

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), aims to bring together multi-disciplinary collaborations of experts with a range of scientific, methodological, and specialist knowledge and skills to build a network of *Multimorbidity Research Collaboratives* across the UK. The first Panel for this two-stage competition process met on 30 March 2020. Members were pleased to receive a number of strong outline proposals and applications for short-term development (Consolidator) grants. Several applications were invited to submit full Research Collaborative Award proposals towards Wave 1 deadline. Eleven proposals were selected to receive Consolidator grants to provide research groups with additional resource and time to develop their research ideas and prepare full Research Collaborative applications for Wave 2.

Funded Consolidator proposals

Frayling, Timothy (MR/V005359/1; 6 months)

Genetic Evaluation of Multimorbidity towards Individualisation of Interventions - GEMINI

Principal Investigator Professor Timothy Frayling (University of Exeter)
Co-Investigator Professor Clive Ballard (University of Exeter)
Co-Investigator Professor Andrew Hattersley (University of Exeter)
Co-Investigator Professor David Melzer (University of Exeter)
Co-Investigator Professor Jose Valderas (University of Exeter)
Co-Investigator Dr Luke Pilling (University of Exeter)
Co-Investigator Professor Jack Bowden (University of Exeter)
Co-Investigator Dr William Strain (University of Exeter)
Co-Investigator Professor Louise Allan (University of Exeter)
Co-Investigator Professor Chris Fox (University of East Anglia Norwich)
Co-Investigator Professor Sarah Lamb (University of Exeter)

Summary:

Researching the co-existence of multiple chronic conditions in a single individual (multimorbidity) is challenging using conventional study designs. Confounding, bias and reverse causality are often complex and severe and may partly explain apparently paradoxical associations. People with type 2 diabetes and additional conditions, for example, tend to have lower HbA1c than those with diabetes alone, and we and others have shown that there is marked weight loss and declining blood pressure for a decade before diagnosis of dementia. Our vision is to address these challenges by combining genetic and conventional approaches and using large-scale data resources from the UK, Spain, US and Canada, including 3 multi-million patient GP data sources. We will identify clusters of disease, use novel causal inference methodology to identify shared biological determinants, and study in-depth a set of disease clusters. By understanding biological determinants of multimorbidity clustering and identifying which are associated with markedly altered clinical outcomes, we will help clarify which multi-morbidity combinations are of most clinical importance to understand.

We will define multimorbidity as the presence of 2 or more chronic conditions (1) but focus on those each occurring in >1% of men or women aged 40 plus and that are genetically

correlated with other conditions. To address inequalities of multimorbidity we will study the excess burden in women and ethnic minorities. A multi-modal, data driven approach will be critical. Clustering that is consistent across genetic and observational data will be more reflective of shared determinants. Genetic approaches provide a test of lifelong exposure to risk factors and provide strong causal inferences. The widespread availability of genome wide information also means that we can study shared risk factors that are not measured in many studies (e.g. insulin resistance) and calculate disease clustering between, as well as within, databases (2).

To achieve our vision we have formed a new multi-disciplinary research team (supported by outstanding external advisors), including researchers with extensive experience in multimorbidity in three GP databases; physical and mental decline in the elderly; specialists in key diseases (diabetes, vascular, dementia, musculo-skeletal) and with expertise in genetics and causal inference.

Goodwin, Laura (MR/V005170/1; 6 months)

An investigation of the multimorbidity of mental disorders and alcohol attributable conditions

Principal Investigator Professor Laura Goodwin (University of Liverpool)

Co-Investigator Dr Laura Bonnett (University of Liverpool)

Co-Investigator Professor Iain Buchan (University of Liverpool)

Co-Investigator Dr Kate Fleming (University of Liverpool)

Co-Investigator Professor Sir Ian Gilmore (University of Liverpool)

Co-Investigator Professor Colin Drummond (King's College London)

Summary:

Alcohol is the main cause of death in young people. In England in 2017 there were almost 6000 deaths across all age groups caused by alcohol, with around a fifth of the population drinking more alcohol than is recommended by government guidelines. We know that individuals who drink too much are also more likely to have a mental health problem, but we know less about the future health of people who have both of these problems and specifically whether physical diseases caused by alcohol are more common in this group. We do know that individuals with both alcohol and mental health problems may not always be able to access the treatments they need and that GPs currently do not routinely ask people with depression and anxiety about their drinking. This work will help us to understand what diseases are more common in this group of people and how best to treat them.

Multimorbidity refers to people having at least two health conditions at the same time and it is important we understand how these multiple conditions interact to affect someone's overall health. This work will investigate the most common patterns of multimorbidity, including mental health problems, depending on whether someone does or does not drink excessively. We know that people may use alcohol to help cope with mental health problems and conversely that drinking too much can make mental health worse. We will therefore look at whether the ordering of the alcohol and mental health problem, in addition to other information regarding employment, housing, smoking, and physical health affects whether people die earlier than they should.

