

# **Obesity Disease Perspective; Position of Liraglutide among modern obesity medications**

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# Outlines

- Prevalence of obesity
- Definition of obesity/Obesity as a spectrum of medical presentations
- Liraglutide structure
- SCALE trial design
- Scale cardiovascular analysis
- Other GLP1/GIP receptor agonist CV outcomes
- Benefits of liraglutide vs the other anti-obesity available drugs
- Conclusion

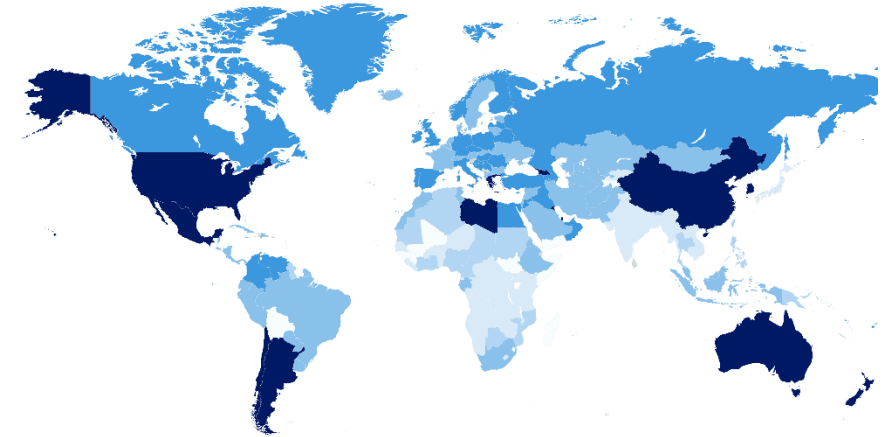
# Global prevalence of obesity

Among adults

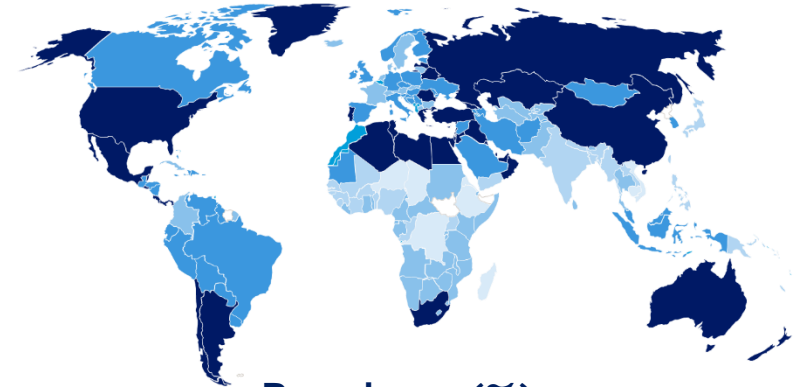
764

million people  
live with obesity<sup>1</sup>

Men<sup>2</sup>



Women<sup>3</sup>

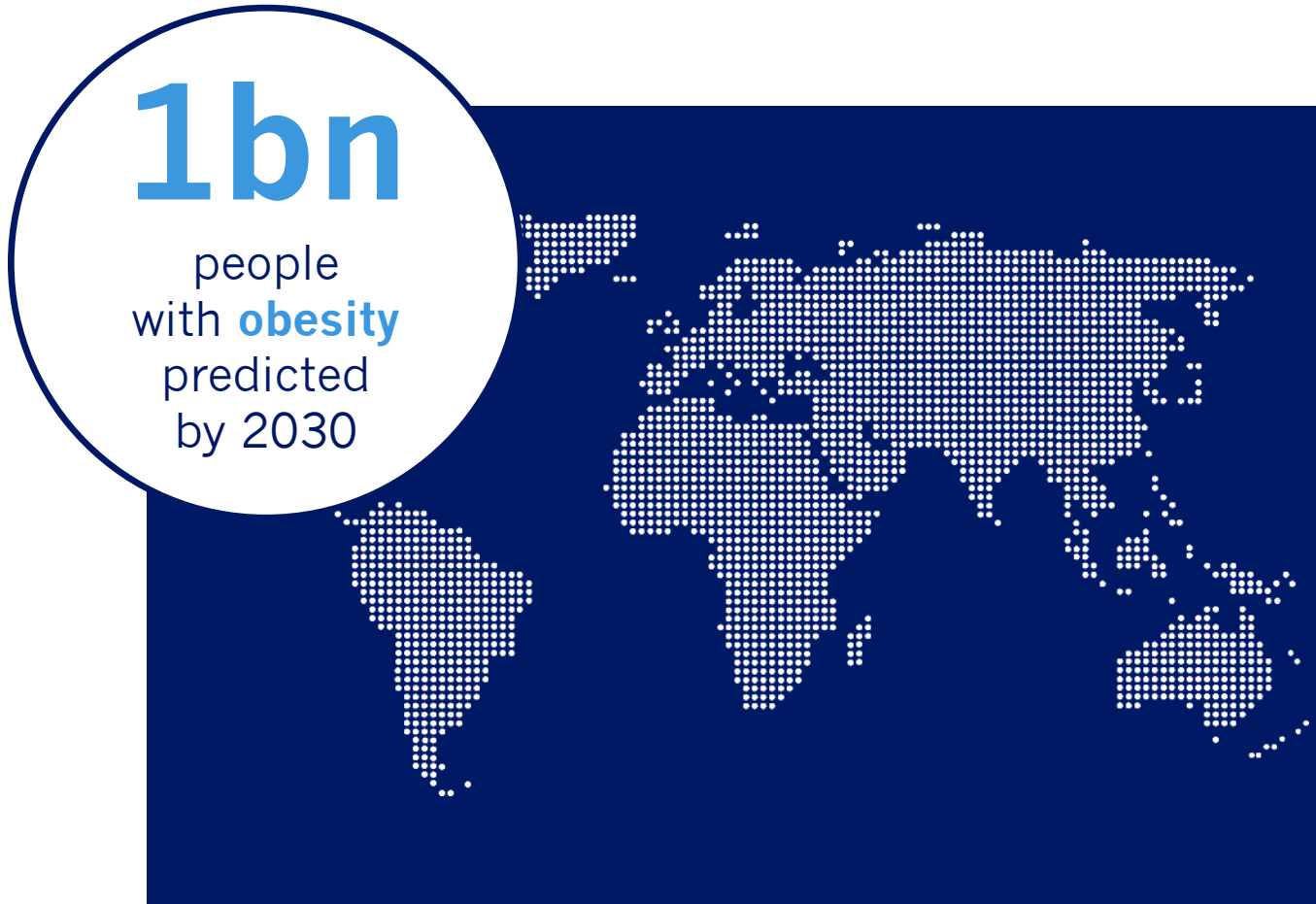


Prevalence (%)

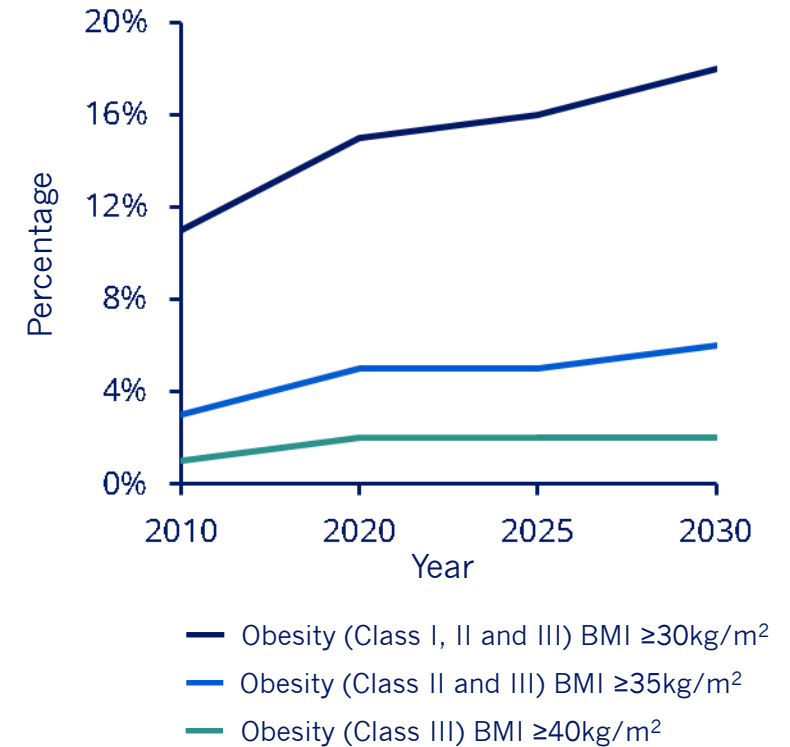


1. World Obesity Federation: World Obesity Atlas, 2022. Available from: [https://s3-eu-west-1.amazonaws.com/wof-files/World\\_Obesity\\_Atlas\\_2022.pdf](https://s3-eu-west-1.amazonaws.com/wof-files/World_Obesity_Atlas_2022.pdf). Accessed October 2022; 2. World Obesity Federation: Men living with obesity. Newest available data. Available from: <https://data.worldobesity.org/maps/?area=trends&group=M&year=2020>. Accessed October 2022; 3. World Obesity Federation: Women living with obesity. Newest available data. Available from: <https://data.worldobesity.org/maps/?area=trends&group=F&year=2020>. Accessed October 2022.

# Predictions for global prevalence of obesity



**Prevalence over time<sup>1</sup>**  
Global obesity prevalence is predicted to steadily increase over the next decade



BMI, body mass index; bn, billion.

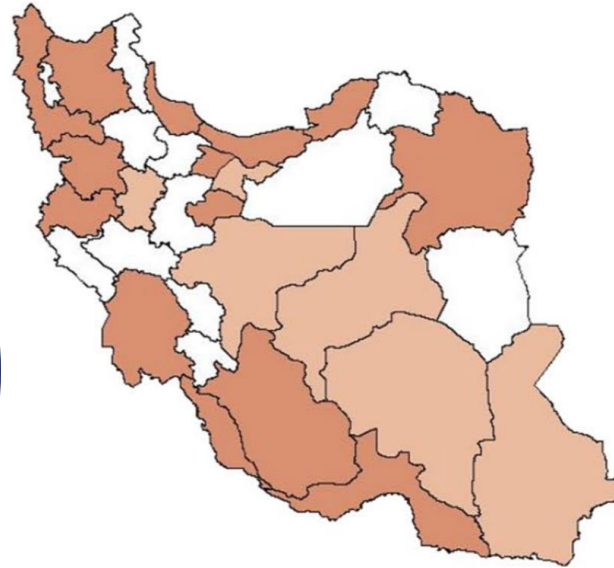
1. World Obesity Federation: World Obesity Atlas, 2022. Available from: [https://s3-eu-west-1.amazonaws.com/wof-files/World\\_Obesity\\_Atlas\\_2022.pdf](https://s3-eu-west-1.amazonaws.com/wof-files/World_Obesity_Atlas_2022.pdf). Accessed October 2022.

# National prevalence of obesity

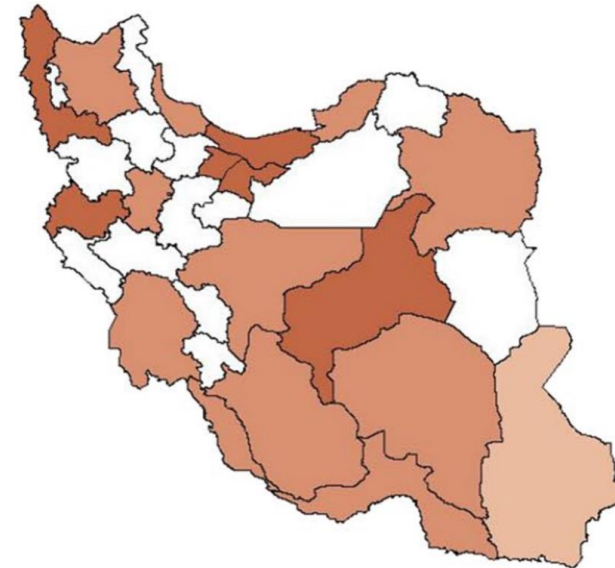
Among adults

**14.5** million people live with **obesity** (21.38% of the adult population)

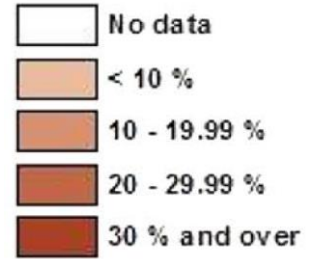
**24** million people live with being **overweight** (35.26% of the adult population)



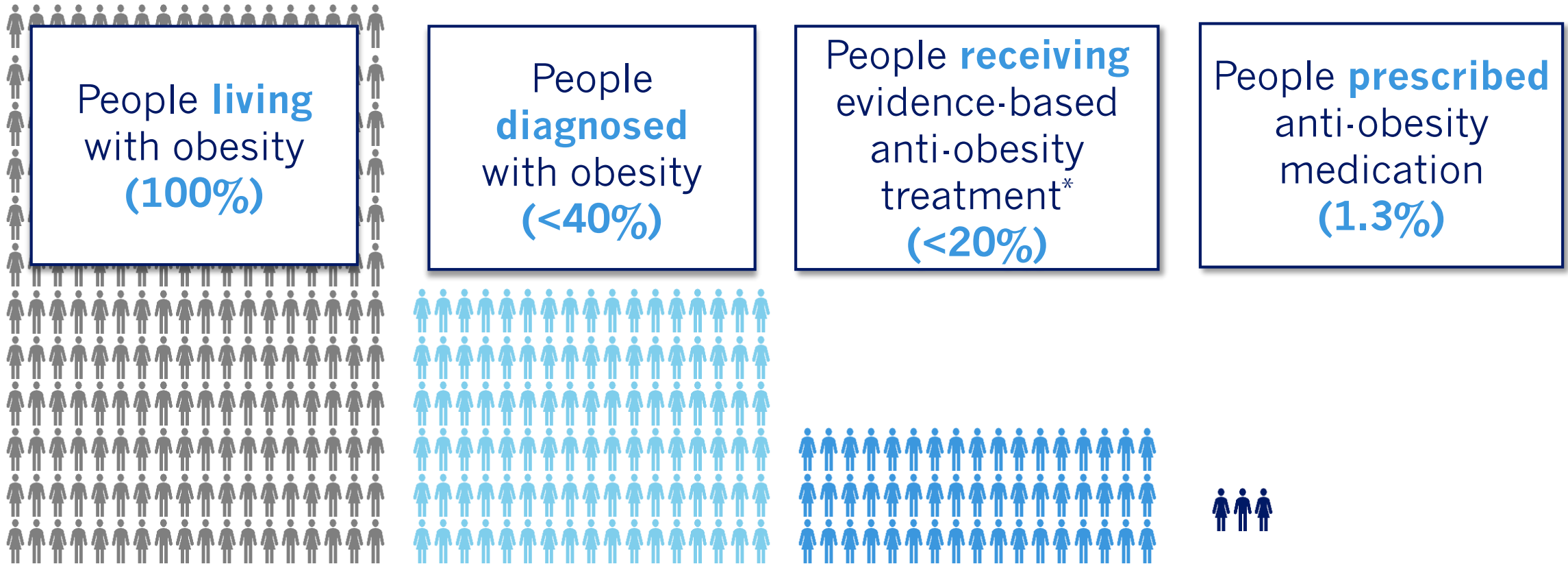
Geographical dispersion of obesity in adults



Geographical dispersion of overweight in adults



# Obesity remains underdiagnosed and undertreated



\*Includes lifestyle and behavioral counselling, anti-obesity medications and bariatric surgery.

