Precision Phenotyping: Are we treating the wrong obesity?

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Personal Disclosures

Research/Educational Grants: Medtronic, Johnson & Johnson,

Scientific Advisory Board: Keyron, GT Metabolic Solution, Kailera
Speaking honoraria: Medtronic, Johnson & Johnson, Novo Nordisk, Eli Lilly, Astra Zeneca

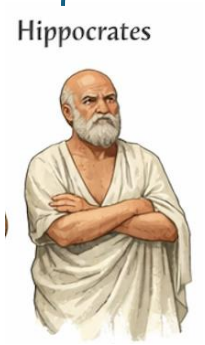
The Heterogeneity of Obesity Across Medicine, Art and Society

- *Harbinger of other diseases*
- *Protective against other maladies*
- *Disease itself*

"Some types of fatness are healthy 'humoral conditions' not an illness"

"Corpulence, when in extraordinary degree may be reckoned a disease"

"Obesity is not a disease in all instances"



M. Fleming, 1760

WG. Campbell 1934

20,000 BC | 500 BC | 200 AD | 1100 | 1500 | 1700 | 1800 | 1870 | 1920

Obelix

Friar Tuck
(Robin Hood Tales)

Rubens
1577-1640

Joe (Dicken's
Pickwick Papers)

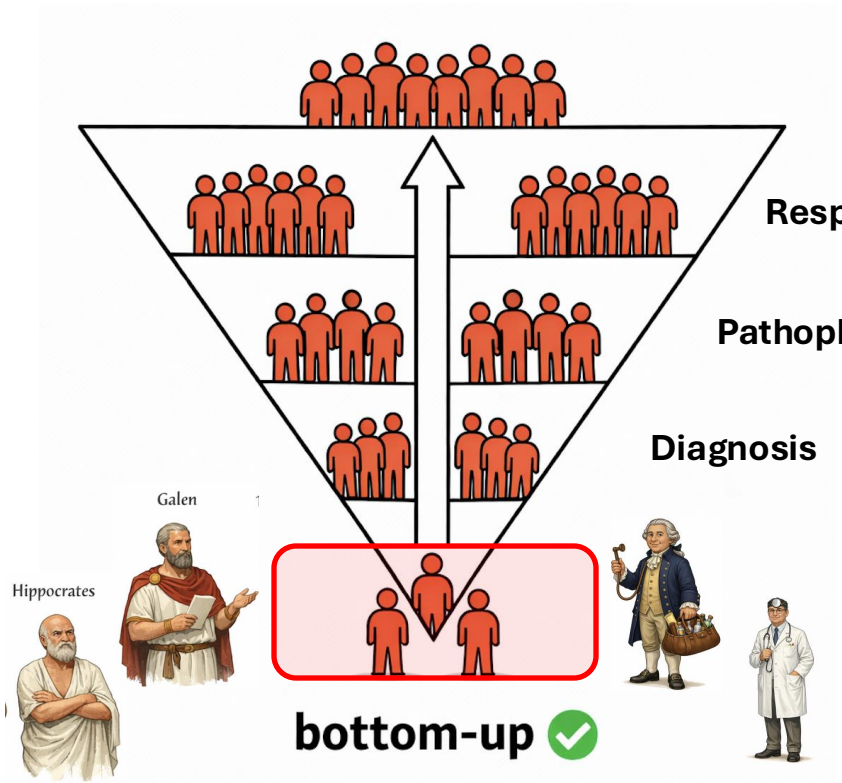
Queen Victoria

Allison, D.B., et al.
Obesity, 16: 1161-1177.

Practical Purpose of Disease Definition: Medicine vs Obesity

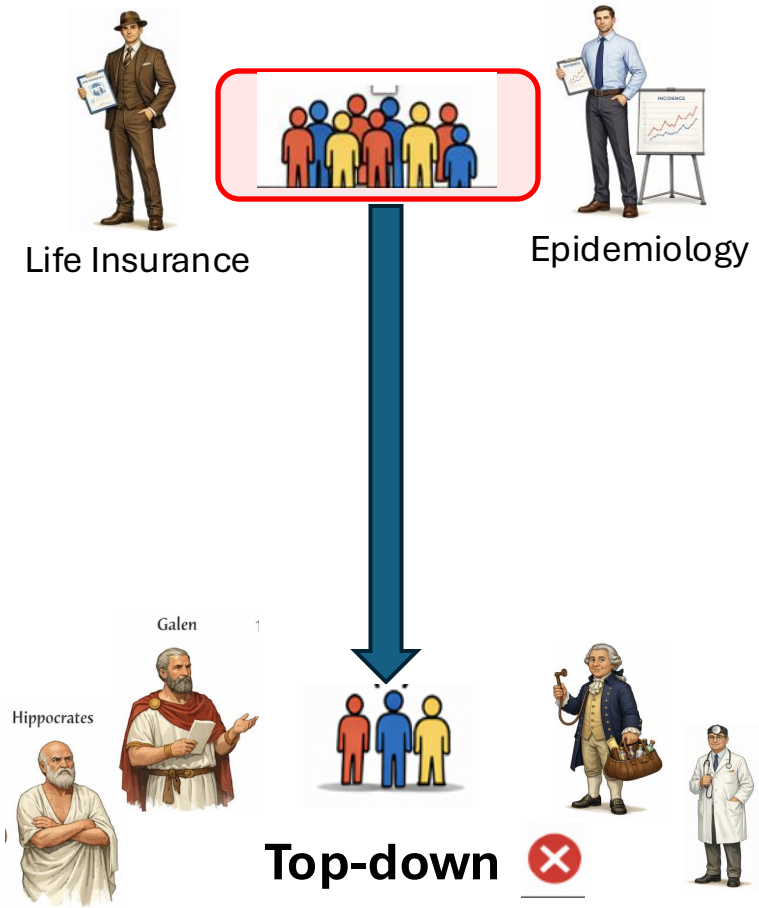
The health impact of obesity has been defined in reverse

Medicine



High Consistency

Obesity



High Heterogeneity

Rose G. Sick individuals and sick populations. International Journal of Epidemiology. 1985;14(1):32–38.

Obesity

Top-down

High Heterogeneity

(Risk, Health, Disease)

- Co-morbidities are not disease's signs/symptoms
- Other diseases have their own etiology
- Could be explained by co-exposure rather than direct cause-effect

Low specificity

Phenotype (risk) vs disease

Everyone with an obesity phenotype

Manifestation

Caused by the adiposity

Resolves

Treating the condition works

Comorbidity

Only associated with it

May not resolve

The cause lies elsewhere

Nothing

No manifestation at all

Nothing to resolve

No benefit is available

Obesity

Top-down

High Heterogeneity

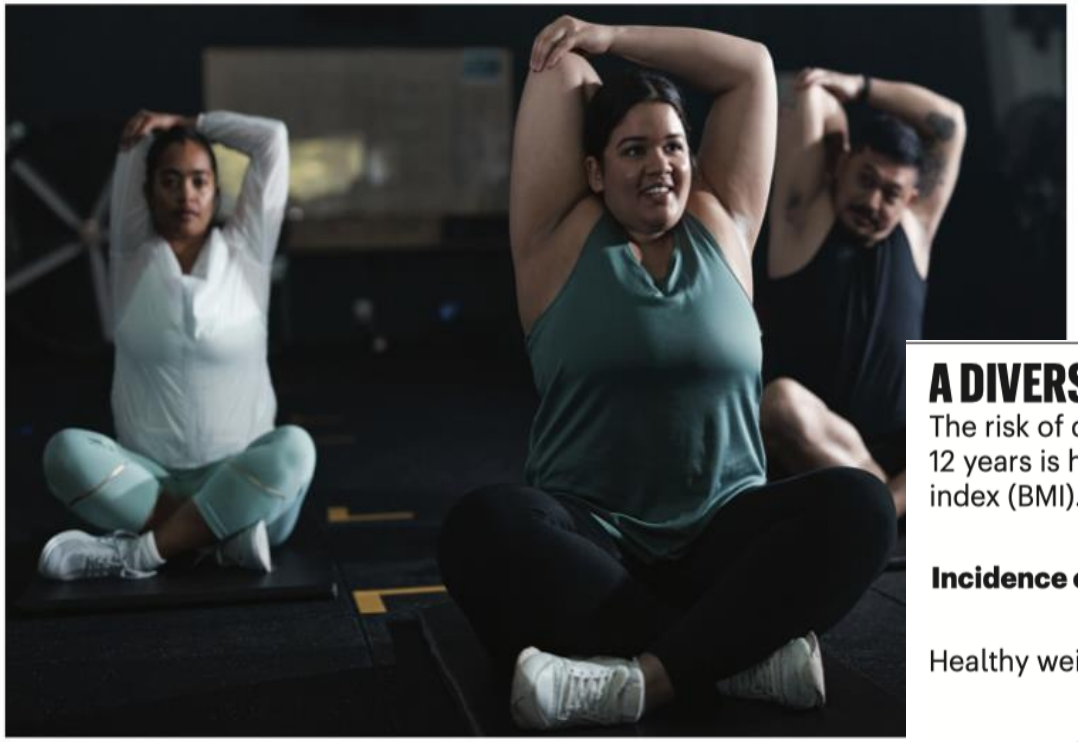
(Risk, Health, Disease)

Disease **CANNOT** be defined by population-level associations

Evidence that Physical Phenotype **CANNOT** be a disease diagnosis

SENSITIVITY

nature



HERAMAN/GETTY

People with the same body mass index can have radically different health statuses.