Our research will use national surveys, cohort studies (which follow people throughout their lives) and electronic healthcare records (which include data from when you visit your GP or are admitted to hospital). We will use statistical methods to understand more about multimorbidity in relation to alcohol and mental health and to identify different groups of individuals who have experienced similar types of health conditions. We will also conduct workshops with healthcare staff to ask them whether our findings reflect what they see in their practice. We will then determine whether individuals who have experienced many disadvantages in their lives and those with other behavioural risk factors (e.g. smoking and

poor diet) are more likely to experience multimorbidity and whether they develop these conditions at a younger age.

We will follow individuals who have been admitted to hospital who already have a disease caused by alcohol to look at whether they are more likely to experience particular patterns of multimorbidity, and which of these people use the most health services and treatments and so may require support at an earlier stage. We will then use what we have discovered about the patterns and pathways of multimorbidity to think about what effect that changes in the way we treat people who drink excessively or have mental health problems might have on outcomes for those patients and the impact this might have on the NHS.

Our work may show that we need to do more to ensure that alcohol and mental health services are better joined up than they currently are. Further impacts of our work will be in developing web-tools that can be used by GPs to understand which patients are likely to have the poorest outcomes and in selecting the best treatment options for their patients. We can also help inform the development of government policies and in selecting which treatments and services to provide, to avoid individuals with mental health problems experiencing more harms as a result of their drinking.

Gregg, Edward (MR/V005057/1; 6 months)

Pathways and Levers for prevention of Multi-morbidity from Young and Middle Adulthood

Principal Investigator Professor Edward Gregg (Imperial College London)

Co-Investigator Professor Majid Ezzati (Imperial College London)

Co-Investigator Professor Timothy Hallett (Imperial College London)

Co-Investigator Dr Francesco Zaccardi (University of Leicester)

Co-Investigator Professor Kamlesh Khunti (University of Leicester)

Co-Investigator Dr Marc Chadeau (Imperial College London)

Co-Investigator Dr Clare Gillies (University of Leicester)

Co-Investigator Professor Alex Bottle (Imperial College London)

Co-Investigator Dr Jonathan Pearson-Stuttard (Imperial College London)

Co-Investigator Dr Jonathan Valabhji (Imperial College Healthcare NHS Trust)

Co-Investigator Professor Azeem Majeed (Imperial College London)

Summary:

Multimorbidity is the presence of two or even several more major health condition at the same time within a single person. It is a growing problem in the United Kingdom in part of the combination of increasing lifespans with unhealthy lifestyles. Although multimorbidity is most common in older age, poor diet, physical inactivity, and obesity in young adulthood and middle-age are likely important causes of the tendency to multimorbidity. We suspect that 3 conditions in particular - diabetes, hypertension, and depression - cause a large portion of multimorbidity because of the way that they work together to affect so many systems of the body. If this is the case, then programmes for focused lifestyle interventions could make a big difference in preventing multimorbidity. Unfortunately, it is difficult to know how these conditions in young and middle-age affect multimorbidity and what works to prevent it because no studies track population across many stages of life, while measuring the impact of interventions. This research programme will tackle these questions with 3 parts. First, it will use long-term data from the UK and London populations to uncover the most common combinations of diseases occurring and whether there are particular steps and pathways in their formation. After finding those combinations and estimating how rapidly they develop at different times in life, we will construct a new computer-based model, called a "lifecourse simulation model" that can identify the optimal times in life, combinations of behaviors, risk factors, and diseases that cause the greatest illness over life. The computer model will also examine the effect of different ways of preventing the accumulation of multimorbidity, such as using focused support to change lifestyle in people at risk for hypertension, diabetes, and

depression. The third part of the research programme will use these data and the computer model to measure the effect of two National Health Service initiatives that support people at risk of diabetes or with diabetes to change lifestyle diabetes. Since lifestyle behaviors are also crucial to hypertension, depression, and other conditions, these "natural experiments" may have a big effect on multimorbidity as well. This work will require a team with expertise in diverse areas - including medical care, epidemiology, behaviour change, mathematics, and computer modelling. This study will answer important questions about what types of conditions are causing the most multimorbidity and what are the best ways to act to prevent them. The computer model and research that results will give doctors, health planners, and the public new way to improve health in communities for the years to come. The work will be first-of-its-kind in the way that it assesses chronic conditions as they form in combination from young adulthood to older adulthood. It will also be new in the way it uses computer models and natural experiments in combination to find out what works best to reduce multimorbidity.

