



Why Do Incretin Mimetics Work Brilliantly in Some but Poorly in Others?

David E. Cummings, MD, FASMBS

**University of Washington
VA Puget Sound Health Care System**



Disclosures

- **Scientific Advisory Boards**
- Lumen Bioscience
- Morphic Medical
- Gila Therapeutics
- Endogenex

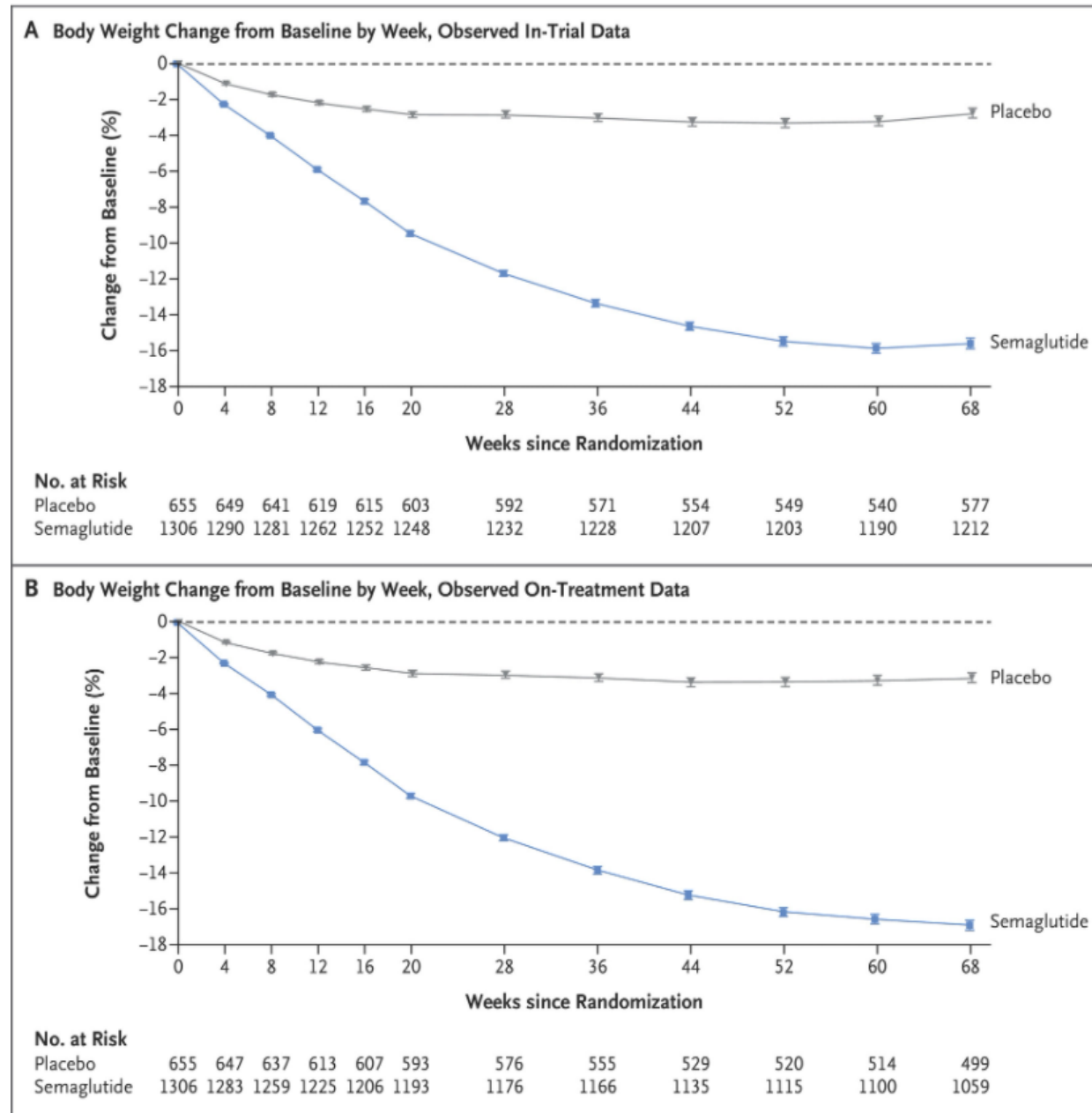
STEP 1: Semaglutide vs. Placebo – *No Diabetes*

n=1,961

Body
Weight
Change
(%)

