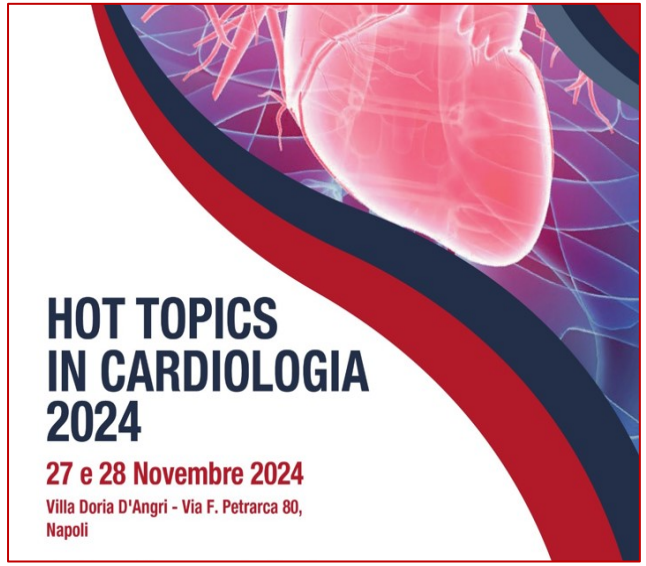

new insights in cardiology

nutrizione e malattie metaboliche

International Journal of *Molecular Sciences* Int. J. Mol. Sci. 2024

Review

The Role of Obesity in Type 2 Diabetes Mellitus—An Overview

Preethi Chandrasekaran [1,*] and Ralf Weiskirchen [2,*]

the rapid development of global urbanization and modernization has lasting effects on lifestyle aspects such as unhealthy eating habits, lack of exercise increased stress and environmental factors

these factors contribute to the **alarming growth of obesity and type 2 DM worldwide**

obese individuals develop insulin resistance, which is characterized by impaired insulin action in the liver and reduced glucose uptake in fat and muscle

while lifestyle changes and medications are recommended for prevention, **they have not been successful in suppressing the increasing incidence conditions**

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Review

The Role of Obesity in Type 2 Diabetes Mellitus—An Overview

Preethi Chandrasekaran [1,*] and Ralf Weiskirchen [2,*]

✓ **multiple** in vivo and clinical studies have demonstrated **a cause-and-effect relationship between obesity and type 2 DM,** unraveling their intimate connections

it is shocking to note that according to the WHO fact sheet, at least 41 million children under the age 5 are overweight or obese (BMI ≥ 35 kg/m2) as of 2016

✓ **if** this trend continues, **60%** of the world's population **will be obese or overweight by 2030**

according to WHO, obesity accounts for 44% of diabetes and the incidence of obesity-related diabetes is expected to double to 300 million by 2025

PERSPECTIVE N Engl J Med; 2007

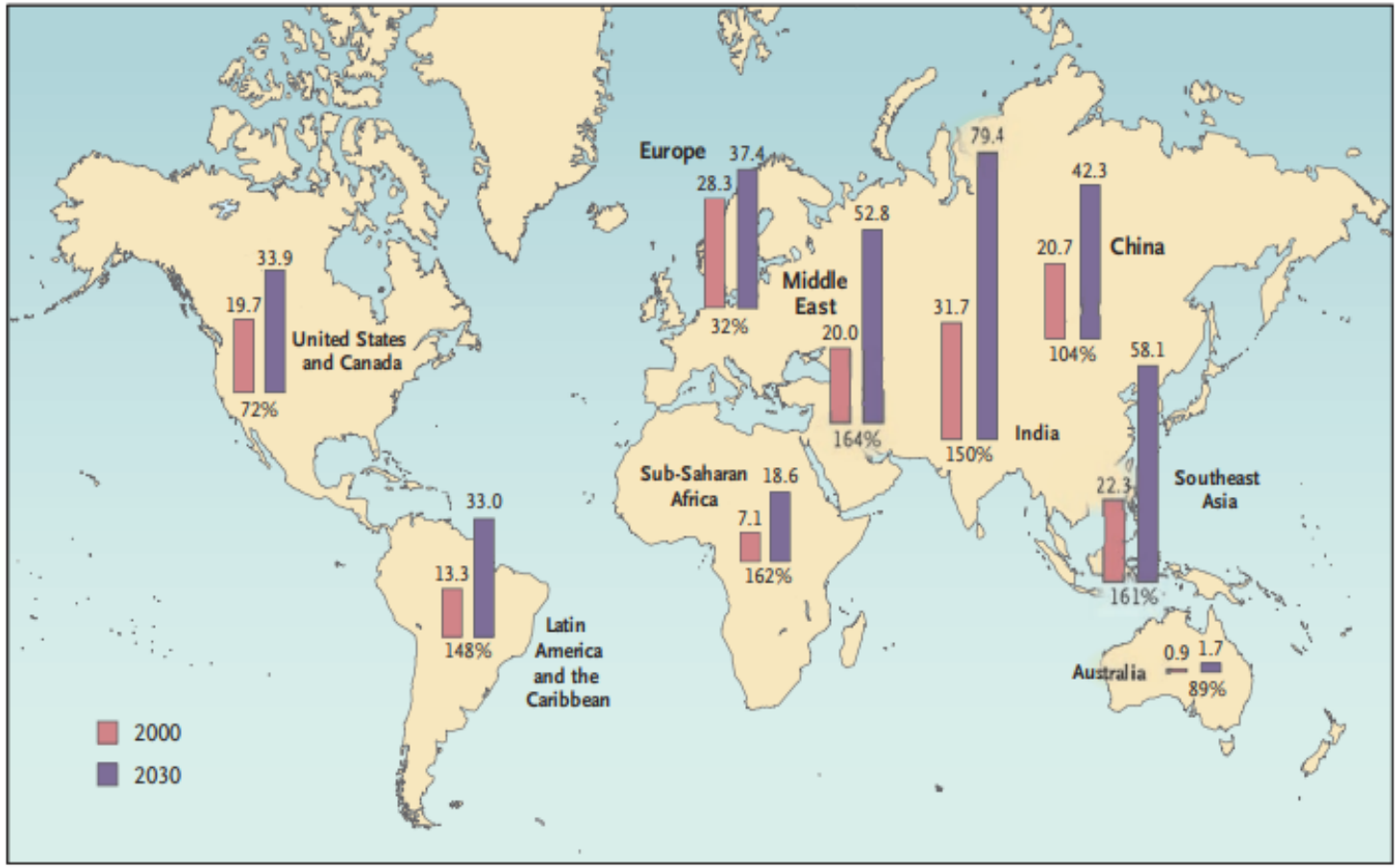
Obesity and Diabetes in the Developing World — A Growing Challenge

Parvez Hossain, M.D., Bisher Kawar, M.D., and Meguid El Nahas, M.D., Ph.D.

about 90% of type 2 diabetes is attributable to excess weight

✓ **approximately 197 million people worldwide**
have impaired glucose tolerance
most commonly because of obesity
and the associated metabolic syndrome

this number is expected to increase to 420 million by 2025



million of cases of diabetes in 2000 and **projections for 2030**, with projected percent changes

International Journal of
Molecular Sciences
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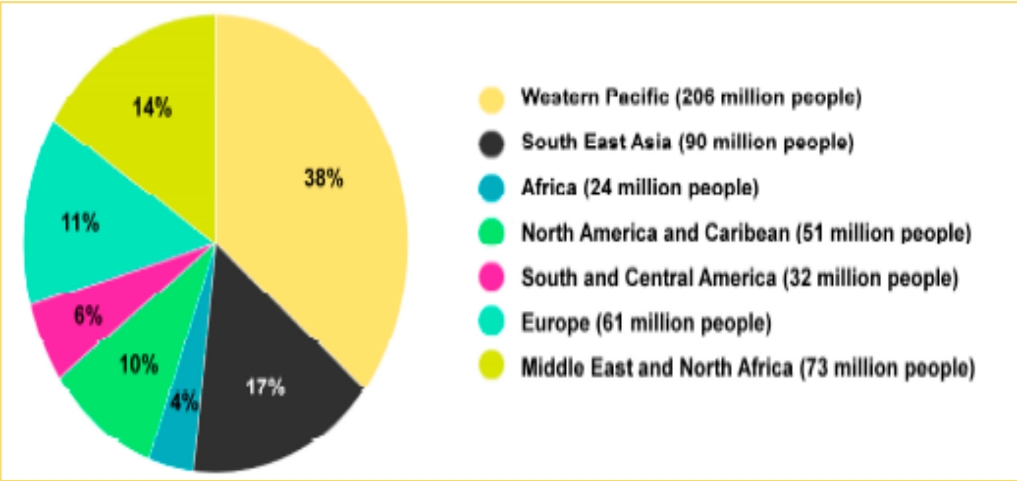
Review

The Role of Obesity in Type 2 Diabetes Mellitus—An Overview

Preethi Chandrasekaran [1,*] and Ralf Weiskirchen [2,*]

this is the fastest-growing pandemic and health emergency globally

✓ obesity plays an inevitable role in the increased prevalence of type 2 DM



prevalence of diabetes worldwide in 2021

a total of 573 million people suffered from diabetes

according to the latest estimates by the International Diabetes Federation :

in 2030 the number of diagnosed cases of DM is predicted to reach 643 million

in 2045 ..... of DM is predicted to reach 783 million

additionally, the majority of undiagnosed type 2 DM cases are concentrated in Africa Southeast Asia and the Western Pacific

International Journal of
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Review

The Role of Obesity in Type 2 Diabetes Mellitus—An Overview

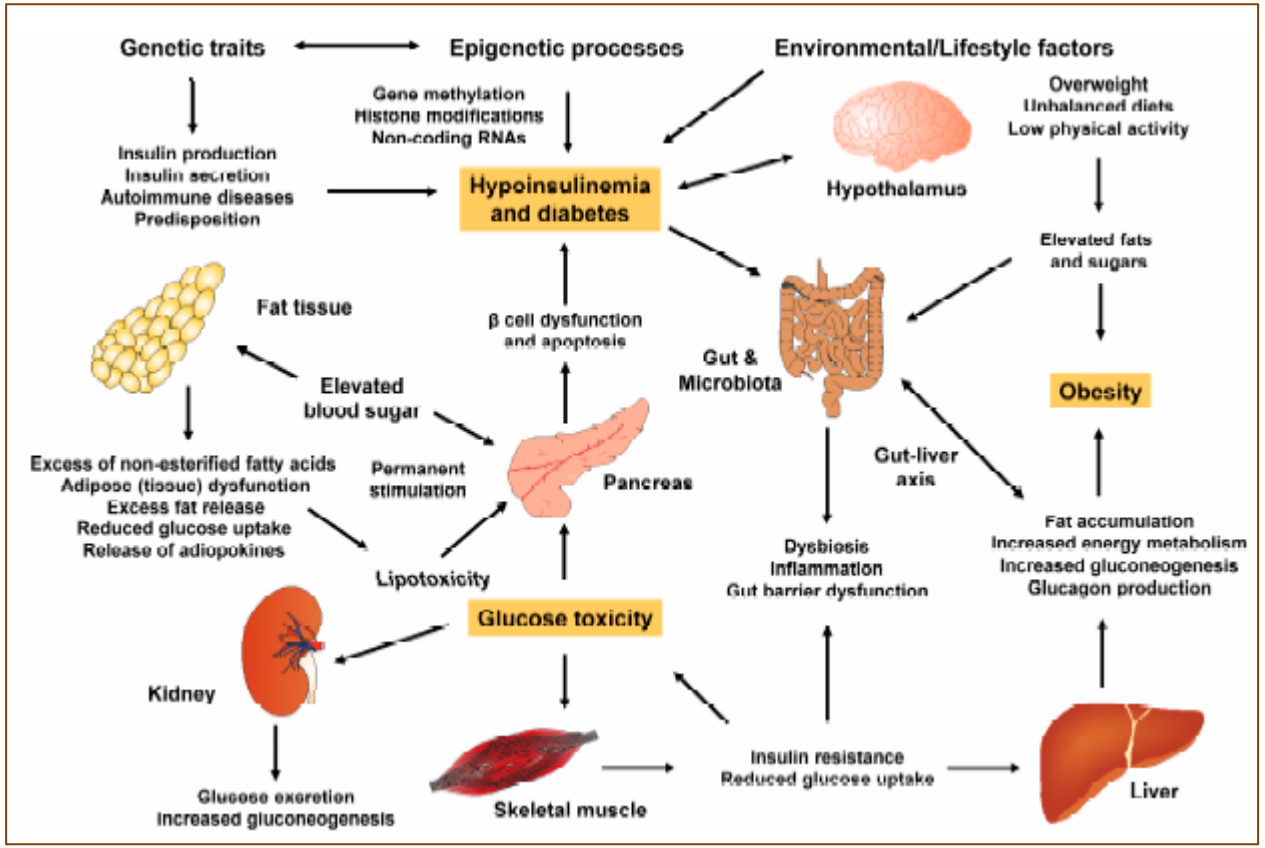
Preethi Chandrasekaran [1,*] and Ralf Weiskirchen [2,*]

the close relationship between obesity and diabetes has led to the term "diabesity" which highlights that the **majority of individuals with diabetes are obese or overweight**