Jakobs, Rowena (MR/V004964/1; 6 months)

Multimorbidity Among People with Serious mental illness (MAPS): Mapping disease clusters, risk factors, trajectories, service barriers and outcomes

Principal Investigator Professor Rowena Jacobs (University of York)

Co-Investigator Dr Claire de Oliveira (University of York)

Co-Investigator Dr Jo Taylor (University of York)

Co-Investigator Dr Najma Siddiqi (University of York)

Co-Investigator Professor Nicholas Pleace (University of York)

Co-Investigator Professor Nigel Rice (University of York)

Co-Investigator Dr Peter Coventry (University of York)

Co-Investigator Professor Piran White (University of York)

Co-Investigator Professor Rachel Churchill (University of York)

Co-Investigator Professor Simon Gilbody (University of York)

Co-Investigator Dr Tim Doran (University of York)

Co-Investigator Dr Emily Peckham (University of York)

Co-Investigator Dr Stephanie Prady (University of York)

Co-Investigator Professor Robert Stewart (King's College London)

Co-Investigator Dr Brendon Stubbs (King's College London)

Co-Investigator Dr Mark Ashworth (King's College London)

Co-Investigator Professor David Osborn (University College London)

Summary:

The impact of having many long-term conditions on health, use of health care and costs, and life expectancy is well understood in the general population, where this burden of "multimorbidity" is recognised as leading to poorer health outcomes. However, far less is known about how having multiple long-term conditions, both mental and physical, affects people with serious mental illness (SMI). This is despite there being a recognised 'mortality gap', where people with SMI tend to die at younger ages compared to the general population. This means it is vital to understand how having different combinations, or 'clusters' of illnesses for example cardiac diseases or respiratory diseases, might affect people with SMI, to understand who may be most at risk due to this 'disease burden' and how they can be supported. In this programme of work, we will bring together large data sets that capture many aspects of health and illness for people with SMI, to identify clusters of long-term conditions among people with SMI, identify the risk factors that contribute to these groupings, and understand their impacts on both health and illness, as well as on broader problems such as homelessness. The goal of this work is to help develop improved ways of delivering care and decrease the mortality gap. By working with service users, health professionals and policy makers, we will identify how our understanding of these 'clusters' can be translated into actions that improve service, lead to better care, and help reduce the risk and burden of illness.

To do this, we will 1) summarise and examine all existing evidence on this topic to help us come up with potential disease groupings, prevalence and outcomes. We will then 2) use health care records from people with SMI to understand how these patients use health care, the disease groupings they belong to, and whether certain risk factors affect some people more than others, as well as follow people over time to understand who is more at risk of being hospitalised or dying. We will also 3) hold interviews with people with SMI to understand in more depth their use of the health care system, their experiences with the NHS, how they acquired their long-term conditions over time, the experience of living with multiple health conditions, how their living situation affects their health and what help they would have needed. Finally, we will 4) combine all the findings to agree what these disease groupings mean for patients and services and find ways to improve how the NHS delivers care for patients in these groupings. This will include improving care pathways that both help existing service users within the 'clusters' and help to plan ways to reduce the number of people who end up with multiple illnesses, through enhanced prevention. Throughout the programme of work, service users will play an integral role in developing the research, helping to interpret and disseminate findings and co-producing solutions for improved care. This research will have an impact on many levels. It will provide NHS health care professionals with information to help prevent the development of multiple long-term conditions among people with SMI, by better understanding who is most at risk. It will help the NHS understand how to improve the care of people with SMI who have many long-term conditions, by recognising how different 'clusters' have different needs. The core goal of this work is to improve the lives of people with SMI, by improving understanding of the burden of multimorbidity for this group and identifying ways to decrease that burden, support people living with complex combinations of illness, and help people live longer and healthier lives.

Jenkins, Gisli (MR/V005324/1; 6 months)

DEMISTIFI Multi Morbidity: DEfining MechanIsms Shared across mulTI-organ Fibrotic disease to prevent the development of long term multi-morbidity

Principal Investigator Professor Gisli Jenkins (University of Nottingham)
Co-Investigator Professor Dorothee Auer (University of Nottingham)
Co-Investigator Professor Penny Gowland (University of Nottingham)
Co-Investigator Professor Susan Francis (University of Nottingham)
Co-Investigator Professor Guruprasad Aithal (University of Nottingham)
Co-Investigator Dr Neil Guha (University of Nottingham)
Co-Investigator Dr Nicholas Selby (University of Nottingham)
Co-Investigator Dr Gordon Moran (University of Nottingham)
Co-Investigator Dr Stamatios Sotiropoulos (University of Nottingham)
Co-Investigator Dr Philip Quinlan (University of Nottingham)

