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# Obesità metabolicamente sana: esiste?

27 - 29 novembre 2025

Padova Congress
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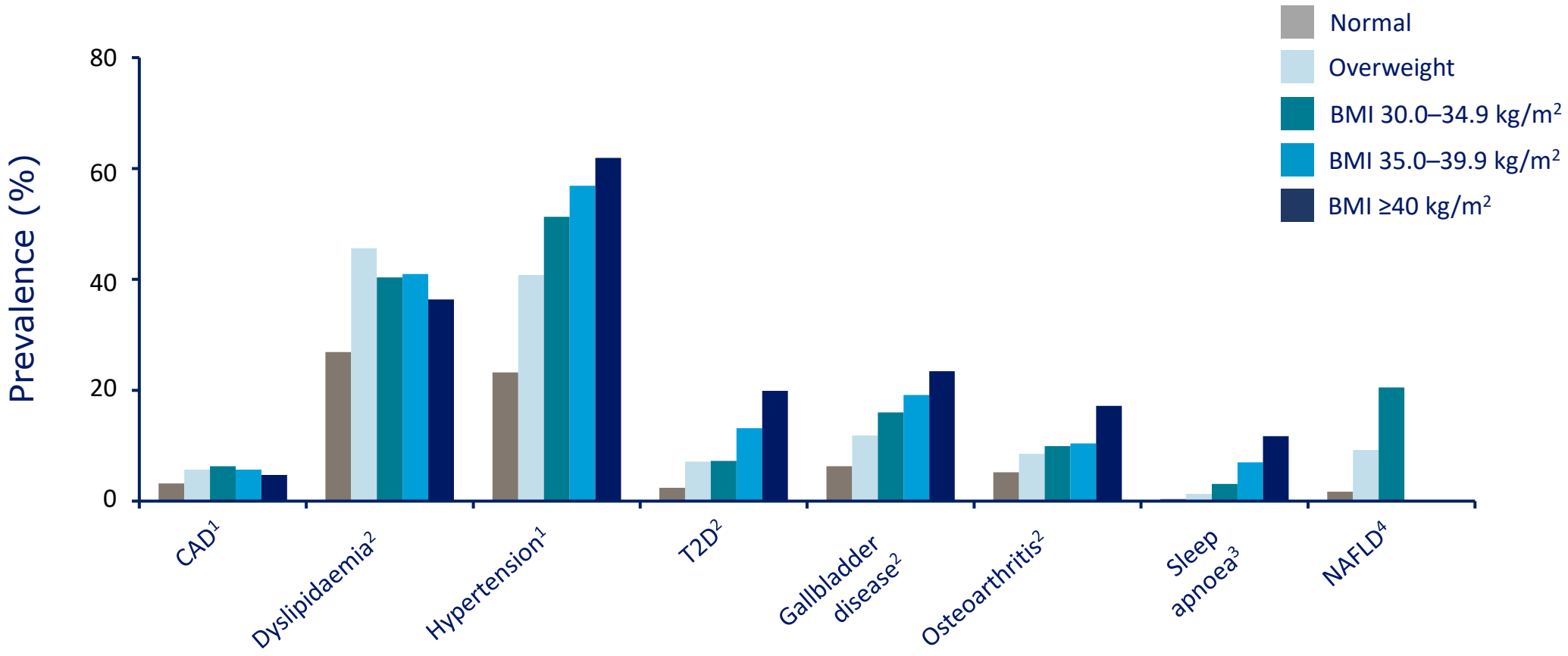
Ricerca e cura per la tua salute IRCCS




Data taken from the female[1,2,3] and male[4] population.
BMI, body mass index; CAD, coronary artery disease; NAFLD, non-alcoholic fatty liver disease; T2D, type 2 diabetes

1. Pantalone *et al. BMJ Open. 2017;7:e017583*; 2. Must *et al. JAMA* 1999;282:1523–9; 3. Li *et al. Prev Med* 2010;51:18–23;
4. Church *et al. Gastroenterology* 2006;130:2023–30

# Multi-morbidity is prevalent with high BMI

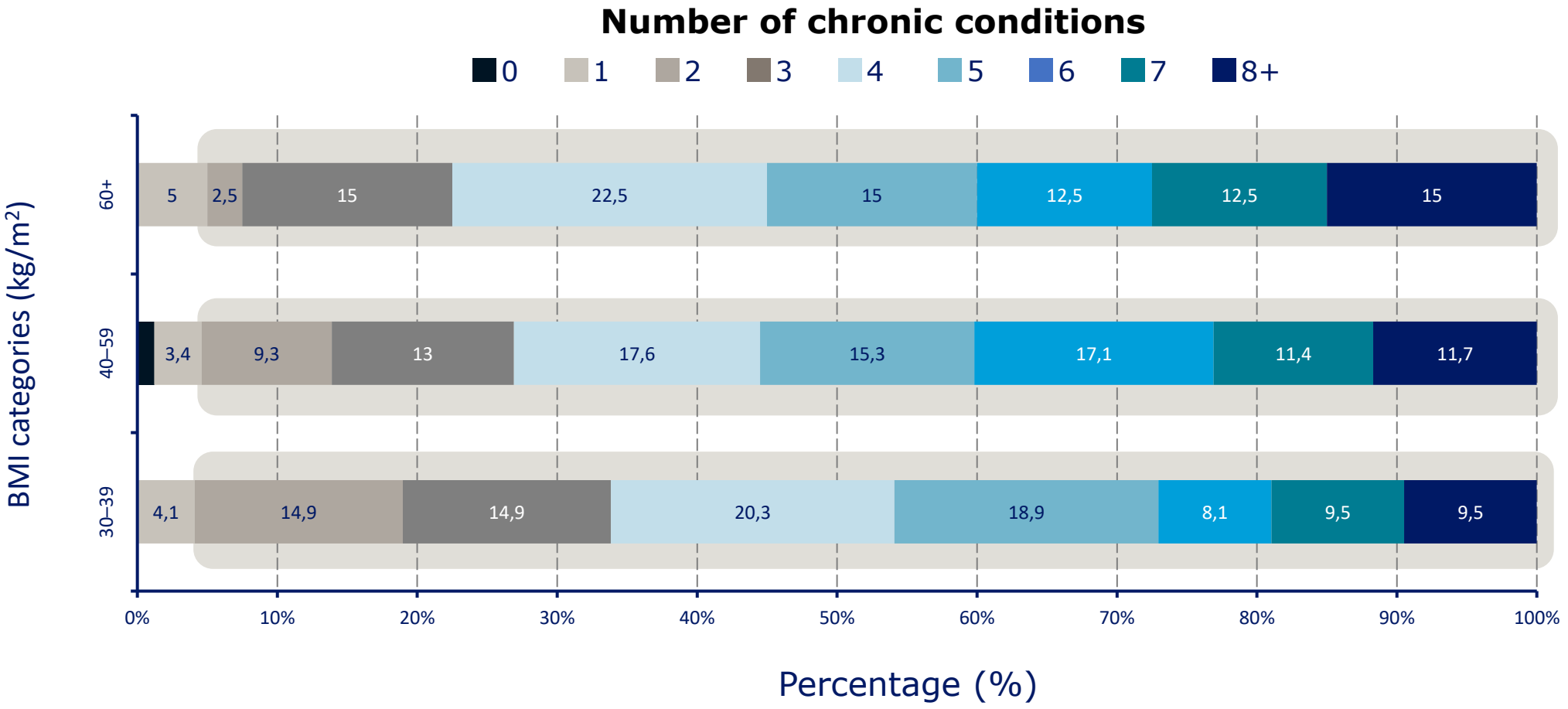
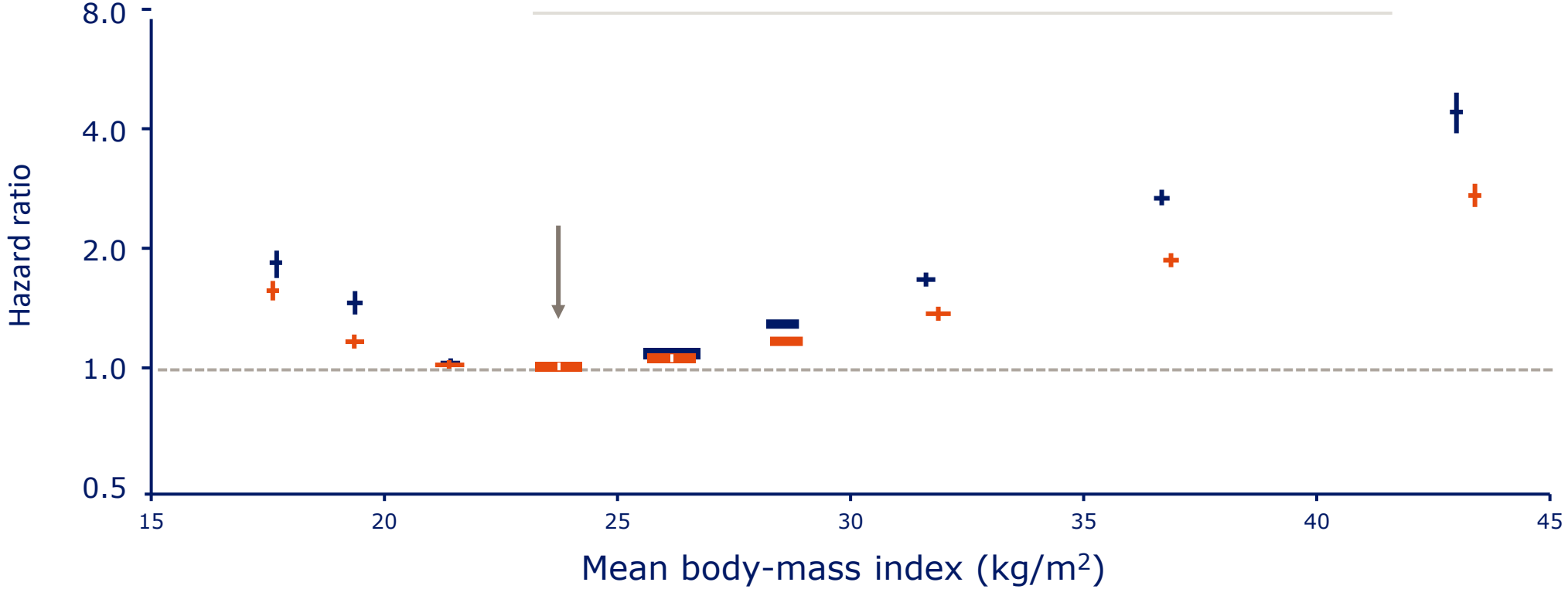



