

Advancing research to tackle multimorbidity: the UK and LMIC perspectives

Workshop report

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This report is a summary of a workshop held in June 2018 and reflects the views expressed, but does not necessarily represent the views of all participants, the Academy of Medical Sciences, the MRC (now part of UK Research and Innovation), the National Institute for Health Research (NIHR), or Wellcome.

We are most grateful to the meeting co-Chairs, Professor Stephen MacMahon FMedSci, Professor Paul Elliott FMedSci, and Professor Naomi Levitt for their contributions and commitment to this workshop.

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Preface

More and more people in countries across the globe are suffering from multiple long-term conditions also called multimorbidity - making this issue a day-to-day reality for billions of patients, their families, and healthcare providers.

I am sure that many of you reading this will have some experience of multimorbidity, either personally, or through a family member or friend. The impact and severity of the issue is therefore easy to grasp, and yet it has long been a neglected area within the research community. As such, we still do not fully understand the true scale of the issue, or the rate at which multimorbidity is becoming more common. It is not always clear what causes multimorbidity, nor how healthcare systems can be better prepared to respond. Unfortunately, these gaps in our understanding mean that the care and outcomes of patients with multimorbidity are often sub-optimal. This is unacceptable.

I am therefore pleased to have Chaired a working group project established by the Academy of Medical Sciences in 2016 with the aim of better understanding multimorbidity in an international context. Our report, published in April 2018, reaffirmed to me just how little we currently know about the scale and impact of multimorbidity, or how to prevent and manage it. We therefore used the report as an opportunity to set out a series of research areas that we believe must be addressed as a matter of urgency if we are to understand the issue better and ultimately improve the lives of patients.

However, we appreciate that multimorbidity research is complex and currently not well supported. I am therefore delighted that we have since been able to work so closely with key research funders including the MRC, NIHR, and Wellcome, to host this follow-on workshop. Through this successful partnership, the workshop was able to bring the research community together, and enable them to identify the areas where research can have the most impact and identify ways in which they can be better supported to drive the research agenda forward. I am particularly pleased that many researchers from low-and middle-income countries were able to participate, allowing us to identify areas where lessons can be shared between different settings across the globe, as well as revealing region-specific opportunities.

As a result of this meeting, numerous UK funders – including the MRC, NIHR, Wellcome, and many single disease charities - have already committed to working more collaboratively to foster research to drive a step change towards the prevention and optimal management of multimorbidity. This effort will help support researchers and provide the necessary resources needed to build the research infrastructure that will enable key questions to be addressed.



I have stated from the outset of this work that we cannot afford to ignore multimorbidity. I strongly believe that the working group, report and this workshop have gone a long way to raising the profile of this vital global health issue, and I am proud that it has been able to generate such immediate impact in the form of joint working.

Professor Stephen MacMahon FMedSci

Principal Director, The George Institute for Global Health Professor of Medicine and James Martin Professorial Fellow, University of Oxford Chair of the Academy of Medical Sciences '*Multimorbidity: a priority for global health research*' working group

Executive summary

In April 2018, the Academy of Medical Sciences published a strategic agenda outlining six key priorities for research on multimorbidity, covering aspects from epidemiology, impact, causes, prevention, treatment and management. This follow-up workshop, held jointly with the MRC (now part of UK Research and Innovation), the National Institute for Health Research (NIHR), and Wellcome, brought together representatives from funding agencies, researchers from high- as well as low- and-middle income countries (HICs and LMICs, respectively), and policymakers.

It focused on three research priorities outlined in the Academy's report, those centering on how to better understand the epidemiology of multimorbidity, its impact and burden, and its causes. Specifically, the workshop aimed to discuss obstacles precluding multimorbidity research in these areas and ways they might be overcome to advance the research agenda in both regional and global contexts.

Multimorbidity: what is already known

To help frame discussions about the most urgent research needs, participants first discussed what is known about the epidemiology and impact of multimorbidity across different settings, identifying similarities between the UK and LMICs, as well as context-specific issues, challenges, and opportunities for progress.

- While the risk of multimorbidity increases with age, multimorbidity is also a common concern in younger adults both in the UK and LMICs.
- Medical specialisation, notably at the tertiary healthcare level, is a challenge to the management of multimorbidity in all locations although fields such as geriatric medicine (UK) and paediatric care (LMICs) have pioneered more integrated approaches to care from which lessons can be learned.
- Many clusters of conditions are common to both LMICs and the UK, although others are more location-specific; for example, infectious diseases such as HIV, tuberculosis (TB) and hepatitis make a greater population level contribution to multimorbidity in LMICs.
- Understanding multimorbidity from the patient's point of view and developing patient-centred models of care will be critical in all settings.
- Multimorbidity research capacity is limited in both the UK and LMICs; nonetheless, it was noted that health researchers in low-resource settings typically have wide experience and a more multidisciplinary mind-set to those in HICs.
- Indeed, this may represent an important opportunity whereby the healthcare systems of LMICs may be more adaptable and able to employ healthcare workers more flexibly, enabling integrated models of care to be introduced more readily.

Priorities for multimorbidity research in the UK

Participants identified several areas where more evidence is needed, leading to the development of a range of priorities and specific research questions. Participants noted that while some such questions are likely to be answered fairly rapidly by drawing on existing data sources, others are more difficult to address and should be considered as more long-term priorities for research. Priorities included:

- Using existing data sources to identify and refine patterns and trends in disease clusters.
- Exploring possible common mechanistic factors underlying concurrent conditions (e.g. inflammation).
- Understanding the implications of polypharmacy (e.g. drug–drug interactions, adverse reactions).
- Developing and evaluating strategies for the prevention and treatment of multimorbidity, initially focusing on the most common clusters of conditions and defined populations, such as pregnant women.

