

Tackling multimorbidity at scale: Understanding disease clusters, determinants & biological pathways

2019 Strategic Priorities Fund call

This [Strategic Priorities Fund \(SPF\) initiative](#), jointly funded by the UK Research and Innovation (UKRI) and the Department of Health and Social Care (DHSC) through the National Institute for Health Research (NIHR), builds a network of Multimorbidity Research Collaboratives by bringing together multi-disciplinary teams of researchers and clinical experts with diverse knowledge and skills that will address various multiple long-term conditions. The Panel assessed Wave 2 applications on 6-7 May 2021 and made four awards.

Funded Wave 2 Proposals

Van den Bree, Marianne Bernadette (MR/W014416/1,48 months)

Physical and mental health multimorbidity across the lifespan (Lifespan multimorbidity research Collaborative (LINC)).

Principal Investigator Professor Marianne Van den Bree (Cardiff University)
Co-Investigator Professor Andrés Ingason (Capital Region Denmark Psychiatric Hosp)
Co-Investigator Professor David van Heel (Queen Mary University of London)
Co-Investigator Professor George Kirov (Cardiff University)
Co-Investigator Professor Golam Khandaker (University of Bristol)
Co-Investigator Dr Hilary Martin (Wellcome Trust Sanger Institute)
Co-Investigator Professor Ines Baroso (University of Exeter)
Co-Investigator Professor James Walters (Cardiff University)
Co-Investigator Dr Jane Lynch (Cardiff University)
Co-Investigator Professor John Macleod (University of Bristol)
Co-Investigator Dr Julie Patricia Clayton (University of Bristol)
Co-Investigator Professor Mark Mon-Williams (University of Leeds)
Co-Investigator Professor Sir Michael Owen (Cardiff University)
Co-Investigator Professor Nicholas Timpson (University of Bristol)
Co-Investigator Professor Peter Holmans (Cardiff University)
Co-Investigator Dr Rupert Payne (University of Bristol)
Co-Investigator Dr Sarah Finer (Queen Mary University of London)
Co-Investigator Professor Thomas Werge (Capital Region Denmark Psychiatric Hosp)
PPI Co-Investigator Mrs Jane Sprackman (Private Address)
PPI Co-Investigator Mr Shahid Khan (Private Address)
Researcher Dr Adam Cunningham (Cardiff University)

Summary:

Multimorbidity (MM) happens when two or more different diseases are present at the same time in an individual. This is common between physical and psychiatric diseases with almost half of people with a psychiatric disease also having a physical disease. As well as about a third of people with a physical disease also having a psychiatric disease. These patients have worse quality of life than those with a single disease, they often struggle to get the best care and are at risk of living less long. A common and serious type of MM is between internalizing diseases (depression and anxiety) and cardiovascular disease (ICV-MM). Still, very little is understood as to how ICV-MM develops and why it happens. We do know however that both internalizing disease and cardiovascular risk (e.g., obesity, cholesterol) tend to begin before adulthood.

To really understand how ICV risk develops, we need large studies of people of all ages

whose health has been followed over time. Studies of children are crucial because they can tell us about early risks for development of ICV-MM later in life. This is important for developing better plans to prevent at-risk children developing ICV-MM.

We know that genes influence risk of both internalizing and cardiovascular disease and that some people are at high genetic risk. We also know that certain conditions that start early in life (neurodevelopmental conditions) such as intellectual disability, autism and ADHD increase risk of developing ICV MM later. Children's environments can also increase this risk, for example, stressful experiences such as poverty and physical or sexual abuse. But how exactly genes, neurodevelopmental conditions and early environmental risks influence the development of ICV-MM over the lifespan is still not understood.

Certain groups are known to be at increased risk of ICV-MM, such as people of South Asian heritage and women, but we don't know why this is. Better understanding of how ICV-MM develops in different groups in society will help doctors give patients care that is matched to their specific needs. It will also help doctors, governments and schools prevent ICV-MM in at-risk children in ways that work best for them.

To really understand the complexities of ICV-MM development, a team of researchers with a wide range of expertise is needed who together understand physical and psychiatric diseases as well as how genetics, neurodevelopmental conditions and the environments people live in influence them throughout their lives.

Our Lifespan multimorbidity research Collaborative (LINC) combines wide-ranging medical and research expertise in physical and psychiatric diseases. We have brought together five very large studies in which the health of many people has been followed over time. Rich medical data is available, including from medical records. Genetic information is also available for these people. Other important information has also been collected such as on people's living environments, life events and lifestyles.

