# Analyzing Real-World Evidence Regarding Efficacy, Adherence and Usage of GLP-1 Drugs and New Therapeutic Directions

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SVP Translational Medicine, Wave Life Sciences

2nd annual Obesity and Weight Loss Drug Development Summit

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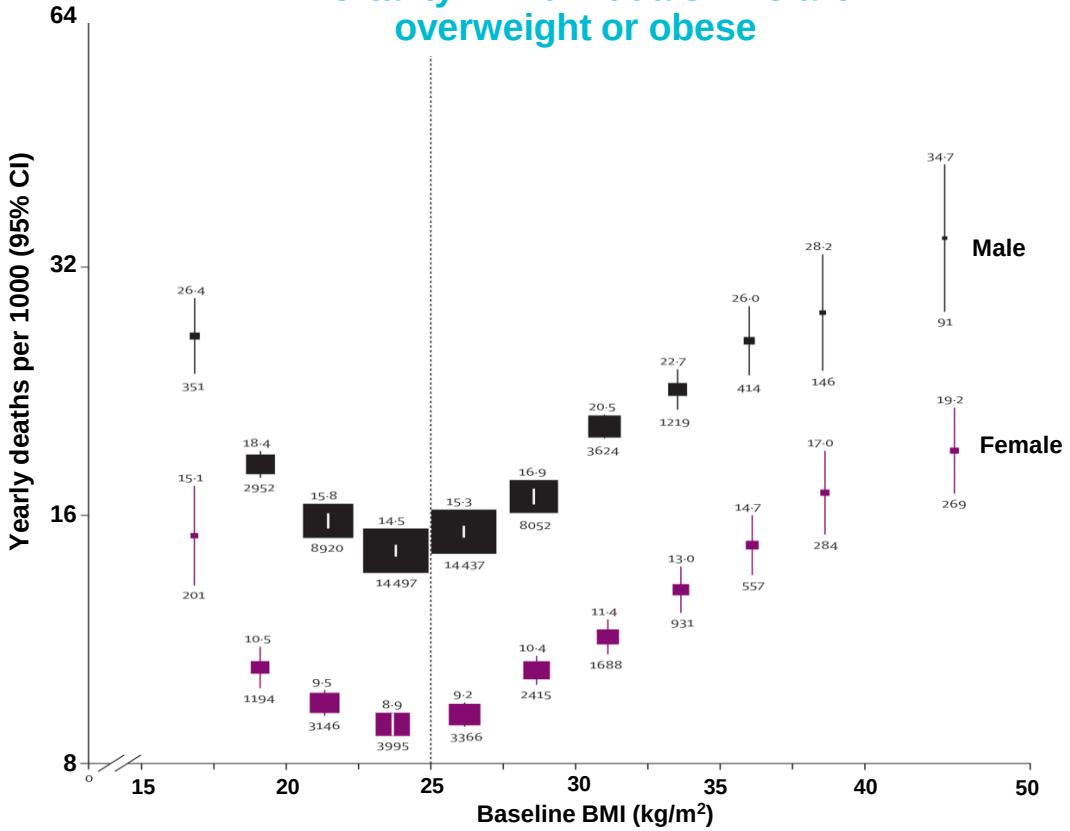
# Obesity is not just “too much weight”

- Defined as ‘**abnormal or excessive fat accumulation** that presents a risk to health’.[2]
- More than 200 complications are linked to obesity -- explains increased, related morbidity and mortality and 4 million related deaths worldwide in 2015.[3,4]
- QoL of people with obesity or overweight is often impaired and lifespan significantly reduced.[5]
- High BMI is associated with decreased life expectancy of up to 10 years
- For every 5 kg/m$^2$ BMI increment above the range of 22.5–25.0 kg/m$^2$, overall mortality is increased by 30%.[6]

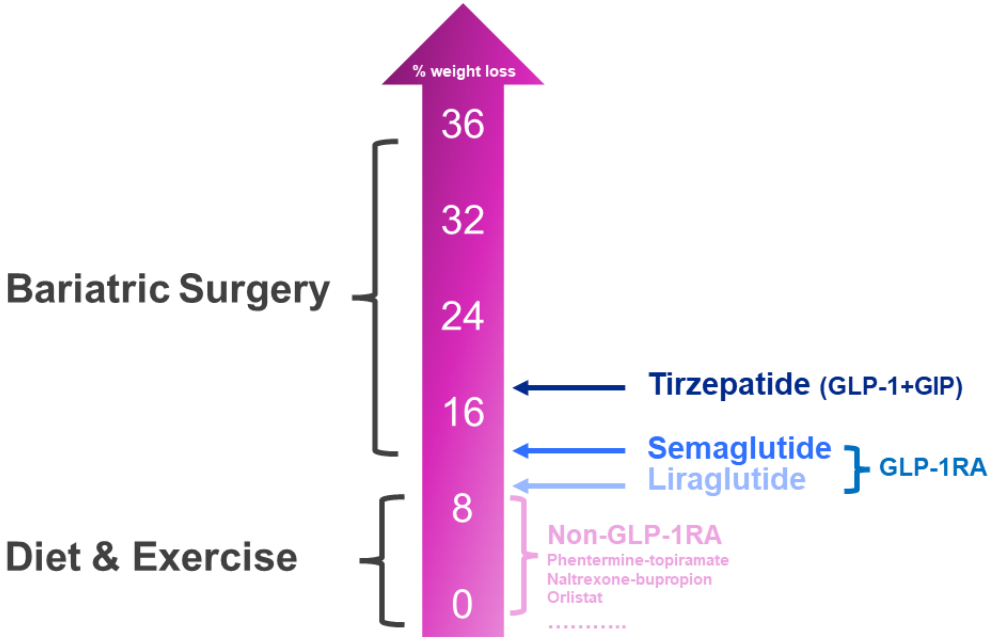
## BMI is associated with increased mortality in individuals who are overweight or obese






1. touchREVIEWS in Endocrinology. 2022; 18(1):35–42 ; 2. World Health Organization. Obesity and overweight. 2021. www.who.int/news-room/fact-sheets/detail/obesity-and-overweight ; 3. Yuen MS, Lui DT, Kaplan LM, et al. Obesity Week 2016, New Orleans, LA, 31Oct-4 Nov. Poster T-P-3166; 4. Afshin A, Forouzanfar MH, Reitsma MB, et al. N Engl J Med. 2017;377:13–27; 5. Lancet. 2016;388:776–86; 6. Lancet. 2009;373:1083–96

# Future weight loss medications aim to improve efficacy, tolerability, and adherence




**Real world evidence for approved GLP-1RA drugs provide key directions for further improvements**

# Real-World Evidence on the impact of the GLP-1 class on patient experience

- Positive experience – impressive weight loss
- Negative experience – adverse events

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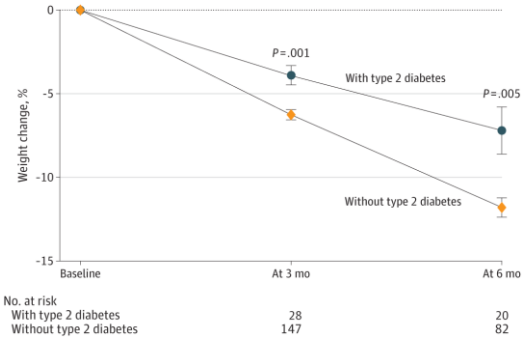
# Real-World Weight Loss Outcomes for Individuals who are Overweight or Obese Treated with Semaglutide

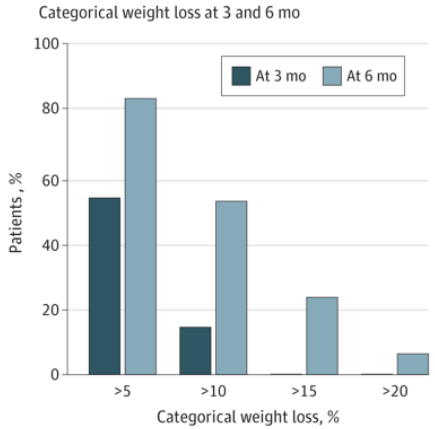
## Patients with T2D experience smaller magnitude of weight loss than those without T2D




