Review Articles

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Multimorbidity in the Era of Multiple Chronic Conditions: From Methodological Advances to Precision Prevention

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A B S T R A C T

Multimorbidity refers to the presence of two or more chronic diseases in a single individual. It has surpassed the single-disease model and become a major public health challenge worldwide. In recent years, notable progress has been made in disease clustering analyses based on large cohorts and electronic health records. However, significant challenges remain, including high methodological heterogeneity, limited clustering stability, and unclear pathways for clinical application. This paper systematically reviews the epidemiological transition of multimorbidity, compares the applicability and limitations of common clustering methods such as hierarchical clustering, latent class analysis, K-centroids clustering, and network analysis, summarizes the heterogeneous characteristics of clustering patterns across populations and regions, and explores translational pathways from disease clustering to precision prevention. Based on this, we propose future research directions, including methodological standardization, integration of longitudinal data, development of stratified precision prevention strategies, and establishment of policy translation mechanisms. The goal is to provide a theoretical framework and methodological guidance for precision prevention in the era of multimorbidity.

1. Introduction

Multimorbidity, defined as the co-occurrence of two or more chronic conditions within one individual, represents the dominant clinical and epidemiological reality of modern healthcare. Although definitional thresholds vary (⩾2 or ⩾3 conditions), the ⩾2 definition is now widely adopted in large-scale analyses. Currently, over half of the global population aged 60 years or older lives with multimorbidity, a proportion projected to rise concomitantly with population aging [1]. Critically, distinct disease combinations exert differential impacts on health outcomes, functional status, and mortality risk. Consequently, identifying which diseases cluster together, elucidating their interactive mechanisms, and characterizing the temporal trajectories of disease have become imperative research priorities.

The application of unsupervised statistical clustering to multimorbidity research has accelerated substantially. In 2025, Ferris et al. published a landmark systematic review and meta-analysis in Nature Communications, synthesizing 79 studies and identifying six moderately stable multimorbidity clusters (Jaccard index ⩾0.51) from 1,226 reported clusters, with cardiometabolic patterns demonstrating the highest stability [错误!未找到引用源。]. Complementarily, Mikula-Noble et al. (2025) conducted a systematic review in PLOS ONE, revealing significant heterogeneity in clustering patterns stratified by age, sex, and socioeconomic status [3].

Despite these advances, critical challenges persist. Methodological heterogeneity across studies—encompassing divergent disease definitions, variable inclusion criteria, and inconsistent analytical workflows—has severely limited cross-study comparability and reproducibility [4]. Notably, no disease cluster has yet achieved high stability (Jaccard index ⩾0.75), and only a minority of studies have incorporated disease temporality into clustering frameworks. These methodological bottlenecks constrain the clinical translation of clustering findings. This review systematically integrates recent advances across four dimensions: epidemiological transition, methodological comparison, cross-population pattern heterogeneity, and translational pathways to precision prevention, and proposes actionable directions for future research.

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2. Epidemiological Transition: From Single-Disease Models to the Multimorbidity Era

2.1. Global Prevalence and Demographic Burden

Multimorbidity has become the prevailing norm in chronic disease epidemiology. A systematic review and meta-analysis estimated that over 50% of adults aged ⩾60 years worldwide live with multimorbidity. The prevalence of multiple long-term conditions (MLTCs)—a term frequently used interchangeably with multimorbidity in the literature—is anticipated to double within the next two decades amid population aging. Among individuals with multimorbidity, 30%–40% concurrently experience physical and mental health disorders. Prevalence is consistently higher among women and socioeconomically disadvantaged populations, with low-income individuals demonstrating multimorbidity levels comparable to those of populations approximately 20 years older in high-income settings [5].

2.2. Healthcare System Challenges

The management of multimorbidity presents multifaceted dilemmas: polypharmacy burden, fragmented care delivery, misalignment of priorities between patients and clinicians, and the absence of harmonized clinical guidelines. These factors collectively contribute to suboptimal care quality, elevated healthcare utilization, increased hospitalization risk, and adverse health outcomes [6]. In resource-constrained settings, limited primary care access frequently renders acute hospitalization the first clinical manifestation of multimorbidity, further straining fragile health systems.

2.3. Conceptual and Strategic Value of Disease Clustering

Given the heterogeneous health impacts of different disease combinations, identifying non-random disease clusters constitutes a critical strategy for optimizing multimorbidity management. Disease clustering reflects systematic associations arising from shared genetic predispositions, lifestyle risk factors, common pathophysiological pathways, drug-disease interactions, or causal disease cascades. Elucidating these patterns not only advances mechanistic understanding but also informs the design of targeted prevention strategies and health service optimization. A 2025 systematic review by Ioakeim-Skoufa et al. emphasized that characterizing multimorbidity trajectories enables anticipatory prevention strategies, supports the identification of patients with predictable progression patterns, and facilitates intervention design to reduce health disparities [6].

