Published in final edited form as:
Nat Rev Dis Primers. 2022 July 14; 8(1): 48. doi:10.1038/s41572-022-00376-4.

Multimorbidity

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Competing interests
The authors report no conflicts of interest.

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Abstract

Multimorbidity (≥2 co-existing conditions in an individual) is a growing global challenge with substantial impact on individuals, carers and society. It occurs a decade earlier in socioeconomically deprived communities, 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 can be considered related to aging and underlying biological mechanisms and to broader determinants of health, e.g. socioeconomic deprivation. Little is known about prevention, but focusing on psychosocial and behavioral factors, particularly population level interventions and structural changes, is likely to be beneficial. Most clinical practice guidelines and healthcare training and delivery focuses on single diseases, leading to care that is sometimes inadequate and potentially harmful. Multimorbidity requires person-centered care, prioritizing what matters most to the individual and their carers, ensuring care that is effectively coordinated and minimally disruptive, and aligns with patient values. Interventions are likely to be complex and multifaceted. While an increasing number of studies examining multimorbidity interventions are available, there is still limited evidence to support any approach. Greater investment in multimorbidity research and training along with reconfiguration of healthcare supporting management of multimorbidity is urgently needed.

Introduction

In recent years, there has been increasing interest in multimorbidity, commonly defined as the co-occurrence of at least two chronic conditions in the same individual,[1] due to its substantial impact on the individual and their families, 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] In 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.

Compared to people with a single chronic condition, people with multimorbidity are more likely to die prematurely, be admitted to hospital and have an increased length of stay.[9,10] Multimorbidity is also associated with poorer function and health-related quality of life (HRQoL), depression and intake of multiple drugs (polypharmacy) as well as greater socioeconomic costs.[11–18] Unfortunately, most healthcare is designed to treat individual conditions rather than providing comprehensive, person-centered care,[2,19,20] which often leads to fragmented and sometimes contradictory care for people with multimorbidity and increases their treatment burden.[21] Treatment burden refers to the workload of self-management and the increased use of medical treatments and healthcare services, which is strongly associated with the number of chronic conditions.[22,23] We also know from qualitative research that treating one condition at a time is inefficient and unsatisfactory for both people with multimorbidity and their health care providers.[24–26]

Multimorbidity is increasingly common, due 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.[2,19,27,28] There is clear evidence of a link between multimorbidity, socioeconomic status and age.[3,19,27,29] However, although age is the strongest driver of multimorbidity, in absolute numbers, more people under 65 years of age are affected by multimorbidity than people 65 years or older, partly due to the fact that more people in the general population are in that age group. Moreover, this highlights that multimorbidity is not just a feature of ageing.[19,28]

The landscape of multimorbidity is further complicated in low- 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.[30–33] LMICs also have higher prevalence of multimorbidity-related financial burden,[34,35] and have weaknesses in health systems including a greater focus on managing acute health conditions and chronic infectious diseases[3,4,35,36] and in some countries complete absence of services for people with multimorbidity.[37]

The burden associated with multimorbidity, including family carer burden and widespread limited awareness amongst healthcare providers and the general public, particularly in LMICs, reveals levers and opportunities for innovation across the whole health system. Advancing towards high-quality health systems requires an emphasis on what matters most to people, such as continuity of care,[37] competent care, user experience, health outcomes, and confidence in the system,[38] and thus, addressing multimorbidity is a unique entry point towards the goal of high-quality health systems.

During the COVID-19 pandemic those with multimorbidity have been at greater risk of infection, and adverse outcomes including hospitalization; and 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 where COVID-19 impact has often been catastrophic.[39–43] The COVID-19 pandemic has 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.[43–45]

Overall, the pandemic highlights the urgent need to take action to deal with the increasing burden of chronic conditions and multimorbidity worldwide through better prevention and management with a reconfiguration of healthcare to achieve an appropriate balance of disease-orientated specialist care and person-centered generalist and primary care.[46,47] This paradigm shift in healthcare delivery also requires updating the training of the next generation of healthcare providers and increasing emphasis on primary prevention strategies, including lifestyle-focused and population-wide prevention efforts, many of which will be deployed outside of the healthcare delivery system.

This primer provides a global overview of the epidemiology, potential underlying mechanisms and pathophysiology, diagnosis, prevention, management, and outcomes of multimorbidity; sets the scene for a call to action for future research; and highlights the need for improved management and enhanced support to primary care and public health. For consistency, we will use the term ‘multimorbidity’ throughout, acknowledging that

'multiple chronic conditions' is also often used in the literature and considered more lay person friendly.[48] In this primer we will define multimorbidity as the co-occurrence of at least two chronic conditions in the same individual, since this is the most commonly applied definition and the accepted definition used by the World Health Organization.[1,49] Given that multimorbidity should have a person-centered approach and does not intrinsically prioritize one individual condition over others,[5,6] the primer does not follow a structure focusing on certain individual diseases or conditions separately, but we refer to individual conditions, comorbidities and clusters of conditions, when relevant.

Epidemiology

Defining and measuring multimorbidity can be considered both from a research or epidemiological perspective and a clinical perspective and we cover clinical diagnosis in later sections. Although the presence of two or more chronic conditions is the most widely cited and accepted definition (Box 1), the way multimorbidity is defined (e.g. number of co-existing conditions needed to qualify as having multimorbidity) and measured is highly variable depending on the number of conditions considered and how they are measured.[50–52] The simple two or more chronic condition definition has been criticized for including large numbers of people with combinations of conditions that do not significantly affect the individual (e.g. well-controlled hypertension, pre-diabetes and high cholesterol), which has led to the suggested alternative definition of "complex multimorbidity".[53] Regardless, on the patient (and household) side, dealing with more than one condition, including mental health ones, translates into more healthcare load and a larger burden of treatment, which is equally important, if not more important, than the precision in the 'technical' definition of multimorbidity.[37,54,55]

Although plausible, the clinical or research utility of the concept of complex multimorbidity is not well established.[56,57] A systematic review of 566 studies of multimorbidity found that simple or weighted condition counts dominate the literature, but the number of conditions included in measures varies from 2 to 285 (median 18). In more than 50% of studies, only eight physical conditions were included (diabetes, stroke, cancer, chronic obstructive pulmonary disease, hypertension, coronary heart disease, chronic kidney disease, and heart failure), and a quarter of studies did not include any mental health condition.[58] There is debate about the relative value of simple condition counts (i.e. counting the number of conditions an individual has) versus weighted indexes (i.e. introducing a weighting for included conditions based on severity and/or impact).[5,46,59–61] The evidence regarding whether simple counts or weighted measures are preferable remains mixed. 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 on this subject reported that there was no consensus on this issue, and suggested that choice of measure should be determined based on study aims.[59–61] There is also uncertainty about how indices should be weighted (for example, by HRQoL or other outcomes) and the most appropriate weighting likely varies depending on the purpose of the study,[51,62] the source and type of data available, the population source, and the impact being considered.[51,59,63,64] Further adding to the variability is whether risk factors and symptoms such as urinary incontinence are included. A large cohort study found that while including risk factors only

increased the prevalence of multimorbidity, including symptoms increased both prevalence and association with patient outcomes.[50]

This great variability makes comparison of prevalence and impact across populations difficult and highlights the importance of considering and clarifying which multimorbidity framework is used in the individual studies as well as calls for a consensus process in terms of identifying the most relevant definitions to use in future studies..

Prevalence

The estimated prevalence of multimorbidity depends on how a particular study has defined multimorbidity[29] but, overall, consistent findings have been made across studies (Figure 1).[29] Systematic reviews focusing on community-based studies in both high-income countries (HICs) and LMICs, have reported a prevalence of multimorbidity in the order of 15-43%.[30,65–67] A scoping review in LMICs reported that the prevalence of multimorbidity in adults ranged from 3% to 68%, with Brazil, China, South Africa, India, Mexico, and Iran providing most of the evidence,[68] and 43% for Latin America and the Caribbean.[66] Prevalence estimates are generally lower in LMICs compared to HICs as displayed in Figure 1 a) and b). The reasons for this difference have not been addressed in prevalence studies but methodological factors and differential survival are plausible hypotheses. Overall, about one-third of the world's adult population,[65] including a substantial proportion in LMICs,[69–71] and more than half of all adults with any chronic condition[19] have multimorbidity, thereby affecting hundreds of millions of people and leading to significant disability worldwide.[27] Of note, depression is two to three times more common in people with multimorbidity compared to people without multimorbidity or those who have no chronic physical condition.[18] Although less commonly reported, available evidence suggests that some children and adolescents are affected by multimorbidity and risk of associated disability.[19,29,72,73] Multimorbidity is strongly associated with age, with prevalence rising rapidly in middle-age and being the norm in older people, with a prevalence of 30% among people aged 45-64 years, 65% among 65-84 years old, and 82% among those aged 85 years or older.[19,29] In addition, multimorbidity is more common in women than in men, with 21 out of 25 studies demonstrating a higher prevalence in women and a weighted difference in prevalence of 6.5%.[74] There is also strong social patterning, with 64% higher frequency in groups with lower education compared with those with higher education.[75] Individuals living in the most deprived areas consistently experience higher prevalence of multimorbidity compared with their more affluent counterparts across the life span (See Fig 1.c), 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,[68] studies in LMICs also find that multimorbidity is common and associated with age, gender and social status, although with a higher prevalence of multimorbidity among adults with higher socioeconomic status in some countries, but not in others.[30,70,76] Reasons for these differences are largely unknown, but might relate to differences in access to health care, getting a diagnosis, health seeking behaviour as well as longevity.[77]

