Multimorbidity

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Abstract | Multimorbidity (two or more coexisting conditions in an individual) is a growing global challenge with substantial effects on individuals, carers and society. Multimorbidity occurs a decade earlier in socioeconomically deprived communities and is associated with premature death, poorer function and quality of life and increased health-care utilization. Mechanisms underlying the development of multimorbidity are complex, interrelated and multilevel, but are related to ageing and underlying biological mechanisms and broader determinants of health such as socioeconomic deprivation. Little is known about prevention of multimorbidity, but focusing on psychosocial and behavioural factors, particularly population level interventions and structural changes, is likely to be beneficial. Most clinical practice guidelines and health-care training and delivery focus on single diseases, leading to care that is sometimes inadequate and potentially harmful. Multimorbidity requires person-centred care, prioritizing what matters most to the individual and the individual's carers, ensuring care that is effectively coordinated and minimally disruptive, and aligns with the patient's values. Interventions are likely to be complex and multifaceted. Although an increasing number of studies have examined multimorbidity interventions, there is still limited evidence to support any approach. Greater investment in multimorbidity research and training along with reconfiguration of health care supporting the management of multimorbidity is urgently needed.

Treatment burden
The workload associated with managing treatments and health-care recommendations and the impact of this on an individual and their supporters.

Interest in multimorbidity — commonly defined as the co-occurrence of at least two chronic conditions in the same individual[1] — has increased in the past few years owing to its substantial effect on the individual and the individual's family, as well as on health systems and on society, particularly in resource-poor settings[2–4]. Multimorbidity is distinct from the related concept of comorbidity, which refers to the combined effects of additional conditions in relation to the index condition in an individual[5–8]. By contrast, care for multimorbidity is patient-centred and does not routinely give priority to any single condition, although in clinical care, patients and clinicians will usually focus on the most pressing problems that the patient is experiencing.

People with multimorbidity are more likely to die prematurely, be admitted to hospital and have an increased length of stay than people with a single chronic condition[9,10]. Multimorbidity is also associated with poorer function and health-related quality of life (HRQOL), depression and intake of multiple drugs (polypharmacy) and greater socioeconomic costs[11–18]. Most health care is designed to treat individual conditions rather than providing comprehensive, person-centred care[2,19,20], which often leads to fragmented and sometimes contradictory care for people with multimorbidity and increases their treatment burden[21] Moreover, treating one condition at a time is inefficient and unsatisfactory for both people with multimorbidity and their health-care providers[22–24].

Multimorbidity is increasingly common owing to changes in lifestyle risk factors, notably physical inactivity and obesity, and population ageing that in part reflects improvements in survival from acute and chronic conditions[2,19,25,26]. Multimorbidity is associated with socioeconomic status and age[3,19,25,27]. However, although age is the strongest driver of multimorbidity, in absolute numbers, more people <65 years of age have multimorbidity than people ≥65 years of age, partly because more people in the general population are in that age group. Moreover, this emphasizes that multimorbidity is not just a feature of ageing[19,26].

Multimorbidity is further complicated in low-income and middle-income countries (LMICs) by the overlap of compounding factors, including adverse environmental and early life stressors linked to poverty, limited social infrastructure and poorer family coping mechanisms, that translate into chronic diseases occurring at earlier ages[28–31]. LMICs also have a higher prevalence of multimorbidity-related financial burden[32,33] and have weaknesses in health systems including a greater focus

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on managing acute health conditions and chronic infectious diseases[3,4,33,34] and, in some countries, complete absence of services for people with multimorbidity[35].

Of note, during the COVID-19 pandemic individuals with multimorbidity had greater risk of infection and adverse outcomes including hospitalization. Moreover, there has been a deficit in standardized health advice and clinical guidelines for some of the most vulnerable people with multimorbidity, notably for people in care homes, in which the effect of COVID-19 was catastrophic[36–40]. The COVID-19 pandemic also demonstrated the fragility of public health systems worldwide, and the prioritization of acute care has further compromised long-term chronic care, including mental health care[40–42].

Overall, the pandemic highlights the urgent need for action to deal with the increasing burden of chronic conditions and multimorbidity worldwide through better prevention and management and a reconfiguration of health care to achieve an appropriate balance of disease-oriented specialist care and person-centred generalist and primary care[43,44]. Moreover, health systems should take into account what matters most to people, such as continuity of care[35], competent care, user experience, health outcomes and confidence in the system, to advance towards high-quality health care[45]. Changing health-care delivery requires updating the training of the next generation of health-care providers and increasing emphasis on primary prevention strategies, including lifestyle-focused and population-wide prevention efforts, many of which will be deployed outside the health-care delivery system.

This Primer provides a global overview of the epidemiology, potential underlying mechanisms and pathophysiology, diagnosis, prevention, management and outcomes of multimorbidity. Moreover, this Primer highlights the need for improved management and enhanced support to primary care and public health and ends with a call to action for future research. For consistency, the term 'multimorbidity' is used throughout, acknowledging that 'multiple chronic conditions' is also often used in the literature and considered more lay person friendly[46]. In this Primer, multimorbidity is defined as the co-occurrence of at least two chronic conditions in the same individual, as this definition is the most commonly used and is the accepted definition used by WHO[1,47]. Given that multimorbidity should have a person-centred approach and does not intrinsically prioritize one individual condition over others[5,6], this Primer does not follow a structure focusing on certain individual diseases or conditions separately, but refers to individual conditions, comorbidities and clusters of conditions when relevant throughout.

Epidemiology

Although the presence of two or more chronic conditions is the most widely cited and accepted definition of multimorbidity (BOX 1), the way multimorbidity is defined (for example, the number of coexisting conditions needed to qualify as having multimorbidity) and measured is highly variable depending on the number of conditions considered and how they are measured[48–50]. The simple two or more chronic condition definition has been criticized for including people with combinations of conditions that do not meaningfully affect the individual (such as well-controlled hypertension, mild eczema and high cholesterol), which has led to suggestions of alternative definitions of 'complex multimorbidity', such as the "co-occurrence of three or more chronic conditions affecting three or more different body systems within one person"[51]. Regardless, at the patient (and household) level, having more than one condition, including a mental health disorder, translates into a higher health-care load and treatment burden, which is equally important to or more important than the precision in the 'technical' definition of multimorbidity[35,52,53].

Although plausible, the clinical or research use of the concept of complex multimorbidity is not well established[54,55]. One systematic review of 566 studies of multimorbidity found that simple counts (counting the number of conditions an individual has) or weighted condition counts (introducing a weighting for included conditions based on severity and/or impact) are commonly used in research, but the number of conditions included in measures varies from 2 to 285 (median 18)[56]. Only eight physical conditions were included (diabetes mellitus, stroke, cancer, chronic obstructive pulmonary disease, hypertension, coronary heart disease, chronic kidney disease and heart failure) in >50% of studies, and 21.5% of studies did not include any mental health condition[56]. The relative value of simple condition counts versus weighted indexes is debated[5,43,57–59]. Some systematic reviews have concluded that counts and weighted measures are equally effective at predicting the majority of outcomes and an overview of systematic reviews could not identify consensus on this issue, and suggested that choice of measure should be determined based on study aims[57–59]. How indices should be weighted (for example, by HRQOL or other outcomes) is also debated, and the

most appropriate weighting is likely to vary depending on the purpose of the study[49,60], the source and type of data available, the population source and the effect being considered[49,57,61,62]. Further adding to the variability is whether risk factors and symptoms such as urinary incontinence, pain or obesity are included. A large cohort study found that including risk factors increased only the prevalence of multimorbidity, whereas including symptoms increased both prevalence and association with patient outcomes[48].

This variability makes comparison of prevalence and effect of multimorbidity across populations difficult. Moreover, it highlights the importance of considering and clarifying which multimorbidity framework is used in individual studies as well as calls for a consensus process to identify the most relevant definitions to use in future studies. A modified Delphi study aimed to develop consensus on the definition and measurement of multimorbidity in research. In this study, consensus was reached among professionals and people with chronic conditions that multimorbidity should be defined as two or more chronic conditions. Furthermore, consensus was also reached on a list of conditions to always include and usually include in multimorbidity measures[63].

Box 1 | **Multimorbidity definitions**

World Health Organization[47]
"…the coexistence of two or more chronic conditions in the same individual…"

Academy of Medical Sciences[43]
The coexistence of two or more chronic conditions, each one of which is either
- A physical non-communicable disease of long duration, such as a cardiovascular disease or cancer.
- A mental health condition of long duration, such as a mood disorder or dementia.
- An infectious disease of long duration, such as HIV or hepatitis C.

National Institute for Health and Care Excellence guideline[181]
Multimorbidity refers to the presence of 2 or more long-term health conditions, which can include
- Defined physical and mental health conditions such as diabetes or schizophrenia.
- Ongoing conditions such as learning disability.
- Symptom complexes such as frailty or chronic pain.
- Sensory impairment such as sight or hearing loss.
- Alcohol and substance misuse.

Johnston et al.[58], citing definitions used in systematic reviews
- "The co-occurrence of multiple chronic or acute diseases and medical conditions in one person"[325].
- "The coexistence of two or more chronic diseases in the same individual"[326].
- "The co-occurrence of multiple diseases or medical conditions within 1 person"[59].
- "Multimorbidity is defined as any combination of chronic disease with at least one other disease (acute or chronic) or biopsychosocial factor (associated or not) or somatic risk factor…"[327].
- "Comorbidity may be defined as the total burden of illnesses unrelated to the principal diagnosis"[61].

Complex multimorbidity[51,62]
Complex multimorbidity has been defined as the "co-occurrence of three or more chronic conditions affecting three or more different body systems within one person", although others simply count the presence of three or more conditions. It is still unclear whether this definition can identify patients with greater complexity of care need and worse health, but it can be expected that additional information around disease severity and socioeconomic–psychological stressors would be important.

