The Academy of Medical Sciences

'Addressing the global challenge of multimorbidity': Call for written evidence summary

Overall summary and recurring themes

- The terminology used to describe the co-existence of multiple diseases in any given patient is variable, and a consensus definition of multimorbidity is lacking.
- Many noted however that a definition should include pathological conditions in addition to all factors that will contribute to poor health, including social, environmental, political and economic factors.
- Many respondents noted that efforts to reach a more uniform operationalisation of multimorbidity may help facilitate surveillance and monitoring efforts, leading to the development of more accurate prevalence and longitudinal trend data. It could also improve the identification and classification of studies on multimorbidity, and improve the ability to make comparisons across different settings.
- However, it may be difficult to develop one definition that is both clinically and methodologically useful, especially across all geographic locations.
- Most data on multimorbidity are collected from the primary care setting, which is also largely considered by most respondents as the most appropriate sector for providing generalist care to multimorbid patients. However, respondents also noted a desire to increase the collection and integration of data from secondary and community care sectors as well, in addition to reducing the fragmentation of these sectors to improve care provision.
- Broadly, respondents noted that it may be possible to make certain assumptions about the determinants, prevention, and management of multimorbidity from single disease evidence. However, making such assumptions may be naive and there is a clear need to increase the body of empirical evidence to specifically support whether these assumptions hold true in the context of multimorbidity.
- However, the complexity of multimorbidity means that efforts to undertake such work will require new research strategies, new analytical tools, new animal models that better represent the complexity of multimorbidity, and a move away from trials that focus only on single diseases.
- Such a change will be facilitated by funding strategies that encourage and reward collaborative efforts in terms of discipline, as well as supporting multi-centre and cross-border collaborations.
- Future research should use a combination of clinical endpoints, patient-defined outcomes, and economic (e.g. cost-effectiveness) metrics when evaluating the success and sustainability of prevention and management interventions.
- There is a keen desire to ensure that future work considers multimorbidity across the entire life course, and in low resource settings.

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Introduction

This document contains each of the full submissions received in response to the call for written evidence, which was launched on 14 September 2016 to inform the Academy of Medical Science's working group project *'Addressing the global challenge of multimorbidity'.* The call for evidence was widely disseminated to both national and international stakeholders, and was officially closed on 30 November 2016.

22 responses have been received from the individuals and organisations listed below:

Individuals

1. Professor Martin Dawes, Head of Department of Family Practice, University of British Columbia
2. Dr Nafeesa Dhalwani, Lecturer in Epidemiology, Diabetes Research Centre, University of Leicester
3. Professor Martin Fortin, Applied Research Chair in Health Services and Policy Research on Chronic Diseases in Primary Care
4. Professor Jane Gunn, Chair of Primary Care Research, University of Melbourne
5. Professor Stewart Mercer, Professor of Primary Care Research, University of Glasgow
6. Professor Mahfuzar Rahman, Head of Health, Nutrition and Environment Research Unit, BRAC, Bangladesh
7. Professor Rajesh Sagar, Professor of Psychiatry, All India Institute of Medical Sciences
8. Professor Christopher Salisbury, Professor of Primary Health Care, University of Bristol
9. Professor Marjan van den Akker, Associate Professor, Maastricht University
10. Professor Graham Watt FMedSci, Norie Miller Professor of General Practice, University of Glasgow
11. Dr Madhavi Bajekal, on behalf of the UCL Multimorbidity Research Team
12. Professor Umesh Kadam, Professor of Clinical Epidemiology and Health Services Research, Keele University

Organisations

13. Professor Dame Anna Dominiczak DBE FRSE FMedSci, on behalf of the University of Glasgow's College of Medical, Veterinary and Life Sciences
14. The National Institute for Health and Care Excellence (NICE)
15. Royal College of General Practitioners
16. The Stroke Association
17. British Pharmacological Society
18. The AGE group, Institute of Neuroscience, Newcastle University
19. The Scottish School of Primary Care (SSPC)
20. Professor Katherine Payne, on behalf of a research team at the University of Manchester
21. The Society for Academic Primary Care (SAPC)
22. Kathryn Nicholson, on behalf of a team of researchers from Australia, Belgium and Canada

Questions 1 and 6: Which definitions (or aspects of definitions) do you think are most helpful to efforts to understand and describe multimorbidity? What should the definition of 'multimorbidity' be? How would this definition improve research and/or treatment?