1. Adapted from: Colby and Ortman. 2014. Available from [www.census.gov/content/dam/Census/library/publications/2015/demo/p25-1143.pdf](http://www.census.gov/content/dam/Census/library/publications/2015/demo/p25-1143.pdf). Accessed October 2022; 2. Centers for Disease Control and Prevention. Available from [www.cdc.gov/nchs/fastats/obesity-overweight.htm](http://www.cdc.gov/nchs/fastats/obesity-overweight.htm). Accessed on October 2022; 3. Ma et al. Obesity (Silver Spring) 2009;17:1077-85; 4. IMS Xponent Dec-15; 5. Caterson et al. Diabetes Obes Metab 2019; 21:1914-24; 6. Saxon et al. Obesity (Silver Spring, Md.) 2019;27:1975-81.

# Obesity is recognised as a disease and a health issue



“Obesity is a chronic, relapsing, progressive disease process ....need for immediate action for prevention and control of this global epidemic”

World Obesity Federation<sup>1</sup>



“Obesity is a progressive chronic disease, similar to diabetes or high blood pressure, ...”

Obesity Canada<sup>3</sup>



“Obesity is a multifactorial, chronic, relapsing, non-communicable disease marked by an abnormal and/or excessive accumulation of body fat, that presents a risk to health.”

European Association for the Study of Obesity<sup>4</sup>



“Obesity and overweight as a chronic medical condition (de facto disease state) and urgent public health problem...”

American Medical Association<sup>2</sup>



“It (obesity) is not a lifestyle choice caused by individual greed but a disease caused by health inequalities, genetic influences and social factors..”

Royal College of Physicians UK<sup>5</sup>



“The Treat and Reduce Obesity Act would allow a variety of qualified practitioners, including registered dietitian nutritionists, to more effectively treat this disease, which impacts more than one-third of our nation.”

Academy of nutrition and dietetics<sup>6</sup>



“Obesity is a chronic relapsing disease, which in turn acts as a gateway to a range of other non-communicable diseases, such as diabetes, cardiovascular diseases and cancer.”<sup>3</sup>

European Commission<sup>7</sup>



“A pathological state (obesity disease) in which a person suffers health problems caused by or related to obesity thus making weight loss clinically desirable ...”

Asia Oceania Association for the Study of Obesity<sup>8</sup>

1. Bray et al. *Obes Rev* 2017;18:715–23; 2. AMA resolutions. June 2012. Available at [https://www.ama-assn.org/sites/ama-assn.org/files/corp/media-browser/public/hod/a12-resolutions\\_0.pdf](https://www.ama-assn.org/sites/ama-assn.org/files/corp/media-browser/public/hod/a12-resolutions_0.pdf). Accessed March 2024; 3. Obesity Canada. Available at <https://obesitycanada.ca/guidelines/>. Accessed March 2024; 4. Busetto L et al. *Nat Med* 2024; doi: 10.1038/s41591-024-03095-3. Online ahead of print; 5. Royal College of Physicians. Anon. *BMJ* 2019;364:l45; 6. Raynor et al. *J Acad Nutr Diet* 2016;116:129–47; 7. European Commission. Obesity prevention. Available from [https://knowledge4policy.ec.europa.eu/health-promotion-knowledge-gateway/obesity\\_en](https://knowledge4policy.ec.europa.eu/health-promotion-knowledge-gateway/obesity_en). Accessed March 2024; 8. AOASO position statement, Nagoya Declaration 2015.



# Defining obesity

WHO guidelines for classifying obesity\*

WHO classification	BMI cut-off points for definition (kg/m <sup>2</sup> )	Cardiovascular disease risk	Asian BMI cut-off points for action (kg/m <sup>2</sup> )
<b>Underweight</b>	<18.5		<18.5
<b>Normal range</b>	18.5–24.9	Low	18.5–22.9
<b>Overweight</b>	25.0–29.9	Moderate	≥23.0
<b>Obesity class I</b>	30.0–34.9	High	27.5–32.4
<b>Obesity class II</b>	35.0–39.9	Very high	32.5–37.4
<b>Obesity class III</b>	≥40.0	Very high	≥37.5

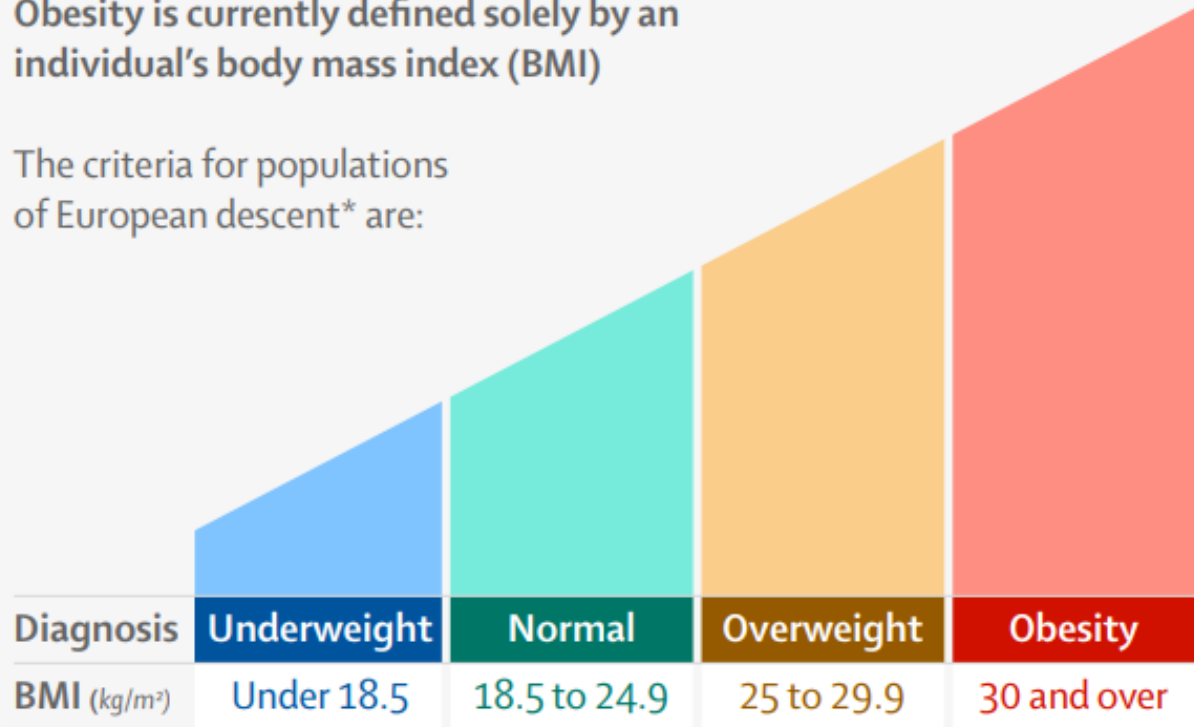
\*Additional cut-off points for public health action and for reporting purposes to facilitate international comparisons.  
BMI, body mass index; WHO, World Health Organization.  
World Health Organisation. Obesity fact files. Available [here](#). (Accessed March 2024).

# Diagnosing clinical obesity

## Limitations of the current definition of obesity

Obesity is currently defined solely by an individual's body mass index (BMI)

The criteria for populations of European descent\* are:



\*Criteria for other ethnic groups are different



Although BMI is **useful** for identifying individuals at increased risk of health consequences...



It **is not** a direct measure of fat



It **does not** establish the distribution of fat around the body



It **cannot** determine when excess body fat is a health problem

# Limitations of BMI-Based Definition of Obesity



**No "Obesity"**  
*(Normal Fat Mass)*



**Obesity**  
*(Excess Fat Mass)*



**No ongoing illness**      **Ongoing illness**



OBESITY (BMI)



EXCESS ADIPOSITY

HEALTH

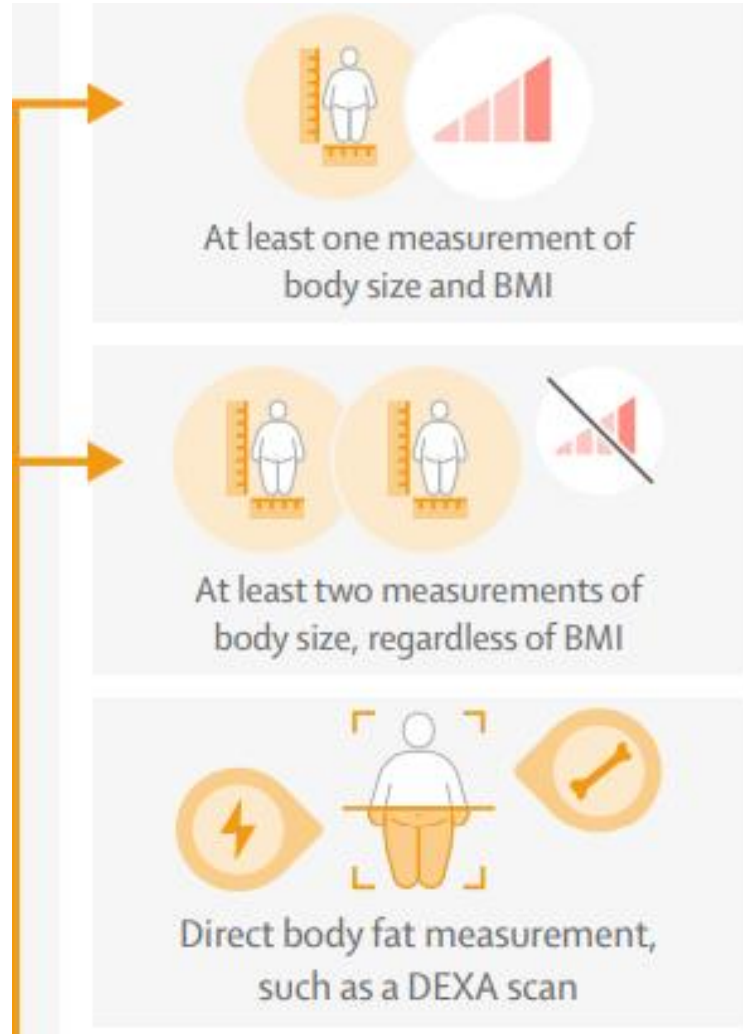
ILLNESS

# Who is obese?

#	1	2	3	4
BMI (kg/m <sup>2</sup> )	28.2	30.1	36.2	36.2
Diagnosis	Overweight	Obesity	Obesity	Obesity
Excess body fat?	✓ Yes	✗ No	✓ Yes	✓ Yes
Signs and symptoms?†	✗ No	✗ No	✗ No	✓ Yes
Notes	Under-diagnosis of obesity	Over-diagnosis of obesity	Obesity with preserved health	Obesity with ongoing illness

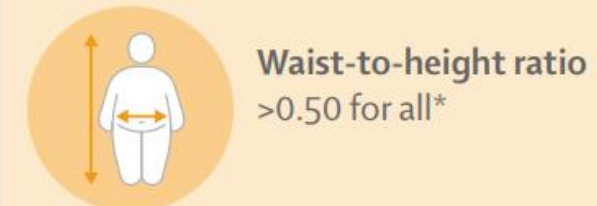
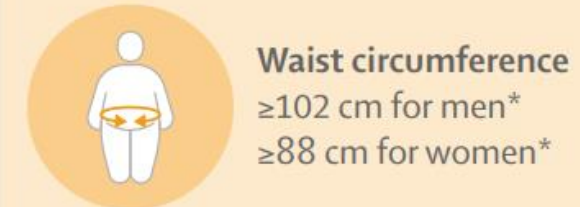
## Excess body fat?

The first step in such a diagnosis is confirming excess body fat, which can be achieved via one of the following three criteria:



### Measurements of body size

The commission defines three measurements of body size that can be used to confirm excess body fat:



*Excess body fat can pragmatically be assumed if BMI is >40 kg/m<sup>2</sup>*

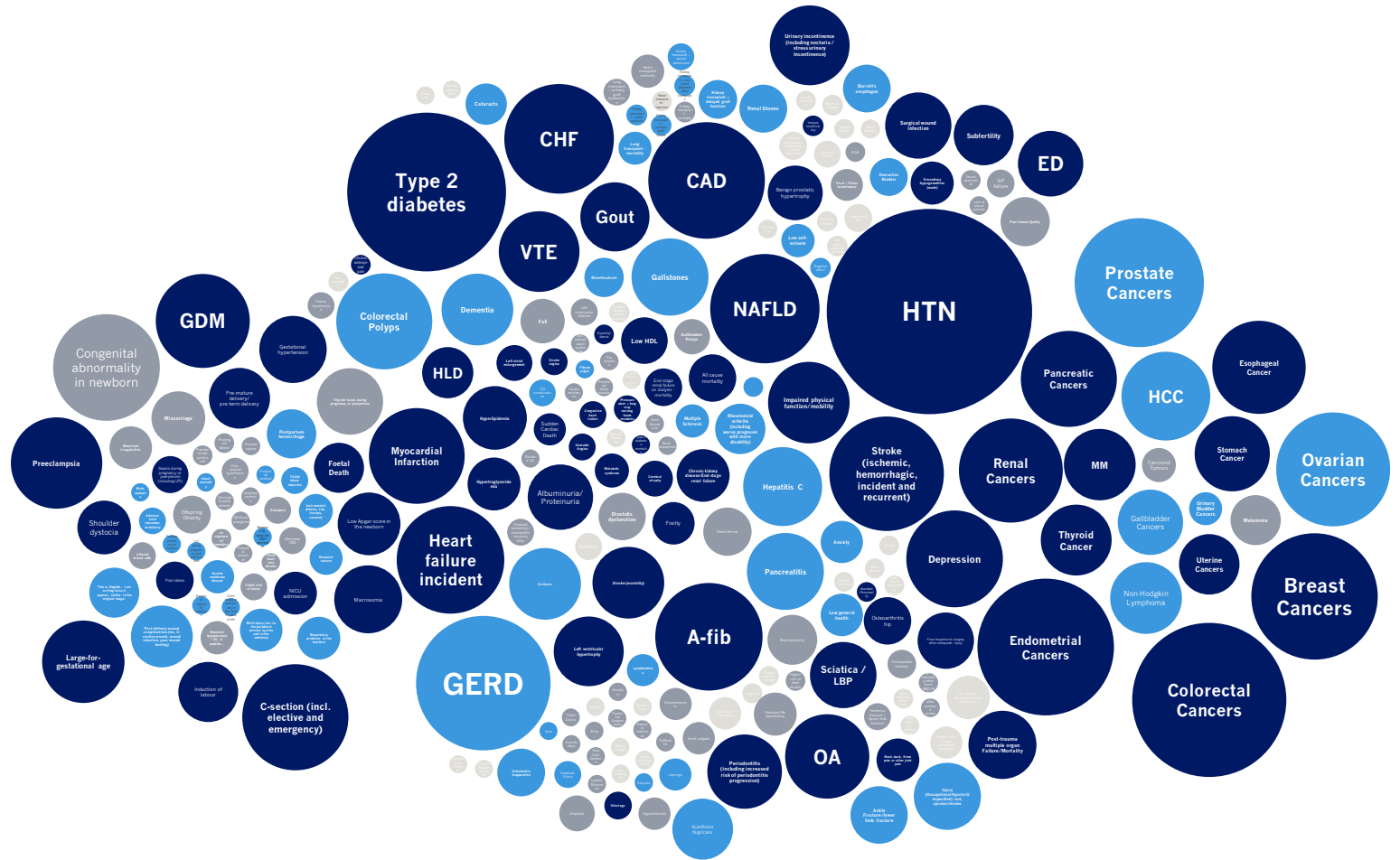
# Two obesity categories

- The commission introduces two categories:
  - **Preclinical obesity:** Excess adiposity without evident organ dysfunction or activity limitations. Individuals in this category are at increased risk of developing clinical obesity and associated diseases.
  - **Clinical obesity:** Excess adiposity accompanied by apparent organ dysfunction or activity limitations.
- This category defines obesity as a chronic disease.
- Indicators include shortness of breath, joint pain, and metabolic issues such as T2 diabetes.

