

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

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\* *Mandatory fields*

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\* Is this input submitted as an organisational or individual response? ~~Organisation~~ Individual  
(on behalf of the UCL Multimorbidity Research Team)

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## Definitions

**1. There is no standard definition of 'multimorbidity' – various different definitions are used. Which definitions (or aspects of definitions) do you think are most helpful to efforts to describe and understand multimorbidity?**

*Please provide references for any published research, and highlight any other initiatives related to multimorbidity that the Academy may be interested in.*

**Other Initiatives** that the Academy may be interested in:

**UCL Multimorbidity Research Initiative:** Socioeconomic inequalities in life expectancy with and without multimorbidity.

I am the Principal Investigator on this study, working in collaboration with a multidisciplinary team of clinical epidemiologists, statisticians, academic GPs and data scientists.

### **Background and research questions**

This research aims to understand the transitions between health-states (from 'healthy' to being diagnosed with one, two or more chronic diseases, to death) and the patterns of disease accumulation.

Our main scientific questions are:

- i. Do socio-economically advantaged and multiply disadvantaged die from the same combinations of diseases, whereby the latter die earlier because of earlier onset of multimorbidity?  
Or

- ii. Do disadvantaged groups have a greater number or more 'lethal' combinations of chronic diseases?
- iii. Do mental health disorders act synergistically with chronic physical conditions to hasten death?
- iv. How do survival curves diverge between socioeconomic groups once multimorbidity sets in?

We are using the Clinical Practice Research Datalink (CPRD) for the analysis, including those 1.3 million patients aged 45 and over who are registered in general practices with records linked to Hospital Episode Statistics and ONS mortality.

This is an open-cohort study, with patients followed up from 2001 to March 2010 (using CALIBER data available in FARR Institute, London).

The study is part of the NIHR CLAHRC-North Thames Methodological Innovation theme and an overview of the project can be found here:

<http://www.clahrc-norththames.nihr.ac.uk/health-inequalities-multiple-morbidities/>

The study commenced in March 2015 and will report all findings by Dec 2017. Two papers are currently being drafted.

***Issues with the working definition of multimorbidity:***

The general definition of multimorbidity – patients having two or more chronic or long-term conditions concurrently – serves a valuable purpose in highlighting the burden of multimorbidity across the age range or between sub-groups of the population.

However, this definition is based solely on counting the number of diseases a person has. Hence, estimates of multimorbidity incidence and prevalence are dependent on how many and which diseases are included in the study definition – and, as there is no consensus on these, estimates vary widely between studies and the setting in which the primary data were collected (eg self-reported versus hospital visits versus primary care records).

Our study focuses on inequalities in onset, duration and survival with multiple chronic conditions. Some of the definitional challenges we faced included:

- if we included a large number of diagnosed chronic conditions and pre-cursors of disease (eg hyperlipidemia or hypertension) and symptoms associated with ageing (eg sensory deficits) as many previous studies have, then, for older age groups, we would soon hit a ceiling, with almost all of the population characterised as multimorbid by a certain age (eg 70 years). Hence, we would lose discriminatory power for the stratified socioeconomic analysis on life years spent in various health-states prior to death.
- By definition, the most prevalent single diseases will be found most often in combination with other diseases; but selecting on prevalent combinations alone would miss important combinations with a high case fatality rates.

- We sought to avoid double-counting by not including both the disease and its symptom as separate conditions – eg pain and arthritis.

Based on criteria specific to the aims of our study, 30 major chronic diseases were identified as being in-scope for our analyses. Those without any of these 30 diseases were categorised as 'healthy' or 'not morbid'.

We believe that the count-based definition of multimorbidity falls short of providing a framework for the identification and analysis of common disease clusters and/or timed trajectories of multimorbidity and the impact of several disease interactions on survival. New evidence generated by disease-based (rather than count-based) analyses is urgently needed, together with analyses on how disease patterns vary by age, gender and socioeconomic status, to provide the evidence base for the treatment of multimorbidity and potentially for the reconfiguration of health services.

We are using two approaches to identifying the common sequences of disease accumulation:

1. Grouping our 30 diseases into eight clinically pre-defined disease clusters. The disease clusters are loosely based on the ways that clinical specialities are defined. They include cardiovascular diseases (including diabetes), cancers, chronic respiratory diseases, neurological disease, mental health conditions, disease of immune system, musculoskeletal diseases and 'other'. Patients with diseases in one cluster are assumed to have aetiologically linked conditions or sequelae of disease progression. In contrast, patients with diseases in multiple and random clusters are thought to have complex multimorbidity. Little is known of the burden of random and non-random clusters of multiple morbidity, its implications for longevity or the challenges it may pose for clinical management and care coordination.

We will use multi-state modelling to identify age of onset, years spent with a disease in each cluster and the sequence of cross-cluster accumulation and finally, the life expectancy (by socioeconomic group) of each specific disease-cluster trajectory. It will help answer questions on whether the order in which diseases are acquired have an impact on survival and may help with designing interventions to halt or slow down the process of disease accumulation.

2. Rather than pre-group diseases into defined clusters, our second approach is to use unsupervised machine learning algorithms to identify common disease accumulation trajectories for all 30 diseases. This is discovery-driven research which may help to provide new insights to hitherto intractable question of complex disease patterns and sequences. This approach is methodologically innovative and is being developed with colleagues in UCL computer science.

