Strategies for the early detection of type 2 diabetes in an at risk population

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by

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Chapter 1

Introduction

1.1 Introduction

Type 2 diabetes is one of the most common chronic diseases in the western world. It is a complex, multi-factorial disease which affects the quality, quantity and style of an individual’s life. Its prevalence continues to rise worldwide and in the United Kingdom the number of people known to have diabetes was 1.67 million in 2002. (Diabetes UK 2002) In 2005 the National Diabetes Audit calculated the prevalence of diabetes in England alone to be 4.67% or 2.35 million people, of whom over 650 000 people are either undiagnosed or whose diabetes is not registered with a GP practice. (National Diabetes Audit 2005, National Statistics 2005, YHPRO 2006) The International Diabetes Federation have forecasted that by 2025 the number of people with diabetes will increase by more than 30% in the UK. (IDF 2005)

Type 2 diabetes is often preceded by a long asymptomatic period, with many individuals having established complications at diagnosis. (Verhoeven 1991) Data from the UKPDS suggests that the onset of diabetes may be up to seven years before the clinical diagnosis is made. (UKPDS 16, 1995) Extrapolation of the association between prevalence of retinopathy and the duration of diabetes suggests that glucose intolerance may start to decline up to twelve years before clinical recognition. (UKPDS 16, 1995) With the increasing prevalence of diabetes and increasing life expectancy of the population, it is vital that those individuals with diabetes are identified as early in the disease process as possible in order to improve their quality and quantity of life. The duration of time between onset and diagnosis of diabetes provides an ideal opportunity to identify glucose intolerance early and to intervene to improve long-term outcomes.

However, despite this compelling information, there is still no national screening programme for diabetes in the United Kingdom, to identify these people early and there is controversy and debate with regard to who and how to screen for diabetes. There is also a lack of outcome data showing that screening confers long term benefits and reduced complications. The National Screening Committee have looked at the issues around screening for diabetes and requested more studies be done before decisions are formulated. (National Screening Committee 1998) They are meeting again to consider current
evidence and much of the data in this thesis will be shared with the National Screening Committee. The Screening Those At Risk (STAR) study was designed to provide informed answers to the questions around methodology and outcomes of screening. The ethnic population within Leicester provides an ideal environment for a screening study whose findings will be applicable throughout the United Kingdom and applicable to other minority ethnic communities in other parts of the world.

1.2 General Aims
The main aims of this thesis are to provide answers to the questions below which will contribute to information for the Department of Health and National Screening Committee.

The screening process
- Which risk factors for diabetes are most important and do these differ between South Asians and White Europeans?
- Can risk scores and questionnaires be used as screening tools to decrease the number of blood tests required, and does the performance of such tools vary between ethnic groups?
- Are fasting plasma glucose and HbA1c sensitive enough to be used as screening tools, and if so what cut-points would be recommended in ethnic groups?
- Is there a simple and effective screening strategy for diabetes that is applicable across ethnic groups? and if so to describe such a strategy.

Patients found to have abnormal glucose tolerance through screening
- What are the baseline characteristics of patients found to have diabetes through a screening programme?
- Does the prevalence of metabolic syndrome at diagnosis of abnormal glucose tolerance differ between the ethnic groups?
- Does screening for diabetes cause anxiety and what are the health beliefs in those screened for diabetes?
This thesis will review the current literature on different screening methods for abnormal glucose tolerance, around preventing the progression of and delaying the onset of complications of diabetes after people have been identified with abnormal glucose tolerance or early diabetes.

1.3 Summary
This thesis will develop and evaluate a simple and effective stepwise strategy for the detection of diabetes. A strategy will be described detailing the optimal method of screening an at risk multi-ethnic population for diabetes in the United Kingdom. This will contribute to the current debate in the Department of Health and within the National Screening Committee on the need for a national policy for screening for type 2 diabetes mellitus.
Chapter 2

Screening for Abnormal Glucose Tolerance
Introduction and Review of the Literature

2.1 Introduction
Type 2 diabetes mellitus is one of the most common chronic diseases in the western world. It is a complex, multi-factorial disease which affects the quality, quantity and style of life. Its prevalence continues to rise worldwide. It is estimated the total number of people worldwide with diabetes will rise from 151 million in the year 2000, to 221 million by the year 2010 and 300 million by 2025. (Amos 1997, King 1998) The National Diabetes Audit calculated the prevalence of diabetes in England in 2005 to be 4.67% or 2.35 million people, of whom just over 650 000 are either undiagnosed or not registered with GP practice. (NDA 2005, YHPRO 2006, National Statistics 2005) Other estimates are nearer to one million individuals with undiagnosed diabetes. (Diabetes UK 2002) The prevalence of Impaired Glucose Tolerance (IGT), which is one of the precursors to diabetes, varies depending on the study population and the survey methods used. In European populations the prevalence of IGT increases with age and varies from 7.2% to 17.2%. (Unwin 2002) IGT is commoner in females than in males in European populations with the exception of the age range 80 to 89 years where it is more prevalent in men (Unwin 2002).

Type 2 diabetes is a chronic disease often preceded by a long asymptomatic period. It is well known that type 2 diabetes presents late, with many people having established complications at diagnosis (Verhoeven 1991). Cardiovascular risk is increased at the time of diagnosis and appears to be independent of the duration of the diagnosis of diabetes (West 1983). One reason for this is that a long period of undiagnosed diabetes may be preceded by even longer intervals of prediabetes [Impaired Fasting Glycaemia (IFG) and IGT] (Harris 1993). (table 2.1) Data from the UKPDS suggest that the onset of diabetes may be up to seven years before the clinical diagnosis is made. Extrapolation of the association between prevalence of retinopathy and the duration of diabetes suggests that glucose tolerance may start to decline up to 12 years before clinical recognition. (UKPDS 16, 1995) This provides a window of opportunity to identify glucose intolerance early and to intervene to improve long-term outcomes.
Type 2 diabetes is associated with a significant burden of premature mortality, morbidity and financial cost. People with type 2 diabetes have a life expectancy that can be shortened by as much as 10 years. (DOH 2001) Macrovascular disease accounts for most of the excess mortality and morbidity associated with type 2 diabetes. Over 60% of individuals with diabetes will die from coronary heart disease (Laing 1999), and there is a 2-4 fold increase risk of cerebrovascular disease in those with diabetes compared to those with normal glucose tolerance. (Folsom 1999) There is increasing evidence from large clinical trials suggesting that earlier detection of diabetes and treatment of hyperglycaemia and the related metabolic abnormalities may be beneficial in reducing the development and progression of cardiovascular events and complications of diabetes. Recent large trials have shown that lifestyle interventions can delay or prevent diabetes in people with prediabetes. (Pan 1997, Tuomilehto 2001, DPPRG 2002, Ramachandran 2006) However, it is less clear whether the increased prevalence of cardiovascular disease in prediabetes will respond to treatments that lower blood glucose. (ADA 2002, Engelgau 2000) Studies are in progress but macrovascular outcome data are not yet available. (Navigator 2002) To reduce the impact of type 2 diabetes in the 21st century we need not only to optimally treat the person with established diabetes but also to prevent diabetes and the associated complications from occurring in the first place.

The current best evidence for the prevention of diabetes is for interventions that target those individuals at highest risk. Patients at highest risk include those with IGT, targeting them with lifestyle changes including physical activity and dietary factors have been shown to be effective in the Chinese, North American, Finnish and Indian populations. (Pan 1997, Tuomilehto 2001, DPPRG 2002, Ramachandran 2006) In order for such lifestyle interventions to be successful in other populations, they need to be culturally sensitive, individualized and sustained. Some pharmacological agents including metformin and acarbose have also been shown to be effective, although the profile of those who respond is different. (Holman 2003, Chiasson 2002, DPPRG 2002)

This chapter will review the current literature on different screening methods for diabetes, including how, who and when to screen. Then the evidence on preventing the progression of prediabetes to diabetes will be reviewed. Lastly the literature regarding screening for abnormal glucose tolerance in order to identify individuals with prediabetes so that progression to diabetes can be prevented will be presented.
2.2 Definitions of abnormal glucose tolerance

The plasma glucose values for defining diabetes, IGT and IFG are shown in table 2.1 and discussed in section 2.2. (WHO 1998, ADA 2005)

Table 2.1 The plasma glucose values for defining diabetes, IGT and IFG

<table>
<thead>
<tr>
<th>Glucose concentration – mmol/l</th>
<th>Plasma venous</th>
<th>Whole blood venous</th>
<th>Capillary</th>
</tr>
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<tbody>
<tr>
<td><strong>Diabetes mellitus</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting and/or</td>
<td>≥ 7.0</td>
<td>≥ 6.1</td>
<td>≥ 6.1</td>
</tr>
<tr>
<td>2-h post glucose load</td>
<td>≥ 11.1</td>
<td>≥ 10.0</td>
<td>≥ 11.1</td>
</tr>
<tr>
<td><strong>Impaired Glucose Tolerance</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting</td>
<td>&lt; 7.0</td>
<td>&lt; 6.1</td>
<td>&lt; 6.1</td>
</tr>
<tr>
<td>2-h post glucose load</td>
<td>7.8 – 11.1</td>
<td>6.7 – 9.9</td>
<td>7.8 - 11.0</td>
</tr>
<tr>
<td><strong>Impaired fasting glycaemia</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting</td>
<td>6.1 – 6.9</td>
<td>5.6 – 6.0</td>
<td>5.5 – 6.0</td>
</tr>
<tr>
<td>2-h post glucose load</td>
<td>&lt; 7.8</td>
<td>&lt; 6.7</td>
<td>&lt; 7.8</td>
</tr>
<tr>
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<td>5.1 – 5.5</td>
<td>5.0 – 5.5</td>
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2.2.1 Diabetes

It was not until 1979 that a widely accepted diagnosis for diabetes was available. Prior to this the diagnosis of diabetes was inconsistent. Different cut-off glucose values at different time intervals and differing glucose loads given either intravenously or orally were used. This made research and comparisons between geographical and ethnic populations difficult to interpret.