Current landscape

- The terminology used to describe the co-existence of multiple diseases in any given patient is variable, and a consensus definition of multimorbidity is lacking.[1,2,3]
- Nonetheless, a commonality between the various definitions is that they are typically composed of two components; a count of diagnoses and a list of specific diseases for inclusion in the definition.
- Most definitions are aligned in terms of disease count, with the most common definition of multimorbidity being *'two or more chronic or long-term diseases/conditions'*.
- Conversely, there is much variations between definitions in terms of the 'type' and 'list' of diseases that are included.
    - Most definitions focus on diseases that are chronic, and exclude acute and cyclical diseases. However, there is not complete agreement over what constitutes a chronic disease, nor whether this distinction is helpful or not - especially in clinical settings.
    - While some include mental health issues in addition to somatic diseases, others do not.
    - There is also disagreement as to whether to include states of ill-health, such as pain, or psychosocial issues.
    - In an attempt to offer clarification, most papers define multimorbidity using a restricted list of specific diseases. These lists are variable however, which leads to difficulties in comparing different studies (see below).
- It was broadly agreed that, despite the lack of an agreed definition, the concept of multimorbidity differs from co-morbidity in that it does not consider any one disease to be a 'primary' or 'index' condition.
    - It was noted, however, that publications and other resources often conflate the two definitions, leading to the incorrect classification of research and leading to difficulties comparing research outputs.
- Example definitions submitted to the call included:
    - In an English based study on the epidemiology of multimorbidity, Chris Salisbury *et al* defined multimorbidity (in a primary approach) as more than one of 17 important chronic conditions for which care is incentivised under the Quality and Outcomes Framework, which includes physical illnesses, mental health issues, and learning difficulties.[4]
    - In a Scottish study on the epidemiology of multimorbidity, Karen Barnett *et al* broadened this definition to include the presence of two or more of 40 selected conditions, which also encompassed both physical and mental disorders.[5]

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[1] Almirall J & Fortin M (2013). *The coexistence of terms to describe the presence of multiple concurrent diseases*. Journal of Comorbidity **3(1)**,4-9. http://jcomorbidity.com/index.php/test/article/view/22

[2] Valderas JM, *et al.* (2009). *Defining comorbidity: implications for understanding health and health services.* Ann Fam Med **7(4)**,357-63. https://www.ncbi.nlm.nih.gov/pubmed/19597174

[3] Huntley AL, *et al.* (2012). *Measures of multimorbidity and morbidity burden for use in primary care and community settings: A systematic review and guide*. Annals of Family Medicine **10(2)**,134-41. https://www.ncbi.nlm.nih.gov/pubmed/22412005

[4] Salisbury C, *et al.* (2011). *Epidemiology and impact of multimorbidity in primary care: a retrospective cohort study.* Br J Gen Pract **61(582),** e12-21. https://www.ncbi.nlm.nih.gov/pubmed/21401985

[5] 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. https://www.ncbi.nlm.nih.gov/pubmed/22579043

- The recent NICE guidelines define multimorbidity broadly - and includes medical and social factors - as the presence of two or more long-term health conditions, which can include: defined physical and mental health conditions such as diabetes or schizophrenia; ongoing conditions such as learning disability; symptom complexes such as frailty or chronic pain; sensory impairment such as sight or hearing loss; alcohol and substance misuse.
- A study to compare the global prevalence of multimorbidity instead used a more restrictive definition of the presence of two or more of the six conditions: arthritis, angina or angina pectoris, asthma, depression, schizophrenia or psychosis, and diabetes.[6]
- Submission 11 was provided in the form of a paper looking to explore the burden of multimorbidity in Bangladesh, and defined multimorbidity as two or more of the following non-communicable diseases; hypertension, diabetes, COPD, cancer, heart diseases and stroke.

Issues with current definitions

- Definitions may be helpful epidemiologically, but are often less useful in clinical settings as the severity and complexity of multimorbidity (which is subjective and context dependent) is poorly captured and communicated by definitions based on disease count and type.
  - For example, the burden, impact, and clinical requirements of multimorbidity are influenced by the disease combination suffered from. While some multimorbidity patients suffer from impaired quality of life, others may not. Similarly, some multimorbid patients are complex to care for while others require less complex or minimal clinical interventions.
- Estimates of multimorbidity incidence and prevalence are dependent on how many, and which, diseases are included in the study definition. The lack of consensus in this regard creates highly variable figures between studies and the setting in which the primary data were collected (e.g. self-reported versus hospital visits versus primary care records).
- These difficulties are further exacerbated by the finding that only half of the published literature on multimorbidity actually provide a definition, with many more papers failing to provide a rationale for the definition or measure of multimorbidity used within the publication.[7]

Looking forward - what should the definition be and why?

