Valutazione del rischio cardiovascolare nel prediabete

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Outline

- Prediabetes Definition and Epidemiology
- Prediabetes and Cardiovascular Disease
  - Dysglycemia, Inflammation, and Cardiovascular Disease
  - Causal Relationships between prediabetes and vascular complications
- Prevention or Treatment
- Conclusions

Prediabetes Definition

Prediabetes is an impaired state of glucose metabolism defined by elevated but not yet diabetic levels of fasting or 2-h glucose, or HbA1c.

American Diabetes Association (ADA) definitions are:

Impaired Fasting Glucose (IFG) = fasting glucose 100-126 mg/dL;

Impaired Glucose Tolerance (IGT) = 2-h glucose 140-200 mg/dL;

HbA1c = 39–46 mmol L−1 (or 5.7–6.4%).

The cooccurrence of IFG and IGT is termed “impaired glucose regulation”

Prediabetes Epidemiology

- ✓ The global prevalence of prediabetes in adults is 7.3% **(n = 352 million people),**
- ✓ In Europe, 4.6% (n = 36 million people) ,
  In the US, 33.9% (n = 84.1 million people)[1].
- ✓ In the short term, 5–10% annually will progress to full-blown type 2 diabetes (T2D); however, after five years, **about half will have developed T2D[2].**
- ✓ **Five years of a therapeutic window!** (T2D and related CVD complication prevention)

1) International Diabetes Federation. IDF Diabetes Atlas 8th edn, 150 (International Diabetes Federation, Brussels, Belgium, 2017).
2) Prediabetes: a high-risk state for diabetes development. Lancet 379, 2279–2290 (2012).

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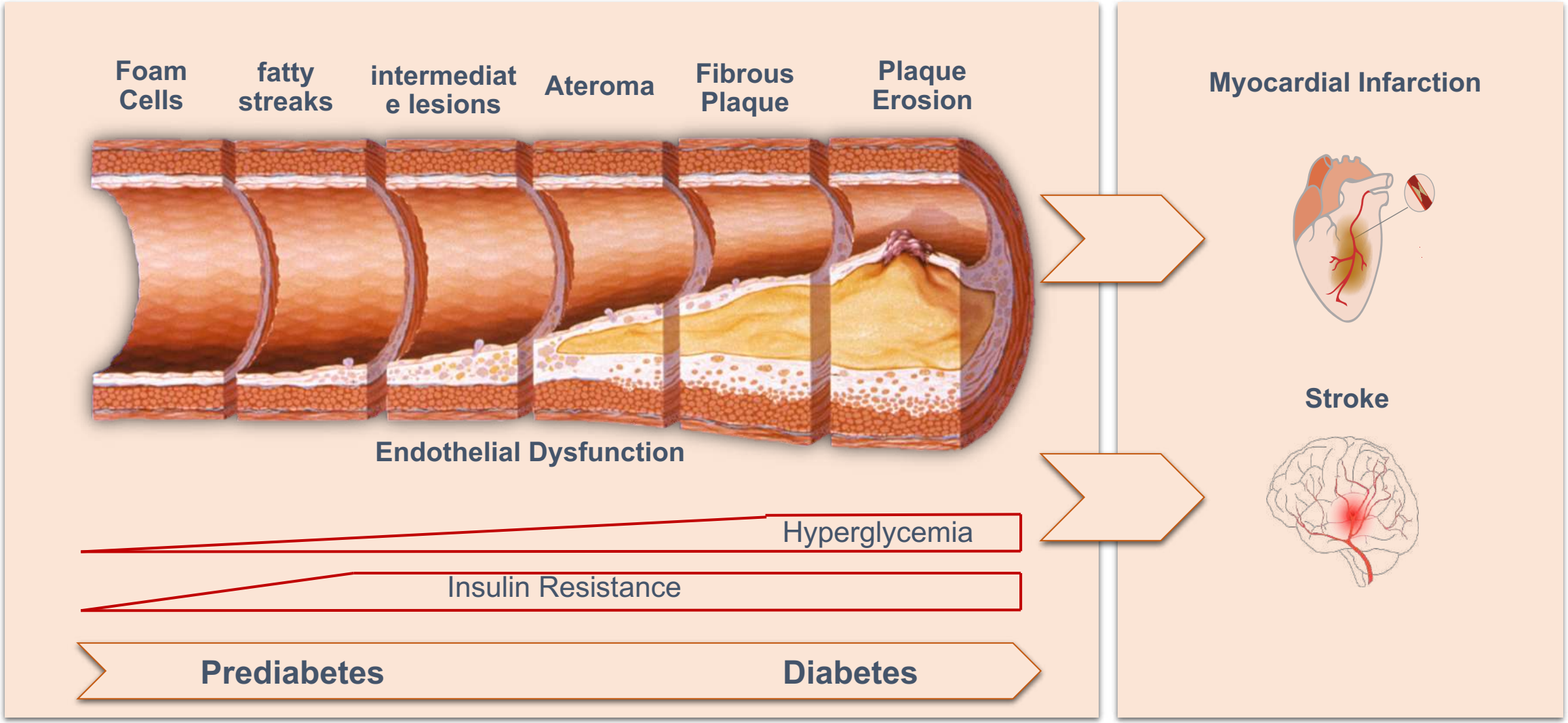
Atherosclerotic and Cardiometabolic Disease Evolution

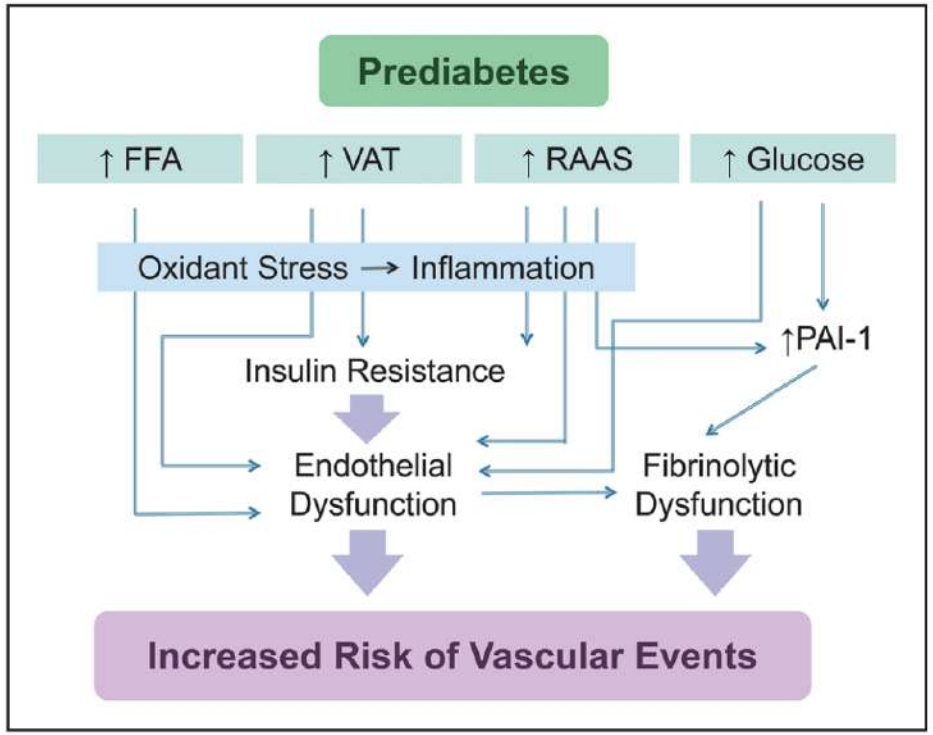


1.Libby P, et al. *Nature*. 2011;473(7347):317-325. **2.** Libby P, et al. *Nat Rev Dis Primers*. 2019;5:56. **3.** Ference BA, et al. *J Am Coll Cardiol.* 2018;72(10):1141-1156. **4.** Badimon L, et al. *J Intern Med.* 2014;276(6):618-632. Stary HC et al. Circulation. 1995;92:1355-1374.

Characteristics of atheromatosis in the prediabetes stage

In the **ILERVAS study** 33.9% (n = 2269) had prediabetes; Those with presented a higher prevalence of subclinical atheromatous disease than participants with HbA1c < 5.7% (70.4 vs. 67.5%, p = 0.017).

