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REVIEW ARTICLE

Modelling the Economics of Type 2 Diabetes Mellitus Prevention: A Literature Review of Methods

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Abstract Our objective was to review modelling methods for type 2 diabetes mellitus prevention cost-effectiveness studies. The review was conducted to inform the design of a policy analysis model capable of assisting resource allocation decisions across a spectrum of prevention strategies. We identified recent systematic reviews of economic evaluations in diabetes prevention and management of obesity. We extracted studies from two existing systematic reviews of economic evaluations for the prevention of diabetes. We extracted studies evaluating interventions in a non-diabetic population with type 2 diabetes as a modelled outcome, from two systematic reviews of obesity intervention economic evaluations. Databases were searched for studies published between 2008 and 2013. For each study, we reviewed details of the model type, structure, and methods for predicting diabetes and cardiovascular disease. Our review identified 46 articles and found variation in modelling approaches for cost-effectiveness evaluations for the prevention of type 2 diabetes. Investigation of the variables used to estimate the risk of type 2 diabetes suggested that impaired glucose regulation, and body mass index were used as the primary risk factors for type 2 diabetes. A minority of cost-effectiveness models for diabetes prevention accounted for the multivariate impacts of interventions on risk factors for type 2 diabetes. Twenty-eight cost-effectiveness models included cardiovascular events in addition to type 2 diabetes. Few cost-effectiveness models have flexibility to evaluate different intervention types. We conclude that to compare a range of prevention interventions it is necessary to incorporate multiple risk factors for diabetes, diabetes-related complications and obesity-related co-morbidity outcomes.

Key Points for Decision Makers:

Forty-six studies have evaluated the cost effectiveness of public health interventions that prevent type 2 diabetes mellitus; however, model type and natural history detail are variable.

Type 2 diabetes models have predominantly assumed either impaired fasting glucose or body mass index as a univariate risk factor for diabetes, but few models adopt a multivariate risk function.

There was variability in whether diabetes-related complications and diabetes co-morbidities were included in the model.

Few models have a sufficiently flexible structure to allow evaluation of multiple preventative interventions in alternative high-risk sub-populations.

1 Introduction

The global prevalence of type 2 diabetes mellitus is anticipated to rise to 366 million by 2030 [1]. There is an urgent need for effective and cost-effective public health interventions to reduce the burden of the disease.

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This review was conducted as part of a project to develop a public health policy model to evaluate strategies with an aim to prevent type 2 diabetes. Previous models have either assessed (1) high-risk identification strategies to target individuals with hyperglycaemia, such as impaired fasting glucose (IFG), and/or impaired glucose tolerance (IGT) using the fasting plasma glucose (FPG) or oral glucose tolerance test (OGTT) [2], (2) diet and physical activity interventions for individuals who demonstrate metabolic risk factors associated with cardiovascular disease and type 2 diabetes [3], or (3) preventative interventions within the general population. In the past public health assessments from the National Institute for Health and Care Excellence (NICE) have evaluated the effectiveness and cost effectiveness of these strategies independently [4, 5]. The objective of the new economic model was to evaluate, within one common framework, both population-level strategies and targeted strategies in high-risk groups for the prevention of diabetes.

Previous systematic reviews of obesity interventions and diabetes risk identification programmes have focussed upon critical appraisal of economic models and evaluation of cost-effectiveness outcomes [6–8]. However, it has been suggested that given the limitations to the generalisability of evidence from economic evaluations, it is perhaps more appropriate to conduct a review of economic models with the aim of informing the development of a new decision model [9]. This review aims to inform the development of a new model to evaluate diabetes prevention interventions targeting population, communities, and high-risk individuals. The objectives of this economic review were based on a new framework for developing the structure of public health economic models [10]:

1. To compare how other modellers have chosen to structure the model and estimate key variables. This may involve considering the use of mathematical relationships such as risk equations or parameters, which have been included within previous models if their source and justification has been appropriately explained.
2. To identify which variables are important in influencing model results (including any which have not been highlighted during the understanding of the problem phase) and which do not substantially affect the differences in outcomes between the interventions and comparators.
3. To provide an insight into the sort of data available, which may inform the level of detail included within the model.
4. To consider the strengths and limitations of existing economic evaluations.
5. To determine whether there is already a model that could be used, either in part or as a whole, for the decision problem described.

2 Methods

2.1 Search Strategy

The search strategy was designed to identify published model-based economic evaluations of screening and prevention interventions for type 2 diabetes, including population level and targeted strategies. We were aware of four existing systematic reviews on obesity and diabetes prevention interventions [6–8, 11]. These four systematic reviews together with a systematic literature review of recent publications (see Fig. 1) were used to identify economic models.

Waugh [8] evaluated the value of screening for undiagnosed diabetes and whether it should be extended to identify IGT or metabolic syndrome [8]. Gillett [6] reviewed the clinical effectiveness and cost effectiveness of non-pharmacological interventions, including diet and physical activity, for the prevention of type 2 diabetes in people with intermediate hyperglycaemia. Two recent systematic reviews of economic evaluations of adult weight management interventions were used to identify economic evaluations in obese populations [7, 11]. We decided to include obesity studies in the review because interventions to reduce obesity are anticipated to impact on the incidence of type 2 diabetes as a result of the relationship between body mass index (BMI) and type 2 diabetes [12]. The articles identified in these searches were screened for inclusion in this review.