Single Agonist

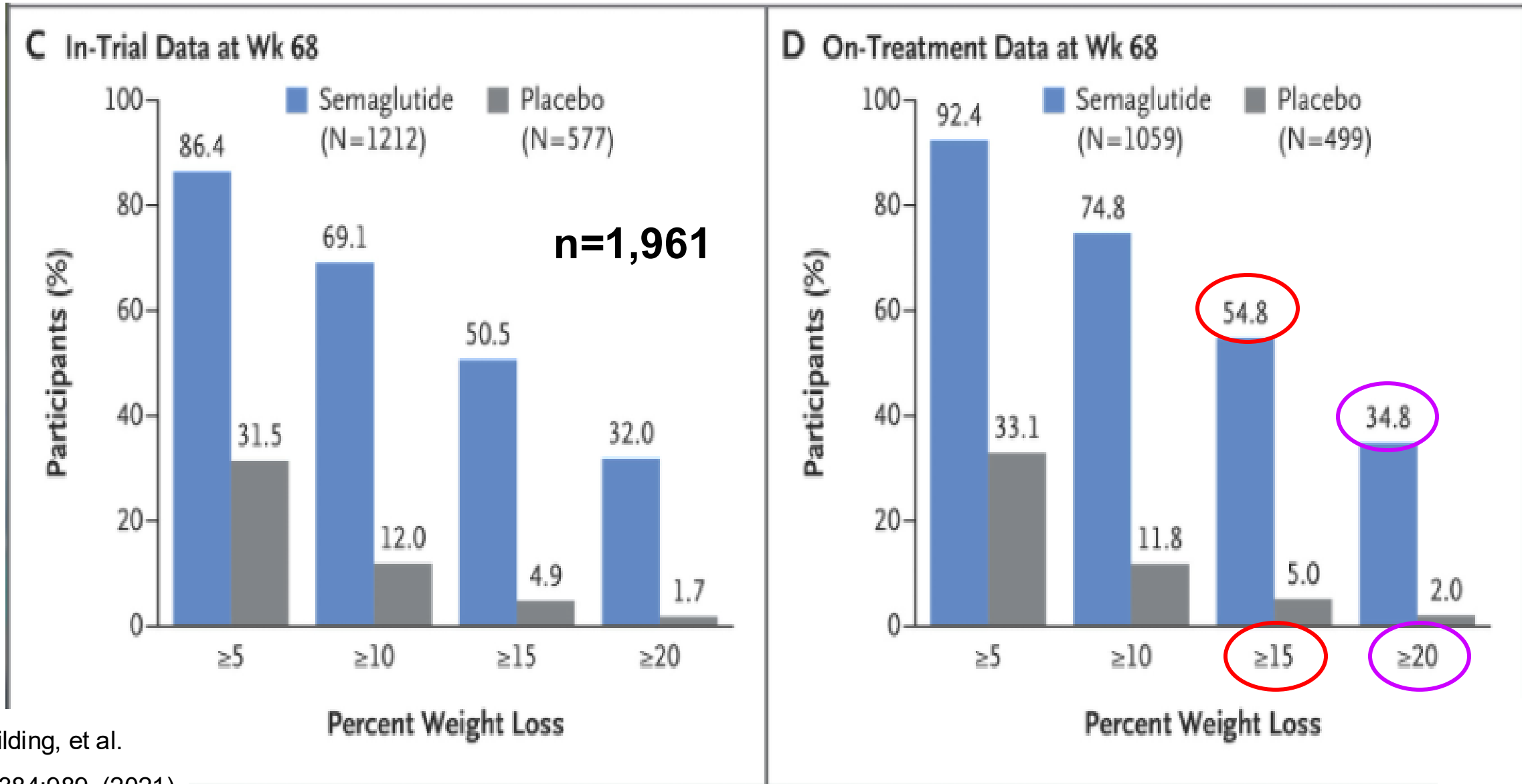
15%
weight
loss



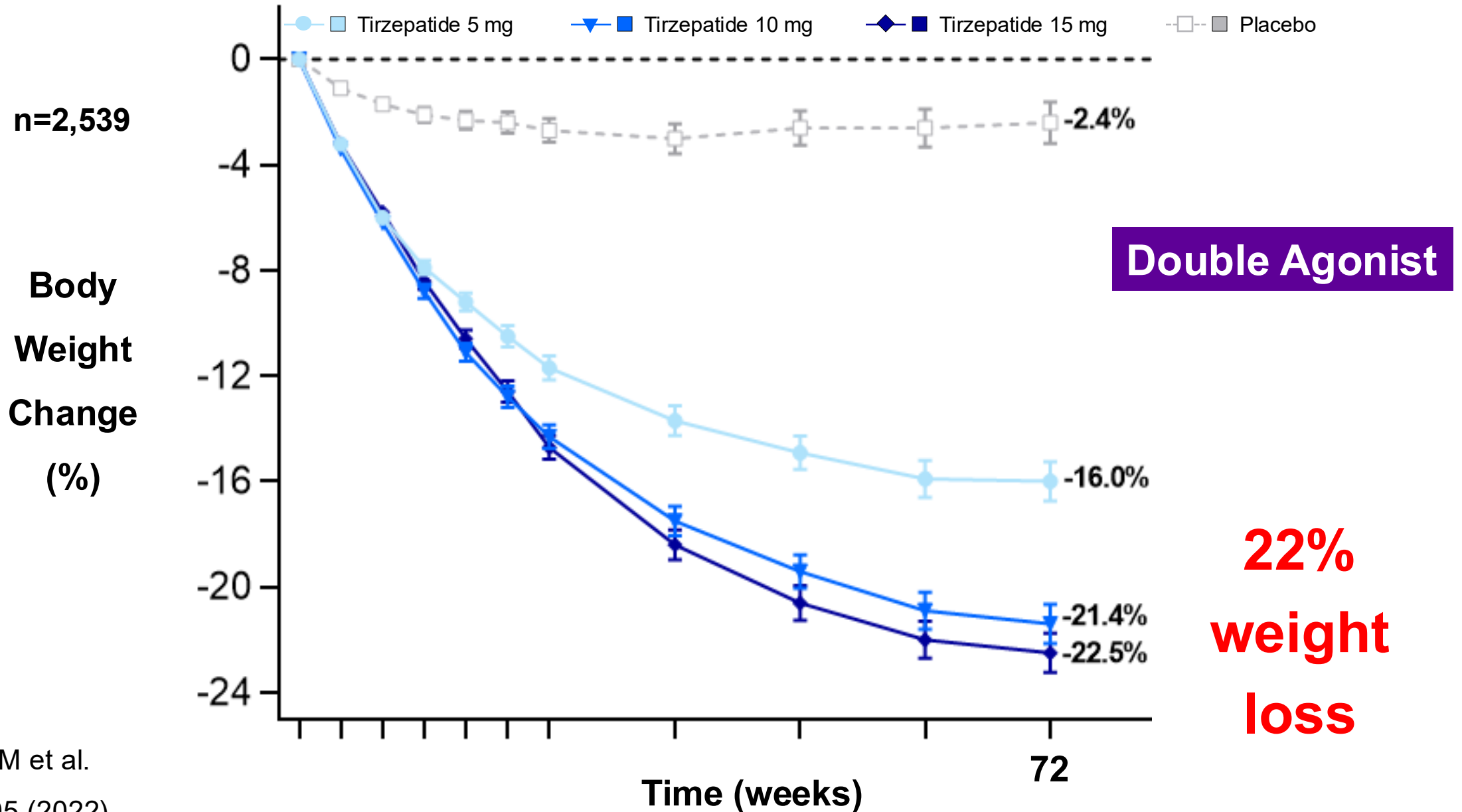
Wilding, et al.

NEJM 384:989 (2021)

STEP 1: Semaglutide vs. Placebo – *No Diabetes*



SURMOUNT-1: Tirzepatide vs. Placebo – *No Diabetes*



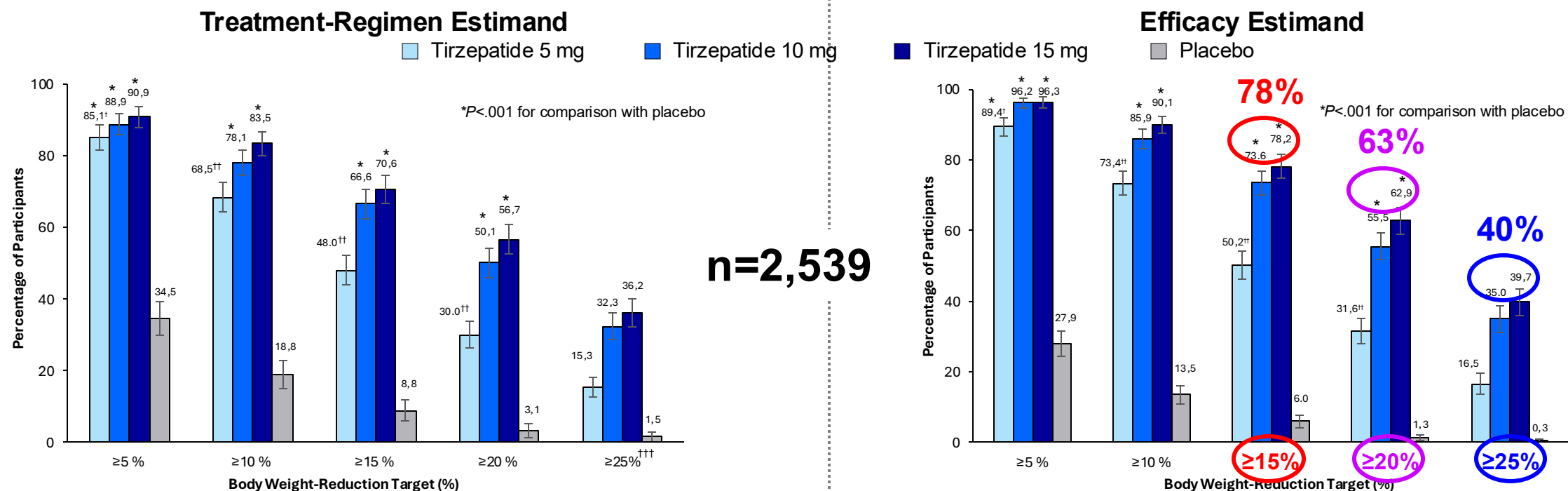
Jastreboff AM et al.

NEJM 387:205 (2022)

Tirzepatide vs. Placebo – No Diabetes

SURMOUNT-1

Percentage of Participants Achieving Body Weight Reductions Targets

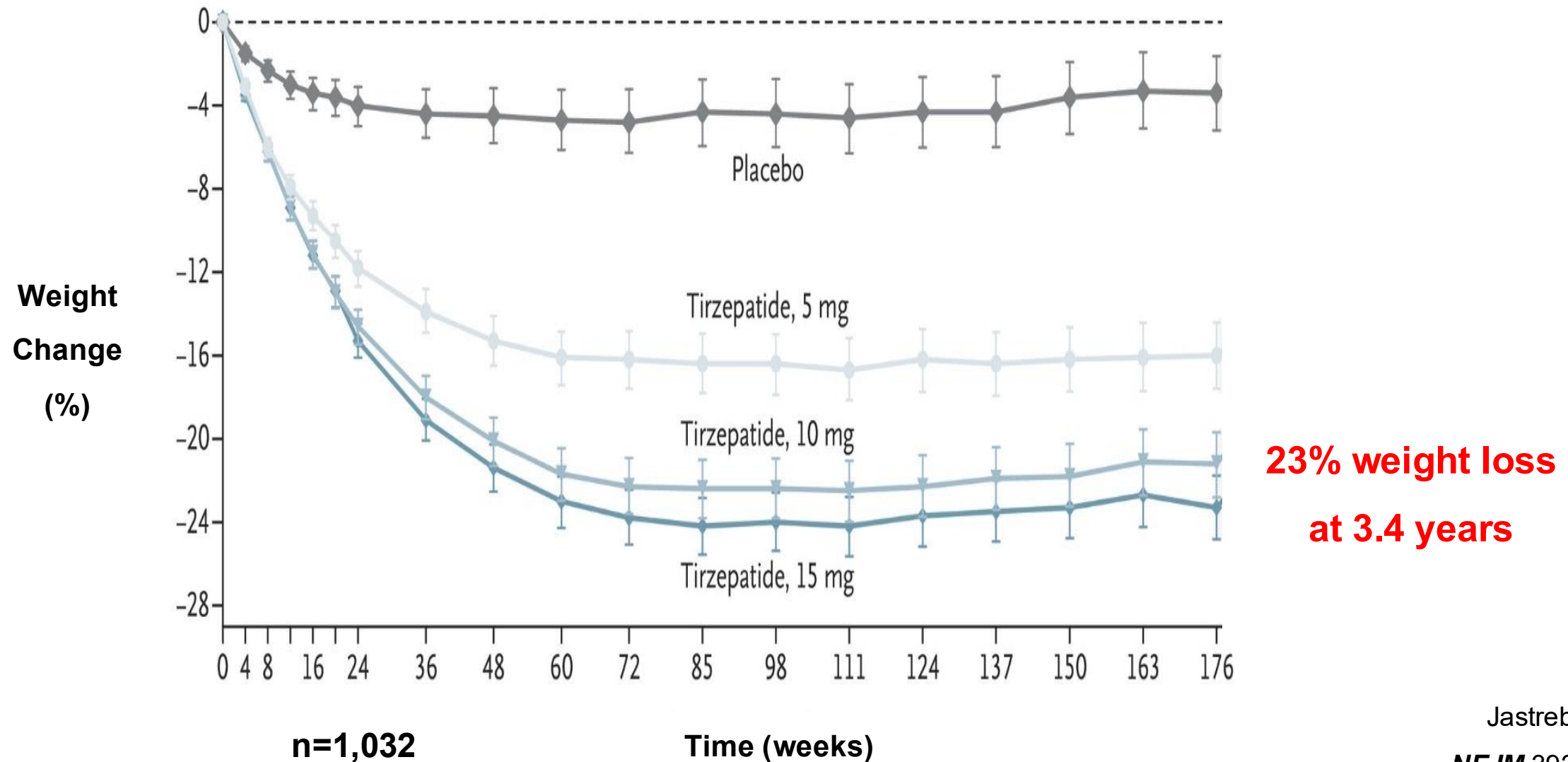


Jastreboff AM et al.

