nature medicine

Brief Communication

https://doi.org/10.1038/s41591-025-03913-2

Tirzepatide leads to weight reduction in people with obesity due to MC4R deficiency

Received: 10 November 2024

Accepted: 24 July 2025

Published online: 26 August 2025

Check for updates

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The magnitude of weight reduction in the SURMOUNT-1 trial of the dual GLP-1 and GIP receptor agonist tirzepatide suggests that this treatment may be particularly effective in addressing the treatment needs of people with severe obesity (body mass index >40 kg m^{-2}), some of whom may carry rare penetrant genetic variants. Here we investigated the clinical response of men and women in the SURMOUNT-1 trial who carried pathogenic mutations in the melanocortin 4 receptor (*MC4R*) gene, the most common genetic cause of obesity. We found that 32 of 2,291 people (1.4%) for whom data were available carried pathogenic *MC4R* mutations. At baseline, *MC4R* mutation carriers exhibited a higher body mass index compared with noncarriers (40 kg m^{-2} versus 38 kg m^{-2}; $P = 0.036$). In the treatment arm, the weight loss trajectory over 72 weeks was comparable in both groups: 18.3% weight reduction in *MC4R* mutation carriers versus 19.9% in noncarriers. We conclude that tirzepatide is an effective treatment for the most common genetic subtype of obesity, MC4R deficiency.

The new generation of obesity medications that target the glucagon-like peptide-1 (GLP-1) receptor and/or the glucose-dependent insulinotropic polypeptide (GIP) receptor are transforming the clinical care of people with obesity and its complications[1]. In clinical trials, the dual GIP and GLP-1 receptor agonist tirzepatide has been shown to result in substantial weight reduction (~20%) in people with obesity, with and without type 2 diabetes[2,3]. This magnitude of weight reduction suggests that tirzepatide may be particularly beneficial in people with severe obesity (defined as a body mass index (BMI) >40 kg m^{-2}), who have the highest burden of complications and highest mortality from cardiovascular disease.

Twin, family and adoption studies have consistently demonstrated that genetic factors influence the variation in body weight seen in an obesogenic environment[4]. The heritable contribution to body weight is greatest in people with severe obesity who have both a higher burden of common obesity susceptibility alleles and a higher prevalence of rare penetrant alleles that drive weight gain from childhood[5]. The melanocortin 4 receptor (MC4R) is expressed in the hypothalamus, brainstem and other brain regions and plays a pivotal role in the regulation of hunger, satiety and food preference[6]. Heterozygous *MC4R* mutations that are dominantly inherited and cause loss of function (LoF) in cells are defined as pathogenic[7,8]. Pathogenic *MC4R* mutations have been found in both clinical and population-based cohorts[9] at varying frequencies depending on ascertainment criteria: 0.3% of an unselected UK birth cohort[10], 1% of adults with a BMI >30 kg m^{-2}, 2% of children with obesity[11] and up to 5% of children with severe obesity[7]. MC4R deficiency, which represents the most common genetic form of obesity, is characterized by hyperphagia (increased drive to eat), weight gain that begins in the first 5 years of life, disproportionate hyperinsulinemia and accelerated linear growth in childhood[7,12,13]. Adults with MC4R deficiency often have severe obesity but with a lower prevalence of hypertension and reduced systolic and diastolic blood pressure associated with impaired sympathetic nervous system tone[14,15].

Obesity due to MC4R deficiency is challenging to treat. Two studies have shown that intense dietary and physical activity interventions[11,16] are less effective in children with MC4R deficiency, and weight reduction is harder to maintain in this group. While melanocortin receptor agonists can act as pharmacological chaperones to rescue signaling by some MC4R-mutant receptors in cells[17,18], clinical trials of a MC4R agonist have not demonstrated efficacy in this patient group[17].