Error bars = SD

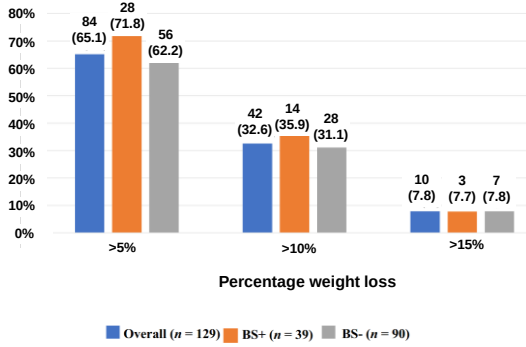
eHR Mayo Clinic Health System 01/01/2021 to 03/15/2022

## Categorical Percentage Weight Loss at 3 and 6 Months (semaglutide)




eHR Mayo Clinic Health System 01/01/2021 to 03/15/2022

## Semaglutide delivers similar weight-loss for patients without bariatric surgery, as well as in those with inadequate body weight reduction after bariatric surgery




BS, bariatric surgery; BS+, patients with a history of BS; BS, patients without a history of BS

# Negative experience associated with GLP-1RA treatment - Adverse events (AE)

## Mechanism-related AE - NON-CNS

- Hypoglycaemia[1]
- ***Gastrointestinal***[1] – abdominal pain, nausea, vomiting, diarrhea, belching, heartburn, and GI bleeding
- Pancreatitis, gallbladder disease or biliary diseases[1,2]
- *Pulmonary aspiration* - intestinal blockage, paralytic ileus[3]
- Neoplasms - pancreatic cancer, and/or thyroid cancer/carcinoma, and medullary thyroid cancer[1]
- ***Loss of muscle***[9,10,11]

## Mechanism-related AE - CNS

- Psychiatric adverse events
  - depression[4]
  - suicidal thoughts and actions[4,5]
  - self-injurious ideations[5]
  - *Suppression of general reward system*[5]

## Induced by Rapid weight loss

- ***Hair loss*** - Telogen Effluvium[6,7]
- ***Cosmetic*** - Ozempic butt or face[8]

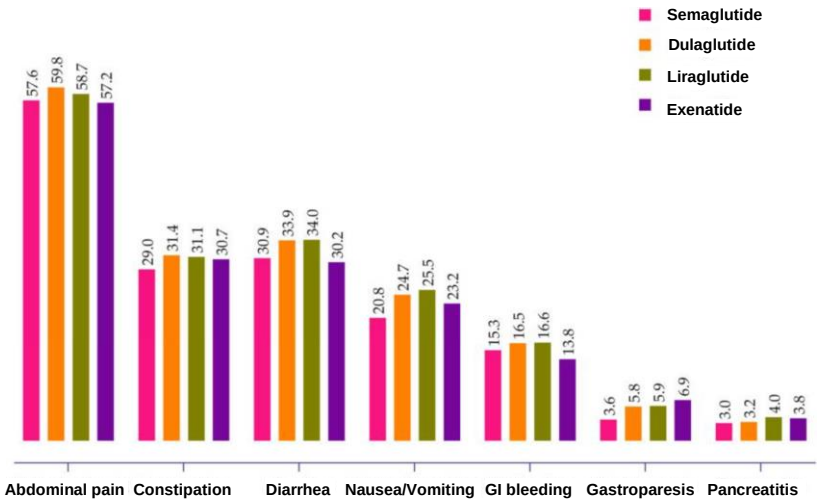


1. Front Endocrinol (Lausanne) (2021)12:645563; 2. Front Endocrinol (Lausanne) (2023) 14:1214334; 3. Anaesth Rep (2024) 12(1):e12278; 4. Front. Psychiatry 14:1238353; 5. EuropeanNeuropsychopharmacology82(2024)82–91; 6. Cureus (2021) 13(4):e14617; 7. Medicina (Kaunas) (2024) 60(2):325; 8. Plast Reconstr Surg Glob Open. (2024) 12(1): e5516; 9. Eur Rev Med Pharmacol Sci (2023) 27(20):9908-9915; 10. Curr Diabetes Rev (2021) 17(3):293-303; 11.Osteoporos Int (2018) 29(12):2639-2644

# Non-CNS Mechanism related Adverse Events for GLP-1RA

Incidence of gastrointestinal adverse events due to treatment with GLP-1RA

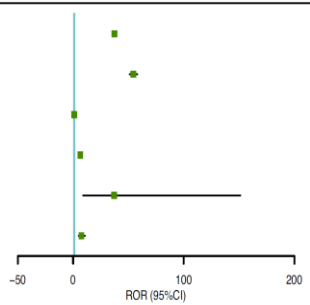
## GI related AE




ALL of Us Research Program Database Version 7, 10,328 new GLP-1RA users. 36.2% were on semaglutide (n = 3739), 29.8% were on dulaglutide (n = 3079), 29.3% were on liraglutide (n = 3031), and 4.6% were on exenatide (n = 479)

## Risk of pancreatic cancer

| Drug | n | ROR (95% CI) | PRR (95% CI) | IC (IC025) | EBGM (EBGM05) |
|---|---|---|---|---|---|
| Exenatide | 1719 | 37.32 (35.47, 39.28) | 36.45 (34.67, 38.32) | 5.00 (4.76) | 32.10 (30.76) |
| Liraglutide | 1148 | 54.45 (51.21, 57.90) | 52.52 (49.49, 55.73) | 5.59 (5.26) | 48.30 (45.88) |
| Albiglutide | 6 | 0.94 (0.42, 2.09) | 0.94 (0.42, 2.09) | −0.09 (–) | 0.94 (0.48) |
| Dulaglutide | 167 | 6.47 (5.56, 7.54) | 6.45 (5.54, 7.51) | 2.67 (2.29) | 6.38 (5.62) |
| Lixisenatide | 2 | 37.07 (9.09, 151.09) | 36.09 (9.20, 141.64) | 5.17 (1.27) | 36.09 (11.14) |
| Semaglutide | 31 | 7.43 (5.22, 10.57) | 7.39 (5.20, 10.50) | 2.88 (2.02) | 7.38 (5.49) |




**FAERS adverse event** (AE) reports (between 1 January 2004 and 31 December 2020) were used to investigate the correlation between GLP-1RAs and pancreatic carcinoma. A total of 3073 pancreatic carcinoma cases were related to GLP-1RAs. ROR reporting odds ratio, CI confidence interval, PRR proportional reporting ratio, IC information component, IC025 the lower limit of a 95% credibility interval for the IC, – not available, EBGM empirical Bayesian geometric mean, EBGM05 the lower limit of a 90% one-sided CI of EBGM

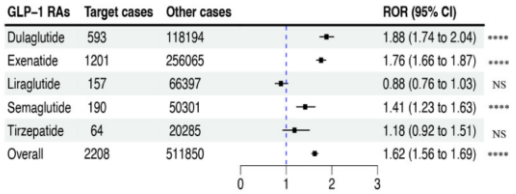



Pharmaceuticals (Basel). 2024 Feb; 17(2): 199; International Journal of Clinical Pharmacy (2023) 45:689–697

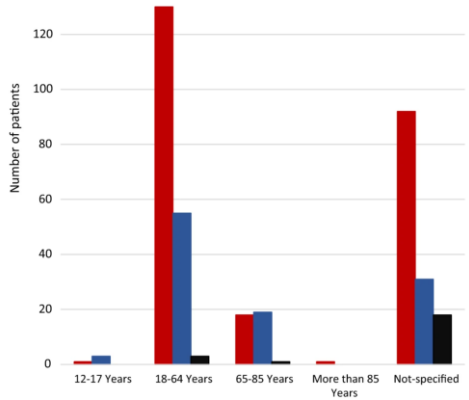
# Real-World Evidence for GLP-1RA-related psychiatric adverse events demonstrates fast onset and reversibility

Psychiatric AEs have fast onset, do not appear to increase with improved efficacy, and are rare

