Understanding changes in complex care needs over time: key research insights into multimorbidity trajectories

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Multimorbidity, the coexistence of multiple chronic diseases or conditions, poses a major challenge for health-care systems worldwide. Traditional research has largely relied on cross-sectional studies, offering limited insight into multimorbidity evolution over time. This Personal View advocates for a paradigm shift towards longitudinal approaches that capture multimorbidity trajectories. Tracking the sequence, pace, and severity of disease accumulation can enhance our understanding of underlying mechanisms, inform early interventions, and improve patient care. Drawing on expert discussions from an international workshop held in Bielefeld, Germany, in May, 2024, we outline key themes and findings to guide future research on the dynamic processes underlying multimorbidity trajectories. Specifically, we summarise previous work, examine the challenges and opportunities of existing data resources, and highlight priority areas for further investigation. Advancing this field will require the standardisation of longitudinal multimorbidity phenotypes, integration of health and social care processes, and testing the usefulness of trajectories for patient-relevant outcomes and risk stratification. Progress will also depend on methodological innovation, patient and public involvement, harmonisation of diverse data sources, and close interdisciplinary collaboration. Ultimately, a trajectory-based framework for multimorbidity research can enable more personalised, efficient, and equitable health-care strategies, improving outcomes in ageing populations.

Introduction

Multimorbidity, defined as the coexistence of multiple chronic diseases or conditions in an individual,[1] is common among people aged 65 years and older. Data from 15 European countries between 2004 and 2017 showed that the prevalence of multimorbidity among adults aged 50 years and older ranged from 24·7% to 55·6%, depending on the country.[2] Although multimorbidity is increasingly recognised as a crucial and growing challenge in health-care provision, most clinical guidelines primarily focus on single diseases, with only few references to modifying diagnostic and treatment strategies for individuals with a substantial morbidity burden.[3] Some guidelines have begun to acknowledge frequent comorbid combinations, such as diabetes and cardiovascular disease, by providing limited but expanding recommendations that emphasise whole-person care, as reflected in recent updates from the American Diabetes Association and the European Society of Cardiology.[4,5]

Research has identified several risk factors for multimorbidity and revealed that specific combinations or patterns of diseases are more prevalent than others.[6] However, a major limitation of current multimorbidity research is its predominant reliance on cross-sectional studies, which provide snapshots of health states at specific timepoints. Although useful, these studies provide a static view, neglecting the changing interactions between multiple diseases and disregarding that a rapid accumulation of diseases could serve as a dynamic biomarker for deteriorating health.[7] As a result, the studies offer limited insights into how diseases evolve and interact over time. This Personal View advocates for a paradigm shift towards incorporating the dimension of time into multimorbidity research, emphasising the need to understand dynamic health trajectories and their implications for patient care and outcomes.

Why do we need to incorporate the dimension of time into multimorbidity research?

Previous studies have shown that tracking health trajectories—ie, monitoring changes in diseases and functional status over time, including the direction (deterioration *vs* improvement) and pace of change—yields a more comprehensive understanding of multimorbidity than static health snapshots.[8,9] A dynamic approach that addresses health and care trajectories in their interactions would highlight the pace at which multiple diseases occur, provide insights into underlying disease mechanisms, and facilitate the identification of early markers and modifiable predictors of accelerated deterioration. This approach would also acknowledge that health and multimorbidity evolve not only naturally but also in response to care interventions, enabling a more accurate assessment of individual care needs. Rapid accrual of diseases or a faster worsening in the severity of particular diseases might point to different underlying factors, including health behaviours, care interventions, and their intersection, resulting in more complex clinical states that demand prompt action. In contrast, slower changes might reflect chronic, stable diseases that could benefit from maintenance treatment only.[10] The dynamic analysis of associations might also uncover and help to mitigate the burden of treatment and avoid iatrogenic cascades triggered by applying disease-specific clinical practice guidelines (eg, the increase in diabetes incidence following the initiation of high-dose statins for dyslipidaemia treatment and coronary disease prevention[11]).

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See **Online** for appendix

Our understanding of the timing and sequence in which chronic diseases co-develop also remains limited. Multimorbidity involves a complex interplay in which shared underlying causes can contribute to multiple diseases. Both illnesses and their treatments might lead to additional conditions, and broader contextual factors, such as environmental, socioeconomic, cultural, and structural influences, play crucial roles.[12,13] Furthermore, our understanding should extend to how disparities in health-care access, along with associated practices, such as the overuse of case detection and diagnostic testing, can contribute to the accelerated accumulation of multiple diseases.[14] As a result, the timing, rate of occurrence, and sequence of disease onset can vary between individuals, carrying important implications for treatment and prognosis. Indeed, the sequence of diseases, such as whether cardiovascular disease precedes or follows diabetes, can substantially influence health trajectories and outcomes.[15–17]

