ASU FC
Azienda sanitaria
universitaria
Friuli Centrale

Obesità, Prediabete, Rischio Cardiovascolare

Dr Andrea Da Porto

Responsabile SOSD Diabetologia

Azienda Sanitaria Universitaria Friuli Centrale

- Il /la dr./sa Andrea de Porto dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:

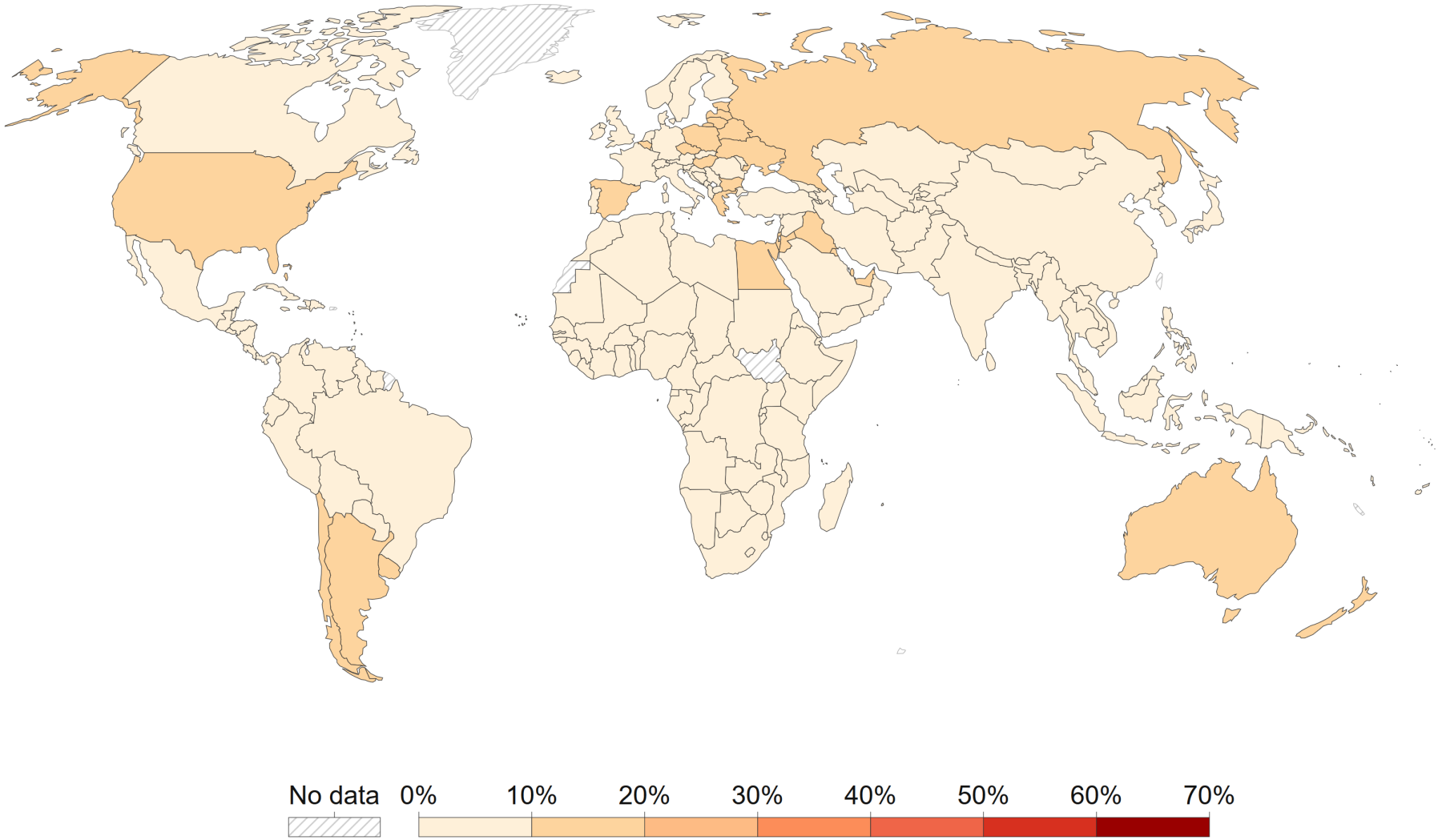
  - - Lilly
  - - Sanofi
  - - Roche Diagnostics
  - - NovoNordisk
  - - Boeringer-Ingelman

Dichiara altresì il proprio impegno ad astenersi, nell'ambito dell'evento, dal nominare, in qualsivoglia modo o forma, aziende farmaceutiche e/o denominazione commerciale e di non fare pubblicità di qualsiasi tipo relativamente a specifici prodotti di interesse sanitario (farmaci, strumenti, dispositivi medico-chirurgici, ecc.).

Share of adults that are obese, 1975

Obesity is defined as having a body-mass index (BMI) equal to, or greater than, 30. BMI is a person's weight (in kilograms) divided by their height (in meters) squared.

Our World in Data



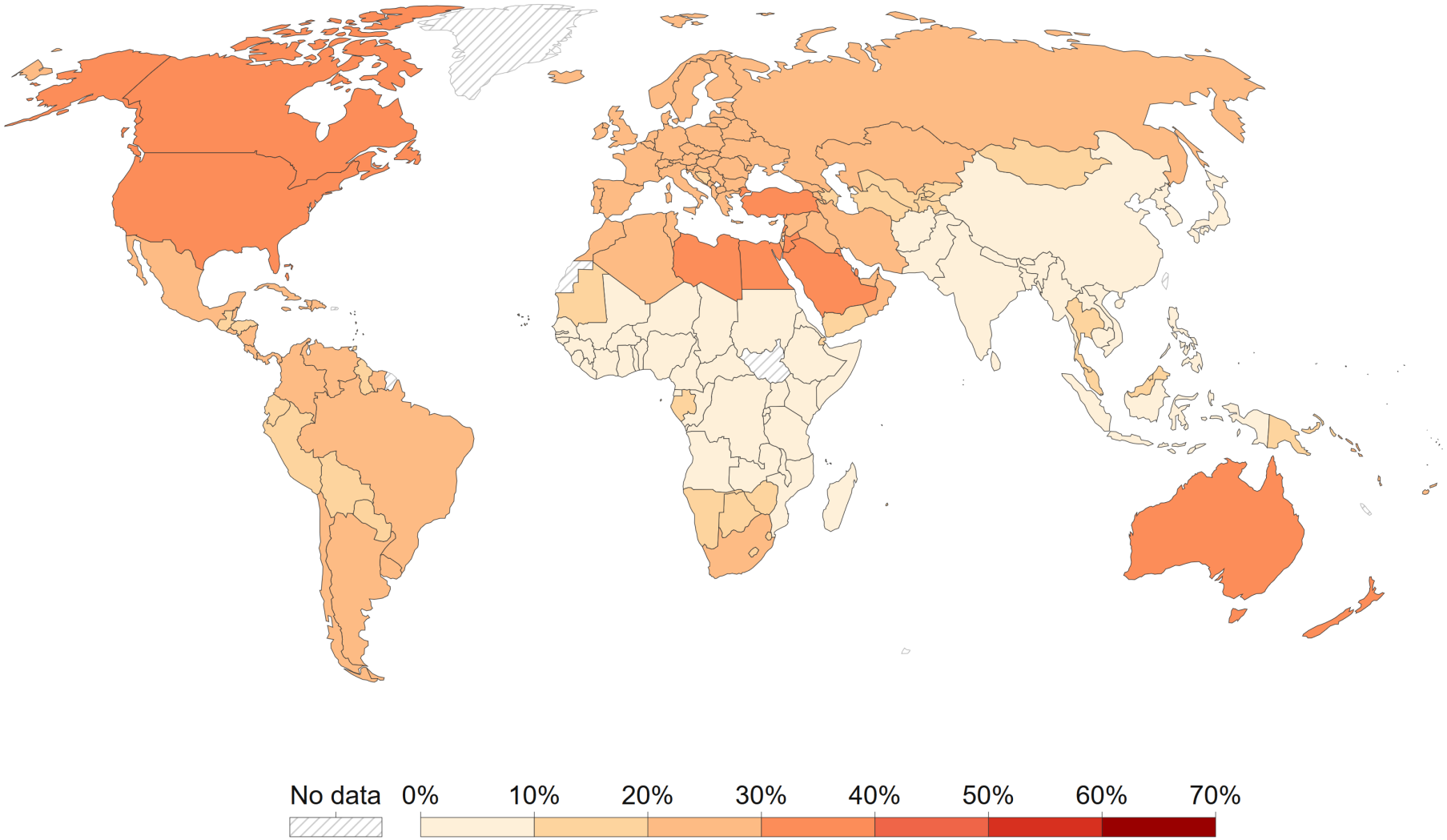
Source: WHO, Global Health Observatory (2022)

OurWorldInData.org/obesity • CC BY

Share of adults that are obese, 2016

Obesity is defined as having a body-mass index (BMI) equal to, or greater than, 30. BMI is a person's weight (in kilograms) divided by their height (in meters) squared.

Our World in Data



Source: WHO, Global Health Observatory (2022)

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

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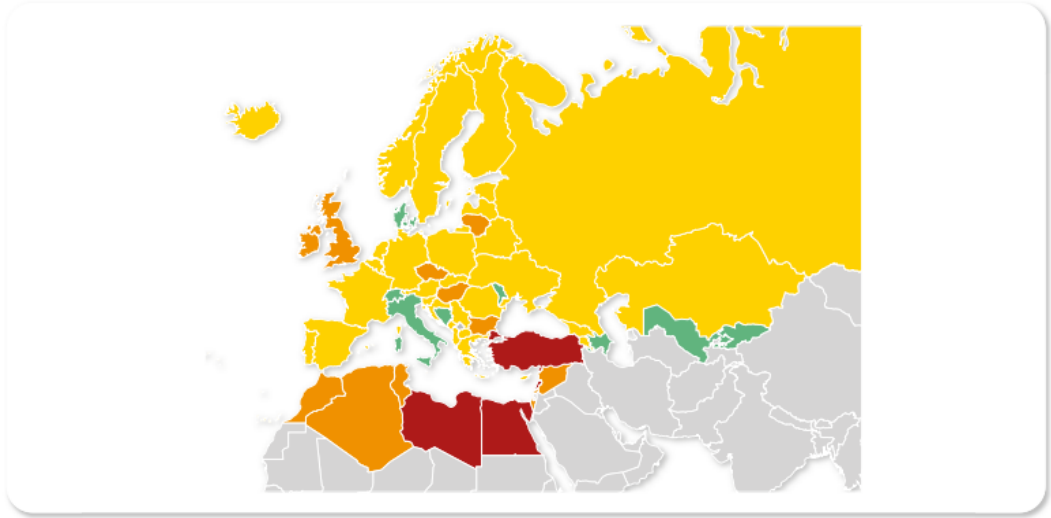

Prevalence of obesity (BMI ≥30 kg/m^2) across ESC member countries in 2019. Adapted from Timmis *et al.*[6]

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 6, 2017 VOL. 377 NO. 1

Health Effects of Overweight and Obesity in 195 Countries over 25 Years

The GBD 2015 Obesity Collaborators*

ABSTRACT

BACKGROUND

Although the rising pandemic of obesity has received major attention in many countries, the effects of this attention on trends and the disease burden of obesity remain uncertain.

METHODS

We analyzed data from 68.5 million persons to assess the trends in the prevalence of overweight and obesity among children and adults between 1980 and 2015. Using the Global Burden of Disease study data and methods, we also quantified the burden of disease related to high body-mass index (BMI), according to age, sex, cause, and BMI in 195 countries between 1990 and 2015.

RESULTS

In 2015, a total of 107.7 million children and 603.7 million adults were obese. Since 1980, the prevalence of obesity has doubled in more than 70 countries and has continuously increased in most other countries. Although the prevalence of obesity among children has been lower than that among adults, the rate of increase in childhood obesity in many countries has been greater than the rate of increase in adult obesity. High BMI accounted for 4.0 million deaths globally, nearly 40% of which occurred in persons who were not obese. More than two thirds of deaths related to high BMI were due to cardiovascular disease. The disease burden related to high BMI has increased since 1990; however, the rate of this increase has been attenuated owing to decreases in underlying rates of death from cardiovascular disease.

CONCLUSIONS

The rapid increase in the prevalence and disease burden of elevated BMI highlights the need for continued focus on surveillance of BMI and identification, implementation, and evaluation of evidence-based interventions to address this problem. (Funded by the Bill and Melinda Gates Foundation.)

*The names, academic degrees, and affiliations of the authors, who are members of the Global Burden of Disease (GBD) 2015 Obesity Collaborators, are listed in the Appendix. The authors assume responsibility for the content and integrity of this article. Address reprint requests to Dr. Murray at the Institute for Health Metrics and Evaluation, University of Washington, 2301 5th Ave., Suite 600, Seattle, WA 98121, or at cjlm@uw.edu.

This article was published on June 12, 2017, at NEJM.org.

