

REVIEW ARTICLE

Multimorbidity in dementia: Current perspectives and future challenges

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Abstract

Multimorbidity—the co-occurrence of two or more chronic health conditions—affects > 86% of people with dementia. It is associated with cognitive and functional decline, reduced health-related quality of life, increased health-care use, and higher mortality. The relationship between multimorbidity and dementia is potentially bidirectional; conditions such as hypertension and diabetes increase the risk of developing dementia, and cognitive impairment can complicate their management. This complexity presents challenges in health care and research, affecting treatment decisions and often leading to the exclusion of these individuals from clinical trials. Understanding multimorbidity through long-term prospective studies is crucial to clarify its relationship with dementia. Investigating specific disease combinations, environmental and genetic factors, and their impacts on cognitive health will guide the development of effective prediction models and inclusive intervention strategies for diverse global populations across the life course.

KEYWORDS

all-cause dementia, comorbidity, multimorbidity, multiple long-term conditions

Highlights

- Multimorbidity affects > 86% of individuals with dementia, worsening outcomes.
- The relationship between multimorbidity and dementia is potentially bidirectional.
- Chronic conditions hinder dementia management and clinical trial inclusion.
- Life-course multimorbidity research is key to dementia risk reduction strategies.
- Prospective studies are needed to improve prediction models and interventions.

1 | INTRODUCTION

As global populations age, both dementia and multimorbidity are gaining attention as priorities for research and public health. Dementia is a clinical syndrome characterized by cognitive, psychological, behavioral, and functional impairments.¹ The most common causes of dementia include Alzheimer's disease (AD), vascular disease, Lewy body spectrum disorders, frontotemporal lobar degeneration, and mixed pathologies.²

1.1 | Defining comorbidity and multimorbidity

Multimorbidity is usually defined as the co-existence of two or more chronic health conditions in one person.^{3,4} Some definitions specify that these can comprise long-term physical diseases as well as mental health conditions, which in certain diagnostic systems include dementia.^{1,3–5} When physical conditions are considered alone, this can be termed physical or somatic multimorbidity, and when both physical and mental conditions co-exist, mental–physical (or somatic–mental) multimorbidity may be used.^{6,7} Other terminology, often preferred by patients and the public, includes multiple long-term conditions and multiple chronic conditions. Because the usage of these terms differs

internationally, we use the broader term “multimorbidity” throughout this paper for consistency.⁸

Comorbidity, however, is described as the presence of any disease that may interact with a primary condition of interest.³ Therefore, in the context of other conditions, dementia can be considered either one component of multimorbidity or the primary condition of interest (known as an index condition) in relation to comorbidities.

A meta-analysis of epidemiological studies from both high- and low- and middle-income countries (HICs and LMICs) reported a pooled prevalence of multimorbidity of 33.1%, which increased with age regardless of sex.⁹ Multimorbidity is associated with poorer health outcomes, including increased mortality, impaired activities of daily living, delirium, reduced quality of life, and increased health-care costs.^{8,10} Due to the large number of possible combinations of conditions, people with multimorbidity often have unique phenotypes and may not be well served by specialty care that is oriented around a single diagnosis. Comorbidities are often part of exclusion criteria for clinical trial participation, leading to insufficient evidence to guide treatment decisions for people with multimorbidity.^{11,12} In this era of increasing research and policy focus on the impact of both multimorbidity and the projected increase in dementia prevalence, this is a pertinent time to reflect on their relevance to each other and to consider ways to mitigate their future impacts.

1.2 | Relevance of multimorbidity to dementia

Dementia is a significant health and societal issue and a leading cause of death worldwide. People with dementia commonly have multiple comorbidities, with one study of nearly 150,000 primary care patients reporting that 86.7% of people with dementia had at least two other conditions, compared to 63.9% of matched controls without dementia, and that 74.8% of people with dementia had three or more different conditions, compared to 53% of controls.¹³ Other research has reported that people with dementia have a mean of four comorbidities, compared to two in those without dementia,^{14,15} and that people with dementia alongside six or more chronic conditions have particularly poor health.¹⁶ The combination of chronic conditions in an older adult with dementia adds complexity due to interactions between comorbidities and the use of multiple prescribed medications, increasing the risk of adverse health outcomes.

Due to the heterogeneity of multimorbidity phenotypes, there are likely to be multiple mechanisms underpinning its association with dementia. These may include causative relationships between certain conditions and neurodegeneration, common risk factors for multimorbidity and dementia, or the impact of specific conditions or treatments on cognitive reserve and function. In turn, the variety of clinical manifestations and neuropathological presentations of dementia represents complex pathways between systemic conditions and causes of neurodegeneration. For example, hypertension, diabetes, and heart disease are often comorbid with vascular dementia, and the presence of these conditions may influence the clinical diagnostic process. Furthermore, diagnosing specific subtypes of dementia, especially when cognitive impairment occurs in the context of multimorbidity, can be difficult and is often impractical in many settings, particularly in LMICs.

The interplay between multimorbidity and all-cause dementia may be bidirectional; not only is there an established link between multimorbidity and developing dementia,¹⁷ but the presence of cognitive impairment can impair the optimal management of other comorbidities or risk factors, thereby contributing to a greater burden of multimorbidity and impeding dementia risk reduction strategies.¹⁸ Balancing the prioritization of dementia or other conditions poses challenges in implementing person-centered care and for health-care systems.¹⁹ Recognizing that dementia usually presents within a complex clinical context is essential for providing comprehensive care.

Figure 1 summarizes the interactions, common causes, and consequences of co-existent multimorbidity and dementia.

1.3 | Neuropathological multimorbidity

Although the concept of multimorbidity encompasses conditions across body systems, the co-existence of multiple pathologies within the brain is also common, and systemic conditions may influence the accumulation of specific pathologies in numerous ways.²⁰ AD is neuropathologically characterized by the presence of misfolded amyloid beta (A β) and tau proteins, although there is increasing evidence of co-pathologies including α -synuclein,²¹ transactive response DNA-

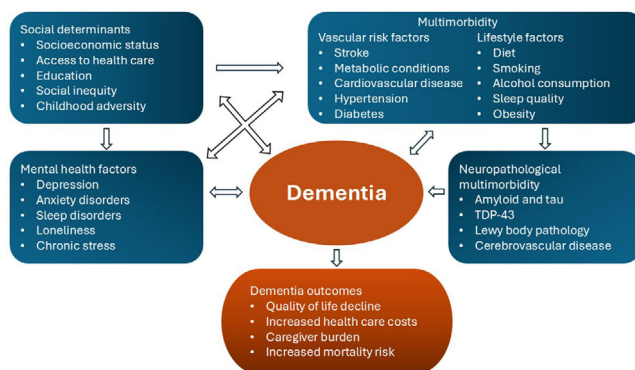


FIGURE 1 Flowchart of interactions, common causes, and consequences of co-existent multimorbidity and dementia. TDP-43, transactive response DNA-binding protein 43 kDa.

binding protein 43 kDa (TDP-43),²² and cerebrovascular disease.²³ The relevance of this comorbid neuropathology is acknowledged by the 2024 revised criteria for the diagnosis and staging of AD.²⁴ These pathologies often co-occur to varying degrees as “mixed” disease, are more common than single “pure” pathologies,²⁵ and are associated with more severe dementia and faster disease progression.²⁶

It is unknown how physical conditions affect the risk for multiple neurological pathologies. An autopsy analysis of 767 brain tissue donors concluded that physical multimorbidity was not associated with dementia-related neuropathological changes; instead, conditions that may be clinical or prodromal manifestations of dementia-related neuropathology (Parkinson’s disease, cerebrovascular disease, depression, and other psychiatric conditions) better predicted dementia-related neuropathology at autopsy.²⁰ This poses uncertainties about the role of comorbidities in increasing neuropathology, although a floor effect could take place in end-stage disease. Vascular risk factors are strongly linked to markers of cerebrovascular disease (such as white matter hyperintensities), suggesting a complex relationship between multiple risk factors.

