


ORIGINAL ARTICLE

Decision models of prediabetes populations: A systematic review

Jose Leal DPhil¹  | Liam Mc Morrow PhD¹  | Waqar Khurshid MSc¹ |
Eva Pagano MSc² | Talitha Feenstra PhD^{3,4} 

¹Health Economics Research Centre, Nuffield Department of Population Health, University of Oxford, Oxford, UK

²Unit of Clinical Epidemiology and CPO Piemonte, Città della Salute e della Scienza Hospital, Turin, Italy

³Groningen University, UMCG, Department of Epidemiology, Groningen, The Netherlands

⁴RIVM, Bilthoven, The Netherlands

Correspondence

Talitha Feenstra, PhD, Groningen University, UMCG, Department of Epidemiology, Groningen, The Netherlands.
Email: talitha.feenstra@rivm.nl

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Aims: With evidence supporting the use of preventive interventions for prediabetes populations and the use of novel biomarkers to stratify the risk of progression, there is a need to evaluate their cost-effectiveness across jurisdictions. Our aim is to summarize and assess the quality and validity of decision models and model-based economic evaluations of populations with prediabetes, to evaluate their potential use for the assessment of novel prevention strategies and to discuss the knowledge gaps, challenges and opportunities.

Materials and methods: We searched Medline, Embase, EconLit and NHS EED between 2000 and 2018 for studies reporting computer simulation models of the natural history of individuals with prediabetes and/or we used decision models to evaluate the impact of treatment strategies on these populations. Data were extracted following PRISMA guidelines and assessed using modelling checklists. Two reviewers independently assessed 50% of the titles and abstracts to determine whether a full text review was needed. Of these, 10% was assessed by each reviewer to cross-reference the decision to proceed to full review. Using a standardized form and double extraction, each of four reviewers extracted 50% of the identified studies.

Results: A total of 29 published decision models that simulate prediabetes populations were identified. Studies showed large variations in the definition of prediabetes and model structure. The inclusion of complications in prediabetes (n = 8) and type 2 diabetes (n = 17) health states also varied. A minority of studies simulated annual changes in risk factors (glycaemia, HbA1c, blood pressure, BMI, lipids) as individuals progressed in the models (n = 7) and accounted for heterogeneity among individuals with prediabetes (n = 7).

Conclusions: Current prediabetes decision models have considerable limitations in terms of their quality and validity and do not allow evaluation of stratified strategies using novel biomarkers, highlighting a clear need for more comprehensive prediabetes decision models.

KEYWORDS

biomarker, decision model, economic evaluation, prediabetes, stratified treatment, systematic review

1 | INTRODUCTION

Diabetes is one of the most prevalent chronic diseases, with over 90% of individuals with diabetes having type 2 diabetes (T2D).¹ Major cardiovascular events such as myocardial infarction and stroke are common in individuals with diabetes and there is a highly significant

association between glycaemic levels and the development of diabetes-related complications.²

Early identification and management of individuals at risk of T2D provides an opportunity to prevent or delay its development. Individuals with prediabetes, a condition characterized by intermediate hyperglycaemia, that is, impaired fasting glucose (IFG) and/or impaired glucose

tolerance (IGT), are at high risk of developing diabetes.³ In addition, individuals with prediabetes may face an increased risk of cardiovascular disease, early stage nephropathy, chronic kidney disease and diabetic retinopathy.³

Lifestyle interventions in the form of diet and physical activity⁴⁻⁷ and/or pharmacological interventions^{8,9} have been shown to prevent or delay the onset of T2D in individuals with prediabetes. New developments concerning biomarkers for glycaemic deterioration potentially allow a more detailed stratification of the risk of developing diabetes, its progression and evaluation of novel treatments.¹⁰⁻¹² Such risk stratification strategies, based on biomarkers and clinical characteristics, could allow optimizing the management of individuals with prediabetes and diabetes based on expected treatment response, pharmacological or non-pharmacological, the likelihood of developing diabetes or complications and the potential for disease remission.^{13,14}

As the number of preventive interventions for individuals with prediabetes grows, based on risk stratification or not, there is an increased need to assess whether the potential health gains justify the cost of implementation. Decision analysis models, based on computer simulations, are well suited to provide such evidence in the setting and time frame of interest to decision makers.¹⁵ This is particularly relevant in prediabetes and diabetes, which develop over a long period of time.^{1,16,17}

Several models have been developed and validated for T2D populations and used in a variety of ways, such as estimating long-term clinical outcomes and costs of a clinical trial and aiding decision makers in choosing between available interventions in these populations.^{16,18-20} Similar to the situation with T2D, computer models of prediabetes populations must be clinically credible, based on the best available evidence, and must be reproducible and validated against clinical data. Furthermore, novel biomarkers and risk stratification introduce new requirements for these models, such as explicit modelling of screening and management of individuals at risk, simulating glycaemic deterioration trajectories over time and translating these trajectories into diabetes onset and progression. Evaluating novel diabetes-prevention programmes requires more comprehensive models capable of translating changes in several risk factors (eg, BMI, blood pressure) into lifetime costs and outcomes in a way that allows the possible inclusion of benefits broader than simply the prevention of diabetes itself (eg, heart disease, cancer). In addition, it must be ensured that the estimated prevention of cardiovascular and non-cardiovascular events is not overestimated in these populations.

The aim of this systematic review was to summarize and assess the quality and validity of peer-reviewed and published decision models that simulate progression from prediabetes onset onwards and report health economics outcomes. We also evaluated the potential of these models to inform the evaluation of novel prevention strategies that use stratification and/or target more than one risk factor. Finally, we identified and discussed the research gaps to be addressed to inform future evaluations targeting prediabetes populations, based on computer models.