- ✓ **while type 2 DM** is influenced by genetic predisposition and ethnicity which are non modifiable risk factors, it can still be prevented or managed by addressing **modifiable risk factors such as obesity**

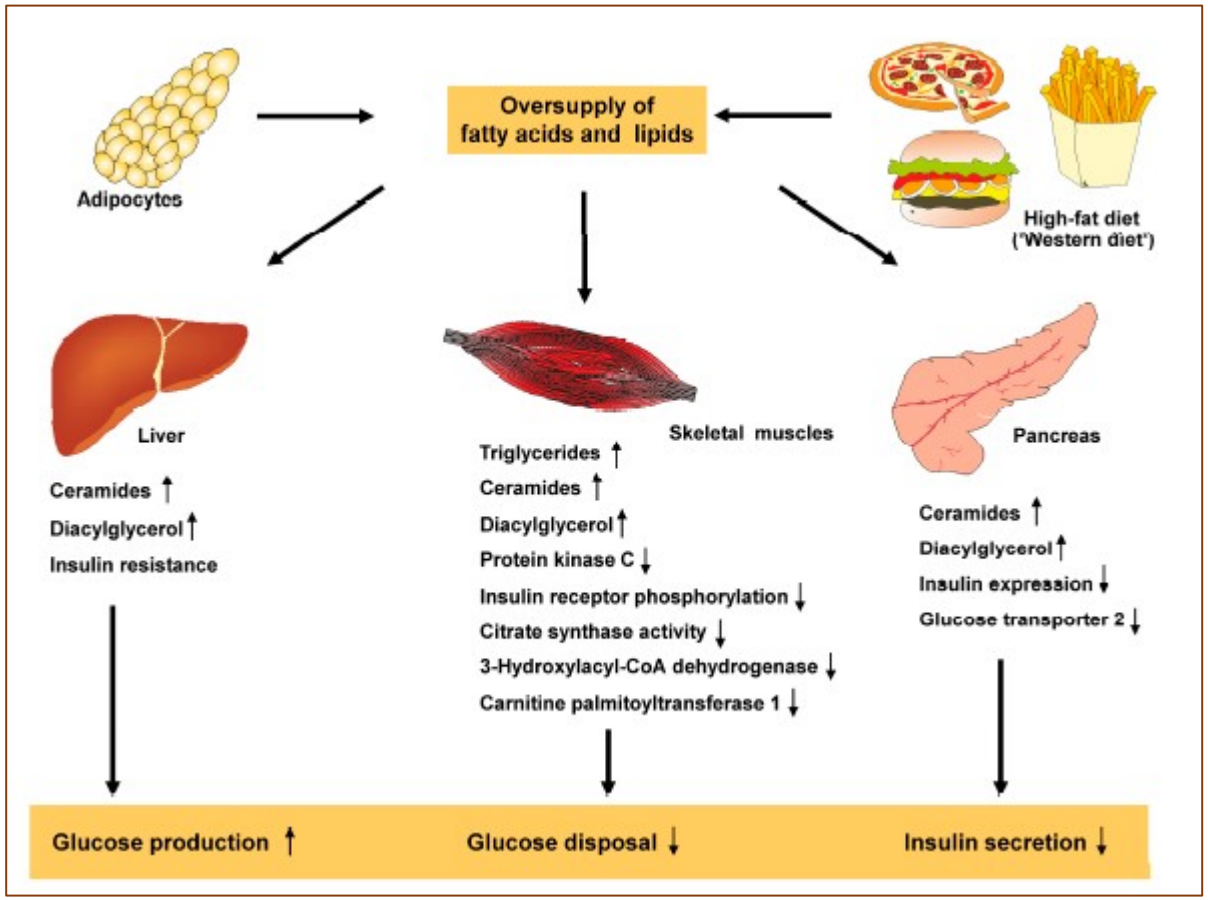
despite recent advancement in management strategies, obesity and diabetes remain a significant interconnected public health challenge worldwide

multifactorial pathophysiology of obesity and type 2 diabetes



- ✓ various factors, including adipokines, pro-inflammatory cytokines, non-esterified fatty acids (NEFA) and others contribute to visceral fat accumulation, β-cell dysfunction and changes in gut microbiota and gut barrier leakage
- ✓ in addition, inflammatory reactions in the hypothalamus might contribute to the onset of diabetes and vice versa
- ✓ diabetes impacts energy homeostasis and hyper-activates regulatory neurons as well as the surrounding microglia in the hypothalamus

genetic and epigenetic factors, along with an unhealthy lifestyle play significant roles in the development of obesity and DM2



fats and lipids in the pathogenesis of type 2 diabetes

an overabundance of fatty acids and lipids, resulting from a high-caloric diet enriched in fat

(which cannot be stored in adipocytes), lead to increased levels of circulating fat that accumulate in peripheral tissues such as the liver, muscles and pancreas

this accumulation triggers numerous molecular changes that result in increased glucose production lowered glucose disposal and impaired insulin secretion

these factors are hallmarks of diabetes

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classification of obesity based on body mass index and waist circumferences

Condition	BMI (kg/m^2)	Disease Risk Relative to Normal Weight and Waist Circumference Men ≤ 40 inches (≤102 cm) Women ≤ 35 inches (≤88 cm)
Normal	18.5–24.9	data
Overweight	25.0–29.9	Increased
Obese	30.0–34.9 (class 1)	High
	35.0–39.9 (class 2)	Very high
Extremely Obese	≥40	Extremely high

✓ **however,** due to the role of adipose tissue in lipid and glucose metabolism, and grade inflammation

it is necessary to classify obesity on the basis of body fat composition and distribution, rather than the simply increase of body weight and the Body Mass Index

✓ **the new term of adiposopathy** (‘‘sick fat’’) clearly defines the pathogenic role of adipose tissue

four phenotypes of obese individuals have been described: (1) normal weight obese (NWO)
(2) metabolically obese normal weight (MONW) - (3) metabolically healthy obese (MHO)
(4) metabolically unhealthy obese (MUO)

moreover, sarcopenic obesity has been related to all the phenotypes

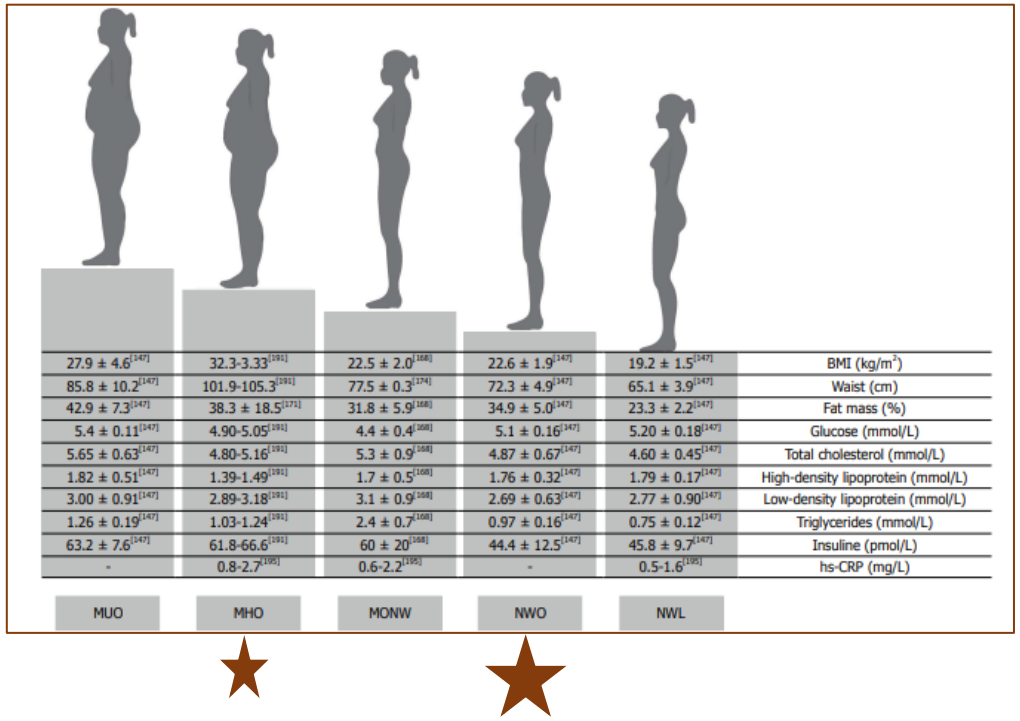
World Journal of Gastroenterology

World J Gastroenterol 2016 J

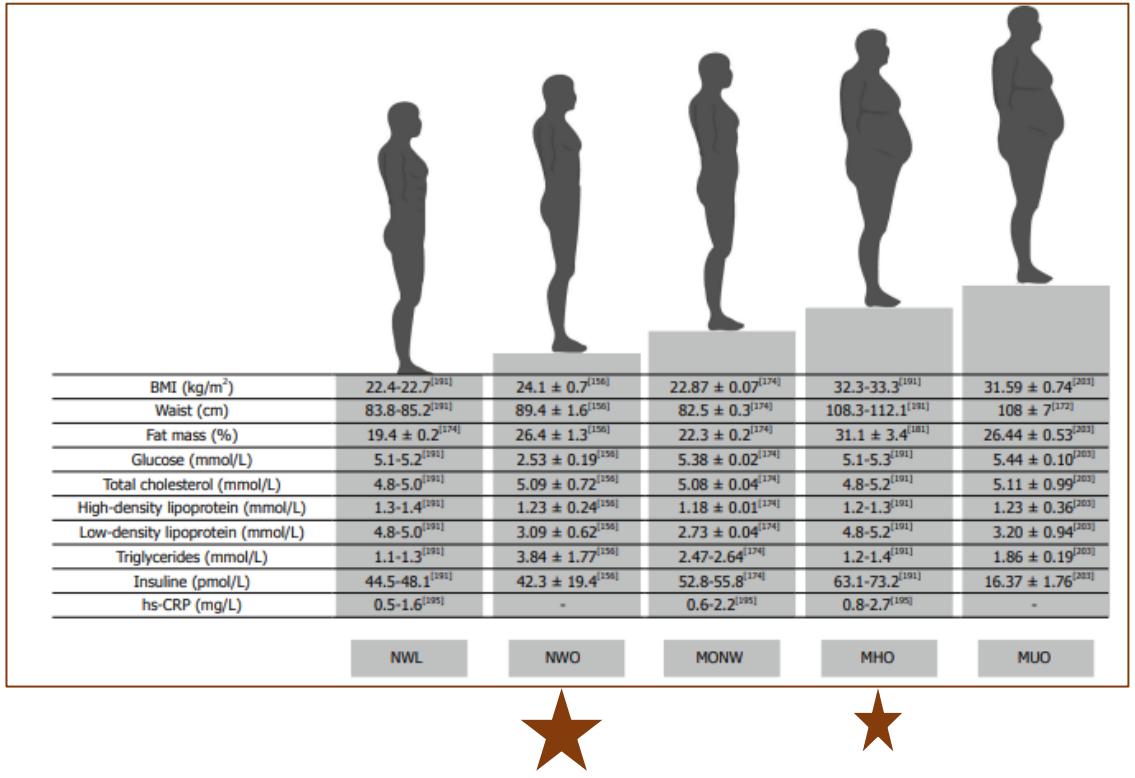
New obesity classification criteria as a tool for bariatric surgery indication

