INSELSPITAL
UNIVERSITÄTSSPITAL BERN
HÔPITAL UNIVERSITAIRE DE BERNE

HERZ GEFÄSS ZENTRUM

FOKUS HERZ BERN

Adipositas und kardiovaskuläre Erkrankungen

Konstantinos Koskinas, MD

Universitätsklinik für Kardiologie

INSELSPITAL Bern

16.05.2025

Adipositas

- **Prävalenz**
- Auswirkungen auf das kardiovaskuläre Risiko
- Behandlungsmöglichkeiten

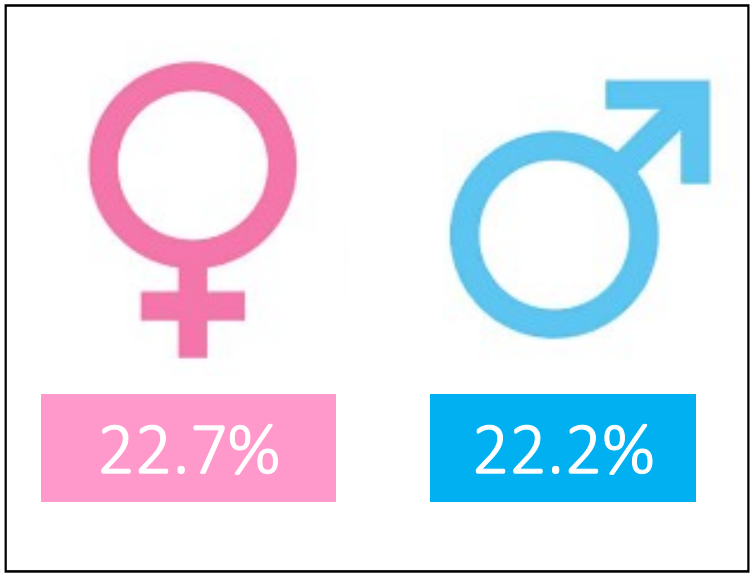
Worldwide trends in underweight and obesity from 1990 to 2022: a pooled analysis of 3663 population-representative studies with 222 million children, adolescents, and adults

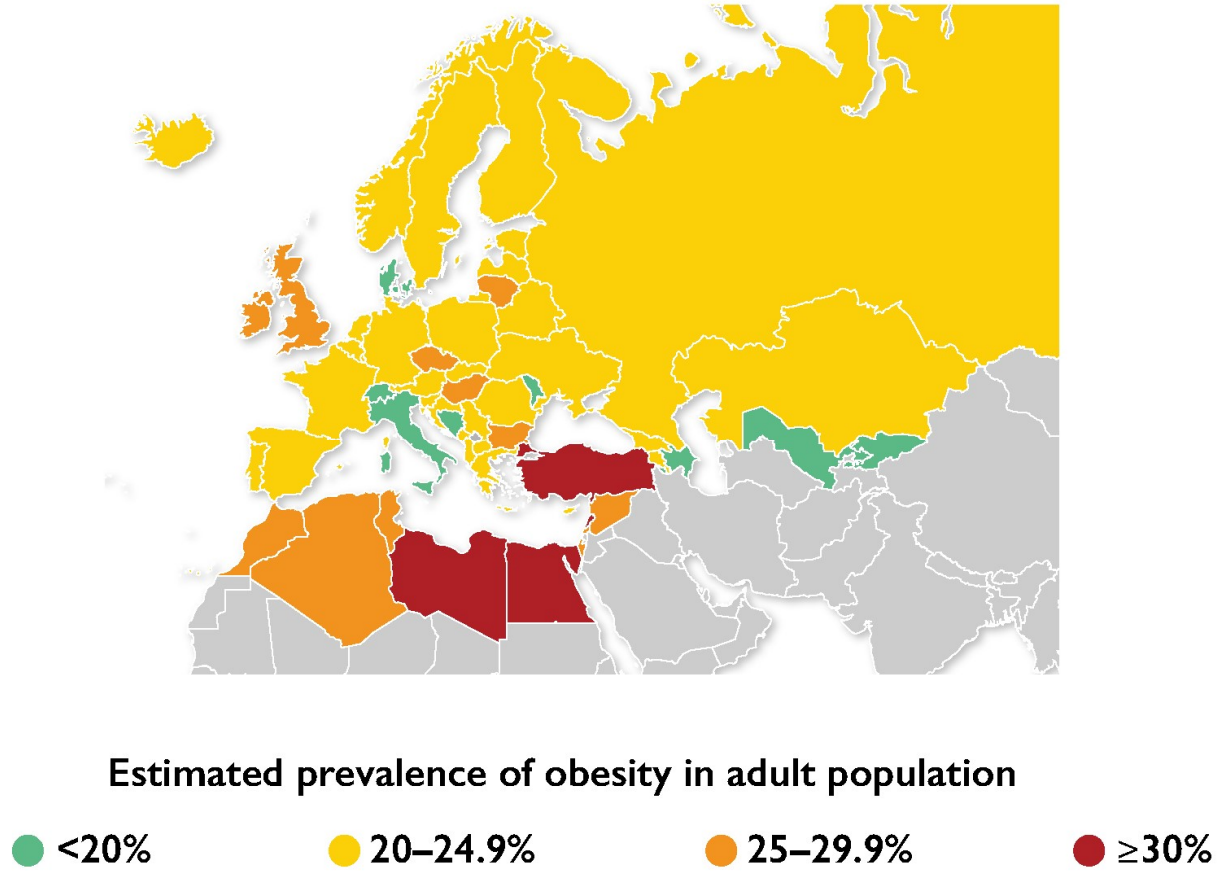
NCD Risk Factor Collaboration (NCD-RisC)*

Lancet 2024: 403: 1027–50

- In 2022, more than **1 billion** people (one in 8 adults) in the world were living with **obesity**
- The prevalence of **overweight** is estimated at **42%**
- Worldwide, obesity has more than **doubled** since 1990 among adults, and has **quadrupled** among children and adolescents

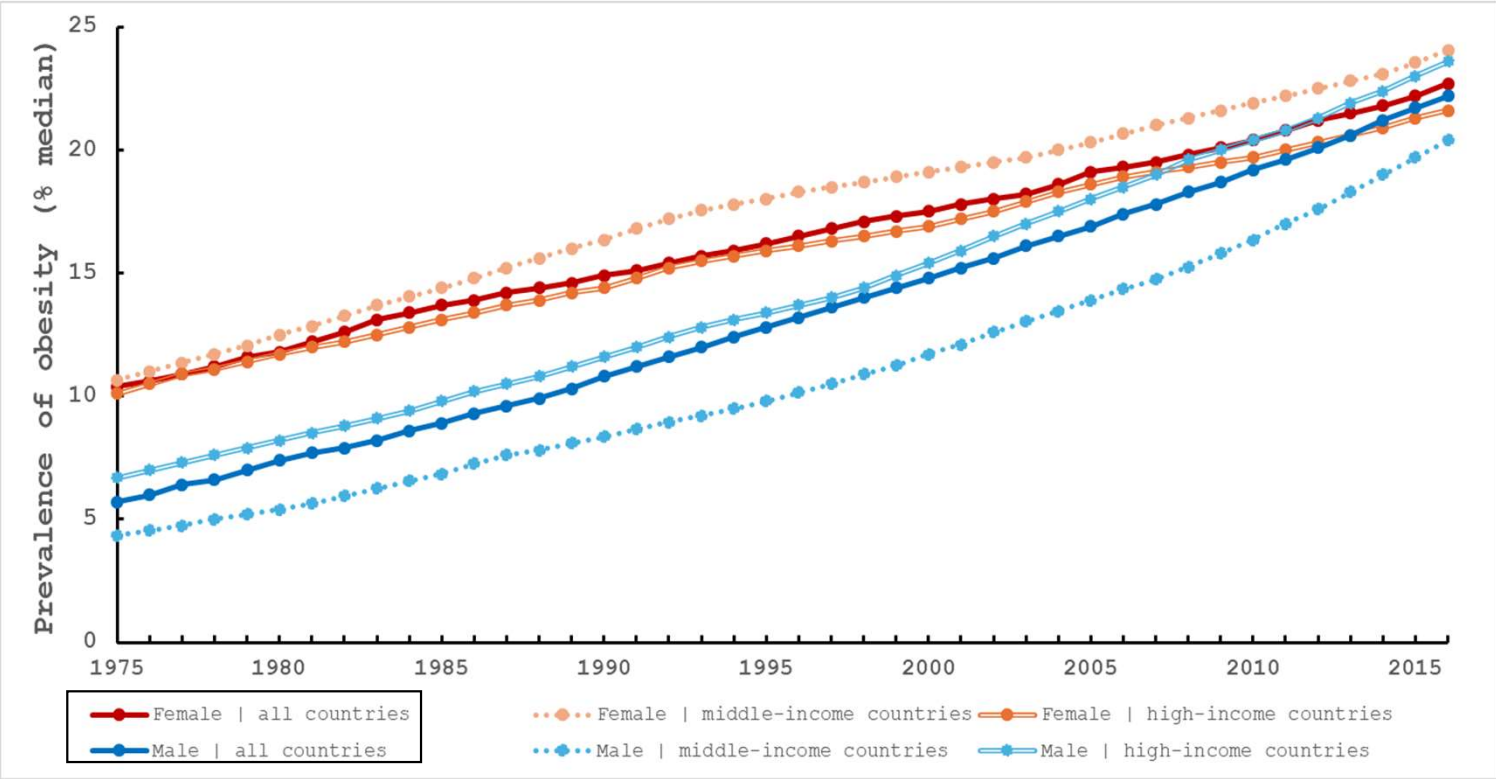
Prevalence of obesity across ESC member countries in 2019





Koskinas KC, et al. *Eur Heart J* 2024;45(38):4063-4098

Changes in the prevalence of obesity in ESC member countries between 1975 and 2016