- Most respondents expressed the opinion that multimorbidity should encompass both physical and mental conditions as a dose-response relationship exists between the number of chronic physical problems and depressive symptoms.[8] The addition of mental health concerns may

[6] Afshar S, *et al.* (2015). *Multimorbidity and the inequalities of global ageing: a cross-sectional study of 28 countries using the World Health Surveys.* BMC Public Health **15**,776. http://bmcpublichealth.biomedcentral.com/articles/10.1186/s12889-015-2008-7

[7] Almirall J & Fortin M (2013). *The coexistence of terms to describe the presence of multiple concurrent diseases*. Journal of Comorbidity **3(1)**,4-9. http://jcomorbidity.com/index.php/test/article/view/22

[8] Gunn JM, *et al*. (2012). *The association between chronic illness, multimorbidity and depressive symptoms in an Australian primary care cohort.* Soc Psychiatry Psychiatr Epidemiol. **47(2)**,175-84. https://www.ncbi.nlm.nih.gov/pubmed/21184214

also place different, or additional, requirements on the clinical management of physical diseases.[9]

- Others felt that the definition of multimorbidity should be even wider, and also include social, environmental, political, and economic factors in recognition that these also contribute to poor health and impact on the clinical management of patients.
    - The definitions provided by both the European General Practice Research Network and the NICE guidelines on multimorbidity were noted as examples that encompass this value.[10,11,12]
- Broad definitions that encompass diagnosed conditions, ill-health 'states' (e.g. hypertension and sensory deficits etc), and socioeconomic factors were largely considered to be desirable by many respondents. However, others raised caution that such a broad definition would lead to a very high population prevalence, especially in the elderly.
    - It was also noted that several disease pre-cursors and ill-health 'states' such a pre-diabetes are controversial. A desire for a definition to be broad and encompass such issues may also lead to an over-diagnosis of multimorbidity.
- In turn, there is a concern that any such definition would lose discriminatory power and may preclude accurate stratified and longitudinal analyses.
- A more useful definition could therefore be achieved either by increasing the disease count to three or more conditions[13], or by developing a weighted definition (e.g. weighted by impact on life expectancy (similar to the Charlson index) or by disease severity) to better identify patients with complex health needs.
- Respondents noted that reaching an agreed definition would be needed to better facilitate the identification and classification of studies on multimorbidity, and reduce the confusion between this issue and co-morbidity. In turn, a more standardised and accurate collection of research would be available for comparison, which is needed to advance further research and treatment.
- A standard definition was also considered to help better facilitate surveillance and monitoring efforts, leading to improved prevalence and longitudinal trend data to be developed. Such data is needed to more accurately model the future burden of multimorbidity and develop appropriate prevention and management strategies.

Is it feasible or possible to reach a consensus definition?

- While many respondents noted the benefits of reaching an agreed definition, others raised concern as to whether it is feasible to develop one, non-arbitrary consensus definition which is applicable and relevant across all settings (e.g. research and clinical care) and geographic locations.

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[9] Mercer S (2012). *Managing patients with mental and physical multimorbidity.* BMJ **345**. http://www.bmj.com/content/345/bmj.e5559

[10] Le Reste JY (2013). *The FPDM (family practice depression and Multimorbidity) Study: Project for systematic review of literature to find criteria for multimorbidity definition.* Eur J Gen Pr **17(3)**,180.

[11] Le Reste J, *et al*. (2013). *The European General Practice Research Network presents a comprehensive definition of Multimorbidity in Family Medicine and Long-Term Care, following a systematic review of relevant literature.* J Am Med Dir Assoc 14(5), 319–325.

[12] Le Reste J, *et al* (2015). *The European General Practice Research Network Presents the Translations of Its Comprehensive Definition of Multimorbidity in Family Medicine in Ten European Languages*. PLOSOne. http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0115796#pone.0115796.ref014

[13] Harrison, *et al* (2014). *Examining different measures of multimorbidity, using a large prospective cross-sectional study in Australian general practice*. BMJ Open **4**:e004694. http://bmjopen.bmj.com/content/4/7/e004694.full

- For example, the list of which conditions should be included would be dependent on context and disease prevalence. LMICs will have different diseases that need to be considered, including infectious diseases that are uncommon in developed countries.
- Reaching an agreed definition is also complicated by the conflict between providing a definition that is comprehensive enough to capture the highly complex clinical reality of multimorbidity and a definition that is specific and pragmatic enough for the development of functional tools for research. That is, it may be difficult to develop a definition that is both clinically and methodologically useful.
- Lastly, it was also noted that, since multimorbidity is not a disease *per se* (but rather a concept that more broadly describes ill-health), any definition may benefit from being adaptive in nature, and amendable to change as our understanding of the issue improves.

