatory chemokine receptor when CCL5/RANTES was identified as its ligand. Through GPR75, RANTES was shown to activate MAPK signaling to protect hippocampal HT22 cells from amyloid-β-induced cell death and to stimulate insulin secretion in pancreatic islet cells. Now it has been established that 20-HETE, a member of the cytochrome (CYP) P450-derived eicosanoids, acts through the same receptor to elicit vascular effects.

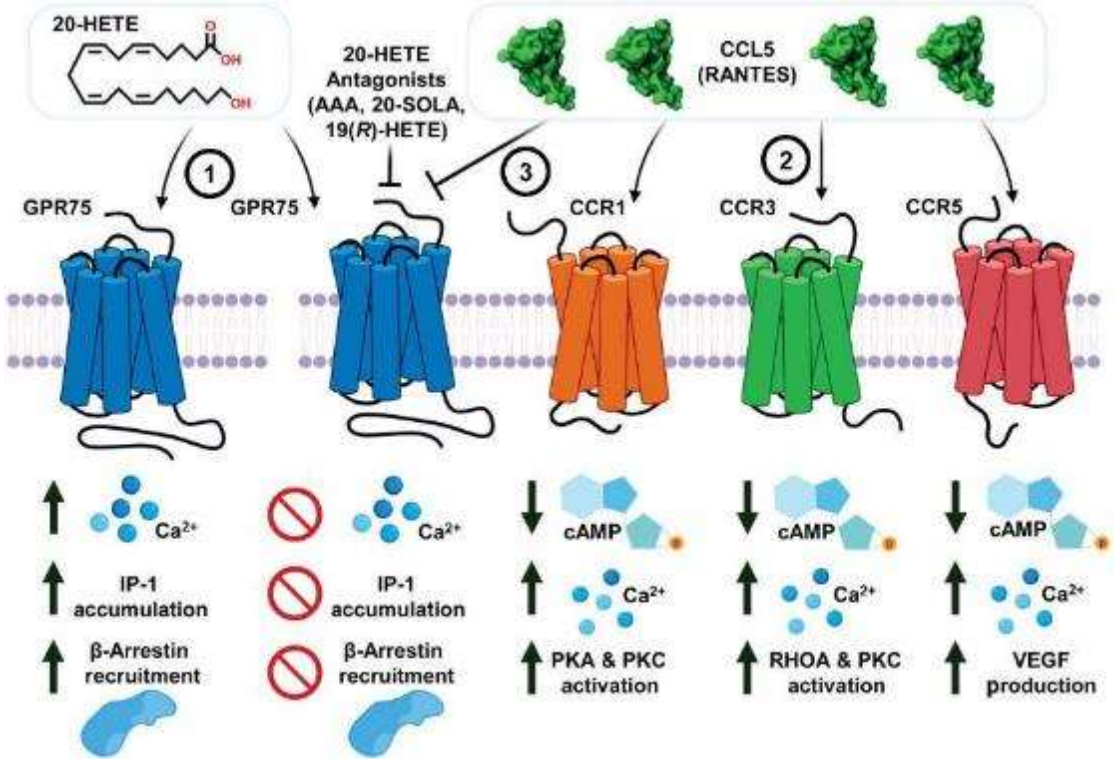


Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5766006/

20-HETE Antagonists Could Inhibit GPR75 Activity

Pascale JV, Park EJ, Adebesin AM, Falck JR, Schwartzman ML, Garcia V. Uncovering the signalling, structure and function of the 20-HETE-GPR75 pairing: Identifying the chemokine CCL5 as a negative regulator of GPR75. *Br J Pharmacol.* Sep 2021, pp. 3813-3828.

The G-protein-coupled receptor GPR75 (Gq) and its ligand, the cytochrome P450-derived vasoactive eicosanoid 20-hydroxyeicosatetraenoic acid (20-HETE), are involved in the activation of pro-inflammatory and hypertensive signalling cascades contributing to diabetes, obesity, vascular dysfunction/remodelling, hypertension and cardiovascular disease. Little is known as to how, where and with what affinity 20-HETE interacts with GPR75. PR confirmed 20-HETE binding to GPR75 with an estimated KD of 1.56 × 10-10 M. In GPR75-transfected HTLA cells, 20-HETE stimulated intracellular Ca2+ levels, IP-1 accumulation and β-arrestin recruitment, all of which were negated by known 20-HETE functional antagonists. Computational modelling of the putative ligand-binding pocket and mutation of Thr212 within the putative 20-HETE binding site abolished 20-HETE's ability to stimulate GPR75 activation. The chemokine CCL5, a suggested GPR75 ligand, binds to GPR75 (KD of 5.85 × 10-10 M) yet fails to activate GPR75; however, it inhibited 20-HETE's ability to activate GPR75 signalling. We have identified 20-HETE as a high-affinity ligand for GPR75 and CCL5 as a low-affinity negative regulator of GPR75, providing additional evidence for the deorphanization of GPR75 as a 20-HETE receptor.

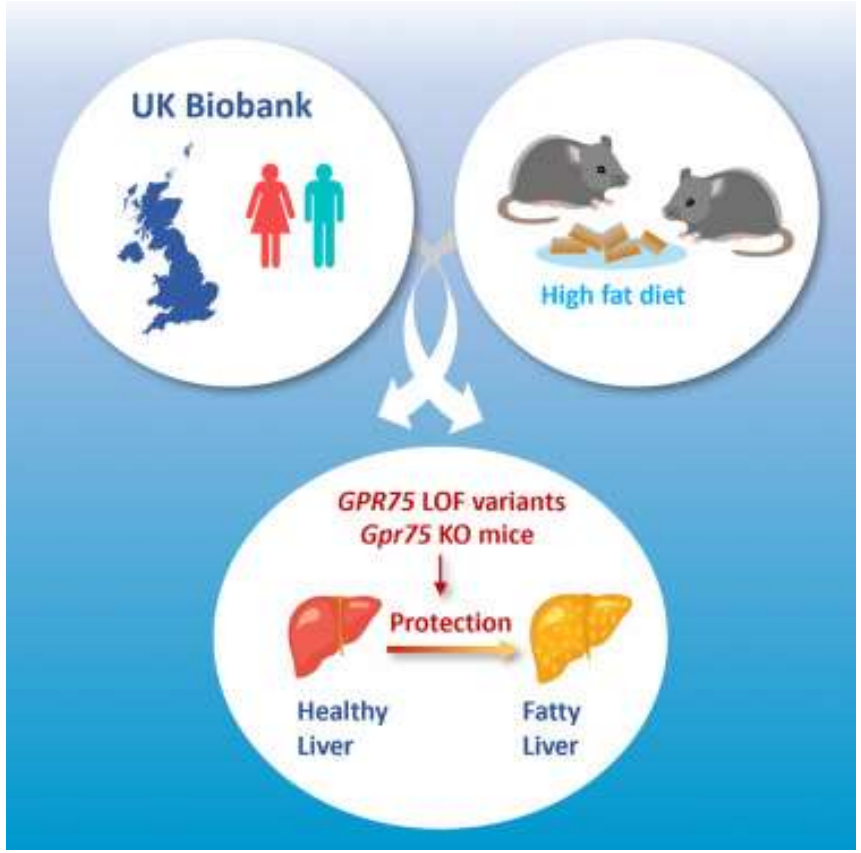


Source: https://pubmed.ncbi.nlm.nih.gov/33974269/

Recent Paper in *Cell Metabolism* Identifies GPR75 as Key Protein in NAFLD

Leeson-Payne A. et.al., "Loss of GPR75 protects against non-alcoholic fatty liver disease and body fat accumulation," *Cell Metabolism*, May 7, 2024

Approximately 1 in 4 people worldwide have non-alcoholic fatty liver disease (NAFLD). This study investigated the role of adiposity-associated orphan G protein-coupled receptor 75 (GPR75) in liver lipid accumulation. We profiled *Gpr75* expression and report that it is most abundant in the brain. Next, we generated the first single-cell-level analysis of *Gpr75* and identified a subpopulation co-expressed with key appetite-regulating hypothalamic neurons. CRISPR-Cas9-deleted *Gpr75* mice fed a palatable western diet high in fat adjusted caloric intake to remain in energy balance, thereby preventing NAFLD. Consistent with mouse results, analysis of whole-exome sequencing data from 428,719 individuals (UK Biobank) revealed that variants in *GPR75* are associated with a reduced likelihood of hepatic steatosis. Here, we provide a significant advance in understanding of the expression and function of GPR75, demonstrating that it is a promising pharmaceutical target for NAFLD treatment.



Source: https://www.cell.com/cell-metabolism/abstract/S1550-4131(24)00120-7

Metformin and GPR75 Antagonism May Work in Part Through Similar MOA: Could Also Reduce Cancer Risk

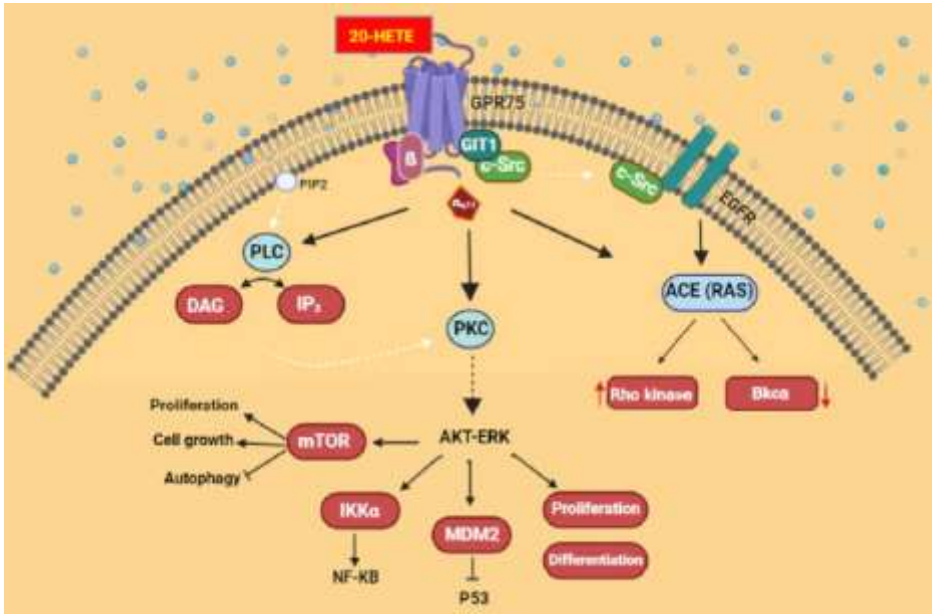
Ghorbanzadeh F, et.al, "Advanced nano-therapeutic delivery of metformin: potential anti-cancer effect against human colon cancer cells through inhibition of GPR75 expression," *Med Oncol.* Jul 29, 2023;40(9):255.

"Cancer risk is reduced by Metformin treatment, as first shown by Evans et al. The anti-cancer activities of Metformin are associated with both AMPK-dependent and AMPK-independent pathways. Protein synthesis and cell proliferation are regulated by Metformin through the AMPK/mTOR pathway. Despite its wide use, Metformin has poor intestinal absorption due to its high aqueous solubility and weak membrane permeability. In order to reduce these limitations, it is necessary to develop new methods of drug delivery.

Using Metformin-loaded nanoparticles would allow for higher intratumoral drug concentrations and a targeted therapy within the tumor, ultimately improving the efficiency of Metformin.

Several studies have shown G-protein-coupled receptors (GPCRs) to be potential therapeutic targets. There has been much interest in GPR75 as a novel member of the GPCR family. A study showed that the inhibition of GPR75 may be an effective therapeutic strategy for obesity. A further study demonstrated that the 20-HETE-GPR75 receptor plays an important role in initiating intracellular signaling in PC-3 cells, manifesting a shift toward an increasingly aggressive phenotype when they undergo malignant transformations. GPR75 signaling pathways that influence the development and progression of cancer are shown in Fig. 1.

A number of genes are expressed in CRC that affect apoptosis and cell cycle rate; for example, a major function of Cyclin D1 is to regulate transition from G1/S phase, interacting with CDKs4 and 6. Many types of tumors, including colon cancer, show an overexpression of cyclin D1."



Source: https://link.springer.com/article/10.1007/s12032-023-02120-8

GPR75 Drug Pipeline is Early But Has High Promise

Hit-to-Lead Stage

ConfometRx

Lead to IND Stage

ORION biotechnology

REGENERON science to medicine

SHUIMU BIOSCIENCES

Phase 1

TAISHO PHARMACEUTICAL

(20-Hete inhibitor, abandoned)

Both Regeneron and Shuimu are generating highly promising GPR75 antagonist small molecules. Orion's pre-clinical animal data with their GPR75 peptide agonist are highly impressive and suggest that drugs in this area are likely to work well for obesity.

Regeneron is pursuing three modalities to target GPR75:

- *siRNA collaboration with Alnylam*
- *Small molecule collaboration with AstraZeneca*
- *Antibody approach*

The Next Generation of Obesity Drugs: Where Next?

Up to 2034: Where Does the Market Go?

Forgive us for taking so many pages to describe what we think is going to matter in the 2028 to 2034 period in the obesity market.

The most likely scenario, we think, is that drugs like Retatrutide, MariTide and CagriSema will take substantial market share around 2029 and will not look back. Today's market leaders, semaglutide and tirzepatide, won't disappear. They will just lose share and become less relevant. Sort of like liraglutide today. If forced to pick a winner, we would think that upcoming MariTide data will vault Amgen to a #1 position while Lilly enjoys a very strong #2 spot on the back of great data and results with retatrutide and orforglipron.* Novo will very much be in the hunt as a #3 because, if nothing else, it's built out so much manufacturing capacity – which will remain essential. Novo's CB1 is also possible best in class as an oral.

There are a bunch of coin flips coming up that are going to influence the market's direction:

1. How well do the monotherapy GIP antagonists fare?
2. Can Roche deliver superior long-run results with a biased GLP-1 agonist in CT-288?
3. Will the GPR75's work?
4. How does BioAge's apelin agonist fare in the clinic?
6. Do any of the ideas less in the foreground like gut blockers, mitochondrial uncouplers, TASR modulators, AMPK's Juvena's JUV-112, NLRP3 inhibitors, INHBE's, LPL activators, microRNA ASO's, SCD-1 inhibitors, D5D inhibitors, MCR4's, MASP inhibitors or PTPb1's work out? While the history of obesity drug development is littered with failures, presumably some of these will work.
7. Will the muscle augmentation drugs play a major role? We are not so sure in a world where MariTide or amylin's do well but there will be room for these drugs.
8. What hidden pipeline is laying in wait from groups like Amgen and Pfizer that might shake up the market?

It seems very likely to us that small molecule companies are going to club up. This is a major source of potential deal-making over the next three or four years. A Novo with its CB1 franchise might well benefit from partnering with a group that has a true small molecule GLP-1 agonist. Novo's oral amycretin is a very complex molecule and doesn't solve the fundamental capacity constraint in the marketplace.** There is also an opportunity for a large pharma that still doesn't have a seat at the table to come in and disrupt things by combining two or three drugs in a combo pill. One might be able, for example, combine Corbus' CB1 with Structure's GLP-1 and apelin agonist to create a dominant small molecule polypill. Sort of like Gilead has done with Biktarvy® in HIV.

* We disagree with the view that Lilly and Novo hold an unchangeable duopoly on obesity drugs (see https://www.morningstar.com/markets/obesity-drug-stocks-why-it-will-be-exceptionally-difficult-dethrone-eli-lilly-novo-nordisk). While there are incumbency advantages from building out manufacturing capacity, building a commercial force and running giant marketing studies, history would tell us that a company with a substantially better drug can take the top spot, particularly if they market well. Biohaven's experience in migraine drugs is a good example of how this can happen.

**See, for example: https://patents.google.com/patent/US20230331803A1

Imagine it's 2034. What Does Society Look Like?

Today, the GLP-1's have been transformative. With the extra weight loss with tirzepatide the excitement for what the obesity drug revolution means for our society is extraordinary.

Obese diabetics across the United States, and many other countries, for the first time are getting down to normal weight reliably. And millions more obese non-diabetics are benefitting.

If ten years ago a walk around Los Angeles revealed a suspiciously large number of blond people, today a walk down Park Avenue in New York reveals a suspiciously large number of thin people.

Where have all the overweight people gone?

For those who can afford it, the GLP-1's have been metabolically transformational.

OK, so now imagine, its 2034.

How has the world changed because of obesity drugs in the last decade? By 2034 semaglutide generics would have been on the market for two years.* The price will be quite low and, at this point, most of the planet *will* have access to this drug. Online access to these drugs will be routinized and increasingly global.

Interestingly, tirzepatide will still be on patent. Its last Orange Book patent doesn't expire until 2039.

There is widespread worry today about what obesity drugs mean for companies like Conagra, McDonald's etc.

It shouldn't be that big of a worry because people on Park Avenue don't hit McDonald's that much anyway.

Most of the world is busy getting *less healthy* while the lucky few have access to drugs that allow them to get *more healthy*. It's definitely not time to short the fast-food industry.

But, by 2034, we expect it will be a different world. By 2034, most people would prefer not to drink sugary sodas and eat fast food.

There will be meaningful access to life-changing obesity drug medications for those that need them.

On the side of the world where people can afford to pay (or have really good health insurance), there will be a myriad of great choices. These are likely to include amazing small molecule products from companies like Lilly and Structure Therapeutics, muscle enhancers from companies like BioAge, Regeneron, Scholar Rock and Veru and much better injectables from companies like Amgen, Lilly and Novo Nordisk.

For those that can't tolerate GLP-1's there will be good options involving amylin agonists, DACRA's and GIP antagonists.

* We think this what happens. USPTO has turned down Viatris' challenge to the 2031 patents and is looking at a challenge to its 2033 patent. Our read is that 2031 is the year when generics will be able to enter the market. See https://www.fiercepharma.com/pharma/novo-nordisk-patent-semaglutide-invalid-viatris-request-uspto-will-review.

More on Life in 2034

If obesity drugs are a craze today, we haven't seen anything yet. This is because the new generation of incretin drugs will be *so* good. To be able to take off 30%+ body weight in a year is materially better than what can be expected today with semaglutide and tirzepatide.

The idea that humanity can and will get healthy will be understood by 2034 as civilization changing.

We should start to see the relatively poor life expectancy situation in the United States improve. Today, a female born in Japan can expect to live for 90 years. Notably, there is almost a zero chance she will be obese. Japan is the world's least obese country. As more people face metabolic lives like that of today's Japanese female, what it means to be human will change.

Knowing that you can live without chronic disease into your 80's will give enormous swaths of society meaningfully more time to live well, enjoy family and become fulfilled. And it is going to save society a fortune on medical spending.

That guy on Park Avenue is going to be even more fit.

And buff too – thanks to muscle enhancing drugs, assuming the approvals come through with a good adverse event profile. (See the next page for a tongue-in-cheek vision of what happens to Park Avenue Guy).

Much more importantly, whether it's Peoria, Atlanta or Topeka you are going to see fewer morbidly obese people.

The all too familiar scenes in our society of 200-pound children and 350-pound security guards will become less common. A little at first. A lot, later. Hopefully, places like McDonald's will have got the message and will be serving up "fast food" that is GLP-1 friendly and nutritious to boot. Soft drinks made with high fructose corn syrup might start to go away and new consumer products optimized for health will be available and popular.*

There will obviously be major consequences for the pharma industry and Wall Street. Thanks to the obesity drug revolution, by 2034 we will have long passed the moment when we saw a pharma company achieve a trillion-dollar market cap.

Companies that ignored the "big drugs for big diseases" theme in 2022 and stuck to their rare disease and oncology guns will still be relevant – but just a lot smaller than those that got serious then about doing something for chronic disease.

Of course, obesity will still be with us. If anything, there will be more obese people – and that's because it's a global phenomenon. There will still be a lot of unmet need in the market for future innovators to chew on.

* See https://www.bloomberg.com/news/articles/2024-06-23/big-food-tries-to-offset-obesity-drug-blow-with-vitamins-meals

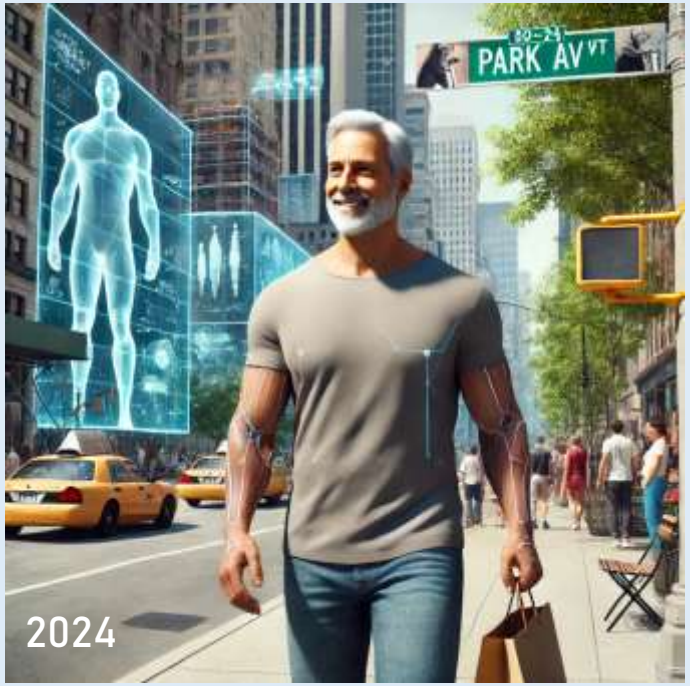
The Hypothetical Man on Park Avenue in Different Eras

2010: Pre-Ozempic®

Tries to eat right but not winning the battle of the bulge.

2024: On Zepbound®

Fitter and getting healthier.



2034: On Retatrutide/MariTide And a Myostatin Inhibitor

Super fit and even healthier.

These pictures are intended to give a light-hearted rendition of what successive generations of obesity / metabolic health drugs might mean over time for those who can afford them. In 2010, our hypothetical person walking down Park Avenue didn't bother with liraglutide as it didn't make a difference. But, today, he's definitely heard about Zepbound® and got a prescription - lost a good 70 pounds. He's now working out and eating right. By 2034, he decided to use that myostatin inhibitor and got really muscular and has taken off even more weight. Uses his InBody scale monthly to monitor body composition and keep body fat in the desired range. He's feeling great and now looking forward to the fourth generation of drugs which will help optimize inflammation, oxidative stress and insulin sensitivity to avoid risks of old age such as Alzheimer's disease. Not that this guy needs to worry that much.

Beyond 2035: What's Next for the Obesity Problem?

We already know that we are going to have something like 4 billion obese people on the planet by 2035.

The problems we have today with kids drinking sugary soda, society eating too much fast food and adults maintaining poor lifestyles will still be with us in 2035.

The world appears likely to become a wealthier, more harried, more divided, more anxious and more socially conscious place. Today's 15-year-old anxious tech-savvy kid, glued to their iPhone and video games is going to become a parent by 2035 – interested in the good life, eating and society. There is still a very good chance that that kid will be struggling with obesity as a young adult.

This socially conscious person is going to be very interested in taking off weight or keeping off weight. This person will know words like Ozempic, Zepbound and soon, MariTide, by heart.

The obesity drug market of 2035 will be gigantic, highly politicized, fragmented and more globalized than today. All of this plays in a backdrop of fiscal stress on governments as it just so happens that 2035 is the year that the U.S. Social Security system is predicted to go broke.*

* See https://www.cnbc.com/select/will-social-security-run-out-heres-what-you-need-to-know

Unhealthy eating will be around for a long time.
Interest in obesity drugs will continue for decades to come.

Three Visions of the Next Generation of the Obesity Market

1 Self Pay Market Dominates — The hell with reimbursement

- Self pay market is over $100bn in U.S. alone.
- Current market is being consumerized rapidly. Ro.co and Hims&Hers exemplify the trend
- Poor reimbursement for GLP-1s is the problem of payors and the U.S. government – not Lilly and Novo
- Self pay market takes over mainstream market. Reimbursement is reserved for those with severe co-morbities
- The market evolves to better self-pay drugs – with a variety of price points so even less well off participate

2 Better Drugs — Orals, less nausea, more muscle, no rebound

- Even faster weight loss or sustained weight loss when you go off your GLP-1
- Work to fix the liabilities of the GLP-1 class over time
- This is the predominant idea driving investment in obesity drugs today. Better drugs. Better features
- The key area of remaining need is to deal with the rebound effect: weight regain when one stops drugs
- Fourth generation sponsors likely to pursue novel ideas to limit post-GLP1 rebound

3 Harm Management — Target reimbursement to people who need it most

- Obesity kills. But obesity doesn't kill all people
- There are multiple theories as to why obesity kills (e.g. auto-inflammatory response and insulin resistance)
- A viable strategy is to direct GLP-1's (and other MOAs) to persons who would most benefit from harm reduction
- Precision obesity medicine approaches have high potential to reshape the market – similar thing happened in oncology
- Design add-on drugs that address specific causes of harm and use with obesity drugs
- Employers and governments much more likely to pay for drugs that maximally reduce harm

This section delves into the growing self pay market for obesity drugs and contemplates how this market will evolve.

We will talk about the payor-mediated segment of the market which is relatively small today.

A key issue is dealing with the rebound effect – the tendency of patients to put weight back on after stopping GLP-1 agonists.

If the mantra of third generation obesity drugs is "take it off" then the mantra of the fourth is "keep it off" and "get healthy".

To this end, we discuss strategies that drug companies can use to optimize outcomes for patients through harm reduction in detail.

The Obesity Drug Market Will Fragment

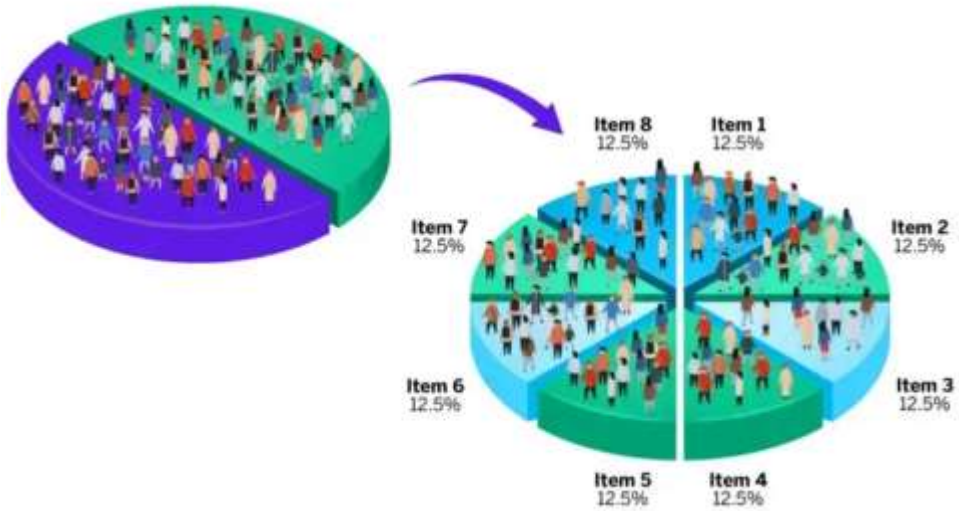
Our prediction is that the obesity market is going to fragment and become increasingly segmented.

Today, some private health insurers cover Wegovy® and Zepbound® for obesity in the United States. But the coverage isn't good. Employers try hard to create barriers to these drugs for employees because they are expensive. And the U.S. government won't pay for them at all – unless you have Type 2 diabetes (or soon, heart disease, kidney disease or sleep apnea).

It's for this reason that we have seen a huge private pay obesity market market crop up in the last two or three years. Based on industry trends and conversations we believe that the online compounded semaglutide market is going to become an ever-larger fraction of the branded market.*

The price point in this market is well below that in the branded prescription market. One can buy a month's supply of semaglutide online for as little as $149 – far less than the discounted price your friendly drug wholesaler is paying today for branded semaglutide in the United States. We have seen some data on growth and scale in this market and can say it's growing at more than 10% a month as consumer word-of-mouth counteracts industry and FDA messaging that product from this market is unsafe, unreliable and illegitimate. The reality is that the sale of compounded product is perfectly legal; is mainstream and safety issues are very rare.

The Obesity Drug Market is Likely to Fragment



In the last quarter, the largest players in the ePrescribing market, Hims and Ro have both indicated that they are stepping up efforts to sell compounded semaglutide.* The compounding phenomenon reminds one of what happened when the pharma industry tried to replace cigarettes with FDA-regulated nicotine inhalers. As companies like Aradigm were struggling with the capital costs of entering the market, electronic cigarette makers exploited legal loopholes and started offering eCigarettes directly to consumers.

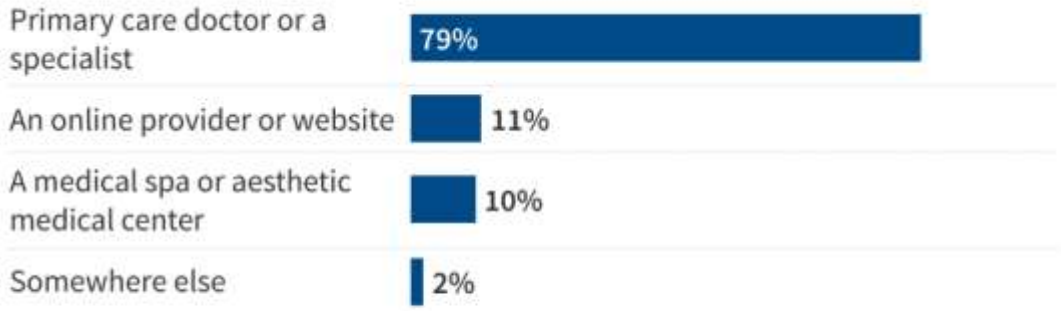
* See: https://investors.hims.com/news/news-details/2024/Hims--Hers-Announces-Access-to-GLP-1-Injections-Passing-Cost-Savings-Onto-Customers/default.aspx. One industry source indicated to us that ro.co alone has done over a million-month years of semaglutide sales in the last 12 months. We spoke to another relatively new vendor who is doing about a third that volume with 30% monthly growth throughout 2024.

KFF Tracking Poll: 19% of GLP-1 Users Paid Out of Pocket / 21% Did Not Get Them From Their Doctor

Figure 5

Most Adults Who Have Taken GLP-1 Drugs Say They Got Them From Their Primary Doctor or Specialist, About One In Four Say They Got Them From Another Source

Did you get these drugs or a prescription for them from any of the following places?



Note: Among those who have ever used GLP-1 agonists. Percentages will add up to more than 100 due to multiple responses. See topline for full question wording.

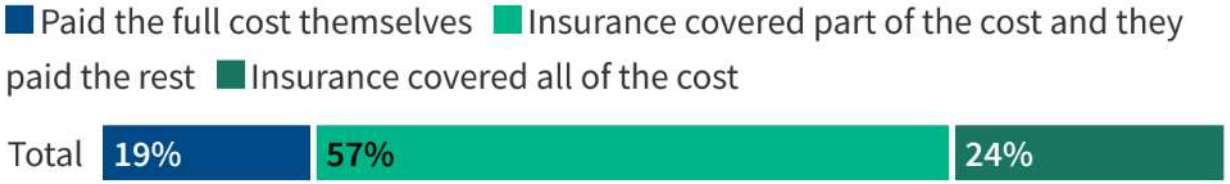
Source: KFF Health Tracking Poll (April 23-May 1, 2024)

KFF

Figure 6

Most Insured Adults Who Have Taken GLP-1s Say Their Insurance Covered at Least Part of the Cost, but Fewer Say Their Insurance Covered All the Cost

How did you pay for the cost of these drugs?



Note: Among those who have ever used GLP-1 agonists who are covered by health insurance. See topline for full question wording.

Source: KFF Health Tracking Poll (April 23-May 1, 2024)

KFF

Source: https://www.kff.org/health-costs/poll-finding/kff-health-tracking-poll-may-2024-the-publics-use-and-views-of-glp-1-drugs/

How the Market Could Segment

Before we knew it, a large unregulated market popped up. For all the criticism, the reality is that eCigarettes have gotten many off of real cigarettes and have likely saved many lives. The eCigarette market is now more than $25 billion in size and is expected to more than double by 2032.*

For the compounded market to be shut down in the U.S., semaglutide would need to come off of the FDA shortage list. This is not expected to happen for years. With generics expected to enter the market in 2031, the consumerized obesity market is likely to grow indefinitely.

The Consumer Market for Obesity Drugs

In our obesity report last year, we forecast that the self-pay U.S. consumer market for obesity drugs will eventually end up with sales over $100 billion. The TAM is actually much larger based on survey data, but surveys don't always end up forecasting actual consumer behavior.

The botox market is $4.3 billion today and is expected to hit $13 billion by 2035.** Almost all of the spend in this market is self-pay.

Think of the obesity market as being a much larger version of the botox market.

* See https://www.custommarketinsights.com/press-releases/e-cigarette-and-vape-market-size/
** See https://finance.yahoo.com/news/botox-market-size-hit-usd-150100661.html

How the Market Could Evolve

Can We Shut Down the Consumer Market?

Imagine, hypothetically, that a group of frustrated pharmaceutical companies decided to try to boost sales of GLP-1 agonists by successfully lobbying Congress to change compounding rules so that it would be no longer possible to sell semaglutide online while the drug is in shortage.

We predict that the consumer market would likely evolve but not go away.

And, how the market evolves, wouldn't necessarily be good for drug companies. One way to think about this is by analogy – to the music business. Traditional labels like Warner Music hit their heyday in the 1990s.

Then, in 1999 consumers discovered that they could enjoy music by illegally downloading it from a filesharing service called Napster.

Download they did. By 2000, the idea of online music had spread like wildfire and buying music CDs from the local music shop became passé.*

What ensued was a legal battle in which record companies successfully (and correctly) caused Napster to be shut down.

Unfortunately, record companies never were able to return to the previous days of high profits from selling tapes and CD's in physical stores.

The consumer wants to buy their obesity drugs online and they would like the price to be affordable.

* https://www.theguardian.com/music/2013/feb/24/napster-music-free-file-sharing

Consumer Market is Resilient

Instead, the market morphed. And got larger.

Much larger.

At first, Pandora emerged with an online streaming service.

Also, Apple entered the market with iTunes that allowed anyone to buy an individual song themselves.

Soon, Spotify entered and after great success, Apple also decided to open a streaming service.

This business ended up growing through evolution.

Apple's music business is easily worth more than $100 billion – far more than the old record companies were ever worth.

Spotify's market cap today is $27 billion, far larger than the record companies ever got.

Pandora probably exited too soon, selling to XM Sirius in 2019 for $3.5 billion.

Online music today is a gigantic business that parallels the video streaming industry.

The desire of some to shut down the burgeoning consumer market for obesity drugs reminds of the desire of record companies to shut down streaming services 20 years ago.

The Consumer Market is Here to Stay

You get the idea. There is a giant and rapidly growing consumer market for buying obesity drugs online – created by compounding rules in response to the semaglutide shortage.

The allure of losing weight is intoxicating to the general public.

And it's going to be very hard to put this genie back in the bottle.

How the Consumer Market Could Work in the Future

The consumer seems to accept a price point of $150 a month for their drugs.* If possible, they would like the drugs to be oral and without side effects.

That works out to an $1,800 opportunity. There are at least 140 million adult Americans (according to recent CDC data) with a BMI over 27. Let's suppose you got half of them to buy (consistent with consumer survey data discussed in our report in 2023).

That math translates to a $126 billion total addressable market.

And that's with conservative assumptions on price point and for the United States only.

Presumably, there is an equally large market to be had in other countries.

As we said last year, the consumer market for obesity drugs is really big – on par with the iPhone.

* Most online sites we looked at in June 2024 charge between $199 a month and $349 a month.

The Consumer Wants Big Weight Loss

There are obvious opportunities for those that are enterprising to participate in this market.

Small Molecule Market Entry Options

If Novo is right, for example, that Monlunabant can generate 19% weight loss in a year, then that drug would definitely get consumers' interest.

It looks like most of the small molecule GLP-1's can get to 15% to 22% weight loss in a year (based on orforglipron's 14.7% average weight loss at 9 months).*

With small molecule manufacturing economics, one could turn either one of these drug types into a $10 billion+ drug in the self-pay market alone.

Obviously, one can combine them and compete on efficacy and, probably, charge more. There is obvious potential to offer regular, premium and supreme options to the consumer.

There are powerful incentives to take some of the more derisked small molecule classes (e.g,. GLP-1's or CB1's) and get an FDA approval in order to be able to sell the drugs to the self-pay market. As we say, the hell with reimbursement.

* Compare these stats to 12-month weight loss of 8 to 10% with QSYMIA, a small molecule weight loss option available today.

The Consumer Wants to Buy Online

Marketing Large Molecules Directly to the Consumer

There is also a major opportunity to develop a large molecule drug and supply it directly to the consumer.

Lilly is doing this now with its LillyDirect program for tirzepatide.* But the online cost from the site is $6,000 annually and Lilly does not promote the service on social media as do direct-to-consumer marketers of compounded semaglutide. To our knowledge, there are no TV or online ads for LillyDirect. Awareness of the service is low. We love the idea of LillyDirect, but the service must be promoted to really take off.**

It would seem logical to develop one of the many effective injectable GLP-1's invented by groups like Altimmune, Gan & Lee or Hanmi for this direct-to-consumer market.

A particularly intriguing possibility is raised by Sun Pharma's Utreglutide, which is now in Phase 2 studies. This GLP-1R agonist peptide is manufactured in India and Sun is capable of building out large manufacturing capacity in that country.

Sun is also fully capable of seeking an approval that would not present drug in pre-filled syringes but instead create vial presentations that are made for the online market. This could cause the drug to generate margin at a lower price point.***

* Pfizer has also started a direct-to-consumer telehealth type service (https://www.biopharmadive.com/news/pfizer-eli-lilly-direct-to-consumer-glp-1/716866/).

** There are interesting parallels in the music and video streaming businesses. Warner music responded to the streaming movement with its Topsify. Disney has created its own service called Disney+. But these services have not become large and profitable for reasons involving a desire to avoid cannibalization, use of internal content only and lack of investment in consumer marketing.

*** A further point is that the dose of Utreglutide required for efficacy is about a third lower than with other GLP-1's. This means that the capital cost of manufacture could be lower. The drug is showing some differentiated efficacy as well on lipid lowering.

OTC Market Another Possibility

Most large pharma have been exiting OTC businesses as quickly as they can. It's clear enough why. Margins aren't great. Growth is low. And the battle for shelf space in retail outlets is challenging.

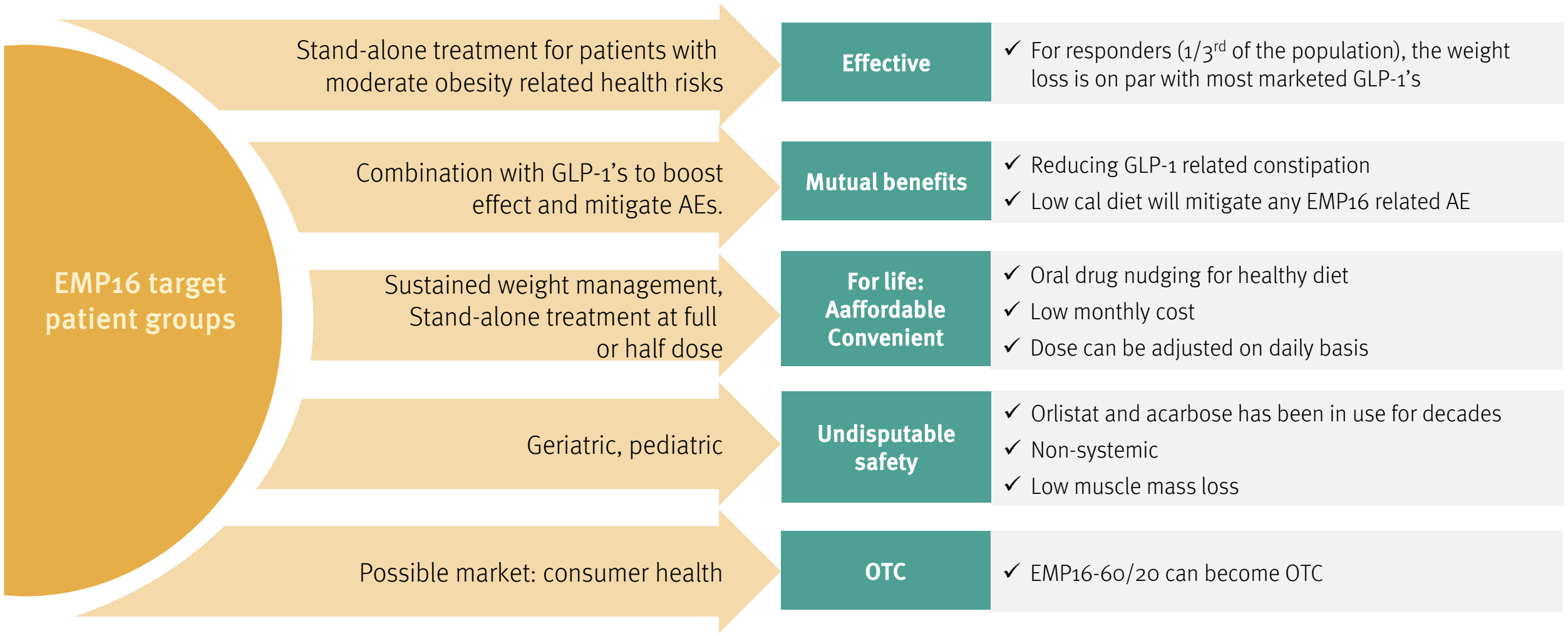
We think the economics of this business could change if an effective OTC weight loss product could be designed - particularly if it were sold and promoted in the manner that today's online marketers are operating.

As proven by the online compounded semaglutide market, there is, theoretically, quite a large market for a good OTC weight loss product that would be marketed online.

Today's OTC weight loss market leader Alli®, sold by Haleon, generates 4% placebo-adjusted weight loss at one year via a lipase inhibitor. That's not enough to excite a consumer. Alli® sales are modest.

We've been intrigued by small Swedish company, Empros Pharma, which has combined a lipase inhibitor with acarbose, an alpha-glucosidase inhibitor. Acarbose is not an OTC drug today but has a very benign side effect profile and likely could be. Empros showed 7.7% weight loss with their combo pill EMP16 at 24-weeks. That's not too far off from semaglutide. Another OTC product, Plenity®, has an orthogonal MOA (stomach filling agent) and has good weight loss numbers. Sigrid Therapeutics is also interesting. It would be interesting to explore whether one could create a combo pill using something like EMP16 + Plenity with Sigrid in support. One should be able to get near to the kind of weight loss Novo is forecasting with monlunabant.

Empros Pharma EMP16 Product Profile



Source: Empros Pharma corporate presentation, June 2024

The Larger Opportunity

There are so many good ways to connect to the consumer who is interested in weight loss.

One approach, advocated by Hims and Hers, is to provide customized care that is physician driven. This care integrates online training, access to physicians to discuss weight and the drugs themselves. Others, like Weight Watchers have switched to combining meal plans with GLP-1 drugs and general health advice. Calibrate and Noom combine GLP-1's with advice and nutritional training.

Another approach would be to use more "high tech medicine" – advanced diagnostics if you will, to understand the whole patient and to generate recommendations for drugs that integrate back into the patients existing care ecosystem. Today, we are seeing quite a few websites that are focused on specific customer subgroups. For example, we know of one website that is mainly offering drugs just to the U.S. Chinese community. In Chinese. Likewise, there are many different types of obese persons. Cultural differences. Health differences. Differences based on blood markers, genetic analysis, body composition analysis and co-morbitities. It should be possible to address various subtypes with customized pharmacology.

The movement towards self-pay obesity drugs marks a sea change in the larger context of medicine, consumer health and the integration of technology into our everyday lives. Authors such as Hemant Taneja and Steve Klasko of General Catalyst or Daisy Wolf and Vijay Pande of Andreessen Horowitz have thought deeply about this area and how healthcare could be better organized and delivered to the active consumer-patient of today using novel business models.* Their thoughts are highly germane in the context of the integration of obesity drugs into optimal patient care.

* See, for example, https://www.healthassurance.ai/book/, https://a16z.com/the-biggest-company-in-the-world/, https://a16z.com/consumer-health-areas-of-opportunity/ and https://a16z.com/hey-tech-its-time-to-build-in-healthcare/.

What About the Rest of the Market?

We see at least two other major segments of the obesity market in the United States:

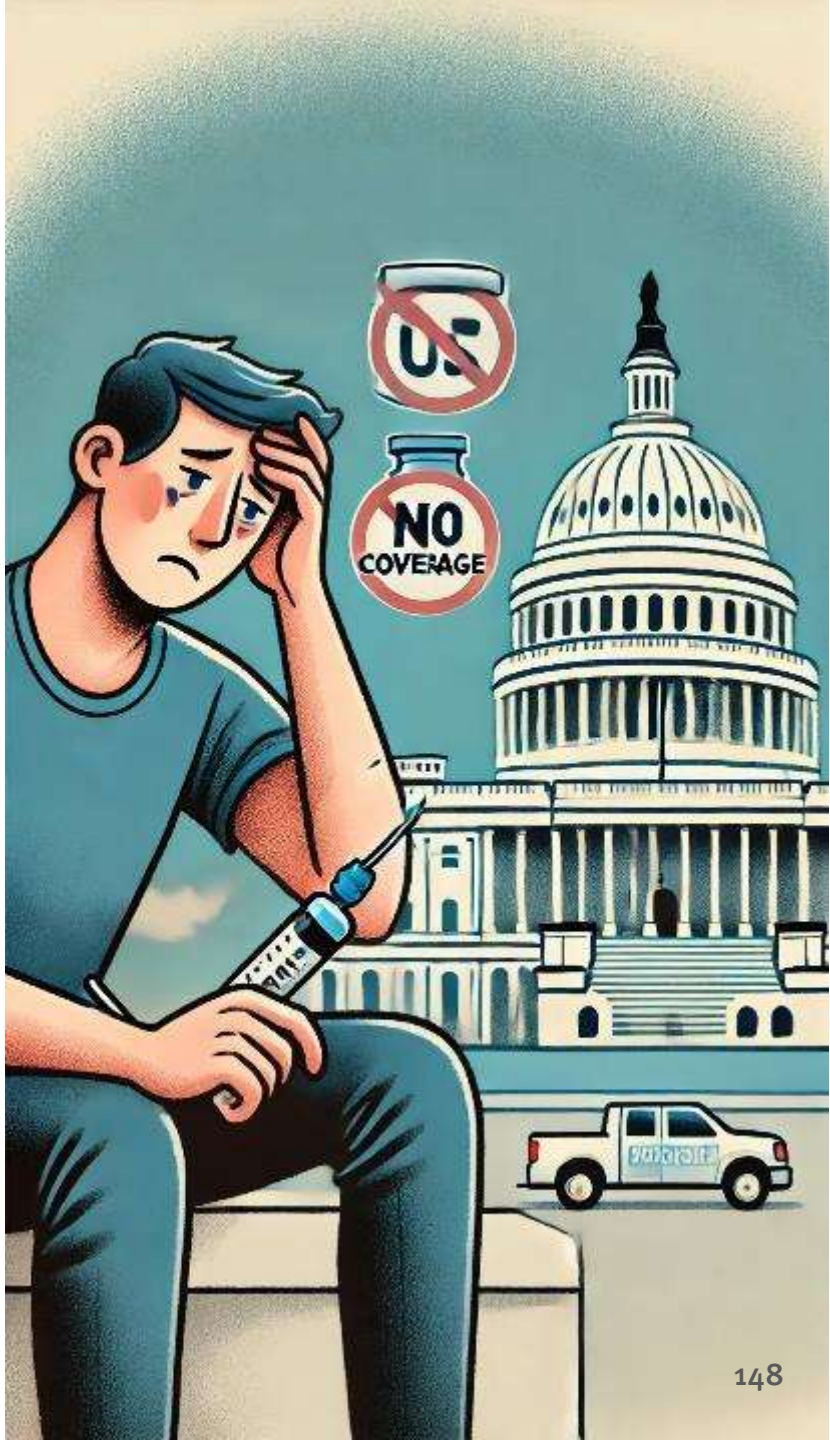
(1) The U.S. government reimbursed market
(2) The private reimbursed market

In practice, private insurers tend to take their lead from CMS reimbursement and coverage decisions, but in the case of obesity this is not possible.

The reason is that the government is legally prohibited from covering obesity drugs while private insurers are under high pressure to do so.

We spoke to a senior executive at one of the largest payors in the United States in early 2024. He described intense incoming pressure from CEOs of corporate customers to cover drugs like Wegovy® and Zepbound® but no willingness in their shop to do so. He said simply: "we don't pay people to lose weight."

We think that eventually, the U.S. government, most international governments and private payors *will* pay for obesity drugs. However, this will be an interactive process and is highly unlikely to involve a day when CMS says "darn it, Lilly and Novo – we give in. We'll give you the $6,000 a year that you want". The consequences of doing so could be quite financially costly for the payors involved given the large number of persons who are obese in the U.S. Similar logic holds for other countries where willingness to cover obesity drugs is low.*



* In Germany, interestingly, the government will consider reimbursement for GLP-1's for weight loss among the morbidly obese. However, the law prohibits private insurers from paying for obesity drugs at all. See https://www.reuters.com/business/healthcare-pharmaceuticals/german-health-ministry-insurance-coverage-weight-loss-drugs-not-agenda-2024-01-30/. The UK's NICE recommends Wegovy for weight management alongside diet and exercise and patients must have one weight-related comorbidity and a BMI over 35. Even then patients only get reimbursed for two years and must take drugs within a specialist weight management service.

What About the Rest of the Obesity Market?

So, ultimately, there will be reimbursement for GLP-1's and other drugs, but that payment is likely to be segmented based on who the patient is, what stage of therapy the patient needs (e.g., induction vs. maintenance) and the like.

We are quite aligned with the perspective expressed at right by Markus Gores of IQVIA who writes:

> "The shape of the future obesity market will be very different from today's. The intersect of these three dimensions will create a more stratified market, reflecting nuanced patient needs, different therapy goals and who pays (Figure 3)."

Most fundamentally, the private pay obesity market will be a consumer goods market. Competition on price, features and reputation will govern this market.

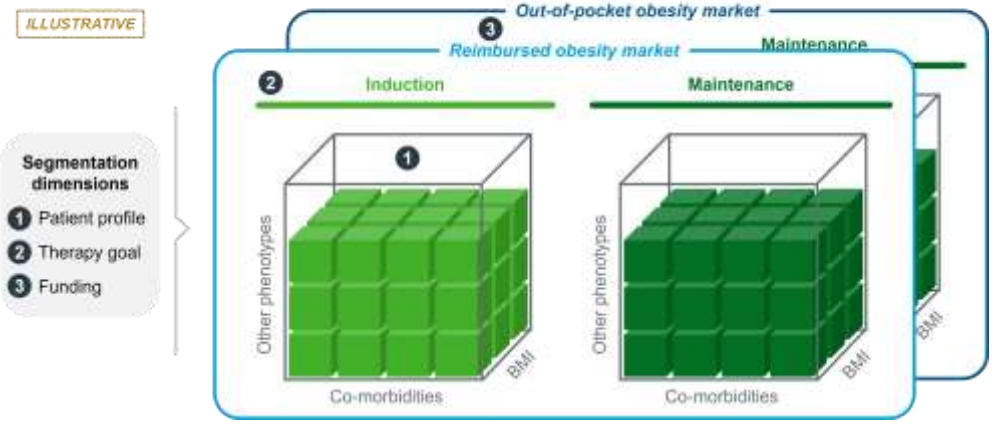
In contrast, the government and insurance-mediated markets will be governed by *value*. How much benefit do patients and payors gain from covering all or part of the payments on obesity drugs?

Whether legally done under the auspices of the IRA, there will necessarily be a conversation about how coverage decisions are made and the pharmaco-economics of coverage.

Markus Gores, IQVIA, "When the dust settles: The future shape of the obesity market," Blog Post, May 13, 2024

Figure 3

The future obesity market: more segmented



Payor Behavior and Interests in the Obesity Market

If the goal of the government is to get the most value for their patient dollar, then this behooves pharmaceutical companies to think about how to maximize the payor's benefit.

Of course, this also maps to what is good for the patient.

We would suggest a single strategy for accomplishing this?

Harm reduction.

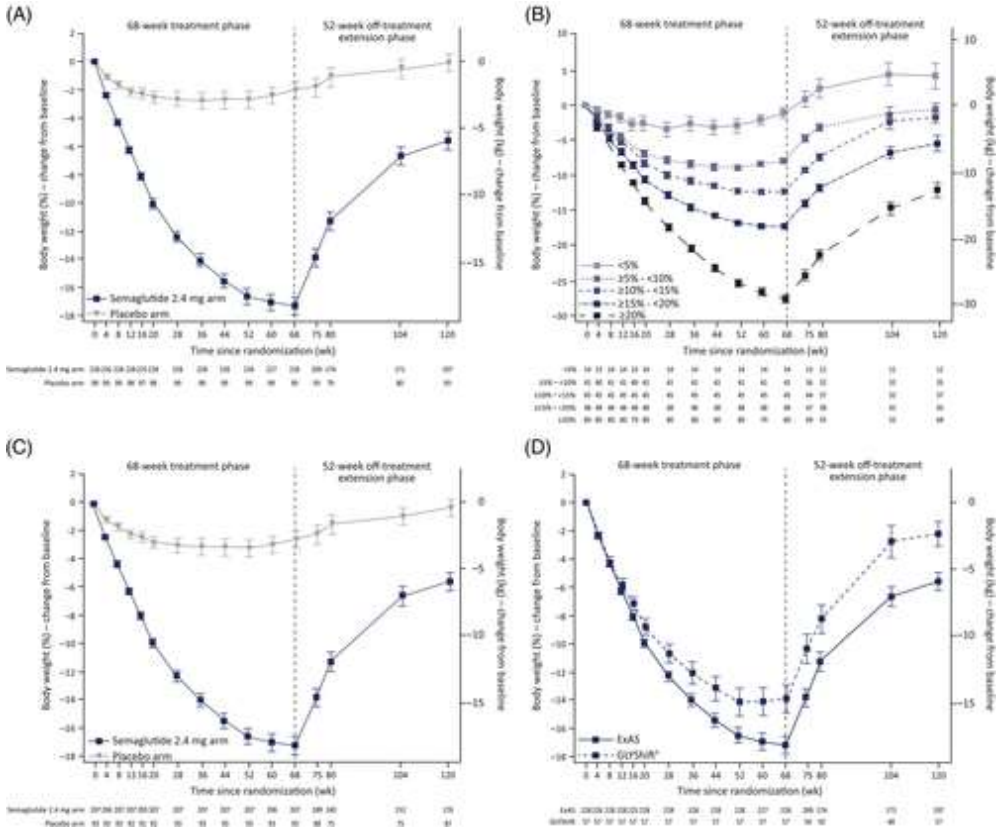
That is, how can obesity drugs (or drugs in closely related areas such as those involved in muscle augmentation) best deliver benefit to patients?

It's fair to say that there are number of obvious issues to deal with.

First, is there a way to solve the rebound problem? That is, within a few years of stopping the use of GLP-1's patients put all or most of the weight back on.

Second, is there a way to segment the obese population and identify patients *ex ante* who are most likely to be harmed by their disease?

Likewise, are there other patients who could live a full healthy life uninterrupted by chronic disease even though they are obese?



Source: https://dom-pubs.onlinelibrary.wiley.com/doi/10.1111/dom.14725

What Payors and Politicians Want in the Obesity Drug Field

One can quickly see the dichotomy between payor interests (desire to reduce morbidity/mortality and future system costs) and consumer interests (desire to weigh less no matter the benefit).

Our thought then is that in the fourth generation of the obesity market, there will be products that are designed for the healthy consumer who wishes to be thin and look thin. These products will be sold based on efficacy and consumer-relevant features such as absence of nausea and price.

These may not be the same products that garner reimbursement by payors, hence our thesis of segmentation and fragmentation of the market. On the payor mediated side of the business, there are some obvious grand scientific challenges to grapple with:

1. Is there a way to reset a person's weight "setpoint" so that after losing weight they don't put it all back on?
2. Is there a way to identify patients who will benefit most from weight loss interventions?
3. Is there a way to design interventions that deliver even greater benefit than those provided today?
4. Is there a way to use precision medicine techniques to customize the interventions to the patient so that the payor achieves maximum benefit for their dollar?

Research on the science of weight and overnutrition has been underway for more than fifty years. We don't pretend that all of these questions can be answered satisfactorily anytime soon.

Rather, as we contemplate the next several decades of progress on the obesity epidemic, we simply mean to say that these are going to be some of the main questions that will matter.

The Politics of Obesity Drugs

The Covid epidemic became a major political problem for Donald Trump who didn't handle it well. Likewise, we think the unwillingness of the government to pay for obesity drugs could eventually become the government's problem.

There are obvious issues of social justice, public health and economics that should be considered as governments around the world grapple with an important opportunity for their citizenry: the chance to slim down to healthier weights.

The rest of this report takes on the issues on this page: (1) Is there a way to change the weight setpoint that people have to avoid the rebound problem? (2) Are there opportunities for targeted harm reduction with obesity drugs and related drugs? And (3) Given the politics, how might government coverage of obesity drugs play out in the decades ahead?

Strategies to Change the Weight Setpoint

Gigantic Unmet Need: Blocking Rebound

This section is all about strategies to prevent rebound after weight loss.

Consumers, physicians and payors are all too aware that “rebound” is the most important unmet need in weight loss pharmacology.

This is such a large problem because adherence to GLP-1 agonists is not great. Thus, we see patients in a cycle where they lose weight on a drug or diet, then put it back on, lose weight again, put it back on etc.

It’s as if us human beings have a weight setpoint that our body keeps going back to.

There is an obvious need which is to design strategies that allow patients to “take it off” and “keep it off”.

The only strategy we have today for permanent weight loss is bariatric surgery. We’ve now figured out how to match bariatric surgery weight loss with a pharmaceutical. Now, we need to figure out how to match the permanence of bariatric surgery with a pharmaceutical.

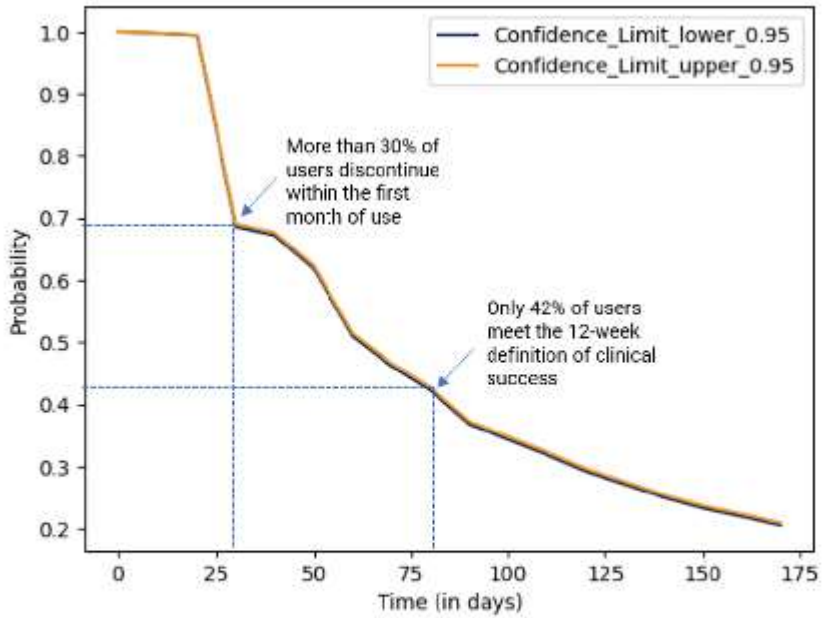
This “grand challenge” of pharmacology will obviously be difficult.

Patient Adherence to Use of GLP-1's is Far from Ideal

ISSUE BRIEF: MAY 2024

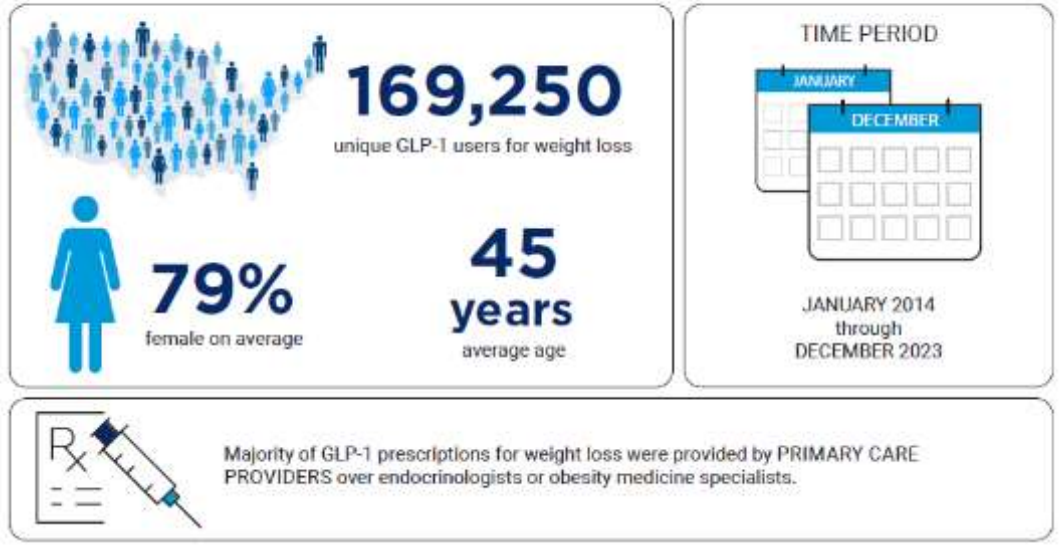
Real-World Trends in GLP-1 Treatment Persistence and Prescribing for Weight Management

Figure 5: Overall time to treatment discontinuation in GLP-1 users for weight management.

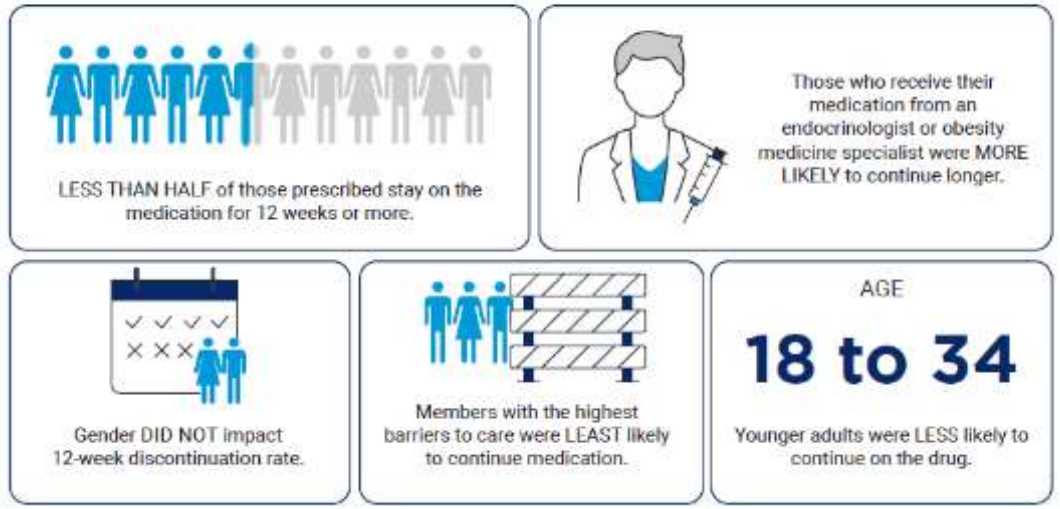


The probability of staying on a GLP-1 drug drops drastically between zero and six weeks. These individuals are not on a GLP-1 long enough to see a clinically meaningful benefit.

GLP-1 Medication for Weight Loss: Profile of Users and Prescribers



GLP-1 Medication Persistence: Factors Affecting Discontinuation



Source: https://www.bcbs.com/sites/default/files/BHI_Issue_Brief_GLP1_Trends.pdf

Weight Loss with GLP-1's is Often Not Kept Off

Dual Team Study, Epic Research, Jan 23, 2024

Proportion of Patients by Weight Change After Stopping Semaglutide (after losing 5 pounds or more in the first place)

Over half of Semaglutide users keep off the weight they lost a year after starting on the drug. Around 20% gain all the weight they lost back. But that's the first year. There is further rebound in weight later.

The amount of regain is much lower for those with very high obesity to start.

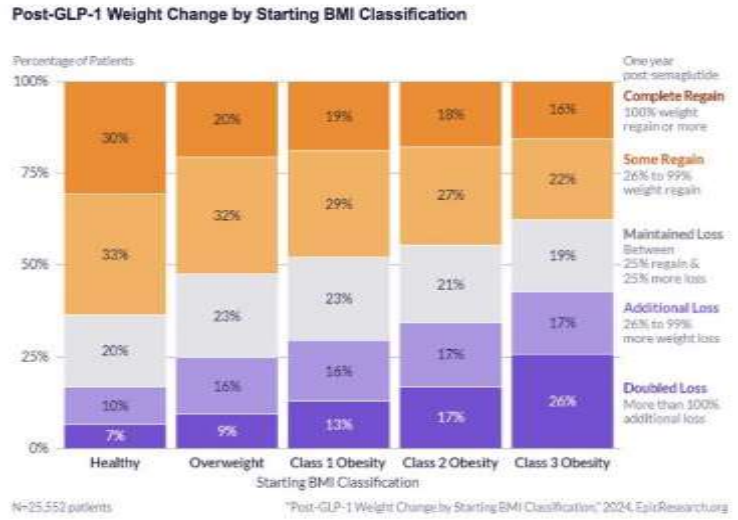
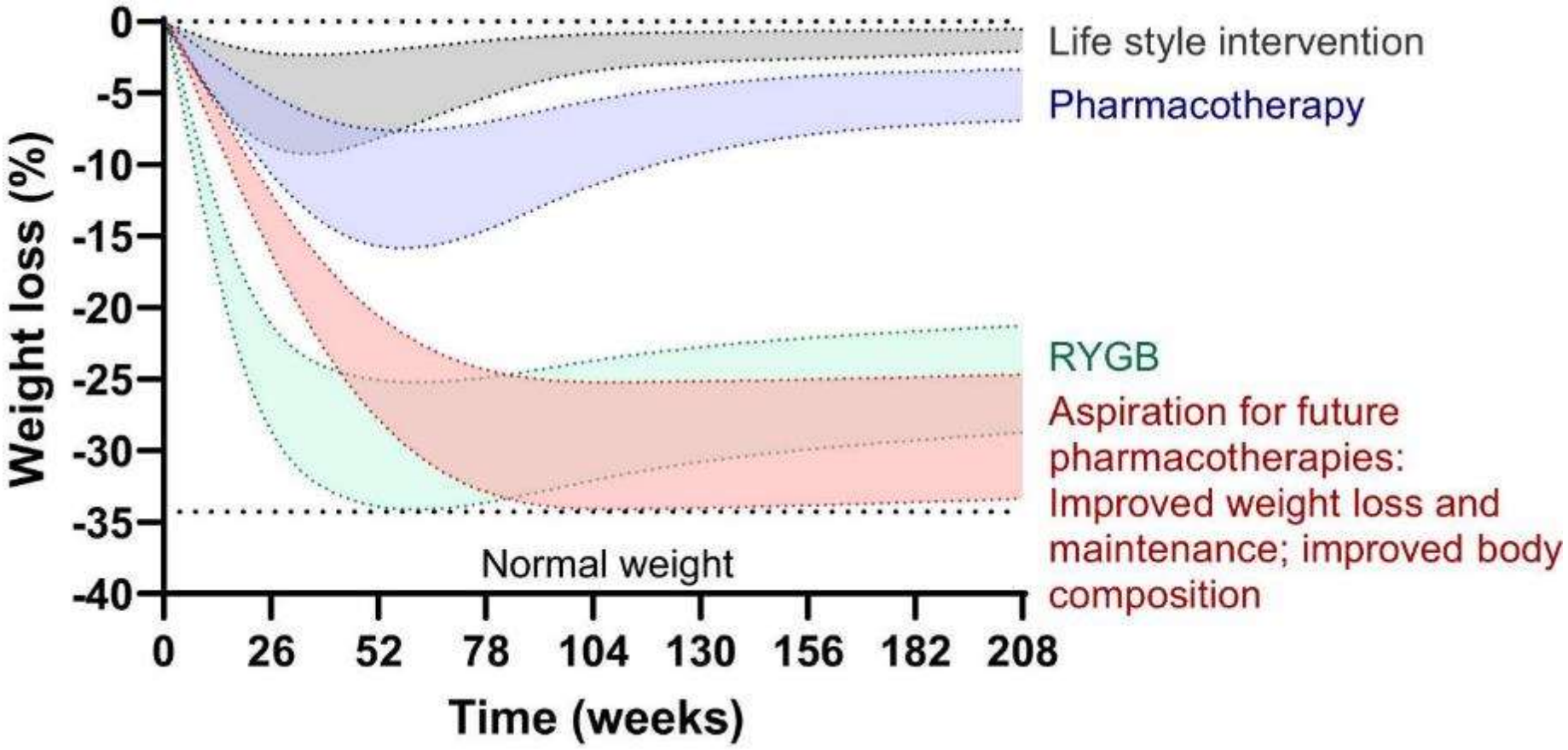


Figure 1. Weight change one year after stopping GLP-1 by starting BMI classification.

Sources: https://www.epicresearch.org/articles/many-patients-maintain-weight-loss-a-year-after-stopping-semaglutide-and-liraglutide, https://www.epicresearch.org/articles/patients-with-higher-initial-bmis-and-greater-weight-loss-while-on-glp-1s-most-likely-to-maintain-or-continue-weight-loss-after-stopping-glp-1s

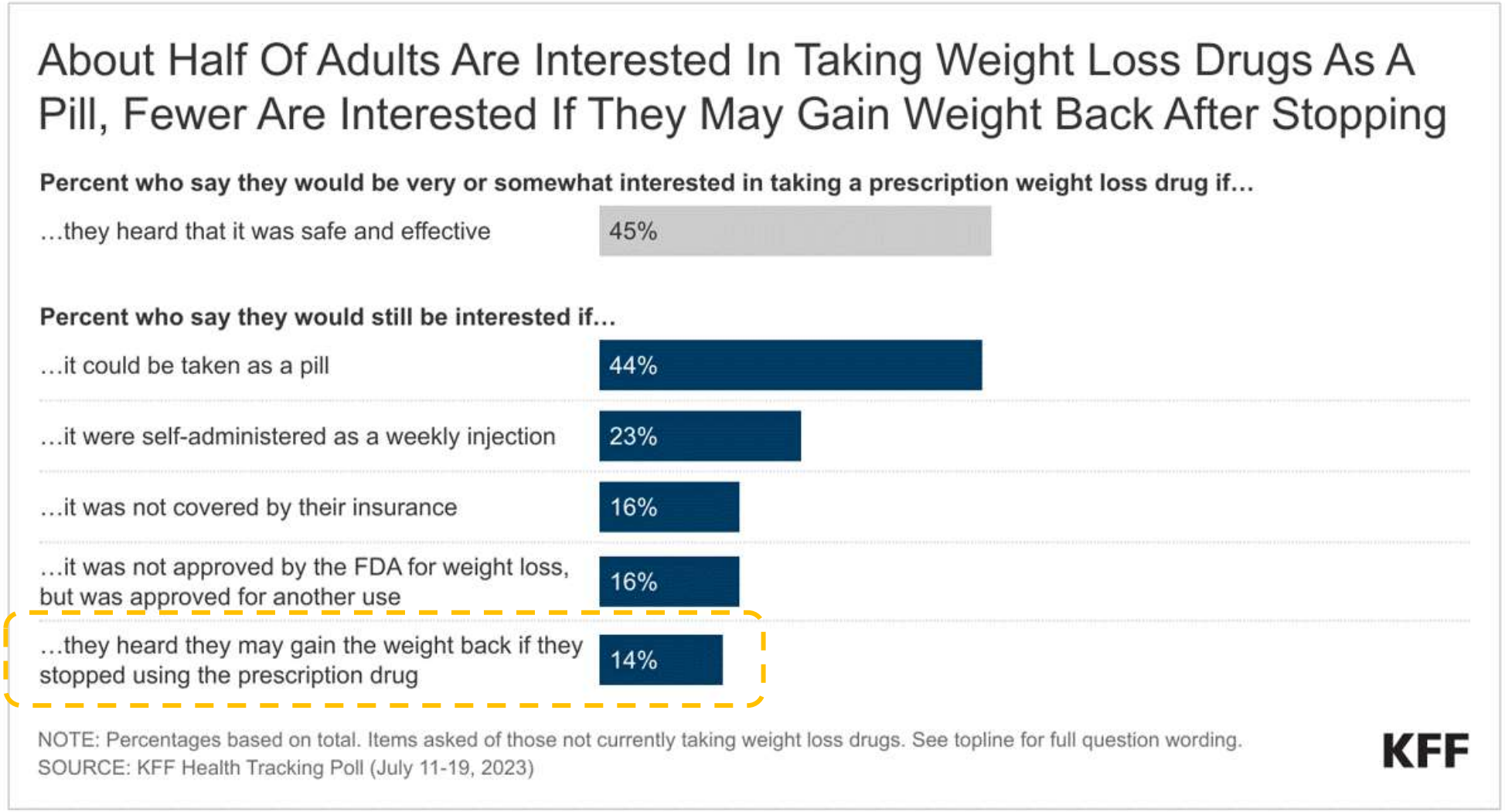
The Market Wants a Drug That Can Deliver Lasting Weight Loss

Christoffersen BØ, Sanchez-Delgado G, John LM, Ryan DH, Raun K, Ravussin E., "Beyond appetite regulation: Targeting energy expenditure, fat oxidation, and lean mass preservation for sustainable weight loss," *Obesity*, April 2022, pp. 841-857.



Source: https://onlinelibrary.wiley.com/doi/10.1002/oby.23374

KFF Poll: Weight Regain Is a Huge Issue for Those Interested in Weight Loss Drugs



Could There be a Pharmaceutical Intervention That Could Take Weight Permanently Off Without Chronic Medication?

A fourth-generation obesity solution could involve "one and done" or, at least, infrequent therapy to induce and maintain weight loss. Figuring out whether this might work needs to start with a broad root cause analysis of obesity.

The search for a permanent pharmacologic approach to weight loss is a grand challenge for academia and industry.

We would suggest that the place to start is to try to understand why some people have abnormally high weight in the first place.

Presumably, there is some root cause that needs to be fixed.

Think of the difference between gene therapy which fixes a loss of function mutation so that an enzyme can be made versus enzyme replacement therapy.

Could there be some approach that would alter the underlying cause of the disease in a permanent way. Ideally, this would be one and done.

While this might not be good for some makers of chronic drug therapies it would be great for patients and society which is saddled with the burden of obesity.

The market opportunity is obviously gigantic. If you could fix the obesity problem with a pill of some sort, the ability to charge society would be enormous.

Root Cause Theories of Obesity

A pharmacologic approach to permanent normalization of weight needs to recognize the root cause of obesity. Here are five theories of obesity causality that are found in the scientific literature.

1 Set Point Theory: There is No Hope

The set point people would tell all of us not to bother with attempts to permanently alter weight. They argue that we all have some set point for our weight and that no matter hard you might try, you will put the weight back on.

The only way to keep it off is to permanently keep your body in disequilibrium.

For example, you could stay on GLP-1 drugs for life. That should work.

Set point theorists argue that evolutionarily we are programmed to put on weight to avoid starvation and death in case of famine

2 Genetic Theory: It's Both Genes and Epigenetics

There is significant genetic influence on whether you become obese. This evidence suggests that some persons have high polygenic risk to be obese and that others do not.

This does not necessarily suggest that alteration of gene products could provide a "one and done" solution to obesity but it points towards solutions.

A separate literature points to epigenetic risk factors that are somatically alterable after birth. This helps to explain why some identical twins end up with differences in weight later in life.

3 Addiction Theory & Gut-Brain Communication

Sugars, particularly fructose, in the gut leads to brain communication that causes an addictive state. These states are augmented by life stress that is all the more common in modern society.

This theory is not necessarily incompatible with the fatty brain theory nor the set point theory.

Sugar addiction could be the root cause of fatty brain. The hedonic desire of the brain to continue to gather abnormal amounts of food can turn into DSM-IV addiction. A number of therapeutic options are possible.

4 Fatty Brain Theory

The fatty brain theorists indicate that there is something that happens in the brain of some people that causes their minds to want to be fat.

The idea is that environment or perhaps genetics lead some people to weigh more. These factors regulate the hypothalamus's normal "set point" factors to be heavier or lighter.

There is substantial evidence linking dopaminergic and glutaminergic neurotransmitters to weight and this may be a key validating part of the "fatty brain hypothesis".

5 Adipocyte Theory: It's Lipolysis & Oxidation

Obese people tend to metabolically adapt to higher levels of fat stores. When they lose weight, those adaptations do not necessarily disappear leading to an "obese memory" that makes it difficult to keep weight off.

There is reasonably convincing evidence that obese people tend to oxidize fat less and, also, have lower rates of lipolysis than normal weight persons. This tends to stay even after weight loss.

There are a number of emerging strategies that could help fix this memory.

Some Background Factors to Consider

Obesity rates have risen rather quickly across OECD countries since the 1980s

Among major countries, obesity is highest in the United States

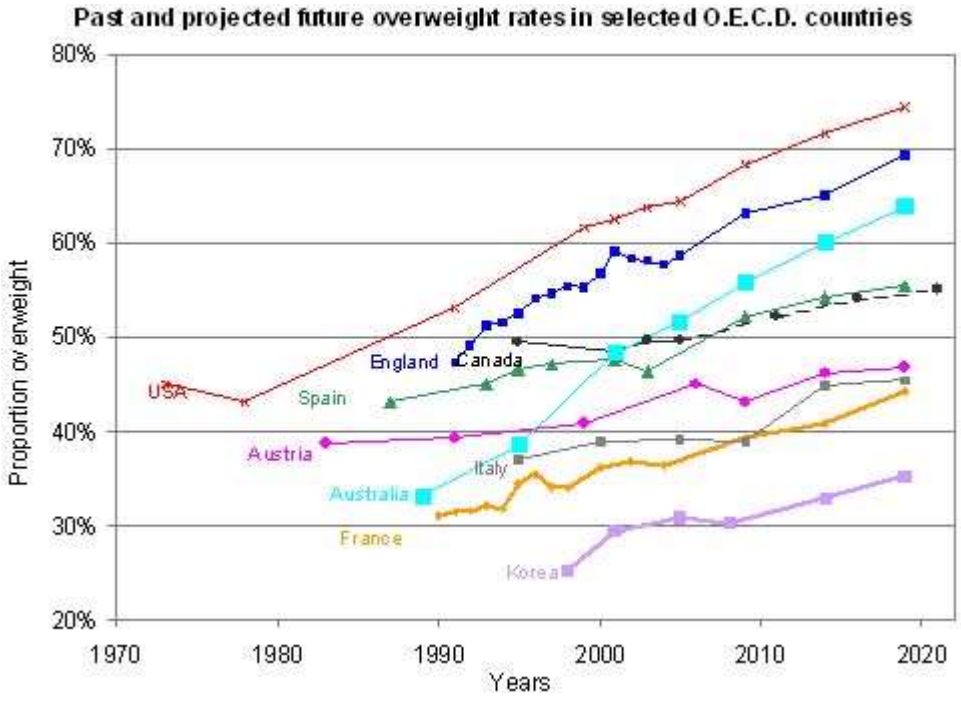
Obesity rates are rising fastest among adolescents and their health is not great

Obesity rates are higher, on average, in the U.S. among the poor and among ethnic minorities

In less wealthy countries, obesity rates are higher among the wealthy

Difference in obesity among identical twins point to genetic factors as relevant in weight

Bariatric Surgery generally results in permanent weight loss

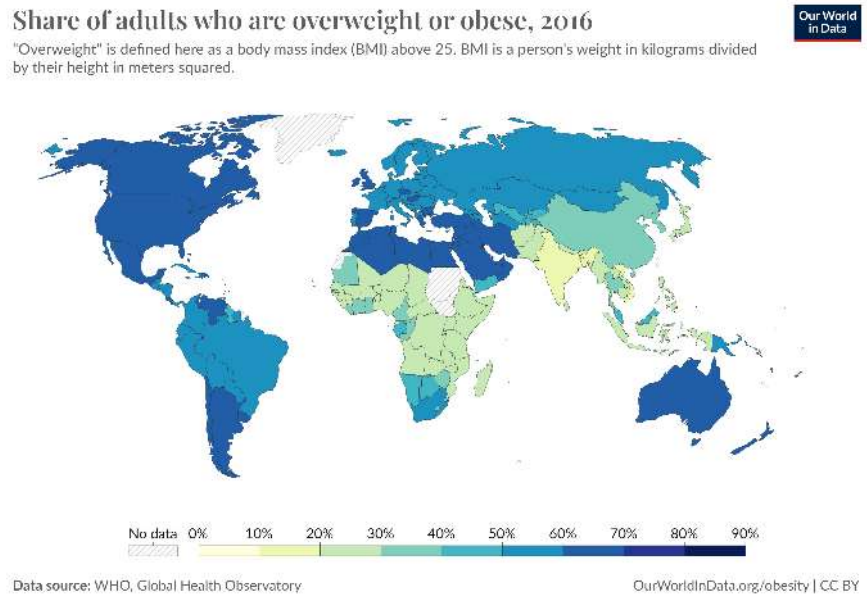


Source: https://archive.nytimes.com/economix.blogs.nytimes.com/2010/09/23/the-world-is-fat/

Human Behavioral Ecology Theory Helps Explain Obesity Differentials by Wealth

Bentley, R.A., Ormerod, P. & Ruck, D.J. Recent origin and evolution of obesity-income correlation across the United States. Palgrave Commun 4, 146 (2018).