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Condition clusters

The identification of clusters of conditions is an alternative to both simple counts and weighted indices. For example, conditions may share a common etiology, or the clustering of physical and mental chronic conditions may impose challenging burdens on individuals, families and health systems, particularly in LMICs with resource poor environments.[30,46,78] There is much debate about the most appropriate methods to identify and analyze clusters. In recent systematic reviews, factor-analysis or hierarchical-clustering methods dominated,[79–81] with smaller numbers using latent class, network, and multiple correspondence analysis. The two most consistent and replicable clusters across available studies included cardio-metabolic conditions and mental health conditions, respectively, while clusters including musculoskeletal conditions and allergic conditions have also been identified.[79–81] Although the evidence is still limited, there are indications that certain clusters, in particular those including mental health conditions (e.g. depression), are associated with poorer health.[82,83], functional limitations[84] and higher health care costs.[85] However, there are few replication studies, and those that have been done suggest that observed condition clusters are not usually replicable using different methods and/or in different datasets. [79,81,86–88] There is a need to better understand multimorbidity clusters, their importance for care, and their trajectories over time across different age ranges, sex, genders and racial groups.[89–91] This will identify opportunities for early intervention to address sex and gender, ethnic and socioeconomic inequality in multimorbidity.[92,93]

Multimorbidity trajectories

Only a few studies have taken a longitudinal approach and examined multimorbidity trajectories, i.e. repeated measures of disease count and status, disease transitions and order of disease occurrence over time. A recent 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.[94] No studies were from the LMIC contexts and the methods used were heterogeneous. Additional longitudinal data and analysis will be important to better understand multimorbidity's development and acceleration and its inequalities based on social status.[75,95–97]

Healthcare utilization and economic impact

People with multimorbidity are more likely to die prematurely.[56,98] Furthermore, there is a clear link with increased health care utilization.[10,17,99] Multimorbidity accounts for 78% of all consultations in primary care in HICs,[99] more frequent hospital admissions with longer lengths of hospital stay,[10,99,100] and an almost exponential relationship between the number of chronic conditions and their associated costs because of increased healthcare utilization.[17] This higher healthcare utilization, coupled with multiple pharmacological treatments, common among people with multimorbidity,[15,17] leads to higher treatment burden.[21,101,102] and also places financial strain on patients and healthcare systems.

Households can experience catastrophic health expenditures when faced with the management of chronic conditions and multimorbidity.[34,103,104] Informal caregiving, provided by family relatives mostly without financial compensation, many of whom have

to stop working to devote to caregiving,[105,106] adds to the societal and household economic burden of multimorbidity.

Mechanisms/Pathophysiology

Considering the mechanisms and pathophysiology that underlie epidemiology and clinical impact is complicated by the heterogeneity of people with multimorbidity. 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) where the conditions have unrelated pathophysiology and differing treatments that may even be contradictory.[107] Nonetheless, the emerging literature on pathophysiology and mechanisms in multimorbidity does provide evidence of some common multifactorial pathways (Figure 2).[108] Mechanisms can be considered in three broad areas: 1) Ageing and inflammation; 2) Socioeconomic, psychosocial and behavioural determinants of health; and 3) Medication-related. Each of these issues is discussed in turn in the sections below.

Mechanisms of ageing, inflammation and multimorbidity

There is a growing literature on the mechanisms connecting ageing and the development of multimorbidity.[109–112] The ‘hallmarks of ageing’[113] 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 of ageing” have been postulated to be possible targets for future pharmacological developments to prevent or slow development of multimorbidity.[114] Genomic instability (the build-up of genetic damage) is important because genomic stability is key to maintain the health of cells and tissues, but it can be adversely affected by a range of internal and external factors.[115] Internal factors that can have negative effects include generation of reactive oxygen species (ROS) and spontaneous hydrolytic reactions while external factors include things like chemicals in the environment or ultraviolet radiation.[114] Long term epigenetic changes (how a combination of behaviours and environment influence gene function) have been postulated to have an important role in understanding development of multimorbidity and are said to affect gene function through effects on histones (proteins found in cell nuclei); DNA methylation, microRNA dysregulation.[116] Both genomic instability and epigenetic changes have been associated with development of certain cancers[117] and chronic inflammatory disease.[118] Telomere attrition (accrual of DNA damage that affects part of the chromosome known as telomeres) can be increased by oxidative stress. [119] Telomeres are known to shorten with age,[120] but the mechanisms underpinning these changes and the ultimate effects on human health remain uncertain.[121,122] A study examining the relationship between telomere length and development of multimorbidity did not find an association between telomere length and multimorbidity, although, in men, longer telomeres were associated with lower risk of multimorbidity that included mental health problems.[123] However, another study did show a relationship between telomere shortening in people with multimorbidity who also experienced sarcopenia or frailty.[124]

However, while the literature on direct mechanisms connecting telomere shortening to chronic disease remains relatively sparse there is growing evidence of links between telomere shortening and carcinogenesis,[125] inflammatory conditions such as inflammatory bowel disease[126] and kidney fibrosis,[127] and certain neurodegenerative disorders such as Alzheimer's disease.[128] There is growing interest 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 (problems with regulation of cell proteins) which includes impaired autophagy, proteins misfolding and reduced translation fidelity of proteins is associated with aging and age-related diseases. Difficulties in relation to proteostasis have been suggested to have a role in the development of a range of neurodegenerative diseases such as Parkinson's or Alzheimer's Disease.[129] While altered intercellular communication (which can be neuronal, endocrine or neuroendocrine) that occurs with aging can lead to decreases in tissue health. These changes are often associated with an increase in inflammatory signalling known as "inflammaging".[130] Deregulated nutrient sensing (problems with the processes affecting nutrition that can affect metabolism) refers to a range of signalling pathways, for example, involving insulin-like growth factors that seem to affect longevity. It has been suggested that anabolic signalling promotes ageing while decreased nutrient signalling secondary to calorie restricted diets or stimulation of sirtuins 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.[131]

Mitochondrial dysfunction (problems with mitochondrial energy production) can be exacerbated by oxidative stress[132] and have a role in stem cell function and cellular senescence. The mechanisms underpinning adverse effects associated with mitochondrial dysfunction have only recently become clearer, albeit based on mouse research.[133] This work demonstrated that mice with T cells that were deficient in a mitochondrial DNA-stabilizing protein showed many features associated with aging including abnormalities of neurological, metabolic, muscular and cardiovascular function and that these changes produced effects similar to "inflammaging".[133] This work suggested that mitochondrial dysfunction was controlled by mitochondrial transcription factor A (TFAM) which was associated with inflammaging and is a predictor of multimorbidity and contributes to the evidence that mitochondria play a causal role in senescence.[134]

Cellular senescence (accumulation of unrepaired damage to cells and limitations in repair functions which may be exacerbated by oxidative stress) is associated with chronic inflammation.[112,135] Cellular senescence results in senescent cells that can remain metabolically active and may affect other cells through a "senescence-associated secretory phenotype" (SASP)[136] that can secrete inflammatory mediators and has been suggested to promote a pro-inflammatory state that may be associated with age-related chronic diseases and in turn multiple chronic diseases (multimorbidity).[112,136] Multiple internal and external signals can stimulate a cell to become senescent. External factors include metabolic signals (e.g. high levels of glucose), hypoxia and reactive oxygen species (ROS), while examples of internal factors are telomeric dysfunction, DNA damage and mitochondrial dysfunction.[137]

Senescent cells have been noted to accumulate in multiple chronic diseases such as diabetes and cardiovascular disease.[138,139]

Finally, stem cell exhaustion (depletion of stem cells numbers and the regeneration potential of tissues)[113] is a typical attribute of aging 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, then 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, once again illustrating the interplay and connections between the various “hallmarks of aging”. Stem cell exhaustion has been linked with development of chronic lung diseases like chronic obstructive pulmonary disease.[140]

A recent study explored the relationship, if any, between the aforementioned hallmarks of ageing and multiple age related diseases through text mining the literature, genome wide association studies and examination of electronic health records.[141] The researchers found that five of the ageing hallmarks (altered intercellular communication; mitochondrial dysfunction; deregulated nutrient sensing; cellular senescence; and stem cell exhaustion) occurred more often in multimorbidity across different age groups.[141]

There is increasing interest in the “geroscience hypothesis” which suggest that health can be enhanced by focusing on the mechanisms of ageing rather than single diseases and there are a growing number of studies looking at “geroscience-informed therapeutic approaches”[114] aiming to reduce or slow effects of or development of multimorbidity and it seems likely that research in these domains will intensify in the years to come.

We remain uncertain about whether the “hallmarks of ageing” work individually, together or interactively and only some have been validated in clinical studies.[142] Biomarker studies have suggested that the build-up of senescent cells affects allostasis, the adaptive physiological response activated when homeostasis is disrupted during acute stress.[143] This can result 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] that can be assessed by measuring multi-system biomarkers which are an indicator of multi-system physiological dysregulation. Allostatic load is a measure of the cumulative effect of chronic stress and likely also life events (as described in the socioeconomic, psychosocial and behavioural determinants section). It has been associated with a range of health conditions spanning diabetes, 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]

While our understanding of the “hallmarks of ageing” and their relationship with multimorbidity is currently limited, there are some biomarkers, especially those related to oxidative stress, which may be markers of some of these mechanisms of ageing and inflammation. These biomarkers are presented in the section on diagnosis, screening and prevention, and may have future potential.