Prevalence

The estimated prevalence of multimorbidity depends on the definition used[27] but, overall, many findings are consistent across studies[27] (FIG. 1). Globally, about one-third of adults[64], including a substantial proportion in LMICs[65–67], and more than half of all adults with any chronic condition[19] have multimorbidity[25]. Systematic reviews focusing on community-based studies in both high-income countries (HICs) and LMICs have found a prevalence of 15–43%[28,64,68,69]. A scoping review in LMICs found a prevalence of 3% to 68% in adults, with most of the evidence from Brazil, China, South Africa, India, Mexico and Iran[70], and 43% in adults in Latin America and the Caribbean[68]. Prevalence estimates are generally lower in LMICs than in HICs (FIG. 1a,b). The reasons for this difference are not known but methodological factors and differential survival are plausible hypotheses. Of note, depression is two to three times more common in people with multimorbidity than in people without multimorbidity or those with no chronic physical condition[18].

Although less commonly reported, some children and adolescents have multimorbidity and risk of associated disability[19,27,71,72]. Multimorbidity is strongly associated with age, with a prevalence of 30% among people aged 45–64 years, 65% among those aged 65–84 years and 82% among those aged ≥85 years[19,27]. In addition, multimorbidity is more common in women than in men, with a weighted difference in prevalence of 6.5%[71]. Moreover, multimorbidity has a higher odds in groups with lower education levels than in those with higher education levels[73]. Individuals living in the most deprived areas consistently experience higher prevalence of multimorbidity than their more affluent counterparts across the lifespan (FIG. 1c), and also experience more complex combinations of physical and mental health multimorbidity[19].

Although the available literature on multimorbidity is largely dominated by studies in HICs[70], studies in LMICs have also found that multimorbidity is common and associated with age, sex and social status, although the prevalence of multimorbidity is higher among adults with higher socioeconomic status in some countries, but not in others[28,66,74]. Reasons for these differences are largely unknown, but might relate to differences in access to health care, obtaining a diagnosis, health-seeking behaviour and longevity[75].

Condition clusters

The identification of clusters of conditions is an alternative to both simple counts and weighted indices[28,43,76]. The most appropriate methods to identify and analyse clusters is debated. Factor analysis or hierarchical clustering methods were predominantly used in studies included in recent systematic reviews[77–79], with smaller numbers of studies using latent class, network and multiple correspondence analysis. The two most consistent and replicable clusters across available studies included cardiometabolic conditions and mental health conditions, respectively, although clusters including musculoskeletal conditions and allergic conditions have also been identified[77–79]. Although the evidence is still

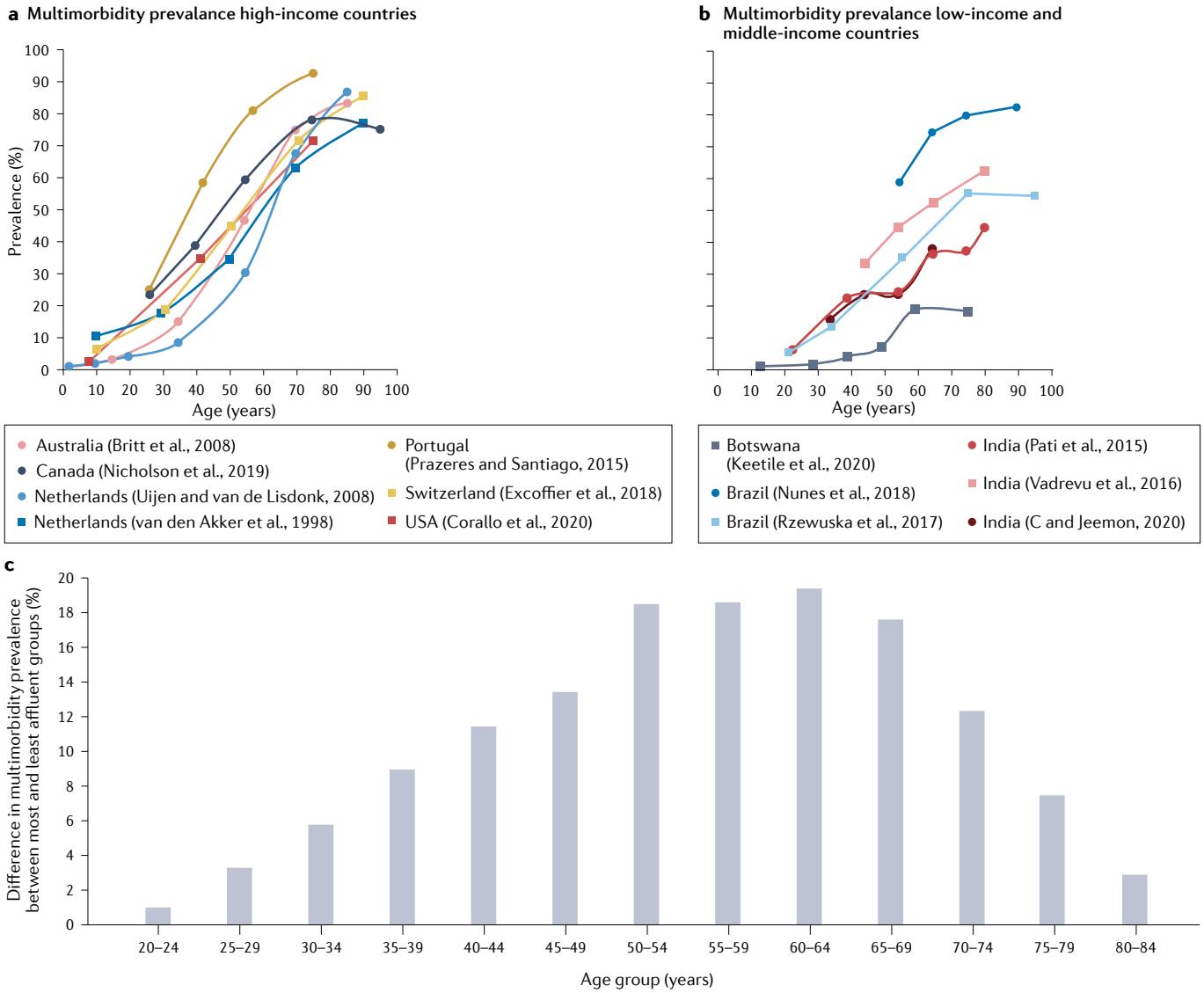

Fig. 1 | **Prevalence of multimorbidity. a** | Prevalence estimates of multimorbidity according to age in high-income countries; data from REFS.[27,313–319]. **b** | Prevalence estimates of multimorbidity according to age in low-income and middle-income countries; data from REFS.[66,67,320–323]. The prevalence of multimorbidity increases with age, although estimates vary among studies. Apart from differences across regions, differences among studies may arise from the recruitment method and sample size, data collection and the operational definition of multimorbidity used, which includes the number of diagnoses considered (such as two or more, or three or more), and the conditions considered. The most appropriate estimates for a given population are probably those obtained from a large sample and using the most prevalent long-term conditions with a high effect or burden in that population. When comparing prevalence estimates of multimorbidity between high-income countries and low-income and middle-income countries, lower age-specific rates are observed in low-income and middle-income countries. To our knowledge, the reason for this difference has not been addressed in prevalence studies, and whether the difference is due to factors such as ascertainment of conditions (such as fewer conditions diagnosed), effects linked to survival (such as shorter survival after acute events), or to a true difference, remains to be determined. **c** | Prevalence of multimorbidity (defined as 2 or more of 40 conditions)[19] by age between the most and least affluent tenths of the population. Multimorbidity prevalence increases steeply with age in all groups, and, apart from in the very oldest, is consistently higher in the less affluent with the largest difference between groups in middle age.

limited, some data suggest that certain clusters, in particular those including mental health conditions (such as depression), are associated with poorer health[80,81], functional limitations[82] and higher health-care costs compared with other clusters[83]. However, few replication studies have been carried out, and available studies suggest that observed condition clusters are not usually replicable using different methods and/or in different datasets[77,79,84–86]. Further research is needed to obtain a better understanding of multimorbidity clusters, their importance for care and their trajectories over time across different age ranges, sex, genders and racial groups[87–89]. This research will identify opportunities for early intervention to address sex and gender, ethnic and socioeconomic inequality in multimorbidity[90,91].

Genomic instability
An increased tendency for DNA mutations (changes) and other genetic changes to occur during cell division.

Telomere attrition
Accrual of DNA damage that affects part of the chromosome known as telomeres.

Proteostasis
Regulation of cell proteins.

Mitochondrial dysfunction
Problems with mitochondrial energy production.

Deregulated nutrient sensing
Problems with the processes affecting nutrition that can affect metabolism.

Cellular senescence
Accumulation of unrepaired damage to cells and limitations in repair functions, which may be exacerbated by oxidative stress.

Stem cell exhaustion
Depletion of stem cell numbers and the regeneration potential of tissues.

Multimorbidity trajectories

Relatively few studies have thoroughly examined multimorbidity trajectories over time. One scoping review on multimorbidity trajectories compiled evidence from 34 studies, and found significant associations between multimorbidity and adverse outcomes, such as reduced reported health, and increased risk of disability and mortality[92]. However, no studies were from LMICs and heterogeneous methods were used. Additional longitudinal data and analysis are important to obtain a better understanding of the development and acceleration of multimorbidity and its inequalities based on social status[73,93–95].

Health-care utilization and economic effect

People with multimorbidity are more likely to die prematurely[54,96]. Furthermore, multimorbidity is linked with increased health-care utilization[10,17,97]. Multimorbidity accounts for 78% of all consultations in primary care in HICs[97], people with multimorbidity have more frequent hospital admissions with longer lengths of hospital stay than people with one or no conditions[10,97,98], and there is an almost exponential relationship between the number of chronic conditions and their associated costs due to increased health-care utilization[17]. This higher health-care utilization, coupled with multiple pharmacological treatments that is common among people with multimorbidity[15,17], leads to higher treatment burden[21,99,100], and also places financial strain on patients and health-care systems. Households can experience very high health expenditures associated with the management of chronic conditions and multimorbidity[32,101,102]. Informal caregiving, provided by family relatives mostly without financial compensation, many of whom have to stop working to devote to caregiving[103,104], adds to the societal and household economic burden of multimorbidity.