Priorities for multimorbidity research in LMICs

Participants also suggested a range of immediate and long-term priorities for multimorbidity research in LMICs:

- Performing an audit of existing data sources to confirm their suitability and potential utility in multimorbidity research (e.g. (longitudinal) population studies, health and demographic surveillance surveys).
- Understanding the local, context-specific burdens and risk factors of multimorbidity, and determining what mechanisms can be employed to best address them.
- Performing a systematic assessment of the impact of upstream, population-based primary prevention strategies on multimorbidity.
- Developing and evaluating simple, scalable, and technologically enabled interventions, including new models of care and community-centred approaches, initially targeting common disease clusters or defined populations, such as pregnant women.
- Performing health economic analyses and economic modelling to understand financial implications of multimorbidity and models of care, and communicating this with policymakers.

Enablers of multimorbidity research

Participants noted that there are many challenges and barriers impeding progress in the identified priority areas. As such, they suggested several systematic and methodological approaches which should be encouraged to better enable and accelerate multimorbidity research:

- Establishing consistent definitions, standards and research methodologies will facilitate research globally; global collaborations will enable all parties to share knowledge and learn from each other.
- Enhancing existing population studies or creating new bespoke cohorts to generate longitudinal data will allow better understanding of chains of causation and tackling key multimorbidity questions.
- Building new health data science capabilities, while capitalising on existing ones for multimorbidity research to better understand the epidemiology and determinants of multimorbidity.
- Promoting capacity-building, interdisciplinary research collaborations and partnerships, and wider engagement of academic research with existing health research infrastructure (e.g. NIHR Biomedical Research Centres, Applied Research Centres).
- Re-considering clinical trial parameters to be more inclusive of multimorbidity and to reflect the 'real-life' situation.
- Exploring greater use of routinely gathered data and 'trial emulation' methodologies.
- Promoting more holistic health technology assessments that focus on efficacy in patients with multimorbidity.

While the above methodological issues are felt in both the UK and LMICs, it was also noted that there is a particular urgent need, in LMIC settings, to promote capacity building and connect researchers to international partnerships.

The role of funders

Ways in which funding agencies could help advance multimorbidity research were also part of the workshop discussion. It was noted that funders could play an invaluable role by:

- Coordinating their activities and investments to maximise impact.
- Promoting greater recognition among disease-specific charities of the importance of multimorbidity to their communities.
- Engaging across various biomedical communities and with additional funding organisations outside the medical sphere (e.g. in economic and social research, computer and data science).
- Encouraging grant application and review methods that are more appropriate for multidisciplinary proposals.
- Being flexible with their approaches to funding according to research community needs (e.g. direct commissioning, support for exploratory hypothesis-generating studies).
- Supporting supplementary activities (e.g. international meetings, sandpits to broker new partnerships).
- Capitalizing on existing investments (e.g. UK Biobank, Health Data Research UK) in support of multimorbidity research.

The challenges of multimorbidity are well-recognised in clinical practice, but multimorbidity has arguably not received the attention it deserves within the research community. This requires addressing as a matter of increasing urgency given the rising global multimorbidity burden.

This workshop focused on how best to support research priorities 1 to 3 identified in the Academy of Medical Sciences multimorbidity report. It aimed to discuss the structural and methodological obstacles to multimorbidity research and, as a way to overcome them, outline the way in which funders and researchers can jointly facilitate and stimulate the field, both in the UK and internationally.

Introduction

Multimorbidity, the presence of two or more concurrent long-term health conditions, is a significant and growing problem in both HICs and LMICs. The presence of multiple conditions adds to patients' care-seeking burden, complicates interactions with healthcare systems, and is associated with both poorer outcomes and heavier use of healthcare resources.¹

In light of the growing challenges presented by multimorbidity, the Academy of Medical Sciences established an international working group to examine the global picture of multimorbidity and to identify the key evidence gaps that need to be addressed in order to better understand the extent of the issue, and ultimately generate the knowledge to prevent and better manage multimorbidity to improve care and patient outcomes. Following an extensive evidence-gathering and consultation exercise, the working group published a report in 2018 – titled 'Multimorbidity: a priority for global health research' - setting out a series of strategic research priorities for multimorbidity (Box 1) and a proposed standardised definition of multimorbidity and reporting system (Box 2).²

Box 1: Strategic research priorities for multimorbidity

The Academy of Medical Sciences '*Multimorbidity: a priority for global health research*' report identified a number of globally relevant research priorities designed to produce a better understanding of the burden, determinants, prevention and treatment of patients with multimorbidity.

- 1. What are the trends and patterns in multimorbidity?
- 2. Which multimorbidity clusters cause the greatest burden?
- 3. What are the determinants of the most common clusters of conditions?
- 4. How do we prevent multimorbidity?
- 5. How can we maximise the benefits and limit the risks of treatment?
- 6. How can healthcare systems be better organised?

^{1.} Barnett K, et al (2012). Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. Lancet **380**(9836), 37-43.

^{2.} Academy of Medical Sciences (2018). Multimorbidity: a priority for global health research. https://acmedsci.ac.uk/policy/policy-projects/multimorbidity

To further explore and progress this research agenda, the Academy of Medical Sciences, the MRC (now part of UK Research and Innovation), the National Institute for Health Research (NIHR), and Wellcome jointly organised a two-day workshop with the active participation of researchers from the UK and LMICs, several disease-focused charities, and policymakers. The aims of the workshop were to focus in more detail on the strategic research priorities 1 to 3 identified in the Academy's report, to consider how methodological and other challenges to research presented by multimorbidity could be tackled, and how research funders could facilitate and accelerate multimorbidity research in the UK and globally.

The workshop comprised a series of scene-setting presentations followed by 'solutions-orientated' breakout sessions. These sessions were structured to help identify specific areas where research can have the most impact in tackling multimorbidity, and to better understand the methodological and funding issues within this space. Day 1 was dedicated to multimorbidity in the UK and day 2 focused on the issue within LMICs. An agenda for each of the two days in provided in Annex 1, and a full participants list in Annex 2. Copies of all presentations can be downloaded from the Academy's website.³

Box 2: Definition and reporting 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, the Academy of Medical Sciences '*Multimorbidity: a priority for global health research*' report recommend the adoption of a uniform definition and reporting system for multimorbidity, as outlined below.