In 1978 the World Health Organization (WHO) and in 1979 The US National Diabetes Data Group (NDDG) published their diagnostic criteria and a new classification system for diabetes was established. (NDDG 1979, WHO 1980) However the diagnostic criteria still varied. In 1985 the WHO altered their criteria to more closely match the NDDG criteria. (WHO 1985)

In 1997 the WHO criteria were altered again when it was acknowledged that people with diabetes were developing symptoms and both macrovascular and microvascular
complications at fasting plasma glucose (FPG) levels of 7.0 mmol/l. These levels were below the 7.8 mmol/l previously recognised as diagnostic for diabetes. (ADA 1997, Alberti 1998) The American Diabetes Association, (ADA) who used the NDDG classification, and the WHO criteria unfortunately differed again as the ADA decided that diabetes could be diagnosed using only the lower level of FPG (7.0 mmol/l) and the 2-hour glucose value was no longer necessary, whereas the WHO maintained the use of both FPG and 2-hour glucose values. At present this discrepancy remains in the diagnosis of diabetes between the ADA and WHO criteria. Throughout this thesis the WHO criteria are used, which are widely accepted across the United Kingdom and Europe.

The diagnosis of diabetes should only be based on a single glucose value if an individual is already symptomatic with hyperglycaemia. If there are no symptoms present then two glucose values within the diabetic range are needed on two separate days.

2.2.2 Impaired Glucose Tolerance and Impaired Fasting Glycaemia
The term IGT was introduced in 1979 by the US NDDG (NDDG 1979) and can be identified with a glucose tolerance test. It was first introduced as a term to replace ‘borderline’ or ‘chemical’ diabetes. It was recognised from epidemiological studies that people with glucose values above normal but below those recognised for diabetes were at risk of macrovascular disease, but not at risk of microvascular complications. (Jarrett 1976). However, it was not until 1985 that the precise definition was outlined by the WHO (WHO 1985). IGT was defined as a venous FPG of < 7.8 mmol/l and a level of between 7.8 and 11.1 mmol/l two hours after a 75-gram oral glucose load (WHO 1985). The definition of glucose intolerance changed in 1997 when the ADA proposed a change in the diagnostic FPG (ADA 1997). The diagnosis of IGT remained the same in terms of the two-hour post glucose value (≥ 7.8 and < 11.1 mmol/l) but the FPG level for a diagnosis of diabetes was lowered to < 7 mmol/l. There was also an introduction of a new category of abnormal glucose tolerance called Impaired Fasting Glucose (IFG) defined as an elevation of the FPG between 6.1 to 6.9 mmol/l with a 2-hour plasma glucose of less than 7.8 mmol/l. (ADA 1997). However, the underlying pathological processes that cause diabetes may be recognisable in people who have glucose levels even lower than this. The threshold for defining IFG may need to be decreased if we want ‘normal glucose tolerance’ to mean there is no increased risk of progression to diabetes. In recognition of this in 2002 the ADA lowered the definition of IFG to a FPG value of ≥ 5.6 mmol/l. (ADA 2005) However this lower threshold has not accepted internationally.
Maintaining normoglycaemia requires a balance between glucose production and disposal mediated by skeletal muscle, pancreatic B-cells, and the liver. IGT and IFG may represent different abnormalities of glucose regulation. Since this was suggested by O’Rahilly in 1994 there has been much support for this concept. (O’Rahilly 1994) IGT is thought to reflect abnormal post-prandial glucose control mainly secondary to insulin resistance in the skeletal muscles and liver and IFG reflects abnormal FPG control due to pancreatic B-cell abnormality. (Turner 1976, Ferranini 1985) Those with IFG have been shown to have equivalent insulin resistance, but depressed B-cell function with greater impairment in first-phase insulin secretion and higher basal hepatic endogenous glucose output compared with IGT. (Weyer 1999, Davies 2000) Both IFG and IGT are stages in the natural history of abnormal glucose metabolism and are associated with an increased risk of progression to diabetes and macrovascular disease. Progression to diabetes does not always occur and therefore the phrase ‘prediabetes’, which is recognised by the ADA to include both IGT and IFG, (ADA 2005) is not accepted by all specialists within the field of diabetes.

2.2.3 Normal glucose tolerance
Apart from in the United States a FPG concentration less than 6.1 mmol/l is currently classified as ‘normal’. (WHO 1998) Individuals with a normal FPG may have elevated 2-hour post-prandial glucose values. Therefore to be certain an individual has normal glucose tolerance both a FPG and 2-hour post challenge plasma glucose are needed. The 2-hour value should be < 7.8 mmol/l. (Alberti 1998) It may be that the definition of normal glucose tolerance will change alongside the lower FPG criteria for the definition for IFG. Detecting those people with early changes is likely to be beneficial in that the pathological processes have a greater chance of being reversible at this stage, but has the disadvantage of identifying more individuals, some of whom will be at low risk of subsequently developing diabetes or cardiovascular disease.

2.3 Why screen for diabetes?
Diabetes is associated with a substantial burden of mortality and morbidity. Diabetes UK and the British Heart Foundation report that in the UK up to 35,000 deaths a year are attributable to diabetes – around one in seven of all deaths. Individuals with type 2 diabetes are at significantly higher risk for coronary heart disease, peripheral vascular disease and stroke, and they have increased risk of having hypertension, dyslipidaemia and obesity. (DeFronzo 1991, Eastman 1997, UKPDS 23 1998, DECODE 2001) At the time of
diagnosis of diabetes there are often already established complications (see figure 2.1). Recent trials suggest that much of the potential benefit of detecting undiagnosed diabetes is likely to accrue from intensive management of cardiovascular risk factors in addition to treatment of hyperglycaemia (Hansson 1998, UKPDS 38 1998)

Figure 2.1 The prevalence of complications at diagnosis in the UKPDS

2.4 Criteria for screening in asymptomatic populations
The National Service Framework (NSF) for Diabetes standard two states that the NHS will develop, implement and monitor strategies to identify people who do not know they have diabetes. (Department of Health 2003) The National Screening Committee has recently appraised the evidence for effectiveness and appropriateness of screening for type 2 diabetes. The criteria to judge whether a screening programme is justified or not are based on the classic criteria published by the WHO in 1966. (Wilson 1966) Generally screening is appropriate in asymptomatic populations when certain conditions are met. These are shown in Table 2.2 (Engelgau 2000) In the case of diabetes the first three criteria are clearly met. The next three criteria are probably met, or met in part. And the last criteria is uncertain. Each of these will be discussed.
Table 2.2 Criteria for screening in asymptomatic populations

<table>
<thead>
<tr>
<th>The disease represents an important health problem that imposes a significant burden on the population</th>
</tr>
</thead>
<tbody>
<tr>
<td>The natural history of the disease is understood</td>
</tr>
<tr>
<td>There is a recognizable pre-clinical stage during which the disease can be diagnosed</td>
</tr>
<tr>
<td>Treatment after early detection yields benefits superior to those obtained when treatment is delayed.</td>
</tr>
<tr>
<td>The benefit of screening outweighs the physical and psychological harm caused by the tests, diagnostic procedures and treatment.</td>
</tr>
<tr>
<td>Tests are available that can detect the pre-clinical stage of a disease and the tests are acceptable and reliable</td>
</tr>
<tr>
<td>The costs of case finding and treatment are reasonable and are balanced in relation to health expenditures as a whole</td>
</tr>
</tbody>
</table>

2.4.1 The disease represents an important health problem that imposes a significant burden on the population.

There is no doubt that diabetes is an important common condition. There is significant burden of premature mortality, morbidity and a large financial cost through both macrovascular and microvascular complications.

2.4.2 The natural history of the disease is understood

The natural history of diabetes is understood and has been well described and diabetes can be seen to progress through several identifiable stages. (Knowler 1990) The incidence of diabetes is strongly related to IFG, IGT and gestational diabetes. There are well recognised risk factors that are associated with the development of diabetes, such as age, family history of diabetes, obesity and blood pressure. (Shaw 1999, Gabir 2000, deVegt 2001)

2.4.3 There is a recognizable pre-clinical stage during which the disease can be diagnosed

Using the same diagnostic criteria diabetes can be diagnosed in both symptomatic and asymptomatic individuals. Between a third and a half of cases of type 2 diabetes are currently undiagnosed, which in England is thought to be over 650,000 people. (ADA 1997, Diabetes UK 2002, YHPRO 2006) Diabetes may have been present for up to 7 years before it is diagnosed (Harris 1992) and glucose tolerance has been estimated by
extrapolation from the prevalence of retinopathy at clinical diagnosis to begin to decline up to 12 years prior to diagnosis. (UKPDS 16 1995)

2.4.4 Treatment after early detection yields benefits superior to those obtained when treatment is delayed.

This is a more difficult criteria to fulfil for screening for diabetes. The benefits of improved glycaemic control and blood pressure treatment in patients with clinically diagnosed diabetes are established. The benefits and risk of screening and early treatment are less clear. Schneider, from Germany, looked at the 32-year follow up of 166 people with diabetes diagnosed in a screening program in 1962-63, and also a retrospective 12-year study on 488 patients diagnosed in 1976. The 32-year follow up showed a lower but not statistically significant average loss of life years, whereas the 12-year data did show a significantly lower loss of life years for patients screened in comparison with those conventionally diagnosed diabetes. (Schneider 1996)