Life-course epidemiology has emerged as a fundamental approach to understanding the mechanisms that should be targeted for the prevention of age-related chronic diseases.[18] For instance, individuals who had intrauterine growth restriction have a higher risk of developing cardiovascular diseases, type 2 diabetes, and hypertension in adulthood, attributable to fetal programming mechanisms linked to metabolic processes and growth patterns.[19] Likewise, adverse childhood experiences (eg, abuse, neglect, or household dysfunction) can lead to heightened stress responses and have been linked to various chronic diseases, including cardiovascular and mental health disorders, and their accumulation speed in later life.[20,21] The impact of life-course factors might explain why seemingly similar patients experience different health outcomes despite having equivalent diseases at some point in time.[21,22]

Cohort, period, and age effects, firmly established for specific conditions, are also seldom considered in multimorbidity research. More recently born cohorts bear a greater burden of multiple chronic conditions and tend to develop multimorbidity at earlier ages than earlier born cohorts, with depressive symptoms and diabetes contributing disproportionately to those cohort differences.[23] Such differences might reflect both true cohort patterns and shifts in diagnostic practices. A clear example of a period effect is the COVID-19 pandemic, which substantially shaped the experiences, attitudes, values, and behaviours of survivors through factors such as unemployment, rising divorce rates, enforced physical distancing, and restricted access to health and social care, with likely lasting effects on health trajectories.[24] The pandemic has indeed accelerated the onset of some chronic diseases and worsened existing ones. Moreover, age is frequently considered a simple covariate in multimorbidity research, which fails to capture the complex ways in which ageing interacts with multiple chronic diseases. Age is not only a key indicator of biological, phenotypic, and functional resilience but also reflects the historical, societal, and medical context at the time of birth and across successive life stages (eg, development, working life).[25]

Study of multimorbidity trajectories

Research examining multimorbidity trajectories focuses on the pathways of health changes that individuals experience over time, documented at multiple timepoints to capture the dynamic nature of patients' health status. These trajectories can involve changes in the rate of chronic disease accumulation, shifts in the severity of existing diseases, or the development of new diseases. Therefore, the study of multimorbidity trajectories ideally involves a comprehensive ascertainment of all diseases, their timing of diagnosis and their severity at diagnosis, together with a functional assessment that traces an individual's health status over time. This requires considering both exogenous factors, such as clinical changes (eg, new diagnoses and treatment adjustments), and endogenous factors, such as shifts in biological parameters. In addition, it is crucial to consider the social determinants of health that shape these trajectories.

We herein outline key themes and insights that can inform a future research agenda aimed at characterising the dynamic processes underlying multimorbidity trajectories. By summarising previous relevant work, we reflect on the challenges and opportunities of current data resources and identify key areas that might warrant further investigation.

Methodological considerations

This Personal View is based on insights gathered at an international workshop held in Bielefeld, Germany, in May, 2024. The workshop brought together 24 experts from three continents with backgrounds spanning general practice, geriatrics, clinical pharmacology, internal medicine, nursing, public health, and epidemiology. The workshop primarily addressed the concept of multimorbidity trajectories as a way to define the dynamic processes involved. Discussions also emphasised the importance of longitudinal analyses that consider time-varying diagnostic information, the broader health system, and social contexts, which resulted in a list of potential research questions and approaches. Following the workshop, the methodological focus of this Personal View was further shaped by the authors' in-depth knowledge and extensive experience in the field of multimorbidity. The workshop discussions were meticulously documented through detailed notes and recordings, capturing the dynamic interplay of ideas and emerging research trends discussed by leading experts. This rich repository of expert deliberations provided a foundational layer for the analytical depth and comprehensive coverage of the work.

When summarising previous work (appendix pp 1–7), the authors comprehensively reviewed the literature over the past two decades, focusing on longitudinal studies that shed light on the progression and impacts of multiple chronic diseases over time. The cited studies were selected by experts to illustrate various analytical approaches using different databases across multiple countries, with the goal of informing and expanding the

discussions initiated during the workshop. We specifically selected an equal number of studies for each analytical approach discussed in the following section, considering study relevance, journal impact factor, diversity of data sources, geographical balance, and equitable representation of first authors. To facilitate interpretation, each study type is accompanied by an ad hoc example (figures 1–3) based on original data from the Swedish National study on Aging and Care in Kungsholmen (SNAC-K).[26] This study, with its strong track record in multimorbidity research, covers a population-based ageing cohort of adults aged 60 years and older.

This Personal View explores the concept of multimorbidity trajectories, which lacks a widely recognised definition. We define a multimorbidity trajectory as the longitudinal characterisation of an individual's health status through the chronological development, sequence, and severity progression of multiple diagnosed chronic diseases. These trajectories consider not only clinical aspects, such as new diagnoses and changes in the treatment of existing diseases, but also the social determinants of health that shape them. For research feasibility and conceptual clarity, we propose that a trajectory begins at a defined index point (eg, the diagnosis of a second chronic condition), includes multiple observation nodes (ie, at least two) spaced over time to capture meaningful change, and incorporates, to the extent possible, information on diagnoses and disease severity, as well as treatments and relevant contextual factors. This construct differs from single-disease progression or cross-sectional multimorbidity clustering by capturing the dynamic, longitudinal interplay of multiple conditions within real-life contexts. Consequently, the methodological approaches used to study these trajectories fall within the fields of epidemiology (including clinical epidemiology) and health services research.