Socioeconomic, psychosocial and behavioral determinants

Socioeconomic, psychosocial and behavioral determinants of health have all been shown to be associated with development of multimorbidity.[110] Socioeconomic deprivation, measured by household income, total household wealth or household area level[146], and lower education level have been associated with higher multimorbidity prevalence [75,146–149] and with the development of multimorbidity at a younger age.[19] The converse may apply in LMICs where there has been some work to suggest that higher income may be associated with multimorbidity.[75] A systematic review of 24 studies examining the relationship between socioeconomic deprivation, education level, or income showed that lower versus higher education level was associated with a 64% increased risk of multimorbidity,[75] while another review including 42 studies showed that multimorbidity was over four times more likely in people with the lowest incomes compared to those with the highest incomes.[146] Others have shown that multimorbidity occurs a full decade earlier in those from more socioeconomically deprived backgrounds.[19]

A growing range of lifestyle factors including smoking status, alcohol intake, decreased physical activity, and diet have all been associated with development of multimorbidity.[150,151] However, findings are mixed, and it remains unclear which factors are the most important with a great deal of heterogeneity in the literature, in relation to method of multimorbidity ascertainment and lifestyle factors assessed, making it difficult to draw firm conclusions. A Canadian study involving 1196 participants examined the association between common lifestyle factors such as smoking, alcohol, physical activity and fruit and vegetable consumption and found smoking to be the most important factor but also reported that the presence of combinations of unhealthy lifestyles (e.g. smoking and physical inactivity) increased the risk of multimorbidity.[152] This study did not show an increased risk of multimorbidity with physical inactivity, yet others have, such as a study using data from the China Health and Retirement Longitudinal Study which showed that low levels of physical activity were associated with a 45% increased risk of multimorbidity.[153] While a recent Australian study involving 53,867 participants (45–64 years) from the 45 and Up Study who were free of eleven predefined chronic conditions at baseline (2006–2009) showed that the top multimorbidity predictors were smoking (in men), and age, body mass index, chicken and red meat intake in both sexes, but that other behavioural factors like physical activity, alcohol consumption and sleep duration were also important.[154] A study from India of 699,686 women showed that women who smoked or chewed tobacco had 87% higher risk of multimorbidity and those who consumed alcohol had a 18% greater risk.[155] Factors such as smoking are known to promote cellular senescence through inflammatory effects, oxidative stress and DNA damage[156], while exercise is known to prevent cellular senescence, [156,157] thus highlighting the likely interplay of socioeconomic, psychosocial and behavioral determinants with the “hallmarks of aging”.

In recent years, interest in “emerging lifestyle factors” as potentially preventable factors in the development of chronic illness, such as cardiovascular and metabolic disease, has increased,[158,159] and also their role in development of multimorbidity. Emerging lifestyle factors include issues such as television viewing time[160] or sedentary behaviour, sleep duration[161] (both too much and too little), and levels of social participation (e.g.

loneliness).[110,158,162 153,163,164] Short sleep duration has been associated with extent of multimorbidity in 1,508 respondents of the European Health Examination Survey.[164] Data from the US 2005–2006 National Health and Nutrition Examination Survey (NHANES) has suggested 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[166] and social isolation have been suggested as being associated with multimorbidity. However, a systematic review exploring these matters identified only 8 studies that examined these issues and reported that while cross sectional and longitudinal studies suggested an association between loneliness and multimorbidity the evidence for social isolation was under researched.[166] The mechanisms underpinning many of these associations remain uncertain with some suggesting, for example, that the relationship between multimorbidity and sleep disturbance could be bidirectional.[167] While others have suggested that sleep disturbance could be a surrogate measure of loss of resilience or multisystem homeostatic dysregulation.[163] It has been suggested that social relationships may moderate against the effects of stress on health and wellbeing through what has been referred to as the stress buffering hypothesis.[168]

Adverse childhood experiences (ACEs) [169,170] have also been shown to be associated with increased severity and complexity of multimorbidity.[170] There are a range of hypotheses in the literature regarding potential underlying mechanisms.[171] These range from suggestions that persistent stress secondary to ACEs might result in chronic activation of the hypothalamic-pituitary-adrenal axis, leading to increased allostatic load. Other work has proposed that ACEs are associated with increased cortisol levels and chronic inflammation[172] or with DNA methylation in certain genes and with telomere length shortening, possibly increasing the risk of conditions of aging[173,174].

Lacking control over one’s life[148] has also been implicated in development of multimorbidity. Lack of control may exacerbate anxiety promoting a chronic stress response and increase the risk of unhealthy behaviours such as smoking.[110] The interplay of “stress” and multimorbidity has only just begun to be explored and has been associated with increased hospitalizations and mortality.[175,176] It has been suggested that stress could be a modifiable risk factor, particularly as it might be associated with decisions about unhealthy behaviours—but its effects may also be explained through consideration of implications of its effects on allostatic load as discussed in the preceding section on ageing and inflammation.[177]

Some have posited that the aforementioned “social hallmarks of ageing” should be integrated with the work on biology of ageing to enhance our understanding of the factors associated with human ageing and the development of multimorbidity.[178]

While there is growing evidence o the f social determinants of multimorbidity, more research is required to help us understand which factors or combination of factors are the most important to target. A key gap relates to our knowledge of determinants of different multimorbidity patterns, particularly with reference to LMICs[179]

Medication-related mechanisms

Medications and polypharmacy may also contribute to development of multimorbidity. A number of medications are associated with increased risk of diabetes and dyslipidaemia, e.g. antipsychotics.[181] Similarly, medications with anticholinergic effects have been associated with increased risk of cardiovascular events and cognitive impairment/dementia.[170]

In practical terms what this means is that patients who are prescribed medications for specific single conditions, for example, oral steroids for polymyalgia rheumatica, may end up developing additional chronic conditions, such as diabetes, cataracts, and osteoporosis, as a direct consequence of a medication correctly prescribed for the initial condition. 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 adding to the extent of multimorbidity. For example, co-prescription of Non-Steroidal Anti-inflammatory medication for arthritis and SSRI antidepressants for depression can result in gastrointestinal bleeding.

There are clearly many inter-relationships between mechanisms related to 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 development of multimorbidity. Mechanisms underpinning development of multimorbidity are frequently inter-related 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 which is significant or severe from a patient or clinician perspective, and which therefore requires an approach to care which is more than simply optimising care for every individual condition present.

Diagnosis in clinical practice

Since multimorbidity is the coexistence of two chronic conditions, ‘diagnosing’ multimorbidity (in the sense of identifying it is present) in clinical practice is rarely a problem because the clinician and patient usually agree which conditions are currently active or relevant. What is more difficult is deciding (or diagnosing) when multimorbidity is sufficiently severe or impactful that it requires specific attention, or that single-disease management needs adapting including not following single-disease guidelines or shifting to more palliative approaches to care.[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,[182] if a patient requests such care or if they have any of a number of markers: 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. Frailty is a

state of reduced resilience and increased vulnerability to stressors secondary to deterioration in function across several physiological systems.[183] Although frailty and multimorbidity are highly associated,[46,184] they are not the same. While 72% of individuals with frailty have multimorbidity, only 16% of individuals with multimorbidity have frailty,[185] with both being associated with lower socioeconomic status and neither being restricted to older adults.[19,184,187] However, when frailty and multimorbidity co-exist, there is an increased risk of mortality,[184] even after adjusting for the number of conditions, sociodemographic factors and lifestyle. Therefore, it is important to identify pre-frailty and frailty in patients with multimorbidity to prevent frailty progression, reduce the risk of adverse outcomes and optimize treatment.

NICE recommended that clinicians can screen for patients who might require such an approach to care using electronic health records (EHRs), or opportunistically identify patients during routine care. The recommended screening tools for use in EHRs were UK-validated tools predicting emergency hospital admission and identifying polypharmacy, but the same principles apply internationally.

Opportunistically, key markers are consideration of condition burden, treatment burden, and frailty (where 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 well correlated with gold-standard frailty assessment and useful screening tools).[182] Condition burden (the impact of the conditions on an individual, e.g. a pain score) and treatment burden (the impact of the treatment and care for those conditions) can only be assessed by asking the patient and/or carer about their experience of health and care.[182] Clinicians should agree with the patient whether condition burden, treatment burden or frailty require a different approach rather than existing, usually disease-focused care (Figure 3). However, NICE did not consider that very intensive evaluation such as that carried out in Comprehensive Geriatric Assessment (CGA) could be recommended for diagnosis of problematic multimorbidity in all patients because it is too resource-intensive to be used routinely. Instead, NICE considered CGA to be a combined assessment and intervention, and it is discussed further in the management section.