Figure adapted from Agborsangaya *et al. Obesity (Silver Spring)* 2015;23:707–12

# Association of BMI with all-cause mortality

| | Studies | Participants | Deaths | HR per 5 kg/m$^2$ |
|---|---|---|---|---|
| Men | 157 | 913,174 | 115,328 | 1.51 (1.46-1.56) |
| Women | 141 | 2,743,371 | 264,657 | 1.30 (1.26-1.33) |

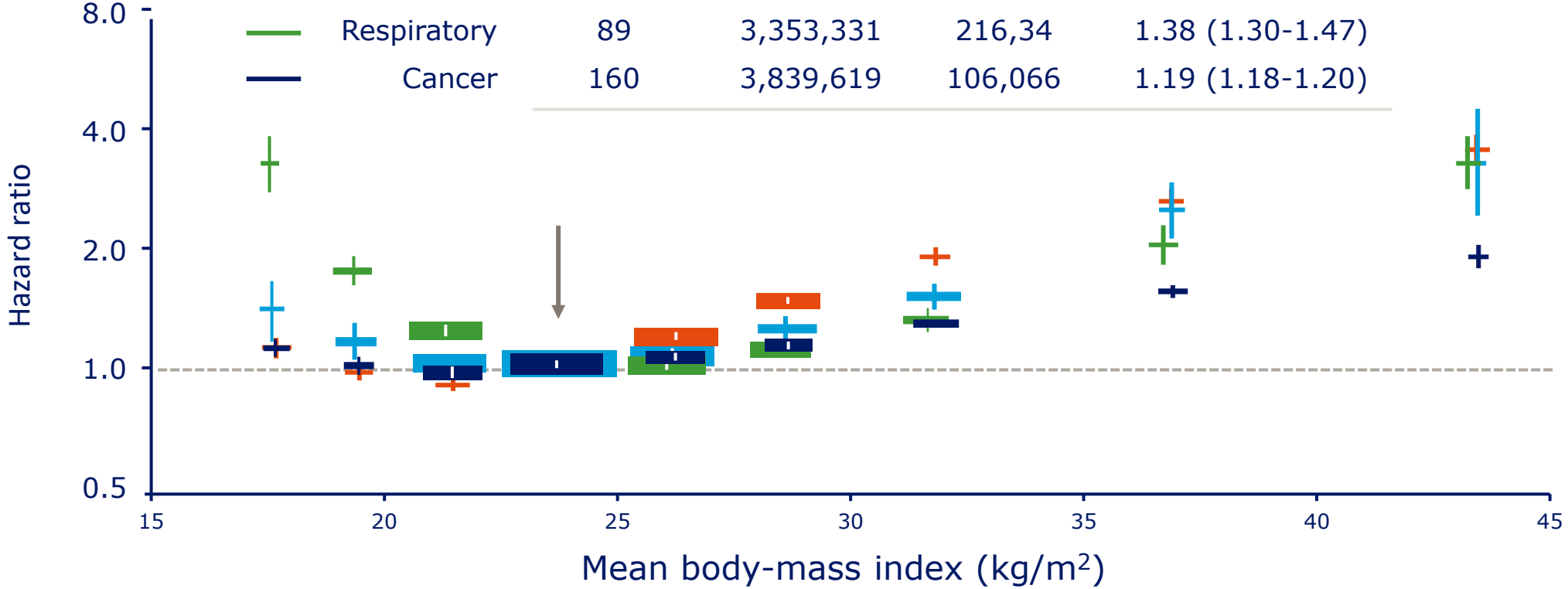



The reference category is shown with the arrow and is 22.5–<25.0 kg/m$^2$. HR; hazard ratio

Global BMI Mortality Collaboration. *Lancet*. 2016. pii: S0140-6736(16)30175-1.

# Association of BMI with all-cause mortality

| | Studies | Participants | Deaths | HR per 5 kg/m$^2$ |
|---|---|---|---|---|
| CHD | 124 | 3,599,426 | 54,872 | 1.42 (1.35-1.49) |
| Stroke | 114 | 3,580,423 | 40,084 | 1.42 (1.35-1.50) |
| Respiratory | 89 | 3,353,331 | 216,34 | 1.38 (1.30-1.47) |
| Cancer | 160 | 3,839,619 | 106,066 | 1.19 (1.18-1.20) |




The reference category is shown with the arrow and is 22.5–<25.0 kg/m$^2$. HR; hazard ratio

Global BMI Mortality Collaboration. *Lancet*. 2016. pii: S0140-6736(16)30175-1.

# OBESITA' METABOLICAMENTE SANA MHO

«*However, although obese subjects, as a group, are at increased risk for cardio-metabolic complications compared with normal-weight subjects,* ***not all obese individuals will ultimately develop these complications***»

Current Obesity Reports (2020) 9:109–120
https://doi.org/10.1007/s13679-020-00375-0

METABOLISM (M DALAMAGA, SECTION EDITOR)

Check for updates

## Metabolically Healthy Obesity: Criteria, Epidemiology, Controversies, and Consequences

Agathocles Tsatsoulis[1] · Stavroula A. Paschou[2]

Published online: 16 April 2020

# Criteria

The term MHO applies to individuals who are obese (BMI > 30 kg/m2) and in whom cardio-metabolic risk factors are absent.

Currently, there are **not universally accepted criteria to identify individuals with MHO.**

In addition to BMI, the criteria used in most studies to define metabolic heath are frequently based on

1) absence of the MS
2) insulin sensitivity.



**Table 2** Criteria used for the definition of metabolically healthy obesity

| Criteria | Meigs [18] | Karelis [17] | Aguilar-Salinas [19] | Wildman [20] |
|---|---|---|---|---|
| WC, cm | ≥102 (M)<br>≥88 (F) | - | - | - |
| FPG, mg/dL | ≥100 or treatment | - | < 126 and no | ≥100 or treatment |
| BP, mmHg | ≥130/85 or treatment | - | < 140/90 and no | ≥130/85 or treatment |
| TG, mg/dL | ≥150 | < 150 | ≥150 | ≥150 |
| HDL, mg/dL | < 40 (M)<br>< 50 (F) | ≥50 | ≥40 | < 40 (M)<br>< 50 (F) |
| HOMA-IR | - | < 1.95 | - | 90th percentile |
| Others | - | TC < 200 mg/dL<br>LDL < 100 mg/dL | - | hsCRP < 90th percentile |
| MHO criteria: | < 3 of the above | ≥4 of the above | All of the above | < 2 of the above |
| BMI, kg/m2 | ≥30 | ≥30 | ≥30 | ≥30 |

*WC*, waist circumference; *FPG*, fasting plasma glucose; *BP*, blood pressure; *TG*, triglycerides; *HDL*, high-density lipoprotein; *HOMA-IR*, homeostasis model assessment of insulin resistance; *TC*, total cholesterol; *LDL*, low-density lipoprotein; *hsCRP*, high-sensitivity C-reactive protein; *MHO*, metabolically healthy obesity; *BMI*, body mass index

# CRITERIA

The need for harmonizing MHO definitions has been addressed by **the BioShare-EU project**, an international collaboration between European and Canadian institutes and cohort studies

**163,000 individuals in ten population-based cohort studies** from different countries in Europe have been evaluated to characterize clinical and metabolic factors associated with MHO and compare key characteristics defining MHO.