Antonino De Lorenzo, Laura Soldati, Francesca Sarlo et al.

the anthropometric assessment of percentage body fat is a more accurate measure of adiposity than BMI



MUO	MHO	MONW	NWO	NWL	
27.9 ± 4.6[147]	32.3-3.33[191]	22.5 ± 2.0[168]	22.6 ± 1.9[147]	19.2 ± 1.5[147]	BMI (kg/m^2)
85.8 ± 10.2[147]	101.9-105.3[191]	77.5 ± 0.3[174]	72.3 ± 4.9[147]	65.1 ± 3.9[147]	Waist (cm)
42.9 ± 7.3[147]	38.3 ± 18.5[171]	31.8 ± 5.9[168]	34.9 ± 5.0[147]	23.3 ± 2.2[147]	Fat mass (%)
5.4 ± 0.11[147]	4.90-5.05[191]	4.4 ± 0.4[168]	5.1 ± 0.16[147]	5.20 ± 0.18[147]	Glucose (mmol/L)
5.65 ± 0.63[147]	4.80-5.16[191]	5.3 ± 0.9[168]	4.87 ± 0.67[147]	4.60 ± 0.45[147]	Total cholesterol (mmol/L)
1.82 ± 0.51[147]	1.39-1.49[191]	1.7 ± 0.5[168]	1.76 ± 0.32[147]	1.79 ± 0.17[147]	High-density lipoprotein (mmol/L)
3.00 ± 0.91[147]	2.89-3.18[191]	3.1 ± 0.9[168]	2.69 ± 0.63[147]	2.77 ± 0.90[147]	Low-density lipoprotein (mmol/L)
1.26 ± 0.19[147]	1.03-1.24[191]	2.4 ± 0.7[168]	0.97 ± 0.16[147]	0.75 ± 0.12[147]	Triglycerides (mmol/L)
63.2 ± 7.6[147]	61.8-66.6[191]	60 ± 20[168]	44.4 ± 12.5[147]	45.8 ± 9.7[147]	Insuline (pmol/L)
-	0.8-2.7[195]	0.6-2.2[195]	-	0.5-1.6[195]	hs-CRP (mg/L)



NWL	NWO	MONW	MHO	MUO	
22.4-22.7[191]	24.1 ± 0.7[156]	22.87 ± 0.07[174]	32.3-33.3[191]	31.59 ± 0.74[203]	BMI (kg/m^2)
83.8-85.2[191]	89.4 ± 1.6[156]	82.5 ± 0.3[174]	108.3-112.1[191]	108 ± 7[172]	Waist (cm)
19.4 ± 0.2[174]	26.4 ± 1.3[156]	22.3 ± 0.2[174]	31.1 ± 3.4[181]	26.44 ± 0.53[203]	Fat mass (%)
5.1-5.2[191]	2.53 ± 0.19[156]	5.38 ± 0.02[174]	5.1-5.3[191]	5.44 ± 0.10[203]	Glucose (mmol/L)
4.8-5.0[191]	5.09 ± 0.72[156]	5.08 ± 0.04[174]	4.8-5.2[191]	5.11 ± 0.99[203]	Total cholesterol (mmol/L)
1.3-1.4[191]	1.23 ± 0.24[156]	1.18 ± 0.01[174]	1.2-1.3[191]	1.23 ± 0.36[203]	High-density lipoprotein (mmol/L)
4.8-5.0[191]	3.09 ± 0.62[156]	2.73 ± 0.04[174]	4.8-5.2[191]	3.20 ± 0.94[203]	Low-density lipoprotein (mmol/L)
1.1-1.3[191]	3.84 ± 1.77[156]	2.47-2.64[174]	1.2-1.4[191]	1.86 ± 0.19[203]	Triglycerides (mmol/L)
44.5-48.1[191]	42.3 ± 19.4[156]	52.8-55.8[174]	63.1-73.2[191]	16.37 ± 1.76[203]	Insuline (pmol/L)
0.5-1.6[195]	-	0.6-2.2[195]	0.8-2.7[195]	-	hs-CRP (mg/L)

NWO: **normal weight obese** - MONW: **metabolically obese normal weight** - MHO: **metabolically healthy obese** - MUO: **metabolically unhealthy obese**

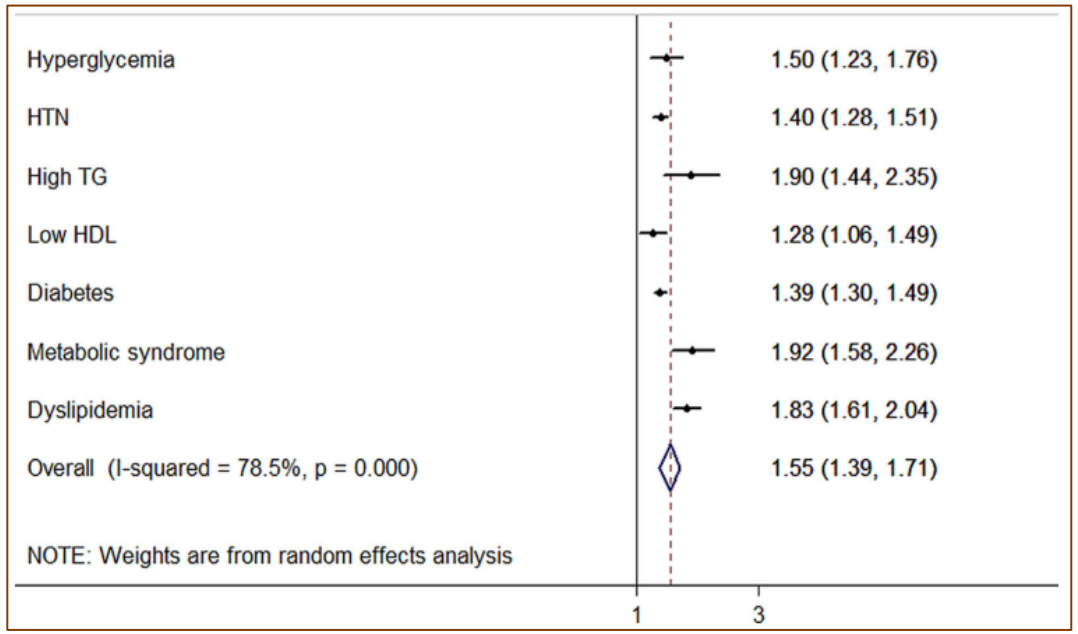
frontiers in Endocrinology March 2022

Nami Mohammadian Khonsari, Patricia Khashayar, Ehsan Shahrestanaki et al

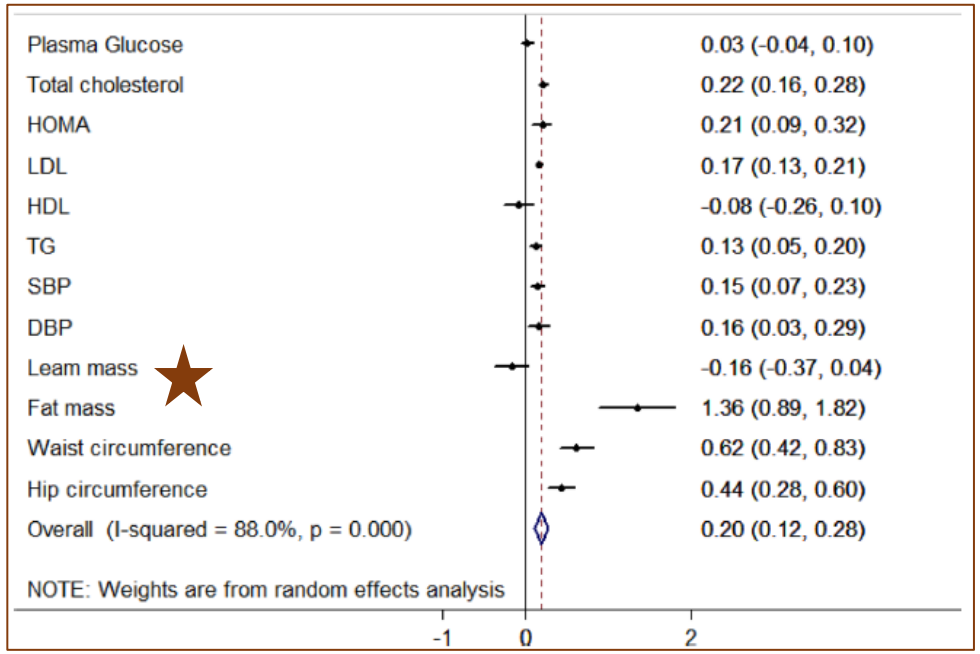
Normal Weight Obesity and Cardiometabolic Risk Factors: A Systematic Review and Meta-Analysis

background: a new type of obesity, normal weight obesity (NWO), which is defined as having a normal BMI, but a high-fat percentage increases the risk of cardiometabolic risk factors (CMRFs)

Forest plot detailing the pooled association between NWO with CMRFs.



the random effect meta-analysis showed ...



increased odds of dyslipidemia by 83% (OR:1.83, 95% CI:1.61 20.4), of HTN by 40% (OR:1.40, 95% CI:1.28, 1.51) and of metabolic syndrome by 92% (OR:1.92, 95% CI:1.58, 2.26)

NWO statistically increased the mean of HOMA (SMD: 0.12, 95% CI: 0.09, 0.32), TG (SMD: 0.13, 95% CI: 0.05, 0.20), SBP (SMD: 0.15, 95% CI: 0.07, 0.23) DBP (SMD: 0.16, 95% CI: 0.03, 0.29) the relationship between plasma glucose, HDL and lean mass was not statistically significant

