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Screening for type 2 diabetes: literature review and economic modelling

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Abstract

Screening for type 2 diabetes: literature review and economic modelling

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Objectives: To reconsider the aims of screening for undiagnosed diabetes, and whether screening should be for other abnormalities of glucose metabolism such as impaired glucose tolerance (IGT), or the 'metabolic syndrome'. Also to update the previous review for the National Screening Committee (NSC) on screening for diabetes, including reviewing choice of screening test; to consider what measures would be taken if IGT and impaired fasting glucose (IFG) were identified by screening, and in particular to examine evidence on treatment to prevent progression to diabetes in these groups; to examine the cost-effectiveness of screening; and to consider groups at higher risk at which screening might be targeted.

Data sources: Electronic databases were searched up to the end of June 2005.

Review methods: Literature searches and review concentrated on evidence published since the last review of screening, both reviews and primary studies. The review of economic studies included only those models that covered screening. The new modelling extended an existing diabetes treatment model by developing a screening module. The NSC has a set of criteria, which it applies to new screening proposals. These criteria cover the condition, the screening test or tests, treatment and the screening programme. Screening for diabetes was considered using these criteria.

Results: Detection of lesser degrees of glucose intolerance such as IGT is worthwhile, partly because the risk of cardiovascular disease (CVD) can be reduced by treatment aimed at reducing cholesterol level and blood pressure, and partly because some diabetes can be prevented. Several trials have shown that both lifestyle measures and pharmacological treatment can reduce the proportion of people with IGT who would otherwise develop diabetes. Screening could be two-stage, starting with the selection of people at higher risk. The second-stage choice of test for blood glucose remains a problem, as in the last review for NSC. The best test is the oral glucose tolerance test (OGTT), but it is the most expensive, is inconvenient and has weak reproducibility. Fasting plasma glucose would miss people with IGT. Glycated haemoglobin does not require fasting, and may be the best compromise. It may be that more people would be tested and diagnosed if the more convenient test was used, rather than the OGTT. Five economic studies assessed the costs and short-term outcomes of using different screening tests. None examined the long-term impact of different proportions of false negatives. All considered the costs that would be incurred and the numbers identified by different tests, or different cut-offs. Results differed depending on different assumptions. They did not give a clear guide as to which test would be the best in any UK screening programme, but all recognised that the choice of cut-off would be a compromise between sensitivity and specificity; there is no perfect test. The modelling exercise concluded that screening for diabetes appears to be cost-effective for the 40–70-year age band, more so for the older age bands, but even in the 40–49-year age group, the incremental cost-effectiveness ratio for screening versus no screening is only £10,216 per quality-adjusted life-year. Screening is more cost-effective for people in the hypertensive and obese subgroups and the costs of screening are offset in many groups by lower future treatment costs. The

cost-effectiveness of screening is determined as much by, if not more than, assumptions about the degree of control of blood glucose and future treatment protocols than by assumptions relating to the screening programme. The very low cost now of statins is also an important factor. Although the prevalence of diabetes increases with age, the relative risk of CVD falls, reducing the benefits of screening. Screening for diabetes meets most of the NSC criteria, but probably fails on three: criterion 12, on optimisation of existing management of the condition; criterion 13, which requires that there should be evidence from high-quality randomised controlled trials (RCTs) showing that a screening programme would reduce mortality or morbidity; and criterion 18, that there should be adequate staffing and facilities for all aspects of the programme. It is uncertain whether criterion 19, that all other options, including prevention, should have been considered, is met. The issue here is whether all methods of improving lifestyles in order to reduce obesity and increase exercise have been sufficiently tried. The rise in overweight and obesity suggests that health promotion interventions have not so far been effective.

Conclusions: The case for screening for undiagnosed diabetes is probably somewhat stronger than it was at the last review, because of the greater options for reduction of CVD, principally through the use of statins, and because of the rising prevalence of obesity and hence type 2 diabetes. However, there is also a good case for screening for IGT, with the aim of preventing some future diabetes and reducing CVD. Further research is needed into the duration of undiagnosed diabetes, and whether the rise in blood glucose levels is linear throughout or whether there may be a slower initial phase followed by an acceleration around the time of clinical diagnosis. This has implications for the interval after which screening would be repeated. Further research is also needed into the natural history of IGT, and in particular what determines progression to diabetes. An RCT of the type required by NSC criterion 13 is under way but will not report for about 7 years.

Contents

List of abbreviations

1,5-AG	1,5-antrydroglicitol
ACE	angiotensin-converting enzyme
ACEI	ACE inhibitor
ADA	American Diabetes Association
AHRQ	Agency for Healthcare Research and Quality
ARB	angiotensin receptor blocker
AUROC	area under receiver operating characteristic
BG	blood glucose
BMI	body mass index
BNF	British National Formulary
CA	cardiac arrest
CBG	capillary blood glucose
CDC	(US) Centers for Disease Control and Prevention
CHD	coronary heart disease
CI	confidence interval
CRS	Cambridge Risk Score
CT	computed tomography
CVD	cardiovascular disease
DBP	diastolic blood pressure
DCCT	Diabetes Control and Complications Trial
DPP	Diabetes Prevention Program
DPS	Diabetes Prevention Study
DRS	Diabetes Risk Score
EASD	European Association for the Study of Diabetes
ESRD	end-stage renal disease
FBG	fasting blood glucose
FPG	fasting plasma glucose
FRA	fructosamine
HbA_{1c}	glycosylated haemoglobin
HDL	high-density lipoprotein
HOMA	homeostasis model analysis
HRQoL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
IFG	impaired fasting glucose
IGT	impaired glucose tolerance
IHD	ischaemic heart disease
LADA	latent autoimmune diabetes in adults
LDL	low-density lipoprotein
LEA	lower extremity amputation
LYG	life-year gained
MI	myocardial infarction
NCEP-ATP	National Cholesterol Education Program Adult Treatment Panel
NDDG	National Diabetes Data Group
NGSP	National Glycohemoglobin Standardization Program
NGT	normal glucose tolerance
NHANES	National Health and Nutrition Examination Survey

continued

List of abbreviation *continued*

NICE	National Institute for Health and Clinical Excellence
NNS	number-needed-to-screen
NSC	National Screening Committee
OGTT	oral glucose tolerance test
OHA	oral hypoglycaemic agent
OR	odds ratio
PCDP	preclinical detectable phase
PCT	Primary Care Trust
PG	plasma glucose
PVD	peripheral vascular disease
QALY	quality-adjusted life-year
QWBI	Quality of Wellbeing Index
RCT	randomised controlled trial
RPG	random plasma glucose
RR	relative risk
SBP	systolic blood pressure
SD	standard deviation
SRQ	Symptom Risk Questionnaire
STOP-NIDDM	Study To Prevent Non-insulin Dependent Diabetes Mellitus
T2DM	type 2 diabetes mellitus
UKPDS	United Kingdom Prospective Diabetes Study
WHO	World Health Organization
YHPHO	York and Humber Public Health Observatory

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices in which case the abbreviation is defined in the figure legend or at the end of the table.

Executive summary

Background

The National Screening Committee (NSC) is responsible for providing advice on screening policy to all parts of the UK. A review of policy on screening for type 2 diabetes is due shortly, and this document was commissioned by the NHS R&D HTA Programme in order to support that review.

It is known that a proportion of people with type 2 diabetes are undiagnosed. Blood glucose levels can rise to diabetic levels with little or nothing in the way of symptoms. Sometimes by the time people are diagnosed with diabetes, they have developed complications such as the eye damage known as retinopathy, due to an effect of diabetes on small blood vessels (microvascular disease). However, the main risk to health in undiagnosed type 2 diabetes is an increased risk of cardiovascular disease, in particular ischaemic heart disease, because of damage to the arteries (macrovascular disease). Early detection of diabetes would lead to measures to reduce the risk of heart disease, such as the use of statins to lower cholesterol, and also reduction of blood glucose levels by, initially, diet and exercise, supplemented with hypoglycaemic drugs if necessary.

Microvascular disease such as retinopathy is specific to diabetes. However, the macrovascular disease seen in diabetes is broadly the same disease as seen in people without diabetes; the difference in diabetes is the increased risk. An important issue when considering whether there should be screening for diabetes is that unlike with retinopathy, the increase in risk starts below the level of blood glucose used to define diabetes. There are groups of people who have higher than normal blood glucose levels but who are not diabetic. They are classified according to whether their blood glucose level is raised when fasting [impaired fasting glucose (IFG)] or is normal when fasting but raised after meals, or after testing with a 75-g glucose drink. The second group are said to have impaired glucose tolerance (IGT).

The risk of heart disease is increased slightly in IFG but by about 60% in IGT.

Hence if reduction of heart disease is one of the aims of screening, then we should consider screening not just for diabetes, but also for IGT.

Objectives

The objectives of this review were as follows:

- to reconsider the aims of screening for undiagnosed diabetes, and whether screening should be for other abnormalities of glucose metabolism such as IGT, or the 'metabolic syndrome'
- to update the previous review for the NSC on screening for diabetes, including reviewing choice of screening test
- to consider what measures would be taken if IGT and IFG were identified by screening, and in particular to examine evidence on treatment to prevent progression to diabetes in these groups
- to examine the cost-effectiveness of screening, by a review of previous economic models, and by new modelling to take account of recent developments in treatment such as the use of statins
- as part of the economic analysis, to consider groups at higher risk at which screening might be targeted
- to identify research needs.

Methods

The literature searches (carried out up to the end of June 2005) and review concentrated on evidence published since the last review of screening, both reviews and primary studies. The review of economic studies included only those models that covered screening. The new modelling extended an existing diabetes treatment model by developing a screening module.

The NSC has a set of criteria, which it applies to new screening proposals. These criteria cover the condition, the screening test or tests, treatment and the screening programme. Screening for diabetes was therefore considered using these criteria.

Results

As was known before this review, undiagnosed diabetes can be detected by screening several years before it would become apparent after the development of symptoms. Earlier detection and treatment reduces the development both of specific diabetes problems such as eye disease and of cardiovascular disease. Treatment to reduce the risk of cardiovascular disease has become much less costly since the arrival of generic statins, which are now very cheap.

Detection of lesser degrees of glucose intolerance such as IGT is worthwhile, partly because the risk of cardiovascular disease can be reduced by treatment aimed at reducing cholesterol level and blood pressure, and partly because some diabetes can be prevented. Several trials have shown that both lifestyle measures and pharmacological treatment can reduce the proportion of people with IGT who would otherwise develop diabetes.

Screening could be two-stage, starting with the selection of people at higher risk, based on primary care records of age, weight and other indicators of metabolic risk such as hypertension. Screening might be targeted at those above a certain body mass index threshold, while recognising that any cut-off would be an arbitrary line on a continuum of risk. The second-stage choice of test for blood glucose remains a problem, as in the last review for NSC. All of fasting plasma glucose, the oral glucose tolerance test and glycated haemoglobin would be acceptable, but none is perfect. The best test is the oral glucose tolerance test (OGTT), but it is the most expensive, is inconvenient and has weak reproducibility. Fasting plasma glucose would miss people with IGT. Glycated haemoglobin does not require fasting, and may be the best compromise. It may be that more people would be tested and diagnosed if the more convenient test was used, rather than the OGTT.

A review of previous economic models showed that screening for diabetes appeared to be cost-effective. The models differed in some aspects but reached broadly similar conclusions. The strongest and most comprehensive came from the USA, and there were some doubts over their applicability to the UK.

Five previous modelling studies examined the costs and benefits of identification and screening of people with IGT. All predicted that diabetes prevention measures would provide good value for money. One was conducted from a UK perspective. Diet and exercise treatment is the most cost-effective option. Treatment with metformin may be less cost-effective than lifestyle changes, but would be appropriate in some groups. To some extent, the models may have underestimated benefit by focusing mainly on prevention of diabetes, and not taking full account of the benefits of lifestyle changes on risk factors for cardiovascular disease.

Five economic studies assessed the costs and short-term outcomes of using different screening tests. None examined the long-term impact of different proportions of false negatives. All considered the costs that would be incurred and the numbers identified by different tests, or different cut-offs. Results differed depending on different assumptions. They did not give a clear guide as to which test would be the best in any UK screening programme, but all recognised that the choice of cut-off would be a compromise between sensitivity and specificity; there is no perfect test.

The modelling exercise concluded that:

- Screening for diabetes appears to be cost-effective for the 40–70-year age band, more so for the older age bands than the 40–49-year band, but even in the 40–49-year age group, the incremental cost-effectiveness ratio for screening versus no screening is only £10,216 per quality-adjusted life-year.
- Screening is more cost-effective for people in the hypertensive and obese subgroups.
- The costs of screening are offset in many groups by lower future treatment costs.
- The cost-effectiveness of screening is determined as much by, if not more than, assumptions about the degree of control of blood glucose and future treatment protocols than by assumptions relating to the screening programme.
- The very low cost now of statins is an important factor.

Although the prevalence of diabetes increases with age, the relative risk of cardiovascular disease falls, reducing the benefits of screening.

Screening for diabetes meets most of the NSC criteria, but probably fails on three:

- criterion 12, on optimisation of existing management of the condition
- criterion 13, which requires that there should be evidence from high-quality randomised

controlled trials showing that a screening programme would reduce mortality or morbidity
- criterion 18, that there should be adequate staffing and facilities for all aspects of the programme.

It is uncertain whether criterion 19 – that all other options, including prevention, should have been considered – is met. The issue here is whether all methods of improving lifestyles in order to reduce obesity and increase exercise have been sufficiently tried. The rise in overweight and obesity suggests that health promotion interventions have not so far been effective.

Conclusions

The case for screening for undiagnosed diabetes is probably somewhat stronger than it was at the last review, because of the greater options for reduction of cardiovascular disease, principally through the use of statins, and because of the rising prevalence of overweight and hence type 2 diabetes. However, there is also a good case for screening for IGT, with the aim of preventing some future diabetes and reducing cardiovascular disease.

Research needs

One key uncertainty concerns the duration of undiagnosed diabetes, and whether the rise in blood glucose levels is linear throughout or whether there may be a slower initial phase followed by an acceleration around the time of clinical diagnosis. This has implications for the interval after which screening would be repeated.

Another uncertainty is the natural history of IGT, and in particular what determines progression to diabetes.

Research needs include the above, and

- Research into ways of reducing the prevalence of insulin resistance. For example, what forms and amounts of exercise are required to prevent or reduce insulin resistance?
- How can public health campaigns on lifestyle measures be made more effective? Most cases of type 2 diabetes are preventable. What balance should be struck between the public health, prevention by lifestyle approach, and the more medical model of care focused on the individual?
- If screening were to be introduced, should it be repeated, and, if so, at what interval? More data on the natural history of IGT may emerge from current research.
- If a decision were taken in principle that selective screening should commence, further modelling as suggested in Chapter 5 could help with selection.
- A trial in which populations were cluster randomised by practice to different screening tests, with economic evaluation built in, might be useful for showing which test was best in terms of both screening parameters and practicality.

A randomised controlled trial of the type required by NSC criterion 13 is under way but will not report for about 7 years.

Chapter 1
Background

The purpose of this review is to underpin forthcoming discussions at the UK National Screening Committee (NSC) on a review of policy on screening for type 2 diabetes mellitus (T2DM). The main aim was to look at evidence which had emerged since the last review, and so the first aim was to examine recent reviews and any new primary evidence not included in these reviews. However, as discussed in more detail below, screening for diabetes could, depending on the cut-off chosen for tests being positive, detect more people with lesser degrees of glucose intolerance, such as impaired glucose tolerance (IGT), than with diabetes. The main aim of screening is to reduce the burden of disease from cardiovascular disease (CVD), to which people with diabetes are more susceptible. Those with IGT are also at increased risk, and although their relative risk (RR) is less than those with diabetes, there are far more of them than there are people with undiagnosed diabetes, and so there will be more cardiovascular events in those with IGT than in those with diabetes. They are also at risk of progression to diabetes.

Screening is therefore addressed from a somewhat wider perspective than in some previous reviews. A section has also been included that covers recent evidence on prevention of diabetes in those with what has been called 'pre-diabetes', although since most will not become diabetic, the term is not entirely satisfactory.

A key issue (details later) is that there is a continuum of CVD risk across all levels of blood glucose (BG). Hence there is no simple threshold at which people can be split into at risk and not at risk. In such circumstances, the final decision on whom to screen and treat (or at what level of risk to do so) can be illuminated by economic analysis, since that can provide data indicating when interventions become cost-effective.

Reviews of previous economic models of screening have been included. Considerable new modelling has also been carried out.

Finally, the extent to which screening for diabetes and IGT meets the NSC criteria is also considered.

Screening for type 2 diabetes – the issues

The NSC reviewed screening for T2DM a few years ago, and the current policy statement is on the NSC website (www.nsc.nhs.uk). The case for screening was assessed, as usual, against clearly defined criteria, looking in turn at;

- the condition
- the screening test
- the treatment
- the screening programme.

This review therefore does not start from a zero base, but from the present NSC policy, underpinned by the work of Wareham and Griffin[1] for the last policy review.

An assessment of the case for screening, judged against the criteria, and based on the previous review, is available on the NSC website. Many of the criteria were met, but there were concerns or doubts over:

- whether all the cost-effective primary prevention interventions had been applied (criterion 3)
- the screening test, and in particular which threshold of BG should be used, bearing in mind the need to focus more on large vessel disease such as ischaemic heart disease (IHD) (criterion 6)
- whether screening and treatment should be specifically aimed at diabetes, or a wider range of factors predisposing to IHD risk (criterion 11)
- whether treatment of existing diabetes was optimised (criterion 12)
- the lack of randomised controlled trials (RCTs) of screening (criterion 13)
- the balance between benefits and harms of widespread screening (criterion 15)
- the ability of the NHS to cope with a large number of people with newly diagnosed diabetes (criterion 18).

Note that the NSC criteria are updated from time to time, for example to cover new scenarios such as genetic testing, and the numbering used above

reflects the current set, which are different from those used at the time of the last review. The current criteria are listed for convenience in Appendix 2.

In this review, the case for screening will be assessed against the criteria, but focusing mainly on those where there were concerns last time, or on those where the evidence base may have changed. We do not address type 1 diabetes, where screening is not required, or gestational diabetes, which was the subject of a previous review.[2]

The NSC criteria now fall into groups as follows:

- the condition (criteria 1–4)
- the test (criteria 5–9)
- the treatment (criteria 10–12)
- the screening programme (criteria 13–22).

Some of the criteria are not applicable to this review. Criteria 4, 9 and 22 deal with genetic screening. Criteria 17, 18 and 20 are concerned with the running of screening programmes and need not be addressed until a decision in principle to provide it is taken.

The criteria that seem most important to the current review are discussed below. The others that are relevant, and the evidence which relates to them, will be dealt with in Chapter 6.

The condition

NSC criterion 1 – the condition should be an important health problem

The importance of T2DM has not diminished. Indeed, the trend in the prevalence is upwards, with a rise in all-age prevalence due to demographic change, and almost certainly a rise in age-specific prevalences due to increasing levels of obesity. It has been estimated that there will be an increase in prevalence of 16% for England between 2001 and 2010, based on ONS census projections and current obesity trends.[3]

However, it may be worth reflecting on what we would be trying to achieve by screening for T2DM. People with T2DM are less prone than those with type 1 diabetes to the acute metabolic complications such as diabetic ketoacidosis, which still causes deaths in the young. However, if good glycaemic control is not achieved, they are at risk of the specific diabetic microvascular complications such as retinopathy and nephropathy. An increasing proportion (in some centres over half) of diabetic people on renal dialysis have T2DM.[4]

However, the biggest problem in T2DM is large vessel disease, and most people with T2DM die of coronary heart disease. Diabetes is also important in peripheral vascular disease (PVD) and stroke.[5,6] In most studies looking at the relationship between BG and mortality in T2DM, the higher the glucose level, the higher is the mortality, but the rise per unit of glucose [e.g. per mmol/l of fasting plasma glucose (FPG) or per 1% of glycosylated haemoglobin (HbA_{1c})] is modest.[7]

The importance of large vessel disease can be seen in the end-points reported in the UK Prospective Diabetes Study (UKPDS). *Table 1* shows the numbers for most of the end-points in the conventionally treated group (UKPDS 33).[8]

Hence the majority of adverse events were due to large vessel disease. Most of the microvascular end-points were made up of retinal photocoagulation for retinopathy, the risk of which is probably less in the group who would be detected by screening. It should be noted that amongst the UKPDS patients, there were some who might now be classified as latent autoimmune diabetes in adults (LADA), rather than true T2DM.

However, if we take only those who were in the overweight group who were randomised to

TABLE 1 *Numbers of end-points in UKPDS*

Endpoint	Number
Macrovascular	
Fatal MI	91
Non-fatal MI	101
Sudden death	18
Heart failure	36
Angina	72
Stroke	59
Amputations and death from PVD	21
Microvascular	
Death from renal disease	2
Renal failure	9
Blindness in one eye	38
Vitreous haemorrhage	10
Photocoagulation for retinopathy	117
All macrovascular	397
All microvascular	176

MI, myocardial infarction.

TABLE 2 *End-points in the overweight UKPDS group – controls only (N = 411)*

End-point	Number
Macrovascular	
All IHD (MI, heart failure, angina)	121
Stroke	25
PVD	11
Microvascular	
Renal failure	3
Blind in one eye	13
Vitreous haemorrhage	3
Photocoagulation	36
All macrovascular	157
All microvascular	52

metformin or conventional treatment if their FPG at 3 months was higher than 6.0 mmol/l, and who may be more similar to those who would be found by screening, then the picture is similar. Overweight was defined as more than 120% of ideal body weight. *Table 2* shows the numbers of end-points in the control group (UKPDS 34).[9] Again, the end-points are dominated by large vessel disease.

Hence it could be argued (and has been in the past – see reviews by Goyder and Irwig[10] and Jarrett[11]) that the most important reason for screening for T2DM is in order to be able to intervene earlier with a view to reducing the risk of macrovascular disease, and mainly IHD.

What is diabetes?

A digression into the underlying rationale for the definition of diabetes is now necessary.
The only constant feature of diabetes is a raised BG level. There may or not be any of the classical symptoms such as the passing of larger volumes of urine and thirst. Many people with T2DM have no symptoms when diagnosed. Conversely, many people without diabetes report similar symptoms, and so the symptoms, at least in milder forms, are not specific to diabetes.[12,13]

However, the problem comes when defining what is meant by 'raised'.

Successive reports by working parties for the WHO[14,15] and the American Diabetes Association (ADA)[16,17] have examined the problems of diagnostic criteria for diabetes. The earlier history has been reviewed by Keen,[18] who noted that the classifications in the late 1970s, from the National Diabetes Data Group (NDDG) in the USA,[19] and the second report of the WHO Expert Committee[20] were based on a hybrid approach, being primarily based on clinical description according to treatment, but with some elements based on assumed aetiology. The classification divided diabetes mainly into insulin-dependent and non-insulin-dependent. However, these reports did at least produce diagnostic criteria in terms of a threshold for true diabetes (a fasting blood glucose level of 7.8 mmol/l or over, and a 2-hour post-load level of 11.1 mmol/l or over), hence removing the uncertainty over what should be classed as diabetes. The term 'impaired glucose tolerance' (IGT) was used to describe the situation where BG was raised above normal but was below the threshold for diabetes. This replaced terms such as 'borderline' diabetes. However, the lower limit for IGT was left somewhat vague.[18] The normal FPG level is up to 5.6 mmol/l.

The key feature of the classifications was that the diagnosis of diabetes was based on the level at which the risk of **retinopathy** started. At the risk of some over-simplification, people with glucose levels below the threshold did not get retinopathy; those above were at risk of retinopathy, with the risk increasing as glucose levels rose further. This was based on three studies, described in the report of the ADA's expert committee.[17]

Despite the rationalisation which the WHO and ADA classifications brought to a previously somewhat confused situation, some dissatisfactions remained. One was the 'hybrid' nature of the classification, and the confusion that arose because many people with non-insulin-dependent diabetes were being treated with insulin in order to achieve better control. A second was that the classification was too dependent on the oral glucose tolerance test (OGTT), which is an inconvenient and unphysiological test (involving drinking 75 g of glucose in water over a short period) with poor reproducibility. Another was that the two thresholds – 7.8 mmol/l for fasting and 11.1 mol/l for 2 hours after a glucose load – had imperfect correlation, in that the fasting level implied a greater degree of hyperglycaemia than the 2-hour level.

The ADA and WHO[14] groups reviewed their classifications. Their conclusions were fairly consistent (there was cross-representation between the expert groups), and the new classifications made a number of changes. First, diabetes was subdivided clearly, according to the need for insulin, into:

- Type 1 diabetes, where insulin treatment was required for survival, because the pancreatic islets cells have been destroyed by the disease process; this covers the insulin-dependent group from the previous definitions.
- T2DM, where pancreatic insulin production continues, but may be insufficient for control of blood sugar levels; most of this group will be treated with diet alone, or with tablets, but some will need insulin for control of BG. In the UKPDS patients, the trend was for glucose to rise over time.[21]

Second, the ADA threshold for the FPG level at which diabetes was diagnosed was lowered to 7.0 mmol/l, to be more compatible with the 2-hour level. It was anticipated that fasting glucose levels would be used as the main method of diagnosis, being more convenient and more reproducible. The ADA group envisaged that FPG would be the main method of diagnosis, with OGTTs being usually unnecessary.

The WHO group recommended the same fasting and 2-hour cut-off levels but, for epidemiological and screening purposes, preferred the 2-hour value.

The new ADA classification gives four groups;

- Those with both fasting and post-load levels above the thresholds – the diabetics, of whom those with FPGs between 7.0 and 7.8 mmol/l could be called the 'new' diabetics.
- Those with fasting above the upper limit of normal (6.1 mmol/l) but below 7.0 mmol/l; this group is said to have impaired fasting glucose (IFG).
- Those with a normal fasting glucose under 6.1 mmol/l, but with the post-load level above 7.8 but under 11.1 mmol/l; this group is described as having IGT.
- Those with fasting levels under 6.1 and post-load under 7.8 mmol/l, who are classed as normal.

A collaborative project by the European Diabetes Epidemiology Group, the DECODE study,[22] pooled data from 13 cohort studies, in order to examine the risks of mortality in the various groups, relative to those with normal (defined as under 6.1 mmol/l) glucose levels. Hazard ratios were as given in *Table 3*.

Taking IFG and IGT statuses in combination, a somewhat simplified version of some of their findings is as given in *Table 4*.

TABLE 3 *DECODE – hazard ratios for different glycaemic states*

State	Men	Women
Normal	1.0	1.0
IFG	1.21	1.08
IGT	1.51	1.60
'New diabetes'	1.81	1.79[a]

[a] Those with fasting glucose between 7.0 and 7.8 mmol/l.

TABLE 4 *Relative risks of mortality*

IFG status	IGT status	
	Normal 2-hour level	IGT
Normal fasting level	1.0	1.56 (1.33 to 1.83)
IFG	1.18 (0.99 to 1.42)[a]	

[a] 95% confidence intervals.

Hence IFG alone, without IGT, is associated with a slight increase in mortality [although the confidence intervals (CIs) overlap with no increase), but IGT carries more risk. Similar findings were reported from a meta-analysis by Coutinho and colleagues[23] of 20 studies examining cardiovascular mortality (19 studies) or morbidity (four studies). A fasting glucose level of 6.1 mmol/l carried 1.33 times the risk of the reference one of 4.2 mmol/l; a 2-hour glucose level of 7.8 mmol/l carried an RR of 1.58 compared with a 2-hour level of 4.2 mmol/l.

In both IFG and IGT, there is insulin resistance, but with different distributions. Pima Indians with IFG have higher fasting insulin levels than those with IGT, but the latter have higher post-prandial insulin levels.[24] There are also differences in other cardiovascular risk factors, with higher triglyceride and fibrinogen levels in IGT than IFG, reflecting the higher insulin resistance in IGT than IFG.[25]

IGT is common – it affects 17% of Britons aged 40–65 years.[26] This has implications for choice of a screening test – if FPG were to be used, a group of people whose FPG is normal but who have IGT would be missed. In the Rancho Bernardo study,[27] the RR of a cardiovascular event in women aged 50–89 years with normal FPG but IGT was 2.9. Similarly, a Paris study found that the heart disease mortality rate in men with normal fasting glucose but IGT was double that of those with

normal glucose tolerance.[28] However, an earlier paper from Paris[29] noted that fasting insulin levels were a better predictor of future heart disease than glucose levels, presumably reflecting the varying degrees of insulin resistance.

The Helsinki Police Study found the same.[30] In the 22-year follow-up, 10% of those in the lowest quintile of baseline insulin had an IHD event compared with 25% of those in the highest insulin quintile. Also, in the San Antonio Heart Study, Haffner found that the baseline insulin level predicted not only future T2DM, but also hypertension, low high-density lipoprotein (HDL) and high triglycerides.[31]

The DECODE group[32] carried out a meta-analysis of 11 studies and compared the cardiovascular mortality in the highest and lowest quartiles of plasma insulin levels. After adjustment for other risk factors, the risks were 1.54 in men and 2.66 in women in the highest quartiles.

In Japan, Tominaga and colleagues[33] found that IGT was a risk factor for CVD but that IFG was not. Numbers of deaths were fairly low and CIs wide, but by the 7-year follow-up, the cumulative survival in those with IGT was significantly lower then that of those with normal glucose levels, whereas the survival in those with IFG was not different from normal.

Unlike with retinopathy, there is no sudden inflection in the risk curve according to blood glucose levels, but rather a continuum of risk.

Indeed, even within what is regarded as being the entirely normal range, higher BG levels correlate with higher IHD rates. In the EPIC study in Norfolk,[34] the relationship between HbA_{1c} and cardiovascular risk started well within the non-diabetic range (*Table 5*).

A similar finding was reported by Piche and colleagues in Quebec,[35] although using 2-hour plasma glucose. They compared groups with low normal 2-hour plasma glucose (PG) (<5.6 mmol/l), 'high normal' (5.6–7.7 mmol/l) and with IGT. The high normal group were more obese (as measured by waist, visceral fat by computed tomography (CT) scan, and subcutaneous fat) than those with low normal PG. Their cholesterol:HDL ratio was also higher.

The same applies to PVD. Muntner and colleagues[36] reported data from the 1999–2002 NHANES survey. The figures in *Table 6* are after multivariate adjustment. PVD was defined as an ankle:brachial blood pressure ratio under 0.9. However, the CIs were wide and only the last figures had a 95% CI which did not overlap with 1.0.

TABLE 5 *EPIC study – relative risks by bands of glycated HbA_{1c}*

HbA_{1c} (%)	RR of CVD	
	Men	Women
<5%	1.0	1.0
5–5.4%	1.23	0.89
5.5–5.9%	1.56	0.98
6.0–6.4%	1.79	1.63
6.5–6.9 %	3.03	2.37
>7% (newly diagnosed diabetes)	5.01	7.96
Prior diabetes	3.32	3.36

TABLE 6 *NHANES – relative risks of PVD by bands of HbA_{1c}*

HbA_{1c} (%)	RR of PVD
<5.3%	1.0
5.3–5.4	1.41
5.5–5.6	1.39
5.7–6.0	1.57

There have been suggestions that the threshold for IFG should be reduced to 5.6 mmol/l.[37] This would greatly increase the prevalence of IFG. For example, in the DESIR study of French men and women aged 30–64 years, the prevalence of IFG would rise from the 13% in men and 4% in women seen using the old IFG threshold of 6.1 mmol/l to 40% in men and 16% in women.[38] Balkau and colleagues[38] noted that the risk of progression to diabetes is much less in old IFG than in new (*Table 7*). However the progression to IHD may show a different gradient.

It may be that IGT and IFG reflect different aetiologies. Piche and colleagues[39] followed a cohort of men who initially had normal glucose tolerance for 6 years. Some developed IFG and some IGT; most remained normal. Those who developed IFG tended to be leaner than those who developed IGT [baseline body mass index (BMI) 26 versus 28], and on CT had much less visceral fat. Those who developed IFG tended to have lower baseline fasting insulin, whereas those who developed IGT had higher levels. Hence IFG may reflect a production problem with insulin whereas IGT reflects insulin resistance. Numbers in this study were small: eight with IFG and 12 with IGT.

TABLE 7 *DESIR study – incidence of diabetes according to glycaemic status at baseline.*

		Incidence of diabetes per 1000 person-years		
IFG status	**Glucose level (mmol/l)**	**30–44 years**	**45–54 years**	**55–64 years**
Men				
Normal	<5.6	2.3	1.7	1.1
New IFG	5.6–6.0	4.9	8.5	11.5
Old IFG	6.1–6.9	24.7	38.9	63.9
Women				
Normal	<5.6	0.4	1.4	0.7
New IFG	5.6–6.0	5.5	7.0	5.9
Old IFG	6.1–6.9	35.7	52.3	66.7

The metabolic syndrome

The metabolic syndrome has been described as a cluster of cardiovascular risk factors associated with insulin resistance.[40] An operational definition was devised by the National Cholesterol Education Program Adult Treatment Panel (NCEP-ATP),[41] based on the presence of three or more of the following:

- Abdominal obesity – waist circumference over 40 inches (~100 cm) in men, and 35 inches (~90 cm) in women
- Triglycerides over 150 mg/dl (1.68 mmol/l)
- HDL cholesterol <40 mg/dl (1.03 mmol/l) in men, <50 µg/dl (1.29 mmol/l) in women
- Blood pressure 130 or more systolic, 85 or more diastolic
- Fasting glucose over 110 mg/dl (6.1 mmol/l).

Hypertension and diabetes are common components, and about 40% of those with the metabolic syndrome have diabetes.[40] Others will have lesser degrees of glucose intolerance. However, some will have normal glucose tolerance. The question therefore arises as to whether one should be screening for the metabolic syndrome because of the increased risk of CVD, rather than just for abnormalities of glucose metabolism.

Another issue concerns the choice of treatment for hypertension. People with hypertension have long been known to be at increased risk of diabetes, and in several studies it was noted that substantial proportions of newly diagnosed diabetic patients were on anti-hypertensive drugs (see Jarrett and Fitzgerald[42] for a review). This raised the possibility that some of the older drugs for hypertension such as thiazides might be causing some diabetes.[42]

A meta-analysis of recent trials has cast new light on this problem. Scheen[43] pooled results from eight RCTs of angiotensin-converting enzyme inhibitors (ACEIs) and reported that ACEIs and the more specific angiotensin receptor blockers (ARBs) appear to reduce the incidence of diabetes, albeit only modestly, from 9.6% in those not treated with an ACEI or ARB to 7.4% in those who were. This finding applied whether the controls were given placebo or older drugs such as thiazides. Those on thiazides or beta-blockers had no greater incidence of diabetes than those on placebo.

In a more recent meta-analysis, Gillespie and colleagues[44] included 14 trials of ACEIs or ARBs and found that these drugs reduced the incidence of T2DM by 22% [odds ratio (OR) 0.78; 95% CI 0.73 to 0.83].

Hence screening for diabetes might provide benefit to those with hypertension who are found to have IGT or IFG; their hypertensive treatment could be changed to an ACEI or ARB, which should reduce the risk of progression to diabetes.

The WHO definition of the metabolic syndrome is couched more in terms of insulin resistance:

- T2DM, IFG or IGT, or normal glucose level but high insulin level plus two or more of
- elevated blood pressure – systolic 160 or over, diastolic 90 or over
- elevated triglycerides – 1.7 mmol/l or over
- low HDL cholesterol – <0.9 mmol/l in men and <1.0 mmol/l in women
- obesity – BMI >30, or central obesity with waist:hip ratio >0 .90 in men and, >0.85 in women
- microalbuminuria.

Scuteri and colleagues[45] from the Cardiovascular Health Study in Americans over 65 years old followed a cohort of 2175 subjects for just over

4 years. At baseline, 28% had the metabolic syndrome by NCEP ATP III criteria and 21% had it by WHO criteria; 81% of those considered to have metabolic syndrome by one set of criteria also had it by the other. Using the metabolic syndrome alone gave RRs for CVD of 1.9 and 1.89 for NCEP and WHO, respectively. Taking into account age, sex, family history of myocardial infarction (MI), smoking and low-density lipoprotein (LDL) cholesterol, increased the RR with the NCEP criteria to 2.04 (95% CI 1.7 to 2.5) but reduced the RR with the WHO set to 1.63 (95% CI 1.3 to 2.0).

The increased risk of vascular disease in the metabolic syndrome has been reviewed recently by Ford.[46] The increase in risk depends on which groups are included. If those with diabetes are excluded, the RR is less (1.58) than if those with diabetes are included (2.02). Overall, the RR of cardiovascular risk is about 1.7–1.9.

Data from the National Health and Nutrition Examination Survey (NHANES) (unpublished but quoted by Haffner[31]) showed that in individuals aged over 20 years, the prevalences of IHD were:

- without metabolic syndrome – 8.5%
- with metabolic syndrome by WHO criteria – 12.5%
- metabolic syndrome by ATP III (NCEP) criteria – 16.6%.

In the San Antonio Heart Study, Stern and colleagues[47] found that the metabolic syndrome as defined by NCEP was not as good a predictor of future diabetes as the Diabetes Predicting Model (which includes family history) or as good a predictor of heart disease as the Framingham Risk Score (which includes age, sex, smoking and cholesterol), but information on those factors could easily be collected at the same time.

The prevalence of the metabolic syndrome has been studied in middle-aged (40–69 years) people in different ethnic groups in London (Brent and Southall) using both definitions. Tillin and colleagues[48] found the highest prevalence amongst South Asians (46% in men, 31% in women; WHO definition) and the lowest in European women (9%). However, the rates were not standardised for obesity. Central obesity was much commoner in the Asian groups. Hence their higher prevalence may reflect obesity not ethnicity (although the tendency towards central obesity could be due to either genetic or lifestyle factors).

But would including screening for the metabolic syndrome go far enough? Reaven[49] pointed out that many individuals who are both insulin-resistant and dyslipidaemic do not meet the NCEP criteria, but are still at increased risk of vascular disease. The answer may lie in economics – at what level of risk does screening and treatment cease to be cost-effective?

The value of having a condition called the metabolic syndrome, rather than just dealing with the individual components, has been called into question by a joint statement from the ADA and the European Association for the Study of Diabetes (EASD), published simultaneously in *Diabetologia* and *Diabetes Care*. The statement concludes that:

> Until much-needed research is completed, clinicians should evaluate and treat all CVD risk factors without regard to whether a patient meets the criteria for diagnosis of the 'metabolic syndrome'.
>
> Kahn and colleagues (2005).[50]

The converse of the metabolic syndrome has also been studied. Perry and colleagues[51] from Cork in Ireland identified factors, from previous studies, which protected against diabetes: BMI <25; waist:hip ratio <0.85 for women and 0.90 for men; never smoking; medium- to high-level physical activity; light drinking (3–5 to 7 units per week); and a prudent diet. In their sample of middle-aged Irish men and women, drawn from general practice populations, 7.5% had none of these protective factors. Insulin resistance was calculated using the homeostasis model analysis (HOMA) score (based on fasting levels of both insulin and glucose). Taking the 7.5% with no protective factors as the reference group, multivariate analysis gave ORs for insulin resistance of 0.59 with one protective factor, 0.48 with two, 0.14 with three and 0.04 with four or more. About 13% had four or more protective factors.

Hence there is little doubt that lifestyle measures could prevent most cases of T2DM. Weight loss would also benefit those who already have diabetes, or hypertension, and improvements can follow even modest weight loss. Goldstein[52] reviewed studies in which large and small amounts of weight were lost, and concluded that even modest weight reductions, of 10% or less, resulted in significant benefit in a substantial subset. Even loss of a few kilograms can provide benefit.

In addition to the total calorie intake, the quality of the diet can affect the incidence of diabetes. In the EPIC-Potsdam study, Heidemann and colleagues[53] found that a healthy pattern diet

(high intake of fresh fruit and low intake of high-calorie soft drinks, beer, red meat, poultry, processed meat) reduced the incidence of diabetes. ORs from the poorest to the best diet ranged from 1.0 to 0.26. Adjusting for BMI reduced the difference only slightly, implying that those who do not succeed in dieting to lose weight could still reduce their risk of diabetes by changing the content of the diet.

Decision point

Hence if the aim of screening is to reduce heart disease, it could be argued that one should look not only at diabetes, but at all degrees of glucose intolerance, and perhaps wider still for the metabolic syndrome.

This has implications for the test to be used, for the choice of definitive test and for the treatments to be given to screen-positives. The aims of treatment might be:

1. For those with definite diabetes, reduction of the risk of retinopathy and nephropathy, by reduction of PG to normal, initially trying diet and exercise, but using drug therapy when indicated.
2. For those with PG levels in the IFG and IGT ranges, prevention of progression to diabetes, by diet and exercise, or by drug therapy if indicated.
3. For all of the above, measures to reduce cardiovascular risk, by measures other than the glucose control measures already mentioned, such as qualitative improvements in diet; aspirin; cholesterol-lowering measures such as statins; blood pressure control; and anti-obesity measures.

Decision analysis 1.
Should the aim of screening be to identify people with diabetes, or should there be a broader aim to reduce heart disease in a wider group, or both? Diabetes would then be regarded as the higher glycaemic end of a spectrum of glucose intolerance that is in turn part of a wider metabolic syndrome.

NSC criterion 2 – the epidemiology and natural history of the condition, including development from latent to declared disease, should be adequately understood and there should be a detectable risk factor, disease marker, latent period or early symptomatic stage

If the condition is diabetes, then this criterion is partially met, although the terminology is not exactly right. Undiagnosed diabetes is not 'latent' in the sense that it can be causing damage (for example, people with newly diagnosed diabetes may already have retinopathy). It is latent only in the sense of being asymptomatic (although some may have mild symptoms such as polyuria without realising the significance, or indeed that it is abnormal). The 'disease marker' is BG, measured in various ways.

The main reason for using the word 'partially' is that there is uncertainty about the duration of diabetes before diagnosis.

The duration of undiagnosed diabetes

The most quoted estimate of the duration of diabetes before diagnosis is from Harris and colleagues,[54] who used data from two population-based groups, one in the USA (Wisconsin) and the other in Australia, supplemented with data from published studies from other areas or studies, including UKPDS and Edinburgh. In brief, they plotted prevalence of retinopathy against known duration, and then extrapolated back to estimate when diabetes started. The prevalences at diagnosis were different – 21% in Wisconsin and 10% in Australia. Possible explanations for the difference might be that the Wisconsin group was very thoroughly studied by Klein and colleagues[55] in the series of studies from the Wisconsin epidemiology of retinopathy study, and so they may have detected more. Another contributor may have been that some (7.5%) of the Australian group were not diabetic by NDDG/WHO criteria of the time – some probably had IGT.

In the UKPDS, the prevalence of retinopathy at diagnosis (or, strictly, referral – but GPs were asked to refer newly diagnosed patients) was 24%, close to that in Wisconsin (even though, strictly, not all the UKPDS patients had diabetes either – the entry criterion was an FPG of 6.0 mmol/l). It might be worth noting that the UKPDS group was not population based, but relied on referral to hospital clinics, and many had hypertension, which would increase the risk of retinopathy.

Extrapolating back gave estimates of onset of diabetes of 6.5 years prior to diagnosis in Wisconsin and 4.2 years in Australia. The authors concluded, cautiously, that onset occurred "at least 4–7 years" before diagnosis. However, as they noted in the discussion, it takes time for metabolic changes to give rise to detectable retinopathy, so the onset is probably earlier still.

Ideally, studies of onset of retinopathy would start from the actual onset of diabetes. This requires prospective studies, and there are not many of those. Jarrett[56] followed up a cohort of men with IGT, with repeated OGTTs, so that the date of development of diabetes in those who progressed could be more accurately determined. Most of the men (180 of 240) did not develop diabetes over 10 years. Of the 60 who did, none had detectable retinopathy in the first 5 years after onset. That suggests that onset of diabetes could be 9–12 years before clinical diagnosis.

Thompson and colleagues[57] used data from Egypt, and a similar backwards extrapolation method to that of Harris and colleagues, but estimated that the onset of retinopathy was only 2.6 years before clinical diagnosis. The 95% CI was wide at 0.3 to 8.4 years; they had data on 218 patients. Prevalence of retinopathy at diagnosis was 12%. They estimated that onset preceded diagnosis by 7.6 years, using the data on duration of diabetes to retinopathy from Jarrett's study.

One method used for estimating date of onset uses the data from UKPDS on decline of beta cell function. UKPDS paper 16[21] showed a steady rise in HbA_{1c}, irrespective of treatment, of about 0.22% per year. The mean HbA_{1c} level in those symptomatic at diagnosis was 9.6. The upper limit of normal HbA_{1c} in UKPDS was 6.1. Hence, if it is assumed that the decline in beta cell function was linear throughout, then one obtains an estimate of 16 years from first elevation above normal (note: not the same as diabetes – there would be an intervening period of IFG and IGT).

