Looking Beyond the Scale to Chronic Disease

——Health Gain From an Endocrinologist's Perspective

Yingying Luo

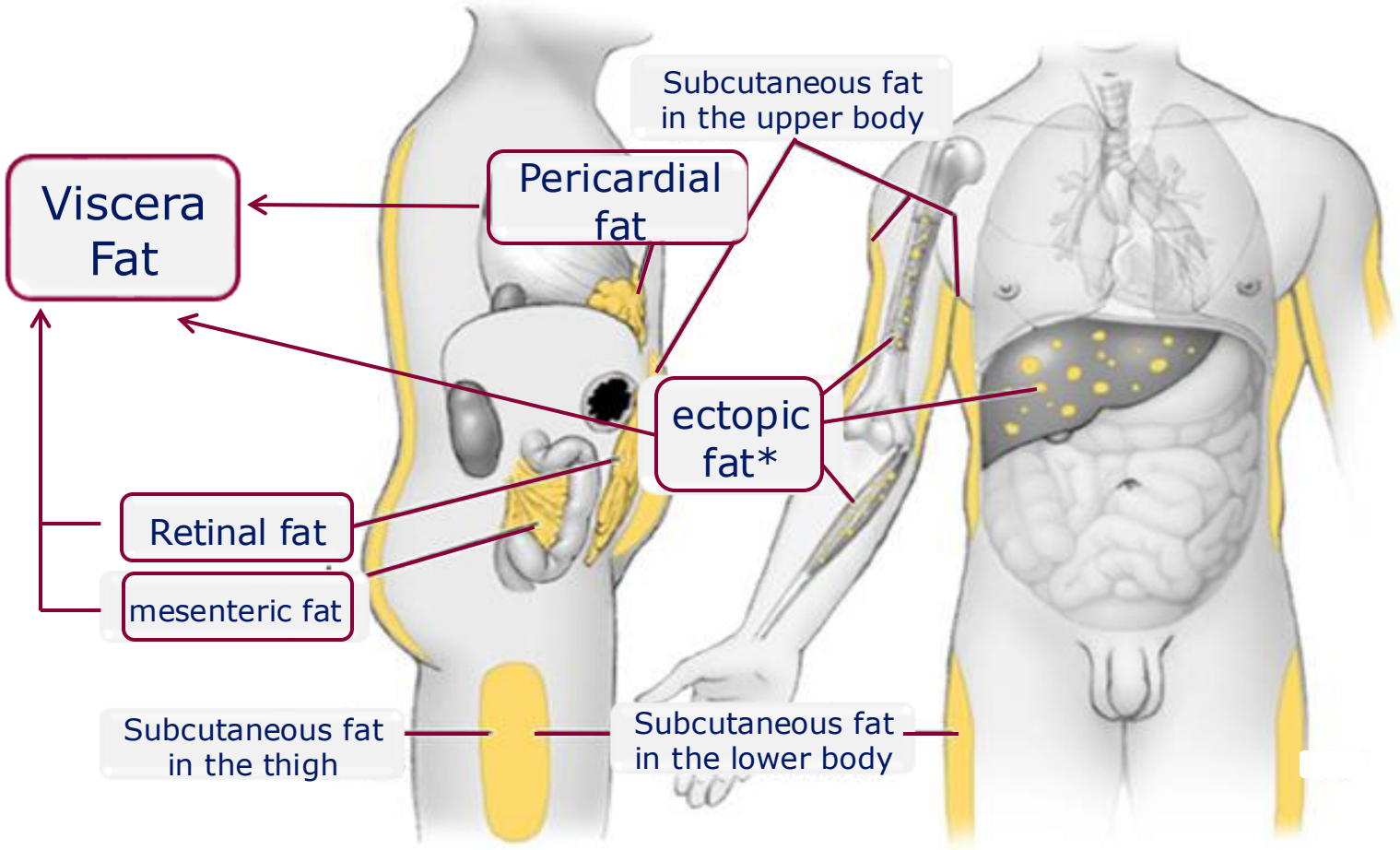
Peking University People's Hospital

北京大学人民医院
PEKING UNIVERSITY PEOPLE'S HOSPITAL

Conflicts of Interest

I have no conflicts of interest to declare related to this presentation.

The distribution of human adipose tissue



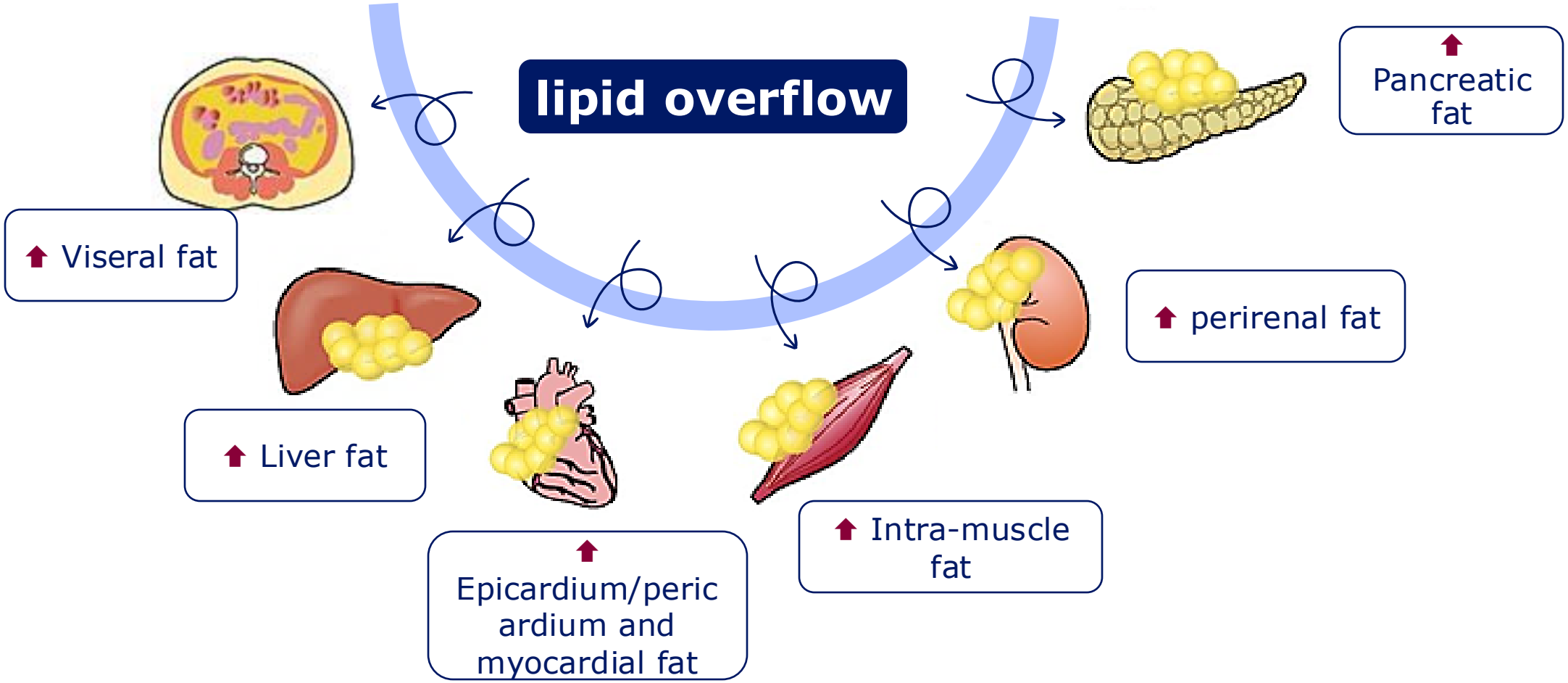
Whole body adipose tissue is generally classified as follows:

- Subcutaneous adipose tissue (>80%)
- **Visceral adipose tissue** (in men: <20%; in women: <10%)

*Most ectopic fat is visceral fat.