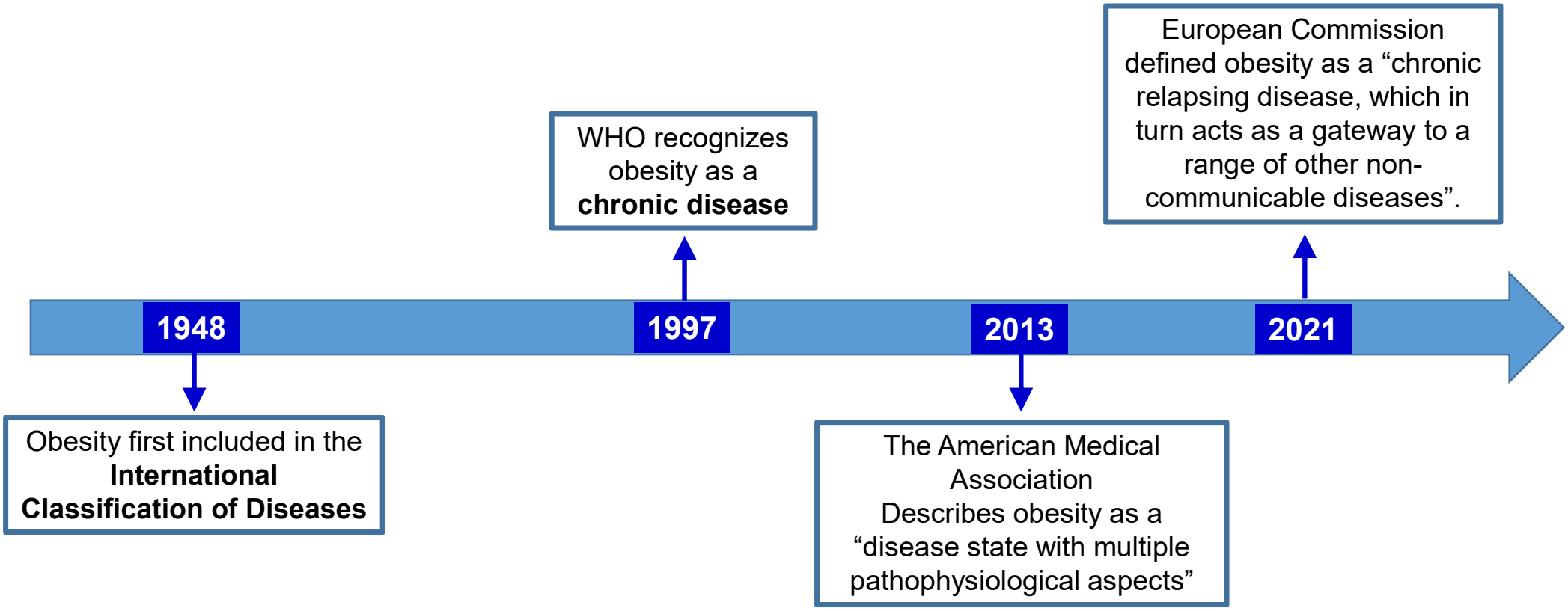


Timmis A et al. *Eur Heart J.* 2022: 43(8):716-799

Adipositas

- Prävalenz
- **Auswirkungen auf das kardiovaskuläre Risiko**
- Behandlungsmöglichkeiten

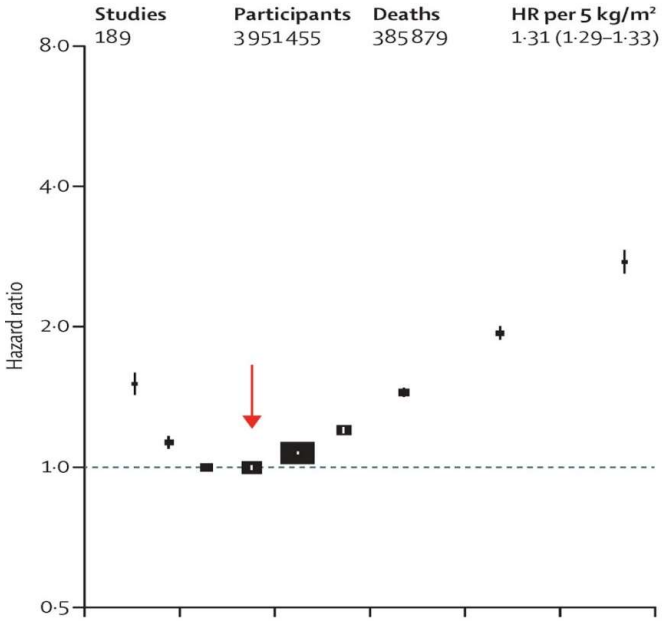
Is obesity a disease?



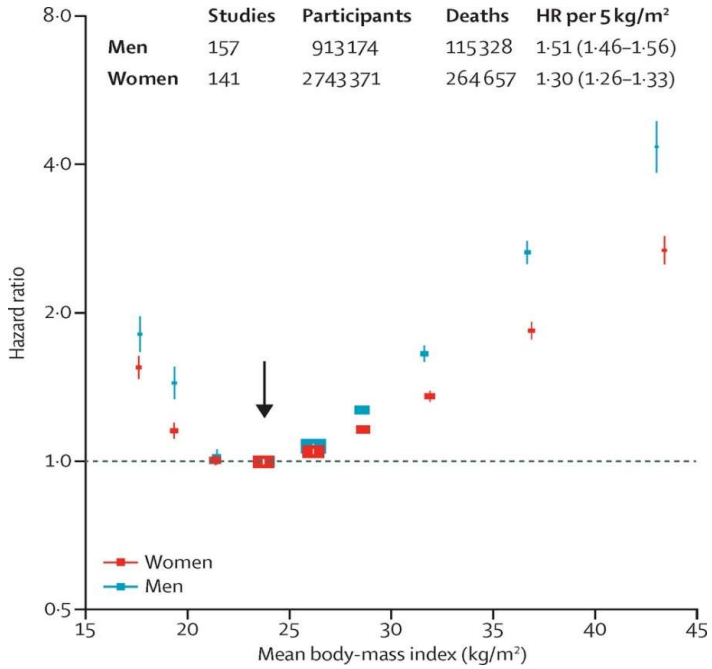
Association of BMI with all-cause mortality

The risk of all-cause death increased by ≈ 30% for every 5 kg/m2 increase in BMI for BMI >25 kg/m2

Overall



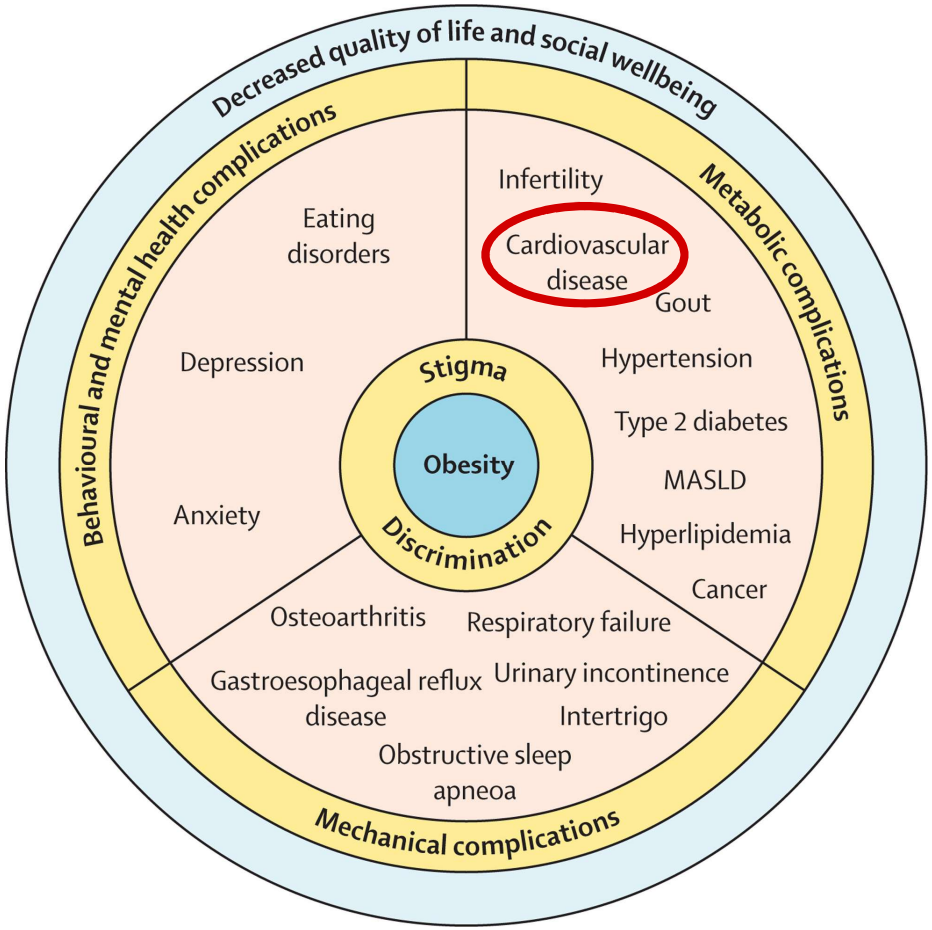
By sex



Meta-analysis including >10 million individuals

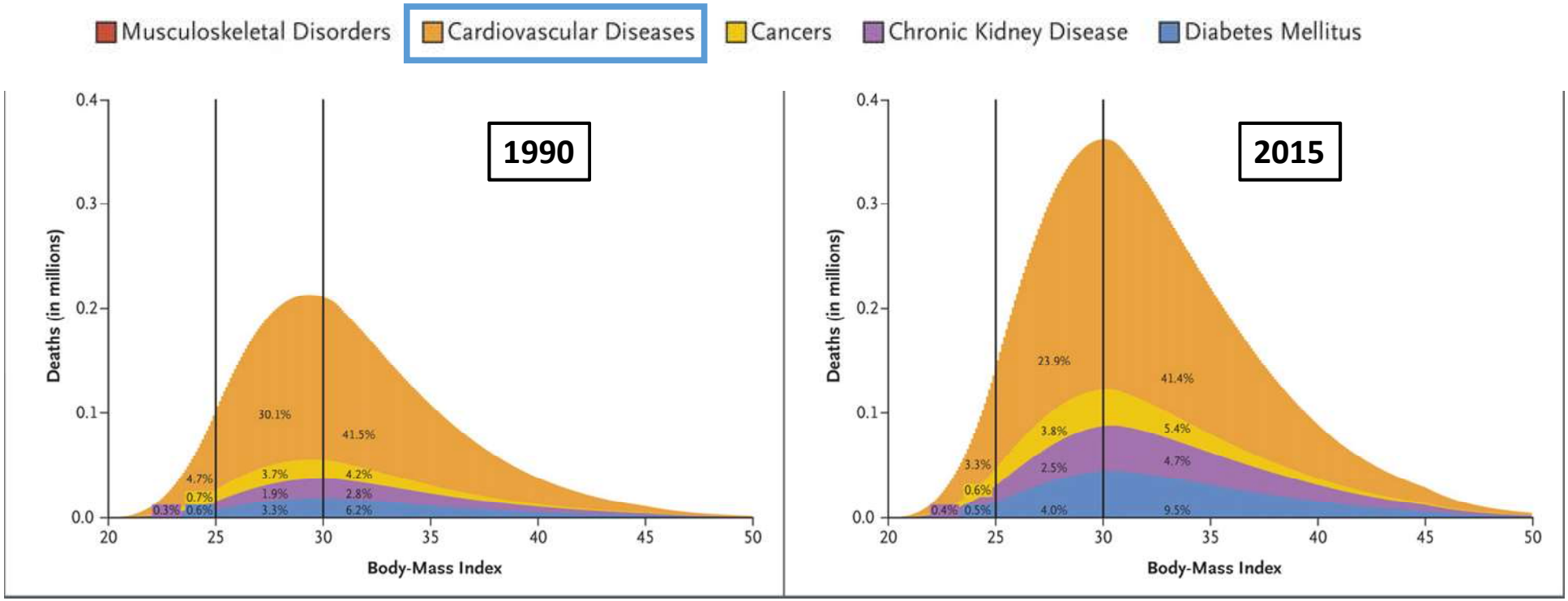
Di Angelantonio E, et al. *Lancet* 2016; 388: 776–86

Obesity is a risk factor for several chronic diseases



Lingvayc I, et al. *Lancet* 2024:S0140-6736(24)01210-8

67.5% of deaths related to high BMI are attributable to CVD



Percentages indicate the proportion of deaths that were contributed by each of the listed disorders

Afshin A, et al. *N Engl J Med*. 2017 Jul 6;377(1):13-27.

