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Computer simulation models of prediabetes populations: a systematic review protocol

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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 computer simulation models due to their ability to forecast long-term health outcomes and costs beyond the time-frame limitations of clinical trials. However, to support good implementation and reimbursement decisions of interventions in these populations, models should be clinically credible, based on the 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 and NHS EED. We extracted peer-reviewed studies published between 2000 and 2016 that describe computer simulation models of the natural history of individuals with prediabetes and/or used decision models to evaluate the impact of interventions, risk stratification and/or screening on these populations. Two reviewers independently assessed each study for inclusion. Data will be extracted using a pre-defined 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.

Systematic review registration: CRD42016047228

Keywords: diabetes, economic evaluation, decision model, systematic review, health economics, prediabetes

Strengths 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.

Limitations of the study

- 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 more than 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 over 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 America Diabetes Association, prediabetes is defined as a fasting plasma glucose level of 100 to 125 mg/dL (known as impaired fasting glucose - IFG), a 2-h plasma glucose level after a 75-g oral glucose tolerance test of 140 to 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 primary prevention intervention. However, pharmaceutical interventions, such as oral antidiabetic drugs and anti-obesity drugs, either compared to 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 have to be clinically credible,

based on the best available evidence, reproducible and validated against clinical data. 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 such as 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.[10-12] or assessing their potential to model multiple preventive interventions in high risk populations.[13] However, the discussion about the quality of the decision models upon 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,[14] no formal assessments have been made of their quality and validity using recognised checklists.[15-17] Our review will focus on understanding the current evidence base and highlighting key limitations, opportunities and challenges that need to be addressed for future evaluations, such as potential stratified preventive and treatment strategies based on novel biomarkers.[18] Hence, the aim of this systematic review is to assess the quality and validity of decision models and model-based economic evaluations that simulate prediabetes populations from disease onset onwards. Our objectives are listed as:

- Summarise decision models and model-based economic evaluations of populations of individuals with prediabetes.
- Assess the quality and validity of the decision models using best practice guidelines.
- 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 2015 (PRISMA-P) guideline.[19] We provide in Appendix 1 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 Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement.[20-22] 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 impaired fasting glucose, impaired glucose tolerance, 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 mature onset diabetes of the young (MODY).

Type of intervention

Studies describing models of natural history of prediabetes but not presenting economic evaluations of interventions will be included. Model-based economic evaluations of any intervention(s) aimed at prediabetes 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 prediabetes populations and/or model-based economic evaluations of preventive interventions (e.g. 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.

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 23] The following electronic databases were searched from 1st January 2000 until 1st August 2016: Medline, Embase and The Cochrane Library (for NHS EED). Articles were restricted to English-language literature but no geography restrictions were applied to the search. Abstracts or conference presentations were not included as sufficient data is not presented to allow critical appraisal of the decision models. The exact search terms used in all databases are described in Appendix 2. 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, 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,[20] 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. Data extracted will include details on (see Appendix 3):

- Study: title, author and publication details
- Economic evaluation: objective/scope of model, location and setting, study design, perspective of analysis, primary outcomes, strategies/comparators, patient population characteristics, prediabetes definition used, time horizon and information on discounting.
- 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 (e.g. progression dependent on multiple risk factors for a given individual) and how.

- Data: methods used for identifying data, data sources used, evidence synthesis and calibration. We will use the hierarchy of evidence from Cooper et al.[24] 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.
- Model uncertainty and validation: methods used to address methodological uncertainty, structural uncertainty, parameter uncertainty and heterogeneity; model internal and external validation.
- Results, quality checklist score and comments and limitations of the study

Risk of bias (quality) assessment

The Philips et al.[16] 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. [17] 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 guidance.[15] 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 is 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

Ethics and dissemination

This systematic review is exempt from ethics approval and consent to participate because the work is carried out on published documents. We will disseminate the findings in a related peer-reviewed journal.

Declarations

Funding

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Competing interests

The authors declare that they have no competing interests.

Authors' contributions

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.

Ethics approval and consent to participate

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

Acknowledgments

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Appendices

Appendix 1: PRISMA-P checklist

Table A.1: PRISMA-P 2015 checklist

Section and topic	Item No.	Checklist Item	Reported on page #
A) Administrative Information			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	Identify protocol as an update of a previous systematic review if applicable	n/a
Registration	2	Name of registry and registration number	2+4
B) Authors			
Contact		Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions		Describe contributions of protocol authors and identify the guarantor of the review	8
Amendments		If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	n/a
Support			
- Sources	5a	Indicate Sources of financial or other support for the review	8
- Sponsor	5b	Provide name for the review funder and/or sponsor	8
- Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s) and/or institution(s), if any, in developing the protocol	n/a
C) Introduction			
Rationale	6	Describe the rationale for the review in the context of what is already known	4
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	4
D) Methods			
Eligibility Criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	5
Information Sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	5+6
Search Strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	5 + 6 + Appendix 2
E) Study Records			
Data Management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	6
Selection Process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	6
Data Collection Process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	6
Data Items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	6 + 7+ Appendix 3
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	6 + 7
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study	7

		level, or both; state how this information will be used in data synthesis	
Data Synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	7
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency	n/a
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	n/a
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	7
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	n/a
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed	7

Appendix 2: Search strategy

Table A.2.1: Ovid MEDLINE

Searches	Search Terms
1	exp prediabetic state/
2	exp insulin resistance/
3	prediab$.ti,ab.
4	pre diab$.ti,ab.
5	(glucose adj2 impair$).ti,ab.
6	(glucose adj2 intol$).ti,ab.
7	IGT.ti,ab.
8	IFG.ti,ab.
9	IGR.ti,ab.
10	(impair$ adj2 glycem$).ti,ab.
11	(impair$ adj2 glycaem$).ti,ab.
12	(insulin adj2 resistan$).ti,ab.
13	impaired fasting glucose.ti,ab.
14	impaired fasting glycaem$.ti,ab.
15	impaired fasting glycem$.ti,ab.
16	impaired glucose tolerance.ti,ab.
17	impaired glucose regulation.ti,ab.
18	glucose intolerance.ti,ab.
19	borderline diabetes.ti,ab.
20	impaired fasting insulin.ti,ab.
21	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20
22	Type 2 Diab$.ti.
23	diabetes.ti.
24	exp insulin resistance/
25	Type II diab$.ti.
26	NIDDM.ti.
27	Non insulin dependent diabetes.ti.
28	T2DM.ti.
29	exp diabetes mellitus, Type 2/
30	obese diabetes.ti.
31	obesity diabetes.ti.
32	((adult or mature or late) and onset).ti.
33	MODY.ti.
34	22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33
35	screen$.ti,ab.
36	prevent$.ti,ab.
37	lifestyle.ti,ab.
38	early detection.ti,ab.
39	(risk adj2 stratifi$).ti,ab.
40	(risk adj2 identification$).ti,ab.
41	35 or 36 or 37 or 38 or 39 or 40
42	34 and 41
43	simulation model$.ti,ab.
44	markov.ti,ab.
45	monte carlo.ti,ab.
46	decision tree$.ti,ab.
47	decision analy$.ti,ab.
48	qaly$.ti,ab.
49	(valu$ adj2 quality).ti,ab.
50	utility value$.ti,ab.
51	((disability or quality) adj adjusted).ti,ab.
52	((life adj2 year$) or health year equivalent$).ti,ab.
53	(health adj utilit$).ti,ab.
54	hui$1.ti,ab.