Previous work on multimorbidity trajectories

Several longitudinal studies have examined the onset and progression of multimorbidity over time, primarily focusing on its effects on individual outcomes in middle-aged and older adults. These studies typically assume the chronic nature of diseases as their starting point. As a result, acute conditions (eg, infections and injuries) are seldom considered; rather, they tend to be viewed as isolated or short-term episodes, although they might represent pivotal points in multimorbidity trajectories by precipitating the development of new chronic conditions or accelerating the progression and severity of existing ones.

Previous efforts to classify existing longitudinal studies on multimorbidity trajectories have been mainly based on applied statistical methods or modelling techniques.[27–29] Herein, we propose an alternative classification focused on how multimorbidity development and progression have been so far operationalised in research, along with the specific research questions and goals addressed. In particular, we categorise the existing literature into three groups according to the methodological approaches used to conceptualise and analyse the dynamics of multimorbidity over time: (1) studies that define multimorbidity as a count

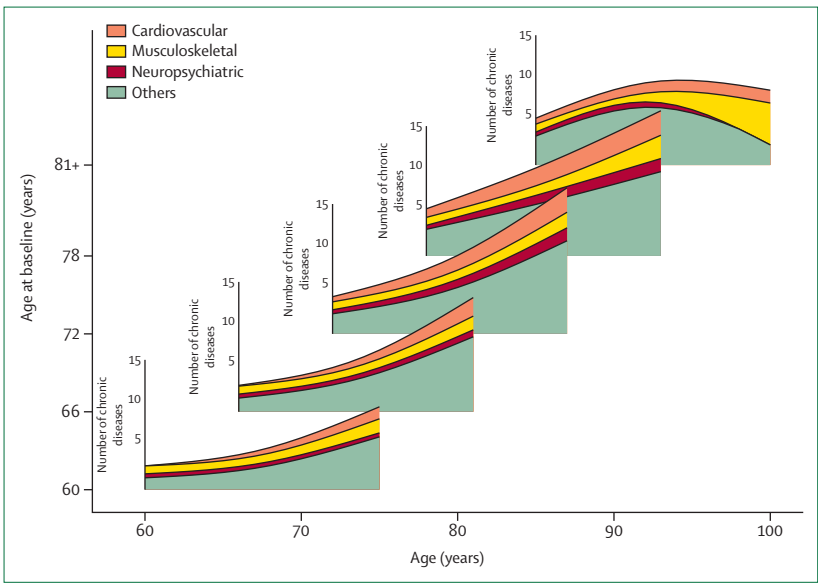

Figure 1: **Median yearly accumulation of chronic diseases by disease types during 2001–19 among participants in the SNAC-K ageing cohort**

Note: Estimates were obtained using quantile mixed models with random intercept and random slope. The non-linear effect of time was operationalised through regression splines. SNAC-K=Swedish National study on Aging and Care in Kungsholmen.

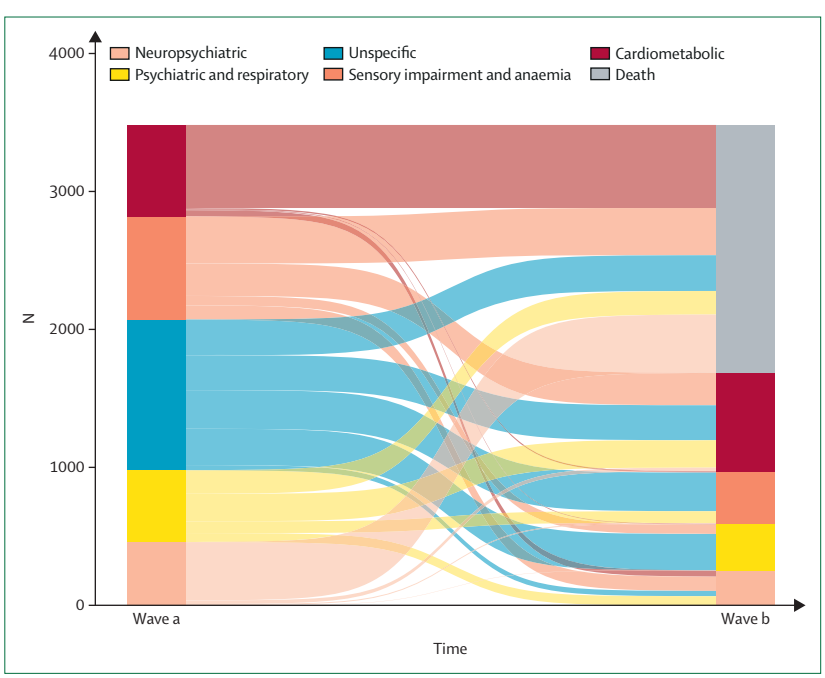

Figure 2: **Alluvial plot representing the volume of transitions among multimorbidity patterns and death during 2001–19 among participants in the SNAC-K ageing cohort**

Note: Multimorbidity patterns were identified using latent class analysis. Chronic diseases were considered to characterise the patterns if they had an observed or expected ratio of at least 2 and an exclusivity of at least 25%. The optimal number of patterns was determined using the adjusted Bayesian information criterion and theoretical interpretability. Participants were assigned to the pattern with the highest posterior probability of membership. SNAC-K=Swedish National study on Aging and Care in Kungsholmen.

