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Multidisciplinary ecosystem to study lifecourse determinants and prevention of early-onset burdensome multimorbidity

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Registration date 16/12/2022	**Overall study status** Ongoing	[_] Statistical analysis plan [_] Results
Last Edited 09/09/2024	**Condition category** Other	[_] Individual participant data [X] Record updated in last year

Plain English summary of protocol

Background and study aims

A growing number of people are living with several long-term health conditions like diabetes, heart disease, depression or dementia. We call this multimorbidity. Many things throughout a person's life influence the chances of developing health conditions. This includes their biology (e.g.age, ethnicity), things that happen to them (e.g.infections, accidents), behaviours (e.g.smoking, diet) and broader experiences (e.g. the environment people grew up in, their education, work, and income). People from more disadvantaged backgrounds and/or certain ethnicities are more likely to develop multimorbidity and to develop it earlier in life. The impact (or 'burden') of multimorbidity, and the order that people develop
conditions, also vary. We don't know what all the possible opportunities are to prevent burdensome multimorbidity.

We aim to understand more about what things influence the way people develop early multimorbidity over their lifetime and the burden this has on them. By 'early' we mean before age 65. This will identify key time points in a person's life where prevention efforts should be targeted or strengthened to reduce the risk of that person developing burdensome multimorbidity.

Who can participate?

Patients who have multiple long-term condition multimorbidity, their carers and multimorbidity experts will be recruited into the initial part of the study

What does the study involve?

To understand what 'burdensome' means for people with multimorbidity and how it could be prevented or reduced, we will ask patients, carers and multimorbidity experts their views and carefully summarise previous research on this issue. Ideally, we would study very large numbers of people from birth to death. However, not enough of this type of data is available. Therefore, we will use Artificial Intelligence (AI) methods (using computers to learn patterns from data) to help us connect information and knowledge from two very big General Practitioner datasets with information from three 'birth cohorts' – research studies of people all born in the same year (e.g. 1970) and followed throughout their lives. We will also use AI methods to help us

understand the order in which people develop conditions and how they group together to become ‘burdensome’. We will have experts and members of the public in a ‘People, Policy and Impact’ group identify opportunities to prevent burdensome multimorbidity.

Patient and public involvement
A diverse ten-person Patient and Public Advisory Board will oversee the project. Members of the Board will actively engage with each element of the project and be asked to discuss results as they emerge. This will ensure that the experiences and priorities of people living with multimorbidity will always be considered. Their input will ensure all decisions consider the experiences and priorities of people with multimorbidity.

Dissemination
Our ‘People, Policy and Impact’ group will share our learning and influence policy and practice on preventing burdensome multimorbidity by co-producing public health advice. We will share findings through academic channels, a website and social media.

What are the possible benefits and risks of participating?
The benefits and risks provided are for taking part in the Delphi study. The possible benefits of participation are to contribute to the understanding of how multiple long-term condition multimorbidity develops across the lifecourse of the study. The possible risks are considered minimal and are those of using a computer to answer survey questions.

Where is the study run from?
University of Southampton (UK)

When is the study starting and how long is it expected to run for?
April 2022 to November 2025

Who is funding the study?
National Institute for Health and Care Research (NIHR) (UK)

Who is the main contact?
Dr Simon Fraser, s.fraser@soton.ac.uk

Study website
https://www.southampton.ac.uk/publicpolicy/support-for-policymakers/policy-projects/Current%20projects/meld-b.page

Contact information

Type(s)
Principal Investigator

Contact name
Dr Simon Fraser

ORCID ID
http://orcid.org/0000-0002-4172-4406

Contact details

School of Primary Care
Population Sciences and Medical Education
Faculty of Medicine
Southampton General Hospital
Tremona Road
Southampton
United Kingdom
SO16 6YD
+44 (0)2381206530
s.fraser@soton.ac.uk

Type(s)
Public

Contact name
Dr Simon Fraser

Contact details
School of Primary Care
Population Sciences and Medical Education
Faculty of Medicine
Southampton General Hospital
Tremona Road
Southampton
United Kingdom
SO16 6YD
+44 (0)2381206530
s.fraser@soton.ac.uk

Type(s)
Principal Investigator

Contact name
Prof Nisreen Alwan

Contact details
School of Primary Care
Population Sciences and Medical Education
Southampton General Hospital
Tremona Road
Shirley
Southampton
United Kingdom
SO16 6YD
+44 (0)2381206530
n.a.alwan@soton.ac.uk

Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number
312785

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
NIHR 203988, IRAS 312785

Study information

Scientific Title
Multidisciplinary ecosystem to study lifecourse determinants and prevention of early-onset burdensome multimorbidity

Acronym
MELD-B

Study objectives
This Research Collaboration is being undertaken to answer the following research questions:

What does ‘burdensome’ and ‘complex’ mean for people living with multimorbidity, carers and health professionals?