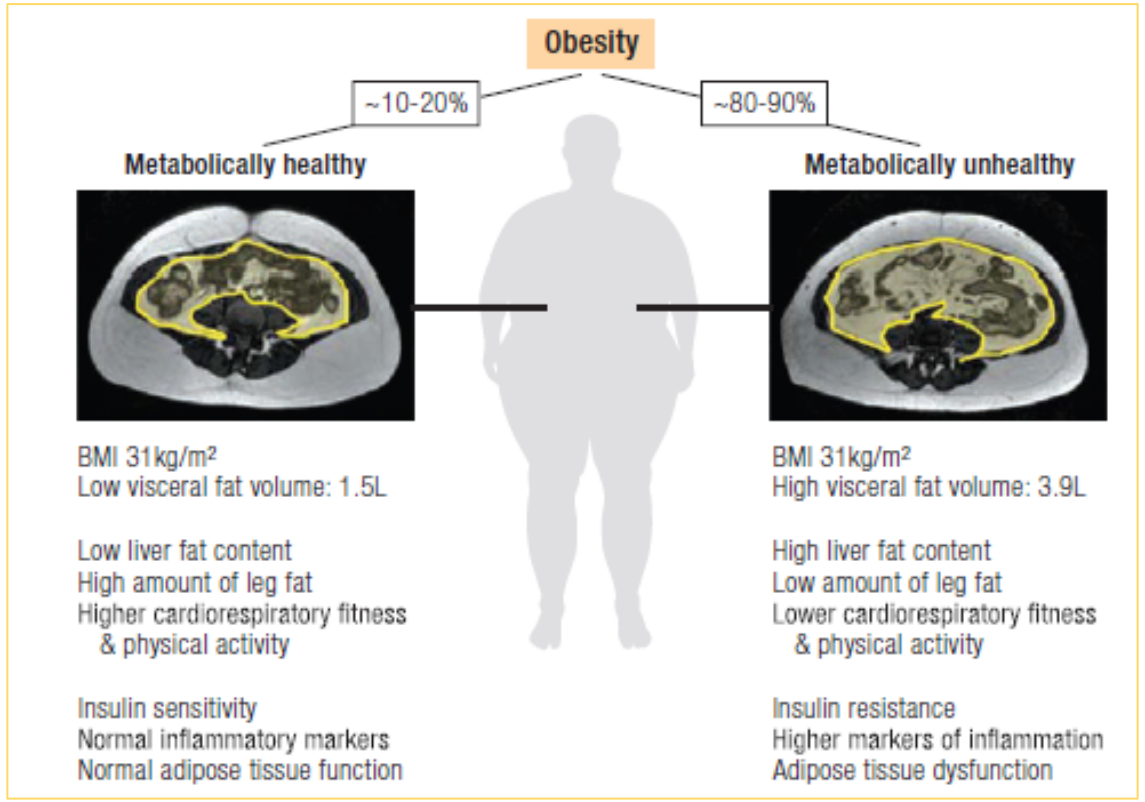
conclusion: NWO increased the odds of CMRFs ….. the inadequacy of the BMI measurement and the need for body fat assessment for a better obesity risk assessment

Metabolically Healthy Obesity

Matthias Blüher

Essential Points

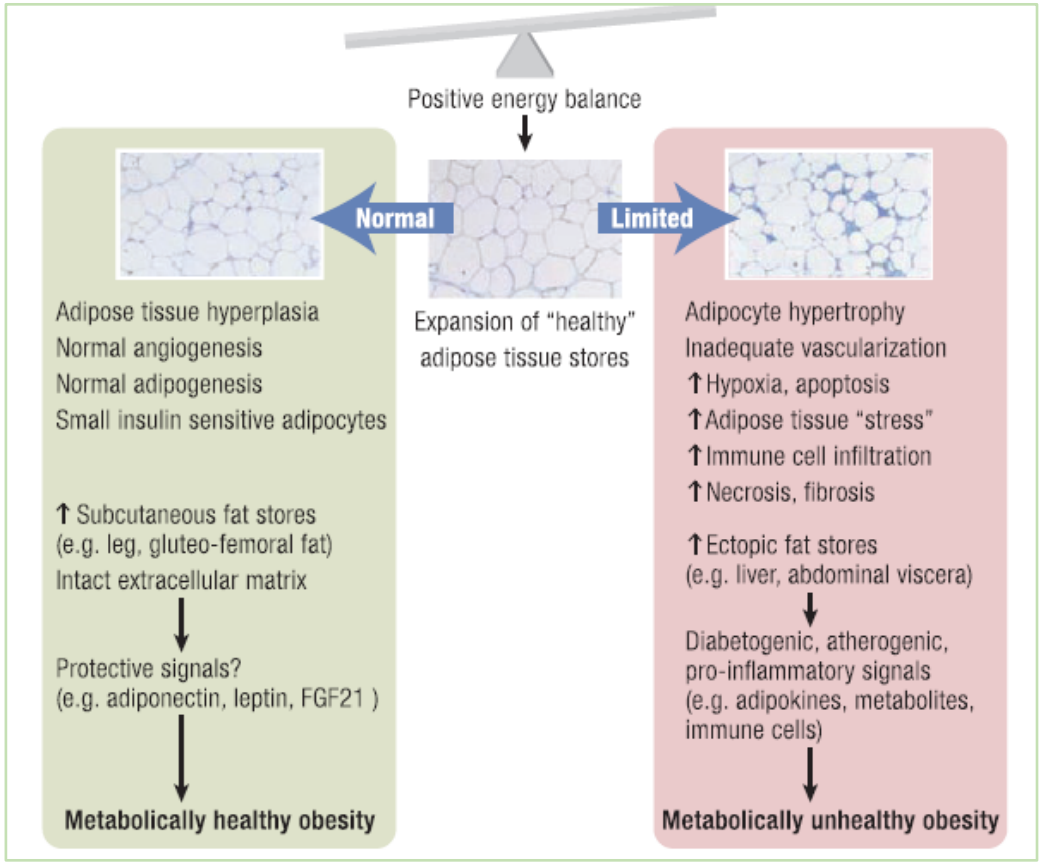
- Metabolically healthy obesity (MHO) is a concept derived from clinical observations that a subgroup of people with obesity do not exhibit overt cardiometabolic abnormalities.
- Although there is no standardized definition of MHO, the following criteria have been proposed in addition to the diagnosis of obesity (BMI ≥30 kg/m^2): fasted serum triglycerides ≤1.7 mmol/l (≤150 mg/dl); HDL cholesterol serum concentrations >1.0 (>40 mg/dl) (in men) or >1.3 mmol/l (>50 mg/dl) (in women); systolic blood pressure (SBP) ≤130 mmHg; diastolic blood pressure ≤85 mmHg; fasting blood glucose ≤ 6.1 mmol/l (≤100 mg/dl); no drug treatment for dyslipidemia, diabetes, or hypertension; and no cardiovascular disease manifestation.
- With an age- and gender-dependent prevalence between ~10% to 30%, MHO is not a rare condition.
- Individuals with MHO are characterized by lower liver and visceral fat, but higher subcutaneous leg fat content, greater cardiorespiratory fitness and physical activity, insulin sensitivity, lower levels of inflammatory markers, and normal adipose tissue function compared to patients with metabolically unhealthy obesity (MUO).
- Metabolically healthy obesity most likely represents a transient phenotype, and individuals with MHO still have an indication for weight-loss interventions because their risk of developing cardiometabolic diseases may be lower compared to MUO, but it is still higher than in metabolically healthy lean people.



Metabolically Healthy Obesity

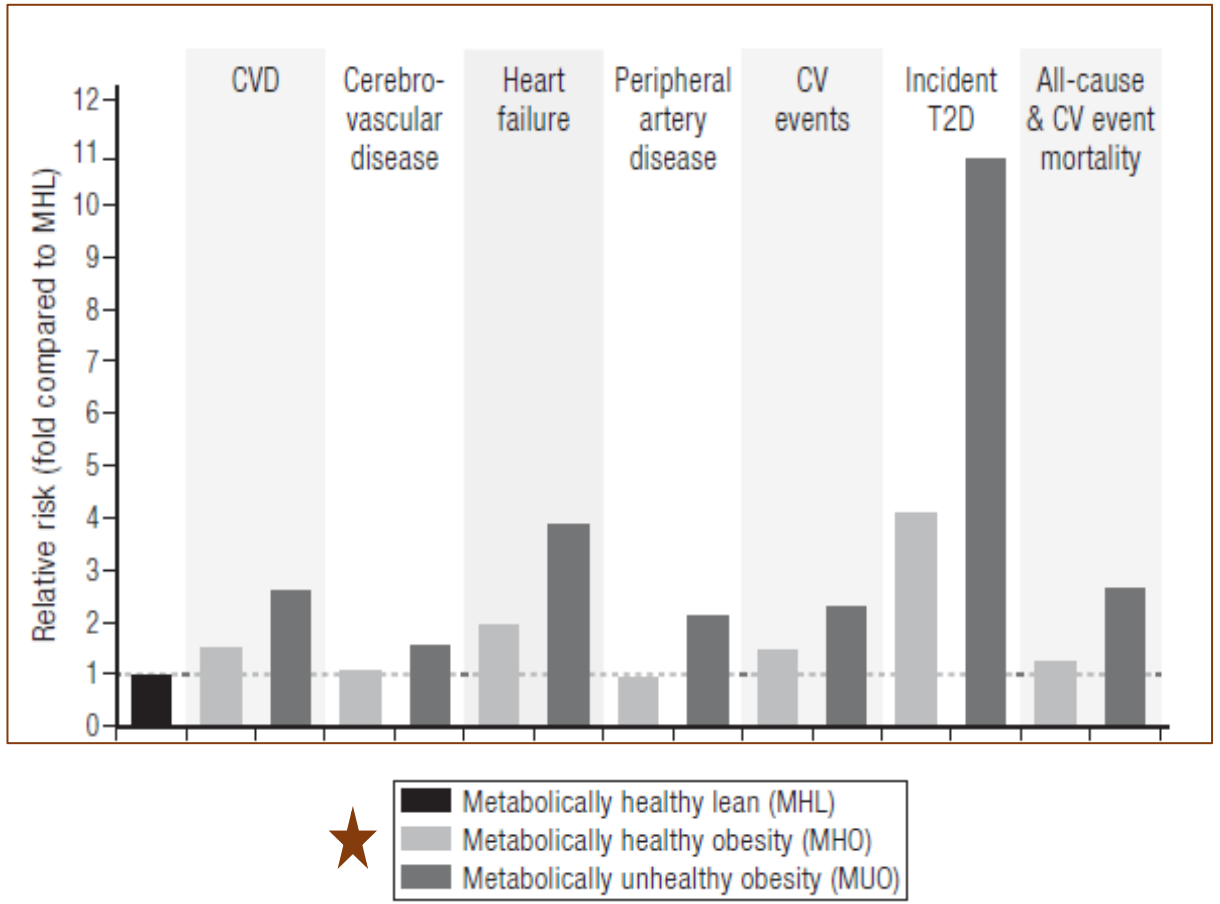
Matthias Blüher

REVIEW



adipose tissue dysfunction and development of metabolically unhealthy obesity
a **chronically positive energy balance requires expansion of adipose tissue (AT) to store excess energy**

risk of CVD and cardiovascular events, type 2 diabetes (T2D) and all-cause and/or CVD event mortality in MHO



