Multimorbidity: a priority for global health research

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Multimorbidity: a priority for global health research

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Executive summary

The term multimorbidity broadly refers to the existence of multiple medical conditions in a single individual. For many regions of the world, there is evidence that a substantial, and likely growing, proportion of the adult population is affected by more than one chronic condition. However, the true extent of multimorbidity is difficult to gauge as there is no agreed definition or classification system for reporting. Consequently, the existing evidence base is fragmented and often difficult to interpret.

This report was undertaken to summarise the existing research evidence about the burden, determinants, prevention, and treatment of multimorbidity, and to identify areas of weakness in which additional data are required. The report has been informed by an expert international working group, as well as by meetings with researchers and research funders from a range of countries.

What do we know about multimorbidity?

Within the primary healthcare services of most high-income countries (HICs), multimorbidity is considered the norm not the exception. It appears to be more common in older adults, suggesting that the incidence and prevalence may be increasing, at least in part, because of population ageing. Other evidence suggests that it is often more prevalent in those of lower socioeconomic status, and may be influenced by other variables such as sex, ethnicity, and several health-related behaviours already known to increase the risk of single chronic conditions. Multimorbidity also appears to be increasingly common in low- and middle-income countries (LMICs), where the burden of chronic physical conditions (or non-communicable diseases (NCDs)) such as diabetes and heart conditions is rising and augmenting existing burdens of infectious diseases, maternal and child health problems, and nutritional conditions.

While there are limited data about the most commonly occurring clusters of conditions, it is accepted that multimorbidity is highly heterogeneous and patients can experience a wide array of different combinations of conditions. In some cases, the co-existing conditions might be similar in their origin treatment requirements; a scenario referred to as concordant multimorbidity. Indeed, there is evidence that certain conditions, such as coronary heart disease and cerebrovascular disease, which share a common aetiology (e.g. high blood pressure), frequently co-exist. In other cases – termed discordant multimorbidity – the co-existing conditions appear to be unrelated to each other or require different management approaches. In this regard, it is notable that there are data indicating that chronic physical and mental health conditions commonly co-exist. Some common clusters of conditions appear to vary by region – for example, the clustering in some LMICs of chronic physical conditions, such as coronary heart disease, with chronic infectious diseases, such as HIV.

There is evidence that some types of multimorbidity are associated with increased disability and functional decline, as well as reduced wellbeing and quality of life. There is also evidence that some patients with multimorbidity account for a disproportionately higher share of the healthcare workload and healthcare costs than would be expected from the individual component conditions.

What are the evidence gaps?

Most studies of the prevalence of multimorbidity have focused on older populations in HICs, while data from younger adults and LMICs are much more limited. Data identifying the most common clusters of conditions in populations and subgroups are also limited, as are data on the burden (e.g. years of life lost) generated by such clusters. While there are some data that suggest the prevalence of some types of multimorbidity has increased over time, these are limited.

Similarly, few data are available about modifiable factors that predict the risk of different types of multimorbidity. While some common condition clusters will simply represent the chance co-occurrence of common individual conditions, others will represent shared causal factors. However, it remains unknown whether there are biological, environmental, or behavioural factors that predict the risk of some types of multimorbidity independently of factors that alter the risk of the individual component conditions. The identification of any such factors, and the assessment of the likelihood of causality, requires data from prospective observational studies but the large majority of studies conducted to date are cross-sectional.

When conditions share common causal factors, prevention strategies targeting these causes clearly have the potential to reduce the risk of the development of multimorbidity clusters comprised of these conditions. However, the paucity of information available about the most common clusters of conditions – in particular, those that do not appear to share a common aetiology – has limited the development and evaluation of intervention strategies designed specifically to prevent the relevant conditions simultaneously. Similarly, the absence of data about factors that may increase the risk of multimorbidity independently of its component conditions means that it has not been possible to develop and evaluate prevention strategies targeting such factors.

With respect to the treatment of patients with multimorbidity, there is some evidence that such patients are less likely to receive guideline-based care. However, there have been very few randomised trials of interventions designed specifically to enhance the management of this important patient group. Additionally, randomised trials of interventions targeting individual conditions have frequently excluded patients with multimorbidity, leading to concerns about the relevance of data from clinical trials for the treatment of patients with multiple conditions. For some treatments, such as statins, large meta-analyses using individual patient data from randomised trials have enabled the assessment of treatment effects across a broad range of patient subgroups including those with different types of multimorbidity. Yet, for many other treatments, no similar databases exist and the effects of treatment in those with multimorbidity have to be extrapolated from the effects observed in those with a single condition.

There are also very few data about the effectiveness of health services and systems for patients with multimorbidity. In most parts of the world, large components of the health system are designed around single conditions or body systems. This focus extends to the training of doctors, particularly those working in hospitals where subspecialisation is now common, leaving the coordination of care for patients with multiple chronic conditions to general practitioners and geriatricians. This seems likely to result in many missed opportunities to provide care for co-existing conditions that may not have been the focus of a hospital admission or a specialist consultation, but there are few relevant data.

Conclusions

It appears likely that many populations in both HICs and LMICs are experiencing multimorbidity on a massive scale. Given this likelihood, the available evidence about the burden, determinants, prevention and treatment of patients with multimorbidity is inadequate. Research funders should consider prioritising research on multimorbidity across a wide range of perspectives from biological mechanisms to healthcare systems.

Recommendations and research priorities

Recommendation: Towards a standardised definition and classification system for multimorbidity

The research base on multimorbidity is fragmented, difficult to interpret, and difficult to synthesise. A core contributor to this situation is the absence of an agreed definition of multimorbidity and inconsistencies in the information reported by authors of research papers on this topic. To mitigate these difficulties, we therefore recommend the adoption of a uniform definition and reporting system for multimorbidity, as outlined below.

Adherence to this definition and reporting framework will help ensure that research reports provide consistent data on multimorbidity, which will in turn facilitate the synthesis from multiple sources. This will produce a much richer dataset from which to assess questions about the burden of multimorbidity, its determinants, and the prevention and treatment of patients with multimorbidity. Importantly, the proposed reporting system allows researchers the flexibility to consider multimorbidity in a way that is most appropriate for the precise research question and the specific context in which the study is conducted.

Definition

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.

This definition is consistent with that adopted by the World Health Organization (WHO). It also approximates that which has been used most often by researchers to date. The only material difference in this proposed definition is the inclusion of chronic infections, which are of particular importance in regions where infectious conditions such as HIV and hepatitis C are endemic.

Reporting system
We recommend that all research reports on multimorbidity should, wherever possible, include details of the following:

- Co-existing chronic conditions as described above, preferably coded using a standardised classification scheme such as the International Classification of Diseases (ICD-10) or the International Classification of Primary Care, Second edition (ICPC-2) (where relevant and applicable).[1,2]
- Functional deficits or disabilities, preferably coded using a standardised classification scheme such as the WHO Disability Assessment Schedule 2.0 (WHODAS 2.0) or the International Classification of Functioning, Disability and Health (ICF).[3,4]
- Frailty, also preferably coded using a standardised classification scheme such as the cumulative deficit model of frailty or Fried's phenotype model.[5,6]
- Other states of poor health (e.g. obesity or poor blood lipid profiles) and health-related behaviours (e.g. smoking) linked to one or more chronic conditions. There is no widely adopted comprehensive classification scheme for such factors, but there are numerous schemes for the classification of behaviours including tobacco use, diet, alcohol consumption and substance abuse, and environmental exposures such as that used in the Comparative Risk Assessment component of the Global Burden of Disease Project.[7]

If information on any of these is not collected, this should be recorded.

Recommended research priorities

This report summarises the existing evidence about multimorbidity and highlights areas where better evidence is required. We have identified a number of research priorities designed to produce a better understanding of the burden, determinants, prevention and treatment of patients with multimorbidity. While these are intended to be of global relevance, it is recognised that there may be differences between settings in the relative weight assigned to individual priority areas and the conditions, causes and strategies that are the focus of research. We strongly support the conduct of research in each of the priority areas across a broad landscape encompassing the full spectrum of epidemiological, geographic, sociodemographic and economic factors that may be relevant to the development, consequences or control of multimorbidity.

For each of these priority areas, we define multimorbidity on the basis of the definition described above.

Research priority 1: What are the trends and patterns in multimorbidity?

- Which clusters of conditions are most common at the population level, and has their prevalence changed over time?
- Do the most common clusters of conditions experienced by an individual change over the life course?
- Are there different time trends for concordant and discordant multimorbidity, and for mental health and physical multimorbidity?
- How has the age-specific prevalence and incidence of multimorbidity changed over time?

Research priority 2: Which multimorbidity clusters cause the greatest burden?

- Which clusters of conditions have the worst prognosis in terms of death and disability, as quantified by metrics such as 'years of life lost' (YLL) and 'years lost due to disability' (YLD)?
- Which clusters have the greatest impact on patient- and carer-centric outcomes such as treatment burden and quality of life?
- Which clusters result in the greatest healthcare utilisation and the greatest costs?
- Is the impact of clusters of conditions on these outcomes greater or less than that which would be predicted from the cumulative impact of the individual conditions?

Research priority 3: What are the determinants of the most common clusters of conditions?

- What are the main behavioural, environmental, sociodemographic, and biological factors associated with the most common clusters of conditions, and those clusters that generate the greatest burden at the population level?
- Which of these factors are causally related to multimorbidity, and which are surrogates for other causal factors?
- To what degree do these factors interact, either in a synergistic or additive way, to influence the risk of multimorbidity clusters?
- Are there factors for which their association with multimorbidity is greater than expected or explained by their association with the individual component 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?

- Are there strategies for the prevention of clusters of conditions that will generate greater benefits than those achieved by focusing on single conditions in isolation?
- Where clusters are already known, can single-condition guidelines be refined or better integrated – and healthcare professionals (HCPs) better supported – to prevent conditions that a patient may not yet have but are at a higher risk of developing in the future?
- What approaches should be taken to prevent discordant morbidities where the nature of any causal relationship is unknown?
- How might mental health conditions be prevented among those who have a chronic physical condition, and how might chronic physical conditions be prevented among those who have a mental health condition?

Research priority 5: What strategies are best able to maximise the benefits and limit the risks of treatment among patients with multimorbidity?

- Can tools be developed to assist healthcare professionals (HCPs) to deliver comprehensive integrated care to multimorbid patients that takes full account of all relevant clinical guidelines for the management of component conditions?
- Can strategies be developed to maximise the benefits and minimise the risks associated with the multiple treatments often received by patients with multimorbidity?
- How can patient and carer priorities be better captured and incorporated into care plans for patients with multimorbidity, and do these optimise clinical and patient-centred outcomes?

Research priority 6: How can healthcare systems be better organised to maximise the benefits and limit the risks for patients with multimorbidity?

- What strategies can be deployed to improve the integration of services for patients with multimorbidity, including those aspects of care directed to physical health, mental health, and social independence?
- Do any such strategies improve clinical outcomes, patient-centred outcomes, and the cost- effectiveness of care?
- How does the composition of the healthcare team affect outcomes for patients with multimorbidity? How should the roles of generalist and specialist HCPs be defined to maximise the effectiveness and safety of care?
- How can different financing models incentivise systems and providers to provide better care for those with multimorbidity?

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Further research is urgently required to better understand the growing challenge of multimorbidity and improve the care of patients across the globe.

1. Introduction

1.1 Background and rationale of report

Advances in public health, together with improvements in clinical interventions, have led to an increase in life expectancy in almost all regions of the world. This has already resulted in major demographic changes, and this is expected to continue. Between 2015 and 2050 the global population of people aged 60 years and older is projected to almost double, reaching around 2.1 billion.8

As a consequence, ever-greater numbers of people are reaching middle and older ages when chronic physical conditions – including, but not limited to, cancers, cardiovascular diseases, chronic respiratory diseases, and type 2 diabetes – are most likely to occur. The impact of these changes are most pronounced in low- and middle-income countries (LMICs), where populations are not only ageing but also experiencing a change in lifestyle and environmental exposures which contribute to NCDs (such as an increase in obesity and physical inactivity). As a result, many LMICs are experiencing an increasing burden of NCDs in addition to the existing burden of infectious diseases, which continue to affect millions of people every year.

As a result of these demographic and epidemiological changes, many people are now living with more than one chronic condition – a scenario broadly referred to as multimorbidity.[9,10]

The prevalence of multimorbidity appears to have increased in many regions of the world over the past 10 to 20 years, and it is anticipated to continue rising. Evidence from high-income countries (HICs) suggests that while multimorbidity is highly prevalent in older populations (typically those over 65 years of age), it also affects younger people.[11] As such, multimorbidity from chronic conditions is now the norm in most HICs, with at least 50 million people affected in the European Union (EU) alone.[12] Multimorbidity is also an increasing problem in LMICs, where already fragile healthcare systems are further stretched by the dual burden of NCDs and infectious diseases.[13,14,15]

These global trends suggest that multimorbidity is an expanding health challenge in many, and possibly most, regions of the world.

However, to date, the issue has received relatively little attention from health researchers and policymakers, particularly in LMICs, and there are still many aspects of this new healthcare challenge that are not fully understood. This situation is made more complicated by the lack of an agreed definition of multimorbidity, which prevents the interpretation and synthesis of research findings. This has resulted in a fragmented evidence base that has made it difficult to develop evidence-based health policies to address the challenges of multimorbidity **(Chapter 2).**

As discussed in **Chapter 3**, data on longitudinal trends in multimorbidity, while suggestive of increasing prevalence, are inadequate. There are few data on trends in major population subgroups and, more broadly, in the populations of LMICs. Knowledge of which conditions are most likely to co-exist is also incomplete, as are reliable estimates of the burden of death and disability attributable to multimorbidity. Similarly, and as discussed in **Chapter 4**, the determinants of common types of multimorbidity are often not fully understood, particularly when these involve seemingly unrelated conditions. Such knowledge gaps limit the capacity to identify individuals or populations at particular risk of multimorbidity, and limit the ability to develop specific interventions to prevent multimorbidity.

In most regions of the world, many aspects of clinical practice and healthcare organisation have been developed with a focus on specific conditions or specific body systems. This focus has also extended to research, including clinical research, where patients with multimorbidity have been frequently excluded from participation. This has led to unnecessary uncertainty about the relevance of clinical trial data for the treatment of patients with multiple conditions.

The management of multiple chronic conditions is inevitably complex, and a research base that enables the generation of data that can inform strategies for the simultaneous management of multiple conditions is necessary. Without this, treatment guidelines and health service polices are unlikely to fulfil the needs of patients, HCPs, or health systems **(Chapter 5)**. The resulting risks include poorer health outcomes and reduced quality of life for patients, and increased healthcare costs for patients, families, and communities.

Research is urgently required to generate better evidence about the burden and causes of multimorbidity, and the effectiveness of strategies designed to improve patient outcomes and control the healthcare costs associated with multimorbidity.

This working group project was initiated by the Academy of Medical Sciences following an exploratory roundtable meeting, 'Multiple morbidities as a global health challenge', held on 7 October 2015.[16] This workshop recognised that multimorbidity was likely to be a global health challenge, and acknowledged that realisation of the Sustainable Development Goals,[17] and other broader development targets, is likely to require more research on multimorbidity. On this basis, an international working group project was established to explore in greater depth the challenges and evidence gaps associated with multimorbidity.

1.2 Terms of Reference and project ambitions

The project's Terms of Reference are detailed in **Box 1** below.

Box 1: Terms of Reference

1. Summarise:

a. How multimorbidity has been defined within research to date, and how the existing intellectual framework might impact future progress within the field.
b. The existing evidence on the burden and determinants of multimorbidity in populations throughout the world, including in high-, middle-, and low- income countries.
c. The existing evidence about the most appropriate prevention and treatment strategies among individuals with multimorbidity.

2. Make recommendations about the implications for future research by:

a. Identifying ways to think about multimorbidity, potentially through an improved intellectual framework or greater consistency in the research methods used.
b. Identifying the most significant gaps in the existing evidence about multimorbidity and the associated research priorities, which might include prevalence, burden, determinants, prevention, management and healthcare delivery strategies.

As noted above, and detailed more fully in **Chapter 2**, there is no agreed definition of multimorbidity and the terminology used in the literature to describe the co-existence of multiple conditions is inconsistent and often ambiguous. For the purposes of this report we have chosen to use a simple and focused definition of 'multimorbidity' – **the co-existence of two or more chronic conditions.**

However, some constraints were imposed on the scope of the project and certain aspects were excluded from consideration, specifically: multimorbidity in paediatric and adolescent populations (aged less than 18 years of age), multimorbidity in those requiring end-of-life palliative care, and multimorbidity with acute conditions. These exclusions were deemed necessary to ensure the project was manageable, but should not be taken as an implication that the working group did not consider these issues important.

Despite these constraints, the wide scope of this project has allowed exploration of how inconsistent definitions of multimorbidity and a sparse evidence base have, to date, precluded efforts to reach clarity on the true scale and impact of the problem. Such difficulties have also meant that research-led healthcare and evidence-based medical policies designed to address multimorbidity have remained largely elusive. It is clear that to reduce the burden of multimorbidity and improve outcomes for the expanding population of multimorbid patients, more research is needed to understand the issue.

In order to address the global challenge of multimorbidity, we must understand the problem better.

As such, the **overarching aim of this report is to make recommendations about future research priorities.** It was clear from our evidence-gathering activities that the majority of research funding is siloed and directed to the investigation of single conditions, and that specific funding for multimorbidity research is lacking.

Our recommendations are therefore principally aimed at research funders whom we would like to encourage to provide greater funding and support for multimorbidity research. As will become clear throughout this report, despite its complexity, multimorbidity is not an intangible problem and greater efforts to better understand its causes and impact have the potential to improve patients' lives across the globe. Our recommendations for research should therefore also be of interest to researchers in both academic and industrial settings,

medical charities, governments, and other international organisations, particularly those providing guidance on health research.

While this report places an emphasis on a need for more research, we hope it will also be of interest to policymakers, professional and regulatory bodies, public health service providers, and commercial organisations who will be increasingly required to act on the outcomes of such research to develop evidence-based policies to elicit improvements in healthcare delivery and patient outcomes.

This policy project and its report was led by a working group of international experts, and supported by a series of evidence-gathering activities including a call for written evidence, oral evidence sessions, and two workshops held to explore multimorbidity in several LMICs. The evidence gathered through these activities formed the basis of this work, and additional references were sought through desk-based research performed by the secretariat and expert working group. While these efforts were comprehensive, a formal academic literature search has not been performed and the references provided in this work should not be considered as wholly exhaustive. More detailed information about the project's conduct and timeline is provided in **Annex 1**. The membership of the working group is provided in **Annex 2**.

1.3 Structure of the report

Excluding the introduction, the report includes four chapters, each of which explores a specific aspect of multimorbidity as proposed in the Terms of Reference. Each chapter has been written in a similar format. Firstly, the current evidence base of the specific theme is provided to set the scene and help identify areas where evidence is particularly sparse or lacking. These evidence gaps are then subsequently considered in more detail to provide the necessary context and rationale for the chapter's recommendations for research.

- **Chapter 2: Definition of multimorbidity and associated terminology.** This chapter explores how multimorbidity has been defined in research to date, discusses the problems caused by inconsistent terminology and the simultaneous use of different definitions, and proposes a standardised definition and classification system for multimorbidity.
- **Chapter 3: The scale and impact of the problem.** This chapter considers the burden of multimorbidity in the broadest sense, and summarises both the descriptive epidemiology of multimorbidity and its impact on patients, carers, HCPs, and healthcare systems. The social and economic impact of multimorbidity is also considered.
- **Chapter 4: Determinants of multimorbidity.** This chapter explores what is known and what is not known about the causes of multimorbidity and how these differ from determinants of single chronic conditions.
- **Chapter 5: Management of multimorbidity.** This chapter discusses what is known about strategies for the prevention and treatment of multimorbidity, and discusses their limitations. It also explores what evidence is required to guide the management of multimorbidity beyond that required for the management of single conditions.

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Research funders should support research on multimorbidity across a wide range of perspectives, from biological causes to how best to design healthcare systems to support patients.

> Not having an agreed definition of multimorbidity has hampered research and patient care.

2. Definition of multimorbidity and associated terminology

Overview

- The terminology describing the presence of multiple, co-existing conditions is variable, inconsistent and confusing.
- 'Multimorbidity' is the most commonly used descriptor, but there is variation in the number and type of conditions included in definitions.
- Inconsistent approaches to the definition and classification of multimorbidity complicate the comparison and synthesis of research findings. This limits conclusions about the scale and impact of multimorbidity.
- To overcome the problems caused by the multiplicity of definitions, **we recommend the use of a standardised definition and classification system for multimorbidity.**
- The adoption of a standardised definition and classification system will increase the comparability of data on multimorbidity, resulting in a more coherent evidence base for researchers, policymakers, healthcare providers and healthcare consumers to use.

2.1 Terminology and definitions of multimorbidity are variable

Multimorbidity has not been uniformly defined in the medical literature, and this chapter outlines some of the challenges created by this inconsistency. In this report, however, we have adopted a clear, coherent, and widely relevant definition. After much discussion within the working group, and with stakeholders, it was agreed, that for the initial purposes of this project, multimorbidity would be defined simply as the **co-existence of two or more chronic conditions.**

We therefore consider multimorbidity to be a scenario whereby a person experiences any possible combination of chronic conditions, which could encompass diagnosed and undiagnosed physical, infectious, and mental health conditions (such as those defined by ICD codes).[18] Within any one person, these component conditions may or may not interact with each other, either in their pathophysiology, clinical management, or impact on the patient.

We chose this broad definition to allow the report to explore the breadth and complexity of multimorbidity, and ensure that it is relevant to a wide range of research, clinical, and policy issues.

2.1.1 Inconsistent terminology

The terminology used in the medical literature to describe the co-existence of multiple conditions in any given patient is inconsistent and often ambiguous.[19,20,21,22]

While the most common term is 'multimorbidity', a number of different terms are also used interchangeably including polymorbidity, polypathology, pluripathology, multipathology, and multicondition.[23] Most recently, ***The Lancet*** has coined the term 'syndemics' to describe a conceptual framework for the presence of two or more disease states that adversely interact with each other, and are exacerbated by their social, economic, environmental, and political context.[24]

While the use of numerous terms to describe the same concept is unhelpful, it was noted in our evidence-gathering activities that further confusion arises when terms such as multimorbidity are conflated with other related terms such as comorbidity and frailty.[25,26,27] However, sufficient differences exist between these concepts to justify them being considered as distinct clinical scenarios.

More specifically, the term comorbidity was proposed in 1970 to describe the co-occurrence of additional conditions alongside a primary, or index, condition.[28] The term multimorbidity was later proposed as a way to differentially describe situations where several conditions co-exist but there is no single focus of attention on one condition over and above the others.[29] Consequently, while these two terms are related (because in both, the person affected has two or more conditions) they are not synonymous (see **Box 2** for further details).

Multimorbidity can also be confused with frailty, but while multimorbidity is the co-existence of distinct chronic conditions, frailty is the increased vulnerability of individuals to stressors from the accumulated consequences of morbidities or their treatments.[30] Therefore some, but not all, people with multimorbidity will be considered frail, and many, but not all people with frailty will have multimorbidity.[31]

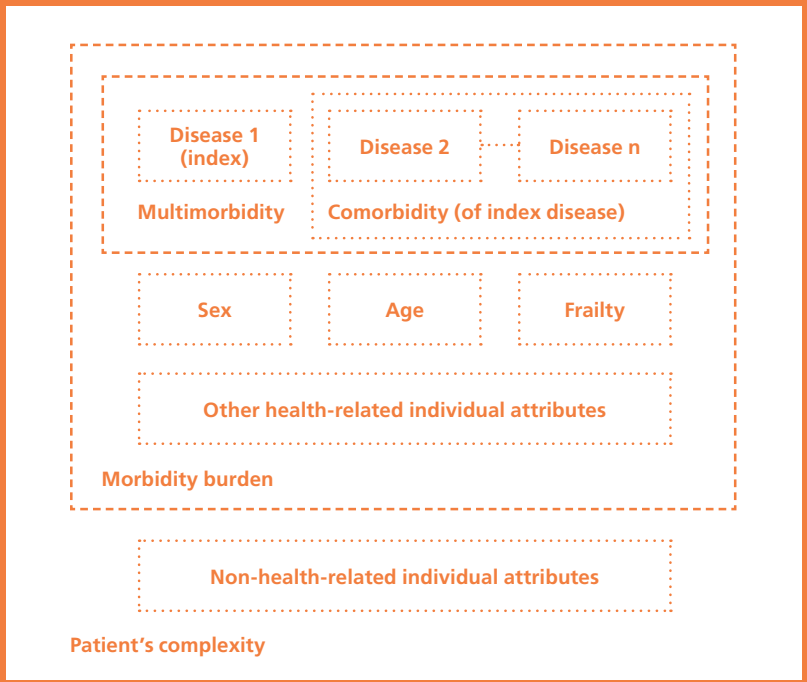
Box 2: Multimorbidity vs. comorbidity

Multimorbidity and comorbidity are not synonymous terms, but neither are they mutually exclusive or contradictory – the terms provide two different perspectives through which to consider a patient with more than one condition at the same time.[32,33]

Comorbidity is the co-existence of other conditions with an index condition that is the specific focus of attention.

Multimorbidity is the co-existence of several conditions where none are considered an index condition that is the specific focus of attention.

Multimorbidity is therefore a highly heterogeneous concept, and can be used to describe a wide array of patients experiencing a multitude of different combinations of conditions. As described in **Section 2.1.2**, co-existing conditions can be similar in their origin and/or treatment (concordant multimorbidity) or appear to be unrelated from each other (discordant multimorbidity). Multimorbidity constitutes a more generic, patient-centred concept and in doing so also acknowledges that the impact of a condition is influenced not only by health-related characteristics but also by socioeconomic, cultural, and environmental factors, and patient behaviour.



Source: Valderas JM, *et al.* (2009).[34]

Comorbidity: Presence of additional diseases in relation to an index disease in one individual.
Multimorbidity: Presence of multiple diseases in one individual.
Morbidity burden: Overall impact of the different diseases in an individual taking into account their severity.
Patient's complexity: Overall impact of the different diseases in an individual taking into account their severity and other health-related attributes.

The above figure has been included to illustrate the conceptual differences between comorbidity and multimorbidity, and the influence of a range of non-health attributes on patients' perception of their health and quality of life.

2.1.2 Variations in the meaning of multimorbidity

In addition to the confusion caused by multiple terminologies, further problems have arisen due to the numerous different ways in which authors choose to use (or operationalise) the definition of multimorbidity – that is, there are many different ways in which multimorbidity is defined (see **Box 3** for some example definitions).

Most definitions of multimorbidity include two components: a count of the relevant conditions, and a choice of which conditions to include. The most common definitions of multimorbidity use the presence of 'two or more conditions' within one individual, although there are other examples in which multimorbidity has been defined as '***three*** or more conditions', and even '***four*** or ***five*** and more'.[35]

However, even in cases where the approach to quantifying conditions is comparable, definitions can still vary as different authors may restrict cases of multimorbidity to the co-occurrence of conditions from different predefined lists. Such lists often differ in length and also in the type and name of conditions they specify.[36,37]

For example, while some definitions are restricted to physical conditions, others also include mental health conditions. Even when conditions are agreed, there can be variation in how discrete conditions are actually defined and diagnosed between different research papers. Notably, there is variation with regard to whether definitions include acute conditions as well as 'long-term' or 'chronic' conditions, the definitions of which are also subject to considerable ambiguity given the heterogeneous set of conditions such classifications include.[38,39] Further still, in an effort to capture a more holistic concept of multimorbidity, some definitions have expanded the criteria beyond recognised medical conditions to include poor health states and socioeconomic factors. The definitions provided by the European General Practice Research Network (EGPRN) and the UK National Institute for Health and Care Excellence (NICE) guidelines on multimorbidity are examples of such holistic definitions (see **Box 3**).[40,41] As a result, papers describing 'multimorbidity' are often not directly comparable and can, in fact, be describing vastly different scenarios.

