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Systematic literature review of methodologies and data sources of existing economic models across the full spectrum of Alzheimer's disease and dementia from apparently healthy through disease progression to end of life care: a systematic review protocol.

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ABSTRACT

Introduction Dementia is one of the greatest health challenges the world will face in the coming decades, as it is one of the principal causes of disability and dependency among older people. Economic modelling is used widely across many health conditions to inform decisions on health and social care policy and practice. The aim of this literature review is to systematically identify, review and critically evaluate existing health economics models in dementia. We included the full spectrum of dementia, including Alzheimer's disease (AD), from preclinical stages through to severe dementia and end of life. This review forms part of the Real world Outcomes across the Alzheimer's Disease spectrum for better care: multimodal data Access Platform (ROADMAP) project.

Methods and analysis Electronic searches were conducted in Medical Literature Analysis and Retrieval System Online, Excerpta Medica dataBASE, Economic Literature Database, NHS Economic Evaluation Database, Cochrane Central Register of Controlled Trials, Cost-Effectiveness Analysis Registry, Research Papers in Economics, Database of Abstracts of Reviews of Effectiveness, Science Citation Index, Turning Research Into Practice and Open Grey for studies published between January 2000 and the end of June 2017. Two reviewers will independently assess each study against predefined eligibility criteria. A third reviewer will resolve any disagreement. Data will be extracted using a predefined data extraction form following best practice. Study quality will be assessed using the Phillips checklist for decision analytic modelling. A narrative synthesis will be used.

Ethics and dissemination The results will be made available in a scientific peer-reviewed journal paper, will be presented at relevant conferences and will also be made available through the ROADMAP project.

Strengths and limitations of this study

- This systematic literature review of published economic models of dementia and Alzheimer's disease (AD) is broad in terms of disease stages since the searches are being conducted across the full spectrum of dementia, including AD, from preclinical stages through to severe dementia and end of life.
- The searches cover a wide range of databases using detailed search strategies and include studies from any Organisation for Economic Co-operation and Development (OECD) country published in English language between January 2000 and June 2017.
- The review will be reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement and will use the Phillips checklist for decision analytic modelling to assess the quality of the models reported in the studies.
- We are excluding conference abstracts, commentaries and studies in languages other than English.

PROSPERO registration number CRD42017073874.

INTRODUCTION

Dementia is a progressive neurodegenerative disease that encompasses cognitive and functional impairment and behavioural symptoms.[1] People living with dementia may have difficulty with language, memory, perception, behaviour and activities of daily living. Impairments increase as the disease progresses,[1] and

there is no curative treatment. Caring for a person with dementia may also considerably affect the quality of life and health of caregivers who experience increased rates of depression and financial difficulties.[2]

An estimated 47 million people are believed to be living with dementia worldwide, and—as a result of demographic shifts towards an ageing society and increased survival of people with dementia—that number is expected to rise to around 131 million by 2050.[3] Dementia exerts a considerable toll on people living with dementia and their caregivers, its impact reaches health and social care systems and the wider society[1]; the global cost of dementia was estimated to be US$818 billion in 2015 and is projected to rise to US$2 trillion by 2030.[4]

Alzheimer's disease (AD) is the most common cause of dementia. AD is a spectrum; the earliest stage of the disease is mild cognitive impairment (MCI) where patients experience a reduction in their cognitive abilities beyond the expected cognitive decline for their age and education.[1] The symptoms may be subtle, and MCI may go unrecognised for some time.[1] While MCI may be due to the early stages of AD,[5–8] MCI can result from other clinical conditions including depression and medication side effects, which—unlike AD—may be reversible. The need for early detection and intervention in MCI is therefore crucial.[1]

Economic models can examine progression of AD from early stages such as MCI to severe dementia, in order to quantify the impact of AD across the spectrum of clinical severity. Robust economic models guide policymakers in deciding how best to allocate scarce public funds. While economic models have been used extensively for other health conditions—such as stroke, diabetes, obesity and cardiovascular diseases[9]—such modelling has been relatively less used for AD.[10] However, as the number of people living with dementia increases, high-quality economic models will be required to provide the tools for governments and other decision makers to implement cost-effective solutions to make the best use of scarce resources.