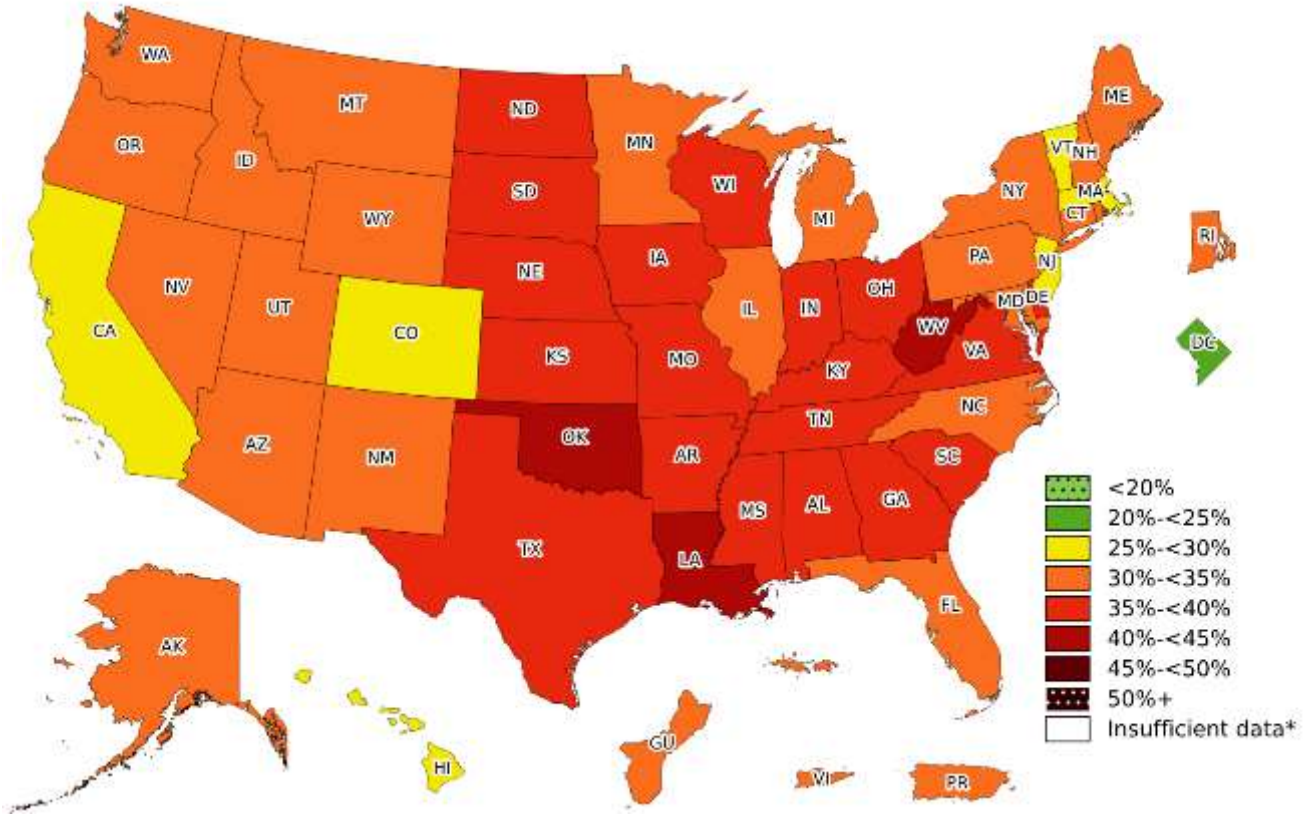
Cultural evolution potentially offers a less proximate, more ultimate explanation for the recent rise in obesity. Evolutionary approaches to behavioral change include human behavioral ecology and cultural evolutionary theory; the former tends to prioritize optimality of adaptive behavior while the latter tends to prioritize social learning. Generally speaking, human behavioral ecology (HBE) emphasizes the plasticity of human physiology and behavior, by which individuals minimize risk to survival and optimize their long-term reproductive payoffs (Higginson et al., 2017). As wealth mitigates survival risk, HBE predicts a positive correlation between BMI and wealth, as humans have evolved to store calories as insurance against future famine or food shortage (Shrewsbury and Wardle, 2012; Higginson et al., 2017; Tapper, 2017). In the poorest 80% of the world's societies, body mass index (BMI) generally increases with household wealth (Subramanian et al., 2011)—except below about 400 USD per capita, when poverty is such that BMI is uniformly low (Hruschka et al., 2014). **In high-income countries, HBE predicts greater obesity among the poor, partly because humans have evolved behavioral "rules" that lead to overeating in rich environments and partly because poorer people have more immediate risks and concerns than outweigh long-term mortality risk of being obese** (Dittmann and Maner, 2017; Dohle and Hafmann, 2017; Higginson et al., 2017; Mani et al., 2013; Smith, 2017).



Source: https://www.nature.com/articles/s41599-018-0201-x

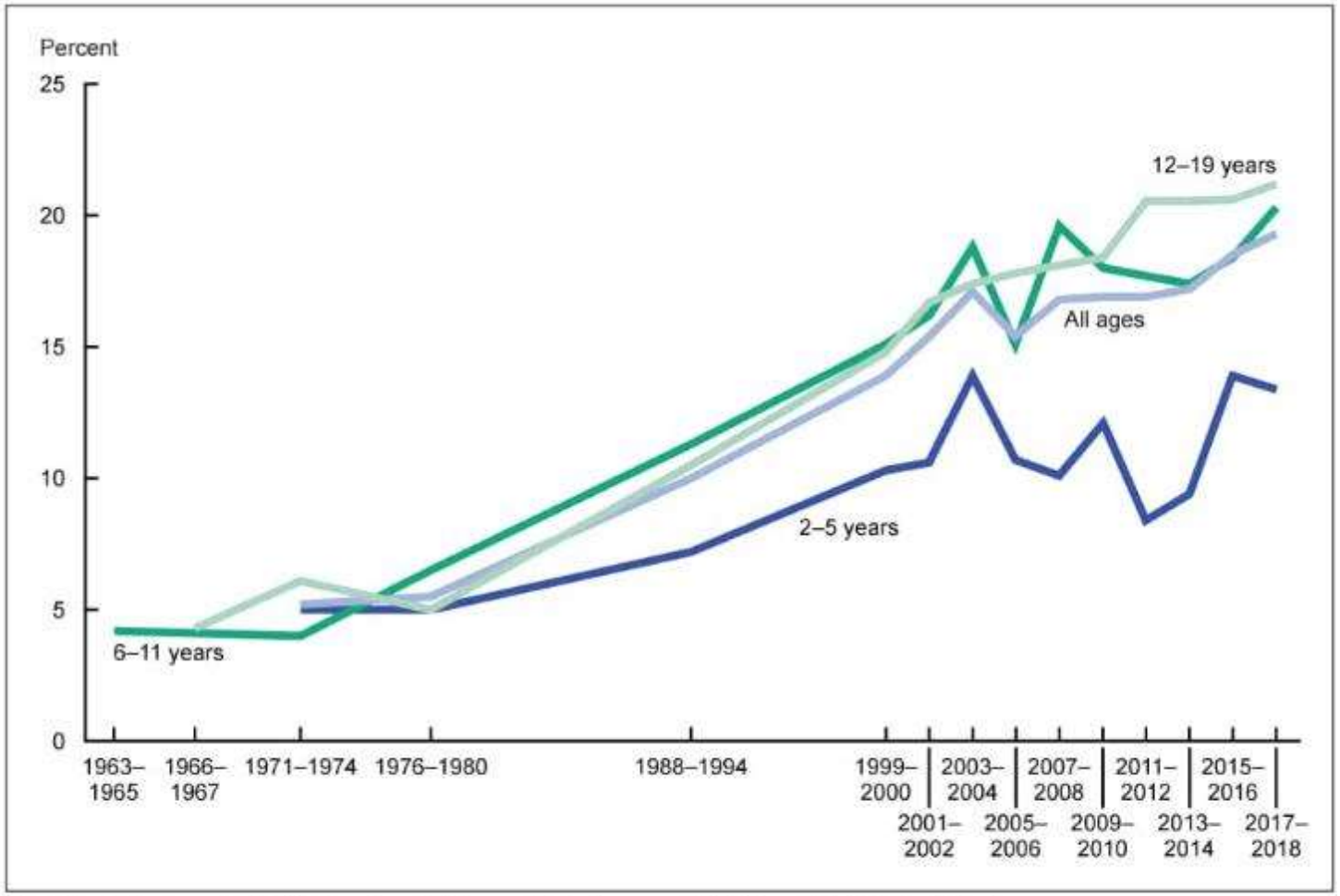
State Level Obesity Data in the U.S. Support Human Behavioral Ecology Theory

CDC data for 2022 show highest obesity rates in less wealthy states.

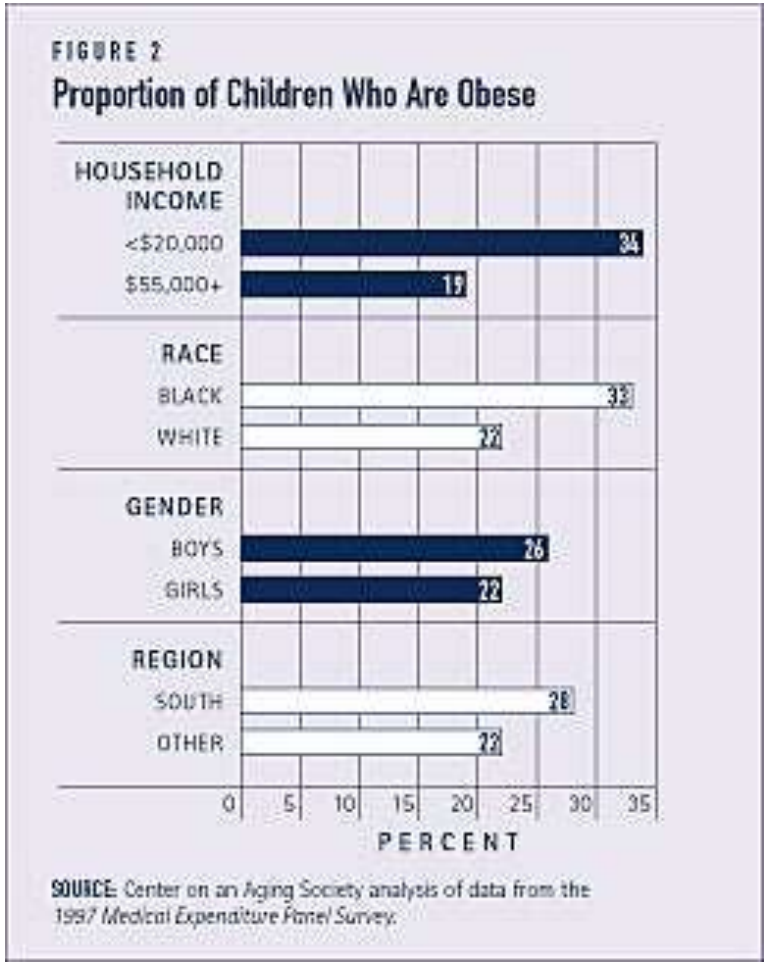


Source: https://www.cdc.gov/obesity/php/data-research/adult-obesity-prevalence-maps.html

CDC: Adolescent Obesity Has Quadrupled Since 1965. Most Common Among Poor, Minorities and Those in South



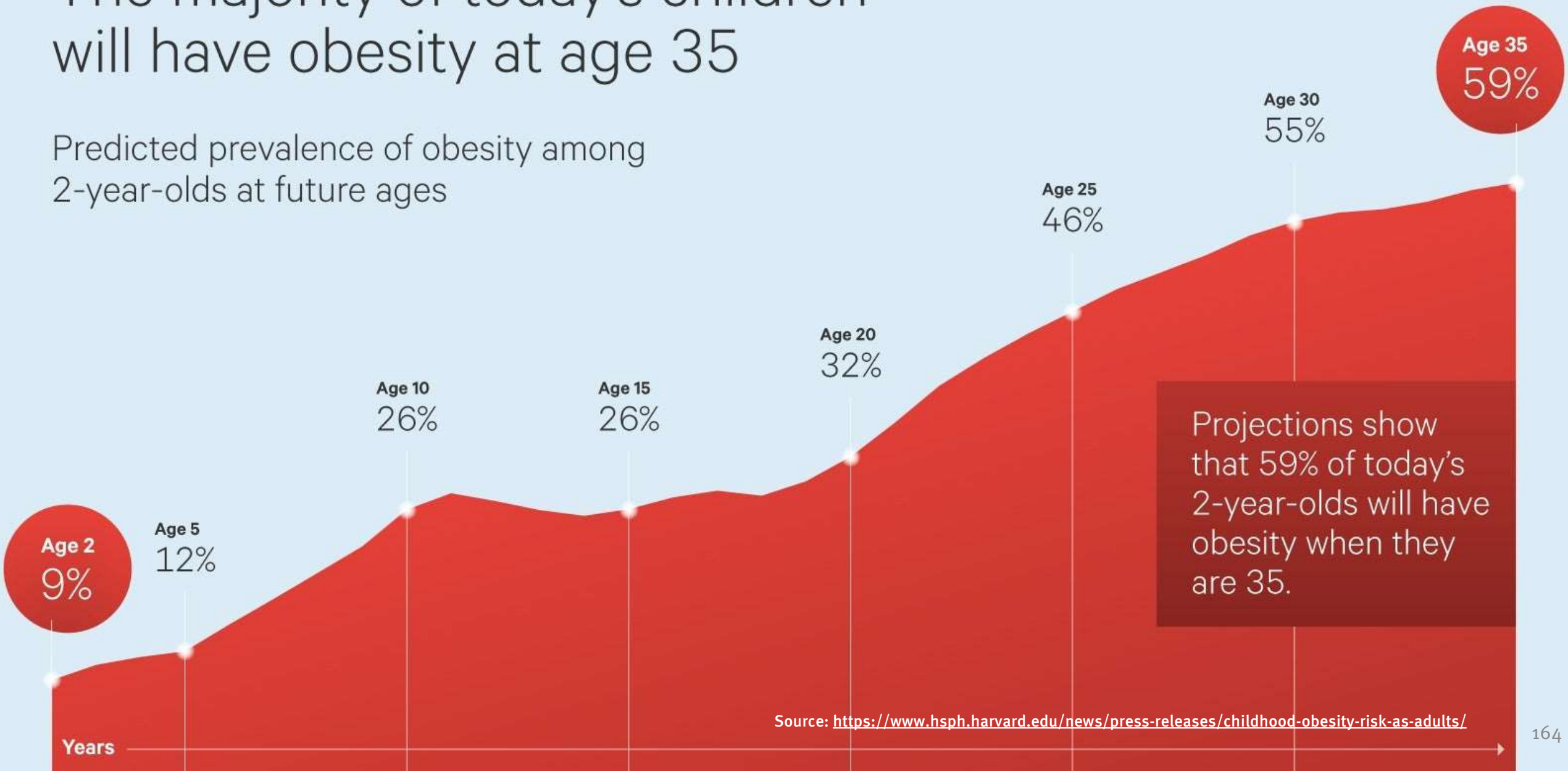
NOTE: Obesity is body mass index (BMI) at or above the 95th percentile from the sex-specific BMI-for-age 2000 CDC Growth Charts.
SOURCES: National Center for Health Statistics, National Health Examination Surveys II (ages 6–11), III (ages 12–17), and National Health and Nutrition Examination Surveys (NHANES) I–III, and NHANES 1999–2000, 2001–2002, 2003–2004, 2005–2006, 2007–2008, 2009–2010, 2011–2012, 2013–2014, 2015–2016, and 2017–2018.



Sources: https://www.cdc.gov/nchs/data/hestat/obesity-child-17-18/obesity-child.htm, https://hpi.georgetown.edu/obesity/

The majority of today's children will have obesity at age 35

Predicted prevalence of obesity among 2-year-olds at future ages

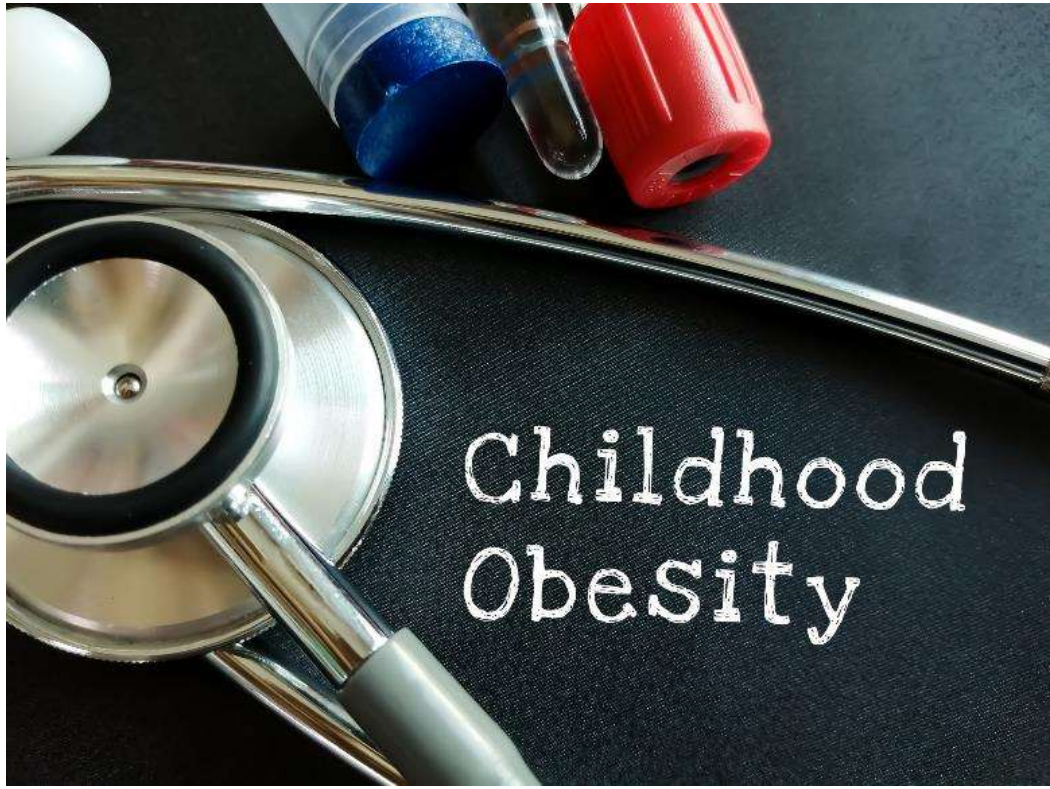


Source: https://www.hsph.harvard.edu/news/press-releases/childhood-obesity-risk-as-adults/

Childhood Obesity Linked to Heart Disease Later in Life

Nadeau, K., Maahs, D., Daniels, S. et al. Childhood obesity and cardiovascular disease: links and prevention strategies. *Nat Rev Cardiol* 8, 513–525 (2011).

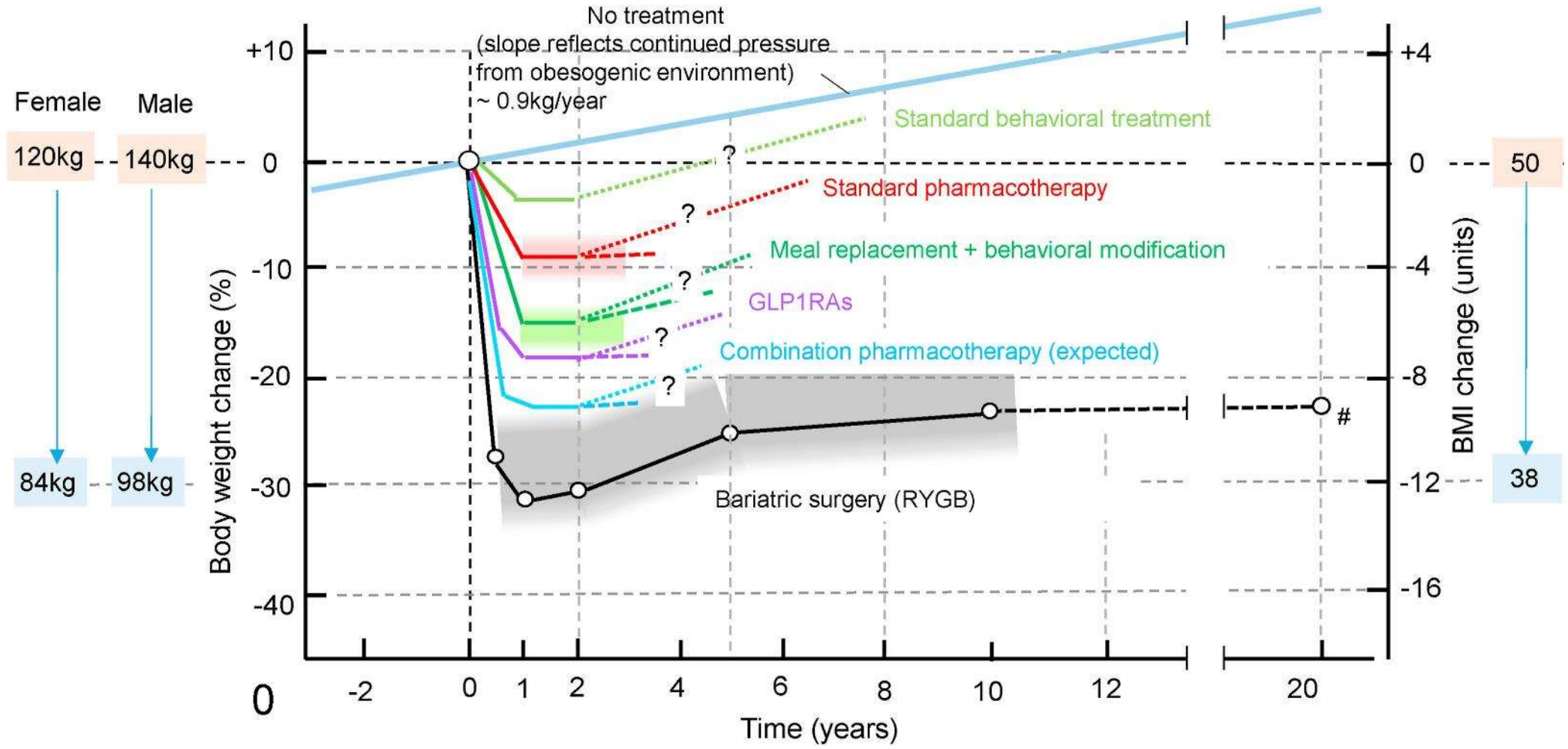
The prevalence and severity of pediatric obesity have dramatically increased since the late 1980s, raising concerns about a subsequent increase in cardiovascular outcomes. Strong evidence, particularly from autopsy studies, supports the concept that precursors of adult cardiovascular disease (CVD) begin in childhood, and that pediatric obesity has an important influence on overall CVD risk. Lifestyle patterns also begin early and impact CVD risk. In addition, obesity and other CVD risk factors tend to persist over time. However, whether childhood obesity causes adult CVD directly, or does so by persisting as adult obesity, or both, is less clear. Regardless, sufficient data exist to warrant early implementation of both obesity prevention and treatment in youth and adults. In this Review, we examine the evidence supporting the impact of childhood obesity on adult obesity, surrogate markers of CVD, components of the metabolic syndrome, and the development of CVD. We also evaluate how obesity treatment strategies can improve risk factors and, ultimately, adverse clinical outcomes.



Source: https://www.nature.com/articles/nrcardio.2011.86

Bariatric Surgery is Most Effective at Keeping Weight Off

Albaugh et. al., "Regulation of body weight: Lessons learned from bariatric surgery," *Molecular Metabolism*, Feb 2023.



Source: https://www.sciencedirect.com/science/article/pii/S2212877822000862

Fractyl is One of the Few Companies Working on the Rebound Problem

Press Release: "Fractyl Health Presents New Preclinical Data on Sustained Weight Maintenance and Improved Body Composition from its Rejuva® Single-Administration GLP-1 Pancreatic Gene Therapy in President's Select Oral Presentation at the American Diabetes Association's 84th Scientific Sessions," June 23, 2024

BURLINGTON, Mass., June 23, 2024 (GLOBE NEWSWIRE) -- Fractyl Health, Inc. (Nasdaq: GUTS) (the "Company"), a metabolic therapeutics company focused on pioneering new approaches for the treatment of obesity and type 2 diabetes (T2D), today presented new data from its preclinical Rejuva pancreatic gene therapy program in an oral presentation at the American Diabetes Association (ADA)'s 84th Scientific Sessions in Orlando, FL.

Rejuva is the Company's adeno-associated virus (AAV)-based GLP-1 pancreatic gene therapy program (PGTx), designed to enable durable production of GLP-1 in the pancreas for the treatment of obesity and T2D. The study presented at ADA compared the effects of a single dose of Rejuva and daily semaglutide treatment on body composition and glycemic parameters in the well-validated mouse model of diet-induced obesity (DIO). It also examined the effects of single-dose Rejuva in the DIO mice after semaglutide was discontinued.

"These data demonstrate that Rejuva can durably improve body composition and fasting glucose, compared to or better than semaglutide, by restoring GLP-1 production in a 'one-and-done' treatment," said Harith Rajagopalan, M.D., Ph.D., co-founder and Chief Executive Officer of Fractyl. "These data also show Rejuva could help maintain improvements after semaglutide is withdrawn, highlighting our therapy's potential to fill an emerging and critical need in the management of obesity and T2D: a reliable, 'off ramp' from chronic GLP-1 drugs that allows people to maintain the weight loss and blood sugar benefits, even as they stop taking these medicines."

At week 4, the Rejuva arm experienced reduced fat mass of 21% versus 16% of body weight with semaglutide (both $p<0.0001$ versus placebo, $p<0.05$ Rejuva versus semaglutide) while both Rejuva and semaglutide preserved lean mass with a loss of only 5% of body weight (both, $p<0.0001$ versus placebo). **At week 8, fat mass rebounded to 1% below baseline (n.s.) in the semaglutide withdrawal group (Arm 2a), whereas semaglutide-withdrawn mice treated with Rejuva (Arm 2b) maintained fat reduction of 17% ($p<0.01$) and weight loss of 22% ($p<0.0001$) at week 8.**

Source: https://www.globenewswire.com/news-release/2024/06/23/2902704/0/en/Fractyl-Health-Presents-New-Preclinical-Data-on-Sustained-Weight-Maintenance-and-Improved-Body-Composition-from-its-Rejuva-Single-Administration-GLP-1-Pancreatic-Gene-Therapy-in-Pr.html

1

Why Do So Many People Regain Weight After Dieting? Set-Point Theory

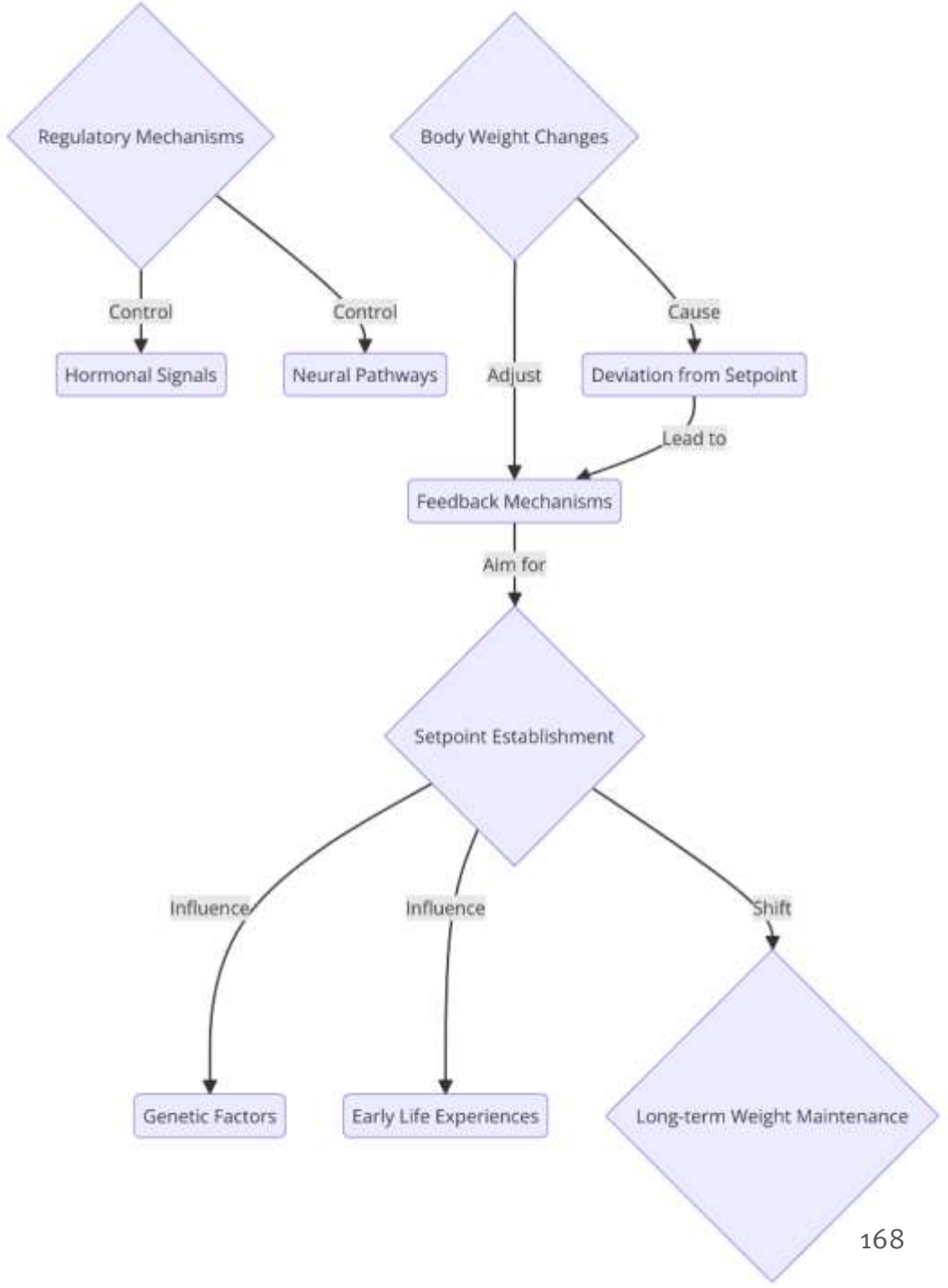
Venu Ganipisetti and Pratyusha Bollimunta, Baystate Health, 2023

“The set-point theory is related to homeostasis. The theory posits that the human body has a predetermined weight or fat mass set-point range. Various compensatory physiological mechanisms maintain that set point and resist deviation from it. Feedback systems are vital in driving the body weight back toward the set point. In 1953, Kennedy proposed that body fat storage is regulated.

In 1982, nutritional researchers William Bennett and Joel Gurin expanded on Kennedy's concept when they developed the set-point theory.

Notably, the rate at which one regains weight following weight loss is considerably high, with over 80% of individuals eventually regaining the weight they lost.

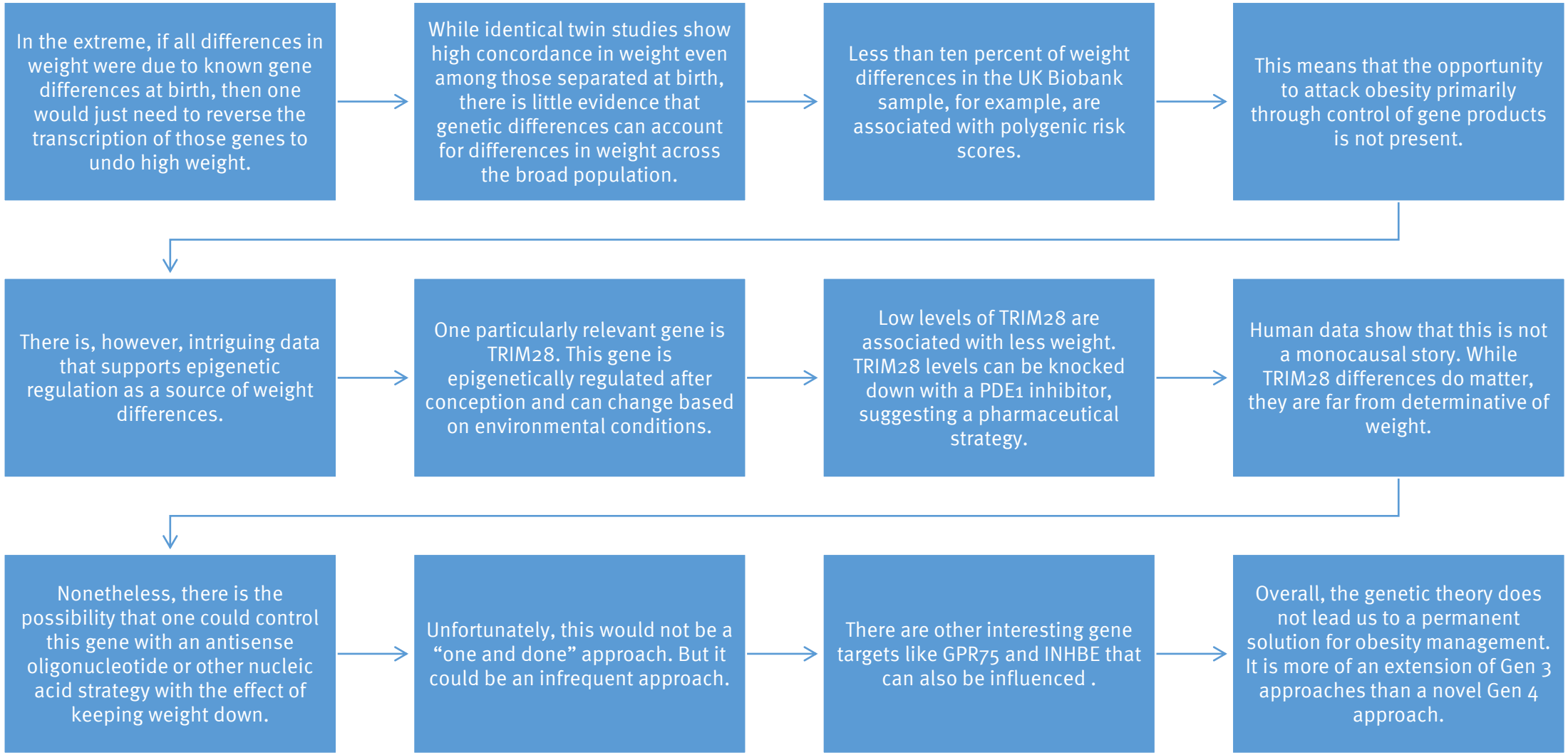
The set-point theory may explain the high incidence of regained weight. When an individual loses weight, the body triggers increased appetite through modulation of satiety hormones, altered food preferences through behavioral changes, and overcompensated reduction in metabolism to drive the body weight back toward the set-point range. On the other hand, weight gain also triggers compensatory mechanisms, but these are weaker than those protecting weight loss. This asymmetry could be due to the evolutionary advantage of storing fat for survival during prolonged caloric restriction periods.”



Source: https://www.ncbi.nlm.nih.gov/books/NBK592402/

Obesity and Genetics

2 Genetic Theory of Obesity



Identical Twin Studies and Obesity

Sylvia Karasu, Twin Studies and the "Heritage of Corpulence", *Psychology Today*, June 22, 2019

In their classic twin study, Stunkard et al (NEJM, 1990) evaluated 93 pairs of identical twins reared apart (one of the most effective means of determining the importance of shared genes from that of a shared environment); 154 pairs of identical twins reared together; 218 pairs of fraternal twins reared apart, and 208 pairs of fraternal twins reared together, all of whom were from the Swedish Registry that combined twin studies with adoption studies. Twins were evaluated in their late 50s, with 60% women. The researchers noted, though, that even when twins are reared apart, they can resemble each other if their rearing environments are similar (e.g. if twins were placed "selectively" in homes that tended to resemble those of their biological parents.) Of those twins who were separated from their biological parents, almost half of the twins were separated in the first year of life, often due to death, disease, or financial hardship in the family of origin. Stunkard et al found strong evidence for the influence of heredity on BMI, and they found that genetic influences extend across all weight categories, i.e., from those thin to those obese. They also noted that identical twins reared apart had intra-pair correlation coefficients of 0.70 for men and 0.66 for women for BMI and concluded in this study that childhood environments had little or even no influence. They do caution, though, "heritability does not imply an invariant, immutable genetic influence," but rather genetic influences under certain environmental conditions. (Stunkard et al, 1990)

Table 1. Body-Mass Index and Intrapair Correlations in Monozygotic and Dizygotic Pairs of Twins Reared Apart or Together.*

Type	Men			Women		
	No. of Pairs	Body-Mass Index	Intrapair Correlation	No. of Pairs	Body-Mass Index	Intrapair Correlation
Monozygotic						
Reared apart	49	24.8±2.4	0.70	44	24.2±3.4	0.66
Reared together	66	24.2±2.9	0.74	88	23.7±3.5	0.66
Dizygotic						
Reared apart	75	25.1±3.0	0.15	143	24.9±4.1	0.25
Reared together	89	24.6±2.7	0.33	119	23.9±3.5	0.27

*Plus–minus values are means ±SD.

Source: https://www.psychologytoday.com/ca/blog/the-gravity-weight/201906/twin-studies-and-the-heritage-corpulence, https://www.nejm.org/doi/full/10.1056/NEJM199005243222102

› Int J Obes Relat Metab Disord. 1999 Jul;23(7):746-53. doi: 10.1038/sj.ijo.0800923.

Environmental factors in the development of obesity in identical twins

P Hakala [1], A Rissanen, M Koskenvuo, J Kaprio, T Rönnemaa

Affiliations + expand

PMID: 10454109 DOI: 10.1038/sj.ijo.0800923

Abstract

Objective: To study environmental factors promoting obesity when genetic factors are identical.

Design: Monozygotic (MZ) twins discordant for overweight were examined during a 3-day stay in an inpatient setting.

Subjects: The subjects were selected from the Finnish Twin Cohort. The study sample consisted of 23 healthy adult MZ twin pairs (14 female, nine male) with a difference of at least 3 kg/m2 in BMI. The mean BMI was 29.5 kg/m2 for the overweight twins and 22.9 kg/m2 for their lean co-twins.

Measurements: Interviews and standardized questionnaires were used to obtain information about energy and nutrient intake, eating behaviour, physical activity history, smoking and other background factors.

Results: The overweight co-twins had higher disinhibition scores (P = 0.007) and hunger scores (P = 0.005) in the 3-Factor Eating Questionnaire than their lean co-twins. Among women the mean daily energy intake was higher in the overweight twins than in their lean co-twins (8.8 vs 7.4 MJ; P = 0.045). In the twins discordant for smoking the mean BMI was higher in non-smokers than in smokers (BMI 29.7 +/- 4.4kg/m2 vs 23.8 +/- 3.1 kg/m2; P = 0.031).

Conclusions: Difficulty in controlling eating in both sexes and high energy intake in women were related to overweight, independent of genetic background. Smoking explained the BMI difference among smoking discordant pairs. It is probable that individual twin pairs had different reasons behind the variation in weight gain resulting in non-significant intrapair differences in single obesity-promoting factors. Difference in living conditions (e.g. family-and work-related factors) may have promoted different living habits, especially eating behaviour, and may have led to different weight gain in identical twins.

Not all identical twins weight the same. Differences in weight are linked to the ability to control eating and smoking.

Source: https://pubmed.ncbi.nlm.nih.gov/10454109/

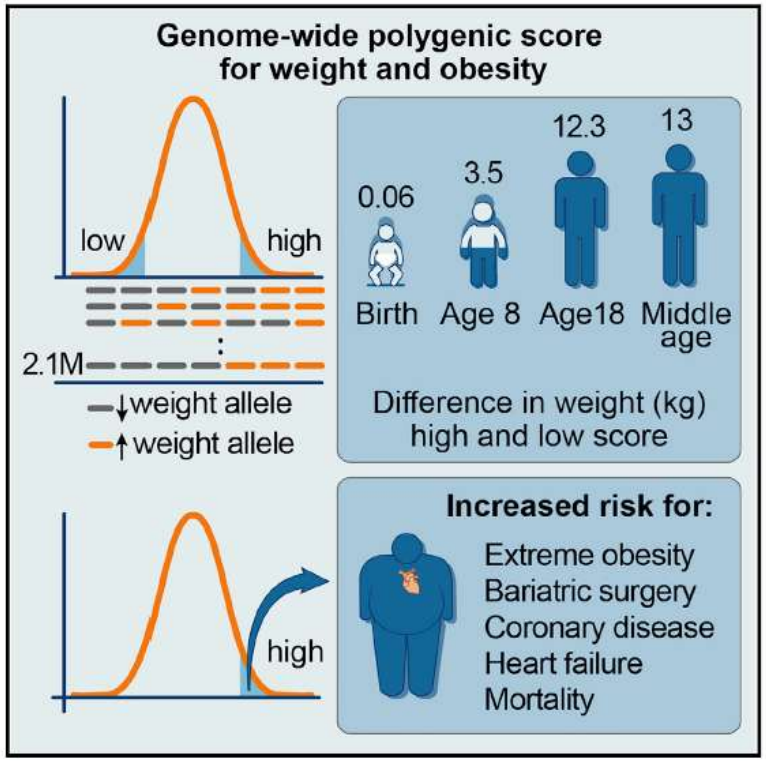
Polygenic Risk Scores are Relevant in Explaining Obesity…

Article

Cell

Polygenic Prediction of Weight and Obesity Trajectories from Birth to Adulthood

Graphical Abstract



Authors

Amit V. Khera, Mark Chaffin, Kaitlin H. Wade, ..., Nicholas J. Timpson, Lee M. Kaplan, Sekar Kathiresan

Correspondence

avkhera@mgh.harvard.edu (A.V.K.), skathiresan1@mgh.harvard.edu (S.K.)

In Brief

A genome-wide polygenic score quantifies inherited susceptibility to obesity, integrating information from 2.1 million common genetic variants to identify adults at risk of severe obesity.

Source: https://www.cell.com/cell/fulltext/S0092-8674(19)30290-9

Severe obesity is a rapidly growing global health threat. Although often attributed to unhealthy lifestyle choices or environmental factors, obesity is known to be heritable and highly polygenic; the majority of inherited susceptibility is related to the cumulative effect of many common DNA variants. Here we derive and validate a new polygenic predictor comprised of 2.1 million common variants to quantify this susceptibility and test this predictor in more than 300,000 individuals ranging from middle age to birth. **Among middle-aged adults, we observe a 13-kg gradient in weight and a 25-fold gradient in risk of severe obesity across polygenic score deciles.** In a longitudinal birth cohort, we note minimal differences in birthweight across score deciles, but a significant gradient emerged in early childhood and reached 12 kg by 18 years of age. This new approach to quantify inherited susceptibility to obesity affords new opportunities for clinical prevention and mechanistic assessment.

… But Polygenic Risk Scores Far from Determinative in Explaining Cross-Sectional Obesity

Khera AV, Chaffin M, Wade KH, Zahid S, Brancale J, Xia R, Distefano M, Senol-Cosar O, Haas ME, Bick A, Aragam KG, Lander ES, Smith GD, Mason-Suares H, Fornage M, Lebo M, Timpson NJ, Kaplan LM, Kathiresan S. Polygenic Prediction of Weight and Obesity Trajectories from Birth to Adulthood. *Cell*. 2019 Apr 18;177(3):587-596.e9.

Table S3. Association of genome-wide polygenic score with BMI in participants stratified by age, Related to Figure 1

The 288,016 UK Biobank testing dataset participants were stratified into 6 strata based on age at time of enrollment, and the Pearson correlation with BMI calculated in each.

Age	Number of participants	Pearson Correlation
< 45 years	27,465	0.307
≥ 45 and < 50 years	35,724	0.302
≥ 50 and < 55 years	42,225	0.302
≥ 55 and < 60 years	51,906	0.290
≥ 60 and < 65 years	72,675	0.281
≥ 65 years	58,021	0.278

Most of population variation in weight is not related to genetic differences.

Source: https://pubmed.ncbi.nlm.nih.gov/31002795/

Genes Alone Have Only Moderate Explanatory Power of Actual Obesity

ASSOCIATION STUDIES ARTICLE *Human Molecular Genetics*, 2018, Vol. 27, No. 20 3641–3649

Meta-analysis of genome-wide association studies for height and body mass index in ~700 000 individuals of European ancestry

Loic Yengo[1,*], Julia Sidorenko[1,2], Kathryn E. Kemper[1], Zhili Zheng[1], Andrew R. Wood[3], Michael N. Weedon[3], Timothy M. Frayling[3], Joel Hirschhorn[4], Jian Yang[1,5], Peter M. Visscher[1,5] and the GIANT Consortium

[1]Institute for Molecular Bioscience, The University of Queensland, Australia, [2]Estonian Genome Center, Institute of Genomics, University of Tartu, Estonia, [3]Genetics of Complex Traits, University of Exeter Medical School, University of Exeter, UK, [4]Broad Institute, USA and [5]Queensland Brain Institute, The University of Queensland, Australia

Table 2. Number, percentage of variance explained and accuracy of genetic predictors from SNPs found associated ($P < 10^{-8}$) with height or BMI in a random sample of 250 000 unrelated participants of the UKB

	Height		BMI	
	Random sample from UKB	Wood et al. (5)	Random sample from UKB	Locke et al. (6)
Number of near-independent genome-wide significant SNPs (GWS; GCTA $P < 10^{-8}$)	850	594	160	82
Variance explained by GWS	14.0%	12.8%	2.3%	1.8%
Prediction accuracy (r^2)	14.0%	10.9%	2.5%	1.8%

For comparison, similar statistics are reported from GWAS-hits identified in (6) and the Bonferroni-corrected (squared correlation coefficient between genetic predictors and traits) and variance explained (estimated using GCTA software) is assessed in 8552 unrelated participants of the HRS.

Recent genome-wide association studies (GWAS) of height and body mass index (BMI) in ~250 000 European participants have led to the discovery of ~700 and ~100 nearly independent single nucleotide polymorphisms (SNPs) associated with these traits, respectively. Here we combine summary statistics from those two studies with GWAS of height and BMI performed in ~450 000 UK Biobank participants of European ancestry. Overall, our combined GWAS meta-analysis reaches N ~700 000 individuals and substantially increases the number of GWAS signals associated with these traits. We identified 3290 and 941 near-independent SNPs associated with height and BMI, respectively (at a revised genome-wide significance threshold of $P < 1 \times 10^{-8}$), including 1185 height-associated SNPs and 751 BMI-associated SNPs located within loci not previously identified by these two GWAS. The near-independent genome-wide significant SNPs explain ~24.6% of the variance of height and ~6.0% of the variance of BMI in an independent sample from the Health and Retirement Study (HRS). Correlations between polygenic scores based upon these SNPs with actual height and BMI in HRS participants were ~0.44 and ~0.22, respectively. From analyses of integrating GWAS and expression quantitative trait loci (eQTL) data by summary-data-based Mendelian randomization, we identified an enrichment of eQTLs among lead height and BMI signals, prioritizing 610 and 138 genes, respectively. Our study demonstrates that, as previously predicted, increasing GWAS sample sizes continues to deliver, by the discovery of new loci, increasing prediction accuracy and providing additional data to achieve deeper insight into complex trait biology. All summary statistics are made available for follow-up studies.

JAMA Network Open.

Original Investigation | Nutrition, Obesity, and Exercise

June 28, 2024

Heritability of Body Mass Index Among Familial Generations

Gabriel Chodick, PhD; Maya Simchoni, MD; Britt Wang Jensen, PhD; Estela Derazne, MSc; Orit Pinhas-Hamiel, MD; Regev Landau, MD; Alon Abramovich, MD; Arnon Afek, MD, MHA; Jennifer Lyn Baker, PhD; Gilad Twig, MD, PhD

Abstract

IMPORTANCE Studies on the familial effects of body mass index (BMI) status have yielded a wide range of data on its heritability.

OBJECTIVE To assess the heritability of obesity by measuring the association between the BMIs of fathers, mothers, and their offspring at the same age.

DESIGN, SETTING, AND PARTICIPANTS This cohort study used data from population-wide mandatory medical screening before compulsory military service in Israel. The study included participants examined between January 1, 1986, and December 31, 2018, whose both parents had their BMI measurement taken at their own prerecruitment evaluation in the past. Data analysis was performed from May to December 2023.

MAIN OUTCOMES AND MEASURES Spearman correlation coefficients were calculated for offsprings' BMI and their mothers', fathers', and midparental BMI percentile (the mean of the mothers' and fathers' BMI cohort- and sex-specific BMI percentile) to estimate heritability. Logistic regression models were applied to estimate the odds ratios (ORs) and 95% CIs of obesity compared with healthy BMI, according to parental BMI status.

RESULTS A total of 447 883 offspring (235 105 male [52.5%]; mean [SD] age, 17.09 [0.34] years) with both parents enrolled and measured for BMI at 17 years of age were enrolled in the study, yielding a total study population of 1 343 649 individuals. Overall, the correlation between midparental BMI percentile at 17 years of age and the offspring's BMI at 17 years of age was moderate ($\rho = 0.386$). Among female offspring, maternal-offspring BMI correlation ($\rho = 0.329$) was somewhat higher than the paternal-offspring BMI correlation ($\rho = 0.266$). Among trios in which both parents had a healthy BMI, the prevalence of overweight or obesity in offspring was 15.4%; this proportion increased to 76.6% when both parents had obesity and decreased to 3.3% when both parents had severe underweight. Compared with healthy weight, maternal (OR, 4.96; 95% CI, 4.63-5.32), paternal (OR, 4.48; 95% CI, 4.26-4.72), and parental (OR, 6.44; 95% CI, 6.22-6.67) obesity (midparent BMI in the ≥95th percentile) at 17 years of age were associated with increased odds of obesity among offspring.

Key Points

Question What is the association between parents' body weight at 17 years of age and the likelihood of offspring obesity, accounting for the influence of shared environmental and lifestyle factors?

Findings In this cohort study of more than 1.3 million individuals, offspring born to parents with obesity at 17 years of age exhibited a substantial 77% probability of having obesity at the same age compared with 15% when both parents were in the healthy weight range.

Meaning In this study, the weight status of parents at 17 years of age was associated with obesity risk for both female and male offspring, emphasizing that parental factors may influence the next generation's health outcomes.

+ Supplemental content

Author affiliations and article information are listed at the end of this article.

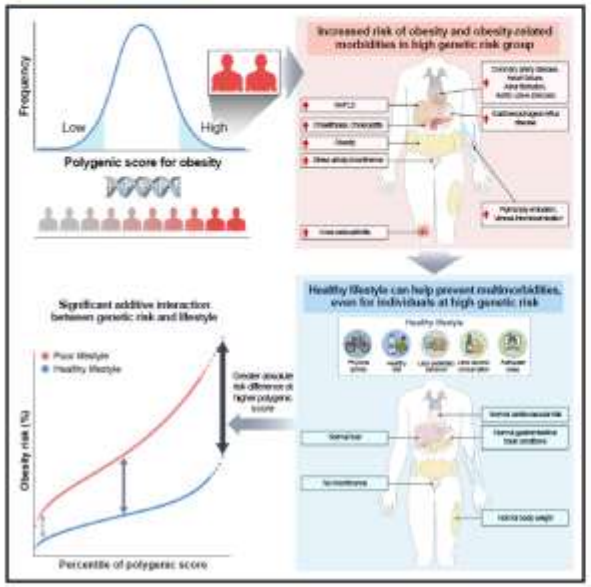
Sources: https://academic.oup.com/hmg/article/27/20/3641/5067845, https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2820556

Lifestyle Interacts with Polygenic Risk Score to Determine Lifetime Probability of Obesity*

Cell Metabolism Clinical and Translational Report
July 2, 2024

Association of genetic risk, lifestyle, and their interaction with obesity and obesity-related morbidities

Graphical abstract



Authors
Min Seo Kim, Injeong Shim, Akl C. Fahed, ..., Pradeep Natarajan, Amit V. Khera, Hong-Hee Won

Correspondence
avkhera@partners.org (A.V.K.), wonhh@skku.edu (H.-H.W.)

In brief
Kim et al. demonstrate modifiable lifestyle factors can offset the determined genomic risk for obesity. Adherence to a healthy lifestyle (minimal obesogenic behaviors) is associated with a reduced risk of obesity and obesity-related morbidities across all genetic backgrounds.

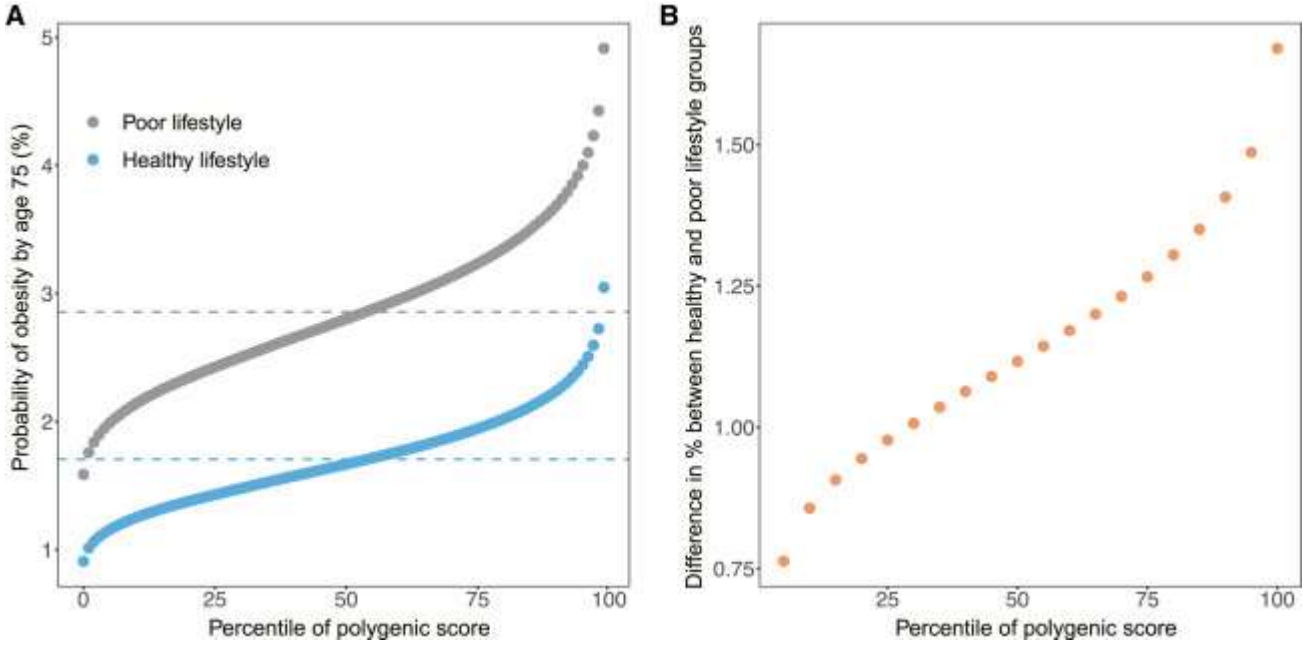


Figure 3: Predicted probability of obesity risk by lifestyle:

(A) Probability of incident obesity (%) by polygenic score for the healthy (blue) and poor (gray) lifestyle groups.

(B) Differences in percentage units between the healthy and poor lifestyle groups by polygenic score.

* Also see https://pubmed.ncbi.nlm.nih.gov/38677521/

Source: https://www.cell.com/cell-metabolism/fulltext/S1550-4131(24)00229-8

Epigenetics Matter Too

Mitch Leslie, "Fat? Thin? Molecular switch may turn obesity on or off," *Science*, Jan 28, 2016

Identical twins may be alike in everything from their eye color to their favorite foods, but they can diverge in one important characteristic: their weight. A new study uncovers a molecular mechanism for obesity that might explain why one twin can be extremely overweight even while the other is thin.

Heredity influences whether we become obese, but the genes researchers have linked to the condition don't explain many of the differences in weight among people. Identical twins with nonidentical weights are a prime example. So what accounts for the variation? Changes in the intestinal microbiome—the collection of bacteria living in the gut—are one possibility. Another is epigenetic changes, or alterations in gene activity. These changes occur when molecules latch on to DNA or the proteins it wraps around, turning sets of genes "on" or "off."

Triggered by factors in the environment, epigenetic modifications can be passed down from one generation to the next. This type of transmission happened during the Hunger Winter, a famine that occurred when the Germans cut off food supplies to parts of the Netherlands in the final months of World War II. Mothers who were pregnant during the famine gave birth to children who were prone to obesity decades later, suggesting that the mothers' diets had a lasting impact on their kids' metabolism. However, which epigenetic changes in people promote obesity remains unclear.

So when—many decades later—physiologist J. Andrew Pospisilik of the Max Planck Institute of Immunobiology and Epigenetics in Freiburg, Germany, and colleagues noticed an odd pattern of weight gain in some mutant mice, they were intrigued. The mice had only one copy of a gene called Trim28, and the researchers found that most them were either obese or lean, with few animals in between.

To discover why, the scientists measured gene activity in the animals. **Trim28 controls the activity of several other genes, making it an epigenetic modifier. In the obese mice, the activity of an interacting set of genes was turned down. Pospisilik and colleagues hypothesize that Trim28 helps form an epigenetic switch that can flip on obesity by suppressing these genes.**

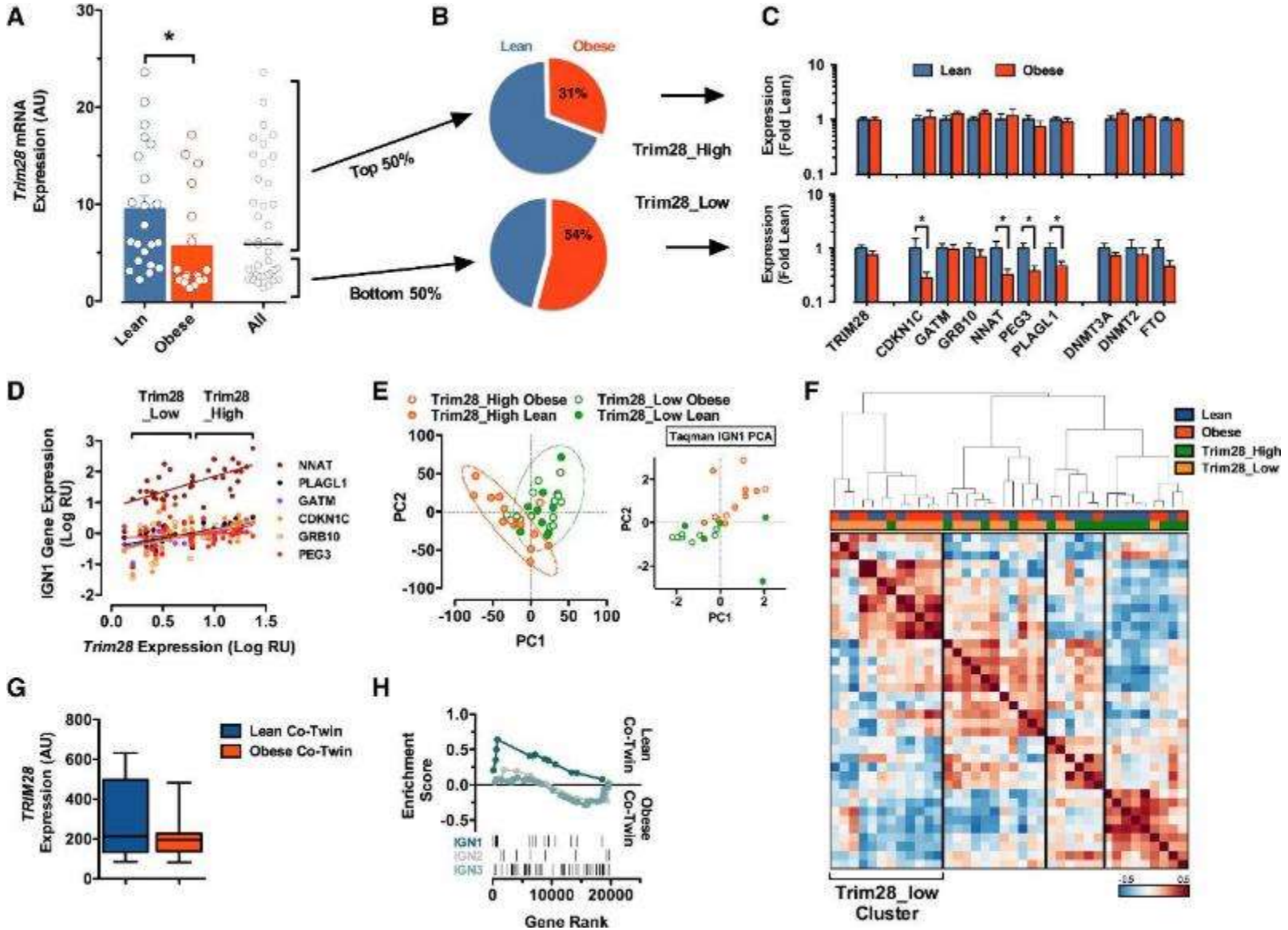
But could the same mechanism foster obesity in humans? After all, the mice have only one copy of the Trim28 gene, whereas people have two copies. To find out, the team took fat samples from children who were in the hospital for surgery. TRIM28 activity was abnormally low in fat from kids who were obese. "There's a subset of children who look very much like the obese mice" in their TRIM28 measurements, Pospisilik says. The researchers also analyzed data on 13 pairs of identical twins in which one twin was obese. TRIM28 activity was diminished in fat from the obese twins, the scientists report online today in Cell.

Pospisilik suggests several risk factors for obesity in children, such as their mothers' smoking and eating habits during pregnancy. But "the big question now is what is the trigger" that flips the obesity switch, says genetic epidemiologist Paul Franks of the Lund University Diabetes Center in Malmö, Sweden. "If you could determine what that was, you'd have the basis for intervention."

Source: https://www.science.org/content/article/fat-thin-molecular-switch-may-turn-obesity-or

Trim28 Epigenetics Influential in Explaining Weight Differences

Trim28-Low Human Children Are Obesity Susceptible and Exhibit a Distinct Transcriptome Landscape



Dalgaard K et.al., Trim28 Haploinsufficiency Triggers Bi-stable Epigenetic Obesity. *Cell*. 2016 Jan 28;164(3):353-64.

We examined gene expression by Taqman qPCR in subcutaneous adipose tissue samples from a cohort of pre-pubertal Caucasian children of European ancestry entering the clinic for elective surgery (typically orthopedic); the cohort included 22 lean and 18 obese individuals. The children were disease and medication free and have been described in detail as part of the Leipzig Childhood AT cohort (Landgraf et al., 2015). When measured against three housekeeping genes (ACTB, HPRT, TBP), we found both a significant reduction in adipose tissue TRIM28 levels in obese children (Figure 4A) and an apparent cluster of very low TRIM28-expressing individuals in the obese group. Individuals in the lower 50th percentile of TRIM28 expression appeared more likely to be obese than high TRIM28 expressors (Figure 4B).

Source: https://www.cell.com/cell/fulltext/S0092-8674(15)01689-X

Low Intracellular TRIM28 Expression Linked to Obesity by Disabling Hormone-Stimulated Lipolysis

SCIENCE ADVANCES | RESEARCH ARTICLE

MOLECULAR BIOLOGY

Transcriptional determinants of lipid mobilization in human adipocytes

Alison C. Ludzki[1], Mattias Hansen[1], Danae Zareifi[1], Jutta Jalkanen[1], Zhiqiang Huang[2], Muhmmad Omar-Hmeadi[1], Gianluca Renzi[1], Felix Klingelhuber[3,4], Sebastian Boland[5], Yohannes A. Ambaw[5,6], Na Wang[1], Anastasios Damdimopoulos[2], Jianping Liu[1], Tomas Jernberg[7], Paul Petrus[1], Peter Arner[1], Natalie Krahmer[3,4], Rongrong Fan[2], Eckardt Treuter[2], Hui Gao[2], Mikael Rydén[1]*†, Niklas Mejhert[1]*†

Defects in adipocyte lipolysis drive multiple aspects of cardiometabolic disease, but the transcriptional framework controlling this process has not been established. To address this, we performed a targeted perturbation screen in primary human adipocytes. Our analyses identified 37 transcriptional regulators of lipid mobilization, which we classified as (i) transcription factors, (ii) histone chaperones, and (iii) mRNA processing proteins. On the basis of its strong relationship with multiple readouts of lipolysis in patient samples, we performed mechanistic studies on one hit, *ZNF189*, which encodes the zinc finger protein 189. Using mass spectrometry and chromatin profiling techniques, we show that ZNF189 interacts with the tripartite motif family member TRIM28 and represses the transcription of an adipocyte-specific isoform of phosphodiesterase 1B (PDE1B2). The regulation of lipid mobilization by ZNF189 requires PDE1B2, and the overexpression of PDE1B2 is sufficient to attenuate hormone-stimulated lipolysis. Thus, our work identifies the ZNF189-PDE1B2 axis as a determinant of human adipocyte lipolysis and highlights a link between chromatin architecture and lipid mobilization.

Source: https://www.science.org/doi/full/10.1126/sciadv.adi2689

SCIENCE ADVANCES | RESEARCH ARTICLE

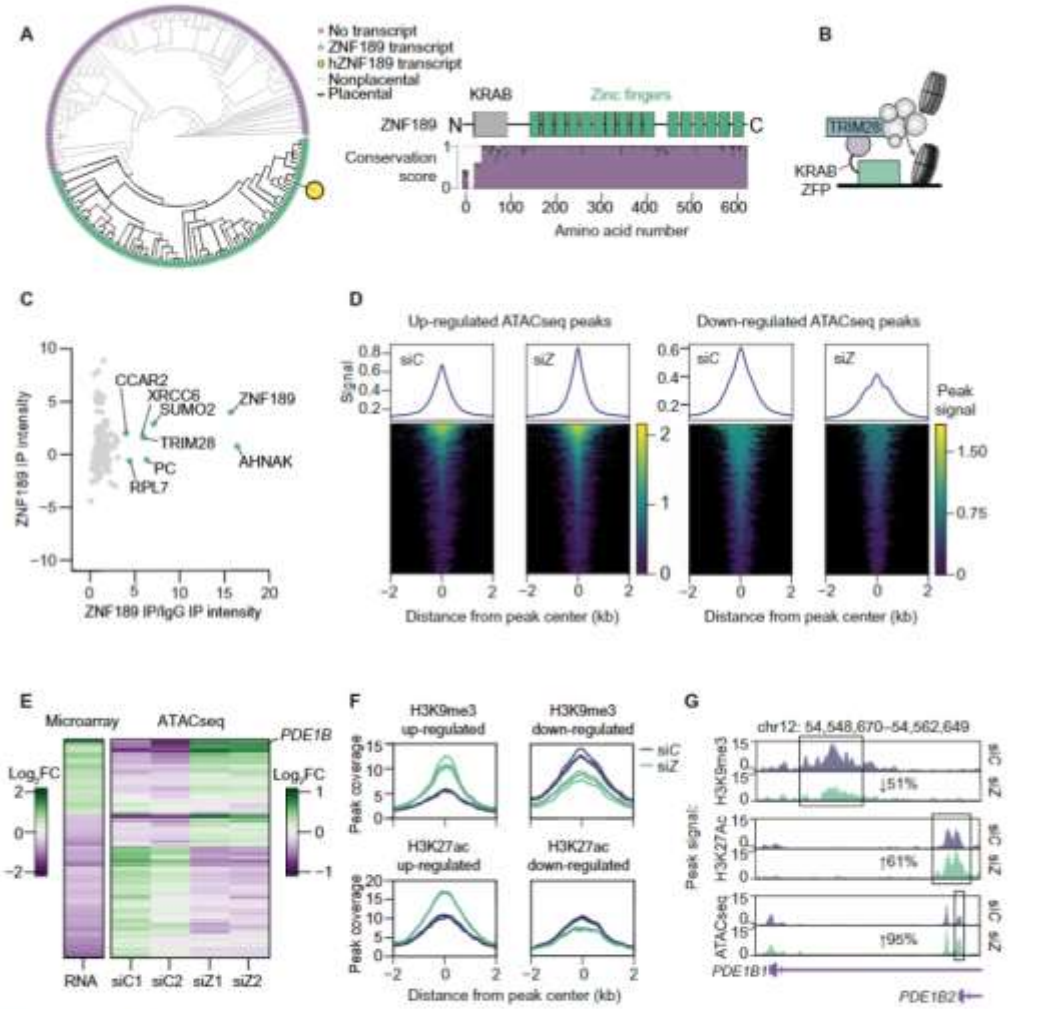


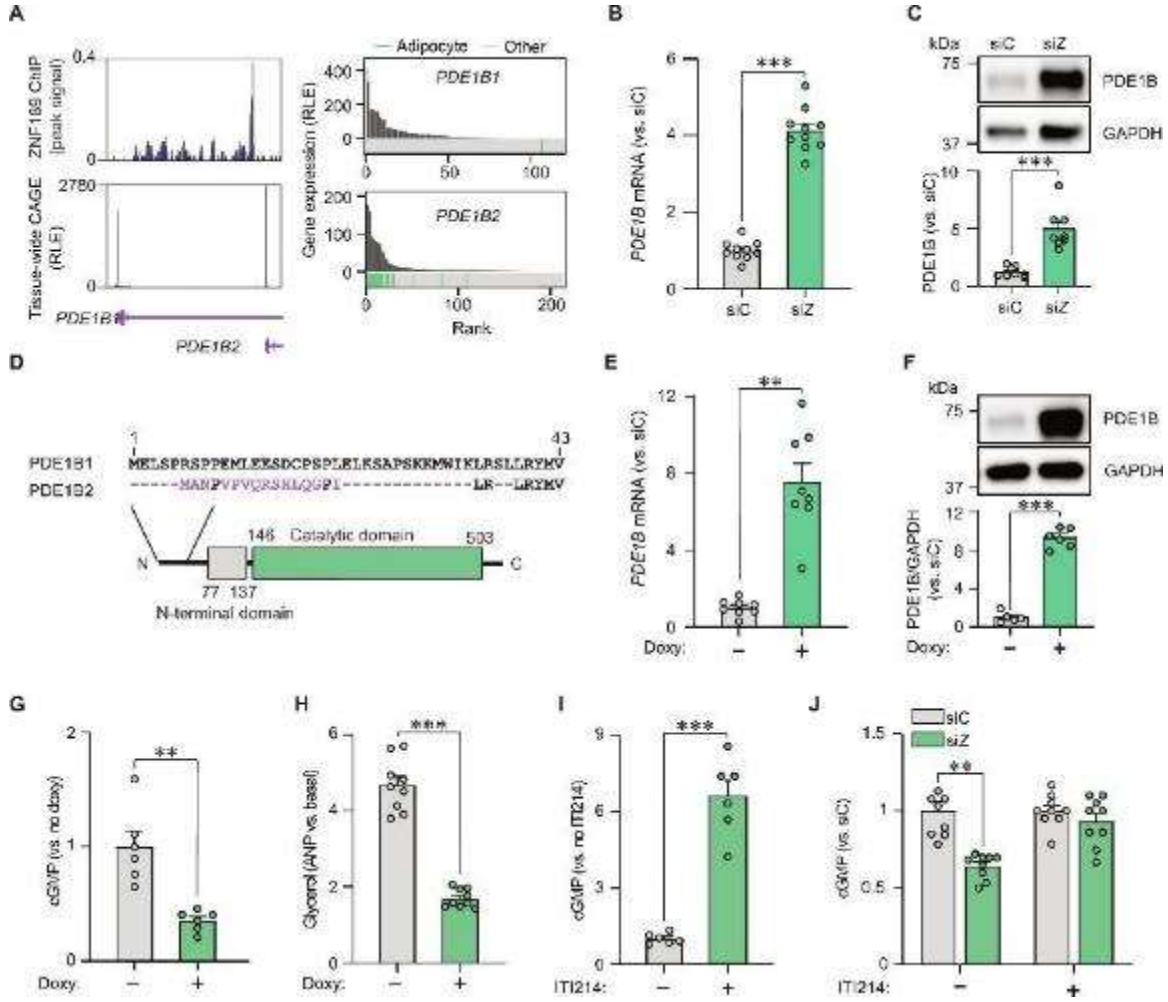
Fig. 5. ZNF189 contains a KRAB domain and interacts with TRIM28. (**A**) Left: Phylogenetic tree showing gain of *ZNF189* gene in placentals (eutheria). Right: ZNF189 protein conservation (Valdar scores from 10 homologs) aligned with ZNF189 protein domains (Uniprot O75820). (**B**) Schematic overview of the KRAB-TRIM28 protein complex showing ZNF189 interacting with DNA and the TRIM28 complex. TRIM28 is depicted maintaining closed chromatin via a protein complex. (**C**) Normalized protein intensities from MS on ZNF189 immunoprecipitation (IP) samples ($n = 4$). (**D**) Peak density plots and heatmaps for increased and decreased ATACseq peaks in control (siC) and si*ZNF189* (siZ) cells ($n = 2$). (**E**) Fold change [$\log_2$(FC)] from the microarray and ATACseq for genes with significant regulation by both assays. RNA data reflects fold changes versus siC and ATACseq data reflects fold changes versus the mean of the comparison condition. (**F**) Peak coverage plots for regulated H3K9me3 and H3K27ac peaks by CUT&Tag ($n = 3$). (**G**) Average peak signal for chromatin profiling at the *PDE1B* locus, which contains two promoters encoding *PDE1B1* and *PDE1B2*.

Multiple Therapeutic Targets Emerge from TRIM28 Literature Including PDE1 Inhibition

Ludzki AC et.al, *Sci Adv.* 2024 Jan 5;10(1):eadi2689.

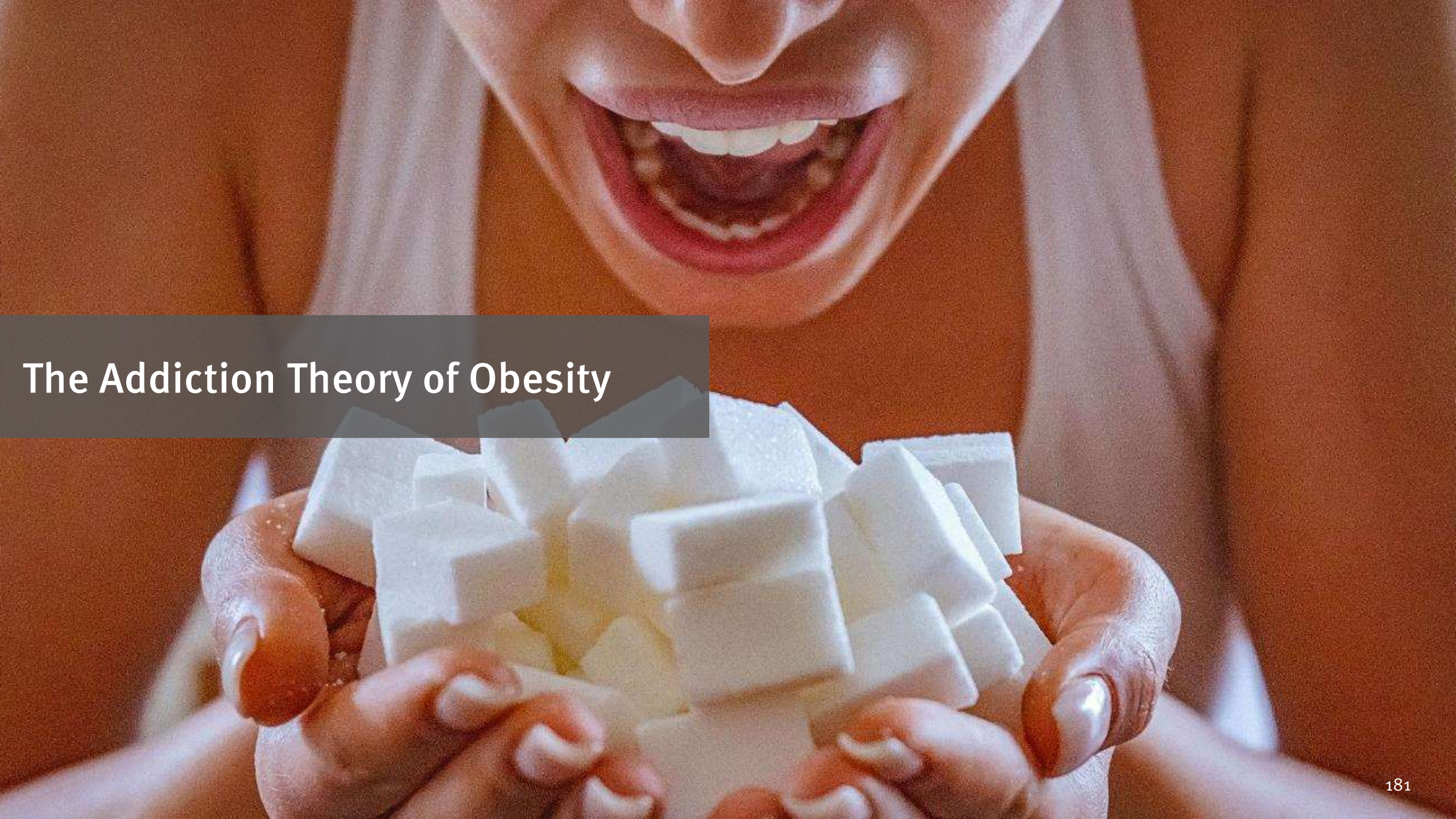
We and others have linked impairments in hormone-stimulated lipolysis to metabolic derangements in humans. It is therefore possible that treatments restoring hormone-stimulated lipolysis could mitigate adipose tissue-related metabolic disease. In addition to physical activity, which is known to improve WAT lipolysis and has beneficial effects on cardiovascular risk markers, our data suggest that PDE1B2 inhibition could be explored. In line with this, a recent study in mice showed that the nonspecific PDE1 inhibitor, vinpocetine, had positive effects on adiposity and in vivo measures of lipolysis, including circulating fatty acids and triacylglycerols. The development of selective PDE inhibitors is an ongoing challenge due to high structural similarities in PDE substrate-binding pockets between family members.

Nevertheless, rapid advancements in phosphodiesterase pharmacology make the development of a selective PDE1B2 inhibitor feasible.



The ZNF189-PDE1B2 axis regulates adipocyte lipolysis.
(A) Left: ZNF189 ChIP signal shown above tissue-wide cap analysis of gene expression signals [expressed as relative log expression (RLE)] at the two PDE1B promoters (encoding PDE1B1 and PDE1B2). Right: Gene expression of PDE1B1 and PDE1B2 across tissue/cell samples from the FANTOM5 database. Adipose samples are highlighted in green. (B and C) PDE1B mRNA (B) and protein (C) levels for siZNF189 (siZ) versus control cells (siC). (D) Sequence alignments for PDE1B1 and PDE1B2 shown above protein domains from InterPro. Purple characters represent deviations from the canonical protein isoform. Conserved protein domains are indicated with colored boxes. (E to H) PDE1B mRNA (E) and protein (F) as well as cGMP (G) and glycerol (H) in cells engineered to overexpress PDE1B2 under a doxycycline (doxy)-inducible promoter

Source: https://www.science.org/doi/full/10.1126/sciadv.adi2689



The Addiction Theory of Obesity

3 Addiction Theory and the Gut-Brain Axis

The addiction theory of food suggests that certain types of food ingredients are addictive.

Starting in the 1970s the U.S. decided to promote high fructose corn syrup. Even today, HFCS is subsidized by the U.S. government.

By the 1980s consumption of HFCS began to grow rapidly, particularly in sugary soda as this was an inexpensive ingredient.

This coincides quite closely with growth in obesity.

At the same time, consumption of other highly processed foods, fast food and convenience items began to rise.

County level data on consumption of sugary soda and fast-food lines up surprisingly well with the obesity epidemic.

The U.S. consumes the most HFCS by far of any major country and has the highest obesity rate.

Sugar consumption levels by country are correlated with obesity rates.

These data are consistent with the theory that these bad foods induce an addiction of sort.

That is, the worse food you eat, the worse food you want to eat.

What is particularly challenging is that access to this bad food is high among children and adolescents.

This is when an addictive process appears to begin.

When children are taken off sugary soda, they go through a withdrawal process very similar to that of going off addictive drugs.

There are multiple MOA's of this addictive process. The science is particularly strong.

First, exposure to high fructose in the gut signals the release of L-glutamine in the lumen. Some of this gets to the brain.

