Review Articles

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Cardiometabolic Multimorbidity: Clustering Phenotypes, Shared Pathways, and Integrated Management Strategies

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ABSTRACT

Cardiometabolic multimorbidity (CMM), defined as the co-occurrence of hypertension, type 2 diabetes mellitus, dyslipidemia, obesity and related disorders in the same individual, has become an increasingly severe global public health challenge in the era of multimorbidity. Recent large-scale cohort studies have gone beyond simple counting of disease counts and identified heterogeneous phenotypic clusters, such as metabolically healthy obesity (MHO) and metabolically unhealthy normal weight (MUNW), which show significantly different risks of progressing to overt cardiometabolic multimorbidity. This review compares mainstream clustering analysis methods, explores the common pathophysiological mechanisms underlying these phenotypes, including insulin resistance, chronic low-grade inflammation and neuroendocrine disorders, and summarizes evidence-based integrated management strategies tailored to different comorbidity clusters. By integrating phenotype-specific characteristics with multi-target lifestyle interventions, pharmacotherapy and digital health interventions, this framework promotes a shift from fragmented specialty-based management to precision collaborative management, which is expected to reduce cardiovascular events, renal function decline and premature mortality.

1. Introduction

Hypertension, type 2 diabetes, dyslipidemia, and obesity rarely occur in isolation; instead, they frequently coexist as cardiometabolic multimorbidity (CMM) [1], amplifying risks of cardiovascular disease (CVD), chronic kidney disease (CKD), and functional decline. Compared with individuals who have a single cardiometabolic condition, patients with CMM experience a markedly higher mortality risk, with a reduction in life expectancy of 12–15 years at age 60 [2]. CMM not only increases disease burden but is also linked to neurodegenerative diseases and mental health disorders [3]. Traditional single-disease management—cardiology for coronary disease, endocrinology for glycemia, nephrology for renal decline—overlooks the interconnected nature of these conditions, leaving comprehensive care a clinical blind spot.

Recent data-driven approaches have identified distinct comorbidity clusters and metabolic phenotypes, revealing that metabolic status often outweighs body mass index (BMI) alone and that not all obesity confers equal risk. This review focuses on two complementary pillars—clustering phenotyping and integrated comorbidity management—to provide clinicians and researchers with actionable insights for precision prevention and care [1][4][5].

2. Methods

This narrative review was conducted to synthesize evidence on clustering phenotypes, shared pathways, and integrated management of cardiometabolic multimorbidity. We searched PubMed, Embase, and Scopus from January 2015 to April 2026 using the terms “cardiometabolic multimorbidity,” “clustering phenotypes,” “metabolically healthy obesity,” “MUNW,” “MHO,” “CKM syndrome,” “insulin resistance,” “metaflammation,” and “integrated management.” Studies were included if they were large cohort studies, systematic reviews, meta-analyses, clinical guidelines, or expert consensuses addressing clustering methods, pathophysiological pathways, or management strategies in adults with CMM. We prioritized longitudinal data, high-impact publications, and recent (2023–2026) evidence on the American Heart Association (AHA) CKM framework and multidisciplinary consensuses. Non-English articles, case reports, and small cross-sectional studies without outcome data were

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excluded. Reference lists of included articles were hand-searched for additional sources.

3. Clustering Phenotypes of Cardiometabolic Multimorbidity: Methods, Findings, and Clinical Utility

3.1. Overview of Clustering Methods

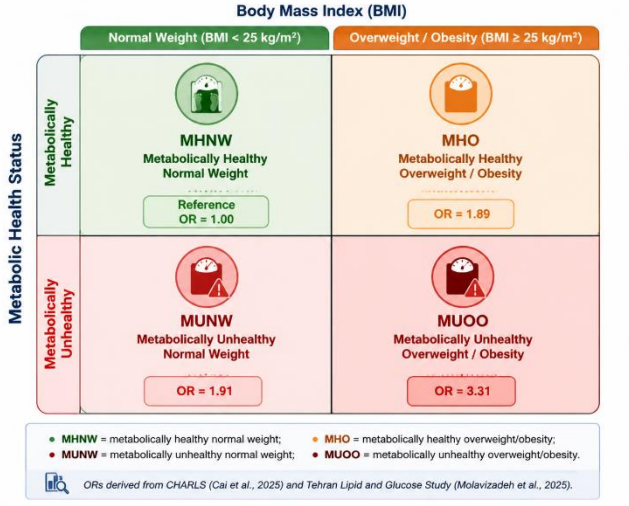
Clustering analyses of large cohorts have evolved from descriptive cross-sectional patterns to predictive longitudinal trajectories. Key methods and their characteristics are summarized in Table 1.