Figure 3: Chronic disease sequencesChronic disease sequences for anaemia (A), COPD (B), heart failure (C), and ischaemic heart disease (D) based on diagnostic data from the Swedish National Patient Register* (1997–2016) of participants from the SNAC-K ageing cohort.

Note: Sequences were generated using a greedy algorithm that identifies the three most frequently occurring diagnoses that typically follow or precede the primary diagnosis for a given individual. Each step in the sequence represents a single pair of consecutive diagnoses. These sequences were constructed by merging pairs of diagnoses that overlapped. To extend the sequences, additional overlapping pairs were incorporated, ensuring that the sequences remained within a maximum distance of two diagnoses from the primary one. Pairs with frequencies below the tenth percentile were not considered. Figure created with BioRender.com. COPD=chronic obstructive pulmonary disease. SNAC-K=Swedish National study on Aging and Care in Kungsholmen. *The Swedish National Patient Register includes all care episodes taking place within Swedish inpatient or outpatient specialist care.

of diseases or an index, examining longitudinal dynamics through changes in the number of diseases or index values over time; (2) studies that operationalise multimorbidity as specific clusters of diseases, investigating longitudinal dynamics by tracking individuals' transitions between patterns; and (3) studies that analyse longitudinal dynamics by examining the chronological sequence in which multiple chronic diseases or conditions are acquired.

Studies investigating the rate of change in the number of chronic diseases

In the first group of studies, some examples of which are illustrated in the appendix (pp 2–3), multimorbidity is operationalised as a weighted index or count of diagnoses from a predefined list of chronic diseases. Metrics of multimorbidity can include weighted indexes, such as the Charlson Comorbidity Index,[30] but more often consist of unweighted counts of diagnosed diseases, treating all diseases as equivalent without considering their severity. In these studies, repeated measures of such indexes or disease counts are available for each individual at multiple timepoints. The number of diseases included in the multimorbidity count and the number of timepoints vary considerably between studies. Data in these studies mainly derive from epidemiological cohort studies in middle-aged and older people.[31,32] Traditional statistical methods might cover simple descriptive measures of change (eg, subtraction or percentage of change), multilevel regression models that estimate the average rate of change in the number of diseases over time, as well as more sophisticated longitudinal group-based methodologies (eg, latent class growth analysis, growth mixture modelling) that identify interindividual differences in intraindividual trajectories of disease accumulation.

These studies mainly aim to examine individual changes in multimorbidity metrics over time, regardless of the disease onset or the order in which diseases accumulate. The goal is to identify predictors of accelerated multimorbidity accumulation, such as age,[31] ethnicity,[33] inflammation,[31] sleep disturbances,[34] BMI,[35,36] physical activity,[37] early-life and lifelong psychosocial factors,[21,22] and adverse childhood experiences.[38] Additionally, these studies explore the association between a faster increase in the number of chronic diseases and specific adverse outcomes, such as accelerated cognitive decline[39] and functional dependence.[32] Notably, few of these studies include participants with no diseases or only one disease at baseline, as they primarily focus on the expansion and progression of multimorbidity over time.

The trajectories of chronic disease accumulation over an 18-year follow-up in the SNAC-K cohort are shown in figure 1. These trajectories are categorised by types of chronic diseases (cardiovascular, musculoskeletal, neuropsychiatric, and others) and by different baseline age groups. As expected, individuals who were older at baseline showed the greatest accumulation of multimorbidity over time, regardless of disease type.

Studies investigating multimorbidity patterns and clusters longitudinally

This second group of studies, some examples of which are illustrated in the appendix (pp 4–5), investigates the longitudinal evolution of multimorbidity patterns and clusters. The concept of multimorbidity patterns was developed empirically from cross-sectional studies using interdependence techniques (eg, factor analysis, cluster analysis, principal component analysis). These studies found that chronic diseases tend to cluster in individuals at higher rates than expected by chance (ie, associative multimorbidity).[40] Several studies have examined patterns of empirically driven and systematically co-occurring chronic diseases longitudinally by following the evolution of such patterns over time and the transitions of participants across patterns.[41] The variable of interest in these studies is not the individual count of diseases but rather group membership based on shared co-occurring diseases. These studies usually include large populations followed up for a long period (8–16 years). Data sources include both population-based epidemiological studies[41–43] and electronic health records (EHRs) from primary and specialised care.[44,45] The statistical methods facilitating this approach might include transition and data mining methodologies (eg, state transition modelling), visual approaches (eg, alluvial plots, Sankey diagram), or group-based methodologies (eg, group-based trajectory model, latent class growth analysis).