These studies follow the health over time of children, adolescents and adults. We can therefore study how internalizing and cardiovascular disease happen together in adulthood. Importantly we can then also study early risk factors in the children before they develop these conditions. Because our child and adult samples differ in ethnicity and economic situation, we can also study how the development of ICV-MM differs for different groups in society. Finally, because we have genetic data, we can study how genes influence ICV-MM development in people at risk.

Our study will help us understand how ICV-MM develops and which circumstances influence this. What we learn will be important for the prevention of ICV-MM in children who are at risk because of genetics, their sex, or ethnic or economic reasons. We will work with patients, doctors and charities to develop specific health advice in order to reduce ICV-MM in at risk groups in the future.

Nirantharakumar, Krishnarajah (MR/W014432/1, 36 months)

Multimorbidity and Pregnancy: Determinants, Clusters, Consequences and Trajectories (MuM-PreDiCT)

Principal Investigator Dr Krishnarajah Nirantharakumar (University of Birmingham)

Co-Investigator Dr Amaya Azcoaga Lorenzo (University of St Andrews)

Co-Investigator Professor Catherine Nelson-Piercy (Guy's & St Thomas' NHS Foundation Trust)

Co-Investigator Professor Christopher Yau (The University of Manchester)

Co-Investigator Professor Colin McCowan (University of St Andrews)

Co-Investigator Professor Dermot O'Reilly (Queen's University of Belfast)

Co-Investigator Ms Gillian Santorelli (Bradford Teaching Hosp NHS Found Trust)

Co-Investigator Professor Helen Dolk (University of Ulster)
Co-Investigator Dr Holly F Hope (The University of Manchester)
Co-Investigator Professor Kathryn Abel (The University of Manchester)
Co-Investigator Dr Kelly-Ann Eastwood (Univ Hosp Bristol & Weston NHS Fdn Trust)
Co-Investigator Professor Louise Locock (University of Aberdeen)
Co-Investigator Dr Mairead Black (University of Aberdeen)
Co-Investigator Dr Maria Loane (University of Ulster)
Co-Investigator Mrs Ngawai Moss (University of Birmingham)
Co-Investigator Professor Peter Brocklehurst (University of Birmingham)
Co-Investigator Mrs Rachel Plachcinski (University of Birmingham)
Co-Investigator Dr Rebecca (Beck) Taylor (University of Birmingham)
Co-Investigator Professor Richard Riley (Keele University)
Co-Investigator Professor Shakila Thangaratinam (University of Birmingham)
Co-Investigator Professor Sinead Brophy (Swansea University)
Co-Investigator Ms Zoe Vowles (Guy's & St Thomas' NHS Foundation Trust)
Researcher Dr Siang Ing Lee (University of Birmingham)
Researcher Dr Utkarsh Agrawal (University of St Andrews)

Summary:

What is the problem?

One in five pregnant women have two or more active long-term health conditions. These can be both physical conditions (like diabetes or raised blood pressure), and mental health conditions (such as depression or anxiety). Often women also have to take several medications to manage their different health needs. Having two or more health conditions is also becoming increasingly common in pregnant women as women are increasingly older when they start having a family and as obesity and mental health conditions are on the rise in general.

We don't really understand what the consequences are of multiple health conditions or medications for mothers and babies. This can make pregnancy, healthcare and managing medications more complicated. Without deeper understanding of the problem, women with several long-term health conditions may not have the best and safest experience of care before, during and after pregnancy because services have not been designed with their health needs in mind.

What will we do?

Our research is divided into five work packages. The first work package will examine how health conditions accumulate over time and identify what makes a woman more at risk of developing two or more long-term health conditions before pregnancy.

The second work package will explore women's experiences of care during pregnancy, birth and after birth. We will work together with families and health professionals to establish how care could be improved.

The third work package will look further at how having two or more long-term health conditions may affect pregnant women and their children. We will do this in three ways: we will identify outcomes that women, health professionals and researchers feel should be reported in research; we will examine how often women experience pregnancy complications; and we will explore how frequently women and their children develop additional long-term ill health.

In the fourth work package we will describe how medications are prescribed. We will investigate how taking combinations of medication may affect pregnant women and their babies.

In our fifth work package, we will build a prediction model to help identify how likely a previously healthy pregnant woman will develop multiple long-term conditions after pregnancy. We can do this by using health information collected during or just after pregnancy. This is because we know that some complications in pregnancy may be a warning sign of future illnesses.

What will our research achieve?

We will help women and their healthcare professionals make informed decisions about their care and medication use by providing accessible information on risk. For example, the risks associated with pregnancy; the risks associated with combinations of medications during pregnancy; and the future risk of developing long-term health conditions after a pregnancy complication.