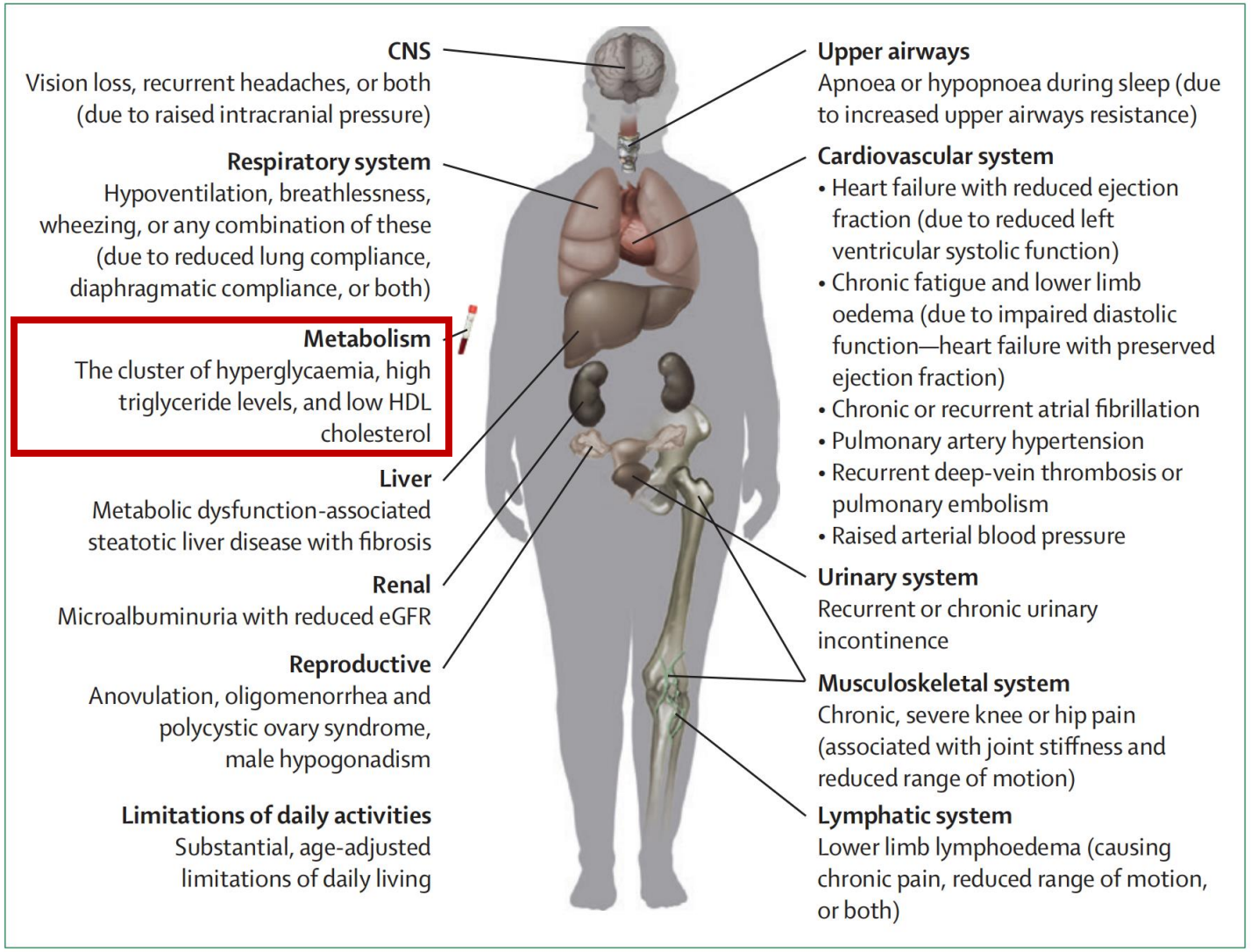
1.Tchkonia T, et al. Cell Metab. 2013;17(5):644-56; 2. Iacobellis G, et al. J Am Soc Echocardiogr.2009;22(12):1311-9; 3. Iacobellis G, et al. Nat Rev Endocrinol.2015 Jun;11(6):363-371.

Lipid overflow results in the ectopic deposition of adipose tissue



Tchernof A, et al. Physiol Rev. 2013;93(1):359-404.

Obesity is a Multisystem Disease Associated With Metabolic Complications



Future Indications for weight loss medications:

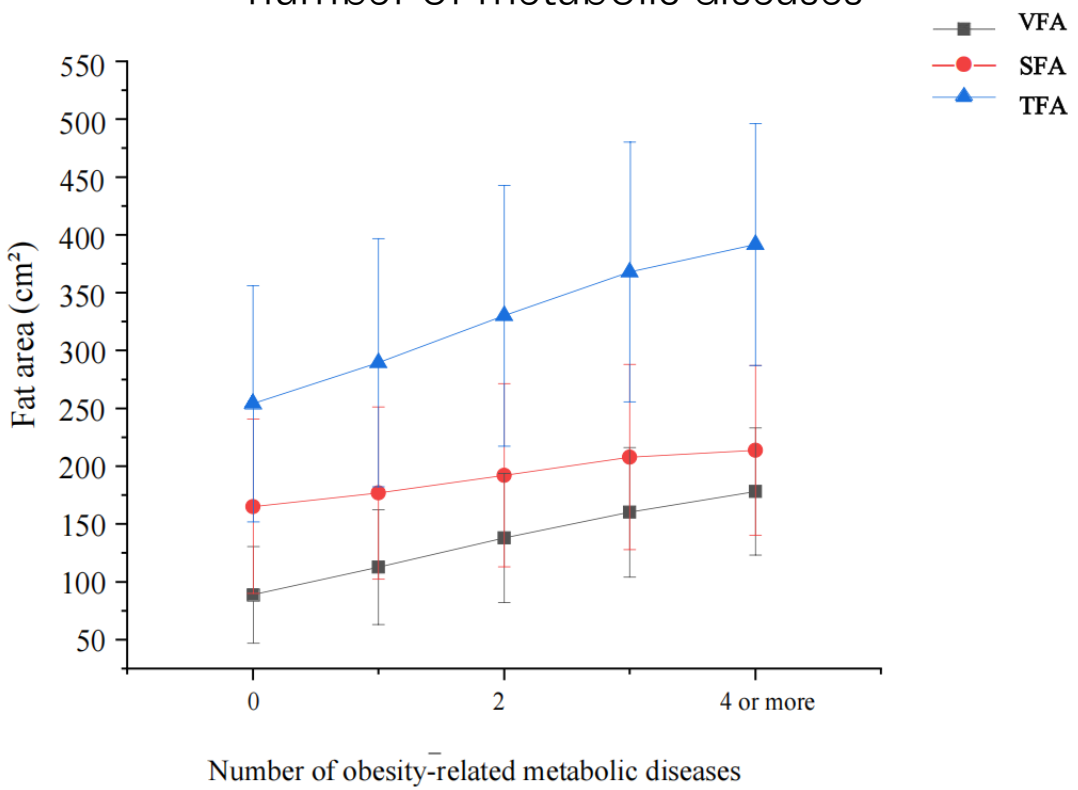
- Weight loss
- Weight induced illness
  - N=18

www.thelancet.com/diabetes-endocrinology Published online January 14, 2025 https://doi.org/10.1016/S2213-8587(24)00316-4

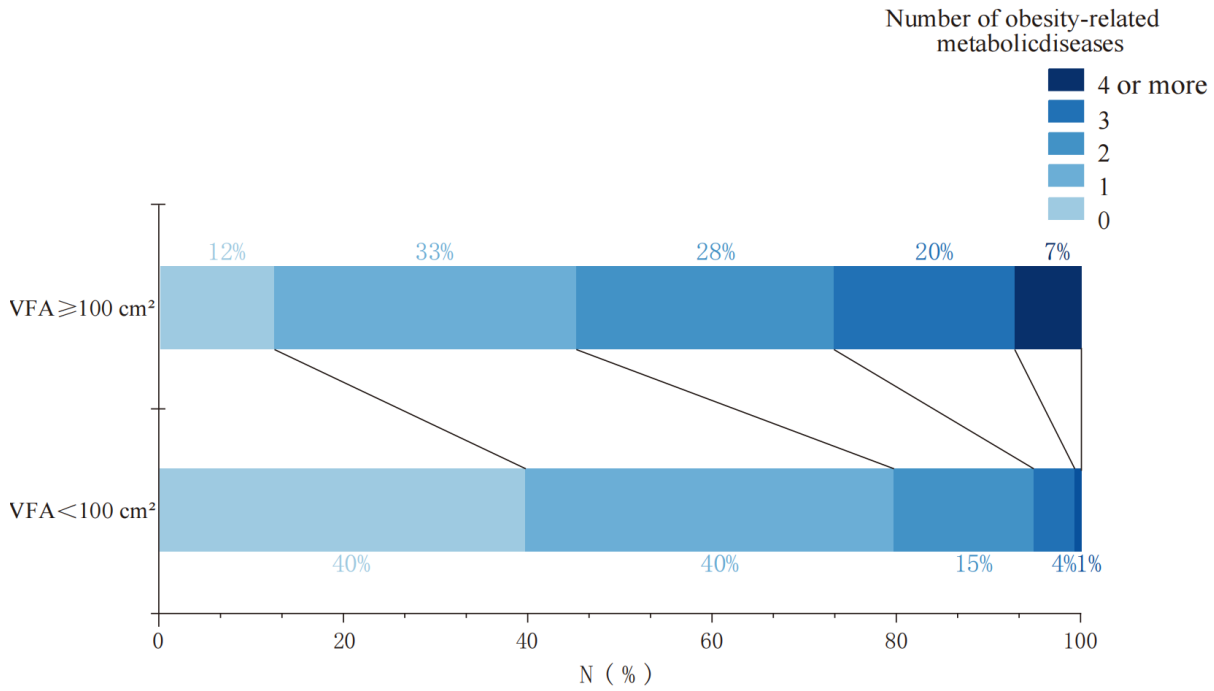
Visceral fat accumulation is strongly associated with weight-related metabolic diseases

To explore the relationship between visceral fat and obesity-related metabolic diseases, a cross-sectional study involved 3,371 participants from Beijing was conducted. Anthropometric measurements and metabolic indicators were assessed, and visceral fat area (VFA) was calculated from non-contrast abdominal computed tomography scans.