Question 2 and 7: What data exist - and what are the key data sources - on the prevalence, burden, and determinants of multimorbidity? Are there significant gaps in such data; if so, what are they? What are the priorities for research about the prevalence, burden and determinants of multimorbidity?

Prevalence

What is currently known, and where are the gaps?

- Responses noted that the prevalence of multimorbidity is particularly high in the elderly, and growing internationally.
    - A study has recently been published which found that while the prevalence of multimorbidity is highest in high income countries, figures from low- and middle-income countries are gradually approaching the figures of richer countries.[14]
- However, responses noted that while these trends may be apparent, actual figures on prevalence are highly variable. This may be, in part, due to inconsistencies in definition - prevalence figures will depend on the number and types of conditions included in any given definition.[15,16,17]
- Many studies are also often restricted to elderly populations, meaning prevalence data in younger cohorts is particularly lacking.
- Figures from LMICs are also lacking, as efforts to investigate the issue are often impeded by a lack of comprehensive medical records and a reliance on self-report.
- There are some recent studies investigating the longitudinal trends of multimorbidity, but broadly this is an area where the evidence is very limited.[18,19]
- Certain clusters of diseases occur more commonly together.[20,21,22]
- Multimorbidity that is comprised of both physical illness and mental health issues is common.[23]

[14] Garin N, *et al*. (2016). *Global Multimorbidity Patterns: A Cross-Sectional, Population-Based, Multi-Country Study*. J Gerontol A Biol Sci Med Sci **271(2)**, 205-14. https://www.ncbi.nlm.nih.gov/pubmed/26419978

[15] Salisbury C, *et al.* (2011). *Epidemiology and impact of multimorbidity in primary care: a retrospective cohort study.* Br J Gen Pract **61(582),** e12-21. https://www.ncbi.nlm.nih.gov/pubmed/21401985

[16] Fortin M, *et al* (2012). *A systematic review of prevalence studies on multimorbidity: toward a more uniform methodology*. Ann Fam Med. **10(2)**, 142-151. https://www.ncbi.nlm.nih.gov/pubmed/22412006

[17] Stewert M, *et al.* (2013). *Comparisons of multi-morbidity in family practice--issues and biases.*Fam Pract. **30(4)**, 473-480. https://www.ncbi.nlm.nih.gov/pubmed/23666805

[18] Dhalwani NN, *et al*. (2016). *Long terms trends of multimorbidity and association with physical activity in older English population.* Int J Behav Nutr Phys Act **13(1)**, 8. https://ijbnpa.biomedcentral.com/articles/10.1186/s12966-016-0330-9

[19] Melis R, *et al.* (2014). *Incidence and Predictors of Multimorbidity in the Elderly: A Population-Based Longitudinal Study. PloS one* **9(7)**, e103120. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4109993/

[20] Van den Akker & Muth C (2014). *'How common is multimorbidity?'* In Mercer S. W, Salisbury C and Forton M edited *ABC of Multimorbidity*. Wiley Blackwell

[21] Violan C, *et al.* (2014). *Prevalence, Determinants and patterns of multimorbidity in primary care: A systematic Review of Observational Studies.* PLoS One. http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0102149

[22] 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. http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(12)60240-2/abstract

[23] King's Fund. (2012). *Long term conditions and mental health*. http://www.kingsfund.org.uk/sites/files/kf/field/field_publication_file/long-term-conditions-mental-health-cost-comorbidities-naylor-feb12.pdf

Determinants

What is currently known, and where are the gaps?

- It is broadly accepted that there is a positive association between multimorbidity and several modifiable and non-modifiable factors including age; social deprivation; gender (with women more commonly affected); and low levels of physical activity.[24,25,26]
- One respondent noted that many cardio-metabolic diseases, and other chronic conditions, are most common in South Asian populations, meaning certain ethnic groups may also be at an inherently higher risk of multimorbidity.
- One respondent also noted recent work suggesting that those with adverse childhood experiences are more likely to present with multimorbidity in later life.[27]
- Many respondents noted that while it can be predicted that many determinants of single chronic diseases may also contribute to multimorbidity, more research needs to be done in this area, particularly in an effort to develop more effective primary prevention strategies.

Burden

What is currently known, and where are the gaps?