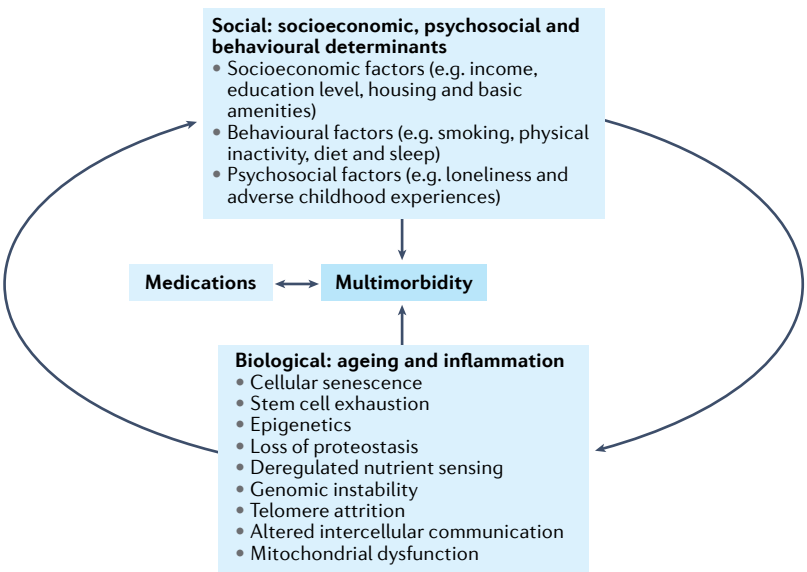

Fig. 2 | **Determinants of multimorbidity.** Development of multimorbidity is affected by several factors. Mechanisms underlying the development of multimorbidity are frequently interrelated and may be synergistic. Mechanisms can be considered in three areas: underlying biological mechanisms relating to ageing and inflammation; broader determinants of health such as socioeconomic, psychosocial and behavioural social determinants; and medication-related.

Mechanisms/pathophysiology

Studying the mechanisms and pathophysiology of multimorbidity is complicated by the heterogeneity of patients. Patients may have concordant multimorbidity (for example, cardiovascular multimorbidity (such as a combination of atrial fibrillation, coronary heart disease and heart failure)) where conditions have a shared pathophysiology or shared approaches to management, or discordant multimorbidity (such as a combination of chronic obstructive pulmonary disease, depression, dyspepsia and osteoarthritis) whereby the conditions have unrelated pathophysiology and differing treatments that may even be contradictory[105]. Nonetheless, the emerging literature on pathophysiology and mechanisms of multimorbidity provides evidence of some common multifactorial pathways[106] (FIG. 2). Mechanisms can be considered in three broad areas: ageing and inflammation; socioeconomic, psychosocial and behavioural determinants of health; and medication-related. Each of these issues is discussed in turn in the sections below.

Ageing, inflammation and multimorbidity

The body of literature on the mechanisms connecting ageing and the development of multimorbidity is increasing[107–110]. The 'hallmarks of ageing'[111] include genomic instability, epigenetic effects, telomere attrition, loss of proteostasis, altered intercellular communication, mitochondrial dysfunction, deregulated nutrient sensing, cellular senescence and stem cell exhaustion. These hallmarks have been postulated to be possible targets for future pharmacological developments to prevent or slow development of multimorbidity[112].

Genomic instability is important because it is key to maintaining the health of cells and tissues, but it can be adversely affected by a range of internal and external factors[113]. Internal factors that can have negative effects include generation of reactive oxygen species (ROS) and spontaneous hydrolytic reactions, whereas external factors include chemicals in the environment or ultraviolet radiation[112]. Long-term epigenetic changes, which is how behaviours and environment influence gene function, have been postulated to have an important role in understanding development of multimorbidity and affect gene function through effects on histones, DNA methylation and microRNA dysregulation[114]. Both genomic instability and epigenetic changes are associated with development of certain cancers[115] and chronic inflammatory disease[116].

Telomere attrition can be increased by oxidative stress[117] and telomeres shorten with age[118], but the mechanisms underpinning these changes and the effects on human health remain uncertain[119,120]. A study examining the relationship between telomere length and development of multimorbidity did not find an association; however, in men, longer telomeres were associated with a lower risk of multimorbidity, including mental health conditions[121]. However, another study did show a relationship between telomere shortening in people with multimorbidity who also experienced sarcopenia

Frailty
A state of reduced resilience and increased vulnerability to stressors secondary to deterioration in function across several physiological systems.

Allostasis
The adaptive physiological response activated when homeostasis is disrupted during acute stress.

or frailty[122]. Although the literature on direct mechanisms connecting telomere shortening to chronic disease remains sparse, there is growing evidence of links between telomere shortening and carcinogenesis[123], inflammatory conditions (such as inflammatory bowel disease[124] and kidney fibrosis[125]) and certain neurodegenerative disorders (such as Alzheimer disease)[126]. Interest is growing in the potential of telomere shortening to serve as a prognostic marker, and this may be an area worthy of further investigation in relation to multimorbidity.

Loss of proteostasis, including impaired autophagy, protein misfolding and reduced translation fidelity, is associated with ageing and age-related diseases[112,127,128]. Moreover, alterations in proteostasis have been suggested to have a role in the development of neurodegenerative diseases such as Parkinson disease and Alzheimer disease[127]. Altered intercellular communication (which can be neuronal, endocrine or neuroendocrine) that occurs with ageing can also lead to decreases in tissue health and are often associated with an increase in inflammatory signalling known as 'inflammageing'[129]. Deregulated nutrient sensing can affect multiple signalling pathways that seem to affect longevity (for example, the insulin-like growth factor signalling pathway). Anabolic signalling has been suggested to promote ageing, whereas decreased nutrient signalling secondary to calorie-restricted diets or stimulation of sirtuins (signalling proteins involved in maintaining cellular haemostasis) promotes longevity. The role of insulin-like growth factors on the cells of bone development have been the subject of clinical studies aimed at treating osteoporosis, but benefits remain uncertain[128].

Mitochondrial dysfunction can be exacerbated by oxidative stress[130] and has a role in stem cell function[131] and cellular senescence[132]. The mechanisms underlying the adverse effects of mitochondrial dysfunction have been studied in mice[133]. This research demonstrated that mice with T cells deficient in a mitochondrial DNA-stabilizing protein have features associated with ageing including abnormalities of neurological, metabolic, muscular and cardiovascular function and that these changes produce effects similar to inflammageing[133]. This research suggested that mitochondrial dysfunction was controlled by mitochondrial transcription factor A, which is associated with inflammageing, and is a predictor of multimorbidity, contributing to the evidence that mitochondria have a causal role in senescence[134].

Cellular senescence is associated with chronic inflammation[110,135]. Cellular senescence results in senescent cells that can remain metabolically active and affect other cells through a senescence-associated secretory phenotype[136] that can secrete inflammatory mediators. This can lead to the promotion of a pro-inflammatory state that may be associated with age-related chronic diseases and, in turn, multiple chronic diseases (multimorbidity)[110,136]. Multiple factors can stimulate cellular senescence. External factors include metabolic signals (such as high levels of glucose), hypoxia and ROS whereas internal factors include telomeric dysfunction, DNA damage and mitochondrial dysfunction[137]. Senescent cells accumulate in multiple chronic diseases such as diabetes mellitus and cardiovascular disease[138,139].

Stem cell exhaustion[111] is a typical attribute of ageing that is associated with cellular senescence. Stem cells are required to generate new cells as old cells are lost or damaged, and without sufficient proliferating stem cells responses to damage or injury will be inadequate, resulting in impaired cell replacement and recovery[139]. Genomic stability and proteostasis are important for stem cell function, illustrating the connection between the various hallmarks of ageing. Stem cell exhaustion has been linked with development of chronic lung diseases such as chronic obstructive pulmonary disease[140].

One study explored the relationship between the hallmarks of ageing and multiple age-related diseases through text mining the literature, genome-wide association studies and examination of electronic health records (EHRs)[141]. This study found that five hallmarks of ageing (altered intercellular communication, mitochondrial dysfunction, deregulated nutrient sensing, cellular senescence and stem cell exhaustion) occurred more often in multimorbidity than expected by chance across different age groups[141]. Interest is increasing in the geroscience hypothesis, which suggests that health can be enhanced by focusing on the mechanisms of ageing rather than single diseases. A growing number of studies are investigating geroscience-informed therapeutic approaches[112] aiming to reduce or slow the effects of or development of multimorbidity. Research in these domains is likely to further intensify in the future.

Whether the hallmarks of ageing work individually, together or interactively is unclear, and only some have been validated in clinical studies[142]. Biomarker studies have suggested that the build-up of senescent cells affects allostasis[143] resulting in increased allostatic load, which has been proposed as a gauge of the aggregate physiological burden on the body required to maintain internal stability[144]. Allostatic load can be assessed by measuring multisystem biomarkers that are an indicator of multisystem physiological dysregulation. Allostatic load is a measure of the cumulative effect of chronic stress and probably also life events (as described in the section Social, psychosocial and behavioural factors). It has been associated with a range of health conditions including diabetes mellitus, musculoskeletal disorders, cancer, and mood and anxiety disorders, with evidence that those experiencing high levels of stress and psychological distress have higher allostatic loads[145].

Although our understanding of the hallmarks of ageing and their relationship with multimorbidity is limited, some biomarkers, particularly those related to oxidative stress, may be markers of some of these mechanisms of ageing and inflammation (see the section Diagnosis, screening and prevention, below).

Social, psychosocial and behavioural factors

Socioeconomic, psychosocial and behavioural determinants of health are associated with development of multimorbidity[108]. Socioeconomic deprivation (measured by household income, total household wealth or household area[146]) and lower education level are associated with higher multimorbidity prevalence[73,146–149] and development of multimorbidity at a younger age[19]. The opposite may apply in LMICs, whereby some studies

have suggested an associated between multimorbidity and higher incomes[73]. A systematic review of 24 studies examining the relationship between socioeconomic deprivation, education level or income found that a lower education level was associated with a 64% increased odds of multimorbidity compared with a higher education level[73], whereas another review including 42 studies found that multimorbidity was over four times more likely in people with the lowest incomes than in those with the highest incomes[146]. Other studies have shown that multimorbidity occurs a decade earlier in those from more socioeconomically deprived backgrounds[19].