Lancet Diabetes Endocrinol
2023; 11: 426–40

Review

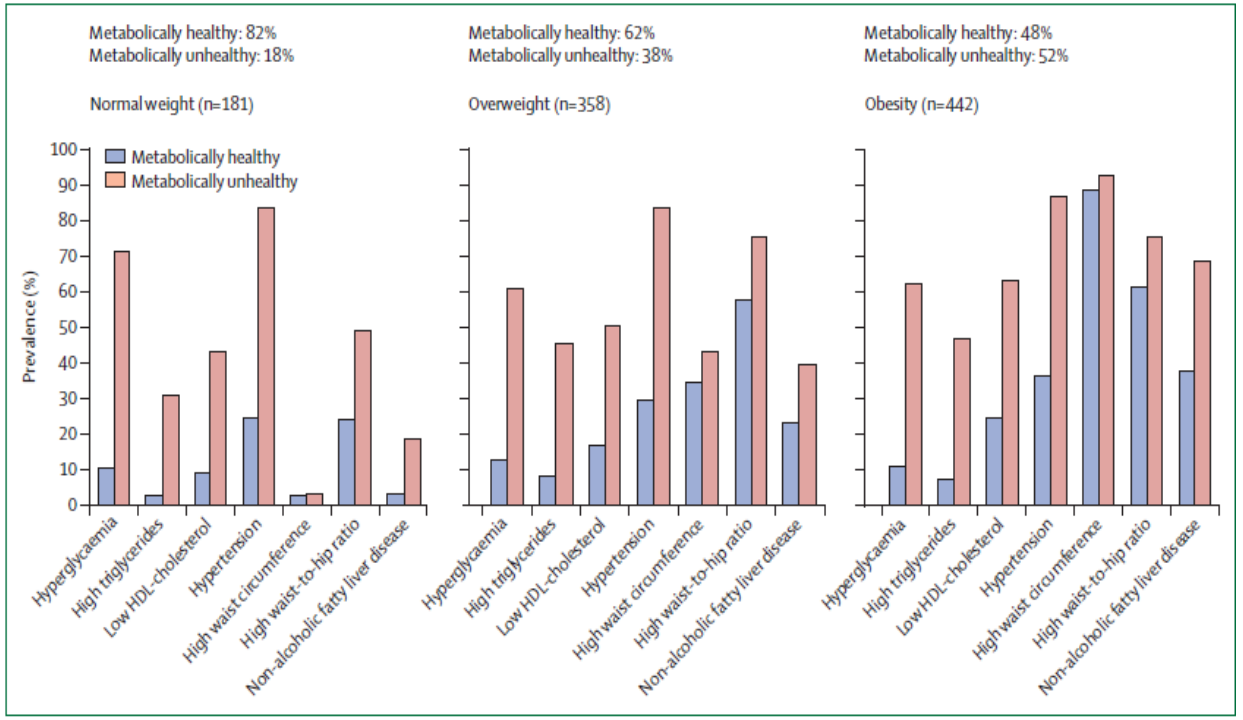
Metabolic health and cardiometabolic risk clusters: implications for prediction, prevention, and treatment

Norbert Stefan, Matthias B Schulze

the crucial point now **is whether these subphenotyping strategies** are superior to established cardiometabolic risk stratification methods regarding the prediction prevention, and treatment of cardiometabolic diseases

the approaches to identify **cardiometabolic risk clusters** in particular have provided some evidence: they **could be used to allocate individuals to specific pathophysiological risk groups**

but whether this allocation is helpful for prevention and treatment still needs to be determined



Circulation Research

immagine modificata dal web

EARLY DETERMINANTS OF CARDIOVASCULAR DISEASE COMPENDIUM

Diet and Food and Nutrition Insecurity and Cardiometabolic Disease

Eric J. Brandt, Dariush Mozaffarian, Cindy W. Leung, Seth A. Berkowitz, Venkatesh L. Murthy

healthy food

junk food

you are what you eat …

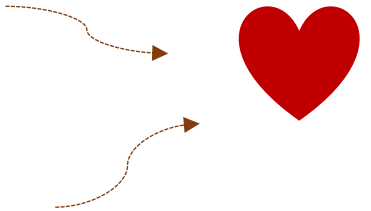
DIET AND EARLY CMD

the role of **diet and nutrition in the development of CVD** can be challenging to study

nonetheless, **randomized controlled trials such as PREDIMED** (Prevención con Dieta Mediterránea) and **CORDIOPREV** (CORonary Diet Intervention with Olive Oil and Cardiovascular PREVention) **have established that dietary patterns reduce CVD events in primary and secondary prevention**

randomized studies of youth evaluating different diets for future CVD as adults would be extremely challenging

✓ **there is substantial direct and indirect observational evidence connecting both diet and nutrition during childhood to CVD later in life**



nutrizione …

Circulation Research. 2023

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EARLY DETERMINANTS OF CARDIOVASCULAR DISEASE COMPENDIUM

Diet and Food and Nutrition Insecurity and Cardiometabolic Disease

Eric J. Brandt, Dariush Mozaffarian, Cindy W. Leung, Seth A. Berkowitz, Venkatesh L. Murthy

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ABSTRACT

poor nutrition is the leading cause of poor health, health care spending, and lost productivity in the United States and globally, **which acts through cardiometabolic diseases as precursors to cardiovascular disease**, cancer, and undernutrition

there is great interest in how the **social determinants of health** (**SDOH** - the conditions in which people are born, live, work, develop and age) **impact cardiometabolic disease**

✓ **food insecurity** is an example of a powerful social determinant of health that impacts health outcomes

✓ **nutrition insecurity**, a distinct but related concept to food insecurity, is a direct determinant of health

" food insecurity, is one powerful SDOH, distinct from food insecurity, nutrition insecurity is a direct determinant of health thus, while related, these factors should be considered jointly "

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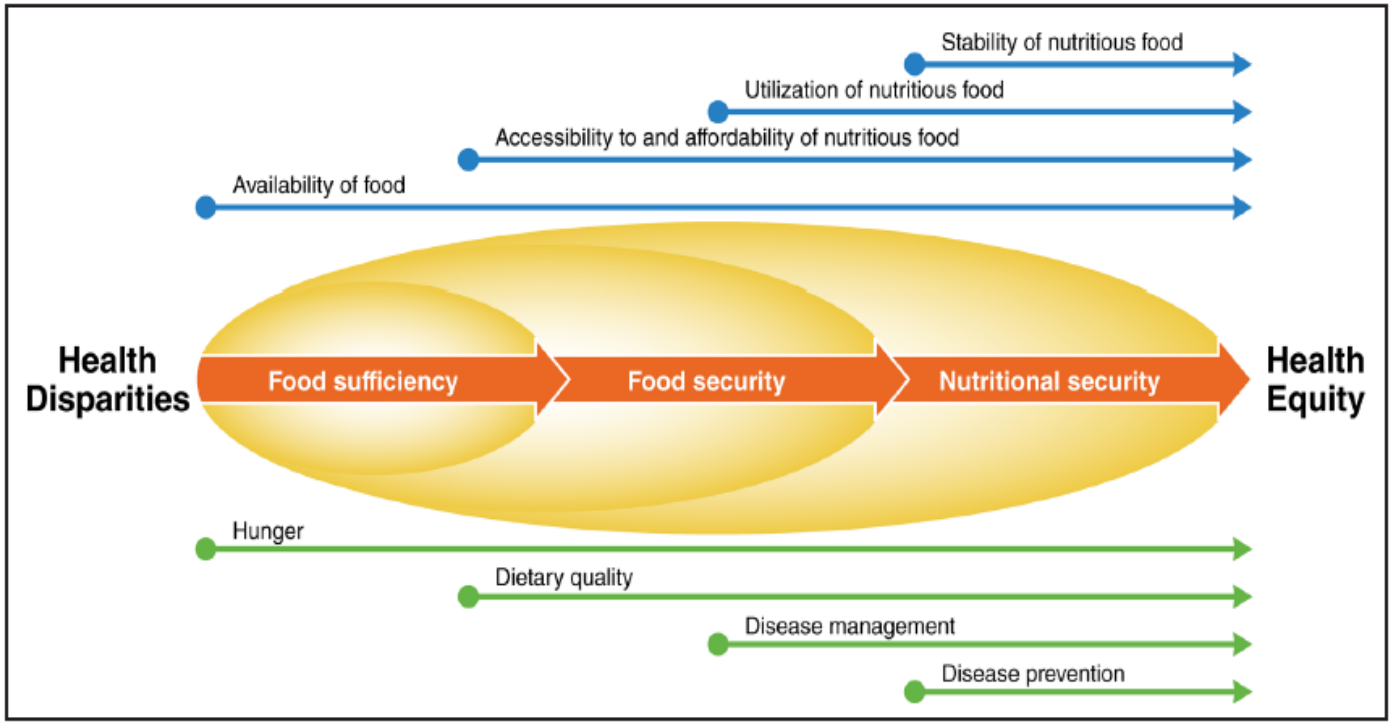
EARLY DETERMINANTS OF CARDIOVASCULAR DISEASE COMPENDIUM

Diet and Food and Nutrition Insecurity and Cardiometabolic Disease

Eric J. Brandt, Dariush Mozaffarian, Cindy W. Leung, Seth A. Berkowitz, Venkatesh L. Murthy

moving from food sufficiency to nutrition security



early determinants of cardiovascular disease

Two Question Food Insecurity Screener

Question	Responses
Within the past 12 mo, we worried whether our food would run out before we got money to buy more	a. Never true
	b. Sometimes true
	c. Often true
Within the past 12 mo, the food we bought just didn't last and we didn't have money to get more	a. Never true
	b. Sometimes true
	c. Often true

the growing recognition of the importance of directly assessing nutrition security—access to healthy food— has spurred a clinical and public health evolution toward the **new, complementary concept of nutrition security**

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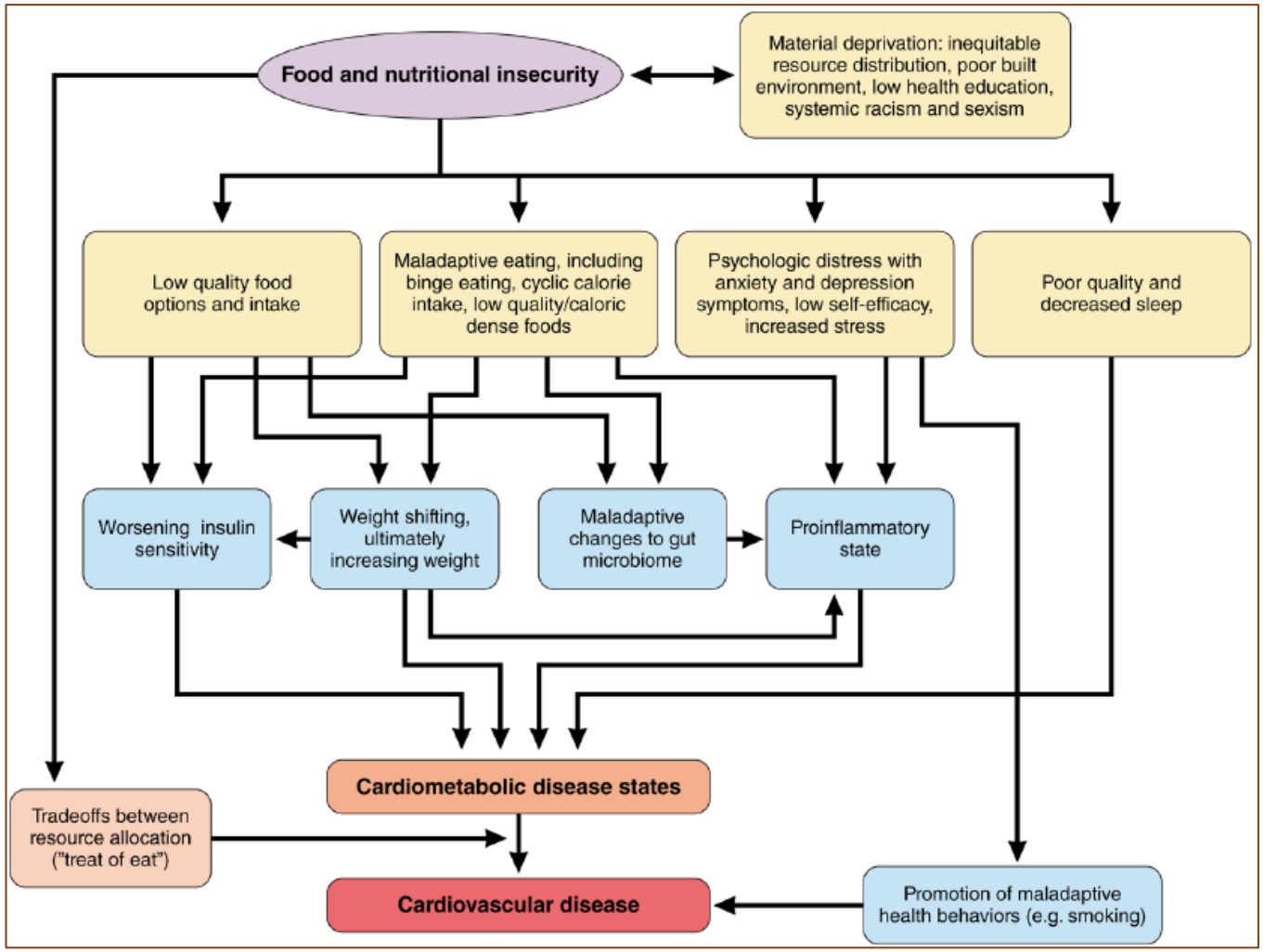
- ✓ *mechanisms by which food and nutrition insecurity connect to **cardiometabolic disease** (CMD)*