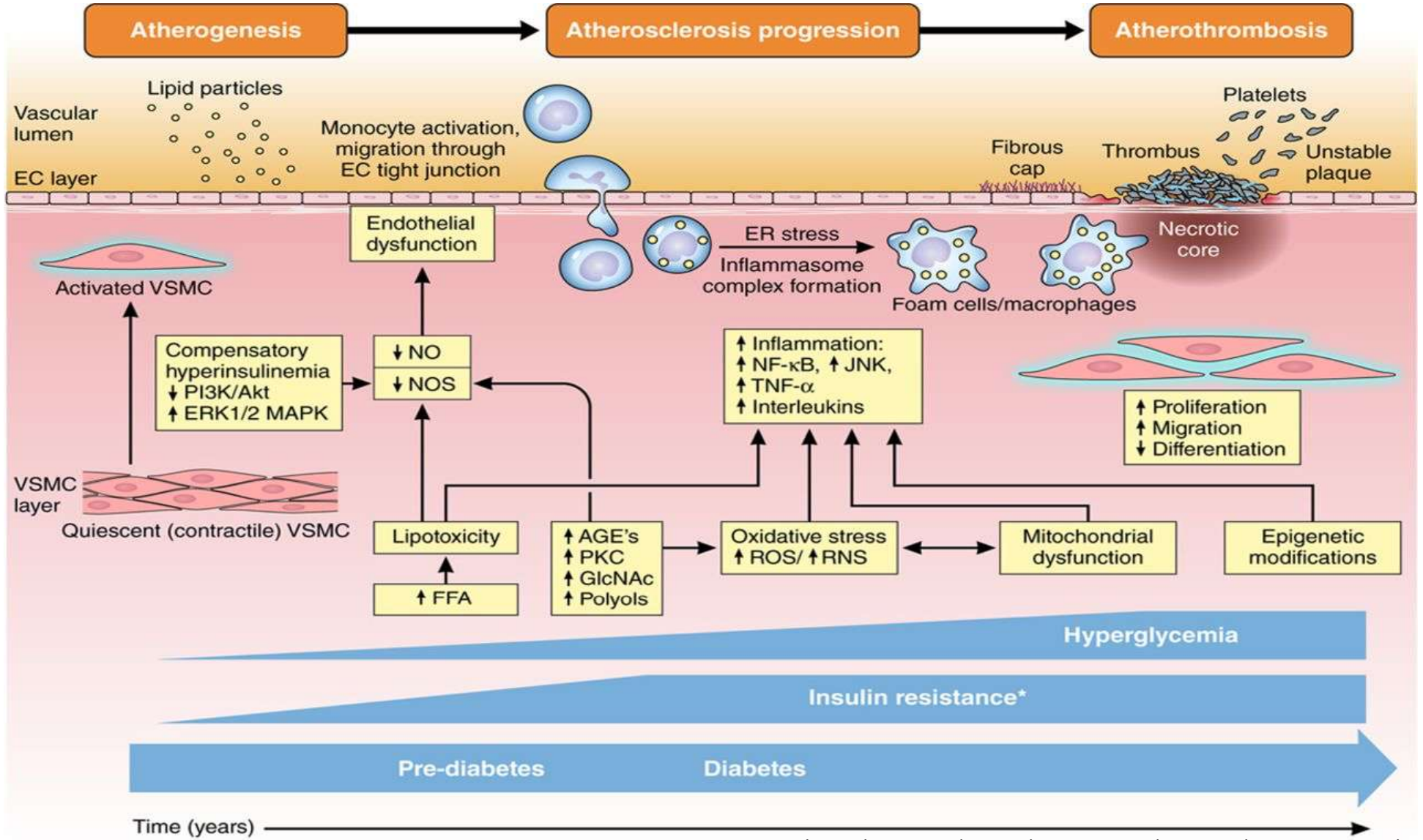
	Prediabetes (n=979)	Control group (n=2,268)	p-value
Presence of subclinical atheromatous disease, n (%)	797 (81.4)	1,715 (75.6)	<0.001
Carotid territory affected, n (%)	545 (55.7)	1,100 (48.5)	<0.001
Femoral territory affected, n (%)	675 (68.9)	1,438 (63.4)	0.002
Number of affected territories	2 [1;4]	2 [1;3]	<0.001
Total plaque area, (cm^2)	0.71 [0.30;1.37]	0.65 [0.28;1.23]	0.034



Endothelial insulin resistance, hyperglycemia and the formation of advanced glycation products, and increased free fatty acids (FFAs) give rise to oxidative stress,inflammation and endothelial vasodilator, and fibrinolytic dysfunction in prediabetes. PAI-1 indicates plasminogen activator inhibitor-1; RAAS renin–angiotensin–aldosterone system; and VAT, visceral adipose tissue.

Sánchez et al. Characteristics of atheromatosis in the prediabetes stage: a cross-sectional investigation of the ILERVAS project Cardiovasc Diabetol. 2019 Nov 15;18(1):154.
David H. Wasserman et al. The Vasculature in Prediabetes Circulation Research. 2018;122:1135–1150

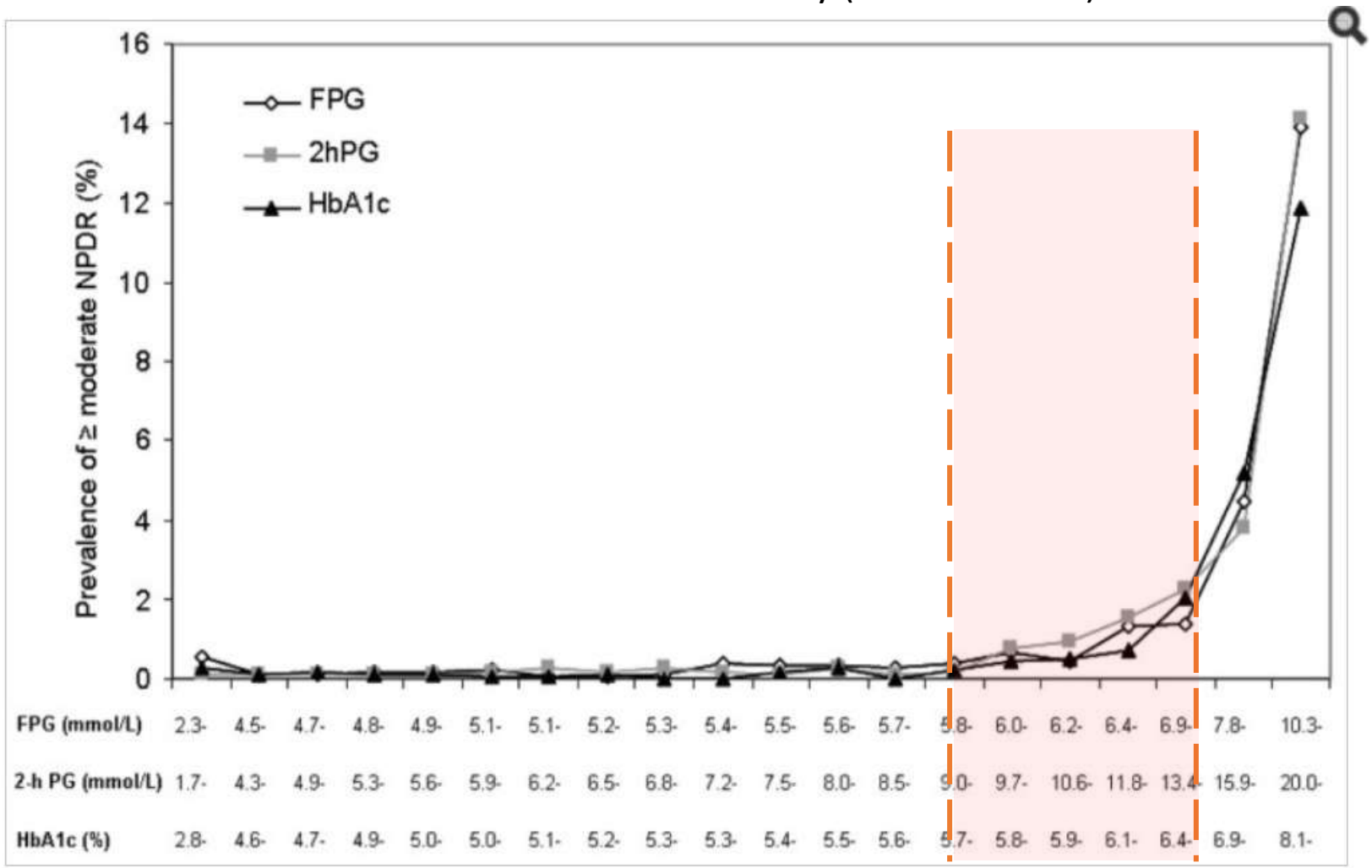
Vascular complications in prediabetes and type 2 diabetes: a continuous process arising from a common pathology



Atherosclerotic Cardiovascular Disease and Heart Failure in Type 2 Diabetes Mellitus – Mechanisms, Management, and Clinical Considerations 2016

Prediabetes and Cardiovascular Disease

National Health and Nutrition Examination Survey (NHANES 1992)



(NHANES 2020)