55	(quality adj3 well$).ti,ab.
56	qwb.ti,ab.
57	(qald$ or qale$ or qtime$).ti,ab.
58	(well being or wellbeing).tw.
59	(health adj2 stat$).tw.
60	((adjusted adj2 life) or qaly$).ti,ab.
61	(daly or qol or hql or hqol or hrqol or hr ql or hrql).tw.
62	cost-utility.ti,ab.
63	cost-effectiveness.ti,ab.
64	cost-benefit.ti,ab.
65	cost-minimisation.ti,ab.
66	cost-minimization.ti,ab.
67	modelling.ti,ab.
68	modeling.ti,ab.
69	decision model.ti,ab.
70	QALY.ti,ab.
71	quality adjusted life year$.ti,ab.
72	cost.ti,ab.
73	life year$.ti,ab.
74	incremental cost-effectiveness ratio.ti,ab.
75	(qtwist or q twist).ti,ab.
76	(quality adj2 life).ti,ab.
77	43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76
78	21 or 42
79	77 and 78
80	non-diabet$.ti,ab.
81	79 not 80
82	exp animals/ not human.sh.
83	81 and 82
84	limit 83 to yr="2000 -Current"
85	limit 84 to english language

ti: title; ab: abstract

Table A.2.2: Embase

Searches	Search Terms
1	exp impaired glucose tolerance/
2	exp insulin resistance/
3	prediab$.ti,ab.
4	pre diab$.ti,ab.
5	(glucose adj2 impair$).ti,ab.
6	(glucose adj2 impair$).ti,ab.
7	IGT.ti,ab.
8	IFG.ti,ab.
9	IGR.ti,ab.
10	(impair$ adj2 glycem$).ti,ab.
11	(impair$ adj2 glycaem$).ti,ab.
12	(insulin adj2 resistan$).ti,ab.
13	impaired fasting glucose.ti,ab.
14	impaired fasting glycaem$.ti,ab.
15	impaired fasting glycem$.ti,ab.
16	impaired glucose tolerance.ti,ab.
17	impaired glucose regulation.ti,ab.
18	glucose intolerance.ti,ab.
19	borderline diabetes.ti,ab.
20	impaired fasting insulin.ti,ab.
21	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20
22	Type 2 Diab$.ti.
23	diabetes.ti.
24	exp insulin resistance/
25	Type II diab$.ti.
26	NIDDM.ti.
27	Non insulin dependent diabetes.ti.
28	T2DM.ti.
29	exp non insulin dependent diabetes mellitus/
30	obese diabetes.ti.
31	obesity diabetes.ti.
32	((adult or mature or late) and onset).ti.
33	MODY.ti.
34	22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33
35	screen$.ti,ab.
36	prevent$.ti,ab.
37	lifestyle.ti,ab.
38	early detection.ti,ab.
39	(risk adj2 stratifi$).ti,ab.
40	(risk adj2 identification$).ti,ab.
41	35 or 36 or 37 or 38 or 39 or 40
42	34 and 41
43	simulation model$.ti,ab.
44	markov.ti,ab.
45	monte carlo.ti,ab.
46	decision tree$.ti,ab.
47	decision analy$.ti,ab.
48	qaly$.ti,ab.
49	(valu$ adj2 quality).ti,ab.
50	utility value$.ti,ab.
51	((disability or quality) adj adjusted).ti,ab.
52	((life adj2 year$) or health year equivalent$).ti,ab.
53	(health adj utilit$).ti,ab.
54	hui$1.ti,ab.
55	(quality adj3 well$).ti,ab.
56	qwb.ti,ab.
57	(qald$ or qale$ or qtime$).ti,ab.
58	(well being or wellbeing).tw.
59	(health adj2 stat$).tw.
60	((adjusted adj2 life) or qaly$).ti,ab.
61	(daly or qol or hql or hqol or hrqol or hr ql or hrql).tw.
62	cost-utility.ti,ab.
63	cost-effectiveness.ti,ab.
64	cost-benefit.ti,ab.

65	cost-minimisation.ti,ab.
66	cost-minimization.ti,ab.
67	modelling.ti,ab.
68	modeling.ti,ab.
69	decision model.ti,ab.
70	QALY.ti,ab.
71	quality adjusted life year$.ti,ab.
72	cost.ti,ab.
73	life year$.ti,ab.
74	incremental cost-effectiveness ratio.ti,ab.
75	(qtwist or q twist).ti,ab.
76	(quality adj2 life).ti,ab.
77	43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76
78	21 or 42
79	77 and 78
80	non-diabet$.ti,ab.
81	79 not 80
82	exp animals/ not human.sh.
83	81 not 82
84	limit 83 to yr="2000 -Current"
85	limit 84 to english language

ti: title; ab: abstract

Table A.2.3: NHS EED (via the Cochrane Library)

Searches	Search Terms
#1	MeSH descriptor: [Prediabetic State] explode all trees
#2	MeSH descriptor: [Insulin Resistance] explode all trees
#3	(prediab*) .ti,ab
#4	(pre diab*) .ti,ab
#5	(glucose near/2 impair*) .ti,ab
#6	(glucose adj2 intol*) .ti,ab
#7	(IGT) .ti,ab
#8	(IFG) .ti,ab
#9	(IGR) .ti,ab
#10	(impair* near/2 glycem*) .ti,ab
#11	(impair* near/2 glycaem*) .ti,ab
#12	(insulin near/2 resistan*) .ti,ab
#13	(impaired fasting glucose) .ti,ab
#14	(impaired fasting glycemia) .ti,ab
#15	(impaired fasting glycaemia) .ti,ab
#16	(impaired glucose tolerance) .ti,ab
#17	(impaired glucose regulation) .ti,ab
#18	(glucose intolerance) .ti,ab
#19	(borderline diabetes) .ti,ab
#20	(impaired fasting insulin) .ti,ab
#21	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20
#22	Type 2 Diab*.ti
#23	diabetes.ti
#24	MeSH descriptor: [Insulin Resistance] explode all trees
#25	Type II diab*.ti
#26	NIDDM.ti
#27	Non insulin dependent diabetes.ti
#28	T2DM.ti
#29	MeSH descriptor: [Diabetes Mellitus] explode all trees
#30	obese diabetes.ti
#31	obesity diabetes.ti
#32	((adult or mature or late) and onset) .ti
#33	MODY.ti
#34	#22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33
#35	(screen*) .ti,ab.
#36	(prevent*) .ti,ab
#37	lifestyle.ti,ab
#38	(early detection) .ti,ab
#39	(risk near/2 identification$) .ti,ab
#40	(risk near/2 stratif$*) .ti,ab
#41	#35 or #36 or #37 or #38 or #39 or #40
#42	#34 and #41
#43	#21 or #42
#44	(non-diabet*) ti.ab
#45	animals.sh. not (humans.sh. and animals.sh.)
#46	#43 not #44
#47	#46 not #45
#48	*:ti,ab,kw Publication Year from 2000 to 2016 (Word variations have been searched)
#49	#47 and #48
#50	*:ti,ab,kw in Economic Evaluations (Word variations have been searched)
#51	#49 and #50

ti: title; ab: abstract

Appendix 3: Pro-forma for Data Extraction

Reviewer:	
Date form completed:	
Study Details:	
Title:	
Author:	
Year Published:	
Journal:	
Citation:	
Language:	