Table 1 - Comparison of Clustering Methods for Cardiometabolic Multimorbidity

Method	Advantages	Limitations	Best Use Cases	Representative References
Hierarchical clustering	Intuitive dendrograms; no pre-specified cluster number	Sensitive to outliers; limited statistical testing	Exploratory pattern discovery	Ferris et al., 2025 [6]
Latent class / model-based analysis	Probabilistic assignment; goodness-of-fit statistics	Requires predefined cluster count; computationally intensive	Hypothesis-driven phenotyping	Nichols et al., 2022 [7]
Longitudinal sequence / Markov models	Captures disease progression trajectories over time	Demands complete follow-up data	Predictive risk modeling	Ioakeim-Skoufa et al., 2025 [8]
Network / machine-learning approaches	Visualizes direct disease interconnections	Limited causal inference	Multimorbidity network mapping	Marengoni et al., 2025 [9]

A 2025 systematic review and meta-analysis identified six stable cardiometabolic-dominated clusters with moderate stability across studies [10]. Longitudinal analyses, such as those from the China Health and Retirement Longitudinal Study (CHARLS), delineated eight distinct progression sequences leading to CMM [5].

Figure 1. Four-Quadrant Metabolic Phenotypes and Risk of Cardiometabolic Multimorbidity



3.2. BMI-Metabolic Phenotype Framework (Four-Quadrant Model)

The most clinically translatable framework combines BMI with metabolic health status to define four phenotypes: metabolically healthy normal weight (MHNW), metabolically healthy overweight/obesity (MHO), metabolically unhealthy normal weight (MUNW), and metabolically unhealthy overweight/obesity (MUOO). These phenotypes were first introduced in the four-quadrant model and have been validated in multiple cohorts.

Analyses of CHARLS data (n=5,850) showed a graded risk of CMM progression: MUOO conferred the highest odds (OR 3.31, 95% CI 2.60–4.24), followed by MUNW (OR 1.91) and MHO (OR 1.89) relative to MHNW [5]. The Tehran Lipid and Glucose Study (14.3-year follow-up, n=6,343) reported similarly elevated risks of cardio-renal-metabolic multimorbidity for MHO (HR 2.04) and MUNW (HR 2.29), challenging the concept of truly "benign" obesity [11]. Metabolic health appears more prognostic than BMI alone; dynamic transitions in metabolic status (rather than weight change per se) drive CMM incidence. These phenotypes also predict differential intervention responses, supporting risk stratification.

3.3. Limitations and Future Directions in Phenotyping

Limitations include heterogeneity in definitions of "metabolic health" (e.g., metabolic syndrome criteria vs. waist-to-hip ratio), predominance of data from high-income and East Asian populations, and insufficient incorporation of social determinants of health. Emerging multi-omics and machine-learning models promise more granular, dynamic phenotyping.

4. Shared Pathophysiological Pathways Linking Phenotypes to CMM

Three interconnected mechanisms form the common soil of cardiometabolic clusters.

4.1. Insulin Resistance as the Central Hub

Insulin resistance, estimated to affect 26–40% of adults globally (with regional variation from ~16% in some populations to >47% in high-risk groups) [12][13], impairs phosphatidylinositol 3-kinase/protein kinase B (PI3K/Akt) signaling while activating stress kinases such as c-Jun N-terminal kinase (JNK) [14]. This leads to hyperglycemia, dyslipidemia, and endothelial dysfunction. Phenotype differences are notable: MHO individuals often retain higher adiponectin and lower ceramide levels, partially preserving insulin sensitivity despite obesity, whereas MUNW shows early adipose dysfunction and ectopic fat deposition.