The resistance versus resilience framework is an alternative approach to understanding the co-existence of multiple neuropathologies.²⁷ Resistance refers to high-risk individuals not developing neuropathology as expected, and resilience is defined as those with evidence of neuropathological damage who do not manifest clinical dementia. In research that focuses on single neuropathological processes, apparent resilience to one cause of dementia may in fact represent resistance to another comorbid pathology that was not under study.²⁸

2 | EPIDEMIOLOGY THROUGH THE LIFE COURSE

2.1 | Methodological challenges

In the last decade, as research and policy interest in multimorbidity has grown, there has been an influx of evidence on the associations between multimorbidity and dementia, with two 2025 systematic

reviews capturing their characteristics.^{17,29} The complexity of multimorbidity is reflected in the various methods of measuring it, with inconsistencies affecting prevalence estimates and reported associations with relevant outcomes. A 2021 systematic review on multimorbidity found that only 47.3% of studies used the accepted definition of two or more co-existing conditions, with more than one third of the papers not defining their threshold at all.⁶ The review also highlighted the importance of determining how many and which candidate conditions were included (this ranged from 2 to 285) and how these were grouped (e.g., counting myocardial infarction and angina as two separate conditions or grouping them into coronary heart disease). Because most multimorbidity studies have been designed to capture a range of diseases without reference to an index condition, dementia may appear as one contributor among a list of conditions. Therefore, when examining dementia alongside comorbidities, there is a risk of double-counting if dementia itself, or related neurodegenerative disorders—for example, Parkinson's disease or stroke—appear among the included conditions.^{20,30}

Although two thirds of the 566 studies in the 2021 systematic review measured multimorbidity using counts of conditions, 155 (27%) studies used weighted indices, most commonly the Charlson Comorbidity Index, which assigns weights to each condition according to its association with mortality.³¹ Decisions about whether to use counts or indices depend on the study's aim and the data available.³² Disease counts are considered most appropriate when estimating prevalence, studying clusters of conditions, or measuring trajectories of multimorbidity accumulation, and indices are better suited for risk adjustment, assessing the severity of disease burden, or predicting the specific outcome for which the index was designed.³³

For both multimorbidity and dementia ascertainment, attention should be paid to the sources of diagnostic data, such as self-report (present in 55% of multimorbidity studies), extraction from health-care records, or expert clinical diagnoses. Each of these approaches has its distinct limitations that may bias the results.⁶ A combination of methods may be used to explore multimorbidity and dementia together, such as clinical dementia diagnosis alongside multimorbidity ascertained from health records.

A further methodological challenge is the consideration of age. Multimorbidity research often focuses on older people, although its prevalence is high at younger ages in socioeconomically deprived groups.⁴ Although studying older adults captures most people with dementia, age limits in epidemiological studies of multimorbidity may exclude people with young-onset dementia (often defined as onset before 65 years).

When examining the epidemiology of multimorbidity and dementia, questions arise about causation and correlation. To support a causative role, evidence should show that comorbid conditions pre-date dementia. Due to the long prodromal phase of dementia, longitudinal studies of ≥ 10 years are likely necessary to account for the substantial impact of reverse causation driving observed associations. It may be that some apparently comorbid conditions diagnosed before dementia, for example depression, are in fact early manifestations of the dementia and

are misrepresented in epidemiological studies as independent risk factors. Most longitudinal studies on multimorbidity and dementia to date have examined relationships between condition counts and incident dementia,^{17,29} with consideration of the accumulation of specific conditions over time less well studied.^{34,35}

2.2 | Importance of age with multimorbidity on dementia risk

As populations age, the prevalence of both multimorbidity and dementia is increasing.³⁶ Emerging research suggests a link between multimorbidity in mid-life (the prevalence of which is reported as 33% to 72%^{37–39}) and dementia.

Existing evidence is largely based on participants with multimorbidity measured at late mid-life (≥ 60 years) or late life (≥ 70 years). The 2024 Lancet Commission on Dementia positioned individual risk factors within a life-course framework, proposing that, among other conditions, hypertension, hearing loss, diabetes, and depression in mid-life, and visual loss in late life, increase dementia risk.⁴⁰ Addressing these conditions may reduce the risk of both dementia and comorbidities in later life.

Among 10,308 UK-based participants from the Whitehall II study, multimorbidity onset at ages 55, 60, 65, and 70 years was associated with increased dementia incidence, with the strongest associations observed at younger ages, which progressively attenuated at older ages.⁴¹ For example, at age 65 years, participants with multimorbidity onset before age 55 (duration over 10 years) had a hazard ratio of 2.46 for subsequent dementia, compared to 1.51 for those with onset between 60 and 65 years.

Similar findings were observed among 23,196 participants of the Survey of Health, Ageing, and Retirement in Europe, in which multimorbidity was associated with increased incidence of dementia over 15 years of follow-up, particularly in people aged < 55 years.⁴² Longitudinal studies like this provide additional knowledge toward understanding causality beyond what is shown in cross-sectional research.

Multimorbidity in mid-life might be a particularly strong risk factor for dementia due to the cumulative effects of protracted exposure. Understanding the accumulation of conditions over the life course can provide insights into whether there are critical risk periods and cumulative effects. Among 5923 participants of the US Health and Retirement Survey, rapid onset of conditions over time, but not slow or steady onset, was associated with increased dementia incidence.³⁵

Future longitudinal studies should assess the relationship between multimorbidity across different life stages and dementia in later life, considering nuances such as the number, type, severity, patterns, and rate of accumulation of chronic conditions, and their relationship with different dementia subtypes. This precision evidence would inform intervention strategies to prevent or delay both multimorbidity and dementia at the earliest opportunity.

2.3 | Multimorbidity patterns

Multimorbidity is heterogeneous, but its association with dementia might only be driven by the presence of certain conditions. Several studies have used the UK Biobank cohort of half a million participants to identify multimorbidity patterns. Within each study, a “cardiometabolic,”⁴³ a “mental health,”⁴⁴ and a broadly defined multi-system multimorbidity pattern⁴⁵ displayed the strongest associations with dementia. These variable results are likely due to the use of different methodological approaches to identify patterns. However, vascular and metabolic conditions were consistently related with dementia. Among 2478 participants from the Swedish National Study on Aging and Care in Kungsholmen, individuals with “neuropsychiatric,” “cardiovascular,” and “sensory impairment/cancer” patterns had higher rates of dementia.⁴⁶ Understanding the role of patterns is important for identifying individuals at a higher risk of dementia and for the development of targeted preventative interventions. In addition, most epidemiological evidence to date is from HICs, and further investigation in a greater diversity of settings is a crucial next step.

2.4 | Common risk factors for multimorbidity and dementia

As certain conditions, such as hypertension and diabetes, are established risk factors for all-cause dementia, their co-existence or interaction with other conditions may have an additive effect on dementia risk.⁴⁰ Vascular risk factors such as smoking and hypercholesterolemia have been associated with the development of both AD and vascular dementia,⁴⁷ highlighting that optimization of cerebrovascular risk factors could reduce dementia incidence through multiple mechanisms, as well as improve overall health.

Multimorbidity composition may vary in HICs and LMICs with different contributing conditions, although some demographic, socioeconomic, and lifestyle factors are common to all settings (for example, physical activity as a protective factor).⁴⁸ In HICs, socioeconomic status and inequalities are linked with higher prevalence of multimorbidity, frailty, disability, and dementia,^{49,50} suggesting a complex interplay of all these factors. Comprehensive investigations of multimorbidity risk in LMICs are lacking, but existing evidence highlights the role of socioeconomic status, social inequities, childhood adversity, lifestyle behaviors, obesity, and dyslipidemia.⁵¹

The impact of shared genetic pathways between risk factors for multimorbidity and dementia has been less explored. However, a genomic structural equation modeling study demonstrated a high level of genetic overlap between known modifiable risk factors for dementia.⁵² A twin study suggests that cardiometabolic multimorbidity, particularly in mid-life, is associated with an increased incidence of dementia and that a genetic background underpins this association.⁵³ In another UK Biobank study, there were stronger associations between multimorbidity and dementia in participants with a lower genetic risk of dementia (defined as non-carriers of apolipoprotein E ϵ 4). In those with high genetic predisposition, the direction of associations remained

similar, albeit weaker in strength.⁴³ Mendelian randomization studies in a multivariable framework might help researchers understand the role of genetic risk factors for multimorbidity and dementia and the mediating effects of environmental, socioeconomic, and lifestyle factors.⁵⁴

Several studies have highlighted the role of multimorbidity in mild cognitive impairment (MCI). A longitudinal study and a cross-sectional study of older adults in HICs reported the risk of MCI in people with multimorbidity to increase by 1.38 and 3.03 times, respectively,^{55,56} with a study of adults across six LMICs finding the risk increased by 1.40 times.⁵⁷ Variations in the strength of association between studies could be related to participants' disease profiles, sample age, sex, quality and accessibility of health care, poverty, and education levels.