ESC European Society of Cardiology

European Heart Journal (2024) **00**, 1–36
https://doi.org/10.1093/eurheartj/ehae508

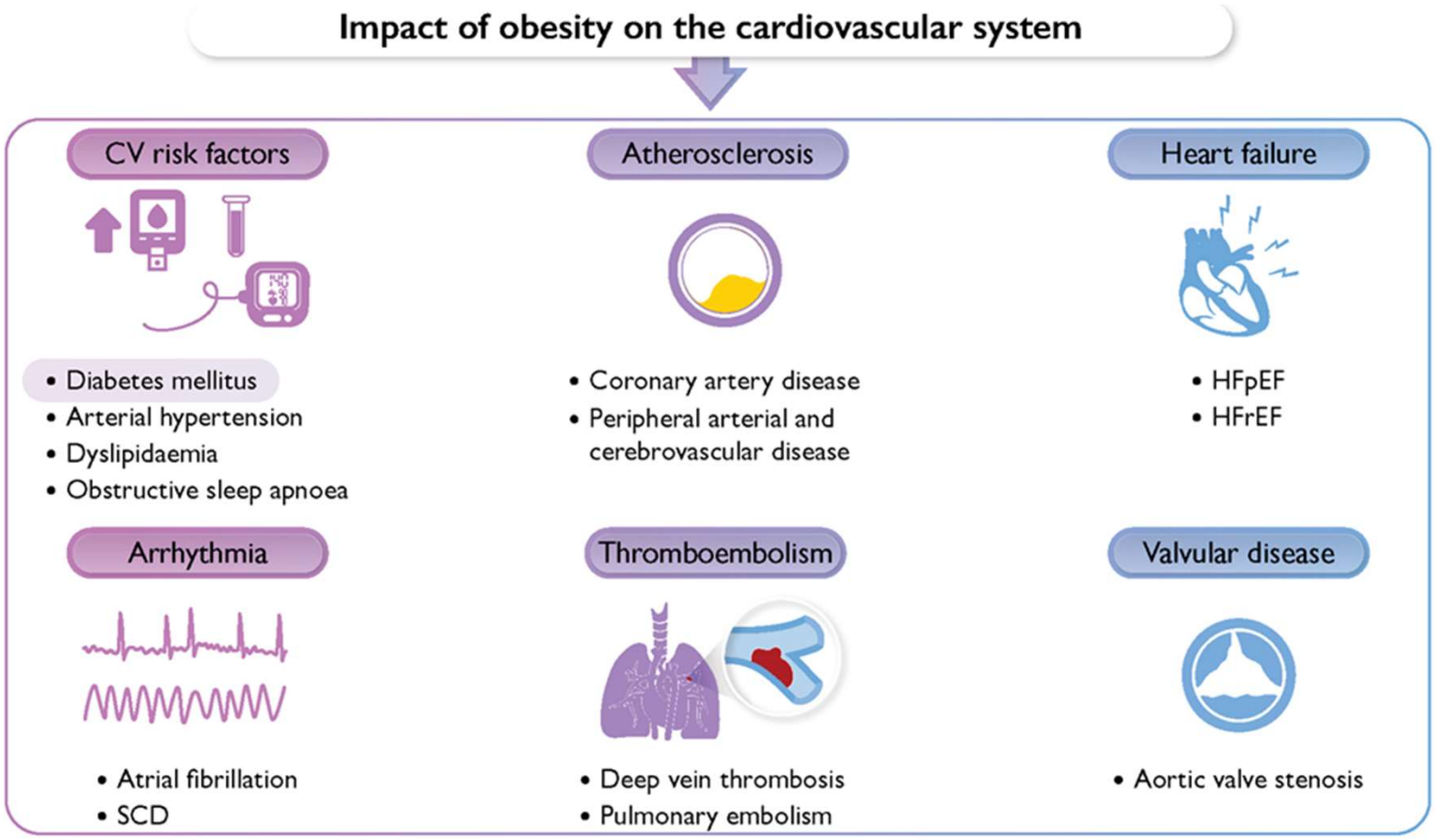
SPECIAL ARTICLE
Diabetes and metabolic disorders

Obesity and cardiovascular disease: an ESC clinical consensus statement

Konstantinos C. Koskinas[1]*†, Emeline M. Van Craenenbroeck[2,3]*†, Charalambos Antoniades[4], Matthias Blüher[5], Thomas M. Gorter[6], Henner Hanssen[7], Nikolaus Marx[8], Theresa A. McDonagh[9,10], Geltrude Mingrone[11,12], Annika Rosengren[13,14], Eva B. Prescott[15]*‡, and the ESC Scientific Document Group

[1]Department of Cardiology, Bern University Hospital—INSELSPITAL, University of Bern, Freiburgstrasse 18, Bern 3010, Switzerland; [2]Department of Cardiology, Antwerp University Hospital, Drie Eikenstraat 655, Antwerp 2650, Belgium; [3]Research group Cardiovascular Diseases, GENCOR, University of Antwerp, Antwerp, Belgium; [4]Acute Multidisciplinary Imaging and Interventional Centre Radcliffe Department of Medicine, University of Oxford, Oxford, UK; [5]Helmholtz Zentrum München at the University of Leipzig and University Hospital Leipzig, Leipzig, Germany; [6]Department of Cardiology, University Medical Center Groningen, Groningen, The Netherlands; [7]Department of Sport, Exercise and Health, University of Basel, Basel, Switzerland; [8]Department of Internal Medicine I—Cardiology, RWTH Aachen University, Aachen, Germany; [9]Cardiology Department, King's College Hospital, London, UK; [10]King's College, London, UK; [11]Cardiovascular and Metabolic Medicine & Sciences, King's College London, London, UK; [12]Department of Medical and Surgical Sciences, Fondazione Policlinico Universitario A. Gemelli & Catholic University, Rome, Italy; [13]Department of Molecular and Clinical Medicine, Institute of Medicine, University of Gothenburg, Gothenburg, Sweden; [14]Sahlgrenska University Hospital/Ostra, Västra Götaland Region, Gothenburg, Sweden; and [15]Bispebjerg Frederiksberg Hospital, University of Copenhagen, Bispebjerg Bakke 23, Copenhagen 2400, Denmark

Received 14 May 2024; revised 8 July 2024; accepted 26 July 2024

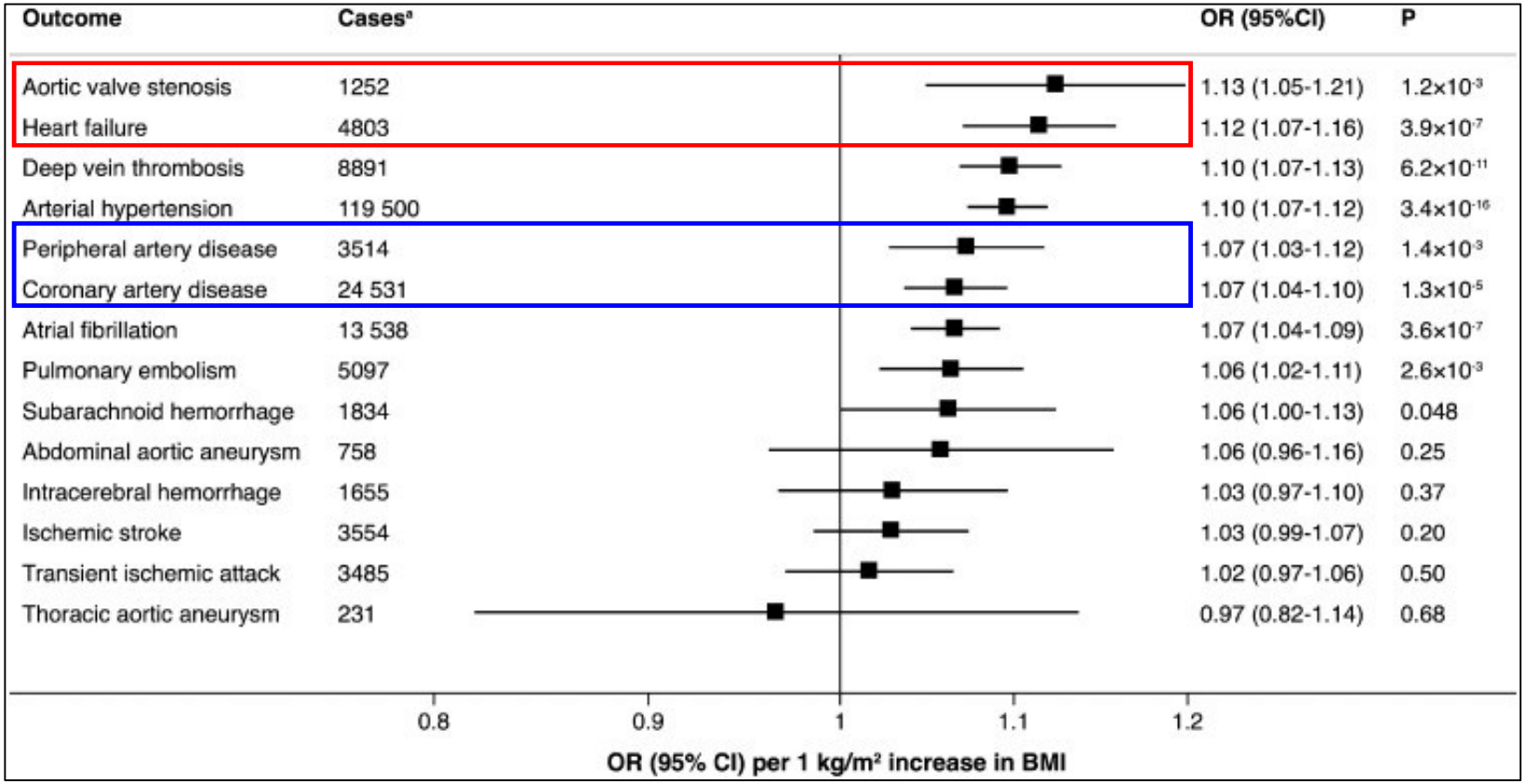


Koskinas KC, et al. *Eur Heart J* 2024;45(38):4063-4098

Associations of genetically predicted 1 kg/m2 increase in BMI with CV conditions
(n=367,703)