Relationship between fat area and number of metabolic diseases



Relationship between fat area and number of metabolic diseases



Bingying Yang, Yingying Luo, et al. Metab Target Organ Damage. 2025;5:40. Doi:10.20517/mtod.2025.70

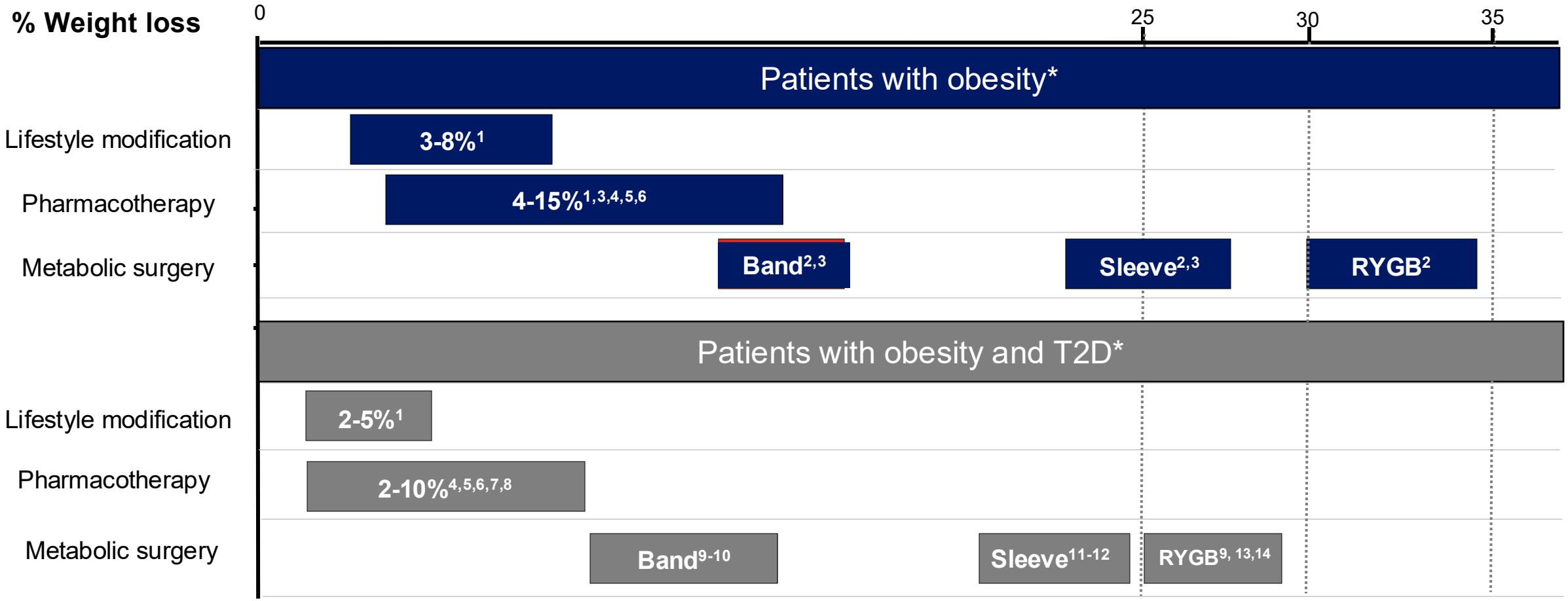
BMI alone is not enough. The diagnosis of overweight and obesity may require additional anthropometric assessments

Condition	Criteria for people with non-Asian background	Criteria for people with Asian background*
Excess adiposity	BMI ≥25 kg/m^2	BMI ≥23 kg/m^2
Overweighty	BMI 25–29.9 kg/m2 with WHtR <0.5 or BMI 25–29.9 kg/m2 with WC <88 cm in women; BMI 25–29.9 kg/m2 with WC <102 cm in men	BMI 23–27.4 kg/m2 with WHtR <0.5 or BMI 23–27.4 kg/m2 with WC <80 cm in women; BMI 23–27.4 kg/m2 with WC <90 cm in men
Obesity	BMI ≥30 kg/m2 or BMI 25–29.9 kg/m2 with WHtR ≥0.5 or BMI 25–29.9 kg/m2 with WC ≥88 cm in women; BMI 25–29.9 kg/m2 with WC ≥102 cm in men	BMI ≥27.5 kg/m2 or BMI 23–27.4 kg/m2 with WHtR ≥0.5 or BMI 23–27.4 kg/m2 with WC ≥80 cm in women; BMI 23–27.4 kg/m2 with WC ≥90 cm in men

Elevated WC in women with a non-Asian background is ≥35 inches and in men with a non-Asian background is ≥40 inches. Elevated WC in women with an Asian background is ≥31.5 inches and in men with an Asian background is ≥35.5 inches. WC, waist circumference; WHtR, waist-to-height ratio.
*The BMI and WC thresholds identified for people with Asian backgrounds represent general targets, and health care professionals should be aware that specific values may exist for certain Asian countries that differ from the values listed above (40, 41, 55). Asian background includes Asia (e.g., China, Japan, Korea) and the South Asian subcontinent (e.g., India, Pakistan, Bangladesh). Clinicians should be aware of the evidence gap regarding individuals who identify as having mixed race or ethnicity. At this time, clinicians should use the background from which the individual identifies.

Source: ADA Standards of Care in Overweight and Obesity—2026

Weight Loss in People with Obesity



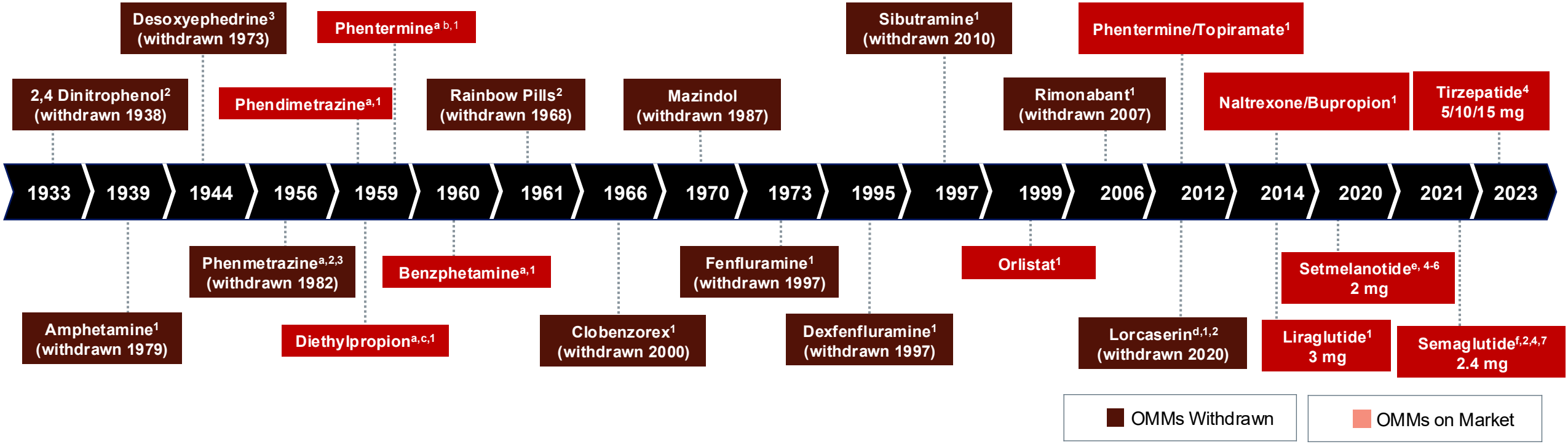
* Not head to head trials. Between trial comparisons should be interpreted carefully.

RYGB: Roux-en-Y gastric bypass; T2D: Type 2 diabetes.

1. Jensen et al. Circulation 2014;129(25 Suppl 2):S102–38; 2. Courcoulas et al. JAMA 2013;310:2416–25; 3. Obesity Drug Outcome Measures: A Consensus Report of Considerations Regarding Pharmacologic Intervention. Available at: https://publichealth.gwu.edu/pdf/obesitydrugmeasures.pdf Accessed February 28, 2023; 4. Wegovy Product Monograph. Novo Nordisk Canada, Mississauga, ON – Revision date June 30, 2022 5. Saxenda Product Monograph. Novo Nordisk Canada, Mississauga, ON; Revision date December 9, 2022. 6. Xenical Product Monograph. CHEPLAPHARM Arzneimittel GmbH Germany – Revision date Sept 27, 2017 7. Qysmia Prescribing Information: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/022580s016lbl.pdf Accessed February 28, 2023 8. Wentworth JM, et al. Obes Surg. 2015 Dec;25(12):2400-7; 9. Courcoulas AP, et al. JAMA Surg. 2015 Oct;150(10):931-40; 10. Sally Abbott et al. / Surgery for Obesity and Related Diseases 16 (2020) 1723–1730; 11. Schauer PR, et al. N Engl J Med. 2017 Feb 16;376(7):641-651; 12. Keidar A, et al. Diabetologia. 2013 Sep;56(9):1914-8. doi: 13.1007/s00125-013-2965-2; 14. Hofsø D, et al. Lancet Diabetes Endocrinol. 2019 Dec;7(12):912-924;