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https://doi.org/10.1038/s41591-025-03913-2

Table 1 | Characteristics of SURMOUNT-1 participants at baseline

Characteristic	*MC4R* mutation carriers (n=32)[a]	Noncarriers (n=2,259)[a]	P value[b]
Age, years	41.06 (13.12)	45.23 (12.36)	0.043
Female sex, no. (%)	20 (62%)	154 (68%)	
Duration of obesity, years	16.38 (9.17)	14.40 (10.88)	0.11
BMI, kg m^{-2}	40.04 (6.21)	38.04 (6.88)	0.036
BMI category, no. (%)			0.084
<35	7 (22%)	907 (40%)	
≥35 to <40	10 (31%)	631 (28%)	
≥40	15 (47%)	721 (32%)	
Waist circumference, cm	120.44 (15.95)	114.02 (15.18)	0.012
Glycated hemoglobin, %	5.57 (0.48)	5.56 (0.37)	0.71
Fasting glucose, mg dl^{-1}	95.20 (10.54)	95.50 (10.10)	0.72
Fasting insulin, mIU l^{-1}	15.40 (9.08)	14.02 (10.44)	0.31
Blood pressure, mm Hg			
Systolic	121.31 (13.35)	123.59 (12.62)	0.43
Diastolic	79.5 (8.10)	79.56 (8.14)	0.91
Heart rate, beats min^{-1}	72.50 (10.13)	72.13 (9.52)	0.83
Lipid levels, mg dl^{-1}			
Total cholesterol	183.56 (36.94)	191.91 (38.94)	0.22
HDL cholesterol	45.87 (11.99)	48.96 (13.04)	0.23
LDL cholesterol	108.71 (33.35)	114.52 (32.81)	0.31
Triglycerides	148.14 (73.44)	145.80 (107.45)	0.52

[a]For all characteristics, mean (s.d.) are shown; no., number (%). [b]Wilcoxon rank-sum test; Pearson's chi-squared test; Fisher's exact test, two-sided. Lipid levels are shown as geometric means (coefficient of variation, %). HDL, high-density lipoprotein; LDL, low-density lipoprotein.

