Research Advances on Cognitive Impairment in Patients with Chronic Disease Comorbidities: A Postprint

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Abstract

Chronic disease comorbidity accelerates cognitive decline and increases the risk of cognitive dysfunction. However, existing research predominantly investigates the cognitive status of patients with single or specific chronic diseases, leaving the cognitive domain in patients with chronic disease comorbidity as an urgent area for exploration. This study delineates the epidemiological characteristics of cognitive dysfunction in patients with chronic disease comorbidity, summarizes the influencing factors, collates the association patterns between chronic disease comorbidity patterns and cognitive dysfunction, expounds on its underlying mechanisms, and finally proposes prevention and control strategies, with the aim of providing a reference for future prevention and treatment of cognitive dysfunction in this patient population.

Full Text

Review and Monograph: Research Advances in Cognitive Impairment Among Patients with Chronic Disease Multimorbidity

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Abstract

Multimorbidity accelerates cognitive decline and leads to an increased risk of cognitive impairment. However, existing studies have mainly explored the cognitive status of patients with a single or specific chronic disease, and the cognitive domain in patients with multimorbidity remains urgently understudied. The present study describes the epidemiological characteristics of cognitive impairment in multimorbidity, summarizes the influencing factors, organizes the association patterns between multimorbidity and cognitive impairment, elucidates the underlying mechanisms, and finally proposes preventive and control strategies. The findings of this study are intended to serve as a valuable reference for future efforts in preventing and treating cognitive impairment in patients with multimorbidity.

Keywords: Multimorbidity; Cognitive impairment; Multimorbidity pattern; Review

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Introduction

As population aging accelerates alongside advances in healthcare, public health policies, and living conditions, the phenomenon of individuals suffering from two or more chronic diseases simultaneously—termed multimorbidity—has become increasingly prevalent [1]. Recent research has found that multimorbidity accelerates cognitive decline, with faster accumulation of chronic diseases associated with more severe cognitive deterioration and higher risk of cognitive impairment [2]. However, existing studies have primarily focused on cognitive function in patients with single or specific chronic diseases, largely overlooking the impact of multimorbidity on cognition [3]. The combined effects of multimorbidity and cognitive impairment lead to losses in healthy life expectancy, reduced quality of life, premature mortality, and increased healthcare costs, imposing severe medical and economic burdens on individuals, families, and society [4]. Given these concerns, this review examines cognitive impairment in patients with multimorbidity from multiple perspectives, including epidemiological characteristics, influencing factors, pathogenic mechanisms, multimorbidity patterns, and prevention strategies, to inform the development of targeted, multidisciplinary, comprehensive prevention and management measures.

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1. Literature Search Strategy

We conducted computerized searches of Chinese databases including CNKI, Wanfang Data Knowledge Service Platform, and VIP, using Chinese search terms related to multimorbidity such as “慢性病共病” and “多重慢病,” and cognitive impairment-related terms including “认知功能障碍,” “认知障碍,” and “痴呆.” English databases searched included PubMed, Web of Science, Embase,

PsychINFO, CINAHL, and Cochrane Central, with English search terms for multimorbidity including "multimorbidity," "multiple chronic conditions," "concurrent chronic conditions," and "concurrent chronic disorders," and cognitive impairment terms including "cognitive impairment," "cognitive defect," "cognition dysfunction," and "dementia." The search timeframe spanned from database inception to October 20, 2023. Inclusion criteria comprised studies investigating the relationship between multimorbidity and cognitive impairment in Chinese or English. Exclusion criteria comprised studies not focusing on chronic noncommunicable diseases, those unrelated to the topic, studies of poor quality, and those without full-text availability.

