

# Thoughts on dietary interventions for metabolic syndrome (MetS) in an era of metabolic heterogeneity

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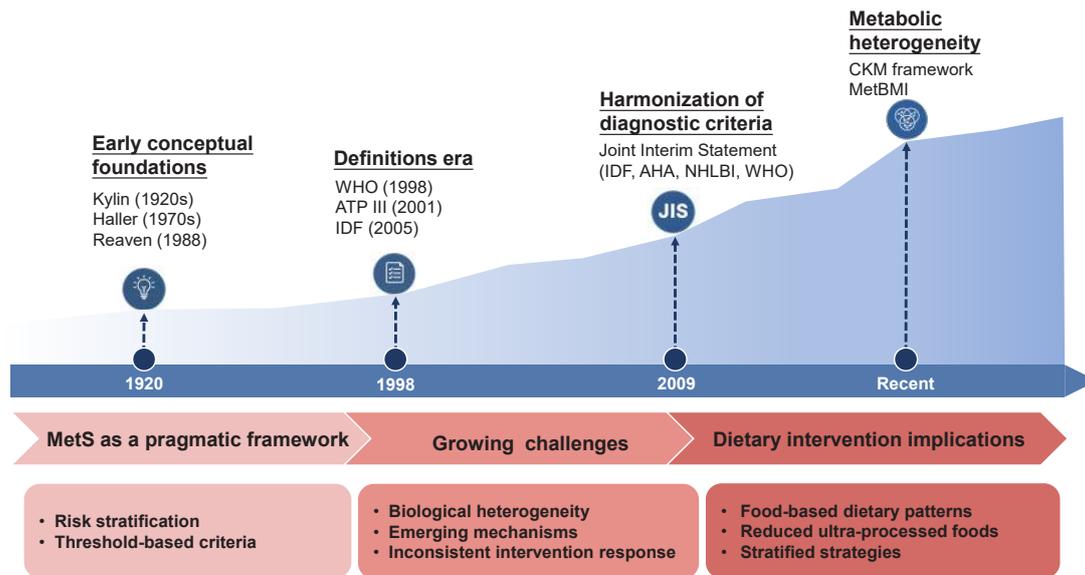
**SUMMARY:** Metabolic syndrome (MetS) has long been used as a pragmatic tool for population-level cardiometabolic risk stratification, rather than as a mechanistically defined disease entity. However, mounting evidence suggests the existence of marked biological heterogeneity among individuals meeting identical MetS criteria, encompassing diverse metabolic phenotypes, disease trajectories, and responses to interventions. Such heterogeneity helps explain the limited and inconsistent effectiveness of uniform dietary strategies. In parallel, dietary research has shifted from a nutrient-centric approach to a food-based dietary pattern, emphasizing higher intakes of whole foods and reduced consumption of ultra-processed foods. In the context of metabolic heterogeneity, these shared food-level characteristics may confer relatively consistent metabolic benefits across diverse phenotypes. Future research may shift from uniform dietary recommendations to stratified strategies, grounded in dietary principles and informed by mechanistic insights, to better address metabolic heterogeneity.

**Keywords:** metabolic syndrome (MetS), metabolic heterogeneity, dietary patterns, ultra-processed foods, stratified strategies

Metabolic syndrome (MetS) was not originally conceived of as a precise clinical diagnosis but rather as a pragmatic framework for identifying individuals at elevated cardiometabolic risk. From the early observations of Kylin in the 1920s, through Haller's metabolic clustering hypothesis, to Reaven's landmark description of insulin resistance syndrome, the central aim of MetS has consistently been population-level risk stratification rather than mechanistic classification (1-3). Beginning with the World Health Organization's first formal definition in 1998, subsequent decades saw the development of additional diagnostic criteria by organizations such as the National Cholesterol Education Program Adult Treatment Panel III (ATP III) and the International Diabetes Federation (IDF) (4-6). The 2009 Joint Interim Statement sought to harmonize these definitions, acknowledging that no single threshold could fully capture the biological complexity underlying metabolic risk (7) (Figure 1).