Our work will also identify important time points to intervene and ways to prevent pregnancy complications or developing future long-term health conditions. This will reduce the health burden for women, partners, carers and reduce avoidable healthcare and economic cost in the long run for society. Working together with women and healthcare professionals, we will produce recommendations on how to plan and design services that meet the needs of women and their families before, during and after pregnancy.

Frayling, Timothy (MR/W014548/1, 48 months)

Genetic Evaluation of Multimorbidity towards Individualisation of Interventions (GEMINI)

Principal Investigator Professor Timothy Frayling (University of Exeter)
Co-Investigator Professor Andrew Hattersley (University of Exeter)
Co-Investigator Professor Chris Fox (University of East Anglia)
Co-Investigator Professor Clive Ballard (University of Exeter)
Co-Investigator Dr Concepción Violán Fors (IDIAPJGol)
Co-Investigator Professor Daniel Prieto-Alhambra (University of Oxford)
Co-Investigator Professor David Melzer (University of Exeter)
Co-Investigator Professor Frank Dudbridge (University of Leicester)
Co-Investigator Professor Jack Bowden (University of Exeter)
Co-Investigator Dr Joao Delgado (University of Exeter)
Co-Investigator Professor Jose Valderas (University of Exeter)
Co-Investigator Professor Lee Shepstone (University of East Anglia)
Co-Investigator Mr Leonard Farmer (Private Address)
Co-Investigator Professor Louise Allan (University of Exeter)
Co-Investigator Dr Luke Pilling (University of Exeter)
Co-Investigator Ms Mary Mancini (Private Address)
Co-Investigator Professor Sarah Lamb (University of Exeter)
Co-Investigator Dr William Strain (University of Exeter)
Co-Investigator Dr Sara Khalid (University of Oxford)
PPI Co-Investigator Ms Kate Boddy (University of Exeter)

Summary:

More than 50% of people over the age of 65 are living with more than one long term condition (multimorbidity). Despite this, people with multimorbidity are often excluded from clinical trials and there has been limited research into identifying the causes of multimorbidity. For example, we often do not know if two common long-term conditions occur together by chance as we get older, whether one leads to the other, or if they share a risk factor. This problem is partly because health care professionals and researchers tend to focus on one condition at a time. For example, there has been a lot of research into the causes and consequences of osteoarthritis but not why people with osteoarthritis have a higher frequency of asthma, even when accounting for sex, age and obesity.

The aim of our research is to uncover new links between long term conditions that could lead to improved interventions including drug treatments or other more focused treatments. These new links could include a better understanding of which cells in the body are most critical to the presence of two conditions in the same patient.

To achieve our aims, we have formed a partnership called the GEMINI (Genetic Evaluation of Multimorbidity towards INdividualisation of Interventions) collaborative. This team includes two people with multimorbidity, health care professionals including those in primary care and experts in statistics and genetics. In GEMINI we will study the causes of multimorbidity with a new approach. We will use existing databases of DNA sequence information linked to diseases from 10,000s of people. Using this genetic approach our initial research has identified many new and interesting links between conditions that were not previously well known. For example, between Rheumatoid arthritis and stroke (but not Rheumatoid arthritis and heart disease), gastro-reflux disease and depression, and between asthma and osteoarthritis. We will complement the genetic approach with data from millions of patients in primary care. These patients are representative of the UK as a whole and will allow us to study large numbers of people with combinations of conditions even if these combinations are quite rare.

Our research plans are divided into three parts. We will involve patients and carers in all stages to ensure we are using their data appropriately and to help us remain focused on the important conditions and outcomes of multimorbidity. First, we will use three sources of data from patients in primary care (GPs) to define the conditions we will study. We will start from all conditions that are long term and present in more than 1% of the people over 65 years. We will then use millions of DNA sequence changes - the genetic information we inherit from our parents - to identify which conditions share broad biological mechanisms. Second, we will use a similar number of genetic variants to identify the specific mechanisms involved. These techniques are based on the principle that inherited DNA sequence changes are fixed for life and so provide us with a way of assessing the causal direction of associated risk factors and diseases. For example, we will use genetics to test whether one disease leads to a second disease, or whether a shared risk factor leads to both. These risk factors will include well known risks such as obesity and more detailed measures of biology, such as how genes are switched on and off in different cells and tissues. Third, we will study in more depth patients with the conditions highlighted in the first two steps using primary care databases. We will hold workshops with patients and carers to understand in depth the most important outcomes of these conditions, for example is reduced lifespan more or less important than risk of frequent hospitalisation? We will then study patients with new combinations of conditions to see if they suffer from worse outcomes.