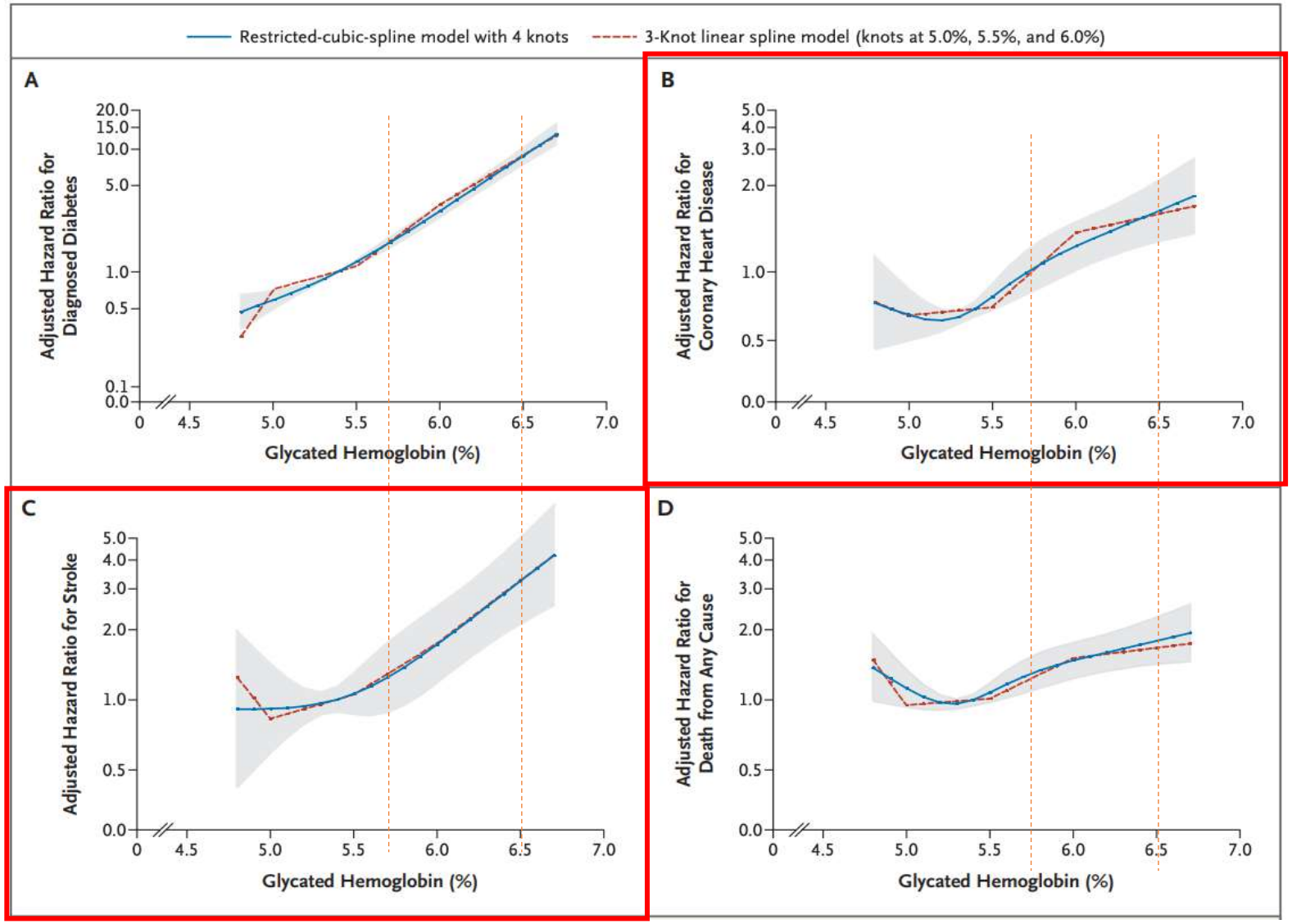
	Adjusted OR (95% CI)	p-value
HbA1c	1.50 (0.82, 2.74)	0.1778
Gender		
Male	1.39 (1.04, 1.85)	0.0267
Female	Ref	
Age	1.03 (1.01, 1.05)	0.0203
Ethnicity		
Caucasian	Ref	
African American	1.74 (0.97, 3.11)	0.5376
Mexican American	0.93 (0.52, 1.64)	0.7881
Other	1.49 (0.67, 3.32)	0.3233
HOMA-IR	1.09 (1.03, 1.16)	0.0030
HOMA-IR		
<3 (n=1258)	Ref	
3-5 (n=388)	1.49 (0.73, 2.69)	0.3038
>5 (n=268)	1.64 (1.03, 2.62)	0.0393

incident retinopathy was present 9.4% of patients without diabetes, and these lesions were directly related to HOMA-IR but independent of HbA1c.

Multivariable Logistic Regression Model for Retinopathy in Participants Aged 40 Years and Older in the Fasting Cohort and Without Diabetes, NHANES 2005-2008 ; HbA1c = glycated hemoglobin, HOMA-IR = homeostatic model assessment of insulin resistance

Hanssen KF, et al. Blood glucose control and diabetic microvascular complications: long-term effects of near-normoglycaemia. Diabet Med, 1992, 9:697-705. ;
Use of Glycated Haemoglobin (HbA1c) in the Diagnosis of Diabetes Mellitus: Abbreviated Report of a WHO Consultation. Geneva: World Health Organization; 2011.
Yicheng K. Bao, BA Association of retinopathy and insulin resistance: NHANES 2005-2008 Curr Eye Res. 2020 February ; 45(2): 173–176.

Prediabetes and Cardiovascular Disease



Prognostic value of glycated hemoglobin and fasting glucose for identifying adults at risk for T2D or **CVD** of the Atherosclerosis Risk in Communities (ARIC) study. (2010)

Adjusted Hazard Ratios for Self-Reported Diagnosed Diabetes and Coronary Heart Disease, Ischemic Stroke, and Death from Any Cause, According to the Baseline Glycated Hemoglobin Value. The hazard ratios are per each absolute increase of 1 percentage point in the glycated hemoglobin value at baseline. The shaded area is the 95% confidence interval from the restricted-cubic-spline model. Both models are centered at the median (5.4%) and the plot was truncated at the 2.5th and 97.5th percentiles of glycated hemoglobin (4.7% and 6.8%, respectively). The hazard ratios were adjusted for age, sex, and race (black or white), low-density and high-density cholesterol levels, log-transformed triglyceride level, body-mass index, waist-to-hip ratio, hypertension (yes or no), family history of diabetes (yes or no), education (less than high school, high school or equivalent, or college or above), alcohol use (currently, formerly, or never), physical-activity index score, and smoking status (current smoker, or never smoked). The data are shown on a natural-log scale.

Elizabeth Selvin et al. Glycated hemoglobin, diabetes, and cardiovascular risk in nondiabetic adults N Engl J Med. 2010 Mar 4;362(9):800-11.

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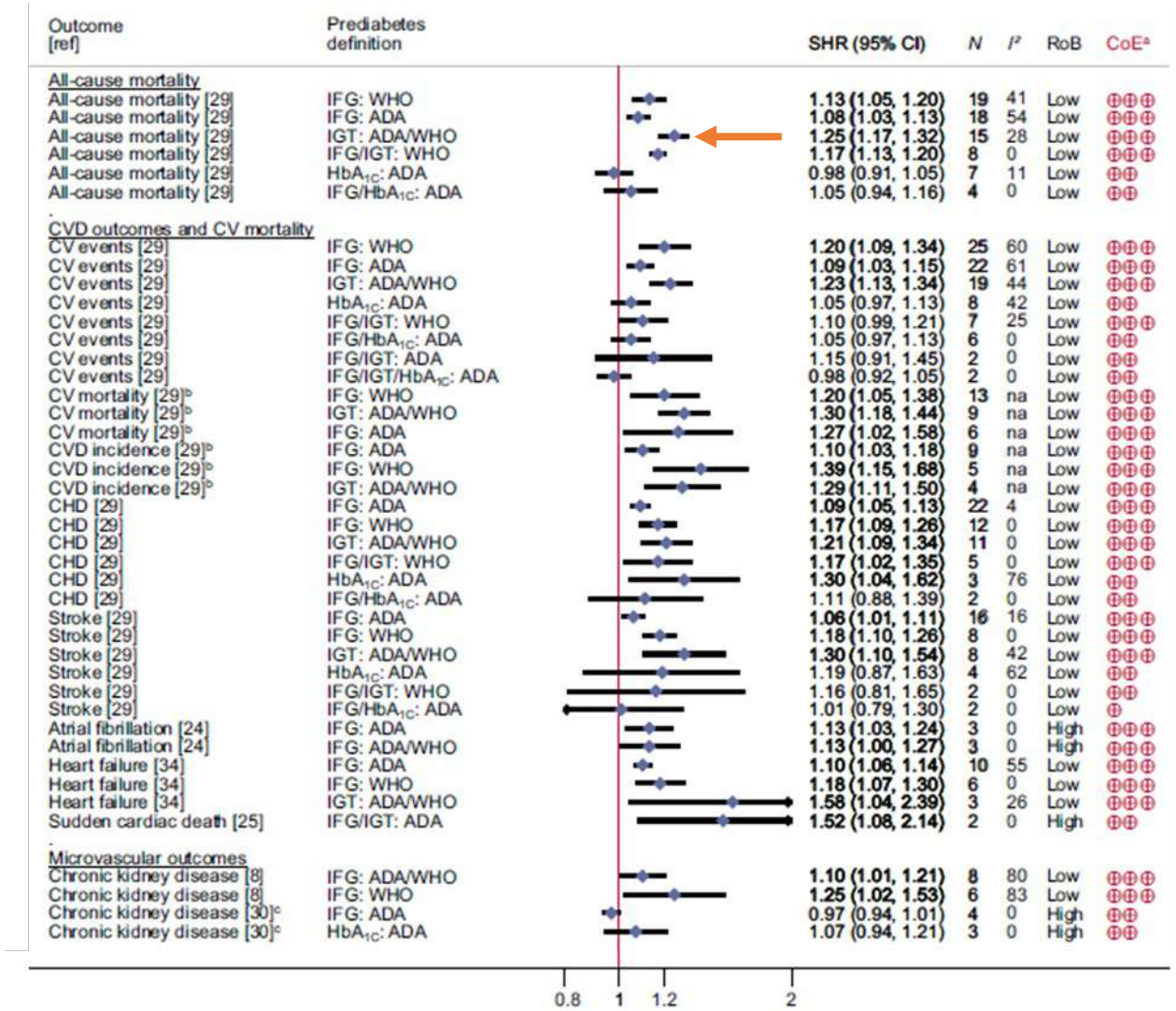
Prediabetes and Cardiovascular Disease (CVD)

umbrella review of meta-analyses of prospective studies



Interpretation of the certainty of evidence is denoted by crossed circles: four symbols, high; three symbols, moderate; two symbols, low; and one symbol, very low. CoE, certainty of evidence; CV, cardiovascular; N, number of primary studies; RoB: Risk of bias