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2. Overview of Cognitive Impairment in Multimorbidity Patients

Currently, most domestic and international scholars examining the relationship between physical health status and cognitive impairment have focused on single or specific chronic diseases, with limited investigation into how multimorbidity affects cognitive function [4]. A cross-sectional study found that multimorbidity was closely associated with higher risk of cognitive impairment, with the probability of cognitive impairment gradually increasing from one chronic disease [OR (95%CI) = 1.21 (1.03–1.42)] to $ $4 chronic diseases [OR (95%CI) = 2.07 (1.70–2.52)] compared to individuals without chronic diseases [5]. However, longitudinal studies exploring the relationship between multimorbidity and cognitive impairment remain scarce, and previous findings have been inconsistent. Some studies found that multimorbidity was associated with higher risk of cognitive impairment after five years, with risk [HR (95%CI) = 1.38 (1.05–1.82)] exceeding that of patients with single or no chronic diseases [6]. The incidence of cognitive impairment in multimorbidity patients is approximately twice that of those without multimorbidity [IR (95%CI) = 3.41 (3.30–3.53) versus IR (95%CI) = 1.87 (1.80–1.94)], with multimorbidity-related cognitive impairment risk increasing by 59% (95%CI = 1.47–1.71) when follow-up exceeds 10 years [7]. Some studies also indicate associations between multimorbidity and poorer processing speed [8] and subjective memory complaints [9]. However, ELDHOLM et al. [10] found no association between the two. Therefore, future research requires more prospective cohort studies to investigate the relationship between multimorbidity and subsequent risk of cognitive impairment.

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3. Influencing Factors

3.1 Sociodemographic Factors Sociodemographic factors influencing the relationship between multimorbidity and cognitive impairment primarily involve age and gender. First, HASSEN et al. [11] analyzed Whitehall II prospective cohort data with over 100,000 participants followed for up to 30 years, finding that multimorbidity (particularly when onset occurs in middle age) was closely

associated with cognitive impairment risk, with the strongest correlation at age 55 that gradually weakened with advancing age. Compared to healthy populations, individuals developing multimorbidity in middle age face nearly five times higher risk of cognitive impairment, whereas risk increases 1.7-fold when multimorbidity begins in older age [12]. This may be because the association between multimorbidity and brain volume is stronger in middle-aged individuals than in older adults [13]. Additionally, MARIA et al. [6] found sex differences in cognitive impairment risk among multimorbidity patients, with stronger associations between multimorbidity and cognitive impairment in men. This may be because correlations between multimorbidity patterns, metabolic disturbance patterns, and total brain volume, gray matter, and white matter hyperintensities are stronger in men than in women [13]. Therefore, implementing targeted interventions in middle-aged multimorbidity patients is crucial for preventing or delaying cognitive impairment development, while strengthening attention to male multimorbidity patients is needed to avoid cognitive impairment onset and progression.

3.2 Disease Count Factors The number of chronic diseases is closely associated with increased cognitive impairment risk—the more diseases present, the greater the risk [14]. A study in Hunan Province, China found that cognitive impairment incidence among adults over 65 increased with the number of chronic diseases [15]. VASSILAKI et al. [6] reported that individuals with $ $2 and $ $4 chronic diseases had 1.38-fold (95%CI = 1.05–1.82) and 1.61-fold (95%CI = 1.21–2.13) higher risk of cognitive impairment, respectively, compared to those with one or no chronic diseases. SHANG et al. [14] also found that individuals with $ $6 diseases had 3.97 times higher dementia probability (95%CI = 3.51–4.48) than normal individuals. Furthermore, one study reported that certain health problems not individually considered cognitive impairment risk factors could increase frailty index scores when combined, thereby elevating cognitive impairment risk [16]. This suggests that high disease burden may increase cognitive impairment risk, while improving overall health status may beneficially reduce this burden. However, examining relationships based on disease count has limitations, as methods for quantifying multimorbidity burden vary considerably across studies. Common numerical indices like the Charlson Index [17] or simple disease counts (0, 1, 2, 3, 4+ diseases) are limited because they cannot establish direct links between specific diseases and outcomes.