A range of lifestyle factors including positive smoking status, high alcohol intake, decreased physical activity and poor diet quality are associated with development of multimorbidity[150,151]. However, findings are mixed, and it remains unclear which factors are the most important, making it difficult to draw firm conclusions. A Canadian study involving 1,196 participants examined the association between common lifestyle factors (such as current or past smoking, high-risk alcohol consumption, physical inactivity and low fruit and vegetable consumption) and found that smoking was the most important factor[152]. This study also found that the presence of combinations of unhealthy lifestyles (such as current or past smoking and physical inactivity) increased the risk of multimorbidity[152]. Of note, this study did not show an increased risk of multimorbidity with physical inactivity, which is in contrast to the findings of other studies, such as one study using data from the China Health and Retirement Longitudinal Study that demonstrated a 45% increased risk of multimorbidity with low levels of physical activity[153]. By contrast, an Australian study involving 53,867 participants aged 45–64 years who were free of 11 predefined chronic conditions at baseline showed that among the top multimorbidity predictors were current or past smoking, and increased age, high BMI and high intake of chicken or red meat in both sexes, but that other behavioural factors including physical inactivity, alcohol consumption and excessive or insufficient sleep duration were also important[154]. A study from India in 699,686 women showed that the risk of multimorbidity was 87% higher in women who smoked or chewed tobacco and was 18% higher in those who consumed alcohol than in women who did not smoke or chew tobacco or consume alcohol, respectively[155]. Factors such as smoking promote cellular senescence through inflammatory effects, oxidative stress and DNA damage[156], whereas exercise prevents cellular senescence[156,157], highlighting the probable interplay between socioeconomic, psychosocial and behavioural determinants and the hallmarks of ageing.

Interest is increasing in emerging lifestyle factors as potentially preventable factors in the development of chronic illness, such as cardiovascular and metabolic disease[158,159] and their role in development of multimorbidity. Emerging lifestyle factors include high television viewing time[160] or sedentary behaviour, sleep duration[161] (both too much and too little), and levels of social participation (such as loneliness)[108,153,158,162–164]. Short sleep duration was associated with the number of multimorbid conditions in 1,508 respondents of the European Health Examination Survey[164]. Moreover, data from the US 2005–2006 National Health and Nutrition Examination Survey (NHANES) suggests that sedentary behaviour is associated with multimorbidity, after adjusting for light-intensity physical activity and adherence to moderate-to-vigorous physical activity guidelines[165]. Loneliness and social isolation have also been suggested to be associated with multimorbidity[166]; however, 1 systematic review found that only eight studies have examined these issues and found that, although cross-sectional and longitudinal studies suggested an association between loneliness and multimorbidity, the evidence for social isolation is under-researched[166]. The mechanisms underlying many of these associations remain uncertain with some suggesting, for example, that the relationship between multimorbidity and sleep disturbance could be bidirectional[167], and others suggesting that sleep disturbance could be a surrogate measure of loss of resilience or multisystem homeostatic dysregulation[163]. Moreover, social relationships have been suggested to moderate the effects of stress on health and well-being in the stress buffering hypothesis[168].

Adverse childhood experiences (ACEs)[169,170] are also associated with increased severity and complexity of multimorbidity[170]. There are a range of hypotheses for potential underlying mechanisms[171], including chronic activation of the hypothalamic–pituitary–adrenal axis by persistent stress secondary to ACEs, leading to increased allostatic load. Other work has suggested that ACEs are associated with increased cortisol levels and chronic inflammation[172] or with DNA methylation of certain genes and telomere length shortening, possibly increasing the risk of conditions of ageing[173,174].

Lacking control over one's life (the extent to which people believe what happens in their life is determined by factors outside their control)[148] has also been implicated in development of multimorbidity. Lack of control may exacerbate anxiety, thereby promoting a chronic stress response and increasing the risk of unhealthy behaviours such as smoking[108]. Research into the interplay between stress and multimorbidity is in its infancy, but has indicated an association with increased hospitalizations and mortality[175,176]. Stress could be a modifiable risk factor for multimorbidity, particularly as it might be associated with decisions about unhealthy behaviours, but its effects may also be explained through an effect on allostatic load[177]. Some have posited that the social hallmarks of ageing should be integrated with the work on the biology of ageing to enhance understanding of the factors associated with human ageing and the development of multimorbidity[178].

Although evidence for the social determinants of multimorbidity is increasing, more research is required to help understand which factors or combination of factors are the most important to target. A key gap in knowledge is of determinants of different multimorbidity patterns, particularly in LMICs[92].

Medication-related mechanisms

Medications and polypharmacy may also contribute to development of multimorbidity. Several medications are associated with increased risk of diabetes mellitus and dyslipidaemia (for example, antipsychotics[179]).

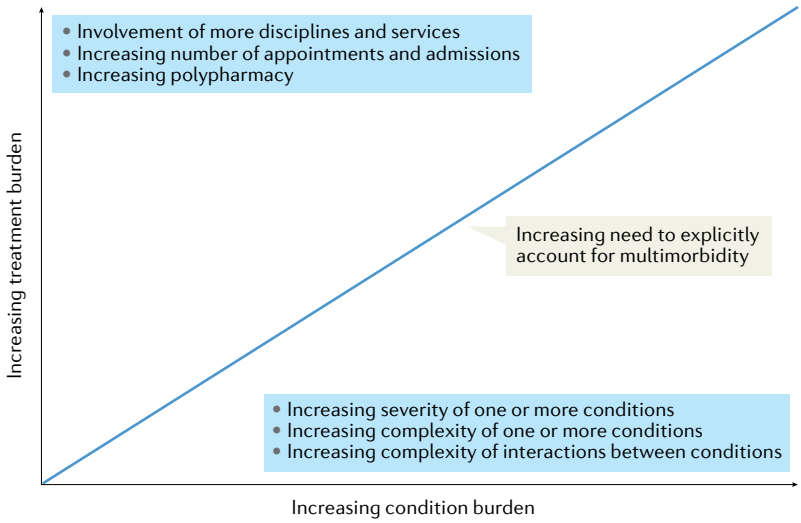

Fig. 3 | **Identifying who needs an approach to care that accounts for multimorbidity.** Adaptation of care to account for multimorbidity may be needed because the patient experiences a high condition burden and/or because the patient experiences a high treatment burden. Condition burden is related to the severity, complexity and interaction of the effects of individual conditions. For example, diabetes mellitus and hypertension is a combination that is relatively unproblematic because cardiovascular disease prevention is a common goal, whereas combinations such as diabetes mellitus, schizophrenia and chronic obstructive pulmonary disease (COPD) have more complex interactions between conditions (for example, schizophrenia has effects on motivation that may make lifestyle change difficult) and between medications (for example, antipsychotics adversely affect glucose metabolism, and share anticholinergic adverse effects with some COPD medications). Treatment burden is related to the effect of treatments, including the complexity of follow-up in relation to the number of different professionals, services, appointments and admissions, and complexity of treatment, particularly in relation to polypharmacy.

Similarly, medications with anticholinergic effects are associated with increased risk of cardiovascular events and cognitive impairment or dementia[170].

In practical terms, this could lead to patients receiving treatment for specific single conditions, and developing additional chronic conditions as a direct consequence of the treatment of the initial condition (for example, oral steroids for polymyalgia rheumatica contributing to the development of diabetes mellitus, cataracts and osteoporosis). In this way, medications can contribute to the development of multimorbidity. Equally, polypharmacy can increase the risk of drug–drug interactions or drug–condition interactions, also causing or adding to multimorbidity. For example, co-prescription of NSAIDs for arthritis and selective serotonin reuptake inhibitors for depression can result in gastrointestinal bleeding[180].

In summary, many interrelationships are involved in the development of multimorbidity, including ageing and inflammation, socioeconomic, psychosocial and behavioural social determinants and medications. FIGURE 2 summarizes key influences on development of multimorbidity, and illustrates the shared pathways to the development of multimorbidity. Mechanisms underpinning development of multimorbidity are frequently interrelated and may be synergistic.

Diagnosis, screening and prevention

Multimorbidity is not a condition or disease in the usual sense, so conventional ideas of diagnosis and screening are not strictly relevant. The focus of this section is, therefore, on the detection and diagnosis of multimorbidity that is significant or severe from the perspective of the patient or the clinician, and that, therefore, requires an approach to care which is more than simply optimizing care for every individual condition present.

Diagnosis in clinical practice

As multimorbidity is the coexistence of two or more chronic conditions, 'diagnosing' multimorbidity in clinical practice is rarely a problem because the clinician and patient usually agree which conditions are currently active or relevant. However, deciding (or diagnosing) when multimorbidity is sufficiently severe or impactful that it requires specific attention or when the management of a single disease needs to be adapted (including not following single-disease guidelines or shifting to more palliative approaches to care) is more difficult[20].

From this perspective, the UK National Institute for Health and Care Excellence (NICE) guideline on multimorbidity recommends that clinicians actively consider whether an individual patient requires an approach to care that specifically accounts for multimorbidity[181], if the patient requests such care or if the patient has any of the following features: finding it difficult to manage treatment or usual activities; receiving care from multiple services; having both physical and mental health chronic conditions; frequently seeking unplanned or emergency care; taking multiple medicines; or having frailty[182]. Of note, although frailty and multimorbidity are highly associated, they are not the same[43,183]. Although 72% of individuals with frailty have multimorbidity, only 16% of individuals with multimorbidity have frailty[184]. Both conditions are associated with lower socioeconomic status and neither is restricted to older adults[19,183,185]. However, the coexistence of frailty and multimorbidity is associated with increased risk of mortality[183], even after adjusting for the number of conditions, sociodemographic factors and lifestyle. Thus, identifying pre-frailty and frailty in patients with multimorbidity is important to prevent frailty progression, reduce the risk of adverse outcomes and optimize treatment.