While many definitions provide a simple count of conditions in any given patient, others have used weighted disease counts as an alternative approach to quantifying multimorbidity. These weighted measures aim to characterise the impact associated with different combinations of conditions, using outcomes such as mortality, quality of life, and resource utilisation.[42,43] Many different weighted measures have been developed, including the Charlson Index,[44] the Chronic Disease Score,[45] the Adjusted Clinical Groups (ACG) System,[46] the Cumulative Illness Rating Scale (CIRS),[47] and the Functional Comorbidity Index (FCI).[48] A detailed description and appraisal of such measures is beyond the scope of this report, but each differ with respect to the study population and setting in which they have been most robustly validated (e.g. primary or secondary care) and the outcome variable with which they are weighted (e.g. mortality, healthcare utilisation, quality of life). Consequently, the relative merit of weighted counts is dictated by the outcome variable of interest and there appears to be no single optimal weighted count that is uniformly relevant to all studies.[49,50,51]

In addition to the above inconsistencies in the definition of multimorbidity, some research reports use the term multimorbidity (or similar) without any explanation of how it is defined.[52,53] Lastly, while there has been a MeSH (Medical Subject Headings) term for comorbidity since 1990, there was no MeSH term dedicated to the indexing of papers exploring multimorbidity until January 2018.[54] The lack of a specific MeSH term has previously contributed to difficulties in the identification, categorisation, and assimilation of multimorbidity research papers.[55]

Concordant and discordant multimorbidity

There have also been efforts to develop definitions of multimorbidity that better specify the relationship between component conditions. For example, co-existing diagnoses that are similar in their origin or that can be addressed by similar treatment plans have been described as being 'concordant' (for example, coronary heart disease and cerebrovascular disease). Conversely, 'discordant' multimorbidity has been used to describe co-existing conditions that appear to be unrelated from each other and require different management approaches (for example, type 2 diabetes and chronic obstructive pulmonary disease (COPD)). However, while the two terms were originally used to describe approaches to the management of diabetes comorbidity,[56] simple descriptors of concordant and discordant can conflate shared management and shared aetiology. For example, conditions that are concordant in some aspects of their aetiology may not be concordant in their management – e.g. smoking is a cause of both coronary heart disease and lung cancer, but their treatments are entirely different. Furthermore, upstream determinants of health, such as social deprivation, can predispose to a broad range of conditions that share neither an obvious aetiological relationship nor a common approach to treatment.

Box 3: Variable definitions of multimorbidity

At the simplest level, multimorbidity is used to describe the co-existence of 'more than one chronic condition'. However, there is variation in how authors define multimorbidity in scientific literature. For example, differences exist with respect to:

- The number of conditions included in the definition.
- The types of conditions included and the way they are defined.
- The inclusion of functional status or other non-disease factors (such as socioeconomic status) in the definition.
- The use of weighted counts to infer the severity of each condition.
- Whether the nature of the relationship between the component conditions is described.

Examples of definitions include:

The World Health Organization (WHO)

The WHO defines multimorbidity as 'being affected by two or more chronic health conditions in the same individual'.[57]

European General Practice Research Network (EGPRN)

Following an interactive and iterative process designed to identify key themes that should be communicated by a definition of multimorbidity, the EGPRN proposed a definition composed of three parts, intended not only to define multimorbidity but also to detail potential modifiers and outcomes of multimorbidity.[58]

- Multimorbidity is any combination of chronic disease with at least one other disease (acute or chronic) or biopsychosocial factor (associated or not) or somatic risk factor.
- Any biopsychosocial factor, any somatic risk factor, the social network, the burden of diseases, the healthcare consumption, and the patient's coping strategies may function as modifiers (of the effects of multimorbidity).
- Multimorbidity may modify the health outcomes and lead to an increased disability or a decreased quality of life or frailty.

UK National Institute for Health and Care Excellence (NICE)

NICE has issued clinical guidelines for optimising care for adults with multimorbidity, which was described as the presence of two or more chronic health conditions, which can include:[59]

- 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.

2.2 Challenges arising from a lack of consensus regarding definition

It was clear from our evidence gathering that the diversity of terminology, multiplicity of definitions, and the inconsistency in how these terms and definitions are used, makes the scientific literature about multimorbidity difficult to navigate and assimilate.

Inconsistent approaches to the definition and classification of multimorbidity have made the comparison and synthesis of findings from different research efforts challenging.

This, in turn, has created difficulties for reaching conclusions about the scale and impact of multimorbidity, and makes developing recommendations about management strategies difficult. Additionally, without a standard definition it is difficult to compare the burden of multimorbidity experienced by different subgroups of patients or different global communities. It also makes it difficult to synthesise or contrast the effects of different interventions for the prevention and treatment of multimorbidity. The same challenge extends to meaningful analysis of evidence about the causes or predictive factors for multimorbidity. Without these analyses, there are major challenges in the development of evidence-based guidelines for the management of multimorbidity, as well as in the development of healthcare policy regarding the provision of preventive and therapeutic services.

A more coherent evidence base is required in order to develop appropriate strategies for the prevention and treatment of multimorbidity.

The routine use of a single definition of multimorbidity would greatly reduce these challenges. However, the application of any such definition needs to include a mechanism by which information about the conditions experienced by an individual are documented in a standardised way, and adherence to a uniform reporting framework would also be of benefit.

Recommendation: Towards a standardised definition and classification system for multimorbidity

The research base on multimorbidity is fragmented, difficult to interpret, and difficult to synthesise. A core contributor to this situation is the absence of an agreed definition of multimorbidity and inconsistencies in the information reported by authors of research papers on this topic. To mitigate these difficulties, we therefore recommend the adoption of a uniform definition and reporting system for multimorbidity, as outlined below.

Adherence to this definition and reporting framework will help ensure that research reports provide consistent data on multimorbidity, which will in turn facilitate the synthesis from multiple sources. This will produce a much richer dataset from which to assess questions about the burden of multimorbidity, its determinants, and the prevention and treatment of patients with multimorbidity. Importantly, the proposed reporting system allows researchers the flexibility to consider multimorbidity in a way that is most appropriate for the precise research question and the specific context in which the study is conducted.

Definition

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.

This definition is consistent with that adopted by the World Health Organization (WHO). It also approximates that which has been used most often by researchers to date. The only material difference in this proposed definition is the inclusion of chronic infections, which are of particular importance in regions where infectious conditions such as HIV and hepatitis C and endemic.

Reporting system

We recommend that all research reports on multimorbidity should, wherever possible, include details of the following:

- Co-existing chronic conditions as described above, preferably coded using a standardised classification scheme such as ICD-10 or the International Classification of Primary Care, Second edition (ICPC-2) (where relevant and applicable).[60,61]
- Functional deficits or disabilities, preferably coded using a standardised classification scheme such as the WHO Disability Assessment Schedule 2.0 (WHODAS 2.0) or the International Classification of Functioning, Disability and Health (ICF).[62,63]
- Frailty, also preferably coded using a standardised classification scheme such as the cumulative deficit model of frailty or Fried's phenotype model.[64,65]
- Other states of poor health (e.g. obesity or poor blood lipid profiles) and health-related behaviours (e.g. smoking) linked to one or more chronic conditions. There is no widely adopted comprehensive classification scheme for such factors, but there are numerous schemes for the classification of behaviours including tobacco use, diet, alcohol consumption and substance abuse, and environmental exposures such as that used in the Comparative Risk Assessment component of the Global Burden of Disease Project.[66]

If information on any of these is not collected, this should be recorded.

Example of the use of the definition and reporting system

Sex
Female

Age
71 years

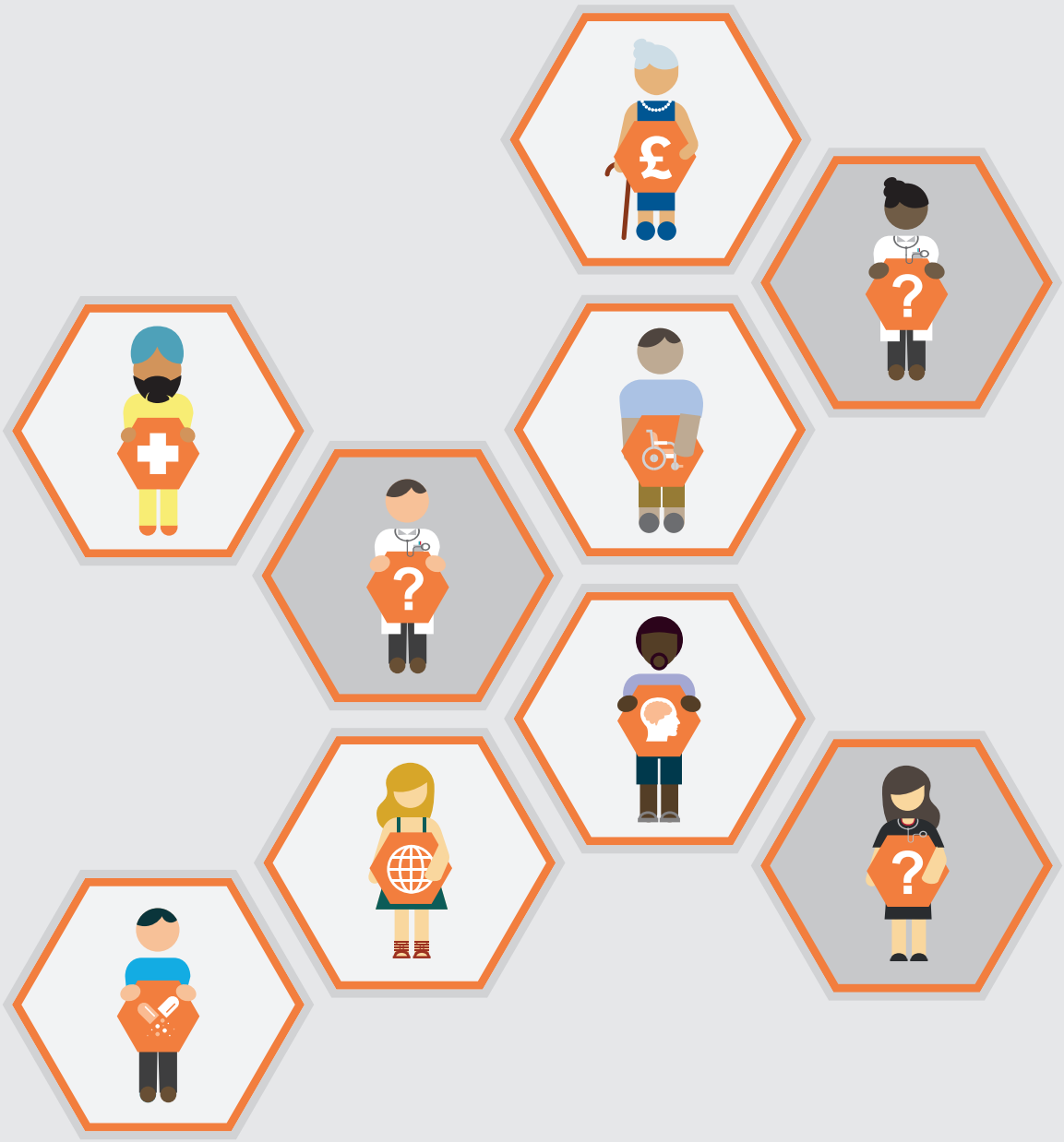
Co-existing chronic conditions (ICD-10)
Chronic obstructive pulmonary disease (ICD-10 J44)
Recurrent depressive disorder (ICD-10 F33.1

Disability
Emotional functions (ICF b152); moderate impairment
Mobility (ICF d4500); severe impairment walking short distances
Self-care (ICF d540); mild impairment (dressing)
Basic interpersonal interactions (ICF d710); moderate impairment

States of poor health
Former smoker (stopped 2009)

“

Multimorbidity affects people of all ages, and has negative impacts on patients, carers, healthcare providers, and healthcare systems.



3. The scale and impact of the problem

Overview

What is known?

- Irrespective of the way in which multimorbidity is measured, it appears to be common in many regions of the world.
- There is evidence that the prevalence of multimorbidity is particularly high in older adults (typically those over 60 years of age), although it is also present in younger people.
- The prevalence of multimorbidity is likely to be increasing due to ageing populations, although relevant incidence data are few.
- Some conditions are known to cluster more frequently together than others, with different patterns of clustering in different geographical locations, as well as in different demographic groups.
- Some physical and mental health conditions commonly cluster. Among those affected, both quality of life and life expectancy are reduced.
- Multimorbidity has a negative impact on the health and wellbeing of carers as well as patients.
- Multimorbidity is associated with increased healthcare utilisation and expenditure.

What are the evidence gaps?

- The lack of an agreed approach to the definition and classification of multimorbidity has led to highly variable estimates of prevalence.
- Much of the data on multimorbidity come from a fragmented evidence base, in which variations in the definition and classification of multimorbidity make it difficult to draw generalisable conclusions.
- The evidence base is heavily skewed towards older populations and HICs. The scale and impact of multimorbidity in younger adults and LMICs is less well documented.
- Most of the available data are on prevalence, and few are on incidence, burden (e.g. disability-adjusted life years (DALYs)), or healthcare costs.
- More data are required from longitudinal studies (including repeated cross-sectional and cohort studies) to better understand the changing prevalence, incidence, burden and cost of multimorbidity over time.

Research priorities

- **Research priority 1: What are the trends and patterns in multimorbidity?**
- **Research priority 2: Which multimorbidity clusters cause the greatest burden?**
- Repeated cross-sectional population surveys and longitudinal cohort studies using a standardised approach to definition and classification are required in both HICs and LMICs.
- Studies of the experiences and preferences of patients with different types of multimorbidity are required in HICs and LMICS.
- Collectively, these studies would enable the creation of a ‘global atlas’ of multimorbidity that would provide data on the extent and impact of different multimorbidity clusters in different population subgroups, in different parts of the world.
- This would help identify those clusters that are priority targets for research on causes, prevention, and treatment.

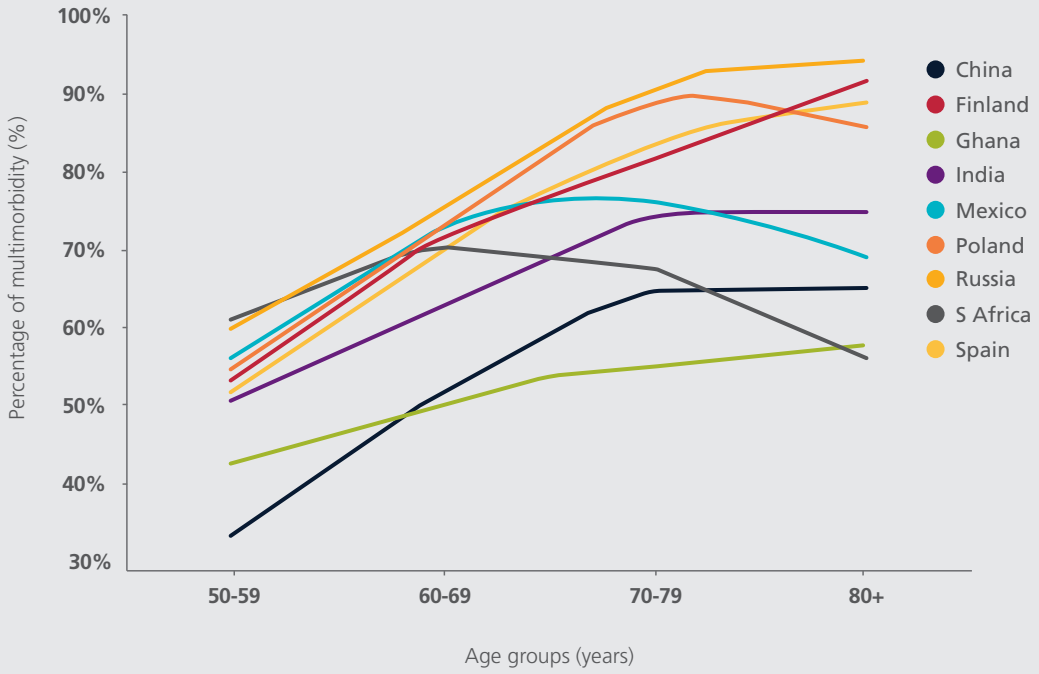
3.1 Descriptive epidemiology: prevalence and incidence

Reaching a consensus on the prevalence of multimorbidity in populations is difficult not only because of variable levels of access to healthcare and rates of chronic condition diagnosis across the world, but also because highly variable definitions and classifications of multimorbidity lead to highly variable prevalence estimates. For example, a systematic review of 39 observational studies across 12 countries reported estimates ranging from around 13% to 95%.[67] Another systematic review reported similarly variable estimates, with prevalence estimates in the general population ranging from 13% to 72%.[68] While some variations may reflect real differences in the prevalence of multimorbidity between populations, this cannot be disentangled from the variation that results from differences in definition. Not surprisingly, the prevalence of multimorbidity is higher when the number of conditions eligible for inclusion in the definition is higher.[69,70] For example, a retrospective cohort study in the UK reported prevalence estimates ranging from 16% to 58%, depending on whether multimorbid patients were identified using the 17 conditions included in the UK Quality and Outcomes Framework (QOF) pay-for-performance programme or using the wider Johns Hopkins University Adjusted Clinical Groups (ACG) Case-Mix System respectively.[71] Similarly, the prevalence of multimorbidity will be dictated by the prevalence of the single conditions included in the list – the inclusion of highly prevalent conditions will increase the prevalence of multimorbidity.[72]

The adoption of a standardised definition and classification system for multimorbidity, as recommended in Chapter 2, will enable much more reliable comparisons of multimorbidity prevalence between regions and population subgroups. Without such a standardised approach, it will remain difficult to draw conclusions about the extent of the problem in different populations or at different points in time.

That said, it appears that patients with multiple conditions are now the rule rather than the exception in HICs. Most older adults have more than one chronic condition, and data from Scotland have revealed that of people with at least one morbidity, half in fact have multimorbidity.[73,74] A similar burden is also observed in LMICs,[75,76,77,78] where the prevalence of multimorbidity has been reported to be gradually approaching that of HICs (see **Figure 1**).[79] Multimorbidity prevalence is thought to be increasing in LMICs not only as a result of a demographic shift to older ages, but also due to a growing prevalence of NCDs adding to the well-known burden of infectious diseases. This change in condition patterns may, in turn, be indicative not only of the ageing population but also of changing lifestyle and cultural behaviours, changing environmental exposures and urbanisation, and healthcare-related advances contributing to an increased prevalence of chronic conditions.[80,81] As such changes progress further in LMICs, the scale of the problem of multimorbidity seems likely to increase.

Figure 1. Multimorbidity prevalence across high-, middle-, and low-income countries



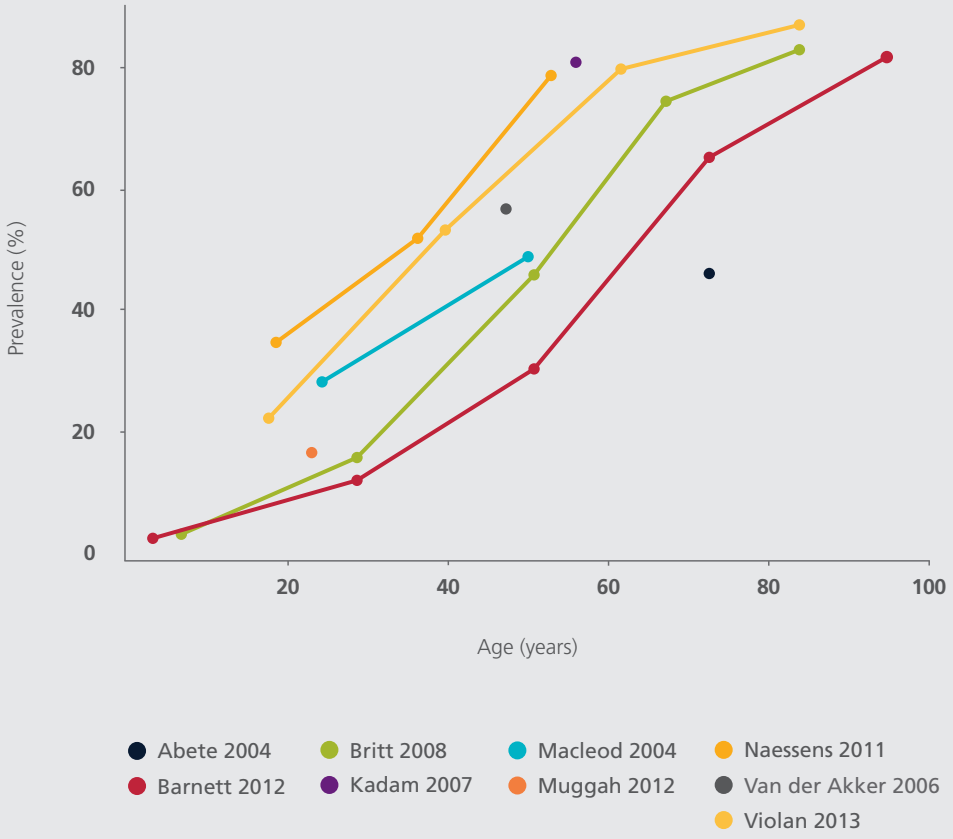
Source: Garin N, *et al.* (2016).[82]

Multimorbidity prevalence is shown across age groups for several low-, middle-, and high-income countries. The data are taken from a cross-sectional analysis of studies including 41,909 adults (aged 50 years and older) and illustrate that a high prevalence of multimorbidity occurs in older adults across the countries, with figures in LMICs gradually approaching those of HICs. Multimorbidity has been defined as the co-existence of at least two of the following conditions: angina, arthritis, asthma, cataract, COPD, depression, diabetes, edentulism, hypertension, cognitive impairment, obesity, and stroke.

Most studies investigating the prevalence of multimorbidity have involved older populations – typically those over 60 or 65 years of age – where a strong relationship between multimorbidity and increasing age has been observed (see **Figure 2**).[83,84] Although data from younger populations are comparatively sparse, and difficult to compare due to the variable use of multimorbidity definitions, there is evidence showing a similar relationship among people under 65 years. Moreover, while the proportion of those with multimorbidity is generally higher at older ages, in some populations the absolute number of people affected by multimorbidity is greater among those under 65 years of age due to the age structure of the population.[85,86,87,88,89]

Multimorbidity is not exclusive to older people, and appears to affect a much broader cross-section of the population.

Figure 2. Multimorbidity prevalence by age group



Source: Violan C, *et al.* (2014).[90]

The data are taken from a systematic review of 39 observational studies across 12 HICs, and illustrate a well-established positive association between age and prevalence of multimorbidity. This association is commonly seen despite the definition of multimorbidity differing between the included studies.[90]

There is, therefore, an emerging consensus that multimorbidity is common and poses a challenge to most HICs and many LMICs. However, there is also a recognition that the existing evidence about prevalence is inadequate for many regions of the world, while data on incidence is lacking entirely for most regions. Additionally, the lack of data on longitudinal trends in multimorbidity was raised repeatedly during our evidence-gathering process.[91,92,93]

That said, despite the limitations of the data on longitudinal trends, the available evidence suggests that the prevalence of multimorbidity has increased over the past 10 to 20 years in many countries.[94,95,96,97,98] Particularly compelling evidence of increasing prevalence in the UK was provided by a study of multimorbidity among 230,000 primary care patients who had a first diagnosis of CVD during the period 2000 and 2004.[99]

Over this four-year period, the incidence of CVD decreased, while the prevalence of multimorbidity increased: for example, the prevalence of multimorbidity with five or more conditions quadrupled from 6% to 24%.

Such increases in prevalence are cause for significant concern as this evidence suggests higher age-specific death rates among people with multimorbidity of various types.[100,101,102] The largest study of the impact of multimorbidity on mortality was conducted among 413,000 patients admitted to UK hospitals with acute myocardial infarction during the period 2003 to 2013: patients with one additional condition were 32% more likely to die, while those with two or more additional conditions were twice as likely to die compared to those without multimorbidity.[103]

While better data are required about time trends in the prevalence and incidence of multimorbdity, as well as its impact on major clinical and personal outcomes, the available evidence underlines the urgent need for better evidence about the causes and prevention of multimorbidity as discussed in **Chapters 4 and 5**.

Improved data on prevalence, incidence and longitudinal trends in multimorbidity across a range of regions are required to estimate the future impact of multimorbidity on populations and healthcare systems. This is essential for planning future resource requirements for the provision of healthcare to those with multiple conditions.

The best evidence about longitudinal trends in the prevalence of multimorbidity is likely to come from the data provided by repeated cross-sectional studies of random samples of the population, which can also identify trends in the prevalence of the individual component conditions. Many countries perform longitudinal health surveys which might be exploited to such effect, and examples include the United States National Health and Nutrition Examination Survey (NHANES),[104] the Korean National Health and Nutrition Examination Survey (KNHANES),[105] Japan's National Health and Nutrition Survey (NHNS),[106] the Russia Longitudinal Monitoring Survey – Higher School of Economics (RLMS),[107] the New Zealand Health Survey,[108] the Health Survey for England,[109] and the Scottish Health Survey.[110]

Data from longitudinal cohort studies could also provide relevant evidence on both the prevalence and incidence of multimorbidity. However, if the cohorts involved in such studies are not representative of the populations from which they are drawn, the observed absolute rates of multimorbidity may not be generalisable. Nonetheless, relative changes in rates over time may be more generalisable. Analyses of existing datasets from both repeated cross-sectional studies and longitudinal cohort studies should be prioritised to gain clarity on country-specific and global trends in multimorbidity. For helpful reference, **Box 4** provides further detail on the differences between cross-sectional and longitudinal studies.

Cohort studies may also be able to provide a range of other relevant information. For example, it is possible that such studies could provide data on the temporal relationships between the occurrence of an initial condition and the occurrence of subsequent conditions, and on the factors that might predispose an individual with one condition to develop a second. Such studies should also be able to provide data on the longitudinal associations of factors such as age, sex, obesity, health-related behaviours, and socioeconomic status with the incidence of multimorbidity. Additionally, cohort studies of patients with already existing multimorbidity should be able to provide estimates of the associations of multimorbidity with outcomes such as death, serious acute events, and disability. Such data can be used to estimate the burden associated with different types of multimorbidity using metrics such as disability-adjusted life years (DALYs) or years lost due to disability (YLD).[111] Our evidence-gathering exercises did not identify any studies that provide formal estimates of the burden of multiple conditions.[112]

Box 4: Cross-sectional and longitudinal studies

Cross-sectional studies
Cross-sectional studies involve the collection of data from a single sample of a population of interest at one specific point in time.

If the sample is representative of the broader population, it will provide estimates of the prevalence of conditions and of the factors associated with these conditions in the population as a whole. Cross-sectional studies can therefore provide data about those conditions that are most likely to co-exist, and the prevalence of multimorbidity of different types. These studies can also provide estimates of the cross-sectional associations of factors such as age, sex and socioeconomic status with multimorbidity.

While a single cross-sectional study cannot provide evidence about longitudinal trends in the prevalence of conditions, repeated cross-sectional studies of multiple representative samples can provide such evidence and are the best way of estimating changing population needs. However, only cohort studies (described below) can provide evidence about the incidence of conditions, and their precursors and outcomes.

Longitudinal cohort studies
Cohort studies involve the collection of data from a single sample of a population of interest at multiple points in time. When performed in initially unaffected populations, the incidence of individual conditions and multiple conditions can be measured over time.[113] If the sample is representative of the broader population, and does not suffer from high attrition over the course of the study, it will provide useful estimates of the incidence of individual conditions and multimorbidity in the population as a whole. Cohort studies can also provide evidence about the longitudinal associations of factors (such as obesity and tobacco use) measured at one or more points in time with the subsequent incidence of individual and multiple conditions. For this reason, cohort studies are particularly useful for the identification of causal factors for individual conditions, as well as for multimorbidity. Cohort studies using patient populations can also provide evidence about the longitudinal association of multimorbidity with outcomes such as death and disability.

3.2 Descriptive epidemiology: patterns of multimorbidity

3.2.1 Clusters of conditions

Multimorbidity can encompass many different combinations of conditions, but there is evidence that certain conditions are more likely to cluster than others – in ways that can be either concordant or discordant in nature, as discussed in **Chapter 2**.[114,115,116,117,118,119,120,121,122,123,124,125] This may be due to shared causal factors (which could be biological or environmental (see also **Chapter 4)**) or, alternatively, due to pathological pathways or networks, whereby one condition increases the risk of another.

Annex 4 summarises some multi-country systematic reviews, and one cross-sectional study, performed with the aim of providing evidence about the most common clusters of conditions.[126,127,128,129] Much of this work has focused on clusters comprised of just two conditions, and has found depression, cardiometabolic disorders, and musculoskeletal disorders to be common components of multimorbidity clusters across the globe. Nonetheless, it should be noted that it is perhaps more evident from the available data that the frequency of specific combinations of conditions is highly influenced by the setting and population in which the research is performed.