**In addition to BMI > 30 kg/m2, the harmonization effort proposed four parameters based on the NCEP ATP III criteria to define the metabolic phenotype**

**Table 3** Criteria for harmonizing MHO definitions in the BioShare-EU project

| Criteria | Thresholds |
|---|---|
| Blood pressure | SBP ≥ 130 mmHg or DBP ≥ 85 mmHg or use of antihypertensives |
| Blood glucose | ≥ 110 mg/dL or use of antidiabetic medications |
| HDL-cholesterol | < 40 mg/dL in men or < 50 mg/dL in women or treatment |
| Triglycerides | > 150 mg/dL or medication for elevated triglycerides |
| Diagnosis of CVD | Yes |

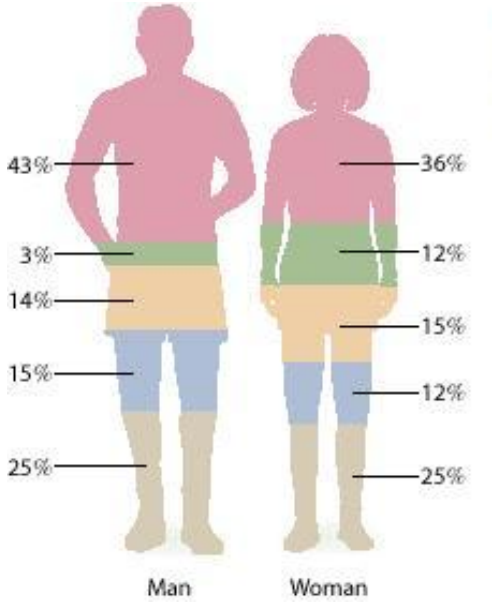
Metabolically healthy obesity is defined as having BMI ≥ 30 kg/m$^2$, none of the criteria of MS, and no cardio-vascular disease

van Vliet-Ostaptchouk JV,, et al. The prevalence of metabolic syndrome and metabolically healthy obesit in Europe: a collaborative analysis of ten large cohort studies. BMC Endocr Disord. 2014;14:9.

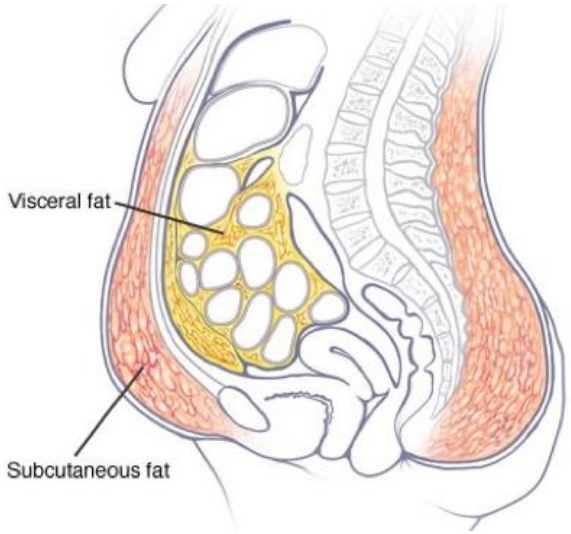
# CRITERIA
# Limiti

## BMI to define obesity can also be misleading

BMI cannot distinguish between fat and lean tissue




BMI cannot provide information on body fat distribution.




**Individual with high BMI may have increased muscle mass and be physically fit or may have increase fat mass but very little accumulation in visceral fat depots**

# CRITERIA
## Limiti

The absence of the MS alone does not exclude the presence of individual risk factors.

- Lifestyle
- Gender
- Ethnicity
- Age
- Insulin resistance indices
- Inflammatory
- cardio-respiratory fitness

Are generally accepted but these variables are not included in the current criteria of **MS**.

# Epidemiology
# Prevalence of MHO

**The proportion of obese subjects diagnosed to have MHO varies considerably depending on the criteria used to define MHO.**

**Third National Health and Nutrition Examination Survey (NHANES III), the prevalence of MHO**

- ❑ **47%** classified based on the absence of the MS as defined by the ATP III criteria
- ❑ **32%** classified based on insulin sensitivity (using HOMA-IR cut-off of 2.5),
- ❑ **10%** classified based on **all components** of the MS being absent.

- ❑ **50%** of obese subjects are MH when classified using DEXA for the measurement of body fat percentage
- ❑ **30%** when classified using BMI



Caution should be used how obesity is defined

# Epidemiology
# Prevalence of MHO

**BioShare-EU project.**

11,465 men and 16,612 women with obesity, age-standardized **prevalence on MHO was 12% across all cohorts**, with great variation between cohorts from different regions of Europe.

**MHO highest prevalence**

Women compared with men.

-Men (19%) was found in Italy,

**MHO prevalence decreases**

with age in both genders independent of geographic region and MHO criteria

van Vliet-Ostaptchouk JV,, et al. The prevalence of metabolic syndrome and metabolically healthy obesit in Europe: a collaborative analysis of ten large cohort studies. BMC Endocr Disord. 2014;14:9.

The prevalence of MHO ranged from **6 to 75%,** and this may vary according to several socio demographic variables such as gender, age, and race/ethnicity.

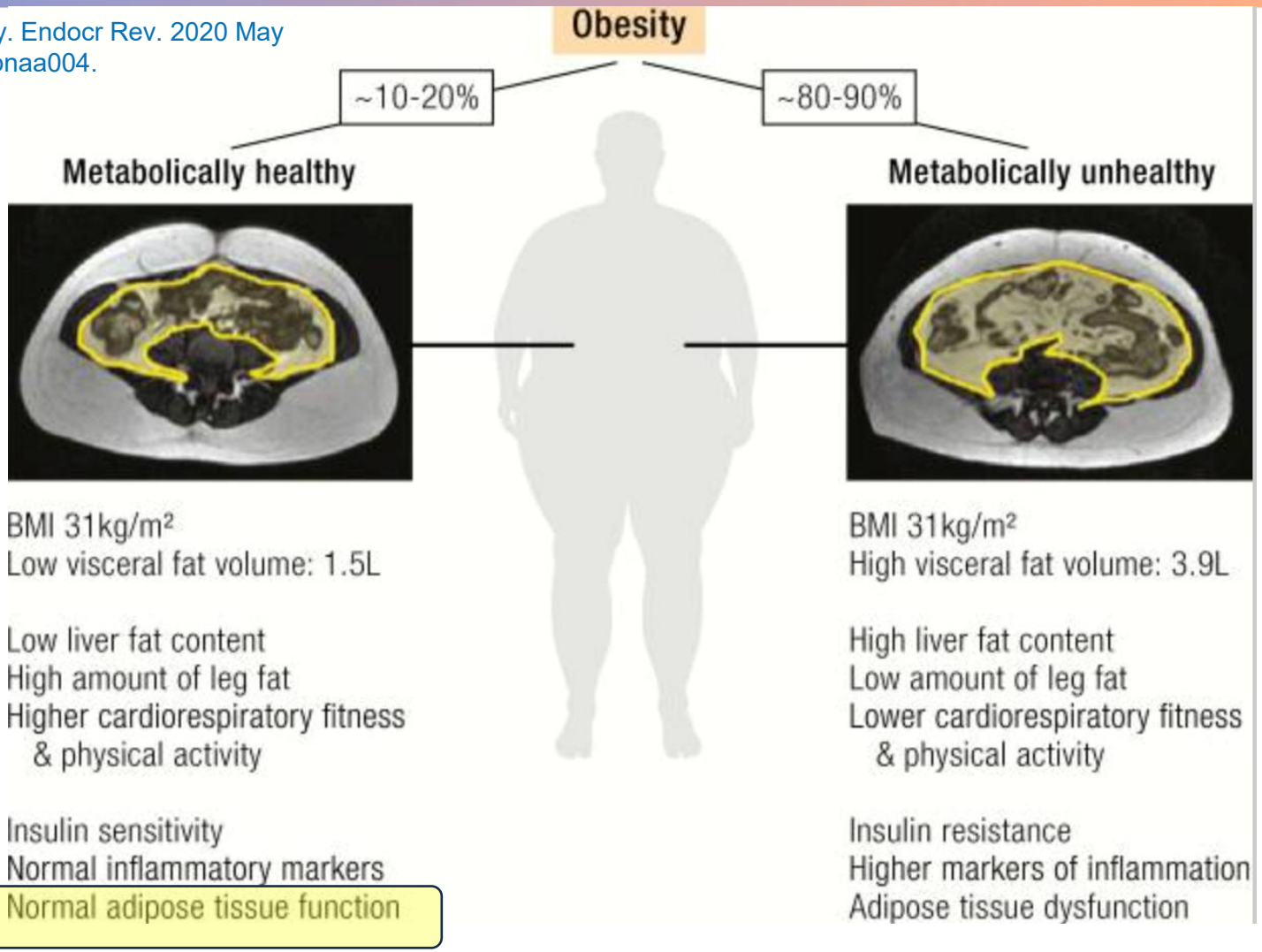
The prevalence of MHO **was higher in women and younger aged subjects**, and regarding race/ethnicity, the prevalence was higher in **Asian populations** compared with Caucasians or multi-ethnic groups

Rey-lopez JP et al . The prevalence of metabolically healthy obesity: a systematic review and critical evaluation of the definitions used. Obes Rev. 2014;15:781–90.