Another UKPDS paper (UKPDS 61[58]) examined initial FPGs. The patients in the lowest tertile of initial FPG were more likely to be asymptomatic and more likely to be found by screening (such as at medical examinations for insurance or employment purposes). However, their progression of glycaemia was similar over time to that of patients with higher initial levels, so it appears that they may simply have been at an earlier stage in the disease. A shift forward of 5 years would overlay the lowest tertile on the highest, implying that there may be a gap of 5 years between their initial HbA_{1c} of 6.7% and the 10% in the highest, more symptomatic group. That would suggest a rise per annum in HbA_{1c} of 0.6%

Another possible method is to use GP records preceding the date of diagnosis. Gulliford and colleagues[59] used this approach to examine contacts with and prescriptions from primary care in the UK in the 5 years before diabetes was diagnosed. However, they included only patients who at some stage were treated with oral hypoglycaemic agents (OHAs); those on diet alone were excluded. They then compared the OHA group with controls who never had any diabetes medication. The diabetic group had higher consultation rates 5 years before diagnosis and more hypertension, hyperlipidaemia, obesity and IHD. However, they were not (as far as is known from the GP data) screened for diabetes, so some may have had undiagnosed diabetes or IGT. Records showed that 0.6% had IGT and 5% had 'hyperglycaemia' recorded. The authors concluded that none of the non-glycaemic factors was sufficiently predictive of future diabetes – which for our purposes means that these factors cannot be used for retrospective estimates of onset.

There are two problems with some of the above estimations.

First, the means for HbA_{1c} for such groups will conceal variations within them. In particular, those left on diet alone include both those who lost weight and took exercise and those who did not. UKPDS does not separate these subgroups. A long-term model of beta cell decline has been devised by Bagust and Beale[60] using data from the Belfast diet study, in which patients who managed to stay on diet alone for 6 years or more had comparatively little decline in beta cell function.

Second, it is not known if the decline in beta cell function is linear throughout the course of the condition. Is the decline in the 'pre-diabetes' and undiagnosed diabetes stages at the same rate? Bagust and Beale[60] hypothesise that there are two stages – an initial slow decline over perhaps 10 years or more, and then a rapid decline over the next 10 years.

The rate of decline in the period before diagnosis (and hence the rate of increase of HbA_{1c} and vascular damage) could have considerable effects on the cost-effectiveness of screening. This will be examined in the economic model.

It may be worth considering the difference between the duration of undiagnosed disease in the natural history situation and the undiagnosed duration in practice. The duration of undiagnosed disease, that is, the interval between onset of the

TABLE 8 *Health Survey for England: proportions of people who are overweight or obese trends over time*

	Men (%)		Women (%)	
	BMI 25–30	**BMI 30+**	**BMI 25–30**	**BMI 30+**
1993	44.4	13.2	32.2	16.4
1994	44.3	13.8	31.4	17.3
1995	44	15.3	32.9	17.5
1996	44.6	16.4	33.6	18.4
1997	45.2	17.0	32.8	19.7
1998	45.5	17.3	32.1	21.2
1999	43.9	18.7	32.8	21.1
2000	44.5	21.0	33.8	21.4
2001	46.6	21.0	32.9	23.5
2002	43.4	22.1	33.7	22.8

metabolic problem and the appearance of symptoms, depends on the natural history and is presumably fairly constant (unless other contributory factors have changed over time, such as levels of exercise). However, the undiagnosed duration may depend on clinical or patient behaviour, which may have changed over time because of increasing awareness of risk factors, public concern about undiagnosed diabetes (prompted by campaigns such as the Diabetes UK 'missing million'), and easy accessibility of glucose testing. Hence the proportion undiagnosed now may be less than in the past, although absolute numbers may be greater, due to increasing prevalence.

If the condition includes impaired glucose tolerance, there is again reasonable understanding of the condition – it is known that it can progress to diabetes, and is associated with an increased risk of CVD. It is known that many people go back from IGT to normality. In the 10-year follow-up to the Bedford study, far more men with IGT returned to normal (128) than progressed to diabetes (36).[61] And as discussed above, it is not known if the decline in those who do progress is linear.

However, we know that a sizeable proportion will develop diabetes. Edelstein and colleagues[62] analysed six studies, with 2389 individuals with IGT, followed up for between 2 and 27 years, and noted that 23–62% progressed to diabetes over time, at a rate of 4–9% per year. Admittedly, the higher progression rates were seen in ethnic groups at particularly high risk, such as the Pimas and Naurans. Progression was increased if BMI was higher, but was not affected by age or family history of diabetes.

The test

NSC criterion 5. There should be a simple, safe, precise and validated screening test
NSC criterion 6. The distribution of test values in the target population should be known and a suitable cut-off level defined and agreed
NSC criterion 7. The test should be acceptable to the population
NSC criterion 8. There should be an agreed policy on the further diagnostic investigation of individuals with positive test results and the choices available to those individuals
Screening tests are addressed in Chapter 3. The position as regards these criteria depends partly on what we are screening for – T2DM, IGT and IFG, or the metabolic syndrome.

Treatment

NSC criteria 10–12

Treatments for diabetes itself are soundly evidence based, and will not be addressed in this review. However, Appendix 3 examines the management of lesser degrees of glucose intolerance such as IGT, since any screening programme would find more people with that than with diabetes.

Trends in overweight and obesity

The prevalence of T2DM is closely linked with that of overweight. Data from the Health Survey for England[63] show that the proportion of the population which is overweight or obese (BMI 30 or over) has been increasing in recent years (*Table 8*).

TABLE 9 *Mortality by weight*

	Weight as percentage of average						
	<80%	80–89	90–109	110–119	120–129	130–139	140+
IHD							
Men	0.88	0.90	1.0	1.23	1.32	1.55	1.95
Women	1.01	0.89	1.0	1.23	1.39	1.54	2.07
Diabetes							
Men	0.88	0.84	1.0	1.65	2.56	3.51	5.19
Women	0.65	0.61	1.0	1.92	3.34	3.78	7.90

The risks of being overweight are well known. Lew and Garfinkel[64] reported mortality data from a very large study from the American Cancer Society with over 750,000 men and women, classified in terms of whether their weights were average, above or below. The reference group comprised those with weights 90–110% of average. *Table 9* shows the mortality ratios for IHD and diabetes.

However, these figures will reflect a mixture of overweight people – some just overweight, others with diabetes or hypertension. It may be more the diseases associated with overweight that increase the risk. Obesity alone is less risky than obesity with a co-morbidity, such as diabetes. Oldridge and colleagues[65] looked in the 1992 Health and Retirement Study in the USA (it is not clear from the results paper whether the study sampled people only in Michigan) at the effects of obesity, diabetes and hypertension in middle age (51–70 years). Compared with people with none of the three, those with obesity had a 24% increased risk of hospital admission, whereas those with diabetes and obesity had double the risk. Those with all three had three times the risk. Some of the obese probably had undiagnosed diabetes. The diagnosis in the study was made if respondents said that a doctor had previously told them that they had diabetes.

Hence the main risk of obesity may be from the increased risk of diabetes, rather than obesity itself.

The prevalence of diabetes – diagnosed and undiagnosed

The York and Humber Public Health Observatory (YHPHO) (www.york.ac.uk/yhpho) has developed a prevalence model for diabetes. The current estimated prevalence of diabetes (diagnosed and undiagnosed) is 4.37% of the population, 0.33% under 30 years, 3.3% from 30 to 59 years and 13.8% in those over 60 years. Prevalence also varies by ethnicity: whites 4.2%, blacks 5.6% and Asians 6.6% (not corrected for obesity). The YHPHO estimates that there are currently about 2.14 million people with diabetes in England, or about 1 in 20 of the population.

By 2010, population ageing alone will have increased the proportion to 4.63%. If overweight trends continue, the proportion due to ageing and weight combined will rise to 5.05%. If the prevalence of overweight and obesity were to fall to the levels before 1995, the expected prevalence of diabetes would fall, to 4.24%, despite the ageing change.

Rises in the prevalences of diabetes and IGT have been reported in other Western countries. Dunstan and colleagues in Australia[66] reported a prevalence in the over 25-year-olds of diabetes of 8% in men and 6.8% in women, with an additional 17% of men and 15% of women having IGT or IFG. These data were based on a very large population-based survey of 11,247 participants who had the 75 g OGTT (the authors say that it is the largest OGTT study in the world). Only 0.8% were indigenous Australians.

Half of those identified as having diabetes were undiagnosed. The prevalence of IFG was 8% in men and 3.4% in women; for IGT the figures were 9% and 12%. The prevalence was much higher than the 3.4% seen in two (smaller) previous Australian studies (Busselton and Victoria, in 1981 and 1992, respectively)[67,68] and than self-reported diabetes in health surveys in 1989 and 1990 (2%).

The authors note that rises in obesity and the ageing of the population explain part of the rise. However, they conclude that these do not fully explain the rise, and they hypothesise that two other factors are reduced physical activity levels

and obesity at younger ages (and hence longer duration of obesity).

In Canada, a large study was carried out with the aid of a sample of physicians who looked after a representative sample of the population.[69] Screening was sequential – a casual BG; those with results over 5.5 mmol/l were asked to return for an FPG; those with FPG 6.1–6.9 mmol/l were invited back for a 2-hour post-glucose load sample. However, screening was offered only to those who attended for routine care for other reasons, who by definition are less healthy than the rest of the population, and may be at higher risk. That may increase the proportion with diabetes. Conversely, the number detected may have been reduced by the failure of about one-quarter who had casual BG levels over 5.5 mmol/l to return for an FPG, and half those who did have an FPG did not have the 2-hour post-load test.

It was believed that the prevalence of known diabetes in Canada was 5%. This study found another 2.2% with undiagnosed diabetes and at least 3.5% with undiagnosed glucose intolerance (based on IFG and IGT combined).

Similar results were reported from the NHANES surveys in the USA,[70] summarised in a Centers for Disease Control and Prevention (CDC) report. The prevalence of known diabetes in the over-20s was 5.9%; testing by FPG found another 2.2%. The prevalence of IFG was 6.1%. No 2-hour post load testing was done, so there may also have been undiagnosed IGT.

The costs of diabetes

Some cost of illness studies include both type 1 and type 2 diabetes. Those which focus on type 2 include a review by Raikou and McGuire,[71] who noted some of the problems in such studies:

- Cost of illness studies based only on diabetes as primary diagnosis will underestimate costs, because most of the cost arises from complications.
- Diabetes is under-recorded on hospital discharge data, so costs will be underestimated.
- When considering the cost of complications, the attributable proportion needs to be estimated, rather than the total cost. This can be done by estimating the excess treatment costs for people with diabetes compared with a matched group without diabetes (it could also be done using RR – if the RR of a heart attack is 4, then 75% of the cost could be attributed to diabetes).

Amongst the studies identified by Raikou and McGuire[71] as being of good quality, only one came from the UK, and it only looked at drug costs. Evans and colleagues in Tayside[72] used DARTS/MEMO data and showed that patients with T2DM accounted for just over 7% of the total drugs budget. However, they noted that the excess prescribing costs were not just for diabetic medications, and in particular that there was a 10% higher use of cardiovascular drugs than in the general population.

Raikou and McGuire[71] appear to have missed the study by Bagust and colleagues,[73] which reports the creation of a model, and the results from running it, for T2DM. The model appears well thought out and inevitably complex. The authors estimate that the lifetime cost of healthcare after people have been diagnosed with T2DM is double that of the non-diabetic population. However, the economics of screening are not addressed.

Williams and colleagues[74] noted that much of the cost of healthcare for people with diabetes is not for the diabetes itself, but for the complications. Using data from the Cost of Diabetes in Europe Type 2 study (CODE-2), they noted that 72% of patients in the study had at least one complication, of whom 34% had macrovascular disease. In those with complications, the cost of care was increased by up to 250% compared with those without complications. Hence there are financial reasons in addition to human factors for seeking to prevent the complications of diabetes, and the cost of complications has implications for the cost-effectiveness of screening.

Chapter 2

Previous reviews

Some of the more important (recent) reviews are summarised below, and position statements from the ADA and Diabetes UK are also included.

Wareham and Griffin (2001)[1]

This paper[1] summarises a review done for the UK NSC, and is structured along the lines of the NSC criteria (Appendix 2). Wareham and Griffin noted that screening for T2DM meets many of the criteria, but that a number of problems remain:

- The criterion that "cost-effective primary prevention interventions should have been implemented" is not met, because there are known methods of reducing the incidence of T2DM, such as diet and exercise.
- There is no clear threshold at which the risk of CVD takes off (unlike with microvascular disease), which is a problem if the aim of screening is to reduce cardiovascular risk.
- The cost-effectiveness of screening would probably depend mainly on that reduction in cardiovascular risk, by a range of measures not specific to diabetes, such as cholesterol and blood pressure lowering.
- Universal screening would be unlikely to be worthwhile, so target populations should be identified.
- There are definite harms of screening, such as being labelled as diabetic.
- The NSC criterion on optimising present forms of care for the condition before finding new cases was not met.[75]
- The criterion that screening should be supported by evidence from RCTs was not met.

Wareham and Griffin concluded that on the evidence available in 2001, it was not clear whether screening would be worthwhile.

Engelgau and colleagues (2000)[76]

Engelgau and colleagues[76] carried out a series of reviews of screening for diabetes. In the version of 2000, they provide a thorough review examining how well screening for T2DM matches the screening criteria. Although this was a balanced and well-argued review, it cannot be classed as systematic; no details of search strategy, of inclusion and exclusion criteria or indeed of any methods were given.

They conclude that the criteria on whether the disease is a significant health burden, the natural history being known, and there being a recognisable asymptomatic but detectable stage, are met. That on whether early treatment has advantages over waiting until symptoms appear is probably met, but with some doubts over compliance, and they note the absence of RCTs of screening and early treatment.

They conclude that the criterion on a suitable test is met, while recognising that none of the tests are perfect. They regard urine testing as being of limited value; consider that FPG is not as good as post-prandial measurement because subjects with undiagnosed diabetes are more likely to exceed the 2-hour cut-off than the FPG one; and conclude that HbA_{1c} is acceptable, although not as good as the post-load PG, but that there is a need to standardise methods. They conclude that questionnaires are unsatisfactory, but they consider these as a one-stop screening test, whereas they are probably more useful as part of a two-stage screen.

They have considerable doubt as regards the criterion on cost-effectiveness – possibly met with opportunistic screening, but not with population-based screening, even on a selective basis.

Their overall conclusion is that:

> The effectiveness of screening for diabetes has not been directly demonstrated.

They accept that the early detection of diabetes and improved glycaemic control "may modestly reduce" future microvascular disease, but that there is little evidence for benefits in macrovascular disease. However, they do note that treatment of hypertension and hyperlipidaemia may be of benefit. Their review was written before some of the recent trials of statins in diabetes, such as CARDS,[77] DALI[78] and HPS,[79] were published.

Engelgau and colleagues[76] noted that several expert bodies have recommended screening but that none of the recommendations had been formally evaluated.

Harris and colleagues (2003)[80]

Note: The first author of this review is Russell Harris, not to be confused with Maureen Harris, another noted contributor to the debate on screening.

Harris and colleagues[80] provided a high quality systematic review, with details on sources searched and search strategy, study selection, data extraction and synthesis and other aspects of methods. One weakness is that only MEDLINE was searched. This is a common American failing and will lead to some trials being missed.[81] They seem to have searched the Cochrane Library but only for reviews, not for trials in CENTRAL.

The review was published as a journal article,[80] but is also available at the full technical report on the website of Agency for Healthcare Research and Quality (AHRQ).[82]

Harris and colleagues address several of the screening issues. They recognise that there is an asymptomatic but detectable stage, but note that the true average length of this is unknown, and that different people will have different durations of this stage. They note that none of the tests are perfect; that the 2-hour PG is regarded as the reference standard but that it is less reproducible than the FPG; and that there are fewer logistical problems with HbA_{1c}.

As regards the benefits of early treatment, they summarise the trials of tighter control in T2DM (with the UKPDS being by far the largest), but correctly point out that these trials were mainly about the benefits in those whose diabetes had been diagnosed, and hence that the findings might not be applicable to those detected by screening and who would have lower glycaemia levels. This is a fair point. Even if there is still benefit at lower levels of glycaemia, the relative benefits of lowering glucose might be similar in terms of reducing microvascular complications, but since the absolute benefits would be less, the cost-effectiveness of intervention would be much less.

The AHRQ review[82] also addresses wider aspects of risk reduction through screening, by considering what benefits might accrue to those found to be diabetic through treatments for hypertension and hyperlipidaemia. The authors note that the diagnosis of diabetes can affect both how vigorously hypertension is treated and the choice of drug. They report the findings of the Hypertension Optimal Treatment trial,[83] that the optimal level of blood pressure may be lower for those with diabetes than those without. They also report on the controversy as to whether ACEIs are more beneficial than other anti-hypertensive agents, and conclude that they should still be favoured. This topic has been reviewed more recently by Ravid and Rachmani,[84] who also concluded that ACEIs probably had advantages and, as Harris and colleagues[82] point out, the side-effects of ACEIs (such as cough) are less than with other anti-hypertensive drugs. They do note in an addendum that the ALLHAT trial, published in 2002,[85] showed no advantage of ACEIs over calcium channel blockers.

Another potential consequence of being diagnosed with diabetes would be that the vascular risk score would be raised, and this could mean the difference between being treated with a statin and not, using the current consensus on levels of risk [National Institute for Health and Clinical Excellence (NICE) guidance recommend that people with a 10-year risk of 20% of CVD should be treated with a statin].[86]

The same could apply to aspirin prophylaxis, which reduces the risk of heart disease in diabetes.

Hence one result of screening for diabetes might be the benefits from reduction of CVD by non-diabetic treatment, as a consequence of crossing the threshold of risk at which these treatments are recommended.

Harris and colleagues[82] also review the harms of treatment. They are unconvinced that 'labelling' is a significant problem, at least in terms of quality of life (although noting possible problems with life insurance costs) and they consider that the side-effects of drugs such as statins and ACEIs are not a great problem. They comment on the hypoglycaemic side-effects of diabetic drugs, but base that on the UKPDS, where many patients were on insulin. These results are less likely to apply to people found by screening, who would, at least initially, have lower BG levels, controllable by diet or metformin (which would be the drug of choice when a drug was needed, assuming that screening was selective and that a key selection criterion was BMI).

This review also considers cost-effectiveness, not in monetary terms, but through estimation of numbers needed to screen to prevent one event. They use various assumptions (in the absence of good evidence) to show that to prevent one case of blindness from retinopathy, by screen detection then tight glycaemic control, would have numbers-needed-to-screen (NNS) ranging from 4300 to 61,400. However, they note that since macrovascular is much commoner than microvascular disease, the NNS for that are much lower, with a range in hypertensive people of 500 to 7200 (which does not include the effect of statins).

Harris and colleagues[82] came to no firm conclusions, perhaps because the purpose of their review was to provide a basis for the US Preventive Task Force to do so, but the thrust of their review is that there are clear arguments in favour of screening, but also remaining doubts about cost-effectiveness.

The CDC Working Group[87]

The Primary Prevention Working Group of the Centers for Disease Control and Prevention (2004)[87] carried out a review of primary prevention of T2DM. They summarise the three recent trials aimed at preventing IGT progressing to diabetes, as follows.

Da Qing Study[88]

This was an RCT over 6 years, with four groups – controls; diet; exercise; and diet plus exercise – with the incidence of diabetes reduced in the three intervention groups by 31, 46 and 42%, respectively.

Finnish Diabetes Prevention Study (DPS)[89]

An RCT was performed over 3 years with two groups – control versus lifestyle intervention (physical activity, weight loss, diet) – with incidence of diabetes reduced by 58% compared with controls.

Diabetes Prevention Program (DPP)[90]

This was an RCT of control versus metformin versus intensive lifestyle; incidence of diabetes was reduced by 31% in the metformin group and 58% in the lifestyle group.

Fuller details of the trials are given in Appendix 3.

The CDC review has some useful thoughts on policy implications or challenges. These were as follows:

1. Identification of subjects for preventive interventions
   The Working Group[87] notes that there remains uncertainty over best screening test, because of the inconvenience of the OGTT. They note that there have been no trials of prevention of progression from IFG to diabetes, but that 24% of those with pre-diabetes have IFG.
   They then pose the question as to whether "the blood glucose criterion should be eliminated". They note that many (61%) Americans are overweight or obese, and that the lifestyle interventions of the DPP would be beneficial to all. They wonder if the target should be not just those with abnormal glucose levels, but all the 47 million with the metabolic syndrome. However, they then wonder if intervening with such large numbers might dilute the intervention too much.
   No definite conclusion is reached.
2. The delivery of lifestyle interventions
   The Working Group[87] note that lifestyle interventions are effective, but that physicians may not be the best people to deliver them, because they are more accustomed to the medical role of disease management and drug prescribing. While physicians may have a role in helping motivate people, the lifestyle interventions might be better provided by non-medical staff such as dietitians, nurses or undefined "community health workers". But perhaps the key question is whether a more public health-based approach is required. Instead of trying to provide lifestyle interventions as part of medical care, should the aim be to reduce diabetes by "changing the underlying environmental factors that contribute to obesity and sedentary behaviour in the general population"?
3. Are lifestyle interventions cost-effective?
   The review comments on the scarcity of economic evaluations of preventing diabetes, but cites a 1998 reference in support of this statement, and may therefore have missed some of the more recent economic studies (see Chapter 4 of this report). It notes that the incremental costs of the intervention arms of the DPP were modest at US$2191 and $2269 for metformin and lifestyle interventions, respectively.
4. The ethical implications
   Two main issues are considered by the Working Group. The first is what strength of evidence is needed for lifestyle interventions. For any campaign aimed at the general public, or at a high-risk subset of it – but in either case at people who are not actually ill – should the

strength of evidence required be as good as or greater than that required for conventional medical care?
The second is about the ethics of extrapolation. If there is good evidence that lifestyle interventions benefit those with IGT, can this be extrapolated to those with lesser risks of progression to diabetes or cardiovascular disease, or are RCTs needed? As the review says:

> Is it ethical to await results of a new, extensive series of randomised controlled trials to evaluate intervention efficacy in groups at lower risk of diabetes? Or is it acceptable to infer intervention efficacy in groups other than those defined by the eligibility criteria of the Diabetes Prevention Program?

However the review makes no firm recommendations but only summarises some of the evidence.

Other reviews

One of the advocates of screening for diabetes has been Maureen Harris, who has also been first author of several studies on the prevalence of undiagnosed diabetes in the USA. Her reviews are editorials or commentaries rather than systematic reviews, but they deserve comment. In 1994, with Michaela Modan,[91] she argued that there should be a national programme in the USA, basing this assertion on what was known about the prevalence of undiagnosed diabetes and the presymptomatic phase, on the presence of complications in some at diagnosis, and the availability of effective treatments. They did not consider cost-effectiveness or the possible harms of treatment. They recommended the OGTT, although simplified to a 2-hour glucose, as the best test, while accepting its drawbacks. They noted that if cost and efficiency were to be considered, then there could be selection of people for screening on the basis of obesity and hypertension.

In a later (non-systematic) review, Harris and Eastman[92] make similar points about the health burden of diabetes, the latent phase and the damage which can accrue during it, the natural history and the effectiveness of treatments, updating the previous editorial with data on the benefits of statins, and the lowered blood pressure goal in those with diabetes. Another update concerns the new criteria of the ADA[93] and the recommendations on which test to use. Harris and Eastman make the point that although the 2-hour PG test is still better in theory (because it is more sensitive), the FPG test may in practice detect a greater proportion because the simplicity makes it more likely to be used. They do not consider HbA_{1c} in this review.

Another recent review is by Borch-Johnsen and colleagues.[94] This was a short but good-quality review, with a clear search strategy and with the WHO screening criteria used for assessing the case for screening. It focused mainly on the criteria, on a suitable test, on treatment and the indications for that and on the ethical and psychological consequences of screening.

They concluded that suitable tests were available, but that:

- FPG should not be used as the only test because one out of three cases of diabetes will be missed.
- Random blood glucose was of limited value, as was urine testing.
- HbA_{1c} would be useful when used as part of a stepwise process, for example combined with FPG; they envisaged selecting individuals for OGTT testing.
- Questionnaires would help select high-risk people, but might need to be validated in other countries.

Borch-Johnsen and colleagues[94] had more reservations about treatment aspects. They noted the beneficial results from trials in newly diagnosed diabetes (UKPDS) and in the treatment of hyperlipidaemia and hypertension. However, they identified a major gap in that there were no trials, then, of non-pharmacological intervention in the early stages of the disease, but that the ADDITION (an Anglo–Danish–Dutch trial of intervention in those with T2DM detected by screening)[95] had started. They concluded that:

> Until such data are available, any recommendation regarding screening and early intervention will depend on speculative interpretation of secondary intervention studies.

As regards the ethical and psychological consequences, they considered that there was a need for further research. They also noted that there were shortfalls in care for many individuals with existing diabetes, which needed correction before adding to the number by screening. Their final conclusions were that T2DM met many of the criteria but not all, that mass screening could not be recommended, but that testing for diabetes should be offered to those with hypertension, dyslipidaemia and CVD and those with many risk factors for diabetes.

Diabetes UK

Diabetes UK issued a position statement on "Early identification of people with type 2 diabetes" in November 2002.[96] In brief, it advocated a screening programme for both undiagnosed diabetes, and also for IGT, with a view to reducing progression to diabetes. It did not support general population screening, but recommended targeted case finding, with screening for those with two or more risk factors, such as:

1. White people aged over 40 years and people from black, Asian and minority ethnic groups aged over 25 years, with:
   (a) a first degree family history of diabetes and/or
   (b) who are overweight (BMI 25–20 and above) and who have a sedentary lifestyle and/or
   (c) who have IHD, CVD, PVD or hypertension.
2. Women who have had gestational diabetes.
3. Women with polycystic ovary syndrome who are obese.
4. Those known to have IGT or IFG.

Diabetes UK noted that there was a lack of evidence on the best method of screening, but as regards tests, they favoured the 2-hour post-load glucose test (noting that a full OGTT would be the best possible test but was impractical) followed by fasting PG measurement. Glycosuria was also listed as having some value. HbA_{1c} was not included in their list of recommended tests.

The American Diabetes Association

The ADA publishes clinical practice recommendations each year, in a supplement to *Diabetes Care*. The 2005 edition[97] has the following statement on screening for diabetes in asymptomatic adults:

> 1. Testing for diabetes should be considered in all individuals at age 45 years and above, particularly in those with a BMI of 25 or over, and if normal should be repeated at 3-year intervals.
> 2. Testing should be considered at a younger age or be carried out more frequently in individuals who are overweight (BMI ≥25) and have additional risk factors, as follows:
> - are habitually physically inactive
> - have a first degree relative with diabetes
> - are members of a high-risk ethnic population
> - have delivered a baby weighing >9 lb or have been diagnosed with GDM
> - are hypertensive (≥140/90)
> - on previous testing, had IGT or IFG
> - have history of vascular disease.
>
> (ADA, 2005; abbreviated)[97]

The ADA said that either an FPG or a 2-hour OGTT (75 g) was appropriate, but that the FPG was the preferred test for screening for pre-diabetes:

> The FPG is more convenient to patients, more reproducible, and easier to administer than the 2-h OGTT. Therefore the recommended screening test for non-pregnant adults is the FPG.

Exercise

A very useful collation of the evidence on physical activity and health was published as a book by Hardman and Stensel.[98] They examined the evidence for the benefits of exercise for various conditions:

- CHD – exercise protects. It need not be vigorous (although vigorous exercise protects more) and so walking is sufficient to give some protection. However, protection is lost shortly after exercise is stopped. The RR of heart disease amongst the inactive is at least 2.
- Hypertension – the risk of developing hypertension amongst the inactive is about 1.5. Exercise is an effective way of reducing blood pressure, although the reductions are modest compared with pharmacological treatment – about 3.4 mmHg systolic and 2.4 mmHg diastolic.
- Lipid levels – exercise increases HDL and lowers triglycerides.
- Coagulation of blood – exercise lowers platelet aggregation and fibrinogen.
- T2DM – cohort studies show a reduction in risk. Vigorous exercise four times per week cuts the risk of T2DM by 40% in men (from the Physicians' Health Study[99]). Taking more than 7 hours of exercise a week reduces the risk of diabetes in women (from the Nurses Health Study[100]) by 30%. Having the combination of a good diet, a BMI under 25 and high physical activity (over 30 minutes per day of moderate or more strenuous exercise) in the Nurses Health Study gave an RR of diabetes of about 0.1; Hu and colleagues[100] suggest that 87% of T2DM in avoidable. In those already having T2DM, remission was seen after exercise in half of those recently diagnosed with diabetes after screening (but numbers were small – only 41 in total; from the Malmo feasibility study[101]).

Hardman and Stensel[98] quote the National Audit Office report on possible reasons for the reduction in physical activity:

- a reduction in occupational exercise
- greater car ownership and use
- a decline in walking as a mode of transport
- energy-saving devices in public places, such as escalators, lifts and automatic doors
- fewer opportunities for young people to take exercise
- the substitution of physically active leisure activities with sedentary ones such as computer games, television and the Internet.

Chapter 3

Screening tests

Organised screening would be a two-stage process, with the first stage being selection from the general population (using general practice registers) of those likely to be more at risk than average, and the second being testing of glucose levels, usually in blood. However, some studies have used urinary glucose testing as the second screen, followed by BG testing.

There is already some *ad hoc* screening on offer, such as by pharmacies, or urine testing at new patient registration in general practice.

Stage 1 – selection by risk factors

Testing only people who are at higher than average risk means that a higher proportion of those who will be tested for glucose will be positive, the NNS to detect each true positive will be lower and the whole programme will be more cost-effective.

1. Age is always a key factor, because the risk of T2DM increases steeply with age. The cost-effectiveness of screening will be lower at younger ages since the NNS to find each case will increase, and also because the event rate from CVD will be lower.
   However, although the prevalence of diabetes is greater in the older ages groups, the excess mortality may fall. Tan and colleagues[102] found that in men diagnosed with T2DM over the age of 65 years in Tayside, there was no excess mortality compared with the general population. This might represent a survival selection effect. The situation in women was different, with an RR of death of 1.29 (95% CI 1.15 to 1.45). The implication of this might be that if the main aim of screening is to reduce heart disease mortality and morbidity, screening in men should not include those aged over 65 years.
   Vijan and colleagues[103] also looked at this in their model of T2DM. Improving glycaemia control improves life expectancy, but the gains from a 2% improvement (HbA_{1c} 11–9%) are very different at different ages of onset (*Table 10*).

TABLE 10 *Life-years gained by age of onset*[103]

Age of onset (years)	Life-years gained
45	1.3
55	0.9
65	0.5
75	0.2

   This modelling is based mainly on microvascular disease, and is more concerned with poorly controlled patients with higher HbA_{1c} levels than those who would be found by screening. However, it does illustrate a general principle that because most serious microvascular disease comes on a decade or two after the onset of diabetes, those who become diabetic at older ages have less risk and hence less to gain from screening. Hence one could argue that screening at 65 years or over is not worthwhile. It should be noted that in *Table 11* the insulin-treated group are a mixture of patients with type 1 and type 2 diabetes.
2. BMI is the second factor, reflecting overweight and obesity. The risk of T2DM is greatly increased by excess weight. However, there is also a link with the distribution of body fat, with abdominal (especially visceral) fat distribution carrying a higher risk. Waist measurement could be used as a risk factor, for example, more than 40 inches (approximately 100 cm) in men or 35 inches (approximately 90 cm) in women. However, men tend to know their waist measurement, by which they buy trousers, more than women, who use overall size.
3. Co-morbidities. The risk of diabetes is associated with other aspects of the metabolic syndrome such as hypertension and hyperlipidaemia, and with the presence of vascular disease, such as peripheral vascular disease or IHD.
4. Family history of diabetes, or of premature vascular disease or hypertension, is a predictor.
5. Ethnicity is also a predictor, in that some ethnic groups have a higher risk of T2DM than others, although this is less if adjustments are made for BMI and fat distribution. In the Manchester survey,[104] the prevalence of known diabetes in a poor inner city area was 8 and 3.7% in European men and women,

TABLE 11 *Prevalence of insulin- and non-insulin-treated diabetes per 1000 population, 1998*

		Age (years)							
Diabetes	**Sex**	**16–24**	**25–34**	**35–44**	**45–54**	**55–64**	**65–74**	**75–84**	**85+**
Insulin-treated	Males	3.5	4.6	6.2	7.2	10	13.3	10.9	6.8
	Females	3.2	4.3	5.2	5.7	9.4	12.1	9.4	5.9
Non-insulin-treated	Males	0.2	0.6	3.6	11.8	30.5	47.5	47.4	43.1
	Females	0.2	0.6	2.8	7.9	20.3	35.7	37.1	33.8

Source: Office of National Statistics.

respectively. and 14 and 18.2% in Pakistani men and women, respectively. The Pakistani women had higher BMI than the Europeans (29.6 versus 27.2) and a higher waist:hip ratio (0.88 versus 0.81). Pakistani and European men had similar BMIs (27.4 and 27.5, respectively), but the Pakistani waist:hip ratio was higher (0.96 versus 0.92; 95% CIs 0.94 to 0.97 and 0.92 to 0.94). However, the most striking differences were in physical activity. The proportions taking at least 20 minutes of exercise three times per week were 38 and 29% for European men and women, respectively, and 7 and 5% for Pakistani men and women, respectively. Physical activity reduces insulin resistance even if there is little or no weight loss.[98]

6. Drug treatments such as for hypertension, or corticosteroids.

There are two ways in which such selection criteria could be applied. Questionnaires could be sent out, albeit perhaps only to those above a certain age. However, increasingly, computer systems in general practices will have much of the necessary data – certainly age, drug treatment, co-morbidities and usually BMI. They are less likely to have waist measurements and family history. However, it means that the first stage of any screening system could use existing data at little extra cost. This was demonstrated by Baan and colleagues[105] in the Rotterdam study, where data from a population screening study were used in three progressively more complex screening tools:

(a) Level 1 had only data available in general practice records, age, sex, use of anti-hypertensive and anti-hyperlipidaemia medications, previous gestational diabetes, CVD and obesity.
(b) Level 2 had additional items which could be obtained from a simple questionnaire, family history, smoking, cardiovascular symptoms and exercise (cycling).
(c) Level 3 added data that would need to be obtained from physical examination, blood pressure and waist and hip measurements (for waist:hip ratio).

Baan and colleagues[105] found that the addition of level 3 data did not improve the predictive value over level 2. Level 2 had little advantage over level 1, despite physical activity having a strong predictive power. In level 2, not cycling had an OR of 2.83, which was the highest OR of all the factors.

Patients at higher risk could then be approached opportunistically when they consulted for other reasons. Those who did not consult within, say, 2 years of the threshold age could be invited to attend for screening.

Hence one option for the first stage could be to rely only on data already in general practice records, which would provide an inexpensive method. However, questionnaires could provide more data.

Questionnaires

Several systems have been used.

The Hoorn study[106] used the Symptom Risk Questionnaire (SRQ), which, despite the name, covered more than symptoms, age, height, weight, pain on walking, shortness of breath, frequent thirst, family history of diabetes, use of anti-hypertensive drugs and cycling. They then used a cut-off of >6 mmol/l for selection for glucose testing.

Herman and colleagues[107] used data from NHANES 2 to examine different combinations of risk factors. The combination of age, sex, previous delivery of large infant, obesity, lack of exercise and family history identified a high-risk group which contained 79% of people with newly

diagnosed diabetes. Adding hypertension and a history of glucose intolerance made little difference (83% sensitivity). Ethnic difference had little effect once other factors such as weight had been allowed for (although in this case the ethnic groups were black people, Hispanics and American Indians).

Burden and Burden[108] reported that the ADA questionnaire had low sensitivity (46%) in a study in Leicestershire for detecting those with raised casual BG levels.

The Diabetes Risk Score (DRS) is designed to be self-administered, and so could be sent out by practices to people at the appropriate age. It has questions on age, BMI, waist circumference, medications for hypertension, any history of high BG, physical activity and daily consumption of vegetables, fruit or berries. The IGLOO group (Impaired Glucose Tolerance and Long-term Outcomes Observational study)[109] used the DRS and compared the findings with the results of OGTT, in people selected on the basis of having one or more risk factors for CVD, and being aged 55–74 years. Of 1377 patients, but without known diabetes, 15.4% had IGT, 11.1% had IFG, 11% had IGT and IFG and 17.4% had diabetes.

The cost per case detected, irrespective of method, was low (under €23). However, they applied their results to scenarios of 1000 people with different prevalences of undiagnosed T2DM and IGT. For the 10% prevalence (which is closer to the UK one), they concluded that using the DRS would reduce the proportion of patients needing a fasting blood glucose (FBG) test by about 43%, and then OGTTs by about 90 people (from 270 to 180). The total cost would fall by about one-third, and the cost per case detected from €87 to €65, but there would be a drop in sensitivity from 68 to 55%. This is mainly because a DRS cut-off of 9 gives a sensitivity of 86% for diabetes but 77% for diabetes + IGT. It is worth noting that a DRS cut-off of 9 is more sensitive for diabetes + IGT than an FBG with cut-off of 6.1 mmol/l or more.

Griffin and colleagues[110] developed a new risk score for diabetes, the Cambridge Risk Score (CRS), based on data available in general practice records (assuming that family and smoking history are recorded), and then validated it on another group of people. Using a low threshold, 30% of the practice population in Ely would go on to diagnostic testing and 77% of those with undiagnosed diabetes would be detected. Using a higher threshold, 15% would be called for diagnostic testing but only 41% of the undiagnosed diabetics would be detected. Hence, as usual, there is a trade-off between sensitivity and cost, with cost including not just money but also the adverse effects of screening amongst the false positives. Griffin and colleagues[110] also note the danger of normal results in those at high risk because of unhealthy lifestyles – they may see a normal result as justifying continuing with such lifestyles.

A different approach was used by Spijkerman and colleagues.[111] They used a three-step approach, with step 1 being an SRQ, step 2 being an FPG and step 3 being an OGTT (unless the FPG was so high that an OGTT was not considered necessary). The aim of the study was not to assess the accuracy of the SRQ (already done in a previous study), and those with scores <6 were not tested further. The usefulness for this review is two-fold. First, the group identified by screening had a lowish HbA_{1c} of 6.7% [standard deviation (SD) 1.4]. Second, they had high prevalences of hypertension (70%), high cholesterol levels (73%) and obesity (40%). Hence many would have been identified as being at high risk of CVD even without diabetes screening. If the aim of screening for diabetes is so that measures to reduce cardiovascular risk, such as statins, can be started, then in this case screening may have made little difference.

Greaves and colleagues[112] also based initial selection on data now available in general practice computer systems. They tested a simple system using age and BMI only, with four groups selected by the combination of age (over 70, over 65, over 60 and over 50 years) and BMI (over 33, 31.29 and 27). Hence the oldest and fattest group excluded the other three, but the other three groups could overlap with those above. They then invited patients to attend for FPG measurement. Those with FPG over 6.1 mmol/l were invited back for a repeat FPG. Those with FPG at 7.0 mmol/l or over on both occasions were classed as diabetic. Those with one or two levels between 6.1 and 6.9 mmol/l were classed as IFG. The uptake of screening was 61%.

Greaves and colleagues[112] then looked at the efficiency of screening in terms of the NNS in each group, and found that for diabetes it ranged from an NNS of 22 in the age over 70 years/BMI over 33 group to 38 in the 50+ years/BMI 27 group. For detecting diabetes or IFG, the respective NNS were 8 and 13. There was little

difference in the oldest/heaviest three groups. Screening became slightly less efficient in the over 50 years/BMI over 27 group. However, the three oldest groups were reported as comprising 6.66% of the practice populations (which seems low) and so restricting screening to them would detect fewer people with hyperglycaemia than screening all over 50 years with BMI over 27.

The authors do not present data separately for the group with ages between 50 and 59 years BMI over 27 and under 29. Hence, the marginal benefits of applying each age/BMI cut-off could not be examined. It is possible that most of the patients found in the most inclusive group (over 50 years/BMI over 27) were actually from the higher groups.

The Atherosclerosis Risk in Communities (ARIC) Study[113] looked at the marginal advantages of adding laboratory data to a clinical risk score. In terms of area under a receiver operating characteristic (AUROC) curve, the results were as follows:

- Clinical risk score alone [age, waist measurement, parental history, ethnic group, systolic blood pressure (SBP)] gave an AUROC of 0.71.
- FPG alone gave 0.74.
- Clinical plus FPG gave 0.78.
- Adding triglycerides and HDL cholesterol increased that to 0.80.
- Scores based on the metabolic syndrome gave AUROCs of 0.75 and 0.78.

Hence adding laboratory results improved the predictive power, but only slightly.

Schmidt and colleagues[113] also tested the San Antonio clinical score (age, sex, family history, BMI, HDL cholesterol and hypertension) and found that that gave an AUROC, for whites only, of 0.80.

Stage 2 – glucose testing

Urine testing has been advocated, but in most reviews has been discounted because of low sensitivity.[1,76,94] It would in effect be another preliminary screen, with screen positives going on to blood testing. Nevertheless, it has been shown to be of some use, especially as it can be done by post.[114] However, it would be much less useful if screening were to be for all degrees of elevated BG. It also retains a place in the investigation of polyuria, but by definition people with symptoms are not included in the screening situation.

The tests for blood glucose include;

- casual (non-fasting) BG – more sensitive than glycosuria but less specific
- FPG or FBG
- glucose tolerance tests, combining fasting and 2-hour levels
- HbA_{1c}, which reflects BG over the previous 3 months (assuming red blood cells of normal longevity, and in the absence of haemoglobin variants)
- fructosamine
- 1,5-anhydroglucitol.

Casual BG is usually discounted because of its variability and poor sensitivity (at levels which give acceptable specificity).[115]

The choice of test depends on what one is screening for. FPG is reliable, in the sense of showing less day-to-day variability than OGTTs, and will identify people with diabetes and IFG. However, it will miss those with IGT, who have a higher IHD risk than those with IFG.

The use of HbA_{1c}

The use of HbA_{1c} as a screening test has been reviewed by various expert groups.

The WHO Expert Group[14] did not recommend HbA_{1c} for diagnosis, commenting that:

> An alternative to the single blood glucose estimation or OGTT has long been sought to simplify the diagnosis of diabetes. Glycated haemoglobin, reflecting average glycaemia over a period of weeks, was thought to provide such a test. Although in certain cases it gives equal or almost equal sensitivity and specificity to glucose measurement, it is not available in many parts of the world and is not sufficiently well standardised for its use to be recommended at this time.

However, screening was not addressed in this report. Its perspective was world-wide; HbA_{1c} is routinely available in the UK. Systems for standardisation are available such as the National Glycohemoglobin Standardization Program (NGSP),[116] which aims to standardise results to make them comparable with the Diabetes Control and Complications Trial (DCCT) Trial. Most UK laboratories use this system to align their results to DCCT.

In a recent report, the ADA Expert Committee[117] on the diagnosis and classification of diabetes mellitus summarised the advantages and disadvantages of HbA_{1c} for the diagnosis of diabetes. The Committee listed the advantages as:

- HbA_{1c} measures average glycaemic levels over a period of 10 weeks or so, and is therefore more stable than FPG, and especially than 2-h OGTT.
- Fasting is not required, and the test can be done at any time of day.
- The precision of HbA_{1c} can be as good as that of PG (Note the use of the word "can" – is there an implication that results may not be as good in routine practice?).
- HbA_{1c} is the test used for monitoring control of diabetes and correlates well with the microvascular complications; it may be useful to use the same test for diagnosis and monitoring.
- It has been shown by meta-analysis that when using a statistical cut-point of 2 SDs above the non-diabetic mean value, HbA_{1c} is as good as FPG and 2-hour PG in terms of sensitivity (66%) and specificity (98%).

The disadvantages were identified as:

- Internationally, there is a profusion of assay methods and reference ranges. However, this can be overcome by standardisation to the DCCT assay.
- HbA_{1c} may be affected by other conditions which affect the life of the red blood cell; results may then be misleading. This could be a particular problems in ethnic groups in which haemoglobinopathy is common.
- A chemical preparation for uniform calibration standards has only recently become available and is not universally available.

However, with the exception of the other conditions, these disadvantages need not apply in a national screening system. There is therefore a case for using HbA_{1c} as the screening test, particularly in view of its correlation with cardiovascular risk across a wide spectrum. In the Norfolk study, Khaw and colleagues[118] noted that the rise in cardiovascular events with rising HbA_{1c} started well below the diabetic range. Indeed, they pointed out that when both diabetes and HbA_{1c} are included in the statistical analysis, HbA_{1c} dominates, as Gerstein[119] argues in an editorial:

> the glycosylated hemoglobin level is an independent progressive risk factor for cardiovascular events, regardless of diabetes status.

So, if the aim of screening is to identify people at high risk of vascular disease, is HbA_{1c} more useful than diabetes?

Rohlfing and colleagues[120] noted that two changes would affect the performance of HbA_{1c} as a screening test. The first was the standardisation system (NGSP) mentioned above. The second was the change in the definition of diabetes, with the lowering of the FPG threshold to 7.0 mmol/l. Using data from NHANES 3, they showed that a cut-off of 1 SD above the HbA_{1c} mean would give 83% sensitivity and 84% specificity, compared with FPG. Using a cut-off of 2 SD would give 63% sensitivity and 97% specificity. The 2 SD cut-off level would be an HbA_{1c} level of 6.1%.

One weakness of this study was that most patients did not have an OGTT. Of those who had HbA_{1c} $\leq$6.1%, 96% had non-diabetic FPGs. The 4% with FPGs under 7.0 mmol/l but HbA_{1c} over 6.1% may have included people with IGT.