As the prevalence and incidence of many single conditions vary between countries, the prevalence and incidence of specific clusters also varies between countries. Since serious infectious diseases with long duration such as HIV/AIDS, tuberculosis (TB), and hepatitis C are much more common in LMICs than in HICs, clusters that include one of these conditions are also more common in LMICs.[130,131] In South Africa, for example, there are many people with both cardiovascular disease and HIV.[132] This is explained in part by the very large increase in life expectancy produced by antiviral therapy, which has resulted in many HIV-infected individuals living to older ages when the risks of chronic NCDs are greatest.[133] However, the clustering of cardiovascular disease and HIV appears to be magnified by the adverse effects of antiretroviral therapies that predispose to atherosclerosis and other cardiometabolic conditions.[134,135,136,137,138] It was noted at both our evidence-gathering workshops that improved treatments for such infectious diseases mean they can often be considered as a manageable, chronic condition and so they markedly contribute to multimorbidity in some LMICs (including in South Africa as discussed in **Box 5**).[139,140,141]

In general, population subgroups have differential levels of exposure to potential causal factors such as smoking and obesity which is likely to result in differences in the prevalence of specific clusters of conditions, as will differences between population subgroups in terms of demographic factors such as age, sex, ethnicity, and socioeconomic factors such as family income and social status (see **Chapter 4**).[142,143,144,145] However, such evidence requires further exploration and there is a particular need for further work in younger populations, and greater efforts to explore multimorbidity clusters composed of more han two conditions.

There is also a paucity of evidence about how clusters of conditions develop and change over time, meaning it can be difficult to predict how the disease burden might change over the course of a patient's life, and difficult to identify when interventions might be best applied.[146] Additionally, it has been established that certain chronic conditions tend to cluster in families and communities,[147,148] but it remains uncertain whether multimorbidity ***per se*** also clusters in this way.

However, once again, there is likely to be a body of relevant data already available from existing cohort studies and repeated cross-sectional surveys. Of particular value would be analyses designed to identify the most common clusters not only in whole populations but also more specifically in major population subgroups.

Understanding which conditions most commonly occur together, and which population subgroups are most affected, could be valuable for identifying those patients with a single condition who are at greatest risk of developing a second. Moreover, being able to identify specific additional conditions that are most likely to occur could usefully inform decisions about strategies for prevention (see also **Chapter 5**).

Furthermore, as discussed in **Section 3.3.1**, different clusters of conditions are likely to differentially affect physical functioning and quality of life, meaning greater evidence on the occurrence and impact of common clusters could inform decisions about service provision, resource allocation, and management strategies to ensure multimorbid patients are optimally cared for.

Evidence about which conditions most commonly cluster together in different populations, what their impact is, and how they change over time is needed to inform decisions about how to optimise prevention and treatment programmes, and systems of healthcare delivery.

It should be noted that much of the work performed to date to identify multimorbidity clusters has been largely descriptive and has not extended to the investigation of common causal factors or pathological processes. The need to also understand the mechanistic foundations of multimorbidity clusters is explored in **Chapter 4.**

Box 5: The dual burden of infectious and non-communicable diseases in South Africa – consequences and approaches to tackle it

Many LMICs, including South Africa, are experiencing a rising burden of NCDs against a background of infectious disease epidemics, including HIV and TB. The second National Burden of Disease Study for South Africa reported that 43% of all deaths in 2012 were attributable to NCDs and 33.6% were attributable to HIV/AIDS and TB.[149] While such conditions may occur together in an individual through chance, there is growing evidence that chronic infectious diseases can causally contribute to the development of NCDs, and multimorbidity comprising both NCDs and infectious diseases is a growing concern in many LMICs. While estimates of multimorbidity prevalence are sparse in South Africa, several studies have shown that hypertension, diabetes, HIV and TB frequently co-occur.[150,151,152,153,154] Notably, multimorbidity comprising these conditions is evident from early adulthood due to the younger age distribution of HIV-infected persons. The risk of such conditions is generally higher in those of socioeconomic disadvantage, who often have a lower capacity to access healthcare and deal with the burden of ill health.[155]

The co-occurrence of NCDs and infectious diseases, notably HIV/AIDS and TB, presents complex challenges to the South African healthcare system, which, like many others, faces a difficult task in integrating care across the spectrum of chronic conditions. Notably, sustained efforts to revise single condition guidelines – which tend to treat NCDs and infectious diseases as unrelated conditions – are called for. The public health sector, which provides free primary healthcare and referral services to over 80% of the population, lacks the resources to address the complexity of multimorbidity.[156] While the service has made substantial progress in addressing the effects of HIV/AIDS, it remains to be seen how best to harness this success to serve chronic care more broadly. There is also a need for a more integrated health service that provides adequate treatment and management, and also has an improved capability for screening and monitoring multimorbidity.

Encouragingly, discussions at the *'Addressing the global challenge of multimorbidity: Lessons from South Africa'* workshop showed that while many gaps remain, South Africa is at the cutting edge of implementation research in relation to chronic conditions and the integration of care.[157,158] For example, the South African Department of Health is currently re-engineering primary healthcare to more effectively and equitably address the growing burden of multiple NCDs by integrating chronic care, although it has been noted that it does not sufficiently incorporate issues of multimorbidity including infectious diseases.[159,160]

An evidence-based guideline known as the Practical Approach to Care Kit (PACK) has also been put in place to enable HCPs (primarily nurses) working in primary care to better integrate the management of commonly encountered conditions.[161,162] As heard during the workshop, four pragmatic randomised controlled trials (RCTs), completed between 2003 and 2013, have shown that the implementation of PACK improves health outcomes and strengthen health systems, and has brought about consistent and reproducible improvements across various behaviours such as prescribing, referral, and screening.[163] It was added, however, that further improvements could be made to the extent to which PACK provides specific advice on multimorbidity.

There are reasons to expect that such reforms in healthcare organisation and delivery will bring demonstrable benefit to multimorbid patients in South Africa, although frameworks to more comprehensively address multimorbidity composed of both NCDs and infectious diseases are still needed. While such work should consider how best to organise care and support HCPs in a cost-effective and sustainable manner, it should also look to incorporate patient perspectives and consider patients' capacity to respond to ill health, given the pervasive influence of the social determinants of health. Participants at the South Africa workshop also highlighted that such work will need to consider adults of all ages and assess how best to apply life course approaches to improve the diagnosis and care of multimorbidity.

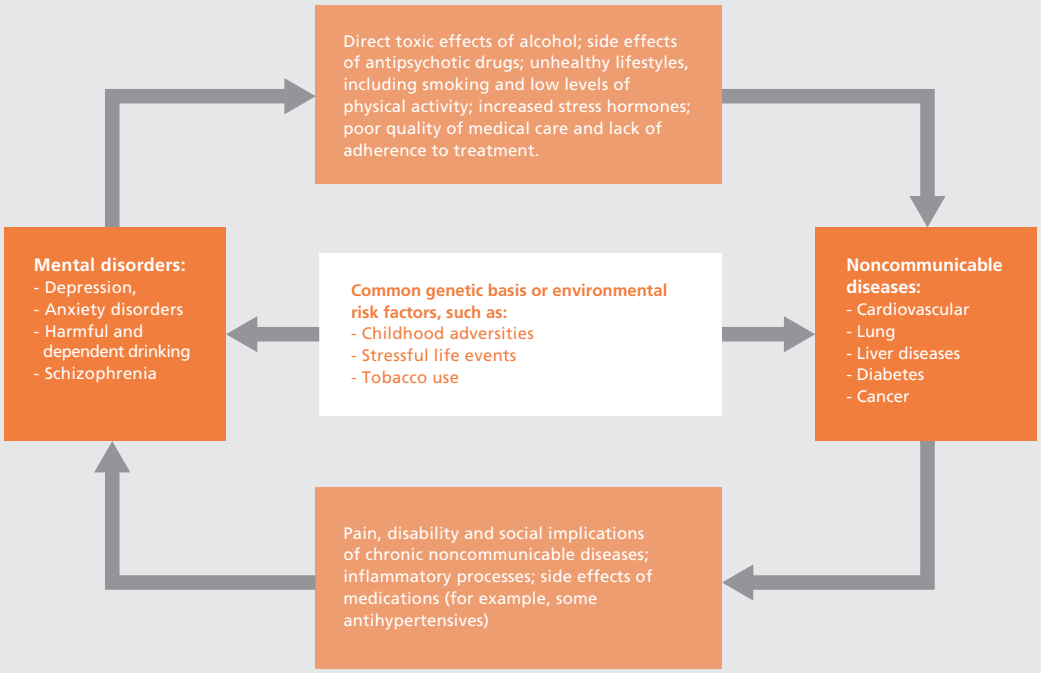
3.2.2 Co-existing mental and physical health multimorbidity

Throughout our evidence-gathering process, the importance of mental health conditions as a component of multimorbidity was emphasised.

Mood disorders such as depression, severe psychiatric conditions such as schizophrenia, and alcohol and substance abuse appear to cluster with a range of physical NCDs as well as with chronic infections such as HIV.[164,165] Discussions during our evidence-gathering workshop held with representatives from the BRICS countries (Brazil, Russia, India, China, and South Africa) also called for greater recognition that multimorbidity that includes poor mental health from conditions that result in cognitive decline (such as dementia) is increasingly a concern as older populations grow.[166,167]

Although its existence is recognised, most of the available data on the clustering of mental and physical health conditions are derived from cross-sectional studies (see **Annex 5**).[168,169,170,171,172,173] As such, it does not provide good evidence about causality or the direction of relationships (i.e. does physical ill health lead to poor mental health, or vice versa) although it is expected to be bidirectional (see **Figure 3**). While the risk of mental health conditions (such as depression and anxiety) and cognitive decline has frequently been reported to increase as the number of chronic conditions increases,[174,175,176,177,178] some cohort studies have also provided evidence that mental health conditions can increase the risk of subsequent physical conditions and multimorbidity, possibly as a result of both lifestyle and treatment specific factors (see **Annex 5**).[179,180,181,182,183] There is also evidence that poor mental health and psychosocial risk factors such as feeling dissatisfied with life, not feeling calm, having sleep problems that affect work, and financial concerns are predictive of multimorbidity in various age groups.[184,185] Other evidence has similarly shown that living in a family compared to living alone, and being part of a large social network, are protective factors for multimorbidity occurrence.[186]

Figure 3. The mechanisms of comorbidity of mental disorders with other non-communicable diseases



Source: Patel V & Chatterji S (2015).[187]

The relationship between mental health and physical conditions is complex, but appears to be bidirectional and may arise due to shared biological factors, or mediated by various lifestyle and treatment specific factors.

Regardless of causality, the available data suggest that patients with concurrent physical and mental health conditions typically have a poorer health-related quality of life, worse clinical outcomes, and an increased risk of premature mortality than those who have physical conditions alone.[188,189,190,191,192,193]

These outcomes could be linked to the reduced capacity for managing the symptoms of physical conditions, worsening of functional status, decreased adherence to medications, and compromised self-management among individuals experiencing psychological distress.[194] Similarly, some studies have found that those with multimorbidity including a mental health condition are at particular risk of adverse drug events,[195] and are at risk of receiving suboptimal care for co-existing physical conditions,[196,197] which may also contribute to poor health outcomes and increased mortality. Higher rates of healthcare utilisation have also been observed among patients with co-existing mental and physical conditions compared to those with physical conditions alone, which can also result in adverse financial implications (see **Section 3.6**). Some evidence suggests that the co-existence of mental and physical health conditions is more common in younger adults than in those over 50 years of age, and is more frequent in women than men.[198,199,200,201]

Further research on multimorbidity involving both mental and physical health conditions is required to better quantify the extent of the problem in different population groups, and to better define which mental health conditions are most likely to be associated with which physical conditions.

Further research is also required to determine whether the relationship between mental health and physical conditions are causal and, if so, what mechanisms underlie the relationship.

Recommended research priority 1

Clarity about the true scale, trajectory, and patterns of multimorbidity is required to define at-risk populations and ensure that healthcare can be delivered in an optimal and targeted manner, both in the immediate future and over longer timeframes.

We therefore consider it a priority for future research in this area to investigate:

What are the trends and patterns in multimorbidity?

- Which clusters of conditions are most common at the population level, and has their prevalence changed over time?
- Do the most common clusters of conditions experienced by an individual change over the life course?
- Are there different time trends for concordant and discordant multimorbidity, and for mental health and physical multimorbidity?
- How has the age-specific prevalence and incidence of multimorbidity changed over time?

To help address this evidence gap, new research should generate data that will determine whether trends and patterns differ between populations and subsets of the population defined by factors such as age, sex, race/ethnicity, migrant status, and household, as well as modifiable risk factors such as tobacco smoking, obesity, and salt intake. Such information will help inform efforts to identify factors that may underlie trends and patterns, and help target preventive strategies appropriately.

The initial priority should be to use existing longitudinal data for this purpose. Looking forward, a registry-based approach to support the routine documentation and surveillance of multimorbidity could help facilitate prospective studies.

3.3 Impact of multimorbidity on patients' lives

3.3.1 Impact on quality of life

While studies investigating the burden of disease as measured by factors such as years of life lost (YLL) and years lost due to disability (YLD) often do not account for multimorbidity,[202] others have revealed that the co-existence of multiple conditions is associated with an increase in disability and functional decline,[203,204,205,206,207,208] and an increased risk of mortality even after accounting for age.[209,210,211,212] It has been further shown that multimorbidity is associated with reduced wellbeing, as assessed by measures of self-rated health and quality of life (QoL).[213,214,215,216,217,218] While much of the available data have been generated in HICs across Europe and the United States, data from the WHO Study on Global AGEing and Adult Health (SAGE) Wave 1 show an association between multimorbidity and poor self-rated health and reduced QoL across numerous LMICs.[219]

Different clusters of conditions can be expected to differentially affect QoL,[220,221,222] with some reports using weighted counts to define multimorbidity revealing that the severity of the conditions influences QoL in those with multimorbidity.[223,224] Others have found that certain combinations of conditions appear to have a larger negative impact on QoL than that which would be expected from the sum of each condition considered independently.[225,226,227,228] However, most such studies have only investigated a narrow range of conditions, and have been limited to pairwise comparisons of common conditions or have grouped conditions into organ-specific domains.

As with other outcomes among people with multimorbidity, there is uncertainty as to how much of the association between multimorbidity and QoL is the result of confounding factors. For example, variables such as socioeconomic status, age and sex are thought to influence QoL, in addition to multimorbidity (see **Chapter 4**).[229] Nonetheless, the current literature is somewhat contradictory with respect to how much of the association between multimorbidity and QoL is explained by such socioeconomic and demographic variables. As in other areas discussed throughout this report, there is a paucity of longitudinal research on multimorbidity and QoL, which prevents characterisation of the relationship between multimorbidity and QoL over time.

Further work is needed to better characterise the impact of multimorbidity on QoL, and determine the degree to which the association can be explained by confounding factors.

3.3.2 Treatment burden

'Treatment burden' has been defined as the negative impact on a patient's time and energy due to accessing care from multiple providers, complying with complex treatment plans involving multiple drugs, and coordinating other aspects of their own care.[230,231,232,233,234] Evidence from studies of patients with single conditions such as diabetes, heart failure, and cancer reveal that treatment burden is an important clinical concern as patients who feel overwhelmed are less likely to adhere to medications and are less able to maintain self-care.[235] Treatment burden may also contribute to reports of reduced perceptions of the clinical care provided – for example, there is some evidence from the UK that patients with multiple chronic conditions have a less positive experience in primary care than patients with a single condition or no chronic conditions.[236,237]

However, evidence about the extent and impact of treatment burden specifically among patients with multimorbidity is limited.[238]

Providing such evidence is made difficult by a lack of tools with which to generate a quantitative measure of treatment burden beyond drug-induced side effects. Although some preliminary attempts have been made to develop a measure of treatment burden for the specific use in patients with multiple chronic conditions,[239,240,241] greater clarity as to how patients experience treatment burden and how it affects clinical outcomes is needed.

3.4 Impact of multimorbidity on caregivers

Caregivers can also suffer negative consequences as a result of caring for people with chronic conditions. While not specific to multimorbidity, it is nonetheless important to recognise this given the large body of evidence demonstrating that caring for someone with a chronic condition is associated with increased rates of both mental health and physical conditions in the carer, and is associated with increased mortality.[242,243,244,245] One study on the experiences of multimorbid patients in their last year of life reported that both patients and carers struggle with managing multiple medications, and note a lack of coordination and continuity of care.[246] This was consistent with an earlier study based in Canada, which also found that carers frequently expressed frustration as a result of poor communication between medical specialties and a lack of care coordination.[247]

However, there has been little other work exploring the specific experiences of carers of individuals living with multimorbidity, and whether caregiver burden in this population is yet further amplified due to the complexity of having to consider multiple conditions. A study of an intervention to improve the management of patients aged 18 years and older with multimorbidity in general practice is currently underway, which will include a study of carers and the impact on their QoL.[248]

3.5 Impact of multimorbidity on healthcare professionals

Caring for patients with multimorbidity can pose substantial challenges for HCPs who often have limited time and resources, and can experience difficulties when trying to apply multiple clinical guidelines to one patient.[249,250,251,252] Specialist HCPs may also face difficulties in managing co-existing conditions outside of their area of specialty, or adjusting treatments for their condition of interest in the face of multimorbidity and co-prescribing. A systematic review including ten studies across seven HICs found that clinicians face a diverse range of challenges when dealing with multimorbid patients including: difficulties caused by fragmented healthcare services and systems; problems resulting from the complexity of following multiple guidelines which focus on the management of single conditions; challenges in delivering patient-centred care; and barriers to shared decision making.[253] This study also revealed that general practitioners (GPs) feel a sense of professional isolation when managing multimorbid patients. There is also some evidence suggesting that the difficulties faced by HCPs when managing multimorbid patients can lead to reduced quality of care.[254]

3.6 Economic burden of multimorbidity

3.6.1 Health service utilisation

Patients with multimorbidity account for a disproportionately high share of the healthcare workload in HICs. Numerous studies show increased primary care visits and hospital admissions among multimorbid patients, and several have reported that this is independent of sociodemographic factors such as age, sex and socioeconomic status.[255,256,257,258,259,260,261,262] There is also evidence that unplanned hospital admissions for a physical condition are particularly high in patients who have co-existing mental health conditions such as depression,[263] as well as among those who have problems with alcohol and psychoactive substances, dementia, schizophrenia, and learning disabilities.[264]

Most studies of healthcare utilisation by patients with multimorbidity have been restricted to older adults (older than 50 years and often older than 65 years), and there has been less attention on younger age groups. There is some evidence that increasing numbers of chronic conditions are associated with increasing healthcare utilisation in LMICs, although this is limited in comparison to that available from HICs.[265,266,267]

Further work is required to better quantify healthcare usage by multimorbid patients, and assess to what degree it is, or is not, appropriate given their multiple conditions. This should include comparison of usage by patient groups with different clusters of conditions as well as comparisons of usage by patient groups defined by sociodemographic characteristics.

3.6.2 Financial implications of multimorbidity

An association between multimorbidity and healthcare costs in older adults (most commonly 65 years of age and older) has been reported by a systematic review of studies from HICs including the United States, Canada, Europe, Australia, South Korea, and Hong Kong.[268] The authors noted that most of the studies reported an almost exponential relationship, suggesting that the cost of care for patients with multimorbidity is more than

would be predicted based on the cost of managing the individual component conditions alone. Data from the UK indicates that multimorbidity is a key driver and predictor of health and social care costs, beyond that explained by age alone.[269] This finding indicates the need for studies among younger patient groups. Other data suggest that multimorbidity can increase social care costs, such as those associated with professional care providers as well as informal caregivers, such as family members and friends.[270,271]

The personal financial burden of multimorbidity is greatest among individuals who have to pay out-of-pocket (OOP) costs for healthcare.[272] Evidence from the United States has shown that while OOP expenditure depends on insurance and coverage, average OOP expenditure increases with the number of chronic conditions, irrespective of age.[273,274,275] A direct relationship between the number of chronic conditions and OOP spending has also been reported in older adults in a number of other countries where patients are, at least partially, responsible for covering their own healthcare costs.[276,277,278] Several analyses of data from the WHO SAGE study have shown that outpatient OOP expenditure increases with an increasing number of NCDs, with medication costs often accounting for the largest proportion of spending.[279,280] Indirect costs also increase among patients with multimorbidity – for example, costs associated with transport and accommodation when seeking care, and lost productivity of patients and carers.[281,282]

Data about costs associated with multimorbidity are, however, mostly from HICs and mostly from older populations. More data are required from LMICs and younger populations. Data are also required on costs associated with different multimorbidity clusters, as different combinations of conditions are likely to differentially influence the financial implications of multimorbidity (see **Box 6**). Longitudinal data on time trends in costs for the management of multimorbidity are also required for a range of settings.

Greater clarity about the economic burden of multimorbidity across different countries and ages is needed to help inform decisions about service provision and resource allocation.

Box 6: The financial cost of multimorbidity – a UK example

A retrospective observational study based in the UK has shown that the management of multimorbidity is often associated with a significantly different cost than that required for the treatment of the individual component conditions.[283] The cost per person was estimated based on primary care resource use i.e. the number of consultations and the cost of medications and tests.

- It was observed that some combinations of conditions were cost-increasing, i.e. that the cost of treating two conditions in one person was higher than treating two patients each with only one condition.
    - For example, the co-existence of depression in combination with another chronic condition was almost always associated with an increase in cost relative to treating each of the conditions independently.
- In other cases, however, some combinations were cost-limiting i.e. the cost of treating one person with two conditions was lower than treating two patients each with only one of the component conditions.
    - **Dementia was found to be cost-limiting in combination with all other chronic conditions.** The reason for this was unclear but may reflect that such patients experience inadequate care and have unmet needs, or that clinicians and families are less willing to start, or more willing to stop, the intensive treatment of other conditions in those with (late-stage) dementia.
    - Hypertension was found to be cost-limiting in combination with most other conditions, potentially as a result of treatment overlap.
- The direction and extent of the association between multimorbidity and cost was **age-dependent.**
    - For example, the co-existence of diabetes and stroke was found to be cost-increasing in those 60 years and older, but cost-limiting in those aged 40–59 years.
- The proportion of multimorbidities that were cost-limiting was greater in those aged 60 years and older. **This suggests that the financial burden of multimorbidity may be greater in younger adults**, supporting the need for multimorbidity research to consider a broader age range for such differential impacts to be understood.

The complexity with which specific combinations of conditions influence healthcare costs is also evident from data generated from two studies involving older populations in the United States and Germany.[284,285] However, evidence from other countries, particularly LMICs, is sparse.

Recommended research priority 2

A better understanding of the burden brought about by multimorbidity is required. This should include the burden on the population as a whole and within subgroups, as well as the burden on individual patients, caregivers, and HCPs. The definition of burden should be taken to include both prevalence and incidence, as well as outcomes such as death, disability, reduced quality of life, hospital admissions, primary care utilisation, the need for social care, and costs (both direct and indirect). Better data on the burden of multimorbidity will help inform healthcare policy and investment decisions.

In the first instance, the priority for research should be to determine:

Which multimorbidity clusters cause the greatest burden?

- Which clusters of conditions have the worst prognosis in terms of death and disability, as quantified by metrics such as 'years of life lost' (YLL) and 'years lost due to disability' (YLD)?
- Which clusters have the greatest impact on patient- and carer-centric outcomes such as treatment burden and quality of life?
- Which clusters result in the greatest healthcare utilisation and the greatest costs?
- Is the impact of clusters of conditions on these outcomes greater or less than that which would be predicted from the cumulative impact of the individual conditions?

Differences in the impact of specific disease combinations in different populations (e.g. HICs and LMICS) should be explored, as should the impact in different population subgroups (e.g. defined by sex, ethnicity, and SES). Most of these questions can only be answered by data generated from longitudinal studies, and the analyses of existing longitudinal datasets are therefore a priority. Analyses should not be restricted to physical chronic conditions but should include consideration of mental health conditions, since conditions such as depression and anxiety disorders appear to cluster very frequently with chronic physical conditions.

“

Research on the causes of multimorbidity is sparse and there are many evidence gaps.

4. Determinants of multimorbidity

Overview

What is known?

- A clear association between increasing age and higher rates of multimorbidity has been established in many different populations across a range of countries and contexts.
- Multimorbidity has generally been reported to be more prevalent in women and those of lower socioeconomic status, although such findings show inter-country differences highlighting that the associations of some factors with multimorbidity are context dependent.

What are the evidence gaps?

- Broadly, research on the determinants of multimorbidity is sparse, conflicting, and limited to cross-sectional studies.
- Whether there are factors that influence the risk of multimorbidity independently of the risk of individual component conditions is uncertain.
- While some clusters of conditions (e.g. coronary heart disease and COPD) are explained by common aetiological factors (e.g. smoking) the causes underlying other clustering is either currently speculative (e.g. coronary heart disease and depression sharing common inflammatory origins) or currently unexplained (e.g. coronary heart disease and osteoarthritis).
- Much of the work conducted to date on the causes of multimorbidity has not taken into account the specific morbidities involved.

Research priorities

- **Research priority 3: What are the determinants of the most common clusters of conditions?**
- Longitudinal studies are needed to better understand the direction and magnitude of associations with multimorbidity and to assess causality and temporal trends.
- Given the heterogeneity of multimorbidity, most value may be seen if the initial focus of research is directed to the determinants of the most common clusters and/or those of greatest impact.
- Progress may also be readily achieved by focusing attention on those clusters for which there may be an existing reason to suspect they share an underlying mechanism, for example inflammation.
- The use of a standardised approach to the definition and classification of multimorbidity, such as that proposed in **Chapter 2,** will greatly facilitate the clear interpretation of such work.

4.1 Challenges in understanding the determinants of multimorbidity

An association between increasing age and higher rates of multimorbidity has been established in many populations across a range of countries, and multimorbidity is typically the norm in older individuals regardless of how it has been defined.[286,287,288,289,290,291,292]

Nonetheless, as described in **Chapter 3**, multimorbidity is not unique to older adults and there is evidence indicating that the increasing prevalence of multimorbidity cannot be explained solely by an ageing population.[293,294] In some cases of multimorbidity, conditions may simply co-occur through chance, especially if the component conditions are individually common at the population level. Should such conditions increase in prevalence, then it is likely that the prevalence of multimorbidity will also increase. Further, it is possible that an increase in multimorbidity has arisen through improved survival from acute events like myocardial infarction, or from the more systematic diagnosis of asymptomatic conditions like hypertension. Still, it is also possible that there are additional and specific determinants of certain multimorbidity clusters in the same manner that there is for all other common chronic conditions.

As summarised below in **Section 4.2**, there has been some effort to explore associations between multimorbidity and risk factors known to contribute to single chronic conditions, such as ethnicity, socioeconomic status, smoking and alcohol use, physical activity, obesity, and nutrition. Although this current evidence base on the causes of multimorbidity beyond ageing remains sparse and often contradictory, because these variables are already associated with several chronic conditions, they may also be associated with multimorbidity if they result in the accumulation of individual conditions with shared causal factors.

However, much of the research performed to date has sought to identify causes of multimorbidity without reference to the specific morbidities involved. Given the heterogeneous nature of multimorbidity, considering multimorbidity in the abstract and pooling individuals who may well have entirely different clusters of conditions is unlikely to provide generalisable evidence. It also clouds efforts to understand whether there are factors that contribute to specific clusters of multimorbidity in a manner that is above and beyond what might be expected given any associations with single conditions. That is, are they associated with multimorbidity in a way that cannot be explained by the simple accumulation of multiple conditions? The standardised approach to the definition and classification of multimorbidity proposed in **Chapter 2** should be used in order to improve the interpretation and generalisability of data on the causes of multimorbidity and specific clusters.

The available data on potential determinants of multimorbidity are largely limited to cross-sectional studies. While such studies can provide descriptive associations, the direction of such relationships can often be interpreted in different ways, as illustrated in the remainder of this chapter. It is also difficult to discern from the current data the degree to which the investigated variables directly influence multimorbidity risk, as opposed to acting as a proxy for another causal factor. For example, numerous explanations at the sociocultural, behavioural, economic, and environmental level could plausibly explain some of the observed associations between multimorbidity and variables such as sex, ethnicity, and socioeconomic status, and greater clarity as to why multimorbidity may be more common in certain sub-populations is needed.