Jenkins, Gisli (MR/W014491/1, 48 months)

DEfining MechanlsmS Shared across mulTI-organ Fibrosis to prevent the development of long-term multi-morbidity (DEMISTIFI-Multi Morbidity)

Principal Investigator Professor Gisli Jenkins (Imperial College London)

Co-Investigator Dr Aloysious Aravinthan (University of Nottingham)
Co-Investigator Dr Christopher Scotton (University of Exeter)
Co-Investigator Professor Dorothee Auer (University of Nottingham)
Co-Investigator Dr Fasihul Khan (University of Nottingham)
Co-Investigator Dr Gordon Moran (University of Nottingham)
Co-Investigator Professor Guruprasad Aithal (University of Nottingham)
Co-Investigator Dr Hilary J. Longhurst (University of Auckland)
Co-Investigator Dr Iain Stewart (University of Nottingham)
Co-Investigator Professor Jennifer Quint (Imperial College London)
Co-Investigator Professor Louise Wain Taylor (University of Leicester)
Co-Investigator Dr Maria Kaiser (NHS Blood and Transplant NHSBT)
Co-Investigator Dr Neil Guha (University of Nottingham)
Co-Investigator Dr Nicholas Selby (University of Nottingham)
Co-Investigator Professor Nick Oliver (Imperial College London)
Co-Investigator Professor Penny Gowland (University of Nottingham)
Co-Investigator Dr Philip Quinlan (University of Nottingham)
Co-Investigator Professor Richard Hubbard (University of Nottingham)
Co-Investigator Professor Rutger Ploeg (University of Oxford)
Co-Investigator Dr Stamatios Sotiropoulos (University of Nottingham)
Co-Investigator Professor Susan Francis (University of Nottingham)
Co-Investigator Dr Tom Giles (University of Nottingham)
Co-Investigator Dr Xin Chen (University of Nottingham)
Researcher Co-Investigator Dr Richard Allen (University of Leicester)

Summary:

Scarring (“fibrosis”) of the internal organs occurs in many common diseases, including diabetes (scarring in the pancreas), high blood pressure (blood vessels), chronic kidney disease (kidney), cirrhosis (liver) and pulmonary fibrosis (lungs). Scarring of the internal organs can stop these organs working properly and causes about one third of all deaths world-wide. People can be affected by scarring in more than one organ.

Factors believed to contribute to scarring include smoking, alcohol, obesity and infections such as COVID-19. These external factors are known as “environmental” factors. There are also a number of genetic factors (known as genetic mutations or ‘variants’) that can run in families with people affected more likely to have scarring in different organs, at a younger age.

Genetic factors that cause scarring are often seen in short telomere syndrome, a form of accelerated aging, which leads to scarring throughout the body. In severe cases, this can start in childhood, with scarring affecting different parts of the body. It often starts with the bone marrow, causing severe anaemia, infections and bleeding, and later in the liver leading to cirrhosis or the lung leading to death.

Other people could have milder genetic problems that they may not know about. These might be quite common and cause scarring only in old age or if triggered by external (environmental) factors such as smoking, obesity or drinking too much alcohol. It is likely that both genetic and environmental/external risk factors cause scarring of different organs and may happen at different times.

If patterns of scarring can be identified when young, development of more extensive scarring, in multiple organs in later life, could be prevented. This could be done by identifying groups of people at risk of scarring and working out which specific treatments or medications will work best for each group. Having identified these groups of people, targeted therapies would be used to encourage people to change their lifestyle or to take the medicines that are most likely to be effective for each particular person.

The aim of our research is to identify patterns of scarring in different organs, which we have termed Fibrotic Multi-Morbidity (FMM). We will use new technology such as Magnetic Resonance Imaging (MRI) scans to measure the extent of scarring in different organs, in order to generate a “Fibrotic Multi-Morbidity” Score (i.e., to measure the severity of the scarring). This will enable us to ascertain the full extent of scarring, provide an early warning and detect the spread of scarring from one organ to another. We will map the genetic and environmental/external triggers of scarring in different organs and investigate the underlying biological causes of the scarring so that we can find the treatments to prevent or cure it. We suspect that many medications that are already in use could help prevent or treat scarring but before we can recommend them, we need to prove that these medicines work.

In this way, we hope to provide the right treatment to the right person to stop scarring from destroying the organ in which it is found and to prevent it spreading to other organs. These treatments could involve lifestyle changes, such as weight loss and exercise, and/or medications. We hope that by treating and preventing scarring- ‘fibrosis’, we may be able to help a lot of people stay healthy and live longer, healthier lives.