Second, this is associated with GABA release in the brain.

This, in turn, is associated with a hedonic phenotype in the brain that creates a self-reinforcing process leading to eating.

The normal homeostatic mechanism that would downregulate hunger in the presence of overnutrition fails to kick in and is overcome by hedonic impulses.

What is important about this theory is that an addiction might be broken with a "one and done" type approach.

One intervention that works through the gut-brain axis and alters hedonistic food addiction is RGBY bariatric surgery. This is not ideal for most people.

Further, our society does not have great addiction drugs but there are some. These drugs do appear to work and could be useful to try in the case of obesity.

Typically, addiction specialists couple pharmaceutical treatments with cognitive therapy. Something similar could work here.

Another intervention that could work highlighted in Tan et.al. is a specific microbiome treatment.

We should note that the addiction theory is not at all mutually exclusive with some versions of the "fatty brain" theory of obesity.

Growth in Use of High Fructose Corn Syrup in U.S. Associated with Obesity Trend

Bray GA, Nielsen SJ, Popkin BM. Consumption of high-fructose corn syrup in beverages may play a role in the epidemic of obesity. Am J Clin Nutr. April 2004, pp. 537-43.

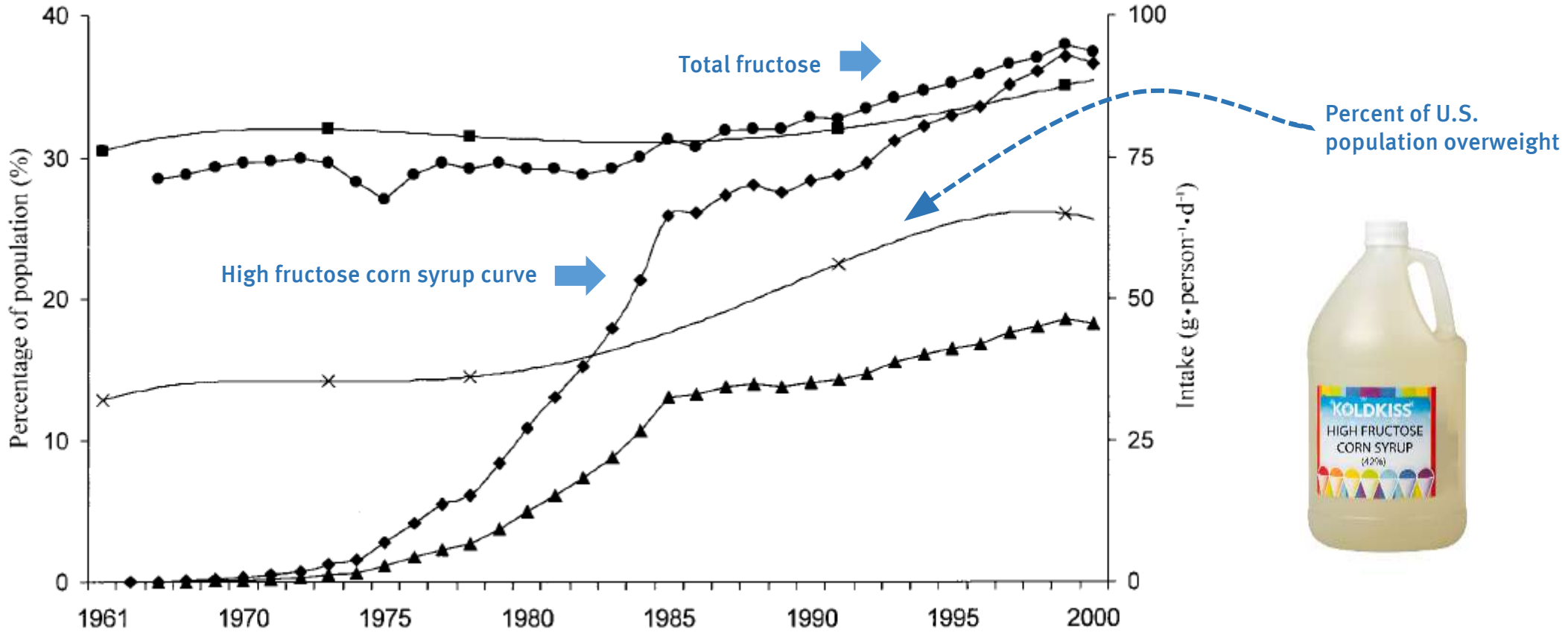
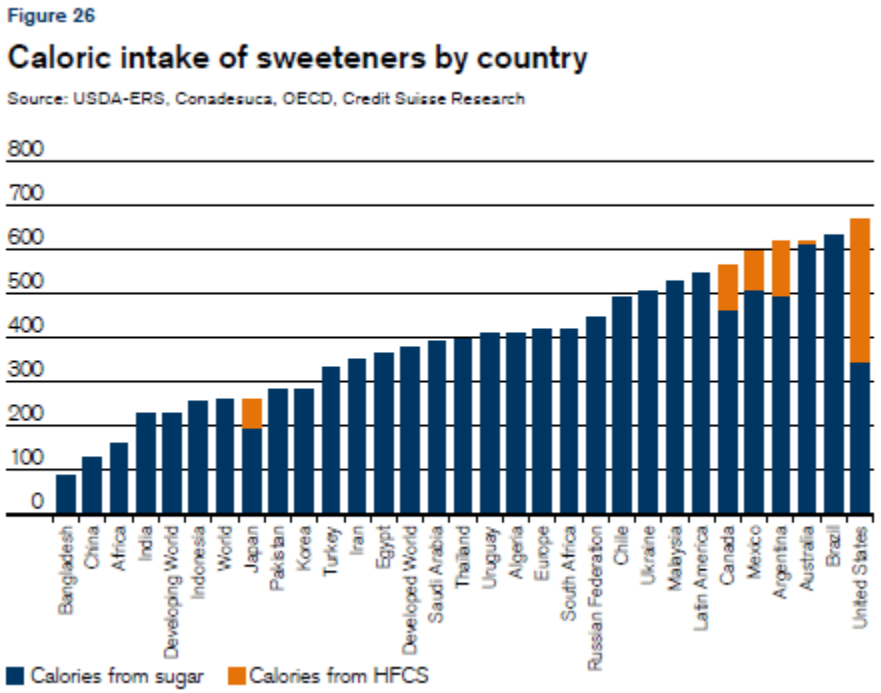


FIGURE 1. Estimated intakes of total fructose (●), free fructose (▲), and high-fructose corn syrup (HFCS, ♦) in relation to trends in the prevalence of overweight (■) and obesity (x) in the United States. Data from references 7 and 35.

Source: https://pubmed.ncbi.nlm.nih.gov/15051594/

U.S. Has Exceptionally High Sweetener Intake and Consumes More High Fructose Corn Syrup Than Any Major Country



Landrigan, Satlin and Bofetta, Mt Sinai, 2016

Since 1980, obesity rates in children have tripled. Today, 13 million children are obese, including 14 percent of all 6- to 11-year-olds, and 17 percent of adolescents. Over 70 percent of these children will be obese adults, with increased risks of diabetes, heart disease, and certain cancers.

But an **especially powerful driver is the abundance of cheap, unwholesome food sweetened by the synthetic sugar substitute high-fructose corn syrup** (HFCS). Consumption of HFCS has increased tenfold since 1974. The obesity epidemic in America's children precisely tracks this trend.

HFCS was invented in the 1960s. Production increased dramatically in the 1970s, after the U.S. Department of Agriculture (USDA) ended controls on corn, wheat, and soy production and replaced them with a policy that encouraged — and paid — farmers to grow as much of these commodity crops as possible. **Today, these subsidies total $19 billion per year. They have led to enormous increases in production of cheap corn starch.** No subsidies are paid to fruit or vegetable farmers despite the clear health benefits of eating fresh fruits and vegetables.

Source: https://www.quora.com/How-much-high-fructose-corn-syrup-does-the-average-American-consume-per-year-How-does-that-compare-to-other-countries

Just Two Weeks of High Fructose Corn Syrup Leads to Meaningful Weight Gain in Children

Sigala DM et.al., "Effects of Consuming Sugar-Sweetened Beverages for 2 Weeks on 24-h Circulating Leptin Profiles, Ad Libitum Food Intake and Body Weight in Young Adults," *Nutrients*. 2020 Dec 19;12(12):3893.

Sugar-sweetened beverage (sugar-SB) consumption is associated with body weight gain. In a parallel, double-blinded, intervention study, participants (n = 131; BMI 18–35 kg/m2; 18–40 years) consumed three beverages/day containing aspartame or 25% energy requirement as glucose, fructose, high fructose corn syrup (HFCS) or sucrose (n = 23–28/group). Body weight, ad libitum food intake and 24-h leptin area under the curve (AUC) were assessed at Week 0 and at the end of Week 2. The Δbody weight was not different among groups (p = 0.092), but the increases in subjects consuming HFCS- (p = 0.0008) and glucose-SB (p = 0.018) were significant compared with Week 0. Subjects consuming sucrose- (+14%, p < 0.0015), fructose- (+9%, p = 0.015) and HFCS-SB (+8%, p = 0.017) increased energy intake during the ad libitum food intake trial compared with subjects consuming aspartame-SB (–4%, p = 0.0037, effect of SB). Fructose-SB decreased (–14 ng/mL × 24 h, p = 0.0006) and sucrose-SB increased (+25 ng/mL × 24 h, p = 0.025 vs. Week 0; p = 0.0008 vs. fructose-SB) 24-h leptin AUC.

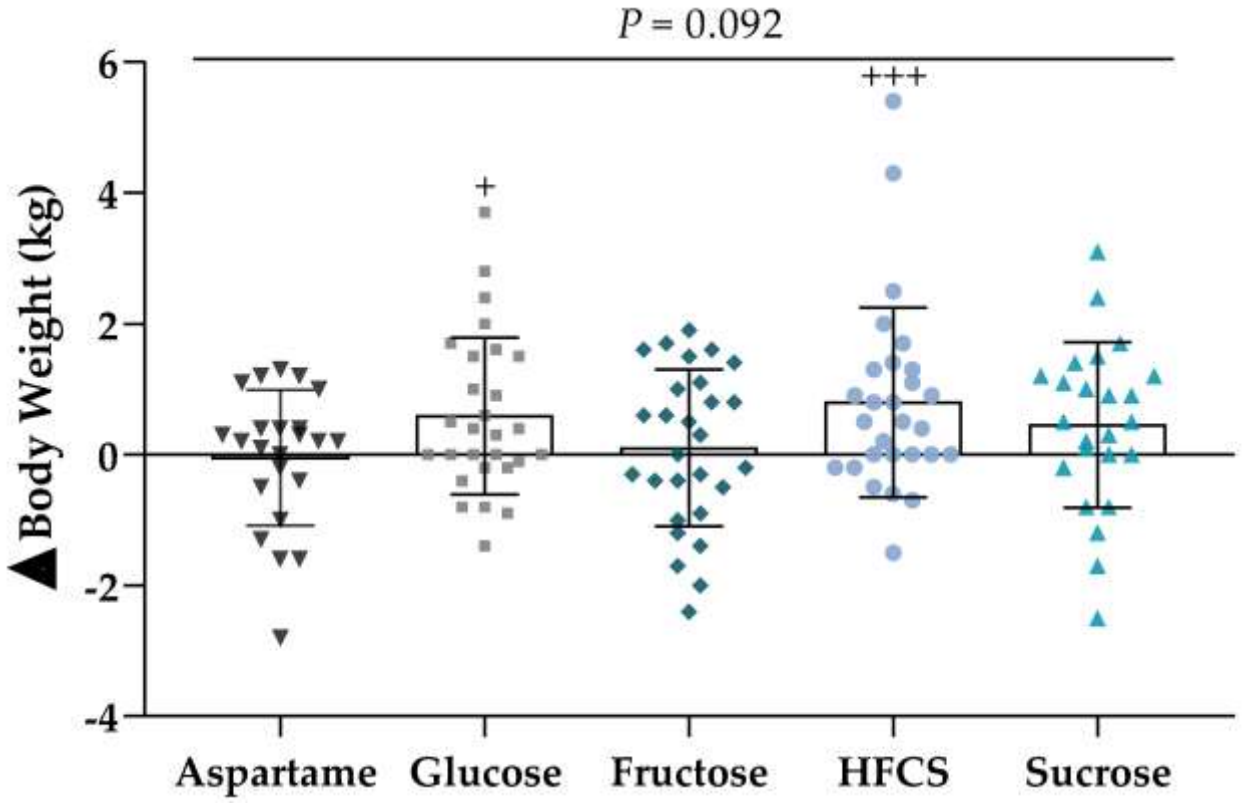


Figure 2. Body weight: The mean ± SEM of the absolute change (Week 2–Week 0) in body weight in subjects consuming either glucose-, fructose-, high fructose corn syrup (HFCS)-, sucrose-, or aspartame-sweetened beverages for 2 weeks. Two-factor (SB group, sex) analysis of covariance with adjustment for outcome at Week 0; $^{+}$ $p < 0.05$, $^{+++}$ $p < 0.001$, least squares (LS) mean different from zero.

Source: https://www.mdpi.com/2072-6643/12/12/3893

40 years of adding more fructose to high fructose corn syrup than is safe, through the lens of malabsorption and altered gut health–gateways to chronic disease

Luanne Robalo DeChristopher[1*]

Nutrition Journal (2024) 23:16

The displacement of sucrose with HFCS, its ubiquitous presence in the US food supply, and the industry practice of adding more fructose to HFCS than is generally-recognized-as-safe, combined with the increased use of apple juice as a sweetener in foods and beverages, and growing use of crystalline fructose, agave syrup (70–90% fructose) and apple powder, have all contributed to unprecedented excess-free-fructose daily intake levels. Dosages have exceeded and continue to exceed levels that trigger fructose malabsorption (~5 g-10 g)—a condition with far reaching consequences. Excess-free-fructose promotes gut formation of asthma provoking, proinflammatory advanced glycation end-products (FruAGE) and causes gut dysbiosis – a disease associated with a growing list of chronic diseases including asthma, COPD, autoimmune disease, IBD, IBS, CVD, NAFLD, CKD, and cardiometabolic and mental health disorders.

Figure 1

Major sources of added sugar in the American diet

Source: Johnson et al, Circulation, 2009: 120:1011-1020. Food groups that contribute more than 5% of the added sugars to the American diet are listed in decreasing order.

Food categories	Contribution to added sugar intake (% of total added sugar consumed)
Regular soft drinks	33.0
Sugars and candy	16.1
Cakes, cookies, pies	12.9
Fruit drinks (fruitades and fruit punch)	9.7
Dairy desserts and milk products (ice cream sweetened yogurt, and sweetened milk)	8.6
Other grains (cinnamon toast and honey-nut waffles)	5.8

Sources: https://nutritionj.biomedcentral.com/articles/10.1186/s12937-024-00919-3, https://conversableeconomist.blogspot.com/2013/10/the-global-sugar-market-and-us-sugar.html

Fructose Leads to Excess Adiposity by Expanding the Surface Area of the Gut

Taylor, S.R., Ramsamooj, S., Liang, R.J. et al. Dietary fructose improves intestinal cell survival and nutrient absorption. *Nature* 597, 263–267 (2021).

Fructose consumption is linked to the rising incidence of obesity and cancer, which are two of the leading causes of morbidity and mortality globally. Dietary fructose metabolism begins at the epithelium of the small intestine, where fructose is transported by glucose transporter type 5 (GLUT5; encoded by SLC2A5) and phosphorylated by ketohexokinase to form fructose 1-phosphate, which accumulates to high levels in the cell. Although this pathway has been implicated in obesity and tumour promotion, the exact mechanism that drives these pathologies in the intestine remains unclear. Here we show that dietary fructose improves the survival of intestinal cells and increases intestinal villus length in several mouse models. The increase in villus length expands the surface area of the gut and increases nutrient absorption and adiposity in mice that are fed a high-fat diet. In hypoxic intestinal cells, fructose 1-phosphate inhibits the M2 isoform of pyruvate kinase to promote cell survival. Genetic ablation of ketohexokinase or stimulation of pyruvate kinase prevents villus elongation and abolishes the nutrient absorption and tumour growth that are induced by feeding mice with high-fructose corn syrup. The ability of fructose to promote cell survival through an allosteric metabolite thus provides additional insights into the excess adiposity generated by a Western diet, and a compelling explanation for the promotion of tumour growth by high-fructose corn syrup.

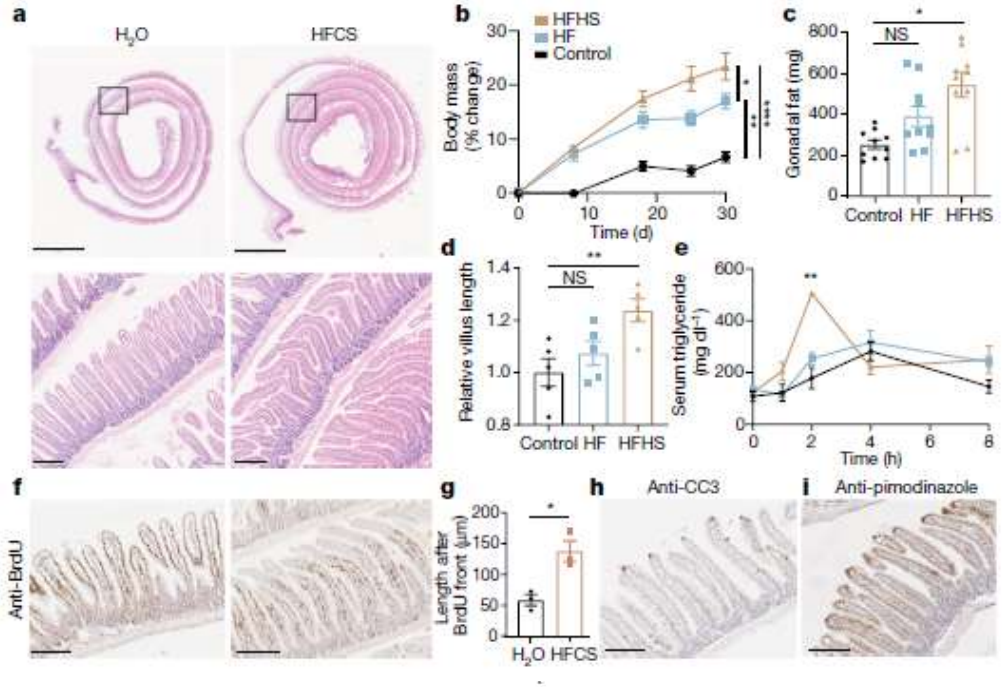


Fig. 1 | Dietary fructose increases intestinal villus length and lipid absorption. a, Haematoxylin and eosin (H&E)-stained duodenum from mice that were fed normal chow with ad libitum H_2O or 25% HFCS for four weeks. Scale bars, 3 mm (top); 200 μm (bottom). **b**, Relative change in the body mass of mice that were fed a control diet, a high-fat diet (45% kcal fat) (HF) or a high-fat, high-sucrose diet (HFHS) ($n = 5$ mice per group). **c**, Mass of white adipose tissue from the gonadal depot after five weeks on each diet ($n = 5$ mice per group; two depots per mouse). **d**, Relative duodenal villus length after five weeks on each diet ($n = 5$ mice per group). **e**, Serum triglyceride levels in fasted mice after an oral gavage with olive oil ($n = 3$ mice per group). **f**, BrdU immunohistochemistry (IHC) of duodenal sections from H_2O or HFCS-treated mice 72 h after intraperitoneal BrdU injection. Scale bars, 200 μm. **g**, Duodenal villus length distal to the BrdU front ($n = 3$ mice per group; 40 villi per mouse). **h**, **i**, IHC for CC3 (**h**) and pimodinazole (**i**) in duodenal sections from H_2O-treated mice. Scale bars, 200 μm. **b**–**e**, One-way ANOVA followed by Holm–Sidak post-hoc test for multiple comparisons; **g**, two-sided Student's *t*-test. NS, not significant; $^*P < 0.05$, $^{**}P < 0.01$, $^{****}P < 0.0001$; exact *P* values are provided in the Source Data for all figures. All data are mean ± s.e.m.

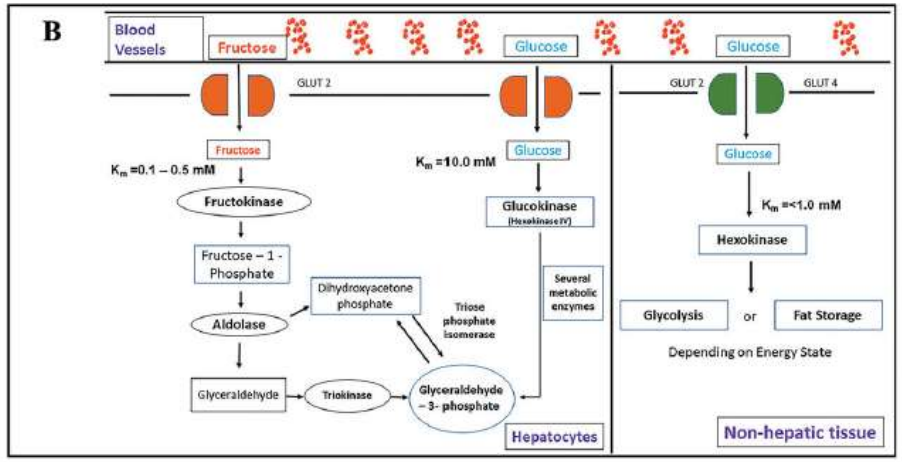
Source: https://www.nature.com/articles/s41586-021-03827-2

Compared to Glucose, Fructose is Preferentially Turned to Fat

Faruque S, Tong J, Lacmanovic V, Agbonghae C, Minaya DM, Czaja K. The Dose Makes the Poison: Sugar and Obesity in the United States - a Review. *Pol J Food Nutr Sci.* 2019;69(3):219-233.

In the liver, both fructose and glucose are converted to an important intermediate; glyceraldehyde-3-phosphate (Figure at right). However, unlike glucose, fructose metabolism is not subjected to fructose kinase regulations. Therefore, energy status does not regulate fructose uptake by the liver and subsequent de novo lipogenesis (DNL), which means that a high level of consumed fructose enters the liver with little reaching the systematic circulation [Stanhope et al., 2013]. The increased rate of DNL induced by fructose generates fatty acids for hepatic triglyceride production and thus leads to postprandial hypertriglyceridemia. **Fructose can yield greater amounts of fat when consumed in larger quantities than glucose [Berg et al., 2015]. Fructose consumption fosters an imbalance between hepatic lipid input and output, creating a net liver fat accumulation [Stanhope et al., 2013].** In addition, increased consumption of fructose leads to decreased secretion of insulin and leptin, hormones known to regulate energy homeostasis by decreasing food intake and increasing energy expenditure [Elliott et al., 2002].

Glucose and fructose have different regional adipose distribution: fructose promotes lipid deposition in visceral adipose tissue, while glucose favors subcutaneous adipose tissue deposition [Stanhope et al., 2009]. Individuals who consumed high-fructose diets showed increased hepatic de novo lipogenesis (DNL), postprandial triglycerides, insulin resistance, and markers or altered lipid metabolism [Basciano, et al., 2005].



Fructose and glucose leave blood vessels and enter hepatic or non-hepatic tissue dependent on the affinities of those cells for the monosaccharides. Fructose almost exclusively moves into hepatic tissue due to fructokinase's high affinity (low Km) for the sugar. In hepatic tissue fructokinase is converted to glyceraldehyde and subsequently glyceraldehyde-3-phosphate both of which are involved in the process of glycolysis.

Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6959843/

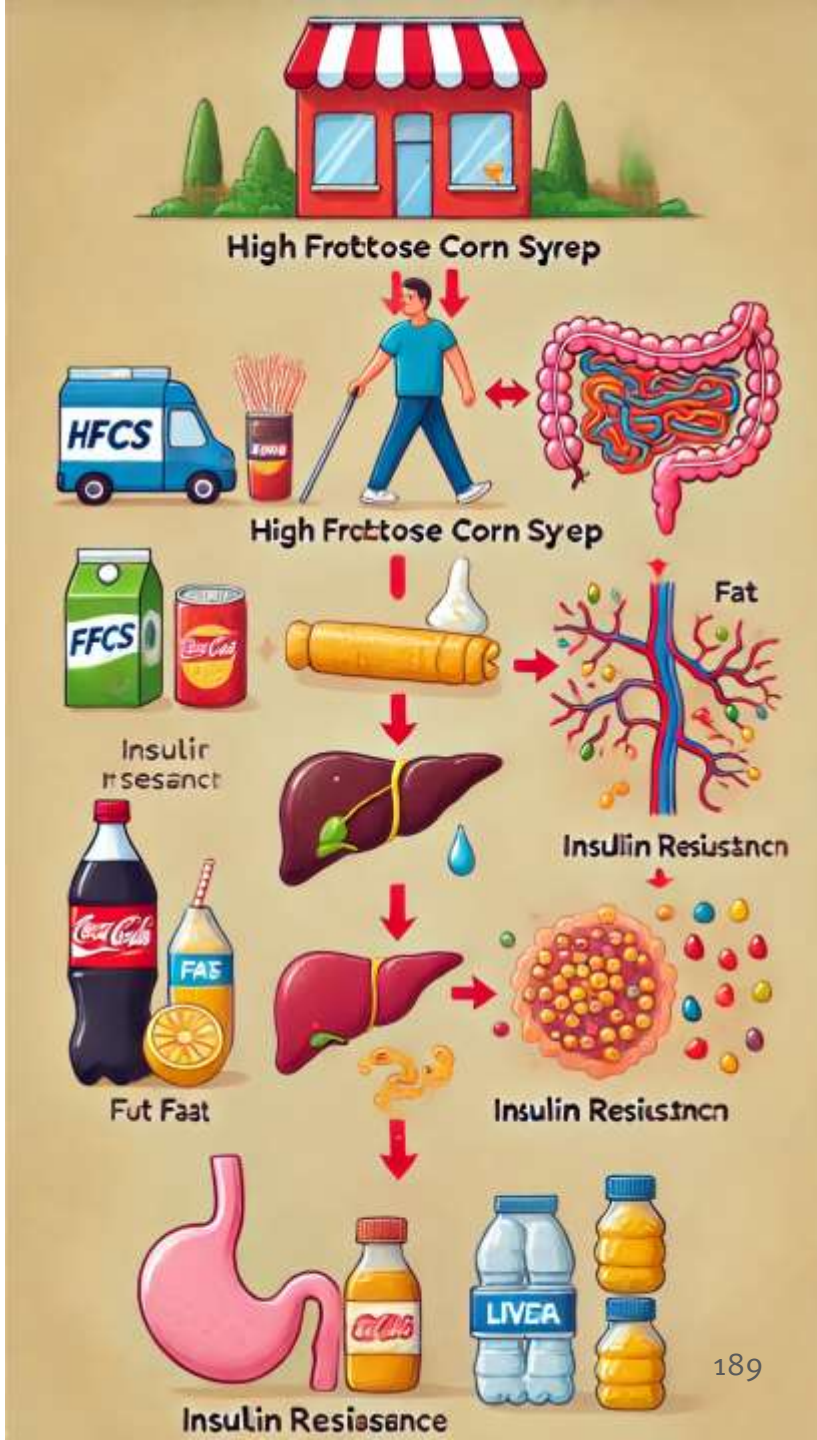
Even if You Don't Overeat, Corn Syrup Leads to Insulin Resistance

Hidaka M, Oshima Y, Hanai Y, Kataoka H, Hattori H., "Effects of Excessive High-fructose Corn Syrup Drink Intake in Middle-aged Mice," *In Vivo*. May-Jun 2024;38(3):1152-1161

Early middle-aged mice were divided in HFCS and control groups; they were provided either 10% HFCS water or deionized water ad libitum for 12 weeks, respectively. Total energy intake was controlled using a standard rodent diet. Oral glucose tolerance test (OGTT), insulin tolerance test (ITT), tissue weight measurements, serum parameter analyses, and mRNA expression assessments were performed.

No increase in body and adipose tissue weight was observed with excessive HFCS intake under energy restriction. Moreover, serum lipid parameters did not differ from those of controls. However, in the OGTT and ITT, the HFCS group showed higher blood glucose levels than the control group. Moreover, the pancreatic weight and insulin II mRNA expression were reduced.

The excessive HFCS drink intake under energy restriction did not induce obesity; however, it induced impaired glucose tolerance, indicating its negative effects on the pancreas in early middle-aged mice. When translated in human physiology, our results show that even if one does not become obese, excessive HFCS may affect the overall metabolic mechanism; these effects may vary depending on age.



Source: https://pubmed.ncbi.nlm.nih.gov/38688615/

Regional Data Lines Up Soda and Fast-Food Consumption Well with the Obesity Epidemic

Althoff T, Nilforoshan H, Hua J, Leskovec J. Large-scale diet tracking data reveal disparate associations between food environment and diet. *Nat Communications*, Jan 18, 2022;13(1):267.

We leverage smartphones to track diet health, operationalized through the self-reported consumption of fresh fruits and vegetables, fast food and soda, as well as body-mass index status in a country-wide observational study of 1,164,926 U.S. participants and 2.3 billion food entries to study the independent contributions of fast food and grocery store access, income and education to diet health outcomes. This study constitutes the largest nationwide study examining the relationship between the food environment and diet to date. We find that higher access to grocery stores, lower access to fast food, higher income and college education are independently associated with higher consumption of fresh fruits and vegetables, lower consumption of fast food and soda, and lower likelihood of being affected by overweight and obesity.

Source: https://www.nature.com/articles/s41467-021-27522-y

An unhealthy diet is a major risk factor for chronic diseases including cardiovascular disease, type 2 diabetes, and cancer. Limited access to healthy food options may contribute to unhealthy diets. Studying diets is challenging, typically restricted to small sample sizes, single locations, and non-uniform design across studies, and has led to mixed results on the impact of the food environment. Here we leverage smartphones to track diet health, operationalized through the self-reported consumption of fresh fruits and vegetables, fast food and soda, as well as body-mass index status in a country-wide observational study of 1,164,926 U.S. participants (MyFitnessPal app users) and 2.3 billion food entries to study the independent contributions of fast food and grocery store access, income and education to diet health outcomes. This study constitutes the largest nationwide study examining the relationship between the food environment and diet to date. We find that higher access to grocery stores, lower access to fast food, higher income and college education are independently associated with higher consumption of fresh fruits and vegetables, lower consumption of fast food and soda, and lower likelihood of being affected by overweight and obesity. However, these associations vary significantly across zip codes with predominantly Black, Hispanic or white populations. For instance, high grocery store access has a significantly larger association with higher fruit and vegetable consumption in zip codes with predominantly Hispanic populations (7.4% difference) and Black populations (10.2% difference) in contrast to zip codes with predominantly white populations (1.7% difference). Policy targeted at improving food access, income and education may increase healthy eating, but intervention allocation may need to be optimized for specific subpopulations and locations.

Numerous Studies Confirm Link Between Ultra-Processed Food Intake (esp. Sugary Beverages) and Adverse Health Outcomes

Molecular Nutrition & Food Research

Research Article

Association of Ultra-Processed Food Intake with Cardiovascular and Respiratory Disease Multimorbidity: A Prospective Cohort Study

Huiping Li, Shu Li, Hongxi Yang, Yuan Zhang, Yue Ma, Yabing Hou, Xinyu Zhang, Li Sun, Yan Borné, Yaogang Wang

ASN American Society for Nutrition
Excellence in Nutrition Research and Practice
www.nutrition.org

NUTRITION 2024

Where the Best in Science & Health Meet
June 29 - July 2 • McCormick Place • Chicago, IL

NEWS RELEASE 30-JUN-2024

Intake of ultra-processed foods linked with increased risk of death

Processed meats and soft drinks show strongest association with increased mortality

Reports and Proceedings
AMERICAN SOCIETY FOR NUTRITION

Association of ultra-processed food consumption with all cause and cause specific mortality: population based cohort study

Zhe Fang,[1] Sinara Laurini Rossato,[2,3] Dong Hang,[3,4] Neha Khandpur,[3,5,6] Kai Wang,[1] Chun-Han Lo,[7] Walter C Willett,[1,3,8] Edward L Giovannucci,[1,3] Mingyang Song[1,3,9]

Sources: https://onlinelibrary.wiley.com/doi/abs/10.1002/mnfr.202200628, https://www.bmj.com/content/385/bmj-2023-078476, https://www.eurekalert.org/news-releases/1048890

One Can Test for Addiction by Looking for Withdrawal Symptoms

Parnarouskis L, Leventhal AM, Ferguson SG, Gearhardt AN. Withdrawal: A key consideration in evaluating whether highly processed foods are addictive. *Obes Rev*. Nov 2022:e13507.

Researchers are currently debating whether theories of addiction explain compulsive overeating of highly processed (HP) foods (i.e., industrially created foods high in refined carbohydrates and/or fat), which contributes to obesity and diet-related disease.

A subset of individuals consumes HP foods with behavioral phenotypes that mirror substance use disorders. Withdrawal, the emergence of aversive physical and psychological symptoms upon reduction or cessation of substance use, is a core component of addiction that was central to historical debates about other substances' addictive potential (e.g., nicotine and cocaine). However, no one has systematically considered evidence for whether HP foods cause withdrawal, which represents a key knowledge gap regarding the utility of addiction models for understanding compulsive overeating. Thus, we reviewed evidence for whether animals and humans exhibit withdrawal when reducing or eliminating HP food intake. **Controlled experimental evidence indicates animals experience HP food withdrawal marked by neural reward changes and behaviors consistent with withdrawal from other addictive substances. In humans, preliminary evidence supports subjective withdrawal-like experiences.**

Source: https://pubmed.ncbi.nlm.nih.gov/36196649/

Drug withdrawal in the addicted is associated with headaches, cravings, lack of motivation and irritability.

Sugary Soft Drinks Can Cause Addiction in Adolescents

Falbe J, Thompson HR, Patel A, Madsen KA., "Potentially addictive properties of sugar-sweetened beverages among adolescents," *Appetite*, Feb 1, 2019 pp. 130-137.

Sugar-sweetened beverages (SSBs) increase risk of cardiometabolic disease. Young people consume the largest amounts of SSBs and have experienced the greatest relative gains in obesity in the past several decades. There is evidence of addictive properties of both caffeine and sugar, the primary ingredients in SSBs, but little research into such properties of SSBs in naturally occurring consumption patterns. Thus, in this exploratory study, we sought to examine potentially addictive properties of SSBs during a 3-day SSB cessation intervention in overweight and obese adolescents who typically consume ≥3 SSBs daily. Participants (n = 25) were aged 13-18 years, mostly female (72%), and African American (56%) or Hispanic (16%) with a BMI≥95th percenttile (76%). Withdrawal symptoms and SSB craving were assessed approximately 1-week apart, during both regular SSB consumption and a 3-day period of SSB cessation in which participants were instructed to drink only plain milk and water. **During SSB cessation, adolescents reported increased SSB cravings and headache and decreased motivation, contentment, ability to concentrate, and overall well-being** (uncorrected Ps ‹ 0.05). This study provides preliminary evidence of withdrawal symptoms and increased SSB cravings during cessation in a diverse population of overweight or obese adolescents.

Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6488513/

Sugar Begets Sugar ➡ Obesity

Herman MA, Birnbaum MJ. Molecular aspects of fructose metabolism and metabolic disease. *Cell Metab*. 2021 Dec 7;33(12):2329-2354.

The hedonic reward derived from consuming sugars containing fructose contributes to its overconsumption, leading to excessive energy intake, overweight, and obesity. Additional mechanisms independent of its hedonic value have also been invoked to explain why fructose might be particularly obesogenic. For instance, fructose ingestion may have distinct effects on anorexigenic and orexigenic hormones, such as leptin and ghrelin, that impact feeding behaviors. Meal-associated increases in leptin are diminished by fructose compared with glucose and fructose may induce leptin resistance (Chotiwat et al., 2007; Shapiro et al., 2008; Teff et al., 2004). Fructose ingestion less potently suppresses ghrelin secretion compared with glucose ingestion (Teff et al., 2004). All these effects could promote excessive food intake and weight gain.

Recent evidence derived from human genetics and non-clinical model organisms has suggested a negative feedback loop, whereby the consumption of fructose suppresses further sugar consumption. FGF21 is a liver-derived hormone that regulates systemic fuel homeostasis (Flippo and Potthoff, 2021). In humans, non-human primates, and rodents, fructose consumption acutely and robustly increases hepatic production of FGF21 in a ChREBP-dependent manner (Dushay et al., 2015; Iizuka et al., 2009; Kim et al., 2017; Talukdar et al., 2016). FGF21 signals via neural circuitry, including through glutamatergic neurons in the ventromedial hypothalamus, to suppress further carbohydrate intake (von Holstein-Rathlou et al., 2016; Jensen-Cody et al., 2020; Talukdar et al., 2016).

Gillespie KM, Kemps E, White MJ, Bartlett SE. The Impact of Free Sugar on Human Health-A Narrative Review. Nutrients. 2023 Feb 10;15(4):889.

The evidence for an impact of sugars on obesity appears to be stronger when investigating the impacts of SSBs (as opposed to total sugar intake or other forms of carbohydrate). **Numerous studies have been conducted, with multiple systematic reviews and meta-analyses concluding that SSB consumption promotes weight gain.** Sucrose and high-fructose corn syrup from SSBs are the major source of fructose in our diets, which are thought to have a more detrimental impact on physical and neurological health given the unique way they are metabolised in the body.

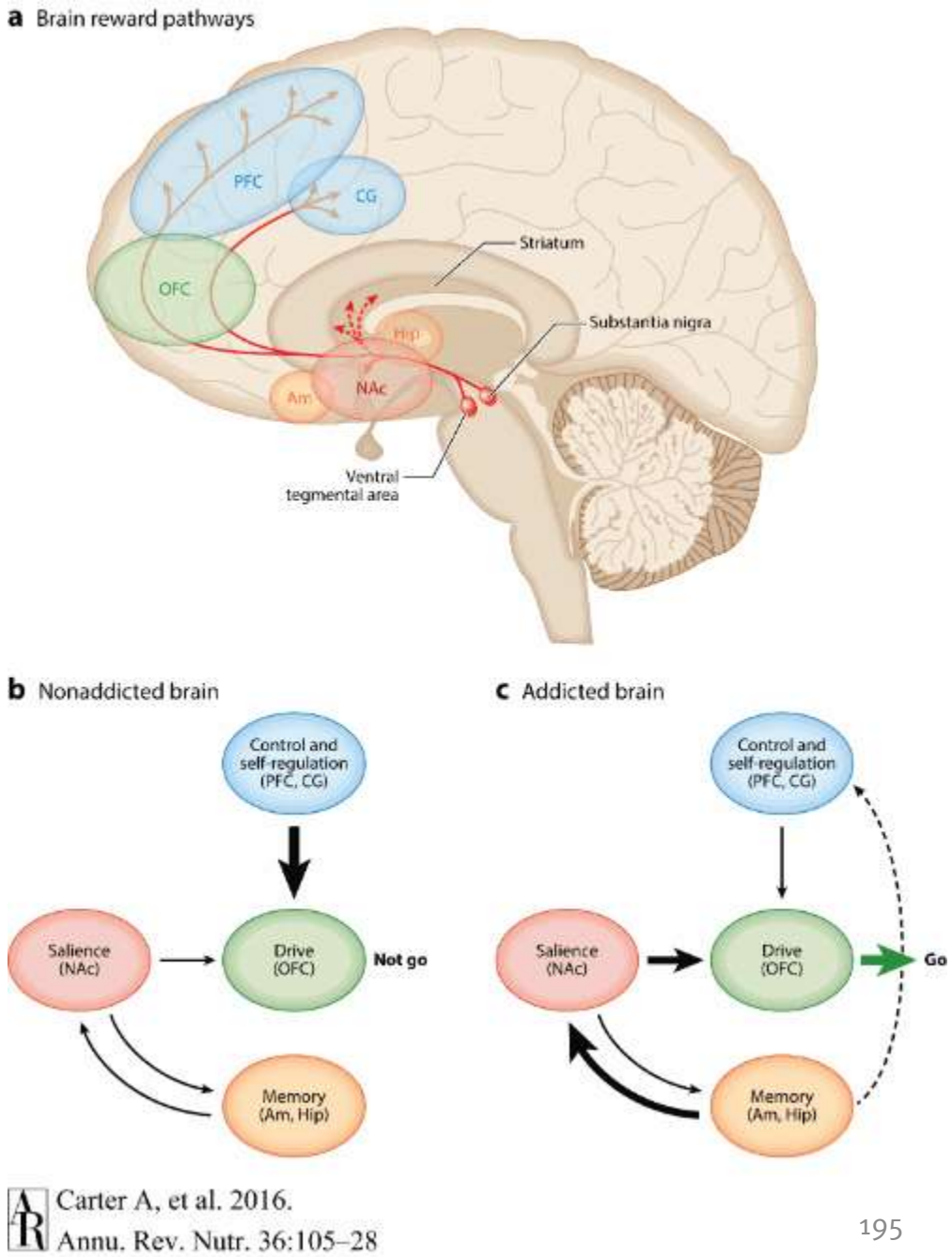
Source: https://www.cell.com/cell-metabolism/fulltext/S1550-4131(21)00429-0, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9966020/

Food Addiction is Driven by Loss of Prefrontal Cortex Control of Eating

Carter A, Hendrikse J, Lee N, Yücel M, Verdejo-Garcia A, Andrews ZB, Hall W. The Neurobiology of "Food Addiction" and Its Implications for Obesity Treatment and Policy. *Annu Rev Nutr*. Jul 17, 2016;36:105-28.

Figure 1

Model of brain circuits implicated in drug addiction and obesity. (a) The structures of the brain involved in addiction and obesity. The nucleus accumbens (NAc) is thought to play an important role in identifying activities that are rewarding or salient (the feature of a thing that makes it stand out from all others). The orbitofrontal cortex (OFC) is involved in decision making and determining the expected rewards/punishments of an action. The amygdala (Am) and hippocampus (Hip) are involved in forming memories of the stimulus/reward relationship; inhibitory control and emotional regulation are provided by the prefrontal cortex (PFC) and the anterior cingulate gyrus (CG). Addictive drugs and food, particularly in obese individuals, are believed to cause neurons from the ventral tegmental area to release the neurotransmitter dopamine in the NAc. These regions regulate activity in the frontal cortical regions. This pathway is referred to as the mesolimbic reward pathway (marked with red arrows). (b,c) Schematics showing the reward pathways in the (b) nonaddicted and the (c) so-called addicted brain. **In a person suffering from addiction, the reward pathway is disrupted such that the PFC and CG are no longer controlling factors, and compulsive behavior is driven by the enhanced activation of the reward/saliency and memory/conditioning regions of the brain.** As such, when an individual is exposed to the reinforcing stimulant (a drug or food, for example), the system goes into overdrive.



Source: https://www.annualreviews.org/content/journals/10.1146/annurev-nutr-071715-050909

Food Addiction and Drug Addiction Have Concordance with DSM-IV Criteria for “Addiction”

A critique of this view is presented by Graham Finlayson in 2017 (https://pubmed.ncbi.nlm.nih.gov/28549063).

Carter A, Hendrikse J, Lee N, Yücel M, Verdejo-Garcia A, Andrews ZB, Hall W. The Neurobiology of "Food Addiction" and Its Implications for Obesity Treatment and Policy. *Annu Rev Nutr*. 2016 Jul 17;36:105-28.

The suggestion that obesity may be a form of food addiction was initially based on phenotypic similarities between patterns of overeating in obese individuals and addictive drug use. These can be seen in a number of similarities between the eating behavior of obese individuals and diagnostic criteria for substance dependence in the fourth and fifth editions of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV and DSM-5). **Both patterns of behavior show signs of tolerance; withdrawal; substances taken in larger amounts or for longer than intended; unsuccessful efforts to control use; a large amount of time spent obtaining, using, or recovering from use of the substance; a neglect of social, occupational, or recreational activities; and continued use despite a “recurrent physical or psychological problem [...] caused or exacerbated by the substance”.**

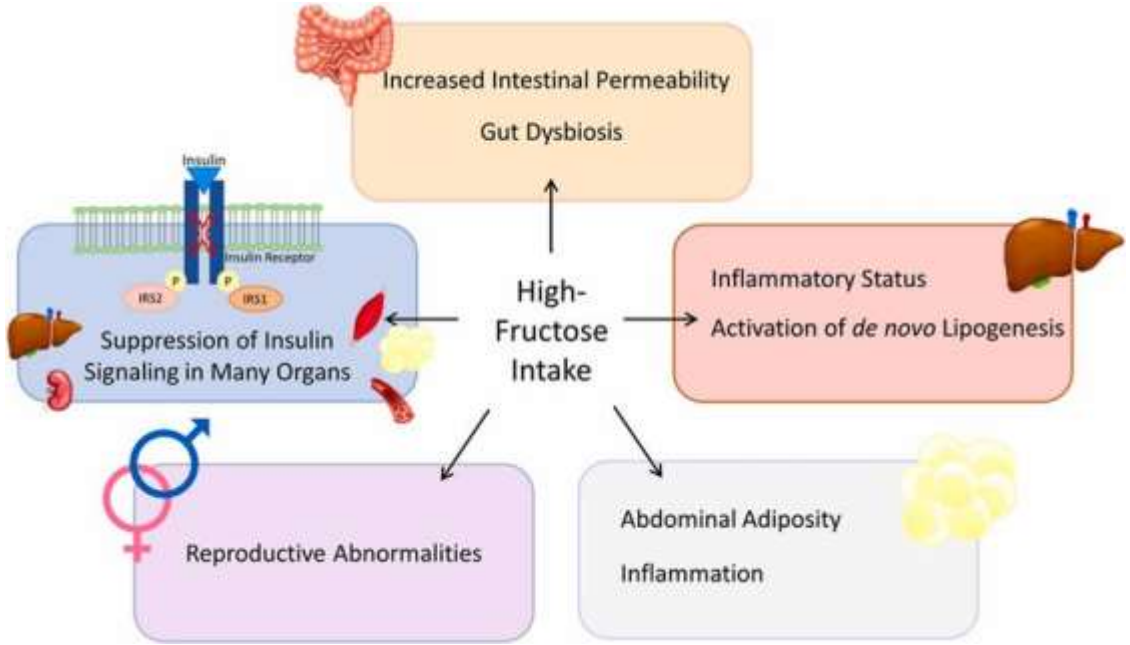
Gearhardt and colleagues adapted the DSM-IV criteria for substance dependence to create the Yale Food Addiction Scale (YFAS), a tool for diagnosing food addiction. Comparisons have also been made between maladaptive eating styles, such as binge eating disorder (BED), and the impaired impulse control and compulsivity of substance-dependent individuals.

Addictive patterns of eating are associated with obesity, but the overlap between the two is incomplete. Not all persons who are obese meet the criteria for food addiction, and not all individuals who meet the criteria for food addiction are overweight. The same is true for BED. These observations demonstrate that excess body mass index (BMI) is an inadequate marker of compulsive or addictive-like overeating. A larger correlation exists between BED and food addiction. Further research on the development of these disorders is needed to establish if they represent separate diagnoses or are part of the same processes. The validity of the YFAS does not establish that food addiction is a coherent concept. Research is needed to identify neural processes that are similarly involved in both food and drug addiction.

Source: https://www.annualreviews.org/content/journals/10.1146/annurev-nutr-071715-050909

Strong Evidence Links High Fructose Consumption to Microbiome Dysbiosis

- **Fructose and Microbiome**: Fructose induces gut microbiota dysbiosis, increasing the susceptibility to metabolic disorders like non-alcoholic fatty liver disease (NAFLD) and obesity.*
- **Metabolic Effects**: Research published in *Cell Metabolism* highlights how high fructose consumption promotes hepatic steatosis and insulin resistance through changes in gut microbiota composition and function.**
- **Gut Permeability and Inflammation**: A study in The Journal of Nutrition describes how fructose consumption can increase intestinal permeability and systemic inflammation, contributing to metabolic diseases.#
- **Obesity Mechanisms**: Reviews in Nutrients and The American Journal of Clinical Nutrition detail the role of fructose in promoting lipogenesis, altering appetite regulation, and inducing insulin resistance, all of which contribute to obesity.



* See https://www.mdpi.com/2227-9059/9/7/728, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9904196/, https://pubmed.ncbi.nlm.nih.gov/36839247/
** See https://www.cell.com/cell-metabolism/fulltext/S1550-4131(21)00423-X
# See https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10447940/

Fructose Impact on Microbiome Not Subtle

cmgh
CELLULAR AND MOLECULAR GASTROENTEROLOGY AND HEPATOLOGY

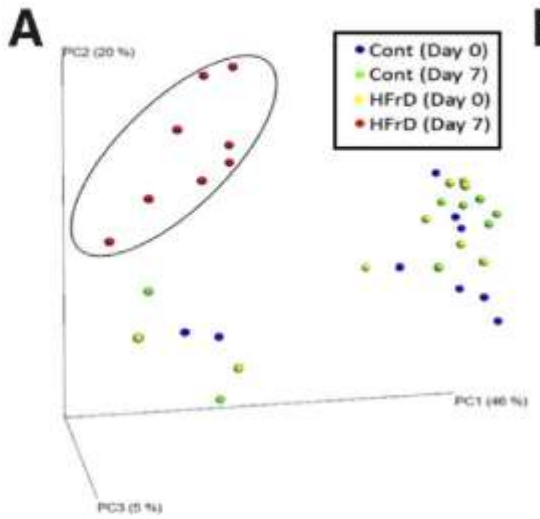
ORIGINAL RESEARCH

Dietary Fructose Alters the Composition, Localization, and Metabolism of Gut Microbiota in Association With Worsening Colitis

David C. Montrose,[1,a] Ryohei Nishiguchi,[1,a] Srijani Basu,[1] Hannah A. Staab,[1] Xi Kathy Zhou,[2] Hanhan Wang,[2] Lingsong Meng,[2] Melanie Johncilla,[3] Juan R. Cubillos-Ruiz,[4] Diana K. Morales,[4] Martin T. Wells,[5] Kenneth W. Simpson,[6] Shiying Zhang,[6] Belgin Dogan,[6] Chen Jiao,[7] Zhangjun Fei,[7] Akihiko Oka,[8] Jeremy W. Herzog,[8] R. Balfour Sartor,[8] and Andrew J. Dannenberg[1]

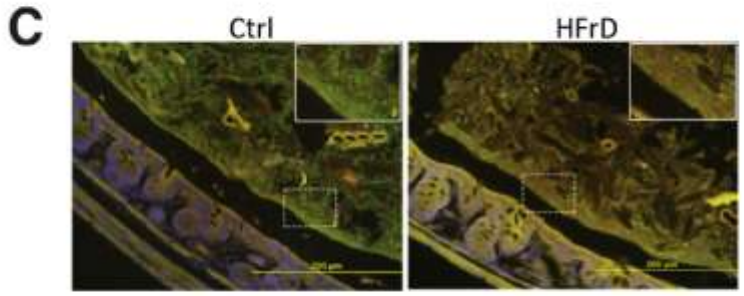
[1]Department of Medicine, [2]Department of Healthcare Policy and Research, [3]Department of Pathology, [4]Department of Obstetrics and Gynecology, Weill Cornell Medicine, New York, New York; [5]Department of Biological Statistics and Computational Biology, [6]Department of Clinical Sciences, [7]Boyce Thompson Institute for Plant Research, Cornell University, Ithaca, New York; and [8]Departments of Medicine, Microbiology, and Immunology, University of North Carolina, Chapel Hill, North Carolina

Cell Mol Gastroenterol Hepatol 2021;11:525–550



B

Species	Control (% Abundance)	HFrD (% Abundance)
*Clostridium disporicum**	11.48	0.27 ↓
*Akkermansia muciniphila**	14.66	31.12 ↑
Barnesiella spp.	5.33	4.33
*Lactobacillus johnsonii**	3.19	0.31 ↓
Robinsoniella peoriensis	1.13	1.44
*Clostridium sp.**	3.50	6.90 ↑
*Bacteroides acidifaciens**	32.06	2.56 ↓
Ruminococcus flavefaciens	0.86	1.14
*Lachnoclostridium clostridium aldenense**	1.25	3.29 ↑
Oscillospira spp.	0.77	1.61
Eubacterium rectale	1.00	1.90
Clostridium spp.	1.60	4.59
*Roseburia sp.**	0.27	1.20 ↑
*Lactococcus lactis**	0.85	7.84
Lachnoclostridium clostridium scindens	0.96	2.45 ↑
*Alloboculum sp**	2.42	0.62 ↓
Eubacterium coprostanoligenes	0.77	4.40
Sporobacter termitidis	0.75	2.03
Others	17.15	22.02



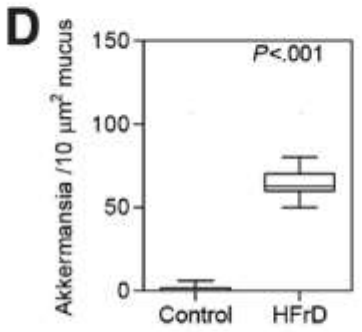


Figure 10. Consumption of a HFrD alters fecal gut microbiota. (*A* and *B*) Proportions of fecal bacterial populations were determined in mice at baseline and after feeding control or HFrD for 1 week using 16S rRNA analysis. (*A*) Microbial abundance is shown by principal coordinate analysis (n = 8–9/group). (*B*) Proportion of fecal bacterial species in mice given control or HFrD for 1 week is shown as percent of total microbes. Those bacteria that are at least 1% of the total are listed by name, and those below 1% were placed into the "others" category. *Abundance is significantly different comparing samples from control vs HFrD. (*C*) FISH using *A muciniphila*-specific probe was carried out on sections from mice fed control or HFrD for 1 week. (*D*) Number of FISH positive *A muciniphila* at mucus interface was quantified in colonic sections from control or HFrD fed mice (N = 8 per group, median ± standard deviation). Data were generated from single experiments.

Source: https://www.cmghjournal.org/article/S2352-345X(20)30145-4/fulltext

Microbiome Can be Positively Influenced by a Low Carb Diet

Li, X., Yang, J., Zhou, X. et al. Ketogenic diet-induced bile acids protect against obesity through reduced calorie absorption, *Nature Metabolism*, June 27, 2024

The low-carbohydrate ketogenic diet (KD) has long been practiced for weight loss, but the underlying mechanisms remain elusive. Gut microbiota and metabolites have been suggested to mediate the metabolic changes caused by KD consumption, although the particular gut microbes or metabolites involved are unclear. Here, we show that KD consumption enhances serum levels of taurodeoxycholic acid (TDCA) and tauroursodeoxycholic acid (TUDCA) in mice to decrease body weight and fasting glucose levels. Mechanistically, KD feeding decreases the abundance of a bile salt hydrolase (BSH)-coding gut bacterium, Lactobacillus murinus ASF361. The reduction of L. murinus ASF361 or inhibition of BSH activity increases the circulating levels of TDCA and TUDCA, thereby reducing energy absorption by inhibiting intestinal carbonic anhydrase 1 expression, which leads to weight loss. TDCA and TUDCA treatments have been found to protect against obesity and its complications in multiple mouse models. Additionally, the associations among the abovementioned bile acids, microbial BSH and metabolic traits were consistently observed both in an observational study of healthy human participants (n = 416) and in a low-carbohydrate KD interventional study of participants who were either overweight or with obesity (n = 25). In summary, we uncover a unique host–gut microbiota metabolic interaction mechanism for KD consumption to decrease body weight and fasting glucose levels. Our findings support TDCA and TUDCA as two promising drug candidates for obesity and its complications in addition to a KD.

Source: https://www.nature.com/articles/s42255-024-01072-1

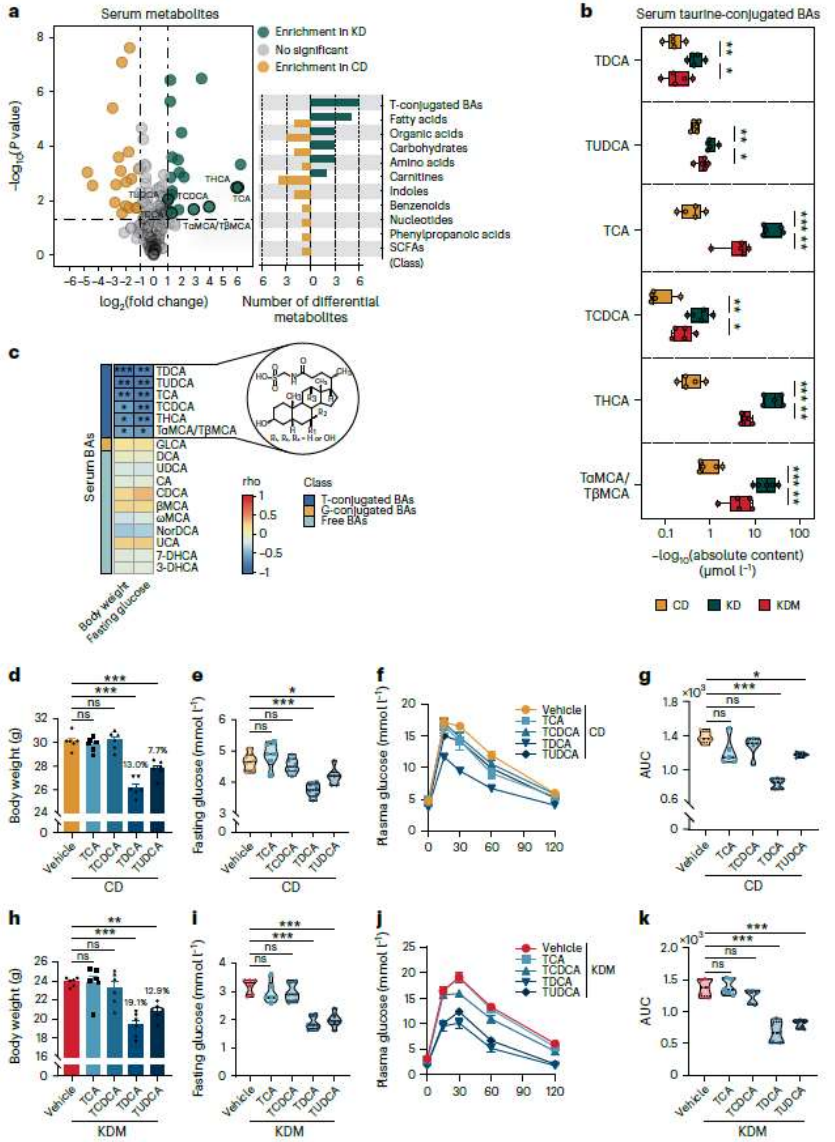


Fig. 1 | KD enhances serum TDCA and TUDCA levels to decrease body weight and fasting glucose levels. a, Volcano plot (fold change versus significance) of the serum metabolites enriched in CD-fed and KD-fed mice (six biological replicates for each group). Each point represents one metabolite. Taurine-conjugated BAs with significantly different levels in two groups are highlighted with black open circles. The right bar chart displays the number of enriched metabolites in multiple classes. **b**, Boxplot showing the serum levels of six taurine-conjugated BAs in CD-fed, KD-fed and KDM-fed mice (five biological replicates for each group; data are $\log_{10}$ transformed). Boxplot, median and quartiles; whiskers, data range. **c**, Heatmap displaying the correlations between serum levels of BAs and body weight or fasting glucose levels in CD-fed, KD-fed and KDM-fed mice (five biological replicates for each group). The chemical structure of taurine-conjugated BAs is shown on the right; created using ChemDraw. **d**–**g**, Body weight (**d**), fasting glucose (**e**), glucose tolerance test (GTT) (**f**) and the associated area under the curve (AUC) values (**g**) of CD-fed mice after 3 weeks of TCA, TCDCA, TDCA or TUDCA treatments (six biological replicates for each group). **h**–**k**, Body weight (**h**), fasting glucose (**I**), GTT (**j**) and the associated AUC values (**k**) of KDM-fed mice after 3 weeks of TCA, TCDCA, TDCA or TUDCA treatments (five biological replicates for each group). Error bars, s.e.m.; ns, not significant; *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$ determined by two-tailed Student's *t*-test (**a**), one-way ANOVA with Tukey's post-hoc test (**b**, **d**–**k**) and Spearman's rank correlation (**c**).

Obesity Linked to Microbiome Dysbiosis Through a Glutamate Mechanism

Gwenola Le Dréan & Hervé M. Blottière, Glutamate from the microbiome controls host metabolism, *Nature Metabolism*, June 2024; 987-989.

The intricate interplay between the gastrointestinal tract and the brain, known as the gut–brain axis, plays a fundamental role in regulating metabolic processes, including appetite control and energy homeostasis. Enteroendocrine cells (EECs) are key players in this axis, responsible for sensing luminal contents and secreting various hormones that signal to the brain to modulate feeding behaviour. Scattered throughout the lining of the gastrointestinal tract, these specialized cells express a large battery of receptors and transporters to detect nutrients and bacterial derivatives, depending on their location in the digestive tract, and covering the full range of stimuli in the lumen.

Tan et al., in a new study published in this issue of *Nature Metabolism*, discovered that a microbiota-derived metabolite, namely l-glutamate, could induce hyperphagia and obesity. Using elegant approaches of deletion of colonic EECs by crossing Neurog3fl/fl mice with Cdx2Cre transgenic mice (EECΔCol), the authors revealed that the absence of colonic EECs induced severe alteration in host metabolism, including dysregulation of appetite control and energy balance, leading to obesity accompanied by liver steatosis and adipose tissue hypertrophy. These findings point towards an enteroendocrine–microbial axis.

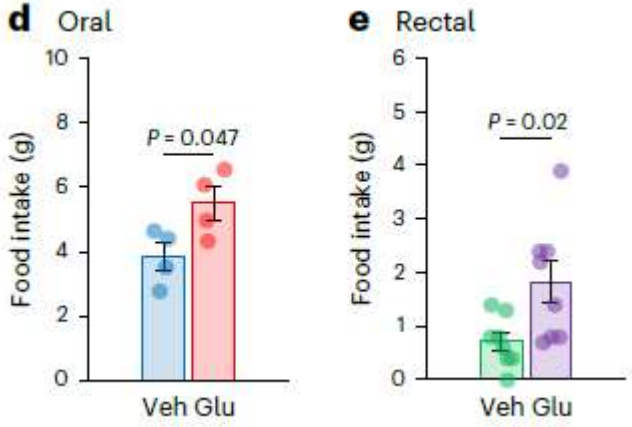
Moreover, the authors demonstrated that the mechanisms driving obesity were caused by gut microbiome dysbiosis. Using antibiotic treatment, germ-free rederivation and transfer to germ-free recipients, as well as co-housing of wild type and EECΔCol mice, the authors showed that the microbiome was necessary and sufficient to induce these metabolic effects.

Glutamate is the main excitatory neurotransmitter in the CNS and the ENS, both systems producing their endogenous glutamate and being preserved from luminal glutamate by a blood barrier. Vagal afferent neurons (VAN) terminate on neurons of the nucleus of the solitary tract (NTS), relaying peripheral signals to mediate appropriate physiological responses, including food intake. VAN connecting with the gut controls homeostatic eating behaviour by initiating satiation. **As glutamate is the primary neurotransmitter of vagal afferent signalling to the NTS, the contribution of the microbiota-derived l-glutamate on presynaptic glutamate receptor may disrupt the balanced regulation of endogenous glutamate.**

Source: https://doi.org/10.1038/s42255-024-01050-7

Tan et.al. Paper Links Glutamate Administration to Higher Food Intake

Glutamate increases food intake (Fig 7)



Interaction between the gut microbiota and colonic enteroendocrine cells regulates host metabolism

nature metabolism

Received: 26 June 2023

Accepted: 9 April 2024

Published online: 22 May 2024

Check for updates

Shuai Tan[1,2,17], Jacobo L. Santolaya[3], Tiffany Freeney Wright[3], Qi Liu[2], Teppei Fujikawa[4,5], Sensen Chi[6], Colin P. Bergstrom[2], Adam Lopez[2], Qing Chen[2], Goncalo Vale[7,8], Jeffrey G. McDonald[7,8], Andrew Schmidt[9], Nguyen Vo[9], Jiwoong Kim[10], Hamid Baniasadi[11], Li Li[1], Gaohui Zhu[1], Tong-Chuan He[12], Xiaowei Zhan[10], Yuuki Obata[9], Aishun Jin[6], Da Jia[13], Joel K. Elmquist[4,5,14,15], Luis Sifuentes-Dominguez[3,17] & Ezra Burstein[2,16,17]

Nutrient handling is an essential function of the gastrointestinal tract. Hormonal responses of small intestinal enteroendocrine cells (EECs) have been extensively studied but much less is known about the role of colonic EECs in metabolic regulation. To address this core question, we investigated a mouse model deficient in colonic EECs. Here we show that colonic EEC deficiency leads to hyperphagia and obesity. Furthermore, colonic EEC deficiency results in altered microbiota composition and metabolism, which we found through antibiotic treatment, germ-free rederivation and transfer to germ-free recipients, to be both necessary and sufficient for the development of obesity. Moreover, studying stool and blood metabolomes, we show that differential glutamate production by intestinal microbiota corresponds to increased appetite and that colonic glutamate administration can directly increase food intake. These observations shed light on an unanticipated host–microbiota axis in the colon, part of a larger gut–brain axis, that regulates host metabolism and body weight.

Illustration of Gut-Brain Interplay Via Microbiota as Identified in Tan Paper

Gwenola Le Dréan & Hervé M. Blottière, Glutamate from the microbiome controls host metabolism, *Nature Metabolism*, June 2024; 987-989.

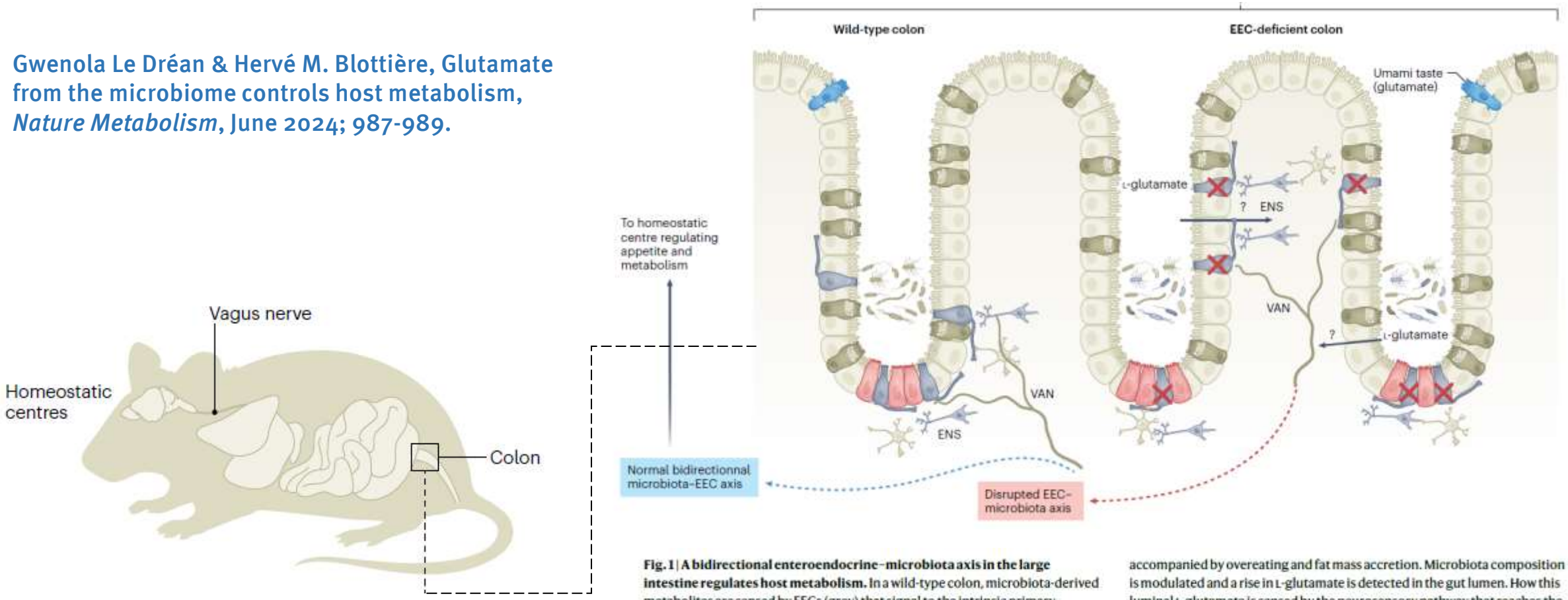


Fig. 1 | A bidirectional enteroendocrine–microbiota axis in the large intestine regulates host metabolism. In a wild-type colon, microbiota-derived metabolites are sensed by EECs (grey) that signal to the intrinsic primary afference of the ENS and VAN in the submucosa, relaying luminal cues to the homeostatic centres that control host appetite and energy balance. In EECs-deficient colon ($EEC\Delta_{col}$), host metabolism is significantly altered, and this is accompanied by overeating and fat mass accretion. Microbiota composition is modulated and a rise in L-glutamate is detected in the gut lumen. How this luminal L-glutamate is sensed by the neurosensory pathway that reaches the brain remains to be discovered. Tuft cells (blue), which express the umami taste receptor, may be potential candidates.

Source: https://doi.org/10.1038/s42255-024-01050-7

Efficacy of Bariatric Surgery Compatible with Gut-Brain Axis

Albaugh et. al., "Regulation of body weight: Lessons learned from bariatric surgery," *Molecular Metabolism*, Feb 2023.

Although no clear and unique mechanism has yet emerged, there is moderately convincing evidence that increased GLP-1 signaling plays a significant role in orchestrating reduced food intake and loss of body weight after RYGB in humans, and in improving glucose homeostasis after RYGB and VSG in rodents and humans. There is also some evidence from transgenic mouse models for the partial involvement of other signaling pathways, including bile acids, gut microbes, leptin, melanocortin, and IGFBP2.

However, besides perhaps melanocortin signaling, none of these signaling pathways seems to account for the bulk of the beneficial effects of bariatric surgery. We speculate that, similar to the genetics of obesity, dozens of signaling pathways contribute to these beneficial effects, each with a small size effect and making their experimental demonstration difficult.

This was quite unexpected because the initial intervention in bariatric surgery is limited to the gut. If correct, the scenario reveals a much richer cross-communication between the gut and the rest of the body, at least as far as body weight regulation is concerned. As with the genetics of obesity, it is still possible that we are currently missing a signaling pathway(s) with a larger size effect, as methodological advances in clinical and preclinical research become available.

While bariatric surgery works well there is no single hormone that explains its effect.

Rather, broad crosstalk between gut hormones and metabolites and the brain appears to explain the permanent weight loss.

Source: https://www.sciencedirect.com/science/article/pii/S2212877822000862

Bariatric Surgery Deprograms Hedonistic Eating

Albaugh et. al., "Regulation of body weight: Lessons learned from bariatric surgery," *Molecular Metabolism*, Feb 2023.

3.3.2. Hedonic and cognitive mechanisms

Besides a reduction in caloric intake, many clinical studies also report changes in food preferences and food choice, as well as in the 'liking' and 'wanting' of specific nutrients and foods after bariatric surgery [130—137]. Homeostatic mechanisms centering around the hypothalamus have been dominating research in the 20th century, but there is now much interest in the role of hedonic and cognitive brain functions in the controls of food intake and regulation of energy balance [138—140]. The interrelated concepts of food reward [141,142], cue-induced conditioned eating [143,144], executive/inhibitory control [145,146], and their relationship with homeostatic circuits which are mainly controlled by interoceptive signals [147—149], have been in the center of this effort.

After bariatric surgery, patients seem to want food far less often.

Something breaks in the gut-brain axis to cause a patient to lose interest in food.

Source: https://www.sciencedirect.com/science/article/pii/S2212877822000862

Absence of Specific Microbe Is Associated with Glutamate in the Bloodstream and Obesity

Nature Medicine, Jul 2017, pp. 859-868.

Gut microbiome and serum metabolome alterations in obesity and after weight-loss intervention

Ruixin Liu[1,16], Jie Hong[1,16], Xiaoqiang Xu[2,3,16], Qiang Feng[2,4,16], Dongya Zhang[2,16], Yanyun Gu[1,16], Juan Shi[1], Shaoqian Zhao[1], Wen Liu[1], Xiaokai Wang[2,3], Huihua Xia[2,5], Zhipeng Liu[2], Bin Cui[1,6], Peiwen Liang[1], Liuqing Xi[1], Jiabin Jin[7], Xiayang Ying[7], Xiaolin Wang[8], Xinjie Zhao[8], Wanyu Li[1], Huijue Jia[2,5,9], Zhou Lan[2], Fengyu Li[2], Rui Wang[1], Yingkai Sun[1], Minglan Yang[1], Yuxin Shen[1], Zhuye Jie[2,5], Junhua Li[2,5,9], Xiaomin Chen[2], Huanzi Zhong[2,5], Hailiang Xie[2], Yifei Zhang[1], Weiqiong Gu[1], Xiaxing Deng[7], Baiyong Shen[7], Xun Xu[2,5], Huanming Yang[2,10], Guowang Xu[8], Yufang Bi[1], Shenghan Lai[11], Jian Wang[2,10], Lu Qi[12,13], Lise Madsen[2,14,15], Jiqiu Wang[1], Guang Ning[1,6], Karsten Kristiansen[2,5,15] & Weiqing Wang[1]

Emerging evidence has linked the gut microbiome to human obesity. We performed a metagenome-wide association study and serum metabolomics profiling in a cohort of lean and obese, young, Chinese individuals. We identified obesity-associated gut microbial species linked to changes in circulating metabolites. The abundance of *Bacteroides thetaiotaomicron*, a glutamate-fermenting commensal, was markedly decreased in obese individuals and was inversely correlated with serum glutamate concentration. Consistently, gavage with *B. thetaiotaomicron* reduced plasma glutamate concentration and alleviated diet-induced body-weight gain and adiposity in mice. Furthermore, weight-loss intervention by bariatric surgery partially reversed obesity-associated microbial and metabolic alterations in obese individuals, including the decreased abundance of *B. thetaiotaomicron* and the elevated serum glutamate concentration. Our findings identify previously unknown links between intestinal microbiota alterations, circulating amino acids and obesity, suggesting that it may be possible to intervene in obesity by targeting the gut microbiota.

Source: https://www.nature.com/articles/nm.4358

This paper links closely to the Tan et.al. work on microbiome, glutamate and obesity.

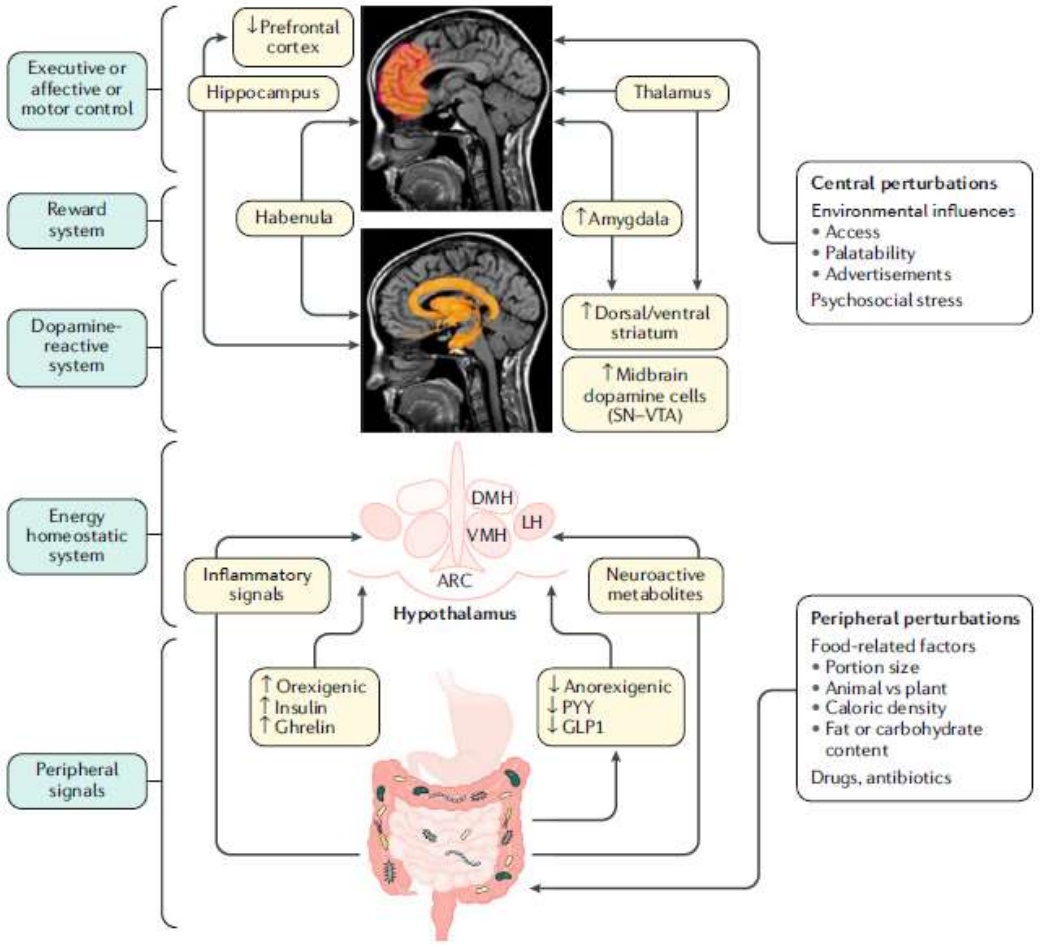
Liu et.al. find that a specific microbe might be added to overcome dysbiosis of the gut and change the link to obesity.

Interestingly, the deficiency of the same microbe is altered in humans by bariatric surgery.

Recent Comprehensive Review Consistent with Food Addiction Theory of Obesity

Gupta, A., Osadchiy, V. & Mayer, E.A. Brain–gut–microbiome interactions in obesity and food addiction. Nat Rev Gastroenterol Hepatol 17, 655–672 (2020).

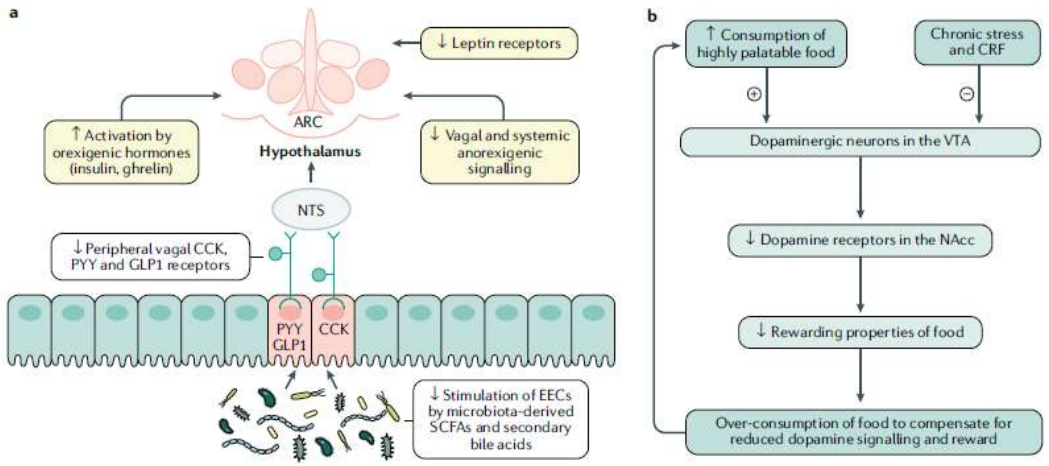
Normal eating behaviour is coordinated by the tightly regulated balance between intestinal and extra-intestinal homeostatic and hedonic mechanisms. By contrast, food addiction is a complex, maladaptive eating behaviour that reflects alterations in brain–gut–microbiome (BGM) interactions and a shift of this balance towards hedonic mechanisms. Each component of the BGM axis has been implicated in the development of food addiction, with both brain to gut and gut to brain signalling playing a role. Early-life influences can prime the infant gut microbiome and brain for food addiction, which might be further reinforced by increased antibiotic usage and dietary patterns throughout adulthood. The ubiquitous availability and marketing of inexpensive, highly palatable and calorie-dense food can further shift this balance towards hedonic eating through both central (disruptions in dopaminergic signalling) and intestinal (vagal afferent function, metabolic endotoxaemia, systemic immune activation, changes to gut microbiome and metabolome) mechanisms. In this Review, we propose a systems biology model of BGM interactions, which incorporates published reports on food addiction, and provides novel insights into treatment targets aimed at each level of the BGM axis.



Source: https://www.nature.com/articles/s41575-020-0341-5

Gupta Review Suggests Targets for Intervention

Gupta, A. et.al, "Brain–gut–microbiome interactions in obesity and food addiction," *Nat Rev Gastroenterol Hepatol* 17, 655–672 (2020).