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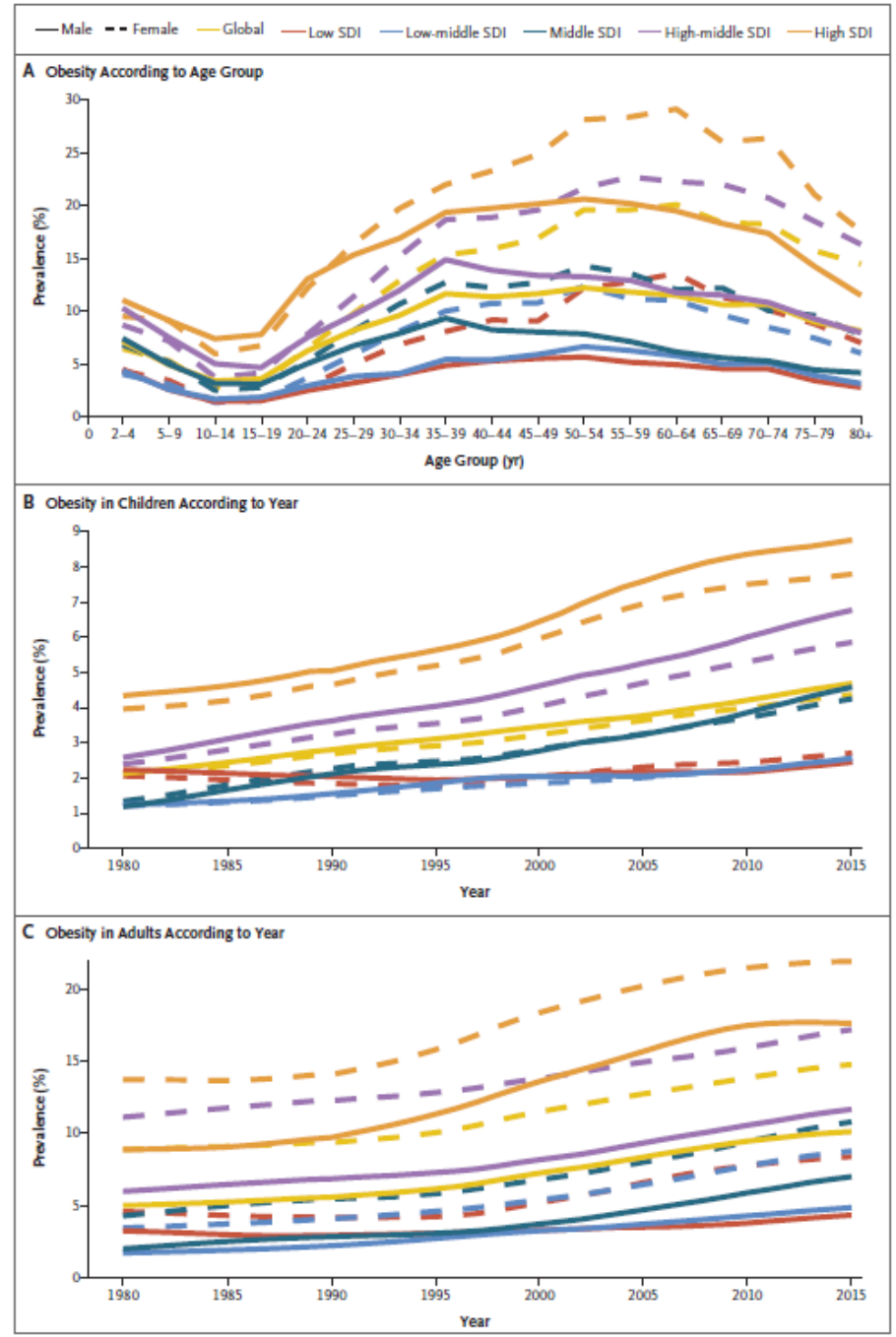
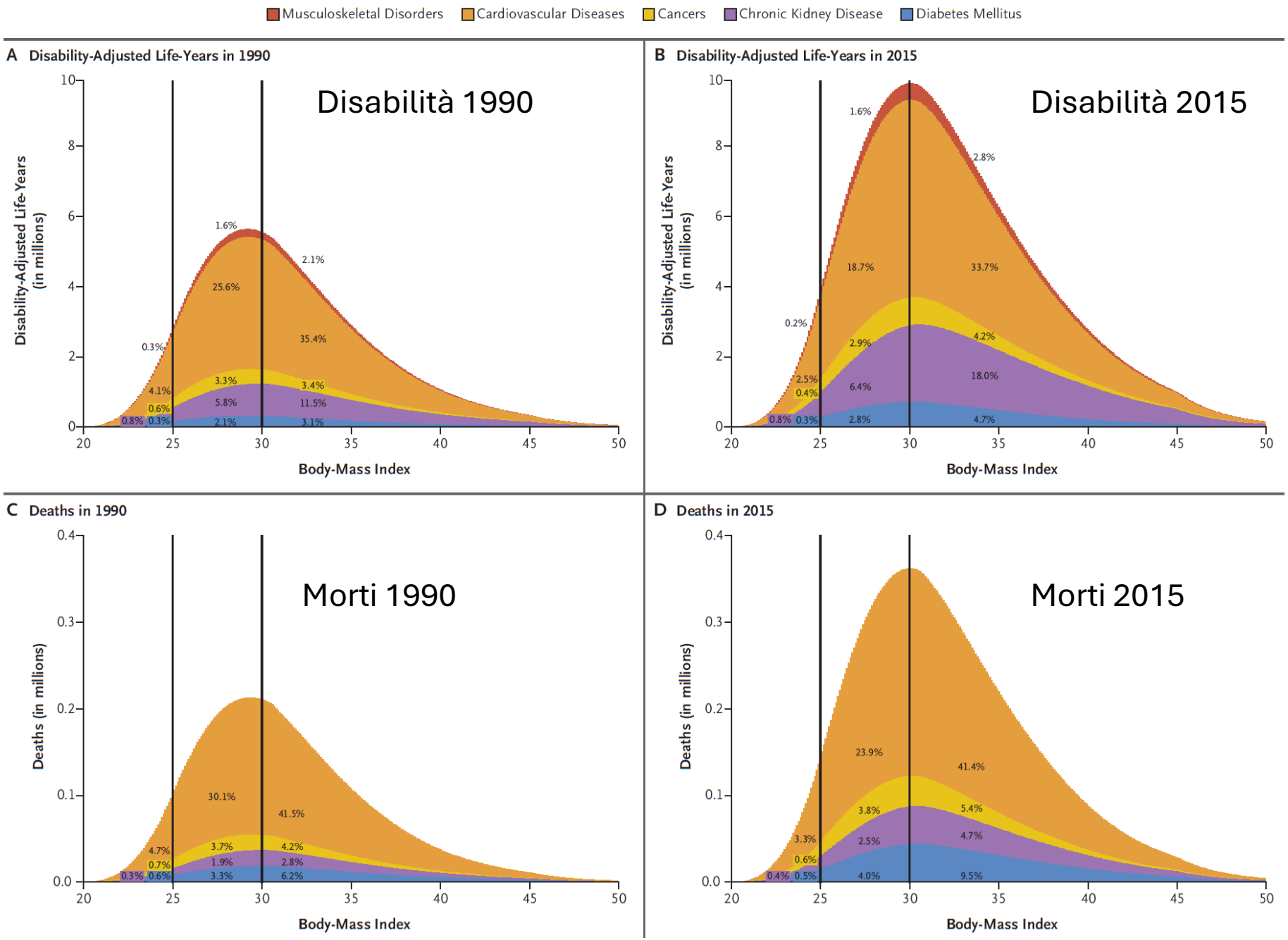
N Engl J Med 2017;377:13-27.
DOI: 10.1056/NEJMoa1614362





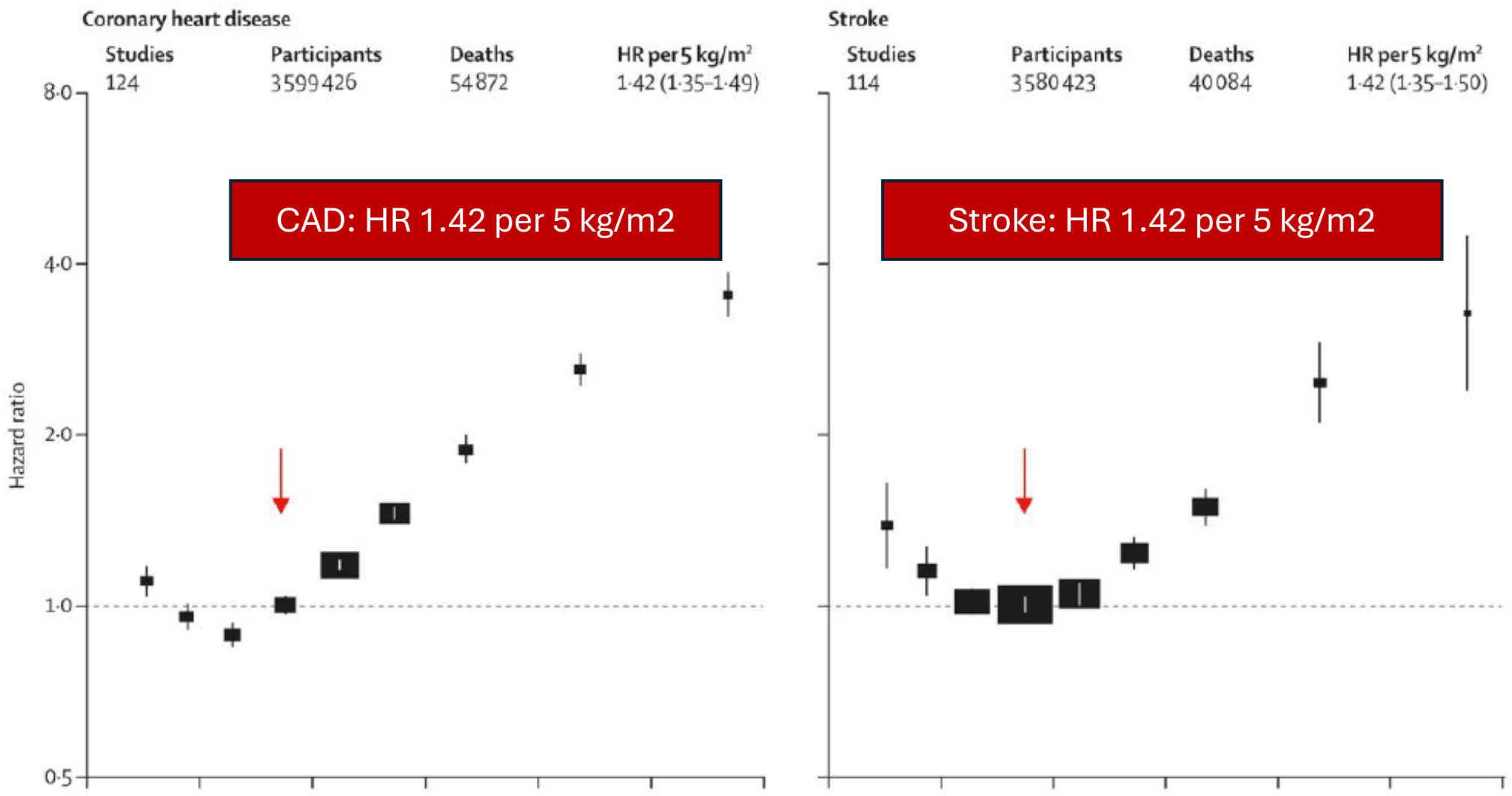
Cardiovascular disease was the leading cause of death and disability-adjusted life-years related to high BMI and accounted for ***2.7 million deaths*** (95% uncertainty interval, 1.8 to 3.7)

Diabetes was the second leading cause of BMI-related deaths in 2015 and contributed to ***0.6 million deaths***

Chronic kidney disease was the second leading cause of BMI-related disability-adjusted life-years in 2015

N Engl J Med 2017;377:13-27.

Obesità e CV Outcomes: dati Prospettici



Lancet. 2016; 388:776–786.

Body mass index and all-cause mortality: Individual-participant-data **meta-analysis of 239 prospective studies** in four continents. Over 3,5 million of partecipants. Over than 100.000 CV events.

Impatto dell'Obesità sulla malattia cardiovascolare

CV risk factors

- Diabetes mellitus
- Arterial hypertension
- Dyslipidaemia
- Obstructive sleep apnoea