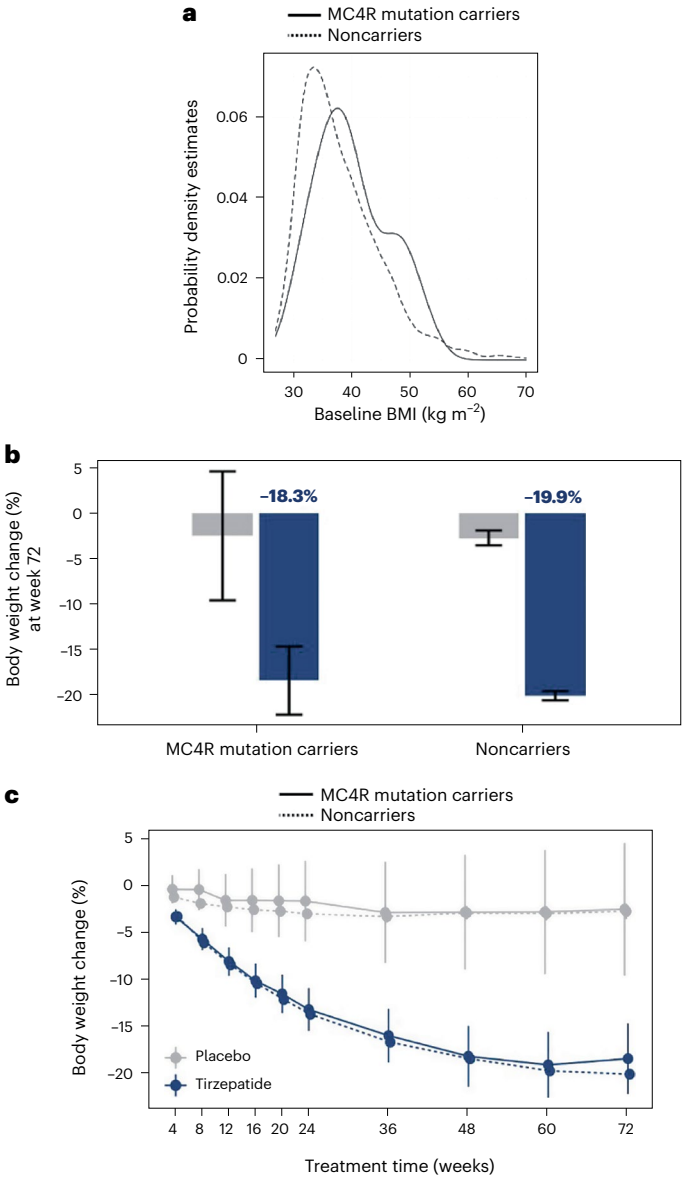

Fig. 1 | Baseline BMI distribution and tirzepatide-induced weight loss in *MC4R* mutation carriers versus noncarriers. a, The distribution of BMI at baseline for *MC4R* mutation carriers and noncarriers. **b**, Least-squares mean estimands of the percentage change in body weight from baseline to week 72, with error bars representing 95% confidence intervals (CI). Genetic effects on change in body weight were assessed using aggregated data on carriers of 14 *MC4R* LoF mutations (beta coefficient −0.88, SEM 3.2); statistical significance was assessed using a REGENIE collapsed burden test incorporating the treatment interaction effect (unadjusted two-sided P value 0.79). **c**, Time course effect on body weight change. Least-squares mean estimands were generated for each time point based on a three-way interaction among *MC4R* carrier status, pooled treatment and visit. Blue and gray bars represent tirzepatide treatment and placebo arms, respectively, with error bars representing 95% CI.

As such, there is currently no licensed treatment for people with obesity due to MC4R deficiency. GLP-1 receptor agonists predominantly target non-MC4R-dependent neural pathways in mice[19], and there is evidence from a small clinical study with liraglutide[20] that they may be effective in people with MC4R deficiency. Here, to investigate the efficacy of tirzepatide in people with MC4R deficiency, we examined genetic data obtained from participants in a randomized controlled trial (SURMOUNT-1) of people with a BMI ≥30 kg m^{-2}, or ≥27 kg m^{-2} with at least one weight-related comorbidity[2], treated with tirzepatide versus placebo.

DNA samples of sufficient quality were obtained on 2,291 people (90%) randomized in the SURMOUNT-1 trial. These samples were genotyped using the Axiom genotyping array from Affymetrix. We identified 24 different missense, frameshift and amino acid insertion or deletion mutations; 14 of these mutations have been shown to reduce MC4R function in cells (that is, LoF; https://www.mc4r.org.uk/), giving a prevalence of pathogenic *MC4R* mutations of 1.4% (n = 32/2,291) in adults with obesity in the SURMOUNT-1 study (Extended Data Table 1). People carrying either of the two prevalent gain-of-function *MC4R* variants (V103I and I251L; n = 88), associated with lower BMI in cohort studies[21], were excluded from all analyses.

We found that, at baseline, the BMI distribution differed between *MC4R* mutation carriers and noncarriers (P = 0.036); a greater proportion of people with MC4R deficiency had severe obesity and increased waist circumference (P = 0.012); they were also slightly younger at recruitment (Table 1 and Fig. 1a). A trend toward lower total cholesterol was observed, consistent with findings from larger clinical case series of individuals with MC4R deficiency and from *MC4R* mutation carriers in the UK Biobank population cohort (accompanying paper, Zorn et al.[22]). Otherwise, the clinical characteristics of carriers of MC4R mutations and noncarriers were broadly similar (Table 1 and Extended Data Table 2).

We compared the weight loss trajectory at 72 weeks in the 32 *MC4R* mutation carriers and 2,259 noncarriers. People with MC4R deficiency responded to tirzepatide similarly to those with a normal *MC4R* genotype, demonstrating the effectiveness of tirzepatide in this subgroup of people with obesity (Fig. 1b,c). Furthermore, there was no differential

impact of treatment (versus placebo) on metabolic parameters in *MC4R* mutation carriers versus noncarriers (Extended Data Table 3). All the *MC4R* mutation carriers in the placebo-treated group were female (Extended Data Table 2). This probably represents a chance occurrence given the rarity of MC4R deficiency and the fact that the SURMOUNT-1 cohort recruited twice as many females as males (males 825, females 1,714, total 2,539).