A large-scale trial of HbA_{1c} as a screening test was carried out in New Zealand, somewhat serendipitously as an add-on to a large screening programme for hepatitis B.[121] In the North Island, 50,819 subjects being tested for hepatitis B also had HbA_{1c} measured. Of these, 300 who lived close to the testing laboratories were invited to attend for a standard 75 g OGTT. Most (82%) of the participants were Maori.

Thirty-two were found to have undiagnosed diabetes. Of these, 30 had HbA_{1c} over 6.1% – an apparent sensitivity of 94% and specificity of 77%, if the OGTT is taken as the gold standard. A total of 67 (22%) people had FG 6.1–6.9 mmol/l; only 33 of these had HbA_{1c} over 6.1%. To detect those with IFG, a lower HbA_{1c} cut-off would be required. A cut-off of 5.6% would give a sensitivity of 98% but a poor specificity of 30%. A cut-off of 5.9% would give a more reasonable compromise with sensitivity 82% and specificity 73%.

McCance and colleagues[122] compared FPG, 2-hour PG and HbA_{1c} as diagnostic tests in Pima Indians, and found very little difference in the predictive power for retinopathy of FPG, 2-hour PG and HbA_{1c}.

Peters and colleagues[123] carried out a meta-analysis of the use of HbA_{1c} (and also HbA_1) in the diagnosis of diabetes. They found that a cut-point of 7.0% for HbA_{1c} would give a group in whom 89% were diabetic by the OGTT, 7% had IGT and 4% were normal. Of those with diabetes by the OGTT, only 42% had an HbA_{1c} over 7%, but the authors argue that this cut-off identifies those who would be likely to require pharmacological treatment – although this is an assumption, based on a position that those with HbA_{1c} under 7% are rarely treated with drugs. They considered that

the inconvenience of the OGTT might be one of the reasons for under-diagnosis of diabetes.

Woerle and colleagues[124] reported that the 2-hour PG explained more of rises in HbA_{1c} than FPG. They also give data on further testing in those with HbA_{1c} levels between 6.0 and 7.0%. None had normal glucose tolerance (NGT); 43% had IGT, 49% were diabetic and 8% had IFG. However, numbers were small (23, 26 and four, respectively). There was a steep rise in the proportion abnormal between the sixth and seventh deciles of HbA_{1c}:

- Sixth decile: mean HbA_{1c} 5.34 %; 30% had abnormal glucose tolerance.
- Seventh decile: mean HbA_{1c} 5.48%; 70% had abnormal glucose tolerance.

Hence an HbA_{1c} of 5.5% might be a suitable cut-off for screening.

One advantage of HbA_{1c} is that it is used as the target for glycaemic control. The ADA Position Statement of 2005[97] recommends that the aim should be an HbA_{1c} level under 7% (referenced to a non-diabetic range of 4.0–6.0%, using a DCCT aligned assay). However, the relationship between complications and HbA_{1c} is closer for microvascular disease than macrovascular disease.

HbA_{1c} has become part of the routine of diabetes care. However, some concerns remain, and a useful critical review by Jeffcoate[125] summarises these as follows:

- Analytical variability – which should be reduced by standardisation methods.
- Biological variability, in particular that due to differences in the longevity of the red blood cell, but also uncertainties over the relative contributions to HbA_{1c} of preprandial (such as fasting) and postprandial BG elevations. He notes an ADA conclusion that FPG is a closer correlate than postprandial.
- Clinical variability – and in particular the poorer correlation with macrovascular disease.

If postprandial glucose levels are better predictors of macrovascular disease than FPG, and if HbA_{1c} is more influenced by preprandial than postprandial PG, then using HbA_{1c} as a screening test might be fine for predicting and preventing future diabetes, but not so good as a basis for predicting and preventing future heart disease.

However, the relative contributions of fasting and preprandial (taking fasting to be before breakfast and preprandial to be before other meals) and postprandial to overall glycaemia, as reflected in HbA_{1c}, varies according to stage of disease. Monnier and colleagues[126] reported that the higher the HbA_{1c}, the greater is the contribution of fasting and preprandial – which is logical, since most people spend most of the day in a non-postprandial state. At low levels of HbA_{1c}, under 7.3%, postprandial has twice as much effect on HbA_{1c} as fasting and preprandial. In the lowest quintile (mean HbA_{1c} of 6.45%), postprandial glucose contributed 70% of the elevation in HbA_{1c}.

This has implications for using HbA_{1c} as a screening method, since at the lower levels expected in those found by screening, postprandial will have more effect, and therefore the level may reflect an IGT pattern more than an IFG pattern, which could be useful.

Do we actually need blood glucose testing?

An interesting paper from the Hoorn study[127] looked at those who were first-stage screen positive by the CRS, but who did not have diabetes on glucose testing. Spijkerman and colleagues[127] found that this group had almost as high a CVD rate as the true positives. Taking the RR in true negatives as 1.0, the newly diagnosed diabetics had an RR of 1.73 and the false positives had an RR of 1.56. Furthermore, the false positives made up about half of the population, so their number of events was much greater than that of the true positives (175 versus 24 events). As the authors noted, screening might do harm to this group:

> In current screening practice this large group of people would be sent home feeling reassured about diabetes but unaware of their increased risk of mortality.

They might then feel less inclined to improve their lifestyles. The CRS includes remediable factors in BMI and smoking. Given that this group have been identified by the CRS as being at increased risk, they could be reminded of that post-screening and given appropriate advice. Would that lead to lifestyle changes? Perhaps research is needed.

Since 63% of the total deaths occurred in the false-positive group, the authors comment that:

> It may be of greater public health benefit to intervene in the screen positive group as a whole rather than only in the relatively small group who on subsequent biochemical testing have an increased glucose concentration.

If so, it could be argued that glucose testing is not necessary. However, this is based on a macrovascular focus. Detection of diabetes would lead to screening for and intervention in the (admittedly less common) microvascular disease such as retinopathy.

Conclusions

There is no perfect test. The gold standard test might be the OGTT (or the modified version with just FPG and 2-hour PG) but repeated a week later, because of its imperfect reproducibility. However, it is impractical and, as Hanson and colleagues[128] pointed out, the emphasis on the OGTT may be part of the reason why so many people in the USA are undiagnosed. A slightly less good test may in practice be more useful by being applied more frequently.

As regards evidence on tests, there is little to change since the last NSC review by Wareham and Griffin in 2001.[1] The FPG and the 2-hour PG are equally useful for assessing the risk of microvascular complications such as retinopathy, but the 2-hour PG level is better for assessing macrovascular risk, because of the difference in heart disease risk between IFG and IGT. HbA_{1c} has advantages in terms of convenience and reproducibility compared with the OGTT or its modified form, the 2-hour PG. FPG is also more reproducible than the OGTT.

In practice, HbA_{1c} may be the best test, but costs more than FPG, although less than OGTT.

Chapter 4

Review of economic models and evaluations

Overview

The aim of this chapter is to identify and appraise economic studies relevant to the decision of whether or not to screen for undiagnosed diabetes and or IGT. The chapter is divided into three sections based around three principal questions:

1. Is it a cost-effective use of resources to screen for and treat people with undiagnosed diabetes?
2. Is it a cost-effective use of resources to screen for and treat people with IGT?
3. If a screening programme were to be implemented, what screening tests and cut-off points should be used?

First, modelling studies that assess the long-term cost and consequences of screening for T2DM are reviewed. Second, similar models that assess the long-term costs and consequences of treating people with IGT or IFG are reviewed. Finally, studies that consider the short-terms costs and outcomes of alternative screening tests (and cut-off points) for diabetes and IGT/IFG are reviewed.

Methods

A systematic literature search (up to the end of June 2005) was undertaken to identify any economic assessments of screening for diabetes and/or IGT/IFG. Databases searched were MEDLINE, EMBASE, NHSEED and Science and Social Science Citation Index; no time limit was set but there was little prior to the first model being published in 1998. Abstracts were reviewed and any studies that were potentially relevant to any of the three questions outlined above were retrieved. Articles cited by other relevant studies were also retrieved for review. In addition, a broader search was conducted for any economic models within the area of T2DM, to ascertain if any such models had been used to address any of the questions of interest.

Inclusion and exclusion criteria

To be included, studies generally had to assess the costs and outcomes (long or short term) of screening strategies for either undiagnosed diabetes or IGT/IFG. However, given the lack of economic evaluations that had assessed screening for undiagnosed diabetes (question 1), studies that assessed only the long-term outcomes [life-years or quality-adjusted life-years (QALYs)] or costs of screening (where relevant to the UK setting) were also considered eligible for inclusion. In addition, no studies explicitly assessed the long-term costs and outcomes of screening for IGT/IFG, so studies that assessed the costs and outcomes of treating patients already identified as having IGT/IFG were considered eligible for inclusion. Studies reported in languages other than English were not included.

Data extraction

Data were extracted from the long-term modelling studies of screening for diabetes or IGT under the following headings:

1. author and year
2. decision problem (comparators, population, setting, objectives)
3. cohort information (characteristics and numbers)
4. model structure, perspective and scope (basic structure and assumptions)
5. modelling of disease progression (details of structure and assumptions used for modelling diabetes progression)
6. modelling of diabetes complications (details of structure and assumptions used to model progression of diabetes complications)
7. mortality (details of how mortality was modelled)
8. costs (details of costs considered in the model).
9. outcomes (outcomes reported and methods for calculating life-years or QALYs)
10. findings (reported results of the base-case analysis)
11. sensitivity analysis (details and results of any sensitivity analysis conducted).

For the studies that assessed only the short-term costs and outcomes of alternative screening strategies, data were extracted under the following headings:

1. author and year
2. setting (country for which analysis was conducted)
3. objectives (specific questions addressed)

4. strategies (alternative strategies considered)
5. costs (cost included in the analysis, currency and year)
6. Outcomes considered
7. time horizon and perspective of study
8. results/authors' conclusions (details of main findings and authors' conclusions).

Quality assessment of included studies

One reviewer critically appraised all the economic evaluations included using the *BMJ* guidelines for reviewers of economic evaluations.[129] The economic models included in the review were appraised by the same reviewer using a published checklist for good practice in decision analytic modelling in health technology assessment.[130]

Economic models assessing long-term costs and/or consequences of screening for type 2 diabetes

Background

Proponents of screening for diabetes argue that the additional investments needed to implement screening programmes are justified by the potential reductions in future diabetic complications, mortality and associated treatment costs. However, although there is direct evidence that various treatments are effective in reducing complications and mortality in people who have been clinically diagnosed with diabetes, there is no direct evidence relating to the magnitude of any further benefit that might be derived from starting these treatments earlier, after detection by screening. In the absence of direct evidence, economic models have been used to estimate the long-term costs and outcomes associated with screening. These models are based on available evidence relating to the progression of diabetes and its complications and various assumptions about the impact of treating diabetes in its early preclinical phase.

Search results

The search for economic studies that assessed the long-term costs and consequences of screening for diabetes identified six potential studies. However, one of the models only considered the benefits of screening in terms of reduction in the incidence of blindness, and another study considered only the long-term costs of screening for a US population. This left four studies for inclusion in this section of the review – three that assessed the long-term cost-effectiveness of screening and one which considered only the long-term outcomes of implementing a screening policy at the population level. These are discussed and compared with each other and previous diabetic modelling studies below.

Statement of the decision problem

The characteristics of the four modelling studies included in this review are summarised in *Table 12*. Three of the studies used similar Markov models to assess the long-term costs and outcomes of screening for T2DM.[131–133] These models used similar assumptions to a previously published model by Eastman and colleagues,[134,135] but incorporated a screening module to assess the impact of identifying and treating patients earlier than they otherwise would have been. The Center for Disease Control Diabetes Cost-Effectiveness Study Group (CDC) was the first to construct a model assessing the impact of screening.[131] This model concentrated on the long-term costs and benefits associated with the provision of glucose-controlling interventions in the early preclinical phase of diabetes. Conventional treatments were assumed to begin after early identification by screening and were compared with the current clinical practice in the USA at the time (conventional treatment commencing after clinical diagnosis). The authors assumed that screening, followed by early treatment for hyperglycaemia, would only impact upon the incidence of microvascular complications and have no effect on CVD.

Chen and colleagues[132] later used the same basic model structure as the CDC to investigate the impact of repeated universal screening as opposed to once-off opportunistic screening. This study also addressed the question of how frequently screening should be carried out.

More recently, Hoerger and colleagues[133] updated the original CDC model to incorporate wider benefits of screening. They used new data for various model parameters and incorporated the finding that, for people with diabetes, tighter blood pressure control provides substantial benefit (relative to standard control) in terms of reducing CVD morbidity and mortality. The model assessed the cost-effectiveness of targeting screening at patients with hypertension compared with once-off opportunistic screening for all adults and the practice of relying on clinical diagnosis.

The fourth study identified used a different approach to model the QALY gains associated with screening. Goyder and Irwig[136] used a decision tree to weigh the potential benefits against the potential harms of screening. The

TABLE 12 *Summary of screening models reviewed*

Study	Comparators	Model type	Economic outcomes	Complications modelled	Benefits of early treatment modelled
CDC, 1998[131]	1. Clinical diagnosis (case finding) 2. Once-off opportunistic screening	Markov (Monte Carlo simulation)	Cost per life-year and cost per QALY	Retinopathy, nephropathy, neuropathy, all CVD	Reduced microvascular complications
Chen *et al.*, 2001[132]	1. Clinical diagnosis (case finding) 2. Universal repeat screening	Markov (Monte Carlo simulation assumed)	Cost per life-year and cost per QALY	Retinopathy, nephropathy, neuropathy, all CVD	Reduced microvascular complications
Hoerger *et al.*, 2004[133]	1. Clinical diagnosis (case finding) 2. Once-off opportunistic screening 3. Targeted screening to people with hypertension	Markov (cohort analysis)	Cost per QALY	Retinopathy, nephropathy, neuropathy, CHD (angina and MI), stroke	Reduced microvascular and cardiovascular complications
Goyder and Irwig, 2000[136]	1. Clinical diagnosis (case finding) 2. Screening for all 45–50-year-olds	Decision tree (cohort analysis)	QALYs gained	All microvascular complications (not distinguished), all CVD (including angina, MI, chronic heart failure and stroke)	Reduced microvascular and cardiovascular complications

baseline characteristics of the cohort were varied to ascertain in which populations the benefits of screening would be likely to outweigh the harm. They assumed that an early diagnosis with screening would lead to improved treatment of other CVD risk factors in addition to BG-controlling measures. Therefore, benefits in the model (QALY gains) accrued from reductions in both microvascular and cardiovascular complications. The potential harms of screening included in the model were assumed reductions in quality of life associated with early diagnosis and adverse effects of the early treatment. None of the other studies considered potential harms of screening.

Cohort information

The characteristics of the cohorts for which these modelling studies were conducted are summarised in *Table 13*. The CDC group[131] simulated screening for a hypothetical population with the demographic characteristics of the US population over 25 years of age. The population was assigned to either screening or current clinical practice. For 10,000 people with diabetes within this population, the disease progression model simulated the development of complications from onset of diabetes under each of the alternative options (screening and current practice). Different screening cohorts defined by age (10-year age groups), race and ethnicity are also considered separately in the model.

The cohort simulated by Hoerger and colleagues[133] was based on 1997 population estimates projected from the 1990 US Census and data on the distribution of people with diabetes by hypertension, cholesterol level and smoking status. Different cohorts defined by age, sex, race and hypertension status were simulated through the model using cohort simulation (all at once) rather than Monte Carlo simulation methods (one patient at a time).

The cohort used by Chen and colleagues[132] consisted of 30,000 individuals with demographic characteristics reflecting the population of Taiwan.

The decision tree analysis by Goyder and Irwig[136] was conducted for a predominantly Caucasian UK cohort aged between 45 and 60 years. The prevalence of diabetes in this cohort was based on a prevalence survey of the population of the Isle of Ely.

Model structure, scope and perspective

The CDC[131] developed a semi-Markov model and used Monte Carlo simulation to model disease progression, treatment costs, life-years and QALYs for the two alternative options considered –

TABLE 13 *Cohort information used in the published screening models*

Study	Cohort demographic characteristics based on	Source of cohort information	Cohort age range (years)	No. of patients in cohort
CDC, 1998[131]	US population	National Health and Nutrition Examination Survey II	25 and over	10,000
Chen *et al.*, 2001[132]	Taiwanese population	Not stated	30 and over	30,000
Hoerger *et al.*, 2004[133]	US population	1997 population estimates projected from the 1990 US Census and data on distribution of people with diabetes in the USA	Separate cohort analyses for screening at 35, 45, 55, 65 and 75	Not stated
Goyder and Irwig, 2000[136]	Caucasian UK population	Isle of Ely Diabetes Project	45–60	10,000

opportunistic screening of all adults versus reliance on clinical diagnosis. The disease progression module consisted of a series of Markov processes, which were used to simultaneously model disease progression on three diabetes complication pathways starting at onset of diabetes. The complication pathways modelled were retinopathy, nephropathy and neuropathy. Individuals from the hypothetical cohort were simulated one at a time through the screening module, where they were first assigned various characteristics weighted on the demographic characteristics of the US population. They were also assigned a diabetes status (undiagnosed) based on the prevalence of undiagnosed diabetes in the US population (adjusted for age, race, ethnicity, obesity and hypertension status). Individuals with diabetes in the screening arm of the model could either be identified by screening (true positives) or missed (false negatives) based on the sensitivity/specificity of the test (FPG test with a cut-off value 6 mmol/l). A total of 10,000 patients with diabetes, as assigned by the model, were then simulated one at a time through the disease progression submodels. Patients who received a diagnosis of diabetes as a result of screening were assumed to begin conventional glucose-controlling treatment (diet and exercise) immediately, whereas those given a false-negative test result began treatment at clinical diagnosis. All those with diabetes in the no-screening arm were assumed to begin treatment at clinical diagnosis. It was assumed that on average clinical diagnosis would occur 10.5 years after diabetes onset. This estimate was based on a study which looked at the relationship between the prevalence of retinopathy and time from clinical diagnosis and used extrapolation to estimate the time at which the prevalence would be zero (9–12 years before clinical diagnosis).[54] Diagnosis by screening was assumed to occur 5 years earlier at 5.5 years after onset (*Figure 1*). Those identified through screening were simulated to receive an extra 5 years of treatment compared with those diagnosed clinically and, thus, have a slower rate of progression in the disease progression submodels.

The model used by Chen and colleagues[132] has the same basic structure as the CDC model, although it is unclear if cohort simulation or Monte Carlo simulation was used for the analysis. Very little information was provided in the published paper regarding the structure of the model and the methods for estimation of parameter values and transition probabilities. This lack of transparency makes it very difficult to assess the quality of the model. The authors used an estimate of 1.1% for the annual incidence of diabetes, which does not seem to have been varied as a function of age, sex or any other patient characteristics. A hypothetical cohort of 30,000 subjects was randomly allocated to one of two screening arms (screen every 2 years or screen every 5 years) or a control arm (no screening). The screening test used was FBG but it is unclear from the paper what cut-off point was used and what sensitivity/specificity values were assumed. Presumably, screening was assumed to result in diagnosis of the incident diabetes cases at a time from onset consistent with the screening intervals. However, it was unclear whether or not the analysts considered the impact that introducing mass screening would have on the undiagnosed prevalent cases in the population. Furthermore, the time from onset at which clinical diagnosis was assumed to occur in the absence of screening was

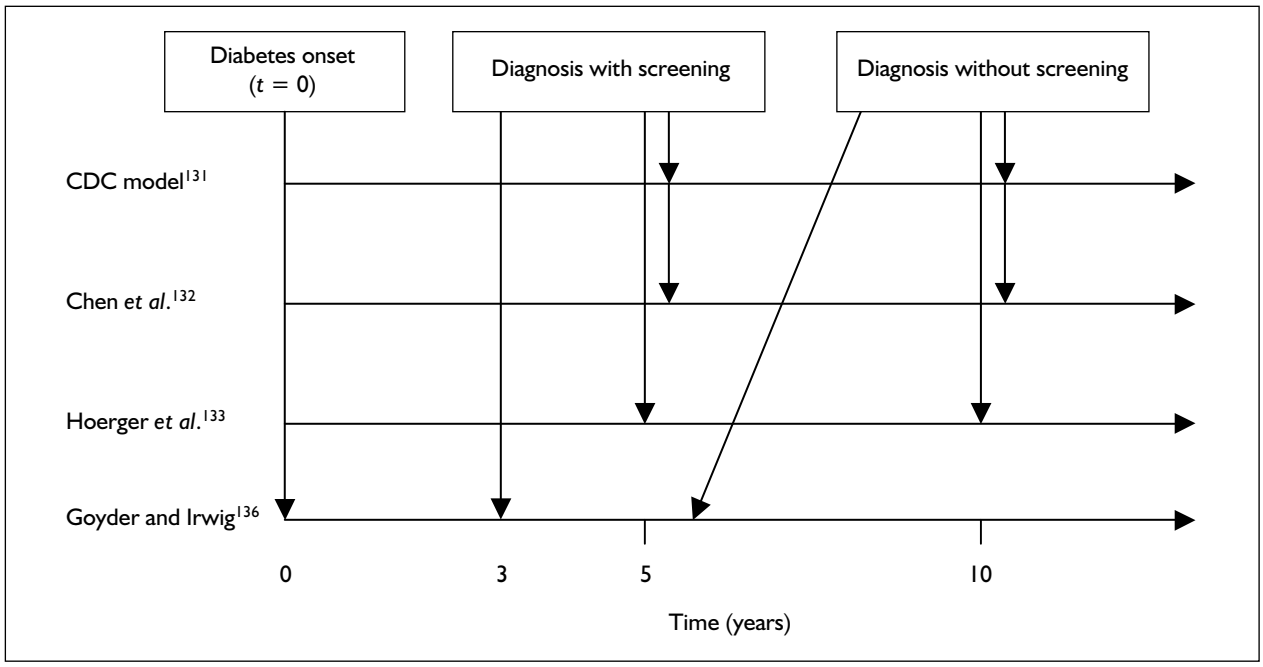

FIGURE 1 *Screening module summaries (indicates time after onset at which diagnosis is assumed to occur in the presence and absence of screening for each of the models)*

not stated. However, it was assumed that screening would result in early treatment that would slow the development of microvascular complications.

The model conducted by Hoerger and colleagues[133] followed the same basic structure as that of the CDC but differed in number of important ways. First, cohort simulation was used to evaluate the model as opposed to Monte Carlo simulation. This means that whole cohorts were passed through the model simultaneously, as opposed to one individual at a time. The model was evaluated for different screening cohorts defined by age, hypertension status and race/ethnicity separately. As shown in *Figure 1*, there were also slight differences in the assumptions about when diagnosis would occur in the presence (average of 5 years after onset as opposed to 5.5 years) and absence of screening (average of 10 years after onset as opposed to 10.5 years). Hoerger and colleagues[133] also made the assumption that upon diagnosis individuals would immediately receive intensive glycaemic control, as defined in the UKPDS trial,[8] as opposed to the conventional treatment assumed in the CDC model. Furthermore, all hypertensive individuals that received a diagnosis of diabetes were assumed to change from standard treatment for hypertension to more intensive therapy [target diastolic blood pressure (DBP) of 80 mmHg as opposed to 90 mmHg].[83] The disease progression module of the model used by Hoerger and colleagues[133] differed from that of the CDC model with respect to added complication pathways for CHD and stroke.

The three Markov models all took the perspective of a single healthcare payer and incorporated inputs consistent with this perspective. The inputs included were sensitivity/specificity of screening tests, costs of the screening tests, transition probabilities relating to the progression of diabetes and its complications, diabetes- and non-diabetes-related mortality risks, utilities and data relating to the effectiveness of glucose- and hypertension-controlling treatments. The models all adopted a lifetime horizon and assessed the lifetime incidence of diabetes-related complications, and also life-years and QALYs, for age- and race-specific cohorts under the different screening and no-screening scenarios.

The decision tree model developed by Goyder and Irwig[136] was used to assess the short-term harms and long-term benefits of once-off screening for people aged between 45 and 60 years. The cohort was assigned to screening or no screening. Those assigned to screening were modelled to receive a single FBG test (using a cut-off giving sensitivity 90%), followed by a gold standard diagnostic test for those screening positive. A prevalence of diagnosed diabetes of 4% was assigned to the cohort based on the findings of a prevalence study conducted on the Isle of Ely.[137] For every prevalent

case of diagnosed diabetes, it was assumed that there would be an undiagnosed case, based on a meeting of an expert committee on diagnosis and classification of diabetes. Therefore, the probability of diabetes being undiagnosed at the time of screening was estimated to be 50%. The model assumed that treatment for diabetes and other cardiovascular risk factors (e.g. hypertension or hyperlipidaemia) would be implemented upon diagnosis, thus reducing morbidity and mortality from microvascular and cardiovascular complications. The authors made the assumption that early treatment for cardiovascular risk factors would only reduce the incidence of cardiovascular events within the time from screening to the time clinical diagnoses would occur in the absence of screening. After the time of clinical diagnosis, it was assumed that the incidence of cardiovascular events would be the same regardless of whether or not early treatment of risk factors was received. This may be an inappropriate assumption if the incidence of CVD is a function of the duration that risk factors have been present.

Goyder and Irwig[136] made two assumptions regarding the impact that screening would have on the time from onset at which diagnosis would occur. First, they assumed that 50% of those who are undiagnosed in the population would never receive a clinical diagnosis in the absence of screening – that is, they would die of mainly cardiovascular causes before receiving a diagnosis and before any end-stage microvascular complications would occur. Hence, screening in this first group of patients would not result in gains from reductions in the incidence in microvascular complications, only gains due to reductions in CVD risks. This differs somewhat from the assumptions made in the Markov models, that all the undiagnosed patients in the population would receive a diagnosis 10 years after onset unless they died before this time. If Goyder and Irwig's[136] assumption is correct, it may be that the CDC model overestimates the impact that screening would have on reducing microvascular complications. It adds weight to the argument that more benefit can be derived from screening by treating risk factors for CVD in those screening positive, rather than from reducing microvascular complications. However, this assumes that it is more cost-effective to diagnose diabetes and then treat risk factors rather than just treat risk factors in those who have them without first screening for diabetes. The second assumption made by Goyder and Irwig[136] is that for the 50% of undiagnosed patients who would receive a clinical diagnosis in the absence of screening, this would occur on average 6 years after onset. This is shorter than the 10/10.5 years assumed in the other models. The effect is that screening results in a shorter window of opportunity (3 years as opposed to 5 years) to provide extra treatment from which patients can gain extra benefit (*Figure 1*).

Modelling of disease progression

In the three Markov models,[131–133] all patients are assumed to have no complications at onset of diabetes. In the CDC model, progression of complications in the early prediagnosis phase is modelled as a function of the prevalence of complications observed at clinical diagnosis in various epidemiological studies.[54,91,138] Hoerger and co-workers[133] only state that they made assumptions about transition probabilities between disease states in the period before usual clinical diagnosis based on knowledge that progression is relatively slow during this phase. After the time when clinical diagnosis would usually occur, disease progression is modelled in relation to the time from normal clinical diagnosis based on the findings of various epidemiological studies (see below). Some transition probabilities in the original CDC model are also adjusted for race/ethnicity to permit the estimation of cost-effectiveness of screening in different racial/ethnic groups. Transition probabilities for race/ethnicity were adjusted using multipliers derived by Eastman and colleagues[134,135] to reflect the higher incidence rates of complications observed in African Americans, American Indians and Hispanic Americans. In the analysis by Hoerger and colleagues,[133] the cost-effectiveness of screening by different racial/ethnic groups was not explored. Little detail was given on how progression was modelled before the time of normal clinical diagnosis in the model by Chen and Colleagues,[132] but the transition probabilities are reported to vary by time.

In the models by the CDC and Hoerger and colleagues, the transition probabilities for progression of microvascular complications were also adjusted for glycaemic control – as measured by HbA_{1c} levels. Initiation of treatment after screening or clinical diagnosis reduces the HbA_{1c} level and thus reduces the transition probabilities for disease progression. Adjustments for HbA_{1c} levels were made using a power function derived by Eastman and colleagues.[134] As evidence relating to the benefits of reducing HbA_{1c} in T2DM patients was lacking at the time of the CDC analysis, the relative benefits (reduced incidence) per unit difference in HbA_{1c} levels were derived

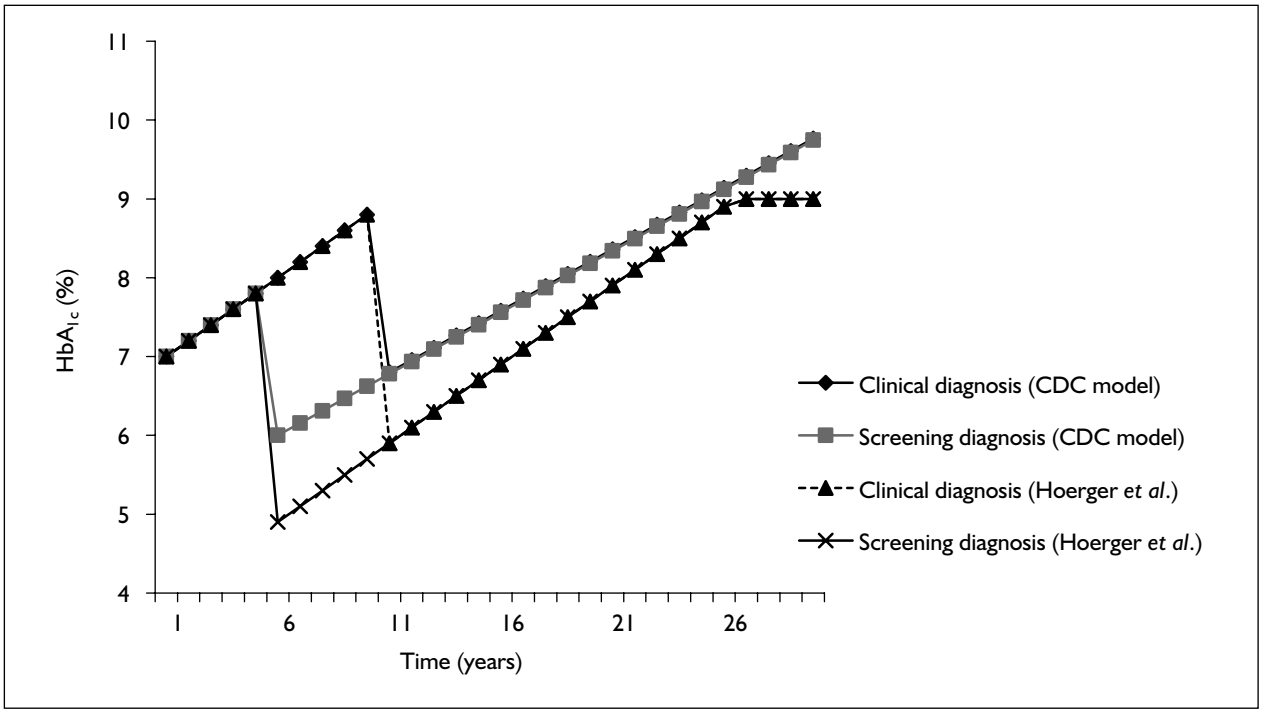

FIGURE 2 *HbA_{1c} levels over time for the screening and no screening strategies in the models by the CDC[131] and Hoerger and colleagues[133]*

from a trial of treatments in patients with type 1 diabetes.[139] Hoerger and colleagues[133] updated this using more recent data on the effects of intensive glycaemic control on disease progression in patients enrolled in the UKPDS trial of T2DM.[8] This reportedly results in smaller reductions in the incidence of complications per unit difference in HbA_{1c} level, compared with the original CDC model.

Figure 2 gives an indication of how the HbA_{1c} levels were modelled over time in the studies by the CDC[131] and Hoerger and colleagues.[133] The figure is based on our own calculations using data provided in the papers. In the original CDC model,[131] the HbA_{1c} levels were assumed to be 6.8% at onset of diabetes with an annual increase of 0.2% points resulting in a level of 8.9% at clinical diagnosis (consistent with data reported in the UKPDS)[140] and 7.8% at diagnosis by screening. From the authors' report, it appears that the HbA_{1c} level was assumed to drop by 2.1% points on initiation of treatment and then increase slowly again by 0.156% points per year – again based on an earlier report of the UKPDS.[141] The HbA_{1c} levels were not allowed to go above 11% or below 6% with treatment. Patients were modelled to receive one of four treatment modalities: diet and exercise, oral hypoglycaemic agents, oral hypoglycaemic agents with insulin or insulin alone. The proportion using each treatment modality varied by duration of diabetes, but exactly how each treatment affected HbA_{1c} levels and how HbA_{1c} levels were used to adjust transition probabilities for disease progression were unclear from the report.

In the updated model by Hoerger and colleagues,[133] the same approach was used to model the HbA_{1c} levels, except that more intensive treatment upon diagnosis resulted in a greater fall of 2.9% points in HbA_{1c} levels.[8] In addition, after the initiation of treatment in the model by Hoerger and colleagues,[133] the HbA_{1c} level is increased by 0.2% points per year (as opposed to 0.156% points) but is never allowed to rise above 9%. Transition probabilities for the development of CHD and stroke were also adjusted for the presence of hypertension and intensity of hypertensive treatment in the model by Hoerger and colleagues (see below).

It was not possible to ascertain the approach used to model the beneficial effects of implementing treatment early in the model by Chen and colleagues.[132] The authors only stated that treatment efficacy parameters were based on those used in Eastman and colleagues' model and findings from the UKPDS.

Goyder and Irwig[136] populated their decision tree model with probabilities derived from literature

sources and various assumptions. Although little information was given in the published journal paper as to how these probabilities were derived, a technical report was obtained from the authors providing more detail. The shorter duration of undiagnosed diabetes (6 years) used in the model was estimated by dividing estimates of the prevalence of undiagnosed diabetes (cases per 1000 individuals) by the incidence (cases per 1000 per year) as estimated from various population surveys.[142–145] However, the authors point out that the incidence estimates were based on clinically diagnosed cases, which will not accurately reflect the true incidence of diabetes, since many cases will never receive a clinical diagnosis. In order to reflect the uncertainty surrounding this parameter, the authors examined the impact of a wide range of estimates in sensitivity analysis.

In terms of the risks of microvascular complications, Goyder and Irwig[136] assumed a lifetime risk of 13% for any complication in intensively treated, clinically diagnosed individuals. This was taken from Eastman and colleagues' model[134] based on the results from the DCCT trial of treatment in type 1 diabetes. This may be inappropriate given more recent findings that suggest intensive glycaemic control is less effective in reducing the lifetime risks of complications in T2DM as it is in type 1 diabetes.[8] The authors assumed that the effectiveness of early treatment to reduce HbA_{1c} would be 50% relative to the effectiveness of treatment later in the disease course. They also assumed that the maximum effect of treatment in the early post-screening phase (before clinical diagnosis) would be to postpone microvascular complications by 3 years (the assumed length of the early treatment window). However, since it was assumed that treatment during this early period would only be half as effective as treatment around the time complications develop, avoidable microvascular complications were assumed to be postponed by 1.5 years with early treatment.

For cardiovascular complications, Goyder and Irwig[136] assumed that the risk of CVD in undiagnosed and diagnosed cases would be the same. In the base case this was assumed to be 2% per year. This was varied in sensitivity analysis to assess the impact that screening might have in groups at higher risk of CVD. It was assumed that an RR reduction of 33% could be achieved during the early treatment period by implementing tighter treatment for hypertension and or hyperlipidaemia. This assumption is based on the findings from several trials showing the effectiveness of these treatments in clinically diagnosed patients.[146–150] The applicability of these findings to patients detected by screening is uncertain. The authors also assumed that the CVD events avoided as a result of early treatment would have been survived by 15 years on average and that the RR of CVD due to early treatment would last only for the period before clinical diagnosis would normally be made. After the time of normal clinical diagnosis, the CVD risk is modelled as being the same, regardless of whether or not early treatment had been received.

In terms of the time horizon of the model, the authors assumed a mean survival time of 17 years from the time of clinical diagnosis based on the model of Eastman and colleagues.[134] Implementation of early treatment is assumed to impact upon morbidity only, and has no effect on life expectancy in the model. The authors estimated that the impact of screening and early treatment on the development of microvascular complications would occur after 15 years. Cardiovascular complications avoided due to early treatment were also assumed to last for 15 years.

Structure of complication submodels (Markov models only)

Nephropathy

The three studies using Markov models adopted the same structure for their nephropathy submodels. Patients follow a path through a Markov process with four consecutive states: no nephropathy, microalbuminuria, proteinuria and end-stage renal disease (ESRD). In the CDC model, Monte Carlo simulation is used to determine whether patients progress from one state to the next or not. Hoerger and colleagues[133] use a cohort simulation where the whole cohort progresses at once. The simulation method used by Chen and colleagues[132] is unclear. In the early preclinical phase, the models by the CDC[131] and Hoerger and colleagues[133] use transition probabilities that yield the prevalence of complications observed at clinical diagnosis in several epidemiological studies.[54,91,138] It is unclear in the model by Chen and colleagues[132] how transition probabilities were modelled during this period. After the time of normal clinical diagnosis (10 years after onset), the CDC model uses the same transition probabilities for developing nephropathy complications as those used by Eastman and colleagues.[135] Chen and colleagues[132] also use these same transition probabilities, although it is not possible to tell if these have been used appropriately, that is, after the time clinical diagnosis would normally occur. Eastman and colleagues[134,135] give details in their

papers on how transition probabilities for progression to each state in the pathway were calculated by duration since clinical diagnosis, and made conditional on the patient being in the immediately prior state. Transition probabilities are also adjusted for race, ethnicity and glycaemic control, as discussed above.

In Hoerger and colleagues' updated version of the model,[133] some of the transition probabilities in the nephropathy module are the same (e.g. proteinuria to end-stage renal disease), but others have been changed without explanation. For example, the transition probability for microalbuminuria to proteinuria is substantially lower. The transition probabilities for microalbuminuria and proteinuria also vary depending on hypertension status and the intensity of hypertensive treatment received (standard before diabetes diagnosis, intensive after) based on data from the UKPDS.[151]

Neuropathy

The neuropathy submodel adopted by all three Markov models again follows the same structure as that used in the study by Eastman and colleagues.[135] The states included are no neuropathy, symptomatic neuropathy, history of lower extremity amputation (LEA) and death from LEA. An individual with neuropathy can experience an LEA during any 1-year cycle, from which they either die (transit to death from LEA) or survive (transit to history of LEA). Patients with a history of LEA can also experience a second LEA from which they can again die or survive. Transitions between these states, after time when normal clinical diagnosis would have occurred, are again based on the transition probabilities calculated by Eastman and colleagues.[134] They calculated these from data on the incidence of neuropathy and LEAs reported in the Rochester Diabetic Neuropathy Study.[152–154] The prevalence of neuropathy at clinical diagnosis was assumed to be 3.5% based on data from the NHANES II survey.[155] An annual hazard rate was then assigned which would result in a cumulative incidence at 8 years after diagnosis that was consistent with the Rochester study.[152,153] Transition probabilities for progression from symptomatic neuropathy to first LEA were again based on the cumulative incidence of this event observed in the Rochester study and made conditional on the presence of neuropathy. The neuropathy module in the updated study by Hoerger and colleagues[133] is essentially the same but the transition probability for peripheral neuropathy is slightly higher as calculated from data reported in the UKPDS study.[151] Hypertension and its control are assumed to have no effect on the development of neuropathy.

Retinopathy

The CDC group based their retinopathy submodel on the model by Eastman and colleagues.[134] The states included are no retinopathy, non-proliferative retinopathy, proliferative retinopathy, significant macular oedema and blindness. The transition probabilities used for these events are those reported by Eastman and colleagues.[135] These were calculated appropriately using data from the Wisconsin Epidemiologic Study of Diabetic Retinopathy[156] and were again made dependent on duration of diabetes since clinical diagnosis. In the model, people who develop proliferative retinopathy and receive eye examinations are assumed to be treated with appropriate photocoagulation, thus reducing their risk of progression to blindness. However, it is not clear what the probability of being identified by an eye examination is.

The retinopathy submodel used by Chen and colleagues[132] follows the same basic structure as that of the CDC model, but the transition probabilities used appear to be different. No details were provided by Chen and colleagues[132] on how these were calculated.

The retinopathy module in the model by Hoerger and colleagues[133] differs from the other two models in that only three states are included. These are normal, photocoagulation and blindness. Transition probabilities are updated with data from the UKPDS trial and also vary according to hypertension status and treatment.

Cardiovascular disease

Specific cardiovascular complications of diabetes are not modelled in the original CDC analysis. However, cumulative incidence of all CVD and CVD mortality is modelled. It is not entirely clear from the paper how this is done, but presumably the same approach as by Eastman and colleagues is used.[134,135] In the latter model, each person is assigned CVD risk factors (smoking status and mean SBP, total cholesterol and HDL cholesterol), based on their age, race and sex by sampling from probability distributions. A previously published multivariate model based on the Framingham Heart Study is then used to calculate the incidence of all CVD.[157] For patients who develop ESRD, 50% are assumed to have CVD based on the observation that 50% of deaths in patients with diabetes-related ESRD are due to CVD. The model assumes that glycaemic

levels have no impact on CVD. This may be an inappropriate assumption and more recently published risk equations for CVD in patients with diabetes include HbA_{1c} levels as a predictor variable.[158]

The model by Chen and colleagues[132] also follows this same structure and makes the same assumptions about CVD in patients with ESRD.

The model described by Hoerger and colleagues[133] (see http://www.annals.org/cgi/content/figsonly/140/9/689 for additional details) includes a fairly complex submodel for CHD and stroke. It is based on previous published models of CHD.[159,160] States in the CHD model include normal, angina, history of CHD/MI and death from CHD. Within a 1-year cycle, individuals in the normal state can experience a CHD event, which could be angina, or a fatal or non-fatal MI (MI modelled as state). The Framingham risk equations are used to calculate the probabilities for these events based on the demographic and epidemiological characteristics of the cohort being analysed.[157] Following an initial MI, patients can either die within 30 days, in which case they transit to the state death from CHD, or they can survive over 30 days. Patients who survive over 30 days can either die from chronic conditions related to MI within the year, experience a second MI within the year (from which they have probabilities of dying or surviving), or continue on with no further events for the remainder of the year. Those who survive move to the state history of MI. Patients whose first CHD event is angina can either survive with angina for the remainder of the year, or experience a MI within the year. Those surviving with angina transit to the angina state, whereas those who have subsequent MI within the year can either survive (transit to history of MI) or die within the year (death from CHD). In the subsequent cycle of the model, patients in each of the states have further chances of staying where they are, experiencing an initial or subsequent MI, or dying. The probabilities for all the events in this model are based on published multivariate equations, which incorporate age, various CVD risk factors and CHD history.[157,159,160]

The effects on blood pressure control are modelled as reductions in the risks of CHD events. The efficacy of intensive hypertension control in preventing CHD comes from the HOT trial, which found that relative to standard control, it reduces the risk of CHD by 51%.[83]

The stroke module included in the model by Hoerger and colleagues[133] includes three states: normal, history of stroke and death. Within each 1-year cycle individuals can either stay in the normal state or experience a stroke from which they die or transit to having a history of stroke. Again, no details are provided for how risks of these events are calculated in the published paper of the screening model. The technical report describes how the Framingham equation is used to calculate the transition probability from normal to stroke. The other transition probabilities were calculated appropriately from another published source.[161] In the base-case analysis, it was assumed that intensive hypertension control has no effect on the incidence of stroke relative to standard control, but a 30% RR reduction was explored in sensitivity analysis, based on the findings of studies showing such benefits for intensive hypertension control.[151,162]

Mortality

Mortality in the CDC screening study is modelled as a competing risk for each of the major complications of diabetes. Increased mortality rates among people with diabetes are attributed to increased mortality due to CVD, ESRD, LEA and other causes. A mortality rate is assigned to individuals in a sequential fashion. If, for example, a patient undergoes an LEA during the year, the model will assign that person a mortality rate based on the anatomical level of amputation. If a patient does not have an LEA or survives the operation, the model assigns that person either the mortality rate for ESRD, if it is present, or a mortality rate determined from the increased risk of CVD mortality plus non-CVD morality. Data sources used for the mortality risks for ESRD and LEA are given in the report, but no details are given for any calculations required. The cardiovascular mortality rate is estimated using equations from the Framingham Heart Study[83] as a function of age, sex, SBP, total cholesterol level, HDL levels and left ventricular hypertrophy. It is not clear how these characteristics are assigned and modelled over time for individuals in the cohort, but presumably the same approach as by Eastman and colleagues is taken whereby patient characteristics are sampled from probability distributions. The authors of the CDC model[131] also assume that diabetic patients have an increased risk of non-CDV mortality 2.75 times that of non-diabetic individuals, which is presumably used to adjust age- and sex-specific mortality rates published in life tables. Eastman and colleagues[135] originally introduced this factor to achieve consistency with a reported 5–10-year

reduction in life expectancy observed for middle-aged people with diabetes.

Chen and colleagues[132] provide too little detail in their paper to ascertain how mortality from competing causes was modelled.

