BMJ Open

Computer simulation models of pre-diabetes populations: a systematic review protocol

Jose Leal,[1] Waqar Khurshid,[1] Eva Pagano,[2] Talitha Feenstra[3,4]

To cite: Leal J, Khurshid W, Pagano E, *et al*. Computer simulation models of pre-diabetes populations: a systematic review protocol. *BMJ Open* 2017;**7**:e014954. doi:10.1136/bmjopen-2016-014954

► We have an online supplement to complement the paper.

► Prepublication history and additional material are available. To view these files please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2016-014954).

Received 31 October 2016
Revised 13 February 2017
Accepted 9 May 2017

[1]Nuffield Department of Population Health, Health Economics Research Centre, University of Oxford, Oxford, UK
[2]Unit of Cancer Epidemiology, "Città della Salute e della Scienza" Hospital and CPO Piemonte, Piemonte, Italy
[3]Department of Epidemiology, University Medical Centre Groningen, Groningen, The Netherlands
[4]Department for Prevention and Health Services Research, National Institute for Public Health and the Environment (RIVM), Bilthoven, The Netherlands

Correspondence to
and Dr Jose Leal;
jose.leal@ndph.ox.ac.uk

ABSTRACT

Introduction Diabetes is a major public health problem and prediabetes (intermediate hyperglycaemia) is associated with a high risk of developing diabetes. With evidence supporting the use of preventive interventions for prediabetes populations and the discovery of novel biomarkers stratifying the risk of progression, there is a need to evaluate their cost-effectiveness across jurisdictions. In diabetes and prediabetes, it is relevant to inform cost-effectiveness analysis using decision models due to their ability to forecast long-term health outcomes and costs beyond the time frame of clinical trials. To support good implementation and reimbursement decisions of interventions in these populations, models should be clinically credible, based on best available evidence, reproducible and validated against clinical data. Our aim is to identify recent studies on computer simulation models and model-based economic evaluations of populations of individuals with prediabetes, qualify them and discuss the knowledge gaps, challenges and opportunities that need to be addressed for future evaluations.

Methods and analysis A systematic review will be conducted in MEDLINE, Embase, EconLit and National Health Service Economic Evaluation Database. We will extract peer-reviewed studies published between 2000 and 2016 that describe computer simulation models of the natural history of individuals with prediabetes and/or decision models to evaluate the impact of interventions, risk stratification and/or screening on these populations. Two reviewers will independently assess each study for inclusion. Data will be extracted using a predefined pro forma developed using best practice. Study quality will be assessed using a modelling checklist. A narrative synthesis of all studies will be presented, focussing on model structure, quality of models and input data, and validation status.

Ethics and dissemination This systematic review is exempt from ethics approval because the work is carried out on published documents. The findings of the review will be disseminated in a related peer-reviewed journal and presented at conferences.

Reviewregistration number CRD42016047228.

Strengths and limitations of the study

- This systematic review of computer simulation models of prediabetes populations was based on a detailed search strategy complemented with a comprehensive data extraction and analysis of the studies and technical reports.
- The review followed the latest guidelines and assessed the quality and validity of the computer models using published modelling checklists.
- The quality and validity of the computer models identified may depend on the reporting quality and transparency of the main study and technical reports.

INTRODUCTION

Diabetes affected >415 million worldwide in 2015 and was responsible for 5 million deaths.[1] It is one of the most prevalent chronic diseases and type 2 diabetes is the most common form of diabetes mellitus, with >90% of individuals with diabetes having this type of condition.[1] Cardiovascular disease, retinopathy, nephropathy and lower limb amputation are common diabetes-related complications and there is a highly significant association between glycaemic levels and the development of each of these complications.[2]