Chronology of OMMs

Based on First Approval



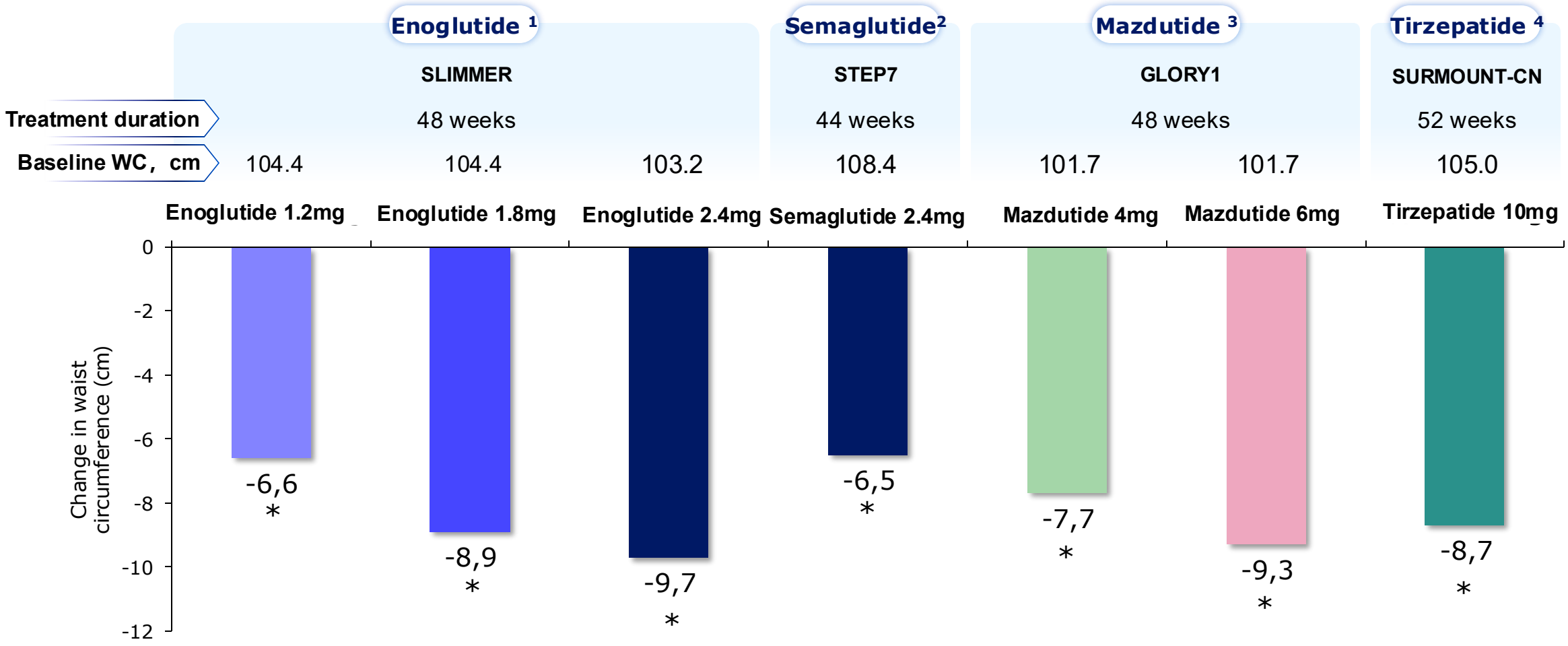
[a]Approved for short-term use in the United States. [b]Withdrawn in 1981 in Sweden, United Arab Emirates, Mauritius, Turkey, Oman, United Kingdom, Venezuela. [c]Withdrawn in 1975 in Sweden, Norway, United Arab Emirates, Turkey, Oman, United Kingdom, Venezuela, France, and Brazil. [d]Withdrawn from market in February 2020 for safety issue related to increased cancer incidence. [e]Setmelanotide was first approved for syndromic or monogenic forms of obesity by the FDA. [f]Sema 1.7 mg was approved as a maintenance dose in adults in July 2023.

OMM=Obesity Management Medication; SEMA=Semaglutide.

1. Pilitsi E, et al. *Metabolism.* 2019;92:170-192. 2. Müller TD, et al. *Nat Rev Drug Discov.* 2022;21(3):201-223. 3. Onakpoya IJ, et al. *BMC Med.* 2016;14(1):191. 4. Tchang BG, et al. *Endotext*. 2024. 5 Imcivree [US PI]. Boston, Massachusetts, USA: Rhythm Pharmaceuticals, 2025. 6. Imcivree [SmPC]. Amsterdam, The Netherlands: Rhythm Pharmaceuticals Netherlands B.V. 7. https://www.fda.gov/media/185422/download (Accessed September 23, 2025).

GLP-1 based medication can significantly reduce waist circumference – data from Chinese population

eliminating the placebo effect



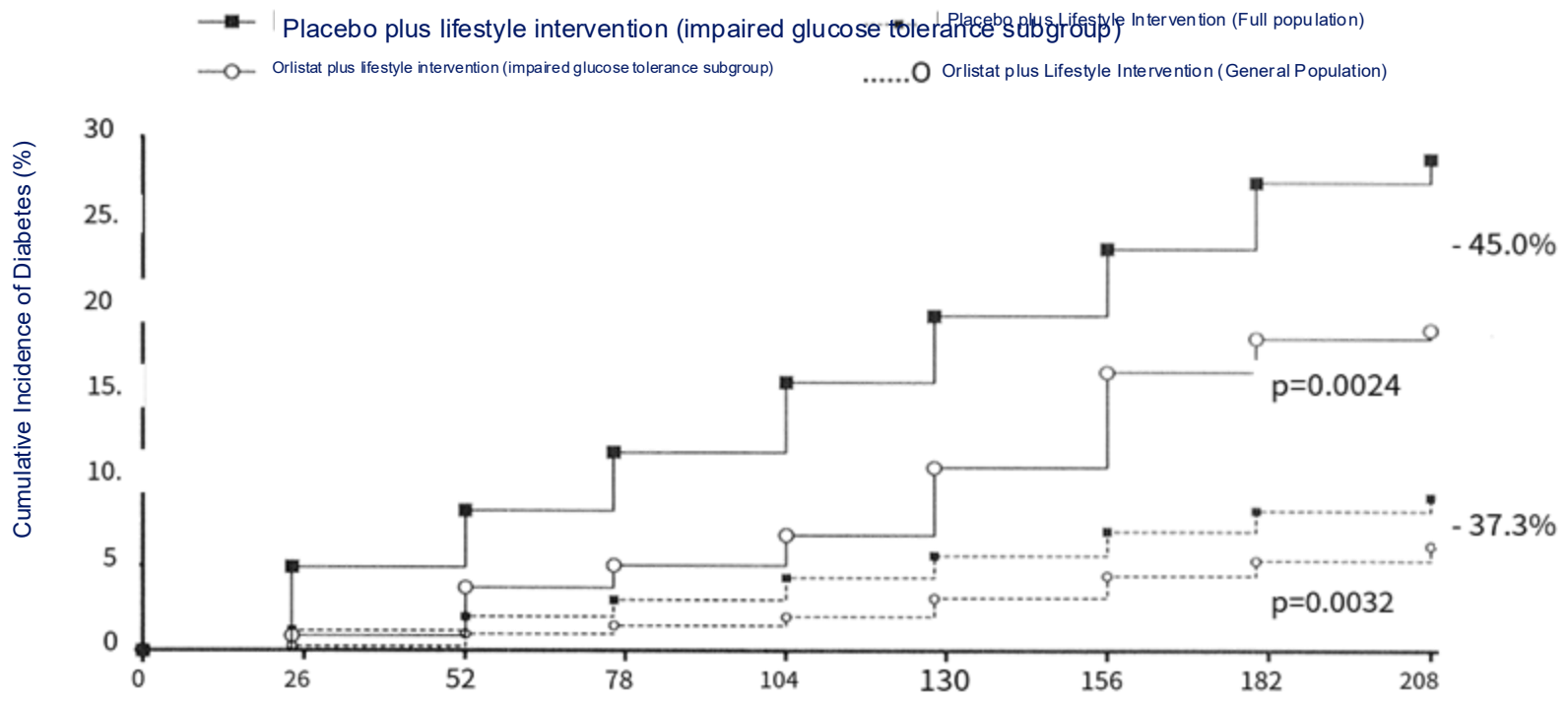
* P <0.05;

1.Ji L, et al. Lancet Diabetes Endocrinol. 2025 Sep;13(9):777-789. 2.Gu W, et al. Diabetes Obes Metab. 2025 May;27(5):2540-2551. 3.Ji L, et al. N Engl J Med. 2025 Jun 12;392(22):2215-2225. 4.Zhao L, et al. JAMA. 2024 Aug 20;332(7):551-560.