Longitudinal studies have an important role to play in unravelling causal and non-causal factors associated with multimorbidity. One example is an Australian cohort study that followed up 13,700 women with multimorbidity for 20 years over the period 1996 to 2016 and monitored the sequential development of multimorbidity with diabetes, stoke and coronary heart disease. The results indicated that the risk of developing mutlimorbidity with these three conditions was significantly greater in women who were separated, divorced, or widowed; were born outside Australia; had difficulty managing financially; were overweight or obese; had hypertension; were physically inactive; used tobacco; or had prior chronic conditions such as mental disorders, asthma, cancer, osteoporosis, or arthritis.[295]

More data from longitudinal studies are required to draw conclusions about the direction of the relationships between multimorbidity and potential risk factors, establish causation, and identify how trends and patterns change over time.

Lastly, the mechanisms by which potential determinants contribute to multimorbidity are also largely unknown. In particular, it was noted throughout our evidence gathering that there is a need to investigate whether factors such as those discussed in **Section 4.2** might affect the risk of multimorbidity via specific biological

mechanisms, and whether these are independent of the mechanisms by which they cause component conditions (also see **Section 4.3.1**).

Given the ubiquity of multimorbidity, the policy implications of gathering better evidence about its determinants, and their mechanisms, are far reaching. Such evidence may help improve the identification of individuals and populations at particular risk of developing multimorbidity, guide the development and targeting of intervention strategies, and optimise resource allocation and healthcare delivery strategies to improve patient outcomes.

4.2 Potential determinants of multimorbidity

4.2.1 Sex

Some studies have reported a sex disparity in the prevalence of multimorbidity, with reports from both HICs and LMICs indicating that multimorbidity is more common in women (see **Annex 6**).[296,297,298,299,300,301,302,303,304,304,305] However, other studies have not observed such differences (also see **Annex 6**).[306,307,308,309,310] A systematic review of observational studies performed across Europe, the United States, Canada, and Australia reported that multimorbidity prevalence was significantly higher in women in nine studies, but not in another five.[311]

The explanation for these apparent differences is uncertain, and it is unclear whether sex directly influences multimorbidity risk or whether differing findings instead reflect a failure of some studies to adjust for age or other confounding factors, inadequate statistical power to identify differences, or the inclusion of differential numbers of sex-specific conditions in each study. However, it is also possible that, rather than sex fundamentally influencing multimorbidity risk at the biological level, it instead acts as a context-dependent proxy for another social or behavioural characteristic that influences multimorbidity risk or detection. For example, higher rates of care-seeking shown by women in some countries may mean they are more likely to have a condition diagnosed than men.[312,313] Alternatively, in some settings women may suffer more adverse effects of poverty and income inequality, leading to more frequent multimorbidity compared to men.

Determining whether sex is a non-modifiable determinant of multimorbidity, or is instead acting as a surrogate for another potentially modifiable characteristic, will be important to ensure that prevention and management measures can be designed and targeted in the most optimal manner.

4.2.2 Ethnicity

In addition to sex, several epidemiological studies have explored whether there are associations between multimorbidity and ethnicity, and examples of these studies are detailed more fully in **Annex 7**.[314,315,316,317,318,319,320,321] However, differences in study methodology and in the terminology used to describe ethnicity have meant that such work is difficult to synthesise and interpret. As a result, whether there are real inter-ethnic differences in the risk of developing multimorbidity – as opposed to rates of diagnosis or differential survival – remains to be determined. The following examples highlight the complexity of synthesising research in this area.

At any given body mass index (BMI), South Asian populations tend to have a higher body fat percentage than other ethnicities. They are also more prone to developing abdominal obesity, which is associated with several NCDs.[322,323] It is therefore feasible that as ethnicity influences susceptibility to certain chronic conditions, when these NCDs cluster there might also be an association between ethnicity and multimorbidity.

However, many of the studies reporting an association between ethnicity and multimorbidity have investigated different ethnic groups within a single country or geographically defined population. Ethnicity, like sex, could therefore be acting as a context-specific proxy for other psycho-socioeconomic factors such as social deprivation, or even migrant status which has been the focus of a limited number of studies.[324,325,326,327] During the evidence-gathering workshop held in South Africa, it was noted that across Southern and sub-Saharan Africa there is a large population of migratory workers who have an increased risk of multimorbidity and face barriers to care, resulting in a greater burden of disease.[328]

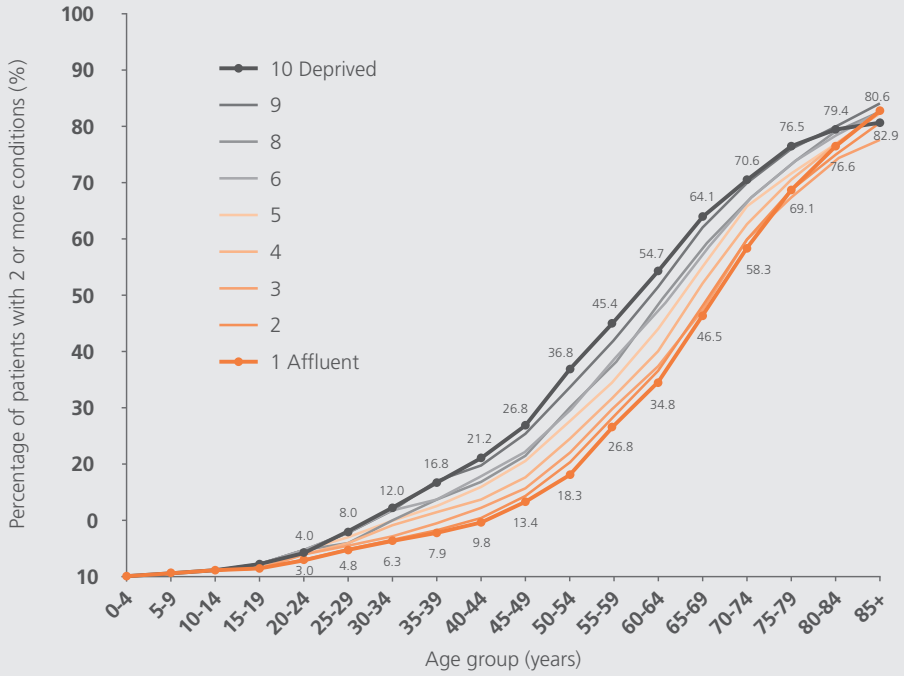
There therefore remains a need to better establish whether there are reproducible differences in multimorbidity risk between different ethnic groups, and whether they are caused by non-modifiable biological factors or by modifiable factors that affect groups defined by ethnicity differently. As for sex, clarity here is important to identify whether there are risk factors or behaviours which can be used as targets for preventive interventions, and to confirm whether management strategies need to be more optimally directed to certain sub-populations.

4.2.3 Socioeconomic status

Cross-sectional studies investigating multimorbidity prevalence in HICs have shown a negative (or inverse) relationship between multimorbidity and socioeconomic status (SES); that is, lower SES is associated with an increased prevalence of multimorbidity.[329,330,331,332,333,334,335,336,337,338]

Notably, one cross-sectional study of a primary care population in Scotland found that the onset of multimorbidity occurred 10 to 15 years earlier in those living in the most deprived areas compared with the most affluent (see **Figure 4**), and that the prevalence of multimorbidity including mental health conditions was almost twice as high in the most deprived areas compared with the most affluent areas.[339] Additional studies based in other UK populations have similarly indicated that social deprivation is particularly strongly associated with multimorbidity that included depression, anxiety, drug misuse, or pain.[340,341,342]

Figure 4. Multimorbidity prevalence by age and socioeconomic status



Source: Barnett K, *et al.* (2012).[343]

Multimorbidity prevalence is shown by age and socioeconomic status, whereby one on the SES scale represents the most affluent and ten represents the most deprived. The data are taken from a cross-sectional study performed using a dataset consisting of complete clinical data for all patients registered at 314 primary care practices, collectively caring for about a third of the population in Scotland, UK. The data illustrate a clear positive association between multimorbidity and SES, and that young and middle-aged adults living in the most deprived areas had rates of multimorbidity equivalent to those aged 10 to 15 years older in the most affluent areas. Multimorbidity was defined as two or more conditions from a list of 40 chronic physical and mental health conditions.

However, other studies have revealed that associations between multimorbidity and SES are complex and, at least in some contexts, multimorbidity may be more commonly seen in individuals of higher SES (see **Annex 8**).[344,345,346,347]

Differences between countries, or contexts, in the rate and direction of the association between multimorbidity and SES might be explained by differences in the demographic and epidemiological changes that predispose to chronic conditions. Yet, since most of the research to date has been cross-sectional, care should be taken when making inferences about the direction of the association between SES and multimorbidity. The following examples illustrate the complexity.

Situations where multimorbidity is more common in those of lower SES may arise due to the adverse influence of numerous factors which are often more commonly experienced by those of lower SES and contribute to chronic condition susceptibility, such as increased rates of smoking, poor diet, psychosocial issues including increased levels of stress and poor sleep, and reduced health literacy (some of these factors are also explored in more detail in **Section 4.2.4**). However, it is also possible that the development of multimorbidity occurs first, and subsequently results in a reduction in SES as a consequence of factors such as reduced earning capacity due to disability, or increased healthcare expenditure as a result of an increased need for high-cost healthcare (as discussed in **Chapter 3**).

Conversely, increased rates of multimorbidity at higher SES, particularly in LMICs, might be explained by those with higher income having greater access to high-calorie foods, tobacco, alcohol, and other lifestyle factors that contribute to multiple chronic conditions. An association between multimorbidity and high SES might also reflect that individuals with higher incomes have greater access to healthcare and are more likely to receive a disease diagnosis, and/or have higher survival rates from acute infections and accidents resulting in them being more likely to develop multiple chronic conditions associated with ageing. As an extension of this hypothesis, those of lower SES may have less access to healthcare, which could lead to an increased rate of mortality from acute conditions, or a lesser likelihood of disease diagnosis and underestimates of multimorbidity prevalence.

However, an added consideration is that the specific metric or component used to assess SES can also markedly influence findings, and studies that use different metrics for the assessment of SES may not be directly comparable. For example, the WHO SAGE Wave 1 data (generated in China, Ghana, India, Mexico, Russia, and South Africa) showed that while multimorbidity is less prevalent in those with higher levels of education in all six LMICs, multimorbidity was only associated with household wealth in China and Russia.[348] Another study, involving individuals aged 60 years and older in Bangladesh, showed that when SES was defined using a household assets index, multimorbidity is more common in those of higher SES, yet when SES was assessed using a measure of literacy, multimorbidity was more prevalent in those of lower SES.[349]

Longitudinal studies are required to better assess the true direction of the association between multimorbidity and SES, and provide additional data to help resolve the precise way in which SES might mediate an increased risk of multimorbidity.

Any association between multimorbidity and complex measures such as SES raises the need for a multi-sectorial approach to optimally managing multimorbidity.[350] Nonetheless, improved clarity about the precise factors mediating an association between SES and multimorbidity will be needed to ensure that the allocation of resources and application of management strategies is optimally targeted to those most likely to benefit from them.

4.2.4 Health-related behaviours and environmental exposures

As alluded to above, the health inequalities observed between those of differing SES might be influenced by several intermediary factors that affect the day-to-day experiences of individuals, including engagement in risky health-related behaviours such as smoking, and environmental exposures such as air pollution.[351]

Yet despite a large body of work on the contribution of various health-related behaviours and environmental exposures to the development of individual chronic conditions, the influence of such variables on multimorbidity – either in their own right or as intermediary factors for SES – has received less attention. A brief discussion of the work performed to date is provided below, although the extent to which – and how – such variables might individually contribute to multimorbidity, or interact with each other to exacerbate an individual's health, remains a key evidence gap.

Tobacco and alcohol use

Annex 9 provides a summary of predominately cross-sectional studies that have explored associations between multimorbidity prevalence and tobacco or alcohol consumption, and highlights that the evidence on a potential association between multimorbidity and such health-related behaviours is conflicting.[352,353,354,355,356,357] These inconsistencies may reflect different study populations and methodologies, or be a consequence of a failure to adjust for confounding variables.

Furthermore, as with other factors discussed above, a paucity of longitudinal data means that the direction of any relationship may be obscured.

Nonetheless, given the causal relationship between smoking and many chronic conditions, it is likely that some evidence of an increased prevalence of multimorbidity among either previous or current smokers indicates that smoking directly contributes to the development of multimorbidity (see **Annex 9**). One longitudinal study has indeed found that smoking is a predisposing factor for incident multimorbidity among an initially condition-free population in Finland.[358] However, it remains uncertain whether the co-occurrence of multimorbidity in smokers is greater than would be predicted by its impact on the risk of individual conditions.

Alternatively, it may also be true that an association between multimorbidity and smoking reflects the later development of a smoking habit as a potential coping mechanism in those with complex health needs. A similar scenario might apply to associations of alcohol consumption with multimorbidity. Once again, without longitudinal studies to clarify the direction of the relationship, it remains difficult to predict the likely impact of preventive strategies targeting tobacco or alcohol use on multimorbidity rates.

Physical activity

The consequences of sedentary behaviour – and the benefits of physical activity – on chronic conditions have been extensively studied. While it is therefore likely that these factors will also be relevant to those with multimorbidity, relevant data in this population are currently limited, inconsistent, and open to different interpretations (see **Annex 10**).[359,360,361,362,363,364,365,366]

For example, studies reporting an increased prevalence of multimorbidity in those who are less physically active could indicate either that leading a sedentary lifestyle contributes to the development of multimorbidity, or that multimorbidity reduces the capacity to exercise. One study investigating longitudinal trends in multimorbidity in an English population aged ≥50 years found a dose-response association between levels of physical activity and multimorbidity, with the odds of multimorbidity in people who engaged in vigorous activity being 55% lower compared to physically inactive individuals.[367] Another involving Australian women aged 45–50 years of age similarly found that physical inactivity is associated with increased odds of multimorbidity.[368] A lack of physical activity and obesity have both been identified as predisposing factors for incident multimorbidity in an initially condition-free Finnish population aged 25–64 years old.[369] This work was limited, however, to the consideration of multimorbidity comprising just two or more of five common conditions: diabetes, cardiovascular diseases, asthma/COPD, cancer, and rheumatoid arthritis.

However, while data from a multinational cross-sectional study involving 46 LMICs have similarly shown an increased risk of multimorbidity at low levels of physical activity (<150 minutes of moderate to vigorous physical activity per week), it noted that a proportion of this association was mediated by multimorbid patients reporting depression, mobility difficulties, pain, and sleep issues.[370]

Nutrition and obesity

The evidence that we received during the course of this project suggested that comparatively little work has been conducted on the influence of nutrition (to mean both malnutrition and undernutrition) on multimorbidity risk. One study has reported that in those with cardiovascular disease, low fruit and vegetable consumption is associated with the progression to multimorbidity as defined as the subsequent development of either diabetes, asthma/COPD, cancer or rheumatoid arthritis.[371] Others have indicated that the consumption of fruit, vegetables, and whole-grain products is associated with a reduced risk of developing multimorbidity.[372] An additional study has reported a positive association between the consumption of soft drinks and multimorbidity among adults in South Australia, noting that this relationship was most evident in those under 60 years old.[373] However, others have failed to demonstrate a link between nutrition and multimorbidity.[374,375]

Conversely, there are more data on the association between obesity and multimorbidity, despite such work being complicated due to a lack of consensus as to whether obesity should be considered as a risk factor for developing multimorbidity or be included in the definition of multimorbidity as a condition in its own right. Nonetheless, studies in HICs have reported that multimorbidity prevalence increases as BMI increases in both men and women,[376,377,378,379,380] with some suggesting that obese individuals develop multimorbidity

at an earlier age.[381] There is also some evidence that increasing BMI may act as an intermediate factor in the inverse association between education and multimorbidity.[382] A cross-sectional study involving data from LMICs has similarly reported that obese individuals in Russia, China, and Ghana have a significantly higher likelihood of having multimorbidity compared to those of normal weight.[383] However, as with other variables discussed here, it is possible that there is reverse causality in that multimorbidity might lead to reduced physical function or depression, in turn leading to reduced exercise or adverse nutrition choices, and ultimately obesity. Longitudinal studies are needed to provide clarity.

Associations between BMI and multimorbidity have led some to consider whether an emphasis on maintaining a healthy weight, or encouraging weight loss, could be a helpful means to reduce the risk of multimorbidity. One study has shown that weight loss in individuals who are initially severely obese can facilitate a reduction in the number of chronic conditions suffered from and therefore a reduction in the 'severity' of multimorbidity.[384] Such evidence is however limited, and more work is required to confirm this hypothesis and help predict whether public health measures to promote healthy weight will have a meaningful impact on multimorbidity prevalence.

Area of residence and environmental exposures

Variations in SES often accompany divisions in rural/urban habitation and differential exposures to certain environmental factors, meaning it is possible that such variables also influence multimorbidity risk. Indeed, as mentioned in **Chapter 3**, there are reports – albeit conflicting – of rural/urban divides in multimorbidity prevalence.[385,386,387,388] There is evidence that urbanisation and residential density can influence the risk of certain conditions,[389,390,391] and so clarity as to what degree rural/urban divides in multimorbidity risk are reproducible across different settings would be helpful given the rapid urbanisation taking place in many LMICs. Such work would benefit from exploring the various environmental, social and cultural factors that differ between rural and urban settings to better determine the mediating factors contributing to any differences.[392]

Exposure to environmental exposures such as outdoor and indoor air pollutants has been linked to the increased risk of several chronic conditions, including respiratory conditions such as COPD but also hypertension, stroke, and kidney diseases.[393,394,395] As with other variables in this report, these exposures could therefore be associated with multimorbidity through the accumulation of such conditions. The results from the KORA-Age Study, which involved adults aged 65–94 years in Germany, has reported that long-term exposure to NO_2 (nitrogen dioxide) and PM_{10} (inhalable particle matter with a diameter of between 2.5 and 10 micrometres) is significantly associated with multimorbidity, when defined as two or more conditions from a list of six conditions: heart disease, stroke, diabetes, hypertension, joint disease, and kidney disease.[396] Notably, when analysing the six chronic conditions separately, only the association between stroke and PM_{10} remained significant. However, to date, there is an evident lack of similar studies that have specifically investigated an association between multimorbidity and environmental exposures.

More optimal care for multimorbid patients will require greater efforts to determine which factors are most strongly, and most directly, associated with multimorbidity while recognising that these may be context dependent and moderated by each other (see also Section 4.3.2).

4.3 Determinants of clusters of conditions

Much of the work on the determinants of multimorbidity has focused on 'macro' level social, behavioural, and environmental factors already known to contribute to one or more chronic conditions. As recognised above, it can therefore be conceptualised that such factors might also contribute to multimorbidity through the simple accumulation of chronic conditions, and common conditions would be more likely to cluster together as a consequence of their greater frequency. Indeed, the association between multimorbidity prevalence and age could be explained by the greater opportunity of older individuals to accumulate chronic conditions over the lifespan.

However, as discussed in **Chapter 3**, certain clusters of conditions might occur for other reasons, such as shared aetiological factors. Nonetheless, there has been little work on which clusters represent aetiologically unrelated conditions and which represent conditions that share a common cause. As **research priority 1** in **Chapter 3** highlights, more clarity is needed on which combinations of conditions are commonly seen together, but such descriptive work would also benefit from a greater understanding of the mechanistic basis underlying such clustering. As discussed in **Section 4.3.1** certain conditions may cluster in individuals due to biological factors, such as a genetic predisposition or shared cellular responses (which may be evoked by some of the demographic and environmental exposures detailed above). Alternatively, certain conditions may occur commonly together as a result of the combined effect of numerous determinants which, when considered in an integrated manner, result in the context-specific clustering of conditions at the population and sub-population level (**Section 4.3.2**).

Notably, most epidemiological studies of disease risk and clustering focus either at the population or individual level. However, there is also growing evidence to suggest that factors that operate at the household level can also be drivers of disease risk – individuals who live with people with a chronic physical or mental health condition have been found to be at an increased risk of experiencing the same condition themselves, in both HICs[397,398,399] and LMICs.[400] Although living with others and having a large social network may be protective for multimorbidity (as noted in **Section 3.2.2**), it will be valuable to consider whether factors that operate at the household level can also influence multimorbidity clusters in a similar manner as to single conditions.

4.3.1 Biological mechanisms underlying multimorbidity

There is some evidence that common biological mechanisms – such as signalling pathways and cellular pathologies including oxidative stress – may be contributors to multimorbidity, even when the co-occurring conditions appear unrelated.

For example, there is a recognised link between chronic kidney disease (CKD) and cardiovascular disease that appears to be mediated, at least in part, by the clustering of traditional cardiovascular disease risk factors (such as hypertension, diabetes, and dyslipidaemia). However, it has been proposed that the clustering might also be mediated by additional risk factors unique to those with CKD, including mineral malabsorption, oxidative stress, and inflammation.[401] It has also been suggested that chronic inflammation and oxidative stress may underlie a number of other chronic conditions and cancers, and could therefore also contribute to several multimorbidity clusters.[402,403,404,405]

There is also growing evidence of interactions between type 2 diabetes and TB. Type 2 diabetes is a recognised risk factor for TB, and has been reported to increase the risk of incident TB by around threefold.[406] Although less robust, there is some evidence to suggest that patients with TB have higher rates of glucose intolerance, which may predispose them to developing type 2 diabetes.[407] In any case, the co-existence of type 2 diabetes and TB can exacerbate the severity of both conditions, and provides a clear example of the importance of understanding the determinants of multimorbidity clusters composed of both NCDs and infectious diseases.

Yet, notwithstanding these examples, the evidence provided to us highlighted that data on the various possible biological mechanisms that underpin different types of multimorbidity are lacking. Better understanding in this area is needed to improve risk stratification efforts and drive advances in preventive strategies. Further, the identification of common biological mechanisms between several conditions could permit the development of novel approaches to treatment targeting common pathways, with resulting benefits for numerous conditions simultaneously.

In this regard, it should also be noted that some pharmacological treatments used to manage a particular condition can predispose to poor health states (for example by causing weight gain or insulin resistance) and/or increase the risk of another seemingly unrelated condition, meaning that drug-related causes of multimorbidity also warrant consideration (see **Box 7**).

Box 7: The influence of pharmaceutical treatments on multimorbidity

There are examples of some pharmaceutical treatments which, when used over long durations, increase the risk of other conditions or lead to poor states of health. For example, the use of antiretroviral therapies (ART) for the treatment of HIV has been associated with insulin resistance, elevated blood lipids, and central fat accumulation, each of which can ultimately contribute to the development of type 2 diabetes and cardiovascular diseases.[408] These conditions appear to cluster in many LMICs in which HIV infection is common and the use of ART widespread.[409]

Some psychotropic medications, most notably antipsychotics, have also been reported to be associated with increased risk of several physical conditions including obesity, diabetes, cardiovascular diseases, and haematological diseases.[410,411] Given the common co-occurrence of mental and physical health conditions in the context of multimorbidity, there is a need for better evidence about causality and confounding in order to identify the exacerbatory effects of medications on those with multimorbidity.

Inadvertent adverse effects of medications on comorbidities exacerbates the complexities faced when managing multimorbid patients, underlining the need for collaborative care and improved integration not only for NCDs but also for the management of infectious diseases and mental health conditions. An improved understanding of the precise scenarios in which treatments might be expected to cause multimorbidity will help efforts to identify at-risk patients and optimise patient management.

4.3.2 Interactions between determinants of multimorbidity

Although most epidemiological research has focused on the contribution of discrete factors (e.g. smoking, blood pressure, diabetes) to the risk of specific conditions (e.g. coronary heart disease, stroke), individuals are not exposed to single risk factors in isolation. Instead, patients typically experience multiple risk factors in different and dynamic combinations often resulting in multiple conditions at different time points.

How the many biological, psychological, behavioural, socioeconomic and environmental risk factors interact to influence health outcomes is being increasingly recognised (see **Box 8**),[412] although how they may act in the genesis of multimorbidity is inevitably complex and not fully understood. Variances in the prevalence of individual conditions and the differential exposure of population subgroups to diverse combinations of risk factors increases this complexity, and is likely to mean that the frequency of multimorbidity clusters will similarly vary between different countries and population subgroups.

Future efforts to understand how risk factors interact to produce specific clusters of conditions are required, both in the general population and in specified population subgroups. One focus could be on the identification of factors, or groups of factors, that predispose to multimorbidity clusters independently of the individual component conditions. To do this will require the use of a standardised approach to the definition and classification of multimorbidity (see **Chapter 2**) as well as the collection of comprehensive information on different classes of risk factors. It will also require long-term follow-up for health outcomes and a large sample size to enable the reliable detection of interactions. In this regard, resources such as the UK Biobank offer a potential to make progress in our understanding of the determinants of multimorbidity of varying kinds.[413] Additionally, a standardised approach to definition, classification, and data collection would allow meta-analyses of data from multiple studies, both as a means to increase statistical power to detect interactions and to enable comparisons between population subgroups.

Box 8: The interaction of type 2 diabetes, depression, and societal factors

In a recent ***The Lancet*** series, a 'syndemic framework' was proposed as a way to visualise the presence of two or more conditions that adversely interact not only with each other, but also with the various social, economic, environmental, and political factors experienced by patients.[414] This holistic and highly contextual approach provides a way to consider not only how multimorbidity impacts on patients' lives, but also how their lives impact on their conditions by acknowledging the socioeconomic and environmental factors that contribute to the onset and development of multimorbidity.

One example of how many such variables can interact is type 2 diabetes and depression, and the influence of external factors - such as socioeconomic deprivation - on both the development and severity of the conditions.

Bidirectional link between type 2 diabetes and depression

There is increasing evidence that type 2 diabetes and depression exhibit a bidirectional relationship.[415] Type 2 diabetes has been reported to increase the risk of depression,[416] while adults with depression have been estimated to be 37% more likely to develop type 2 diabetes compared to those without depression.[417] There is also evidence that the co-existence of depression and diabetes can worsen diabetes outcomes, in part through treatment non-adherence,[418] but potentially through a direct effect of antidepressants on blood glucose levels.[419] Depression has also been shown to increase the risk of morbidity and mortality in populations with type 2 diabetes.[420]

Poor diabetes control has, in turn, also been reported to intensify the symptoms of depression, leading to a cyclical relationship between the two conditions.[421,422]

The additional influence of external factors

As well as the exacerbatory interactions between type 2 diabetes and depression, the context in which the patient lives also influences the prevalence and burden of these conditions. For example, poverty, migration, discrimination, and both chronic and acute trauma (including violence) have all been identified as risk factors either for type 2 diabetes or mental health conditions, or in some cases both.[423]

Although work to explore these various interactions has mostly been performed in HICs, a review of the limited evidence available in LMICs has replicated some associations, with both depression and the combination of depression and type 2 diabetes, being associated with lower SES.[424] The co-existence of depression and type 2 diabetes has also been shown to be more likely among older individuals, those with low family income, non-professional/administrative professions, those not currently employed and dependent, and those living alone.[425]

Further research in LMICs is needed to help elucidate the connections between depression, type 2 diabetes, and external factors such as poverty. Nonetheless, the co-existence of diabetes and depression can be predicted to be a growing challenge for healthcare systems in such countries. The burden of depression is continuing to increase globally,[426] and the growing burden of diabetes is most evident in LMICs. Three-quarters of all people with diabetes currently live in LMICs,[427] and it is projected that by 2040 one in ten adults globally will have diabetes, with the biggest increases in countries transitioning from low- to middle-income levels.[428] It is also predicted that the largest rise in mental health burden over the coming years will be seen in LMICs, as a result of population growth and ageing, and the inability of under-resourced healthcare systems to respond to this concern.[429,430]

Identifying interactions between conditions that result in particularly adverse outcomes has relevance for the way healthcare services are organised and delivered. In the case of concurrent type 2 diabetes and depression, there is a strong case for encouraging the greater integration of services for mental healthcare and physical healthcare.[431,432,433] In primary healthcare settings, depression and type 2 diabetes can often go undiagnosed; in LMICs up to 40% of patients with diabetes have unrecognised depression,[434] and those with depression also often have unrecognised diabetes as they have difficulties in accessing healthcare and effectively communicating with HCPs.[435] However, the improved identification of such patients leads to fewer complications and a reduced burden of disease, an advantage that could be gained from service integration.[436,437]

Recommended research priority 3

The identification of factors predictive of multimorbidity will improve the detection of those individuals most at risk of developing multimorbidity, facilitate predictions of future multimorbidity trends and burden (see **Chapter 3**), and identify populations that will benefit from targeted management strategies (see **Chapter 5**). Greater insight into the mechanisms by which such factors work will also aid in the development of innovative approaches to the prevention of multimorbidity.