Summary:

Scarring (fibrosis) affects every organ in the body and has been estimated to cause approximately one third of all deaths world-wide. Scarring classically affects the lungs and liver in response to environmental injury such as cigarette smoke, industrial dusts (eg asbestos) and alcohol. However, scarring also affects the heart and kidneys leading to heart and renal failure, the bone marrow leading to blood disease, the pancreas leading to diabetes, the blood vessels leading to strokes and heart attacks and the brain in multiple sclerosis and motor neurone disease. Multi-morbid fibrotic disease defines groups (clusters) of conditions that occur together and are characterised by scarring in various organs. Some are known such as short telomere syndromes leading to liver, lung and bone marrow scarring and connective tissue disease related scarring in muscle and joint disease. However, many scarring clusters are not well recognised (eg lung fibrosis and diabetes) and it is possible that there are completely unknown clusters that may reflect distinct genetic or environmental risk factors for scarring.

Scarring is often progressive, notably in the lungs, liver and kidneys where it frequently leads to death or the need for organ transplantation. In some cases if the environmental trigger can be removed the scarring will stop, or even improve, but in other situations the scarring will progress regardless of whether the environmental cause is removed. This may reflect advanced disease which is 'beyond repair' or specific genetic interactions with the environmental triggers.

The aim of this proposal is to understand how genetic and environmental risk factors interact to promote the development of progressive fibrosis across a number of different organs. These studies will address a focused question which will define which groups of scarring diseases are linked by genes that cause telomeres to shorten and cause premature ageing and are known to be responsible for the known cluster of lung liver and bone marrow scarring. We will investigate the interaction between these genes and known environmental triggers including cigarette, alcohol and dusts as well as other triggers that may not yet have been identified. We will determine whether the biological pathways which are responsible for lung, liver or bone marrow fibrosis may also lead to scarring in other organs and whether they link expanded clusters of scarring involving the lung, liver, pancreas, kidney, bone marrow, brain, heart, gastrointestinal tract, or whether there are other genes that promote different clusters of scarring disease.

We will then investigate whether medicines that are known to protect against certain fibrotic diseases within these clusters (for example metformin for diabetes and simvastatin for heart disease and stroke) might have beneficial effects across the full spectrum of fibrotic disease by targeting disease pathways that are shared across the different organs.

These studies will require a collaboration between academics and clinicians with expertise in studying populations, genetics, cells, specific diseases, radiology, and 'big data' analysis to take a team science approach to solving a very important and challenging problem. The DEMISTIFI consortium will provide the expertise to deliver the evidence needed to understand multi organ scarring to improve treatment approaches that will help prevent this devastating scarring process throughout the body.

Kolehmainen, Niina (MR/V004883/1; 6 months)

Understanding early life determinants and mechanisms to preventing life course multimorbidity

Principal Investigator Dr Niina Kolehmainen (Newcastle University)

Co-Investigator Professor Judith Rankin (Newcastle University)

Co-Investigator Professor Mark Pearce (Newcastle University)

Co-Investigator Professor Dawn Craig (Newcastle University)

Co-Investigator Professor Michael Taggart (Newcastle University)

Co-Investigator Dr Kianoush Nazarpour (Newcastle University)

Co-Investigator Dr Timothy Cheetham (Newcastle University)

Co-Investigator Dr Ian Robson (Northumbria University)

Co-Investigator Dr Helen Phillips (Newcastle University)

Co-Investigator Dr Louise Coats (Newcastle University)

Researcher-Co-Investigator Dr Bronia Arnott (Newcastle University)

Summary:

The early part of life—from tiny embryo, to baby in the womb, to birth, through infancy and early childhood—is a time when many events happen that can have important, lasting effects on our lives. We want to find ways to make these early parts of our lives as good as they can be, so that we enter adulthood healthy and able to cope well with things that life may throw at us.

Our research will investigate the early life events that affect our hearts, blood vessels, mental health, and metabolism (how our bodies convert food to energy and to building blocks such as proteins, and eliminate waste). We want to find ways to prevent early life events that lead us

to have several health problems in later life. We call this "multi-morbidity", meaning two or more long-term conditions or disabilities.

The idea of looking at health from early life into adulthood has been around for a while, but it is still fairly rare to actually link information from early life events with multimorbidity. We are a new group of people with complementary expertise in early life and adult health. For example, we have lab scientists studying hearts and blood vessels; psychologists investigating how movement and physical activity affects mothers and children; children's doctors providing front line care while also researching the best ways to help their patients; a data engineer; and public health researchers working on studies that follow people's health for decades. We know that to answer the big questions about early life events and multimorbidity we need to collaborate in new ways across our areas of expertise. We are now proposing a 6-month project to bring together what we know and our different techniques ('methods'), and to refine our bigger 4-year plan. Our bigger plan has four related parts:

A. We will find and make sense of different types of existing evidence about early life drivers of multimorbidity. We will work with stakeholders (parents, carers, children, policy makers, professionals) to draw up a map that will help people to think more clearly about early life events that cause or prevent multimorbidity, see the gaps in our knowledge, and decide which questions to answer next.

