The University Of Sheffield.

The University of Sheffield ScHARR School of Health and Related Research

Public Health Collaborating Centre

Preventing the progression of pre-diabetes to type 2 diabetes in adults.

Identification and Risk Assessment of adults with pre-diabetes.

Commissioned by:	NICE Centre for Public Health Excellence
Produced by:	ScHARR Public Health Collaborating Centre
Authors:	Maxine Johnson Emma Everson-Hock Roy Jones Helen Buckley Woods Elizabeth Goyder Jim Chilcott Nick Payne
Correspondence to:	Vivienne Walker School of Health and Related Research (ScHARR) University of Sheffield Regent Court 30 Regent Street Sheffield S1 4DA v.walker@sheffield.ac.uk

Version 5: 26.08 2011

About the *ScHARR Public Health Collaborating Centre*

The School of Health and Related Research (ScHARR), in the Faculty of Medicine, Dentistry and Health, University of Sheffield, is a multidisciplinary research-led academic department with established strengths in health technology assessment, health services research, public health, medical statistics, information science, health economics, operational research and mathematical modelling, and qualitative research methods. It has close links with the NHS locally and nationally and an extensive programme of undergraduate and postgraduate teaching, with Masters courses in public health, health services research, health economics and decision modelling.

ScHARR is one of the two Public Health Collaborating Centres for the Centre for Public Health Excellence (CPHE) in the National Institute for Health and Clinical Excellence (NICE) established in May 2008. The Public Health Collaborating Centres work closely with colleagues in the Centre for Public Health Excellence to produce evidence reviews, economic appraisals, systematic reviews and other evidence based products to support the development of guidance by the public health advisory committees of NICE (the Public Health Interventions Advisory Committee (PHIAC) and Programme Development Groups).

Contribution of Authors

Maxine Johnson was the systematic review lead. Emma Everson-Hock and Roy Jones were reviewers on the project. Helen Buckley Woods developed and undertook literature searches. Nick Payne and Jim Chilcott were the senior leads. Elizabeth Goyder was the topic expert.

Acknowledgements

This report was commissioned by the Centre for Public Health Excellence of behalf of the National Institute for Health and Clinical Excellence. The views expressed in the report are those of the authors and not necessarily those of the Centre for Public Health Excellence or the National Institute for Health and Clinical Excellence. The final report and any errors remain the responsibility of the University of Sheffield. Elizabeth Goyder and Jim Chilcott are guarantors.

CONTENTS

TABLES AND FIGURES

LIST OF ABBREVIATIONS

ADA	American Diabetes Association
AGT	Abnormal Glucose Tolerance
AUC	Area Under the Curve
BME	Black and Minority Ethnic groups
BMI	Body Mass Index (kg / m^2)
CBG	Capillary Blood Glucose
CHD	Coronary Heart Disease
CI	Confidence Interval
CRS	Cambridge Risk Score
CVD	Cardiovascular Disease
DBP	Diastolic Blood Pressure
DH	Department of Health
DRS	Diabetes Risk Score
EMR	Electronic Medical record
FBG	Fasting Blood Glucose
FCG	Fasting Capillary Glucose
FINDRISC	Finnish Diabetes Risk Score
FPG	Fasting Plasma Glucose
FRA	Serum Fructosamine
GCT	50 g oral Glucose Challenge Test
GP	General Practitioner
Hr	Hour
HbA1c	Glycosylated Haemoglobin
IFG	Impaired Fasting Glucose
IGR	Impaired Glucose Regulation
IGT	Impaired Glucose Tolerance
ITT	Intention to Treat
LRA	Leicester Risk Assessment
MS	Metabolic Syndrome
PG	Post Glucose
PPV	Positive Predictive Value
POCT	Point of Care Testing
NFG	Normal Fasting Glucose
NGT	Normal Glucose Tolerance
n-RCT	Non-Randomised Controlled Trial
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
NPV	Negative Predictive Value
OGTT	75g Oral Glucose Tolerance Test
OR	Odds Ratio
RF	Risk Factors
RCT	Randomised Controlled Trial
RCBG	Random Capillary Blood Glucose
ROC	Receiver operating Characteristics
SAGE	Spectroscopic measurement of dermal advanced glycation end products
SD	Standard Deviation
T2DM	Type 2 Diabetes
WC	Waist Circumference
WHO	World Health Organization

2. EXECUTIVE SUMMARY

2.1 Background

Type 2 diabetes is associated with significant clinical and social consequences. The National Institute for Health and Clinical Excellence has been asked by the Department of Health to develop public health guidance on the prevention of type 2 diabetes among high-risk groups. The referral is divided into two separate pieces of guidance. The first addresses the prevention of pre-diabetes (raised and impaired glucose levels) in populations and communities of high risk adults using community based interventions. The second piece of guidance will address how to prevent the progression from pre-diabetes to type 2 diabetes. To inform development of this second piece of guidance, four reviews of international evidence will be carried out that address the prevention of progression to type 2 diabetes as well as a health economic / modelling review. This document reports on the first of these reviews. It focuses on the effectiveness and cost-effectiveness of strategies and tools designed to identify individuals at risk for pre-diabetes.

Type 2 diabetes has a long preclinical phase, with the condition remaining undiagnosed for many years in a significant number of cases (Woolthius *et al* 2007). A group of conditions defined by blood glucose levels that fall between normal and those defining type 2 diabetes are typically known as Impaired Fasting Glucose (IFG) and Impaired Glucose tolerance (IGT) or collectively as ‘pre-diabetes’.

Impaired Glucose Tolerance (IGT) is defined as a fasting plasma glucose of <7.0mmol/l (126mg/dl) if measured, and a 2–hour plasma glucose (Venous plasma glucose 2–h after ingestion of 75g oral glucose load) ≥7.8 and <11.1mmol/l (140mg/dl and 200mg/dl) (WHO 2003).

Impaired Fasting Glucose (IFG) is defined as a fasting plasma glucose 6.1 to 6.9mmol/l (110mg/dl to 125mg/dl) (if measured) and 2–h plasma glucose <7.8mmol/l (140mg/dl) (WHO 2003).

In 1999 WHO adapted the recommended definition of Impaired Fasting Glucose (IFG) originally introduced by the ADA Expert Committee (2007). IFG thus describes the zone between the upper limit of normal fasting plasma glucose and the lower limit of the diabetic fasting plasma glucose, believed to be analogous to between the upper limit of normal 2–h plasma glucose and the lower limit of the diabetic 2–h plasma glucose described by IGT.

An additional statement has been released by WHO (2011) recently that allows the diagnosis of type 2 diabetes to be made using the HbA1c blood test at a cut point of 5.6%. There was no statement regarding the diagnosis of IFG or IGT using HbA1c due to insufficient evidence. This statement was made after the publication of the included studies in this review.

IGT and IFG are risk factors for future diabetes and/or adverse outcomes rather than a clinical entity. Studies suggest that IGT is associated with muscle insulin resistance and defective insulin secretion, resulting in less efficient disposal of the glucose load during OGTT. IFG is associated with impaired insulin secretion and impaired suppression of hepatic glucose output (WHO 2006)

It is recognised that the term 'pre-diabetes' is not ideal, as not everyone with raised or impaired blood glucose levels will go on to develop type 2 diabetes. However, the term 'pre-diabetes' has been chosen because of its widespread use and recognition by a broad range of stakeholder groups and because of the lack of consensus on a suitable alternative.

The terms 'risk assessment' and 'risk reduction' are used in preference to the term 'screening'. Screening terminology tends to imply that results are either positive or negative and that it is possible to place all individuals into categories of low and high risk with only those at high risk requiring further intervention. "Risk assessment" implies an individualised approach that takes into account individual risk factors. In relation to type 2 diabetes, risk lies on a continuum according to known risk factors, many of which also present on the continuum of risk for other conditions, such as CVD (UK NSC 2008). Many individuals with risk factors will still be at high risk of developing diabetes in the future even if their glucose tolerance is currently still in the normal range. A person is therefore never totally risk-free, and prior to a diagnosis of type 2 diabetes can move either way on the continuum. Risk reduction is the aim of health promotion advice, which needs to be communicated according to a person's perception of their own risk as well as formally assessed risk.

A number of large studies have been carried out internationally that aim to identify effective interventions to delay or prevent development of type 2 diabetes in individuals at high risk. Such interventions require an effective method to identify at risk individuals. In order to meet this requirement for effective methods to identify those at high risk, a range of identification and risk assessment methods have been developed building on methods developed initially to screen for Type 2 diabetes. Tools and tests used to identify individuals with type 2 diabetes will also identify those with pre-diabetes since the risk factors and diagnostic tests are essentially the

same and the diagnoses of ‘pre-diabetes’ or ‘diabetes’ represent clinically and epidemiologically defined cut-offs on a continuous spectrum of hyperglycaemia and impaired glucose tolerance.

It is increasingly accepted that testing for pre-diabetes in those most at risk is an important step in preventing progression to type 2 diabetes. This may provide an appropriate time to intervene with behaviour change advice when progression to clinical diabetes can still be prevented.

2.2 Aims and Objectives

The aim of this first review was to undertake an assessment of the evidence for the relative performance and costs of strategies and tools designed to identify individuals at high risk of progression to diabetes due to the presence of pre-diabetes. The review focuses on risk assessment and identification strategies as well as the barriers and facilitators to such strategies. The objectives were to assess and synthesise evidence pertaining to each of the three steps that can occur in risk assessment strategies, the use of demographic information, risk score tools as well as diagnostic tools. Evidence from included studies that addresses response rates, acceptability, yield and costs of both risk assessment and diagnostic testing will also be reported where evidence is available.

Review Question:

What is the evidence for the effectiveness and cost-effectiveness of methods to identify adults with pre-diabetes, especially the evidence for how to increase identification and the uptake of risk assessment in high-risk groups?

2.3 Methods

A systematic review of evidence of effectiveness to address the above review question has been undertaken. A search strategy was developed and carried out in a number of databases (see Appendix 3) to identify literature from 1998-August 2010 relating to the review question. Keywords were used from an initial search (undertaken in July 2010) to develop a more refined search for Review 1.

References were scrutinised at title and abstract stage for inclusion / exclusion (see Section 4). Papers were included if the study assessed the utility of identification and risk assessment in adults at risk of, but with no diagnosis of type 2 diabetes, using a range of strategies. Most had been evaluated in terms of their sensitivity and specificity, and some also reported positive and negative predictive values and Area under the curve. The review does not include studies that assess clinical assessment

of insulin resistance or prediction of the progression of pre-diabetes to type 2 diabetes. Studies that focussed on the identification of type 2 diabetes only were excluded.

Papers were retrieved at full title if, from the abstract it was clear that they met the criteria (i.e. included sensitivity and specificity as well as other outcomes such as positive predictive value) or possible that they required further assessment.

Data were extracted from included studies using a piloted template, and all papers were assessed for quality using a tool developed for a previous NICE work reviewing a range of risk assessment tools. Data that related to efficacy, uptake, acceptability and costs as well as barriers and facilitators to implementation were extracted where available.

2.4 Results

From an initial total of 2828 references generated from an overarching search and a more focussed search carried out between August and September 2010, as well as reference list checks, 29 papers of varying study type and quality met the inclusion criteria for the review of strategies for identification and risk assessment for pre-diabetes.

The quality of papers was moderate, with 2 papers rated as very good (++), 24 as good (+) and 3 as poor (-).

Two papers assessed the use of routine demographic data found in practice records as an approach for identifying patients that might be at risk for pre-diabetes. Two studies assessed the use of a validated score derived from such records. Seven studies evaluated risk assessment scores using a questionnaire. Eighteen studies assessed a range of strategies using blood glucose indicators, including non-fasting methods (6), fasting plasma glucose (2), HbA1c alone (4), comparison of HbA1c with non-fasting blood glucose measures (1), comparison of HbA1c with fasting blood glucose measures (7), combination of HbA1c and fasting blood glucose measures (3), and stepped strategies using at least two approaches (6). Nine studies reported on study response rates.

Risk assessment strategies were carried out through 3 main stages, the use of routine medical data, questionnaire type risk scores and blood glucose indicator tests. Comparisons between and combinations of individual measures were assessed. The results section reflects the complexity of the range of assessments available in the included literature.

Risk assessment was carried out in either the general population, or a study population. Some populations were randomly selected whilst others were targeted following initial risk assessment. The performance of each strategy was calculated for a range of cut points, with an optimal cut point identified. Optimal cut points were reported as those where the trade off between sensitivity and specificity was minimal. Variations in optimal cut point were typically due to variations in population characteristics.

Risk for pre-diabetes as well as type 2 diabetes can be assessed using data recorded in the medical records, which are mainly now computerised. This strategy requires no input from the participant at the identification stage since the data is readily available. However, optimum performance is dependant upon accurate and comprehensive recording of data that is associated with high risk, such as BMI. Misclassification of data was an issue in 20% of cases in one study.

Medical data can also be used to develop a risk score, such as the validated Cambridge Risk Score (CRS) in the UK. This strategy measures risk as well as identifying those characteristics associated with risk. Again the strategy relies upon accurate recording of data. Two studies assessed the CRS, one in the UK and one in Denmark. The UK study found no benefit compared to assessing BMI alone, though the population were all 45 years old, therefore with relatively low risk. The Danish study identified 42% of adult participants with impaired glucose regulation, at a higher cut point than the UK study.

Questionnaire based risk scores require more input from participants than medical record generated scores. This could mean that more time is required to implement and supervise questionnaire completion. A number of questionnaires are assessed in the literature. The FINDRISC tool was evaluated in four different populations, each one having a different optimal cut point. A shortened German version provided the largest Area under the Curve at cut point 12 than the Italian and Finnish versions at cut point 9 and 11 respectively. The Finnish version provided the highest positive predictive value. The Leicester Risk Assessment score was developed for a UK multi-ethnic population and provided a PPV of 27.7% at cut point 16.

Seven papers described non-fasting approaches to blood glucose indication. Point of Care testing was found to underestimate the true blood glucose levels in one study with a Maori population. Random Capillary Blood Glucose testing was found to have different optimal cut points for detection of IGT compared to IFG with similar sensitivity and specificities. Assessment of a non-fasting, 50g 1 hr Glucose

Challenge Test (GCT) in the US showed a superior AuC to HbA1c, the random plasma glucose test (RPG) and the fasting plasma glucose test (FPG) for detection of pre-diabetes. The test was claimed to be relatively inexpensive. There was insufficient evidence to assess SAGE and Fructosamine indicators.

Eight studies compared fasting blood glucose testing with HbA1c for identification of pre-diabetes. In Japan, there were differences in optimal cut off points by sex for the FPG whilst performance of the HbA1c differed by age in respect to specificity. In one US study, the sensitivity of FPG and HbA1c in detecting IGT was influenced by age and BMI. One study performed in China concluded that the simultaneous measurement of FPG and HbA1c might be a more sensitive and specific screening tool for identifying high-risk individuals with diabetes and IGT at an early stage, whilst another in the same country concluded that, as a mass screening tool, a Fasting Capillary Glucose test performed better than the Hba1c test in the general Chinese population. In an Italian study, the authors concluded that whilst FPG and HbA1c alone do not identify IGT particularly well, the combined use of HbA1C (threshold 5.5%) and FPG (threshold 6.1 mmol/l) improves the sensitivity of risk assessment of individuals with IGT.

Three studies assessed the use of different cut points for FPG and four assessed HbA1c alone. In a UK multi-ethnic population, the HbA1c optimal cut point was lower for White Europeans than south Asians, resulting in better identification of IGT in the latter group.

Six studies assessed multi-component or stepped strategies that included a risk calculation and at least one blood indicator test. Overall, the highest sensitivity and specificity was attained in one study by combining HbA1c, FPG and various combinations of other risk factors such as age, systolic blood pressure and waist circumference. In this study sensitivity ranged from 79% to 83% and specificity ranged from 74% to 76%.

Response rates were discussed in nine of the 29 included papers. Response was reported to differ by age, ethnicity, gender and socio-economic circumstances. Some suggestions to improve response to risk assessment programmes included follow-up calls and providing specific appointments. Uptake for diagnostic testing could be improved through raising awareness during consultations.

2.5. Discussion

The aim of this review was to assess the evidence for the effectiveness, and where available, cost-effectiveness of methods for identifying adults with pre-diabetes, and how to increase identification and the uptake of risk assessment in high-risk groups. Papers assessed the use of routine demographic data found in practice records as an approach for identifying patients that might be at risk for pre-diabetes, the use of routine data to provide a risk score, and questionnaire based risk scores. In addition, a range of blood glucose measures was assessed in at risk and general populations as compared to the OGTT. Comparisons were made between fasting and non-fasting tests, and stepped strategies that included risk assessment as well as blood glucose indicators were assessed.

The studies were heterogeneous in study design, population, prevalence of pre-diabetes, and aims, therefore pooling of data was not deemed appropriate. The results of this review highlight the complexity of risk assessment, and in particular, blood glucose measures that are available for identifying those at risk of pre-diabetes. There was very little useful evidence within the papers on costs, or on how to increase uptake in at risk groups.

There was evidence that use of medical records may be a useful start to the identification process, provided that risk factors such as BMI are recorded accurately and that records are regularly up-dated. The Cambridge Risk score took this method a step further by applying a score to risk data. Implementation of questionnaire based risk scores requires adequate resource. However, more information can be obtained using this method. The FINDRISC was more specific for women than men. A shortened 8-item version developed for the German population gave a higher sensitivity, specificity and AuC than the original. In the UK, a version that targeted a lay multi-ethnic population showed a PPV of 27.7%. Other risk scores have been developed in the US and Denmark. One US version was more specific than the Italian FINDRISC based score.

Improved uptake for risk assessment may occur when participants are followed up by telephone and specific appointments are made within the invitation letter. Low responses were reported in ethnic minority, younger, and unskilled manual populations. Returning for blood testing may be encouraged by discussion of risk during consultations with general practitioners.

It is acknowledged that papers are available that describe other tools, such as the QRISK, developed for assessing cardiovascular risk (Hippisley - Cox *et al* 2009). However, we did not identify papers describing such tools that met the inclusion

criteria for this review, i.e. papers that present an evaluation in terms of detecting pre-diabetes.

A range of non-fasting blood glucose measures gave PPVs of less than 50%. Prevalence of pre-diabetes was high in all the studies. HbA1c was assessed in five studies including the UK. Specificity increased with a rise in cut point and PPV was around 50% in all the studies. Compared to fasting blood glucose, a PPV of 79% was achieved at a cut point of 6.0% in a German high risk population. A similar PPV was found in the same study when combining the two tests. A combination of FPG and HbA1c following risk assessment for BMI gave the highest specificity (98%).

In blood glucose test studies, improved responses may occur in trial and other study populations. Acceptability of the test was also discussed as a motivation, particularly in terms of time required. European males responded least well in one stepped programme, and in another, the women who did not attend had a high rate of morbidity and mortality, though not related to diabetes.

Six studies assessed stepped strategies that commenced with risk assessment. All six studies reported high specificity, though one study reported a higher specificity for the HbA1c alone at a cut point of 6.0% or more.

It appears that a stepped strategy might be useful in terms of identifying risk prior to blood testing, so that resources may be focussed on those at risk. The risk of false positive is reduced by this process and it may be more acceptable to participants to adapt gradually to a potential diagnosis (Eborall *et al* 2007).

As fasting blood glucose measures and HbA1c use different techniques and are measuring different aspects of blood glucose level, there remains uncertainty around whether these two tests should be carried out together rather than alone.

Since this review was initiated, an addendum to the WHO recommendations Definition and diagnosis of diabetes mellitus and intermediate hyperglycemia (2006) has been published in relation to the use of HbA1c for diagnostic purposes. Evidence for the use of HbA1c to diagnose pre-diabetes is inconclusive. However, given that a diagnosis of diabetes can be made at a cut point of 6.5%, previous suggestions of a cut point of HbA1c ≥ 6.5% to diagnose diabetes (or pre-diabetes) will need to be re-evaluated.

The applicability of findings to UK settings is variable since assessments have taken place internationally. In particular, health care delivery will differ from that in the UK. In addition, populations included in the studies vary in terms of risk profile.

2.6 Conclusion

A range of risk assessment tools and blood glucose indicators are available for the identification of pre-diabetes in individuals. Findings from international studies provide multiple combinations of assessment tools and indicators for use in a range of settings, with general and at risk populations, at a number of optimal cut points. However a strategy that assesses initial risk followed by diagnostic testing appears to have acceptable specificity. Response rates indicate that some groups are less likely to attend for risk assessment and testing. A number of strategies are available to increase uptake, mainly based on improved communication.

2.7 Evidence statements

The following evidence statements result from a synthesis of available evidence and are presented by type of strategy. The evidence statements will be repeated in section 6 alongside the relevant narrative synthesis of included studies.

Evidence statement 1:

Approaches to identification based on demographic and routine data

There was moderate evidence [+] from two observational studies of the usefulness of demographic data from routine medical recording systems in identifying people at risk of Impaired Fasting Glucose (IFG) (Greaves *et al* 2004 UK +; Woolthuis *et al* 2007 Netherlands +).

The studies were carried out with mainly Caucasian patient populations and used data on characteristics associated with diabetes risk. Greaves *et al* (2004 UK +) reported an overall uptake rate of 61% (95% CI 55.7-65.6) from 15 practices. There was no reported response bias associated with age or gender. BMI data was available in 76.8% (95% CI 71.7 – 81.9) of cases. There was data misclassification in 20% of these cases. Of the 199 participants with abnormal blood glucose, 100% attended for a follow up blood test.

Woolthuis *et al* (2007 Netherlands +) reported that the Electronic Medical Record (EMR) with additional risk assessment was successful in identifying risk in 28% of the total population from 11 general practices.

Evidence statement 2:

Barriers and facilitators to identification based on demographic and routine data

There was moderate evidence [+] from two observational studies (Greaves *et al* 2004 UK +; Woolthuis *et al* 2007 Netherlands +) that barriers to using routine data for identification of pre-diabetes risk are inconsistent and inaccurate record keeping. In particular, data referring to obesity and family medical history was often missing, requiring that the practitioner complete the records during patient visits.

ES 1 / 2 Applicability Rating:

These studies are directly applicable to the UK context, with one being based in the UK. One study was based in the Netherlands. Both studies sampled from general practice populations, though the majority of the samples were Caucasian. Feasibility of the strategy is good since the aim is utilisation of available data.

Evidence statement 3:

Approaches to identification based on validated scores for demographic and routine data

There was moderate evidence [+] from two studies for the relative performance of the Cambridge Risk Score (Thomas *et al* 2006 UK +; Heldegaard *et al* 2006 Denmark +).

One UK evaluation (Thomas *et al* 2006 UK +) utilised a survey sample of 45 year old individuals. Of the 84% of the respondents that received an HbA1c measurement, 3% were identified as having HbA1c ≥ 6.0%. The Cambridge Risk Score at a cut off ≥ 0.128 was reported to have sensitivity of 78.2%, specificity 63.9%, PPV 6.4% (no NPV reported), and Area under the Curve 0.76 for identifying hyperglycaemia (HbA1c ≥ 6.0%). A total of 22.6% of the sample were identified as at risk for diabetes compared to BMI alone which identified 23.7%.

An evaluation of the CRS in a general practice population (Heldegaard *et al* 2006 Denmark +) with a 69% response rate to the initial questionnaire found that 42% of the sample had Impaired Glucose Regulation (IFG and / or IGT) based on assessment of high risk. An optimal cut off of ≥ 0.246 on the risk score gave

sensitivity 47.1%, specificity 83.9%, PPV 29.8%, NPV 91.6%, Area under the Curve 0.74.

Evidence statement 4:

Barriers and facilitators to identification based on validated scores for demographic and routine data

There was moderate evidence [+] from one Danish study (Heldegaard *et al* 2006 Denmark +) that validated scores developed from demographic and routine data (such as the Cambridge Risk Score) was a convenient method of identifying high risk individuals. This method does not require a questionnaire to be completed by patients.

ES 3 / 4 Applicability Rating:

These studies are partially applicable to the UK context, with one being based on a UK survey focussing on mid-life women. One study was carried out in a Danish general practice population; characteristics of the sample were not reported. Feasibility of the strategy is good as the risk score was developed in the UK and was designed for use with available data. However, applicability to specific populations other than midlife women cannot be assessed.

Evidence statement 5:

Questionnaire Risk Scores for the identification of pre-diabetes based on FINDRISC

There was strong evidence [++; +] from four studies (Franciosi *et al* 2005 Italy +; Saaristo *et al* 2005 Finland ++; Schwarz *et al* 2007 Finland +; Gray *et al* 2010 UK +) of the FINDRISC score.

The Italian Diabetes Risk Score, adapted for a CVD risk population, had a 77% specificity, 45% specificity at cut point 9 for identifying diabetes or IGT, with PPV 48%, AuC 0.67 (Franciosi *et al* 2005 Italy +).

The 8-item FINDRISC score (Saaristo *et al* 2005 Finland ++) with a maximum score of 26 was more sensitive and specific at cut point 11 for women than for men in a

general population survey for identifying Abnormal Glucose Tolerance (IFG / IGT). The PPV was higher for men (65.9 at cut point 11 compared to 45.2 for women) The NPV was correspondingly lower in men (57.7 compared to 72.4). AuC was 0.65 in men and 0.66 in women.

A shortened German version (Schwarz *et al* 2007 Finland +) with maximum score of 23 was more sensitive and specific at cut point 12 than the Finnish version at identifying IFG / IGT in a population with a family history of T2DM. There was evidence of good association between progressively higher scores and disease progression (P<0.01). 1996 data produced an optimal cut off point of 12 with 77.5% sensitivity and 67.8% specificity, PPV 19.7% and NPV 96.8%, AuC 0.78. 1997 data produced an optimal cut point of 9, with sensitivity 72.7%, specificity 68.2%, PPV 29.4 and NPV 88.1, AuC 0.74.

In the UK, the Leicester Risk Assessment (LRA) with a maximum score of 47 aimed at identification of Impaired Glucose Regulation / T2DM in a lay multi-ethnic population. A sensitivity of 72.1% and specificity 54.1% at cut point 16 was reported, with a PPV of 27.7% and an NPV of 88.8%. AuC was not reported. (Gray *et al* 2010 UK +).

ES 5 Applicability Rating:

These studies are partially applicable to the UK context, with one being based in the UK and focussing on multi-ethnic populations. The other three were carried out in EU populations. Feasibility of the LSA is good as the risk score was developed in the UK, though for a specific at risk population. Two studies were carried out in European countries, with one adapting the score for an at risk population. Applicability of the FINDRISC may depend upon adaptation to the target population.

Evidence statement 6:

Questionnaire based Risk Scores for the identification of pre-diabetes

There was moderate [+] evidence from three studies (Heikes *et al* 2008 US +; Glumer *et al* 2004 Denmark +; Rolka *et al* 2001 US +) relating to questionnaire based risk scores.

In one US population survey study (Heikes *et al* 2008 US +) the US Diabetes Risk Calculator at cut point 0.254 had a similar sensitivity (75%) but higher specificity

(65%) for identifying IFG / IGT as the Italian Diabetes Risk Calculator (77% and 45% respectively; Franciosi 2005 Italy +) at a cut point of 9 for identifying glucose abnormalities. PPVs were similar at 49% and 48% respectively. NPVs were 85% and 76% respectively.

The Danish Diabetes Risk Score (Glumer *et al* 2004 Denmark +) at cut point 31 and with 50% uptake had sensitivities between 45.2% and 47.8% across the two study groups and pilot. No other data for identifying IGT was given. The 7 item ADA questionnaire at cut point ≥10 gave a maximum specificity of 54% for dysglycaemia in a general US population (Rolka *et al* 2001 US +).

Evidence statement 7:

Barriers and facilitators to the use of questionnaire based Risk Scores for the identification of pre-diabetes

There was strong evidence [++] to suggest that requesting that patients complete a questionnaire based risk score may require someone to supervise the process. Such supervision has an impact on available resources. (Saaristo *et al* 2005 Finland ++).

ES 6 / 7 Applicability Rating:

These studies are less applicable to the UK context, with none being based in the UK. Implications of feasibility within the UK health service compared with, in particular, the US are therefore a consideration. However, all the studies were carried out in OECD countries.

Evidence statement 8:

Blood Glucose Indicators for identification of pre-diabetes: Non-fasting methods

Moderate evidence was found from six studies (+; -) (Simmons 2004 New Zealand +; Zhou 2010 China +; Rush 2008 US -; Somanavaar 2009 India +; Rolka 2001 US +; Phillips 2009 US +) that random or capillary blood testing alone to identify those at risk of pre-diabetes using a range of optimal cut points (5.6mmol/l to ≥7.8 mmol/l) had a sensitivity of between 24% and 64.6%. Specificity ranged from 59% to 97%. A specificity of 97% was reported by one study (Rolka 2001 US +) using a cut point of 7.8 mmol/l, and 94% was in another study (Rush 2008 US -) with an at risk Maori population. Sensitivities however were less than 50% in both cases.

The 1 hour oral glucose tolerance test was assessed in one general population study (Phillips *et al* US +). At cut off 7.8 mmol/l, reported sensitivity and specificity was 73% and 68% respectively with PPV 34%, NPV 92%, and AuC 0.73.

There was insufficient evidence from one study [-] of the general population (Maynard *et al* 2007 US -) relating to the use of a non-invasive blood glucose indicator technique (spectroscopic measurement of dermal advanced glycation end products - SAGE) which showed a sensitivity of 68%, with no further information provided.

ES 8 Applicability Rating:

These studies are not directly applicable to the UK context, with none being based in the UK, or European countries. The implications of feasibility within the UK health service compared with, in particular, the US and India therefore requires consideration. The targeted populations in these studies may also differ in prevalence of pre-diabetes to those in UK and also to those in general practice. However, feasibility of non-fasting methods may be high in general practice compared to fasting methods.

Evidence statement 9:

Blood Glucose Indicators for identification of pre-diabetes: Fructosamine

There was insufficient evidence to determine the effect of fructosamine alone. One [-] study from Poland (Herdzik 2002 -) using fructosamine alone at a cut point of 247 µmol/l produced sensitivity and specificity for identifying those at risk of pre-diabetes of 58.3% and 83.6%.

ES 9 Applicability Rating:

This study is not partially applicable to the UK context, being based in Poland where the characteristics of health service delivery may be different from those in the UK.

Evidence statement 10:

Studies assessing Fasting Plasma Glucose

There was moderate evidence [+] from two studies (Guerreo-Romero 2006 Mexico +; Mannucci *et al* 2003 Italy +) relating to the use of FPG measures.

One study (Guerreo-Romero 2006 Mexico +) reported that for the identification of impaired glucose tolerance (IGT), lowering the criterion for normal fasting plasma glucose (FPG) to 5.6 mmol /l from 6.1 – 6.9 mmol/l increased the sensitivity from 32.9% to 82%, but lowered specificity from 82.7 to 64.2%, with a related increase in PPV from 31% to 37.5%.

At a cut point of 6.1mmol/l, one study (Mannucci *et al* 2003 Italy +) reported different sensitivity and specificity for men and women when identifying IGT (sensitivity 40.9% and 29.0% respectively; specificity 25.0% and 18.0%). PPV and NPV were not reported.

ES 10 Applicability Rating:

These studies are partially applicable to the UK context, with one being carried out in Mexico where the target population and the health care system is very different from

the UK. One study was carried out in Italy which may differ from the UK in terms of health care delivery, but the target population is characteristically similar.

Evidence statement 11:

Studies assessing HbA1c alone

There was strong evidence [+] from four studies (Mostafa *et al* 2010 UK ++; Zhou *et al* 2009 China +; Mohan *et al* 2010 India +; Luders *et al* 2005 Germany +) relating to the performance of HbA1c.

In one UK study population, two Asian general population studies and one German high risk population HbA1c alone at a range of optimal cut off points (5.6% - 6.4%) were reported to give sensitivities of between 39% and 65.6% and specificities 56.5% - 84%.

Lower sensitivities and higher specificities were associated with higher cut points. The highest specificity (84%) and PPV (79%) for the highest cut point (6.0%) were obtained in a German population at high risk (hypertensive). One UK study (Mostafa *et al* 2010 ++) found that the optimal cut point and corresponding specificity was higher in south Asian groups than in white Europeans for detection of IGR (PPV 50%). A sensitivity of 65.1%, specificity 63.4% was obtained using the ADA criterion for identification of IFG (cut point 5.6%) in an Indian general population (Mohan *et al* 2010 India +). However the PPV was only 8.0% as the sample identified with IFG was very small.

Since these studies were published, WHO (2011) have issued a statement that HbA1c at cut point 6.5% can be used, in optimal conditions, to diagnose type 2 diabetes.

ES 11 Applicability Rating:

These studies are partially applicable to the UK context, with one study being carried out in the UK. One study was carried out in a German general practice which may differ from the UK in terms of health care delivery, but the target population is characteristically similar. Two studies were carried out in Asia. Feasibility of the test is high with no requirement for fasting.

Evidence statement 12:

Studies comparing non-fasting capillary blood glucose indicators to HbA_{1c}

There was moderate evidence [+] from one general population study (Zhou *et al* 2010 China +) that HbA1c at cut point ≥ 5.6 mmol/l had a very low sensitivity for men and women (4.5% and 5.7%) respectively in a sample with 29.5 % prevalence of pre-diabetes compared to Capillary Glucose measurements at cut point ≥6.0 mmol/l (66.3%) in a sample with 22.4% prevalence. However the PPV for HbA1c was 50.3% for men and 46.7% for women.

Since this study was published, WHO (2011) have issued a statement that HbA1c at cut point 6.5% can be used, in optimal conditions, to diagnose type 2 diabetes.

ES 12 Applicability Rating:

This study is not applicable to the UK context, being carried out in Eastern Asia where the health care system and the target population differ from the UK.

Evidence statement 13:

Studies comparing Fasting Blood Glucose (Fasting Capillary Glucose / Fasting Plasma Glucose) and HbA1c tests

Moderate evidence was available from seven studies [+; -] that compared fasting glucose testing with HbA1c (Herdzik *et al* 2002 Poland -; Simmons 2004 New Zealand +; Hu *et al* 2009 China +; Gomyo 2004 Japan +; Saydah 2002 US +; Luders 2005 Germany +; Colagiuri 2004 Australia +). All fasting blood measures were taken from plasma apart from one study (Herdzik *et al* 2002 Poland -) that measured capillary blood.

In six studies of high risk populations, FCG / FPG with cut points ranging from 5.5 mmol/l to 6.1 mmol/l and HbA1c cut points ranging from 5.3% to 6.1% (Herdzik *et al* 2002 Poland -; Hu *et al* 2009 China +; Gomyo *et al* 2004 Japan +; Saydah *et al* 2002 US +; Luders *et al* 2005 Germany +), the highest sensitivity was for the FPG in a Japanese trial population (69%) using a cut point of 5.7mmol/l (Gomyo *et al* 2004 +).

The highest specificity was 99% (obtained via capillary testing applying a low cut point of 5.5mmol/l; Herdzik *et al* 2002 Poland -), and with plasma testing at cut point 6.1mmol/l following risk assessment (100%).

The highest positive predictive value was 79% (NPV 66%) for HbA1c at a cut point of 6.0% in a German high risk population (Luders *et al* 2005 Germany +). Sensitivity and specificity were 58% and 84% with AuC 0.614.

Two studies carried out in the general population (Simmons 2004 + New Zealand +; Colagiuri *et al* 2004 Australia +), using cut points ≥ 5.3 mmol/l and 6.1 mmol/l for FPG and 5.3% for HbA1c reported that sensitivity was 66.3% and 50.9% (Simmons 2004 New Zealand +) and 34.6% and 42.0% (Colagiuri *et al* 2004 Australia +).

PPV was 36.8% for FPG and 46.6% for HbA1c, with an AuC of 0.88 and 0.68, with specificity and NPV not report (Simmons 2004 + New Zealand +). In Colagiuri *et al* (2004 Australia +), PPV was 45.5%, NPV 100% for FPG, with PPV 43.2% for HbA1c. NPV and AuC were not reported.

Since these studies were published, WHO (2011) have issued a statement that HbA1c at cut point 6.5% can be used, in optimal conditions, to diagnose type 2 diabetes.

ES 13 Applicability Rating:

Six of these studies are partially applicable to the UK context, having been carried out in OECD countries. However, health care delivery and prevalence for pre-diabetes may differ from the UK, particularly in the Maori and US populations. One study was carried out in China, where the characteristics of the health care system and the target population may be very different from the UK.

Evidence statement 14:

Studies assessing a combination of fasting blood glucose indicators and HbA_{1c}

Moderate evidence was found [+] in three studies that assessed the combined performances of Fasting Blood Glucose and HbA1c indicators in high risk populations (Hu *et al* 2009 China +; Luders *et al* 2005 Germany +; Coligiuri *et al* 2004 Australia +).

Sensitivity and PPV were highest (61%, 78%) with a combination of FPG cut point 6.1mmol/l and HbA1c 6.0% (Luders *et al* 2005 Germany +). Specificities were high in all three studies (>78%), though not as high as for HbA1c alone in one study (Luders *et al* 2005 Germany +). The highest specificity (88.4%) was obtained following assessment of risk factors in a stepped strategy (Coligiuri *et al* 2004 Australia +).

It may therefore be beneficial to combine tests in a staged strategy.

Since these studies were published, WHO (2011) have issued a statement that HbA1c at cut point 6.5% can be used, in optimal conditions, to diagnose type 2 diabetes.

ES 14 Applicability Rating:

Two of these studies are partially applicable to the UK context, having been carried out in OECD countries. However, health care delivery and prevalence for pre-diabetes may differ from the UK. One study was carried out in China, where the characteristics of the health care system and the target population may be very different from the UK.

Evidence statement 15:

Stepped / multi-component strategies

Moderate to good evidence [+; ++] was found from six studies of multi-component / staged strategies to identify IGT / IFG (Colagiuri *et al* 2004 +; Franciosi *et al* 2005 +; Lidfelt *et al* 2001+; Luders *et al* 2005 +; Rolka *et al* 2001 +; Simmons *et al* 2004+).

Three studies were carried out in at risk populations (Lidfelt *et al* 2001 Sweden +;

Luders *et al* 2005 Germany +; Franciosi *et al* 2005 Italy +). All six studies utilised assessment of risk prior to evaluation of one or more blood glucose indicators. A combination of FPG cut point 6.1 mmol/l, HbA1c cut point 6.0% and risk assessment for age gave a sensitivity of 82%, specificity 76%, PPV 79% in one study (Luders *et al* 2005 Germany +). This compares to sensitivity 58%, specificity 84% for HbA1c alone (≥ 6% cut point) and 62%, 57% for FPG alone (6.1mmol/l cut point).

Franciosi *et al* (2005 Italy +) reported increased specificity (65% at cut point ≥5.6mmol/l and 84% at cut point ≥6.1mmol/l) with the addition of the Diabetes Risk Score to FBG compared to the risk score (45% at cut point 9) or FBG alone (44% at cut point ≥5.6mmol, 75% at cut point ≥6.1mmol/l). PPV was highest (69%) for the FBG at ≥6.1mmol/l and the risk score, with NPV 74%. AuC was not reported for this combination.

Rolka *et al* (2001 US +) reported similar specificity for the addition of the ADA questionnaire (94-5%) to capillary blood glucose testing at cut point 7.8 mmol/l (96-7%), which was higher than that for the ADA questionnaire alone (51-4%) at cut point ≥ 10. Sensitivity reduced with each stage, from 72-8% for the questionnaire alone, to 28-41% and 32-45% for the CBG and the CBG with the questionnaire. PPV, NPV and AuC were not reported.

Since these studies were published, WHO (2011) have issued a statement that HbA1c at cut point 6.5% can be used, in optimal conditions, to diagnose type 2 diabetes.

ES 15 Applicability Rating:

All of these studies are partially applicable to the UK context, having been carried out in OECD countries. The target populations will be relatively similar to those in the UK, though health systems may vary.

Evidence statement 16:

Costs of implementation of blood glucose indicator and stepped strategies for identification of pre-diabetes.

There was moderate evidence [+] from one study Australian stepped study (Colagiuri *et al* 2004 +) that costs were $A 8.05 for FPG, $A 14.15 for HbA1c. A return visit to obtain the result of the blood test was reported as costing $A 25.05; OGTT $A 15.90, and return final visit to the primary care physician for the result $A 25.05. Total cost for each person identified with IGT or IFG was reported as $A 260.

ES 16 Applicability Rating:

This study is partially applicable to the UK context, having been carried out in an OECD country. The target populations will be relatively similar to those in the UK, though the health system may vary.

Evidence statement 17:

Barriers and facilitators to implementation of blood glucose indicator and stepped strategies for identification of pre-diabetes.

There was no available evidence within the included studies for barriers or facilitators to implementation of blood glucose indicator and stepped strategies for identification of pre-diabetes.

Evidence Statement 18: Uptake

Moderate evidence was found [+;-] from nine studies (Glumer *et al* Denmark 2004 +; Gray *et al* 2010 UK; Mohan *et al* 2007 India +; Phillips *et al* 2009 US +; Rush *et al* 2008 US -; Simmons *et al* 2004 New Zealand +; Somanavaar 2009 India + ; Thomas *et al* 2006 UK +; Zhou *et al* 2010 China +).

For risk assessment, response rates ranged between 50% and 89%. The highest response rate reported was for the Cambridge Risk Score (Thomas *et al* 2006 UK +), and the lowest reported was for the Diabetes Risk Score (Glumer *et al* Denmark 2004 +). In an evaluation of the Leicester Risk Assessment, 22% of the initial South Asian sample remained in the study following a series of tests including the OGTT. (Gray *et al* 2010 UK +).

For blood glucose measures, there was a 52.5% response rate to the first visit for a 1 hour oral glucose tolerance test (Phillips *et al* 2009 US +). Random / Point of care testing was reported to have a response rate of 89% (Somanavaar 2009 India +) and 61% (Rush *et al* 2008 US -)

Response rates for assessment of the HbA1c were reported as 87% (Zhou *et al* 2010 China +) and 93% (Mohan *et al* 2007 India +), though the Chinese based study also included assessment of fasting blood glucose, for which there was a response of 91%.

Simmons *et al* (2004 New Zealand +) conducted OGTT, fasting blood glucose and HbA1c measures from one blood sample. The response rate for this visit was 68% in those aged 40-59 years and 71% in those aged 60-79 years. There were no reported differences in response between Maori, European and Pacific Islander groups or between age groups. Response rate was reported to be similar between males and females apart from in the European group, where males were less likely to respond (66.5% rate compared to females 73.9%, p=0.012).

ES 18 Applicability Rating:

These studies are partially applicable to the UK context, with two being carried out in the UK. In the remaining studies, health care delivery and prevalence for pre-diabetes may differ from the UK. Uptake rates may differ due to a range of factors, including targeting a study population rather than the general population.

Evidence statement 19:

Barriers and facilitators to uptake for strategies for identification of pre-diabetes.

Potential facilitators to increasing uptake were suggested in two studies. Woolthuis *et al* (2007 +) found that one facilitator was carrying out risk assessment in a familiar clinic environment. Greaves *et al* (2004+) reported that their good uptake rate may be due to confirmation of appointments and follow-up contact with patients by telephone.

ES 19 Applicability Rating:

These studies are directly applicable to the UK context, with one being based in the UK. One study was based in the Netherlands. Both studies sampled from general practice populations, though the majority of the samples were Caucasian.

3. INTRODUCTION

Type 2 diabetes is associated with significant clinical and social consequences. The National Institute for Health and Clinical Excellence has been asked by the Department of Health to develop public health guidance on the prevention of type 2 diabetes among high-risk groups. The referral is divided into two separate pieces of guidance. The first addresses the prevention of pre-diabetes (raised and impaired glucose levels) in populations and communities of high risk adults using community based interventions. The second piece of guidance will address how to prevent the progression from pre-diabetes to type 2 diabetes. To inform development of this second piece of guidance, four reviews of international evidence will be carried out that address the prevention of progression to type 2 diabetes as well as a health economic / modelling review. This document reports on the first of these reviews. It focuses on the effectiveness and cost-effectiveness of strategies and tools designed to identify individuals at risk for pre-diabetes.

Type 2 diabetes has a long preclinical phase, with the condition remaining undiagnosed for many years in a significant number of cases (Woolthius *et al* 2007). A group of conditions defined by blood glucose levels that fall between normal and those defining type 2 diabetes are typically known as Impaired Fasting Glucose (IFG) and Impaired Glucose tolerance (IGT) or collectively as 'pre-diabetes'. It is recognised that the term 'pre-diabetes' is not ideal, as not everyone with raised or impaired blood glucose levels will go on to develop type 2 diabetes. However, the term 'pre-diabetes' has been chosen because of its widespread use and recognition by a broad range of stakeholder groups and because of the lack of consensus on a suitable alternative.

The terms 'risk assessment' and 'risk reduction' are used in preference to the term 'screening'. Screening terminology tends to imply that results are either positive or negative and that it is possible to place all individuals into categories of low and high risk with only those at high risk requiring further intervention. "Risk assessment" implies an individualised approach that takes into account individual risk factors. In relation to type 2 diabetes, risk lies on a continuum according to known risk factors, many of which also present on the continuum of risk for other conditions, such as CVD (UK NSC 2008). Many individuals with risk factors will still be at high risk of developing diabetes in the future even if their glucose tolerance is currently still in the normal range. A person is therefore never totally risk-free, and prior to a diagnosis of type 2 diabetes can move either way on the continuum. Risk reduction is the aim of

health promotion advice, which needs to be communicated according to a person's perception of their own risk as well as formally assessed risk.

A number of large studies have been carried out internationally that aim to identify effective interventions to delay or prevent development of type 2 diabetes in individuals at high risk. Such interventions require an effective method to identify at risk individuals and to meet this requirement for effective methods to identify those at high risk a range of identification and risk assessment methods have been developed building on methods developed initially to screen for Type 2 diabetes. Tools and tests used to identify individuals with type 2 diabetes will also identify those with pre-diabetes since the risk factors and diagnostic tests are essentially the same and the diagnoses of 'pre-diabetes' or 'diabetes' represent clinically and epidemiologically defined cut-offs on a continuous spectrum of hyperglycaemia and impaired glucose tolerance.

An additional statement has been released by WHO (2011) recently that allows the diagnosis of type 2 diabetes to be made using the HbA1c blood test at a cut point of 5.6%. There was no statement regarding the diagnosis of IFG or IGT using HbA1c due to insufficient evidence. This statement was made after the publication of the included studies in this review.

Assessment of a person's risk for diabetes can be carried out opportunistically, or through a structured strategy, such as the UK "Health Check" programme. Risk assessment can be carried out using risk tools, and / or a range of blood tests. Blood tests are also required for diagnosis; for example the fasting plasma glucose (FPG) blood test for impaired fasting glucose (IFG) and the Oral Glucose Tolerance Test (OGTT) for impaired glucose tolerance (IGT). They are also used to diagnose type 2 diabetes. Other blood glucose tests, such as random capillary, fasting capillary, and HbA1c are being assessed for their utility in both risk assessment and diagnosis of IFG / IGT (pre-diabetes). Therefore, the risk assessment / diagnosis process can involve a number of non-invasive and invasive tests in isolation or combination that may require regular repetition for those presenting with risk factors and / or symptoms (Williamson & Narayan 2009), since risk is ever-present and blood glucose levels will represent risk of progression to type 2 diabetes over time.

Evaluating strategies for risk assessment and diagnosis of pre-diabetes involves comparing the test's ability to identify with that of a recognised diagnostic test (such as the FPG or the OGTT). The OGTT is known as the 'Gold Standard' for identifying IGT, but has resource and acceptability limitations. Alternatives may be more acceptable and / or economical, but less reliable (Williamson & Narayan 2009).

In order to identify an optimal cut off point, a trade off needs to be made between the sensitivity and specificity of a test. The sensitivity can be defined as the proportion of people (%) with the disorder who test positive on the test. A highly sensitive test is unlikely to miss someone who does have pre-diabetes. Specificity can be defined as the proportion of people (%) who do not have the disorder who test negative on the test. A highly specific test is unlikely to misclassify someone who does not have pre-diabetes as having pre-diabetes. The sensitivity and specificity of tests therefore have ethical implications in regard to the potential mis-diagnosis of persons that do not in fact have a condition, or the potential missed diagnosis of persons that do have the condition. In addition, a more sensitive test will identify more cases, and therefore resources need to be in place to deal with this in terms of follow up and interventions. Higher cut-off points for risk scores and diagnostic tests will lower sensitivity whilst improving specificity, while lower cut-off points will have the opposite effect (Williamson & Narayan 2009).

Whilst it is desirable to have a test that is both highly sensitive and specific this is not usually possible. The relationship between the two is shown in the receiver operator characteristic curve (ROC). The true positive rate (sensitivity) is plotted on the y axis against the false positive rate (1-specificity) over a range of cut-off points. On the curve, tests that discriminate well crowd toward the upper left corner. Ideally, as sensitivity increases there is little decrease in specificity until high levels of sensitivity are reached. Tests that perform no better than chance give a diagonal line. In some studies, the Area under the Curve (AuC) is also reported. The AUC ranges from 0 to 1, with 0.5 indicating a poor test where the accuracy is equivalent to chance (CRD 2009).

Studies also sometimes report the predictive values of a test. This relates to the probability that a person has or does not have the disorder given the result of the test, with the Positive Predictive Value (PPV) being the probability of the disorder in a person with a positive test result. The Negative Predictive Value (NPV) is the probability of a person not having the disorder with a negative test result (WHO 2003). To increase the positive predictive value and therefore the number of positives that are true positives (or yield), assessment of risk would be carried out in a population with known higher prevalence, such as older, obese adults (Williamson & Narayan 2009).

It is increasingly accepted that testing for pre-diabetes in those most at risk is an important step in preventing progression to type 2 diabetes, particularly as risk is a

continuum that can be identified by blood glucose measurements over time. Provision of support needs to be in place for those identified with pre-diabetes and therefore at risk of developing type 2 diabetes. For example, identification of pre-diabetes may be an appropriate time to intervene with behaviour change advice whilst progression to clinical diabetes can still be prevented.

3.1 Aims and objectives

The aim of this first review was to undertake an assessment of the evidence for the effectiveness and cost-effectiveness of strategies and tools designed to identify individuals at high risk of progression to diabetes due to the presence of pre-diabetes. The review focuses on risk assessment and identification strategies as well as the barriers and facilitators to such strategies. The objectives were to assess and synthesise evidence pertaining to each of the three steps that can occur in risk assessment strategies, the use of demographic information, risk score tools as well as diagnostic tools. Evidence from included studies that addresses costs, acceptability and uptake of both risk assessment and diagnostic testing will also be reported.

Research questions:

What is the evidence for the effectiveness and cost-effectiveness of methods to identify adults with pre-diabetes, especially the evidence for how to increase identification and the uptake of risk assessment in high-risk groups?

How does the effectiveness and cost-effectiveness of strategies vary according to the following:

a) For tools, cut-off points that are deemed most effective?

b) Sensitivity, specificity, PPV, NPV and area under the curve if appropriate?

c) Whether the strategy is based on an underlying theory or conceptual model?

d) Diversity of the population (e.g. in terms of the user's age, gender or ethnicity) for whom the strategy is designed?

e) Status of the person (or organization) delivering the strategy and the way it is delivered?

f) Settings, and whether these are transferable to other settings?

4. BACKGROUND

4.1 Description of the health problem

The NICE scope (2009b), which sets out what the guidance will and will not cover, highlights that every year, 100,000 people in the UK are diagnosed with type 2 diabetes and many more may have the condition (Diabetes UK 2006). It can lead to long-term complications including micro- and macrovascular diseases such as eye problems, kidney disease, foot ulcers and cardiovascular pathologies. Between 33% and 66% of people with pre-diabetes – raised or impaired blood glucose levels – will go on to develop type 2 diabetes over a period of 3–6 years (Diabetes Prevention Programme Research Group 2002; Lindstrom *et al* 2003; Pan *et al* 1997; Ramachandran *et al* 2006). During that time they will also be at increased risk of cardiovascular disease (Waugh 2007).

In addition to the personal cost to individuals, families and communities, diabetes is estimated to account for at least 5% of UK healthcare expenditure. Up to 10% of hospital budgets are used for the care of people with the condition – drug costs alone for people with type 2 diabetes have been estimated to account for about 7% of the total NHS drugs budget (Waugh *et al* 2007). Preventing pre-diabetes among groups at high risk of developing type 2 diabetes could help save some of these NHS resources.