2.5 | Mental illness within multimorbidity

Most multimorbidity measures include mental illnesses. These disorders have a complex relationship with dementia; they may manifest as an early symptom of dementia, exist as a separate condition alongside dementia and additively reduce brain reserve, or act as a risk factor for dementia. Notably, meta-analyses demonstrate that people with depression have a higher risk of developing dementia in later life compared to those without,^{58,59} and, albeit less well studied, anxiety disorders have also been associated with cognitive decline and subsequent dementia.⁶⁰ Additionally, depression has been documented as a risk factor for mortality in people with dementia.⁶¹ Mental illnesses may affect other health behaviors such as physical activity, smoking, and alcohol use,⁶² which may influence the progression of dementia.⁶³ Addressing mental health, psychosocial factors, and related health behaviors in multimorbidity may mitigate adverse outcomes.

2.6 | Potential causative pathways

The heterogeneity of multimorbidity means that there are multiple potential causative pathways toward dementia. Inflammation has been proposed as a primary mechanism for their interaction and is being explored as a potential target for dementia treatments.^{46,64} Both alone and in combination, chronic conditions are associated with increased inflammatory cytokines, such as interleukins, tumor necrosis factor alpha, and plasminogen activator inhibitor-1.⁶⁵ Microglial inflammation is posited to occur concurrently with or after systemic symptoms appear.⁶⁶

Normal cognitive function depends on the efficiency of cerebral blood perfusion and neuronal viability, as well as the availability of glucose, the primary fuel for the brain. Other mechanisms affecting the relationship between chronic diseases and cognition include hormonal alterations, such as insulin resistance or fluctuating blood glucose; reduced insulin-like growth factor 1 in non-alcoholic fatty liver disease; vitamin and protein deficiencies, such as decreased vitamin B12 and folate and increased homocysteine levels; autonomic dysfunction; fat accumulation in tissues and blood vessels⁶⁷; and immune

system activation.^{68,69} Preclinical investigations of multimorbidity mechanisms have focused on the common vascular pathways with neurodegeneration.⁷⁰ The gut microbiome has also been identified as a potential regulator of AD pathology and may be influenced by other factors, including genetics, lifestyle, and drugs.⁷¹ Although less biologically certain, there is evidence of a bidirectional association between medication use and functional impairment.¹⁸ People with multiple conditions usually take several medications (known as polypharmacy), and this has been identified as associated with dementia, with potential causation through anticholinergic burden.⁷²

3 | IMPACT OF COMORBIDITIES ON PEOPLE WITH ESTABLISHED DEMENTIA

Multimorbidity is associated with poorer physical, mental, and social health outcomes and reduced independence.^{73,74} This decline in health-related quality of life (HRQoL) is exacerbated in individuals with dementia, as both cognitive and physical health deteriorate simultaneously.⁷⁵ Additionally, people with dementia and multimorbidity often experience social isolation, which can lead to loneliness, mobility problems, pain, mood disturbances, and challenges in managing daily activities.^{16,75,76} Certain comorbid conditions, such as genitourinary, sight, or oral health problems, are associated with substantially diminished HRQoL and affected social interactions.¹⁶ Accurate evaluation of HRQoL in people with dementia can be influenced by reliance on self-assessment of health status and the potential bias introduced by proxy reporting from caregivers.¹⁶

Increased comorbidity contributes to mortality in dementia beyond the impact of dementia alone.^{77,78,79} This may be explained by undertreatment of comorbidities, impaired self-management and decision making, and challenges with following recommended treatment plans.^{80,81,82}

3.1 | Person-centered perspectives

Managing both dementia and comorbidities can be complicated. There is little guidance for clinicians on how to optimize prescribing for this population, and several barriers exist to shared decision making about taking multiple medications.⁸³ Deprescribing might reduce the risk of adverse events but requires culturally sensitive communication within a trusted patient–physician relationship.⁸⁴

Data from the National Health and Aging Trends Study and the National Study of Caregiving show that among people with dementia, each additional comorbidity adds physical and psychological demands on caregivers.⁸⁵ Qualitative research on the experiences of people with multimorbidity has shown the importance of a person-centered and family-centered approach to community care. This includes coordination of health and social services tailored to the needs of older adults and their informal caregivers.⁸⁶ Another study on the care needs of nursing home residents showed differences between the perspectives of residents with mental and physical comorbidity and nursing

staff.⁸⁷ It recommended developing a dialogue about needs, wishes, and expectations to optimize individually tailored care plans.

People with dementia and multimorbidity require multidisciplinary teams to address their complex needs. Care strategies should focus on managing comorbidities and may benefit from care coordination around hospital admissions, caregiving, and health-care provision, particularly in advanced dementia.

3.2 | Health-care use and costs

Multimorbidity research has shown that as the number of chronic conditions increases, so do health-care use and costs.⁸⁸ This association varies by country and increases with national gross domestic product, and most evidence comes from the United States.⁸⁹ For example, a longitudinal study of older adults with multimorbidity and dementia estimated the total societal cost per beneficiary at US\$44,786 in 2011, with the majority of costs arising from hospital admissions for physical illnesses.⁹⁰

Dementia itself is associated with increased health-care use and costs.^{91,92} In the United States, Medicare costs escalate with the severity of dementia and increase further with higher numbers of comorbidities, with annual expenditures between 1999 and 2010 ranging from \$2612 for no comorbidities to \$30,244 for three or more comorbidities.⁹³ Matching people with dementia to controls without dementia found a higher mean per-person cost for each of the 15 comorbidities studied.⁹⁴ Population-based data from Hong Kong between 2010 and 2019 corroborated that an increasing number of comorbidities alongside dementia was associated with increased emergency department attendances and hospital admissions.⁹⁵

Although dementia can be a terminal disease, with survival post-diagnosis ranging between 1.8 and 7.2 years⁹⁶ and post-symptom onset $\approx$ 6.3 years,⁹⁷ health-care costs may decrease as the disease progresses. Studies from Sweden⁹⁸ and Denmark⁹⁹ reported higher costs related to dementia for up to 4 and 5 years, respectively, out of 10 years of follow-up. This may reflect the fact that the focus of care often moves from medical intervention to assistance with activities of daily living as dementia progresses.¹⁰⁰

4 | CHALLENGES IN EMERGING CLINICAL DEVELOPMENTS

4.1 | Relevance of multimorbidity to dementia clinical trials

People with chronic conditions are often excluded from drug trials.¹⁰¹ This is particularly relevant in the era of new disease-modifying treatments for dementia, in which clinical trials often under-report comorbidities.¹⁰² In 2022, the US Food and Drug Administration (FDA) granted accelerated approval of two monoclonal antibodies, aducanumab and lecanemab, the latter subsequently receiving traditional approval.¹⁰³ Notable exclusion criteria for both drugs' phase 3 trials

included other neurodegenerative conditions or brain disorders, cardiovascular disease, cardiopulmonary contraindications, and a history of cancers, all of which are common in older adults. A simulation study applying these criteria to people with early-stage AD in a population-based cohort found that only 5% and 8% of their participants ($N = 237$) met eligibility for aducanumab and lecanemab, respectively.¹⁰⁴

Similarly, a study applying aducanumab clinical trial criteria to a retrospective database from a specialist cognitive service found that although 57% of patients met appropriate use criteria for aducanumab, only 27% met clinical trial inclusion criteria.¹⁰⁵ In comparison, another study showed that the proportion of memory clinic patients who would be excluded was as high as 99%.¹⁰⁶ Such findings expose the uncertainty surrounding the external validity of dementia therapies in current trial pathways. To reduce variability and safety risks, the stringent criteria in such trials compromise the representation of common comorbidities and generalizability, thereby creating a gap in risk-benefit information for broader patient populations. In addition, people with vascular comorbidities are at higher risk of significant adverse effects from these monoclonal antibodies, with implications for their health and increased costs associated with enhanced monitoring.^{107,108}

4.2 | Impact of multimorbidity on dementia biomarkers

4.2.1 | Blood biomarkers

Another recent advance in the management of dementia is the development of blood biomarkers of AD.¹⁰⁹ Their introduction into clinical practice will help refine diagnoses and may be used to provide biomarker evidence of AD pathology before prescribing monoclonal antibodies. However, two studies of cognitively unimpaired people have found that blood concentrations of these biomarkers vary with comorbidities, namely chronic kidney disease, dyslipidemia, hypertension, and diabetes.^{110,111} Further results in people without dementia also suggest that levels of four biomarkers (phosphorylated tau 181, total tau, neurofilament light chain, and glial fibrillary acidic protein) increase with the number of comorbid chronic conditions.¹¹² Given the high prevalence of comorbidities in people likely to undergo blood biomarker testing for AD, it will be crucial to consider these findings when interpreting test results.