- ✓ Systematic reviews with meta-analyses reporting summary risk estimates for the associations between prediabetes and incidence of mortality, CVD outcomes and CV mortality
- ✓ Prediabetes was associated with a 6–101% increased risk for all-cause mortality and the incidence of cardiovascular outcomes with **moderate certainty of evidence** (GRADE tool)
- ✓ The association with all-cause mortality was stronger for prediabetes, defined by impaired glucose tolerance, than for prediabetes defined by HbA1c. ←
- ✓ *LIMITATION* study participants with prediabetes may have developed T2D during the follow-up period

Sabrina S et al Diabetologia (2022) 65:275–285

Prediabetes and Cardiovascular Disease (CVD)

- ✓ Many observational studies have shown that prediabetes is a risk factor for CVD,[1,2]
- ✓ These observations cannot be directly interpreted as causal effects owing to the limitations of observational epidemiology.
- ✓ Following a cohort of participants who remain in the prediabetic state for many years would help determine if blood glucose variations within the prediabetic range are associated with CVD.
- ✓ Such a study is probably unfeasible and would (owing to its observational nature) be prone to confounding and reverse causality.

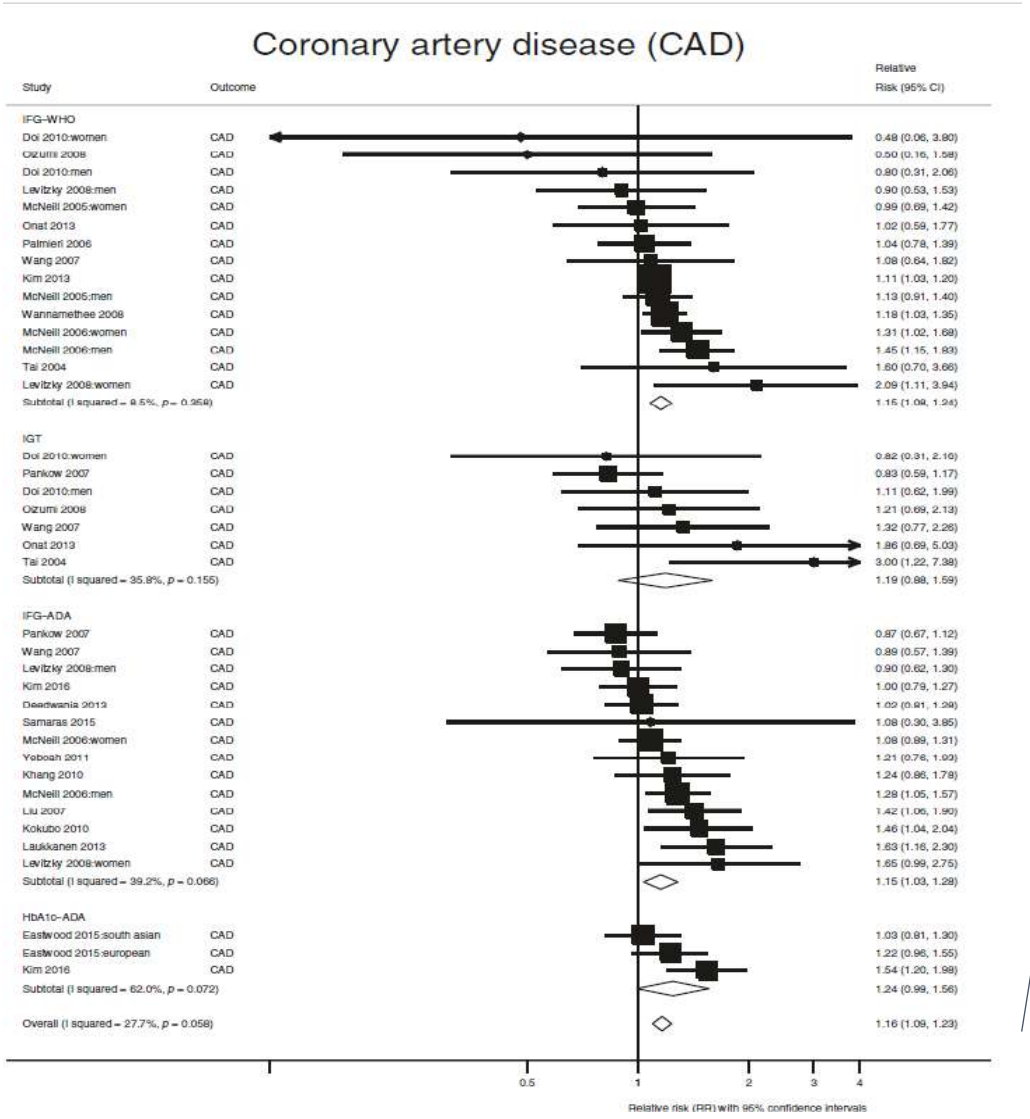
1) Haffner, S. et al JAMA 263, 2893–2898 (1990), 2) Sabrina S et al Diabetologia (2022) 65:275–285

Causal relationships between prediabetes and vascular complications (observational data meta-analysis & Mendelian Randomization)

- ✓ Studies included participants from the general population, with **prediabetes at baseline** and **outcomes measured at follow-up** (CAD, CKD, or stroke) compared with the group of normoglycaemic participants.
- ✓ Studies with **individuals with diabetes at baseline or follow-up were excluded** from the analysis.
- ✓ The pooled sample size was **1,326,915 participants**, with a mean (SD) age of 53.2 ± 10.2 years and a follow-up duration of 9.6 ± 4.8 years.

Pascal M. Mutie, et al. Nature Communications volume 11, Article number: 4592 (2020)