In 2007, 60% of primary care trusts (PCTs) had programmes in place to raise public awareness of the risk factors for diabetes and 37% were raising awareness of its signs and symptoms. Only 42% had specifically assessed the needs of their population in relation to diabetes and less than 40% had developed a diabetes strategy (Innove 2008).

An individual's risk factors for pre-diabetes include: obesity (a body mass index [BMI] of more than 30 kg/m2); a high waist circumference measurement (more than 80 cm in women and 94 cm in men); a sedentary lifestyle; a close family history of type 2 diabetes; a history of gestational diabetes in women; and being older than 40 (or older than 25 for some black and minority ethnic groups). In addition, certain groups of people are at greater overall risk of developing pre-diabetes, for example people of south Asian, African–Caribbean and black African descent. With rates of obesity on the increase and the population becoming more sedentary (The Health and Social Care Information Centre 2009) type 2 diabetes (and pre-diabetes) is becoming more prevalent.

For many people, both pre-diabetes and type 2 diabetes can be prevented by being supported in changing lifestyle behaviours such as improving diet and increasing physical activity levels (Tuomilehto 2001). In some cases where these are not possible or have not been successful, certain drug therapies and surgical procedures are available that aim to reduce BMI.

In order to identify individuals with pre-diabetes that are therefore at risk from progressing to type 2 diabetes, a range of tools and strategies have been developed. These are sometimes used in sequel as part of a stepped programme (Sandbaek *et al* 2008). The first part of the strategy involves identification of individuals from data in practice registers that have identified risk factors such as a raised BMI and / or waist circumference, a family history of type 2 diabetes, and previous gestational diabetes. In addition, basic demographic data such as age, sex and ethnicity are used in this identification process.

Once identified, those at increased risk can be further assessed using specific risk assessment tools. A range of these exist; the review aims to explore the reported aims and outcomes for individual known tools.

A high risk score could mean that an individual has (or is likely to have) pre-diabetes or type 2 diabetes. To test this several tests are available each having different characteristics in terms of costs and benefits for both the user and provider organisation.

5. METHODS

5.1 Methods for identification of evidence

A systematic review of the effectiveness of strategies to identify and assess risk for pre-diabetes was undertaken according to the general principles recommended in the methods guide for development of NICE public health guidance (2009a). Methods followed the development of a review protocol and search protocol and are detailed below.

5.1.1 Search Strategy

The standard NICE Methods, as outlined in the Methods for the Development of NICE Public Health Guidance (2009) were used to guide the development of the search methods. The aim of the search strategy was to retrieve the best available evidence to inform the effectiveness and cost effectiveness reviews, the views review and the economic model.

An initial search was carried out supplemented by an additional more focussed search for gaps found in the literature in order to ensure that the review topic was fully explored as the reviews progressed. The search strategies were developed in conjunction with NICE Information Specialists.

Instead of aiming to identify the relevant literature for a specific question using one search, we adopted an emergent approach which attempts to identify key literature. The initial search strategy, using concepts taken from the scope, formed the basis of the search strategies for the review questions. A further review focussed search was then generated for review one by identifying free text and subject headings from studies identified from the initial search and key known literature as being relevant to the review question. Iterations were then repeated as new concepts were identified, within the time frame of the study.

The questions to be addressed in the reviews have differing existing evidence bases. Therefore, decisions on the type of evidence (e.g. RCTs, observational studies) to be used in the reviews were made through an iterative searching process that allows decisions to be made based on the available evidence.

The initial overarching search was limited from 1990-2010, English language and human studies. All other searches for review one were limited to English Language, 1998-2010 and human studies. This date was chosen due to changes made in diagnostic cut-off points for the diagnosis of type 2 diabetes, IGT and IFG at this

time. Literature based on earlier criteria would not be comparable with that relating to research carried out since the changes.

A thorough audit trail of the search process was maintained; this includes all searches, number of results and number of relevant references identified. This process ensures that the search process is transparent, systematic and replicable.

In addition to the database searching, additional searches were undertaken in specialist websites in order to identify evidence not indexed in the bibliographic databases. The ScHARR team also conducted reference and citation searching for those studies identified for inclusion in the reviews using Web of Science (via Thomson ISI), Scopus (via Elsevier) and Google Scholar.

An overview of evidence sources are below, with detailed information including location of websites and sample search strategies presented in Appendix 3.

List of Databases Searched for Review One

Medline via OVID SP

Embase via OVID SP

CINAHL via EBSCO

British Nursing Index via OVID SP

The Cochrane Library via Wiley

Science Citation Index via Thomson ISI

Social Science Citation Index via Thomson ISI

PsycINFO via OVID SP

Selected EPPI Centre Databases

5.2 Study selection

All of the retrieved literature was screened by one of three reviewers (MJ, EEH, and RJ) and double-checked by one other reviewer at title and abstract level for relevance, and those relevant were taken through to full paper appraisal (see section 5.4 for full process details).

Study inclusion and exclusion was based on the following criteria, which were presented in the initial scope document:

5.2.1 Individuals / groups that will be covered

a) Adults aged 18 years and over with a diagnosis of pre-diabetes using current World Health Organization criteria (World Health Organization 2006), that is either or both:

- Impaired fasting glucose (IFG) – a fasting plasma glucose (FPG) between 6.1 and 6.9 mmol/litre.

- Impaired glucose tolerance (IGT) – FPG less than 7.0 mmol/litre and a plasma glucose (2 hours after ingestion of a 75 g oral glucose load, the oral glucose tolerance test) between 7.8 and 11.0 mmol/litre.

The diagnostic criteria for IFG and IGT and type 2 diabetes are expected to be revised by the World Health Organization in 2010. Any forthcoming changes to current diagnostic criteria that might result in possible changes in interpretation of the evidence will be dealt with by taking advice from the PDG and following their direction on this matter.

b) The review will focus on the following populations:

- South Asian, African–Caribbean, Chinese or black African descent and older than 25 years, or white and aged 40 years or older, and who have one or more of the following characteristics:
  obesity (a body mass index [BMI] of 30 kg/m^2 or above, or 27.5 kg/m^2 or above if of south Asian or Chinese descent)
  a waist circumference:
  - ◊ greater than 80 cm for women of European or African descent
  - ◊ greater than 94 cm for men of European or African descent
  - ◊ equal to or greater than 80 cm for women of south Asian or Chinese descent
  - ◊ equal to or greater than 90 cm for men of south Asian or Chinese descent (Alberti *et al* 2007)

  a history of cardiovascular disease
  abnormal blood lipids or lipoprotein level (for example low high-density lipoprotein [HDL] cholesterol)
  hypertension
  a first-degree relative with type 2 diabetes
  sedentary lifestyle.

c) If the evidence allows, people with the following characteristics will be covered:

- severe mental health problems
- learning disabilities
- taking medication that can increase the risk of developing diabetes such as steroids, anti-retrovirals and some antipsychotics
- polycystic ovary syndrome
- low birth weight, that is less than 2.5 kg (5.5 lbs)
- women with a history of diabetes in pregnancy and women who have had a baby over 4.5 kg (9 lbs).

5.2.2 Groups that will not be covered

- People younger than 18 years of age.
- People with a diagnosis of type 2 diabetes or other forms of diabetes.
- Pregnant women.

5.2.3 Strategies / Tools that will be covered

Interventions delivered at individual, family, community and population levels in primary, secondary and tertiary care, the community, residential care sector, and prisons. For this review, this will focus on:

- Identification and risk assessment of adults with IFG/IGT or raised glycated haemoglobin (HbA1c).

5.2.4 Strategies / Tools that will not be covered

Identification and risk assessment for individuals with type 2 diabetes, gestational diabetes or any other form of diabetes. (Type 1 diabetes, type 2 diabetes and diabetes in pregnancy are the subjects of previously published NICE guidance).

5.3 Data Extraction

Data were extracted with no blinding to authors or journal. Data were extracted by one of three reviewers (MJ, EEH, RJ) using a standardised form. As highlighted in the Cochrane Collaboration guidelines for systematic reviews of health promotion and public health interventions, extraction forms should be developed for each review

in order to make them relevant to the information that is required. The forms for extracting data on diagnostic tools were based on the example forms presented within the NICE public health guidance (2009a).

The forms were piloted on two randomly selected articles that assess identification and risk assessment strategies in order to confirm appropriateness for use. Information relating to the review question, study design, outcomes and conclusions were collated. The data extracted for effectiveness evidence included information relating to the strategy under study, namely objectives, content, intervener, tool components, mode of delivery, setting and population. Data extracted by each reviewer was checked by a second reviewer to ensure reliability. Any studies giving rise to uncertainty were reviewed independently by a third reviewer, and discrepancies, for example where studies were not clearly reported, were resolved by discussion.

5.4 Quality assessment

The quality of included studies was assessed by one of three reviewers (MJ, EEH, RJ) using quality criteria based on those developed for the critical appraisal of risk assessment evaluation studies in previous guidance. The criteria used items from the QUADAS checklist (Whiting *et al* 2003), a quality assessment tool designed for reviews of diagnostic accuracy studies. All quality assessments were double checked by a reviewer not involved in the initial assessment.

Studies were graded with ++, + or – as recommended by NICE (see Table 1). Greater consideration was given to the performance of the study on criteria fundamental to the robustness of the findings. Study quality did not determine inclusion into or exclusion from the review, and was carried out with reference to the review question, therefore the same paper may have received a different grading for the effectiveness review than for the views part of the question.

While it is noted that criteria may not be judged as having equal value in quality assessment, in the interests of consistency, a subjective score of 5 or 6 out of 6 criteria fulfilled was rated as ++, 3 or 4 rated as + and below 3 rated as -. Quality assessment is confirmed by a second reviewer in order to minimise any potential bias.

Table 1: Study quality

Grade	Criteria
++	All of the criteria have been fulfilled. Where they have not been fulfilled the conclusions are thought very unlikely to alter.
+	Most of the criteria have been fulfilled. Those criteria that have not been fulfilled or adequately described are thought unlikely to alter the conclusions.
–	Few or no criteria have been fulfilled. The conclusions of the study are thought likely or very likely to alter.

The criteria used were:

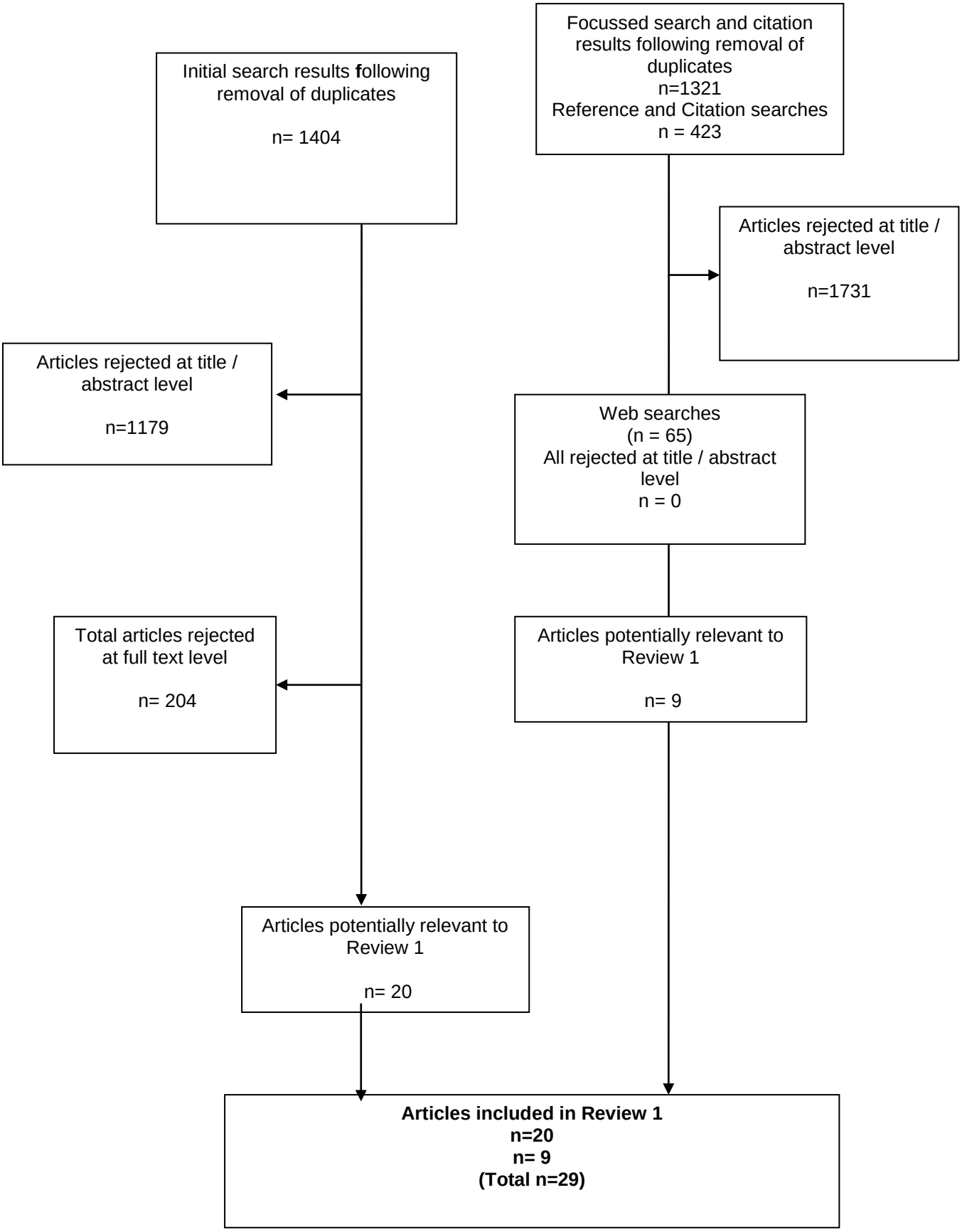
1. Were demographics provided?
2. Was co-morbidity described?
3. Were eligibility criteria and participation rate provided?
4. Criterion standard evaluation of all screened subjects?
5. Analysis of pertinent subgroups?

5.5 Data analysis and synthesis

A synthesis of available evidence is presented in Section 6. Data synthesis was informed by the methods advocated by NICE public health guidance (2009a). Pre-specified outcomes are tabulated in evidence tables and presented within a preliminary narrative synthesis. For the data synthesis, papers were classified according to the type of risk assessment strategy and specific measures such as single strategy, comparisons and combinations. Because of the considerable heterogeneity of the study populations and study designs it was not possible to conduct a meta-analytical review. Therefore, a narrative approach to synthesis was adopted, where key outcomes and findings are reported in the text of the report, summarised in the tables and this information is used to consider and address the review questions in the discussion section.

6. RESULTS

Figure 1: Flow chart of paper selection



6.1 Included studies

From an initial total of 2725 references, a total of 29 papers of varying study type and quality met the inclusion criteria for the review of strategies for identification and risk assessment for pre-diabetes. One further paper was included following citation searches.

Two papers assessed the use of routine demographic data found in practice records as an approach for identifying patients that might be at risk for pre-diabetes. Two studies assessed the use of a validated score derived from such records. Seven studies evaluated risk assessment scores using a questionnaire. Eighteen studies assessed a range of strategies using blood glucose indicators, including non-fasting methods (6), fasting plasma glucose (2), HbA1c alone (4), comparison of HbA1c with non-fasting blood glucose measures (1), comparison of HbA1c with fasting blood glucose measures (7), combination of HbA1c and fasting blood glucose measures (3), and stepped strategies using at least two approaches (6). Nine studies reported on study response rates.

6.1.1 Quality of included studies

The quality of papers was reasonable, with 2 papers rated as very good (++), 24 as good (+) and 3 as poor (-).

6.1.2 Limitations to study quality

A key limitation found in included studies was a lack of clarity in reporting progressive stages within the study. The studies typically had complex designs that were often difficult to follow. The distinction between performances of diagnostic tools in identifying pre-diabetes rather than type 2 diabetes was often vague. In addition PPV, NPV and AuC values were often missing from the findings.

6.2 Narrative summaries of included studies

The following is a list of the included studies, described in narrative form in alphabetical order. This will be followed by tables that display study findings in relation to different types of tools and strategies.

Colagiuri *et al* (2004 +) assessed the AusDab protocol for identifying type 2 diabetes and impaired glucose metabolism. The protocol is based on a three stage stepped

approach where the first stage is risk assessment. Those considered at risk move to the next stage of FPG measurement and possible further testing according to the FPG results. The authors also included an assessment of HbA1c and other variations to the protocol.

The study utilized a representative sample of 11,247 people from the general population aged 25 and over from 42 randomly selected areas in Australia. Of these, 475 had known diabetes and data was unavailable for another 264, leaving 10,508 to be included in the analyses. Each participant completed a health questionnaire and underwent physical examination to assess blood pressure, weight and height, calculation of BMI. Blood was collected for measurement of lipids and HbA1c.Those that were not taking insulin or hypoglycaemic agents for diabetes had an OGTT performed, the results of which found that 7.4% had diabetes, half of whom were unaware of their condition prior to the programme.

Beginning with opportunistic risk factor identification, 5,604 had at least one risk factor specified in the AusDab protocol, which indicated the need for FPG measurement. When weighted to the Australian population, this meant that 47.4% of adults ≥ 25 years would require testing. Of the 5,604 with risk factors, 2,723 (48.6%) had an FPG ≤5.5 mmol/l and so were deemed at low risk. A further 210 (3.7%) had an FPG ≥ 7.0 mmol/l, indicating diabetes. The remaining 2,671 (47.7%) had FPG 5.5 - 6.9 mmol/l and would have been recommended to have an OGTT. The effect of various modifications to the current guideline was assessed; the optimal FPG cut point for detecting previously undiagnosed diabetes and IGT/IFG was ≥ 5.5, and for HbA1c the cut point was 5.3%.

Of the 10,508 people included in the study, 1,372 (11.0%) had IGT and 642 (5.9%) had IFG. Assessing risk factors and performing FPG at cut off ≥5.5% (in line with the Australian protocol) gave a sensitivity of 51.9% and specificity 86.7% with a PPV of 45.5% for detecting IGT / IFG. Increasing the FPG cutoff to ≥ 6.1 mmol/l decreased the sensitivity to 34.6%, though specificity was reported as 100%. Assessing risk factors and performing HbA1c at cut off ≥5.3% gave a sensitivity of 42.0% and specificity 88.2% with a PPV of 43.2%. AuC was not reported.

The single risk factor that identified most people (71.5%) as being at high risk for undiagnosed diabetes was age ≥ 55 years, and another 24.2% were identified because they were age 45–54 years with one of the following: BMI≥ 30 kg/m2, hypertension, or family history of diabetes.

Costs: The cost in Australian dollars ($A) to the health care system for the screening options for detecting each person with newly diagnosed diabetes or IGT/IFG was calculated using the following scenario. Risk factor assessment was done opportunistically at the time of a routine visit to the primary care physician without incurring an additional cost, the blood test was ordered as an additional test (cost $A 8.05 for FPG, $A 14.15 for HbA1c), the person returned for a visit to the primary care physician specifically to obtain the result of the blood test (cost $A 25.05), and individuals with an equivocal FPG had an OGTT (cost $A 15.90) and then returned for a final visit to the primary care physician for the result (cost $A 25.05). These costs are based on the published national fees specified by the Health Insurance Commission of Australia.

The cost for detecting each person with newly diagnosed diabetes using the current Australian protocol is $A 746, and $A 260 for each person with IGT or IFG. Increasing the FPG cut point to≥6.1mmol/l alters costs to $A 700 for diabetes and $A 292 for IGT or IFG, whereas the corresponding costs for a protocol based on risk factor assessment followed by measurement of HbA1c are $A 828 and $A 352, respectively. It should be noted that the cost of making a clinical diagnosis of diabetes will be slightly higher because of the repeat testing required to confirm the diagnosis. The authors conclude that the costs of screening associated with protocols that used HbA1c were predictably higher than those that relied on FPG, but, overall, the costs were not particularly high and generally could be considered affordable in the context of opportunistic screening programs.

The authors conclude that overall, the protocol identified around 8 out of 10 people with type 2 diabetes, 5 out of 10 who had IGT, and 7 out of 10 of those who had IFG. They state that strategies for detecting IGT/IFG using HbA1c alone to identify those needing further testing with an OGTT was less sensitive than strategies using the FPG to identify those needing further testing.

Franciosi *et al* (2005 +) carried out a study which formed part of the IGLOO Impaired Glucose Tolerance and Long-Term Outcomes Observational) study, to evaluate an opportunistic screening strategy applied by general practitioners for individuals with one or more cardiovascular risk factor. The tool being tested was the Diabetes Risk Score (DRS), a questionnaire based tool adapted from the FINDRISC to identify individuals with type 2 diabetes or impaired glucose tolerance (IGT).

Of the initial 1,840 recruited individuals, 1,377 completed the evaluation (DRS and OGTT) giving a response rate of 74.5%. The effectiveness of a three-step screening strategy to identify individuals with undiagnosed diabetes or IGT, while reducing the number of those needing an OGTT was also tested. The first step was assessment of the DRS. The second step was the measurement of fasting blood glucose (FBG) and the third step was an OGTT follow up in selected subgroups.

Prevalence rates of 20%, 10% and 5% glucose abnormalities (IGT + T2DM) were tested for the likely behaviour of the proposed risk assessments. Patients excluded from the analyses did not differ from those included in terms of age, BMI, waist circumference, levels of cholesterol and triglycerides, dyslipidemia, or presence of metabolic syndrome. Patients not included in the analyses were reported to be less often men (45.6% males were not included vs 51.7% women p=0.02) implying that women were less likely to be included. The authors tested the DRS and FBG alone as well as in combination, giving values for both results being positive and for both results being negative to identify the degree of certainty that participants either do or do not have pre-diabetes.

The DRS alone at a cut off ≥ 9 points showed a sensitivity of 77% (95% CI 0.74–0.81) and specificity 45% (95% CI 0.41–0.48), PPV 48% (95%CI 0.44–0.51) and NPV 76% (95%CI 0.71–0.79), AUC 0.67 (95% CI 0.64–0.70) at cut-off >9.

FBG alone at ≥6.1 mmol/l had a sensitivity of 68% (95% CI 0.64–0.72), specificity 75% (95% CI 0.72-0.78), PPV 0.64, NPV 0.78. Using a cut-off of FBG 5.6 mmol/l, a sensitivity of 86% (95% CI 0.84–0.89) and specificity 44% (95% CI 0.41 – 0.48), PPV 0.50, NPV 0.83 was shown.

Combined use of the DRS at cut-off >9 with an FBG cut off of ≥6.1 mmol/l led to 90% (95% CI 0.88–0.93) sensitivity with both tests negative. The specificity in this case was 78% (95% CI 0.76–0.81), PPV 0.48, NPV 0.85. To raise the specificity to 84% (95% CI 0.81–0.86) with both tests positive meant a reduction in sensitivity to 55% (95% CI 0.51–0.59), PPV 0.69, NPV 0.74.

Combined use of the DRS at cut-off >9 with an FBG cut off of ≥5.6 mmol/l led to 95% (95% CI 0.93–0.97) sensitivity, 24% specificity (95% CI 0.21–0.27), PPV 55%, NPV 88% with both tests negative.

Combined use of the DRS at cut-off >9 with an FBG cut off of ≥5.6 mmol/l led to 69% (95% CI 0.65–0.73) sensitivity, 65% specificity (95% CI 0.62–0.69), PPV 56%, NPV 76% with both tests positive.

Glumer *et al* (2004 +) reported on a Danish study that aimed to develop a simple self-administered questionnaire that would assist in the identification of individuals with undiagnosed diabetes. The rationale behind the study was that the crude prevalence rate of diabetes in Denmark was 6.3 and that 65% of individuals with diabetes were unaware of the disease. Regular screening in Denmark is not recommended and before screening is implemented a number of uncertainties have to be resolved, such as who should be screened, whether a high-risk group needs to be identified to minimise the extent of subsequent blood glucose testing to diagnose or rule out pre-diabetes or type 2 diabetes, and whether screening is feasible. A further aim of the study was that the questionnaire would identify at least 75% of individuals with diabetes and reduce the number of subsequent blood tests to 25%.

A large Danish population sample of 12,934 individuals aged 30-60 years (the Inter99 study) stratified by age and sex were invited to take part. A total of 6,784 (52.5%) agreed to participate in the questionnaire study. Those with known diabetes (n=139) or without a classification (n=374) were excluded from the study. A further 147 had missing data, leaving 6,124 for analysis.

Those included into the study were divided into two groups according to birth years (the reporting of this process in the paper seems to be flawed; years ending in 4 or 9 and 5 or 0 should probably be 4-9 and 5-0); one group was tested in 1999 and the other group in 2000. Participants underwent a standardised oral glucose tolerance test (OGTT) according to the World Health Organisation (WHO) 1998 criteria. They also completed a questionnaire containing items on risk factors and symptoms for type 2 diabetes, and underwent physiological examination. The risk score was derived from the first 3,250 participants, 135 of whom, following OGTT, were diagnosed with type 2 diabetes. Data from the remaining 2,874 participants was compared to that from the first group; it is not clear from reporting in the paper how this group participated in terms of risk score evaluation.

External validation was carried out on individuals from the Anglo-Danish-Dutch Study of Intensive Treatment in People with Screen Detected Diabetes in Primary Care (ADDITION) pilot study. In the ADDITION study, individuals aged 40-69 years had been invited to participate; those that agreed to participate (1,028) completed a questionnaire containing the risk score and underwent measurement of random capillary blood glucose. A standardised OGTT was performed if the random blood glucose level was ≥4.5 mmol/l.

The final risk score included age, sex, BMI, known hypertension, physical activity at leisure time, and family history of diabetes, as well as items independently and significantly (P <0.05) associated with the presence of previously undiagnosed diabetes. For identification of IGT at an optimal cut point of 31, sensitivity was 46.5% (95% CI 41.5 – 51.4) for the first half of the Inter99 study, 47.9% (95% CI 42.3 – 53.6) for the second half of the Inter99 study, and 45.2% (95% CI 27.3 – 64.0) for the ADDITION pilot. No other data for identification of IGT was reported. The authors concluded that they had developed a simple one-page questionnaire that could be used in a stepwise screening strategy for type 2 diabetes in Denmark.

Gomyo *et al* (2004 +) used a sample from the JDPP trial to evaluate the abilities of the Fasting Plasma Glucose and HBA1c indicators to diagnose IGT. The sample of 997 were aged between 30-59 years (stratified into 3 age groups; 30-39; 40-49; 50-59), and were not randomized to conditions. Those with IGT were defined as having FPG < 7.0 mmol/l and 7.8 mmol/l, ≤ 2 h PG < 11.1mmol/l. Those with impaired fasting glucose (IFG) were defined as having 6.1 mmol/l ≤ FPG < 7.0 mmol/l, and 2 h PG < 7.8 mmol/l. According to the 1997 criteria of ADA, 140 subjects were classified as diabetes (14.0%), 256 as having IGT (25.7%), 87 as having IFG (8.7%) and 514 as having NGT (51.6%).The aim was to identify differences in sensitivity and specificity across sex, age groups and BMI at the optimal cut off point.

For FPG, there were differences in optimal cut off by sex, with the cut-off for females being lower (5.5 mmol/l) than that of males (5.8 mmol/l). Sensitivity at these cut points was 66.9% for females and 68.3% for males. Specificity was 63.4% for females and 61.9% for males. Optimal cut point for both males and females together was 5.6 mmol/l (sensitivity 69.1%; specificity 61.6% PPV was 54%, NPV 46%, AuC 0.72 (± 0.02).

For HbA1c, optimal cut points were 5.2 for males (sensitivity 61.7%; specificity 64.6%), 5.3 for females (sensitivity 62.3%; specificity 63.2%). For both together, optimal cut point was 5.3 with sensitivity 57.2%; specificity 64.4%, PPV 47%, NPV 54%, AuC 0.65 (± 0.02).

Sensitivity and specificity of each test were higher when the state of glucose tolerance was worse. In screening with FPG, females had lower sensitivity and higher specificity than males. In screening with HbA1c, the specificity was lower in the groups of 40–49 and 50–59 year-olds (70.2% and 60.9 % respectively) than the group of 30–39 year-olds (90.7%) and lowest (58.3%) (in the obese group (BMI ≥ 25 kg/m2). In screening with HbA1c, the optimal cut off points of the groups of 40–49

and 50–59 year-olds were higher (5.3) than the group of 30–39-year-olds (5.2). The obese group had higher optimal cut off points in both FPG and HbA1c than the other groups of BMI.

This study showed that the discriminating ability of FPG was superior to that of HbA1c, although each test can discriminate between IGT and non-IGT (NGT plus IFG). The authors concluded that the FPG was better than HbA1c for screening for IGT and IGT plus diabetes mellitus, and sex, age and BMI had effects on the performance of the screening test. The optimal IGT cut off point for FPG (5.6 mmol/l) was lower than the FPG values for IFG (between 6.1.mmol/l and 6.9.mmol/l) in the report by the WHO.

If a two-step strategy is adopted to screen for IGT plus diabetes mellitus, the authors suggest selecting all those with a FPG value of 5.8 mmol/l or greater for the first screening, at least in Japanese subjects. Limitations to the study were that the population was not randomly selected but a preselected group with some risk of glucose intolerance. The age range (30–59 years) was also narrow. Despite these limitations, the authors conclude that results presented in this study should be a valuable piece of information to identify subjects of IGT.

Gray *et al* (2010 +) developed the Leicester Risk Assessment, a risk score based on the FINDRISC to be used by lay members of multiethnic populations as part of the ADDITION study. The Leicester Risk Assessment (LRA) included FINDRISC items as well as smoking status, alcohol consumption, occupational status, ethnicity, physical activity and scales to measure well-being and anxiety. The tool was tested on a sample of 6186 participants aged 40 -75 (mean 57.3; SD 9.6) and almost equally balanced male to female, with a mean BMI of 28.1 (SD 5.0). The LRA was delivered by trained researchers to the participants, the majority of whose ethnicity was reported as White (73.4%).

The reference standard used was 75g OGTT. The authors assessed utility for diagnosis of T2DM, and claimed that a cut-off point of equal to or more than 16 was the optimum for identifying Impaired Glucose Regulation (a composite of IGT and IFG) as well as T2DM. At this cut off point, the sensitivity is reported as 72.1% (95% CI 69.6–74.6), with specificity 54.1% (95% CI 52.7–55.5), PPV 27.7 (95% CI 26.2–29.3) and NPV 88.8 (95% CI 87.7–89.9) At this cut-off point the tool is comparable to FINDRISC at cut off equal to or more than 12. The area under the curve is reported for the identification of T2DM only, at 0.72.

The authors conclude that the score is a way of identifying those that are at risk before further testing.

Greaves *et al* (2004 +) randomly selected 16 practices in the South West of England with lists containing at least 3500 patients to sample 100 patients each. Each sample was divided into four groups according to stepped BMI and age. Group 1 included patients who were >70 years with BMI ≥ 33; group 2 were >65 with BMI ≥ 31; group 3 were >60 years with BMI ≥29 and group 4 were >50 years with BMI ≥ 27. Using this type of categorisation, patients could be selected for more than one group (251 were in 2 groups; 47 in 3 groups and 4 in all 4 groups) due to the nested age and BMI points. Computer searching generated lists of patients meeting the inclusion criteria; those diagnosed with diabetes, non-Caucasians and patients with learning difficulties were excluded.

Patients that met the criteria were invited to clinic where practice nurses assessed age, weight and height and obtained fasting venous blood samples. Repeat tests were suggested for those having FPG ≥6.1 mmol/l. Those with FPG ≥7.0 mmol/l on both tests were diagnosed with diabetes, while those having FPG 6.1 – 6.9 mmol/l on both tests or one reading of 6.1 – 6.9 mmol/l and one of or >7.0 mmol/l were diagnosed with Impaired Fasting Glucose (IFG).

A total of 1287 patients were recruited (39.5% male). The uptake rate was 60.6% from 15 practices. No significant sampling biases were found. BMI data were available for 76.8% of patients >50 years. When compared to current data from assessment visits, 20% of the sample had data in their practice record that was recorded incorrectly. This did not substantially affect the results. Data on age was available for 100% of the patients, though in 27 cases this differed from self-reported age by one year.

In each group, new cases of IFG were identified as follows: 25 (8.3%) in group 1; 41 (8.4%) in group 2; 39 (8.3%) in group 3; and 20 (5.2%) in group 4. This represented a total of 93 patients (7.2%) across the practices. In addition, 55 (4.3%) new cases of diabetes were identified. The number needed to screen to detect either IFG or diabetes ranged between 15 and 28 across the four groups. The authors state that only brief nurse training was required to run the clinics. Computerised identification took less than I hour per practice, and patient clinic time was around 10 to 15 minutes compared to minimum 2 hours and two appointments for OGTT.

Detection rates may be increased by improving the recording of BMI as well as software development to allow searches for 'latest BMI'. In addition, OGTT could be added to the strategy, as FPG and OGTT detection only overlaps by 20-25%, with FPG tending to under-estimate the true prevalence of type 2 diabetes. The authors conclude that this study was carried out with data as used in practice, with its limitations, yet detected a substantial number of cases.

Guerrero-Romero *et al* (2006 +) aimed to determine the effect of lowering the criterion for normal fasting plasma glucose (FPG) to 5.6 mmol/L on the identification of individuals with impaired glucose tolerance (IGT) and metabolic syndrome (MS). A cross-sectional analysis of a population-based study from Durango, Mexico was carried out. The study enrolled 844 healthy men and non-pregnant healthy women aged 34 to 64 years. According to the individual's FPG concentrations, participants were allocated to one of three groups:

a) FPG <5.6 mmol/l (492, 58.3% of sample)

b) FPG 5.6-6.0 mmol/l (181, 21.4% of sample)

c) FPG 6.1-6.9 mmol/l (171, 20.3% of sample)

The authors reported that there were no significant statistical differences between the groups in terms of age.

The reference standard used was the OGTT. The authors claimed that using the cut off point FPG 5.6 mmol/L to identify subjects with IGT increased sensitivity from 32.9% to 82%, though specificity decreased from 82.7% to 67.8%, and PPV increased from 31.7% to 37.5%. The AUC was not reported.

The authors concluded that, taking into account that the main goal of screening such as the early detection of risk factors in an apparently healthy population requires diagnostic tests of high sensitivity, lowering the normal criterion for FPG to 5.6 mmol/L increases the identification of subjects with IGT, improving the success of FPG as a screening tool for T2DM.

Heikes *et al* (2008 +) describe the development of a Diabetes Risk Calculator (DRC), a paper questionnaire for use in general practice or to be developed as an online tool for the public. The risk score tool was developed using items known to be associated with risk of developing Type 2 Diabetes, and validated using the NHANES 1999-2004 data (7,092 participants in the US who were aged ≥20 years and had

FPG results; no uptake data available). This data includes OGTT levels for approximately half of the sample aged 40-75, and FPG results for the remainder.

Two methods of analysis were used to validate the tool; Logistic Regression and Classification and regression tree (CART). The tool includes an algorithm that leads the user along branches of a node tree, depending on responses to the perceived presence of well known risk factors.

The DRC sorts people into 14 different categories and reports for each category the probability that an individual is at low risk or high risk for either undiagnosed diabetes or pre-diabetes.

The authors claim that using a cut off score of 25% for the probability of having pre-diabetes, the accuracy of the classification tree for pre-diabetes or undiagnosed diabetes is sensitivity 75%, specificity 65%, PPV 49%, NPV 85%, and area under the ROC curve 0.75.

For increased plasma glucose, the difference in the odds of a positive versus a negative result is a factor of approximately 6. They claim that the DRC can be used by physicians to assess the risks of their patients or can be self-administered by individuals to assess their own risks. Use of this tool enables the identification of individuals who might benefit from confirmatory tests and treatment to delay or prevent the onset of type 2 diabetes and its complications. Development of a patient-friendly, electronic version is being developed for broader use in clinical practice.

Heldegaard *et al* (2006 +) tested the CRS in a Danish practice population to identify individuals with undiagnosed diabetes, IGT, IFG, and metabolic syndrome in order to implement preventive interventions where appropriate. A response rate of 69% was obtained from invited patients (n=1355). Physical examination included height, weight, waist circumference, blood pressure and OGTT. Self administered questionnaires were completed for medical and family medical history as well as lifestyle behaviours. The CRS was calculated for all participants.

Participants with IGT / IFG were older (mean 50.1 vs 43.4 years), had higher total cholesterol readings (5.55 mmol/l vs 5.24 mmol/l), higher systolic blood pressure (130 vs 120 mmHg), larger waist circumference (93cm vs 84cm female and 100cm vs 93cm male), higher BMI (28.3 vs 25.3) and were more likely to have a family history of diabetes (34.8 vs 16.9) that those with normal glucose tolerance (NGT).

A total of 141 (2.29% 95%CI 1.56-3.23) patients had pre-diabetes; 90 (6.64% 95%CI 5.38 – 8.10) were diagnosed with IGT; 51 (3.76% 95%CI 2.81 - 4.91) with IFG. The authors state that using a threshold of ≥0.246 (sensitivity 47.1%; specificity 83.9%; PPV 29.8, NPV 91.6%, Area under the Curve 0.74 (95% CI 69.9 – 78.0), a total of 271 participants would have required further testing, whilst 59 people (42%) with IGT or IFG, 81 (47.1%) with impaired glucose regulation and 91 (50.3%) with metabolic syndrome would have been detected.

The authors concluded that the CRS performs reasonably well in identifying those with pre-diabetes. Calculating risk scores automatically using electronic medical records followed by diagnostic testing on a proportion of the population is more practical than inviting all the adults on the general practice list for blood glucose tests. The CRS in addition does not entail distribution or analysis of questionnaires. General practitioners should be encouraged to collect and record risk factor information necessary to calculate predictive models.

Herdzik *et al* (2002 -) assessed the measurement of Fasting Capillary Glycaemia (FCG) along with fructosamine (FRA) and / or HbA1c to detect glucose tolerance abnormalities better than FCG alone. A total of 538 adults over 18 years (males 55.5%) referred to an Outpatient Clinic in Western Pomerania in Poland between 1993-9 took part in the study. The authors do not specify a response rate. All patients received an OGTT test, apart from those with fasting capillary glucose ≥11.1 mmol/l. Pregnant women, patients with previously diagnosed diabetes and patients receiving hypoglycaemic treatment were excluded from the study. Due to financial limitations, determinations of fructosamine (FRA) and glycosylated haemoglobin HbA1c were available only in subsets of these patients (FRA in 480 patients, 263 of whom were men).and depended on the doctors' recommendation.

For Fasting Capillary Glucose (FCG), the optimum cut point was 5.6 mmol/l (ADA criterion) with a sensitivity of 62.6%, specificity 100%, PPV 40.6%, NPV 60.0% (reviewer calculation), AuC 0.865 (± 0.017). For Fructosamine (FRA), the optimum cut point was 247 µ (maximal effectiveness) with a sensitivity of 58.3%, specificity 83.6%, PPV 42.7%, NPV 58.0% (reviewer calculation), AuC 0.748 (± 0.024). For HbA1c, the optimum cut point was 5.29 (maximal effectiveness) with a sensitivity of 51.3%, specificity 95.8%, PPV 36.4%, NPV 64.2% (reviewer calculation), AuC 0.777 (± 0.03).

The authors state that in this sample, for patients in whom 2h-OGTT values were in the IGT range, the FCG value in 74.74% of them was within normal range, and

25.26% in the IFG range according to ADA. Combined use of FCG, FRA and HbA1c did not significantly improve prediction of 2-hour post-load glycaemia compared to combined use of FCG and FRA. In cases of discriminating diabetes from the other glucose tolerance abnormalities and NGT, FCG had the greatest diagnostic value. However, it only identified 29% of those in IFG range. Taking FRA as an additional criterion in detecting glucose tolerance abnormalities in case of normal FCG allows for significant, although comparatively small, increase in the sensitivity of their detection.

Hu *et al* (2009 +) used medical records data from a Shanghai hospital to identify 2,298 Chinese Han nationality individuals (no uptake data), aged over 18 years of age, that had at least one known risk factors for diabetes (family history of diabetes, BMI ≥ 25 kg/m2 or waist – height ratio (WHR) ≥ 0.9 for males and 0.85 for females) as well as a history of impaired glucose tolerance that agreed to attend diabetes screening. The mean age for the group of individuals was 54.2 years (SD 13.3).

The screening test was performed after three days of normal carbohydrate intake and physical activity and venous blood samples were drawn after an overnight fast of at least 10 hours. Fasting Plasma Glucose (FPG) and HbA1c at 2 cut points (for IGT and diabetes), and both tests combined were assessed. At an optimal cut point for IGT of ≥ 5.6 mmol/l, FPG gave a sensitivity of 64.1%, specificity 65.4%, PPV 51.4%, NPV 49.3% (reviewer calculation), AUC 0.701.

At an optimal cut point for IGT of ≥ 5.6%, HbA1c gave a sensitivity of 66.2%, specificity 51.0%, PPV 58.4%, NPV 42.3% (reviewer calculation), AuC 0.647. Combined use of FPG at ≥ 5.6 mmol/l and HbA1c at ≥ 5.6% gave a sensitivity of 87.9%, specificity 33.4%, PPV 74.2%, NPV 26.5% (reviewer calculation)

The authors concluded that compared with FPG or HbA1c alone, the simultaneous measurement of FPG and HbA1c (FPG and/or HbA1c) might be a more sensitive and specific screening tool for identifying high-risk individuals with diabetes and IGT at an early stage.

Lidfelt *et al* (2001++) assessed a strategy for identifying unknown metabolic dysfunction in middle aged Swedish women. Women aged 50-59 from five designated geographical areas (n= 10,766) were invited to participate. The programme consisted of two stages. In the first, 6,917 participating women (64%) received a questionnaire that included items concerned with medical history, drug treatment and family history of diabetes. A physical examination was also carried out to measure body weight, height, minimal waist and maximal hip circumference (to

calculate WHR), blood pressure, random capillary blood glucose and non-fasting lipids. Women with one or more risk factor for type 2 diabetes (n=3593) were invited to attend for OGTT after 1-4 weeks. A total of 2923 women attended at this stage.

Of the 3324 women without risk factors, a randomly selected group of 300 was designated as a control group (i.e. were invited for OGTT), of whom 221 attended. Lack of time was given as a reason for not attending the follow-up by the remaining 79 women. During the period 1995-99, 99 non-participants and 12 participants died. The main cause of death was cancer, though 14 non-participants (0 participants) also died of CVD (non-diabetes related).

Women with identified risk factors who attended follow-up (n=2923) had higher diastolic blood pressure (DBP) ($p<0.001$), B-glucose ($p<0.01$) and S-triglycerides ($p<0.05$) compared to those that did not attend follow-up (n=536). In women without risk factors, WHR was lower ($p<0.05$) in the control group attending follow-up (n=221) compared to the 3016 remaining women without risk factors and the 79 women who did not attend follow up (total n=3095).

The OGTT tests resulted in 1940 (66.4%) women with NFG/NGT; 134 (4.6%) with IFG/IGT; 517 (17.7%) with NFG/IGT; 109 (3.7%) with IFG/IGT and 223 (7.6%) with diabetes. The authors state that the prevalence of IGT and diabetes was around four times higher in women with risk factors compared to those women without risk factors. Risk factors in this study were reported as not associated with presence of IFG.

The authors state that the sensitivity of the instrument was 70%, with 55% specificity (no information given on which condition this is for). The PPV was 34%, however the figures were based on presumed prevalence in the non-participating and negative results groups. AuC was not reported. In addition, changing the risk factor variables (deleting drug treatment of hyperlipidaemia, family history of diabetes and hyper-triglyceridaemia) would give a specificity of 66%, with sensitivity lowered to 62%. Both sensitivity and specificity would be higher (80% and 56% respectively) if IFG/NGT was deleted, with these participants being regarded as normal. In summary, the authors state that a high prevalence of unknown impaired glucose metabolism was found in middle-aged women with a positive risk assessment profile.

Luders *et al* (2005 +) carried out a multi-component evaluation in Germany (Pre-Diabetes Score or PreDiSc study) to identify the sensitivity of a range of potential models for predicting IGT in people with hypertension. The five assessed models were: 1) HBA1c alone 2) FPG alone, 3) HBA1c and FPG combined, 4) HBA1c + FPG

+ age, 5) HBA1c + FPG + age + systolic blood pressure, 6) HBA1c + FPG + age + systolic blood pressure + waist circumference.

Patients aged18 years or more with known or untreated hypertension (≥140/ ≥90mm Hg), from 34 general practices were recruited for the study. Mean age was 60.9 years, mean BMI 30.7 kg/m2. A capillary fasting glucose value was determined with a commercial STIX device. In the cases where this value was 100-130 mg/dl, further screening was carried out and if BMI was ≥25 kg / m2 or a previous history of IGT or DM in parents or siblings was present, the patient was eligible for the PreDiSc study.

A total of 267 patients were eligible for inclusion in the study, with an OGTT value being determined for 260 of these patients. Of these, 148 patients also had elevated venous blood glucose values. For HbA1c alone (Model 1), the optimal cut off was 6mmol/l with a sensitivity of 58% and specificity 84%, PPV 79% and NPV 66%. For fasting glucose of≥110 mg/dl alone (Model 2), there was a sensitivity of 62%, specificity 57%, PPV 60% and NPV 59%. A combination of HbA1c and FBG (Model 3) gave sensitivity 61%, specificity 78%, PPV 78%, NPV 59%. Model 4) gave sensitivity 82%, specificity 76%, PPV 81% and NPV 74%. Model 5) gave sensitivity 79%, specificity 74%, PPV 79%, NPV 74%. Model 6) gave sensitivity 83%, specificity 76%, PPV 80% and NPV 82%.

The authors state that a combination of HbA1c of ≥6%, FPG of≥110 mg/dl and age of ≥55 years, systolic blood pressure and a large waist size (model 6) is highly predictive of IGT (sensitivity 83%, specificity 76%, PPV 80% and NPV 82%. AuC 0.72).

Mannucci *et al* (2003 +) invited all the 67,000 residents of Bagno a Ripoli, Florence to partake in a study to assess the utility of FPG and HbA1c in identifying diabetes and IGT/IFG. A sample of 567 males and 648 females aged 30–70 years took part in the study (no uptake data available). The mean age was 52.2 (±19.5) in men and 52.0 (±17.6) in women.

A detailed personal and family medical history was collected; weight and height were measured and waist and hip circumferences were measured according to WHO recommendations. Mean BMI was 26.7 (±3.5) in men and 25.4 (±4.5) in women.

Glucose tolerance was assessed in all participants. A 75-g oral glucose load (was administered, and plasma glucose was again measured after 120 min rest. After an overnight fast, venous blood samples were drawn for the determination of HbA1C, lipid profile, and plasma glucose. The upper limit of the reference range for HbA1C in those without diabetes was 5.5%. Impaired fasting glucose (fasting glycaemia, 6.3–

6.9 mmol/l) was diagnosed in 161 subjects including 107 men (19.0%) and 54 women (8.4%). Impaired glucose tolerance was diagnosed in 96 participants, including 61 men (10.8%) and 31 women (4.8%). The prevalence of diabetes, IFG, and IGT was significantly (p<0.05) higher in obese (BMI>30 kg/m2) or overweight (BMI=25–30 kg/m2) participants when compared to the rest of the sample.

The majority of participants with IGT had FPG levels within the normal range, while most of those with IFG had normal glucose tolerance. In those without a diagnosis of diabetes, IGT and IFG were more frequently associated in obese subjects among men (p<0.05 vs. the rest of the sample), but not among women. Prevalence of IFG in individuals with IGT was 23.0%, 40.0%, and 61.1% in men, and 25.0%, 44.4%, and 20.0% in women, among normal-weight, overweight, and obese subjects, respectively. Those with combined IFG and IGT had signifìcantly (p<0.05) higher BMI and HbA1C (29.1±4.3 kg/m2, and 5.7%±0.4%, respectively), when compared to those with IFG (27.9±4.2 kg/m2 and 5.5%±0.4%) and IGT (27.6±4.6 kg/m2 and 5.5%±0.5%) only.

FPG with a threshold of 6.1 mmol/l, had a sensitivity for IGT of 40.9%, specificity 25.0%, in men. For women, sensitivity was 29.0%, specificity 18.0%. The authors conclude that determination of FPG is not useful in the screening of IGT, and that HbA1c alone does not provide any advantage over FPG in the screening of IGT. The combined use of HbA1C and FPG with a threshold of 5.5% (upper limit of normal range) for HbA1C and 6.1 mmol/l for FPG, improves the sensitivity of screening, facilitating the identification of individuals with IGT. While this procedure can be useful for case finding in clinical research, it still fails to detect over one-third of individuals with IGT. Furthermore, the specificity of combined FPG and HbA1C for IGT is not sufficient to recommend this method for systematic screening in the general population.

Maynard *et al* (2007 -) assessed the spectroscopic measurement of dermal advanced glycation end products (SAGE). This is a non-invasive device that detects the fluorescence of skin advanced glycation end products. Performance of the device compared with fasting plasma glucose (FPG) and HbA1C using the 2-hour oral glucose tolerance test (OGTT) for identifying impaired fasting glucose (IFG).

Participants were recruited through flyers and newspaper advertising (although uptake was not reported) and were selected on the basis of having one or more risk factors for diabetes according to the American Diabetes Association standard-of-care guidelines and not having had a previous diagnosis for diabetes. Recruitment

concluded once 84 participants with abnormal glucose tolerance had been identified, with 351 participants overall.

At the IFG threshold (FPG = 5.5 mmol/l reviewer conversion), sensitivity for the non-invasive device was 74.7%. (sensitivity advantage over blood tests, $p<0.05$). Comparable sensitivity for the FPG was 58% (specificity 77.4%), and for the HbA1c sensitivity was 63.8% for A1C. As specificity for SAGE and HbA1c was not reported, it was not feasible to calculate PPV or NPV and therefore it is difficult to assess relative performances.

The authors concluded that the non-invasive technology identified 28.8% more individuals in the OGTT-defined positive screening class than FPG testing and 17.1% more than A1C testing and that the device is suited for opportunistic screening.

Mohan *et al* (2010 +) examined cut points for glucose intolerance (diabetes, impaired glucose tolerance [IGT], and impaired fasting glucose [IFG]) in Asian Indians relative to oral glucose tolerance test (OGTT). Participants were recruited using systematic stratified random sampling in Chennai, India, as part of the as part of the Chennai Urban Rural Epidemiology Study (CURES), a cross-sectional population-based study representative of Chennai (formerly Madras), the largest city in southern India, with a population of ~5 million people. Forty-six of the 55 wards in Chennai, India were selected for sampling, providing a total sample size of 26,001 individuals aged ≥20 years. From this pool, every 10th participant recruited (2600) was invited for detailed testing, including an oral glucose tolerance test (OGTT) in those without self-reported diabetes, and the response rate was 90% (2,350 of 2,600 participants). Of the 2,350 subjects who received an OGTT, A1C was measured in 2,188 participants (response rate 93.1%).

Different cut points for HbA1c were evaluated against IGT (2-hr plasma glucose) and IFG (fasting plasma glucose at both WHO and ADA cut points). For IGT, the HbA1c cut point was 5.6%, with sensitivity was 65.6%, specificity 62.1%, PPV 19.9%. AuC was 0.708. Using the IFG (WHO) criterion of FPG ≥ 6.1mmol/l and < 7.0 mmol/l, the optimal HbA1c cut point was 5.6%, giving a sensitivity of 60.0%, specificity 56.5%, PPV 8.0%. The authors state that the IFG group was very small. For the IFG (ADA) criterion of FPG≥ 5.6 mmol/l and < 7.0 mmol/l, the HbA1c cut point was 5.6%, giving a sensitivity of 65.1%, specificity 63.4%, PPV 8.3%.

The authors concluded that an HbA1c cut point of 5.6% would identify Asian Indians with IGT and/or IFG with 69–74% accuracy at optimal specificity and sensitivity.

Mostafa *et al* (2010 +) compared the prevalence of Impaired Glucose Regulation (IGR) when using two ranges of HbA1c cut points (6.0 - 6.4% and 5.7 – 6.4%) compared to the OGTT in a multi-ethnic population. The 1896 sample, aged 40 – 75 years (mean 57.3 years) were recruited from the LEADER study population (primary care) in the UK. The sample comprised 52.3% females, 74.7% White Europeans, and 22.8% south Asians. The mean HbA1c was 5.71% (SD 0.61), though this was significantly lower in White Europeans (5.66%; SD 0.61) than in south Asians (5.86%; SD 0.62) ($p<0.0001$).