4.2.2 | Neuroimaging biomarkers

Neuroimaging studies of people without dementia have revealed a link between multimorbidity and biomarkers of neurodegeneration and cerebrovascular pathology.^{113–115} Multimorbidity was associated with smaller brain volumes, including total brain tissue and hippocampal volume, lower cortical thickness, and 18F-fluorodeoxyglucose positron emission tomography hypometabolism.^{113–115} These studies also reported an association between multimorbidity and markers of

vascular pathology, such as white matter hyperintensities and cortical infarcts. No association was observed with imaging markers of amyloid deposition.¹¹⁵ Notably, the association with neuroimaging biomarkers appeared stronger when multimorbidity affected multiple body systems¹¹³ or in the presence of specific multimorbidity patterns.¹¹⁴ Multimorbidity may therefore influence brain structure independently of neurodegenerative diseases.

5 | GLOBAL EQUITY

Multimorbidity is context dependent, and rates differ among ethnic groups and between countries.^{116,117} Disparities exist not only between HICs and LMICs but also within nations, often reflecting underlying social inequalities. Health equity is defined as the absence of unfair, avoidable, or remediable differences between groups of people, which will allow all individuals to attain their full potential for health and well-being.¹¹⁸ Marginalized and socioeconomically disadvantaged communities, including those affected by structural racism, frequently experience a higher prevalence of both multimorbidity and dementia.^{4,119} These disparities are often masked, as many national datasets do not provide sufficiently detailed data on different ethnic and socioeconomic groups, thereby hampering efforts to understand and address the challenges faced by these populations. For example, multimorbidity is common among older South Asian Indians,¹²⁰ but in many US national datasets, data are aggregated for all Asian groups. Furthermore, race and ethnic categories are social rather than biological constructs, and their definitions may vary according to the geopolitical context of research.¹²¹ These differences mean that ethnic categories are often not transferable between countries. For example, the precise composition of who is included in the “Asian” category may differ between the United States and UK. There is, therefore, a need for disaggregated and longitudinal data on subgroups of minority populations in the United States and globally to examine the prevalence, incidence, and modifiers of multimorbidity and the relationship to other age-related chronic conditions, including dementia.¹²²

Given the projected rapid population aging in LMICs in the coming decades, preventing and managing chronic diseases is a global research and public health priority.¹²³ Addressing inequity requires culturally sensitive, affordable, and accessible health-care interventions tailored to the needs of diverse populations. Integrated policy and system-level approaches to managing multimorbidity and dementia include care models that combine medical, social, and community resources, with skilled care coordinators overseeing both dementia and co-existing conditions.⁸² Continuity of care is known to reduce hospitalizations and emergency visits,¹²⁴ so enhanced training for community health-care providers on managing multimorbidity is needed, fostering generalist skills alongside specialization.¹²⁵ Finally, system-level changes, such as expanding health services and promoting interprofessional cooperation, are necessary to improve care delivery.¹²⁶ By prioritizing equity in research, health-care delivery, and policy making, it will be possible to reduce health disparities and improve outcomes for individuals affected by these complex conditions.

6 | PREVENTION AND PUBLIC HEALTH STRATEGIES

There is some evidence for a decline in dementia incidence rates in HICs, attributed to national policy changes like compulsory education and reduced smoking rates, as well as healthier lifestyle and improved management of cardiovascular conditions.¹²⁷ Given the common risk factors for multimorbidity and dementia, prevention efforts at individual and population levels will benefit both brain health and overall physical health cost-effectively.¹²⁸ For example, trials of multi-domain risk reduction programs for dementia have shown that interventions can improve not only cognition but also improve cardiovascular risk factors and reduce the accumulation of chronic conditions.^{129,130}

Multimorbidity and the interaction between physical health, mental disorders, and brain health should be considered in dementia prevention strategies at global and national policy levels (primary prevention), among people with identified risk factors for dementia (secondary prevention), and in the care of people who have already developed cognitive impairment (tertiary prevention).

7 | FUTURE RECOMMENDATIONS

7.1 | Recommendations for more equitable research

Research can be a powerful tool in addressing inequities in multimorbidity and dementia. Modifiable risk factors for dementia disproportionately affect LMICs, as well as marginalized and socially disadvantaged communities in HICs.^{40,131,132} Despite the greater potential for risk reduction in these communities, they are often under-researched in dementia studies. Therefore, incorporating equity, diversity, and inclusion considerations and collaborating internationally is crucial for conducting rigorous, relevant, and impactful research that is generalizable to all population groups.¹³³ Key research recommendations are shown in Box 1, including those with general reach and with specific reference to multimorbidity, highlighting the fact that measures to improve multimorbidity research and outcomes can be relevant and beneficial to other areas of health.¹⁹

7.2 | Recommendations for reporting methods

As the field of multimorbidity and dementia continues to grow, research should be designed to promote quality, consistency, and reproducibility.¹³⁴ Studies should report their definition of multimorbidity, the use of a list or an index, and the candidate conditions, including whether multiple conditions are grouped under a larger category or assessed individually.⁶ As in any study of an index disease, the definition and ascertainment of dementia should be specified, acknowledging that prevalence and resulting associations may vary by the methods used.¹³⁵ In most dementia studies or trials, the term comorbidity will be most appropriate to describe co-existing conditions

BOX 1 Equity, diversity, and inclusion (EDI) recommendations for multimorbidity and dementia¹⁹

- Promoting, funding, and enabling equitable research by governing bodies and agencies.
- Ensuring equitable access to funding opportunities for all researchers and trainees.
- Recruiting and training a diverse workforce to effectively engage with under-researched groups.
- Building and maintaining relationships with under-researched groups to foster trust, establish research priorities, and facilitate longitudinal data collection.
- Integrating EDI considerations into multimorbidity research design and data analyses.
- Developing and testing interventions and multimorbidity-related outcomes in diverse populations.

alongside dementia (that is, with dementia being the index condition). We recommend that studies explicitly include important operational definitions in their inclusion criteria. In keeping with open research practices, study reports should publish their definition and measurement strategy for both multimorbidity and dementia, including clinical code sets and mapping to classification systems such as International Classification of Diseases 10th Revision. Advances in computational power will continue to facilitate more sophisticated assessment of the accumulation of conditions over time, using machine learning or artificial intelligence techniques. Studies using artificial intelligence should report the description of the datasets (test and training), relevant algorithms used, performance metrics, and the rationale and relevance of the applied method as recommended by existing reporting guidelines.¹³⁶

7.3 | Areas of research need

There is growing evidence for the association between multimorbidity and dementia, but their interactions are complex, requiring further exploration. Prospective longitudinal studies with repeat measures over long follow-up periods could focus on the effects of accumulation of specific combinations of conditions as well as environmental and genetic factors to improve evidence around risk and causation, which will in turn better inform prevention and policy changes.

Now that the scale of multimorbidity among people with dementia has been better elucidated, more work is needed to ensure that the clinical application of new biomarkers and treatments accurately accounts for interacting conditions. Clinical trials for dementia treatments should consider matching inclusion criteria more closely to the characteristics of the affected population.