VHD
HF

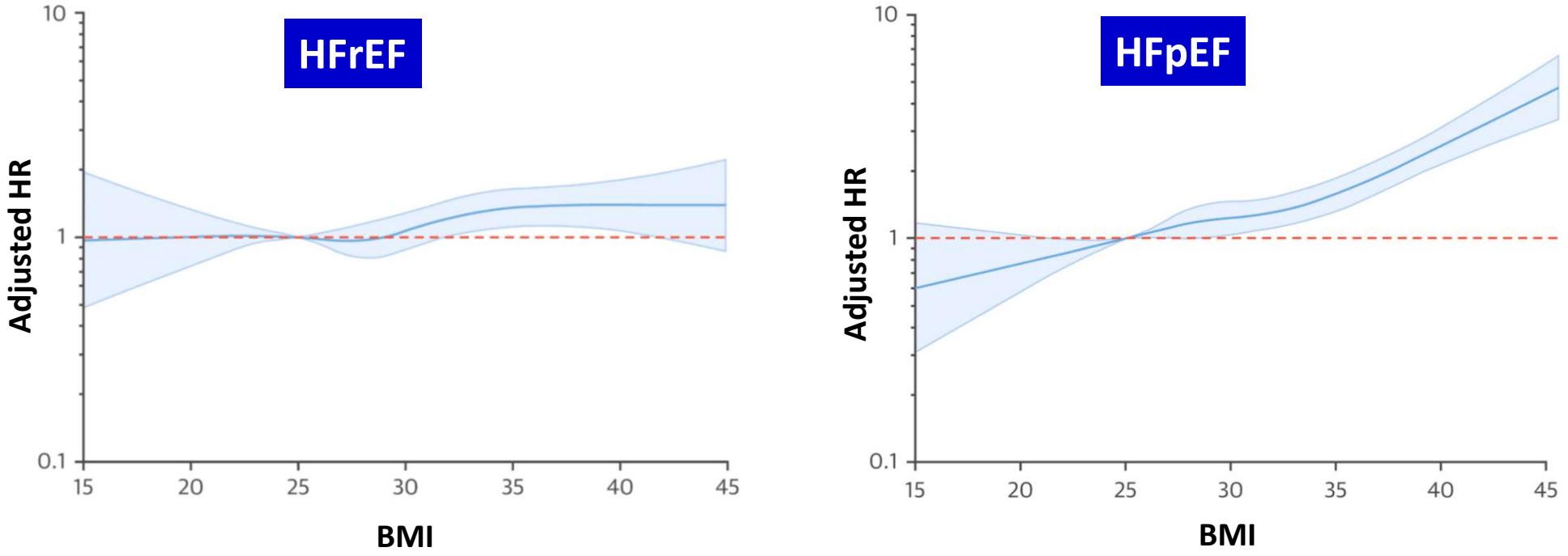
ASCVD



Larsson SC, et al. *Eur Heart J.* 2020;41(2):221-226.

Heart Failure

Obesity increases the risk of incident HF, particularly **HFpEF**



Associations between BMI and risk of HFpEF and HFrEF

Pandey A, et al. *JACC Heart Fail* 2018;6(12):975-982

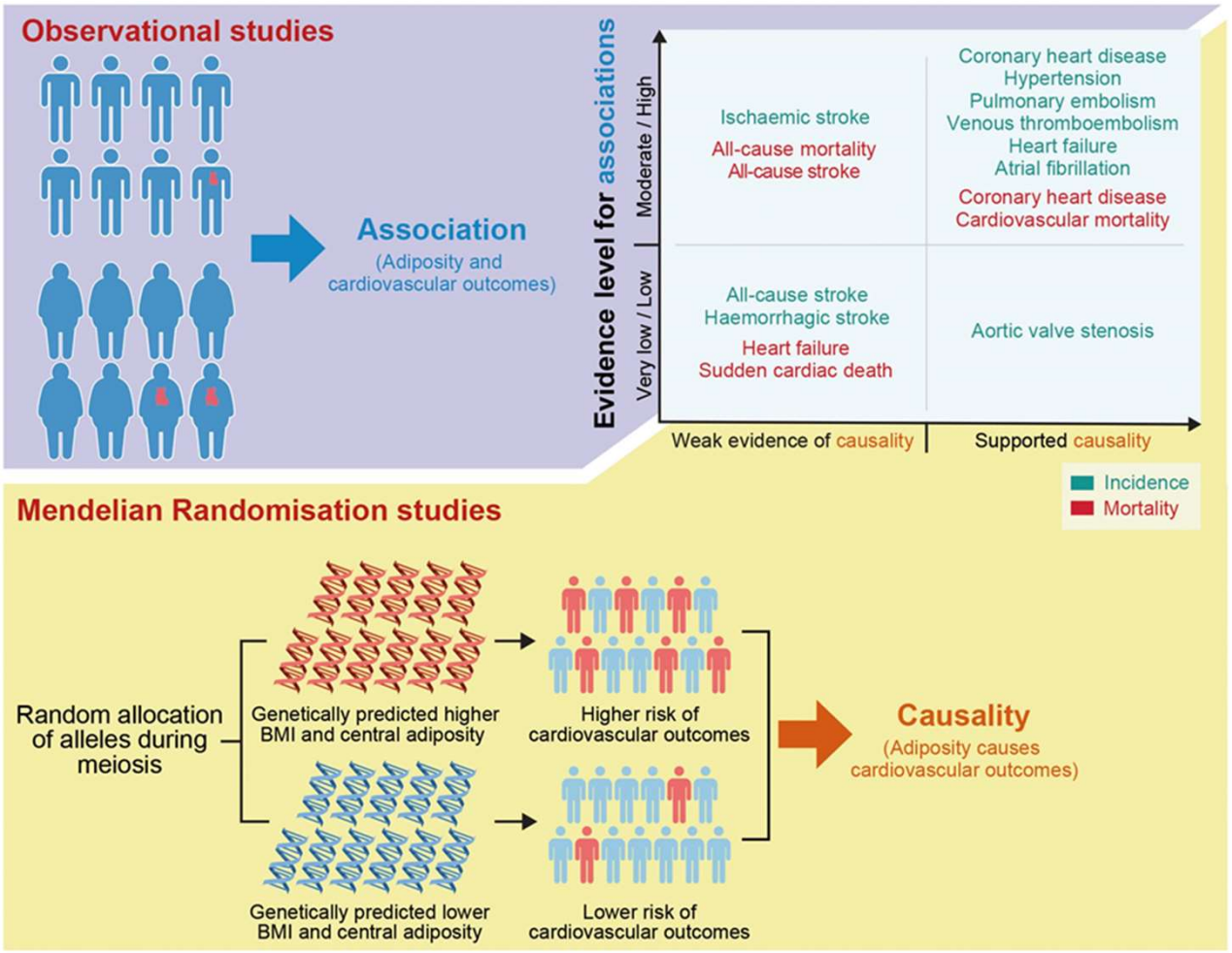
ESC European Society of Cardiology
European Heart Journal (2021) **42**, 3388–3403
doi:10.1093/eurheartj/ehab454

META-ANALYSIS
Epidemiology and prevention

Association between adiposity and cardiovascular outcomes: an umbrella review and meta-analysis of observational and Mendelian randomization studies

Min Seo Kim[1,2], Won Jun Kim[1,3], Amit V. Khera[4,5,6], Jong Yeob Kim[7], Dong Keon Yon[8], Seung Won Lee[9], Jae Il Shin[10], and Hong-Hee Won[2,11]*

Observational studies (informing associations) and **Mendelian randomization studies** (informing causality) provided mutually complementary insight and enabled a more reliable interpretation of perplexing epidemiological relationships



Kim MS et al. *Eur Heart J* 2021;42:3388-3403

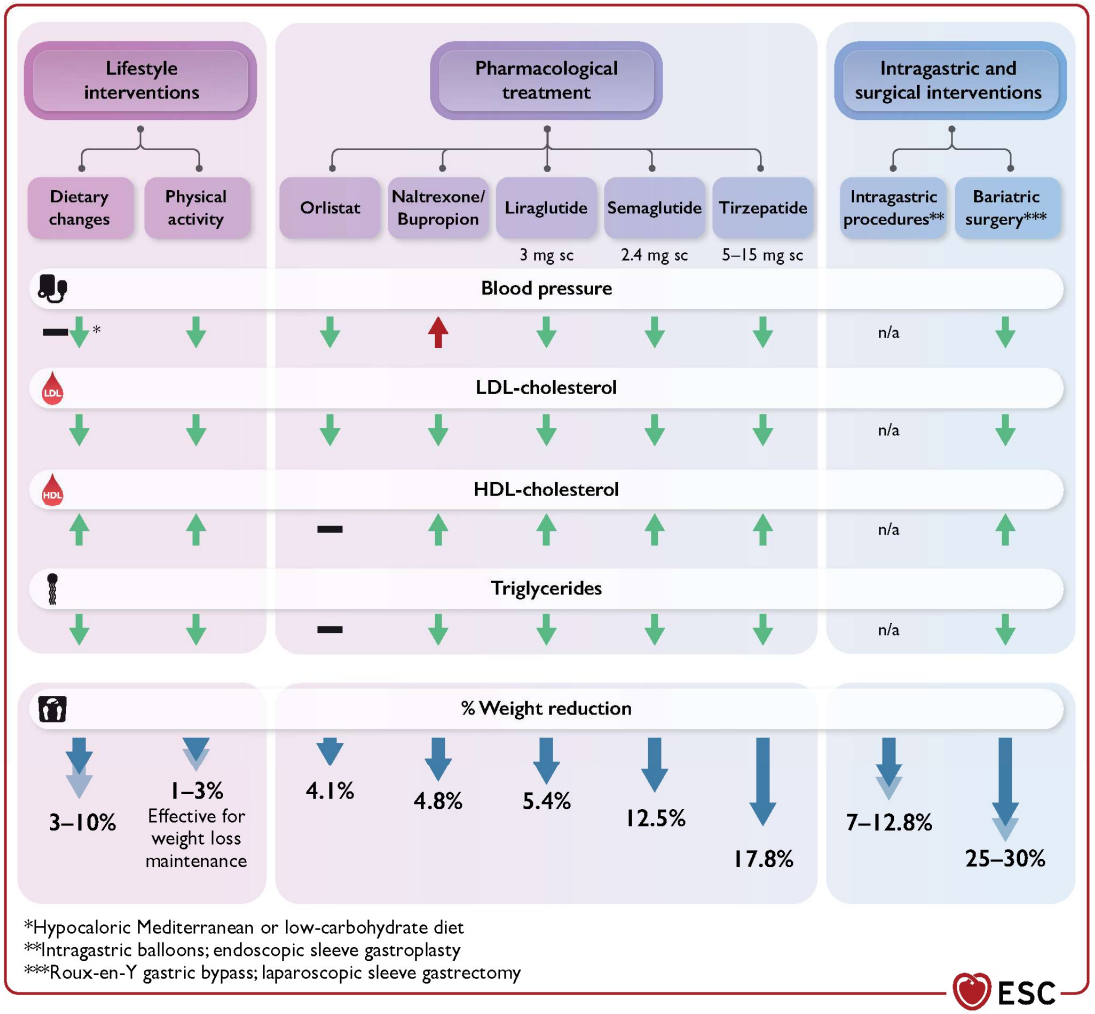
Adipositas

- Prävalenz
- Auswirkungen auf das kardiovaskuläre Risiko
- **Behandlungsmöglichkeiten**