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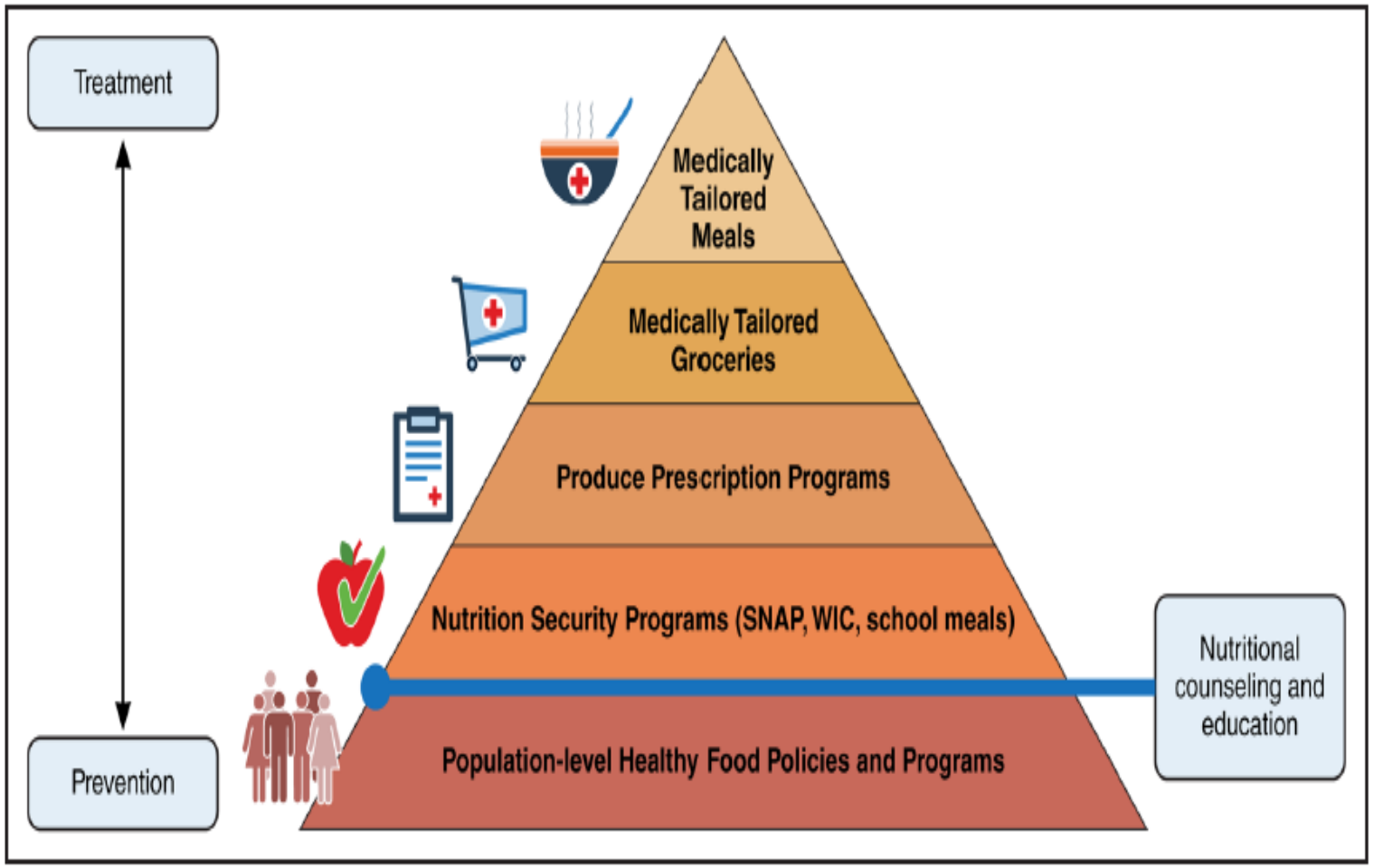
INTERVENTIONS TO IMPROVE NUTRITION SECURITY

✓ strategies to address nutrition insecurity can be conceptualized as a **pyramid of programs and interventions targeting both treatment and prevention** across different populations

adapted from Mozaffarian et al, Nat Med 2022



Circulation Research. 2023

JACC STATE-OF-THE-ART REVIEW

"Food Is Medicine" Strategies for Nutrition Security and Cardiometabolic Health Equity

Dariush Mozaffarian, Karen E. Aspry, Kathryn Garfield et al.

"Food Is Medicine" (FIM) represents a spectrum of food-based interventions integrated into health care for patients with specific health conditions and often social needs

programs include **medically tailored meals groceries, and produce prescriptions, with varying levels of nutrition and culinary education**

HIGHLIGHTS

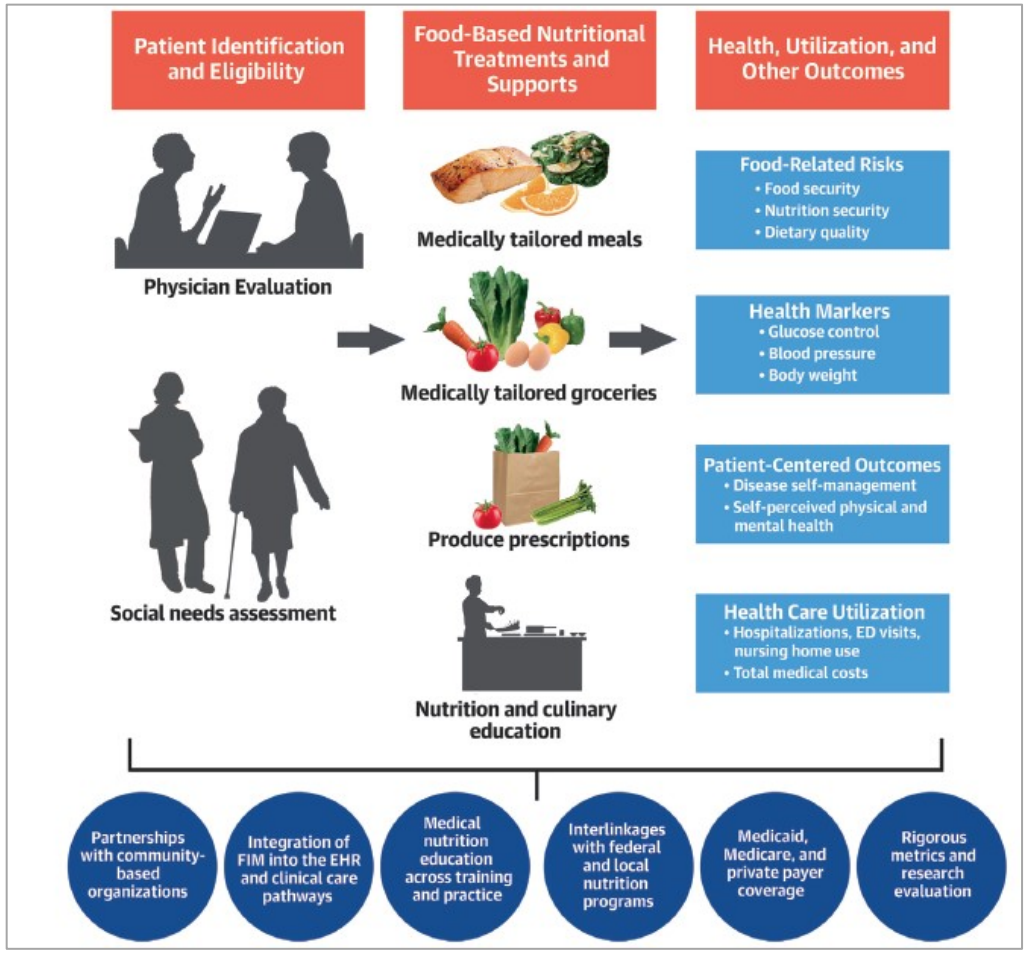
- "Food is Medicine" interventions integrate food-based treatments into health care systems.
- Preliminary evidence suggests significant positive impacts of these programs.
- Clinicians, health systems, and payers should support current and future directions of this strategy.

evidence **supports positive effects of FIM on metabolic diseases**, food insecurity, diet quality, glucose control, hypertension body weight, disease self-management, self-perceived physical and mental health and cost effectiveness or cost savings

✓ new national and local programs and policies are rapidly accelerating FIM within health care

✓ **successful incorporation of FIM into health care** will require multiparty partnerships to assess optimize and scale these promising treatments to advance health and health equity

A "Food is Medicine" Approach in Health Care



✓ FIM interventions are **food-based nutritional treatments integrated into health care** to treat and advance **health equity** among patients with specific disease conditions and often social needs

these programs often **include nutrition and culinary education** and can benefit from **supportive partnerships**, e-screening and care pathways, **medical nutrition education for clinicians, interlinkages with food assistance programs** and payer coverage

Mozaffarian D, et al. J Am Coll Cardiol. 2024

clinical practice and population guidelines also **emphasize nutrition for primary and secondary prevention of CVD and as a cornerstone of cardiovascular health across the lifespan**

✓ **cardiometabolic risk is attributable to low intakes of protective dietary factors**
(fruits, vegetables, whole grains, legumes, unsaturated fatty acids, fish)

✓ **and high intakes of** harmful components
(refined grains, processed meats, saturated fat, sodium, added sugars)

✓ … burdens of poor nutrition for patients are rarely driven by individual knowledge or choice alone

but influenced by complex social, environmental, cultural, agricultural, political, and economic determinants

Systematic Review

J Prev Med Public Health 2024;

Journal of Preventive Medicine & Public Health

Food is Medicine Initiative for Mitigating Food Insecurity in the United States

Vidya Sharma[1], Ramaswamy Sharma[2]