The NICE guideline on multimorbidity also recommends that clinicians screen for patients who might require an approach to care that accounts for multimorbidity using EHRs or opportunistically identify patients during routine care. The recommended screening tools for use with EHRs have been validated in the UK to predict emergency hospital admission and to identify polypharmacy, but the same principles apply internationally. Key markers to opportunistically identify patients who require such a different approach (FIG. 3) are consideration of condition burden, treatment burden and frailty. Condition burden and treatment burden can only be assessed by asking the patient and/or carer about their experience of health and care[181]. For assessing the presence of frailty, then simple measures such as informal or formal assessment of gait speed, self-reported health, timed up-and-go tests or the PRISMA-7 questionnaire are recommended in the NICE guideline and are well correlated with gold standard frailty assessment, and are useful screening tools[181]. Of note, very intensive evaluation (such as that carried out in Comprehensive Geriatric

Condition burden
Also called disease burden. The effect of the condition on an individual, for example, on symptoms, activities of daily living or quality of life.

Assessment (CGA)) is not recommended in the NICE guideline for diagnosis of problematic multimorbidity in all patients, as CGA is too resource-intensive for routine use. Instead, NICE considers CGA to be a combined assessment and intervention to be used in selected patients where there is agreement that a different approach to care is needed (see Management, below).

Less-specific guidance on diagnosis or screening of multimorbidity is present in other guidance documents internationally, which tend to start from the recognition that the patient has multiple conditions. However, other guidelines recommend agreement with the patient about their most important outcomes or priorities, which may be associated with specific conditions or may not be condition specific[186–188]. Such a patient-centred approach is critical to ensuring that care is tailored to the individual. The range of personal circumstances that are important to the individual and relevant to care will often include diagnosed conditions but also potentially broader issues that affect health and care, for example living circumstances, social disadvantage and health literacy, all of which can influence an individual's capacity to cope with a given level of treatment burden[99,100].

However, some combinations of conditions may not be immediately problematic for the individual patient but carry considerable future risk that may need to be managed (such as hypertension, hyperlipidaemia, obesity, impaired glucose tolerance and previous myocardial infarction without current symptoms). Patient-centred care that focuses on high condition and/or treatment burden as experienced by the patient, therefore, has to be balanced against managing disease and future risk. Accordingly, predicting poor health outcomes and limited life expectancy is an important parallel strategy in identifying patients with multimorbidity who need an approach to care different from the more common disease or specialty-oriented models of care as reflected in condition-specific clinical guidelines.

A practical example of the diagnostic and management challenges facing clinicians is a patient with heart disease and chronic respiratory disease who has breathlessness and fatigue. A generalist approach is needed to identify the likely cause of these symptoms, which could relate to either condition and/or be compounded by coexisting depression and anxiety. Similarly, people with a combination of diabetes mellitus, heart disease and arthritis often find that pain caused by active arthritis limits their capacity to exercise and in some this contributes to difficulties maintaining a healthy body weight, thereby adversely affecting their diabetes and heart disease. Accordingly, even in someone with poor diabetes control, pain management might be the immediate priority. This approach, which focuses on improving outcomes prioritized by the patient and improving experience of care, rather than focusing on the condition count, parallels a change in thinking about polypharmacy from considering the total number of medications (often used in research studies) to focusing on appropriate polypharmacy from a patient perspective[189,190].

From a patient and clinical perspective, multimorbidity may, therefore, be present but not problematic, and the diagnostic problem is identification of multimorbidity, which requires a specific approach to care that goes beyond single-condition treatments. A combination of systematic screening of EHR data to identify patients for review, and opportunistic case finding during routine care is required. However, the core of diagnosis comprises the clinician actively working with the patient (and/or carer) to understand their experience while also using clinical judgement and agreeing a management plan with the patient.

Physiological and serum biomarkers

Several physiological and serum biomarkers may in the future be useful to help us understand determinants of multimorbidity and could also potentially be used to identify individuals at risk of adverse outcomes. Several physiological biomarkers are associated with development of multimorbidity[191], including higher baseline blood pressure, reduced hand grip strength[192–194], high waist–hip ratio and high BMI[150,191,195,196], and lung function indices, such as reduced forced expiratory volume in 1 s (REF.[197]). Some evidence suggests a link between the levels of a range of serum biomarkers and multimorbidity including higher cystatin C, C-reactive protein and lipoprotein levels, lower dehydroepiandrosterone sulfate levels, higher IL-6 levels[198], lower serum glutathione levels[199], and higher diacron reactive oxygen metabolite and HbA_{1c} levels[200]. This area is rapidly evolving with the potential for new biomarkers to be identified. For example, one study found an association between high total serum homocysteine and low methionine levels with more rapid development of cardiovascular multimorbidity[201]. Data on the use of some biomarkers for multimorbidity, such as vitamin D, are conflicting[202,203].

Of note, as yet there is no clear evidence to support the use of physiological and serum biomarkers to target treatments or interventions in patients with multimorbidity. Two systematic reviews have highlighted the insufficient literature on this topic[191,198] and suggest that there is an urgent need for additional good quality studies to aid understanding and inform targeting of potential future interventions (for example, to help individualize care) aimed at reducing or delaying development of multimorbidity. Future research on biomarkers for multimorbidity may identify biomarkers of sufficient predictive value to be used as screening tools in clinical practice or research.

Prevention

Primary prevention of multimorbidity has not been studied robustly, in part because such studies would potentially need long-term interventions and decades of follow-up to evaluate possible long-term benefits. Preventive measures for multimorbidity are related to psychosocial and behavioural factors, including the broad social determinants of health perspective, as described in Mechanisms/pathophysiology. The a healthy lifestyle (engaging in physical activity, not smoking, eating five portions of fruit and vegetables per day and not consuming alcohol in excess) seems to be associated with an increased life expectancy regardless of multimorbidity[204]. Moreover, as physical inactivity is

a risk factor for several chronic conditions, it is of particular relevance for the prevention of multimorbidity in all age groups[205], especially in individuals from socioeconomically deprived backgrounds who are more vulnerable to unhealthy lifestyle factors[204], given the negative health effects associated with social deprivation.

Population level and structural changes are necessary to effectively prevent multimorbidity and limit its progression. These changes could focus on influencing the determinants of health by reducing the effects of a particular risk factor across the whole population[206–208] (focusing, for example, on hypertension[209], smoking[210] and obesity[211,212] at the population level). Moreover, population-level approaches may be needed to overcome structural racism and economic barriers[213] and to address early determinants of multimorbidity, including socioeconomic deprivation and lower education level, to aid with the prevention of multimorbidity[70,214,215].

Management

Most clinical practice guidelines and organization of health care focus on managing single diseases[216]. Cumulatively implementing a single-disease approach for patients with multimorbidity can lead to care that is impractical or even harmful[20,186,217–219], particularly as the number and complexity of conditions increase. Management of multimorbidity requires an appropriate balance between a single-disease focus and multimorbidity care. Moreover, multimorbidity requires care that is both patient-centred and family-centred, prioritizing what matters most to the individual and the individual's carers, ensuring care that is effectively coordinated and minimally disruptive, and aligns with patient values and priorities[220]. Recognizing the social, family and care context in which health-care activities are managed, decisions are made and care is experienced is essential, particularly in those with more complex health needs. The need for an individualized, patient-centred approach to care means that there is no single multimorbidity management pathway. The patients and care settings are heterogeneous and care approaches will vary from potentially curative to palliative approaches. This paradigm shift from a management approach focusing on a single condition to a multimorbidity approach to care challenges conventional approaches to care delivery and needs to be supported by research that can inform evidence-based treatments for multimorbidity with a broad focus on identifying and addressing the needs of the patient and the patient's carers.

Evidence-based multimorbidity care

Given the challenges of managing multimorbidity, potential interventions are likely to be complex and multifaceted if they are to address the varied needs of the individual. Although an increasing numbers of studies have examined interventions for multimorbidity, evidence is still too limited to support any specific approach. One 2016 Cochrane review (which was corrected and re-published in 2021) included studies targeting multimorbidity (eight studies) and comorbidity (eight studies)[221], and suggested that interventions targeting comorbidity or common clusters of conditions that include depression may improve mental health outcomes, but found no clear evidence of effectiveness for interventions targeting multimorbidity more broadly. Comorbidity interventions can be designed to address the challenges of patients with those specific conditions; for example, an intervention for people with diabetes mellitus and comorbid depression will combine elements of diabetes-focused care with psychotherapy or escalation of antidepressant medication. The most consistent evidence for comorbidity studies relates to collaborative care approaches for comorbid depression, which improve depression outcomes[95]. Interventions for comorbidity that have targeted depression[222] or dementia care[223], have tended to target the index condition (depression or dementia) with less focus on the other comorbid conditions, meaning they do not really address the multimorbidity experienced by the patient.

A 2021 systematic review included studies published up to 2019 and focused on trials of interventions targeting multimorbidity only (excluding comorbidity studies) and identified 8 further studies totalling 16 randomized controlled trials (RCTs)[224]. Most of these trials included older patients (mean age >70 years in 11 of the 16 studies) and individuals with at least three conditions. Interventions targeting multimorbidity need to be focused, yet generic, and, in this systematic review, interventions were provided by a range of disciplines based in established primary care systems in HICs. Interventions were divided broadly into three groups: care coordination[225] combined with self-management support[226], self-management support alone and medicines management[227]. Although there was no clear evidence of effectiveness for any specific intervention type, a combination of care coordination and self-management support was suggested to improve the patient experience of care. Another focus of multimorbidity trials has been enhancing self-management support; however, despite 12 of the 16 RCTs having this aim, no clear evidence of effect on self-management or health behaviours was found[221]. CGA involves specialist multidisciplinary assessment of older patients and care to address biopsychosocial needs and can be considered in older patients with multimorbidity. There is evidence that CGA improves outcomes in hospitalized patients[228], although the effect on outcomes in primary care and community settings is less clear, and it is a very resource-intensive intervention[229].

Four of the 16 RCTs in the 2021 systematic review evaluated medicines management-type interventions with mixed effects, which may have related to inappropriate patients being targeted, for example, in those with little room for improvement. A more recent RCT from Ireland also evaluated a medicines management intervention in individuals with multimorbidity, targeting older adults taking at least 15 medicines, and found a significant small reduction in the number of medicines, although no significant effect on the appropriateness of medicines was reported[230].