## GLP-1 RA)-related psychiatric adverse events (AEs) based on the FAERS database (2004-2023)[1]

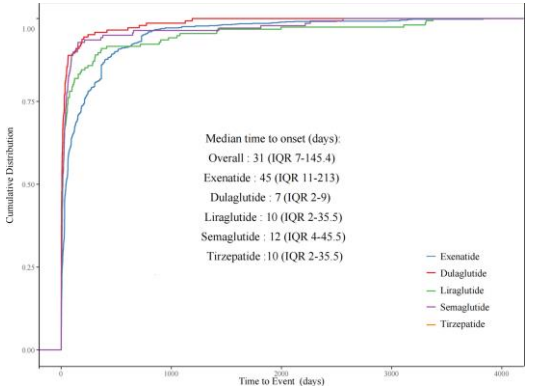



## Age and sex distribution for psychiatric adverse events, semaglutide, liraglutide and tirzepatide[2]




Red – women, blue – men, Black - unspecified

## Fast onset for GLP-1 RA-related psychiatric adverse events[3]



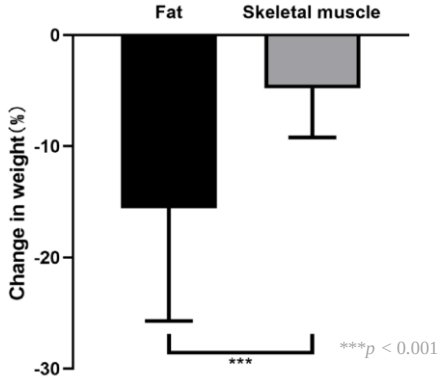



1. Front. Endocrinol.(2024) 15:1330936; 2. International Journal of Clinical Pharmacy (2024) 46:488–495; 3. Front. Endocrinol.(2024) 15:1330936

# Semaglutide-induced weight loss is associated with reduction in muscle mass

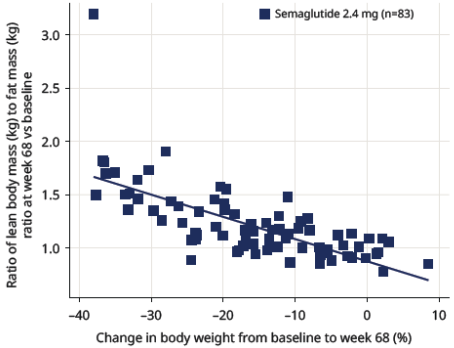
Body-weight loss represents combination of a larger loss of fat mass and a smaller loss of muscle mass

### Treatment with semaglutide led to significant loss of fat and skeletal muscles (RWE)[1]

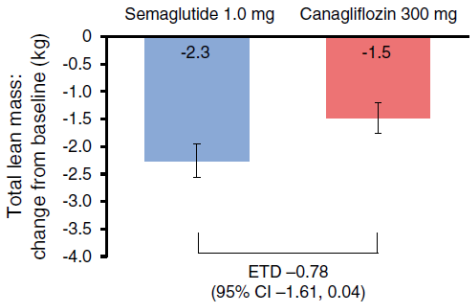



From November 2021 to November 2022, a total of 53 patients with obesity (BMI ≥ 28 kg/m2) who received 24 weeks of treatment with semaglutide at the Second Affiliated Hospital of Guangxi Medical University

### Higher degree of lean mass loss is associated with greater body weight reduction (STEP1)[2]




### Reduction of total lean mass is greater with semaglutide treatment compared to SGLT2i (SUSTAIN8)[3]



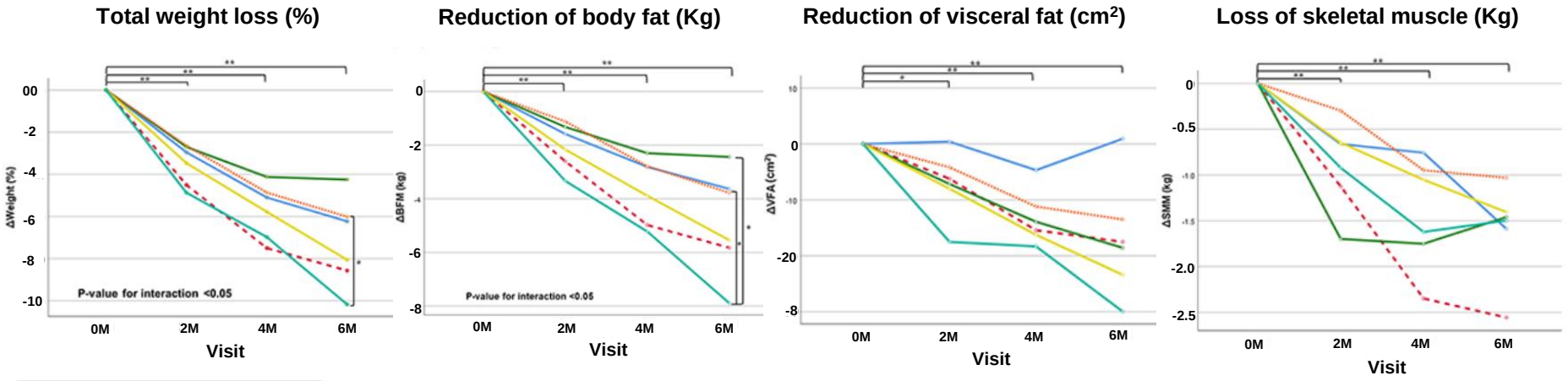

**Loss of muscle mass due to reduced nutritional status is a general physiological response**




1. European Review for Medical and Pharmacological Sciences (2023) 27: 9908-9915; 2. N Engl J Med 2021;384:989. 3. Diabetologia (2020) 63:473–485

# Medications inducing reduction in the intake of nutrients also bring on reduction in skeletal muscles mass

## Medication-induced reduction in nutrition appears to activate general physiological response




205 adults aged 19–65 years who had obesity or overweight with obesity-related comorbidities, who were prescribed AOMs by two family medicine specialists at the obesity clinics of Kyungpook National University Hospital and Kyungpook National University Chilgok Hospital between March 2015 and December 2020. Orlistat (12), Lorcaserin (24), Naltrexone/Bupropion (17), Liraglutide (62), Phentermine/Topiramate (51), Phentermine (39)

# Real-World Evidence of the usage of the GLP-1 class on patient adherence

- Patients' behavior
- Treatment adherence
- Weight regain after termination

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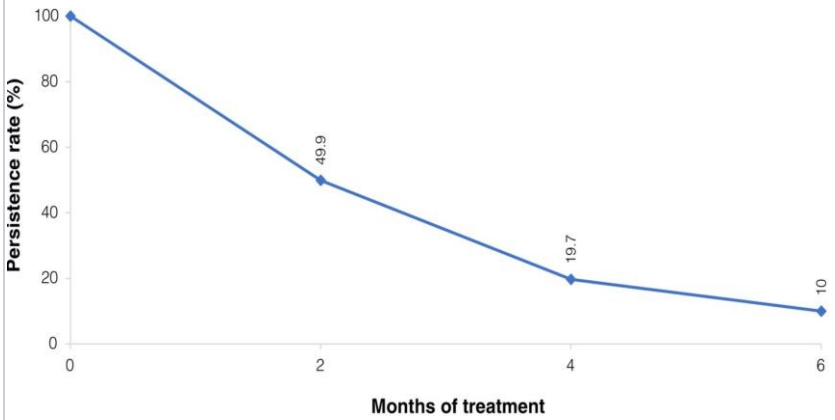
# Low efficacy and adverse events are among leading causes leading to discontinuation of treatment

Rapid treatment discontinuation for patients treated with Saxenda (liraglutide)

## Treatment persistence for Liraglutide 3.0mg




## Reasons for dropping out of liraglutide 3.0 mg treatment within 6 months

| Reason | Adherence group | | | *P** | *P* for trend |
|---|---|---|---|---|---|
| | <2 Months (n=63) | 2–4 Months (n=242) | 4–6 Months (n=234) | | |
| Unknown | 57 (90.5) | 124 (51.2) | 111 (47.4) | <0.001 | <0.001 |
| Cost | 0 | 22 (9.1) | 21 (9.0) | | |
| Failure to lose weight | 0 | 20 (8.3) | 30 (12.8) | | |
| Adverse event | 2 (3.2) | 42 (17.4) | 36 (15.4) | | |
| Switch to another treatment | 4 (6.3) | 34 (14.0) | 36 (15.4) | | |