# Obesity is associated with multiple complications

GRADE	Strength of evidence
4	Very strong
3	Strong
2	Moderate
1	Weak

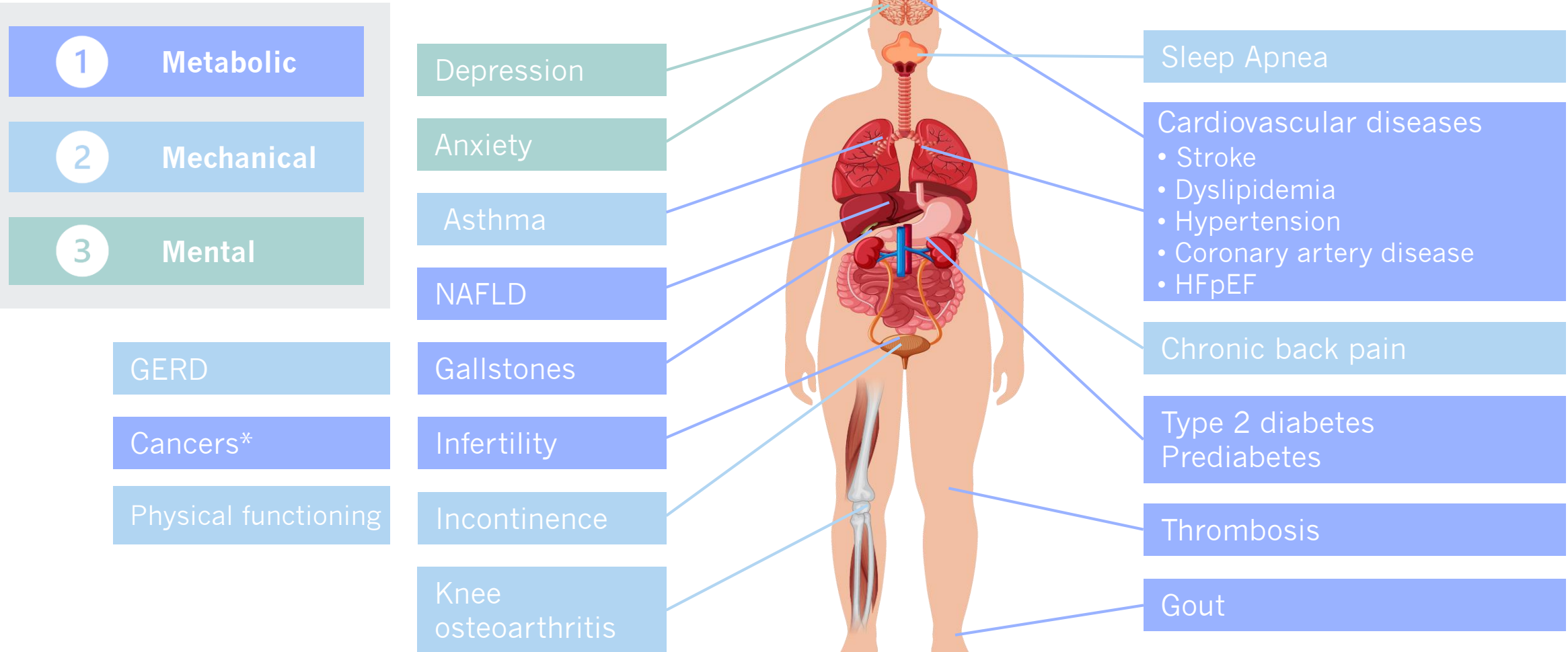
Size of circle reflects number of articles



**229+**  
 complications affecting **EVERY** organ system and medical specialty

A-fib, atrial fibrillation; CAD, coronary artery disease; CHF, congestive heart failure; ED, erectile dysfunction; EOM, eosinophilic otitis media; GDM, gestational diabetes mellitus; GERD, gastroesophageal reflux disease; HCC, hepatocellular carcinoma; HTN, hypertension; HLD, hyperlipidemia; MM, multiple myeloma; NAFLD, non-alcoholic fatty liver disease; OA, osteoarthritis; VTE, venous thromboembolism.  
 Horn et al. Postgrad Med 2022;134:359–75.

# Obesity is associated with multiple complications



\*Including breast, colorectal, endometrial, oesophageal, kidney, ovarian, pancreatic and prostate.

GERD, gastro-oesophageal reflux disease; HFpEF, heart failure with preserved ejection fraction; NAFLD, non-alcoholic fatty liver disease.

Adapted from Sharma AM. *Obes Rev* 2010;11:808–9; Guh DP et al. *BMC Public Health* 2009;9:88; Luppino FS et al. *Arch Gen Psychiatry* 2010;67:220–9; Simon GE et al. *Arch Gen Psychiatry* 2006;63:824–30; Church TS et al. *Gastroenterology* 2006;130:2023–30; Li C et al. *Prev Med* 2010;51:18–23; Hosler AS. *Prev Chronic Dis* 2009;6:A48.

# Prevalence of complications in people with

Body mass index  $\geq 30$

**3%** Stroke



**3.5%** Congestive heart failure



**8%** Ischemic heart disease



**9%** PCOS



**19%** Major depression



**21%** Diabetes



**21%** Myocardial infarction



**29%** NAFLD



**35%** GERD symptoms\*



**~40%** OSAS



**51%** Hypertension



**52%** Knee osteoarthritis

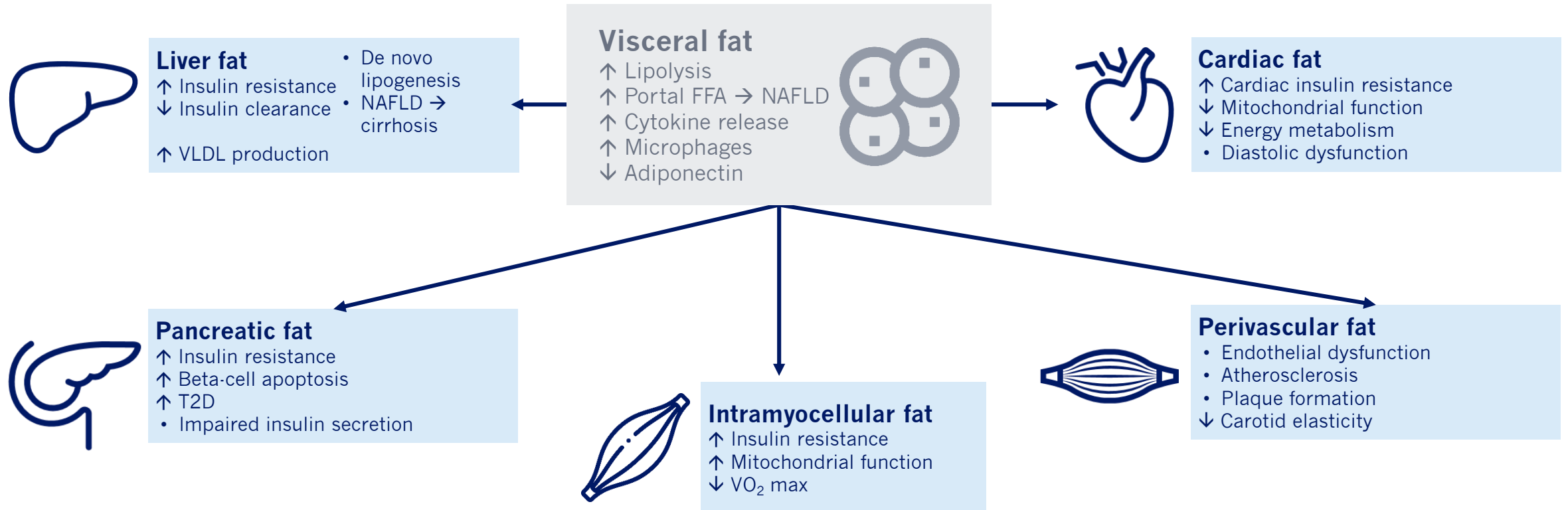


\*Weekly heartburn and regurgitation.

GERD, gastro-oesophageal reflux disease; NAFLD, nonalcoholic fatty liver disease; OSAS, obstructive sleep apnoea syndrome; PCOS, polycystic ovary syndrome.

1. Simon GE et al. Arch Gen Psychiatry 2006;63:824–30; 2. Su W et al. J Med Economics 2015;18:886–97; 3. López-Velázquez JA et al. Ann Hepatol 2014;13:166–78; 4. Yildiz BO et al. J Clin Endocrinol Metab. 2008;93:162–68; 5. El-Serag HB et al. Am J Gastroenterol. 2005;100:1243–50; 6. Prieto-Alhambra D et al. Ann Rheum Dis 2014;73:1659–64; 7. Modena DAO et al. Rev Assoc Med Bras 1992;63:852–8.

# Obesity-related health risk also depends on lipotoxicity



Accumulation of VAT is associated with fat accumulation in other organs leading to metabolic dysfunction and lipotoxicity



# 2025 Lancet Commission

## Management of clinical and preclinical obesity

### Preclinical obesity management

**Focus on risk reduction and prevention of progression to clinical obesity or other obesity-related diseases**



Health counselling for weight loss or prevention of weight gain



Monitoring over time



Active weight loss interventions in people at higher risk of developing clinical obesity, and other obesity-related diseases

### Clinical obesity management

**Focus on improvement or reversal of organ dysfunction**



Evidence-based treatment and management, with an aim to fully regain or improve functions



Treatment type should be informed by individual risk — benefit assessments and decided via an active discussion with the patient



Success should be assessed by improvement of signs and symptoms, rather than measures of weight loss

This new diagnosis approach will support evidence-based, personalised prevention and treatment, ensuring more efficient and cost-effective use of resources

# Liraglutide Overview

# What is GLP-1?

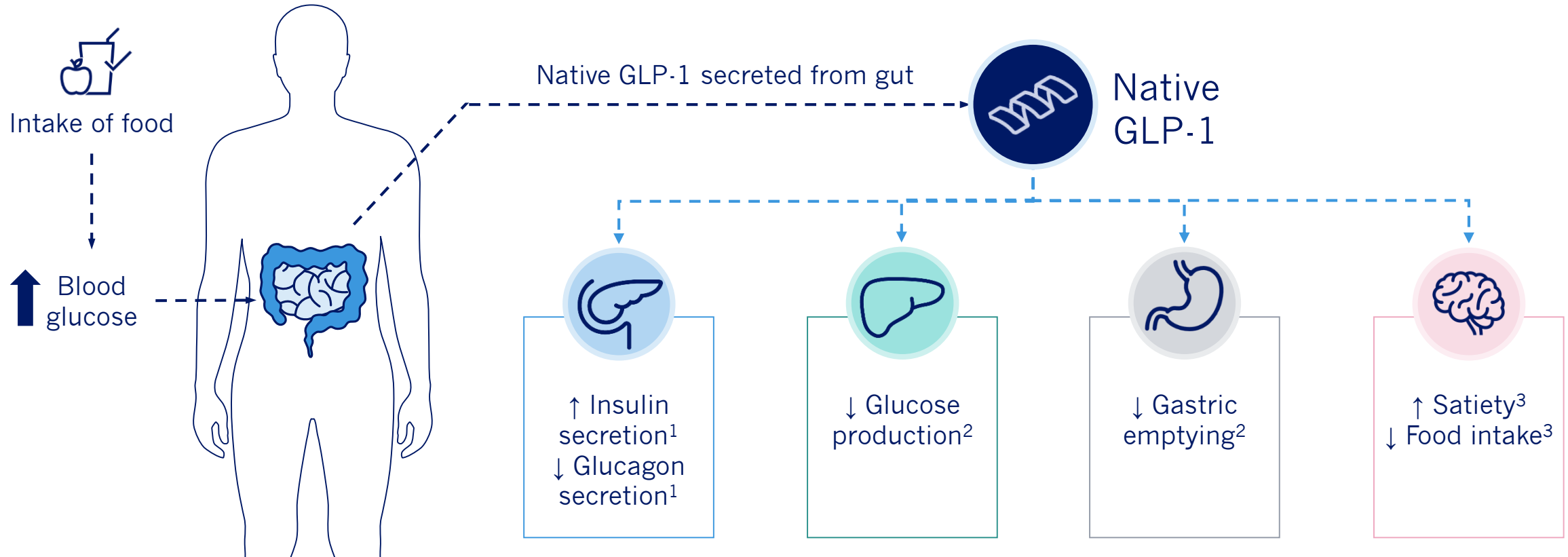
- GLP-1 is a peptide comprised of 31 amino acids
- Member of incretin family
- Secreted predominantly from L-cells in the gut, but also the brain (nucleus tractus solitarius)

## Human endogenous GLP-1



Enzymatic degradation by DPP-4  
 $t_{1/2} = 1.5\text{--}2 \text{ min}$

# Tissue specific effects of native GLP-1



GLP-1 is an endogenous incretin hormone secreted in the gut in response to food intake<sup>4</sup>

GLP-1, glucagon-like peptide-1

1. Vilsbøll T et al. *Diabetologia*, 2002; 45:1111–1119; 2. Wajchenberg BL. *Endocr Rev*, 2007; 28:187–218; 3. Baggio LL, Drucker DJ. *Gastroenterology*, 2007; 132:2131–2157; 4. van Bloemendaal L et al. *Journal of Endocrinology*, 2014; 221(1):T1-T16

# Role of GLP-1RA beyond appetite regulation

## Multifactorial effects

### Pancreas

- ↑ Beta-cell function<sup>1</sup>
- ↓ Beta-cell death<sup>1</sup>
- ↑ Insulin secretion and production<sup>1</sup>
- ↓ Glucose-dependent glucagon secretion<sup>1</sup>
- ↑ Glucose-dependent insulin secretion<sup>1</sup>

- ↓ Cardiovascular risk<sup>2</sup>
- ↓ Fatty acid metabolism<sup>2</sup>
- ↑ Cardiac function<sup>3</sup>
- ↓ Systolic blood pressure<sup>3</sup>
- ↓ Inflammation<sup>4</sup>

### Heart

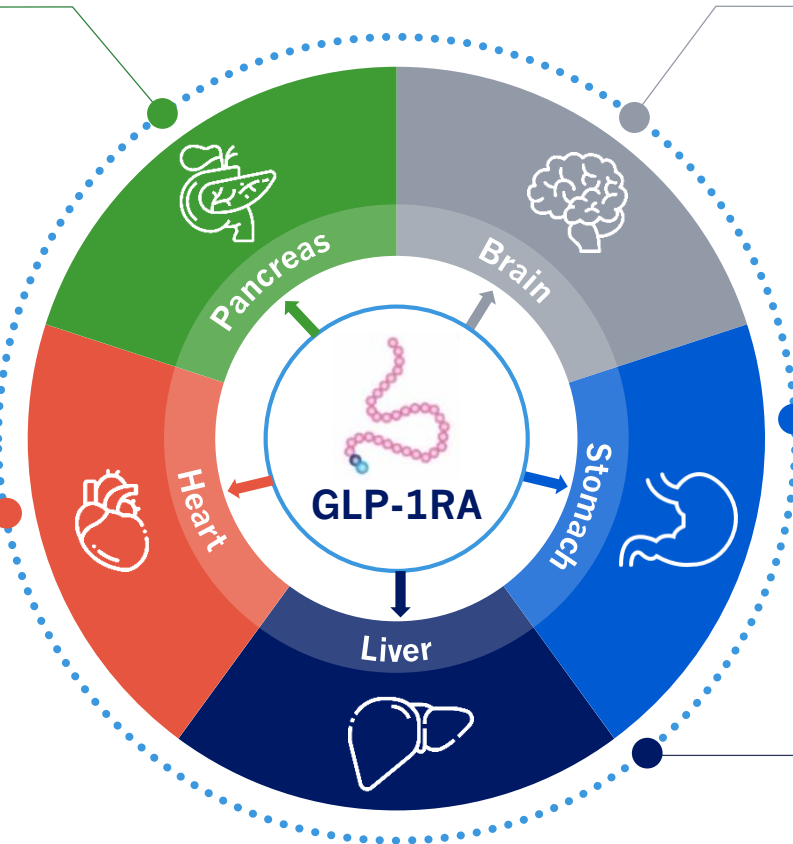
### Brain

- ↓ Body weight<sup>5</sup>
- ↓ Food intake<sup>6</sup>
- ↑ Satiety<sup>7,8</sup>