Why obesity shouldn't always be considered a disease

Francesco Rubino

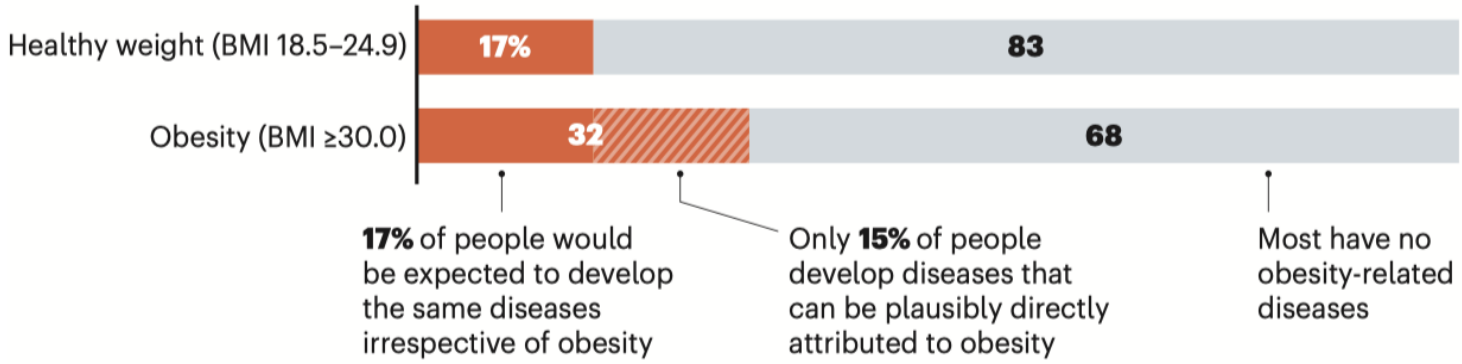
Biological and clinical heterogeneity >>

Calling all obesity a disease serves no-one

A DIVERSE LANDSCAPE

The risk of developing one or more of 21 common 'obesity related diseases' over 12 years is higher in people with obesity than in those with a healthy body mass index (BMI). But these population-level statistics obscure a varied clinical picture.

Incidence of obesity-related disease in UK Biobank data



Individual-Level Perspective

12-year incidence of ≥1 of 21 obesity-related diseases — 100 people with obesity*

Replication across two independent cohorts

Finnish Cohorts

Finnish Public Sector Study

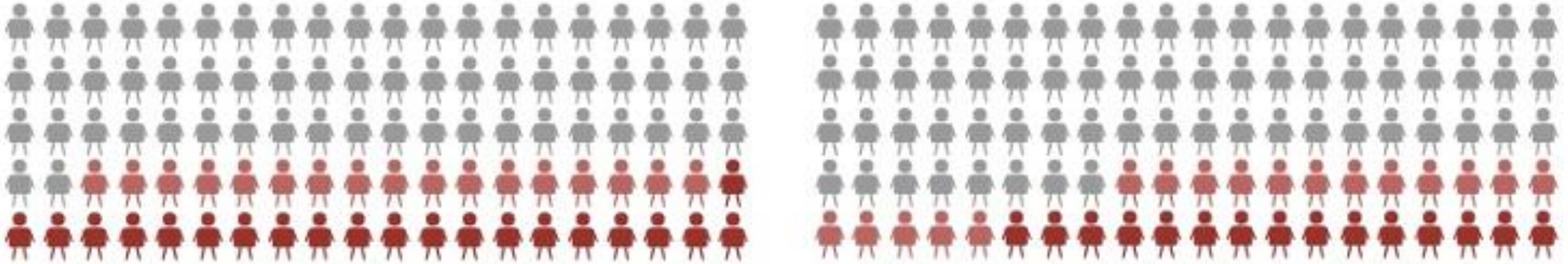
n = 114,657 · mean follow-up 12.1 yrs

62	17	21
of 100	of 100	of 100
No obesity-related disease	Background incidence	Attributable to obesity

UK Biobank

n = 499,357 · mean follow-up 11.8 yrs

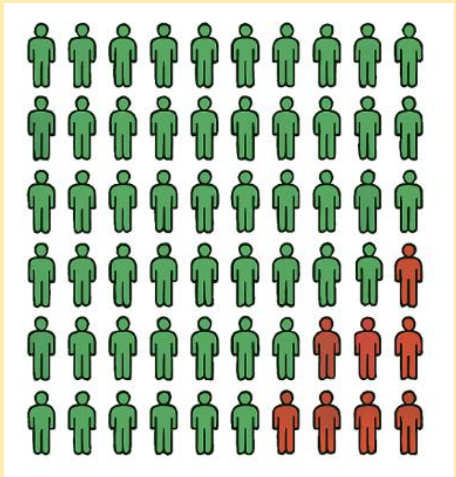
68	17	15
of 100	of 100	of 100
No obesity-related disease	Background incidence	Attributable to obesity



No obesity-related disease **Background incidence** **Excess incidence attributable to obesity**

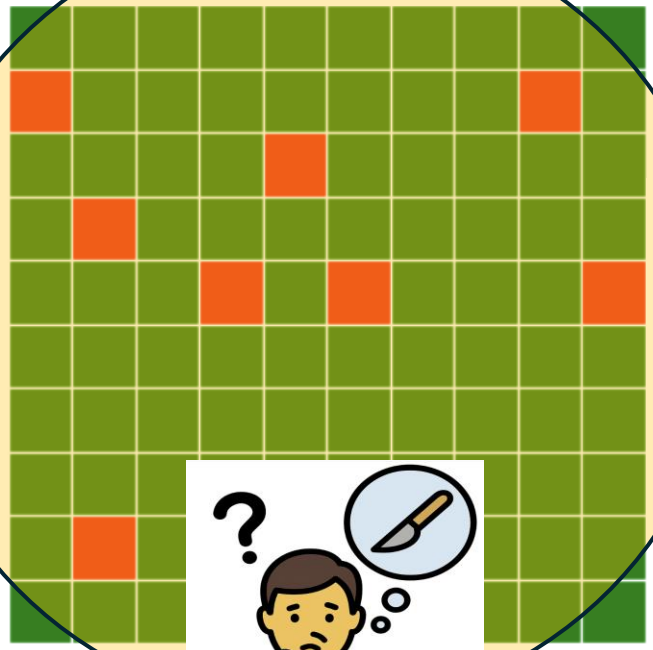
OBESITY: PUBLIC HEALTH vs CLINICAL APPROACH