Given the heterogeneity of multimorbidity, the initial focus of research should be on the determinants of clusters that are most common and/or of greatest impact. Progress may also be more readily achieved by focusing attention to those clusters for which there may be an existing reason to suspect they share an underlying mechanism.

We therefore consider it a priority for future research in this area to investigate:

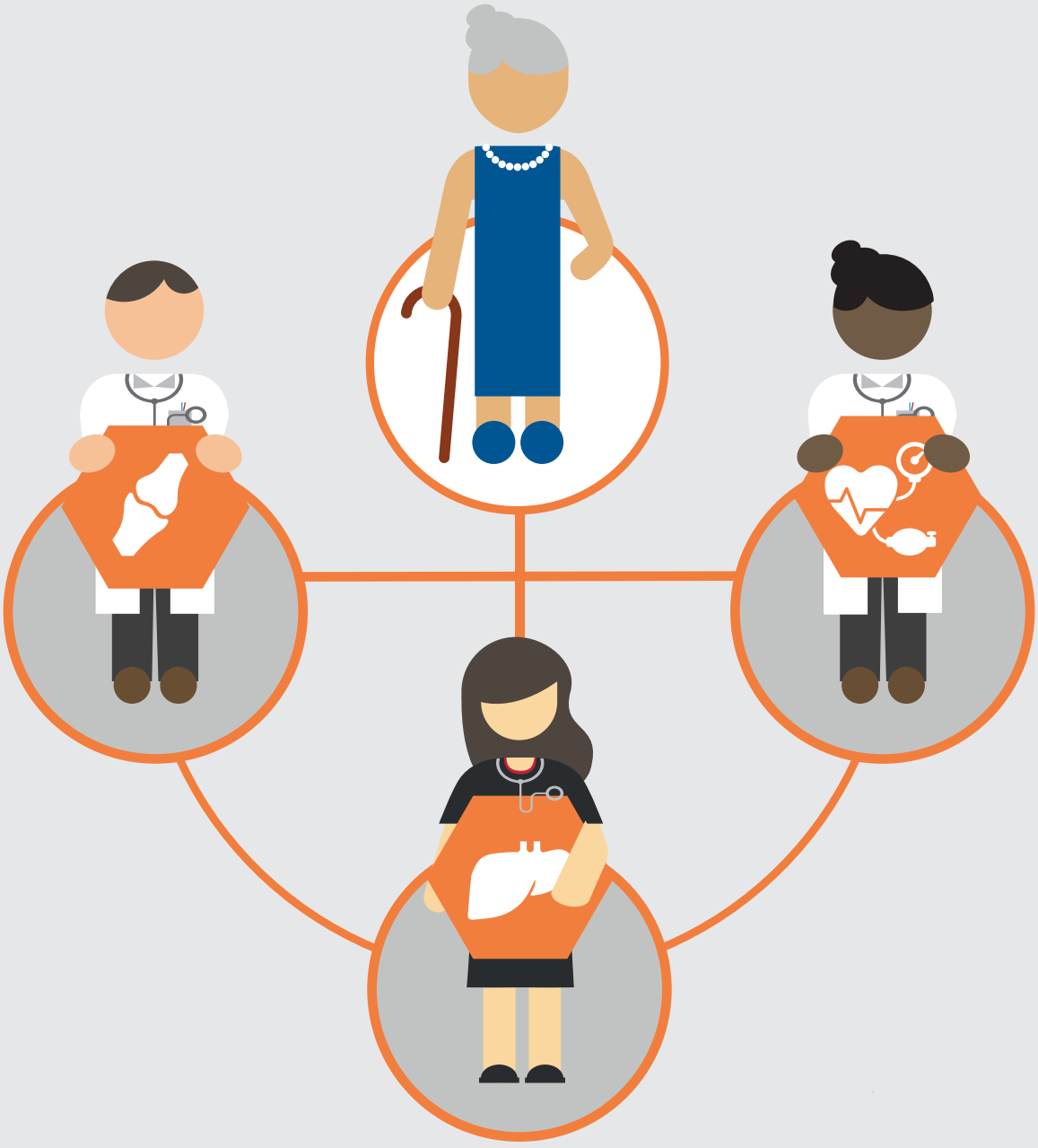
What are the determinants of the most common clusters of conditions?

- What are the main behavioural, environmental, sociodemographic, and biological factors associated with the most common clusters of conditions, and those clusters that generate the greatest burden at the population level?
- Which of these factors are causally related to multimorbidity, and which are surrogates for other causal factors?
- To what degree do these factors interact, either in a synergistic or additive way, to influence the risk of multimorbidity clusters?
- Are there factors for which their association with multimorbidity is greater than expected or explained by their association with the individual component conditions?

To ensure future work can disentangle and better understand the determinants of multimorbidity, the use of a standardised approach to the definition and classification of multimorbidity, such as that proposed in **Chapter 2**, is essential. Longitudinal studies are needed to better understand the direction and magnitude of associations and to assess causality.

“

Research is needed to design effective approaches for the personalised treatment of those with multiple conditions.



5. Management of multimorbidity

Overview

What is known?

- There is evidence from clinical trials about the effectiveness of preventive and therapeutic strategies developed for the management of most individual conditions that contribute to common clusters of conditions.
- However, many of these clinical trials have excluded patients with multimorbidity, and most healthcare systems are designed around the treatment of particular groups of conditions. The extent to which current single condition guidelines and strategies are also relevant to those with multimorbidity is not always clear.
- Although an approach to care that takes explicit account of multimorbidity is not always required, current management strategies may be suboptimal for those with complex healthcare needs as a result of multimorbidity.

What are the evidence gaps?

- Few trials have set out to assess the effectiveness of strategies specifically designed to prevent multimorbidity.
- It is therefore unclear whether it is possible to develop integrated preventive strategies for multimorbidity that are more effective than preventive strategies focused on individual component conditions.
- Similarly, few trials have set out specifically to assess the effectiveness of treatment strategies among patients with multimorbid conditions.
- It remains to be established whether it is possible to develop integrated treatment strategies for patients with multimorbidity that are more effective than treatment strategies targeting individual component conditions.
- The evidence gap also extends to how healthcare delivery services should be best organised to deliver care for multimorbid patients, given that specialist services are typically organised by body system and are therefore not conducive to the simultaneous management of multiple conditions affecting different body systems.
- Importantly, there is little evidence about how to ensure that the priorities and preferences of patients are integrated in prevention and treatment strategies.

Research priorities

- **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?**
- **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?**
- There is a need to formulate and evaluate preventive strategies that are specifically designed to reduce the incidence of multimorbidity.
- Similarly, there is a need to formulate and evaluate clinical strategies designed specifically for the personalised treatment of individuals with multimorbidity. Such efforts should take account of the priorities and preferences of patients.

5.1 Prevention of multimorbidity

The evidence presented in this report suggests that there is an increasing prevalence of multimorbidity, and describes how the wide-ranging downstream consequences represent a substantial global health challenge. Consequently, strategies to prevent the development of multimorbidity are needed.

An initial, key component of any strategy for the prevention of multimorbidity is the deployment of strategies already proven to reduce the incidence of individual conditions that compose common clusters. For example, tobacco cessation has been shown to prevent cardiovascular, respiratory and several neoplastic diseases, and their associated mortality.[438,439,440] A reduction in blood pressure prevents coronary disease, ischaemic stroke, cerebral haemorrhage, congestive heart failure and chronic kidney disease,[441,442,443] while LDL-cholesterol lowering prevents coronary heart disease and ischaemic stroke.[444,445]

Given that we know that many of the conditions listed above frequently cluster together, these three example interventions are expected to each reduce the risk of multimorbidity clusters composed of the conditions they have been shown to effect. The benefits will be particularly large when these preventive strategies are delivered in parallel. For example, the combination of smoking cessation, a 15mmHg reduction in systolic blood pressure and a 1mmol/L reduction in LDL-cholesterol will reduce the incidence of cardiovascular diseases, COPD and smoking-related cancers by more than half.

While such interventions can be expected to elicit benefits at the individual level, wider reductions in multimorbidity prevalence at the population level are likely to be achieved in other ways, such as through the introduction of taxes directed to unhealthy products. For example, there is evidence that tobacco taxation can reduce smoking and its related conditions,[446,447,448] and such benefits might also extend to a reduction in certain multimorbidity clusters. It is possible that taxation on other causes of common chronic conditions might similarly result in behaviour changes and a reduction of the incidence of these conditions, and therefore ultimately also reduce multimorbidity comprised of such conditions. For example, sugar taxes might be expected to reduce a number of chronic cardiometabolic conditions through the prevention of obesity, which is a driver of both high blood pressure and type 2 diabetes. It was noted in the evidence-gathering workshop held in South Africa that the recent introduction of a 20% tax on high sugar content drinks in this country has created an opportunity to collect data that would allow an assessment of the impact of this legislation on multimorbidity incidence.[449] Such work may also be possible in other countries that have recently introduced, or are expected to introduce, a sugar tax such as the UK, Mexico, Finland, Hungary, and France. However, gaining clarity on whether such public health approaches are indeed an effective and sustainable approach to preventing multimorbidity – and how they can be well-implemented to take into consideration the needs of communities – is important given the potential for such measures to present enormous financial challenges to LMICs.[450]

There are other conditions that are also components of common clusters for which there is much less evidence about how to prevent them, for example depression, lower back pain, and cognitive impairment. While data from randomised trials are few, there is some evidence that the risk of dementia is reduced through lowering blood pressure.[451,452] It is also possible that interventions that prevent obesity may prevent depression, since obesity can increase the risk of developing depression.[453] Additionally, it is possible that interventions that prevent depression may prevent lower back pain, since the risk of lower back pain is 50% greater among individuals with depression.[454] However, there is no evidence of efficacy from randomised trials for either of the latter possibilities.

It was noted through our evidence gathering that an optimal approach to multimorbidity prevention may require greater synergy across the NCD and infectious disease perspectives, as infectious diseases can also contribute to the development of certain NCDs and ultimately multimorbidity. At the evidence-gathering workshop with the BRICS countries, it was noted that some cancers are caused by viral infections (e.g. HPV and cervical cancer), and other chronic cardiovascular and respiratory conditions may be caused by bacterial infections (e.g. coronary heart disease and periodontal infections). Infections can also trigger longer-term autoimmune changes leading to chronic conditions such as Guillain-Barré syndrome.[455] Therefore, it follows that efforts to improve the control of infectious diseases through vaccination, early detection, and effective treatment, could reduce the risk of multimorbidity clusters composed of infectious and non-infectious conditions.

Nonetheless, the prevention of multimorbidity clusters that include a chronic infection may also require strategies focused on reducing the risk of associated non-infective chronic conditions. For example, it was noted at the workshop in South Africa (see **Section 3.2.1 and Box 7**) that among patients with HIV infection, antiretroviral therapy appears to increase the risks of several cardiometabolic conditions.[456,457,458,459,460,461] In many other situations, drugs such as statins and antihypertensive treatment have been shown to produce large reductions in myocardial infarction, stroke and other serious outcomes of cardiometabolic conditions. There is, therefore, a rationale for expecting that the same treatments will reduce the risks of the same outcomes among individuals on ART. Such treatment could, conceivably, be delivered by community clinics established to treat patients with HIV, although this possibility would first need to be explored in one or more qualitative research projects. A recent demonstration programme conducted in Malawi concluded that it was possible to implement a hypertension management programme in HIV clinics.[462] There would be value in assessing whether a broader cardiometabolic management programme could be implemented in a scalable and cost-effective manner in similar settings. If proven feasible, a controlled study, such as a cluster randomised controlled trial, could be designed to determine the impact of a cardiometabolic disease prevention program on clinical outcomes among patients receiving ART.

Further progress in the prevention of multimorbidity will benefit from an increased understanding of which conditions most commonly cluster together and which account for the greatest proportion of the total disease burden in the population (see **research priority 1** and **research priority 2** in **Chapter 3**), as such information will aid in the prioritisation of early diagnosis/screening efforts and preventive strategies. Where there are proven preventive interventions for the individual component conditions, the challenge remains to find the most effective way to deliver multiple preventive intervention strategies in parallel. Where there is a specific causal link between one condition and another, the challenge is to find the most effective way to prevent the second condition while treating the first.

By applying existing research about the prevention of individual conditions in the context of increasing understanding about clusters of conditions, it may be possible to develop and evaluate integrated preventive strategies to reduce the incidence of multimorbidity. It is hoped that such multimorbidity-specific interventions might be more effective than prevention strategies focused on individual component conditions alone.

Recommended research priority 4

The formulation of strategies for the prevention of multimorbidity requires improved evidence about the specific chronic conditions that are most likely to cluster, and the reasons for such clustering. Better evidence about the order in which conditions develop within clusters would also help guide strategies for the prevention of additional morbidities among those who have already developed one or more relevant conditions.

We therefore consider it a priority for future research in this area to investigate the following:

What strategies are best able to facilitate the simultaneous or stepwise prevention of chronic conditions that contribute to the most common multimorbidity clusters?

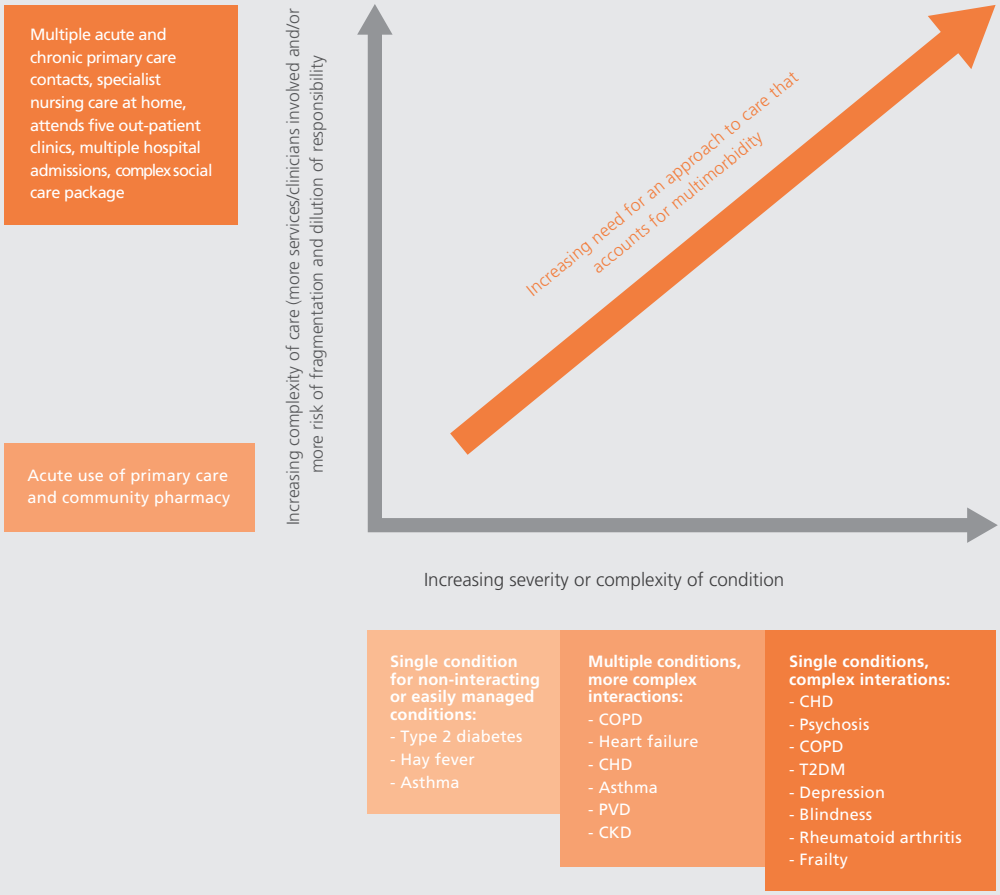
- Are there strategies for the prevention of clusters of conditions that will generate greater benefits than those achieved by focusing on single conditions in isolation?
- Where clusters are already known, can single-condition guidelines be refined or better integrated – and healthcare professionals (HCPs) better supported – to prevent conditions that a patient may not yet have but are at a higher risk of developing in the future?
- What approaches should be taken to prevent discordant morbidities where the nature of any causal relationship is unknown?
- How might mental health conditions be prevented among those who have a chronic physical condition, and how might chronic physical conditions be prevented among those who have a mental health condition?

Given that the most common clusters of conditions are likely to differ by sex, age, geographical and socioeconomic circumstances, it is also likely that the most impactful preventive strategies will differ by these (and other) population subgroups. Research on the prevention of multimorbidity therefore needs to take account of the context in which it will be performed. Similarly, the availability of the relevant resources required to prevent multimorbidity is also likely to dictate the success of any preventive strategies and should be considered.

5.2 Current treatment strategies for multimorbidity

When considering options for the care of multimorbid patients, an approach that takes explicit account of multimorbidity is not always required.[463,464,465] Yet, as the complexity or impact of multiple conditions increases, or as the complexity of treatment or care increases, so does the need for management strategies that take specific account of multimorbidity (see **Figure 5**). However, it is not always clear, for the reasons outlined below, how to provide optimal care for multimorbid patients with complex healthcare needs.

Figure 5. Relationship of complexity of care and complexity of conditions



Source: NICE (2016).[466]

Patients with multimorbidity may not always need an approach to care that goes beyond the optimal management of their individual conditions in isolation. Yet as the severity or complexity of their conditions and their interactions increases, the need for a management strategy that specifically considers multimorbidity becomes more apparent. This may especially be the case where the clusters of conditions are discordant in their management strategies, and where a patient presents with both mental health and physical conditions. Uncoordinated and fragmented care from healthcare systems centred on single conditions may be suboptimal for such patients.[466]

5.2.1 The exclusion of patients with multimorbidity from clinical trials

As for prevention, a key component of any strategy for the treatment of patients with multimorbidity is the deployment of strategies already proven to be safe and effective in the management of single component conditions. However, evidence about the safety and efficacy of such treatments is often generated by randomised trials that have, to varying degrees, excluded patients with multimorbidity.[467,468,469,470]

The exclusion of multimorbid patients from clinical trials is generally based on a belief that comorbid conditions may dilute or mask treatment benefits for the primary condition under investigation, or cause or exacerbate the side effects of the treatment under study. However, whether such concerns are justified

is often not certain. Strict eligibility criteria mean that trial populations often do not include major subgroups of patients with the condition of interest, resulting in large differences between the study's population and the populations in which the evaluated treatment will ultimately be used.[471,472,473,474] As a result, questions have been raised about the appropriateness of extrapolating data from some clinical trials to broader clinical populations with the target disease and comorbidities. There has been particular uncertainty about the generalisation of data on the balance of risks and benefits, given that absolute rates of conditions increased or decreased by treatment may vary substantially between clinical populations, with resulting differences in the balance of benefits and risks between patient subgroups.

Nonetheless, exclusion criteria often vary from trial to trial and so meta-analyses of all the relevant trials may still be able to assess the effects of treatment in subgroups defined by multimorbidity. For example, in meta-analyses of trials to lower blood pressure and LDL-cholesterol, treatment effects have been assessed across a range of patient subgroups including some defined by clusters of conditions.[475,476] In general, the results demonstrate that the relative reductions in cardiovascular disease risk for any given reduction of blood pressure or LDL-cholesterol are similar in those with and without major comorbid conditions. However, the absolute benefits are typically greater in those with common comorbidities, such as established coronary disease or cerebrovascular disease, because the absolute incidence of cardiovascular disease events is higher.

Conversely, however, when relative increases in adverse effects are similar in those with and without major comorbidities, the absolute increases can be very different. For example, if a treatment for diabetes were to increase the risk of falling by 20%, this may represent a very small absolute increase in risk in a young person with no major comorbidities, but could represent a very large increase in risk in an older person with a post-stroke functional impairment.

A partial solution to the problem of generalising results from highly selective trial populations to real-world multimorbid populations is to apply estimates of relative effects observed in the trials to estimates of absolute risks observed in real-world populations. This assumes that the direction and size of relative treatment effects is broadly consistent between groups. This approach provides a way to estimate a treatment's likely balance of benefits and risks in different patient groups, which is likely to be of greatest relevance to individuals when making decisions about the initiation or termination of treatment.

5.2.2 The single condition model of care and clinical guidelines

Most healthcare systems and guidelines are designed around the treatment of particular groups of conditions rather than the overall, holistic treatment of condition clusters. This is most apparent in the tertiary care sector where healthcare structures are designed around condition-specific medical specialities and subspecialties. Patients often cite frustrations due to having to see multiple different HCPs as a result of their multimorbidity, and having to navigate complex healthcare systems.[477,478,479,480,481,482] As discussed in **Section 3.3.2**, these frustrations can contribute to treatment burden,[483] and can have adverse effects on patients' perception of care. For example, one study from England reported that fewer multimorbid patients cite a positive experience of care from their GP compared to those with a single chronic condition or no chronic condition.[484] HCPs also share in these frustrations and, as discussed in **Section 3.5**, often raise concerns about time-limited consultations and feeling ill-equipped to manage complex, multimorbid patients who may have conditions beyond their immediate speciality.[485,486,487,488,489]

Single condition guidelines, which typically pay little attention to the management of co-existing conditions,[490] can also create challenges for HCPs when treating multimorbid patients. The comprehensive guideline-based management for many patients requires HCPs to have a knowledge of all guidelines for the most common chronic conditions, and the capacity to process these simultaneously to provide a personalised care plan for each patient. The complexity of these guidelines, the frequency of their revision, and the inconsistencies that may exist between guidelines with respect to the management of comorbid conditions, make this a difficult challenge.

When healthcare is organised around single condition specialties and guidelines, there is a concern that patients may be at risk of inappropriate polypharmacy. While the use of multiple drugs is often necessary and appropriate in patients with several conditions,[491] the potential for adverse drug effects grows as the number of drugs prescribed increases, thereby placing those with multimorbidity at particular risk.[492,493] This risk is likely to be exacerbated when multimorbid patients receive multiple prescriptions from different HCPs working in different parts of the healthcare system.[494] The risks may be particularly elevated in older

populations, disabled people, or those with mental health conditions that may limit self-management efforts and adherence to treatment. Indeed, there is evidence that multimorbidity is associated with increased rates of adverse drug events among patients who have both physical and mental chronic health conditions.[495] There is also evidence that the greater number of chronic conditions, the greater the likelihood of patient-reported safety incidents.[496] Evidence from populations aged 65 years or older also suggests that treatment by multiple prescribing physicians is an independent predictor of reports of adverse drug events.[497]

Several studies have reported that HCPs are concerned about using single condition guidelines for patients with multimorbidity, because of fears that this may result in inappropriate care.[498,499,500] Such concerns could be addressed through the development of guidelines focused on common clusters of conditions rather than individual conditions alone. However, that would require much more evidence from trials designed specifically to assess the effectiveness of treatment programmes that target multiple conditions in parallel or in a series.

Collectively, the current challenges in providing integrated care for patients with multimorbidity may result in suboptimal management.[501,502,503] Notably, the division between physical and mental healthcare services in many countries means that those with concurrent mental and physical health conditions are at particular risk of poor care, despite having higher rates of interaction with healthcare services.[504,505]

Greater efforts need to be taken to explore how best to provide care for those with complex multimorbidity (see Section 5.3). A particular priority will be to generate evidence from trials of treatment strategies designed for the management of patients with common multimorbidity clusters.

5.3 Better models of healthcare for treating patients with multimorbidity

There are three main levels of healthcare provision at which changes could be introduced to improve the care of patients with multimorbidity: the patient level, the provider level and the organisation level.[506] While these are outlined in more detail below, the working group was unconvinced that the current evidence is sufficient to recommend the adoption of any such strategies as an effective means to improve health outcomes for multimorbid patients. Research into interventions for multimorbidity remains sparse, and the evidence that does exist is largely limited to interventions targeting older patients in HICs.[507,508,509,510] Evidence from LMIC settings, which are experiencing a growing burden of multimorbidity, remains particularly limited.[511] Nonetheless, the working group is encouraged by the number of ongoing intervention trials identified during the course of this project (see **Annex 11**).

It was noted throughout our evidence gathering that, when exploring models of care for multimorbidity, there may be opportunities to take guidance from fields such as geriatric and palliative medicine where multimorbidity is largely the norm. Similarly, multimorbidity is frequently encountered by HCPs treating patients with rare diseases, such as lysosomal storage disorders where multiple bodily systems are typically affected in any given patient. In the UK, and several other countries around the world, the care for such conditions is often managed via specialist referral centres that are well established and highly effective at providing patient-centred, integrated care across multiple disciplines. Such specialist centres may therefore provide another helpful paradigm from which to design appropriate healthcare systems for the care of multimorbidity in the general population.[512]

Nonetheless, the precise context in which care is delivered will influence its success. Greater efforts to empirically evaluate novel or innovative multimorbidity interventions across a breadth of settings and patient populations are still clearly needed. We note that both the design and evaluation of interventions for the treatment of multimorbidity are likely to be complex, and such efforts might be facilitated by the adoption of an agreed framework for designing and reporting models of care for multimorbidity.[513] Such research should also consider drawing on the Medical Research Council (MRC) guidance on developing and evaluating complex interventions,[514,515,516] and be assessed using a range of carefully considered outcomes including clinical endpoints, patient-reported outcomes, and economic metrics (e.g. cost-effectiveness), as called for by the COMET (Core Outcome Measures in Effectiveness Trials) Initiative.[517]

A role for digital technologies in supporting multimorbidity management was repeatedly emphasised by those we received evidence from. Although an in-depth discussion is beyond the scope of this report, some additional information is provided in **Box 9**.

5.3.1 Patient-level interventions

Patient-level interventions can be formulated to encourage and support patient self-management and facilitate discussions about personal preferences and priorities with HCPs, which could involve non-medical factors that may be relevant to their needs, such as the social and environmental context in which they live.[518]

A 2016 Cochrane Review identified six studies of patient-level approaches to the management of multimorbidity, which included efforts such as educational support and self-management interventions.[519] The results of these six studies suggested that these interventions had little or no impact on clinical symptoms, mental health, or quality of life, indicating that patient-level interventions have limited impact when delivered in isolation. However, some studies published since the Cochrane Review have reported that 'whole-of-system' approaches, which embed patient-oriented interventions within larger scale organisation-level interventions may be more effective. These are discussed further in **Section 5.3.3**.

5.3.2 Provider-level interventions

Provider-level interventions aim to support individual HCPs in their provision of care to multimorbid patients, but there is currently little evidence as to whether such interventions improve care or outcomes.

Nonetheless, there are a number of areas in which provider-level support for HCPs might be expected to improve the quality of care for multimorbid patients. For example, because of the complexity of integrating multiple, potentially conflicting clinical guidelines for individual conditions (as outlined in **Section 5.2.2**), interventions that support improved clinical decision making could generate benefits for the treatment of multimorbid patients. This could help avoid 'clinical inertia', a concept ordinarily framed as a reluctance to initiate or intensify therapy for a patient receiving inadequate treatment, or a reluctance to stop or reduce treatment for a patient at risk of adverse treatment effects.[520] In this regard, there have been some efforts to encourage HCPs to consider 'quaternary prevention', whereby HCPs are supported to recognise situations where it might be appropriate to choose not to perform certain investigations or provide certain treatments.[521] As detailed in **Box 9**, the use of digital tools to support clinical decisions about treatment intensity and related issues could be valuable, although there has been limited research to date on digital approaches to the management of multimorbidity.

Additionally, provider-level support could involve efforts to help HCPs incorporate individual patient priorities and preferences in personalised treatment plans for multimorbid patients. Given that multimorbidity is a patient-centred construct, it is hoped that such an approach could help prioritise treatment goals which might in turn improve patient satisfaction and quality of life and increase adherence to medication, with the ultimate aim of potentially improving clinical outcomes. Of relevance to this is evidence showing that some patients with multimorbidity feel their views are not adequately considered by HCPs, indicating a desire to be more involved in decisions about care plans.[522,523,524]

A number of different theoretical frameworks have been developed to support the broader inclusion of patient preferences into care plans. For example, 'minimally disruptive medicine' is a patient-centred concept which aims to tailor treatment regimens to the realities of patients' daily lives by placing a greater focus on improving patient wellbeing, and achieving patient-reported goals, while imposing the smallest possible treatment burden.[525,526,527] This approach has been suggested as particularly helpful for patients who are heavily burdened by their conditions and associated treatments, which is often the case for those with multimorbidity. However, it remains uncertain as to whether improvements in wellbeing are offset by a more rapid clinical deterioration that might occur when patients do not receive treatments proven to prevent this.