Lifestyle, pharmacological, intragastric and surgical bariatric interventions

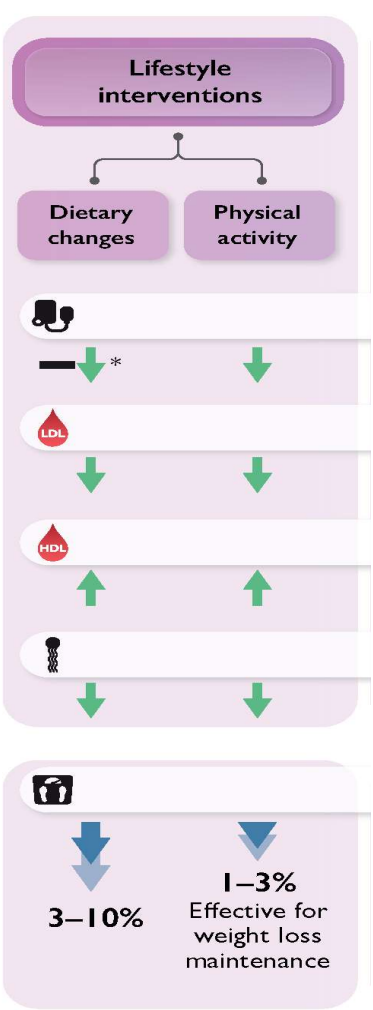
Effects on risk factors

Effects on body weight



Koskinas KC et al. *Eur Heart J* 2024 Aug 30:ehae508. doi: 10.1093/eurheartj/ehae508

Impact of weight loss interventions on cardiovascular outcomes



- Intensive **lifestyle interventions** combining nutritional interventions and physical activity in obesity have shown improved weight loss and improvement in cardiometabolic risk factors
- No significant effect on hard CV outcomes according to RCT evidence

Koskinas KC et al. *Eur Heart J* 2024 Aug 30:ehae508. doi: 10.1093/eurheartj/ehae508

Main bariatric surgery procedures

Sleeve gastrectomy | Roux-en-Y gastric bypass

Main endoscopic procedures

Intragastric balloon | Sleeve gastroplasty

Indications

- BMI ≥ 40 kg/m²
- BMI ≥ 35 kg/m² with obesity associated comorbidities

- BMI ≥ 30 kg/m² (USA)
- BMI ≥ 27 kg/m² (Europe)

- BMI ≥ 30 kg/m²
- People with obesity considered as high risk for invasive bariatric surgery

Contraindications

No absolute contraindications

Relative contraindications:

- Severe heart failure
- Unstable coronary artery disease
- End-stage lung disease
- Active cancer treatment
- Portal hypertension
- Drug/alcohol dependency
- Impaired intellectual capacity
- Crohn's disease (only for RYGB)
- Contraindication to receiving general anaesthesia

- Prior gastric surgery
- Upper gastrointestinal bleeding lesions
- Coagulopathies
- Severe liver disease
- Pregnancy
- Alcoholism, drug addiction
- Contraindication to undergo oesophagogastroscopy

- Acute, potentially bleeding gastric mucosal lesions
- Ulcers
- Acute gastritis
- Neoplastic lesions
- Hiatus hernia >3 cm
- Coagulopathies
- Psychiatric disorders

ESC

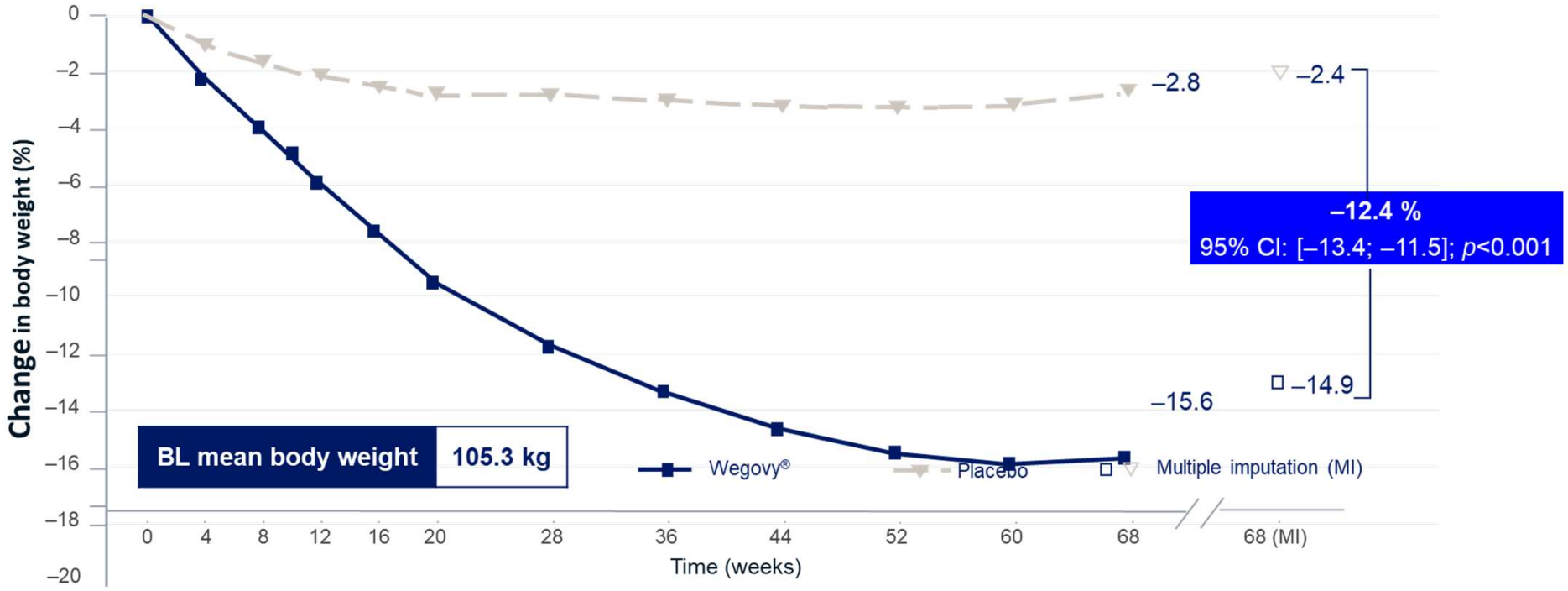
Impact of weight loss interventions on cardiovascular outcomes

- Bariatric surgery has been associated with improved CV outcomes in **observational** studies.
- RCTs assessing CV outcomes are not available.

Koskinas KC et al. *Eur Heart J* 2024 Aug 30:ehae508. doi: 10.1093/eurheartj/ehae508

STEP 1: Semaglutide 2.4 mg for weight reduction

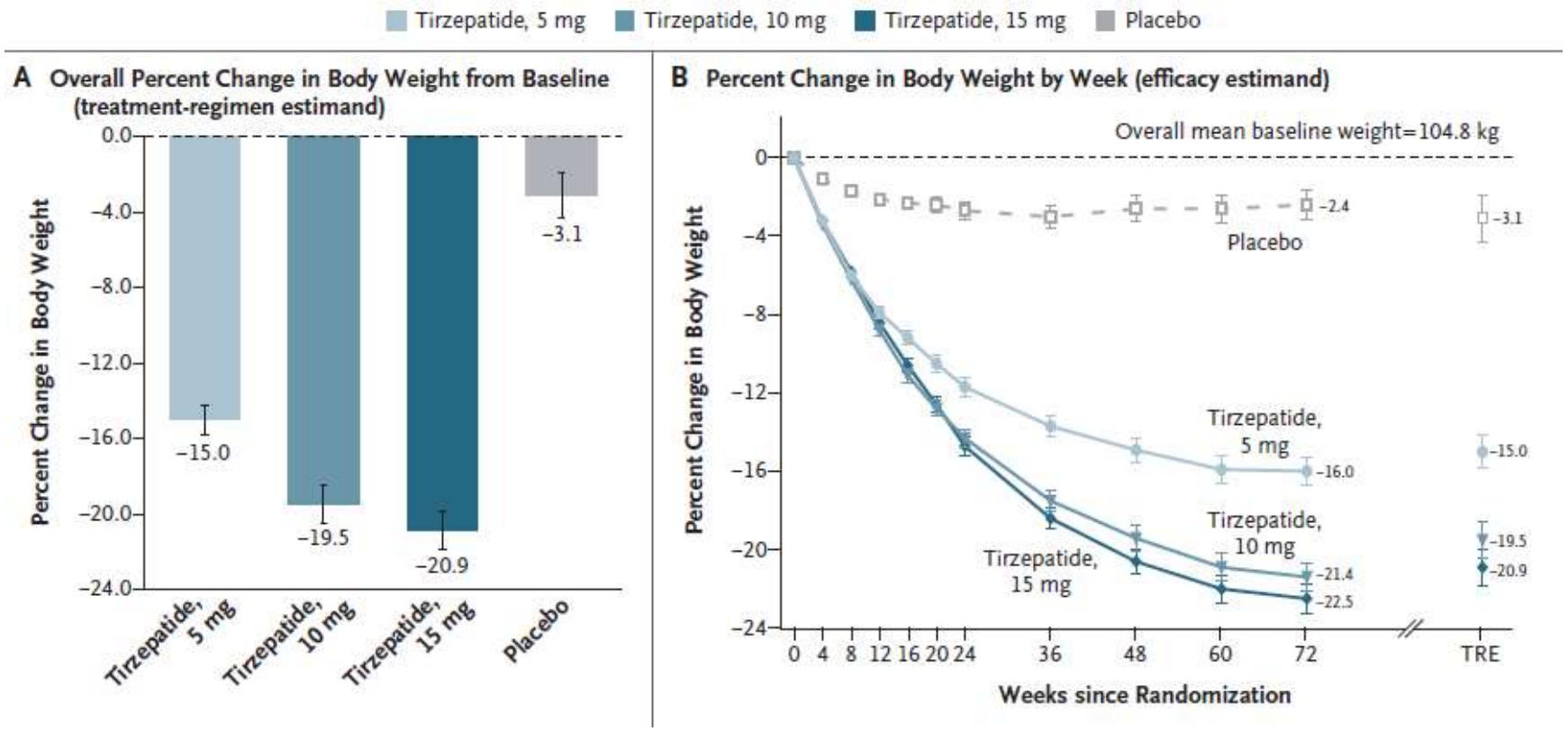
- Adult patients (n=1961) with BMI >30 kg/m2 or ≥27 kg/m2 with ≥1 weight-related comorbidity randomised (2:1) to semaglutide 2.4 mg or placebo
- 16-week dose escalation period, followed by a 52-week treatment period, and a 7-week off-treatment follow-up period



Wilding JPH et al. *N Engl J Med* 2021;384:989-1002

SURMOUNT 1: Tirzepatide for weight reduction

N = 2,539 patients, BMI >30 kg/m2 or ≥27 kg/m2 with ≥1 weight-related comorbidity, no diabetes



Jastreboff AM et al. *N Engl J Med*. 2022;387(3):205-216.