The OGTT detected 1407 (16.2%) people with IGR (66.8% of these with IGT; 17.4% IFG; 15.8% both IFG/IGT). More were detected using the HbA1c at 6.0 – 6.4% than with the OGTT (n = 1610; 18.5%); an increase of 1.1 fold in White Europeans and 1.5 in south Asians ($p<0.0001$). Only 477 people (5.8%) were detected as IGR using both HbA1c and OGTT, showing discordance between the tests. A total of 758 were no longer classified as IGR using HbA1c cut point <6.0%.

A total of 3904 (44.9%) were detected as IGR using the range HbA1c 5.7 – 6.4% (the ADA recommended range). This led to a 2.8 fold increase in White Europeans and 3.0 fold in south Asians ($p<0.0001$). Concordance with the OGTT was found in 873 (10.7%) people, with an extra 3031 people being identified as IGR with the HbA1c at this range than the OGTT, and 363 (4.4%) no longer classified as IGR.

HbA1c had an AuC of 0.69 (95% CI 0.68 – 0.71) for detecting IGR. For south Asians, this was 0.72 (95% CI 0.69 – 0.75). For IGT alone, the AuC was 0.67 (95% CI 0.64 – 0.69) for White Europeans and 0.67 (95% CI 0.66 – 0.73). Sensitivity and specificity at cut point of ≥ 6.0% for White Europeans was 39.5% (95% CI 36.3 – 42.7) and 83.5% (95% CI 82.5 – 84.5) respectively, for identifying IGR. The optimal cut point however was ≥ 5.8%, giving sensitivity 61.5% (95% CI 58.2 – 64.4) and specificity 67.9% (95% CI 66.6 – 69.1). Stratifying by age gave a lower optimal cut point for 40 – 59 years (5.7%) than in the 60 – 75 year group (5.8%) in White Europeans.

For the south Asian group, the corresponding sensitivity and specificity at an optimal cut point of ≥ 6.0% was 63.8% (95% CI 58.6 – 68.7) and 69.4 (95% CI 67.1 – 71.6). Stratifying by age gave a similar optimal cut point for both age groups in south Asians.

The authors conclude that HbA1c had a low AuC (>0.7), suggesting that this is a weak tool for detecting IGR, particularly in White Europeans. The range 6.0 – 6.4% appeared to miss many of this group, but was a reasonable option for the south Asian group, where the optimal cut point was higher.

Phillips *et al* (2009 +) aimed to determine if risk assessment could be undertaken using a strategy similar to that used for gestational diabetes, in this instance, an oral glucose challenge test (GCT). Posters, flyers, presentations and notices in the media were used to raise awareness of the programme among employees of the Grady Health System, Emory HealthCare, and Emory University and Morehouse Schools of Medicine, as well as members of the community. Of those expressing interest, uptake was 52.5% (2,111/4,024).

Individuals were eligible if they had no prior diagnosis of diabetes, were not pregnant or nursing, not taking glucocorticoids and were well enough to have worked during the previous week (without requiring actual employment). At the first visit, (which did not require a prior fast), and scheduled during the work day, participants had random plasma glucose and random capillary glucose (RCG) measured. Participants then drank 50 g oral glucose within five minutes, with measurement of plasma (GCTplasma) and capillary glucose (GCTcap) after one hour. Of those scheduled for first visit uptake was 78.5% (1,658/2,111).

Of these, a total of 1,581 participants aged 18 to 87 years (mean age 48 years) completed the protocol, though 8 did not complete both GCT and OGTT tests. Analyses were reported on the remaining 1,573 participants who attended for the second visit (average of 13 days after first visit), and returned 1hr GCT values. Blood was also obtained for measurement of plasma lipids and HbA1c. Of those completing both sessions and having complete data, uptake was 94.9% (1,573/1,658).

Optimal GCTplasma cut-off 7.8 mmol/l provided a sensitivity of 73%, specificity 68 %, and PPV 34%, NPV 92%. Area under the curve for detecting pre-diabetes was 0.79. Optimal GCTcap cut off was 8.9 mmol/l (160 mg/dl), giving a sensitivity of 67%, specificity 64 %, and PPV 30%, NPV 89%. Area under the curve for detecting pre-diabetes was 0.73.

The authors concluded that screening performance was generally consistent across different times after meals and different times of day, as well as in subgroups with higher and lower pre-test probability of glucose intolerance. GCT plasma screening appeared to be accurate, convenient and widely applicable, with the test being

relatively inexpensive in populations such as the study population ($84 per case of diabetes or pre-diabetes identified).

Rolka *et al* (2001 +) describe a stepped strategy using the American Diabetes Association (ADA) risk assessment questionnaire and capillary blood glucose testing. The recommended CBG cut point of 140 mg/dl, and an alternative CBG cut point of 120 mg/dl were evaluated against several diagnostic criteria for diabetes (FSG ≥126 mg/dl, 2-h SG ≥200 mg/dl, or either) and dysglycemia (FSG ≥110 mg/dl, 2-h SG ≥140 mg/dl, or either). Volunteers (n=1471) aged ≥20 years were recruited by health care systems serving communities in Springfield, MA; Robeson County, NC; and Providence, Pawtucket, and Central Falls, RI during routine health centre visits and at community health fairs. Those with self-reported previously diagnosed diabetes or who had been pregnant or breastfeeding within the previous 3 months, or had been hospitalised within the previous six months were not eligible to participate in the study. Screening tests were administered at recruitment. Participants returned for a 75-g OGTT on a subsequent morning (usually within 7 days) after fasting overnight for ≥10 h. Fasting and 2-h post-load venous blood specimens were collected during this visit and FSG and 2-h SG concentrations were analyzed in a clinical laboratory using glucose oxidase methodology.

The sensitivity and specificity of the ADA risk assessment questionnaire, CBG cut point of 140 mg/dl and CBG cut point of 120 mg/dl were evaluated against OGTT 2-hr serum glucose (SG) concentrations analysed from 2-hr postload venous blood specimens, where IGT was defined as 2-h postload serum glucose ≥140 mg/dl and <200 mg/dl and IFG was defined as 110–125 mg/dl.

For dysglycemia (IFG/IGT), the ADA questionnaire had a sensitivity of 69% and specificity of 51% for pre-diabetes criterion FSG ≥ 110 mg /dl; sensitivity 72% and specificity 53% for criterion 2-h SG≥ 140 mg/dl and sensitivity 69%, specificity 54% for criterion FSG ≥ 110 mg /dl or 2-h SG ≥140 mg/dl.

The recommended CBG cut point of 140 mg/dl had a sensitivity of 41% and a specificity of 97% for pre-diabetes criterion FSG ≥ 110 mg /dl, with lower sensitivities for the other 2 criteria; specificities remained similar. For the alternative CBG cut point of 120 mg/dl, the better performance was for pre-diabetes criterion FSG ≥ 110 mg /dl with a sensitivity of 62% and a specificity of 90%.

A combination of the ADA questionnaire and CBG cut point of 120 mg/dl yielded a sensitivity of 45% and a specificity of 95% with the pre-diabetes criterion FSG ≥ 110

mg /dl. The alternative 2 criteria gave lower sensitivities while specificities remained similar (~95%).

Some differences for age and gender were noted but sensitivities and specificities varied little by race or ethnicity.

The authors concluded that whilst the usefulness of the ADA questionnaire may be limited by low specificity, lowering the cut point for the CBG test (e.g., to 120 mg/dl) may improve sensitivity and still provide adequate specificity.

Rush *et al* (2008 -) aimed to determine the accuracy of a modern point of care test (POCT) glucose meter and whether it was suitable for screening for dysglycaemia (term used by the authors to describe diabetes, IGT or IFG) using a large cohort from a randomised cluster controlled trial of intensive lifestyle change. A total of 3,225 Maori Participants aged 28 years and over were recruited from those already enrolled in the in the Te Wai o Rona Diabetes Prevention Strategy, New Zealand (total 60.7% uptake, reviewer calculation).

An Accu-chek Advantage meter and strips was used for glucose measurement, and whole blood values were reported. In addition, venous blood was sampled followed by a 2hr-OGTT.

With venous glucose ≥ 6.1 mmol/l as the criterion for diagnosis of pre-diabetes, the POCT identified 14.9% compared with 17.8% in the OGTT (46.4% agreement between tests). At an optimal cut point of 6.2 mmol/l, sensitivity of the POCT for detecting any dysglycaemia was 44%, specificity 94%, PPV 32.9%, NPV 67.7% (reviewer calculation) AuC was 0.76 (95% CI 0.74-0.79).

The authors identified the participant burden of the OGTT, and the benefit of finger-prick samples that are relatively easy to obtain compared with venous samples, particularly in the obese. However, the authors suggest that POCT significantly underestimated the true blood glucose at diagnostic levels for diabetes, and cannot be recommended as a means of screening for or diagnosing diabetes or pre-diabetes.

Saaristo *et al* (2005 ++) evaluated the Finnish Diabetes Risk Score (FINDRISC) in a Finnish population of 3092 participants, aged 45-74 years without known diabetes. The risk score was developed for use in primary care though it can be self-administered. An optimal score of 11 gave sensitivity for men of 45.6% (95% CI 41.7 – 49.5) and for women 53.4% (95% CI 49.1 – 57.7) in terms of identification of

Abnormal Glucose Tolerance. Specificity was 24.6% (95% CI 21.3 – 27.9) for men and 34.2% (95% CI 31.3 – 37.1) for women. Positive predictive values were 65.9% (95% CI 61.5 – 70.4) for men and 57.7% (95% CI 54.4 – 61.10) for women. Negative predictive values were 45.2% (95% CI 41.3 – 49.1) for men and 72.4% (95% CI 69.6 – 75.3) for women. Area under the Curve was reported as 0.65 in men and 0.66 in women.

The authors concluded that (depending on the cut off point chosen), the FINDRISC recognises undetected diabetes and glucose abnormalities fairly well. Waist circumference is probably not commonly recognised by the general public as a risk factor for T2D. In clinical practice, therefore, it is recommended that the questionnaire responses should be checked by a practitioner.

Saydah *et al* (2002 +) Assessed the FPG and HbA1c (both tests using venous plasma) as alternatives to the OGTT for identifying Impaired Glucose Tolerance in people defined by the DPP as high risk (i.e. BMI ≥24 kg/m2). Of 2,844 high risk 40-74 year olds in the US, 10.6% received the 2h OGTT as Reference Standard. The authors stratified results by age and body mass index.

For the FPG, the optimum cut-off point was ≥ 5.8 mmol/l (37.5% of the sample) with a sensitivity of 56.0 % (± 5.1), specificity 72.0% (± 1.9), PPV 17.1% (±2.9). For the HbA1c, the optimum cut-off point was ≥ 5.5% (38.3% of the sample) with a sensitivity of 60.0% (± 3.4), specificity 55.0% (± 4.3), PPV was 21.4% (±2.2).

The authors concluded that age and BMI influence the sensitivity of both tests in detecting IGT. Both tests had relatively higher sensitivity and specificity when used to screen people aged 60 to 74 years than for people between 40 and 59 years, but the differences were not substantial. Sensitivity also increased when BMI increased from ≥ 24 to ≥ 27, or to ≥ 30 kg/m2.

To determine those who might be eligible for a DPP intervention in the general U.S. population to reduce their risk of developing diabetes, measurement of height and weight could immediately eliminate from further testing the 27.2% of individuals with BMI ≥24 kg/m2. Measurement of fasting plasma glucose in those with BMI ≥24 kg/m2 would eliminate 41.1% of this group who are below or above the DPP fasting plasma glucose criteria.

The authors predict that, for the 95 million people aged 40–74 years without diagnosed diabetes in the US, 15 million would have to undergo an OGTT by this scheme. A similar procedure could be followed using HbA1c ≥5.5%, which does not require an individual to be fasting and can be measured in a blood sample collected

without regard to time of the prior meal. However, the authors acknowledge that these findings were based on a specific age range (40-74 years) and conclude that neither fasting plasma glucose nor HbA1c alone are ideal screening tests.

Schwarz *et al* (2009 +) adapted the FINDRISC questionnaire for a German survey by reducing the number of items from 8 to 6. Variables relating to diet and physical activity were omitted because both items did not add much power for the prediction of diabetes risk in previous studies. The maximum score that could be achived was 23. The questionnaire was completed by 771individuals with a family history of metabolic syndrome from the 1996 survey, and 526 with a family history of type 2 diabetes from the 1997 survey.

All participants underwent physiological examination to determine BMI, and were given the OGTT to determine blood glucose levels. Individuals with IGT and/or IFG were analyzed as a combined glucose intolerance group using criteria according to WHO / ADA guidelines. A total of 286 participants were diagnosed with IGT / IFG in 1996, increasing to 306 in 1997.

From the 1996 data, a cut off point of 12 was found to be optimal in achieving 77.5% sensitivity and 67.8% specificity in 1996, with a PPV of 19.7% and NPV of 96.8% in 1996. Data from 1997 showed an optimal cut point of 9, with sensitivity 72.7%, specificity 68.2%, PPV 29.4 and NPV 88.1. AUC values were 0.78 for 1996 data and 0.74 in 1997.

There was a significant association between higher scores and disease progression ($p<0.01$) with mean FINDRISC values for NGT (n = 116) 5.32 (SD 3.68); for those remaining IFG / IGT (n = 175) 7.54 (SD 4.08) and those with disease progression (n = 76) 8.49 (SD 5.24).

According to the authors, participants with the highest FINDRISC value were the highest proportion of individuals with diabetes at baseline, and the largest proportion of them remained within the diabetes criteria during the 3 year follow-up, whereas those with a low FINDRISC value comprised the highest proportion of individuals remaining within normal glucose tolerance criteria. They state that the most relevant application field of FINDRISC is on the primary care level, where population-based screening strategies are needed and widely implemented. The use by primary care physicians or other health care professionals would facilitate the detection of high-risk subjects and the institution of early preventive measures.

Simmons *et al* (2005+) carried out a multi-component study in which risk factors and laboratory measures of glycaemia were compared for detection of undiagnosed

diabetes and dysglycaemia (IGT/IFG). European, Maori and Pacific Islands residents of inner urban South Auckland were randomly selected for invitation to participate in the study using a stratified sampling frame by age and ethnicity. Of the 1928 individuals aged 40–59 years and 809 aged 60–79 years invited to participate, 1321 (68.5%) and 578 (71.4%) were screened for diabetes, 534 (67.9%) of whom attended the OGTT. ROCs were calculated using sensitivity and 1-specificity (in %) using weighted and unweighted data.

Three risk factors were identified for the study: a) treated for hypertension; b) obesity (BMI ≥30 kg/m^2); c) first-degree relative with diabetes.

Seven different screening strategies were employed:

1. Single blood test (immediate random glucose), followed by OGTT

2. Single blood test (fasting glucose) and HbA1c) followed by OGTT

3. Single blood test (HbA1c), followed by OGTT

Strategies 1–3 had sensitivities of 50.9%-66.3% for IFG/IGT

4. Straight to OGTT if any of the three risk factors (see above) are present

Strategy 4 gave a sensitivity of 71.6%.

5. Risk factor screening, followed by a single blood test (immediate random glucose), followed by OGTT

6. Risk factor screening, followed by a single blood test (fasting glucose), followed by OGTT

7. Risk factor screening, followed by a single blood test (HbA1c), followed by OGTT

Strategies 5–7 gave sensitivities of 44.2%-60.8%.

Risk factor screening was associated with approximately 9–12% less OGTTs. Screening with a fasting glucose with a threshold for OGTT of 5.5 mmol/l had substantially superior sensitivity to any other approach, whereas screening using HbA1c with a threshold of 5.3% was also consistently superior to risk factor screening. Use of random glucose testing followed by fasting glucose testing was inferior to risk factor screening and screening only those with risk factors would have missed 4/22 (18%) of those with an HbA1c of ≥8.0%.

The authors concluded that using risk factors as an initial stage in screening prior to blood testing adds little to direct screening with the risk of missing some with

significant hyperglycaemia, thus screening for dysglycaemia may best be undertaken using blood tests without initial risk factor symptom screening.

Somannavar *et al* (2009 +) assessed random capillary blood glucose (RCBG) cut points that discriminate diabetes, impaired glucose tolerance (IGT), and impaired fasting glucose (IFG) relative to the oral glucose tolerance test (OGTT). Participants were recruited through opportunistic diabetes screening camps in Chennai, India, as part of the Prevention Awareness Counselling and Evaluation (PACE) Diabetes Project. Of the 103,878 people who attended, 73.8% (76,645) underwent an RCBG test. Those self-reporting diabetes were excluded (n=13,340), and from the remaining 63,305, 1500 were randomly selected to attend for an OGTT, with an uptake of 1333 (88.9%).

Different cut points for RCBG were evaluated against IGT (2-hr plasma glucose) and IFG (fasting plasma glucose at both WHO and ADA cut points). For IGT, and at an RCBG cut point of 6.6 mmol/l, sensitivity was 64.7%,specificity 65.5%, PPV 27%, AUC 0.715.

Using the IFG (WHO) criterion of FPG ≥ 6.1 mmol/l and <7.0 mmol/l, at an RCBG cut point of 6.6 mmol/l, sensitivity was 62.8%, specificity 62.9%, PPV 25%, AUC 0.683. For the IFG (ADA) criterion of FPG≥ 5.6 mmol/l and <7.0 mmol/l, the RCBG optimal cut point was 6.3 mmol/l, giving a sensitivity of 62.8%, specificity 58.6%, PPV 47%, AUC 0.619 .

The authors concluded that Asian Indians with a risk assessment result RCBG > 6.1 mmol/l can be recommended to undergo definitive testing, in order to help limit the number of individuals who must arrive for screening in a fasting state and reduce the costs of screening.

Thomas *et al* (2006 +) assessed how well the Cambridge Risk Score and BMI could detect individuals in midlife with HbA_{1c} levels greater than or equal to 6.0% (pre-diabetes) as well as 7.0% and 5.5%.

Participants in the study were drawn from the 1958 Birth Cohort, which consists of data on approximately 17,000 individuals born during a single week in March 1958 in England, Scotland, and Wales. Survivors have been interviewed regularly at 7, 11, 23, 33, and 42 years of age, and at 45 years of age, a survey of biomedical risk factors and disease outcomes was undertaken that included physical assessments and blood collection. Data were available from 7,452 individuals without known diabetes who participated in a biomedical survey and gave a blood sample from which an HbA_{1c} measure was obtained.

Of the total sample, 3.8% (95% CI, 3.2%-4.5%) had HbA1c levels of 6.0% or more. The Cambridge Risk Score at an optimal cut point of ≥ 0.128 detected individuals with elevated HbA_{1c} levels with reasonable accuracy (AUC, 0.76 for HbA_{1c} level ≥6.0%). Similar AUC values were obtained using BMI alone (0.79 for HbA_{1c} level ≥6.0%). Sensitivity at this level was 78.2%, specificity 63.9% and PPV 6.4 (NPV not reported).

When tested using the lower HbA_{1c} threshold of 5.5% or more, the Cambridge Risk Score and BMI did not perform well (AUC, 0.65 and 0.63 for Cambridge Risk Score and BMI, respectively). The CRS identified 22.6% of the sample at increased risk of diabetes, whilst BMI alone identified 23.7%.

Woolthius *et al* (2007 +) examined use of the ProMedico EMR software in 11 practices in the Netherlands to detect IFG and type 2 diabetes. Whilst diagnoses and medication were consistently coded within the software system, family history of T2DM and history of gestational diabetes were not and could not therefore be used as risk factors for identification. Patients were mainly Caucasian so that ethnicity was not included as a risk factor. Risk status (risk / no risk) was marked in the EMR with an alert to trigger GPs at the next usual care visit. Measurement of FPG was requested for at-risk patients. For those coded 'no risk', GPs were requested to verify coded information and complete missing risk factor data. If this assessment revealed risk, FPG was requested as if for those with EMR coded risk.

The total patient population aged 45 to 75 years was 14,457, 6% of whom had a diagnosis of diabetes. The remaining 13,581 were included in the study. EMR risk identified 3858 (28%) at risk; those with known diabetes were older (mean 61.4 years) than those with EMR derived risk (mean 60.5 years), who were in turn older than those without EMR derived risk (mean 55.2 years). There was little inter-practice variation. In total, 1886 patients (91%) with an EMR derived risk and 1449 patients at risk after additional assessment (88%) returned for FPG measurement. Patients in the first group were more often male (44.2% vs 39.9%) and older (mean 60.3 vs 55.6 years) than the second group. In the first group, 13.5% exceeded the cut-point for IFG; in the second group, 9.6% exceeded the cut point.

Limitations to the study included poor recording of obesity and family history of diabetes; this data was mainly retrieved at the additional assessment during consultation. Although patients had to return in a fasting state for the FPG, the authors state that they were willing to do so, with 90% attendance.

The authors state that over 3 years this method would result in all patients coded at risk attending the GP, which is in line with the ADA recommendation for a 3-year interval in diabetes risk assessment. The universal access and continuity of patient registration enabled the programme to take place. Other health care systems may differ in terms of feasibility. The FPG was performed rather than the OGTT due to being easier and quicker, more acceptable to patients and cheaper, with use of portable glucose meters available in general practice. A barrier is the variability in performance of such meters, with risk of false-negatives and false-positive outcomes. The issue of false positives was addressed by repeat testing of those that had results above the cut-point. Repeat testing could also take place to limit false negatives, though this was not within the study strategy.

During the 1-year study period, 5,277 (39%) patients had an encounter with a family practitioner during which screening was discussed. According to initial risk assessment, 3,724 (71%) of these were at high risk for diabetes and 1,553 (29%) were at low risk; 90% (3335) of the high-risk patients and 86% (398) of the 465 invited low-risk patients returned for a first capillary FPG measurement after invitation.

Among high-risk patients, a second capillary FPG was performed in 496 high-risk patients, or 88% of those invited and venous sample was collected in 125 (74%) of these patients. Of these, 81% had undiagnosed type 2 diabetes, 16% had IFG, and 3% had a normal fasting glucose level.

Zhou *et al* (2009 +) recruited individuals who had participated in a diabetes survey conducted in Beijing, to determine the performance of glycated haemoglobin (HbA1c) as a screening tool for detecting newly diagnosed diabetes and pre-diabetes. A total of 903 out of a possible 915 individuals, aged 21 – 79 years, without previously diagnosed diabetes were recruited from the survey population. HbA1c and other required covariates had already been measured. The mean age for the individuals was 55.0 years (95% CI 54.3 to 55.6), mean BMI was 26.3 (95% CI 26.1 to 26.5) and 26.5% were male.

The reference standard used was 75g OGTT. A total of 22.4% of the sample were diagnosed with pre-diabetes. Those with pre-diabetes and diabetes tended to be older, more obese, dyslipidaemic and hypertensive compared to those with normal glucose tolerance. The authors claimed that the optimal cut-off point for pre-diabetes was HbA1c ≥ 5.7%, giving a sensitivity of 59.4%, specificity 73.9%, PPV 46.0%, NPV 54.7% (reviewer calculation). AuC was 0.73. The authors concluded from this study

that HbA1c as a single screening test was adequate to detect newly diagnosed diabetes but was not able to properly identify pre-diabetes in an obese Chinese population.

Zhou *et al* (2010 +) recruited individuals who had participated in a diabetes survey conducted in Qingdao, China, to evaluate the performance of A1C and fasting capillary blood glucose (FCG) tests as mass screening tools for diabetes and pre-diabetes. Of the 6,100 individuals, who had participated in the diabetes survey, 2,332 (aged 35 to 74 years) without a prior history of diabetes met the inclusion criteria for the study. The response rate overall was 87.8%. Mean age for the study participants was 49.5 years (95% CI 48.9 – 50.2) for males (986), and 49.3 years (95% CI 48.8 – 49.8) for females (1,346). The mean BMI was 25.7 (95% CI 25.5 – 25.8) for males, and 25.8 (95% CI 25.6 – 26.0) for females.

The reference standard used was a two hour 75g OGTT. At cut point ≥ 6.0%, sensitivity of the Fasting Capillary Glucose indicator was 60.5%, specificity 62.3%, PPV 50.3%, NPV 50.4% (reviewer calculation) for males. For females, sensitivity was 56.7%, specificity 67.8%, PPV 46.7%, NPV 54.0% (reviewer calculation). AuC was 0.64 for men and 0.65 for women.

At cut point ≥ 6.5%, sensitivity of the HbA1c was 4.5%, specificity 88.3%, PPV 5.0%, NPV 95% (reviewer calculation) for males. For females, sensitivity was 5.7%, specificity 89.4%, PPV 6.0%, NPV 96% (reviewer calculation). AuC was 0.47 for men and 0.51 for women. The HbA1c was reported not to distinguish between pre-diabetes and normal glycaemia.

6.3 Characteristics of included studies by strategy

A stepped approach to identification and risk assessment moves patients through stages of risk assessment depending on the results at each stage. The first step is the use of routine medical records to identify those patients at heightened risk from type 2 diabetes due to age, raised BMI and family history of type 2 diabetes. Step 2 would be further assessment of those potentially at heightened risk using a validated risk score. A score that is equal to or greater than the cut-off described in guidelines would then lead to step 3, further investigation using proven diagnostic methods to determine blood glucose levels.

This section presents the characteristics of included studies for each step in the identification and risk assessment process as well as those that assess a strategy of two or more steps.

Reference Standards

Oral Glucose Tolerance Test (OGTT / 2h-OGTT)

The OGTT is regarded as the 'gold standard' for diagnosis of type 2 diabetes / impaired glucose tolerance and is often used in evaluation studies as a 'Reference Standard'. Participants need to fast from midnight prior to an OGTT and on arrival for the test, a blood test is taken. Liquid containing 75g glucose is then consumed and further blood testing takes place every 30 – 60 minutes. It takes up to three hours to complete the test. The performances of tools that are being evaluated in the included studies (Index and comparators) for identification of IGT are compared with results from the OGTT.

Fasting Plasma Glucose (FPG)

The Fasting Plasma Glucose test is used to identify Impaired Fasting Glucose (IFG) with criteria 6.1- 6.9 mmol/l. However it can also identify IGT at cut point of <7,0 mmol/l or diabetes at >7,0 mmol/l. In the included studies the FPG is used either as Reference Standard for IFG, or as an index / comparator test.

Approaches based on demographic and routine data

Individuals with IFG, IGT or IGR (collectively known as pre-diabetes) are at high risk of developing type 2 diabetes. Identification of those patients with known risk factors associated with the development of type 2 diabetes can be followed up with further diagnostic tests. This limits the need to perform diagnostic tests on everyone. Risk factors include age, a raised BMI and / or waist circumference, family history of

T2DM, history of gestational diabetes and ethnicity (see introduction for full list of risk criteria). Whilst patients may be assessed for risk on an *ad hoc* basis during visits to their general practitioner or practice nurse, more systematic approaches are suggested within the literature.

Computerized searching of routinely kept records within general practice may show that a patient is at increased risk for type 2 diabetes or pre-diabetes due to being older (over 40 years), having a raised BMI and / or a family history of type 2 diabetes. The patient's degree of risk can be assessed further using a validated risk score prior to the measurement of blood glucose levels.

Five included studies assessed the use of routine medical data in the identification of individuals at risk of pre-diabetes. Two studies used the presence of risk factors without designating a score for identification of IFG. A further two studies assessed the Cambridge Risk Score, which is a tool using data routinely held in general practice, based on the probability of having type 2 diabetes using co-efficients developed from a UK prevalence survey (Griffin *et al*, 2000). The score uses risk variables such as age, sex, BMI, family history of diabetes, smoking and prescribed anti-hypertensive medication and is the sum of the co-efficients described in the model. A higher score denotes a higher probability of having type 2 diabetes. In the two included studies, the score was tested for its ability to detect hyperglycaemia.

Table 2: Characteristics of Demographic Routine Data studies

Study	n	Delivery setting	Target population	Age range	Index / Comparitor	Reference Standard
Greaves 2004	1287	SW England	6 GP practice lists	27-70	Medical Records	FPG
Heldegaard 2006	1355	Denmark	1 GP practice list	20-69	Cambridge Risk Score	OGTT
Thomas 2006	7,452	UK	Mid life Survey	45	Cambridge Risk Score	HbA1c
Woolthius 2007 / 2009	13,581	Netherlands	11 GP Practices	45-75	ProMedico EMR software	FPG

Approaches using Risk Score Tools

Whilst use of routine medical data does not require patients to become involved prior to the score being determined, the risk scores described in this section consist of a questionnaire that requires information from the patient. Questionnaires can usually be completed by the patient with or without assistance from a practitioner.

Seven included studies assessed the use of questionnaire-based risk scores to identify individuals at increased risk from pre-diabetes in population or primary care

based studies. Variables included in the questionnaires are described in specific sections on each study; all included age and some measure of obesity (e.g. BMI). Two studies were carried out in the UK, the remainder in Europe.

Finnish Risk Score (FINDRISC)

The FINDRISC questionnaire was developed in Finland to identify those at high risk of type 2 diabetes prior to intervention (Lindstrom & Tuomilehto 2003b). It consists of 8 questions relating to risk factors for Type 2 Diabetes. Scores for each question are weighted according to the strength of association between risk factor and the condition. The range of scores is 0-26 with a cut off ≥ 12 points identifying high risk. The FINDRISC has been adapted for use in a range of populations, providing variations on the risk score that are assessed in this review. Shortened Finnish and German versions (Saaristo *et al* 2005; Schwarz *et al* 2007) have been assessed. A UK version, the Leicester Risk Assessment (LRA) tool, with scores 0-47, and an optimal cut point of ≥ 16 to identify high risk was adapted for the lay multi-ethnic population (Gray *et al* 2010). An Italian version (Diabetes Risk Score) with a range 0-20 and a cut off point of ≥ 9 points targeted a population with one or more CVD risk factor (Franciosi *et al* 2005).

Other Risk Scores

A Diabetes Risk Score was developed in the Netherlands using samples from the Inter99 and ADDITION study populations (Glumer *et al* 2004). The aim was to develop a one page questionnaire that was self-administered, with 75% sensitivity for identifying undiagnosed type 2 diabetes. A similar aim inspired the US Diabetes Risk Calculator, which was developed using logistic regression with the NHANES III dataset to identify the probability of developing diabetes or pre-diabetes (Heikes *et al* 2008). A risk score recommended by the American Diabetes Association (ADA) questionnaire was evaluated alongside Capillary Glucose Blood tests at different cut-points by Rolka *et al* (2001). The ADA risk score has 7 weighted items that reflect risk for diabetes, with a cut point of ≥ 10 denoting a positive result.

Table 3: Characteristics of Risk Score studies

Study	n	Delivery setting	Target population	Age range	Index / Comparitor	Reference Standard
Franciosi 2005 +	1,377	Italy	Random Primary care	55-75	Diabetes Risk Score (Italian; adapted from FINDRISC)	OGTT
Gray 2010 +	6,390	UK	Multi-ethnic	40-75	Leicester Risk Assessment	OGTT
Glumer 2004 +	6,784 1,028	Denmark	Population based	30-60 40-69	Diabetes Risk Score (not adapted from FINDRISC)	OGTT
Heikes 2008 +	7,092	US	Population survey	40-75	Diabetes Risk Calculator	OGTT
Rolka 2001 +	1,471	US	Health care users	≥ 20	ADA questionnaire	OGTT
Saaristo 2005 ++	3,092	Finland	Population based	45-74	FINDRISC	OGTT
Schwarz 2009 +	771 526	Germany	1996 & 1997 Population surveys	NR	Adapted FINDRISC	OGTT

Approaches using Blood Glucose Indicator tests

Whilst the OGTT and the FPG are the standard measures for identification of IGT and IFG respectively, alternatives to the OGTT are being evaluated for risk assessment purposes due to time and cost implications. A range of blood glucose indicators from simple random tests using capillary blood samples and pocket size monitors through fasting blood glucose tests to HbA1c were assessed in the included studies for their ability to detect pre-diabetes. Studies varied in terms of setting and population as well as included age groups. Some studies targeted random populations and others high risk individuals.

Non-fasting blood tests

Point of care / random testing

Point of care (POCT) and random blood glucose tests are not necessarily associated with a particular time of the day, such as a mealtime. They can be carried out at any time to confirm hyperglycemia. Random testing that results in blood sugar readings of 11 mmol/l or more usually indicate the need for further testing.

Glucose Challenge Test (GCT)

Similar to the OGTT though without the requirement to fast, glucose challenge tests have been traditionally used to screen for gestational diabetes. A range of variations are being evaluated in terms of the amount of glucose consumed and the length of time elapse between consumption and blood glucose testing.

Spectroscopic measurement of skin advanced glycation end products (SAGE)

A non-invasive method of identifying biomarkers for diabetes utilizes spectroscopic measurement of skin fluorescence, which alters in respect to the speed at which advanced glycated end products (AGEs) are produced. AGEs accumulate faster in individuals with diabetes, and are reported to correlate with integrated glycaemic exposure (Maynard *et al* 2007)

Table 4: Characteristics of studies assessing Non-fasting blood tests

Study	n	Delivery setting	Target population	Age range	Index / Comparitor	Reference Standard
Maynard 2007 -	351	US	Opportunistic through advertising	21-86	Spectroscopic measurement of dermal advanced glycation end products (SAGE).	OGTT
Phillips 2009 +	1,573	US	Health system, Health Care, University and Schools of Medicine employees. Members of the community.	18-87	Oral glucose challenge test	OGTT
Rush 2008 -	3,225	New Zealand	Maoris from Te Wai o Rona Diabetes Prevention Strategy	≥28	POCT using Accu-chek Advantage meter	OGTT
Somannavar 2009 +	76,645	Chennai, India	Opportunistic diabetes screening camps	NR	Random capillary blood glucose (RCBG)	OGTT

Fasting Blood Glucose Indicators

Plasma or capillary blood taken following a fast of between 8 and 10 hours can be used as an indicator of pre-diabetes or type 2 diabetes. Levels of blood glucose of 6.1 mmol/l to 6.9 mmol/l indicate impaired glucose tolerance (IGT). Blood glucose levels below this are regarded as normal, whilst those above 7.0 mmol/l indicate type 2 diabetes. However, an oral glucose tolerance test is may be carried out to confirm the diagnosis.

HbA1c

The HbA1c test measures the amount of glycated haemoglobin present in venous blood. Glycated haemoglobin is a substance found in red blood cells that is formed when blood glucose attaches to haemoglobin. This process occurs slowly over several weeks, therefore the test gives an average reading of blood glucose over the previous 8 to 12 weeks.

An HbA1c result of ≤ 6% is considered normal. The recommended criterion for diagnosing diabetes is an HbA1c level above 6.5%. The method of presenting HbA1c measures will change in May 2011 from percentages to mmol/l.

Table 5: Characteristics of studies assessing Fasting Blood Glucose and HbA1c tests

Study	n	Delivery setting	Target population	Age range	Index / Comparitor	Reference Standard
Gomyo 2004 +	997	Japan	JDPP trial	30-59	Combination of FPG and HbA1c	OGTT
Guerreo-Romero 2006 +	844	Mexico	Cluster sample	34-64	FPG at different cut-points	OGTT
Herdzik 2002 +	538	Poland	At risk for diabetes; hospital clinic	≥ 18	FCG FRA HbA1c	OGTT
Hu 2009 +	2,298	China	General population with ≥ 1 risk factor	≥ 18	FPG HbA1c	OGTT
Mannucci 2003 +	1,215	Italy	General population	30–70	FPG HbA1c	OGTT
Mohan 2010 +	2,350	India	Chennai Urban Rural Epidemiology Study (CURES)	≥ 20	HbA1c	OGTTfor IGT FPG for IFG
Mostafa 2010 +	8,696	UK	Study population (LEADER)	40 - 75	HbA1c across 2 ranges	OGTT
Saydah 2002 +	2,844	US	High risk for diabetes	40-74	FPG HbA1c	OGTT
Zhou 2009 +	903	China	General population	21-79	HbA1c	OGTT
Zhou 2010 +	2,332	China	General population	35-74	FCG HbA1c	OGTT

Stepped strategies

Using a stepped strategy for identification of pre-diabetes allows those at highest risk to be followed through, cutting down the extent of blood glucose testing required. A typical strategy would begin with a risk assessment using demographical data from medical records and/or a risk score questionnaire to identify individuals who have at least one risk factor (e.g. age over 40 years, BMI ≥ 25, family history of type 2 diabetes). Only those fulfilling the criteria of the first step are tested for raised blood glucose levels using one or more of a range of tests, as previously described.

Six studies were included that assessed at least 2 strategies within one study. The characteristics of these studies are listed below.

Table 6: Characteristics of studies assessing stepped strategies

Study	n	Delivery setting	Target population	Age range	Index / Comparitor	Reference Standard
Colagiuri 2004 +	10,508	Australia	At risk for diabetes; AusDab sample	≥ 25	Risk assessment, FPG and HbA1c.	OGTT
Franciosi 2005 +	1,377	Italy	Random Primary care	55-75	Diabetes Risk Score FBG at 2 cut points DRS + FBG at 2 cut points	OGTT
Lidfelt 2001 ++	6.917	Sweden	Mid –age women	50-59	Risk assessment questionnaire, physical examination, RCBG	OGTT
Luders 2005 +	260	Germany	General practice population with hypertension	≥ 18	6 Multi-component models including FPG, HbA1c, age, BMI and WC	OGTT
Rolka 2001 +	1,471	US	Routine health care cases	≥ 20	ADA questionnaire and CBG at 2 different cut points	OGTT
Simmons 2005 +	1,899	New Zealand	European, Maori, Pacific Islanders (age and ethnicity)	40-79	Single blood test Risk factors Risk factors + blood test	OGTT

6.4 Study findings

Tables 7-17 display the performances of risk assessment tools as well as blood glucose measures. Each strategy is presented within a separate table to allow comparisons to be made between performances, which are stated as the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and Area under the curve (AuC). Where possible, the tools and measures are listed in rising order of reported optimal cut point.

Whilst some studies assess a single tool or measure (typically using the OGTT as reference standard to detect abnormal glycaemia), many compare at least one tool or measure and some assess a combination of measures that are carried out in a stepped approach. For example, having a high risk score could lead to a fasting blood sugar measure and / or an HbA1c measure. Some studies assess the identification of a range of risk factors to determine the most predictive factor for pre-diabetes.

Whilst WHO have stated that HbA1c at cut point 6.5% can be used, in optimal conditions, to diagnose type 2 diabetes, the studies included in this review were published previous to this statement and therefore do not use HbA1c as a diagnostic tool (though they may assess the possibility of this approach). In any case, the new statement precludes the use of HbA1c for the diagnosis of pre-diabetes, with which this review is concerned.

Approaches based on demographic and routine data

Three included studies assessed the use of routine medical data to identify risk factors either alone (Greaves *et al* 2004), or prior to further testing of blood glucose (Lidfelt *et al* 2001; Simmons *et al* 2005). Such risk factors include age, BMI and family history of diabetes (see section 5.2). Individuals having at least one of these factors are considered at increased risk from type 2 diabetes and pre-diabetes and can therefore be targeted for further assessment, which may be a questionnaire, and / or blood glucose measures.

Table 7: Findings from studies assessing Demographic Routine Data

Study	Measure	Target population	Optimal cut point	Sensitivity	Specificity	Prevalence	AuC	PPV (NPV)
Greaves 2004	Medical Records	16 GP practice lists	NA	NA	NA	7.2% IFG	NA	NA
*Lidfelt 2001	Risk factors	Sweden Mid-life women	BMI ≥ 30 Waist / hip ≥ 90	70%	55%	3.7% IFG / IGT	NR	33.6% (85.1%)
*Simmons 2005	Risk factors	Maori, Pacific general population	Any of 3	71.6%	NR	20% IFG / IGT	0.61	43.5% for IFG / IGT / DM

**Part of a stepped strategy*

No performance data was given for using medical records alone. In the two stepped strategies, assessing risk factors gave similar sensitivity (around 70%) and PPV (33-43%). The NPV for use of this approach in Swedish middle aged women was 85.1%. The populations in these studies differed in that Lidfelt *et al* (2001) focussed on mid-age women whilst Simmons *et al* (2005) targeted three populations; Maori, Pacific Islanders, and a European white sample. For Lidfelt *et al* (2001), the optimum cut point was BMI of at least 30, which represents an obese population.

Evidence statement 1:

Approaches to identification based on demographic and routine data

There was moderate evidence [+] from four studies of the usefulness of demographic data from routine medical recording systems in identifying people at risk of Impaired Fasting Glucose (IFG) (Greaves *et al* 2004 UK +; Lidfelt *et al* 2001 +; Simmons *et al* 2005 +; Woolthuis *et al* 2007 Netherlands +). The studies used data on characteristics associated with diabetes risk. Two studies used this process as part of a stepped strategy.

Greaves *et al* (2004 UK +) reported an overall uptake rate of 61% (95% CI 55.7-65.6) from 15 practices. There was no reported response bias associated with age or gender. BMI data was available in 76.8% (95% CI 71.7 – 81.9) of cases. There was data misclassification in 20% of these cases. Of the 199 participants with abnormal blood glucose, 100% attended for a follow up blood test.

Lidfelt *et al* (2001 Sweden +) reported 70% sensitivity, 55% specificity for the assessment of risk factors in mid age women prior to further testing. Prevalence of pre-diabetes in this sample was low (3.7%). PPV was 33%; no AuC was reported.

Simmons *et al* (2005 New Zealand +) reported a similar sensitivity of 71.6% and PPV 43.5% for risk assessment prior to further testing in a population of Maori, White European and pacific Islanders with high prevalence of pre-diabetes (20%). AuC was 0.61.

Woolthuis *et al* (2007 Netherlands +) reported that the Electronic Medical Record (EMR) with additional risk assessment was successful in identifying risk in 28% of the total population from 11 general practices.

Approaches using risk score tools

The Cambridge Risk Score (CRS)

The CRS was developed in the UK for use with routine medical data. Further details of the score are described in section 6.3. The score was assessed in two included studies, one based in the UK and targeting the midlife general population (Thomas *et al* 2006) and one based in Denmark general practices (Heldegaard *et al* 2006).

Table 8: Findings from studies assessing risk scores based on medical data

Study	Measure	Target population	Optimal cut point	Sensitivity	Specificity	Prevalence	AuC	PPV (NPV)
Thomas 2006	Cambridge Risk Score	Mid life Survey	≥0.128	78.2%	63.9%	3.1% with HbA1c ≥ 6 mmol/l	0.76	6.4% (NR)
Heldegaard 2006	Cambridge Risk Score	1 GP practice list	0.246	47.1%	83.9%	10.4% IGT / IFG	0.74	29.8% (91.6)

The two studies reported optimal cut-points of ≥ 0.128 and ≥ 0.246 respectively. Area under the curve was similar in both studies (around 0.75). Prevalence of pre-diabetes was higher in the practice population (Heldegaard *et al* 2006). The UK study (Thomas *et al* 2006) reported higher sensitivity but the practice based tool was more specific and had a higher PPV A total of 22.6% of the sample were identified as at risk for diabetes compared to BMI alone which identified 23.7% (see Table 8).

Evidence statement 2:

Approaches to identification based on validated scores for demographic and routine data

There was moderate evidence [+] from two studies for the relative performance of the Cambridge Risk Score (Thomas *et al* 2006 UK +; Heldegaard *et al* 2006 Denmark +).

One UK evaluation (Thomas *et al* 2006 UK +) utilised a survey sample of 45 year old individuals. Of the 84% of the respondents that received an HbA1c measurement, 3% were identified as having HbA1c ≥ 6.0%. The Cambridge Risk Score at a cut off ≥ 0.128 was reported to have sensitivity of 78.2%, specificity 63.9%, PPV 6.4% (no NPV reported), and Area under the Curve 0.76 for identifying hyperglycaemia (HbA1c ≥ 6.0%). A total of 22.6% of the sample were identified as at risk for diabetes compared to BMI alone which identified 23.7%.

An evaluation of the CRS in a general practice population (Heldegaard *et al* 2006 Denmark +) with a 69% response rate to the initial questionnaire found that 42% of the sample had Impaired Glucose Regulation (IFG and / or IGT) based on assessment of high risk. An optimal cut off of ≥ 0.246 on the risk score gave sensitivity 47.1%, specificity 83.9%, PPV 29.8%, NPV 91.6%, AuC 0.74.

Questionnaire-based Risk Scores for the identification of pre-diabetes

As described in section 6.3, questionnaire based risk score tools are completed by participants though they may require some supervision. Seven studies assessed the use of such questionnaires, mainly in the general population.

Table 9: Findings from studies assessing Questionnaire based risk scores

Study	Measure	Population	Optimal cut point	Sensitivity	Specificity	Prevalence	AuC	PPV (NPV)
Franciosi 2005	Diabetes Risk Score	Italy At least 1 CVD risk factor	>9	77%	45%	11% IFG/IGT	0.67	DRS only: 48% (76%)
†Gray 2010	Leicester Risk Assessment	UK Lay multi-ethnic	≥16	72%	54%	19.5% IGR / T2DM	0.72 for T2DM	27.7% (88.8%)
Glumer 2004	Danish Diabetes Risk Score	Denmark Inter99 a) and b) c) ADDITION pilot	≥31	a) 46.5% b) 47.9% c) 45.2%	NR	a)12.6% b) 10.9% c) 9.2% IGT	NR	NR
Heikes 2008	Diabetes Risk Calculator	US General population	25% risk probability	75%	65%	26.14% IFG and / or IGT	0.75	49% (85%)
*Rolka 2001	ADA risk assessment questionnaire	US General population	ADA ≥ 10	69%	54%	15% IFG / IGT	NR	†58.2% (42.6%)
Saaristo 2005	FINDRISC	Finland General population	Score of 11	45.6% men; 53.4% women	24.6% men; 34.2% women	50.6% men 33.3% women AGT	0.65 men 0.66 women	65.9% (57.7%) men 45.2% (72.4%) women
Schwarz 2009	Adapted FINDRISC (6-item)	Germany Risk of metabolic syndrome	12	77.5%	67.8%	37.2% IGT /IFG	0.78	19.7% (96.8%)
			9	72.7%	68.2%		0.74	29.7% (92.9%)

NR = Not Reported †

* Part of stepped strategy / multi-component study

† This study assessed IGR and T2DM together

Questionnaire Risk Scores for the identification of pre-diabetes based on FINDRISC

One assessment (Franciosi *et al* 2005) was carried out in primary care and reported the lowest optimal cut-point to obtain relatively high sensitivity (77%) but low specificity (45%). This study reported the lowest prevalence (11%) of pre-diabetes and the tool gave the lowest AuC (0.67).

Saaristo *et al* (2005) reported that the FINDRISC, developed and tested in Finland, at an optimal score of 11 gave low sensitivity and specificity though PPV and were relatively high. There was a differential performance between men and women with men having higher PPV (65.9%) and women higher NPV (72.4%).

A shortened version of FINDRISC (6 items rather than 8) adapted in Germany (Schwarz *et al* 2009) was sensitive (73% and 78%) at cut points 9 and 12 and had a NPV of over 90% at both scores. AuC was over 74 for both scores. The prevalence of pre-diabetes was relatively high in this general population sample identified at risk of metabolic syndrome.

In the UK, the Leicester Risk Assessment (Gray *et al* 2010) was developed specifically for a lay multi-ethnic population. At optimal cut-point 16, the tool had an AuC of 0.72 for type 2 diabetes, and an NPV of 88.8%. The remaining studies reported a range of performances that are presented in Table 9.

Evidence statement 4:

Questionnaire Risk Scores for the identification of pre-diabetes based on FINDRISC

There was strong evidence [++; +] from four studies (Franciosi *et al* 2005 Italy +; Saaristo *et al* 2005 Finland ++; Schwarz *et al* 2007 Finland +; Gray *et al* 2010 UK +) that assessed the FINDRISC score.

The Italian Diabetes Risk Score, adapted for a CVD risk population, showed 77% specificity, 45% specificity at cut point 9 for identifying diabetes or IGT, with PPV 48%, AuC 0.67 (Franciosi *et al* 2005 Italy +).

The 8-item FINDRISC score (Saaristo *et al* 2005 Finland ++) with a maximum score of 26 was more sensitive and specific at cut point 11 for women than for men in a general population survey for identifying Abnormal Glucose Tolerance (IFG / IGT). The PPV was higher for men (65.9 at cut point 11 compared to 45.2 for women) The NPV was correspondingly lower in men (57.7 compared to 72.4). AuC was 0.65 in men and 0.66 in women.

A shortened German version (Schwarz *et al* 2009 Finland +) with maximum score of 23 was more sensitive and specific at cut point 12 than the Finnish version at identifying IFG / IGT in a population with a family history of T2DM. There was evidence of good association between progressively higher scores and disease progression ($P<0.01$). 1996 data produced an optimal cut off point of 12 with 77.5% sensitivity and 67.8% specificity, PPV 19.7% and NPV 96.8%, AuC 0.78. 1997 data produced an optimal cut point of 9, with sensitivity 72.7%, specificity 68.2%, PPV 29.4 and NPV 88.1, AuC 0.74.

Gray *et al* (2010 UK +) assessed the Leicester Risk Assessment (LRA) with a maximum score of 47 aimed at identification of Impaired Glucose Regulation / T2DM in a lay multi-ethnic population. A sensitivity of 72.1% and specificity 54.1% at cut point 16 was reported, with a PPV of 27.7% and an NPV of 88.8%. AuC was not reported.

Other questionnaire based risk scores

Heikes *et al* (2008) assessed the US Diabetes Risk Calculator. At cut point 0.254 the score had a similar sensitivity (75%) but higher specificity (65%) for identifying IFG / IGT as the Italian Diabetes Risk Calculator (77% and 45% respectively; Franciosi 2005) at a cut point of 9. PPVs were similar at 49% and 48% respectively. NPVs were 85% and 76% respectively.

Glumer *et al* (2004) assessed the Danish Diabetes Risk Score. At cut point 31 sensitivity was reported to be between 45.2% and 47.8% across the two study groups and pilot. No other data for identifying IGT was given. The 7 item ADA questionnaire at cut point ≥10 gave a maximum specificity of 54% for dysglycaemia in a general US population (Rolka *et al* 2001).

Evidence statement 6:

Other questionnaire based Risk Scores for the identification of pre-diabetes

There was moderate [+] evidence from three studies (Heikes *et al* 2008 US +; Glumer *et al* 2004 Denmark +; Rolka *et al* 2001 US +) relating to questionnaire based risk scores not based on FINDRISC.

In one US population survey study (Heikes *et al* 2008 US +) the US Diabetes Risk Calculator at cut point 0.254 had a similar sensitivity (75%) but higher specificity (65%) for identifying IFG / IGT as the Italian Diabetes Risk Calculator (77% and 45% respectively; Franciosi 2005 Italy +) at a cut point of 9 for identifying glucose abnormalities. PPVs were similar at 49% and 48% respectively. NPVs were 85% and

76% respectively.

The Danish Diabetes Risk Score (Glumer *et al* 2004 Denmark +) at cut point 31 and with 50% uptake had sensitivities between 45.2% and 47.8% across the two study groups and pilot. No other data for identifying IGT was given. The 7 item ADA questionnaire at cut point ≥10 gave a maximum specificity of 54% for dysglycaemia in a general US population (Rolka *et al* 2001 US +).

Approaches using Blood Glucose Indicator tests

A range of blood glucose indicators were assessed in the included studies for their ability to detect pre-diabetes as compared to the gold standard OGTT. As described in section 6.3, indicators can be differentiated by the requirements of the test and the kind of measures that can be made. For example, some tests require the participant to fast prior to taking blood, and others do not. HbA1c does not require patients to be fasting and provides an aggregated measure of blood glucose over time, whilst other tests provide a measure that is current, and therefore prone to fluctuation over time and with changes in eating and physical activity behaviours.

Non-fasting tests

A convenient non-fasting indicator in terms of time and instant results is the point of care test. Four studies assessed the use of capillary blood tests either alone or within a multi-component study. In addition, one study (Phillips *et al* 2009) assessed the one hour plasma OGTT which has been mainly used to detect gestational diabetes. One further study (Maynard *et al* 2007) assessed the use of spectroscopic technology that measures changes in skin fluorescence with changes in blood glucose. The fructosamine test photometrically measures the absorption of formazane to determine the concentration of glycated proteins in plasma, of which albumin plays a major part. In a similar way to glycated haemoglobin, glycated albumin can serve as a marker to monitor blood glucose. It usually provides a retrospective measure of average blood glucose concentration over a period of 1 to 3 weeks. (Reinauer *et al* 2002).