# MHO Phenotype

Blüher M. Metabolically Healthy Obesity. Endocr Rev. 2020 May 1;41(3):bnaa004. doi: 10.1210/endrev/bnaa004.

**Healthy lifestyle**
-healthy diet*
-high level of physical activity
-no smoking



frontiers | Frontiers in Nutrition

ORIGINAL RESEARCH
published: 25 April 2022
doi: 10.3389/fnut.2022.858206

# Adherence to the Mediterranean Diet and Risk of Metabolically Unhealthy Obesity in Women: A Cross-Sectional Study

*Alessandro Leone[1]*, Ramona De Amicis[1], Alberto Battezzati[1] and Simona Bertoli[1,2]*

**TABLE 1 |** Diagnostic criteria for metabolic phenotypes of obesity.

| **Definition of MHO** | |
|---|---|
| A women has been classified as MHO if **met 0 of the 4 MetS criteria** (WC excluded), which are the following: | |
| • Elevated triglycerides or drug treatment for elevated triglycerides | ≥150 mg/dl (1.7 mmol/l) |
| • Reduced high-density lipoprotein cholesterol or drug treatment for reduced HDL | <50 mg/dl (1.3 mmol/l) |
| • Elevated blood pressure or antihypertensive drug treatment | Systolic blood pressure ≥ 130 mm Hg and/or diastolic blood pressure ≥ 85 mm Hg |
| • Elevated fasting glucose or drug treatment of elevated glucose | ≥100 mg/dl (5.6 mmol/l) |
| **Definition of MUO** | |
| A women has been classified as MUO if **met 1 to 4 of the MetS criteria** reported above (WC excluded). | |

**TABLE 3 |** Characteristics of patients.

| | **MHO *N* = 449** | | **MUO *N* = 1666** | | |
|---|---|---|---|---|---|
| | **Median** | **IQR** | **Median** | **IQR** | ***P*-value** |
| Age (years) | 41 | 34; 49 | 51 | 42; 60 | <0.001 |
| BMI (kg/m$^2$) | 32.3 | 31.0; 34.1 | 33.7 | 31.6; 36.8 | <0.001 |
| Fat Free Mass (%) | 59.3 | 57.5; 61.0 | 57.3 | 55.3; 59.1 | <0.001 |
| Waist circumference (cm) | 100.5 | 96.0; 105.7 | 105.6 | 100.2; 112.0 | <0.001 |
| Visceral fat (mm) | 45.3 | 35.0; 58.2 | 63.7 | 48.5; 80.6 | <0.001 |
| Subcutaneous fat (mm) | 36.4 | 29.1; 43.5 | 33.9 | 26.9;42.1 | <0.001 |
| VAT:SAT ratio | 1.2 | 0.9; 1.8 | 1.8 | 1.3; 28 | <0.001 |

**TABLE 4 |** Association between the adherence to the Mediterranean diet risk of metabolically unhealthy obesity.

| | | **Adherence to the Mediterranean diet** | | |
|---|---|---|---|---|
| | | **Not adherent** | **Adherent** | ***P*-value** |
| Overall | MHO/MUO | 404/1470 | 45/196 | |
| | Median score | 6 | 9 | |
| | OR (95%CI) | 1 (ref.) | 0.91 (0.62; 1.34) | 0.624 |
| Premenopausal women | MHO/MUO | 321/683 | 26/57 | |
| | Median score | 6 | 9 | |
| | OR (95%CI) | 1 (ref.) | 1.18 (0.70; 1.99) | 0.532 |
| Postmenopausal women | MHO/MUO | 83/787 | 19/139 | |
| | Median score | 7 | 9 | |
| | OR (95%CI) | 1 (ref.) | 0.55 (0.31; 0.96) | 0.034 |

*Models adjusted for age, BMI, fat free mass (%), VAT:SAT ratio, past diet, marital status, education, smoking, physical activity, menopausal status, familiarity for diabetes and cardiovascular disease and antidepressants use.*

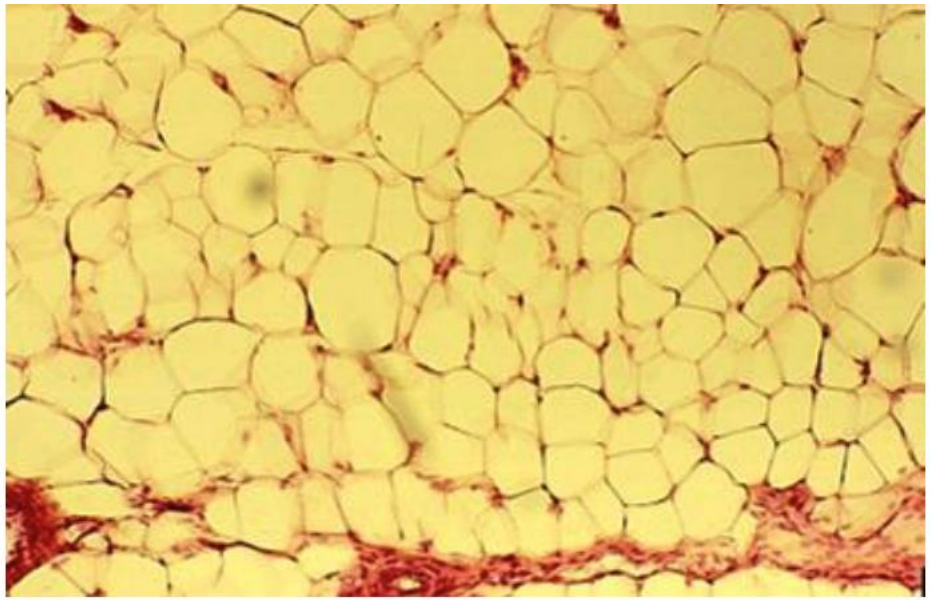
## Conclusion

In this study, the adherence to the Mediterranean diet was favorably associated with metabolic phenotype of obesity in older women. More specifically, the adherence to the Mediterranean diet was associated with a lower likelihood of MUO in postmenopausal women, independent of wide range on known confounders. Moreover, the result appears

# Adipocyte MHO Phenotype

**Role of Genetic Factors**

The amount and distribution of body fat and the number of adipocytes appear to be controlled by various factors, including sex and age but also **genetic factors and epigenetic influences**