Interventions for managing the combination of multimorbidity and dementia are limited, so there is a need for person-centered study

BOX 2 Key recommendations for advancing research on dementia and multimorbidity

- Design prospective, longitudinal studies to evaluate how combinations of chronic conditions, along with genetic and environmental factors, influence dementia risk.
- Engage individuals with dementia in setting research priorities and developing person-centered interventions.
- Ensure clinical trial inclusion criteria reflect real-world combinations and interactions of chronic conditions in people with dementia.
- Standardize definitions and measurement approaches for both multimorbidity and dementia across studies.
- Account for methodological variability when interpreting prevalence estimates of dementia and multimorbidity.
- Explore interactions among physical, mental, and brain health.

design in this area.¹³⁷ In addition, the importance of including people with dementia when setting research priorities is increasingly acknowledged. It is especially relevant when considering dementia alongside multiple comorbidities in the current context of resource allocation decisions about costly new treatments.¹³⁸ Recommendations for research and policy are summarized in Box 2.

8 | CONCLUSION

Multimorbidity significantly impacts the development, progression, and management of dementia, presenting complex challenges for individuals, caregivers, health-care providers, and systems worldwide. The bidirectional relationship between multimorbidity and dementia underscores the necessity of comprehensive and integrated approaches to care that address both cognitive and physical health needs. There is compelling evidence of epidemiological associations throughout the life course, indicating that multimorbidity not only increases the risk of developing dementia,¹⁷ but also exacerbates cognitive decline,¹³⁹ reduces HRQoL,⁷⁵ and leads to higher health-care use and costs.^{93–95}

Emerging research on biomarkers and neuropathology enhances our biological understanding of how multimorbidity interacts with dementia, which is crucial for the development and clinical application of new diagnostic tools and treatments.^{20,110–112} However, excluding individuals with multimorbidity from clinical trials limits the generalizability of findings and the effectiveness of interventions in real-world settings.¹⁰¹ Therefore, future research must prioritize inclusivity and representation, ensuring that study populations reflect the diversity of those affected by both multimorbidity and dementia.

Addressing disparities and promoting equity are essential components of this effort. Policies and system-level changes should focus on implementing integrated care models, adapting clinical guidelines

to the needs of patients with multimorbidity and dementia, enhancing continuity of care, and fostering patient-centered approaches.¹⁹ Training and education for health-care providers on the complexities of managing these co-existing conditions are also imperative.¹²⁶

Future efforts should also concentrate on longitudinal studies to investigate the complex interactions between specific combinations of chronic conditions and dementia, considering behavioral, cultural, social, environmental, and biological factors.¹⁴⁰ Inclusive clinical trials and person-centered interventions will help tailor treatments to individual needs and preferences, improving outcomes and quality of life for those affected.

Optimizing physical and brain health through prevention strategies and integrated care models can achieve synergistic benefits that extend beyond individual patients to communities and health-care systems.¹³⁰ Embracing an approach that prioritizes equity and inclusivity will not only enhance understanding of multimorbidity and dementia but also pave the way for effective interventions that mitigate the societal and economic burdens of these intertwined conditions.

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CONFLICT OF INTEREST STATEMENT

The authors declare the following competing interests: G.R.R. and M.T. are currently employed at a company, Oxford Brain Diagnostics Ltd. All

other authors declare no competing interests. Author disclosures are available in the [supporting information](#).

CONSENT STATEMENT

This paper does not report any original research with human participants so consent was not necessary.

REFERENCES

1. ICD-11 for mortality and morbidity statistics. ICD-11. Accessed May 26, 2025. <https://icd.who.int/browse11>
2. Brunnström H, Gustafson L, Passant U, Englund E. Prevalence of dementia subtypes: a 30-year retrospective survey of neuropathological reports. *Arch Gerontol Geriatr*. 2009;49:146-149.
3. Johnston MC, Crilly M, Black C, Prescott GJ, Mercer SW. Defining and measuring multimorbidity: a systematic review of systematic reviews. *Eur J Public Health*. 2019;29:182-189.
4. Barnett K, Mercer SW, Norbury M, Watt G, Wyke S, Guthrie B. Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. *Lancet*. 2012;380:37-43.
5. Academy of Medical Sciences. Multimorbidity: A priority for global health research. 2018. Accessed May 26, 2025. <https://acmedsci.ac.uk/file-download/8222577>
6. Ho IS-S, Azcoaga-Lorenzo A, Akbari A, et al. Examining variation in the measurement of multimorbidity in research: a systematic review of 566 studies. *Lancet Public Health*. 2021;6:e587-e597.
7. Chen S, Nagel CL, Liu R, et al. Mental-somatic multimorbidity in trajectories of cognitive function for middle-aged and older adults. *PLoS One*. 2024;19:e0303599.
8. Skou ST, Mair FS, Fortin M, et al. Multimorbidity. *Nat Rev Dis Primers*. 2022;8:48.
9. Nguyen H, Manolova G, Daskalopoulou C, Vitoratou S, Prince M, Prina AM. Prevalence of multimorbidity in community settings: a systematic review and meta-analysis of observational studies. *J Comorb*. 2019;9:2235042x19870934.
10. Dasgupta M, Hillier LM. Factors associated with prolonged delirium: a systematic review. *Int Psychogeriatr*. 2010;22:373-394.
11. Tan YY, Papez V, Chang WH, Mueller SH, Denaxas S, Lai AG. Comparing clinical trial population representativeness to real-world populations: an external validity analysis Encompassing 43 895 Trials and 5 685 738 individuals across 989 Unique Drugs and 286 Conditions in England. *The Lancet Healthy Longevity*. 2022;3:e674-e689.
12. Swarbrick C, Poulton T, Martin P, Partridge J, Moppett IK. Study protocol for a national observational cohort investigating frailty, delirium and multimorbidity in older surgical patients: the third sprint national anaesthesia project (SNAP 3). *BMJ Open*. 2023;13:e076803.
13. Beerten SG, Helsen A, De Lepeleire J, Waldorff FB, Vaes B. Trends in prevalence and incidence of registered dementia and trends in multimorbidity among patients with dementia in general practice in Flanders, Belgium, 2000-2021: a registry-based, retrospective, longitudinal cohort study. *BMJ Open*. 2022;12:e063891.
14. Sabatini S, Martyr A, Hunt A, et al. Comorbid health conditions and their impact on social isolation, loneliness, quality of life, and well-being in people with dementia: longitudinal findings from the IDEAL programme. *BMC Geriatr*. 2024;24:23.
15. Subramaniam H. Co-morbidities in Dementia: time to Focus More on Assessing and Managing co-morbidities. *Age Ageing*. 2019;48:314-315.
16. Martín-García S, Rodríguez-Blázquez C, Martínez-López I, Martínez-Martín P, Forjaz MJ. Comorbidity, health status, and quality of life in institutionalized older people with and without dementia. *Int Psychogeriatr*. 2013;25:1077-1084.
17. Xin B, Zhang D, Fu H, Jiang W. Association between multimorbidity and the risk of dementia: a systematic review and meta-analysis. *Arch Gerontol Geriatr*. 2025;131:105760.
18. Calderón-Larrañaga A, Vetrano DL, Ferrucci L, et al. Multimorbidity and functional impairment-bidirectional interplay, synergistic effects and common pathways. *J Intern Med*. 2019;285:255-271.
19. Quiñones AR, Kaye J, Allore HG, Botoseneanu A, Thielke SM. An agenda for addressing multimorbidity and racial and ethnic disparities in Alzheimer's disease and related dementia. *Am J Alzheimers Dis Other Dement*. 2020;35:1533317520960874.
20. Hamilton CA, Matthews FE, Attems J, et al. Associations between multimorbidity and neuropathology in dementia: consideration of functional cognitive disorders, psychiatric illness and dementia mimics. *Br J Psychiatry*. 2024;224:237-244.
21. Chung EJ, Babulal GM, Monsell SE, Cairns NJ, Roe CM, Morris JC. Clinical features of Alzheimer disease with and without lewy bodies. *JAMA Neurol*. 2015;72:789-796.
22. Nelson PT, Dickson DW, Trojanowski JQ, et al. Limbic-predominant Age-related TDP-43 Encephalopathy (LATE): consensus working group Report. *Brain*. 2019;142:1503-1527.
23. Attems J, Jellinger KA. The overlap between vascular disease and Alzheimer's Disease—lessons from pathology. *BMC Med*. 2014;12:206.
24. Jack CR, Andrews JS, Beach TG, et al. Revised criteria for diagnosis and staging of Alzheimer's Disease: Alzheimer's association workgroup. *Alzheimers Dement*. 2024;20:5143-5169.
25. Robinson JL, Lee EB, Xie SX, et al. Neurodegenerative disease concomitant proteinopathies are prevalent, age-related and APOE4-associated. *Brain*. 2018;141:2181-2193.
26. Kapasi A, DeCarli C, Schneider JA. Impact of multiple pathologies on the threshold for clinically overt dementia. *Acta Neuropathol*. 2017;134:171-186.
27. Arenaza-Urquijo EM, Vemuri P. Improving the resistance and resilience framework for aging and dementia studies. *Alzheimers Res Ther*. 2020;12:41.
28. Montine TJ, Cholerton BA, Corrada MM, et al. Concepts for brain aging: resistance, resilience, reserve, and compensation. *Alzheimers Res Ther*. 2019;11:22.
29. Zhou Y, You Y, Zhang Y, Yuan C, Xu X. Multimorbidity and risk of dementia: a systematic review and meta-analysis of longitudinal cohort studies. *J Prev Alzheimers Dis*. 2025:100164.
30. Griffith LE, Gruneir A, Fisher KA, et al. Key factors to consider when measuring multimorbidity: results from an expert panel and online survey. *J Comorb*. 2018;8:2235042x18795306.
31. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40:373-383.
32. Stirland LE, González-Saavedra L, Mullin DS, Ritchie CW, Muniz-Terrera G, Russ TC. Measuring multimorbidity beyond counting diseases: systematic review of community and population studies and guide to index choice. *BMJ*. 2020;368:m160.
33. Ho ISS, Azcoaga-Lorenzo A, Akbari A, et al. Measuring multimorbidity in research: delphi consensus study. *BMJ Med*. 2022;1:e000247.
34. Klee M, Markwardt S, Elman MR, et al. Examining multimorbidity contributors to dementia over time. *Alzheimers Dement*. 2025;21:e14589.
35. Chen H, Zhou Y, Huang L, Xu X, Yuan C. Multimorbidity burden and developmental trajectory in relation to later-life dementia: a prospective study. *Alzheimers Dement*. 2023;19:2024-2033.
36. Chowdhury SR, Chandra Das D, Sunna TC, Beyene J, Hossain A. Global and regional prevalence of multimorbidity in the adult population in community settings: a systematic review and meta-analysis. *EClinicalMedicine*. 2023;57:101860.
37. Bowling CB, Deng L, Sakhuja S, Morey MC, Jaeger BC, Muntner P. Prevalence of activity limitations and association with