Another theoretical construct, termed the 'Ariadne principles', has been proposed as a framework to support clinical decision making when specifically dealing with multimorbid patients.[528] This model focuses on agreeing realistic treatment goals that take account of the patient's conditions and treatment options, as well as the patient's preferences and prioritisation of health problems. A study is currently ongoing that will implement the Ariadne principles in a population of multimorbid patients taking five or more drugs. Its primary aim is to evaluate whether this construct can reduce concerns of inappropriate polypharmacy by improving the 'appropriateness' of prescribing in these patients, as assessed by a prescribing quality measure known as the Medication Appropriateness Index (MAI) (also see **Annex 11**).[529]

Some initial work has shown that the routine capture and assessment of patient-reported outcome measures (PROMs) from patients with multimorbidity is considered helpful by both patients and clinicians,

as a means to support the prioritisation of patients' health problems and monitor their health conditions.[530] However, it is not a simple task to enumerate and address the numerous, potentially conflicting priorities of individuals with multiple conditions, particularly as patient preferences change over time.[531,532,533,534]

While there are a number of tools to measure patient preferences with respect to treatment for a single condition, a systematic review performed in 2016 noted that there are very few practical tools to support HCPs in capturing patient priorities across a number of co-existing conditions.[535]

The development and evaluation of clinically applicable tools for eliciting patient priorities and preferences in a multimorbidity setting is a priority.

Recommended research priority 5

Efforts to better support HCPs providing care to multimorbid patients are needed. However, the wide array of combinations of conditions experienced by such patients complicates the development of generic interventions that are applicable and helpful to all those with multimorbidity. Nonetheless, improvements in patient care may be more readily realised through the development of treatment strategies, and potentially clinical guidelines, that address specifically defined clusters of conditions, such as those that are most common and/or those known to cause the most burden for patients or HCPs. In order to do so, greater efforts are needed to include patients with multimorbidity in clinical trials and to develop tools to capture patient preferences and priorities in a clinical context.

We therefore consider it a priority for future research in this area to investigate the following:

What strategies are best able to maximise the benefits and limit the risks of treatment among patients with multimorbidity?

- Can tools be developed to assist healthcare professionals (HCPs) to deliver comprehensive integrated care to multimorbid patients that takes full account of all relevant clinical guidelines for the management of component conditions?
- Can strategies be developed to maximise the benefits and minimise the risks associated with the multiple treatments often received by patients with multimorbidity?
- How can patient and carer priorities be better captured and incorporated into care plans for patients with multimorbidity, and do these optimise clinical and patient-centred outcomes?

We appreciate that intervention trials for the prevention or treatment of multimorbidity are likely to be more difficult to design and evaluate compared to conventional clinical trials focusing on single conditions. Such research should therefore draw on the MRC guidance on developing and evaluating complex interventions,[536,537,538] and be assessed using a range of carefully considered outcomes including clinical endpoints, patient-reported outcomes, and economic metrics (e.g. cost-effectiveness), as called for by the COMET (Core Outcome Measures in Effectiveness Trials) Initiative.[539] The simultaneous use of such metrics will help build a clearer picture of where interventions are most likely to succeed and fail. Such work should also recognise that many interventions designed to manage specific concerns will be most successful when embedded within the wider healthcare system.

5.3.3 Organisational-level interventions and healthcare reform

As introduced in Section 5.2.2, most healthcare systems are predominately designed around the treatment of single conditions as opposed to clusters of conditions. Such structures are a barrier to the provision of the integrated care required by patients with multimorbidity. For example, while patients admitted to hospital will receive comprehensive guidelines-based care for the condition that led to the admission, other concurrent conditions that may be of similar or greater relevance to the patient's overall health may be overlooked.[540] In particular, when healthcare is focused on the treatment of individual conditions, there is, inevitably, a reduced likelihood that attention will be paid to managing functional deficits (e.g. climbing stairs, self-dressing) that may be of much greater importance to the patient than the treatment of a condition that is not a cause of the deficit.[541] Greater attention to such deficits is warranted given that they have been associated with an increased risk of readmission and long hospital stays.[542,543,544]

Research is required to find innovative strategies for the comprehensive integrated care of patients with multiple conditions, ensuring that due attention is paid to the management of co-existing conditions and deficits, in addition to treatment of the condition of primary concern at any given time.

The integration of care can be achieved in a number of different ways and at a number of different levels, for example at organisation, service, and HCP levels.[545] Some qualitative studies have suggested that improving the continuity of care between HCPs across different parts of the health system may improve the perception of care and improve clinical outcomes in multimorbid patients.[546,547,548,549] Changes to the way primary care consultations are provided has also been proposed for patients with multimorbidity, who might benefit from or require longer consultation times or an adjustment of consultation times in proportion to the complexity of multimorbidity.[550,551,552,553]

More substantively, it has been proposed that a move towards service integration and the provision of coordinated care by multidisciplinary teams (including generalists, specialists, and allied healthcare workers) could maximise the efficiency and effectiveness of care for patients with multimorbidity. In this regard, improved communication between team members, allowing them to 'speak with one voice', may also promote trust amongst patients.[554]

Some have commented that such changes in the way healthcare is organised and provided will require a significant shift away from the currently dominant 'specialism' perspective to a greater emphasis on 'generalism', whereby contributions from a range of HCPs could be provided under the supervision of a generalist physician.[555,556,557,558] While an in-depth consideration is beyond the scope of this report, it is noteworthy that healthcare system reforms and calls for increasing the number of generalist physicians would have substantial implications for medical education, insofar as there would need to be a better balance between training focused on specific conditions and body systems, and training focused on multiple conditions and the specific skills required to manage multiple conditions simultaneously. This would be needed to ensure that the next generation of HCPs can collectively create a workforce that is better equipped and prepared to deal with the complexities of multimorbidity.[559,560]

Efforts to evaluate organisational level changes have formed the predominant focus of much of the, albeit limited, research to date. Of the 18 RCTs included in the aforementioned 2016 Cochrane Review, the main intervention in 12 of the trials involved a change to the organisation of care, for example through promoting case management[561] or by employing strategies designed to enhance multidisciplinary team work.[562]

The authors of the review noted that substantial methodological variations between studies complicated direct comparisons, which in turn precluded drawing robust conclusions regarding the effectiveness of the interventions. That said, it was noted that broad organisational interventions designed with an aim of producing standardised changes in care delivery for all patients with multimorbidity were less likely to be effective. This is understandable given the broad clinical heterogeneity of multimorbid patients, and the inevitable need for some flexibility in the provision of care. Indeed, the Cochrane Review revealed that the most likely way to elicit positive outcomes for patients might be to more specifically target interventions at particular combinations of conditions, notably those including depression, or at specific functional difficulties that may be common across various conditions, such as limitations in performing physical activity. However, work in this area remains sparse and requires great attention.

As already noted in **Section 5.3.1**, there have also been efforts to embed patient-oriented interventions within larger scale organisation-level interventions in an attempt to evaluate whether 'whole-of-system' approaches can improve the care of multimorbid patients. For example, the CARE Plus study was performed with the aim of investigating whether a 'whole-of-system' approach involving longer GP consultations, more training and support for HCPs, and additional self-management support for patients, has the potential to increase wellbeing and improve quality of life.[563] While the intervention was reported to be cost-effective, it was challenging to implement. Another, smaller RCT involving 50 participants with two or more chronic conditions, found that a self-management programme involving regular interaction with occupational therapists produced improvements in self-efficacy, health-related quality of life, and patient-reported goal attainment.[564] A larger trial to evaluate this intervention further is currently ongoing.[565] The Joint Action on Chronic Diseases and Promoting Healthy Ageing across the Life Cycle (JA-CHRODIS) has developed a 'Multimorbidity Care Model' with the aim of improving the coordination of care while also supporting self-management. There are plans to roll this programme out across EU member states, and ongoing evaluation of its success will be required.[566] Several other studies evaluating the success of complex, whole-system approaches that embed patient and professional level interventions within wider organisational changes are ongoing at the time of writing, and are included in **Annex 11**.

Advances in this area could help progress towards the WHO's Framework on 'integrated people-centred health services', which aims to shift the emphasis of health systems designed around conditions and health institutions towards health systems designed around people.[567] The WHO has recognised that such an approach is crucial to the development of health systems that can respond to emerging and varied health challenges, including multimorbidities.

Further research to evaluate and compare the outcomes elicited by different approaches to providing care to multimorbid patients is required.

Notably, such work will need to recognise that system-level strategies for managing multimorbidity need to take account of the strength and availability of the resources available, the way in which healthcare is provided, and the way in which HCPs are incentivised. As such, the precise opportunities and barriers to improving the organisation, integration, and delivery of multimorbidity care will differ between HICs and LMICs, but also between different HICs (e.g. the UK and the United States) and LMICs at different stages in the development of their health systems. Lessons from HICs that already have strong and well-resourced healthcare systems may not be applicable to LMICs, where the integration of care is likely to also require capacity building and improvements in the quality of services. Alternatively, however, given that many LMICs are in the process of redeveloping their healthcare systems, now may be an opportune time for such countries to formulate and evaluate innovative strategies for the management of multimorbid patients that might be less achievable in more established HIC settings. Indeed, at the evidence-gathering workshop for BRICS countries, it was agreed that there could be an opportunity for LMICs to 'leapfrog' the systems typical of HICs and establish integrated models of care more suitable for populations experiencing high levels of multimorbidity.[568]

For this reason, research on the development and evaluation of intervention strategies for the management of multimorbidity must be context-specific. Similarly, research into the scaling-up of effective intervention strategies also needs to be context-specific. Implementation research is required to determine how best to promote new intervention strategies and embed them in routine care in a way that is sustainable and scalable.[569] Research is also required to determine how best to introduce organisational changes in an equitable manner to avoid widening health inequalities between those of differing SES that might arise as a result of the inverse care law – a term referring to the scenario whereby optimal medical care is most readily accessible to those with the least need for it.[570,571] Ensuring efforts are taken to mitigate or limit the impact of the inverse care law on those with multimorbidity is vital given the observed SES gradient in multimorbidity prevalence and its potential impoverishing impact (**Chapter 3**).[572] Such efforts are also relevant within wider ambitions to achieve universal health coverage, where all can have equitable access to quality healthcare services.[573]

Financing care for multimorbid patients

It was recognised throughout the course of this work that the redesign of health systems to improve the care of patients with multimorbidity cannot be done without consideration of strategies for financing the provision of both health and social care in an attainable, sustainable, and equitable manner for all.[584] For example, new models of care shown to be effective in research projects will not necessarily be scalable without financial incentives for healthcare providers to coordinate the care of patients in a more appropriate manner. In the absence of such financial strategies, the sustainability of any system reforms will be compromised.[585]

Encouragingly, however, there have been some efforts across Europe to improve the care for patients with multimorbidity by using innovative financing strategies to create a stimulus to promote the coordination and integration of care.[586,587,588] One example is the provision of 'add-on payments' which are given to HCPs who achieve specific outcomes related to improved care.[589] This includes pay-for-performance schemes where provider payments are adjusted for the quality of provided care. It should be noted, however, that the metrics typically used to evaluate quality of care are focused on the management of individual conditions, and new initiatives are required to develop and evaluate specific indicators of the quality of care for multimorbid patients.

Another approach is to use 'bundled payments' where separate payments to individual providers or services are grouped together.[590] This can create shared incentives to HCPs to provide collaborative, integrated care for those with multimorbidity. 'Population-based payments' (or 'capitation payments') extend this concept to that of a single payment that covers the care provided to all patients living in a particular area over a defined period of time. Since fragmented care for patients with multimorbidity is unlikely to be cost-effective, such payment systems may encourage the provision of better integrated care. However, for both bundled and population payments, the incorporation of specific financial incentives linked to the care of multimorbid patients is necessary for optimal outcomes to be achieved. Many LMICs are currently in the process of expanding health insurance coverage, and are moving away from input-based payments (such as salaries for individual HCPs, and fixed budgets for secondary care) towards remuneration mechanisms, which include capitation payments for primary care and payment schemes based on 'diagnosis-related groups (DRGs)' for inpatient care. Reforming payment schemes to more efficiently use resources will be a step towards universal health coverage, and encouraging efforts to design and evaluate such innovative financing solutions in LMICs may provide them with another opportunity to leapfrog countries where the financing schemes for healthcare are more established.

While many payment and incentive mechanisms show promise for improved care for patients with chronic conditions, each will have its own limitations, and one standard approach is unlikely to be suitable and effective in all settings. More specifically, work by the Organisation for Economic Co-operation and Development (OECD) on financing the care for patients with multimorbidity has observed that country-specific demographic and epidemiological considerations will influence the most appropriate choice of financial model.[591] More research is needed to understand how different payment schemes can best improve the care of those with multimorbidity.

Box 9: The role of digital technologies in managing multimorbidity

An output from the ICARE4EU consortium study has recently recognised that digital and electronic technologies can facilitate the provision of tailored, patient-centred, and integrated healthcare to people with complex care needs including those with multimorbidity.[574] Importantly, the growth in mobile telecommunications and increased access to the internet across many LMICs means that digital technologies might afford valuable opportunities to reach, monitor, and treat patients in areas where resources and access to care are otherwise low.[575] The complexity of multimorbidity and the immense difficulty in combining multiple guidelines highlights a role for technology in identifying and helping deliver optimal healthcare.

Improving access to care

In low-resource settings and other scenarios where access to care is limited or difficult, digital technologies can provide an alternative way to access high-quality care and treatment. Examples of such innovations include: telehealth and telemedicine systems; health, activity and behaviour monitoring systems; environmental sensors; and e-prescriptions. Given that those with multimorbidity often require numerous consultations which can be time-consuming and expensive, the benefits of improved access through the use of technologies may be particularly significant to such patients. However, there has been little research to evaluate their utility in multimorbid patients.

Supporting clinical decision making

Clinical decision support (CDS) systems are computerised aids that are designed to improve clinical decisions by providing HCPs with actionable recommendations or management options based on patient-specific information, which is intelligently filtered or presented at appropriate times.[576,577]

To support HCPs in dealing with the complexity of treating multimorbidity, a CDS system could be developed to generate a synthesised recommendation that takes into account guidelines for all relevant conditions. In turn, such a system could help mitigate risks of safety resulting from inappropriate polypharmacy.[578] Developing such a CDS system is challenging as it must be capable of handling the breadth and complexity of multimorbid patients. Indeed, multimorbidity has been recognised as one of the 'grand challenges' of clinical decision support.[579] To date, a high-quality CDS system for the management of multimorbidity is yet to be developed and more innovative approaches may be needed.[580,581]

Improving the coordination and integration of care

Digital technologies can also be used to enhance integrated care by providing a platform for multiple HCPs to exchange and discuss patient information, and ultimately make shared recommendations. In doing so, such platforms could be expected to improve the continuity of care while also reducing the management inefficiencies often experienced by multimorbid patients.

A large international project, C3-Cloud, involving 12 partner organisations in seven countries is currently evaluating a system designed to allow personalised care plans to be developed through the input of a multidisciplinary care team, and supported by the systematic and semi-automatic condensation of clinical guidelines.[582] The proposed cloud-based system will also include active patient engagement and goal setting, helping this innovative approach to be patient-centred.

Improving patient self-management

Digital technology designed for use by patients can help support various aspects of self-care. Such tools can include computerised and mobile technologies (e.g. website resources and apps, and online support communities), wearable devices, and a range of other tools that track and monitor symptoms, provide health advice or psychological support, and help promote adherence to medication and wider health promoting behaviours through reminders and alerts. Such technologies offer the potential to reduce the burden of multimorbidity on healthcare services by reducing the workload of HCPs and avoiding unnecessary appointments or hospitalisations.

An example of such an approach is ProACT (Integrated Technology Ecosystems for ProACTtive Patient Centred Care), a digital health research programme that aims to develop and evaluate digital health solutions to improve home-based integrated care to support older adults (aged 65+) with multimorbidity to remain living independently in their community for as long as possible.[583] The project includes a focus on self-management, and runs from January 2016 to July 2019.

Recommended research priority 6

Healthcare systems across the world are typically designed around the care of single conditions, or organ systems. Conversely, the heterogeneity of multimorbidity often necessitates a more holistic and integrated approach to ensure that optimal care is provided for all co-existing conditions. Further work is now needed to develop, evaluate, and compare different healthcare organisation structures to determine whether they can elicit positive benefits to patients and the HCPs responsible for their care. To what degree such healthcare reforms are economically viable and sustainable also warrants consideration.

We therefore consider it a priority for future research in this area to investigate the following:

How can healthcare systems be better organised to maximise the benefits and limit the risks for patients with multimorbidity?

- What strategies can be deployed to improve the integration of services for patients with multimorbidity, including those aspects of care directed to physical health, mental health, and social independence?
- Do any such strategies improve clinical outcomes, patient-centred outcomes, and the cost-effectiveness of care?
- How does the composition of the healthcare team affect outcomes for patients with multimorbidity? How should the roles of generalist and specialist HCPs be defined to maximise the effectiveness and safety of care?
- How can different financing models incentivise systems and providers to provide better care for those with multimorbidity?

Future research in this area should be cognisant of differences in care delivery and resource availability between different countries, and recognise that the most optimal organisation of healthcare will be context dependent. While not a priority within the scope of this report, we are also aware that calling for research to evaluate large-scale changes in healthcare system design and healthcare delivery may ultimately have wider ramifications in areas such as medical education. We would therefore urge other interested stakeholders, such as medical schools and professional medical colleges, to remain mindful of this and consider supporting research to identify strategies that might best support such system changes.

Acronyms

ADLs: Activities of daily living
ART: Antiretroviral therapies
BMI: Body mass index
BRICS countries: Brazil, Russia, India, China, South Africa
CDS: Clinical decision support
CIRS: Cumulative Illness Rating Scale
CKD: Chronic kidney disease
COPD: Chronic obstructive pulmonary disease
DALY: Disability-adjusted life year
EGPRN: European General Practice Research Network
EU: European Union
FCI: Functional Comorbidity Index
GP: General practitioner
HCP: Healthcare professional
HIC: High-income country
ICD: International Classification of Diseases
LMIC: Low- and middle-income country
MeSH: Medical Subject Heading; a hierarchically-organised terminology for indexing and cataloguing biomedical information
MRC: Medical Research Council
NICE: National Institute for Health and Care Excellence
OECD: Organisation for Economic Co-operation and Development
OOP: Out-of-pocket
PACK: Practical Approach to Care Kit
PROMS: Patient-reported outcome measures
QOF: Quality and Outcomes Framework
QoL: Quality of life
RCT: Randomised controlled trial
SAGE: World Health Organization's Study on Global AGEing and Adult Health
SES: Socioeconomic status
TB: Tuberculosis
WHS: World Health Organization's World Health Survey
WHO: World Health Organization
YLD: Years lost due to disability
YLL: Years of life lost

Glossary of terms

Adherence
When patients follow a recommended course of treatment.

Aetiology
The modifiable and non-modifiable cause of a medical condition.

Cluster
A group of conditions that co-occur.

Chronic
The term 'chronic' can be interpreted in a number of ways. However, throughout this report we use the term loosely to refer to any physical, mental, or infectious health condition of long duration.

Cochrane Review
A systematic review of research findings on a specific health topic using a defined methodology.

Cohort study
An observational study in which data are collected from a group of participants over a period time.

Comorbidity
The co-occurrence of additional conditions alongside a primary, or index, condition that is the focus of attention.

Condition
Throughout this report, the term condition should be read to encompass physical non-communicable diseases (NCDs) of long duration, mental health conditions of long duration, and infectious diseases of long duration.

Cross-sectional
An observational study in which data are collected from a group of participants at a single moment in time.

Demographic
A sector of the population that shares specific characteristics such as income, age, education, or ethnicity.

Epidemiology
The study of the distribution, causes, and impacts of health and disease conditions in defined populations.

Frailty
A situation in which a patient exhibits increased vulnerability to stressors from the accumulated consequences of morbidities or treatments.

Healthcare professional (HCP)
Qualified individuals specialising in the maintenance of human health through the use of evidence-based medicine and caring. Healthcare professionals may provide advice, preventive and curative strategies for a condition, or conduct research, with the aim of improving health outcomes for patients and the wider community.

Incidence
The probability of occurrence of a particular medical condition in a population over a certain period of time.

Longitudinal study
An observational study where data are gathered from a single group of participants at multiple time points.

Modifiable determinants
Factors that can predispose an individual to a condition, but can be changed e.g. smoking, physical inactivity, obesity.

Multimorbidity
In the context of this report, multimorbidity is defined as the co-existence in adults of two or more chronic conditions, where no one condition is considered an index condition.

Non-modifiable determinants
Factors that can predispose an individual to a condition, but that are unchangeable e.g. age, sex, ethnicity.

Polypharmacy
The concurrent use of multiple medications by a patient.

Prevalence
The proportion of a given population with a particular medical condition at a given point in time.

Primary care
Care provided by a healthcare professional (HCP) in the community such as a general practitioner (GP).

Secondary care
Medical care provided by a medical specialist or in a hospital.

Shared decision making
Shared decision making is a process whereby healthcare providers and patients work together to select tests, treatments, management or support packages, taking account of both the clinical evidence and the patient's informed preferences.

Treatment burden
The adverse impact on wellbeing experienced by a patient as a result of receiving medical care.

Annex 1: Project conduct and timeline

This policy project and its report were led by an expert working group, which included both UK and international members who collectively contributed a broad set of experience and expertise. Details of the working group members, their affiliations, and areas of expertise are in **Annex 2**. The working group was supported by a secretariat of Academy staff. Their details are also provided in **Annex 2**.

The working group met five times over the course of 15 months, and was also informed by a range of additional activities to gather external input including a call for written evidence, several workshops, oral evidence, and desk-based research. These evidence-gathering activities were comprehensive but a formal literature review has not been performed, and as such the references used throughout this report should not be considered as exhaustive.

The project was formally launched in September 2016 with a **call for written evidence**, which aimed to gather external input on the definition(s) of multimorbidity and the current evidence base on multimorbidity, and to seek opinions about future research priorities and opportunities. The call was widely disseminated to a range of national and international stakeholders including researchers, healthcare professionals, research institutions, funders, industry, and patient groups. A total of 22 responses were received, all of which can be accessed on the Academy's website alongside a summary developed by the secretariat.[592] The working group also gathered additional input on the effectiveness of clinical management strategies when dealing with multimorbidity and on how best to incorporate patient views into clinical care through an **oral evidence session**. A summary of this session can also be accessed on our website.[593]

Lastly, this report has also been informed by **two workshops** developed using the funding the Academy has been granted from the Global Challenges Research Fund (GCRF).[594] The first workshop, *'Addressing the global challenge of multimorbidity: Lessons from South Africa'*, was held over two days in November 2016, in Johannesburg, South Africa.[595] The second workshop was held in London in March 2017, and extended its focus to the BRICS countries (Brazil, Russia, India, China, and South Africa); the five major emerging national economies.[596] Both workshops provided valuable insight into the issue of multimorbidity across LMICs, importantly allowing the commonalities between these countries to be clearly identified. The input from these workshops has been instrumental in ensuring that the recommendations of this report are globally relevant.

A number of useful resources on multimorbidity were submitted to us during these evidence-gathering activities. While these are not exhaustive, they have been provided in **Annex 3**.

To help ensure the report's recommendations were relevant, both to the target audience and on a global scale, **the early stages of the project were also supported by the attendance of several observers at working group meetings**. Observers contribute to working group projects as representatives of their organisations, with these organisations being considered as key stakeholders for the report's recommendations. Input from observers is therefore critically valuable to ensure that the recommendations are relevant and can be feasibly implemented, allowing the project to achieve its desired outcome. However, observers were not present when the report's recommendations were finalised by the working group, and only contributed to early deliberations. We are grateful to those observers who supported the project in this manner; their names and affiliations are provided in **Annex 2**.

The report has been reviewed, and approved, by an external review group which was appointed by the Council of the Academy of Medical Sciences. Care was taken to ensure this group benefited from international representation, and details of the review group are provided in **Annex 2**.

Annex 2: Membership of the working group, secretariat, and review group

Working group

Members
Job titles and affiliations were correct at the time of publication. Members participated in a personal capacity and not on behalf of their affiliated organisations.

Professor Stephen MacMahon FMedSci [Chair], Principal Director, The George Institute for Global Health.
Stephen MacMahon is Principal Director and co-founder of The George Institute for Global Health. He also holds positions as Professor of Medicine and James Martin Fellow at the University of Oxford and Professor of Cardiovascular Medicine at the University of New South Wales. The George Institute is a research and development organisation with 650 staff located at centres in Australia, China, India and the UK. Its primary goal is the improvement of healthcare provided in major emerging economies, and its focus is on the management of those chronic conditions responsible for most premature deaths. Stephen is also the founder of George Health Enterprises Limited, a wholly-owned subsidiary of The George Institute devoted to building social enterprises that deliver products and services designed to reduce the global burden of disease. Stephen has published more than 300 scientific papers and delivered more than 200 invited lectures. For his work in the field of cardiovascular disease, he has received numerous awards, fellowships and honours from various governments, universities and learned societies. For his research achievements in cardiovascular medicine, Stephen has been elected a Fellow of the Australian Academy of Science, the British Academy of Medical Sciences and the Australian Academy of Health and Medical Sciences. He was made an Officer of the Order of Australia in the 2017 Queen's Birthday Honours list.

Professor Peter Calverley FMedSci, Professor of Respiratory Medicine, University of Liverpool.
Peter Calverley is Professor of Respiratory Medicine within the Institute of Ageing and Chronic Disease at the University of Liverpool. He was an Honorary Consultant Physician at Aintree University Hospital, Liverpool until 2015 when he retired clinically. His major research interests have been in applied respiratory physiology, sleep and breathing disorders and chronic obstructive pulmonary disease (COPD) and he has published extensively in these areas. He authored the first textbook devoted to COPD and chaired the Department of Health group which developed the national COPD strategy. He chaired the National Institute for Health Research (NIHR) Clinical Research Network Respiratory Specialty Group for five years and served on the Department of Health Respiratory Programme Board. He is a past President of the British Thoracic Society and is currently an Associate Editor of the American Journal of Respiratory and Critical Care Medicine.

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Nishi Chaturvedi is Professor of Clinical Epidemiology in the Institute of Cardiovascular Science at University College London (UCL). She qualified in Medicine at the University of London in 1985 and has subsequently specialised in clinical epidemiology, obtaining first an MSc and subsequently an MD in epidemiology. Professor Chaturvedi began her epidemiological career at UCL, moving to Imperial College as a professor in 2000, and then returning to UCL in 2013. Professor Chaturvedi leads one of the largest tri-ethnic older age cohorts (SABRE, Southall And Brent REvisited), and was appointed to lead the oldest national UK birth cohort (National Survey of Health and Development) in 2017. Her work highlights the marked ethnic contrasts in risks of cardiometabolic disease. This was used to inform lower obesity thresholds for diabetes screening in the UK. Previously, she led the largest cohort of type 1 diabetes (the EURODIAB cohort), which informed two trials of interventions to reduce the burden of diabetes complications, the EUCLID trial and the DIRECT programme, all of which were published in *The Lancet*. She has also worked on the aetiology of and interventions for cardiometabolic disease in low- to middle-income countries such as the Caribbean, Egypt and Pakistan. Her current key interest is the exploitation of detailed, non-invasive precision

phenotyping to understand disease aetiology and mechanisms for the identification of novel interventions. Additional current roles include Vice Dean for Research for the Faculty of Population Health Sciences, Associate Editor of Diabetologia and Chair of the British Heart Foundation Fellowships Committee.

Professor Zhengming Chen, Professor of Epidemiology and Director of China Programmes, University of Oxford.
Zhengming Chen qualified in medicine at Shanghai Medical University in 1983 (now Fudan University), and gained his DPhil in epidemiology at the University of Oxford in 1993. He is now Professor of Epidemiology at the University of Oxford. His research focuses on the environmental and genetic causes of chronic conditions, evidence-based medicine and evaluation of widely practicable treatments for chronic conditions. Over the past 20 years, he has initiated and led several large randomised trials in heart disease, stroke, and cancer and has been the lead principal investigator for the Kadoorie Biobank, which involves over 512,000 adults recruited from ten diverse areas of China during 2004–08 with extensive data collection by questionnaire and physical measurements, and with long-term storage of biological samples and linkages to any episodes of hospitalisation.