2 | MATERIALS AND METHODS

The protocol for the literature review was registered in the PROSPERO international prospective register of systematic reviews

(registration number CRD42016047228) and has been published elsewhere.²¹ We did not deviate from the published protocol. Briefly, we searched Medline (via OVID), Embase (via OVID), EconLit (via ProQuest) and NHS EED (via the Cochrane Library) between 2000 and 2018 for peer-reviewed studies that reported computer simulation models of the natural history of individuals with prediabetes and/or used decision models to evaluate the impact of interventions on these populations. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed.²² Search terms are described online in Supporting Information (Appendix S1; Supporting Information Tables SA1.1-SA1.4). Studies were restricted to those published in the English language since 2000. No geography restrictions were applied to the search. Abstracts or conference presentations were not included as these are without sufficient data to allow critical appraisal of the decision models. The reference lists of the studies identified in the review were also searched, as well as those of previous literature reviews.

The inclusion criteria used to identify relevant studies were as follows:

- Studies with decision models of disease progression of prediabetes populations that reported health economics outcomes such as costs, (quality-adjusted) life expectancy and diabetes-related complications;
- Studies with model-based economic evaluations of intervention(s) aimed at prediabetes populations such as cost-consequences, cost-utility, cost-effectiveness and cost-minimization studies.

Any recognized method of establishing prediabetes in an individual was considered, including, but not limited to, impaired fasting glucose (IFG), impaired glucose tolerance (IGT), raised fasting plasma glucose or raised glycated haemoglobin (HbA1c). Studies concerning pre-existing diagnosis of diabetes were excluded as well as studies in gestational diabetes or mature onset diabetes of the young (MODY). Economic evaluations that reported solely short-term outcomes such as incidence of type 2 diabetes and/or cases detected and costs following screening/detection were excluded.

References were managed using ENDNOTE X7, Thomson Reuters. Duplicates were removed by one reviewer, after which two reviewers independently assessed 50% of the titles and abstracts to determine whether a full text review was necessary. A further 10% was assessed by each reviewer to cross-reference the decision to proceed to full review. Any disagreement between the two reviewers was resolved by inclusion of a third reviewer for assessment.

Data extraction was performed using a standardised form (Appendix S3). If a decision model was found to be associated with multiple publications, data were extracted from the study that described the model in greater detail, the model supported by other publications and online documentation that was judged to be relevant. Four reviewers each extracted 50% of the identified studies, with each study seen by two reviewers. Any disagreements were resolved by consensus.

The main outcomes analysed were: 1) prediabetes definition used; 2) model structure and rationale; 3) incorporation of individual heterogeneity; 4) hierarchy of evidence informing baseline clinical

data, primary effect size and duration of primary effect, resource use, costs and quality of life/utilities; 5) model uncertainty and validation. We used a hierarchy of evidence developed for economic analyses in which the data source used to inform a certain aspect of the model is awarded a score of one (highest quality) to six (lowest quality, expert opinion).²³ See "Data Details" in the Data Extraction form for full definitions of the hierarchy scale and respective rank (Appendix S3).

Two reviewers independently performed a quality appraisal of the studies. The Philips et al.²⁴ checklist was used to assess the quality of reporting of the decision models and model-based economic evaluations, as recommended in the Cochrane Handbook for Systematic Reviews of Interventions.²⁵ The AdViSHE (A Validation-Assessment Tool of Health-Economic Models for Decision Makers and Model Users)²⁶ checklist was used to assess model validation. The AdViSHE checklist was developed to support structured reporting of the model validation efforts performed and to increase model transparency. For the current review, it was used as a checklist to determine which aspects of model validity were reported in the publications. Disagreements were resolved by consensus and arbitration by a third reviewer. We had problems in consistently scoring the Phillips checklist, given the potential interpretations of its 57 items and we needed additional rounds of consensus seeking to reach the final agreement. Findings from the review were synthesised in a narrative format.

This systematic review is exempt from ethics approval and consent of participants because the work was carried out with published documents.

3 | RESULTS

A total of 29 studies were identified that reported decision models simulating prediabetes populations from at least the onset of prediabetes onwards. Figure 1 shows the flow of studies throughout the review. An overview of each model is outlined in Table 1, sorted by year of publication. Models were set in the USA (n = 6, 21%),^{29,30,32,42,44,50} the UK (n = 3, 10%),^{35,51,52} Australia (n = 3, 10%),^{34,37,46} other European countries (n = 7, 24%),^{33,36,39,41,43,47,54} the Americas (n = 3, 10%),^{27,38,45} Asia (n = 5, 17%)^{40,48,49,53,55} and in multiple countries (n = 2, 7%).^{28,31} The type of intervention evaluated included screening programmes (n = 3, 10%), interventions (lifestyle and/or pharmacological) (n = 8, 28%), screening plus intervention (n = 17, 59%) and current care only (n = 1, 3%) (more detail in Appendix S2; Supporting Information Table SA.2.1). A total of 14 (48%) models presented results from the perspective of the healthcare payer (ie, included medical costs reimbursed by public single payer or third-party payers); 12 (41%) models used the societal perspective; one (3%) model used the perspective of the healthcare provider; one (3%) model did not report the perspective; and one (3%) model did not include costs. Cohort Markov models (n = 12, 41%) and micro-simulation models (n = 9, 31%) were the most common. The majority of models implemented an annual cycle length (n = 26, 90%), accounted for costs and outcomes over 20 years or more (n = 20, 69%), and involved cost-utility (n = 23, 79%) or cost-effectiveness analysis (n = 3, 10%). Almost all studies reported that interventions were cost-effective relative to usual care or to no intervention