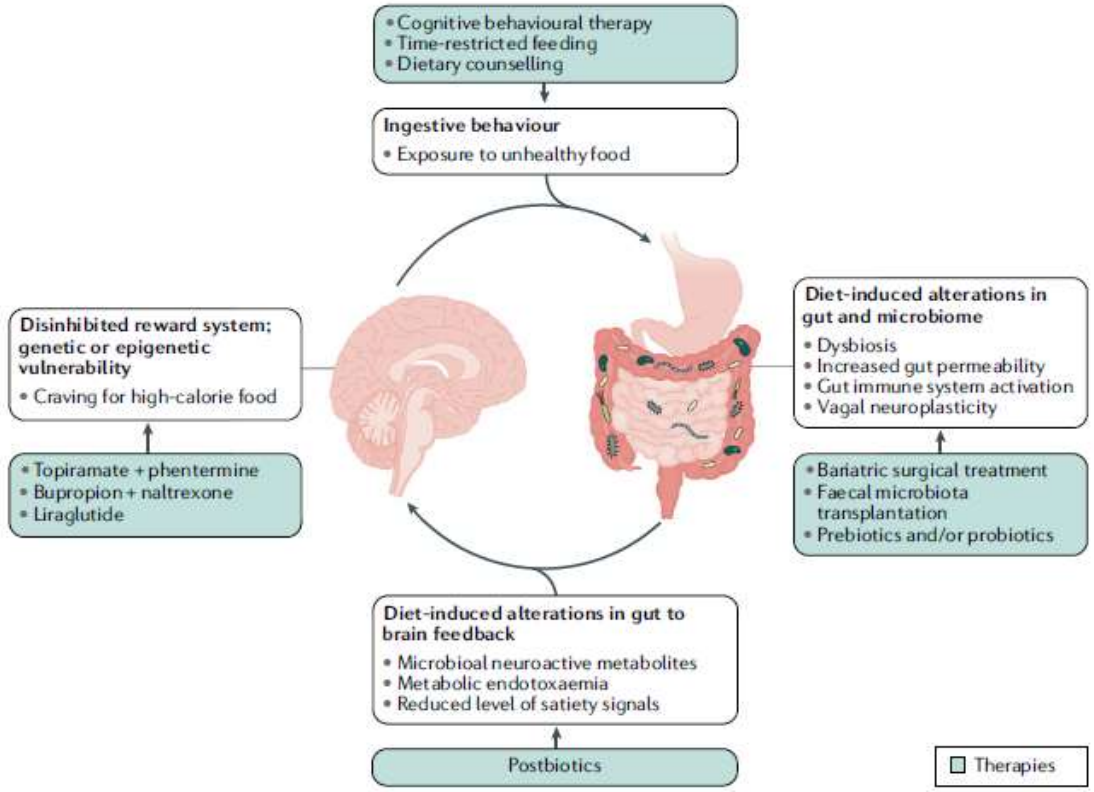


Fig. 3 | Mechanisms in the homeostatic and hedonic systems leading to food addiction. a | Diet- induced disinhibition of vagal and hypothalamic satiety mechanisms. A high- fat, low- fibre diet reduces the release of satiety hormones (glucagon- like peptide 1 (GLP1), peptide YY (PYY), cholecystokinin (CCK)) from enteroendocrine cells (EECs) in the gut by dietary fibre- derived short- chain fatty acids (SCFAs), leading to downregulation of receptors for satiety hormone molecules on vagal afferents innervating the EECs, and to downregulation of the vagal- mediated satiety signalling via the nucleus tractus solitarius (NTS) to the arcuate nucleus of the hypothalamus (ARC). Hypothalamic receptors mediating the effect of other anorexigenic signals (leptin) reaching the ARC via the systemic circulation are also downregulated, resulting in an unrestrained effect of orexigenic signals (ghrelin, insulin, cortisol). Thus, chronic exposure to a high- fat, low- fibre diet downregulates the inhibitory mechanisms of homeostatic regulation of ingestive behaviours. b | Diet- induced changes in the extended reward system. According to the dopamine deficiency hypothesis, a reduction in dopaminergic stimulation of neurons in the nucleus accumbens (NAcc) as a result of reduced dopamine release from the ventral tegmental area (VTA), and downregulation of dopamine receptors on NAcc neurons, reduces the rewarding effects of ingested foods, and leads to craving and over- consumption of unhealthy food in an attempt to compensate for the reduced dopamine signalling. Chronic stress- induced release of corticotropin- releasing factor (CRF) and glucocorticoid levels also have an inhibitory effect on dopamine signalling. Upward arrows and downward arrows inside boxes indicate reported upregulation and downregulation of respective mechanisms.

Source: https://www.nature.com/articles/s41575-020-0341-5

Novel Therapeutic Options for Treating Drug Addiction Emerging

The landscape of therapeutics for treating drug addiction is rapidly evolving, with several promising approaches showing significant potential. Key options under investigation include:

- **Deep Brain Stimulation**: Deep brain stimulation (DBS) is emerging as a promising treatment for addiction. This method involves electrically stimulating specific brain regions to disrupt the dopamine release that drives addictive behaviors. Preliminary studies in both animal models and humans have shown that DBS can reduce drug-seeking behavior and may help prevent relapse by modifying the brain's reward system.

- **Psychedelic-Assisted Therapy**: Psychedelic substances like Ibogaine, Noribogaine, Ketamine, DMT, and Psilocybin are gaining traction for their potential in treating addiction. These substances, often used in controlled therapeutic settings, have shown promise in helping individuals break the cycle of addiction by promoting profound psychological insights and emotional healing.

- **Orexin-1 Receptor Antagonists**: Targeting the orexin-1 receptor has been found to be effective in reducing drug-seeking behavior. Orexin-1 receptor antagonists block the signaling pathways involved in the reinforcement and craving associated with addiction, providing a novel approach to treatment. For example, Nivasorexant is a selective orexin-1 receptor antagonist drug developed by Idorsia Pharmaceuticals Ltd. It's an oral drug that can penetrate the brain and is the first SO1RA to enter clinical development. As of May 2024, its global R&D status is Phase 1. The drug recently was not successful in treating binge eating disorder.

These are examples of a broad range of possibilities under investigation.* These therapies offer significant hope in how we approach addiction treatment, focusing not only on the behavioral aspects but also addressing the underlying biological mechanisms.

* See https://pubmed.ncbi.nlm.nih.gov/30382181/

Sources: Brain Stimulation (https://medicalxpress.com/news/2024-03-brain-drug-addiction.html, https://www.neurotherapeuticsjournal.org/article/S1878-7479(23)01076-0/, https://www.neuromodulationjournal.org/article/S1094-7159(22)00724-3/, https://pubmed.ncbi.nlm.nih.gov/26030707/); Psychedelics (https://www.frontiersin.org/journals/psychiatry/articles/10.3389/fpsyt.2023.1183740/full, https://www.nytimes.com/2022/03/31/well/mind/psilocybin-mushrooms-addiction-therapy.html, https://www.frontiersin.org/journals/psychiatry/articles/10.3389/fpsyt.2023.1134454/full) and Orexin-1 antagonism (https://www.sciencedirect.com/science/article/abs/pii/S0166223621001697, https://www.nature.com/articles/s41398-022-02090-x, https://pubs.acs.org/doi/10.1021/acs.jmedchem.3c01894).

Does the Food Addiction Theory Offer a Viable Fourth Generation Strategy for Obesity Management?

- The addiction theory of obesity fits the facts of the U.S. obesity epidemic reasonably well.
- Recent research on gut-brain communication, microbiome, glutamate and obesity is quite interesting and supportive of the addiction hypothesis.
- We know from other addictive behaviors that there are effective treatments but “one and done” approaches have been elusive.
- The pipeline of novel approaches to addiction treatment is interesting and some approaches have a “one and done” element. Some might have application to the obesity area.*
- Perhaps, most interestingly, is the idea that interventions could be possible in the gut and microbiome itself to interrupt the communication between gut and brain. Several possibilities have emerged in the literature.

* See, for example: https://pubmed.ncbi.nlm.nih.gov/33719688/

Fatty Brain Theory

4 Fatty Brain Theory

It's well-known that eating behavior is controlled by the brain and, by implication, obesogenic behavior also must be controlled in the brain.*

There are a variety of effective pharmacologic obesity interventions that work through control of the brain in some way. These include CB1 inverse agonist class and QSYMIA® which includes topiramate.

There is also overwhelming evidence that GLP-1 receptors are present in the brain and that changes associated with GLP-1 receptor agonist impact weight through changes in brain activity and associated chemistry.**

But we also know that cessation of GLP-1's often leads to weight regain.

So, the real question isn't do some drugs reduce obesity through the brain? Rather, we wish to ask: Can obesity be thought mainly as a brain disease like depression which largely has an endogenous cause?

Think of cancer. One school of thought is that cancer is caused by mutations in growth factor receptors that lead to uncontrolled cell growth. A different school of thought portrays cancer as an immunologic disease – a failure of the immune system to recognize cancerous cells and kill them. So, to define, the idea here is that there is an unrecognized endogenous CNS disease called "fatty brain" that makes some people fat.

We all try to treat obesity with diet, exercise and all sorts of modern incretin drugs. But the fatty brain theorists would suggest that if you don't treat the underlying brain condition, you won't really help the patient. You'll lose weight on those incretin drugs but as soon as you stop them, the weight will come right back.

To take the analogy further, in advanced cancer we see true long-term cures with PD-1 antibodies, for example, but rarely get them with growth factor inhibitors.

Let's suppose, hypothetically, that we figured out the biology of fatty brain. We might then be able to improve on pharmacology in a manner that created the possibility of a permanent cure.

As hinted already, one could see the "food addiction" theory discussed previously as a version of fatty brain. The normal homeostatic weight regulation mechanism is disrupted, perhaps by too much fructose, and the person becomes fat. Addiction is a serious disease and is, in theory, treatable.

But are there other endogenous brain causes of obesity that could be treated pharmacologically? We are looking for narratives that, like depression, could involve external stimuli, but fundamentally, involve dysregulation of eating for some neurobiological reason.

*See, for example: Kim MS. The neural basis of weight control and obesity. Exp Mol Med. 2022 Apr;54(4):347-348.
**See, for example: https://www.science.org/doi/10.1126/sciadv.adh0980, https://www.nature.com/articles/s41598-023-34070-6, https://www.nature.com/articles/d41586-024-02106-0.

Theories of Fatty Brain

We have conducted a literature review and have talked to a few experts in this area. The following narratives came up:

1. Dopamine Dysfunction can cause obesity;
2. Disregulation of NMDA / glutaminergic receptors

The **dopamine dysfunction theory** is appealing. The idea is that we become obese for some reason – perhaps too much fast food in adolescence. Then, we try to take the weight off through diet or GLP-1 drugs. But the weight keeps coming back. The theory states that the first episode of obesity changes our dopamine expression system in a manner that stays with us when we lose weight. The striatal dopamine system, specifically, becomes less expressive in the presence of excess fat. This creates a self-reinforcing feedback loop that causes the fat to stay fat. So, if you artificially force yourself to lose weight (say with that handy semaglutide prescription) it will initially work. But the dopamine dysfunction doesn't go away. So, as a result, you will slowly put the weight back on. One would need to deal with the underlying dopamine dysfunction to realize long-term weight loss.

What's appealing about the theory is that can (1) explain why diets don't work, (2) be consistent with the rise in obesity but also explain why obesity isn't going down despite a recent drop in sugar use, (3) explain why almost all weight loss interventions fail – no matter what their etiology. Interestingly, the theory is also consistent with the success of bariatric surgery. After this surgery, patients see reactivation of their dopaminergic systems in a way that restrains eating.*

The **NMDA receptor theory** has been around for about five years. N-methyl-D-aspartate receptors (NMDAR) are glutamate-gated ion channels permeable to Ca2+ found throughout the brain.

Glutamate is the principal excitatory neurotransmitter by binding to postsynaptic NMDARs, contributing to NMDAR excitatory postsynaptic currents, and participating in almost all brain physiological functions.

In addition, NMDAR has been implicated in synaptic plasticity, which is the key substrate for learning and memory processes. Several observers have argued that NMDA receptor antagonism can increase neural plasticity which in turn could cause a neurological state sustaining pathological obesity to change.

Numerous studies have reported NMDAR signaling in the regulation of appetite. NMDAR signaling regulates food intake at several appetite-suppressing nodes, including the solitary tract nucleus, the parabrachial nucleus, the ventromedial nucleus of the hypothalamus and the lateral habenula.

* See https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2926260/

Theories of Fatty Brain (continued)

Interestingly, ketamine is a well-known NMDA receptor antagonist (as are several approved drugs like memantine, amantadine and dextromethorphan). Ketamine is used medically with positive effect to manage depression but is not without liabilities.

An idea championed by Christoffer Clemmensen of the University of Copenhagen is that one might be able to enhance the effect of NMDA receptor antagonists by co-administering them with a jointly bound GLP-1 agonist. A recent paper authored by Clemmensen and colleagues found that doing so was able to improve weight loss in mice over a GLP-1 alone or an NMDA receptor antagonist alone.

Importantly, the effect was long-lasting suggesting the possibility of a long-lasting or even permanent therapy – as has been seen with drugs like ketamine for depression. Whether or not this might work in humans is not known although, interestingly, there is clinical evidence that amantadine and memantine are associated with rather impressive weight loss in obese persons.

As you might imagine, the area of NMDA receptor pharmacology is fertile and efforts are underway to innovate – developing more specific, better binding oral options at companies like Gate Neuroscience and Gilgamesh Pharma.

We would close by noting that the theories of fatty brain proposed here (dopamine and NMDA) are intended to be illustrative rather than comprehensive.

We hope that readers might be motivated to identify other relevant theories or to develop novel theories that involve brain function and the persistence of obesity despite the use of dietary and pharmacologic interventions.

An important complexity is that it is likely that multiple neurotransmitters and MOA's contribute to obesity in the brain. It is unlikely that there is a single factor that contributes to fatty brain.

A 2020 paper by Labban and colleagues noted, for example: "Obesity and the brain are linked since the brain can control the weight of the body through its neurotransmitters. In brain tissue, significantly high levels of dopamine and glutamate as well as significantly low levels of serotonin were found in the obese group compared to those in the lean group and were discussed in relation to the biochemical profile in the serum. It was also noted that the HFD affected bacterial gut composition in comparison to the control group… The results of the present study confirm that obesity is linked to inflammation, oxidative stress, dyslipidemic processes, and altered brain neurotransmitter levels that can cause obesity-related neuropsychiatric complications."*

* See: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7705990/

Dopamine is a Central Mediator Between Food Reward Signals and Endocannabinoids

Coccurello R, Maccarrone M. Hedonic Eating and the "Delicious Circle": From Lipid-Derived Mediators to Brain Dopamine and Back. *Front Neurosci.*, April 24, 2018, pp. 271.

Palatable food can be seductive and hedonic eating can become irresistible beyond hunger and negative consequences. This is witnessed by the subtle equilibrium between eating to provide energy intake for homeostatic functions, and reward-induced overeating. In recent years, considerable efforts have been devoted to study neural circuits, and to identify potential factors responsible for the derangement of homeostatic eating toward hedonic eating and addiction-like feeding behavior. Here, we examined recent literature on "old" and "new" players accountable for reward-induced overeating and possible liability to eating addiction. Thus, the role of midbrain dopamine is positioned at the intersection between selected hormonal signals involved in food reward information processing (namely, leptin, ghrelin, and insulin), and lipid-derived neural mediators such as endocannabinoids. The impact of high fat palatable food and dietary lipids on endocannabinoid formation is reviewed in its pathogenetic potential for the derangement of feeding homeostasis.

The dopaminergic system forms the crossroads of a complicated interplay of brain signal transmitters that control the eating motivation (hunger) system.

Source: https://pubmed.ncbi.nlm.nih.gov/29740277/

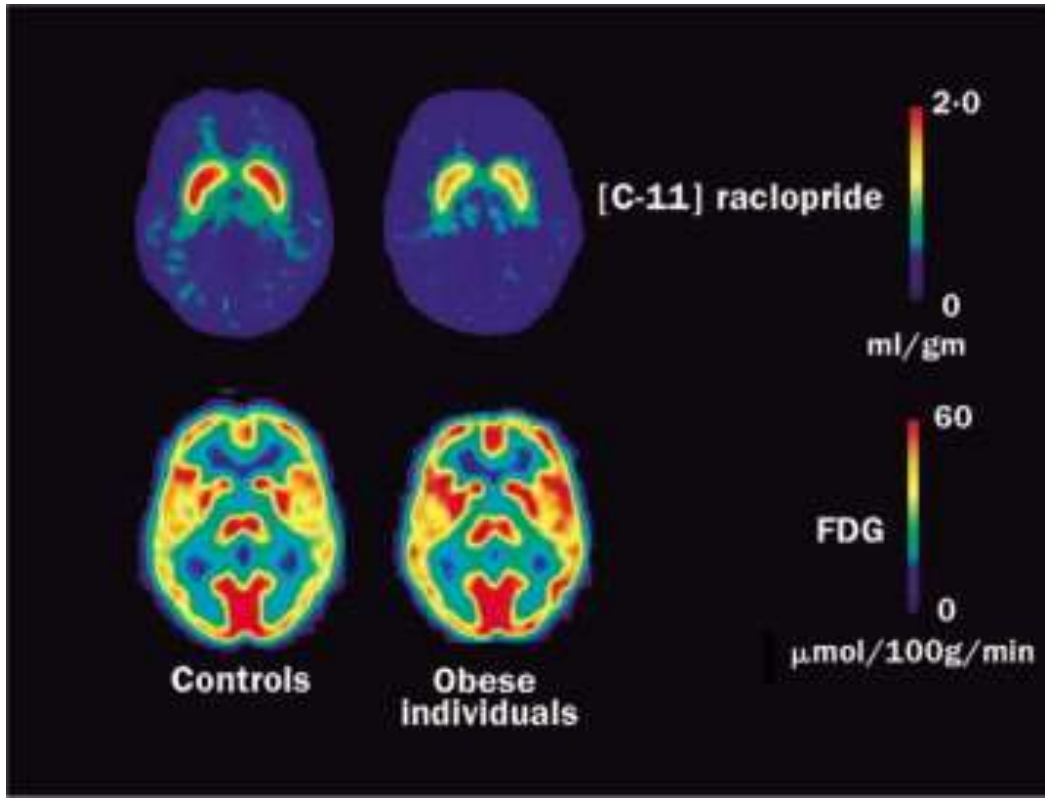
Dopamine Receptor Density Lower in Obese Individuals

Wang et.al., "Brain dopamine and obesity," *Lancet*, Feb 3, 2001.

The cerebral mechanisms underlying the behaviours that lead to pathological overeating and obesity are poorly understood. Dopamine, a neurotransmitter that modulates rewarding properties of food, is likely to be involved. To test the hypothesis that obese individuals have abnormalities in brain dopamine activity we measured the availability of dopamine D_2 receptors in brain.

Striatal dopamine D2 receptor availability was significantly lower in the ten obese individuals (2·47 [SD 0·36]) than in controls (2·99 [0·41]; p<0·0075). In the obese individuals body mass index (BMI) correlated negatively with the measures of D2 receptors (r=0·84; p⩾0·002); the individuals with the lowest D2 values had the largest BMI. By contrast, neither whole brain nor striatal metabolism differed between obese individuals and controls, indicating that striatal reductions in D2 receptors were not due to a systematic reduction in radiotracer delivery.

The availability of dopamine D_2 receptor was decreased in obese individuals in proportion to their BMI. Dopamine modulates motivation and reward circuits and hence dopamine deficiency in obese individuals may perpetuate pathological eating as a means to compensate for decreased activation of these circuits. Strategies aimed at improving dopamine function may be beneficial in the treatment of obese individuals.



Source: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(00)03643-6

Obesity Begets Obesity: High Calorie Diets Reduce Capacity for Dopamine Transmission Which Stimulates Eating

Wallace CW, Fordahl SC. Obesity and dietary fat influence dopamine neurotransmission: exploring the convergence of metabolic state, physiological stress, and inflammation on dopaminergic control of food intake. *Nutr Res Rev.* 2022 Dec;35(2):236-251.

Prolonged consumption of highly palatable diets may disrupt dopamine reward signalling. Chronic HFD intake and diet-induced obesity impact VTA dopamine neuron activity and interfere with mechanisms regulating dopamine at synaptic terminals within the NAc. Changes include lowered D2R binding potential as well as reduced dopamine transporter (DAT) function and membrane localisation. Furthermore, HFD intake activates inflammatory processes that may contribute to neuronal insulin resistance. Central insulin and leptin resistance attenuate satiation and reward valuation of palatable foods by altering NAc synaptic dopamine and disrupt orexigenic and anorectic communication between the LH, ARC and VTA. Finally, chronic HFD intake shifts opioid control of NAc dopamine neurotransmission, which could amplify stress-induced feeding and have consequences for obese individuals on energy restricted diets. Overall, studies presented below demonstrate HFD consumption acutely increases NAc dopamine , but prolonged intake reduces capacity for dopamine neurotransmission through repeated stimulation of dopamine receptors, resistance to hormonal and homeostatic signals , and up-regulated inflammatory signalling·

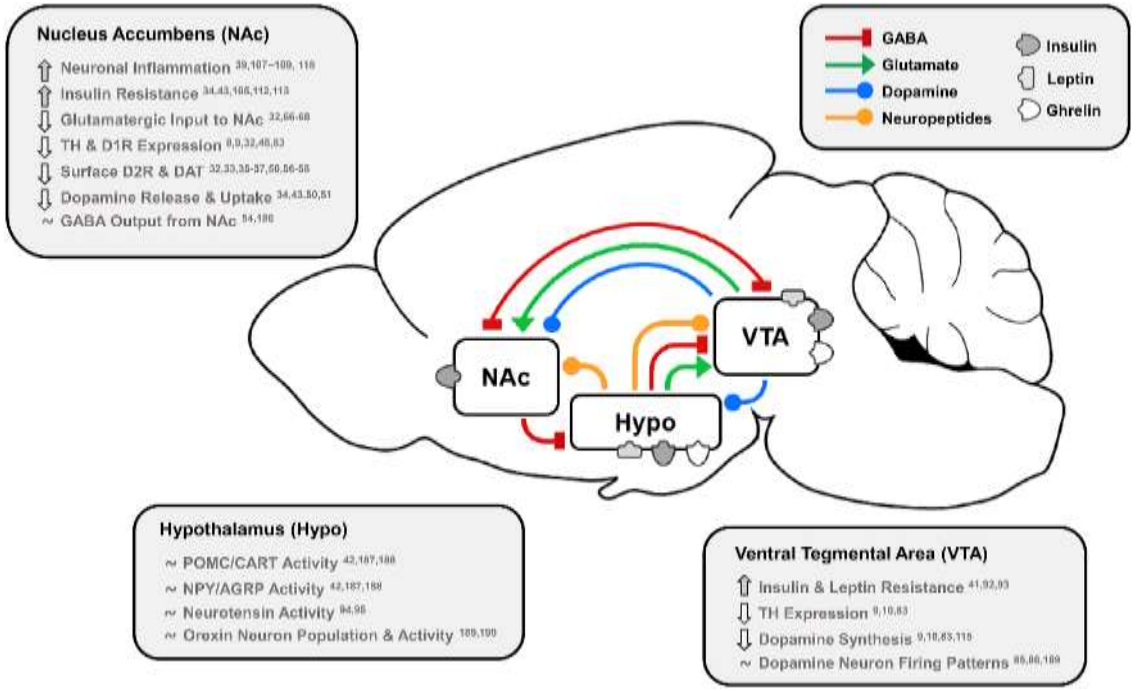


Fig. 1. Effects of dietary fat and obesity on hedonic and homeostatic dopamine circuits: homeostatic, dopamine-motivated feeding and reward learning circuits overlap as insulin and leptin convey body energy status to the hypothalamus (Hypo) and VTA. In response, hypothalamic nuclei send appetitive neuropeptides to the VTA and NAc to influence food intake, and NAc dopamine neurotransmission is directly stimulated by hormonal action in the NAc and VTA. This information is also conveyed via dopamine, GABA and glutamate from the VTA to NAc, and the NAc responds by sending GABA to hypothalamic feeding regions, the VTA as a regulatory feedback circuit, and thalamic, motor and cognitive cortical regions. Effects of long-term HFD or palatable food consumption are highlighted by region. This characterises how diet-induced obesity dysregulates key neurotransmitters, neuropeptides and hormones that regulate food intake to reduce dopamine neurotransmission leading to overeating and further weight gain.

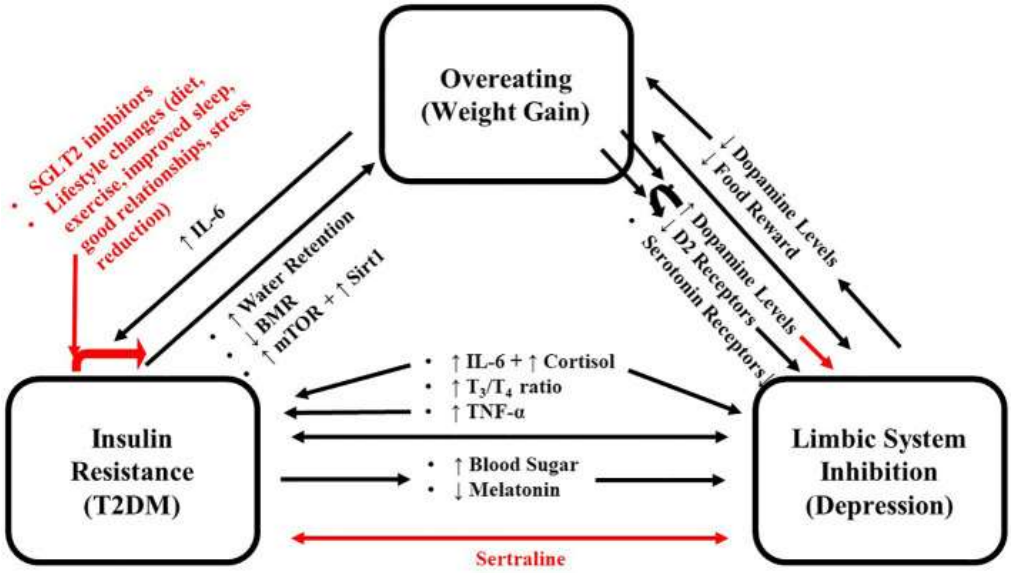
Source: https://pubmed.ncbi.nlm.nih.gov/34184629/

Dopamine Inhibition Helps Explain Why Depression is So Common in Obesity and Diabetes

Wilson JB, Epstein M, Lopez B, Brown AK, Lutfy K, Friedman TC. The role of Neurochemicals, Stress Hormones and Immune System in the Positive Feedback Loops between Diabetes, Obesity and Depression. *Front Endocrinol,* Aug 17, 2023, p. 1224612.

Type 2 diabetes mellitus (T2DM) and depression are significant public health and socioeconomic issues. They commonly co-occur, with T2DM occurring in 11.3% of the US population, while depression has a prevalence of about 9%, with higher rates among youths. Approximately 31% of patients with T2DM suffer from depressive symptoms, with 11.4% having major depressive disorders, which is twice as high as the prevalence of depression in patients without T2DM. Additionally, over 80% of people with T2DM are overweight or obese. This review describes how T2DM and depression can enhance one another, using the same molecular pathways, by synergistically altering the brain's structure and function and reducing the reward obtained from eating.

Work on the neuronal basis of eating addiction has also been conducted. Traditionally this has involved studying both central and peripheral molecules involved in hunger and satiety, such as leptin, orexin (also known as hypocretin), insulin, alpha-melanocyte-stimulating hormone (α-MSH), glucagon-like peptide -1 (GLP-1), amylin, glucose-dependent insulinotropic polypeptide (GIP, also known as a gastric inhibitory polypeptide), adiponectin and cholecystokinin (CCK). However, it is well known in psychiatry that neurotransmitters are also involved. Soon after the introduction of atypical antipsychotics, which antagonize serotonin receptors and dopamine D2 receptors (D2R), numerous case reports appeared showing that the use of these drugs were associated with increased obesity and the development of type 2 diabetes mellitus (T2DM)



Also see https://pubmed.ncbi.nlm.nih.gov/38674096/

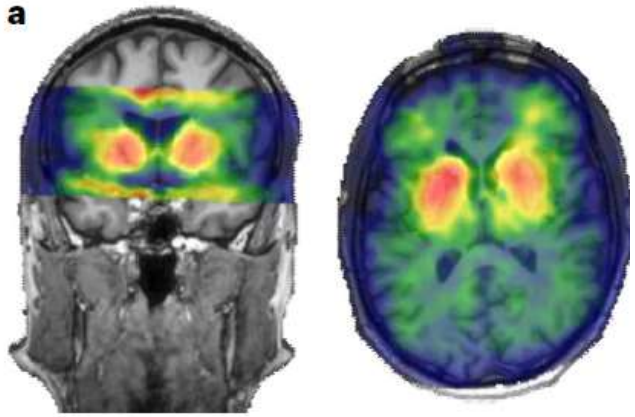
Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10470111/

Dopamine System Impairment Not Restored After Weight Loss

van Galen, K.A., Schrantee, A., ter Horst, K.W. et al., "Brain responses to nutrients are severely impaired and not reversed by weight loss in humans with obesity: a randomized crossover study," *Nat Metabolism*, June 12, 2024, 1059–1072.

Post-ingestive nutrient signals to the brain regulate eating behaviour in rodents, and impaired responses to these signals have been associated with pathological feeding behaviour and obesity. To study this in humans, we performed a single-blinded, randomized, controlled, crossover study in 30 humans with a healthy body weight (females $N = 12$, males $N = 18$) and 30 humans with obesity (females $N = 18$, males $N = 12$). We assessed the effect of intragastric glucose, lipid and water (noncaloric isovolumetric control) infusions on the primary endpoints cerebral neuronal activity and striatal dopamine release, as well as on the secondary endpoints plasma hormones and glucose, hunger scores and caloric intake.

To study whether impaired responses in participants with obesity would be partially reversible with diet-induced weight loss, imaging was repeated after 10% diet-induced weight loss. We show that intragastric glucose and lipid infusions induce orosensory-independent and preference-independent, nutrient-specific cerebral neuronal activity and striatal dopamine release in lean participants. In contrast, participants with obesity have severely impaired brain responses to post-ingestive nutrients. Importantly, the impaired neuronal responses are not restored after diet-induced weight loss. Impaired neuronal responses to nutritional signals may contribute to overeating and obesity, and ongoing resistance to post-ingestive nutrient signals after significant weight loss may in part explain the high rate of weight regain after successful weight loss.



Representative example of a T1-weighted anatomical brain MRI overlaid with the co-registered SPECT image of a lean participant showing the distribution of radiotracer uptake, with strongest uptake of [123I]IBZM in the bilateral striata.

Discussion

In this study, we demonstrate the differential post-ingestive (that is, orosensory and preference-independent) effects of isocaloric intragastric glucose and lipids on neuronal activity in brain regions involved in the regulation of eating behaviour, as well as on striatal dopamine release in lean adults. Moreover, we show that most of these physiological responses to intragastric nutrients are impaired in humans with obesity, with no signs of reversibility after 12 weeks of dietary weight loss. Taken together, these findings support the hypotheses that: (i) glucose and lipid differentially affect brain regions involved in the regulation of eating behaviour through post-ingestive signals; (ii) impaired post-ingestive nutrient signalling may contribute to pathological eating behaviour, overeating and obesity; and (iii) the persistence of these disturbances after diet-induced weight loss may contribute to the high incidence of weight regain after dietary interventions.

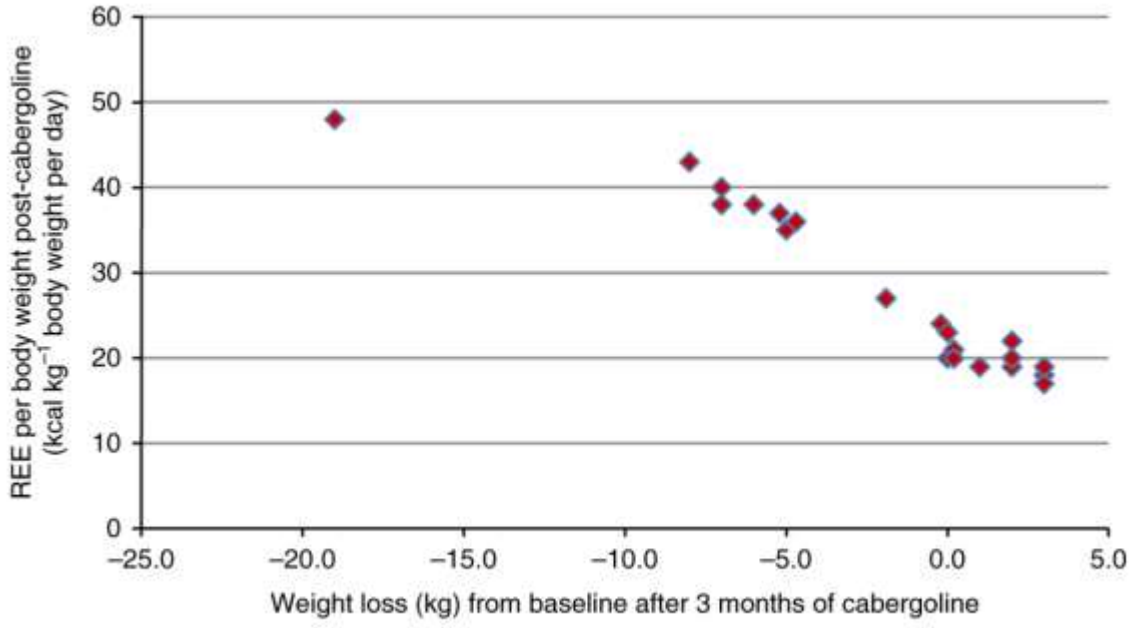
Source: https://www.nature.com/articles/s42255-023-00816-9

Folgueira Study: Dopamine Agonists Associated With Weight Loss

Folgueira, C., Beiroa, D., Porteiro, B. et al. Hypothalamic dopamine signalling regulates brown fat thermogenesis. Nat Metab 1, 811–829 (2019).

In line with the findings made in rodents, dopamine agonism in both our retrospective and prospective studies of patients with hyperprolactinemia have decreased body weight and improved glucose and lipid metabolism. The weight loss was accompanied by a reduction in both total body fat and visceral adiposity. Interestingly, dopamine agonism achieved by cabergoline treatment in patients with hyperprolactinemia resulted in an increase in REE that is consistent with the bromocriptine-induced effects on BAT observed in rodents. Moreover, in patients treated with cabergoline, the weight loss is positively correlated to REE. Our observations are in agreement with previous studies of bromocriptine or cabergoline treated patients. Note, while cabergoline decreases body weight in both lean and overweight patients irrespective of BMI a clear variability in this response is observed, and patients with higher BMIs are in a position of losing more excess weight.

Dopamine Agonist Associated with Weight Loss in Human Study When Resting Energy Expenditure Rises



Source: https://www.nature.com/articles/s42255-019-0099-7

Folgueira Study: Dopamine Agonists Impact on Weight Loss Governed by Brown Adipose Tissue Thermogenesis

Simonds SE, Cowley MA. Speed-dieting: dopamine agonists promote weight loss. *Nat Metab*. 2019 Sep;1(9):851-852.

Folgueira et al. show that dopamine increases brown adipose tissue (BAT) temperature via orexin signalling, a pathway involved in the regulation of sleep and arousal states. Activation of lateral hypothalamic area (LHA) neurons has previously been shown to increase BAT temperature through the propagation of signals to the raphe pallidus (RPa) in the hindbrain. The dorsomedial hypothalamus has also been demonstrated to have strong BAT-controlling projections that run through the RPa.

Folgueira et al. have found that D2R activation in the LHA or the zona incerta (ZI), but not in the dorsomedial hypothalamus, increases BAT temperature3. Orexin A was previously demonstrated to increase BAT temperature through activation of neurons in the Rpa and the sympathetic nervous system. D2R activation in the LHA and ZI acts directly through GABA (γ-aminobutyric acid)-expressing neurons but requires an intact orexin pathway to alter BAT temperature. These findings highlight potential neural pathways through which D2 may regulate BAT temperature and therefore energy expenditure and ultimately body weight. D2R activation inhibits the activity of GABAergic neurons and in turn activates Orexin A neurons in the LHA and ZI. The Orexin A signal is propagated via the Rpa to the sympathetic trunk and onto BAT cells, thus promoting thermogenesis and potentially glucose uptake (Fig. 1). The increase in glucose uptake may also explain the beneficial effects of bromocriptine, a D2R agonist, on glucose tolerance in people with type 2 diabetes.

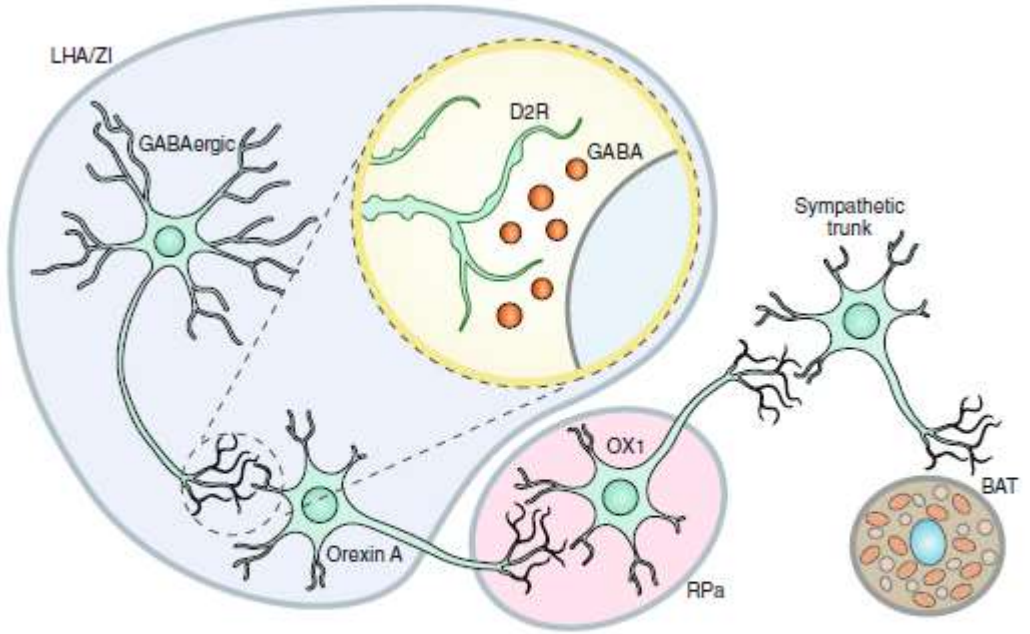
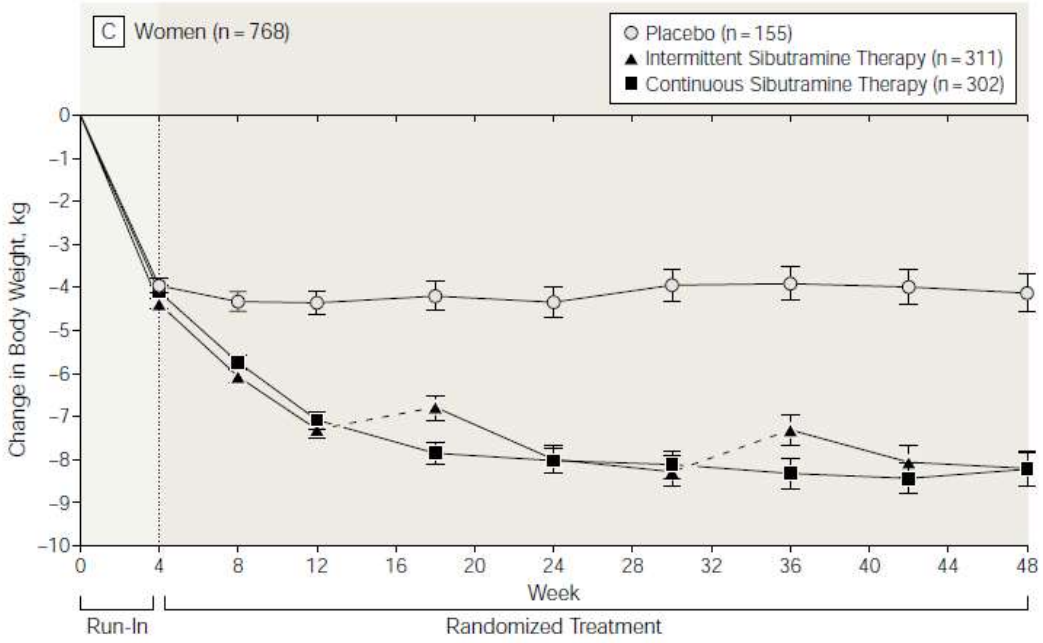


Fig. 1 | Schematic of the potential circuitry through which LHA/ZI D2R agonism might increase BAT temperature in an Orexin A/Orexin 1 receptor-dependent manner. D2Rs on GABAergic neurons in the LHA are disinhibited by activation of D2R, thus causing increased Orexin A activity via the RPa to the sympathetic trunk and BAT. OX1, orexin 1.

Source: https://pubmed.ncbi.nlm.nih.gov/32694744/

Lack of Rebound Seen in Weight Loss with Sibutramine (Partial Dopamine Agonist)

Wirth A, Krause J. Long-term weight loss with sibutramine: a randomized controlled trial. *JAMA*, Sep 19, 2001, pp. 1331-9.



The mean (SE) changes for the intent-to-treat population are shown for the 4-week run-in period with 15 mg of sibutramine hydrochloride (week 0-4) and the randomized treatment period. The broken line in the intermittent therapy curves denote the two 6-week placebo periods.

(Reprinted) JAMA, September 19, 2001—Vol 286, No. 11 **1335**

Source: https://pubmed.ncbi.nlm.nih.gov/11560538/

Sibutramine is a serotonin–norepinephrine reuptake inhibitor (SNRI) that, in humans, reduces the reuptake of norepinephrine (by ~73%), serotonin (by ~54%), and dopamine (by ~16%), thereby increasing the levels of these substances in synaptic clefts and helping enhance satiety; the serotonergic action, in particular, is thought to influence appetite.

Mean weight loss in the intention-to-treat population during the 44-week randomized treatment period was 3.8 kg (4.0%) in patients receiving continuous therapy and was 3.3 kg (3.5%) in patients receiving intermittent therapy, vs a mean weight gain of 0.2 kg (0.2%) in patients receiving placebo (with a 4-week sibutramine run-in).

Note: Sibutramine was approved by FDA for weight loss as MERIDIA but later taken off due to cardiac side effects.

NMDA Receptor Blockers Can Reduce Weight in the Obese

Petersen et. al., "GLP-1-directed NMDA receptor antagonism for obesity treatment," *Nature*, May 15, 2024, pp. 1133-1141.

Non-competitive, open-channel NMDA receptor blockers are used clinically for the management of Alzheimer's disease and treatment-resistant depression. It is believed that this class of small-molecule drugs improves brain disorders through mechanisms involving neurostructural changes and synaptic plasticity.

Notably, genome-wide association study (GWAS) analyses for body mass index (BMI) have linked glutamatergic signalling and NMDA receptor-related neuroplasticity to regulation of body weight and obesity.

In rodents, disparate effects of NMDA receptor antagonism on food intake have been observed. Specifically, antagonizing NMDA receptors in the brainstem has been associated with an increase in short-term food intake; by contrast, antagonizing NMDA receptors in the hypothalamus has been linked to a reduction in food intake and a decrease in body weight.

In the context of prolonged systemic administration, NMDA receptor antagonists, such as memantine and MK-801 (also known as dizocilpine), induce anorexia and weight loss in rodents.

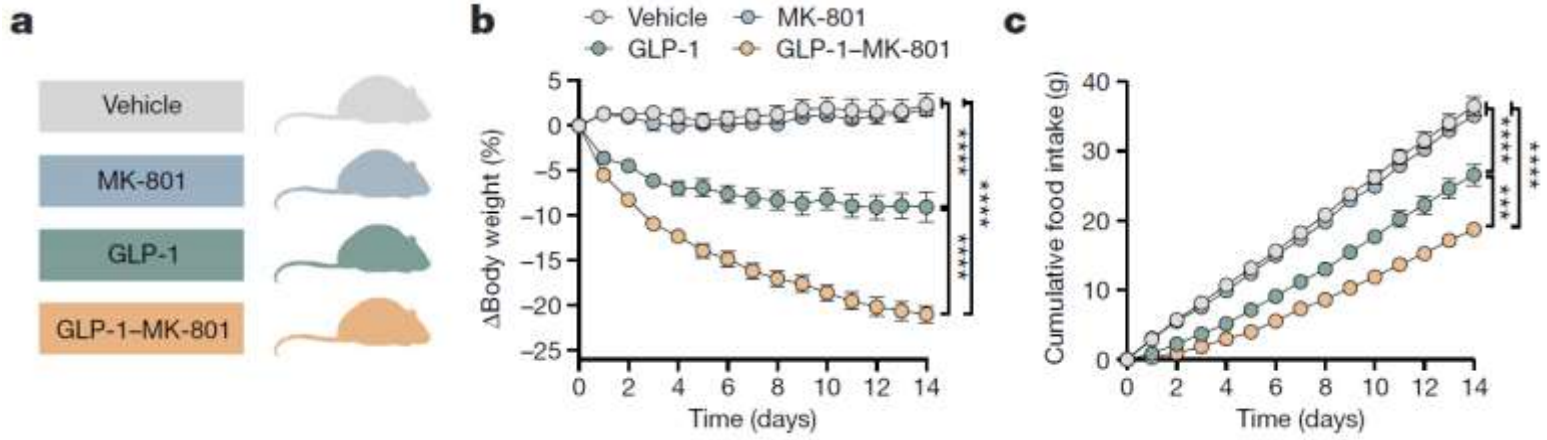


Fig. 1 | GLP-1–MK-801 corrects metabolic disease when DIO mice were treated once-daily with s.c. injections of MK-801, GLP-1, GLP-1–MK-801 or vehicle for 14 days. n = 10 mice per group. 100 nmol kg–1 dose. a, Schematic. b, Change in body weight. c, Cumulative food intake.

Source: https://www.nature.com/articles/s41586-024-07419-8

Obesity GWAS Studies Point to NMDA / AMPA Receptors

Faduhunsi et.al., "Targeting postsynaptic glutamate receptor scaffolding proteins PSD-95 and PICK1 for obesity treatment," Science Advances, March 10, 2024.

Over the past decade, genome-wide association studies (GWAS) have revealed numerous biological pathways that might contribute to obesity pathogenesis. Notably, many of the genes and pathways identified through genetic studies are enriched or exclusively expressed in the brain, emphasizing a key role of the central nervous system (CNS) in the pathobiological mechanisms underlying obesity.

Genes relating to glutamatergic signaling and postsynaptic plasticity that are linked to α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and N-methyl-d-aspartate (NMDA) receptors are particularly enriched in genetic studies of obesity, pointing to an important role of the glutamatergic neurotransmitter system in the homeostatic mechanisms governing energy balance. Although incompletely mapped, a role for glutamate receptor–linked synaptic plasticity has also been identified in rodent studies related to energy metabolism.

Rodent studies confirm the potential weight-lowering benefits of disrupting NMDA receptor signaling.

In addition, there is evidence supporting the idea that antagonizing AMPA receptors could mitigate food-motivated behavior.

However, AMPA and NMDA receptors are ubiquitously expressed throughout the CNS, and chemical modulators of these receptors are typically marred with off-target effects.

Source: https://www.science.org/doi/full/10.1126/sciadv.adg2636

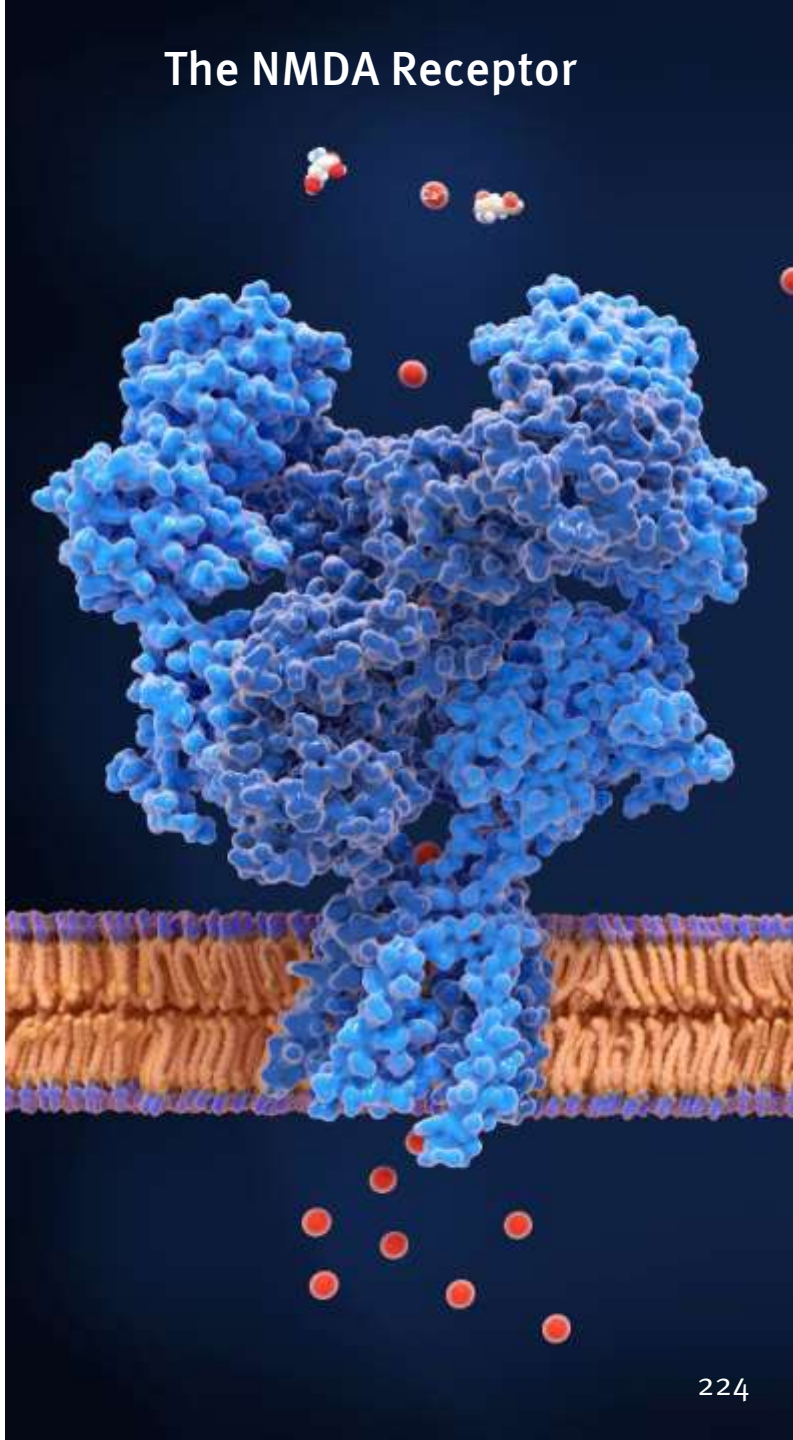
Recent Paper Tests a Coupled GLP-1 Agonist with NMDA Antagonist

Tysoe, O. "NMDA receptor antagonist coupled to GLP1 analogue in highly effective experimental weight loss drug," *Nature Reviews Endocrinology*, Jun 4, 2024.

Small-molecule drugs targeting the N-methyl-D-aspartate (NMDA) receptor, a glutamate-activated cation channel broadly expressed in neurons in the brain, had previously been investigated for weight loss in preclinical studies, but were not considered translationally viable due to adverse physiological and behavioural effects. Now, a study in Nature has combined an NMDA receptor antagonist (MK-801) with a glucagon-like peptide 1 (GLP1) analogue to produce potent weight loss without these adverse effects.

The drug, GLP1–MK-801, conjugates MK-801 to a novel GLP1 analogue via a disulphide linker. This approach allows MK-801 to be targeted only to the neurons in the brain expressing GLP1 receptors, including appetite-regulating regions of the brain such as the hypothalamus. "Chemically masking the secondary amine of MK-801 renders it inactive until the linker is cleaved by the higher concentration of thiol-containing compounds in the intracellular environment," explains first author Jonas Petersen.

Source: https://www.nature.com/articles/s41574-024-01007-6



'Trojan Horse' Weight Loss Drug More Effective Than Available Therapies in Mice

Science Daily, May 15, 2024.

Christoffer Clemmensen and colleagues developed an interest in molecules that are used to treat chronic depression and Alzheimer's disease.

The molecules block a receptor protein called the NMDA receptor, which play a key role in long-term changes in brain connections and have received scientific attention within fields of learning and memory. Drugs targeting these receptors will strengthen and/or weaken specific nerve connections.

This family of molecules can have a permanent effect on the brain. Studies have demonstrated that even a relative infrequent treatment can lead to persistent changes to the brain pathologies. We also see molecular signatures of neuroplasticity in our work, but in this case in the context of weight loss," he explains.

The human body has evolved to protect a certain body weight and fat mass. From an evolutionary perspective, this has probably been to our advantage, as it means that we have been able to survive periods of food scarcity. Today, food scarcity is not a problem in large parts of the world, where an increasing part of the population suffers from obesity.

"I consider the drugs available on the marked today as the first generation of weight-loss drugs. Now we have developed a new type of weight-loss drug that affects the plasticity of the brain and appears to be highly effective."

Christoffer Clemmensen

Associate Professor, Novo Nordisk Foundation Center for Basic Metabolic Research at the University of Copenhagen

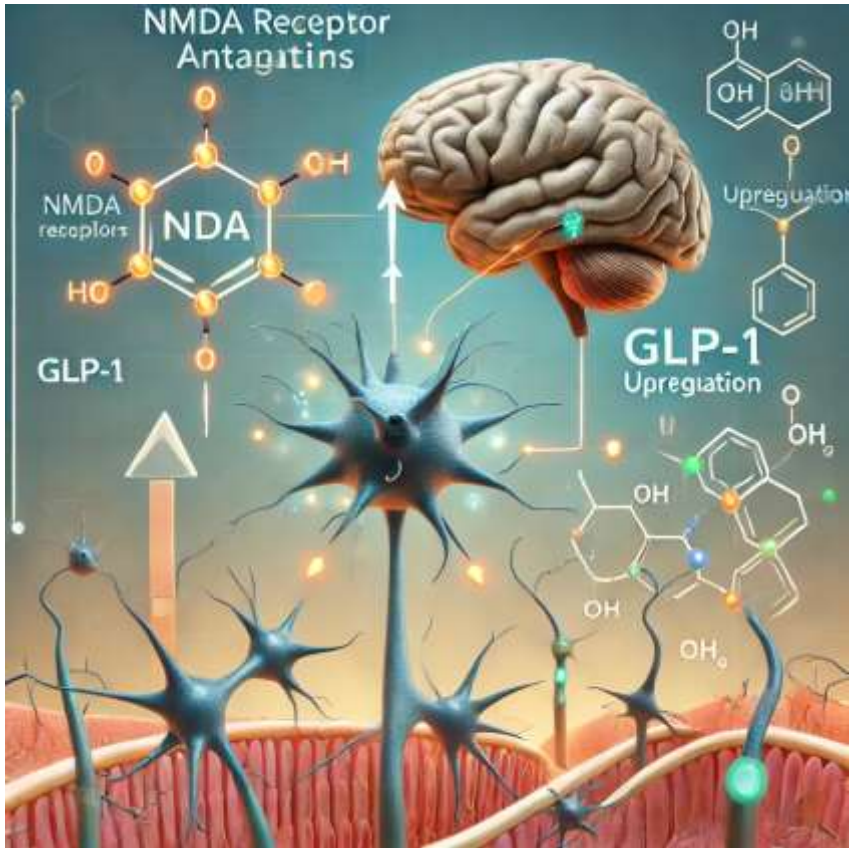
Source: https://www.sciencedaily.com/releases/2024/05/240515225107.htm

NMDA Receptor Blockers Agonize GLP-1

An important finding in this paper written by Novo Nordisk scientists is that NMDA expression outside the brain is involved with incremental GLP-1 release.

Cyranka et. al., "NMDA Receptor Antagonists Increase the Release of GLP-1 From Gut Endocrine Cells," *Frontiers in Psychology*, April 26, 2022.

Type 2 diabetes mellitus (T2DM) remains one of the most pressing health issues facing modern society. Several antidiabetic drugs are currently in clinical use to treat hyperglycaemia, but there is a need for new treatments that effectively restore pancreatic islet function in patients. Recent studies reported that both murine and human pancreatic islets exhibit enhanced insulin release and β-cell viability in response to N-methyl-D-aspartate (NMDA) receptor antagonists. Furthermore, oral administration of dextromethorphan, an over-the-counter NMDA receptor antagonist, to diabetic patients in a small clinical trial showed improved glucose tolerance and increased insulin release. However, the effects of NMDA receptor antagonists on the secretion of the incretin hormone GLP-1 was not tested, and nothing is known regarding how NMDA receptor antagonists may alter the secretion of gut hormones. This study demonstrates for the first time that, similar to β-cells, the NMDA receptor antagonist MK-801 increases the release of GLP-1 from a murine L-cell enteroendocrine model cell line, GLUTag cells. Furthermore, we report the 3′ mRNA expression profiling of GLUTag cells, with a specific focus on glutamate-activated receptors. We conclude that if NMDA receptor antagonists are to be pursued as an alternative, orally administered treatment for T2DM, it is essential that the effects of these drugs on the release of gut hormones, and specifically the incretin hormones, are fully investigated.



Source: https://www.frontiersin.org/journals/pharmacology/articles/10.3389/fphar.2022.861311/full

Memantine Associated with Substantial Weight Loss

Deng SN, Yan YH, Zhu TL, Ma BK, Fan HR, Liu YM, Li WG, Li F. Long-Term NMDAR Antagonism Correlates Weight Loss With Less Eating. Front Psychiatry. Feb 8, 2019.

Our results show that long term NMDAR antagonism by memantine significantly decreased the weight of obese mice. Our results are in accordance with clinical reports. Long term NMDAR antagonism by memantine increases weight loss in mice obesity induced by high fat diet. Memantine decreases food intake without inducing abdominal discomfort and anxiety, suggesting that this compound would be a good candidate drug for obesity control. However, the molecular mechanism and brain circuit involved in the regulation of weight loss by memantine need further study.

Schaefer et.al, "Memantine-associated reversal of clozapine-induced weight gain," *Pharmacopsychiatry*. Jul 2007, pp. 149-51.

We report on a treatment-resistant schizophrenic patient who received an add-on treatment with the low-affinity NMDA antagonist memantine because of cognitive disturbances. During this treatment we observed a marked decrease of clozapine-induced weight gain. The causal relationship to memantine could be demonstrated using an on-off-on design with a significant increase of weight after discontinuation and again a substantial weight loss after re-exposition with memantine. Beside weight, also negative symptoms improved.

Hermanussen M, Tresguerres JA. A new anti-obesity drug treatment: first clinical evidence that, antagonising glutamate-gated Ca2+ ion channels with memantine normalises binge-eating disorders. Econ Hum Biol. 2005 Jul;3(2):329-37.

The regulation of appetite relies on complex hypothalamic neurocircuitry of which the arcuate nucleus, and the hormone leptin play important roles. Arcuate nucleus neurones are essential for the regulation of eating behaviour, but they can be intoxicated by elevated serum levels of the amino acid glutamate (GLU). Neurotoxic effects of GLU are mediated by the N-methyl-D-aspartate receptor (NMDA-R). But the neurotoxic effects of GLU can be prevented… In view of a previously published hypothesis that human obesity results from chronic over-consumption of GLU, **we performed a therapeutic trial in five obese, but otherwise healthy women. Memantine treatment markedly decreased appetite within few hours and complete suppressed the binge-eating disorder within 24 h.** Body weight decreased markedly within a few days. The findings strongly support the hypothesis that elevated levels of nutritional GLU play an important role in the pathomechanism of human obesity.

GSK Dopamine Transport Inhibitor Lowers Weight in Obese Persons with a Polymorphism in NMDA Receptor

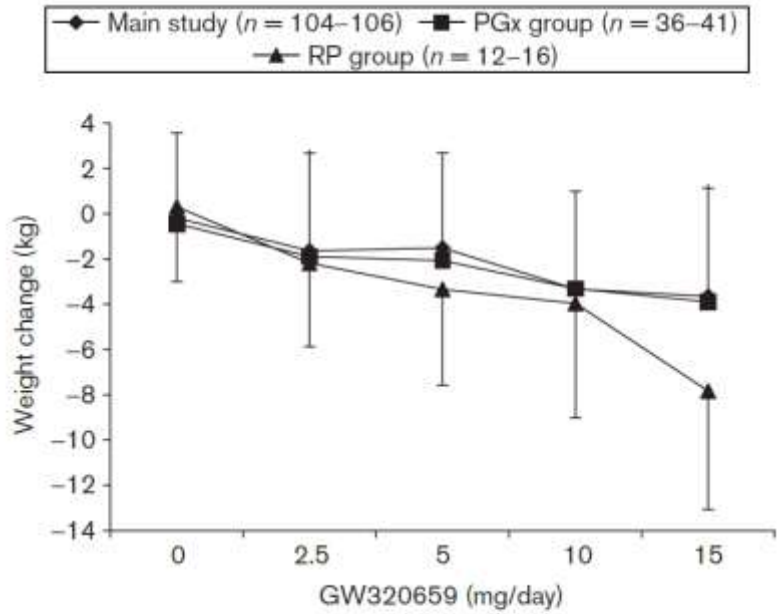
Pharmacogenetics and obesity: common gene variants influence weight loss response of the norepinephrine/ dopamine transporter inhibitor GW320659 in obese subjects

Colin F. Spraggs, Sreekumar G. Pillai, David Dow, Christal Douglas, Linda McCarthy, Penelope K. Manasco, Michael Stubbins and Allen D. Roses

Pharmacogenetics and Genomics
December 2005 | Volume 15 | Issue 12 | pp: 883-889

Background: GW320659, a highly selective neuronal norepinephrine and dopamine re-uptake inhibitor, has been evaluated for the treatment of obesity. Scrutiny of the weight loss data from a phase II study (GlaxoSmithKline study OBS20001) showed a wide variation in weight loss response following GW320659 treatment and the possibility that the study population might include subgroups with enhanced weight loss response.

Results: Common genetic polymorphisms in the drug target (norepinephrine transporter protein 1, SLC6A2) and mechanism pathway (NMDA receptor channel NR1 subunit, GRIN1) were associated with increased weight loss following GW320659 treatment in a proportion (36%) of the study population. In the patient subgroup selected for these genotypes, GW320659 (15 mg/day) produced a significant difference in mean weight loss of 7.84 kg (SD 5.23, n = 14), compared to 2.53 kg (SD 5.17, n = 24) in the subgroup that did not possess the genotypes (P = 0.006). This subgroup also showed a highly significant weight loss response for GW320659 compared to placebo (+0.31 kg, SD 3.32, n = 16) with the same genotypes (P < 0.0001). In addition, there was no difference in placebo response between either subgroup.



Dose-response curves for the Main Study, PGx and RP selected population. Points are mean with SD bars. RP selected subgroup comprised subjects with the genotypes: CC for SLC6A2 IVS13+66T>C or AA for SLC6A2 G1287A or AA for GRIN1 IVS9–38G>A.

Source: https://pubmed.ncbi.nlm.nih.gov/16272960/

Potential for Obesity Treatment Via Glutamate Receptor Scaffolding Proteins PSD-95 and PICK1

Fadahunsi et.al., "Targeting postsynaptic glutamate receptor scaffolding proteins PSD-95 and PICK1 for obesity treatment," *Science Advances*, March 10, 2024.

However, AMPA and NMDA receptors are ubiquitously expressed throughout the CNS, and chemical modulators of these receptors are typically marred with off-target effects.

To circumvent these, scientists have begun exploring therapeutic targeting of intracellular receptor protein complexes to attain precise interference of postsynaptic receptor signaling.

Both AMPA and NMDA receptors directly interact with intracellular scaffolding proteins, which participate in the anchoring and trafficking of glutamate receptors at the membrane. Many of these scaffolding proteins contain postsynaptic density protein-95 (PSD-95)/disc large/ZO-1 (PDZ) domains.

PDZ domain–containing proteins support the formation and stability of postsynaptic glutamate receptor complexes and are emerging as promising targets for a variety of CNS disorders such as stroke and neuropathic pain.

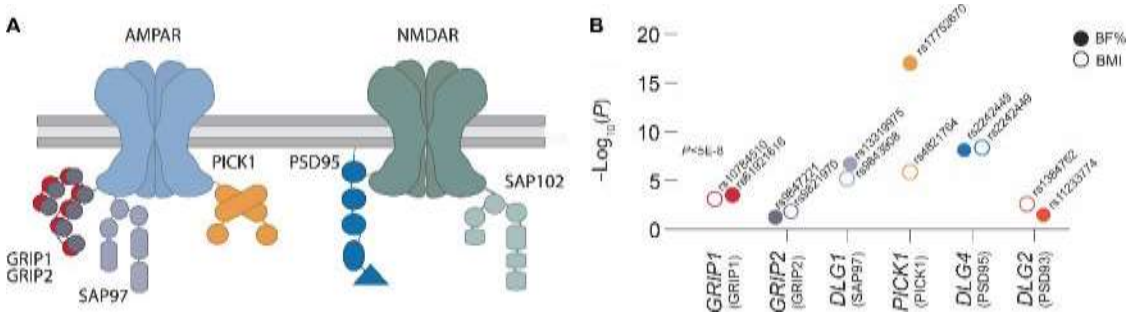


Fig. 1. Overview of PDZ domain–containing proteins and the associations of genetic variants in the corresponding gene regions with BF% and BMI.
(A) PDZ domain–containing proteins that interact with glutamatergic AMPA or NMDA receptors: GRIP1, GRIP2, PICK1, PSD-95 (DLG4), SAP97 (DLG1), and SAP102 (DLG3). (B) Genetic variants in the PICK1 (rs17752670) and DLG4 (rs2242449) loci reached genome-wide significance [shown as –log10(P)] for association with BF% and BMI.

Source: https://www.science.org/doi/full/10.1126/sciadv.adg2636

Pharmacological Inhibition of PSD-95 Lowers Body Weight in Obese Mice

Fadahunsi et.al., "Targeting postsynaptic glutamate receptor scaffolding proteins PSD-95 and PICK1 for obesity treatment," *Science Advances*, March 10, 2024.

PSD-95, the protein product of the DLG4 gene, is a highly abundant component of the postsynaptic density (27). PSD-95 is involved in the regulation of NMDA and AMPA (via the protein stargazin) receptor trafficking and stabilization mediated via its PDZ domains (28, 29). The physiological and pharmacological role of PSD-95 in energy balance regulation remains elusive, and it has not yet been investigated as a drug target for weight loss. To probe the functional relevance of the link between DLG4 and obesity, we explored whether pharmacological targeting of PSD-95 lowers body weight in diet-induced obese (DIO) mice. Here, we demonstrate that daily subcutaneous injections of UCCB01-147 dose-dependently lower body weight and food intake in DIO mice, and show that 25 mg kg–1 appears to be well tolerated for chronic dosing (fig. S1, A to G). Next, we assessed the effects of 14 days of repeated UCCB01-147 dosing on energy balance, glycemic control, and plasma lipid markers in DIO mice (Fig. 4C). We observed a 9% reduction in body weight, which was accompanied by a decrease in food intake (Fig. 4, D to G). The reduction in body weight was reflected in a selective loss of fat mass (Fig. 4H).

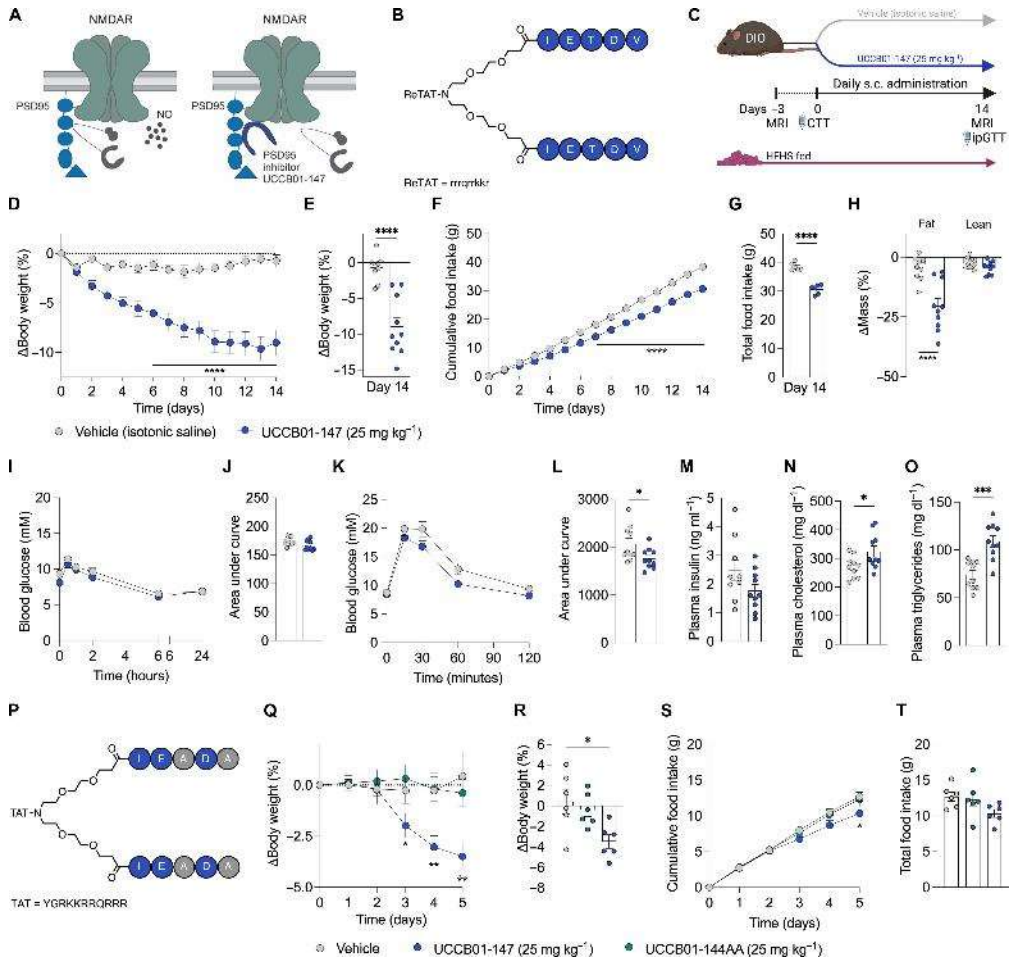
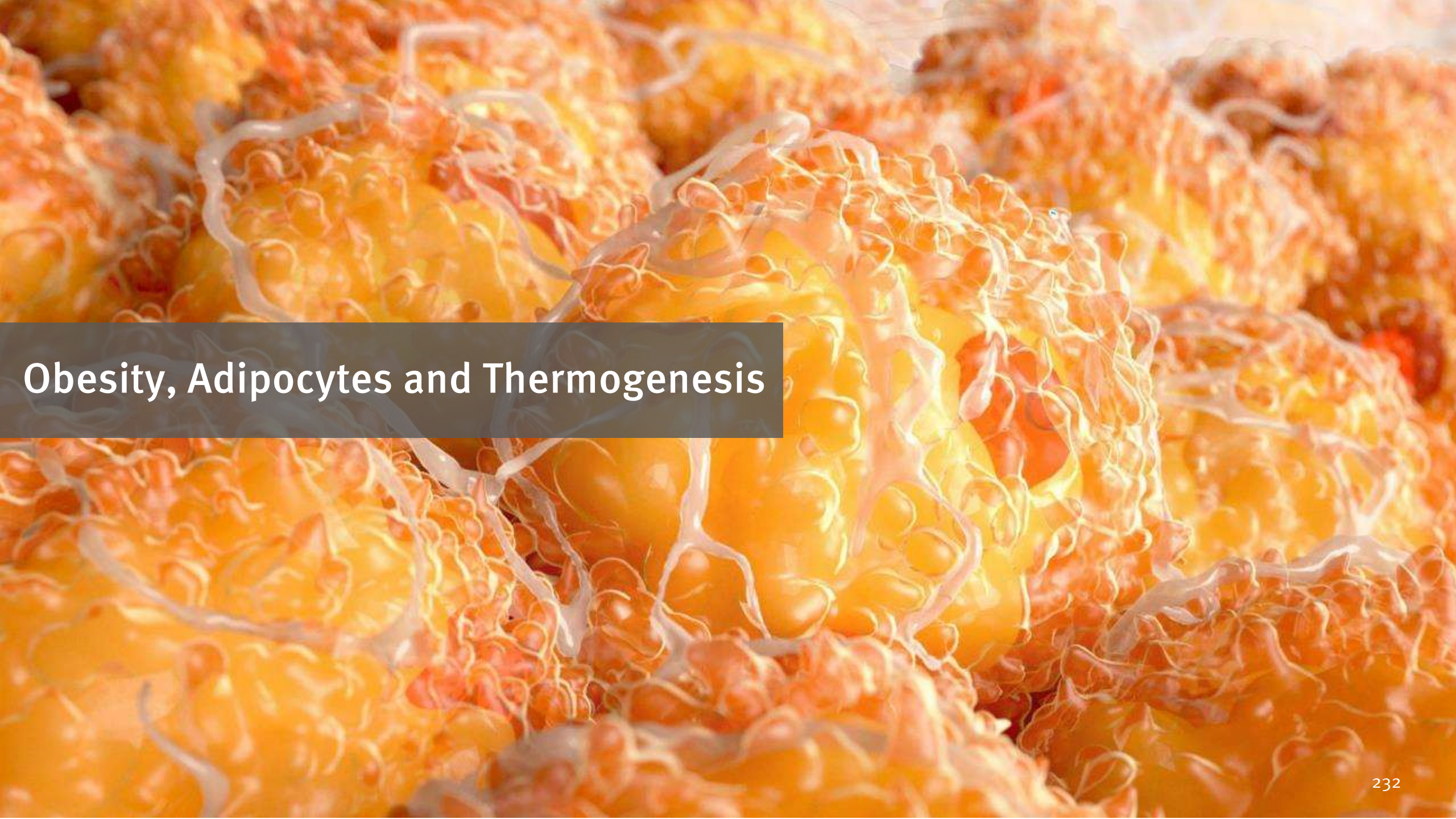


Fig. 4. Pharmacological inhibition of the PSD-95/nNOS/NMDA receptor complex reduces adiposity in DIO mice. (A) Mechanism of action of PSD-95 inhibitor UCCB01-147 disrupting the PSD-95/nNOS/NMDA receptor complex. (B) Chemical structure of UCCB01-147. (C) Experimental design of the study in which DIO male C57BL/6J mice were treated with once-daily subcutaneous (s.c.) injections of UCCB01-147 (25 mg kg–1; n = 10 mice and n = 7 cages) or vehicle (isotonic saline, n = 9 mice and n = 6 cages) over 14 days. (D) Change in body weight. (E) Total change in body weight. (F) Cumulative food intake. (G) Total food intake. (H) Change in body composition. (I) Compound tolerance test on day 0. (J) Area under the curve of (I). (K) Intraperitoneal glucose tolerance test on day 14. (L) Area under the curve of (K). (M) Plasma insulin levels. (N) Plasma cholesterol levels.

Source: https://www.science.org/doi/full/10.1126/sciadv.adg2636

Does the Fatty Brain Theory Offer a Viable Fourth Generation Strategy for Obesity Management?

- The idea that the brain is some how permanently reset in the obese and is hard to change back to a “thin brain” resonates with the experience of many who have been overweight.
- The fatty brain theory differs from the food addiction theory in that it relates more to high fat diets (or high calorie diets in general) rather than high fructose diets.
- The evidence that the dopamine system and glutamate system reset in obesity is reasonably strong but not overwhelming.
- One can explain key background information, like the rise in obesity over time or the high prevalence in the U.S. simply by noting that what causes obesity isn’t the same as what prevents loss.
- We find the evidence in the Clemmensen paper regarding the NMDA receptor theory to be highly encouraging. Fusing an NMDA receptor antagonist to a GLP-1 agonist was a novel and interesting idea.
- While Clemmensen has been quoted in the press as suggesting that this might lead to permanent weight loss, we could not find evidence in the paper supporting this claim. On the other hand, evidence of long-term depression remission with NMDA receptor antagonists is solid.

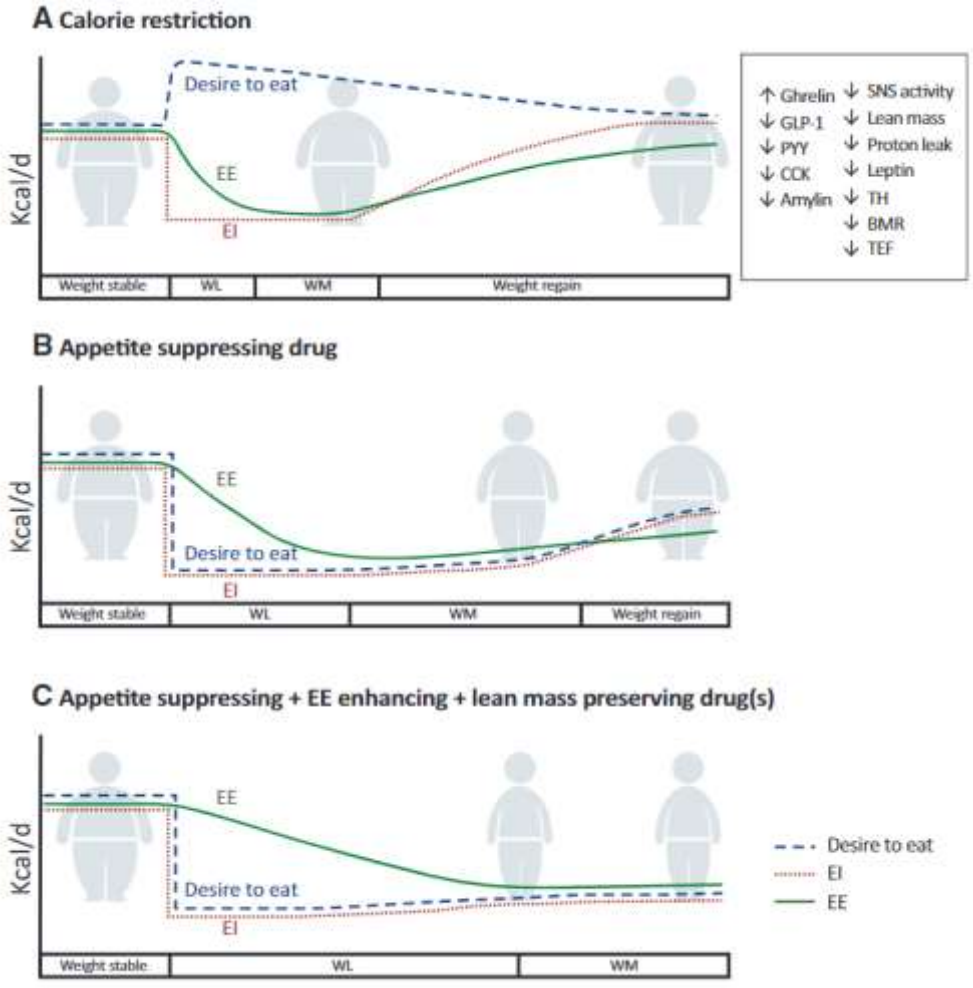


Obesity, Adipocytes and Thermogenesis

Aspiration: Calorie Restriction + Appetite Suppressants + Drugs that Increase Energy Use Could Lead to Sustainable Weight Loss

Christoffersen BØ, Sanchez-Delgado G, John LM, Ryan DH, Raun K, Ravussin E., "Beyond appetite regulation: Targeting energy expenditure, fat oxidation, and lean mass preservation for sustainable weight loss," *Obesity*, April 2022, pp. 841-857.

Trends in energy balance regulation in response to different weight-loss regimens. Energy intake and energy expenditure are balanced in weight-stable obesity. (A) The reduction in energy intake during calorie restriction; (B) When the weight loss is induced by continuous treatment with an appetite-reducing compound, the hunger is decreased and the satiation is increased, enabling a longer period with reduced energy intake. However, energy expenditure is typically still reduced owing to loss of body mass/lean mass, neurohormonal changes, and some degree of metabolic adaptation. Consequently, the reduction in body weight is still limited, and usually, over time, weight regain occurs despite continued treatment, albeit at a slower rate compared with the regain observed with calorie restriction in panel A. (C) The future aspiration for pharmacotherapy that combines appetite-reducing, energy-expenditure–boosting, and lean-mass–preserving mechanisms. Such a combination will decrease hunger, increase satiety, and protect lean mass, resulting in less suppression of energy expenditure, which (together with an actual energy-expenditure–boosting component) will have the potential to cause greater and more sustainable weight loss.



Source: https://onlinelibrary.wiley.com/doi/10.1002/oby.23374

Adipose Tissue Plays a Major Role in Weight Regain

van Baak MA and Mariman ECM, "Obesity-induced and weight-loss-induced physiological factors affecting weight regain," ***Nature Reviews Endocrinolology*****, Nov 19, 2023 pp. :655-670.**

Weight regain after successful weight loss resulting from lifestyle interventions is a major challenge in the management of overweight and obesity. Knowledge of the causal mechanisms for weight regain can help researchers and clinicians to find effective strategies to tackle weight regain and reduce obesity-associated metabolic and cardiovascular complications.