Economic evaluation details					**Location in text** (page/figure/ table/other)
Objective/scope of model:					
Location (country/city)					
Economic study design:	CEA	☐	CBA	☐	
	CUA	☐	CMA	☐	
	CCA	☐	Cost(s) only		
	Health outcomes(s)				
Perspective of analysis:	Societal	☐	Individual clinician	☐	
	Patient and patient family	☐	Insurer/third party payer	☐	
	Healthcare system	☐	Other:		
	Healthcare provider				
Primary costs/consequences/outcome measure(s) *(please list):*					
Strategies/comparators:					
Setting *(describe):*					
Patient population characteristics *(describe):*					
Prediabetes definition *(describe):*					
Time horizon of analysis:					
Was discounting used?	Discount rate for costs: ……		No discounting	☐	
	Discount rate for health outcomes: …….		N/A (no information, not relevant)	☐	

Modelling details			Location in text *(page/figure /table/other)*
Rationale for model structure:	Yes ☐ No ☐	If Yes please specify:	
Model structure *(paste structure):*			
Structural assumptions *(describe):*			
Have experts been asked to judge the appropriateness of the model?	Yes ☐ No ☐	If Yes please specify: 1. Who: 2. Why they are experts: 3. Level of agreement:	
Has the model been compared with other models found in the literature?	Yes ☐ No ☐	If Yes please provide reference/citation:	
Model type	Cohort-based decision tree (DT) ☐ Cohort-based State Transition model (MM) ☐ Individual patient-level DT ☐ Individual patient-level MM ☐ Discrete event simulation ☐ Agent-based model ☐ System dynamics model ☐ Other:		
Rationale for model type:	Yes ☐ No ☐	If Yes please specify:	
Cycle length *(if relevant):*			
Well defined disease states/pathways?	Yes ☐ No ☐	If Yes please specify:	
Natural history of diabetes evolution *(describe, e.g. discrete, homogeneous)*			
Likelihood of glycaemia returning to normal?	Yes ☐ No ☐	If Yes please specify from which state:	
Well defined complications in prediabetes state?	Yes ☐ No ☐	If Yes please specify:	
Well defined complications in type 2 state?	Yes ☐ No ☐	If Yes please specify:	

Modelling details			Location in text *(page/figure /table/other)*
Was patient heterogeneity modelled?	Prediabetes: Yes ☐ No ☐	If Yes please specify:	
	Type 2 diabetes: Yes ☐ No ☐	If Yes please specify:	

Data details			Location in text *(page/figure /table/other)*
Are methods for identifying input data reported?	Yes ☐ No ☐ If Yes please specify:		
Have experts been asked to judge the appropriateness of the input data?	Yes ☐ No ☐	If Yes please specify: 1. Who: 2. Why they are experts: 3. Level of agreement:	
When input parameters are based on regression models, have statistical tests been performed?	Yes ☐ No ☐	If Yes please specify tests:	
Source of baseline clinical data: Prediabetes state(s)	**1** Case series or analysis of reliable administrative databases specifically conducted for the study covering patients solely from the jurisdiction of interest.	☐	
	2 Recent case series or analysis of reliable administrative databases covering patients solely from the jurisdiction of interest.	☐	
	3 Recent case series or analysis of reliable administrative databases covering patients solely from another jurisdiction.	☐	
	4 Old case series or analysis of reliable administrative databases. Estimates from RCTs	☐	
	5 Estimates from previously published economic analyses: unsourced	☐	
	6 Expert opinion	☐	
	Other: Specify relevant data sources: More than 1 data source per parameter? Reasons for excluding data sources? Evidence synthesis performed? Calibration?	☐	

Data details			Location in text *(page/figure /table/other)*
Source of baseline clinical data: Type 2 diabetes state(s)	**1** Case series or analysis of reliable administrative databases specifically conducted for the study covering patients solely from the jurisdiction of interest	☐	
	2 Recent case series or analysis of reliable administrative databases covering patients solely from the jurisdiction of interest	☐	
	3 Recent case series or analysis of reliable administrative databases covering patients solely from another jurisdiction	☐	
	4 Old case series or analysis of reliable administrative databases. Estimates from RCTs	☐	
	5 Estimates from previously published economic analyses: unsourced	☐	
	6 Expert opinion	☐	
	Other: Specify relevant data sources: More than 1 data source per parameter? Reasons for excluding data sources? Evidence synthesis performed? Calibration?	☐	
Source of data for duration of primary effect (i.e. after end of follow-up of source of primary effect size)	**1** Analysis of reliable administrative databases specifically conducted for the study covering patients solely from the jurisdiction of interest	☐	
	2 Recent analysis of reliable administrative databases covering patients solely from the jurisdiction of interest	☐	
	3 Recent analysis of reliable administrative databases covering patients solely from another jurisdiction	☐	
	4 Old analysis of reliable administrative databases.	☐	
	5 Estimates from previously published economic analyses: unsourced	☐	
	6 Expert opinion	☐	
	Other: Specify relevant data sources: More than 1 data source per parameter? Reasons for excluding data sources? Evidence synthesis performed? Calibration?	☐	

Data details			Location in text *(page/figure /table/other)*
Source of data for primary effect size measure(s):	**1**+ Meta-analysis of RCTs with direct comparison between comparator therapies, measuring final outcomes.	☐	
	1 Single RCT with direct comparison between comparator therapies, measuring final outcomes	☐	
	2+ Meta-analysis of RCTs with direct comparison between comparator therapies, measuring surrogate outcomes	☐	
	Meta-analysis of placebo-controlled RCTs with similar trial populations, measuring final outcomes for each individual therapy	☐	
	2 Single RCT with direct comparison between comparator therapies, measuring surrogate outcomes	☐	
	Single placebo-controlled RCTs with similar trial populations, measuring final outcomes for each individual therapy	☐	
	3+ Meta-analysis of placebo-controlled RCTs with similar trial populations, measuring surrogate outcomes	☐	
	3 Single placebo-controlled RCTs with similar trial populations, measuring surrogate outcomes for each individual therapy		
	4 Case-control or cohort studies		
	5 Non-analytic studies, for example, case reports, case series		
	6 Expert opinion Specify relevant data sources: More than 1 data source per parameter? Reasons for excluding data sources? Evidence synthesis performed? Calibration?		