Prediabetes, a condition characterised by intermediate hyperglycaemia, is associated with a high risk of developing diabetes.[3] According to the American Diabetes Association, prediabetes is defined as a fasting plasma glucose level of 100–125 mg/dL (known as impaired fasting glucose (IFG)), a 2-hour plasma glucose level after a 75 g oral glucose tolerance test of 140–199 mg/dL (known as impaired glucose tolerance (IGT)) or haemoglobin A1c (HbA1c) 5.7 to <6.5%. In 2015, 318 million people worldwide were estimated to have IGT.[1] In addition to the high risk of developing diabetes, research shows it to be also associated with increased risk of cardiovascular disease, early stage nephropathy and retinopathy.[3] However, there is strong evidence from clinical trials that lifestyle interventions (diet and physical activity) can prevent or delay the development of type 2 diabetes,[4–7] and as a result, lifestyle changes

are considered to be the first-lineprevention intervention. However, pharmaceutical interventions, such as oral antidiabetic drugs and anti-obesity drugs, either compared with standard care or as an addition to lifestyle changes, were also shown to reduce the rate of progression to diabetes in individuals with IGT.[8 9]

As the number of preventive interventions in prediabetes populations grows and evidence accumulates, there is a need to assess whether the potential health gains from adding these interventions to healthcare policies justify their implementation costs. Such considerations are important to inform national policy and local decisions in many jurisdictions where evidence on both the effectiveness and cost-effectiveness of interventions is needed. Computer simulation models, such as decision analytic models, are well suited to provide cost-effectiveness evidence in the setting and time frame of interest to decision makers. They allow extrapolating short-term outcome data from clinical trials over lifetimes and across different populations as well as forecasting the long-term health gains and costs of preventive interventions. This is particularly relevant in (pre)diabetes which develops over a long period of time, has substantial costs and is associated with high morbidity and mortality.[1] However, to support decisions on whether to implement or reimburse interventions targeting prediabetes populations, computer models reporting health economics outcomes have to be clinically credible, based on the best available evidence, reproducible and validated against clinical data.[10] Recently, an increasing amount of research effort is being put into the discovery of biomarkers that allow stratification of both prediabetes and diabetes. Stratified groups may be amenable to different treatment strategies. Such targeted treatments do put specific requirements on health economic decision models, such as the ability to model trajectories of risk factors like HbA1c, blood pressure, lipid levels, body mass index and history of complications.

Previous systematic reviews have assessed economic evaluations of diabetes prevention programmes with the aim of comparing the cost-effectiveness results across interventions and studies[11–13] or assessing their potential to model multiple preventive interventions in high-risk populations.[14] However, there may be decision models that report health economic outcomes (eg, costs, life years, quality adjusted life years and so on) but have not been used to inform economic evaluations. Furthermore, the discussion in previous reviews about the quality of the decision models on which the cost-effectiveness results were based has thus far been limited. Items such as type and structure of the computer simulation models, how disease progression in prediabetes and diabetes states was simulated, the evidence base used to inform the models and their clinical and model validity were seldom discussed in detail. Furthermore, despite their relevance to inform decision making in diabetes,[15] no formal assessments have been made of their quality and validity using recognised checklists.[16–18] Our review will focus on understanding the current evidence base and highlighting key limitations, opportunities and challenges for health economics models that need to be addressed for future evaluations, such as potential stratified preventive and treatment strategies based on novel biomarkers.[19] Hence, the aim of this systematic review is to summarise and assess the quality and validity of decision models that simulate prediabetes populations from disease onset onwards and report health economics outcomes. Our objectives are listed as:

1. Summarise peer-reviewed and published health economics decision models and model-based economic evaluations of populations of individuals with prediabetes.
2. Assess the quality and validity of the decision models using best practice guidelines.
3. Identify and discuss research gaps that need to be addressed to inform future economic evaluations targeting prediabetes populations.

METHODS

Protocol and registration

When developing the protocol we followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis for Protocols (PRISMA-P) 2015 guideline.[20] We provide the completed PRISMA-P checklist. We registered the protocol with the PROSPERO international prospective register of systematic reviews (registration number CRD42016047228). The final review will follow the PRISMA statement.[21–23] Important amendments to this protocol will be reported and published with the results of the review.