Hoerger and colleagues[133] model mortality from LEA, ESRD, CHD, stroke and other causes. Details of how these events were modelled were provided in the technical report only. Mortality estimates for CVD/CHD are based on equations originally published by Weinstein and colleagues[159] and updated by Hunink and colleagues.[160] These equations predict probabilities of CHD-related deaths based on age, sex and history of CHD events. It is not clear if these risks are directly relevant to patients with diabetes, as diabetic patients may have greater risks of death following CHD events than non-diabetic patients. Diabetic patients in the cohort who experience a stroke, LEA or ESRD also have a higher mortality risk than patients without these complications. The death rates for LEA were obtained from published literature[154] and appropriately transformed for incorporation into the model. Mortality rates from ESRD are specific for the cohort's age, sex and race/ethnicity. Finally, patients in the cohort can experience death from other causes from any state in the model. These rates are taken from life tables and do not appear to be adjusted in the same way as in the original CDC study.[131]

Costs

The costs included in the original CDC model are those for screening, glucose-controlling treatment (including drugs, self-monitoring costs, outpatient visits), costs associated with microvascular complications, costs associated with CVD and other routine medical costs not specific to diabetes. Costs are presented in 1995 US dollars and are discounted at a rate of 3%. Assumptions regarding extra resources required for screening and treatment are described and justified in the model, and the unit costs used are presented and referenced. However, it is very difficult to comment on the appropriateness of these unit costs given the lack of detail on how they were calculated.

Chen and colleagues[132] use exactly the same cost data (1995 US dollars) as used in the CDC model[131] and also discount at a rate of 3%. However, they do not provide any information on how treatment regimens are assumed to change over time.

In addition to the costs considered in the CDC model, Hoerger and colleagues[133] also include the costs of standard and intensive hypertension control for patients with hypertension. Also, the updated study assumes that intensive glycaemic control would be implemented upon diagnosis of diabetes, thus increasing resource use and costs associated with treatment. Costs in the updated study are provided in 1997 US dollars and unit costs are derived from various sources in the literature. In some cases the sources are the same as in the original CDC study,[131] but in other cases different sources have been used. It is not clear why such choices have been made, but a number of costs in the earlier study were derived from studies of patients with type 1 diabetes, so the more recent estimates in the updated model may be more appropriate. Costs in the updated study by Hoerger and colleagues[133] are also discounted at 3%.

Outcomes

The primary outcomes in the CDC model[131] were additional life-years and QALYs measured from onset of diabetes. Outcomes were discounted at 3%. The scarcity of data available for utility scores at the time this model was constructed meant that certain assumptions had to be made. Utility scores were assumed to be 1 for each year of life lived without a major end-stage complication. Utility adjustments were only made for years lived with blindness (0.69),[163] ESRD (0.61)[164] and LEA (0.8).[165] No details are given in the paper as to how these utility scores were calculated, so it is not possible to comment on their suitability for estimating QALYs. The assumption was also made that when a patient develops more than one major complication, the lower utility score applies. These assumptions are unrealistic. First, reductions in utility are likely in the earlier phases of diabetes and its complications (possibly due to having the diagnosis or side-effects of treatments), and second, if two major complications are experienced, it is not likely that a patient would value this the same as having only one complication. The model is therefore likely to underestimate the quality of life impact of diabetes.

Chen and colleagues[132] use the same utility adjustments and discount QALYs at 3%. They do not provide any detail as to how they deal with patients who experience multiple complications.

Hoerger and colleagues[133] consider the same outcomes as the earlier model and use the same utility values for blindness, LEA and ESRD. They

also add utility adjustment values for angina (0.947),[135] history of MI (0.880)[166] and history of stroke (0.50).[167] QALYs were also discounted at a rate of 3%. The approach used for adjusting utility values in patients with multiple complications is not given in the paper.

A simplifying assumption of the decision tree model by Goyder and Irwig[136] is that no distinction is made between different types of microvascular complications and different types of macrovascular complications. It assumes that early intervention reduces the incidence of all of them. A utility weight for all microvascular complications was estimated by taking the average of the weights for blindness, LEA and ESRD as estimated in the Global Burden of Disease study.[168] This was a weighted average based on the relative prevalence of these complications as estimated by Eastman and colleagues.[135] For the macrovascular utility weight the same method was used, taking the average of weights for angina, acute MI, chronic heart failure and stroke. For the disutility assumed to be associated with early diagnosis and treatment, a value of 0.01 was used. This was taken from a study assessing the impact of treatment for hypertension given a lack of direct evidence relating to the impact of diabetes. Benefits, in terms of QALY gains, associated with avoidance of micro- and macrovascular complications, were discounted at 3%.

Findings/conclusions

The results for the four studies are as follows (costs in US dollars).

CDC Diabetes Cost-Effectiveness Group[131]

The incremental cost-effectiveness ratio (ICER) reported in the CDC study was $236,449 per life-year gained (LYG) and $56,649 per QALY for screening of all adults over 25 years of age. Screening was found to be more cost-effective in younger cohorts – $35,768 per LYG ($13,376 per QALY) for a 25–34-year-old age cohort compared with $64,878 per LYG ($18,707 per QALY) in 35–44-year-olds and $681,989 per LYG ($116908 per QALY) for those aged 55–64 years. This result is explained by the fact that the CDC model assumes that early treatment after screening only benefits patients by postponing occurrence of microvascular complications. Screening, therefore, has little impact on mortality/life expectancy but does improve quality of life. More favourable ICERs are observed in younger cohorts because they have more expected life-years in which to remain complication free. More favourable ICERs were also observed in African Americans due to the increased prevalence of diabetes and increased risks of developing complications in this group.

Chen and colleagues[132]

Compared with control, both the screening regimens are reported to reduce the incidence of microvascular complications. The reported reduction in incidence was particularly high for ESRD (65%). This is much higher than the reduction reported in the CDC model (35%), despite the fact that a very similar modelling approach was reportedly used. No clear explanation is given for this anomaly. The ICERs reported for biennial and 5-yearly screening, compared with no screening, are $17,883 and $10,531 per QALY, respectively. Chen and colleagues[132] also found that screening younger cohorts was more cost-effective than screening older cohorts.

Hoerger and colleagues[133]

The authors found that in cohorts of all ages, the ICERs were more favourable for screening targeted to people with hypertension than universal screening – ICERs ranging from $87,096 per QALY (35-year-old cohort) to $32,106 per QALY (75-year-old cohort) compared with no screening. The equivalent ICERs for universal screening were $126,238 and $48,146 per QALY. The ICERs for universal screening versus targeted screening range from $143,839 per QALY (35-year-old cohort) to $443,433 per QALY (75-year-old cohort). Screening in general (targeted and universal) was found to be more cost-effective in older cohorts, a very different finding to that reported in the CDC study. The main reason for this is that in the new model, most of the benefits of screening come from reducing CHD events with intensive hypertension control as opposed to reducing microvascular complications with glycaemic control. Younger people have lower risk for CHD and so benefit less. A second reason for the difference is that in the new model, glycaemic control results in smaller reductions in the incidence of microvascular complications. This is based on more appropriate data from the UKPDS trial, which was not available at the time of the previous analysis.

Goyder and Irwig[136]

The base-case analysis found that for every 10,000 individuals screened, a net of 10 QALYs would be gained: four from postponed microvascular complications and 17 from avoided cardiovascular complications balanced against a loss of 11 from early diagnosis due to screening. This seems to be

consistent with the findings of Hoerger and colleagues,[133] that the main benefits of screening will be obtained from reducing cardiovascular events as opposed to microvascular complications.

Sensitivity analysis

The authors of the CDC study report that the cost-effectiveness of screening was sensitive to several parameters including the screening test used, the sensitivity/specificity of the test and particularly the length of prediagnosis interval and the intensity of treatment received after screening (more intensive treatments increasing the cost per QALY). This is an important finding since the standard of care for T2DM patients should now be intensive treatment in the light of the results from the UKPDS study. A weakness of the CDC model is the limited sensitivity analysis carried out. Only univariate sensitivity analysis was conducted on a small number of parameters, which does not adequately characterise the uncertainty inherent in the modelling approach.

Chen and colleagues[132] reported no sensitivity analysis.

Hoerger and colleagues[133] provided a much more thorough sensitivity analysis. In addition to performing univariate analysis, they performed probabilistic sensitivity analysis by simultaneously varying 129 parameters over probability distributions estimated from published 95% CIs. However, it is not clear if they took into account interdependence between parameters. From univariate sensitivity analysis, it was found that the cost-effectiveness of targeted screening was moderately sensitive to the duration of the prediagnosis phase, and highly sensitive to the intensity of glycaemic treatment individuals receive after diagnosis (ICERs halved if conventional treatment was assumed). It is not entirely clear why this assumption had such a great effect on the ICER. Results were also very sensitive to the risk reduction associated with intensive hypertension control. This is an important finding given that the reduction used in the model was taken from a single trial and that adherence to drugs may be lower in general populations. Based on 1000 iterations of second-order Monte Carlo simulation, the median ICER for targeted screening of 55-year-olds was $34,229 (95% of ICERs falling between $21,594 and $76,099 per QALY).

Goyder and Irwig[136] conducted one-way sensitivity analysis on most of the parameters included in their model and found that with all else remaining constant (at baseline values), the benefits of screening would no longer outweigh the harms if the annual risk of CVD fell below 0.8%, the RR of CVD could not be reduced by 13% or more with early treatment, the disutility of early diagnosis is more than 2% or the annual discount rate applied to QALY gains was greater than 7%. From this, the authors concluded that the decision on who to screen should be based on the baseline risk of CVD, the presence of other treatable CVD risk factors and the disutility that is assigned to diagnosis. In addition to their main analysis, Goyder and Irwig used these threshold values to calculate the interval at which the benefits of repeat screening would be likely to outweigh the harms.

Conclusions of critical appraisals

This section summarises the critical appraisals of the four modelling studies reviewed in this chapter in terms of a checklist provided for assessing the quality of decision analytic models.[130]

CDC Diabetes Cost-Effectiveness Group[131]

The authors provide a reasonable overview of the decision problem and the structure and assumptions of their model, which are consistent with the underlying theory of diabetes disease progression. However, there is a lack of transparency regarding the details of how specific components of the model work. For example, it is not clear how mortality risks are calculated or how the glycaemic levels are used to adjust the progression of complications.

Another problem is a lack of transparency regarding the data incorporation process. Although sources are generally referenced well, values used in the model are not presented in many cases and it is not always clear how/whether data from original epidemiological, clinical or costing studies have been synthesised for incorporation into the model. The generalisability of US cost data to the UK is also questionable, especially since it is unclear how costs were calculated. The limited sensitivity analysis is also a weakness, making it difficult to express confidence in the results presented.

Although there is no evidence presented that directly assessed the internal and external consistency of the model, the model does not produce any counterintuitive results and certain components of the model were calibrated to be consistent with data reported in epidemiological studies (e.g. glycaemic levels and mortality). In summary, due to the study weaknesses mentioned

above and the exclusion of any benefits in terms of reduced risk of CVD (as a direct consequence of glycaemic control or by initiation of treatments aimed at other CVD risk factors), the conclusions of this model cannot be taken as authoritative. The model is somewhat outdated by the more up-to-date analysis which incorporates more recent and relevant data.

Chen and colleagues[132]

The model clearly outlines the decision problem of whether mass screening should be introduced, how often it should take place and who should be screened. The objectives of the model are also clearly laid out. However, the main problem with this model is the lack of transparency in the paper reporting it. Many assumptions have not been made explicit, making it impossible to ascertain the appropriateness of the results. In general, the structure is the same as in the original CDC model, but there are differences in the screening component with regard to repeat screening. It is unclear if the authors have used the same assumptions regarding the time after onset that clinical diagnosis occurs in the absence of screening. It is also unclear whether they have considered the impact that screening would have on prevalent undiagnosed cases already present in the population or only considered its impact on incident cases in a cohort, which starts with no diabetes.

The data incorporation process is not recorded in sufficient detail, with no information on the calculation of transition probabilities, although many of these were taken directly from a previous model. Another weakness is the fact that no sensitivity analysis was conducted, which is particularly important given that assumptions about the uptake for screening and adherence to subsequent treatment are likely to impact upon the cost-effectiveness of mass screening for the whole population.

The model also appears to deliver some surprising results, which seem inconsistent with the CDC model, despite the apparent similarities between the two models. First, the model predicts a proportionally much larger reduction in the incidence of ESRD. Second, the ICERs reported for mass repeat screening are substantially lower than those reported by the CDC for once-off opportunistic screening. The opposite might be expected if one considers that the cost of mass repeat screening is likely to be much higher, and might not detect very many more cases. Furthermore, with repeated screening, the cost per case detected is likely to increase with time, as there will be fewer undiagnosed cases in the population. Without knowing what the assumptions were regarding the prevalence of undiagnosed diabetes in the cohort, the costs of implementing mass screening and the uptake for it, it is impossible to tell if these findings are credible. With regard to the finding that mass screening was more cost-effective in younger cohorts, the same criticisms that applied to the CDC model also apply here.

Hoerger and colleagues[133]

This analysis is more comprehensive than the original CDC model due to the inclusion of submodels for CHD and stroke and the incorporation of benefits accruing from tight blood pressure control. However, there is a lack of justification given for excluding other potentially cost-effective screening strategies from the analysis. For example, screening for diabetes could be targeted at other high/higher risk groups using risk scores that take into account obesity, smoking status, cholesterol level, etc. Screening could be potentially more cost-effective in such groups who have a higher risk for diabetes and CVD than people who have hypertension alone. The cost-effectiveness of repeated screening or organised mass screening have not been explored either. In addition, the assumption in the screening module seems to be that implementing opportunistic screening will result in 100% of those eligible for it being offered it, and 100% agreeing to uptake, which may be unrealistic. However, people already attending their GP for other reasons are likely to be a fairly accessible population.

Access to a technical report on the model provided a better understanding of the finer detail. There is more transparency regarding the data incorporation process in this analysis, with point estimates, distributions and sources being presented in tables. However, there was little detail given in the published paper about how certain parameters were derived from the literature. The technical report gave a better account of the derivation of model parameters. However, some of the parameters used in the screening model appear to be different to those published in the technical report, so it is still unclear how some parameter values used in the model were derived. A further advantage of the updated model is the incorporation of many parameter values as distributions, which appear to have been appropriately estimated from published 95% CIs where available. This allowed second-order probabilistic sensitivity analysis to be conducted,

giving a better indication of the uncertainty surrounding the cost-effectiveness estimate.

In terms of internal consistency, the model appears to work in a predictable manner but does produce one slightly counterintuitive result. There is no clear explanation as to why the ICER for screening is so much lower when conventional glucose-controlling treatment, as opposed to intensive treatment, is assumed. However, this is consistent with the findings of sensitivity analysis reported in the original CDC model. The results that do differ from the previous version of the model are adequately explained in terms of the inclusion of benefits relating to the intensive treatment of blood pressure. So, given the findings from the model, the authors conclude that screening of people with hypertension between the ages of 55 and 75 years is likely to be a more efficient strategy than universal screening. This conclusion seems reasonably valid given the data presented in the model. However, the conclusion is based on an assumption that intensive hypertension control provides as much added benefit to people with preclinical diabetes as it does to people with clinical diabetes. There is also the same problem of the generalisability of US cost data to the UK.

Goyder and Irwig[136]

The authors of this model use a simpler model structure than the other analyses. This means that more simplifying assumptions were required and these are not transparent and appropriately justified in all cases. For example, the basis for the assumption that 50% of undiagnosed cases will never be clinically diagnosed in the absence of screening is not clear. Furthermore, it is not clear how long this group would be expected to live in the absence of screening. It is difficult to assess the appropriateness of some of the assumptions given this lack of transparency and justification.

For parameters based on evidence from the literature, details of sources and calculations required for incorporation in the model were provided in the technical report. Appropriate methods appear to have been used to identify sources and the data sources used are perhaps more applicable to the UK setting than those used in the other models. However, the prevalence estimates are based on a sample that is not representative of the UK population as a whole. Another problem is that where numerous data sources exist for one parameter, the choice of estimate used in the model is not always justified. Although the impact of using a full range of plausible values has been considered for most parameters, only one-way sensitivity analysis was used.

In terms of consistency, there is no evidence that the authors have tested the model prior to conducting their analysis. In general, the decision tree approach used by Goyder and Irwig[136] provides a less comprehensive and realistic way of modelling the impact of diabetes screening than the model by Hoerger and colleagues. Given the larger number of simplifying assumptions, it is difficult to assess the validity of the results. However, it is based on data that are perhaps more relevant to the UK setting and it does produce findings that are broadly consistent with the findings of Hoerger and colleagues.

Summary and recommendations

Of the four studies reviewed in this chapter, the model of Hoerger and colleagues is the strongest and most comprehensive. However, it is difficult to assess the applicability of the results to the UK setting given that the model was designed to reflect the epidemiology of, and the resource use patterns for, diabetes in the USA. There are various reasons why the cost estimates used for long-term complications in Hoerger and colleagues' model may not apply to the UK. First, the treatment protocols for various complications of diabetes may differ in the UK (i.e. be less or more resource intensive). Second, the methods used to estimate the costs to attach to resources used may be based on inappropriate methods for transferral to the UK setting (i.e. user charges). Third, different price structures exist in the USA compared with the UK. Although Hoerger and colleagues conducted probabilistic sensitivity analysis and showed that their findings were fairly robust to simultaneous variation in 192 parameters (including all cost parameters), a definitive conclusion on whether or not screening for diabetes would be cost-effective in the UK is not possible from this review. On the other hand, the conclusion that selective screening is likely to be more cost-effective than universal screening is likely to be applicable to the UK. However, exactly how screening should be targeted is still unclear, as the model by Hoerger and colleagues only considered one targeted screening strategy. It would be possible to target treatment at individuals with cardiovascular risk factors other than hypertension (e.g. obese patients or those with elevated lipids).

Given the shortcomings of the models included in this review and the difficulties surrounding the

generalisability of the results, it would be advisable to conduct a new modelling study to assess the cost-effectiveness of screening in the UK setting before drawing any conclusions on cost-effectiveness. This analysis should include all possible screening options and in particular should look at the cost-effectiveness of screening targeted at other groups at high risk of CVD (not just hypertensive patients). Modelling such strategies will require some assumptions about the added benefit of providing a diabetes diagnosis on top of the other known cardiovascular risk factors. If it is assumed that diabetes diagnosis would result in better treatment, or better adherence to treatment for other CVD risk factors present (e.g. obesity or hyperlipidaemia), then targeted screening could potentially be cost-effective in these groups. On the other hand, the question remains as to whether or not it would be more cost-effective to try and improve treatment for CVD risk factors in all patients who have them, without screening for diabetes. Thus a relevant comparator in models of targeted diabetes screening could be no screening but improved treatment of all CVD risk factors in those who have them.

Another potential screening option that has not been included in any of the screening models to date is the possibility of widening screening to identify those with IFG or IGT. Several clinical studies have demonstrated the effectiveness of lifestyle interventions or pharmacological treatments for reducing the incidence of T2DM in those who are known to have IFG or IGT.[89,90] Cost-effectiveness modelling studies have also been conducted and estimate favourable cost per QALY and cost per LYG ratios for such programmes.[169–172] These models are reviewed in detail in the next section. It would be relatively straightforward to adapt one of the existing screening models, or another diabetes model, to estimate the extra costs and the added benefits of detecting and treating individuals with IGT or IFG. Such models would require data on the prevalence of these conditions, the sensitivity/specificity of tests to detect them and the prevalence of cardiovascular risk factors in these groups. Finally, a future analysis could also investigate the effects of repeat screening as opposed to once-off screening.

The main gap in the evidence relating to the cost-effectiveness of screening for diabetes is the uncertainty surrounding the effects of implementing or improving treatment for hyperglycaemia, hypertension and hyperlipidaemia in the preclinical phase of diabetes.

Economic models assessing the cost-effectiveness of identifying and treating people with impaired glucose tolerance

Background

Several RCTs have demonstrated the effectiveness of lifestyle interventions or pharmacological treatments for reducing the incidence of diabetes over the short to medium term.[89,90,169] Thus, a potential benefit that could be gained from screening for hyperglycaemia would be to prevent progression to diabetes in those found to have IGT or IFG. A within-trial cost-effectiveness analysis, carried out alongside the largest diabetes prevention trial to date,[170] estimated the cost per diabetes case prevented and the cost per QALY gained for the lifestyle and metformin interventions compared with placebo. The reported ICERs were $34,500 per case prevented ($99,200 per QALY) for the metformin arm and $24,400 per case prevented ($51,600 per QALY) for the lifestyle arm. However, this analysis only considered the costs of treatment and the benefits accrued over the 3-year follow-up period of the trial. It did not consider future IGT treatment costs, future costs avoided from delaying or preventing the onset of diabetes or gains in quantity and/or quality of life associated with the avoidance of future complications of IGT or diabetes. This section appraises and discusses the findings of several modelling studies that have been carried out to assess the long-term costs and consequences of preventing or delaying the onset of diabetes.

Search results

Five modelling studies were identified by literature searches for inclusion in this section. The characteristics of the five modelling studies included in this section are summarised in *Table 14*. The studies all used modelling approaches broadly similar to those used in the studies assessing the long-term costs and health impact of screening for diabetes. The main difference is that the models reviewed in this section assessed the progression of disease from a time prior to the onset of diabetes, when subjects would have IGT or IFG. Three of the studies assessed the long-term costs and benefits that would be expected with the use of lifestyle or pharmacological interventions for the prevention of diabetes,[171–173] one study considered lifestyle interventions and surgery[174] and one only assessed the impact that delaying the onset of diabetes would have[175] – without actually incorporating in the model the interventions that

TABLE 14 *Summary of prevention models reviewed*

Study	Comparators	Model type	Economic outcomes	Complications modelled	Benefits of early treatment modelled
Segal *et al.*, 1998[174]	1. Intensive diet and behaviour modification (seriously obese individuals with and without IGT) 2. Intensive diet and behaviour modification (women with previous gestational diabetes) 3. Surgery for severely obese individuals 4. Group behavioural modification for overweight and obese men 5. GP advice 6. Media campaign with community support (general population)	Markov model (cohort analysis)	Cost per life-year	None	Reduced mortality due to prevention of diabetes
Caro *et al.*, 2004[173]	1. Lifestyle intervention (DPS trial) 2. Metformin intervention (DPP trial) 3. Acarbose intervention (STOP-NIDDM trial) 4. Control (no intervention)	Markov model (Monte Carlo simulation)	Cost per life-year	Retinopathy, neuropathy, nephropathy, foot ulcers, hypoglycaemia, stroke, transient ischaemic attacks, MI and angina (only the costs of these events were considered)	Reduced mortality due to prevention of diabetes
Palmer *et al.*, 2004[172]	1. Lifestyle intervention (DPP trial) 2. Metformin intervention (DPP trial) 3. Placebo (DPP trial)	Markov model	Cost per life-year	None	Reduced mortality due to prevention of diabetes
Herman *et al.*, 2005[171]	1. Lifestyle intervention (DPP trial) 2. Metformin intervention (DPP trial) 3. Placebo (DPP trial)	Markov model (cohort analysis)	Cost per QALY	Retinopathy, nephropathy, neuropathy, CHD (angina and CA/MI), stroke	Reduced mortality due to prevention of diabetes and QALY gains from reduced diabetes complications
McEwan *et al.*, 2005[175]	No interventions but four delay scenarios assessed: 1. no delay 2. 2-year delay 3. 5-year delay 4. 10-year delay	Semi-Markov microsimulation model	Cost per QALY	Retinopathy, nephropathy, neuropathy, MI and stroke	Reduced mortality due to prevention of diabetes and QALY gains from reduced diabetes complications

would be required to do this. The models used in these studies are discussed in detail below.

Statement of decision problem

Segal and colleagues[174] conducted the first cost-effectiveness modelling study in the area of diabetes prevention. They developed their model to assess the cost-effectiveness of several different types of diabetes prevention programme relative to a control. The objective was to ascertain which types of programme were likely to be most cost-effective. The interventions considered in the model were intensive diet and behaviour modification (targeted at all seriously obese individuals with and without IGT), intensive diet and behaviour modification (targeted at women with previous gestational diabetes), surgery for severely obese individuals (BMI >40), group behavioural modification for overweight and obese men (mixed and with IGT only), GP advice (targeted at high-risk adults) and a media campaign with community support (general population). The study did not consider any pharmacological interventions for the prevention of diabetes.

A subsequent modelling study, conducted by Caro and colleagues,[173] assessed the cost-effectiveness of a lifestyle intervention, a metformin intervention and an acarbose intervention relative to no intervention. The lifestyle intervention was based on that used in the DPS trial.[89] This intervention involved seven dietician visits in the first year and four visits per year thereafter, in addition to individualised exercise programmes. For the acarbose and metformin interventions, it was assumed that patients would be prescribed the daily doses reported in various diabetes preventions trials.[89,90,169] An additional analysis carried out by the authors also assessed the costs of screening that would be required to identify people with IGT for treatment. This model concentrated on the benefits that could be gained from preventing patients progressing from IGT to diabetes.

Palmer and colleagues[172] used a similar approach to Caro and colleagues[173] to extrapolate the findings from the DPP trial over the lifetime of patients. They assessed the long-term costs and outcomes of the lifestyle and metformin interventions, as reported in the DPP trial,[90] relative to the control arm. The analysis was conducted separately for an Australian, French, German, Swiss and UK population/setting. It should be noted that the lifestyle intervention used in the DPP trial was more resource intensive than that used in the DPS trial (see below). The metformin intervention consisted of a target dose of 850 mg twice per day and also included standard advice on diet and exercise. The control arm of the trial was the same as the metformin arm but a placebo was given instead of metformin.

In a more recent study, Herman and colleagues[171] also assessed the benefits that could be gained from preventing progression to diabetes using the lifestyle and metformin interventions reported in the DPP trial. They used the same model (Research Triangle International/CDC diabetes model) as that used by Hoerger and colleagues[133] to assess the cost-effectiveness of screening for diabetes. However, in this analysis the model was modified to predict disease progression prior to the onset of diabetes.

In the most recent study reviewed here, McEwan and colleagues[175] used their model to assess the impact that delaying diabetes would have on costs and outcomes over a 20-year period. The report was only available as a poster presentation at time of writing, so limited detail was available regarding the model's structure and assumptions. Their analysis was not an economic evaluation in the sense it did not assess the cost-effectiveness of different interventions relative to each other. However, it did assess the costs, clinical outcomes and QALYs that would accrue for four different scenarios relating to the timing of diabetes onset. The four scenarios were no delay in diabetes onset (control), a 2-year delay in onset, a 5-year delay in onset and a 10-year delay in onset.

Cohort information

The characteristics of the cohorts synthesised in the modelling studies of diabetes prevention programmes are summarised in *Table 15*. The cohorts modelled by Segal and colleagues[174] varied for the different types of interventions modelled, which were targeted at different groups (see above). The authors did state that a single age group was assumed for all the different target populations, but it was unclear what this was.

Caro and colleagues[173] conducted their analysis for a cohort of 1000 patients with the characteristics of those enrolled in a recent randomised trial of interventions to prevent diabetes, the Study To Prevent Non-insulin Dependent Diabetes Mellitus (STOP-NIDDM).[169] Participants were predominantly Caucasians from Canada, Germany, Austria, Norway, Denmark, Sweden, Finland, Israel and Spain, with a mean age of 54.5 years and a BMI between 25 and 40 kg/m^2. All participants had IGT defined as

TABLE 15 *Cohort information used in the published prevention models*

Study	Cohort demographic characteristics	Source of cohort information	Cohort age range (years)	No. of patients in cohort
Segal *et al*., 1998[174]	Varied by intervention being assessed (see text)	Not reported	Not reported	Not reported
Caro *et al*., 2004[173]	Predominantly Caucasians from Canada, Germany, Austria, Norway, Denmark, Sweden, Finland, Israel and Spain. Mean age 54.5 years and BMI between 25 and 40 kg/m^2	Patients enrolled in the STOP-NIDDM trial	40–70	1000
Palmer *et al*., 2004[172]	Mean age 50.6 years, mean body weight 92 kg and mean BMI 34 kg/m^2; 32% men and 45% from minority groups	Patients enrolled in the DPP trial	25 and older	Not reported
Herman *et al*., 2005[171]	Mean age 50.6 years, mean body weight 92 kg and mean BMI 34 kg/m^2; 32% men and 45% from minority groups	Patients enrolled in the DPP trial	25 and older	Not reported
McEwan *et al*., 2005[175]	Not reported	Not reported	Not reported	Not reported

2-hour plasma glucose concentration of 7.8 mmol/l or greater, and less than 11.1 mmol/l after a 75-g glucose load. Patients also had to have a fasting plasma glucose concentration of 5.6–7.7 mmol/l. For their screening analysis, the authors assumed that the prevalence of IGT was 11% of the population based on an epidemiological study conducted in the USA.[176]

The cohort modelled by Palmer and colleagues[172] was constructed to resemble the study population of the DPP: 3234 patients over the age of 25 years with IGT and fasting glucose levels between 5.27 and 6.94 mmol/l.[90] The mean age of the cohort was 50.6 years, the mean body weight 92 kg and the mean BMI 34 kg/m^2; 32% of the cohort were men and 45% were from minority groups. Hence the cohort modelled by Palmer and colleagues is substantially different from that modelled by Caro and colleagues.[173]

Herman and associates[171] also conducted their analysis for a cohort based on the characteristics of patients enrolled in the DPP trial. The demographic characteristics and modifiable risk factors of the cohort modelled by McEwan and colleagues[175] were not reported in the available poster but the model cohort consisted of 1000 patients.

Model structure, perspective and scope

Segal and colleagues[174] used a Markov model, with cohort analysis, to explore diabetic status and survival in an intervention and control group for each programme type they considered. Limited details were provided in the published paper but it appears that their model had four main states: NGT, IGT, diabetes and death. Obesity and weight loss/gain also seem to have been modelled but there is no detail provided of how this was done. Progression between the states was modelled to occur on 5-yearly cycles over a period of 25 years. This does not seem an appropriate cycle length and no explanation or justification was provided for this choice. However, the cohort was subject to an annual mortality risk so as to yield an annual tally of the number of survivors in each group, in addition to expected life-years. The intervention group was divided into two streams in the model: those who would complete/adhere to treatment and those who would fail to complete/adhere to treatment. The authors conservatively assumed that those failing to complete treatment would experience the same outcomes as the control group. Beyond the 25-year period for which the model was run, the remaining life expectancy of survivors was calculated by adjusting the age-specific life expectancy of the general population for diabetic state and whether or not weight loss had occurred. The assumptions made regarding the time horizon and continued effectiveness of treatments, beyond the follow-up periods of the clinical studies on which effectiveness estimates were based, were not made clear in the paper by Segal and colleagues.[174] Although not explicitly stated, the model seems to have been conducted

from the perspective of the health service, including only direct medical costs (apart from the media campaign programme).

Caro and co-workers[173] used Monte Carlo simulation to evaluate a Markov process with four main states that simulated patients could move amongst on an annual basis. The four states were IGT, NGT, diabetes and death. Individuals in the cohort began in the IGT state, from where they could either transit to diabetes or regress back to NGT. Patients who regressed from IGT back to NGT could also revert back to IGT again. For patients who progressed to diabetes, it was assumed to be irreversible and they were assigned the corresponding lifetime costs and clinical outcomes associated with diabetes. The estimated costs and outcomes associated with diabetes were based on a previous diabetes model developed by the authors.[177,178] The diabetes submodel consisted of several Markov processes that were used to model disease progression on several complication pathways including retinopathy, nephropathy, neuropathy and CVD (stroke, transient ischaemic attacks, MI and angina). Individuals progressed through the model based on their starting characteristics (age, sex, HbA_{1c}) and were tracked until death. All patients who progressed to diabetes were assumed to be diagnosed at time of onset, as their BG would be regularly monitored if they were being treated for IGT. For the screening analysis, the authors considered the cost of identifying individuals in a starting population with undiagnosed IGT. The prevalence in the population was set at 11% based on a prevalence survey.[176] A once-off screen was assumed and those testing positive were entered into the model to commence treatment. This was compared with a scenario with no screening where individuals with IGT progressed to diabetes at the base rate observed in the placebo arm of the STOP-NIDDM trial. However, assumptions about the time after diabetes onset when this undiagnosed group would receive a diagnosis were not made clear. If these patients were not diagnosed with IGT, it is unlikely they would receive a diagnosis of diabetes at onset, as do those with diagnosed IGT. Therefore, individuals with undiagnosed IGT might not have their diabetes treated as early as those progressing to diabetes from diagnosed IGT. The effect might be that complications would develop at a higher rate in this group. It is unclear whether this has been considered in the model. If not, the model could underestimate the benefits associated with screening for IGT. The interventions to prevent progression to diabetes were modelled to continue for 5 years and then stop. It is not clear whether or not this is an appropriate assumption and little justification is given for it in the paper. The model followed up individuals in the cohort over a period of 10 years but if they progressed to the diabetes module, they accumulated lifetime costs and outcomes associated with diabetes. It is unclear why this 10-year period was chosen for follow-up in the IGT model.

Palmer and co-workers[172] also adopted a Markov model structure to explore the long-term costs and outcomes that could be expected from the DPP interventions. Three states, IGT, T2DM and deceased, were included in the model. Simulated patients started in the IGT state and progressed to diabetes at different rates depending on the treatment received. Transitions between states were modelled to occur on an annual basis though it is unclear whether cohort analysis or Monte Carlo simulation was used to model progression. State-specific annual mortality rates were applied to patients with IGT and diabetes. In the first 8 years after transition to diabetes, patients were simulated to have a mortality risk higher than that for IGT, but lower than that for clinically diagnosed diabetes. This period reflects the estimated preclinical phase of diabetes.[54,179] In the base-case analysis, the DPP interventions were assumed to continue for only 3 years (the trial period). Thereafter, patients were simulated to progress from IGT to diabetes at the baseline rate and accrue no intervention costs. The model took the perspective of a single healthcare payer, and considered the direct medical costs and benefits (LYGs) over the lifetime of patients. The costs included were the costs of the DPP interventions, costs associated with side-effects of the interventions (gastrointestinal and musculoskeletal), the average annual costs associated with diabetes and the average annual costs associated with IGT.

The study by Herman and colleagues[171] used a modified version of the model used by Hoerger and colleagues[133] to evaluate screening for diabetes. A prediabetes module was added based on data from the DPP on disease progression, costs and quality of life associated with IGT. Several parameters relating to the progression of diabetes and the quality of life associated with diabetes were also updated using recently published findings. In the prediabetes module patients were followed from IGT to diabetes or death, whichever came first. Unlike in the model by Caro and colleagues,[173] patients in this model could not revert to NGT. Patients were modelled to receive either the lifestyle, metformin or

placebo intervention of the DPP trial during the prediabetes phase. The interventions were assumed to continue until onset of diabetes or death. This is perhaps a more realistic assumption than those of Caro and colleagues.[173] and Palmer and colleagues.[172] It was assumed by the authors that the microvascular and neuropathic complications would not progress during the prediabetes phase. However, hypertension and dyslipidaemia were modelled to progress at the rates observed in the DPP and patients could develop CHD and CVD. At onset of diabetes, patients move to the early diabetes module of the model, where complications progress slowly for a period of 10 years (preclinical phase). After the early preclinical phase, patients enter the normal diabetes progression module, where progression of complications occurs at the rate observed in epidemiological studies of clinically diagnosed diabetes patients.

McEwan and colleagues[175] used a modified version of their model, which was originally used to simulate the impact of treatments on the occurrence of diabetes-related complications in patients with clinically diagnosed diabetes. This model was based on the diabetes model developed by Eastman and colleagues.[134,135] The complications included in the model were stroke, MI, PVD, peripheral neuropathy, nephropathy and retinopathy. The model was modified to assess the impact of delaying diabetes by allowing CVD events to occur before the onset of diabetes. It was presumably assumed by the authors that microvascular complications would not progress during this period. The study assessing the impact of delaying diabetes was conducted from the perspective of the UK NHS over a 20-year time horizon and assumed the existing pattern of care for people with diabetes. The costs that would be incurred in delaying the onset of diabetes do not appear to have been included in the model. These would include the costs of identifying those at risk and treating them appropriately with lifestyle and/or pharmacological treatments. Thus, this study does not address the question of whether or not it would be cost-effective to screen for IGT and treat people found to be positive.

Modelling disease progression

Segal and colleagues[174] conducted their analysis before results were available from any of the large diabetes prevention trials. Therefore, the transition probabilities between the NGT, IGT and diabetes states were based on smaller trials and epidemiological studies. The authors provided very little information on how transition probabilities between these states were calculated for each of the programmes considered. Only one example was provided in the paper of how transition probabilities were calculated for the behavioural modification programme aimed at overweight and obese men. A Swedish study, of an intensive weight loss and fitness programme for overweight persons with IGT, relative to a standard care group, was used.[101] The finding from the Swedish study was that at 5–6 years' follow-up, persons in the intensive intervention group had a significantly reduced rate of progression to T2DM compared with the control group (10.6% compared with 21.4%). These figures were used directly as the 5-yearly probabilities of progressing from IGT to T2DM in the intervention and control groups of the model. No detail was provided on the quality of the study or the precise characteristics of the participants, so it is unclear if these findings would be generalisable to the cohort considered in the model. Furthermore, it is unclear how transition probabilities were calculated for the other possible transitions in the model (IGT to NGT and NGT to IGT).

In the model by Caro and colleagues,[173] the baseline risk of developing diabetes, from a state of IGT, was modelled based on the placebo arm of the STOP-NIDDM trial.[169] Based on the results of this trial, the annual probability of progressing from IGT to diabetes was calculated at 0.063. Diabetes was defined in the model as two consecutive positive OGTTs. The annual probability of transiting from IGT to NGT was estimated to be 0.162 and back from NGT to IGT 0.163. It is unclear exactly how these estimates were derived. The impact of interventions was incorporated in the model as relative reductions/increases in the risks of transition between IGT, NGT and diabetes. The RR reductions were taken from the DPP, DPS and STOP-NIDDM trials[89,90,169] using the results for Caucasian subgroups where available. The acarbose, metformin and lifestyle interventions reduced the probability of transiting from IGT to diabetes by 36%,[169] 24%[90] and 58%,[89] respectively. In addition to reducing the risk of transiting to diabetes, acarbose, metformin and lifestyle interventions were all modelled to increase the transition from IGT to NGT by 9% and reduce reversion back to IGT by 7%.[169] On transition to diabetes, the progression of complications was modelled based on the patient's HbA_{1c} level and other characteristics at time of diagnosis. However, it is unclear from the paper how these characteristics were assigned to simulated patients

and modelled to progress over time. From review of a previous version of the diabetes model used in this analysis,[177,178] it appears that patient characteristics were assigned by sampling from probability distributions. However, there is no mention in the current analysis of the distributions used for the IGT cohort. Going by the previous version of the diabetes model, HbA_{1c} was modelled to increase by 0.15% points per year regardless of treatment, but it is unclear what HbA_{1c} level was assumed at transition to diabetes from the IGT state. There was also a lack of clarity regarding assumptions about the standard of care that individuals would receive for hyperglycaemia and other CVD risk factors after the onset of diabetes. Regarding the time horizon and the continued effectiveness of treatment, the relative effects of the interventions were modelled to be the same over their entire course (assumed to be 5 years). However, the underlying risk of progressing to diabetes was assumed to increase over time, reaching 20% by 10 years of follow-up.

The probability of transit from IGT to diabetes in the model by Palmer and colleagues[172] was based on the rates per 100 patient years reported in the DPP.[90] These were 10.8, 7.8 and 4.8 in the placebo, metformin and lifestyle groups, respectively. The authors state that these rates were converted into annual transition probabilities using the *ratetoprob* function in DATA (the software used for the analysis). The side-effects of the interventions were modelled using the rates of adverse events reported in the DPP trial for the lifestyle, metformin and control group. For gastrointestinal side-effects the rates were 30.7, 77.8 and 12.9 events per 100 patient years for the control, metformin and lifestyle interventions, respectively. The corresponding rates for musculoskeletal side-effects were 21.1, 20 and 14.1 per 100 patient-years.

In the analysis by Herman and colleagues,[171] the DPP was used to estimate an annual baseline hazard of diabetes onset of 10.8%.[90] This is higher than the hazard rate calculated by Caro and colleagues,[173] using data from the STOP-NIDDM trial.[169] The lifestyle and metformin interventions were modelled to reduce the probability of transit to diabetes by 58 and 29.9%, respectively.[90] In their analysis, Herman and colleagues[171] assumed that these treatments would continue until the onset of diabetes, and would continue to be as effective. Patients were modelled already to have some complications at diagnosis of IGT – microalbuminuria (6%), nephropathy (0.4%) neuropathy (8.5%), hypertension 28%, dyslipidaemia (45%), history of CVD (1.1%) and history of MI (2%) – based on the participants in the DPP at baseline.[90] Microvascular complications and neuropathy were assumed not to progress during the prediabetes phase, whereas CVD risk factors and CHD and CVD were allowed to progress to be consistent with the rates observed in the DPP. The authors estimated that the incidence of CHD and CVD in patients with IGT would be 58 and 56%, respectively, of the rates observed in patients with diabetes. These estimates were based on two large epidemiological studies.[180,181] It was assumed that the non-diabetes-related mortality rate would be the same for persons with IGT and diabetes. On entry to the diabetes module, patients in Herman and colleagues' model were assumed to have an HbA_{1c} level of 6.4%, the level observed at diagnosis of diabetes in patients enrolled in the DPP.[90] Patients were assumed to be treated for diabetes during the early preclinical phase (estimated to be 10 years) and their HbA_{1c} levels were modelled to rise at a rate resulting in the HbA_{1c} level observed at randomisation in the UKPDS, after the dietary run-in period (7.1%). Thus the annual rate of increase in HbA_{1c} was estimated to be 0.07% per year in the early preclinical phase of diabetes. During this 10-year period, microvascular and neuropathic complications were modelled to progress slowly, to yield the prevalence observed at randomisation in the UKPDS.[8,182,183] Hypertension and hyperlipidaemia were assumed to progress at the same rates as observed in the DPP trial.[183] The risks of CHD and stroke were modelled using the UKPDS risk equations.[184,185] These equations estimate absolute risk of CHD and stroke based on race, sex, age, smoking status, HbA_{1c} levels, SBP and lipid ratios. However, they were derived using data for people diagnosed with clinical diabetes so it is unclear how appropriate they are for modelling risk in the period immediately after onset of diabetes. It is possible that they overestimate the risk of CVD for patients with preclinical diabetes. If this is the case, the cost-effectiveness of delaying the onset of diabetes might decrease. This was not an assumption that the authors explicitly tested through sensitivity analysis. McEwan and colleagues[175] made the same assumptions (see below). After the 10-year preclinical phase of diabetes, patients were assumed to receive intensive management of their diabetes, with changes in treatment and HbA_{1c} levels modelled to reflect those observed in the UKPDS.[8] An initial drop in HbA_{1c} of 2.9% was observed in the UKPDS, followed by increases of 0.2% per year. Complications were also modelled to develop at the rates observed in the UKPDS.[8,151,183–185]

The factors that have a direct effect on the events simulated in the model by McEwan and colleagues[175] include HbA_{1c}, HDL cholesterol, total cholesterol, SBP, race or ethnicity, age, gender and tobacco use. The modifiable risk factors were also programmed to increase/decrease over the simulation period, depending on treatments received. However, the assumptions and methods used to model change over time were not described in the available poster. Originally the model used the UKPDS risk equations to estimate the risk of stroke[185] and CHD[184] after onset of diabetes – based on the characteristics and modifiable risk factors of simulated diabetes patients. The authors adapted the model so that they could assess the impact that delaying diabetes would have on lifetime costs and outcomes. They did this by incorporating the Framingham risk equations[157] into the model, so that cardiovascular events could be modelled prior to the onset of diabetes. This is an appropriate use of these equations since they were derived for a non-diabetic population. In order to account for the increased risk of CVD that would be expected with the development of metabolic syndrome, prior to the onset of diabetes, the authors assumed a linear increase in the risk of CVD over the delay period – culminating in the risks predicted by the UKPDS equations[184,185] at diabetes onset. The authors also addressed a methodological uncertainty in their model by assessing the impact that a different set of risk equations for CHD and stroke would have on predicted costs and outcomes.[158] The UKPDS outcomes model is a further development of the UKPDS risk engine.[184] It predicts the occurrence and timing of diabetes complications and death, and also life expectancy and quality-adjusted life expectancy. It was unclear from the available report how progression of microvascular complications was modelled (perhaps using the transition probabilities estimated by Eastman and colleagues[134,135]) but it was reported to be consistent between both versions of the model assessed.

Diabetes complication submodels

The diabetes complication submodels, of the prevention models that include them, are very similar to those used in the diabetes screening models reviewed in the pervious section. Therefore, less detailed discussion is given to the individual complication pathways here.