NEJM 387:205 (2022)

Weekly Tirzepatide vs. Placebo

SURMOUNT-1: >3-Year Extension – Only People with Pre-DM (41%)



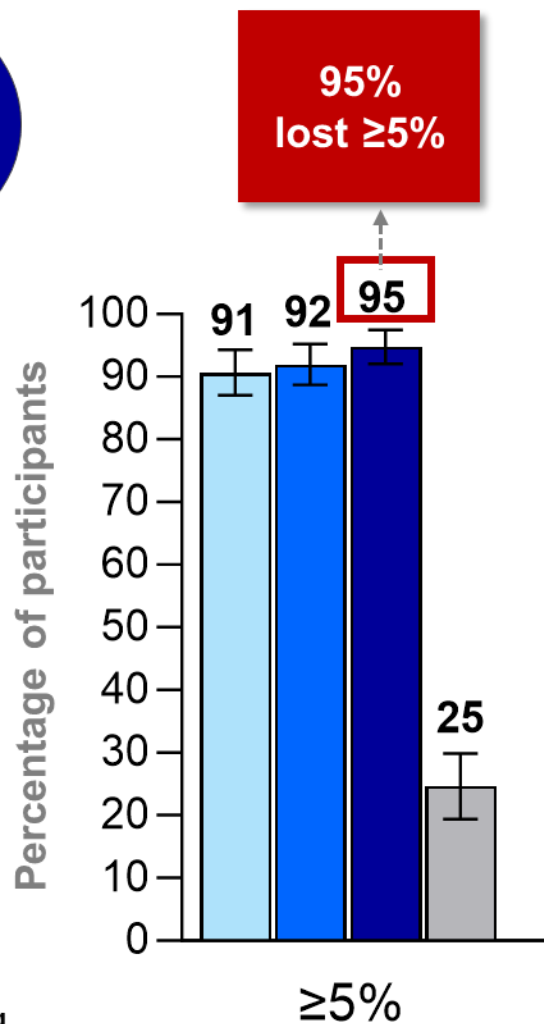
Jastreboff, et al.

NEJM 392:958 (2025)

Percent of Participants Reaching Weight Reduction Thresholds

at 3.4 years

On Treatment
Efficacy Estimand



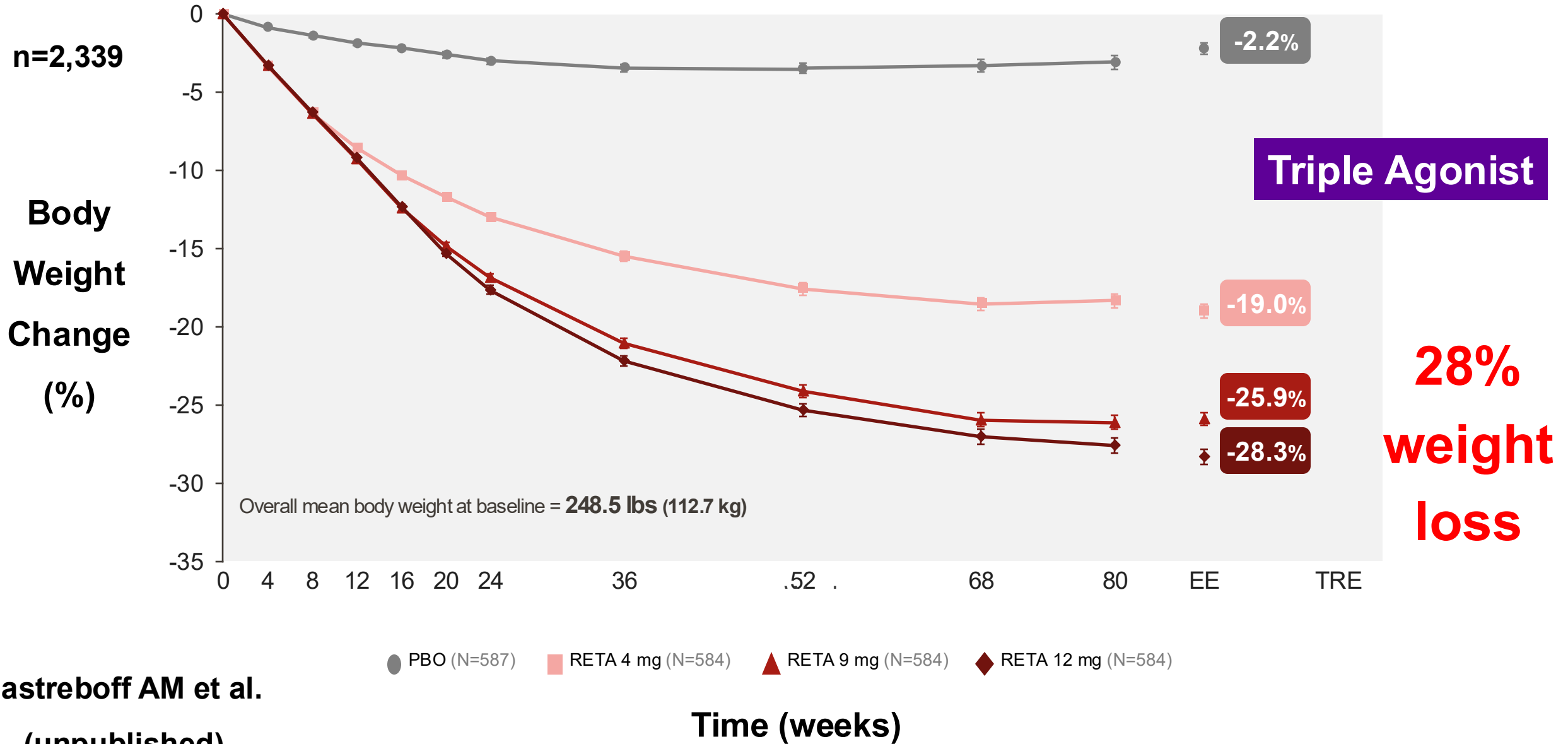
placebo
tirzepatide 5 mg
tirzepatide 10 mg
tirzepatide 15 mg

Body weight-reduction thresholds

Jastreboff, et al.

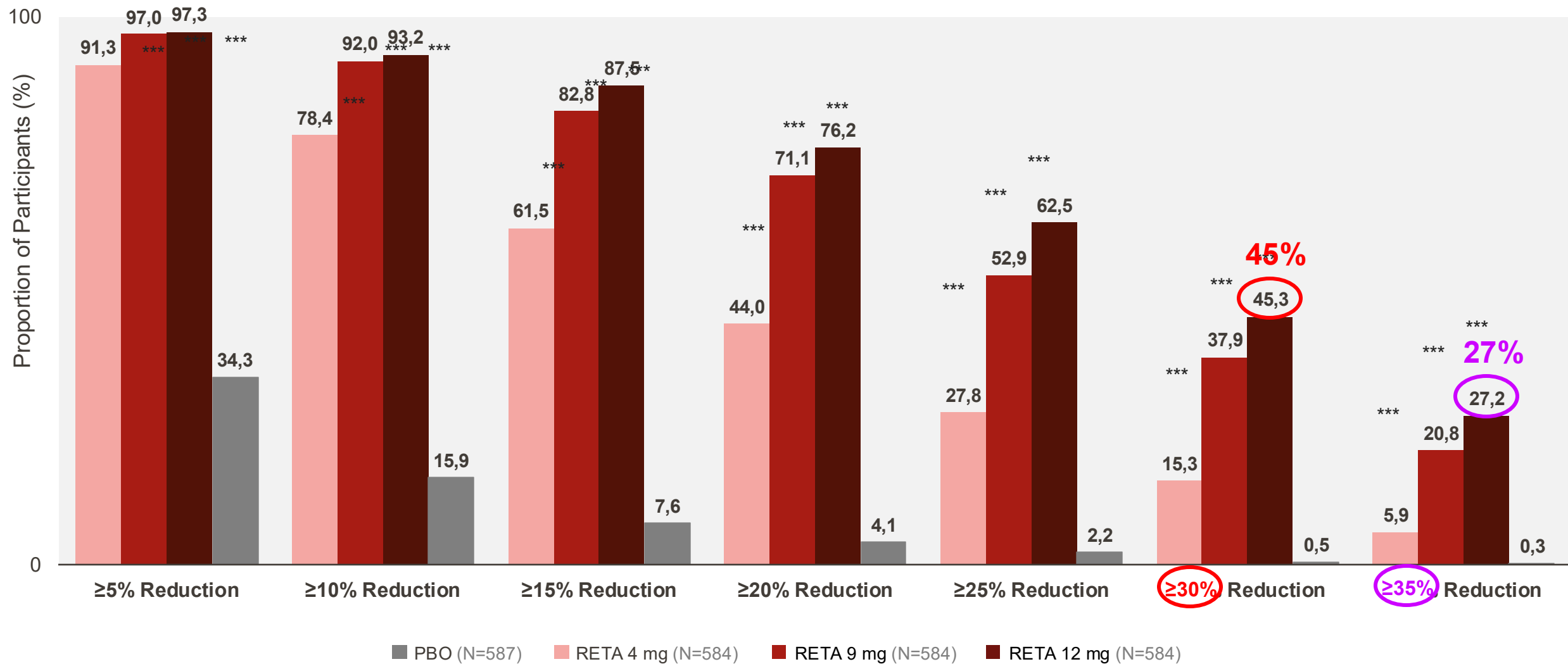
NEJM 392:958 (2025)