Data details			Location in text *(page/figure /table/other)*
Source of data for resource use:	**1** Prospective data collection or analysis of reliable administrative data from same jurisdiction for specific study	☐	
	2 Recently published results of prospective data collection or recent analysis of reliable administrative data – same jurisdiction	☐	
	3 Unsourced data from previous economic evaluations – same jurisdiction	☐	
	4 Recently published results of prospective data collection or recent analysis of reliable administrative data – different jurisdiction	☐	
	5 Unsourced data from previous economic evaluation – different jurisdiction	☐	
	6 Expert opinion		
	Other: Specify relevant data sources: More than 1 data source per parameter? Reasons for excluding data sources? Evidence synthesis performed? Calibration?		
Source of data for costs:	**1** Cost calculations based on reliable databases or data sources conducted for specific study – same jurisdiction	☐	
	2 Recently published cost calculations based on reliable databases or data sources – same jurisdiction	☐	
	3 Unsourced data from previous economic evaluation – same jurisdiction	☐	
	4 Recently published cost calculations based on reliable databases or data sources – different jurisdiction	☐	
	5 Unsourced data from previous economic evaluation – different jurisdiction	☐	
	6 Expert opinion		
	Other: Specify relevant data sources: More than 1 data source per parameter? Reasons for excluding data sources? Evidence synthesis performed? Calibration?		

Data details							Location in text *(page/figure /table/other)*
Costs included:	Direct medical	☐	Direct non-medical	☐	Productivity losses	☐	
	Direct treatment	☐	Social care	☐	Income forgone due to illness	☐	
	In-patient	☐	Social benefits	☐	Income forgone due to death	☐	
	Out-patient	☐	Travel costs	☐	Income forgone due to death	☐	
	Day care	☐	Caregiver out-of-pocket	☐			
	Community healthcare	☐	Criminal Justice	☐			
	Medication	☐	Training of staff	☐			
	Side effect costs	☐					
	or						
	Staff	☐					
	Medication						
	Labs/diagnostic	☐					
	Overhead	☐					
	Capital equipment	☐					
	Real estate	☐					
	Other:	☐					
		☐					
		☐					
		☐					
Currency/Price year:							
Were QOL estimates derived:	Yes	☐					
	No	☐					

Data details				Location in text *(page/figure /table/other)*
Source of data for quality of life/utilities:	**1** Direct utility assessment for the specific study from a sample:			
	a) of the general population		☐	
	b) with knowledge of the disease(s) of interest		☐	
	c) of patients with the disease(s) of interest		☐	
	1 Indirect utility assessment from specific study from a patient sample with disease(s) of interest: using a tool validated for the patient population		☐	
	2 Indirect utility assessment from specific study from a patient sample with disease(s) of interest using tool not validated for the patient population		☐	
	3 Direct utility assessment from a previous study from a sample either:		☐	
	a) of the general population		☐	
	b) with knowledge of the disease(s) of interest		☐	
	c) of patients with the disease(s) of interest		☐	
	3 Indirect utility assessment from previous study from patient sample with disease(s) of interest: using tool validated for the patient population		☐	
	4 Indirect utility assessment from previous study from patient sample with disease(s) of interest: using tool not validated for the patient population or method of elicitation unknown		☐	
	5 Patient preference values obtained from a visual analogue scale		☐	
	6 Delphi panels, expert opinion Specify relevant data sources: More than 1 data source per parameter? Reasons for excluding data sources? Evidence synthesis performed? Calibration?		☐	
If validated tools were used, which instrument(s):	Rosser Index	☐	Health Utilities Index (HUI) ☐	
	EQ-5D	☐	Quality of Well Being (QWB) ☐	
	15D	☐	SF-36 ☐	
	SF-12	☐	SF-6 ☐	

Data details		Location in text *(page/figure /table/other)*
Converted into utilities?	Yes ☐ No ☐ If Yes report value set:	
If direct elicitation was used, which approach(s):	Standard Gamble ☐ VAS ☐ Time trade-off ☐ Person trade-off ☐	
Utility values combined with survival to form QALYs?	Yes ☐ No ☐	
Were all data sources described and reported?	Yes ☐ No ☐	
Were mutually inconsistent data reported in the model?	Yes ☐ No ☐	If Yes were the choices justified?
Were data incorporated as point estimate or distribution?	Point estimate ☐ Distribution ☐ Both ☐	Which model inputs were incorporated as distributions (delete)? All; majority; minority; none Was the choice of distribution justified?
Model uncertainty	Methodological uncertainty ☐ If yes, describe: Structural uncertainty ☐ If yes, describe: Heterogeneity ☐ If yes, list subgroups: Parameter uncertainty ☐ If yes, list method:	
Model internal validation (mathematical logic and accuracy of coding)	Mathematical logic tested thoroughly before use ☐ Computerised model examined by modelling experts ☐ Model run for specific, extreme sets of parameter values to detect coding errors ☐ Patients tracked through model to determine if its logic is correct ☐ Tested individual sub-modules of the computerised model ☐ Other:	
Model external validation	Model outcomes compared with the outcomes of other models that address similar problems ☐ Counterintuitive results from model explained and justified ☐ Model outcomes compared with the outcomes obtained when using alternative input data ☐ Model outcomes compared with empirical data ☐ Model calibrated against independent data with differences explained and justified ☐ Other:	

Data details	Location in text *(page/figure /table/other)*
Result(s):	

Quality checklist score			
Risk of bias	High ☐	Medium ☐	Low ☐
Comments, limitations of the study			
Study, natural history and effectiveness data:			
Cost, Effects, methodology, uncertainty:			
Generalizability:			

Appendix 1: PRISMA-P checklist

Table A.1: PRISMA-P 2015 checklist

Section and topic	Item No.	Checklist Item	Reported on page #
A) Administrative Information			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	Identify protocol as an update of a previous systematic review if applicable	n/a
Registration	2	Name of registry and registration number	2+4
B) Authors			
Contact		Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions		Describe contributions of protocol authors and identify the guarantor of the review	8
Amendments		If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	n/a
Support			
- Sources	5a	Indicate Sources of financial or other support for the review	8
- Sponsor	5b	Provide name for the review funder and/or sponsor	8
- Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s) and/or institution(s), if any, in developing the protocol	n/a
C) Introduction			
Rationale	6	Describe the rationale for the review in the context of what is already known	4
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	4
D) Methods			
Eligibility Criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	5
Information Sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	5+6
Search Strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	5 + 6 + Appendix 2
E) Study Records			
Data Management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	6
Selection Process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	6
Data Collection Process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	6
Data Items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	6 + 7+ Appendix 3
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	6 + 7

Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	7
Data Synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	7
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency	n/a
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	n/a
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	7
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	n/a
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed	7

BMJ Open

Computer simulation models of prediabetes populations: a systematic review protocol

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Complete List of Authors:	Leal, Jose; University of Oxford, UK, Khurshid, Waqar; University of Oxford, UK Pagano, Eva; Unit of Cancer Epidemiology, "Città della Salute e della Scienza" Hospital and CPO Piemonte Feenstra, Talitha; National Institute for Public Health and the Environment (RIVM), Centre for Prevention and Health Services Research
Primary Subject Heading:	Diabetes and endocrinology
Secondary Subject Heading:	Health economics, Health policy, Public health
Keywords:	diabetes, economic evaluation, decision model, systematic review, HEALTH ECONOMICS, prediabetes

Computer simulation models of prediabetes populations: a systematic review protocol

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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 NHS EED. 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 used 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 pre-defined 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.