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.

 Academy of Medical Sciences (2018). Advancing research to tackle multimorbidity: the UK and LMIC perspectives. https://acmedsci.ac.uk/policy/policy-projects/advancing-research-to-tackle-multimorbidity-the-uk-and-lmic-perspectives

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 (where relevant and applicable).⁴
- 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).^{5,6}
- Frailty, also preferably coded using a standardised classification scheme such as the cumulative deficit model of frailty or Fried's phenotype model.^{7,8}
- 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 diseases. 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.⁹

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

- 4. World Health Organisation (2010). International Statistical Classification of Diseases and Related Health Problems 10th Revision. http://apps.who.int/classifications/icd10/browse/2010/en
- 5. World Health Organisation. WHO Disability Assessment Schedule 2.0 (WHODAS 2.0). http://www.who.int/classifications/icf/whodasii/en/
- 6. World Health Organisation. International Classification of Functioning, Disability and Health (ICF). http://www.who.int/classifications/icf/en/
- 7. Rockwood K, et al (2005). A global clinical measure of fitness and frailty in elderly people. CMAJ 173(5), 489-495.
- 8. Fried LP, et al (2001). Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci 56, M146–156.
- 9. Murray CJL, et al (2003). Comparative quantification of health risks: Conceptual framework and methodological issues. Population Health Metrics 1, 1

Multimorbidity in the UK and LMICs: what are the challenges and where are the opportunities?

To help frame discussions about the most urgent research needs, participants discussed the similarities and differences between the UK and LMICs, highlighting areas where knowledge and lessons can be shared for mutual benefit and revealing context-specific issues, challenges, and opportunities for progress.

Multimorbidity patterns and trends

Thanks to medical successes in areas such as cardiovascular disease and cancer, life expectancy is continuing to rise in the UK, leading to larger numbers of older people with multiple health conditions. Further, modelling studies suggest that complex multimorbidity in old age will increase significantly over the next 20 years.¹⁰ Notably however, multimorbidity is also common in younger age groups, and affects substantial numbers of middle-aged people.4 The issue is also a concern amongst certain 'at risk groups', such as pregnant women.

Multimorbidity in the UK is characterised by distinct clustering of health conditions.¹¹ Some clusters are particularly common, and often share a mechanistic basis (concordant conditions). Mechanistically distinct (discordant) morbidities may sometimes be a secondary consequence of ill-health (e.g. depression), whereas adverse reactions to treatment may also underlie some common clusters. Importantly, some clusters show no obvious connection, hinting at currently unknown risk factors or causal linkages.

Multimorbidity shows a non-random geographic distribution in the UK. It is particularly common in rural and semi-rural areas, in part reflecting the age distribution of the UK, as well as in areas of deprivation. It is less common in urban centres where research institutions are typically located, leading participants to note that this necessitates that UK-based researchers will need to reach beyond local communities to ensure they access communities most affected by multimorbidity.

Given their diversity, the multimorbidity challenges in LMICs vary considerably. In many countries, the high burden of infectious disease is a major contributor: HIV/AIDS, hepatitis B and TB are highly prevalent and chronic infections often co-exist with other morbidities. Additionally, many neglected infectious diseases, which collectively affect a billion people worldwide, establish chronic infections.

As access to treatments in many LMICs improves, people with (chronic) infectious conditions, particularly HIV/AIDS, are living longer with additional morbidities, and with health consequences triggered by slowed disease progression and long-term treatment.

^{10.} Kingston A, et al (2018). Projections of multi-morbidity in the older population in England to 2035: estimates from the Population Ageing and Care Simulation (PACSim) model. Age Ageing **47(3)**, 374–380.

^{11.} Farmer C et al (2016). Clinical assessment and management of multimorbidity: summary of NICE guidance. BMJ 354, i4843.

Multimorbidity tends to affect younger people in LMICs compared to HICs, partly because of infections such as HIV and TB. Furthermore, epidemiological, demographic and nutritional transitions significantly affect patterns of ill-health. Migration to cities and increased exposure to more affluent diets and lifestyles are shifting risk exposures and contributing to a marked rise in cardiometabolic diseases (and hence multimorbidity). Furthermore, many LMICs are facing the simultaneous challenge of widespread under-nutrition particularly in children coexisting with growing rates of obesity later in life, both of which have implications for the development of multimorbidity.

Managing multimorbidity

Although multimorbidity is an everyday reality for the UK healthcare system, there is limited evidence available to guide treatment and the delivery of care. Clinical trials routinely exclude individuals with multimorbidity, and clinical guidelines typically focus on management of individual conditions. The National Institute for Health and Care Excellence (NICE) has developed guidelines on management of multimorbidity that focus on general principles rather than specific treatment recommendations.¹² Older patients are typically prescribed a wide range of medications – polypharmacy – despite a lack of data on their interactions and their effect on other conditions. Polypharmacy has been increasing substantially in recent years and is projected to increase still further.¹³

Medical specialisation has been a dominant characteristic of UK healthcare, and now also features in primary care with, for example, the emergence of diabetes specialist nursing staff. While this may benefit the treatment and prevention of individual conditions, such 'vertical' approaches are suboptimal for delivering care to patients with multimorbidity and fails to provide integrated patient-centric care. Possible exceptions include comprehensive geriatric assessments for older frail patients and pathways developed by palliative care teams.

In LMICs, little evidence is available on interactions between common conditions, on how the co-existence of multiple conditions affects treatment responses, and how services can best be integrated. Many settings face the challenges of poorly resourced healthcare systems, limited health infrastructure, and limited human health resources.

Even so, it was suggested that LMICs may be better positioned to respond to the growing threat of multimorbidity compared to HICs such as the UK for a number of reasons. Firstly, many LMICs are currently developing their health infrastructures and considering how to apply the principles of universal health coverage. This presents a clear opportunity for such countries to build more integrated healthcare systems that are better able to manage multimorbidity, leapfrogging the highly specialised approaches that are now a major obstacle to integrated care in HICs.