There is less specific guidance on diagnosis or screening in the other available guidance documents internationally, which tend to have a starting point from the recognition that the patient has multiple conditions. However, other guidelines similarly recommend agreement with the patient about the most important outcomes or priorities to the patient, which are sometimes, but not always, tied to specific conditions.[188–190] Such a patient-centred approach is critical to ensuring that care is tailored to the individual. The range of personal circumstances which are important to the individual and relevant to care will often go beyond ‘conditions’ defined by clinical diagnosis, potentially including consideration of broader issues that impact on 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.[101,102]

However, there are combinations of conditions which may not be immediately problematic for the individual patient (e.g. hypertension, hyperlipidemia, obesity, impaired glucose

tolerance and previous myocardial infarction without current symptoms) but which carry significant future risk that may need to be managed. 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. Predicting poor health outcomes and limited life expectancy is, therefore, an important parallel strategy in identifying patients with multimorbidity who need a different approach to care, in contrast to the more common disease or specialty-oriented models of care, which have been developed across most health systems and are reflected in condition-specific clinical guidelines. A practical example of the diagnostic and management challenges facing clinicians occurs in a patient with both heart disease and chronic respiratory disease, who is experiencing breathlessness and fatigue. A generalist approach is needed to tease out the likely underlying cause of these symptoms, which could relate to either condition and/or be compounded by co-existing depression and anxiety. Similarly, a combination of diabetes, heart disease and arthritis is relatively common but pain caused by active arthritis may limit the patient's capacity to exercise and maintain a healthy body weight, thus impacting on their diabetes and heart disease. Even in the face of poor diabetes control, pain management may therefore be agreed to be the immediate priority. This approach which focuses on improving outcomes prioritised by the patient and improving experience of care, rather than focusing on the condition count parallels a shift in thinking that has occurred in the context of polypharmacy away from considering the total number of medications (often used in research studies) towards focusing on appropriate polypharmacy from a patient perspective.[191,192]

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 which 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, but the core of diagnosis is 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

A range of physiological and serum biomarkers may be useful to help us better understand determinants of and prognosis in people with multimorbidity and could potentially be used to identify individuals at risk. Several physiological biomarkers have been associated with development of multimorbidity,[193] including blood pressure, hand grip strength,[194–196] waist-hip ratio and body mass index,[197 150,193, 198] and lung function indices, such as reduced FEV1.[199] There is some evidence linking a range of serum biomarkers with multimorbidity including cystatin C (Cyst-C); C-reactive protein (CRP); lipoprotein (Lp); dehydroepiandrosterone sulfate (DHEAS); and interleukin 6 (IL-6)[200], serum glutathione,[201] diacron reactive oxygen metabolites (D-ROMS) and HBa1c[202]. This is a rapidly evolving area with the potential for new biomarkers to be identified. For example, a recent study reported that high total serum homocysteine (tHcy) and low methionine (Met) levels were associated with more rapid cardiovascular multimorbidity development.[203] While for biomarkers such as Vitamin D the literature remains mixed,.[204,205]

However, there is currently no clear evidence to support the use of physiological and serum biomarkers to target treatments or interventions in multimorbidity. Two systematic reviews have highlighted that there is insufficient literature on this topic[193,200] and suggested that there is an urgent need for additional good quality studies to aid understanding and inform targeting of potential future interventions (e.g. 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 need to cover decades, given interventions would need to include supports for physical activity, healthy eating, and other behaviors with long term horizons to benefit. Preventive measures against multimorbidity are connected to the complex effect of psychosocial and behavioral factors, including the broad social determinants of health perspective described in the Mechanisms section. The effect of a healthy lifestyle (engaging in physical activity, not smoking, eating five portions of fruits and vegetables per day and not consuming alcohol in excess) appears to be associated with an increased life expectancy regardless of multimorbidity.[206] Given that physical inactivity is a risk factor for a multitude of chronic conditions, this is an area of particular relevance in terms of preventing multimorbidity in all age groups,[207] especially individuals from socioeconomically deprived backgrounds who have been shown to be more vulnerable to unhealthy lifestyle factors,[206] particularly given the repercussions of deprivation across the entire lifespan on an individual.

Population level and structural changes will be necessary to effectively prevent multimorbidity and to limit its progression. These could focus on influencing the determinants of health across communities aiming to reduce the effects of a given risk factor across the whole population,[208–210] as shown for hypertension,[211] smoking,[212] as well as sugar taxes and food labelling to counter obesity.[213,214] As another example, structural racism and economic barriers, evident in disparities in educational systems, social communities and built environments, and the stress resulting from structural racism may have effects that individual-focused prevention and intervention cannot overcome.[215] Furthermore, the early determinants of multimorbidity, including socioeconomic deprivation and lower education level, outlined in the Mechanisms section, and relevant for both HICs and LMICs,[68] could lead to wider prevention efforts embracing life-course approaches[216] and social determinants of health,[217] particularly poverty reduction.

Management

Most clinical practice guidelines and organization of health care focus on managing single diseases.[218] Cumulatively implementing a single-disease approach for patients with multimorbidity leads to care that is often impractical or even harmful for people with multimorbidity,[20,23,188,219,220] especially as the number and complexity of conditions increase. Management of multimorbidity requires an appropriate balance between a single-disease focus and multimorbidity care. Multimorbidity requires care that is both patient-

centred and family-centred, prioritizing what matters most to the individual and their carers, ensuring care that is effectively coordinated and minimally disruptive, and aligns with patient values and priorities.[221] It is essential to recognize the social, family and care context in which health care activities are managed, decisions are made, and care is experienced, particularly for those with more complex health needs. The need for an individualised, 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 potential curative to palliative approaches. This paradigm shift towards a multimorbidity approach to care away from a single condition focused approach 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 their 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. While there are increasing numbers of studies examining interventions for multimorbidity, there is still limited evidence to support any specific approach. A 2016 Cochrane review (corrected and re-published in 2021) included studies targeting both multimorbidity (8 studies) and comorbidity (8 studies).[222] It suggested that interventions targeting comorbidity or common clusters of conditions that include depression may improve mental health outcomes but there is 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, to address both conditions, an intervention for people with diabetes 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 have been reported to improve depression outcomes.[97] Interventions in comorbidity that have targeted depression[223] or dementia care,[224] have had less focus on the overall impact in other comorbid conditions and multimorbidity.

A recent 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 randomised controlled trials (RCTs).[225] The majority of these trials included older patients, with a mean age >70 years reported in 11 of the 16 studies. The majority also targeted those with at least three conditions and reported complex, multifaceted interventions provided by a range of disciplines, based in established primary care systems in HICs. Interventions targeting multimorbidity need to be focused, yet generic, and, in this systematic review, they were divided broadly into three groups: care coordination combined with self-management support, self-management support alone and medicines management. While there was no clear evidence of effectiveness for any specific intervention type, there was a suggestion that a combination of care coordination and self-management support may improve the patient experience of care. Another focus of multimorbidity trials has been on enhancing self-management support; however, despite 12 of the 16 RCTs having this aim, there was no clear evidence of effect on self-management

or health behaviours.[222] CGA is an intervention that could be considered in older patients with multimorbidity. It involves specialist multidisciplinary assessment and care to address bio-psychosocial needs and there is evidence that it improves outcomes in hospitalised patients.[226] There is less clear evidence of effect on outcomes in primary care and community settings and it is a very resource intensive intervention.[227]

Four of the 16 RCTs in the 2021 multimorbidity systematic review reported on medicines management type interventions with mixed effects, which may have related to inappropriate patients being targeted, i.e those with little room for improvement. A more recently published RCT from Ireland also reported on a medicines management intervention in multimorbidity, targeting older adults taking at least 15 regular medicines and found a small but significant drop in the number of medicines (incidence rate ratio 0.95; 95% CI 0.899-0.999, p=0.045), though no significant effect on the appropriateness of medicines.[229]

Most existing trials have focused on older people but it is important to address the needs of younger individuals as well, as they will have different challenges, often having to work as well as manage their multimorbidity, particularly those in the poorest socioeconomic groups, who develop multimorbidity earlier.[19] The CarePlus study in Scotland specifically targeted socioeconomically disadvantaged adults with multimorbidity with a multi-level intervention supporting practitioners and patients.[230] which was cost-effective within recommended UK funding thresholds, though this finding needs to be replicated in larger trials in other settings. The challenges that have arisen in existing trials of multimorbidity interventions are presented in Table 1. Of note, interventions for multimorbidity have mostly been conceived within well-established healthcare delivery structures with strong primary care networks in HICs and there has been limited development of interventions in LMICs.[46]

Evidence-based Clinical Guidelines

The limited available evidence has created a challenge for clinical guideline development though a small number of these have been developed internationally.[182,190,231] The consensus across these guidelines is presented in Box 2.[232]

The general lack of evidence as a basis of guideline recommendations has led to a reliance on consensus.[232] While the evidence that multimorbidity care offers major advantages over parallel care for single chronic conditions remains weak and inconsistent, qualitative research with patients and practitioners highlights the need for change. It emphasizes the challenges people face managing multiple conditions in fragmented medical systems that have largely been designed around single chronic condition care and have not prioritized care coordination.[233,234] The NICE Guidance on Multimorbidity calls for a re-orientation of care to address multimorbidity and highlights the importance of recognizing and addressing treatment burden for patients.[102,182]

Managing medicines is another key part of managing multimorbidity and features as a key element of existing clinical guidelines for multimorbidity with an emphasis on targeting those with complex polypharmacy, that is, those taking ≥10 medicines regularly. Medicines management in multimorbidity tends to include 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 reported impact on validated measures of appropriate prescribing, but there is less clear evidence of effect on clinical outcomes and well-being.[191,192,235,236] Given the overlap between multimorbidity and polypharmacy, clinical guidelines for each often overlap.[232] A systematic review identified eight guidelines, four for polypharmacy and four for multimorbidity with overlapping principles and recommendations including targeting those in need of intervention, holistic assessments of conditions, physiological status (frailty), medicines, patient priorities, individualized management and monitoring plans.[232]

