Multimorbidity in the UK population: understanding disease clustering

2018 call

Funded proposals

This joint MRC-NIHR call in 2018 aimed to pump-prime research into identifying and exploring disease clusters, their trajectories and risk factors to enable progress in understanding common mechanistic pathways in multimorbidity. It also aimed to mobilise the research community to establish new and develop existing collaborations between clinical and academic experts to promote a multidisciplinary approach. The Panel, which met in February 2019, was pleased to note that many excellent research groups, including those new to the field, responded to the call. Five proposals were awarded forming a portfolio that consists of a mixture of studies ranging from methodological research to studies that focus on specific disease clusters. The funded proposals had a good geographical spread and used diverse UK data sources (UK Biobank, SAIL, CPRD, THIN, etc.).

Details of the funding projects can be found below:

Dregan, Alexandru (MR/S028188/1; 24 months) Mechanisms and consequences of depression-related multimorbidity over the life course: coordinated analysis of population and primary care data

Principal Investigator Dr Alexandru Dregan (King's College London)
Co-Investigator Dr Matthew Prina (King's College London)
Co-Investigator Dr Stephani Hatch (King's College London)
Co-Investigator Professor Matthew Hotopf (King's College London)
Co-Investigator Professor David Armstrong (King's College London)
Co-Investigator Professor Andrew Pickles (King's College London)
Co-Investigator Dr Lauren Rayner (King's College London)
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Multimorbidity (MM), defined as the co-existence of two or more mental and/or physical chronic conditions, represents a complex challenge for clinicians, participants, and their families. Current preventive efforts have partly failed because they have focused on one disease at a time and too late in life. For this reason, there is a critical need to identify groups of individuals at risk of MM earlier in life, and to develop interventions to prevent MM and its adverse health outcomes.

A number of surveys have shown that not only clinical depression the most common illness in any MM cluster, it also is the most important for harming a patient's quality of life. Compared with most diseases that occur (and begin to cluster) in later years, depression tends to begin much earlier in adult life. As most existing research on MM has focused on older adults (over 60 years), this means an important component has been relatively ignored. What exactly is the relationship between the onset of depression in early adult years and later MM clusters? A life course approach that follows groups of people over many years is the best way of addressing this question.

In the proposed study we will analyse three of the world largest birth cohorts (all based in the UK) that contain around 40,000 participants who have been regularly studied in the decades

since their birth. We will identify those participants with a record of depression in young and mid-adult years (20 to 64 years of age) and examine how their early onset psychological difficulties interacted with later illnesses, both physical and mental. In particular, we will explore these relationships across time and within different subgroups, defined by gender and socioeconomic background. In addition, we plan to evaluate the clinical value of the cohort findings with data collected from routine general practice.
The CPRD database now contains millions of patients' records and we anticipate examining in excess of 200,000 patients with depression. These large numbers should be sufficient to identify important mechanisms and consequences of depression related MM with reasonable precision. Dr Dregan (PI) has developed a protocol for accessing electronic health records from the primary care database, which will inform this part of the proposed study. Thus, we are confident that we will access to a large number of individuals in order to identify the important risk factors (including physiological, behavioural habits, treatment, and social support) for depression-related multimorbidity clusters across young and mid-adult years. We should be able to determine which depression-related MM clusters have the most harmful impacts during young or mid-adult years and test how these relationships are affected by gender, social class, and specific attributes of depression (such as sleep disturbance).

We will use advanced statistical methods to produce the most reliable results possible. With the large cohort and primary care databases, these important questions that will inform future clinical trials and improve public health, can be addressed at a considerably lower cost than a randomised trial. We will also use the requested resources to enable other researchers to use cohort data to address important research questions.