Table 10: Findings from Non-fasting blood test studies

Study (Population)	**Index / comparator**	**Optimal cut point**	**Sensitivity**	**Specificity**	**Prevalence**	**AuC**	**PPV (NPV)**
Capillary Blood							
Simmons 2004 + (NZ; EU, Maori, Pacific general population)	Random Blood Glucose	≥ 5.6 mmol/l	66.3%	NR for IGT	20% IFG / IGT	0.72	41.3% for IFG / IGT / DM
†Rush 2008 - (NZ; at risk Maori population)	Point of care test (POCT) glucose meter	6.2 mmol/l	44%	94%	3.6% IFG 9.3% IGT 26.1% IGT and IFG	0.76	ǂ32.9% (67.7%)
Somannavar 2009 + (India; general population)	RCBG – IFG (ADA criterion – FPG ≥5.6 mmol/l and < 7.0 mmol/l	6.3 mmol/l	58.3%	58.6%	28.9% IFG	0.619	47%
	RCBG – IFG (WHO criterion – FPG 6.1 mmol/l and 7.0 mmol/l	6.6 mmol/l	62.8%	62.9%		0.683	25%
	Random capillary blood glucose (RCBG) – IGT	6.6 mmol/l	64.7%	65.5%	28.1% IGT	0.715	27%
Rolka 2001 + (US; General population)	Capillary Blood Glucose (CBG)	*6.6mmol/l* *7.8mmol/l*	48% 33% when compared to 2h OGTT	89% 96% when compared to 2h OGTT	15%	NR	NR
Plasma Blood							
Phillips 2009 + (US; general population)	Oral glucose challenge test (GCTplasma)	7.8 mmol/l	73%	68%	18.7% pre-diabetes	0.73	34% (92%)
Herdzik 2002 - (Poland; at risk population)	Fructosamine (FRA)	247 µmol/l	58.3%	83.6%	17.65% IGT	0.899	*42.7% (58.0%)*
Non-Invasive							
Maynard 2007 - (US; General population)	Spectroscopic measurement of dermal advanced glycation end products (SAGE).	50	74.7%	NR	15.6% IGT	0.797	NR

† This study assessed identification of dysglycaemia

ǂ *Figures calculated / converted by reviewer*

Prevalence of pre-diabetes was relatively high in all the studies (at least 15%). Point of care testing had the highest specificity (94%) and AuC (0.76) in one study targeting a Maori population that were already identified at risk (Rush *et al* 2008). Higher cut-points in the remaining studies generally were more specific and AuC was at least 0.61, though AuC was not reported in one study (Rolka *et al* 2001). All the studies were carried out within the general population though three of these are regarded as at higher risk (Rush *et al* 2008; Somannavar *et al* 2009; Simmons *et al* 2005) for diabetes.

The one hour OGTT showed a good balance of sensitivity and specificity at cut point 7.8 mmol/l, and had an NPV of 92% (see Table 10). Whilst the spectroscopic approach reported a high AuC (0.79) there was insufficient evidence from which to draw conclusions of performance.

Evidence statement 8:

Blood Glucose Indicators for identification of pre-diabetes: Non-fasting methods

Moderate evidence was found from five studies (+; -) (Simmons 2005 New Zealand +; Rush 2008 US -; Somanavaar 2009 India +; Rolka 2001 US +; Phillips 2009 US +) that random or capillary blood testing alone to identify those at risk of pre-diabetes using a range of optimal cut points (5.6mmol/l to ≥7.8 mmol/l) had a sensitivity of between 24% and 64.6%. Specificity ranged from 59% to 97%. A specificity of 97% was reported by one study (Rolka 2001 US +) using a cut point of 7.8 mmol/l, and 94% was in another study (Rush 2008 US -) with an at risk Maori population. Sensitivities however were less than 50% in both cases.

The 1 hour oral glucose tolerance test was assessed in one general population study (Phillips *et al* US +). At cut off 7.8 mmol/l, reported sensitivity and specificity was 73% and 68% respectively with PPV 34%, NPV 92%, and AuC 0.73.

There was insufficient evidence from one study [-] of the general population (Maynard *et al* 2007 US -) relating to the use of a non-invasive blood glucose indicator technique (spectroscopic measurement of dermal advanced glycation end products - SAGE) which showed a sensitivity of 68%, with no further information provided.

There was insufficient evidence [-] to determine the effect of fructosamine alone. One study (Herdzik 2002 Poland -) using fructosamine alone at a cut point of 247 µmol/l produced sensitivity and specificity for identifying those at risk of pre-diabetes of 58.3% and 83.6%.

Fasting Blood Glucose Indicators

Fasting plasma glucose measures require that the participant is fasted prior to testing. This method is described in section 6.3. Three included studies assessed this method alone (see Table 12), though FPG was also used as a comparator or in combination with other assessment tools in other studies (see Tables 15 and 16).

Table 12: Findings from studies assessing fasting blood glucose alone

Study (Population)	**Index / comparator**	**Optimal cut point**	**Sensitivity**	**Specificity**	**Prevalence**	**AuC**	**PPV (NPV)**
Franciosi 2005 +	FBG following risk assessment	5.6 mmol/l 6.1 mmol/l	86% 68%	44% 75%	11%	NR	50% (83%) 64% (78%)
Guerreo-Romero 2006 + (Mexico; population sample)	FPG at different cut-points	5.6 mmol/l	82%	67.8%	19.1% IGT 20.3% IFG	NR	37.5% (94.1%)
Mannucci 2003 + (Italy: General population)	FPG – men	6.1 mmol/l	40.9%	25.0%	13.25% IFG 7.6% IGT	NR for this cut point	NR
	FPG – women	6.1 mmol/l	29.0%	18.0%			

† *Figures calculated / converted by reviewer*

Two of the studies assessing FPG alone were carried out in Italy (Franciosi *et al* 2005; Mannucci *et al* 2003) and one in Mexico (Guerreo-Romero *et al* 2006). Two were carried out in the general population (Mannucci *et al* 2003; Guerreo-Romero *et al* 2006), and one in primary care (Franciosi *et al* 2005). The FPG gave the highest specificity (75%) in the Italian primary care population at cut point 6.1 mmol/l, though this followed risk assessment. However the highest reported prevalence for pre-diabetes was in the Mexican general population study (Guerreo-Romero *et al* 2006); this study reported an NPV of 94%. Sensitivity and specificity were low in the Italian

general population study (Mannucci *et al* 2003) and no PPV or NPV was reported. AuC was not reported in any of these three studies.

Evidence statement 10:

Studies assessing Fasting Plasma Glucose

There was moderate evidence [+] from three studies (Franciosi *et al* 2005 Italy +; Guerreo-Romero 2006 Mexico +; Mannucci *et al* 2003 Italy +) relating to the use of FPG measures.

Franciosi *et al* (2005 Italy +) assessed the FPG at two cut points in a risk assessed population. Sensitivity was higher at the lowest reported cut point (77% for 5.6 mmol/l) though specificity was 45%. Prevalence for pre-diabetes was lowest in this study (11%). AuC was 0.67.

One study (Guerreo-Romero 2006 Mexico +) reported that for the identification of impaired glucose tolerance (IGT), lowering the criterion for normal fasting plasma glucose (FPG) to 5.6 mmol /l from 6.1 – 6.9 mmol/l increased the sensitivity from 32.9% to 82%, but lowered specificity from 82.7 to 64.2%, with a related increase in PPV from 31% to 37.5%. AuC was not reported.

At a cut point of 6.1mmol/l, one study (Mannucci *et al* 2003 Italy +) reported different sensitivity and specificity for men and women when identifying IGT (sensitivity 40.9% and 29.0% respectively; specificity 25.0% and 18.0%). PPV, NPV and AuC were not reported.

HbA1c

The HbA1c test does not require fasting prior to testing, and the measure of glucose is an average of the previous 2-3 months. For more details of this measure, see section 6.3.

Four included studies measured the performance of HbA1c alone. Three were carried out in the general population in India, UK and China respectively (Mohan *et al*

2010; Mostafa *et al* 2010; Zhou *et al* 2009) and one with hypertensive primary care patients in Germany (Luders *et al* 2005).

Table 13: Findings from studies assessing HbA_{1c} alone

Study (Population)	**Index / comparator**	**Optimal cut point**	**Sensitivity**	**Specificity**	**Prevalence**	**AuC**	**PPV (NPV)**
Mohan 2010 + (India; General population)	HbA_{1c} – IGT	5.6%	65.6%	62.1%	11.8% IGT	0.708	20% (92.6%)
	HbA_{1c} – IFG (WHO criterion – FPG ≥ 6.1 mmol/l and <7.0 mmol/l)	5.6%	60.0%	56.5%		0.632	8% (99.6%)
	HbA_{1c} – IFG (ADA criterion – FPG ≥ 5.6 mmol/l and < 7.0 mmol/l)	5.6%	65.1%	63.4%		0.708	8% (97.3%)
Mostafa 2010 + UK Study population	HbA1c 5.7 – 6.4% or HbA1c 6.0 – 6.4%	5.8% in White Europ. 6.0% in south Asians	61.5% 63.8%	67.9% 69.4%	16.2% IGR	0.69 (0.69 white Europ ean; 0.72 south Asian)	*0.50 (0.51)* *0.50 (0.51)*
Zhou 2009 + China General population	HbA1c	≥ 5.7%	59.4%	73.9%	22.4% pre-diabetes	0.73	46.0% (54.7%)
Luders 2005 + (Germany; high risk patients)	HbA_{1c} alone	≥6%	58%	84%	37% with HbA1c ≥ 6mmol/l	0.614	79% (66%)

Figures in italics calculated by reviewer

Specificity was shown to increase with higher cut-points but also with increased prevalence. AuC was similar across all studies, ranging from 0.614 in Germany to 0.73 in China (see Table 13). The UK based study (Mostafa *et al* 2010) assessed performance of the test with white Europeans and the South Asian population. The optimal cut-point was 5.8% in the former and 6.0% in the latter, both of which were relatively sensitive and specific (≥ 61%). The PPV and NPV were around 0.50 in both groups.

Evidence statement 11:

Studies assessing HbA1c alone

There was strong evidence [+] from four studies (Mostafa *et al* 2010 UK ++; Zhou *et al* 2009 China +; Mohan *et al* 2010 India +; Luders *et al* 2005 Germany +) relating to the performance of HbA1c.

In one UK study population, two Asian general population studies and one German high risk population HbA1c alone at a range of optimal cut off points (5.6% - 6.4%) were reported to give sensitivities of between 39% and 65.6% and specificities 56.5% - 84%.

Lower sensitivities and higher specificities were associated with higher cut points. The highest specificity (84%) and PPV (79%) for the highest cut point (6.0%) were obtained in a German population at high risk (hypertensive). One UK study (Mostafa *et al* 2010 ++) found that the optimal cut point and corresponding specificity was higher in south Asian groups than in white Europeans for detection of IGR (PPV 50%). A sensitivity of 65.1%, specificity 63.4% was obtained using the ADA criterion for identification of IFG (cut point 5.6%) in an Indian general population (Mohan *et al* 2010 India +). However the PPV was only 8.0% as the sample identified with IFG was very small.

Since these studies were published, WHO (2011) have issued a statement that HbA1c at cut point 6.5% can be used, in optimal conditions, to diagnose type 2 diabetes.

Comparing non-fasting capillary blood glucose indicators to HbA_{1c}

None of the included studies compared non-fasting capillary blood glucose indicators to HbA_1c.

Evidence statement 10:

Comparing non-fasting capillary blood glucose indicators to HbA_{1c}

There was no evidence available comparing non-fasting capillary blood glucose indicators to HbA_1c.

Comparison of fasting blood glucose indicators and HbA1c

Eight included studies compared fasting blood glucose and HbA1c in the detection of pre-diabetes. Two studies assessed fasting capillary blood testing and six assessed plasma blood tests. The performance of each test and comparator is listed below.

Table 15: Findings from studies comparing Fasting plasma blood glucose indicators to HbA_{1c}

Study (Population)	**Index / comparator**	**Optimal cut point**	**Sensitivity**	**Specificity**	**Prevalence**	**AuC**	**PPV (NPV)**
Capillary							
Herdzik 2002 - (Poland; at risk population)	FCG	5.5 mmol/l	63.5%	99.4%	17.65% IGT	0.865	*40.6% (60.0%)*
	HbA_{1c}	5.29%	51.3%	95.8%		0.748	*36.4% (64.2%)*
Zhou 2010 + China General population	FCG	≥6.0 mmol/l	60.5% men 56.7% women	62.8% men 67.8% women	29.5% pre-diabetes	0.64 men 0.65 women	NR
	HbA_{1c}	≥ 6.5%	4.5% men 5.7% women	88.3% men 89.4% women		0.47 men 0.51 women	
Plasma							
Simmons 2004 + (NZ; EU, Maori, Pacific general population)	FPG	≥ 5.3 mmol/l	66.3%	NR	20% IFG / IGT	0.88	36.8% for IFG / IGT / DM
	HbA1c	5.3%	50.9%	NR		0.68	46.6% for IFG / IGT / DM
Hu 2009 + (China; high risk population)	FPG	≥ 5.6 mmol/l	64.1%	65.4%	16.5% IGT / IFG	0.701	51.4% (49.3%)
		≥ 6.1 mmol/l	32.4%	88.3%			28.3% (72.5%)
	HbA_{1c}	≥5.6%	66.2%	51.0%			58.4% (42.3%)
Gomyo 2004 + (Japan; sample from JDPP study)	FPG	*5.7 mmol/l*	69.1%	61.6%	25.7% IGT 8.7% IFG	0.72	†54.0% (46.0%)
	HbA_{1c}	5.3%	57.2%	67.4%		0.65	*47.0% (54.0%)*
Saydah 2002 + (US; at risk population)	FPG	≥*5.83mmol/l*	56%	72%	24.8% IGT	0.665	17%
	HbA_{1c}	≥5.5%	60%	55%		0.593	21%
Luders 2005 +	FPG	≥ *6.1 mmol/l*	62%	57%	37% with HbA1c ≥	0.671	60% (59%)

Study (Population)	**Index / comparator**	**Optimal cut point**	**Sensitivity**	**Specificity**	**Prevalence**	**AuC**	**PPV (NPV)**
(Germany; high risk patients)	HbA_{1c}	6.0%	58%	84%	6mmol/l	0.614	79% (66%)
Colagiuri 2004 + (Australia; general population)	Risk assessment and FPG	≥5.5 mmol/l	51.9%	86.7%	47.7% IFG/IGT	NR	45.5% (NR)
	Risk assessment, and HbA_{1c}	≥5.3%	42.0%	88.2%			43.2% (NR)

Figures in italics calculated by reviewer

It is difficult to make any firm conclusions from the data since the results of comparisons vary from study to study. Most of the populations targeted were high risk, and this is reflected in the prevalence rates. PPV was highest (79%) for HbA1c at a cut point 6.0% in a German stepped strategy with hypertensive patients. Specificity in this study was also much higher (84%) than for the FPG (57%) at a cut point 6.1 mmol/l.

Evidence statement 13:

Studies comparing Fasting Blood Glucose (Fasting Capillary Glucose / Fasting Plasma Glucose) and HbA1c tests

Moderate evidence was available from eight studies [+; -] that compared fasting glucose testing with HbA1c (Herdzik *et al* 2002 Poland -; Simmons 2004 New Zealand +; Hu *et al* 2009 China +; Gomyo 2004 Japan +; Saydah 2002 US +; Luders 2005 Germany +; Colagiuri 2004 Australia +; Zhou *et al* 2010 China +). All fasting blood measures were taken from plasma apart from one study (Herdzik *et al* 2002 Poland -) that measured capillary blood.

In six studies of high risk populations, FCG / FPG with cut points ranging from 5.5 mmol/l to 6.1 mmol/l and HbA1c cut points ranging from 5.3% to 6.1% (Herdzik *et al* 2002 Poland -; Hu *et al* 2009 China +; Gomyo *et al* 2004 Japan +; Saydah *et al* 2002 US +; Luders *et al* 2005 Germany +), the highest sensitivity was for the FPG in a Japanese trial population (69%) using a cut point of 5.7mmol/l (Gomyo *et al* 2004 +). The highest specificity was 99% (obtained via capillary testing applying a low cut point of 5.5mmol/l; Herdzik *et al* 2002 Poland -), and with plasma testing at cut point 6.1mmol/l following risk assessment (100%).

The highest positive predictive value was 79% (NPV 66%) for HbA1c at a cut point of 6.0% in a German high risk population (Luders *et al* 2005 Germany +). Sensitivity and specificity were 58% and 84% with AuC 0.614.

Three studies were carried out in the general population (Simmons *et al* 2005 + New Zealand +; Colagiuri *et al* 2004 Australia +; Zhou *et al* 2010 China +). One study compared FPG cut point ≥ 5.5 mmol/l to HbA1c at ≥ 5.3%, reporting sensitivity 66.3% (specificity not reported), PPV 36.8% (NPV not reported), AuC 0.88 for the FPG and sensitivity 50.9%, no specificity reported, PPV46.6% and Auc 0.68 for HbA1c (Simmons *et al* 2005 + New Zealand +).

Another study reported 51.9% sensitivity, 86.7% specificity; PPV 45.5%, (NPV not reported) for risk assessment and FPG ≥ 5.3 mmol/l; 42.0% sensitivity, 88.2% specificity, PPV 45.5% (NPV not reported) for risk assessment and FPG ≥ 6.1 mmol/l, compared to sensitivity 42.0%, specificity 88.2%, PPV 43.2%, (NPV not reported, AuC not reported for any values) for HbA1c at ≥ 5.3% (Colagiuri *et al* 2004 Australia +).

Zhou *et al* (2010 China +) reported separate results for men and women. FCG at cut point 6.0 mmol/l was more sensitive for men (60.5%) than for women (56.7%) and more specific for women (67.8%) than for men (62.8%). Specificity was higher for the HbA1c in both men and women (88.3% for men, 89.4% for women) but with low sensitivity (less than 5%). AuC was 0.64-5 for the FCG and 0.47-0.51 for the HbA1c. PPV and NPV were not reported.

Since these studies were published, WHO (2011) have issued a statement that HbA1c at cut point 6.5% can be used, in optimal conditions, to diagnose type 2 diabetes.

Assessing the combination of fasting blood glucose indicators and HbA_1c

Four studies assessed a strategy that included a combination of FPG and HbA1c. All populations were high risk; three studies (Luders *et al* 2005; Colagiuri *et al* 2004; Saydah *et al* 2002) assessed risk prior to testing.

Table 16: Findings from studies assessing a combination of fasting blood glucose indicators and HbA_{1c}

Study (Population)	**Index / comparator**	**Optimal cut point**	**Sensitivity**	**Specificity**	**Prevalence**	**AuC**	**PPV (NPV)**
Hu 2009 + (China; high risk population)	FPG and HbA_{1c}	≥5.6 mmol/l ≥5.6%	42.4%	82.4%	16.5% IGT / IFG	0.701	35.6% (82.4%)
Luders 2005 + (Germany; high risk patients)	FPG and HbA_{1c}	≥*6.1 mmol/l* 6.0%	61%	78%	37% with HbA1c ≥ 6mmol/l	0.688	78% (60%)
Risk Assessed population							
Colagiuri 2004 + (Australia; Survey population)	Risk assessment FPG and HbA_{1c}	≥5.5 mmol/l ≥5.3%	42.0%	88.2%	47.7% IFG/IGT	NR	54.8% (NR)
Saydah 2002 + US General population	BMI ≥ 24 kg/m^2 Age 40-74 years FPG and HbA1c	≥5.8 mmol/l ≥5.5%	33.4%	84.8%			37.9% (NR)
		≥5.8 mmol/l ≥6.0%	11.2%	97.5%			45.1% (NR)
		≥6.1 mmol/l ≥5.5%	21.1%	93.5%			42.3% (NR)
		≥6.1 mmol/l ≥6.0%	6.2%	98.7%			42.3% (NR)

Figures in italics calculated by reviewer

All four studies showed high specificity (at least 78%). PPV was highest (78%) for HbA1c at a cut point 6.0% and FPG at a cut point 6.1 mmol/l in a German strategy with hypertensive patients. AuC was only reported in two studies (Hu *et al* 2009; Luders *et al* 2005) at 0.70 and 0.68 respectively.

Evidence statement 14:

Studies assessing a combination of fasting blood glucose indicators and HbA_{1c}

Moderate evidence was found [+] in four studies that assessed the combined performances of Fasting Blood Glucose and HbA1c indicators in high risk populations (Hu *et al* 2009 China +; Luders *et al* 2005 Germany +; Coligiuri *et al* 2004 Australia +; Saydah *et al* 2002 US +).

Sensitivity and PPV were highest (61%, 78%) with a combination of FPG cut point 6.1mmol/l and HbA1c 6.0% (Luders *et al* 2005 Germany +). Specificities were high in all four studies (>78%). The highest specificity (98.7%) was obtained with a population that had BMI ≥ 24 kg/m^2 and age 40-74 years (Saydah *et al* 2002 US+) It may therefore be beneficial to combine tests following risk assessment.

Since these studies were published, WHO (2011) have issued a statement that HbA1c at cut point 6.5% can be used, in optimal conditions, to diagnose type 2 diabetes.

Stepped strategies

Six studies assessed stepped strategies that used a risk assessment followed by at least one blood glucose indicator depending on the result of the risk score.

Table 17. Stepped strategies

Study (Population)	**Index / comparator**	**Optimal cut point**	**Sensitivity for prediabetes**	**Specificity for prediabetes**	**Prevalence**	**AuC**	**PPV (NPV)**
Colagiuri 2004 + (Australia; Survey population)	Risk assessment		NR (87.4% for T2DM)	NR (58.4% for T2DM)	47.7% IGT/IFG	NR	NR
	Risk assessment and FPG	≥5.5 mmol/l	51.9%	86.7%			45.5% (NR)
	Risk assessment, FPG and HbA_{1c}	≥5.5 mmol/l ≥5.3%	42.0%	88.2%			43.2% (NR)
Franciosi 2005 + Italy At least 1 CVD risk factor	Diabetes Risk Score	>9	77%	45%	11% IGT/IFG	0.67	48% (76%)
	FBG + DRS>9	≥5.6 mmol/l ≥6.1 mmol/l	69% 55%	65% 84%		NR	56% (76%) 69% (74%)

Study (Population)	**Index / comparator**	**Optimal cut point**	**Sensitivity for prediabetes**	**Specificity for prediabetes**	**Prevalence**	**AuC**	**PPV (NPV)**
	FBG	≥5.6 mmol/l ≥6.1 mmol/l	86% 68%	44% 75%		NR	50% (83%) 64% (78%)
Lidfelt 2001 ++ (Sweden; Mid-life women)	Risk factors and Random Capillary Blood Glucose	≥8.0 mmol/l	70%	55%	3.7% IGT/IFG	NR	33.6% (85.1%)
Luders 2005 + (Germany; high risk patients)	HbA_{1c} alone	≥6%	58%	84%	37% with HbA1c ≥ 6%	0.614	79% (66%)
	FPG alone	*6.1 mmol/l*	62%	57%		0.671	60% (59%)
	HbA_{1c} and FPG combined		61%	78%		0.688	78% (60%)
	HbA_{1c} + FPG + age		82%	76%		0.716	81% (74%)
	HbA_{1c} + FPG + age + systolic blood pressure		79%	74%		0.722	79% (74%)
	HbA_{1c} + FPG + age + systolic blood pressure + waist		83%	76%		0.724	80% (82%)
Rolka 2001 + (US; General population)	ADA risk assessment questionnaire	ADA ≥ 10	*FBG 6.6mmol/l* 69% 2h OGTT 7.8mmol 72%	*FBG 6.6mmol/l* 51% 2h OGTT 7.8mmol 53%	15% IGT/IFG	NR	NR
	Capillary Blood Glucose (CBG)	*6.6mmol/l* *7.8mmol/l*	FBG *6.6mmol/l* 62% 2h OGTT 7.8mmol 48% FBG *6.6mmol/l* 41% 2h OGTT 7.8mmol 33%	FBG *6.6mmol/l* 90% 2h OGTT 7.8mmol 89% FBG *6.6mmol/l* 97% 2h OGTT 7.8mmol 96%		NR	NR
	ADA questionnaire + CBG	ADA ≥ 10 ≥ 140 mg/dl *7.8mmol/l*	*FBG 6.6mmol/l* 45% 2h OGTT 7.8mmol 36%	*FBG 6.6mmol/l* 95% 2h OGTT 7.8mmol 94%		NR	NR
Simmons 2005 + (NZ; EU,	Risk Factors	Any of 3 factors	71.6%	NR for IGT	20% IGT/IFG	0.61	43.5% for IFG / IGT /

Study (Population)	**Index / comparator**	**Optimal cut point**	**Sensitivity for prediabetes**	**Specificity for prediabetes**	**Prevalence**	**AuC**	**PPV (NPV)**
Maori, Pacific general population)							DM
	Random Blood Glucose	≥ 5.6 mmol/l	66.3%	NR for IGT		0.72	41.3% for IFG / IGT / DM
	Random Blood Glucose + factor	≥ 5.6 mmol/l	52%	NR for IGT			56.3% for IFG / IGT / DM
	Fasting Glucose	≥ 5.3 mmol/l	66.3%	NR for IGT		0.88	36.8% for IFG / IGT / DM
	Fasting Glucose + factor	≥ 5.3 mmol/l	60.8%	NR for IGT			48.9% for IFG / IGT / DM
	HbA1c	≥ 5.3%	50.9%	NR for IGT		0.68	46.6% for IFG / IGT / DM
	HbA1c + factor	≥ 5.3%	44.2%	NR for IGT			61.4% for IFG / IGT / DM

Colagiuri reported high specificity for risk assessment followed by either FPG at cut point 5.5 mmol/l (86.7%), or FPG and HbA1c at cut point 5.3% (88.2%). PPV was less than 46% for both these strategies. AuC improved with each step in the Luders strategy that added the risk factors age, blood pressure and waist circumference to the assessment of HbA1c and FPG. However, HbA1c alone had a similar PPV to the full set of risk factor and dual blood glucose measures (80% compared to 79%).

Evidence statement 15:

Stepped / multi-component strategies

Moderate to good evidence [+; ++] was found from six studies of multi-component / staged strategies to identify IGT / IFG (Colagiuri *et al* 2004 +; Franciosi *et al* 2005 +; Lidfelt *et al* 2001+; Luders *et al* 2005 +; Rolka *et al* 2001 +; Simmons *et al* 2005 +).

Three studies were carried out in at risk populations (Lidfelt *et al* 2001 Sweden +; Luders *et al* 2005 Germany +; Franciosi *et al* 2005 Italy +). All six studies utilised assessment of risk prior to evaluation of one or more blood glucose indicators. A combination of FPG cut point 6.1 mmol/l, HbA1c cut point 6.0% and risk assessment

for age gave a sensitivity of 82%, specificity 76%, PPV 79% in one study (Luders *et al* 2005 Germany +). This compares to sensitivity 58%, specificity 84% for HbA1c alone (≥ 6% cut point) and 62%, 57% for FPG alone (6.1mmol/l cut point).

Franciosi *et al* (2005 Italy +) reported increased specificity (65% at cut point ≥5.6mmol/l and 84% at cut point ≥6.1mmol/l) with the addition of the Diabetes Risk Score to FBG compared to the risk score (45% at cut point 9) or FBG alone (44% at cut point ≥5.6mmol, 75% at cut point ≥6.1mmol/l). PPV was highest (69%) for the FBG at ≥6.1mmol/l and the risk score, with NPV 74%. AuC was not reported for this combination.

Rolka *et al* (2001 US +) reported similar specificity for the addition of the ADA questionnaire (94-5%) to capillary blood glucose testing at cut point 7.8 mmol/l (96-7%), which was higher than that for the ADA questionnaire alone (51-4%) at cut point ≥ 10. Sensitivity reduced with each stage, from 72-8% for the questionnaire alone, to 28-41% and 32-45% for the CBG and the CBG with the questionnaire. PPV, NPV and AuC were not reported.

Since these studies were published, WHO (2011) have issued a statement that HbA1c at cut point 6.5% can be used, in optimal conditions, to diagnose type 2 diabetes.

Evidence statement 16:

Costs of implementation of blood glucose indicator and stepped strategies for identification of pre-diabetes.

There was moderate evidence [+] from one study Australian stepped study (Colagiuri *et al* 2004 +) that costs were $A 8.05 for FPG, $A 14.15 for HbA1c. A return visit to obtain the result of the blood test was reported as costing $A 25.05; OGTT $A 15.90, and return final visit to the primary care physician for the result $A 25.05. Total cost for each person identified with IGT or IFG was reported as $A 260.

Evidence statement 17:

Barriers and facilitators to implementation of blood glucose indicator and stepped strategies for identification of pre-diabetes.

There was no available evidence within the included studies for barriers or facilitators to implementation of blood glucose indicator and stepped strategies for identification of pre-diabetes.

6.4.4 Response rates

Details of response rates to study participation invites and / or participation in the various stages of the study, such as blood glucose testing, was reported in 20 included papers. Other studies reported data such as how many participants were eligible to participate due to the presence of risk factors or the results of blood glucose testing. These figures are not presented here since they are not depicting the participant's choice or ability to take-up risk assessment strategies. In some studies it was a challenge to identify the pattern of recruitment and take-up from the reported information. There was scarce reporting of the issues raised through recruitment in the included papers. Only those studies reporting response rates or data are presented in Table 18. Figures in italics have been calculated from the data by a reviewer.

Table 18. Response rates reported in included studies

Study	Population	Measure	Recruitment (participated /invited)	Uptake
Risk assessment				
Greaves 2004	UK 16 GP practices	Medical Records	15 / 16 practices (n=1287)	60.6% initial 100% repeat testing
Glumer 2004 (ADDITION pilot)	Denmark General Population	Diabetes Risk Score	6,124 (Inter99) 1,028	Inter99 52.5% ADDITION pilot, 50%
Gray 2010 (ADDITION – Leicester)	UK Lay Multi-ethnic	Leicester Risk Assessment	6,390 / 30,950	22%
Heldegaard 2006	Denmark 1 GP practice list	Cambridge Risk Score	1355 / 2082	69%

Saaristo 2005 FINRISK-2002	Finland General Population	FINDRISC	3,092 / 4,622	67% initial participation. Of these, 85% completed FINDRISC.
Schwarz 2009	Germany 1996 & 1997 General population	Adapted FINDRISC	1997: 515 / 526	*97.9%*
Thomas 2006	UK Mid life women General Population	Cambridge Risk Score	9,377 / 12,070	84.2% of which 7,899 (84.2%) gave blood sample
Woolthuis 2007	Netherlands 11 GP Practices	ProMedico EMR software	3,337 total at risk	88% returned for FPG.
Blood Glucose indicators				
Mohan 2007 (CURES)	India Chennai Urban Rural	OGTT	2,350 / 2,600	90%
		HbA1c	2,188 / 2,350	93.1%
Phillips 2009	US Health care employees; Members of the community	1 hour oral glucose challenge test	2,111 / 4,024	*52.5%* participation. Of these, 78.5% (1,658) attended first visits and *74.9%* (1,581) completed the protocol.
Rush 2008 (Te Wai o Rona)	New Zealand At risk Maori	OGTT POCT	3,225 / 5,309 completed both tests	*60.7%*
Somannavaar 2009	Chennai, India Opportunistic diabetes screening camps	Random capillary blood glucose (RCBG)	1,333 / 1,500	88.9%
Zhou 2009	China General population	HbA1c	903 / 915 total data collected	
Zhou 2010	China General population	OGTT/ FPG HbA1c FCG	6,100 invited	87.8% of which 87.4%had HbA1c 90.9% had FCG
Multi-component				
Coligiuri 2004 (AusDab)	Australia General population	Risk assessment FPG HbA1c	11,247 10,508 participated after exclusions	55.3%
Franciosi 2005 (IGLOO)	Italy Primary care ≥1 CVD risk factor	Diabetes Risk Score FBG FBG + DRS	1,377 / 1,840	*74.5%*
Lidfelt 2001	Sweden Mid –age	Questionnaire OGTT	6,917/ 10,766 2,923 / 3,593	64.2%

	women		had OGTT	
Luders 2005	Germany Primary care Hypertensive	Risk factors 2-hr OGTT	260 / 267 had OGTT	
Simmons 2005	New Zealand European, Maori, Pacific Islanders	Risk factors OGTT RBG FBG HbA1c	1,899 / 2,737	67.9% attended OGTT
Somannavaar 2009	Chennai, India Opportunistic diabetes screening camps	Random capillary blood glucose (RCBG)	1,333 / 1,500	88.9%

Comparison of response rates requires caution due to the wide variation in study types, study design and reporting. However, there are details within the studies that differentiate between participating and non-participating populations or offer an explanation for some of the reported rates. These are presented where available in the following, relating to the type of risk assessment strategy.

Risk assessment

Greaves *et al* (2004) reported that the good uptake rate in their evaluation of the use of medical records for risk assessment may be due to confirmation of appointments by telephone. In addition, patients that did not initially attend were followed up and re-contacted. The recruitment rate was lower in men (39.5%) than women. The authors report that the response rate compares favourably with population screening for cervical cytology and mammography.

Gray *et al* (2010) developed a diabetes risk score (LRA) based on data from a population with 23% ethnic minority representation, mainly South Asian. The reported uptake for actual screening in the ADDITION-Leicester study was low in this group (22%). There are no known reported reasons for the low rate.

Heldegaard *et al* (2006) reported an acceptable response rate (69%) to invitations for the CRS. Non-responders were younger (20-39 years) than participants, though as the authors suggest, younger people are at less risk than those aged over 40 years. This may have had an impact on the positive predictive value achieved when assessing the risk score.

In the CRS evaluation carried out by Thomas *et al* (2006), there was a higher reported attrition rate in those from unskilled manual backgrounds. The authors suggest that this group are more at risk from type 2 diabetes are than the UK general

population, therefore the results of the evaluation may underestimate the extent of risk.

Woolthuis *et al* (2007) reported that following the use of EMR to identify at risk patients, most of the 28% of those at risk (88%) were willing to return for blood glucose testing. There are no details of the willingness of particular groups in this study, though an additional strategy in this study was to discuss diabetes risk at every consultation with the GP. This may have increased willingness to participate through raised awareness of personal risk.

Blood Glucose Testing

Although a high response rate (90%) was reported by Mohan *et al* (2010), recruitment was from a population that was already taking part in an Indian epidemiological study (CURES). Though the authors do not discuss this, there is possibly more motivation for this group to participate in further testing than in the general population.

Rush *et al* (2008) attribute the relatively high response rate (61%) in their study to the acceptability of the strategy being tested. Point of care testing requires no fasting or waiting and therefore may be more acceptable than some other types of blood glucose testing.

Stepped /multi-component strategies

Lidfelt *et al* (2001) reported a relatively high response rate. Women who did not attend for OGTT had a higher mortality rate, mainly from malignancy, indicating that prevention of diabetes may not be a priority for these women. Non-attenders also cited lack of time as a barrier to attending.

In the Simmons *et al* (2004) study, there was a relatively high reported response rate (68%) for attending the OGTT. However, the authors found that the highest rate of non-attenders was in European males. There was no explanation offered for this finding.

Evidence Statement 18:

Response rates

Moderate evidence was found [+;-] from nine studies (Glumer *et al* Denmark 2004 +; Gray *et al* 2010 UK; Mohan *et al* 2007 India +; Phillips *et al* 2009 US +; Rush *et al*

2008 US -; Simmons *et al* 2004 New Zealand +; Somanavaar 2009 India + ; Thomas *et al* 2006 UK +; Zhou *et al* 2010 China +).

For risk assessment, response rates ranged between 50% and 89%. The highest response rate reported was for the Cambridge Risk Score (Thomas *et al* 2006 UK +), and the lowest reported was for the Diabetes Risk Score (Glumer *et al* Denmark 2004 +). In an evaluation of the Leicester Risk Assessment, 22% of the initial South Asian sample remained in the study following a series of tests including the OGTT. (Gray *et al* 2010 UK +).

For blood glucose measures, there was a 52.5% response rate to the first visit for a 1 hour oral glucose tolerance test (Phillips *et al* 2009 US +). Random / Point of care testing was reported to have a response rate of 89% (Somanavaar 2009 India +) and 61% (Rush *et al* 2008 US -)

Response rates for assessment of the HbA1c were reported as 87% (Zhou *et al* 2010 China +) and 93% (Mohan *et al* 2007 India +), though the Chinese based study also included assessment of fasting blood glucose, for which there was a response of 91%.

Simmons *et al* (2004 New Zealand +) conducted OGTT, fasting blood glucose and HbA1c measures from one blood sample. The response rate for this visit was 68% in those aged 40-59 years and 71% in those aged 60-79 years. There were no reported differences in response between Maori, European and Pacific Islander groups or between age groups. Response rate was reported to be similar between males and females apart from in the European group, where males were less likely to respond (66.5% rate compared to females 73.9%, p=0.012).

Evidence statement 19:

Barriers and facilitators to uptake for strategies for identification of pre-diabetes.

Potential facilitators to increasing uptake were suggested in two studies. Woolthuis *et al* (2007 / 2009+) found that one facilitator was carrying out risk assessment in a familiar clinic environment. Greaves *et al* (2004+) reported that their good uptake rate may be due to confirmation of appointments and follow-up contact with patients by telephone.

7. DISCUSSION

The aim of this review was to assess the evidence for the effectiveness, and where available, cost-effectiveness of methods for identifying adults with pre-diabetes, and how to increase identification and the uptake of risk assessment in high-risk groups. From an initial total of 2828 references generated from two searches, as well as reference list checks, 29 studies, of varying study type and quality, met the inclusion criteria. Many published studies focus on detection of type 2 diabetes rather than pre-diabetes. This review did not assess such papers. The quality of papers was moderate, with 2 papers rated as very good (++), 24 as good (+) and 3 as poor (-).

Papers assessed the use of routine demographic data found in practice records as an approach for identifying patients that might be at risk for pre-diabetes, the use of routine data to provide a risk score, and questionnaire based risk scores. In addition, a range of blood glucose measures was assessed in at risk and general populations as compared to the OGTT. Comparisons were made between fasting and non-fasting tests, and stepped strategies that included risk assessment as well as blood glucose indicators were assessed.

The studies were heterogeneous in study design, population, prevalence of pre-diabetes, and aims, therefore pooling of data was not deemed appropriate. The results of this review highlight the complexity of risk assessment, and in particular, blood glucose measures that are available for identifying those at risk of pre-diabetes. It is difficult to make comparisons since the results from comparison studies did not show a particular trend. There was very little useful evidence within the papers on costs, or on how to increase uptake in at risk groups.

There was evidence that use of medical records may be a useful start to the identification process, provided that risk factors such as BMI are recorded accurately and that records are regularly up-dated. The Cambridge Risk score took this method a step further by applying a score to risk data. This method was evaluated in the UK and Denmark, with both studies reporting AuC of around 0.75. However, the optimal cut points differed. The UK study reported no difference in effect than using BMI alone as a risk indicator.

Questionnaire based risk scores require more resource to implement, as they are administered to patients who may need some supervision. However, more information can be obtained using this method. The FINDRISC was developed in Finland and is more specific for women than men. A shortened 8-item version

developed for the German population gave a higher sensitivity, specificity and AuC than the original, at a cut point one point higher. In the UK, a version that targeted a lay multi-ethnic population showed a PPV of 27.7% at a cut point higher than the Finnish or German versions. Other risk scores have been developed in the US and Denmark. One US version was more specific than the Italian FINDRISC based score.

Improved uptake for risk assessment may occur when participants are followed up by telephone and specific appointments are made within the invitation letter. Low responses were reported in ethnic minority, younger, and unskilled manual populations. Returning for blood testing may be encouraged by discussion of risk during consultations with general practitioners.

It is acknowledged that papers are available that describe other tools, such as the QRISK, developed for assessing cardiovascular risk (Hippisley - Cox *et al* 2009). However, we did not identify papers describing such tools that met the inclusion criteria for this review, i.e. papers that present an evaluation in terms of detecting pre-diabetes.

A range of non-fasting blood glucose measures gave PPVs of less than 50%. Prevalence of pre-diabetes was high in all the studies. It was difficult to compare the performance of fasting blood glucose indicators due to differences in the populations studied, optimal cut points and assessment criteria. HbA1c was assessed in five studies including the UK. Specificity increased with a rise in cut point and PPV was around 50% in all the studies. Compared to fasting blood glucose, a PPV of 79% was achieved at a cut point of 6.0% in a German high risk population. A similar PPV was found in the same study when combining the two tests. A combination of FPG and HbA1c following risk assessment for BMI gave the highest specificity (98%).

In blood glucose test studies, improved responses may occur in trial and other study populations. Acceptability of the test was also discussed as a motivation, particularly in terms of time required. European males responded least well in one stepped programme, and in another, the women who did not attend had a high rate of morbidity and mortality, though not related to diabetes.

Six studies assessed stepped strategies that commenced with risk assessment. All six studies reported high specificity, though one study reported a higher specificity for the HbA1c alone at a cut point of 6.0% or more.

It appears that a stepped strategy might be useful in terms of identifying risk prior to blood testing, so that resources may be focussed on those at risk. The risk of false

positive is reduced by this process and it may be more acceptable to participants to adapt gradually to a potential diagnosis (Eborall *et al* 2007).

As fasting blood glucose measures and HbA1c use different techniques and are measuring different aspects of blood glucose level, there remains uncertainty around whether these two tests should be carried out together rather than alone.

Since this review was initiated, an addendum to the WHO recommendations *Definition and diagnosis of diabetes mellitus and intermediate hyperglycemia* (2006) has been published in relation to the use of HbA1c for diagnostic purposes. A consultation concluded that:

" *HbA1c can be used as a diagnostic test for diabetes provided that stringent quality assurance tests are in place and assays are standardised to criteria aligned to the international reference values, and there are no conditions present which preclude its accurate measurement. An HbA1c of 6.5% is recommended as the cut point for diagnosing diabetes. A value less than 6.5% does not exclude diabetes diagnosed using glucose tests. The expert group concluded that there is currently insufficient evidence to make any formal recommendation on the interpretation of HbA1c levels below 6.5%"* WHO 2011 (p.3).

The implication of the above statement for this review is that evidence for the use of HbA1c to diagnose pre-diabetes is inconclusive. However, given that a diagnosis of diabetes can be made at a cut point of 6.5%, previous suggestions of a cut point of HbA1c ≥ 6.5% to diagnose diabetes (or pre-diabetes) will need to be re-evaluated.

The applicability of findings to UK settings is variable since assessments have taken place internationally. In particular, health care delivery will differ from that in the UK. In addition, populations included in the studies vary in terms of risk profile.

Conclusion

A range of risk assessment tools and blood glucose indicators are available for the identification of pre-diabetes in individuals. Findings from international studies provide multiple combinations of assessment tools and indicators for use in a range of settings, with general and at risk populations, at a number of optimal cut points. However a strategy that assesses initial risk followed by diagnostic testing appears to have acceptable specificity. Response rates indicate that some groups are less likely to attend for risk assessment and testing. A number of strategies are available to increase uptake, mainly based on improved communication.

8. REFERENCES

Alberti KG, Zimmet P, Shaw J. International Diabetes Federation: a consensus on Type 2 diabetes prevention. Diabet Med. 2007 May;24(5):451-63.

Centre for Reviews and Dissemination (CRD) *Systematic Reviews: CRD's guidance for undertaking reviews in health care.* CRD. York: 2009

Department of Health (2002) National service framework for diabetes: standards London: Department of Health

Diabetes UK (2006) Diabetes and the disadvantaged: reducing health inequalities in the UK. A report by the All Party Parliamentary Group for Diabetes and Diabetes UK [online]. Available from www.diabetes.org.uk/Documents/Reports/Diabetes_disadvantaged_Nov2006.pdf

Griffin SJ, Little PS., Hales CN., Kinmomth AL., Wareham NJ. Diabetes risk score: towards earlier detection of type 2 diabetes in general practice. Diabetes Metab. Res. Rev. 2000: 16; 164 – 171.

Hippisley – Cox J., Coupland C., Vinogradova Y., Robson J., May M., Brindle. P.Derivation and validation of QRISK, a new cardiovascular disease risk score for the United Kingdom: prospective open cohort study. 2009: bmj.com doi:10.1136/bmj.39261.471806.55

Lindstrom J, Eriksson JG, Valle TT *et al*. (2003a) Prevention of diabetes mellitus in subjects with impaired glucose tolerance in the Finnish Diabetes Prevention Study: results from a randomized clinical trial. Journal of the American Society Nephrology 14 (supplement 2): 108–13

Lindstrom J., Tuomilehto J. (2003b) The diabetes risk score: a practical tool to predict type 2 diabetes risk. *Diabetes Car*e 26; 725 – 731.

Model Group (2007) Diabetes: finding excellence? Facing the multi-faceted challenge of diabetes [online]. Available from www.diabetes.nhs.uk/downloads/diabetes_finding_excellence.pdf

National Institute for Health and Clinical Excellence 2009. *Methods for development of NICE public health guidance* (second edition) National Institute for Health and Clinical Excellence, London.

National Institute for Health and Clinical Excellence 2009b. Developing NICE Guidance.

http://www.nice.org.uk/nicemedia/live/12067/45087/45087.pdf (Accessed 13.05.10).

http://www.nice.org.uk/guidance/index.jsp?action=download&o=34605 Accessed 12/1/10

Reinauer H., Home P.D., Kanagasabapathy A.S., Heuck C-C. *Laboratory Diagnosis and Monitoring of Diabetes Mellitus.* 2002: World Health Organization.

Sandbaek A., Griffin SJ., Rutten G., Davies M., Stolk R., Khunti K., Borch-Johnsen K., N. J. Wareham NJ., Lauritzen T. Stepwise screening for diabetes identifies people with high but modifiable coronary heart disease risk: the ADDITION study. *Diabetologia*. 2008 51:1127–1134

The Health and Social Care Information Centre (2009) Statistics on obesity, physical activity and diet: England February 2009. London: The Information Centre.

Tuomeilheto J., Lindstrom J., Eriksson JG., Valle TT., Hamaleinen H., Hanne-Parikka P. *et al*. 2001 Prevention of type 2 diabetes by changes in lifestyle among subjects with impaired glucose tolerance. *N Eng J Med* 2001 344: 1343-1350

UK National Screening Committee. The Handbook for Vascular Risk Assessment, Risk Reduction and Risk Management. University of Leicester; UK. 2008.

Waugh N, Scotland G, McNamee P *et al* (2007) Screening for type 2 diabetes literature review and economic modelling. Health Technology Assessment 11: 17 [online]. Available from www.ncbi.nlm.nih.gov/pubmed/17462167

Whiting P., Rutjes AWS., 2 Reitsma JB., Bossuyt PMM., Kleijnen J. The development of QUADAS: a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. BMC Medical Research Methodology 2003, 3:25

Williamsom DF., Venkat Narayan KM. Identification of persons with dysglycaemia: Terminology and practical significance. *Primary Care Diabetes* 2009, 3: 211-217.

World Health Organisation.Screening for Type 2 Diabetes: Report of a WHO/IDF meeting. (2003) WHO Geneva

World Health Organisation. Definition and diagnosis of diabetes mellitus and intermediate hyperglycemia: Report of a WHO/IDF Consultation (2006) WHO / IDF

World Health Organisation. Use of Glycated Haemoglobin (HbA1c) in the diagnosis of Diabetes Mellitus. (Addendum to "*Definition and diagnosis of diabetes mellitus and intermediate hyperglycemia*") 2011 WHO / IDF

9. APPENDICES

Appendix 1: Included studies

Colagiuri S.Hussain Z., Zimmet P., Cameron A., Shaw J. Screening for type 2 diabetes and impaired glucose metabolism. The Australian experience. *Diabetes Care* 2004; 27(2):367-371.

Franciosi M, De Berardis G, Rossi MC, Sacco M, Belfiglio M, Pellegrini F, *et al*. Use of the diabetes risk score for opportunistic screening of undiagnosed diabetes and impaired glucose tolerance: the IGLOO (Impaired Glucose Tolerance and Long-Term Outcomes Observational) study. *Diabetes Care* 2005 28(5):1187-1194

Glumer C, Carstensen B, Sandbaek A, Lauritzen T, Jorgensen T, Borch-Johnsen K. A Danish Diabetes Risk Score for Targeted Screening: The Inter99 study. *Diabetes Care* 2004 Mar: 27(3):727 – 733

Gomyo MS., Sakane N., Kamae I., Sato S., Suzuki K., Tominaga S *et al* Effects of sex, age and BMI on screening tests for impaired glucose tolerance. *Diabetes research and clinical practice* 2004; 64(2):129-136.

Gray LJ., Taub NA., Khunti K., Gardiner E., Hilest S., Webb DR., Srinivasan BT., Davies MJ. The Leicester Risk Assessment Score for detecting undiagnosed Type 2 diabetes and impaired glucose regulation for use in a multiethnic UK setting. *Diabetic Medicine* 2010 27: 887-895

Greaves CJ., Stead JW., Hattersley AT., Ewings P., Brown P., Evans PH. A simple pragmatic system for detecting new cases of type 2 diabetes and impaired fasting glycaemia in primary care. *Family Practice* 2004: 21: 57-62

Guerrero-Romero FR-M., Rodriguez-Moran M. Lowered criterion for normal fasting plasma glucose: Impact on the detection of impaired glucose tolerance and metabolic syndrome. *Archives of Medical Research* 2006: 37(1):140-144.

Heikes KE, Eddy DM, Arondekar B, Schlessinger L, Heikes KE, Eddy DM *et al*. Diabetes Risk Calculator: a simple tool for detecting undiagnosed diabetes and pre-diabetes. *Diabetes Care* 2008: 31(5):1040-1045.

Heldgaard, PE., Griffin SJ. Routinely collected general practice data aids identification of people with hyperglycaemia and metabolic syndrome. *Diabetic Medicine* 2006. 23(9): 996-1002

Herdzik E., Safranow K., Ciechanowski K. Diagnostic value of fasting capillary glucose, fructosamine and glycosylated haemoglobin in detecting diabetes and other glucose tolerance abnormalities compared to oral glucose tolerance test. *Acta Diabetol* 2002; 39(1):15-22.

Hu Y, Liu W, Chen Y, Zhang M, Wang L, Zhou H, *et al* Combined use of fasting plasma glucose and glycated haemoglobin A1c in the screening of diabetes and impaired glucose tolerance *Acta Diabetol* 2010: 47:231–236

Lidfeldt, J., Nerbrand C., Samsioe G., Schersten B., Agardh C-D. A screening procedure detecting high-yield candidates for OGTT. The Women's Health in the Lund Area (WHILA) study: A population based study of middle-aged Swedish women*. European journal of epidemiology* 2001: 17(10): 943-951.

Luders S., Hammersen F., Kulschewski A., Venneklass U., Zuchner C., Gansz A., *et al* Diagnosis of impaired glucose tolerance in hypertensive patients in daily practice. *Int J Clin Practice* 2005: 59 (6) 632-8

Mannucci E, Ognibene A., Sposato I., Brogi M., Gallori G., Bardini G, *et al*. Fasting plasma glucose and glycated haemoglobin in the screening of diabetes and impaired glucose tolerance. *Acta Diabetol* 2003: 40: 181-186

Maynard JD, Rohrscheib M, Way JF, Nguyen CM, Ediger MN. Noninvasive type 2 diabetes screening: superior sensitivity to fasting plasma glucose and A1C. *Diabetes Care* 2007 May 30(5):1120 -1124

Mohan V, Vijayachanrika V, Gokulakrishnan K, Anjana RM, Ganesan A, Weber MB, Venkat Narayan KM. A1c cut points to define various glucose intolerance groups in Asian Indians. *Diabetes Care* 2010 33 (3); 515-519

Mostafa SA., Khunti K., Srinivasan BT., Webb D., Gray LJ., Davies MJ. The potential impact and optimal cut-points of using glycated haemoglobin, HbA1c, to detect people with impaired glucose regulation in a UK multi-ethnic cohort. *Diabetes Research and Clinical Practice* 2010: 90; 100 - 108

Phillips LS, Ziemer DC, Kolm P, Weintraub WS, Vaccarino V, Rhee MK, *et al*. Glucose challenge test screening for prediabetes and undiagnosed diabetes. *Diabetologia* 2009 Sep 52 (9):1798-807.