Secondly, some LMICs have developed innovative 'task-shifting' approaches, a process of delegation nd reorganising the workforce such that certain tasks are given to less specialised health workers.¹⁴ Such an approach can help to overcome shortages of trained healthcare workers and help integrate services, ensuring that each point of patient contact with the healthcare system is as productive as possible. The 'Practical Approach to Care Kit' (PACK), developed in South Africa, is one such example.¹⁵ In addition, groups such as community health workers provide a key infrastructure for delivering integrated packages of care and prevention within local communities, tailored to local needs and cultures.

The rollout of malaria and HIV/AIDS treatment and prevention programmes has created new health infrastructures in many countries, often supported by international development assistance. This infrastructure could provide a framework for integrating additional services. There may also be opportunities to learn from the innovations pioneered by the HIV/AIDS community, for example in community engagement and task-shifting.

^{12.} NICE (2016). Multimorbidity: clinical assessment and management. https://www.nice.org.uk/guidance/ng56

^{13.} Guthrie B et al (2015). The rising tide of polypharmacy and drug-drug interactions: population database analysis 1995-2010. BMC Med 13, 74.

^{14.} World Health Organisation (2008). Task Shifting: Global Recommendations and Guidelines. http://www.who.int/healthsystems/TTR-TaskShifting.pdf?ua=1

^{15.} Knowledge Translation Unit. PACK Adult – Western Cape, South Africa. http://knowledgetranslation.co.za/programmes/pack-adult-wc-sa/

In fact, successful models of integrated care have been implemented in LMICs. Perhaps most notable is the Integrated Management of Childhood Illness strategy, developed by WHO and partners, which promotes an integrated, whole-child perspective on child health and wellbeing. The continuum of antenatal, delivery and post-natal care is another area with a strong emphasis on integrated care.

LMICs have also been swift to adopt mobile phone and digital technologies, highlighting that exciting opportunities exist to build on this new digital infrastructure, such as 'mobile health' (mhealth) applications in treatment and prevention. Multiple mhealth studies have been undertaken, but to our knowledge none yet has been scaled up to a population level. Importantly, digital tools will also facilitate community- and population-based research, underpinned by digital data collection, curation, linkage and sharing.

Determinants of multimorbidity and prevention

The risk factors for multimorbidity are likely to overlap or be the same as those for individual chronic conditions, particularly non-communicable diseases (NCDs). Hence, primary prevention is unlikely to differ from the traditional public health agenda, focusing on physical exercise, diet, smoking cessation, protection from infections and reducing social isolation. Conversely, secondary prevention – preventing multimorbidity once one long-term condition has been diagnosed – may offer opportunities for more specific interventions once multimorbidity clusters and chains of causation are identified.

Social and environmental factors have a strong influence on the development of multimorbidity in all settings. Poverty, for example, is associated with earlier onset of multimorbidity and greater severity at most ages in most high income settings. However, links between poverty and multimorbidity may be more complex in LMICs, as increasing prosperity frequently leads to the adoption of more affluent diets and lifestyles likely to increase NCDs. Tackling multimorbidity will therefore require a focus also on social and environmental determinants, emphasising the need for a true multidisciplinary approach for multimorbidity research.

Participants noted that cultural practices and social attitudes across LMICs influence the development of multimorbidity and its management. As well as context-specific risk behaviours and exposures, the conceptualisation of mental health disorders varies widely across cultures, as do expectations of physician–patient relationships. The status of women in society, as well as family and social support mechanisms, may also have an important influence on exposure to risk factors and access to treatment.

In terms of prevention, the agendas established by NCD and infectious disease control programmes also apply to multimorbidity in LMICs. All countries face the same public health challenges and can draw upon established policies and other instruments, adapted for local contexts. Given the potentially enormous cost of treatments, participants suggested that primary prevention would be particularly attractive to LMICs.

The need for a life-course perspective

Multimorbidity affects all ages, but is likely to be experienced differently at different stages of life. In both the UK and LMICs, it was suggested that there is a need to understand common clusters, risk factors (biological and social) and disease mechanisms at different life stages, to inform prevention and models of care, including continuum of care as individuals transition into and out of care pathways (e.g. from juvenile to adult care).

The life-course perspective also emphasises that, as is clear from individual NCDs, the roots of multimorbidity may lie in much earlier influences – even as far back as in utero. A focus on multimorbidity across the life course, together with mechanistic studies, could reveal early predictors and biomarkers of multimorbidity, and whether the impact of early influences relates solely to their effects on individual conditions or whether they have a more complex relationship with multimorbidity.

This understanding could support the use of targeted interventions at different points in the life-course, to influence long-term disease trajectories. Again, it will be important to determine the impact of these interventions on multimorbidity as well as individual conditions.

Box 3: People-centric approaches

A recurring theme at the meeting was the need to consider the patient's perspective of multimorbidity, including how combinations of conditions impact on functional capabilities and quality of life. It will be important to accurately capture such outcomes in clinical practice, and to use patient-defined outcome measures in trials.

Participants also noted that new digital technologies and 'wearables' are opening up multiple opportunities to gather information directly from patients, in trials and routine care settings. Standardisation and validation of such tools is needed to ensure reliability and comparability of data.

The patient perspective was felt to be particularly important in the development of new models of care. Managing multiple long-term conditions can impose a considerable 'care burden' on individuals when healthcare systems are organised predominantly around management of single conditions.

Patient consultations can provide insight into the evidence gaps requiring the most urgent focus. The James Lind Alliance recently undertook a systematic, multistage consultation with patients to identify priority research questions . This highlighted several issues – particularly related to the psychosocial consequences of multimorbidity and maintaining psychological wellbeing – additional to those identified by the Academy of Medical Sciences and NICE. Importantly, considering patient voices could help to identify which condition should be prioritised for treatment in patients affected by multiple morbidities in the context of varying environmental and social risk factors. This would require novel linkages to data sources outside the health domain, and engagement with other sectors, including social and economic researchers and funders.