Causal relationships between prediabetes and CAD: observational analysis

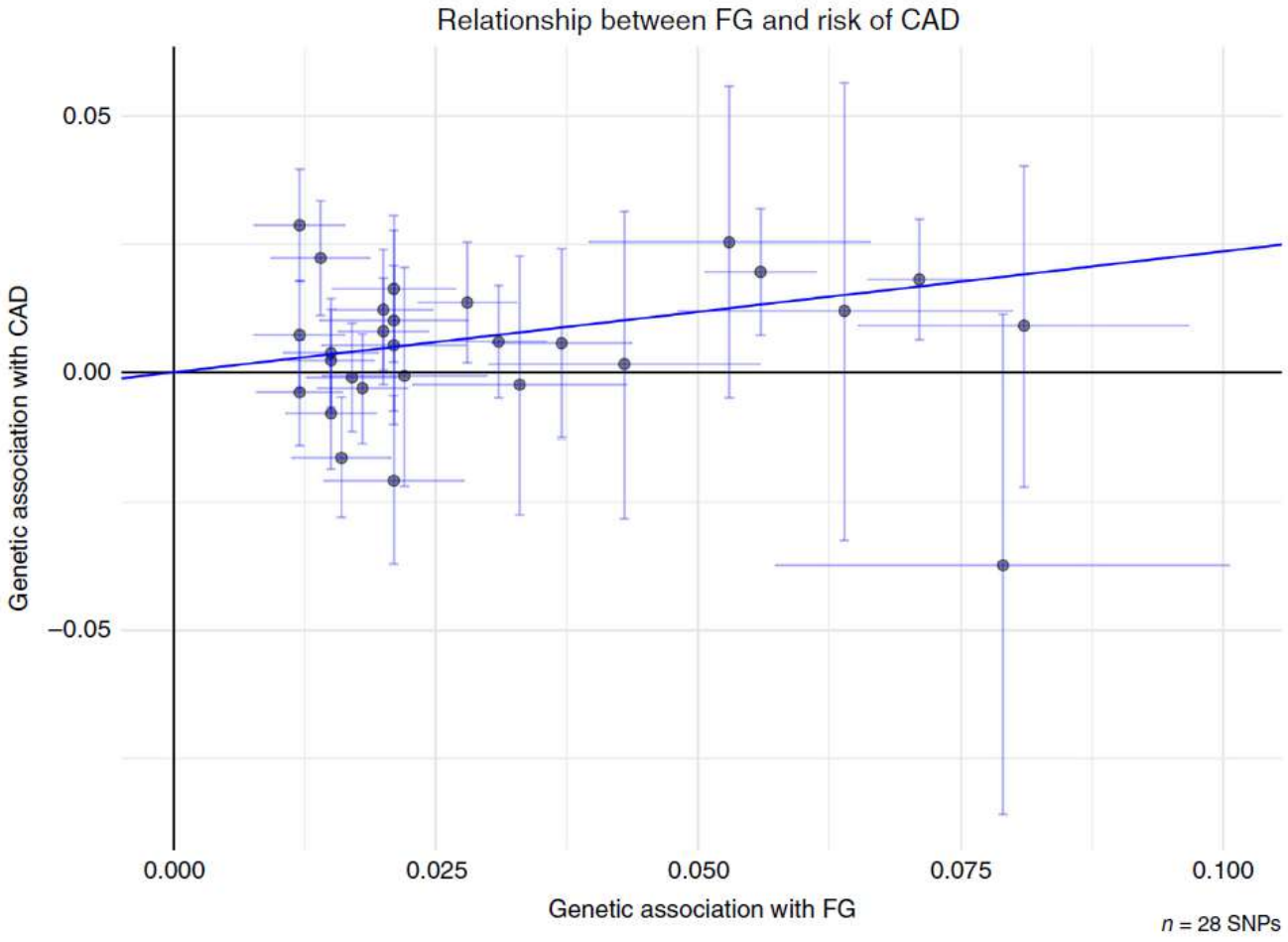


Meta-analysis of the association between prediabetes and CAD. The square and diamond shapes represent effect size (relative risk estimates), while the horizontal bars represent the 95% confidence intervals. A total of 21 studies are included. All P values are two-sided. Source data are provided as Source Data file. CAD, Coronary Artery Disease

- ✓ In the observational data meta-analysis, prediabetes was associated with a 16% elevated risk of coronary artery disease (CAD) (RR = 1.16; 95% CI: 1.09, 1.23; Q = 52.5, PQstat = 0.058; I2 = 27.7%).
- ✓ Prediabetes conveyed a RR of 1.11 (95% CI: 1.03, 1.18; Q = 28.5, PQstat = 0.23; I2 = 16%) for stroke.
- ✓ Prediabetes was not associated with chronic kidney disease (CKD) (RR = 1.05; 95% CI: 0.98, 1.12; Q = 27.2, PQstat = 0.002; I2 = 63.3%),

Pascal M. Mutie, et al. Nature Communications volume 11, Article number: 4592 (2020)

Causal relationships between prediabetes and CAD: Mendelian Randomization

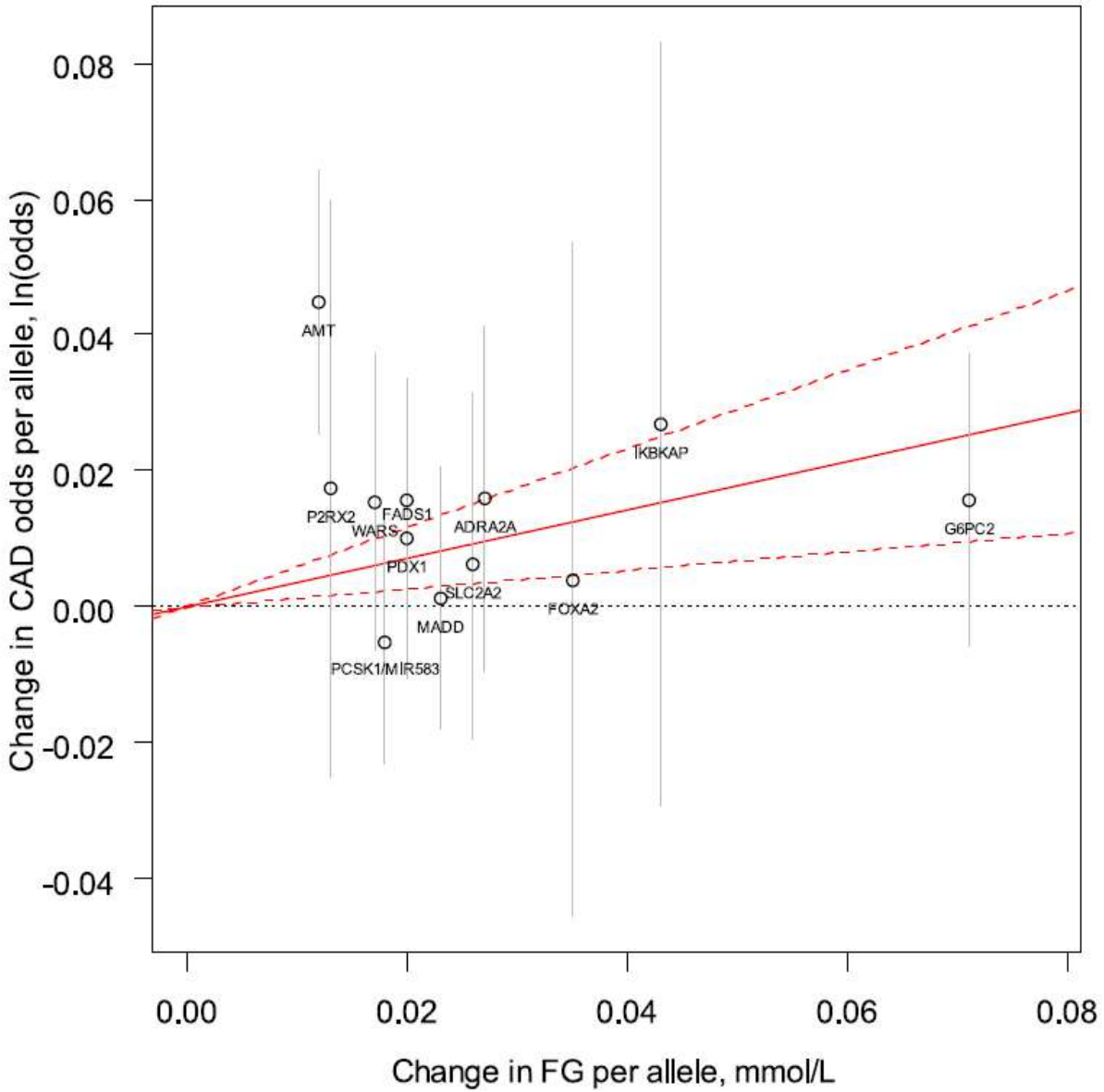


Relationship between genetic effects of prediabetes only and CAD. Data are represented as log-odds and 95% confidence intervals for each trait. Slope of the line represents an estimate of the causal effect of fasting glucose on risk of CAD. The points represent effect sizes for each individual genetic variant (SNPs) for each of the traits on both axes. The horizontal and vertical bars at each point represent the 95% confidence intervals for genetic associations with FG and CAD, respectively. FG fasting glucose, CAD coronary artery disease. Source data are provided as Source Data file.

- ✓ Mendelian Randomization (MR) is a popularized adjunct to randomized controlled trials (RCTs) that makes use of epidemiological data for causal inference.
- ✓ In the MR analysis, **non diabetic fasting glucose variation was significantly associated with CAD**, such that 1 mmol L−1 (18 mg/dL) higher fasting glucose conveyed an OR of 1.26 (95% CI: 1.16, 1.38) for CAD.
- ✓ In the MR analysis, stroke and CKD were not associated with prediabetes

Pascal M. Mutie, et al. Nature Communications volume 11, Article number: 4592 (2020)

Causal relationships between prediabetes and CAD: Mendelian Randomization



- ✓ MR analysis using summary-level statistics from the largest published meta-analyses of genome-wide association studies (GWAS) for fasting glucose (FG) (n = 133,010 participants free of diabetes) and CAD (n = 63,746 case subjects and 130,681 control subjects)
- ✓ GWAS for type 2 diabetes were excluded
- ✓ In an instrumental variable analysis comprising 12 FG-raising variants, **a 1 mmol/L (18 mg/dL) increase in FG revealed an effect-size estimate of 1.43 CAD odds (95% CI 1.14–1.79).** Corrected for other CAD risk factors.

Jordi Merino et al. Diabetes Care 2017;40:687–693

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DIABETES Prevention in Prediabetes (phenotyping)

- ✓No **medicinal products** are approved for the treatment of prediabetes in the EU or US[1].

- ✓**Lifestyle measures** are clearly recommended as a first-line intervention to improve glycemia in people at high risk of developing diabetes[1,2,3,4]

- ✓**Additional drug therapy** is widely acknowledged that may be beneficial to those at high risk of developing diabetes (BMI 35 ≥kg/m ^{2}, those at higher glucose levels (e.g., fasting plasma glucose110–125 mg/dL, 2-h post-challenge glucose173-199 mg/dL, A1c > 6.0%)[1,2,3,4] (metformin, alpha-glucosidase inhibitors, pioglitazone, liraglutide, semaglutide, tirzepatide, orlistat, phentermine/topiramate).