These results suggest that tirzepatide may be an effective treatment option for the most common form of monogenic obesity, MC4R deficiency. Given the severity of obesity in mutation carriers, equitable access to obesity medications should be a priority for this group, in whom diet and exercise interventions are unlikely to be effective. Roux-en-Y bypass surgery is effective in carriers of heterozygous but not homozygous mutations in *MC4R*, suggesting that central melanocortin circuits mediate some of the effects of bariatric surgery[23]. In a case report, a homozygous *MC4R* mutation carrier not responding to RYGB surgery was found to respond to GLP-1 receptor agonist treatment[24].

Ongoing studies of the safety and efficacy of chronic treatment with obesity medications will be important for the management of patients with MC4R deficiency and other clinical groups. As MC4R deficiency presents with severe obesity from childhood, trials of tirzepatide (NCT06439277 and NCT06075667) and other obesity medications in children and adolescents with obesity, including those with MC4R deficiency, are needed to provide the evidence base for earlier, and potentially chronic, treatment in genetically driven obesity.

Online content

Any methods, additional references, Nature Portfolio reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at https://doi.org/10.1038/s41591-025-03913-2.

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Methods

Study cohort (SURMOUNT-1 clinical trial)

Ethical approval and study populations. The study was conducted in accordance with the principles of the Declaration of Helsinki, Good Clinical Practice guidelines and all applicable regulatory requirements Study protocol and informed consent documents were approved by independent ethics committees and institutional review boards at all participating trial sites. Trial site investigators obtained consent, recruited participants, collected data and adhered to ethical standards. The sponsor conducted centralized monitoring with strict ethical oversight.

Genotyping. DNA was extracted from whole blood samples from participants enrolled in the SURMOUNT-1 trial (supported by Eli Lilly and Company.; ClinicalTrials.gov number NCT04184622) who consented to genetic analyses. Samples were quantified using a Quant-iT PicoGreen dsDNA assay to measure the DNA concentration. Samples were genotyped using the customized Axiom Biobank genotyping array (version 3) from Affymetrix. The array was customized using an Affymetrix UK BioBank backbone and incorporated all known genetic variants associated with genes or pathways related to various pathophysiological manifestations of obesity and related complications. A total of 2,474 patient samples along with duplicates and HapMap controls were genotyped, and data on 726,107 variants were generated. Standard metrics for genome-wide level data quality control were applied. After excluding variants with a call rate below 95% (n = 1,931), discordant variants in duplicate samples (n = 493) and monomorphic variants (n = 77,179), 646,504 variants and 2,291 samples passed quality control screening.

Statistical methods and details. *Mixed-model repeated-measures weight loss imputation*. A mixed model was run using SAS, including baseline weight, country, sex, prediabetes status, treatment, visit and the treatment-by-visit interaction as fixed effects, with a subject-level random effect. Any visits that did not have a recorded weight value were imputed as the predicted value from the mixed effect model. The value for the imputed weight percentage change from baseline was computed as (Predicted − Baseline) × 100/Baseline for all imputed visits. To ensure enough visits for imputation, we used only participants with a visit at week 24 or later (n = 2,291).

Genetic analysis. REGENIE was used to perform statistical association analyses for gene-level and single mutation-level testing[25]. For both models, the imputed weight loss percentage change from baseline at week 72 was used as the outcome. The model tested for genetic interaction with pooled treatment (collapsed 5, 10 and 15 mg treatment groups versus placebo), adjusting for age, sex, study country, baseline weight, prediabetes status and the first ten principal components.

$$\text{Outcome} = \beta_0 + \text{Variant} \times \beta_{\text{SNP}} + \text{Treatment} \times \beta_{\text{Trt}} + \text{Variant} \times \text{Treatment} \times \beta_{\text{inter}} + \text{Covariates} \times \beta_{\text{cov}}$$

Default settings were used in REGENIE genotypic data preparation and testing. For gene-level MC4R carrier testing, 14 LoF mutations were used to define the MC4R mask for collapsed burden testing, which measures the genotype–treatment interaction effect.