Can we develop a suite of burdensomeness/complexity indicators for routine healthcare data as burdensomeness/complexity domains for use in clustering and clinical practice?

Can specified long-term conditions (LTCs) be harmonised across birth cohort datasets and routine data?

Can individuals be matched between birth cohorts and routine datasets to identify early-life and later determinants of burdensome multiple long-term condition multimorbidity (MLTC-M) clusters using semi-supervised learning methods?

Can lifecourse trajectories of LTC and burden accrual towards burdensome clusters be modelled?

Can we identify and characterise clusters of early-life risk and characterise population groups at risk of future burdensome MLTC-M in early- life?

Can critical time points and key lifecourse targets for MLTC-M prevention be identified?

Can we model counterfactual prevention scenarios acting on combined risk factors at specified timepoints?

How do AI and causal inference modelling methods compare for potential early-life (0-18) ‘preventable moments’?

Ethics approval required
Old ethics approval format

Ethics approval(s)
1. Approved 14/07/2022, the University of Southampton Faculty of Medicine Ethics Committee (Faculty of Medicine Ethics Committee, Southampton General Hospital, Mailpoint 801, South Academic Block, Tremona Road, Southampton, SO16 6YD, UK; +44 (0)23 8059 2819; rgoinfo@soton.ac.uk), ref: ERGO 66810
2. Confirmed 24/05/2022, East Midlands - Derby Research Ethics Committee (Equinox House, City Link, Research Ethics Office, Nottingham, NG2 4LA, UK; +44 (0)207 1048 154; derby.rec@hra.nhs.uk); an application was submitted through IRAS to REC/HRA who confirmed that approval was not required because participants in the WP1 Delphi are not being recruited through the NHS and the datasets being used all have their own approval/governance processes, and does not require additional ethics approval under the UK's law.

Study design
A 'Research Collaboration' funded by NIHR involving five work packages (WPs) that include:
1. Undertaking a qualitative evidence synthesis and a consensus study (Delphi) to develop a deeper understanding of what 'burdensomeness' and 'complexity' means to people living with early-onset (by age 65) multiple long-term condition multimorbidity (MLTC-M), carers and healthcare professionals
2. Developing safe data environments and readiness for artificial intelligence (AI) analyses across large, representative routine healthcare datasets (Secure Anonymised Information Linkage (SAIL) and Clinical Practice Research Datalink (CPRD)) and birth cohorts (National Child Development Study (NCDS), Aberdeen Children of the 1950s (ACONF), 1970 British Cohort Study (BCS70)) then harmonising specified long-term conditions (LTCs) across birth cohorts and routine data.
3. In those safe data environments, using the WP1 burdensomeness/complexity indicators and applying AI methods to identify novel early-onset, burdensome MLTC-M clusters and match individuals in birth cohorts into routine data MLTC-M clusters, identify determinants of burdensome clusters using matched datasets, and model trajectories of LTCs and burden accrual.
4. Characterising clusters of early-life (pre-birth to 18 years) risk factors for early-onset, burdensome MLTC-M and sentinel conditions (the first LTC to occur in the lifecourse), defining population groups in early life at risk of future MLTC-M, identifying critical time points and targets for prevention, and modelling counterfactual prevention scenarios of interventions acting on combined risk factors at key timepoints
5. Engaging key stakeholders to prioritise timepoints and targets to prevent/delay specified sentinel conditions and early-onset, burdensome MLTC-M. Partnering with our PPI Advisory Board, and maintaining stakeholder engagement, we will co-produce public health implementation recommendations

Primary study design
Observational

Secondary study design
Cohort study

Study setting(s)
Other

Study type(s)
Prevention

Participant information sheet

Not available in web format, please use contact details to request a participant information sheet

Health condition(s) or problem(s) studied
Multiple long-term condition multimorbidity

Interventions
This is an observational study.
The aim is to safely deliver an Artificial Intelligence (AI)-enhanced epidemiological analytic system in which optimal lifecourse time points and targets for prevention of early-onset, burdensome multimorbidity are identified through multidisciplinary synthesis and analysis of birth cohorts and electronic health records, and to disseminate the results to key stakeholders.