The model by Caro and colleagues[173] included complication pathways for retinopathy, neuropathy, nephropathy, foot ulcers, hypoglycaemia and macrovascular complications (stroke, transient ischaemic attacks, MI and angina). Little detail was provided on the structure and assumptions of these submodels but the transition probabilities for the various complications were based on observed outcomes in various trials and epidemiological studies.[139,141,156] The transition probabilities for the microvascular complications were made dependent on HbA_{1c} levels using the risk gradients observed in the DCCT trial of type 1 diabetes.[139] The precise method of adjustment is not reported, but the problems associated with applying this risk gradient to patients with T2DM were discussed in the previous section. Another possible problem with the complication risks used in this model is that they are based on studies of clinically diagnosed patients. It is unclear whether or not the transition probabilities were appropriately adjusted to reflect the lower risks that would be observed in the preclinical phase of diabetes. The risks of macrovascular complications were reportedly based on the Framingham equations,[157] but again too little detail is provided to assess if these have been used appropriately. The main problem with using the Framingham equations to estimate CVD risks in people with diabetes is that the equations only include diabetes as a dichotomous variable, and the risks for people with diabetes are based on only 337 people with diabetes included in the study. More appropriate CVD risk equations for people with diabetes are now available, as discussed above.[158,184,185]

The model by Palmer and colleagues[172] did not incorporate a diabetes submodel and so the incidence of complications associated with diabetes was not assessed. However, the costs of diabetes and its associated complications were captured (see below).

Herman and colleagues[171] used exactly the same diabetes complication submodels as used in their previous analysis of screening for diabetes.[133] However, some were populated with more recent data from the UKPDS. For example, the progression of nephropathy was based on data from the UKPDS 64[183] as opposed to data from the DCCT[139] and UKPDS 38.[151] The risks of CHD and stroke were based on the UKPDS 56[184] and 60[185] as opposed to risk equations developed for people without diabetes.[157,159,160]

No details were available regarding the structure of the complication submodels used by McEwan and colleagues,[175] but they are likely to have been similar to those used in other models described in the previous section.

Mortality

In the study by Segal and colleagues,[174] mortality was modelled by deriving annual age-specific mortality risks for each of the three states (NGT, IGT and T2DM). Two sets of mortality risks were estimated for each intervention programme, one for people who successfully achieve and maintain the intervention targets and the other for the control and those for whom the intervention is unsuccessful (i.e. do not reach or maintain target weight). The mortality risks were calculated by adjusting age/sex-specific mortality rates for the Australian population with the relative risks associated with IGT, T2DM and obesity (weight loss). The relative risks were obtained from published epidemiological studies.[186–190]

The mortality risk associated with IGT in the model by Caro and colleagues[173] was obtained by adjusting age- and sex-dependent mortality estimates from Canadian life tables. Mortality risks from the life tables were increased by 45% based on the findings of an epidemiological study.[191] This increased risk was assumed to be lost in patients that reverted back to NGT. For those who developed diabetes, mortality was presumably modelled using the diabetes submodels and mortality risks appropriate to individual complications, but no detail was provided on this.

Mortality in the model by Palmer and colleagues[172] was modelled in the same way. The average annual probability of dying with IGT or diabetes was calculated by adjusting age-, sex- and country-specific all-cause mortality (taken from appropriate life tables) with published RRs for all-cause mortality reported for patients with IGT or diabetes relative to the normoglycaemic population.[191] During the first 8 years after onset of diabetes, patients were assigned the RR of mortality reported for people with undiagnosed diabetes in the NHANES II survey (1.76). After the assumed 8-year preclinical phase, patients were assigned the RR associated with clinically diagnosed diabetes (2.26). The RR of mortality for IGT was estimated to be 1.37.

Herman and colleagues[171] used a more sophisticated approach to model mortality. Their approach enabled them to keep track of different causes of death. In their model, patients could die from ESRD, LEA, CHD, stroke and other causes. For patients who developed diabetes, the CVD mortality risks were modelled using the UKPDS risk equations.[184,185] For the prediabetes submodel, CVD mortality risks were estimated by applying RR reductions[180,181] to the CVD mortality risks predicted by the UKPDS risk equations. The mortality risks associated with LEA and ESRD were obtained from published epidemiological studies.[154,192]

The model of McEwan and colleagues[175] uses the same approach as that of Herman and colleagues to model the CVD mortality associated with diabetes. The Framingham equations[157] and the assumptions about increasing risk with metabolic syndrome (discussed earlier) were presumably used to predict mortality in the period before diabetes onset.

Costs

Segal and co-workers[174] used descriptions of programmes reported in the literature to estimate resource use and then attached unit costs to reflect the cost of implementing such programmes in an Australian setting. Costs included in their analysis were the intervention costs and average annual diabetes management costs for those that transit to diabetes. Screening costs were also included for the programmes targeted at obese and overweight men with IGT and the GP advice programme. Potential cost savings from reducing the incidence of CVD in patients with IGT were not included in the analysis. Reducing CVD in patients with IGT is a potential benefit of such programmes, aside from preventing progression to diabetes. All costs in the model by Segal and colleagues were expressed in Australian dollars, but no cost year was specified. Future costs were reportedly discounted at 5% per annum.

The costs included in the model by Caro and colleagues[173] were treatment costs for the IGT interventions, test costs to monitor progression of hyperglycaemia, screening costs to identify individuals with IGT and lifetime diabetes management costs for those who transit to diabetes. The costs of the pharmacological interventions were based on the daily doses reported in the diabetes prevention trials[89,90,169] and the unit costs for these drugs in Canada. The cost of the lifestyle intervention was modelled on the resource use reported for the lifestyle intervention used in the DPS trial.[90] This included seven dietician visits in the first year of treatment and four per year thereafter. Costs of two exercise classes per week were also incorporated using the cost of monthly gym membership in Canada. The cost of an OGTT was based on the test cost and the estimated physician time and all patients were assumed to undergo one such test a year, and to undergo a subsequent OGTT if the first one was positive. The unit costs for tests were based on

Canadian fee schedules. For those who developed diabetes, the cost estimates for its management were based on previously developed cost profiles for each of the complication pathways considered in the diabetes submodel.[193,194] For each complication, the average direct cost of managing such an event from the acute phase until death was estimated. Costs included in these calculations included hospitalisation costs, home healthcare services, outpatient services, nursing home care, laboratory tests, drugs, emergency room visits and diagnostic and therapeutic procedures. The main source of cost data was physician and laboratory fee schedules. Use of such fees to estimate cost makes it difficult to assess generalisability. It is also unclear what cost assumptions, if any, were made for treatment of uncomplicated diabetes (e.g. intensive control of hyperglycaemia, treatment of other CDV risk factors). All costs in the analysis by Caro and colleagues[173] were reported in 2000 Canadian dollars and discounted at a rate of 5% per annum.

Palmer and co-workers[172] estimated the cost of implementing the DPP interventions in a primary care setting in Australia, France, Germany, Switzerland and the UK. However, the costs of identifying people with IGT through screening did not appear to have been incorporated in the model. All costs were reported in 2002 euros, and only the direct medical costs were considered. The assumptions were that the lifestyle intervention would require six review sessions with the GP in year one, 16 lessons on diet and exercise with a practice nurse, and monthly reviews with the GP in subsequent years. The resource use for the metformin intervention was assumed to include 850 mg of metformin twice per day per patient, one titration visit with the GP in year one, three subsequent follow-up visits with the GP in year one and four follow-up consultations with the GP in subsequent years. The resource use in the control arm was assumed to be one annual visit with the GP for standard advice. It was assumed that patients who experienced side-effects would have additional consultations with their GPs and incur the corresponding costs. Patients who progressed to diabetes in the model by Palmer and colleagues incurred an annual cost that reflects the average annual medical costs for people with diabetes.[195] The annual direct medical costs associated with IGT were taken to be 46% of those for patients with T2DM. This estimate was based on a single study that found that medical costs 8 years prior to diabetes diagnosis, at the time patients would have IGT, were 46% of the annual costs of a patient with T2DM.[196] In this study, costs increased over the 8 years and peaked at the time of diabetes diagnosis. Palmer and colleagues[172] used these findings to model annual increases in costs throughout the preclinical diabetes phase. The costs of the DPP interventions and diabetes management in each of the country settings considered in the model were estimated from a variety of sources appropriate to the country for which the analysis was being conducted. Sources included the Cost of Diabetes in Europe Study (CODE-2),[195] which examined resource use in people with T2DM using population-based registers in eight European countries including the UK.

The costs included in the model by Herman and colleagues[171] were the costs of identifying and treating individuals with IGT, costs of complications (hypertension and CVD) associated with IGT and costs associated with T2DM. The authors also considered direct patient costs for a separate analysis adopting a societal perspective. The costs of identifying people with diabetes were based on screening a large and diverse population with OGTTs.[170] The direct medical costs of identifying one person with IGT were calculated by multiplying the number of OGTTs required to identify one DPP participant by the unit cost of an OGTT. The OGTT unit cost was based on Medicare reimbursement rates. The costs of interventions were calculated based on the resources use profiles reported in the DPP trial. The costs of the metformin intervention included drug costs, costs of ensuring adherence and costs of monitoring and treating side-effects.[170] The cost of the lifestyle intervention was based on a core curriculum consisting of 16 one-on-one lessons covering diet, exercise and behaviour modification.[170] Monthly individual and group sessions with case managers followed this. The future costs of IGT associated complications were calculated using a multiplicative cost model developed by the authors. Multipliers were estimated and applied to the baseline costs of the DPP interventions to account for the costs associated with incident hypertension and CVD. A similar, previously developed, cost model was used for the diabetes module.[197] A multiplicative prediction model was used to estimate annual direct medical costs according to demographic characteristics, diabetes treatment (as per UKPDS intensive group), cardiovascular risk factors and microvascular and macrovascular complications. This a more comprehensive cost model than that used by Caro and colleagues as it includes the costs treating CVD associated with IGT. All costs are presented in 2000 US dollars and are discounted at a rate of 3%.

The only detail available on the costs included in the model by McEwan and colleagues[175] was that only direct healthcare costs were considered. The total costs avoided under each delay scenario were presented in 2005 UK pounds. As mentioned earlier, the costs that would need to be incurred in order to delay the onset of diabetes do not seem to have been incorporated in the model. Costs were discounted at 3.5% per annum, the current recommended rate for the UK.

Outcomes

In terms of outcomes, Segal and colleagues[174] modelled the number of diabetic years avoided and the LYGs for each intervention programme compared with its control. Outcomes were discounted at 5% per annum.

The outcomes considered in the model by Caro and colleagues[173] were the number of cases of T2DM prevented over a 10-year period, life-years and years free of diabetes. However, it was unclear what assumptions were made about life expectancy in the absence of diabetes in order to calculate life-years gained by preventing it. Life-years are reportedly discounted at 5% per annum.

Palmer and colleagues[172] used their model to estimate the number of years free of diabetes, the percentage of patients developing diabetes over their lifetime and life expectancy for each of the comparators. The ICER of the interventions versus the control arm was reported as cost per life-year.

Herman and colleagues[171] reported outcomes in QALYs. The utilities associated with IGT were based on the Quality of Wellbeing Index (QWBI), which was administered to patients enrolled on the DPP trial.[170] The utility scores associated with diabetes were based on another study that used the QWBI to assess utility in patients with both type 1 and type 2 diabetes recruited from a medical centre.[198] The authors constructed an additive health utility model to predict health utility scores associated with IGT beyond the 3-year follow-up period of the trial. For each complication that a patient experienced in the model, a utility decrement was applied to their utility score. The decrements were estimated by fitting a regression model of the QWBI4-derived health utility scores to indicator variables for diabetes and each demographic variable, treatment and complication. The same process was used for assigning utility scores to diabetes and its complications.

McEwan and colleagues'[175] model predicted the absolute number of CHD, stroke, CVD deaths, retinopathy, nephropathy and neuropathy events for each delay scenario considered. The model also predicted the number of QALYs gained for each delay scenario versus the control. The source of utility scores for IGT and diabetes was not provided in the available poster. In addition, the assumptions used for estimating utility scores for multiple complications were also not made explicit. The QALYs were discounted at 3.5% per annum.

Findings

The programmes considered by Segal and colleagues[174] were estimated to yield between 43 (GP advice for those with IGT) and 423 (surgery for seriously obese) life-years per 100 patients treated. Relative to the control groups, the incremental cost per LYG varied from interventions that both increased life expectancy and led to net savings (intensive diet and behaviour change for seriously obese with IGT, group behaviour change intervention for overweight men and the media campaign) to $12,300 per life-year (surgery for seriously obese).

Caro and colleagues[173] predicted from their model that over the 10-year period considered, 70 of the 1000 IGT patients in the cohort would be expected to die in the absence of treatment and 543 would develop diabetes. Intensive lifestyle modification was estimated to prevent 117 of these cases and metformin and acarbose were estimated to prevent 52 and 74 cases, respectively. The lifestyle modification intervention was found to be the most expensive in addition to being the most effective (ICER $749 per LYG compared with no treatment). The metformin and acarbose interventions were found to be cost saving compared with the no-treatment option. The ICERs reported for lifestyle modification versus metformin and acarbose were $7725 and $9988 per life-year, respectively.

Palmer and colleagues[172] estimated that the lifestyle and metformin interventions would increase both the number of years free from diabetes and life expectancy. The mean number of years free from diabetes was 8.14, 9.94 and 9.02 for the control, lifestyle and metformin group, respectively. The corresponding improvements in non-discounted life expectancy for the lifestyle and metformin interventions were 0.22 and 0.11, respectively. They also estimated that in many countries the interventions would be cost saving. However, for the UK setting they predicted that

the interventions would lead to small increases in net costs of €1021 and €378 for the lifestyle and metformin interventions versus control, respectively. This translates to a net ICER of €6381 and €5400 per life-year for the lifestyle and metformin interventions, respectively, in the UK setting.

Herman and colleagues[171] found that approximately 50% of their cohort would be expected to develop diabetes within 7 years if treated with placebo. In contrast, they estimated it would take 18 years for 50% of lifestyle-treated patients to develop diabetes and 10 years for 50% of the metformin-treated participants to develop diabetes. These findings are broadly similar to those of Caro and colleagues,[173] despite the differences between the models and the populations for which they were conducted. Over a lifetime, Herman and colleagues[171] estimated that 83% of participants treated with placebo would develop diabetes compared with 63% of those treated with lifestyle intervention and 75% of those treated with metformin. They also estimated that the lifestyle intervention would increase life expectancy by 0.5 years and reduce the cumulative incidence of blindness by 38%, ESRD by 38%, LEA by 35%, stroke by 9% and CHD by 8%. The metformin intervention was found to increase life expectancy by 0.2 years and reduce the cumulative incidence of blindness by 16%, ESRD by 17%, LEA by 16%, stroke by 3% and CHD by 2%. Compared with the placebo intervention, the lifestyle intervention was found to cost $635 more over a lifetime and produce a gain of 0.57 QALYs ($1100 per QALY). The metformin intervention cost $3922 more over a lifetime and resulted in a gain of 0.13 QALYs ($31,300 per QALY). The lifestyle intervention dominated the metformin intervention.

As mentioned earlier, McEwan and colleagues[175] evaluated their model using the original UKPDS risk equations for CHD and stroke[184,185] and also using the newer equations from the UKPDS outcomes model.[158] Using the original equations, the no-delay scenario resulted in discounted costs of £13,076 and 7.6 discounted QALYs over the 20-year time horizon. The total costs were found to decrease to £11,291 per subject with a 2-year delay in diabetes, £9998 with a 5-year delay and £8395 with a 10-year delay. This translates to discounted cost savings of £1785, £3078 and £4681 for the three delay scenarios, respectively. It should be noted that the cost savings would decrease or disappear if the costs required to delay diabetes were to be included in the analysis. The predicted QALYs for the three delay scenarios were 8.3 for the 2-year delay, 9.1 for the 5-year delay and 10.1 for the 10-year delay, representing gains relative to the no-delay scenario of 0.7, 1.5 and 2.5, respectively. When the equations from the UKPDS outcomes model[158] were used, fewer cardiovascular and microvascular events were predicted over the 20-year time period. The cost savings associated with the three delay scenarios were subsequently less using these equations. However, the QALY gains were similar using the equations from the UKPDS outcomes model.

Sensitivity analysis

Segal and colleagues[174] assessed the sensitivity of their findings to variations in several model parameters using one-way sensitivity analysis. The results were found to be sensitive to the assumed success rates of the programmes. However, even when it was assumed that only 20% of patients would achieve the weight loss/exercise targets for the behaviour modification programmes, the cost per life-year stayed within the range considered favourable.[198] This was presumably due to the avoidance of high costs associated with diabetes management.

Caro and colleagues[173] conducted one-way sensitivity analysis on many of the parameters in their model. They also found that the ICERs of all the interventions remained in acceptable bounds relative to no treatment. However, the intervention of choice changed when effectiveness results were varied within the upper and lower bounds of their CIs. For example, at the lower bound of the CI for the lifestyle intervention, all else remaining constant, the acarbose intervention would be dominant. However, no multivariate or probabilistic sensitivity analysis was conducted to characterise better the uncertainty in the decision between the options.

Palmer and colleagues[172] conducted their analysis for different subgroups to characterise the impact that the heterogeneity in outcomes, observed in the DPP trial,[90] would have on their findings. They assessed the cost-effectiveness of the interventions for cohorts of different age and BMI groups using the findings reported for these different subgroups in the DPP trial. They found that the metformin intervention had a better impact on costs and life expectancy than the lifestyle intervention in younger more obese patients but led to less benefit and higher costs than the lifestyle intervention in the older cohort (aged 65 years at baseline). In a cohort with a BMI

<30 kg/m^2, the metformin intervention led to minimal improvements in life expectancy and increased costs, whereas the lifestyle intervention had a greater impact on life expectancy and was cost saving. However, even in this group the ICER of metformin still remained attractive (€47,200 per life-year) compared with other interventions for diabetes.[199] In a group with BMI >30 kg/m^2, the metformin intervention led to a greater improvement in life expectancy and greater cost savings than the lifestyle intervention. Palmer and colleagues also conducted extensive one-way sensitivity analysis on many of the individual cost and probability parameters included in their model. They found that the findings were most sensitive to the probabilities of developing diabetes, the RRs of mortality associated with IGT and diabetes, the annual costs of managing diabetes and the costs of implementing the DPP interventions. However, they found that when these parameters were varied within plausible ranges, the ICERs of the DPP interventions remained in the range considered cost-effective by international standards.[199] They also showed that greater improvements would be seen in diabetes-free years and life expectancy if the DPP interventions were to continue, and continue to be effective, for longer than the 3-year follow-up period of the DPP trial. They also found that the total lifetime net costs associated with the lifestyle intervention decreased as the assumed duration of the effect of the intervention increased. This was due to the higher number of diabetes cases being prevented offsetting the costs of ongoing delivery of the intervention.

Herman and colleagues[171] conducted fairly extensive univariate and bivariate sensitivity analysis. First they ran the model for different age groups and then they assessed the impact of altering various treatment effectiveness and cost assumptions. They found that the lifestyle intervention would be cost saving in participants younger than 45 years and that metformin would not be cost-effective in patients aged over 65 years (>$100,000 per QALY). The authors also reported that the cost-effectiveness of the interventions improved if they were modelled as they might be implemented in routine clinical practice – group sessions as opposed to one-on-one lessons for the lifestyle intervention and generic metformin for those on pharmacological treatment. Even if effectiveness was assumed to be 50% less than reported in the DPP trial, they estimated that both interventions would remain in the cost-effective range.[198] The authors also conducted probabilistic sensitivity analysis where 81 parameters were simultaneously varied over probability distributions for 500 iterations of the model. They found that 95% of the cost per QALY ratios fell between $587 and $9456 for the lifestyle intervention and between $16,509 and $84,583 for the metformin intervention.

Apart from assessing the methodological uncertainty surrounding the use of different risk equations in their model, McEwan and colleagues[175] reported no details of any further sensitivity analysis conducted.

Conclusions of the critical appraisals

The five modelling studies reviewed in this chapter were appraised using a quality assessment checklist for decision analytic models.[130] The results of this process are summarised below.

Of the five models reviewed, four clearly highlighted the decision problem that they were addressing, and had objectives consistent with this problem.[171–174] The fifth study, by McEwan and colleagues,[175] was not a decision analytic model in that it did not consider a choice between alternative treatment options. In terms of the structures of the models, most were broadly similar but some were more comprehensive than others. Two of the models seemed rather simplistic in that they did not model individual complications associated with IGT and diabetes[172,174] or did not incorporate the quality-of-life impacts that these complications would have.[173] The models by Herman and colleagues[171] and McEwan and colleagues[175] are preferred on these grounds. The model by Segal and colleagues,[174] in particular, seemed over-simplistic, using just one set of 5-yearly transition probabilities to model transitions between three states. Furthermore, the assumptions regarding the probabilities of transition were not made clear for many of the interventions considered by Segal and colleagues.[174] There is also a lack of transparency in the reporting of the model by Caro and colleagues.[173] In this model, some of the assumptions used to model life expectancy and LYGs were unclear and not explicitly justified. In the model by McEwan and colleagues,[175] it was not possible to ascertain the methods used to model the microvascular complications. This was because we only had access to a poster presentation of this modelling study at the time of writing. The models by Palmer and colleagues[172] and Herman and colleagues[171] were reported very transparently, allowing a clearer assessment of their quality and the appropriateness of the data they incorporated.

In terms of the data incorporation process, none of the models provided much detail on the methods used to identify sources for the parameters included. In addition, the details of methods used to synthesise data for incorporation into the models were not provided in many of the reports. The exceptions were the models by Herman and colleagues[171] and, to a slightly lesser extent, Palmer and colleagues.[172] Herman and colleagues provided all the details of how model parameters were estimated in a technical report published alongside the published paper.[133] It was clear from this report that, as far as possible, appropriate sources had been used and incorporated into the model correctly. This is not to say that there were not some potential problems with the model as discussed in the previous sections of this review. Another strength of the model by Herman and colleagues[171] was the extensive use of sensitivity analysis. A strength of the model by Palmer and colleagues[172] was that good-quality resource use and cost data were incorporated, which was more relevant to the UK setting. Although individual complications were not included in the model, the costs of treating these were captured.

In terms of consistency, most of the models produced results that made intuitive sense based on the data that had been incorporated, and they all produced findings that were broadly consistent with one another.

In conclusion, the model by Herman and colleagues[171] was the most comprehensive and transparent of the models reviewed. The model by McEwan and colleagues[175] was also very comprehensive but the lack of detail available at the time of writing made it difficult to assess its quality and the appropriateness of its assumptions. The model by Palmer and colleagues,[172] although simple, was presented very transparently and made assumptions that seemed reasonable in the light of the decision that the model was designed to inform. The report on the model by Caro and colleagues[173] lacked transparency and made some assumptions that were not appropriately justified. Finally, the model by Segal and colleagues[174] was over-simplistic and lacked transparency.

Summary and recommendations

The models reviewed all estimated long-term costs and outcomes associated with the delay or prevention of diabetes. Four of the studies modelled the short-term costs and effects of delivering interventions to prevent/delay the onset of diabetes, and balanced these additional treatment costs against expected future health outcomes and cost savings.[171–174] Although these models were of variable quality, and varied in their structure and assumptions, all predicted that diabetes prevention interventions would provide good value for money. The fifth study included in the review only assessed the impact that delaying diabetes would have on future health outcomes and medical costs.[175] However, it also produced findings that were broadly consistent with those of the other models – that delaying the onset of diabetes by even modest periods would substantially reduce the incidence of vascular complications (microvascular and cardiovascular), improve quality of life and avoid future medical costs. These results certainly seem to suggest that if a screening programme were implemented for people at risk of developing diabetes, it would be a good use of resources to treat those found to have IGT with lifestyle or pharmacological interventions.

Based on the models reviewed, there appears to be some uncertainty surrounding the preferred intervention for people identified as having IGT. First, the characteristics of the cohort seem to have some bearing on which option is to be preferred,[172] and second, the relative effectiveness of the alternative treatments in routine clinical practice may also prove important. The evidence from the diabetes prevention trials and above modelling studies suggests that lifestyle interventions are likely to be the best option for most people with IGT. However, for select groups a pharmacological treatment might be preferred.[172] Furthermore, if lifestyle interventions prove very difficult to implement effectively in routine clinical practice, and pharmacological treatments are well accepted, then these might prove the better option or be used in combination with lifestyle change. Another point worth mentioning is that lifestyle interventions could have substantial impacts on other CVD risk factors such as obesity, blood pressure and lipid ratios. It is not entirely clear if these potential benefits have been captured in the models reviewed here. If not, they could underestimate the benefits of the lifestyle interventions.

Some of the models reviewed also included the costs that would be incurred in identifying people with IGT (screening costs).[171,173,174] Even when these costs were included, the reported ICERs remained favourable. However, none of the models appeared to compare directly an IGT screening and treatment scenario with a no-screening scenario. Although the model by

Herman and colleagues[171] included costs of identifying patients for treatment, the control arm in the model also assumed that patients would be identified as having IGT. Therefore, patients in the control arm also received intensive treatment for diabetes upon onset. If no screening programme were in place to identify patients with IGT, then they would not receive a diagnosis of diabetes at onset, and would not receive treatment until they were clinically diagnosed. In this absence of screening, individuals progressing from IGT to diabetes would probably develop diabetic complications at a higher rate than those progressing to diabetes after having been diagnosed with IGT. Hence, if screening followed by treatment for IGT were to be compared with a no-screening scenario, then the cost-effectiveness estimates might be more favourable than those reported in the studies reviewed here. However, there remains a question over who to screen that needs further clarification.

The prevalence of IGT will be highest in groups who have other CVD risk factors. As the previous section of the review concluded, screening for diabetes is more likely to be cost-effective in these groups. The question is, with the cost-effectiveness of treating IGT having been demonstrated, should the target population for screening be wider than it would otherwise be if it were only those with undiagnosed diabetes who would benefit? This question requires a more thorough exploration of the cost-effectiveness of different screening strategies, where the benefits of treating those identified with both IGT and undiagnosed diabetes are incorporated.

In conclusion, several modelling studies all predicted favourable ICERs for the identification and treatment of people with IGT. Two of the studies in particular were transparently presented, allowing a thorough assessment of quality. Both of these studies appeared to use appropriate data and assumptions and used fairly extensive sensitivity analysis to characterise uncertainty. Both studies reported consistent findings and one was conducted from the UK NHS perspective. Based on the findings of these two studies, lifestyle interventions similar to those reported in the DPP trial[90] would appear to be the best option for treating people identified with IGT. Their cost-effectiveness of the metformin intervention appears less certain, although there may be particular groups for whom this intervention would be the preferred option. Based on the available evidence, it seems reasonable to conclude that screening and treating people for IGT would be cost-effective in the UK setting. However, before proceeding with such a programme, the question of who to screen requires further consideration. A modelling approach could be used to assess the relative cost-effectiveness of screening targeted at different populations.

Studies assessing the costs and short-term outcomes of diabetes screening tests

Background

If a decision is made to implement a screening programme for diabetes or IGT/IFG, then there remains a question of what screening tests and cut-off points to use. One way to help inform this decision is to consider the costs of alternative test strategies and the associated outcomes in terms of the numbers of true cases that would be detected, and also the numbers of false positives, false negatives and true negatives. In this section, studies that have assessed these costs and outcomes for different tests and test cut-off points are reviewed.[200]

Search results

The searches identified five studies for inclusion in this section of the review[201–205] These studies are summarised in *Table 16* and discussed in detail below.

The studies

Shirasaya and colleagues[203] conducted an economic evaluation alongside a study to establish the efficacy of alternative screening tests for IGT and T2DM. They established the sensitivity and specificity of three indicators, which do not require fasting beforehand, in order to identify the best option for screening in situations where fasting tests are not practical. The three indicators compared were 1,5-anhydroglucitol (1,5-AG), glycosylated haemoglobin (HbA_{1c}) and fructosamine (FRA). The sensitivity and specificity of the three indicators were assessed on a sample of 891 men who had been assigned diabetes status according to WHO criteria. The optimum cut-off point for each of the indicators was established by plotting receiver operating characteristic curves and then determining the point on the curve that was closest to the point where sensitivity was 100% and the false-positive rate 0. The optimum cut-off points for the three indicators were calculated for detecting diabetes only and also diabetes and IGT together.

An economic evolution was then conducted using the sensitivities and specificities at the optimum

cut-off points for the three test indicators. The authors adopted a healthcare payer perspective and developed a model to estimate the cost-effectiveness of screening with the three indicators for a hypothetical cohort of 1000 men with a given prevalence of undiagnosed diabetes and IGT. The numbers of true positives, true negatives, false positives and false negatives were estimated based on the previously calculated sensitivities and specificities. For those who screened positive using each of the indicators, an OGTT was assumed to follow. Those who screened negative (false and true negatives) were assumed to undergo the same screening test in subsequent years (annual screening assumed) and the model was run until more than 99% of diabetes cases in the cohort would be identified. The cost per case detected for each of the indicators was established for IGT and diabetes together, and for diabetes alone. For the analysis using the optimum cut-offs for IGT and diabetes together, the authors also calculated the number of cases of IGT detected that would progress to diabetes (over a 10-year period) to give the prospective number of diabetes cases that would be detected. The prospective and present cases were added together to give the total number of diabetes cases that would be identified through each screening alternative.

The costs included in the analysis were the costs of each of the screening tests and the costs of the OGTT for those screening positive. Those who screened negative were assumed to incur the same test costs in subsequent years. In the case of false negatives, individuals were assumed to incur the screening test costs in subsequent years until they screened positive, in which case they would also incur the cost of an OGTT that year. The future costs were discounted at 5% per annum.

The results of the study were that, out of the three indicators, HbA_{1c} and 1,5-AG resulted in the highest number of diabetes cases identified. However, when the optimum cut-off points for IGT and diabetes were used, 1,5-AG identified the highest number of cases – closely followed by FRA. The authors concluded that in Japan, FRA would be the most cost-effective strategy for screening when fasting was not practical due to the low cost of the test. However, the study findings were not clearly presented, making it very difficult to ascertain the validity of this conclusion. Moreover, the results would depend on several assumptions. For example, one assumption was that testing would be conducted on an annual basis and so the negative consequences/costs of false negatives would be minimised. In addition, the costs and number of cases that would be detected, at the different cut-off points for the different tests, were not presented. The authors did report some sensitivity analysis and reported that the choice between indicators depended on the costs of the tests and the cut-off points chosen, but again these analyses were poorly reported. Moreover, other important parameters such as the screening interval were not addressed in sensitivity analysis. Given the lack of transparency in the reporting of this study, it is impossible to comment on the applicability of the findings to the UK setting.

In another similar study, Johnson and colleagues[202] set out to assess the efficacy and cost of several different strategies for identifying diabetes that would not require fasting. They carried out their analysis for the US population aged between 45 and 74 years, estimating that 72.6 million people would be eligible for screening. The prevalence of undiagnosed diabetes and IGT in the population was estimated to be 10 and 22%, respectively, at baseline. Johnson and colleagues[202] estimated the number of true positives, false positives and false negatives that would be obtained using three different cut-off points ($\geq$100, $\geq$130 and $\geq$160 mg/dl) on a random plasma glucose (RPG) test, at 1-, 3- and 5-yearly intervals over a period of 15 years. In addition they also assessed the screening performance of a multivariate logistic equation, which incorporated RPG level, postprandial time, age, sex and BMI. The sensitivity and specificity of the different cut-offs, and the logistic equation, were calculated by applying them to a large dataset, which had all the appropriate information, including results of OGTTs performed on consecutive days (gold standard for diagnosis of diabetes). The total direct medical costs and patient costs associated with each strategy were calculated.

Johnson and colleagues[202] found that for each incremental improvement in sensitivity, using cut-offs below 130 mg/dl, there were substantial reductions in specificity. The multivariate equation was also shown to be more sensitive than RPG alone at any given level of specificity and vice versa. The absolute difference in the number of true positive screening tests between the most sensitive (RPG $\geq$100 mg/dl every year) and least sensitive strategy ($\geq$160 mg/dl every 5 years) was 4.5 million over the 15 years. The absolute difference in the number of false positives between the most sensitive and least sensitive strategy was 476 million. Hence cut-off points with a higher specificity were found to decrease minimally the

number of true-positive screening tests but to decrease substantially the number of false-positive tests. Based on these efficacy findings, the authors concluded that an RPG cut-off point of 130 mg/dl, or the multivariate equation, applied every 3 years would be the optimal screening strategy. It was not entirely clear what criteria the authors used to arrive at this conclusion. The costs of each of the strategies were estimated by assessing the direct medical and patient costs associated with each strategy. It was estimated that 54.4 million of the eligible population would seek routine medical care within any given year, and would therefore be eligible for opportunistic screening. For this group, the only direct medical costs were the costs of the screening test and, when necessary, a diagnostic test. The remaining population were assumed to incur the cost of an arranged outpatient visit, in addition to the test costs. Based on the baseline prevalence of undiagnosed diabetes, the prevalence of IGT, an estimated rate of progression from IGT to diabetes, and the number of cases detected at each screening examination, the authors calculated the prevalence of undiagnosed diabetes in the population for each screening examination following baseline. The costs of the different screening strategies were estimated to vary from US$6.9 to 42.7 billion. A weakness was that no cost year and no discounting of future costs were reported. The strategies that the authors declared optimal based on sensitivity and specificity data (RPG cut-off point of 130 mg/dl and the multivariate equation applied every 3 years) cost US$11.1 and 9.7 billion, respectively. This translates into $642 and $563 per true positive, respectively. However, it should be noted that this was not an economic evaluation designed to identify the most cost-effective screening strategy. It is not possible to answer that question without considering the longer term costs and consequences associated with false negatives relative to the costs and consequences of true and false positives. The costs and consequences of false negatives will depend on the length of the screening interval, the uptake of screening at subsequent recalls and the rate of development of diabetes-related complications in undiagnosed individuals (relative to those who are diagnosed and treated).

Another study, conducted by Icks and colleagues,[201] compared several once-off screening strategies in terms of cost per case of undiagnosed diabetes detected. A simple decision analytic model was developed to compare four different strategies over a time horizon of 1 year. The strategies considered were a single FPG test (using a cut-off of 7 mmol/l), an FPG test followed by an OGTT for those with FPG ⩾6.1 and <7.0 mmol/l (diabetes assumed if FPG ⩾7.0 or OGTT ⩾11.1 mmol/l), an OGTT alone (⩾11.1 mmol/l) and an HbA_{1c} test followed by an OGTT for those with an HbA_{1c} level >5.6%. For each of these four strategies, two different models for their delivery were also assessed – screening of everyone in the population and screening targeted at those at increased risk (as defined by various risk factors for diabetes).

The authors estimated the total cost and the number of cases that would be detected for each of the strategies. The characteristics of patients, the prevalence of the various levels of hyperglycaemia (defined by each of the indicators) and the sensitivities/specificities of the various tests were estimated from a population prevalence survey of inhabitants (aged between 55 and 74 years) of the German city of Augsburg.[206] They also used data from a UK-based study to reflect different levels of uptake for the different test strategies.[200] The uptake of HbA_{1c} testing was estimated to be 100% based on the assumption that everyone in Germany between the ages of 55 and 74 years would visit their physician at least once per year and so be accessible to testing. This may be an over-optimistic assumption. The authors conducted their analysis from both the healthcare payer and societal perspectives, including direct medical costs and indirect productivity costs associated with each strategy.

One of the main findings of this study was that the population screening options dominated all the targeted options. This was probably due to the assumption that the patient-level information required for the targeted options would not be routinely available, and so its collection would require additional assessments and incur extra costs. These costs were estimated to be greater than the extra costs it would take to screen everyone in the population. However, the assumption seemed to be that in order to target screening, everyone in the population would require their BMI, blood pressure and triglycerides to be measured. This would unlikely be the case in reality, so this finding should not be taken as authoritative. In terms of the relative cost-effectiveness of the different strategies for population-based screening, the strategies requiring FPG tests were dominated by the single OGTT from the perspective of the healthcare payer. The HbA_{1c} test followed by an OGTT was found to identify more true cases but at greater cost (€771 per additional case detected). It was

more effective due to the assumption that uptake of HbA_{1c} testing would be 100% and that those with a positive HbA_{1c} test would have a much higher uptake for the OGTT. Similar results were also obtained when the cost-effectiveness of the strategies was considered from the societal perspective. One of the weaknesses of the study by Icks and colleagues[201] was the lack of detail given regarding the estimation of the model effectiveness and cost parameters, making it difficult to assess the internal and external validity of the results. A fairly comprehensive sensitivity analysis was carried out, which showed that the results were reasonably robust to changes in the prevalence of disturbed glucose metabolism, uptake for the various strategies and productivity costs. However, the strategy considered to be most cost-effective was sensitive to changes in the participation rates. The same weakness that applies to the other studies discussed in this section also applies here. That is, by failing to consider the relative long-term costs and consequences of the different screening outcomes, it is not possible to answer the question of which strategy is best. Moreover, given the lack of transparency regarding the parameter estimates included in the model, and the use of charges as opposed to costs, it is not possible to ascertain with confidence which of the strategies would be the most efficient in the UK in terms of the cost per case detected.

Zhang and colleagues[204] addressed a similar question to that of Icks and colleagues.[201] However, they assessed the efficacy, effectiveness and efficiency of various strategies for detecting both cases of prediabetes (IGT and/or IFG) and cases of undiagnosed diabetes. Like Icks and colleagues they assessed once-off screening for the US population but assumed that only those who seek healthcare would be screened. Based on data from the US 2000 census,[207] the third national health and nutrition examination survey (NHANES III)[208] and other published literature, they estimated that there would be 54.4 million adults aged between 45 and 74 years who would be eligible for screening. They further estimated that the eligible number would be 37.4 million if screening were to be restricted to those with a BMI $\geqslant$25 kg/m^2. It was also estimated that there would be 12.1 million cases of prediabetes and 5.4 million cases of undiagnosed diabetes in the whole population and 9.6 and 4.7 million cases in the population with BMI $\geqslant$25 kg/m^2. The methods used for calculating these figures were not clearly reported.

The screening strategies assessed by Zhang and colleagues[204] were as follows: (1) an OGTT for everyone in the study population; (2) an FPG test for everyone followed by an OGTT for those with fasting glucose levels above the cut-off used (95 mg/dl) but below the level used to diagnose impaired fasting glucose (110 mg/dl); (3) an HbA_{1c} test with an OGTT for those with an HbA_{1c} level above 5%; (4) a capillary blood glucose (CBG) test with an OGTT for those with capillary glucose above 100 mg/dl; and (5) a risk assessment questionnaire followed by an OGTT for those who scored above a certain limit. The cut-off points used for the FPG, HbA_{1c} and CBG tests were reportedly selected on the basis that they incurred the lowest cost per case detected out of a range of cut-off points tested, but the analysis used to inform this decision was not reported in the paper.

Zhang and colleagues[204] assessed the effectiveness of the different strategies by estimating the proportion and number of prediabetes and undiagnosed diabetes cases that would be detected using each screening strategy. The sensitivities and specificities of the various tests were taken from published sources and it was assumed that the OGTT was 100% sensitive and specific for identifying IGT, IFG and undiagnosed diabetes. Some assumptions were also made about the sensitivity and specificity of the FPG test, but these were not entirely clear. The direct medical costs that would be incurred through each screening strategy were calculated by using charges for the different laboratory tests and physician time requirements. The patient costs were calculated based on estimates of patient time required for each strategy and transportation costs. Since the unit costs for the laboratory tests and physician time were based on charges, it is difficult to generalise them to settings outwith the USA. It was unclear how patient time and travel costs were estimated.

The estimated number of cases that would be detected with each of the screening strategies applied to the whole population ranged from 12.1 to 17.5 million. The equivalent range for the targeted screening option was 9.8 to 14.3 million cases. In both cases the OGTT on its own was found to be the most effective strategy, followed by HbA_{1c}, FPG and CBG. The total costs of each of the strategies from the single payer's perspective ranged from $2.16 billion (risk assessment questionnaire) to $3.44 billion ($HbA_{1c}$ with OGTT) for the whole population. This translates into costs per case averted ranging from $176 (CBG with OGTT) to $236 ($HbA_{1c}$ with OGTT). When

societal costs were included, all the strategies were more costly and the costs per case averted ranged from $247 (CBG with OGTT) to $332 ($HbA_{1c}$ with OGTT). The cost per case identified was lower when screening was restricted to those with a BMI $\geqslant$25 kg/m^2 but the rank order remained the same. This finding differs from that of Icks and colleagues,[201] who estimated that targeted screening would be dominated by population screening. This is probably due to the differing assumptions about the costs involved in identifying people for the targeted strategy.

Based on these findings, the authors concluded that the OGTT test alone was superior (more effective and less costly) to a strategy involving HbA_{1c} followed by OGTT. The choice between the other options, they concluded, would depend on the objective of the screening programme because the less effective strategies were also more efficient in terms of the cost per case detected. However, these results were found to be sensitive to assumptions about uptake of the different tests. In the base case, 100% uptake was assumed for all the tests, but when these assumptions were varied during sensitivity analysis (75% uptake for FPG and 50% uptake for OGTT), the FPG test became the more effective and efficient strategy. However, the authors did not seem to consider the possibility that uptake of OGTTs would be higher after positive screening tests than it would be without. Had this been investigated, the strategy involving the HbA_{1c} test may have appeared more favourable. Due to the lack of transparency surrounding some of the calculations and assumptions in this analysis, and the limited sensitivity analysis, it is not possible to say with confidence which of the strategies would be most effective and efficient (in terms of cost per case identified) in the context of a national screening programme in the UK.

Zhang and colleagues conducted a subsequent analysis[205] using a very similar approach to their previous study. However, in this later study they examined the efficiency of a wider range of cut-off points for three different screening tests – presenting the cost per case detected for each cut-off point assessed. In addition, they looked at how the efficiency of the different cut-offs would change if the goal of the screening programme were to identify cases of undiagnosed diabetes alone, as opposed to both prediabetes and undiagnosed diabetes. The three tests they assessed were FPG, HbA_{1c} and random CBG. The most efficient cut-off point on each of these tests was defined as the point that yielded the lowest cost per positive case identified. The sensitivities and specificities for each of the cut-off points assessed in the analysis were obtained from the published literature,[8,10] but little detail was given on these studies. As in the previous analysis, subjects with an FPG above the cut-off, but below the value used to define prediabetes (or undiagnosed diabetes), were assumed to undergo an OGTT. For the other two screening tests, all subjects above the different cut-offs assessed were assumed to undergo an OGTT. The numbers of individuals above the different cut-off points were presumably modelled based on the reported sensitivities and specificities for the different cut-off points on the different tests. As before, the costs and effects of the three strategies were modelled for all eligible adults in the US population – 54.4 million adults aged between 45 and 74 years who seek healthcare at least once per year – from both single-payer and societal perspectives. The costs were all reported in 2000 US dollars.