Obesity is accompanied by changes in the innate and adaptive immune systems of adipose tissue in humans and in mice. A massive invasion of macrophages is characteristic, attracted by adipocytes stressed by hypoxia, hypertrophy or cell death. Crown-like structures can be seen under the microscope when the adipocytes are surrounded by macrophages. At the same time, tissue resident macrophages differentiate into a continuum of multiple macrophage populations. These populations include the M2 and M1 states that utilize oxidative phosphorylation and glycolysis, respectively, and macrophages with both M2 and M1 metabolic characteristics, which secrete pro-inflammatory cytokines including IL-1, IL-6 and tumour necrosis factor (TNF). In addition to macrophages, the proportion and function of many other classes of immune cells are changed in adipose tissue during the development of obesity10.

In mice, there is evidence that an obesity memory imprinted in immune cells during obesity and weight loss is involved in an increased risk of weight regain. A 2017 study found that after a cycle of weight gain and weight loss, mice on a high-fat diet (HFD) gained body weight faster than mice of similar body weight that had not passed through such a previous cycle of weight gain and loss.

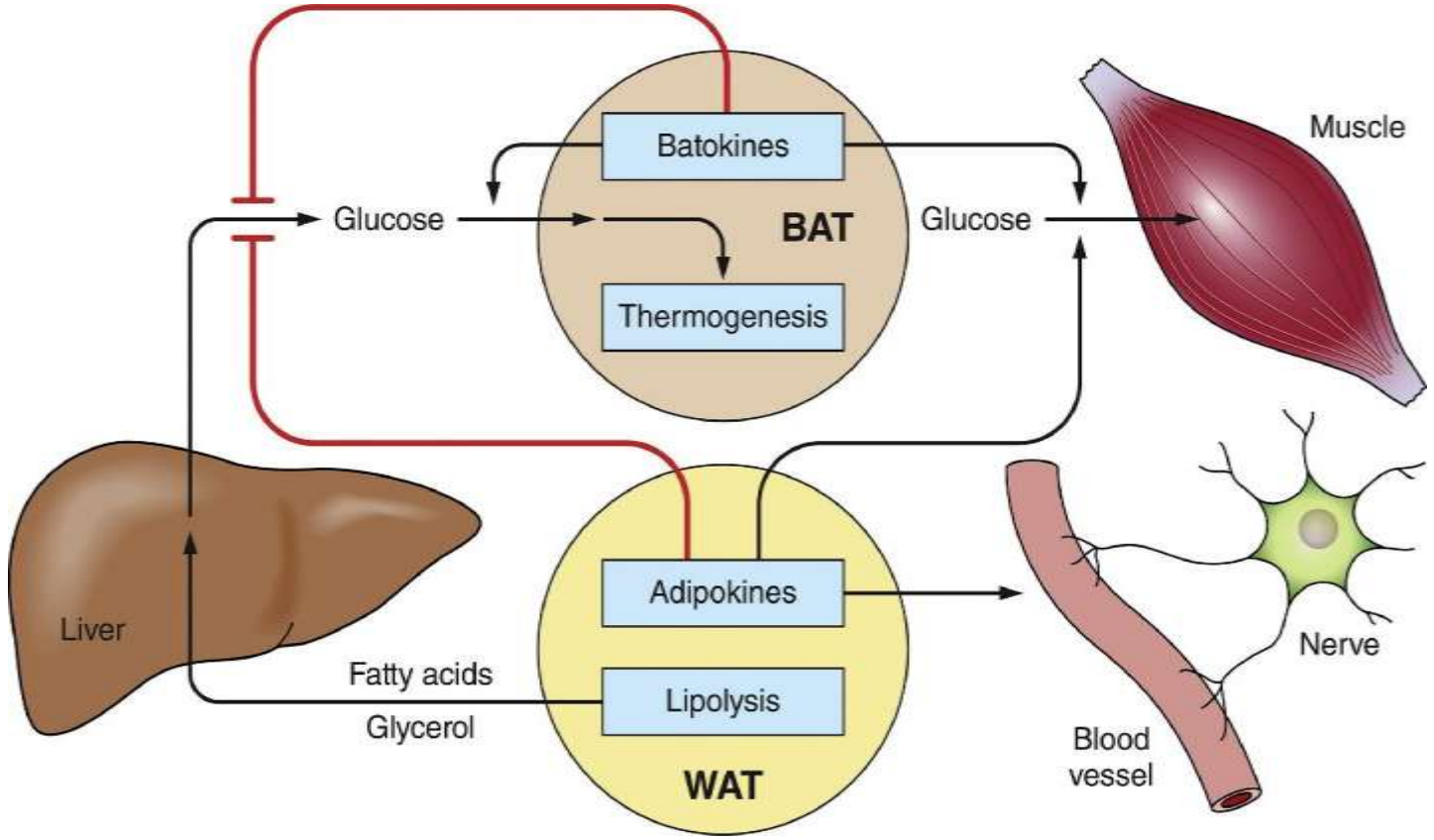
In humans, a link between the immune status of adipose tissue and weight regain after weight loss has been suggested by the YoYo study, a dietary intervention study in which individuals with overweight or obesity lost 8% of body weight on a low-calorie diet or a very-low-calorie diet (VLCD) (weight loss phase), then remained for 4 weeks on a balanced diet to maintain weight loss (weight-stable phase), after which they were followed up for 9 months during which weight regain was recorded. The expression of 277 ECM genes in the subcutaneous adipose tissue was investigated. In people who lost weight on a VLCD, the change in expression of a cluster of integrin genes during the weight-stable phase correlated positively with percentage weight regain. The findings indicated that people with the lowest reduction in the expression of leukocyte-specific genes in the weeks after weight loss (weight-stable phase) were more prone to weight regain.

Source: https://www.nature.com/articles/s41574-023-00887-4

Adipose Tissue Signals Are Important Metabolic Regulators

Czech MP. Mechanisms of insulin resistance related to white, beige, and brown adipocytes. Mol Metab. Apr 2020, 27-42.

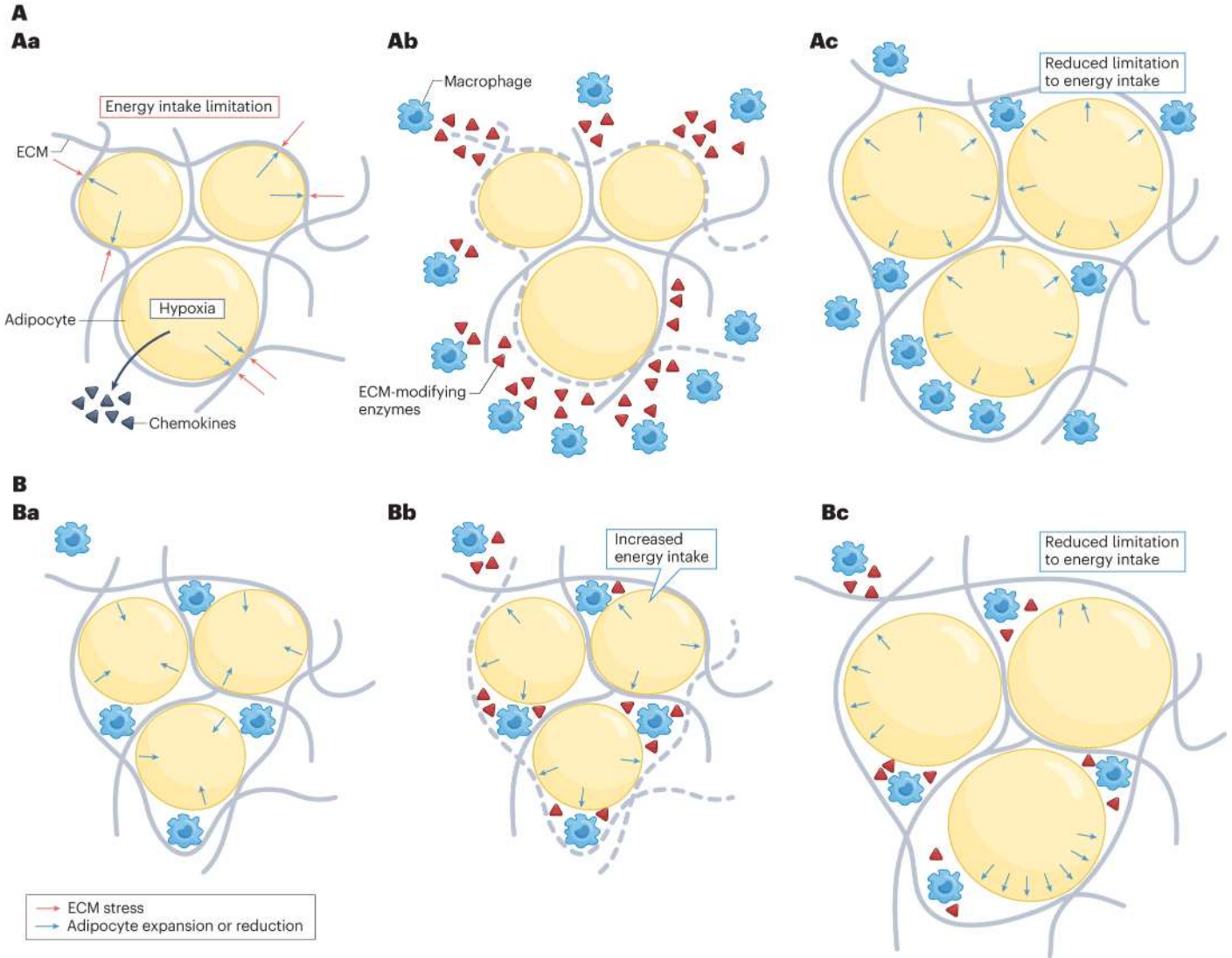
Pathways by which WAT and BAT depots serve as major nodes of systemic metabolic regulation. Adipokines and batokines regulate hepatic lipogenesis and glucose output as well as glucose uptake and disposal by muscle. Secreted factors from adipocytes can also act in a paracrine fashion to regulate other cell types within adipose depots such as vascular cells and nerve fibers. BAT thermogenesis may contribute to systemic glucose disposal and oxidize lipids to lower systemic toxicity. WAT lipolysis in obesity can contribute to fatty acid and glycerol overload in the liver to enhance gluconeogenesis and glucose output. WAT-derived fatty acids also contribute to skeletal muscle insulin resistance (not shown). The combination of the actions of peptides, lipids, small RNA, and other factors from adipocytes plus the released lipolytic products (fatty acids and glycerol) have major influences on local cell types within adipose tissue as well as on distant tissues.



Source: https://pubmed.ncbi.nlm.nih.gov/32180558/

Multiple Adipocyte MOA's May Influence Regain Risk

van Baak MA and Mariman ECM, "Obesity-induced and weight-loss-induced physiological factors affecting weight regain," *Nature Reviews Endocrinolology*, Nov 19, 2023 pp. :655-670.



A, Adipose tissue expansion during weight gain. Aa, A positive energy balance leads to expansion of adipocytes, generating extracellular matrix (ECM) stress. Consequently, signals from the stressed adipose tissue reduce energy intake and storage. Chemokines, also secreted by the stressed adipocytes, attract macrophages. Ab, Macrophages secrete ECM-modifying enzymes, weakening the ECM and reducing the stress. Ac, Reduced ECM stress enables increased energy intake and further adipocyte growth. B, Macrophage persistence in adipose tissue facilitates weight regain after weight loss. Ba, After weight loss, adipocyte size is reduced and the ECM is remodelled and tightened around the shrunken adipocytes. However, macrophages persist in the tissue. Bb, If overeating occurs again, this challenge leads to rapid secretion of ECM-modifying enzymes by the persistent macrophages already present and weakening of the ECM. Bc, This ECM weakening enables rapid adipocyte growth and weight regain.

Source: https://www.nature.com/articles/s41574-023-00887-4

Decreases in Lipid Oxidation That Happen with Weight Loss Tend to Persist – Increasing the Likelihood of Weight Regain

van Baak MA and Mariman ECM, "Obesity-induced and weight-loss-induced physiological factors affecting weight regain," *Nature Reviews Endocrinolology*, Nov 19, 2023 pp. :655-670.

For a condition of weight stability, a balance between energy intake and energy expenditure is required. Such a balance can only be obtained if the levels of macronutrient intake and expenditure are also balanced. Carbohydrate and protein stores are closely regulated by adjusting levels of oxidation to levels of intake and thus any day-to-day energy imbalances are mainly resolved by changes in storage and utilization of lipids.

Over the long term, changes in levels of free fatty acids (FFA) and in insulin sensitivity, due to gains or losses of adipose tissue, influence the average rate of lipid oxidation. Subsequently, body composition will drift towards the degree of adiposity where lipid oxidation matches dietary fat intake. Lipid oxidation is restrained by high levels of glycogen, so a greater expansion of adipose tissue mass is needed in individuals who maintain relatively high glycogen reserves.

One of the first studies showing a potential connection between lipid oxidation and obesity was a study in Pima Indians that found that a higher 24-h respiratory quotient (a measure of the mixture of substrates oxidized), thus a lower level of lipid oxidation, was associated with weight gain, independent of whether REE was high or low.

Weight loss was found to decrease lipid oxidation at rest and during exercise and 24-h respiratory quotient was higher in adults who had lost a large amount of weight and had maintained this weight loss for at least 2 months than in a weight-matched control group who had not lost weight previously. Similarly, weight-reduced obese rats showed a lower 24-h lipid oxidation when fed a low-fat diet (LFD) ad libitum after the energy restriction than obese rats on the same ad libitum diet that were also matched for energy intake. This finding suggests that the weight-loss-induced adaptation in lipid oxidation is independent of energy imbalance.

However, participants with a less-pronounced weight-loss-induced reduction in respiratory quotient and lower FFA after weight loss had a larger weight regain. Therefore, weight-loss-induced changes in FFA metabolism might influence weight regain. This result was supported by the finding that adipose tissue-specific gene expression indicated a main role for weight-loss-induced adaptations of fatty acid metabolism in weight regain.

Source: https://www.nature.com/articles/s41574-023-00887-4

Decreases in Lipolysis Persist After Weight Loss and Make it Difficult to Lose Weight and Keep it Off

van Baak MA and Mariman ECM, "Obesity-induced and weight-loss-induced physiological factors affecting weight regain," *Nature Reviews Endocrinology*, Nov 19, 2023, pp. :655-670.

Lipid oxidation in the fasted state is mainly fuelled by adipose tissue lipolysis and driven by high circulating levels of FFA. An interesting question therefore is whether the reduction in lipid oxidation that is often found in people with obesity, and which can be further reduced after weight loss, is accompanied by reductions in lipolysis.

For decades it has been observed that obesity is associated with an impairment in adipose tissue lipolysis. Basal lipolysis in adipose tissue, which is mediated mainly by adipose triglyceride lipase (ATGL), does not seem to be affected by obesity based on microdialysis studies of subcutaneous adipose tissue.

However, although in a 2008 glycerol tracer study, total rate of appearance of glycerol at baseline was similar in men with or without obesity, it was significantly lower in men with obesity when corrected for body adipose tissue mass. An explanation for the lower basal lipolysis in obesity could be obesity-associated insulin resistance. Insulin resistance has been found to be associated with reduced expression of ATGL mRNA and protein.

A 2007 study found that the expression of ATGL mRNA and protein in subcutaneous adipose tissue is reduced by diet-induced weight loss (in negative energy balance). In agreement with these findings, basal lipolysis of subcutaneous adipose tissue, as derived from interstitial concentrations of glycerol measured by microdialysis, was reduced after diet-induced weight loss in women with obesity (in negative energy balance) and the reduction was maintained during weight regain.

With respect to stimulated lipolysis, a 1997 study found that in vitro adrenaline-stimulated lipolysis in isolated subcutaneous abdominal and gluteal adipocytes was reduced in adipocytes isolated from participants who had undergone diet-induced weight loss compared with pre-weight-loss values. In agreement with this finding is the observation that subcutaneous adipose tissue expression of HSL mRNA and protein was reduced by weight loss (in negative energy balance) in individuals with overweight or obesity

Source: https://www.nature.com/articles/s41574-023-00887-4

Reductions in Lipolysis Tend to Lead to Weight Regain

van Baak MA and Mariman ECM, "Obesity-induced and weight-loss-induced physiological factors affecting weight regain," *Nature Reviews Endocrinolology*, Nov 19, 2023 pp. :655-670.

A 2019 study compared lipolysis by measuring the ex vivo adipose tissue FFA production in mice going through an intervention of 8 weeks on a HFD followed by 4 weeks on a LFD with lipolysis in mice that were kept on the LFD for 12 weeks. After 12 weeks, noradrenaline-stimulated lipolysis activity did not differ between the two groups. However, when both groups of mice were subsequently put on a HFD, stimulated lipolysis in the intervention-treated group was significantly lower than in the control group. In addition, HSL phosphorylation and the expression of the genes for the β1-adrenergic, β2-adrenergic and β3-adrenergic receptors were lower in the treated mice, although the expression of the anti-lipolytic α2-adrenergic receptor was also reduced.

The differences in these parameters between the groups closely resembled the situation after the initial 8 weeks on a HFD or LFD. Therefore, it was proposed that obesity memory not only has an inflammatory component but also a metabolic component, in particular with respect to lipolysis.

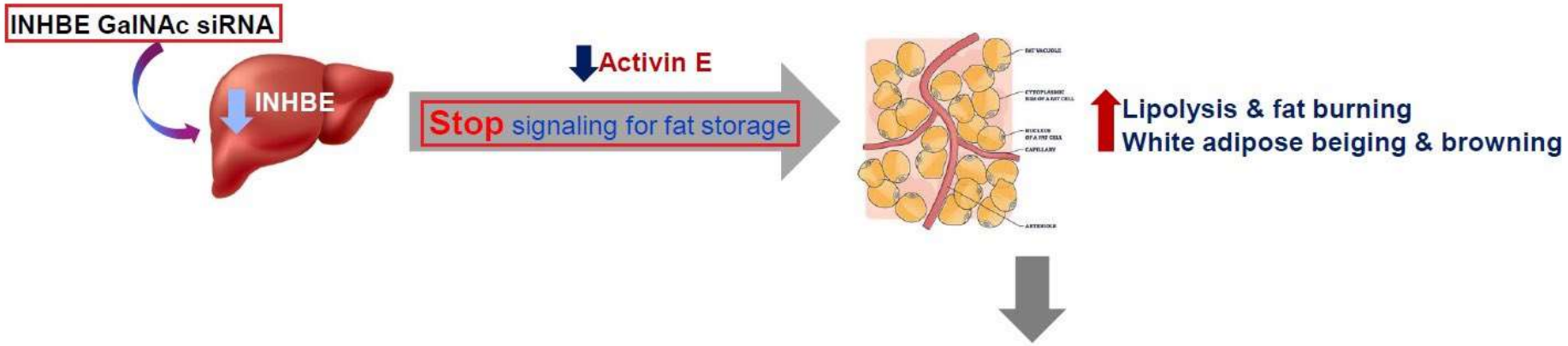
The impairments in lipolysis after weight loss observed in humans with overweight or obesity also suggest that reduced lipolysis might have a role in weight regain. It is hypothesized that a reduction in the lipolytic activity of adipocytes after weight loss could shift the net balance of adipose tissue FFA uptake and storage versus FFA secretion and utilization towards uptake and storage, in particular because FFA oxidation is also reduced. So far, however, direct evidence for this hypothesis from studies in humans is limited. A 2013 study found that the change in ATGL protein expression in adipose tissue during weight loss predicted weight regain: the larger the reduction in ATGL, the higher the weight regain. **In the YoYo study, a larger weight loss-induced reduction in plasma levels of FFA, which is likely to reflect reduced lipolysis, predicted more weight regain.**

In summary, people with obesity are on average characterized by low levels of lipolysis and lipid oxidation. Both lipolysis and lipid oxidation are further impaired upon weight loss, and there is some evidence that this impairment persists after weight loss has ceased and that a stronger impairment of lipolysis after weight loss is associated with more weight regain (Fig. 2).

Source: https://www.nature.com/articles/s41574-023-00887-4

Wave Life Sciences: INHBE Silencing Promotes Lipolysis and Fat Browning

Silencing INHBE increases adipose lipolysis, induces white adipose beiging & browning, and improves serum lipid profile & metabolic health



INHBE silencing displays distinct mechanism of body weight regulation and may offer excellent obesity treatment option

Cell Reports (2018) 25, 1193–1203; PNAS 2023 Vol. 120 No. 32 e2309967120; Nat Commun 2022. https://doi.org/10.1038/s41467-022-32398-7; Nat Commun 2022. https://doi.org/10.1038/s41467-022-31757-8

Various Pharmacologic Strategies Available for Overcoming Adipocyte Factors Hindering Weight Loss Maintenance

van Baak MA and Mariman ECM, "Obesity-induced and weight-loss-induced physiological factors affecting weight regain," *Nature Reviews Endocrinolology*, Nov 19, 2023 pp. :655-670.

Studies in animals have revealed several ways to influence body weight regulation that can be explored to find novel targets for the prevention of weight regain. A 2022 study[146] identified obesity-induced genes in mouse adipocytes, the expression of which did not change during weight loss. For 19 of these persisting genes, knockout of the homologous gene in the worm *Caenorhabditis elegans* led to a decrease in food intake. Knocking out of one of these genes, *Atp6v0a1*, the gene coding for a component of the vacuolar-ATPase complex, which serves to pump protons across membranes in several cellular organelles by hydrolysing ATP, decreased both food intake and body weight in HFD-fed mice. Gene and protein expression of adipocyte *ATP6v0a1* is also increased in adipocytes from people with obesity compared with those from lean controls, and persists after weight loss in human obese adipose tissue. Pharmacological inhibition of vacuolar-ATPase by bafilomycin in HFD-fed mice that had passed through a cycle of weight gain and loss lowered food intake, reduced fat mass and blunted weight regain.

Table 2 | Potential strategies to tackle weight regain

Strategy	Examples	Mechanisms
Changing diet composition	High protein content, low glycaemic index, anti-inflammatory diets	Reduce appetite
		Increase energy expenditure
		Reduce adipose tissue inflammation
Physical activity	Aerobic exercise, high-intensity interval exercise, resistance exercise	Improve leptin sensitivity
		Increase sympathetic nervous system tone
		Reduce appetite
		Increase lipid oxidation
		Preserve muscle mass
		Increase energy expenditure
Pharmacotherapy	Targeting gastrointestinal hormones (for example, GLP1 receptor agonists), leptin supplementation, leptin sensitizers, NSAIDs, vacuolar-ATPase	Reduce appetite
		Target the immune system to block or prevent obesogenic memory in adipose tissue
		Influence expression of weight-regulating genes
Biomedical strategies	Coating cells in vivo with apoptotic peptides or lipids, photothermal ablation of nanoparticle-treated adipocytes	Target relevant cell types (such as endothelial cells and adipocytes) in adipose tissue, resulting in cell death

GLP1, glucagon-like peptide 1.

Source: https://www.nature.com/articles/s41574-023-00887-4

Many Past Efforts at Raising Thermogenesis Have Been Challenged

Targets explored in clinical trials for increased energy expenditure and induction of weight loss

Target	Mode of action	Indication	Clinically relevant weight loss	If withdrawn, reasons for discontinuation; Remarks
TH mimetics	Increased REE via SNS activation, mitochondrial biogenesis and uncoupling	Currently, dyslipidemia; NASH	Yes	Lack of safety window on cardiac and bone parameters; thyrotoxicosis
Dinitrophenol	Mitochondrial uncoupling	Obesity, NASH	Yes	Steep dose response, hyperthermia, mortality
Monoaminergic system				
Fenfluramine/Fen-Phen	Potentiation of thermic effect of food; appetite suppression	Obesity	Yes	Cardiac valvulopathies, increased blood pressure/heart rate
Sibutramine	Appetite suppression; increased REE in some trials	Obesity	Yes	Increased risk of heart attack and stroke
β3-AR agonists	BAT activation	Obesity; diabetes	No	Lack of efficacy and off-target effects on blood pressure and heart rate (β3-AR not relevant for human BAT activation)
MC3/4 agonists Setmelanotide	Appetite suppression and presumed increase in SNS activity in animal models	Obesity	No (general obesity)	Several programs withdrawn for general obesity due to lack of efficacy (including setmelanotide), cardiovascular effects and/or hyperpigmentation.
			Yes (genetic obesity)	Setmelanotide approved for rare genetic obesity
GLP-1/glucagon coagonists (w/wo GIP)	Appetite suppression, fat oxidation, increased EE	Obesity, Diabetes, NASH	Yes	Some programs discontinued for obesity due to lack of glycemic control, ongoing trials for NASH
FGF21 analogues	Diverse effects on appetite, browning and/or increased REE in animal models	Obesity, Diabetes, NASH	No	Programs discontinued for obesity due to lack of efficacy, ongoing trials for NASH
MetAP2 inhibitors	Fat oxidation, lipolysis	Obesity	Yes	Venous thromboembolisms with beloranib; ZGN-1061 in trials for obesity

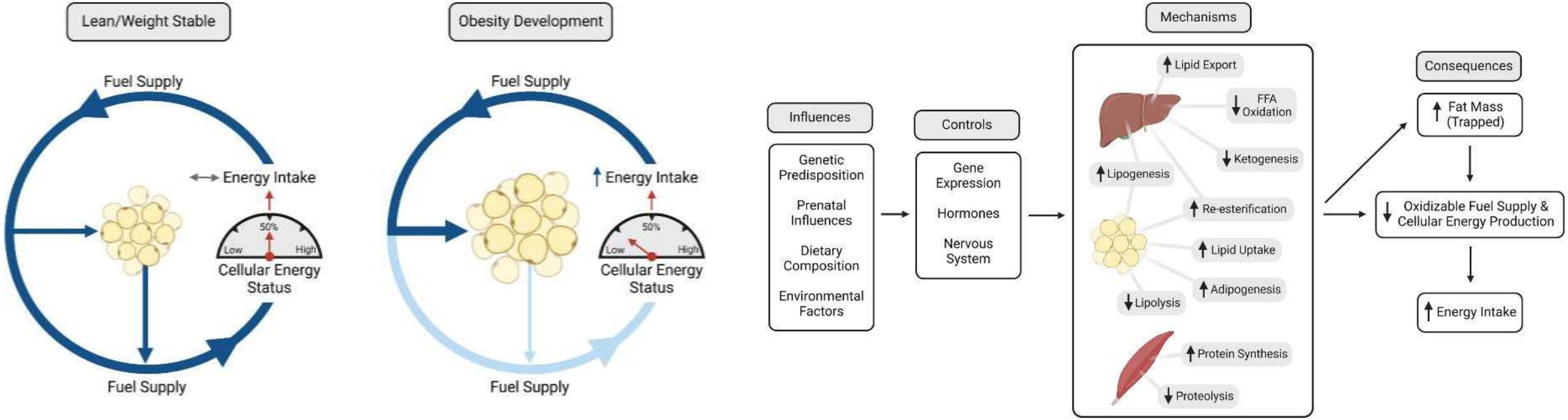
Abbreviations: AR, adrenergic receptor; BAT, brown adipose tissue; EE, energy expenditure; Fen-phen, combination of fenfluramine and phentermine; FGF21, fibroblast growth factor 21; GIP, gastric inhibitory polypeptide; GLP-1, glucagon-like peptide 1; MC, melanocortin; MetAP2, methionine aminopeptidase 2; NASH, non-alcoholic steatohepatitis; REE, resting energy expenditure; SNS, sympathetic nervous system; TH, Thyroid hormones; w/wo, with/without.

Source: https://onlinelibrary.wiley.com/doi/10.1002/oby.23374

Related Theory Portrays Obesity as a Problem of Fuel Partitioning

Friedman MI, Sørensen TIA, Taubes G, Lund J, Ludwig DS. Trapped fat: Obesity pathogenesis as an intrinsic disorder in metabolic fuel partitioning. Obes Rev. Jul 3, 2024.

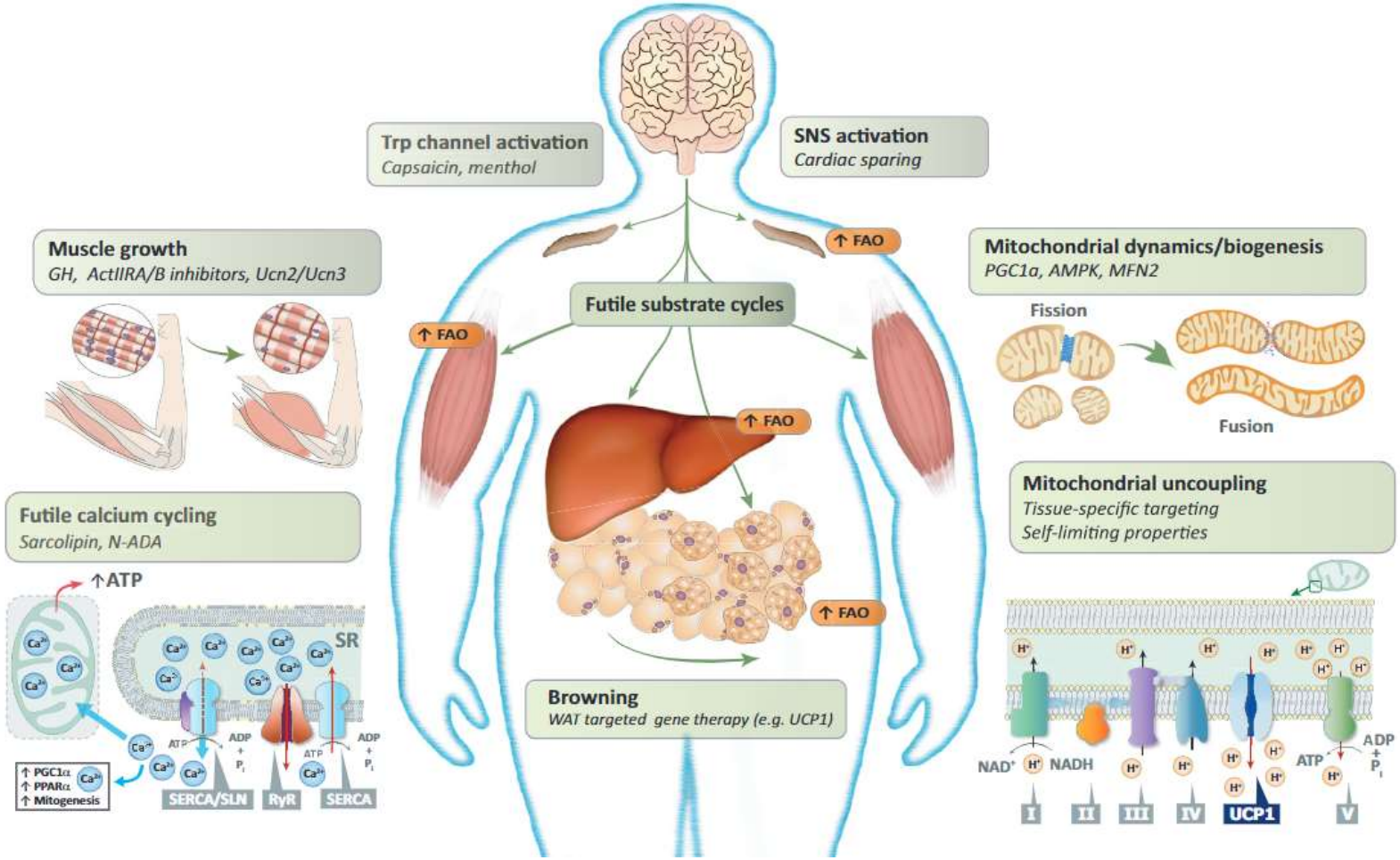
Our understanding of the pathophysiology of obesity remains at best incomplete despite a century of research. During this time, two alternative perspectives have helped shape thinking about the etiology of the disorder. The currently prevailing view holds that excessive fat accumulation results because energy intake exceeds energy expenditure, with excessive food consumption being the primary cause of the imbalance. The other perspective attributes the initiating cause of obesity to intrinsic metabolic defects that shift fuel partitioning from pathways for mobilization and oxidation to those for synthesis and storage. The resulting reduction in fuel oxidation and trapping of energy in adipose tissue drives a compensatory increase in energy intake and, under some conditions, a decrease in expenditure. This theory of obesity pathogenesis has historically garnered relatively less attention despite its pedigree. Here, we present an updated comprehensive formulation of the fuel partitioning theory, focused on evidence gathered over the last 80 years from major animal models of obesity showing a redirection of fuel fluxes from oxidation to storage and accumulation of excess body fat with energy intake equal to or even less than that of lean animals. The aim is to inform current discussions about the etiology of obesity and by so doing, help lay new foundations for the design of more efficacious approaches to obesity research, treatment and prevention.



Source: https://onlinelibrary.wiley.com/doi/10.1111/obr.13795

Numerous Attractive Targets for Increasing Cellular Energy Expenditure and Thermogenesis

Christoffersen BØ, Sanchez-Delgado G, John LM, Ryan DH, Raun K, Ravussin E., "Beyond appetite regulation: Targeting energy expenditure, fat oxidation, and lean mass preservation for sustainable weight loss," *Obesity*, April 2022, pp. 841-857.



Rethinking approaches for weight maintenance by targeting energy expenditure and lean mass preservation. Potential ways of maintaining or increasing energy expenditure include a diversity of targets ranging from sympathetic nervous system and transient receptor potential channel activation over browning of white adipose tissue to increased nonshivering thermogenesis in various organs. Nonshivering thermogenesis in skeletal muscle and other tissues can be brought about by increasing mitochondrial proton leak, by pharmacologically induced futile calcium cycling or various other futile substrate cycles, all of which would increase fatty acid oxidation andenergy expenditure. Mitochondrial biogenesis and improved mitochondrial function are needed to support this increased energy demand. Potential targets for maintaining or increasing muscle mass include growth hormone, activin type II receptors A/B, and urocortin 2 and 3,which will secondarily lead to maintenance of the energy expenditure. ActIIR A/B, activin type II receptors A/B; AMPK, AMP-activated protein kinase; FAO, fatty acid oxidation; GH, growth hormone; MFN2, mitofusin 2; N-ADA, N-arachidonoyl dopamine; PGC1α, peroxisome proliferator-activated receptor gamma coactivator 1α; PPARα, peroxisome proliferator-activated receptor alpha; RyR, ryanodine receptor; SERCA, sarcoplasmic/endoplasmic reticulum Ca2+-dependent ATPase; SLN, sarcolipin; SNS, sympathetic nervous system; SR, sarcoplasmic reticulum; TRP, transient receptor potential; Ucn2/3, urocortin 2 and 3; UCP1, uncoupling protein 1; WAT, white adipose tissue

Source: https://onlinelibrary.wiley.com/doi/10.1002/oby.23374

Thermogenic Enhancement Strategies

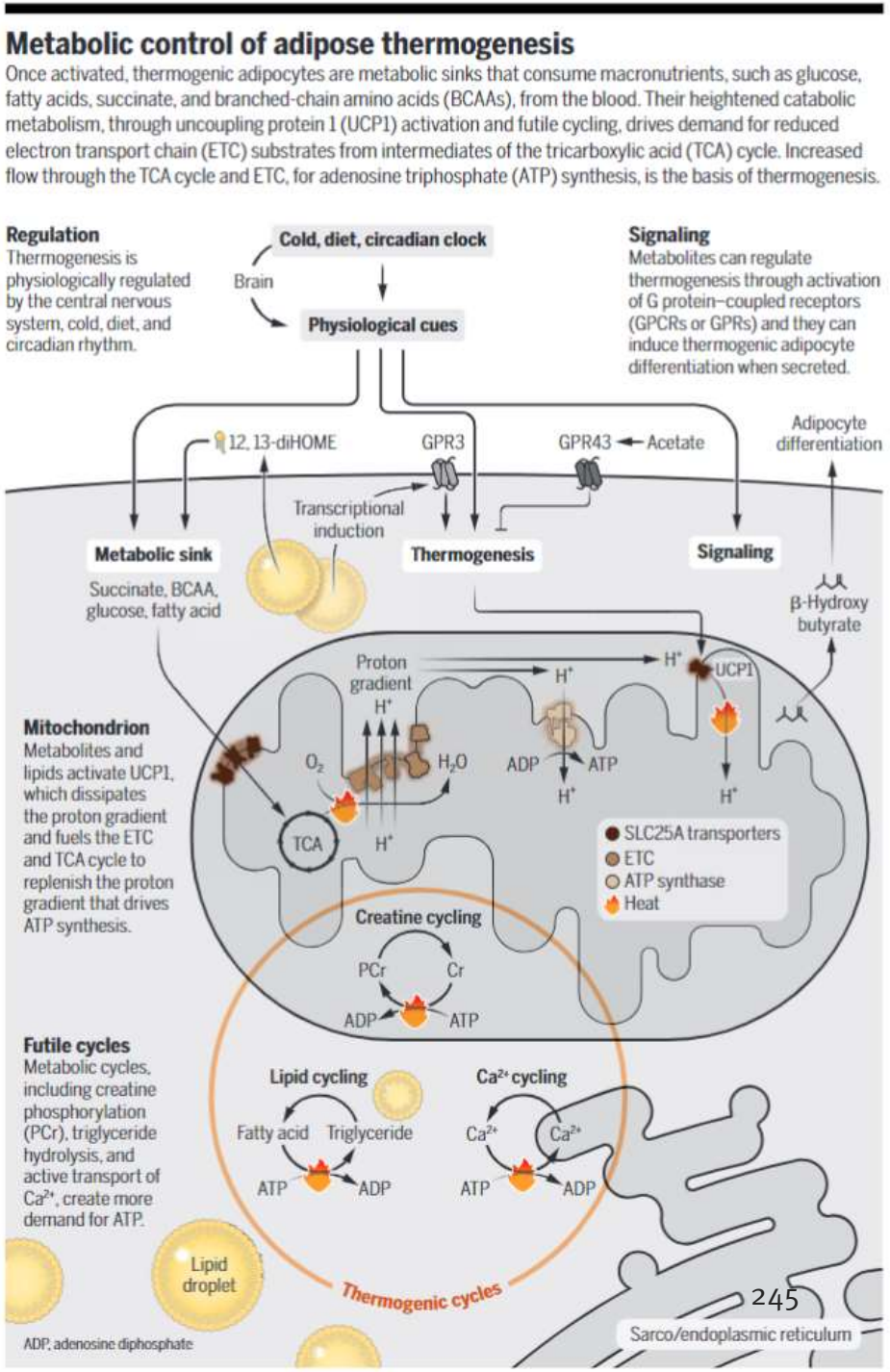
Numerous Druggable Mechanisms Exist to Enhance Heat Dissipation – Altering Energy Balance in the Adipocyte Microenvironment

Discussed Elsewhere in this Report

AMPK Activation: AMPK mimics the transcriptional signature induced by exercise
Activin Receptor IIA Antagonism: Thermogenesis increases + BAT adipogenesis
Apelin Agonism: Enhances thermogenesis
CB1 Antagonists: Decrease appetite, enhance thermogenesis and diminish lipogenesis
Dopamine Agonists: Directly linked to higher thermogenesis
GPR75 Antagonism: Causes body to burn fat and turn to heat
INHBE: Mediates liver-adipose tissue communication and lipolysis
Mitochondrial Uncouplers: Increase heat dissipation
PKCa: Augments oxygen use and β3-adrenergic receptor signaling
UCP1: As noted at right, UCP1 fuels ATP synthesis and hence thermogenesis

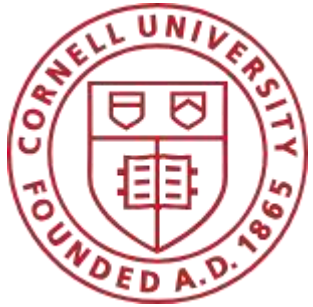
Other Strategies

Adispp: Key batokine controls thermogenesis and glucose homeostasis
β-adrenoceptor: Activates glucose clearance in brown adipose tissue
Claudin1: Highly upregulated in WAT in the case of obesity
CXCL12: Restores brown adipose tissue homeostasis
ERR Agonism: Increases fatty acid oxidation and increase oxidation
GPR43: Hinders thermogenesis as a key negative regulator
HDAC11: Hinders thermogenesis and degrades adipocyte quality
STAT5: Key substrate for lipid breakdown in adipocytes



Source of picture: https://www.science.org/doi/10.1126/science.abl7108

CXCL12 a Key Protein in Brown Adipocyte Thermogenesis



Cornell University Press Release, "Communication between tissues facilitates thermogenesis, June 20, 2024

Daniel Berry, assistant professor in the Division of Nutritional Sciences, and graduate students in his lab have identified the cellular and molecular mechanisms that govern adaptive thermogenesis, a biological process that researchers believe could be the key to treating obesity, type 2 diabetes and other metabolic disorders.

Their study, published in the journal Cell Reports, outlines the complex intra-organ communication that allows brown adipose tissue to burn calories to produce heat to maintain body temperature and provides a potential clue to why mammals lose the tissue.

Brown adipose tissue contains adipocytes, as well as blood vessels and nerve fibers that connect it to the sympathetic nervous system. Berry said that the team was working on a different research question when they noticed that some of the smooth muscle cells that make up those blood vessels produce adipocytes, but others do not.

They found that vascular smooth muscle cells expressing alpha-smooth muscle actin (SMA) don't generate new brown adipocytes, but instead support brown adipose tissue homeostasis and thermogenesis.

Further research revealed that these vascular cells regulate thermogenesis by secreting the signaling protein Cxcl12, which supports and retains local anti-inflammatory macrophages and maintains the sympathetic nerve fibers that stimulate thermogenesis. The team found that mice without Cxcl12 were more susceptible to metabolic dysfunction when fed a high-fat diet, while administering the protein to these mice restored homeostasis in their brown adipose tissue. Furthermore, administering the protein to obese male mice improved the rodents' ability to maintain their body temperature and increased their energy expenditure when exposed to cold. In other words, Cxcl12 improved their thermogenic response.

"It was surprising to see how much cells communicate with each other to coordinate immunological, metabolic and sympathetic processes," Berry said. "It's quite the circuit to think about."

Overall, the study suggests that using Cxcl12 to maintain supportive macrophages in brown adipose tissue could improve brown adipocyte persistence and metabolic homeostasis. Investigating Cxcl12 regulatory pathways could help explain why the tissue declines with age.

Source: https://www.human.cornell.edu/news/imported/2024/06/communication-between-tissues-facilitates-thermogenesis

HDAC11: Negative Regulator of Thermogenesis

Bagchi et.al., "Reversible lysine fatty acylation of an anchoring protein mediates adipocyte adrenergic signaling," PNAS Feb 15, 2022.

N-myristoylation on glycine is an irreversible modification that has long been recognized to govern protein localization and function. In contrast, the biological roles of lysine myristoylation remain ill-defined. We demonstrate that the cytoplasmic scaffolding protein, gravin-α/A kinase-anchoring protein 12, is myristoylated on two lysine residues embedded in its carboxyl-terminal protein kinase A (PKA) binding domain. Histone deacetylase 11 (HDAC11) docks to an adjacent region of gravin-α and demyristoylates these sites.

In brown and white adipocytes, lysine myristoylation of gravin-α is required for signaling via β2- and β3-adrenergic receptors (β-ARs), which are G protein-coupled receptors (GPCRs). Lysine myristoylation of gravin-α drives β-ARs to lipid raft membrane microdomains, which results in PKA activation and downstream signaling that culminates in protective thermogenic gene expression. These findings define reversible lysine myristoylation as a mechanism for controlling GPCR signaling and highlight the potential of inhibiting HDAC11 to manipulate adipocyte phenotypes for therapeutic purposes.

Results of initial imaging studies confirming the presence of BAT that can be activated by cold temperature in humans further fueled interest in developing therapies for obesity based on increasing

The biotech company Myracle Therapeutics is developing HDAC11 inhibitors for the treatment of obesity.

Myracle THERAPEUTICS

Targeting adipocytes for weight management and healthy aging

energy expenditure in BAT or "beiged" WAT. Pharmacological approaches to promote BAT formation and function have focused heavily on the use of β3-AR agonists. Nonetheless, while β3-AR agonists were shown to acutely increase energy expenditure and insulin sensitivity in humans, they failed to promote weight loss upon chronic administration. Results of more recent human studies with mirabegron, a β3-AR agonist that is approved by the US Food and Drug Administration for the treatment of overactive bladder, have renewed interest in stimulating this GPCR pathway in adipose tissue as a means to treat metabolic disease.

Targeting of HDAC11 should be considered as an alternative or complementary strategy to augment thermogenesis in BAT and WAT to stimulate energy expenditure. HDAC11 is ostensibly a safe therapeutic target, since its global deletion in mice is well tolerated, and the discovery of FT895, which is ›10,000-fold selective for HDAC11 over other zinc-dependent HDACs, has established the feasibility of selectively inhibiting this enzyme.

Source: https://pubmed.ncbi.nlm.nih.gov/35149557/

HDAC11 Suppresses the Thermogenic Program of Adipose Tissue via BRD2

Bagchi et.al., "HDAC11 suppresses the thermogenic program of adipose tissue via BRD2," *JCI Insight,* Aug 9, 2018.

There is intense interest in developing alternative pharmacotherapy for obesity based on increasing energy expenditure via brown adipose tissue (BAT). In contrast to white adipose tissue (WAT), which functions mainly to store energy in the form of triglycerides in unilocular white adipocytes, brown adipocytes within BAT harbor small, multilocular lipid droplets and an abundance of mitochondria, which produce heat through nonshivering thermogenesis. Heat production by BAT is governed by uncoupling protein–1 (UCP1), which resides in the inner mitochondrial membrane in brown adipocytes and functions as a long-chain fatty acid/H+ symporter to catalyze mitochondrial proton leak and thereby uncouple electron transport from ATP synthesis. BAT is highly metabolically active and has been shown to contribute to energy expenditure in humans. Additional studies in humans have revealed that body mass index and percent body fat negatively correlate with BAT abundance , and a polymorphism in the gene encoding UCP1 is associated with fat gain and obesity. Together, these findings validate the potential of BAT-targeted therapies for the treatment of obesity.

Pharmacological approaches to promote BAT formation and function have included the use of β3-adrenergic receptor (β3-AR) agonists. β3-AR stimulation directly enhances lipolysis and energy expenditure, and also triggers downstream signaling events.

Here, using multiple in vivo, ex vivo, and cell-based approaches, we demonstrate that histone deacetylase 11 (HDAC11) functions as a repressor of the thermogenic gene program in BAT and prevents beiging of WAT. Compared with WT controls, mice lacking HDAC11 are lean and harbor excess BAT. Accordingly, HDAC11 deficiency leads to enhanced cold-induced thermogenesis, reduced weight gain and lipid accumulation in response to high-fat feeding, and improved glucose tolerance. The global metabolic effects of HDAC11 deletion correlate with enhanced UCP1 expression in BAT, a profound increase in beiging of WAT, and augmented thermogenic gene expression in response to β3-AR signaling. Using cell-based models, we provide evidence for cell-autonomous roles for HDAC11 as a repressor of brown adipocyte differentiation and thermogenic gene expression, functions that are dependent on association of HDAC11 with the bromodomain and extraterminal (BET) family member BRD2. These data demonstrate a previously unrecognized role for HDAC11 as an epigenetic regulator of whole-body metabolism. Furthermore, since HDAC11-deficient mice are healthy (32), and HDAC11 has a unique catalytic domain compared with other HDAC isoforms (33), the findings suggest the possibility that selective HDAC11 inhibitors could be developed to increase energy expenditure for the treatment of obesity and metabolic disease.

Source: https://insight.jci.org/articles/view/120159

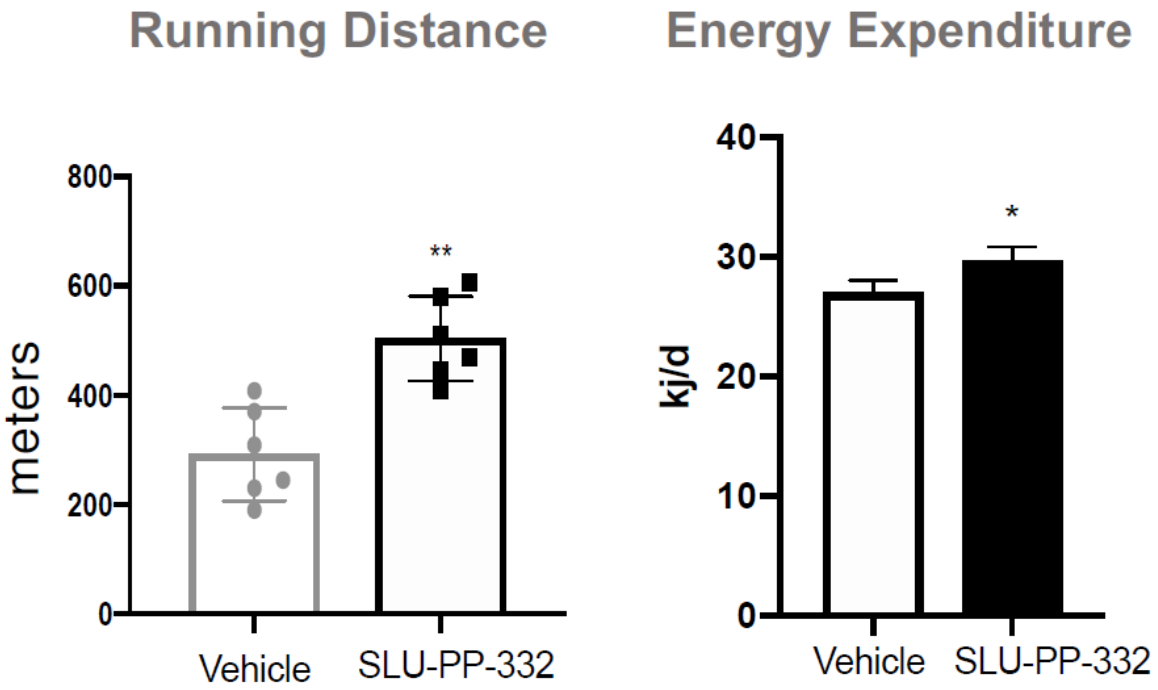
ERR Agonist Increasing Energy Expenditure in Animal Model

The biotech company Pelagos Pharma is developing first-in-class ERR agonists as an "exercise in a pill" approach.

Billon C, Schoepke E, Avdagic A, Chatterjee A, Butler AA, Elgendy B, Walker JK, Burris TP. A Synthetic ERR Agonist Alleviates Metabolic Syndrome. *J Pharmacol Exp Ther,* Jan 17, 2024, pp. 232-240.

Physical exercise induces physiologic adaptations and is effective at reducing the risk of premature death from all causes. Pharmacological exercise mimetics may be effective in the treatment of a range of diseases including obesity and metabolic syndrome. Previously, we described the development of SLU-PP-332, an agonist for the estrogen-related receptor (ERR)α, β, and γ nuclear receptors that activates an acute aerobic exercise program. Here we examine the effects of this exercise mimetic in mouse models of obesity and metabolic syndrome. Diet-induced obese or ob/ob mice were administered SLU-PP-332, and the effects on a range of metabolic parameters were assessed. SLU-PP-332 administration mimics exercise-induced benefits on whole-body metabolism in mice including increased energy expenditure and fatty acid oxidation. These effects were accompanied by decreased fat mass accumulation. Additionally, the ERR agonist effectively reduced obesity and improved insulin sensitivity in models of metabolic syndrome. Pharmacological activation of ERR may be an effective method to treat metabolic syndrome and obesity.

Use of SLU-PP-332 in WT Mice

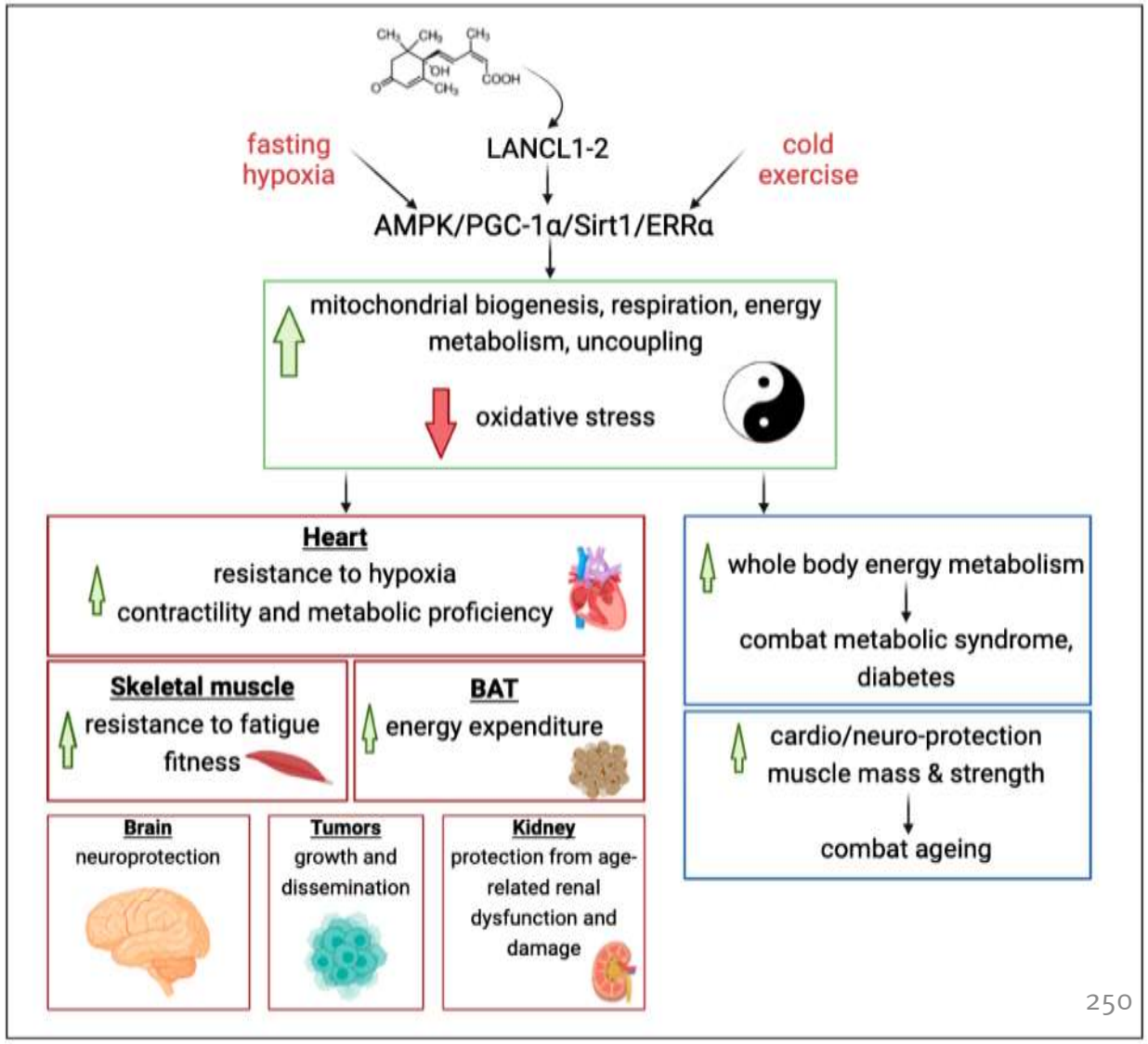


Source: https://insight.jci.org/articles/view/120159

Estrogen-Related Receptor α: A Key Transcription Factor in the Regulation of Energy Metabolism at an Organismic Level

Spinelli et.al., Int J Mol Sci. 2024 Apr 27;25(9):4796.

The orphan nuclear receptor ERRα is the most extensively researched member of the estrogen-related receptor family and holds a pivotal role in various functions associated with energy metabolism, especially in tissues characterized by high energy requirements, such as the heart, skeletal muscle, adipose tissue, kidney, and brain. Abscisic acid (ABA), traditionally acknowledged as a plant stress hormone, is detected and actively functions in organisms beyond the land plant kingdom, encompassing cyanobacteria, fungi, algae, protozoan parasites, lower Metazoa, and mammals. Its ancient, cross-kingdom role enables ABA and its signaling pathway to regulate cell responses to environmental stimuli in various organisms, such as marine sponges, higher plants, and humans. Recent advancements in understanding the physiological function of ABA and its mammalian receptors in governing energy metabolism and mitochondrial function in myocytes, adipocytes, and neuronal cells suggest potential therapeutic applications for ABA in pre-diabetes, diabetes, and cardio-/neuroprotection. The ABA/LANCL1-2 hormone/receptor system emerges as a novel regulator of ERRα expression levels and transcriptional activity, mediated through the AMPK/SIRT1/PGC-1α axis.



Source: https://pubmed.ncbi.nlm.nih.gov/38732013/

MiR-22 a Key Regulator of Thermogenesis

Resalis is developing miR-22 inhibitors for obesity and fatty liver disease and is in Phase 1 clinical testing.

Lou P et.al., "MiR-22 modulates brown adipocyte thermogenesis by synergistically activating the glycolytic and mTORC1 signaling pathways," *Theranostics*, Jan 25, 2021 Jan 25, pp. 3607-3623.

Brown adipose tissue (BAT) dissipates chemical energy as heat and has the potential to be a protective strategy to prevent obesity. microRNAs (miRNAs) are emerging as important posttranscriptional factors affecting the thermogenic function of BAT. However, the regulatory mechanism underlying miRNA-mediated energy metabolism in BAT is not fully understood. Here, we explored the roles of miR-22 in BAT thermogenesis and energy metabolism. Using global and conditional knockout mice as in vivo models and primary brown adipocytes as an in vitro system, we investigated the function of miR-22 in BAT thermogenesis in vivo and in vitro. miR-22 expression was upregulated in BAT in response to cold exposure and during brown preadipocyte differentiation. Both global and conditional knockout mice displayed BAT whitening, impaired cold tolerance, and decreased BAT thermogenesis. Moreover, we found that miR-22 deficiency impaired BAT glycolytic capacity, which is critical for thermogenesis. The mechanistic results revealed that miR-22 activated the mTORC1 signaling pathway by directly suppressing Tsc1 and concomitantly directly suppressing Hif1an, an inhibitor of Hif1α, which promotes glycolysis and maintains thermogenesis.

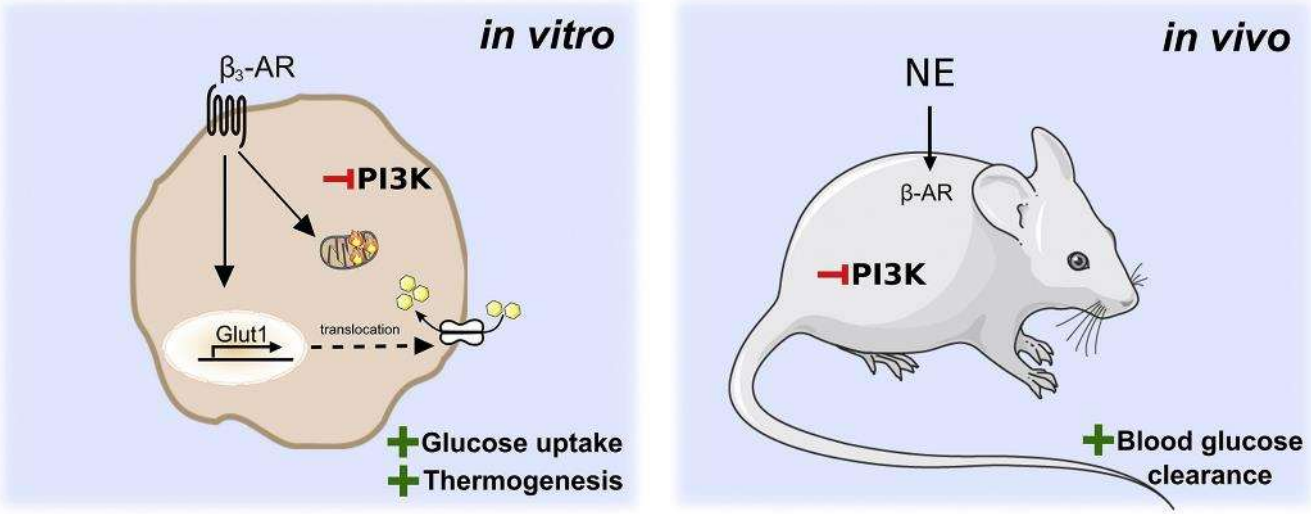
We examined the histology of brown adipose tissue (BAT) from miR-22 KO mice. On gross examination, BAT from miR-22 KO mice exhibited profound morphological whitening. The whitening was accompanied by a switch from a multilocular to a unilocular morphology and an increase in lipid areas. To test the BAT thermogenesis-related function of miR-22, we assessed NST by measuring BAT O_2 consumption in vitro. The O_2 consumption of BAT isolated from miR-22 KO mice was significantly lower than that of BAT isolated from littermate controls. Consistently, BAT-selective genes were significantly downregulated in miR-22 KO mice. The protein expression of Ucp1 and Prdm16 was also attenuated in miR-22 KO mice. In line with these findings, the BAT from miR-22-AKO mice also exhibited profound morphological whitening, downregulation of BAT-selective genes and decreased O_2 consumption. Furthermore, miR-22 BKO mice also exhibited the whitening of BAT and downregulation of BAT-selective genes, compared to control mice, suggesting a specific role of miR-22 in BAT. Together, these in vivo findings demonstrate that miR-22 plays an important role in modulating thermogenic function of BAT.

See: https://pubmed.ncbi.nlm.nih.gov/33664851/, https://www.resalistherapeutics.com/

Acute β-Adrenoceptor Signalling Mediates Glucose Clearance in Brown Adipose Tissue

β-adrenoceptor mediated activation of brown adipose tissue (BAT) has been associated with improvements in metabolic health in models of type 2 diabetes and obesity due to its unique ability to increase whole body energy expenditure, and rate of glucose and free fatty acid disposal. While the thermogenic arm of this phenomenon has been studied in great detail, the underlying mechanisms involved in β-adrenoceptor mediated glucose uptake in BAT are relatively understudied. As β-adrenoceptor agonist administration results in increased hepatic gluconeogenesis that can consequently result in secondary pancreatic insulin release, there is uncertainty regarding the importance of insulin and the subsequent activation of its downstream effectors in mediating β-adrenoceptor stimulated glucose uptake in BAT. Therefore, in this study, we made an effort to discriminate between the two pathways and address whether the insulin signaling pathway is dispensable for the effects of β-adrenoceptor activation on glucose uptake in BAT. We conclude that the β-adrenergic pathway is still functionally intact upon the inhibition of PI3Kα, showing that the activation of downstream insulin effectors is not required for the acute effects of β-adrenoceptor agonists on glucose homeostasis or thermogenesis.

Olsen JM, Åslund A, Bokhari MH, Hutchinson DS, Bengtsson T. Acute β-adrenoceptor mediated glucose clearance in brown adipose tissue; a distinct pathway independent of functional insulin signaling. Mol Metab. 2019 Dec;30:240-249.

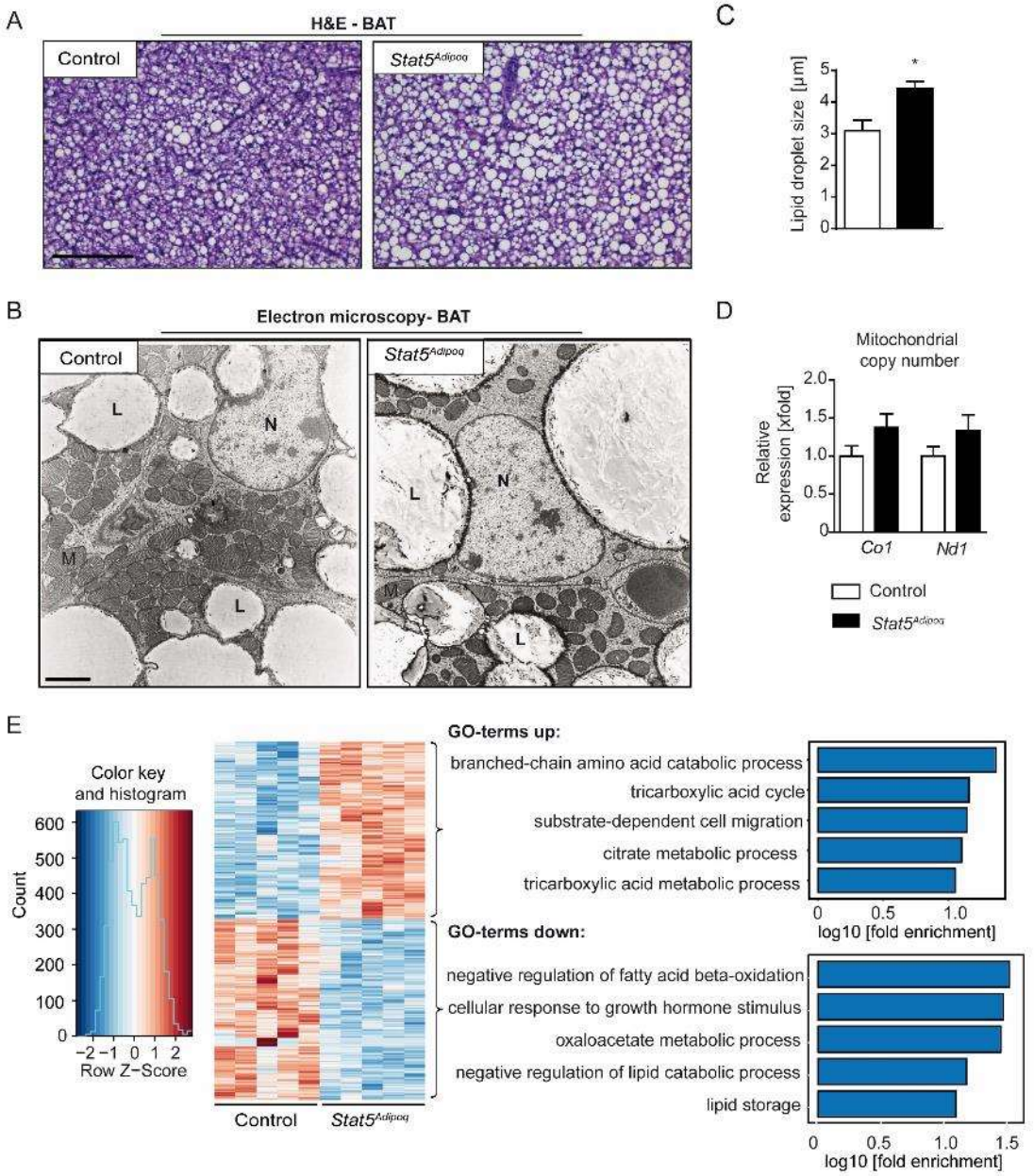


Source: https://pubmed.ncbi.nlm.nih.gov/31767175/

STAT5 is Required for Lipid Breakdown and Beta-Adrenergic Responsiveness of Brown Adipose Tissue

Kaltenecker D et.al., "STAT5 is required for lipid breakdown and beta-adrenergic responsiveness of brown adipose tissue," *Mol Metab*. Oct 2020.

We have shown that adipose STAT5 deficiency impaired temperature maintenance upon acute exposure to cold, which coincided with a diminished usage of BAT lipid stores and reduced UCP1 expression. Interestingly, the lipolytic response upon β3-adrenergic stimulation was blunted in STAT5-deficient BAT, which was partly attributed to diminished PKA activity. Accordingly, the respiratory capacity, as a readout for mitochondrial function, was reduced in primary differentiated adipocytes from Stat5Adipoq mice. Moreover, STAT5 deficiency diminished brown remodelling of ScWAT upon chronic β3-adrenergic stimulation. This, however, was not associated with an impaired induction of UCP1 expression, but with a diminished respiratory activity.



Source: https://www.sciencedirect.com/science/article/pii/S2212877820301009

Figure 1

PAQR4 is a Novel Target for Adipocyte Health

Zhu, Q., Chen, S., Funcke, JB. et al. PAQR4 regulates adipocyte function and systemic metabolic health by mediating ceramide levels., *Nature Metabolism*, July 3, 2024

PAQR4 is an orphan receptor in the PAQR family with an unknown function in metabolism. Here, we identify a critical role of PAQR4 in maintaining adipose tissue function and whole-body metabolic health. We demonstrate that expression of Paqr4 specifically in adipocytes, in an inducible and reversible fashion, leads to partial lipodystrophy, hyperglycaemia and hyperinsulinaemia, which is ameliorated by wild-type adipose tissue transplants or leptin treatment.

By contrast, deletion of Paqr4 in adipocytes improves healthy adipose remodelling and glucose homoeostasis in diet-induced obesity. Mechanistically, PAQR4 regulates ceramide levels by mediating the stability of ceramide synthases (CERS2 and CERS5) and, thus, their activities. Overactivation of the PQAR4–CERS axis causes ceramide accumulation and impairs adipose tissue function through suppressing adipogenesis and triggering adipocyte de-differentiation. Blocking de novo ceramide biosynthesis rescues PAQR4-induced metabolic defects. Collectively, our findings suggest a critical function of PAQR4 in regulating cellular ceramide homoeostasis and targeting PAQR4 offers an approach for the treatment of metabolic disorders.

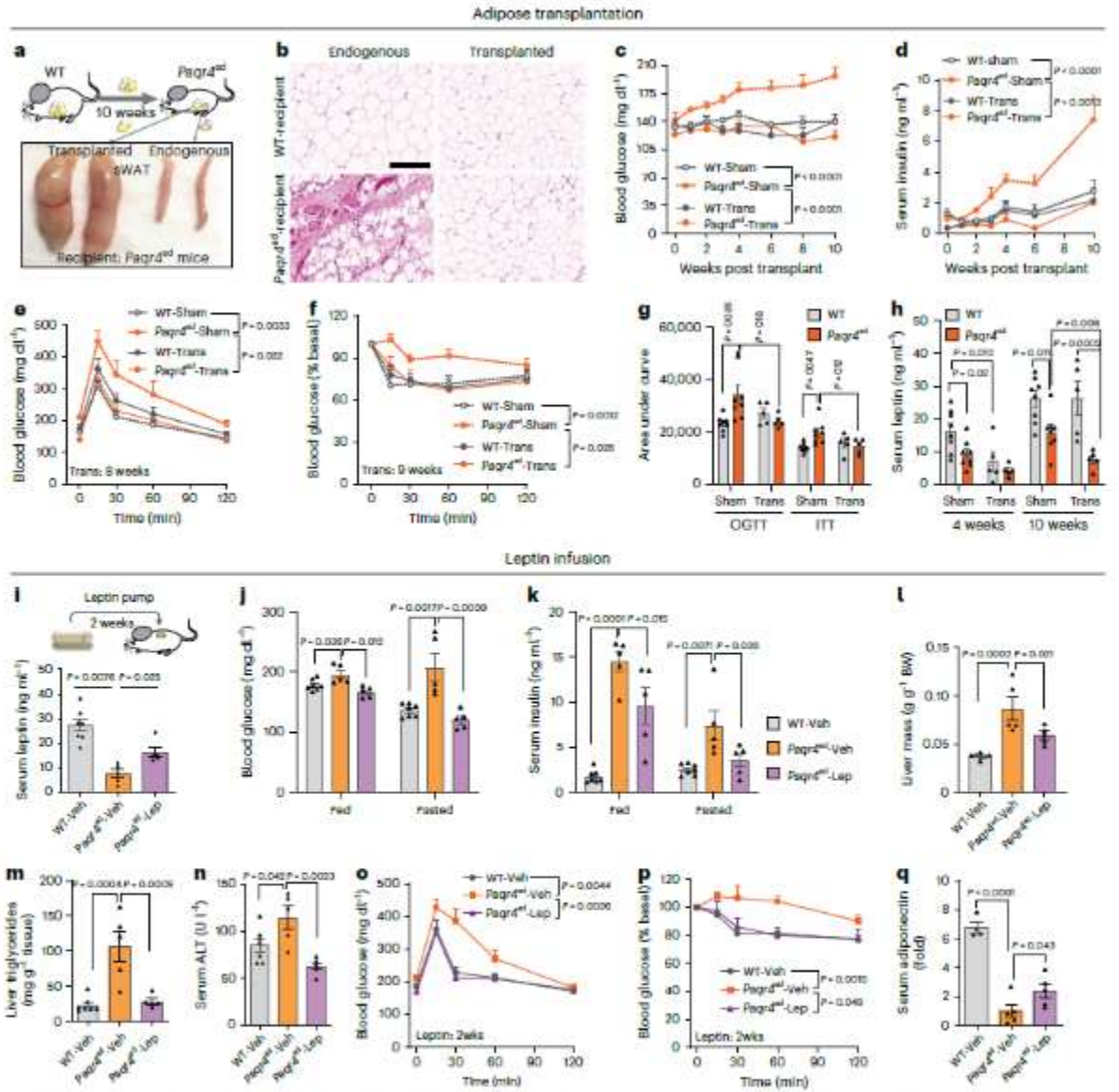


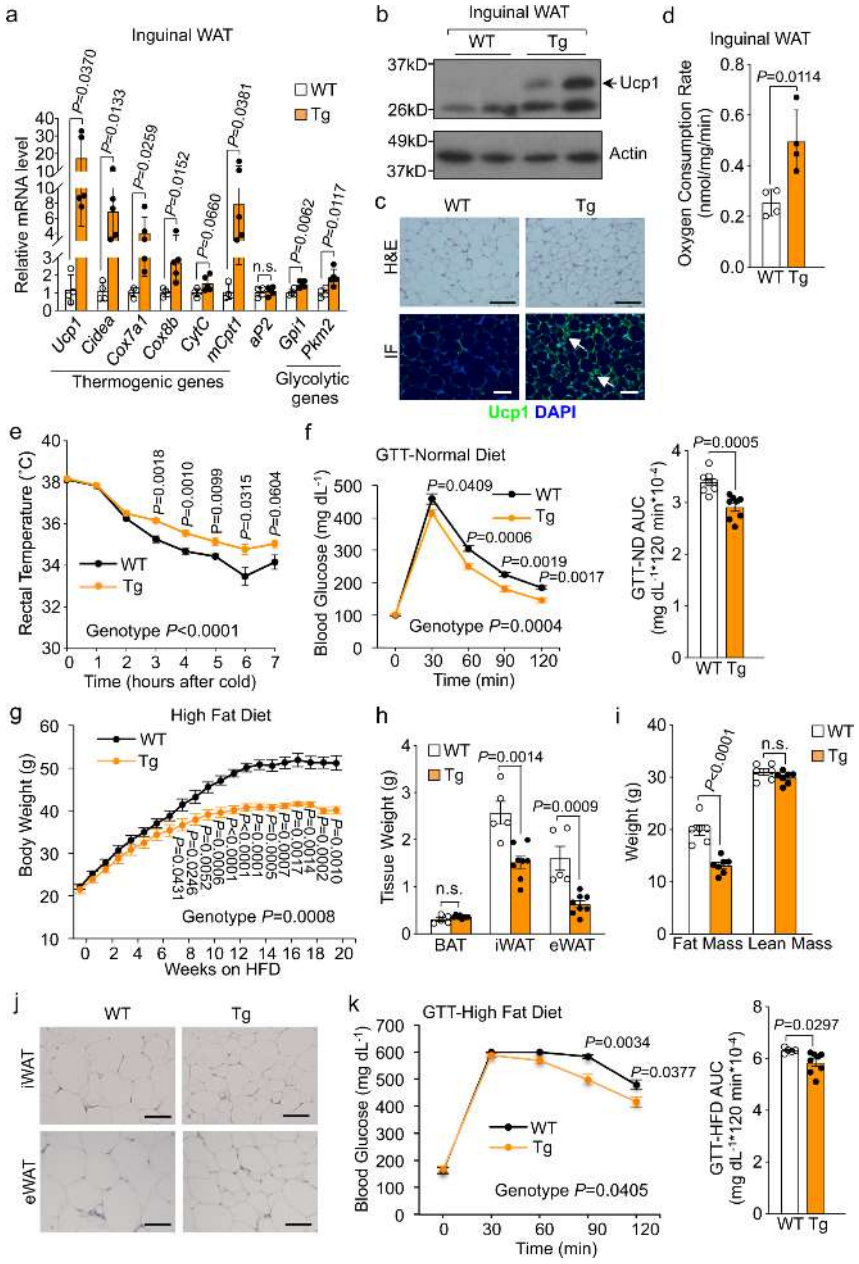
Fig. 3 | Amelioration of PAQR4-induced metabolic dysfunction with adipose tissue transplants or leptin administration. Mice receiving subcutaneous adipose tissue transplants (sWAT) were fed dox chow for 10 weeks. **a**, Endogenous and transplanted sWAT in *Paqr4*^{ad} mice. **b**, Transplanted sWAT displays healthy morphology in both wild-type (WT) and *Paqr4*^{ad} mice ($n = 3$). Scale bar, 200 µm. **c**–**g**, Adipose transplant normalizes hyperglycaemia (**c**), hyperinsulinaemia (**d**), glucose tolerance (**e**,**g**) and insulin-mediated glucose disposal (**f**,**g**) in *Paqr4*^{ad} mice (sham, $n = 8$ per group; transplant, $n = 5$ per group). ITT, insulin tolerance test; OGTT, oral glucose tolerance test; **h**, Adipose transplant does not recover serum leptin in *Paqr4*^{ad} mice (sham, $n = 8$ per group; transplant, $n = 5$ per group). **i**, Two weeks of leptin infusion increases serum leptin levels in *Paqr4*^{ad} mice that were previously exposed to dox chow for 14 weeks (WT, $n = 7$; *Paqr4*^{ad}, $n = 5$ per group). **j**,**k**, Leptin improves hyperglycaemia (**j**) and hyperinsulinaemia (**k**) in *Paqr4*^{ad} mice (WT, $n = 7$; *Paqr4*^{ad}, $n = 5$ per group). **l**–**n**, Leptin reduces liver/body weight (BW) ratio (**l**), liver triglyceride content (**m**) and serum ALT levels (**n**) in *Paqr4*^{ad} mice (WT, $n = 7$; *Paqr4*^{ad}, $n = 5$ per group). **o**,**p**, Leptin normalizes glucose tolerance and insulin-mediated glucose disposal in *Paqr4*^{ad} mice (WT, $n = 7$; *Paqr4*^{ad}, $n = 5$ per group). **q**, Leptin slightly increases serum adiponectin levels in *Paqr4*^{ad} mice (WT, $n = 4$; *Paqr4*^{ad}, $n = 5$ per group). Data are mean ± s.e.m. and analysed by two-way ANOVA (**c**–**h**,**o**,**p**) and one-way ANOVA followed by a Holm–Sidak multiple-comparison test (**i**–**n**,**q**).

Source: https://www.nature.com/articles/s42255-024-01078-9

A Brown Fat-Enriched Adipokine Adissp Controls Adipose Thermogenesis and Glucose Homeostasis

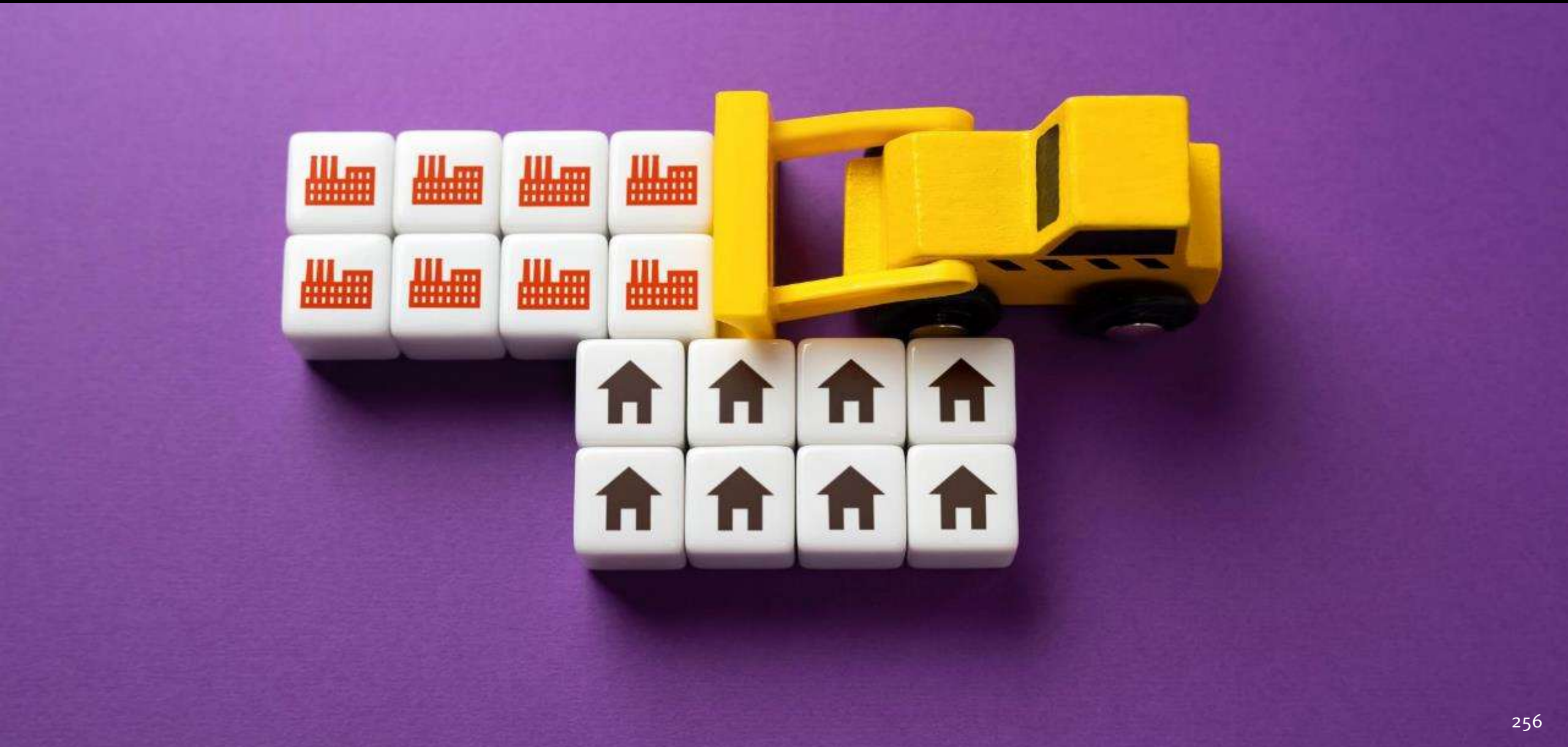
Chen, Q., Huang, L., Pan, D. et al. A brown fat-enriched adipokine Adissp controls adipose thermogenesis and glucose homeostasis. *Nat Commun* 13, 7633 (2022).