**Positive energy balance**

↓

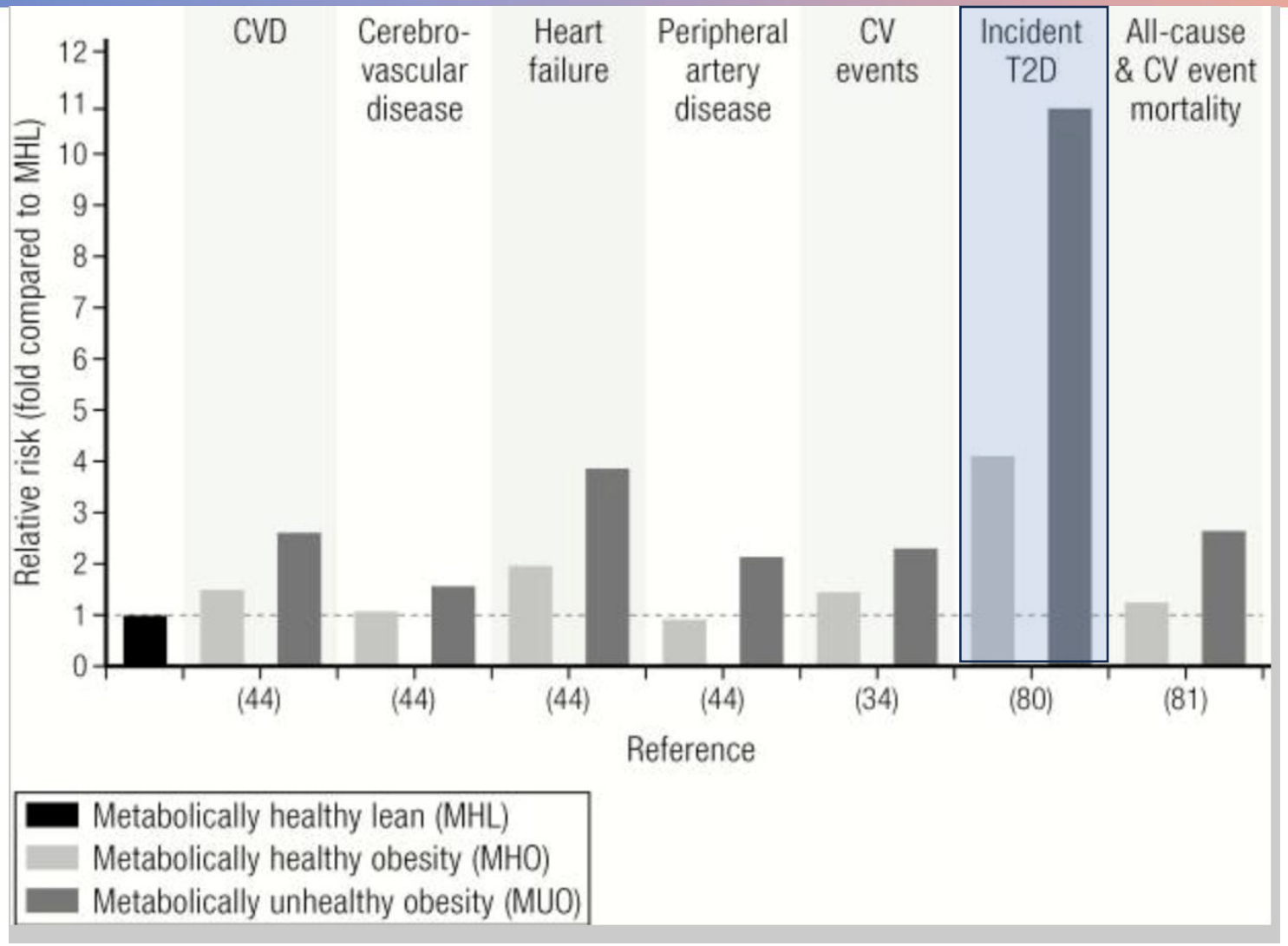
**Defective adipogenesis (Adiposopathy)**

(-) ↙ ↘ (+)

| | |
|---|---|
| **adipocyte hyperplasia** | **adipocyte hypertrophy (visceral adipocity)** |
| ↓ | ↓ |
| **adipose tissue expansion** | **adipose tissue dysfunction** |
| ↓ | ↓ |
| **storage of energy surplus** | **excess FFA release, reduced adiponectin secretion** |
| ↓ | ↓ |
| **normal liporegulation** | **ectopic lipid deposition + low grade inflammation** |
| ↓ | ↓ |
| **insulin sensitivity** | **induction of insulin resistance/hyperinsulinemia** |
| ↓ | ↓ |
| ***MHO phenotype*** | ***MUO phenotype*** |

Both genomewide and gene-expression studies showed that body fat distribution is influenced by a number of genetic loci and developmental genes, independently of BMI.

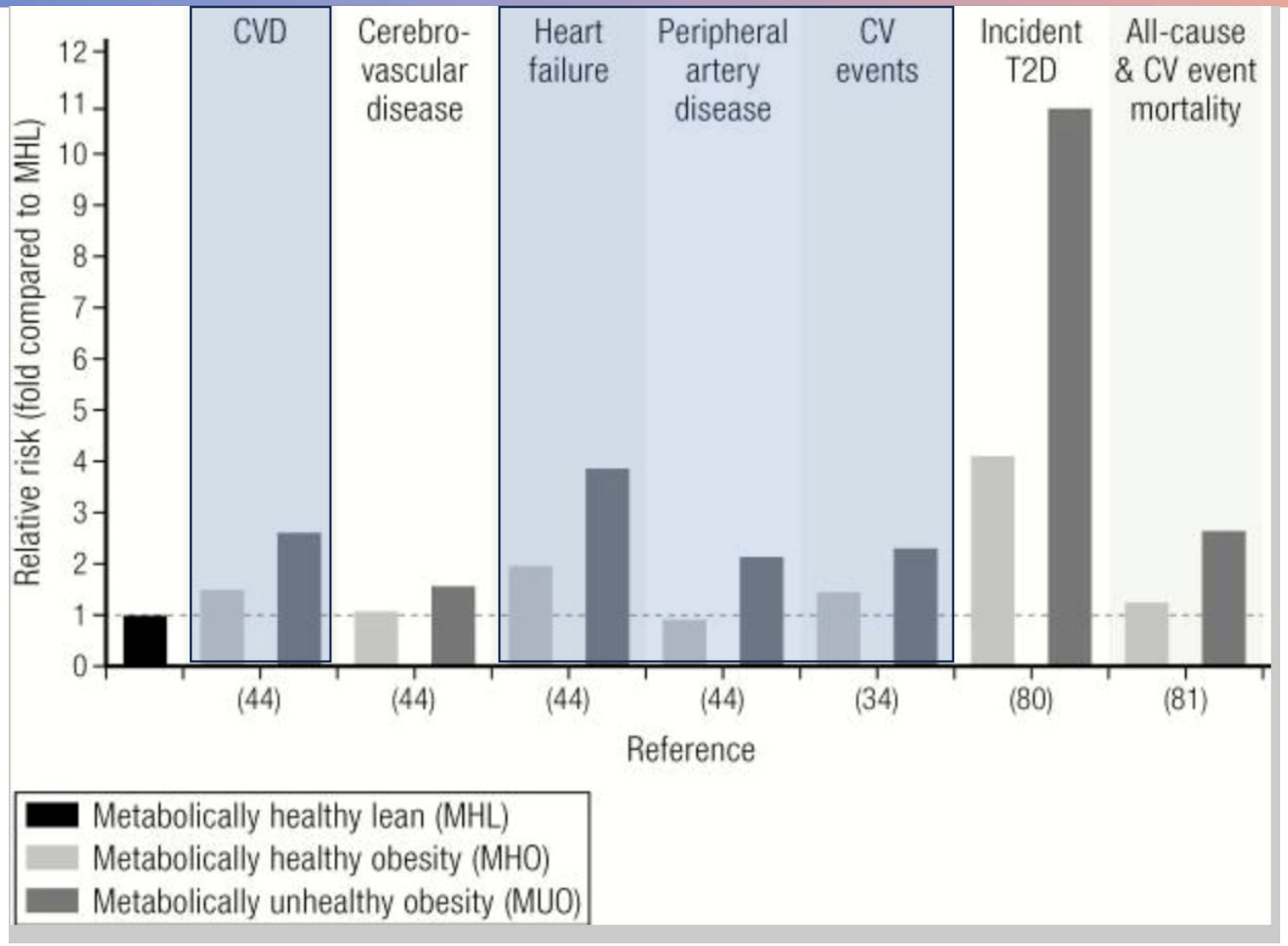
# MHO Phenotype




## T2DM

MHO were at more than **4 times greater risk of** developing T2DM over time than healthy normal-weight adults, although the risk was about **half that of MUO individuals**

# MHO Phenotype




## CV events

MHO is not necessarily a low-risk condition . The metabolically benign phenotype has and increased risk of CVD and death