Preventing diabetes: Orlistat (XENDOS)

- The XENDOS study was a 4-year, double-blind, randomized, placebo-controlled, prospective study involving 3305 obese patients who were randomly assigned to receive either placebo plus lifestyle modification or orlistat at a dose of 120 mg three times daily plus lifestyle modification
- With orlistat, the incidence of diabetes decreased from 9% to 6.2%, with a 37.3% relative risk reduction

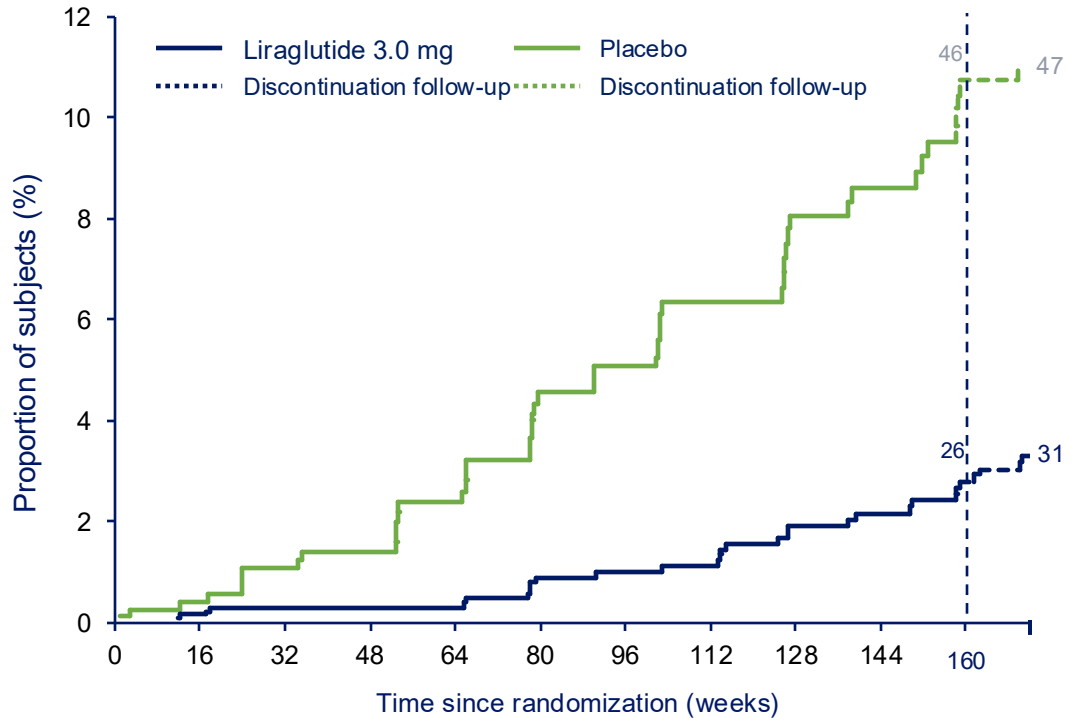
Orlistat reduces diabetes incidence in obese patients



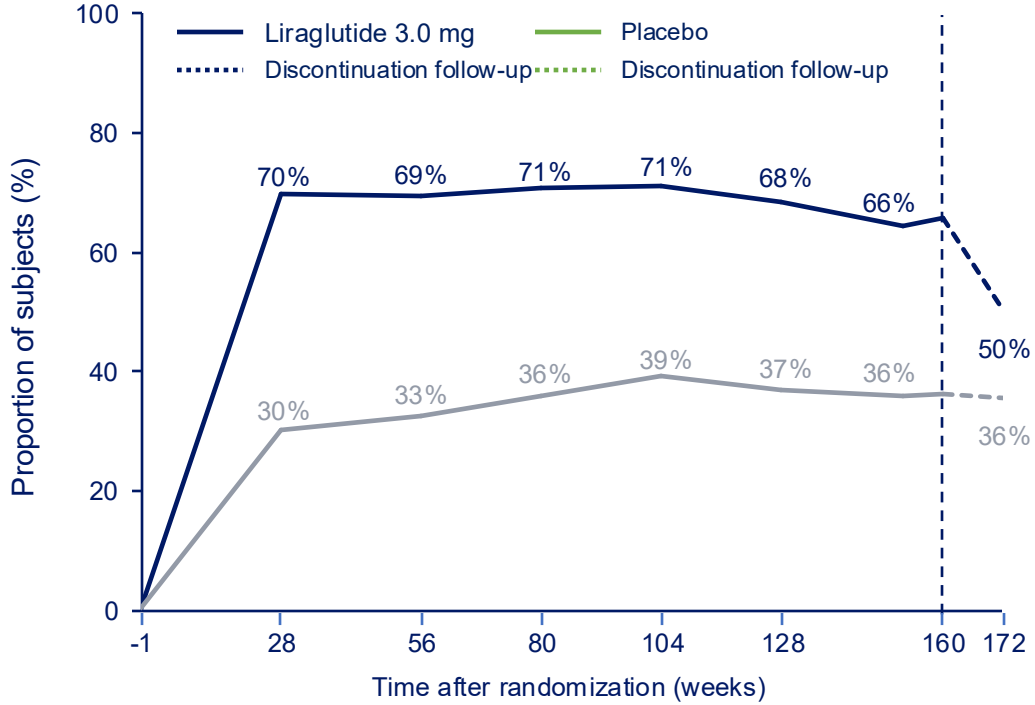
Diabetes Care 27: 155-161, 2004

Diabetes prevention: liraglutide 3.0 mg (SCALE Obesity and Prediabetes study)

Liraglutide 3.0 mg delayed progression to T2D by 2.7 times



Two thirds of subjects in liraglutide 3.0 mg group returned to normal blood glucose



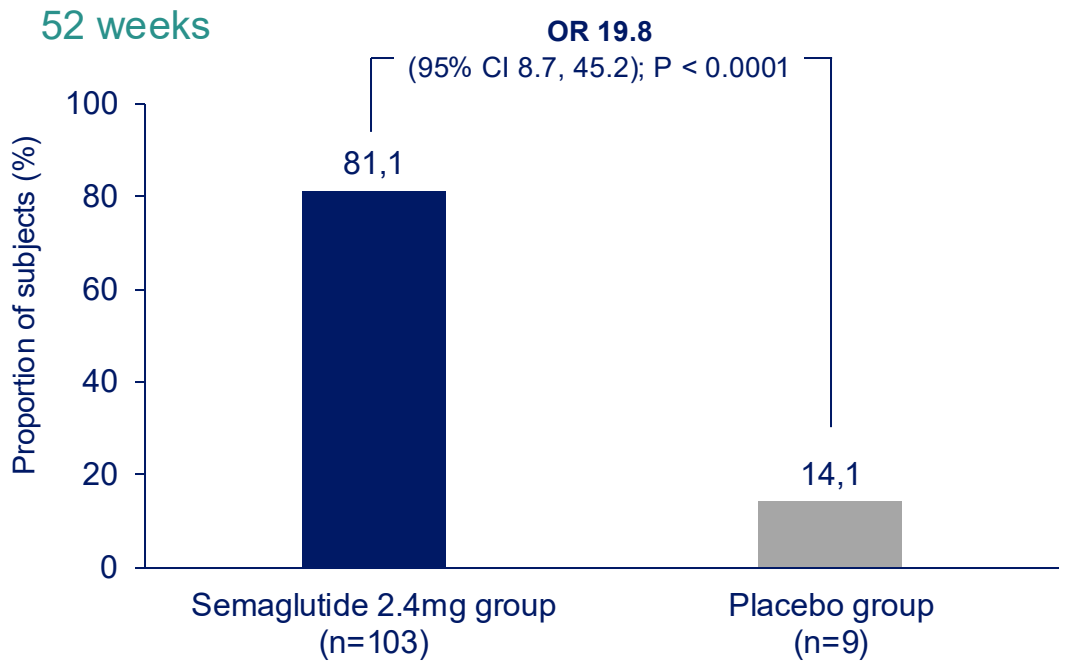
T2D, type 2 diabetes mellitus

le Roux, et al. Lancet. 2017; 389:1399-1409.

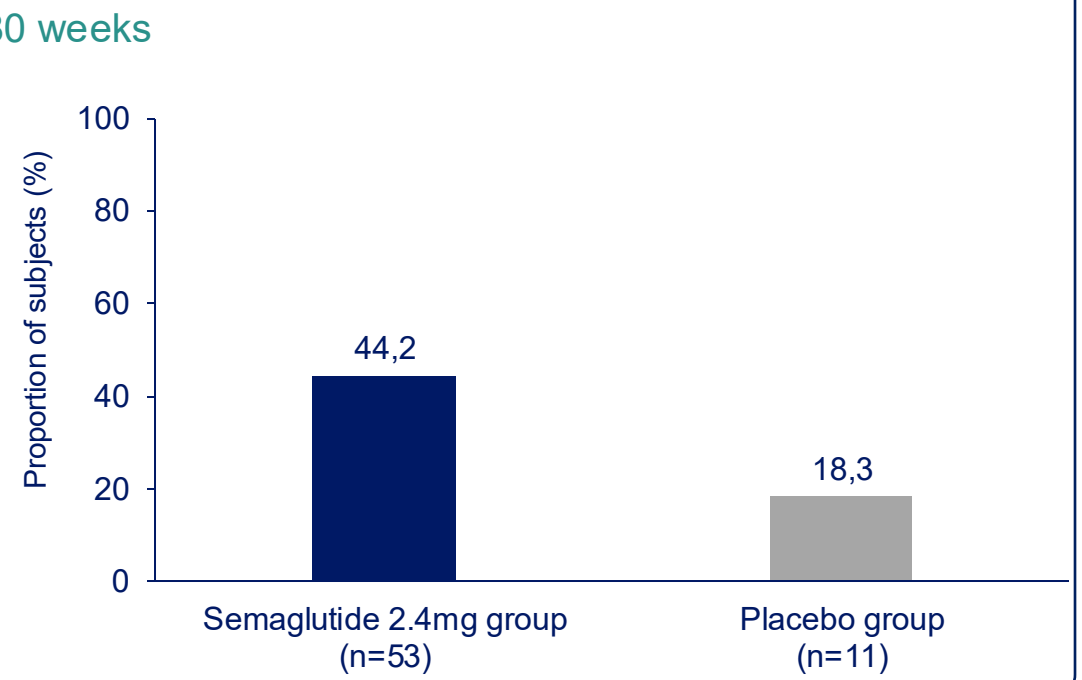
Normalization of blood glucose: semaglutide 2.4mg(STEP 10)