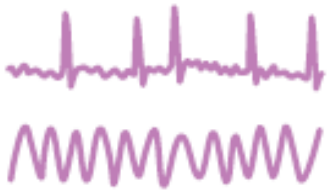
Atherosclerosis

- Coronary artery disease
- Peripheral arterial and cerebrovascular disease

Heart failure

- HFpEF
- HFrEF

Arrhythmia



- Atrial fibrillation
- SCD

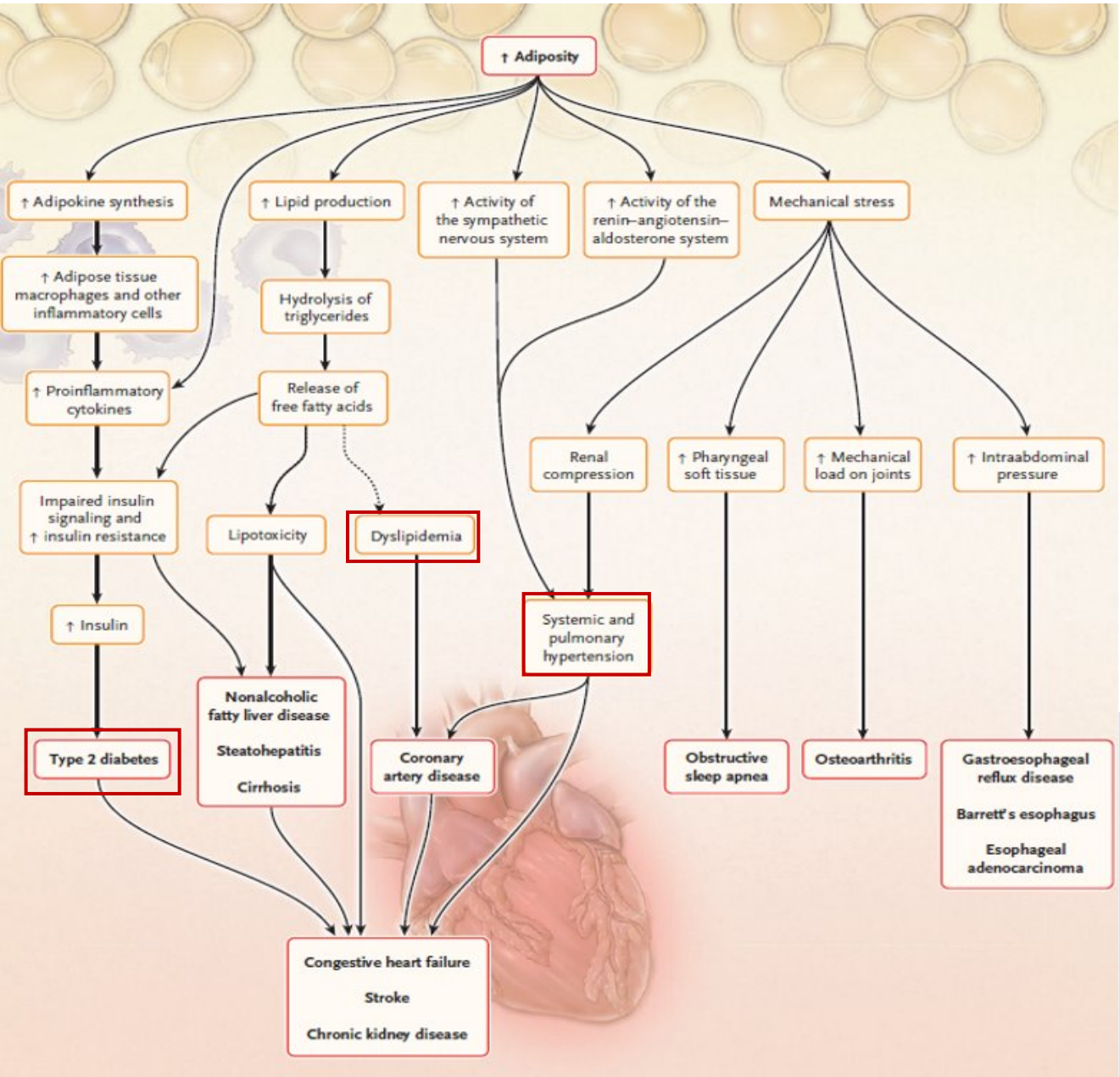
Thromboembolism

- Deep vein thrombosis
- Pulmonary embolism

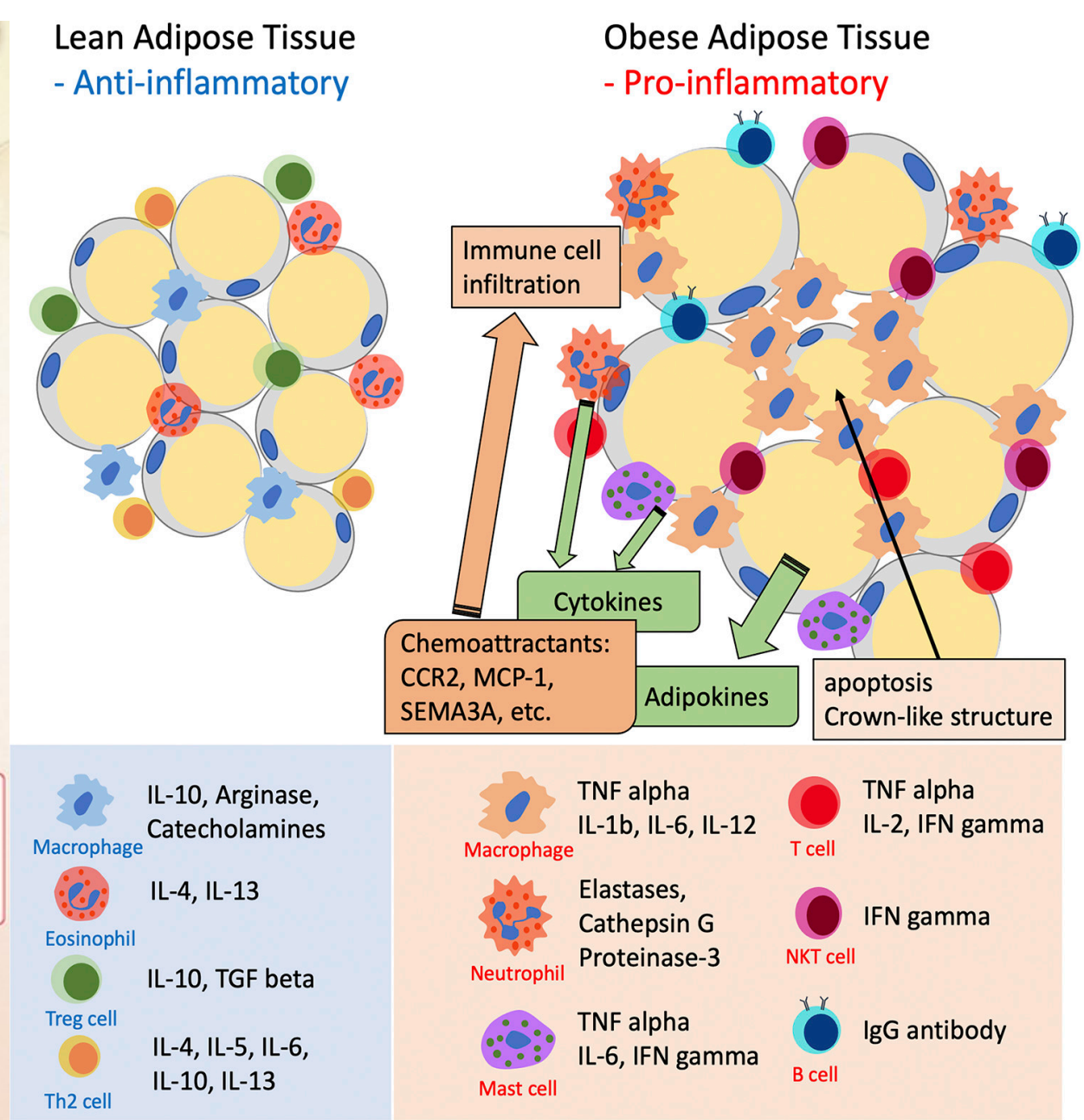
Valvular disease

- Aortic valve stenosis

ESC

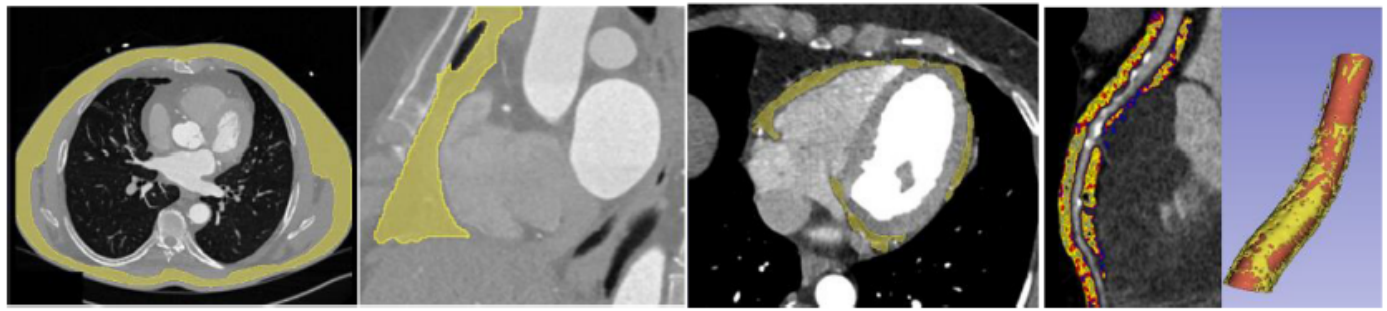


N Engl J Med 2017;376:254-66.



Am J Physiol Cell Physiol 320: C375–C391, 2021

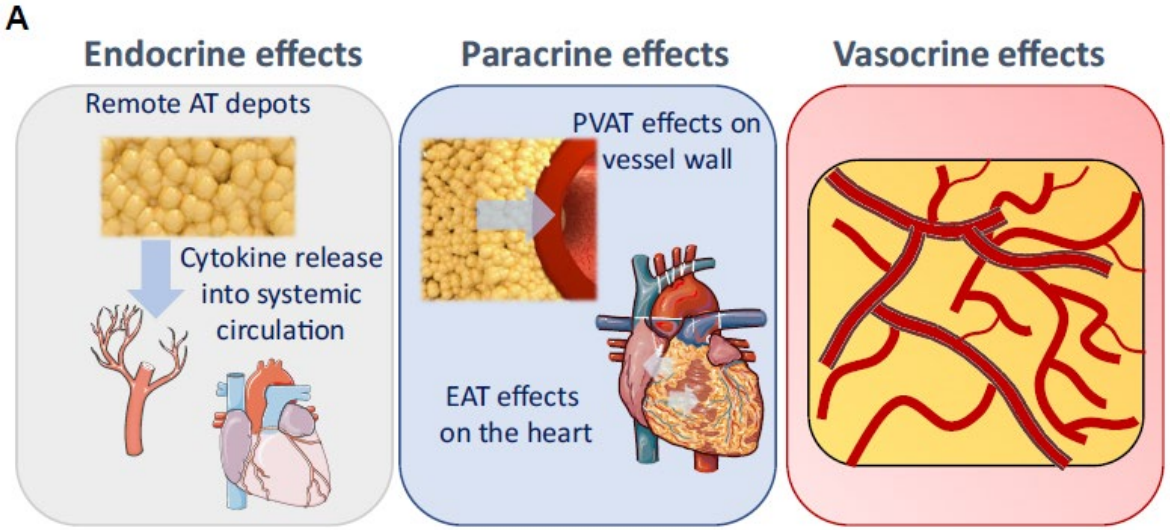
Table 2 Morphological and functional differences between adipose tissue depots in the chest



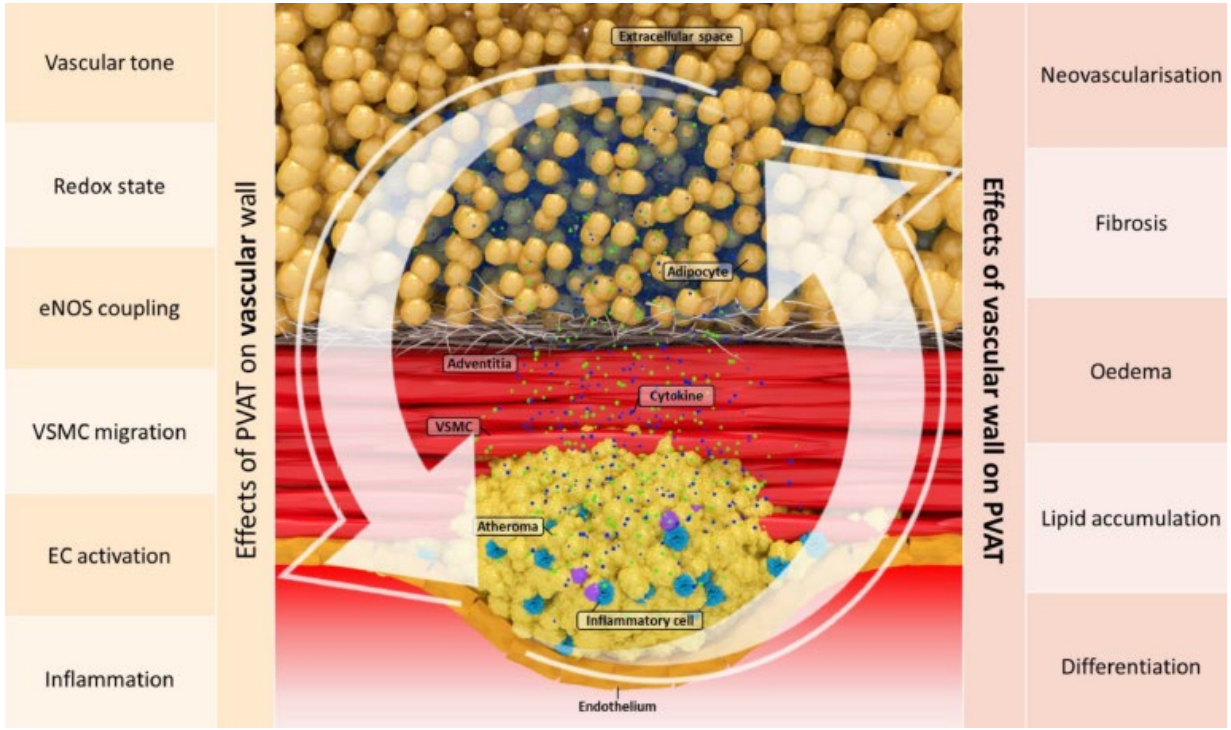
	Subcutaneous adipose tissue (SAT)	Pericardial adipose tissue (PAT)	Epicardial adipose tissue (EAT)	Perivascular adipose tissue (PVAT)
Relation with sex	More in females	Abdominal obesity in males	No difference	No difference
Relation with age	Less with age	Increasing with age	Increasing with age	Unclear
Adipocyte size	Large	Small	Comparable to PAT	Gradient in adipocyte size (smaller closer to the vascular wall)
Adipocyte differentiation status	Well differentiated	Poorly differentiated	Comparable to PAT	Dependent on vascular biology
Vascular-stromal cell content	Less rich vs. VAT	Rich vasculature, high immune-cell content	Comparable to PAT	Dependent on vascular biology
Biological profile	Less metabolically active, thermogenic potential (beiging)	High metabolic activity, inflammatory profile, lipolytic potential	High metabolic activity, inflammatory profile, lipolytic potential	High secretory profile with non-adipocytes (pre-adipocytes and inflammatory cells) driving its secretome
Association with metabolic status	Neutral/protective	Strong, negatively associated with (IR)—biology driven by systemic stimuli	Strong (less than PAT)—biology largely driven by myocardial signals	Less than EAT—biology largely driven by vascular signals
Association with cardiovascular risk	Neutral	Strong	Strong	Strong

Perivascular Adipose Tissue and Pathogenesis of ASCVD

Sistemic Level



Perivascular Level



European Heart Journal (2023) 44, 3827–3844

Prediabetes is associated with elevated risk of clinical outcomes even without progression to diabetes

Baseline characteristic	No prediabetes (HbA_{1c} <39 mmol/l [<5.7%] and FG <5.6 mmol/l)	Prediabetes (HbA_{1c} 39–47 mmol/mol [5.7–6.4%] or FG 5.6–6.9 mmol/l)
N	4142	6168
FG, mmol/l	5.2 (0.3)	5.9 (0.4)
HbA_{1c}, mmol/mol	33.8 (3.0)	37.0 (4.1)
HbA_{1c}, %	5.2 (0.3)	5.5 (0.4)
Age, years**	56.0 (5.6)	57.1 (5.7)
Female sex**	66.3	49.4
White race**	85.5	77.3
BMI, kg/m^2**	25.9 (4.4)	28.1 (5.1)
BMI category**		
<25 kg/m^2	46.9	27.3
25–29.9 kg/m^2	37.5	43.4
≥30 kg/m^2	15.6	29.3
Cigarette smoking status**		
Current	20.2	23.2
Former	35.6	39.1
Never	44.2	37.8
Alcohol consumption**		
Current	61.9	59.8
Former	16.3	19.6
Never	21.8	20.5
Physical activity level**		
Poor (<75 min/week)	31.3	36.3
Intermediate (75 to <150 min/week)	27.7	23.9
Recommended (≥150 min/week)	41.0	39.8
Total cholesterol, mmol/l**	5.36 (0.97)	5.43 (0.99)
HDL-cholesterol, mmol/l**	1.41 (0.45)	1.25 (0.42)
Lipid-lowering medication use*	4.7	6.1
Hypertension**	22.4	33.5