Rolka DB, Narayan KM, Thompson TJ, Goldman D, Lindenmayer J, Alich K, *et al*. Performance of recommended screening tests for undiagnosed diabetes and dysglycemia. *Diabetes Care* 2001 24(11):1899 -1903

Rush E. Crook N., Simmons D. Point-of-care testing as a tool for screening for diabetes and pre-diabetes. *Diabet Med* 2008: 25(9):1070-1075.

Saaristo TP., Peltonen M., Lindstrom J., Saarikoski L., Sundvall J., Eriksson JG., Tuomilehto J. Cross-sectional evaluation of the Finnish Diabetes Risk Score: A tool to identify undetected type 2 diabetes, abnormal glucose tolerance and metabolic syndrome. *Diabetes and Vascular Disease Research* 2005: 2(2):67-72.

Saydah SH., Byrd-Holt D., Harris MI. Projected impact of implementing the results of the Diabetes Prevention Programme in the US population. *Diabetes Care* 2002: 25; 1940-45

Schwarz PEH., Li J., Reimann M., Schutte AE., Bergmann A., Hanefeld M., *et al* The Finnish Diabetes Risk Score is associated with insulin resistance and progression toward Type 2 diabetes. *J Clin Endocrinol Metab* 2009: 94: 920-6

Simmons D., Thompson CF., Engelgau MM. Controlling the diabetes epidemic: how should we screen for undiagnosed diabetes and dysglycaemia? *Diabetic Medicine* 2005: 22; 207-212

Somannavar, S., Ganesan A., Deepa M., Datta M., Mohan V. Random capillary blood glucose cut points for diabetes and pre-diabetes derived from community-based opportunistic screening in India. *Diabetes Care* 2009:32(4) 641-643.

Thomas C, Hypponen E, Power C. Type 2 diabetes mellitus in midlife estimated from the Cambridge Risk Score and body mass index. *Arch Intern Med* 2006: 166(6):682-688.

Woolthuis EPK., de Grauw WJC., van Gerwen WHEM., van den Hoogen HJM., van de Lisdonk EH., Metsemakers JFM., van Weel C. Identifying people at risk for undiagnosed type 2 diabetes using the GP's electronic medical record. *Family Practice* June 14, 2007

Zhou XH, Ji LN, Luo YY, Zhang XY, Han XY, Qiao Q *et al*. Performance of HbA1c for detecting newly diagnosed diabetes and pre-diabetes in Chinese communities living in Beijing. *Diabet Med* 2009; 26(12):1262-1268.

Zhou X, Pang Z, Gao W, Wang S, Zhang L, Ning F *et al*. Performance of an A1C and fasting capillary blood glucose test for screening newly diagnosed diabetes and pre-diabetes defined by an oral glucose tolerance test in Qingdao, China. *Diabetes Care* 2010: 33(3) 545-550.

Appendix 2: Excluded studies

Studies excluded after review of full paper

Author	Ref ID	Reason for exclusion
Abdul-Ghani 2005	1931	Not risk assessment tool
Adam *et al* 2008	2250	Discussion paper
Ader *et al* 2008	3262	Not risk assessment
Akao *et al* 2001	3536	No sensitivity/specificity
Alberti *et al* 2007	2264	Review article
Aldasouqi *et al* 2008	2245/2492	Discussion paper
Allen *et al* 1998	3626	Descriptive
Allsema *et al* 2010	Suggested paper	Not enough detail for IGT (focus on T2DM)
Anand *et al* 2003	2975	Not enough detail for IGT
Armstrong *et al* 2005	3412	No sensitivity/specificity
Balkau *et al* 2008	2251	Prediction of T2DM
Bang *et al* 2009	3774	Not aimed at identifying prediabetes
Barrett-Connnor 2002	3513	Descriptive
Bartnik & Ryden 2005	3431	No sensitivity/specificity
Belfiore 2000	3570	Not risk assessment
Bergmann *et al* 2000	3507	Population with existing prediabetes
Bergmann *et al* 2007	2265	Not aimed at identifying prediabetes
Bethel *et al* 2008	3243	No sensitivity/specificity
Bianchi *et al* 2009	3222	No sensitivity/specificity
Birkeland *et al* 2009	3224	No sensitivity/specificity
Borsch-Johnsen 2001	2384	Review article
Borsch-Johnsen 2004	2343	Discussion paper
Boston & Moate 2008	3267	No sensitivity/specificity
Breda *et al* 2002	3519	No sensitivity/specificity
Buell *et al* 2007	3777	Not aimed at identifying prediabetes
Bur *et al* 2003	2358	Not prediabetes
Cagnacci *et al* 2001	3537	No sensitivity/specificity
Casari *et al* 2001	3544	No sensitivity/specificity
Chapelot *et al* 2001	3535	No sensitivity/specificity
Charfen *et al* 2009	2228	Prevalence study
Chase *et al* 1999	3608	No sensitivity/specificity
Chen *et al* 2006	2295	Clinical research
Cheng *et al* 2004	3459	No sensitivity/specificity
Chevenne *et al* 1998	3634	No sensitivity/specificity
Chiu *et al* 2002	3528	No sensitivity/specificity
Christofordis *et al* 2006	3376	No sensitivity/specificity
Ciampelli *et al* 2005	3437	Not risk assessment
Cohen *et al* 1999	3614	No sensitivity/specificity
Cretti *et al* 2000	3579	No sensitivity/specificity
Cretti *et al* 2000	3567	No sensitivity/specificity
Cretti *et al* 2001	3550	No sensitivity/specificity
Daniel & Rowley 2002	2721/2370	Not aimed at identifying prediabetes
Davidson 2002	3488	Descriptive
Davidson *et al* 1999	3605	No sensitivity/specificity
Davidson *et al* 2000	3574	No sensitivity/specificity
De La Hera *et al* 2008	3258	No sensitivity/specificity

Author	Ref ID	Reason for exclusion
Del Rio *et al* 2009	3237	No sensitivity/specificity
Delgado *et al* 2007	3343	No sensitivity/specificity
Disoteo *et al* 207	3349	No sensitivity/specificity
Donado *et al* 2007	3581	No sensitivity/specificity
Drivsholm *et al* 1999	3599	No sensitivity/specificity
Dunstan *et al* 2004	2666	Cross sectional study
Ediger *et al* 2009	2211/2426	Not prediabetes
Ekstrom *et al* 1999	3598	No sensitivity/specificity
El Bassuoni *et al* 2008	3775	Discussion paper
Elkind-Hirsch & Webster 2003	3485	No sensitivity/specificity
Escalada *et al* 2008	3272	No sensitivity/specificity
Featherstone & Goyder 2000	3044	Discussion paper
Fica *et al* 2008	3260	No sensitivity/specificity
Fonseca 2007	2544	Discussion paper
Fonseca 2008	2242	Discussion paper
Forouhi 2006	2601	Discussion paper
Frabregate *et al* 2006	3373	No sensitivity/specificity
Garcia-Alcala *et al* 2006	3374	No sensitivity/specificity
Giessauf *et al* 2008	3257	No sensitivity/specificity
Ginde *et al* 2008	3263	No sensitivity/specificity for prediabetes
Ginde *et al* 2008	2241	Correlates study
Glumer *et al* 2004	3656	No sensitivity/specificity for prediabetes
Gong *et al* 2008	3271	No sensitivity/specificity
Greenberg *et al* 2002	2380	Review paper
Hammana *et al* 2009	3650	No sensitivity/specificity
Hansen *et al* 1999	3592	No sensitivity/specificity
Heish *et al* 2008	3301	No sensitivity/specificity
Henareh *et al* 2004	3461	No sensitivity/specificity
Henderson *et al* 2004	3473	No sensitivity/specificity
Hippisley-Cox 2009	3841	Prediction study
Hische *et al* 2010	3828	No separate IGT data
Hoffman-Snyder *et al* 2006	3381	No sensitivity/specificity
Hovorka *et al* 1998	3641	No sensitivity/specificity
Howell *et al* 1998	3647	No sensitivity/specificity
Iglesias *et al* 2006	179	No sensitivity/specificity
Iida *et al* 2005	3411	Not risk assessment
Imano *et al* 1999	3594	No sensitivity/specificity
Kanauchi *et al* 2002	3526	No sensitivity/specificity
Kanauchi *et al* 2002	3489	No sensitivity/specificity
Karakaya *et al* 2007	3316	No sensitivity/specificity for prediabetes
Kenealy *et al* 2007	125	Descriptive
Kim *et al* 2005	3419	No sensitivity/specificity
Kim *et al* 2008	3277	No sensitivity/specificity
Kiser *et al* 2003	3494	No sensitivity/specificity
Koh *et al* 2009	3228	No sensitivity/specificity
Kokkoris *et al* 2005	3418	No sensitivity/specificity
Kokkoris *et al* 2005	3405	No sensitivity/specificity
Koopman *et al* 2000	3147	No sensitivity/specificity for prediabetes
Kumar *et al* 2010	3787	No sensitivity/specificity for prediabetes
Lakitsch *et al* 2009	3223	No sensitivity/specificity
Lecube *et al* 2008	3302	No sensitivity/specificity
Ledson *et al* 2007	3308	No sensitivity/specificity

Author	Ref ID	Reason for exclusion
Li *et al* 2009	2237 / 3811	Not prediabetes
Li *et al* 2010	2218	Prediction study
Lindstrom & Tuomilehto 2003		No pre-diabetes data
Little *et al* 1994	381	Prediction study
Lopatynski *et al*	258	Descriptive
Lorenzo *et al* 2004	3452	No sensitivity/specificity
Lyon *et al* 1994	2338	Review paper
Mari *et al* 1999	3609	No sensitivity/specificity
Mari *et al* 2005	3433	No sensitivity/specificity
Martin *et al* 2009	3230	No sensitivity/specificity
Mathur *et al* 2008	3278	No sensitivity/specificity
Matsuda & Defronzo 1999	3604	No sensitivity/specificity
Matsuda & Defronzo 2000	3571	No sensitivity/specificity
Mazurek *et al* 2008	3290	Not enough detail, no specificity
McNeely *et al* 2003	3491	No baseline cross-sectional sensitivity/specificity
Meigs *et al* 2004	2677	Prediction model
Mohan *et al* 2007	3304	No sensitivity/specificity
Motala *et al* 2002	3506	No sensitivity/specificity
Nagy *et al* 2007	3314	No sensitivity/specificity
Naj *et al* 2006	3369	No sensitivity/specificity
Narayan *et al* 2006	3182	Discussion paper
Natarajan *et al* 2006	3370	No sensitivity/specificity
Nigrini *et al* 2008	3246	No sensitivity/specificity
Norberg *et al* 2006	3367	Erratum
Norbert *et al* 2006	3378	No sensitivity/specificity for prediabetes
Oberlinner & Neumann 2008	2538	No sensitivity/specificity for prediabetes
Olijhoek *et al* 2005	3430	No sensitivity/specificity
Orisaka *et al* 2006	157	Prediction model
Pan 2007	2262	Review paper
Park *et al* 2000	3130	Discussion paper
Park *et al* 2002	2375	No sensitivity/specificity for prediabetes
Periwal *et al* 2005	3417	No sensitivity/specificity
Piche *et al* 2007	3323	No sensitivity/specificity
Pontiroli *et al* 2001	3545	No sensitivity/specificity
Pontiroli *et al* 2001	3532	No sensitivity/specificity
Pratley 2007	2555	Discussion paper
Prigeon *et al* 1998	3638	No sensitivity/specificity
Procopio *et al* 2002	3509	No sensitivity/specificity
Radaelli & Catalano 2004	3436	No sensitivity/specificity
Rahman *et al* 2008	2852	No sensitivity/specificity for prediabetes
Rasmussen *et al* 2007	798	No sensitivity/specificity
Rathmann *et al*		Not assessing pre-diabetes
Reslin *et al* 2008	3248	No sensitivity/specificity
Retnakaran *et al* 2008	3266	No sensitivity/specificity
Rice *et al* 2003	3482	No sensitivity/specificity
Rohlfing *et al* 2000	2396	No sensitivity/specificity for prediabetes
Rolandsson *et al* 2001	3552	No sensitivity/specificity reported for prediabetes
Roubicek *et al* 1998	2417	Descriptive
Rovetti *et al* 2006	3375	No sensitivity/specificity

Author	Ref ID	Reason for exclusion
Rowley *et al* 2005	2323	Not prediabetes
Salmasi & Dancy 2005	3360	No sensitivity/specificity
Salmasi *et al* 2005	199/2624	No sensitivity/specificity for prediabetes
Sandbaek *et al* 2008	2253	Risk of CHD
Saudek *et al* 2008		Review paper
Saxena *et al* 2009	3220	No sensitivity/specificity
Sayeed *et al* 2004	2331	No sensitivity/specificity
Schmidt *et al* 2003	3773	Discussion paper
Schulze *et al* 2007	3975	Prediction paper
Schwarz *et al* 2008	110	Discussion paper
Schwarz *et al* 2009	2479	Prediction study
Schwarz *et al* 2009	3788	Review paper
Sesti *et al* 2008	2257	Not risk assessment
Shimazaki *et al* 2007	147	Prediction study
Sievenpiper	3580	No sensitivity/specificity
Simeoni *et al* 1999	3610	No sensitivity/specificity
Simeoni *et al* 1999	3600	No sensitivity/specificity
Soonthornpun *et al* 2003	3501	No sensitivity/specificity
Sorkin *et al* 1999	3607	No sensitivity/specificity
Sorodoc *et al* 2009	3234	No sensitivity/specificity
Stern *et al* 2002	3525/3015	No sensitivity/specificity
Stern *et al* 2002	3486	No sensitivity/specificity
Stern *et al* 2003	3492	Descriptive
Stevic *et al* 2007	3326	No sensitivity/specificity
Stumvoll *et al* 1999	3612	No sensitivity/specificity
Stumvoll *et al* 2000	3590	No sensitivity/specificity
Stumvoll *et al* 2001	3554	No sensitivity/specificity
Takada *et al* 2007	3305	No sensitivity/specificity
Taniguchi *et al* 2001	3530	No sensitivity/specificity
Temelkova-Kurktschiev *et al* 2002	3516	No sensitivity/specificity
Teo *et al* 2004	3475	No sensitivity/specificity
Thomas *et al* 2010	2203	Paediatric population
Thomaseth *et al* 2006	3366	Diabetic population
Toffolo *et al* 1999	3601	No sensitivity/specificity
Toffolo *et al* 2001	3543	No sensitivity/specificity
Tringham 2004	2670	Discussion paper
Tschritter *et al* 2004	3466	Erratum
Tsigos *et al* 2001	3546	No sensitivity/specificity
Tuomilehto 2002	3487	Descriptive
Tura *et al* 2008	3261	Diabetic & prediabetic participants
Turchin *et al* 2005	2321	Not relevant
Twigg *et al* 2007	2271	Position statement
Vaccaro *et al* 2000	3585	No sensitivity/specificity
Van Haeften & Stumvoll 2001	3549	No sensitivity/specificity
Vannai *et al* 2002	3508	No sensitivity/specificity
Velasquez-Mieyer *et al* 2002	3520	No sensitivity/specificity
Vermunt 2010	PDG	No sensitivity/specificity
Viswanath *et al* 2000	2972	No sensitivity/specificity for prediabetes
Wang *et al* 2002	2712	No sensitivity/specificity for prediabetes
Wang *et al* 2010	4014	No sensitivity/specificity for prediabetes
Warner *et al* 2008	3242	No sensitivity/specificity
Waterworth *et al* 2005	3424	No sensitivity/specificity

Author	Ref ID	Reason for exclusion
Weisnagel *et al* 2004	3453	No sensitivity/specificity
Wilke *et al* 2007	2276	Diabetic population
Woerle *et al* 2000	2974	No sensitivity/specificity for prediabetes
Yung *et al* 1999	3624	Some participants diabetic & no sensitivity/specificity for prediabetes
Zhang *et al* 2005	2327	Clinical research
Zhou *et al* 2006	3389	Theoretical
Zhou *et al* 2006	3384	No sensitivity/specificity
Ziemer 2010	2491	Cross-sectional study

Excluded studies

Abdul-Ghani MAS. High frequency of pre-diabetes, undiagnosed diabetes and metabolic syndrome among overweight Arabs in Israel. *Israel Medical Association Journal* 2005; 7(3):143-147.

Adam, J. M., *et al* "Isolated post-challenge hyperglycemia: concept and clinical significance." *Acta Medica Indonesiana* 2008: 40; 171-75.

Ader, M., *et al* "Oral glucose tolerance test fails to detect substantial metabolic abnormalities induced by antipsychotic agents." *Diabetologia* 2008: 51; 775.

Akao, M., *et al* "Usefulness of glucose tolerance test for diagnosing diabetes - Analysis of 12,156 cases." *Diabetologia* 2001: 44; 883.

Alberti, K. G. and K. G. M. M. Alberti. "Screening and diagnosis of prediabetes: where are we headed?." *Diabetes, Obesity & Metabolism* 2007: 9 Suppl 1: 12-16.

Aldasouqi, S. A., *et al* "Hemoglobin A1c: past, present and future." *Annals of Saudi Medicine* 28.6 (2008): 411-19.

Allen, H. F. "Glycosylated hemoglobin levels and new diagnostic criteria - Should the oral glucose tolerance test be performed as a routine screening test for diabetes in cystic fibrosis patients? Response." *Diabetes Care* 1998: 21; 2199-200.

Anand SS., Razak F *et al*, Diagnostic strategies to detect glucose intolerance in a multiethnic population. Diabetes Care 2003: 26; 290 – 296.

Armstrong, K., *et al* "Clinical variables add incremental value to fasting blood glucose in predicting a positive glucose tolerance test in established renal transplant recipients." *American Journal of Transplantation* 2005: 5; 198

Balkau, B., *et al* "Predicting diabetes: clinical, biological, and genetic approaches: data from the Epidemiological Study on the Insulin Resistance Syndrome (DESIR)." *Diabetes Care* 2008: 31; 2056-61.

Bang, H., *et al* "Development and validation of a patient self-assessment score for diabetes risk." *Annals of Internal Medicine* 2009: 151; 775-83.

Barrett-Connor, E. "The oral glucose tolerance test, revisited." *European Heart Journal* 2002: 23; 1229-31.

Bartnik, M. and L. Ryden. "Oral glucose tolerance test or metabolic syndrome criteria to predict risk in patients with coronary heart disease?: reply." *European Heart Journal* 2005: 26; 623-24.

Belfiore, F. "Insulin sensitivity indexes calculated from oral glucose tolerance test data." *Diabetes Care* 2000: 23; 1595.

Bergmann, A., *et al* "A simplified Finnish diabetes risk score to predict type 2 diabetes risk and disease evolution in a German population." *Hormone & Metabolic Research* 2007: 39; 677-82.

Bergmann, G. B., V. Guethnason, and R. Benediktsson. "Diagnosis of impaired glucose tolerance and diabetes mellitus in Iceland: fasting specimen or glucose tolerance test?" *Diabetologia* 2002: 45: 298.

Bethel, M. A., *et al* "High Frequency of Unrecognized Diabetes in Cardiovascular Patients: Should All Have an Oral Glucose Tolerance Test?" *Circulation* 2008: 118; S1080.

Bianchi, C., *et al* "FINDRISC (Finnish Diabetes Risk Score) Predicts Diabetes Risk and Cardiovascular Risk in an Italian Population." *Diabetes* 2009: 58; A257.

Birkeland, K. I., *et al* "Relationship between Vitamin D Status and Insulin Secretion and Action Assessed by the Frequently Sampled Intravenous Glucose Tolerance Test in Subjects with the Metabolic Syndrome." *Diabetes* 2009: 58; A364.

Borch-Johnsen, K. and K. Borch-Johnsen. "The new classification of diabetes mellitus and IGT: a critical approach." *Experimental & Clinical Endocrinology & Diabetes* 2001: 109 Suppl 2; S86-S93.

Borch-Johnsen, K., *et al* "Creating a pandemic of prediabetes: the proposed new diagnostic criteria for impaired fasting glycaemia." *Diabetologia* 2004: 47; 1396-402.

Boston, R. C. and P. J. Moate. "NEFA minimal model parameters estimated from the oral glucose tolerance test and the meal tolerance test." *American Journal of Physiology-Regulatory Integrative and Comparative Physiology* 2008: 295; R395-R403.

Breda, E., *et al* "Minimal model insulin sensitivity from oral glucose tolerance test: Validation against hyperinsulinemic, euglycemic clamp." *Diabetes* 2002: 51; 1431.

Buell, C., D. Kermah, and M. B. Davidson. "Utility of A1C for diabetes screening in the 1999-2004 NHANES population." *Diabetes Care* 2007: 30; 2233-34.

Bur A, Herkner H, Woisetschlager C, Vlcek M, Derhaschnig U, Hirschl MM *et al* Is fasting blood glucose a reliable parameter for screening for diabetes in hypertension? *American Journal of Hypertension* 2003; 16(4):297-301.

Cagnacci, A., *et al* "Insulin sensitivity in women: a comparison among values derived from intravenous glucose tolerance tests with different sampling frequency, oral glucose tolerance test or fasting." European Journal of Endocrinology 145.3 (2001): 281-87.

Casari, G., *et al* "First-phase insulin response (FPIR) to intravenous glucose tolerance test (IVGTT) can track the identification of MODY families not linked to known MODY genes." *Diabetes* 2001: 50; A91-A92.

Chapelot, D., C. Marmonier, and P. Valensi. "Within-subject variations of plasma glucose and insulin following a spontaneous mixed meal: Consequences for the postprandial glucose tolerance test." *Diabetologia* 2001: 44; 881.

Charfen, M.A., Ipp, E., Kaji, A.H., Saleh, T., Qazi, M.F. & Lewis, R.J. Detection of undiagnosed diabetes and prediabetic states in high-risk emergency department patients. *Academic Emergency Medicine* 2009; 16: 394-402.

Chase, H. P., *et al* "First phase insulin release (FPIR) during the initial intravenous glucose tolerance test (IV-GTT) in the diabetes prevention trial (DPT-1)." *Diabetes* 1999: 48; 1041.

Chen, X., *et al* "Abnormal glucose tolerance in Chinese women with polycystic ovary syndrome." *Human Reproduction* 2006: 21; 2027-32.

Cheng, C., *et al* "Correlation of oral glucose tolerance test-derived estimates of insulin sensitivity with insulin clamp measurements in an African-American cohort." *Metabolism-Clinical and Experimental* 2004: 53; 1107-12.

Chevenne, D., *et al* "Proinsulin and specific insulin responses to an oral glucose tolerance test in a healthy population." *Diabetes & Metabolism* 1998: 24; 260-61.

Chiu, K. C., *et al* "Relative contribution of insulin sensitivity and beta-cell function to plasma glucose and insulin concentrations during the oral glucose tolerance test." *Metabolism-Clinical and Experimental* 2002: 51; 115-20.

Christoforidis, A., *et al* "Evolution of oral glucose tolerance test (OGTT) in patients with beta-thalassaemia major in relation to chelation therapy." *Hormone Research* 2006: 65; 57.

Ciampelli, M., *et al* "Assessment of insulin sensitivity from measurements in the fasting state and during an oral glucose tolerance test in polycystic ovary syndrome and menopausal patients." *Journal of Clinical Endocrinology & Metabolism* 2005: 90; 1398-406.

Cohen, O., *et al* "The need for OGTT in screening for diabetes in high-risk populations." *Diabetes* 1999: 48; 1735.

Cretti, A., *et al* "A novel tool to assess beta-cell function during the oral glucose tolerance test (OGTT)." *Diabetes* 2000: 49; 357.

Cretti, A., *et al* "A novel tool to assess beta-cell function during the oral glucose tolerance test (OGTT)." *Diabetologia* 2000: 43; 542.

Cretti, A., *et al* "Assessment of beta-cell function during the oral glucose tolerance test by a minimal model of insulin secretion." *European Journal of Clinical Investigation* 2001: 31; 405-16.

Daniel, M. Rowley. "Fasting criteria for screening: Test properties and agreement with glucose tolerance." *Biomedicine and Pharmacotherapy* 2002: 58; 139-48.

Davidson, M. B. "Counterpoint: The oral glucose tolerance test is superfluous." *Diabetes Care* 2002: 25; 1883-85.

Davidson, M. B., *et al* "Revisiting the oral glucose tolerance test (OGTT) criterion for the diagnosis of diabetes." *Diabetes* 1999: 48; 0377.

Davidson, M. B., *et al* "Revisiting the oral glucose tolerance test criterion for the diagnosis of diabetes." *Journal of General Internal Medicine* 2000:15; 551-55.

De La Hera, J., *et al* "Impact of unknown diabetes diagnosis with oral glucose tolerance test in coronary patients: Identification of possible improvements in secondary prevention measures." *Circulation* 2008: 118; E232.

del Rio, M. J., *et al* "Glycaemic Responses and Insulin Sensitivity As Assessed by Oral Glucose Tolerance Test and Insulin Suppression Test in Patients with Reproductive Pathologies." *Journal of Andrology* 2009: 30; 83.

Delgado, E., *et al* "Utility of the oral glucose tolerance test versus fasting plasma glucose in the diagnosis of the unknown diabetes in population with coronary artery disease." *Diabetes* 2007: 56; A594.

Disoteo, O., *et al* "Influence of waist circumference on glucose metabolism evaluated with oral glucose tolerance test in a group of obese patients." *International Journal of Obesity* 2007: 31; S120.

Drivsholm, T., *et al* "Assessment of insulin-sensitivity and beta-cell function from an oral glucose tolerance test." *Diabetologia* 1999: 42; 692.

Dunstan, D. W. S. "Physical activity and television viewing in relation to risk of undiagnosed abnormal glucose metabolism in adults." *Diabetes Care* 2004: 27; 2603-09.

Ediger, M.N., Olson, B.P. & Maynard, J. D. Noninvasive optical screening for diabetes. *Journal of Diabetes Science and Technology* 2009; 3(4): 776-780.

Ekstrom, C. T., *et al* "Familiality of quantitative traits derived during an oral glucose tolerance test in normoglycaemic relatives of one type 2 diabetic parent." *Diabetologia* 1999 42; 412.

El Bassuoni, E. A., *et al* "The "metabolic syndrome" is less useful than random plasma glucose to screen for glucose intolerance." *Primary care diabetes* 2008: 2 147-53.

Elkind-Hirsch, K. and B. Webster. "A new insulin sensitivity index obtained from the oral glucose tolerance test (OGTT) is applicable for evaluating women with polycystic ovary syndrome (PCOS)." *Fertility and Sterility* 2003: 79; O5.

Escalada, J., *et al* "Usefulness of an oral glucose tolerance test in morbidly obese patients." *Diabetes* 2008: 57; A295.

Fabregate, M., *et al* "Bioelectrical impedance analysis (BIA) and oral glucose tolerance test." *Diabetes* 2006: 55; A526.

Featherstone, J. J. and E. Goyder. "Is waist circumference a useful screening tool for diabetes mellitus in an overweight multi-ethnic population?" *Quality in Primary Care* 2000: 15; 137-44.

Fica, S. V., *et al* "Should an oral glucose tolerance test be performed in all patients with polycystic ovary syndrome?" *Diabetologia* 51 (2008): 351.

Fonseca, V. A. "Early identification and treatment of insulin resistance: Impact on subsequent prediabetes and type 2 diabetes." *Clinical Cornerstone* 2007: 8.SUPPL. 7; S7-S18.

Fonseca, V. A. and Vivian A. Fonseca. "Identification and treatment of prediabetes to prevent progression to type 2 diabetes." *Clinical Cornerstone* 2008: 9; 51-59.

Forouhi, N. G. B. "The threshold for diagnosing impaired fasting glucose: A position statement by the European Diabetes Epidemiology Group." *Diabetologia* 2006: 49; 822-27.

Garcia-Alcala, H., A. Rodriguez-Gallegos, and I. Parra-Ortega. "Combination of fasting and two hours diagnosis criteria in the oral glucose tolerance test increase the frequency of diagnosis of diabetes and glucose intolerance states." *Diabetes* 2006: 55; A532.

Giessauf, H., *et al* "Characteristics of glucose metabolism measured by an intra-dialytic glucose tolerance test." *Wiener Klinische Wochenschrift* 2008: 120;15-16 A55-A56.

Ginde, A. A., *et al* "Point-of-care glucose and hemoglobin A1c in emergency department patients without known diabetes: implications for opportunistic screening." *Academic Emergency Medicine* 2008: 15; 1241-47.

Ginde, A. A., *et al* "Value of risk stratification to increase the predictive validity of HbA1c in screening for undiagnosed diabetes in the US population." *Journal of General Internal Medicine* 2008: 23; 1346-53.

Glümer, C., T. Jørgensen, and Johnsen K. Borch. "Targeted screening for undiagnosed diabetes reduces the number of diagnostic tests. Inter99(8)." *Diabetic medicine : a journal of the British Diabetic Association* 2004: 21; 874-80.

Gong, Q. H., *et al* "HbA1c in screening for and predicting diabetes." *Diabetes* 2008: 57; A273.

Greenberg, R. A., *et al* "Screening for diabetes: is it warranted?". *Clinica Chimica Acta* 2002: 315; 61-69.

Hammana, I., *et al* "Validation of insulin secretion indices in cystic fibrosis patients." *Journal of cystic fibrosis: official journal of the European Cystic Fibrosis Society* 2009: 8; 378-81.

Hansen, T., *et al* "Familialty of quantitative traits derived during an oral glucose tolerance test in normoglycaemic relatives of one type 2 diabetic parent." *American Journal of Human Genetics* 1999: 65; 1123.

Heish, M. Y., *et al* "Revisit of oral glucose tolerance test: A must for diagnosis of type 2 diabetes in patients with chronic hepatitis C." *American Journal of Gastroenterology* 2008: 103; 487-88.

Henareh, L., M. Berglund, and S. Agewall. "Should oral glucose tolerance test be a routine examination after a myocardial infarction?" *International Journal of Cardiology* 2004: 97; 21-24.

Henderson, D. C., *et al* "Glucose metabolism in schizophrenia patients treated with atypical antipsychotics: A frequent sampled intravenous glucose tolerance test and minimal model analysis." *Biological Psychiatry* 2004: 55; 229.

Hippisley-Cox J, Coupland C, Robson J, Sheikh A, Brindle P. Predicting risk of type 2 diabetes in England and Wales: prospective derivation and validation of QDScore. *British Medical Journal* 2009; 338.b880 doi: 10.1136/bmj.b880

Hische M *et al*, Decision trees as a simple-to-use and reliable tool to identify individuals with impaired glucose metabolism or type 2 dibetes mellitus. *European Journal of Endocrinology* 2010 163; 565 - 571

Hoffman-Snyder, C., *et al* "Value of the oral glucose tolerance test in the evaluation of chronic idiopathic axonal polyneuropathy." *Archives of Neurology* 2006: 63; 1075-79.

Hovorka, R., *et al* "Reproducibility and comparability of insulin sensitivity indices measured by stable-label intravenous glucose tolerance test." *Diabetic Medicine* 1998: 15; 234-46.

Howell, W. M., *et al* "Comparison of estimates of insulin sensitivity and B-cell function derived from the oral glucose tolerance test versus the intravenous glucose tolerance test and minimal model." *Diabetes* 1998: 47; 697.

Iglesias N, Petersen PH, Jorgensen LG, Brandslund I, Iglesias N, Petersen PH *et al* Comments on 'HbA1c predicts the likelihood of having impaired glucose tolerance in high-risk patients with normal fasting plasma glucose'. *Ann Clin Biochem* 2006; 43(Pt 1):87-88.

Iida, S., *et al* "Oral glucose tolerance test (OGTT) and post-transplant diabetes mellitus (PTDM) in tacrolimus-treated renal transplant recipients." *American Journal of Transplantation* 2005: 5; 160.

Imano, E., *et al* "Significance of oral glucose tolerance test for the diagnosis of diabetes mellitus in patients with liver cirrhosis." *Internal Medicine* 1999: 38; 918.

Kanauchi, M. "A new index of insulin sensitivity obtained from the oral glucose tolerance test applicable to advanced type 2 diabetes." *Diabetes Care* 2002: 25; 1891-92.

Kanauchi, M., N. Tsujimoto, and T. Hashimoto. "Validation of simple indices to assess insulin sensitivity based on the oral glucose tolerance test in the Japanese population." *Biomedicine and Pharmacotherapy* 2002: 55; 229-35.

Karakaya, J., *et al* "Predictive ability of fasting plasma glucose for a diabetic 2-h postload glucose value in oral glucose tolerance test: spectrum effect." *Journal of Diabetes and its Complications* 2007: 21; 300-05.

Kenealy T, Elley CR, Arroll B, Kenealy T, Elley CR, Arroll B. Screening for diabetes and prediabetes. *Lancet* 2007; 370; 1888-1889.

Kim, H. Y., *et al* "Usefulness of insulin sensitivity indexes from oral glucose tolerance test in women with polycystic ovary syndrome." *Diabetes* 2005: 54; A620.

Kim, S. Y., *et al* "Value of HbA1c for diabetes screening in subjects with normal fasting glucose." *Diabetes* 2008: 57; A555-A556.

Kiser, K. M., R. L. Prigeon, and S. E. Kahn. "Insulin sensitivity quantified with the minimal model is lower with the insulin-modified than the tolbutamide-modified frequently sampled intravenous glucose tolerance test." *Journal of Investigative Medicine* 2003: 51; 15.

Koh, A., *et al* "Mixed Meal Tolerance Test (MMTT) vs. Oral Glucose Tolerance Test (OGTT) after Successful Clinical Islet Transplantation (CIT)." *Diabetes* 2009: 58; A501-A502.

Kokkoris, P., *et al* "Body mass, index is not a reliable index to predict the response to oral glucose tolerance test." *Obesity research* 2005: 13; A115.

Kokkoris, P., *et al* "Estimation of insulin resistance in oral glucose tolerance test." *Diabetes* 2005: 54; A592.

Koopman, R. J., *et al* "Tool to Assess likelihood of fasting Glucose ImpairmenT (TAG-IT)." *Annals of Family Medicine* 2000: 6; 555-61.

Kumar PR, Bhansali A, Ravikiran M, Bhansali S, Dutta P, Thakur JS *et al* Utility of Glycated Hemoglobin in Diagnosing Type 2 Diabetes Mellitus: A Community-Based Study. *J Clin Endocrinol Metab* 2010; 95(6):2832-2835.

Lakisch, M., *et al* "Screening for Diabetes with an Oral Glucose Tolerance Test in Daily Cardiological Practice: Two Simple Parameters Alleviate the Implementation of Current Guidelines." *Diabetes* 2009: 58; A274.

Lecube, A., *et al* "Revisit of oral glucose tolerance test: A must for diagnosis of type 2 diabetes in patients with chronic hepatitis C - Reply." *American Journal of Gastroenterology* 2008; 103; 488.

Ledson, M. J., *et al* "Comparison of the oral glucose tolerance test and serial glucose monitoring in CF patients." *Pediatric Pulmonology* 2007: 532.

Li J, Bergmann A, Reimann M, Bornstein SR, Schwarz PE, Li J *et al* A more simplified Finnish diabetes risk score for opportunistic screening of undiagnosed type 2 diabetes in a German population with a family history of the metabolic syndrome. *Hormone & Metabolic Research* 2009; 41 98-103.

Li, H. Y., *et al* "Validation of diabetes risk scores for predicting diabetes diagnosed by oral glucose tolerance test." *Diabetes Care* 2010: 33; e26.

Lindstrom J, Tuomilehto J. The diabetes risk score: A practical tool to predict type 2 diabetes risk. *Diabetes Care* 2003: 26; 725 - 731

Little, R. R., *et al* "Glycated haemoglobin predicts progression to diabetes mellitus in Pima Indians with impaired glucose tolerance." *Diabetologia* 1994: 37; 252-56.

Lorenzo, C., *et al* "A simple multivariate model is as good as the oral glucose tolerance test and better than the metabolic syndrome for predicting type 2 diabetes: The Mexico city diabetes study." *Diabetes* 2004: 53; A249.

Lopatynski J *et al,* A comparative evaluation of waist circumference, waist-to-hip ratio, waist to height ratio and body mass index as indicators of impaired glucose tolerance and dibetes mellitus type 2 risk factors. *Annales Universitatis Marie-Curie-Sklodowska Lublin-Polonia* Sectio D. Vol. LVIII, N 1, 77

Lyon, A. W., *et al* "The impact of new guidelines for glucose tolerance testing on clinical practice and laboratory services." *CMAJ Canadian Medical Association Journal* 2004:171; 1067-69.

Mari, A., *et al* "Comparative evaluation of simple insulin sensitivity methods based on the oral glucose tolerance test." *Diabetologia* 2005: 48; 748-51.

Mari, A., G. Pacini, and J. J. Nolan. "A new method for assessing insulin sensitivity from the oral glucose tolerance test (OGTT)." *Diabetes* 1999: 48; 1251.

Martin, C. A., *et al* "Isolated Clinic Hypertension Is Associated with Elevated Two-Hour Glucose Post Oral Glucose Tolerance Test." *Hypertension* 2009: 53; 065.

Mathur, D., *et al* "Using capillary blood glucose for eligibility screening in community-based diabetes prevention study." *Diabetes* 2008: 57; A677.

Matsuda, M. and R. A. Defronzo. "Insulin sensitivity indexes calculated from oral glucose tolerance test data - Response." *Diabetes Care* 2000: 23; 1595-96.

Matsuda, M. and R. A. Defronzo. "Insulin sensitivity indices obtained from oral glucose tolerance test: Comparison with the euglycemic insulin clamp." *Diabetes* 1999: 48; 0338.

Mazurek, J. A., *et al* "Feasibility of HbA1c for diabetes screening on an inpatient hospital service in a high risk urban community." *Journal of General Internal Medicine* 23 (2008): 304.

McNeely, M. J., *et al* "Comparison of a clinical model, the oral glucose tolerance test, and fasting glucose for prediction of type 2 diabetes risk in Japanese Americans." *Diabetes Care* 26.3 (2003): 758-63.

Meigs, J. B. W. "Using metabolic syndrome traits for efficient detection of impaired glucose tolerance." *Diabetes Care* 27.6 (2004): 1417-26.

Mohan, K., *et al* "Comparison of the oral glucose tolerance test and serial glucose monitoring in cystic fibrosis patients." *Thorax* 62 (2007): A102-A103.

Motala, A. A., *et al* "Insulin response during the Oral Glucose Tolerance Test (OGTT) in south African Indians: results from a population study." Diabetologia 45 (2002): 292.

Nagy, S., *et al* "Correlation of body mass index (BMI) with 2-hour glucose tolerance test (GTT) results among obese women with polycystic ovarian syndrome (PCOS)." Fertility *and Sterility* 88 (2007): S188-S189.

Naj, A. C., *et al* "Genetic variation in IGF1R is associated with differences in insulin levels at 30 minutes in an oral glucose tolerance test in the old order Amish." *Diabetes* 55 (2006): A223.

Narayan K M.V. "How generally applicable is a simple diabetes detection questionnaire?" *Nature Clinical Practice Endocrinology and Metabolism* 2.4 (2006): 196.

Natarajan, G., *et al* "Screening for diabetes with 75g oral glucose tolerance test in peripheral vascular disease." *Diabetes* 55 (2006): A245.

Nigrini, E., *et al* "Diagnostic Thresholds of Fasting Plasma Glucose Among Women with Abnormal Glucose Screening." *American Journal of Obstetrics and Gynecology* 199.6 (2008): 825.

Norberg, M., *et al* "A combination of HbA1c, fasting glucose and BMI is effective in screening for individuals at risk of future type 2 diabetes: OGTT is not needed." *Journal of Internal Medicine* 260.3 (2006): 263-71.

Norberg, M., J. W. Eriksson, and B. Lindahl. A combination of HbA1c, fasting glucose and BMI is effective in screening for individuals at risk future type 2 diabetes: OGTT is not needed. *Journal of Internal Medicine* 2006: 260; 491.

Oberlinner, C. Neumann. Screening for pre-diabetes and diabetes in the workplace. *Occupational Medicine* 58.1 (2008): 41-45.

Olijhoek, J. K., *et al* Oral glucose tolerance test or metabolic syndrome criteria to predict risk in patients with coronary heart disease? *European Heart Journal* 26.6 (2005): 623.

Orisaka, M., *et al* Risk factors for development of pre-diabetic state from normal glucose regulation." *Tohoku Journal of Experimental Medicine* 210.4 (2006): 279-83.

Pan, C. Y. and Chang Yu Pan. Reducing the risk of type 2 diabetes: early identification of high-risk individuals and treatment with acarbose. *Current Diabetes Reviews* 3.2 (2007): 141-48.

Park, P. J., *et al* The effect of varying the screening interval on false positives and duration of undiagnosed disease in a screening programme for type 2 diabetes. *Journal of Medical Screening* 2000: 91-96.

Park, P. J., *et al* The performance of a risk score in predicting undiagnosed hyperglycemia. *Diabetes Care* 2002: 7; 984-88.

Periwal, V., *et al* Criteria for defining the need for an oral glucose tolerance test in African Americans. *Diabetes* 54 2005: A574-A575.

Piche, M. E., *et al* Measuring insulin sensitivity in postmenopausal women covering a range of glucose tolerance: comparison of indices derived from the oral glucose tolerance test with the euglycemic-hyperinsulinemic clamp. *Metabolism-Clinical and Experimental* 2007: 56;1159-66.

Pontiroli, A. E., *et al* A new approach to assess both insulin sensitivity and insulin release from oral glucose tolerance test indicates reduction of early insulin release in impaired glucose tolerance. *Diabetes* 2001: 50 A100.

Pontiroli, A. E., *et al* Evaluation of insulin sensitivity and insulin release from oral glucose tolerance test: Basal studies and follow-up of impaired glucose tolerance. *Diabetologia* 44 (2001): 214.

Pratley, R. E. M. Pre-diabetes: Clinical relevance and therapeutic approach. *British Journal of Diabetes and Vascular Disease* 7.3 (2007): 120-29.

Prigeon, R. L., W. M. Howell, and S. E. Kahn. A new method for predicting insulin sensitivity from oral glucose tolerance test results. *Diabetes* 47 (1998): 1638.

Procopio, M., *et al* "The oral glucose tolerance test reveals a high frequency of both impaired glucose tolerance and undiagnosed Type 2 diabetes mellitus in primary hyperparathyroidism." *Diabetic Medicine* 19.11 (2002): 958-61.

Radaelli,T. and P. Catalano. Estimates of insulin sensitivity using C-peptide from an oral glucose tolerance test (OGTT). *American Journal of Obstetrics and Gynecology* 191.6 (2004): 154.

Rahman,M. and Griffin, S.J. A simple risk score identifies individuals at high risk of developing type 2 diabetes: A prospective cohort study. *Family Practice* 2008: 25 3

Rasmussen, S. S., *et al* Progression from impaired fasting glucose and impaired glucose tolerance to diabetes in a high-risk screening programme in general practice: the ADDITION Study, Denmark. *Diabetologia* 50.2 (2007): 293-97.

Reslin, M., *et al* "Abnormal Post-Gastric Bypass (RYGB) Glucose Tolerance Test and Weight Recidivism." *Obesity* 16 (2008): S296.

Retnakaran, R., *et al* "Hyperbolic relationship between insulin secretion and sensitivity on oral glucose tolerance test." *Obesity* 16.8 (2008): 1901-07.

Rice, S., *et al* "The role of the oral glucose tolerance test (OGTT) in indentifying glycaemic disorders in acute medical admissions." *Diabetes* 52 (2003): A436.

Rohlfing, C. L., *et al* Use of GHb (HbA1c) in screening for undiagnosed diabetes in the U.S. population.[Erratum appears in Diabetes Care 2000 Jun;23(6):876 *Diabetes Care* 23.2 (2000): 187-91.

Rolandsson, O., *et al* Prediction of diabetes with body mass index, oral glucose tolerance test and islet cell auto-antibodies in a regional population. *Journal of Internal Medicine* 249.4 (2001): 279-88.

Roubicek M, Vines G, Gonzalez SA, Use of HbA1c in screening for diabetes. *Diabetes Care* 1998; 21(9):1577-1578.

Rovetti, R. J., *et al* Minimal model (MM) for oral glucose tolerance test: Validation of insulin sensitivity index (SI) estimation and application to multiethnic population. *Diabetes* 55 (2006): A566.

Rowley KG, Daniel M, O'Dea K, Rowley KG, Daniel M, O'Dea K. Screening for diabetes in Indigenous populations using glycated haemoglobin: sensitivity, specificity, post-test likelihood and risk of disease. *Diabet Med* 2005; 22(7):833-839.

Salmasi AM, Dancy M, Salmasi AM, Dancy M. The glucose tolerance test, but not HbA(1c), remains the gold standard in identifying unrecognized diabetes mellitus and impaired glucose tolerance in hypertensive subjects. *Angiology* 2005; 56(5):571-579.

Salmasi, A. M. and M. Dancy. The glucose tolerance test, but not HbA1c, remains the gold standard in identifying impaired glucose tolerance and diabetes mellitus in subjects with systemic hypertension. *European Heart Journal* 26 (2005): 496-97.

Sandbaek, A., *et al* Stepwise screening for diabetes identifies people with high but modifiable coronary heart disease risk. The ADDITION study. *Diabetologia* 51.7 (2008): 1127-34.

Saudek C.D.*et al* A new look at screening and diagnosing diabetes mellitus. *J Clin Endocrin Metab.* 2008: 2007 - 2174

Saxena, R., *et al* Meta-Analyses of Genome-Wide Association Studies for 2-Hour Glucose Levels during an Oral Glucose Tolerance Test Identify Novel Genetic Loci. *Diabetes* 58 (2009): A48.

Sayeed, M. A., *et al* Fasting cut-offs in determining the prevalence of diabetes and intermediate glucose abnormality in a non-obese population. *Bangladesh Medical Research Council Bulletin* 30.3 (2004): 105-14.

Schmidt, M. A., *et al* Detection of undiagnosed diabetes and other hyperglycemia states. *Diabetes Care* 26 (2003): 1338-43.

Schulze MB, Hoffmann K, Boeing H, Linseisen J, Rohrmann S, Mohlig M *et al* An accurate risk score based on anthropometric, dietary, and lifestyle factors to predict the development of type 2 diabetes. *Diabetes Care* 2007; 30(3):510-515.

Schwarz, P. E., *et al* "The European perspective of type 2 diabetes prevention: diabetes in Europe--prevention using lifestyle, physical activity and nutritional intervention (DE-PLAN) project." Experimental & Clinical Endocrinology & Diabetes 116.3 (2008): 167-72.

Schwarz, P. E., *et al* Tools for predicting the risk of type 2 diabetes in daily practice. *Hormone & Metabolic Research* 41.2 (2009): 86-97.

Sesti, G., Andreozzi, F., Bonadonna, R.C., De Mattia, G., Leonetti, F., Luzi, L., Marini, M.A., Natali, A., Vettor, R. & Bonora, E. Impact of lowering the criterion for impaired fasting glucose in identification of individuals with insulin resistance. The GISIR database. *Diabetes/Metabolism Research and Reviews* 2008; 24: 130-136.

Shimazaki, T., *et al* Hemoglobin A1c (HbA1c) predicts future drug treatment for diabetes mellitus: a follow-up study using routine clinical data in a Japanese university hospital. Translational Research: *The Journal of Laboratory & Clinical Medicine* 149.4 (2007): 196-204.

Sievenpiper, J. L., *et al* Reproducibility of the 75g oral glucose tolerance test (75g-OGTT) is not influenced by body composition*. Diabetes* 49 (2000): 1466.

Simeoni, M., *et al* The intravenous prandial glucose tolerance test (IVPGTT) to measure glucose effectiveness and insulin sensitivity with the minimal models. *Diabetes* 48 (1999): 1259.

Simeoni, M., *et al* The intravenous prandial glucose tolerance test (IVPGTT) minimal model for measuring glucose effectiveness and insulin sensitivity. *Diabetologia* 42 (1999): 695.

Soonthornpun, S., *et al* Novel insulin sensitivity index derived from oral glucose tolerance test. *Journal of Clinical Endocrinology & Metabolism* 88.3 (2003): 1019-23.

Sorkin, J. D., D. C. Muller, and R. Andres. The case for the glucose tolerance test. *Diabetes* 48 (1999): 0710.

Sorodoc, L., *et al* Prolonged Oral Glucose Tolerance Test in Non-Diabetic Patients with Ethanol Poisoning*. Acta Endocrinologica-Bucharest* 5.1 (2009): 61-73.

Stern, M. P., *et al* Predicting future cardiovascular disease - Do we need the oral glucose tolerance test? *Diabetes Care* 25.10 (2002): 1851-56.

Stern, M. P., K. Williams, and S. A. Haffner. Identification of persons at high risk for type 2 diabetes mellitus: Do we need the oral glucose tolerance test? *Annals of Internal Medicine* 136.8 (2002): 575-81.

Stern, M. P., K. Williams, and S. M. Haffner. Do we need the oral glucose tolerance test to identify future cases of type 2 diabetes? *Diabetes Care* 26.3 (2003): 940-41.

Stevic, R., *et al* Oral glucose tolerance test in the assessment of glucose-tolerance in the elderly people*. Age and ageing* 36.4 (2007): 459-62.

Stumvoll, M., *et al* Oral glucose tolerance test indexes for insulin sensitivity and secretion based on various availabilities of sampling times. *Diabetes Care* 24.4 (2001): 796-97.

Stumvoll, M., *et al* Use of the oral glucose tolerance test to assess insulin secretion and insulin sensitivity. *Diabetes* 48 (1999): 1312.

Stumvoll, M., *et al* Use of the oral glucose tolerance test to assess insulin release and insulin sensitivity. *Diabetes Care* 23.3 (2000): 295-301.

Takada, H., *et al* Relation between plasma glucose and insulin secretion in myotonic dystrophy: Evaluation by glucose tolerance test. *Neuromuscular Disorders* 17.9-10 (2007): 854.

Taniguchi, T., *et al* Use of the insulin sensitivity index obtained from oral glucose tolerance test in Japanese subjects. *Biomedicine and Pharmacotherapy* 54.2 (2001): 143-44.

Temelkova-Kurktschiev, T., *et al* Pro12Ala polymorphism of the peroxisome proliferator-activated receptor-gamma 2: Association to type 2 diabetes and response to a glucose tolerance test in a risk population for diabetes. *Diabetes* 51 (2002): 1092.

Teo, K. K., *et al* Importance of an oral glucose tolerance test in identifying high prevalence of dysglycemia in individuals at high cardiovascular risk. *Journal of the American College of Cardiology* 43.5 (2004): 211A.

Thomas C, Hypponen E, Power C,Tsay J, Pomeranz C, Hassoun A, Zandieh SO, Rutledge J, Vogiatzi MG *et al* Screening markers of impaired glucose tolerance in the obese pediatric population. *Hormone research in pdiatrics* 2010; 73(2):102-107.

Thomaseth, K., *et al* Indices of insulin sensitivity of glucose production and disposal from double-tracer oral glucose tolerance test. *Diabetologia* 49 (2006): 0640.

Toffolo, G., *et al* Glucose disposal minimal model insulin sensitivity index from labelled meal glucose tolerance test. *Diabetes* 50 (2001): A65.

Toffolo, G., W. T. Cefalu, and C. Cobelli. beta-cell function during insulin-modified intravenous glucose tolerance test successfully assessed by the C-peptide minimal model. *Metabolism-Clinical and Experimental* 48.9 (1999): 1162-66.

Tringham, J. R. D. Screening for IGT and diabetes. *British Journal of Diabetes and Vascular Disease* 4.4 (2004): 254-58.

Tschritter, O., *et al* Assessing the shape of the glucose curve during an oral glucose tolerance test *Diabetes Care* 27.7 (2004): 1855.

Tsigos, C., *et al* Screening for diabetes in the obese: The two hour post OGTT glucose levels are superior to fasting glucose levels. *Diabetes* 50 (2001): A215.

Tuomilehto, J. Point: A glucose tolerance test is important for clinical practice. *Diabetes Care* 25.10 (2002): 1880-82.

Tura, A., S. Sbrignadello, and G. Pacini. Prediction of the Minimal Model insulin sensitivity index through one hour intravenous glucose tolerance test data. *Diabetologia* 51 (2008): 698.

Turchin A, Kohane IS, Pendergrass ML, Identification of patients with diabetes from the text of physician notes in the electronic medical record. *Diabetes Care* 2005; 28(7):1794-1795.

Twigg, S. M., *et al* Prediabetes: a position statement from the Australian Diabetes Society and Australian Diabetes Educators Association. *Medical Journal of Australia* 186.9 (2007): 461-65.