Guthrie, Bruce (MR/S028013/1; 30 months) Understanding the relationship between depression and trajectories of physical multimorbidity accrual: longitudinal analysis of UK Biobank data

Principal Investigator Professor Bruce Guthrie (University of Edinburgh)
Co-Investigator Professor Cathie Sudlow (University of Edinburgh)
Co-Investigator Professor John Norrie (University of Edinburgh)
Co-Investigator Professor Stewart Mercer (University of Edinburgh)
Co-Investigator Dr Caroline Jackson (University of Edinburgh)
Co-Investigator Dr Daniel Morales (University of Dundee)
Co-Investigator Professor Daniel Smith (University of Glasgow)

Summary:
There are increasing numbers of people who have multimorbidity which means living with multiple physical and/or mental health conditions. Increasing multimorbidity has a number of causes. People are living longer and are more likely to survive life-threatening illness than in the past (for example, anyone who survives a heart attack will then have to live with chronic heart disease). Living longer and surviving life-threatening illness are of course good things, but multimorbidity poses challenges to health services and research which often focuses on single conditions. We need to understand how people develop multiple conditions better, and this is the focus of this research.

The combination of physical conditions with depression is very common. About one in five people with a physical condition have depression, and this combination is associated with worse physical and mental health outcomes. It is therefore important to understand how physical conditions and depression are related. Existing research has often just looked at people at one point in time. This means that it isn't possible to know if depression causes physical disease, or if physical disease causes depression, or both. Existing research also does not always account for things which might be related to both physical disease and depression such as heavy drinking or lack of exercise. The aim of this research is to

examine the relationship between physical disease and depression using data for half a million middle-aged people followed up for ~10 years as part of the UK Biobank study. There are three elements to the planned work:

First, we will develop a number of different ways of measuring the patterns of physical conditions that people get in middle and older age. There are three different ways of doing this: (1) Simply counting how many physical conditions people develop over 10 years; (2) Identifying the 'shape' or trajectory of how they develop new physical conditions (eg developing none vs slowly developing new conditions vs rapidly developing them); and (3) Identifying if there are groups of physical conditions that develop together (for example, different conditions caused by smoking, but there may be unexpected groupings as well). We will also explore different ways of measuring depression in the data, because we don't know whether the severity of depression affects the relationship with physical conditions.
Second, we will examine whether depression before the start of the study predicts how people develop physical conditions over the next 10 years. We will do this using a number of methods, based on the different ways of measuring patterns of physical conditions described above. We will carefully account for the effect of other individual characteristics which might be linked to both depression and patterns of physical condition such as gender, smoking, alcohol, obesity, and how rich or poor a person is.
Third, we will examine whether different patterns of physical condition predict whether or not people develop new or recurrent depression. Again, we will carefully account for the effect of other individual characteristics which might be linked to both depression and patterns of physical conditions.

The study will add significantly to our understanding of the patterns of physical conditions which people develop in middle age, and the links between physical conditions and depression. The same approach can be used in the future to examine how physical conditions are linked to other mental health problems like anxiety or schizophrenia. It will also make possible additional studies that examine if there are common genetic (inherited) causes of both depression and physical conditions, or if there are common mechanisms affecting different diseases like inflammation. Finally, better understanding of patterns of disease will help identify people who may need more help from health services to improve their quality of life and future health.

Finer, Sarah (MR/S027297/1; 36 months) Multimorbidity clusters, trajectories and genetic risk, in British south Asians

Principal Investigator Dr Sarah Finer (Queen Mary University of London)
Co-Investigator Professor David van Heel (Queen Mary University of London)
Co-Investigator Dr Hilary Martin (Wellcome Trust Sanger Institute)
Co-Investigator Ms Rohini Mathur (London Sch of Hygiene and Trop Medicine)
Co-Investigator Dr Sally Hull (Queen Mary University of London)

Summary:
Our research proposal covers an important area of health called 'multimorbidity', which describes where an individual is affected by 2 or more health conditions. Studies have shown that multimorbidity is getting more common in the United Kingdom, and the National Health Service does (NHS) not currently have services designed to tackle it well. Recent research has also shown that multimorbidity exists in 'clusters', with groups of common conditions (e.g. type 2 diabetes, high blood pressure, chronic pain, and depression) often co-exist. However, there is a lot still to learn about multimorbidity, and more research is needed to find out why it occurs, who is at risk, and how to design better health and social care to manage it. Our proposal will produce new knowledge that fills some of the important gaps in our understanding of multimorbidity.