The signaling mechanisms underlying adipose thermogenesis have not been fully elucidated. Particularly, the involvement of adipokines that are selectively expressed in brown adipose tissue (BAT) and beige adipocytes remains to be investigated. Here we show that a previously uncharacterized adipokine (UPF0687 protein / human C20orf27 homolog) we named as Adissp (Adipose-secreted signaling protein) is a key regulator for white adipose tissue (WAT) thermogenesis and glucose homeostasis. Adissp expression is adipose-specific and highly BAT-enriched, and its secretion is stimulated by β3-adrenergic activation. Gain-of-functional studies collectively showed that secreted Adissp promotes WAT thermogenesis, improves glucose homeostasis, and protects against obesity. Adipose-specific Adissp knockout mice are defective in WAT browning, and are susceptible to high fat diet-induced obesity and hyperglycemia. Mechanistically, Adissp binds to a putative receptor on adipocyte surface and activates protein kinase A independently of β-adrenergic signaling. These results establish BAT-enriched Adissp as a major upstream signaling component in thermogenesis and offer a potential avenue for the treatment of obesity and diabetes.

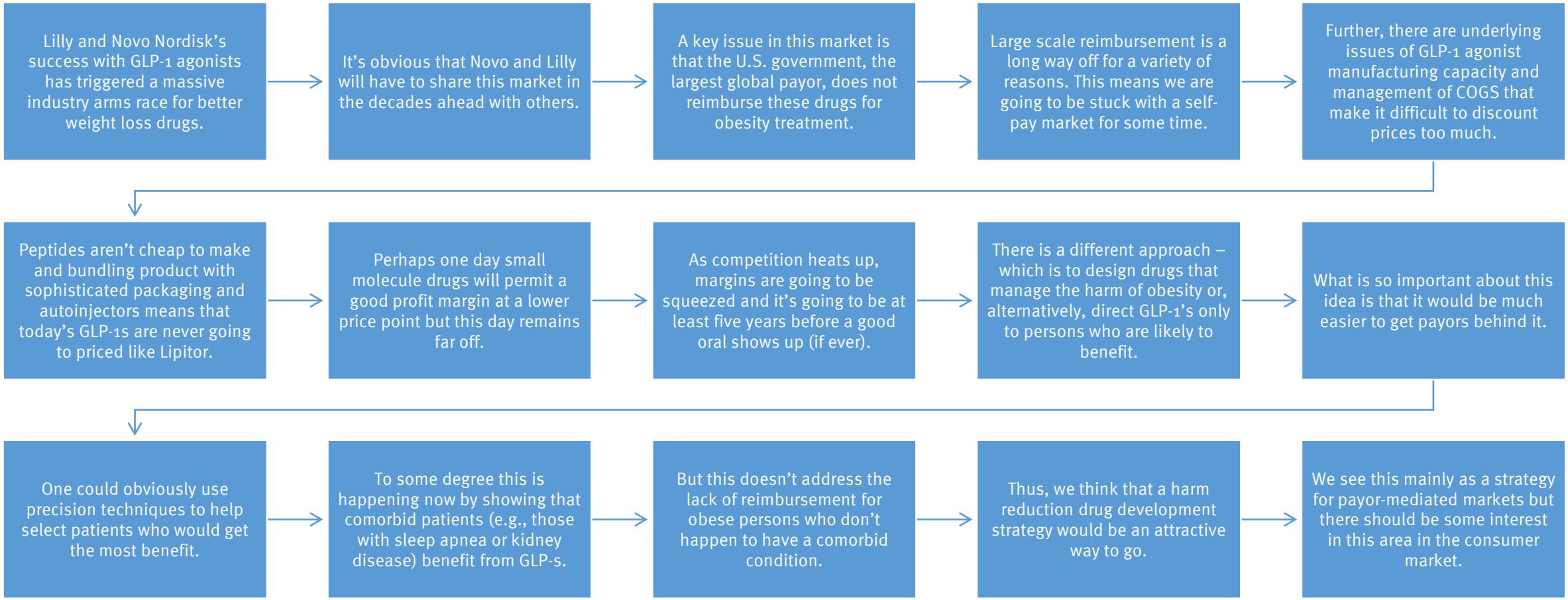


Source: https://www.nature.com/articles/s41467-022-35335-w

Obesity Harm Reduction Strategies



The Idea: Develop Obesity Drugs that Address Specific Causes of Harm



Theories of Obesity Harm

Oxidative Stress / Aldehydes / Superoxides

- Oxidative stress plays an important role in the development of co-morbidities in obesity.
- Contributors to oxidative stress in obesity include hyperglycemia, tissue lipid levels, chronic inflammation, hyperleptinemia and endothelial dysfunction
- Aldeyra's RASP modulators are custom made for this application and are showing promising pre-clinical results
- Emerging superoxide dismutase mimetics and iNOS inhibitors also have high potential here

Insulin Resistance

- Obesity can induce a state of insulin resistance through various mechanisms
- This, in turn, leads to great harm – including cardiovascular disease, liver disease, Alzheimer's, kidney disease
- While GLP-1 agonists improve insulin resistance, are there ways to do better and document specific benefit for resistant patients?
- And could we target patient's *ex ante* that are either insulin resistant now, or likely to become so in the future – in order to maximize payor ROI from covering these drugs?

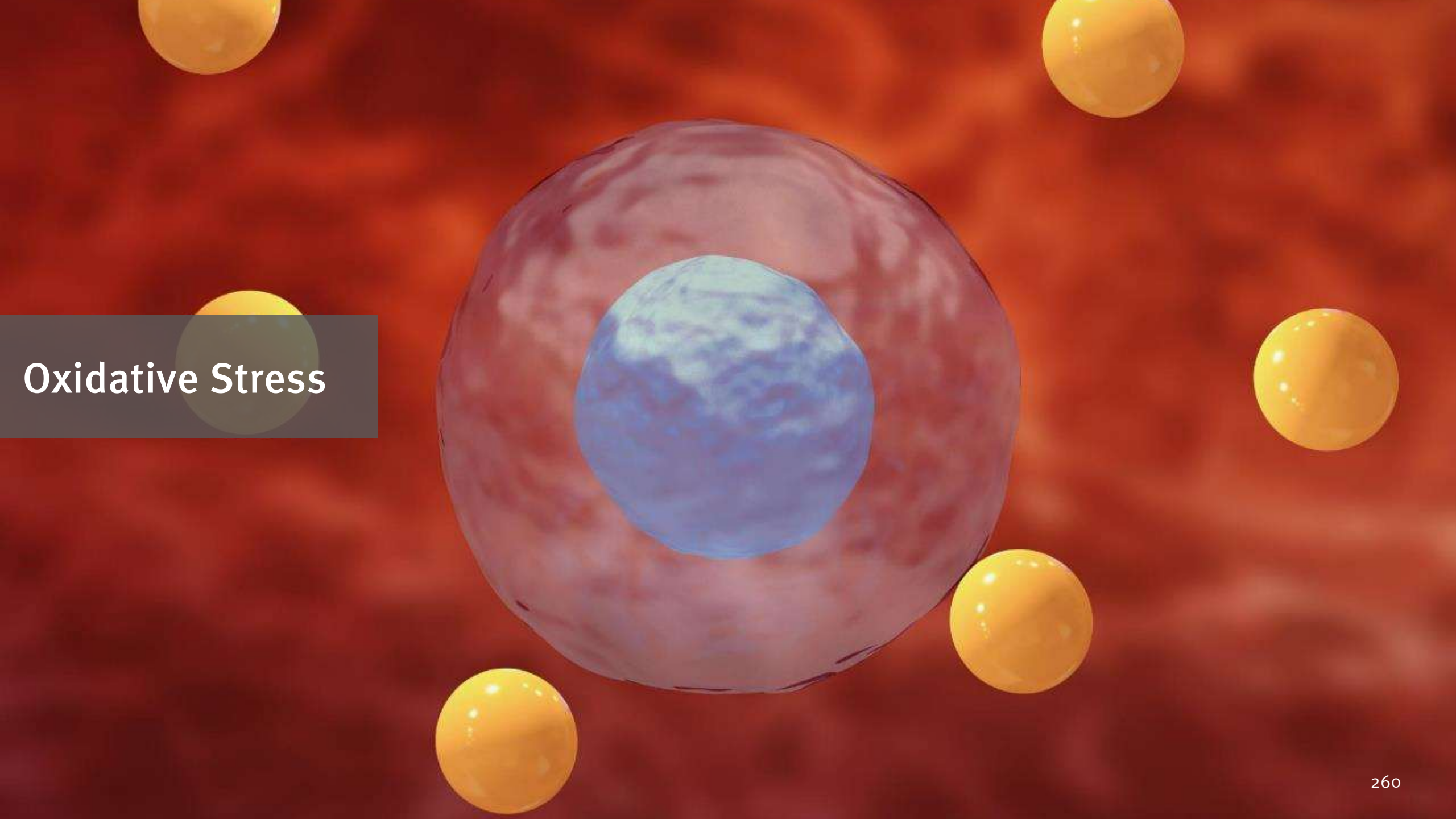
Inflammation / Unhealthy Adipocytes

- Obesity is associated with larger adipocytes
- As adipocytes store more triglyceride, they become stressed
- This stress triggers an inflammatory state that lead to harmful outcomes
- Anti-inflammatory drugs could help

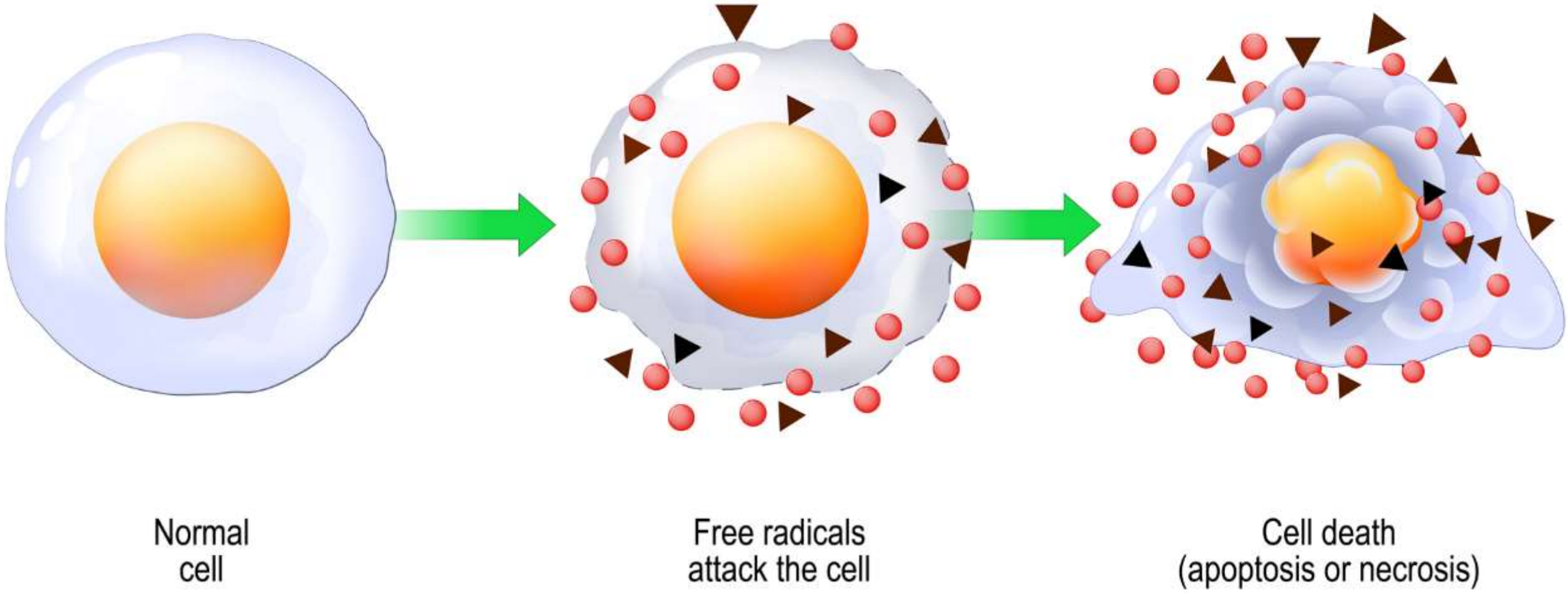
Thank You and Credit

The ideas in this section are partly the result of discussions with:

1. **Dawn Bell**, CEO, Myracle Therapeutics
2. **Bill Chin**, Former Associate Dean for Research, Harvard Medical School and Retired, SVP, Discovery Research and Clinical Investigation, Eli Lilly.
3. **Andrew Dannenberg**, Retired Physician/Scientist, Weill Cornell
4. **Sam Klein**, Director of the Center for Human Nutrition and Chief, Division of Geriatrics and Nutritional Science, Washington University, St. Louis
5. **Paul Ridker**, Brigham and Women's Hospital, Boston


Oxidative Stress

Oxidative Stress Occurs When Free Oxygen Radicals Attack Cells



How Obesity Leads to Oxidative Stress

Manna P, Jain SK. Obesity, Oxidative Stress, Adipose Tissue Dysfunction, and the Associated Health Risks: Causes and Therapeutic Strategies. Metab Syndr Relat Disord. 2015 Dec;13(10):423-44.

Obesity is directly associated with insulin resistance and hyperglycemia. Intracellular glucose overload increases the glycolytic pathway and the tricarboxylic acid cycle, leading to the overproduction of NADH and FADH2; the resulting increase in proton gradient across the mitochondrial inner membrane causes electron leakage at complex III, leading to superoxide production. The free radical thus inhibits glyceraldehyde-3-phosphate dehydrogenase and thereby redirects upstream metabolites into four alternative pathways: (1) glucose is shifted to the polyol pathway; (2) fructose-6-phosphate is shifted to the hexosamine pathway; (3) triose phosphates produce methylglyoxal, the main precursor of advanced glycation end products (AGE); and (4) dihydroxyacetone phosphate is converted to diacylglycol, which activates the PKC pathway. Activation of these alternative pathways induces oxidative/nitrosative stress either by enhancing free radical production or by impairing antioxidant defenses. Activation of the polyol pathway causes NADPH depletion and increases the conversion of glucose to sorbitol, which activates several stress genes and causes oxidative stress, as evidenced in several animal studies. Formation of glucosamine-6-phosphate in the hexosamine pathway inhibits thioredoxin activity and induces oxidative and endoplasmic reticulum (ER) stress; AGE and PKC stimulate the production of ROS/RNS by activating NOX and NF-kB.

Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4808277/

Oxidative Stress Associated with Obesity

Manna P, Jain SK. Obesity, Oxidative Stress, Adipose Tissue Dysfunction, and the Associated Health Risks: Causes and Therapeutic Strategies. Metab Syndr Relat Disord. 2015 Dec;13(10):423-44.

Hyperglycemia and oxidative stress in obesity Obesity is directly associated with insulin resistance and hyperglycemia. Intracellular glucose overload increases the glycolytic pathway and the tricarboxylic acid cycle, leading to the overproduction of NADH and FADH2; the resulting increase in proton gradient across the mitochondrial inner membrane causes electron leakage at complex III, leading to superoxide production. The free radical thus inhibits glyceraldehyde-3-phosphate dehydrogenase and thereby redirects upstream metabolites into four alternative pathways36: (1) glucose is shifted to the polyol pathway; (2) fructose-6-phosphate is shifted to the hexosamine pathway; (3) triose phosphates produce methylglyoxal, the main precursor of advanced glycation end products (AGE); and (4) dihydroxyacetone phosphate is converted to diacylglycol, which activates the PKC pathway. Activation of these alternative pathways induces oxidative/nitrosative stress either by enhancing free radical production or by impairing antioxidant defenses. Activation of the polyol pathway causes NADPH depletion and increases the conversion of glucose to sorbitol, which activates several stress genes and causes oxidative stress, as evidenced in several animal studies.37 Formation of glucosamine-6-phosphate in the hexosamine pathway inhibits thioredoxin activity and induces oxidative and endoplasmic reticulum (ER) stress; AGE and PKC stimulate the production of ROS/RNS by activating NOX and NF-kB. Activation of NOX enzymes increases the production of superoxide radicals (O2•–) by catalyzing the reduction of oxygen using NADPH as an internal electron donor. Glucose auto-oxidation also produces reactive oxidants similar to hydroxyl and superoxide radicals. AGE binds to specific cell surface receptors causing the modification of postreceptor signaling and promotes further generation of ROS.

Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4808277/

Oxidative Stress Leads to Harmful Aldehyde Species

Singh S, Brocker C, Koppaka V, Chen Y, Jackson BC, Matsumoto A, Thompson DC, Vasiliou V. Aldehyde dehydrogenases in cellular responses to oxidative/electrophilic stress. *Free Radic Biol Med*. March 2013, pp. 89-101.

Reactive oxygen species (ROS) are continuously generated within living systems and the inability to manage ROS load leads to elevated oxidative stress and cell damage. Oxidative stress is coupled to the oxidative degradation of lipid membranes, also known as lipid peroxidation. This process generates over **200 types of aldehydes**, many of which are highly reactive and toxic. Aldehyde dehydrogenases (ALDHs) metabolize endogenous and exogenous aldehydes and thereby mitigate oxidative/electrophilic stress in prokaryotic and eukaryotic organisms. ALDHs are found throughout the evolutionary gamut, from single-celled organisms to complex multicellular species. Not surprisingly, many ALDHs in evolutionarily distant, and seemingly unrelated, species perform similar functions, including protection against a variety of environmental stressors such as dehydration and ultraviolet radiation. The ability to act as an "aldehyde scavenger" during lipid peroxidation is another ostensibly universal ALDH function found across species. Upregulation of ALDHs is a stress response in bacteria (environmental and chemical stress), plants (dehydration, salinity, and oxidative stress), yeast (ethanol exposure and oxidative stress), Caenorhabditis elegans (lipid peroxidation), and mammals (oxidative stress and lipid peroxidation). Recent studies have also identified ALDH activity as an important feature of cancer stem cells. In these cells, ALDH expression helps abrogate oxidative stress and imparts resistance against chemotherapeutic agents such as oxazaphosphorine, taxane, and platinum drugs. The ALDH superfamily represents a fundamentally important class of enzymes that contributes significantly to the management of electrophilic/oxidative stress within living systems. Mutations in various ALDHs are associated with a variety of pathological conditions in humans, highlighting the fundamental importance of these enzymes in physiological and pathological processes.

Source: https://pubmed.ncbi.nlm.nih.gov/23195683/

Aldehyde Species Can Promote Obesity and Its Harmful Effects

Arnold Onyango, "Lipid Peroxidation as a Link between Unhealthy Diets and the Metabolic Syndrome," Chapter in "Accenting Lipid Peroxidation," 2021.

Lipid peroxidation is a major contributor to the pathogenesis of the metabolic syndrome, especially through highly reactive and bioactive aldehydes such as acrolein, 4-hydroxy-2-nonenal, malondialdehyde and glyoxal.

Mechanisms of formation of these products are now well-understood. For example, this article has highlighted that formation of MDA from linoleic acid may be easier than previously thought. The mentioned aldehydes propagate oxidative stress and inflammation by inducing insulin resistance, inhibiting sirt1 and AMPK, reducing adiponectin secretion, as well as forming AGEs and ALEs that activate the RAGE receptor.

Inhibiting LPO and the LPO product-associated oxidative stress and inflammation is necessary for preventing and/or ameliorating progression of the metabolic syndrome. This may not be effectively accomplished by dietary agents that merely scavenge free radicals and/or quench singlet oxygen, but also by those that inhibit the signaling pathways that generate non-lipid ROS, or scavenge the reactive carbonyls, ALEs and AGEs.

In addition, saturated fat, sugar, meat, and salt, that fuel the signaling pathways that initiate LPO should be reduced. The metabolic influence of some dietary components such as salt and n-6 PUFAs is particularly influenced by genetics, and this should be duly considered when making dietary recommendations.

Source: https://www.intechopen.com/chapters/76824

Superoxide Dismutase is a Key Factor to Reduce Obesity and Its Harm by Limiting Oxidating Stress

Cui, R., Gao, M., Qu, S. et al. Overexpression of superoxide dismutase 3 gene blocks high-fat diet-induced obesity, fatty liver and insulin resistance. Gene Ther 21, 840–848 (2014).

Oxidative stress has an important role in the development of obesity and obesity-associated metabolic disorders. As an endogenous antioxidant enzyme, superoxide dismutase 3 (SOD3) has the potential to affect diet-induced obesity and obesity-associated complications.

In the current work, we overexpressed SOD3 in C57BL/6 mice fed a high-fat diet (HFD) to study its effect on HFD-induced obesity, fatty liver and insulin resistance. We demonstrated that the Sod3 gene transfer blocked HFD-induced obesity, fatty liver and insulin resistance. Real-time PCR analysis of adipose and liver tissues revealed that overexpression of the Sod3 gene suppressed expression of pro-inflammatory genes in adipose tissue including F4/80, Tnfα, Cd11c, Mcp1 and Il6, and increased expression of anti-inflammatory genes such as adiponectin.

In the liver, high levels of SOD3 activity in animals enhanced expression of the genes responsible for energy expenditure including Cpt1α, Cpt1β, Pgc1α, Pgc1β and Ucp2. These results suggest that overexpression of the Sod3 gene through gene transfer is an effective approach in preventing diet-induced obesity and obesity-associated complications.

Source: https://www.nature.com/articles/gt201464

Superoxide Dismutative Effective in Reducing Oxidative Stress in Mice

Liu Y, Qi W, Richardson A, Van Remmen H, Ikeno Y, Salmon AB. Oxidative damage associated with obesity is prevented by overexpression of CuZn- or Mn-superoxide dismutase. Biochem Biophys Res Commun. 2013 Aug 16;438(1):78-83.

The development of insulin resistance is the primary step in the etiology of type 2 diabetes mellitus. There are several risk factors associated with insulin resistance, yet the basic biological mechanisms that promote its development are still unclear. There is growing literature that suggests mitochondrial dysfunction and/or oxidative stress play prominent roles in defects in glucose metabolism. Here, we tested whether increased expression of CuZn-superoxide dismutase (Sod1) or Mn-superoxide dismutase (Sod2) prevented obesity-induced changes in oxidative stress and metabolism. Both Sod1 and Sod2 overexpressing mice were protected from high fat diet-induced glucose intolerance. Lipid oxidation (F2-isoprostanes) was significantly increased in muscle and adipose with high fat feeding. Mice with increased expression of either Sod1 or Sod2 showed a significant reduction in this oxidative damage. Surprisingly, mitochondria from the muscle of high fat diet-fed mice showed no significant alteration in function. Together, our data suggest that targeting reduced oxidative damage in general may be a more applicable therapeutic target to prevent insulin resistance than by improving mitochondrial function.

Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3768142/

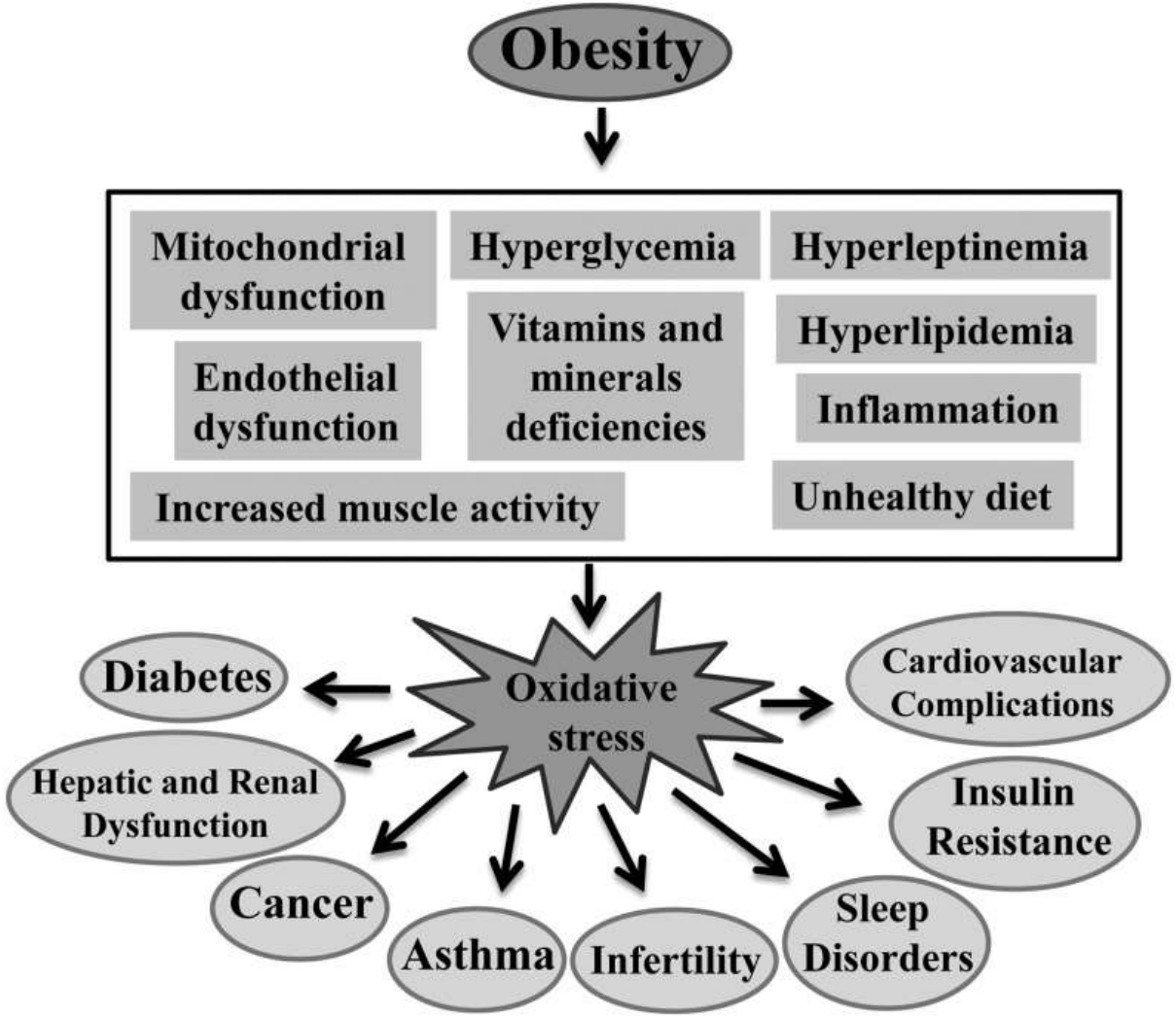
Obesogenic Oxidative Stress Leads to Numerous Diseases

Manna P, Jain SK. Obesity, Oxidative Stress, Adipose Tissue Dysfunction, and the Associated Health Risks: Causes and Therapeutic Strategies. *Metab Syndr Relat Disord.* 2015 Dec;13(10):423-44.

Conditions generating oxidative stress in the pathogenesis of obesity and the role of oxidative stress in the development of obesity associated health risks.

Oxidative stress plays an important role in the development of CVD risk factors among the obese population. Low levels of circulating high-density lipoprotein (HDL), increased clearance of HDL particles, higher levels of postprandial triglycerides, and elevated levels of LDL induce ROS generation in the endothelium. Elevated ROS can directly cause damage to lipids, proteins, or DNA molecules and thereby modulate intracellular signaling cascades, such as MAPK and redox-sensitive transcription factors.

ROS-mediated changes in lipid expression, formation of oxidized lipid products, such as oxidized LDL (Ox-LDL) particles, and activation of macrophages induce the formation of atherosclerotic lesions.



Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4808277/

Aldeyra Platform Focused on Managing Oxidative Stress

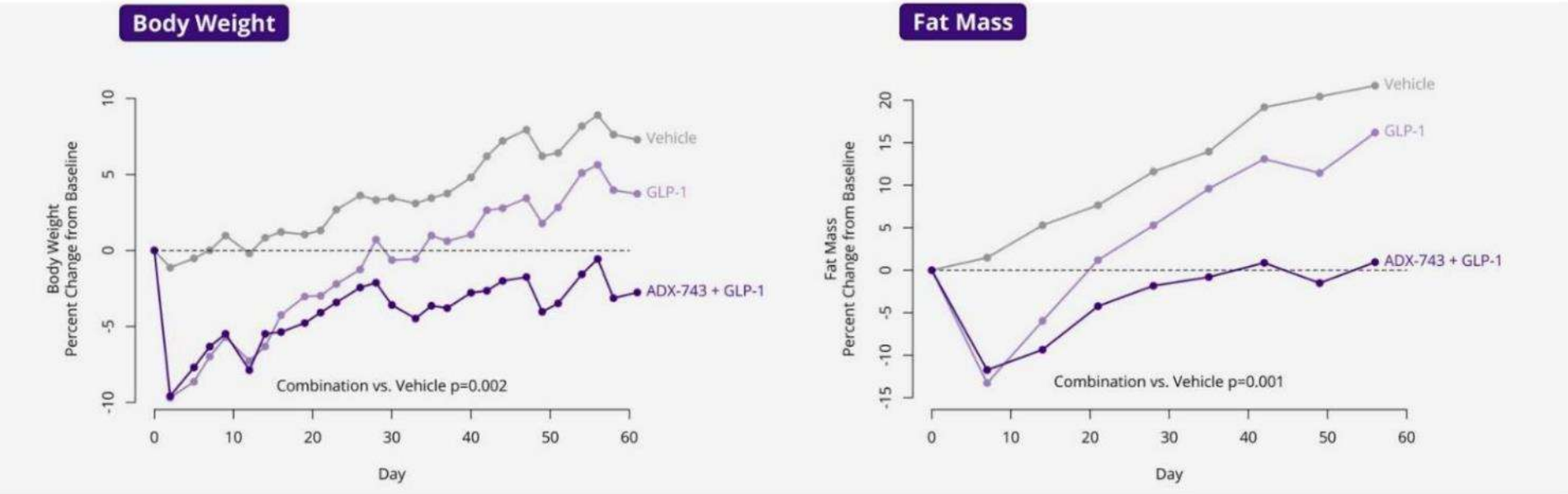
In response to stimuli such as infection, injury, chemicals, and heat. Reactive Aldehyde Species (RASP) are generated through different metabolic processes that include alcohol oxidation, lipid oxidation (enzymatic and non-enzymatic), and certain metabolic pathways involving polyamines and sphingosine. RASP molecules play a crucial role in inflammation signaling by binding covalently to sulfur- and nitrogen-containing residues on proteins, including receptors and enzymes. RASP binding affects the function of proteins, triggering the activation of inflammatory factors within cells, including NF-κB and inflammasomes, which are vital in the inflammatory response. Elevated levels of RASP are typically observed in ocular and systemic inflammatory diseases, which are the focus of our RASP modulator pipeline. Additionally, RASP are linked to metabolic and neurodegenerative disorders and, besides promoting inflammation, can lead to DNA damage, metabolic aggregate accumulation, and other pathological consequences.

Source: https://www.aldeyra.com/

Aldeyra's RASP Inhibitor ADX-629 Associated with Weight Loss

Aldeyra Corporate Presentation, July 5, 2024

ADX-743, an Analog of ADX-629, Demonstrated Preclinical Weight Loss and Reduction of Fat Mass in Combination with GLP-1 Agonist



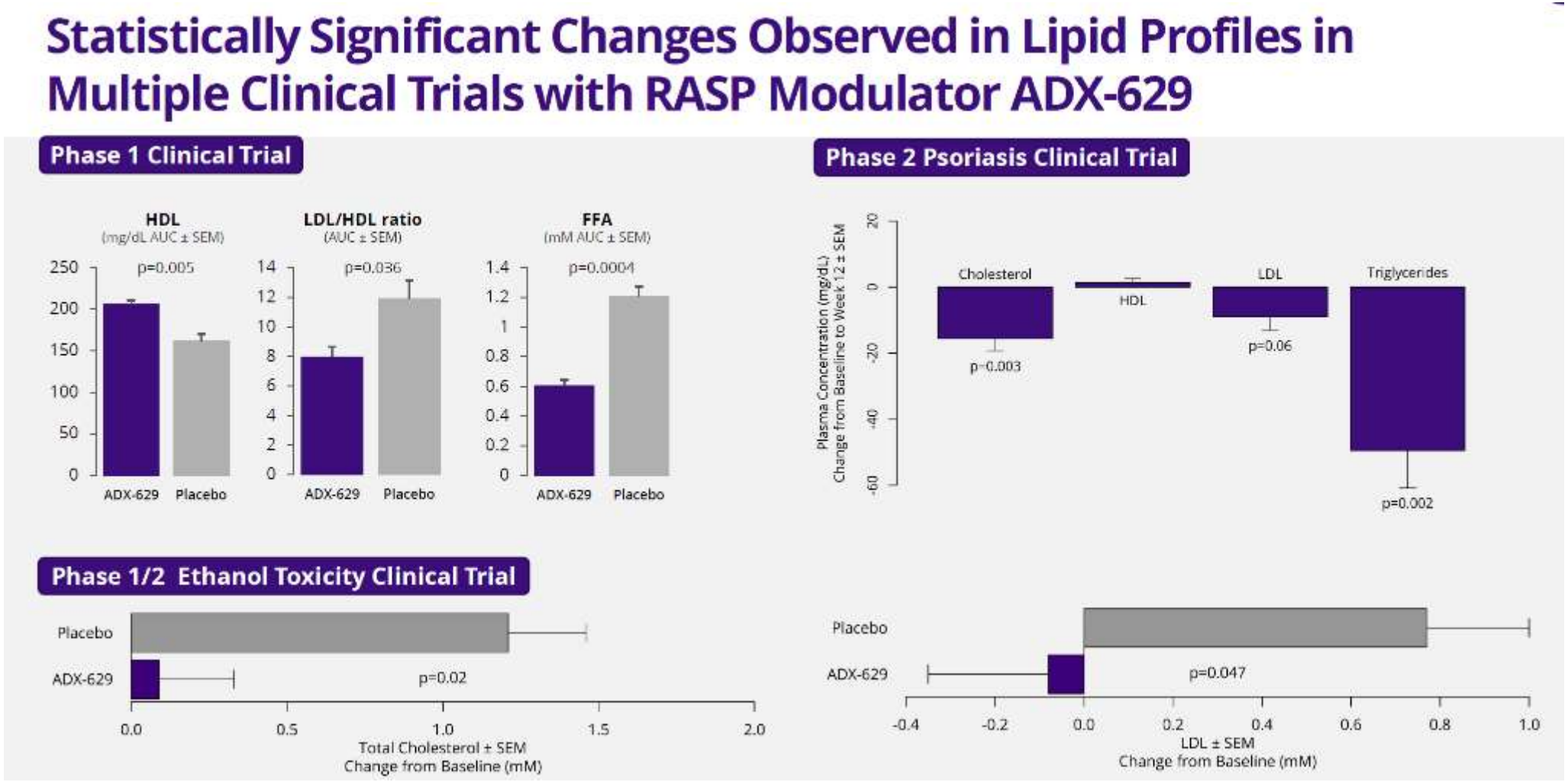
ADX-743 is an investigational drug candidate. SEM = standard error of the mean. GLP-1 = glucagon-like peptide-1 receptor agonist. Data are from murine diet-induced obesity model.

aldeyra

Source: https://www.aldeyra.com/

Aldeyra's RASP Inhibitor ADX-629 Associated with Lipid Changes

Aldeyra Corporate Presentation, July 5, 2024



Source: https://www.aldeyra.com/

Insulin Resistance

Insulin Resistance Leads to Chronic Disease

Insulin Resistance as a Predictor of Age-Related Diseases

FRANCESCO S. FACCHINI, NANCY HUA, FAHIM ABBASI, AND GERALD M. REAVEN

Departments of Medicine (F.S.F., N.H., F.A., G.M.R.), Stanford University, School of Medicine Stanford, California 94305; and San Francisco General Hospital (F.S.F.), University of California–San Francisco, San Francisco, California 94110

The current study was initiated to evaluate the ability of insulin resistance to predict a variety of age-related diseases. Baseline measurements of insulin resistance and related variables were made between 1988–1995 in 208 apparently healthy, nonobese (body mass index ‹ 30 kg/m2) individuals, who were then evaluated 4–11 yr later (mean SEM 6.3 0.2 yr) for the appearance of the following age-related diseases: hypertension, coronary heart disease, stroke, cancer, and type 2 diabetes. The effect of insulin resistance on the development of clinical events was evaluated by dividing the study group into tertiles of insulin resistance at baseline and comparing the events in these 3 groups.

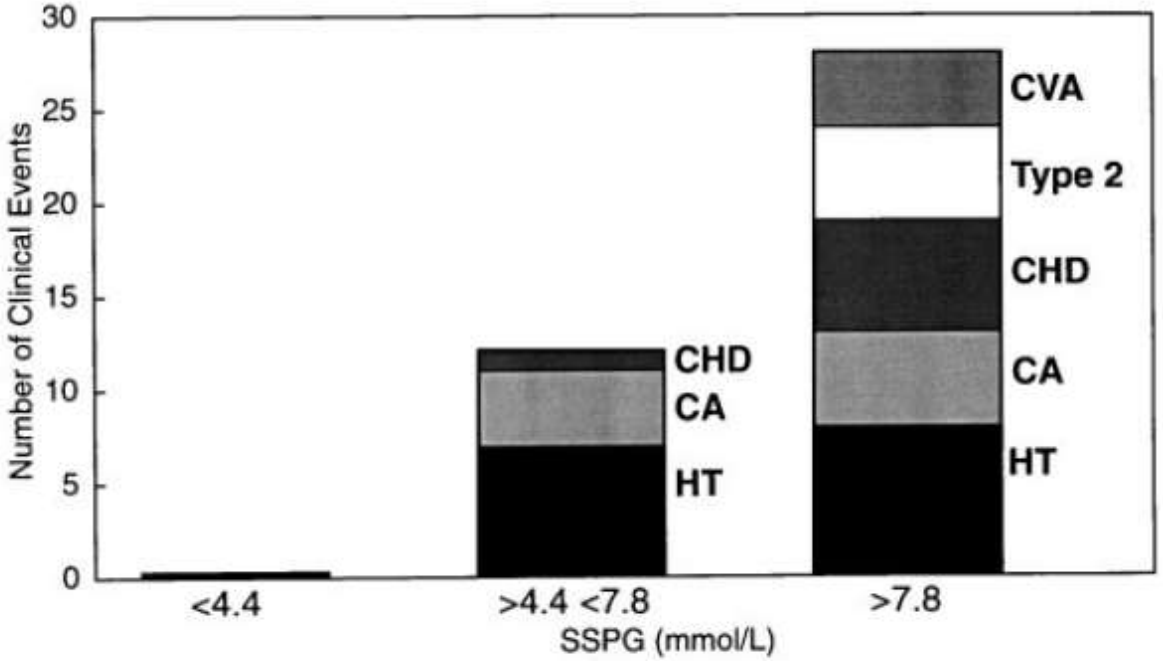


FIG. 1. The number of clinical events observed, as a function of insulin resistance tertile at baseline. CA, Cancer; Type 2, type 2 diabetes. These were 28 events in the highest tertile (SSPG > 7.8 mM), 12 in the intermediate tertile (SSPG > 4.4 < 7.8 mM), and none in the most insulin-sensitive tertile (SSPG < 4.4 mM).

Source: https://academic.oup.com/jcem/article/86/8/3574/2848584

Numerous Studies Show Link Between Insulin Resistance and Mortality

- Shinohara K, Shoji T, Emoto M, Tahara H, Koyama H, Ishimura E, Miki T, Tabata T, Nishizawa Y. Insulin resistance as an independent predictor of cardiovascular mortality in patients with end-stage renal disease. J Am Soc Nephrol. 2002 Jul;13(7):1894-900.
- Ausk KJ, Boyko EJ, Ioannou GN. Insulin resistance predicts mortality in nondiabetic individuals in the U.S. Diabetes Care. 2010 Jun;33(6):1179-85.
- Pan K, Nelson RA, Wactawski-Wende J, Lee DJ, Manson JE, Aragaki AK, Mortimer JE, Phillips LS, Rohan T, Ho GYF, Saquib N, Shadyab AH, Nassir R, Rhee JJ, Hurria A, Chlebowski RT. Insulin Resistance and Cancer-Specific and All-Cause Mortality in Postmenopausal Women: The Women's Health Initiative. J Natl Cancer Inst. 2020 Feb 1;112(2):170-178.
- Moshkovits Y, Rott D, Chetrit A, Dankner R. The insulin sensitivity Mcauley index (MCAi) is associated with 40-year cancer mortality in a cohort of men and women free of diabetes at baseline. PLoS One. 2022 Aug 3;17(8):e0272437.
- Kosmas CE, Bousvarou MD, Kostara CE, Papakonstantinou EJ, Salamou E, Guzman E. Insulin resistance and cardiovascular disease. J Int Med Res. 2023 Mar;51(3):3000605231164548.
- Tsai SF, Yang CT, Liu WJ, Lee CL. Development and validation of an insulin resistance model for a population without diabetes mellitus and its clinical implication: a prospective cohort study. EClinicalMedicine. 2023 Apr 4;58:101934.

Centenarians are Insulin Sensitive

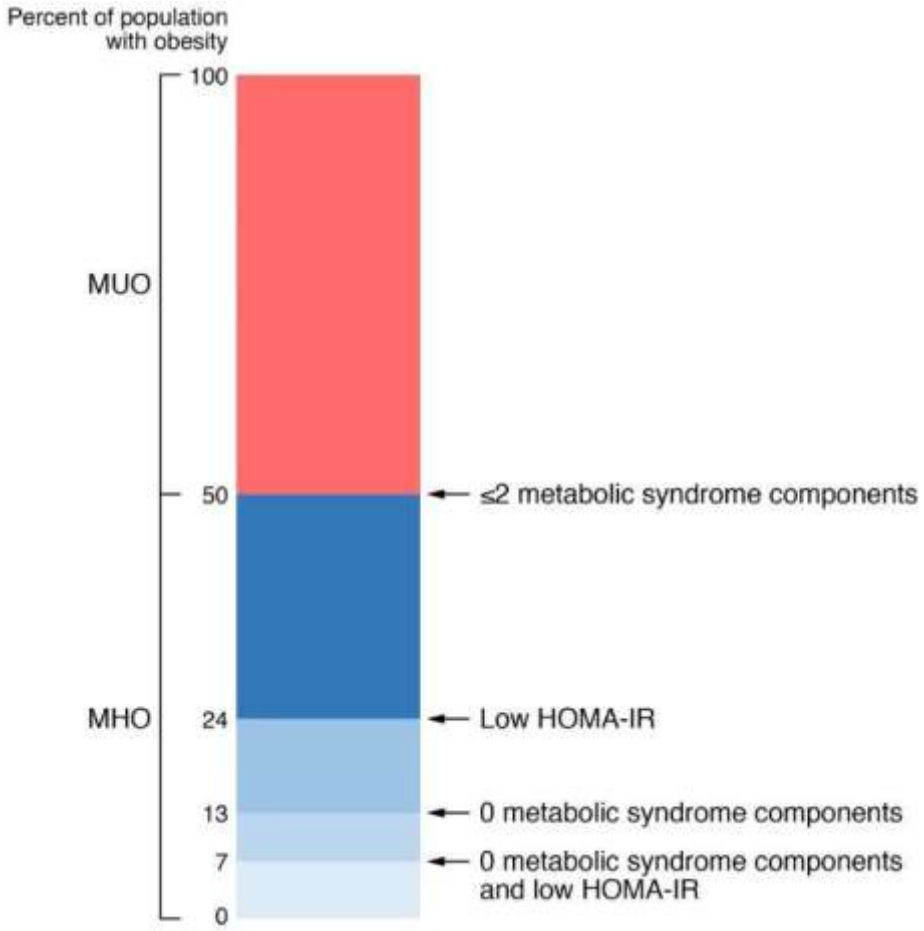
Vitale G, Pellegrino G, Vollery M, Hofland LJ. ROLE of IGF-1 System in the Modulation of Longevity: Controversies and New Insights From a Centenarians' Perspective. Front Endocrinol (Lausanne). 2019 Feb 1;10:27.

Metabolic age-dependent remodeling is a physiological process occurring in the whole population. Aging is frequently associated with a decline in glucose tolerance secondary to an increased insulin resistance, but an exception occurs in long-lived people.

Paolisso et al. found that insulin resistance increased with aging and declined in subjects older than 90 years living in Southern Italy. Indeed, long-lived subjects showed a higher insulin sensitivity and a better preservation of beta-cell function than younger subjects. Such difference was also independent of the main anthropometric and metabolic confounders. Centenarians had a lower 2-h plasma glucose concentration than that aged subjects (mean age 78 years) during oral glucose tolerance test. **In centenarians insulin-mediated glucose uptake was greater than in aged controls during euglycemic glucose clamp, supporting a preserved glucose tolerance and insulin action in this long-lived group.** Similar results, supporting a better insulin sensitivity, were observed in other long-lived populations.

Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6367275/

Many Obese Persons are Metabolically Healthy and Insulin Sensitive



Overwhelming evidence shows that insulin resistance is a key cause of cardiovascular disease in obese (and non-obese) individuals.

There appears to be much more mileage to be had from drugs that impact insulin resistance than GLP-1's alone.

There appears to be little societal gain to be had from reimbursing GLP-1's for persons that are metabolically healthy.

Source: J Clin Invest 2019;129(10):3978-3989.

Metabolically Healthy Obesity and Risk of All-Cause and Cardiovascular Disease Mortality

Mark Hamer and Emmanuel Stamatakis

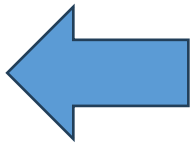
Department of Epidemiology and Public Health, University College London, London WC1E 6BT, United Kingdom

TABLE 3. The association between metabolic health, obesity, and all-cause mortality

	Cases/n	Age- and sex-adjusted HR (95% CI)	Fully adjusted HR (95% CI)[a]
Whole sample			
Metabolically healthy nonobese	777/12716	1.00 (referent)	1.00
Metabolically unhealthy nonobese	656/4201	1.56 (1.40–1.73)	1.59 (1.42–1.77)
Metabolically healthy obese	38/1160	0.60 (0.43–0.83)	0.91 (0.64–1.29)
Metabolically unhealthy obese	397/4128	1.25 (1.11–1.41)	1.79 (1.47–2.17)
P trend		<0.001	<0.001
Men			
Metabolically healthy nonobese	417/5771	1.00 (referent)	1.00
Metabolically unhealthy nonobese	334/1983	1.46 (1.26–1.69)	1.46 (1.25–1.69)
Metabolically healthy obese	23/610	0.69 (0.45–1.05)	1.09 (0.68–1.75)
Metabolically unhealthy obese	203/1669	1.41 (1.20–1.67)	2.09 (1.60–2.73)
P trend		<0.001	<0.001
Women			
Metabolically healthy nonobese	360/6945	1.00 (referent)	1.00
Metabolically unhealthy nonobese	322/2218	1.69 (1.45–1.97)	1.71 (1.45–2.01)
Metabolically healthy obese	15/550	0.51 (0.30–0.86)	0.73 (0.42–1.27)
Metabolically unhealthy obese	194/2459	1.12 (0.94–1.33)	1.56 (1.17–2.08)
P trend		<0.001	<0.001

Sample contains participants without a history of CVD at baseline (n = 22,203).

[a] Contains adjustment for age, sex, smoking, physical activity, socioeconomic group, and BMI.



Obese persons without insulin resistance live much longer, on average, than non-obese persons. On the other hand, the metabolically unhealthy (insulin resistant) live much shorter lives than the others.

The data in this remarkable chart suggest that most of the benefit of today's obesity drugs come treating the insulin resistant rather than all obese persons.

Source: J Clin Endocrinol Metab 97: 2482–2488, 2012 (https://pubmed.ncbi.nlm.nih.gov/22508708/).

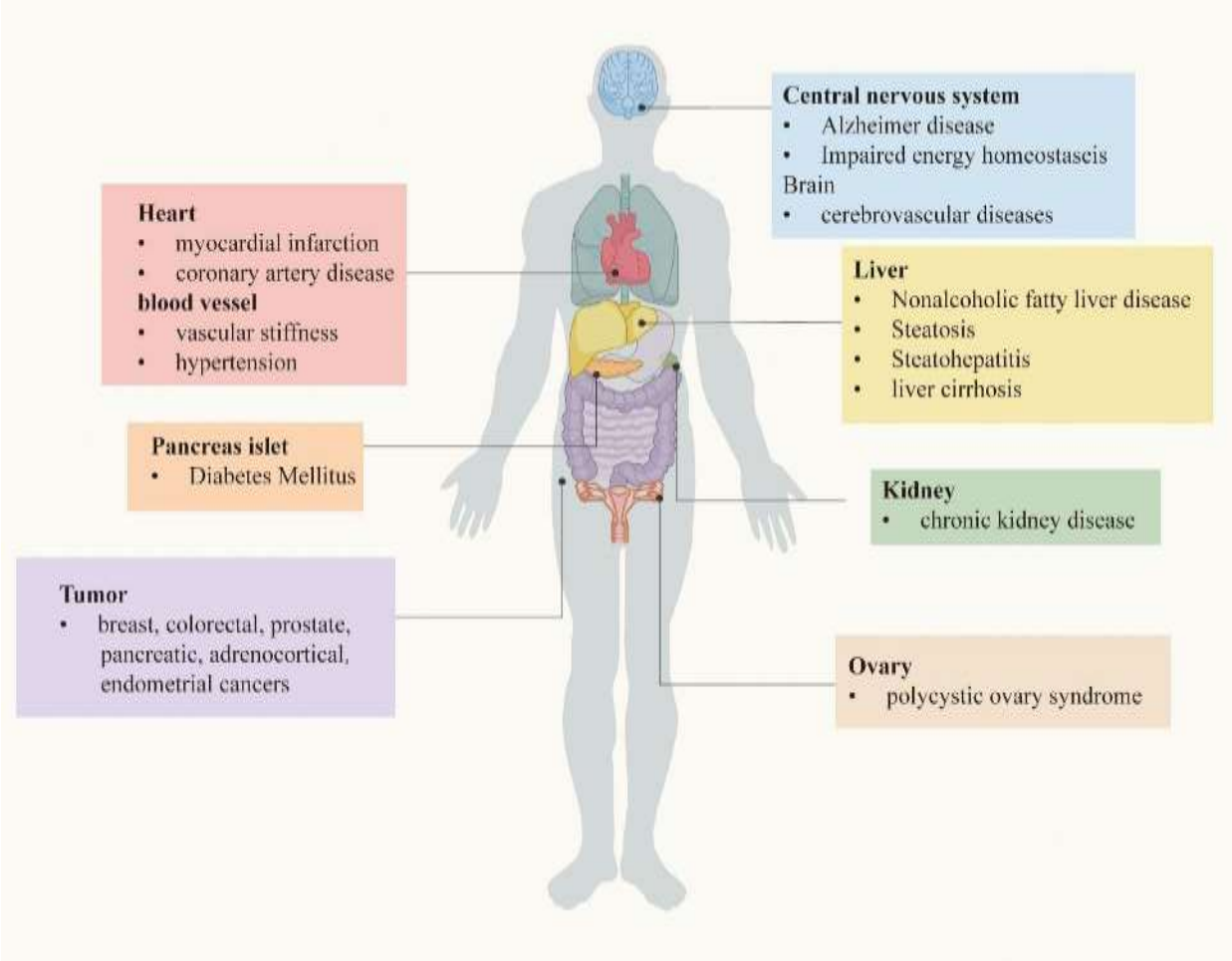
The Harms of Obesity are Largely Due to Insulin Resistance

Melvin A, O'Rahilly S, Savage DB. Genetic syndromes of severe insulin resistance. Curr Opin Genet Dev. June 2018.

Insulin resistance underpins the link between obesity and most of its associated metabolic disorders including type 2 diabetes, fatty liver disease, dyslipidaemia and cardiovascular disease. Despite its importance and extensive scientific endeavour, its precise molecular pathogenesis remains unclear. Monogenic syndromes of extreme insulin resistance, whilst rare in themselves, can provide unique insights into the pathogenesis of human insulin resistance

Source: https://pubmed.ncbi.nlm.nih.gov/29477938/

Diseases Linked to Insulin Resistance



Source: https://www.frontiersin.org/journals/endocrinology/articles/10.3389/fendo.2023.1149239/full

Controlling Insulin Resistance is a Key Aspect of Keeping Weight Off After a Weight Loss Program

Tiedemann LJ, Meyhöfer SM, Francke P, Beck J, Büchel C, Brassen S. Insulin sensitivity in mesolimbic pathways predicts and improves with weight loss in older dieters. *Elife*. Sep 27, 2022, p. e76835.

Central insulin is critically involved in the regulation of hedonic feeding. Insulin resistance in overweight has recently been shown to reduce the inhibitory function of insulin in the human brain. How this relates to effective weight management is unclear, especially in older people, who are highly vulnerable to hyperinsulinemia and in whom neural target systems of insulin action undergo age-related changes. Here, 50 overweight, non-diabetic older adults participated in a double-blind, placebo-controlled, pharmacological functional magnetic resonance imaging study before and after randomization to a 3-month caloric restriction or active waiting group. Our data show that treatment outcome in dieters can be predicted by baseline measures of individual intranasal insulin (INI) inhibition of value signals in the ventral tegmental area related to sweet food liking as well as, independently, by peripheral insulin sensitivity. At follow-up, both INI inhibition of hedonic value signals in the nucleus accumbens and peripheral insulin sensitivity improved with weight loss. These data highlight the critical role of central insulin function in mesolimbic systems for weight management in humans and directly demonstrate that neural insulin function can be improved by weight loss even in older age, which may be essential for preventing metabolic disorders in later life.

Source: https://pubmed.ncbi.nlm.nih.gov/36170006/

Why Does Obesity Lead to Insulin Resistance?

The answer to this question is not fully worked out. When a person is obese, especially when excess fat is stored in the abdominal area (visceral fat), it can interfere with the body's ability to properly use insulin. Here's how it happens:

Increased Fat Cell Size: Adipocytes produce adipokines. When there's an excess fat cell size due to obesity, these adipokines can disrupt insulin signaling.

Inflammation: Fat cells release inflammatory substances that can trigger inflammation throughout the body. Chronic inflammation can interfere with insulin's ability to function correctly.

Elevated Free Fatty Acids (FFAs): In obese individuals, there's often an increased level of free fatty acids circulating in the bloodstream. These FFAs can interfere with insulin's action in tissues, particularly muscles, reducing their ability to take up glucose effectively.

Hormonal Imbalances: Obesity can disrupt hormonal balance, affecting hormones like leptin and adiponectin, which play roles in insulin sensitivity. Changes in these hormones can contribute to insulin resistance.

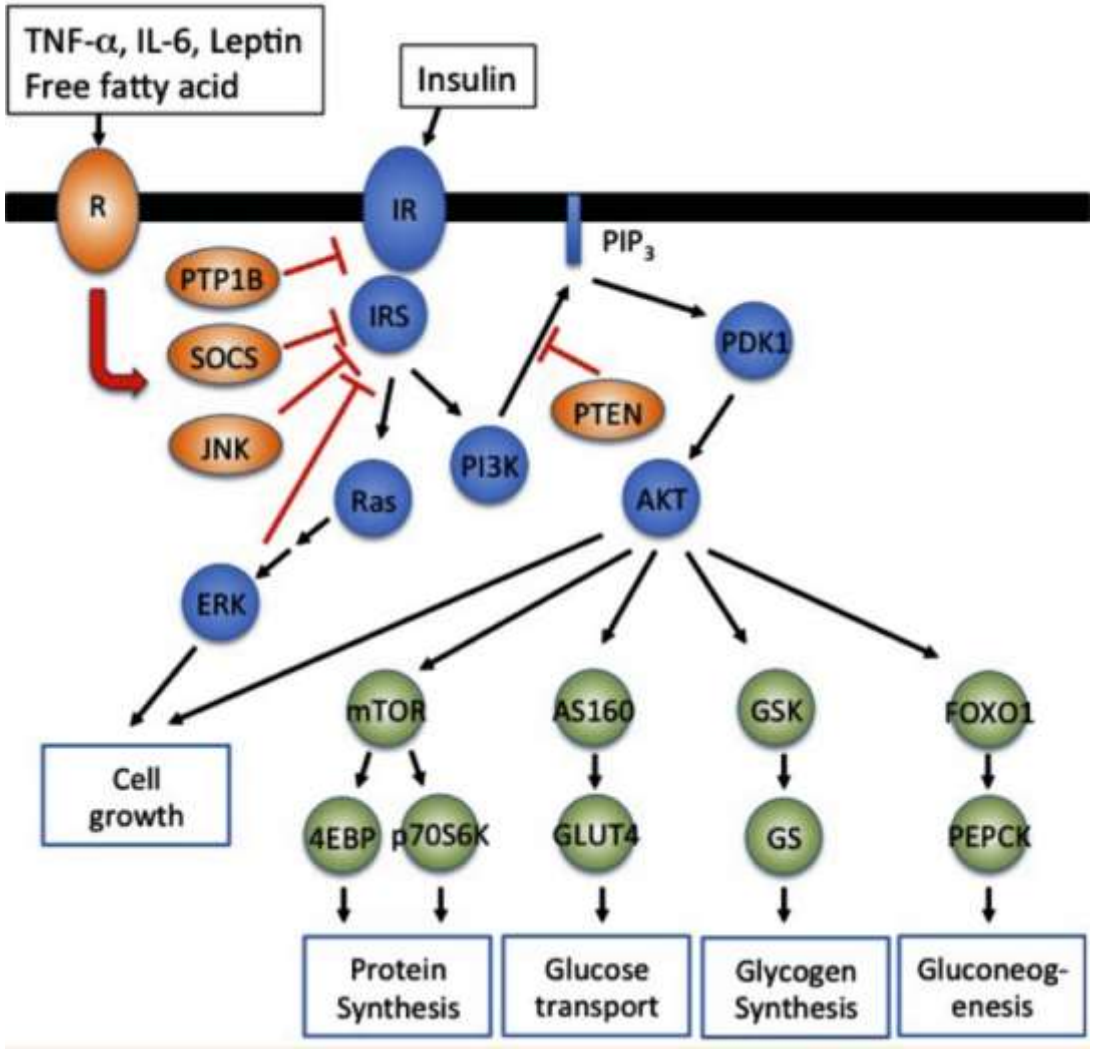
Liver Function: Obesity can also impact liver function, leading to an increased release of glucose into the bloodstream. This can contribute to higher blood sugar levels and insulin resistance.

All these factors combined can disrupt the intricate balance of insulin production and usage in the body, leading to insulin resistance. Over time, this can contribute to the development of type 2 diabetes.

See, for example, Kwon H, Pessin JE. Adipokines mediate inflammation and insulin resistance. *Front Endocrinol,* June 12, 2013, pp. 71.

The Molecular Biology of Insulin Resistance

At the molecular level, insulin binds to the cell surface insulin receptor that exists as an α2β2 heterodimer. Following insulin binding, the tyrosine kinase domain of β subunits autophosphorylates itself in a trans-phosphorylation reaction that activates its intrinsic kinase activity to proximal substrates such as insulin receptor substrate (IRS) family (IRS1-IRS4), Src-homology-2-containing (Shc) adaptor proteins, signal-regulatory protein (SIRP) family, and Grb2-associated binder-1 (Gab1). IRS1/2 phosphorylated on specific tyrosine residues activates two major signaling pathways; (i) the phosphatidylinositol 3-kinase (PI3K)-AKT/protein kinase B (PKB) pathway to modulate most metabolic functions of insulin such as glucose transport, glycogen synthesis, gluconeogenesis, protein synthesis, and cell growth and (ii) Ras-mitogen-activated protein kinase (MAPK) pathway. In addition, there are inhibitory molecules for insulin signaling such as the protein tyrosine phosphatase 1B (PTP1B), the suppressor of cytokine signaling (SOCS) and the growth factor receptor bound protein 10 (Grb10) that suppress insulin signaling by inducing insulin receptor dephosphorylation, physical blocking of substrate phosphorylation, and degradation of the insulin receptor and/or IRS. AKT phosphorylates the AKT substrate of 160 kDa (AS160) to activate Rab small GTPase that initiates the translocation of the glucose transporter 4 (GLUT4) resulting in the glucose uptake in muscle and adipocytes. AKT also suppresses glycogen synthase kinase-3 (GSK3) to activate glycogen synthase resulting in the glycogen synthesis in muscle and liver. The AKT phosphorylation of forkhead box O1 (FOXO1) induces FOXO1 association with 14-3-3 protein, that in turn excludes FOXO1 from the nucleus. In the liver, this suppresses gluconeogenic gene expression and thereby inhibits hepatic glucose output. AKT phosphorylates tuberous sclerosis complex 1 and 2 (TSC1/2), which release the inhibition of Ras homolog enriched in brain (Rheb) for the activation of mTORC1 complex, that in turn enhances protein synthesis through the activation of eukaryotic translation initiation factor 4E binding protein-1 (4E-BP) and p70 ribosomal protein S6 kinase 1 (p70S6K1).



Source: Kwon H, Pessin JE. Adipokines mediate inflammation and insulin resistance. Front Endocrinol (Lausanne). 2013 Jun 12;4:71.

Current Approaches to Managing Insulin Resistance

- **Metformin**: It's often the first-line medication for managing insulin resistance and type 2 diabetes. Metformin works by reducing glucose production in the liver and improving insulin sensitivity in peripheral tissues.
- **Thiazolidinediones** (TZDs): Drugs like pioglitazone improve insulin sensitivity by targeting the peroxisome proliferator-activated receptor-gamma (PPAR-gamma), a nuclear receptor involved in glucose and lipid metabolism.
- **GLP-1 Receptor Agonists**: Medications like semaglutide, liraglutide, and dulaglutide mimic the action of glucagon-like peptide-1 (GLP-1), which enhances insulin secretion and reduces glucagon secretion, leading to improved glucose control and increased insulin sensitivity.
- **SGLT-2 Inhibitors**: These drugs, such as empagliflozin and canagliflozin, work by inhibiting the sodium-glucose cotransporter-2 in the kidneys, reducing glucose reabsorption and promoting its excretion through urine. They have shown benefits in reducing insulin resistance.
- **DPP-4 Inhibitors**: Drugs like sitagliptin, saxagliptin, and linagliptin inhibit dipeptidyl peptidase-4 (DPP-4), an enzyme that degrades incretin hormones. By preserving incretins, they help increase insulin release and decrease glucagon secretion, thereby improving insulin sensitivity.
- **Insulin Sensitizers**: Other medications, such as acarbose, work by delaying the absorption of carbohydrates from the digestive tract, helping to control post-meal blood sugar levels and improve insulin sensitivity.

See, for example, Kwon H, Pessin JE. Adipokines mediate inflammation and insulin resistance. Front Endocrinol (Lausanne). 2013 Jun 12;4:71.

There is an Obvious Need for Novel Insulin Sensitizers

Of the six approaches identified on the previous page, only one class works as **direct** insulin sensitizers (TZDs).

Unfortunately, TZDs are not fully effective and come with important liabilities, particularly tolerability.

All other classes have indirect action and do not interfere with the molecular causes of insulin resistance.

Incremental insulin sensitizers would be highly attractive.

Pharma Interested in Insulin Resistance But Area Remains Nascent

AstraZeneca and Regeneron to research, develop and commercialise new small molecule medicines for obesity

27 July 2021 12:00 BST

Novel small molecule drug candidates will target GPR75 to potentially address obesity and related co-morbidities

AstraZeneca has entered into a collaboration with Regeneron to research, develop and commercialise small molecule compounds directed against the GPR75 target with the potential to treat obesity and related co-morbidities. The companies will evenly split research and development costs and share equally in any future potential profits.

As published in Science, the new target was found by sequencing nearly 650,000 people and identifying individuals with rare protective mutations. Individuals with at least one inactive copy of the GPR75 gene had lower body mass index (BMI) and, on average, tended to weigh about 12 pounds less and faced a 54% lower risk of obesity than those without the mutation.[1] Strong associations were also seen with improvements in diabetes parameters, including glucose lowering.[1] Obesity and insulin resistance are key drivers in the development of type-2 diabetes and often lead to cardiorenal complications, as well as liver disease.

Mene Pangalos, Executive Vice President, BioPharmaceuticals R&D, AstraZeneca, said: "We are pleased to announce this important collaboration with Regeneron to identify small molecule modulators against GPR75, a newly identified target with genetic validation in metabolic disorders. Obesity and insulin resistance remain key drivers in the development of type-2 diabetes and areas of significant unmet medical need."

George D. Yancopoulos, M.D., Ph.D., President and Chief Scientific Officer of Regeneron, said: "The next era of drug development is being fuelled by important genetic findings that direct drug developers on how to deploy our toolkit of biologics, small molecules and gene editing technologies. As experts on genetics and human biology, Regeneron is excited to join forces with the chemistry and small molecule leaders at AstraZeneca, as we seek to develop new medicines tackling the harmful and costly obesity epidemic."

In $500M deal, Novo Nordisk acquires U of Copenhagen start-up developing 'Holy Grail' treatment for diabetes and obesity

By Jesse Schwartz | September 6th, 2023

Pharma giant Novo Nordisk has acquired a University of Copenhagen (UCPH) spinout developing a novel therapeutic for obesity and type 2 diabetes.

Embark Biotech is based on the work of UCPH researchers who discovered a novel target that suppresses hunger, stimulates calorie burning, and increases insulin sensitivity. The start-up initially worked with Novo Nordisk to develop the target into a viable drug. Now it is being acquired by the company in a deal worth up to €456m (over $488M US) that includes a three-year research and development collaboration.

Dewpoint Therapeutics partners with Novo Nordisk to explore the field of biomolecular condensates to treat insulin resistance and diabetes progression

DEWPOINT THERAPEUTICS

NEWS PROVIDED BY
Dewpoint Therapeutics
Mar 22, 2023, 07:09 ET

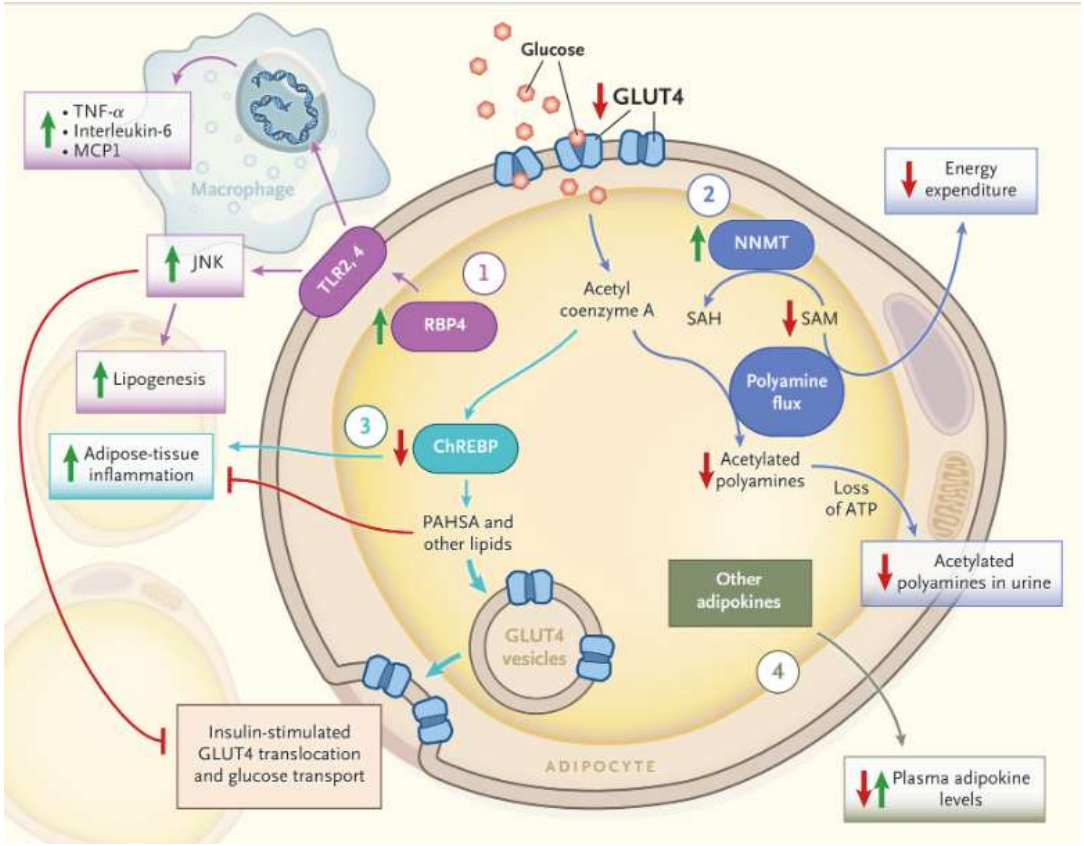
SHARE THIS ARTICLE

Most roads to the insulin resistant phenotype cross through GLUT4 Expression

Adipocyte Regulation of Insulin Sensitivity and the Risk of Type 2 Diabetes

Anna Santoro, Pharm.D., Ph.D., and Barbara B. Kahn, M.D.

N Engl J Med, June 1, 2023; 388:2071-2085



The changes that occur as a result of down-regulation of GLUT4 in adipocytes in the obese and insulin-resistant state are shown. In insulin-sensitive states, insulin stimulates glucose uptake in adipocytes through the GLUT4 glucose transporter. In obesity and type 2 diabetes, GLUT4 expression is decreased in adipocytes. 1. Changes in GLUT4 expression regulate RBP4 expression. In insulin-resistant states, RBP4 levels are elevated in adipose tissue and serum, causing increased adipose-tissue inflammation and impaired GLUT4 translocation to the plasma membrane. RBP4 indirectly impairs insulin signaling by inducing proinflammatory cytokine production from macrophages through the JNK-dependent pathway. Also, higher RBP4 levels promote JNK-induced inhibition of GLUT4 vesicle translocation to the plasma membrane. The RBP4 effect is mediated by TLR4 and other pathways and involves activation of the NLRP3 inflammasome. Higher RBP4 levels in insulin-resistant states result in increased adipose-tissue inflammation and lipolysis and a higher risk of type 2 diabetes. 2. Changes in GLUT4 expression also regulate NNMT expression. NNMT methylates nicotinamide, using SAM as a methyl donor. SAM fuels polyamine biosynthesis. Polyamine flux has a major role in energy metabolism. In insulin-resistant states, higher levels of NNMT decrease adipose SAM levels and polyamine flux, resulting in reduced acetylation of polyamines. Acetylated polyamines are usually excreted in the urine, which “wastes” ATP, thereby increasing oxygen consumption in adipocytes. However, in insulin-resistant states, decreased excretion of acetylated polyamines reduces ATP consumption, which is likely to contribute to obesity. 3. In insulin-sensitive states, increased insulin-stimulated glucose uptake in adipocytes activates ChREBP, a transcriptional regulator of lipogenic and glycolytic genes, resulting in higher synthesis of lipids with favorable metabolic effects, including PAHSAs. These lipids reduce adipose-tissue inflammation and augment insulin-stimulated GLUT4 translocation to the cell membrane. 4. Adipocytes also secrete other adipokines with opposing effects on food intake and energy homeostasis. In insulin-resistant states, adipokine levels with favorable effects on metabolism are decreased, and adipokine levels with unfavorable effects on metabolism are increased.

Use of Retratrutide (GLP-1/GIP/GlucaGon Agonist) Associated with Major Improvement in Insulin Resistance vs. GLP-1 Alone

Retatrutide, a GIP, GLP-1 and glucagon receptor agonist, for people with type 2 diabetes: a randomised, double-blind, placebo and active-controlled, parallel-group, phase 2 trial conducted in the USA

Julio Rosenstock, Juan Frias, Ania M Jastreboff, Yu Du, Jitong Lou, Sirel Gurbuz, Melissa K Thomas, Mark L Hartman, Axel Haupt, Zvonko Milicevic, Tamer Coskun

Summary

Background According to current consensus guidelines for type 2 diabetes management, bodyweight management is as important as attaining glycaemic targets. Retatrutide, a single peptide with agonist activity at the glucose-dependent insulinotropic polypeptide (GIP), GLP-1, and glucagon receptors, showed clinically meaningful glucose-lowering and bodyweight-lowering efficacy in a phase 1 study. We aimed to examine the efficacy and safety of retatrutide in people with type 2 diabetes across a range of doses.

At 36 weeks, treatment with retatrutide increased insulin sensitivity, as indicated by decreases of up to 41·65% (SE 6·49; p<0·0001 in the 8 mg fast escalation group) in fasting insulin concentrations (table 2), 30·55% (6·34; p<0·0001 in the 8 mg fast escalation group) in fasting C-peptide concentrations, and 38·90% (10·52; p=0·0042 in the 8 mg slow escalation group) in homoeostasis model assessment of insulin resistance (HOMA2-IR, computed with insulin),[11] and by increases of up to 53·46% (12·27; p<0·0001 in the 8 mg fast escalation group) in adiponectin concentrations (appendix p 14). These changes were generally dose-dependent and significantly larger in the higher dose retatrutide groups than observed with dulaglutide.

Source: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(23)01053-X/

Rivus' HU6, Controlled Mitochondrial Accelerator, Associated with Improved Insulin Sensitivity

Rivus Pharmaceuticals Announces Positive Data from Phase 2a Clinical Trial of Lead Candidate HU6, Demonstrating Fat Reduction and Weight Loss in High BMI Participants

"This trial provides compelling proof of clinical concept for the efficacy and safety of mitochondrial uncoupling with HU6, our first in class CMA. HU6 pharmacology which selectively reduces fat and weight without appetite suppression is highly differentiated. Given early indications that this biology may reverse insulin resistance and systemic inflammation, we can now explore whether reducing visceral and organ fat can provide clinical benefits to patients across a host of cardiometabolic diseases," said Shaharyar Khan, Ph.D., Rivus' Chief Scientific Officer.

CMAs provide a new, measured approach to safely activating mitochondrial uncoupling, a process in the body that regulates and dissipates energy. By ferrying protons out of the mitochondrial intermembrane space, CMAs increase the oxidation of sugars and fats, while maintaining the same baseline production of adenosine triphosphate (ATP). Activating this process results in the reduction and the prevention of fat accumulation throughout the body.

Source: https://www.rivuspharma.com/wp-content/uploads/2022/09/RIVUS_PHARMACEUTICALS_ANNOUNCES_POSITIVE_DATA_FROM_PHASE_2A_CLINICAL_TRIAL_OF_LEAD_CANDIDATE_HU6.pdf

KHK Inhibition Improves Insulin Sensitivity (with Fructose Diets)

13. Pharmacological inhibition of fructose metabolism reduces liver fat and improves insulin sensitivity in participants with MASLD

E.J.C. Koene[1], J. Basset Sagarminaga[1], K. Brouwers[2], J. Mevenkamp[2], Y.M.H. Op den Kamp-Bruls[2], E. Phielix[1], V. Schrauwen-Hinderling[2], P. Schrauwen[1], M.C.G. Brouwers[3];
[1]Nutrition and Movement Sciences, Maastricht University, Maastricht, Netherlands, [2]Radiology and Nuclear Medicine, Maastricht University Medical Center+, Maastricht, Netherlands, [3]Internal Medicine/Endocrinology, Maastricht University Medical Center+, Maastricht, Netherlands. 10:30 AM-10:45 AM 15m View abstract

Background and aims: Previous studies have shown that fructose intake is associated with metabolic dysfunction-associated steatotic liver disease (MASLD), which is a risk factor for type 2 diabetes (T2D). Of interest, experimental studies demonstrated that pharmacological inhibition of ketohexokinase (KHK), the first committed step in fructose metabolism which converts fructose to fructose-1-phosphate, effectively lowers de novo lipogenesis and intrahepatic lipid (IHL) content, which have recently been confirmed in phase II clinical studies. Here, we investigated the effect of a KHK inhibitor, PF-06835919, on insulin sensitivity.

Materials and methods: We conducted a randomized double-blind, placebo-controlled cross-over trial in which fifteen overweight/obese participants with MASLD (IHL ≥ 5.56%) were treated with PF-06835919 (300 mg, once daily) and placebo. Each 6-week treatment arm was evaluated by assessment of: 1) in vivo intrahepatic fructose phosphorylation (measured with 31P- Magnetic Resonance Spectroscopy (MRS) after an oral fructose load) 2) IHL content (quantified with 1H-MRS), and 3) insulin sensitivity (M-value assessed with two-step hyperinsulinemic-euglycemic clamp).

Results: Hepatic phosphomonoester concentration increased upon an oral fructose load in the placebo arm, which was completely abolished after PF-06835919 treatment ($p<0.001$), showing that the drug inhibits normal fructose metabolism. IHL content was lower after PF-06835919 versus placebo (absolute difference: -2.5 %; 95% CI: -3.3, -1.8; $p<0.001$). Body weight remained stable between both periods (difference: 0.37 kg; 95% CI: -0.12, 0.83 kg; $p=0.12$). Whole body insulin sensitivity (M-value) was significantly higher ($p=0.007$) after 6 weeks of PF-06835919 (mean: 5.2 mg/kg/min) as compared to placebo (mean: 4.4 mg/kg/min).

Source: 60th Annual Meeting, European Association for the Study of Diabetes, Conference Website.

Pfizer in Phase 2 with a KHK Inhibitor

DIABETES, OBESITY AND METABOLISM
A JOURNAL OF PHARMACOLOGY AND THERAPEUTICS

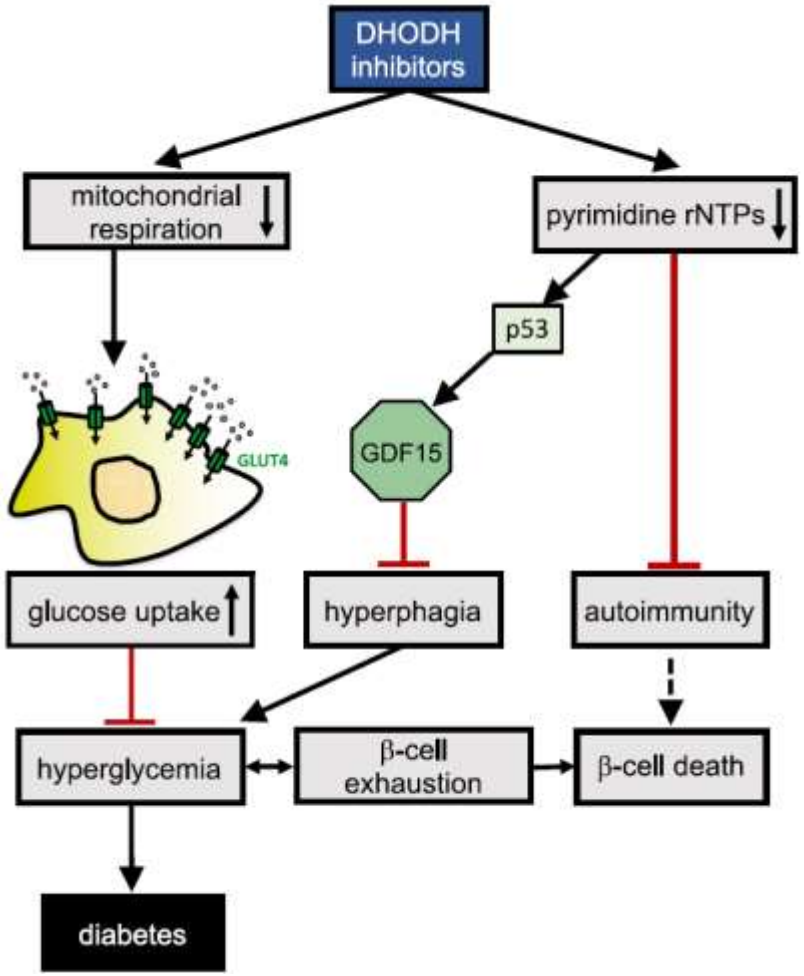
ORIGINAL ARTICLE | Open Access

A phase 2a, randomized, double-blind, placebo-controlled, three-arm, parallel-group study to assess the efficacy, safety, tolerability and pharmacodynamics of PF-06835919 in patients with non-alcoholic fatty liver disease and type 2 diabetes

Aditi R. Saxena MD, Stephanie-An Lyle BA, Kaivan Khavandi MD, Ruolun Qiu PhD, Mark Whitlock PhD, William P. Esler PhD, Albert M. Kim MD

First published: 14 December 2022 | https://doi.org/10.1111/dom.14946

DHODH Inhibitors Enhance GLUT4 Expression Via Effects on Mitochondrial Respiration



Zhang J, Terán G, Popa M, Madapura H, Ladds MJGW, Lianoudaki D, Grünler J, Arsenian-Henriksson M, McCormack E, Rottenberg ME, Catrina SB, Laín S, Darekar S. DHODH inhibition modulates glucose metabolism and circulating GDF15, and improves metabolic balance. iScience. 2021 May 1;24(5):102494.