### Stomach

- ↓ Gastric emptying<sup>9</sup>
- ↓ Endogenous glucose production<sup>10</sup>
- ↑ Hepatic insulin sensitivity<sup>10</sup>
- ↓ *De novo* lipogenesis<sup>10</sup>
- ↓ Lipotoxicity<sup>10</sup>
- ↓ Steatosis<sup>11</sup>

### Liver

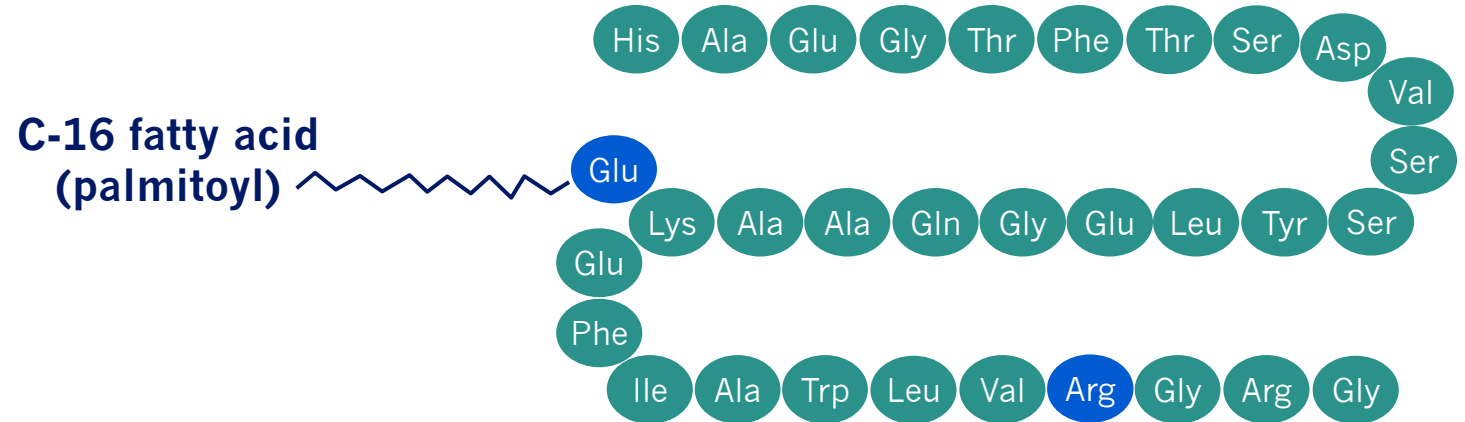


GLP-1RA, glucagon-like peptide-1 receptor agonist.

1. Campbell JE, DJ Drucker. *Cell Metab* 2013;17:819–37; 2. Marso SP et al. *N Engl J Med* 2016;375:311–22; 3. Ryan D, Acosta A. *Obesity* 2015;23:1119–29; 4. Hogan AE et al. *Diabetologia* 2014;57:781–4; 5. Baggio LL, Drucker DJ. *J Clin Invest* 2014;124:4223–6; 6. Bagger JI et al. *Clin Endocrinol Metab* 2015;100:4541–52; 7. Flint A et al. *J Clin Invest* 1998;101:515–20; 8. Blundell J et al. *Diabetes Obes Metab.* 2017;19(9):1242–51; 9. Tong J, D'Alessio D. *Diabetes* 2014;63:407–9; 10. Armstrong MJ et al. *J Hepatol* 2016;64:399–408; 11. Armstrong MJ et al. *Lancet* 2016;387:679–90.

# Liraglutide is a once-daily, human GLP-1 analogue

- 97% amino acid homology to human GLP-1
- $t_{1/2}$  of approximately 13 h



Liraglutide has improved PK: albumin binding through acylation; heptamer formation



Slow absorption from subcutis  
Resistant to DPP-4  
Long plasma half-life



# Liraglutide 3.0mg clinical development

The **S**atiety and **C**linical **A**diposity – **L**iraglutide **E**vidence (SCALE) programme

*The* NEW ENGLAND  
JOURNAL *of* MEDICINE

ESTABLISHED IN 1812

JULY 2, 2015

VOL. 373 NO. 1

A Randomized, Controlled Trial of 3.0 mg of Liraglutide  
in Weight Management

Xavier Pi-Sunyer, M.D., Arne Astrup, M.D., D.M.Sc., Ken Fujioka, M.D., Frank Greenway, M.D.,  
Alfredo Halpern, M.D., Michel Krempf, M.D., Ph.D., David C.W. Lau, M.D., Ph.D., Carel W. le Roux, F.R.C.P., Ph.D.,  
Rafael Violante Ortiz, M.D., Christine Bjørn Jensen, M.D., Ph.D., and John P.H. Wilding, D.M.,  
for the SCALE Obesity and Prediabetes NN8022-1839 Study Group\*

- 
- A 56-week, double-blind trial involving 3731 patients who **did not** have T2D and who had a BMI of at least 30 or a BMI of at least 27 if they had treated or untreated dyslipidemia or HTN.
  - Patients received once-daily liraglutide at a dose of 3.0 mg or placebo
  - The co-primary end points were the change in BW and the proportions of patients losing at least 5% and >10% of their initial body weight.

# Trial design: SCALE Obesity and Prediabetes

Liraglutide 3.0 mg for weight management (56 weeks)



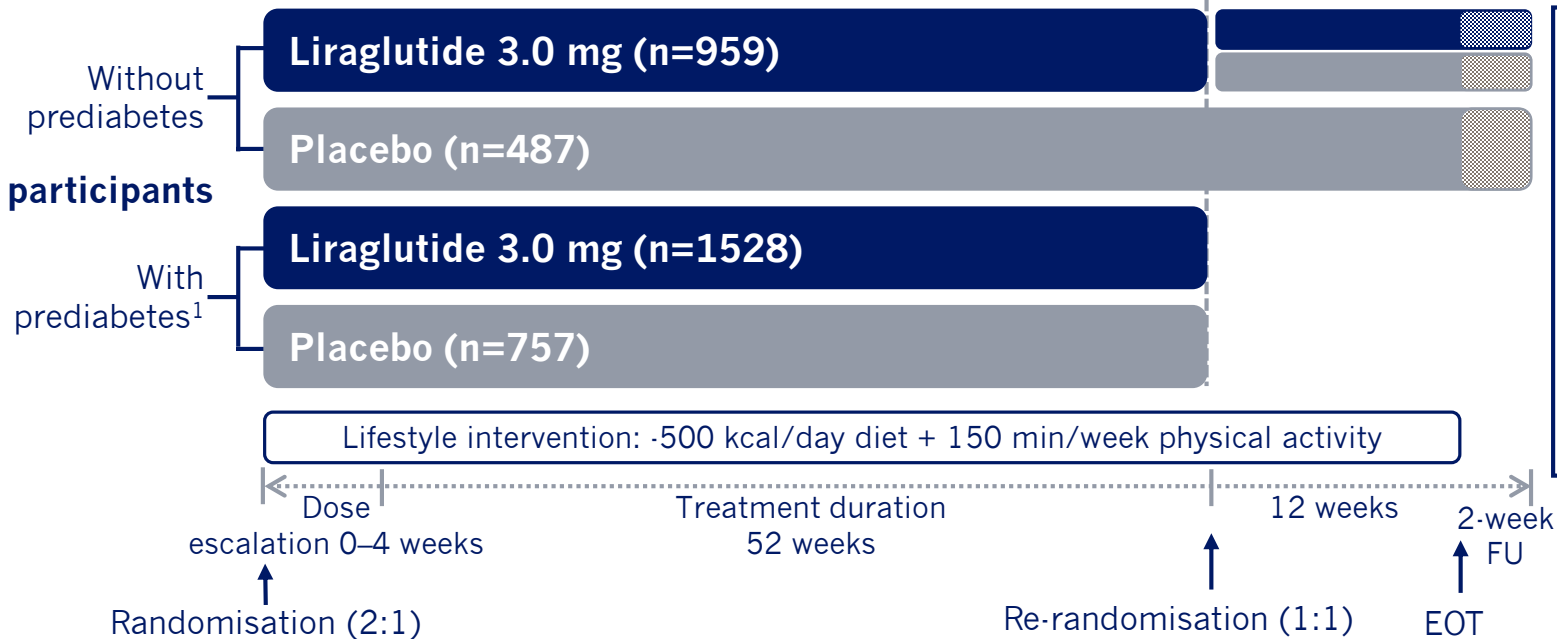
## Trial objective

Efficacy and safety of liraglutide 3.0 mg, as adjunct to D&E, in participants with obesity or overweight plus comorbidities, without diabetes

### Inclusion criteria

- ≥18 years
- Stable BW
- BMI ≥30 kg/m<sup>2</sup> or ≥27 kg/m<sup>2</sup> + comorbidities

3731 participants



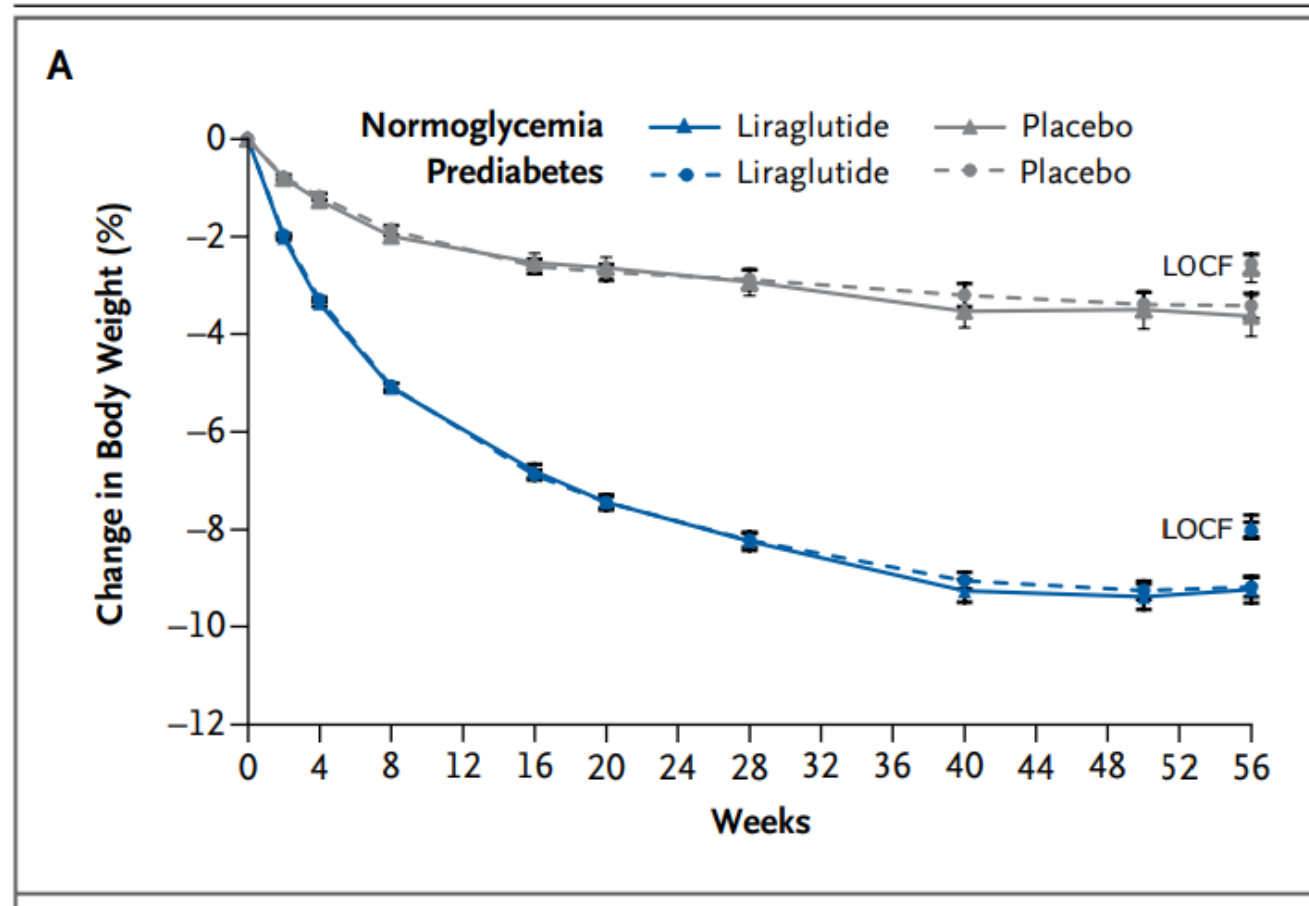
### Trial information

- June 2011 to March 2013
- Randomised controlled double-blind study
- 191 sites in 27 countries
- Duration: 56 weeks (with prediabetes), 68 weeks (without prediabetes)