Most existing trials have focused on older people but it is also important to address the needs of younger individuals who have different challenges, such as working and child-minding as well as managing their

Care coordination
The deliberate organization of patient care activities.

Self-management support
Interventions that equip patients with skills to actively participate and take responsibility in the management of their chronic condition, namely, action plans, goal-setting worksheets, problem-solving, motivational interviewing, reflective listening and selection of effective educational material.

Medicines management
The process through which a medicine is prescribed to optimize health-care delivery and patient outcomes.

multimorbidity, particularly those in the poorest socioeconomic groups who develop multimorbidity earlier[19]. The CarePlus study in Scotland, UK, specifically targeted socioeconomically disadvantaged adults with multimorbidity with a multilevel intervention supporting practitioners and patients that reported a significant

Table 1 | **Challenges to trials of multimorbidity interventions**

Challenges	Description	Evidence from existing trials
Study design (cluster versus individual randomized)	Those delivering interventions can not withhold care to create a control group; in these cases, randomization at the level of care providers addresses this challenge in studies where one care provider is responsible for the treatment (such as the general practitioner)	Eight of the 16 RCTs in a systematic review had a cluster design as this design accounts for contamination between arms within primary care practices[224]; allocating patients at a cluster or practice site level ensures that patients in the control sites are not exposed to the intervention being delivered through care providers
Targeting	The population targeted must have capacity to benefit from the intervention, which can be challenging given the heterogeneity of multimorbidity	In general, existing trials have targeted older patients[308] or those with three or more common long-term conditions, or have used another marker of complexity or severity, such as high health-care utilization[308,309] or polypharmacy[310], to target those more likely to benefit from interventions; for example, inappropriate targeting can occur when included participants have fewer or less-severe baseline problems, making it difficult to improve outcomes[310]
Choice of outcome	Outcomes often need to be generic rather than disease-focused	Common outcomes included in existing studies are HRQOL (EQ-5D and SF-36), mental health outcomes and a range of other PROMs, depending on intervention aims; existing trials have shown no improvement in HRQOL, which may be because this is less responsive to generic than to disease-specific interventions; there is some suggestion of improvements in the patient's experience of care
Choice of intervention components	There are a large number of possible components, and choosing the appropriate intensity of each component is important	Existing trials have all examined complex interventions that can broadly be divided into care coordination, self-management support and medicines management studies
Addressing health system context	Intervention implementation will depend on existing capacity in terms of infrastructure and personnel	Implementing complex interventions may not be possible in systems that are already at capacity, which was cited as a potential reason for lack of effect of the 3D intervention, which was an intervention that included reorganization of primary care to reduce duplication and fragmentation, a focus on patient's priorities, screening and treatment of depression and medicines review[311]; in the Guided Care study in the USA, no effect was found on the main outcome of hospital admissions, but a preplanned subgroup analysis indicated reduced admissions in one of the participating health-care organizations, which may have occurred as this system was more organized and structured than other systems, so that the guided care intervention improved existing care in that system only[309]
Challenges of implementing a new complex intervention for only consented patients (particularly relevant to cluster-randomized trials where not all patients participate)	Delivering an intervention to subgroups of patients can be challenging in clinical settings	In the 3D study, most intervention practices found it difficult to limit implementation of the 3D intervention for the minority of consented patients participating in their practice whilst continuing to provide usual care for patients not participating in the study; these issues need to be anticipated
Duration of intervention	Very complex interventions often need time for both professionals and patients to adapt to the new processes involved	Intervention duration in existing studies ranges from 6 weeks to 18 months, with most lasting for 12 months[221]; these time frames may not be sufficient for an intervention to have an effect, particularly one that is sustained over time
Duration of follow-up	Full intervention effect is unlikely to accrue in 1 year for some interventions (but see 'Usual care is often changing', below)	Most existing studies have had follow-up durations of 1 year owing to affordability and feasibility; this makes it challenging to ascertain the sustained effects of interventions, which may be important when interventions involve changes in management of health behaviours or changes in care delivery or medicines management
Usual care is often changing	Reduces power to detect an intervention effect (but see 'Duration of follow-up', above)	The 3D study showed that several elements were at least partly implemented in control practices at baseline, and the process evaluation showed that control practices were beginning to deliver the same kind of care being implemented in 3D intervention practices
Patient and frontline clinician involvement in intervention design and choice of outcomes	Involvement of patients and clinicians in intervention design is increasingly recognized as critical to development of effective interventions of relevance to key stakeholders	Only a minority of studies have had public and patient involvement in the design of their interventions, for example the 3D study. None has had a clear co-design process with key stakeholders targeted by the intervention

EQ-5D, EuroQol health-related quality of life questionnaire; HRQOL, health-related quality of life; PROM, patient-reported outcome measure; RCT, randomized controlled trial; SF-36, Short-Form Health Survey.

Box 2 | **Summary of key themes in clinical guidelines**

1. Target appropriate patients: consider risk factors and risk stratification
2. Consider interacting conditions and treatments: clinical assessment, consideration of illness and treatment burden, frailty, communication from other caregivers and medication review
3. Consider coexisting depression, which is more prevalent in multimorbidity, creates challenges for self-management and may impede effectiveness of other interventions
4. Incorporate patient preferences and priorities and take account of factors affecting capacity to adhere to management plans: clearly identify patient needs, priorities and values, consider goal setting, and elicit views of family and carers where appropriate
5. Individualized management: consider shared decision-making, effective communication of care plans, balancing benefits with harms of treatment and optimal medicines management
6. Monitoring and follow-up: planned reviews built into care plans, support for ongoing self-management and optimal medicines management

effect on negative well-being, although no effect on a range of other outcomes[231]. The CarePlus intervention was cost-effective within recommended UK funding thresholds, although this finding needs to be replicated in larger trials in other settings. Several challenges have arisen in existing trials of multimorbidity interventions (TABLE 1). Of note, interventions for multimorbidity have mostly been developed within well-established health-care delivery structures with strong primary care networks in HICs, with only limited development in LMICs[43].

Evidence-based clinical guidelines

The limited available evidence on the treatment of multimorbidity makes it challenging for clinical guideline development, although a small number of guidelines have been developed internationally[181,188,232]. The consensus across these guidelines is presented in BOX 2 (REF.[233]).

The general lack of evidence on which to base guideline recommendations has led to a reliance on consensus[233]. Although the evidence that multimorbidity care has major advantages over parallel care for single chronic conditions remains weak and inconsistent, qualitative research with patients and practitioners highlights the need for change. This research emphasizes the challenges patients face managing multiple conditions in fragmented medical systems that have largely been designed for the care of single chronic conditions and have not prioritized care coordination[234,235]. The NICE guideline on multimorbidity calls for a reorientation of care to address multimorbidity and highlights the importance of recognizing and addressing treatment burden for patients[100,181].

Managing medicines is a key part of existing clinical guidelines for multimorbidity with an emphasis on patients with complex polypharmacy (those taking ten or more medicines regularly). Medicines management for multimorbidity typically includes an emphasis on deprescribing and/or addressing indicators of prescribing appropriateness. In the extensive literature on polypharmacy, potentially inappropriate prescribing and deprescribing, some systematic reviews have found an impact on validated measures of appropriate prescribing, but there is less clear evidence of effect on clinical outcomes and well-being[189,190,236,237]. Given the overlap between multimorbidity and polypharmacy, clinical guidelines for each condition often overlap[233]. One systematic review identified four guidelines for polypharmacy and four guidelines for multimorbidity with overlapping principles and recommendations including targeting those in need of intervention, undertaking holistic assessments of conditions and patient priorities, evaluating physiological status (frailty), reviewing medicines, individualizing management and ensuring appropriate monitoring[233].

Multimorbidity and polypharmacy guidelines differ from single disease-oriented guidelines primarily in their generic focus and wider applicability. However, clinicians will still probably use elements of single-condition guidelines based on patient priorities, risk factors and symptoms. However, accounting for multimorbidity in single-disease guidelines is a key challenge. RCTs routinely exclude many patients with the target condition, notably older individuals and those with multimorbidity, co-prescribing or frailty[238–240]. Indeed, one systematic review of 50 studies of trial inclusion and exclusion criteria encompassing 305 trials and 31 physical conditions found that more than half of the trials excluded more than half of patients with the conditions studied[241]. Even patient cohorts in trials that are specifically conducted in older people are likely to significantly differ from the clinical population[242] owing to explicit and implicit exclusion criteria or biases in trial recruitment (such as exclusion of house-bound individuals and those in care homes)[243]. These issues suggest that while treatment benefits observed in trials may be generally applicable to those with multimorbidity, the precise benefit in populations excluded from clinical trials may differ owing to varying baseline risk[244] or increased treatment harms[245].

In guidelines, the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system is used to determine the certainty of the evidence underpinning the clinical recommendations. GRADE accounts for indirectness of evidence, relating to the applicability of the evidence in terms of populations included and differences in trial design, interventions and outcomes[246]. A finding of serious limitations due to indirectness weakens the guideline recommendation for all patients, which may unfairly downgrade strong evidence for the population studied in the trial. The implication is that, rather than downgrading a global recommendation, developers of single-disease guidelines should make nuanced recommendations that explicitly account for variation in the strength of evidence for different groups of patients. Considering coexisting conditions at all major steps in the development of single-disease guidelines is necessary to frame questions so that indirectness to populations with multimorbidity can be identified[247].

Both intervention studies and clinical guidelines need to identify and target patients who have significant treatment burden and who are in danger of being overwhelmed by self-management, which can result in poor adherence to treatment and adverse outcomes[99,100,248]. Patient-reported measures of treatment burden exist[249–251], but their ability to predict adverse outcomes remains uncertain. There is increasing emphasis

Biographical disruptions
A sociological concept referring to a break in social and cultural experience and self-identity.

on understanding factors that influence an individual's capacity to self-manage, which can vary over time as illnesses accumulate and personal circumstances change[99,100,248,252,253] (FIG. 4). These factors include the work involved in taking medicines, self-monitoring, attending appointments and following health professional recommendations. Implications for clinical practice based on available evidence and clinical guidelines are summarized in BOX 3 and global barriers and opportunities for multimorbidity management are summarized in BOX 4.