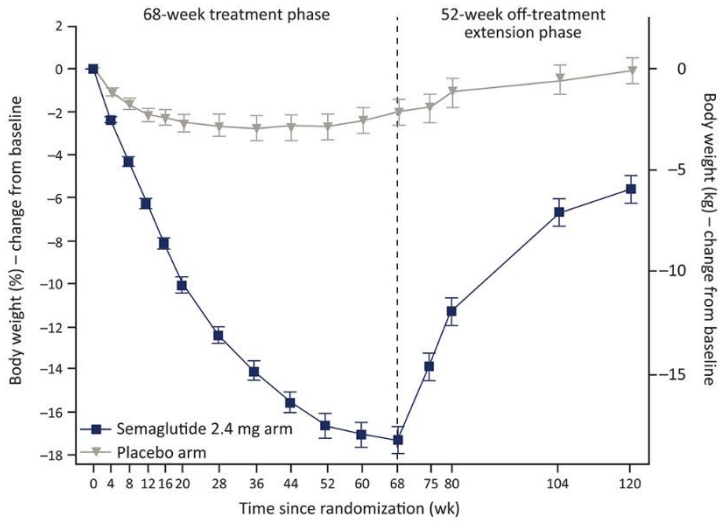


1. Diabetes Obes Metab.2024;26:1346–1354; 2. Journal of Obesity & Metabolic Syndrome 2022;31:254-262;

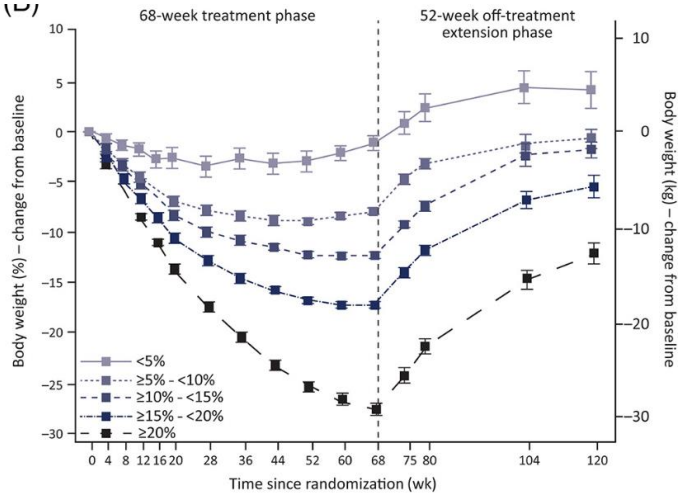
# Discontinuation of treatment with semaglutide leads to a rapid regain of body weight

Weight regain after termination of semaglutide (STEP1 extension)

## Only a fraction of weight-loss is retained after discontinuation of treatment




## Regain of body weight depends on the magnitude of treatment-induced weight-loss



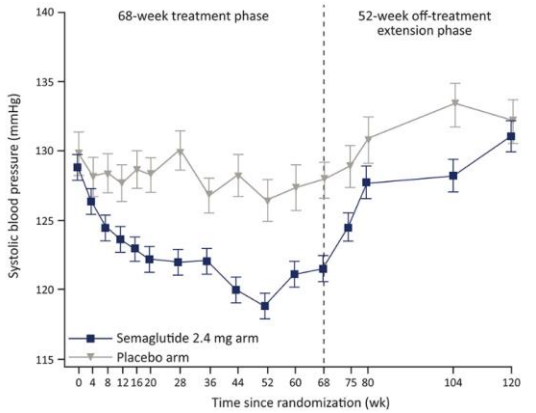



Diabetes Obes Metab. 2022;24:1553–1564

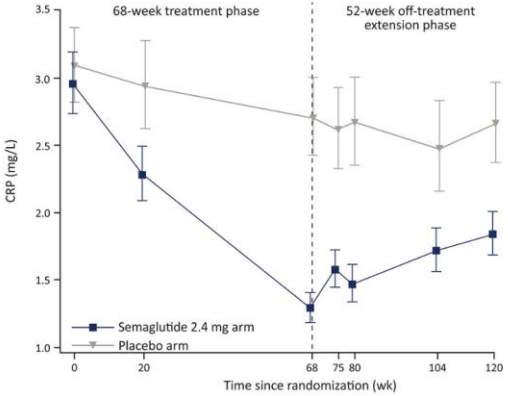
# Rapid loss of beneficial changes in metabolic parameters follows discontinuation of treatment with semaglutide

Data from STEP1 extension trial with semaglutide

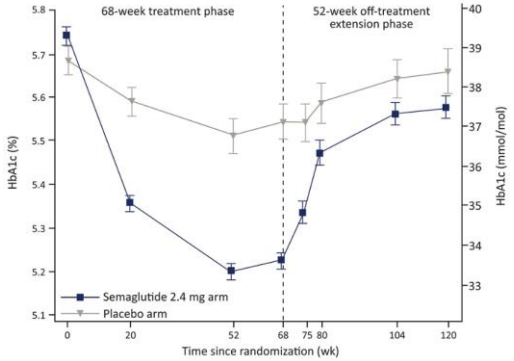
## Systolic blood pressure




## C-reactive protein




## HbA1c







Diabetes Obes Metab. 2022;24:1553–1564

# Progress and lessons learned from marketed anti-obesity drugs

- Effectiveness
- Adherence

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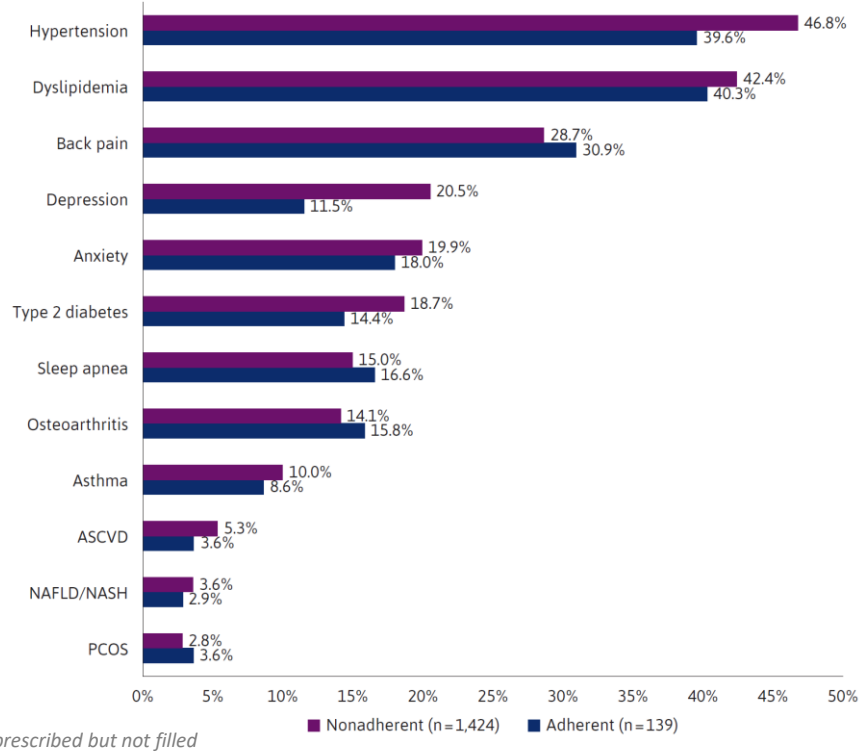
# Baseline Obesity-Related Complications Are Not the Primary Drivers of Adherence in Anti-Obesity Therapy

Optum Integrated Clinical plus Claims database, Individuals with prescription orders between January 1, 2012, and February 28, 2019




*Primary nonadherence (PNA), when a medication is newly prescribed but not filled*