1. ADA. Diabetes Care 2010;33(Suppl. 1):S11-61

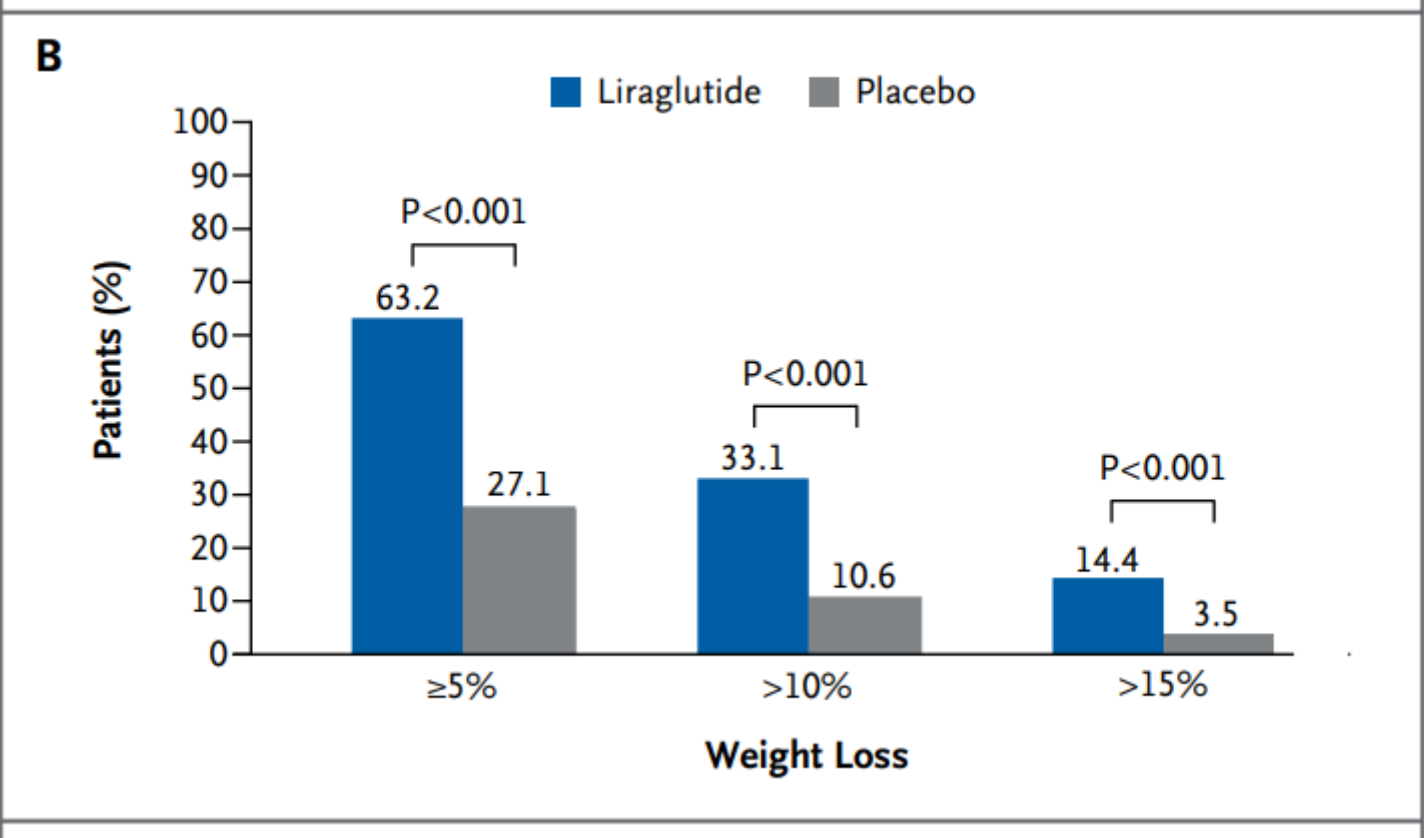
BW, body weight; D&E, diet and exercise; EOT, end of treatment; FU, follow-up; HRQoL, health-related quality of life; WC, waist circumference  
Pi-Sunyer et al. N Engl J Med 2015;373:11-22

# Mean body weight for patients in according to presence or absence of prediabetesb at screening

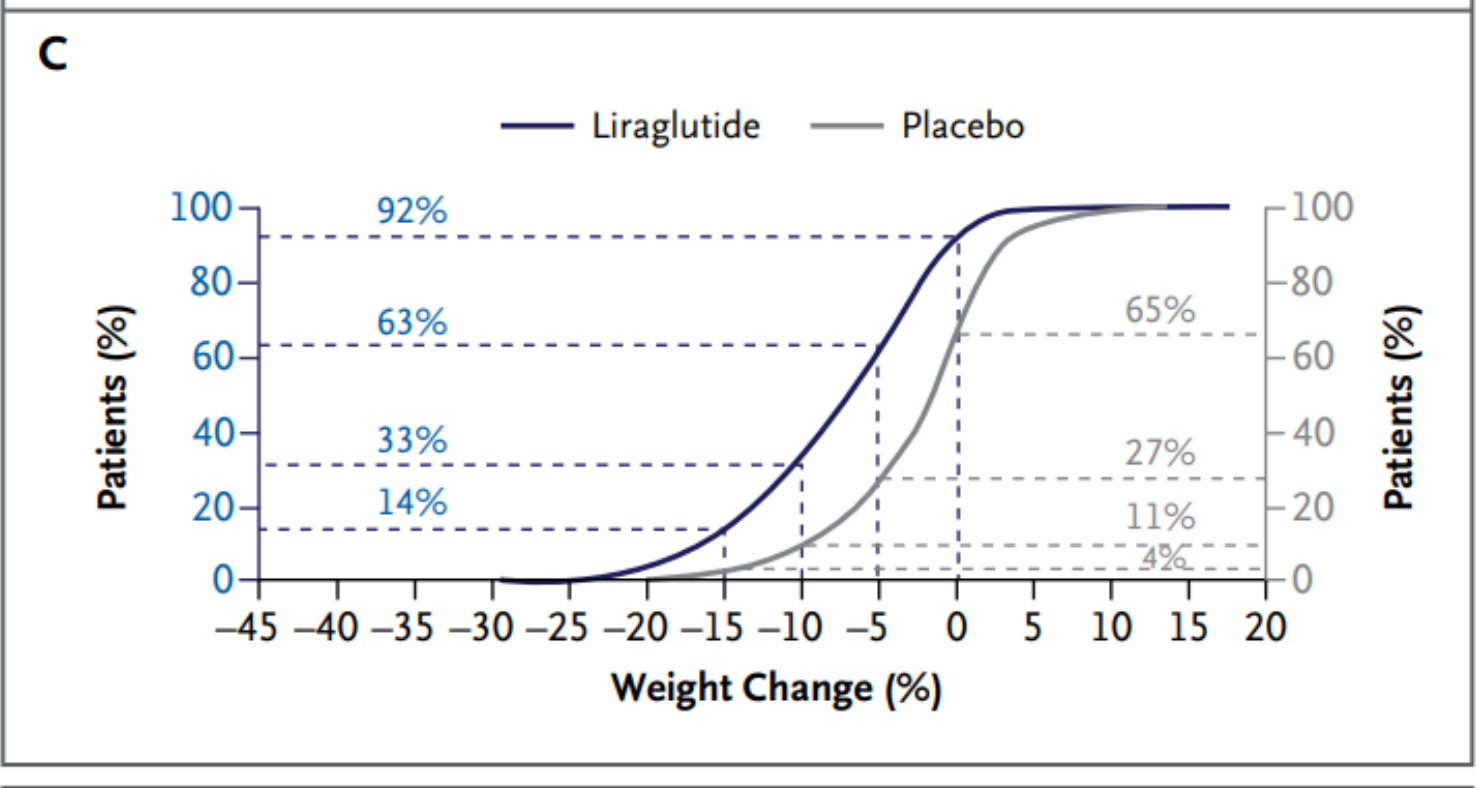


- Pi-Sunyer et al. N Engl J Med 2015;373:11–22

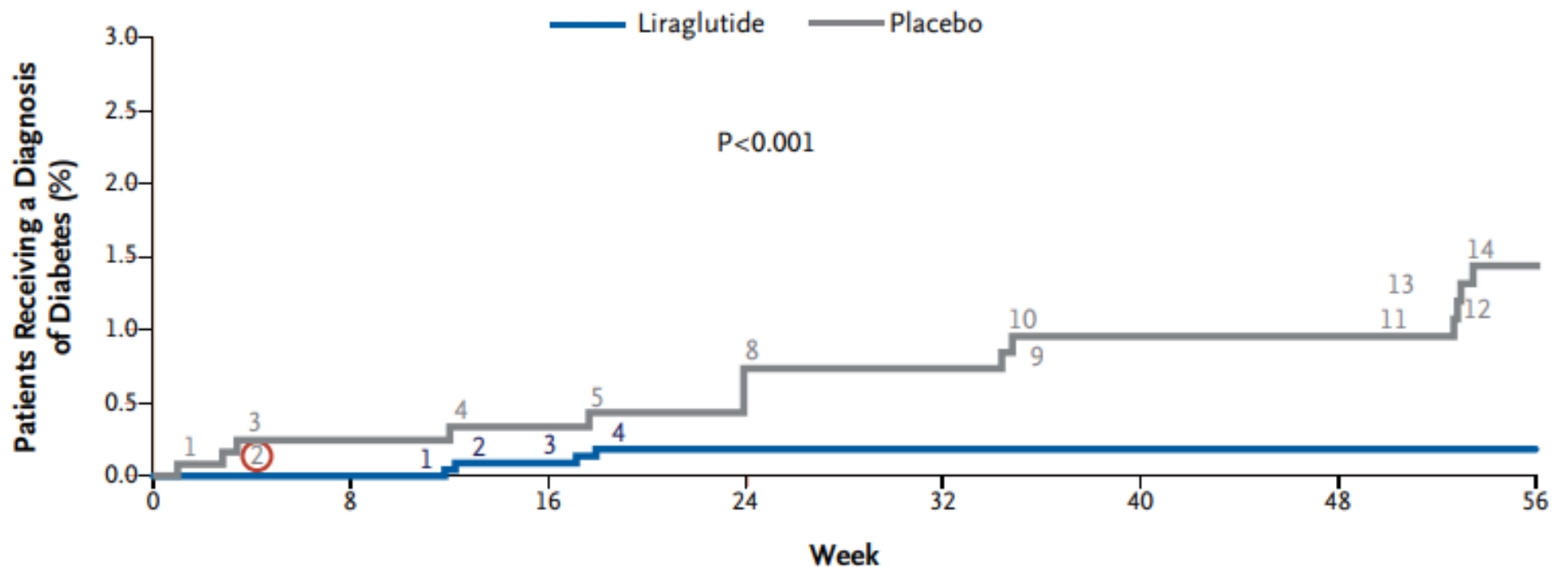
# proportions of patients who lost at least 5, more than 10, and 15% of their baseline body weight



# Cumulative percentage of patients with those changes in body weight after 56 weeks of treatment



The proportion of patients who received a diagnosis of type 2 diabetes during the course of the 56-week main trial period

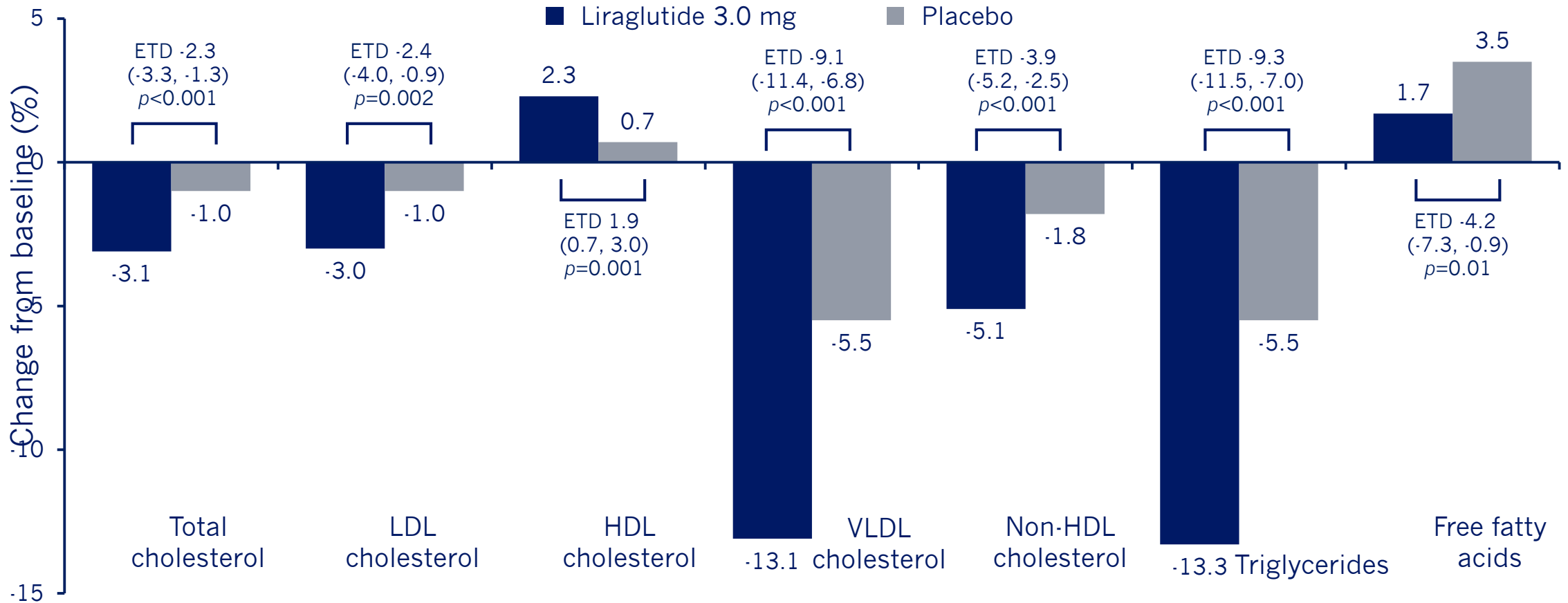


**Cumulative No. of Patients Receiving a Diagnosis of Diabetes over 56 Weeks (No. at Risk)**

Liraglutide	1 (2219)	2 (2210)	3 (2137)	4 (2130)									
Placebo	1 (1225)	2 (1210)	3 (1204)	4 (1096)	5 (1035)	8 (984)	9 (911)	10 (908)	11 (818)	12 (817)	13 (816)	14 (813)	