Some reviews have discussed the use of economic modelling in AD,[10–17] mainly to compare alternative interventions rather than to identify methodological issues and data gaps affecting the economic evaluation.[10–14] Most of the existing systematic literature reviews focused their searches on a limited number of databases (mainly PubMed, Embase and EconLit). In 2011, Green *et al*[10] conducted a systematic literature review on methods of modelling disease progression in AD.

This systematic literature review updates and builds on this existing work. It aims systematically to review existing economic models of dementia—all forms of dementia, including but not limited to AD—across the full spectrum of disease severity, from preclinical stages through to severe dementia and end of life,[18] and including models of the full range of interventions except primary prevention.

This review will inform further stages of the Real world Outcomes across the Alzheimer's Disease spectrum for better care: multimodal data Access Platform (ROADMAP) project, in particular the development of a new proof-of-concept model to evaluate the cost-effectiveness of interventions for the full spectrum of dementia, including AD, from preclinical stages through to severe dementia and end of life.

In this context, the review aims to meet three specific objectives:

1. To systematically identify previous economic modelling studies across the full spectrum of dementia, including AD, from preclinical stages through to severe dementia and end of life care.
2. To describe the key features of those models in terms of their aim, structure, coverage, data sources and outputs.
3. To assess the quality of existing models and describe their main strengths and weaknesses following best practice guidelines for the evaluation of model-based economic evaluations.

METHODS AND ANALYSIS

Protocol and registration

This systematic literature review protocol is reported in accordance with the Preferred Reporting Items for Systematic review and Meta-Analysis Protocols (online supplementary file 1).[19] The protocol has been registered with the PROSPERO international prospective register of systematic reviews (CRD42017073874). The results of this review will be reported following the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement.[20–22] Any amendments to this protocol will be reported and published.

Study selection criteria

Participants

This review focuses on all adults in all care settings in the full spectrum of dementia, including AD, from preclinical stages through to severe dementia and end of life. Although AD is the core of this review, we cover all forms of dementia and include dementia among our search terms.

Study design

The review includes studies reporting existing economic models across any part of the dementia or AD spectrum (from preclinical stages through to severe dementia and end of life).

The following study designs will be considered for inclusion and further consideration: cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost-minimisation analysis, cost analysis, cost-consequences analysis, economic evaluation, health technology appraisal and treatment pathway study.

We will exclude editorials, case studies, phase I and phase II clinical trials, newspaper articles, book sections, patient and expert opinion or commentary, social media and papers describing adaptations of existing economic models. Papers that fail to meet any one of the above

eligibility criteria will be excluded from the review. The number of excluded studies (including reasons for their exclusion) will be recorded.

Outcomes

The outcome measures of interest include:

- Model type and structure.
- Markers/measure used to model disease progression.
- Types of clinical/disease pathways.
- Data used to structure and parameterise the model.
- Summary/synthesis of challenges, limitations and data gaps for developing an economic model for preclinical, MCI and AD/dementia.

Intervention

All types of AD or dementia interventions (both symptomatic and disease modifying) will be included.

Context

Models developed in any OECD country will be included as long as the paper is written in English.

Search strategy

Electronic databases

The following electronic databases were searched for papers published between 1 January 2000 and 27 June 2017: Medical Literature Analysis and Retrieval System Online (Ovid MEDLINE); Excerpta Medica dataBASE (Ovid Embase); Economic Literature Database (EconLit); *NHS* Economic Evaluation Database; *Cochrane Central Register of Controlled Trials*; Cost-Effectiveness Analysis Registry; Research Papers in Economics; Database of Abstracts of Reviews of Effectiveness; Science Citation Index; Turning Research Into Practice; and Open Grey (online supplementary file 2).

The search terms include (but not limited):

- AD, dementia and mild cognitive impairment.
- Cost-effectiveness analysis, cost–utility analysis, cost analysis, economic models, Markov chains, simulation and pharmacoeconomics.

The search strategies are designed such that to be selected for review of title and abstract papers needed to contain a term from each of these two categories. A copy of the search strategies is available on the online supplementary file 2.

Manual searching

The reference lists of studies included in the review are being hand-searched to identify any additional literature.

Study selection

The electronic reference management tool EndNote X7 by Thomson Reuters will be used in order to export and manage the references. Duplicates will be removed by one reviewer (MKa), and all the remaining titles and abstracts identified through the searches will be reviewed against the predefined eligibility criteria by two reviewers (MKa and AP) in order to determine if there is a need for a further full-text review. The relevance of each study will be assessed according to the inclusion and exclusion criteria. For those studies that appear to meet the inclusion criteria, or in cases where a decision cannot be safely made based on the title/abstract only, a full text will be retrieved for the assessment. Studies that do not fulfil the inclusion criteria will be excluded. Disagreements are will be resolved by a third reviewer (RW).