Systematic review registration: CRD42016047228

Keywords: diabetes, economic evaluation, decision model, systematic review, health economics, prediabetes

Strengths 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.

Limitations of the study

- 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 more than 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 over 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 America Diabetes Association, prediabetes is defined as a fasting plasma glucose level of 100 to 125 mg/dL (known as impaired fasting glucose - IFG), a 2-h plasma glucose level after a 75-g oral glucose tolerance test of 140 to 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 primary prevention intervention. However, pharmaceutical interventions, such as oral antidiabetic drugs and anti-obesity drugs, either compared to 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 prediabetic 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 such as 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 (e.g. costs, life years, quality adjusted life years, etc.) but have not been used to inform economic evaluations. Furthermore, the discussion in previous reviews about the quality of the decision models upon 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:

- Summarise peer-reviewed and published health economics decision models and model-based economic evaluations of populations of individuals with prediabetes.
- Assess the quality and validity of the decision models using best practice guidelines.
- 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 2015 (PRISMA-P) 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 Preferred Reporting Items for Systematic Review and Meta-Analysis (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 impaired fasting glucose, impaired glucose tolerance, 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 mature onset diabetes of the young (MODY).

Type of intervention

Decision models of disease progression of prediabetic 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 prediabetic populations and/or model-based economic evaluations of preventive interventions (e.g. 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 the several publications in our literature review but extract data based on the paper that describes the model in greater detail 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 1st January 2000 until 1st August 2016: Medline, Embase, Econlit and The Cochrane Library (for NHS EED). Articles were restricted to English-language literature but no geography restrictions were applied to the search. Abstracts or conference presentations will not be included as sufficient data is not presented to allow critical appraisal of the decision models. The exact search terms used in all databases are described in Appendix 1. 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, 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. Data extracted will include details on (see Appendix 2):

- Study: title, author and publication details
- 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.
- 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 (e.g. progression dependent on multiple risk factors for a given individual) and how.
- 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.
- Model uncertainty and validation: methods used to address methodological uncertainty, structural uncertainty, parameter uncertainty and heterogeneity; model internal and external validation.
- Results, quality checklist score and comments and limitations of the study

Risk of bias (quality) assessment

The Philips et al.[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 guidance.[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 is 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

Ethics and dissemination

This systematic review is exempt from ethics approval and consent to participate because the work is carried out on published documents. We will disseminate the findings in a related peer-reviewed journal.

Declarations

Funding

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Competing interests

The authors declare that they have no competing interests.

Authors' contributions

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.

Ethics approval and consent to participate

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

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Computer simulation models of prediabetes populations: a systematic review protocol

Appendices

Appendix 1: Search strategy

Table A.1.1: Ovid MEDLINE

Searches	Search Terms
1	exp prediabetic state/
2	exp insulin resistance/
3	prediab$.ti,ab.
4	pre diab$.ti,ab.
5	(glucose adj2 impair$).ti,ab.
6	(glucose adj2 intol$).ti,ab.
7	IGT.ti,ab.
8	IFG.ti,ab.
9	IGR.ti,ab.
10	(impair$ adj2 glycem$).ti,ab.
11	(impair$ adj2 glycaem$).ti,ab.
12	(insulin adj2 resistan$).ti,ab.
13	impaired fasting glucose.ti,ab.
14	impaired fasting glycaem$.ti,ab.
15	impaired fasting glycem$.ti,ab.
16	impaired glucose tolerance.ti,ab.
17	impaired glucose regulation.ti,ab.
18	glucose intolerance.ti,ab.
19	borderline diabetes.ti,ab.
20	impaired fasting insulin.ti,ab.
21	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20
22	Type 2 Diab$.ti.
23	diabetes.ti.
24	exp insulin resistance/
25	Type II diab$.ti.
26	NIDDM.ti.
27	Non insulin dependent diabetes.ti.
28	T2DM.ti.
29	exp diabetes mellitus, Type 2/
30	obese diabetes.ti.
31	obesity diabetes.ti.
32	((adult or mature or late) and onset).ti.
33	MODY.ti.
34	22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33
35	screen$.ti,ab.
36	prevent$.ti,ab.
37	lifestyle.ti,ab.
38	early detection.ti,ab.
39	(risk adj2 stratifi$).ti,ab.
40	(risk adj2 identification$).ti,ab.
41	35 or 36 or 37 or 38 or 39 or 40
42	34 and 41
43	simulation model$.ti,ab.
44	markov.ti,ab.
45	monte carlo.ti,ab.
46	decision tree$.ti,ab.
47	decision analy$.ti,ab.
48	qaly$.ti,ab.
49	(valu$ adj2 quality).ti,ab.
50	utility value$.ti,ab.
51	((disability or quality) adj adjusted).ti,ab.
52	((life adj2 year$) or health year equivalent$).ti,ab.
53	(health adj utilit$).ti,ab.
54	hui$1.ti,ab.

55	(quality adj3 well$).ti,ab.
56	qwb.ti,ab.
57	(qald$ or qale$ or qtime$).ti,ab.
58	(well being or wellbeing).tw.
59	(health adj2 stat$).tw.
60	((adjusted adj2 life) or qaly$).ti,ab.
61	(daly or qol or hql or hqol or hrqol or hr ql or hrql).tw.
62	cost-utility.ti,ab.
63	cost-effectiveness.ti,ab.
64	cost-benefit.ti,ab.
65	cost-minimisation.ti,ab.
66	cost-minimization.ti,ab.
67	modelling.ti,ab.
68	modeling.ti,ab.
69	decision model.ti,ab.
70	QALY.ti,ab.
71	quality adjusted life year$.ti,ab.
72	cost.ti,ab.
73	life year$.ti,ab.
74	incremental cost-effectiveness ratio.ti,ab.
75	(qtwist or q twist).ti,ab.
76	(quality adj2 life).ti,ab.
77	43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76
78	21 or 42
79	77 and 78
80	non-diabet$.ti,ab.
81	79 not 80
82	exp animals/ not human.sh.
83	81 and 82
84	limit 83 to yr="2000 -Current"
85	limit 84 to english language