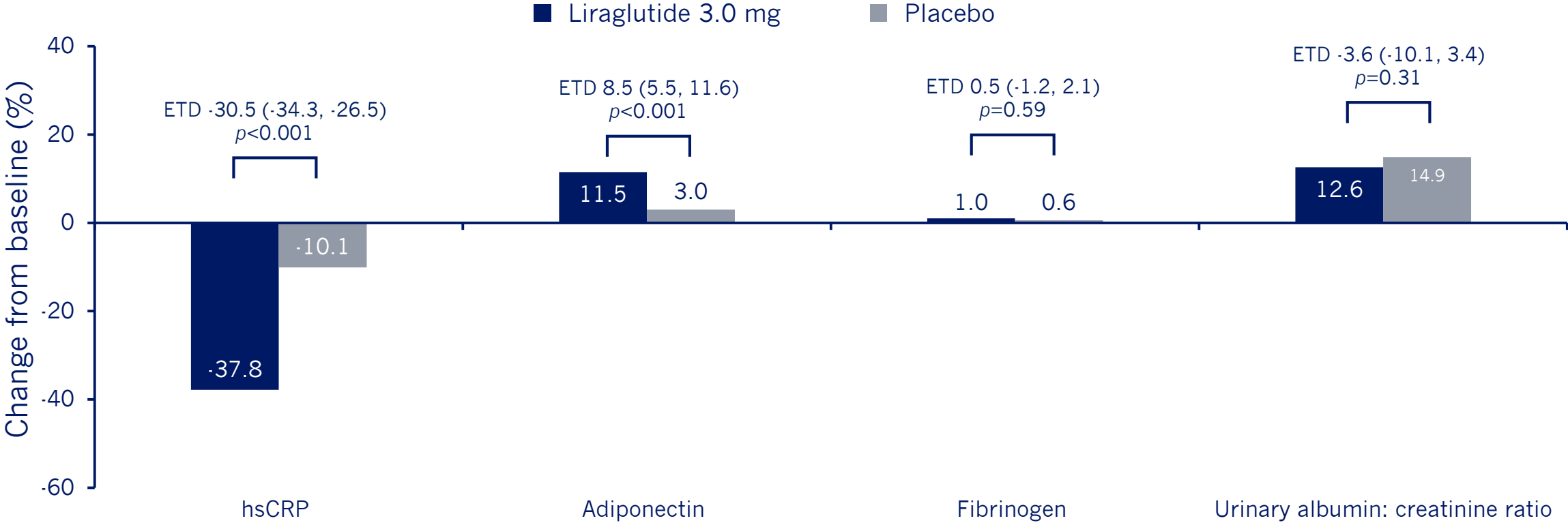
# Change in fasting lipids

SCALE Obesity and Prediabetes: 0-56 weeks



# Change in cardiovascular biomarkers

SCALE Obesity and Prediabetes: 0-56 weeks

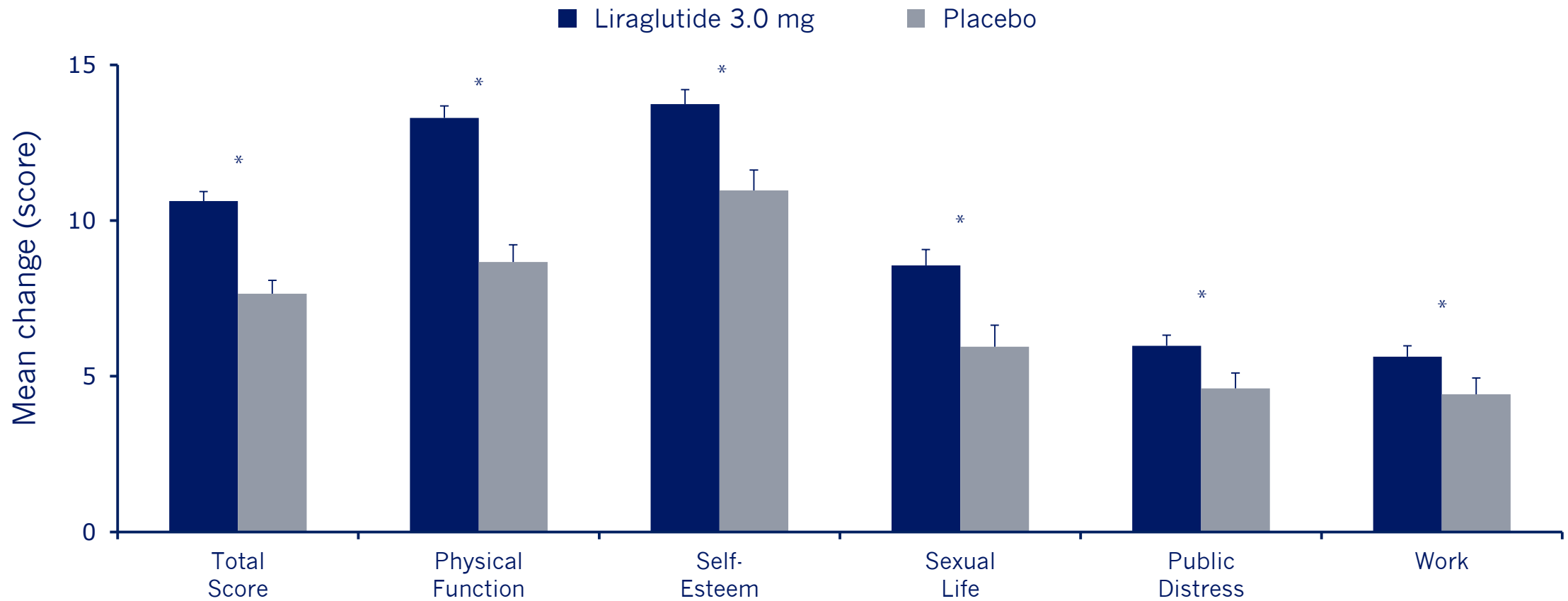


FAS, LOCF. Data are based on observed geometric means. Statistical analysis is ANCOVA. Data for PAI-1 not available. Data are shown as % change from baseline. Units of measure were hsCRP (mg/L); Adiponectin (mg/L); Fibrinogen (g/L); Urinary albumin: creatinine ratio (mg/mol). FAS, full analysis set; ETD, estimated treatment difference (95% CI); LOCF, last observation carried forward. Pi-Sunyer et al. N Engl J Med 2015;373:11-22

# Summary of IWQOL-Lite

SCALE Obesity and Prediabetes: 0-56 weeks

Increase = Improvement

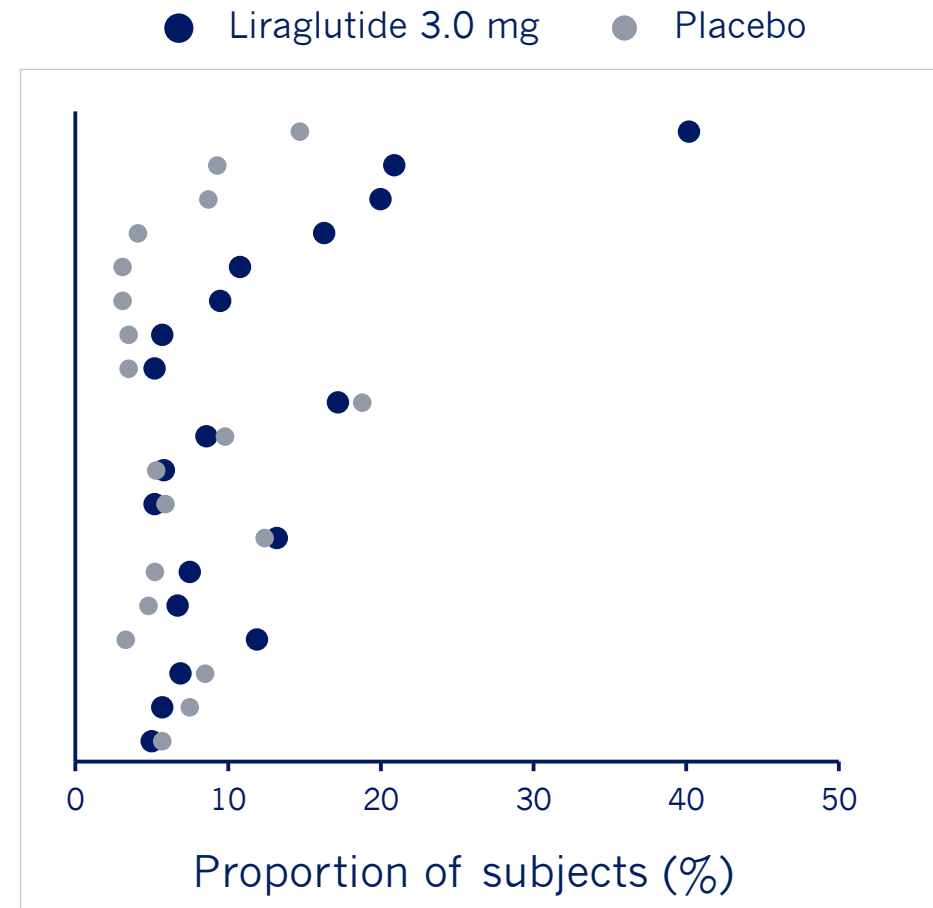


FAS LOCF. Bar graph is observed mean change from baseline. Statistical analysis is ANCOVA. \*p<0.01  
FAS, full analysis set; IWQOL-Lite, Impact of weight on quality of life-lite questionnaire; LOCF, last observation carried forward  
Pi-Sunyer et al. N Engl J Med 2015;373:11-22

# Adverse events were reported in $\geq 5\%$ of participants

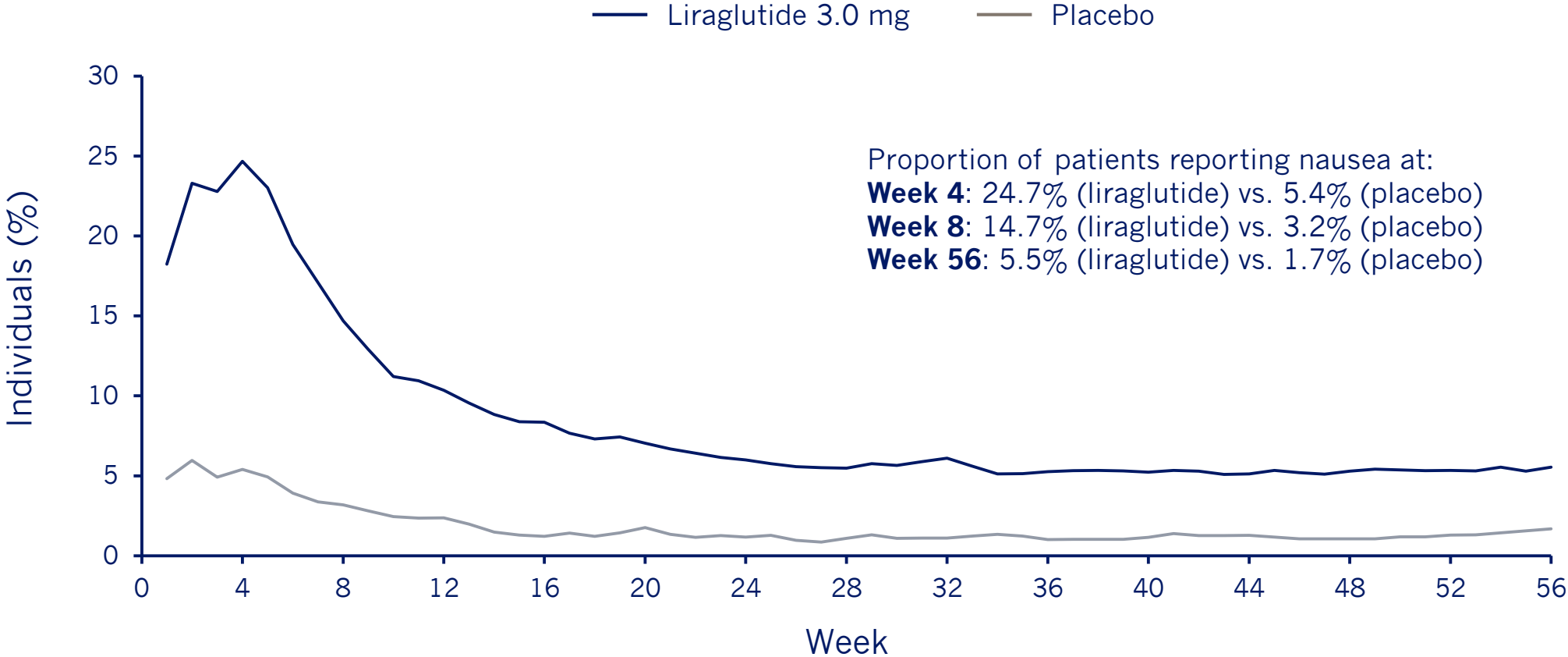
SCALE Obesity and Prediabetes: 0-56 weeks

	Liraglutide 3.0 mg %	Placebo %
Nausea	40.2	14.7
Diarrhoea	20.9	9.3
Constipation	20.0	8.7
Vomiting	16.3	4.1
Decreased appetite	10.8	3.1
Dyspepsia	9.5	3.1
Abdominal pain upper	5.7	3.5
Abdominal pain	5.2	3.5
Nasopharyngitis	17.2	18.8
Upper respiratory tract infection	8.6	9.8
Influenza	5.8	5.3
Sinusitis	5.2	5.9
Headache	13.2	12.4
Fatigue	7.5	5.2
Dizziness	6.7	4.8
Hypoglycaemia	11.9	3.3
Back pain	6.9	8.5
Injection site haematoma	5.7	7.5
Arthralgia	5.0	5.7



# Proportion of individuals with nausea

SCALE Obesity and Prediabetes: 0-56 weeks



# Conclusion

- Liraglutide, as an adjunct to diet and exercise, was associated with clinically meaningful weight loss in overweight or obese patients, with concurrent reductions in glycemic variables and multiple cardiometabolic risk factors, as well as improvements in health-related quality of life.

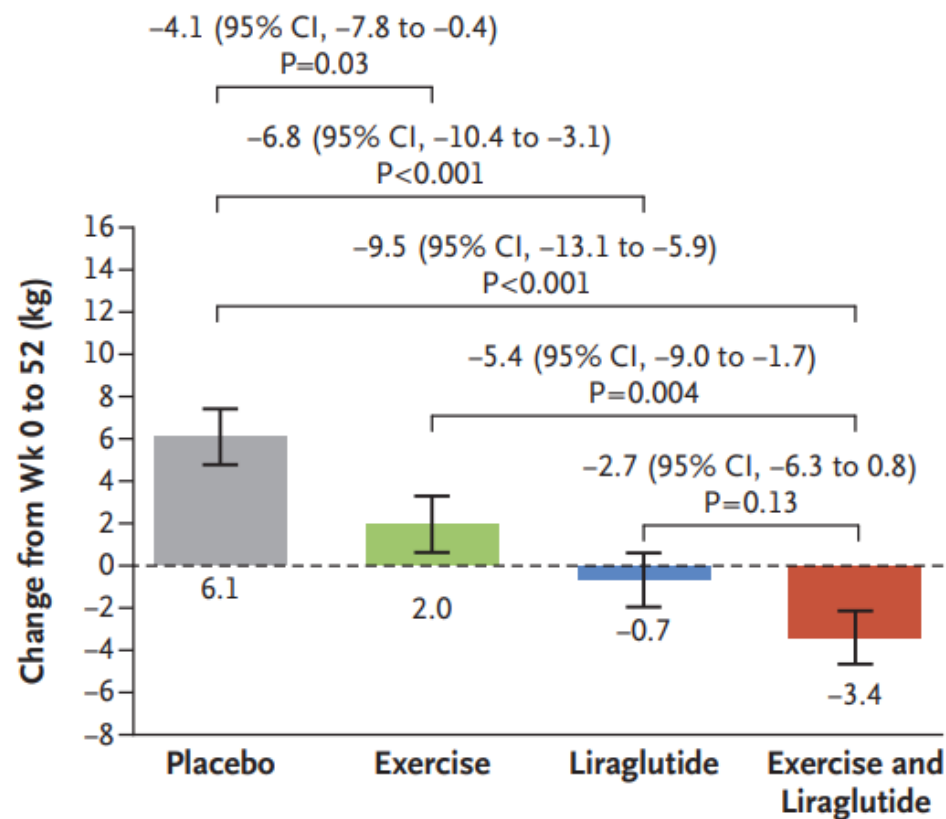
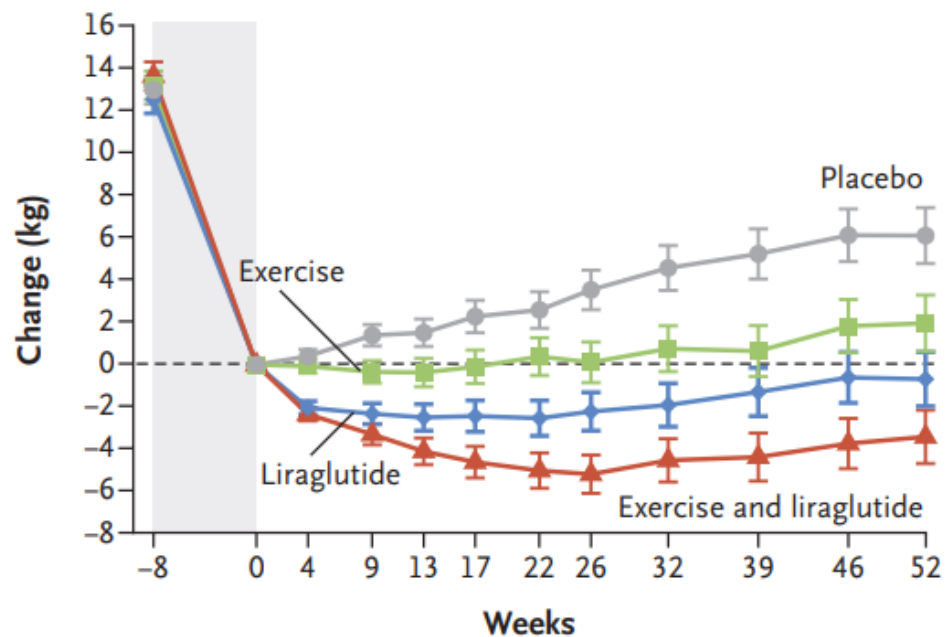
N Engl J Med. 2021 May 6;384(18):1719-1730.