The literature review aimed to identify recently published economic models of population level interventions that were not covered in previous searches. This targeted literature search was undertaken in June 2013 and searched MEDLINE via OVID SP, NHS EED via Wiley Interscience and Econlit via OVID SP. A sample search strategy can be found in the electronic supplementary material. The search approach was to combine terms for diabetes and obesity with terms for prevention. This set was then combined with a peer-reviewed search filter for economic evaluations [13]. Searches were limited to 2008 onwards (based on the date of publication of the reviews described above) and were limited to human studies and English language studies. The search terms used drew heavily on previous work undertaken in the area [6, 8]. References were imported into Reference Manager 12 for consideration for inclusion in the review.

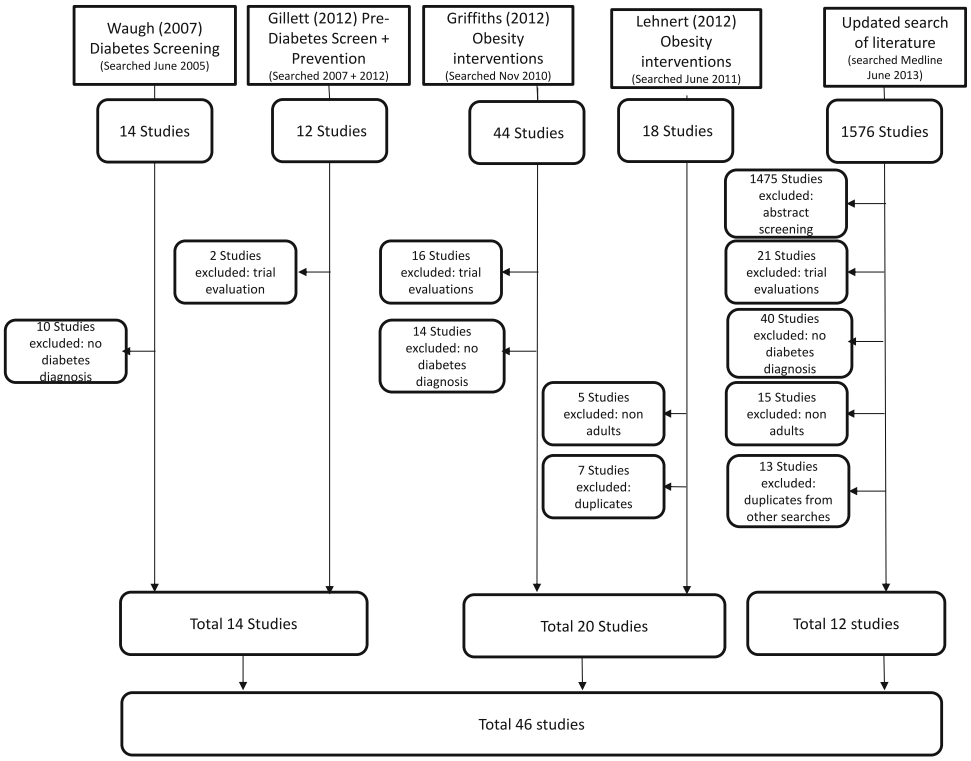

Fig. 1 Search strategy and study selection

We further scrutinised the reference lists of all included studies, and undertook citation searching on all included papers to identify as comprehensive a set of published economic evaluations as possible within the resources available to the project.

2.2 Exclusion Criteria

The following exclusion criteria were used to identify relevant studies.

1. Trial-based evaluations
2. Non-adult populations
3. No type 2 diabetes as a modelled outcome

Trial-based evaluations were not included because the aims of the review were to evaluate modelling methods. Non-adult populations are not within the scope of the study and are likely to have different modelling methods and data sources so were not included in the review. The review was designed to focus on public health prevention policies for type 2 diabetes, therefore diabetes diagnosis was required to be an outcome of the model. Screening programmes for type 2 diagnosis were not included in this review unless preventative interventions were evaluated for individuals identified and diabetes was modelled as a subsequent outcome.

2.3 Data Extraction

One reviewer extracted data (PW) and a second reviewer (HS) checked the data extraction for 10 % of the identified models. Data on the intervention type, target population, model perspective, model structures and model outcomes were extracted to give an overview of the models included in the review. Data extraction for the objectives listed in the introduction included:

1. Objective 1: Model structure and key variables. We extracted the methods for estimating the risk of type 2 diabetes, the methods for estimating cardiovascular disease and details of the other co-morbidities and diabetes-related complications that were included in the model.
2. Objective 2: Sensitive parameters. We extracted data on the reported one-way sensitivity analyses around diabetes co-morbidities to assess whether inclusion is important.
3. Objective 3: Data availability. We extracted data sources for the risk estimates for diabetes and cardiovascular events.

Objectives 4 (model structure strengths and limitations) and 5 (existing model suitability) are considered by reflecting upon the results of these data extractions.