3. Methodological Landscape: From Association Analysis to Network Approaches

3.1. Taxonomy and Application of Clustering Methodologies

The methodological arsenal for disease clustering analysis encompasses three principal categories: (i) association-based methods (association rule mining, network analysis); (ii) classification-based methods (hierarchical clustering, latent class analysis, latent transition analysis); and (iii) dimensionality reduction techniques (principal component analysis, factor analysis, multiple correspondence analysis). Ferris et al.'s systematic review of 79 studies reported hierarchical cluster analysis as the most frequently applied method (25% of analyses), followed by latent class analysis (20%), network analysis (19%), and K-centroids clustering (15%). Percentages sum to >100% because some studies applied multiple method. Mikula-Noble et al.'s review of 125 articles corroborated these findings, identifying latent class analysis as the predominant technique (n=51) [3].

3.2. Comparative Strengths, Limitations, and Temporal Capacities

Hierarchical cluster analysis, the most traditional approach, calculates pairwise disease similarity or distance metrics to construct a dendrogram, enabling exploratory analysis at variable granularity without pre-specification of cluster number. Its strengths include intuitive visualization and flexibility; however, it suffers from high computational complexity, sensitivity to outliers, and limited capacity to integrate covariate information. Critically, standard hierarchical clustering is inherently cross-sectional and cannot incorporate disease temporality or onset sequences.

Latent class analysis (LCA) is a model-based clustering method predicated on the assumption that observed data arise from a mixture distribution determined by a latent categorical variable. Its advantages include robust statistical inference for model fit assessment, probabilistic cluster assignment, and the ability to incorporate covariates to examine clustering determinants. Limitations encompass sensitivity to model assumptions, substantial computational demands, and challenges in managing high-dimensional disease spaces. Comparative studies examining how different methodologies yield divergent clustering results remain scarce [2][4]. Standard LCA is cross-sectional; extensions such as latent transition analysis (LTA) can model disease trajectories over time, albeit with substantially increased computational complexity and sample size requirements.

K-centroids clustering (e.g., K-means, K-medoids) partitions data iteratively to minimize within-cluster variation. Its computational efficiency renders it suitable for large-scale datasets. However, it requires a priori specification of cluster number (K), exhibits sensitivity to initial centroid placement, and performs poorly with non-spherically distributed data. Like hierarchical clustering, standard K-centroids methods are static and cannot accommodate the temporal order of disease onset.

Network analysis conceptualizes diseases as nodes and their associations as edges to construct comorbidity networks. Leveraging electronic health records and genetic biobank data, this approach excels at visualizing complex association architectures, identifying disease modules and central nodes via topological metrics (e.g., modularity, centrality), and integrating multi-omic information through multilayer networks. Key challenges include the lack of consensus on association strength metrics (relative risk, Phi coefficient, Jaccard index differentially influence network topology) and the need for rigorous confounding control. Most comorbidity networks are constructed from cross-sectional data; emerging dynamic network approaches remain methodologically immature for routine application.

Table 1 - Methodological selection framework for multimorbidity clustering

Research objective	Recommended primary method	Temporal capability
Explore hierarchical taxonomy without predefining cluster number	Hierarchical clustering	Cross-sectional only

Research objective	Recommended primary method	Temporal capability
Incorporate covariates; obtain probabilistic class assignment	Latent class analysis (LCA)	Cross-sectional; LTA for longitudinal
Analyze large-scale datasets (>10,000 subjects) efficiently	K-centroids clustering	Cross-sectional only
Visualize complex inter-disease associations; identify central diseases	Network analysis	Mostly cross-sectional; dynamic networks emerging
Model disease onset sequences and temporal transitions	Latent transition analysis (LTA) / Group-based trajectory modeling (GBTM)	Longitudinal

3.3. Methodological Heterogeneity, Stability, and the Temporal Deficit

Multimorbidity clustering studies exhibit profound methodological heterogeneity across multiple dimensions: disease definitions, number of included conditions, clustering algorithms, and data sources. Ferris et al. reported that up to 30% of included studies carried a high risk of bias, raising substantial concerns regarding reproducibility [4]. Critically, stability assessments revealed that no cluster has achieved high stability (Jaccard index ⩾0.75), and only six clusters attained moderate stability (Jaccard index ⩾0.51), all predominantly cardiometabolic [6].