4.2. Chronic Low-Grade Inflammation (Metaflammation)

Adipose tissue in obesity undergoes macrophage infiltration and releases pro-inflammatory cytokines (TNF-α, IL-6), driving systemic metaflammation. This process exacerbates insulin resistance, promotes atherogenesis, and accelerates renal fibrosis. The cGAS-STING pathway acts as a DNA sensor linking mitochondrial stress to inflammation in diabetic cardiovascular complications [15][16], while the NLRP3 inflammasome integrates lipotoxicity and hyperglycemia signals to amplify IL-1β/IL-18 release and pyroptosis [17]. MHO phenotypes exhibit lower metaflammation (reduced macrophage infiltration and preserved anti-inflammatory adipokines) compared with MUOO or MUNW, explaining their relatively lower progression risk.

4.3. Neuroendocrine Dysregulation

Chronic stress activates the hypothalamic-pituitary-adrenal axis and sympathetic nervous system, elevating cortisol and catecholamines. This promotes visceral adiposity, insulin resistance, and hypertension—explaining higher CMM burden in lower socioeconomic groups [18].

These pathways form a self-reinforcing vicious cycle: inflammation worsens insulin signaling, insulin resistance fuels lipotoxicity and further inflammation, and neuroendocrine stress amplifies both. Phenotype-specific modulation of cycle intensity (e.g., lower inflammation in MHO) provides a mechanistic basis for tailored interventions.

5. Integrated Management Strategies

5.1. Conceptual Frameworks

The AHA 2023 Presidential Advisory introduced cardiovascular-kidney-metabolic (CKM) syndrome as a unified pathophysiological continuum encompassing obesity, diabetes, CVD, and CKD, with a four-stage system (Stage 0: no risk factors; Stage 1: excess adiposity; Stage 2: metabolic risk factors ± moderate-to-high-risk CKD; Stage 3: subclinical CVD; Stage 4: clinical CVD) [19]. Complementary European and emerging Asia-Pacific multidisciplinary frameworks emphasize pathophysiology-based risk stratification. Clustering phenotypes inform staging: MUOO patients often progress to higher-risk stages earlier.

5.2. Lifestyle Medicine as Foundation

The American College of Lifestyle Medicine's six pillars—nutrition, physical activity, stress management, restorative sleep, social connection, and avoidance of risky substances—simultaneously target all three pathways [20]. Phenotype-tailored approaches (e.g., visceral fat reduction emphasis in MUOO vs. metabolic correction in MUNW) improve adherence and outcomes.

5.3. Multi-Target Pharmacotherapy

Combination therapy outperforms single-disease approaches. Sodium-glucose cotransporter-2 (SGLT2) inhibitors (e.g., EMPA-REG OUTCOME trial: empagliflozin reduced CV death by 38% and heart failure hospitalization by 35% in type 2 diabetes with CVD) [21] and glucagon-like peptide-1 receptor agonists (e.g., LEADER trial: liraglutide reduced major adverse CV events by 13%) [22] provide cardiorenal-metabolic benefits beyond glucose lowering. Complementary agents include renin-angiotensin system inhibitors, statins ± ezetimibe or PCSK9 inhibitors, and non-steroidal mineralocorticoid receptor antagonists (finerenone). Mechanism-guided, phenotype-prioritized regimens are now recommended in major guidelines.

5.4. Practical Stratified Framework

A stratified approach is recommended: (1) population-level phenotype-based screening, (2) individualized lifestyle plus pharmacotherapy plans, and (3) multidisciplinary teams supported by digital health platforms.

6. Challenges and Future Perspectives

Key barriers include inconsistent phenotyping definitions, implementation gaps in low-resource settings, and health equity issues—CMM disproportionately affects lower socioeconomic groups least able to access integrated care. Future directions include multi-omics precision phenotyping, real-world cost-effectiveness trials of cluster-guided management, and global policies to reduce social determinants-driven disparities.

7. Conclusion

Cardiometabolic multimorbidity demands a paradigm shift from single-disease care to phenotype-informed, pathway-targeted integrated management. By harnessing clustering insights and addressing shared mechanisms through lifestyle medicine, multi-target pharmacotherapy, and digital-multidisciplinary platforms, clinicians can deliver precision co-management that improves outcomes across the CMM spectrum. Realizing this vision requires standardized phenotyping, equitable implementation science, and sustained interdisciplinary collaboration.

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