Zhang and colleagues[205] found that, if the purpose of screening was to identify both prediabetes and undiagnosed diabetes, the cost per case identified by cut-off value ranged from $125 to $321 for the CBG test, from $114 to $476 for the FPG test and from $153 to $536 for the HbA_{1c} test from the single-payer perspective. If the purpose was to identify only undiagnosed diabetes, the cost per case detected from the single-payer perspective ranged from $392 to $671 for the CBG test, from $556 to $717 for the FPG test and from $590 to $817 for the HbA_{1c} test. It was found that for all three screening tests, the cost per case identified first decreased and then increased as the cut-off value of the screening test increased. This was because, to begin with, the decreased sensitivity (decreasing number of cases detected) was outweighed by the decreased costs associated with fewer diagnostic tests. However, after a certain limit, the decreased number of cases detected outweighed the decreased costs, resulting in a rise in cost per case detected. The optimal cut-off point based on the cost per case detected, for detecting both pre- and undiagnosed diabetes, was 100 mg/dl for the FPG test, 5% for the HbA_{1c} test and 100 mg/dl for the CBG test. For detecting undiagnosed diabetes only, the most efficient cut-off points were 110 mg/dl, 5.7% and 120 mg/dl, respectively. The authors did not present the number of cases that would be detected at the different cut-off points or the additional costs of detecting extra cases by increasing sensitivity. Again, the decision as to which screening test to use in a screening programme will depend on the number of cases that would be identified, and not

TABLE 16 *Summary of studies assessing the short-term costs and outcomes of alternative test strategies for the detection of diabetes or IGT/IFG*

Study and setting	Population	Objectives/ questions	Strategies	Costs	Outcomes	Time horizon and perspective	Results/authors' conclusions	Comment
Shirisaya *et al.*, 1999[203] Japan	1000 men (range of prevalence values for prediabetes and undiagnosed diabetes assessed)	When fasting tests are not practical, which screening strategy is most efficient for detecting cases of undiagnosed diabetes alone, and both prediabetes and undiagnosed diabetes together?	1. 1,5-AG + OGTT for those above cut-off 2. HbA_{1c} + OGTT for those above cut-off 3. FRA + OGTT for those above cut-off (different cut-offs used for detecting diabetes alone and diabetes and IGT/IFG)	*Currency and year*: 1997 yen (discount rate 5%) *Unit costs*: FRA 55 yen HbA_{1c} 950 yen 1,5-AG 1450 yen OGTT 2000 yen (assumed no extra physician time requirements) *Sources:* charges/fees	True-positive cases detected	*Perspective*: Single payer *Time horizon*: Until >99% of cases in cohort are eventually diagnosed	FRA had lowest cost per case detected in Japan for both IGT and diabetes together and for diabetes alone. Results found to be sensitive to cost of tests and HbA_{1c} and 1,5-AG were more effective (no ICERs reported)	Presentation of results and sensitivity analysis not transparent. Cannot generalise conclusions to other settings
Johnson *et al.*, 2005[202] USA	US population between 45 and 74 years eligible for population screening (72.6 million)	To assess the costs and outcomes of several screening strategies to detect T2DM based on RPG tests	RPG cut-offs of 100, 130 and 160 mg/dl and a multivariate equation at 1-, 3- and 5-yearly intervals over 15 years (OGTT or FPG to confirm all positive screens)	*Currency and year*: 2000 US$ (no discounting reported) *Unit costs*: Physician time $51 per visit RPG $5.24 FPG $5.24 OGTT $17.22 Patient time $8 per hour (1 hour for RPG/FPG, 2 hours for OGTT) Travel $7 per trip *Sources*: Charges	True positives, false positives, true negatives and false negatives	*Perspective*: Single payer and societal *Time horizon*: 15 years (but no follow-up of individual patients)	RPG ⩾130 mg/dl every 3 years declared optimal strategy based on efficacy findings The total costs of the strategies ranged from $6.9 to $42.7 billion Cases detected ranged from 14 to 18.5 million RPG ⩾130 mg/dl every 3 years cost $642 per true positive (no ICERs were reported for the other strategies)	Increased costs of identifying more cases by moving to more sensitive strategies not presented

continued

TABLE 16 *Summary of studies assessing the short-term costs and outcomes of alternative test strategies for the detection of diabetes or IGT/IFG (cont'd)*

Study and setting	Population	Objectives/ questions	Strategies	Costs	Outcomes	Time horizon and perspective	Results/authors' conclusions	Comment
Icks *et al.*, 2004[201] Germany	Population 1353 individuals between 55 and 74 years from the German city of Augsburg	To assess the cost per true case detected of several opportunistic screening strategies for T2DM	1. Single FPG test (≥7 mmol/l) 2. FPG test + OGTT for those with fasting glucose ≥6.1 and <7 mmol/l 3. Single OGTT (≥11.1 mmol/l) 4. HbA_{1c} + OGTT for those with HbA_{1c} >5.6% (Each strategy assessed for the whole population and also for preselected group with elevated risk for diabetes)	*Currency and year*: 2002 euros (discounting not applicable) *Unit costs*: Preselection testing (including physician time and tests) €12.18 per visit FPG test €14.78 HbA_{1c} €16.00 OGTT €16.34 Patient time €29.19 per hour for employed/€5.37 for those not working (1 hour for HbA_{1c}/FPG, 2 hours for OGTT) Travel $7 per trip *Sources*: Fees/charges	True-positive cases detected	*Perspective*: Single payer and societal *Time horizon*: 1 year	Population-based screening strategies dominated the targeted strategies From single-payer perspective, the single OGTT test dominated the tests involving FPG. The HbA_{1c} + OGTT strategy identified more cases but was also more costly than OGTT alone Results sensitive to assumptions regarding the participation rates for the different tests	A lack of transparency regarding the estimation of model parameters and the use of charges/fees specific to Germany make it difficult to assess the applicability of these results to a UK setting. Also, incremental costs and effects of increasing the test sensitivities were not reported

continued

TABLE 16 *Summary of studies assessing the short-term costs and outcomes of alternative test strategies for the detection of diabetes or IGT/IFG (cont'd)*

Study and setting	Population	Objectives/ questions	Strategies	Costs	Outcomes	Time horizon and perspective	Results/authors' conclusions	Comment
Zhang *et al.*, 2003[204] USA	US population between 45 and 74 years eligible for opportunistic screening (54.4 million)	To assess the costs and consequences of various strategies to identify individuals with prediabetes and undiagnosed diabetes	1. Single OGTT for everyone 2. FPG + OGTT for those with IFG >95 but <110 mg/dl 3. HbA_{1c} + OGTT for those with HbA_{1c} >5% 4. CBG + OGTT for those with CBG >100 mg/dl 5. Risk assessment questionnaire + OGTT for those scoring ⩾10	*Currency and year*: 2000 US$ (discounting not applicable) *Unit costs*: Physician time $51 per visit FPG $5.24 CBG not reported HbA_{1c} not reported OGTT $17.22 Patient time $8 per hour (3.25 hours for all strategies except FPG 4 hours) Travel $7 per trip *Sources*: Charges	Proportion and number of true cases identified from population	*Perspective*: Single payer and societal *Time horizon*: 1 year	The cost per case identified ranged from $176 to $236 from the single-payer perspective Testing all with OGTT was the most effective but CBG test and risk assessment questionnaire were the most efficient Results were sensitive to assumed participation rates for the different tests	Lack of transparency surrounding some of the calculations and assumptions, and only limited sensitivity analysis, make it difficult to assess the internal and external validity of the findings
Zhang *et al.*, 2005[205] USA	US population between 45 and 74 years eligible for opportunistic screening (54.4 million)	To assess the efficiency of a range of cut-off points on three different tests for detecting undiagnosed diabetes alone, and both prediabetes and undiagnosed diabetes together	1. FPG + OGTT for those with IFG above the cut-off but <110 mg/dl 2. HbA_{1c} + OGTT for those with HbA_{1c} above cut-off 3. CBG + OGTT for those with CBG above cut-off (Different cut-offs explored to find the most efficient cut-offs for detecting diabetes alone, and diabetes and prediabetes together)	*Currency and year*: 2000 US$ (discounting not applicable) *Unit costs*: Physician time $51 per visit FPG $5.24 CBG not reported HbA_{1c} not reported OGTT $17.22 Patient time $8 per hour Travel $7 per trip *Sources*: Charges	Cost per case detected (costs and effectiveness results not reported separately)	*Perspective*: Single payer and societal *Time horizon*: 1 year	Most efficient cut-off points for detecting diabetes alone were 110 mg/dl for the FPG test, 5.7% for the HbA_{1c} test and 120 mg/dl for the CBG test Corresponding cut-offs for detecting pre-diabetes and diabetes together were 100 mg/dl, 5% and 120 mg/dl	Costs and effects not presented separately and no incremental costs per extra cases detected from increasing sensitivity presented

just the cost per case identified. It will also be dependent on the costs and consequences of false negatives, which will in turn be dependent on the rate of progression of undiagnosed cases relative to diagnosed cases, and the screening interval. If a decision was made to screen every 2 or 3 years, then the adverse consequences of false negatives would be less severe than they would be if screening was to be just once off.

Summary and conclusions

The studies reviewed in this section[201–205] all assessed the short-term costs and consequences of different approaches to screening for T2DM, or IGT and IFG. All considered the costs that would be incurred and the number of cases that would be identified using different tests or different cut-off points on the same test. The studies all had similar designs although estimates of cost per case detected varied due to different assumptions about costs, prevalence of diabetes/pre-diabetes, sensitivity/specificity of tests and participation rates. Moreover, the efficiency ranks for the different tests varied from study to study and were also found to be sensitive to assumptions within studies. Due to these uncertainties, it is not possible to draw any conclusions as to which test would be most efficient in a screening programme for detecting diabetes and/or IGT/IFG in the UK. One thing that is clear is that when considering an appropriate cut-off point for a test, there is likely to be a trade-off between the number of cases that the test can identify and the efficiency of that test. As the sensitivity of a test is increased beyond a certain limit, by lowering the cut-off point, the cost per case identified is also likely to increase due to the larger number of false positives that will require a definitive diagnostic test. As Zhang and colleagues demonstrated,[205] the opposite effect is seen when the specificity of a test is increased beyond a certain limit. Therefore, the preferred test and the preferred cut-off points for tests will vary depending on the precise objectives and nature of the screening programme. If it is considered very important to detect as many true cases of disease as possible and minimise false negatives, then more sensitive strategies with higher costs per case detected might be appropriate. If the false negatives are not considered to be such an important consequence of screening, then a more specific and efficient screening strategy could be used.

The main problem associated with all the studies reviewed in this section is that by only considering the short-term costs and outcomes associated with the detection process, and failing to consider the longer-term impact of false negatives relative to true positives, these types of studies cannot tell us which screening tests and cut-off point to use in screening programmes for diabetes/IGT. If false negatives result in substantial increases in costs or reductions in life expectancy/quality of life, relative to true positives, then more sensitive and expensive test strategies are likely to be the preferred option. However, if the long-term impact of false negatives is not particularly severe, more specific strategies might be preferred. This might be the case if repeat screening were to be undertaken every 2 or 3 years.

In order to address these questions, the different screening tests and cut-off points need to be assessed in the context of models that consider the lifetime costs and outcomes of screening for T2DM. Such models were reviewed earlier in this report. By incorporating the costs and sensitivities/specificities of different screening strategies into such models, it would be possible to assess the longer term impacts that different test strategies might have relative to each other. This would provide a way of balancing the short-term costs of the different screening strategies against the long-term costs and health outcomes, giving a better indication of how to optimally screen for diabetes.

Chapter 5

Modelling the cost-effectiveness of screening for type 2 diabetes

Introduction

Context of research

The aim has been to produce a basic screening model linked to the existing fully developed treatment model to investigate the order of magnitudes of effects given different scenarios for diabetes screening policies.

Background

T2DM increases the risk of cardiovascular events in addition to causing microvascular complications. The disease remains asymptomatic for a number of years during which the disease progresses and cardiovascular risk is elevated compared with the normal population. It is estimated that up to one million people have undiagnosed T2DM in the UK.[209] Screening for diabetes is potentially beneficial as early treatment may delay progression of diabetes and reduce short- and long-term complications. Treatments include statins, antihypertensive and hypoglycaemic therapy and lifestyle change (dietary modification and increased physical activity).

Although there have been previous assessments of the cost-effectiveness of screening for diabetes, these have some limitations such as being performed before the use of statins.

Objectives

In order to quantify the trade-off between the costs and benefits of screening and early treatment, a diabetes screening model was developed for this study and integrated with an existing diabetes treatment model. This enabled:

- information derived from the screening literature review to be integrated with information on the current and projected prevalence of undiagnosed diabetes and information on the costs and effectiveness of diabetes-related treatment
- the key parameters that will influence the cost-effectiveness of screening for diabetes and the significance of uncertainty around these key parameters to be identified
- the characteristics of the screened population (including the proportion of diabetes undiagnosed in the absence of systematic screening), the characteristics and costs of the screening and diagnostic tests to be varied
- the effectiveness and costs of subsequent treatment to be varied
- initial estimates of the relative cost-effectiveness of a range of different screening options that could be used to inform an option appraisal for diabetes screening to be produced.

Some existing limitations of previous publications on screening modelling were also overcome, such as:

- modelling macrovascular risk reductions
- incorporating the widespread use of generic statins
- accounting for existing policies such as diabetes testing for those with existing CHD, and control of hypertension in the general population.

Model scenarios

Baseline scenario

The baseline model assesses the cost-effectiveness of a single screening round of a population with an age of 40–70 years in order to identify and treat diabetes before clinical diagnosis would occur. The modelling covers a period of 40 years from the decision to screen or otherwise.

Other scenarios

In sensitivity analyses, the cost-effectiveness of screening different populations was assessed, such as those in the 40–49-year age band, the hypertensive subgroup and the obese subgroup. Sensitivity analyses also tested the impact of uncertainty in some of the parameters and model assumptions, such as the costs of statins.

Methods

Model structure

Screening model

The principal approach to model-based evaluations of screening interventions is to (1) develop a natural history model covering the preclinical detectable phase (PCDP) and (2) then

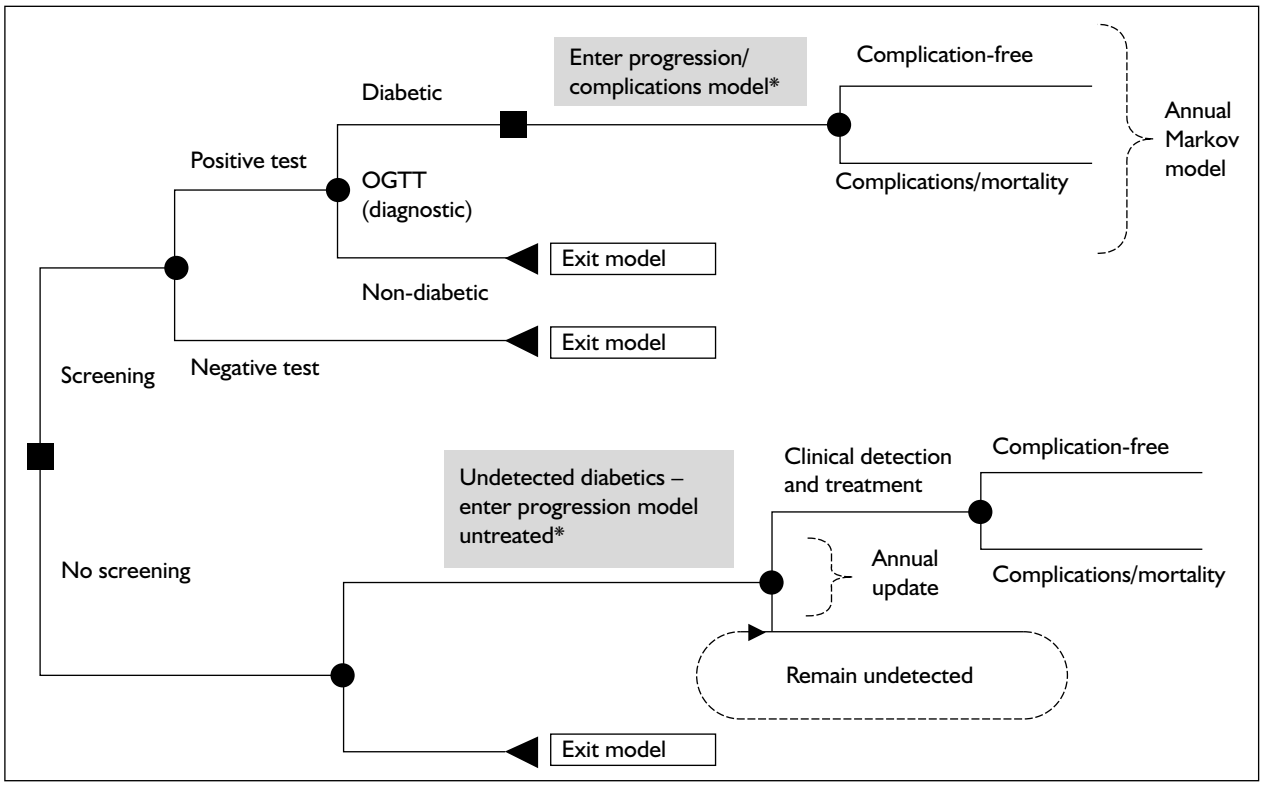

FIGURE 3 *Model structure.* Matched patients in screening and 'no screening' model.*

overlay relevant screening programme interventions (and also the 'no screening' option in which diabetes is detected clinically).

The link between the screening programme and the PCDP provides outcome measures including the proportion of persons detected prior to clinical presentation and the timing of the screen-detection. For diabetes, screening outcomes can be measured in terms of number of new cases diagnosed, distribution of HbA_{1c} levels at diagnosis and distribution of ages at diagnosis compared with ages at which diabetes would otherwise present (i.e. the reduction in time spent in the preclinical phase). These inputs feed into the treatment model so it is possible to compare overall lifetime costs and outcomes of a screened cohort and an unscreened cohort.

Treatment model

This simulates the development of microvascular and macrovascular complications in patients with T2DM. Microvascular risk is based on HbA_{1c} and blood pressure, whereas risk of developing cardiovascular complications uses a modified version of the UKPDS CVD Risk Engine (UKPDS 56[184] and UKPDS 60[185]), which is based on cardiovascular risk and outcomes in the UKPDS trial cohort (including treated and control arms).

The structure of the model is shown in *Figure 3*.

Note that the pathway after screening for the following people is assumed to be the same as if they had not been screened (regardless of whether they have diabetes or not):

- patients who test negative at screening test
- patients who test negative at diagnostic test.

Where these pathways are common regardless of the choice to screen or not, there is no need to model their long-term pathway because the costs and benefits cancel out. It is only necessary to account for the costs of the screening programme itself.

Key model assumptions

Screening and diagnostic process

A single HbA_{1c} measurement was assumed as the screening test, followed by a single OGTT if the HbA_{1c} is above 5.7%. There is much debate about the optimum test strategy[201] and the model can incorporate more complex strategies, including the use of a questionnaire, followed by a screening blood test before diagnostic testing. However, there is agreement that in the absence of symptoms (as is the case in screening) a second glucose measurement is required before anyone is diagnosed as diabetic.

Natural history of HbA_{1c} progression

The potential benefit of earlier diagnosis and treatment of hyperglycaemia will be closely related to the distribution of HbA_{1c} results at screening and its progression up to the point of clinical diagnosis.

Overview of method

To obtain the duration between screening and clinical detection, HbA_{1c} distributions were sampled at screen and clinical detection, and estimated rates of HbA_{1c} progression used to calculate to preclinical duration. This method was chosen as it provides some degree of variability in the preclinical duration which was thought to be an important factor in determining the overall risk profile of patients during the preclinical period. Variability in the rate of HbA_{1c} progression, however, was considered too uncertain to model given that HbA_{1c} progression is the most uncertain aspect of the natural history to estimate (see below).

Although there may be some correlation between HbA_{1c} at screen detection and the HbA_{1c} at which a patient would be clinically detected, this was thought to be low and not significant. Therefore the screen and clinical HbA_{1c} distributions were sampled independently.

HbA_{1c} at screen detection

First, a distribution of HbA_{1c} is assumed for screen-detected patients. Results from screening programmes are summarised in *Table 17*.

It was assumed that HbA_{1c} values were reported on the required DCCT aligned scale (the risk equations in our model are UKPDS-aligned). Data suggest that the FPG test yields a higher HbA_{1c} than an OGTT test – this is expected because postprandial hyperglycaemia is often the more dominant defect in early diabetes. Weighting has been given to studies that used an OGTT test as this test is the most sensitive, and it is assumed that the mean HbA_{1c} of the undiagnosed diabetic population is 6.4%.

The HbA_{1c} test is effectively a 'hybrid' of an FPG and an OGTT test, resulting in a sensitivity below 100%. To obtain a sample of HbA_{1c} values from the undiagnosed population, samples were taken from the upper region (starting from 1 – sensitivity), giving a mean HbA_{1c} through screening of 6.7%.

The 1998 CDC screening evaluation[131] used a similar mean HbA_{1c} of 6.8% at screen detection. An SD of 1.0 was assumed, as reported from the KORA survey,[206] this is consistent with assumptions in the CDC screening modelling. The reviewers have assumed a skewed distribution, as the higher the HbA_{1c} the more likely patients would be symptomatic and be detected clinically, this assumption is supported by the HbA_{1c} distribution shown in Figure 3 of Hofer and colleagues[213] based on NHANES III data.

HbA_{1c} at clinical detection

Patients were randomly assigned to an HbA_{1c} level that would have been found in the absence of screening, that is, clinical detection using the HbA_{1c} distribution from the UKPDS (which was on average 9% but was higher in symptomatic patients). Another study also found that symptomatic patients had a slightly higher HbA_{1c} of 9.9% at diagnosis.[214] A higher HbA_{1c} level of 10.8% was observed in the Poole Diabetes Study,[215] although the scale used here has not been confirmed. The assumption of an average HbA_{1c} of 9% at clinical detection may be slightly conservative in terms of estimating the duration of undiagnosed diabetes.

TABLE 17 *HbA_{1c} at screen detection*

Study	Test	Mean HbA_{1c} (%)	FPG (mmol/l)
KORA survey[201]	OGTT	6.2	
Hoorn[111]	Mixed	6.7	
NHANES III[210]	ADA criteria (FPG levels) WHO criteria (OGTT results)	7.07 6.58	
EDIP[211] (estimated from *Figure 3*)	FPG + HbA_{1c}	6.5	6.6
UKPDS – low FPG group of which 44% asymptomatic[184,185]	Unknown	6.7	
Other UK studies: Ely,[137] Coventry Diabetes Study[212]		Not available	

Although there is some variation in HbA_1 at diagnosis by age group, as shown in the Poole Diabetes Study (their Figure 2),[215] this is considered to be of minimal significance, because there will be little effect on the **incremental** risk between the two cohorts.

HbA_{1c} progression

Having established two HbA_{1c} distributions at screen and clinical detection, the remaining parameter required is the HbA_{1c} progression during the preclinical phase – this will also determine the additional time duration that would pass before clinical detection. Although indirect estimates of the duration have been made, these vary greatly from 6 to 11 years and may involve unjustified assumptions about HbA_{1c} progression.

We believe that the best way to model this uncertainty is firstly to consider the HbA_{1c} trajectory of an average person with diabetes:

- To review evidence on the rates of change in HbA_{1c} where possible – results of patients developing diabetes in IGT studies can give an idea of the rate close to onset of diabetes; the UKPDS gives an idea of the rate of change at clinical detection. A modelling paper by Bagust and Beale[60] using results from the Belfast Diet Study also suggests a possible HbA_{1c} trajectory.
- To explore a range of scenarios for the HbA_{1c} trajectory (for an average patient).
- To identify the scenario which has the best fit with other sources of evidence on disease progression.

Average HbA_{1c} in non-diabetics is around 5.4%. We estimate HbA_{1c} at onset of diabetes to be around 5.85%. Although the DPP reported an HbA_{1c} of 6.4% at onset of diabetes,[90,171] (assumed onset as tested 6-monthly), this could be because those that progressed had more severe beta-cell dysfunction (rather than modifiable insulin resistance), leading to a rapid rise in HbA_{1c}.

There is little hard evidence on which to base the rate of change of HbA_{1c}. Some aspects of the natural history can be inferred from various sources – 'triangulation' using various sources of evidence is considered to be the only approach to estimating the natural history as there is no existing dataset that demonstrates the natural history of untreated diabetes. Various results from studies do seem to suggest a lower rate of change in the earlier part of the preclinical phase.

In the US Diabetes Prevention Program,[90] 38% of placebo patients became diabetic at 4 years. HbA_{1c} change in the placebo group during this period was 0.2%. For the placebo patients, even if it is assumed that HbA_{1c} rose three times faster in those who became diabetic, we estimate that HbA_{1c} would only have risen at an annual rate of about 0.1%.

In the Finnish Diabetes Prevention Study,[89] HbA_{1c} did not change at least up to the end of year 3 in the control group even though diabetes incidence was significant (21, 23 and 42 at 3, 4 and 6 years, respectively), although the control group did receive some dietary information making interpretation more difficult.

Of note is the HbA_{1c} level at screen detection, that is, between 6.0 and 6.5%. This is much closer to the HbA_{1c} level at onset (which is estimated to be about 5.8–5.9%) than the level at clinical detection (9% per UKPDS). This suggests one or both of the following could be happening:

- The rate of HbA_{1c} progression increases either gradually or increases more rapidly at a specific phase of progression such that patients generally are less likely to be detected in the more advanced preclinical phase (because there would be relatively less time in this phase). There is a biological study that supports this hypothesis.[216]
- Some slower progressors may not be detected in the latter stages of the preclinical phase because their raised CHD risk may result in mortality during this period – this would have the effect of detecting patients at relatively low HbA_{1c} levels

The International Diabetes Center, Minneapolis, MN, produced a diagram[217] showing a hypothesised trajectory for glycaemic progression – this appears to be frequently referenced and is consistent with an up-sloping HbA_{1c} trajectory.

The rate of change in HbA_{1c} during the first few years of the UKPDS was around 0.2% p.a., despite antiglycaemic therapy.[8] The expected rate of increase would be greater without treatment.

Taking account of the limited evidence above, it was assumed that, for the baseline analysis,

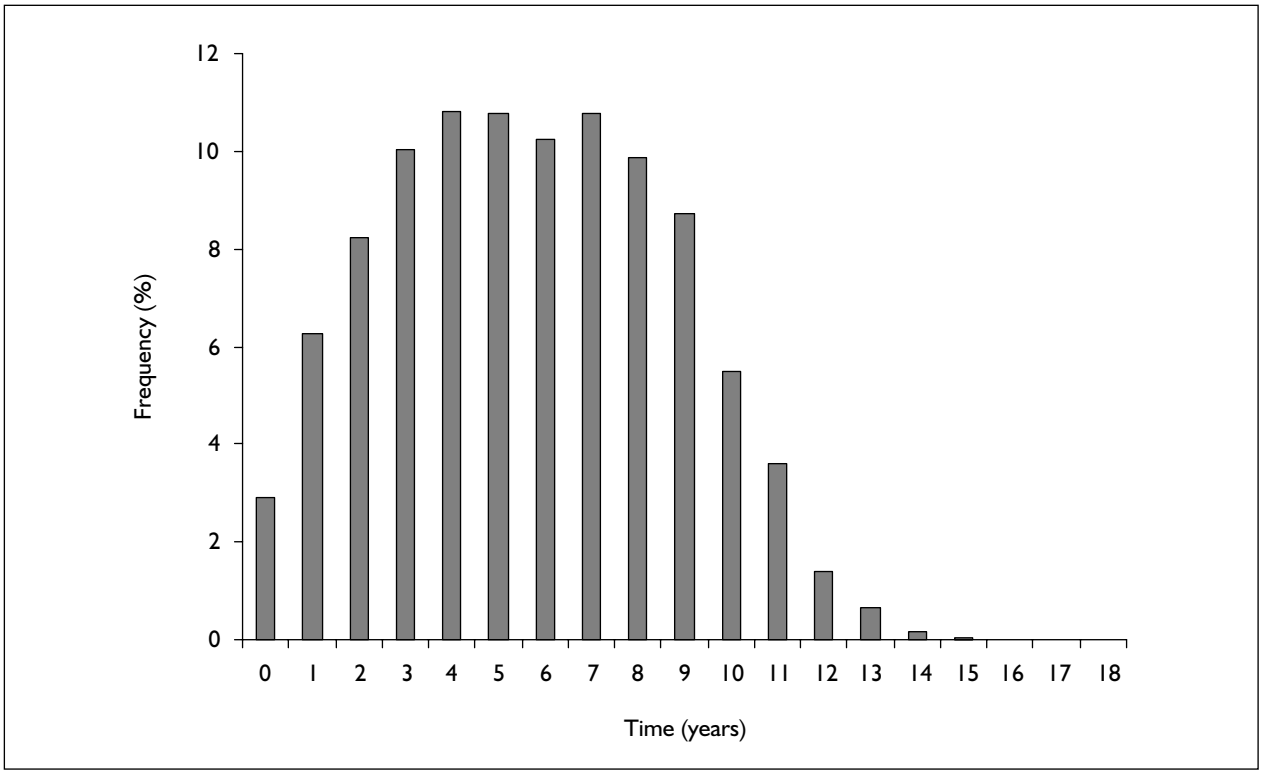

FIGURE 4 *Distribution of reduction in time to diagnosis through screening*

the **rate of HbA_{1c} change** increases exponentially over time from 0.15 p.a. at diabetes onset to 0.45 p.a. at clinical detection (assumed to be at 9.0% HbA_{1c} on average). This is clearly an area for further research. The impact of a more rapid exponential increase (and shorter preclinical period) was examined in the sensitivity analyses.

Reduction in time to diagnosis through screening
Estimates of the expected lead time between screen and clinical detection are an indirect output of this modelling approach and can be compared with the findings with other sources of data using other methods to estimate the preclinical course.

The estimated average delay in diagnosis through not screening is approximately 6–7 years. The estimated sojourn period between onset and clinical detection is around 11 years. The distribution of the delay obtained is shown in *Figure 4*.

Changes to other risk factors during the preclinical period
The assumptions made about baseline characteristics and changes to these during the preclinical period of the unscreened cohort are important.

Systolic blood pressure (SBP)
SBP in the UKPDS at baseline was 136 mmHg. It was assumed that there is reasonably tight SBP control in undetected patients given current NHS incentives for GPs, although not as tight as the recommended level for people with diabetes. It was also assumed that SBP is at most 150 mmHg at baseline.

For annual changes in SBP, data from the Health Survey for England 2003[63] (Volume 2, Risk factors for cardiovascular disease, Figure 7C, p. 186) were used.

Approximate changes (in the general population) were calculated as follows:

- Rise p.a. women = 118 to 137 mmHg from age 40 to 60 years, or approximately 1 mmHg p.a.
- Rise p.a. men = 129 to 138 mmHg, from age 40 to 60 years, or approximately 0.5 mmHg p.a.

It was assumed due to the higher prevalence of hypertension in diabetes, that the SBP rises at twice the general population rate.

Cholesterol
Total cholesterol was 5.4 mmol/l at baseline in the UKPDS.[8]

Changes in cholesterol vary by age and gender in the general population. Further uncertainty arises from some cholesterol monitoring and the impact of diabetes, so no changes in cholesterol levels have been included (this is consistent with observations in UKPDS[218]).

No annual changes in cholesterol level are assumed.

Modelling of treatment and outcomes

Risk equations

Throughout the time horizon of the modelling (i.e. including the preclinical period), the UKPDS CHD and stroke risk equations were used to model the risk of cardiovascular events. The equations published by Eastman for microvascular events were also used.[134,135]

Treatment assumptions from the point of diagnosis

Modelling the no-screening comparator involves initially modelling patients without statin or further antihypertensive therapy or diet/exercise or antiglycaemic therapy. At a patient's determined point of clinical detection, they begin active treatment in the model. The model assumes that from diagnosis, both hyperglycaemia and other CHD risk factors such as hypertension and dyslipidaemia, are treated according to current clinical guidelines. The widespread availability, falling cost and significant cardiovascular risk reduction (30%) of statins is a key factor in the effectiveness of screening.

The model assumes that if proliferative retinopathy or macular oedema develops, then this would be treated using photocoagulation, leading to a 45% reduction in risk of severe vision loss. For the purposes of costing retinopathy screening, it was assumed that this takes place annually.

An area of uncertainty is whether reductions in HbA_{1c} lead to reductions in CHD. A recent review concludes that the evidence suggests that chronic hyperglycaemia is associated with increased CHD risk.[219] A recent analysis reported from the follow-up of DCCT participants (type 1 diabetes), the Epidemiology of Diabetes Interventions and Complications (EDIC) study, may be highly significant – tight HbA_{1c} control (7% versus 9% for conventional control) reduced CVD events by about 50%.[220] For our base-case analysis, the results reported in UKPDS 35[221] were used, namely that each 1% decrease in the observed mean updated HbA_{1c} is associated with a 14% lower incidence of MI. Sensitivity analysis was undertaken to test the impact of varying this assumption.

A detailed description of the Sheffield Treatment model should appear shortly as an on-line Discussion Paper[222] until the full publication is available. The modelling of risk factors post-diagnosis is covered in detail in the 'Background to methods' section at the end of this chapter.

Other assumptions

Pathways following screening

A key assumption is that the only long-term modelling required involves comparing the progression of the true positives under screening with their progression if they had been detected later clinically. This assumes that a negative screening test or a positive screening test followed by a negative diagnostic test does not have any clinically significant long-term consequences, although screening itself will potentially have an impact on both quality of life (by provoking anxiety or reassurance) and risk behaviour (due to individuals becomes more or less motivated to change their diet or lifestyle) depending on the context of screening (these issues are well described in papers by Speight[223] and Edelman and colleagues[224]). It is assumed that these effects can be modified by providing appropriate information and support at the time of screening and have not been included in the modelling. The main impact of diabetes on health-related quality of life (HRQoL) is through the development of complications.

Costs

The model considers costs from an NHS perspective. The costs of screening tests and costs of subsequent treatment for both diabetes and associated complications are included.

Costs borne by patients or society such as costs to the individual of attending for glucose tests or the costs to society of supporting an individual with diabetes-related blindness are not included.

Key model parameters

Population characteristics

The age, sex and ethnicity structure of the screened population is based on the PBS model developed by the Yorkshire and Humber Public Health Observatory,[225] available at www.yhpho.org.uk.[3] Details on how the population prevalence figures were calculated for alternative subgroups are in the 'Background to methods' section at the end of this chapter.

The population size of subgroups based on age group, diagnosed hypertension and BMI were calculated using information from the PBS model and recent data from The Health Survey for England.

As the PBS prevalence figures are at 2001 levels, an uplift of 10% was applied to estimate the prevalence in 2007 based on assumptions published with the PBS prevalence model.[226]

The percentage of the diabetic population that is undiagnosed can be varied. The PBS prevalence model documentation suggests that the figure lies between one-third and half based on Wild and colleagues[227] and King and Rewers.[228] In NHANES III,[210] 35 and 45% of diabetes cases were undiagnosed by ADA and WHO criteria, respectively. More recent estimates, based on a National Diabetes Audit,[229] suggest that with current levels of *ad hoc* screening activity, approximately 25% remain undiagnosed in England. The default figure was set to 35%.

Baseline complication rates

Macrovascular complications

When evaluating the effectiveness of screening older age groups, the increased prevalence of CHD at baseline is important given the increased risk of subsequent MI. However, patients with a CHD history should be screened for diabetes as an element of secondary prevention and it was therefore assumed that the baseline prevalence of CVD amongst the cohorts for potential screening would be negligible.

Similarly, prevalence of prior stroke at diagnosis is assumed to be nil because these people have a CVD profile and in theory should be covered by a broader prevention programme other than a purely diabetic screening programme.

Undiagnosed CHD would be increasingly prevalent at baseline as age increases. As both age at diagnosis and duration since diagnosis are factors in the UKPDS risk engine, this trend is accounted for within the model.

Microvascular complications

Microvascular complications are related to glycaemia and blood pressure. There is debate, however, about the level of glycaemia needed for retinopathy to develop. A recent report from the ADA Conference indicated that retinopathy is present in some prediabetic patients.[230] The assumption was used that the prevalence of (non-proliferative) retinopathy increases linearly from nil at the average HbA_{1c} at onset (5.85%; see end of paragraph) to 17% (330/1919 with Level 35 or worse)[231] in the UKPDS at an HbA_{1c} of 9%. This is close to the 15% prevalence recently reported from the Tayside Diabetes Network[232] and the 17% based on the Early Diabetes Intervention Program (EDIP) study.[211] Analyses from NHANES III and other studies show a marked change in prevalence above an HbA_{1c} of 5.9%,[17] confirming that our assumption above is reasonable.

An individual's presence or otherwise of retinopathy at entry to the simulation is determined by their HbA_{1c} at entry.

A similar relationship is assumed for baseline prevalence of nephropathy, with the prevalence assumed at diagnosis at an HbA_{1c} level of 9% being 6.5% for microalbuminuria and 0.7% for macroalbuminuria.[183]

At an average HbA_{1c} of 6.7% at screen detection, estimated prevalence of retinopathy, microalbuminuria and macroalbuminuria is 4.6, 1.8 and 0.2%, respectively. As the prevalence of neuropathy at diagnosis was only 1.2%,[233] it has been assumed that this is negligible at screen detection.

Uptake of screening

This is set to 50% based on uptake rates within the current UK NSC's diabetes screening pilots in England (the DHDS pilots), where patients are being invited for screening by letter. It has been assumed there is no uptake bias and therefore that the screened population is similar to the general population that would be eligible for screening.

Screening and diagnostic tests

In the baseline model, the screening test assumed is an HbA_{1c} test with a cut-off of 5.7%, as suggested by Zhang and colleagues,[205] as the optimal cut-off. They reported sensitivity and specificity at different HbA_{1c} cut-off levels, these were 66 and 83%, respectively, at a cut-off of 5.7%.

An OGTT is assumed to be performed to confirm (or otherwise) diagnosis in patients who are initially screen positive using the HbA_{1c} test.

Costs

Table 18 shows the key costs associated with screening and early treatment.

It was assumed that no additional costs of case-finding would be incurred on the grounds that suitability for testing would be evident at the time

TABLE 18 *Key cost inputs relating to screening and early treatment*

Resource	Unit	Cost (£)	Note
Case finding	Per case	0	
Screening test (HbA_{1c})	Test	5.00	This is based on a conversation with laboratory colleagues, suggesting a range of costs from about £3.50 to £20 depending on volume and speed of results; a figure has been taken near the lower end of that range assuming that screening would involve large numbers but with no need for speed
Diagnostic test (OGTT)	Test	20.00	HTA Review of screening for gestational diabetes[2]
Cost of statins	Per day	0.17	40 mg generic simvastatin[234]
Non-medication costs of monitoring/managing diabetes (based on two GP visits with HBA_{1c} tests, and retinopathy screening)	Per year	97.00	Calculation based on several sources

of a routine GP appointment (i.e. assuming opportunistic screening rather than a new dedicated mass screening programme).

The costs for an HbA_{1c} test and OGTT test are estimated to be approximately £5 and £20, respectively, including nurse time, transport and laboratory processing costs. No societal costs associated with patients' lost time is included. Additional GP infrastructure costs are assumed to be avoided through adoption of opportunistic screening when patients visit GP practices for 'routine' appointments. No costs of monitoring the screening programme are assumed.

Costs of therapies were obtained from the NHS Drug Tariff[234] (which are generally considerably lower than BNF prices).

The main additional cost of statins arising from screening occurs during the period in which they would otherwise have been undiagnosed (some further additional costs are attributable to improved subsequent survival). It was assumed that 40 mg of (generic) simvastatin is sufficient to manage cholesterol levels during this period and applied this cost throughout the model. Average costs of statins were therefore estimated at £ 0.17 per day.

Insulin cost was based on the average cost of Monotard (£10.50 per 1000 units) and Lantus (Insulin Glargine) (£26 per 1000 units).

Costs of treatment of complications are as specified for the Sheffield Diabetes Treatment Model.

Treatment costs are from an NHS perspective; for example, no costs are included for carers of patients who develop blindness.

Costs are expressed in real terms (i.e. no inflation included).

Discount rates

Costs and benefits were discounted in line with the new NICE guidance for England and Wales of 3.5% for both.

Screening scenarios

In addition to baseline scenarios for the age bands 40–49, 50–59 and 60–69 years, sensitivity analyses were undertaken to demonstrate the relationship between the key parameters and the model outcomes. One-way sensitivity analyses include the impact of screening a higher risk population (hypertensive and obese populations), the impact of varying treatment regimes (more intensive glycaemic control), treatment costs (statin costs) and the impact of varying the assumed natural history (progression of hyperglycaemia prior to clinical diagnosis).

Model outputs

For a given population, the model predicts the number screened, the number of new cases that would be diagnosed by screening, cardiovascular events (MI, and unstable angina and stroke) and mortality in the presence and absence of screening, microvascular complications and the overall costs and QALYs associated with screening. Cost-effectiveness is presented in terms of:

- Marginal net benefit (i.e. the financial value, above that expected to have to be invested, to realise the QALY gains using an acceptability threshold of £ 20,000 per QALY)
- The ICER – the ratio of incremental costs to incremental QALYs.

TABLE 19 *Numbers screened and test results*

Screening scenario	Undiagnosed prevalence (%)	Number to screen (per 100,000 population)[a]	Detected and diagnosed diabetic	Detected and diagnosed as IGT/IFG (approximate estimate)
All 40–70-year olds	2.50	16,869	283	177
40–49 years of age	1.40	6,535	60	37
50–59 years of age	2.20	6,051	88	55
60–69 years of age	4.80	4,283	135	84
Hypertensive (age 40–70 years)	4.40	6,083	176	110
Obese (BMI >30 g/m^2)	4.10	4,004	108	67
Higher uptake (70%)	2.50	23,616	396	247

[a] Assuming 50% uptake of those invited to screening.

The marginal net benefit is more readily interpretable, particularly where the ICER calculation involves negative figures, as is often the case in our results.

Results

Results from baseline scenario

Screening outcomes

Screening a cohort of patients between 40 and 70 years of age in a Primary Care Trust (PCT) population of 100,000 individuals would mean that 33,740 people would be invited for screening, of whom 16,870 would respond and take a screening test; 3078 would need diagnostic testing and 283 (0.3%) would be new cases of diabetes. Based on our model, they would be detected an estimated 6–7 years earlier than in the absence of screening. In practice, only those with BMI over 30 kg/m^2 might be invited.

Cost-effectiveness of screening (per person diagnosed)

Overall £715 would be the cost of additional treatment and monitoring, largely resulting from earlier diagnosis, and £880 would be saved from the reduction in complications and their treatment. The apportioned total cost of screening and diagnosis per diagnosed case would be £516. This represents an overall additional cost of £351 and a gain in QALYs of 0.155 per case detected and treated, giving an incremental cost per QALY ratio of £2266.

Sensitivity analyses

Numbers screened and test results are given in *Table 19*. The relative proportions with undiagnosed diabetes and IGT would vary depending on cut-off level chosen. With lower cut-offs, IGT would be more common.)

The screening strategy (i.e. choice of test and HbA_{1c} cut-off) and assumed uptake rate would leave 575 people in the 40–70-year age band undetected per 100,000 total population; 428 of these would not have taken up screening, with the remainder being those who are screened but whose HbA_{1c} is below the 5.7% cut-off level for a positive result.

The numbers to screen are obtained from the PBS prevalence model by providing weighted averages of age-specific prevalence within 5- or 10-year age bands. As the numbers are based on the mix of the total population of England, they represent the expected number from a 'typical' PCT population.

The results of one-way sensitivity analyses for the treatment of diagnosed patients at screen detection compared with clinical detection (i.e. excluding screening costs) are given in *Table 20*.

This modelling suggests that screening is cost-effective for all populations between 40 and 70 year of age, and for all **one-way** parameter and treatment sensitivity analyses **around the base case**. It cannot be concluded without further analysis, however, that this would be the case for sensitivity analyses around every population. The same applies if some of the sensitivity analysis assumptions were combined (e.g. higher monitoring costs and lower CHD reduction from HbA_{1c} lowering).

Age groups

Table 20 shows additional treatment costs and QALY gains per new case detected. All age groups show a QALY gain of at least 0.12. The 50–59-year and 60–69-year age groups both show cost savings from treatment also. After the costs of screening

TABLE 20 *Results of one-way sensitivity analyses for early treatment compared with treatment at clinical detection per case diagnosed (excludes screening costs)*

Screening scenario	Incremental costs compared with no screening (£)[a]	Incremental QALYs compared to no screening
All 40 to 70 year olds (baseline)	–165	0.155
Age (years)		
40–49	305	0.121
50–59	–198	0.169
60–69	–75	0.179
Risk factors		
Hypertensive patients	–56	0.166
Obese patients	–165	0.155
Natural history		
Faster HbA_{1c} progression prior to clinical detection (shorter delay from screen to clinical detection)	–353	0.175
Treatment effectiveness		
Lower CHD risk reduction achieved from HbA_{1c} reduction	34	0.096
Lower CVD risk reduction from statins	217	0.156
More intensive HbA_{1c} control (adding high-cost drug as third-line combination therapy)	432	0.093
33% lower reduction from screening in microvascular complications	–24	0.138
Treatment and monitoring costs		
Monitoring cost £129 instead of £97 p.a.	0	0.155
Higher statin cost – average 40/80 mg	440	0.155
Insulin cost 1/3 lower (to see effect of fewer patients requiring insulin in long-term through screening)	–121	0.155

[a] Negative incremental costs denote cost saving.

are taken into account, cost-effectiveness appears greatest for the 60–69-year age group (*Table 21*). This is partly because more cases are diagnosed in the 60–69-year age band due to the higher prevalence (see *Table 19*), resulting in the **effective** screening cost **per case detected** being much lower in the 60–69-year age group (£590 and £281 per case detected for 50–59- and 60–69-year age groups, respectively).

The 40–49-year age group yields additional treatment costs, lower QALY gains and higher screening costs per case detected due to lower baseline risk of complications and lower prevalence.

High-risk populations

Populations at higher risk of diabetes are also at higher risk of cardiovascular complications in the presence of diabetes, for example if older or hypertensive. The model suggests that QALY gains will be greater in some higher risk populations, as shown above for the hypertensive subgroup.

Prevalence

The degree of uncertainty in the prevalence of diabetes is unlikely to affect whether screening is cost-effective or not, unless several of the 'pessimistic' assumptions in the sensitivity analyses apply.

Preclinical HbA_{1c} trajectory

A more rapid rise in HbA_{1c} prior to diagnosis will influence both the potential benefit and the potential duration of additional treatment. The model suggests that this will reduce the additional costs largely by reducing the duration of additional treatment (to about 4 years under this assumption) while impacting on later complication rates.

CHD benefit of HbA_{1c} reductions

The assumption that reducing HbA_{1c} will reduce CHD rates is one of the reasons for the significant drop in CHD complications with earlier treatment. However, even after eliminating this benefit, the treatment of associated risk factors (statins, antihypertensives, aspirin) will still produce a significant benefit.