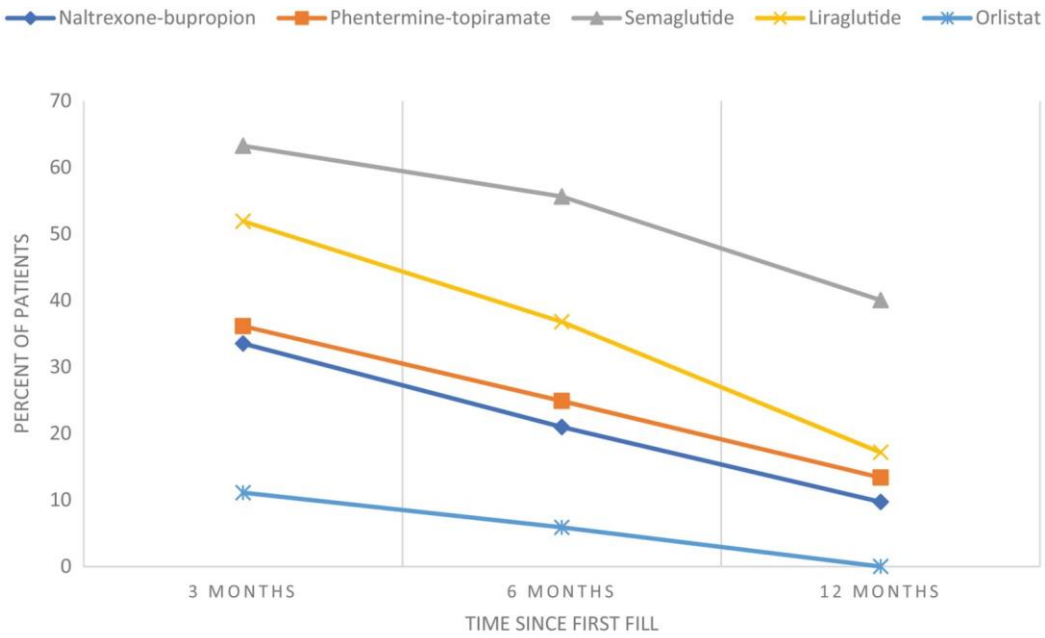
*ASCVD = atherosclerotic cardiovascular disease; NAFLD = nonalcoholic fatty liver disease; NASH = nonalcoholic steatohepatitis; PCOS = polycystic ovary syndrome.*



Real-world primary nonadherence to antiobesity medications. J Manag Care Spec Pharm. 2023;29(10):1099-108.

# Efficacy and side effect profile are key drivers of adherence in anti-obesity therapy

For newer GLP-1RA improved efficacy supports better adherence



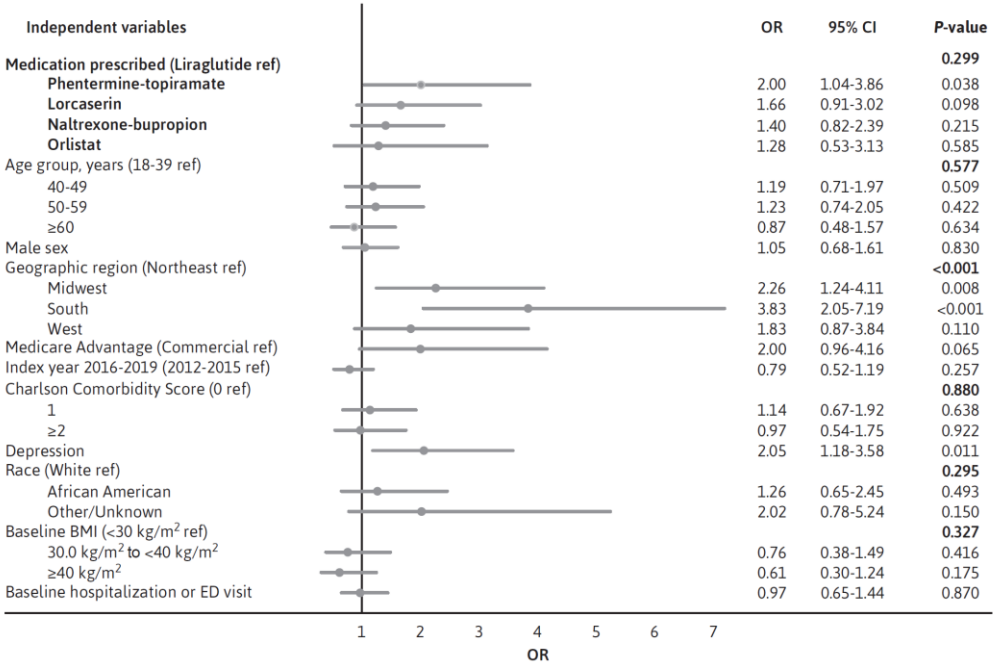

| Drug name | Weight loss (%) |
|---|---|
| Semaglutide (2.4mg, Wegovy) | 15% |
| Liraglutide (3mg, Saxenda) | 10% |
| Phentermine/Topiramate (Qsymia) | 11% |
| Naltrexone/Bupropion (Contrave) | 8% |
| Orlistat (Xenical, Alli) | ~5% |



Obesity (Silver Spring). 2024;32:486–493

# Factors affecting long-term adherence of obesity medications

Positive trend in adherence to treatment with higher initial BMI




## Leading causes for poor adherence

- Inadequate short-term efficacy
- Plateauing of weight loss
- Intolerable side effects, in particular CNS and CV side effects
- Dosing frequency
- Route of administration
- Switch mechanism
- Poor accessibility
- Cost of treatment



Real-world primary nonadherence to antiobesity medications. J Manag Care Spec Pharm. 2023;29(10):1099-108.

# New therapeutic directions and future precision medicine for anti-obesity drugs

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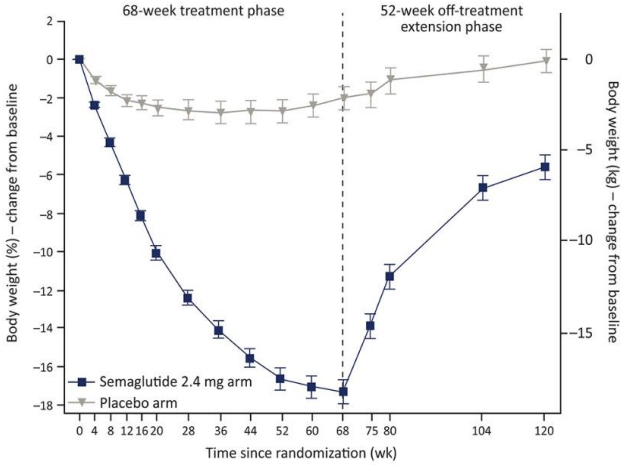
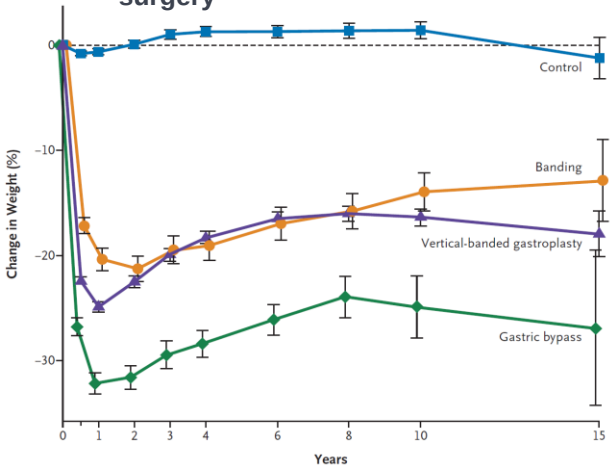
# What are solutions to minimize or prevent weight regain issue?

Even the most effective weight loss treatment, bariatric surgery, is associated with progressive weight regain

**70% weight regain is associated with the discontinuation of semaglutide[1]**




**Weight regain is also observed in different types of bariatric surgery[2]**




## Toward durable weight maintenance

- Improve compliance
- Extend dosing intervals – semi-annual or longer dosing frequency
- Reduce severity of side effects
- Incentivize patients through monitorable therapeutic effect in short-term (i.e. less than 3 months)
- Improve accessibility
- Increase durability of weight loss

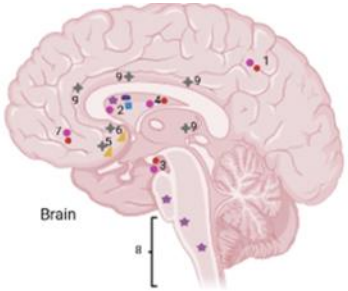


1. Diabetes Obes Metab. 2022;24:1553–1564; 2. N Engl J Med 2007;357:741-52.

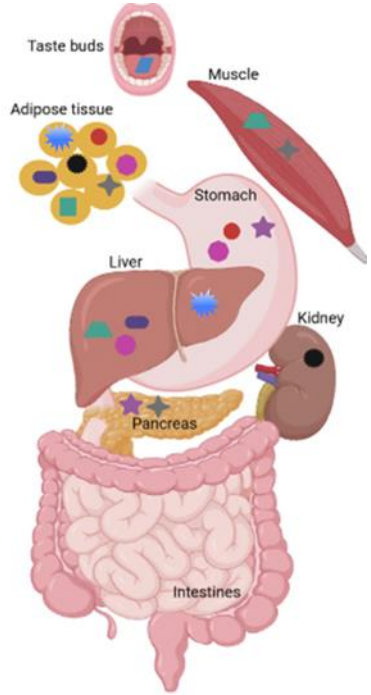
# INHBE silencing – an emerging therapy option for obesity