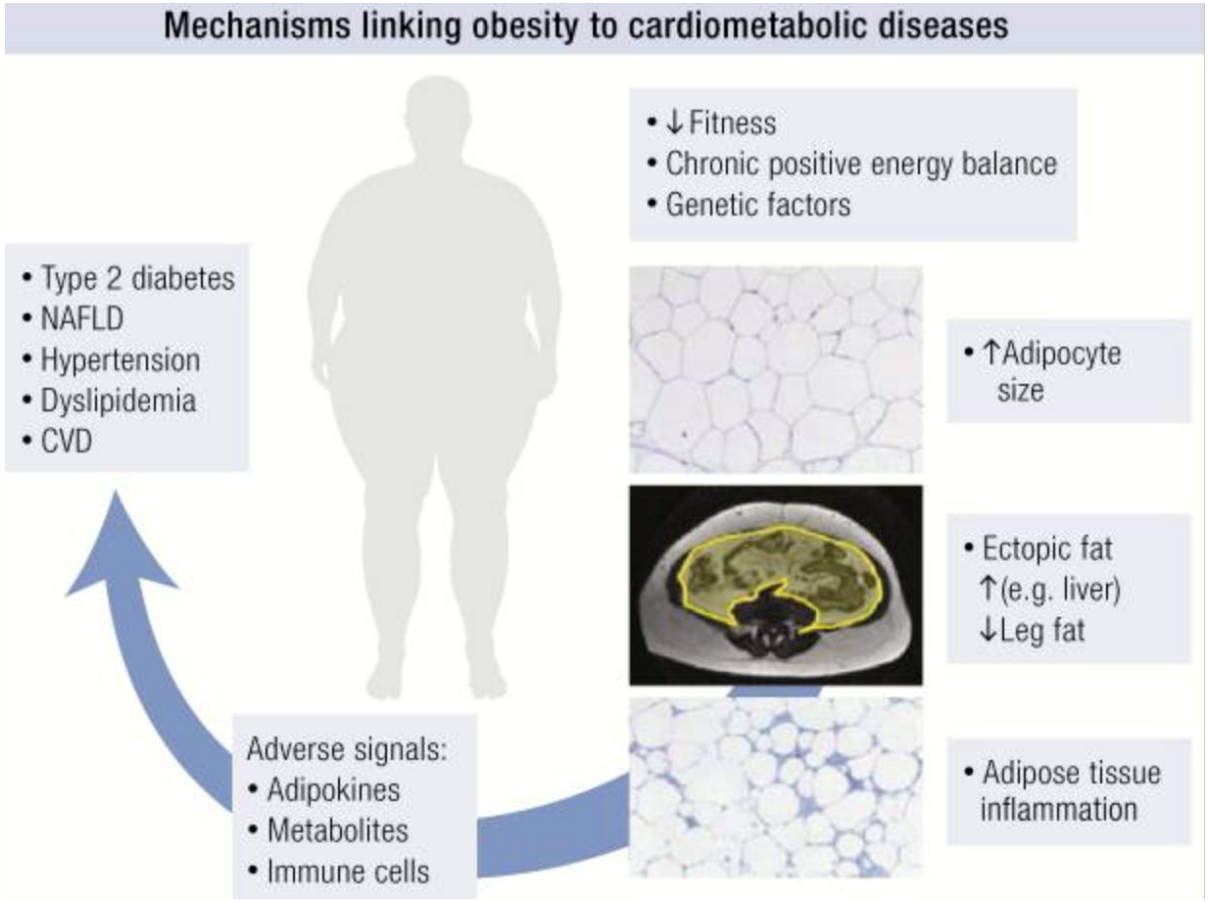
# The Natural History of MHO—Is MHO a Stable Condition?

MHO was initially thought as a **static condition**, but although some individuals can maintain their metabolic health status over time, it is becoming increasingly evident that **MHO status is transient in nature**

- studies with **follow-up up to 10 yea**rs, suggested that between **30% -50%** individuals with MHO convert to an unhealthy phenotype

- studies **with follow-up up to 20 years** suggested that between **50%** individuals with MHO convert to an unhealthy phenotype

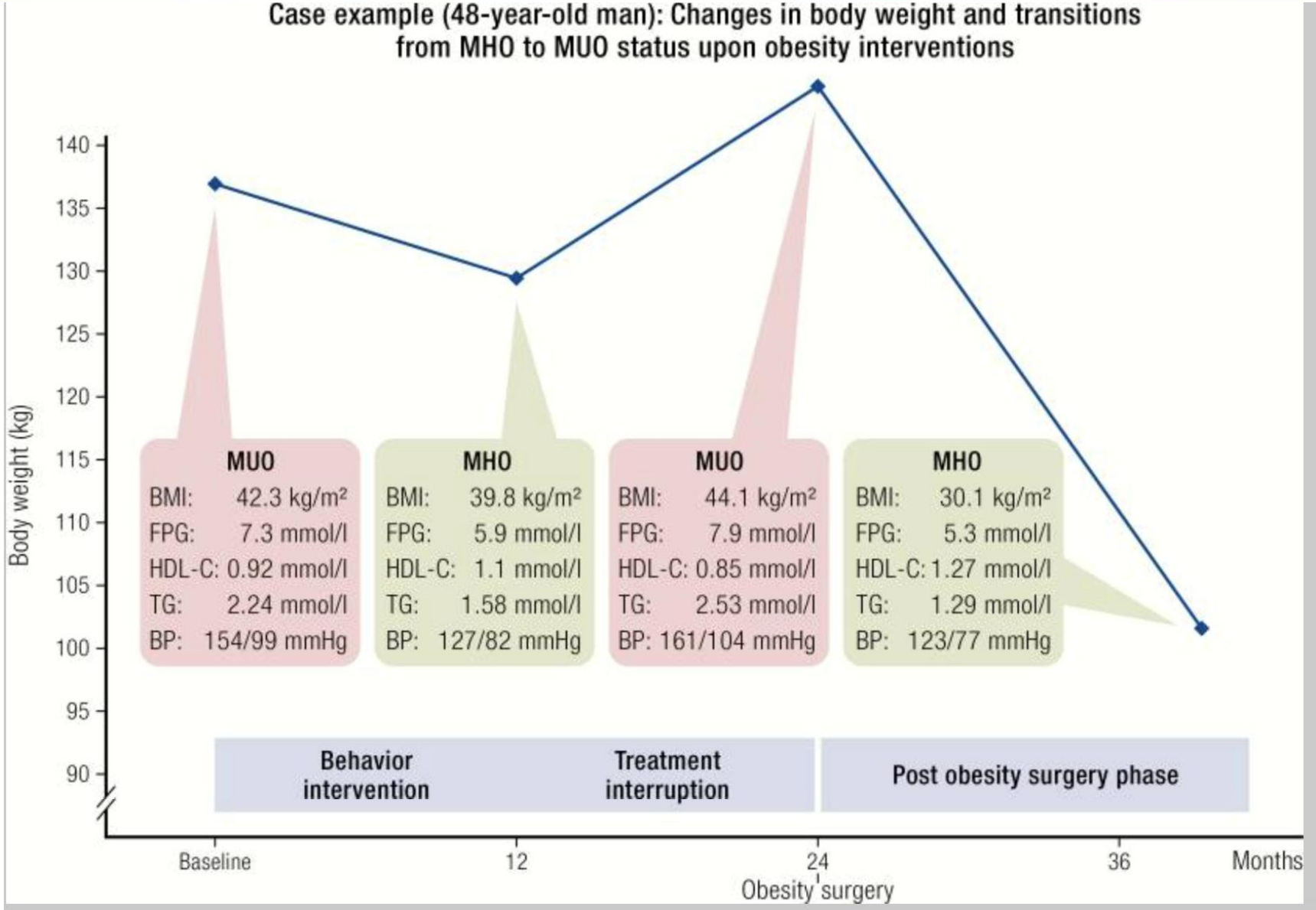
- studies with **follow-up up to 30** 6% of women with MHO remained metabolically healthy 30 years,




*Kramer CK, et al. Are metabolically healthy overweight and obesity benign conditions?: a systematic review and meta-analysis. Ann Intern Med. 2013;159:758–69.*

*Eckel N, et al Metabolically healthy obesity and cardiovascular events: a systematic review and meta-analysis. Eur J Prev Cardiol. 2016;23: 956–66.*

# Is MHO a Stable Condition?



# Conclusioni

**MHO:** sottogruppo di persone con **obesità (BMI ≥30 kg/m²)** ma **senza evidenti alterazioni cardiometaboliche**.

**Prevalenza: 10–30%**, variabile per età, sesso e criteri diagnostici.

## Caratteristiche fisiologiche del fenotipo MHO:

**Minore grasso viscerale** e **minore steatosi epatica**
**Maggior deposito di grasso sottocutaneo periferico** (ginoide, gambe)
**Miglior fitness cardiorespiratoria**
**Maggiore attività fisica spontanea**
**Maggiore sensibilità insulinica**
**Ridotti marker infiammatori** (CRP, IL-6)
**Funzione adipocitaria conservata**