# Healthy Weight Loss Maintenance with Exercise, Liraglutide, or Both Combined

Julie R. Lundgren, M.D., Ph.D., Charlotte Janus, Ph.D., Simon B.K. Jensen, M.Sc., Christian R. Juhl, M.D., Lisa M. Olsen, M.Sc., Rasmus M. Christensen, B.Sc.Med., Maria S. Svane, M.D., Ph.D., Thomas Bandholm, Ph.D., Kirstine N. Bojsen-Møller, M.D., Ph.D., Martin B. Blond, M.D., Ph.D., Jens-Erik B. Jensen, M.D., Ph.D., Bente M. Stallknecht, M.D., D.M.Sc., Jens J. Holst, M.D., D.M.Sc., Sten Madsbad, M.D., D.M.Sc., and Signe S. Torekov, Ph.D.

- Design:
- An 8-week low-calorie diet, then ,participants were randomly assigned for 1 year to one of **four** strategies:
- 1 moderate-to-vigorous–intensity exercise program plus placebo (exercise group); 2 treatment with liraglutide plus usual activity (liraglutide group); 3 exercise program plus liraglutide therapy (combination group); 4 placebo plus usual activity (placebo group).
- End points were the change in body weight (primary end point) and the change in body-fat percentage (secondary end point) from randomization to the end of the treatment period.

### A Change in Body Weight



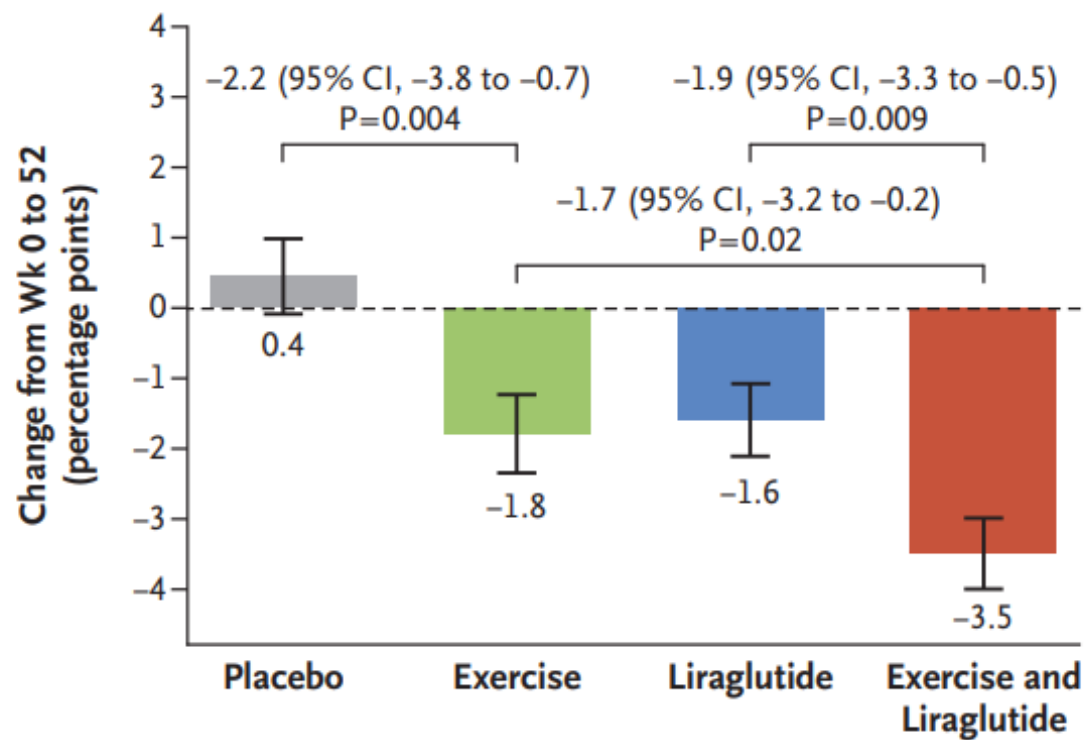
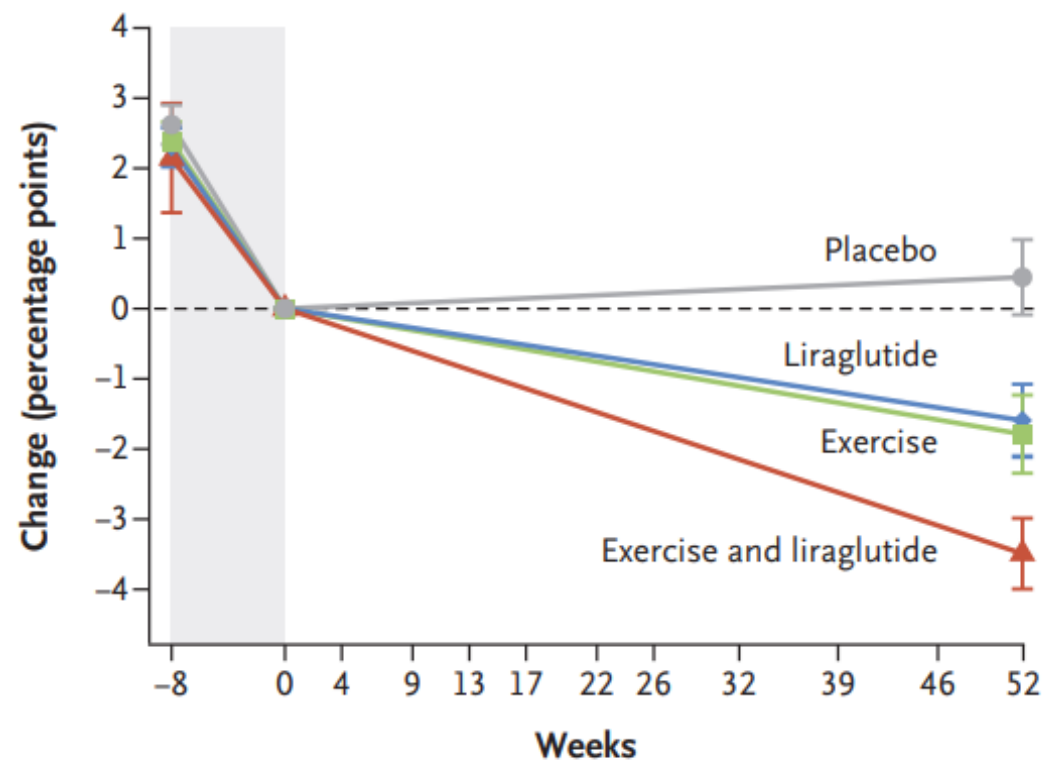
No. of Participants

215 195 187 183 181 178 178 175 171 169 168 166

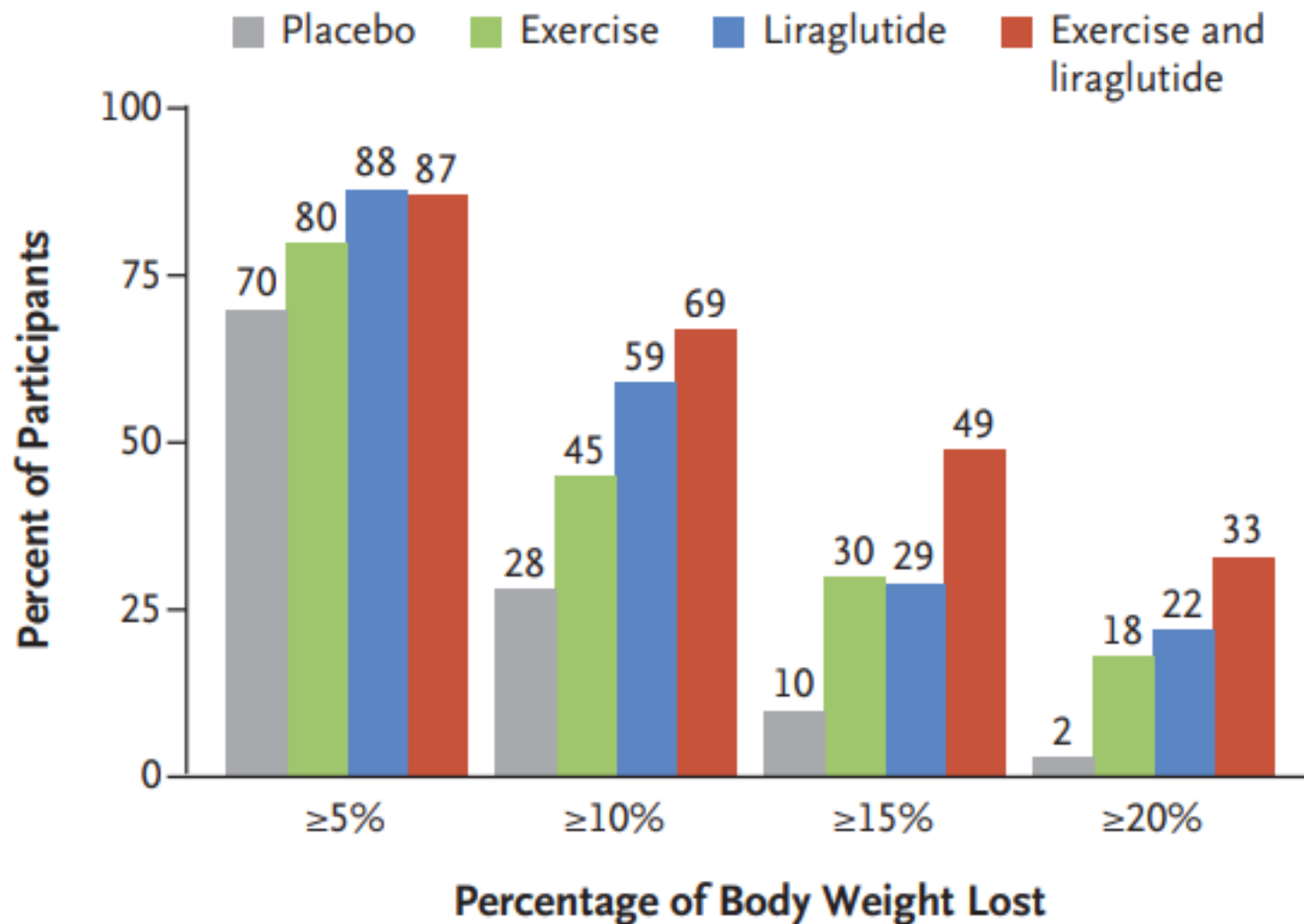
No. Who Underwent Randomization  
No. Who Completed Trial

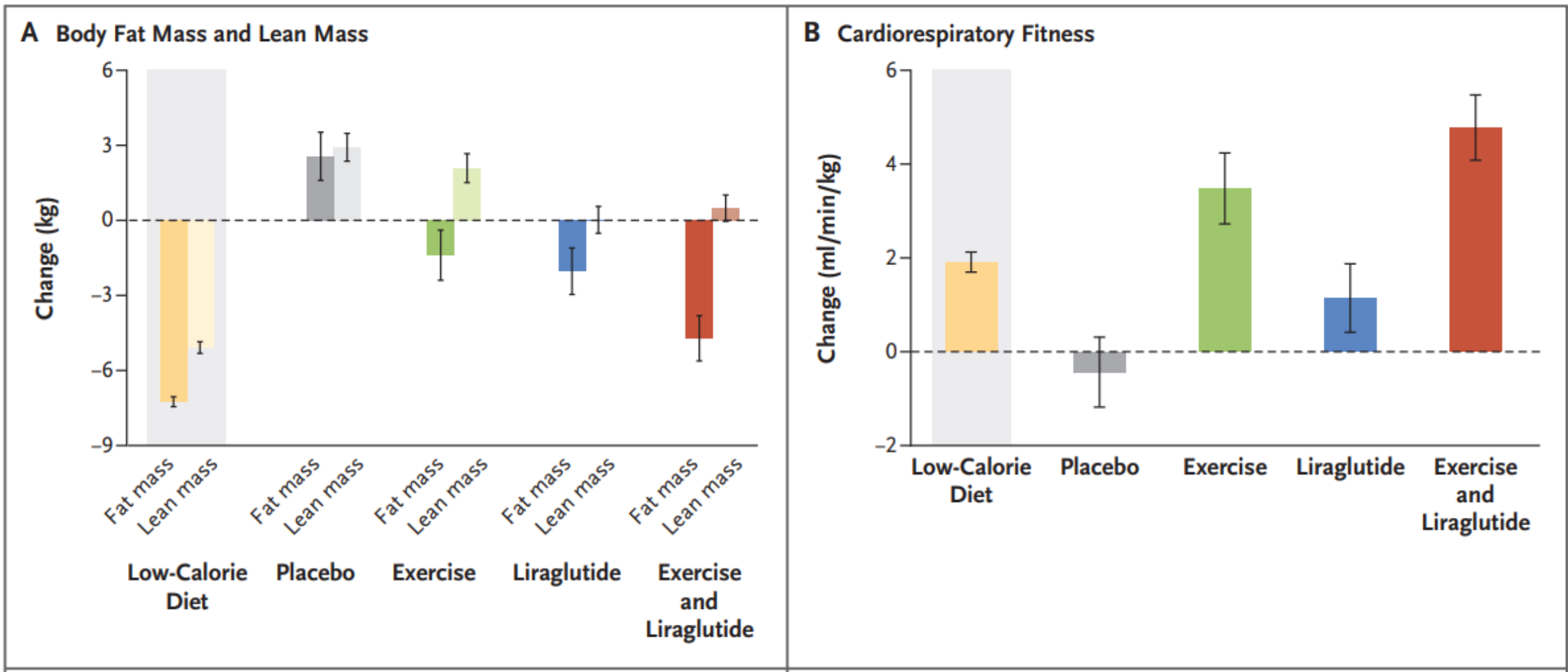
49	48	49	49
40	40	41	45

### B Change in Body-Fat Percentage



### C Change in Body Weight from Wk -8 to Wk 52





**BRIEF REPORT**

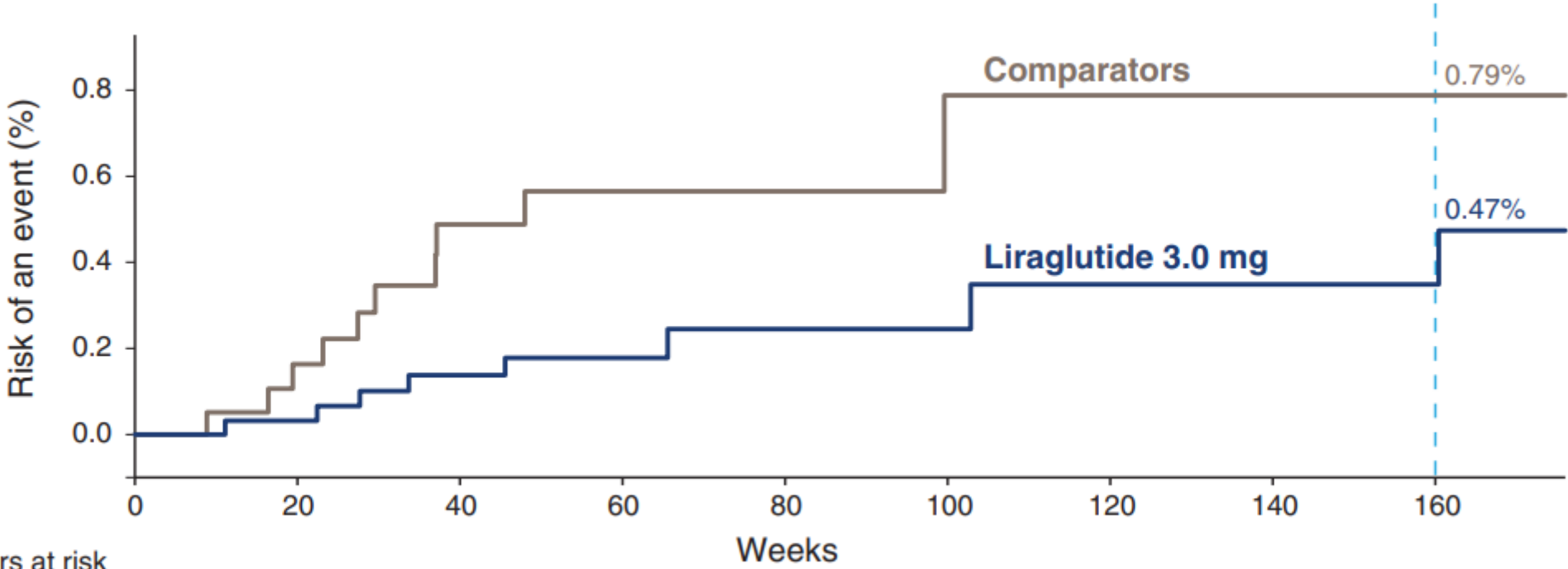
**Liraglutide and cardiovascular outcomes in adults with overweight or obesity: A post hoc analysis from SCALE randomized controlled trials**

M. J. Davies MD<sup>1</sup> | L. J. Aronne MD<sup>2</sup> | I. D. Caterson MD, PhD<sup>3</sup> | A. B. Thomsen MD, PhD<sup>4</sup> |  
P. B. Jacobsen MD, PhD<sup>5†</sup> | S. P. Marso MD<sup>6</sup> | on behalf of the Satiety and Clinical  
Adiposity – Liraglutide Evidence in individuals with and without diabetes (SCALE) study  
groups

The primary composite outcome of this time-to-event analysis was the first occurrence of cardiovascular death, nonfatal MI, or nonfatal stroke.