3 Results

The process of screening existing systematic reviews identified 88 references and the updated literature search identified 1,576 references. After applying the inclusion/exclusion criteria and excluding duplicate references, we identified 46 studies describing 37 independent economic models (Fig. 1). Of the economic models described in multiple publications, Ara [14] reported analyses using a model based on one previously published by Warren [15]. Similarly, Ackerman [16] used a modelling structure based on Herman [17]. Two models with multiple publications were developed for national public health evaluation strategies [18, 19]. The ACE prevention model was developed in Australia to provide a comprehensive analysis of the comparative cost effectiveness of preventative intervention options. The Dutch National Institute of Public Health and Environmental Protection (RIVM) chronic disease model simulated the prevalence of risk factors in a Dutch Population. Both the ACE and RIVM models have been adapted over the years to update data inputs and accommodate changes to the model structure. Details of the studies included in the review are summarised in Table 1.

3.1 Objective 1: Model Structure and Key Variables

To address objective 1, the review of model structures focussed on methods of estimating the incidence of diabetes, cardiovascular disease and the inclusion of other co-morbidities and complications.

3.1.1 The Incidence of Diabetes

3.1.1.1 Impaired Glucose Regulation Status to Model Probability of Incidence of Diabetes Eighteen models evaluated interventions targeting populations with IGR identified with blood glucose tests [6, 16, 17, 20–34].

IGR models were predominantly cohort models with 13 adopting a cohort Markov transition structure [16, 17, 21–25, 27, 28, 31–34] and one decision tree [26]. The structure of these models included discrete health states for IGR, type-2 diabetes and death. Most models assumed a single transition rate for individuals with IGR. Hoerger [25] differentiated risk in IGR according to whether they were IGT and/or IFG, and Sullivan [33] according to a score on a diabetes risk assessment. Only four cohort models included normal glucose tolerance as an additional health state [20, 23, 29, 31].

Four models used an individual patient sampling model structure [6, 20, 29, 30], which could enable a more detailed description of risk of diabetes on a continuous scale. However, only Gillett [6] adjusted risk of diabetes according to the patient's HbA_{1c} test result to enable a continuous relationship between HBA_{1c} and risk of diabetes. The other individual patient sampling models assumed discrete health states preceding diagnosis of type 2 diabetes.

3.1.1.2 Body Mass Index as a Risk Factor for Incidence of Diabetes Sixteen models estimated risk based on the BMI [14, 15, 35–48]. Most of the studies used observational cohort studies to describe diabetes risk according to BMI because long-term diabetes incidence was not recorded within the follow-up of the randomised controlled trial (RCT).

Ten models simulated a cohort using either a decision tree or a state transition model [14, 15, 35, 38–41, 46–48]. Most of the models assumed a single transition rate for the incidence of diabetes in the cohort, determined by mean BMI after the intervention.

Six models used individual patient sampling models to simulate individual patient characteristics [36, 37, 42–45]. Individuals within the models have BMI measured on a continuous scale, which allowed personalised diabetes risks to be calculated according to BMI [36, 40, 42–45]. Three studies adopted relatively sophisticated modelling techniques to estimate diabetes risk conditional on BMI allowing for non-linear relationships [36, 42, 43]. Galani [36] and Picot [43] fit a polynomial function to data from the Nurses Health Survey and Health professional survey to interpolate between reported data [36, 43]. Michaud [42] used a spline in log BMI with a knot at a BMI of 30 U.

3.1.1.3 Other Univariate Risk Factors: Physical Activity Levels and Gestational Diabetes Three studies defined risk using univariate risk factors other than BMI or IGR [49–51]. Lohse et al. [50] treated gestational diabetes as a discrete state with a single risk of progression to type 2 diabetes. Two studies investigated the impact of physical activity on the incidence of type 2 diabetes [49, 51]. Cobiac et al. [49] adapted the ACE prevention model to evaluate the cost effectiveness of physical activity interventions and the risk of diabetes was assumed to decrease linearly with increasing energy expenditure. Roux et al. [51] divided physical activity into four discrete states, and a relative risk of diabetes was applied to each activity state using linear interpolation.

3.1.1.4 Multiple Risk Factors for Diabetes Incidence Six studies included multiple risk factors for diabetes [52–59]. The Dutch RIVM model allowed BMI, physical activity, age and sex to impact on the risk of diabetes. In one adaptation of the ACE prevention model, BMI and physical activity were both assumed to impact the incidence of diabetes [54], whereas other versions of the model assume either BMI or