The objectives are:
1. To develop a deeper understanding of what 'burdensomeness' and 'complexity' mean to people living with early-onset multiple long-term condition multimorbidity (MLTC-M), their carers and healthcare professionals
1.1. To produce a suite of burdensomeness/complexity indicators for routine healthcare data as burdensomeness/complexity domains for use in clustering and clinical practice. These will be achieved through qualitative evidence synthesis and a modified Delphi consensus study

2. To provide a safe data environment and readiness for AI analyses across routine healthcare data (Secure Anonymised Information Linkage (SAIL) and Clinical Practice Research Datalink (CPRD)) and birth cohort data (National Child Development Study (NCDS), Aberdeen Children of the 1950s (ACONF), 1970 British Cohort Study (BCS70))
2.1. To harmonise specified long-term conditions (LTCs) across birth cohorts and routine data. These will be achieved by following the procedures of each of the Trusted Research Environments in which these datasets are housed and adopting and complying fully with principles defined by the Department of Health and Social Care (DHSC) AI Code of Conduct "A guide to good practice for digital and data-driven health technologies" and the "Five Safes" framework. Identification of specified LTCs will be undertaken using code lists that are in the public domain.

3. To use AI methods to cluster individuals within the space of burdensomeness indicators and analyse determinants of clusters and the sequence and trajectories of acquisition of burdensome features and LTCs for individuals in those clusters.
This will be achieved by using the burdensomeness/complexity indicators and applying AI methods to identify novel burdensome early-onset MLTC-M clusters in routine data. We will develop and apply semi-supervised learning to match individuals in birth cohorts into the routine data MLTC-M clusters and identify early-life and later determinants of the burdensome clusters using the matched datasets. We will describe and model trajectories of LTC and burden accrual towards burdensome clusters.

4. To identify the early-life (preconception/interconception, pregnancy, birth, childhood and adolescent) characteristics of population groups at risk of future early-onset multimorbidity and use this characterisation to model targeted public health prevention scenarios of early-onset, burdensome/complex MLTC-M.
We will achieve this by identifying and characterising clusters of early life exposures (risk factors for sentinel conditions (the first to occur in the lifecourse) and early-onset, burdensome MLTC-M and sentinel conditions) and characterise population groups at risk of future MLTC-M in early-life (prebirth-18 years). We will identify critical time points and key lifecourse targets for MLTC-

M prevention and model counterfactual prevention scenarios acting on combined risk factors at the specified timepoints (preconception-18 years).
We will also investigate the influence of sentinel conditions and sequence of accrual of wider determinants, conditions and burdensome factors in the development of early-onset, burdensome MLTC-M clusters and compare AI and causal inference modelling for potential early-life (0-18) 'preventable moments' trajectory and exploring alternative trajectories based on models of policies/strategies/interventions and outcomes.

5. To connect the emerging findings from all work packages with relevant stakeholders to identify appropriate prevention opportunities across the life course and establish effective means of dissemination and policy and practice outputs.
We will achieve this by identifying key stakeholders and engaging them in exploring:
5.1. Timepoints and targets to prevent/delay specified sentinel conditions and early-onset, burdensome MLTC-M
5.2. Opportunities to narrow health inequalities
5.3. Optimal dissemination strategies and pathways to impact

Intervention Type
Mixed

Primary outcome measure
As a research collaboration addressing several research questions as indicated elsewhere in this record there is no single primary outcome measure. The outcomes cannot be specified more precisely in advance because they will be developed as part of the programme of work and cannot be simplified down to one for which method of measurement and timepoint can be provided.
1. Population - people who develop burdensome/complex (to be defined in our work package 1 qualitative evidence synthesis and Delphi study) multiple long-term condition multimorbidity before the age of 65
2. Exposures - multiple exposures occurring at multiple time points across the lifecourse, with a particular interest in exposures occurring pre-birth to age 18 years old (to be defined in our work package 4 using data from three longitudinal birth cohort studies)
3. Comparator - those not exposed
Key outcomes:
1. Burdensome/complex multimorbidity clusters
2. Specific time points in the lifecourse and specific exposures where modelled alternatives demonstrate a reduction in the risk of the development of burdensome multimorbidity (as defined above)
The burdensome multimorbidity outcome will be identified in retrospective cohorts using routine healthcare datasets (SAIL and CPRD) that include approximately 25 years of data between the mid-1990s and 2022.