Recent data strengthens the argument for screening. The UKPDS study group analysed the baseline characteristics, presence of hyperglycaemic symptoms and clinical outcomes in relation to the FPG in 5088 patients. Those patients with lower or intermediate FPG at diagnosis had reduced risk factors, fewer hyperglycaemic symptoms and, of great importance, a reduced risk of developing diabetes complications. This retrospective finding supports the theory that earlier diagnosis of diabetes will lead to improved outcomes, but there remains a lack of prospective trial evidence. (Colagiuri 2002)

As yet there is little trial evidence that earlier detection of diabetes and intervention improves outcomes, or that the cardio-protective effect of intensive blood pressure reduction (UKPDS 38 1998), ACE-inhibition (HOPE 2000) and cholesterol lowering therapy (Pyorala 1997) effective for patients with clinically diagnosed produces the same or greater benefit when commenced in those with screen-detected abnormal glucose tolerance. (Pauker 1993) The STENO study in conventionally diagnosed, but already at high risk because of the presence of microalbuminuria, patients with diabetes found a 20% absolute risk reduction and a 50% relative risk reduction for cardiovascular events after multi-factorial risk reduction compared to the control group. Similarly the relative risk of developing nephropathy, retinopathy and autonomic neuropathy were all reduced by about 50% in the intensively treated group. (Gaede 1999, 2003, 2004, 2004) The ongoing MRC and Department of Health funded ADDITION study, is part of an international
collaborative, and is specifically designed to determine whether earlier multi-factorial intervention in screen-detected diabetes will improve cardiovascular outcomes for patients. In this study patients are randomised to two groups. In one group patients will be treated according to local protocols. In the other group patients will receive more intensive multi-factorial intervention with targets set lower than ‘traditional’ evidence based medicine targets. (Lauritzen 2000)

2.4.5 The benefit of screening outweighs the physical and psychological harm caused by the tests, diagnostic procedures and treatment.

This needs further assessment. Advances and increasing expenditure on health means that many more patients are screened for various conditions to improve quality and quantity of their lives including prostate cancer, breast and bowel cancer. The effects of screening in general and particularly screening for diabetes have not been extensively evaluated. Currently negative effects of screening are poorly understood, but may be considered in the broad categories of physical, psychological and social.

**Physical**

There are only a few potential physical adverse effects involved with the screening for diabetes such as nausea after ingestion of glucose load and repeated blood tests. Following diagnosis there are the risks of hypoglycaemia associated with drug and insulin treatment. Patients with screen detected diabetes may well be on medication for longer periods of time than individuals whose diabetes is diagnosed only when symptoms develop and therefore have greater exposure to oral hypoglycaemic drugs.

**Psychological**

There is limited data on the psychological impact of screening for diabetes and concerns have been expressed about the psychological impact of screening programmes in general. Documented negative effects of screening for diabetes are likely to be similar to those reported for screening for other conditions. These include harmful effects of misdiagnosis (Genuth 2002), negative attitudes among patients diagnosed (Bullimore 1997), a small reduction in perceived health after a false positive result (Kerbel 1997) and a lowering of mood associated with the diagnostic label of diabetes. (Johnston 1984). In addition false reassurance following a false negative result can lead to a worsening of risk (Marteau 1996). The diabetes label also has additional specific adverse consequences, including
employment, particularly among drivers of passenger carrying vehicles and increased health and travel insurance costs.

Little is known about any negative psychosocial consequences of early detection of type 2 diabetes. Some recent studies have been more reassuring; suggesting screening for diabetes was not associated with major adverse psychological events and does not affect the patients’ quality of life. (Edelman 2002). Other studies have suggested that there is little evidence for any negative impact of screening on an individuals’ current emotional well being. (Adriaanse 2002, Farmer 2003, Ludvigsson 2002) As part of this thesis this particular area will be studied further. The diagnosis of diabetes may have effects on the behaviour of health professionals that have consequences for the patients. Following diagnosis patients should get invited to annual review clinics, education sessions and cardiovascular risk factor assessment and treatment, which may lead to more aggressive risk reduction. At annual review appointments individuals with diabetes should be screened for the presence of microvascular complications, including microalbuminuria, retinopathy and neuropathy.

Social
After diagnosis some patients may have increased difficulty or cost in obtaining travel and health insurance or employment. In addition there will be some individuals with false negative or positive results that can have a significant impact. A false positive test exposes individuals to the risks of subsequent unnecessary tests, whereas individuals’ with false negative tests will not receive subsequent diagnostic testing and may be falsely reassured that they do not have diabetes.

The size and nature of the benefits of detecting and treating diabetes earlier and the costs and disbenefits of screening and labelling people as having diabetes should be assessed in a trial prior to establishing definitive screening programmes for diabetes.

2.4.6 Tests are available that can detect the pre-clinical stage of a disease and the tests are acceptable and reliable
For the most part this criteria is met for screening for diabetes. There are a number of tests that could be used for screening. These include both biochemical tests and risk factor assessment tools or questionnaires.
A screening test ideally should be safe and simple whilst being sensitive (high probability of being positive when the subject truly has the disease) and specific (have a high probability of being negative when the subject does not have the disease). It also needs to be reliable and reproducible such that consistent results should be obtained when the test is performed more than once on the same person under the same conditions. (National Screening Committee 1998) When considering a test, the positive predictive value (PPV) needs also to be considered. This is the probability of having diabetes when the screening test is positive. The PPV is determined by the sensitivity and specificity of the screening test and the prevalence of diabetes in the population. When sensitivity and specificity are constant the higher the prevalence of a disease is, the higher the PPV of the screening test. (Lang 1997) Any increase in PPV will translate to more cases detected for each diagnostic test and therefore the PPV has important implications for resource use for a screening programme.

When evaluating studies that have looked at the performance of screening tests for type 2 diabetes the characteristics of the study population, cut-off points of screening tests and the nature of the definitive diagnostic test should all be reviewed. The population characteristics are important because the prevalence of diabetes in the population affects the PPV. The nature of the population may also affect the apparent performance of the test. Such that both sensitivity and specificity will be higher in populations that include subjects with severe hyperglycaemia, which is also the case when patients with diagnosed diabetes are included in the screened population. Studies that include individuals with diabetes should be interpreted cautiously.

Receiver Operator Characteristic (ROC) curves are theoretical tools that can be used to describe the performance of a test over a range of cut-off points. They demonstrate the relationship between sensitivity and specificity and help describe the optimal cut-off point for a test. Generally a trade off has to be made between sensitivity and specificity. Increasing sensitivity reduces specificity and increasing specificity reduces sensitivity. The overall performance of a test can be quantified by the area under the curve (AUC), the greater this value, the better the performance. A test with an AUC of under 0.5 is regarded as worthless, 0.8-0.89 would be a good test and 0.9-1.0 would make an excellent test. (Lang 1997) The optimal test characteristics are considered to exist when there is maximum sensitivity and specificity. (Lang 1997) However when screening for abnormal
glucose tolerance this may not be the optimal cut-off as it is important to have a good sensitivity so that only a few individuals are given false negative results.

2.4.6.1 Urinalysis
Urinalysis is easy to perform and has been shown to be more cost-effective than blood testing. (Davies 1999) Although the specificity may be > 98%, random urinalysis only has a sensitivity of around 20%, (Friderichsen 1997, Andersson 1993) this can be increased to 43–78% if measured after a glucose challenge. (Davies 1999) Two studies of postal screening in which individuals were asked to test their urine one hour after a meal, first in a predominantly Caucasian rural setting and then in a city environment with both Asian and Caucasian individuals found the response rate varied from 30 to 70% and the presence of glycosuria in those responders varied from 0 to 18%. Individuals with glycosuria were invited to attend for an OGTT when the presence of abnormal glucose tolerance was around 45%. The simplicity and cost-effectiveness of such a programme makes postal post-prandial urinalysis an appropriate method of screening for abnormal glucose tolerance in those aged 35-64 years. (Davies 1993, Davies 1999)

2.4.6.2 Fasting Plasma Glucose
FPG is a reasonably simple and inexpensive method to use when screening for diabetes. The only limiting factor is that the individual has to attend after a fast, and this relies on the patient following instructions for the overnight fast. Using the FPG as a screening tool and deciding at what threshold individuals would benefit from further investigation has been investigated. The WHO recommends the threshold is 5.5 mmol/l, whereas the ADA recommendations are for a higher threshold of 6.1 mmol/l. Other studies have recommended values up to 7.8 mmol/l. The sensitivity ranges from 40-65% at a specificity of > 90% depending on the population being studied and the cut-off decided upon. (ADA 2002, WHO 2003, Weiner 1998, Larsson 1998, Pauvilai 1999)

2.4.6.3 Random blood glucose
This is easier and more convenient to obtain than a FPG but has a lower sensitivity and specificity. The accuracy of the blood glucose meter being used would need to be carefully checked before any screening initiatives. A random blood glucose is probably only useful if > 11.1 mmol/l which confirms diabetes or < 5.5 mmol/l which makes a diagnosis of diabetes unlikely. The ADA considers a random plasma glucose \( \geq 8.9 \) mmol/l to require further testing. (ADA 2000) Random blood glucose could be used
opportunistically and is easier and more convenient to obtain and measure. However it has a lower sensitivity and specificity than FPG, with sensitivities ranging from 40 to 79% dependent on age and gender of individuals being tested. (Andersson 1993, Qiao 1995)

Capillary glucose estimations on whole blood, rather than venous blood, have the benefit of only requiring a pin-prick sample, and portable equipment can be used. However, the accuracy of these is generally inadequate for diagnosis. (Campbell 1992). Following a positive screening test with a capillary glucose sample, two further tests would be needed to confirm a diagnosis of diabetes. (Alberti 1998) However there are studies which have used random capillary glucose levels as a screening test. In one study a cut-off of 5.8 mmol/l had sensitivity of 40% in women and 79% in men with specificities 84-86%. (Qiao 1995) A study from the US found a value of 5.6mmol/l to have sensitivities from 68-74% and specificity of 66-77% depending on age. (Engelgau 1995) In both of these studies the specificity is too low for capillary glucose to be useful as a screening tool.