ti: title; ab: abstract

Table A.1.2: OVID Embase

Searches	Search Terms
1	exp impaired glucose tolerance/
2	exp insulin resistance/
3	prediab$.ti,ab.
4	pre diab$.ti,ab.
5	(glucose adj2 impair$).ti,ab.
6	(glucose adj2 impair$).ti,ab.
7	IGT.ti,ab.
8	IFG.ti,ab.
9	IGR.ti,ab.
10	(impair$ adj2 glycem$).ti,ab.
11	(impair$ adj2 glycaem$).ti,ab.
12	(insulin adj2 resistan$).ti,ab.
13	impaired fasting glucose.ti,ab.
14	impaired fasting glycaem$.ti,ab.
15	impaired fasting glycem$.ti,ab.
16	impaired glucose tolerance.ti,ab.
17	impaired glucose regulation.ti,ab.
18	glucose intolerance.ti,ab.
19	borderline diabetes.ti,ab.
20	impaired fasting insulin.ti,ab.
21	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20
22	Type 2 Diab$.ti.
23	diabetes.ti.
24	exp insulin resistance/
25	Type II diab$.ti.
26	NIDDM.ti.
27	Non insulin dependent diabetes.ti.
28	T2DM.ti.
29	exp non insulin dependent diabetes mellitus/
30	obese diabetes.ti.
31	obesity diabetes.ti.
32	((adult or mature or late) and onset).ti.
33	MODY.ti.
34	22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33
35	screen$.ti,ab.
36	prevent$.ti,ab.
37	lifestyle.ti,ab.
38	early detection.ti,ab.
39	(risk adj2 stratifi$).ti,ab.
40	(risk adj2 identification$).ti,ab.
41	35 or 36 or 37 or 38 or 39 or 40
42	34 and 41
43	simulation model$.ti,ab.
44	markov.ti,ab.
45	monte carlo.ti,ab.
46	decision tree$.ti,ab.
47	decision analy$.ti,ab.
48	qaly$.ti,ab.
49	(valu$ adj2 quality).ti,ab.
50	utility value$.ti,ab.
51	((disability or quality) adj adjusted).ti,ab.
52	((life adj2 year$) or health year equivalent$).ti,ab.
53	(health adj utilit$).ti,ab.
54	hui$1.ti,ab.
55	(quality adj3 well$).ti,ab.
56	qwb.ti,ab.
57	(qald$ or qale$ or qtime$).ti,ab.
58	(well being or wellbeing).tw.
59	(health adj2 stat$).tw.
60	((adjusted adj2 life) or qaly$).ti,ab.
61	(daly or qol or hql or hqol or hrqol or hr ql or hrql).tw.
62	cost-utility.ti,ab.
63	cost-effectiveness.ti,ab.

64	cost-benefit.ti,ab.
65	cost-minimisation.ti,ab.
66	cost-minimization.ti,ab.
67	modelling.ti,ab.
68	modeling.ti,ab.
69	decision model.ti,ab.
70	QALY.ti,ab.
71	quality adjusted life year$.ti,ab.
72	cost.ti,ab.
73	life year$.ti,ab.
74	incremental cost-effectiveness ratio.ti,ab.
75	(qtwist or q twist).ti,ab.
76	(quality adj2 life).ti,ab.
77	43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76
78	21 or 42
79	77 and 78
80	non-diabet$.ti,ab.
81	79 not 80
82	exp animals/ not human.sh.
83	81 not 82
84	limit 83 to yr="2000 -Current"
85	limit 84 to english language

ti: title; ab: abstract

Table A.1.3: NHS EED (via the Cochrane Library)

Searches	Search Terms
#1	MeSH descriptor: [Prediabetic State] explode all trees
#2	MeSH descriptor: [Insulin Resistance] explode all trees
#3	(prediab*) .ti,ab
#4	(pre diab*) .ti,ab
#5	(glucose near/2 impair*) .ti,ab
#6	(glucose adj2 intol*) .ti,ab
#7	(IGT) .ti,ab
#8	(IFG) .ti,ab
#9	(IGR) .ti,ab
#10	(impair* near/2 glycem*) .ti,ab
#11	(impair* near/2 glycaem*) .ti,ab
#12	(insulin near/2 resistan*) .ti,ab
#13	(impaired fasting glucose) .ti,ab
#14	(impaired fasting glycemia) .ti,ab
#15	(impaired fasting glycaemia) .ti,ab
#16	(impaired glucose tolerance) .ti,ab
#17	(impaired glucose regulation) .ti,ab
#18	(glucose intolerance) .ti,ab
#19	(borderline diabetes) .ti,ab
#20	(impaired fasting insulin) .ti,ab
#21	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20
#22	Type 2 Diab*.ti
#23	diabetes.ti
#24	MeSH descriptor: [Insulin Resistance] explode all trees
#25	Type II diab*.ti
#26	NIDDM.ti
#27	Non insulin dependent diabetes.ti
#28	T2DM.ti
#29	MeSH descriptor: [Diabetes Mellitus] explode all trees
#30	obese diabetes.ti
#31	obesity diabetes.ti
#32	((adult or mature or late) and onset) .ti
#33	MODY.ti
#34	#22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33
#35	(screen*) .ti,ab.
#36	(prevent*) .ti,ab
#37	lifestyle.ti,ab
#38	(early detection) .ti,ab
#39	(risk near/2 identification$) .ti,ab
#40	(risk near/2 stratif$*) .ti,ab
#41	#35 or #36 or #37 or #38 or #39 or #40
#42	#34 and #41
#43	#21 or #42
#44	(non-diabet*) ti.ab
#45	animals.sh. not (humans.sh. and animals.sh.)
#46	#43 not #44
#47	#46 not #45
#48	*:ti,ab,kw Publication Year from 2000 to 2016 (Word variations have been searched)
#49	#47 and #48
#50	*:ti,ab,kw in Economic Evaluations (Word variations have been searched)
#51	#49 and #50

ti: title; ab: abstract

Table A.1.4: Econlit (via ProQuest)

(ti,ab(prediab*) OR ti,ab(pre-diab*) OR ti,ab(glucose NEAR/2 impair*) OR ti,ab(glucose NEAR/2 intol*) OR ti,ab(voigt) OR ti,ab(ifs) OR ti,ab(igor) OR ti,ab(impair* NEAR/2 glycem*) OR ti,ab(impair* NEAR/2 glycaem*) OR ti,ab(insulin NEAR/2 resistan*) OR ti,ab(impaired fasting glucose) OR ti,ab(impaired fasting glycemia) OR ti,ab(impaired fasting glycaemia) OR ti,ab(impaired glucose tolerance) OR ti,ab(impaired glucose regulation) OR ti,ab(glucose intolerance) OR ti,ab(borderline diabetes) OR ti,ab(impaired fasting insulin))

OR

((ti(Type 2 Diab*) OR ti(diabetes) OR ti(Type II diab*) OR ti(NIDDM) OR ti(Non insulin dependent diabetes) OR ti(T2DM) OR ti(obese diabetes) OR ti((adult OR mature OR late) AND onset) OR ti(MODY))

AND

(ti,ab(screen*) OR ti,ab(prevent*) OR ti,ab(lifestyle) OR ti,ab(early detection) OR ti,ab(risk NEAR/2 identification*) OR (risk NEAR/2 stratif*)))

Restricted to English Language, peer-reviewed and studies published between 1st January 2000 and 1st August 2016.