B. To answer these questions, we will electronically link up existing UK-based data (e.g. heel prick samples, red book questions) and use new methods, such as artificial intelligence, to explore it. We will also collect new data to fill gaps.

C. As the data helps us better understand early life events and how they affect later health, we will co-design new 'interventions' to alter these events. For example, we may develop medicines, health monitors, or ways for people to do things differently. They may be for individuals or populations.

D. We will involve patients and the public throughout to ensure focus on what matters and that the interventions work well in real life.

In the initial 6 months, we will use three particular areas to pilot our ideas and techniques.

These are areas where: early life events are already known to affect later life multimorbidity but how this happens is not clear; there is great potential for better interventions; and we have substantial expertise. The areas are:

- mother's heart and blood vessel health, and influence on baby
- stressful events for the mother/child, and effects on hormones and later child health
- mother/child movement and physical activity, and effects on mother/child heart and blood health and stress

This research will change the way health and care is provided, moving from diagnosing and treating individual conditions as they appear to intervene on early life psychological, social and medical issues. This will prevent multiple problems later in life for large numbers of people. This will improve child and parent health, and reduce the burden on families and services. This research will also help inform what information is important for governments to collect in early life to monitor public health.

Langan, Sinead (MR/V005146/1; 6 months)

Understanding clusters and mechanisms of complex multimorbidity in people with common allergic conditions

Principal Investigator Professor Sinead Langan (London Sch of Hygiene and Trop Medicine)

Co-Investigator Professor Liam Smeeth (London Sch of Hygiene and Trop Medicine)

Co-Investigator Professor Ronan Lyons (Swansea University)

Co-Investigator Dr Jennifer Quint (Imperial College London)

Co-Investigator Professor Aziz Sheikh (University of Edinburgh)

Co-Investigator Mr David Prieto-Merino (London Sch of Hygiene and Trop Medicine)

Co-Investigator Dr David McAllister (University of Glasgow)

Co-Investigator Dr Kathryn Mansfield (London Sch of Hygiene and Trop Medicine)
Co-Investigator Dr Spiros Denaxas (University College London)

Summary:

Multimorbidity is a term used to mean having two or more longterm physical or mental illnesses. Multimorbidity is important because it affects what happens to people throughout their life and how their doctors can treat them.

Conditions which can be associated with allergy, such as asthma and eczema, are very common particularly in children and young adults (at least 1 in 5 children) and are known to have major effects on quality of life and costs to the NHS. Previous work has shown people with allergic diseases are at risk of lots of different mental and physical health problems (multimorbidity), possibly due to their allergic disease. We don't yet understand how these diseases group together ("cluster") and why they occur.

Our work will help us understand how and why allergic diseases are associated with other mental and physical illnesses (multimorbidity) in order to work out how to treat people with allergic diseases better.

In this preparatory phase (also called a consolidator grant), we will first explore how allergic diseases occur in groups together with multiple other medical and psychiatric conditions and how these "clusters" develop over time. Some of these "clusters" will include conditions we already know can be associated with allergic diseases, but we also expect that we might find new associated diseases. We will do this analysis using data collected as part of usual healthcare, which has been stripped of identifiers (e.g., names). We have data collected on large numbers of people (for example 500,000 adults with eczema) over long periods of time with information about health issues, medications, doctors' visits and whether people smoke or drink alcohol.

This work will be complex, so we will need to run workshops involving different kinds of experts, such as data scientists, statisticians, doctors who treat patients with allergic diseases, and patient representatives. In this preparation phase, we will also spend time finalising the most important questions for the main body of work (focusing on working out why people with allergic diseases have other mental and physical conditions) and how we can answer those questions in the best possible way.

In the main body of work (also known as a "collaborative" grant), we will use advanced statistical techniques to understand why common allergic disorders are associated with other physical and mental health problems. We will look at factors in people's environment and lifestyle, or medications that doctors use to treat allergic conditions to see if these might play a role in these "clusters". This collaborative programme will help us move away from doctors focusing on only one problem at a time, to an approach that looks at all of the problems that people have that tend to cluster together. This "joined up" thinking will help us treat people better and might help us avoid some of those health problems in future.