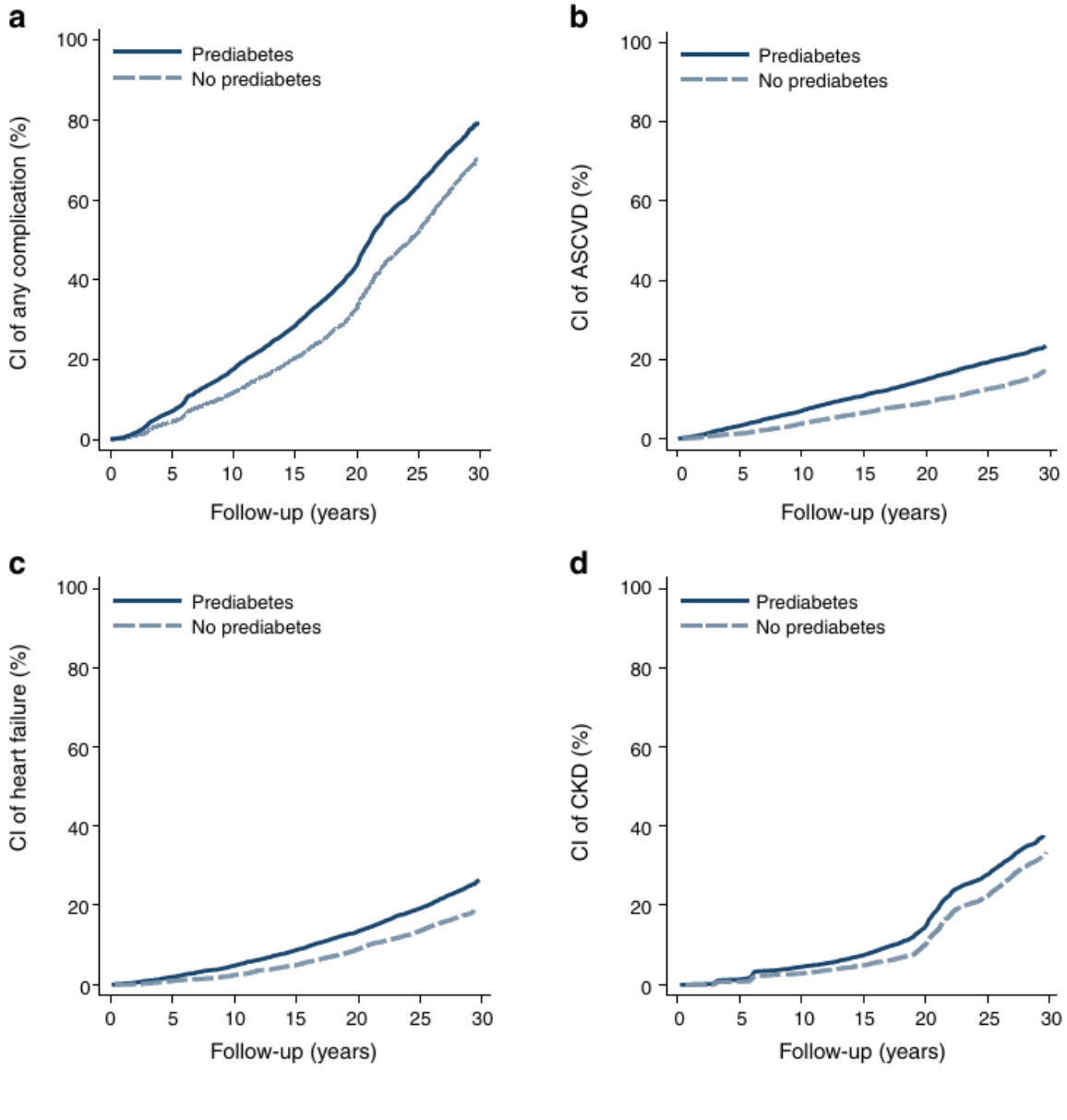
Data are shown as mean (SD) for continuous variables or as percentage for categorical variables

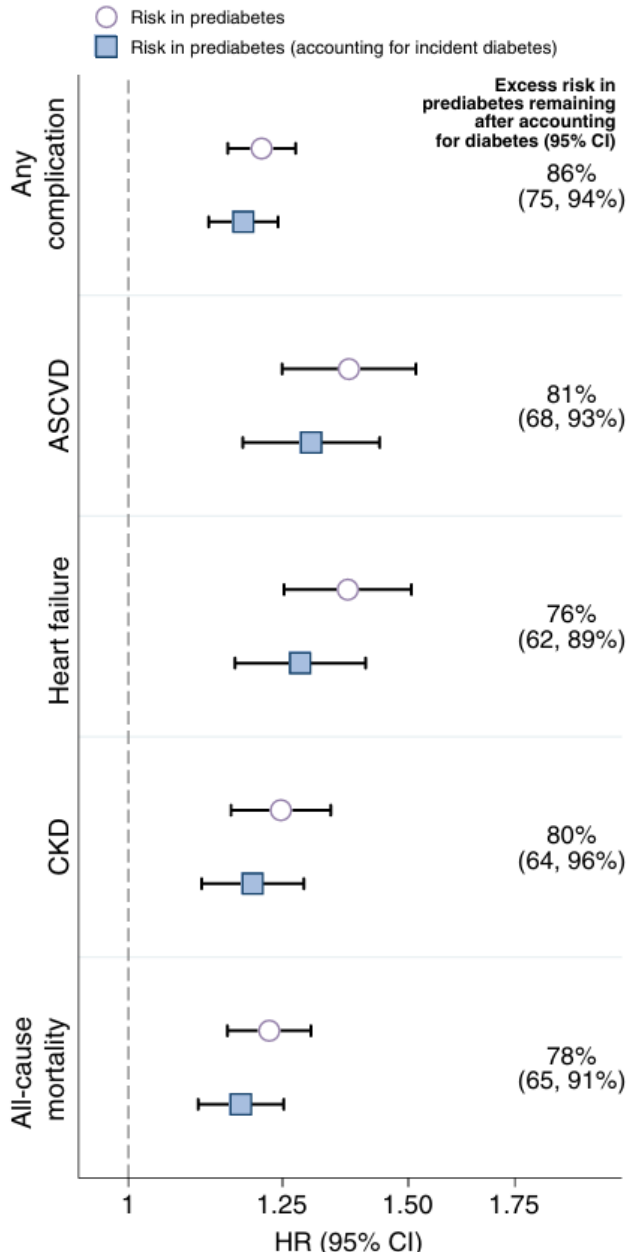
*$p<0.01$ and **$p<0.001$ (two-sample t test for continuous variables and Pearson's χ^2 test for categorical variables)

- **10,310 participants** from the Atherosclerosis Risk in Communities (ARIC) Study (aged 46–70 years, ~55% women, ~20% Black adults) without diabetes at baseline (1990–1992),
- Cox regression to characterise age- and sex-adjusted associations of prediabetes with ~30 year incidence of complications before and after accounting for intervening incidence of diabetes,
- **Outcomes included** atherosclerotic CVD (ASCVD), heart failure, chronic kidney disease (CKD) and all-cause mortality
- calculated the excess risk of complications in prediabetes remaining after accounting for progression to diabetes

Mary M Rooney, *Diabetologia* (2024) 14 Nov Online

Prediabetes is associated with elevated risk of clinical outcomes even without progression to diabetes





HRs (95% CIs) and per cent excess ~30 year risk of complications (composite and individual) in prediabetes (HbA1c 39–47 mmol/mol [5.7–6.4%] or FG 5.6–6.9 mmol/l) remaining after allowing for progression to diabetes in the ARIC study (*N*=10,310; 1990–2020).

Mary M Rooney, *Diabetologia* (2024) 14 Nov Online

0021-972X/07/$15.00/0
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doi: 10.1210/jc.2006-0944

CONTROVERSY IN CLINICAL ENDOCRINOLOGY

Metabolic Syndrome: A Solution in Search of a Problem

Ele Ferrannini

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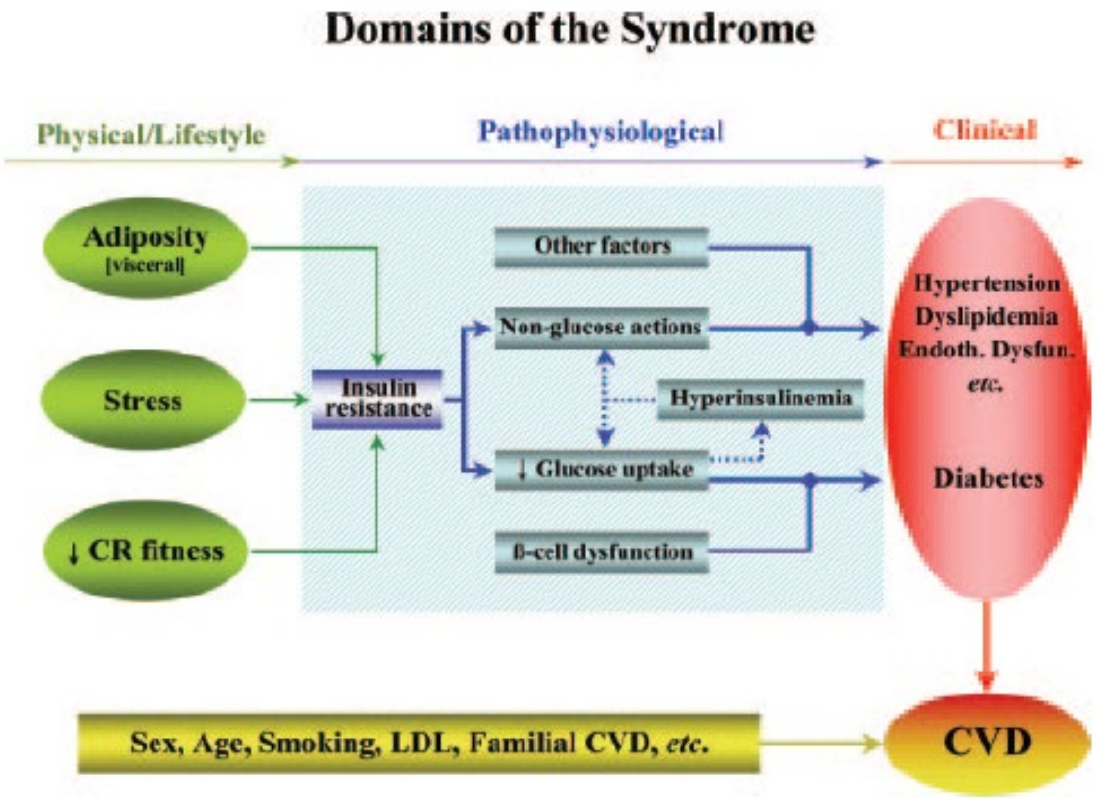
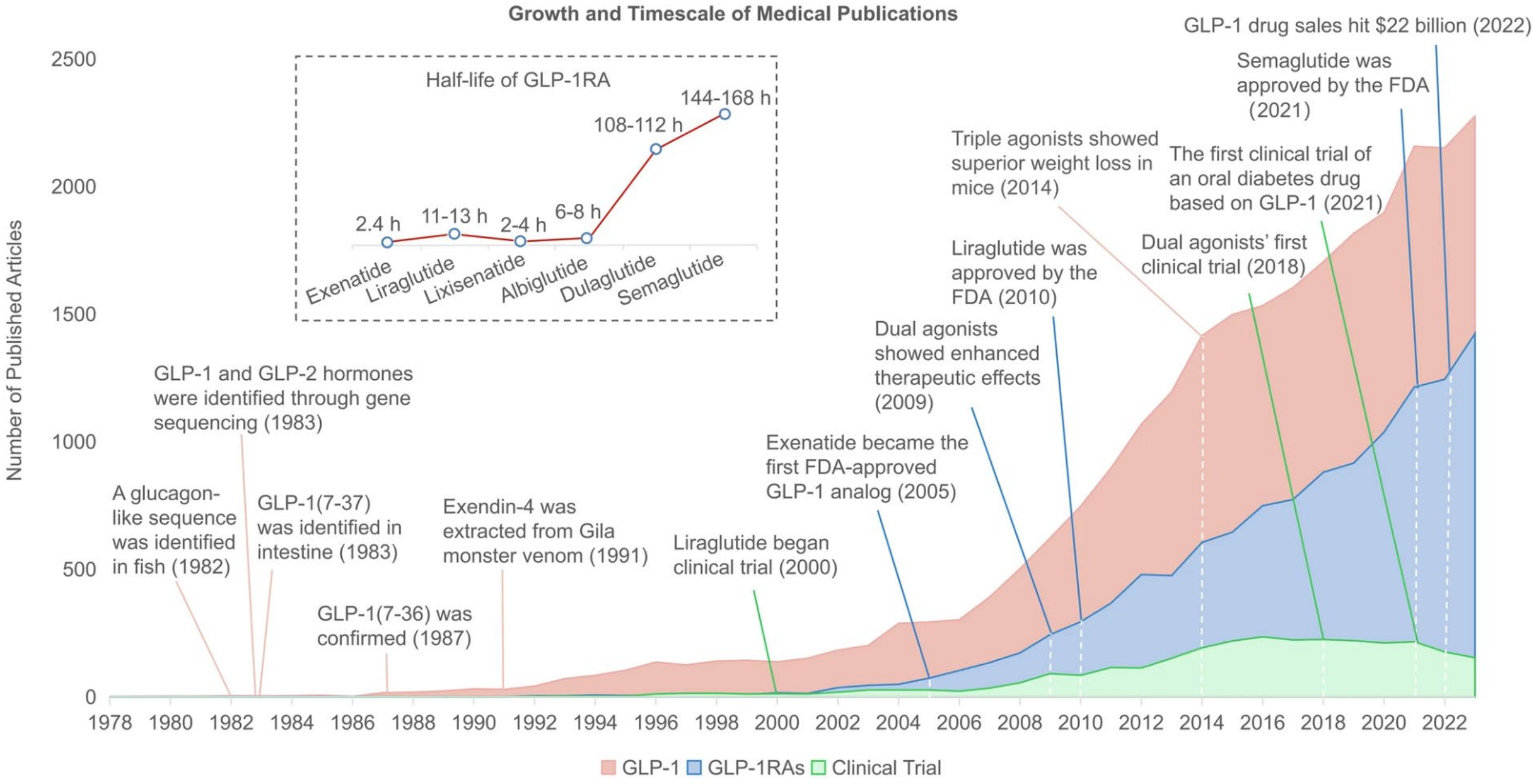
The other day I saw Mrs. R. G., admitted for shortness of breath and fatigue. "A lady of 59," recited the young intern, "has had type 2 diabetes for 15 yr, treated with metformin plus glibenclamide, and hypertension, well-controlled on an angiotensin-converting enzyme inhibitor-thiazide combination. Her body mass index is 30.5 kg/m^2, serum triglycerides are 2.2 mmol/liter and high-density lipoprotein cholesterol is 0.99 mmol/liter." Then, with a triumphant glance at me, "metabolic syndrome," she stated. A clear message, I ever, it is crucial to emphasize that just as insulin resistan alone is insufficient to alter glucose tolerance—for whi some degree of β-cell dysfunction is required—insulin r sistance/hyperinsulinemia is neither strictly necessary n sufficient to alter lipid metabolism, blood pressure, or va cular function. Each of these homeostatic systems is und multifactorial control, and defects in one or more steps of effector pathway (other factors in Fig. 1) are necessary drive the system out of control. Also, each of these systen



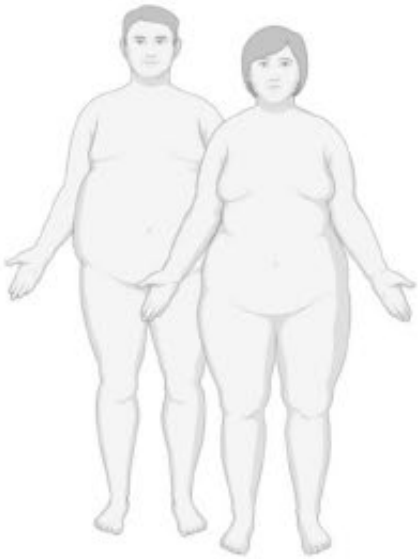
Once a general risk engine capable of capturing cardiometabolic risk with high specificity and accuracy is compiled and validated in multiple datasets from different populations, it could be reduced to a clinical algorithm by peeling off complex or costly measures in a statistically controlled fashion (26). Whereas not yet a disease, a risk syndrome identified by this tool would definitely serve the purpose of designing preventive measures. In addition, it would fertilize pharmaceutical research, as new drugs may target the cluster rather than one or the other of its components. Typically, insulin sensitizers or weight-reducing agents may hit nodal points of the cluster (insulin resistance and ectopic fat, respectively), thereby improving multiple abnormalities. The clinical algorithm could prove useful to monitor efficacy and time course of new treatments.