Dr Lynne Corner, Director of VOICE based at the National Innovation Centre for Ageing, Newcastle University; Director of Engagement, Newcastle University Institute for Ageing.
VOICE is an international organisation established in 2007 to harness the immense experience, ideas and insights of the public, especially older people, to develop evidence based products and services that are needed to support healthy ageing, working with researchers and businesses, and to respond to the challenges and opportunities arising from demographic change. Lynne works closely with the NIHR Innovation Observatory on the Horizon Scanning and public insights programme, and co leads the NIHR James Lind Alliance Priority Setting Partnership on older people living with multiple conditions. Lynne has a special interest in dementia, and through the Dementia Innovation Hub at Newcastle University works with families living with dementia to develop training and support to help people live well with dementia.

Professor Melanie Davies CBE, Professor of Diabetes Medicine, University of Leicester.
Melanie Davies is Professor of Diabetes Medicine at the University of Leicester, and an Honorary Consultant Diabetologist at the University Hospitals of Leicester NHS Trust. She is also an NIHR Senior Investigator Emeritus and Director of the NIHR Leicester Biomedical Research Centre. Professor Davies' research interests include the causes, screening, prevention, self-management and treatment of type 2 diabetes mellitus. Professor Davies has published over 500 original articles in national and international peer-reviewed journals, such as *The Lancet*, The New England Journal of Medicine and the BMJ, and has over £60m of peer-review grant funding.

Professor Majid Ezzati FMedSci, Chair in Global Environmental Health, Imperial College London.
Majid Ezzati is Chair in Global Environmental Health at Imperial College London. He is also the Director of the Wellcome Trust-Imperial Centre for Global Health Research, and the Director of the WHO Collaborating Centre on NCD Surveillance and Epidemiology. He leads an interdisciplinary research programme in global health and the environment. He led the WHO's Comparative Risk Assessment Study, a multi-institution study that developed and applied a framework for consistent and comparable analysis of risk factors, which formed the scientific core of the World Health Report 2002: Reducing Risks, Promoting Healthy Life. Majid leads the NCD Risk Factor Collaboration (www.ncdrisc.org), a worldwide scientific collaboration to strengthen the evidence on the exposure to and health effects of NCD risk factors.

Professor Bruce Guthrie, Professor of Primary Care Medicine and Head of Population Health Sciences Division, University of Dundee.
Bruce Guthrie is a general practitioner and Professor of Primary Care Medicine at the University of Dundee where he leads the Quality, Safety and Informatics Research Group, which conducts applied research to translate basic and clinical research into effective and reliable clinical practice. He was previously an MRC Health Services Research Training Fellow in Edinburgh and a Harkness Fellow in Health Care Policy at the University of California, San Francisco. His research interests focus on the definition, measurement and improvement of quality and safety. His current work primarily examines multimorbidity and prescribing safety, including developing and testing complex interventions in both fields. As well as conducting research, he practices clinically in a former mining village in Scotland, and is a member of a number of NHS advisory bodies, recently chairing the guideline development group for the NICE guideline Multimorbidity: clinical assessment and management.

Professor Kara Hanson, Professor of Health System Economics and Associate Dean for Research, Faculty of Public Health and Policy, London School of Hygiene & Tropical Medicine.
Kara Hanson's research focuses on the economics of health system financing and organisation in LMICs. Her recent research has focused on the potential for strategic purchasing in the context of pathways to universal health coverage. She has worked extensively on the role of the private sector in health systems, and co-edited the recent *The Lancet* series on the private sector in health. She has also researched the economics of delivering maternal and child health and malaria interventions in a range of sub-Saharan African settings. She is co-Research Director of RESYST (Resilient and Responsive Health Systems), a health policy and systems research consortium including partners from seven countries in Africa and Asia. She has published extensively in health economics and health policy journals, and has advised the WHO and UNICEF on health financing issues.

Professor Vivekanand Jha, Executive Director, The George Institute for Global Health, India; James Martin Fellow, The George Institute for Global Health, University of Oxford.
Vivekanand Jha is a physician with a specialisation in the area of kidney diseases and is currently the President-Elect of the International Society of Nephrology. Professor Jha is recognised as a global expert on kidney disease, and focuses on emerging public health threats globally and in India. He currently leads research projects operating in more than 20 countries. He is particularly interested in using multi-disciplinary approaches and innovations to address the major challenge posed to humanity by non-communicable diseases. He is a member of Task Forces and Scientific Advisory Committees of the Department of Science and Technology of the Government of India, is an advisor to the WHO, and has developed guidelines for management of patients with kidney disease.

Professor Vikram Patel FMedSci, Pershing Square Professor of Global Health and Wellcome Trust Principal Research Fellow, Harvard Medical School; Joint Director of the Centre for Chronic Conditions and Injuries at the Public Health Foundation of India.
Vikram Patel is the Pershing Square Professor of Global Health at Harvard Medical School. He is an Adjunct Professor and Joint Director of the Centre for Chronic Conditions and Injuries at the Public Health Foundation of India; Honorary Professor at the London School of Hygiene & Tropical Medicine (where he co-founded the Centre for Global Mental Health in 2008); and a co-founder of Sangath, an Indian NGO which won the MacArthur Foundation's International Prize for Creative and Effective Institutions in 2008 and the WHO Public Health Champion of India award in 2016. He is a Fellow of the UK's Academy of Medical Sciences and has served on several WHO expert and Government of India committees. His work on the burden of mental disorders, their association with poverty and social disadvantage, and the use of community resources for the delivery of interventions for their prevention and treatment has been recognised by: the Chalmers Medal (Royal Society of Tropical Medicine and Hygiene, UK); the Sarnat Medal (US National Academy of Medicine); an Honorary Doctorate from Georgetown University; the Pardes Humanitarian Prize (Brain & Behavior Research Foundation); an Honorary OBE from the UK Government; and the Posey Leadership Award (Austin College). He also works in the areas of child development and adolescent health. He was listed in TIME Magazine's 100 most influential persons of the year in 2015.

Professor Martin Prince, Professor of Epidemiological Psychiatry and Assistant Principal (Global Health), King's College London.
Martin Prince directs King's Global Health Institute and is the Director of the NIHR Global Health Research Unit on Health System Strengthening in Sub-Saharan African Countries at King's College London. His epidemiological research has been oriented to the salience of mental and neurological disorders to health and social policy in low and middle income countries, with a focus on older adults and dementia. His current work focuses on healthcare delivery in resource-poor settings, and system and practice innovations to improve coverage, processes and outcomes of care.

Professor Arnie Purushotham, Professor of Breast Cancer, King's College London and Director of King's Health Partners Comprehensive Cancer Centre; Consultant Surgeon, Guy's & St Thomas' NHS Foundation Trust; Senior Clinical Advisor, Cancer Research UK; Senior Clinical Advisor, Tata Trusts Cancer Program, India.
Arnie Purushotham has been a consultant surgeon and clinical academic for 22 years having worked in Glasgow, Cambridge, London and Mumbai. As a scientific researcher for the last 25 years, Professor Purushotham's goal has been to drive high-quality clinical and translational research that directly impacts on cancer patients. Key areas of research are patterns of metastatic spread, pathophysiology of lymphoedema, sentinel lymph node biopsy, novel optical intra-operative imaging, window-of-opportunity targeted therapy trials, cancer and evolutionary biology, cancer outcomes and cancer policy.

Professor Alan Silman FMedSci, Professor of Musculoskeletal Health, University of Oxford.
Alan Silman is an epidemiologist and a rheumatologist. He was Director of the UK's Arthritis Research Epidemiology Unit at the University of Manchester between 1988 and 2006 and has published over 500 articles in the broad field of arthritis and musculoskeletal diseases. His research interests covered pharmacoepidemiology, genetics and disease outcome; research that spanned several musculoskeletal disorders. He then became Arthritis Research UK's (ARUK) first Medical Director, a post he held from 2007 until the end of 2014. At ARUK he was responsible for the strategic direction of the charity's research activities as well as leading on both healthcare professional and patient education initiatives. Currently he is Professor of Musculoskeletal Health at the University of Oxford. Amongst his other roles, he chairs appeal panels for NICE, advises the Medicines & Healthcare products Regulatory Agency (MHRA) on drug safety and is one of the editors of the leading international postgraduate textbook, Rheumatology (6th Edn. Elsevier 2014).

Professor Stephen Tollman, Director, MRC/Wits Rural Public Health and Health Transitions Research Unit (Agincourt), School of Public Health, University of the Witwatersrand, South Africa.
Steve Tollman directs the MRC/Wits Rural Public Health and Health Transitions Research Unit (Agincourt) and the Health and Population Division in the School of Public Health, University of the Witwatersrand. Internationally, he is guest professor in the Centre for Global Health Research, Umeå University, Sweden, and Principal Scientist of the INDEPTH Network (International Network for the Demographic Evaluation of Populations and Their Health). Steve was founding Board Chair of INDEPTH and is principal investigator for multicentre research for the INDEPTH Programme on Adult Health and Aging. Currently he serves on a panel of the National Academies of Science, USA, addressing the continuing epidemiological transition in sub-Saharan Africa. Major research interests focus on adult health and ageing, non-communicable diseases and chronic care.

Professor Jadwiga Wedzicha FMedSci, Professor of Respiratory Medicine, Imperial College London.
Wisia Wedzicha is Professor of Respiratory Medicine at the National Heart and Lung Institute, Imperial College London. She qualified at Somerville College, University of Oxford and St Bartholomew's Hospital Medical College, Queen Mary University of London. She was elected as a Fellow of the Academy of Medical Sciences in 2013 and is an NIHR Senior Investigator. Professor Wedzicha has a major interest in the causes, mechanisms, impact and prevention of COPD exacerbations, and in the role of bacterial and viral infection in COPD exacerbations. She directs an active research group specialising in COPD exacerbations, and has published extensively on this topic. She chaired the Department of Health Home Oxygen Clinical User Group, and was a member of the guideline development group for the revision of the NICE COPD guideline. She was also a member of the Programme Board for the COPD National Clinical Strategy. Professor Wedzicha was Editor-in-Chief of Thorax from 2002 to 2010, and is a member of the BioMed Central advisory board. She is currently Editor-in-Chief for the American Journal of Respiratory and Critical Care Medicine. In addition, she is on the editorial boards of a number of international journals. She was *The Lancet* Ombudsman until 2014, Publications Director for the European Respiratory Society (ERS) and has also previously been ERS Guidelines Director.

Observers
Observers participated in working group meetings as representatives of their respective organisations. Observers did not contribute to the development of the report's recommendations.

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We are also grateful for the helpful contributions from Dr Jenny Tran, University of Oxford and the contributions of the Academy's policy interns.

Review group

This report was reviewed by an external panel appointed by the Academy's Council. Reviewers were asked to consider whether the report met the Terms of Reference, and whether the evidence and arguments presented in the report were sound and supported the conclusions. Reviewers were not asked to endorse the report or its findings. Reviewers participated in a personal capacity and not on behalf of their affiliated organisations.

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Annex 3: Helpful resources

During the evidence gathering performed for this work, a number of resources about multimorbidity were brought to our attention. We have replicated this list here, although it should not be considered exhaustive.

- International Research Community on Multimorbidity.[597]
- Guidelines International Network (G-I-N) multimorbidity resources.[598]
- Journal of Comorbidity; an international journal that publishes articles on the pathophysiology, diagnosis, prevention and management of patients with comorbidity/multimorbidity.[599]
- Healthcare Quarterly issue on *Complex Care and Multimorbidity.*[600]
- BMC Family Practice Special Collection on *Impact of Comorbidity and multimorbidity on primary care.*[601]
- BMJ collection on multimorbidity.[602]
- A PLoS Medicine Special Issue on *Cardiovascular disease and multimorbidity.*[603]
- healthtalk.org

Annex 4: Clustering of conditions

The table below provides some references to international studies performed to identify common clusters of conditions. These references were identified through our evidence-gathering activities but should not be considered as a fully comprehensive overview of the literature.

Study	Design	Study population and setting
Sinnige J, *et al.* (2013).[604]	A systematic review of 19 articles, representing 23 cross-sectional and observational studies.	Countries included the United States, Canada, Australia, Singapore, and three European countries (Sweden, the Netherlands, and Germany). Component studies were conducted in either the general population (n=13), primary care (n=7), or ambulatory care setting (n=1). Data were collected from various sources depending on the study and included interviews, clinical assessment, health records, insurance claims, and surveys. Population sizes varied from 599 to over one million individuals.
Violan C, *et al.* (2014).[605]	A systematic review of 39 articles, representing 44 observational studies.	Countries included 12 high-income countries: Australia, Canada, Germany, Greece, Ireland, Italy, the Netherlands, Spain, Sweden, Switzerland, the United States and the UK. All studies were conducted in primary care populations. The sources of data differed between the studies and included health records, questionnaires, administrative claims, interviews, clinical examination and ambulatory data. Sample sizes ranged from 328 to 31,313,331 participants.
Prados-Torres A, *et al.* (2014).[606]	A systematic review of 14 cross-sectional studies.	Countries included seven high-income countries: the United States, Australia, and several European countries (Germany, Spain, Sweden, Italy and the Netherlands). Data were collected from various sources depending on the study and included clinical administrative databases, self-administered surveys, and interview-based surveys. Sample sizes varied between 1,039 and 1,645,314.
Garin N, *et al.* (2016).[607]	Secondary analysis of cross-sectional data from the Collaborative Research on Ageing in Europe project (COURAGE) and the WHO Study on Global AGEing and Adult Health (SAGE).	41,909 nationally representative individuals aged 50 years and older from Finland, Poland, and Spain (COURAGE) and China, Ghana, India, Mexico, Russia, and South Africa (SAGE).

	Multimorbidity definition	Aims	Findings
	The review focused on multimorbidity or comorbidity that reported prevalence rates of combinations of two or more conditions.	To describe the prevalence of condition combinations in older patients with multimorbidity and to obtain supportive information towards multimorbidity guideline development.	From a total of 63 conditions, 165 different combinations of two conditions were identified. Depression was found to be most commonly clustered with another condition. Hypertension, diabetes, and coronary artery disease were also commonly seen in disease pairs.
	The definition of multimorbidity differed between studies. In 25 studies, multimorbidity was defined as the presence of at least two chronic conditions; in five studies as the presence of at least three chronic conditions; and in 12 studies by counting the total number of medical conditions and defining groups accordingly. Two studies did not report these data.	To systematically review studies and synthesise evidence on the prevalence, patterns and determinants of multimorbidity in primary care to inform the organisation and delivery of primary care.	Estimates of multimorbidity prevalence and the identification of specific patterns vary widely between studies. The most frequent combinations were those that included osteoarthritis, and a cardiometabolic cluster of conditions such as high blood pressure, diabetes, obesity and ischaemic heart disease. In general, the most frequent pairs were made up of the most frequent single conditions in each study. Clusters involving more than two conditions are less well characterised.
	Definitions varied between included studies.	To identify patterns of 'associative multimorbidity', defined as the non-random association between conditions.	A total of 97 patterns composed of two or more conditions were identified. Among these, 63 patterns were composed of three or more conditions. Three broad groups of non-random associations were found across all studies. One included a combination of cardiovascular and metabolic conditions, a second was related to mental health conditions, and the third with musculoskeletal conditions.
	Two of 12 chronic conditions with high prevalence in most settings (angina, arthritis, asthma, cataract, COPD, depression, diabetes, edentulism, hypertension, cognitive impairment, obesity, and stroke).	To identify and describe multimorbidity patterns in low-, middle- and high-income countries.	A 'cardio-respiratory' pattern – where multimorbidity arises from combinations of angina, asthma, and COPD – was present in all countries investigated except Finland and Russia. A 'metabolic' pattern consisting of diabetes, obesity, and hypertension was found in all countries except Mexico. A pattern including arthritis and depression was found only in China, Ghana, and India.

Annex 5: Clustering of mental and physical health conditions

The table below provides some references to international studies performed to describe the relationship between physical and mental health conditions. These references were identified through our evidence-gathering activities but should not be considered as a fully comprehensive overview of the literature.

Of note, many of these studies are cross-sectional and are unable to provide data on the direction of the relationship between physical health conditions and mental health conditions. A few cohort studies which are able to indicate directionality are included at the end of this table.

Study	Design	Study population and setting
Fortin M, *et al.* (2006).[608]	Performed as part of a larger study involving patients recruited during primary care consultations.	238 participants with a mean age of 59 years across 21 general practices in Québec, Canada.
Barnett K, *et al.* (2012).[609]	A cross-sectional analysis of a national dataset including 1,751,841 individuals held by the Primary Care Clinical Informatics Unit at the University of Aberdeen, UK.	Primary care patients aged 16 years and older across 314 medical practices in Scotland, UK (one-third of the Scottish population).
Gunn JM, *et al.* (2012).[610]	A cross-sectional postal survey.	7,620 primary care patients aged 18–76 years across 30 general practices in Victoria, Australia.
Smith DJ, *et al.* (2014).[611]	A cross-sectional secondary analysis of data from the Primary Care Clinical Informatics Unit at the University of Aberdeen, UK.	1,751,841 patients across 314 primary care practices in Scotland.
Arokiasamy P, *et al.* (2015).[612]	A cross-sectional population based survey using data from the WHO's Study on Global AGEing and Adult Health (SAGE) Wave 1 (2007–10).	42,236 adults aged 18 years and older from six LMICs: China, Ghana, India, Mexico, Russia, and South Africa.
Stubbs B, *et al.* (2016).[613]	A cross-sectional analysis of data from the World Health Survey.	242,952 adults aged 18 years old and older across 48 LMICs.

	Multimorbidity definition	Aims	Findings
	A count of all chronic conditions listed in patients' medical records, and also measured using the Cumulative Illness Rating Scale (CIRS), which takes into account condition severity.	To evaluate the relationship between psychological distress and multimorbidity among patients seen in family practice, taking account of the number and severity of conditions.	Multimorbidity measured by a count of chronic conditions was not related to psychological distress, whereas the risk of psychological distress was associated with multimorbidity when measured using the CIRS to account for severity.
	Two or more conditions from a list of 40, including mental health conditions.	To examine the distribution of multimorbidity, and of comorbidity with physical and mental health conditions, in relation to age and socioeconomic deprivation.	The presence of a mental health condition increased as the number of physical morbidities increased, and was greater in more deprived individuals compared to less deprived individuals.
	Two or more conditions from a list of 12 common chronic physical health conditions.	To assess the link between multimorbidity and depressive symptoms.	A dose-response relationship was observed between the number of chronic physical conditions and the presence of depressive symptoms.
	Two or more conditions from a list of 32 common chronic physical health conditions plus depression.	To assess the associations of multiple physical morbidities with depression in primary care patients.	Individuals with depression were more likely than individuals without depression to have every one of the 32 comorbid physical conditions assessed.
	Two or more conditions from a list of eight chronic conditions.	To examine the prevalence and correlates of multimorbidity and the associations between multimorbidity and self-rated health, activities of daily living (ADLs), quality of life, and depression.	Limitations in ADLs, poor self-rated health, and depression increased in proportion to the number of physical conditions. Conversely, quality of life declined as the number of physical conditions increased.
	Two or more conditions from a list of nine physical conditions. Psychosis and subclinical psychosis assessed separately.	To explore the physical health multimorbidity patterns among people with psychosis or subclinical psychosis across 48 LMICs.	After adjustment for age, sex, education, wealth, and country, psychosis and subclinical psychosis were associated with a higher risk of multimorbidity. Adults aged 18–44 years with psychosis were at greatest risk of physical health multimorbidity.

Study	Design	Study population and setting
Fabbri E, *et al.* (2016).[614]	A longitudinal study using data from the Baltimore Longitudinal Study of Aging.	756 adults aged 65 years or older in Baltimore, United States.
Stubbs B, *et al.* (2017).[615]	A cross-sectional analysis of data from the World Health Survey.	190,593 adults aged 18 years and older across 43 LMICs.
Vancampfort D, *et al.* (2017).[616]	A cross-sectional study using data from the World Health Survey.	181,845 adults aged 18 years or older across 42 countries.
Cohort studies		
van den Akker, *et al.* (2001).[617]	A prospective cohort study, including baseline measurement of psychosocial characteristics and a two-year follow-up period for morbidity.	3,551 individuals aged 20 years and older in the Netherlands.
Melis R, *et al.* (2014).[618]	A longitudinal study performed using data from the Kungsholmen Project (Stockholm, Sweden) and followed-up after three years.	418 adults aged 78 years or older in Stockholm, Sweden. No participants were affected by multimorbidity at baseline.
Vassilaki M, *et al.* (2015).[619]	A prospective cohort study of residents of Olmsted County, Minnesota as identified using the medical records linkage system of the Rochester Epidemiology Project (REP).	2,176 cognitively normal individuals aged 70–89 years old in Minnesota, United States.
Tomasdottir MO, *et al.* (2016).[620]	A prospective cohort study performed over a mean of 11 years using data from the population-based HUNT study.	20,365 individuals aged 20–59 years in Norway. No participants were affected by multimorbidity at baseline.

	Multimorbidity definition	Aims	Findings
	More than one condition from a list of 13 chronic conditions known to have high prevalence and increased risk of disability and death in older adults.	To explore the association between increasing multimorbidity and the decline in cognitive function.	The faster the accumulation of multiple conditions over the follow-up period, the faster the rate of cognitive decline.
	Two or more conditions from a list of nine physical conditions. Depressive symptoms assessed separately.	To explore physical health multimorbidity in people with clinical depression, subsyndromal depression and brief depressive episodes across 43 LMICs.	Compared with those with no depression, subsyndromal depression, brief depressive episodes and depressive episodes were significantly associated with an increased risk of multimorbidity.
	Two or more conditions from a list of nine chronic physical conditions (angina, arthritis, asthma, chronic back pain, diabetes, edentulism, hearing impairment, TB, and visual impairment).	To assess the association of chronic physical conditions with anxiety among community-dwelling adults in 42 countries.	Compared to those with no physical conditions, one condition was associated with a two-fold increased risk of anxiety symptoms. Increasing numbers of chronic physical conditions were associated with a higher risk of anxiety.
	Two or more conditions listed in the Dutch Registration Network of Family Practices database.	To develop a profile of patients that are vulnerable to multimorbidity, and determine the influence of psychosocial characteristics on its occurrence.	Experiencing negative life events, having an external health locus of control (where individuals do not attribute their health to themselves but rather to others such as a doctor), and having a social network of less than five people increased the risk of developing multimorbidity over a two-year follow-up period.
	Two or more chronic conditions.	To calculate the incidence of multimorbidity in older adults, and identify predictors of incident multimorbidity.	Mental health-related symptoms were associated with an increased incidence of multimorbidity among older people.
	Two or more chronic conditions as defined by the ICD-9.	To determine the association between multiple chronic conditions and the risk of developing incident mild cognitive impairment and dementia.	The risk of developing incident mild cognitive impairment and dementia was increased in people with multimorbidity.
	Two or more conditions from a list of 17 including mental health conditions.	To prospectively explore associations between 'existential unease' (a composite of 11 items indicating 'unease' such as low satisfaction with life, poor self-esteem, weak social relationships etc.) and multimorbidity.	Those who reported greater levels of 'existential unease' had an increased risk of developing multimorbidity. The prevalence of multimorbidity increased with the number of 'unease' factors reported.

Annex 6: Sex as a determinant of multimorbidity

The table below provides some references to international studies performed to identify associations between multimorbidity and sex. These references were identified through our evidence-gathering activities but should not be considered as a fully comprehensive overview of the literature.

Study	Design	Study population and setting	Multimorbidity definition
van den Akker M, *et al.* (1998).[621]	Analysis of data from the Registration Network of Family Practices database.	Nationally representative individuals of all ages from the Netherlands.	Two or more conditions.
Fortin M, *et al.* (2005).[622]	Cross-sectional analysis of a primary care population in Québec, Canada.	980 primary care patients aged 18 years and older.	Defined using a simple count-based method, and also the Cumulative Illness Rating Scale (CIRS).
Britt HC, *et al.* (2008).[623]	Secondary analysis of data from a sub-study of the BEACH (Bettering the Evaluation and Care of Health) program.	9,156 individuals seen by 305 general practitioners across Australia.	According to CIRS.
Glynn LG, *et al.* (2011).[624]	Observational study using data from primary care records obtained from ten primary care physicians.	Primary care patients aged 50 years and older, from a mixed urban/rural setting in the west of Ireland.	Two or more conditions described with ICPC-2 codes.
Salisbury C, *et al.* (2011).[625]	A retrospective cohort study using data from the General Practice Research Database.	99,997 individuals aged 18 years or over, registered with 182 general practices in England.	The primary definition was more than one of 17 chronic conditions for which care is incentivised under the QOF. A secondary approach used the Johns Hopkins University Adjusted Clinical Groups Case-Mix System which has a longer list of conditions.
Khanam MA, *et al.* (2011). [626]	Analysis of cross-sectional data obtained from the Poverty and Health in Ageing study.	Individuals aged 60 years and older living in rural Matlab in Bangladesh.	Two or more conditions from a list of nine conditions (arthritis, stroke, obesity, hypothyroidism, obstructive pulmonary symptoms, heart failure, visual impairment, hearing impairment, and high blood pressure).

	Aims	Findings
	To trace determinants of susceptibility to disease in general and to identify vulnerable groups.	When accounting for other socioeconomic factors, sex was not associated with multimorbidity prevalence or incidence.
	To estimate the prevalence of multimorbidity in family practice patients by counting the number of medical conditions and using CIRS, which takes into account disease severity.	When using a simple count of diseases, the frequency of multimorbidity was somewhat higher in women than in men in the 45 to 64 year and 65 year and older age groups; yet in most cases, there is some overlap in the confidence intervals. There was no difference by sex when multimorbidity was defined using CIRS.
	To estimate the prevalence and patterns of multimorbidity in Australia.	The prevalence of multimorbidity did not differ between the sexes.
	To examine the prevalence and associated healthcare utilisation and cost of patients with multimorbidity.	Sex had no significant effect on multimorbidity prevalence rates.
	To gain an understanding of the epidemiology of multimorbidity in England, and the relationships between multimorbidity, consultation rate, and longitudinal continuity in primary care.	Female sex was independently associated with increased odds of having multimorbidity.
	To describe the prevalence and distribution patterns of multimorbidity among older adults in rural Bangladesh.	Multimorbidity was more prevalent in women in both those aged between 60 and 69 years and in those aged 70 years and older.

Study	Design	Study population and setting	Multimorbidity definition
Rizza A, *et al.* (2012).[627]	Analysis of data from the Swiss FIRE project database.	98,152 primary care patients aged 20 years or older in the German-speaking part of Switzerland.	Chronic health conditions were defined using 147 pre-specified ICPC-2 codes and multimorbidity was defined as either two or more conditions as defined by ICPC-2 codes; two or more chronic health conditions from different ICPC-2 chapters; or two or more medical specialties involved in patient care.
Violan C, *et al.* (2014).[628]	Analysis of cross-sectional data obtained from electronic health records.	Individuals aged 19 years and older living in urban areas in Catalonia and under primary care.	Two or more chronic conditions described with ICPC-2 codes.
St Sauver JL, *et al.* (2015). [629]	Historical cohort study using data from the Rochester Epidemiology Project medical records linkage system.	123,716 individuals of all ages from Olmsted County, Minnesota, United States.	Incident multimorbidity was defined as the development of a second condition from a list of 20 chronic conditions selected by the United States Department of Health and Human Services.
Arokiasamy P, *et al.* (2015). [630]	Secondary analysis of cross-sectional data from the WHO's Study on Global AGEing and Adult Health (SAGE) Wave 1 (2007–2010).	42,236 nationally representative individuals aged 18 years and older from six LMICs: China, Ghana, India, Mexico, Russia, and South Africa.	Two or more conditions from a list of eight conditions.
Agrawal S & Agrawal PK (2016).[631]	Analysis of cross-sectional data from the WHO's Study on Global AGEing and Adult Health (SAGE) Wave 1 (2007–2010).	Nationally representative individuals aged 18 years and older from six LMICs: China, Ghana, India, Mexico, Russia, and South Africa.	Two or more chronic physical health conditions from a list of nine conditions (angina pectoris, arthritis, asthma, chronic lung disease, diabetes, hypertension, stroke, depression, and visual impairment).
Ahmadi B, *et al.* (2016).[632]	Cross-sectional analysis of baseline information from the Golestan Cohort Study, Iran.	Individuals aged 40–75 years old living in the Golestan Province, in northern Iran.	Two or more conditions from a list of eight conditions (cardiovascular diseases, diabetes, COPD, CKD, liver disease, gastroesophageal reflux disease, TB, and cancer).
Olivares DE, *et al.* (2017).[633]	Cross-sectional analysis of baseline data from a health promotion activity programme developed in a socioeconomically disadvantaged area of central Argentina.	Individuals aged 18 years and older attending primary care or contacted during community health visits.	Two or more conditions from a list detailing arterial hypertension, cardiovascular diseases, dyslipidemia, diabetes, cancer, chronic respiratory diseases, thyroid dysfunctions, coeliac disease, rheumatoid arthritis, depressive disorders, and other chronic health conditions.
Cassell A, *et al.* (2018)[634]	Retrospective cohort study using data from the UK Clinical Practice Research Datalink (CRPD) database.	403,985 individuals aged 18 years and older registered to primary care across the UK.	Two or more conditions from a list of 36 recorded in patients' medical records.