- multimorbidity among US Adults 50 to 64 Years Old. *J Gen Intern Med*. 2019;34:2390-2396.
38. Boersma P, Black LI, Ward BW. Prevalence of multiple chronic conditions among US Adults, 2018. *Prev Chronic Dis*. 2020;17:E106.
39. King DE, Xiang J, Pilkerton CS. Multimorbidity trends in United States adults, 1988-2014. *J Am Board Fam Med*. 2018;31:503-513.
40. Livingston G, Huntley J, Liu KY, et al. Dementia prevention, intervention, and care: 2024 report of the Lancet standing commission. *Lancet* 404, 572-628 (2024).
41. Ben Hassen C, Fayosse A, Landré B, et al. Association between age at onset of multimorbidity and incidence of dementia: 30 year follow-up in whitehall II prospective cohort study. *BMJ*. 2022;376:e068005.
42. Veronese N, Koyanagi A, Dominguez LJ, et al. Multimorbidity increases the risk of dementia: a 15 year follow-up of the SHARE study. *Age Ageing*. 2023;52.
43. Calvin CM, Conroy MC, Moore SF, Kuźma Elż, Littlejohns TJ. Association of multimorbidity, disease clusters, and modification by genetic factors with risk of dementia. *JAMA Netw Open*. 2022;5:e2232124.
44. Khondoker M, Macgregor A, Bachmann MO, Hornberger M, Fox C, Shepstone L. Multimorbidity pattern and risk of dementia in later life: an 11-year follow-up study using a large community cohort and linked electronic health records. *J Epidemiol Community Health*. 2023;77:285-292.
45. Hu H-Y, Zhang Y-R, Aerqin Q, et al. Association between multimorbidity status and incident dementia: a prospective cohort study of 245,483 participants. *Transl Psychiatry*. 2022;12:505.
46. Grande G, Marengoni A, Vetrano DL, et al. Multimorbidity burden and dementia risk in older adults: the role of inflammation and genetics. *Alzheimers Dement*. 2021;17:768-776.
47. O'Brien JT, Markus HS. Vascular risk factors and Alzheimer's Disease. *BMC Med*. 2014;12:218.
48. Bayes-Marin I, Sanchez-Niubo A, Egea-Cortés L, et al. Multimorbidity patterns in low-middle and high income regions: a multiregion latent class analysis using ATHLOS harmonised cohorts. *BMJ Open*. 2020;10:e034441.
49. Dugravot A, Fayosse A, Dumurgier J, et al. Social inequalities in multimorbidity, frailty, disability, and transitions to mortality: a 24-year follow-up of the whitehall ii cohort study. *Lancet Public Health*. 2020;5:e42-e50.
50. Li R, Li R, Xie J, et al. Associations of socioeconomic status and healthy lifestyle with incident early-onset and late-onset dementia: a prospective cohort study. *Lancet Healthy Longev*. 2023;4:e693-e702.
51. Tan MMC, Barbosa MG, Pinho P, et al. Determinants of multimorbidity in low- and middle-income countries: a systematic review of longitudinal studies and discovery of evidence gaps. *Obes Rev*. 2024;25:e13661.
52. Foote IF, Jacobs BM, Mathlin G, et al. The shared genetic architecture of modifiable risk for Alzheimer's disease: a genomic structural equation modelling study. *Neurobiol Aging*. 2022;117:222-235.
53. Dove A, Guo J, Marseglia A, et al. Cardiometabolic multimorbidity and incident dementia: the Swedish twin registry. *Eur Heart J*. 2023;44:573-582.
54. Desai R, John A, Saunders R, et al. Examining the lancet commission risk factors for dementia using mendelian randomisation. *BMJ Ment Health*. 2023;26:e300555.
55. Vassilaki M, Aakre JA, Cha RH, et al. Multimorbidity and risk of mild cognitive impairment. *J Am Geriatr Soc*. 2015;63:1783-1790.
56. Frisoni GB, Fratiglioni L, Fastbom J, Guo Z, Viitanen M, Winblad B. Mild cognitive impairment in the population and physical health: data on 1,435 individuals aged 75 to 95. *J Gerontol A Biol Sci Med Sci*. 2000;55:M322-8.
57. Koyanagi A, Lara E, Stubbs B, et al. Chronic physical conditions, multimorbidity, and mild cognitive impairment in Low- and Middle-income countries. *J Am Geriatr Soc*. 2018;66:721-727.
58. Jorm AF. History of depression as a risk factor for dementia: an updated review. *Aust N Z J Psychiatry*. 2001;35:776-781.
59. Ownby RL, Crocco E, Acevedo A, John V, Loewenstein D. Depression and risk for Alzheimer disease: systematic review, meta-analysis, and meta-regression analysis. *Arch Gen Psychiatry*. 2006;63:530-538.
60. Gulpers B, Ramakers I, Hamel R, Köhler S, Oude Voshaar R, Verhey F. Anxiety as a predictor for cognitive decline and dementia: a systematic review and meta-analysis. *Am J Geriatr Psychiatry*. 2016;24:823-842.
61. Burns A, Lewis G, Jacoby R, Levy R. Factors affecting survival in Alzheimer's disease. *Psychol Med*. 1991;21:363-370.
62. Scott D, Happell B. The high prevalence of poor physical health and unhealthy lifestyle behaviours in individuals with severe mental illness. *Issues Ment Health Nurs*. 2011;32:589-597.
63. Palmer K, Lupo F, Perri R, et al. Predicting disease progression in Alzheimer's disease: the role of neuropsychiatric syndromes on functional and cognitive decline. *J Alzheimers Dis*. 2011;24:35-45.
64. Maccioni RB, Navarrete LP, González A, González-Canacer A, Guzmán-Martínez L, Cortés N. Inflammation: a major target for compounds to control Alzheimer's disease. *J Alzheimers Dis*. 2020;76:1199-1213.
65. Fabbri E, An Y, Zoli M, et al. Aging and the burden of multimorbidity: associations with inflammatory and anabolic hormonal biomarkers. *J Gerontol A Biol Sci Med Sci*. 2015;70:63-70.
66. Hijioka M, Manabe T, Saito T. Multifactorial glial responses and their contributions to Alzheimer's disease continuum. *Clin Exp Neuroimmunol*. 2023;14:82-91.
67. Bertolotti M, Lonardo A, Mussi C, et al. Nonalcoholic fatty liver disease and Aging: epidemiology to management. *World J Gastroenterol*. 2014;20:14185-14204.
68. Markousis-Mavrogenis G, Bacopoulou F, Kolovou G, et al. Pathophysiology of cognitive dysfunction and the role of combined brain/heart magnetic resonance imaging (Review). *Exp Ther Med*. 2022;24:569.
69. Jensen M, Zeller T, Twerenbold R, Thomalla G. Circulating cardiac biomarkers, structural brain changes, and dementia: emerging insights and perspectives. *Alzheimers Dement*. 2023;19:1529-1548.
70. Shabir O, Moll TA, Matuszyk MM, et al. Preclinical models of disease and multimorbidity with focus upon cardiovascular disease and dementia. *Mech Ageing Dev*. 2020;192:111361.
71. Liang Y, Liu C, Cheng M, et al. The link between gut microbiome and Alzheimer's disease: from the perspective of new revised criteria for diagnosis and staging of Alzheimer's disease. *Alzheimers Dement*. 2024;20:5771-5788.
72. Mur J, Russ TC, Cox SR, Marioni RE, Muniz-Terrera G. Association between anticholinergic burden and dementia in UK Biobank. *Alzheimers Dement: Transl Res Clin Inter*. 2022;8:e12290.
73. Hanlon P, Jani BD, Nicholl B, Lewsey J, Mcallister DA, Mair FS. Associations between multimorbidity and adverse health outcomes in UK Biobank and the SAIL databank: a comparison of longitudinal cohort studies. *PLoS Med*. 2022;19:e1003931.
74. Kanesarajah J, Waller M, Whitty JA, Mishra GD. Multimorbidity and quality of life at mid-life: a systematic review of general population studies. *Maturitas*. 2018;109:53-62.
75. Nelis SM, Wu Y-T, Matthews FE, et al. The impact of co-morbidity on the quality of life of people with dementia: findings from the IDEAL study. *Age Ageing*. 2018;48:361-367.
76. Victor CR, Rippon I, Nelis SM, et al. Prevalence and determinants of loneliness in people living with dementia: findings from the IDEAL programme. *Int J Geriatr Psychiatry*. 2020;35:851-858.
77. Guehne U, Riedel-Heller S, Angermeyer MC. Mortality in dementia. *Neuroepidemiology*. 2005;25:153-162.
78. Snowden MB, Steinman LE, Bryant LL, et al. Dementia and co-occurring chronic conditions: a systematic literature review to identify what is known and where are the gaps in the evidence?. *Int J Geriatr Psychiatry*. 2017;32:357-371.