Table 1 Economic study summary

Study	Year	Population group targeted	Model structures	Type of intervention	Outcome measure
Segal [31]	1998	IGT	Cohort state transition	Lifestyle	Life-year
Clegg [35]	2003	Morbid obese	Cohort decision tree	Obesity surgery	QALY
Caro [21]	2004	IGT	Cohort state transition	Lifestyle and pharmacological	Life-year
Palmer [28]	2004	IGT	Cohort state transition	Lifestyle and pharmacological	Life-year
Warren [15]	2004	BMI 27–40	Cohort decision tree	Pharmacological	QALY
Eddy (Archimedes) [65]	2005	Enrolment criteria for DPP	Individual sampling models	Lifestyle	QALY
Herman [17]	2005	IGT	Cohort state transition	Lifestyle and pharmacological	QALY
Hertzman [39]	2005	BMI ≥30 or ≥28 with CVD	Cohort decision tree	Pharmacological	QALY
Lacey [41]	2005	BMI ≥28 and no T2DM	Cohort decision tree	Pharmacological	QALY
Ackermann [16]	2006	Enrolment criteria for DPP	Cohort state transition	Lifestyle	QALY
Roux [44]	2006	Female BMI ≥25	Individual sampling models	Lifestyle and pharmacological	QALY
Ara [14]	2007	Obese	Cohort state transition	Lifestyle and pharmacological	QALY
Caro [55]	2007	Obese with co-morbidities	Cohort state transition	Pharmacological	QALY
Dalziel [23]	2007	Variable between intervention	Cohort state transition	Lifestyle	QALY
Galani [36]	2007	BMI 27–35	Individual sampling models	Lifestyle	QALY
Hoerger [25]	2007	Age 45–74 years and BMI ≥25	Cohort state transition	Screening and prevention	QALY
Icks [74]	2007	Age 60–74 years, BMI ≥24, pre-diabetic	Cohort decision tree	Lifestyle and pharmacological	Diabetes
Lindgren [27]	2007	Age 60 years, BMI ≥25 FBG >6.1	Cohort state transition	Lifestyle	QALY
van der Brugen (RIVM) [56]	2007	General population	Cohort life table	Lifestyle	QALY
Bemelmans (RIVM) [59]	2008	BMI ≥25	Cohort life table	Lifestyle	QALY
Colagiuri [22]	2008	Age 45–54 years with one or more risk factor, or age 55–74 years	Cohort state transition	Screening and prevention	DALY
Gillies [24]	2008	Age >45 years, high risk	Cohort state transition	Screening and prevention	QALY
Hampp [38]	2008	BMI ≥27, dyslipidaemia, hypertension	Cohort decision tree	Pharmacological	QALY
Iannazzo [40]	2008	BMI ≥30 and no T2DM	Cohort state transition	Pharmacological	QALY
Roux [51]	2008	General population	Cohort state transition	Lifestyle	QALY
van Baal (RIVM) [53]	2008	BMI ≥30	Cohort life table	Pharmacological	QALY
Cobiac (ACE) [49]	2009	General population	Cohort state transition	Policy and lifestyle	DALY
Johansson [52]	2009	General population	Cohort state transition	Lifestyle	QALY
Picot [43]	2009	BMI >35 and T2DM or hypertension	Individual sampling models	Obesity surgery	QALY
Bertram [20]	2010	Age >55 years/age >45 years plus pre-diabetes	Individual sampling models	Screening and prevention	DALY
Cechecci [57]	2010	General population	Individual sampling models	Policy and lifestyle	DALY
Cobiac (ACE) [54]	2010	Mean BMI 34	Cohort state transition	Lifestyle	DALY
Schaufler [30]	2010	Age 35–75 years	Individual sampling models	Screening and prevention	QALY
Smith [32]	2010	Metabolic syndrome and BMI >25	Cohort state transition	Lifestyle	QALY
Trueman [45]	2010	BMI ≥28	Individual sampling models	Lifestyle	QALY
Feenstra (RIVM) [58]	2011	General population	Cohort life table	Lifestyle and pharmacological	QALY

Table 1 continued

Study	Year	Population group targeted	Model structures	Type of intervention	Outcome measure
Forster (ACE) [46]	2011	Overweight or obese	Cohort state transition	Lifestyle	DALY
Lohse [50]	2011	Gestational diabetes	Cohort decision tree	Lifestyle and pharmacological	DALY
Gillet 2011 [37]	2011	IGT	Individual sampling models	Screening and prevention	QALY
Sacks (ACE) [47]	2011	General population	Cohort state transition	Policy	DALY
Sullivan [33]	2011	IFG or IFG and PreDx score	Cohort state transition	Lifestyle	QALY
Veerman (ACE) [48]	2011	Obese adults	Cohort state transition	Pharmacological	DALY
Gillett [6]	2012	IGT	Individual sampling models	Lifestyle	QALY
Michaud [42]	2012	Age >50 years, BMI >30	Individual sampling models	Obesity surgery and pharmacological	Life-year
Palmer [29]	2012	IGT	Individual sampling models	Lifestyle and pharmacological	QALY
Zhuo [34]	2012	General population or age 65–84 years	Cohort state transition	Lifestyle	QALY

BMI body mass index, *T2DM* type 2 diabetes mellitus, *IGT* impaired glucose tolerance, *CVD* cardiovascular disease, *DPP* diabetes prevention programme, *QALY* quality-adjusted life-year

physical activity. The Archimedes model included a detailed individual sampling model of the progression of diabetes through FPG, and insulin function [60].

We identified two multivariate risk equations for diabetes incidence [12, 61]. Johnasson [52] and Caro [55] adopted a multivariate regression with FPG, BMI, high-density lipoprotein (HDL)-cholesterol and systolic blood pressure as covariates in a regression predicting risk of diabetes incidence over 7.5 years. The regression was estimated from the San Antonio longitudinal cohort [61]. Both models were cohort state transition models in which the cohort risk of diabetes was estimated from mean FPG, BMI, HDL-cholesterol and systolic blood pressure estimates.

In a NICE public health evaluation, the economic model adopted the QDScore [12], which estimates diabetes risk based on data routinely collected from primary care databases including: ethnicity, deprivation, BMI, smoking, treated hypertension, family history of diabetes, corticosteroid use and cardiovascular disease [12].