	Aims	Findings
	To explore the age- and sex-related prevalence of multimorbidity and to compare these estimates with the prevalence estimates of other common specific conditions found in Swiss primary care.	Overall, the prevalence of multimorbidity was similar for men and women. However, the proportion of older adults (those over 60 years of age) with multimorbidity was higher for men than women.
	To determine the estimated prevalence and patterns of multimorbidity in urban areas of Catalonia, stratified by sex and adult age groups, and to assess whether socioeconomic status and use of primary health care services were associated with multimorbidity.	Multimorbidity prevalence was higher in women than in men across all age groups, except in those older than 80 years.
	To study the incidence of incident multimorbidity across all ages in a geographically defined population with an emphasis on sex and ethnic differences.	The risk of developing multimorbidity is similar in men and women. However, clusters of conditions differ between the sexes.
	To examine the prevalence and correlates of multimorbidity and the associations between multimorbidity and self-rated health, ADLs, quality of life, and depression.	Compared with men, women were significantly more likely to have multimorbidity than no conditions.
	To establish whether LMICs exhibit a negative association between higher SES and multimorbidity, similar to the evidence from HICs, and whether multimorbidity has positive associations with other health-related outcomes.	Women had consistently higher rates of multimorbidity than men in all six SAGE countries studied.
	To assess multimorbidity and the associated risk factors in Iran.	In all age groups, the proportion of those with multimorbidity was higher in women than in men, and this difference increased with age.
	To investigate chronic diseases and their risk factors in the context of multimorbidity.	Although men presented with more chronic condition risk factors than women, multimorbidity was more prevalent in women.
	To describe the epidemiology of multimorbidity in adults in England, and quantify associations between multimorbidity and health service utilisation.	The prevalence of multimorbidity was higher in females. The prevalence of physical–mental multimorbidity was also highest among females.

Annex 7: Ethnicity as a determinant of multimorbidity

The table below provides some references to international studies performed to identify associations between multimorbidity and ethnicity. These references were identified through our evidence-gathering activities but should not be considered as a fully comprehensive overview of the literature.

Please note, the terminology used to describe ethnicity in the studies is variable, and has been reproduced here in the same way as used in each published research paper; there has been no attempt to standardise it. Further, many have used broad ethnic categories (such as South Asian, Black) which may mask some other valid differences between culturally and epidemiological distinct populations found within the broader ethnic categories, such as Indian, Pakistani, and Bangladeshi subgroups.

Study	Design	Study population and setting
Quiñones AR, *et al.* (2011). [635]	Analysis of longitudinal data from the Health and Retirement Study (1995–2006).	Nationally representative individuals aged 51 years and older from the United States.
Mathur R, *et al.* (2011).[636]	A cross-sectional study of general practices in east London.	843,724 primary care patients aged 18 years and older, and diagnosed with hypertension, ischaemic heart disease, heart failure, stroke, and diabetes.
Lochner KA & Cox CS (2013).[637]	Analysis of administrative claims data for Medicare beneficiaries.	Individuals enrolled in the United States federal health insurance program Medicare.
Rocca WA, *et al.* (2014).[638]	Cross-sectional analysis of data from the Rochester Epidemiology Project medical records linkage system.	138,858 individuals of all ages from Olmsted County, Minnesota, United States.

	Multimorbidity definition	Aims	Findings
	Two or more conditions.	To examine intra- and interpersonal differences in multiple chronic conditions reported by Americans aged 51 and older for a period of up to 11 years.	At baseline, the prevalence of multimorbidity is lower in Mexican-Americans compared to White-Americans, but higher in Black-Americans. The trajectory of condition accumulation, over the 11-year period of observation, was different between the ethnic groups. Both Mexican-American and Black populations showed a slower rate of condition accumulation compared to White-Americans.
	Two or more chronic conditions from five cardiovascular conditions (hypertension, ischaemic heart disease, heart failure, stroke, and diabetes).	To establish the distribution of cardiovascular multimorbidity between ethnic groups; and to explore how the management of key physician-modifiable risk factors varies by both ethnicity and level of morbidity.	Those of Black or South Asian ethnicity are more likely to have multiple cardiovascular related diseases than those of white ethnicity.
	Focused on six or more conditions from a list of 15.	To describe county-level prevalence patterns of Medicare beneficiaries with six or more chronic conditions.	In individuals aged less than 65 years, the prevalence of multimorbidity was highest for non-Hispanic Blacks and Hispanics, and lowest for Asians regardless of sex. In men aged 65 years or older, the prevalence of multimorbidity was highest in non-Hispanic Whites and lowest in Hispanics. In women aged 65 years or older, the prevalence of multimorbidity was highest in non-Hispanic Blacks and lowest in Asian and non-Hispanic Whites.
	Two or more conditions from a list of 20 chronic conditions selected by the United States Department of Health and Human Services.	To describe the prevalence of multimorbidity involving 20 selected chronic conditions in a geographically defined population of the United States, emphasising age, sex, and ethnic differences.	The prevalence of multimorbidity was higher in Blacks compared to Whites, but lower in Asians compared to Whites.

Study	Design	Study population and setting
St Sauver JL, *et al.* (2015). [639]	Historical cohort study using data from the Rochester Epidemiology Project medical records linkage system.	123,716 individuals of all ages from Olmsted County, Minnesota, United States.
Bobo WV, *et al.* (2016).[640]	Cross-sectional analysis of data from the Rochester Epidemiology Project medical records linkage system.	138,858 individuals of all ages from Olmsted County, Minnesota, United States.
Li J, *et al.* (2016).[641]	Analysis of baseline data from the longitudinal Yorkshire Health Study (YHS).	27,806 individuals aged 16–85 years from Yorkshire, England.
Johnson-Lawrence V, Zajacova A & Sneed R (2017).[642]	Analysis of cross-sectional data from the 2002–2014 National Health Interview Surveys.	115,097 nationally representative individuals aged 30–64 years from the United States.

	Multimorbidity definition	Aims	Findings
	Incident multimorbidity was defined as the development of a second condition from a list of 20 chronic conditions selected by the United States Department of Health and Human Services.	To study the incidence of *de novo* multimorbidity across all ages in a geographically defined population with an emphasis on sex and ethnic differences.	Incident multimorbidity (first appearance of multimorbidity) is higher in Blacks compared to Whites, but lower in Asians compared to Whites.
	Two or more conditions from a list of 19 conditions.	To identify how multimorbidity composed of both physical and mental health conditions is influenced by age, sex, and race/ethnicity.	At almost all ages, Asian populations have a lower prevalence of multimorbidity including both a physical and mental health condition (termed by the authors as somatic-mental multimorbidity) compared to Whites and Blacks.
	Two of 13 chronic health conditions listed in the YHS questionnaire.	To use baseline data from the YHS to examine the patterns of multimorbidity and their association with health outcomes for residents in Yorkshire, England.	Baseline data revealed that multimorbidity is more prevalent in those of White ethnicity compared to non-White.
	Two or more conditions from a list of nine conditions: asthma, arthritis, heart disease (angina pectoris, heart attack, coronary heart disease, and 'other' heart disease), stroke, COPD (including emphysema and chronic bronchitis), hypertension, cancer, diabetes, and kidney failure.	To examine the associations of education and race/ethnicity with multimorbidity.	Individuals of non-Hispanic Black ethnicity had greater odds of multimorbidity compared to non-Hispanic Whites. Those of Hispanic ethnicity had lower odds of multimorbidity compared to non-Hispanic Whites.

Annex 8: Socioeconomic status as a determinant of multimorbidity

The table below provides some references to international studies performed to identify associations between multimorbidity and socioeconomic status. These references were identified through our evidence-gathering activities but should not be considered as a fully comprehensive overview of the literature.

Study	Design	Study population and setting	Multimorbidity definition
Afshar S, *et al.* (2015).[643]	Secondary analyses of cross-sectional data from the WHO World Health Survey.	Nationally representative individuals aged 18 years and older from 28 LMICs.	Two or more conditions from a list of six conditions: arthritis, angina or angina pectoris (a heart disease), asthma, depression, schizophrenia or psychosis, and diabetes.
Arokiasamy P, *et al.* (2015). [644]	Secondary analysis of cross-sectional data from the WHO's Study on Global AGEing and Adult Health (SAGE) Wave 1 (2007–2010).	42,236 nationally representative individuals aged 18 years and older from six LMICs: China, Ghana, India, Mexico, Russia, and South Africa.	Two or more conditions from a list of eight conditions.
Lee JT, *et al.* (2015).[645]	Secondary analysis of cross-sectional data from the WHO Study on Global AGEing and Adult Health (SAGE) Wave 1 (2007–2010).	39,213 nationally representative individuals aged 18 years and older from six LMICs: China, Ghana, India, Mexico, Russia, and South Africa.	Two or more conditions from a list of nine conditions (angina, arthritis, asthma, cataract, diabetes, stroke, chronic lung disease, hypertension and depression).
Garin N, *et al.* (2016).[646]	Secondary analysis of data from the Collaborative Research on Ageing in Europe project (COURAGE) and the WHO Study on Global AGEing and Adult Health (SAGE).	41,909 nationally representative individuals aged 50 years and older from Finland, Poland, and Spain (COURAGE) and China, Ghana, India, Mexico, Russia, and South Africa (SAGE).	Two or more conditions from a list of 12 conditions with high prevalence in most settings (angina, arthritis, asthma, cataract, COPD, depression, diabetes, edentulism, hypertension, cognitive impairment, obesity, and stroke).
Kunna R, Sebastian MS & Williams JS (2017).[647]	Secondary analysis of cross-sectional data from the WHO Study on Global AGEing and Adult Health (SAGE) Wave 1 (2007–2010).	Nationally representative individuals aged 50 years and older from China (n = 11,814) and Ghana (n= 4,050).	Two or more chronic conditions from a list of eight conditions (arthritis, diabetes, hypertension, angina, stroke, asthma, depression and chronic lung disease.

	Aims	Findings
	To compare the prevalence of multimorbidity across LMICs, and to investigate patterns by age and education, as a proxy for SES.	The association between SES and multimorbidity shows inter-country and inter-generational differences. In adults aged 55 years and less, multimorbidity prevalence is higher in the least educated adults across all LMICs investigated, although the magnitude of the relationship was variable. However, in those aged 55 years and older, this negative socioeconomic gradient was comparatively reduced and in some cases almost non-existent in all regions except South-East Asia where the relationship was reversed. That is, in adults aged 55 years and older, in South East Asia, increased rates of multimorbidity are observed in those who had completed higher levels of education.
	To examine the prevalence and correlates of multimorbidity and the associations between multimorbidity and self-rated health, ADLs, quality of life, and depression.	The association between SES and multimorbidity shows inter-country differences, but these vary depending on the metric used. Multimorbidity prevalence is higher at lower levels of education in all six LMICs, although the magnitude of the association is highly variable between countries. Household wealth is not associated with multimorbidity prevalence except in China and Russia, where multimorbidity prevalence is highest in those of the lowest wealth quintile.
	To assess the impact of multimorbidity composed of NCDs on healthcare utilisation and out-of-pocket expenditure.	Multimorbidity is not always more prevalent in those of lower SES. In India, Ghana, and Russia, those in the highest wealth quintile are more likely to have multimorbidity than those in the poorest.
	To identify and describe multimorbidity patterns in low-, middle- and high-income countries.	The association between SES and multimorbidity shows inter-country differences, but varies depending on the metric used. Multimorbidity prevalence is higher in those of lower education in all countries investigated except China, Ghana, and Mexico. Multimorbidity prevalence is higher in those with lower income in China. Conversely, multimorbidity prevalence is higher in those of higher income in Ghana and South Africa.
	To measure, compare and decompose socioeconomic inequality in single and multiple NCD morbidity.	Multimorbidity is not always more prevalent in those of lower SES. Multimorbidity is more prevalent in the poorest wealth quintile in the Chinese population. This trend is reversed in Ghana however, as multimorbidity is more prevalent in the wealthiest quintile.

Annex 9: Influence of tobacco and alcohol use on multimorbidity

The table below provides some references to international studies performed to identify associations between multimorbidity and tobacco and alcohol consumption. These references were identified through our evidence-gathering activities but should not be considered as a fully comprehensive overview of the literature.

Study	Design	Study population and setting
Taylor AW, *et al.* (2010).[648]	Secondary analysis of cross-sectional data from the North West Adelaide Health Study (NWAHS).	3,206 individuals aged 20 years and older from the north-west region of Adelaide, South Australia.
Fortin M, *et al.* (2014).[649]	Cross-sectional analysis of results from the Programme of Research on the Evolution of a Cohort Investigating Health System Effects (PRECISE) in Quebéc, Canada.	1,196 randomly selected individuals aged 45 years and older from the general population in Quebéc, Canada.
Booth HP, Prevost AT & Gulliford MC (2014).[650]	A cohort study using data from the UK Clinical Practice Research Datalink (CPRD) database.	300,006 individuals aged 30 years and older registered to primary care across the UK.
Arokiasamy P, *et al.* (2015).[651]	Secondary analysis of cross-sectional data from the WHO Study on Global AGEing and Adult Health (SAGE) Wave 1 (2007–2010).	42,236 nationally representative individuals aged 18 years and older from six LMICS; China, Ghana, India, Mexico, Russia, and South Africa.
Wikström K, *et al.* (2015). [652]	Analysis of longitudinal data recorded as part of the National FINRISK Study in Finland.	32,972 individuals aged 25–64 years of age, randomly selected from one of the five national FINRISK surveys between 1982 and 2002.
Mini GK & Thankappan KR (2017).[653]	Analysis of data collected by the United Nations Population Fund (UNFPA).	9,852 individuals aged 60 years and older from seven states across India.

	Multimorbidity definition	Aims	Findings
	Two or more conditions from a list of seven conditions (asthma, cardiovascular disease, COPD, diabetes, a current mental health condition, arthritis and osteoporosis).	To investigate the prevalence of chronic conditions and associated health- related risk factors, and to monitor the progression of conditions over time.	The association of smoking and multimorbidity is not seen across all ages. In individuals aged 40–59 years of age, a current smoking habit is significantly associated with multimorbidity. An ex-smoking status was not significantly associated with multimorbidity in this age group.
	Three or more conditions from a list of 14 conditions.	To analyse the association between individual lifestyle factors, and their combinations, with the occurrence of multimorbidity.	Both a current and past smoking habit is independently, although weakly, associated with an increased risk of multimorbidity in men but not women. Alcohol consumption is not associated with multimorbidity.
	Two or more conditions from a list of 11 conditions affecting seven organ systems.	To quantify the association between BMI and multimorbidity in a primary care population. Analyses were adjusted for sex, age group, smoking status and socioeconomic deprivation.	Ex-smokers, but not current smokers, have increased odds of multimorbidity compared to non-smokers.
	Two or more conditions from a list of eight chronic conditions.	To examine the prevalence and correlates of multimorbidity and the associations between multimorbidity and self-rated health, ADLs, quality of life, and depression.	A current drinking status is significantly associated with a higher prevalence of multimorbidity compared to a non-drinker status. Tobacco consumption is not associated with a higher prevalence of multimorbidity.
	Two or more conditions from a list of diabetes, cardiovascular disease, asthma/COPD, cancer and rheumatoid arthritis.	To investigate which baseline risk factors predispose to multimorbidity, during a 10-year follow-up of population-based cohorts.	Predisposing factors for incident multimorbidity among an initially condition-free population included smoking, physical inactivity, and obesity. Smoking was also associated with development to multimorbidity in those who already had diabetes but not in those with cardiovascular disease.
	Two or more conditions from a list of 12 NCDs.	To estimate the proportion of older adults with NCD multimorbidity, and identify its correlates and implications in selected Indian states.	Alcohol users and tobacco users are more likely to have multimorbidity than those with no conditions, and those with one chronic condition.

Annex 10: Influence of physical activity on multimorbidity

The table below provides some references to international studies performed to identify associations between multimorbidity and physical activity. These references were identified through our evidence-gathering activities but should not be considered as a fully comprehensive overview of the literature.

Study	Design	Study population and setting	Multimorbidity definition
Kadam UT, Croft PR & North Staffordshire GP Consortium Group (2007).[654]	Cross-sectional analysis of primary care consultation data.	9439 English patients aged 50 years and over attending practices drawn from six of the 12 North Staffordshire General Practice Research Network (NSGPRN) practices, England.	A count based measure was used in addition to a measure based on combinations of 185 selected morbidities classified by severity.
Hudon C, Soubhi H & Fortin M (2008).[655]	Secondary analysis of data from the 1998 Québec Health Survey.	16,782 individuals aged 18–69 years from Québec, Canada.	Two or more conditions from a list of 26 conditions.
Autenrieth CS, *et al.* (2013).[656]	Cross-sectional analysis of data from the KORA-Age Study.	1,007 individuals aged 65 years or older, residing in the region of Augsburg, Germany.	Two or more conditions from a list of 13 conditions.
Cimarras-Otal C, *et al.* (2014).[657]	Cross-sectional study based on data from the 2009 European Health Interview Survey for Spain.	22,190 nationally representative individuals aged 16 years and older, across households in Spain.	Two or more conditions from a list of 22 conditions.
Fortin M, *et al.* (2014).[658]	Cross-sectional analysis of results from the Programme of Research on the Evolution of a Cohort Investigating Health System Effects (PRECISE) in Quebéc, Canada.	1,196 randomly-selected individuals aged 45 years and older from the general population in Quebéc, Canada.	Three or more conditions from a list of 14 conditions.
Wikström K, *et al.* (2015). [659]	Analysis of longitudinal data recorded as part of the National FINRISK Study in Finland.	32,972 individuals aged 25–64 years of age, randomly selected from one of the five national FINRISK surveys between 1982 and 2002.	Two or more conditions from a list of diabetes, cardiovascular disease, asthma/COPD, cancer and rheumatoid arthritis.

	Aims	Findings
	To apply two scales of multimorbidity, one based on simple morbidity counts and the other on the severity classification, to describe the distribution of multimorbidity in family practice and explore whether such classification systems accurately reflect an individual's overall health status.	Multimorbidity as assessed by condition count, and by a severity measure, was associated with poor physical function, independent of age, sex and deprivation.
	To examine the relationship between multimorbidity and physical activity levels, and chronic limitations on activity, self-rated general health, psychological distress, and physical activity levels for each sex in adults, after age, education, income, and employment factors were controlled for.	Multimorbidity was not associated with physical activity levels in either sex, when age, education, income, and employment factors were controlled for.
	To explore an association between physical activity and multimorbidity.	An inverse association between physical activity and multimorbidity was seen among men but not women.
	To examine the association between levels of physical activity and multimorbidity, self-rated health and functional limitations for different age- and sex-based groups of Spanish subjects.	Lower levels of physical activity were associated with increased multimorbidity prevalence in men over 74 years of age, and in women aged 16–24 years.
	To analyse the association between individual lifestyle factors, and their combinations, with the occurrence of multimorbidity.	Physical activity showed no association with the presence of multimorbidity for either men or women.
	To investigate which baseline risk factors predispose to multimorbidity during a 10-year follow-up of population-based cohorts.	Predisposing factors for multimorbidity among the initially condition-free population included physical inactivity, obesity, and smoking. Among men who only had diabetes at baseline, physical inactivity increased the likelihood of incident multimorbidity. The same was not seen for women, nor for either men or women with only cardiovascular disease at baseline.

Study	Design	Study population and setting	Multimorbidity definition
Dhalwani N, *et al.* (2016). [660]	Analysis of data from the English Longitudinal Study of Ageing (ELSA).	15,688 nationally representative individuals aged 50 years and older from England.	Two or more conditions from a list of 17 conditions.
Vancampfort D, *et al.* (2017).[661]	Analysis of cross-sectional data from the WHO World Health Survey (WHS).	228,024 individuals aged 18 years and older from a total of 46 LMICs.	Two or more conditions from a list of nine conditions (arthritis, asthma, diabetes, angina, chronic back pain, visual impairment, hearing impairment, edentulism, and TB).

	Aims	Findings
	To assess the longitudinal trends of multimorbidity and the association between multimorbidity and physical activity in a nationally representative cohort of the English population.	An inverse dose-response association between levels of physical activity and multimorbidity was observed. Individuals who were physically inactive had the highest odds of developing multimorbidity.
	To assess the association between chronic conditions, multimorbidity and low physical activity among community-dwelling adults in 46 LMICs, and explore the mediators of these relationships.	Those with multimorbidity were significantly less physically active. This was observed across all age ranges, but became increasingly notable with age. Mobility issues, pain, depression, and sleep problems were reported to mediate the association between multimorbidity and a lack of exercise.

Annex 11: List of ongoing intervention trials

This annex provides a list of ongoing intervention trials on multimorbidity. Note, this list was correct at the time of publication but should not be considered as fully exhaustive.

Trial name	Participants	Intervention type/aim
The 3D Study: improving whole person care. [662,663,664]	Individuals from the general practice population aged 18 years or older with three or more conditions included in the UK QOF.	To develop and test a new way for GP practices to manage people with multiple chronic conditions.
MAP: Movement through active personalised engagement.[665]	Individuals aged 40–85 years with two or more chronic conditions.	To evaluate the effectiveness of a group education programme to help people with two or more chronic conditions.
Investigating if an internet delivered therapy (ACT) can improve the quality of life for adults living with two or more health conditions (multimorbidity).[666]	Individuals aged 18 years or older with two or more chronic conditions.	To evaluate the effectiveness of an online Acceptance and Commitment Therapy (ACT) programme to help people living with multimorbidity in Ireland.
Goal-setting in care planning for people with multimorbidity.[667]	Individuals aged 18 years or older with two conditions listed in Barnett's analysis of multimorbidity.	To assess the feasibility of undertaking a full-scale study investigating the effectiveness of a goal-setting intervention programme for individuals with multimorbidity and at high risk of hospital admission.
Supporting medicines management in older adults with multiple medical conditions.[668]	Individuals from the general practice population, aged 65 years or older, with prescriptions for 15 or more regular medications.	To determine the effectiveness and acceptability of a programme designed to support GPs to improve medicines management and reduce treatment burden in patients with multimorbidity who are taking 15 or more regular medications.
PRIMA-eDS: Polypharmacy in chronic diseases: Reduction of Inappropriate Medication and Adverse drug events in elderly populations by electronic Decision Support[669,670]	Individuals aged 75 years or older, with continuous prescriptions for seven or more medications.	To investigate the effectiveness of an electronic decision support tool 'PRIMA-eDS' in reducing rates of inappropriate medication and adverse drug events resulting in hospitalisation.
Polypharmacy reduction in patients treated for chronic diseases.[671]	Individuals aged 60 years or older, with prescriptions for five or more medications. Secondary care (hospital) setting.	To determine whether a patient-centred medication review performed by pharmacists and consented with the patient's GP will be effective in sustainably reducing polypharmacy.
Enhancing self-management of multimorbidity in primary care (OPTIMAL).[672]	Individuals aged 18 or older with two or more chronic conditions, and with prescriptions for four or more medications.	To assess the effectiveness of OPTIMAL, an occupational therapy group-based intervention for individuals with multimorbidity.

	Outcome measures	Location
	Health-related quality of life (primary), patient-centredness, illness burden, treatment burden (secondary).	Multiple sites in the UK.
	Engagement in physical activity (primary), self-efficacy for managing chronic disease, medication adherence, quality of life (secondary).	Leicester Diabetes Centre (UK).
	Health-related quality of life (primary), other measures of treatment and illness perceptions, anxiety and depression scores, pain scores (secondary).	Ireland.
	Quality of life, goal achievement rate, patient involvement in care, healthcare resource use, medication prescription rate, mortality (primary).	Six GP practices across the UK.
	Number of repeat medications and rates of inappropriate prescription (primary), other metrics of medication use and healthcare service use (secondary).	30 GP practices across Ireland.
	Composite hospitalisation and mortality (primary), adverse events, quality of life, de-prescription and medication re-uptake rates (secondary).	Numerous GP practices across Germany, the UK, Austria, and Italy.
	Health-related quality of life and prescription rates (primary), patient satisfaction (secondary).	Germany.
	Participation in social and instrumental activities of daily living, quality of life (primary), anxiety/depression, confidence in managing conditions, goal attainment rate, healthcare utilisation (secondary).	Various primary care centres in Ireland.

Trial name	Participants	Intervention type/aim
Multi-PAP RCT: Improving Prescription in Primary Care Patients With Multimorbidity and Polypharmacy.[673,674]	Individuals aged 65–74 years with three or more chronic conditions, and with prescriptions for at least three months for five or more medications.	To assess the effectiveness of a complex intervention in young-old patients with multimorbidity and polypharmacy. To improve physician drug prescription in primary care.
Patient-Centred Innovations for Persons With Multimorbidity – Ontario (PACEinMM-ON).[675]	Individuals aged 18 to 80 years with three or more chronic conditions.	To evaluate the benefit of patients attending a multidisciplinary team meeting to discuss a diverse range of medical, functional, and psychosocial issues for the development of a patient-centred treatment plan.
Improving Communication About Patient Priorities in Multimorbidity (ICOM-APP).[676,677]	Individuals from a primary care setting aged 40 years or older with two or more common chronic conditions including diabetes, heart disease, arthritis, asthma, and COPD, and depression/anxiety.	To develop and test the usability and feasibility of 'Customized Care', an intervention to help patients dealing with depression and/or anxiety in the context of multimorbidity to communicate important issues, such as financial and safety concerns, with their primary care providers.
The PAtient-Centred Team – Effectiveness and Cost-effectiveness Study (PACT).[678,679]	Individuals aged 65 years or older with three or more chronic conditions and an emergency admission within the last year.	To investigate the effectiveness of a patient-centred healthcare team (PACT) service model to ensure safe early discharge and prevent hospital admissions for older patients with multimorbidity.
Enhancing Community Health Through Patient Navigation, Advocacy and Social Support (ENCOMPASS).[680]	Individuals aged 18 years or older, with two of the following conditions: diabetes, CKD, established cardiovascular disease, high cardiometabolic risk.	To evaluate the effectiveness of a community health worker intervention on improving acute care utilisation among patients with complex chronic conditions seen in primary care.
Team Approach to Polypharmacy Evaluation and Reduction (TAPER).[681]	Patients of McMaster Family Health Team aged 70 years or older, with prescriptions for five or more medications.	To test a programme focused on medication reduction with patient, pharmacist and physician involvement using current technology aimed at reducing the harms of polypharmacy.

	Outcome measures	Location
	Medication Appropriateness Index score (primary), quality of life, therapeutic adherence, healthcare utilisation, adverse events, patient perception of shared decision making (secondary).	Three primary care centres in Spain.
	Changes in self-management, self-efficacy, patient-centredness (primary), number of conditions, health-related quality of life, psychological wellbeing, change in health behaviours (secondary).	Ontario, Canada.
	Qualitative assessment of communication during a patient-healthcare provider visit.	University of Rochester, New York, United States.
	Quality of life (primary), hospital admissions, emergency primary care consultation rate, health self-efficacy (secondary).	University Hospital of North Norway, Norway.
	Acute care utilisation (primary), cardiovascular disease risk, health-related quality of life, condition-specific intermediate health outcomes, mortality, medication adherence (secondary).	Canada.
	Successful discontinuation (primary), quality of life, patient experience of de-prescribing, adverse events, health resource utilisation (secondary).	Ontario, Canada.

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