Dihydroorotate dehydrogenase (DHODH) is essential for the de novo synthesis of pyrimidine ribonucleotides, and as such, its inhibitors have been long used to treat autoimmune diseases and are in clinical trials for cancer and viral infections. Interestingly, DHODH is located in the inner mitochondrial membrane and contributes to provide ubiquinol to the respiratory chain. Thus, DHODH provides the link between nucleotide metabolism and mitochondrial function. Here we show that pharmacological inhibition of DHODH reduces mitochondrial respiration, promotes glycolysis, and enhances GLUT4 translocation to the cytoplasmic membrane and that by activating tumor suppressor p53, increases the expression of GDF15, a cytokine that reduces appetite and prolongs lifespan. In addition, similar to the antidiabetic drug metformin, we observed that in db/db mice, DHODH inhibitors elevate levels of circulating GDF15 and reduce food intake. Further analysis using this model for obesity-induced diabetes revealed that DHODH inhibitors delay pancreatic b cell death and improve metabolic balance.

Experimental Findings with DHODH Inhibition

Zhang J, Terán G, Popa M, Madapura H, Ladds MJGW, Lianoudaki D, Grünler J, Arsenian-Henriksson M, McCormack E, Rottenberg ME, Catrina SB, Laín S, Darekar S. DHODH inhibition modulates glucose metabolism and circulating GDF15, and improves metabolic balance. *iScience*. 2021 May 1;24(5):102494.

We observed that when cells were cultured in the presence of DHODH inhibitor, the culture medium became acidified and that there was a reduction in the concentration of glucose in the medium. **This suggested an increase in lactate production and an increase in glucose consumption by cells.** Accordingly, brequinar, like insulin and metformin, induced the translocation of the glucose transporter GLUT4 to the plasma membrane. Supporting that the effect of brequinar was due to inhibition of DHODH, BAY2402234 had the same effect on GLUT4. As induction of the translocation of GLUT4 to the plasma membrane is also a feature of the mitochondrial complex I inhibitor route none (Becker et al., 2001) and DHODH is involved in mitochondrial respiration, we measured oxygen consumption rate (OCR) and extracellular acidification rates in the cell culture medium and observed that both DHODH inhibitors (BAY2402234 and brequinar) partially reduced OCR and promoted a shift toward glycolysis).

Source: https://pubmed.ncbi.nlm.nih.gov/34113829/

Leflunomide-Associated Weight Loss in RA Study

Coblyn JS, Shadick N, Helfgott S. Leflunomide-associated weight loss in rheumatoid arthritis. *Arthritis Rheum*. May 2001, pp. 1048-51.

Objective: To determine the frequency of weight loss in patients treated with leflunomide for rheumatoid arthritis at an arthritis referral center.

Methods: We queried 35 rheumatologists at the Robert Breck Brigham Arthritis Center to determine if weight loss had occurred as an adverse event in patients treated with leflunomide between November 1998 and January 2000. Five such patients were identified, and their clinical course was reviewed.

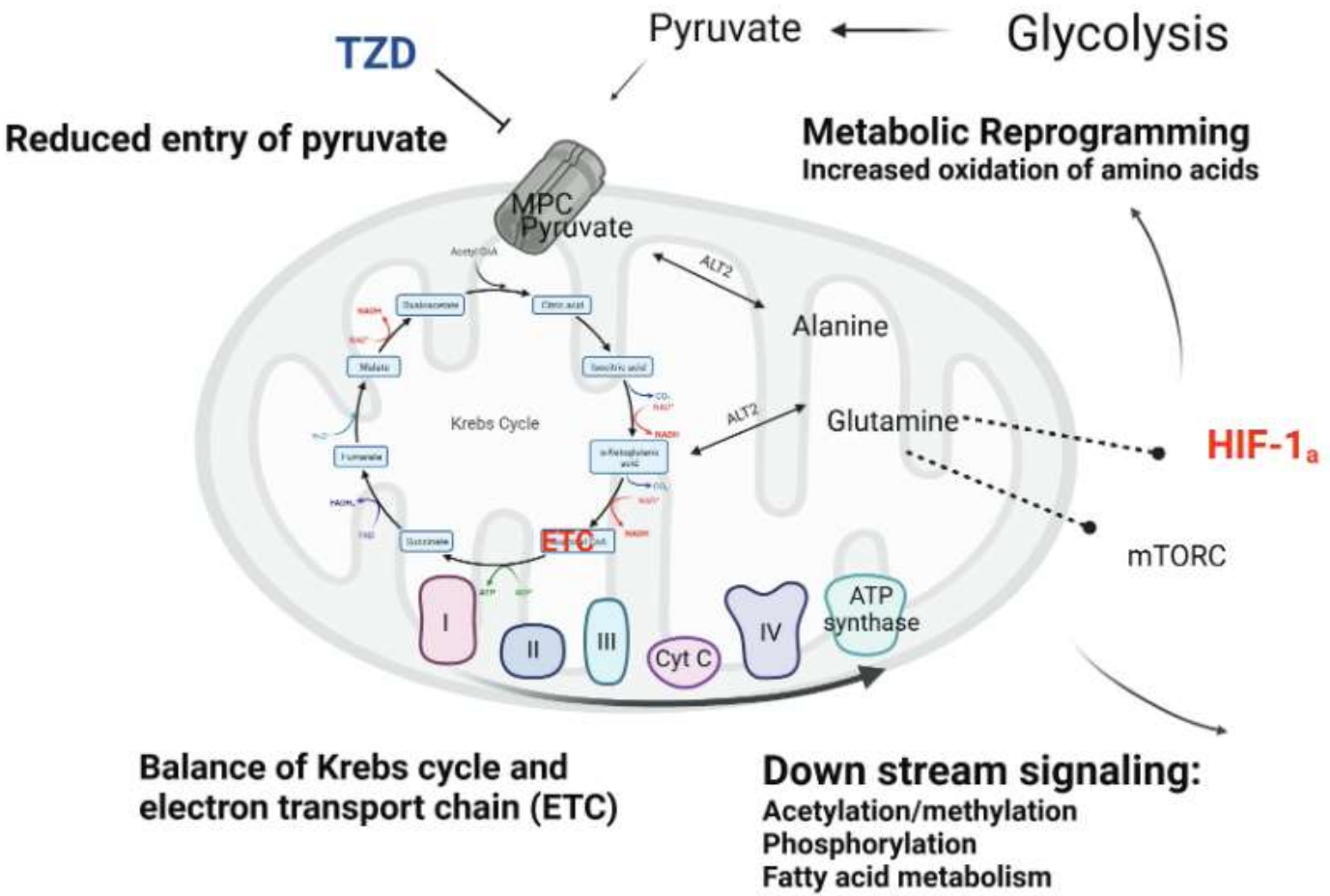
Results: **Five of 70 patients who had begun leflunomide therapy had significant weight loss that could not be linked to other identifiable etiologies. The amount of weight loss was substantial in this group of patients, ranging from 19 pounds to 53 pounds.** All patients had normal levels of thyroid-stimulating hormone and no other gastrointestinal complaints; evaluation revealed no other cause for the weight loss. Despite the significant weight loss, 4 of the 5 patients continued to take the drug due to its efficacy.

Conclusion: Significant weight loss is a potential adverse event in patients with rheumatoid arthritis treated with leflunomide. Awareness of this may obviate the need for extensive medical evaluations

Note: we queried the FDA Adverse Event Reporting System (FAERS) in June 2024 and found exceptionally number of reports for the two approved DHODH inhibitors and weight loss.

Source: https://pubmed.ncbi.nlm.nih.gov/11352235/

Interestingly, TZD's Also Function Through Pyruvate Reduction (Same as DHODH)



. TZD mechanism of action through metabolic reprogramming of pyruvate metabolism.

See https://www.tandfonline.com/doi/10.1080/13543784.2023.2263369

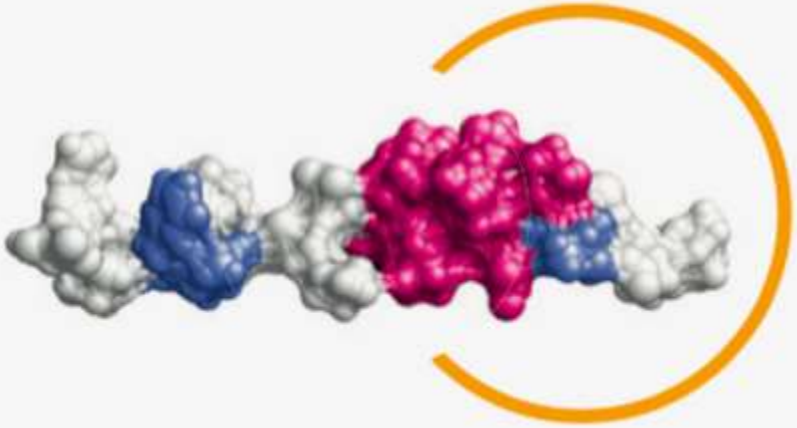
PKCα as a Target

PATAS, a First-in-Class Therapeutic Peptide Biologic, Improves Whole-Body Insulin Resistance and Associated Comorbidities In Vivo

Edwige Schreyer,[1] Cathy Obringer,[2] Nadia Messaddeq,[3] Bruno Kieffer,[3] Paul Zimmet,[4] Alexander Fleming,[5] Tarekegn Geberhiwot,[6,7] and Vincent Marion[1,2]

Diabetes 2022;71:2034–2047 | https://doi.org/10.2337/db22-0058

Adipose tissue is a key regulator of whole-body metabolic fitness because of its role in controlling insulin sensitivity. Obesity is associated with hypertrophic adipocytes with impaired glucose absorption, a phenomenon existing in the ultrarare monogenic disorder Alström syndrome consisting of severe insulin resistance. Inactivation of ALMS1 directly inhibits insulin-mediated glucose absorption in the white adipose tissue and induces severe insulin resistance, which leads to type 2 diabetes, accelerated nonalcoholic liver disease, and fibrosis. These phenotypes were reversed by specific adipocyte-ALMS1 reactivation in vivo. Subsequently, ALMS1 was found to bind to protein kinase C-a (PKCa) in the adipocyte, and upon insulin signaling, PKCa is released from ALMS1. a-Helices in the kinase domain of PKCa were therefore screened to identify a peptide sequence that interfered with the ALMS1-PKCa protein interaction. When incubated with cultured human adipocytes, the stapled peptide termed PATAS, for Peptide derived of PKC Alpha Targeting AlmS, triggered insulin-independent glucose absorption, de novo lipogenesis, and cellular glucose utilization. In vivo, PATAS reduced whole-body insulin resistance, and improved glucose intolerance, fasting glucose, liver steatosis, and fibrosis in rodents. Thus, PATAS represents a novel first-in-class peptide that targets the adipocyte to ameliorate insulin resistance and its associated comorbidities.



AdipoPharma

AdipoPharma SAS is a French biotech company committed to understanding the role of the adipocyte cells in diabetes via their unique effect on lipid biosynthesis and management of whole-body lipid homeostasis. The company was created to commercialize the work of its founder, Dr. Vincent Marion PhD, MSc, and Biochemist and researcher at INSERM, the French National Institute for Health and Medical Research. Dr Marion's team has spent more than a decade identifying therapeutic targets based on the adipocyte's specific role in the metabolic effects of insulin resistance and diabetes. This work began by the detailed genetic investigation of Alström syndrome, an ultra-rare devastating disease characterized by severe insulin resistance, early-onset type 2 diabetes and associated metabolic dysfunctions. The result is AdipoPharma's innovative and first-in-class therapeutic peptide "PATAS", the first Adipeutic drug that will enter clinical trial phase in 2024. This safe and novel therapeutic approach has been shown to restore healthy lipid biosynthesis in the diseased adipocyte leading to reduction of nasty lipids like the ceramides. PATAS is set to be the first anti-diabetic drug to have a significant beneficial effect on insulin resistance, beta cell plaque removal, liver steatosis and fibrosis and ceramides, the leading cause of cardiovascular dysfunction in diabetes.

See https://www.adipopharma.com/

PKCα Inhibition Effective in Reducing Adiposity in Rats

Wang J, et. Al., "A protein kinase C α and β inhibitor blunts hyperphagia to halt renal function decline and reduces adiposity in a rat model of obesity-driven type 2 diabetes," *Sci Rep*. Oct 2023, p. 16919.

Type 2 diabetes (T2D) and its complications can have debilitating, sometimes fatal consequences for afflicted individuals. The disease can be difficult to control, and therapeutic strategies to prevent T2D-induced tissue and organ damage are needed. Here we describe the results of administering a potent and selective inhibitor of Protein Kinase C (PKC) family members PKCα and PKCβ, Cmpd 1, in the ZSF1 obese rat model of hyperphagia-induced, obesity-driven T2D. Although our initial intent was to evaluate the effect of PKCα/β inhibition on renal damage in this model setting, Cmpd 1 unexpectedly caused a marked reduction in the hyperphagic response of ZSF1 obese animals. This halted renal function decline but did so indirectly and indistinguishably from a pair feeding comparator group. However, above and beyond this food intake effect, Cmpd 1 lowered overall animal body weights, reduced liver vacuolation, and reduced inguinal adipose tissue (iWAT) mass, inflammation, and adipocyte size. Taken together, Cmpd 1 had strong effects on multiple disease parameters in this obesity-driven rodent model of T2D. Further evaluation for potential translation of PKCα/β inhibition to T2D and obesity in humans is warranted.

Source: https://pubmed.ncbi.nlm.nih.gov/37805649/

History with PKCα Inhibition

Midostaurin, sold under the brand name Rydapt & Tauritmo both by Novartis, is a multi-targeted protein kinase inhibitor that has been investigated for the treatment of acute myeloid leukemia (AML), myelodysplastic syndrome (MDS) and advanced systemic mastocytosis. It is a semi-synthetic derivative of staurosporine, an alkaloid from the bacterium Streptomyces staurosporeus.

Lilly Announces Enzastaurin Phase III Study Did Not Meet Primary Endpoint in Diffuse Large B-Cell Lymphoma

May 10, 2013

INDIANAPOLIS, May 10, 2013 /PRNewswire/ -- Eli Lilly and Company (NYSE: LLY) announced today Phase III clinical trial results from enzastaurin's PRELUDE study, which explored the molecule as a monotherapy in the prevention of relapse in patients with diffuse large B-cell lymphoma (DLBCL). The study failed to show a statistically significant increase compared to placebo in disease-free survival in patients at high risk of relapse following rituximab-based chemotherapy. There were no new safety findings, and the safety data were consistent with previously disclosed studies.

Download PDF

"We are disappointed in the results that we're announcing today," said Richard Gaynor, M.D., vice president, product development and medical affairs for Lilly Oncology. "However, our oncology pipeline is still one of the most robust across the industry containing more than 20 molecules, including two Phase III molecules in five different tumor types."

IDEAYA BIOSCIENCES

Compared to other PKC inhibitors, such as sotrastaurin and enzastaurin, darovasertib is significantly more potent in inhibiting conventional (α, β) and novel (δ, ϵ, n, θ) PKC proteins and has a better tolerability and safety profile.

GLUT4 Expression is Enhanced by Stimulation of AMPK

Holmes BF, Sparling DP, Olson AL, Winder WW, Dohm GL. Regulation of muscle GLUT4 enhancer factor and myocyte enhancer factor 2 by AMP-activated protein kinase. *Am J Physiol Endocrinol Metab*. Dec 2005, pp. E1071-6.

As the primary glucose transporter in skeletal muscle, GLUT4 is an important factor in the regulation of blood glucose. We previously reported that stimulation of AMP-activated protein kinase (AMPK) with 5-aminoimidazole-4-carboxamide-1-beta-d-ribofuranoside (AICAR) increased GLUT4 expression in muscle. GLUT4 enhancer factor (GEF) and myocyte enhancer factor 2 (MEF2) have been shown to be important for normal GLUT4 expression because deletion or truncation of the consensus sequences on the promoter causes depressed GLUT4 mRNA expression. This led to the current study to investigate possible roles for GEF and MEF2 in mediating the activation of GLUT4 gene transcription in response to AMPK. Here we show that, although AMPK does not appear to phosphorylate MEF2A, AMPK directly phosphorylates the GEF protein in vitro. MEF2 and GEF are activated in response to AMPK as we observed translocation of both to the nucleus after AICAR treatment. Nuclear MEF2 protein content was increased after 2 h, and GEF protein was increased in the nucleus 1 and 2 h post-AICAR treatment. Last, GEF and MEF2 increase in binding to the GLUT4 promoter within 2 h after AICAR treatment. Thus we conclude that GEF and MEF2 mediate the AMPK-induced increase in transcription of skeletal muscle GLUT4. AMPK can phosphorylate GEF and in response to AICAR, GEF, and MEF2 translocate to the nucleus and have increased binding to the GLUT4 promoter.

Source: https://journals.physiology.org/doi/full/10.1152/ajpendo.00606.2004

Amplifier Therapeutics Pursing AMPK Activator

NEW YORK, October 17, 2023 – Amplifier Therapeutics, a Cambrian Bio pipeline company, today announced the dosing of the first patient in the company's Phase 1B clinical trial investigating ATX-304, a peripherally restricted pan-AMPK activator being developed for the treatment of cardiometabolic diseases.

The Phase 1B trial is an 8-week, double-blind, randomized placebo-controlled study in prediabetic, overweight or obese subjects, being conducted in the European Union. The study will focus primarily on the safety and pharmacokinetics of ATX-304 and also will include exploratory outcomes measuring its effect on metabolic parameters and muscle.

"The administration of ATX-304 to the first patient in this trial signifies a pivotal moment in the clinical development of ATX-304," said James Hall, CEO of Amplifier Therapeutics. "We believe our compound could transform the lives of patients, with potential in treating cardiometabolic and aging-related diseases."

Others such as

poxel

Sources: https://www.amplifier-tx.com/news-and-press/amplifier-therapeutics-a-cambrian-bio-pipeline-company-doses-first-patients-in-phase-1b-clinical-trial-and-closes-new-financing-from-future-ventures-and-ra-capital-management, https://www.amplifier-tx.com/

Juvena's JUV-112 Associated with Significant Improvement in Insulin Sensitivity

SAT-791

ENDO2024
JUNE 1–4, 2024 BOSTON, MA

JUV-112 Offers a Distinctive Approach to Weight Loss and Metabolic Health

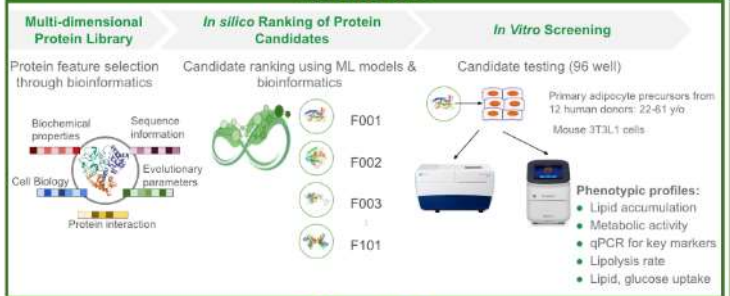
Ritwik Datta, Vengadeshprabhu Karuppagounder, Ashil Koranne, HeeJu Kim, Sharon Louie, Annie Yang, Thach Mai, Mohammad Hassanipour, Rohit Jadhav, Vivian Guo, Sarah Tang, Fengling Liu, Priya Handa, Mo Tabrizi, Hanadie Yousef, **Jeremy D. O'Connell**
The authors have no conflicts. They are employees of Juvena Therapeutics.

Juvena THERAPEUTICS

Introduction

- Obesity and metabolic disorders are major contributors to global morbidity and mortality.
- GIPR/GLP1R agonists have made significant progress in recent years in treating obesity predominantly through appetite suppression.
- High unmet medical need for safe, potent, and durable pharmacotherapies through alternate mechanisms.
- Juvena has developed a biologics-based drug discovery and development platform that integrates machine learning and multi-omics to find potential therapeutic candidates from a unique stem cell-secreted protein library.

Methods



Results

JUV-112 promotes lipid breakdown in adipocytes

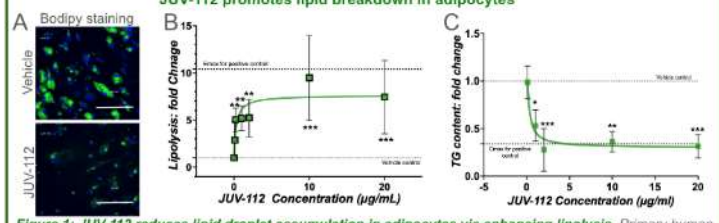


Figure 1: JUV-112 reduces lipid droplet accumulation in adipocytes via enhancing lipolysis. *Primary human adipocytes (36 y/o overweight female) were grown and differentiated under lipid accumulating conditions. Cells were then treated with JUV-112 for 4 days and imaged after Bodipy (green) that stains neutral lipids. Representative images from high-throughput image analysis showing reduced lipid accumulation in JUV-112-treated cells. Hoechst was used as a nuclear counterstain. N=3-6 technical replicates. (B) Differentiated 3T3L1 mouse adipocytes were treated with JUV-112 for 3 days and glycerol content from the media was measured as an indicator of lipolysis in the cell. Forskolin treatment was used as a positive control for the assay (data not shown). N=7 independent experiments. (C) Differentiated 3T3L1 mouse adipocytes were treated with JUV-112 for 3 days followed by measurement of total triglyceride (TG) content in the cell. N=3 independent experiments.*

Results

JUV-112 prevents weight gain and improves body composition in obese mice

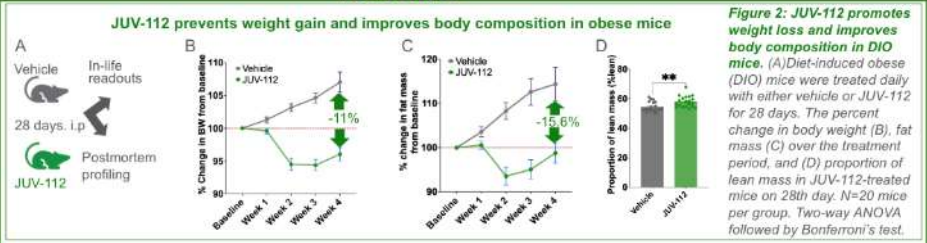


Figure 2: JUV-112 promotes weight loss and improves body composition in DIO mice. *(A)Diet-induced obese (DIO) mice were treated daily with either vehicle or JUV-112 for 28 days. The percent change in body weight (B), fat mass (C) over the treatment period, and (D) proportion of lean mass in JUV-112-treated mice on 28th day. N=20 mice per group. Two-way ANOVA followed by Bonferroni's test.*

JUV-112 improves glucose regulation in obese mice

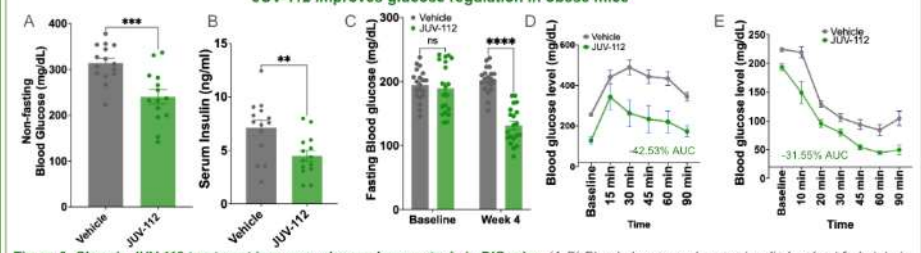


Figure 3: Chronic JUV-112 treatment improves glucose homeostasis in DIO mice. *(A-B) Blood glucose and serum insulin levels at fed-state in JUV-112-treated mice compared to vehicle-treated group.(C) Fasting blood glucose level at baseline and JUV-112-treated DIO mice. (D-E) Glucose tolerance test (GTT) and Insulin tolerance test (ITT) in vehicle and JUV-112-treated mice. One-way ANOVA and two-way ANOVA for for panels A-B and panels C-E respectively, followed by Bonferroni's post test. N=20 mice per group for panel A and C, N=14-15 for panel B, N=5 for panels D-E.*

JUV-112 improves adipocyte and hepatocyte health in obese mice

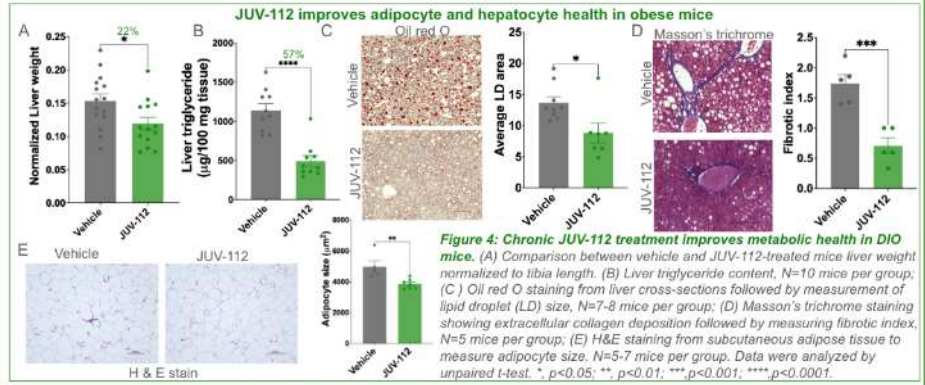


Figure 4: Chronic JUV-112 treatment improves metabolic health in DIO mice. *(A) Comparison between vehicle and JUV-112-treated mice liver weight normalized to tibia length. (B) Liver triglyceride content, N=10 mice per group; (C) Oil red O staining from liver cross-sections followed by measurement of lipid droplet (LD) size, N=7-8 mice per group; (D) Masson's trichrome staining showing extracellular collagen deposition followed by measuring fibrotic index, N=5 mice per group; (E) H&E staining from subcutaneous adipose tissue to measure adipocyte size. N=5-7 mice per group. Data were analyzed by unpaired t-test. *, p<0.05; **, p<0.01; ***,p<0.001; ****,p<0.0001.*

Results

JUV-112 preserves muscle function

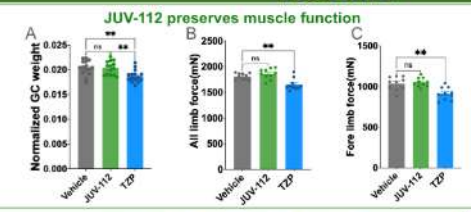


Figure 5: Chronic JUV-112 treatment preserves muscle mass and function despite weight loss. *Diet-induced obese (DIO) mice were treated daily with either vehicle or JUV-112 or Tirzepatide (TZP) for 28 days. (A) Gastrocnemius muscle weight normalized by tibia length. (B-C) Modified Grip strength analysis showing all-limb and forelimb forces. Data were analyzed by one-way ANOVA followed by Bonferroni's post test. N=15 mice in each group for panel A, and N=10 per group for panels B-C.*

JUV-112 does not reduce food intake

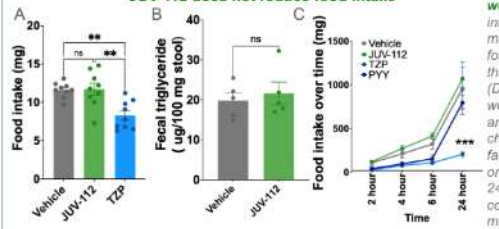


Figure 6: JUV-112 offers a distinctive mechanism for weight loss. *(A-B). Chronic effect of JUV-112 on food intake and fat absorption was measured after treating DIO mice with Vehicle, JUV-112 and Tirzepatide (TZP) daily for 28 days. (A) Food intake was measured by weighing the food pellets in each cage for 3 consecutive days (Days 22-25). Blinded experiment. (B) Stool samples were collected on day 25 after singly-housing mice. N=4-5 animals per group.Triglyceride content from normal chow-fed mice stool remained undetected. (C) Mice were fasted for 16 hours and then treated with vehicle, JUV-112 or TZP before refeeding. Food intake was measured for 24 hours. Peptide YY (PYY) treatment was used as a control for food intake suppression. Blinded study. N=4 mice in each group. **,p<0.01, ***, p<0.001.*

JUV-112 enhances lipid catabolism in adipose tissues

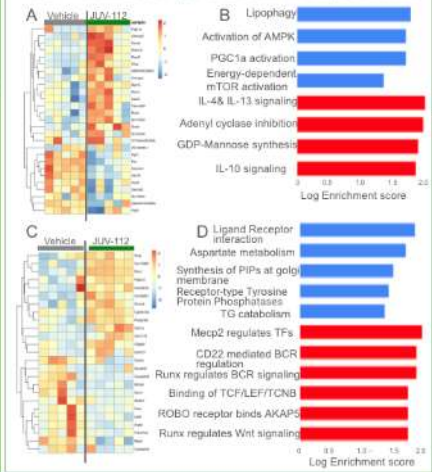
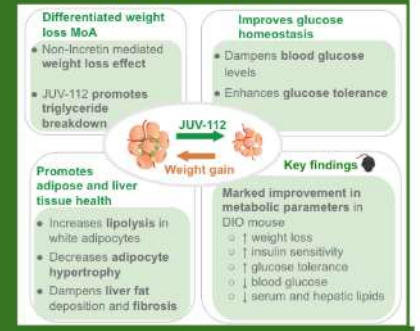


Figure 7: RNA sequencing from brown and subcutaneous adipose tissue showing augmented triglyceride catabolism in JUV-112-treated mice. *DIO mice were treated with JUV-112 or vehicle for 21 days. Differential gene expression in brown adipose tissue (A-B) and subcutaneous adipose tissue (C-D) are shown in heat maps (A&C) alongside the pathway enrichment analysis (B&D). Up and Down regulated pathways are depicted in blue and red respectively.*

Conclusions



Juvena Therapeutics, Inc., Redwood City, CA 94063. juvenatherapeutics.com

https://www.juvenatherapeutics.com

STING-GAS as a Target

RESEARCH ARTICLE | CELL BIOLOGY |

A distinct role of STING in regulating glucose homeostasis through insulin sensitivity and insulin secretion

Jingting Qiao, Ziyin Zhang, Shuhui Ji, +8, and Ming Liu Authors Info & Affiliations

Edited by Zhijian Chen, Department of Molecular Biology, The University of Texas Southwestern Medical Center, Dallas, TX; received January 29, 2021; accepted December 14, 2021

February 10, 2022 | 119 (7) e2101848119 | https://doi.org/10.1073/pnas.2101848119

Herein, using global and β-cell–specific STING knockout mouse models, we revealed a distinct role of STING in the regulation of glucose homeostasis through β-cells and peripheral tissues. Specially, while **global STING knockout beneficially alleviated insulin resistance and glucose intolerance induced by high-fat diet**, it surprisingly impaired islet glucose-stimulated insulin secretion (GSIS). Further analyses revealed that STING deficiency down-regulated expression of β-cell key transcription factor Pax6, impairing Pax6 nuclear localization and binding activity to the promoters of its target genes, including Glut2 and Abcc8, causing impaired GSIS. These data highlight pathophysiological significance of fine-tuned STING signaling in β-cells and insulin target tissues for maintaining glucose homeostasis.

Source: https://www.pnas.org/doi/full/10.1073/pnas.2101848119

PGC-1 Restores GLUT4 Gene Expression

Michael LF, Wu Z, Cheatham RB, Puigserver P, Adelmant G, Lehman JJ, Kelly DP, Spiegelman BM. Restoration of insulin-sensitive glucose transporter (GLUT4) gene expression in muscle cells by the transcriptional coactivator PGC-1. *Proc Natl Acad Sci U S A.* Mar 2001, pp. 3820-5.

Muscle tissue is the major site for insulin-stimulated glucose uptake in vivo, due primarily to the recruitment of the insulin-sensitive glucose transporter (GLUT4) to the plasma membrane. Surprisingly, virtually all cultured muscle cells express little or no GLUT4. We show here that adenovirus-mediated expression of the transcriptional coactivator PGC-1, which is expressed in muscle in vivo but is also deficient in cultured muscle cells, causes the total restoration of GLUT4 mRNA levels to those observed in vivo. This increased GLUT4 expression correlates with a 3-fold increase in glucose transport, although much of this protein is transported to the plasma membrane even in the absence of insulin. PGC-1 mediates this increased GLUT4 expression, in large part, by binding to and coactivating the muscle-selective transcription factor MEF2C. These data indicate that PGC-1 is a coactivator of MEF2C and can control the level of endogenous GLUT4 gene expression in muscle.

Source: https://pubmed.ncbi.nlm.nih.gov/11274399/

PGC-1a Interventions Also Enhance Muscle

Petrocelli JJ, Drummond MJ. PGC-1α-Targeted Therapeutic Approaches to Enhance Muscle Recovery in Aging. *Int J Environ Res Public Health*, Nov 2020, p. 8650.

Impaired muscle recovery (size and strength) following a disuse period commonly occurs in older adults. Many of these individuals are not able to adequately exercise due to pain and logistic barriers. Thus, nutritional and pharmacological therapeutics, that are translatable, are needed to promote muscle recovery following disuse in older individuals. Peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) may be a suitable therapeutic target due to pleiotropic regulation of skeletal muscle. This review focuses on nutritional and pharmacological interventions that target PGC-1α and related Sirtuin 1 (SIRT1) and 5' AMP-activated protein kinase (AMPKα) signaling in muscle and thus may be rapidly translated to prevent muscle disuse atrophy and promote recovery. In this review, we present several therapeutics that target PGC-1α in skeletal muscle such as leucine, β-hydroxy-β-methylbuyrate (HMB), arginine, resveratrol, metformin and combination therapies that may have future application to conditions of disuse and recovery in humans.

Source: https://pubmed.ncbi.nlm.nih.gov/33233350/

Numerous Other Targets for Reducing Insulin Resistance in Literature

- 11β-hydroxysteroid dehydrogenase 1 (https://pubmed.ncbi.nlm.nih.gov/25389364/)
- ACRP30 / Adiponectin (https://pubmed.ncbi.nlm.nih.gov/10092513/, https://pubmed.ncbi.nlm.nih.gov/12238775/)
- Fetuin-A (https://diabetesjournals.org/diabetes/article/57/10/2762/13362/Plasma-Fetuin-A-Levels-and-the-Risk-of-Type-2)
- GPCR119 (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8265056/)
- GPER (https://pubmed.ncbi.nlm.nih.gov/23970785/)
- Metrnl (https://diabetesjournals.org/diabetes/article/64/12/4011/34737/Adipocyte-Metrnl-Antagonizes-Insulin-Resistance)
- MNTR1B (https://pubmed.ncbi.nlm.nih.gov/19060907/)
- Omentin-1 (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6903756/)
- PEDF (https://pubmed.ncbi.nlm.nih.gov/22288782/)
- Serpin a12 (https://pubmed.ncbi.nlm.nih.gov/23370777/)
- Sfrp5 (https://www.mdpi.com/2072-6643/13/7/2459)
- TNFa (https://diabetesjournals.org/diabetes/article/51/5/1319/34580/Tumor-Necrosis-Factor-Suppresses-Adipocyte)

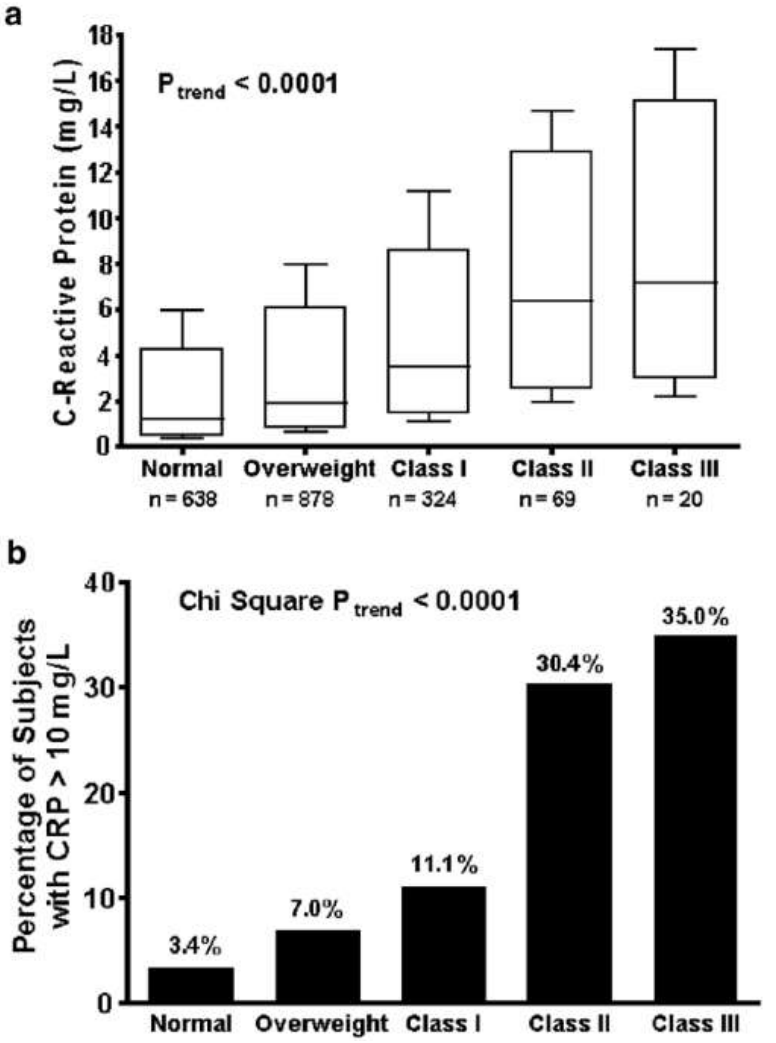
Sources: Dhankhar, S., Chauhan, S., Mehta, D.K. *et al.* Novel targets for potential therapeutic use in Diabetes mellitus. *Diabetol Metab Syndr* **15**, 17 (2023). And Roy, P.K., Islam, J. & Lalhlenmawia, H. Prospects of potential adipokines as therapeutic agents in obesity-linked atherogenic dyslipidemia and insulin resistance. *Egypt Heart J* **75**, 24 (2023).


Obesity Adipocyte Health
and Inflammation

Obesity Strongly Linked to Inflammation

Aronson D, Bartha P, Zinder O, Kerner A, Markiewicz W, Avizohar O, Brook GJ, Levy Y. Obesity is the major determinant of elevated C-reactive protein in subjects with the metabolic syndrome. *Int J Obes Relat Metab Disord.* May 2004; pp. 674-9.

In a total of 1929 subjects undergoing a medical examination in a preventive medicine clinic (age, 50±10 y; 63% males) subjects with obesity had markedly higher CRP level compared to patients without obesity regardless of whether they had the metabolic syndrome. The proportion of subjects with CRP levels above the cut point generally used to indicate an obvious source of infection or inflammation (›10 mg/l) was 3, 7, and 15% in subjects who were normal weight, overweight, and obese, respectively. However, there was no significant difference in CRP levels between nonobese subjects without the metabolic syndrome and subjects in whom the diagnosis of the metabolic syndrome was based on criteria other than obesity (adjusted geometric mean CRP 1.75 vs 2.08 mg/l, P=0.79). Similarly, CRP levels did not differ among obese subjects with and without the metabolic syndrome (adjusted geometric mean CRP 3.22 vs 3.49 mg/l, P=0.99). There was a linear increase in CRP levels with an increase in the number of metabolic disorders (P(trend) ‹0.0001), which was substantially diminished after controlling for body mass index (BMI) (P(trend)=0.1). Stepwise multivariate linear regression analysis identified BMI, triglyceride levels, HDL cholesterol levels (inversely), and fasting glucose as independently related to CRP levels. However, BMI accounted for 15% of the variability in CRP levels, whereas triglycerides, HDL cholesterol and fasting glucose levels accounted for only approximately 1% of the variability in CRP levels.



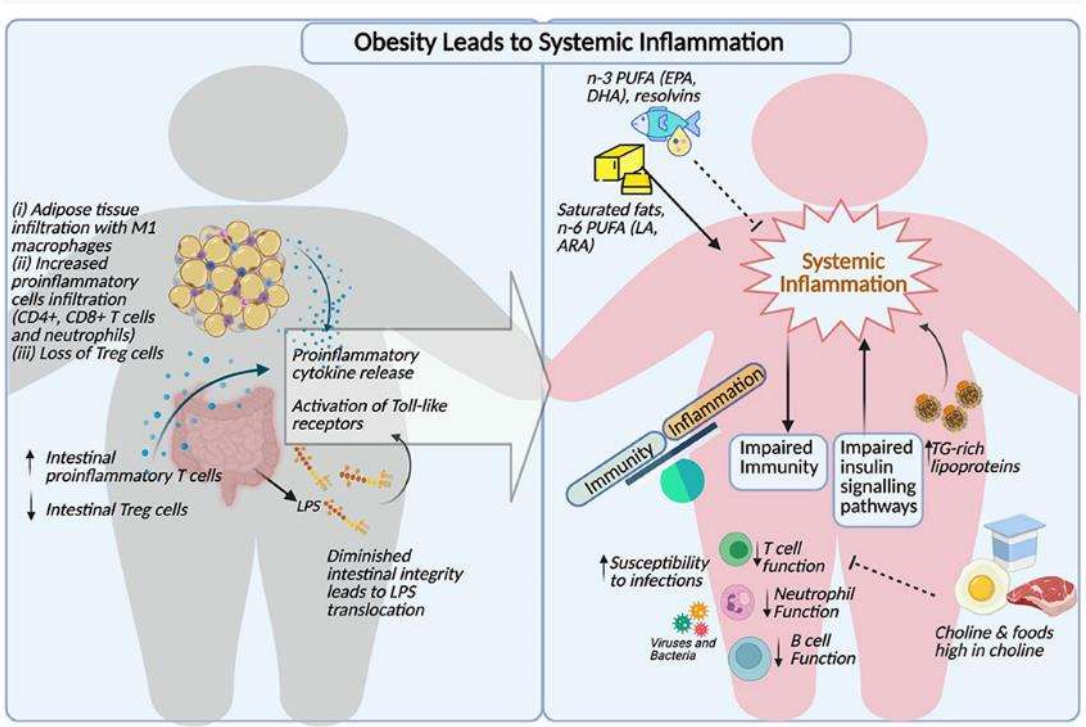
Source: https://pubmed.ncbi.nlm.nih.gov/14993913/

Obesity Leads to Chronic Inflammation Which Leads to Insulin Resistance and Dyslipidemia

She Y, Mangat R, Tsai S, Proctor SD, Richard C. The Interplay of Obesity, Dyslipidemia and Immune Dysfunction: A Brief Overview on Pathophysiology, Animal Models, and Nutritional Modulation. Front Nutr., Feb 17, 2022, p. 840209

Studies have demonstrated that subjects with obesity have elevated circulating pro-inflammatory cytokines, including tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6) and C-reactive protein (CRP). There is the notion that adipose tissue is one main contributor through producing substantial amounts of TNF-α and IL-6. It is known that these pro-inflammatory cytokines impair normal insulin signaling pathways and therefore can lead to insulin resistance as well as dyslipidemia. However, the role of IL-6 per se may depend on the target organ.

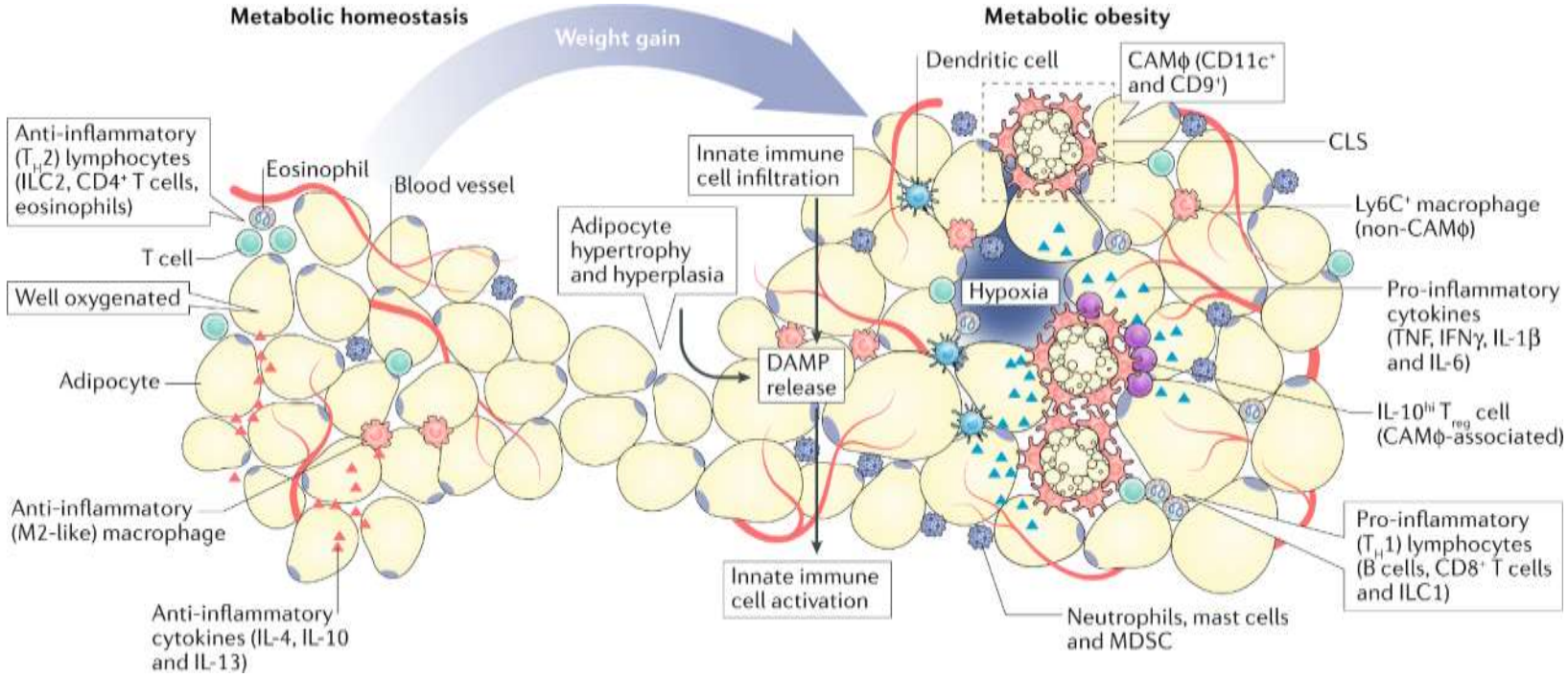
Bornstein et al. were the first to report the involvement of macrophages in adipose tissue leading to inflammation. This discovery has led to an emergent hypothesis that defines the relationship between obesity-related inflammation and impaired immunity. Latter studies found that macrophage infiltration in adipose tissue is increased in obesity. Infiltrating macrophages appear as aggregated crown-like structures and tend to shift from M2 (anti-inflammatory) to M1 (pro-inflammatory) phenotypes. However, recent findings have challenged the initial simplified notion of M1/M2 phenotypes in adipose tissue. The populations of adipose tissue macrophages appear to have more diverse phenotypes (i.e., metabolic activated or oxidized), with distinct surface markers activated by a wide range of stimuli such as free fatty acids or glucose.



Source: https://www.frontiersin.org/journals/nutrition/articles/10.3389/fnut.2022.840209/full

Evolution of the Adipose Tissue Microenvironment During Obesity

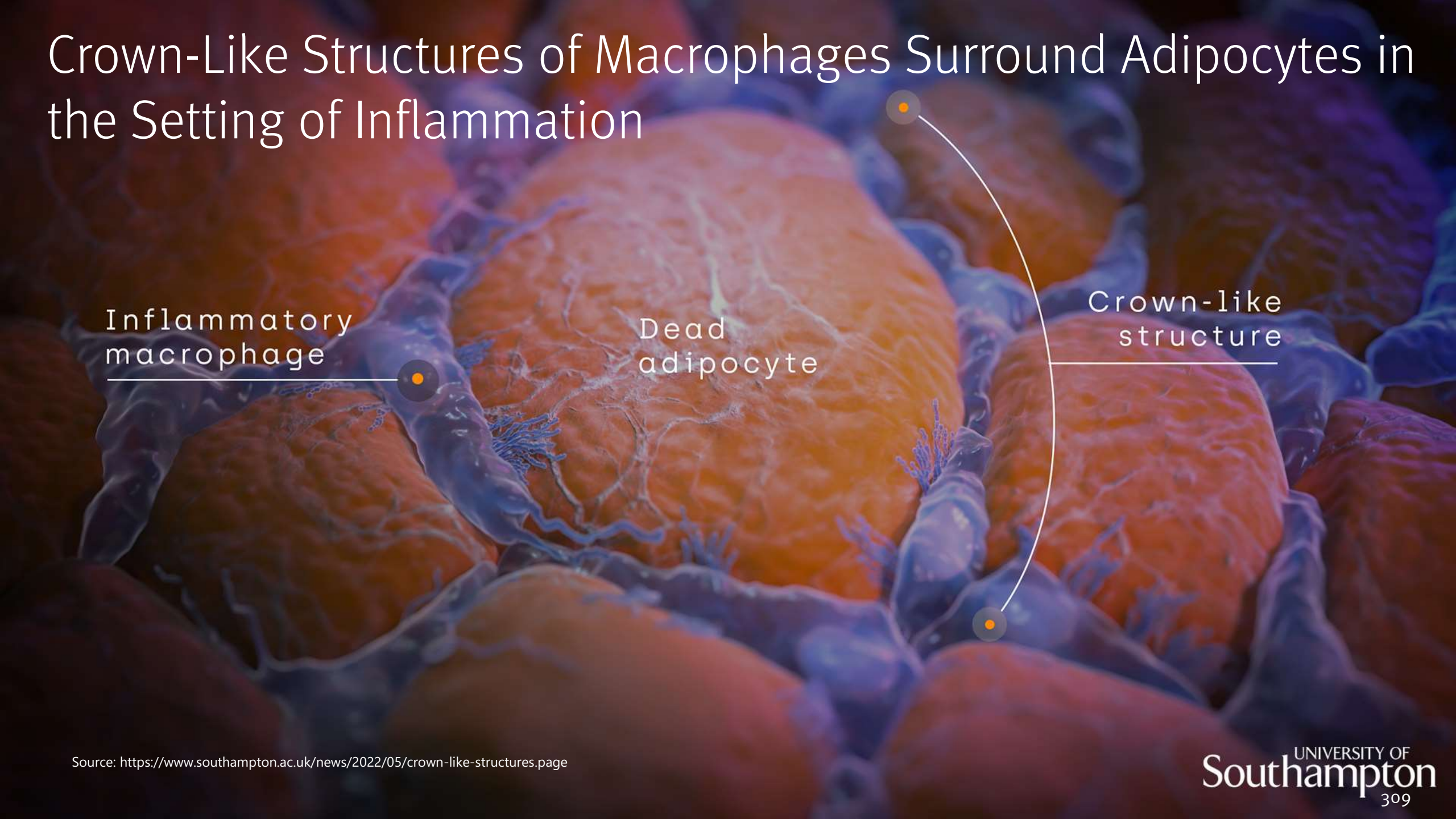
Quail DF, Dannenberg AJ., "The obese adipose tissue microenvironment in cancer development and progression," *Nat Rev Endocrinol.*, March 2019, pp, 139-154.



Source: https://www.nature.com/articles/s41574-018-0126-x

During healthy body-weight conditions (metabolic homeostasis), the adipose tissue microenvironment (ATME) is well-vascularized and rich in anti-inflammatory cytokines (such as IL-4, IL-10 and IL-13), and as a consequence, hosts a variety of type 2 immune cells, including alternatively activated (M2-like) macrophages, group 2 innate lymphoid cells, type 2 T helper (TH2) cells and IL-4-producing eosinophils. In response to body-weight gain or metabolic obesity, adipocytes undergo hyperplasia and hypertrophy; as the vascular supply becomes limited, these cells become stressed or die. This releases damage-associated molecular patterns (DAMP) into the microenvironment, which trigger the infiltration and activation of innate immune cells (for example, dendritic cells, macrophages and granulocytes). These effects promote the development of crown-like structures (CLS) and type 1 (pro-inflammatory) immune responses. This response includes accumulation of type 1 cytokines (for example TNF, IFNγ, IL-1β and IL-6), and pro-inflammatory immune cells, including various granulocytes, group 1 innate lymphoid cells, B cells and CD8+ T cells, which perpetuate chronic inflammatory responses.

Crown-Like Structures of Macrophages Surround Adipocytes in the Setting of Inflammation



Source: https://www.southampton.ac.uk/news/2022/05/crown-like-structures.page

How is Obesity Linked with the Immune System?

de Heredia FP, Gómez-Martínez S, Marcos A. Obesity, inflammation and the immune system. *Proc Nutr Soc.* 2012 May;71(2):332-8.

The link seems to be adipose tissue itself. **There are several connections indeed between adipose tissue and the immune system. For a start, macrophages and lymphocytes can be normally found in the non-adipose fraction of the tissue.** Moreover, white adipocytes have been suggested to share embryonic origin with immune cells, while characterisation of adipose tissue-resident lymphocytes led to the notion that this tissue was an ancestral immune organ. And more recently, immature haematopoietic cells have been found in adipose tissue, hence it has been proposed as a site for formation and maturation of immune cell precursors.

In the early 2000s, histological studies in mice showed that macrophage infiltration in adipose tissue was greater in obese than in lean animals. The **macrophages appeared as crown-shaped aggregates**, similar to those observed in other known inflammatory conditions, such as rheumatoid arthritis, and grew larger with increasing degrees of obesity. This finding led to the idea that macrophage aggregates could partially explain the obesity-related inflammatory state.

In support of this hypothesis, two different phenotypes for adipose tissue-resident macrophages were later described: one that acts as pro-inflammatory (known as M1 or 'classically activated'), and another that acts as anti-inflammatory (M2 or 'alternatively activated'). Interestingly, obesity has been associated with a switch from the M2 to the M1 phenotype; that is, to a more pro-inflammatory profile. Furthermore, the absence of the M2 phenotype has been associated with a higher susceptibility to obesity, inflammation and insulin resistance.

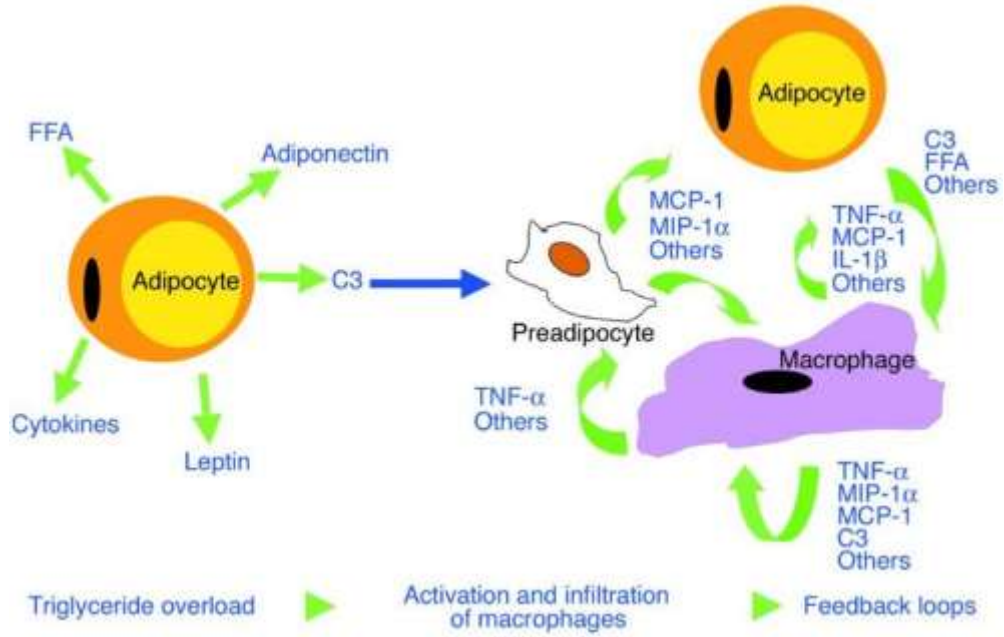
The enhanced macrophage infiltration in the obese adipose tissue explains in part, but not completely, the increased production of cytokines and chemokines. These molecules are mainly produced by immune cells, e.g. monocytes, macrophages and T-lymphocytes, and also by other cells such as mast cells, fibroblasts, endothelial cells, neurons, or adipocytes themselves. Fat cells secrete, among others, TNFα, IL-6, monocyte chemotactic protein 1, transforming growth factor β, or acute phase proteins.

Source: https://pubmed.ncbi.nlm.nih.gov/22429824/

Chronic Inflammation Is a Key Culprit in Insulin Resistance

Xu H, Barnes GT, Yang Q, Tan G, Yang D, Chou CJ, Sole J, Nichols A, Ross JS, Tartaglia LA, Chen H. Chronic inflammation in fat plays a crucial role in the development of obesity-related insulin resistance. J Clin Invest. 2003 Dec;112(12):1821-30.

Insulin resistance arises from the inability of insulin to act normally in regulating nutrient metabolism in peripheral tissues. Increasing evidence from human population studies and animal research has established correlative as well as causative links between chronic inflammation and insulin resistance. However, the underlying molecular pathways are largely unknown. In this report, we show that many inflammation and macrophage-specific genes are dramatically upregulated in white adipose tissue (WAT) in mouse models of genetic and high-fat diet-induced obesity (DIO). The upregulation is progressively increased in WAT of mice with DIO and precedes a dramatic increase in circulating-insulin level. Upon treatment with rosiglitazone, an insulin-sensitizing drug, these macrophage-originated genes are downregulated. Histologically, there is evidence of significant infiltration of macrophages, but not neutrophils and lymphocytes, into WAT of obese mice, with signs of adipocyte lipolysis and formation of multinucleate giant cells. These data suggest that macrophages in WAT play an active role in morbid obesity and that macrophage-related inflammatory activities may contribute to the pathogenesis of obesity-induced insulin resistance. We propose that obesity-related insulin resistance is, at least in part, a chronic inflammatory disease initiated in adipose tissue.



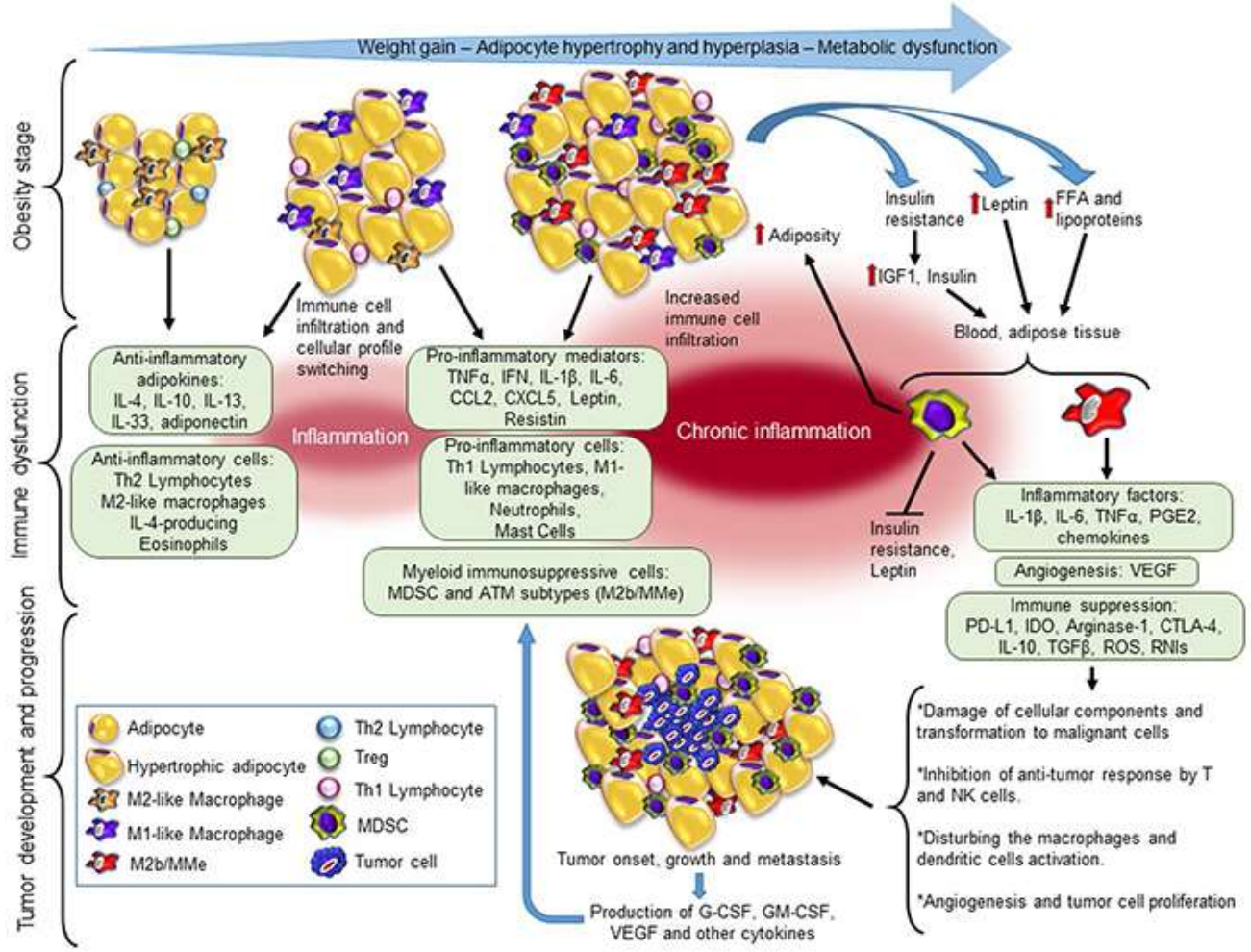
Hypothetical model of chronic inflammation and adipocyte insulin resistance. When adiposity reaches a certain threshold, factors derived from adipocytes induce macrophage activation and infiltration. Activated macrophages secrete cytokines that can impair adipocyte insulin sensitivity and stimulate further activation and infiltration of peripheral monocytes and macrophages into fat. Preadipocytes can also secrete chemokines under the stimulation of TNF-α, which can contribute to macrophage infiltration. These amplifying signals increasingly impair adipocyte insulin signaling and eventually cause systemic insulin resistance.

Source: https://www.jci.org/articles/view/19451

Link Between Obesity, Inflammation and Cancer Runs Through MDSC's

A review study led by Maria D. Sanchez-Pino, PhD, an assistant research professor in the departments of Interdisciplinary Oncology and Genetics at LSU Health New Orleans' School of Medicine …suggest that inflammatory cells with immunosuppressive properties may act as a critical biological link between obesity and cancer risk, progression, and metastasis.

Despite evidence showing that obesity increases the risk of cancer progression, efforts are needed to identify the causal relationship between immunosuppressive cells and the response of immunotherapy in patients with obesity. The function of myeloid cells is shaped by the metabolic microenvironment. Along with macrophages, myeloid cells with immunosuppressive properties called Myeloid-derived suppressor cells (MDSCs) are generated in obesity. One of the major factors associated with the metabolic inflammation of obesity is the expansion of MDSCs. In cancer patients, MDSCs are associated with poor survival and resistance to immunotherapy.



Source: https://www.lsuhsc.edu/newsroom/LSU%20Health%20New%20Orleans%20Describes%20a%20Causal%20Mechanism%20of%20Link%20Between%20Cancer%20and%20Obesity.html

Cancer Link to Obesity is Quite Clear in the Data

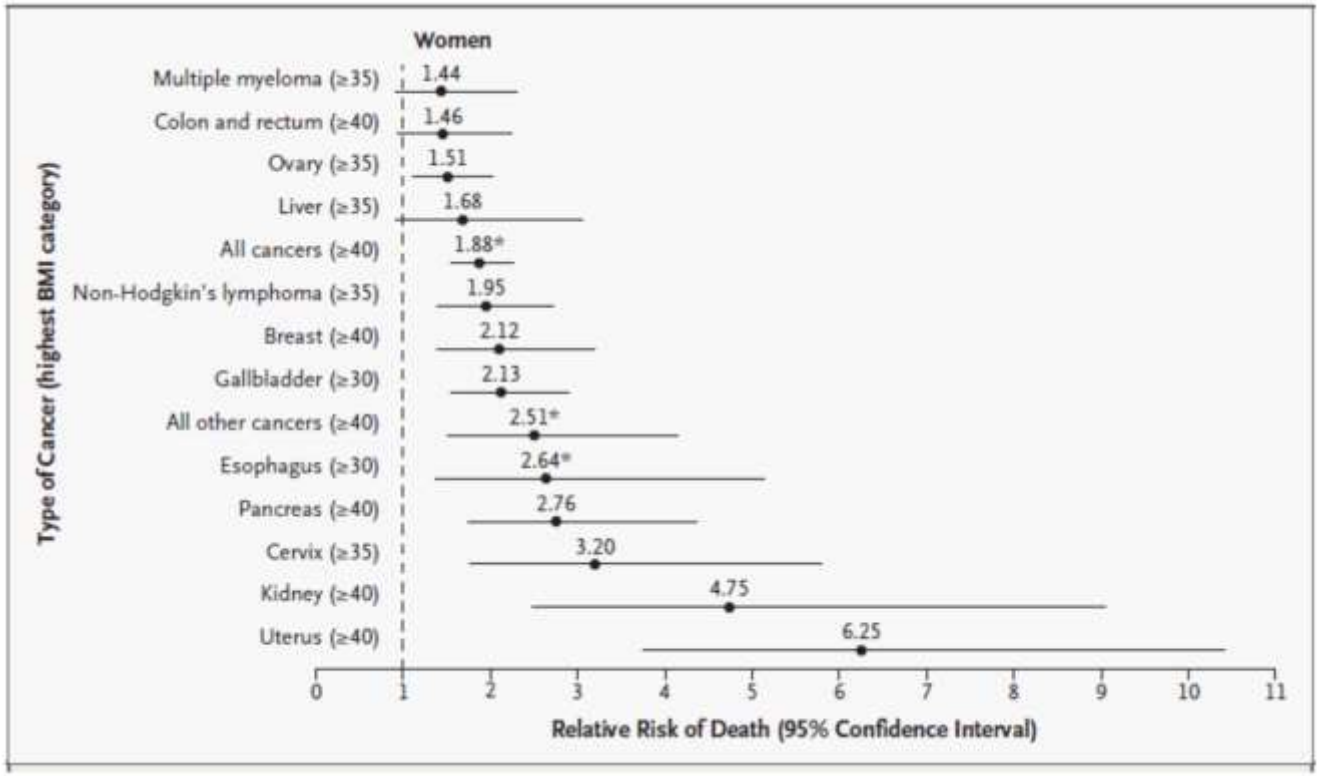
Overweight, Obesity, and Mortality from Cancer in a Prospectively Studied Cohort of U.S. Adults

Authors: Eugenia E. Calle, Ph.D., Carmen Rodriguez, M.D., M.P.H., Kimberly Walker-Thurmond, B.A., and Michael J. Thun, M.D. Author Info & Affiliations

Published April 24, 2003 | N Engl J Med 2003;348:1625-1638 | DOI: 10.1056/NEJMoa021423 | VOL. 348 NO. 17

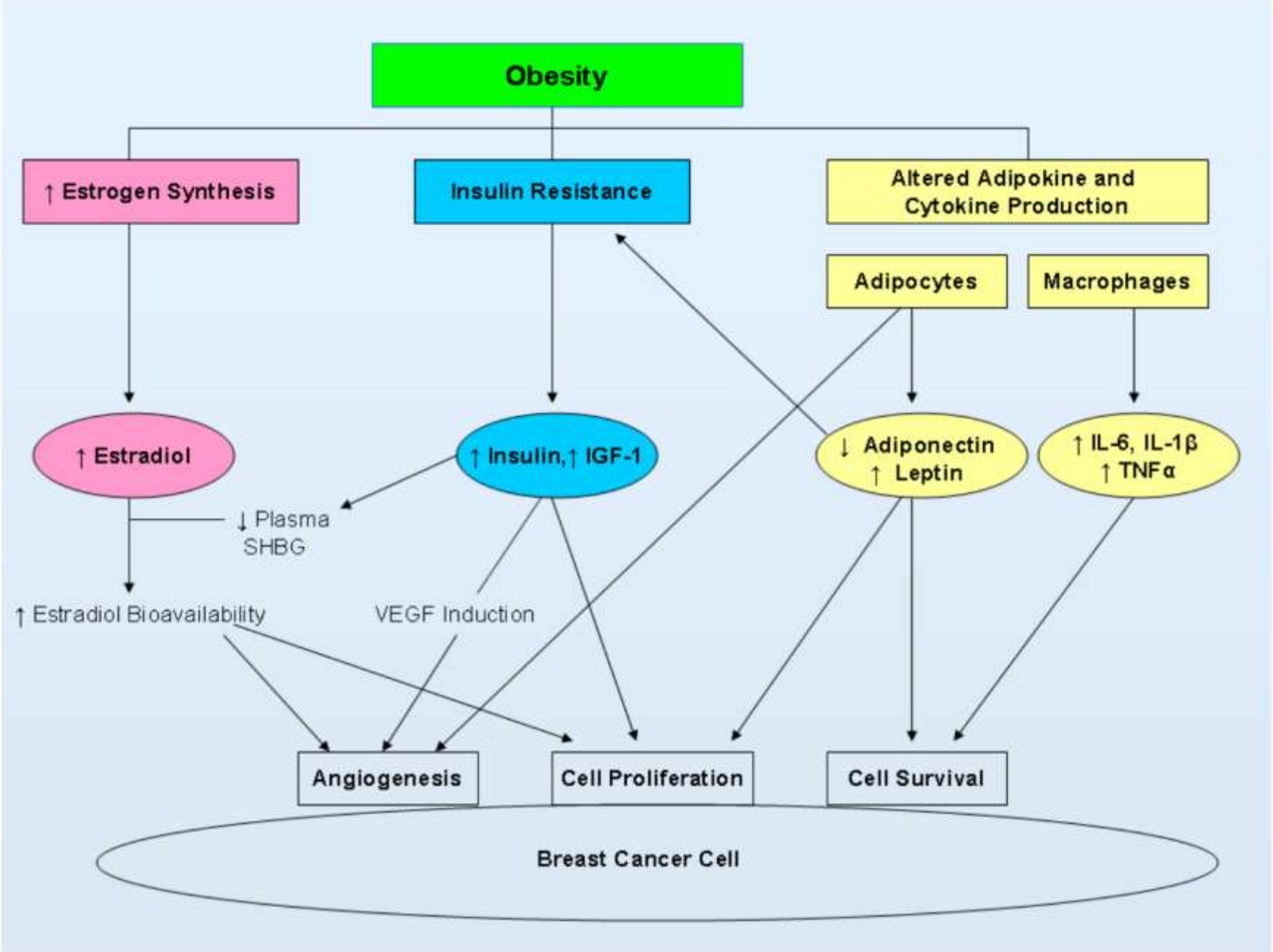
In a prospectively studied population of more than 900,000 U.S. adults (404,576 men and 495,477 women) who were free of cancer at enrollment in 1982, there were 57,145 deaths from cancer during 16 years of follow-up. The heaviest members of this cohort (BMI of at least 40) had death rates from all cancers combined that were 52 percent higher (for men) and 62 percent higher (for women) than the rates in men and women of normal weight. For men, the relative risk of death was 1.52; for women, the relative risk was 1.62. In both men and women, body-mass index was also significantly associated with higher rates of death due to cancer of the esophagus, colon and rectum, liver, gallbladder, pancreas, and kidney; the same was true for death due to non-Hodgkin's lymphoma and multiple myeloma. On the basis of associations observed in this study, **we estimate that current patterns of overweight and obesity in the United States could account for 14 percent of all deaths from cancer in men and 20 percent of those in women.**

Summary of Relative Mortality Risk from Cancer in High Obesity Women in the Cancer Prevention Study II



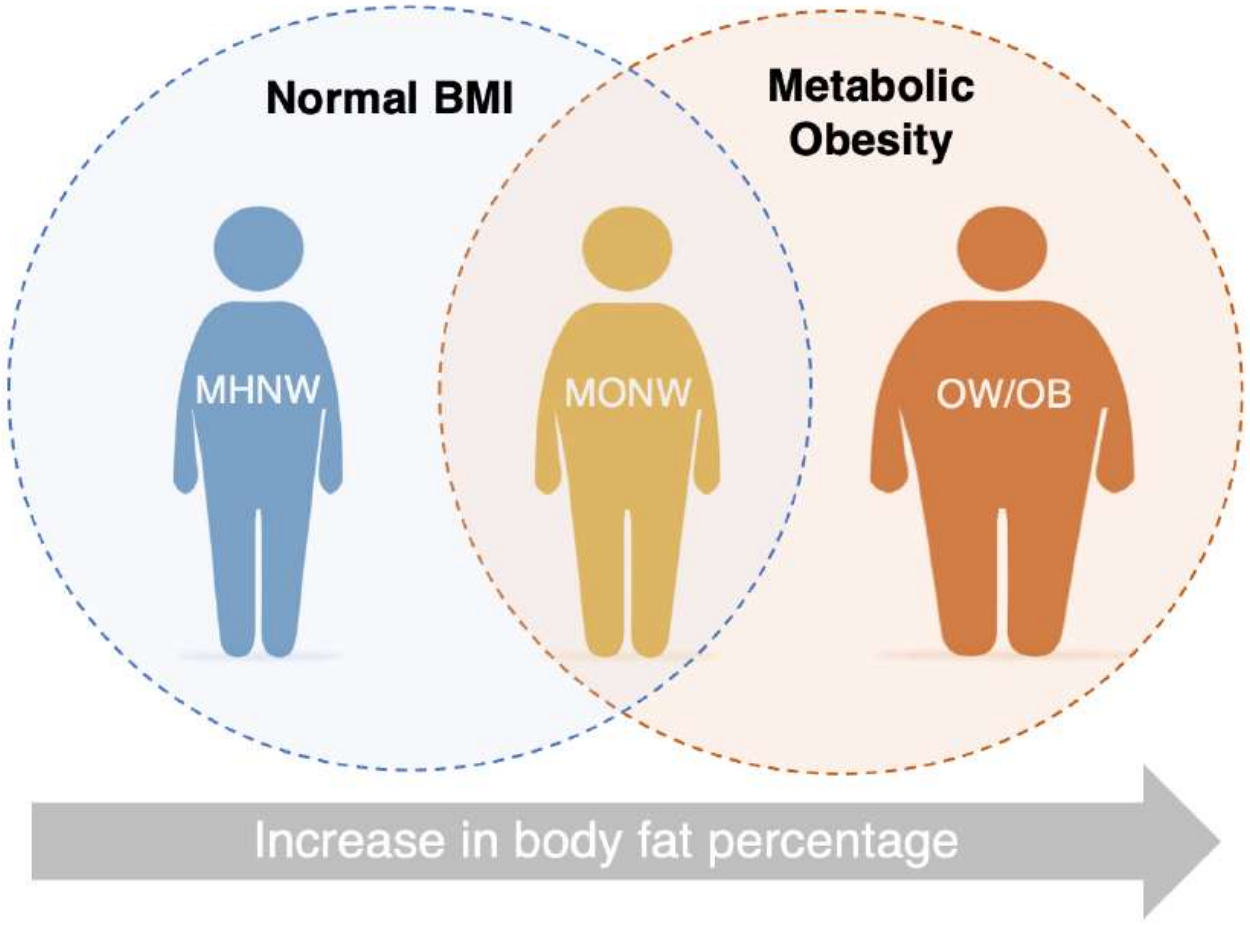
Source: https://www.nejm.org/doi/full/10.1056/NEJMoa021423

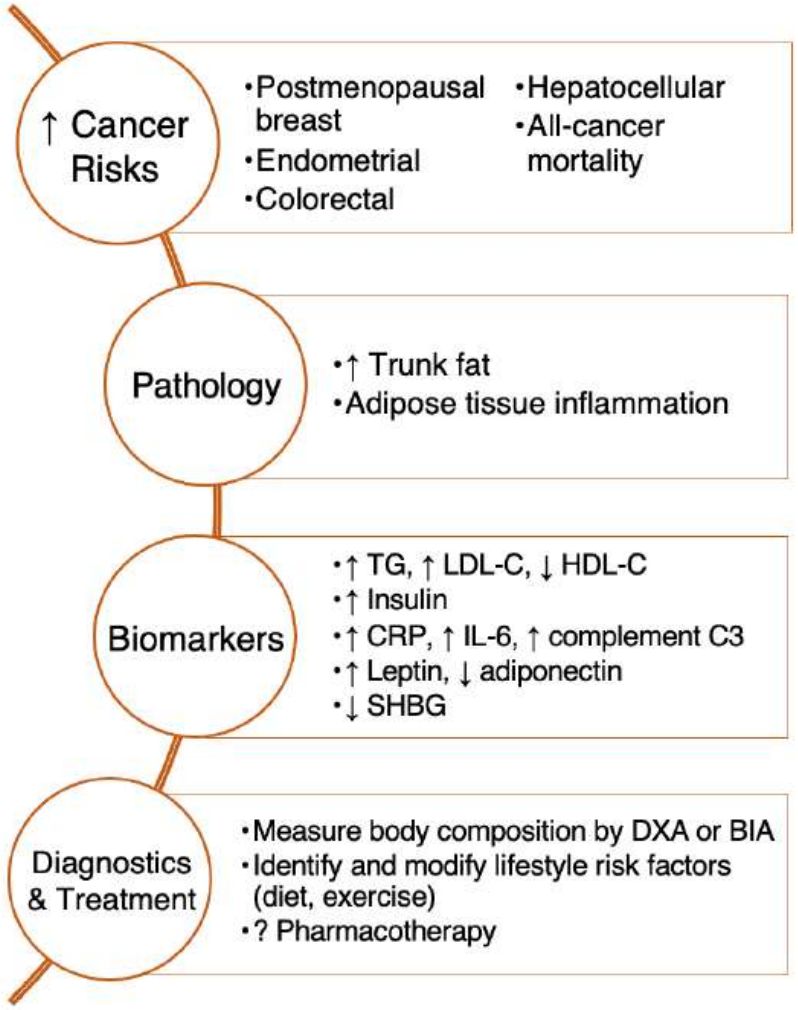
Multiple Pathways Link Obesity to Breast Cancer



Source: Sinicrope FA & Dannenberg AJ. J Clin Oncol 2011

Metabolic Obesity Observed in Those with Normal Weight





Source: Liu B et al. Cancer Prev. Res. 2021.

Link to Breast Cancer Remains in Normal Weight Postmenopausal Women with Excess Body Fat

In the same regard that we saw higher mortality in persons who were insulin resistant but not obese, this paper by Dannenberg and colleagues shows that the risk of cancer is higher in persons with high body fat even if their BMI is normal. This is shown to linked to inflammation. If you will, the primary issue is adipocyte-linked inflammation, not obesity *per se*.

Iyengar NM, Arthur R, Manson JE, Chlebowski RT, Kroenke CH, Peterson L, Cheng TD, Feliciano EC, Lane D, Luo J, Nassir R, Pan K, Wassertheil-Smoller S, Kamensky V, Rohan TE, Dannenberg AJ. Association of Body Fat and Risk of Breast Cancer in Postmenopausal Women With Normal Body Mass Index: A Secondary Analysis of a Randomized Clinical Trial and Observational Study. *JAMA Oncol.* Feb 1, 2019.

Among the 3460 women included in the analysis, multivariable-adjusted hazard ratios for the risk of invasive breast cancer were 1.89 for the highest quartile of whole-body fat and 1.88 for the highest quartile of trunk fat mass. The corresponding adjusted hazard ratios for ER-positive breast cancer were 2.21 and 1.98, respectively. Similar positive associations were observed for serial DXA measurements in time-dependent covariate analyses. Circulating levels of insulin, C-reactive protein, interleukin 6, leptin, and triglycerides were higher, whereas levels of high-density lipoprotein cholesterol and sex hormone–binding globulin were lower in those in the uppermost vs lowest quartiles of trunk fat mass.