TRIUMPH-1: Retatrutide vs. Placebo – *No Diabetes*



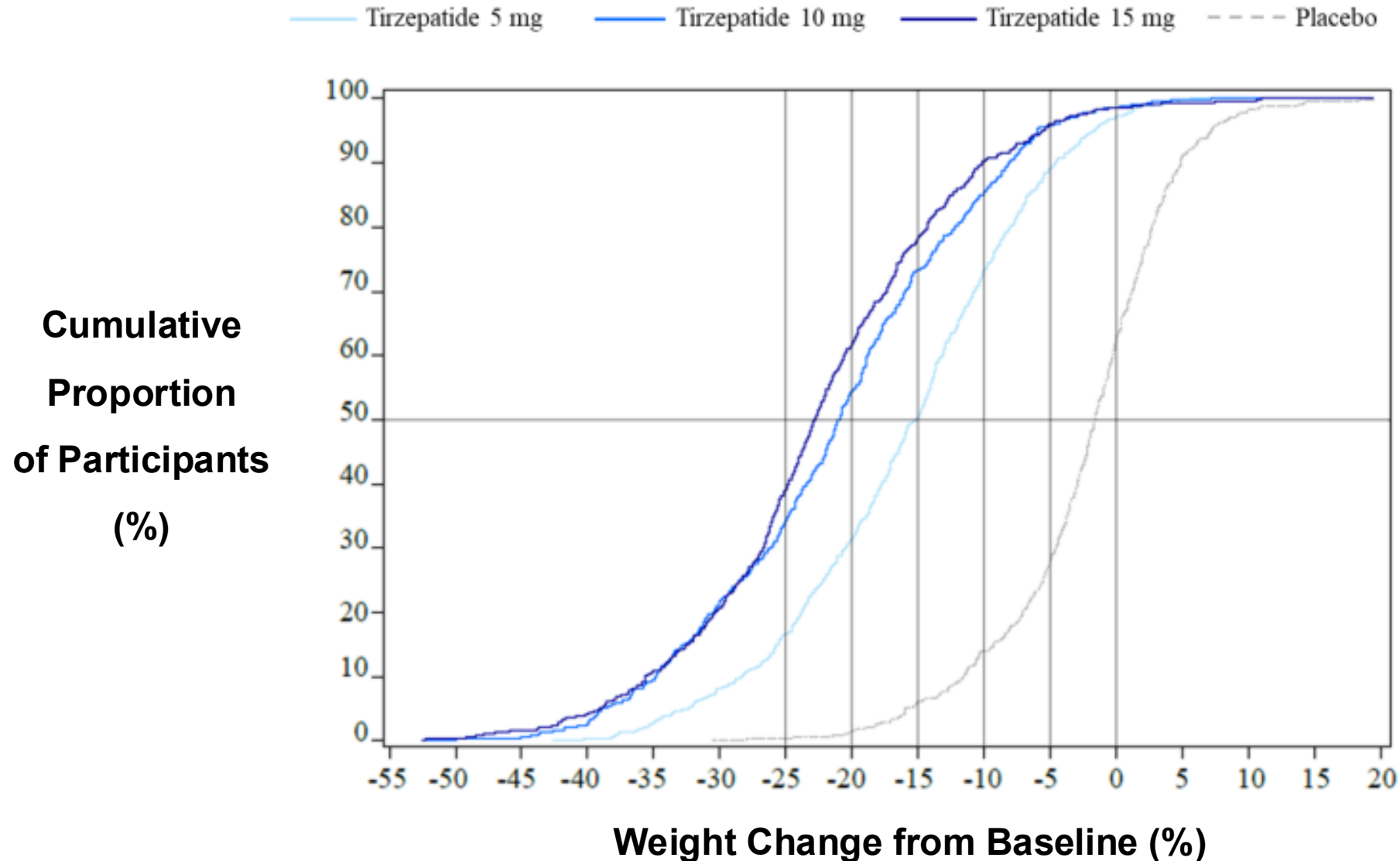
Jastreboff AM et al.
(unpublished)

TRIUMPH-1: Percent of Participants Reaching Weight Reduction Thresholds with Retatrutide at Week 80



Variability in Weight Loss with Tirzepatide

From SURMOUNT-1 Supplementary Appendix

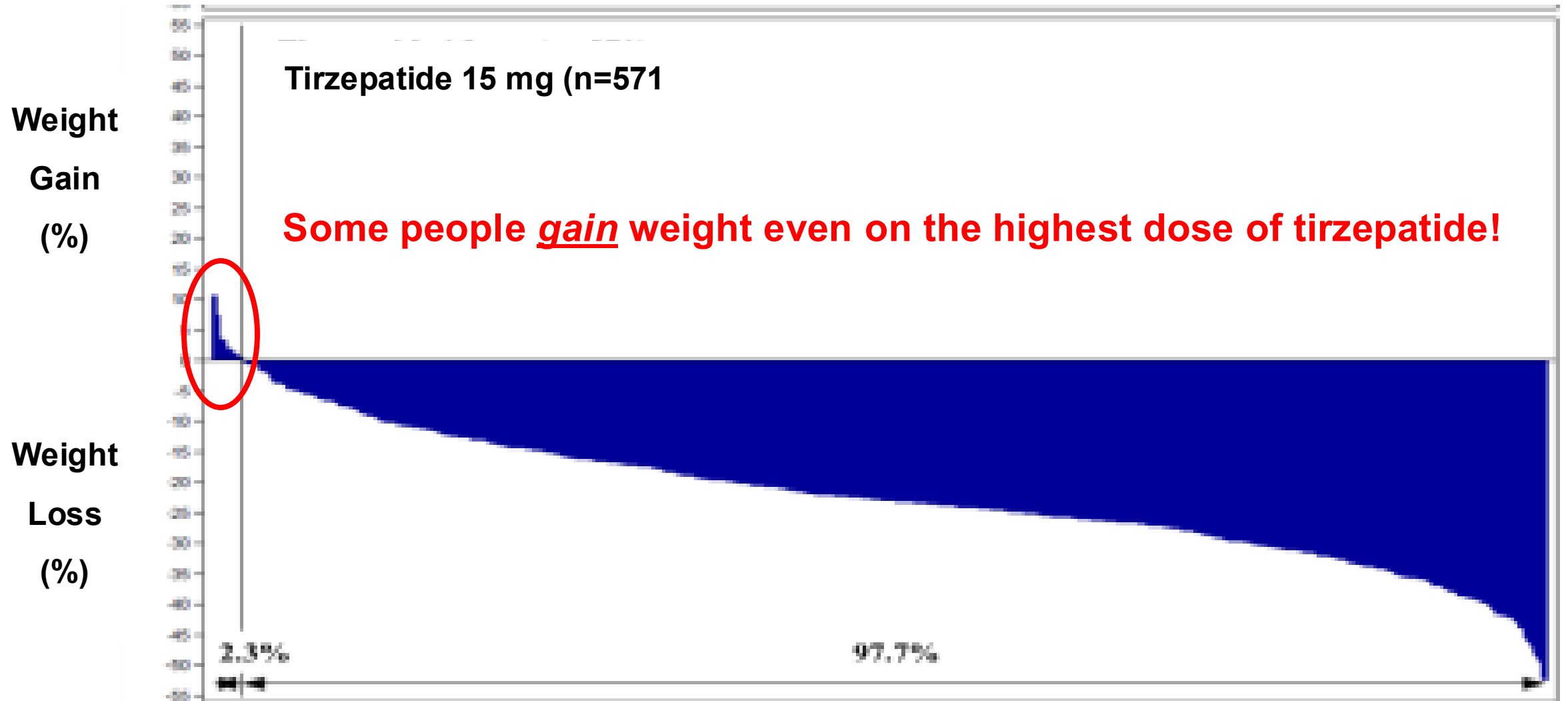


Jastreboff AM et al.