Obesity



Epidemiologist
Public Health Official

Clinician



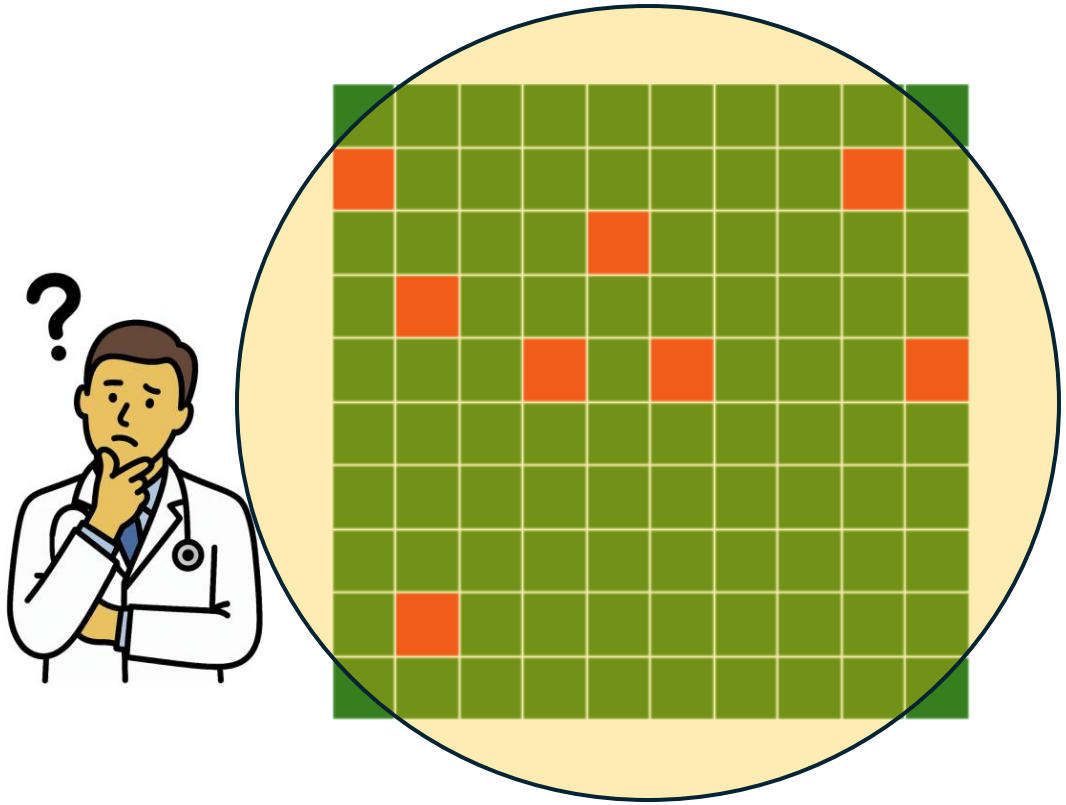
Patient

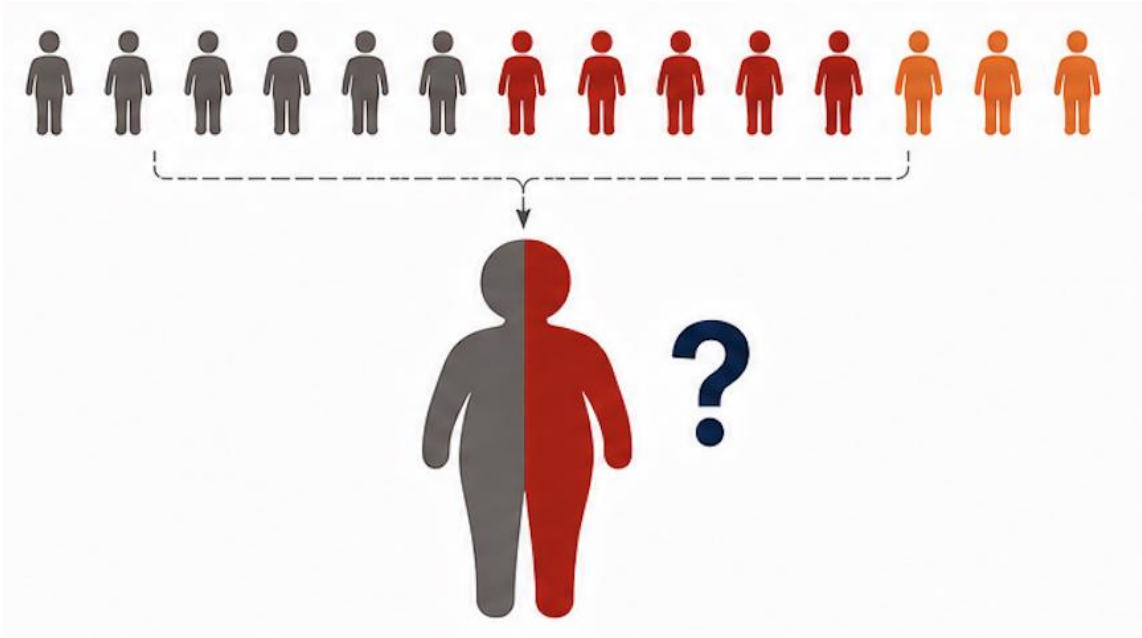
Insurer
Policymaker

Affected

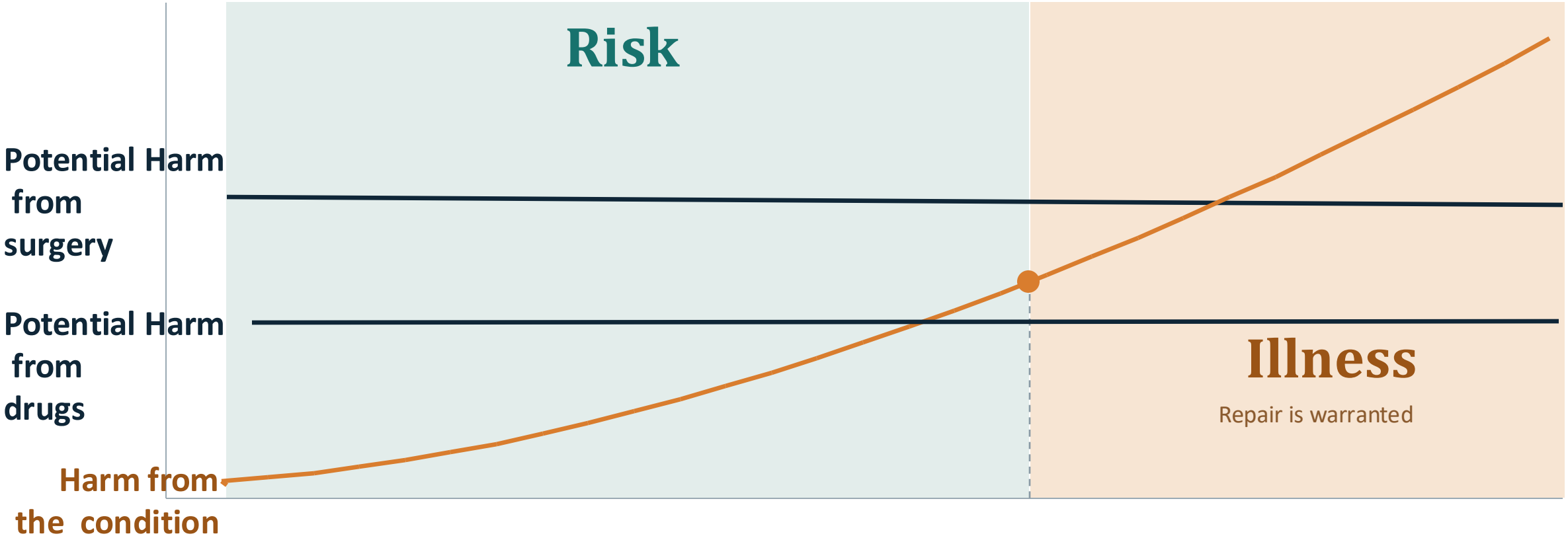
Not Affected

Obesity





Where treatment becomes rational

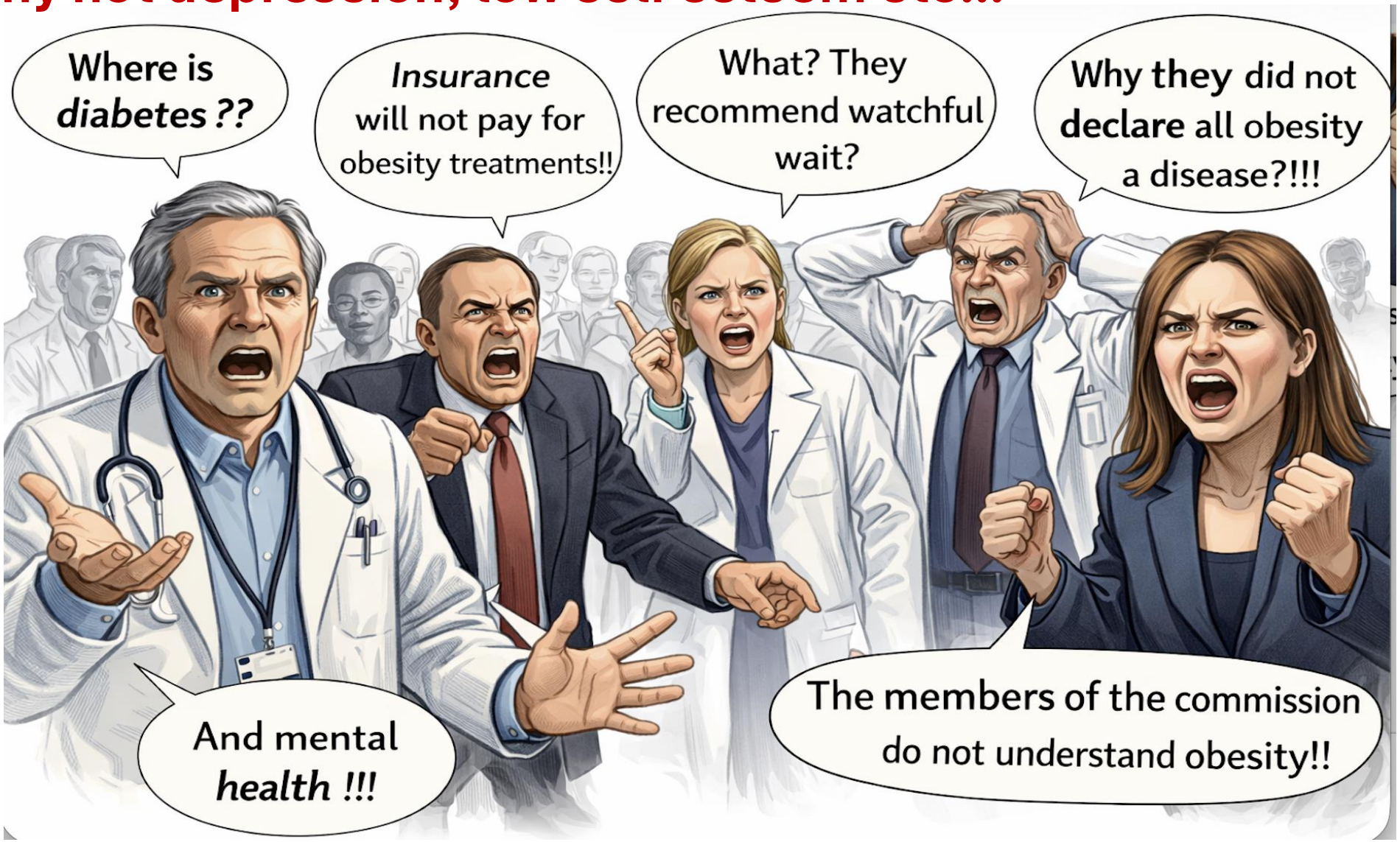


Treatment risk exists whether the patient is ill, or not

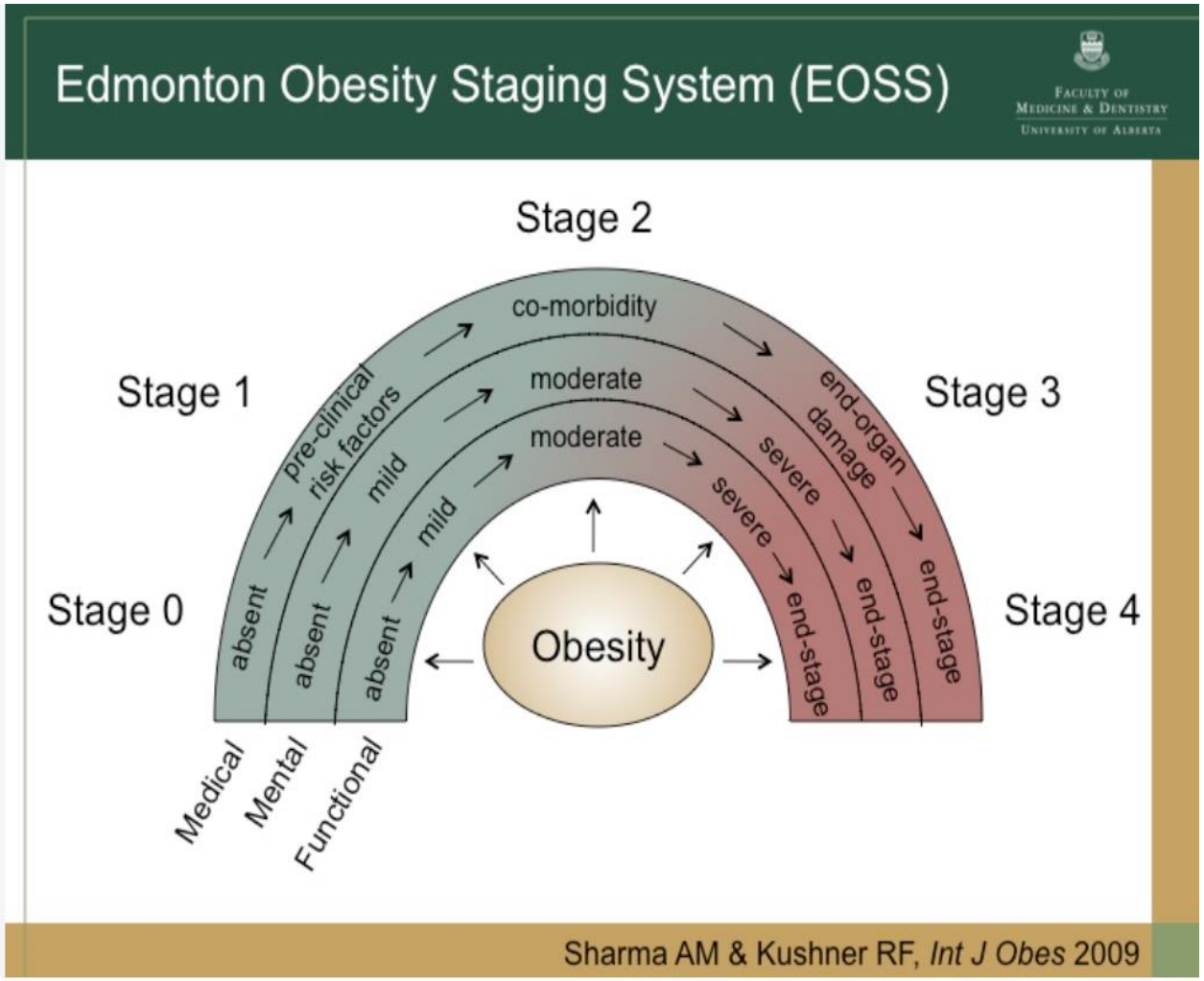
Evidence that Physical Phenotype **CANNOT** be a disease diagnosis

SPECIFICITY

Why diabetes is not part of the definition of clinical obesity … why not depression, low self esteem etc…



… Because Clinical/Preclinical Obesity is not a management framework but a disease diagnosis



Is any of this a Stage 4 Obesity disease?

BMI 30 plus:

- Retinophaty/blindness?
- Severe depression?
- Symptomatic coronary artery stenosis
- Congenital mitral valve defect > Heart failure?
- COPD Emphysema?
- Cancer?

Phenotype (risk) vs disease

Everyone with an obesity phenotype

Manifestation

Caused by the adiposity

Resolves

Treating the condition works