Study selection criteria

Type of population

This systematic review will target populations of individuals with prediabetes. Any recognised method of establishing prediabetes in a patient will be considered, including but not limited to IFG, IGT, raised fasting plasma glucose or raised glycated haemoglobin (HbA1c). Those with a pre-existing diagnosis of diabetes will be excluded as well as individuals with gestational diabetes or maturityonset diabetes of the young.

Type of intervention

Decision models of disease progression of prediabetes populations reporting health economics outcomes and model-based economic evaluations of any intervention(s) aimed at these populations will be included. This may include lifestyle interventions (diet and physical activity), therapeutic interventions (drugs or surgery), use of risk stratification tools for targeted clinical management or screening interventions followed by clinical management.

Type of studies

This systematic review will identify studies reporting decision models simulating the natural history of pre-diabetes populations and/or model-based economic evaluations of preventive interventions (eg, lifestyle changes, drug and surgical interventions), risk stratification and/or screening of these populations. Model-based economic

evaluations may include cost-effectiveness, cost-utility, cost-benefit, cost-minimisation and cost-consequence analysis. If a model is associated with multiple publications, we will identify and cite all these publications in our literature review but extract data based on the paper that describes the model in greatestdetail supported by other publications and any online documentation that may be of relevance. For example, if a publication describes the model in the context of a cost-effectiveness analysis and a second publication reports its validation, the data extraction and quality assessment of the model will take account of both these studies.

Type of outcome measure

We will include only decision models and model-based economic evaluations reporting health economic outcomes such as costs (quality-adjusted), life years and diabetes-related complications. Studies which have developed models solely to predict the risk of detecting undiagnosed type 2 diabetes or the risk of developing type 2 diabetes will not be included. Model-based economic evaluations reporting solely short-term outcomes such as incidence of type 2 diabetes and/or cases detected and costs of screening/detection will not be included.

Search strategy

The selection of electronic databases and the search strategy were developed in conjunction with an information specialist based on previous literature reviews' search strategies.[8 9 24] The following electronic databases were searched from 1 January 2000 to 1 August 2016: MEDLINE, Embase, EconLit and The Cochrane Library (for National Health Service Economic Evaluation Database). Articles were restricted to English-language literature but no geographicalrestrictions were applied to the search. Abstracts or conference presentations will not be included as sufficient data are not presented to allow critical appraisal of the decision models. The exact search terms used in all databases are described in online supplementary appendix. Additional articles will be identified by searching the reference list of the studies included in this review as well as those of previous literature reviews on economic evaluations of interventions to prevent type 2 diabetes.

Study selection

EndNote X7, Thomson Reuters database, was used to manage the references. Duplicates were removed by one reviewer. Two reviewers then independently assessed 50% of the abstracts to determine whether a full-text review is needed. A further 10% was assessed by each reviewer to cross-reference decisions to proceed to full review. Any disagreement between the two reviewers was resolved by using a third reviewer for assessment. Articles chosen for final inclusion were retrieved and reviewed by two reviewers independently and any disagreement was again subject to a third reviewer assessment. Following PRISMA guidelines,[21] we will present a flow diagram reporting the selection process.