1) DiabetesCareVolume 46,Supplement1,January2023 **2)** 1.KnowlerWC et al. Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J M ed 2002;346:393–403 **3)** LindstromJ et al.; Finnish Diabetes Prevention Study Group. Sustained reduction in the incidence of type 2 diabetes by lifestyle intervention: follow-up of the Finnish Diabetes Prevention Study. Lancet 2006;368:1673–1679 **4)** Li G,et al.Cardiovascular mortality, all-cause mortality, and diabetes incidence after lifestyle intervention for people with impaired glucose tolerance in the DaQing Diabetes Prevention Study: a 23-year follow-up study. Lancet Diabetes Endocrinol 2014 ;2:474–480

DIABETES Prevention in Prediabetes

- ✓**DPP,** intensive lifestyle intervention reduced the risk of incident T2D by 58% over 3 years (metformin, intensive lifestyle, and placebo)[1].
- ✓**Metformin** was overall less effective than lifestyle modification in the DPP, differences declined over time in the DPPOS[2], and metformin may be cost-saving overa10-year period[3]. In the DPP, metformin was as effective as lifestyle modification in participants with 35 ≥ kg/m^2 and in younger participants aged 25–44 years[1]. EARLY ACTION!
- ✓Follow-up of 3 large studies of lifestyle intervention for T2D prevention showed 39% reduction at 30 years in the **Da Qing study[4]**, 43% reduction at 7 years in the **Finnish DPS[5]**, and 34 % reduction at 10 years and 27% reduction at 15 years in the U.S. **Diabetes Prevention Program Outcomes Study (DPPOS)[2].**

1) KnowlerWC et al. Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J M ed 2002;346:393–403 **2)** DM Nathan et al., Long-term effects of lifestyle intervention or metformin on diabetes development and microvascular complications over 15-year follow-up: the Diabetes Prevention Program Outcomes Study, Lancet Diabetes Endocrinol . 2015 Nov;3(11):866-75; **3)** DiabetesPreventionProgramResearch Group.The10-yearcost-effectivenessoflifestyle interventionormetforminfordiabetesprevention:anintent-to-treatanalysisoftheDPP/DPPOS.DiabetesCare2012;35:723–730 **4)** Li G,et al.Cardiovascular mortality, all-cause mortality, and diabetes incidence after lifestyle intervention for people with impaired glucose tolerance in the DaQing Diabetes Prevention Study: a 23-year follow-up study. Lancet Diabetes Endocrinol 2014 ;2:474–480; 5) LindstromJ et al.; Finnish Diabetes Prevention Study Group. Sustained reduction in the incidence of type 2 diabetes by lifestyle intervention: follow-up of the Finnish Diabetes Prevention Study. Lancet 2006;368:1673–1679

CVD Prevention in prediabetes

- ✓ The lifestyle interventions for **weight loss** in study populations at risk for T2D showed a reduction in cardiovascular risk factors[1,2] and CVD[3]

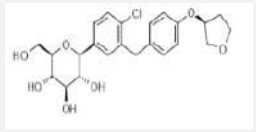
- ✓ In the DaQing DPOS, lifestyle interventions [rand. 1:1:1:1, to a control group or lifestyle intervention groups (diet or exercise or both)] reduced CVD and CV mortality at 23 and 30 years of follow-up[4,5] 6, 7

- ✓ In the DPPOS (10 years follow-up of the DPP) and in the China DaQing DPOS, lifestyle interventions prevented the development of microvascular complications among women [4,5]

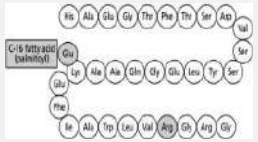
1) DiabetesCareVolume 46,Supplement1,January2023; **2)** OrchardTJ, etal.;Diabetes Prevention Program Outcomes Study Research Group. Long-term effects of the Diabetes Prevention Program interventions on cardiovascular risk factors: a report from the DPP Outcomes Study. Diabet Med 2013;30:46–55 **3)** Salas-Salvadó J, et al. n engl j med 378;25 nejm.org June 21, 2018; **4)** Guangwei Li et al. Cardiovascular mortality, all-cause mortality, and diabetes incidence after lifestyle intervention for people with impaired glucose tolerance in the Da Qing Diabetes Prevention Study: a 23-year follow-up study. Lancet Diabetes Endocrinol . 2014 Jun;2(6):474-80. **5)** Qiuhong Gong et al.,Lancet Diabetes Endocrinol. 2019 Jun;7(6):452-461. Morbidity and mortality after lifestyle intervention for people with impaired glucose tolerance: 30-year results of the Da Qing Diabetes Prevention Outcome Study **6)** DM Nathan et al., Long-term effects of lifestyle intervention or metformin on diabetes development and microvascular complications over 15-year follow-up: the Diabetes Prevention Program Outcomes Study, Lancet Diabetes Endocrinol . 2015 Nov;3(11):866-75 ; **7)** Q. Gong, Long-term effects of a randomized trial of a 6-year lifestyle intervention in impaired glucose tolerance on diabetes-related microvascular complications: the China Da Qing Diabetes Prevention Outcome Study Diabetologia volume 54, pages300–307 (2011) ;