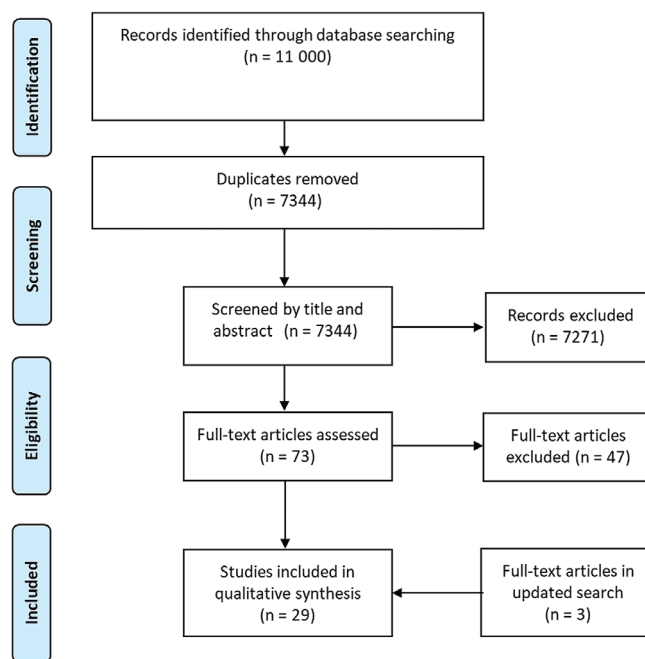


FIGURE 1 PRISMA diagram

(n = 24, 83%) (Appendix S2; Supporting Information Table SA.2.1). Only two studies reported that interventions were not cost-effective, and in three studies no full economic evaluation was performed. Further details concerning discounting and model uncertainty are reported in Appendix S2; Supporting Information Table SA.2.2.

3.1 | Definitions of prediabetes

A total of 21 studies (72%) defined prediabetes using blood glucose measurement criteria (n = 17) from the American Diabetes Association (ADA) (n = 7), the World Health Organisation (n = 5), the Diabetes Prevention Programme (DPP) Trial (n = 4), the UK National Institute for Health and Care Excellence (n = 1) or using blood glucose values and other risk factors (n = 4) (Table 1 and Appendix S2; Supporting Information Table SA.2.3). Among the 17 studies using solely blood glucose measurement criteria, prediabetes was defined according to IGT (n = 7), IGT and/or IFG (n = 7), HbA1c (n = 1), HbA1c and/or IFG (n = 1) or IFG (n = 1). Six studies (21%) did not define prediabetes according to explicit criteria but reported use of IGT (n = 3), IGT and/or IFG (n = 2) or IFG (n = 1). Finally, two studies (7%) did not define prediabetes.

3.2 | Model structure

Table 2 highlights aspects of model structure. The Sheffield group models (Gillett 2015, Breeze 2016) and the CDC/University of Michigan group models (Hoerger 2007, Herman 2005) reported that they explicitly based their diabetes models on previous T2D decision model(s). Three studies (Gillett 2015, Breeze 2016 and Herman 2005) developed new T2D model structures but reported these to be based on previous T2D models, such as Eastman 1997.⁵⁶ The remaining studies reported an apparently new model structure, with the aim of addressing their particular research question.

TABLE 1 Overview of prediabetes models (sorted by year of publication)

Publication (author year)	Setting	Prediabetes definition*	Intervention(s)	Comparator	Cost perspective	Type of model	Horizon (years)	Cycle length	Study design
Caro 2004 ²⁷	Canada	IGT (WHO 1985)	Screening and 1) Lifestyle or 2) Pharmacological	No intervention	Healthcare payer	Cohort Markov Model	10	6 months	CEA
Palmer 2004 ²⁸	Multiple countries	IGT (DPP)	1) Lifestyle 2) Pharmacological	Placebo and Standard advice	Healthcare payer	Cohort Markov Model	Lifetime	Annual	CEA
Eddy 2005 ²⁹	USA	Other	1) Lifestyle 2) No intervention 3) No intervention unless diagnosed with diabetes 4) Pharmacological	No intervention	Societal	Microsimulation	30	Annual	CUA
Herman 2005 ³⁰	USA	IGT (DPP)	1) Lifestyle 2) Pharmacological	Placebo (as in DPP)	Societal	Cohort Markov Model	Lifetime	Annual	CUA
Dalziel 2007 ³¹	Multiple countries	IGT (WHO 1999)	Lifestyle	General dietary advice at initiation	Societal	Cohort Markov Model	20	Annual	CUA
Hoerger 2007 ³²	USA	IGT and/or IFG (ADA 2002)	Screening and Lifestyle	No screening	Societal	Decision Tree Cohort Markov Model	Lifetime	Annual	CUA
Lindgren 2007 ³³	Sweden	Other	Lifestyle (as in DPS)	No intervention	Societal	Microsimulation	Lifetime	Annual	CUA
Colagiuri 2008 ³⁴	Australia	IGT and/or IFG (not defined)	Screening and lifestyle	No intervention	Not reported	Other	10	Annual	CUA
Gillies 2008 ³⁵	UK	IGT (not defined)	Screening and 1) Lifestyle or 2) Pharmacological	No screening	Healthcare payer	Decision Tree Cohort Markov Model	50	Annual	CUA
Iannazzo 2008 ³⁶	Italy	IGT (WHO 1994)	Screening and 1) Lifestyle 2) Pharmacological	Lifestyle modification	Societal	Microsimulation	10	Annual	CUA
Bertram 2010 ³⁷	Australia	IGT and/or IFG (WHO 1999)	Screening and 1) Lifestyle or 2) pharmacological	No intervention	Healthcare payer	Microsimulation	100	Annual	CUA
Castro-Rios 2010 ³⁸	Mexico	IGT and/or IFG (ADA 2010)	Screening and Lifestyle (Mexican Preventative Care Programme)	Usual care	Healthcare payer	Decision Tree Cohort Markov Model	20	Annual	Costs only
Grassi 2010 ³⁹	Austria	IGT and/or IFG (ADA 1997)	Screening	Not applicable	NA	Cohort Markov Model	3	Annual	NA
Ikedo 2010 ⁴⁰	Japan	Other	Pharmacological	Usual care	Healthcare payer	Cohort Markov Model	49	Annual	CEA
Schaufler 2010 ⁴¹	Germany	IGT or IFG (WHO 1999)	Screening and 1) Lifestyle or 2) Pharmacological	No intervention	Healthcare payer	Microsimulation	Lifetime	Annual	CUA
Smith 2010 ⁴²	USA	Other	Screening and Lifestyle (Modified DPP)	Usual care	Healthcare payer	Cohort Markov Model	3	Monthly	CUA