Body Fat Measurement	No. of Cases/ Person-Years	HR (95% CI) Age Adjusted	Multivariable Adjusted[b]
Whole-body fat mass, kg			
≤18.7	23/12 384.9	1 [Reference]	1 [Reference]
18.8-22.0	36/12 733.4	1.55 (0.92-2.62)	1.61 (0.95-2.73)
22.1-25.1	39/12 657.1	1.68 (1.00-2.81)	1.80 (1.07-3.03)
>25.1	48/12 816.8	2.06 (1.25-3.39)	2.21 (1.23-3.67)
P value for trend	NA	.004	.002
C statistic (95% CI)	NA	NA	0.671 (0.625-0.716)
Continuous per 5-unit increase	NA	1.31 (1.12-1.54)	1.35 (1.14-1.60)
Whole-body fat, %			
≤33.7	23/12 716.2	1 [Reference]	1 [Reference]
33.8-37.9	43/13 237.4	1.78 (1.07-2.96)	1.87 (1.12-3.12)
38.0-41.3	36/12 600.9	1.56 (0.92-2.63)	1.69 (1.00-2.88)
>41.3	44/12 037.7	1.98 (1.20-3.28)	2.17 (1.29-3.66)
P value for trend	NA	.02	.01
C statistic (95% CI)	NA	NA	0.665 (0.619-0.711)
Continuous per 5-unit increase	NA	1.22 (1.05-1.42)	1.27 (1.08-1.48)
Fat mass of trunk, kg			
≤7.3	24/12 720.9	1 [Reference]	1 [Reference]
7.4-9.3	31/12 858.8	1.27 (0.75-2.17)	1.40 (0.82-2.39)
9.4-11.4	50/12 686.7	2.07 (1.27-3.36)	2.27 (1.38-3.72)
>11.4	41/12 325.9	1.75 (1.06-1.90)	1.98 (1.18-3.31)
P value for trend	NA	.01	.003
C statistic (95% CI)	NA	NA	0.671 (0.625-0.717)
Continuous per 5-unit increase	NA	1.44 (1.11-1.88)	1.56 (1.18-2.06)

Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6439554/

Semaglutide Lowers Inflammation

Yaribeygi H, Maleki M, Jamialahmadi T, Sahebkar A. Anti-inflammatory benefits of semaglutide: State of the art. J Clin Transl Endocrinol. 2024 Mar 28;36:100340

Semaglutide not only lowers glucose but also shows potential anti-inflammatory effects. Studies suggest it can modulate inflammatory responses and benefit those with diabetes. However, the exact mechanisms of its anti-inflammatory effects are not fully understood.

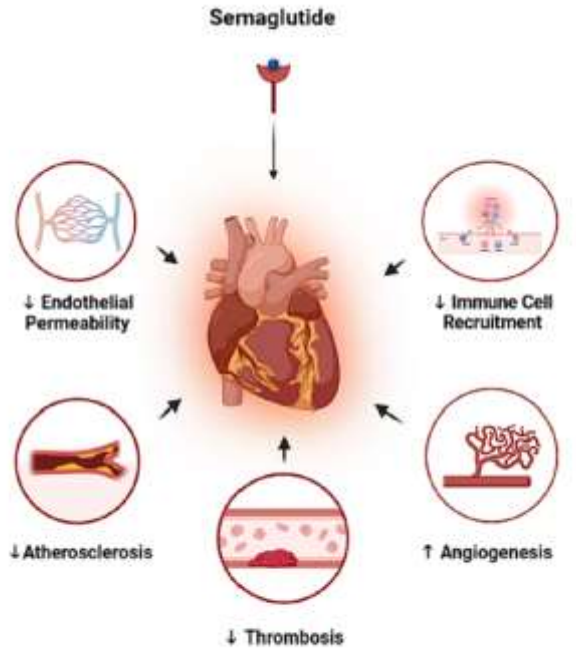


Fig. 2. Semaglutide improves cardiovascular function by its anti-inflammatory benefits thru several mechanisms. It can preserves endothelial permeability, reduce immune cells recruitment into heart tissues, decrease atherosclerotic and thrombotic processes and induce angiogenesis in myocardium.

Table 3
Experimental studies suggesting anti-inflammatory properties of semaglutide (TNF-α = tumor necrosis factor alpha, IL-6 = interleukin-, Nf-κB = nuclear factor kappa b, NLRP3 = NLR family pyrin domain containing 3 inflammasome, MAPK = mitogen activated protein kinase, c-Jun = transcription factor Jun).

Effects	Model	Treatment	Ref.
Reduced the TNF-α, IL-6 and Nf-κB signalings	LPS-induced lung injury in rats	Semaglutide	[73]
Blocked the NLRP3 activity	PTT-induced seizure in C57/BL6J mouse	Semaglutide	[70]
Reduced the TNF-α, IL-6, and IL-1β levels in brain tissues	Endo-toxemia in male Swiss albino mice	Semaglutide	[72]
Reduced p38 MAPK, c-Jun- NF-κB p65 inflammation signaling pathway in brain tissues	Animal model of seizure	Semaglutide	[71]
Reduced intramuscular fat and improved muscle function by lowering the, TNF-α, IL-6, IL-1β levels	Male C57BL/6 mice	Semaglutide	[78]
Declined TNF-α, and IL-6 serum and heart tissues	Obese mouse	Semaglutide	[62]
Decreased vascular inflammation and micro-calcifications	Obese rabbit	Semaglutide	[79]
Attenuated inflammatory markers and improved cardiac function	Obese mice	Semaglutide	[80]

Table 4
Clinical or human evidences explored anti-inflammatory effects of semaglutide (CKD = chronic kidney disease, hsCRP = high-sensitive C-reactive protein).

Treatment	Patients/ samples	Dose/ duration	Effects	Ref.
Semaglutide	40 men with DM	1 mg/week/6 months/ injection	Reduced the inflammatory cytokines of TNF-α and IL-6	[63]
Semaglutide	20 patients with T2DM	1 mg/week/3 months/ injection	Minor changes in some inflammatory cytokines (not meaningful) e.g. CRP and IL-6	[64]
Semaglutide	Patients with T2DM	–	Semaglutide is associated to reduced levels of hsCRP vs baseline in patients with T2DM	[74]
Semaglutide	Obese patients with T2DM	0.25 mg/week for 4 weeks, increased to 0.50 mg/week for 16 weeks, and then to 1 mg/week for 10 months	Semaglutide improved psoriasis and epicardial fat volume and inflammation	[89]
Semaglutide	Patients with T2DM and CKD	3 mg/day/ 9months/orally	Semaglutide improved renal function probably by lowering inflammation	[65]
Semaglutide	Epicardial fat biopsies of patients undergoing open-heart surgery	–	Semaglutide reduced the neutrophils adhesion into endothelial cells and enhances the angiogenesis process	[67]
Semaglutide	Epicardial fat biopsies of patients undergoing cardiac surgery	–	Semaglutide induced anti-thrombotic and anti-atherosclerotic effects by suppressing neutrophils' activity	[87]

Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10992717/

Lilly's Retatrutide Shows Good Performance on Inflammatory Biomarkers

Inflammatory Marker at Week 48, Percent Change from Baseline: Study 1 - OB						
Total Population		PBO	RETA 1 mg	RETA 4 mg	RETA 8 mg	RETA 12mg
	N	56	58	57	60	50
hsCRP, mg/L	% CFB	-7.9 (-24.8, 12.8)	-31.3$^{\#\#\#*}$ (-43.4, -16. 6)	-38.6$^{\#\#\#**}$ (-49.5, -25.3)	-54.8$^{\#\#\#***}$ (-62. 6, -45.4)	-53.2$^{\#\#\#***}$ (-62.1, -42.1)
IL-6, pg/mL	% CFB	-2.1 (-16.2, 14.4)	-13.1 (-24.9, 0.4)	-18.5$^{\#\#}$ (-29.8, -5.4)	-29.6$^{\#\#\#**}$ (-39.0, -18.7)	-21.8$^{\#\#}$ (-33.6, -7.9)
Adiponectin, mg/L	% CFB	11.1$^{\#}$ (0.5, 22.8)	19.4$^{\#\#\#}$ (8.5, 31.5)	45.7$^{\#\#\#***}$ (32.3, 60.4)	71.1$^{\#\#\#***}$ (55.8, 88.0)	56.9$^{\#\#\#***}$ (41.1, 74.4)
Leptin, ng/mL	% CFB	-27.7$^{\#}$ (-46.2, -2.8)	-22.6 (-41.5, 2.4)	-58.0$^{\#\#\#***}$ (-68.3, -44.4)	-68.8$^{\#\#\#***}$ (-76.3, -59.0)	-72.2$^{\#\#\#***}$ (-79.6, -62.1)
Inflammatory Marker at Week 36, Percent Change from Baseline: Study 2 – T2D						
Total Population		PBO	RETA 0.5 mg	RETA 4 mg	RETA 8 mg	RETA 12 mg	DU 1.5 mg
	N	32	39	37	40	32	40
hsCRP, mg/L	% CFB	-15.7 (-35.9, 10.9)	-24.4$^{\#}$ (-41.1, -2.8)	-37.8$^{\#\#\#}$ (-51.7, -19.8)	-33.2$^{\#\#}$ (-47.6, -14.8)	-40.7$^{\#\#\#}$ (-55.1, -21.7)	-21.0 (-38.2, 0.9)
IL-6, pg/mL	% CFB	-13.9 (-35.7, 15.1)	11.8 (-13.2, 44.0)	-24.4$^{\#}$ (-41.7, -2.0)	-29.5$^{\#\#}$ (-44.8, -10.0)	-15.8 (-36.4, 11.4)	-1.4 (-23.2, 26.7)
Adiponectin, mg/L	% CFB	24.7$^{\#\#\#}$ (10.1, 41.3)	11.4 (-0.2, 24.2)	23.6$^{\#\#\#}$ (10.8, 37.9)	56.7$^{\#\#\#**}$ (40.7, 74.4)	41.3$^{\#\#\#}$ (24.9, 59.9)	5.0* (-5.5, 16.5)
Leptin, ng/mL	% CFB	-11.7 (-32.1, 14.8)	-18.2 (-34.6, 2.5)	-23.4$^{\#}$ (-39.8, -2.5)	-52.9$^{\#\#\#***}$ (-62.2, -41.3)	-47.2$^{\#\#\#**}$ (-59.2, -31.7)	10.6 (-12.0, 39.0)

Data are LSM and SE for baseline and LSM (95% CI) percent change from baseline at the treatment end time point.
PBO, placebo; RETA, retatrutide; CFB, change from baseline; DU, dulaglutide.
$^{\#}$p <0.05, $^{\#\#}$p <0.01, $^{\#\#\#}$p <0.001 vs baseline; *p <0.05, **p <0.01, ***p <0.001 vs PBO.

Source: 60th Annual Meeting, European Association for the Study of Diabetes, Conference Website.

GIP Inhibitors are a Viable Strategy to Limit Obesogenic Inflammation and Insulin Resistance

Relevance and consequence of chronic inflammation for obesity development

Lisa Ruck[1,2*], Susanna Wiegand[3] and Peter Kühnen[1] *Molecular and Cellular Pediatrics* (2023) 10:16

Gut-derived hormones such as glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide 1 (GLP-1) also contribute to the development and mitigation of inflammation within the whole body including the hypothalamus (Fig. 7). Studies have demonstrated that GIP is associated with increased expression of pro-inflammatory cytokines and chemokines, while GIP infusion induces elevated levels of adipokines and pro-inflammatory cytokines in adipocytes in vitro. Centrally administered GIP leads to an increase in pro-inflammatory cytokines and factors such as Il-6 and Socs3 in the hypothalamus in mice, diminishes the anorectic effects of insulin in the brain and attenuates the impact of leptin, resulting in leptin resistance. Loss of GIP action is therefore associated with a better outcome in diabetes and resistance towards DIO in mice, but contradictory a transgenic overexpression of GIP also promotes resistance to DIO and leads to a reduced fat mass in mice. Genetic elimination of GIP or its receptor in mice has yielded long-term metabolic protection against diet-induced obesity and insulin resistance.

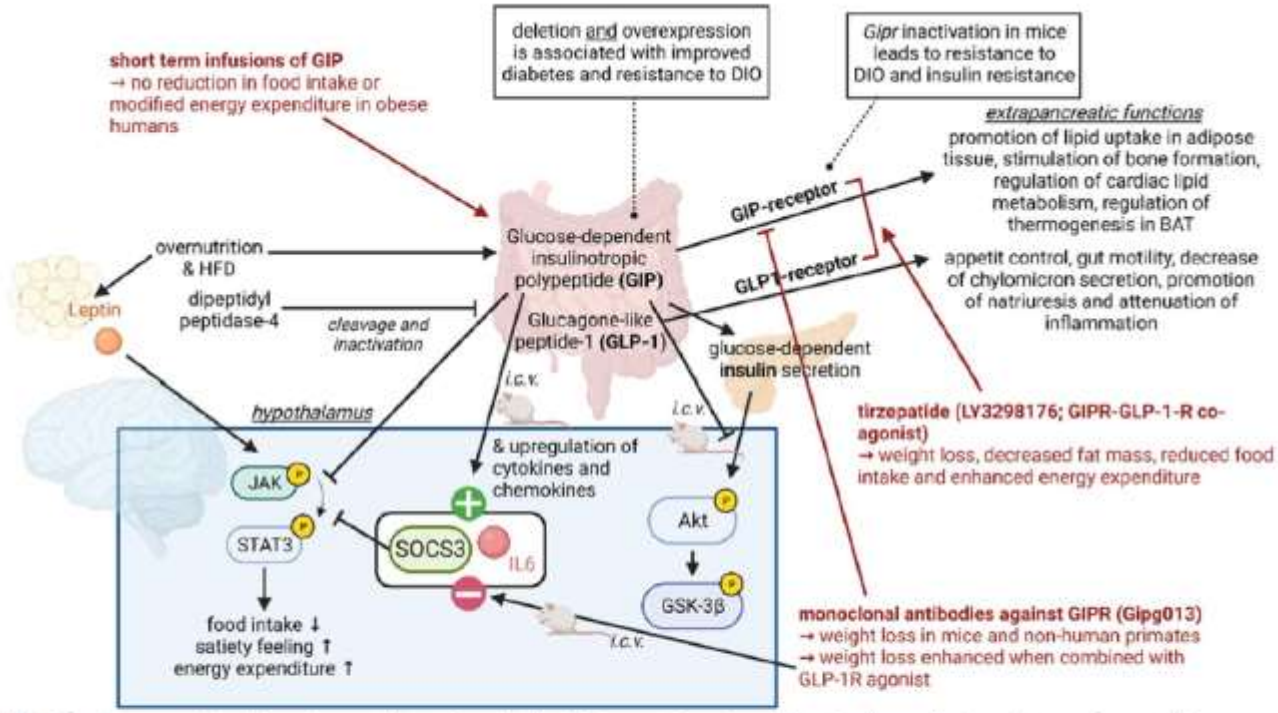


Fig. 7 Gut hormone-derived incretins contribute to hypothalamic inflammation and modulate insulin- and leptin-resistance. Over-nutrition activates GIP production in the gut, which in turn activates glucose-dependent insulin secretion in the pancreas and also exhibits extra-pancreatic functions. Interestingly, in mice, it has been shown that deletion and overexpression of GIP is associated with improved diabetes and resistance to DIO. Centrally administered GIP leads to a reduction of JAK-STAT-activation and therefore diminishes leptin activity in the hypothalamus and upregulates SOCS3 and IL-6 in mice. Concordantly, intracerebral application of monoclonal antibodies against GIPR leads to a suppression of SOCS3 and IL-6 and induces weight loss in mice and non-human primates. This effect is enhanced when combined with GLP-1R agonist. Paradoxically, the GIPR-GLP-1R co-agonist also leads to weight loss, reduced food intake, and a decrease in fat mass. These incretins and their receptors propose immense pharmacological potential in targeting DIO and its co-morbidities

Source: Sinicrope FA & Dannenberg AJ. J Clin Oncol 2011

Peripheral CB1 Inverse Agonists Associated with Control of Inflammation

Han JH, Kim W. Peripheral CB1R as a modulator of metabolic inflammation. FASEB J. 2021 Apr;35(4):e21232.

Obesity is associated with chronic inflammation in insulin-sensitive tissues, including liver and adipose tissue, and causes hormonal/metabolic complications, such as insulin resistance. There is growing evidence that peripheral cannabinoid-type 1 receptor (CB1R) is a crucial participant in obesity-induced pro-inflammatory responses in insulin-target tissues, and its selective targeting could be a novel therapeutic strategy to break the link between insulin resistance and metabolic inflammation. In this review, we introduce the role of peripheral CB1R in metabolic inflammation and as a mediator of hormonal/metabolic complications that underlie metabolic syndrome, including fatty liver, insulin resistance, and dyslipidemia. We also discuss the therapeutic potential of second- and third-generation peripherally restricted CB1R antagonists for treating obesity-induced metabolic inflammation without eliciting central CB1R-mediated neurobehavioral effects, predictive of neuropsychiatric side effects, in humans.

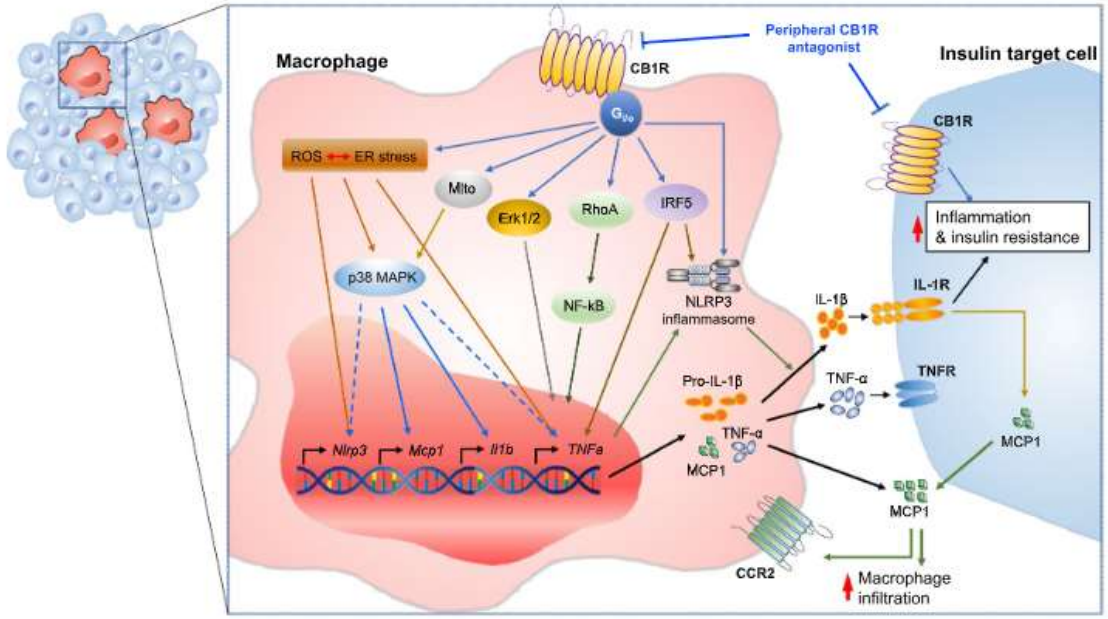
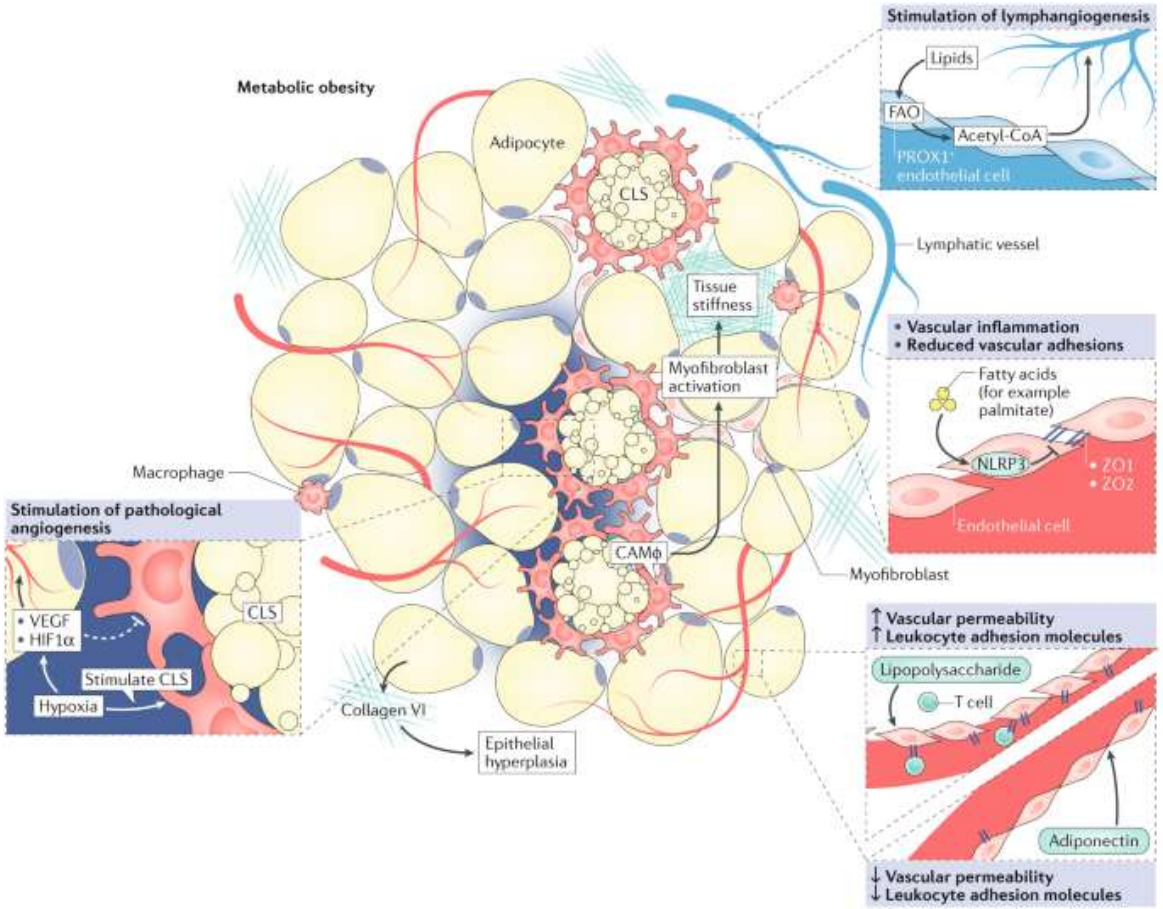


FIGURE 1 A model for peripheral CB1R-mediated pro-inflammatory responses in insulin-target tissues. CB1Rs are present on peripheral insulin-target tissues as well as pro-inflammatory macrophages, where their activation promotes macrophage infiltration and the production of pro-inflammatory cytokines and chemokines via downstream signaling pathways involving Gi/o protein, ER stress, ROS generation, and the NLRP3 inflammasome, leading to obesity-induced metabolic inflammation and insulin resistance

Source: https://faseb.onlinelibrary.wiley.com/doi/epdf/10.1096/fj.202001960R

Inflammation in Adipocyte Microenvironment Can Also Lead to Fibrosis

Quail DF, Dannenberg AJ., "The obese adipose tissue microenvironment in cancer development and progression," *Nat Rev Endocrinol.*, March 2019, pp, 139-154.



During obesity, adipose tissue expands rapidly, leading to high demand for a vascular supply. Similar to a growing tumour, this effect results in regions where vascular supply is insufficient, creating areas of hypoxia. Hypoxia triggers angiogenesis through induction of pro-angiogenic factors (such as vascular endothelial growth factor (VEGF) and hypoxia-inducible factor 1α (HIF1α)); however, resulting blood vessels are poorly functional, and thus low oxygen levels persist. Chronic hypoxia eventually contributes to adipocyte death, and supports the formation of crown-like structures (CLS). Vascular integrity is in part reduced by downregulation of endothelial adhesions (such as zonula occludens 1 (ZO1) and ZO2) in response to obesity-derived factors (for example, lipopolysaccharide and palmitate), while leukocyte adhesion molecules are increased to facilitate infiltration of immune cells (such as T cells). Adiponectin can reverse these effects and improve vascular integrity. In addition, prospero homeobox protein 1 (PROX1)+ lymphatic endothelial cells use lipids to stimulate lymphangiogenesis through fatty acid oxidation (FAO) and production of acetyl-CoA. The extracellular matrix is also aberrant; CLS-associated macrophages (CAMϕ) and myofibroblasts contribute to increased tissue stiffness in the obese adipose tissue microenvironment, and adipocytes produce high levels of collagen VI, which further support adipocyte hyperplasia.

Source: https://www.nature.com/articles/s41574-018-0126-x

Claudin1 Upregulated in Adipocytes Among the Obese

Fernández-García et.al., "Claudin-1 as a novel target gene induced in obesity and associated to inflammation, fibrosis, and cell differentiation," *Eur J Endocrinol.* Mar 2, 2024,.pp. 201-210

T lymphocytes from visceral and subcutaneous white adipose tissues (vWAT and sWAT, respectively) can have opposing roles in the systemic metabolic changes associated with obesity. However, few studies have focused on this subject. Claudin-1 (CLDN1) is a protein involved canonically in tight junctions and tissue paracellular permeability. We evaluated T-lymphocyte gene expression in vWAT and sWAT and in the whole adipose depots in human samples.

A Clariom D-based transcriptomic analysis was performed on T lymphocytes magnetically separated from vWAT and sWAT from patients with obesity (Cohort 1; N = 11). We observed transcriptional differences between T lymphocytes from sWAT compared with vWAT. Specifically, CLDN1 expression was found to be dramatically induced in vWAT T cells relative to those isolated from sWAT in patients with obesity. CLDN1 was also induced in obesity in vWAT and its expression correlates with genes involved in inflammation, fibrosis, and adipogenesis. **This protein may have a crucial role in the crosstalk between T lymphocytes and other adipose tissue cells and may contribute to inflammation, fibrosis, and alter homeostasis and promote metabolic disease in obesity.**

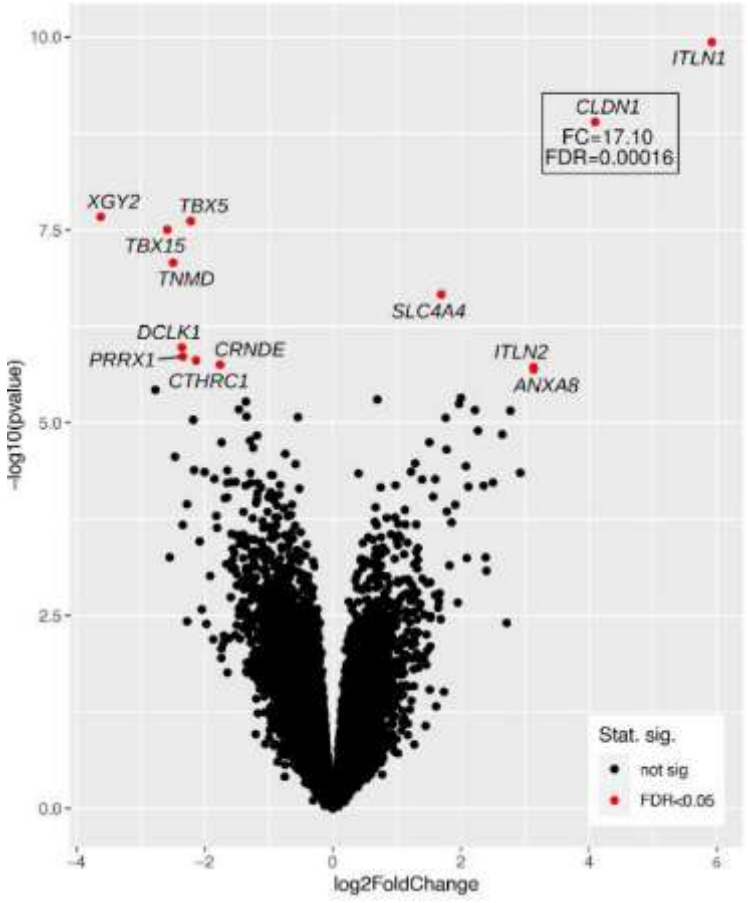


Figure 1. Transcriptomics of T cells infiltrated in WAT from individuals with obesity showed *CLDN1* as a gene modulated in a depot-dependent manner. Volcano plot showing significantly (red) and non-significantly regulated (black) transcripts using Limma statistics in Cohort 1 data set (CLDN1 fold change and FDR values shown in inset box)

Alentis THERAPEUTICS

The Swiss company Alentis is in Phase 1b development of a promising Claudin1 antibody.

Source: https://academic.oup.com/ejendo/article-abstract/190/3/201/7610964

Claudin1 is Induced in T-Cell Infiltrates in Obese Persons

European Journal of Endocrinology, 2024, Vol. 190, No. 3

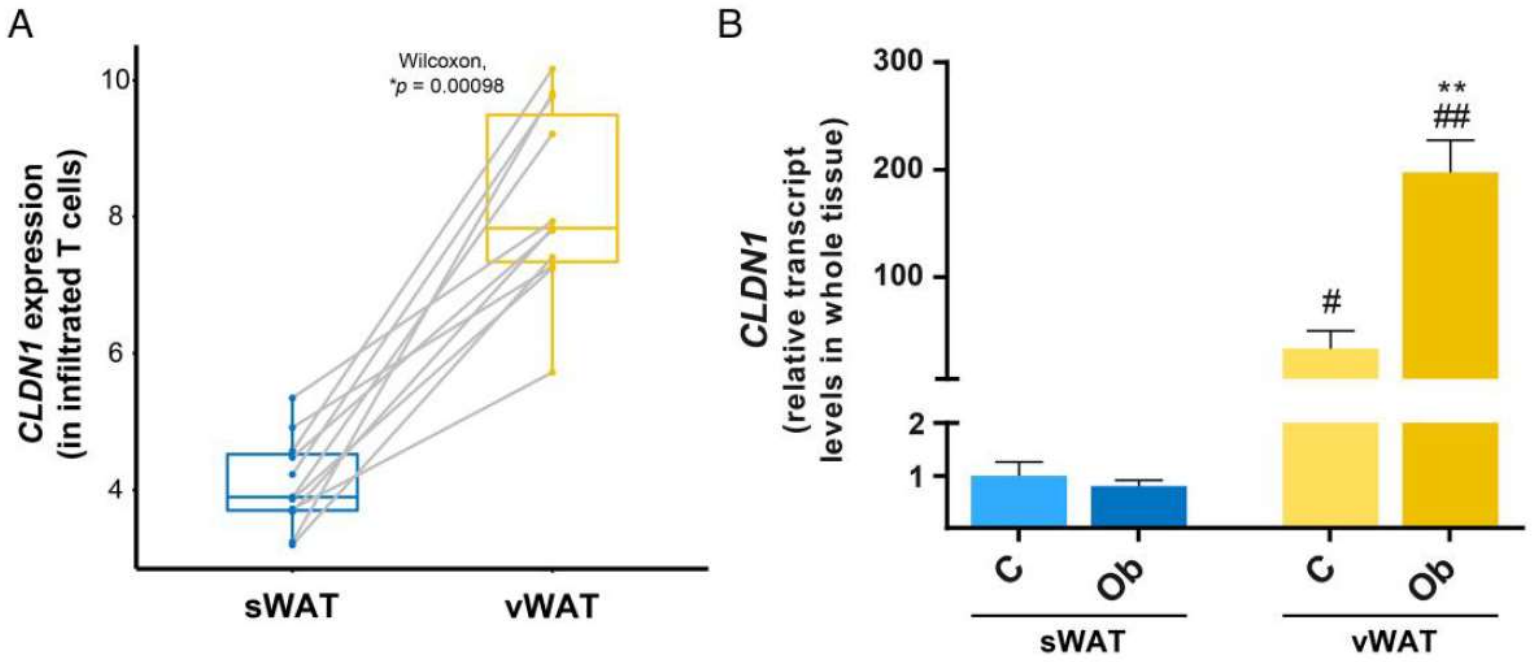


Figure 2. *CLDN1* is induced in obesity, and its expression levels are higher in T lymphocytes infiltrated in vWAT as compared with sWAT. (A) mRNA expression of C*LDN1* in T cells from vWAT compared with those infiltrated in sWAT in patients with obesity. After normality assessment, a paired data (Wilcoxon) test was used to assess statistically significant ($P < .05$) differences. The boxplot depicts the median, interquartile range, and maximum/minimum values and gray lines indicate intra-individual matching. (B) mRNA levels of *CLDN1* in whole adipose tissue from patients with severe obesity compared with controls. A *t*-test was used to assess statistical differences. Error bars indicate means ± SEM. $^{*}P < .05$ and $^{**}P < .01$ obesity vs control group in vWAT; $^{\#}P < .05$ and $^{\#\#}P < .01$ vWAT vs sWAT. sWAT, subcutaneous white adipose tissue; vWAT, visceral white adipose tissue.

Source: https://academic.oup.com/ejendo/article-abstract/190/3/201/7610964

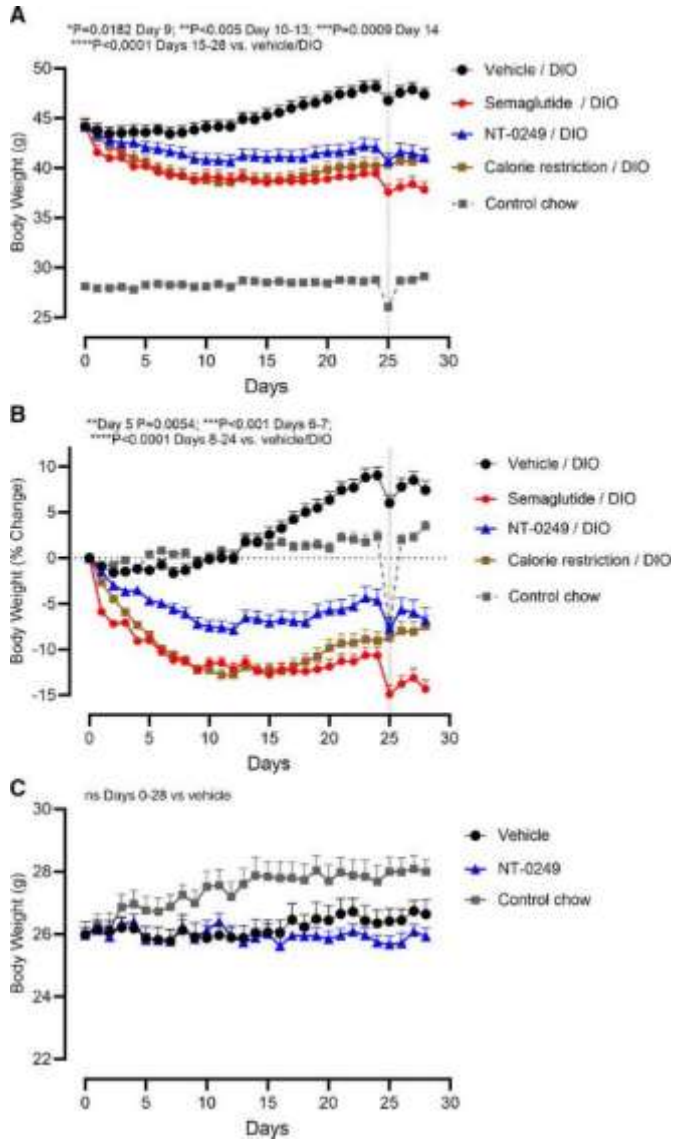
Nodthera: Brain-Penetrant NLRP3 Inhibitors are an Interesting Strategy to Overcome Obesity-Linked Inflammation

Reversal of High Fat Diet-Induced Obesity, Systemic Inflammation, and Astrogliosis by the NLRP3 Inflammasome Inhibitors NT-0249 and NT-0796

Peter Thornton, Valérie Reader, Zsofia Digby, Pamela Smolak, Nicola Lindsay, David Harrison, Nick Clarke, and Alan P. Watt

Journal of Pharmacology and Experimental Therapeutics March 2024, 388 (3) 813-826; DOI: https://doi.org/10.1124/jpet.123.002013

Systemic and cerebral inflammatory responses are implicated in the pathogenesis of obesity and associated metabolic impairment. While the NOD-, LRR-, and pyrin domain-containing protein 3 (NLRP3) inflammasome has been linked to obesity-associated inflammation, whether it contributes to the development or maintenance of obesity is unknown. We provide support for a direct role of saturated fatty acids, such as palmitic acid, as NLRP3 activating stimuli in obese states. To investigate whether NLRP3 activation contributes to the pathogenesis of diet-induced obesity (DIO) in mice, we tested two different clinical-stage NLRP3 inflammasome inhibitors. We demonstrate a contributory role of this key inflammasome to established obesity and associated systemic and cerebral inflammation. By comparing their effects to calorie restriction, we aimed to identify specific NLRP3-sensitive mechanisms contributing to obesity-induced inflammation (as opposed to be those regulated by weight loss per se). In addition, a direct comparison of an NLRP3 inhibitor to a GLP-1 receptor agonist, semaglutide (Wegovy®), in the DIO model allowed an appreciation of the relative efficacy of these two therapeutic strategies on obesity, its associated systemic inflammatory response and cerebral gliosis. We show that two structurally-distinct, NLRP3 inhibitors, NT-0249 and NT-0796, reverse obesity in the DIO mouse model and that brain exposure appears necessary for efficacy.



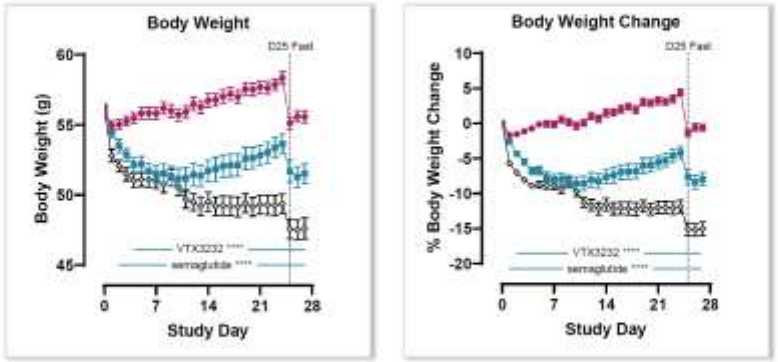
Effects of NT-0249, semaglutide, or calorie restriction on body weights in DIO or control mice. (A) Body weight of normal chow fed mice or DIO mice treated therapeutically with vehicle (by mouth, three times a day), NT-0249 (100 mg/kg by mouth, three times a day), or semaglutide (0.01 mg/kg s.c., every day) for 28 days.

Source: https://jpet.aspetjournals.org/content/388/3/813

Ventyx Also Pursuing a Brain-Penetrant NLRP3 Inhibitor for Weight Loss

Study 1

VTX3232 Reduces Body Weight in DIO Mouse Model

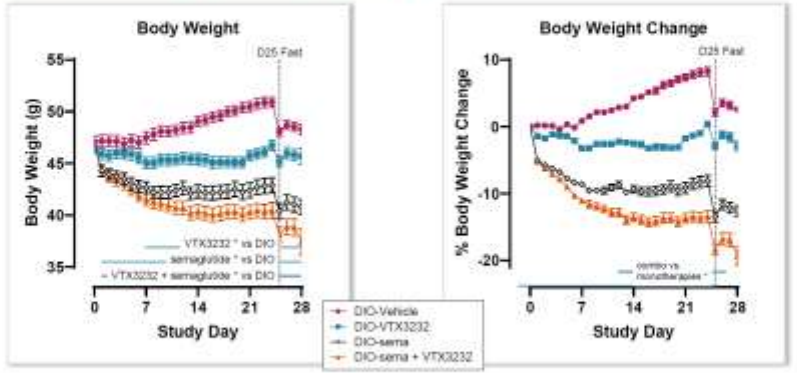


VTX3232 decreases body weight by 5g (~9%) vs. DIO Vehicle

Study 2

VTX3232 + Semaglutide Combo Shows Greater Body Weight Change (%) than Semaglutide Alone

VTX3232 Remains Effective as Monotherapy in Study 2

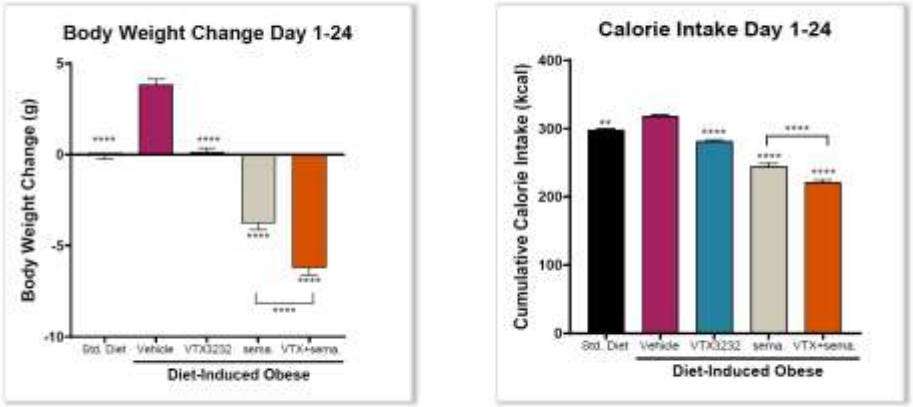


VTX3232[1] and semaglutide[2] combination decreases body weight by 10.5g (~22%) vs. vehicle

Study 2

VTX3232 + Semaglutide Combo Shows Greater Reduction in Body Weight Gain and Caloric Intake Relative to Semaglutide Alone

VTX3232 Remains Effective as Monotherapy in Study 2



VTX3232 and semaglutide combination suppresses BWG and food intake more than either monotherapy

Looking Beyond Mice: Studies with VTX3232 in Obese Participants

- **Proof-of-concept Phase 2a trial in participants with obesity expected to initiate in H2 2024**
  - Endpoints include biomarkers of inflammation (hsCRP, IL-1β, IL-18, IL-6, SAA) and cardiometabolic readouts (lipids, glycemic measurements)
  - Assess potential impact on body weight in a short-duration study
  - Topline results expected in **H1 2025**
- **Planning longer Phase 2 trial for initiation H1 2025**
  - 12-week trial of VTX3232 in participants with obesity
  - Primary endpoint: weight loss with VTX3232
  - Potential to include a combination arm with a GLP-1R agonist
  - Inflammation and cardiometabolic biomarkers

VTX3232 Proposed Phase 2a Trial in Obese Participants*

Source: https://ir.ventyxbio.com/static-files/53fbbof3-d8f7-4151-a18e-43bcf6b4bbd7

NLRP3 Value Proposition Interesting But Unproven in Humans

There has been an upwelling of investor interest in NLRP3 inhibitors for obesity management following Nodthera's recent disclosures. Companies developing brain penetrant molecules include:

BIOAGE JT nodthera ventyx BIOSCIENCES NOVARTIS Roche

An important question raised in Nodthera's recent paper is whether brain exposure is necessary to achieve weight loss. They argue that it is based on mouse experiments.

This creates an intriguing and interesting value proposition for obesity treatment and the mouse data from Nodthera and Ventyx are quite promising.

Several factors deserve consideration in this context.

First, there are well-known gain-of-function and loss-of-function mutations that can over activate or disable NLRP3 function. These are not known to be associated with differential weight in general. Anecdotal evidence associates gain-of-function mutations in NLRP3/NLRC4 with lower weight (not higher weight).

Second, the type of inflammatory processes described in this subsection involve macrophage attack on adipocytes. This is a *local* process – not a central one.* Macrophage activation of pathogenic bacteria and/or cells classically happens without central or neural access.

On the other hand, microglial activation happens in the brain and could only be impacted by a brain penetrant NLRP3 inhibitor, Arguably, be that there is a separate inflammatory process in the brain that impacts eating behavior. Empirical data in man will be highly relevant in this setting.

* https://www.nature.com/articles/s41574-018-0126-x

NLRP3-Inflammasome Inhibition Prevents High Fat and High Sugar Diets-induced Heart Damage Through Autophagy Induction

Pavillard LE et.al., *Oncotarget*. Sep 8, 2017, pp. 99740-99756.

The NLRP3-inflammasome complex has emerged as an important component of inflammatory processes in metabolic dysfunction induced by high-caloric diets. In this study, we investigate the molecular mechanisms by which NLRP3 inhibition may attenuate diet-induced cardiac injury. Here we show the cardiac damage induced by high sugar diet (HSD), high fat diet (HFD) or high sugar/fat diet (HSFD) over 15 weeks. Genetic ablation of NLRP3 protected against this damage by autophagy induction and apoptotic control. Furthermore, NLRP3 inhibition by the selective small molecule MCC950 resulted in similar autophagy induction and apoptotic control in hearts after diets. These data were reproduced in THP-1 cells treated with MCC950 and cultured in media supplemented with serum from mice dosed with MCC950 and fed with diets. NLRP3 inhibition exerted beneficial metabolic, and autophagic adaptations in hearts from obesogenic diets. The inhibition of NLRP3 activation may hold promise in the treatment of metabolic and cardiovascular diseases.

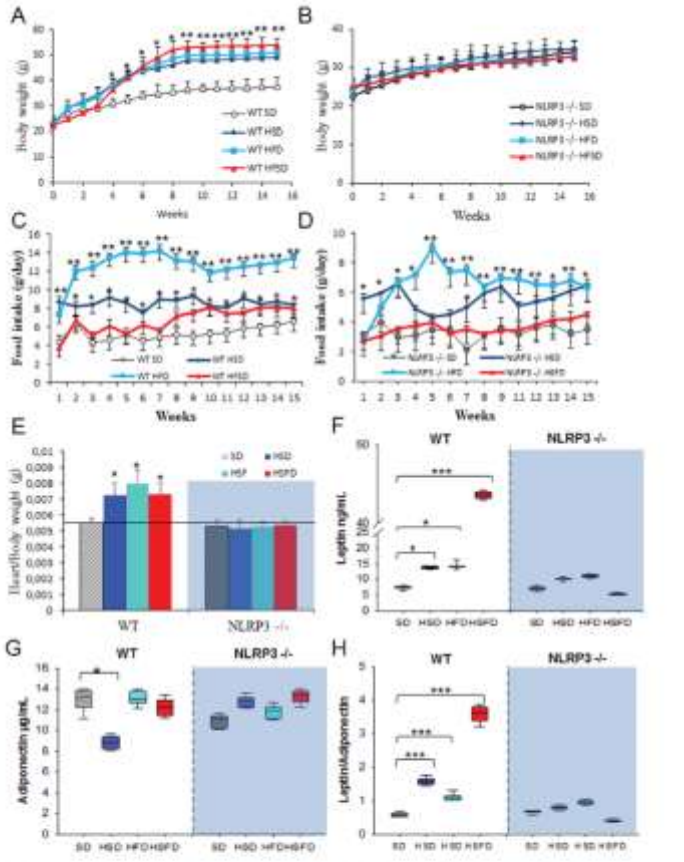


Figure 1: Nlrp3 signaling suppression prevents obesity induced effects of the HSD, HFD and HSFD diets. (A and B) Body weight chart of diets-induced obesity in WT and NLRP3 -/- mice. The mice were fed with the diets for 15 weeks and their body weights were monitored weekly. (C and D) Average daily oral food intake normalized to body weight, measured on the different diets. The food intake of mice was measured was monitored weekly. (E) Heart weight normalized to body weight. (F-H) Levels of leptin, adiponectin, and ratio in plasma. Blood samples were collected after overnight fasting. All data are presented as means ± SEM, n = 10 mice. $^{*}P < 0.05$, $^{**}P < 0.005$, $^{***}P < 0.001$.

This is an interesting paper as it shows that even if NLPR3 inhibitors do not cause weight loss they still can provide significant benefit to patients through improving heart health.

Colchicine is a well-known NLRP3 inhibitor* that is FDA approved for heart benefit but is also known not to cause weight reduction.**

References:

* https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10013297/
** https://www.nature.com/articles/s41366-020-0598-3

Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5725128/

Obesity, Politics and Payors

Recent Editorial from President Biden and Senator Sanders on GLP-1 Prices

President Biden: Novo Nordisk, Eli Lilly must stop ripping off Americans with high drug prices

If Novo Nordisk and other pharmaceutical companies refuse to substantially lower prescription drug prices in our country and end their greed, we will do everything within our power to end it for them.

President Joe Biden and Sen. Bernie Sanders Opinion contributors

Published 5:08 a.m. ET July 2, 2024 | **Updated 10:31 a.m. ET July 2, 2024**

Today, tens of millions of Americans are struggling with Type 2 diabetes and obesity.

The good news is that Novo Nordisk, one of the world's leading pharmaceutical companies, has created new blockbuster drugs, Ozempic and Wegovy, that effectively treat these conditions.

The bad news is that Novo Nordisk is charging the American people unconscionably high prices for these prescription drugs. If your doctor prescribes you a GLP-1, the prices of Ozempic and Wegovy can be up to six times higher than prices in Canada, Germany, Denmark and other major countries. That's unacceptable.

And it's not just Novo Nordisk. Eli Lilly also is charging unconscionably high prices for Mounjaro, a drug with similar health effects as Ozempic. That cost is roughly $1,100 a month.

Why should people in Burlington, Vermont, pay so much more than people in Copenhagen or Berlin for the same drug? The simple fact of the matter is that people in Paris, Texas, shouldn't be paying much higher prices for Ozempic and Wegovy as people in Paris, France.

These inequities are made even more stark when the profit margins of these companies are examined. For example, in March, a study from researchers at Yale University found these drugs could be profitably manufactured for less than $5 a month, or $57 per year.

Moreover, if the prices of these drugs are not substantially reduced, they have the potential to bankrupt the American health care system.

If Novo Nordisk and other pharmaceutical companies refuse to substantially lower prescription drug prices in our country and end their greed, we will do everything within our power to end it for them. Novo Nordisk must substantially reduce the price of Ozempic and Wegovy.

Source: https://www.usatoday.com/story/opinion/2024/07/02/biden-sanders-prescription-drug-cost-ozempic-wegovy/74232827007/

Bernie Sanders “Study” on GLP-1 Prices

United States Senate

HEALTH, EDUCATION, LABOR, AND PENSIONS COMMITTEE

Bernard Sanders, Chair
Majority Staff Report
May 15, 2024

Breaking Point:
How Weight Loss Drugs Could Bankrupt American Health Care

I. Executive Summary

Over the past thirty years, U.S. prescription drug spending has skyrocketed. Spending on prescription drugs jumped from just $47 billion in 1992 to $406 billion in 2022—a 764% increase.[1] Higher prescription drug spending already poses an extraordinary burden on the American people, who are forced to pay higher premiums, taxes, and out-of-pocket costs.

Now, spending on prescription drugs is on the verge of increasing like never before. New drugs for diabetes and weight loss like Novo Nordisk’s Ozempic and Wegovy could be potential game changers for the millions of Americans with diabetes and obesity. But these drugs will not do any good for the millions of patients in America who cannot afford them. Further, the outrageously high prices of these drugs have the potential to bankrupt our entire health care system.

Today, Novo Nordisk charges Americans with type 2 diabetes $969 a month for Ozempic, while this same exact drug can be purchased for just $155 in Canada, $122 in Italy, $71 in France, and $59 in Germany. Meanwhile, Novo Nordisk lists Wegovy for $1,349 a month in the U.S. while this same exact product can be purchased for just $186 in Denmark, $137 in Germany and $92 in the United Kingdom.

Novo Nordisk’s prices are especially egregious given a recent report from researchers at Yale University that found that these drugs can be profitably manufactured for less than $5 a month.[2]

Nearly half of all American adults are interested in taking weight loss drugs.[3] The U.S. Senate Committee on Health, Education, Labor, and Pensions (HELP Committee) Majority Staff modeled how the emerging class of weight loss drugs—led by Novo Nordisk’s Wegovy—could impact prescription drug spending, taking into account estimated manufacturer discounts.

Figure 3: Total retail prescription drug spending from National Health Expenditures data (1992-2022)

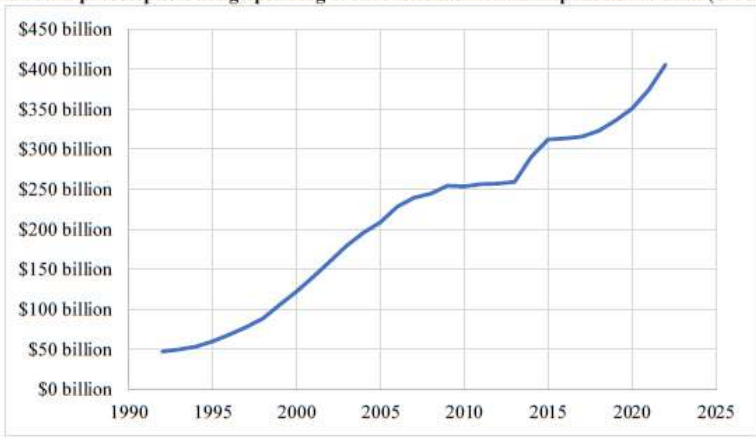
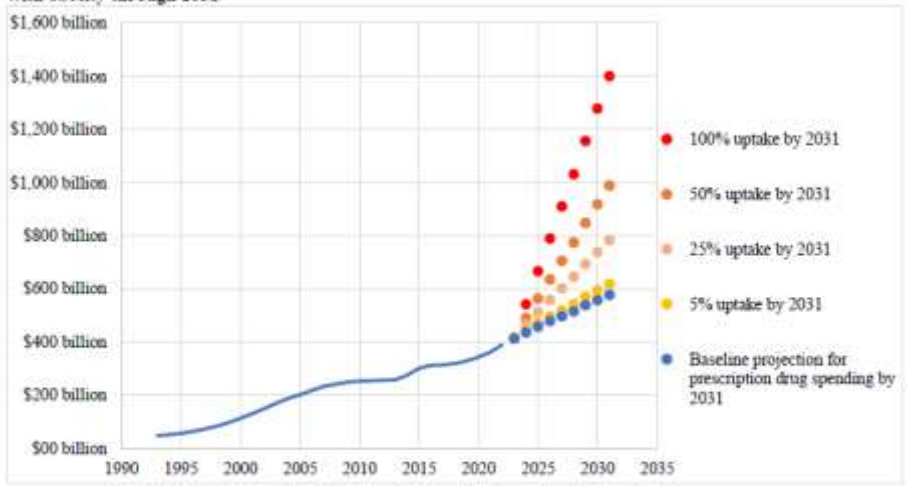


Figure 4: Estimated retail prescription drug spending based on uptake of weight loss drugs among adults with obesity through 2031



Just on new weight loss drugs, the U.S. could cumulatively spend nearly one trillion dollars by 2031 if uptake reached 25 percent, and nearly two trillion dollars if uptake reached 50 percent.[21]

Source: https://www.sanders.senate.gov/press-releases/news-chairman-sanders-releases-report-exposing-how-weight-loss-drugs-could-bankrupt-american-health-care/

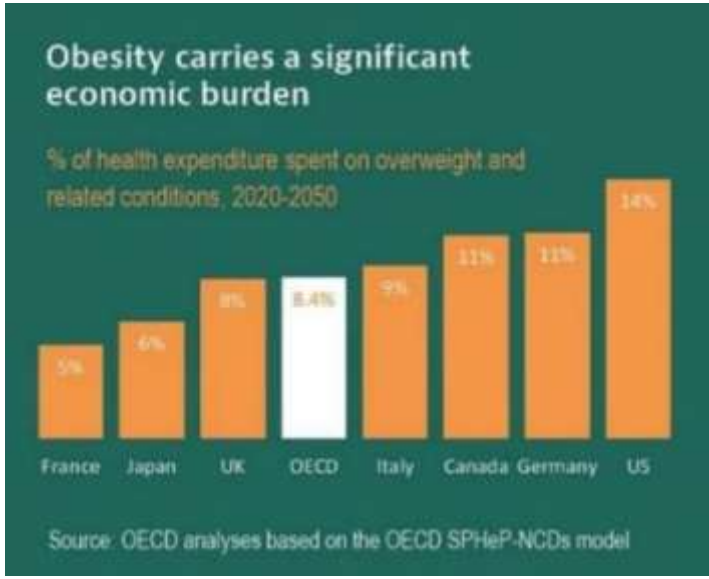
Biden / Sanders Arguments Are Not Sound

- Biden and Sanders cite a *JAMA* paper by three academics arguing what Lilly and Novo Nordisk's API cost is.* The academics, of course, have no idea what the actual API cost is. It's asserted based on biosimilar cost and biosimilar product is likely to be less costly than what Lilly and Novo actually spend.
- Marginal cost of production for pharmaceutical products is often low but the fixed costs for peptide drug production are typically quite high. There are various technical reasons for this including poor yields involved in solid state synthesis of relatively large molecules. If one considers ROI to the pharma as a legitimate topic for discourse one should at least use sound economic reasoning:
  - Specifically, there are gigantic fixed costs of building capacity to make API for incretin peptide drugs. Novo and Lilly are each spending more than $10 billion to build this capacity. Novo's capital expenditures in the last 24 months exceed $8 billion. The buildout of manufacturing capacity is risky and involves long timelines. Notably, Novo now is laying out capital for a $6bn expansion at its Kalundborg site and a $2.5bn expansion at its Chartes site. Further, Novo is spending $11 billion to acquire three plans to expand semaglutide output.** In total, Novo is laying out at least $28 billion in less than five years to try to meet exceptional semaglutide demand.
  - Further, arguing that Novo's profits are obscene is like looking at the winner of a lottery and suggesting that they should give the money back because they received a windfall. This sounds fine until you consider the odds that the winner faced when buying a lottery ticket. Would anyone every buy a lottery ticket again if you had to give your winnings back? This analogy is applicable to pharma since the odds of coming up with a multi-billion dollar revenue drug through R&D efforts are well under one percent.***
- This completely ignores the technology assessment framework that the Biden administration themselves have pushed via the IRA which is to look at the social benefits versus cost of the medication.

* See: https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2816824
** See https://www.bloomberg.com/news/articles/2024-02-05/novo-nordisk-spends-11-billion-on-meeting-obesity-drug-demand
*** See IQVIA Institute, Lifetime Trends in Biopharmaceutical Innovation, 2017. and Standish Fleming, "Why Pharma Risk Is Inherently Unpredictable And Why It Matters," Forbes Nov 6, 2018.

Biden / Sanders Arguments Ignore Societal Upside from Paying for Obesity Drugs

- Biden and Sanders argue that covering GLP-1's would bankrupt the government:
  - To be clear, the government refuses to pay for obesity drugs at all.
  - Presumably, the government price would be well below the list price in the market. The Biden/Sanders editorial absurdly uses the full list price on half the U.S. population to estimate the government would be bankrupted.
  - Even customers off the street can buy tirzepatide from Lillydirect.com at less than 50% of list price.
  - Presumably, the U.S. government would save money on treating diseases avoided by covering the drugs.*
  - There is much to be done to offset the cost. For example, the U.S. government could stop subsidizing the manufacture of high fructose corn syrup and tax obesogenic goods.**
- The critique of "greed" and profitability of Lilly and Novo rings hollow:
  - Novo Nordisk is 28% owned by a *foundation*. Likewise, Lilly has high ownership by a foundation.
  - Their profitability ratios are not out of line with the pharmaceutical industry in any way.
  - Last year, all of Lilly's operating cash flow went to pay for capital expenditures and its balance sheet is being stretched to build manufacturing. Lilly has more ten times more debt than cash and investments today.
- If the U.S. government reimbursed obesity drugs it would likely cause the price of drugs to fall:
  - By paying for the drugs the market would become larger
  - The market would become more just as the poor could access the drugs
  - More competition is likely to enter the market if competition is higher
- Further, obesity drugs bring massive societal benefit:
  - A recent analysis by USC noted more than $1 trillion in direct social benefit over ten years from reimbursing drugs***
  - The USC analysis noted a further $7 trillion of societal gain by covering obesity drugs
  - Others have noted that these drugs could raise GDP by helping to avoiding days lost at work.



The Biden/Sanders editorial completely ignores the massive societal savings that might accrue from spending more on obesity drugs.

* See https://www.barrons.com/articles/wegovy-ozempic-obesity-drugs-healthcare-system-20307eea
** See https://www.nejm.org/doi/full/10.1056/NEJMp2313666, https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2819139, https://www.healthaffairs.org/doi/10.1377/hlthaff.2019.01058.
*** Source: https://healthpolicy.usc.edu/article/medicare-coverage-of-weight-loss-drugs-could-save-billions-of-dollars/

Viewpoint on Obesity Drug Pricing from RA Capital and USC

Dana Goldman (USC) and Peter Kolchinsky (RA Capital), "Want lower obesity drug costs? Medicare holds the key," *Rapport*, Nov 20, 2023

People struggling with obesity have found hope in new, injectable drugs. Clinical trial participants using semaglutide (Wegovy) safely lost 15% or more of their body weight, with similar results for other injectable glucagon-like peptide-1 receptor agonists (GLP-1) medications like tirzepatide (Zepbound). Since 40% of the country has obesity, two thirds are overweight, and the disease kills 300,000 Americans annually, these therapeutics have immense potential to improve nation's health.

But right now, Medicare doesn't cover these drugs and many private insurers point to high list prices to limit access. Not everyone who could benefit from these treatments can get them.

There is a way forward. The federal government can open the door to market forces by being willing to pay for these new, brand-name products.

But would Medicare coverage blow up the federal deficit? Or could the drugs indirectly improve health in other parts of Medicare, like cardiac care, such that overall costs would remain flat or even drop significantly? For example, a new study found that one of the drugs cut the risk of heart attack, stroke or death by 20% among people with obesity and heart disease.

The government's objective should not only be to minimize its costs — after all, Medicare could save billions if more people would die earlier from smoking more cigarettes. But allowing Medicare to start paying for anti-obesity treatments now has the potential to kick off a true weight-loss revolution that can save lives and dramatically drive down the cost of these drugs.

The path from expensive innovative drugs to cheap generic medications is well known. Fifty years ago, diet and exercise were the predominant means of controlling hypertension. The discovery of multiple agents to combat the condition, beginning with diuretics and beta blockers, proved transformative. A similar story emerged for elevated cholesterol. About half the decline in U.S. deaths from coronary heart disease can be attributed to medical therapies that now typically cost a few dollars a month, merely several percent of what they cost when they were novel and branded. And they're a significant contributor to the flattening of Medicare spending over the past 20 years.

The key to drug price declines is robust competition among producers. Competition comes for nearly every drug eventually, and particularly the small molecule treatments we take as pills.

(continued)

Source: https://rapport.bio/all-stories/medicare-obesity-drug-coverage-benefits

Viewpoint on Obesity Drug Pricing (continued)

Dana Goldman (USC) and Peter Kolchinsky (RA Capital), "Want lower obesity drug costs? Medicare holds the key," *Rapport*, Nov 20, 2023

We believe the signs suggest that if Medicare offered coverage, the competition in anti-obesity medications would be robust due to an expanded market, more investors in search of better drugs, and more competitors. These injectable GLP-1s were originally developed to treat diabetes. Now, the FDA has approved three of the drugs for treating obesity, and scores of other obesity drugs are in the pipeline, notably GLP-1 pills. These oral treatments can be more readily scaled than the current injectables, enabling greater price elasticity of coverage (i.e., allowed demand); they eventually would more easily "go generic."

Prices are already wobbling. An analysis at the American Enterprise Institute found that net prices for the new diabetes/obesity treatments are 48-78% below listed prices, meaning insurers have effectively negotiated reduced prices for their customers even with few competitors on the market (those customers could enjoy those savings if insurers decided to pass them through). Eventually, Medicare would also likely subject these treatments to negotiation under the Inflation Reduction Act, which would leverage federal buying power, though currently there's no rule that requires Medicare drug plans to share negotiated savings with beneficiaries.

Obesity and its myriad consequences cost the healthcare system a quarter trillion dollars in 2020. An economic/demographic microsimulation from the USC Schaeffer Center estimates that the cumulative social benefits from solving obesity (e.g., zero obesity rate) would reach almost $1 trillion over the next 10 years, or roughly $100 billion per year. Savings to Medicare alone could be as much as $245 billion in the first 10 years of coverage.

But the benefits and savings don't stop there.

Over 20 years, a period in which we can likely expect both the launch of oral GLP-1s and their eventual genericization, the prices of these medicines would likely spiral down by 80% or more and savings would compound spectacularly. Indeed, calculations based on the Schaeffer model show that the U.S. healthcare system would save $7 trillion over 30 years, on top of all the benefits due to improved quality of life and productivity.

In that context it's easier to see how government spending on branded weight loss drugs in the near term will result in a remarkable, lasting bargain for society.

Source: https://rapport.bio/all-stories/medicare-obesity-drug-coverage-benefits

The Less Well Off Want Access to Obesity Drugs

Unfortunately, diets and access to fresh fruits and vegetables are worst in the very same U.S. regions where economic deprivation is highest. One can see this in the charts at right which show obesity rates, soda's drinks and volume of fast-food visits at the U.S. county level. Poor diet and obesity are highest in the traditional Bible Belt, particularly West Virginia and southern tier states like Louisiana and Alabama.

Fascinatingly, as shown below the same states where obesity is highest and diets worst, are those where interest in obesity drugs is highest. These data highlight the large unmet need in the market.

Google Search Frequency for Term "Ozempic", 2000 to 2024, by State

Sources: https://www.nature.com/articles/s41467-021-27522-y, https://trends.google.com/ (for map on left)

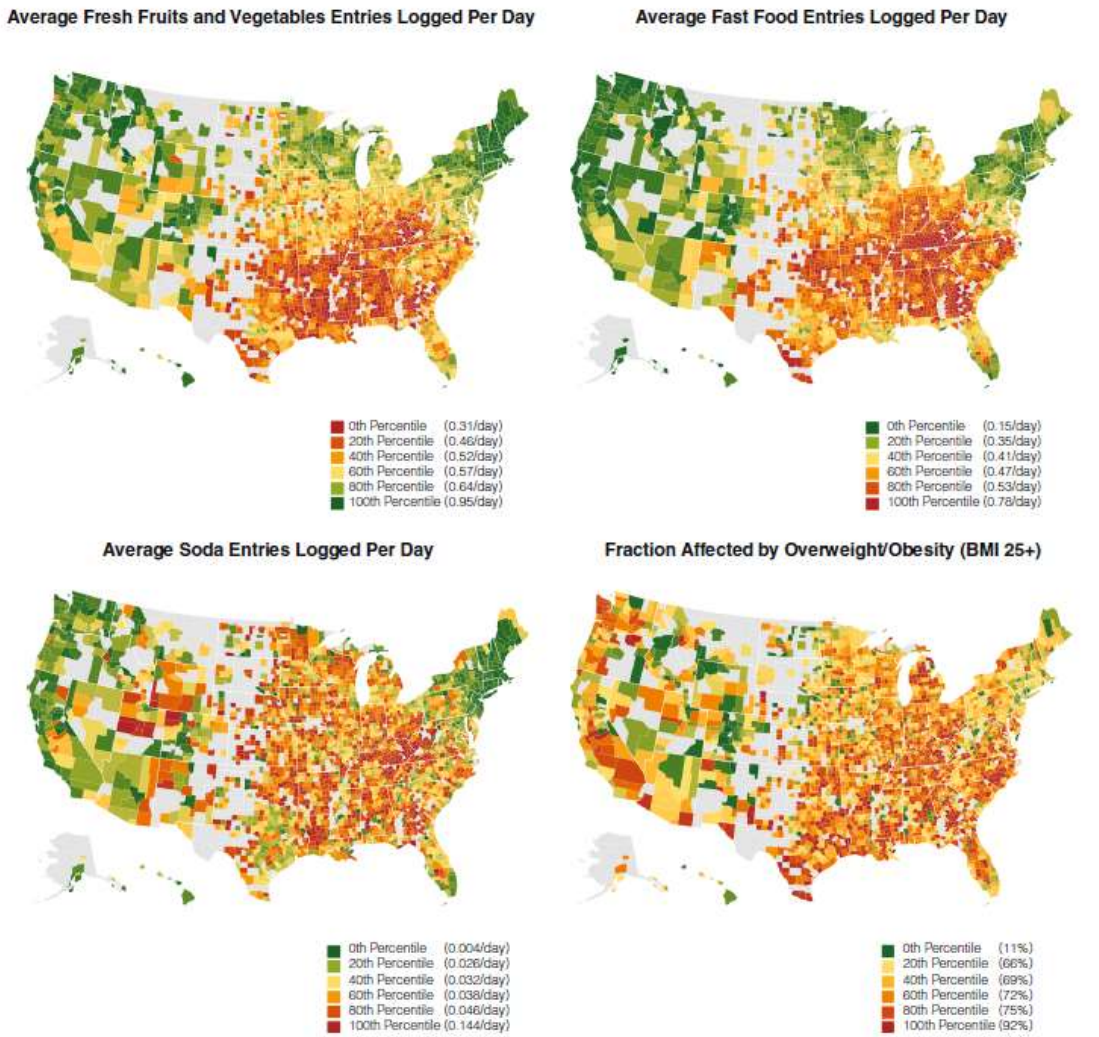


Fig. 2 Dietary consumption and BMI status across U.S. counties. A set of choropleths showing the main study outcomes of the number of entries that are classified as fresh fruit and vegetables, fast food, and soda consumption as well as the fraction affected by overweight/obesity (BMI > 25) participants across the USA by counties with more than 30 participants. We observe that food consumption healthfulness varies significantly across counties in the United States.

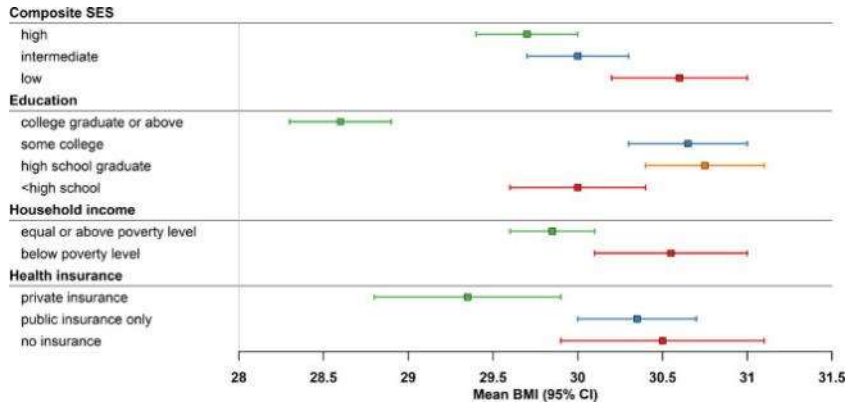
Social Justice and Access to Obesity Drugs

There are obvious issues of social justice insofar as access to obesity drugs has been denied to the least well-off part of the U.S. populace. To compound this problem, those that are less well off have the least access to new drugs. See charts at right.

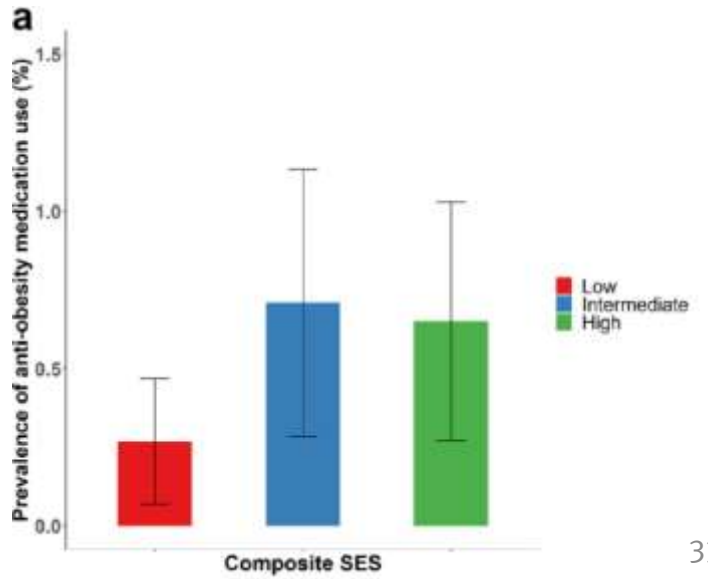
The same justice issues hold at a global level. Jayasree Iyer, Head of the Access to Medicines Foundation, commented on this in a June 2024 editorial in *Stat+*:

> "The fact that resource-poor countries now face an obesity crisis does not mean the age-old problem of undernourishment has been solved. The sad fact is that hundreds of millions of people still do not have enough to eat, even as others struggle with excess weight. The result is that many poor countries are facing double epidemics of hunger and obesity, both of which have serious long-term consequences for health. Obesity is a growing global issue, and the health threats it poses need to be prioritized. The new generation of GLP-1 drugs alone will not solve the problem, but they can contribute to the solution."

Obesity Most Prevalent in Lower Social Economic Status (SES) Populations…



… Yet those populations are least likely to use anti-obesity medications.



Sources: https://www.sciencedirect.com/science/article/pii/S2667193X22000667., https://www.statnews.com/2024/06/07/obesity-drugs-health-care-equity-challenge/

The Pharma Industry, Governments and the Balance of Power

Because the government does not reimburse obesity drugs, we have noted that consumers (aka citizens) are taking matters into their own hands and buying obesity drugs themselves.

This is a critically important trend in our society that has both good and bad implications.

The bad is that the drugs are not necessarily allocated based on medical need. The good is that many patients benefit.

The reality is that today's user of GLP-1 agonists is more likely to be a near normal weight woman in Los Angeles than a morbidly obese poor person in a southern state like Louisiana.

Overwhelmingly, GLP-1 users are private pay patients based in coastal areas where incomes are higher.

Because the private pay market is so large (over $100bn by our estimate), this creates an interesting dynamic in the power relationship between pharma companies, the citizenry and governments. As we have noted using the example of what used to the record business, the entire business model of an industry can be shifted by providing consumers what they really want.

To be thin. To live longer. To enjoy life. To get rid of their diabetes. And so on.

It strikes us that the modern obesity drug is profoundly disruptive to the ecosystem that pays for medicines in the US.

Core power structures of our society could be affected by the rapid shift of drug consumption to the private pay market in the US.

In the same sense that a SpaceX has a seat with governments at the global power table because of its Starlink service, access to large private pay markets are profoundly empowering to pharma while reducing government negotiation leverage.

Basically, pharma companies can market the largest drug class in history and not have to worry about government interference.

Politicians like Biden and Sanders are reduced to complaining about obesity drug prices. The fact that they are doing this and talking about the giant market size is arguably humorous from a pharma view and validates just how large the obesity market is.

But they can't negotiate anything because they aren't at the table. They don't pay for the drugs.

Source: https://www.sciencedirect.com/science/article/pii/S2667193X22000667

The Pharma Industry and the Balance of Power (continued)

Period.

Governments have *zero leverage* in the situation.

With obesity drugs, pharma has found a way to grow their business that involves directly pleasing the end customer.

This is long overdue. Pharma companies have an opportunity to build direct relationships with their customers with services like LillyDirect.

Importantly, the pharma industry in this area is starting to look and feel like what is going in the tech sector:

- Disruptive story.
- Massive market with dynamic competition.
- Power that can rival the role of governments in its relevant to the average citizen.

It will be very interesting to see how the shifting sands of power in the pharma sector evolve over the next decade.

Our gut is that the changed relationship with the consumer and government is of fundamental importance.

You might remember the adage attributed to John Maynard Keynes: "If you owe the bank $100, that's your problem; but if you owe the bank $100 million, that's the bank's problem."*

We'll add a modern corollary: "If you are sick and the government won't pay for it, that's your problem. But, if everyone is sick and the government won't pay for, that's the government's problem."

The Covid epidemic became a major political problem for Donald Trump who didn't handle it well. Likewise, we think the unwillingness of the government to pay for obesity drugs could eventually become a liability for politicians who are in power and something for out of power politicians to campaign about.

* You can read https://quoteinvestigator.com/2019/04/23/bank/ to hear what he actually said.

Justice, Politics and Opportunity

Interestingly, the historical reluctance of the U.S. government to reimburse obesity drugs came from a time when there was less understanding of the causes of excess weight.

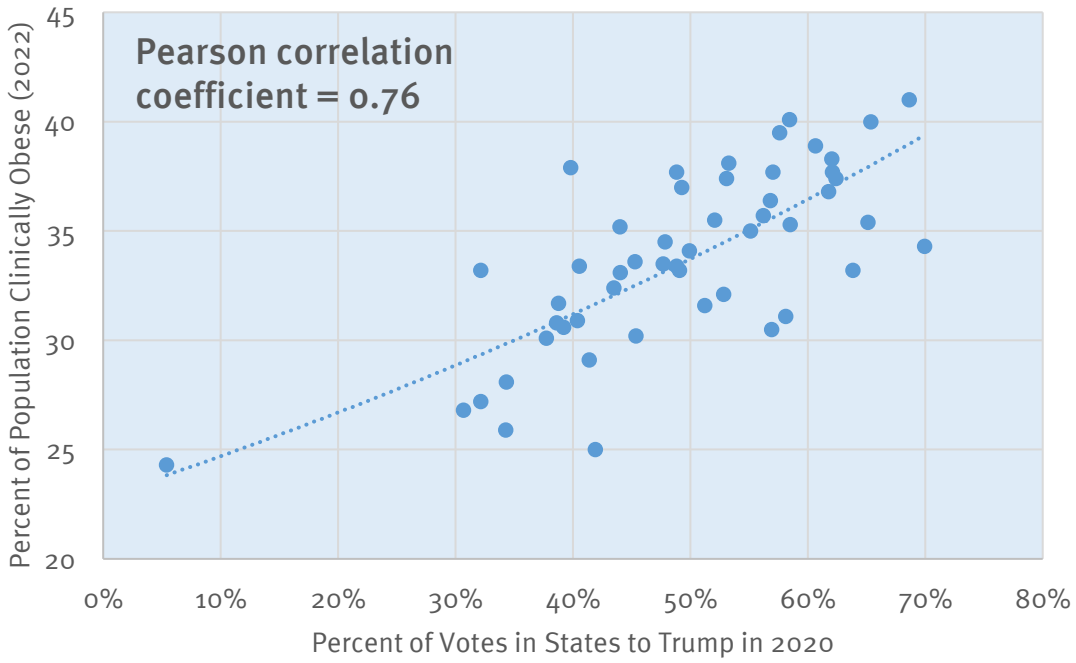
Those who were overweight were seen as undisciplined and not likely to benefit from weight loss interventions. Misconceptions abound in the legislative history.* The current view that obesity has addiction-like characteristics, particularly among children and adolescents, was absent when the rules were set up in 2003.**

Given the extraordinary interest in obesity drugs, there is an obvious opportunity for an enterprising politician to create something like Operation Warp Speed (think "Operation SlimFast") to have the government pay for GLP-1's if citizens commit to get healthy in some way. As with the Pandemic this would need to involve helping to pay for manufacturing capacity and working out a deal with pharma.***

This would be huge vote getter that could appeal to a divided nation.

Importantly, obesity rates are much higher, on average, in red states, creating an issue that a Democratic politician could use broaden their appeal. The correlation coefficient between the percent of voters in a state who voted for Trump in 2020 is extraordinarily high (0.76).

Relationship Between Obesity Rate and Voting for Trump in 2020 by State



At a moment when national election prospects are in some disarray, we encourage politicians to think enterprisingly about the issues of social justice, popular interest and health of the country. Instead of criticizing the pharma industry to garner votes, we encourage politicians on both sides of the aisle to think about working with pharma to help solve one of the largest societal problems that we face: the obesity epidemic.

* https://d84vr99712pyz.cloudfront.net/p/pdf/press/obesity_position_paper_ecri_2022.pdf

** While legislative efforts to remove the ban on obesity drug coverage it is not all obvious that legislation will pass. See https://www.statnews.com/2023/01/26/medicare-obesity-drugs/. CBO's view of this proposed legislation are important as emphasized by Kolchinsky and Goldman's article.

Sources: https://www.cdc.gov/obesity/php/data-research/adult-obesity-prevalence-maps.html (obesity data); https://www.presidency.ucsb.edu/statistics/elections/2020 (voting by state in 2020).

*** One can imagine scenarios where private enterprise initiates this process. One can't help but remember the contracting done by the Medicines Company on inclirisan with the UK government. Interesting and perhaps not coincidentally the obesity company Metsera is run by Clive Meanwell, the CEO of the Medicines company who cut the inclirisan deal.

Disclosure

STIFEL | Healthcare

Stifel collectively refers to Stifel, Nicolaus & Company, Incorporated and other affiliated broker-dealer subsidiaries of Stifel Financial Corp. The information and statistical data contained herein have been obtained from sources that Stifel believes are reliable, but Stifel makes no representation or warranty as to the accuracy or completeness of any such information or data and expressly disclaims any and all liability relating to or resulting from your use of these materials. The information and data contained herein are current only as of the date(s) indicated, and Stifel has no intention, obligation, or duty to update these materials after such date(s). These materials do not constitute an offer to sell or the solicitation of an offer to buy any securities, and Stifel is not soliciting any action based on this material. Stifel may be a market-maker in certain of these securities, and Stifel may have provided investment banking services to certain of the companies listed herein. Stifel and/or its respective officers, directors, employees, and affiliates may at any time hold a long or short position in any of these securities and may from time-to-time purchase or sell such securities. This material was prepared by Stifel Investment Banking and is not the product of the Stifel Research Department. It is not a research report and should not be construed as such. This material may not be distributed without Stifel's prior written consent.

Stifel, Nicolaus & Company, Incorporated | Member SIPC & NYSE | www.stifel.com