Briefly, these studies aim to investigate how multimorbidity patterns dynamically change over time and to identify homogeneous groups of individuals with similar patterns of transitions and prognosis who could benefit from specific primary, secondary, and tertiary preventive strategies or treatments. It is assumed that specific pathology clusters require tailored care plans.[41] Some studies also look at how the evolution of multimorbidity patterns might affect survival.[41,43,45] So far, these studies have focused specifically on disease patterns. However, to fully capture the complexity of the phenomenon in its broader context, future research should incorporate additional factors, such as socioeconomic determinants or nutritional aspects.[46]

The 18-year evolution of various multimorbidity patterns can be seen within the SNAC-K population (figure 2). At baseline, four patterns of co-occurring diseases were identified: cardiometabolic diseases, neuropsychiatric diseases, psychiatric and respiratory diseases, and sensory impairment and anaemia. The remaining individuals were grouped into an unspecific pattern, as they were affected by prevalent diseases, but their occurrence did not exceed the expected rate. The alluvial plot shows the volume of transitions between different multimorbidity patterns and death over the follow-up period. The height of each bar is proportional to the number of individuals in this pattern, and the thickness of a flow is proportional to the number of individuals leaving this pattern. As expected, most individuals in the cardiometabolic and neuropsychiatric patterns died over time due to the severity of these disease

For more on the **Swedish National Patient Register** see https://www.socialstyrelsen.se/en/statistics-and-data/registers/national-patient-register/

groups. Interestingly, individuals in the unspecific pattern transitioned almost equally into the cardiometabolic, psychiatric and respiratory, and sensory impairment and anaemia patterns, as well as to death.

Studies investigating disease sequencing or ordering over time

The third group of studies, some examples of which are illustrated in the appendix (pp 6–7), examine the temporal sequence or chronological order of disease acquisitions. While studies in the second group focus on the non-random co-occurrence of multiple chronic diseases and the longitudinal evolution of such clusters, studies in the third group aim to better understand the chronology of multimorbidity development and progression by examining the order in which diseases occur. The number of diseases included in these studies is highly variable, ranging from very small sets of three diseases—namely, cardiovascular risk factors, cardiometabolic diseases, and cancer[47,48]—to the inclusion of the entire spectrum of possible diseases.[49] Necessarily, most of these studies include large numbers of participants (eg, more than 13 million)[50] enrolled in both population-based studies[47,48] and clinical settings.[49–51] The statistical methods used to analyse the data from these studies emphasise transition and data mining methodologies, such as state transition modelling, disease progression analysis, and network analysis, along with visual approaches.

These studies aim to explore the temporal order and sequence by which multiple diseases develop and progress over time, enhancing our understanding of disease progression from a pathophysiological and clinical perspective. Based on this knowledge, the proclaimed goal is to develop tailored clinical guidelines.[52,53] Furthermore, several studies have examined how lifestyle risk factors[47] and sociodemographic characteristics[48,50] influence the sequences of disease development, as well as the association of these sequences with poorer health outcomes.[48]

Using data from the Swedish National Patient Register (ie, inpatient and outpatient specialist care, years 1997–2016) of participants aged 60 years and older from the SNAC-K ageing cohort, the three most frequently registered chronic diagnoses following or preceding the primary diagnoses of anaemia, chronic obstructive pulmonary disease, heart failure, and ischaemic heart disease are presented (figure 3). Two findings are worth highlighting. First, as expected, hypertension, atrial fibrillation, and ischaemic heart disease preceded heart failure, which is the common outcome for many cardiac morbidities. Moreover, heart failure led to additional cardiovascular and cerebrovascular diseases, perpetuating a cycle of worsening health. Second, one of the conditions preceding anaemia was atrial fibrillation, which could be interpreted, among other factors, as an iatrogenic effect of anticoagulant treatment for stroke prevention. In turn, anaemia preceded heart failure and dementia, further contributing to the burden of multimorbidity.

For more on **Clinical Practice Research Datalink (CPRD)** see https://www.cprd.com

For more on **Swiss Personalized Health Network (SPHN)** see https://sphn.ch

For more on **HDRUK Health Data Research UK** see https://www.hdruk.ac.uk

For more on **European Health Data Space (EHDS)** see https://www.european-health-data-space.com

Challenges and opportunities of currently available datasets

As the challenge of dealing with increasing levels of multimorbidity in the populations becomes more important, new data resources have become available that might help to optimise health outcomes and resource use within strained health-care systems by enabling coordinated care and the development of integrated person-centred pathways.[54] Several countries have developed or are developing comprehensive data resources that interconnect information across multiple levels of health care, aiming to reduce fragmentation. These approaches are mainly supported by national registries (Denmark[55]) or EHRs (CPRD in the UK and LOXO-MULTIPAP in Spain[56]). Currently, country-level (Switzerland and the UK) and multi-country-level (the European Health Data Space) initiatives aim to promote research and enable personalised, patient-centred care. These efforts are essential for better characterising the complex processes that underlie multimorbidity trajectories.