TABLE 1 (Continued)

Publication (author year)	Setting	Prediabetes definition*	Intervention(s)	Comparator	Cost perspective	Type of model	Horizon (years)	Cycle length	Study design
Neumann 2011 ⁴³	Germany	IGT (not defined)	Screening and Lifestyle	No intervention	Societal	Cohort Markov Model	Lifetime	Annual	CUA
Sullivan 2011 ⁴⁴	USA	IFG (ADA 2010)	Screening and Pharmacological	"wait and watch"	Healthcare payer	Other	10	Annual	CUA
Mortaz 2012 ⁴⁵	Canada	IFG (not defined)	Screening	No screening	Healthcare payer	Cohort Markov Model	10	Annual	CUA
Palmer 2012 ⁴⁶	Australia	IGT (ADA 2010)	1) Lifestyle 2) Pharmacological	Usual care	Healthcare payer	Microsimulation	Lifetime	Annual	CUA
Postmus 2012 ⁴⁷	Netherlands	Not defined	Screening and 1) intensive lifestyle for high risk 2) dietary lifestyle for intermediate risk	No intervention for low-risk individuals	Healthcare payer	Cohort Markov Model	Lifetime	Annual	CUA
Liu 2013 ⁴⁸	China	IGT (Other)	Screening and Lifestyle	No intervention	Societal	Decision Tree Cohort Markov Model	40	Annual	CUA
Png 2014 ⁴⁹	Singapore	IGT and IFG (DPP)	1) Lifestyle 2) Pharmacological	Placebo (as in DPP)	Societal	Decision Tree	3	NA	CUA
Dall 2015 ⁵⁰	USA	HbA1c (ADA 2010)	Screening and Lifestyle (as in DPP)	Usual care	Societal	Microsimulation	10	Annual	CUA
Gillett 2015 ⁵¹	UK	HbA1c and/or IFG (NICE)	Screening and Lifestyle	IFG test screening	Healthcare payer	Microsimulation	80	Annual	CUA
Breeze 2016 ⁵²	UK	Not defined	Screening and low, medium and high intensity prevention	No intervention	Healthcare payer	Microsimulation	Lifetime	Annual	CUA
Wong 2016 ⁵³	Hong Kong	IGT (not defined)	Short Messaging Service	Usual care	Healthcare provider	Cohort Markov Model	50	Annual	CUA
Neumann 2017 ⁵⁴	Sweden	IGT and/or IFG (not defined)	Screening and Lifestyle	No intervention	Societal	Markov Model	Lifetime	Annual	CUA
Wong 2017 ⁵⁵	Singapore	IGT (not defined)	Usual care	Not applicable	Societal	Cohort Markov Model	25	Annual	NA

*WHO (1985, 1994): OGTT, 7.8–11.0 mmol/L; WHO (1999): FPG, 6.1–6.9 mmol/L or OGTT, 7.8–11.0 mmol/L; ADA (1997, 2002): FPG, 6.1–6.9 mmol/L or OGTT, 7.8–11.0 mmol/L; ADA (2010, 2012): FPG, 5.6–6.9 mmol/L or OGTT, 7.8–11.0 or HbA1c, 5.7%–6.4%; DPP (2002): FPG, 5.3–6.9 mmol/L or OGTT, 7.8–11.0 mmol/L; NICE (UK): FPG, 5.5–6.9 mmol/L or HbA1c, 6.0%–6.4%; Eddy 2005: DPP including risk factors (BMI >24); Ikeda 2010: ADA 2010 criteria plus one of the following: (i) hypertension, (ii) dyslipidaemia, (iii) obesity, (iv) family history of diabetes; Lindgren 2007: BMI >25; PFG >6.1 mmol/L, no diagnosis of diabetes; Liu 2013: OGTT, 6.8 mmol/L–11.0 mmol/L; Smith 2010: risk factor positive for diabetes and CVD: overweight (BMI ≤ 25 kg/m²) with at least three components of metabolic syndrome: waist circumference (>102 cm for men, >88 cm for women), HDL cholesterol (<40 mg/dL for men, <50 mg/dL for women), FPG (≥ 100 mg/dL), blood pressure ($\geq 130/85$ mmHg) or overweight, having at least two components of metabolic syndrome; FPG, 100–109 mg/dL; physician referral to intervention.

Abbreviations: ADA, American Diabetes Association; BMI, body mass index; CEA, cost-effectiveness analysis; CUA, cost-utility analysis; CVD, cardiovascular disease; DPP, Diabetes Prevention Programme; DPS, Diabetes Prevention Study; FPG, fasting plasma glucose test; IFG – impaired fasting glucose; IGT – impaired glucose tolerance; NA, not applicable; NICE, National Institute for Health and Care Excellence; UK; OGTT, 2-hour oral glucose test; WHO, World Health Organisation.

TABLE 2 Complexity of models (sorted by year of publication)