Mixed-model repeated-measures least-square means. A mixed-effects model for the imputed weight outcome at week 72 was created, including the same fixed covariates as in the genetic analysis, as well as visit, and a subject-level random effect. The least-square means estimands were generated for the three-way interaction for MC4R carrier status, pooled treatment (collapsed 5, 10 and 15 mg treatment groups versus placebo) and visit. Week 72 visit estimands were plotted to visualize the single-time-point treatment and MC4R LoF carrier interaction effect (Fig. 1b), while estimands from all available visits were plotted over time to illustrate the visit interaction effect (Fig. 1c).

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Data availability

The trial sponsor (Eli Lilly and Company) participated in the design and execution of the study, as well as collection, management, analysis and interpretation of the data. Patient-related information was anonymized and collected as part of the SURMOUNT-1 clinical trial and will be subject to confidentiality restrictions. Primary reasons for controlled access of this data are participant confidentiality and ethical compliance. Request for data access can be submitted via Vivli, and expected time for response is around 60 days.

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Acknowledgements

I.S.F. is supported by Wellcome (207462/Z/17/Z), Botnar Fondation, the Bernard Wolfe Health Neuroscience Endowment and a NIHR Senior Investigator Award. The funding bodies had no role in the design or conduct of the study; collection, management, analysis or interpretation of the data; preparation, review or approval of the manuscript; or the decision to submit the manuscript for publication. The views expressed are those of the authors and not necessarily those of the NIHR, the Department of Health and Social Care or the UK government. Eli Lilly and Company was the sponsor of this study. We thank the patients who consented to participate in the SURMOUNT-1 study. We also thank K. M. Kelly for assisting in internal approval processes and informed consent document review, and D. W. Bedwell for coordinating with the contract research organization for sample shipments, genotyping and secure data transfer.

Author contributions

I.S.F. and P.B. conceptualized the project, analyzed the data, interpreted the results and drafted the manuscript. N.N.A provided clinical guidance, facilitated access to the data and assisted in securing funding for the study. N.N.A. and M.C. contributed to formalizing study plans, data analyses and interpretation. X.L. offered operational support to execute the analyses and secure timely delivery of the results. L.M.K. provided critical review of the results and interpretation. All authors reviewed the manuscript for accuracy, edited subsequent revisions of the draft and approved the final paper.

Competing interests

I.S.F. has consulted for Eli Lilly, Novo Nordisk, Sanofi, Nodthera Therapeutics and Rhythm Pharmaceuticals on anti-obesity medications. L.M.K. is a scientific and/or medical consultant to Altimmune, Amgen, Boehringer Ingelheim, Cytoki, Gilead, Johnson & Johnson, Kallyope, Eli Lilly and Company, Novo Nordisk, Optum, Perspectum, Pfizer, Xeno Biosciences and Zealand. N.N.A., M.C., X.L. and P.B. are employees and shareholders of Eli Lilly and Company.

Additional information

Extended data is available for this paper at https://doi.org/10.1038/s41591-025-03913-2.

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41591-025-03913-2.

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Peer review information *Nature Medicine* thanks Anke Hinney, Edra London and the other, anonymous, reviewer(s) for their contribution to the peer review of this work. Primary Handling Editors: Ashley Castellanos-Jankiewicz and Sonia Muliyil, in collaboration with the *Nature Medicine* team.

 https://doi.org/10.1038/s41591-025-03913-2

Extended Data Table 1 | Summary of loss-of-function MC4R mutations identified in SURMOUNT-1 participants