- 'Burden' encompasses several meanings including:
    - The burden of disease on life expectancy and quality of life.
    - Treatment burden, which can affect patients (e.g. polypharmacy) and carers.
    - The burden on both primary and secondary health providers; increased GP appointments and hospital admissions impact on capacity and creates a financial burden.
- Generally, while respondents acknowledged that multimorbidity is associated with this range of burdens, it was noted that more empirical evidence on the true impact of multimorbidity is still needed.
    - Responses noted that much research on burden focuses on older people, and evidence on the impact of multimorbidity in younger cohorts is lacking.
    - Evidence on the burden to different ethnic groups is needed.
    - Similarly, evidence on the burden of multimorbidity in vulnerable populations, such as migrants, those with learning difficulties, and those with poor social support, is lacking.
    - Additional evidence is needed to identify whether particular clusters of diseases are associated with a worse burden (to both patients and healthcare services).
    - More evidence is needed on the economic impact of multimorbidity. In particular, one respondent noted that more is known about the cost to secondary care services as

[24] Salisbury C, *et al.* (2011). *Epidemiology and impact of multimorbidity in primary care: a retrospective cohort study.* Br J Gen Pract **61(582),** e12-21. https://www.ncbi.nlm.nih.gov/pubmed/21401985

[25] 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. http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(12)60240-2/abstract

[26] Violan C, *et al.* (2014). *Prevalence, Determinants and patterns of multimorbidity in primary care: A systematic Review of Observational Studies.* PLoS One. http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0102149

[27] Sinnott C, *et al*. (2015). *Psychosocial complexity in multimorbidity: the legacy of adverse childhood experiences.* Family Practice **32(3)**, 269-75. https://www.ncbi.nlm.nih.gov/pubmed/25900675

opposed to primary care services, despite primary care being the predominant sector caring for patients with multimorbidity.[28,29]

Sources of data

- Respondents noted that in most countries, the epidemiological understanding of multimorbidity has predominately come from primary care data (e.g. CRPD data).
- This may reflect the key role that the primary health care setting plays in both collecting routine data on the care of patients with multimorbidity, and also developing and testing interventions.
- However, it was also deemed important for primary care data to be better supplemented with data from secondary care to provide more accurate, and joined-up, records of multimorbidity.
- It was also noted that CRPD data is of limited utility to understand determinants, as risk factors are incompletely or inconsistently recorded. The UK BioBank database may instead provide a better source of information which could be used to analyse the determinants of multimorbidity in the future (once sufficient death data are available from the longitudinal follow-up). However, this data would be less representative of the population compared to the CPRD, and data on socioeconomically disadvantaged groups would likely be missing.

Future research priorities

- There was a clear desire to improve our understanding across all areas of prevalence, burden, and determinants (biological and social), especially as a mechanism to develop effective prevention strategies.
- All such future research would be greatly facilitated by developing uniform methodologies and a definition to better allow the comparison of studies.
- It was also noted that a potential challenge for studies investigating the basic biological mechanisms and determinants underlying multimorbidity is that they will most likely require new experimental and pre-clinical models that represent the complexity of 'real life' as opposed to modelling strictly defined single diseases.
- There was a desire for more quantitative evidence, as opposed to qualitative evidence, as a means to better define and measure the problem.
    - The use of new scales to measure treatment burden (including the Patient Experience with Treatment and Self-management (PETS) measure and the Treatment Burden Questionnaire) were specifically noted as something that should be considered for use in future studies.[30,31]
- Greater efforts also need to be placed on improving the routine documentation and surveillance of the issue on a global scale. Establishing a registry-based approach may be useful for prospective studies and may be easier to do in low-resource settings where standardised data collection is not always routine.

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[28] Brilleman SL, *et al*. (2014). *Keep it simple? Predicting primary health care costs with clinical morbidity measures.* Journal of Health Economics **35**,109-22. https://www.ncbi.nlm.nih.gov/pubmed/24657375

[29] Brilleman SL, *et al*. (2013). *Implications of comorbidity for primary care costs in the UK: a retrospective observational study.* British Journal of General Practice **63(609)**. https://www.ncbi.nlm.nih.gov/pubmed/23540484

[30] Eton DT, *et al* (2016). *Development and validation of the Patient Experience with Treatment and Self-management (PETS): a patient-reported measure of treatment burden*. Qual Life Res.