Secondary outcome measures
As a research collaboration addressing several research questions as indicated elsewhere in this record there is no specified list of secondary outcome measures. We will also not be able to specify the outcomes fully until the first part of the research is undertaken (qualitative evidence synthesis and Delphi study)
However - other outcomes will include:
1. A list of burdensomeness/complexity indicators for routine healthcare data as burdensomeness/complexity domains for use in clustering and clinical practice.
2. Trajectories of acquisition of burdensome features and long-term conditions for individuals in

those clusters
3. Clusters of early life exposures (risk factors for sentinel conditions (the first to occur in the lifecourse) and early-onset, burdensome multimorbidity and sentinel conditions
4. Time points in the lifecourse and critical targets for MLTC-M prevention
5. Alternative lifecourse trajectory models based on a variety of policies and strategies

Overall study start date
01/04/2022

Completion date
30/11/2025

Eligibility

Key inclusion criteria
For the modified Delphi study:
Participants will include healthcare professionals/MLTC-M experts and adults who live with MLTC-M (or represent people who do, such as carers)

For the rest of the study, we will use data from five sources:
1. The Secure Anonymised Information Linkage (SAIL)
2. Clinical Practice Research Datalink (CPRD) GOLD and Aurum datasets
3. Birth cohort data from the National Child Development Study (NCDS)
4. Birth cohort data from the Aberdeen Children of the 1950s (ACONF)
5. Birth cohort data from the 1970 British Cohort Study (BCS70)

Participant type(s)
Mixed

Age group
All

Sex
Both

Target number of participants
30 for the Delphi study. The SAIL and CPRD datasets contain millions of anonymised records and the birth cohorts included several thousand participants each

Key exclusion criteria
For the Delphi study:
1. People who do not have MLTCM or represent people who do
2. Health professionals or researchers without expertise in the field of MLTCM

Date of first enrolment
03/01/2023

Date of final enrolment
30/09/2024

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
University of Southampton
University Road
Southampton
United Kingdom
SO17 1BJ

Sponsor information

Organisation
University of Southampton

Sponsor details
Research and Innovation Services
University Road
Southampton
England
United Kingdom
SO17 1BJ
+44(0)23 8059 5000
rgoinfo@soton.ac.uk

Sponsor type
University/education

Website
https://www.southampton.ac.uk/

ROR
https://ror.org/01ryk1543

Funder(s)

Funder type
Government

Funder Name
National Institute for Health and Care Research

Alternative Name(s)
National Institute for Health Research, NIHR Research, NIHRresearch, NIHR - National Institute for Health Research, NIHR (The National Institute for Health and Care Research), NIHR

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Publication and dissemination plan
We will undertake broad engagement activities with our Patient and Public Advisory Board and other key stakeholders to identify the potential for impact from outputs.
Dissemination routes will include:
Conferences:
1. Primary care: RCGP/SAPC
2. Public Health Science
3. Society for Social Medicine & Population Health
4. European Society for Mathematical and Theoretical Biology
5. Society for Mathematical Biology
6. Dynamics Days Europe

Academic Papers:
1. Methodology: e.g. development of burdensome/complexity indicators, use of birth cohorts in MLTC-M research, how AI can enhance DAG approaches, early life determinant clustering, matching birth cohort/routine data.
2. Epidemiology: e.g. the influence of wider determinants and sentinel conditions in lifecourse LTC accrual
3. A dynamical model of lifecourse trajectories to MLTC-M

Intention to publish date
30/11/2026

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are not expected to be made available because these data are bound by the governance requirements of the individual data sources which are strictly regulated, please see: CPRD - https://cprd.com/data-access, SAIL - https://saildatabank.com/governance/, and BCS70 - https://bcs70.info/home/privacy/privacy-notice/.

IPD sharing plan summary

Not expected to be made available

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article		25/09/2023	09/09/2024	Yes	No