2.4.6.4 Glycated haemoglobin

HbA1c is a marker of long-term blood glucose control and is used as a measure of an individual’s glycaemic control over the previous three months. Therefore HbA1c is less influenced by recent activity including meals. It is an attractive method of screening as it requires no particular patient preparation, can be taken at any time of the day and has been shown to be directly related to outcome, particularly microvascular and macrovascular complications. (Stratton 2000) It is also a more comprehensive measure of total glycaemic exposure compared to FPG in that it is a measure of plasma glucose not only in the fasting state but also in the post-prandial state. It is more costly than FPG in laboratory terms but this should be balanced against health care professional time and patient convenience. HbA1c is different to the plasma glucose values used to diagnose diabetes, so would minimise confusion that could occur between tests used to screen for and to diagnose diabetes. Now that more laboratories have DCCT/UKPDS aligned assays for measurement of HbA1c the previous difficulties of variability in assays have been minimized. Recent screening studies, including a meta-analysis of papers between 1966 and 1994, have shown that using HbA1c, has sensitivities from 35% to 92%, with specificities of 80 to 100%. (Rohlfing 2000, Peters 1997, Papoz 2000, Sekikawa 1990) The performance of the HbA1c depends on the cut-off point used and the population in whom it is used. HbA1c has been used to detect ‘treatment requiring’ diabetes with a HbA1c of 7%, on the basis that hypoglycaemic medications are not usually prescribed for patients with HbA1c values lower than this. However this approach is changing in recognition of the benefit from
earlier treatment of associated metabolic abnormalities to prevent macrovascular complications and the importance of screening for and treating microvascular complications, which can occur at HbA1c levels below 7%.

2.4.6.5 Oral Glucose Tolerance Test or 2-hour post glucose load test.
The OGTT is the gold standard test in terms of diagnosis, and includes both FPG and 2-hour post glucose load glucose levels. Benefits include that people with early diabetes are more likely to meet the 2-hour glucose value for diabetes than the fasting value; however it is more costly in both financial terms and in healthcare professional and patient time. If a formal OGTT is performed the practicalities of two glucose tests 2 hours apart with a glucose drink at the onset are complicated. The ADA no longer uses the OGTT for routine clinical use because they consider it to be inconvenient to the patient, costly, to take excessive time and because the reproducibility of the test is only about 65%. The reproducibility of the OGTT can be increased by paying attention to the detail. The glucose load should be consumed within 5 minutes, only minimal exertion should take place before the 2-hour glucose level is taken, there should be no smoking and at least an 8-hour fast should precede the test. The practicality of using a relatively complicated test in primary care to screen large numbers of people needs further evaluation.

Individuals could be provided with information to fast overnight, consume 75-g glucose and then attend for a venous glucose test 2 hours later. This decreases the health care professional time but provides opportunity for inconsistency and error. A sensitivity of 50% and specificity of 98% was achieved using glucose tolerance tests for screening. (West 1971) Greater sensitivities were reached but at the expense of lower specificities. (Hanson 1993). However despite these drawbacks the OGTT does remain the gold standard for the diagnosis of diabetes.
Table 2.3 Summary of the performance of screening tests for type 2 diabetes

<table>
<thead>
<tr>
<th>Screening test</th>
<th>Cut-point</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Authors And any Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random urinalysis</td>
<td>Trace glycosuria</td>
<td>18 %</td>
<td>99 %</td>
<td>Andersson 1993</td>
</tr>
<tr>
<td></td>
<td></td>
<td>20.8 %</td>
<td>99.1 %</td>
<td>Friderichsen 1997 Denmark</td>
</tr>
<tr>
<td>Fasting urinalysis</td>
<td></td>
<td>16.7 %</td>
<td>97.9 %</td>
<td>Forrest 1987 Islington Diabetes Survey</td>
</tr>
<tr>
<td>Postprandial urinalysis</td>
<td></td>
<td>43 %</td>
<td>98 %</td>
<td>Davies 1993, 1999 England, White European and South Asian</td>
</tr>
<tr>
<td></td>
<td></td>
<td>72.7 %</td>
<td>77.4 %</td>
<td>Forrest 1987</td>
</tr>
<tr>
<td>Fasting plasma glucose</td>
<td>≥ 5.5 mmol/l</td>
<td>&gt;90 %</td>
<td></td>
<td>WHO 2003</td>
</tr>
<tr>
<td></td>
<td>&gt; 6.1 mmol/l</td>
<td>80 %</td>
<td>96 %</td>
<td>Hanson 1993</td>
</tr>
<tr>
<td></td>
<td>&gt; 6.1 mmol/l</td>
<td>40-65 %</td>
<td>&gt;90 %</td>
<td>ADA 2002</td>
</tr>
<tr>
<td></td>
<td>&gt; 4.8 mmol/l</td>
<td>85.9 %</td>
<td>45 %</td>
<td>Larsson 1998 Sweden, Caucasian females</td>
</tr>
<tr>
<td></td>
<td>&gt; 5.3 mmol/l</td>
<td>77.0 %</td>
<td>77.0 %</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt; 6.0 mmol/l</td>
<td>53.4 %</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥ 6.0 mmol/l</td>
<td>89.9 %</td>
<td>65.9 %</td>
<td>Weiner 1998 Manchester and Liverpool</td>
</tr>
<tr>
<td></td>
<td>&gt; 6.5 mmol/l</td>
<td>83.7 %</td>
<td>80.3 %</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt; 7.0 mmol/l</td>
<td>73.6 %</td>
<td>89.2 %</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt; 7.5 mmol/l</td>
<td>61.8 %</td>
<td>94.2 %</td>
<td></td>
</tr>
<tr>
<td>Random plasma glucose</td>
<td>≥ 8.9 mmol/l</td>
<td>40-79%</td>
<td></td>
<td>ADA 2000</td>
</tr>
<tr>
<td>Random capillary blood</td>
<td>≥ 8.0 mmol/l</td>
<td>69 %</td>
<td>95 %</td>
<td>Andersson 1993</td>
</tr>
<tr>
<td>glucose</td>
<td>≥ 6.2 mmol/l</td>
<td>63 %</td>
<td>92 %</td>
<td>Qiao 1995</td>
</tr>
<tr>
<td>Plasma glucose</td>
<td>≥ 11.1 mmol/l</td>
<td>69 %</td>
<td>97 %</td>
<td>Forrest 1986 Islington Diabetes Survey</td>
</tr>
<tr>
<td>2-hours after glucose</td>
<td>≥ 8.6 mmol/l</td>
<td>90 %</td>
<td>93 %</td>
<td>Hanson 1993</td>
</tr>
<tr>
<td>load</td>
<td>≥ 6.1%</td>
<td>63.2%</td>
<td>97.4%</td>
<td>Rohlffing 2000 NHANES population</td>
</tr>
<tr>
<td></td>
<td>≥ 6.0 %</td>
<td>74 %</td>
<td>93 %</td>
<td>Papoz 2000 Island of La Reunion</td>
</tr>
<tr>
<td>HbA1c</td>
<td>≥ 5.0 %</td>
<td>83.7 %</td>
<td>69.5%</td>
<td>Weiner 1998 Manchester and Liverpool</td>
</tr>
<tr>
<td></td>
<td>≥ 5.5 %</td>
<td>64.0 %</td>
<td>91.0 %</td>
<td>Normal range HbA1c ≤ 5.5 %</td>
</tr>
<tr>
<td></td>
<td>≥ 6.0 %</td>
<td>50.6 %</td>
<td>98.2 %</td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥ 6.2 %</td>
<td>41.0 %</td>
<td>100 %</td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥ 5.6 %</td>
<td>35.0 %</td>
<td>100%</td>
<td>Sekikawa 1990</td>
</tr>
</tbody>
</table>

2.4.6.6 Risk factor assessment tools

The presence of a single risk factor or several risk factors does not always correlate to the development of or presence of diabetes, but the likelihood of an individual without any risk factors having or developing diabetes is low. (Cowie 1994) Using a scoring method, which assesses the combination of risk factors an individual has, can contribute towards identifying individuals who would benefit from further screening. (Griffin 2000, Lindstrom 2003) This information could come from data available in primary care or by
individuals self-completing a questionnaire. A risk score based on questions about phenotypical characteristics for type 2 diabetes will not achieve 100% sensitivity because some individuals with type 2 diabetes have a phenotype more like individuals with type 1 diabetes. (Tuomi 1999) Using a risk score as the first test for screening for diabetes is attractive because it decreases the number of people who will need more invasive time consuming tests and is a simple and low cost test to undertake. (Griffin 2000, Glumer 2004) Several scoring methods have been developed, but they have different methods for allocating a score for each risk factor and different levels of score to indicate an individual is at high risk of diabetes. The methods include self-reported demographic, behavioural or medical information or can be completed using information from a general practice computer database.