Furthermore, the near-universal omission of disease temporality—the sequential order and evolutionary trajectories of disease onset—represents a critical methodological gap that severely limits clinical translation and cross-study comparability. Notably, the field currently lacks consensus on optimal methods for temporal clustering. Latent transition analysis (LTA) and group-based trajectory modeling (GBTM) represent promising approaches for identifying distinct disease progression pathways, yet they remain underutilized in multimorbidity research.

4. Cross-Population Heterogeneity in Clustering Patterns

4.1. Stability and Generalizability of Cardiometabolic Clusters

Cardiometabolic clusters (encompassing hypertension, diabetes, and cardiovascular disease) consistently emerge as the most prevalent and stable multimorbidity patterns across methodologies and populations. The six moderately stable clusters identified by Ferris et al. were composed primarily of cardiometabolic conditions [4]. Mikula-Noble et al. identified 918 disease clusters from 125 studies, grouped into 59 broad categories, with cardiometabolic patterns predominating across all age strata [3].

Longitudinal investigations of cardiometabolic multimorbidity (CMM) demonstrate that CMM occurs across all ages and sexes, conferring the highest rates of mortality and functional decline. Patients with CMM frequently accrue additional cardiometabolic conditions or transition to related clusters, and many subsequently develop neurodegenerative or mental health disorders. Notably, respiratory multimorbidity clusters often evolve into CMM, particularly among socioeconomically disadvantaged populations. Characterizing these evolutionary trajectories is essential for designing temporally targeted interventions [6].

4.2. Effect Modification by Age, Sex, and Socioeconomic Status

Age represents the strongest determinant of clustering patterns. Mikula-Noble et al. demonstrated distinct age-specific preferences: young adults (18–44 years) commonly exhibit clusters involving mental health and musculoskeletal disorders; middle-aged adults (45 – 64 years) most frequently present with diabetes-hypertension co-occurrence; and older adults (⩾65 years) develop clusters involving frailty, cognitive decline, respiratory, or cardiac conditions [3].

Sex-stratified analyses reveal that most clustering patterns are present in both men and women, though mental health-related clusters show modest female predominance, particularly among young women. Multimorbidity prevalence increases with age, is higher in women, and demonstrates a strong inverse socioeconomic gradient. Alarmingly, young and middle-aged adults in low-income groups exhibit multimorbidity burdens comparable to those of individuals ~20 years older in high-income populations [5].

Research on socioeconomic stratification of clustering patterns remains critically deficient: only 4 of 125 studies reviewed by Mikula-Noble et al. stratified clusters by socioeconomic status. Low educational attainment and income are established modifiable risk factors for multimorbidity, yet their mechanistic influence on specific clustering patterns remains largely unexplored.

4.3. Regional Variation and Research Gaps

Clustering patterns vary substantially across regions and populations, reflecting differences in genetic background, environmental exposures, lifestyle, and healthcare system characteristics. Nevertheless, evidence from low- and middle-income countries (LMICs) and non-European populations remains sparse. The 79 studies in Ferris et al.'s review originated predominantly from high-income countries, constraining a comprehensive understanding of global multimorbidity architecture and limiting the generalizability of clustering-derived interventions [错误!未找到引用源。].

5. Translational Pathways: From Cluster Identification to Precision Prevention

5.1. Risk Stratification and High-Risk Population Screening

The primary clinical value of disease clustering lies in high-risk population identification. Defining cluster constituents and evolutionary trajectories enables targeted monitoring and early intervention for individuals most likely to develop specific multimorbidity combinations. For instance, characterizing cardiometabolic cluster trajectories facilitates the identification of high-risk individuals progressing from isolated metabolic disorders to complex CMM. In mental health, emerging risk stratification strategies based on multimorbidity patterns—integrating statistical and machine learning approaches—offer promising avenues for targeted prevention.

5.2. Common Pathway Interventions and Shared Mechanisms

Disease clustering typically reflects shared pathophysiological pathways. Identifying core diseases and common mechanisms within clusters enables the design of pleiotropic prevention strategies. The high stability of cardiometabolic clusters derives largely from shared pathogenic pathways, including insulin resistance, chronic low-grade inflammation, and oxidative stress. Interventions targeting these convergent pathways—lifestyle modification and metabolic-modulating pharmacotherapy—can simultaneously reduce incidence across multiple conditions within a cluster. Advances in multi-omics technologies have provided powerful tools for uncovering the molecular basis of disease clustering. Transcriptomic and proteomic studies have revealed that multiple comorbidities frequently share immune-related molecular pathways. Gene expression profiling to predict disease similarity networks represents an emerging approach for discovering novel comorbidity associations, laying the molecular foundation for precision prevention strategies targeting shared pathways.