- INHBE (called Inhibin βE) is a liver specific gene. The gene product is activin E, which binds to its receptor (ACVR1C) in adipose tissues.
- INHBE LoF variants are associated with decreased abdominal obesity and profound risk reductions for T2D and CVD
- INHBE silencing may offer distinct mechanism of body weight regulation providing an excellent opportunity for future anti-obesity treatment with substantial improvement of metabolic health
- INHBE silencing may enable potent fat reduction, while maintaining muscle mass
- GalNAc siRNA offers high specificity and long duration of pharmacological effects

## Diverse mechanisms of anti-obesity treatments offer opportunities for individualized medicine option




| Medication | Central site of action | Possible peripheral site of action |
|---|---|---|
| GLP-1/glucagon dual agonists | 1,3,4,7 | Adipose tissue, gastrointestinal tract |
| GIP/GLP-1/glucagon tri agonists | 1,2,3,4,7 | Adipose tissue, gastrointestinal tract, liver |
| Y2R agonists | 2 | None |
| Amylin receptor agonists | 2,8 | Stomach, pancreas |
| SGLT-2 inhibitors | None | Adipose tissue, kidneys |
| Methylphenidate | 5,6 | None |
| Glabridin analogue | None | Liver, muscle |
| Oxytocin | 5,6,9 | Adipose tissue, pancreas, muscle |
| Leptin sensitizers | 2 | Adipose tissue, liver |
| Vitamin E | None | Adipose tissue |
| Taste receptor activator | None | Mouth |
| **INHBE** | **NONE** | **Adipose tissue, via liver** |




Modified from eClinical Medicine 2023;58: 101882

# Driven by clinical genetics, Wave's first RNAi program addresses high unmet need in obesity

INHBE program (GalNAc-siRNA) is Wave's first wholly owned program

## GLP-1 receptor agonists have several reported limitations

- × Lead to weight loss at the expense of muscle mass[1]
- × Associated with poor tolerability profile[4] with 68% drop-off after 1 year[3]
- × Discontinuation of therapy leads to rapid weight regain
- × Suppress general reward system[4]

**Wave's INHBE siRNA program may address these limitations and / or work complementarily with GLP-1s**

## INHBE silencing expected to induce fat loss, while maintaining muscle mass

- siRNA to silence INHBE gene is expected to recapitulate the healthy metabolic profile of INHBE loss of function (LoF) heterozygous human carriers, including:[1,2,3]
  - ✓ Reduced waist-to-hip ratio
  - ✓ Reduced serum triglycerides
  - ✓ Elevated HDL-c
  - ✓ Reduced odds ratio of type 2 diabetes and coronary artery disease, in addition to weight loss
- INHBE (Inhibin βE) expressed primarily in liver and gene product (activin E) acts on its receptor in adipose tissue[4]
- Lowering of INHBE mRNA promotes fat burning (lipolysis) and decreases fat accumulation (adiposity) in preclinical obesity models[5,6]

**≥50% reduction of INHBE in patients expected to restore and maintain a healthy metabolic profile**



1. Sargeant, et al. 2019 Endocrinol Metab (Seoul) 34(3):247-262; 2. Prime Therapeutics Claims Analysis, July 2023; 3. Müller, et al. 2019 Molecular Metabolism 30: 72-130.

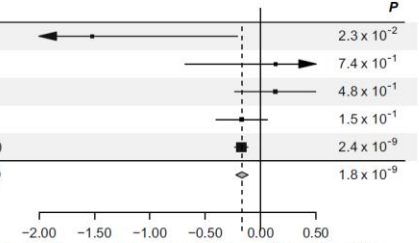
*1. Nat Commun 2022. https://doi.org/10.1038/s41467-022-32398-7; 2. Nat Commun 2022. https://doi.org/10.1038/s41467-022-31757-8; 3. PLOS ONE 2018. https://doi.org/10.1371/journal.pone.0194798; 4. Adam, RC. et.al. Proc Natl Acad Sci USA. 2023, 120(32): e2309967120. 5. Yogosawa et al. 2013 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3526038/ 6. Zhao et al. 2023 https://pubmed.ncbi.nlm.nih.gov/36626233/*

# INHBE LoF variants are associated with decreased abdominal obesity and profound risk reductions for T2D

**BMI−adjusted WHR (*INHBE* − pLOF, AAF < 1%)**

| Cohort | Ancestry | Allele count RR\|RA\|AA | Beta (95% CI) in SD units | Beta (95% CI) in ratio units | P |
|---|---|---|---|---|---|
| UKB | AFR | 8,946\|2\|0 | −1.5 (−2.8, −0.21) | −0.12 (−0.23, −0.017) | $2.3 \times 10^{-2}$ |
| UKB | SAS | 10,110\|5\|0 | 0.14 (−0.68, 0.95) | 0.011 (−0.056, 0.078) | $7.4 \times 10^{-1}$ |
| MDCS | EUR | 28,849\|26\|0 | 0.13 (−0.23, 0.49) | 0.011 (−0.019, 0.04) | $4.8 \times 10^{-1}$ |
| MCPS | AMR | 138,129\|58\|1 | −0.17 (−0.4, 0.06) | −0.014 (−0.033, 0.0049) | $1.5 \times 10^{-1}$ |
| UKB | EUR | 428,437\|1,005\|0 | −0.17 (−0.23, −0.12) | −0.014 (−0.019, −0.0096) | $2.4 \times 10^{-9}$ |
| **Meta−analysis** | **ALL** | **614,471\|1,096\|1** | **−0.17 (−0.22, −0.11)** | **−0.014 (−0.018, −0.0093)** | $1.8 \times 10^{-9}$ |

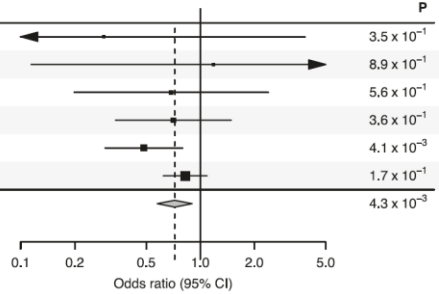
Heterogeneity $I^2$=44.9%; P=0.12




**Type 2 diabetes (INHBE – pLoF, AAF < 1%)**

| Cohort | Ancestry | Cases RR\|RA\|AA | Controls RR\|RA\|AA | Odds ratio (95% CI) | P |
|---|---|---|---|---|---|
| UKB | SAS | 1,936\|0\|0 | 8,195\|5\|0 | 0.29 (0.02, 3.82) | $3.5 \times 10^{-1}$ |
| SINAI | EUR | 978\|1\|0 | 7,492\|6\|0 | 1.18 (0.11, 12.24) | $8.9 \times 10^{-1}$ |
| MDCS | EUR | 3,802\|2\|0 | 21,117\|22\|0 | 0.69 (0.20, 2.38) | $5.6 \times 10^{-1}$ |
| MCPS | AMR | 26,482\|6\|1 | 81,936\|43\|0 | 0.71 (0.34, 1.48) | $3.6 \times 10^{-1}$ |
| GHS | EUR | 26,740\|18\|0 | 64,737\|111\|0 | 0.49 (0.30, 0.80) | $4.1 \times 10^{-3}$ |
| UKB | EUR | 23,862\|45\|0 | 401,975\|953\|0 | 0.82 (0.62, 1.09) | $1.7 \times 10^{-1}$ |
| **Meta−analysis** | **ALL** | **83,800\|72\|1** | **585,452\|1,140\|0** | **0.72 (0.58, 0.90)** | $4.3 \times 10^{-3}$ |