Publication (author year)	Transition from/to		Vascular events, non-vascular events, diabetes-related complications				Annual changes in risk factors		Individual heterogeneity			Disease states modelled explicitly
	Screening and/or screening costs	Pre diabetes to NGT	T2D to pre diabetes	NGT to T2D	Pre diabetes	T2D	Death	Pre diabetes	T2D	Data identification process		
											Pre diabetes	
Caro 2004	✓	✓					✓					NGT, PreD, T2D, D
Palmer 2004							✓					PreD, T2D, D
Eddy 2005				✓			✓	✓				NGT, PreD, T2D, T2 DC, D
Herman 2005				✓			✓	✓		✓		NGT, PreD, Compl, T2D, T2 DC, D
Dalziel 2007		✓	✓				✓					NGT, PreD, T2D, D
Hoerger 2007	✓			✓			✓	✓				NGT, PreD, Compl, T2D, T2 DC, D
Lindgren 2007					✓		✓	✓				NGT, PreD, Compl, T2D, T2 DC, D
Colagiuri 2008	✓						✓	✓				NGT, PreD, T2D, T2 DC, D
Gillies 2008	✓						✓					NGT, PreD, T2D, D
Iannazzo 2008	✓			✓			✓	✓				NGT, PreD, Compl, T2D, T2 DC, D
Bertram 2010	✓	✓					✓	✓				NGT, PreD, Compl, T2D, T2 DC, D
Castro-Rios 2010	✓						✓	✓				PreD, T2D, CVD
Grassi 2010		✓		✓								NGT, PreD, T2D
Ikeda 2010		✓						✓				NGT, PreD, T2D, D
Schaufier 2010	✓						✓	✓		✓		NGT, PreD, T2D, T2 DC, D
Smith 2010	✓						✓	✓				NGT, PreD, T2D, T2 DC, D
Neumann 2011	✓		✓				✓	✓				NGT, PreD, T2D, D
Sullivan 2011	✓						✓	✓				NGT, PreD, T2D, D
Mortaz 2012	✓						✓	✓				NGT, PreD, T2D, T2 DC, D
Palmer 2012		✓	✓				✓	✓				NGT, PreD, T2D, D
Postmus 2012	✓						✓	✓				PreD, T2D, D
Liu 2013	✓						✓	✓				NGT, PreD, T2D, T2 DC, D
Png 2014		✓										NGT, PreD, T2D
Dall 2015	✓						✓	✓				NGT, PreD, Compl, T2D, T2 DC, D
Gillett 2015	✓						✓	✓		✓		NGT, PreD, T2D, T2 DC, D
Breeze 2016	✓						✓	✓ ^a		✓		NGT, PreD, Compl, T2D, T2 DC, D
Wong 2016		✓										NGT, PreD, T2D, D
Neumann 2017	✓		✓				✓	✓				NGT, PreD, T2D, D
Wong 2017							✓	✓				NGT, PreD, T2D, T2 DC, D

Abbreviations: Compl, complications in non-diabetes/prediabetes; D, death; NGT: normal glucose tolerance; PreD: prediabetes; T2 DC: diabetes-related complications. Prediabetes as defined in the study.
^aEvents are modelled for HbA1c less than or equal to 6.5%. Screening is defined as including a screening component or accounting for screening costs in the model (see Appendix S2; Supporting Information Table SA.2.1. Screening Strategy Column for more details).

Complexity of the model structure varied across studies. Table 2 reports the health states explicitly included in the models. All models simulated progression from prediabetes to T2D and could be categorized into six types of model structure according to the health states included (Table 2 and Appendix S2; Supporting Information Figure SA.2). These categories ranged from relatively simple three-state models ($n = 2$), with prediabetes, diabetes and death, to comprehensive models that also included NGT and complications in non-diabetes/prediabetes and diabetes states ($n = 7$).

Modelling of the disease pathway also varied greatly, with 18 (62%) of the 29 models including a screening component and/or screening costs, 12 (41%) models allowing the individual to regress from prediabetes to normal glucose tolerance (NGT), four models (14%) allowing individuals with T2D to return to prediabetes, and two models (7%) allowing direct progression from NGT to T2D. In models with a screening component, individuals were mass screened for IGT, IFG or elevated HbA1c ($n = 4$), or were stratified before screening (eg, by age, BMI, diabetes risk score) ($n = 11$) (Appendix S2; Supporting Information Table SA.2.1 and SA.2.3).

Large variations were seen in the modelling of events and diabetes-related complications stemming from the defined health states (Table 2 and Appendix S2; Supporting Information Table SA.2.4). A minority of models allowed the individual to develop complications in a prediabetes state ($n = 8$, 28%), which were mostly cardiovascular (eg, myocardial infarction, ischaemic heart disease, stroke, heart failure). Two models (Bertram 2010 and Breeze 2016) simulated explicitly the risk of major cardiovascular events (ischaemic heart disease, stroke, heart failure) in non-prediabetes and non-T2D populations, and one (Breeze 2016) also simulated non-vascular events such as cancer (breast and colorectal), osteoarthritis and depression across all states of glucose tolerance. No other model incorporated non-cardiovascular events. More models simulated diabetes-related complications in the T2D state ($n = 17$, 59%) such as macrovascular (eg, myocardial infarction, stroke and heart failure) and microvascular events (eg, retinopathy, nephropathy and neuropathy). However, the number and type of complications varied across models as did the sources used to inform the risk of such events (eg, Framingham Heart Study, UKPDS Risk Engine, UKPDS outcomes model, QRISK2, previous decision models, etc.). Table SA.2.4 in Appendix S2 describes the type of complications simulated by each model, as well as the respective sources used to inform the risk. In models simulating complications in both prediabetes/non-diabetes and diabetes states ($n = 8$), the incidence of diabetes marked the use of a different source for risk of complications in six models (75%). Two studies used the same risk prediction model, with one applying the diabetes covariate to differentiate risk between prediabetes and diabetes states (Iannazzo 2008), while the other assumed equal risks (Lindgren 2007).

Death was included in the majority of models ($n = 26$). All models simulating an NGT health state assumed these individuals to have the same mortality as the general population, even when allowing for regression from a prediabetes state. Eleven models explicitly assumed an increased risk of death in prediabetes populations relative to NGT or general populations, although there was considerable variation in the magnitude of the risk (Bertram 2010, Caro 2004, Dalziel 2007, Herman 2005, Hoerger 2007, Iannazzo 2008, Ikeda 2010, Neumann

2011, Palmer 2004, Palmer 2012, Smith 2010, Wong 2016). Another eleven models assumed no increased risk of death in prediabetes populations (Breeze 2016, Colagiuri 2008, Dall 2015, Gillies 2008, Liu 2013, Mortaz 2012, Neumann 2017, Postmus 2012, Schauffer 2010, Sullivan 2011, Wong 2017) and the remaining seven models did not report whether prediabetes carried an additional risk of death.