We will study multimorbidity in people living in a large east London population of 1.05million people, one-third of whom come from a south Asian ethnic group and who live in high socioeconomic deprivation; both known to be risk factors for multimorbidity. Data collected in electronic health records (e.g. the diagnoses made or treatments given to you when you visit your GP) will be used to inform us about multimorbidity in this population. We will use state-of-the-art statistical techniques that use this data to tell us which are the most common 'clusters' of multimorbidity in east London, and whether they vary in British south Asians compared to Whites. Using historical records, we will study patterns of multimorbidity clusters during a person's life, what risk factors might be associated with them, and how severely they may impact an individual.

The next focus in our research will be to investigate the genetic causes of multimorbidity using cutting edge studies of the genome in volunteers participating in the East London Genes and Health (ELGH) study. ELGH is a large study of people of British-Bangladeshi and -Pakistani origin living in east London, with 32,000 volunteers involved already. Volunteers in ELGH have given consent for us to access their electronic health records and also study their genes using a spit sample donated to the study. We will investigate whether differences in the genetic code of individuals are linked to the risk of multimorbidity. One specific genetic code change we will be looking at is called 'autozygosity', a phenomenon affecting some people in these ethnic groups where parental relatedness is common. Autozygosity increases the chance that gene copies inherited from a person's mother and father are the same, and some studies have shown that this is linked to certain disease. We will study whether the amount of autozygosity in a person's genetic make-up could affect a person's risk of developing multimorbidity. We will also investigate an area of major interest in genetic and health studies at the moment, called polygenic risk scores (PRS). These scores identify multiple, small changes to an individual's genetic code that, when added together using a mathematical formula, strongly predict whether someone is at risk of developing conditions such as heart disease. PRSs have been studied mostly in people of White ethnic groups, and we will contribute to wider efforts to investigate their impact on disease and multimorbidity in south Asians.
Our research will use potentially sensitive data for our studies and we will take very stringent and careful approaches to using this data so that there are no data security issues, and to ensure all data has been collected using appropriate consent and information governance procedures.

We expect that the impact of our research will be wide-ranging, including supporting improvements in health and social care for multimorbidity and perhaps more efficient use of limited NHS funds. We will deliver direct benefits back to our research volunteers through educational programmes and public engagement.

Lyons, Ronan Anthony (MR/S027750/1; 30 months) Application of machine learning to discover new multimorbidity phenotypes associated with poorer outcomes

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Co-Investigator Professor Ann John (Swansea University)
Co-Investigator Dr Alan Watkins (Swansea University)
Co-Investigator Professor John Gallacher (University of Oxford)
Co-Investigator Mr Ashley Akbari (Swansea University)

Summary:
Multimorbidity is a poorly defined concept in which people suffer from more than one ongoing condition at the same time. The true extend of multimorbidity is difficult to assess as

there is no agreed definition for reporting. However, analysis of prescribing for chronic conditions and simple counts of different illnesses show that multimorbidity is becoming more common and is associated with poorer outcomes, such as how long people stay in hospital or premature mortality. It would be helpful to identify factors that predate the development of different morbidities to help understand how morbidities develop, which ones are commonly associated with others, to better understand the effectiveness of health services and individual treatments and to identify opportunities to prevent or delay the onset of these conditions.

Because we know so little about the development of these conditions we propose to use new analytical approaches from computer science, known as machine learning, to identify previously hidden or unknown relationships between different conditions. We will use detailed information from the medical records of the 3 million people of Wales held in the Secure Anonymised Information Linkage (SAIL) system. SAIL is a privacy protecting system in which records that have been stripped of all personal identifiers can be used to understand the development of diseases.
We will use the availability of new data on the results of laboratory investigations, such as changes in blood chemistry, to see if these predict the onset of conditions. If we do find useful patterns we will provide this knowledge back to NHS organisations to allow them to improve their services and intervene earlier to protect people's health.