3.3 Medication Factors Polypharmacy (typically defined as taking $ $5 medications daily) and inappropriate medication use negatively affect cognitive function [18]. Multimorbidity patients take numerous medications, and polypharmacy with drug interactions and/or cumulative effects may increase cognitive decline risk [6]. For example, anticholinergic drugs, antiepileptics, or benzodiazepines are associated with drug-induced cognitive impairment [19]. However, current clinical guidelines typically target single diseases, and adherence may create adverse drug-disease interactions [20]. Failure to optimize med-

ication management for different therapeutic drugs in multimorbidity patients may increase cognitive impairment risk [21]. Therefore, urgent investigation is needed into rational medication use for multimorbidity patients to mitigate negative cognitive effects.

3.4 Lifestyle Factors Multimorbidity and cognitive impairment share many lifestyle risk factors (e.g., sedentary lifestyle, smoking, diet). Approximately 67% of cognitive impairment in multimorbidity patients may be preventable through healthy lifestyle adoption, potentially delaying dementia onset by 3.50 years [22]. SAKAKIBARA et al. [23] emphasized that more unhealthy lifestyle factors correlate with greater cognitive decline associated with multimorbidity, with shared pathogenic pathways playing key roles. Specifically, physical inactivity may increase vascular and metabolic burden, raising cognitive impairment risk; excessive alcohol consumption and smoking cause brain damage through vascular injury and inflammatory processes [24], while inflammation may accelerate neurodegenerative and vascular pathology changes [25], increasing cognitive impairment risk. Regarding social interaction, the cognitive reserve hypothesis suggests that engagement in physical, mental, and socially stimulating activities builds neural resources that can compensate for multimorbidity-related cognitive decline, reducing impairment risk [26]. Additionally, multimorbidity patients adopting active lifestyles and social integration maintain brain volume by activating compensatory networks against neurodegenerative processes [27], while rich social networks encourage interaction and social activity to preserve cognitive integrity. However, self-reported measures of unhealthy lifestyle factors at single time points cannot capture cumulative effects, potentially underestimating associations [28]. Therefore, multi-timepoint longitudinal studies using a life-course approach to healthy aging are needed to investigate cumulative effects of early lifestyle factors on delaying cognitive decline.

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4. Association Patterns Between Multimorbidity and Cognitive Impairment

Identifying multimorbidity patterns is crucial for revealing pathophysiological interactions between disease combinations and exploring regular patterns of cognitive impairment risk in multimorbidity patients, providing scientific evidence for precise intervention strategies.

4.1 Neuropsychiatric-Cardiovascular-Sensory/Cancer Multimorbidity Pattern GRANDE et al. [25] analyzed data from the Swedish National Study on Aging and Care-Kungsholmen (SNAC-K), selecting 2,478 multimorbidity patients to examine their cognitive function after 12 years. They identified three multimorbidity patterns associated with increased cognitive impairment risk: (1) neuropsychiatric disease cluster (primarily neurosis, depression, and other mood disorders); (2) cardiovascular disease cluster

(primarily heart failure, cerebrovascular disease); and (3) sensory impairment/cancer cluster (primarily hearing/vision impairment and various cancers). The neuropsychiatric and cardiovascular clusters showed highest cognitive impairment risk at follow-up, followed by the sensory impairment/cancer cluster. The study also proposed that coexisting inflammation and genetic susceptibility further increase cognitive impairment risk in multimorbidity patients. While SNAC-K is a large-scale, well-characterized population cohort, its results are based on clinical diagnoses lacking biological markers for subtype characteristics. Future research needs biological data to confirm findings and explore mechanisms underlying multimorbidity pattern associations.