2015 is time «zero» for the care of people living with diabetes

EMPA-REG

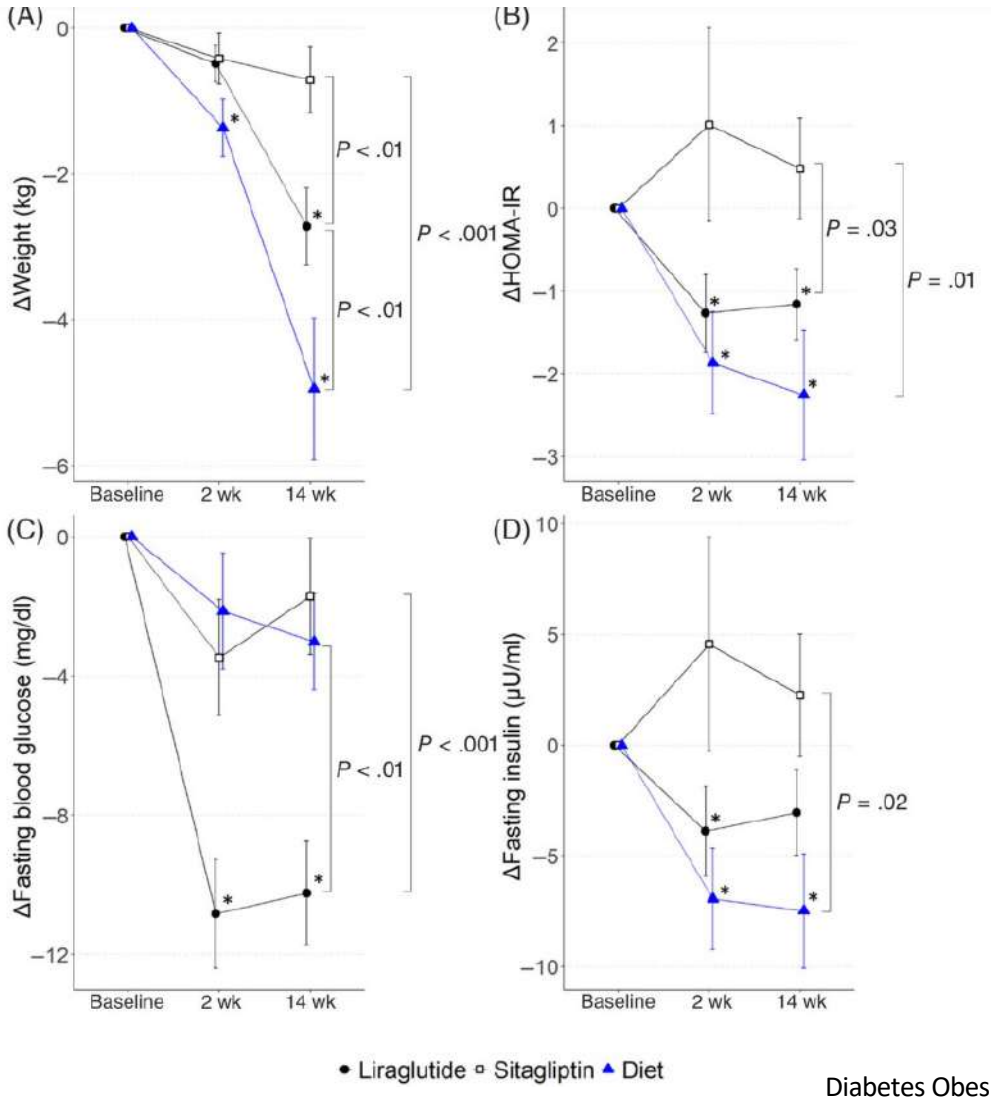


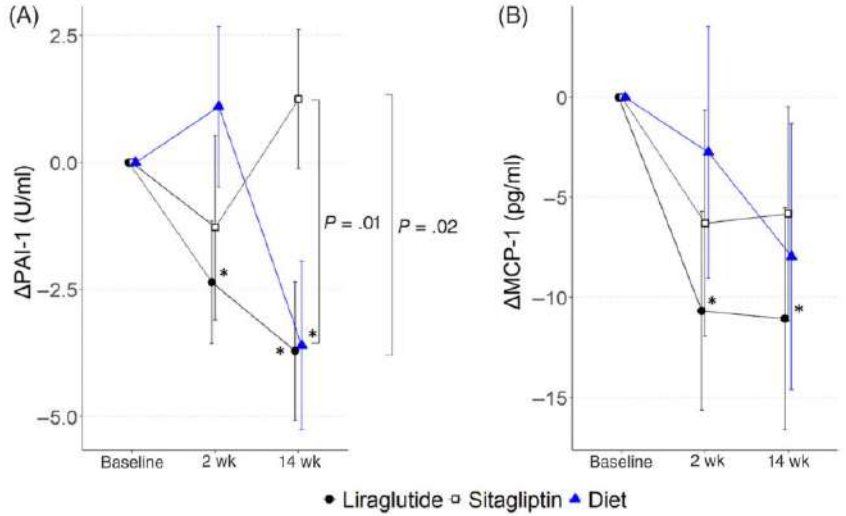
LEADER

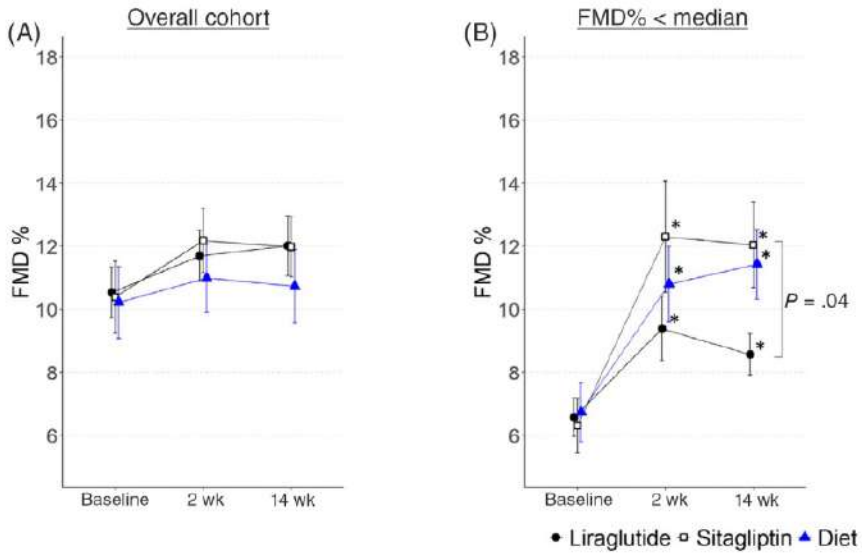


Is 2023 time «zero» for the care of people living with prediabetes and obesity?

Comparative effects of weight loss and **incretin-based therapies on vascular endothelial function, fibrinolysis and inflammation** in individuals with **obesity and prediabetes:** A randomized controlled trial



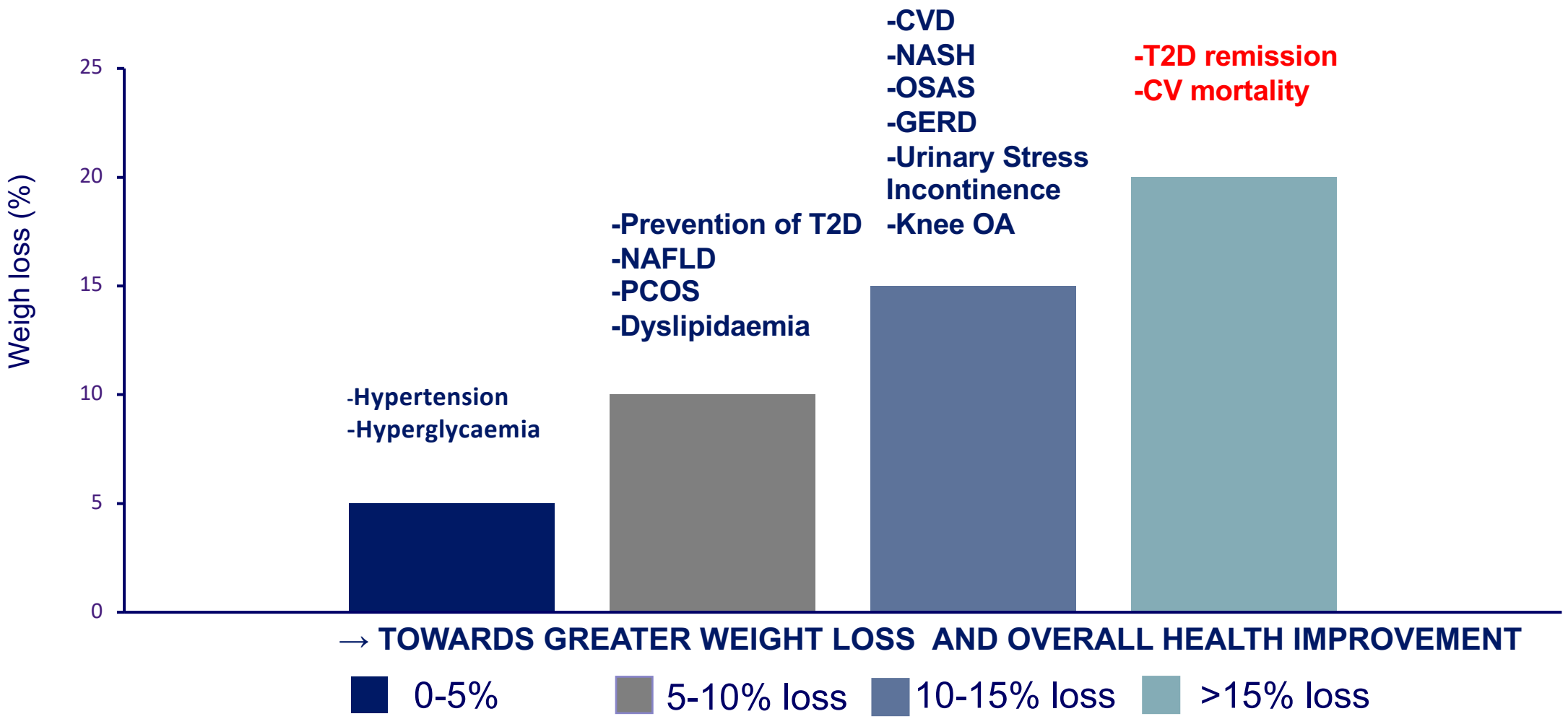




Diabetes Obes Metab. 2023;25:570–580.

Greater weight loss leads to greater benefits [1-5]