By bringing together routinely collected and epidemiologic data at scale, this proposal exploits the potential of the fast-developing UK health informatics environment. Our team includes a mixture of health service researchers, computer scientists, clinical doctors and members of the public who have helped develop this proposal and will continue to be involved in the research and its dissemination.

Marshall, Tom (MR/S027602/1; 36 months) Bringing Innovative Research Methods to Clustering Analysis of Multimorbidity (BIRM-CAM)

Principal Investigator Professor Tom Marshall (University of Birmingham)
Co-Investigator Dr Krishnarajah Nirantharakumar (University of Birmingham)
Co-Investigator Dr Christopher (Yau University of Birmingham)
Co-Investigator Dr Steven Kiddle (University of Cambridge MRC Biostatistics Unit)
Co-Investigator Professor Sylvia Richardson (University of Cambridge MRC Biostatistics Unit)
Co-Investigator Dr Francesca Crowe (University of Birmingham)
Co-Investigator Professor Simon Griffin (University of Cambridge MRC Epidemiology Unit)
Co-Investigator Dr Paul Kirk (University of Cambridge MRC Biostatistics Unit)
Co-Investigator Dr Jessica Barrett (University of Cambridge MRC Biostatistics Unit)
Co-Investigator Dr Duncan Edwards (University of Cambridge)
Co-Investigator Dr Magdalena Teresa Skrybant (University of Birmingham)

Summary:
Multimorbidity is when people suffer from more than one long-term illness. It is increasingly common as people live longer. It is important because individual illnesses have knock-on effects on others, it is more complex managing multiple than single illnesses, and multimorbid patients are heavy users of medications and health services. To understand multimorbidity we need to know which illnesses tend to occur together and which illness combinations most affect health. To adapt health services we need to know which types of people develop multimorbidity: their age, sex, ethnicity, socio-economic status and whether they tend to live in the same households. To learn how to prevent it we need to identify

lifestyle factors (physical activity, diet, smoking, alcohol) linked to multimorbidity and the measurements (laboratory test results, weight, blood pressure) that might be early signs.

Electronic health records are a good source of information on multimorbidity because they include information on the same patient over many years. They include information on illnesses, medications, hospital admissions; measurements (laboratory tests, weight, blood pressure) and lifestyle (smoking, alcohol). Previous research has studied multimorbidity using a variety of statistical methods. It finds some illnesses, such as diabetes and heart disease tend to occur together. But different statistical methods often find different groups of illnesses. We need a single, consistent approach to this type of analysis to ensure we are researching the same groups of illnesses. Previous research generally has not made best use of all the available information. For example, patients are considered either to have or not have diabetes but research did not make use of laboratory measurements (such as blood glucose) identifying some people as likely to develop diabetes. Previous research grouped illnesses according to how commonly they occur together, without giving any special significance to combinations of illnesses linked to risk of death or hospital admission. Clearly such combinations of illness are of more importance. There are more advanced analysis methods which can address these and other shortcomings.

The first part of our research will develop methods of data analysis. We will review research on different statistical methods for grouping illnesses together. We will hold a workshop involving leading UK researchers in the field to try to agree on the best approach to this type of analysis. Informed by this we will analyse two large databases of electronic health records, each including several million patients. In each database we will identify the groups of illnesses that co-occur and check our findings in the other database. This is considered good practice in analysis. At the end of this step we will produce software to analyse and find groups of illnesses in electronic health records and make this freely available for other researchers to use.

The next part of our research will use additional information from two large surveys. Both surveys include details not always available in health records e.g. occupation, diet, lifestyle and measures of frailty. One includes 500,000 people the other has information on the same people over a period of 14 years. We will describe the consequences for patients of different combinations of illnesses: their levels of frailty because it is linked to need for social care; development of further illnesses; medications, use of health services and death. We will work with patient advisors to help guide analysis of patients journeys through health services. We will investigate possible causes of multimorbidity including people's social circumstances, the environment, lifestyle (smoking, alcohol, diet and exercise) and laboratory test results that might help indicate causes. This step will point to the areas of environment and lifestyle which should be investigated further as possible causes.