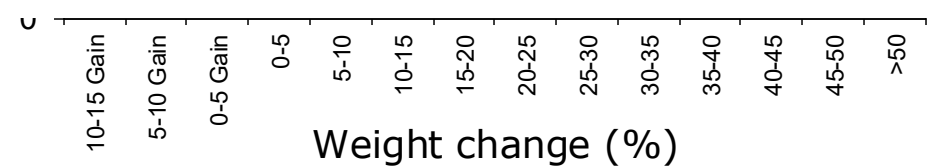
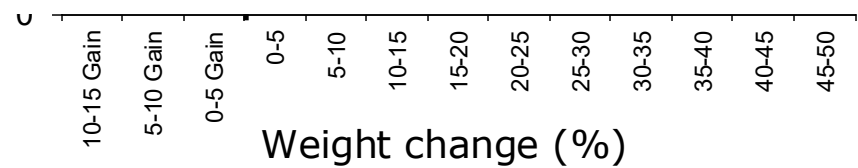
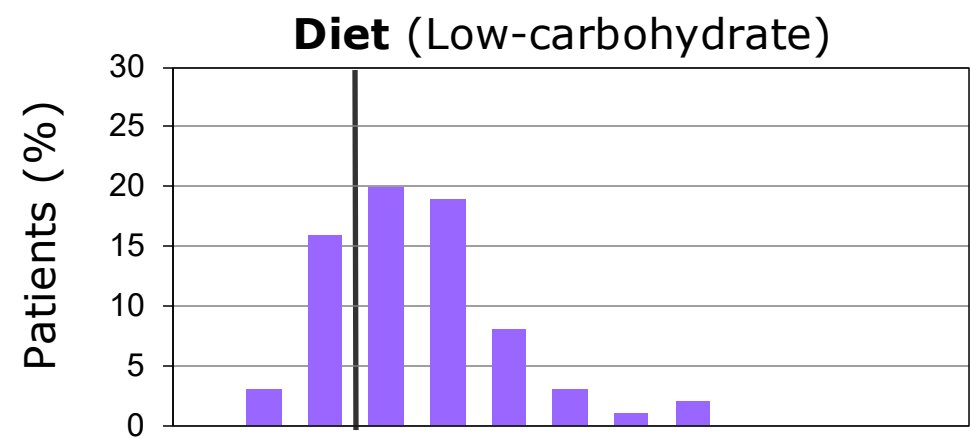
NEJM 387:205 (2022)

Variability in Weight Loss with Tirzepatide

From SURMOUNT-1 Supplementary Appendix



All obesity therapies exhibit wide patient-to-patient variability



Article

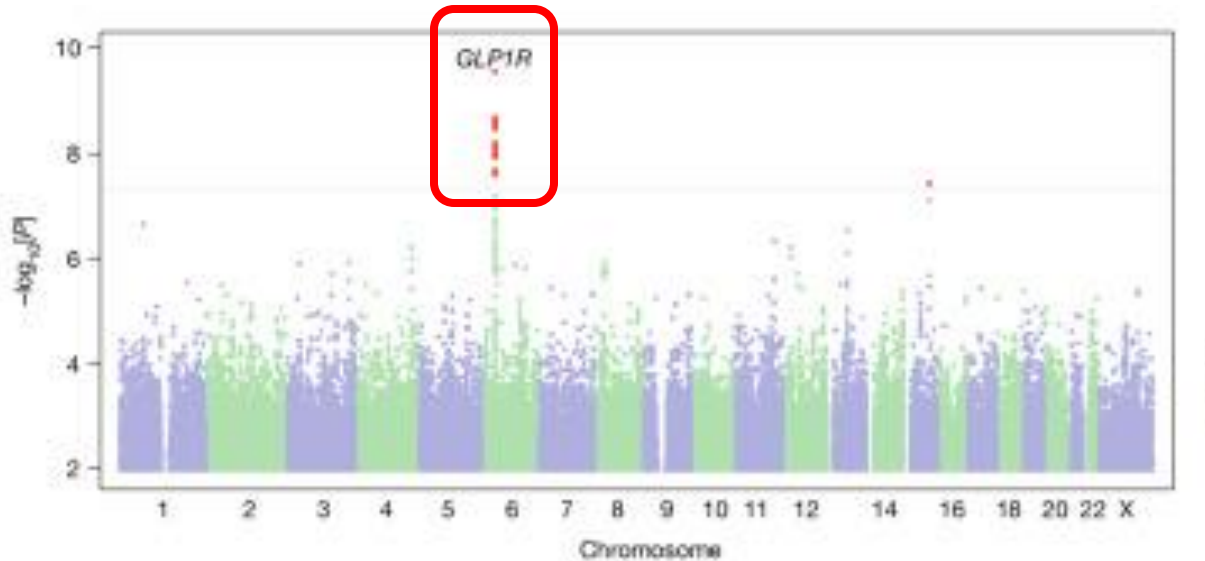
Genetic predictors of GLP1 receptor agonist weight loss and side effects

Qiaojuan Jane Su¹, James R. Ashenhurst¹, Wanwan Xu¹, Vinh Tran¹, R. RYanne Wu¹, Catherine H. Weldon¹, Jingchunzi Shi¹, Barry Hicks¹, 23andMe Research Team*, Noura S. Abul-Husn¹, Stella Aslibekyan¹, Michael V. Holmes¹, Bertram L. Koelsch¹ & Adam Auton¹✉

Nature 653:770 (June 2026)

Genetic Variants in GLP-1 Receptor

Associated with Greater Weight Loss on GLP-1 Agonists



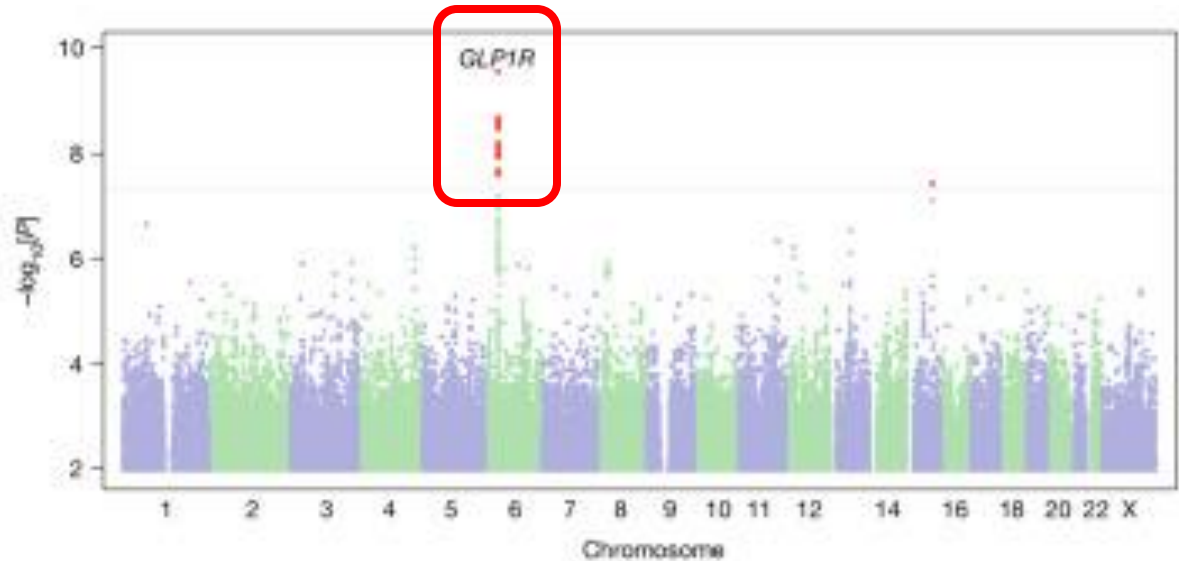
Manhattan Plot

A missense variant in the GLP-1 receptor is significantly associated with greater weight loss on incretin mimetics, with a dose-dependent effect by allele number.

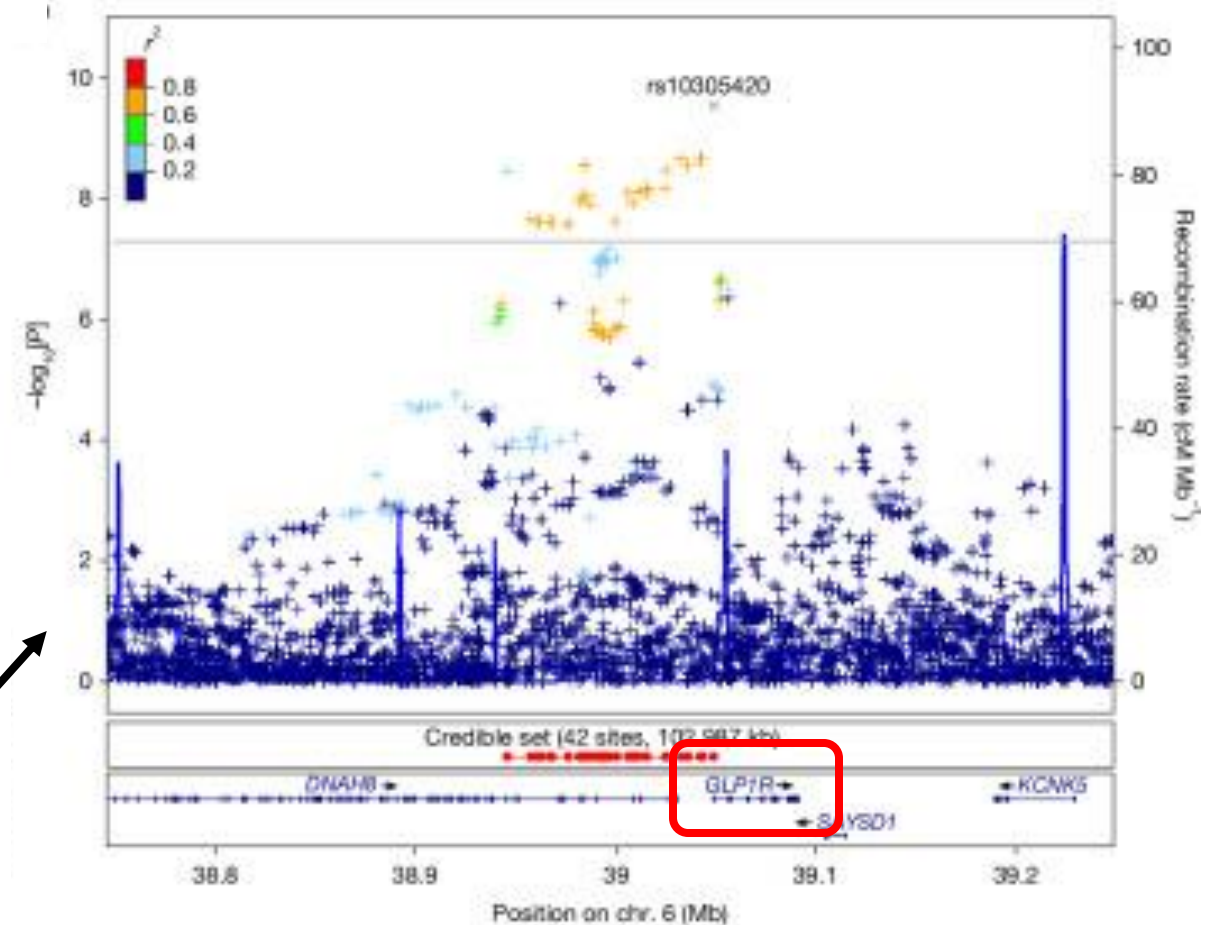
N = 27,885

Su QJ, et al.
Nature 653:770 (2026)