# Cardiovascular events in the pooled weight management trials

## Time to first event is shown for liraglutide 3.0 mg vs all comparators

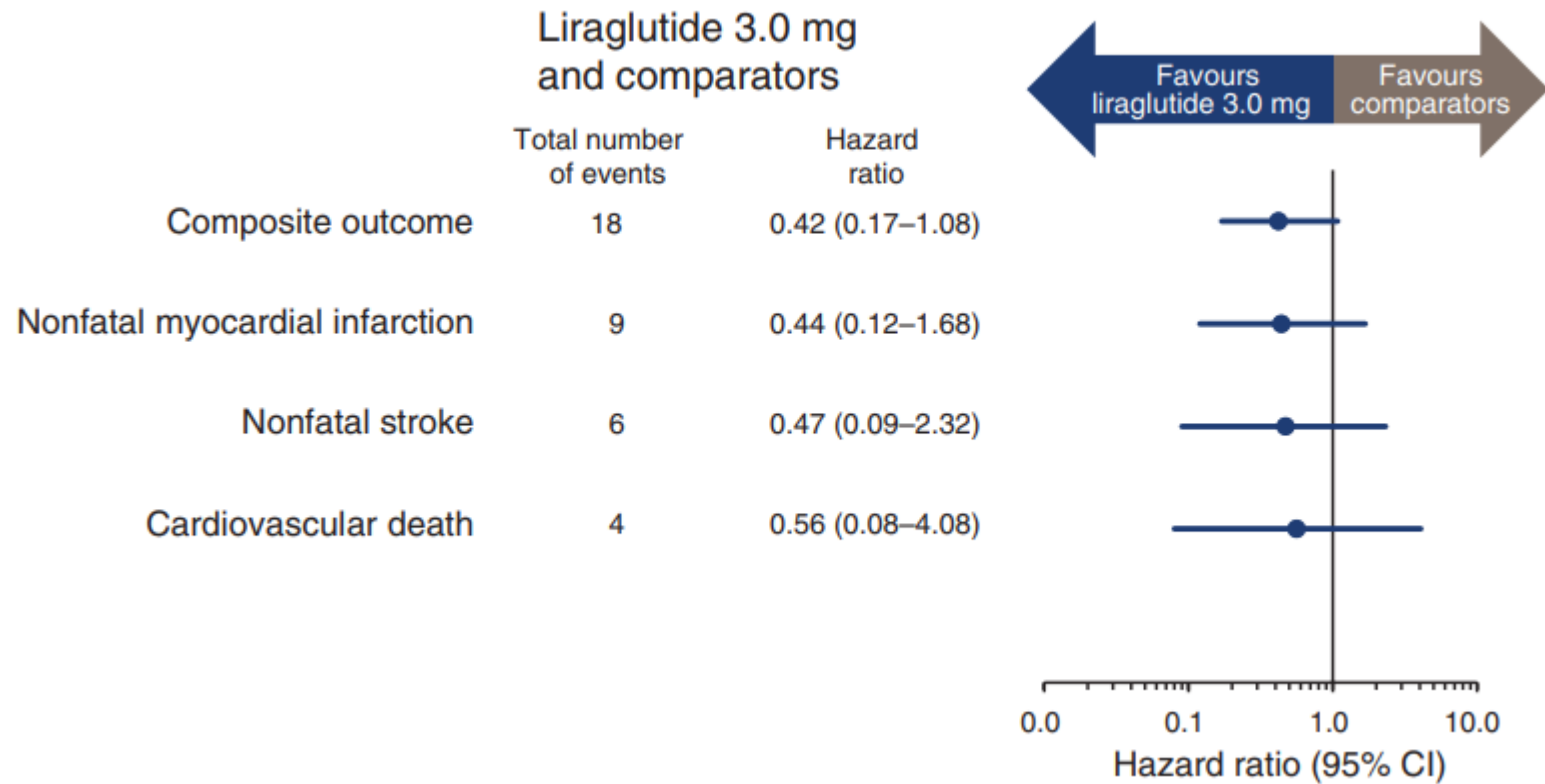


Numbers at risk

	0	20	40	60	80	100	120	140	160
Liraglutide	3384	2960	2559	2171	1067	971	865	828	793
Comparators	2036	1741	1359	1077	504	444	371	350	336

# Cardiovascular events in the pooled weight management trials

## Primary composite analysis and analyses of the 3 individual components



## RESEARCH SUMMARY

## Semaglutide and Cardiovascular Outcomes in Obesity without Diabetes

Lincoff AM et al. DOI: 10.1056/NEJMoa2307563

## CLINICAL PROBLEM

Glucagon-like peptide-1 (GLP-1) receptor agonists can reduce the risk of adverse cardiovascular events in patients with diabetes. Whether the GLP-1 receptor agonist semaglutide can also reduce cardiovascular risk in patients with overweight or obesity but without diabetes is unknown.



## LIMITATIONS AND REMAINING QUESTIONS

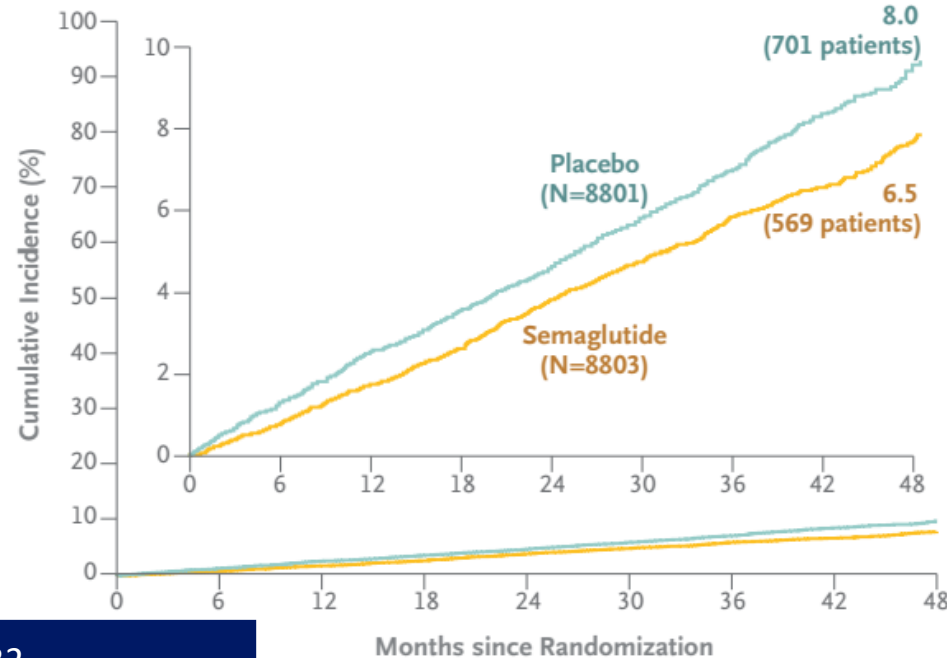
- The trial was limited to patients with preexisting cardiovascular disease.
- The diversity of the trial population did not duplicate a globally representative population; specifically, women and patients identifying as Black were underrepresented.

## CLINICAL TRIAL

**Design:** An international, double-blind, event-driven, randomized, placebo-controlled, superiority trial assessed the safety and efficacy of semaglutide in patients with preexisting cardiovascular disease, overweight or obesity (body-mass index,  $\geq 27$ ), and no history of diabetes.

**Intervention:** 17,604 adults  $\geq 45$  years of age were assigned to receive once-weekly subcutaneous semaglutide (2.4 mg) or placebo. The primary cardiovascular end point was a composite of the first occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke in a time-to-event analysis.

## Death from Cardiovascular Causes, Nonfatal MI, or Nonfatal Stroke

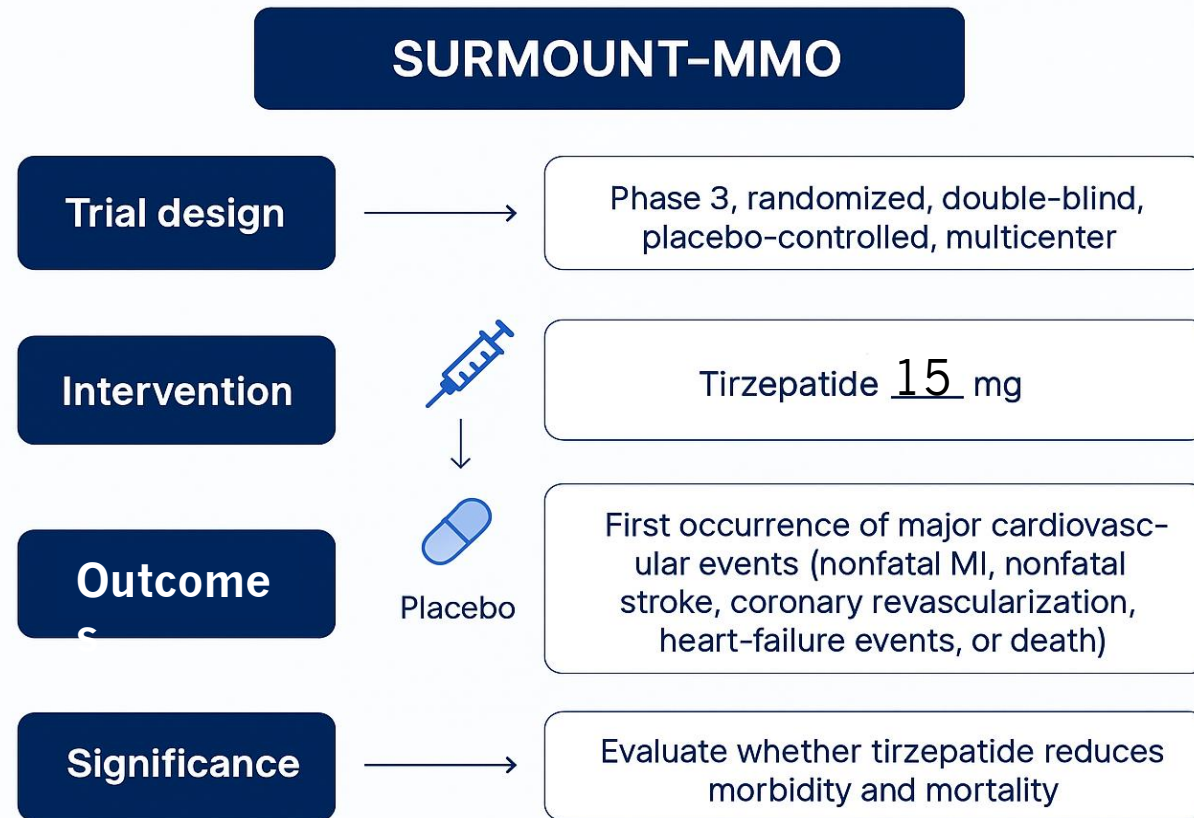
HR, 0.80 (95% CI, 0.72–0.90);  $P < 0.001$  for superiority

# SURMOUNT-MMO

## Primary endpoint:

Time to first occurrence of a 5-component composite outcome including:

**N**onfatal MI, **S**troke, **C**oronary revascularization, **H**eart failure events, **D**eath from any cause  
Once-weekly tirzepatide compared with placebo



- Study population :**
- Established CVD or multiple CV risk factors
  - Sample size: 15,000 participants
  - Conducted at **664 sites across 27 countries**
  - Adults  $\geq 40$  years,
  - BMI  $\geq 27$  kg/m<sup>2</sup>
  - **without diabetes**

# SURMOUNT-MMO trial

- According to trial registries and published design papers, **SURMOUNT-MMO is expected to run for several years with completion roughly around late 2026–2027** (e.g., October 2027).

# Benefits of **Liraglutide** vs **Dual GLP-1/GIP Agonists** in Obesity Treatment

- **Extensive Long-Term Evidence Base**
- **Liraglutide** has been studied for over a decade, with robust data from the **SCALE clinical trial program** demonstrating:
  - Sustained weight loss
  - Improvement cardiometabolic risk factors
  - Efficacy across diverse populations (prediabetes, type 2 diabetes, sleep apnea)
- In contrast, **dual GLP-1/GIP agonists** (e.g., **Tirzepatide**) have **shorter follow-up durations**, and long-term real-world safety data are still emerging.

- Pi-Sunyer X et al., *N Engl J Med*, 2015 — SCALE Obesity & Prediabetes

# Established Safety and Tolerability Profile

- Liraglutide's adverse-event profile is well characterized:
  - Predictable, dose-dependent gastrointestinal effects
  - Extensive post-marketing safety experience
- Dual GLP-1/GIP agonists demonstrate **greater GI adverse effects** in some patients, which may limit tolerability and adherence in real-world practice.

# Dose Titration and Daily Administration Can Improve Tolerability

- Liraglutide's **daily dosing** allows gradual titration and individualized dose adjustments
- This may be advantageous in patients who are sensitive to nausea or vomiting
- Dual agonists are administered **once weekly**, which improves convenience but may lead to **more** intense early GI symptoms due to higher effective doses

# Proven Benefits Beyond Weight Loss

- Reduction in progression from prediabetes to type 2 diabetes
- Improvements in blood pressure and lipid parameters
- Cardiovascular safety
- Dual GLP-1/GIP agonists show promising cardiometabolic effects, but **definitive cardiovascular outcome data in obesity populations are still pending**

# Take Home messages

- The prevalence of obesity is increasing
- The definition of obesity is beyond the measurement of just a BMI
- Obesity has metabolic, mechanical, and mental consequences
- Liraglutide, as an adjunct to diet and exercise, was associated with reduced body weight and improved metabolic control
- liraglutide 3.0 mg treatment was not associated with excess cardiovascular risk
- Liraglutide is more effective when combined with lifestyle changes
- Liraglutide has been studied for over a decade, showing sustained weight loss and Improvement in cardiometabolic risk factors