Multimorbidity and polypharmacy guidelines differ from single disease-oriented guidelines primarily in their generic focus and wider applicability. However, clinicians will still likely use elements of single condition guidelines based on patient priorities, risk factors and symptoms. However, accounting for multimorbidity in single-disease guidelines can also be considered a key challenge. It is well recognised that randomised clinical trials (RCTs) routinely exclude many patients with the condition for which treatment is being evaluated, notably those who are older, and those with multimorbidity, co-prescribing or frailty.[237–239] A systematic review of 50 studies reporting on trial inclusion and exclusion criteria in 305 trials covering 31 physical conditions found that more than half of the trials excluded more than half of patients with the conditions studied.[240] Even when trials are specifically conducted in older people, participants are likely to significantly differ from the clinical population[241] because of explicit and implicit exclusion criteria or biases in trial recruitment (eg exclusion of housebound individuals and those in care homes).[242] Therefore, these issues around generalizability suggest that even if treatment benefits found in trials are generally applicable, net benefit in excluded populations may differ because of varying baseline risk[243] or increased treatment harms.[244]

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 very explicitly accounts for indirectness of evidence, which refers to the applicability of the evidence in terms of populations included and differences in trial design, interventions and outcomes.[245] Furthermore, a finding of serious limitations relating to indirectness weakens the guideline recommendation for all patients, which may unfairly downgrade strong evidence for the population actually studied in the trial. The implication is that rather than weakening a global recommendation, single-disease guideline developers should make nuanced recommendations that draw on epidemiological data about trial-excluded populations, which 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, including nominating and scoping the topic, commissioning the work group, refining key questions, ranking importance of outcomes, conducting systematic reviews, assessing quality of evidence and applicability, summarizing benefits and harms and formulating recommendations and grading their strength is necessary in order to frame questions so that indirectness to populations with multimorbidity can be identified.[246]

Both intervention studies and clinical guidelines need to be able to identify and target people who are experiencing significant treatment burden and who are in danger of being

overwhelmed by the workload of self-management, which can result in poor adherence and adverse outcomes.[101,102,247] Patient reported measures of treatment burden now exist[248–250] but their ability to predict adverse outcomes remains uncertain. There is increasing emphasis on understanding factors that influence an individual's capacity to self-manage which can vary over time as illnesses accumulate and personal circumstances may change (Figure 4).[101,102,247,251,252] These 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 summarised in Box 3 and global barriers and opportunities for multimorbidity management are summarised in Box 4.

Outcomes of care

Outcomes of care can be considered both from a care delivery and a research perspective. In clinical practice, the outcomes to prioritise can be decided between the patient, their carers and clinicians with identification of outcomes, which matter most to the patient. In research, there is a need to systematize and harmonize the use of outcomes to be able 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.[253] Health Related Quality of Life (covered more specifically in a later section), mental health and mortality, are considered to be essential core outcomes in multimorbidity research. The other 17 core outcomes were grouped across the domains of patient-reported impacts 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 electronic health records,[254] and recent[255] and ongoing work[256] aims to identify core outcomes in trials of prevention and treatment of multimorbidity in LMICs. While cost outcomes of care are important to patients and to health systems, there has been limited consideration of cost-effectiveness in trials of multimorbidity interventions and existing studies have focused on health system rather than patient costs or financial burden[222].

From the patient perspective, managing multimorbidity is doubly challenging, as they have to deal with the burden of illness and also the burden of treatment.[257,258] Treatment burden can be measured as an outcome of care[250] in both clinical practice and research as new interventions should reduce rather than add to treatment burden. There is evidence that treatment burden often affects the lives of caregivers as well, and poses a pervasive challenge for health care providers and systems alike.[17,259–268] Further, the psychological distress experienced by patients with problematic multimorbidity and their caregivers may lead to fragmented and ruptured continuity of care and, thus, complicate management.[11,269]

Multimorbidity outcomes include some promising indices of multimorbidity developed to predict mortality, health expenditures and physical functioning.[270–275] but there are few formal prediction tools,[182] 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 on tools intended for 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 on how patients live with multimorbidity while availing of preventive, curative and supportive services.[276] Work undertaken in Sub Saharan Africa examined the utility of theoretical frameworks to aid understanding of chronic disease management and multimorbidity issues, such as the cumulative complexity model and burden of treatment theory[37], in these LMIC contexts.[277] This preliminary work suggests that these frameworks developed in HICs are generally applicable to the LMIC context but that there are some key differences and the absence 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 wellbeing could optimize patient-centric care delivery in these resource constraint settings.[77]

Quality of Life

Management of multimorbidity aims to improve patient outcomes. Health Related Quality of Life, is considered to be essential core outcomes in multimorbidity research. Many observational studies have consistently shown that multimorbidity is associated with poor HRQoL and psychological well-being across the life span.[14,82,295–297] Some studies suggest that this negative association of multimorbidity with HRQoL is stronger in younger subjects,[298] which some have suggested may be due to the accompanying biographical disruptions, a sociological concept referring to a break in social and cultural experience and self-identity, in younger people.[252] Others indicate that in older people there is more of a deterioration in well-being,[82] but a less steep reduction in HRQoL as number of conditions increases.[297] In subgroups based on the number of conditions, a higher number of conditions is associated with greater reductions in HRQoL,[298] and clusters of multimorbidity including both mental and physical conditions are also associated with poorer wellbeing.[82] Grouping individuals based on socioeconomic status found that higher deprivation is associated with a more marked decrease in HRQoL with multimorbidity.[298] The association between HRQoL and multimorbidity is stronger when disease severity is taken into account.[296,299] Furthermore, those with less capacity to cope may be less likely to benefit from treatments in terms of improved well-being and HRQoL.

Outlook

Multimorbidity is a major global health challenge that is increasing in prevalence and evidence is needed, particularly in LMIC, to support effective management and improve patient outcomes (see box 6 for research priorities). Most care for multimorbidity will take place in and be coordinated from primary care, home-based and ambulatory settings and these need to be reconfigured to address both acute episodic illnesses and chronic care, ensuring patient- and family-centred approaches that reduce rather than worsen treatment burden. Specialty care will at times be needed for those with more complex health needs and health systems need better integration of primary and specialty care and improved

communication across the interface. There is an urgent need to move away from siloed care for individual conditions to improve quality of care and safety.

Evidence supporting future multimorbidity management is limited; however, given that multimorbidity has been described as a key challenge for global health systems,[46] clinicians, health managers and policy makers need guidance on how to develop interventions. Going forward, 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 the need to target the appropriate patients and address their priorities, including their caregivers; to support self-management and healthy behaviours; and to deliver 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 and includes various techniques and tools: action plans, goal-setting worksheets, problem-solving to support patients using motivational interviewing, reflective listening, and selection of effective educational material. Motivational interviewing is a critical component given the relationship between the accumulation of unhealthy behaviours and multimorbidity.[152] Of note, the concept of self-management may not entirely match with the lived experience of people with multimorbidity: older adults frequently receive care from family or friends and are more likely to do so as health worsens. While self-management support has the potential to improve outcomes and reduce health care utilization, evidence underpinning its effect in multimorbidity is limited.[222] However, self-management remains a key area for consideration in the evaluation of interventions in chronic diseases.[300]

Healthy behaviours are often a focus of self-management support, for example, improving physical activity and participating in exercise therapy. Exercise has an important health impact across a range of body systems and has been shown to reduce blood pressure, improve pulmonary capacity and oxygen flow, stimulate the metabolism, reduce inflammation, reduce blood glucose in diabetes, reduce constipation, reduce the risk of thrombosis and improve muscle strength, mood and mental health.[301] A meta-analysis suggests that exercise therapy is safe and effective in improving physical and psychosocial health in people with multimorbidity.[302] Given its demonstrated clinical effect on at least 26 chronic conditions,[301] it is particularly promising both for treatment but also for prevention, especially when combined with other self-management supports. An ongoing Horizon 2020 project called MOBILIZE is aimed at investigating the effectiveness of exercise therapy and self-management support for people with multimorbidity (https://www.mobilize-project.dk/). Other health behaviours also need to be considered when optimizing the comprehensive care of patients with multimorbidity: healthy food, avoidance of smoking and responsible alcohol consumption, although, as highlighted earlier, 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 will be essential,[303] and even those targeting individual behaviour will need to take account of potential “prevention burden”, i.e. shifting of responsibility for prevention to individuals, if they are to address health inequality.[304]

While multimorbidity is associated with ageing, we have outlined how, in absolute terms there are more middle-aged people living with multimorbidity and the strong association between multimorbidity and socioeconomic disadvantage, particularly over the life course and for complex combinations of physical and mental health problems. More longitudinal studies are needed that examine multifactorial pathways and disease trajectories across age, sex, gender, racial and socioeconomic groups and the utility and clinical importance of multimorbidity clusters. Especially given the experience of the COVID-19 pandemic, a syndemic approach (i.e. considering interactions between conditions and factors affecting the interactions) is needed to address the shared social determinants of multimorbidity.[33,305]

There is limited evidence regarding effective interventions in multimorbidity, particularly from LMICs. However, there are opportunities to engage in more innovative approaches including those that incorporate digital health solutions. Currently there are concerns about an increasing divide in digital health literacy which is more common in older[306] and in poorer people along with those with learning and other disabilities or those with language barriers.[307,308] Going forward, following experiences of remote care delivery during the COVID-19 pandemic, interventions and care delivery will need to consider the potential of digital health/AI to lessen treatment burden and/or enhance patient capacity to self-manage and negotiate healthcare systems. However, such interventions will need to consider how to prevent the increasing use of digital health from contributing to widening health inequality. Although only in its infancy, personalized treatment, or precision medicine, targeted to the needs of the individual e.g. based on the determinants in Figure 2 holds promise in people with multimorbidity and might lead to health advantages by improving the effectiveness of, and reducing the number of adverse events from, various interventions.[309] We also need to consider how to help the increasing population of people with multimorbidity and concomitant cognitive impairments (e.g. memory problems associated with heart failure or dementia) and address challenges faced by people with multimorbidity that include invisible disabilities like chronic pain (e.g. musculoskeletal pain) and fatigue (associated with many chronic conditions like rheumatoid arthritis, heart failure, multiple sclerosis, depression etc). We need more trials to build an evidence base supporting multimorbidity and clinical guidelines. Current evidence suggests that co-design of interventions with patients, carers and clinicians has been lacking, though may offer potential to improve intervention effectiveness.[310] Trials of interventions directed towards conditions sharing common characteristics and risk factors are also needed, particularly in terms of prevention of further disability, frailty and worsening health outcomes.