Appendix 2: Pro-forma for Data Extraction

Reviewer:	
Date form completed:	
Study Details:	
Title:	
Author:	
Year Published:	
Journal:	
Citation:	
Language:	

Economic evaluation details					**Location in text** (page/figure/ table/other)
Objective/scope of model:					
Location (country/city)					
Economic study design:	CEA	☐	CBA	☐	
	CUA	☐	CMA	☐	
	CCA	☐	Cost(s) only	☐	
	Health outcomes(s)	☐			
Perspective of analysis:	Societal	☐	Individual clinician	☐	
	Patient and patient family	☐	Insurer/third party payer	☐	
	Healthcare system	☐	Other:		
	Healthcare provider	☐			
Costs/consequences/outcome measure(s) *(please list):*					
Strategies/comparators:					
Setting *(describe):*					
Patient population characteristics *(describe):*					
Prediabetes definition *(describe):*					
Time horizon of analysis:					
Was discounting used?	Discount rate for costs: ……	☐	No discounting	☐	
	Discount rate for health outcomes: …….	☐	N/A (no information, not relevant)	☐	

Modelling details				Location in text *(page/figure /table/other)*
Rationale for model structure:	Yes ☐ No ☐		If Yes please specify:	
Model structure *(paste structure):*				
Structural assumptions *(describe):*				
Have experts been asked to judge the appropriateness of the model?	Yes ☐ No ☐		If Yes please specify: 1. Who: 2. Why they are experts: 3. Level of agreement:	
Has the model been compared with other models found in the literature?	Yes ☐ No ☐		If Yes please provide reference/citation:	
Model type	Cohort-based decision tree (DT)	☐		
	Cohort-based State Transition model (MM)	☐		
	Individual patient-level DT	☐		
	Individual patient-level MM	☐		
	Discrete event simulation	☐		
	Agent-based model			
	System dynamics model			
	Other:			
Rationale for model type:	Yes ☐ No ☐		If Yes please specify:	
Cycle length *(if relevant):*				
Well defined disease states/pathways?	Yes ☐ No ☐		If Yes please specify:	
Natural history of diabetes evolution *(describe, e.g. discrete, homogeneous)*				
Likelihood of glycaemia returning to normal?	Yes ☐ No ☐		If Yes please specify from which state:	
Well defined complications in prediabetes state?	Yes ☐ No ☐		If Yes please specify:	
Well defined complications in type 2 state?	Yes ☐ No ☐		If Yes please specify:	

Modelling details			Location in text *(page/figure /table/other)*
Was patient heterogeneity modelled?	Prediabetes: Yes ☐ No ☐	If Yes please specify:	
	Type 2 diabetes: Yes ☐ No ☐	If Yes please specify:	

Data details			Location in text *(page/figure /table/other)*
Are methods for identifying input data reported?	Yes ☐ No ☐ If Yes please specify:		
Have experts been asked to judge the appropriateness of the input data?	Yes ☐ No ☐	If Yes please specify: 1. Who: 2. Why they are experts: 3. Level of agreement:	
When input parameters are based on regression models, have statistical tests been performed?	Yes ☐ No ☐	If Yes please specify tests:	
Source of baseline clinical data: Prediabetes state(s)	**1** Case series or analysis of reliable administrative databases specifically conducted for the study covering patients solely from the jurisdiction of interest.	☐	
	2 Recent case series or analysis of reliable administrative databases covering patients solely from the jurisdiction of interest.	☐	
	3 Recent case series or analysis of reliable administrative databases covering patients solely from another jurisdiction.	☐	
	4 Old case series or analysis of reliable administrative databases. Estimates from RCTs	☐	
	5 Estimates from previously published economic analyses: unsourced	☐	
	6 Expert opinion	☐	
	Other: Specify relevant data sources: More than 1 data source per parameter? Reasons for excluding data sources? Evidence synthesis performed? Calibration?	☐	

Data details			Location in text *(page/figure /table/other)*
Source of baseline clinical data: Type 2 diabetes state(s)	**1** Case series or analysis of reliable administrative databases specifically conducted for the study covering patients solely from the jurisdiction of interest	☐	
	2 Recent case series or analysis of reliable administrative databases covering patients solely from the jurisdiction of interest	☐	
	3 Recent case series or analysis of reliable administrative databases covering patients solely from another jurisdiction	☐	
	4 Old case series or analysis of reliable administrative databases. Estimates from RCTs	☐	
	5 Estimates from previously published economic analyses: unsourced	☐	
	6 Expert opinion	☐	
	Other: Specify relevant data sources: More than 1 data source per parameter? Reasons for excluding data sources? Evidence synthesis performed? Calibration?	☐	
Source of data for duration of primary effect (i.e. after end of follow-up of source of primary effect size)	**1** Analysis of reliable administrative databases specifically conducted for the study covering patients solely from the jurisdiction of interest	☐	
	2 Recent analysis of reliable administrative databases covering patients solely from the jurisdiction of interest	☐	
	3 Recent analysis of reliable administrative databases covering patients solely from another jurisdiction	☐	
	4 Old analysis of reliable administrative databases.	☐	
	5 Estimates from previously published economic analyses: unsourced	☐	
	6 Expert opinion	☐	
	Other: Specify relevant data sources: More than 1 data source per parameter? Reasons for excluding data sources? Evidence synthesis performed? Calibration?	☐	

Data details			Location in text *(page/figure /table/other)*
Source of data for primary effect size measure(s):	**1**+ Meta-analysis of RCTs with direct comparison between comparator therapies, measuring final outcomes.	☐	
	1 Single RCT with direct comparison between comparator therapies, measuring final outcomes	☐	
	2+ Meta-analysis of RCTs with direct comparison between comparator therapies, measuring surrogate outcomes	☐	
	Meta-analysis of placebo-controlled RCTs with similar trial populations, measuring final outcomes for each individual therapy	☐	
	2 Single RCT with direct comparison between comparator therapies, measuring surrogate outcomes	☐	
	Single placebo-controlled RCTs with similar trial populations, measuring final outcomes for each individual therapy	☐	
	3+ Meta-analysis of placebo-controlled RCTs with similar trial populations, measuring surrogate outcomes	☐	
	3 Single placebo-controlled RCTs with similar trial populations, measuring surrogate outcomes for each individual therapy	☐	
	4 Case-control or cohort studies	☐	
	5 Non-analytic studies, for example, case reports, case series	☐	
	6 Expert opinion Specify relevant data sources: More than 1 data source per parameter? Reasons for excluding data sources? Evidence synthesis performed? Calibration?	☐	