Nirantharakumar, Krishnarajah (MR/V005243/1; 6 months)

Multimorbid Pregnancy: Determinants, Clusters, Consequences and Trajectories (MuM-PreDiCCT)

Principal Investigator Dr. Krishnarajah Nirantharakumar (University of Birmingham)

Co-Investigator Professor Shakila Thangaratinam (University of Birmingham)

Co-Investigator Professor Peter Brocklehurst (University of Birmingham)

Co-Investigator Professor Sinead Brophy (Swansea University)

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

Co-Investigator Dr Mairead Black (University of Aberdeen)

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

Co-Investigator Professor Corri Black (University of Aberdeen)

Co-Investigator Dr Christopher Yau (The University of Manchester)
Co-Investigator Professor Richard Riley (Keele University)
Co-Investigator Dr Rebecca (Beck) Taylor (University of Birmingham)
Co-Investigator Professor Louise Locock (University of Aberdeen)
Co-Investigator Dr Amaya Azcoaga Lorenzo (University of St Andrews)
Co-Investigator Dr Kelly-Ann Eastwood Queen's (University of Belfast)

Summary:

The Problem

Multimorbidity is when people suffer from more than one long-term illness. It can be difficult for people with several longterm illnesses to manage their conditions and sometimes they don't receive the best quality care. Patients with multimorbidity may have to coordinate appointments with different specialists and their medications need to be managed carefully. During pregnancy, these challenges may increase for women with multimorbidity. We know that multimorbidity in pregnancy is becoming more common, but we don't understand why this is and what the consequences are for mothers and babies. Without this deeper understanding of the problem, women with several longterm illnesses won't have the best experience of care before, during and after pregnancy because services are not tailored to their specific needs.

Our aims and approach

Our collaboration will bring together experts in data analysis, diseases and public health from 7 academic institutions in the UK. We will work in close partnership with women with experience of multimorbidity in pregnancy.

Firstly, our data specialists will look at electronic health records to find out how many women have multimorbidity in pregnancy and what illnesses they have. We will try and identify if factors such as age, weight, cultural or social background, level of education and number of previous pregnancies influences whether a woman has multimorbidity in pregnancy. We will also find out which illnesses group together(cluster) during pregnancy, which clusters are most common and whether some clusters affect some women more than others.

In the second part of the study, we will compare what happens to mothers with and without multimorbidity during pregnancy. We will find out whether women with multimorbidity are more likely to develop illnesses during the pregnancy (e.g. gestational diabetes), after the pregnancy (e.g. postnatal depression) and also in the longer-term (e.g. heart-disease). We will also look at the health and wellbeing of children of women with multimorbidity in pregnancy.

The third part of our research will focus on medications in pregnancy. We will find out what medicines women with multimorbidity take during pregnancy and how the medications affect the health of the mother and the baby during pregnancy. This knowledge will help doctors prescribe safely during pregnancy. We know that complications in pregnancy are a warning sign of future illnesses in women. As part of this project, we will be able to find out more about how different pregnancy complications affect the longer-term health of women. We can use this knowledge to put preventative measures in place where possible.

Finally, we will meet with women and healthcare professionals to discuss the services available for women with multimorbidity in pregnancy. We will find out how appropriate and accessible these services are and how services can be improved. Going forward, this will help us to jointly design health services with women and their partners.

Involving the public

We will work in partnership with women with experience of multimorbidity in pregnancy. Their insights will help ensure that our project is grounded in the experiences of women and that all stages of the project drive towards improving care for women.

Sharing our findings

Our team has large networks and we will share our findings with healthcare professionals, through professional organisations (e.g. Royal Colleges of Obstetricians and Gynaecologists); through NHS networks (e.g. Local Maternity Services) and through charities and women's networks (e.g. Maternity Voice Partnerships).

Our Impact

This study will give healthcare professionals and women a much better understanding of multimorbidity in pregnancy. Through this enhanced understanding, we will be able to plan and design services that meet the needs of women and their families before, during and after the birth of their babies.

Riboli, Elio (MR/V00509X/1; 6 months)

Investigating shared molecular pathways underlying cardiovascular diseases, diabetes and cancer

Principal Investigator Professor Elio Riboli (Imperial College London)
Co-Investigator Dr Abbas Dehghan Imperial College London
Co-Investigator Professor Julian Griffin Imperial College London
Co-Investigator Dr Konstantinos Tsilidis Imperial College London
Co-Investigator Dr Ioanna Tzoulaki Imperial College London
Co-Investigator Professor Nicholas Wareham University of Cambridge
Co-Investigator Dr Marc Gunter Imperial College London
Co-Investigator Dr Pietro Ferrari Internat Agency for Res on Cancer (IARC)

Summary:

The incidence rates of cardiovascular diseases, diabetes and certain cancers tend to be correlated across countries, that means that countries with higher incidence rates of one disease tend to have higher rates of the other diseases as well. In addition, population studies have found that this correlation also applies at the individual level, that is cardiovascular diseases, type 2 diabetes and some cancers tend to occur in the same patients more frequently than it would be expected by chance. The correlation of diseases is referred to as comorbidities and it is an increasing problem facing the National Health Service as the population lives longer, along with increases in obesity and reduced physical activity.