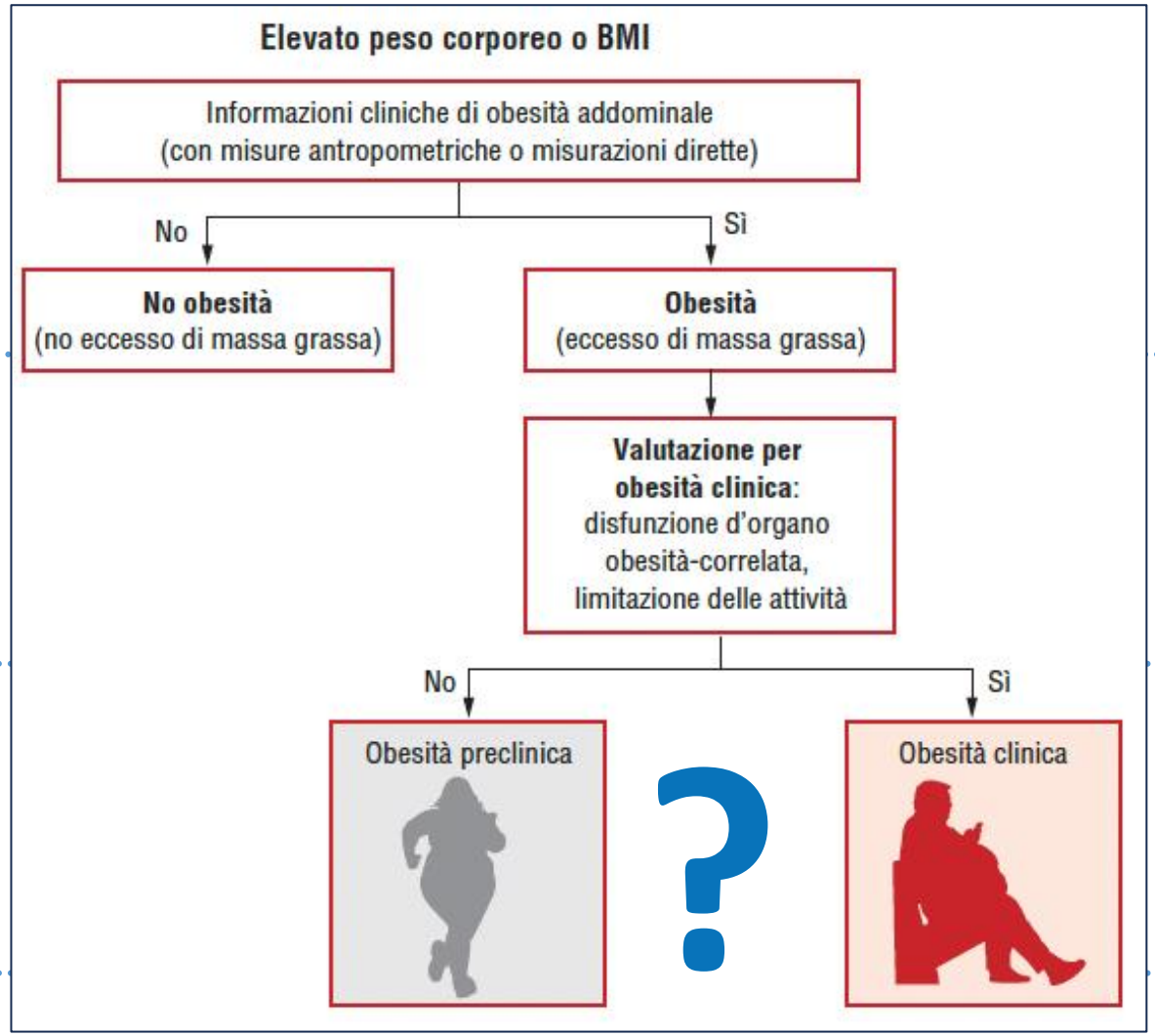
## Implicazioni cliniche:

Il rischio cardiometabolico è **inferiore rispetto alla MUO**,
→ **ma superiore** rispetto ai soggetti normopeso metabolicamente sani.

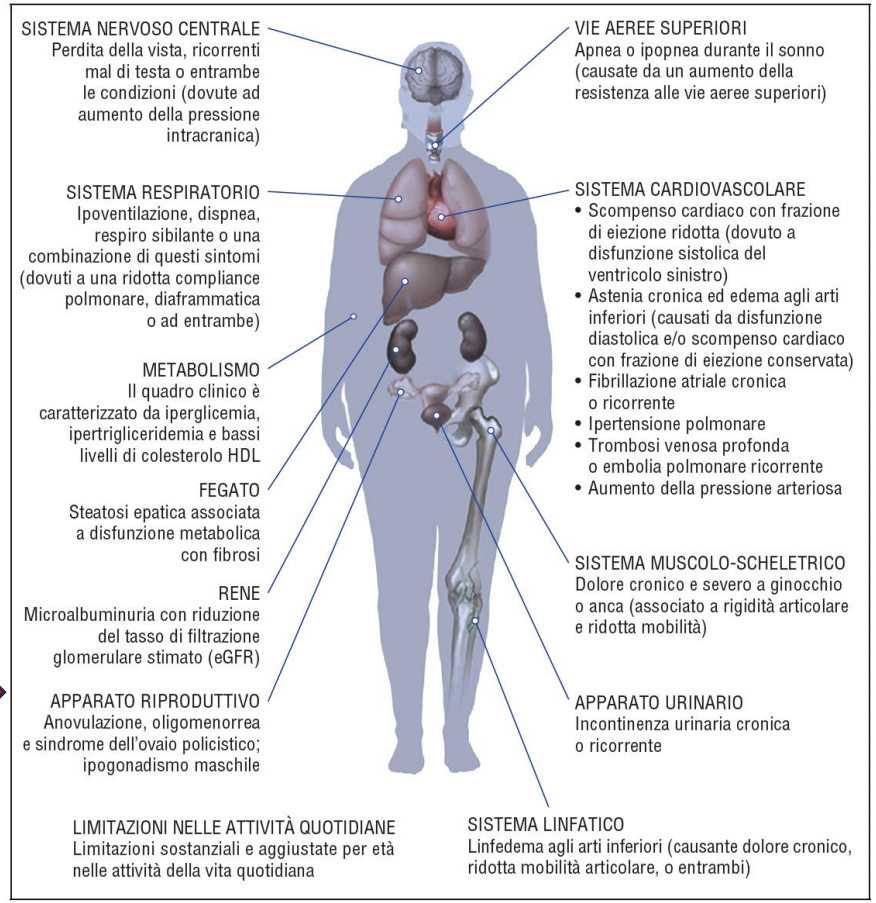
La MHO **non è "obesità benigna"**. È un fenotipo a **rischio intermedio**, con necessità di interventi preventivi mirati e follow-up clinico costante.

# La “nuova” definizione e classificazione dell’obesità: cosa cambia

Rubino F, et al. Definition and diagnostic criteria of clinical obesity. Lancet Diabetes Endocrinol 2025; 13(1):1-12.




= MHO



# Obesità preclinica


Rubino F, et al. Definition and diagnostic criteria of clinical obesity. Lancet Diabetes Endocrinol 2025; 13(1):1-12.

**Preclinical obesity is a heterogeneous condition:**

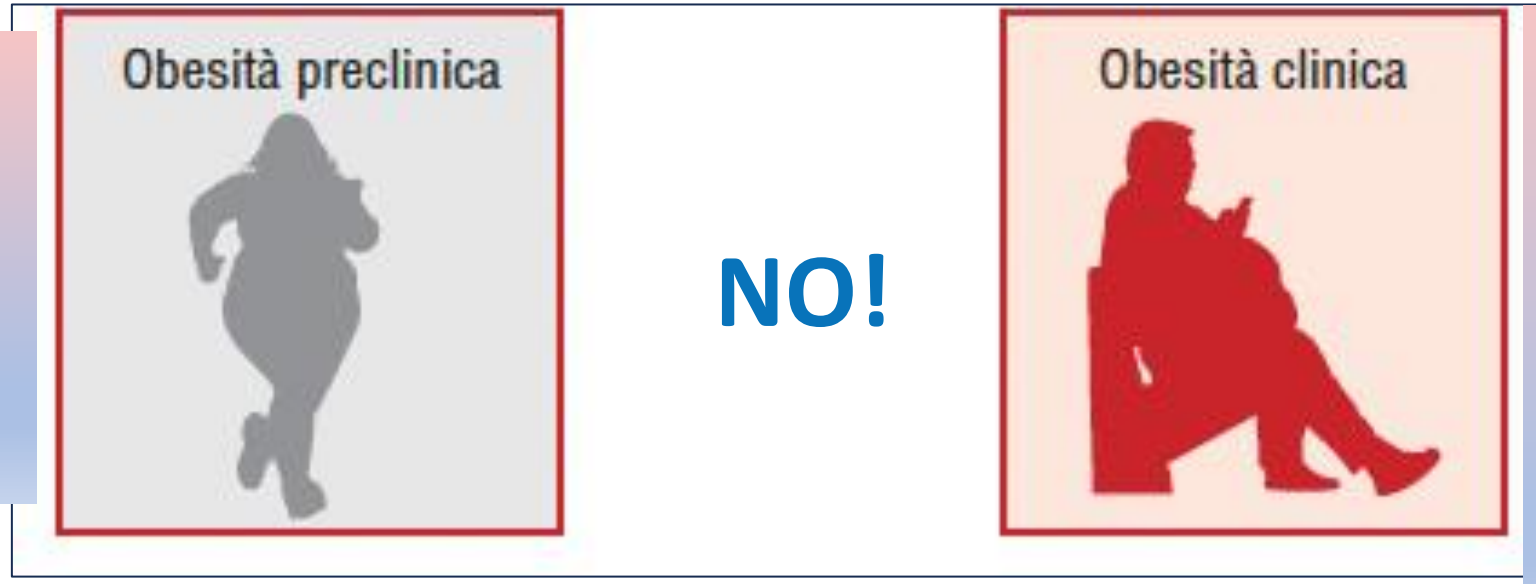
- an earlier stage of clinical obesity (and in that case could be a predisease state)
- a physical phenotype with lower tendency to directly affect organ function
- a sign of other diseases or side-effects of medications.

.