4.2 Arthritis/Asthma/Respiratory Disease/Depression -Obesity/Diabetes/Hypertension/Hypercholesterolemia -Heart Disease/Coronary Disease/Stroke/Kidney Disease Multimorbidity Pattern CRISTIAN et al. [29] used 2019 data from the U.S. Behavioral Risk Factor Surveillance System (BRFSS) to survey 15,621 multimorbidity patients. They identified three multimorbidity patterns associated with increased cognitive impairment risk: (1) arthritis, asthma, respiratory disease, and depression; (2) obesity, diabetes, hypertension, and hypercholesterolemia; and (3) heart disease, coronary disease, stroke, and kidney disease. This study expanded multimorbidity combination patterns, providing evidence for grouping patterns beyond disease counts. However, the cross-sectional design precludes causal inference, and self-reported diseases may introduce recall bias and inaccurate data. Future longitudinal observations are needed for causal inference between multimorbidity patterns and cognitive impairment, using clinical cognitive diagnoses or specialist medical record analysis to reduce recall bias.

4.3 Mental Health-Cardiometabolic-Inflammatory/Autoimmune-Cancer Multimorbidity Pattern MIZANUR et al. [30] analyzed 447,888 dementia-free participants from the UK Biobank cohort baseline (2006-2010), identifying four multimorbidity patterns associated with increased cognitive impairment risk: (1) mental health cluster (primarily schizophrenia and depression); (2) cardiometabolic cluster (primarily heart/circulatory disease, hypercholesterolemia, stroke, diabetes, hypertension); (3) inflammatory/autoimmune cluster (primarily rheumatoid arthritis, other inflammatory polyarthropathies, and psoriasis); and (4) cancer cluster (various cancers). Compared to the no-multimorbidity reference group, mental health and cardiometabolic clusters showed highest cognitive impairment risk, inflammatory/autoimmune cluster showed intermediate risk, and cancer cluster showed lowest risk. This study' s large sample size, long follow-up, and detailed, diverse data support and supplement existing data on potential biological and pathophysiological links between multimorbidity and cognitive impairment. However, the database relies on electronic hospital records and death registries without primary care data linkage, potentially underrepresenting ethnic minorities and socioeconomically disadvantaged groups, which may affect generalizability.

Future research is needed in populations with different demographic structures, disease patterns, and healthcare systems.

4.4 Cardiometabolic Multimorbidity Pattern Analysis of the above multimorbidity patterns reveals that cardiometabolic multimorbidity is most common. The 2020 Lancet Commission on dementia prevention, intervention, and care first emphasized the need to consider combinations of different cardiovascular and metabolic risk factors in relation to cognitive impairment [31]. Recent years have seen growing research focus on the cardiometabolic multimorbidity-cognitive impairment relationship. In 2022, ABIGAIL et al. [32] followed 2,577 dementia-free participants over 60 years old for 12 years using SNAC-K data, finding that: (1) cognitive decline accelerated dose-dependently with increasing cardiometabolic disease count; (2) cardiometabolic multimorbidity nearly doubled cognitive impairment risk and advanced dementia onset by approximately 2 years; and (3) the detrimental effects on cognitive function may be more pronounced in early old age (<78 years) than late old age ($ $78 years). In 2023, ABIGAIL et al. [12] followed 17,913 dementia-free participants $ $60 years old for 18 years using the Swedish Twin Registry (STR), also demonstrating that cardiometabolic multimorbidity increases cognitive impairment risk, with midlife onset showing stronger effects. This study' s unique, genetically informative twin design facilitates exploration of genetic background roles in cardiometabolic multimorbidity-cognitive associations. However, the database includes only hospital and outpatient records without primary care data. Additionally, individuals with cardiometabolic multimorbidity may receive more frequent medical care and thus be more likely diagnosed with cognitive impairment, potentially overestimating results.