**Cambridge Diabetes Risk Score**

A risk factor score was developed for use as a screening tool by Griffin et al (Griffin 2000) and is known as the Griffin or Cambridge Diabetes Risk Score (CDRS). The score is produced using stepwise logistic regression and uses data from the Wessex study on cases of clinically diagnosed type 2 diabetes (Kinmouth 1996), and from the Ely study of prevalent cases of screen-detected type 2 diabetes. (Williams 1995). The score is calculated to produce a value between 0 and 1 to give the probability of having undiagnosed type 2 diabetes. The performance of this CDRS, in detecting diabetes, was evaluated in an independent, randomly selected, population-based sample from the Ely study. Age, gender, body mass index, (BMI) steroid and antihypertensive medication, family history and smoking contributed to the score. When the risk score was used to determine the probability of having undiagnosed diabetes the sensitivity was 77%, specificity 72% and area under receiver operating characteristic (ROC) curve was 80% (95% CI 68 to 91%). (Griffin 2000) When the score was used to predict undiagnosed hyperglycaemia (HbA1c> 7.0%) the sensitivity and specificity was lower at 51% and 78%. (Park 2002)

This score does include BMI and requires the presence of other risk factors to have been entered onto the computer database. It is a difficult formula to use because it involves complex arithmetical calculations and this may be a deterrent to its use. However it is possible that a simple computer programme can be used to calculate this score in a GP environment.
**Finnish Diabetes Risk Score**

The Finnish Diabetes Risk Score (FDRS) was developed in Finland, by Tuomilehto, to characterize individuals according to both their future risk of developing and current risk of having type 2 diabetes. (Lindstrom 2003) It is based on the self assessed risk factors - age, BMI and waist circumference and on questions around the use of blood pressure medication, history of high blood glucose, physical activity, and dietary intake of vegetables, fruit or berries. The FDRS was derived from the coefficients of logistic regression, which were then used to formulate the score which can then be simply calculated. The score ranges from 0 to 20. For the detection of prevalent diabetes, the sensitivity of FDRS was 76 to 77% and the specificity 66 to 67% with a positive predictive value of 7 to 12% and the negative predictive values of 98 to 99%. (Lindstrom 2003) The authors found a cut point of 9 best identifies individuals at higher risk of developing type 2 diabetes, with a sensitivity of 78 to 81% and a specificity of 76 to 77%. Since the original publication of the FDRS, the authors have suggested a modification which includes family history. The presence of a positive family history in a first degree relative contributes five points and increases the possible total score to 25. (unpublished personal communication) The FDRS does not need clinical data collected by a health care professional and is a simple and quick questionnaire completed by the individual. However it has only been used in a predominantly White European population. (Lindstrom 2003, Rathmann 2005, Franciosi 2005)

**Danish Diabetes Risk Score**

In Holland a simple risk score based on a self-administered questionnaire was developed that could identify at least 75% of individuals with diabetes and reduced the number of subsequent blood tests to 28%. (Glumer 2004) A random age- and sex stratified sample of patients who had participated in the Inter99 study were invited to complete the questionnaire containing information on symptoms of diabetes and risk factors for diabetes. Univariate analysis and then multiple logistic regression including only significant variables were used to create the score. (Glumer 2004) The risk score ranged from 0 to 60 and depended on age, sex, BMI, known hypertension, physical inactivity and parental history of diabetes. The advantages of this Danish Risk score are that it was developed in population that includes younger individuals (aged 30 to 60 years), and can be completed by patients at home without any specific measurements. However, this risk score has also only been used in a predominantly White European population.
National Health and Nutrition Survey (NHANES) data Questionnaire
A screening questionnaire was developed from the NHANES data. (Herman 1995) The questionnaire included age, sex, history of delivery of a macrosomic infant, obesity, sedentary lifestyle and family history of diabetes. The questionnaire had a sensitivity of 79% and a specificity of 65%, but when was used in conjunction with a fasting plasma glucose, the sensitivity increased to around 82% (Dominguez-Reyes 1999)

Dutch Questionnaires
In Holland a study was undertaken in which over 1000 patients aged between 55 and 75 years, who were not known to have diabetes, completed a questionnaire on diabetes-related symptoms and risk factors, and then underwent a glucose tolerance test. (Baan 1999) Predictive models were developed using stepwise logistic regression analysis and these predictive models were assessed in 2364 participants in the Hoorn study. This study found that a predictive model based on information only routinely collected by the GP performed similarly to more extensive ones supplemented by information obtained from additional questions and examination. It was felt that this model would be easy to implement in primary care. (Baan 1999). However the specificity of this questionnaire was lower at 55%. Therefore around 45% of the population needed subsequent testing which limits the utility of the questionnaire as a screening tool.

A new Symptom Risk Questionnaire (SRQ) was developed, in Holland, from the above questionnaire. The SRQ contains nine questions about age, sex, BMI, family history of diabetes, frequent thirst, use of antihypertensive medication, shortness of breath when talking to people of the same age, pain during walking with the need to slow down and reluctance to use a bicycle for transportation. Each answer has a fixed score and the total is used as a predictor of undiagnosed type 2 diabetes. This had greater sensitivity and specificity – an SRQ score cut point of six had 66% sensitivity and 70% specificity, 13% positive predictive value and 97% negative predictive value for diabetes. (Ruige 1997) but the SRQ does rely on individuals completing their own questionnaire.

American Diabetes Association Questionnaire
The ADA recommends the use of its questionnaire for community-screening programs to identify high-risk individuals. (Herman 1995) The questionnaire uses a scoring system and assigns different numeric values to the presence of different risk factors; a sum of 10 points
or more indicates a high risk for diabetes. There was a sensitivity of 83% and specificity of 65% when used on the National Health and Nutritional Examination Survey (NHANES) data. (Herman 1995) Using this questionnaire in a community program in New York the sensitivity and specificity changed to 80% and 35% respectively. (Knudson 1998) The use of this risk factor scoring questionnaire has been looked at in a Chinese population with a sensitivity of 74% for identifying undiagnosed diabetes. (Shen 1999)

**Summary of Risk Scores and Questionnaires**

The difference in, and availability of so many questionnaires demonstrates the lack of agreement about the importance in individual risk factors. Some questionnaires may not be applicable to different patient populations in different ethnic groups. It has been recommended that prior to community screening any risk score or questionnaire is validated in each population group involved. (ADA 2000) In the Netherlands not using a bicycle frequently is considered a risk factor for diabetes, however in a society that does not use the bicycle as a common form of transport this may not be such an important risk factor. In Finland not eating berries on a daily basis is included as a risk factor, whereas for example in the UK this would not be so.

The use of any scoring method, either alone or in combination with another screening method, could contribute to early detection or allow targeted screening. These have reasonable positive predictive value and predictive models based on routinely collected data in risk factors can be useful.

**2.4.6.7 Which is the best test?**

Many possible screening methods have been shown to be feasible, acceptable and accurate. Glucose concentrations after fasting and 2 hours after a glucose challenge and HbA1c could be considered for screening tests. Glycosuria detected by urine analysis has a high specificity but a low sensitivity. Testing random blood glucose concentrations is more sensitive but less specific. Risk factor questionnaires and risk scores have reasonable predictive power. Generally questionnaires used as single screening tests tend to perform poorly, whereas biochemical tests perform better. Furthermore, venous and capillary glucose measurements perform better than urinalysis or HbA1c measurements. Post-prandial or post-glucose load levels have an advantage over fasting glucose levels. In all of the tests and studies the test performance still depends on the population being
evaluated, interpretation within and across studies can be difficult. Ultimately the choice of cut-point of any test must be determined by the purpose of the screening programme and the resources required and available to perform further testing on the proportion of the population which would be identified by the choice of cut-point. (Colagiuri 2002)

The laboratory costs of analysing samples in the Leicester Royal Infirmary NHS Trust laboratory in 2004 was £2.39 for HbA1c and £2.14 for two glucose samples in the OGTT. (personal communication) Health care professional time is always going to be the greatest component to a screening programme but if a screening programme is to involve many thousands of individuals then the cost of individual screening tests will have an impact. Screening could be a two-stage process where a less expensive and more sensitive test is used first, which if positive is followed by a more specific test which would decrease the number of invasive tests needed. (Glumer 2004, Christensen 2004) For example, a risk questionnaire followed by a glucose measurement if a certain risk score was reached. Such strategies are unlikely to detect more cases but may allow for more efficient use of resources.

2.4.7 The costs of case finding and treatment are reasonable and are balanced in relation to health expenditures as a whole
The answer to this is unclear, there are few data on the costs of screening for diabetes, and cost effectiveness studies are urgently needed. Diabetes consumes a significant portion of health care funding. It accounts of nearly 9% of total NHS spend and 10% of hospital in-patient costs. (Currie 1997). The TARDIS (Type 2 Diabetes: Accounting for a Major Resource Demand in Society) survey showed that every person with Type 2 diabetes in the UK incurs on average direct costs of over £2000 per year. Over 80% of this accounted for within the NHS, approximately 13% by private expenditure and the remainder by social services. The presence of microvascular and macrovascular complications increases overall NHS costs more than five-fold. (Kings Fund 2002) Early identification of abnormal glucose tolerance has been shown to decrease complications. (UKPDS 28 1998, Tuomilehto 2001, DPPRG 2002) The tight control of blood pressure in hypertensive patients with type 2 diabetes was shown to substantially reduce the cost of complications, increased the interval without complications and had a favourable cost-effectiveness ratio compared to other accepted health care programmes. (UKPDS 40 1998) Similarly intensive blood glucose control in patients with type 2 diabetes significantly increased
treatment costs but substantially reduced the cost of complications and increased the time free from complications. (Gray 2000) With increasing healthcare costs, consideration must be given to screening to identify diabetes early and promote more intensive intervention to decrease overall complications and therefore costs.