Outcomes of care

Outcomes of care can be considered from both a care delivery and a research perspective. In clinical practice, the outcomes to prioritize can be decided between the patient, the patient's carers and clinicians, by identifying the outcomes that matter most to the patient. In research, there is a need to systematize and harmonize outcomes to compare results across studies. A core outcome set for multimorbidity was developed by an expert panel, including multidisciplinary expert clinicians, researchers and patients from 13 countries[254]. HRQOL (see Quality of life, below), mental health and mortality are essential core outcomes in multimorbidity research. The other 17 core outcomes were grouped across the following domains: patient-reported effects and behaviours; physical activity and function; consultation-related; and health systems (BOX 5). Another outcome set has been developed for measuring quality of care in multimorbidity using data from EHRs[255], and recent[256] and ongoing work[257] aims to identify core outcomes in trials of prevention and treatment of multimorbidity in LMICs.

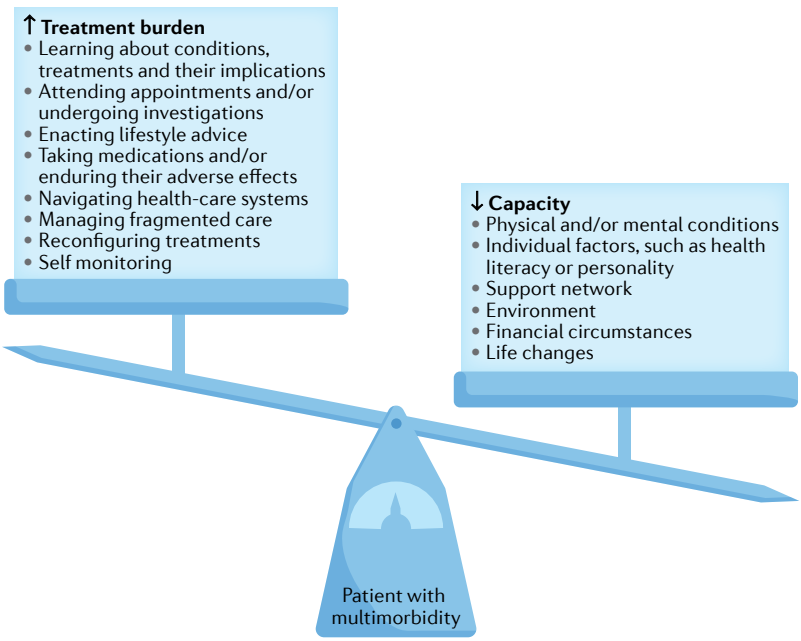

Fig. 4 | **Treatment burden versus capacity in patients with multimorbidity.** Multimorbidity is often associated with high treatment burden, and patients might have lower capacity to self-manage and cope. Treatment burden is strongly associated with the number of chronic conditions[217,324]. Patient-reported measures of treatment burden exist[249–251] but their ability to predict adverse outcomes is uncertain. The individual's capacity to self-manage can vary over time as illnesses accumulate and personal circumstances change[99,100,248,252,253].

Although cost outcomes of care are important to patients and health systems, there has been limited consideration of cost-effectiveness in trials of multimorbidity interventions, and existing studies have focused on health systems rather than patient costs or financial burden[221].

From the patient perspective, managing multimorbidity is challenging owing to the burden of illness and the burden of treatment[258,259]. Treatment burden can be measured as an outcome of care[251] in both clinical practice and research as new interventions should reduce rather than add to treatment burden. Moreover, some evidence shows that treatment burden also affects caregivers, and poses a pervasive challenge for both health-care providers and systems[17,260–269]. Furthermore, psychological distress experienced by patients with problematic multimorbidity and their caregivers may lead to fragmented and ruptured continuity of care and, therefore, complicate management[11,270].

Multimorbidity outcomes include some promising indices of multimorbidity developed to predict mortality, health expenditures and physical functioning[271–276], but there are few formal prediction tools[181], and they require validation using high-quality data before their use can be recommended. These tools are primarily research outcomes and have not been developed or used to support clinical practice. Evidence supporting the use of prediction tools in primary care are particularly important given the opportunity to provide holistic patient-centred care in this setting.

Most of the available evidence on outcomes in multimorbidity pertains to HICs with minimal reports from LMICs[277]. Research in sub-Saharan Africa has examined the use of theoretical frameworks to aid understanding of chronic disease management and multimorbidity issues, such as the cumulative complexity model and burden of treatment theory[35], in LMICs[278]. This preliminary work suggests that frameworks developed in HICs are generally applicable to LMICs but that there are some key differences and the absence of or limited access to required treatments is a key additional identified burden. A contextualized patient-reported measure to assess the effect of multimorbidity treatment and self-management burden on HRQOL and patient well-being could optimize patient-centred care delivery in these resource-constrained settings[75].

Quality of life

Management of multimorbidity aims to improve patient outcomes. HRQOL is an essential outcome in multimorbidity research. Many observational studies have consistently shown that multimorbidity is associated with poor HRQOL and psychological well-being across the lifespan[14,80,279–281]. Some studies have suggested that this effect on HRQOL is stronger in younger individuals[282], which some have suggested may be due to the accompanying life changes or biographical disruptions in younger people[253]. Others have indicated a more severe deterioration in well-being in older individuals[80], with a less steep reduction in HRQOL as the number of conditions increases[281]. A higher number of conditions is associated with greater reductions in HRQOL[282], and clusters of multimorbidity including both mental and physical

Box 3 | **Implications for clinical practice**

Step 1: who to target?

- Consider a multimorbidity approach to care in adults with three or more conditions and other risk factors such as
  - Significant polypharmacy (ten or more medicines)
  - High health-care utilization
  - Social vulnerability

Step 2: plan time for a multimorbidity assessment

- Consider who is best placed to start the clinical assessment if a team-based approach is possible
- Incorporate disease monitoring in the process to reduce treatment burden for patients (for example, may see nurse first for initial review, identification of patient priorities and monitoring blood tests, and then return for physician review with results to complete management plan)

Step 3: how to approach an assessment

- Consider disease and symptom burden
- Identify patient priorities and create plan to address these

Step 4: plan a review

- Tailor this to the individual patient to minimize treatment burden

Approach to care

- Patient, family and carer orientation
- Consider frailty. Informal assessment can consider time taken to walk into the consulting room. More formal assessment of gait speed can be quickly done, with more than 5 s to walk 4 m indicating possible frailty and a need to fully assess whether frailty is present[181].
- Consider physical capacity and daily functioning at all ages and refer to colleagues in allied areas of health such as physiotherapist and occupational therapists who can intervene to improve physical capacity and function if needed. Referral to rehabilitation programmes may also be appropriate depending on patient priorities.
- Consider appropriate risk factor management; for example, glycaemic targets in older people with diabetes mellitus and complex multimorbidity may differ based on risk of hypoglycaemia if aim for tight blood sugar control.
- Consider deprescribing and medication appropriateness based on age and life expectancy. Involve community or practice-based pharmacist if available.
- Consider options for self-management support. Group based approaches may suit some patients if available in local primary care settings.
- Consider comorbid depression and anxiety. Initial assessment could involve use of a brief practical screening tool, asking two questions[328]
  - During the last month, have you often been bothered by feeling down, depressed or hopeless?
  - During the last month, have you often been bothered by having little interest or pleasure in doing things?
- Identify social concerns or isolation and consider social prescribing (referral to non-medical community-based supports, if available)

conditions are also associated with poorer well-being[81]. Moreover, higher deprivation is associated with a more marked decrease in HRQOL with multimorbidity[282]. The association between HRQOL and multimorbidity is stronger when disease severity is taken into account[280,283].

Outlook

Multimorbidity is a major global health challenge that is increasing in prevalence. Further evidence to support effective management and improve patient outcomes is needed, particularly in LMICs (TABLE 2).

Epidemiology and mechanisms

More longitudinal studies are needed that examine multifactorial pathways and disease trajectories across age, sex, gender, racial and socioeconomic groups. Moreover, other studies are needed to evaluate the use and clinical importance of multimorbidity clusters. Especially given the experience of the COVID-19 pandemic, a syndemic approach (considering interactions between conditions and factors affecting the interactions) is needed to address the shared social determinants of multimorbidity[31,284].

Management

Most care for multimorbidity takes place in and is coordinated from primary care, and home-based and ambulatory settings, and these need to be reconfigured to address both acute episodic illnesses and chronic care, ensuring patient-centred and family-centred approaches that reduce treatment burden. Specialty care may be needed for those with more complex health needs and health systems need better integration of primary and specialty care and improved communication between care systems. Moving away from siloed care for individual conditions is urgently needed to improve quality of care and safety.

Interventions for multimorbidity. Clinicians, health managers and policy makers need guidance on how to develop interventions for multimorbidity owing to a paucity of evidence for management of this condition. These interventions should be based on known problems, which include lack of coordination, duplication, treatment burden, single-disease focus and problematic polypharmacy. Three key areas need to be considered, including targeting the appropriate patients and addressing their priorities, including their caregivers; supporting self-management and healthy behaviours; and delivering health and social care with a focus on interdisciplinary care and professional expertise (for example, in medicines management). Self-management support is part of many patient-oriented interventions, and is used widely in many single-disease programmes. Motivational interviewing is a critical component of self-management given the relationship between the accumulation of unhealthy behaviours and multimorbidity[152]. Of note, the concept of self-management may not entirely match the lived experience of people with multimorbidity: older adults frequently receive care from family or friends and are more likely to do so as their health worsens. Although self-management support has the potential to improve outcomes and reduce health-care utilization, evidence underpinning its effect in multimorbidity is limited[221]. However, self-management remains a key area for consideration in the evaluation of interventions in chronic diseases[285].