Genetic Variants in GLP-1 Receptor Associated with Greater Weight Loss on GLP-1 Agonists



Regional plot around
the GLP-1 receptor locus

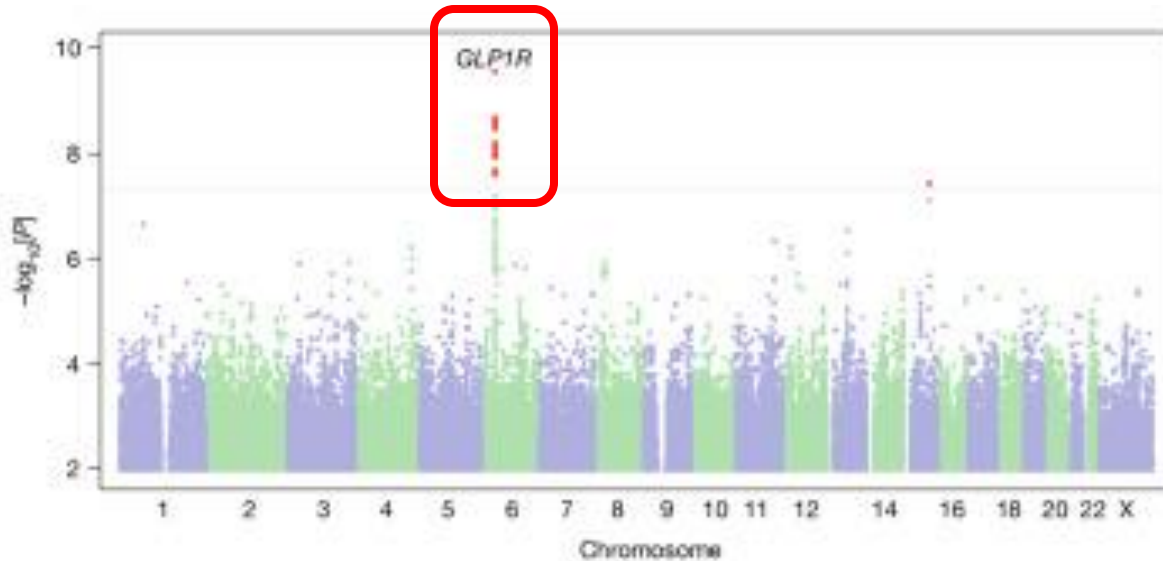


N = 27,885

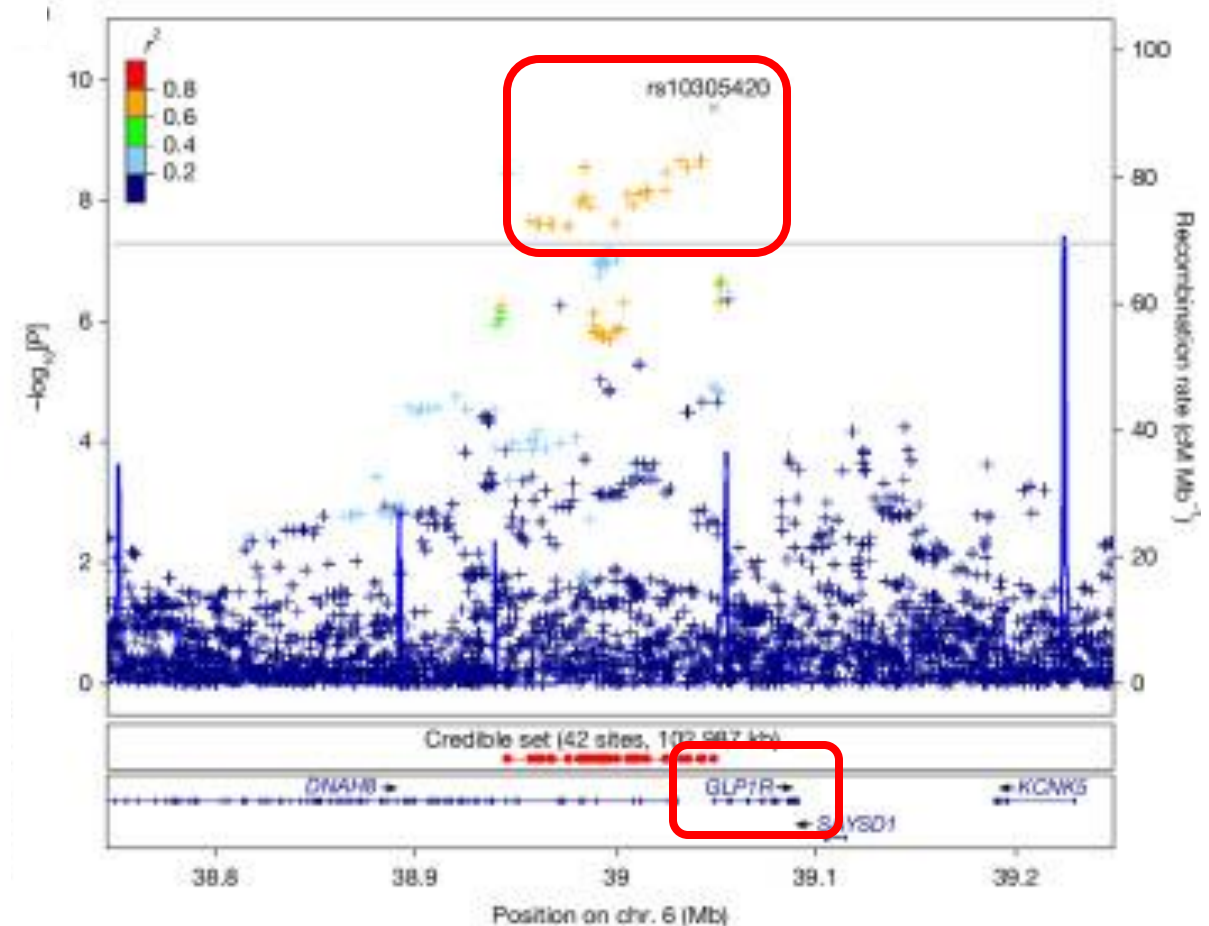
Su QJ, et al.
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Genetic Variants in GLP-1 Receptor

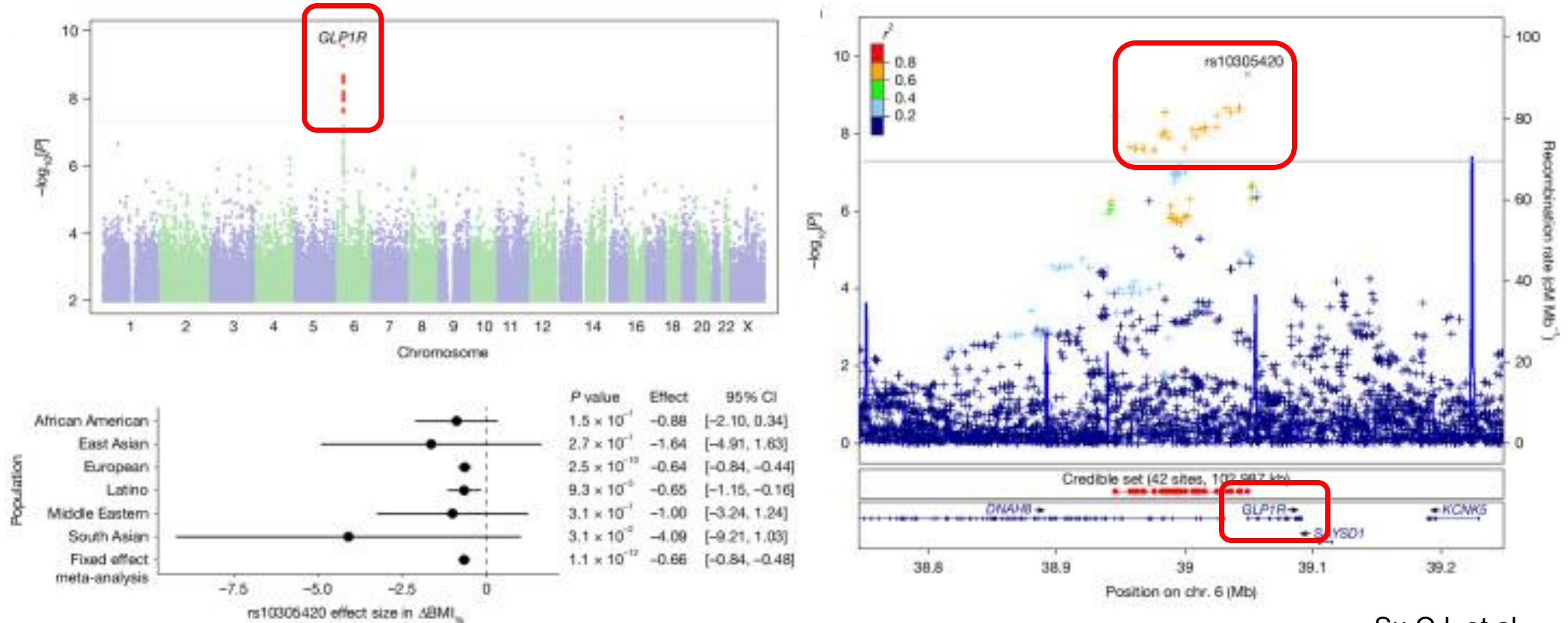
Associated with Greater Weight Loss on GLP-1 Agonists