The full process will be presented in a flow chart and in detail according to PRISMA guidelines.[20]

Data extraction

Two reviewers (AP and MKa) will extract the data from the included studies (online supplementary file 3). They will each independently check the data extraction forms for accuracy and completeness. Any disagreements will be noted and resolved by a third reviewer (RW).

The following information will be extracted:

- Study details: title, author, publication details, language of the study, aim of the study, countries of the study, funding of the study and study funding source.
- Study design: objective of the study, purpose of the modelling, types of modelling study (ie, review of models), type of model, model input data, model output, source of data incorporated into the model, model perspective and model time horizon.
- The intervention evaluated.
- Setting: community setting, institutional setting, primary care, secondary care, tertiary care and mixed setting.
- Participant information: type of participant, number of participants and demographic information.
- Disease-specific information: type of dementia, level of severity and disease progression measurement.
- Outcomes: outcomes modelled and costs (and cost types).
- Approach to model validation and evidence of validation performance.
- Key findings.
- Author's comments on strengths and weaknesses of the model and potential gaps in available data.

Risk of bias (quality) assessment

The quality of the model is the core of our review. Thus, the quality of identified models will be assessed from the perspective of best current practice. The 'Philips checklist',[23 24] as recommended by the *Cochrane Handbook for Systematic Reviews of Interventions*,[25] will be used to assess the quality of the models reported in the studies included in the review. Two researchers will independently review and assess the models. The Phillips checklist was developed for assessing the quality of decision-analytic models in health technology assessment. It was designed to be used both by analysts developing models and by reviewers assessing such models. It comprises nine points on the structure of the model, five on the data used in the model and two on model validation.

Strategy for data synthesis

A narrative synthesis will be used for the present study.

Ethics and dissemination plans

The included studies will be reviewed to ensure ethical considerations were taken into account. The results will be published in the form of a publication in a peer-reviewed journal. In addition, the results will be presented at conferences and will be published in the ROADMAP project's official website (http://roadmap-alzheimer.org/).

Patient and public involvement

Alzheimer Europe, representing patient and carer associations across Europe, is a partner in the ROADMAP consortium and has been fully involved from the beginning in the design and progress of the overall project, including this systematic literature review.

DISCUSSION

Economic models are useful to inform policy decisions by providing evidence on the cost-effectiveness of current and new interventions. The aim of this systematic literature review is to systematically identify and review the existing economic modelling methodologies across the full spectrum of dementia, including AD, from preclinical stages through to severe dementia and end of life.[18] The focus will be on the models, their structure and the information and assumptions used to parameterise them and not on the interventions per se. We will consider modelling of both symptomatic and disease-modifying interventions.[18] The way in which disease progression is represented in economic models will also be covered.[18] This systematic literature review will inform the design and development of future economic modelling across the full spectrum of dementia, including AD, from preclinical stages through to severe dementia and end of life and will identify gaps in data and research.

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Contributors All authors participated in designing this review. MKa and RW wrote this protocol. MKa, RW, AF and A-LP devised the search strategy. PL, RW, AMG, MKn, FITL, IG, JW, AT-H, RH and AYCS critically appraised the protocol and contributed to its development. All authors read and approved the final version of the manuscript.

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Competing interests AT-H is an employee of Eli Lilly and Company Limited and owns stock in Eli Lilly and Company Limited. AYCS is an employee of F. Hoffmann-La Roche Ltd. RH reports grants from ROADMAP (IMI2; public-private collaboration; 2016–2019) to conduct this study, grants from BIOMARKAPD (EU JPND project; 2012–2016), grants from Actifcare (EU JPND project; 2014–2017), grants from European Brain Council (VoT project; public–private collaboration; 2017), grants from Dutch Flutemetamol Study (public–private collaboration; 2012–2017), personal fees from Piramal (advisory; 2016), personal fees from Roche (advisory; 2017), outside the submitted work. PL is employed by, owns stock in and has stock options in Novartis Pharma AG. Novartis Pharma AG, GE Healthcare, Biogen, Eli Lilly and Company Limited and Roche are industry partners in the ROADMAP Project.