Healthy behaviours are often a focus of self-management support interventions (for example, improving physical activity and participating in exercise therapy), and behavioural interventions targeting lifestyle behaviours may improve HRQOL and physical function and reduce depression[286]. Exercise has important health effects, including reducing blood pressure, inflammation, constipation, risk of thrombosis and, in those with diabetes mellitus, blood glucose levels, in addition to improving mood and mental health, pulmonary capacity, oxygen flow, muscle strength and

stimulating metabolism[287]. A meta-analysis has suggested that exercise therapy is safe and effective in improving physical and psychosocial health in people with multimorbidity[288]. Given the demonstrated clinical effects of exercise on at least 26 chronic conditions[287], it is promising both for treatment and prevention, especially when combined with other self-management supports. Importantly, barriers to participation need to be overcome to ensure adherence and effects in the long term[289]. Various international studies aim to investigate exercise therapy and self-management support for people with multimorbidity (such as MOBILIZE and PERFORM). Other health behaviours (healthy food, avoidance of smoking and responsible alcohol consumption) need to be considered when optimizing care of patients with multimorbidity, although an overemphasis on personal behaviours may not be appropriate or as effective as addressing broader socioeconomic determinants of health. Interventions that target both upstream and downstream determinants of health is essential[290], and even those targeting individual behaviour need to take account of potential prevention burden (shifting responsibility for prevention to individuals) if they are to address health inequalities[291].

Box 4 | **Global barriers and opportunities for multimorbidity management**

Patient level barriers

Patient level barriers include lower health literacy and self-efficacy to navigate the health-care system, treatment burden, fragmentation and suboptimal coordination of care, limited social and economic resources to support self-management (such as family support, employment and community support), environment (for example, living in a rural area far from health services or residing in an unsafe area that is a barrier to outdoor physical activity), and inadequacy of financial protection to meet health-care or related costs.

System level barriers

System level barriers include availability of, appropriateness of and access to services[329,330]. In most health systems, consultation times are limited and patients and providers can be frustrated that issues were not addressed adequately[234]. Of note, personal barriers and health-system barriers can combine; for example, patients with multimorbidity often experience functional limitations, which restrict their mobility and ability to access treatment.

Barriers in LMICs

Barriers in LMICs are expected to be augmented and amplified in settings characterized by weak, fragmented and acute-oriented health-care delivery systems[331–333]. Such pressures affect families as well as the precarious and overloaded health system, and require household-level and creative community-level responses to decrease the load on health services. The reach of initiatives such as care coordination[221] often deployed in high-income countries (HICs) may be restricted in low-income and middle-income country (LMIC) settings with fragmented health services or non-existent chronic care, but this can also be a challenge in HICs lacking universal access to health care free at point of delivery. In Peru, more than 90% of care for people with disabilities relies on household relatives, largely women[334].

Opportunities in LMICs

There are opportunities in LMICs to leverage innovative delivery channels, such as technology-enabled tools or mobile health for physical and mental chronic conditions[222,335–337] and the utilization of non-health-care delivery settings such as barbershops to manage risk factors such as hypertension[338], places of religious worship and informal social networks to promote healthy lifestyles[339–341]. These can be aided by co-production approaches, which are likely to yield interventions responsive to people's preferences[342,343], and, therefore, enhance patient-centred approaches. Multilayered interventions in the field of dementia have shown promising results by improving patient-related and caregiver-related outcomes[223,344]. As with other challenges in LMICs, there are opportunities for 'leap-frogging', a concept describing an approach that bypasses arduous and expensive development phases and adopts proven technologies and systems as a way to build better health systems[345].

Box 5 | **17 core outcomes in multimorbidity**

Highest-scoring outcomes (most important)
- Health-related quality of life
- Mental health
- Mortality

Patient-reported impacts and behaviours
- Treatment burden
- Self-rated health
- Self-management behaviour
- Self-efficacy
- Adherence

Physical activity and function
- Activities of daily living
- Physical function
- Physical activity

Consultation-related
- Communication
- Shared decision-making
- Prioritization

Health systems
- Health-care use
- Costs
- Quality health care (patient-rated)

Adapted with permission from REF.[254], Annals of Family Medicine.

Digital health and multimorbidity. More innovative approaches to the management of multimorbidity include interventions that incorporate digital health solutions. Going forward, following experiences of remote care delivery during the COVID-19 pandemic, interventions and care delivery need to consider the potential of digital health and artificial intelligence to reduce treatment burden and/or enhance patient capacity to self-manage and negotiate health-care systems. However, such interventions will need to consider how to prevent the increasing use of digital health from contributing to widening health inequality. Moreover, there are concerns about an increasing digital health literacy gap, which is more common in older individuals[292], people of lower socioeconomic status, those with learning and other disabilities and those with language barriers[293,294].

Personalized approaches. Although only in its infancy, personalized treatment, or precision medicine, targeted to the needs of the individual is promising for people with multimorbidity and might lead to health advantages by improving the effectiveness of, and reducing the number of adverse events from, various interventions[295]. We also need to consider how to help the increasing number of patients with multimorbidity and cognitive impairment and those with invisible disabilities such as chronic pain and fatigue (which is associated with many chronic conditions). More trials are needed to build an

Table 2 | **Research priorities**

Global research priorities on multimorbidity, as per Academy of Medical Sciences Report[43]	Research priorities on multimorbidity sensitive to LMIC contexts[45,312]
Research priority 1: what are the trends and patterns in multimorbidity?	Research agenda to address multimorbidity in LMICs should be sensitive to existing capacities; in the same way in which LMICs differ from HICs, they also differ from each other, and context-specific data are essential; hence, a common definition of multimorbidity, including a few physical and mental chronic conditions is essential to advance the research agenda in LMICs; many LMICs do not have electronic medical records or national surveys for non-communicable diseases, and hence a gradual step to data generation is required; a common definition of multimorbidity would allow basic estimates of a few conditions and, as a country progresses, more conditions can be added whilst maintaining comparability with previous rounds of data collection
Research priority 2: which multimorbidity clusters cause the greatest burden?	
Research priority 3: what are the determinants of the most common clusters of conditions?	
Research priority 4: what strategies are best able to facilitate the simultaneous or stepwise prevention of chronic conditions that contribute to the most common multimorbidity clusters?	Evidence about co-occurring conditions and which combinations most affect health should be generated and aligned with context-specific disease burdens and the capacity of the health system to respond to them
Research priority 5: what strategies are best able to maximize the benefits and limit the risks of treatment among patients with multimorbidity?	
Research priority 6: how can health-care systems be better organized to maximize the benefits and limit the risks for patients with multimorbidity?	A common set of high-quality health system indicators, placing emphasis on what matters most to people, such as competent care, user experience, health outcomes and confidence in the system, in addition to other common outcomes, is essential to advance a context-specific agenda for multimorbidity

HICs, high-income countries; LMICs, low-income and middle-income countries.

evidence base on how to manage multimorbidity and to help produce clinical guidelines. Co-design of interventions with patients, carers and clinicians has been lacking to date, although it may improve the effectiveness of interventions[296]. Trials of interventions for conditions sharing common characteristics and risk factors are also needed, particularly in terms of prevention of further disability, frailty and worsening health outcomes.

Models of care. Owing to the complexity of multimorbidity management, ensuring that clinical practice incorporates interdisciplinary care makes sense. Interdisciplinary teams have been central to the interventions published to date[221]. New models of integrated care that are being developed in many countries include teams of allied professionals joining doctor-led practices[297–299]. Enhancing teamwork could increase the likelihood of effective interventions for multimorbidity. Mechanisms to enhance teamwork are summarized in the Patient-Centred Innovation for Persons with Multimorbidity (PACEinMM) evidence-informed framework[300], which highlights the following aspects: need for a shared team philosophy or vision; strong team relationships with a dedicated person acting as a bridge between the patient and the rest of the team; connectedness with all the components of the health-care system and the community to avoid duplication and work in silos; professional training specific to integrated care and enhanced patient relationships. This framework complements Wagner's Chronic Care Model[301] by identifying conditions under which productive interactions between the patient and the interdisciplinary teams may occur. Moreover, there is an increasing focus on 'minimally disruptive medicine'[218] which calls for clinicians to identify the patient's burden of treatment, taking account of factors that influence capacity to self-manage; encourages a focus on care coordination; and prioritization from the patient perspective. Social prescribing is increasingly being adopted and aligns well with a patient-centred approach to multimorbidity[302]. However, despite its increasing popularity it does not have a strong evidence base and there are a wide range of definitions and types of approaches being adopted[303]. One potential model is the use of practice-based link workers who implement social prescribing, and there are two small trials exploring its effects in multimorbidity[304,305].

Addressing the challenge of multimorbidity facing health systems requires a resilient health workforce and processes to tackle the interplay of health-system emergencies (such as pandemics and the health effects of climate change) with effective management of ongoing multimorbidity. Multimorbidity management will also require augmented skills in multidisciplinary team-based care through inter-professional learning and communication. Globally, health care is still predominantly organized around single conditions, and reimbursement models often reinforce this focus. This approach and structure needs to urgently change to enable a rebalancing between generalism and specialism in health-care systems. All aspects of health-care delivery need this reorientation by clinician training, producing policies and guidelines around clinical care delivery, adapting the places where health care is delivered to incorporate home-based and community-based care, and developing reimbursement models that recognize complexity. Although elements of specialty care delivery

Social prescribing
A process through which clinicians can refer patients for community support from local, non-clinical services.

should be retained, more generalism is required both in primary care and in generalist specialist care across all ages. Beyond the dichotomies within clinical specialties, it remains critical and essential that patients, caregivers and families are at the core of services and receive high-quality care throughout the multiple ongoing interactions between patients and the health system. Closing the physical–mental health divide in health-care systems is also critical for managing complex physical–mental health multimorbidity. This requires both physical and mental health specialists taking at least some responsibility for the other condition (for example, cardiologists thinking about depression and psychiatrists thinking about smoking and cardiovascular risk), particularly in those with enduring serious mental illness. We need clinicians who are able to work effectively across the health-care divide. Relationships have been suggested to be the 'silver bullet' of general practice, enhancing trust, and there is growing evidence that continuity matters and is associated with improved outcomes[306,307]. For multimorbidity, we need to focus on promoting relationships both between practitioners, patient and caregivers and between health professionals to enhance care coordination and reduce fragmentation of care.

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Competing interests

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