Following the harmonization of diagnostic criteria in the 2009 Joint Interim Statement, subsequent advances have increasingly highlighted the limitations of threshold-based definitions in capturing the full spectrum of metabolic risk. These limitations, in turn, have driven the emergence of new conceptual frameworks. More recently, the American Heart Association introduced the concept of cardiovascular-kidney-metabolic (CKM) syndrome, framing MetS as an early upstream stage within a

continuous cardiometabolic disease trajectory (8). In parallel, emerging phenotype-based approaches include metabolomic BMI (MetBMI) (9), a multiomic signature that captures metabolic dysfunction beyond measured BMI. By enabling risk stratification within conventional BMI categories, MetBMI reveals heterogeneity that is not apparent from anthropometric measures alone. One of the fundamental challenges underlying these developments is the pronounced biological heterogeneity of MetS. Even among individuals who meet identical diagnostic criteria, substantial differences may exist in metabolic phenotypes, disease trajectories, and responses to intervention (Table 1). For example, studies in African-American populations have shown that cardiometabolic risk may be underestimated at lower triglyceride levels, suggesting ethnic differences in lipid metabolism and limited generalizability of conventional triglyceride thresholds (10). Likewise, classic phenotypes, such as metabolically healthy obesity and metabolically unhealthy normal weight, provide clinically tangible examples of this heterogeneity, demonstrating that anthropometric measures alone do not reliably capture true metabolic risk (11). Beyond these observable phenotypic differences, age-related changes in body composition, chronic low-grade inflammation, declining insulin sensitivity, and sex-specific hormonal differences add further layers of metabolic complexity (12-14). Individuals with



**Figure 1. Conceptual evolution of metabolic syndrome and its impact on dietary intervention.** The figure illustrates the historical development of MetS from early conceptual observations to the harmonization of diagnostic criteria, the emergence of new frameworks highlighting metabolic heterogeneity, and the resulting shift in the conceptual approach to dietary intervention. *Abbreviations:* MetS: metabolic syndrome; WHO: World Health Organization; ATP III: Adult Treatment Panel III of the National Cholesterol Education Program; IDF: International Diabetes Federation; JIS: Joint Interim Statement; AHA: American Heart Association; NHLBI: National Heart, Lung, and Blood Institute; CKM: cardiovascular–kidney–metabolic syndrome; MetBMI: metabolomic body mass index.

**Table 1. Key sources of heterogeneity in MetS and their implications for dietary intervention**

Heterogeneity	Core issue	Key manifestations	Ref.
Limited applicability of uniform diagnostic criteria	Insufficient cross-population applicability	In African-American populations, metabolic risk may be underestimated at lower triglyceride levels	(10)
Insensitivity of dichotomous thresholds	Phenotypic heterogeneity	Limited ability to identify metabolically unhealthy normal-weight individuals, potentially underestimating risk.	(11)
Limited applicability of standardized intervention strategies	Heterogeneous intervention responses	Age-related muscle loss reduces insulin sensitivity; sex-specific hormonal regulation of metabolism; interindividual differences in chronic low-grade inflammation	(12-14)
Challenges posed by emerging mechanisms	Conventional metabolic indicators inadequately reflect emerging mechanisms	Heterogeneous mechanisms (insulin resistance, adipose dysfunction, inflammation, gut microbiota) despite similar metabolic profiles.	(15-17)

similar fasting glucose or lipid profiles may exhibit fundamentally different underlying mechanisms, including insulin resistance, adipose dysfunction, inflammation, and alterations in gut microbiota (15-17). These mechanistic differences may influence individual responses to dietary interventions. For instance, interindividual differences in the capacity of gut microbial communities to ferment dietary fiber lead to variability in short-chain fatty acid (SCFA) production, which may influence insulin sensitivity and glucose homeostasis (18-20). As a whole, such heterogeneity poses a fundamental challenge to dietary intervention strategies, limiting the long-term efficacy of uniform dietary approaches (21,22).