3.1.2 Cardiovascular Disease

There was variability between studies in the number of complications and co-morbidities that were included as outcomes. Twenty-eight studies included cardiovascular outcomes in the model (Table 2).

Details of how the risk of cardiovascular disease and cerebrovascular disease outcomes were estimated are reported in Columns 6 and 7 of Table 3. The Framingham risk score was used in 14 economic models to estimate the 10-year risk of cardiovascular disease [62]. The UK Prospective Diabetes Study (UKPDS) risk models [63, 64] were used in four economic models. Nine studies used other risk estimates from observational studies, national statistics and simulated estimates. The choice of risk model for cardiovascular outcomes was strongly associated with the underlying risk factor for diabetes in the model. If IGR status determined the risk of diabetes, most models adopted UKPDS risk models to estimate cardiovascular events after onset of diabetes [6, 16, 17, 25, 27, 34]. Three alternative methods included the Framingham equations [20], population prevalence data [22, 30] and one method was not referenced [32].

Five studies that included cardiovascular events in an IGR type framework did not assume a risk of cardiovascular disease before the onset of diabetes [22, 25, 30, 32, 34]. Therefore, cardiovascular events were only treated as a complication associated with diabetes. However, Herman [17], Ackerman [16], Lingdren [27] and Gillett [6] used the UKPDS risk equations to estimate cardiovascular complications in IGR health states. Herman [16] and Ackerman [17] reduced the risk scores by a fixed factor, whereas Lingdren [6] and Gillet [27] used the coefficients of the risk equation (age, duration of disease, metabolic profile) to estimate the reduced risk in an IGR population. Bertram [20] applied the Framingham risk equations to individuals before diabetes diagnosis. Models with BMI or multiple risk factors for diabetes were more likely to use the Framingham risk equations [14, 15, 36, 40, 44, 45, 51, 52, 55]. In these models, cardiovascular disease is better described as co-morbid to diabetes than a complication arising after diagnosis.

Table 2 Non-diabetes complications included as explicit health states in models

Study	Year	Cardiovascular disease	Cerebrovascular disease	Retinopathy	Nephropathy	Neuropathy	Foot ulcer	Hypoglycaemia	Osteoarthritis	Cancers
Segal [31]	1998									
Clegg [35]	2003									
Caro [21]	2004	✔	✔	✔	✔	✔	✔	✔		
Palmer [28]	2004									
Warren/Ara [14, 15]	2004/7	✔								
Eddy [65]	2005	✔	✔	✔	✔	✔	✔	✔		
Herman/Ackerman [16, 17]	2005/6	✔	✔	✔	✔	✔				
Hertzman [39]	2005									
Lacey [41]	2005									
Roux [44]	2006	✔								
Caro [55]	2007	✔								
Daziel [23]	2007									
Galani [36]	2007	✔	✔							
Hoerger [25]	2007	✔	✔	✔	✔	✔				
Icks [74]	2007									
Lindgren [27]	2007	✔	✔							
RIVM [53, 56, 58, 59]	2007	✔	✔						✔	✔
Colagiuri [22]	2008	✔	✔	✔	✔					
Gillies [24]	2008									
Hampp [38]	2008	✔								
Iannazzo [40]	2008	✔								
Roux [51]	2008	✔	✔							✔
ACE [46–49, 54]	2009	✔	✔						✔	✔
Johansson [52]	2009	✔	✔	✔	✔	✔	✔			
Picot [43]	2009	✔	✔							
Bertram [20]	2010	✔	✔		✔					
Cecchini [57]	2010	✔	✔							✔
Schaufler [30]	2010	✔	✔	✔	✔		✔			
Smith [32]	2010	✔	✔	✔	✔	✔				
Trueman [45]	2010	✔								✔
Lohse [50]	2010									
Gillett [37]	2011	✔	✔						✔	✔
Sullivan [33]	2011									
Gillett [6]	2012	✔	✔	✔	✔	✔				
Michaud [42]	2012	✔	✔							
Palmer [29]	2012									
Zhou [34]	2012	✔	✔	✔	✔	✔				