As well as affecting patients, multimorbidity can impose a severe practical and psychological burden on carers. Carers could make an important contribution to the design of interventions and care pathways, and may also benefit from targeted support packages.

Finally, for research to flourish, it was noted that public approval and participation will be essential – both in interventional studies and by allowing access to personal data. Strong public engagement and involvement in developing the research agenda were identified as ways to build trust and promote participation.

Future research priorities

Reflecting on the shared challenges faced in the UK and LMICs, participants suggested that there was considerable scope for researchers in HICs and LMICs to collaborate, to learn from one another, and to jointly tackle key research questions relevant to both settings.

Nonetheless, concern was also raised that addressing the current evidence gaps will be complicated by the limited multimorbidity research capacity both in the UK, mainly due to academic specialisation, and in LMICs, due to overall shortages in research capacity. There was consensus that agreed definitions and standardised metrics – e.g. context-specific disease classifications - would significantly facilitate the global sharing and synthesis of knowledge. Such standards would need to accommodate physiological differences between different ethnic groups and, where necessary, identify reliable population specific cut-offs to diagnose conditions such as hypertension or diabetes. Transparency and an 'open science' approach were seen as important ways to ensure reproducibility and to facilitate data syntheses.

Despite the value in collaborative work and data sharing, participants also reiterated that differences remain between the UK and LMICs in terms of the multimorbidity burden and most pressing needs. There are also opportunities unique to each setting, hence the most relevant, and urgent, research questions may be different between the UK and LMICs, as are the approaches needed to ensure it can be performed effectively.

Below is a summary of several context-specific research questions, and the methodological requirements aimed at answering these.

Research priorities in the UK context

Participants agreed that our current understanding of the patterns and causes of multimorbidity remain incomplete and more evidence is needed, nonetheless, research into the prevention, management and treatment of multimorbidity should and could progress urgently. It was recognised that different research questions would operate over different timescales, and a range of specific research questions which could be simultaneously addressed were proposed.

Cluster characterisation

Participants highlighted the need to increase our understanding of the patterns and trends in disease clusters. To this end, existing data sources could be exploited and further enriched (e.g. through data linkage). Systematic analyses and the use of artificial intelligence algorithms, in particular, could reveal less common, and/or previously unrecognised clusters, as well as patterns specific to different subpopulations and communities. Such research could uncover possible shared pathways of causation, genetic predispositions and potentially inform care practices and secondary prevention.

Mechanisms underlying multimorbidity

To further build on the cluster analysis, an important leap would be the identification and unpicking of common physiological mechanistic processes and pathways contributing to the development of multimorbidity; discovery of early biomarkers indicating development of co-morbidities at their subclinical stage. Rapid progress can be made by initially focusing on the role of processes already known to underlie chronic conditions (for example, inflammation and tissue fibrosis), and by adopting a truly interdisciplinary approach. In a complementary approach, shared pathological mechanisms could be identified by taking a defined cluster of conditions as a starting point of focus.

Studies will need to address the complex interplay between physiological mechanisms, genetic predispositions, environmental, social and behavioural factors. Such work is likely to have considerable crossover with fields such as ageing research, given that age is a strong risk factor for both individual health conditions and multimorbidity itself. This process will require the generation of new tools, including novel animal models, incorporating the investigation of specific combinations of pathologies. The necessity of mechanistic studies was deemed important and complementary to epidemiological research; the outcome of both approaches will collectively influence interventional strategies – illustrating the potential fruitful interplay between population-based, mechanistic and experimental medicine studies.

Polypharmacy

The lack of evidence regarding the use of multiple medications, as well as over-prescribing, were identified as key issues in multimorbidity. Several research goals which should be supported in the immediate future, included laboratory studies of drug–drug interactions, and the investigation of additional risk of adverse reactions caused by multiple conditions. More clinically oriented studies could also be valuable, and examine the implications of changes in drug prescribing in patients taking multiple medications.

Intervention development

While understanding the epidemiology and causes of multimorbidity was agreed to be vital, participants emphasized that, regardless of the outcome of such work, healthcare systems organised around single diseases significantly add to the burden faced by patients with multimorbidity. While some areas of medicine already operate more integrated, patient-centred approaches, such as geriatric medicine and antenatal care, such an approach to care is not routinely offered to those with multimorbidity, although some experimental models of integrated primary care, such as the 3D Study, are being evaluated.¹⁶

Participants also noted that there was scope for more studies addressing known and common risk factors in secondary prevention. Contact with healthcare systems following an initial diagnosis provides opportunities to initiate secondary preventive measures targeting common risks, but it is unclear exactly what kinds of intervention are most appropriate (for example, what forms of exercise are most suitable for particular groups). It was suggested that the UK lacks capacity for translational studies that could answer these kinds of questions, despite their potential to have a significant impact on multimorbidity.

It was suggested that the design and evaluation of innovative and more integrated approaches to care was an urgent priority, and should be performed alongside other work to better understand the epidemiology and mechanistic aspects of multimorbidity. While research to review how best to deliver care and organise healthcare systems are a significant undertaking, it was felt that rapid progress could be made by first focusing on how best to provide care to already known disease clusters and also to discrete populations such as pregnant women. It was suggested that another, longer-term objective might be 'pre-palliative' pathways of care. Intensive treatment of multiple individual conditions towards the end of life may have a major impact on quality of life, as well as absorbing significant healthcare resources.

Research priorities in the LMIC context

It was acknowledged that the understanding of multimorbidity in LMICs is less established than for HICs, with participants noting that increased knowledge of the epidemiology, trends and patterning of multimorbidity in LMICs would help in the prioritisation of resources and optimal targeting of healthcare to those most in need. Nonetheless, a sense of urgency was expressed for a need to develop interventions and improve healthcare delivery immediately, even in the absence of research designed to develop a more detailed picture of patterns and trends in individual settings – which is costly and time consuming. A predominant focus on the development of effective interventions was also considered important given that many LMICs are currently undergoing a development of their healthcare systems, meaning that there is an opportunity for such research to have a clear impact. With this in mind, several ways were highlighted in which evidence on the trends in multimorbidity could be rapidly produced, so that research to develop and evaluate interventions can be done simultaneously, allowing the resultant evidence to be applied in the most effective and timely manner.