The point is, the task still waits to be completed. Should it succeed, we will have a name for it: metabolic syndrome.

Eleuterio Ferranini JCEM. 2007


Growth and Timescale of Medical Publications
Number of Published Articles
2500
2000
1500
1000
500
0
1978
1980
1982
1984
1986
1988
1990
1992
1994
1996
1998
2000
2002
2004
2006
2008
2010
2012
2014
2016
2018
2020
2022
Half-life of GLP-1RA
2.4 h
11-13 h
2-4 h
6-8 h
108-112 h
144-168 h
Exenatide
Liraglutide
Lixisenatide
Albiglutide
Dulaglutide
Semaglutide
GLP-1 and GLP-2 hormones were identified through gene sequencing (1983)
A glucagon-like sequence was identified in fish (1982)
GLP-1(7-37) was identified in intestine (1983)
GLP-1(7-36) was confirmed (1987)
Exendin-4 was extracted from Gila monster venom (1991)
Liraglutide began clinical trial (2000)
Exenatide became the first FDA-approved GLP-1 analog (2005)
Dual agonists showed enhanced therapeutic effects (2009)
Liraglutide was approved by the FDA (2010)
Triple agonists showed superior weight loss in mice (2014)
Dual agonists' first clinical trial (2018)
The first clinical trial of an oral diabetes drug based on GLP-1 (2021)
Semaglutide was approved by the FDA (2021)
GLP-1 drug sales hit $22 billion (2022)
GLP-1
GLP-1RAs
Clinical Trial

Incretin Based Therapy: Global Effects on Health



ASCVD
11-13,18,20-24,26,28,30-33,35-37 ↓ Triglycerides, ↓ total and LDL-c
11-14,16-18,20-24,26-28,30-33,35-37 ↓ SBP, ↓ DBP
11-14,16-1820-24,26-28,30-33,35-37, 39-60 ↓ BW
72 ↓ MACE

CKD
↓ UACR[67]
↔[67,69]/↓ [70] eGFR decline

Most incretin-based therapies
Liraglutide
Semaglutide
Dulaglutide
Tirzepatide

HF
77 ↑ KCCQ
77 ↑ 6 minutes walking test
72 ↓ hHF and CV death

OSA
↓ AHI[16, 38], ↓ hypoxic burden[38]
↑ sleep quality[38]

MASLD
39,79 ↓ Liver fat
39,80 ↓ non-invasive fibrosis markers
39,80 ↓ histological MASH markers
81 ↔/39 ↓ histological fibrosis markers

GERD
↑ Possible AE[94]
↓ [95]

T2D
61 ↓ HOMA-IR, 79 ↓ VAT
13,14,61-63 ↓ incidence of prediabetes and T2D
13,30,35,36,56,59,61 ↑ chances of prediabetes reversal

PCOS, Infertility
↓ Free androgen index, ↑ SHBG[82]
↑ Menstrual frequency[82]
↑ Pregnancy rate[85]

KOA
91 ↓ Inflammation (IL-6, macrophages M1)
93 ↓ Pain

ED, Infertility
↑ NO synthesis → ↑ Endothelial function[86]
↓ Oxidative stress[86]
↓ Smooth muscle cell dysfunction[86]
↓ Incidence of ED[87]

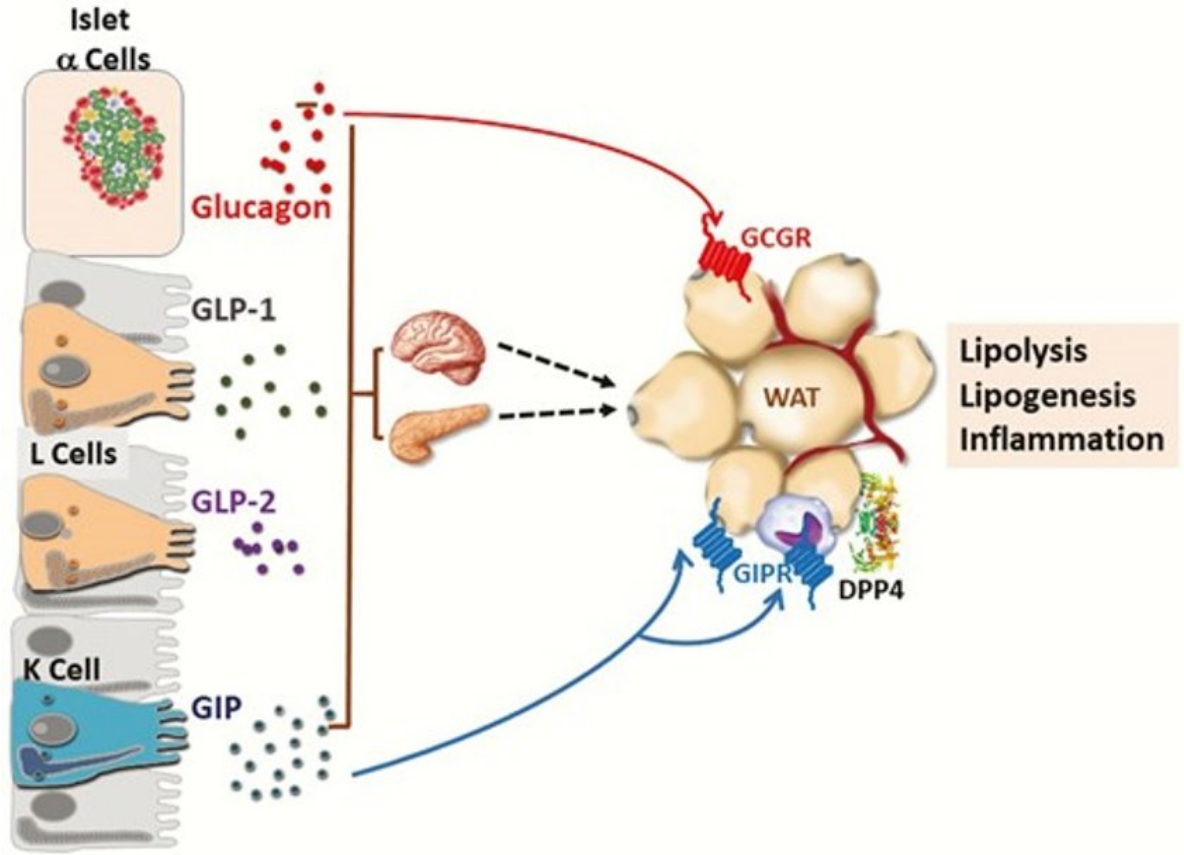
Irene Caruso: *npj Metab Health Dis* **2**, 31 (2024).

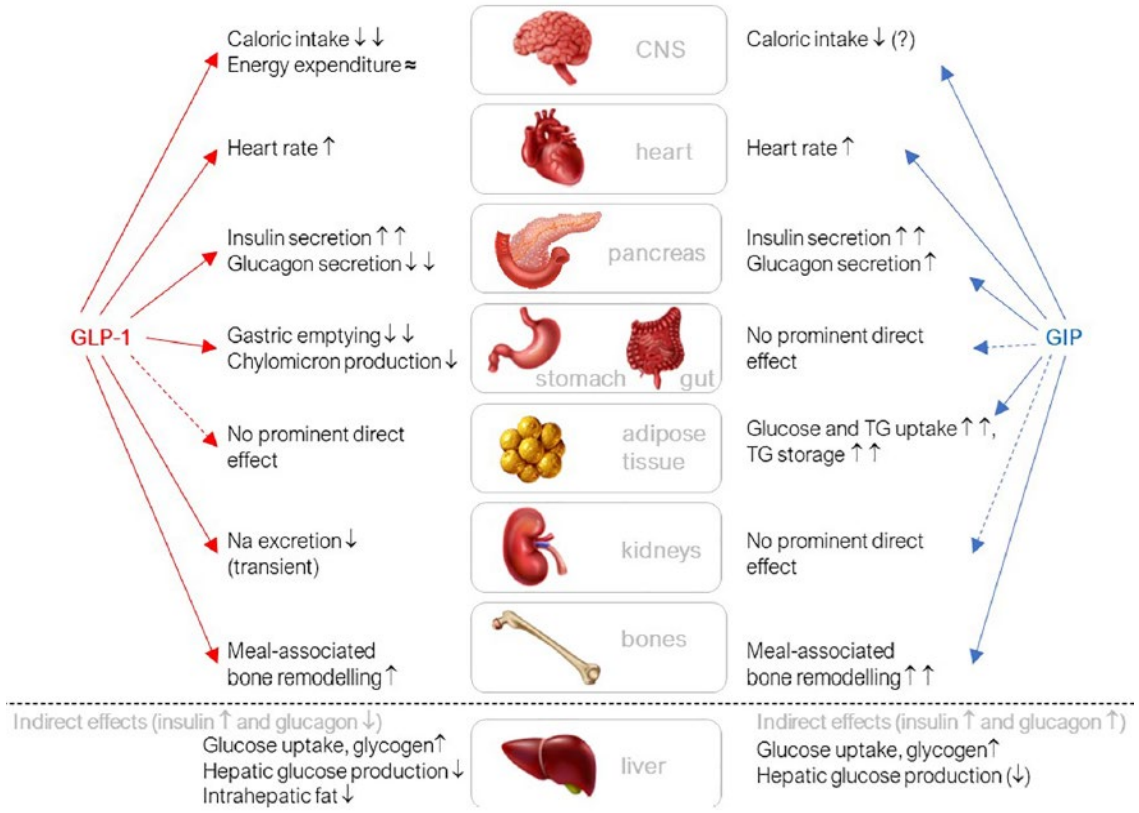
Incretin Based Therapies: One Drug for Met Syndrome?

GLP1 Receptor Agonists

GLP1/Glucagon Agonists

GLP1/GIP Agonists

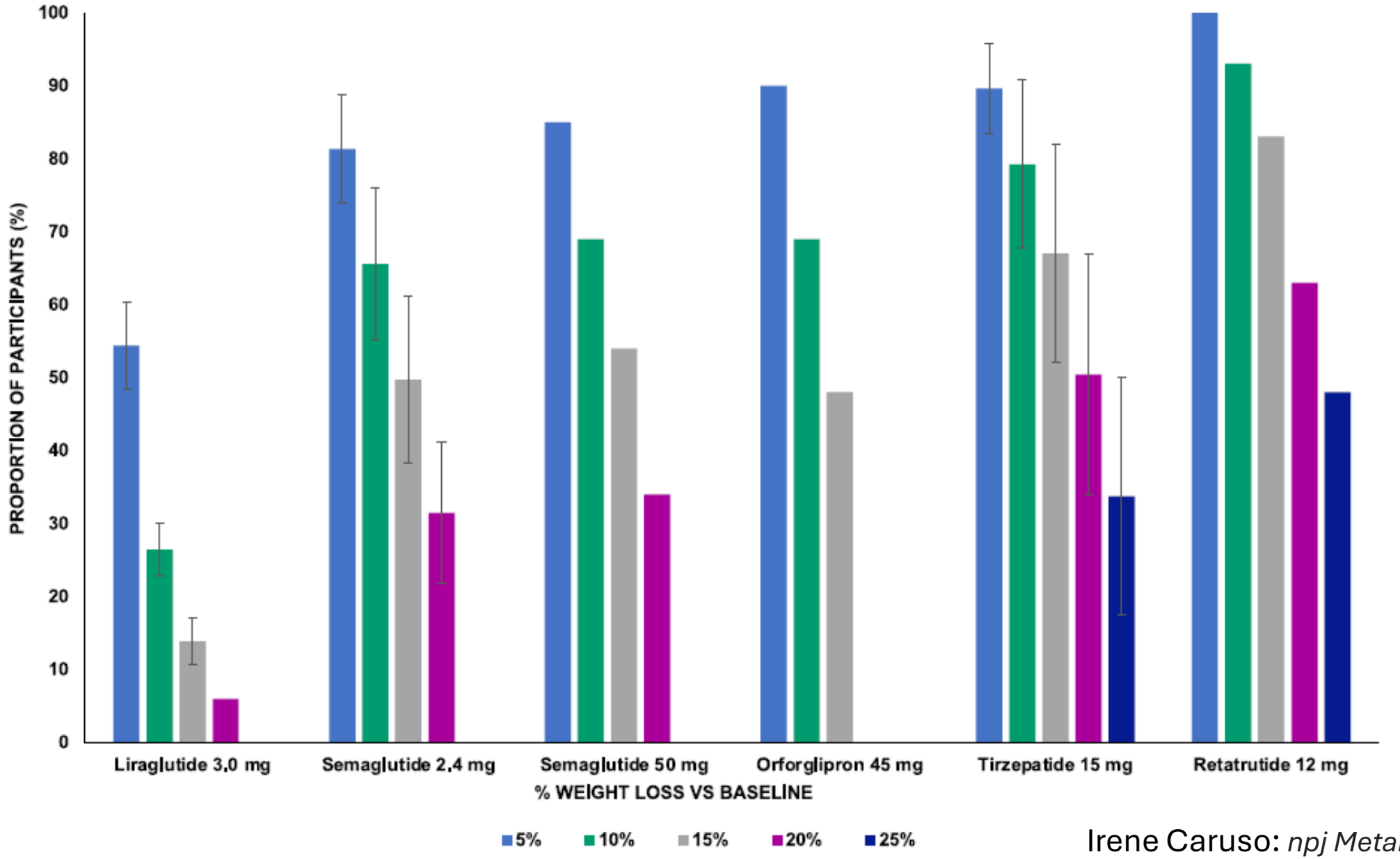




Endocrinology. 2020 Jan 1;161(1)

Diabetes Obes Metab. 2021;23(Suppl. 3):5–29.