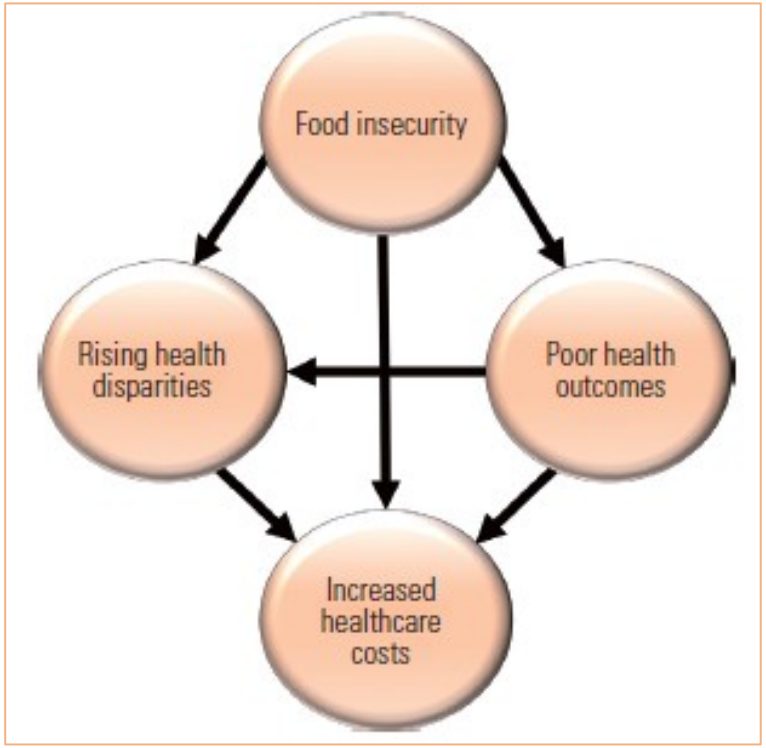
Objectives:

while several food assistance programs in the United States tackle food insecurity, a relatively new program, **"Food is Medicine,"** (FIM) initiated in some cities **not only addresses food insecurity but also targets chronic diseases** by customizing the food delivered to its recipients

Results:

the **FIM program** includes medically tailored meals, medically tailored groceries, and produce prescriptions, data suggest that **it has lowered food insecurity,** promoted **better management of health**, **improved health outcomes** and has, therefore, **lowered healthcare costs**

major consequences of food insecurity

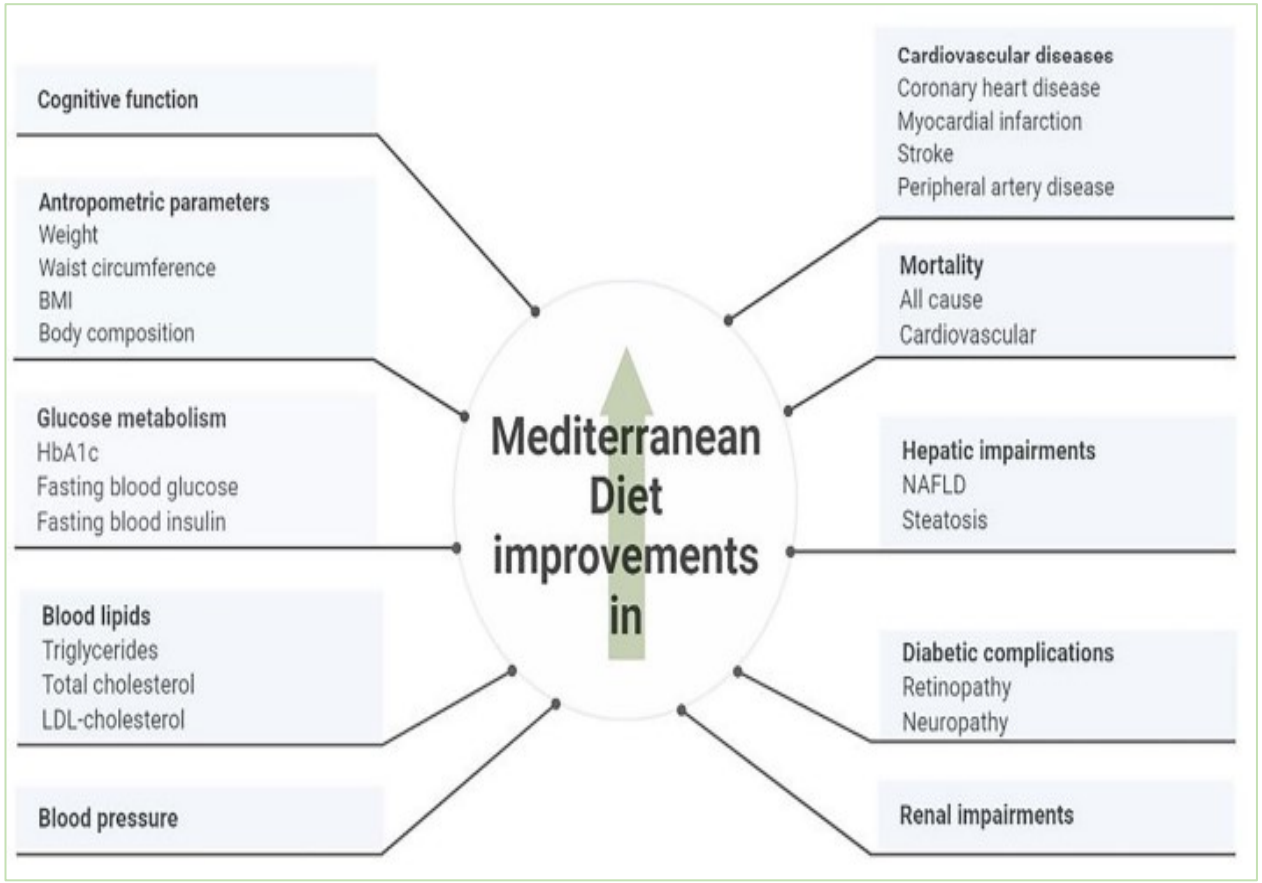


✓ food insecurity contributes to poor health outcomes and further exacerbates health disparities in socioeconomically disadvantaged individuals and families leading to **increased healthcare burden and associated costs**

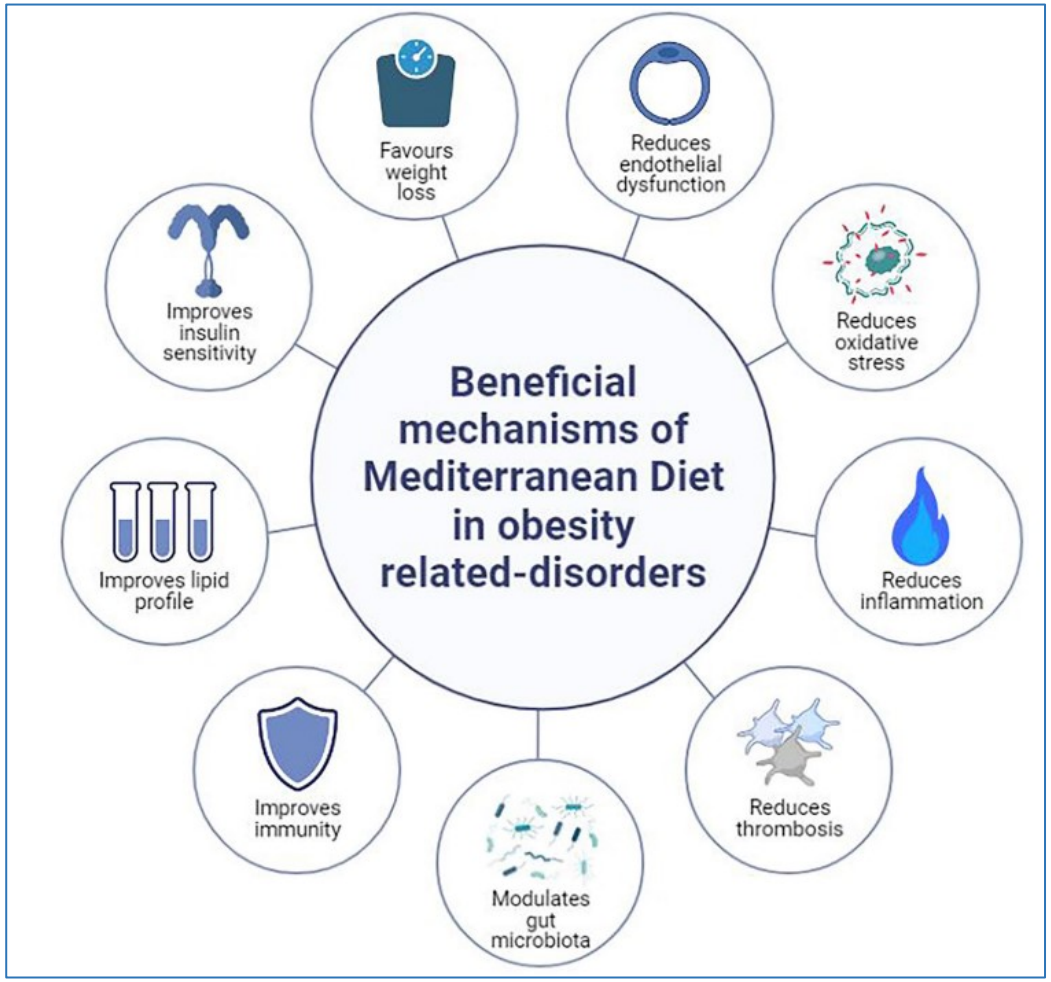
Current Obesity Reports (2022)

Mediterranean Diet and Obesity-related Disorders: What is the Evidence?

G. Muscogiuri, L. Verde, C. Sulu , N.Katsiki, M. Hassapidou, E. F.Toral, G. Cucalón, A. Pazderska, V. D. Yumuk, A. Colao, Luigi Barrea



the beneficial effects of adherence to MD on cardiometabolic factors and diabetic complications in patients with DM2

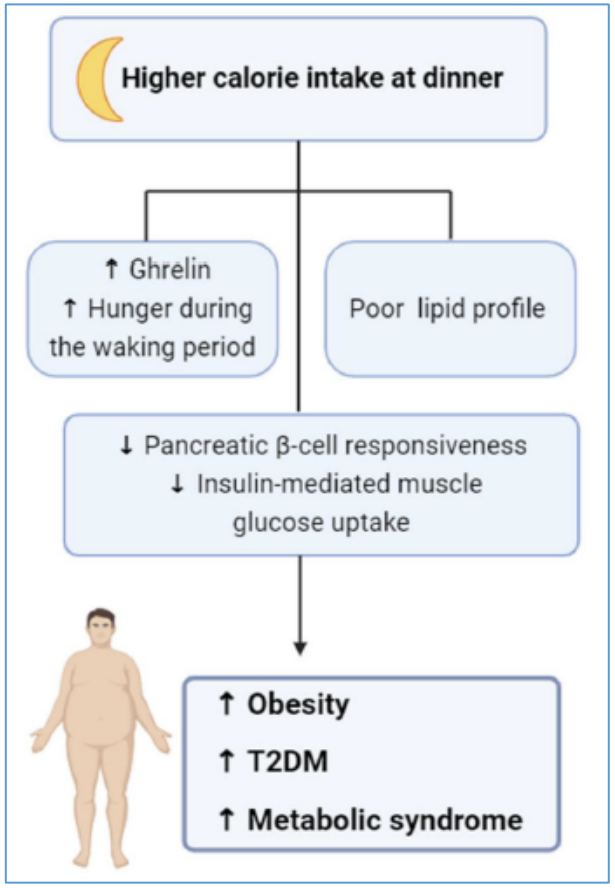


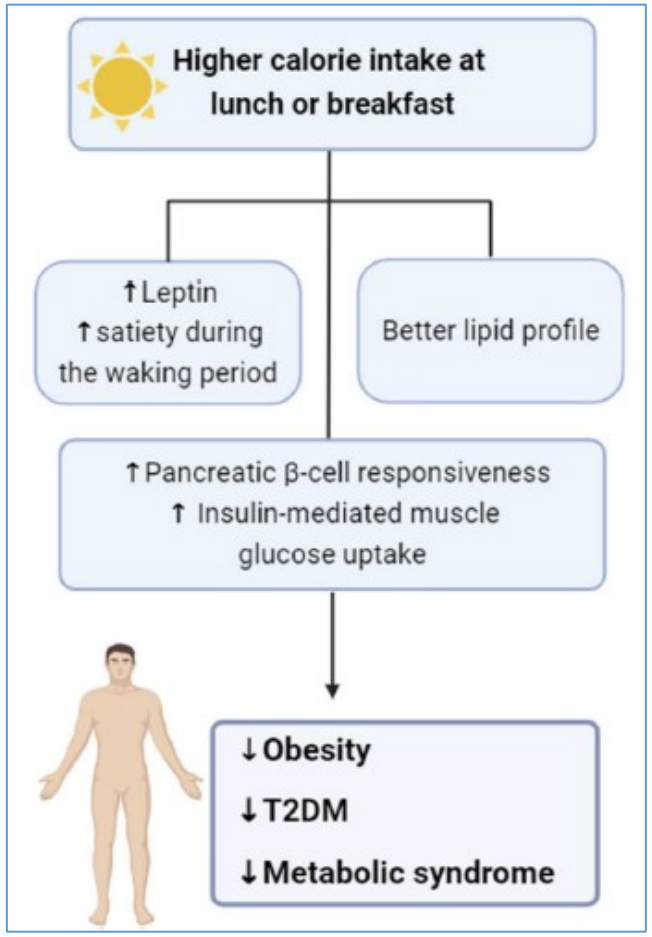
the beneficial mechanisms of Mediterranean diet in obesity-related disorders