- The STEP 10 study was a multicenter, randomized, controlled trial testing the effect of semaglutide 2.4mg, as compared with placebo, on a composite end point of weight and glucose reversion to normal in persons with obesity and prediabetes. The follow-up time was 52 weeks, and the observation period was 28 weeks after treatment discontinuation

At week 52, 81.1% in the semaglutide 2.4-mg group
Blood glucose levels returned to normal

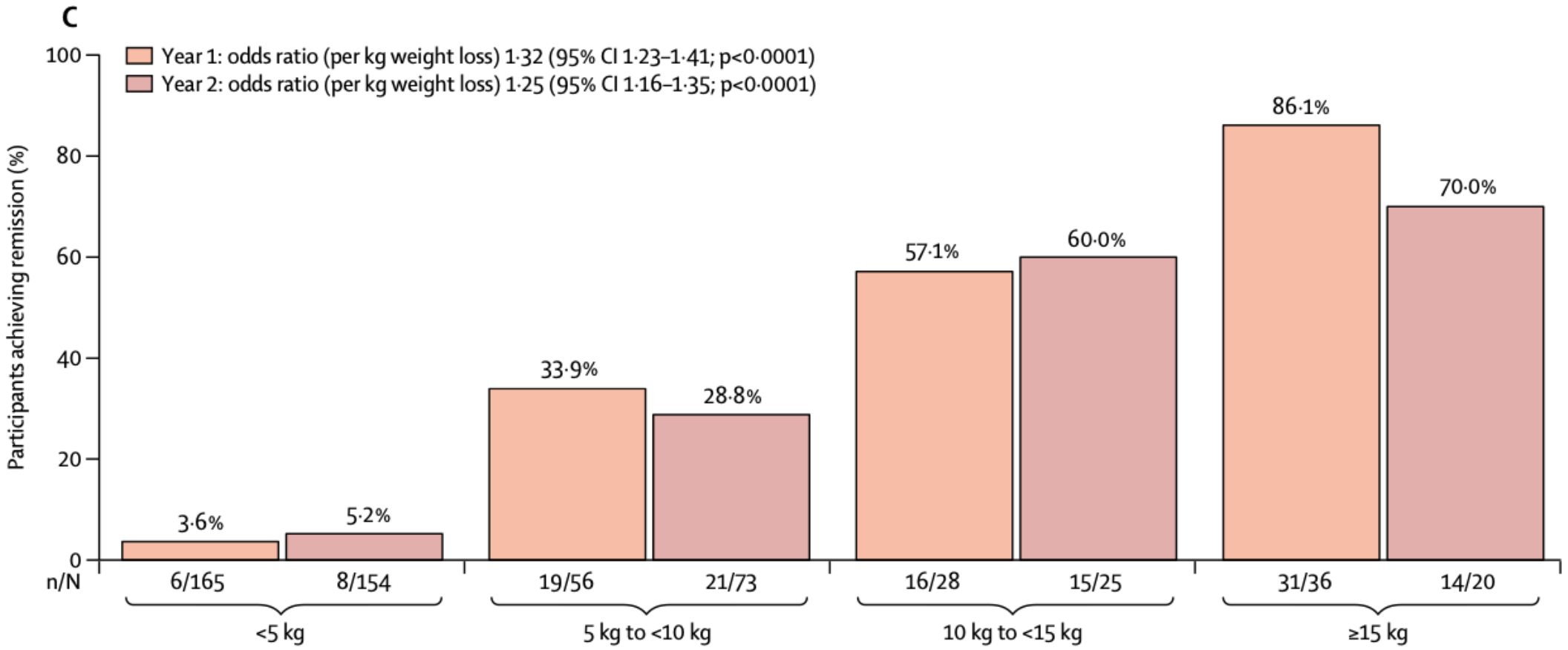


At week 80, 44.2% in the semaglutide 2.4-mg group
Subjects maintained normoglycemia



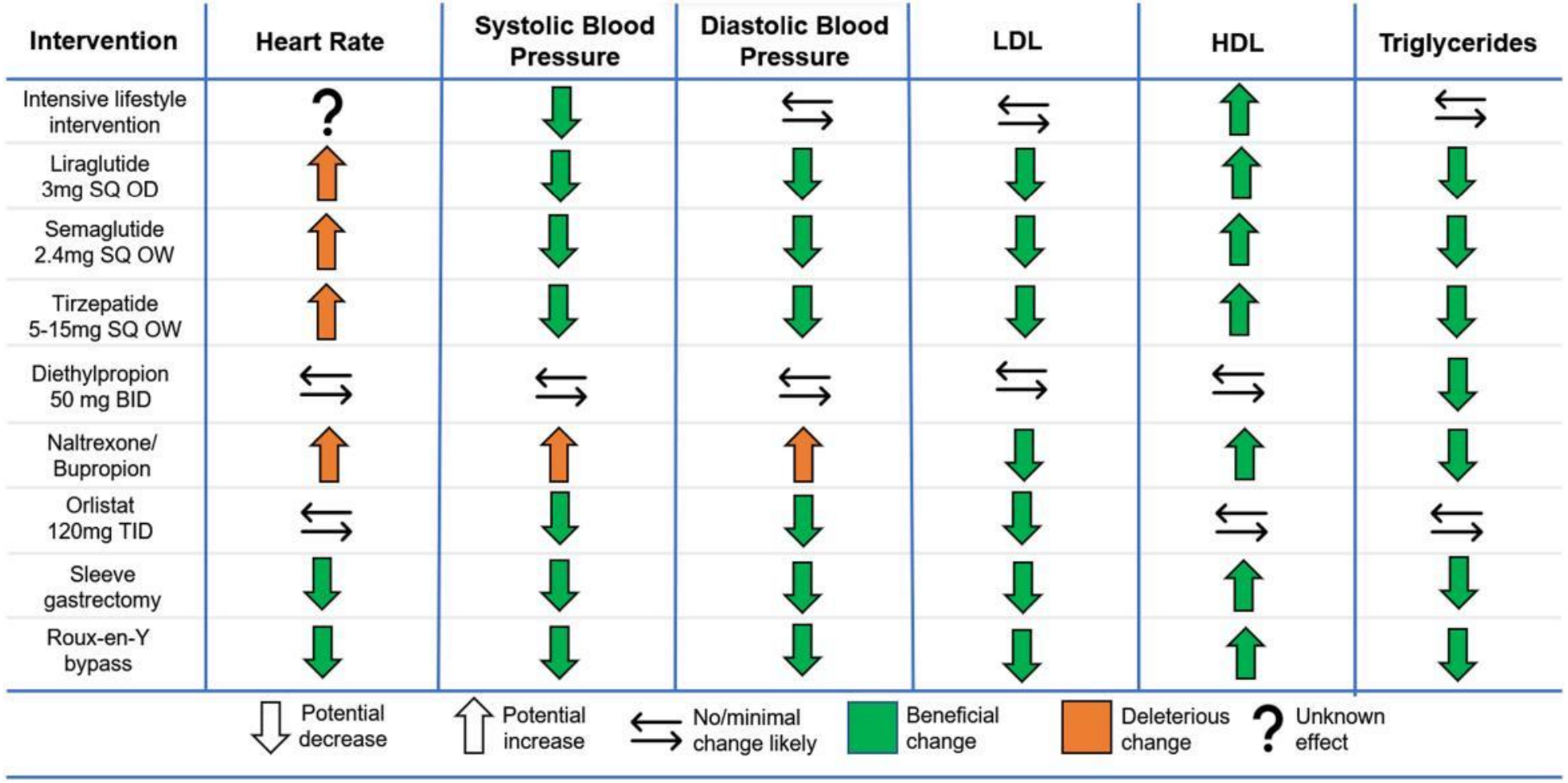
The proportion of participants who returned to normal glucose levels between baseline and weeks 52 and 80 (estimated with theuse of treatment strategies) during the trial observation period. Return to normal glucose levels was defined as an HbA 1c of less than 6.0% (<42 mmol/mol) and an FPG of less than 5.5 mmol/L.
Odds ratio (OR); CI, confidence interval; FPG, fasting plasma glucose; HbA 1c, glycosylated hemoglobin; N, number of subjects; T2D, type 2 diabetes mellitus.
From Figure 3A+B: Proportion of participants who returned to normoglycemia or progressed to T2D in the semaglutide 2.4mg group compared with the placebo group (full analysis set)

Weight Reduction and Diabetes remission from DiRECT trial



Lancet Diabetes Endocrinol 2019 05;7(5)