Comorbidity

Only associated with it

May not resolve

The cause lies elsewhere

Nothing

No manifestation at all

Nothing to resolve

No benefit is available

Refractory Hyperglycemia After Gastric Bypass Surgery: A Novel Subtype of Type 2 Diabetes?

Francesco Rubino,[1] Alpana P. Shukla,[2] David E. Cummings,[3] Matthew W. Rosenbaum,[2] Ashwin Soni,[2] and Geltrude Mingrone[4]

Diabetes Care 2014;37:e254–e255 | DOI: 10.2337/dc14-1481

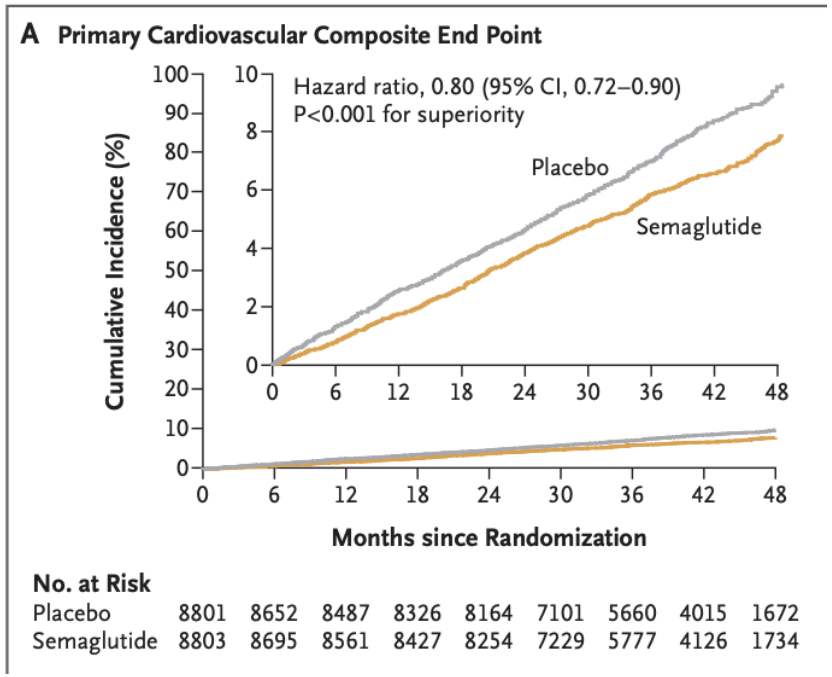
RYGB in pts with T2D
Cases presented documenting **absolute non-responders**
HbA1c and fasting glucose **unchanged or worse at 12 months on the same or more medication,**

Adequate weight loss (28%, with two exceeding 50% excess weight loss.)
All had **normal fasting C-peptide**, so no insulin deficiency.
All but one had no anti-GAD65 (positive case had normal C-peptide).
Duration of diabetes: 3 year - to 10 +
Including insulin-naive.
Hypertension and dyslipidaemia also failed to improve.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 DECEMBER 14, 2023 VOL. 389 NO. 24