Table 3 Data sources for diabetes mellitus and cardiovascular risks

Study	Year	Diabetes risk	Data used to estimate baseline diabetes risk	Source of diabetes risk	Data used to estimate CVD risk	Source of CVD risk
Segal [31]	1998	IGR	RCT	Malmo study [75]		
Clegg [35]	2003	BMI	RCT	RCT follow-up [76]		
Caro [21]	2004	IGR	RCT	Acarbose RCT [77]	RCT	UKPDS [78]
Palmer [28]	2004	IGR	RCT	DPP [67]		
Warren/Ara [14, 15]	2004/7	BMI	Observational	Nurses Health Survey [79] and RCT [80]	Observational	Framingham Heart Study [62]
Eddy [65]	2005	Multiple	Clinical models	Archimedes model [60]	Clinical models	Archimedes model [60]
Herman/Ackerman [16, 17]	2005/6	IGR	RCT	DPP [67]	RCT	UKPDS [63, 64]
Hertzman [39]	2005	BMI	Observational	Nurses Health Survey and Health Professionals Study [69]		
Lacey [41]	2005	BMI	Observational	Nurses Health Survey and Health Professionals Study [69]		
Roux [44]	2006	BMI	Observational	Nurses Health Survey [79, 81]	Observational	Framingham Heart Study [62]
Caro [55]	2007	Multiple	Observational	San Antonio Cohort [61]	Observational	Framingham Heart Study [62]
Dalziel [23]	2007	IGR	RCT	Finnish DPS [82]		
Galani [36]	2007	BMI	Observational	Nurses Health Survey and Health Professionals Study [69]	Observational	Framingham Heart Study [62]
Hoerger [25]	2007	IGR	RCT	DPP [67]	RCT	UKPDS [63, 64]
Icks [74]	2007	IGR	Observational	Hoorn Cohort [70]		
Lindgren [27]	2007	IGR	RCT	Finnish DPS [68]	RCT	UKPDS [63, 64]
RIVM [53, 56, 58, 59]	2007	Multiple	Prevalence	Government report [83]	Prevalence	Government report [83]
Colagiuri [22]	2008	IGR	National statistics	Australian Bureau of Statistics [84, 85]	Prevalence	Australian Bureau of Statistics [84, 85]
Gillies [24]	2008	IGR	Meta-analysis	Meta-analysis [24]		
Hampp [38]	2008	BMI	Observational	Nurses Health Survey [86] and British men cohort [87]	Observational	Nurses Health Study and Physicians Health Study [88, 89]
Iannazzo [40]	2008	BMI	RCT	XENical trial [90]	Observational	Framingham Heart Study [62]
Roux [51]	2008	Activity	National statistics	Centres for disease control and prevention [91]	Observational	Framingham and South London Stroke register [92, 93]
ACE [46–49, 54]	2009	BMI	Meta-analysis	Cohort meta-analysis [94]	Prevalence	Australian Bureau of Statistics [84, 85]
Johansson [52]	2009	Multiple	Observational	San Antonio Cohort [61]	Observational	Framingham Heart Study [62]
Picot [43]	2009	BMI	RCT			
Bertram [20]	2010	IGR	Observational	AusDiab Cohort [95] DISMOD [96]	Observational	Framingham Heart Study [62]
Cecchini [57]	2010	Multiple	Prevalence	DISMOD [96]	Prevalence	DISMOD [96]
Schaufler [30]	2010	IGR	Prevalence	KORA Survey 2000 [97]	Observational	CODE-2 [98]
Smith [32]	2010	IGR	RCT/observational	DPP [67] and Framingham [99]	Not reported	Not reported
Trueman [45]	2010	BMI	Prevalence	NHANES [100]	Observational	Framingham validation [101]
Lohse [50]	2010	GDM	RCT	DPP in GDM [102]		
Gillett [37]	2010	Multiple	Observational	QDScore [12]	Observational	QRISK2 [103]

Table 3 continued

Study	Year	Diabetes risk	Data used to estimate baseline diabetes risk	Source of diabetes risk	Data used to estimate CVD risk	Source of CVD risk
Sullivan [33]	2011	IGR	Observational	Inter 99 cohort [104]		
Gillett [6]	2012	IGR	RCT	Finnish DPS [82]	RCT/ observational	UKPDS [63, 64]/Framingham [62]
Michaud [42]	2012	BMI				
Palmer [29]	2012	IGR	RCT	DPP [67, 105]		
Zhou [34]	2012	IGR	Observational	ARIC cohort (82)	RCT	UKPDS [106]

CVD cardiovascular disease, *IGR* impaired glucose regulation, *DPP* diabetes prevention programme, *DPS* Diabetes Prevention Study, *FPG* fasting plasma glucose, *IGT* impaired glucose tolerance, *BMI* body mass index, *UKPDS* UK Prospective Diabetes Study, *NHANES* National Health and Nutrition Examination Survey, *RCT* randomized controlled trial

Five models included cholesterol and blood pressure in the estimation of cardiovascular risk to account for other risk factors for cardiovascular disease [27, 36, 52, 55, 65]. In two models, the impact of the intervention on cholesterol and blood pressure was modelled from cross-sectional data [37, 44]. One study estimated the reduction in cardiovascular disease risk over 12 months directly from an RCT for sibutramine [15].

3.1.3 Other Complications/Co-morbidities

We also observed a difference in the types of other outcomes included in the models dependent on whether BMI or hyperglycaemia was used to estimate the risk of diabetes. Twelve studies included microvascular complications such as nephropathy, neuropathy, retinopathy or foot ulcers [6, 16, 17, 20–22, 25, 30, 32, 34, 52, 65]. The studies that included microvascular complications all estimated risk of diabetes conditional on glycaemia [6, 16, 17, 21, 22, 25, 30, 34] or glycaemia in combination with other risk factors [52, 65]. These models were used to evaluate high-risk identification strategies to target individuals with hyperglycaemia. However, these models did not include other co-morbid outcomes such as cancer or osteoarthritis.

Nine out of 19 models where BMI and/or physical activity were used to estimate the risk of diabetes included cancer and osteoarthritis [37, 45, 48, 49, 51, 53, 54, 57, 58, 66]. Diabetes-related microvascular complications were not explicitly included in any of these models.