Data extraction

Data extraction will be conducted independently by four reviewers using a standardised form. Each reviewer will assess 50% of the final articles, such that each article will be seen by two reviewers. Any disagreements will be resolved by consensus. A form will be used to extract data from the studies (see online supplementary appendix). Data extracted will include details on the following:

1. Study: title, author and publication details.
2. Economic evaluation: objective/scope of model, location and setting, study design, perspective of analysis, model outcomes, strategies/comparators, patient population characteristics, prediabetes definition used, time horizon and information on discounting.
3. Modelling details: model structure and rationale, structural assumptions, type of model and rationale, natural history of diabetes evolution, complications in prediabetes and type 2 diabetes states modelled, and whether patient heterogeneity was incorporated into the model (eg, progression dependent on multiple risk factors for a given individual) and how.
4. Data: methods used for identifying data, data sources used, evidence synthesis and calibration. We will use the hierarchy of evidence from Cooper *et al*[25] to characterise data sources informing baseline clinical data, primary effect size and duration of primary effect, resource use, costs and quality of life/utilities. We will also extract the category of costs included as well detailed information concerning the use of utilities in the model.
5. Model uncertainty and validation: methods used to address methodological uncertainty, structural uncertainty, parameter uncertainty and heterogeneity; model internal and external validation.
6. Results, quality checklist score and comments and limitations of the study.

Risk of bias (quality) assessment

The Philips *et al*'s[17] checklist will be used to assess the quality of the reporting of the decision models and model-based economic evaluations. Model validation will be assessed using the checklist from Vermer *et al*.[18] Items in the checklists will be marked as Yes, No or Not Applicable. Two reviewers will independently apply the checklist and disagreements will be resolved by consensus or arbitration by a third reviewer.

Data synthesis

The decision models will be synthesised in a narrative format. We will summarise the characteristics of the several elements of the decision models in table format and contrast differences in approach and quality. Also, we will consider how these fit with the diabetes-specific requirements for models reported in the American Diabetes Association guidelines.[16] Finally, we will identify key limitations, opportunities and challenges that need to be addressed for future evaluations of interventions in populations with prediabetes.

DISCUSSION

Economic data are relevant to support decisions concerning which interventions to implement in jurisdictions where healthcare resources are limited. Given the high costs and burden of diabetes, there is significant interest in identifying strategies that work at preventing or delaying the disease and are cost-effective. Such cost-effectiveness evidence relies for the most part on model-based economic evaluations given the chronic nature of the condition and the constraints of clinical trials. This systematic review will identify the state of decision models simulating prediabetes populations and inform on the cost-effectiveness of preventive interventions aimed at these populations. It will focus on the structure of the decision models, the evidence used to inform them, model uncertainty and their validation, with specific focus on suitability for use in evaluating stratified/biomarker-driven intervention strategies. The findings of this review will inform the challenges and opportunities of the economic decision models/computer models that simulate the long-term costs and health outcomes in these populations

Acknowledgements The authors would like to thank their information specialists Eli Bastin and Nia Roberts, University of Oxford, for their help in developing the search strategy and selecting databases.

Contributors JL, TF and EP conceived the initial idea for the study. JL and WK wrote the protocol. TF and EP critically appraised the protocol and also contributed to its development by revising different version. All authors read and approved the final version of the manuscript. JL is the guarantor of the review.

Funding This work is supported by Innovative Medicines Initiative 2 Joint Undertaking under grant agreement no 115881. This Joint Undertaking receives support from the European Union's Horizon 2020 research and innovation programme and EFPIA.

Competing interests None declared.