16. Salisbury C et al (2018). Management of multimorbidity using a patient-centred care model: a pragmatic cluster-randomised trial of the 3D approach. The Lancet **392(10141)**, 41-50.

Data resource auditing

Multiple data sources, including long-standing cohorts and national health and demographic surveillance surveys, may already be available and have the potential to provide insights into the epidemiology of multimorbidity. However, information about such data is not readily available, and it is often unclear from descriptions of large data sources whether they could, in fact, be a useful resource for multimorbidity research. A systematic assessment of the available data was thought to be an important, and urgent, research priority for LMICs, with participants agreeing that such an effort would help clarify the suitability of current data for multimorbidity research.

Local burdens

Epidemiological data generated in HICs cannot be simply extrapolated to LMICs since some conditions and combinations of conditions are unique to, or particularly prevalent in, LMICs, notably those linked to infectious disease. It was noted, therefore, that national and regional studies should be conducted to better understand context-specific burdens and risk factors, and to underpin the design of relevant prevention, management and treatment approaches. It was suggested that identifying interactions between conditions and unpicking causal pathways were important longer-term priorities.

Primary prevention

Approaches to develop primary prevention is a particularly attractive option in LMICs, where treatment of anticipated future disease and multimorbidity burdens would be financially unsustainable. Many populationbased primary preventive interventions could be considered, including policy interventions across domains outside health. In the context of multimorbidity, interventions that simultaneously influence a range of morbidities – such as smoking cessation – would be particularly attractive and could be hugely beneficial at multiple levels, including aspects of sustainability. Performing a systematic assessment of the impact of primary prevention strategies on multimorbidity could generate a key evidence base for LMICs, and should be considered as a priority alongside work to understand the patterns and trends of multimorbidity.

Intervention development

Notwithstanding the value of prevention, participants argued that there is considerable scope – and an urgent need - to develop and evaluate simple and scalable diagnostic, management and treatment packages, incorporating new models of care, integrating community-based approaches and exploiting innovative digital technologies. Well-established and common clusters of conditions were suggested to be a helpful focus of initial studies.

Health economic analyses and policymaker engagement

It was suggested that studies should have a strong focus on effectiveness and cost-effectiveness in real-world settings, ideally paving the way for implementation studies to support wider rollout. To inform health policymaking, the financial implications of multimorbidity and new models of care needed to be rigorously evaluated and communicated to policymakers. Yet, concern was raised that policymakers may be reluctant to increase efforts to identify additional morbidities in patients, due to potential additional healthcare costs. However, participants countered this view by arguing that health economic analyses could highlight the consequences of inactivity, as well as the potential efficiencies of integrated care models and in doing so provide a positive economic argument for placing a greater focus on multimorbidity. Economic modelling may also provide evidence to support investment in primary or secondary prevention.

Enablers of multimorbidity research

After noting areas where additional knowledge is needed and specifying the research priorities, participants also reflected on the current systemic and methodological barriers to multimorbidity research, and discussed possible approaches to overcome these barriers to advance research over the longer term. Many of these barriers are felt in both the UK and LMICs.

Developing population studies

Opportunities exist to expand the range of data collected on current (longitudinal) population studies, although entirely new cohorts may also need to be established to generate data on key multimorbidity questions. In particular, cohorts will provide a key foundation for longitudinal studies that address the time course of multimorbidity development, shedding light on possible pathways of causation in both UK and LMIC settings and providing a potential basis for secondary prevention interventions.

Capitalising on data science

Data science was identified as crucial for understanding key issues such as patterns of disease, the multimorbidity burden, risk factors and the impact of treatment. The need to reduce barriers to data access and sharing was widely recognised. Linkage of primary and secondary care data was seen as helpful, as was the linkage to non-medical data sources such as social care, lifestyle, environmental and education data sources. It was agreed that such an ambition could enhance our understanding of the social and environmental influences on multimorbidity, although there are major practical and methodological hurdles to doing so. Health Data Research UK was widely felt to have a crucial role to play in facilitating multimorbidity-focused data science.

Both routinely collected and cohort data were felt to have advantages and disadvantages - routinely collected data are more comprehensive and cover representative populations, but may be difficult to access and data quality and quantity (e.g. breadth vs depth) may be an issue; cohort data are more rigorous but may not cover all questions of interest or be fully representative of the UK, or LMIC, population(s).

Importantly, participants noted the lack of longitudinal data and a reliance on cross-sectional studies which provide little insight into chains of causation. Longitudinal population studies, including cohorts, can provide more data on the order in which morbidities develop and possible causal linkages. Enhancing existing population studies could generate new data relevant to multimorbidity relatively quickly – entirely new cohorts would be very expensive to establish and would take considerable time to generate evidence. UK Biobank was identified as one specific resource that could play a key role in exploring multimorbidity in the UK.

It was argued that digital infrastructures connecting local healthcare economies could provide opportunities to collect research-quality data from real-world settings. The Salford Lung Study, which has generated evidence of effectiveness of new medicines and safety, was suggested as one possible template.^{17,18,19}

^{17.} Woodcock A et al (2015). The Salford Lung Study protocol: a pragmatic, randomised phase III real-world effectiveness trial in asthma. BMC Pulm Med **15**, 160.

^{18.} Vestbo J et al (2016). Effectiveness of Fluticasone Furoate-Vilanterol for COPD in Clinical Practice. N Engl J Med 375(13), 1253-1260.

^{19.} Collier S et al (2017). Monitoring safety in a phase III real-world effectiveness trial: use of novel methodology in the Salford Lung Study. Pharmacoepidemiol Drug Saf **26(3)**, 344-352.