Cost effectiveness analysis can help inform policy makers on better ways to allocate limited resources. The quality adjusted life year (QALY) is used to compare the effectiveness of a wide range of interventions. Cost effectiveness analysis produces a numerical ratio in pounds per QALY. This ratio is used to express the difference in cost effectiveness between new diagnostic tests or treatments and current ones. The threshold for adopting a diagnostic test or treatment is somewhere between 11 000 and 55 000 British pounds. (Bell 2006) The cost-effectiveness of screening for diabetes has been modelled using data from existing trials of treatment effectiveness and observational studies. (UKPDS 41 2000, UKPDS 33 1998, CDC 1998, Hansson 1998) One cost-effectiveness model of screening for diabetes, found that the cost per QALY for targeted screening was £18,630, while the cost for population screening was more than ten times greater. The authors found that targeted screening for diabetes (of people with hypertension) was more cost-effective than universal screening, and the cost per QALY decreased with increasing age. (Hoerger 2004) Another cost-effectiveness model on opportunistic screening, found the cost per QALY actually increased with increasing age, and varied from £7222 in people aged 25 to 34 years to £31 944 in people aged 65 years of over. (CDC 1998) The conclusions of these studies are highly dependent upon some crucial assumptions and reach different conclusions about whether screening should be undertaken and which sub-groups could potentially benefit. None of these take into account evidence from the Finnish Diabetes Prevention Study and the Diabetes Prevention Programme. (Tuomilehto 2001, DPPRG 2002) The main costs associated with screening are likely to be the costs of prolonged intensive treatment for screen-detected cases rather than the procedures for screening. (Goyder 1998) The same models have yet to be applied to screening for prediabetes.

Early diagnosis through screening and targeted prevention of high-risk groups is likely to be more cost effective than whole population screening. If early treatment of type 2 diabetes reduces the incidence of, or slows the progression of major complications, it might sufficiently reduce the costs of treatment during later years to offset the costs associated with screening and early treatment. (CDC 1998)
2.5 Who to screen

With any screening programme it is important to identify the strategy that is most efficient. The main approaches are population based screening, targeted screening and opportunistic screening.

Population based screening or mass screening is an attempt to screen every individual in the population. This is costly and potentially inefficient due to the relatively low prevalence of diabetes, particularly in some ethnic groups, younger age groups and in those without the traditional recognised risk factors. In 2002 in the United Kingdom there were estimated to be about 1.67 million people known to have diabetes giving a population prevalence of around 2%. (Diabetes UK 2002) Just 2 years later, in 2004, the National Diabetes Audit found, that in England alone, there were just under 1.77 million people known to have diabetes, giving a population prevalence of 3.25%. They also estimate a further 1.01% of the population have diabetes but are undiagnosed. (National Diabetes Audit 2005, National Statistics 2005) By 2006 the YHPRO had increased their prevalence estimates of diagnosed or undiagnosed diabetes to 4.67% of the population. (YHPRO 2006)

Targeted or selective screening is aimed at subgroups of the population with a higher prevalence of risk factors for diabetes. There are many recognised risk factors for diabetes, although different screening guidelines place varying importance on each risk factor. (table 2.4) This strategy may reduce the burden on the population by reducing the number of people who need a diagnostic test. Some authorities recommend screening only patients who have risk factors for type 2 diabetes and not for the population in general, however this does depend on knowing which individuals have risk factors. Different screening guidelines consider different risk factors as being important. Table 2.4 shows those risk factors common to most guidelines and those that are included by some. The utility of these and other risk factors is discussed in chapter 5.
Table 2.4 Risk factors identified for those at risk of having undiagnosed diabetes

<table>
<thead>
<tr>
<th>Risk Factors common to most screening guidelines</th>
<th>Other risk factors included in some screening guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increasing age – actual age varies</td>
<td>Ethnicity</td>
</tr>
<tr>
<td>Overweight - actual body mass index varies</td>
<td>History of gestational diabetes</td>
</tr>
<tr>
<td>History of IGT of IFG</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Family history of diabetes in first degree relative</td>
<td>Hyperlipidaemia</td>
</tr>
</tbody>
</table>

Opportunistic screening or case finding approaches screen individuals during routine visits to healthcare providers. This requires fewer resources to reach individuals but may have poor coverage as it will only include those make contact with the health service.

No study has yet looked explicitly at the age at which screening should commence or the optimal frequency of screening. In the DPS, DPP and STOP-NIDDM trials, participants were much older and heavier than the population initially screened, suggesting that individuals older than 45 years of age and who are substantially overweight were more likely to have abnormal glucose tolerance and therefore meet the inclusion criteria. (Chiasson 2002, DPP Research Group 2002, Tuomilehto 2001) If after screening, individuals found to have abnormal glucose tolerance were to be targeted with lifestyle changes, then the DPP results, would support screening older patients as it was in this age group where lifestyle interventions were more effective. (DPP Research Group 2002) Metformin was as effective as lifestyle intervention in individuals aged 24-44 years and in those with a BMI ≥ 35 kg/m². Whereas it was nearly ineffective in those over the age of 60 years or in those who were less overweight (BMI < 30 kg/m²) If medication is going to be offered then screening could be targeted to those younger individuals who have been found to benefit from medication. Nearly all the data on screening to date has been done on people under the age of 75 years. The UKPDS data suggested that benefits of intensive treatment for diabetes took up to 10 years to become apparent, (UKPDS 33 1998) which may limit the benefit of screening in the very elderly patients.
2.6 Current recommendations for screening for Diabetes

Screening for diabetes has been recommended in several countries due to the increasing prevalence of diabetes. However the guidelines do vary. The World Health Authority position statement on screening states that a FPG should be the initial screening test followed by an OGTT if the FPG is greater than 5.5mmol/l. (WHO 2003) The ADA recommends screening all individuals > 45 years by measuring FPG. The age is lowered if risk factors are present. (ADA 2002) They recommend a FPG of 6.1 mmol/l as the threshold at which the patient does proceed to an OGTT. This decreases the need for an OGTT to around 8% of the population. (ADA 2000) Neither the ADA, WHO or Diabetes UK recommend different cut-off values for ethnic populations. Diabetes UK recommends screening those considered most at risk – those > 40 years, or > 25 years if of non European ethnicity, with one of the following risk factors

- family history of diabetes
- macrovascular disease
- hypertension
- overweight with a sedentary lifestyle
- obesity

Any individual, regardless of their age, with a history of gestational diabetes, IGT, IFG or those individuals with polycystic ovarian syndrome and obesity would also meet the guidelines for being offered screening. (Diabetes UK 2002)

2.7 How often should we screen?

Screening will inevitably miss some individuals with diabetes as sensitivity is less than 100% and because many people do not present themselves for screening and new cases of diabetes replenish the pool of undiagnosed case. Therefore screening programmes should be ongoing. The optimal time interval between screening is uncertain. It is known that IFG and IGT progress to diabetes at rates between 1.6% and 10.4% each year depending on the population studied as shown in table 2.6. One study has examined screening intervals; over 3200 individuals were screened for diabetes with urinalysis testing, when this was repeated 30 months later, 2 further individuals who had negative screening tests on the first screening were found to have diabetes, and a further 0.44% of individuals were diagnosed with diabetes. (Davies 1994) Diabetes UK and the ADA recommend screening should be repeated every three years. The three year interval was selected on the basis of
the negligible likelihood of developing complications within this timescale. (British Diabetes Association 2000) This has not been tested prospectively and is based on retrospective assessment of data. It is likely that optimal screening intervals will vary between populations.

2.8 Summary of screening for diabetes
There remains a lack of evidence on the long-term benefits of screening for diabetes. The National Screening Committee has reviewed the topic of screening for diabetes and noted that although type 2 diabetes fulfils many of the criteria needed for screening, the optimal methods of screening, cut-off points for tests and screening frequency, particularly in different populations, requires further evaluation. Currently available guidelines do not support universal screening, instead they recommend screening and intense treatment in population sub-groups in whom undiagnosed diabetes and risk factors are especially prevalent. Diabetes UK guidelines recommend that an individual above 40 years of age with at least one risk factor for diabetes should be screened. Diabetes UK, ADA and WHO all recommend that a FPG should be the initial test used to screen. The cut-off value varies between guidelines but if this FPG value is reached than the individual should proceed to an OGTT. The guidelines also recommend that screening of at risk individuals should be repeated at three-yearly intervals. (Engelgau 2000, Diabetes UK 2002, ADA 2002) There are as yet no separate cut-off values or thresholds for different ethnic groups or different age ranges.

2.9 Screening for prediabetes
Impaired Fasting Glucose (IFG) and impaired glucose tolerance (IGT) are states of disordered carbohydrate metabolism that result in elevated glucose levels above normal but below those levels diagnostic of diabetes. These are often referred to collectively as prediabetes. (PDM) IGT and IFG appear to have some differences but are both precursors to diabetes and involve both insulin resistance and reduced insulin secretion. The aetiology and relative contribution of insulin resistance and defects of insulin secretion are not clear. Genetic and environmental factors including obesity, physical inactivity and age are important and the background trend of urbanization and industrialization seem to increase the prevalence of abnormal glucose tolerance. IGT has been identified as a specific entity for a considerably longer time than IFG and hence there is more
epidemiological data on the natural history of IGT. Within the DECODE surveys 58% in
the European Study and 73% in the Asian study with IGT reported a normal FPG (<6.1
mmol/L). (DECODE 1998, DECODA 2003). Therefore IGT can only effectively be
identified using a glucose tolerance test. Studies have shown that the concordance between
IGT and IFG varies between 20 and 40%. This variation is important, as it reflects that
the pathophysiological abnormalities of IFG and IGT are different. Elevated hepatic
 glucose output and a defect in early insulin secretion are characteristic of IFG. Whereas
IGT which reflects post-prandial glucose levels is affected more by glucose uptake in
insulin-sensitive tissues and therefore is more likely to be influenced by insulin resistance.