Semaglutide and Cardiovascular Outcomes in Obesity without Diabetes

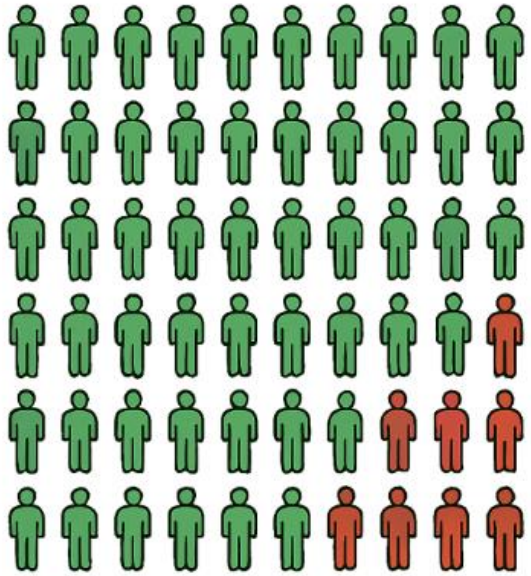


Primary endpoint: death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke

Primary cardiovascular end-point"
569 / 8803 patients (6.5%) in the semaglutide group
701 of the 8801 patients (8.0%) in the placebo group (HR, **0.80**;; P<0.0)0

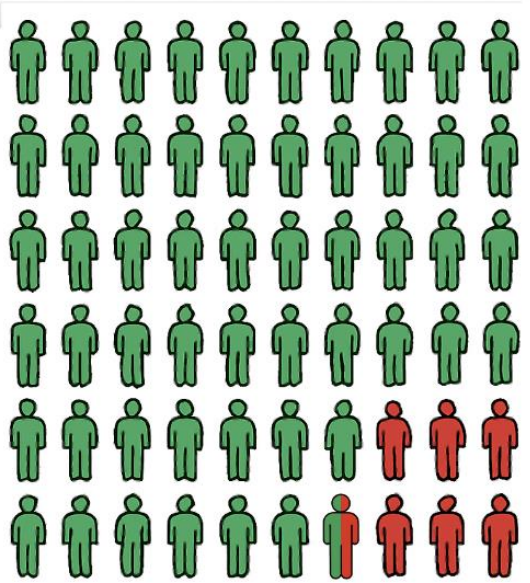
8% have MACE

92% DO NOT have MACE



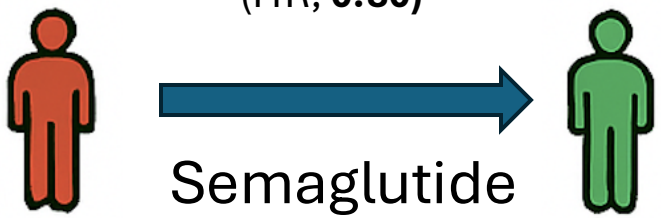
Semaglutide

20% MACE REDUCTION
(HR, **0.80)**

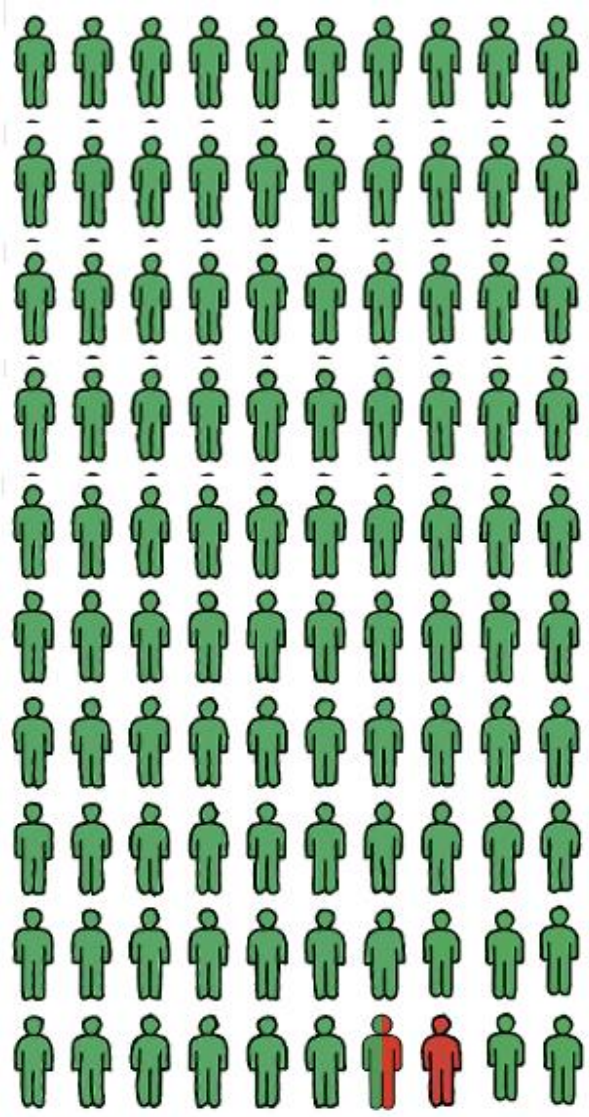


MACE REDUCTION in PERSON WITH OBESITY AT HIGH CV RISK

20% RISK REDUCTION
(HR, **0.80)**



Semaglutide



NNT: 67

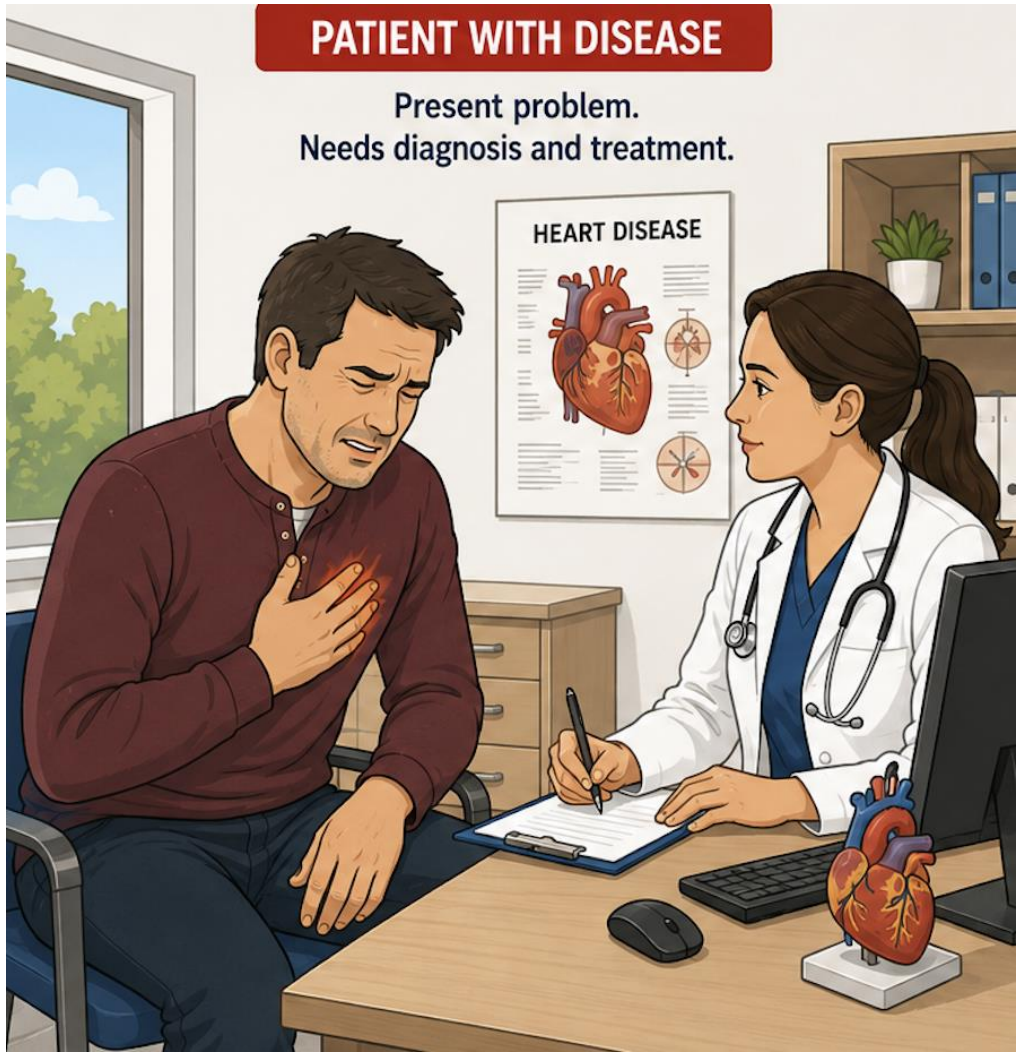
Games of chance:

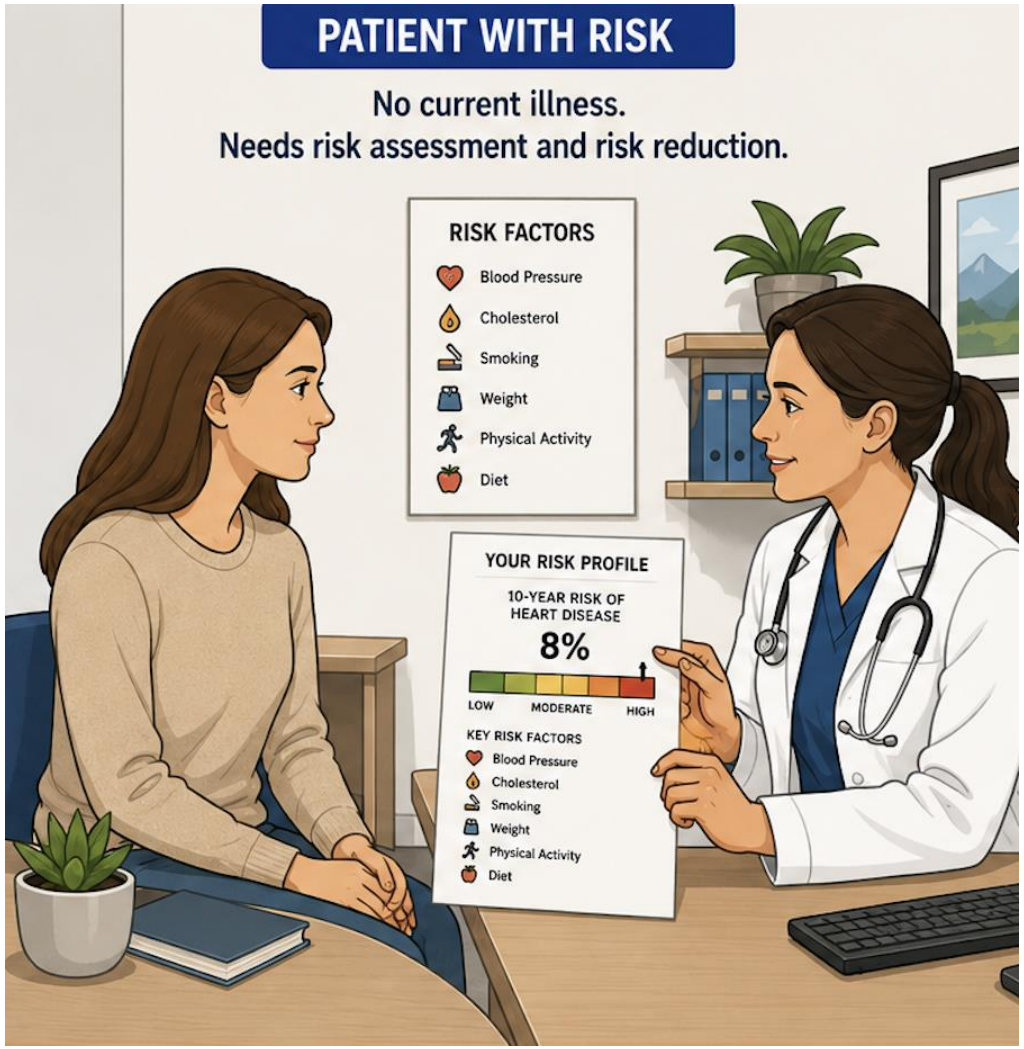
- **Correctly guessing a specific number on two dice added together, twice in a row** (≈ 1.4%)

- **Winning on a single roulette number** 1 in 37 —**is *about twice as likely*** as 1:67

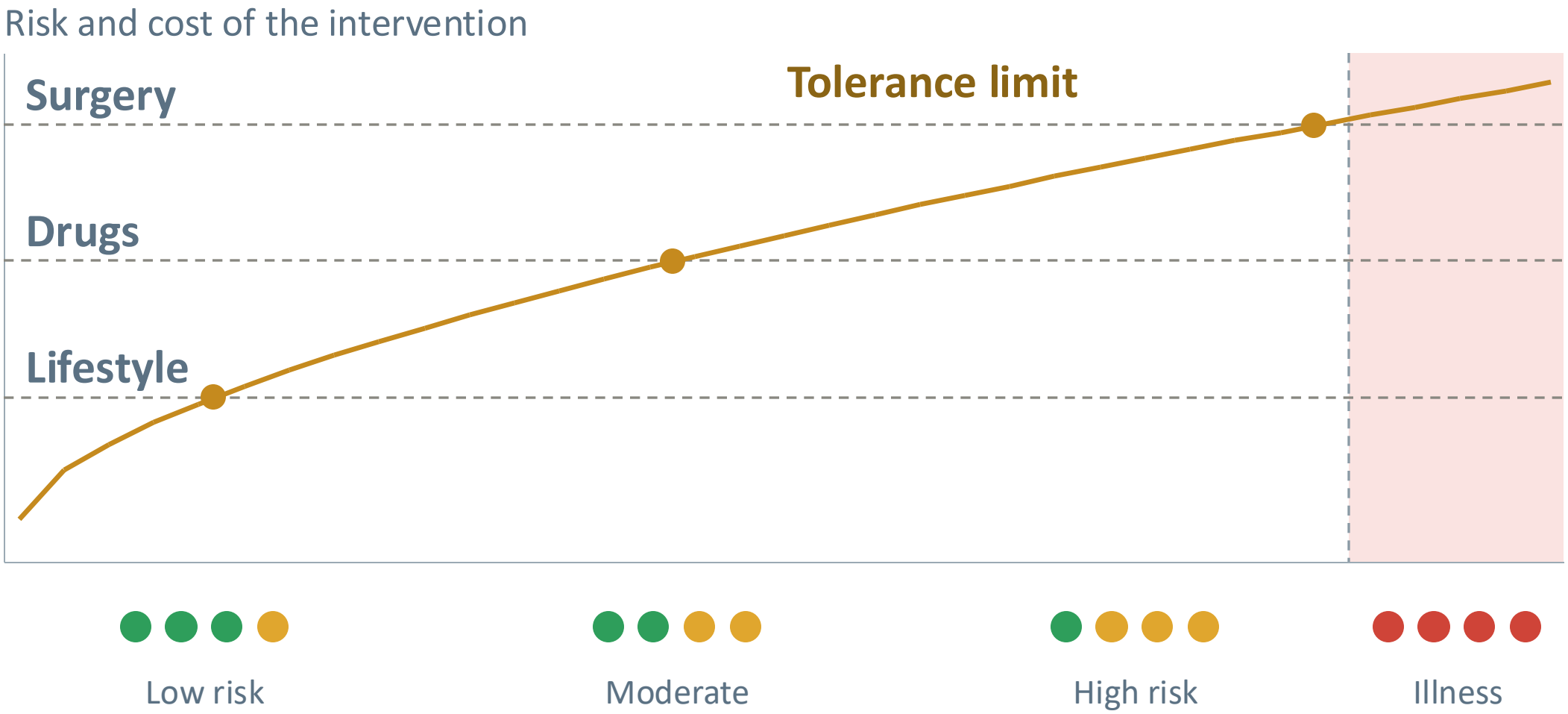
ChatGPT

Disease Treatment vs Risk Management





Tolerance rises as risk rises



TWO ENTERPRISES

Treatment of risk is not disease treatment

Treatment of risk

Prevent what has not happened

Who is in the group

Aim: prevent progression

Success: an event avoided

Harm tolerated: very little

Disease treatment

Repair what is present

Who is in the group

Aim: repair what is present

Success: improvement or remission

Harm tolerated: more

Will not progress

At real risk

Already ill

Every risk-defined group contains people for whom there was never anything to prevent.

JAMA Network Open

Original Investigation | Nutrition, Obesity, and Exercise

New Obesity Definition and Clinical Obesity Prevalence for Global Metabolic Bariatric Surgery

Simone Cremona, MD; Ricardo V. Cohen, MD; Francois Pattou, MD; Anna Casajoana, MD, PhD; Guilherme Sampaio Souza, RN; Violeta Raverdy, MD; Helene Verkindt, MD; Beatriz T. L. Blasio, MD; Pia Roser, MD; Robert Caiazzo, MD, PhD; David Benaiges, MD, PhD; Tarissa B. Zanata Petry, MD; Francesco Rubino, MD