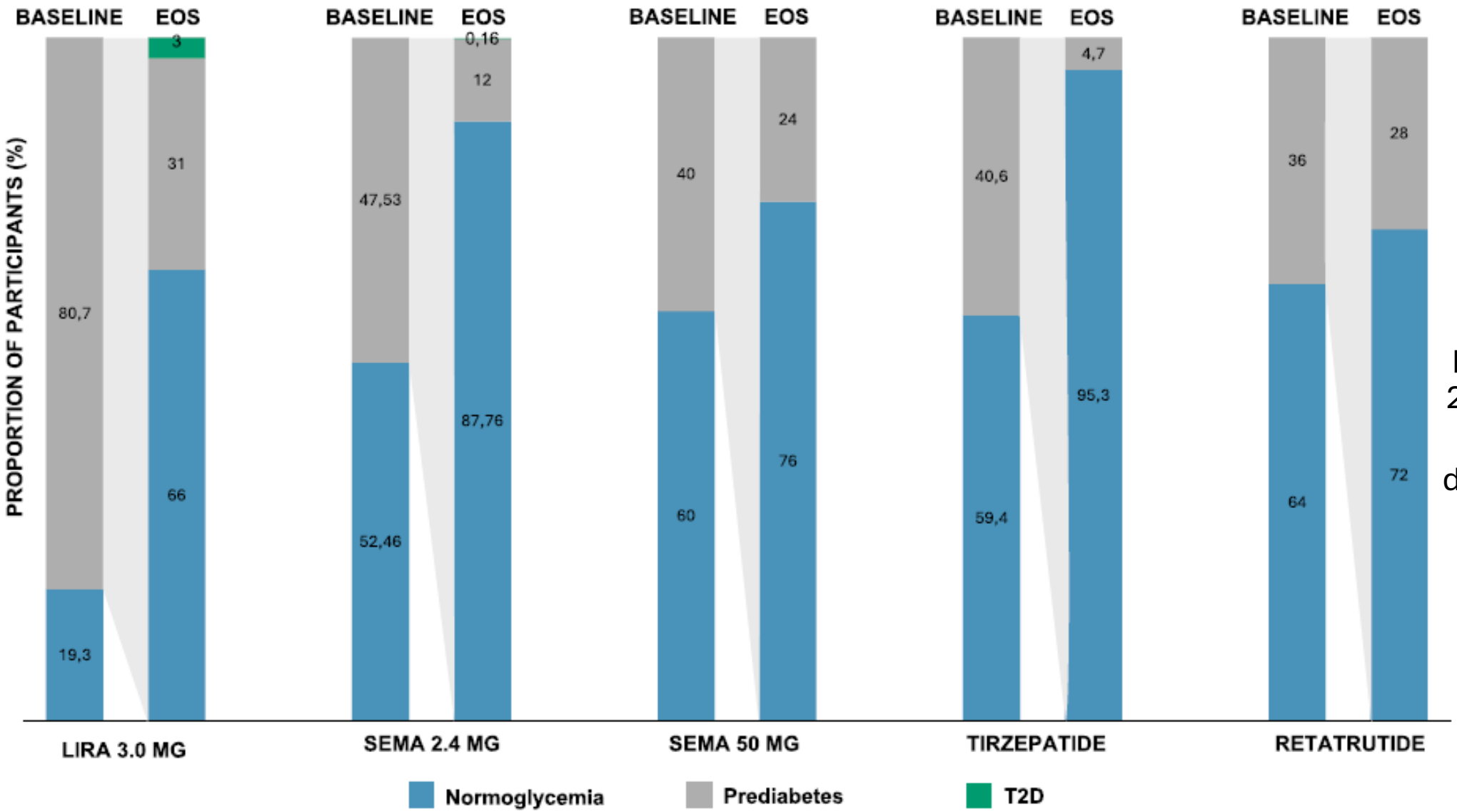
Incretin Based Therapy: Effects on Body Weight



Proportion of participants with at least 5%, 10%, 15%, 20%, 25% body weight loss across dedicated randomized controlled trials with incretin-based anti-obesity medication

Irene Caruso: *npj Metab Health Dis* **2**, 31 (2024).

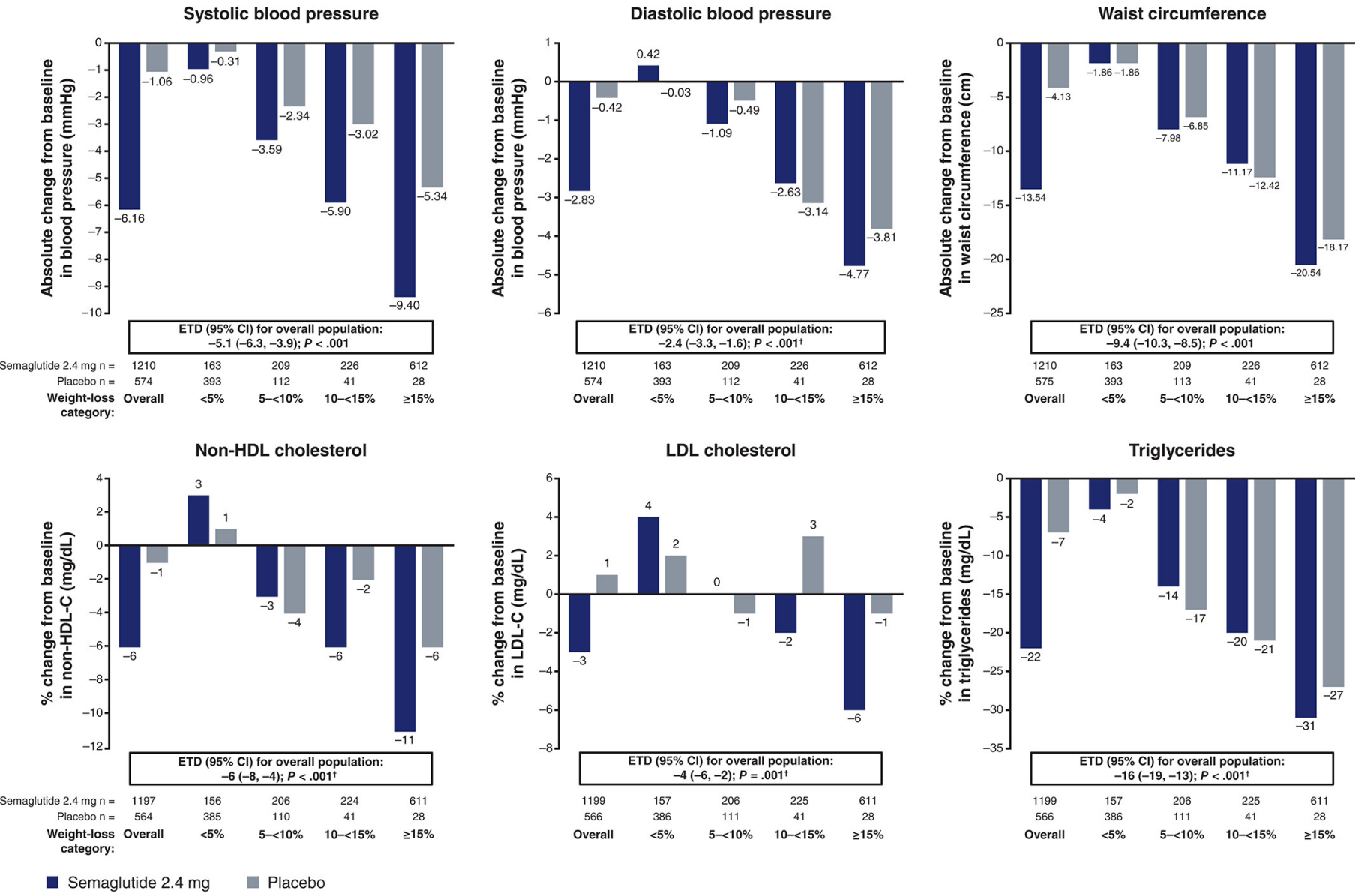
Incretin Based Therapy: Effects on Glucose Metabolism



Proportion of participants with normoglycemia, prediabetes and type 2 diabetes at baseline and end of study in dedicated randomized controlled trials with incretin-based anti-obesity medications

Irene Caruso: *npj Metab Health Dis* **2**, 31 (2024).

Semaglutide in People without Diabetes: effects on CV risk Factors



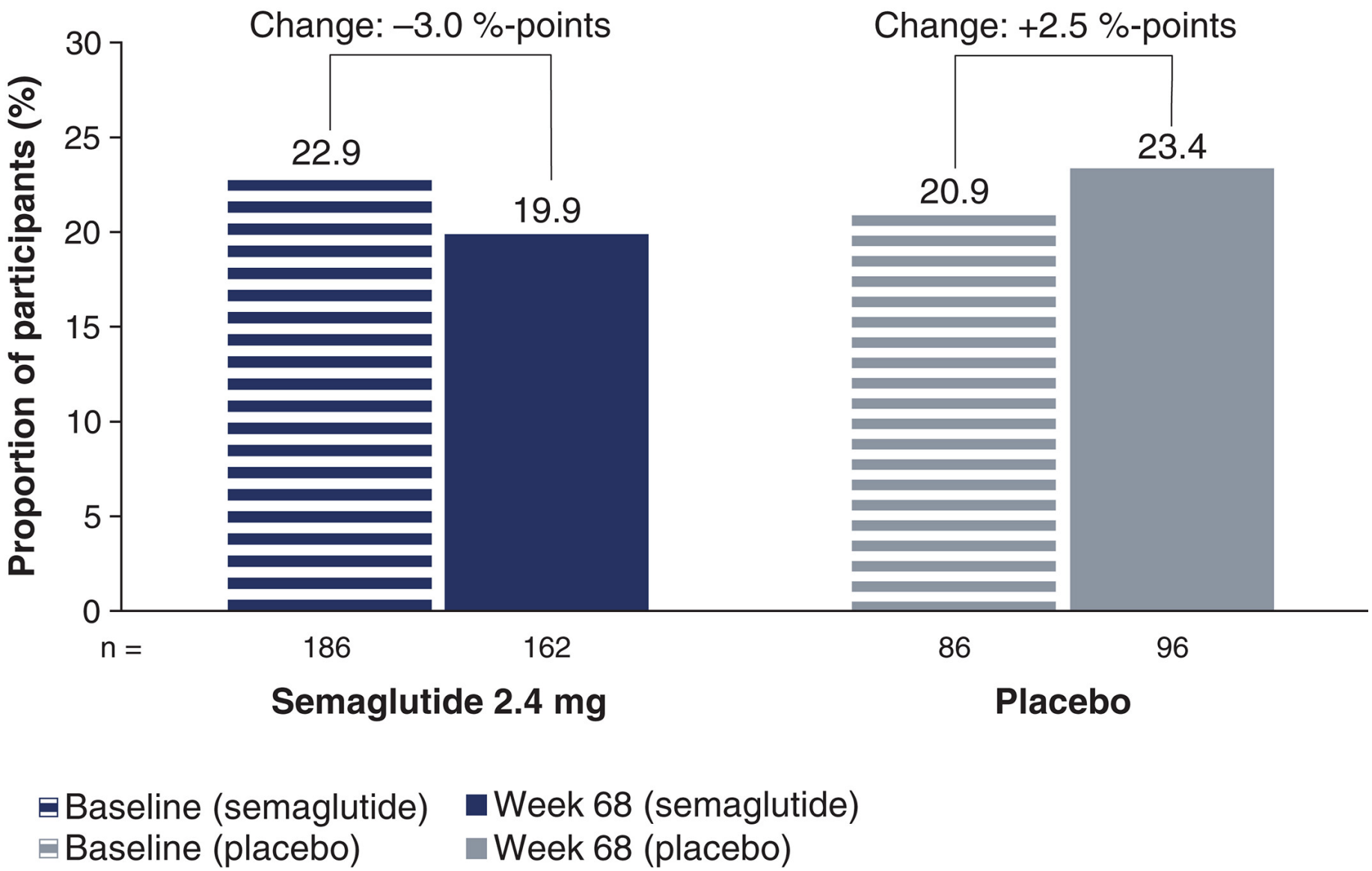
STEP 1 and 4 were phase III, 68-week, placebo-controlled trials of once-weekly **semaglutide 2.4 mg** combined with lifestyle intervention;

STEP 4 had a 20-week semaglutide run-in and 48-week randomized withdrawal period.

Participants had a body mass index ≥30 kg/m2 or ≥27 kg/m2 with one or more weight-related comorbidity, without diabetes.