One area of improvement is data harmonisation. Coding systems vary across these data resources, hindering comparisons within and across countries, which are required to enhance the validity and reproducibility of multimorbidity trajectories. Similarly, the definition, ascertainment, and recording of diseases can also change across and within registries or EHRs over time. For example, the diagnosis of autism spectrum disorder underwent substantial modifications since its initial definition in 1943.[57] Studies in this area that use EHRs have been criticised because their case finding is subject to variability in clinical practice[58] and comparisons across countries rarely take into consideration cultural and contextual factors affecting diagnosis.[59] However, national and international collaborations are taking place to reach some consensus, although coding variations (including those due to differences in clinical culture[60]) will likely remain.

Alongside these national EHRs or registries, multiple ageing cohorts (eg, InCHIANTI, SNAC-K, HRS, ELSA, CHARLS, Helsinki Birth Cohort) and biobanks (eg, UKBiobank, CKBiobank, All of US, Our Future Health) have been created. These data resources focus on creating large cohorts, typically collecting detailed genotypic, biological, and phenotypic data with the aim of combining them to generate new insights for improved diagnosis, treatment, and personalised medicine. Due to the detailed information included, relatively large sizes, and multiple approaches aiming to improve disease ascertainment (compared with, for example, EHRs), these data resources are particularly suited to study multimorbidity, although with some potential limitations. For example, most studies tend to recruit healthier and less socioeconomically disadvantaged participants (compared with the reference population) and often lack detailed information on disease severity (typically reported only as present or absent).[29] Longitudinal data also carry inherent constraints, such as participant attrition and high maintenance costs.

Moreover, some evidence suggests that associations with hard outcomes (eg, mortality, hospitalisations, and major adverse cardiovascular events) in individuals with complex multimorbidities (four or more diseases) are underestimated compared with those in the general population.[61] Furthermore, changes in the number of diagnoses might be due to clinical factors but also due to other contextual factors not typically collected (eg, difficulties in accessing health care).[62] The uncritical use of these data sources will likely exacerbate health inequalities, particularly in the context of black-box methods focusing on prediction.[63]

Other sources of bias can also affect trajectory research. For example, variation in physicians' coding practices and workflows[64] might produce apparent temporal variation in an individual's record that reflects noise rather than true change. Although minimum standards required for some EHRs and purpose-built cohort studies might help, data validation and analytical methods that account for such variations (eg, smoothing techniques) are generally necessary.[65] In addition, EHRs vary substantially in completeness across individuals. Systematic biases arise from unequal access to health services and from distrust of digital systems, both of which are reflected in current records; ignoring these differences in population-level analyses or subgroup comparisons risks reinforcing and perpetuating such biases.[66] Another important source of variation is whether conditions are recorded through clinical diagnoses or self-reports. Neither approach is universally more accurate, and validity depends on the type of condition; for example, self-reports often capture conditions salient to individuals, such as obesity,[67] whereas EHRs might more reliably capture conditions incentivised for administrative reporting.[68]

One clear area of potential opportunity is to combine multiple databases using linkages. The integration of multiple data modalities, such as imaging, clinical notes, and laboratory results, for the diagnosis and management of specific conditions is now a reality.[69] Extending these approaches to the dynamic study of multimorbidity would be a natural next step. For example, integrated data from primary care and hospital inpatient records will generate a more robust understanding of multimorbidity trajectories than a single data source. This integrated approach provides a more complete picture of patients' health, improving the underestimation of multimorbidity that can occur when relying on a single data source.[70] Furthermore, linkage to municipal datasets, covering socioeconomic and sociodemographic data, might reveal relevant insights. Data linkages have been the focus of several initiatives nationally, such as NHS Digital (UK), the Research Program All of US (USA), and My Health Record (Australia),[71] and globally, such as the Observational Health Data Sciences and Informatics (OHDSI) collaboration. By integrating diverse health data, clinicians can improve the quality of care even as the complexity of care needs increases, in line with findings that a greater number of diseases does not necessarily compromise the quality of health care provided.[14] However, essential challenges remain, particularly in the areas of privacy, security, and governance. In Europe, legislation addressing some of these issues has been in place since 2024.[72] Other technical and interoperability barriers remain, but some methods have been created and are continually explored to address these challenges.[29,73] Methods that help use the strengths of different datasets to answer specific questions and triangulate the findings without the need for full linkages are more likely to be the way to do so in the near future.

Although linkages and triangulation methods will advance our understanding of multimorbidity trajectories through the life course, an essential issue is the characterisation of the individual's health status at a given timepoint, beyond the simple accrual of chronic conditions.[74] This characterisation should help to differentiate conditions or individuals with conditions that are well-controlled and managed versus those that are not. Approaches to defining clinical severity tend to point towards the use of patient-reported outcomes and other functional measures, which are typically not collected as part of EHRs, adding to the need for further triangulation methods to incorporate these measures into multimorbidity trajectory analyses.

Advancing key research areas for the future

In this section, we outline potential research areas focused on analytical advancements, enhanced epidemiological reasoning, and the translational capacity of longitudinal multimorbidity research (summarised in the panel). Addressing these areas warrants a coordinated effort to standardise phenotypes, identify patterns of morbidity accrual, explore the predictive capacity of multimorbidity trajectories, and gain a deeper understanding of how socioeconomic and cultural factors and health-care provision interact with these trajectories. By translating these insights into targeted interventions, we could pave the way towards more personalised and efficient care solutions. These efforts will also need to adapt to a rapidly evolving health-care environment, including advances in digital health technologies and the expanding use of artificial intelligence.

