Biomarkers in Multimorbidity: Scoping Review and White Paper Protocol

Issue Date: Jan 2020, Version 1
Protocol Amendment Number: 1

Protocol Author(s): Spencer EA, Heneghan C [1]

Working group: Rafael Perera, [1] Mei Sum Chan [2] Gary Ford, [3] Richard Hobbs, [1] Annette Pluddemann [1]

[1] Nuffield Department of Primary Care Health Sciences, University of Oxford
[2] Nuffield Department of Population Health, University of Oxford
[3] Oxford Academic Health Science Network and Radcliffe Department of Medicine, University of Oxford

Contact: carl.heneghan@phc.ox.ac.uk

Background

Multimorbidity is the co-occurrence of two or more diseases in the same individual where each must be a non-communicable disease (NCD), or a mental health disorder, or a long duration infectious disease. [1] NCDs account for 71% of all deaths globally, and give rise to 15 million premature deaths. [2]

Multimorbidity is more common with ageing and affects two-thirds of the elderly. Around one in four adults in the UK have two or more long-term conditions (LTCs), often known as 'multimorbidity' and this rises to two-thirds of people aged 65 years or over. [3]
Evidence shows multimorbidity decreases quality of life and increases morbidity and mortality.[4][5]

Early recognition, screening and treatment of multimorbidity is vital to reduce the morbidity and minimise the risks to individuals, while reducing costs to the healthcare system. In those with long-term conditions, UK health and social care expenditure is estimated to take up around £7 in every £10 of total. [6]

One way to identify individuals at an earlier stage is through the use of biological and physiological markers that predict risk of developing multimorbidity. [7] The accumulation of chronic disease at older ages has been associated with various markers that may act as an early warning sign to better target interventions, aid identification of preventive strategies and reduce the associated burden of multimorbidity through better treatment.

We, therefore, plan to undertake a scoping review of the literature to identify the available evidence on biological and physiological markers and incident multimorbidity in adults. Specifically we will:

- Identify the biological and physiological markers associated with incident multimorbidity
- Map the literature on biomarkers in multimorbidity, identify key concepts and gaps in the research literature
- Assess the current levels of evidence, the quality of evidence and provide a synthesis of the evidence on biomarkers in multimorbidity
- Describe what the literature shows on the relationship of biomarkers and multimorbidity.

Methods

This protocol (and any necessary amendments) will be published at and is accessible at https://www.cebm.net/category/cebm-protocols/

Eligibility criteria

Eligible studies will include adult individuals with two or more long term conditions compared to those without multimorbidity (i.e. those with no long term conditions or only one long term condition). For a study to be eligible, study participants must be aged 18 years and older; the measurement of the biomarker (the exposure measure) must predate the outcome of multimorbidity and measured in adulthood.

We will include cohort studies (prospective and retrospective); cross-sectional studies; RCTs where we can use data from the control arm; and case control studies. We will also include systematic reviews which contain studies meeting our eligibility criteria not otherwise identified in our searches; and where applicable, guidelines or reports from the grey literature. We will also include protocols or records of relevant ongoing trials and prospective studies.
We will exclude cross-sectional studies; case series and case reports. We will only include studies in English.

Biomarkers are defined by the NIH Working Group definition as: ‘a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.’ [8] We will include studies that use biomarker with ‘measurable and quantifiable biological parameters (e.g., specific enzyme concentration, specific hormone concentration, specific gene phenotype distribution in a population, presence of biological substances) which serve as indices for health- and physiology-related assessments, such as disease risk, psychiatric disorders.’ (see PubMed MESH database for full list) We will also include studies using physiological markers defined as measurable and quantifiable physiological parameters (e.g., oral temperature, blood pressure, heart rate, body weight etc.).

We will exclude biomarkers related to health outcomes (for example prior disease, medication, and treatment), health behaviours, socioeconomic factors, environmental factors, sex and chronological age.

We will exclude studies that do not specify the marker or do not have an objective measure of the marker, or that relate the marker to only one specific disease. We will group biomarkers by physical capability, physiological, endocrine, cognitive and immune (and sensory as a potential group) as per the review of the panel of biomarkers of healthy ageing commissioned by MRC. [9]

Information sources

We will search the following electronic databases: MEDLINE, Register of Controlled Trials (Cochrane CENTRAL), CINAHL, PsycINFO, EMBASE, Scopus, Web of Science, TRIP database. The search will be conducted from the beginning of the databases up until the search date (November 2019). Search terms used are detailed in Appendix 1. We will also screen the reference lists of included studies for possible additional studies to assess for eligibility.