The NEW ENGLAND JOURNAL of MEDICINE

Semaglutide and Cardiovascular Outcomes in Obesity without Diabetes

A. Michael Lincoff, M.D., Kirstine Brown-Frandsen, M.D., Helen M. Colhoun, M.D., John Deanfield, M.D., Scott S. Emerson, M.D., Ph.D., Sille Esbjerg, M.Sc., Søren Hardt-Lindberg, M.D., Ph.D., G. Kees Hovingh, M.D., Ph.D., Steven E. Kahn, M.B., Ch.B., Robert F. Kushner, M.D., Ildiko Lingvay, M.D., M.P.H., Tugce K. Oral, M.D., Marie M. Michelsen, M.D., Ph.D., Jorge Plutzky, M.D., Christoffer W. Tornøe, Ph.D., and Donna H. Ryan, M.D., for the SELECT Trial Investigators*

CONCLUSIONS

In patients with preexisting cardiovascular disease and overweight or obesity but without diabetes, weekly subcutaneous semaglutide at a dose of 2.4 mg was superior to placebo in reducing the incidence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke at a mean follow-up of 39.8 months. (Funded by Novo Nordisk; SELECT ClinicalTrials.gov number, NCT03574597.)

Lincoff AM, et al. *N Engl J Med* 2023; doi 10.1056/NEJMoa2307563

SELECT: Semaglutide and CV Outcomes in Obesity without Diabetes

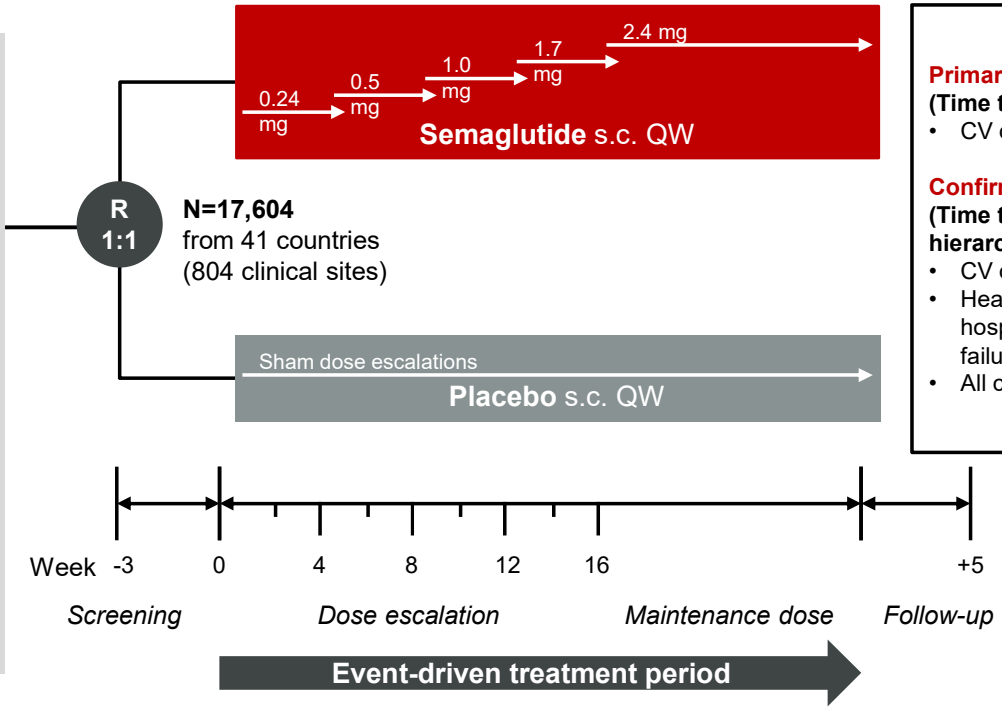
Randomized, double-blind, parallel-group, placebo-controlled superiority trial

Main inclusion criteria

- Aged ≥45 years
- Overweight or obesity, **BMI ≥27 kg/m²**
- Established CVD (at least one of the following: prior MI, prior stroke, symptomatic PAD#)

Main exclusion criteria

- History of T1DM or T2DM
- HbA_{1c} ≥6.5% (≥48 mmol/mol)
- Treatment with glucose-lowering agent
- NYHA Class IV heart failure
- MI, stroke, ACS, TIA within prior 60 days
- Planned revascularization
- ESRD or dialysis
- Pancreatitis
- Malignancy in prior 5 years
- Severe psychiatric disorder
- Pregnancy



Primary composite endpoint
(Time to first event)
- CV death, nonfatal MI, or nonfatal stroke

Confirmatory secondary endpoints
(Time to first event and tested in hierarchical order)
- CV death
- Heart failure composite (CV death or hospitalization or urgent visit for heart failure)
- All cause death

Hypothesis: Addition of semaglutide 2.4 mg s.c. once weekly to standard of care will reduce the incidence of major CV events among patients with overweight or obesity and pre-existing CV disease, who do not have diabetes.

Lincoff AM, et al. *N Engl J Med* 2023; doi 10.1056/NEJMoa2307563

SELECT: Semaglutide and CV Outcomes in Obesity without Diabetes

Baseline characteristics of SELECT trial participants

N=17,605

BMI

33.34 kg/m²

SD 5.0

MI only

n=11,908

67.6%

Stroke only

n=3,135

17.8%

PAD only

n=777

4.4%

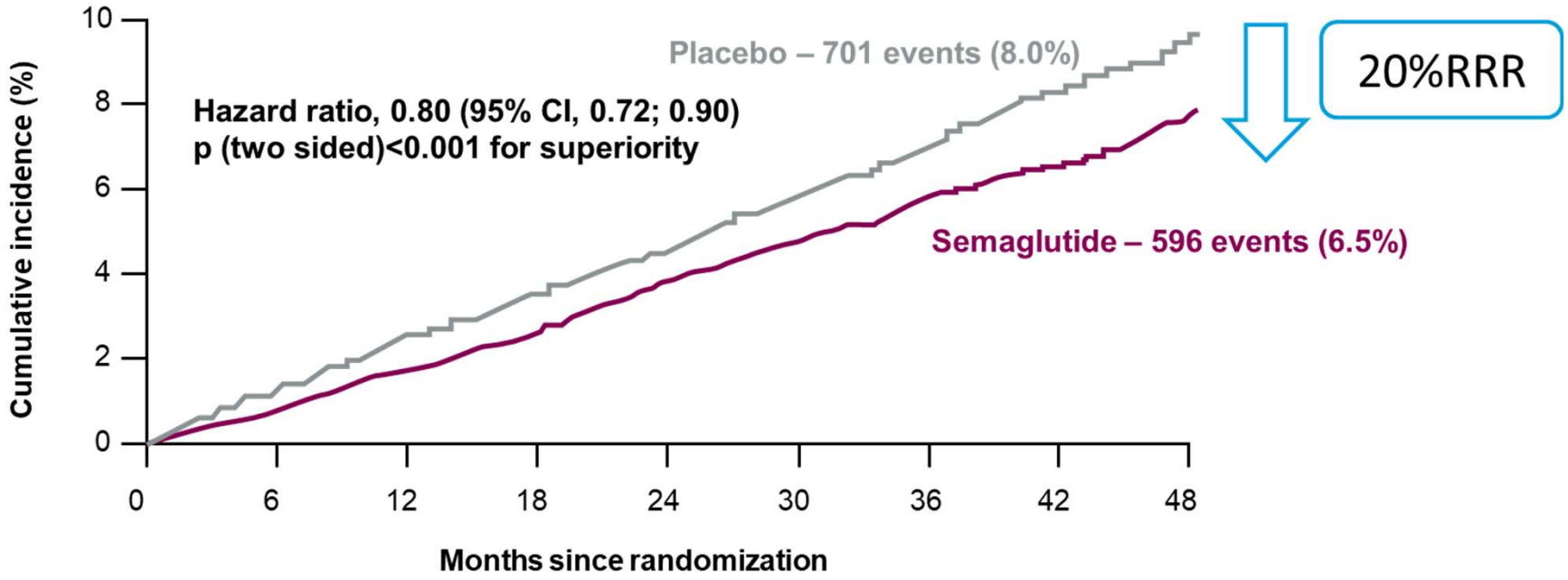
≥2 CV inclusion criteria: n=1,433, 8.1%

Lincoff AM, et al. *N Engl J Med* 2023; doi 10.1056/NEJMoa2307563

SELECT: Semaglutide and CV Outcomes in Obesity without Diabetes

Primary cardiovascular composite endpoint

CV death, nonfatal MI, or nonfatal stroke



Lincoff AM, et al. *N Engl J Med* 2023; doi 10.1056/NEJMoa2307563

ESC European Society of Cardiology
European Heart Journal (2024) **45**, 3415–3537
https://doi.org/10.1093/eurheartj/ehae177

ESC GUIDELINES

2024 ESC Guidelines for the management of chronic coronary syndromes

Developed by the task force for the management of chronic coronary syndromes of the European Society of Cardiology (ESC)

Recommendations	Class	Level
CCS patients without type 2 diabetes		
The GLP-1 receptor agonist semaglutide should be considered in chronic coronary syndrome patients without diabetes, but with overweight or obesity (BMI >27 kg/m2), to reduce CV mortality, myocardial infarction, or stroke	**IIa**	**B**

Vrints C, Andreotti F, Koskinas KC et al. *Eur Heart J* 2024;45(36):3415-37

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 21, 2023 VOL. 389 NO. 12

Semaglutide in Patients with Heart Failure with Preserved Ejection Fraction and Obesity

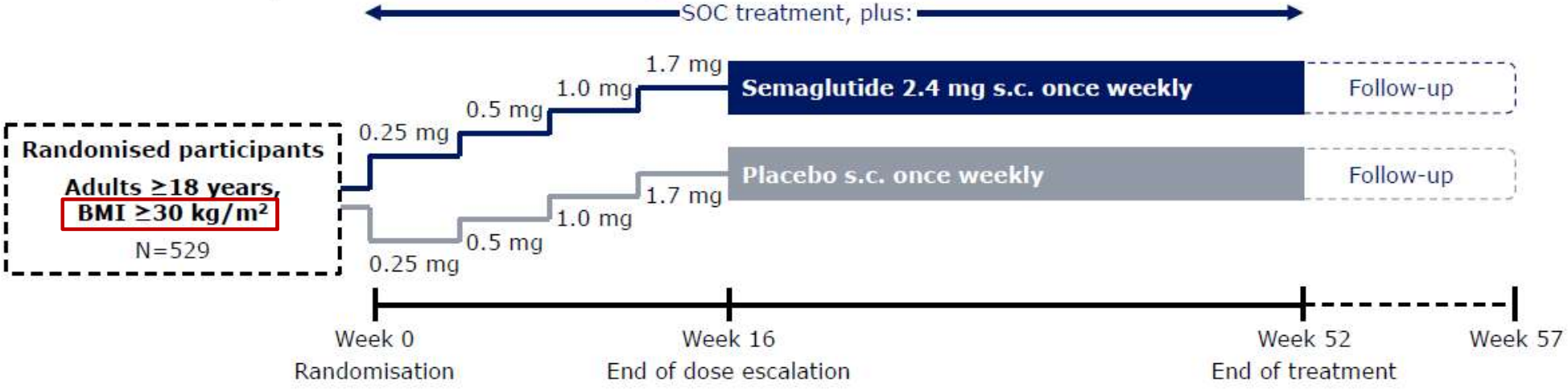
M.N. Kosiborod, S.Z. Abildstrøm, B.A. Borlaug, J. Butler, S. Rasmussen, M. Davies, G.K. Hovingh, D.W. Kitzman, M.L. Lindegaard, D.V. Møller, S.J. Shah, M.B. Treppendahl, S. Verma, W. Abhayaratna, F.Z. Ahmed, V. Chopra, J. Ezekowitz, M. Fu, H. Ito, M. Lelonek, V. Melenovsky, B. Merkely, J. Núñez, E. Perna, M. Schou, M. Senni, K. Sharma, P. Van der Meer, D. von Lewinski, D. Wolf, and M.C Petrie, for the STEP-HFpEF Trial Committees and Investigators*

CONCLUSIONS

In patients with heart failure with preserved ejection fraction and obesity, treatment with semaglutide (2.4 mg) led to larger reductions in symptoms and physical limitations, greater improvements in exercise function, and greater weight loss than placebo. (Funded by Novo Nordisk; STEP-HFpEF ClinicalTrials.gov number, NCT04788511.)