Data details			Location in text *(page/figure /table/other)*
Source of data for resource use:	**1** Prospective data collection or analysis of reliable administrative data from same jurisdiction for specific study	☐	
	2 Recently published results of prospective data collection or recent analysis of reliable administrative data – same jurisdiction	☐	
	3 Unsourced data from previous economic evaluations – same jurisdiction	☐	
	4 Recently published results of prospective data collection or recent analysis of reliable administrative data – different jurisdiction	☐	
	5 Unsourced data from previous economic evaluation – different jurisdiction	☐	
	6 Expert opinion	☐	
	Other: Specify relevant data sources: More than 1 data source per parameter? Reasons for excluding data sources? Evidence synthesis performed? Calibration?	☐	
Source of data for costs:	**1** Cost calculations based on reliable databases or data sources conducted for specific study – same jurisdiction	☐	
	2 Recently published cost calculations based on reliable databases or data sources – same jurisdiction	☐	
	3 Unsourced data from previous economic evaluation – same jurisdiction	☐	
	4 Recently published cost calculations based on reliable databases or data sources – different jurisdiction	☐	
	5 Unsourced data from previous economic evaluation – different jurisdiction	☐	
	6 Expert opinion	☐	
	Other: Specify relevant data sources: More than 1 data source per parameter? Reasons for excluding data sources? Evidence synthesis performed? Calibration?	☐	

Data details							Location in text *(page/figure /table/other)*
Costs included:	Direct medical	☐	Direct non-medical	☐	Productivity losses	☐	
	Direct treatment	☐	Social care	☐	Income forgone due to illness	☐	
	In-patient	☐	Social benefits	☐	Income forgone due to death	☐	
	Out-patient	☐	Travel costs	☐	Income forgone due to death	☐	
	Day care	☐	Caregiver out-of-pocket	☐			
	Community healthcare	☐	Criminal Justice	☐			
	Medication	☐	Training of staff	☐			
	Side effect costs	☐					
	or						
	Staff	☐					
	Medication	☐					
	Labs/diagnostic	☐					
	Overhead	☐					
	Capital equipment	☐					
	Real estate	☐					
	Other:	☐					
Currency/Price year:							
Were QOL estimates derived:	Yes ☐						
	No ☐						

Data details				Location in text *(page/figure /table/other)*
Source of data for quality of life/utilities:	**1** Direct utility assessment for the specific study from a sample:			
	a) of the general population		☐	
	b) with knowledge of the disease(s) of interest		☐	
	c) of patients with the disease(s) of interest		☐	
	1 Indirect utility assessment from specific study from a patient sample with disease(s) of interest: using a tool validated for the patient population		☐	
	2 Indirect utility assessment from specific study from a patient sample with disease(s) of interest using tool not validated for the patient population		☐	
	3 Direct utility assessment from a previous study from a sample either:		☐	
	a) of the general population		☐	
	b) with knowledge of the disease(s) of interest		☐	
	c) of patients with the disease(s) of interest		☐	
	3 Indirect utility assessment from previous study from patient sample with disease(s) of interest: using tool validated for the patient population		☐	
	4 Indirect utility assessment from previous study from patient sample with disease(s) of interest: using tool not validated for the patient population or method of elicitation unknown		☐	
	5 Patient preference values obtained from a visual analogue scale		☐	
	6 Delphi panels, expert opinion Specify relevant data sources: More than 1 data source per parameter? Reasons for excluding data sources? Evidence synthesis performed? Calibration?		☐	
If validated tools were used, which instrument(s):	Rosser Index	☐	Health Utilities Index (HUI)	☐
	EQ-5D	☐	Quality of Well Being (QWB)	☐
	15D	☐	SF-36	☐
	SF-12	☐	SF-6	☐

Data details		Location in text *(page/figure /table/other)*
Converted into utilities?	Yes ☐ No ☐ If Yes report value set:	
If direct elicitation was used, which approach(s):	Standard Gamble ☐ VAS ☐ Time trade-off ☐ Person trade-off ☐	
Utility values combined with survival to form QALYs?	Yes ☐ No ☐	
Were all data sources described and reported?	Yes ☐ No ☐	
Were mutually inconsistent data reported in the model?	Yes ☐ No ☐	If Yes were the choices justified?
Were data incorporated as point estimate or distribution?	Point estimate ☐ Distribution ☐ Both ☐	Which model inputs were incorporated as distributions (delete)? All; majority; minority; none Was the choice of distribution justified?
Model uncertainty	Methodological uncertainty ☐ If yes, describe: Structural uncertainty ☐ If yes, describe: Heterogeneity ☐ If yes, list subgroups: Parameter uncertainty ☐ If yes, list method:	
Model internal validation (mathematical logic and accuracy of coding)	Mathematical logic tested thoroughly before use ☐ Computerised model examined by modelling experts ☐ Model run for specific, extreme sets of parameter values to detect coding errors ☐ Patients tracked through model to determine if its logic is correct ☐ Tested individual sub-modules of the computerised model ☐ Other:	
Model external validation	Model outcomes compared with the outcomes of other models that address similar problems ☐ Counterintuitive results from model explained and justified ☐ Model outcomes compared with the outcomes obtained when using alternative input data ☐ Model outcomes compared with empirical data ☐ Model calibrated against independent data with differences explained and justified ☐ Other:	

Data details	Location in text *(page/figure /table/other)*
Result(s):	

Quality checklist score			
Risk of bias	High ☐	Medium ☐	Low ☐
Comments, limitations of the study			
Study, natural history and effectiveness data:			
Cost, Effects, methodology, uncertainty:			
Generalizability:			

Appendix 1: PRISMA-P checklist

Table A.1: PRISMA-P 2015 checklist

Section and topic	Item No.	Checklist Item	Reported on page #
A) Administrative Information			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	Identify protocol as an update of a previous systematic review if applicable	n/a
Registration	2	Name of registry and registration number	2+4
B) Authors			
Contact		Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions		Describe contributions of protocol authors and identify the guarantor of the review	8
Amendments		If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	n/a
Support			
- Sources	5a	Indicate Sources of financial or other support for the review	8
- Sponsor	5b	Provide name for the review funder and/or sponsor	8
- Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s) and/or institution(s), if any, in developing the protocol	n/a
C) Introduction			
Rationale	6	Describe the rationale for the review in the context of what is already known	4
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	4
D) Methods			
Eligibility Criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	5
Information Sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	5+6
Search Strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	5 + 6 + Appendix 2
E) Study Records			
Data Management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	6
Selection Process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	6
Data Collection Process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	6
Data Items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	6 + 7+ Appendix 3
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	6 + 7

Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	7
Data Synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	7
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency	n/a
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	n/a
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	7
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	n/a
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed	7