TABLE 21 *Results of one-way sensitivity analyses for overall costs and cost-effectiveness of screening versus no screening per 100,000 population*

Screening scenario	Number screened	Total screening cost (£)	Number detected and treated	Total incremental treatment cost (£)[a]	Total incremental QALYs	Marginal net benefit of screening (per screened person) (£)[b]	ICER (screening vs no screening)
All 40–70-year olds (baseline)	16,869	145,898	283	–46,697	44	46	2,266
Age (years)							
40–49	6,535	55,781	60	18,259	7	11	10,216
50–59	6,051	52,141	88	–17,528	15	44	2,324
60–69	4,283	37,981	135	–10,103	24	106	1,152
Risk factors							
Hypertensive patients	6,083	53,708	176	–9,824	29	89	1,505
Obese patients	4,004	35,234	108	–17,791	17	79	1,046
Natural history							
Faster HbA_{1c} progression prior to clinical detection (shorter delay from screen to clinical detection)	16,869	145,898	283	–99,861	50	56	929
Treatment effectiveness							
Lower CHD risk reduction achieved from HbA_{1c} reduction	23,616	204,257	396	13,656	38	23	5,706
Lower CVD risk reduction from statins	16,869	145,898	283	61,281	44	40	4,682
More intensive HbA_{1c} control (adding high-cost drug as third-line combination therapy)	16,869	145,898	283	122,247	26	15	10,214
33% lower reduction from screening in microvascular complications	16,869	145,898	283	–6,837	39	38	3,563
Screening test costs							
Higher HbA_{1c} test cost (£10)	16,869	230,241	283	–46,697	44	41	4,193
Treatment and monitoring costs							
Monitoring cost £129 instead of £97 p.a.	16,869	145,898	283	65	44	43	3,334
Higher statin cost – average 40/80 mg	16,869	145,898	283	124,503	44	36	6,177
Insulin cost 1/3 lower	16,869	145,898	283	–34,307	44	45	2,549

[a] Negative incremental costs denote cost savings.
[b] Assumes a cost-effectiveness acceptability threshold of £20,000/QALY.

Treatment costs

The additional use of statins is a major driver of associated costs and benefits associated with early treatment of patients identified through screening. The potential for a wider range of generic statins over the next 5–10 years and associated reductions in the costs of all statins could potentially further increase the cost-effectiveness.

The results of the sensitivity analysis of the effect of adding a high-cost drug as third-line combination therapy can be explained as follows. If screening is undertaken, long-term HbA_{1c} control is improved. This means that more patients remain below the HbA_{1c} level at which insulin would be added (8.3% was assumed), but many could, if recommended by guidelines, be taking triple combination drugs to control HbA_{1c} to target HbA_{1c} levels applicable to patients using oral agents (7.5% in the model).

Detailed analysis of base-case results

The following analysis relates solely to the costs and benefits of treatment at screen detection compared with treatment only after clinical detection.

The QALY gain in the base case can be broken down as follows:

Survival benefits	
Discounted LYGs during the preclinical period	0.013
Benefit of postclinical detection from improved survival during the preclinical period	0.030
Benefit from being in 'no CVD' state versus 'CVD' at end of preclinical period (improved long-term survival)	0.048
Other	–0.008
Subtotal	0.083
Benefit from reduced complications	
CHD	0.021
Retinopathy	0.027
PVD	0.017
Other	0.007
Subtotal	0.072
Total	**0.155**

The benefit from reduction in first CHD events is shown in *Figure 5*.

Table 22 shows cost and benefits of treating screened detected diabetics compared with no treatment until clinical detection. The results are based on multiple simulations of 10,000 patients. The incremental costs arising from earlier treatment (i.e. at screen detection) can be summarised as follows (note: negative costs denote cost savings):

	£
Additional therapy	193
Additional monitoring	522
Fewer complications:	
Macrovascular	–457
Retinopathy	–120
Dialysis	–147
Other Microvascular	–156
Total	**–165**

There is a significant reduction in microvascular complications as a result of screening attributable to:

- The long-term improved HbA_{1c} control predicted resulting from earlier detection and treatment (see *Figure 6*) as observed in the UKPDS.[158] Similarly in the DCCT, the screening HbA_{1c} value was a major predictor of subsequent HbA_{1c} levels.[235]
- The high sensitivity of retinopathy risk to different levels of HbA_{1c}, even at moderately elevated levels.
- The microvascular risk equations take account of historical HbA_{1c} levels by using 'mean updated' HbA_{1c}, that is, the mean of the annual values. (The HbA_{1c}-based hazard ratios used by Eastman and colleagues[134] are based on the risk gradients from the DCCT using mean updated HbA_{1c} values[235]). This is important because the substantial difference in HbA_{1c} levels during the preclinical period (see *Figure 6*) has some effect on long-term risk. The elevated long-term risk despite improved glycaemic control shown in the DCCT as pre-DCCT exposure (determined by screening HbA_{1c} value and diabetes duration) was a major predictor of subsequent complications.[235]

Note that the complications submodels (i.e. CHD, stroke, etc.) run in parallel to reflect the reality that these are 'competing risks' – this means that the level of risk in, for example, the CHD model affects survival, thereby affecting the number of patients remaining at risk. This can be seen in the results – although CHD events are lower in the screened cohort, stroke incidence is very similar (despite the benefit of statins during the preclinical period) and other-cause mortality is higher in the screened cohort.

The initial drop in the screened curve is due to patients starting diet and exercise and medication after diagnosis.

TABLE 22 *Total lifetime incidence of events and years spent in health states: costs and QALYs arising through treatment per patient*

	Opening prevalence	Prevalence at end		Incidences of all events		'State years' (non-fatal events)		Per patient					
								Total costs (£)			Utility (utility loss): QALYs		
	Screening	Screening	No screening	Screening	No screening	Screening	No screening	Screening	No screening	Difference	Screening	No Screening	Difference
Treatment													
Utility of those alive (unpenalised for complication):	10,000	453	446								10.632	10.549	0.083
Of which 'Complication-free'	–	–	–										
States													
No retinopathy	9,276	229	159			178,286	147,445						
Non-proliferative retinopathy	641	90	86	1,540	3,122	18,217	30,047				0.000	0.000	0.000
Proliferative retinopathy	84	5	8	61	193	1,869	2,807	2	9	–7	–0.002	–0.003	0.001
Significant macular oedema	–	57	85	1,055	2,112	8,647	21,614	51	113	–63	–0.008	–0.022	0.014
Severe vision loss	–	73	108	237	601	2,404	5,741	31	82	–50	–0.007	–0.019	0.012
No history of coronary heart	10,000	313	299			190,394	184,206						
Non-fatal MI	–	140	147	2,032	2,388	19,029	23,448	1,648	1,915	–267	–0.044	–0.056	0.012
Death (from MI only)		3,500	3,558	3,500	3,558					0			
No cerebrovascular history	10,000	166	161			189,635	187,118						
Stroke or transient ischaemic attack	–	287	285	2,752	2,801	19,788	20,535	3,899	4,089	–190	–0.185	–0.194	0.009
Death due to stroke only		708	709	708	709					0			
No nephropathy	9,681	261	226			175,296	164,320						
Microalbumuria	281	142	135	2,124	2,630	29,417	34,586				–0.018	–0.022	0.004
Gross proteinuria	38	46	71	363	726	4,470	8,281				–0.003	–0.005	0.002
Dialysis	–	1	5	32	64	97	207	103	250	–147	–0.000	–0.001	0.000
No nephropathy – post-transplant	–	2	9	18	56	143	260	55	98	–43	–0.000	–0.001	0.000
Death due to nephropathy only		5	34	5	34								
No previous PVD	10,000	366	352			202,825	197,521						
PVD	–	85	90	687	915	6,238	9,353	108	179	–70	–0.019	–0.031	0.012
Amputation (A1 or A2)	–	2	4	79	145	359	780	44	86	–43	–0.005	–0.010	0.005
Death – multiple co-morbidities		19	20	19	20								
Death – involving other causes		5,317	5,234	5,317	5,234								

continued

TABLE 22 *Total lifetime incidence of events and years spent in health states: costs and QALYs arising through treatment per patient (cont'd)*

	Per patient											
	Opening prevalence	**Prevalence at end**		**Incidences of all events**		**'State years' (non-fatal events)**		**Total costs (£)**			**Utility (utility loss): QALYs**		
	Screening	**Screening**	**No screening**	**Screening**	**No screening**	**Screening**	**No screening**	**Screening**	**No screening**	**Difference**	**Screening**	**No Screening**	**Difference**
Managing diabetes including therapy													
Drugs:													
OHMs													
1st line								77	0	77			
2nd line								111	45	66			
3rd line								95	82	14			
4th line								0	227	–227			
All other								0	0	0			
Antihypertensive								398	364	34			
Lipid-related								774	546	228			
Total drug costs								1,455	1,263	193			
Monitoring								1,348	821	526			
Adverse event costs				41	43			316	320	–4			
Totals				20,567	25,350	1,047,111	1,038,268	9,060	9,225	–165	10.339	10.184	0.156

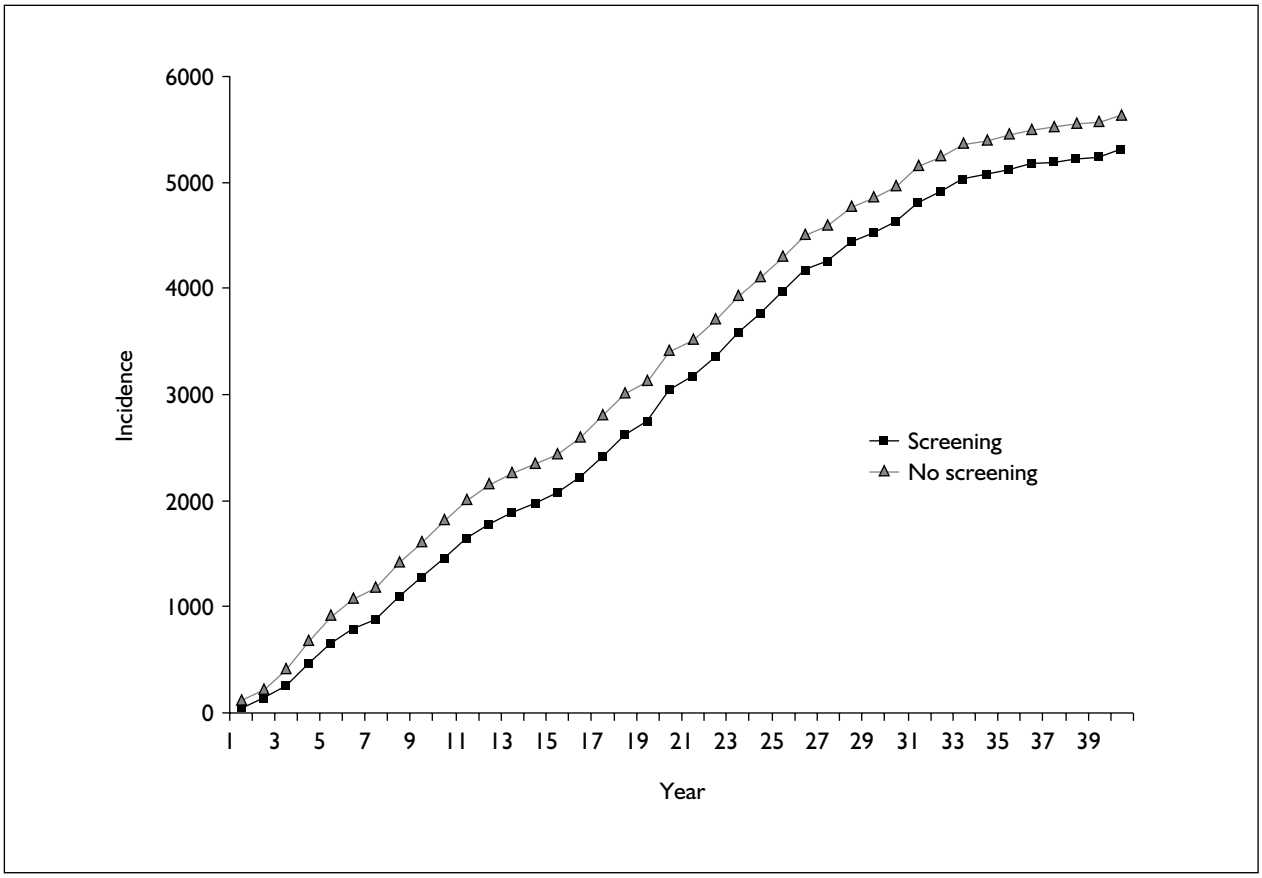

FIGURE 5 *Cumulative Incidence of first CHD events*

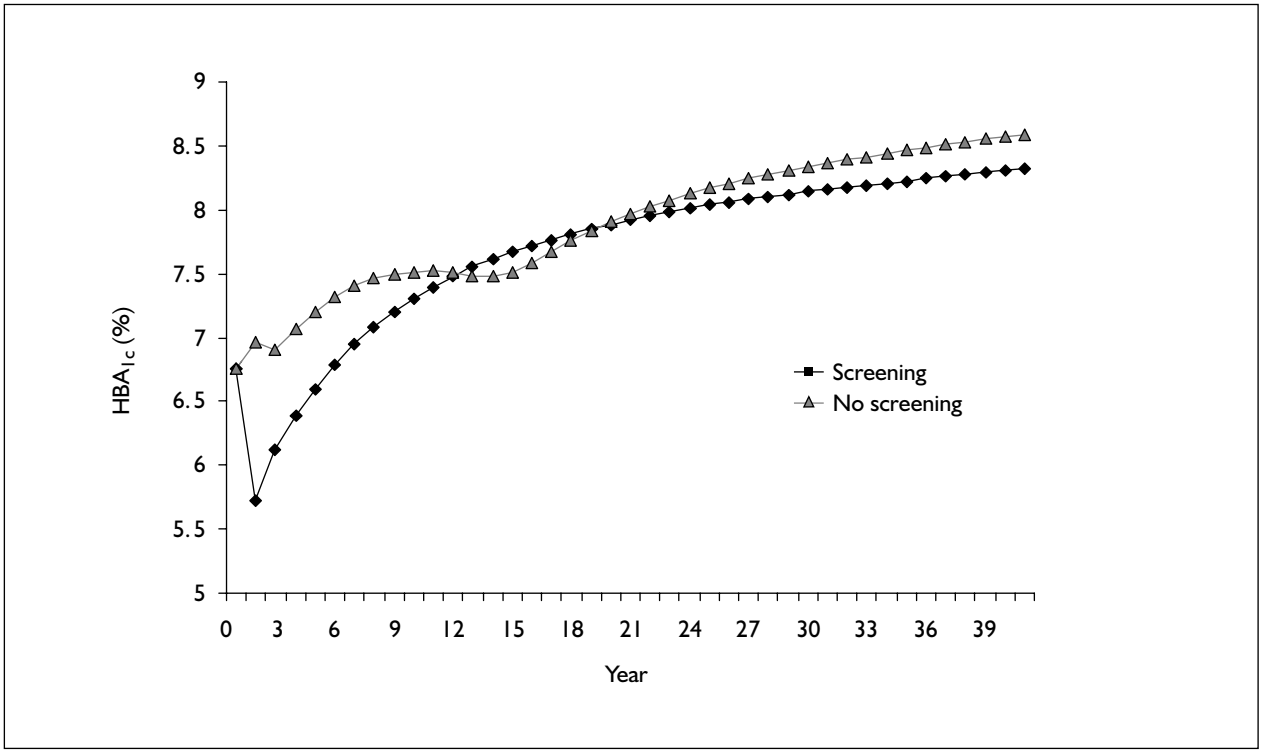

FIGURE 6 *HbA_{1c} trends (from time at which decide to screen or otherwise)*

The HbA_{1c} curves temporarily cross because of the significant short-term fall in HbA_{1c} on initiation therapy at clinical detection in the no-screening cohort. This is only a short-term effect, with HbA_{1c} resuming its upward course within a year or two. As clinical detection is occurring at varying times, the curve of average HbA_{1c} is flattened out over the period during which most unscreened patients are detected. HbA_{1c} is higher than for the screened cohort in the long term.

Discussion

Summary of findings

In the baseline scenario, offering screening to everyone aged 40–70 years, screening appears to represent a cost-effective intervention. This is due to the cost reductions and QALY gains from reductions in complications, largely from fewer cardiovascular events (risk reduced largely by statin treatment during the preclinical period) and fewer individuals developing retinopathy and other microvascular complications (risk reduced by sustained improved glycaemic control).

The main economic trade-off is between:

1. the costs of the screening and diagnostic tests
2. the net cost of statins, other therapy and monitoring costs (such as retinopathy screening) during the period before clinical detection minus the reduction in treatment costs of cardiovascular events and retinopathy
3. the higher QALYs that result from earlier intervention.

In addition to reduced retinopathy during the preclinical period, the decision to screen or not creates a modest but clinically significant difference in HbA_{1c} that leads to sustained differential retinopathy incidence rates after the point of clinical detection.

Sensitivity analyses show that whereas a prevalence has a relatively minor impact on overall cost-effectiveness, the cost-effectiveness of earlier treatment is closely dependent on the costs and effectiveness of subsequent treatment of cardiovascular risk.

The trade-off between size of CVD risk reduction and duration of benefit is seen in the results in *Table 20*. The most cost-effective age groups to screen and treat earlier appear to be the 50–59-year and 60–69-year groups, these have a sufficiently high CVD risk to obtain a significant benefit from earlier intervention while having sufficient remaining life expectancy to realise medium- to long-term benefits. Although seeming to be still cost-effective, the 40–49-year age group is much less so than the other age groups as the uncertainty in the various parameters could affect whether this group, in particular, is cost-effective to screen and treat.

Comparison with previous models

Overall, the importance of key parameters identified by previous models has been confirmed and some additional areas of uncertainty, particularly around the preclinical course of diabetes, have been highlighted. As expected, the cost-effectiveness of screening is strongly related to the costs of screening/additional treatment and the effectiveness of the additional treatment. The costs and usage of statins become key parameters because of the model assumption that one impact of earlier diagnosis will mean that individuals at high risk of CVD are started on statins earlier. This is consistent with the CDC model, which predicted that screening would be most cost-effective in those with pre-existing hypertension who would receive intensive, and cost-effective, earlier treatment to reduce their cardiovascular risk.[131]

Our modelling of the natural history gives an estimated total preclinical duration of around 11 years, with 6–7 years being the average delay between screen detection and symptomatic detection, this is close to the assumption within the CDC model. The average delay is probably greater for younger age groups (the estimate is about 8 years), assuming some correlation between age and HbA_{1c} at detection.

Previous models have also assumed linear HbA_{1c} progression, which could also result in an underestimate of the potential benefits of earlier treatment.

The large reduction in cardiovascular events predicted is due to use of statins from diagnosis. Some other diabetes screening effectiveness evaluations were performed either before statins were in widespread use or before the recent sharp falls in the price (largely through expiry of patents), and therefore would include either lower risk reductions or greater costs.

The population in the present model excludes those with existing CHD at baseline and has reflected the move towards tighter blood pressure

control in the general population. This means that long-term survival in the modelled population is higher. As a result, differences in survival arising through screening (up to the point at which clinical detection is made) result in a greater long-term benefit than would otherwise have been obtained.

Our model incorporates the relationship between HbA_{1c} at diagnosis and long-term HbA_{1c} control. Improved long-term HbA_{1c} control arising through screening is translated into long-term reductions in microvascular complications.

Other models have also not considered the potential benefit of reductions in long-term HbA_{1c} levels on CHD incidence. Although our base case assumed a 14% CHD risk reduction per 1% fall in mean updated HbA_{1c} as per UKPDS 35,[221] sensitivity analysis indicates that screening would still be highly cost-effective if this were only 5%.

Our test cost is low compared with other models. Treatment costs are largely UK based, accounting for some of the difference with other models.

A utility of 0.77 was assigned to a person with diabetes but no complications, whereas other models tend to use 1.0. The latter does not reflect either the reduced age-related quality of life of the general population or the diabetes-specific loss of quality of life arising from taking medication, monitoring and so on. This explains why some models report a utility gain through screening of similar order to our model, despite much lower reductions in complications.

Strengths and weaknesses of analysis

Due to the timescale involved, we have not produced a state of the art model or made use of more sophisticated modelling methods to undertake evidence synthesis to structure or populate the economic model. It has been necessary to make various assumptions and exploration of uncertainty has been limited to simple sensitivity analyses. We have nevertheless produced a screening model linked to the existing fully developed treatment model to investigate the order of magnitude of effects given different scenarios for diabetes screening policies.

The model results are dependent on the choice of model parameters and, although more complex than some previous models, there are a number of areas where complete data are unavailable. In particular, the natural history of diabetes before clinical diagnosis and the clinical characteristics of cases detected by screening remain uncertain, despite review of the best available evidence. For this reason, a number of sources have been used or different methods triangulated to estimate, for example, the duration of disease between screening and clinical detection and the HbA_{1c} trajectory.

Our modelling suggests that screening is cost-effective across all populations between 40 and 70 years of age and across most one-way sensitivity analyses. However, it cannot be concluded without further analysis that this would be the case for sensitivity analyses around every population. The same applies if some of the sensitivity assumptions were combined (e.g. higher monitoring costs and lower CHD reduction from HbA_{1c} lowering). Equally, there is some uncertainty about the **relative** cost-effectiveness of the alternative populations.

A probabilistic sensitivity analysis would be required to determine adequately the **optimum** screening policy (see the subsections 'Optimum screening age' and 'Rescreening interval', p. 82), taking account of the impact of uncertainty and exploring the most significant parameters. Probabilistic sensitivity analysis would effectively be a more comprehensive multivariate extension of the one-way sensitivity analyses that have been conducted so far, and would quantify the likelihood of a screening policy being cost effective. Methods have recently been developed that reduce the heavy computational burden of probabilistic sensitivity analysis for patient-level models based on the algebra of analysis of variance and Bayesian statistics,[236] making a rigorous uncertainty analysis feasible in reasonable time. Our simulations have removed most 'first-order variability' from the results but any probabilitic sensitivity analysis should be large enough to ensure that this is effectively eliminated.

Potential for further modelling

Further development of existing model parameters

Although this model has used the best available published evidence on the natural history of diabetes prior to clinical diagnosis, there is potential to develop more sophisticated models. A gradual upsloping HbA_{1c} curve during the preclinical period was assumed, but there are some suggestions that there could be a slow linear phase followed by a more rapid linear phase (possibly where beta-cell failure becomes more significant

than insulin resistance). It would be useful to incorporate more primary data on aspects of the natural history of the development and early progression of diabetes. Potential sources of data include the Whitehall Study,[237] the UKPDS,[238] the ADDITION trial[95] and the DARTS Tayside Regional Diabetes Network.[239]

Screening for both prevention/delay and earlier detection of diabetes

This model addresses screening and earlier treatment for diabetes. However, any screening programme for diabetes will also identify individuals who would benefit from interventions to delay or prevent the development of diabetes. This issue has been considered separately, but if both prevention and early detection are deemed to be cost-effective, it would be useful to model the overall impact of screening on both prevention and early treatment.

Optimum screening age

Our modelling suggests that screening is cost-effective for all age groups between 40 and 70 years. However, it may be that there is relatively little incremental benefit from screening patients in their 40s compared with waiting until they are around 50 years old (but any future modelling should also consider possible interactions between age and rate of diabetes progression as discussed below in the subsection 'Patient variability in the preclinical phase').

Rescreening interval

Rescreening would not arise as an issue if a single screening intervention to identify prevalence cases of undiagnosed diabetes had not been demonstrated to be cost-effective from a certain age. However, if a prevalence-round screening strategy is cost-effective, then clearly whether rescreening should be done, and if so at what time interval, should also be modelled. In practice, once an individual has been given a screening test, they will expect to be rescreened unless they can assume they are no longer at a significant risk of the condition screened for. This is unlikely, particularly if they have already been offered a screening blood test on the basis of the presence of risk factors for diabetes.

Cardiovascular risk reduction

If screening for diabetes is considered in the context of screening for CVD, then it would be logical to quantify the **additional** value of identifying both i**ndividuals at risk of diabetes** and **individuals with diabetes** within a cardiovascular screening/risk reduction programme. The model would still estimate the overall costs and benefits of screening, but with the objective of cardiovascular risk reduction. Such an approach might reduce the potential for those without diabetes but with other cardiovascular risk factors to be 'falsely reassured' by screening. Our model could be refined to restrict statin use to a person diagnosed with diabetes once their CHD risk exceeds a certain threshold.

Secondary CHD risk

The modelling has shown that the reduction, through earlier treatment, in the prevalence of CHD (non-fatal MI), at the time at which clinical detection would otherwise have occurred, is a significant driver of cost-effectiveness. It would be possible to refine the secondary event rates so that they are dependent on risk factors.

Relationship between nephropathy and CHD

CHD risk increases significantly with progression from overt nephropathy to ESRD. The very high costs of dialysis and renal transplantation are reduced to some extent by screening (through better long-term glycaemic control), but it would be useful to model the risk relationship more precisely. This is especially the case given the relatively high long-term survival of our modelled population (having no symptomatic CHD at baseline and tight blood pressure control), because more patients could live long enough to develop ESRD.

Patient variability in the preclinical phase

It would be useful to consider the between-patient variability in HbA_{1c} changes – this may be important because slow progressors are more likely to be detected through screening as they spend longer in the preclinical phase. Further information on this variability might be obtained using data from trials treating patients with IGT and from UKPDS data.

The literature often refers to younger patients experiencing a faster beta-cell decline than older patients – it would be worth investigating this further to see if this interaction is significant and, if so, to quantify the impact on cost-effectiveness.

Newer agents

Any future work should include new therapeutic developments; for example, if glucagon-like peptide (GLP) analogues or dipeptidyl peptidase IV (DPPIV) inhibitors can stabilise or reverse beta-cell decline, the benefits of early detection may change. Inhaled insulin may change both the costs and effectiveness of glycaemic control (through improved adherence).

Conclusions

The modelling undertaken has led to the following conclusions:

1. Screening for diabetes appears to be cost-effective for the 40–70-year age band subject to limitations of the evidence available and within the one-way (parameter and treatment protocol) sensitivity analyses that we have carried out.
2. Screening for diabetes appears to be most cost-effective for the 50–59-year and 60–69-year age bands and less so for the 40–49-year age group.
3. Screening appears to be even more cost effective for the hypertensive and obese subgroups.
4. Further analysis should explore whether screening is cost-effective under some combined parameters and treatment sensitivity assumptions, particularly for the 40–49-year age band.
5. Assumptions about degree of control and treatment protocols after clinical detection are as important, if not more so, than assumptions relating to the screening programme itself in determining the cost-effectiveness of screening.
6. Although the results suggest that there is a cost-effective screening programme, the optimum age and other criteria are not obtainable from these results and further work is needed to determine this. The optimum policy also needs to take account of the optimum rescreening interval and the benefits of treating patients detected with IFG or IGT.
7. Further uncertainty analysis (including probabilistic sensitivity analysis) is required to explore the robustness of our preliminary conclusions and to prioritise any areas for further research or modelling.
8. There appears to be limited quantified evidence in the public domain describing the natural history of diabetes before clinical detection. Further work to understand this would increase confidence in the estimated time between potential screen detection and clinical detection.
9. Further work to refine central estimates for some parameters (such as CHD risk reduction resulting from HbA_{1c} reductions) would be useful, possibly using expert elicitation.

Further work is also needed to establish the overall cost-effectiveness if diabetes screening is incorporated into a comprehensive risk reduction strategy that includes assessment and management of overall risk of CVD, including assessment and management of IGT. However, it seems plausible that including assessment of glycaemia as an element of a cardiovascular risk assessment and risk reduction intervention would prove cost effective:

1. given the additional benefits (from reduction in long-term complications) from earlier intervention in individuals at significant risk of CVD due to IGT and other associated risk factors and
2. assuming the availability of cost-effective interventions to offer to those identified as being at risk.

Background to methods

Modelling of treatment and outcomes post-diagnosis

We have developed a patient-level Markov simulation model following the lifetime clinical pathways of T2DM patients from diagnosis. Patients' attributes include age, sex, ethnicity, smoking and baseline levels of HbA_{1c}, cholesterol and blood pressure.

Each period, patients have their metabolic variables monitored (which can be varied, but usually 6-monthly or yearly) and if they exceed thresholds on blood pressure or glucose control, patients' therapies are re-examined and switched to the next therapy in a defined sequence; hence the model can compare alternative therapy sequence strategies in addition to alternative tighter or looser control and monitoring of metabolic variables.

The risks of fatal and non-fatal events associated with the key diabetes co-morbidities are examined each period using published evidence on risk. The co-morbidity modules are heart disease, stroke, diabetic retinopathy, nephropathy and neuropathy. These work in parallel and independently, so that any individual patient may have a number of co-morbidities at the same time.

Patients' quality of life is measured based on published evidence of utility values of all of the health states concerned. This enables a final result of overall survival and QALYs to be calculated. Similarly, costs of drugs, monitoring and related co-morbid clinical events are included and tracked, enabling a lifetime cost to be quantified.

Risk factors and treatment for screening detected cases in treatment model

Modelling the screening arm involves running the model in the usual way, with characteristics of

true-positive patients at screening forming the baseline characteristics at diagnosis in the treatment model.

- Cholesterol: following the results of the Heart Protection Study showing that statin therapy is beneficial in diabetics regardless of baseline cholesterol levels,[79] the model assumes that all patients with diabetes will be prescribed statins on diagnosis, and benefit from a 30% cardiovascular risk reduction (Waugh N, University of Aberdeen; personal communication).
- BG: it is assumed that patients are initially treated with diet and exercise followed by monotherapy, then combination oral agents followed by the addition of insulin. Patients progress to the next line of therapy if their HbA_{1c} exceeds the specified threshold in the treatment model, namely 7.5%. The annual HbA_{1c} changes are based around (a) an equation derived from UKPDS results[58] to link HbA_{1c} falls during 3 months' diet and exercise treatment to the level at diagnosis and (b) the equation provided in UKPDS 68,[158] which relates annual changes to HbA_{1c} levels at randomisation and levels in the previous year.
- Smoking: smoking status at baseline is included in the risk calculations. The UKPDS 68 model[158] gives a hazard ratio of 1.4 for current smokers versus non-smokers. We have no information on which to incorporate any changes in smoking behaviour resulting from a diagnosis of diabetes. Adoption of interventions to increase smoking cessation at diagnosis of diabetes would enhance the clinical benefits of screening but entail additional costs.
- Blood pressure: the same threshold is assumed for starting antihypertensive therapy as for clinically detected patients, i.e. 135 mmHg.
- Aspirin efficacy: aspirin is assumed to be taken where the 10-year CHD risk exceeds 15%. The associated risk reduction achieved in primary CHD prevention in patients with diabetes is uncertain, but analyses suggest some benefit.[240] The present model uses a modest default 5% CHD risk reduction as there is no clear evidence that the benefit observed in non-diabetic people is mirrored in diabetic patients. If the risk is significantly greater, this could increase the effectiveness of screening because it would provide further benefit during the preclinical period at negligible additional cost.

Use of relative risk reductions

Where multiple RRs are applied to reflect the effect of statins, HbA_{1c} reductions, aspirin therapy and so on, these have been applied on a multiplicative rather than additive basis.

Calculation of diabetes prevalence in specified population

The total prevalence of T2DM for the population specified by the age, gender and ethnicity variables is obtained from a link to the PBS Prevalence Model[3] (Yorkshire and Humber Public Health Observatory). These calculations have been adjusted to calculate only T2DM prevalence, excluding the type 1 diabetes population.

There are options to filter patients further according to hypertensive status and BMI levels. Adjustments to the prevalence from the PBS model are made using the following RRs:

- RR for diabetes if hypertensive = 1.67, which is estimated from the RRs in the reports in the KORA survey[206] and the Inter99 Study.[241]
- RR for diabetes per unit BMI = 1.25 (based on internal review[242]).
  Where both hypertensive and BMI criteria are specified, these two RRs have been multiplied together and then multiplied by a factor of 0.67 to make a rough adjustment for the correlation between hypertension and obesity, which was estimated from the univariate and multivariate relative risk reported in the Inter99 study.[241]

Chapter 6
Discussion

The aims of screening

As discussed earlier, the aims of screening could include:

- Detection of undiagnosed diabetes, with a view to starting treatment aimed at lowering BG levels and reducing the risk of the microvascular complications of diabetes. Treatment would start with diet and exercise, with hypoglycaemic drugs added if necessary.
- Detection of people at risk of developing diabetes, with a view to starting measures to reduce progression to diabetes. Treatment would be with diet and exercise.
- Identification of a group, comprising both of the above, who are at increased risk of macrovascular disease, and then treatment to reduce subsequent CVD. Treatment would include reduction of BG as above, but control of hypertension and reduction of hyperlipidaemia would probably be more important. A further benefit would arise from treatment of hypertension with ACEIs and ARBs, which would prevent progression to diabetes in some people.
- An additional reason for screening might be that even in those individuals already identified as at high cardiovascular risk, knowledge of the additional risk due to diabetes/hyperglycaemia may motivate individuals to act to reduce risk by increasing the perceived benefit (versus inconvenience/personal cost) of lifestyle change or taking medication – that is, the value of the information to the individual rather than the clinician.

Diabetes and IGT confer an increased risk of macrovascular disease, but the increase with IFG is much less. Hence if the main aim is to reduce future heart disease, detecting IFG is less important. This has implications for the screening test. It makes FPG less attractive. The remaining options are then the OGTT (reduced to a 2-hour challenge test after 75 g of glucose) or HbA_{1c}.

In favour of HbA_{1c} test is that it is simpler to perform than the 2-hour OGTT and is more reproducible, and that we have data from the Norfolk Study showing that it is associated with CVD across a wide spectrum.

As Goyder and Irwig[10] pointed out, people with diabetes detected by screening are at high risk of macrovascular disease but at comparatively low risk of microvascular disease. In the UKPDS, those whose diabetes was asymptomatic had lower FPG and fewer microvascular complications at diagnosis and were at lower risk in the years which followed (admittedly, not all had diabetes – the entry criterion was FPG over 6 mmol/l).

Could it be argued that in people known to be at high risk of heart disease, because of factors such as hypertension, high cholesterol levels and overweight, that testing BG level would provide little additional benefit, since they should already be treated with antihypertensive agents, diet and statins? (Diet because it helps reduce both cholesterol and blood pressure.) Many of this group would be able to control their hyperglycaemia on diet alone.

Arguments against such a position is that they are at some risk of microvascular disease at diagnosis, that the natural history of the disease is that beta-cell failure appears progressive (UKPDS 16),[243] that most require additional antihyperglycaemic therapy over time (UKPDS 16)[243] and that the marginal cost of adding an FPG or an HbA_{1c} test is low when fasting blood is being taken for lipid estimation anyway.

Screening interval

Assuming the first screen is at age 45 years, when should people be rescreened? Rather than have a fixed interval for all, the second screen could depend on the result of the first. If an HbA_{1c} level of 6% is taken as the threshold for intervention (at that level, with diet, exercise and monitoring over time), and if it is assumed that HbA_{1c} rises by 0.2% per year (in those in whom it does rise), then the interval in years could be

$$6.0 - HbA_{1c} \text{ at age } 45/0.2$$

Those whose HbA_{1c} had not risen at second screen could be reassured and not recalled. The recall interval could be based on rate of rise. If the age expected to reach an HbA_{1c} of 6% or more was

over 70 years, then perhaps they could also be discharged (on the grounds that screening for diabetes at age over 70 years is not worthwhile).[102]

However, the above arguments make an assumption that rise in HbA_{1c} is linear. This is not known, and given that the rate of rise may vary amongst patients, and that it may not be linear, it would probably be safer to recall at a fixed interval for the first two rounds of screening. The resulting data should then provide the evidence base for future recall policy.

At present there are insufficient data on which to base any screening interval. A pragmatic approach might be to screen by risk factors at age 45 years, screen by BG in those who were risk-factor positive and then re-screen a random sample of BG-negative people at, say, 5 years as part of a research project.

Research needs

1. Research is needed into ways of reducing the prevalence of insulin resistance. More research is also needed into which forms and amounts of exercise are effective in reducing hyperglycaemia and the effect on cardiovascular risk. Why do some people become insulin resistant when overweight whereas others do not? Is exercise the key factor?
2. The main need is to find ways of achieving compliance with diet and other lifestyle measures in order to reduce overweight and obesity. How can public health campaigns be made more effective?
3. In the UKPDS, HbA_{1c} rose in all treatment groups. However, the groups included those who gained and those who lost weight. Research is needed into whether the rise over time is seen also in those who reduce weight and take exercise. Would return to normal weight, or close to it, coupled with regular exercise to reduce insulin resistance, abort the beta-cell failure over time?
4. If screening is to be introduced, should it be one-off; if not, what should the interval be? Data are needed on the rise in glucose over time, and whether it is linear.
5. If blood is being taken for glucose measurement, what other investigations would be cost-effective at the same time? A lipid profile for HDL, LDL and triglycerides?
6. Where should screening stop? Should it be for undiagnosed diabetes, or that plus IGT, or for the wider metabolic syndrome? What cut-off should be used, to strike the optimum balance amongst sensitivity, specificity and what the NHS can cope with?
7. What is the optimum balance between the clinical approach of identifying and treating individuals and the public health approach of intervention at population level?

Some of the public health questions will be addressed by the Public Health appraisal function now taken over by NICE. The appraisals will inevitably pose another broad question:

8. Which public health or health promotion interventions are not cost-effective and should be stopped? These may include current *ad hoc* screening activities that could be stopped or targeted more efficiently.

Research currently under way includes:

- The ADDITION study – do screening and early diagnosis and intervention reduce cardiovascular risk? (Griffin S and Khunti K: personal communication, 2005).
- The Whitehall Study, which should yield information on the potential benefits of screening (Brunner E: personal communication, 2005).
- The Diabetes Heart Disease and Stroke Prevention Study of screening in a routine setting, including in less affluent areas, and those with a high proportion of ethnic minorities, is already showing differences in uptake of screening, and in percentages of people with new diabetes (Goyder E: personal communication, July 2005).
- The 1958 Birth Cohort Study, which is examining risk scores and their marginal benefits over simply using BMI, and also regional variations in prevalence (Power C: personal communication, 2005).

Does screening for diabetes and IGT meet the NSC criteria?

The UK NSC criteria for evaluating screening programmes were adapted from the WHO criteria published in 1968.[244] The criteria are published by the NSC on their website (http://www.nsc.nhs.uk/pdfs/criteria.pdf).

This section applies the criteria to screening for diabetes and lesser degrees of glucose intolerance and summarises the evidence presented in the previous chapters. Our view on the extent to which the criteria are satisfied is appended in bold at the end of the text on each criterion.

The condition

Criterion 1. The condition should be an important public health problem

Whether the problem is defined as diabetes, all degrees of glucose intolerance, the metabolic syndrome or even wider as overweight and obesity, it is an important public health problem. The level of individual risk will vary according to the scope of the definition – in some cases at the margin, the individual health problem, in terms of excess risk, will be slight. However, because of the very large numbers involved, even slight increases in risk amount to a major public health problem. The 'Rose principle' applies here – there is more to be gained from a leftward shift in the population risk, even if the individual benefits are small, compared with only identifying those at the high-risk right end of the population curve.[245] However, both approaches can be applied.

Criterion met.

Criterion 2. The epidemiology and natural history of the condition, including development from latent to declared disease, should be adequately understood and there should be a detectable risk factor, or disease marker, and a latent period or early symptomatic stage

This was discussed at length in Chapter 1. There are several uncertainties about natural history:

- Is the progression to diabetes linear throughout, or is there a slow initial phase followed by a faster decline in beta-cell function? This would affect screening interval.
- Why do some people with IGT progress to diabetes, whereas about half return to normality? What do the half do that ensures improvement?
- Is the progression always IGT, then IFG, then diabetes? Or are there two pathways?
- In people diagnosed with T2DM, is progression inevitable as shown in UKPDS overall – or do those who lose weight and take exercise have much slower progression, or indeed regression to normal, as shown in the Malmo trial?

However, answers to all of these questions are not needed before screening can start. Enough is known about natural history on a population basis (for example, a sizeable minority of those with IGT will progress to diabetes; many with undiagnosed diabetes will be developing retinopathy; many people with diabetes will have advancing but asymptomatic heart disease, the first manifestation of which may be a fatal MI).

Criterion met.

Criterion 3. All the cost-effective primary prevention interventions should have been implemented as far as practicable

Primary prevention of T2DM involves several aspects:

- Public health campaigns to encourage the public to avoid overweight and take exercise. A review of the evidence on interventions at population level is outwith the scope of this review.
- Intervention on a personal basis in those who can be identified as being at higher risk of T2DM, such as those with IGT as already mentioned. There is good trial evidence that this can be effective, and our review of the economic evidence shows that intervention is cost-effective, but that refers to prevention of diabetes alone.

The main problem with public health measures is not cost-effectiveness (most campaigns would be inexpensive because they are delivered to large numbers) but clinical effectiveness. There have been many campaigns at varying levels, from mass media campaigns about healthy eating to local initiatives at health authority level such as trying to encourage people to 'walk about a bit'. Yet the prevalence of overweight and obesity continues to rise. The research need arising from this has been mentioned above. We know that lifestyle measures **can** work; if they do they would be cost-effective (measures such as diet and exercise being largely cost free to the NHS).

Criterion met? For diabetes, yes. For IGT and IFG, unproven. Prevention certainly possible in theory.

Criterion 4. If the carriers of a mutation are identified as a result of screening, the natural history of people with this status should be understood, including the psychological implications

Not applicable.

The test

Criterion 5. There should be a simple, safe, precise and validated screening test

As discussed in Chapter 3, screening would be two stage – assessment of risk by 'questionnaire' but with most of the necessary data already held on general practice computer systems; and then BG measurement in those at higher risk. The decision on the risk level at which to intervene would be influenced by the capacity of the service to cope with those newly diagnosed.

There have been various ways of achieving the first stage, and the debate is not about validation

but about the marginal benefits of adding or removing additional items.

For the second stage, there are three acceptable tests – FPG, OGTT and HbA_{1c}. All are safe, precise and validated. However, each has its advantages and disadvantages. OGGT is inconvenient, poorly reproducible and has to be repeated, and would probably not qualify as simple. FPG requires people to fast, compliance may be imperfect and those with isolated IGT would be missed. HbA_{1c} is more expensive but can be done at any time of day and reflects glycaemia over a period of several months.

But the debate is about which test is best – all are acceptable.

Criterion met.

Criterion 6. The distribution of test values in the target population should be known and a suitable cut-off level defined and agreed

The distribution of test values is known from population-based research studies. The cut-off level depends on whether screening is for diabetes, diabetes plus IGT or wider. The case for screening for metabolic syndrome is unproven pending further research. Hence it could be assumed that screening is only for diabetes and IGT, using HbA_{1c} or the 2-hour PG. The cut-off would be for debate, partly influenced by what it was felt the NHS could cope with, but might be based more towards the levels shown to increase risk in the EPIC Norfolk study, rather than the HbA_{1c} of 7% suggested on the basis of being the level at which pharmacological treatment might be necessary.

Criterion met.

Criterion 7. The test should be acceptable to the population

The evidence is that the test is acceptable to many, but not all. For example, unpublished data from the Leicester ADDITION study shows a poor uptake (Griffin S and Khunti K, ADDITION Study Group, Cambridge and Leicester: personal communication, July 2005), although that was in the context of a trial and may have been affected by an information overload imposed by ethics committees. There seems to be a wish on behalf of Diabetes UK, the key consumer organisation, for screening to be provided.

In any case, screening would be offered, and those who did not wish it would not need to accept.

Criterion met.

Criterion 8. There should be an agreed policy on the further diagnostic investigation of individuals with a positive test result and on the choices available to those individuals

There is agreement on further investigation, with the key rule being that one abnormal glucose level should always be confirmed. In asymptomatic people, diabetes should not be diagnosed on the basis of one result. If the initial screening test was HbA_{1c}, the follow-up test could be an FPG, for simplicity. If that was normal, a 2-hour post-load PG could be sought.

Criterion met.

Criterion 9. If the test is for mutations, the criteria used to select the subset of mutations to be covered by screening, if all possible mutations are not being tested, should be clearly set out

Not applicable.

The treatment

Criterion 10. There should be an effective treatment or intervention for patients identified through early detection, with evidence of early treatment leading to better outcomes than late treatment

The question of which condition is to be screened for is less important here, because initial treatment for T2DM, IGT and the metabolic syndrome would be the same – diet and exercise. Statins might be added.

There is a good evidence base for treatment of diabetes itself. Several trials have shown that the progression to diabetes from IGT can be reduced by lifestyle changes or drug treatment (see Appendix 3). Lifestyle changes can also improve control of diabetes. A meta-analysis of the effects of exercise[246] showed that it reduced HbA_{1c} by a clinically significant amount of 0.66% (which is not far off the difference between the intensive and control groups in UKPDS). Interestingly, the benefit of exercise was achieved without weight loss.

Other aspects of management of diabetes include screening for complications; the case for eye screening is beyond doubt and has been addressed by previous NSC policy considerations.

The key issue is whether treatment earlier in the disease process is better than later treatment once the condition has become symptomatic. The aim of treatment is to prevent the complications of

diabetes. Some people have retinopathy at diagnosis (UKPDS) but rarely to a sight-threatening stage, so earlier treatment is unlikely to prevent more visual loss than later. Similarly, nephropathy takes time to develop.

However, vascular disease is the main risk in the group which would be affected by screening. IHD is often asymptomatic until an MI occurs, and the first MI may be fatal. The risk can be reduced by about one-third by statin therapy. Hence earlier treatment would have clear advantages. Many of the people in this metabolic group will have other risk factors, but the diagnosis of diabetes or IGT may result in them crossing the NICE 2% per year threshold, and being treated with a statin.