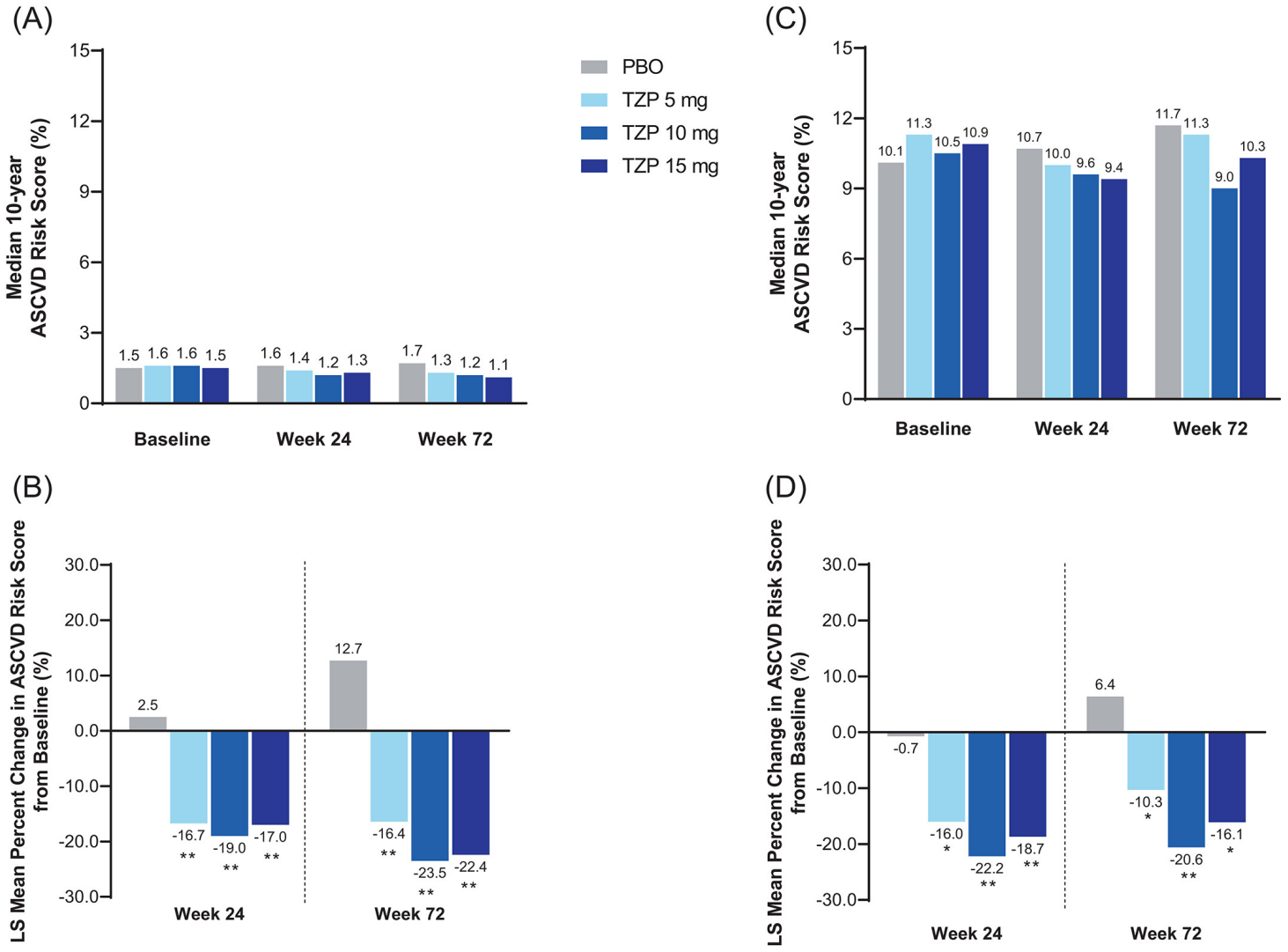
Diabetes Obes Metab. 2023 Feb;25(2):468-478.

Semaglutide in People without Diabetes: effects on ASCVD Score



Proportion of participants at intermediate-high ASCVD risk at baseline and week 68 in STEP 1. Observed in-trial data for participants aged 40-79 years with available data at baseline and week 68. Among 882 participants in the semaglutide group and 472 participants in the placebo group who were aged 40-79 years, 813 (92.2%) and 411 (87.1%), respectively, had ASCVD scores at baseline and week 68 and so were included in the analysis. n, number of intermediate-high-risk participants.

Tirzepatide in People without Diabetes: effects on CV risk Factors



SURMOUNT-1, a phase 3 trial, evaluated the efficacy and safety of tirzepatide in adults with body mass index ≥30 or ≥27 kg/m2 and at least one weight-related complication, excluding diabetes.

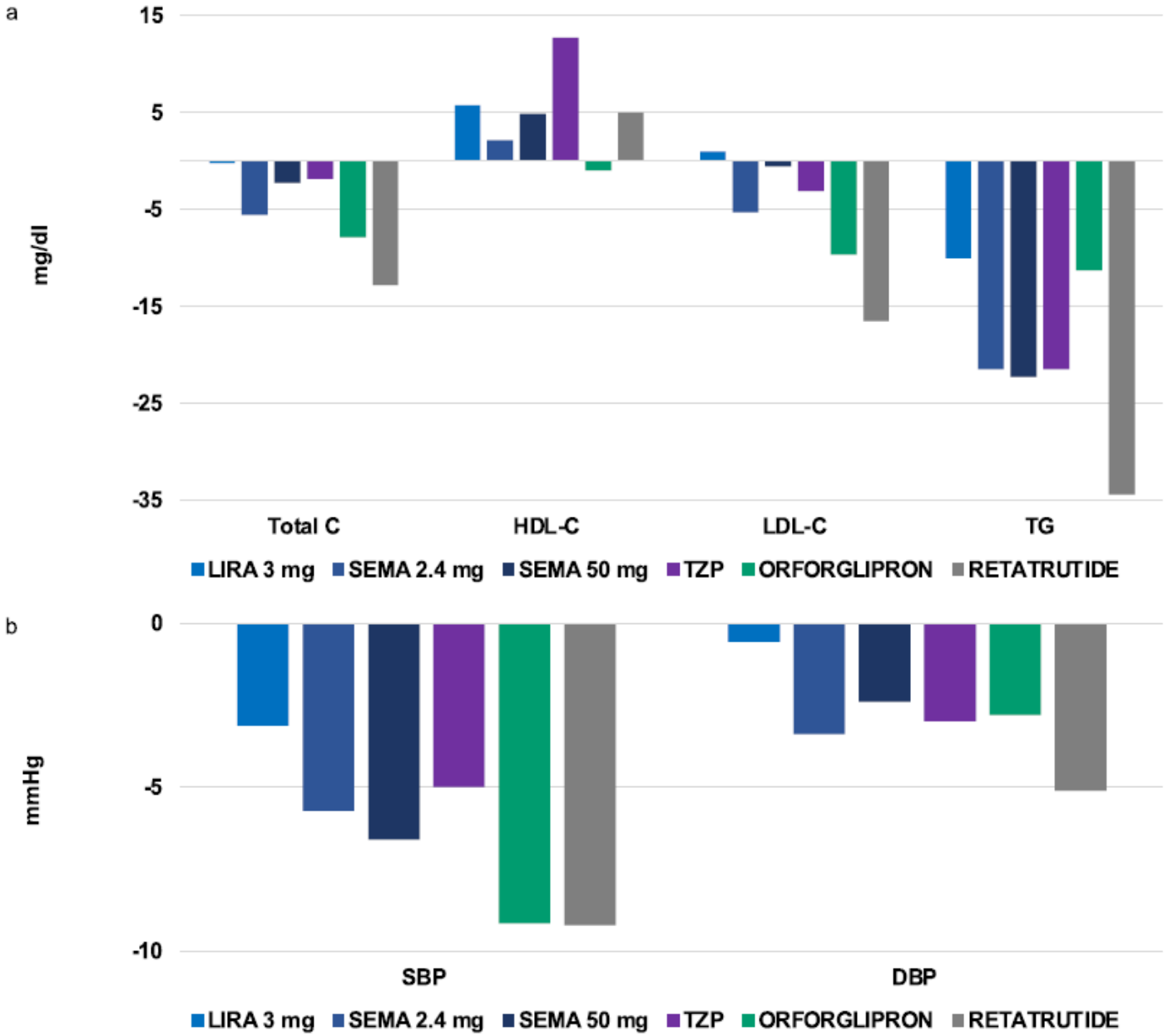
Participants were randomly assigned to tirzepatide (5/10/15 mg) or placebo.

Changes from baseline in cardiometabolic variables were assessed.

The predicted 10-year ASCVD risk scores were calculate.

Diabetes Obes Metab. 2024;26(1):319–28

Incretin Based Therapy: Effects on CV Risk Factors

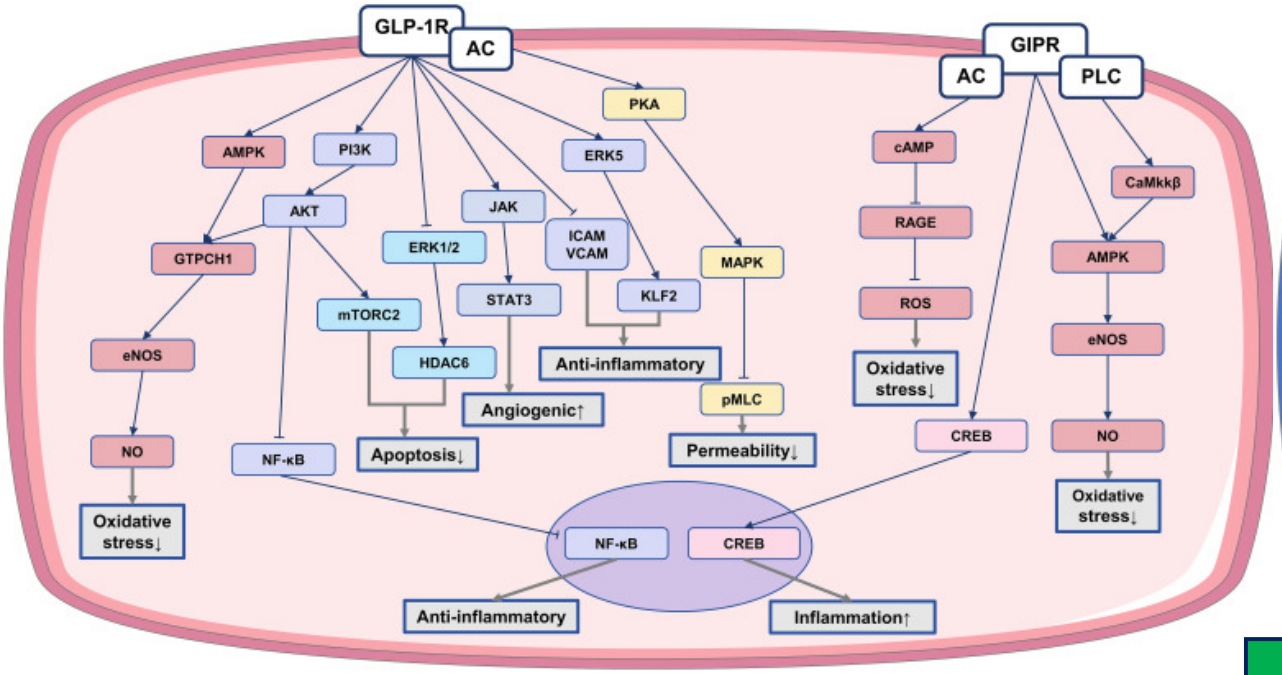


Depict the effect of incretin-based anti-obesity medications on lipid profile and blood pressure, respectively.

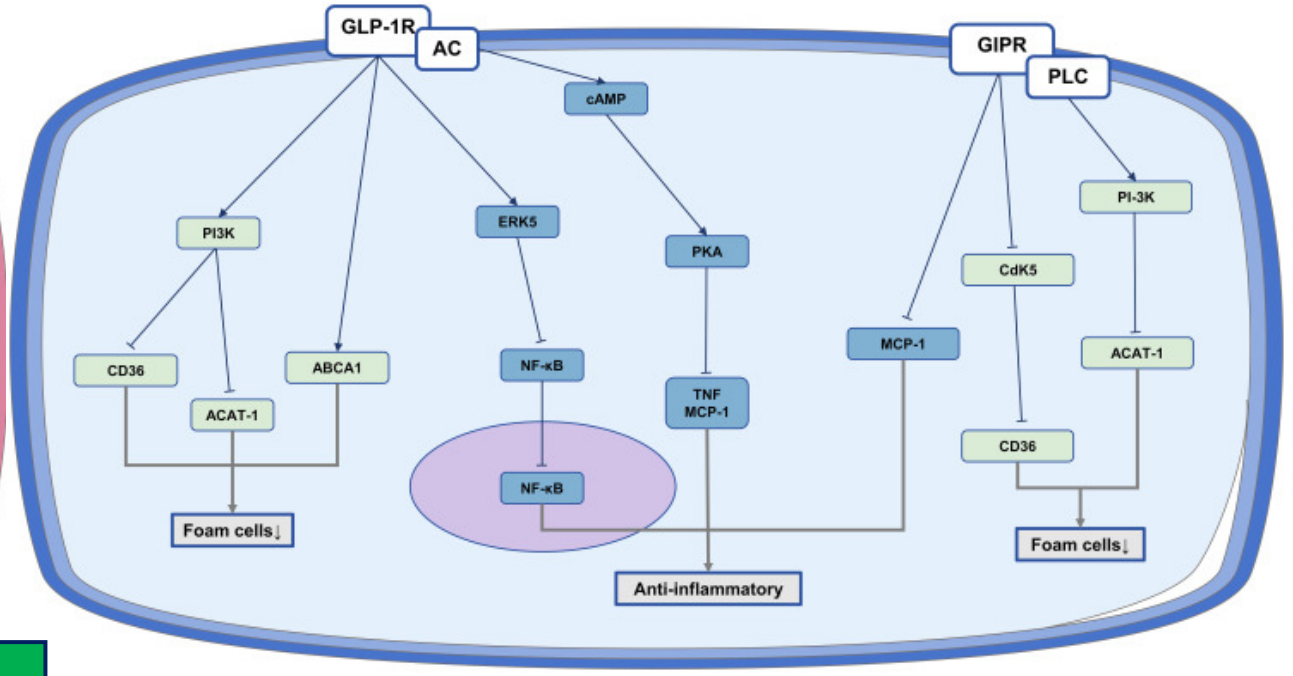
C cholesterol, DBP diastolic blood pressure, HDL-C high-density lipoprotein cholesterol, LDL-C low-density lipoprotein cholesterol, Lira liraglutide, SBP systolic blood pressure, Sema semaglutide, TG triglycerides, TZP tirzepatide.