Heterogeneity I2=0%; P=0.55

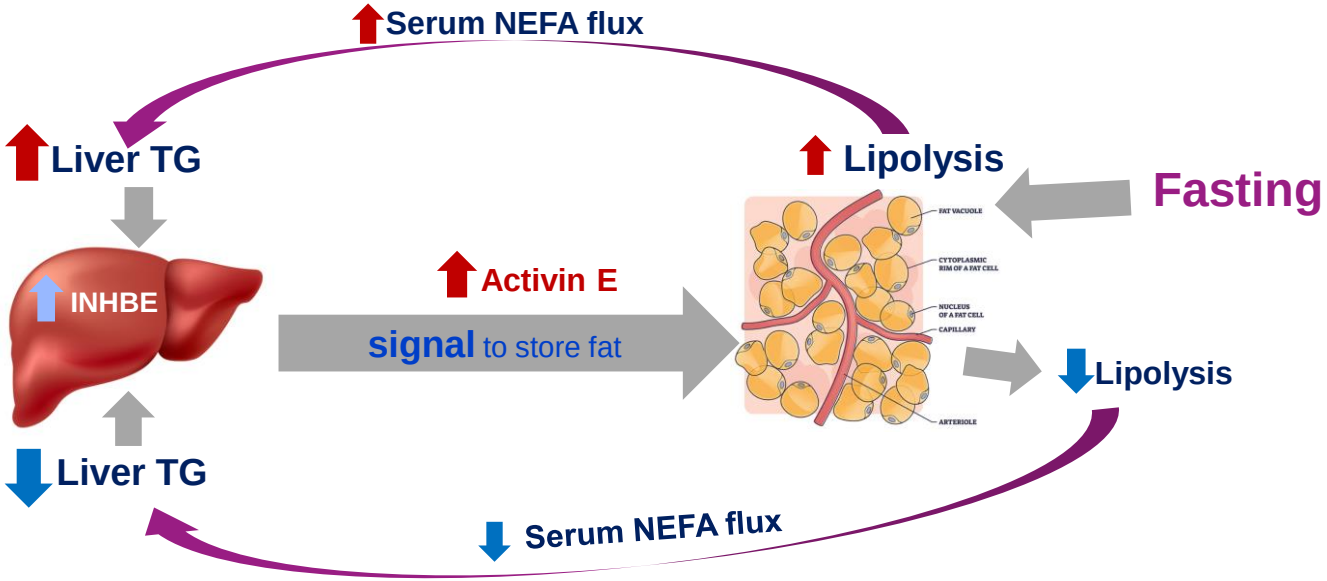



β= -0.17 SD of BMI-adjusted WHR

28% reduction in Odds Ratio for T2D

**Silencing of INHBE mRNA is expected to reduce abdominal obesity and risk for T2D & CAD**

# INHBE (called Inhibin βE) mRNA is a key regulator of adipose lipolysis through serum NEFA, under *normal physiological conditions*

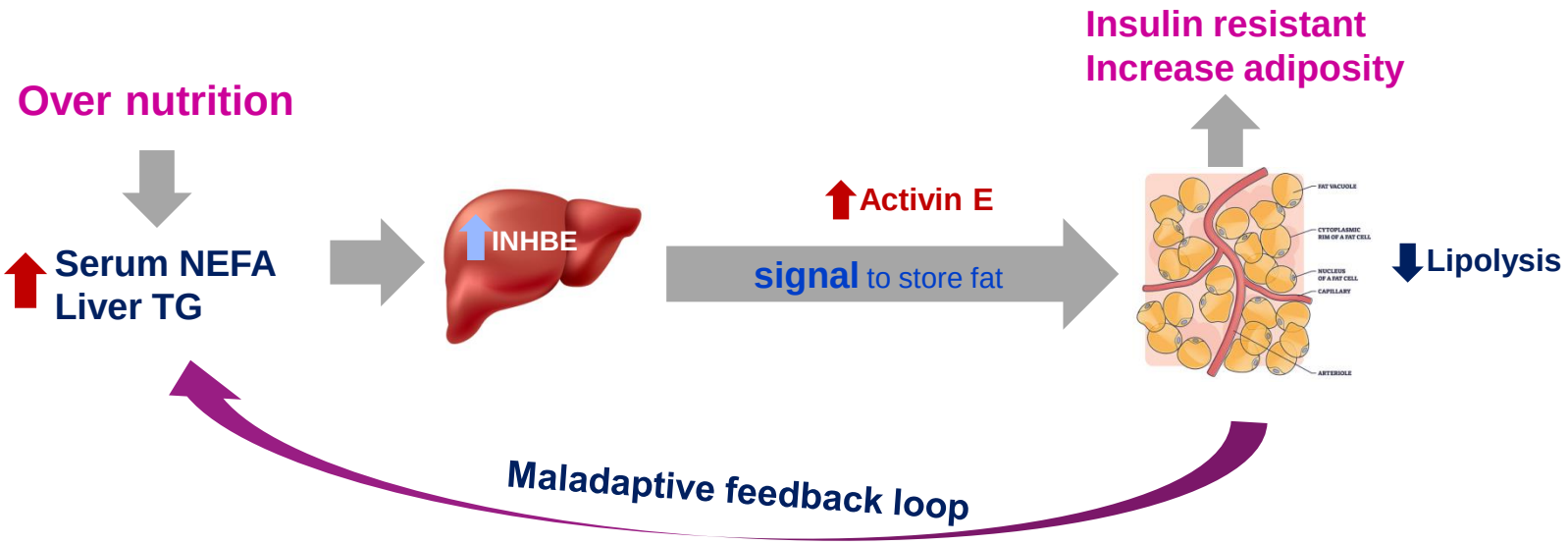



**Fasting induced lipolysis and serum NEFA drives upregulation of liver INHBE, which, in turn, suppresses adipose lipolysis, lowers serum NEFA and brings INHBE mRNA back to normal level.**



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

# Continuous upregulation of INHBE mRNA leads to *maladaptive response* to over nutrition and drives elevation of serum NEFA and liver TG

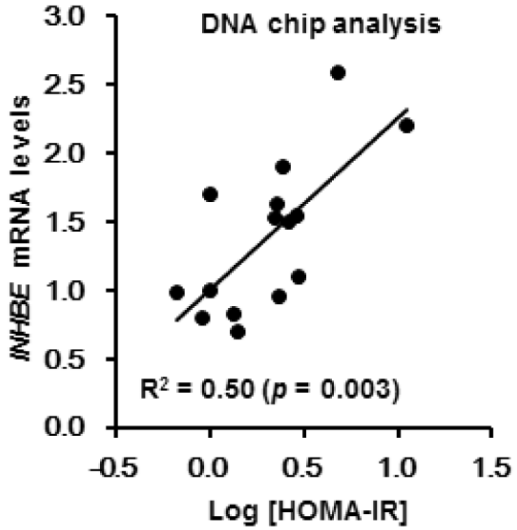


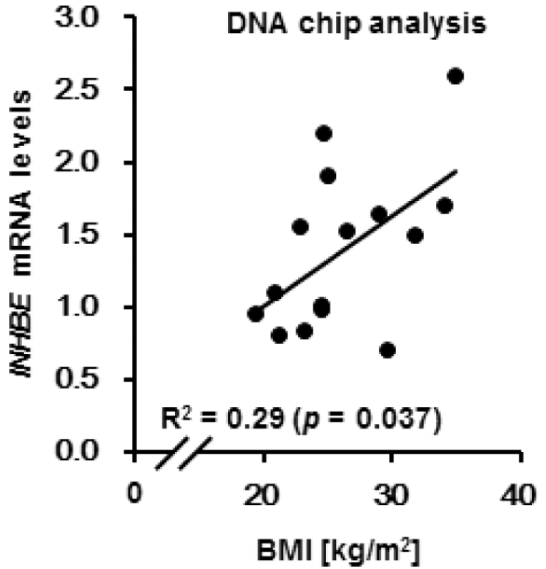

**Under pathological conditions, i.e. increase insulin resistance or adiposity, liver INHBE mRNA is upregulated as a result of maladaptive response and further promotes fat storage and increase of adiposity**



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

# INHBE mRNA increase with insulin resistance and BMI in human



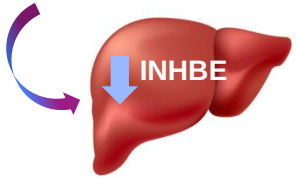




*Data from Sugiyama M et al. PLoS ONE 13(3): e0194798*

**Silencing of INHBE should improve insulin sensitivity and reduce BMI**

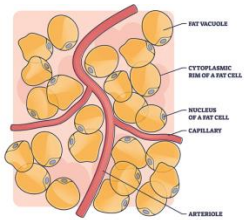
# Silencing INHBE increases adipose lipolysis, induces white adipose beiging & browning, and improves serum lipid profile & metabolic health