3.3 | Incorporation of risk factors, novel biomarkers and individual heterogeneity

Seven of the 29 models simulated annual changes in risk factors such as glycaemia (HbA1c, FPG, and/or 2-hr glucose), blood pressure (systolic and/or diastolic), BMI and lipids (total cholesterol and/or HDL) as individuals progressed in the model (see Table 2 and Appendix S2; Supporting Information Table SA.2.5 for details). No other biomarkers informed the models.

The simulated trajectory of the changing risk factors subsequently informed the risk of onset of diabetes and/or complications. In three of the seven models (Breeze 2016, Dall 2015 and Eddy 2005) the impact of interventions was simulated via reduction in risk factors such as BMI and HbA1c, which then had a knock-on effect on progression to diabetes and complications. In the remaining 26 models, the impact of screening and interventions was simulated through a direct reduction in progression to T2D, which was then translated into fewer diabetes-related complications, higher life expectancy, better quality of life and potential cost-savings compared to usual care. One model (Breeze 2016) also simulated the impact of interventions on non-diabetes-related complications by further assuming that interventions that reduce BMI could also reduce the incidence of cancer and severe osteoarthritis, while interventions that reduce progression to diabetes could also reduce the incidence of severe osteoarthritis and depression.

Six models (Breeze 2016, Dall 2015, Eddy 2005, Gillett 2015, Herman 2005 and Hoerger 2007) simulated HbA1c annual deterioration in T2D populations, of which three (Breeze 2016, Dall 2015 and Gillett 2015) also simulated HbA1c annual deterioration in non-diabetes/prediabetes populations, albeit using different risk factors and equations before diagnosis of diabetes, and after. In prediabetes/non-diabetes populations, the change in HbA1c was also modelled differently across the three models and depended on risk factors such as BMI, previous HbA1c value, smoking, alcohol, family history of T2D, ethnicity, age, sex and total cholesterol values. In diabetes populations, five of six models used the UKPDS study ($n = 3$) or the UKPDS Outcomes Model ($n = 2$) to inform annual changes in HbA1c, with the latter predicting annual changes conditional on previous HbA1c values, time since diagnosis of diabetes and HbA1c value at diagnosis. Two models (Breeze 2016 and Eddy 2005) also simulated annual changes in fasting plasma glucose in non-diabetes/prediabetes populations, with the latter simulating these changes as a function of insulin resistance that was assumed to increase with T2D progression.

Table 2 shows that seven studies accounted for heterogeneity among individuals in a non-diabetes and/or prediabetes health state. Five of these studies (Breeze 2016, Eddy 2005, Gillet 2008, Dall 2015 and Neumann 2017) allowed the progression to T2D to vary as a function of factors such as age, sex, ethnicity, marital status, lipid

levels, plasma glucose levels (IGT, FPG, HbA1c), family history of T2D and BMI. The remaining two studies (Bertram 2010 and Liu 2013) explored heterogeneity by varying the risk of progression to T2D by age group and sex.

3.4 | Hierarchy of evidence informing models

Data from a range of studies were used to inform the prediabetes models. Table 2 shows that a minority of studies (n = 4) outlined a systematic method in which data were identified. The hierarchy of evidence used in the models is summarized in Figure 2, ranging from high quality (rank 1: eg, meta-analysis or single RCT with direct comparison between comparator therapies for effect size) to low quality (rank 6: expert opinion). The majority of studies (86%) reported use of high-quality data to inform the effect size estimates. More details are presented in Appendix S2; Supporting Information Table SA.2.6.

3.5 | Model validation

According to the AdViSHE checklist,²⁶ 21 of 29 studies reported that one or more validation checks had been performed. However, ten studies that reported on validation limited their reporting to single tests, such as comparing model outcomes to other similar models. Two studies (Breeze 2016 and Eddy 2005) presented elaborate validation efforts on all aspects of the modelling cycle (conceptual model validation, input data validation, code verification and operational validation). Appendix S2, Supporting Information Figure SA.2.3, shows the number of studies that undertook each of the validation techniques outlined in the assessment tool (full results in Appendix S2; Supporting Information Table SA.2.7).

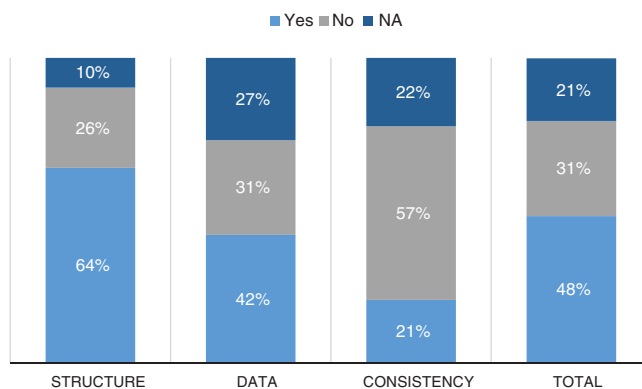


FIGURE 3 Quality of modelling studies according to the Philips checklist. Legend: A “yes” answer was assigned if a criterion was fulfilled. A “no” answer was assigned to criteria that were not fulfilled. NA indicates not applicable

3.6 | Model quality

According to the checklist from Philips et al.,²⁴ the percentage of criteria fulfilled were unequally distributed across studies and dimensions of quality (model structure, model data and model consistency). Figure 3 shows that, on average across all studies, model structure ranked the highest, with 64% of criteria for quality being met, followed by model data (42%) and model consistency (21%). (Full results in Appendix S2; Supporting Information Table SA.2.8).