Furthermore, some studies have examined sex-specific multimorbidity patterns associated with cognitive impairment. CATHERINE et al. [7] analyzed UK Biobank cohort data, finding that compared to patients without multimorbidity, women with hypertension/diabetes/coronary disease clusters and pain/osteoporosis/dyspepsia clusters, and men with diabetes/hypertension clusters and coronary disease/hypertension/stroke clusters showed highest cognitive impairment risk. A Taiwanese scholar [33] also found, based on a prospective cohort study (2011-2019), that male multimorbidity patterns included mental, kidney-vascular, and cancer-urinary patterns, while female patterns included mental, cardiometabolic, and cancer-endocrine patterns.

In summary, multimorbidity pattern classification improves identification of at-risk populations and highlights the necessity of disease-cluster-based rather than single-risk-factor-based prevention strategies, providing references for clinically guided prevention. However, these studies were mostly conducted in localized high-income countries, focused on elderly populations, and used varying multimorbidity assessment methods. Therefore, research is needed within Chinese cultural contexts using scientific multimorbidity clustering methods to explore pattern-cognitive impairment relationships across different age and sex groups,

providing scientific screening criteria and data support for precise interventions.

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5. Mechanisms of Cognitive Impairment in Multimorbidity

The mechanisms underlying cognitive impairment in multimorbidity patients remain understudied, but several potential etiological mechanisms may explain their association. Recent research has found that low-grade chronic inflammation, increased cerebrovascular problems, disease accumulation effects, and cerebral hypoxia may increase cognitive impairment risk in multimorbidity patients [34-35]. For example, chronic diseases often involve low-grade chronic inflammation, and inflammation combined with genetic susceptibility further increases cognitive impairment risk for specific multimorbidity combinations. Multimorbidity may create specific accumulation effects from clustered chronic diseases that ultimately accelerate cognitive decline. Reduced cerebral oxygenation causing neuronal death represents a potential causal mechanism, with cardiopulmonary disease-induced chronic hypoxia predisposing individuals to cognitive impairment. Additionally, cardiometabolic disease represents an important potential mechanism supporting the heart-brain connection in aging [36]. First, cardiometabolic multimorbidity may cause cerebrovascular and neurodegenerative pathology through several overlapping mechanisms [37]. Chronic hyperglycemia characteristic of type 2 diabetes causes oxidative stress, underlying cerebral atherosclerosis and neurodegeneration, and directly causes neuronal death through myelin toxicity. Another type 2 diabetes pathophysiological feature—cerebral insulin resistance—is associated with increased tau hyperphosphorylation and amyloid-β production. Furthermore, chronic cerebral hypoperfusion causing stroke or reduced cardiac output from heart disease alters cerebral blood flow velocity, leading to cerebrovascular pathology [38]. Cerebral hypoperfusion also triggers brain hypoxia, affecting peptide clearance and promoting amyloid-β deposition [39]. Additionally, endothelial dysfunction characteristic of cardiometabolic multimorbidity disrupts blood-brain barrier integrity, impairing amyloid-β clearance [40]. Inflammation represents a convergence point for these mechanisms, playing important roles in cardiometabolic multimorbidity pathogenesis [41] and potentially accelerating neurodegenerative and cerebrovascular pathology progression [42].

In summary, research on potential mechanisms of cognitive impairment in multimorbidity patients remains preliminary. The exact biological pathways through which multimorbidity patterns affect cognitive impairment require clarification, and current literature remains limited. More experimental studies are needed to explore these mechanisms.

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6. Prevention and Control Strategies for Cognitive Impairment in Multimorbidity Patients

6.1 Emphasizing Multidisciplinary Prevention and Lifestyle Importance Healthy lifestyles provide evidence for reducing cognitive impairment risk associated with multimorbidity, highlighting the potential of comprehensive lifestyle interventions rather than single-behavior approaches to prevent cognitive decline in these patients [28]. Many studies have confirmed that multidomain lifestyle interventions (dietary counseling, physical exercise, cognitive training, vascular and metabolic risk monitoring) can improve cognitive function in at-risk populations [43], though this remains unconfirmed in multimorbidity patients. Digital interventions offer feasible solutions for cognitive health interventions in multimorbidity patients. A meta-analysis showed that web-based multidomain lifestyle programs optimized cognition in healthy adults, demonstrating that online lifestyle programs can positively affect cognitive health outcomes and help prevent cognitive impairment onset and progression [43]. Therefore, focusing on shared modifiable lifestyle risk factors for multimorbidity and cognitive impairment, adopting interdisciplinary prevention strategies, and implementing multidomain lifestyle interventions represent feasible approaches to maintain or improve cognitive function.