Chrononutrition in type 2 diabetes mellitus and obesity: A narrative review

Ludovica Verde, Tonia Di Lorenzo, Silvia Savastano, Annamaria Colao, Luigi Barrea, Giovanna Muscogiuri

mechanisms that explain the impact of different energy intakes at dinner versus breakfast or lunch on obesity and T2DM





taking a **greater energy intake in the first part of the day** (at breakfast and lunch) has **beneficial effects on the lipid profile and leads to a greater sense of satiety** which could allow better control of body weight

furthermore, it has been shown that **blood glucose concentrations follow very specific rhythms due to changes in insulin sensitivity and the insulin secretory capacity** of the endocrine pancreas

in fact, **in the morning, pancreatic β cell reactivity and insulin-mediated muscle glucose uptake were at optimal levels,** this may result in a better glycaemic profile, resulting in a reduced risk of T2DM

✓ **these beneficial effects are lost when the greatest energy intake is taken in evening**

REVIEW ARTICLE

Diabetes Metab Res Rev. 2024

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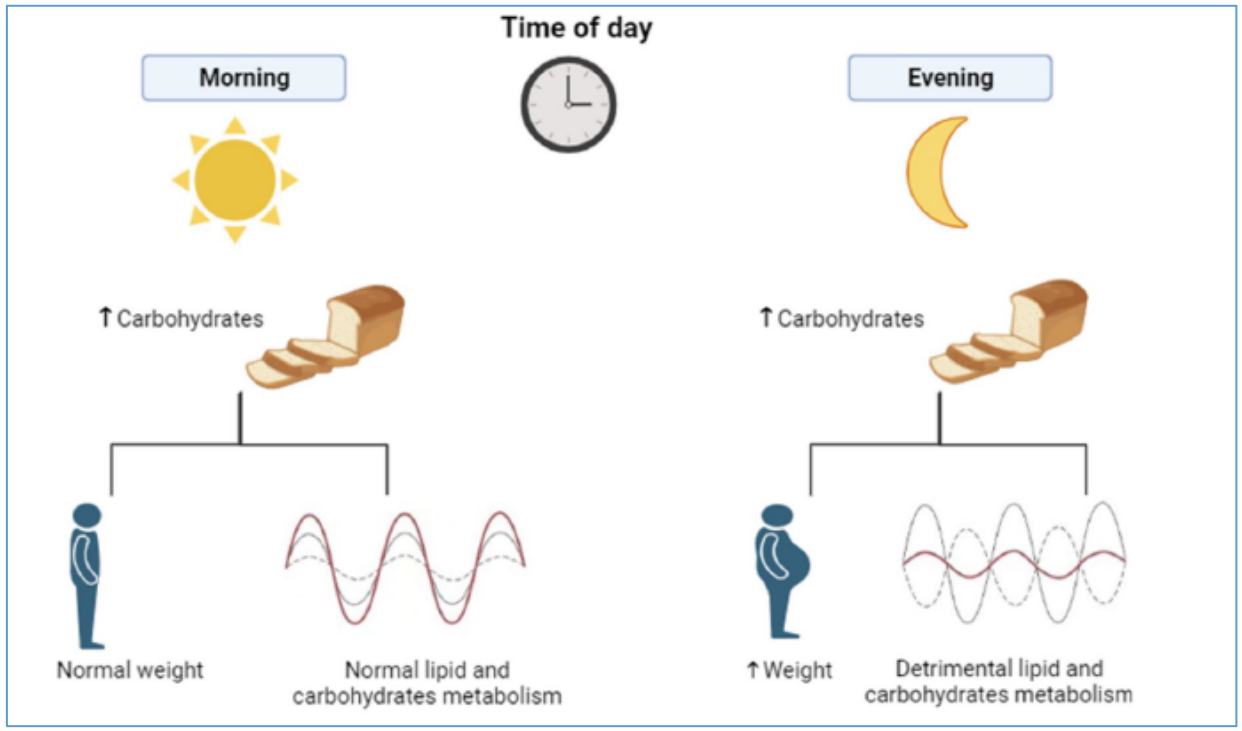


the impact of carbohydrate timing in obesity and T2DM

eating more carbohydrates earlier in the day can reduce the likelihood of weight gain and help maintain better glycometabolic control, reducing the risk of developing T2DM

on the contrary, consuming a greater intake of carbohydrates in the evening can significantly increase the likelihood of suffering from obesity and overweight

✓ **furthermore, concentrating most of the carbohydrates in the evening can have a more negative impact on glycometabolic control, increasing the risk of developing T2DM**

International Journal of
Molecular Sciences

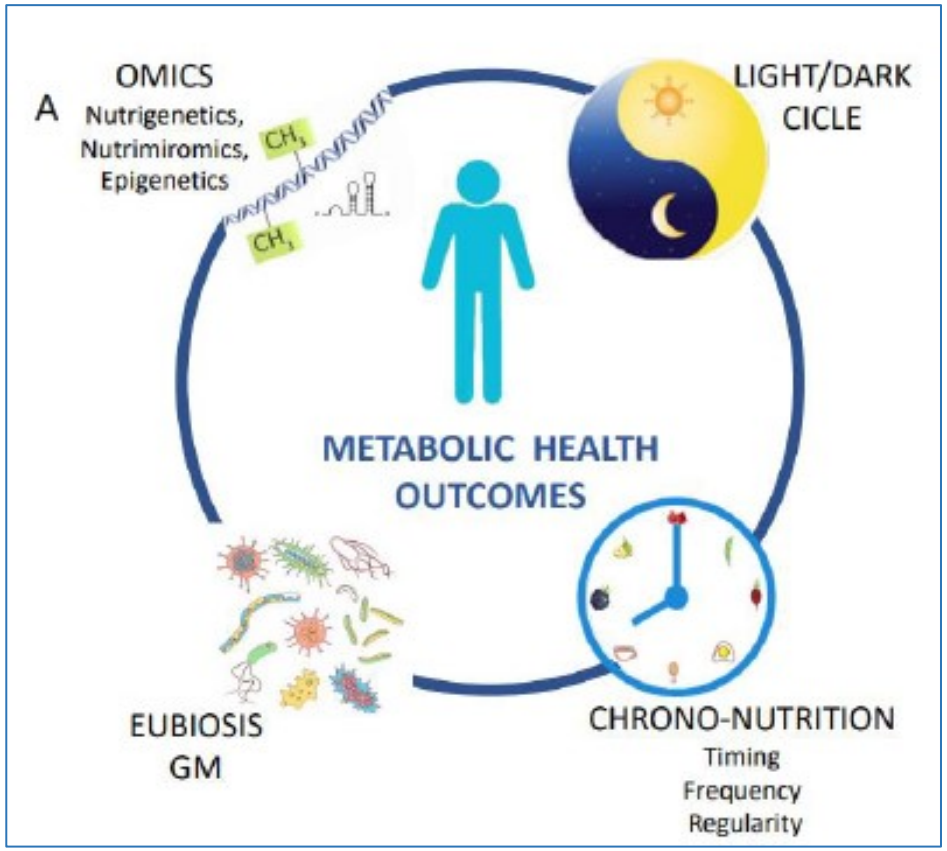
Int. J. Mol. Sci. 2023,

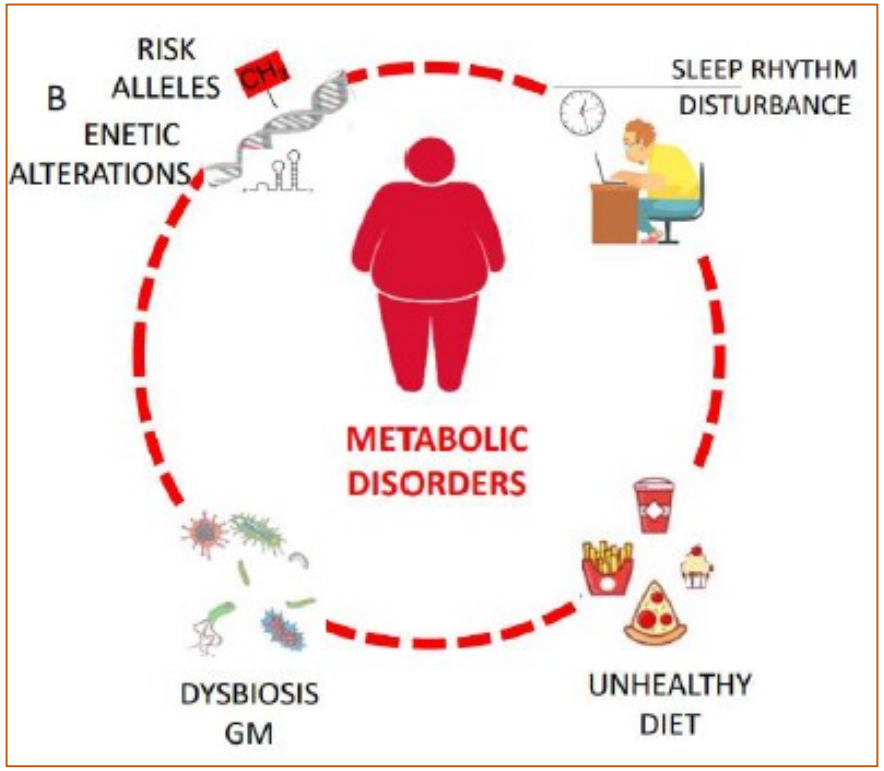
Marica Franzago, Elisa Alessandrelli, Stefania Notarangelo et al

Review

Chrono-Nutrition: Circadian Rhythm and Personalized Nutrition

from a nutritional genomics perspective ....





diet, chronotype, and several environmental disruptions of modern societies can impact the integration of circadian-triggering metabolic alterations and lead the development of chronic disease

CONCLUSIONS

combination of multidisciplinary health care ….. ?

an **epidemic of diet-related cardiometabolic and cardiovascular diseases** is intersecting with high rates of **food and nutrition insecurity**

- ✓ these challenges also provide opportunities for accelerated innovation to address their negative consequences on cardiometabolic and cardiovascular disease, productivity, health inequities, and healthcare spending

together, a **combination of multisector health care, policy,** and **population interventions can advance food security, nutrition security, and health equity**

- ✓ **aiming for equitable access** to and greater consumption of healthier foods and beverages and fewer unhealthy foods and beverages

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success is not final, failure is not fatal
it is the courage to continue that counts

Winston Churcill

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