Given the complexity of multimorbidity management, incorporating interdisciplinary care into clinical practice makes sense. Interdisciplinary teams have been central to interventions published to date.[222] New models of integrated care being developed in many countries include teams of allied professionals joining doctor-led practices.[311–313] There are a few elements that can be considered to enhance teamwork and that may increase the likelihood of effective interventions. They are summarized in the Patient-Centered Innovation for persons with Multimorbidity or PACE in MM evidence-informed framework[314], which highlights the 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 healthcare 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[315] by identifying conditions under which productive interactions between the patient and the interdisciplinary teams may occur. There is also increasing focus on "Minimally Disruptive Medicine,"[219] which similarly calls for clinicians to establish the burden of treatment that patients are experiencing, taking account of factors that will influence capacity to self-manage; encourages a focus on care co-ordination; and prioritization from the patient perspective. Social prescribing is increasingly being adopted and aligns well with a patient-centred approach to multimorbidity. It is a process through which clinicians can refer patients for community supports from local, non-clinical services.[316] 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.[317] One potential model has been the use of practice-based link workers who implement social prescribing and there are two small trials exploring its impact in multimorbidity.[318,319]

Addressing the challenge of multimorbidity facing health systems will require a resilient health workforce and processes to tackle the interplay of health system emergency, e.g. pandemics and health impact 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, healthcare is still predominantly organised around single conditions and reimbursement models often reinforce this focus. We urgently need to change our current approaches and structures to enable a re-balancing between generalism and specialism in healthcare systems. All aspects of healthcare delivery need this re-orientation in systems from training of clinicians, policies and guidelines around clinical care delivery, the places where healthcare is delivered to incorporate home- and community-based care, and reimbursement models that recognise complexity. While we need to retain elements of specialty care delivery, we particularly need more generalism, 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 not once, but throughout the multiple ongoing interactions between patients and the health system, i.e. the chronicity of care needs to be respectful, responsive, meaningful and effective. Closing the physical-mental health divide in healthcare systems is also critical for managing complex physical-mental health multimorbidity. This will require both physical and mental health specialists taking at least some responsibility for the other, for example cardiologists thinking about depression even if someone else treats it; and psychiatrists thinking about smoking and cardiovascular risk, particularly for those with enduring serious mental illness. We need clinicians who are able to work effectively across the healthcare divide. We also need to focus on promoting "relationships", both between practitioners, patient, and caregivers and between health professionals to enhance care coordination and lessen fragmentation of care. 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.[320,321] In conclusion, to tackle the world-wide and increasing challenge of multimorbidity we will need a framework for multimorbidity literacy for policy makers, practitioners and

populations. This needs to incorporate a preventive approach both for the individual patient living with multimorbidity but also one that deals with the structural determinants of multimorbidity across the life course.

Acknowledgements

STS is currently funded by a program grant from Region Zealand (Exercise First), and two grants from the European Union's Horizon 2020 research and innovation program, one from the European Research Council (MOBILIZE, grant agreement No 801790) and the other under grant agreement No 945377 (ESCAPE).

MF was funded by the Canadian Institutes of Health Research.

BPN receives research grants from the Research Support Foundation of Rio Grande do Sul, Brazil (grants 19/2551-0001231-4; 19/2551-0001704-9; and 21/2551-0000066-0 - *Programa Pesquisa para o SUS: gestão compartilhada em saúde - PPSUS)* related to projects on multimorbidity.

CMB is funded by the National Institutes of Health, K24 AG056578, 1P30AG066587 and R24 AG064025.

JJM acknowledges having received support from the Alliance for Health Policy and Systems Research (HQHSR1206660), Biotechnology and Biological Sciences Research Council (BB/T009004/1), Bernard Lown Scholars in Cardiovascular Health Program at Harvard T.H. Chan School of Public Health (BLSCHP-1902), Bloomberg Philanthropies (via University of North Carolina at Chapel Hill School of Public Health), FONDECYT via CIENCIACTIVA/CONCYTEC, British Council, British Embassy and the Newton-Paulet Fund (223-2018, 224-2018), DFID/MRC/Wellcome Global Health Trials (MR/M007405/1), Fogarty International Center (R21TW009982, D71TW010877, R21TW011740), Grand Challenges Canada (0335-04), International Development Research Center Canada (IDRC 106887, 108167), Inter-American Institute for Global Change Research (IAI CRN3036), Medical Research Council (MR/P008984/1, MR/P024408/1, MR/P02386X/1), National Cancer Institute (1P20CA217231), National Heart, Lung and Blood Institute (HHSN268200900033C, 5U01HL114180, 1UM1HL134590), National Institute of Mental Health (1U19MH098780), Swiss National Science Foundation (40P740-160366), UKRI GCRF/Newton Fund (EP/V043102/1), Wellcome (074833/Z/04/Z, 093541/Z/10/Z, 103994/Z/14/Z, 107435/Z/15/Z, 205177/Z/16/Z, 214185/Z/18/Z, 218743/Z/19/Z) and the World Diabetes Foundation (WDF15-1224).

BG was supported by funded by Legal and General PLC (research grant to establish the independent Advanced Care Research Centre at University of Edinburgh).

We would like to acknowledge Mr James Larkin, HRB Collaborative Doctoral Award PhD Scholar (HRB CDA-2013-008, Prof Susan Smith), who supported us in the preparation of manuscript by retrieving, organizing and inserting references via EndNote.

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Box 1

Multimorbidity definitions

World Health Organization [49]

'…the coexistence of two or more chronic conditions in the same individual…'

Academy of Medical Sciences [46]

"The co-existence 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.

NICE guideline [182]

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 [60] *citing definitions used in systematic reviews*

- 'The co-occurrence of multiple chronic or acute diseases and medical conditions in one person'[336]
- 'The coexistence of two or more chronic diseases in the same individual' '[337]
- 'The co-occurrence of multiple diseases or medical conditions within 1 person'.[61]
- '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.'[338]
- 'Comorbidity may be defined as the total burden of illnesses unrelated to the principal diagnosis'[63]

Complex multimorbidity [53,64]

Complex multimorbidity' is the "co-occurrence of three or more chronic conditions affecting three or more different body systems within one person."

It is still unclear whether this definition can identify patients with greater complexity of care and worse health, but it can be expected that additional information around disease severity and socioeconomic/psychological stressors would be important.

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Box 2

Summary of key themes in clinical guidelines

1	Need to target the 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 care givers and medication review
3	Consider co-existing depression which is more prevalent in multimorbidity and 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, elicit views of family and carers where appropriate
5	Individualised 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

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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 (10 or more medicines)
- High healthcare utilisation
- Social vulnerability

Step 2:

Plan time for a multimorbidity assessment

- Consider who is best place 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 minimise 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 can also be completed quickly assessing gait speed with with more than 5 seconds to walk 4 metres indicating frailty (ref NICE guidance)

➡Consider **physical capacity and daily functioning** at all ages and refer to allied health colleagues such as physiotherapist or 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 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 2 questions[339]:

- 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, i.e referral to non-medical community based supports, if available.

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Box 4

Global Barriers and Opportunities for Multimorbidity Management

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 resources to support self-management (e.g. family support, employment and community support), environment (e.g. living in rural areas far from health services or in residing in unsafe areas that are a barrier to outdoor physical activity); or inadequacy of financial protection to meet healthcare or related costs.

System level barriers include availability, appropriateness and access to services.[278,279] In most health systems, consultation times are limited and patients and providers can be frustrated that issues were not addressed adequately.[233]

Personal and health system barriers can combine, for example patients with multimorbidity often experience functional limitations, which restrict their mobility and ability to access treatment.

LMICs barriers are expected to be augmented and amplified in settings, characterized by weak, fragmented, and acute-oriented healthcare delivery systems.[280–282] 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 like care coordination[222] often deployed in HICs, may be restricted in LMIC settings with fragmented health services or non-existent chronic care, but this can also be a challenge in HICs lacking universal access to healthcare free at point of delivery. In Peru, more than 90% of care for people with disabilities relies on household relatives, largely women.[283]

There are ***opportunities in LMICs*** to leverage innovative delivery channels, such as technology-enabled tools or mHealth for physical and mental chronic conditions[223,285–287] and the utilization of non-healthcare delivery settings such as barbershops to manage risk factors like hypertension[288] and places of religious worship and informal social networks to promote healthy lifestyles.[289–291] These can be aided by co-production approaches, which are likely to yield interventions responsive to people's preferences,[292,293] 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.[224,284] As with other LMIC challenges, 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.[294]

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Box 5

17 Core outcomes in multimorbidity.[253]

Highest-scoring outcomes (most important)
Health-related quality of life
Mental health
Mortality
Patient-reported impacts and behaviors
Treatment burden
Self-rated health
Self-management behavior
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)

Box 6

Research priorities

Global research priorities on Multimorbidity, as per Academy of Medical Sciences Report[46]	Research priorities on multimorbidity sensitive to low- and middle-income countries (LMICs) contexts
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, hence a gradual step to data generation is required. A common definition of multimorbidity would allow basic estimates of a few conditions and, as 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 maximise the benefits and limit the risks of treatment among patients with multimorbidity?	
Research priority 6: How can healthcare systems be better organised to maximise the benefits and limit the risks for patients with multimorbidity?	As common set of high-quality health systems 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.