Overall health improvements

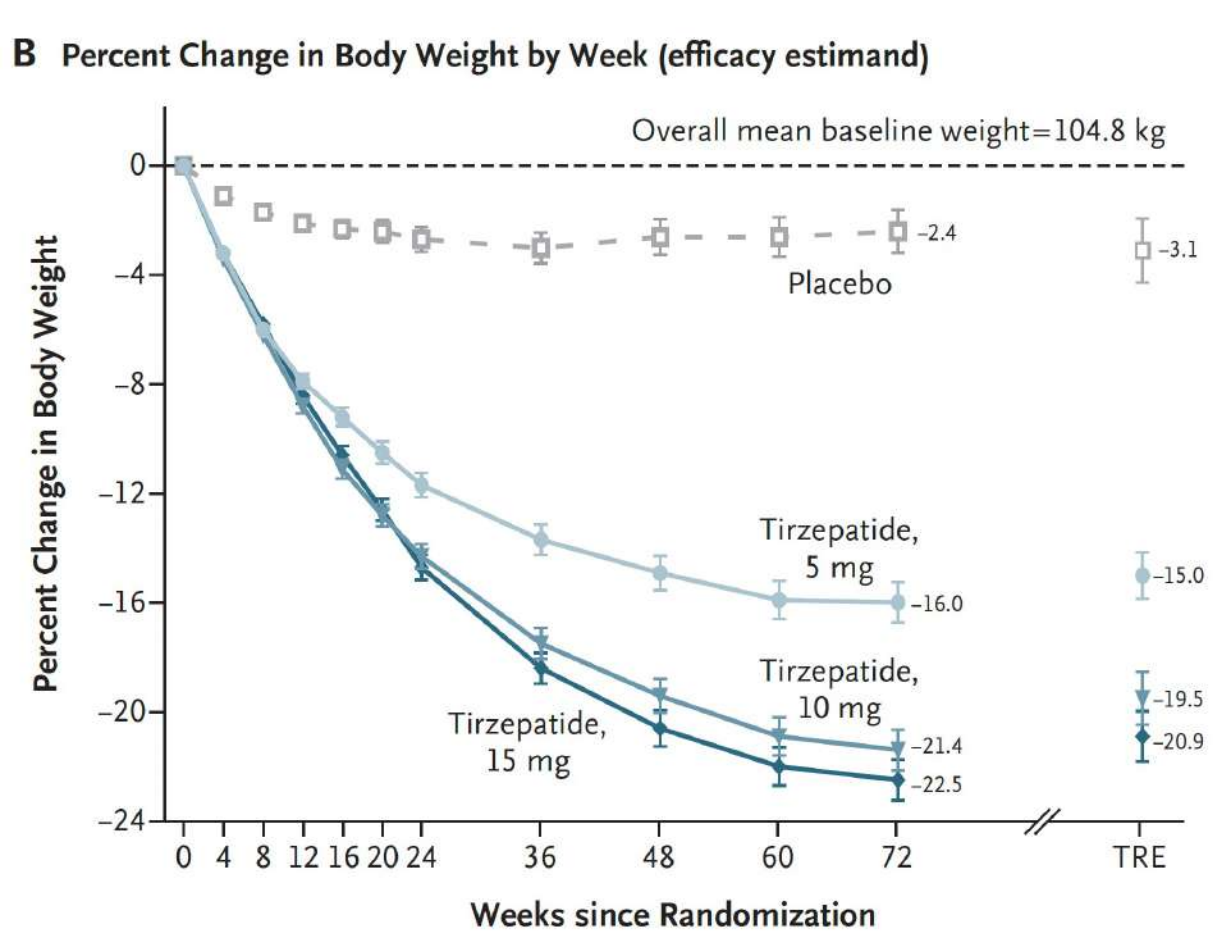


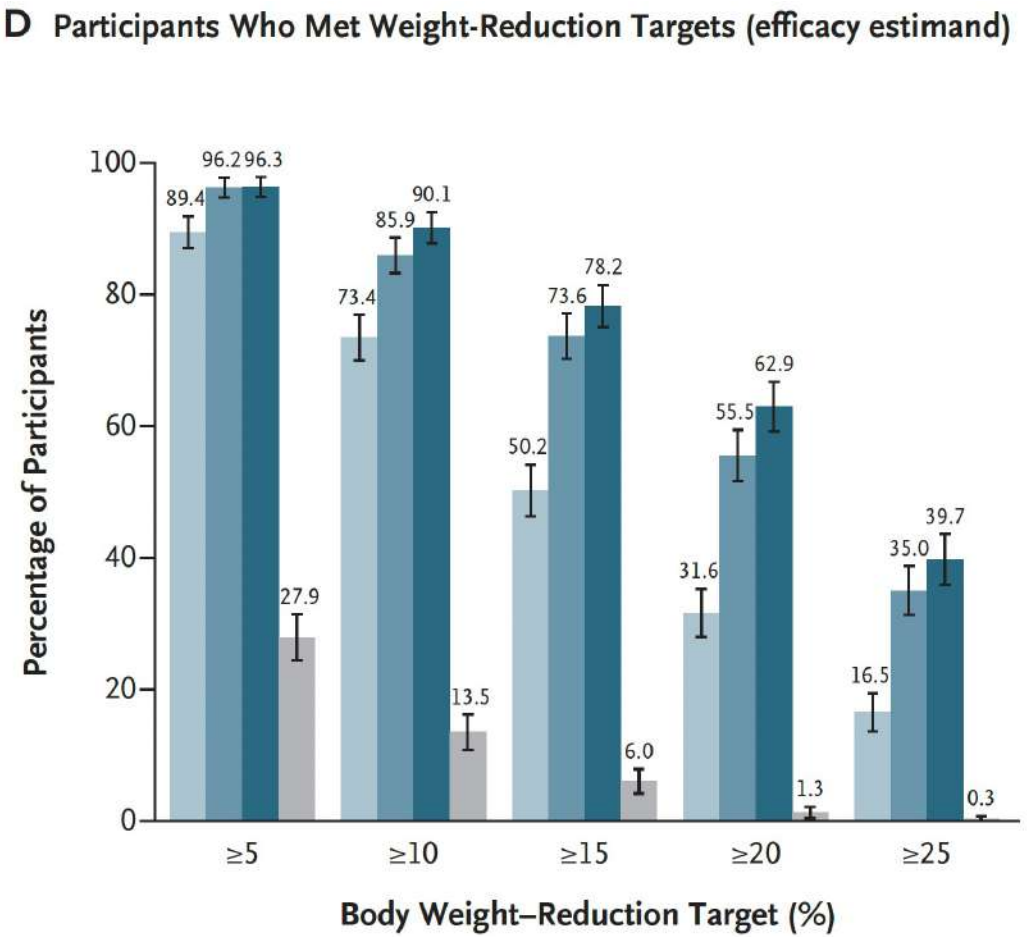
1. Knowler WC et al. *N Engl J Med* 2002;346:393–403; 2. Wing RR et al. *Diabetes Care* 2011;34:1481–1486; 3. Dattilo AM et al. *Am J Clin Nutr* 1992;56:320–328; 4. Li G et al. *Lancet Diabetes Endocrinol* 2014;2:474–480; 5. Foster GD et al. *Arch Intern Med* 2009;169:1619–1626; 6. Kuna ST et al. *Sleep* 2013;36:641–649; 7. Warkentin LM et al. *Obes Rev* 2014;15:169–182; 8. Wright F et al. *J Health Psychol* 2013;18:574–586

Tirzepatide Once Weekly for the Treatment of Obesity SURMOUNT-1

Effect of Once-Weekly Tirzepatide, as Compared with Placebo, on Body Weight

Tirzepatide, 5 mg Tirzepatide, 10 mg Tirzepatide, 15 mg Placebo





NEJM, June 4, 2022

GLP-1RAs have multifactorial effects

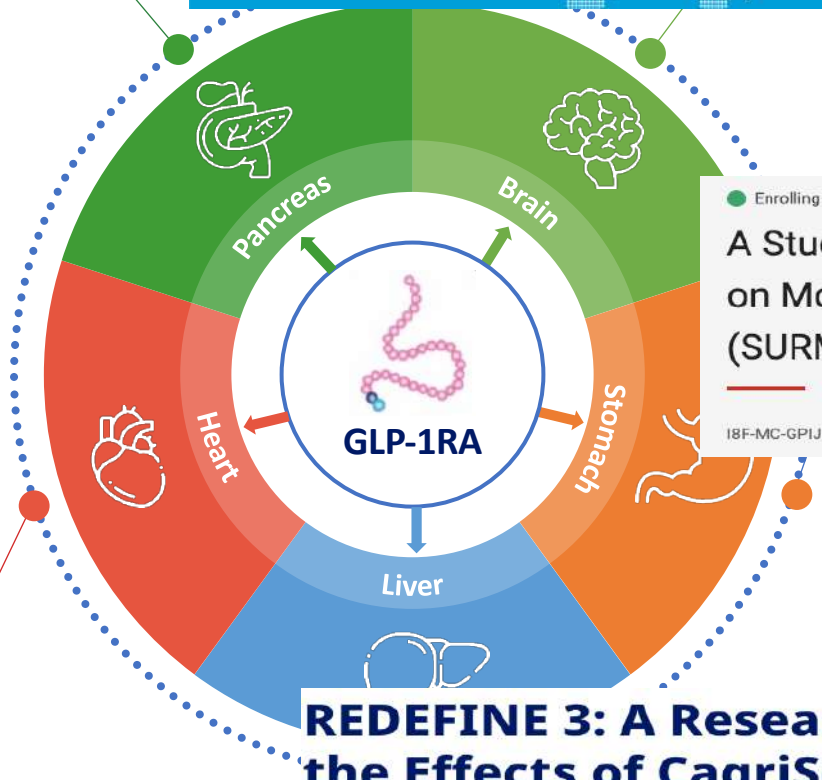
Pleiotropic effects

Pancreas

- ↑ Beta-cell function[1]
- ↓ Beta-cell apoptosis[1]
- ↑ Insulin biosynthesis[1]
- ↑ Glucose-dependent insulin secretion[1]
- ↓ Glucose-dependent glucagon secretion[1]

Brain

- ↓ Body weight[5]
- ↓ Food intake[6]
- ↑ Satiety[7,8]



Enrolling

A Study of Tirzepatide (LY3298176) on the Reduction on Morbidity and Mortality in Adults With Obesity (SURMOUNT-MMO)

I8F-MC-GPIJ - ClinicalTrials.gov - NCT05556512

- ↓ Endogenous glucose production[10]
- ↑ Hepatic insulin sensitivity[10]
- ↓ *De novo* lipogenesis[10]
- ↓ Lipotoxicity[10]
- ↓ Steatosis[11]

Liver

- ↓ Cardiovascular risk[2]
- ↓ Fatty acid metabolism[3]
- ↑ Cardiac function[3]
- ↓ Systolic blood pressure[3]
- ↓ Inflammation[4]

Heart

REDEFINE 3: A Research Study to See the Effects of CagriSema on Heart Disease in People Living With Obesity and Diseases in the Heart and Blood Vessels

GLP-1RA, glucagon-like peptide-1 receptor agonist.
Adapted from Campbell & Drucker. Cell Metab 2013;17:819–37; Pratley & Gilbert. Rev Diabet Stud 2008;5:73–94. Full reference list in

Conclusions

- ✓ CV risk starts early (before dysglycemia appears)
- ✓ Prediabetes correlates with CVD
- ✓ Diabetes Prevention is feasible for people with Prediabetes (Focus on people with 35 ≥ kg/m^2, younger patients, and those with «upper range» prediabetes
- ✓ CVD prevention appears to be possible for people with Prediabetes, however, future RCT data using GLP1 RA - GIP-GLP1 RA – GLP1-Amylin RA are needed to prove it robustly!