Vaccaro, O., G. Ruffa, and G. Riccardi. Is there any use for the oral glucose tolerance test? *Diabetes Care* 23.5 (2000): 714-15.

van Haeften, T. W. and M. Stumvoll. To: Albareda M *et al* (2000) Assessment of insulin sensitivity and beta-cell function from measurements in the fasting state and during an oral glucose tolerance test. *Diabetologia* 43: 1507-1511.

Vannai, J., M. Havasi, and L. Blatniczky. First phase C-peptide release during the intravenous glucose tolerance test as a marker of subclinical beta-cell dysfunction among first-degree relatives of IDDM Patients. *Diabetologia* 45 (2002): 358.

Velasquez-Mieyer, P. A., *et al* Racial differences in glucagon-like peptide-1 (GLP-1) and insulin secretion during oral glucose tolerance test in obese non-diabetic subjects. *Diabetes* 51 (2002): 1482.

Vermunt PWA., Milder IEJ., Wielaard F., van Oers JAM., Westert GP. An active strategy to identify individuals eligible for type 2 diabetes prevention by lifestyle intervention in Dutch primary care: The APHRODITE study. *Family Practice* 2010 1-8

Viswanath, A. K., *et al* Diagnosing diabetes mellitus: contemporary use of the oral glucose tolerance test in a regional diabetes centre. *Practical Diabetes International* 23.7 (2000): 287-90.

Wang, W., Lee, E.T., Fabsitz, R., Welty, T.K. & Howard, B.V. Using HbA_{1c} to improve efficacy of the American Diabetes Association fasting plasma glucose criterion in screening for new type 2 diabetes in American Indians. *Diabetes Care* 2002; 25(8):1365-1370.

Wang JJ, Stancakova A, Kuusisto J, Laakso M. Identification of Undiagnosed Type 2 Diabetic Individuals by the Finnish Diabetes Risk Score and Biochemical and Genetic Markers: A Population-Based Study of 7232 Finnish Men. *J Clin Endocrinol Metab* 2010; 95(8):3858-3862.

Warner, C., *et al* Validation of a Novel Combined Oral Triglyceride Tolerance Test/Glucose Tolerance Test. *Circulation* 118.18 (2008): S567-S568.

Waterworth, D. M., *et al* Interaction between insulin (VNTR) and hepatic lipase (LIPC-514C > T) variants on the response to an oral glucose tolerance test in the EARSII group of young healthy men. *Biochimica et Biophysica Acta-Molecular Basis of Disease* 1740.3 (2005): 375-81.

Weisnagel, S. J., *et al* Surrogate estimates of insulin sensitivity in postmenopausal women: Comparison of fasting and oral glucose tolerance test derived indices with the euglycemic-hyperinsulinemic clamp. *Diabetes* 53 (2004): A354.

Wilke RA, Berg RL, Peissig P, Kitchner T, Sijercic B, McCarty CA *et al* Use of an electronic medical record for the identification of research subjects with diabetes mellitus. *Clinical Medicine & Research* 2007; 5(1):1-7.

Woerle, H. J., *et al* Diagnostic and therapeutic implications of relationships between fasting, 2-hour postchallenge plasma glucose and hemoglobin A1c values. *Archives of Internal Medicine* 164.15 (2000): 1627-32.

Yung, B., *et al* Diagnosis of cystic fibrosis related diabetes: a selective approach in performing the oral glucose tolerance test based on a combination of clinical and biochemical criteria. *Thorax* 54.1 (1999): 40-43.

Zhang, Y. Q., *et al* The role of oral glucose tolerance test in screening for diabetes mellitus in the elderly of Harbin, China. *Chinese Medical Journal* 118.5 (2005): 418-20.

Zhou, W. B., *et al* Assessing 1-h plasma glucose and shape of the glucose curve during oral glucose tolerance test. *European Journal of Endocrinology* 155.1 (2006): 191-97.

Zhou, W. B., *et al* The ROC analysis for different time points during oral glucose tolerance test. *Biomedicine and Pharmacotherapy* 72.1 (2006): 88-92.

Ziemer, D. C. K. Glucose-independent, black-white differences in hemoglobin A1c levels: A cross-sectional analysis of 2 studies. *Annals of Internal Medicine* 152.12 (2010): 770-77.

Appendix 3: Search Strategies and Details of Evidence Sources

List of databases searched

Medline and Medline in Process via OVID

Embase via OVID

CINAHL via EBSCO

British Nursing Index via OVID

Cochrane Library via Wiley

Science Citation Index via Web of Knowledge

Social Science Citation Index via Web of Knowledge

PsycINFO via OVID

EPPI Centre Databases – Bibliomap, Database of Promoting Health Effectiveness Reviews (DoPHER), Trials Register of Promoting Health Interventions (TRoPHI), The database on Obesity and Sedentary behaviour studies

http://eppi.ioe.ac.uk/cms/

Websites

Association of Public Health Observatories

www.apho.org.uk/

NHS Evidence: National Library for Public Health

www.library.nhs.uk/publichealth/

The Joseph Rowntree Foundation

www.jrf.org.uk/

Diabetes UK

http://www.diabetes.org.uk/

Other Sources

Scopus (via Elsevier)

Web of Science (via Thomson ISI)

NHS Economic Evaluation Database (NHS EED via Wiley)

EconLit (via Ovid SP)

Health Economic Evaluations Database (HEED via Wiley)

Google Scholar

http://scholar.google.co.uk/

Initial Search

Sample search strategy Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R)

1. *prediabetic state/

2. (prediabetes or pre diabetes or raised glucose intolerance or impaired glucose level$ or impaired glucose tolerance or IGT or impaired fasting glucose or IFT or FPG or fasting plasma glucose or impaired glucose regulation or impaired glucose metabolism or raised glycated haemoglobin or raised glycated hemoglobin or high glycated Hb or hyperglycaemia or hyperglycemia).ti.

3. (prevention adj3 (type II diabetes or type 2 diabetes or T2D)).ti.

4. 1 or 2 or 3

5. *body mass index/

6. *obesity/

7. (south asia$ or black africa$ or black caribbean$ or pakistan$ or bangladesh$ or india$ or ethnic minorit$ or chinese or obes$ or waist circumference or "bmi > 3?" or BMI).ti.

8. 5 or 6 or 7

9. *Hemoglobin A, Glycosylated/ or *Mass screening/ or *Risk assessment/

10. (((risk assessment or monitoring or screening) adj2 diabetes) or HBA1C).ti.

11. 9 or 10

12. *Exercise/ or *Exercise therapy/ or *Diet therapy/

13. (lifestyle intervention$ or slimming club$ or diet or low glycaemic index or low glycemic index or reduced fat or low carbohydrate or low calorie or physical activit$ or exercise or cardiorespiratory training).ti.

14. (Motivational support adj5 diet).ti,ab.

15. 12 or 13 or 14

16. 8 or 11 or 15

17. 4 and 16

Search Strategy Review One

Sample search Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R)

1. ((risk assessment or screening or identification or uptake) adj5 (diabetes or prediabetes or pre diabetes or raised glucose intolerance or impaired glucose level$ or impaired glucose tolerance or IGT or impaired fasting glucose or IFT or FPG or fasting plasma glucose or impaired glucose regulation or impaired glucose metabolism)).ti,ab.

2. *Prediabetic State/di [Diagnosis]

3. 1 or 2

4. (GP adj2 database).ti,ab.

5. (medical record$ or clinical database$).ti.

6. exp *Medical Records Systems, Computerized/

7. 4 or 5 or 6

8. 3 and 7

9. (findrisc or danish risk questionnaire or cambridge risk score or symptom risk questionnaire or indian score).mp.

10. *Glucose Tolerance Test/st [Standards]

11. (gestational or pregnan$ or postpartum).ti,ab.

12. 10 not 11

13. ((risk assessment or screening or identification or uptake) adj2 (diabetes or prediabetes or pre diabetes or raised glucose intolerance or impaired glucose level$ or impaired glucose tolerance or IGT or impaired fasting glucose or IFT or FPG or fasting plasma glucose or impaired glucose regulation or impaired glucose metabolism)).ti,ab.

14. 2 or 12

15. *Hemoglobin A, Glycosylated/du [Diagnostic Use]

16. HBA1C.ti,ab.

17. 15 or 16

18. 14 and 17

19. (oral glucose tolerance test or ogtt).ti,ab.

20. 14 and 19

21. (fasting plasma glucose or FPG).ti,ab.

22. 14 and 21

23. (oral glucose challenge or ogc).ti,ab.

24. 14 and 23

25. (random blood glucose).ti,ab.

26. 14 and 25

27. (capillary blood glucose or capillary glucose test).ti,ab.

28. 14 and 27

29. (Diabetes risk score assessment tool or ADA risk test).ti,ab.

30. 18 or 20 or 22 or 24 or 26 or 28 or 29

31. 30 not 11

32 8 or 9 or 12 or 31

Limit to 1998-current, English language, human studies

Health Economic Searches

With reference to the Methods for the Development of NICE Public Health Guidance (2009), a simplified search was undertaken for the health economic searches for this review question.

Sample search strategy for EconLit via Ovid

1 (risk assessment or screening or monitoring or diagnostic or diagnosis or glucose test or HBA1C).ti,ab.

2 (diabetes or pre-diabetes or prediabetes or IGT or impaired glucose tolerance or IFG or impaired fasting glucose or FPG or fasting plasma glucose).ti,ab.

3 1 and 2

4 limit 3 to yr="1998 -Current"

References

Evidence for Policy and Practice Information and Coordination (EPPI) Centre. (2008) Available from: http://eppi.ioe.ac.uk/cms/ [Accessed 28th July 2010].

Ramer, Cheryl L. (2005) Site-ation pearl growing, methods and librarianship history and theory. *Journal of the Medical Library Association*, 93 (3), 397–400.

Stott, Ray. (1999) *Citation Pearl Growing*. [online]. Nebraska, Creighton University. Available from: http://newadonis.creighton.edu/HSL/searching/PearlGrowing.html [Accessed 28th July 2010].

Appendix 4: Quality rating of included papers

Study	1	2	3	4	5	Summary quality rating
Coligiuri 2004	P	N	Y	Y	Y	3 / 5 +
Franciosi 2005	Y	N	Y	Y	Y	4 / 5 +
Glumer 2004	Y	Y	Y	Y	N	4 / 5 +
Gomyo 2004	Y	N	P	Y	Y	3 / 5 +
Gray 2010	Y	N	Y	Y	Y	4 / 5 +
Greaves 2004	Y	P	Y	Y	Y	4 / 5 +
Guerreo-Romero 2006	Y	N	Y	Y	N	3 / 5 +
Heikes 2008	N	N	Y	Y	Y	3 / 5 +
Heldegaard 2006	Y	N	Y	Y	N	3 / 5 +
Herdzik 2002	Y	N	P	N	Y	2 / 5 -
Hu 2010	Y	N	Y	Y	N	3 / 5 +
Lidfelt 2001	Y	Y	Y	Y	Y	5 / 5 ++
Luders 2005	Y	P	Y	Y	Y	4 / 5 +
Mannucci 1999	Y	P	Y	Y	P	3 / 5 +
Maynard 2007	P	N	Y/N	Y	N	2 / 5 -
Mohan 2007	Y	N	Y	Y	N	3 / 5 +
Mostafa 2010	Y	Y	P	Y	Y	4 / 5 +
Phillips 2009	Y	P	Y	Y	N	3 / 5 +
Rolka 2001	Y	N	Y	Y	Y	4 / 5 +
Rush 2008	U	N	Y	Y	N	2 / 5 -
Saaristo 2005	Y	Y	Y	Y	Y	5 / 5 ++
Saydah 2002	P	N	Y	Y	Y	3 / 5 +
Schwarz 2009	Y	P	Y	Y	Y	4 / 5 +
Simmons 2004	Y	N	Y	Y	Y	4 / 5 +
Somannavaar 2009	Y	N	Y	Y	N	3 / 5 +
Thomas 2006	Y	N	Y	Y	N	3 / 5 +
Woolthuis 2007	Y	N	Y	N/A	Y	3 / 5 +
Zhou 2009	Y	Y	Y	Y	N	4 / 5 +
Zhou 2010	Y	N	Y	Y	N	3 / 5 +

NR = Not Reported, NA = Not Applicable U = Unclear P = Partial

Appendix 5: Evidence Tables for included studies

Study	**Author:** Colagiuri **Year** 2004 **Country:** Australia **Study design:** Evaluation of a screening protocol	**Comments**
Study Aims	To examine the performance of the Australian screening protocol and variations to this protocol for identifying people with previously undiagnosed type 2 diabetes and people with IGT or impaired fasting glucose (IFG).	
Screening tool	Stepped approach to detecting undiagnosed type 2 diabetes based on assessment of risk status, measurement of fasting plasma glucose (FPG) , HbA1c in individuals at risk.	Related to the AusDab Study
Setting / Delivered by	Part of AusDab survey; Primary Care	
Characteristics targeted	Date and country of birth, language spoken at home, ethnicity, personal and family history of diabetes, smoking habit, past health (including diagnosis and treatment for hypertension and dyslipidemia), cardiovascular disease (angina, heart attack, stroke) and, in women, past history of gestational diabetes.	
Population	**Sample:** 11,247; 10,508 could be included in the analyses. Of these, 5,604 had at least one identifiable risk factor for undiagnosed diabetes specified in the Australian protocol and would be recommended to have an FPG measured. When weighted to the Australian population, 43.4% of adults aged ≥25years would require screening with an FPG.Of the 5,604 with risk factors, 2,723 (48.6%) had an FPG ≥5.5 mmol/l, 210 (3.7%) had an FPG ≥7.0 mmol/l (126 mg/dl), and the remaining 2,671 (47.7%) had an FPG between 5.5 and 6.9 mmol/l and would have been recommended to have an OGTT. **Males** **Mean age**: **Mean BMI**: **Waist circumference:** **Other**: The single risk factor that identified most people (71.5%) as being at high risk for undiagnosed diabetes was age ≥55 years, and another 24.2% were identified because they were age 45–54 years with one of the following: BMI≥ 30 kg/m2, hypertension, or family history of diabetes. Together these two risk factors identified 86.9% of people with newly diagnosed diabetes. Of the 10,508 people included in this study, 1,372 (11.0%) had IGT (FPG ≥ 7.0 and 2-h plasma glucose ≥ 7.8 and <11.1mmol/l) and 642 (5.9%) had IFG (FPG 6.1–6.9 and 2-h plasma glucose ≥7.8). The prevalence of pre-diabetes 47.7%	
No of Items	N/A	
Time to complete	N/A	
Reference standard used	OGTT performed and interpreted according to the 1999 World Health Organization criteria.	
Index and Comparitor tests	Each person underwent a physical examination including measurement of blood pressure, weight and height, and calculation of BMI, and blood was collected for measurement of lipids and HbA1c.	
Sensitivity (%) for diagnosis of IGT / IFG	RF and FPG ≥ 5.5 51.9% RF, FPG and HbA1c 42.0%	

Specificity (%) for diagnosis of IGT / IFG	RF and FPG≥ 5.5 86.7% RF, FPG and HbA1c 88.2%	
Positive and Negative-predictive values (%) for IGT / IFG	RF, FPG and HbA1c PPV 45.5% NPV 43.4%	
AuRoc Value	NR	
Reported optimal threshold	RF and FPG ≥ 5.5 (current guideline) The optimal HbA1c cut point for detecting previously undiagnosed diabetes and IGT/IFG was 5.3%.	
Follow up	NR	
Other properties	NR	
Cost Effectiveness	The cost in Australian dollars ($A) to the health care system for the screening options for detecting each person with newly diagnosed diabetes or IGT/IFG was calculated using the following scenario. Risk factor assessment was done opportunistically at the time of a routine visit to the primary care physician without incurring an additional cost, the blood test was ordered as an additional test (cost $A 8.05 for FPG, $A 14.15 for HbA1c), the person returned for a visit to the primary care physician specifically to obtain the result of the blood test (cost $A 25.05), and individuals with an equivocal FPG had an OGTT (cost $A 15.90) and then returned for a final visit to the primary care physician for the result (cost $A 25.05). These costs are based on the published national fees specified by the Health Insurance Commission of Australia. The cost for detecting each person with newly diagnosed diabetes using the current Australian protocol is $A 746, and $A 260 for each person with IGT or IFG. Increasing the FPG cut point to≥6.1mmol/l alters costs to $A 700 for diabetes and $A 292 for IGT or IFG, whereas the corresponding costs for a protocol based on risk factor assessment followed by measurement of HbA1c are $A 828 and $A 352, respectively. It should be noted that the cost of making a clinical diagnosis of diabetes will be slightly higher because of the repeat testing required to confirm the diagnosis.	
Authors conclusions	The Australian protocol had a sensitivity of 51.9% and specificity of 86.7% for detecting IGT or IFG. Increasing the FPG cutoff to≥ 6.1 mmol/l decreased sensitivity to 34.6%. Similarly strategies for detecting IGT/IFG that relied on HbA1c measurement alone to determine the need for further testing with an OGTT were associated with lower sensitivities compared with protocols that based further testing on FPG measurement. Increasing the FPG cut point to determine the need for an OGTT to 6.1 mmol/l decreased sensitivity, increased specificity, and substantially reduced the proportion of people requiring an OGTT from 21 to 7%. The effect of using measurement of HbA1c to determine the need for an OGTT generally gave similar results to the protocols that used FPG alone, and 12–27% of people required an OGTT. The optimal cut point for HbA1c was 5.3%. The Australian screening protocol performed well in identifying and detecting people with undiagnosed diabetes when applied to a representative sample of the Australian population. Overall, the protocol identified around 8 of 10 people who had previously undiagnosed diabetes, 5 of 10 who had IGT, and 7 of 10 who had IFG. The number needed to screen to identify one new case of diabetes is 32, with 4 of 10 people screened requiring measurement of FPG and 1 in 5 requiring an OGTT.	
Quality Assessment	+	4/6
Study	**Author:** Franciosi **Year:** 2005 **Country:** Italy **Study design:** Evaluation of screening tool and stepped approach aimed at estimating the prevalence of IGT.	Part of IGLOO:(Impaired Glucose Tolerance and Long-Term Outcomes Observational) study.

Study Aims	To evaluate an opportunistic screening strategy addressed to individuals with one or more cardiovascular risk factor, based on the Diabetes Risk Score (DRS) as the initial instrument, for the identification of individuals with type 2 diabetes or impaired glucose tolerance (IGT).	
Screening tool	**Name:** Diabetes Risk Score (DRS) **Type:** Simple fast self-administered questionnaire based on the presence of well known diabetes risk factors. Initially validated in a Finnish population	A copy of the DRS is provided at http://care.diabetesjournals.org. The original version of the questionnaire was developed to characterize individuals according to their future risk of developing type 2 diabetes (Lindstrom 2003 FINRISK programme).
Setting / Delivered by	Primary care; Distributed by General Practitioner Self-administered	
Characteristics targeted	Identification of unknown T2D or glucose intolerance. Age, BMI, waist circumference, use of blood pressure medication, history of high blood glucose, physical activity, and daily consumption of vegetables, fruits, or berries.	
Population	**Sample:** 1,377 patients aged 55-75 years with one or more CVD risk factor but without a CVD history. Consecutive eligible attendees up to max 30 **Males** 712 **Mean age** 62.4 (SD 5.3) **Mean BMI** Men 28.2 (SD 6.4) Women 27.3 (4.6) **Waist circumference:** Mean men 100.6 (11.7) Women 91.8 (12.1).Total of Men equal or >102 cm and women equal or >88 cm =680 **Other**: Patients excluded from the analyses did not differ from those included in terms of age, BMI, waist circumference, levels of cholesterol and triglycerides, dyslipidemia, or presence of metabolic syndrome. Patients not included were less often men. Overall, 54.9% of the patients showed some forms of glucose metabolism alteration; in particular, 15.4% of the patients had impaired fasting glucose (IFG), 11.1% had IGT, 11.0% had IGT and IFG. Mean DRS values showed a marked variation according to glucose metabolism categories, as follows: 8.7 - 3.0 in normoglycemic individuals, 9.5 - 3.1 in individuals with IFG, 9.9 -3.3 in individuals with IGT, 10.3 - 3.3 in individuals with IFG and IGT (*P* <0.0001). The prevalence of pre-diabetes = 11%	
No of Items	N/A	
Time to complete	N/A	
Reference standard used	OGTT, with determination of venous plasma glucose, fasting and 2 h after the ingestion of 75 g glucose. World Health Organization 1999 criteria for the definition of IGT.	
Index and Comparitor tests	The score ranges between 0 and 20, and a cut point of 9 best identifies individuals at higher risk of developing type 2 diabetes, with a sensitivity of 0.78 – 0.81 and a specificity of 0.76–0.77. Prevalence rates of 20%, 10% and 5% were tested.	
Sensitivity (%) for diagnosis of IGT / IFG	DRS only sensitivity 77% (95% CI 0.74–0.81) An FBG ≥ 6.1 mmol/l had a sensitivity of 68% (95% CI 0.64–0.72) for the diagnosis of glucose abnormalities. An FBG cut-off of 5.6 mmol/l gave a sensitivity of 86% (95% CI 0.84–0.89) for the diagnosis of glucose abnormalities. Combined use of DRS and with an FBG cutoff of ≥6.1 mmol/l led to 90% (95% CI 0.88–0.93) sensitivity (both tests	

	negative). Combined use of DRS and with an FBG cutoff of ≥6.1 mmol/l led to 55% (95% CI 0.51–0.59) sensitivity (both tests positive). Combined use of DRS and with an FBG cutoff of ≥5.6 mmol/l led to 95% (95% CI 0.93–0.97) sensitivity (both tests negative). Combined use of DRS and with an FBG cutoff of ≥5.6 mmol/l led to 69% (95% CI 0.65–0.73) sensitivity (both tests positive)..	
Specificity (%) for diagnosis of IGT / IFG	DRS only specificity 45% (95% CI 0.41–0.48) An FBG =or >6.1 mmol/l had a specificity of 75% (95% CI 0.72–0.78) for the diagnosis of glucose abnormalities. An FBG cut-off of = or 5.6 mmol/l gave a specificity of 44% (95% CI 0.41–0.48) for the diagnosis of glucose abnormalities. The combined use of DRS and with an FBG cutoff of ≥6.1 mmol/l led to 78% (95% CI 0.76–0.81) specificity (both tests negative). Combined use of DRS and with an FBG cutoff of ≥6.1 mmol/l led to 84% (95% CI 0.81–0.86) specificity (both tests positive). The combined use of DRS and with an FBG cutoff of ≥5.6 mmol/l led to 24% (95% CI 0.21–0.27) specificity (both tests negative). Combined use of DRS and with an FBG cutoff of ≥5.6 mmol/l led to 65% (95% CI 0.62–0.69) specificity (both tests positive).	
Positive and Negative-predictive values (%) for IGT / IFG	DRS only NPV 76% (95%CI 0.71–0.79) at cut-off 9 DRS only PPV 0.48 (95%CI 0.44–0.51) FPG cutoff of ≥5.6 mmol/l NPV 0.83 (95%CI 0.8–0.87) FPG cutoff of ≥5.6 mmol/l PPV 0.50 (95%CI0.47–0.54) FPG cutoff of ≥6.1 mmol/l NPV 0.78 (95%CI 0.75–0.81) FPG cutoff of ≥6.1 mmol/l PPV 0.64 (95%CI 0.60–0.68) NPV for combined DRS and FPG cutoff of ≥5.6 mmol/l was 0.88 (95%CI 0.84–0.92) (both tests negative) NPV for combined DRS and FPG cutoff of ≥5.6 mmol/l was 0.76 (95%CI 0.73–0.79) (both tests positive). PPV for combined DRS and FPG cutoff of ≥5.6 mmol/l, was 0.55 (95%CI 0.42–0.48) (both tests negative) PPV for combined use of DRS with an FBG cutoff of ≥5.6 mmol/ was 0.56 95%CI (0.53–0.60) (both tests positive). NPV for combined DRS and FPG cutoff of ≥6.1 mmol/l was 0.85 (95%CI 0.81–0.89) (both tests negative) NPV for combined DRS and FPG cutoff of ≥6.1 mmol/l was 0.74 (95%CI 0.71–0.77) (both tests positive). PPV for combined DRS and FPG cutoff of ≥6.1 mmol/l was 0.48 (95%CI 0.45–0.51) (both tests negative) PPV for combined DRS and FPG cutoff of ≥6.1 mmol/l was 0.69 (95%CI 0.64–0.73)(both tests positive).	
AuRoc Value	AUC 0.67 (95% CI 0.64–0.70)	
Reported optimal threshold	A cut-off of 9 ensured the best balance between true-positive and false-positive rates. Different screening strategies to be applied to high-risk individuals: 1) FBG testing in all patients 2) administration of the DRS as an initial screening tool, with FBG measured only in individuals with a score≥9. 3) the need for OGTT according to two different levels of FBG (i.e., OGTT performed in individuals with FBG between 6.1 and 6.9 mmol/l or FBG between 5.6 and 6.9 mmol/l). A strategy based on the DRS as an initial screening instrument, with FBG measured only in individuals with a score≥9, and an OGTT performed in individuals with an FBG value ≥5.6 mmol/l would lead to the identification of 57% of cases of IGT. This strategy would require the measurement of FBG in 64% of the patients and an OGTT in 38%. On the other hand, a strategy based on FBG measurement in all individuals and the performance of OGTT in those with an FBG ≥5.6 mmol/l would allow the identification of 78% of individuals with IGT, but 56% of the patients should undergo an oral test.	

	A strategy based on FBG measurement in all individuals and the performance of OGTT in those with an FBG ≥5.6 mmol/l would allow the identification of 78% of individuals with IGT, but 56% of the patients should undergo an oral test.	
Follow up	NR	
Other properties	NR	
Cost Effectiveness	The best compromise between number of cases detected and cost per case detected is represented by the screening strategy using the DRS as initial instrument, with an FBG performed in individuals with a DRS score ≥9 and an OGTT performed in individuals with an FBG between 5.6 and 7 mmol/l. The difference in cost per case detected in favour of DRS as the initial screening tool tended to increase as the prevalence of the target condition decreased.	See paper p1192 for costings at each level (can IGT be teased out from T2D in these figures?)
Reviewer comments	"Presence of the metabolic syndrome was defined according to Adult Treatment Panel III criteria" This criteria is for cholesterol management, not metabolic syndrome	
Authors conclusions	When used in combination with FBG, the questionnaire allowed the identification of >50% of those with IGT, while limiting the rate of those requiring an OGTT.	
Quality Assessment	+	4/6
Study	**Author:** Glumer **Year**: 2004 **Country:** Denmark **Study design:** Diagnostic accuracy study	
Study Aims	To develop a simple self-administered questionnaire identifying individuals with undiagnosed diabetes with a sensitivity of 75% and minimizing the high-risk group needing subsequent testing.	
Screening tool	**Name:** Danish Diabetes Risk Score **Type:** Self -administered questionnaire	In Denmark, regular screening is not recommended. Those at high risk should be first identified.
Setting / Delivered by	Self -administered	
Characteristics targeted	Participants were split into two groups, one group was examined in 1999 and the other group examined in 2000. Subjects from the additional pilot study underwent measurement of random capillary blood glucose.	Part of Inter99 study Validated using ADDITION pilot sample (40-69 years).
Population	**Sample:** Inter99 Age 30-60 First half: N=3250 **Males:** 49.8% **Mean age**: 46.0 (SD 7.9) **Mean BMI**: 26.2 (SD 4.4) **Waist circumference:** NR Second half: N=2874 **Males** 49.3% **Mean age**: 46.0 (SD 7.8) **Mean BMI:** 26.3 (SD 4.6) **Waist circumference:** NR **Other**: IGT First half 12.6% Second half 10.9% Participants in a population-based primary prevention study of cardiovascular disease (Inter99 study). Without	

	known diabetes Pilot study (ADDITION) of 1028 adults aged 40-69 years of age, from the lists of five general practitioners in the City of Arhus used to validate results. The prevalence of pre-diabetes in 3 groups = 12.6%; 10.9%; 9.2% respectively	
No of Items	Age, sex, BMI, known hypertension, physical activity at leisure time, and family history of diabetes	
Time to complete	NR	
Reference standard used	75g OGTT	
Index and Comparitor tests	RBG of equal or >4.5 mmol/l went on to OGTT	
Sensitivity (%) for diagnosis of IGT / IFG/T2DM	**First half Inter 99** 73.3 (66.1-80.9) **Second half Inter99** 66.7 (58.1-74.5) **Additional study** 75.9 (58.3-90.3)	The Danish Health Care system could only manage to test 25% of the entire adult population. Because the risk score is the first part of a step-wise procedure, the sensitivity had to be no less than 75%.
Specificity (%) for diagnosis of IGT / IFG/T2DM	**First half Inter 99** 74.3 (72.7–75.6) **Second half Inter99** 73.6 (71.9–75.2) **Additional study** 72.2 (69.3–75.1)	
Positive and Negative-predictive values (%) for IGT / IFG/T2DM	**First half Inter 99** PPV 11.0 (9.1–13.2) NPV 98.5 (98.0–98.9) **Second half Inter99** PPV 9.7 (7.5–11.7) NPV 98.1 (97.5–98.7) **Additional study** PPV 7.3 (4.5–10.3) NPV 99.0 (98.3–99.6)	
AuRoc Value	**First half Inter 99** 80.4 (76.5-83.8) **Second half Inter99** 76.1 (72.0-80.3) **Additional study** 80.3 (72.1-87.6)	
Reported optimal threshold	Cutoff 31 picked up IGT: First half190 out of 409 (Sensitivity 46.5% 95% CI 41.5-51.4) Second half, 20.6 %(17.7-23.6) (Sensitivity 47.9% 95% CI 42.3-53.6) ADDITION 5.0% (2.8 – 8.3) (Sensitivity 45.2% 95% CI 27.3-64.0)	
Follow up	NR	
Other properties	NR	
Cost Effectiveness	See Glumer 2006	
Authors conclusions	The authors concluded that they had developed a one page questionnaire that could be used in a stepwise screening strategy for type 2 diabetes in Denmark. The risk score decreases the proportion of the population that need subsequent testing.	

Quality Assessment	+	4/6
Study	**Author:** Gomyo **Year:** 2004 **Country:** Japan **Study design:** Comparative evaluation	
Study Aim	To assess the discriminating abilities of fasting plasma glucose (FPG) and HbA1c on screening tests for impaired glucose tolerance (IGT) and IGT plus diabetes mellitus by the receiver operating characteristic (ROC) curve analysis. To examine the effects of sex, age and BMI on sensitivity and specificity of the optimal cutoff points.	
Screening tool	FPG (fasting Plasma Glucose) HBA1c	
Setting / Delivered by	NR	
Characteristics targeted	The subjects were divided into subgroups according to sex, age (30–39, 40–49, 50–59) and BMI (<20, 20–24.9, 25) to examine effects of these variables on sensitivity and specificity of the optimal cutoff points. A BMI of ≥25 kg/m2 was regarded as obesity in Japanese. Furthermore, the optimal cutoff points by the subgroups were examined.	
Population	**Sample:** 997 subjects, without a previous history of diabetes), who were recruited for OGTT after the first screening of the Japan Diabetes Prevention Program (JDPP). **Males:** 461 **Mean age**: 30–59 years **Mean BMI**: **Waist circumference:** **Other**: Those with IGT were defined as having FPG < 126 mg/dl and 140 mg/dl ≤ 2 h PG < 200 mg/dl; Those with impaired fasting glucose (IFG) were defined as having 110 mg/dl ≤ FPG < 126 mg/dl and 2 h PG < 140 mg/dl. According to the 1997 criteria of ADA, 140 subjects were classified as diabetes (14.0%), 256 as having IGT (25.7%), 87 as having IFG (8.7%) and 514 as having NGT (51.6%).	JDPP is a randomized clinical trial (1999) designed to assess the efficacy of intensive diet and exercise to prevent or delay the onset of type 2 diabetes mellitus in subjects with IGT. The JDPP research group adopted a two-step strategy for identifying subjects with IGT by the findings of previous reports.
No of Items	N/A	
Time to complete	N/A	
Reference standard used	75 g OGTT.	
Index and Comparitor tests	At first screening, the subjects were selected with the criteria decided as (1) 100 mg/dl (5.5mmol/l) ≤ FPG < 126 mg/dl (7.0 mmol/l); (2) 140 mg/dl (7.8 mmol/l) ≤ casual plasma glucose *(*CPG*)* < 200 mg/dl (11.1 mmol/l) (less than 2 h after a meal); (3) 110 mg/dl(6.1 mmol/l) ≤ CPG < 140 mg/dl(7.8 mmol/l) (more than 2 h after a meal)	
Sensitivity (%) for diagnosis of IGT / IFG	FPG: Male optimal cut point 105 mg/dl (5.83 mmol/l) = 68.3% Female optimal cut point 100 mg/dl (5.5mmol/l) = 66.9% Optimal Cut off for both 102 mg/dl (5.6 mmol/l) = 69.1% for both males and females Optimal Cut off 102 mg/dl (5.6 mmol/l) by sex, age and BMI: Male 81.3% (73.3–87.7); Female 57.9% (49.1–66.3) (Significantly different compared with males).	

	Age: 30-39 45.5 % (16.8–76.6), age 40 -49 68.8 % (58.5–77.8); age 50 -59 71.1 %(63.2–78.2) BMI ≥ 25 70.5% (61.2–78.7) HbA1c: at cut off 5.3% = 57.2% Male 51.7 %(42.4–60.9); Female 62.3% (53.4–70.6) Age: 30-39 27.3 %(6.0–61.0); age 40 -49 55.3%(44.7–65.6);age 50 -59 60.7% (52.3–68.6) BMI ≥ 25 59.6 %(49.8–68.9)	
Specificity (%) for diagnosis of IGT / IFG	FPG: Male optimal cut point 105 mg/dl (5.7mmol/l) = 61.9% Female optimal cut point 100 mg/dl (5.5mmol/l) = 63.4% Optimal Cut off for both 102 mg/dl (5.6mmol/l) = 61.6% for both males and females Optimal Cut off 102 mg/dl (5.6 mmol/l) by sex, age and BMI: Male 50.9% (45.1–56.8); Female 69.9% (65.3–74.7) Age: 30-39 50.9 %(45.1–56.8); age 40 -49 62.4% (55.4–69.1);age 50 -59 60.1%(55.1–65.2) BMI ≥ 25 51.3 %(43.1–59.5) HbA1c: at cut off 5.3% = 67.4% Male 74.3 %(67.2–80.5); Female 63.2 %(57.8–68.6) Age: 30-39 90.7% (79.7–96.9); age 40 -49 70.2% (62.3–77.3);age 50 -59 60.9 %(55.0–66.7) BMI ≥ 25 58.3 %(48.7–67.4)	
Positive and Negative-predictive values (%) for IGT / IFG	NR	
AuRoc Value	IGT only: AUC for FPG (0.72 ± 0.02) was significantly larger than that for HbA1c (0.65 ± 0.02) ($P < 0.01$).	
Reported optimal threshold	FPG: 102 mg/dl for IGT (Male 105/ Female 100) HbA1c: 5.3% for IGT (Male 52/ Female 53)	
Follow up	NR	
Other properties	N/A	
Cost Effectiveness	NR	
Authors conclusions	Both sensitivity and specificity of each test were higher when the state of glucose tolerance was worse. In screening with FPG, females had lower sensitivity and higher specificity than males. The specificity for IGT plus diabetes mellitus was the lowest in the obese group (BMI ≥ 25 kg/m2). In screening with HbA1c, the specificity was lower in the groups of 40–49- and 50–59-year-olds than the group of 30–39-year-olds and lowest in the obese group (BMI ≥ 25 kg/m2). The values were influenced by those variables. In screening with FPG, the optimal cut off point of females was lower than that of males. In screening with HbA1c, the optimal cut off points of the groups of 40–49- and 50–59-year-olds were higher than the group of 30–39-year-olds. The obese group had higher optimal cut off points in both FPG and HbA1c than the other groups of BMI. This study showed that the discriminating ability of FPG was superior to that of HbA1c, although each test can discriminate between IGT and non-IGT (NGT plus IFG). The DECODE study has shown that the optimal FPG cutoff point increased with increasing BMI.FPG was better than HbA1c for screening for IGT and IGT plus diabetes mellitus, and sex, age and BMI had effects on the performance of the screening test. A report by the WHO recommended that all those with IFG have an OGTT performed to exclude the diagnosis of IGT or diabetes mellitus. The optimal cutoff points of FPG were lower than the FPG values for IFG in the report by WHO. If the two-step strategy is adopted to screen for IGT plus diabetes mellitus, we suggest selecting all those with a FPG value of 105 mg/dl or greater for the first screening, at least in Japanese subjects. Limitations: The population studied here was not randomly selected but a preselected group with some risk of glucose intolerance. The age range (30–59 years) was also narrow. Despite these limitations, the results presented	

	in this study should be a valuable piece of information to identify subjects of IGT.	
Quality Assessment	+	4/6
Study	**Author:** Gray **Year**: 2010 **Country:** UK **Study design:** Evaluation of Risk Score tool (ADDITION Study)	
Study Aim	To externally validate the LRA score	
Screening tool	**Name:** Leicester Risk Assessment (LRA) **Type:** A risk score developed to be used by lay members of multiethnic populations.	IGR = Impaired Glusose Regulation
Setting / Delivered by	Trained Researcher	
Characteristics targeted	Smoking status; alcohol consumption; occupational status; ethnicity; physical activity; FINDRISC and scales to measure well-being and anxiety.	
Population	**Sample:** 6186 Aged 40 -75 **Males** 3048 (47.7%) **Mean age** 57.3 (9,6) **Mean BMI** 28.1 (5.0) **Waist circumference:** 94.2 (13.1) **Other**: Ethnicity: White European 4687 (73.4%); Other 1499 (23.5%) IGR 1043 (16.3%)	WHO criteria for diagnosis of T2DM, IFG and IGT. IGR refers to a composite of IGT and/or IFG
No of Items	NR	
Time to complete	NR	
Reference standard used	75g OGTT	
Index and Comparitor tests		
Sensitivity (%) for diagnosis of IGT / IFG	Cut point ≥ 12 86.7 (84.7–88.5) Cut point ≥ 13 83.5 (81.3–85.5) Cut point ≥ 14 79.4 (77.1–81.6) Cut point ≥ 15 75.3 (72.8–77.6) Cut point ≥ 16 72.1 (69.6–74.6) Cut point ≥ 17 69.3 (66.7–71.9) Cut point ≥ 18 63.3 (60.6–66.0) Cut point ≥ 19 58.4 (55.6–61.1) Cut point ≥ 20 53.2 (50.4–56.0)	
Specificity (%) for diagnosis of IGT / IFG	Cut point ≥ 12 34.5 (33.2–35.8) Cut point ≥ 13 39.1 (37.7–40.4) Cut point ≥ 14 45.2 (43.8–46.5) Cut point ≥ 15 50.5 (49.1–51.9) Cut point ≥ 16 54.1 (52.7–55.5) Cut point ≥ 17 57.2 (55.8–58.5) Cut point ≥ 18 63.8 (62.5–65.2) Cut point ≥ 19 68.2 (66.9–69.4) Cut point ≥ 20 72.1 (70.9–73.4)	
Positive and Negative-predictive values (%) for IGT / IFG	Cut point ≥ 12 PPV 24.4 (23.2–25.7) NPV 91.4 (90.0–92.6) Cut point ≥ 13 PPV 25.1 (23.8–26.4) NPV 90.6 (89.4–91.8)	

	Cut point ≥ 14 PPV 26.1 (24.7–27.6) NPV 90.0 (88.8–91.1) Cut point ≥ 15 PPV 27.1 (25.6–28.6) NPV 89.3 (88.1–90.4) Cut point ≥ 16 PPV 27.7 (26.2–29.3) NPV 88.8 (87.7–89.9) Cut point ≥ 17 PPV 28.3 (26.7–30.0) NPV 88.4 (87.3–89.5) Cut point ≥ 18 PPV30.0 (28.2–31.8) NPV 87.7 (86.6–88.7) Cut point ≥ 19PPV 30.9 (29.1–32.8) NPV 87.0 (85.9–88.0) Cut point ≥ 20PPV 31.8 (29.8–33.9) NPV 86.3 (85.3–87.3)	
AuRoc Value	0.72 (for T2DM)	
Reported optimal threshold	For IGR alone Cut off point ≥16 sensitivity 72.1 (95% CI 69.6-74.6) Specificity 54.1% (95% CI 52.7-55.5)	Compares to FINDRISC alone at ≥12 Sensitivity 69.7%; Specificity 55.5%; PPV 23.3; NPV 90.4
Follow up	NR	
Other properties	NR	
Cost Effectiveness	NR	
Authors conclusions	Identification of high risk individuals can prevent diabetes. The risk score is a simple and non-invasive way of targeting those in need of further testing.	
Quality Assessment	+	4/6
Study	**Author:** Greaves **Year:** 2004 **Country:** UK **Study design:** Evaluation	
Study Aim	To investigate the idea of computerized searching of routinely collected data as the starting point for a targeted screening programme. To establish the potential feasibility of this system for identifying hyperglycaemic illness, the study assessed the prevalence of previously undetected diabetes and impaired fasting glycaemia (IFG) in four groups of patients with selected age and BMI criteria.	
Screening tool	**Type:** Computerized searching of routinely collected data	
Setting / Delivered by	General Practice	
Characteristics targeted		
Population	**Sample:** 16 practices in Somerset, North and East Devon. Each practice was asked to sample 100 patients for testing, 25 from each of four groups. The groups were specified by stepped age and BMI criteria. A sample of 100 patients from each of 16 practices was calculated to give confidence intervals (CIs) around the estimated percentage of ±2% In total, 1287 patients were recruited (1644 data points across the four groups). As the grouping criteria are nested within each other, a patient could be selected for more than one group. Of the 1287 participants, 251 were selected into two groups, 47 were selected into three groups and four were selected into all four groups. **Males**: 508 (39.5%) **Mean age**: **Mean BMI**: **Waist circumference:** **Other**: Practice data on age were available for 100% of patients. In 27 cases, self-reported age differed from that on the practice computer by >1 year. This could potentially have led to the misclassification of 11 patients (0.7%).	

	BMI data in the over-50 population were available for 76.8% (95% CI 71.7–81.9) of patients. The BMI on record was compared with the current weight and height measured at the clinics. This indicated that 328 (20.0%) of the sample were misclassified due to either out of date or inaccurate BMI data in the practice record. However, when the data were reanalysed excluding those misclassified, this did not substantially affect the results.	
No of Items	NR	
Time to complete	NR	
Reference standard used	N/A	
Index and Comparitor tests	N/A	
Sensitivity (%) for diagnosis of IFG	N/A	
Specificity (%) for diagnosis of IFG	N/A	
Positive and Negative-predictive values (%) for IGT / IFG	N/A	
AuRoc Value	N/A	
Reported optimal threshold	N/A	
Follow up	Number needed to test for either IFG or diabetes Group 1 7.7 (5.8–10.4) Group 2 7.1 (5.7–8.8) Group 3 8.3 (6.5–10.6) Group 4 12.8 (9.1–18.0)	
Other properties	The rate of response to the invitation for screening was 60.6% (95% CI 55.7–65.6), based on data returned by 15 practices. No significant sampling biases due to either age or gender were found.	
Cost Effectiveness	NR	
Authors conclusions	Alternative systems for targeting diabetes screening, including risk questionnaires, and the calculation of risk scores may be considerably more labour intensive, and OGT testing is likely to be less acceptable to patients than the fasting glucose test. However, these options may provide different population coverage, more efficient targeting of at-risk patients or more sensitive identification of cases. Alternatively, the detection rate of the computerized searching system described here could be improved by efforts to improve BMI recording, by the development of software patches to allow searching for 'latest BMI' and potentially by the use of glucose tolerance testing.	
Quality Assessment	+	4/6
Study	**Author:** Guerreo-Romero **Year** 2006 **Country:** Mexico **Study design:** Diagnostic accuracy study	
Study Aims	The aim of the study was to determine the effect of lowering the criterion for normal fasting plasma glucose (FPG) on the identification of subjects with impaired glucose tolerance (IGT) and metabolic syndrome (MS).	
Screening tool	**Name / Type**: Fasting Plasma Glucose	
Setting / Delivered by	Population sample	
Characteristics targeted	BMI, waist circumference,	
Population	**Sample:** 844	

	Males: a) 156 31.7%, b) 81 44.8%, c) 70 40.9% **Mean age**: **Mean BMI**: Males a) 27.6 ± 6.8, b) 28.3 ± 6.0, c) 29.5 ± 4.5 Females a) 27.3 ± 10.2, b) 29.2 ± 5.8, c) 30.6 ± 5.6 **Waist circumference:** Males a) 95.7cm ± 11.8, b) 99.0cm ± 20.2, c) 103.1 ± 12.0 Females a) 91.8cm ± 13.2, b) 98.7cm ± 15.0, c) 102.0 ± 16.3 **Other**: A randomised two-stage cluster sampling process was used resulting 844 individuals aged 30-64 years. According to the individual's FPG concentrations, participants were allocated to one of three groups, group a FPG <5.6 mmol/L (492, 58.3% of sample), group b FPG 5.6-6.0 mmol/L (181, 21.4% of sample) and group c FPG 6.1-6.9 mmol/L (171, 20.3% of sample). The authors reported that there were no significant statistical differences between the groups. The prevalence of pre-diabetes = 19.1% IGT; 20.3 IFG	
No of Items	N/A	
Time to complete	N/A	
Reference standard used	One hour Oral glucose tolerance test (OGTT)	
Index and Comparitor tests	FPG	
Sensitivity (%) for diagnosis of IGT	5.6 mmol/L 82.0% 6.1-6.9 mmol/L 32.9%	
Specificity (%) for diagnosis of IGt	5.6 mmol/L 67.8% 6.1-6.9 mmol/L 82.7%	
Positive and Negative-predictive values (%) for IGT	5.6 mmol/L 37.5% PPV, 94.1% NPV 6.1-6.9 mmol/L 31.0% PPV, 84.0% NPV	
AuRoc Value	Not reported	
Reported optimal threshold	The authors reported an FPG cut-off point of 5.6 mmol/L	
Follow up	Not reported	
Other properties	Not reported	
Cost Effectiveness	Not reported	
Authors conclusions	The authors concluded that, taking into account that the main goal of screening such as the early detection of risk factors in an apparently healthy population requires diagnostic tests of high sensitivity, lowering the normal criterion for FPG to 5.6 mmol/L increases the identification of subjects with IGT, improving the success of FPG as a screening tool for T2DM.	
Quality Assessment	+	
Study	**Author:** Heikes **Year:** 2008 **Country:** US **Study design:** Development and comparison of two different tools using different methods. The one that best served objectives of simplicity and accuracy was selected.	.
Screening tool	**Name:** Diabetes Risk Calculator **Type:** A simple, self-administered, paper-based screening tool that could be used by the public to determine their risk of having pre-diabetes (or undiagnosed diabetes) and to help people decide whether they should see a physician for further evaluation. Additional details about the data collection and analysis are described in a technical report available as an online	Data from the Third National Health and Nutrition Examination Survey (NHANES) (1988–1994) was used to build and internally validate the tool.

	appendix at http://dx.doi.org/10.2337/dc07-1150	
Setting / Delivered by	Self-administered / GP administered	
Characteristics targeted	BMI, height, weight, waist circumference, waist-to-hip ratio, age, sex, race/ethnicity, taking blood pressure medication, taking cholesterol medication, gestational diabetes, high blood pressure, high cholesterol, history of diabetes (any blood relative), history of diabetes (parent or sibling), history of diabetes (parent), history of diabetes (sibling), and exercise compared with peers. Not all variables were used in the final tool; their inclusion in the final models depended on their value as predictors of pre-diabetes and undiagnosed diabetes.	The definitions of pre-diabetes are based on fasting plasma glucose (FPG) and glucose tolerance, as measured by a 2-h plasma oral glucose tolerance test (OGTT). IFG is defined as FPG of 100-125 mg/dl. IGT is defined as 2-h OGTT result of 140–199 mg/dl. Pre-diabetes is defined as IFG and/or IGT without diabetes.
Population	**Sample:** 7,092 participants who were aged ≥20 years and had FPG results. **Males** **Mean age** **Mean BMI** **Waist circumference:** **Other**: Two-hour OGTT data were available for approximately half of those aged 40–75 years. For people for whom 2-h OGTT results were missing, the diagnoses were based on FPG alone. The prevalence of pre-diabetes in the NHANES III dataset was 26.14%.	Analysis of the group for whom both FPG and OGTT data were available revealed that the lack of OGTT data for some of the participants did not materially affect the stability of the results; the overall effect of the missing data was to underestimate the prevalences of pre-diabetes by app. 2%.
No of Items	The DRC includes questions on age, waist circumference, gestational diabetes, height, race/ethnicity, hypertension, family history, and exercise. The tree begins in upper left corner. An individual moves through the tree in directions determined by answers to questions at each branch, until ending in a terminal node (oval). The probabilities an individual at any terminal node has undiagnosed pre-diabetes are shown in the nodes.	
Time to complete	NR	
Reference standard used	FPG	
Index and Comparitor tests	OGGT	
Sensitivity (%) for diagnosis of IGT / IFG	With use of a cut point of 0.254, sensitivity was 80% Using risk of pre-diabetes as probability >29% Training 75.36%; NHANES 1999-2004 77.65%	
Specificity (%) for diagnosis of IGT / IFG	With use of a cut point of 0.254, specificity was 64% Using risk of pre-diabetes as probability >29% Training 64.59%; NHANES 1999-2004 51.36%	
Positive and Negative-predictive values (%) for IGT / IFG	Training PPV 49% NPV 85% Using risk of pre-diabetes as probability >29%; NHANES 1999-2004 PPV 40.5%, NPV 84.3%	
AuRoc Value	With use of a cut point of 0.254, area under receiver operating characteristic (ROC) was 0.793 Using risk of pre-diabetes as probability >29% Training 0.7503; NHANES 1999-2004 0.6991	
Reported optimal threshold	Cut point of 0.254 Each terminal node can designate an individual to be at high risk of either 1) diabetes or pre-diabetes (if the probability of undiagnosed diabetes is >8%) or 2) pre-diabetes (if the risk of pre-diabetes is >29% and the risk of undiagnosed diabetes is = or <2.5%), or 3) neither diabetes or pre-diabetes (if the risk of pre-diabetes is ≥29%and the risk of undiagnosed diabetes is <1%).	Validations were performed using split datasets, in which the model was “trained” on a randomly selected subset of the data and tested on the remaining data.
Follow up	NR	
Other properties	NR	