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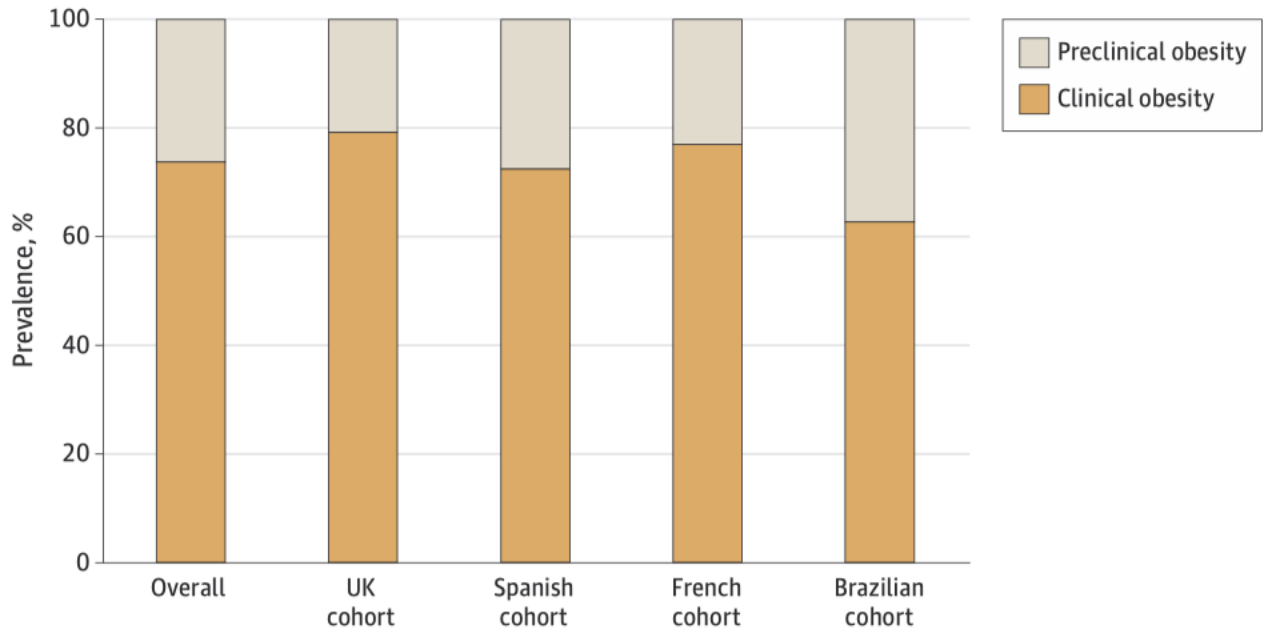
Figure 1. Bar Graph of Prevalence of Clinical and Preclinical Obesity Among Metabolic Bariatric Surgery Candidates Across International Metabolic Bariatric Surgery Centers



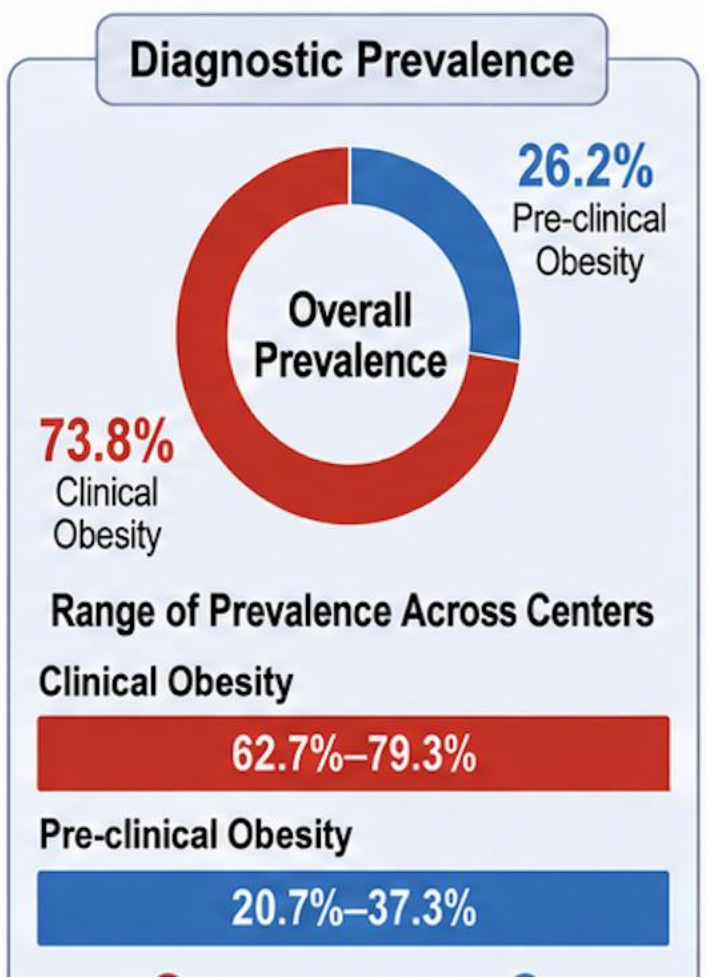


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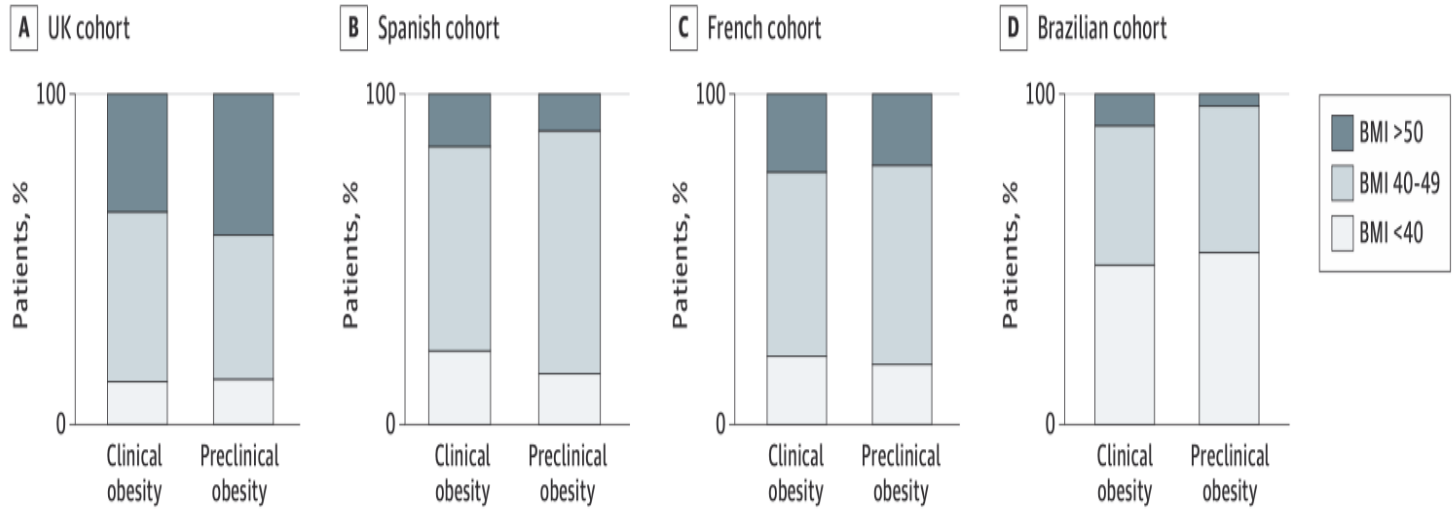
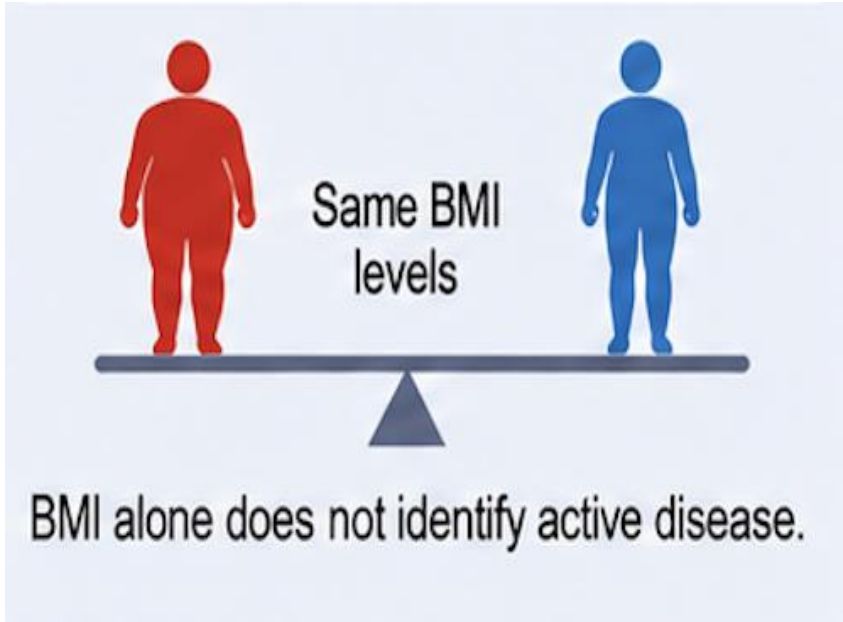
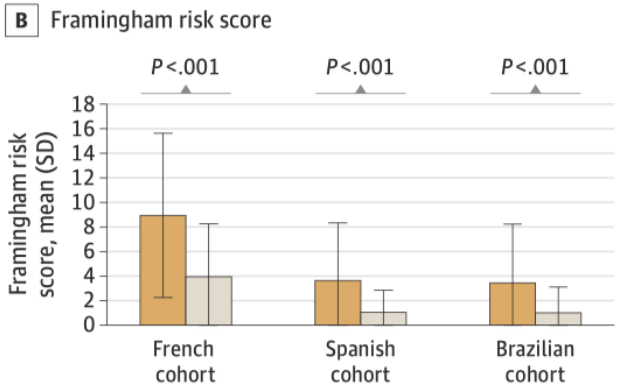
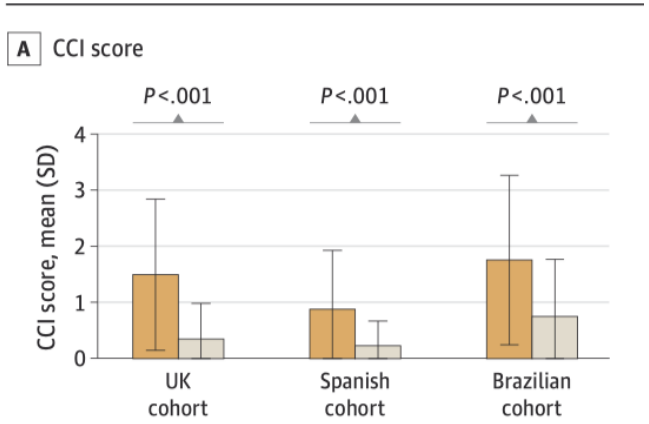
Figure 2. Bar Graphs of the Distribution of Body Mass Index (BMI) Categories Among Patients With Clinical and Preclinical Obesity Across International Metabolic Bariatric Centers