Incretins effects on Vascular and Systemic Inflammation

Cellula Endoteliale



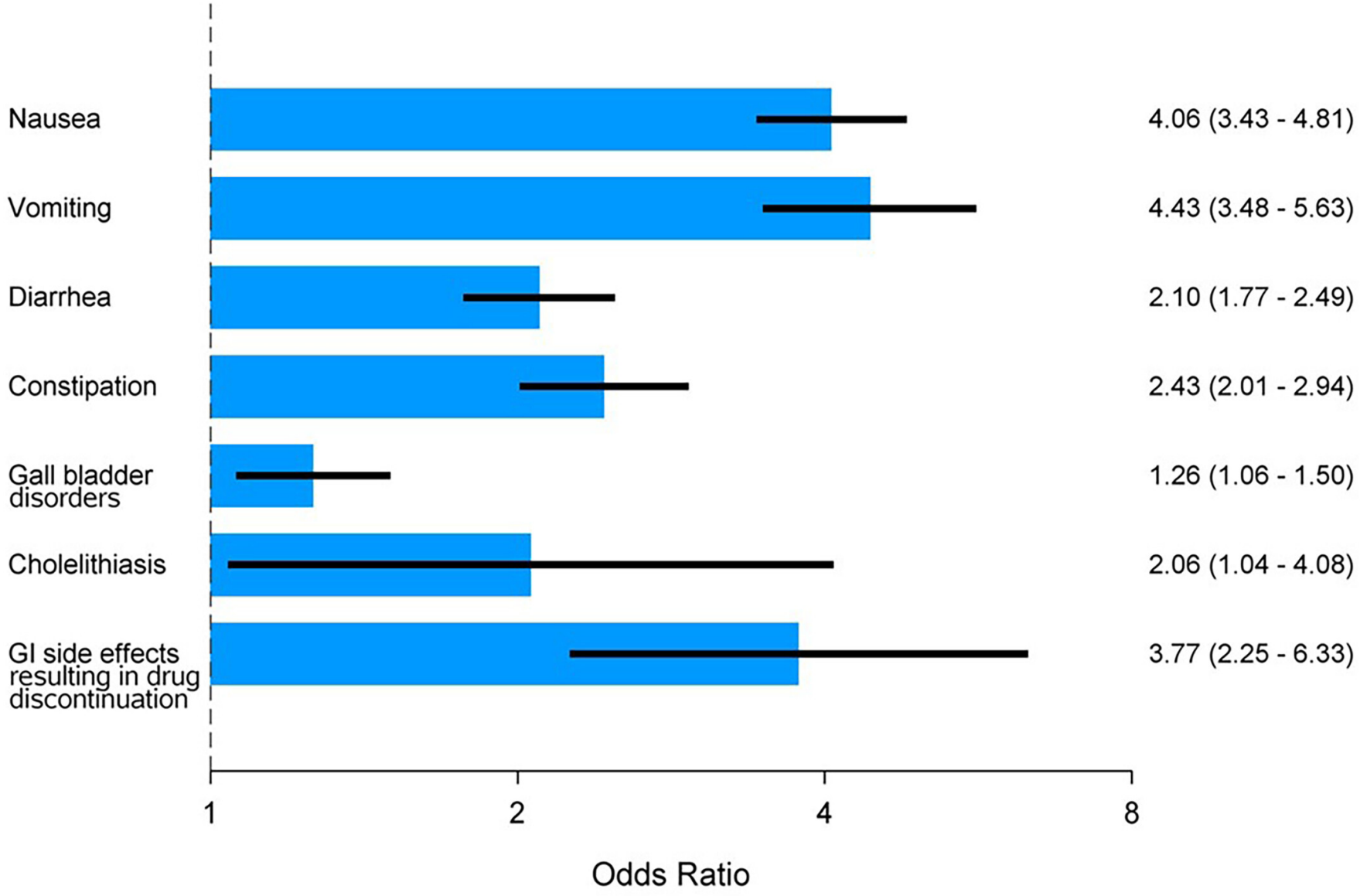
Monociti-Macrofagi



Riduzione Infiammazione della placca

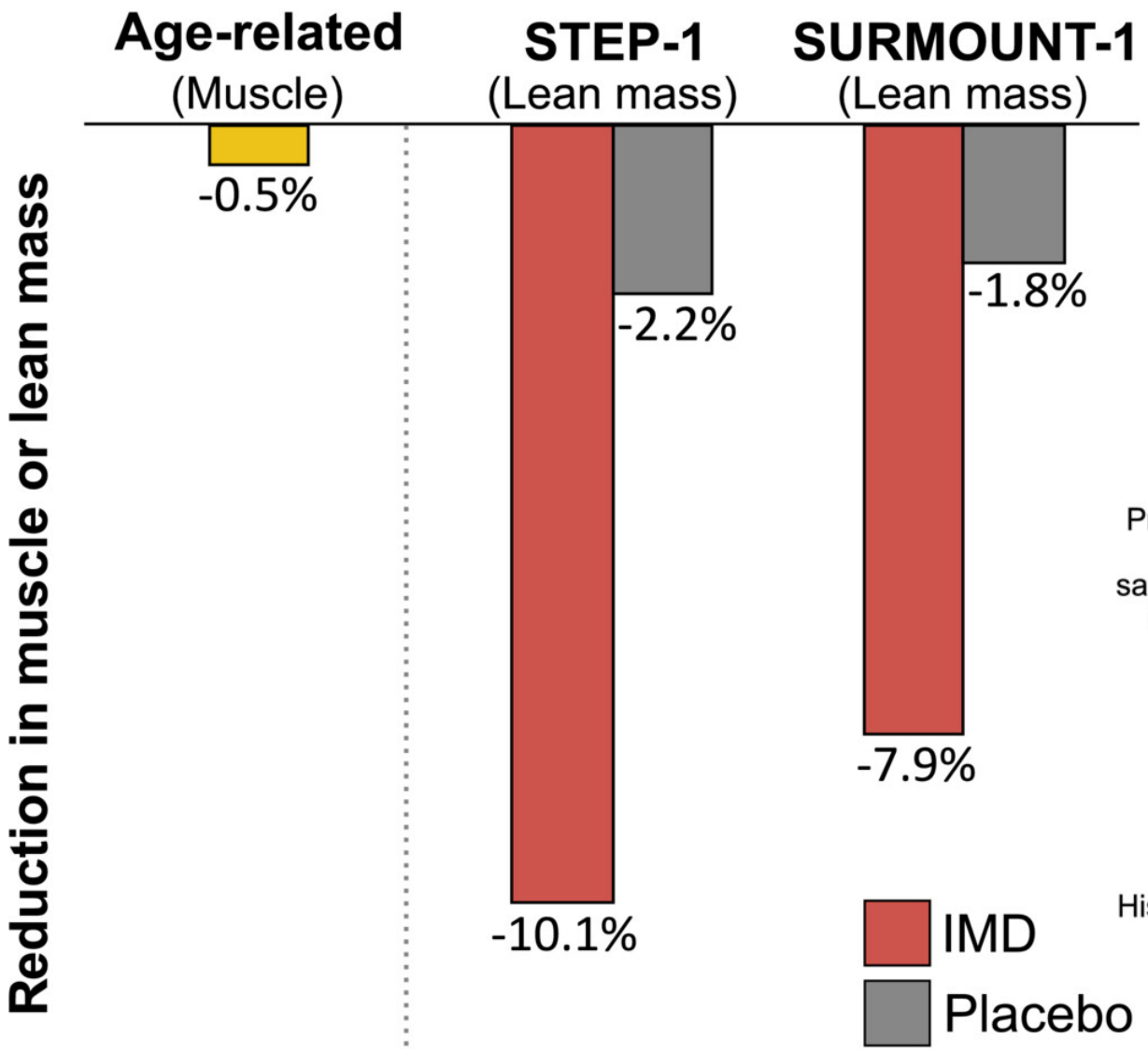
Front Endocrinol (Lausanne). 2024 Oct 18;15:1463547.

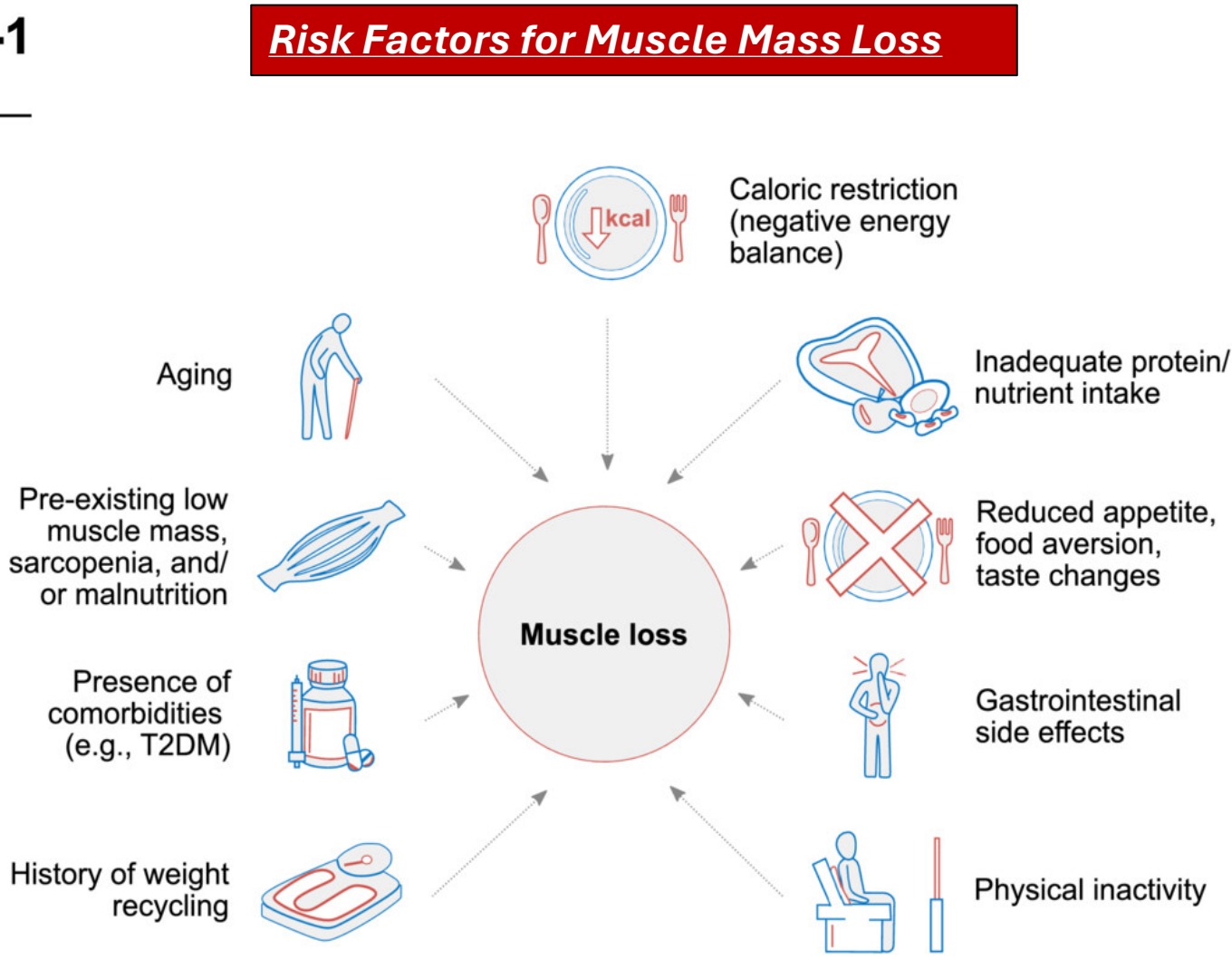
Semaglutide Side effects in People without Diabetes



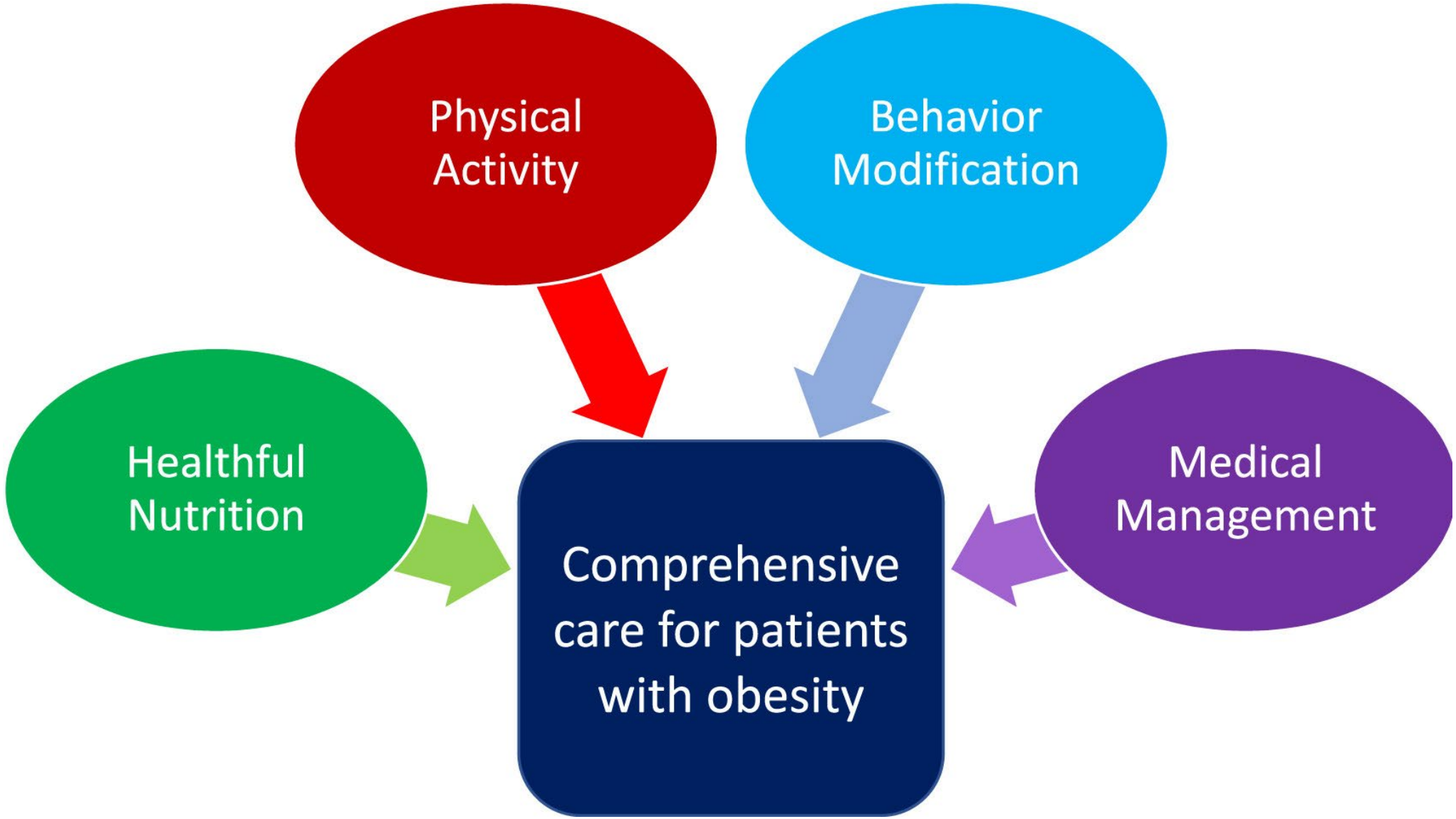
Obes Rev. 2024 Sep;25(9):e13792.

Consequences of Uncontrolled Weight Loss with IBT





Obes Rev. 2024 Sep 19:e13841


Physical Activity
Behavior Modification
Healthful Nutrition
Medical Management
Comprehensive care for patients with obesity

Grazie