[31] Tran VT, *et al* (2012). *Development and description of measurement properties of an instrument to assess treatment burden among patients with multiple chronic conditions.* BMC medicine **10**:68. http://bmcmedicine.biomedcentral.com/articles/10.1186/1741-7015-10-68

- The documentation of treatment prescribing should also be supplemented with data on treatment adherence, so that treatment burden and polypharmacy can be more accurately investigated.
- One respondent noted that future research should concentrate on elderly populations, as the prevalence and burden of multimorbidity is worse in such patients.
- However, overall there was a clear desire for future research to focus on multimorbidity at all stages of the life-course, and also for longitudinal studies.
- Many respondents expressed a desire for future studies to investigate which combinations of diseases are associated with the worst outcomes, and why. One respondent conversely noted that further work to understand clustering might be of limited utility in better understanding risk factors and causal pathways, and that future work should instead focus on means to improve patient care.
- Future research should also be performed to better understand what the prevalence, and impact, of multimorbidity is in vulnerable groups and ethnic minorities.

Questions 3 and 8: What are the key data, and what data sources exist, on the prevention of multimorbidity? Are there significant gaps in such data and, if so, what are they? What are the priorities for research about the prevention of multimorbidity?

What is currently known, and where are the gaps?

- This was an area in which many respondents noted a particular lack of established evidence, although several interventions were suggested that might be predicted to positively influence the trajectory of multimorbidity.
- For example, certain factors such as smoking, obesity, and physical inactivity etc, are known to play a role in the development of individual diseases, which then commonly occur together in multimorbid patients. There is additional, although limited, evidence to suggest that the same risk factors are associated with incident multimorbidity.[32,33]
- Therefore, a number of respondents predicted that targeting modifiable risk factors to prevent individual diseases would simplify the problem and also inherently work as a primary prevention strategy for multimorbidity.
    - In turn, it is likely that prevention strategies will need to target individual health-related risk factors but also within the context of wider public health interventions, as recently acknowledged by the National Prevention Research Initiative.[34]
- However, caution was raised that assuming an intervention that is proven to work in a single disease group will also work for multimorbidity is naive.
- While we know a lot about how to promote healthy lifestyles - and the influence of such interventions on single diseases - there is still a need for more quantitative research to establish whether these interventions are indeed able to elicit a positive influence in the context of multimorbidity.
- With this in mind, more research is also needed to explore the relative benefits of such public health interventions i.e. which ones work best?
- It should also be remembered that some determinants of multimorbidity are not modifiable e.g. age, gender, and ethnicity and therefore a need for effective secondary prevention and management strategies should not be forgotten.

Future research priorities

- Research to investigate prevention strategies should address issues at all levels, from public health, primary and secondary care, and community/social care.
- However, a particularly beneficial avenue for future research might be to better understand the degree to which lifestyle factors contribute to multimorbidity, and the mechanism by which they do so. As these factors are largely modifiable, such information may help develop particularly impactful preventative strategies. As they could be introduced at a public health level, they may also be more effective than efforts that require behaviour change at the individual level.

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[32] Wikstrom K, *et al*. (2015). *Clinical and lifestyle-related risk factors for incident multimorbidity: 10-year follow-up of Finnish population-based cohorts 1982-2012.* Eur J Intern Med **26(3)**,211-216. https://www.ncbi.nlm.nih.gov/pubmed/25747490

[33] Fortin M, *et al.* (2014). *Lifestyle factors and multimorbidity: a cross sectional study.* BMC Public Health **14(1)**, 686. http://bmcpublichealth.biomedcentral.com/articles/10.1186/1471-2458-14-686

[34] National Prevention Research Initiative. Initiative outcomes and future approaches, 2015. https://www.mrc.ac.uk/publications/browse/national-prevention-research-initiative-npri-report-2015/

- Research should be performed to determine at what stage of the life course interventions should be targeted.
    - For example, one submission noted that exploring the impact of family based interventions to reduce adverse childhood events on later longer-term multimorbidity could be an area to consider.
- One of the NICE recommendations for research is to explore whether it is possible to *'analyse primary care data to identify characteristics that affect life expectancy and to develop algorithms and prediction tools for patients and healthcare providers to predict reduced life expectancy*'. The rationale for this recommendation was given as predicting reduced life expectancy could allow healthcare providers to better target preventative medicines to patients who are most likely to benefit from them.
- Some effort should also be given to identifying whether particular groups of people are more likely to develop multimorbidity, allowing increased preventative efforts to be targeted to these areas.
- Future research should use a combination of clinical endpoints, patient-defined outcomes, and economic (e.g. cost-effectiveness) metrics when evaluating the success and sustainability of preventative interventions.

Questions 4 and 9: What are the key data, and what data sources exist, on the management of multimorbidity? Are there significant gaps in such data and, if so, what are they? What are the priorities for research about the management of multimorbidity?