Previous studies and recent research conducted by us has found that the co-occurrence of these diseases in the same population and even in the same patients, may be due to the fact that these diseases share several lifestyle and metabolic risk factors, such as smoking, excessive alcohol drinking, some aspects of diet, nutrition, overweight and obesity and lack of physical activity. In addition, it has been postulated that co-morbidity may also be due to the possibility that these diseases share biological and pathological mechanisms. In this project, we plan to take advantage of shared risk factor to discover if these diseases also share pathological mechanisms that lead to their clinical development. These would be powerful targets for treating both diseases.

Technological advances have recently allowed us to measure thousands of small molecules in thousands of human samples at a reasonable cost and in a short period of time. This approach is termed "metabolomics" and will be applied to the stored blood samples provided by a large number of volunteers belonging to studies called "population cohorts". In a population cohort study design, the health of the participants is monitored across time to see who will develop the diseases of interest and how this might be related to various measures already performed in this population at the entry into the study, such as the genes they possess, their diet, physical activity, smoking, drinking and many other measures. We will use the "metabolomics" technology to investigate a large number of small molecules comprising a wide range of normal and abnormal biological pathways in human blood plasma providing us with a unique insight into the common pathways of these very different diseases.

We will study the patterns of biological markers associated with the genetic susceptibility to each of the diseases under study and apply advanced statistical methods to find any high-level structural similarities between them. We will use powerful bioinformatic methods to

identify pathological pathways that are characterized by the presence of metabolites and biomarkers that are common between diseases. Such pathways may guide us to uncover some of the biological bases of the comorbidity between different diseases.

This project may also help us understand why increased population prevalence of obesity, type 2 diabetes and some cardiovascular conditions is linked to increased risk of developing certain cancers.

We expect that the results of these investigations, by deepening our knowledge of the causes and mechanisms leading to CVD, Diabetes and cancer, may eventually help to identify and implement new prevention and treatment strategies that could address more than one of the disorders at once.

Steves, Claire Joanne (MR/V005030/1; 6 months)

GErosience and Multi-Morbidity: identifying targets for intervention (GEMM)

Principal Investigator Dr Claire Joanne Steves (King's College London)

Co-Investigator Dr Jordana Bell (King's College London)

Co-Investigator Professor Linda Partridge (University College London)

Co-Investigator Professor Janet Lord (University of Birmingham)

Co-Investigator Professor Warwick Dunn (University of Birmingham)

Co-Investigator Professor Georgios Gkoutos (University of Birmingham)

Co-Investigator Dr Thomas Jackson (University of Birmingham)

Co-Investigator Dr Davide Liborio Vetrano (Karolinska Institute)

Researcher-Co-Investigator Dr Ruth Bowyer (King's College London)

Summary:

Currently medicine tends to treat distinct diseases individually. We are increasingly aware that people do not suffer from one disease in isolation. Current treatment means that many people are taking multiple medications, which increases side effects and can lead to harmful drug interactions.

We now know that groups of diseases tend to cluster together, such that an individual with one disease is more likely to have others in the cluster. We think this is because there are underlying mechanisms which are root causes of many diseases at the same time.

Age is the major risk factor for getting many diseases. Biologists have studied ageing in model organisms and humans for many years. This body of work is called Geroscience. Geroscience has now identified key mechanisms which occur in ageing and contribute to changes in physiology and health. We want to investigate how these processes relate to the development of disease clusters. By understanding the mechanisms behind the development of these disease clusters we aim to develop strategies to combat the root causes, thereby preventing or treating multiple diseases at once.

Geroscience has identified three key changes which occur with ageing and contribute to health problems: cell senescence (where old cells do not die but remain in tissues secreting molecules which upset healthy cells); changes in nutrient sensing (where the cell system inappropriately assesses the balance between growth and health), and altered autophagy (problems recycling proteins in the cells such that they accumulate and affect cell function). All three of these mechanisms have possible therapies which could be used to stop the underlying process. Importantly, some of these therapies are drugs like metformin or lifestyle changes such as diet alterations which are already used in humans and known to be relatively safe.

Our consortium contains internationally recognised expertise across five universities with experts from discovery science, ageing biology, computational biology, clinical trial design, and medicine who will work together to develop a new strategy for treatment. Our vision is to bring a paradigm shift in the clinical management of age-related multimorbidity, via modulation

of the upstream drivers of the major disease clusters, replacing the current approach of treating diseases separately.