79. Taudorf L, Nørgaard A, Brodaty H, Laursen TM, Waldemar G. Dementia increases mortality beyond effects of comorbid conditions: a national registry-based cohort study. *Eur J Neurol*. 2021;28:2174-2184.
80. Fortinsky RH. Health care triads and dementia care: integrative framework and future directions. *Aging Ment Health*. 2001;5:S35-48.
81. Bunn F, Burn AM, Goodman C, et al. Comorbidity and dementia: a scoping review of the literature. *BMC Med*. 2014;12:192.
82. Tsunawaki S, Abe M, Dejonckheere M, et al. Primary care physicians' perspectives and challenges on managing multimorbidity for patients with dementia: a Japan-Michigan qualitative comparative study. *BMC Prim Care*. 2023;24:132.
83. Green AR, Lee P, Reeve E, et al. Clinicians' perspectives on barriers and enablers of optimal prescribing in patients with dementia and coexisting conditions. *J Am Board Fam Med*. 2019;32:383-391.
84. Green AR, Boyd CM, Gleason KS, et al. Designing a primary care-based deprescribing intervention for patients with dementia and multiple chronic conditions: a qualitative study. *J Gen Intern Med*. 2020;35:3556-3563.
85. Zhang J, Wang J, Liu H, Wu C. Association of dementia comorbidities with caregivers' physical, psychological, social, and financial burden. *BMC Geriatr*. 2023;23:60.
86. Ploeg J, Canesi M, D Fraser K, et al. Experiences of community-dwelling older adults living with multiple chronic conditions: a qualitative study. *BMJ Open*. 2019;9:e023345.
87. Van Den Brink AMA, Gerritsen DL, De Valk MMH, Mulder AT, Oude Voshaar RC, Koopmans R. What do nursing home residents with mental-physical multimorbidity need and who actually knows this? a cross-sectional cohort study. *Int J Nurs Stud*. 2018;81:89-97.
88. McPhail SM. Multimorbidity in chronic disease: impact on health care resources and costs. *Risk Manag Healthc Policy*. 2016;9:143-156.
89. Tran PB, Kazibwe J, Nikolaidis GF, Linnosmaa I, Rijken M, Van Olmen J. Costs of multimorbidity: a systematic review and meta-analyses. *BMC Med*. 2022;20:234.
90. Macneil-Vroomen JL, Thompson M, Leo-Summers L, Marottoli RA, Tai-Seale M, Allore HG. Health-care use and cost for multimorbid persons with dementia in the national health and aging trends study. *Alzheimers Dement*. 2020;16:1224-1233.
91. Bynum JPW, Rabins PV, Weller W, Niefeld M, Anderson GF, Wu AW. The relationship between a dementia diagnosis, chronic illness, medicare expenditures, and hospital use. *J Am Geriatr Soc*. 2004;52:187-194.
92. Zhu CW, Cosentino S, Ornstein K, Gu Y, Andrews H, Stern Y. Use and cost of hospitalization in dementia: longitudinal results from a community-based study. *Int J Geriatr Psychiatry*. 2015;30:833-841.
93. Zhu CW, Cosentino S, Ornstein KA, Gu Y, Andrews H, Stern Y. Interactive effects of dementia severity and comorbidities on medicare expenditures. *J Alzheimers Dis*. 2017;57:305-315.
94. Salber PR, Selecky CE, Soenksen D, Wilson T. Impact of dementia on costs of modifiable comorbid conditions. *Am J Manag Care*. 2018;24:e344-e351.
95. Zhang Y, Luo H, Lum TY, et al. Association of comorbidity with healthcare utilization in people living with dementia, 2010-2019: a population-based cohort study. *Dementia*. 2024;23:422-437.
96. Brodaty H, Seeher K, Gibson L. Dementia time to death: a systematic literature review on survival time and years of life lost in people with dementia. *Int Psychogeriatr*. 2012;24:1034-1045.
97. Loi SM, Tsoukra P, Chen Z, et al. Mortality in dementia is predicted by older age of onset and cognitive presentation. *Aust N Z J Psychiatry*. 2022;56:852-861.
98. Persson S, Saha S, Gerdtham U-G, Toresson H, Trépel D, Jarl J. Health-care costs of dementia diseases before, during and after diagnosis: longitudinal analysis of 17 years of swedish register data. *Alzheimers Dement*. 2022;18:2560-2569.
99. Sopina E, Spackman E, Martikainen J, Waldemar G, Sørensen J. Long-term medical costs of Alzheimer's disease: matched cohort analysis. *Eur J Health Econ*. 2019;20:333-342.
100. Jönsson L, Tate A, Frisell O, Wimo A. The costs of dementia in Europe: an updated review and meta-analysis. *Pharmacoeconomics*. 2023;41:59-75.
101. Hanlon P, Hannigan L, Rodriguez-Perez J, et al. Representation of people with comorbidity and multimorbidity in clinical trials of novel drug therapies: an individual-level participant data analysis. *BMC Med*. 2019;17:201.
102. Canevelli M, Ancidoni A, Valletta M, et al. Reporting of comorbidities and health status of participants in clinical trials testing amyloid- and tau-targeting monoclonal antibodies for Alzheimer's disease: a systematic review. *J Alzheimers Dis*. 2024;102:587-596.
103. Van Dyck CH, Swanson CJ, Aisen P, et al. Lecanemab in early Alzheimer's disease. *N Engl J Med*. 2023;388:9-21.
104. Pittcock RR, Aakre JA, Castillo AM, et al. Eligibility for anti-amyloid treatment in a population-based study of cognitive Aging. *Neurology*. 2023;101:e1837-e1849.
105. Togher Z, Dolphin H, Russell C, Ryan M, Kennelly SP, O'Dowd S. Potential eligibility for aducanumab therapy in an Irish specialist cognitive service-utilising cerebrospinal fluid biomarkers and appropriate use criteria. *Int J Geriatr Psychiatry*. 2022;37.
106. Canevelli M, Rossi PD, Astrone P, Consorti E, Vanacore N, Cesari M. "Real world" eligibility for aducanumab. *J Am Geriatr Soc*. 2021;69:2995-2998.
107. Doran SJ, Sawyer RP. Risk factors in developing amyloid related imaging abnormalities (ARIA) and clinical implications. *Front Neurosci*. 2024;18:1326784.
108. Ko D, Pascual-Leone A, Shah SJ. Use of lecanemab for patients with cardiovascular disease: the challenge of uncertainty. *JAMA*. 2024;331:1089-1090.
109. Teunissen CE, Verberk IMW, Thijssen EH, et al. Blood-based biomarkers for Alzheimer's disease: towards clinical implementation. *Lancet Neurol*. 2022;21:66-77.
110. Syrjanen JA, Campbell MR, Algeciras-Schimnich A, et al. Associations of amyloid and neurodegeneration plasma biomarkers with comorbidities. *Alzheimers Dement*. 2022;18:1128-1140.
111. O'Bryant SE, Petersen M, Hall J, Johnson LA, HABS-HD Study Team. Medical comorbidities and ethnicity impact plasma Alzheimer's disease biomarkers: important considerations for clinical trials and practice. *Alzheimers Dement*. 2023;19:36-43.
112. Valletta M, Vetrano DL, Rizzuto D, et al. Blood biomarkers of Alzheimer's disease in the community: variation by chronic diseases and inflammatory status. *Alzheimers Dement*. 2024;20:4115-4125.
113. Valletta M, Vetrano DL, Calderón-Larrañaga A, et al. Association of Mild and Complex Multimorbidity With Structural Brain Changes in Older Adults: a Population-based Study. *Alzheimers Dement*. 2024;20:1958-1965.
114. Shang X, Zhang X, Huang Y, et al. Association of a wide range of individual chronic diseases and their multimorbidity with brain volumes in the UK biobank: a cross-sectional study. *EClinicalMedicine*. 2022;47:101413.
115. Vassilaki M, Aakre JA, Mielke MM, et al. Multimorbidity and neuroimaging biomarkers among cognitively normal persons. *Neurology*. 2016;86:2077-2084.
116. Ho IS-S, Azcoaga-Lorenzo A, Akbari A, et al. Variation in the estimated prevalence of multimorbidity: systematic review and meta-analysis of 193 international studies. *BMJ Open*. 2022;12:e057017.
117. Caraballo C, Herrin J, Mahajan S, et al. Temporal trends in racial and ethnic disparities in multimorbidity prevalence in the United States, 1999-2018. *Am J Med*. 2022;135:1083-1092.e14.
118. Health equity. <https://www.who.int/health-topics/health-equity>