6.2 Strengthening Active Health Concepts and Innovating Self-Management Models Chronic disease patients need to adhere to self-management protocols to maintain optimal health and avoid disease progression and complications. Growing evidence shows that self-management programs can promote higher levels of health and well-being, motivating patients to take proactive roles in their healthcare [44]. For multimorbidity patients, effective self-management is an effective strategy for maintaining health status and preventing cognitive impairment. Raising awareness about the increased risk of cognitive impairment associated with multimorbidity represents a highly feasible preventive measure for cognitive health maintenance [29]. Therefore, healthcare professionals need to innovate new self-management models that integrate self-health monitoring, chronic disease management, and cognitive function prevention based on multimorbidity patient characteristics. Encouraging active health concepts and helping patients engage with and utilize new technologies to support self-management can reduce cognitive impairment risk and improve quality of life.

6.3 Exploring China-Specific Multimorbidity Patterns Related to Cognitive Impairment and Optimizing Precision Pharmacotherapy Current research on multimorbidity patterns related to cognitive impairment predominantly focuses on Western countries. However, health behaviors, dietary habits, and environmental factors differ across populations, and patterns identified in Western countries may not apply to Chinese multimorbidity patients [25,29-30]. Additionally, a Taiwanese study had small sample size (449 individuals), limiting representativeness and comprehensive reflection of

Chinese multimorbidity patient characteristics [33]. Therefore, future research should use large Chinese prospective cohort data to explore multimorbidity patterns related to cognitive impairment and provide personalized cognitive prevention and control plans for specific patterns. Rational prevention, control, intervention, and management of multimorbidity represent key priorities for promoting health and reducing cognitive impairment risk. Regarding pharmacotherapy, a meta-analysis indicated that medication optimization or intervention can improve cognitive function in elderly chronic disease patients, though it remains unclear how much improvement is specifically attributable to medication optimization versus non-pharmacological approaches [45]. Research on medication optimization or intervention (excluding anti-dementia drugs) remains extremely limited, and large-scale, high-quality prospective clinical trials using comprehensive assessment tools are urgently needed to evaluate validated medication optimization methods. Therefore, exploring rational medication use in multimorbidity patients is critical for preventing (or reversing) cognitive impairment onset and progression to effectively improve cognitive function.

Summary

This review focused on cognitive impairment in multimorbidity patients, examining epidemiological characteristics, influencing factors, multimorbidity patterns, mechanisms, and prevention strategies to inform targeted interventions for reducing or delaying cognitive impairment risk. Age, gender, polypharmacy, disease count, and lifestyle factors affect cognitive impairment risk in multimorbidity patients. Different multimorbidity patterns differentially impact cognitive function, with particular attention needed for cardiometabolic patterns. We recommend that healthcare professionals recognize the necessity of multimorbidity pattern-based cognitive impairment prevention, actively identify at-risk multimorbidity populations, address shared modifiable risk factors, and develop innovative interdisciplinary, multidomain intervention models centered on self-management to strengthen cognitive impairment prevention and promote healthy aging.

Author Contributions

XIN Bo was responsible for conceptualization, design, literature organization, and manuscript writing. WU Yixin, ZHANG Di, HE Yuxin, and YANG Shan conducted literature collection. LI Mengchi performed manuscript revision. JIANG Wenhui was responsible for quality control and review, overall accountability, and supervision. The authors declare no conflicts of interest.

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Note: Figure translations are in progress. See original paper for figures.