Kosiborod MN et al. *N Engl J Med* 2023; 389:1069–84

STEP-HFpEF trial design



Key inclusion criteria

- LVEF ≥45%, NYHA functional class II–IV, KCCQ-CSS <90 points, 6MWD ≥100 metres, and ≥1 of the following:
  - Elevated left ventricular filling pressures (invasively measured)
  - Elevated natriuretic peptide levels and structural echocardiographic abnormalities
  - HF hospitalisation (previous 12 months) and ongoing requirement for diuretics and/or structural echocardiographic abnormalities

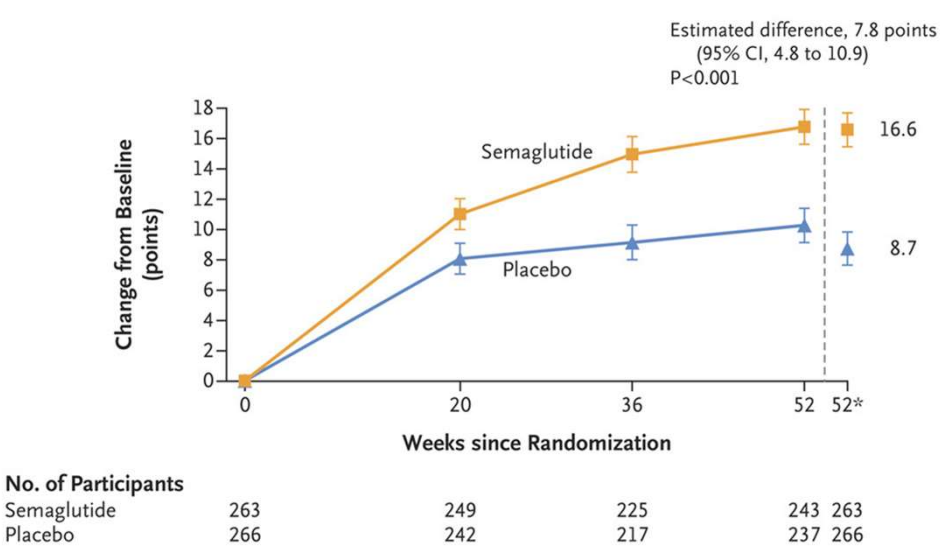
Key exclusion criteria

- Prior/planned bariatric surgery
- Recent self-reported weight change >5 kg (11 lbs)
- Recent adverse CV event or HF hospitalisation
- SBP of >160 mmHg at screening
- HbA_{1c} ≥6.5% or known medical history of diabetes

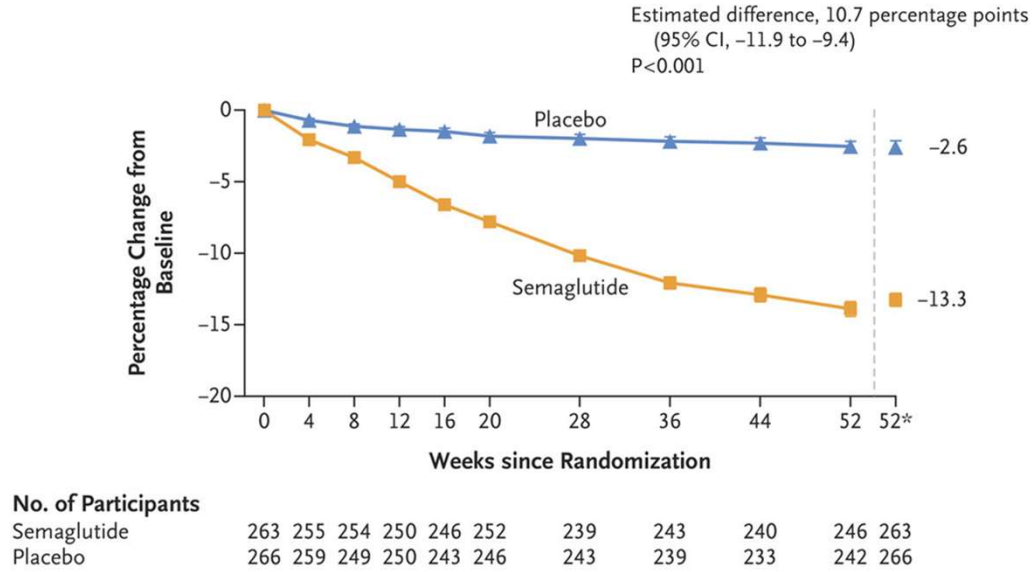
6MWD, 6-minute walk distance; BMI, body mass index; CV, cardiovascular; echo, echocardiographic; HbA_{1c}, glycated haemoglobin; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire Clinical Summary Score; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; SBP, systolic blood pressure; s.c., subcutaneous; SOC, standard of care; STEP, Semaglutide Treatment Effect in People with obesity.

Kosiborod MN et al. *N Engl J Med* 2023; 389:1069–84

STEP-HFpEF: Co-Primary Endpoints



Change in KCCQ-CSS



Change in Body Weight

Kosiborod MN et al. *N Engl J Med* 2023; 389:1069–84

Semaglutide versus placebo in patients with heart failure and mildly reduced or preserved ejection fraction: a pooled analysis of the SELECT, FLOW, STEP-HFpEF, and STEP-HFpEF DM randomised trials

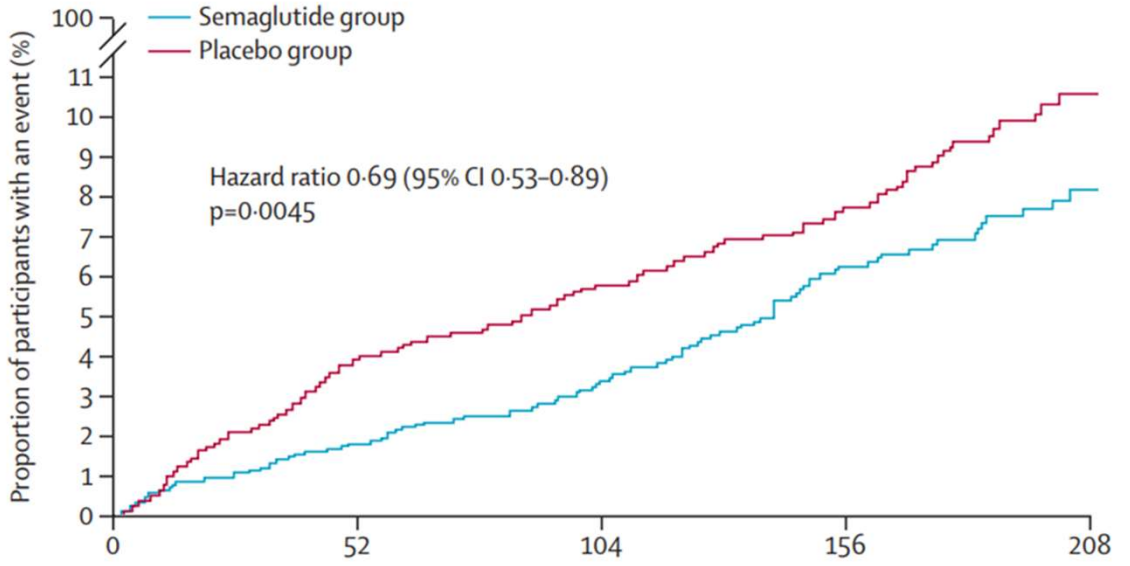
Mikhail N Kosiborod, John Deanfield*, Richard Pratley, Barry A Borlaug, Javed Butler, Melanie J Davies, Scott S Emerson, Steven E Kahn, Dalane W Kitzman, Ildiko Lingvay, Kenneth W Mahaffey, Mark C Petrie, Jorge Plutzky, Søren Rasmussen, Cecilia Rönnbäck, Sanjiv J Shah, Subodh Verma, Peter E Weeke, A Michael Lincoff, for the SELECT, FLOW, STEP-HFpEF, and STEP-HFpEF DM Trial Committees and Investigators*

Lancet 2024; 404: 949-61

- **Study population** (n=3,743):
  - STEP-HFpEF and STEP-HFpF DM trials: patients with obesity-related HFpEF
  - SELECT trial: patients with atherosclerotic cardiovascular disease and overweight / obesity
  - FLOW trial: patients with type 2 diabetes and chronic kidney disease
- **Intervention**: subcutaneous semaglutide (2.4 mg in SELECT, STEP-HFpEF, and STEP-HFpEF DM; 1.0 mg in FLOW) or placebo
- **Main outcome**: composite endpoint of time to cardiovascular death or first worsening heart failure event (defined as hospitalisation or urgent visit due to heart failure)

Pooled analysis of STEP-HFpEF, STEP-HFpEF Diabetes, SELECT, and FLOW

CV death or first worsening HF event



Number at risk (number censored)									
Semaglutide group	1914	1886	1854	1296	1272	1127	892	640	299
	(0)	(9)	(27)	(575)	(587)	(716)	(933)	(1179)	(1513)
Placebo group	1829	1785	1734	1190	1162	1029	823	584	271
	(0)	(7)	(23)	(559)	(572)	(691)	(889)	(1114)	(1421)