Developing standardised longitudinal multimorbidity phenotypes

One of the central questions in multimorbidity research is whether we can establish standardised longitudinal phenotypes that support comparability and replicability across different datasets and contexts. Generally, a major challenge in studying the epidemiology of multimorbidity is the lack of consensus on how diseases should be defined and measured or even the definition of multimorbidity itself.[27,75,76] While true for cross-sectional data analyses, longitudinally examining multimorbidity is even more complex. Thus, how can we balance the need for focused research on chronic diseases while also assessing the effects of acute conditions that might complicate, yet also shed light on, the trajectories of chronic diseases, particularly in terms of treatment burden and patient care strategies? How can we

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For more on the **All of Us Research Program** see https://allofus.nih.gov

For more on **Observational Health Data Sciences and Informatics (OHDSI)** see https://www.ohdsi.org

Panel: **Future research areas, key questions, and potential analytical approaches**

Standardised longitudinal phenotypes

- Can we develop standardised sets to support comparability and replicability across different datasets and contexts?
- Which diseases should be included in these standardised sets (eg, chronic, acute), and how should these diseases be measured (eg, clinical diagnoses, biomarkers, patient-reported outcomes)?
- What are the optimal rules to manage overlaps and changing diagnoses?
- How should we tailor multimorbidity phenotypes for different purposes (eg, predicting outcomes, assessing health-care costs)?

Patterns and determinants of morbidity accrual

- What trajectories of morbidity accrual (eg, linear, accelerating, variable) do people experience?
- Which factors (eg, genetics, environment, inequalities, medication) can drive different patterns of morbidity accrual?
- Are different trajectories associated with different outcomes (eg, mortality, quality of life, morbidity)?

Predictive value of multimorbidity trajectories

- Does characterising multimorbidity trajectories (eg, dynamic health information) improve the prediction of future events compared with simpler approaches (eg, static health information)?
- Should the sequence and timing of diseases be additionally considered to improve predictive insights?

Linkage with health and social care and wider contextual information

- How do health care, social care, and treatment trajectories relate to morbidity accrual?
- What is the directionality of the associations between health and social care provision and multimorbidity trajectories?
- How do wider contextual variables influence the relationships between care provision and multimorbidity trajectories?

Translating knowledge of multimorbidity trajectories into interventions for equitable, efficient, and effective care services

- Can a better understanding of multimorbidity trajectories inform the target population and nature of preventive and care interventions?
- Can different preventive and care interventions be implemented at various stages of the multimorbidity trajectory to create tailored health-care strategies? And does it improve outcomes?
- How can the knowledge of multimorbidity trajectories inform policy to ensure equitable, efficient, and effective delivery of health-care services?

best determine the accuracy and consistency of clinical diagnoses across different health-care settings to ensure that they effectively contribute to our understanding of multimorbidity? Furthermore, developing and refining mapping frameworks between diagnostic systems and categories is essential to ensure consistency and accuracy in interpreting and integrating data. Such frameworks help standardise how overlapping diagnoses are identified and managed when diseases are labelled differently or evolve over time, ensuring comparability across health information systems. These foundations might allow us to tailor longitudinal multimorbidity phenotypes for various purposes, whether we aim to look retrospectively to enhance our understanding of pathophysiological developments or prospectively to predict a range of health outcomes.

Patterns and determinants of morbidity accrual

An essential area of investigation involves better characterisation of the patterns of morbidity accrual that individuals experience over time, in terms of both the type and the timing of new disease development. These trajectories might follow a linear progression with a steady accumulation of diseases over time, but they might also accelerate after severe health events, such as cancer, infection, acute kidney injury, or delirium, or due to accelerated biological ageing or changes in social circumstances (eg, transition to nursing home, loss of informal caregiver). Alternatively, multimorbidity trajectories might be variable, with periods of stability interrupted by sudden deterioration.[28] Moreover, the severity of each condition can intensify, further complicating the management and understanding of multimorbidity. Improving our knowledge of the role played by various factors, including genetics, environmental influences, social capital conditions, socioeconomic inequalities, medication (ie, iatrogenic causes), and their interactions, is a clear priority. Understanding the relationship between specific trajectories and future morbidity development can also offer crucial insights into improving preventive care, especially in terms of secondary and tertiary prevention.

Predictive capacity of multimorbidity trajectories for adverse health outcomes

Whether characterising multimorbidity trajectories improves the prediction of future health events better than simpler approaches, such as using health information at a single baseline timepoint, remains unclear.[77–79] For instance, does investigating the rate of change in the number of chronic diseases (ie, the pace at which diseases accumulate) provide meaningful additional predictive power compared with the assessment of the total number of diseases at a given timepoint? How does the predictive capacity of multimorbidity trajectories compare to that of simpler, easily

administered measures, such as self-rated health, which encompasses wider determinants and predicts mortality optimally?[80] Similarly, does analysing the sequence and timing of disease accrual offer deeper insights than the cross-sectional assessment of the presence of diseases? Furthermore, future research should examine whether different multimorbidity trajectories are associated with variations in distinct outcomes, such as quality of life, functional independence, wellbeing, or premature death. These questions are crucial for improving predictive models and designing early interventions for patients at risk of deteriorating health.