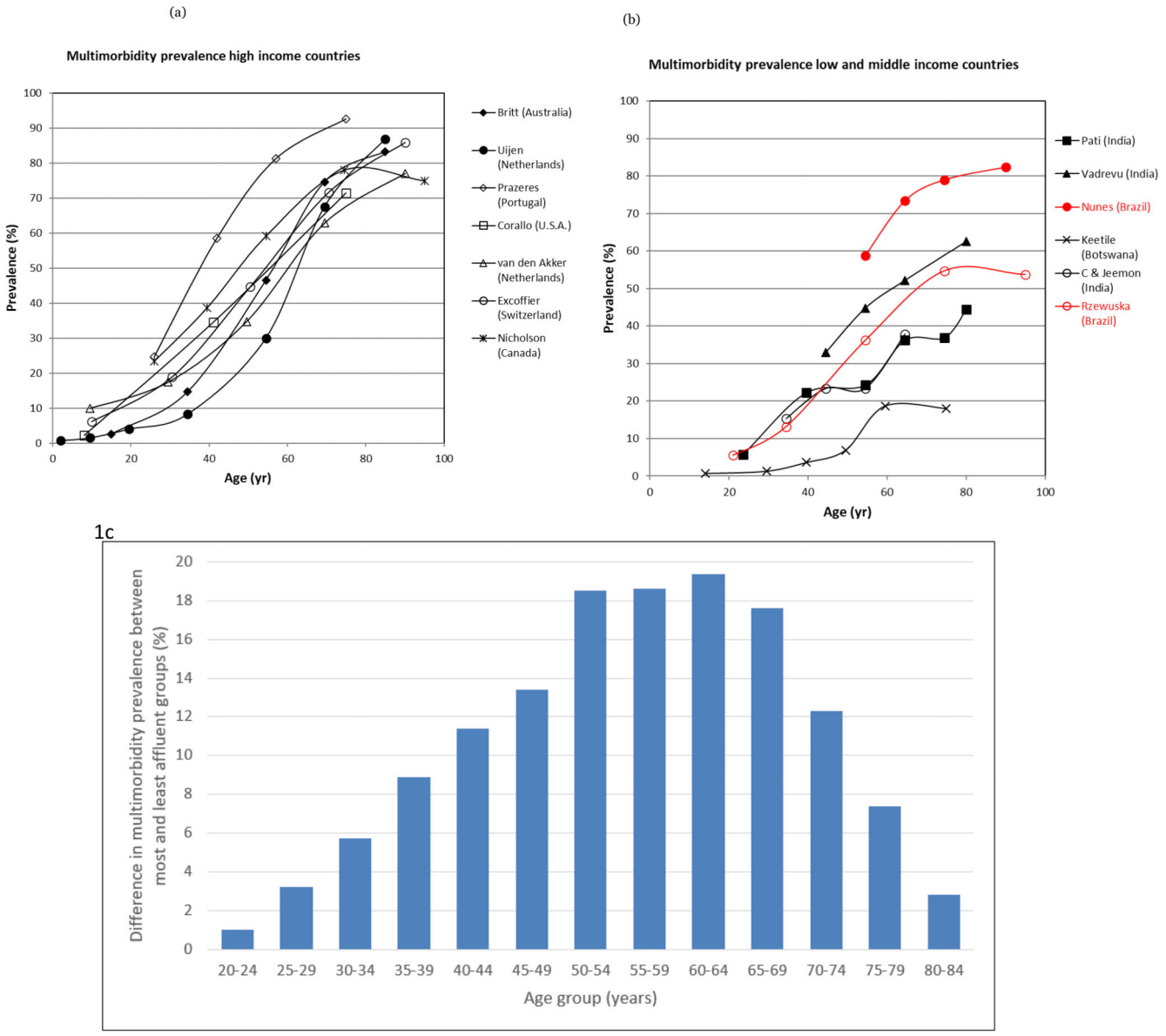

Figure 1. Prevalence of multimorbidity.

Figures 1a and b show prevalence estimates of multimorbidity according to age in high-income countries (HICs; a; data from [29,325–332]) and low-income and middle-income countries (LMICs; b; data from [70,71,333–335]). In general, it can be readily observed that the prevalence of multimorbidity increases with age, although estimates vary among studies. Apart from differences in geographic settings, 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 (e.g. 2 or more, 3 or more), and the conditions considered in the list. 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 impact or burden in that population. When comparing prevalence estimates of multimorbidity between HICs and LMICs, lower age

specific rates are observed in LMICs. To our knowledge, the reason of this difference has not been addressed in prevalence studies, and the question whether the difference is due to factors such as ascertainment of conditions (e.g. fewer conditions diagnosed), effects linked to survival (e.g. shorter survival after acute events), or if it is a true difference, remains to be answered.

Figure 1c shows the difference in prevalence of multimorbidity (defined as two 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.

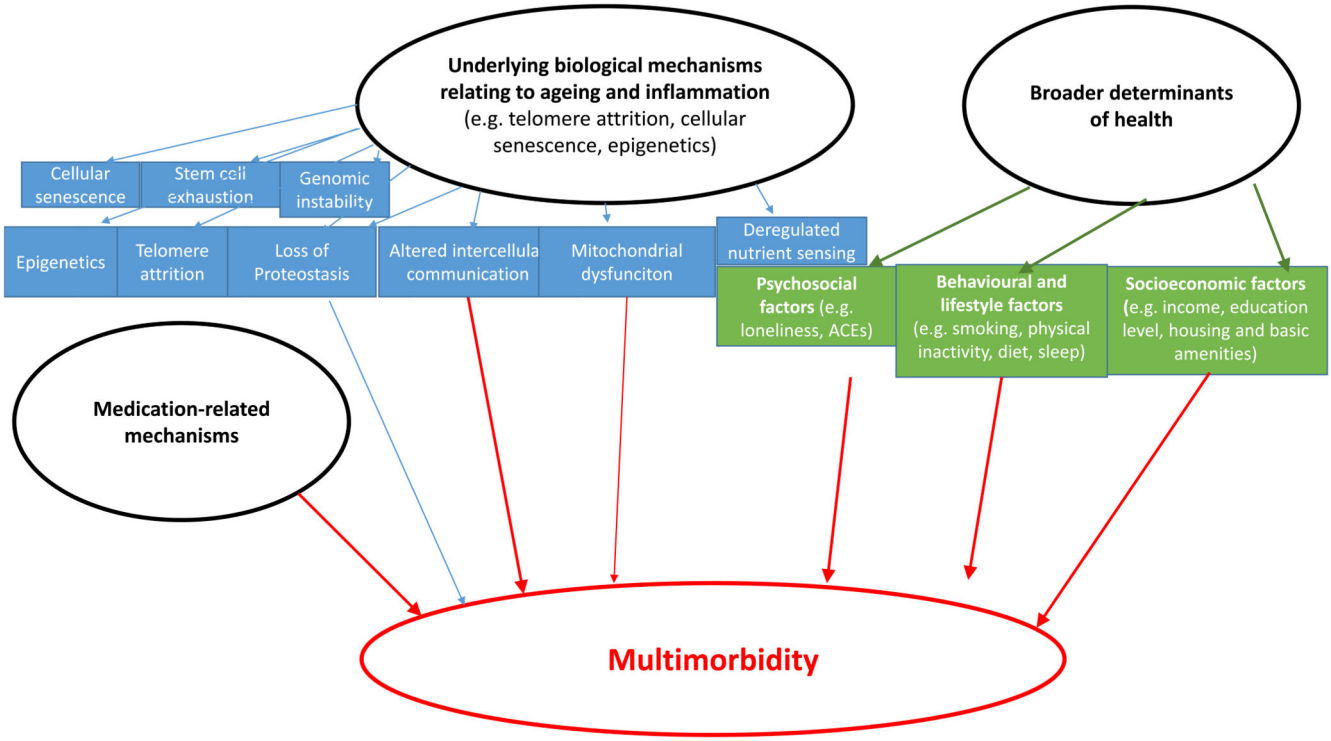

Figure 2. Determinants of Multimorbidity.

The figure summarizes key influences (red arrows) on development of multimorbidity and illustrates the shared pathways to development of multimorbidity. Mechanisms underpinning development of multimorbidity are frequently inter-related and may be synergistic (black arrows). Mechanisms can be considered in three areas (black ovals): 1) Underlying biological mechanisms relating to ageing and inflammation (blue boxes); 2) Broader determinants of health such as socioeconomic, psychosocial and behavioural social determinants (green boxes); and 3) Medication related.