5.3. Design and Implementation of Cluster-Based Precision Interventions

Translating disease clustering phenotypes into clinical practice requires a coherent pathway from "cluster identification" to "stratified management." Marengoni et al. (2025) systematically outlined this translational framework in European Geriatric Medicine, positing that multimorbidity clusters can enhance clinical research and practice by refining disease classification, optimizing treatment strategies, and improving risk prediction [8].

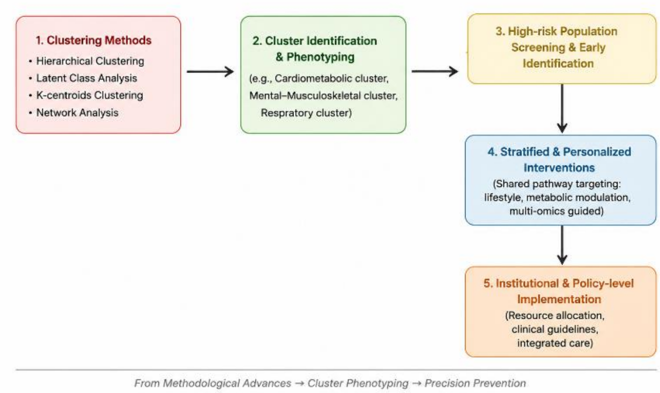
This translational framework operates at three levels: (i) individual level—developing personalized treatment priorities and follow-up protocols based on a patient's cluster phenotype; (ii) institutional level—designing integrated specialist services aligned with the most prevalent disease combinations within specific clusters; and (iii) policy level—guiding healthcare resource allocation and prevention program deployment based on population-level cluster distributions. Tailoring healthcare services to the most common clusters within specific demographic strata may yield more efficient, comprehensive care and improved patient outcomes.

Nevertheless, this translation faces substantial barriers: insufficient clinical interpretability of clustering outputs, absence of evidence-based clinical guidelines for cluster-based phenotyping, and unresolved questions regarding effective implementation within primary care settings [9].

5.4. Recommendations for Methodological Standardization

To enhance methodological rigor and translational potential, Ferris et al. proposed critical improvements: harmonization of disease definitions and inclusion criteria; enhanced transparency in reporting clustering methodologies; systematic incorporation of disease temporality and longitudinal evolution; and rigorous external validation across diverse data sources. Cross-study methodological standardization and transparent reporting are prerequisites for advancing the field. Chinese scholars have additionally advocated for the comparative application of multiple clustering methods to identify optimal methodological combinations for specific research contexts [10]. Figure 1 presents a conceptual framework summarizing the stepwise translational pathway from disease clustering methods to precision prevention implementation.

Fig. 1 Conceptual framework for translational pathways from disease clustering to precision prevention.



6. Conclusions and Future Directions

Multimorbidity has evolved from an individual clinical concern to a defining global public health challenge of the 21st century. Disease clustering analysis, as a pivotal tool for elucidating the intrinsic architecture of multimorbidity, has achieved substantial progress: large-scale cohort studies have identified relatively stable patterns, particularly cardiometabolic clusters, and cross-population heterogeneity across age and sex has been increasingly characterized. However, the field remains in a methodological exploration phase. Critical bottlenecks include: high methodological heterogeneity and inadequate clustering stability; severe underrepresentation of socioeconomic stratification research; near-absence of longitudinal temporal analysis; and unclear translational pathways from cluster identification to clinical implementation.

Future research should prioritize five directions. First, promote methodological standardization by harmonizing disease definitions and analytical workflows to enhance reproducibility and cross-study comparability. Second, integrate longitudinal data to embed disease temporality and evolutionary trajectories within clustering frameworks, enabling dynamic rather than static phenotyping; the routine adoption of latent transition analysis and group-based trajectory modeling should be explored. Third, expand stratified research to systematically examine effect modification by socioeconomic status (income, education, occupation), ethnicity, and geography on clustering patterns, with particular emphasis on addressing critical evidence gaps in LMICs and non-European populations, including multinational comparative studies to elucidate how social inequalities shape disease clustering architectures. Fourth, develop and validate cluster-based stratified precision prevention strategies, establishing complete translational pathways from cluster identification and high-risk screening to personalized intervention, supported by randomized clinical trials. Fifth, build robust mechanisms for translating research evidence into public health policy and clinical guidelines, enabling disease clustering phenotyping to serve as a practical instrument for precision prevention in routine clinical decision-making and health system planning.

In the era of precision medicine, advancing disease clustering phenotyping from methodological research to clinical application and public health practice represents both a cutting-edge scientific frontier and an urgent practical necessity. When clustering phenotypes are fully integrated into routine care and population health planning, the vision of precision prevention in the multimorbidity era will transition from aspiration to reality.

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