Linkage with health and social care and wider contextual information

Health is a biological phenomenon influenced by the care that individuals receive.[81] Investigating how care pathways relate to morbidity accrual can provide insights into how health-care systems and societies support or hinder patients' health over time. To acknowledge that claims-based measures of multimorbidity trajectories are not immune to external influences is also important. For example, the coding of morbidities in the USA substantially differs between the Medicare Advantage and traditional Medicare programmes, largely driven by the differing financial incentives inherent in each system. This variation underscores the need for careful consideration of how economic factors and coding systems might shape our understanding of disease prevalence and progression. These care and treatment pathways can be explored neutrally, without judgement on whether the care is beneficial or detrimental or can alternatively be framed in terms of treatment burden,[82–84] assessing how the complexity and frequency of medical or social interventions affect patient health and wellbeing. Another potential approach is to investigate whether health and social care directly influence multimorbidity trajectories, and vice versa. In this context, long-term care services play a particularly important role, as demand increases with the accumulation of chronic conditions and rising severity; these care-related factors might reflect and shape the course of multimorbidity. Better understanding of these reciprocal relationships might be crucial for developing more efficient and effective care models that reduce the burden on patients while improving outcomes.

Translating knowledge of multimorbidity trajectories into interventions for equitable, efficient, and effective care services

Whether and how a better understanding of multimorbidity trajectories can optimise preventive measures and care interventions is not yet understood. If some trajectories or transitions are associated with poorer outcomes, interventions could be strategically implemented at specific points to improve long-term health and reduce adverse events. For example, a patient following a trajectory from diabetes to heart failure and subsequently to depression (often triggered by declining physical function and quality of life) could benefit from early, integrated cardiometabolic and mental health interventions that might alter the course of deterioration. Tailoring interventions to different stages of the trajectory is also essential. Preventive strategies during stable phases might help delay or avoid deterioration, whereas targeted support after acute events can aid recovery and reduce complications. Patients experiencing frequent transitions between hospital and home care, for instance, might benefit from case management or transitional care models that, when informed by common multimorbidity trajectories, can proactively identify those at risk of deterioration and implement preventive measures to mitigate progression. A longitudinal perspective thus enables stage-sensitive and personalised care that adapts to patients' evolving needs. Moreover, identifying trajectories that are more prevalent in socioeconomically disadvantaged populations might inform the design of targeted public health programmes or community-based services aimed at reducing inequities. At the health system level, robust longitudinal evidence integrating multiple data sources will be crucial to evaluate pragmatic, practice-based interventions co-designed with patients and clinicians. In addition, attention to complex multimorbidity phenotypes and treatments, as experienced by patients and caregivers, is essential to align interventions with lived realities and ensure that these interventions address what matters most.[85,86] Finally, knowledge of multimorbidity trajectories can inform health policy by guiding the development of regulations and frameworks for resource allocation and professional training, thereby promoting equitable, efficient, and effective service delivery and ensuring access to high-quality care across diverse populations.

Conclusions

Multimorbidity represents a considerable challenge for patients, clinicians, researchers, and health policy makers. Although clinicians are familiar with the challenge of managing multiple conditions in individual patients, medical education and health service organisations are still fundamentally focused on understanding and treating one disease at a time. Research on multimorbidity is further complicated by the dynamic and complex longitudinal interplay of coexisting health conditions with time-varying factors, such as environmental exposures, and health and social care. This calls for innovative, evidence-informed approaches to improve patient care and outcomes, while alleviating the burden on health systems.

Looking ahead, a focus is on leveraging our understanding of multimorbidity development and progression to strengthen predictive models for distinct, patient-relevant outcomes. The standardisation of longitudinal multimorbidity phenotypes and the study of interacting health and social care processes are essential for a comprehensive understanding of the origin and evolution of multimorbidity trajectories. Addressing these challenges requires a

concerted effort to harmonise data sources and refine analytical methods to study multimorbidity trajectories. National and international initiatives, such as EHRs, ageing cohorts, and biobanks, as well as the linkage across such databases, offer promising opportunities to better understand the dynamics of multimorbidity trajectories.

These insights can inform our health policy and decision making about the wider determinants of health at a population level and pave the way for personalised interventions tailored to the progression of patients' conditions to enhance their quality of life and reduce the burden on health systems. Achieving this goal will, however, require not only methodological innovation but also meaningful public and patient involvement in service development and close interdisciplinary and interprofessional collaboration between researchers, health-care providers, and policy makers.

Contributors

ACL, EF, AIG, RPS, SP, and MvdA wrote the first draft of the paper. All authors provided input at the international workshop (Bielefeld, Germany in May, 2024) that gave rise to this paper, and they contributed through subsequent revisions. ACL, CG, and DLV had full access to all the data in the study. All authors had final responsibility for the decision to submit for publication.

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