Many variants with
linkage disequilibrium to
the index SNP, mostly in
the upstream regulatory region



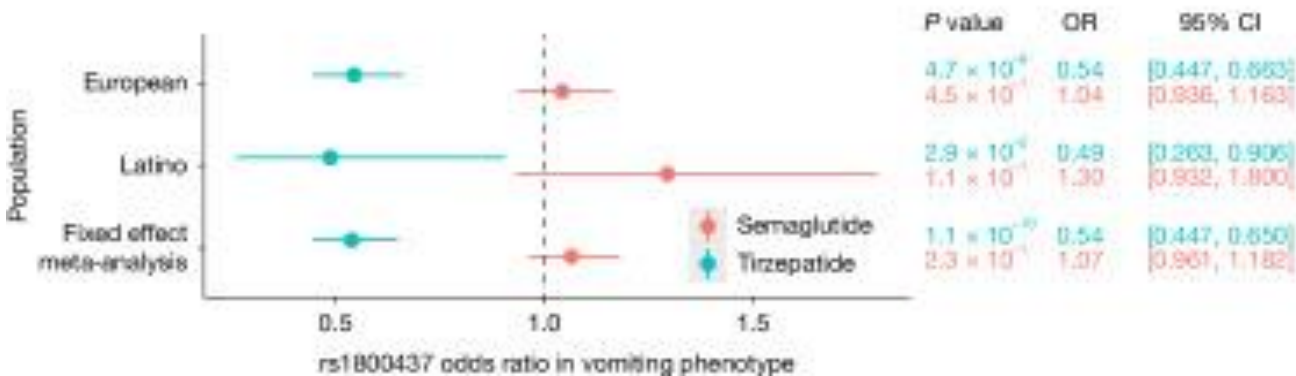
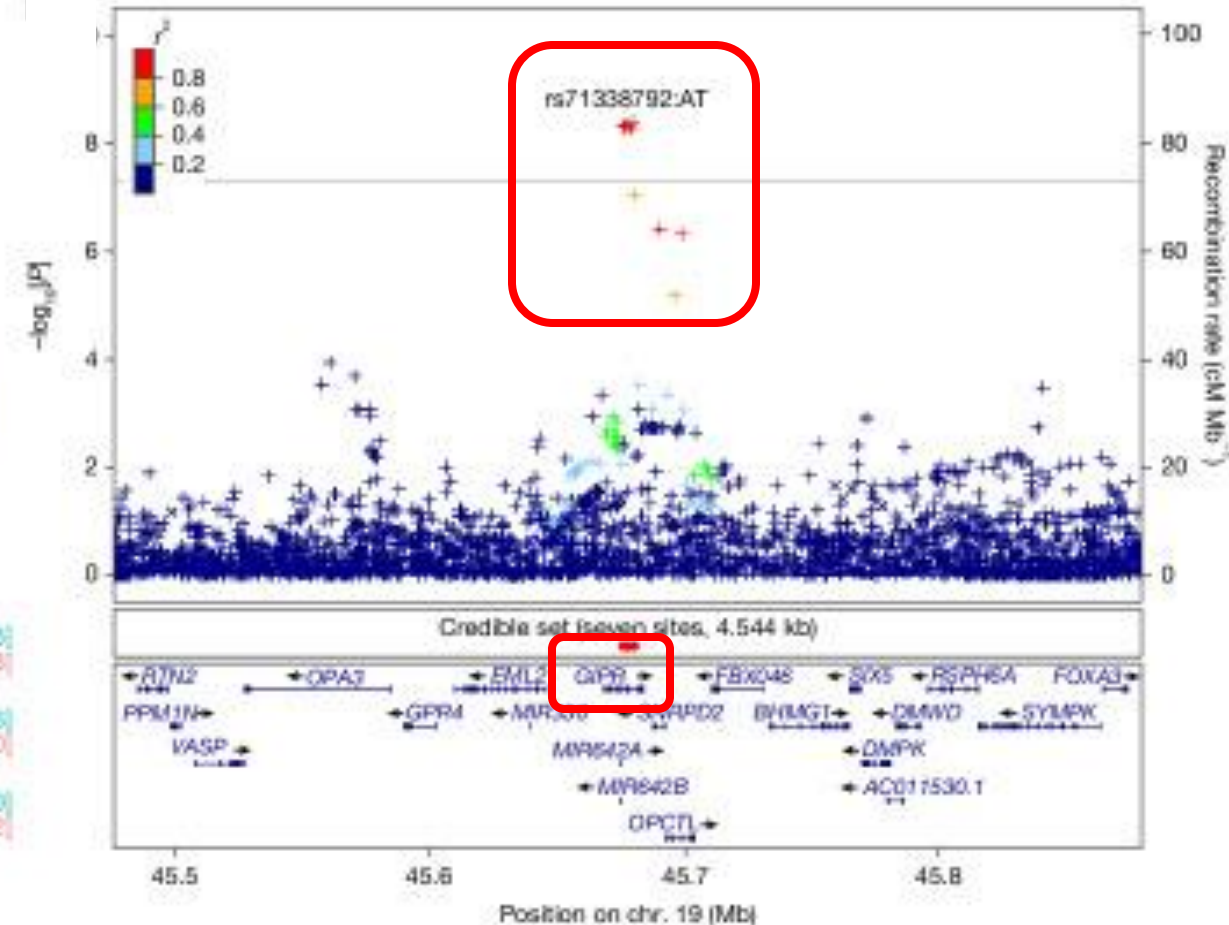
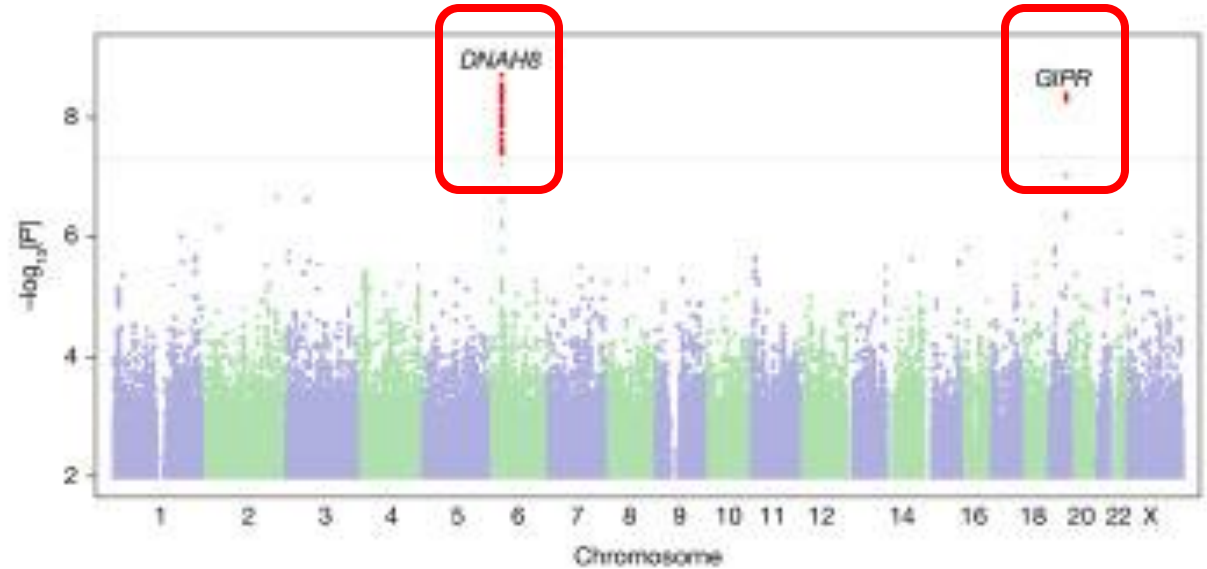
Genetic Variants in GLP-1 Receptor Associated with Greater Weight Loss on GLP-1 Agonists