# Obesità preclinica = MHO

«Because **health or illness** is not solely defined by metabolic abnormalities, **preclinical and clinical obesity do not coincide with the previously proposed distinctions of metabolically healthy or metabolically unhealthy obesity»**

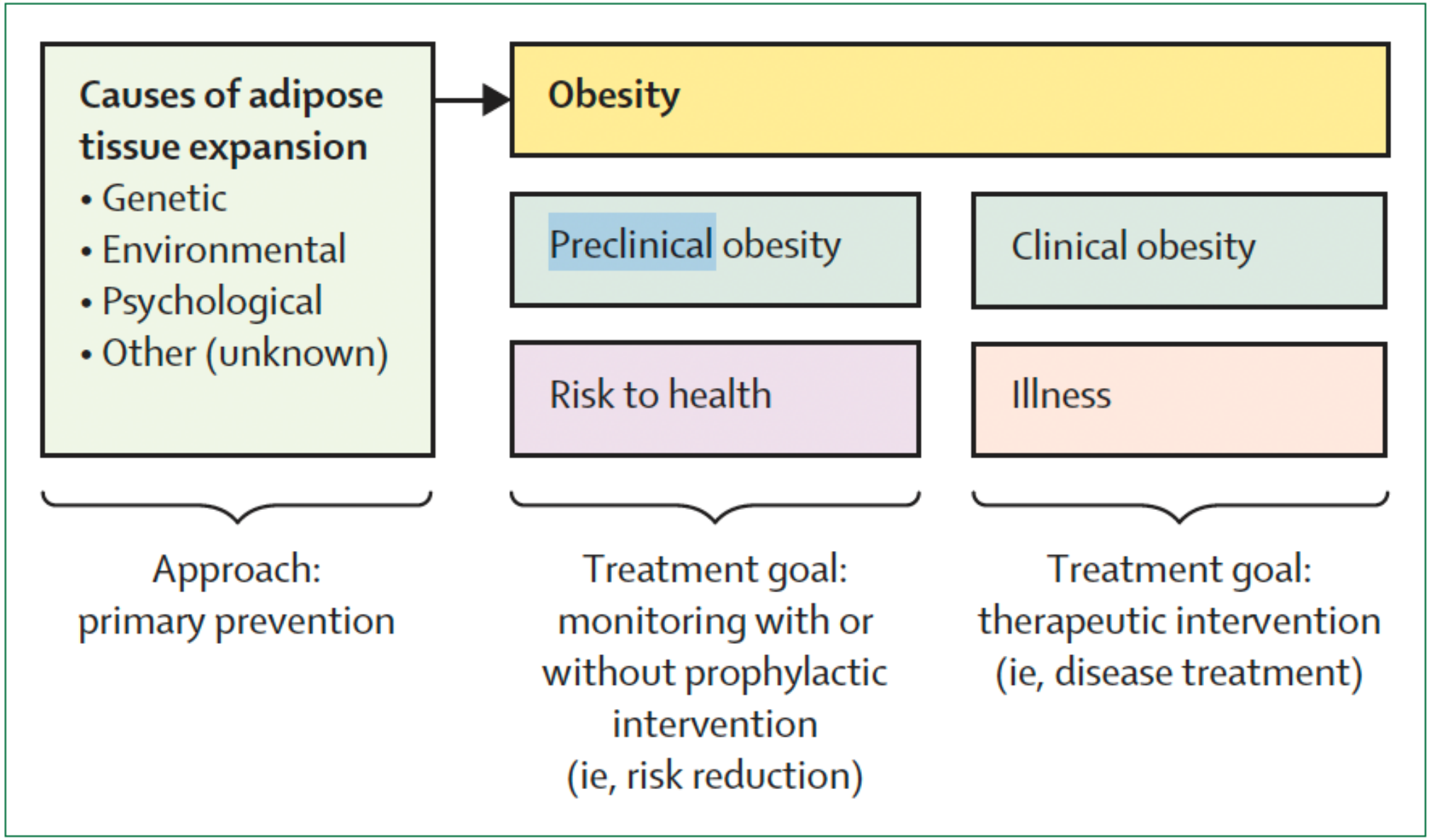
**Preclinical obesity** is, defined by the absence of any substantial organ dysfunction (not just metabolic abnormalities).




**clinical obesity** can exist in the absence of metabolic dysfunction, if other non-metabolic dysfunctions such as cardiovascular, respiratory, or musculoskeletal dysfunctions are present

Rubino F, et al. Definition and diagnostic criteria of clinical obesity. Lancet Diabetes Endocrinol 2025; 13(1):1-12.

Rubino F, et al. Definition and diagnostic criteria of clinical obesity. Lancet Diabetes Endocrinol 2025; 13(1):1-12.



Rubino F, et al. Definition and diagnostic criteria of clinical obesity. Lancet Diabetes Endocrinol 2025; 13(1):1-12.

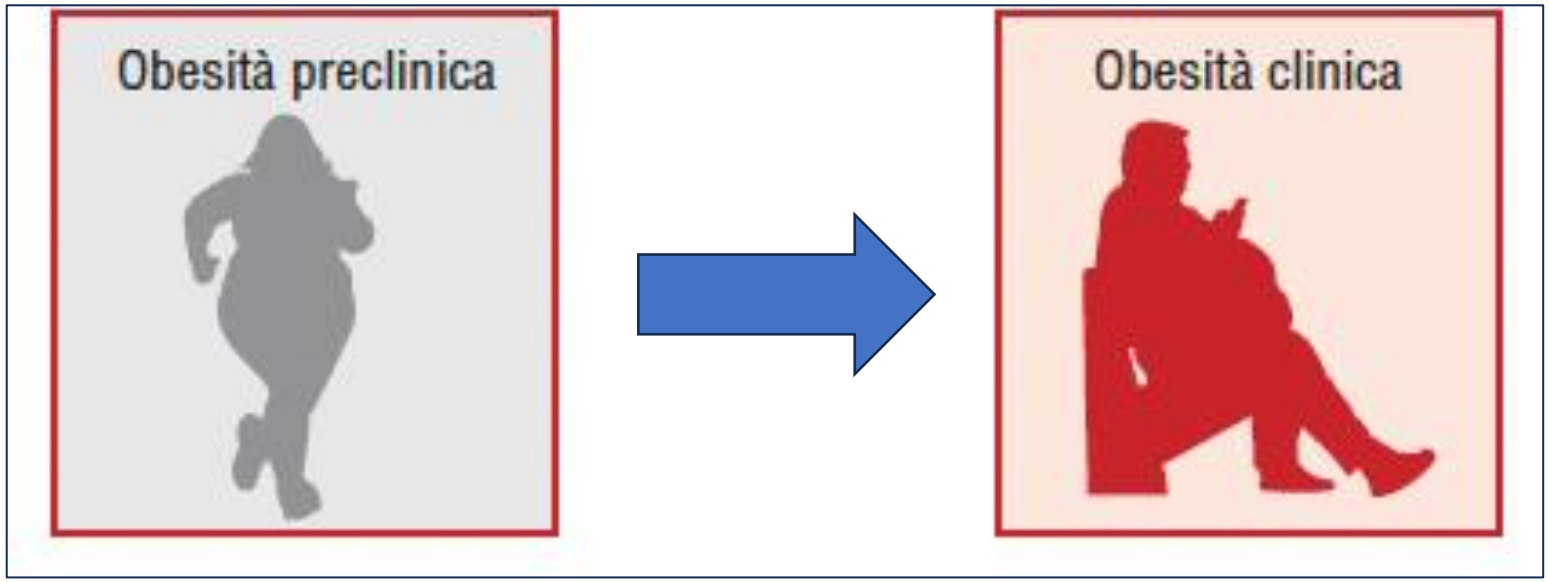

**Obiettivi principali:**
Ridurre il rischio di evoluzione verso obesità clinica e malattie correlate.

**Scelta terapeutica:**
- Basso rischio: Modifiche dello stile di vita
- Rischio elevato: possibile intervento farmacologico o chirurgico.

**Obiettivi principali:**
Migliorare le manifestazioni cliniche, non solo sulla perdita di peso

**Scelta terapeutica:**
- Modifiche dello stile di vita
- Terapie farmacologiche
- Interventi riabilitativi
- Chirurgia bariatrica.

# CONCLUSIONE




La **probabilità** e la **velocità** di progressione dalla **obesità preclinica** alla **obesità clinica** non sono ancora note e richiedono ulteriori studi.

Il rischio di evoluzione dipende da:

- **Età**
- **Etnia**
- **Predisposizione familiare**
- **Distribuzione del grasso corporeo** (viscerale > sottocutaneo)
- **Stile di vita** (attività fisica, qualità della dieta)

## Take-Home Message

La **obesità preclinica** non è una fase innocua: rappresenta una **finestra critica di intervento precoce**, prima della comparsa di obesità clinica o complicanze metaboliche.

# Grazie per l’attenzione