The overarching aim of our proposal is to build a multidisciplinary collaborative to identify whether these ageing mechanisms underpin the development of distinct multimorbidity clusters. The consortium is led by doctors and will involve clinical trial experts to keep us focused on developing new treatment strategies quickly.

Our plan is to use data from large cohorts which already have many biological and health measures characterised, to investigate the biology behind multimorbidity clusters. We will start with the TwinsUK cohort which has had molecular biology assayed in detail, from genes, to expression of genes, proteins, metabolites and cell subsets. In the first six-month consolidation phase, we will construct the clusters in this dataset and look at the relationships between biology and the clusters. We will also extend the team to involve additional scientific experts.

In the consortium phase we will extend this to other cohorts and perform experiments on cells derived from participants and then in clinical studies to demonstrate cause and effect, and investigate how we can modify and treat multiple diseases safely (Figure 1). Combining this understanding with our collaborative's expertise in novel clinical trial designs, we will develop protocols for testing treatments targeting the identified mechanisms in people suffering from multiple diseases.

Van den Bree, Marianne (MR/V004905/1; 6 months)
Investigating five large population-based cohort studies to understand for the precursors of multimorbidity risk.

Principal Investigator Professor Marianne Van den Bree (Cardiff University)
Co-Investigator Professor James Walters (Cardiff University)
Co-Investigator Professor George Kirov (Cardiff University)
Co-Investigator Professor Peter Holmans (Cardiff University)
Co-Investigator Professor Sir Michael Owen (Cardiff University)
Co-Investigator Professor David van Heel (Queen Mary University of London)
Co-Investigator Dr Sarah Finer Queen Mary (University of London)
Co-Investigator Professor Mark Mon-Williams (University of Leeds)
Co-Investigator Professor Nicholas Timpson (University of Bristol)
Co-Investigator Professor John Macleod (University of Bristol)
Co-Investigator Dr Kate Northstone (University of Bristol)

Summary:

Multimorbidity refers to different diseases being present at the same time in a person. For example, we know that almost half of people with a mental health disorder also have a long-term physical health problem and a third of people with a physical health problem have a psychiatric disorder. Life is often more difficult for people with both physical and psychiatric disorders. They can struggle to get the best possible care and are at risk of living less long.

We don't know enough about why multimorbidity happens. To fully understand why changes in physical and mental health happen over time we need large studies of people whose health has been followed over time. Studies of children are very important because they can tell us about early risks for development of multimorbidity later in life. This is important for creating the best plans to prevent at-risk children developing multimorbidity.

To really understand how multimorbidity develops, studies need to have information about the many important behaviours and events that can influence health. For example, we need to know about someone's living environment (e.g., low income), lifestyle (e.g., lack of exercise) or life events (e.g., stressful experiences).

We know that genes can increase risk of physical and psychiatric disorder. We also know that some groups in society are at greater risk of multimorbidity, such as people of Asian and Minority Ethnic groups and people who live in poverty. We don't currently understand why this is and in this study we aim to get answers by studying the development of physical and psychiatric disorders in children at genetic risk. To understand differences in multimorbidity development in people from different ethnic and socio-economic backgrounds, we need studies in which all these groups are well represented.

If we understand better how multimorbidity develops in different groups in society (people at genetic risk, those from different ethnic and socio-economic backgrounds) this will help doctors give patients care that is matched to their specific needs. It will also help doctors, schools and others prevent multimorbidity in at-risk children in ways that suit their backgrounds best.

Finally, to conduct these studies, a team of researchers with a range of expertise is needed, who together understand the range of physical and psychiatric disorders, as well as how genes, the living environment, life style and life events influence these disorders over time.

We are a team with wide-ranging medical and research expertise in physical and psychiatric disorders. We have brought together five very large studies in which the health of close to 700,000 people has been followed over time. Rich medical data is available, including from medical records. Other important information has also been collected such as on the living environment, lifestyle and life events of these people. Genetic information is also available for all people in these studies.

These studies follow the health over time of both adults and children. We can therefore study how physical and psychiatric disorders happen together in adulthood. Importantly we can then also study the early stages of the development of multimorbidity in children. Because our child and adult samples differ in ethnic and socio-economic background, we can also study if the development of multimorbidity differs for different groups in society. Finally, because we have genetic data we can study how genes influence multimorbidity development in people at risk.

Our study will help us understand how multimorbidity develops and which behaviours and events influence this. What we learn will be important for the prevention of multimorbidity in children who are at risk because of genetic, ethnic or economic reasons. We will create health messages for specific groups in society and this can reduce multimorbidity in at risk groups in the future.