Despite long-running debate regarding its clinical definition, the relevance of MetS is underscored by its sheer epidemiological scale. Recent global modeling studies estimate that more than 1.5 billion adults

worldwide now meet diagnostic criteria for MetS, reflecting a dramatic rise over the past two decades (23). Importantly, MetS is not merely a descriptive label but a powerful predictor of adverse outcomes. Large prospective studies and meta-analyses have consistently shown that individuals with MetS face approximately a two-fold higher risk of cardiovascular events and a markedly elevated risk of developing type 2 diabetes, with estimates approaching a five-fold increase (7,24). Evidence from the Global Burden of Disease studies clearly indicates that core components of metabolic syndrome, including elevated systolic blood pressure, hyperglycemia, and obesity, now account for a substantial share of global mortality and DALYs. According to the GBD 2019 risk factor analysis, elevated fasting plasma glucose ( $\geq 5.4$  mmol/L) contributes to approximately 6.5% of global DALYs and 2.4 million deaths, whereas

elevated systolic blood pressure ( $\geq 110$ -115 mmHg) is associated with around 10.8 million deaths and more than 200 million DALYs globally (25). Elevated low-density lipoprotein cholesterol (LDL) causes approximately 4.4 million deaths annually (26). In parallel, overweight and obesity ( $\text{BMI} \geq 25 \text{ kg/m}^2$ ) contribute to around 5 million deaths and 160 million disability-adjusted life years (DALYs) globally, with particularly pronounced increases observed in low- and middle-income countries (27). These observations explain why, despite its conceptual imperfections, MetS continues to serve as a pragmatic framework for population-level risk stratification.

Against the backdrop of growing metabolic heterogeneity and the limited capacity of uniform dietary interventions to deliver consistent and sustained benefits, dietary intervention research has increasingly shifted toward a pattern-based perspective in recent years. Attention has shifted to how foods are combined, processed, and embedded in daily eating patterns instead of a single nutrient. An increasing number of prospective studies and international dietary guidelines support a dietary pattern-based approach, advocating that public health strategies should prioritize improving food quality and dietary diversity rather than overly emphasizing upper limits on individual nutrient intake (28-30). Despite substantial differences in macronutrient composition, diverse healthy dietary patterns, including the Mediterranean, DASH, plant-based diets, and healthy eating indices importantly converge at the food level, consistently emphasizing higher intakes of whole foods, such as vegetables, fruits, legumes, and whole grains, while limiting ultra-processed foods and added sugars (31-33). This convergence at the food level is particularly relevant in the context of metabolic heterogeneity, as it suggests that food-based characteristics such as higher fiber intake and minimal processing may have relatively consistent metabolic effects across diverse metabolic phenotypes even when individuals differ in their responses to macronutrient composition (21,34,35). From this perspective, the growing focus on ultra-processed foods represents not merely a shift in nutritional trends but a pragmatic dietary strategy aimed at reducing overall metabolic risk at the population level in the context of pronounced metabolic heterogeneity. A substantial body of evidence consistently links a high intake of ultra-processed foods to adverse metabolic outcomes, including obesity, type 2 diabetes, and cardiovascular disease (36-38). Accordingly, recent scientific statements from the American Heart Association and the 2025-2030 Dietary Guidelines for Americans have explicitly called for limiting ultra-processed foods while prioritizing "eat real food"-based dietary patterns, underscoring a broader shift toward dietary interventions that are both metabolically relevant and feasible at the population level (39).

Overall, increasing metabolic heterogeneity challenges the notion of metabolic syndrome as a target

for uniform dietary intervention. While MetS remains useful for population-level risk stratification, its biological diversity limits the effectiveness of standardized dietary strategies. A shift toward real food-based, pattern-oriented strategies may offer a more adaptable and scalable framework for reducing metabolic risk across biologically heterogeneous populations. Future research may move beyond universally optimal diets toward principle-based, mechanism-informed stratified approaches that retain shared food-level recommendations while incorporating metabolic and gut microbial features (40,41), thereby better accommodating metabolic heterogeneity while preserving population-level feasibility.

*Funding:* None.

*Conflict of Interest:* The author has no conflicts of interest to disclose.

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Received February 6, 2026; Accepted February 22, 2026.

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Released online in J-STAGE as advance publication February 25, 2026.