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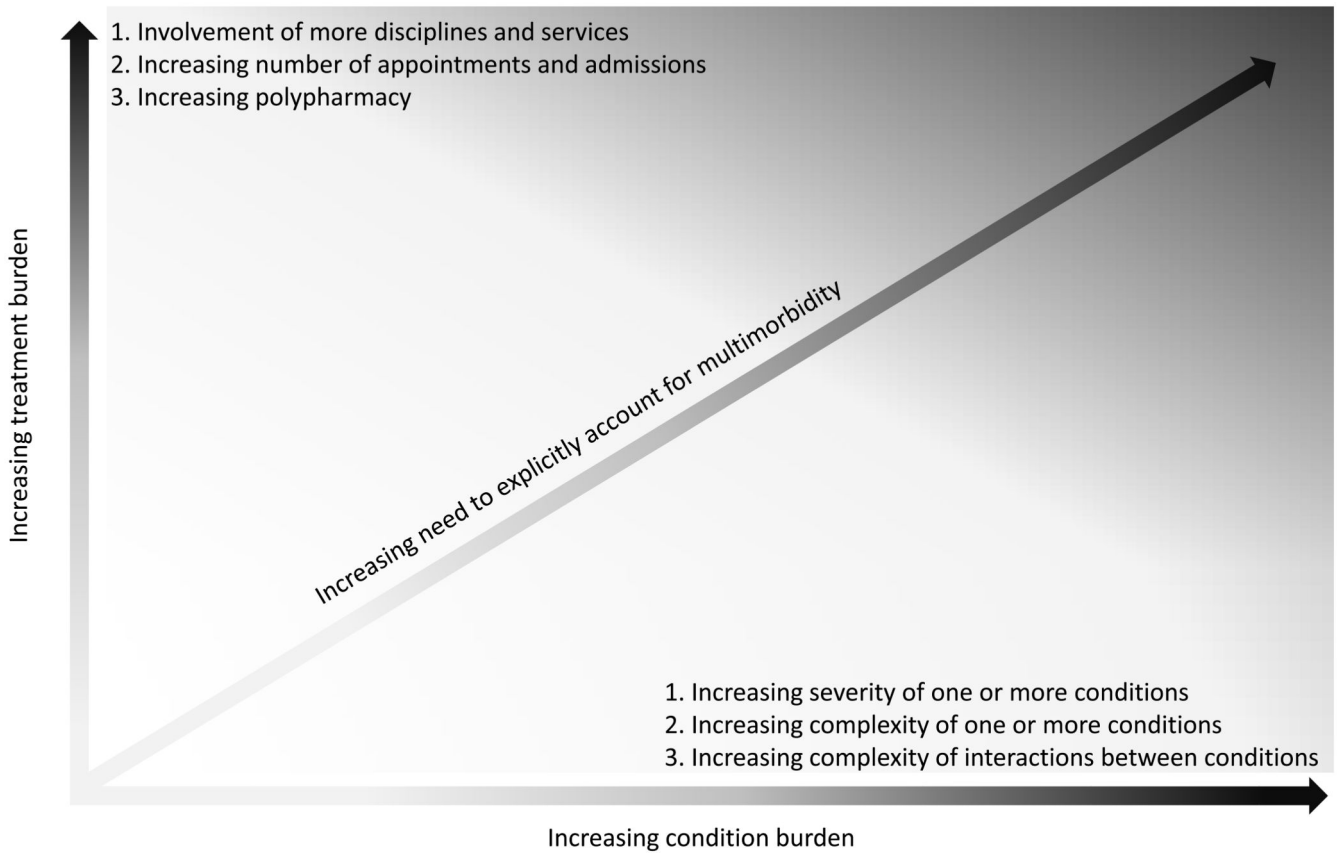

Figure 3. Identifying who needs an approach to care that accounts for multimorbidity.

The Figure emphasises that adaptation of care to account for multimorbidity may be needed because the patient experiences (a) high condition burden and/or because they experience (b) high treatment burden. (a) Condition burden is related to the severity and complexity of impact of individual conditions, but also to how they interact. For example, diabetes and hypertension is a combination where the combination is relatively unproblematic, whereas combinations like diabetes, schizophrenia and chronic obstructive pulmonary disease have more complex interactions. (b) Treatment burden is related to the impact 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. Adapted from.[182]

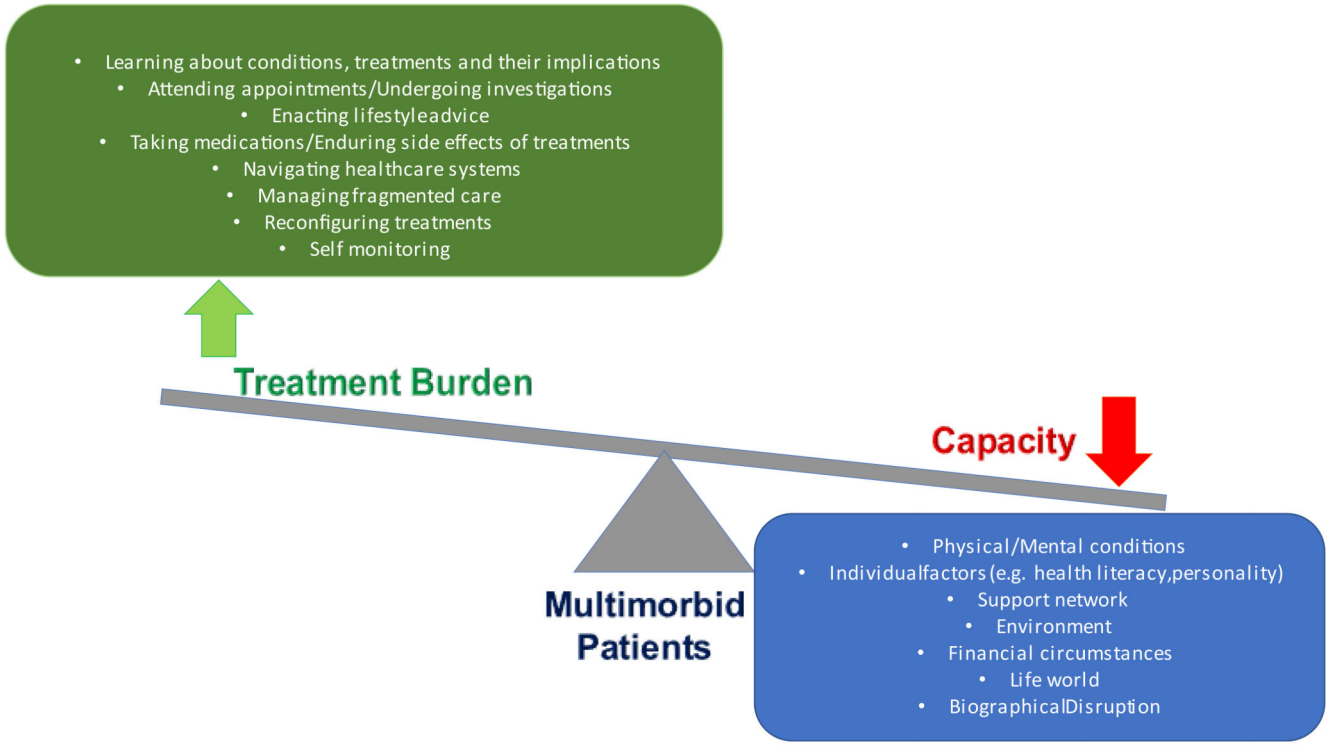

Figure 4. Treatment burden vs. capacity in patients with multimorbidity.

Multimorbidity is often associated with high treatment burden, while the patients might have lower capacity to self-manage and cope with their situation. Treatment burden refers to the workload of self-management and the health care we ask people to undertake, which is strongly associated with the number of chronic conditions.[22,23] Patient reported measures of treatment burden now exist[248–250] but their ability to predict adverse outcomes remains uncertain. The individual's capacity to self-manage can vary over time as illnesses accumulate and personal circumstances may change.[101,102,247,251,252] These include the work involved in taking medicines, self-monitoring, attending appointments and following health professional recommendations.

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Table 1

Challenges to trials of multimorbidity interventions.

Challenges	Description	Evidence from existing trials
Study design (cluster vs individual randomised)	Those delivering interventions can't 'turn-off' how they provide care to create a control group and in these cases randomization at the level of care providers addresses this challenge in studies where one care provider is responsible for the treatment (e.g. the general practitioner).	8 of the 16 RCTs in a recent systematic review had a cluster design as this accounts for contamination between arms within primary care practices.[225] Allocating patients at a cluster or practice site level ensures that patients in the control sites do not get 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 inherent in multimorbidity.	In general, existing trials have targeted older patients[322] or those with three or more common long-term conditions, or used another marker of complexity or severity, such as high healthcare utilization[322,323] or polypharmacy[228], to target those more likely to benefit from interventions. For example, inappropriate targeting can occur when included participants have less baseline problems making it difficult to improve outcomes.[228]
Choice of outcome	Outcomes often need to be generic rather than disease focussed.	Common outcomes included in existing studies are HRQoL (EQ5D and SF36), 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 compared with 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.[324] In the Guided Care study in the USA, there was no effect on the main outcome of hospital admissions, but a pre-planned sub-group analysis indicated reduced admissions in one of the participating health care organizations, which may have occurred because the particular health system was already more organized and structured, so that the Guided Care intervention simply improved the existing care, in contrast to less organized systems.[323]
Challenges of implementing a new complex intervention for only consented patients (particularly relevant to cluster-randomised trials where not all patients participate)	Delivering an intervention to sub-groups 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 while 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 12 months.[222] These timeframes may not be sufficient to have an effect, particularly one that is sustained over time.
Duration of follow-up	Full intervention effect is unlikely to accrue in one year for some interventions (but see next)	Most existing studies have follow-up durations of one 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 previous)	In the 3D study, data 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	Involvement of patients and clinicians in intervention design is increasingly recognised as critical to development of effective	Only a minority of studies had public and patient involvement in the design of their interventions, for example the 3D study. None have had a clear co-design process with key stakeholders targeted by the intervention

Challenges	Description	Evidence from existing trials
design and choice of outcomes	interventions of relevance to key stakeholders.	

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