3.2 Objective 2: Parameter Sensitivity

One-way sensitivity analyses were extracted from all of the studies included in this review. Six of the studies did not report sensitivity analyses on individual parameters of the model [23, 36, 37, 40, 46, 57]. Ten studies reported a very small number of sensitivity analyses that were not informative about the sensitivity of the model to diabetes-related co-morbidities [16, 26, 27, 30, 45, 47, 51, 58, 59, 66]. The remaining studies reported multiple one-way sensitivity analyses; however, only a small number of these tested parameters related to diabetes-related co-morbidities. Sensitivity analyses such as the impact of discount rates, time horizons, intervention efficacy and intervention costs were frequently reported but are not summarised here because they do not inform the model structure.

Four studies reported the sensitivity of the model results to the baseline risk of diabetes [21, 28, 33, 52]. Three of these found that the baseline risk of type 2 diabetes was an influential parameter in the model [21, 28, 33], whereas Johansson (2007) reported that changing the data source for the risk of diabetes did not impact on outcomes [52]. It is noteworthy that the three models in which the risk of diabetes was more sensitive had substantially simpler model structures and did not include complications or co-morbidities for diabetes.

Warren [15] excluded the costs and quality-adjusted life-years (QALYs) of type 2 diabetes and cardiovascular disease from the analysis and found that the model was highly sensitive to these variables and their exclusion produced a higher cost-per-QALY estimate.

Gillett [6] tested assumptions regarding the risk of cardiovascular outcomes whilst in an IGR health state. In the base case, the UKPDS risk score was used allowing the coefficients to estimate a lower incidence of coronary heart disease and stroke because of age and duration of diagnosis. In a sensitivity analysis the authors reduced the risk of coronary heart disease and stroke by 30 %. The intervention was more cost effective, reducing the incremental cost-effectiveness ratio from £1,819 to £419, suggesting that risk of cardiovascular disease before diabetes diagnosis is influential on model results.

No studies tested the impact of the inclusion of retinopathy, nephropathy, neuropathy, osteoarthritis or cancers

upon the model results. It is not appropriate to compare results from studies including and excluding these co-morbidities because of the heterogeneity between them.

3.3 Objective 3: Data Sources

The review has identified several useful data sources for economic evaluations of diabetes prevention policies. Details of the data sources used to estimate the risk of diabetes and cardiovascular disease are reported in Table 3. The United States Diabetes Prevention Program [67] and the Finnish Diabetes Prevention Study [68] were the main sources of data for the incidence of diabetes from IGR. The relationship between BMI and diabetes risk most often came from the Nurses Health Survey and Health professional survey, which are longitudinal cohorts from the US [69]. We identified four longitudinal cohort studies with multiple metabolic risk factors measured at baseline that were associated with diabetes incidence at a future time point [12, 61, 70, 71].

The UKPDS and Framingham risk equations were the most commonly used equations for estimating the incidence of cardiovascular events [62–64]. The UKPDS was most commonly used to estimate the risk of cardiovascular events after diabetes, with adjustments for pre-diabetic states. The QRISK2 algorithm was used in Gillett (2011) because it was a more representative risk model for a UK population [37].

Of the data sources identified in the QResearch cohort, the UKPDS trial and the British regional heart study collected data on individuals from the UK. The QResearch cohort is representative of a UK population because it is based on anonymised health records; therefore the risk equations are more representative of UK incidence of diabetes and cardiovascular disease than the Framingham risk equations. The UKPDS trial is representative of a UK population with diagnosed diabetes and can be used to estimate cardiovascular risk amongst diabetic patients. However, the cohort started collecting data in 1977 and therefore may not be representative of a current prevalent cohort of type 2 diabetic patients. Whilst the QResearch is more representative of the UK general population, it only includes a binary variable for diagnosed diabetes. Therefore, it is not sensitive to the impact of HbA_{1c}, which has been estimated from the UKPDS analysis. As a consequence, different cohorts may not be appropriate for all individuals at all stages of a simulation model. The British regional heart study collected a representative sample of men aged 40–59 years from multiple locations in Britain. However, the absence of women in the survey limits its application to estimating the risk of diabetes and cardiovascular risk in the general population.

3.4 Objective 4: Strengths and Weaknesses

3.4.1 The Incidence of Diabetes

The models using IGR to define diabetes risk produced a relatively inflexible model structure because the incidence of diabetes was only representative of individuals meeting the RCT inclusion criteria. The structure does not describe other patient attributes such as BMI, ethnicity, or age that are known to impact on the incidence of diabetes. Changing the target population to receive intervention with the IGR structured model would require a new set of data inputs to describe the incidence of diabetes in the revised population.

The studies that describe BMI as the only risk factor for diabetes are slightly more flexible than the IGR approach because alternative baselines can easily be specified. The data inputs for these models tended to come from longitudinal cohort studies in which a continuous relationship between BMI and diabetes incidence could be specified, which means that it is possible to run analyses of multiple target groups with different baseline BMI. However, by focussing on BMI as the risk factor for diabetes it is not possible to estimate the risk according to other risk factors. Therefore, the broader effects of an intervention on lowering cholesterol or blood pressure will be disadvantaged because these effects will not be accounted for in the model. None of these models included a discrete health state for IGR prior to diagnosis of diabetes.