2.10 Prevalence of Impaired Glucose Tolerance and Impaired Fasting Glucose
The reported prevalence of IGT varies greatly between studies, depending on the
population and the survey methods used. Worldwide the prevalence has been shown to
vary as shown in table 2.5. (Unwin 2002) In European populations the prevalence of IGT
increases with age and is commoner in females than in males, with the exception of those
aged 80 to 89 years, where it is more prevalent in men. (Unwin 2002)
Table 2.5 The prevalence of IGT and IFG in different populations

<table>
<thead>
<tr>
<th>Population studied</th>
<th>Age of cohort</th>
<th>Size of study population</th>
<th>Prevalence of IGT</th>
<th>Prevalence of IFG</th>
<th>Overall prevalence of prediabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hong Kong (Ko 1998)</td>
<td>18 – 66 years</td>
<td>1486</td>
<td>7.2 %</td>
<td>2.0 %</td>
<td>8.1%</td>
</tr>
<tr>
<td>Hoorn Study, Holland (deVegt 1998)</td>
<td>50 – 75 years</td>
<td>1342</td>
<td>8.3 %</td>
<td>10.2 %</td>
<td>---</td>
</tr>
<tr>
<td>Italy (Vaccaro 1999)</td>
<td>40 – 59 years</td>
<td>560</td>
<td>8.8 %</td>
<td>3.6 %</td>
<td>10.7%</td>
</tr>
<tr>
<td>Paris, France (Eschwege 2001)</td>
<td>44 – 55 years</td>
<td>6881</td>
<td>9.1 %</td>
<td>3.8%</td>
<td>12.9%</td>
</tr>
<tr>
<td>Australia (Dunstan 2002)</td>
<td>≥ 25 years</td>
<td>11247</td>
<td>10.6 %</td>
<td>8.3 %</td>
<td>16.3%</td>
</tr>
<tr>
<td>DECODE (DECODE Study Group 1999)</td>
<td>≥ 30 years</td>
<td>25364</td>
<td>11.9 %</td>
<td>10.0 %</td>
<td>18.8%</td>
</tr>
<tr>
<td>Pima Indians (Gabir 2000)</td>
<td>≥15 years</td>
<td>5023</td>
<td>13.2 %</td>
<td>4.4 %</td>
<td>15.1%</td>
</tr>
<tr>
<td>NHANES III, USA (Harris 1998)</td>
<td>40 – 74 years</td>
<td>2844</td>
<td>14.9 %</td>
<td>8.3 %</td>
<td>19.3%</td>
</tr>
<tr>
<td>Ely, UK (Wareham 1999)</td>
<td>40 – 65 years</td>
<td>908</td>
<td>17.1 %</td>
<td>24.2%</td>
<td>--</td>
</tr>
<tr>
<td>Mauritius (Shaw 1999)</td>
<td>25 – 74 years</td>
<td>3229</td>
<td>17.2 %</td>
<td>7.5%</td>
<td>21.4%</td>
</tr>
</tbody>
</table>

The prevalence of IFG again varies between populations, is commoner in men and tends to increase in frequency until middle age, where the frequency then plateaus. (Unwin 2002) The prevalence of IFG in a cohort of 60-79 year olds across 24 British towns was 20%. This cohort was predominantly Caucasian and the rate amongst ethnic minority groups is likely to be greater. (Thomas 2005) The Coventry Diabetes Study compared the prevalence of diabetes and IGT in Asians and Europeans and found that Asian males were 3.9 times as likely to have diabetes and females 2.4 times as likely to have diabetes as age matched Europeans. In addition there was a greater prevalence of IGT in Asians under the age of 60 but the proportion of abnormal glucose tolerance due to diabetes was greater than in White Europeans. The age of diagnosis was younger in Asians. (Simmons 1991)
2.11 Why screen for Prediabetes?
In the UKPDS aggressive treatment successfully lowered blood glucose levels in type 2 diabetes and reduced the risk of complications, but there was still a steady deterioration in glucose control. The rate of change did not depend on which hypoglycaemic agent was used. (UKPDS 33 1998). Any intervention, including lifestyle changes, that either reduces insulin resistance or protects the beta-cells should theoretically prevent or delay the progression to diabetes. Intervention prior to the onset of diabetes may be the only way of preventing people commencing this steady decline. The identification of IGT is therefore important because it can identify those individuals who have an increased risk of progression to type 2 diabetes but also because of its own association with an increased risk of macrovascular complications (Jarrett 1979, Keen 1982, Fuller 1983). This is in contrast to people with diabetes who have an increased risk of both microvascular and macrovascular problems.

2.12 Prediabetes and the progression to diabetes
Individuals with IGT have a greatly increased risk of progression to type 2 diabetes compared to those with normal glucose tolerance. The progression rate of IGT to diabetes varies from 2 to 10% per year depending on racial and ethnic origin and age of the individuals, with some of the lowest rates being reported in the United Kingdom (table 2.6) (Unwin 2002). However which individuals are going to progress to diabetes and which will revert to normal glucose tolerance is not predictable and there is much variation even within ethnic groups. Studies looking at delaying the progression of IFG to diabetes are ongoing. (Table 2.10)
Table 2.6 The annual progression of IGT to diabetes in different populations

<table>
<thead>
<tr>
<th>Population</th>
<th>Number of participants (normal glucose tolerance, IFG, IGT or IFG+IGT)</th>
<th>Isolated IGT</th>
<th>IGT and IFG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ely, UK (Wareham 1999)</td>
<td>908</td>
<td>1.6%</td>
<td>2.8%</td>
</tr>
<tr>
<td>Paris, France (Eschwege 2001)</td>
<td>5139</td>
<td>2.2%</td>
<td>6.0%</td>
</tr>
<tr>
<td>Italy (Vaccaro 1999)</td>
<td>560</td>
<td>2.8%</td>
<td>3.9%</td>
</tr>
<tr>
<td>Pima Indians (Gabir 2000)</td>
<td>5023</td>
<td>4.0%</td>
<td>8.2%</td>
</tr>
<tr>
<td>Mauritius (Shaw 1999)</td>
<td>3229</td>
<td>4.2%</td>
<td>7.6%</td>
</tr>
<tr>
<td>Holland (deVegt 1998)</td>
<td>1342</td>
<td>5.5%</td>
<td>10.4%</td>
</tr>
</tbody>
</table>

As well as there being a clear relationship of progression of IGT to type 2 diabetes, there is also good evidence that IFG progresses to type 2 diabetes. (DeVegt 1998, Gimeno 1998, Shaw 1999, Vaccaro 1999, Wareham 1999, Gabir 2000, Eschwege 2001). Although the sensitivity of IFG as a predictor for progression to diabetes is inferior to that of IGT. (Shaw 1999) The pattern seen in all of these studies is that if a subject has both IFG and IGT they are at the higher risk of subsequent development of diabetes. In most populations this ranged from 40 to 70% over a 5 to 11 year follow-up. The exception being the UK white population, which was considerably lower at 12.7% over a 4.5-year follow-up (Wareham 1999).

2.13 Prediabetes and Cardiovascular disease

IGT is a significant risk factor for cardiovascular morbidity and mortality. The Whitehall Study showed after 20 years of follow-up an age-adjusted hazard ratio of coronary heart disease (CHD) mortality of 2.14 when compared to normal controls (Jarrett 1979). The Da Qing Study shows a 10-fold increase in the prevalence of electrocardiogram abnormalities in Chinese subjects with IGT, compared to normal controls (Pan 1997). The Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe (DECODE) study was one of the largest prospective studies of hyperglycaemia to be conducted. Data from 13 prospective studies across Europe was amalgamated and included over 25,000 participants and up to 28 years of follow-up. The main finding was that all cause mortality was determined primarily by the 2-hour plasma glucose level. Compared to people with normal glucose tolerance, men with IGT had a 1.51 and women with IGT had a 1.60 hazard ratio for death from all cause mortality. (DECODE 1999). FPG had only a weak
relationship with all cause mortality. This was not an isolated finding. The Honolulu Heart Program study showed a continuously increasing gradient between post-challenge glucose levels and subsequent CHD that was independent of other known risk factors. Other studies including the Diabetes Intervention Study, Paris Prospective Study and Cardiovascular Health Study showed that it was post-prandial rather than FPG at baseline that was associated with subsequent CHD. (Hanefeld 1996, Barrett-Connor 1998, Fontbonne 1989) The epidemiological data are clear. There is a specific, and as yet unexplained relationship between post-challenge hyperglycaemia and cardiovascular outcomes.

A number of hypotheses have been suggested to explain the link between glucose intolerance and CHD, but the one most widely accepted is that of ‘Syndrome X’ or the insulin resistance syndrome proposed by Reaven (Reaven 1988). In the Paris Prospective Study subjects with IGT had higher blood pressure, higher serum triglyceride and central obesity compared to normal controls (Fontbonne 1989). This has been confirmed in a number of other studies showing that subjects with IGT have an adverse cardiovascular risk profile (Jarrett 1996, Davies 1993). Small mechanistic studies have also confirmed that early abnormalities of cardiac structure and function are present in subjects with IGT. (Celanto 1995)

Effect of glycaemic control on cardiovascular events

Whether IFG has the same increased risk, as IGT for cardiovascular disease is controversial. Data from the Funagata Diabetes Study, which followed a cohort in which they classified people as normal, IFG or IGT, showed that whilst the risk of death from cardiovascular disease was 2.2 fold higher in the IGT group after a 7-year follow-up, in the IFG group it was not significantly different to those with normal fasting glucose levels. Their conclusion was that whilst IGT was a risk factor for cardiovascular disease, IFG was not (Tominaga 1999). However, other data would suggest that both elevated fasting and 2-hour plasma glucose are associated with total cardiovascular mortality.