4 | DISCUSSION

Given the high cost and burden of diabetes, there is significant interest in identifying strategies that prevent or delay the disease and that

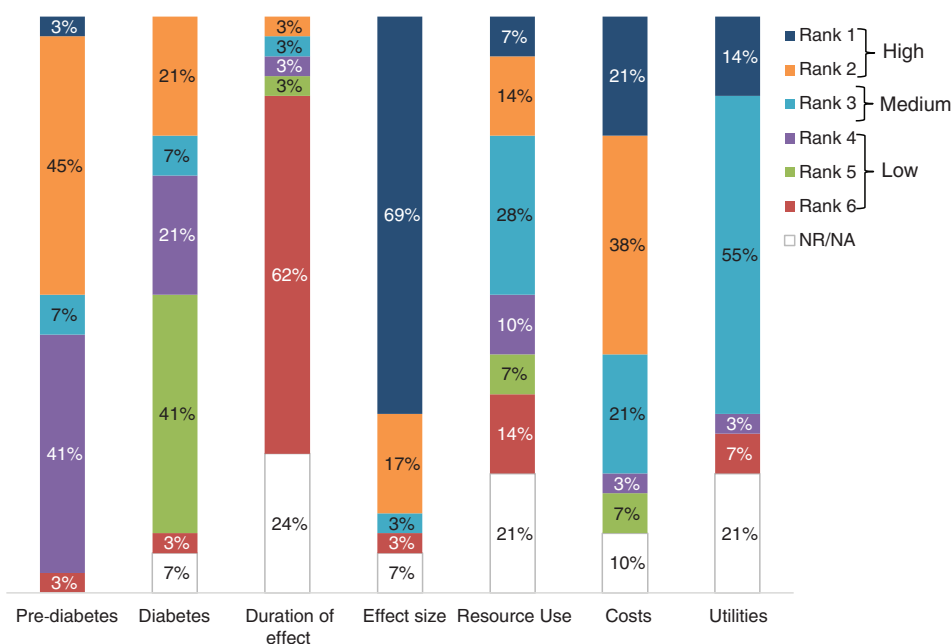


FIGURE 2 Hierarchy of evidence informing the 29 models. Legend: Quality of data input is ranked from 1 (highest: eg, meta-analysis of RCTs with direct comparison between comparator therapies, measuring final outcomes for effect size) to 6 (lowest: expert opinion). Abbreviations: NR, data source not reported; NA, not applicable. See Data Extraction form in Appendix S3 for full definitions of each rank

are cost-effective. Economic decision models simulating disease progression from normal glucose tolerance throughout the period of prediabetes to diabetes and its complications may support the economic evaluation of various screening and prevention strategies. Such computer models enable extrapolation from short-term empirical studies to predict health benefits and cost consequences over the lifetime of an individual. However, in order to assess stratified prevention strategies, such models should have a scope wide enough to capture the identification of individuals, their management and their response to treatment. Also, they should allow individual heterogeneity in risk of progression, according to biomarkers levels and their changes over time, to be taken into account. Furthermore, prediabetes models should consider all relevant outcomes, including onset of relevant comorbidities, in addition to the onset of T2D.

Our review identified 29 studies that use decision models to predict the progression of prediabetes and to evaluate prevention strategies. An assessment of these studies indicates considerable limitations in current models in terms of their quality and validity. Furthermore, their potential to evaluate the impact of novel biomarkers, and of stratified prevention strategies using such biomarkers, seems limited, despite the growing evidence base linking biomarkers to prediabetes disease progression.^{10–12}

We found that the definitions of prediabetes varied considerably across the 29 models. Some models defined prediabetes as IGT, others as IFG, or both. Furthermore, studies used different glycaemic threshold values to define these states. The variation seemed to be largely a function of the clinical studies used to inform the model and their inclusion criteria, as well as changes in the classification and diagnosis of (pre)diabetes over time. This is relevant, as disease progression will differ according to the definition of prediabetes.⁵⁶ For example, IFG and IGT are considered distinct pathophysiological mechanisms and may lead to differing risks of developing diabetes or complications.³ Thus, there is a need for agreement and standardization concerning the way prediabetes is defined in these models. This will also allow a better understanding of their findings, facilitate comparisons across models and allow transparent assessments of their validity. With increasing attention being given to heterogeneity among individuals with diabetes, heterogeneity in prediabetes may also require attention and current definitions may need to allow for larger variety in prediabetes subtypes.⁵⁷

The complexity of risk prediction models for diabetes incidence and the variety of covariates used^{58,59} were in stark contrast with the assumption, made in the majority of models, that the rate of progression to T2D was constant across the entire prediabetes population. Furthermore, several well-validated T2D computer models allow prediction of many types of diabetes complications (eg, MI, stroke, heart failure, ischaemic heart disease, renal failure, blindness, etc.),¹⁹ as well as second events,^{16,18,20} conditional on baseline and/or time variant risk factors (eg, age, sex, cholesterol levels, HbA1c, history of complications, physical activity, etc.). However, the models identified in this review did not share the same complexity, and either simulated complications as a whole or simulated fewer complications, or simply did not simulate any complications. This is probably due, in part, to challenges in identifying suitable input data sources for prediabetes populations, as this requires a representative cohort that has been

appropriately tested for prediabetes. While a diabetes cohort can be relatively easily recruited from diagnosed patients, a prediabetes cohort inevitably requires some form of screening and a longer follow up sufficient to identify the onset of diabetes and/or any subsequent complications.

Changes in glycaemia, blood pressure, BMI and/or lipids were simulated in seven models, but no other biomarkers were identified in our review. In terms of glycaemic deterioration, only three models simulated trajectories of HbA1c in the non-diabetes/prediabetes populations and based these on different methods and data sources. However, these models allowed for a discontinuity in disease progression before and after diagnosis by simulating HbA1c deterioration after diabetes diagnosis, using risk factors and populations other than those informing HbA1c progression prior to diagnosis. Furthermore, of the six models simulating HbA1c deterioration after diagnosis of diabetes, five used data from a single source, the UK Prospective Diabetes Study, and one relied on assumptions. Concern about the lack of continuity in disease progression extended to the remaining risk factors being modelled, before and after diagnosis of diabetes. Here, either the same source was used to inform the trajectories without any adjustments for progression after diagnosis of diabetes or very different sources and populations informed trajectories before and after diagnosis. This makes the case for more comprehensive models that are capable of better capturing the continuity in disease progression and, also, of incorporating the identification of novel biomarkers and the respective development of new risk-stratification tools. Such models will need to simulate individual-level glycaemic deterioration trajectories and account for heterogeneity, given that disease progression and risk of complications depend on a range of factors within prediabetes and diabetes populations.