Chr	Position Start (GRCh 38)	Position End (GRCh 38)	Mutation Type	rsID	Protein consequence	Carriers in SURMOUNT-1 (N=32/2,291) Total (Tirzepatide | Placebo)
18	60,372,261	60,372,261	Missense	rs13447323	p.Ser30Phe	1 (0 | 1)
18	60,372,135	60,372,135	Missense	rs775933215	p.Asn72Ser	1 (1 | 0)
18	60,372,015	60,372,015	Missense	rs13447329	p.Thr112Met	1 (1 | 0)
18	60,371,970	60,371,970	Missense	rs13447331	p.Ser127Leu	2 (1 | 1)
18	60,371,857	60,371,857	Missense	rs13447332	p.Arg165Trp	1 (1 | 0)
18	60,371,827	60,371,827	Missense	rs121913563	p.Ala175Thr	3 (3 | 0)
18	60,371,659	60,371,660	Missense	rs1363347811	p.Gly231Ser*	1 (0 | 1)
18	60,371,631	60,371,631	Missense	rs202228712	p.Asn240Ser	3 (3 | 0)
18	60,371,596	60,371,596	Missense	rs13447336	p.Gly252Ser	2 (1 | 1)
18	60,371,544	60,371,544	Missense	rs79783591	p.Ile269Asn	11 (8 | 3)
18	60,371,513	60,371,514	Frameshift	---	p.Phe280AlafsTer12	1 (1 | 0)
18	60,371,474	60,371,477	Inframe Deletion	rs754899496	p.Ile291del**	3 (3 | 0)
18	60,371,433	60,371,433	Missense	rs940167950	p.Ser306Asn	1 (1 | 0)
18	60,371,428	60,371,428	Missense	rs375095163	p.Glu308Lys	1 (1 | 0)

* This is a multiallelic site (p.Gly231Ser and p.Gly231AlafsTer11); we only observed Gly231Ser in our study ** This is a multiallelic site (p.Ile291del, or p.Met292SerfsTer9, or p.Met292Ile); we observed p.Ile291del in our study. MC4R variants were classified as loss-of-function if they had previously been shown to impair binding /signaling or other mechanisms in cells (as reported on www.mc4r.org.uk)

https://doi.org/10.1038/s41591-025-03913-2

Extended Data Table 2 | Characteristics of SURMOUNT-1 participants at baseline by treatment allocation

Characteristic[1]	Placebo		Tirzepatide		p-value[2]
	MC4R mutation carriers (n = 7)[1]	Non-carriers (n = 562)	MC4R mutation carriers (n = 25)	Non-carriers (n = 1,697)[1]	
Age - years	37.1 (15.0)	45.0 (12.5)	42.2 (12.6)	45.3 (12.3)	0.2
Female sex - no. (%)	7 (100%)	377 (67%)	13 (52%)	1,160 (68%)	
Body mass index (kg/m^2)	39.8 (5.4)	38.2 (6.9)	40.1 (6.5)	37.9 (6.8)	0.2
Body mass index <35 kg/m^2 (%)	1 (14%)	220 (39%)	6 (24%)	687 (40%)	
Body mass index >=35– 40 kg/m^2 (%)	3 (43%)	152 (27%)	7 (28%)	479 (28%)	
Body mass index >=40 kg/m^2 (%)	3 (43%)	190 (34%)	12 (48%)	531 (31%)	
Waist circumference - cm	118.9 (17.1)	114.1 (14.9)	120.9 (15.9)	114.0 (15.3)	0.09
Glycated hemoglobin - %	5.41 (0.3)	5.58 (0.4)	5.6 (0.5)	5.5 (0.4)	0.2
Fasting glucose - mg/dl	93.4 (7.4)	95.8 (9.7)	95.7 (11.3)	95.4 (10.2)	0.6
Systolic blood pressure (mm Hg)	114.8 (14.6)	123.3 (12.4)	123.1 (12.7)	123.7 (12.6)	0.3
Diastolic blood pressure (mm Hg)	76.6 (6.1)	79.7 (7. 8)	80.3 (8.5)	79.5 (8.2)	0.5
Total cholesterol (mg/dl)	173.3 (28.2)	190.4 (38.6)	186.4 (39.0)	192.4 (39.0)	0.3
HDL cholesterol (mg/dl)	48.5 (14.6)	48.1 (12.9)	45.1 (11.4)	49.2 (13.0)	0.14
LDL cholesterol (mg/dl)	97.2 (21.8)	113.5 (33.3)	111.9 (35.6)	114.8 (32.6)	0.3
Triglycerides (mg/dl)	137.4 (62.7)	146.4 (84.3)	151.1 (77.1)	145.5 (114.1)	0.7