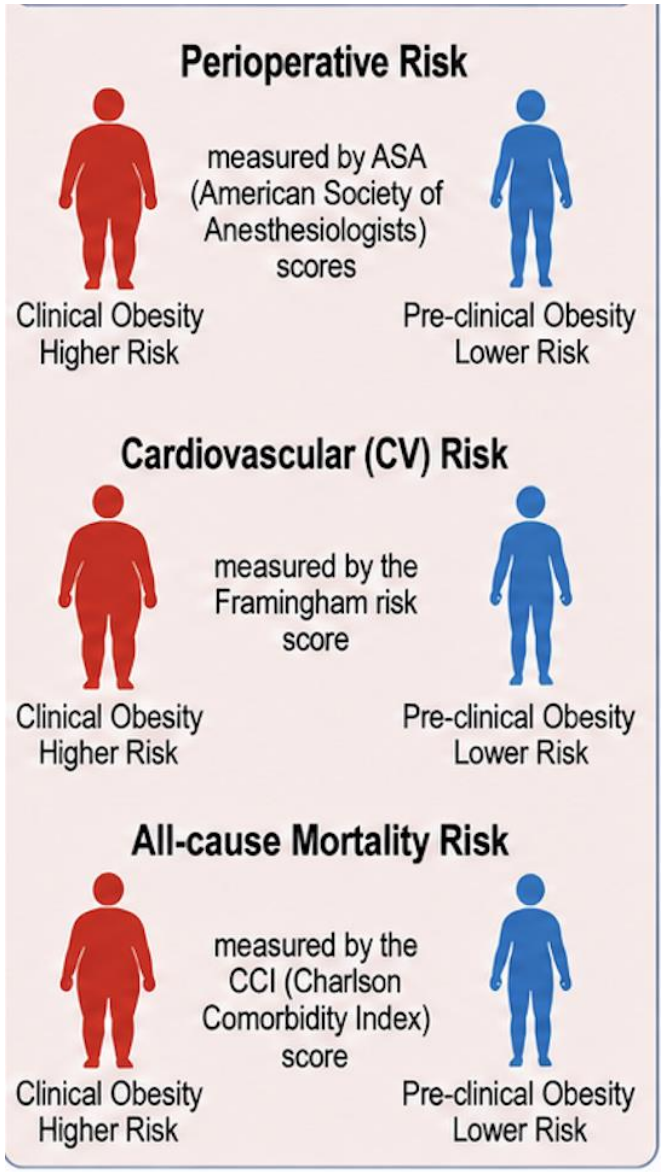


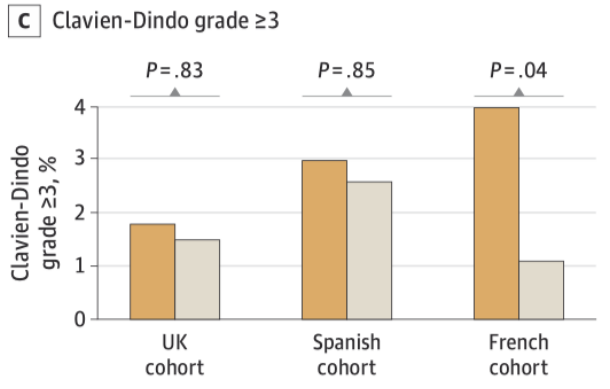
Proportion of patients within each BMI (calculated as weight in kilograms divided by height in meters squared) category.

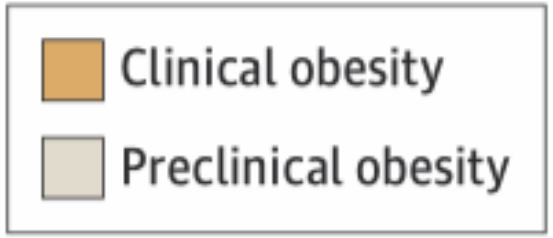



B Framingham risk score
P<.001
P<.001
P<.001
Framingham risk score, mean (SD)
18
16
14
12
10
8
6
4
2
0
French cohort
Spanish cohort
Brazilian cohort

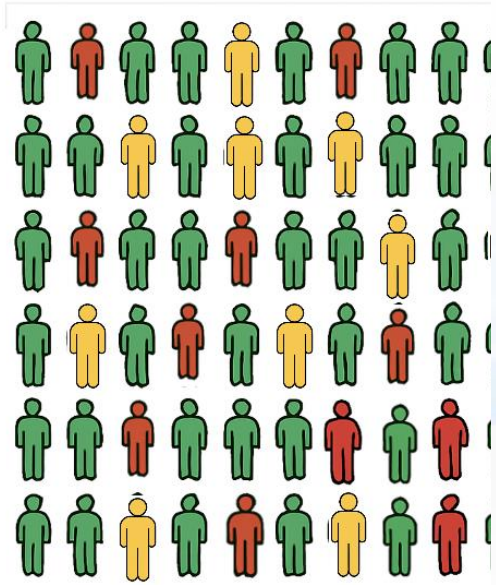

A CCI score
P<.001
P<.001
P<.001
CCI score, mean (SD)
4
3
2
1
0
UK cohort
Spanish cohort
Brazilian cohort


Perioperative Risk
measured by ASA (American Society of Anesthesiologists) scores
Clinical Obesity Higher Risk
Pre-clinical Obesity Lower Risk
Cardiovascular (CV) Risk
measured by the Framingham risk score
Clinical Obesity Higher Risk
Pre-clinical Obesity Lower Risk
All-cause Mortality Risk
measured by the CCI (Charlson Comorbidity Index) score
Clinical Obesity Higher Risk
Pre-clinical Obesity Lower Risk


C Clavien-Dindo grade ≥3
P=.83
P=.85
P=.04
Clavien-Dindo grade ≥3, %
4
3
2
1
0
UK cohort
Spanish cohort
French cohort


Clinical obesity
Preclinical obesity

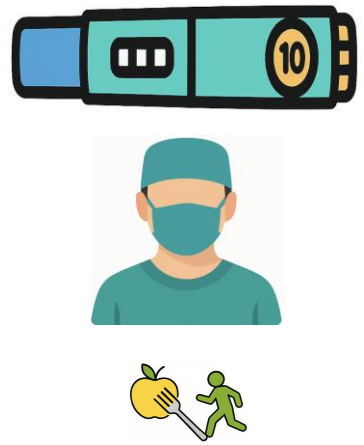
Obesity



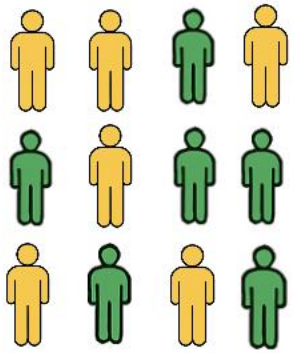
Diagnosis

Clinical Obesity

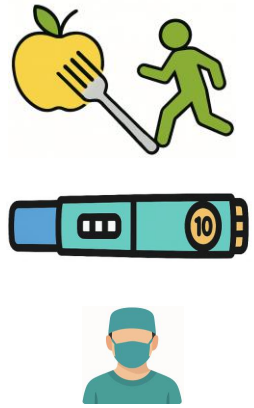
Disease Staging



Pre-Clinical Obesity



Risk-Scoring



The Future of Obesity Care