Cost Effectiveness	NR	
Reviewer comments	This appears to be the fore-runner of the ADA on-line tool (US).	
Authors conclusions	The DRC sorts people into 14 different categories and reports for each category the probability that an individual is at low risk or high risk for either undiagnosed diabetes or pre-diabetes. The screening tool can be used by physicians to assess the risks of their patients or can be self-administered by individuals to assess their own risks. Use of this tool enables the identification of individuals who might benefit from confirmatory tests and treatment to delay or prevent the onset of type 2 diabetes and its complications. Development of a patient- friendly, electronic version is underway for broader use in clinical practice.	
Quality Assessment	+	3/6
Study	**Author:** Heldgaard **Year**: 2006 **Country:** Jutland, Denmark **Study design:** Cross-sectional study	
Screening tool	**Name:** Cambridge Risk Score (CRS) **Type**: Routinely collected data recorded in general practices**.**	
Setting / Delivered by	NR	
Characteristics targeted		
Population	**Sample:** Danish general practice population (1,355) **Males:** **Mean age**: **Mean BMI**: **Waist circumference:** **Other**: Population characteristics not reported for sample as a whole. Prevalence of pre-diabetes in sample = 10.4%	2,082 patients (aged 20 to 69 years) from a single general practice were invited to take part. After exclusions, 1,355 people were assessed and include din the analysis.
No of Items	Age (years), sex, BMI (4 categories), prescribed anti-hypertensives or steroids, diabetes family history (parents or siblings*), smoking (non-smoker, ex-smoker, or current smoker)	
Time to complete	NR	
Reference standard used	A 10 hour overnight fast and a standard 75g Oral glucose tolerance test.	
Index and Comparitor tests	As above	
Sensitivity (%) for diagnosis of IGT / IFG	CRS Threshold 0.058 80.2 (73.6-83.5) 0.086 71.5 (64.4-77.7) 0.143 58.7 (51.3-65.8) 0.246 47.1 (39.8-54.5) 0.428 30.8 (24.4-38.1)	
Specificity (%) for diagnosis of IGT / IFG	CRS Threshold 0.058 54.4 (51.5-57.2) 0.086 64.6 (61.8-67.3) 0.143 74.2 (71.6-76.6) 0.246 83.9 (81.7-85.9) 0.428 93.1 (91.5-94.4)	
Positive and Negative-predictive	CRS Threshold PPV NPV	

values (%) for IGT / IFG	0.058 20.4 (18.0-23.0) 95.0 (93.1-96.4) 0.086 22.7 (20.2-25.4) 94.0 (92.1-95.4) 0.143 24.8 (22.2-27,6) 92.5 (90.7-94.0) 0.246 29.8 (27.0-32.7) 91.6 (89.8-93.1) 0.428 39.0 (36.0-42.1) 90.2 (88.5-91.8)	
AuRoc Value	74.0% (69.9-78.0)	
Reported optimal threshold	0.246	
Follow up	NR	
Other properties	NR	
Cost Effectiveness	NR	
Authors conclusions	The authors conclude that glucose disorders are common within the Danish population, and that the CRS performs well in identifying both undiagnosed type 2 diabetes as well as reasonably well in identifying those with pre-diabetes. Calculating risk scores automatically using electronic medical records followed by diagnostic testing on a proportion of the population is more practical than inviting all the adults on the general practice list for blood glucose tests. The CRS in addition does not entail distribution or analysis of questionnaires. General practitioners should be encouraged to collect and record risk factor information necessary to calculate predictive models.	
Quality Assessment	+	
Study	**Author:** Herdzik **Year** 2002 **Country:** Poland **Study design:** Assessment of a screening strategy.	
Study Aims	To determine if measuring fasting capillary glycaemia (FCG) along with fructosamine and/or glycosylated haemoglobin allows the detection of glucose tolerance abnormalities better than FCG alone.	
Screening tool	**Name**: FCG; FSA; HbA1c	
Setting / Delivered by	Outpatient Clinic	
Characteristics targeted	N/A	
Population	**Population**: Caucasian men and women over 18 years of age, living in Western Pomerania in Poland, referred between January 1993 and December 1999 to the Outpatients' Clinic or to the Department of Internal Medicine at Pomeranian Academy of Medicine because of suspicion of having diabetes due to symptoms or having known risk factors for glucose intolerance. **Sample:** 538 subjects. Due to financial limitations, determinations of fructosamine (FRA) and glycosylated haemoglobin HbA1c were available only in subsets of these patients and depended on the doctors' recommendation. OGTT was not performed on patients with fasting capillary glucose ≥11.1 mmol/l (200 mg/dl). Pregnant women, patients with previously diagnosed diabetes and patients receiving hypoglycaemic treatment were excluded from the study. **Males:** (n=299) 55.5% **Mean age**: **Mean BMI**: Males 28.9 (2.7) Females 27.6 (2.1) **Waist circumference:** **Other:** The serum fructosamine concentration was determined in 480 of these patients (54.8% were men; n =263). Prevalence of pre-diabetes in sample = 17.65%	
No of Items	N/A	

Time to complete	N/A	
Reference standard used	OGTT	
Index and Comparitor tests	FCG; FRA; HbA1c	
Sensitivity (%) for diagnosis of IGT / IFG	**FCG** Cut-off: 4.9 Sensitivity 75.8% Cut-off:5.4 Sensitivity 66.7% Cut-off: 5.5 (maximal effectiveness) Sensitivity 63.5% Cut-off:5.6 (ADA criterion) Sensitivity 62.6% **Fructosamine (FRA)** Cut-off: 234 Sensitivity 69.0% Cut-off: 276 Sensitivity 33.7% Cut-off: 247 (maximal effectiveness) Sensitivity 58.3% **HbA1c** Cut-off 4.81 Sensitivity 67.0% Cut-off 5.28 Sensitivity 51.3% Cut-off 5.29 Sensitivity 51.3% Cut-off	
Specificity (%) for diagnosis of IGT / IFG	**FCG** Cut-off: 4.9 Specificity 77.1% Cut-off:5.4 Specificity 96.2% Cut-off: 5.5 (maximal effectiveness) Specificity 99.4% Cut-off:5.6 (ADA criterion) Specificity 100% **Fructosamine (FRA)** Cut-off: 234 Specificity 69.3% Cut-off: 276 Specificity 95.2% Cut-off: 247 (maximal effectiveness) Specificity 83.6% **HbA1c** Cut-off 4.81 Specificity 67.2% Cut-off 5.28 Specificity 95.0% Cut-off 5.29 Specificity 95.8%	
Positive and Negative-predictive values (%) for IGT / IFG	NR	
AuRoc Value	FCG 0.865 (± 0.017) FRA 0.748 (± 0.024) HbA1c 0.777 (± 0.03)	
Reported optimal threshold	FCG 5.6% FRA 247 HbA1c 5.29%	
Follow up	NR	
Other properties	NR	
Cost Effectiveness	NR	
Authors conclusions	In our study, in patients in whom 2h-CG values were in IGT range, FCG value in 74.74% of them was within normal range, and in 25.26% in the IFG range according to ADA. These results are similar to those of the analysis conducted by DECODE Study Group (70% and 23%, respectively). Our study confirms that FPG value is limited in identification of the patients with IGT. Therefore, in detecting mild abnormalities of glucose tolerance OGTT seems	

	still to have importance. We found higher correlation between FCG and HbA1c (r=0.66) than between 2h-CG and HbA1c (r=0.602). We also found higher correlation between 2h-CG and fructosamine than between FCG and fructosamine. Combined use of FCG and fructosamine allowed better prediction of 2-hour post-load glucose combined use of FCG and HbA1c. Although HbA1c alone correlated better with 2h-CG than FRA (the difference was not statistically significant), in contrast to FRA it was strongly correlated with FCG, so adding HbA1c to FCG did not bring more information in predicting 2h-CG because of the effect of redundance. Adding FRA to FCG helped in higher degree to predict 2h-CG, because its high values probably reflected high post-load glycaemia even in patients with normal fasting glucose. Combined use of FCG, FRA and HbA1c did not significantly improve prediction of 2-hour post-load glycaemia compared to combined use of FCG and FRA. These findings could have importance in case of IGT patients, in whom FPG alone allows to qualify only 29% of them to IFG group. It would allow to increase sensitivity in detecting this abnormality, being potential risk factor of developing diabetes. In summary, our study showed that among three examined parameters, FCG is the most effective in detecting glucose tolerance abnormalities and predicting 2-hour postload glycaemia in OGTT. An additional parameter, whose determination combined with FCG measurement brings some benefits in detecting IGT, is serum fructosamine concentration. The oral glucose tolerance test remains an irreplaceable diagnostic tool in detecting diabetes, and particularly other glucose tolerance abnormalities (IGT).	
Quality Assessment	-	2/6
Study	**Author:** Hu **Year** 2009 **Country:** China **Study design:** Diagnostic accuracy study	
Study Aim	To assess the validity of combined use of fasting plasma glucose (FPG) and glycated hemoglobin A1c (HbA1c) as screening tests for diabetes and impaired glucose tolerance (IGT) in high-risk subjects.	
Screening tool	Combined use of fasting plasma glucose (FPG) and HbA_{1c}	
Setting / Delivered by	Subjects went to the Diabetes and Endocrine Department of Shanghai Renji Hospital for screening	
Characteristics targeted		
Population	**Sample:** 2,298 Chinese Han nationality subjects aged over 18 years of age with known risk factors for diabetes **Males:** All subjects 956/2298 (41.6%), NGT 304/830 (36.6%), IFG 43/110 (39.1%), IGT 149/380 (39.2%), IFG+IGT 78/183 (42.6%), undiagnosed diabetes 382/795 (48.1%). **Mean age**: All subjects 54.2 years (SD 13.3), NGT 48.7 ± 14.9, IFG 55.5 ± 9.7, IGT 52.8 ± 13.5, IFG+IGT 57.1 ± 10/9, undiagnosed diabetes 54.7 ± 11.3. **Mean BMI**: Not reported **Waist circumference:** Not reported **Other**: Prevalence of pre-diabetes in sample = 16.5%	Data on subjects came from a hospital's medical examination database. High risk subjects were those that had the risk factors that included a family history of diabetes, a history of gestational diabetes, obesity (BMI ≥ 25 kg/m^2), and a history of impaired glucose tolerance. Subjects were split into five groups using 1999 World Health organisation criteria, the groups were normal glucose tolerance (NGT), impaired fasting glucose (IFG), impaired glucose tolerance (IGT), IFG and IGT, and newly diagnosed diabetes.
No of Items	N/A	
Time to complete	N/A	
Reference standard used	The test was performed after three days of normal carbohydrate intake and physical activity and venous blood	

	samples were drawn after an overnight fast of at least 10 hours. Oral glucose tolerance test (OGTT was performed with 75-g glucose and FPG and two hour PG were measured together with $HbA_{1c,}$ 1999 WHO criteria were used.	
Index and Comparitor tests	FPG HbA_{1c} was measured by the high-performance liquid chromatography (HPLC) method with a BIO-RAD analyser.	
Sensitivity (%) for diagnosis of IGT	FPG ≥ 5.6 mmol/l 64.1% (95% CI 61.7 – 66.5) FPG ≥ 6.1 mmol/l 32.4% (95% CI 30.0 – 34.8) HbA_{1c} ≥ 5.6% 66.2% (95% CI 63.8 – 68.6) FPG ≥ 5.6 mmol/l and HbA_{1c} ≥ 5.6% 42.4% (95% CI 39.9 – 44.9) FPG ≥ 5.6 mmol/l or HbA_{1c} ≥ 5.6% 87.9% (95% CI 86.3 – 89.5)	Subjects with undiagnosed diabetes were excluded in the calculation of sensitivity and specificity for IGT.
Specificity (%) for diagnosis of IGT	FPG ≥ 5.6 mmol/l 65.4% (95% CI 63.0 – 67.8) FPG ≥ 6.1 mmol/l 88.3% (95% CI 86.7 – 89.9) HbA_{1c} ≥ 5.6% 51.0% (95% CI 48.5 – 53,5) FPG ≥ 5.6 mmol/l and HbA_{1c} ≥ 5.6% 82.4% (95% CI 80.5 – 84.3) FPG ≥ 5.6 mmol/l or HbA_{1c} ≥ 5.6% 33.4% (95% CI 31.0 – 35.8)	
Positive and Negative-predictive values (%) for IGT	Not reported	
Roc Value	Poorly reported	Poorly reported
Reported optimal threshold	The optimal cut point of FPG for detecting IGT diagnosed by OGTT was 5.6 mmol/l and for HbA_{1c} it was 5.6%	
Follow up	Not reported	
Other properties		
Cost Effectiveness	Not reported	
Reviewer comments	The authors make the point that only Shanghai Han nationality subjects participated and that the high risk group in the study were not representative of the general population.	
Authors conclusions	The authors concluded that compared with FPG or HbA_{1c} alone, the simultaneous measurement of FPG and HbA_{1c} (FPG and/or HbA_{1c}) might be a more sensitive and specific screening tool for identifying high-risk individuals with diabetes and IGT at an early stage.	
Quality Assessment	+	
Study	**Author:** Janssen **Year** 2007 **Country:** Netherlands **Study design:** Diagnostic accuracy study	
Study Aim	To evaluate the efficiency of population-based screening for Type 2 diabetes.	
Screening tool	Two stepwise population-based screening procedures were performed. The first screening procedure consisted of four steps, a questionnaire, random glucose measurement, fasting glucose measurement and oral glucose tolerance test (OGTT) and was carried out from May 2002 to January 2003. The second procedure (from July 2003 to April 2004) consisted of three steps (without random glucose measurement).	
Setting / Delivered by	A regional laboratory	
Characteristics targeted	Age, gender, BMI.	
Population	**Sample:** 17,883, of these, 11,028 were on the four step screening procedure and 6,855 were on the three step screening procedure. **Males**: 44.7% four step screening procedure, 45.1% three step screening procedure. **Mean age**: Not reported **Mean BMI**: Not reported	

	Waist circumference: Not reported **Other**:	
No of Items	N/A	
Time to complete	N/A	
Reference standard used	N/A	
Index and Comparitor tests	In the four-step screening procedure, the first step consisted of the questionnaire (Step 1). Participants with a score >4 points were invited for a random blood glucose (RBG) measurement (Step 2). If RBG >5.5 mmol/l, a fasting blood glucose (FBG) was measured (Step 3). Participants with an RBG >11.1 mmol/l and FBG >6.0 mmol/l were diagnosed as diabetic patients. Those with FBG >6.0 mmol/l but RBG <11.1 mmol/l were invited for further diagnostic testing by means of a standard 75-g oral glucose tolerance test (OGTT) (Step 4). The three-step screening procedure, only capillary blood samples were taken, due to cost implications, Participants with a score >6 points on the questionnaire (Step 1) were invited for FBG measurement (Step 2). RBG measurement was not performed. If FBG >6.0 mmol/l, a capillary OGTT followed (Step 3).	
Sensitivity (%) for diagnosis of IGT	Not reported	
Specificity (%) for diagnosis of IGT	Not reported	
Positive and Negative-predictive values (%) for IGT	Not reported	
AuRoc Value	Not reported	
Reported optimal threshold	Not reported	
Follow up	Not reported	
Other properties	Not reported	
Cost Effectiveness	Not reported	
Reviewer comments	The authors reported that approximately one-third (31.4%, 17,883/56,978) of patients from the general practices showed up to undergo glucose testing. A further three quarters (76.6%, 1300/1698) of those invited for the OGTT showed up. This indicates a drop-out rate of 23.4% of people invited for an OGTT. It was reported that the yield of the diabetes screening programme was low, (1.0% of those invited were diagnosed with diabetes), the yields from the two procedures were not significantly different (1.0% for the four step procedure and 1.1% for the three step procedure). It was commented on by the authors that a considerable number of people who might be at high risk for diabetes did not attend the screening at all. Since dropout rates were high among high-risk individuals within both screening procedures, it is unlikely that the comparison is distorted.	
Authors conclusions	The authors concluded that in the Netherlands, the yield of population-based screening is low. The dropout among high-risk individuals was high. Given the decreasing prevalence of undiagnosed diabetes and the possibility of opportunistic screening on a continuous basis, opportunistic screening for diabetes might be more appropriate than population-based screening.	
Quality Assessment	-	
Study	**Author:** Lidfelt **Year:** 2001 **Country:** Sweden **Study design:**	
Aim of Study	To evaluate a screening procedure for detecting high-yield candidates for an OGTT in a population of middle-aged Swedish women.	Women of 50-59 are stated to be at increased risk of CVD, losing their previous advantage over men.

Screening tool	**Name /Type:** 2-step procedure: 1) Questionnaire – present and previous diseases, drug treatment, family history of T2D. 2) Laboratory examination and physical examination; weight, height, waist hip circumference (WHR), BP, Random Capillary Blood Glucose, non-fasting lipid profile. Those with one or more positive screening variable were offered OGTT.	
Setting / Delivered by	NR	
Characteristics targeted	Weight, height, waist hip circumference (WHR), BP, Random Capillary Blood Glucose, non-fasting lipid profile.	
Population	**Sample:** All women aged 50-59 years (1935-1945) from 5 communities of Lund, Sweden. 6917 out of 10,766 (64.2%) women agreed to participate. **Males:** N/A **Mean age**: All: 56.4 (SD 3.0). 56.4 (SD 2.9) in NFG/NGT; rising through the groups to 57.7 (SD2.9) in diabetes. **Mean BMI**: All: 25.4 (4.1) Highest mean was for IFG/IGT (29.7; SD 5.3) **WHR**: All: 0.78 (0.06) Highest mean was for IFG/IGT (0.84; SD 0.07) **Other**: Those with known diabetes, stroke or MI previous year, severe concurrent disease were excluded. Prevalence of pre-diabetes in the sample = 3.7%	
No of Items	N/A	
Time to complete	N/A	
Reference standard used	OGTT NGT = <5.6 mmol/l and normal 2h-glucose <6.7 mmol/l. IFG/NGT = normal fasting glucose and 2h-glucose 6.7-9.9 mmol/l IFG/IGT = fasting glucose 5.6-6.0 mmol/l and 2h-glucose 6.7-9.9 mmol/l.	
Index and Comparitor tests	2 step as above	
Sensitivity (%) for diagnosis of IGT / IFG	5.29% for RF and RCBG 70.1% based on findings of the control sample (n=300) If IFG/NGT was added to the 'normal' group, making OGTT obligatory for diagnosis, sensitivity would be 79.7%	
Specificity (%) for diagnosis of IGT / IFG	55.1% based on findings of the control sample (n=300) if IFG/NGT was added to the 'normal' group, making OGTT obligatory for diagnosis, specificity would be 55.5%	
Positive and Negative-predictive values (%) for IGT / IFG	PPV 33.6%; NPV 85.1% based on findings of the control sample (n=300) f IFG/NGT was added to the 'normal' group, making OGTT obligatory for diagnosis, PPV would be 29.0%, NPV 92.3%	
AuRoc Value	NR	
Reported optimal threshold	N/A	
Follow up	3593 had a positive screening outcome, of whom 2923 had an OGTT. 3324 had a negative screening outcome. Of these, from 300 control group women, 221 had an OGTT. Lack of time was given as a reason for not attending the follow-up. More non-participants than participants died during 1995-99 (2.6% vs. 0.2% p<0.001) as well as during the following 2 years. The main cause of death was cancer in non-participants (64/99) and participants (10/12) 14/99 non-participant deaths were due to CVD (not diabetes related), vs. 0 in the participating group. Women with positive screening outcome who attended follow-up (n=2923) had higher DBP (p<0.001), B-glucose (p<0.01) and S-triglycerides (p<0.05) compared to those that did not attend follow-up (n=536). In women with negative screening outcome, WHR was lower (p,0.05) in the control group attending follow-up (n=221) compared to other women with negative screening outcome (n=3016 + 79 = 3095).	Take-up data

	OGTT results in positive screens: – 1940 (66.4%) had NFG/NGT; 134 (4.6%) had IFG/IGT; 517 (17.7%) had NFG/IGT; 109 (3.7%) had IFG/IGT and 223 (7.6%) had diabetes.	
Other properties	The 2 most striking positive variables were S-triglycerides and BP, occurring in 18.4% and 18.1% respectively.	
Cost Effectiveness	NR	
Authors conclusions	In this population-based study, 64% participated. The non-participating group had a higher death rate, though not due to diabetes-related diseases. Women who were invited to, but did not attend for OGTT (536 with positive screening and 79 controls with negative screening outcomes) were no different to attendees in terms of primary screening variables (risk factors). In the positive screening outcome group, 17.7% had NFG/IGT, 3.7% IFG/IGT and almost 8% had previously unknown diabetes (about x4 of those negatively screened). There were no differences in groups for IFG/NGT. The risk factor variables were not associated in this study with the presence of IFG. The sensitivity (70%) of the instrument was sufficient, though the PPV was only 34%, suggesting a high rate of false positives. However the figures were based on presumed prevalence in the non-participating and negative screening groups. In addition, changing the risk factor variables (deleting drug treatment of hyperlipidaemia, family history of diabetes and hypertriglyceridaemia) would give a specificity of 66%, with sensitivity lowered to 62%. Both sensitivity and specificity would be higher (80% and 56% respectively) if IFG/NGT was deleted, with these participants being regarded as normal. In summary, a high prevalence of unknown impaired glucose metabolism was found in middle-aged women with a positive screening profile.	
Quality Assessment	++	5/6
Study	**Author:** Luders **Year** 2005 **Country:** Germany **Study design:** Evaluation	
Screening tool	**Name:** PreDiSc study **Type:** STIX	
Setting / Delivered by		
Characteristics targeted		
Population	**Sample:** 34 practices, involving general medical practitioners, internists and diabetes consultants. 267 patients with known treated hypertension (≥140/ ≥90mmHg), or untreated hypertension (≥140/ ≥90mmHg), and older than 18 years. **Males:** 48% **Mean age**: 60.9 **Mean BMI**: 30.7 kg/m2. **Waist circumference:** **Other**: Eligibility: If the STIX value was in the range of 100–130 mg/dl, the patients would have been screened for further inclusion criteria. The patients would have been eligible to participate in the PreDiSc study, if at least one of the following inclusion criteria had been found – body mass index (BMI) of ≥25 kg/m2 or a previous history of impaired glucose tolerance or diabetes mellitus in parents or siblings. Prevalence of pre-diabetes in the sample = 37% (HbA1c ≥ 6 mmol/l)	
No of Items	N/A	
Time to complete	N/A	

Reference standard used	OGTT	
Index and Comparitor tests	The capillary fasting glucose value was determined with a commercial Stix measuring device (STIX, Glucostix, Bayer, Leverkusen, Germany).	
Sensitivity (%) for diagnosis of IGT / IFG	HbA1c of ≥6%, glucose in the venous blood of≥110 mg/dl and age of ≥55 years has a sensitivity of 82%. HbA1c 58% Fasting glucose 62% HbA1c1 + fasting glucose 61% HbA1c1 + fasting glucose + age 82% HbA1c1 + fasting glucose+ age + SBP 79% HbA1c1 + fasting glucose + age + SBP + waist 83%	SBP = Systolic Blood Pressure
Specificity (%) for diagnosis of IGT / IFG	HbA1c of ≥6%, glucose in the venous blood of≥110 mg/dl and age of ≥55 years has a specificity of 76% HbA1c 84% Fasting glucose 57% HbA1c1 + fasting glucose 78% HbA1c1 + fasting glucose + age 76% HbA1c1 + fasting glucose+ age + SBP 74% HbA1c1 + fasting glucose + age + SBP + waist 76%	
Positive and Negative-predictive values (%) for IGT / IFG	PPV78% ; NPV 60% HbA1c 79 66 Fasting glucose 60 59 HbA1c1 + fasting glucose PPV 78% NPV 60% HbA1c1 + fasting glucose + age PPV 81% NPV 74% HbA1c1 + fasting glucose+ age + SBP PPV 79% NPV 74% HbA1c1 + fasting glucose + age + SBP + waist PPV 80% NPV 82%	
AuRoc Value	HbA1c 0.614 Fasting glucose 0.671 HbA1c1 + fasting glucose 0.688 HbA1c1 + fasting glucose + age 0.716 HbA1c1 + fasting glucose+ age + SBP 0.722 HbA1c1 + fasting glucose + age + SBP + waist 0.724	
Reported optimal threshold	HbA1c ≥ 6mmol/l	
Follow up	NR	
Other properties	An OGTT value was determined for 260 patients (148 of these had been in the 'suspect' range following the STIX test). A comparison of the percentage frequency of concomitant risk factors (familial diabetes, familial hyperlipidaemia and familial hypertension) in the two groups did not show any significant differences.	
Cost Effectiveness	NR	
Authors conclusions	The close correspondence between STIX screening and enzymatic determination in the venous blood was confirmed by the fact that the absolute differences were <10%. The difference in the percentage frequency of the normal 2-h OGTT category (<140 mg/dl) may be explained by the lower cut-off for the STIX measurement. As this started at 100 mg/dL, whereas the glucose determination method only started at 110 mg/dL, it is no surprise that the rate of 'normal' OGTT findings is higher in the STIX group. Because impaired glucose tolerance in patients suffering from hypertension results in an increased risk of cardiovascular disease, it needs to be recognized and treated at an early stage. The OGTT, which is regarded as the diagnostic gold standard in this context, is not fully accepted in daily clinical practice because of its cumbersome	

	nature. Therefore, various specialist associations, such as the American Diabetes Association or the Deutsche Diabetes Gesellschaft (German Diabetes Association), recommend that screening for impaired glucose tolerance be simplified in the form of the easier-to-perform and less expensive determination of fasting glucose. Impaired glucose tolerance should be suspected, if fasting glucose is ≥126 mg/dl on a second measurement. Although this screening method is much simpler to perform than the OGTT, it does have the drawback that its diagnostic sensitivity is very low (19%). Sole use of an HbA1c value of ≥6% or the sole use of an isolated fasting glucose value of ≥110 mg/dl is only sensitive to the existence of impaired glucose tolerance. Only 50% (51/101) of all patients with impaired glucose tolerance were identified with the sole use of an HbA1c value of >6%. Sixty-seven per cent (68/101) of patients were identified with a fasting glucose value of >110 mg/dl. This result confirms the criticism voiced by other investigators with regard to the use of the isolated measurement of only one of the two parameters. If both parameters are used, the diagnostic value increases significantly (sensitivity 61%, specificity 78%, positive predictive value 78% and negative predictive value 60%).	
Quality Assessment	+	4/6
Study	**Author:** Mannucci **Year** 2003 **Country:** Italy **Study design:** Assessment of a screening strategy.	
Study Aims	To assess the sensitivity and specificity of FPG and HbA1C in diagnosing diabetes and IGT, determined by oral glucose tolerance test (OGTT).	
Screening tool	**Name**: FPG and HbA1c Type: Plasma and whole blood tests.	
Setting / Delivered by	Medical doctors with general practices	
Characteristics targeted	N/A	
Population	**Sample:** All 67 000 residents of Bagno a Ripoli (a suburban community in the outskirts of Florence) aged 30–70 years were invited, through newspaper and television announcements and posters, to participate in the study. **Males:** Men (n=567) Women (n=648) took part in the study. **Mean age**: Men 52.2 (±19.5) Women 52.0 (±17.6) **Mean BMI**: Men 26.7 (±3.5) Women 25.4 (±4.5) **Waist circumference:** Men 92.8 (±10.4) Women 85.0 (±11.4) **Other**: A detailed personal and family medical history was collected; weight and height were measured without shoes and in light clothing, while waist and hip circumferences were measured according to WHO recommendations. Diagnosis of diabetes was made in 53 men (9.3%) and 27 women (4.2%). Impaired fasting glucose (fasting glycaemia, 6.3–6.9 mmol/l) was diagnosed in 161 subjects including 107 men (19.0%) and 54 women (8.4%). Impaired glucose tolerance was diagnosed in 96 participants, including 61 men (10.8%) and 31 women (4.8%). The prevalence of diabetes, IFG, and IGT was significantly (p<0.05) higher in obese (BMI>30 kg/m2) or overweight (BMI=25–30 kg/m2) subjects when compared to the rest of the sample. The majority of subjects with impaired glucose tolerance had fasting plasma glucose levels within the normal range, while most of those with impaired fasting glucose had normal glucose tolerance. In non-diabetic subjects, IGT and IFG were more frequently associated in obese subjects among men (p<0.05 vs. the rest of the sample), but not among women; prevalences of IFG in individuals with IGT were 23.0%, 40.0%, and 61.1% in men, and 25.0%, 44.4%, and 20.0% in women, among normal-weight, overweight, and obese subjects, respectively. Subjects with combined IFG and IGT had significantly (p<0.05) higher BMI and HbA1C (29.1±4.3 kg/m2, and 5.7%±0.4%, respectively), when compared to those with IFG (27.9±4.2 kg/m2 and 5.5%±0.4%) and IGT (27.6±4.6 kg/m2 and 5.5%±0.5%) only.	

	Prevalence of pre-diabetes = 13.25% IFG, 7.6% IGT	
No of Items	N/A	
Time to complete	N/A	
Reference standard used	OGTT. Glucose tolerance was assessed in all participants. A 75-g oral glucose load (50% solution in water) was administered, and plasma glucose was again measured after 120 min rest.	
Index and Comparitor tests	In the morning, after an overnight fast, venous blood samples were drawn for the determination of HbA1C, lipid profile, and plasma glucose. The upper limit of the reference range for HbA1C in nondiabetic subjects was 5.5%.	
Sensitivity (%) for diagnosis of IGT / IFG	FPG with a threshold of 6.1 mmol/l, has a sensitivity for IGT of 40.9% and 29.0% in men and women, respectively. Using HbA1C >5.5% or FPG >6.1 mmol/l as screening criteria for IGT, sensitivity was 59% and 54.8% respectively, in men and women.	
Specificity (%) for diagnosis of IGT / IFG	FPG with a threshold of 6.1 mmol/l, has a specificity of 25.0% and 18.0%, in men and women, respectively. Using HbA1C >5.5% or FPG >6.1 mmol/l as screening criteria for IGT, specificity was 19.3% and 9.3%, respectively, in men and women.	
Positive and Negative-predictive values (%) for IGT / IFG	NR	
AuRoc Value	NR	
Reported optimal threshold	HbA1c > 5.5%; FPG≥ 6.1; for IGT	
Follow up	NR	
Other properties	N/A	
Cost Effectiveness	NR	
Authors conclusions	The determination of fasting plasma glucose is not useful in the screening of IGT, as previously reported. While glycated haemoglobin alone does not provide any advantage over FPG in the screening of IGT, the combined use of HbA1C and FPG with a threshold of 5.5% (upper limit of normal range) for HbA1C and 6.1 mmol/l for FPG, improves the sensitivity of screening, facilitating the identification of individuals with IGT. While this procedure can be useful for case finding in clinical research, it still fails to detect over one-third of individuals with IGT. Furthermore, the specificity of combined FPG and HbA1C for IGT is not sufficient to recommend this method for systematic screening in the general population. Considering the clinical relevance of diagnosing IGT, periodical screening with OGTT can be recommended in all persons at high risk.	
Quality Assessment	+	4/6
Study	**Author:** Maynard, Rohrscheib, Way, Nguyen & Ediger **Year:** 2007 **Country:** USA **Study design:** Diagnostic accuracy study	
Study Aim	To compare the performance of a novel noninvasive technology to fasting plasma glucose (FPG) and A1C tests for detecting undiagnosed diabetes and impaired glucose tolerance.	
Screening tool	**Name:** Spectroscopic measurement of dermal advanced glycation end products (SAGE) **Type:** A non-invasive device that detects the fluorescence of skin advanced glycation end products	
Setting / Delivered by	University setting? Not reported who delivered the test	
Characteristics targeted	Comparison of SAGE with FPG and A1C assessed using the 2-hour OGTT	
Population	**Sample:** Participants were selected from individuals who responded to flyers and newspaper advertising. Subjects were recruited until the target prevalence of abnormal glucose tolerance was comfortably achieved. Selection criteria were one or more risk factors for diabetes per the American Diabetes Association standard-of-care guidelines.	Reference: American Diabetes Association: Standards of Medical Care in

	Individuals with aprevious diagnosis of diabetes were excluded. When recruiting concluded, 84 subjects with abnormal glucose tolerance had been identified within a cohort of 351 participants. **Males:** 128/351 or 36.5% **Mean age**: NR (range 21 to 86 years) **Mean BMI**: NR **Waist circumference:** NR **Other**: To demonstrate superior sensitivity at 80% power with 95% CI, an abnormality in 80 subjects was required. At that prevalence and for a projected SAGE sensitivity of 68%, the power calculations yield a 95% CI for test sensitivity of 57.8–78.2%. Prevalence of pre-diabetes = 15.6% IGT	Diabetes: 2006 (Position Statement). Diabetes Care 29 (Suppl. 1):S4–S42, 2006 Reference for power calculation: Schatzkin A, Connor RJ, Taylor PR, Bunnag B: Comparing new and old screening tests when a reference procedure cannot be performed on all screenees: example of automated cytometry for early detection of cervical cancer. Am J Epidemiol 125: 672–678, 1987
No of Items	N/A	
Time to complete	Approximately 1 minute	
Reference standard used	OGTT	
Index and Comparitor tests	FPG and A1C assessed using the 2-hour OGTT The screening performance of FPG and A1C tests and SAGE were assessed by comparing their respective sensitivities at a relevant clinical threshold. An appropriate comparative threshold for screening is the FPG threshold for impaired fasting glucose (IFG). All three tests were evaluated at the specificity corresponding to this FPG value (100 mg/dl). SAGE values could range from a possible 0 to 100, and a value of 50 was used for sensitivity The IFG threshold of 100 mg/dl corresponds to an FPG specificity of 77.4%, the critical specificity for comparing the tests.	
Sensitivity (%) for diagnosis of IFG	**SAGE** 74.7% (95% CI 65.4–84%) **FPG** 58.0% **A1C** 63.8% The SAGE had a performance advantage of 16.7% over FPG and 10.9% over A1C in terms of absolute sensitivity and 28.8% over FPG and 17.1% over A1C in terms of relative sensitivity. The sensitivity advantage of the noninvasive device over both blood tests for detecting diabetes and precursors was statistically significant ($P < 0.05$).	
Specificity (%) for diagnosis of IFG	**FPG** 77.4%	
Positive and Negative-predictive values (%) for IGT / IFG/T2DM	NR	
AuRoc Value	**SAGE** 79.7% **FPG** 72.1% **A1C** 79.2% The general performance metric of area under the curve (AUC) shows a statistically significant advantage ($P < 0.05$) for SAGE versus FPG testing. The AUC values for SAGE versus A1C testing were not statistically separable. The Hoorn coefficient of variation of SAGE, quantifying the intersession reproducibility of the non-invasive instrument, was 9.4%.	
Reported optimal threshold	Not an outcome – a threshold of 50 was used as a critical specificity threshold	
Follow up		

Other properties		
Cost Effectiveness	Not assessed	
Authors conclusions	The noninvasive technology showed clinical performance advantages over both FPG and A1C testing. The sensitivity differential indicated that the noninvasive device is capable of identifying 28.8% more individuals in the OGTT-defined positive screening class than FPG testing and 17.1% more than A1C testing. The combination of higher sensitivity and greater convenience—rapid results with no fasting or blood draws—makes the device well suited for opportunistic screening.	
Quality Assessment	-	2/6
Study	**Author:** Mohan, Vijayachandrinka, Gokulakrishnan, Anjana, Ganesan, Weber & Narayan **Year:** 2010 **Country:** India **Study design:** Diagnostic accuracy study	
Study Aim	To determine A1C cut points for glucose intolerance in Asian Indians.	
Screening tool	**Name:** A1C	
Setting / Delivered by	Setting not reported, although data was collected as part of the CURES study – referenced. Not reported who delivered the test.	
Characteristics targeted	A1C cut points to determine glucose intolerance in Indian Asians relative to fasting plasma glucose (FPG).	
Population	**Sample:** Participants were recruited through systematic stratified random sampling, where 46 of the 55 wards in Chennai, India were selected for sampling, providing a total sample size of 26,001 individuals aged ≥20 years. From this pool, every 10th participant recruited (2600) was invited for detailed testing, including an oral glucose tolerance test (OGTT) in those without self-reported diabetes, and the response rate was 90% (2,350 of 2,600 participants). Of the 2,350 subjects who received an OGTT, A1C was measured in 2,188 participants (response rate 93.1%). **Males:** NR **Mean age**: 37 ± 12 years in those with normal glucose tolerance (NGT), 43 ± 13 in those with prediabetes (IFG & IGT) and 45 ± 11 in those with newly diagnosed diabetes (NDD) **Mean BMI**: 22.6 ± 4.0 kg/m^2 in those with NGT, 24.2 ± 3.5 in those with prediabetes and 24.2 ± 3.1 in those with NDD **Waist circumference:** 81.6 ± 11.4 cm in those with NGT, 86.9 ± 10.3 in those with prediabetes and 88.5 ± 9.0 in those with NDD **Other:** Among the 2,188 participants who had both OGTT and A1C tests, 1,710 (78.2%) had NGT, 258 (11.8%) had IGT, and 220 (10.1%) had newly diagnosed diabetes (NDD). Prevalence of pre-diabetes = 11.8% IGT	
No of Items	N/A	
Time to complete	NR	
Reference standard used	OGTT measuring FPG and 2-hr postload (75-g) plasma glucose (glucose oxidase-peroxidase method). IGT was defined as 2-h postload plasma glucose ≥140 mg/dl (7.8 mmol/l) and <200 mg/dl (11.1 mmol/l) by WHO Criteria. IFG was defined using ADA criteria if FPG was ≥100 mg/dl (5.5 mmol/l) and <126 mg/dl (7 mmol/l) and using WHO criteria if FPG was ≥110 mg/dl (6.1mmol/l) and <126 mg/dl (7 mmol/l).	
Index and Comparitor tests	A1C Receiver operating characteristic curves were plotted using sensitivity and 1 - specificity for different cut points of A1C, taking the diagnosis of diabetes, IGT, or IFG based on various plasma glucose criteria as the gold standard.	
Sensitivity (%) for diagnosis of IFG/IGT	**IGT** **2-hr PG** ≥140 mg/dl and <200 mg/dl, **A1C** 5.9 ± 0.6, **optimal A1C cut point** 5.6 – 65.6%	

	IFG **FPG (WHO)** ≥110 mg/dl and <126 mg/dl, **A1C** 5.7 ± 0.3, **optimal A1C cut point** 5.6 – 60.0% **FPG (ADA)** ≥110 mg/dl and <126 mg/dl, **A1C** 5.8 ± 0.5, **optimal A1C cut point** 5.6 – 65.1% Considerable overlap was identified among those with NGT, IGT, and diabetes with respect to the A1C levels. Using a cut point of 5.6%, 73.6% of those with IGT and/or IFG (using WHO criteria) and 72.8% of subjects with IFG (using ADA criteria) would be correctly identified.	
Specificity (%) for diagnosis of IFG/IGT	**IGT** **2-hr PG** ≥140 mg/dl and <200 mg/dl, **A1C** 5.9 ± 0.6, **optimal A1C cut point** 5.6 – 62.1% **IFG** **FPG (WHO)** ≥110 mg/dl and <126 mg/dl, **A1C** 5.7 ± 0.3, **optimal A1C cut point** 5.6 – 56.5% **FPG (ADA)** ≥110 mg/dl and <126 mg/dl, **A1C** 5.8 ± 0.5, **optimal A1C cut point** 5.6 – 63.4%	
Positive and Negative-predictive values (%) for IGT / IFG/T2DM	**PPVs:** **IGT** **2-hr PG** ≥140 mg/dl and <200 mg/dl, **A1C** 5.9 ± 0.6, **optimal A1C cut point** 5.6 – 19.9 **IFG** **FPG (WHO)** ≥110 mg/dl and <126 mg/dl, **A1C** 5.7 ± 0.3, **optimal A1C cut point** 5.6 – 0.8 **FPG (ADA)** ≥110 mg/dl and <126 mg/dl, **A1C** 5.8 ± 0.5, **optimal A1C cut point** 5.6 – 8.3	
AuRoc Value	**IGT** **2-hr PG** ≥140 mg/dl and <200 mg/dl, **A1C** 5.9 ± 0.6, **optimal A1C cut point** 5.6 – 0.708 **IFG** **FPG (WHO)** ≥110 mg/dl and <126 mg/dl, **A1C** 5.7 ± 0.3, **optimal A1C cut point** 5.6 – 0.632 **FPG (ADA)** ≥110 mg/dl and <126 mg/dl, **A1C** 5.8 ± 0.5, **optimal A1C cut point** 5.6 – 0.708	
Reported optimal threshold	A1C cut points of 5.6 for IGT (119 mg/dl [6.6 mmol/l]) and 5.6 and 5.6 respectively for two definitions of IFG (WHO 118 mg/dl and ADA 113 mg/dl) maximized the sensitivity and specificity.	
Follow up		
Other properties		
Cost Effectiveness	Not assessed	
Reviewer comments		
Authors' conclusions	This population based data suggest that an A1C cut point of 5.6% would identify those with IGT and/or IFG with optimal specificity and sensitivity, but the accuracy is only 69–74%.	
Quality Assessment	+	
Study	**ID:** # 3778 **Author:** Mostafa **Year** 2010 **Country:** UK **Study design:** Assessment of a blood glucose indicator	
Study Aims	To investigate the potential impact of the use of (a) HbA1c 6.0– 6.4% and (b) HbA1c 5.7–6.4% on the prevalence, phenotype, clinical characteristics and cardiovascular disease (CVD) risk of people classified as having 'IGR'. To briefly examine the impact on prevalence using the ADA definition of IFG (5.6–6.9 mmol/l). To determine the optimal HbA1c cut-points for detecting IGR within a multi-ethnic cohort.	
Screening tool	**Name**: HbA1c	
Setting / Delivered by	Leicestershire, UK Primary Care	

Characteristics targeted	Ethnicity	
Population	**Sample:**.Leicester Ethnic Atherosclerosis and Diabetes Risk (LEADER) cohort First screening programme (n = 8696 under 40 and completing OGTT) 74.7% white European 22.8% South Asian White Europeans (5.66%, SD 0.61) had a significantly lower mean HbA1c compared to south Asians (5.86%, SD 0.62), p < 0.0001. 66.8% isolated IGT, 17.4% isolated IFG and 15.8% combined IGT/IFG HbA1c 6.0–6.4%, identified, n = 1610 (18.5%) more cases (1.1-fold increase in prevalence of people classified as having 'IGR' (1.1- and 1.5-fold in white Europeans and south Asians, respectively, p < 0.0001). 75% with at least one risk factor for diabetes (n = 2413) 71.3% white European 25.9% South Asian 2.8% Other ethnicities 29 (1.3%) with IFG / IGT **Males:**.47.7% **Mean age**: 40 – 75 years (57.3) **Mean HbA1c** = 5.71% (SD 0.61) Second screening programme - unselected population from ADDITION (n = 6283) 73.6% white European 20.9% South Asian 5.5% Other ethnicities 216 (3.4%) with IFG / IGT **Mean BMI**: **Waist circumference:** **Other**:	
No of Items	N/A	
Time to complete	N/A	
Reference standard used	OGTT (75g) according to WHO 1999 criteria	
Index and Comparitor tests	HbA1c	
Sensitivity (%) for diagnosis of IGT / IFG	HbA1c ≥ 6.0% White Europeans = 39.5% (CI 36.3–42.7) Optimal cut point HbA1c ≥5.8% = 61.5% (CI 58.2–64.4) south Asians 63.8% (CI 58.6–68.7) HbA1c ≥5.7%, White Europeans 70.5% (CI 67.4–73.4%) south Asians 85.6% (CI 81.4–88.9)	
Specificity (%) for diagnosis of IGT / IFG	HbA1c ≥ 6.0% White Europeans 83.5% (CI 82.5–84.5)	

	south Asians HbA1c ≥ 6.0% 69.4% (CI 67.1–71.6) Optimal cut point White European HbA1c ≥5.8% =67.9% (CI 66.6–69.1) HbA1c ≥5.7%, White Europeans 57.9% (CI 56.6–59.2); south Asians 41.3 (CI 38.9–43.7)	
Positive and Negative-predictive values (%) for IGT / IFG	White Europeans PPV 0.80; NPV 0.21 south Asians PPV 0.30; NPV 0.73	
AuRoc Value	0.69 (CI 0.68–0.71) however in white Europeans and south Asians these were 0.69 (CI 0.67–0.71) and 0.72 (CI 0.69–0.75) respectively.	
Reported optimal threshold	White Europeans HbA1c ≥ 5.8% south Asians ≥ HbA1c ≥ 6.0% white Europeans aged 40–59 = 5.7% 60–75 years = 5.9% south Asians produced similar optimal HbA1c cut-points of 6.0% in each age group	
Follow up	NR	
Other properties	NR	
Cost Effectiveness	NR	
Reviewer comments		
Authors conclusions	Only 477 (5.8%) people with both IGR detected on OGTT and HbA1c 6.0– 6.4%, showing a degree of discordance between the two tests. When IGR detected on OGTT was separated into isolated IFG (n = 245), isolated IGT (n = 940) and combined IFG/IGT (n = 222), the latter category had the least proportion of people with HbA1c < 6.0% (30.6%) but the highest proportion with (a) HbA1c 6.0–6.4% (41.4%) and (b) HbA1c ≥ 6.5% (27.9%), p < 0.000. In contrast, individuals with isolated IGT had the highest proportion with HbA1c < 6.0% (61.5%), but the lowest proportion with (a) HbA1c 6.0–6.4% (30.6%) and (b) HbA1c ≥ 6.5% (7.9%), p < 0.0001. Individuals with isolated IGT also had the highest proportion with HbA1c < 5.7% (32.2%) and the lowest proportion with HbA1c 5.7–6.4% (59.9%), p < 0.0001. Within each IGR subtype, there were a significantly higher proportion of white Europeans with HbA1c < 6.0% (or HbA1c < 5.7%) in comparison to south Asians; in contrast, there was a significantly lower proportion of white Europeans with HbA1c ≥ 6.5% (all p < 0.0001, except for isolated IFG using ADA HbA1c recommended criteria: p = 0.002). Due to the large degree of discordance in people identified between glucose testing and a single HbA1c cut-point, an alternate method of using two HbA1c cut-points for diagnosis has been suggested. A lower cut-point would 'rule out' diabetes producing high sensitivity, while the upper cut-point would 'rule in' diabetes producing high specificity; so far HbA1c ≥5.5% and ≤ 7.0% respectively have been suggested from an Australian population HbA1c had a sub-optimal AUC (<0.7) suggesting it is a weak tool for detecting IGR, particularly in white Europeans.	
Quality Assessment	+	
Study	**Author:** Phillips **Year:** 2009 **Country:** US **Study design:** Evaluation	
Study Aim	To test the hypothesis that screening could be done with a strategy similar to that used near-universally for gestational diabetes, i.e. a 50 g oral glucose challenge test (GCT) performed at any time of day, regardless of	

	meal status, with one 1 h sample.	
Screening tool	**Name:** A 50 g oral glucose challenge test (GCT) **Type:** 50 g glucose given at any time of day, without a prior fast, and glucose levels are measured one hour later.	
Setting / Delivered by	At the first visit, (which did not require a prior fast), and scheduled during the work day, participants had random plasma glucose and random capillary glucose (RCG) measured. Participants then drank 50 g oral within five minutes, with measurement of plasma and capillary glucose after one hour. At a second visit (average of 13 days after first visit), a 75 g OGTT was begun before 11.00 hours following an overnight fast, with samples at baseline, one and two hours; blood was also obtained for measurement of plasma lipids and HbA1c.	
Characteristics targeted		
Population	**Sample:** 1,573 **Males** 42% **Mean age** 48 years (18 to 87 years range) **Mean BMI** 30.3 **Waist circumference:** **Other**: Prevalence of pre-diabetes = 18.7% pre-diabetes	
No of Items		
Time to complete		
Reference standard used	OGTT	
Index and Comparitor tests	GCT plasma; GCTcap	
Sensitivity (%) for diagnosis of Pre-diabetes	GCT plasma Cut-off, 6.7 mmol/l (mg/dl) 6.7 (120) 89 Cut-off, 7.2 mmol/l (mg/dl) 7.2 (130) 83 Cut-off, 7.8 mmol/l (mg/dl) 7.8 (140) 73 Cut-off, 8.3 mmol/l (mg/dl) 8.3 (150) 59 Cut-off, 8.9 mmol/l (mg/dl) 8.9 (160) 46 Cut-off, 9.4 mmol/l (mg/dl) 9.4 (170) 35 Cut-off, 10.0 mmol/l (mg/dl) 10.0 (180) 28 Cut-off, 10.6 mmol/l (mg/dl) 10.6 (190) 19 GCTcap Cut-off, 7.8 mmol/l (mg/dl) 7.8 (140) 87 Cut-off, 8.3 mmol/l (mg/dl) 8.3 (150) 77 Cut-off, 8.9 mmol/l (mg/dl) 8.9 (160) 67 Cut-off, 9.4 mmol/l (mg/dl) 9.4 (170) 56 Cut-off, 10.0 mmol/l (mg/dl) 10.0 (180) 45 Cut-off, 10.6 mmol/l (mg/dl) 10.6 (190) 31 Cut-off, 11.1 mmol/l (mg/dl) 11.1 (200) 21 Cut-off, 11.7 mmol/l (mg/dl) 11.7 (210) 16	Of the 1,573 participants 4.6% had diabetes, 18.7% pre-diabetes and 23.3% dysglycaemia
Specificity (%) for diagnosis of Pre-diabetes	GCT plasma Cut-off, 6.7 mmol/l (mg/dl) 6.7 (120) 47 Cut-off, 7.2 mmol/l (mg/dl) 7.2 (130) 58 Cut-off, 7.8 mmol/l (mg/dl) 7.8 (140) 68 Cut-off, 8.3 mmol/l (mg/dl) 8.3 (150) 76 Cut-off,8.9 mmol/l (mg/dl) 8.9 (160) 83 Cut-off, 9.4 mmol/l (mg/dl) 9.4 (170) 87	

	Cut-off, 10.0 mmol/l (mg/dl) 10.0 (180) 91 Cut-off, 10.6 mmol/l (mg/dl) 10.6 (190) 94 GCTcap Cut-off, 7.8 mmol/l (mg/dl) 7.8 (140) 44 Cut-off,8.3 mmol/l (mg/dl) 8.3 (150) 56 Cut-off, 8.9 mmol/l (mg/dl) 8.9 (160) 65 Cut-off, 9.4 mmol/l (mg/dl) 9.4 (170) 72 Cut-off, 10.0 mmol/l (mg/dl) 10.0 (180) 80 Cut-off,10.6 mmol/l (mg/dl) 10.6 (190) 86 Cut-off, 11.1 mmol/l (mg/dl) 11.1 (200) 90 Cut-off, 11. 7 mmol/l (mg/dl) 11.7 (210) 93	
Positive and Negative-predictive values (%) for Pre-diabetes	GCT plasma Cut-off, 6.7 mmol/l (mg/dl) PPV 28 NPV 95 Cut-off, 7.2 mmol/l (mg/dl) PPV 31 NPV 94 Cut-off, 7.8 mmol/l (mg/dl) PPV 34 NPV 92 Cut-off, 8.3 mmol/l (mg/dl) PPV 37 NPV 89 Cut-off, 8.9 mmol/l (mg/dl) PPV 39 NPV 87 Cut-off, 9.4 mmol/l (mg/dl) PPV 38 NPV 85 Cut-off, 10.0 mmol/l (mg/dl) PPV 42 NPV 84 Cut-off, 10.6 mmol/l (mg/dl) PPV 41 NPV 83 GCTcap Cut-off, 7.8 mmol/l (mg/dl) PPV 26 NPV 93 Cut-off, 8.3 mmol/l (mg/dl) PPV 29 NPV 91 Cut-off, 8.9 mmol/l (mg/dl) PPV 30 NPV 89 Cut-off, 9.4 mmol/l (mg/dl) PPV 32 NPV 88 Cut-off, 10.0 mmol/l (mg/dl) PPV 34 NPV 86 Cut-off, 10.6 mmol/l (mg/dl) PPV 33 NPV 84 Cut-off, 11.1 mmol/l (mg/dl) PPV 32 NPV 83 Cut-off, 11.7 mmol/l (mg/dl) PPV 33 NPV 82	
AuRoc Value	The AROCs were: 0.79 (95% CI 0.76–0.82) to identify pre-diabetes (GCTplasma); 0.73 (95% CI 0.702 – 0.763) (GCTcap)	
Reported optimal threshold	A relatively high-specificity GCTplasma cut-off of 7.8 mmol/l (140 mg/dl) provided good specificity, sensitivity and NPV, with acceptable PPV.	
Follow up	NR	
Other properties	During recruitment, 4,024 individuals expressed initial interest in the study, 2,111 were scheduled for first visits (selected largely on the basis of need to balance participant sex and race), 1,658 completed first visits, 1,581 completed the protocol and 1,573 had complete GCT and OGTT data	Of those expressing interest, uptake was 52.5% (2,111/4,024) Of those scheduled for first visit uptake was 78.5% (1,658/2,111) Of those completing both sessions and having complete data, uptake was 94.9% (1,573/1,658)
Cost Effectiveness	Using current Medicare reimbursements of US$6.64 for a gestational diabetes GCT (including 50 g glucose) and $17.99 for the OGTT, assumed five minutes of medical assistant time would be needed ($1.13) for administration of the glucose and expressed costs per case identified, cases being defined as diabetes and pre-diabetes. The Center for Disease Control group projected the minimum cost of identifying a case of diabetes or pre-diabetes as $176 (comparing RCG, HbA1c, FPG and OGTT) [42] or $172 (comparing RCG, FPG and HbA1c) [35]. However, GCTplasma screening followed, if positive, by an OGTT would incur direct costs of only $84 per case identified; the GCTplasma approach is both more accurate and less expensive.	