In the absence of RCTs of screening versus no screening, we have to try to obtain evidence on whether earlier treatment gives better outcomes from other studies. Data from the UKPDS have been used for this purpose[58] by examining outcomes according to FPG at diagnosis. Those in the lowest tertile of initial FPG were more likely to be asymptomatic and found by screening (such as insurance or employment medical examinations). They had less retinopathy at diagnosis and had fewer complications during the study. However, this may just mean that they were at an earlier stage of the disease – lead time bias. It could also be because they had a milder form of the disease, but their rise in PG over time was similar to that in the other groups, so that seems unlikely. Nevertheless, they were diagnosed with fewer complications, and there is scope to reduce the future development of complications by intervention.

Criterion met.

Criterion 11. There should be agreed evidence-based policies covering which individuals should be offered treatment and the appropriate treatment to be offered

Initial treatment would be diet and exercise, and monitoring for progression to levels at which pharmacological treatments would be given. For statins, this might be at a risk level of 2% or more per annum, aiming at a total cholesterol of 5 mmol/l or less. For HbA_{1c}, the aim might be to keep it under 7% (ADA) or 7.5% (NICE), with metformin the first-line drug. The meglitinide analogues might be considered if the problem is mainly post-prandial hyperglycaemia.

Criterion met.

Criterion 12. Clinical management of the condition and patient outcomes should be optimised in all healthcare providers prior to participation in a screening programme

Many patients with T2DM are not well controlled, and many may not be on, for example, statin therapy. Only 43% of people with diabetes in Scotland for whom an HbA_{1c} result was available for the Scottish Diabetes Survey, had an HbA_{1c} under 7.5%, the NICE guidelines target. These data also include people with type 1 diabetes, but are numerically dominated by T2DM. However, guidelines for management of diabetes have been issued by NICE, as has guidance on statin use.[86] It may take some time for these to work through the system.

Hence there is more to be done to optimise care and outcomes thereof for existing patients, and it could be argued that they should take first priority. Adding an additional load of new patients would make it more difficult to achieve this.

Criterion not met.

The screening programme

Criterion 13. There should be evidence from high-quality randomised controlled trials that the screening programme is effective in reducing mortality or morbidity

As yet, no RCTs of screening for diabetes have been reported. However, one is under way. The ADDITION Study is an RCT of systematic screening and targeted cardiovascular risk reduction in primary care, being carried out in Cambridge, Denmark and the Netherlands.[95] However, the screening phase was not due to be completed until late 2006, after which there will be a 5-year follow-up period. Hence results will not be available for the next review of NSC policy.

Criterion not met.

Criterion 14. There should be evidence that the complete screening programme (test, diagnostic procedures, treatment/intervention) is clinically, socially and ethically acceptable to health professionals and the public

Screening would only be offered, not imposed, and details of follow-up investigations and treatments would be included with the invitation. Hence only those who found the complete programme acceptable would attend for screening.

Criterion met.

Criterion 15. The benefit from the screening programme should outweigh the physical and psychological harm (caused by the test, diagnostic procedures and treatment)

Any screening programme has the potential to convert a healthy person into 'a patient'. Being labelled as diabetic could cause anxiety, in addition to possibly having adverse effects on some forms of employment (although that is more of a problem with insulin-treated diabetes). The anxiety would depend on the perceived seriousness of diabetes to the newly diagnosed person.

In the Hoorn study,[106] the psychological impact of screening was assessed by qualitative methods (semi-structured interviews) in 20 patients newly diagnosed (mean age 62 years) and 20 at increased risk of diabetes but who tested negative. The main limitation of the study was the small numbers involved. The results indicate that the fact of the diagnosis caused little alarm. This may have been, as the authors report, because only one of the new diabetic patients regarded the disease as serious, and because about half felt that they had control, in the sense that they believed they could take effective action to deal with it, such as dieting. Their mean BMI was 28.6 kg/m^2, so their belief seems justified.

More harm might ensue in the group who were at risk but who tested negative. Adriaanse and colleagues[106] note that this group may have been so reassured by the result that they saw no reason to adjust their lifestyles.

Criterion met? Uncertain.

Criterion 16. The opportunity cost of the screening programme (including testing, diagnosis and treatment, administration, training and quality assurance) should be economically balanced in relation to expenditure on medical care as a whole (i.e. value for money)

The economic analysis suggests that screening for IGT and prevention of diabetes would be cost-effective, although not all costs have been identified. If screening was, as assumed, based in primary care, there would presumably be a form of target or points-based systems to remunerate practices. The cost of the programme would depend on the number of people invited for screening and the response rate. Screening might only be offered to those with BMI 30 kg/m^2 or over, although any such cut-off would be an arbitrary line in a continuum of risk. The modelling exercise in Chapter 5 shows that screening would be more cost-effective in the obese or the hypertensive, but not dramatically so.

Criterion met.

Criterion 17. There should be a plan for managing and monitoring the screening programme and an agreed set of quality assurance standards

Not applicable until a decision is made in principle to provide screening. A quality assessment system for HbA_{1c} exists.

Not applicable.

Criterion 18. Adequate staffing and facilities for testing, diagnosis, treatment and programme management should be available prior to the commencement of the screening programme

Primary care services and diabetes clinics are already under pressure. It is unlikely that they could cope with a large extra load at present. Screening could be brought in slowly, and a high threshold for positivity used, at least in the early stages.

Criterion not met.

Criterion 19. All other options for managing the condition should have been considered (e.g. improving treatment, providing other services), to ensure that no more cost-effective intervention could be introduced or current interventions increased within the resources available

The main option other than screening would be a public health programme to encourage people to keep weight down and take exercise. The rise in overweight and obesity implies that past and present public health campaigns have failed. Is it worth trying harder, or trying new options such as 'exercise prescriptions'? Is there a danger of 'medicalising' unhealthy life style and reducing the emphasis on personal responsibility for health?

It was noted that the best way to identify people for screening would be to identify them from general practice records. Instead of inviting them for screening, the data could be used for targeted health promotion interventions such as for weight loss or exercise.

Criterion met? Uncertain.

20. Evidence-based information, explaining the consequences of testing, investigation and treatment, should be made available to potential participants to assist them in making an informed choice.

The evidence exists and would be supplied when people were being invited to attend.

Criterion met.

Criterion 21. Public pressure for widening the eligibility criteria for reducing the screening interval, and for increasing the sensitivity of the testing process, should be anticipated. Decisions about these parameters should be scientifically justifiable to the public

The problem here might be that the decisions of screening policy, such as whom to invite, would depend partly on cost-effectiveness aspects, which may not be understood by the public.

Criterion met? Uncertain

Criterion 22. If screening is for a mutation the programme should be acceptable to people identified as carriers and to other family members

Not applicable.

Summary

Of the 22 criteria:

- 12 are met.
- Three are not met.
- In three there is uncertainty.
- Four are not applicable.

Conclusions

Targeted screening for T2DM meets most but not all of the NSC criteria. The main failure is that there is no RCT of screening. Screening also appears to be cost-effective.

However, several issues need to be resolved. The main aim of screening would be to reduce CVD, and that is increased not only in diabetes but also in IGT, and to a lesser extent in IFG. Depending on which test for BG was used and what cut-off was used to define 'positives', many more people with IGT would be found than with diabetes. A decision is needed on what to do for them.

The first national policy decision might therefore be whether to screen for diabetes, or to have a broader, integrated approach to reduction of CVD. The next decision might be the balance of investment in public health/health promotion measures, versus individual screening and care.

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Contribution of authors

Norman Waugh (Professor of Public Health) was responsible for Chapters 1–3 and 6 and for the final draft of the whole report. Graham Scotland (Research Fellow) and Paul McNamee (Senior Research Fellow) reviewed the previous economic models in Chapter 4. Mike Gillett (Operational Research Analyst), Elisabeth Goyder (Senior Lecturer in Public Health) and Alan Brennan (Director of Health Economics and Decision Science) were responsible for the new economic modelling in Chapter 5. Rhys Williams (Professor of Clinical Epidemiology) and Ann John (Specialist Registrar in Public Health Medicine) reviewed the literature on prevention of type 2 diabetes in Appendix 3. Chapters were exchanged for internal review. Elisabeth Goyder reviewed Chapters 1–3. Graham Scotland and Norman Waugh reviewed Chapter 5.

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Appendix 1

Search strategies

MEDLINE

1. exp *Diabetes Mellitus, Type 2/
2. exp Mass Screening/
3. (diabetes and screening).m_titl.
4. 1 and 2
5. 1 and 3
6. 4 or 5
7. limit 6 to (english language and yr="2000 – June 2005")

EMBASE

1. exp *Non Insulin Dependent Diabetes Mellitus/
2. exp Mass Screening/
3. (diabetes and screening).m_titl.
4. 1 and 2
5. 1 and 3
6. 4 or 5
7. limit 6 to (english language and yr="2000 – June 2005")

The Cochrane Library 2005, Issue 2 – all sections

#1 MeSH descriptor Diabetes Mellitus, Type 2 explode all trees in MeSH products
#2 MeSH descriptor Mass Screening explode all trees in MeSH products
#3 (#1 AND #2)
#4 screening in Record Title and diabetes in Record Title in all products
#5 (#3 OR #4)

Appendix 2
The NSC criteria

The UK NSC criteria for evaluating screening programmes were adapted from the WHO criteria published in 1966. The criteria are published by the NSC on their website (http://www.nsc.nhs.uk/pdfs/criteria.pdf).

The condition

1. The condition should be an important health problem.
2. The epidemiology and natural history of the condition, including development from latent to declared disease, should be adequately understood and there should be a detectable risk factor, disease marker, latent period or early symptomatic stage.
3. All the cost-effective primary prevention interventions should have been implemented as far as practicable.
4. If the carriers of a mutation are identified as a result of screening the natural history of people with this status should be understood, including the psychological implications.

The test

5. There should be a simple, safe, precise and validated screening test.
6. The distribution of test values in the target population should be known and a suitable cut-off level defined and agreed.
7. The test should be acceptable to the population.
8. There should be an agreed policy on the further diagnostic investigation of individuals with a positive test result and on the choices available to those individuals.
9. If the test is for mutations the criteria used to select the subset of mutations to be covered by screening, if all possible mutations are not being tested, should be clearly set out.

The treatment

10. There should be an effective treatment or intervention for patients identified through early detection, with evidence of early treatment leading to better outcomes than late treatment.
11. There should be agreed evidence-based policies covering which individuals should be offered treatment and the appropriate treatment to be offered.
12. Clinical management of the condition and patient outcomes should be optimised in all healthcare providers prior to participation in a screening programme.

The screening programme

13. There should be evidence from high-quality RCTs that the screening programme is effective in reducing mortality or morbidity.
14. There should be evidence that the complete screening programme (test, diagnostic procedures, treatment/ intervention) is clinically, socially and ethically acceptable to health professionals and the public.
15. The benefit from the screening programme should outweigh the physical and psychological harm (caused by the test, diagnostic procedures and treatment).
16. The opportunity cost of the screening programme (including testing, diagnosis and treatment, administration, training and quality assurance) should be economically balanced in relation to expenditure on medical care as a whole (i.e. value for money).
17. There should be a plan for managing and monitoring the screening programme and an agreed set of quality assurance standards.
18. Adequate staffing and facilities for testing, diagnosis, treatment and programme management should be available prior to the commencement of the screening programme.
19. All other options for managing the condition should have been considered (e.g. improving treatment, providing other services), to ensure that no more cost-effective intervention could be introduced or current interventions increased within the resources available.
20. Evidence-based information, explaining the consequences of testing, investigation and treatment, should be made available to potential participants to assist them in making an informed choice.

21. Public pressure for widening the eligibility criteria for reducing the screening interval, and for increasing the sensitivity of the testing process, should be anticipated. Decisions about these parameters should be scientifically justifiable to the public.

22. If screening is for a mutation, the programme should be acceptable to people identified as carriers and to other family members.

Appendix 3

Management of impaired fasting glucose and impaired glucose tolerance

Early detection and primary prevention of type 2 diabetes

This section starts by looking at the conclusions of reviews published since the last NSC review of the topic; then at primary studies published since then; and lastly at studies on the management of 'prediabetes'.

Background (reviews of studies published prior to 2002)

Two of the reviews mentioned in this opening section are chapters contained in Williams and colleagues.[247] They are not, in the true sense of the term, 'systematic reviews' in that they were not planned and carried out according to guidelines such as those advocated by the Cochrane Collaboration. Nevertheless, they provide a reasonably comprehensive and critical coverage of the literature up until the date of publication of that text. The third is a consensus statement issued as part of the WHO (World Health Authority) diabetes programme. It was the result of the deliberations of an expert group which met in May 2002 in Geneva.

'Prevention of type 2 diabetes', RF Hamman[248]

The work cited by Hamman is summarised in *Table 23* and the studies that he cited in *Table 24*. His overall summary of this body of evidence was as follows:

> SUMMARY
> The available data now provide a firm answer that type 2 diabetes can be delayed or prevented in high-risk subjects. Trials currently underway should provide substantial evidence about the impact of specific pharmacologic interventions on diabetes prevention.
>
> With the current level of information, it is reasonable to recommend a programme of moderate levels of physical activity, weight maintenance or modest weight loss (for overweight people), and a low-fat, calorie-moderated diet for the positive effects this will have on cardiovascular and other risks for large numbers of people. In addition, subjects at high risk should have specific risk factors for cardiovascular disease treated (e.g. lipids, blood pressure). The recent results from ACE-inhibitor trials suggest that such agents may also lower diabetes risk as an important benefit.

The phrase "… for the positive effects this will have on cardiovascular and other risks for large numbers of people." is interesting in the light of the fact that very few of the studies identified had cardiovascular risk factors as primary end-points. These included RCTs carried out as a follow-up to the Bedford study[249,250] in which tolbutamide (500 mg twice daily) with and without dietary advice was compared with placebo with and without dietary advice. No significant differences were found between any of the groups. Paasikivi[251] investigated the same dose of tolbutamide versus placebo and found that the difference in CVD mortality seen at 18 months did not persist beyond that time. The Malmöhus study,[252] which made similar comparisons, found no significant differences in CVD mortality.

'The evidence to screen for type 2 diabetes', Engelgau and Narayan[253]

Table 25 provides a summary of the results (costs in US dollars and cost per QALY gained) derived from the lifestyle simulation model described in their reference 76 (CDC Diabetes Cost-Effectiveness Study Group, 1998).[131] These results and scrutiny of other evidence as it was then led to the following conclusions:

> CONCLUSIONS
> The effectiveness of diabetes screening has not been directly demonstrated. Indirect examination of the potential benefits of screening using data from RCTs of treatment of diagnosed diabetes, observational studies and disease models lend some support to the idea that early improvement in glycaemic control may help reduce the lifetime occurrence of microvascular disease. There is little convincing evidence that there will be macrovascular disease reductions. The physical, psychological and social effects of screening and early diagnosis and treatment remain unclear. Thus, on balance, there is only modest evidence, at best, supporting screening for type 2 diabetes. (Level of evidence II-3; Strength of Recommendation B.)

TABLE 23 *Search strategy and results*

Search question: To identify existing guidelines for prediabetes/T2DM: prevention, screening, early identification	
Keywords – thesaurus/free text/MeSH	Prediabetes, prediabetic state, type 2 diabetes, non-insulin-dependent diabetes mellitus, prevention and control, primary prevention, screening, impaired glucose tolerance, impaired fasting tolerance
Publication types – guidelines, systematic reviews, press releases, conference proceedings, published statistics, etc.	Studies, reviews or best evidence only
Limitations	
Language	English
Dates covered	1999 →
Non-UK	Worldwide
Other limitations	–
Sources of information	
Evidence-based resources including Cochrane, Clinical Evidence and guidelines	
Public health and health management and knowledge bases (HMIC , NPHS Library catalogues	HMIC
Clinical databases (MEDLINE, EMBASE, CINAHL)	MEDLINE, EMBASE
Specialist databases Grey Literature Sources (SIGLE, HMIC), specific Databases (Dissertation Abstracts, NRR Research Registers and ASSIA, CRD)	
Internet – health gateways – OMNI	
Specialised collections relevant to topic (Royal Colleges, professional Associations)	
UK Health Departments	
Affiliated organisations – HPA, HP	
Wider NHS – NeLH, PHOs, HDA	
Non-NHS – LAs, academia	
European/international authoritative sources – EU, WHO	
Expert opinion Frequently cited authors within specialist field, colleagues, E-bulletin boards (project work details)	

Search results
EMBASE

	Search history	Results
1	prediabetes.mp. or *Impaired Glucose Tolerance/	1,165
2	"PREVENTION AND CONTROL"/ or PRIMARY PREVENTION/	5,385
3	1 and 2	7
4	limit 3 to (human and english language and yr=1999–2004)	6
5	from 4 keep 1–3	3
6	*SCREENING/	3,907
7	Non Insulin Dependent Diabetes Mellitus/ or type 2 diabetes.mp.	32,844
8	(7 or 1) and 6	21
9	8	21
10	limit 9 to (human and english language and yr=1999–2004)	4
11	from 10 keep 1–2	2

continued

TABLE 23 *Search strategy and results (cont'd)*

MEDLINE		
	Search history	**Results**
1	Mass Screening/	20,579
2	Prediabetic State/or prediabetes.mp.	310
3	*DIABETES MELLITUS, TYPE II/pc [Prevention & Control]	676
4	2 or 3	972
5	*PRIMARY PREVENTION/	1,692
6	(2 or 3) and (5 or 1)	91
7	limit 6 to (human and english language and yr=1999–2004)	48
HMIC		
	Search history	**Results**
1	prediabetes.mp. or exp PREDIABETIC STATE/	2
2	exp DIABETES/	834
3	prevention.mp. or exp PREVENTIVE MEASURES/	12,489
4	exp SCREENING/	2,750
5	type 2.mp.	124
6	1 and (3 or 4)	0
7	impaired glucose.mp.	17

TABLE 24 *Studies cited by Hamman*[248]

1. Intervention: combined lifestyle interventions (mainly dietary modification aimed at weight loss and increased physical activity)				
Type	**Study group**	**Outcome**	**No. of studies**	**References**[a]
Randomised trials	Normal glucose tolerance	Glucose	9	45–50, 52–54, 56, 63, 64, 67, 280
	Overweight, normal glucose tolerance	Glucose	2	60, 62
	Hyperinsulinaemia	Glucose	2	43, 44
	Glucose intolerance	Diabetes	1	42
	IGT	Diabetes	3	55, 59, 68, 69
Non-randomised trials or cohort studies	Glucose intolerance	Diabetes	1	73
	IGT	Diabetes	1	57
	IGT	Mortality	1	77
	Family history of diabetes	Diabetes	1	78,79
2. Intervention: physical activity alone				
Type	**Study group**	**Outcome**	**No. of studies**	**References**[a]
Randomised trials			None	
Non-randomised trials or cohort studies	Various (mostly mixtures of subjects with normal and abnormal glucose tolerance)	Diabetes	19	76, 103–111, 113, 114, 116–122, 125

continued

TABLE 24 *Studies cited by Hamman[248] (cont'd)*

3. Intervention: dietary modification alone				
Type	**Study group**	**Outcome**	**No. of studies**	**References[a]**
Randomised trials			None	
Non-randomised trials			None	
Cohort studies	Various (mostly mixtures of subjects with normal and abnormal glucose tolerance)	Diabetes	20	5, 107, 114, 123, 140–143, 146–150, 154, 155, 157–159, 161, 162, 238
4. Intervention: pharmacological agents (with or without lifestyle modification)				
Type	**Study group**	**Outcome**	**No. of studies**	**References[a]**
Tolbutamide vs placebo	Glucose intolerance	Glucose, diabetes or mortality (one study[190,192,194] – Bedford study – had CVD as outcome)	5	181, 184–186, 190, 192, 194, 196, 197
Tolbutamide vs phenformin vs placebo	Glucose intolerance	Diabetes	1	187, 188
Chlorpropamide vs tolbutamide vs phenformin	Glucose intolerance	Normalisation of glucose tolerance	1	195
Glicazide vs placebo	IGT, IFG or fasting hyperglycaemia	Glucose tolerance	2	56, 199, 281
Glibenclamide (G) vs Biguanide (B) vs G + B vs placebo	Glucose intolerance	Glucose tolerance	1	202
Phenformin vs placebo	Glucose intolerance	Diabetes	1	204, 205
Phenformin + diet	Glucose intolerance	Glucose tolerance	1	206
Metformin vs placebo	High waist:hip ratio; subjects with IGT or IGT + overweight or obesity	Glucose tolerance, lipids, diabetes	4	70–72, 207–210, 212
Troglitazone vs placebo	Normal, overweight or IGT or GDM	Glucose or diabetes	5	216, 218, 217, 221, 220
Acarbose vs placebo	IGT	Diabetes	2	222, 223
Captopril vs 'conventional' treatment (for hypertension)	Hypertensive patients	Diabetes	2	224, 226
Ramipril vs placebo	Mixed normal and hypertensive	Diabetes	1	225
Pravastatin vs placebo	Non-diabetic men with elevated cholesterol	Diabetes	1	240

[a] These are references numbered as in the original review,[248] not in the present report.

TABLE 25 *Effectiveness of screening for type 2 diabetes from lifestyle simulation models*

	Lifetime cumulative incidence (%)			LYG	QALYs gained	Cost (US$)	
	ESRD	Blindness	LEA			Per LYG	Per QALY gained
Total population age ⩾25 years							
Without screening	3.5	9.1	4.6				
With screening	2.6	5.9	3.6				
Absolute risk reduction	0.9	3.2	1.0				
NNT	111	31	100	0.02	0.08	236,449	56,649
Total population age 25–34 years							
Without screening	19.2	32.4	19.0				
With screening	15.9	25.9	16.0				
Absolute risk reduction	3.3	6.5	3.0				
NNT	30	15	33	0.12	0.35	35,768	13,376
Total population age ⩾65 years							
Without screening	0.3	1.7	1.0				
With screening	0.2	1.1	0.7				
Absolute risk reduction	0.1	0.5	0.3				
NTT	1000	200	333	0.00	0.01	NA	575,241

NA, not applicable; NNT, number-needed-to-treat.
Adapted from Engelgau and Narayan (2002).[253]

'Screening for type 2 diabetes. Report of a WHO and IDF meeting'

The consensus report of this meeting (May 2002) led to the following conclusions and recommendations:

CONCLUSIONS

1. Screening for T2DM is important in terms of individual health, day-to-day clinical practice and public health policy.
2. There is currently no direct evidence that individuals will benefit from the early detection of T2DM through screening (direct evidence is that from RCTs specifically designed to answer questions related to early detection through screening).
3. Despite this lack of direct evidence, early detection through screening is already taking place both by inviting individuals from the general population to come forward for screening and, opportunistically, when individuals perceived to be at high risk of developing diabetes attend for healthcare (usually primary healthcare) for other reasons.
4. These activities present opportunities for collecting observational data, which, although no substitute for direct RCT evidence, can provide important, circumstantial evidence.
5. Following a demonstration of any benefits of screening, the most important **epidemiological considerations** determining whether to screen in any given population will be (a) the prevalence of undiagnosed T2DM in a population and (b) the degree to which T2DM is associated with risk of CVD and other important health outcomes in that population.
6. The most important **health systems considerations** will be the capacity (a) to carry out the screening, (b) to provide effective healthcare for those who screen positive, (c) to address the psycho-social needs of all those who undergo screening and (d) to implement effective prevention in those who, although not confirmed to have diabetes at the time, are at high risk of its future development.
7. The most important **economic considerations** are (a) the cost of early detection to the health system and to the individual, (b) the extra costs of treatment following early detection and (c) the relative cost-effectiveness of early detection compared with that of improving the care of clinically detected (as opposed to screen-detected) cases.
8. Screening for T2DM is a dynamic topic in which new evidence will become available and further considerations will arise over time.

RECOMMENDATIONS

1. Health authorities and professional organisations should formulate policies on screening for T2DM even if the policy is that screening is not currently to be advocated.
2. There is an urgent need for direct RCT evidence on the effects of early detection of T2DM through screening. (Such evidence should include health outcomes related to diabetes CVD, psychosocial outcomes and economic considerations for individuals, health systems and the wider society. Although RCTs directed to answering these questions may be costly and logistically difficult, there is, in the current state of knowledge, no ethical reason why they should not be undertaken.)

3. Since the results of such RCTs will not be available for some time (if ever), there is also an urgent need to develop a framework (or model) which would permit countries to evaluate the cost-effectiveness of the early detection of diabetes compared with other preventive and therapeutic interventions.
4. The testing of apparently unaffected individuals at increased risk of having diabetes when these individuals attend for healthcare for other reasons (sometimes called 'opportunistic screening') **may** be justified provided that (a) the reasons for testing are adequately explained to the individual, (b) the health system has the capacity for the clinical management of those who screen positive, (c) methods with adequate sensitivity and specificity are available, (d) the psychosocial needs of those who screen positive and those who screen negative can be met and (e) the health system can implement effective preventive strategies for those confirmed to be at high risk for the future development of diabetes.
5. If such opportunistic screening is being advocated, then this should be carried out according to a policy which should (a) be clear and relevant in its aims and objectives, (b) be based as far as possible on sound evidence, (c) take into account the epidemiology of T2DM and related CVD risk in the population and (d) be sensitive to competing local health priorities.
6. Where screening is already taking place, formal evaluation should be integral to these activities. The results of such evaluations could contribute to the general assessment of the value of early detection and should, when appropriate, contribute to the modification or curtailment of the local activities being evaluated.
7. Given the dynamic nature of this topic, policies for screening for T2DM must be reviewed from time to time as new evidence accumulates.

Early detection and primary prevention of type 2 diabetes (review of work published from 2002 onwards with particular emphasis on published guidelines for the detection of 'prediabetes')

Search strategy

The complete search strategy is given in *Table 23*. In brief, the search question was:

> To identify existing guidelines for prediabetes/T2DM: prevention, screening, early detection

and was of publications, available in English and published in the major databases such as Cochrane, HMIC, MEDLINE and EMBASE. The search was for items published from 1999 onwards. This summary concentrates on those published from 2002 onwards.

Summary of findings

Reviews and position statements

The ADA, in its review of the prevention or delay of T2DM,[254] concluded that there was substantial evidence that T2DM could be prevented or delayed but commented that it was "not yet known" whether the interventions (lifestyle change and/or pharmaceutical interventions) that had been shown to be successful "will cost-effectively reduce the morbidity and mortality associated with diabetes". However, it did comment that lifestyle modifications which were specifically directed towards modest weight loss and increased physical activity were likely to have additional health benefits over and above their specific effects in relation to type diabetes. It recommended "some" of the following prevention policies (listed in Table 2 of the original publication – strength of the evidence given as A–E in descending order of certainty):

- Individuals at high risk of developing diabetes need to become aware of the benefits of modest weight loss and participating in regular physical activity (A).
- Screening based on current screening guidelines for diabetes [(reference 49 in the original – Expert Committee on the Diagnosis and Classification of Diabetes Mellitus (2003)], men and women ⩾45 years of age, particularly those with BMI ⩾25 kg/m^2, are candidates for screening to detect prediabetes (IFG or IGT). Screening should be considered in younger individuals with a BMI ⩾25 kg/m^2 who have additional risk factors [given in Table 3 of the original] (B).
- In individuals with normoglycaemia, rescreening at 3-year intervals is reasonable (C).
- How to screen: screening should be carried out only as part of a healthcare office [*sic*] visit. Either an FPG test or a 2-hour OGTT (75-g glucose load) is appropriate, and positive test results should be confirmed on another day (B).
- Intervention strategy: patients with prediabetes (IFG or IGT) should be given counselling on weight loss and also instruction for increasing physical activity (A).
- Follow-up counselling appears important for success (B).
- Monitoring for the development of diabetes should be performed every 1–2 years (E).
- Close attention should be given to, and appropriate treatment given for, other CVD risk factors (e.g. tobacco use, hypertension, dyslipidaemia (A).
- Drug therapy should not be routinely used to prevent diabetes until more information is known about its cost-effectiveness (E).

Among the eight recommendations for further research, the most relevant to this review is the first mentioned [particularly the section in (our) italics]:

> What is the cost-effectiveness of a DPP-like lifestyle intervention? Are there more cost-effective strategies, and *how would they affect the morbidity and mortality associated with diabetes?* The issue of whether the preventive or delaying strategies are effective in preventing or delaying CVD is not directly tackled in this review, thus recognising the relative lack of evidence relating to the effect on CVD risk of interventions shown to be effective in preventing or delaying the onset of diabetes itself.

A further position statement issued by the ADA[255] concludes that "there is sufficient indirect evidence to justify opportunistic screening in a clinical setting of individuals at high risk". The screening test advocated for this opportunistic screening is the FPG. Again, no direct reference is made to the management of prediabetes in relation to reduction of CVD risk.

Davies and colleagues[256] reviewed the evidence with a specific focus on its relevance to the UK setting. They point out that none of the available RCTs have been carried out in the UK and question whether their findings can be replicated in the UK given possible difference in the pathophysiology of IGT (which, frankly, seems unlikely), a lower rate of progression to diabetes (which is possible) and low levels of awareness of the importance of IGT (which are documented[257,258]). The authors conclude that it is unlikely that a study of the effects on diabetes incidence or CVD outcomes of 'upstream' interventions (i.e. primary prevention measures in total populations) will ever be conducted.

Key publications 2002 onwards

In addition to the studies listed in *Table 24*, key publications from 2002 onwards are summarised in *Table 26*.

Studies specifically dealing with management of 'prediabetes'

In relation to reducing diabetes risk

Davies and colleagues[256] present a comparison, in terms of number-needed-to-treat of the interventions tested in the Da Qing,[88] TRIPOD,[259] Diabetes Prevention Programme (DPP),[90] Diabetes Prevention Study (DPS),[89] STOP-NIDDM[169] and XENDOS[260] trials. These are summarised in *Table 27*.

Further pharmacological interventions are summarised by Gerstein.[261] These include:

- Metformin: as in DPP mentioned above.
- Acarbose: as in STOP-NIDDM mentioned above.
- Orlistat: as in XENDOS mentioned above.
- Thiazolidinediones: troglitazome (as in DPP, withdrawn as a result of adverse effects) and TRIPOD.
- ACEIs: ramipril (as in HOPE); lisinopril (as in ALLHAT); captopril (as in CAPP); enalapril (as in D-SOLVD); and others.
- Insulin and insulin secretagogues: of theoretical benefit.
- Statins and fibrates: pravastatin (as in WOSCOPS), significant reduction in conversion to diabetes; no effect found for atorvostatin (ASCOT), simvastatin (Heart Protection Study), pravastatin (LIPID).
- Oestrogen: reduction in conversion to diabetes found by Kanaya and colleagues.[262] Adverse effects on CVD risk render this an unsuitable therapeutic approach.

In relation to reducing cardiovascular disease risk

The only diabetes prevention RCT which has reported a positive effect on CVD risk is the STOP-NIDDM trial of acarbose. Chiasson and colleagues[169] reported a significant reduction in new cases of hypertension, MI and any CVD event in those taking acarbose. Given the fact that 30% of those randomised to the active intervention stopped taking the drug and this analysis was based on intention-to-treat, the effect of acarbose on CVD incidence may well be even greater than that described. However, this unexpectedly large effect needs to be replicated in other trials and has not been reported as a result of lifestyle changes or in relation to other pharmacological interventions.

Ongoing work with the DiabetesForcaster™ model (McEwan and colleagues, in preparation) provides numerical estimates of the effects on CVD morbidity and mortality of delaying the onset of type 2 diabetes. Shown in *Table 28* are the expected cardiovascular events, total simulation costs and QALYs obtained by running the model over a 20-year time horizon for two scenarios: scenario 1 provides a linear increase in risk over the time after the onset of diabetes whereas scenario 2 provides a stepwise change in risk at diagnosis. For scenario 1, a 10-year delay in the onset of diabetes roughly halves the number of deaths from CVD, reduces direct healthcare costs to around one-third and provides an average gain in QALYs per person of 3.31.

TABLE 26 *Key studies published from 2002 onwards*

Group	Study/level evidence	Title Country Multi-centred	Authors	Year	Source	Population studied	Intervention given	Outcomes	Follow-up/ analysis	Comments: blinding, groups treated equally	Treatment effect
Interventions in IGT population	RCT II	The Diabetes Prevention Program and its global implications USA Multi-centred – 5	Moltich *et al*.[263]	2003	*J Am Soc Nephrol* **14**:S103–7	3234 ⩾25 years, mean 51 years BMI ⩾24, mean 34 kg/m^2 IGT 68% women, 45% BM ethnic groups	1. Lifestyle goals: 7% weight loss, 150 minutes' exercise/week Behaviour modification individual and group sessions 2. Metformin 3. Placebo	Developing DM, annual OGTT	Av. 3.8 years ITT analysis	Double-blinded for metformin and placebo Groups not treated equally, i.e. lifestyle was intensive	Av. weight loss 5.6 kg in Lifestyle group Incidence DM Lifestyle 58% (95% CI 48 to 66) incidence reduced Metformin 31% lower (95% CI 17 to 43) compared with placebo Lifestyle effect seen across ethnic groups Treating 6.9 people for 3 years, prevents 1 case with lifestyle 13.9 with metformin
Economics of primary prevention		Costs associated with the primary prevention of T2DM in DPP USA	American Diabetes Association[264]	2003	*Diabetes Care* **26**:37–47		To describe costs of DPP	Direct medical costs, direct non-medical costs and indirect costs, placebo, metformin and intensive lifestyle interventions			Direct medical costs, laboratory tests to identify 1 person with IGT $139 Over 3 years, costs per participant relative to placebo was $2191 in metformin, $2412 in lifestyle for a healthcare system

continued

TABLE 26 *Key studies published from 2002 onwards (cont'd)*

Group	Study/level evidence	Title Country Multi-centred	Authors	Year	Source	Population studied	Intervention given	Outcomes	Follow-up/ analysis	Comments: blinding, groups treated equally	Treatment effect
											Considered modest incremental costs but need to evaluate costs relative to health benefits to determine real value
Interventions in IGT population	RCT II	Prevention of diabetes mellitus in subjects with impaired glucose tolerance in the Finnish Diabetes Prevention Study: results from a randomised clinical trial	Lindstrom *et al.*[265]	2003	*J Am Soc Nephrol* **14**:S108–13	522 men and women, 67% women. Av. age 55 years. Av. BMI 31 kg/m^2. IGT	1. Lifestyle. *N* = 265, diet (reduced fat intake to 30% energy intake), exercise (over 4 hours per week), weight loss (at least 5%) in 7 sessions in year 1, then 4 times per year, included nutritionist. Food diaries	Incidence of DM by WHO criteria. Changes in weight, diet, exercise	3.2 years 90% follow-up	Achieved 4.2 kg weight loss in intervention group People with best compliance to lifestyle change had greatest reduction in incidence	Lifestyle incidence rate = 3.2/100 PY versus control = 7.8/100 PY Hazard ratio = 0.4 (0.3–0.7) for incident DM ARR = 4.6/100 PY Risk of diabetes reduced by 58% in intervention group over the trial ($p < 0.001$) Also improved CV risk factors – reduced TG and blood pressure
		Prevention of Type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance Finland Multi-centres 5	Tuomilehto *et al.*[89]	2001	*N Engl J Med*, **344**: 1343–50		2. Control. *N* = 257. Annual information – verbal and written				

continued

TABLE 26 *Key studies published from 2002 onwards (cont'd)*

Group	Study/level evidence	Title Country Multi-centred	Authors	Year	Source	Population studied	Intervention given	Outcomes	Follow-up/ analysis	Comments: blinding, groups treated equally	Treatment effect
Screening IGT in high-risk population Interventions in IGT population to follow	Observational, cross-sectional IV RCT II	Study on lifestyle-intervention and IGT Maastrict (SLIM): design and screening results The Netherlands 3 centres	Mensink *et al.*[266]	2003	*Diabetes Res Clin Pract* **61**:49–58	2820 aged over 40+, BMI >25 kg/m^2 or family history DM screened with OGTT Identified 226 (8.3%) T2DM, 215 (7.9%) IFG, 385 (14.2%) IGT 2nd OGTT 144 with IGT entered into study	1. Lifestyle-dietary (aim 5–7% weight loss), exercise (aim 30 minutes ×5 per week moderate physical activity), free access to training programme, individual advice 2. Control – oral and written information re benefits of weight loss and exercise. No additional appointments	Results/yield screening	6108 invited over 40+, BMI >25 kg/m^2 or family history DM 3288 (53.8%) non-responders, mean age lower 55.7 ± 0.1 vs 56.8 ± 0.1 years, gender equivalent 1st OGTT in 2820: 226 (8.3%) T2DM, 215 (7.9%) IFG, 385 (14.2%) IGT 379 for 2nd OGTT		In men and women with BMI over 30 kg/m^2, DM 3× and IFG/IGT 2× more prevalent than than if BMI below 27 kg/m^2 Prevalence of newly diagnosed DM 2× higher in men than women for each BMI/age group. Positive relation between age and prevalence DM and IGT, IFG highest 55–59 years Strong upward trend for age and BMI was seen from NGT to T2DM with IGT and IFG in between IGT more prevalent than IFG, limited overlap. Tables of yield given

continued

TABLE 26 *Key studies published from 2002 onwards (cont'd)*

Group	Study/level evidence	Title Country Multi-centred	Authors	Year	Source	Population studied	Intervention given	Outcomes	Follow-up/ analysis	Comments: blinding, groups treated equally	Treatment effect
Screening for T2DM and IFG	Observational cross-sectional survey IV	A simple pragmatic system for detecting new cases of type 2 diabetes and impaired fasting glycaemia in primary care UK	Greaves *et al.*[112]	2004	*Fam Pract* **21**:57–62	16 practices in Somerset with prevalent DM 2.36% 100 patients from each practice, 25 for each of 4 groups stepped by age and BMI criteria 1287 patients recruited, 39.5% male	Computerised searching of routinely collected data as starting point for a targeted screening programme. Selected patients received invitation and call to attend for test. Weight, height, age, FBG If first IFG abnormal, repeated for dx	Results yield of screening	RR to invite 60.6% (95% CI 55.7 to 65.6) like breast cancer screening BMI data available for 76.8% of over-50 population. 1287 attended screening clinic, 199 abnormal FBG, 199 attended 2nd test 55 (4.3% attenders) T2DM 93 (7.2% attenders) IFG No gender differences		For those attending NNT to detect IFG/T2DM in over 70s, BMI $\geqslant$33 kg/m^2 was 7.7, 16.5 if one includes non-attenders NNT if age $>$50 years and BMI $\geqslant$27 kg/m^2 12.8 but greater proportion of population-screening trade-off Authors favour wide screening criteria for over-50s, BMI $\geqslant$27 kg/m^2

continued

TABLE 26 *Key studies published from 2002 onwards (cont'd)*

Group	Study/level evidence	Title Country Multi-centred	Authors	Year	Source	Population studied	Intervention given	Outcomes	Follow-up/ analysis	Comments: blinding, groups treated equally	Treatment effect
Evaluation of strategies to screen prediabetes	Evaluation	Costs of screening for prediabetes among US adults	Zhang *et al.*[204]	2003	*Diabetes Care* **26**:2536–42	Age 47–74 years visited healthcare provider ×1 in previous year with no previous diagnosis T2DM= 54.4 million With BMI ⩾25 kg/m^2 eligible population = 37.4 million	5 strategies: 1. all OGTT 2. all FBG if positive but no IFG then OGTT 3. HbA_{1c} if positive OGTT 4. CBG if positive OGTT 5. risk assessment score then OGTT	Effectiveness of each strategy defined by proportion of cases identified. Assumed OGTT and FBG 100% sensitive for detecting IGT, IFG and T2DM Evaluated if limited strategies to those aged 45–74 years, BMI ⩾25 kg/m^2 Medical and non-medical costs		Weaknesses: no-one under 45 or over 75 years, family history not included Costs of undetected cases not included	Proportion identified of pre-DM and T2DM ranged 69–100% Cost per case identified ranged $176–236 from single-payer perspective Testing all with OGTT most effective, CBG and risk assessment most efficient If people much less willing to take an OGTT than an FPG test, then FBG strategy most effective Trade-off between effectiveness and efficiency depending on whether aim is to identify more cases or pursue lowest cost per case Screening overweight individuals had lower cost per case

continued

TABLE 26 *Key studies published from 2002 onwards (cont'd)*

Group	Study/level evidence	Title Country Multi-centred	Authors	Year	Source	Population studied	Intervention given	Outcomes	Follow-up/ analysis	Comments: blinding, groups treated equally	Treatment effect
Detection IGT in ethnic population	IV	Diagnostic strategies to detect glucose intolerance in a multiethnic population Canada	Anand *et al.*[267]	2003	*Diabetes Care* **26**:290–6	936 Canadians of South Asian, Chinese and European descent	Using ROC curves to determine sensitivities/ specificities and cut-off values				Sensitivity of ADA criteria to diagnosis T2DM is low and there is substantial variation between ethnic groups FBG and HbA_{1c} can be used to identify those with DM but OGTT needed for IGT
Prevalence study	Cross-sectional IV	High prevalence of undiagnosed DM in Southern Germany: target population for efficient screening. The Kora study Germany	Rathman *et al.*[206]	2003	*Diabetologia* **46**:182–9	OGTT to random sample 1353 subjects in the KORA study 2000 Age 55–74 years	Prevalences (WHO 1999) and NNTS (screen) to identify 1 person calculated		62% agreed to participate; 'healthy participant effect'		Prevalences: Known DM 9% Unknown DM 9.7%, IGT 16.8%, IFG 9.8% in men 7.9, 6.9, 16.0, 4.5% in women NNT in men +2.9 if have abdominal obesity, parental DM and hypertension Cardiovascular risk factors worsen among glucose tolerance categories? Justify screening strategies

DM, diabetes mellitus; ITT, intention-to-treat; PY, person-year; ROC, receiver operating characteristic; TG, triglycerides.

TABLE 27 *Number-needed-to-treat (NNT) to avoid one case of progression from IGT to T2DM in published trials*

Study	Cumulative incidence of T2DM vs placebo (%)	Intervention	NNT	Duration (years)
Da Qing (Pan *et al*., 1997)[88]	66 vs 44	Lifestyle	4.5	6
TRIPOD (Azen *et al*., 1998)[259]	30 vs 14	Troglitazone	6	2.5
Diabetes Prevention Program (DPP Research Group, 2002)[90]	29 vs 14	Lifestyle	7	3
Diabetes Prevention Study (Tuomilehto *et al*., 2001)[89]	42 vs 32	Lifestyle	8	4
STOP-NIDDM (Chiasson *et al*., 2003)[169]	42 vs 32	Acarbose	11	4
Diabetes Prevention Program (DPP Research Group, 2002)[90]	29 vs 22	Metformin	14	3
XENDOS (Sjostrom *et al*., 2002)[260]	9 vs 6	Xenical	36	3

Adapted from Davies and colleagues (2004).[256]

TABLE 28 *Summary of cardiovascular results, total costs and QALYs obtained over a 20-year time horizon running the model with no delay in diabetes and 1, 3, 5 and 10 years' delay for scenarios 1 and 2: values shown are expected cumulative events (when running the model with no delay), and expected events/costs avoided and gain in QALYs*

Events	Events avoided (or QALYs per person gained)								
	No delay	1-year delay		3-year delay		5-year delay		10-year delay	
		Scenario 1	Scenario 2	Scenario 1	Scenario 2	Scenario 1	Scenario 2	Scenario 1	Scenario 2
CHD	421	24	15	44	61	81	95	121	181
Stroke	269	18	20	49	56	88	84	151	159
CVD death	271	17	10	40	47	73	70	133	131
Costs and QALYs	**Effect on costs and QALYs**								
Costs per subject:									
Non-discounted (£)	18,303	–£703.48	–839.69	–2119	–2237	–3441	–3616	–6026	–6604
Discounted (£)	13,145	–605.91	–687.02	–1722	–1823	–2717	–2869	–4547	–4978
QALYs per subject:									
Non-discounted	9.74	0.41	0.37	1.13	1.19	1.85	1.85	3.17	3.31
Discounted	7.53	0.34	0.32	0.93	0.98	1.48	1.49	2.43	2.53

Adapted from McEwan and colleagues (in preparation).[268]

Conclusions

1. There is still no evidence from RCTs specifically designed to show whether early detection through screening is worthwhile and that individuals will benefit from the early detection of T2DM. The definitive RCT is unlikely to be undertaken.
2. Given that opportunistic screening and screening by invitation are happening in primary care in the UK, standards and guidelines are required in order to achieve equitable access to good practice.
3. Screening activities, whether opportunistic or by invitation, may, depending on cut-offs used, identify more people with IGT and/or IFG than people with previously undiagnosed diabetes.
4. There is convincing RCT evidence that interventions relating to lifestyle change and some pharmacological treatments (as yet unlicensed for this use) are effective in delaying transition from IGT to diabetes, particularly in people who are overweight or obese.
5. It is, as yet, an unanswered question as to whether the efficacy of these interventions in the RCT context can be translated into effectiveness (and cost-effectiveness) in everyday clinical practice.

6. It is also an unanswered question as to whether delaying transition to diabetes delays or prevents the cardiovascular outcomes associated with diabetes.
7. It is highly likely that the effectiveness and cost-effectiveness of early identification of diabetes, IGT and IFG will be enhanced by combining this with the early identification and management of CVD risk.
8. A care pathway for the early detection and prevention of T2DM and associated CVD risk based on the best evidence available (or at least consensus) is required to guide primary care professionals and others on current and future practice.

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