N = 27,885

Genetic Variants in GLP-1 & GIP Receptors

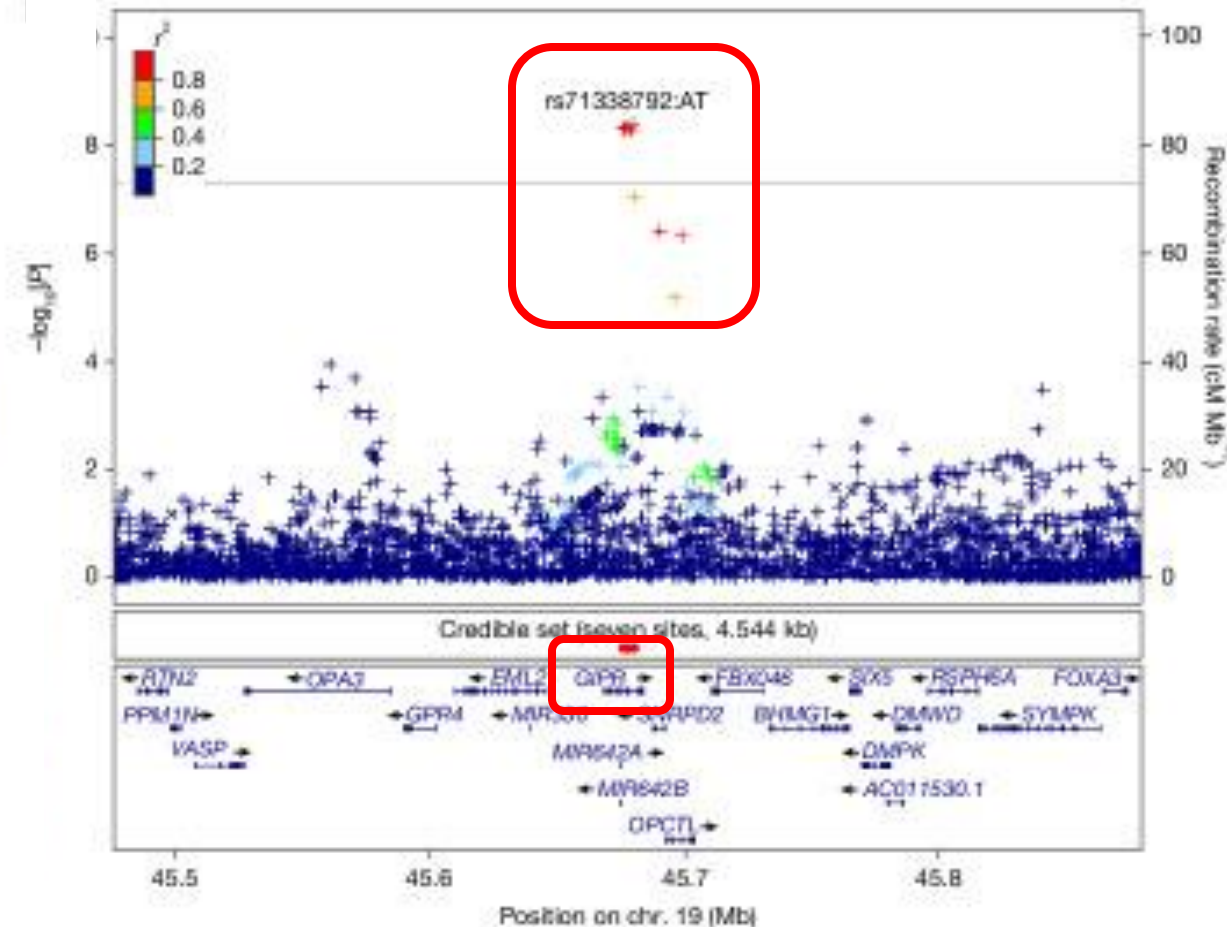
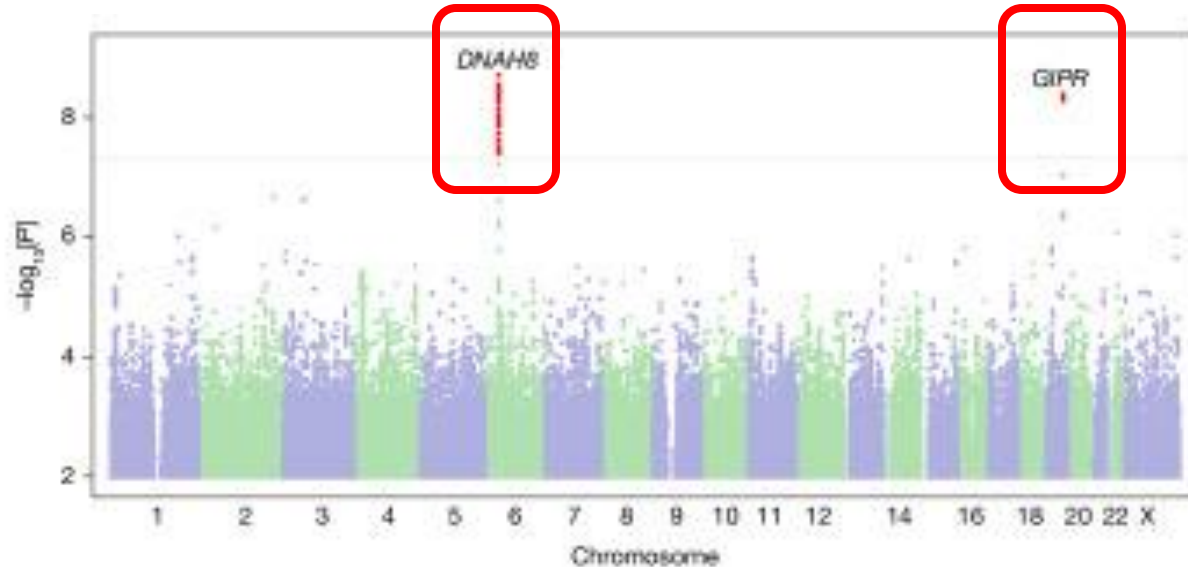
Associated with More Side Effects on Incretin Mimetics



N = 27,885

Genetic Variants in GLP-1 & GIP Receptors

Associated with More Side Effects on Incretin Mimetics



Variations near the GLP-1 and GIP receptors associated with more nausea on incretin mimetics (GIP-R only for TZP)



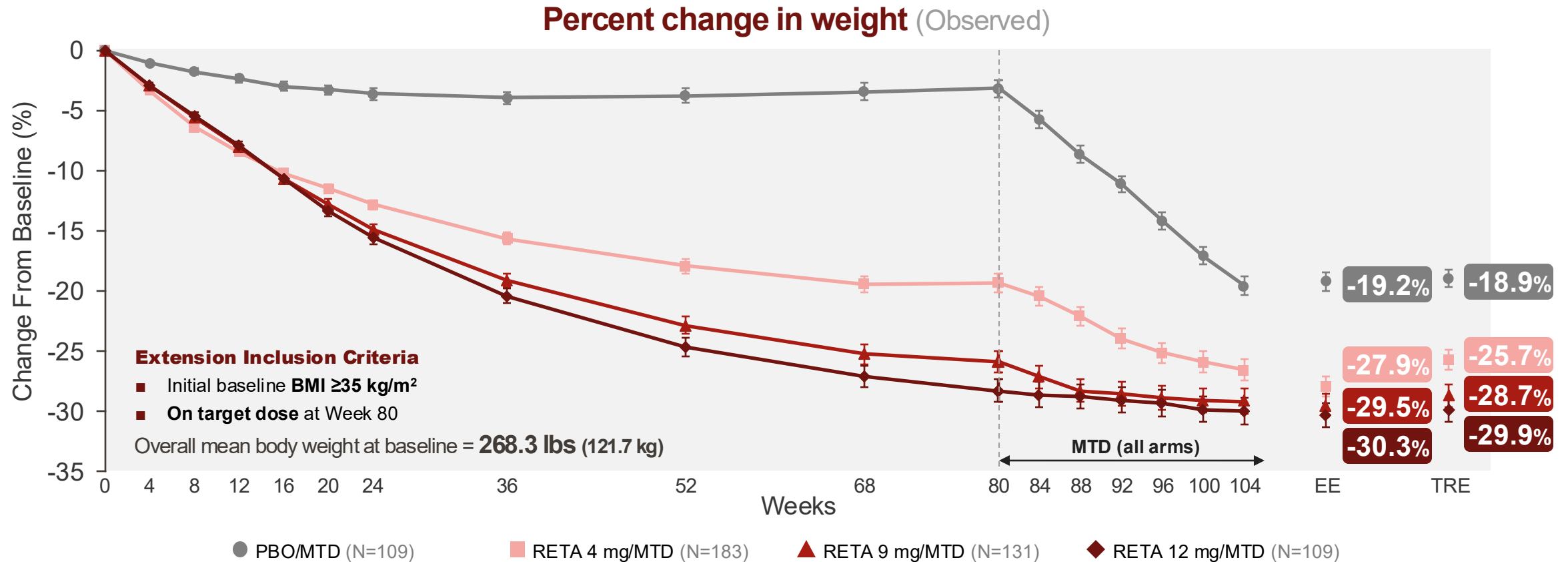
Thank you

Weight Reduction Over 104 Weeks With Retatrutide

TRIUMPH-1 Extension

All Addendum Participants

N=532
total



Participants in the extension lost up to an average of 30% of their initial weight at 104 weeks

All groups $p < 0.001$ vs. PBO.

BMI=body mass index; EE=Efficacy Estimand; MTD=maximum tolerated dose; PBO=placebo; RETA=retatrutide; TRE=Treatment Regimen Estimand.