## **Current knowledge base**

*When answering these questions, please consider both national and international populations of high, middle, and low income countries. Please provide examples and case studies to illustrate your arguments where appropriate. Please provide references for any published research.*

**2. What are the key data, and what data sources exist, on the prevalence, burden (including costs and impact on health systems) and determinants of multimorbidity? Are there significant gaps in such data and, if so, what are they?**

The accompanying AMS's round-table discussion summarises the benefits and limitations of the various types of data sources. Of these, linked electronic health records from routine collections (eg CPRD), whilst not perfect, are the best available source for estimating incidence, prevalence, disease accumulation trajectories, and developing prognostic models. Clarification of the chronic conditions with the largest adverse impacts on life expectancy (by socio-economic group) will directly lead to evidence based decisions on the most appropriate combinations of pharmaceutical treatments to provide and of the most appropriate medications to stop in cases of adverse drug interactions or side effects.

However, CPRD provides little useable data for the analysis of determinants of multimorbidity ie bio-markers, health behaviours and environmental risk factors are incompletely or inconsistently recorded.

In contrast, the UK biobank database offers rich data on social, biomedical and genetic attributes of individuals 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, these data are less representative of the population than the CPRD, particularly the most socioeconomically disadvantaged groups.

**3. 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?**

**4. What are the key data, and what data sources exist, on the management of multimorbidity? Are there significant gaps in such data; if so, what are they?**

*The term 'management' here could refer to clinical interventions designed to specifically treat patients with multimorbidity as well as strategies for the delivery of healthcare services patients with multimorbidity. The term also refers to a wide range of management approaches that may differ by the specific diseases that co-exist.*

Data on treatment adherence (for both prevention and management of disease) is scarce (e.g. generally prescribed medication is available, but rarely of medication taken).

**5. What are the key sources of funding for research into multimorbidity? Are there gaps in funding and, if so, where?**

ESRC supports research on healthy ageing; NIHR supports research on the clinical *management* of multimorbidity and polypharmacy; MRC does not mention multimorbidity as a research topic, the closest it comes to it is in the Population and Systems Medicine strand but specifically excludes diseases of the brain and immune system in its remit; and the BBSRC on capacity building in bioinformatics (eg machine learning using big data). Thus, whilst basic research on disease accumulation trajectories in multimorbidity is of relevance to each funding body, is not their core concern.

Given the relative 'newness' of the topic, its complexity and the lack of evidence on almost all aspects – epidemiology, clinical management and economics - multimorbidity research requires sustained funding to build capacity within multidisciplinary teams. Currently there is

very limited funding to exploit routine administrative data sources for multimorbidity research or to develop/validate algorithms and novel methodologies necessary to exploit them. Most current funding has been invested in infrastructure.

## Looking forward

### **6. What should the definition of 'multimorbidity' be? How would this definition improve research and/or treatment?**

The simplicity of the current definition of multimorbidity as a count of concurrent diseases has served well to identify the scale of a major health challenge for an ageing population. If agreement were reached on a set of diseases to include, the current definition could provide a useful tool to monitor trends and variations in prevalence between sub-populations and across countries.

However, age is the single biggest predictor of multimorbidity; and by using the 2+ count measure, the vast majority of older people are classed as multimorbid by early-old age (ie about 10-15 years before the median age at death in the UK). We feel the low threshold of disease counts in the current definition fails to help identify people with complex healthcare needs, and blunts its utility as a population monitoring tool to capture the total (and growing) burden of chronic illness. A weighted multimorbidity score (eg weighted by impact on life expectancy, similar to the Charlson index) might be one way forward for monitoring and comparative purposes.

Most importantly however, research based on either a simple or weighted count measure will not address needs for evidence to guide clinical practice and treatment priorities; and neither will it provide insights for policy makers to better understand the determinants of common disease trajectories to identify key targets for interventions which halt or slow its progress.

Better definitions of multimorbidity would enable us to better address research/treatment questions, eg :

- Characterising trade-offs between improving quality and quantity of life in multimorbidity
- What are patients' priorities for treatment of multimorbidity – to improve quality or quantity of life?
- where polypharmacy is a feature of multimorbidity, what should the priority be in rationalising medication?

This issue is circular in that answers to questions such as these would influence the definition adopted. There would also be implications for data collection procedures eg currently there are few data repositories that record disease sequences in multimorbidity together with quality of life and survival.

### **7. What are the priorities for research about the prevalence, burden and determinants of multimorbidity?**

### **8. What are the priorities for research about the prevention of multimorbidity?**

**9. What are the priorities for research about the management (as defined above) of patients with multimorbidity?**

Some questions for which evidence is urgently needed in order to 'tailor' management of patients with multimorbidity include:

- does single disease preventative activity (e.g. cardiovascular disease secondary prevention) improve quality of life or just add to the polypharmacy burden?
- Are symptom treatment targets (eg for blood pressure, cholesterol levels, HbA1c) of any benefit in managing multimorbidity?
- Where is the threshold (with respect to age, number of comorbidities, functional status) beyond which treatment should be supportive rather than actively managed?
- Is there a ceiling effect (with respect to QOL/ life expectancy benefit) when treating multimorbidity after 6, 7, 8 etc medications?

**10. What should be the strategic response of both national and international research funders and agencies be to multimorbidity?**