Selection of sources of evidence

Two reviewers (ES, CH) will independently screen the initial retrieved studies for eligibility. The first screen will select based on study title; the next screen will use title and abstract; the next screen will use full texts. Any disagreements will be resolved by consensus, if necessary by discussion with a third reviewer. Inclusion and exclusion of retrieved studies will be shown in a flow diagram.

Data extraction and mapping

We will assess the quality of the evidence using the OCEBM levels of evidence appraisal tool for aetiological studies.

We will provide a table of characteristics by biomarker grouping. We will extract data on the type of study, country and setting, publication year, sample size, baseline characteristics of the population: age, sex, diseases at baseline and multimorbidity outcomes at follow up, with ascertainment and measurement methods. Where necessary, we will use the ICD-11 classification to group rarely reported conditions and to group closely associated conditions. [10] We will report the relationship of exposure to the outcome as reported in the original paper. These data will be extracted by one reviewer (ES) and checked by a second reviewer (CH).

We will report any assumptions and simplifications made during the data extraction process.

Synthesis and dissemination of results

We will summarise data narratively by biomarker or group where applicable, and report the outcomes as stated in the paper. Where feasible we will summarise the range of outcomes and provide weighted averages.

We will assess the relationship between the biomarkers and multimorbidity and report the effects by age (and other reported variates that were accounted for in the analysis)

We will provide a table of research implications (from each paper we will extract the information on research priorities); and where relevant, we will report implications for practice.

We will report the scoping review according to the PRISMA statement on reporting scoping reviews (see https://drive.google.com/drive/folders/1ek6bAZ26ht5PnCuqTpkJQ7JNhRQTWQCD)

Funding
UK Spine Knowledge Exchange FUND

Competing Interests
CH receives funding support from the NIHR (National Institute for Health Research) School for Primary Care Research Evidence Synthesis Working group (NIHR SPCR ESWG project 390) and the NIHR Oxford Biomedical Research Centre. He is an NIHR senior investigator, editor in chief of BMJ Evidence-Based Medicine, and an NHS urgent care GP and has received payments for his media work (full declaration at www.phc.ox.ac.uk/team/carl-heneghan).

References

1 https://apps.who.int/iris/bitstream/handle/10665/252275/9789241511650-eng.pdf;jsessionid=B72C21D47211990535AA47913161BEDE?sequence=1 (accessed 15 Nov 2019).

2 Non communicable diseases. https://www.who.int/news-room/fact-sheets/detail/noncommunicable-diseases (accessed 15 Nov 2019).

3 England NHS. NHS England » Multimorbidity – the biggest clinical challenge facing the NHS? https://www.england.nhs.uk/blog/dawn-moody-david-bramley/ (accessed 5 Nov 2019).

4 Nunes BP, Flores TR, Mielke GI, Thumé E, Facchini LA. Multimorbidity and mortality in older adults: A systematic review and meta-analysis. *Arch Gerontol Geriatr* 2016;**67**:130–8.

5 van den Akker M. MTSSZMSS. Multimorbidity and quality of life: Systematic literature review and meta-analysis. *Ageing Research Reviews* 2019;**53**:100903.

6 Long-term conditions and multi-morbidity. The King's Fund. https://www.kingsfund.org.uk/projects/time-think-differently/trends-disease-and-disability-long-term-conditions-multi-morbidity (accessed 15 Nov 2019).

7 Ferreira GD, Simões JA, Senaratna C, *et al.* Physiological markers and

multimorbidity. Journal of Comorbidity. 2018;**8**:2235042X1880698. doi:10.1177/2235042x18806986

8 Biomarkers and surrogate endpoints: Preferred definitions and conceptual framework. Clinical Pharmacology & Therapeutics. 2001;**69**:89–95. doi:10.1067/mcp.2001.113989

9 Lara J, Cooper R, Nissan J, *et al.* A proposed panel of biomarkers of healthy ageing. *BMC Med* 2015;**13**:222.

10 WHO | International Classification of Diseases, 11th Revision (ICD-11). Published Online First: 11 October 2019.http://www.who.int/classifications/icd/en/ (accessed 28 Nov 2019).

11 Heneghan C, Badenoch D. *Evidence-Based Medicine Toolkit*. John Wiley & Sons 2013.

12 Ward AM, Takahashi O, Stevens R, *et al.* Home measurement of blood pressure and cardiovascular disease: systematic review and meta-analysis of prospective studies. *J Hypertens* 2012;**30**:449.