Ethics approval This systematic review is exempt from ethics approval and consent to participate because the work is carried out on published documents.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1. International Diabetes Federation. IDF Diabetes Atlas (seventh edition) Brussels: International Diabetes Federation. 2015. http://www.diabetesatlas.org/.
2. Stratton IM, Adler AI, Neil HA, *et al*. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ* 2000;321:405–12.
3. Tabák AG, Herder C, Rathmann W, *et al*. Prediabetes: a high-risk state for diabetes development. *Lancet* 2012;379:2279–90.
4. Knowler WC, Barrett-Connor E, Fowler SE, *et al*. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 2002;346:393–403.
5. Tuomilehto J, Lindström J, Eriksson JG, *et al*. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N Engl J Med Overseas Ed* 2001;344:1343–50.
6. Saito T, Watanabe M, Nishida J, *et al*. Lifestyle modification and prevention of type 2 diabetes in overweight Japanese with impaired fasting glucose levels: a randomized controlled trial. *Arch Intern Med* 2011;171:1352–60.
7. Ramachandran A, Snehalatha C, Mary S, *et al*. The Indian Diabetes Prevention Programme shows that lifestyle modification and metformin prevent type 2 diabetes in Asian Indian subjects with impaired glucose tolerance (IDPP-1). *Diabetologia* 2006;49:289–97.
8. Gillies CL, Abrams KR, Lambert PC, *et al*. Pharmacological and lifestyle interventions to prevent or delay type 2 diabetes in people with impaired glucose tolerance: systematic review and meta-analysis. *BMJ* 2007;334:299.
9. Stevens JW, Khunti K, Harvey R, *et al*. Preventing the progression to type 2 diabetes mellitus in adults at high risk: a systematic review and network meta-analysis of lifestyle, pharmacological and surgical interventions. *Diabetes Res Clin Pract* 2015;107:320–31.
10. Caro JJ, Briggs AH, Siebert U, *et al*. Modeling good research practices--overview: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force-1. *Med Decis Making* 2012;32:667–77.
11. Li R, Zhang P, Barker LE, *et al*. Cost-Effectiveness of interventions to prevent and control Diabetes Mellitus: a systematic review. *Diabetes Care* 2010;33:1872–94.
12. Alouki K, Delisle H, Bermúdez-Tamayo C, *et al*. Lifestyle interventions to prevent type 2 diabetes: a systematic review of economic evaluation studies. *J Diabetes Res* 2016;2016:1–14.
13. Saha S, Gerdtham UG, Johansson P. Economic evaluation of lifestyle interventions for preventing diabetes and cardiovascular diseases. *Int J Environ Res Public Health* 2010;7:3150–95.
14. Watson P, Preston L, Squires H, *et al*. Modelling the economics of type 2 diabetes mellitus prevention: a literature review of methods. *Appl Health Econ Health Policy* 2014;12:239–53.
15. Palmer AJ, Clarke P, Gray A, *et al*. Computer modeling of diabetes and its complications: a report on the fifth mount hood challenge meeting. *Value Health* 2013;16:670–85.
16. American Diabetes Association Consensus Panel. Guidelines for computer modeling of diabetes and its complications. *Diabetes Care* 2004;27:2262–5.
17. Philips Zoë, Bojke L, Sculpher M, *et al*. Good Practice guidelines for Decision-Analytic modelling in Health Technology Assessment. *Pharmacoeconomics* 2006;24:355–71.
18. Vemer P, Corro Ramos I, van Voorn GA, *et al*. AdViSHE: a validation-assessment tool of health-economic models for decision makers and model users. *Pharmacoeconomics* 2016;34:349–61.
19. Guasch-Ferré M, Hruby A, Toledo E, *et al*. Metabolomics in prediabetes and diabetes: a systematic review and meta-analysis. *Diabetes Care* 2016;39:833–46.
20. 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.
21. Moher D, Liberati A, Tetzlaff J, *et al*. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ* 2009;339:b2535.
22. Liberati A, Altman DG, Tetzlaff J, *et al*. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ* 2009;339:b2700.
23. 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.
24. Abdul Pari AA, Simon J, Wolstenholme J, *et al*. Economic evaluations in bipolar disorder: a systematic review and critical appraisal. *Bipolar Disord* 2014;16:557–82.
25. Cooper N, Coyle D, Abrams K, *et al*. Use of evidence in decision models: an appraisal of health technology assessments in the UK since 1997. *J Health Serv Res Policy* 2005;10:245–50.

BMJ Open

Computer simulation models of pre-diabetes populations: a systematic review protocol

Jose Leal, Waqar Khurshid, Eva Pagano and Talitha Feenstra

*BMJ Open*2017 7:
doi: 10.1136/bmjopen-2016-014954