We found that normal glycaemia, prediabetes and T2D were largely handled as discrete events in the models. Although this was a convenient simplification of reality, it fails to model glycaemia deterioration as a continuum of risk and to account for the differing risk levels of disease progression among individuals with plasma glucose readings towards the upper limit of the normal range.⁶⁰ Also, with models informed by a variety of data sources and populations, it may introduce bias in terms of rates of disease progression when these are dependent on the study and the population informing the model rather than on the stage of disease. For example, models predicted vascular events using risk equations from T2D-only populations (eg, UKPDS Risk Engine and UKPDS Outcomes Model) together with equations from populations with subgroups of individuals with diabetes (eg, Framingham Heart Study or QRISK2) depending on whether the individuals had progressed to T2D. Furthermore, even for models using the same data source (eg, UKPDS Risk Engine or Framingham Heart Study) to predict vascular events, validity is likely to vary across non-diabetes and diabetes populations,⁶¹ and we did not identify a model that used the same data source to inform disease progression during both prediabetes and T2D.

All interventions under evaluation in the models discussed in this review required identification of individuals with prediabetes within the general population. However, several models did not include or account for identification strategies. This is another necessary layer of complexity in prediabetes models; in particular, if the usefulness of

novel biomarkers is to be evaluated, the screening and identification of individuals at risk must be accounted for. Furthermore, some interventions may have an impact beyond diabetes. There is then the question of how comprehensive the models must be to provide reliable estimates for decision making. This reinforces the need for a clear rationale for model structure, for thorough consistency checks, to ensure that cardiovascular and non-cardiovascular events are not overestimated in these populations when informed by varied sources, and for incorporation of relevant aspects of natural history such as regression from prediabetes or diabetes, aspects that were largely ignored by the majority of studies in this review.

The Philips and AdViSHE checklists highlighted concerns about the data and the validation status of the models. Few studies reported any model validation, despite ADA guidelines on modelling diabetes.¹⁷ This raises questions about the validity of the models as being representative of relevant populations and in providing estimates sufficiently robust to inform policy making.

Previous systematic reviews have assessed economic evaluations of diabetes prevention programmes, with the aim of comparing cost-effectiveness results across interventions and studies.^{62–66} Roberts et al.⁶⁵ also utilized an ISPOR checklist⁶⁷ to evaluate the relevance and credibility of results for policy makers. Our review contributes to existing reviews as it focuses on the health economic decision models. It uses recognized modelling checklists,^{24,26} to provide a formal assessment of the models used to inform decision making in the prevention of diabetes.²⁰

Our findings highlight the need to develop models that allow prediction of disease progression at an individual level and identification of new sub-classifications of prediabetes and diabetes based on novel biomarkers and clinical characteristics. Glycaemic deterioration should be modelled as a continuum before the diagnosis of diabetes, whether or not the diagnosis of diabetes implies discrete changes in the risk of complications, and treatment response should be carefully considered and validated. To inform these models, prediabetes cohorts with a follow-up period sufficiently long and measurement rounds sufficiently frequent are needed. To evaluate stratified treatment strategies, models should include sufficient detail all along the simulated patterns of care, from identification of prediabetes cases to assessment of all relevant outcomes, beyond diabetes per se. Finally, it is key to perform extended validation of any developed model to assess robustness and to inform policy.

Concerning strengths and limitations, this is the first systematic review to critically assess the quality and validation of existing prediabetes models. It highlights that current prediabetes models have considerable limitations and may not be suitable to evaluate novel interventions such as those derived from the discovery of new biomarkers, an area of research that is receiving increased attention. This review has a number of limitations. First, risk prediction models for diabetes incidence and budget impact models were excluded from the review. Prediction models could have provided insights into the variables that are relevant to economic models that aim to evaluate novel biomarker strategies,⁵⁸ whereas budget impact models could have made apparent the variables relevant to assessment of financial impact. However, the aims of such models differ from the evaluation of novel prevention strategies and require different extraction forms,

as well as quality and validation checklists. Second, only studies published in English were included in this review. Third, there may be a degree of publication bias as models that show an intervention to be cost-effective may be more likely to be published. Finally, the assessment of study quality may be biased as some studies were not described in full detail because of word count constraints; however, in the current era of online appendices, this bias should be less relevant.

Findings from this review have identified the need for validation of existing prediabetes models and for the development of more comprehensive models to more accurately evaluate novel biomarker-based stratified interventions. Furthermore, use of the Philips checklist demonstrated the lack of quality data being used in current prediabetes models. Future research can focus on gathering high-quality data in order to build a more robust decision model.

To conclude, novel biomarkers have the potential to identify cost-effective strategies that aim to prevent or delay the disease. Current prediabetes decision models have considerable limitations in terms of quality and validity, and they are not equipped to evaluate novel biomarkers for glycaemic deterioration, highlighting the clear need for the development of more comprehensive prediabetes decision models.

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CONFLICT OF INTEREST

The authors declare that they have no competing interests.

AUTHOR CONTRIBUTIONS

J. L., E. P. and T. F. designed the study, J. L., W. K. and L. M. collected the studies. All authors conducted data extraction. J. L., W. K. and L. M. performed the analysis, E. P. and T. F. critically commented on analysis results. J. L., L. M., E. P. and T. F. wrote the manuscript.

ORCID

Jose Leal  <https://orcid.org/0000-0001-7870-6730>

Liam Mc Morrow  <https://orcid.org/0000-0003-0252-613X>

Talitha Feenstra  <https://orcid.org/0000-0002-5788-0454>

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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