What is currently known, and where are the gaps?

- This is an additional area where respondents noted a clear paucity of empirical research.
- Many made reference to the recent Cochrane review which summarises the existing interventions and evidence of their effectiveness. The review reported that there have only been 18 RCTs on this topic, and that the resulting evidence is conflicting and inconclusive, in addition to being limited by virtue that most studies focus only on multimorbidity in older people.[35]
    - However, a number of trials that were ongoing at the time of the Cochrane review have since been published, including the CARE PLUS Study and the 3D Study.[36,37]
- While few clinical guidelines specifically take multimorbidity into account, there is a general consensus that certain strategies should be expected to improve the care of multimorbid patients e.g.:
    - Improving the continuity of care.
    - Providing longer consultation times.
    - Addressing the current fragmentation of healthcare services by improving the integration between, for example, primary care and social care.
    - Providing care through multi-disciplinary teams.
    - Encouraging patient self-management.
    - Paying greater attention to the potential problems of polypharmacy and a lack of medication adherence.
    - Making changes to healthcare delivery, both in terms of service organisation but also in the training of GPs and other healthcare professionals.
- However, although there is some evidence to support the effectiveness of these interventions, the evidence base underlying the utility of these strategies is largely sparse, especially with respect to longer term outcomes.
- One of the primary barriers to developing this information is that patients with multimorbidity are often excluded from single disease clinical research, which aims to understand how to treat an 'average uncomplicated patient'.
- There is also little agreement on what outcomes or end-points should be used to determine the effectiveness of management strategies, which also complicates comparisons between studies. Many respondents noted however that patient-defined outcomes should gain greater recognition.
- As noted in multiple areas in this summary, there is a particular lack of research into management strategies for younger adults, those from poorer socioeconomic backgrounds, and ethnic minorities.
- There is a lack of evidence about the cost-effectiveness of new models of care.

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[35] Smith S, *et al.* (2016). *Interventions for improving outcomes in patients with multimorbidity in primary care and community settings*. Cochrane Database of Systematic Reviews. https://www.ncbi.nlm.nih.gov/pubmed/22513941

[36] Mercer, SW, *et al.* (2016). *The Care Plus study - a whole system intervention to improve quality of life of primary care patients with multimorbidity in areas of high socioeconomic deprivation: exploratory cluster randomised controlled trial and cost-utility analysis.* BMC Medicine, **14**, 88. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4916534/

[37] Man, MS, *et al.* (2016). *Improving the management of multimorbidity in general practice: protocol of a cluster randomised controlled trial (The 3D Study)*. BMJ Open, **6(4)**, e011261.

Future research priorities

- Most respondents felt that primary care is the most appropriate sector to offer management strategies for multimorbidity (as it can provide a generalist approach), but noted that future research should prioritise how changes in service organisation and delivery can be introduced to ensure care for multimorbid patients is optimised.
    - In addition to clinically defined outcomes, the evaluation of such alternative interventions should also consider how they impact on patient-defined goals, such as day-to-day function and social participation etc.
    - Several respondents raised that evaluation strategies should also consider cost-effectiveness, particularly as there is some evidence, for example arising from the WISE trial of care planning, that it is difficult to achieve sustained organisational or attitude changes.[38]
    - Large, well-designed trials of management interventions may be of most value to perform in defined patient groups (for example, people with multimorbidity who find it difficult to manage their treatment, people with multiple providers or services involved in their care, people with both long-term physical and mental health problems etc).[39]
- However, the responses also noted that future research should explore how care could be improved at all system levels, including how best to employ community based measures to manage multimorbidity.
- Similarly, the role of self-management was also raised as something that requires more research. While many predict that increasing patients health literacy and ability to self-manage may be beneficial, one respondent noted that care should be taken not to impose too much responsibility on patients and carers.
- Additional research is needed to address both the clinical benefits and cost-effectiveness of *stopping* preventative medicines.
- It will also be beneficial for future research to explore whether technology and digital health measures - including electronic medical records, computerised decisions support, mobile phone apps, and telecare services etc - can improve both healthcare delivery and self-management (and in turn whether this leads to improved clinical outcomes).
- As also discussed in the context of preventative strategies, future research should use a combination of clinical endpoints, patient-defined outcomes, and economic (e.g. cost-effectiveness) metrics when evaluating the success and sustainability of any intervention.
    - With this in mind, the COMET initiative, which aims to establish a core outcome set for studies examining multimorbidity, may be helpful.[40]
- The recent NICE guidelines have several research recommendations that are relevant in the context of this question.[41]