We identified two studies that had adopted a multivariate risk equation for diabetes incidence that included BMI, FPG, systolic blood pressure, HDL-cholesterol, age and sex [52, 55]. This model structure allowed the incidence of diabetes to vary according to individual characteristics. Alternative policies targeting BMI or IFG could be evaluated within a common framework. A second advantage of this modelling approach was that by including risk factors impacting upon both diabetes and cardiovascular disease such as systolic blood pressure and HDL, the model correlates risk of diabetes with risk of cardiovascular disease. Although these models offered a more flexible method for estimating diabetes risk, we identified other limitations that precluded immediate adoption of this modelling structure. First, the risk equation requires data on the effect of an intervention on all of the metabolic risk factors that may not be collected in intervention trials. These effects would need to be estimated using additional data sources. Second, the equation only includes FPG to measure glycaemia, whereas the HbA_{1c} test is becoming favoured for high-risk identification strategies [72]. Further statistical modelling would be required to estimate the relationships between HbA_{1c} and FPG scores. Third, some additional risk factors for diabetes such as ethnicity, social deprivation and a

family history of diabetes were not included, but may be targeted as part of public health policies.

3.4.2 *Cardiovascular Disease, Other Complications and Co-morbidities*

The data sources and structural assumptions regarding cardiovascular outcomes were different according to whether the studies used IGR, BMI or multiple risk factors for estimating diabetes outcomes. IGR models conceptualised cardiovascular outcomes as diabetes-related complications and consequently several models assumed that cardiovascular events did not occur prior to diabetes. This assumption may affect the model results because the benefits of remaining in IGR are over-estimated. However, in contrast the IGR models were more likely to include a detailed description of diabetes that included explicit modelling of micro-vascular events. This is likely to be because the IGR models were often adaptations of diabetes treatment models or used in conjunction with assessment of diabetes screening policies, which justified a more detailed approach to modelling diabetes complications.

4 Discussion

In answer to objective 5, we did not identify an economic model whose design and structure was completely suitable for comparing the cost effectiveness of diabetes prevention interventions within the general population, for individuals with hyperglycaemia, and for individuals who demonstrate metabolic risk factors associated with cardiovascular disease and type 2 diabetes. The majority of the models identified in this review could estimate the incidence of diabetes for a set of individuals or cohort according to the metabolic risk profile (i.e. BMI) or a blood test for glycaemia (FPG, OGTT or HbA_{1c}), but not both. This structural limitation for the current decision problem can be resolved with a multivariate risk equation for diabetes. We identified two multivariate risk scores for diabetes. Stern [61] included several metabolic risk factors that was useful because both BMI and glycaemic status were included. However, one of the limitations of this risk equation was that it did not include many of the non-clinical risk factors for diabetes that can be used to identify individuals for a screening programme. In contrast, the QDiabetes score used in Gillett included BMI, ethnicity, deprivation, smoking and a family history of diabetes [12, 37]. However, this risk equation did not include data on FPG or HbA_{1c} test results. Consequently, we propose that further statistical analysis is required to pool together the strengths of both approaches. Including other risk factors will increase the complexity of the model, but will account for within-individual correlations between the risks of diabetes and cardiovascular disease. A multivariate risk model for diabetes diagnosis would describe the independent effects of multiple risk factors for diabetes, thus allowing a range of policies impacting upon different risk factors to be assessed.

There are some methodological advantages and also limitations in relation to the review. The search process adopted broad inclusion criteria for intervention type and target population to capture interventions in a range of at-risk populations. Rather than conducting a large new systematic review, we updated recent, good-quality, systematic reviews of diabetes and obesity prevention interventions. We have updated the reviews to identify recently published articles and articles that did not meet the inclusion criteria of previous reviews, given our objective to identify models that include diabetes diagnosis as an outcome. The review excluded evaluations of interventions in children because the time horizon and diabetes progression in children is markedly different to an adult population. We identified two reviews of interventions in IGR [6, 8] and two in obesity [7, 11]. As a consequence we have identified a broad distinction between models that describe risk through IGR or BMI. A previous systematic review of cost-effectiveness studies of obesity compared modelling methods and identified methodological deficiencies in the models [11].

It is clear that to change population-wide behaviour patterns, prevention is needed across a spectrum of population-wide and targeted interventions [73]. What is less clear is how to allocate resources across this spectrum. To answer this question, models are required that are flexible to consider multiple populations and intervention types. This review of economic studies provided an important step in the design and development of a future policy analysis model. However, further research is needed to develop an economic model of a broad range of diabetes prevention interventions, including literature searches for data on the epidemiology of diabetes prevention and its co-morbidities, input from stakeholders to develop our understanding of the decision problem and a clinically appropriate model structure, the development of a description of current resource pathways, and new statistical analyses to develop a bespoke tool for predicting diabetes, conditional on multiple risk factors.

5 Conclusion

We have undertaken a review to identify issues of importance for future health economic models of diabetes prevention. Existing models either use the metabolic risk profile (i.e. BMI) or a blood test for glycaemia to estimate

diabetes outcomes, and as such are not able to compare targeted and population-wide diabetes prevention interventions. We found that cardiovascular events were commonly modelled, whereas microvascular outcomes and cancer were only included in a minority of models. Examination of sensitivity analyses did not provide sufficient evidence to conclude if complications and co-morbidities were influential on model results. We conclude that to compare a range of prevention interventions it is necessary to incorporate multiple risk factors for diabetes, diabetes-related complications and obesity related co-morbidity outcomes. None of the identified papers included all of these features.

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