**INHBE GalNAc siRNA**




**Activin E**

**Stop** signaling for fat storage




**Lipolysis & fat burning**
**White adipose beiging & browning**

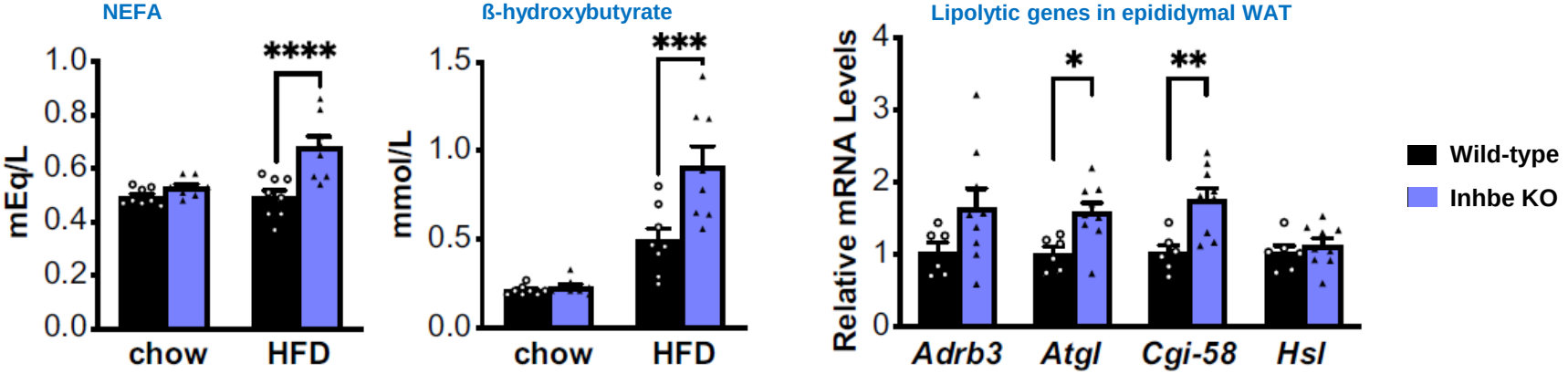
- **Improved serum lipid profile**
- **Reduced visceral and subcutaneous adipose tissues**
- **Lowered adipose inflammation**

**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

# Activin E–ACVR1C cross talk controls energy storage via suppression of adipose lipolysis in mice

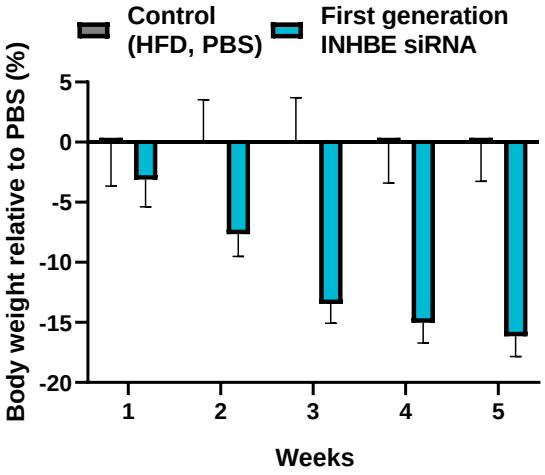



*Data from Adam RC et al, PNAS (2023) 120(32): e2309967120*

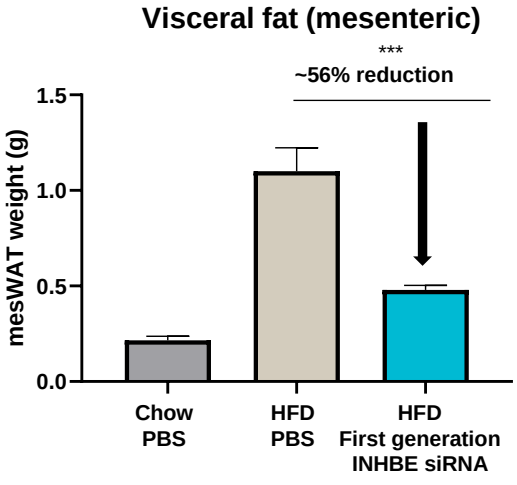
**Loss of activin E promotes fat burning, weight loss and may offer an excellent combination or switch therapeutic option for weight maintenance and improvement of metabolic health**

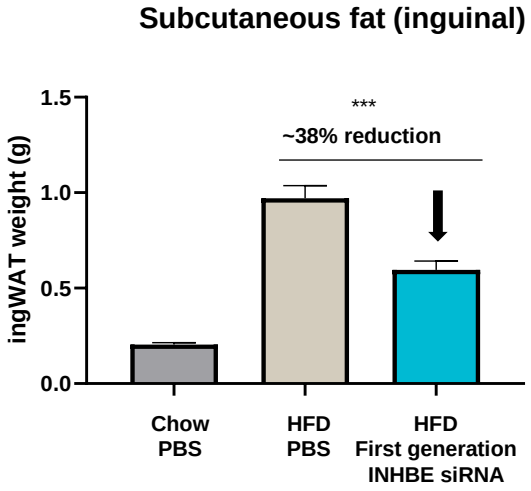
# First generation INHBE GalNAc-siRNA led to lower body weight and significant decrease in visceral fat in DIO mouse model

**Lower body weight as compared to control**




**Reduction in fat mass across multiple types of white adipose tissue, with preferential effect on visceral fat reduction**



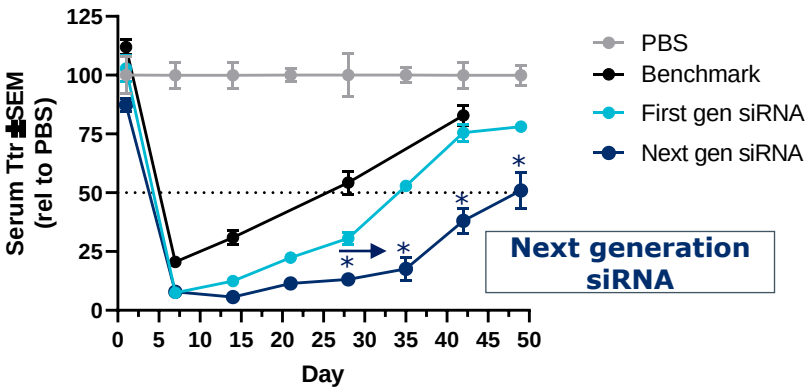

**Results of *in vivo* preclinical study are consistent with UK Biobank human data on loss-of-function carriers**



Right: Reduction in fat mass at Week 5; DIO: Diet-induced obesity

# INHBE lead clinical candidate has Wave's next generation siRNA format and best-in-class profile

## Next generation siRNA results in more potent and durable target knockdown




## INHBE program: Data from DIO mouse model supports best-in-class profile

- ✓ Highly potent silencing ($ED_{50}$ < 1mg/kg)
- ✓ Durable silencing following one, low-single-digit dose, supporting every-six-month or annual dosing
- ✓ Weight loss similar to semaglutide with no loss of muscle mass
- ✓ Reduction in fat mass, with preferential effect on visceral fat
- ✓ Curtailed rebound weight gain upon cessation of semaglutide

**Expect to initiate clinical trial for INHBE candidate in 1Q 2025**



Left: Benchmark: Foster, DJ. et.al. Mol Ther. 2018, 26(3), 708. B6 mice administered PBS or 0.5 mg/kg of siRNA (subcutaneous). Stats: Mixed Two-way ANOVA followed by post hoc test comparing siRNA vs. Next gen siRNA per day derived from linear mixed effects model * P < 0.0001; DIO: diet-induced obesity

# Emerging ideas for future obesity treatments - Enabling healthy, sustainable weight loss

Future obesity treatments geared toward effective improvement of body composition (decrease fat / maintain or increase muscle mass) - INHBE silencing has potential to address many of treatment goals

## Infrequent administration – semi-annual or annual dosing

**Goal to enhance**

- Compliance
- Effectiveness
- Adherence
- Durability

## Precision medicine approach for treatment initiation based on

- Co-morbidity(ies)
- Severity of obesity and treatment goal
- Route of administration consideration
- Tolerance of specific side effect(s)

## Individualized selection of add-on, switch or maintenance therapy based on

- Complementarity of MoAs
- Synergistic MoAs
- Side effect profiles
- Severity of obesity and treatment goal
- Treatment frequency and route of administration

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