119. Hinton L, Tran D, Peak K, Meyer OL, Quiñones AR. Mapping racial and ethnic healthcare disparities for persons living with dementia: a scoping review. *Alzheimers Dement*. 2024;20:3000-3020.
120. Pati S, Swain S, Hussain MA, et al. Prevalence and outcomes of multimorbidity in South Asia: a systematic review. *BMJ Open*. 2015;5:e007235.
121. Sharghi S, Khalatbari S, Laird A, et al. Race, ethnicity, and considerations for data collection and analysis in research studies. *J Clin Transl Sci*. 2024;8:e182.
122. Zanwar PP, Taylor R, Heyn PC. Call for collecting and reporting disaggregated data for centering racial inclusion and equity in the U.S. and globally: examining multimorbidity and risk for cognitive impairment in the Asian American populations. *Alzheimers Dement*. 2023;19.
123. Public health and aging: Trends in aging—United States and worldwide. Centers for Disease Control and Prevention. <https://www.cdc.gov/mmwr/preview/mmwrhtml/mm5206a2.htm> (2003).
124. Mondor L, Maxwell CJ, Hogan DB, et al. Multimorbidity and health-care utilization among home care clients with dementia in Ontario, Canada: a retrospective analysis of a population-based cohort. *PLoS Med*. 2017;14:e1002249.
125. Langenberg C, Hingorani AD, Whitty CJM. Biological and functional multimorbidity—from mechanisms to management. *Nat Med*. 2023;29:1649-1657.
126. Dinh TS, Brünn R, Schwarz C, et al. How do middle-aged patients and their healthcare providers manage multimorbidity? results of a qualitative study. *PLoS One*. 2023;18:e0291065.
127. Mukadam N, Wolters FJ, Walsh S, et al. Changes in prevalence and incidence of dementia and risk factors for dementia: an analysis from cohort studies. *Lancet Public Health*. 2024;9:e443-e460.
128. Veronese N, Soysal P, Demurtas J, et al. Physical activity and exercise for the prevention and management of mild cognitive impairment and dementia: a collaborative international guideline. *Eur Geriatr Med*. 2023;14:925-952.
129. Yaffe K, Vittinghoff E, Dublin S, et al. Effect of personalized risk-reduction strategies on cognition and dementia risk profile among older adults: the SMARRT randomized clinical trial. *JAMA Intern Med*. 2024;184:54-62.
130. Marengoni A, Rizzuto D, Fratiglioni L, et al. The Effect of a 2-year Intervention Consisting of Diet, Physical Exercise, Cognitive Training, and Monitoring of Vascular Risk on Chronic Morbidity—the FINGER randomized controlled trial. *J Am Med Dir Assoc*. 2018;19:355-360.e1.
131. Mayeda ER, Glymour MM, Quesenberry CP, Whitmer RA. Inequalities in dementia incidence between six racial and ethnic groups over 14 years. *Alzheimers Dement*. 2016;12:216-224.
132. GBD 2021 Nervous System Disorders Collaborators. Global, regional, and national burden of disorders affecting the nervous system, 1990-2021: a systematic analysis for the global burden of disease study 2021. *Lancet Neurol* 23, 344-381 (2024).
133. Best Practices in Equity, Diversity and Inclusion in Research. <https://www.sshrc-crsh.gc.ca/funding-financement/nfrf-fnfr/edi-eng.aspx>
134. Dunn R, Clayton E, Wolverson E, Hilton A. Conceptualising comorbidity and multimorbidity in dementia: a scoping review and syndemic framework. *J Multimorb Comorb*. 2022;12:26335565221128430.
135. Davis KAS, Mueller C, Ashworth M, et al. What gets recorded, counts: dementia recording in primary care compared with a specialist database. *Age Ageing*. 2021;50:2206-2213.
136. Hernandez-Boussard T, Bozkurt S, Ioannidis JPA, Shah NH. MINIMAR (MINimum information for medical AI reporting): developing reporting standards for artificial intelligence in health care. *J Am Med Inform Assoc*. 2020;27:2011-2015.
137. Parker KJ, Hickman LD, Phillips JL, Ferguson C. Interventions to optimise transitional care coordination for older people living with dementia and concomitant multimorbidity and their caregivers: a systematic review. *Contemp Nurse*. 2020;56:505-533.
138. Jessen F, Georges J, Wortmann M, Benham-Hermetz S. What matters to patients with Alzheimer's disease and Their Care Partners? Implications for understanding the value of future interventions. *J Prev Alzheimers Dis*. 2022;9:550-555.
139. Vargas-González J-C, Stranges S, Speechley MR, et al. The association between multimorbidity and cognitive decline: a systematic review. *Alzheimers Dement*. 2022;18.
140. Adkins-Jackson PB, George KM, Besser LM, et al. The structural and social determinants of Alzheimer's disease related dementias. *Alzheimers Dement*. 2023;19:3171-3185.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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