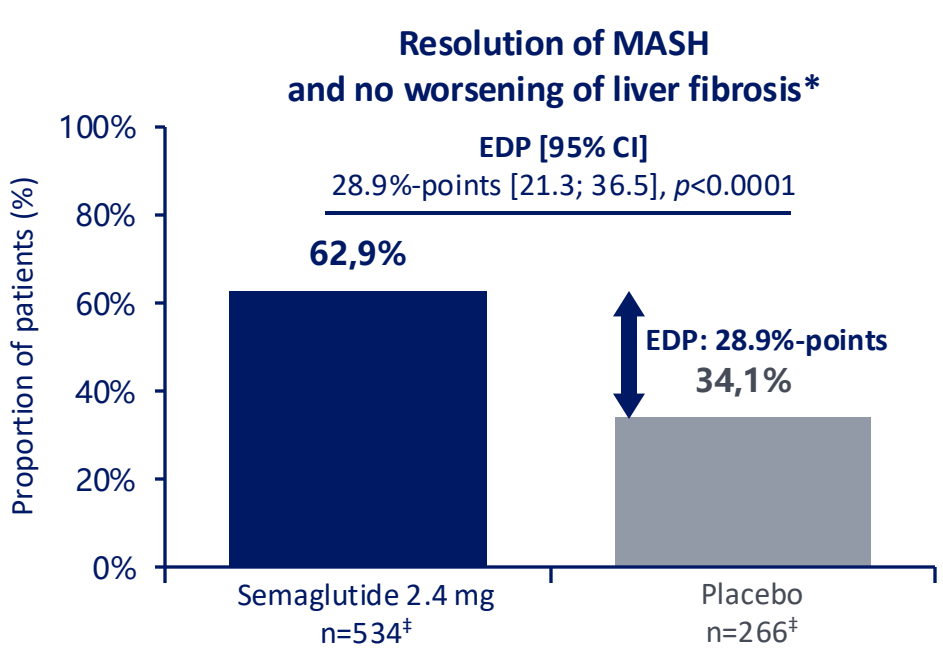
Effects of weight loss medications on cardiovascular risk factors

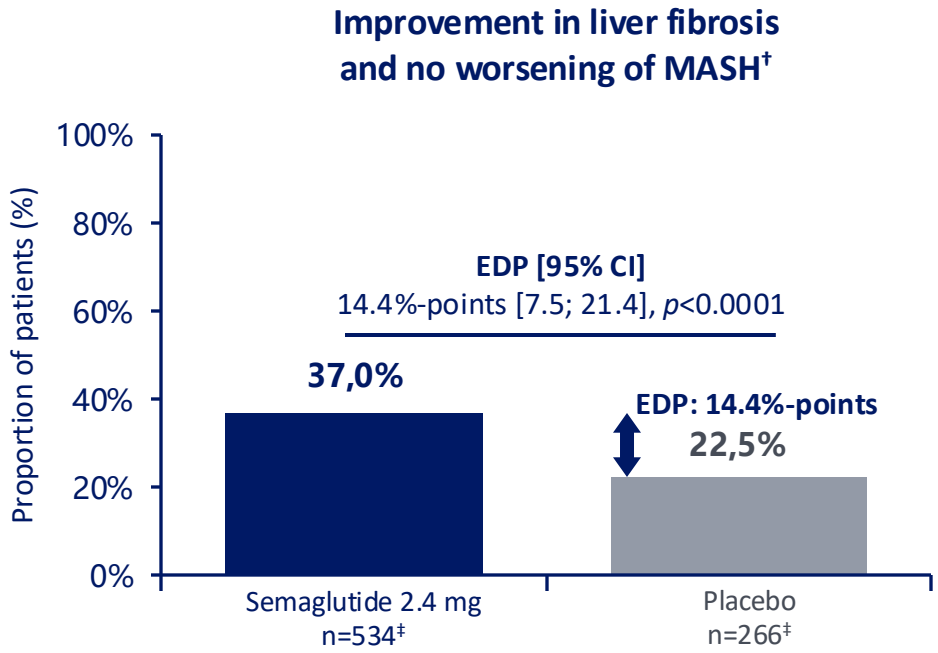


European Heart Journal (2023) **44**, 5036–5048

Steatohepatitis resolution and improvement in liver fibrosis

Proportion of patients at Week 72 (full analysis set)

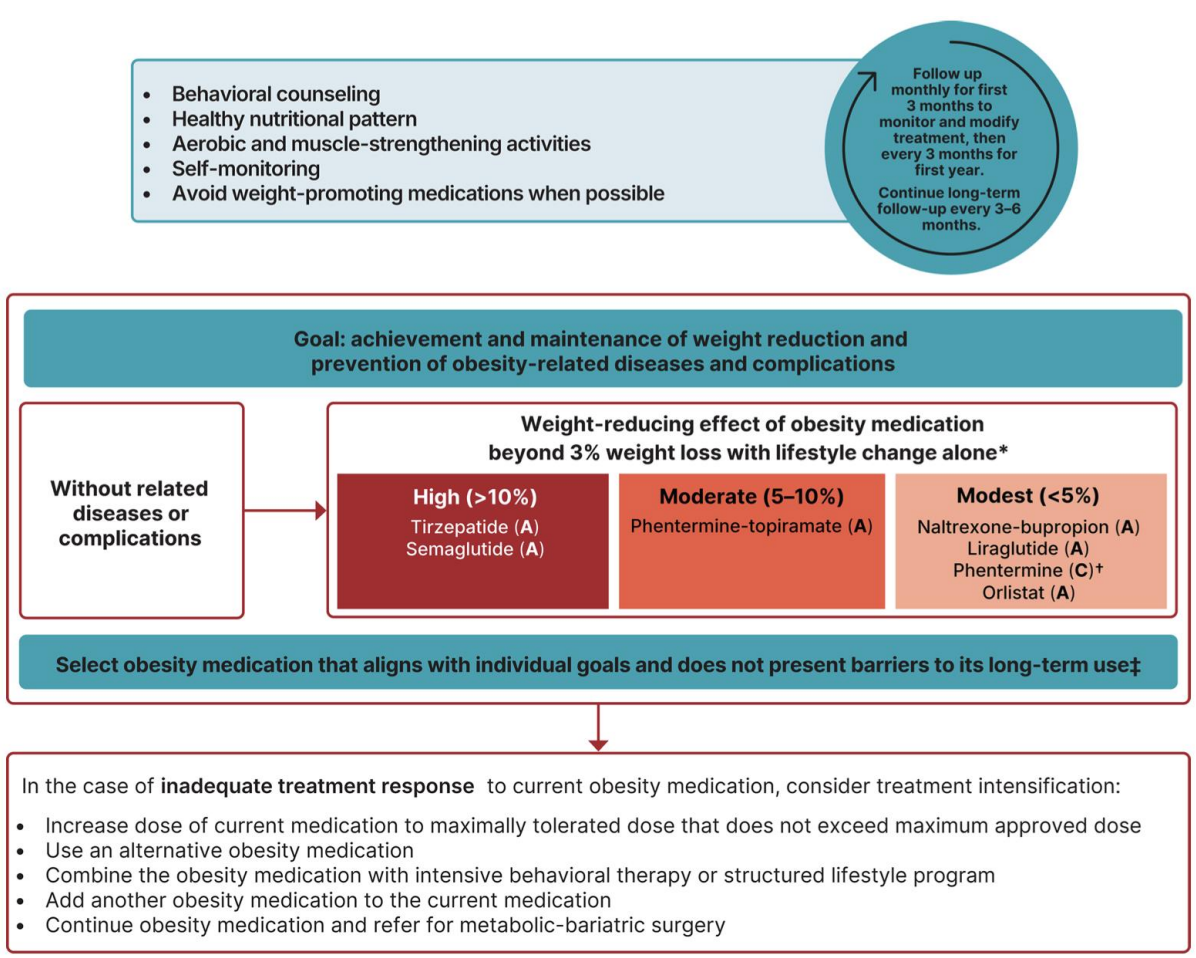


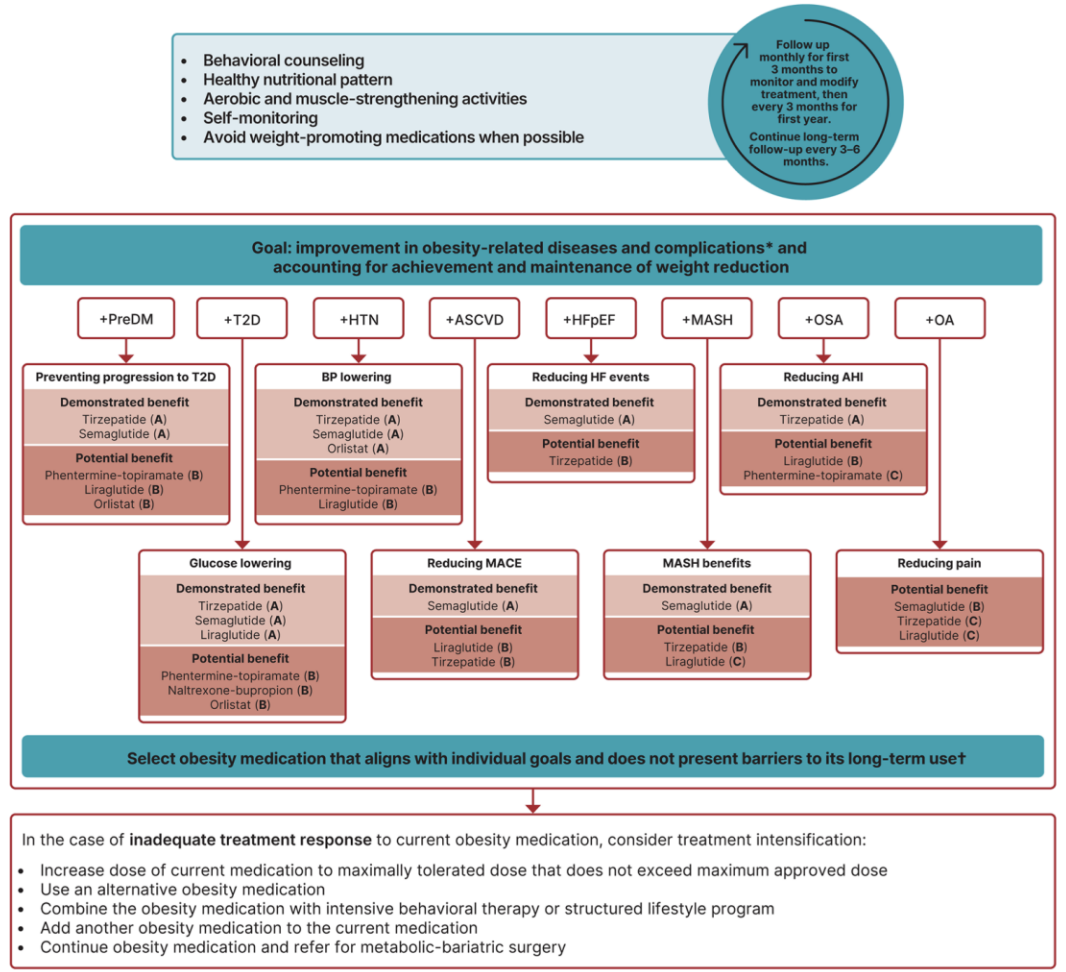


Significantly more patients with MASH F2–F3 treated with semaglutide 2.4 mg achieved **both primary endpoints of MASH resolution (62.9%) and improvement in liver fibrosis (37.0%)** than those treated with placebo **(34.1%, 22.5% respectively)**