Kosiborod MN et al. *Lancet* 2024; 404: 949–61

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 30, 2025 VOL. 392 NO. 5

Tirzepatide for Heart Failure with Preserved Ejection Fraction and Obesity

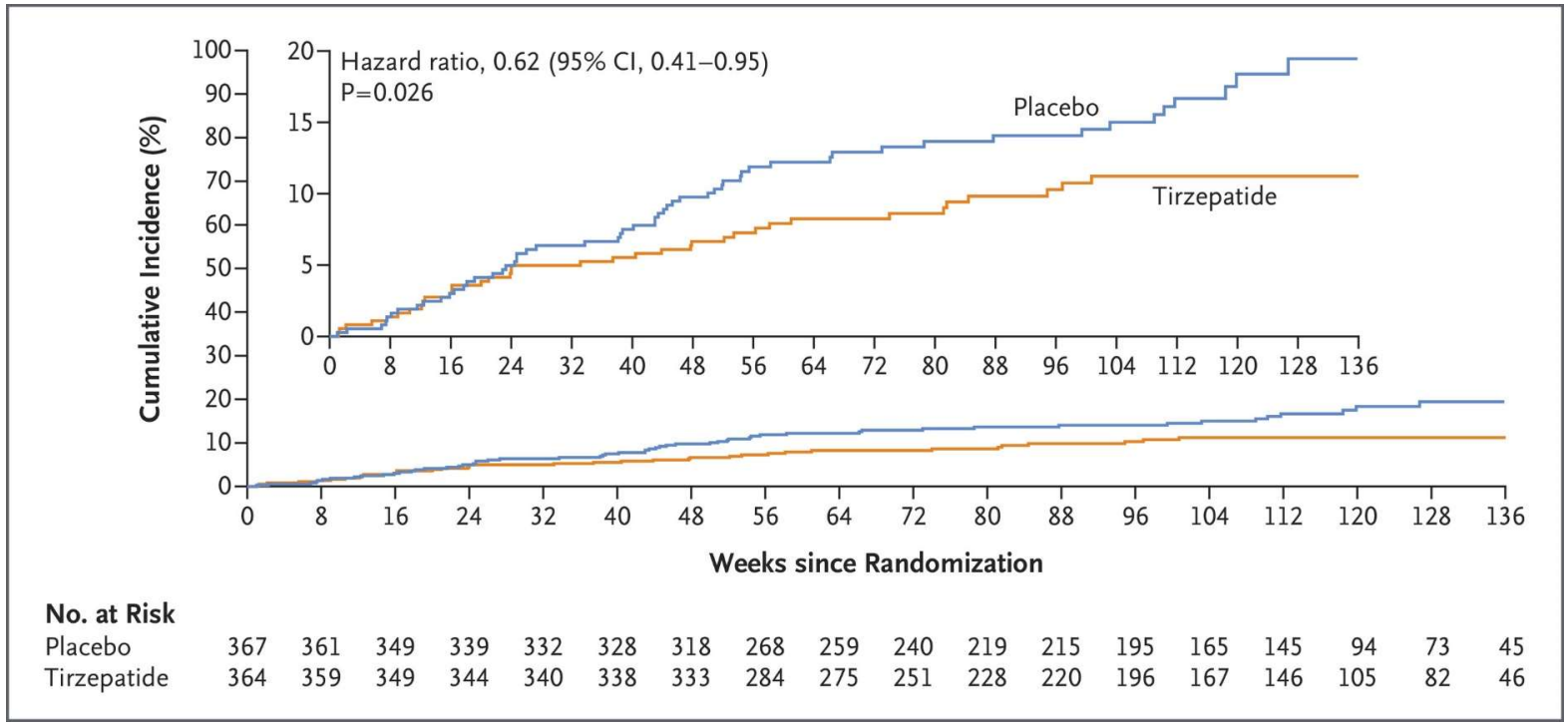
Milton Packer, M.D., Michael R. Zile, M.D., Christopher M. Kramer, M.D., Seth J. Baum, M.D., Sheldon E. Litwin, M.D., Venu Menon, M.D., Junbo Ge, M.D., Govinda J. Weerakkody, Ph.D., Yang Ou, Ph.D., Mathijs C. Bunck, M.D., Karla C. Hurt, B.S.N., Masahiro Murakami, M.D., and Barry A. Borlaug, M.D., for the SUMMIT Trial Study Group*

- 731 patients with HFpEF (LVEF $\geq$ 50%)
- BMI $\geq$ 30

CONCLUSIONS

Treatment with tirzepatide led to a lower risk of a composite of death from cardiovascular causes or worsening heart failure than placebo and improved health status in patients with heart failure with preserved ejection fraction and obesity. (Funded by Eli Lilly; SUMMIT ClinicalTrials.gov number, NCT04847557.)

Composite of Death from Cardiovascular Causes or a Worsening Heart-Failure Event



Packer M, et al. N Engl J Med. 2025;392(5):427-437

TAKE-HOME MESSAGES

- Obesity has reached **pandemic proportions**, affecting more than **1 in 5 adults** in ESC member countries and 1 in 8 adults worldwide
- People living with obesity have a **50%–100% increased risk of death** compared to normal-weight individuals
- Obesity is a high risk condition that is **causally linked to various CV risk factors and CVD manifestations** including atherosclerotic disease, HF, arrhythmias, and valvular heart disease
- **Two-thirds of deaths related to high BMI are due to CVD**
- Despite the increasingly appreciated link between obesity and CVD, obesity has been **under-recognised and sub-optimally addressed** by cardiologists. **Cardiologists need to become more pro-active in addressing obesity as a major modifiable CV risk factor**

INSELSPITAL
UNIVERSITÄTSSPITAL BERN
HOPITAL UNIVERSITAIRE DE BERNE
BERN UNIVERSITY HOSPITAL

Vielen Dank für Ihre Aufmerksamkeit

konstantinos.koskinas@insel.ch

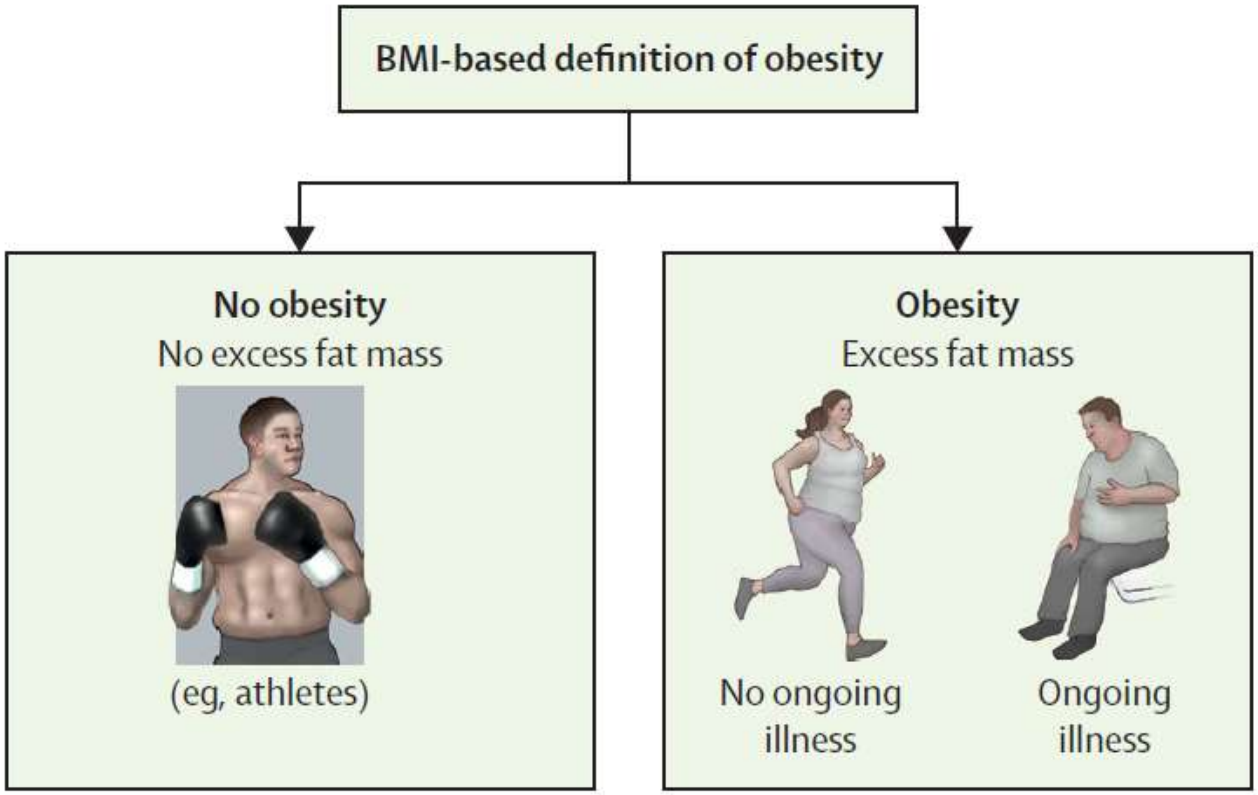
BACK-UP SLIDES

Obesity: Definition and WHO classification in adults

BMI 20 to <25 kg/m^2: **Normal weight**
BMI 25 to <30 kg/m^2: **Overweight**
BMI ≥30 kg/m^2: **Obesity**
• BMI 30 to <35 kg/m^2: **Obesity class 1**
• BMI 35 to <40 kg/m^2: **Obesity class 2**
• BMI ≥40 kg/m^2: **Obesity class 3** (severe obesity)

- Lower, country-specific cut-off points apply to Asian subpopulations
- Different cut-off values for children and pregnant women

Limitations of the BMI-based definition

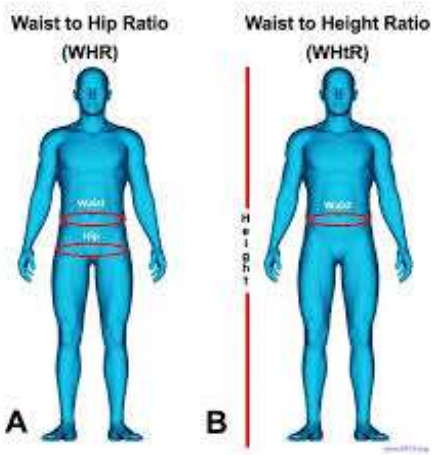


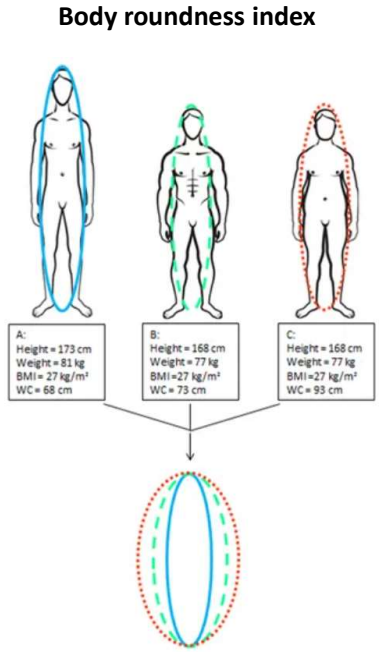
Rubino F et al. Lancet Diabetes Endocrinol 2025; 13: 221–62

Obesity: Definition and WHO classification in adults

Metrics of **abdominal adiposity** are useful to refine risk stratification:

- Waist circumference
- Waist-to-height ratio
- Waist-to-hip ratio
- Body roundness index





Ross R, *Nat Rev Endocrinol.* 2020;16:177–89

Wormser D, et al. *Lancet.* 2011;377:1085–95

Zhang X, et al. *JAMA Netw Open* 2024;7:e2415051.