[1]For all characteristics, mean (SD) are shown; no, number (%); [2] Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test, two-sided Lipid levels are shown as geometric means (coefficient of variation, %). Abbreviations: HDL: High density lipoprotein; LDL: Low density lipoprotein.

 https://doi.org/10.1038/s41591-025-03913-2

Extended Data Table 3 | Tirzepatide induced changes in metabolic parameters

Percent change from baseline (at 72 weeks)		Estimated Marginal Means[1]	SE	95% CI		N	p-value[2] (interaction)
				LCI	UCI		
Total Cholesterol (mg/dl)	Non carrier	-4.2	0.72	-5.63	-2.80	1,549	0.52
	MC4R mutation carriers	-2.9	3.20	-9.18	3.36	24	
Triglycerides (mg/dl)	Non carrier	-20	1.83	-23.89	-16.69	1,545	0.12
	MC4R mutation carriers	-13	7.60	-27.51	2.31	24	
Systolic Blood Pressure (mm Hg)	Non carrier	-4.8	0.43	-5.62	-3.95	1,583	0.28
	MC4R mutation carriers	-4.5	1.83	-8.11	-0.95	24	
Diastolic Blood Pressure (mm Hg)	Non carrier	-4.7	0.49	-5.61	-3.70	1,583	0.33
	MC4R mutation carriers	-5	2.06	-9.06	-0.98	24	
Glycated hemoglobin (%)	Non carrier	-7.9	0.23	-8.34	-7.44	1,558	0.19
	MC4R mutation carriers	-7	1.05	-9.04	-4.93	23	

[1]Estimated marginal means are for the tirzepatide treatment arm only [2]P-value represents MC4R mutation carrier status and treatment interaction effect from REGENIE collapsed burden test, two-sided, no multiple testing adjustment N represents the participants allocated to the tirzepatide treatment arm and with available MC4R genetic and clinical data Total cholesterol and Triglycerides levels are shown as geometric means (coefficient of variation, %) Abbreviations: SE: Standard Error for estimated marginal means; LCI: Lower bound 95% confidence interval; UCI: Upper bound 95% confidence interval

Materials & experimental systems

n/a	Involved in the study
☒	☐ Antibodies
☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☒	☐ Animals and other organisms
☐	☒ Clinical data
☒	☐ Dual use research of concern
☒	☐ Plants

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

Clinical data

Policy information about clinical studies

All manuscripts should comply with the ICMJE guidelines for publication of clinical research and a completed CONSORT checklist must be included with all submissions.

Clinical trial registration	NCT04184622
Study protocol	Protocol for: Jastreboff AM, Aronne LJ, Ahmad NN, et al. Tirzepatide once weekly for the treatment of obesity. N Engl J Med 2022;387:205-16. (https://www.nejm.org/doi/suppl/10.1056/NEJMoa2206038/suppl_file/nejmoa2206038_protocol.pdf)
Data collection	All data was collected at specific clinics by investigators, with baseline defined as the last non-missing data collected at randomization (before the first dose of study drug) and post-treatment at 72 weeks. Data from a contracted vendor was stored electronically in the vendor's database system and then transferred to a centralized database.
Outcomes	Primary outcome: % change in body weight from baseline to week 72 (taken at fasted state using a calibrated electronic scale capable of measuring weight in kg to 1 decimal place) Key secondary end points were metabolic parameters: waist circumference, HbA1c, fasting glucose, fasting insulin, BP, heart rate, and lipid levels

Plants

Seed stocks	N/A
Novel plant genotypes	N/A
Authentication	N/A