Patient consent The study is a systematic literature review. It did not involve any contact with patients.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1. World Health Organization. Dementia: A Public Health Priority. 2012 whqlibdoc.who.int/publications/2012/9789241564458_eng.pdf.
2. Mahoney R, Regan C, Katona C, *et al*. Anxiety and depression in family caregivers of people with Alzheimer disease: the LASER-AD study. *Am J Geriatr Psychiatry* 2005;13:795–801.
3. Prince M, Comas-Herrera A, Knapp M, *et al*. *World Alzheimer report 2016: improving healthcare for people living with dementia: coverage, quality and costs now and in the future*. London: Alzheimer's Disease International, 2016.
4. Prince M. *World Alzheimer Report 2015: the global impact of dementia: an analysis of prevalence, incidence, cost and trends*. London: Alzheimer's Disease International, 2015.
5. Petersen RC, Smith GE, Waring SC, *et al*. Mild cognitive impairment: clinical characterization and outcome. *Arch Neurol* 1999;56:303–8.
6. Sperling RA, Aisen PS, Beckett LA, *et al*. Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement* 2011;7:280–92.
7. Albert MS, DeKosky ST, Dickson D, *et al*. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement* 2011;7:270–9.
8. McKhann GM, Knopman DS, Chertkow H, *et al*. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement* 2011;7:263–9.
9. Drummond M, Sculpher M, Claxton K, *et al*. *Methods for the economic evaluation of health care programmes*. Oxford: Oxford university press, 2015.
10. Green C, Shearer J, Ritchie CW, *et al*. Model-based economic evaluation in Alzheimer's disease: a review of the methods available to model Alzheimer's disease progression. *Value Health* 2011;14:621–30.

11. Gustavsson A, Green C, Jones RW, *et al*. Current issues and future research priorities for health economic modelling across the full continuum of Alzheimer's disease. *Alzheimers Dement* 2017;13:312–21.
12. Green C, Zhang S. Predicting the progression of Alzheimer's disease dementia: a multidomain health policy model. *Alzheimers Dement* 2016;12:776–85.
13. Hernandez L, Ozen A, DosSantos R, *et al*. Systematic Review of Model-Based Economic Evaluations of Treatments for Alzheimer's Disease. *Pharmacoeconomics* 2016;34:681–707.
14. Handels RL, Wolfs CA, Aalten P, *et al*. Diagnosing Alzheimer's disease: a systematic review of economic evaluations. *Alzheimers Dement* 2014;10:225–37.
15. Cohen JT, Neumann PJ. Decision analytic models for Alzheimer's disease: state of the art and future directions. *Alzheimers Dement* 2008;4:212–22.
16. Hyde C, Peters J, Bond M, *et al*. Evolution of the evidence on the effectiveness and cost-effectiveness of acetylcholinesterase inhibitors and memantine for Alzheimer's disease: systematic review and economic model. *Age Ageing* 2013;42:14–20.
17. Bond M, Rogers G, Peters J, *et al*. The effectiveness and cost-effectiveness of donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease (review of Technology Appraisal No. 111): a systematic review and economic model. *Health Technol Assess* 2012;16:1–470.
18. Real world Outcomes across the AD spectrum for better care: Multi-modal data Access Platform (ROADMAP) proposal. 2016:35–8.
19. Shamseer L, Moher D, Clarke M, *et al*. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ* 2015;349:g7647.
20. Moher D, Liberati A, Tetzlaff J, *et al*. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009;6:e1000097.
21. Liberati A, Altman DG, Tetzlaff J, *et al*. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLoS Med* 2009;6:e1000100.
22. Welch V, Petticrew M, Tugwell P, *et al*. PRISMA-Equity 2012 extension: reporting guidelines for systematic reviews with a focus on health equity. *PLoS Med* 2012;9:e1001333–7.
23. Philips Zo??, Bojke L, Sculpher M, *et al*. Good Practice Guidelines for Decision-Analytic Modelling in Health Technology Assessment. *Pharmacoeconomics* 2006;24:355–71.
24. Philips Z, Ginnelly L, Sculpher M, *et al*. Review of guidelines for good practice in decision-analytic modelling in health technology assessment. *Health Technol Assess* 2004;8:1–58.
25. Higgins JP, Green S. eds. *Cochrane handbook for systematic reviews of interventions*. New Jersey: John Wiley & Sons, 2011.