Reviewer comments	The study excluded participants that were too ill to attend work.	
Authors conclusions	The authors concluded that widespread use of GCT screening could help improve disease management by permitting early initiation of therapy aimed at preventing or delaying the development of diabetes and its complications.	
Quality Assessment	+	
Study	**Author:** Rolka, Narayan, Thompson, Goldman, Lindenmayer, Alich, Bacall, Benjamin, Lamb, Stuart & Engelgau **Year:** 2001 **Country:** USA **Study design:** Diagnostic accuracy study (risk scores)	
Study Aim	To evaluate the performance, in settings typical of opportunistic and community screening programs, of screening tests currently recommended by the American Diabetes Association (ADA) for detecting undiagnosed diabetes.	
Screening tool	**Name:** American Diabetes Association (ADA) risk assessment questionnaire and capillary blood glucose (CBG) at two cut points.	
Setting / Delivered by	Health centres and community health fairs. Not reported who delivered the test.	
Characteristics targeted	Delivery of a macrosomic (≥9lb) infant (in females) [scoring 1 point], having one or more siblings with diabetes [1 point], having one or more parents with diabetes [1 point], a BMI of ≥27kgm^2 [5 points], aged <65 years and little or no physical activity in most weeks [5 points], being aged 45-64 years [5 points] or being aged ≥65 years [9 points].	
Population	**Sample:** 1,471 volunteers aged ≥20 years were recruited by health care systems serving communities in Springfield, MA; Robeson County, NC; and Providence, Pawtucket, and Central Falls, RI during routine health centre visits and at community health fairs. Those with self-reported previously diagnosed diabetes or who had been pregnant or breastfeeding within the previous 3 months, or had been hospitalised within the previous six months were not eligible to participate in the study. Screening tests were administered at recruitment. **Males:** 30% **Mean age**: 44 years **Mean BMI**: 51% of participants had BMI ≥27kgm^2 **Waist circumference:** NR **Other:** A total of 52% of all participants had a positive score (≥10 points) on the ADA questionnaire; 9.5% had CBG ≥140 mg/dl, and 18.4% had CBG ≥120 mg/dl. Prevalence of pre-diabetes = 15% IFG / IGT	
No of Items	7	
Time to complete	NR	
Reference standard used	OGTT – 2-hr serum glucose (SG) concentrations analysed from 2-hr postload venous blood specimens. IGT was defined as 2-h postload serum glucose ≥140 mg/dl and <200 mg/dl and and IFG was defined as 110–125 mg/dl.	
Index and Comparitor tests	ADA risk assessment questionnaire Whole blood glucose level from a capillary (finger prick) sample (CBG) To investigate how covariates may effect performance characteristics and the choice of appropriate cut points for the CBG, multiple regression models were fit relating CBG to diabetes (FSG ≥126 mg/dl), age (<45 or ≥45 years), postprandial time (<8or ≥8 h), sex, and race/ethnicity (Hispanic, non-Hispanic white, or African-American). We also computed the sensitivity and specificity of the four screening tests for FSG ≥126 mg/dl separately by sex and race/ethnicity.	
Sensitivity (%) for diagnosis of	**Dysglycemia (IFG/IGT)**	

IFG/IGT	**ADA questionnaire** **FSG ≥126 mg/dl** – 72% (69-75) **2-hr SG ≥200 mg/dl** 78% (73-84) **FSG ≥126 mg/dl or 2-hr SG ≥200 mg/dl** 75% (72-79) **CBG ≥140 mg/dl** **FSG ≥126 mg/dl** – 41% (39-43) **2-hr SG ≥200 mg/dl** 33% (31-35) **FSG ≥126 mg/dl or 2-hr SG ≥200 mg/dl** 28% (27-29) **CBG ≥120 mg/dl** **FSG ≥126 mg/dl** – 62% (57-66) **2-hr SG ≥200 mg/dl** 48% (45-50) **FSG ≥126 mg/dl or 2-hr SG ≥200 mg/dl** 44% (41-47) **ADA questionnaire *and* CBG ≥120 mg/dl** **FSG ≥126 mg/dl** – 45% (42-48) **2-hr SG ≥200 mg/dl** 36% (34-39) **FSG ≥126 mg/dl or 2-hr SG ≥200 mg/dl** 32% (30-34) The ADA questionnaire was moderately sensitive (69–78%) for all diagnostic criteria for diabetes and dysglycemia; however, its specificity did not exceed 54%. The cut point of 140 mg/dl for CBG was quite specific (95–97%) for all of the diagnostic criteria but only 56–65% sensitive for diabetes and 28–41% sensitive for dysglycemia. Empirical receiver operating characteristic curves suggest that a CBG cut point of 120 mg/dl may yield a good balance of sensitivity and specificity. Indeed, this test was 75–84% sensitive for diabetes, 44–62% sensitive for dysglycemia and 86–90% specific for all of the diagnostic criteria. Among study participants who had not eaten for ≥8 h (37% of all participants), CBG ≥110 mg/dl was 82–95% sensitive and 86–89% specific for diabetes and 51–80% sensitive and 89–94% specific for dysglycemia. Cut points for the CBG test that were optimal (maximizing the sum of sensitivity and specificity) tended to be lower for younger participants and those with longer postprandial times and higher for men. CBG performed somewhat better (larger areas under the curves) for men than for women and for participants with postprandial time ≥8 h than for those with postprandial time <8 h. The sensitivities and specificities of the four screening tests varied little by race or ethnicity, and we did not find substantial racial or ethnic differences in the performance of CBG for diabetes (FSG ≥126 mg/dl) after controlling for age, postprandial time, and sex.	
Specificity (%) for diagnosis of IFG/IGT	**Dysglycemia (IFG/IGT)** **ADA questionnaire** **FSG ≥126 mg/dl** – 51% (20-52) **2-hr SG ≥200 mg/dl** 53% (52-54) **FSG ≥126 mg/dl or 2-hr SG ≥200 mg/dl** 54% (53-55) **CBG ≥140 mg/dl** **FSG ≥126 mg/dl** – 97% (96-97) **2-hr SG ≥200 mg/dl** 96% (96-97) **FSG ≥126 mg/dl or 2-hr SG ≥200 mg/dl** 97% (97-97) **CBG ≥120 mg/dl** **FSG ≥126 mg/dl** – 90% (89-91) **2-hr SG ≥200 mg/dl** 89% (88-90) **FSG ≥126 mg/dl or 2-hr SG ≥200 mg/dl** 90% (90-91) **ADA questionnaire *and* CBG ≥120 mg/dl** **FSG ≥126 mg/dl** – 95% (94-95) **2-hr SG ≥200 mg/dl** 94% (94-95) **FSG ≥126 mg/dl or 2-hr SG ≥200 mg/dl** 95% (95-96) Detail above also covers specificity	

Positive and Negative-predictive values (%) for IGT / IFG/T2DM	NR	
AuRoc Value	NR (represented diagrammatically but specific values not reported)	
Reported optimal threshold	The combination of a positive ADA questionnaire and CBG ≥120 mg/dl was less sensitive and more specific than either the questionnaire or CBG ≥120 mg/dl alone. A positive score on the ADA questionnaire was a total of ≥10 points.	
Follow up	NR	
Other properties	NR	
Cost Effectiveness	Not assessed	
Authors' conclusions	Low specificity may limit the usefulness of the ADA questionnaire. Lowering the cut point for a casual CBG test (e.g., to 120 mg/dl) may improve sensitivity and still provide adequate specificity.	
Quality Assessment	+	4/6
Study	**Author:** Rush **Year:** 2008 **Country:** New Zealand **Study design:** Evaluation	
Study Aim	To determine the utility of finger-prick point-of-care testing (POCT) of blood glucose for the detection of dysglycaemia.	
Screening tool	**Name:** Finger--prick point-of-care testing (POCT) **Type:** The finger was cleaned and warmed and a blood droplet obtained using a Softclix Pro disposable lancet. An Accu-chek Advantage meter and strips (Roche Diagnostics, Mt Wellington, New Zealand) was used for glucose measurement.	
Setting / Delivered by	At a screening venue (not specified)	
Characteristics targeted	None specified	
Population	**Sample:** 3,225 Self-identified Maori aged ≥28 years **Males** **Mean age** **Mean BMI** **Waist circumference:** **Other**: Self-identified Maori aged ≥ 28 years on 30 September 2004, without known diabetes, members of households with at least one Maori resident, Maori with past gestational diabetes mellitus or with two parents with known diabetes, were also considered eligible. Those terminally ill, unfit to sign a consent form or with known diabetes were excluded. Prevalence of pre-diabetes = 3.6% IFG; 9.3% IGT; 26.1% IGT and IFG	Participants were recruited from the 5,309 enrolled in the Te Wai o Rona Diabetes Prevention Strategy, a randomised cluster controlled trial of intensive lifestyle change, Population characteristics not entered due to inconsistencies in numbers in table
No of Items	N/A	
Time to complete	N/A	
Reference standard used	Glucose was measured using the Hitachi 911 (Hitachi Limited, Tokyo, Japan).	
Index and Comparitor tests	Venous blood sampling and laboratory analysis in screening for and diagnosing diabetes, impaired glucose tolerance (IGT) and impaired fasting glucose (IFG)	
Sensitivity (%) for diagnosis of IGT/IFG	0.44 (0.65, 0.68)	Fasting venous glucose ≥ 6.1 mol/l

Specificity (%) for diagnosis of IGT/IFG	0.94 (0.93–0.94)	
Positive and Negative-predictive values (%) for IGT / IFG	Not reported	
AuRoc Value	For any dysglycaemia was 0.76 (95% CI 0.74–0.79) for the POCT glucose and 0.866 (95% CI 0.85–0.89) for venous laboratory glucose.	
Reported optimal threshold	The optimal screening criteria for IGT and diabetes (where sensitivity equalled specificity) was at 5.4 mmol/l using POCT (68% sensitivity/specificity) and 5.4 mmol/l using venous glucose (77% sensitivity/specificity).	
Follow up	NR	
Other properties	Authors identified one possible barrier in that asking people to report to a screening site, to fast in the morning and then to wait for two hours after drinking the oral glucose would increase participant burden. The identified benefit was that finger-prick samples are relatively easy in collection compared with venous samples, particularly in the obese.	
Cost Effectiveness		
Barriers / Facilitators	Individual variation in terms of time and physiology affecting blood glucose. Variation in instrument precision. Differences between plasma and blood glucose make comparisons difficult.	
Reviewer comments	Data not clearly reported	
Authors conclusions	The authors believed that screening using POCT and then applying a diagnostic test is unlikely to save time and money and that POCT for the diagnosis of both diabetes and pre-diabetes is too inferior to standard laboratory measures to be recommended for use.	The analysis is limited by the fact that the testing was only undertaken once.
Quality Assessment	-	
Study	**Author:** Saaristo **Year:** 2005 **Country:** Finland **Study design:** Evaluation of Risk Score tool	
Study Aim	To assess the performance of the Finnish Diabetes Risk Score as a screening tool for undetected type 2 diabetes (T2D), abnormal glucose tolerance (AGT) and metabolic syndrome in the general population.	
Screening tool	**Name:** Finnish Diabetes Risk Score (FINDRISC) **Type:** A simple risk calculator that can be conveniently used in primary care and also by individuals themselves.	
Setting / Delivered by	Primary care Practitioner or self-administration	
Characteristics targeted	Age, BMI, waist circumference, physical activity, daily consumption of fruits, berries or vegetables, history of antihypertensive drug treatment, history of high blood glucose, and family history of diabetes.	
Population	**Sample:** 4,622 subjects were invited to a screening visit that included an OGTT and completion of the FINDRISC form. Of these subjects, data on glucose tolerance status were obtained for 3,092 (67%) people without a prior history of diabetes. 2,640 (85%) completed the FINDRISC form. **Males** 1349 **Mean age** Men 57.7 (7.5) Women 56.7 (7.6) **Mean BMI Men** 27.7 (3.8) Women 27.6 (4.9) **Waist circumference: Men** 97.9 (10.7) Women 86.7 (12.2) **Other**: In men with risk score > 15, the prevalence of SDM was 30%.In women, the corresponding prevalence was 16% Prevalence of pre-diabetes = 50.6% men; 33.3% women, AGT	People who had either SDM, impaired fasting glucose (IFG, fasting plasma glucose > 6.1 and < 7.0 mmol/L) or impaired glucose tolerance (IGT; two-hour plasma glucose > 7.8 and < 11.1 mmol/L) were classified as having abnormal glucose tolerance (AGT). Body mass index (BMI) was calculated as weight (kg) divided by height2 (m2).
No of Items	One-page questionnaire containing eight questions, with categorised answers weighted, corresponding to the risk	

	increase associated with the respective variable in the original model. The total risk score is a simple sum of the individual weights, and values range from 0 to 26.	
Time to complete	NR	
Reference standard used	OGTT was carried out according to World Health Organization (WHO) recommendations	
Index and Comparitor tests	N/A	
Sensitivity (%) for diagnosis of IGT / IFG	Cutoff value=11 Men 45.6 (41.7 – 49.5) Women 53.4 (49.1 – 57.7) Cutoff value=13 Men 27.8 (24.4 – 31.3) Women 39.4 (35.3 – 43.6) Cutoff value=15 Men 16.9 (14.0 – 19.8) Women 26.7 (22.9–30.4)	
Specificity (%) for diagnosis of IGT / IFG	Cutoff value=11 Men 24.6 (21.3 – 27.9) Women 34.2 (31.3 – 37.1) Cutoff value=13 Men 13.4 (10.8 – 16.0) Women 19.9 (17.4 – 22.4) Cutoff value=15 Men 6.6 (4.7 – 8.6) Women 11.9 (9.9 – 14.0)	
Positive and Negative-predictive values (%) for IGT / IFG	Cutoff value=11 Men PPV 65.9 (61.5 – 70.4) NPV 57.7 (54.4 – 61.0) Women PPV 45.2 (41.3 – 49.1) NPV 72.4 (69.6 – 75.3) Cutoff value=13 Men PPV 69.7 (63.9 – 75.5) NPV 54.4 (51.4 – 57.4) Women PPV 52.1 (47.0 – 57.3) NPV 71.4 (68.8 – 74.0) Cutoff value=15 Men PPV 74.2(67.0 – 81.4) NPV 52.8 (49.9 – 55.6) Women PPV 57.3 (50.7 – 63.8) NPV 69.7 (67.2 – 72.1)	
AuRoc Value	(IFG/IGT) = 0.65 in men and 0.66 in women	
Reported optimal threshold	Cutoff value=11	
Follow up	Two cutoff values of the FINDRISC are being used in the programme, followed by different intervention strategies: subjects with score values in the range 7–14 are offered written information about healthy lifestyle, whereas subjects scoring 15 or above are candidates for further testing for a possible glucose abnormality and are referred for more intensive interventions.	
Other properties	NR	
Cost Effectiveness	NR	
Authors conclusions	The study shows that, depending on the cutoff point chosen, the FINDRISC recognises undetected diabetes and glucose abnormalities fairly well, and there is marked association between the score and several CVD risk factors. Both IGT and the metabolic syndrome are independently associated with future risk of T2D. The ability of the FINDRISC to identify the metabolic syndrome, as defined by the NCEP criteria, was in fact as good as its ability to identify undetected T2D. Waist circumference is probably not commonly recognised by the general public as a risk factor for T2D. In clinical practice, therefore, it is recommended that the answers should be checked by a nurse or a physician.	Use WC suggestion in barriers data?
Quality Assessment	++	5/6
Study	**Author:** Saydah **Year:** 2002 **Country:** US **Study design:** Observational analysis	

Study Aim	To determine the feasibility of using FPG or HbA1c to identify individuals in US population who meet the DPP criteria for intervention (BMI ≥ 24, FPG 96-125mg/dl, and 2h glucose level 140-199 mg/dl in an OGTT.	Based on NHANES III, 27.2% of the U.S. population aged 40–74 years with no medical history of diabetes had BMI ≥24 kg/m2 and 72.8% had BMI ≥24 kg/m2
Screening tool	**Name:** HbA1c and FPG	
Setting / Delivered by	General Practice	
Characteristics targeted	BMI, age, ethnicity	
Population	**Sample:** *n* =2,844 **Males:** **Mean age**: 40–74 years **Mean BMI**: **Waist circumference:** **Other**: Of those with BMI≥24 kg/m2, 6.2% had a FPG level ≥126 mg/dl and would be classified as having newly diagnosed diabetes. 34.9% had FPG level <96 mg/dl and would not meet the DPP eligibility criteria for intervention. The remainder (58.9%) had FPG level 96 –125 mg/dl; 69.6% of these had 2-h plasma glucose level <140 mg/dl (normal glucose tolerance), 24.8% had 2-h glucose level 140–199 mg/dl (impaired glucose tolerance), and 5.6% had 2-h glucose level ≥200 mg/dl (newly diagnosed diabetes). Prevalence of pre-diabetes = 24.8% IGT	
No of Items	N/A	
Time to complete	N/A	
Reference standard used	OGTT	
Index and Comparitor tests	FPG and HbA1c	
Sensitivity (%) for diagnosis of IGT / IFG	**FPG** Cut off ≥100 (66.2% distribution) 76.5% (± 3.5) Cut off ≥105 (37.5% dis) 56.0 % (± 5.1) Cut off ≥110 (20.7% dis) 34.9% (± 4.5) Cut off ≥115 (10.2% dis) 19.9% (± 3.6) Cut off ≥120 (4.5% dis) 7.5% (± 2.7) **HbA1c (%)** Cut off ≥4.5 (97.7% dis) 98.0% (± 1.2) Cut off ≥5.0 (80.2% dis) 90.2% (± 2.3) Cut off ≥5.5 (38.3% dis) 60.0% (± 3.4) Cut off ≥6.0 (8.2% dis) 16.7% (± 2.4) Cut off ≥6.5 (0.9% dis) 1.6% (± 0.5)	For identifying individuals who have a 2-h glucose of 140–199 mg/dl among U.S. adults aged 40–74 years with BMI>24 kg/m2 and a fasting glucose of 96–125 mg/dl, according to fasting plasma glucose and HbA1c cut points
Specificity (%) for diagnosis of IGT / IFG	**FPG** Cut off ≥100 37.9% (± 2.8) Cut off ≥105 72.0% (± 1.9) Cut off ≥110 86.9% (± 1.5) Cut off ≥115 95.4 % (±1.0)	

	Cut off ≥120 97.4% (± 0.9) **HbA1c (%)** Cut off ≥4.5 1.8% (± 0.9) Cut off ≥5.0 17.2% (± 2.4) Cut off ≥5.5 55.0% (± 4.3) Cut off ≥6.0 92.9 (±1.3) Cut off ≥6.5 99.3% (± 0.4)	
Positive and Negative-predictive values (%) for IGT / IFG	**FPG** Cut off ≥100 17.9% (± 2.9) Likelihood ratio 1.23 Cut off ≥105 17.1% (±2.9) LR 2.00 Cut off ≥110 31.4% (±4.7) LR 2.66 Cut off ≥115 33.9% (± 6.5) LR 4.33 Cut off ≥120 54.3% (± 7.6) LR 2.88 **HbA1c (%)** Cut off ≥4.5 24.2% (± 18.9) LR 1.00 Cut off ≥5.0 14.9% (±4.5) LR 1.09 Cut off ≥5.5 21.4% (±2.2) LR 1.33 Cut off ≥6.0 27.6% (±4.4) LR 2.35 Cut off ≥6.5 39.8% (± 5.3) LR 2.29	
AuRoc Value	FPG 0.665 (95% CI 0.630 – 0.700) HbA1c 0.593 (0.557 – 0.629)	
Reported optimal threshold	FPG Cut off ≥ 105 mg/dl; HbA1c cut off ≥5.5%	
Follow up	NR	
Other properties	N/A	
Cost Effectiveness	NR	
Authors conclusions	At fasting glucose level ≥105 mg/dl, which included 37.5% of participants, the sensitivity of fasting glucose to identify the individuals with 2-h glucose of 140– 199 mg/dl was 56.0%, the specificity was 72.0%, and the PPV was 17.1%. Similarly, at HbA1c ≥5.5%, which included 38.3% of participants, the sensitivity of HbA1c to identify the individuals with 2-h glucose level 140–199 mg/dl was 60.0%, the specificity was 55.0%, and the PPV was 21.4%. Requiring either fasting glucose level ≥105 mg/dl or HbA1c ≥5.5% increased the sensitivity to 82.6% but decreased the specificity to 42.3% and did not substantially change the PPV (31.3%). Using a higher fasting glucose cut point of ≥110 mg/dl decreased the sensitivity further, increased the specificity, and did not substantially change the PPV. Similarly, using a higher HbA1c cut point of ≥6.0% also decreased the sensitivity, increased the specificity, and did not substantially change the PPV. For those aged 60–74 years, sensitivity, specificity, and PPV for fasting glucose and HbA1c were somewhat better than for those aged 40–59 years, but the differences were not substantial. The effect of race was minor for fasting plasma glucose but, for HbA1c, non-Hispanic whites had lower sensitivity and higher specificity than all others. The DPP recruited participants at high risk for developing diabetes based on BMI, fasting plasma glucose level, and response to an OGTT. To determine those who might be eligible for a DPP intervention in the general U.S. population to reduce their risk of developing diabetes, measurement of height and weight could immediately eliminate from further testing the 27.2% of individuals with BMI ≥24 kg/m2. Measurement of fasting plasma glucose in those with BMI ≥24 kg/m2 would eliminate 41.1% of this group who are below or above the DPP fasting plasma glucose criteria. For the remaining 41 million individuals with BMI ≥24 kg/m2 and fasting plasma glucose level 96–125 mg/dl, setting the fasting glucose cut off value at ≥105 mg/dl would eliminate 62.5% from further testing by the OGTT while including fully 56.0% of those with 2-h glucose level 140–199 mg/ dl. Thus, for the 95 million people aged 40–74 years without diagnosed diabetes, 15 million would have to undergo an OGTT by this scheme. A similar	

	procedure could be followed using HbA1c ≥5.5%, which does not require an individual to be fasting and can be measured in a blood sample collected without regard to time of the prior meal. If HbA1c is used, the method for measuring HbA1c would have to be standardized to the Diabetes Control and Complications (DCCT) method. The prevalence of diabetes and abnormal glucose tolerance increases with increasing age and BMI and is higher in those of minority race/ethnicity. The DPP lifestyle intervention for reducing the incidence of diabetes was almost equally effective in each gender, BMI, and race/ethnicity group and showed the greatest reduction in incidence of diabetes for individuals aged ≥60 years. Overall, the fasting glucose cut off level proposed seems to be a balance between sensitivity and specificity with 2:1 odds of identifying an individual with 2-h glucose between 140 and 199 mg/dl. Neither fasting plasma glucose nor HbA1c alone are ideal screening tests. Limitations: Only have results on adults aged 40-74 years.	
Quality Assessment	+	3/6
Study	**Author:** Schwarz, **Year:** 2009 **Country:** Germany **Study design:** Cohort	
Study Aim	To evaluate the usefulness of the FINDRISC to predict insulin resistance in a population at increased diabetes risk.	
Screening tool	**Name:** Finnish Diabetes Risk Score (FINDRISC) **Type:** Questionnaire adapted for German population used in survey.	
Setting / Delivered by	Community	
Characteristics targeted	Age, body mass index (BMI), waist circumference, physical activity, diet, use of antihypertensive medication, history of high blood glucose, and family history of diabetes.	
Population	**Sample:** Two different samples were analyzed. The first sample (n=771) drawn in 1996 consisted of 921 subjects with a family history of metabolic syndrome. The second sample (n=526) drawn in 1997 was used for validation purposes and consisted of 735 subjects from German families with a family history of type 2 diabetes or related insulin resistance disorders such as obesity or dyslipidemia. **Males / Females 1996 :** 326/445 **Males / Females 1997:** 256/270 **Mean age 1996**:43 (30 –57) **Mean age 1997**: 59 (51– 63) **Mean BMI 1996:**25 (22–28) **Mean BMI 1997:** 26 (24 –28) **Waist circumference:** NR **Other**: Individuals with IGT and/or IFG were analyzed as a combined glucose intolerance group. NGT/IFG-IGT/T2D 1996: 417/287/67 NGT/IFG-IGT/T2D 1997:159/306/61 Mean HBA1c 1996: 5.2 (4.9 –5.5) Mean FPG 1997: 5.6 (5.3– 6.0) Mean FPG 1996: 5.38 (4.99 –5.85) Mean FPG 1997: 5.84 (5.48–6.39) The mean FINDRISC total score of the 1996 survey was 9.33 (SD 5.92); score range 1-23 In the1997 baseline survey, the mean FINDRISC was 7.27 (SD 4.45). The total score ranged from one to 17. Prevalence of pre-diabetes = 24.8% IGT	
No of Items	The FINDRISC comprises eight items as above. In the current study, a modified and validated German version of the questionnaire was applied. In this shortened version, the variables diet and physical activity were omitted because both items did not add much power for the prediction of diabetes risk in previous studies. Thus, the	

	maximal achievable score of the modified questionnaire is 23.	
Time to complete	NR	
Reference standard used	75-g oral glucose tolerance test (OGTT)	
Index and Comparitor tests	Each participant completed the FINDRISC questionnaire, a physical examination, blood samples for measurement of glucose, insulin, proinsulin C peptide, and free fatty acids (FFAs). the subjects were categorized as having either normal glucose tolerance (NGT), impaired glucose tolerance (IGT), including those with impaired fasting glucose (IFG) and type 2 diabetes mellitus according to the World Health Organization/American Diabetes Association criteria of 1997/1999.	
Sensitivity (%) for diagnosis of IGT / IFG	1996 Survey: 77.5% at cut off 12. 1997 Survey: 72.7% at cut off 9.	
Specificity (%) for diagnosis of IGT / IFG	1996 Survey: 67.9% at cut off 12 1997 Survey: 68.2% at cut off 9.	
Positive and Negative-predictive values (%) for IGT / IFG	1996 Survey: PPV 19.7% NPV 96.8%, 1997 Survey: PPV 29.4% NPV 88.1%,	
AuRoc Value	AUC values were 0.78 (1996) and 0.74 (1997 baseline).	
Reported optimal threshold	The optimal cut points were 12 in 1996 and 9 in 1997.	
Follow up	A follow-up examination was performed 3 yr after the initial survey. Subjects with follow-up examination were also defined according to the evolution of their diabetic status as unchanged, progression, or regression.	
Other properties	NA	
Cost Effectiveness	NR	
Authors conclusions	Subjects with the highest FINDRISC value had the highest proportion of individuals with diabetes at baseline, and the largest proportion of them remained diabetic during the follow-up, whereas those with a low FINDRISC value comprised the highest proportion of individuals remaining NGT. The FINDRISC is significantly associated with markers of insulin resistance and with disease evolution. Because insulin resistance always precedes IGT (7), the FINDRISC may be a useful instrument to identify people at the earliest stage of disease development. The most relevant application field of FINDRISC is on the primary care level, where population-based screening strategies are needed and widely implemented. The use by primary care physicians or other health care professionals would facilitate the detection of high-risk subjects and the institution of early preventive measures. Limitations: 1) It may be argued that analysis of only six risk items in the FINDRISC questionnaire is not reliable because the two excluded variables, diet and physical activity, have an evidenced impact on diabetes development. It could be shown in two independent studies using the FINDRISC that these two items did not add much power to the prediction of diabetes risk. Other studies also reported similar observations. 2) All subjects of the two cohorts had high risks for type 2 diabetes mellitus, thus, the selection bias may lead to an underestimation of associations. The mean BMI showed that the 1996 and 1997-baseline samples were “overweight,” corresponding to 25 (22–28) and 26 kg/m2 (24–28), respectively. The benefits of completing a questionnaire compared with a single BMI measure is a possible increase in awareness regarding individual risk factors. Therefore, it is necessary to validate the association of FINDRISC and insulin resistance in a randomized study and also in other populations.	
Quality Assessment	+	4/6
Study	**Author:** Simmons, Thompson and Engelgau **Year:** 2004 **Country:** New Zealand **Study design:** Diagnostic accuracy study (risk scores)	
Screening tool	**Name:** Risk factor screening, HbA_{1c} and random glucose (compared with fasting glucose)	

Setting / Delivered by	Setting was not reported. Not reported who delivered the test.	
Characteristics targeted	Risk factor screening: family history of diabetes, known hypertension, past gestational diabetes mellitus, BMI (from measured weight and height).	
Population	**Sample:** European, Maori and Pacific Islands residents of inner urban South Auckland were randomly selected for invitation to participate in the study from a prior household census. The target sample size was 450 aged 40–59 years, and 150 aged 60–79 years for each ethnic group. A stratified sampling frame was used, randomly selecting households within each age and ethnic group using SPSS for Windows. Of the 1928 individuals aged 40–59 years and 809 aged 60–79 years invited to participate, 1321 (68.5%) and 578 (71.4%) were screened for diabetes. This included 658 Europeans, 485 Maori and 726 Pacific Islands people. Overall, 534 (67.9% of 786 invited) attended the OGTT. **Males:** 40.2% of those with new diabetes, 49.2% of those with IGT/IFG and 43.3% of those with normal GT or no OGTT **Mean age**: 55 ± 9 in those with new diabetes, 56 ± 10 in those with IGT/IFG and 54 ± 10 in those with normal GT or no OGTT **Mean BMI**: 31.5 ± 6.6 kg/m^2, 36.8 ± 7.7 and 36.8 ± 6.9 in European, Maori and Pacific Islands people with new diabetes respectively, 29.7 ± 5.6, 33.8 ± 7.8 and 37.6 ± 8.4 in European, Maori and Pacific Islands people with IGT/IFG respectively and 27.8 ± 5.6, 32.4 ± 6.4 and 33.9 ± 7.0 in European, Maori and Pacific Islands people with normal glucose tolerance or no OGTT respectively **Waist circumference:** NR **Other:** A total of 52% of all participants had a positive score (≥10 points) on the ADA questionnaire; 9.5% had CBG ≥140 mg/dl, and 18.4% had CBG ≥120 mg/dl. Prevalence of pre-diabetes = 20% IFG / IGT	
No of Items	3 (treated for hypertension; obesity [BMI ≥30 kg/m^2]; first-degree relative with diabetes)	
Time to complete	NR	
Reference standard used	OGTT – fasting and 2-hr post glucose (75-g) challenge glucose	
Index and Comparitor tests	Risk factor screening Random blood glucose HbA_{1c} ROCs were calculated using sensitivity and 1-specificity (in %) using weighted and unweighted data. Area under the curve (AUC) was calculated using the SPSS ROC Curve function for the continuous variables (e.g. HbA_{1c}). An AUC of < 0.50 is considered worthless, 0.60–0.69 poor, 0.70–0.79 fair, 0.80–0.89 good and 0.90–1 excellent. Optimal test characteristics were considered to exist where sensitivity was equivalent to specificity. Comparison of the AUCs adjusting for correlation of the different measures was made using ROCKIT which creates a Z statistic. Adjustment for the six comparisons was made using the Bonferroni correction (making P < 0.0083 significant).	
Sensitivity (%) for diagnosis of IFG/IGT	**IGT/IFG** **Strategy 1: screen with random glucose and OGTT if ≥ 5.6 mmol/l** 66.3% **Strategy 2: screen with HbA_{1c} and OGTT if ≥ 5.3%** 50.9% **Strategy 3: screen with fasting glucose and OGTT if ≥ 5.5 mmol/l** 66.3% **Strategy 4: OGTT if any of the 3 risk factors** 71.6% **Strategy 5: Those with any of the 3 risk factors screened as in strategy 1 (random glucose)** 52.0% **Strategy 6: Those with any of 3 risk factors screened as in strategy 2 (HbA_{1c})** 44.2%	

	Strategy 7: Those with any of 3 risk factors screened as in strategy 3 (fasting blood glucose) 60.8% Seven different screening strategies were employed: • Single blood test (immediate random glucose, fasting glucose and HbA_{1c}) followed by OGTT (strategies 1–3) • Straight to OGTT if any of the three risk factors are present (strategy 4) • Risk factor screening, followed by single blood test, followed by OGTT (strategies 5–7). Risk factor screening was associated with approximately 9–12% less OGTTs. Screening with a fasting glucose with a threshold for OGTT of 5.5 mmol/l had substantially superior sensitivity to any other approach. Overall, 17% of participants had a fasting glucose of ≥7.0 mmol/l and would probably not have needed an OGTT, although a second test would still have been required for a clinical diagnosis. Screening using HbA_{1c} with a threshold of 5.3% was also consistently superior to risk factor screening. Use of random glucose testing was inferior to risk factor screening when followed by fasting glucose testing. Screening only those with risk factors would have missed 4/22 (18%) of all participants and 1/3 of Europeans with an HbA_{1c} of ≥8.0%.	
Specificity (%) for diagnosis of IFG/IGT	Reported but combined for IGT, IFG & diabetes – not reported separately for prediabetes	
Positive and Negative-predictive values (%) for IGT / IFG/T2DM	PPV reported but combined for IGT, IFG & diabetes – not reported separately for prediabetes	
AuRoc Value	Reported but combined for IGT, IFG & diabetes	
Reported optimal threshold	Screening with a fasting glucose with a threshold for OGTT of 5.5 mmol/l had substantially superior sensitivity to any other approach. Screening using HbA_{1c} with a threshold of 5.3% was also consistently superior to risk factor screening. Use of random glucose testing was inferior to risk factor screening when followed by fasting glucose testing. Screening only those with risk factors would have missed 4/22 (18%) of all participants and 1/3 of Europeans with an HbA_{1c} of ≥8.0%.	
Follow up	NR	
Other properties	NR	
Cost Effectiveness	Not assessed	
Authors' conclusions	Using risk factors for the identification of who should receive a blood test for dysglycaemia adds little to direct screening with the risk of missing some with significant hyperglycaemia. Screening for dysglycaemia may best be undertaken using blood tests without initial risk factor symptom screening.	
Quality Assessment	+	
Study	**Author:** Somannavar, Ganesan, Deepa, Datta & Mohan **Year:** 2009 **Country:** India **Study design:** Diagnostic accuracy study	
Study Aim	To determine random capillary blood glucose (RCBG) cut points that discriminate diabetic and pre-diabetic subjects from normal individuals.	
Screening tool	**Name:** Random capillary blood glucose (RCBG)	
Setting / Delivered by	Opportunistic diabetes screening camps Not reported who delivered the test, although detailed methodology is reported in another paper. OGTT was performed in Dr. Mohan's Diabetes Specialities Centre, a tertiary referral centre for diabetes care	Detail reported in: Narayanan V, Rema M, Mohan V: Prevention Awareness Counselling and Evaluation (PACE) Diabetes Project: a mega multi-pronged program for diabetes awareness and prevention in South India

		(PACE-5). J Assoc Physicians India 56:429– 435, 2008
Characteristics targeted	RCBG cut points that discriminate diabetes, impaired glucose tolerance (IGT), and impaired fasting glucose (IFG) were determined using receiver operating characteristic curves, in comparison with venous plasma glucose OGTT	
Population	**Sample:** Participants were recruited through opportunistic diabetes screening camps in Chennai, India, as part of the Prevention Awareness Counselling and Evaluation (PACE) Diabetes Project. Of the 103,878 people who attended, 73.8% (76,645) underwent an RCBG test. Those self-reporting diabetes were excluded (n=13,340), and from the remaining 63,305, 1500 were randomly selected to attend for an OGTT, of which 1333 (88.9%) responded. **Males:** 45.2% **Mean age**: 45.5 ± 10.7 years **Mean BMI**: 24.8 ± 4.0 kg/m^2 **Waist circumference:** NR **Other:** 27.2% (n=363) had RCBG <100 mg/dl (5.6 mmol/l), 65.9% (n=878) had RCBG in the range of 100–200 mg/dl (5.6 –11.1 mmol/l), and 6.9% (n=92) had RCBG >200 mg/dl (11.1 mmol/l). Prevalence of pre-diabetes = 28.1% IGT; 28.9% IFG	
No of Items	N/A	
Time to complete	NR	
Reference standard used	FPG assessed by 2-hour venous plasma glucose OGTT.	
Index and Comparitor tests	RCBG. Receiver operating characteristic curves were plotted using sensitivity and 1-specificity for different cutoff values of RCBG. Comparison of sensitivity with specificity was made over the entire range of RCBG cut points, and areas under the curve were plotted.	
Sensitivity (%) for diagnosis of IFG/IGT	**IGT** **2-hr PG** ≥140 mg/dl and <200 mg/dl, **RCBG** 168.4 ± 62.6 mg/dl, **RCBG cut point** 119 – 64.7% **IFG** **FPG (WHO)** ≥110 mg/dl and <126 mg/dl, **RCBG** 165.0 ± 63.1, **RCB cut point** 118 – 62.8% **FPG (ADA)** ≥110 mg/dl and <126 mg/dl, **RCBG** 146.9 ± 57.1, **RCBG cut point** 113 – 62.8% For IGT, the RCBG cut point was 119 mg/dl (6.6 mmol/l). Using the IFG (WHO) criterion of FPG ≥110 (6.1 mmol/l) and <126 mg/dl (7.0 mmol/l), the RCBG cut point was 118 mg/dl (6.6 mmol/l), while for the IFG (ADA) criterion of FPG≥100 mg/dl (5.6 mmol/l) and <126 mg/dl (7.0 mmol/l), the RCBG cut point was 113 mg/dl (6.3 mmol/l).	
Specificity (%) for diagnosis of IFG	**IGT** **2-hr PG** ≥140 mg/dl and <200 mg/dl, **RCBG** 168.4 ± 62.6 mg/dl, **RCBG cut point** 119 – 65.5% **IFG** **FPG (WHO)** ≥110 mg/dl and <126 mg/dl, **RCBG** 165.0 ± 63.1, **RCBG cut point** 118 – 62.9% **FPG (ADA)** ≥110 mg/dl and <126 mg/dl, **RCBG** 146.9 ± 57.1, **RCBG cut point** 113 – 58.6%	
Positive and Negative-predictive values (%) for IGT / IFG/T2DM	**PPVs:** **IGT** **2-hr PG** ≥140 mg/dl and <200 mg/dl, **RCBG** 168.4 ± 62.6 mg/dl, **RCBG cut point** 119 – 27.2 **IFG** **FPG (WHO)** ≥110 mg/dl and <126 mg/dl, **RCBG** 165.0 ± 63.1, **RCBG cut point** 118 – 25.4 **FPG (ADA)** ≥110 mg/dl and <126 mg/dl, **RCBG** 146.9 ± 57.1, **RCBG cut point** 113 – 46.9	
AuRoc Value	**IGT** **2-hr PG** ≥140 mg/dl and <200 mg/dl, **RCBG** 168.4 ± 62.6 mg/dl, **RCBG cut point** 119 – 0.715 **IFG** **FPG (WHO)** ≥110 mg/dl and <126 mg/dl, **RCBG** 165.0 ± 63.1, **RCB cut point** 118 – 0.683	

	FPG (ADA) ≥110 mg/dl and <126 mg/dl, **RCBG** 146.9 ± 57.1, **RCBG cut point** 113 – 0.619	
Reported optimal threshold	RCPG cut points for IGT (119 mg/dl [6.6 mmol/l]) and two definitions of IFG (WHO 118 mg/dl and ADA 113 mg/dl) maximized the sensitivity and specificity.	
Follow up	NR	
Other properties	NR	
Cost Effectiveness	NR	
Authors' conclusions	Based on the findings, in opportunistic screening studies in Asian Indians, all those with RCBG values >110 mg/dl (6.1 mmol/l) should receive more definitive tests for diabetes and pre-diabetes. This could not only help limit the number of individuals who must arrive for screening in a fasting state but also reduce the costs of screening, as only 60% of those screened would have RCBG >110 mg/dl.	
Quality Assessment	+	3/6
Study	**Author:** Thomas **Year:** 2006 **Country:** **Study design:** Diagnostic accuracy study	
Study Aim	To assess the ability of the CRS to predict glycosylated haemoglobin (HbA1c) levels and determined whether the RS was better than body mass index (BMI) at predictingHbA1c levels in midlife.	
Screening tool	**Name:** Cambridge Risk Score was compared to body mass index (BMI) to determine which was better at predicting HbA1c levels in midlife.	
Setting / Delivered by		
Characteristics targeted	Cambridge Risk Score and BMI	
Population	**Sample:** Subjects from the 1958 Birth Cohort who participated in the biomedical survey when aged 45. of 9337 who did participate, 7492 subjects without known diabetes were included in the study **Males:** **Mean age**: **Mean BMI**: **Waist circumference:** **Other**: Prevalence of pre-diabetes = 3.1% at HbA1c ≥ 6 mmol/l	
No of Items	**Cambridge Risk Score:** Age (years), sex, BMI (4 categories), prescribed antihypertensives or steroids, diabetes family history (parents or siblings*), smoking (nonsmoker, ex-smoker, or current smoker)	
Time to complete	NR	
Reference standard used	HbA1c	
Index and Comparitor tests	CRS	
Sensitivity (%) for diagnosis of IGT / IFG/T2DM	**HbA1c levels ≥6%** **Cambridge Risk Score** 78.2 %(72.2-83.3) **BMI ≥30** 71.2 %(64.8-77.0) **HbA1c levels ≥7%** **Cambridge Risk Score** 76.9 % (64.8-86.5) **BMI ≥30** 78.5% (66.5-87.7)	
Specificity (%) for diagnosis of	**HbA1c levels ≥6%**	

IGT / IFG/T2DM	**Cambridge Risk Score** 63.9 % (62.7-65.0) **BMI ≥30** 74.8 %(73.8-75.8) **HbA1c levels ≥7%** **Cambridge Risk Score** 77.8 %(76.9-78.8) **BMI ≥30** 73.9 %(72.8-74.9)	
Positive and Negative-predictive values (%) for IGT / IFG/T2DM	**HbA1c levels ≥6%** **Cambridge Risk Score** PPV 6.4 (5.5-7.4) NPV not reported **BMI ≥30** PPV8.2 (7.0-9.5) NPV not reported **HbA1c levels ≥7%** **Cambridge Risk Score** PPV 3.0 (2.2-3.9) NPV not reported **BMI ≥30** 2.6 (1.9-3.4) NPV not reported	
AuRoc Value	**HbA1c levels ≥6%** **Cambridge Risk Score** **BMI ≥30** **HbA1c levels ≥7%** **Cambridge Risk Score** **BMI ≥30**	
Reported optimal threshold	≥0.128 was the optimal cutoff for Cambridge Risk Score to detect HbA1c levels of 6% or more For BMI a cutoff of 30 or more was estimated.	
Follow up	NR	
Other properties	NR	
Cost Effectiveness	NR	
Authors conclusions	The authors concluded that for adults in midlife the Cambridge Risk Score preformed reasonably well in identifying individuals with elevated HbA1c but had no advantage compared to BMI alone in identifying diabetes risk.	
Quality Assessment	+	3/6
Study	**Author:** Woolthius Two papers reporting on same study **Year:** 2007 / 2009 **Country:** Netherlands **Study design:** Screening yield assessment and uptake	
Screening tool	**Name / Type:** EMR-derived Risk assessment	
Setting / Delivered by	Family practices Practice assistants within patients' own family practice.	
Characteristics targeted	Patients with one or more known risk factor/s (family history of diabetes, hypertension, cardiovascular disease, lipid metabolism disorders, obesity [BMI <27] and a history of gestational diabetes mellitus) and without risk factors (opportunistic screening) (not extracted) and uptake of screening.	
Population	**Sample:** Participants were recruited from 11 family practices in the Netherlands that were part of academic research networks of university departments of family medicine. The practices had a total population of 49,229 patients, cared for by 25 family practitioners, and had not previously performed systematic screening for diabetes. All patients aged 45 to 75 years inclusive who were listed with these practices and were not known to have diabetes were considered for inclusion in the study. The 11 participating practices had 49,229 registered patients (2,500-9,750 per practice), of whom 14,457 (957-1,831 per practice) were aged 45 to 75 years. The prevalence of known diabetes before our screening program was 6.1%, leaving 13,581 patients for the study. During the 1-year study period, 5,277 (39%) of these patients had an encounter with a family practitioner during which screening was discussed. Risk assessment indicated that 3,724 (71%) were at high risk for diabetes and 1,553 (29%) were at low risk; 90% (3335) of the high-risk patients and 86%	

	(398) of the 465 invited low-risk patients returned for a first capillary FPG measurement after invitation. Sex and mean age did not differ significantly between high-risk and low-risk patients, but mean FPG was slightly higher in the former group. Among high-risk patients, a second capillary FPG was performed in 496 high-risk patients, or 88% of those invited. A venous sample was collected in 125 (74%) of these patients but not in 44 (26%). Of the 125 patients with a venous sample, 81% had undiagnosed type 2 diabetes, 16% had IFG, and 3% had a normal fasting glucose level. These groups differed significantly in terms of mean FPG values and the prevalence of lipid metabolism disorders. **Males:** 42.3% and 42.2% of high- and low-risk patients respectively, in whom a first capillary fasting glucose level was measured **Mean age**: 58.2 ± 8.2 and 57.5 ± 7.2 of high- and low-risk patients respectively, in whom a first capillary fasting glucose level was measured **Mean BMI**: 28.0 ± 4.5 and 23.5 ± 2.2 **Waist circumference:** NR **Other:** Mainly Caucasian Prevalence of pre-diabetes = 16% IFG	
No of Items	N/A	
Time to complete	N/A	
Reference standard used	N/A	
Index and Comparitor tests	N/A	
Sensitivity (%) for diagnosis of IFG/IGT	N/A	
Specificity (%) for diagnosis of IFG/IGT	N/A	
Positive and Negative-predictive values (%) for IGT / IFG/T2DM	N/A	
AuRoc Value	N/A	
Reported optimal threshold	N/A	
Follow up	1886 patients with EMR-derived risk (91%) and 1449 at risk after additional assessment (88%) returned for an FPG measurement. In both groups, patients were found with an FPG above the cut off for FPG (13.5% and 9.6%).	
Other properties		
Cost Effectiveness	Not assessed	
Authors' conclusions	Obesity and family history of diabetes were poorly recorded and were mainly retrieved with additional risk assessment during consultation.	
Quality Assessment	+	3/6
Study	**Author:** Zhou **Year:** 2009 **Country:** China **Study design:** Diagnostic accuracy study	
Study Aim	The aim of the study was to determine the performance of glycated haemoglobin (HbA_{1c}) as a screening tool for detecting undiagnosed diabetes and pre-diabetes.	
Screening tool	HbA1c	
Setting / Delivered by	Unclear where measurements and testing of study participants was carried out.	

Characteristics targeted	HbA_{1c} , BMI, waist circumference, oral glucose tolerance test, impaired glucose tolerance, impaired fasting glucose.	
Population	**Sample:** 903 Individuals aged 21 to 79 years of age, living in two urban communities of Beijing that had participated in a diabetes survey that was conducted from March to May in 2008 and had no prior history of diabetes. **Males**: 26.5% (239) **Mean age**: 55.0 years (95% CI 54.3 to 55.6) **Mean BMI**: 26.3 (95% CI 26.1 to 26.5) **Waist circumference:** Males mean 89.5 cm (95% CI 88.3 to 90.7), Females mean 83.4 cm (95% CI 82.7 to 84.1) **Other**: Prevalence = 22.4% pre-diabetes	The 903 individuals who had no history diabetes along with HbA_{1c} and all required measurements out of the 1107 who participated in the diabetes survey.
No of Items	N/A	
Time to complete	N/A	
Reference standard used	HbA_{1c} was measured by boronate affinity high-pressure liquid chromatography method.	
Index and Comparitor tests	A 75-g oral glucose tolerance test (OGTT), performed in the morning after the study participants had at least three days of unrestricted diet and an overnight fast of 10 to 12 hours, for newly diagnosed diabetes. For pre-diabetes the World Health Organisation 1999 criteria (impaired glucose tolerance [IGT] and impaired fasting glucose [IFG]) was used.	
Sensitivity (%) for diagnosis of IGT / IFG	$HbA_{1c} \geq 5.7\%$ 59.4 $HbA_{1c} \geq 6.0\%$ 25.2 $HbA_{1c} \geq 6.5\%$ 2.0	
Specificity (%) for diagnosis of IGT / IFG	$HbA_{1c} \geq 5.7\%$ 73.9 $HbA_{1c} \geq 6.0\%$ 94.8 $HbA_{1c} \geq 6.5\%$ 100.0	
Positive and Negative-predictive values (%) for IGT / IFG	Not reported	
AuRoc Value	Not reported	
Reported optimal threshold	Optimal cut off for undiagnosed diabetes was $HbA_{1c} \geq 6.0\%$ and for pre-diabetes it was $HbA_{1c} \geq 5.7\%$.	
Follow up	Not reported	
Other properties		
Cost Effectiveness	Not reported	
Reviewer comments	The authors noted that the performance of a HbA_{1c} as a diagnostic test for diabetes and pre-diabetes was compared against the results of one OGTT test, and given that the reproducibility of the OGTT test itself is poor, individuals could have been misclassified. Furthermore as participation in the study was voluntary, the prevalences of undiagnosed diabetes and pre-diabetes (as well as obesity and hypertension) was high in the study population. In the study, HbA_{1c} detected more individuals with elevated waist circumference and/or BMI, and the authors believe that the result could not be extrapolated to a general population. The small sample size may also a limitation of the study.	
Authors conclusions	The authors concluded from this study that HbA_{1c} as a single screening test was adequate to detect newly diagnosed diabetes but was not able to properly identify pre-diabetes in an obese Chinese population.	
Quality Assessment	+	
Study	**Author:** Zhou **Year:** 2010	

	Country: China **Study design:** Diagnostic accuracy study	
Study Aim	To evaluate the performance of A1C and fasting capillary blood glucose (FCG) tests as mass screening tools for diabetes and pre-diabetes, as determined by the standard oral glucose tolerance test (OGTT).	
Screening tool	**Name:** A1C is the mean of the long-term glucose level and does not require the subject to be in a fasting state with only one blood sample drawn. The capillary blood glucose test is a point-of-care determination that involves only one finger prick. As it is easy to use and cheap, it is applied as a first-step screening test for mass screening of subjects in either the fasting or the random state. Prevalence = 29.5% pre-diabetes	
Setting / Delivered by	Unclear	
Characteristics targeted	BMI, waist circumference,	
Population	**Sample:** The study population was drawn from 6,100 residents of Qingdao city in China, who had participated in a diabetes survey. Of these, 2,332 individuals (aged 35 to 74 years) without a prior history of diabetes made the inclusion criteria for the study. **Males**: 42.3% (986) **Mean age**: Males 49.5 years (95% CI 48.9 – 50.2), Females 49.3 years (95% CI 48.8 – 49.8) **Mean BMI**: Males 25.7 (95% CI 25.5 – 25.8), Females 25.8 (95% CI 25.6 – 26.0) **Waist circumference:** Males 87.2 cm (95% cI 86.6 – 87.8), Females 81.9 cm (95% cI 81.5 – 82.4) **Other**:	
No of Items	N/A	
Time to complete	N/A	
Reference standard used	Standard oral glucose tolerance test (OGTT)	
Index and Comparitor tests	After an overnight fast of at least 10 hours, participants were given the FCG test over the 0700–0930 period, using a Bayer Ascensia BRIO blood glucose monitoring system that was calibrated to give capillary plasma/serum glucose equivalent results. A standard OGTT was also performed on the same day over the 0700–1130 period, and blood samples for glucose determinations were collected from the antecubital vein into a vacuum tube containing sodium fluoride.	
Sensitivity (%) for diagnosis of IFG	For males the A1C cutoff of 6.5% gave a sensitivity of 4.5% and at 5.6% it gave 33.5%. For females the A1C cutoff of 6.5% gave a sensitivity of 5.7% and at 5.6% it gave 36.2%.	
Specificity (%) for diagnosis of IFG	For males the A1C cutoff of 6.5% gave a specificity of 88.3% and at 5.6% it gave 59.4%. For females the A1C cutoff of 6.5% gave a specificity of 89.4% and at 5.6% it gave 62.9%.	
Positive and Negative-predictive values (%) for IGT / IFG	Not reported	
AuRoc Value	For males the AUC for A1C was 0.53 and 0.69 for FCG, for females the AUC for A1C was 0.55 and 0.68 for FCG	
Reported optimal threshold	The optimal A1C cutoff point for newly diagnosed diabetes in this study population was 5.6% (lower than the recommended value of 6.5%). The optimal FCG cutoff point was 6.3 mmol/l for men and 6.6 mmol/l for women.	
Follow up	Not reported	
Other properties	Not reported	
Cost Effectiveness	Not reported	
Authors conclusions	The authors concluded that, as a mass screening tool, the FCG test performed better than the A1C test in the general population of Chinese. In consideration of its high cost and poor performance, the A1C test is not a suitable	

	test for mass screening, particularly with the purpose of detecting pre-diabetes for early intervention.	
Quality Assessment	+	