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[38] Kennedy A, *et al* (2013). *Implementation of self management support for long term conditions in routine primary care settings: cluster randomised controlled trial*. BMJ **346**:f2882. http://www.bmj.com/content/346/bmj.f2882

[39] https://www.nice.org.uk/guidance/ng56/evidence/full-guideline-2615543103

[40] http://www.jcomorbidity.com/index.php/test/article/view/21

[41] https://www.nice.org.uk/guidance/ng56/evidence/full-guideline-2615543103

Question 5 and 10: What are the key sources of funding for research into multimorbidity. Are there gaps in funding, and if so where? What should the strategic response of both national and international research funders and agencies be to multimorbidity?

Sources of funding

- The responses to the question *'What are the key sources of funding for research into multimorbidity*' were varied, although broadly reflected a lack of *specific* funding opportunities (with single disease funding being more available) and a lack of international funding.
- Within the UK, the NIHR was noted as the primary source of funding for academic research into multimorbidity. However, one respondent noted that this funding stream received few applications, postulating that this reflected a paucity of research teams with experts in this area (in turn, perhaps reflecting a need for a wider culture change to improve future research).
- In Scotland, the Chief Scientist Office (CSO) is another potential source of funding for multimorbidity research.
- Some frustration was apparent that many other sources of funding - including Wellcome, the Research Councils, and medical charities - focus on single disease specific research. However, others implied that while multimorbidity may not be a core concern for such funders, they could nonetheless still be appropriate sources of funding to inform certain elements or aspects of multimorbidity.
- The Richmond Group of Charities, Nesta, National Voices, Health Foundation, The King's Fund, and Nuffield Trust were all raised as additional sources of funding into other aspects of multimorbidity.
- The EU has funded the Joint Action on Chronic Disease (JA-CHRODIS) which has a multimorbidity work package.[42] It is currently working towards creating a multimorbidity care model which could potentially be implemented in European Health Care Settings.
- One respondent raised a positive vision that, since a wider range of funding bodies are now recognising the importance of multimorbidity, an expansion in research capacity will follow (although it was noted that this will take time).

Future strategic response

- Many respondents to this question noted a strong desire for funding that both encourages and rewards collaborative efforts in terms of discipline, as well as supporting multi-centre and cross-border collaborations.
    - Such funding opportunities should be made available across the spectrum of medical research, from basic science to clinical research to public health and epidemiological research.
    - Many respondents expressed a particular desire for more international funding.
- Respondents felt that collaborative research will progress multimorbidity research by presenting opportunities to learn from more established fields (such as geriatrics), while also providing a mechanism to attract new ways of thinking, encourage the use of novel and innovative technologies, and build the much needed research capacity in this area.
- One respondent noted however that funders should help build a framework that supports a consistent but gradual expansion in research capacity through investment in training and

[42] http://chrodis.eu/our-work/06-multimorbidity/

infrastructure as it will be important to avoid a sudden influx of too much funding in advance of there being researchers with relevant interests and expertise.[43]

- Lastly, some respondents noted that many journals are either entirely focussed on specific diseases or have a strong preference for papers relating to single diseases as these tend to be highly cited due to the larger mass of other researchers that refer to this work. Therefore, to ensure the impact of future research it may be necessary to develop a wider culture change.

[43] Medical Research Council. Primary Health Care: Topic Review. London, 1997.

Helpful resources

A number of helpful resources for further information emerged throughout the submissions and are listed below.

- The recent NICE guidelines on multimorbidity.
- A report by the Royal College of General Practitioners on '*Responding to the needs of patients with multimorbidity*'.
- Guidelines Imitative Network (GIN), especially the 'Resources' page.[44]
- The International Research Community on Multimorbidity publication list, which details all the available literature.[45]
- The Journal of Comorbidity, an international journal that publishes on articles on the pathophysiology, diagnosis, prevention and management of patients with comorbidity/multimorbidity.[46]
- A Healthcare Quarterly Issue on 'Complex Care and Multimorbidity'.[47]
- The COMET Initiative on '*Establishing a Core Outcome set for studies examining multimorbidity'.*[48]

[44] http://www.g-i-n.net/working-groups/multimorbidity/mulimorbidity-resources
[45] www.usherbrooke.ca/crmcspl/fileadmin/sites/crmcspl/documents/Publications_on_multimorbidity_01.pdf
[46] http://jcomorbidity.com/index.php/test
[47] http://www.longwoods.com/publications/healthcare-quarterly/24653
[48] http://www.cometinitiative.org/studies/details/822