Improving research capacity and training

A lack of multimorbidity research capacity was widely acknowledged. Training, including clinical training, and research institutional structures tend to promote specialisation, and multimorbidity is not recognised as a discrete discipline. Research into single diseases will remain vital, and progress in multimorbidity will most likely – at least initially - be made from promoting interdisciplinary collaborations, including partnerships spanning clinical, laboratory, data science and epidemiology. Input from the social sciences will also be needed to generate a deeper understanding of social and environmental influences on multimorbidity.

Training for scientists, academics, clinicians and beyond could be multifaceted. Dedicated multimorbidity training modules; reciprocal 'hands-on' visits in research, clinical and community environments; targeted funding calls; educational series on multimorbidity in widely-read journals (e.g. The Lancet) and more could enable a cadre of researchers and health care professionals to work individually and in teams on multimorbidity. This would also be relevant to LMIC settings, where specialization in work in 'disease silos' is less prominent, hence reciprocal and joint learning would be beneficial across different settings.

Trial data

To avoid potentially confounding influences, efficacy trials typically exclude patients over a certain age, those with particular conditions and therefore those with multimorbidity. In some areas of medicine, these criteria exclude the vast majority of patients. As a result, there is very little clinical trial evidence on the efficacy and safety of medicines in 'real-life' settings.

Various ways to address this deficiency were suggested, including a wider and more representative range of participants in trials or other research studies, and increasing the use of pragmatic effectiveness studies. Including outcome measures relevant to a range of conditions would further be beneficial in generating more evidence relevant to multimorbidity. Agencies involved in health technology assessments could also be encouraged to take a broader view of efficacy and effectiveness, and to emphasise the importance of evidence related to use in 'real world' populations with multimorbidity.

Virtual trials

Every day, potentially valuable information on treatment choices and outcomes is being captured in electronic health records, but very little informs future treatments. It was suggested that there was scope to exploit this source of evidence through 'learning health systems' and other approaches.

One option discussed was embedding clinical trials within primary health care, with patients being assigned different treatment options on a random basis (as in the StatinWISE trial.)²⁰ Alternatively, retrospective 'trial emulation' methodologies could be adopted, in which electronic health record data on selected groups of patients – such as those with particular combinations of morbidities – could be extracted and analysed.²¹

Additional enablers of multimorbidity research in LMICs

Participants agreed that the methodological barriers mentioned above will be similarly felt in both the UK and LMICs, meaning that there will be opportunities for the outcomes of work to overcome them to be shared between settings to advance the global research agenda. However, participants also recognised that there are some additional barriers that are more specific to LMICs, or felt more strongly in such settings. In particular, participants noted an urgent need to address capacity shortages and to connect researchers to international partnerships.

^{20.} Herrett E et al (2017). Study protocol for statin web-based investigation of side effects (StatinWISE): a series of randomised controlled N-of-1 trials comparing atorvastatin and placebo in UK primary care. BMJ Open **7(12)**, e016604.

^{21.} Hernán MA & Robins JM (2016). Using big data to emulate a target trial when a randomized trial is not available. Am J Epidemiol 183(8), 758–764.

Capacity-building

Capacity for multimorbidity research (and research in general) remains low in most LMICs. It was suggested that a broad-ranging capacity-building programme is needed, enabling health researchers to expand their areas of interest and to build capabilities in areas such as data science and implementation science. Training needs would need to be addressed and could benefit from approaches covering HICs and LMICs jointly or interconnectedly as outlined above.

Partnership-building

Complementing capacity-building, it was recognised that interdisciplinary research collaborations also needed to be nurtured, and that wider international communities need to be built to generate a global critical mass of researchers to support coordinated action and sharing of knowledge.

Role of funding agencies

Funding agencies, including disease-specific charities, were felt to have a vital role to play in progressing the multimorbidity research agenda, both in the UK and internationally. Importantly, the coordination of activities and investments in research was felt to be important, this would provide a concerted push to the field and maximise impact. Disease-specific charities could also consider funding research of multimorbidity including their priority diseases (as several are already moving towards), as health conditions are rarely experienced in isolation and additional morbidities can have a significant impact on quality of life.

Given that multimorbidity research will need to be multidisciplinary in nature, participants also suggested that there is a need to overcome internal disciplinary barriers, and that this could be facilitated by ensuring that multiple funding programmes and panels are involved within individual funding agencies. It was suggested that important contributions could be made by funding agencies outside the medical sciences, including the humanities, social sciences, and computer sciences.

Furthermore, joint funding schemes involving multiple organisations were identified as a necessary mechanism to foster an increased cross-talk between scientific fields needed to overcome barriers inhibiting multimorbidity research. Flexible funding mechanisms could also be considered, such as the direct commissioning for specific activities that would advance the field, support for initial exploratory hypothesis-generating studies, support of longitudinal studies, or funding to establish new interdisciplinary collaborations.

While it was raised that the multidisciplinary nature of such grants present challenges to traditional peer review, it was noted that this could be addressed by ensuring that peer review processes and the make-up of funding committees are suitably tailored to assess multidisciplinary grant applications.

In addition to larger scale research projects, it was also recognised that funders have a role in 'human capacity-building and training' with there being value in supporting novel training approaches such as dedicated PhD programmes in multimorbidity. Specific funding might also be earmarked for resource (e.g. accessible databases) or methodology development.

Finally, and importantly, there is urgent need to capitalise on existing investments in research - such as the Health Data Research UK and UK Biobank - and both established and new research consortia and dedicated conferences to accelerate multimorbidity research.

Conclusion

The challenges of multimorbidity are well-recognised in clinical practice, but multimorbidity has arguably not received the attention it deserves within the research community. In large part, this reflects numerous structural factors that encourage a focus on individual conditions – including specialist training, disciplinary 'silos', the reductionist nature of much biomedical science, paradigms of pharmaceutical development, and the absence of elements that 'glue' a defined scientific community together (such as learned societies, dedicated journals and funding streams).

Because of the multiple different factors relevant to multimorbidity, the field is most likely to develop initially as a coalition based on interdisciplinary collaborations rather than through the emergence of multimorbidity polymaths. Nevertheless, broadening the perspective of individual researchers will be critical to their successful integration into such networks.