*Analysis set: FAS (interim), first 800 randomised subjects. EDP: Estimated difference in responder proportions with 95% confidence interval and two-sided p-value. *Resolution of steatohepatitis is defined as a NAS of 0-1 for inflammation, 0 for ballooning and any value for steatosis according to NASH CRN. No worsening of liver fibrosis is defined as no increase in fibrosis score. Fibrosis is graded on the NASH CRN fibrosis scale from 0-4. †Improvement in fibrosis is defined as >= 1 grade improvement on the NASH CRN fibrosis scale. No worsening of steatohepatitis is defined as no increase from baseline in NAS score for ballooning, inflammation or steatosis. The absolute difference between responder proportions, 95% confidence interval, P value was generated with the use of Cochran-Mantel-Haenszel (CMH) test stratified by baseline diabetes status (medical history) and fibrosis stage (eligibility read). ‡Missing data were handled by reference-based multiple imputation and Rubin' s rule based on the Mantel-Haenszel estimator and Sato's estimate of the standard error (reference) were used to aggregate results. CI, confidence interval; EDP, estimated difference in responder proportions; F, fibrosis stage; MASH, metabolic dysfunction associated steatohepatitis; NASH CRN, Non-Alcoholic Steatohepatitis Clinical Research Network. Newsome PN et al. Oral Presentation at American Association for the Study of the Liver The Liver Meeting; Late Breaker 5018; November 19 2024; San Diego, USA.*

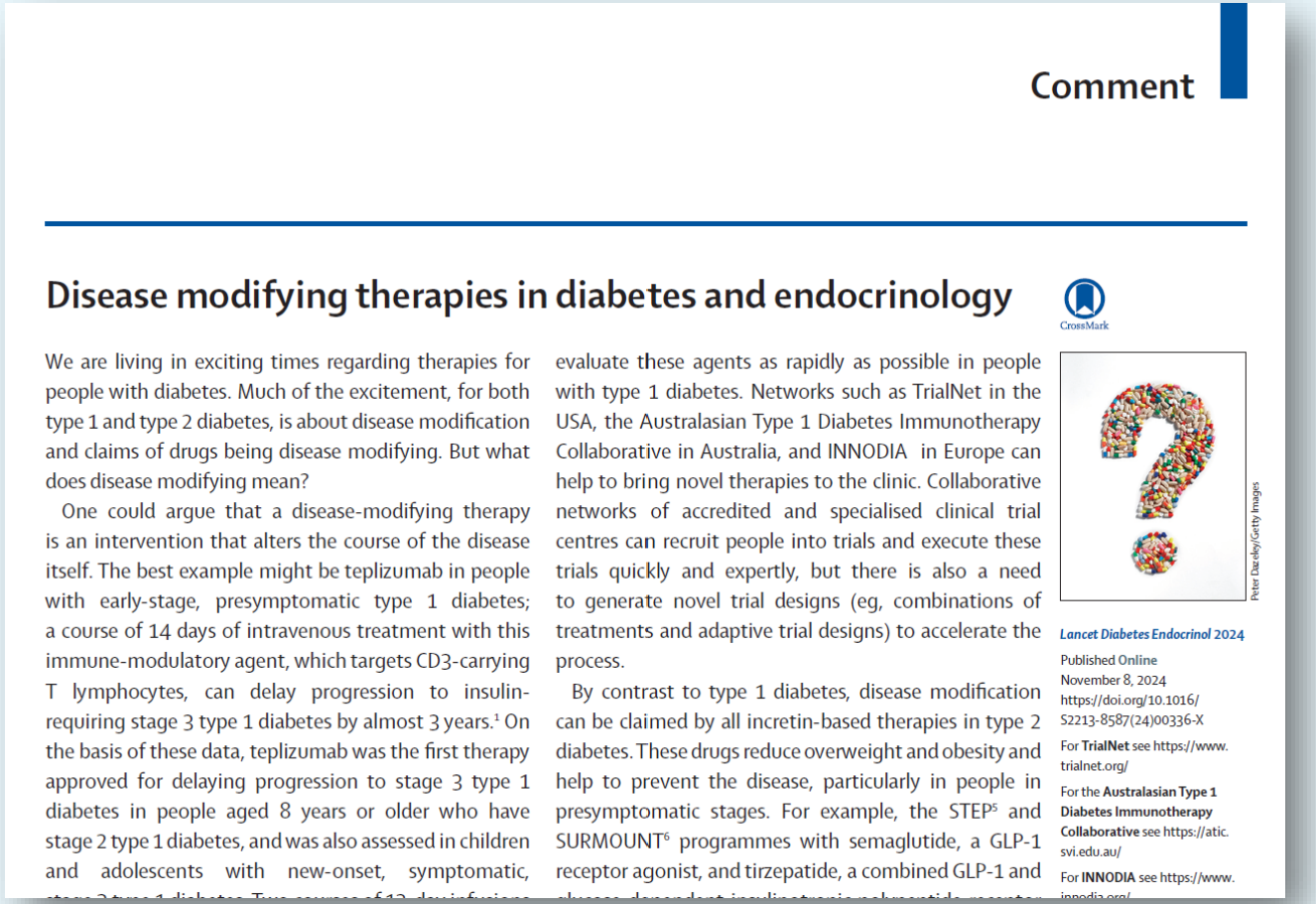
The ADA's latest treatment recommendations for obese individuals





Pharmacologic Treatment of Obesity in Adults: Standards of Care in Overweight and Obesity. DOCM CARE 2026; doci250008

"Disease modification" has emerged as a direction in the management of metabolic diseases



Comment

Disease modifying therapies in diabetes and endocrinology

We are living in exciting times regarding therapies for people with diabetes. Much of the excitement, for both type 1 and type 2 diabetes, is about disease modification and claims of drugs being disease modifying. But what does disease modifying mean?

One could argue that a disease-modifying therapy is an intervention that alters the course of the disease itself. The best example might be teplizumab in people with early-stage, presymptomatic type 1 diabetes; a course of 14 days of intravenous treatment with this immune-modulatory agent, which targets CD3-carrying T lymphocytes, can delay progression to insulin-requiring stage 3 type 1 diabetes by almost 3 years.[1] On the basis of these data, teplizumab was the first therapy approved for delaying progression to stage 3 type 1 diabetes in people aged 8 years or older who have stage 2 type 1 diabetes, and was also assessed in children and adolescents with new-onset, symptomatic,

evaluate these agents as rapidly as possible in people with type 1 diabetes. Networks such as TrialNet in the USA, the Australasian Type 1 Diabetes Immunotherapy Collaborative in Australia, and INNODIA in Europe can help to bring novel therapies to the clinic. Collaborative networks of accredited and specialised clinical trial centres can recruit people into trials and execute these trials quickly and expertly, but there is also a need to generate novel trial designs (eg, combinations of treatments and adaptive trial designs) to accelerate the process.

By contrast to type 1 diabetes, disease modification can be claimed by all incretin-based therapies in type 2 diabetes. These drugs reduce overweight and obesity and help to prevent the disease, particularly in people in presymptomatic stages. For example, the STEP[5] and SURMOUNT[6] programmes with semaglutide, a GLP-1 receptor agonist, and tirzepatide, a combined GLP-1 and

Peter Dazeley/Getty Images

Lancet Diabetes Endocrinol 2024

Published Online November 8, 2024 https://doi.org/10.1016/S2213-8587(24)00336-X

For **TrialNet** see https://www.trialnet.org/

For the **Australasian Type 1 Diabetes Immunotherapy Collaborative** see https://atic.svi.edu.au/

For **INNODIA** see https://www.innodia.org/

In 2024, The Lancet Diabetes & Endocrinology redefined the therapeutic goal as **disease modification** — which, in obesity care, hinges on **visceral fat reduction to halt or reverse metabolic disease progression**.

Lancet Diabetes Endocrinol. 2024 Dec;12(12):876-877

北京大学人民医院
PEKING UNIVERSITY PEOPLE'S HOSPITAL

Thank you for your attention