Both HICs and LMICs face a major multimorbidity challenge, the nature of which shares many similarities but also some distinctive features. At the same time, there is considerable scope to advance multimorbidity at a global level, through the sharing of knowledge and expertise, and for researchers in all settings to learn from each other.

The Academy of Medical Sciences 'Multimorbidity: a priority for global health research' report has previously highlighted the key evidence gaps and future priorities for multimorbidity research across the globe. However, in order to advance this research agenda, the structural obstacles to multimorbidity research call for concerted efforts to facilitate and stimulate the field, both in the UK and internationally. This workshop provided an invaluable platform to discuss these obstacles further, and identify ways in which they may be overcome. Furthermore, as a result of this workshop, a range of UK funders who co-organised or actively participated in the workshop have signalled their intention to work collaboratively to advance the multimorbidity research field.

Annex 1: Agenda

Wednesday 20 June 2018 – Multimorbidity and the UK context		
08.30 – 09.00	Registration	
09.00 - 09.40	 Welcome and Introductory Presentation: Multimorbidity: a priority for global health research Professor Stephen MacMahon FMedSci, Principal Director, George Institute for Global Health; Chair, Academy's report on multimorbidity 	
09.40 – 10.10	 Keynote Presentation: Multimorbidity: where science and policy meet Professor Chris Whitty CB FMedSci, Chief Scientific Adviser, Department of Health and Social Care 	
10.10 – 10.30	 Presentation: MRC's interest and future plans Professor Paul Elliott FMedSci, Chair, MRC Population and Systems Medicine Board 	
10.30 - 11.00	 Presentation: What do we know in the UK context and what are the gaps? Professor Avan Sayer, Professor of Geriatric Medicine, Newcastle University 	
11.00 – 11.30	Refreshment break	
11.30 – 12.00	 Presentation: Methodological approaches to multimorbidity research Professor Sylvia Richardson FMedSci, Director, MRC Biostatistics Unit, University of Cambridge 	
12.00 – 13.30	 Breakout groups To discuss: Group 1: What are the trends and patterns in multimorbidity? Group 2: Which multimorbidity clusters cause the greatest burden? Group 3: What are the determinants (underlying mechanisms and risk factors) of the most common clusters of conditions? Group 4: How best to enable multimorbidity research in the UK? Each group to explore: Where research can have the most impact in addressing multimorbidity, The barriers to such research, and how they can be overcome, The technical and methodological approaches needed to ensure such research can be performed in an effective and informative manner. 	
13.30 - 14.15	Lunch	
14.15 – 15.15	Breakout group feedback Chair: Professor Paul Elliott FMedSci	
15.15 – 15.35	Refreshment break	
15.35 – 16.35	 Discussion session: Prevention and management opportunities Chair: Professor Chris Whitty CB FMedSci A chance to explore what we know about strategies for the clinical management of people with multimorbidity, and to identify opportunities to improve care. 	
16.35 – 17.15	 General discussion, conclusions, and next steps Chair: Professor Paul Elliott FMedSci 	
17.15 – 17.30	Final remarks Professor Paul Elliott FMedSci and Professor Stephen MacMahon FMedSci	
17.30 – 19.00	 Networking reception To facilitate collaboration across disciplines and experts interested in addressing multimorbidity 	

Thursday 21 June 2018 – Multimorbidity and the LMIC context		
08.30 – 09.00	Registration	
09.00 - 09.40	 Welcome and Introductory Presentation: Multimorbidity: a priority for global health research Professor Stephen MacMahon FMedSci, Principal Director, George Institute for Global Health; Chair, Academy's report on multimorbidity 	
09.40 - 10.00	 Introductory Presentation: TB and Diabetes Intersection, an African Perspective Professor Naomi Levitt, Professor, Division of Diabetes and Endocrinology, University of Cape Town; Director, Chronic Diseases Initiative for Africa 	
10.00 – 10.30	 Keynote Presentation: What do we know about multimorbidity in the LMIC context and what are the gaps? Dr Sanghamitra Pati, Indian Council of Medical Research 	
10.30 – 11.00	 Keynote Presentation: Methodological considerations for performing multimorbidity research in LMIC settings. Dr Vilma Irazola, Director, Department of Chronic Diseases, South American Center of Excellence for Cardiovascular Health (CESCAS), Institute for Clinical Effectiveness and Health Policy (IECS) 	
11.00 – 11.30	Refreshment break	
11.30 – 13.00	 Breakout groups To discuss: Group 1: What are the trends and patterns in multimorbidity? Group 2: Which multimorbidity clusters cause the greatest burden? Group 3: What are the determinants (underlying mechanisms and risk factors) of the most common clusters of conditions? Group 4: How to best enable multimorbidity research in LMICs? Each group to explore: Where research can have the most impact in addressing multimorbidity, The barriers to such research, and how they can be overcome, The technical and methodological approaches needed to ensure such research can be performed in an effective and informative manner. 	
13.00 - 13.45	Lunch	
13.45 – 14.45	Breakout group feedbackChair: Professor Naomi Levitt	
14.45 – 15.15	Refreshment break	
15.15 – 16.15	 Discussion session: Prevention and management opportunities Chair: Professor Chris Whitty CB FMedSci A chance to explore what we know about strategies for the clinical management of people with multimorbidity, and to identify opportunities to improve care. 	
16.15 – 17.15	 General discussion and conclusions Chair: Professor Naomi Levitt 	
17.15 – 17.30	Final remarks Professor Naomi Levitt and Professor Stephen MacMahon FMedSci	
17.30	Meeting close	
17.30 – 18.30	Funders post-meeting wash-up An opportunity for funders to reflect and agree on ways forward.	

Annex 2: Participant list

Day 1 – 20 June

Dr Ana Antunes-Martins

Programme Manager, Population Sciences and Public Health; Programme Manager, Global Health (Non-Communicable Diseases), Medical Research Council, UK Research and Innovation

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Professor Philip Conaghan Professor of Musculoskeletal Health, University of Leeds

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