A recent meta-analysis of 20 studies looked at data relating glucose to CHD events with a mean follow-up of 12 years (Coutinho 1999). This showed a continuous positive relationship with both initial fasting and 2-hour plasma glucose and CHD events, which extended below the current threshold for both IFG and IGT. (Coutinho 1999)
In contrast to the clear benefits of glucose lowering to prevent or retard the progression of microvascular complications associated with diabetes, it is less clear whether the high rate of CVD in people with IGT and IFG is caused by elevated blood glucose levels or will respond to treatments that lower blood glucose. Epidemiological studies have shown a clear relationship, whereas intervention trials in people with diabetes suggest, but have not demonstrated, a clear benefit of glycaemic control. Additionally, there are no studies that have investigated a benefit of glucose lowering on macrovascular disease in subjects with only IFG or IGT but not diabetes. There are ongoing prospective studies that are designed to look at this area. The aim of the Outcome Reduction with Initial Glargine Intervention (ORIGIN) trial is to determine if insulin mediated normoglycaemia can reduce cardiovascular mortality in individuals with prediabetes or early diabetes. The Diabetes REduction Assessment with Medication trial (DREAM) which involves an ACE-inhibitor and PPAR-gamma receptor blocker (ramipril and rosiglitazone) and the Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) (involving an insulin secretagogue and angiotensin-II receptor blocker) are both powered for progression rates of prediabetes and the NAVIGATOR study is also powered for cardiovascular events. (NAVIGATOR 2002, Aventis 2004, DREAM 2004)

### 2.14 Preventing the progression of prediabetes to diabetes

There are a number of intervention studies that have targeted people with prediabetes. These can be divided into those trials that included lifestyle intervention with dietary and physical activity advice, those that included glucose lowering drugs and those that produced incidental findings when post hoc analysis was performed of larger cardiovascular trials.

**Studies That Involved Lifestyle changes with or without Glucose Lowering Therapy**

These are summarised in table 2.8. Early attempts in the UK in the 1970’s and 1980’s with dietary intervention, tolbutamide, and phenformin showed no benefits. (Keen 1982, Jarrett 1977) Studies in Sweden in the same era were more successful and tolbutamide and dietary changes with increased exercise were associated with a lower incidence of diabetes. (Sartor 1980, Eriksson 1991) In the 1990’s diet and exercise were again found to have beneficial effects on the progression of IGT to diabetes (Pan 1997, Tuomilehto 2001) The DPP used both lifestyle intervention and metformin with benefits on progression. (DPPRG 2002) The STOP-NIDDM found a decreased risk of progression to diabetes in those
patients taking acarbose. (Hanefeld 2002) Although in EDIT when the whole cohort of patients with either IFG or IGT or both were studied there was no change in those patients taking either acarbose or metformin. If just those patients with IGT at baseline were studied there was a 25% relative risk reduction in progression to diabetes in those individuals receiving acarbose, but not with metformin and not if acarbose was given in combination with metformin. (Holman 2003) The Indian Diabetes Prevention Programme found that lifestyle modification and metformin significantly reduced the incidence of diabetes in Asian Indians with IGT. In this study there was no added benefit from combining lifestyle changes with metformin. (Ramachandran 2006) A meta-analysis of randomized controlled trials that involved lifestyle education reported that intervention was effective and reduced the 2-hour plasma glucose after a 75-g glucose tolerance test by 0.84 mmol/l compared to control groups and the one-year incidence of diabetes was reduced by around 50% compared to the control group. (Yamaoka 2005) Although the interventions and methods of lifestyle education varied in these studies, the results suggested that lifestyle education as well as dietary education improved 2-hour glucose and reduced the risk of type 2 diabetes in high risk individuals. (Yamaoka 2005)
<table>
<thead>
<tr>
<th>Study</th>
<th>Number of people</th>
<th>Years of follow up</th>
<th>Intervention</th>
<th>Mean age and BMI</th>
<th>Frequency of intervention</th>
<th>Specified targets other than to delay progression to diabetes</th>
<th>Effect of intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malmohus, Sweden (Sartor 1980)</td>
<td>267 men</td>
<td>10</td>
<td>Diet, exercise, weight loss, tolbutamide</td>
<td>54.1 years (mean weight 76 kg)</td>
<td>Every 12/12</td>
<td>None</td>
<td>Decreased progression to diabetes per group; 29% - control. 13% - diet, 0% diet+tolbutamide. No weight loss</td>
</tr>
<tr>
<td>Malmo, Sweden (Eriksson 1991)</td>
<td>181 men</td>
<td>6</td>
<td>Diet, exercise</td>
<td>48 years 26 kg/m²</td>
<td>Monthly for 6/12, then every 12/12</td>
<td>Unspecified weight loss</td>
<td>37% reduction in diabetes incidence in intervention group, 2-3.3kg weight loss</td>
</tr>
<tr>
<td>Whitehall (Jarrett 1977)</td>
<td>200</td>
<td>5</td>
<td>Low carbohydrate diet, phenformin</td>
<td>56 years 26.2 kg/m²</td>
<td>Once at start of study</td>
<td>Unspecified weight loss</td>
<td>No benefit in progression to diabetes, weight loss 1.2kg</td>
</tr>
<tr>
<td>Bedford Study, UK (Keen 1982)</td>
<td>241</td>
<td>10</td>
<td>Dietary intervention and tolbutamide</td>
<td>56 years 27kg/m²</td>
<td>Every 6/12</td>
<td>No effect on progression to diabetes after 10 years</td>
<td></td>
</tr>
<tr>
<td>FHS (Dyson 1997)</td>
<td>188</td>
<td>6</td>
<td>Diet, exercise, gliclazide</td>
<td>50 years (mean weight 81.7 kg)</td>
<td>Every 3/12</td>
<td>Lose weight if BMI&gt;22kg/m², low fat diet, exercise 3-4 times/week</td>
<td>No benefit in progression to diabetes, no weight loss</td>
</tr>
<tr>
<td>DPP, US (DPPRG 2000, 2002)</td>
<td>3234</td>
<td>2.8</td>
<td>Diet, exercise, metformin</td>
<td>51 years 34 kg/m²</td>
<td>16 diet sessions in 6/12 then monthly. Twice weekly supervised exercise sessions</td>
<td>7% weight loss, low fat diet, 150 minutes exercise/week</td>
<td>Decreased progression to diabetes per group; 58% - diet+exercise. (71% in people&gt;age 70 years) 31% - metformin, 3.8kg weight loss – diet+exercise. 1.8 kg weight loss – metformin. (metformin had greater efficacy in the younger, more obese individuals compared with older less overweight patients.)</td>
</tr>
<tr>
<td>STOP-NIDDM (Chiasson 2002, Hanefeld 2002)</td>
<td>1429</td>
<td>3.3</td>
<td>Diet, weight loss, activity, acarbose</td>
<td>55 years 31 kg/m²</td>
<td>Every 12/12</td>
<td>None</td>
<td>Acarbose decreased progression to diabetes by 25%. Weight loss 0.5kg. 35% risk reduction in new cases of hypertension and 49% risk reduction in cardiovascular events</td>
</tr>
<tr>
<td>Da Qing, China (Pan 1997)</td>
<td>577</td>
<td>6</td>
<td>Diet, exercise</td>
<td>45 years 25.6 kg/m²</td>
<td>7 sessions in 3/12, then every 3/12</td>
<td>BMI&lt; 23kg/m², healthier diet</td>
<td>Reduction in diabetes incidence per group; 31% diet, 46% exercise, 42% diet+exercise. 1.7kg weight loss – diet+exercise. 1.8 kg weight loss – metformin. (metformin had greater efficacy in the younger, more obese individuals compared with older less overweight patients.)</td>
</tr>
<tr>
<td>DPS, Finland (Tuomilehto 2001)</td>
<td>522</td>
<td>3.2</td>
<td>Diet, exercise</td>
<td>55 years 31 kg/m²</td>
<td>7 sessions in 12/12 then every 3/12. Free gym subscription + supervised activity sessions.</td>
<td>5% weight loss, decrease fat intake, increase fibre intake, &gt;150 minutes exercise/week</td>
<td>Reduction in diabetes incidence in intervention group; 63% men and 54% women. 3.5kg weight loss after 2 years</td>
</tr>
<tr>
<td>New Zealand (Swinburn 2001)</td>
<td>103</td>
<td>5.0</td>
<td>diet</td>
<td>52 years 29 kg/m²</td>
<td>Monthly for first 12/12</td>
<td>Unspecified weight loss, reduced fat intake</td>
<td>No benefit in progression to diabetes. No weight loss</td>
</tr>
<tr>
<td>EDIT (Holman 2003)</td>
<td>631</td>
<td>6</td>
<td>Metformin, acarbose</td>
<td>52 years 28.6 kg/m²</td>
<td>unspecified</td>
<td>none</td>
<td>No difference in whole cohort (IFG and/or IGT) in progression to diabetes with either acarbose and/or metformin. In those with IGT at baseline there was significant 25% risk reduction with acarbose but not with metformin</td>
</tr>
<tr>
<td>TRIPOD (Buchanan 2002)</td>
<td>235 women</td>
<td>2.5</td>
<td>Troglitazone</td>
<td>35 years 30 kg/m²</td>
<td>unspecified</td>
<td>None</td>
<td>56% reduction in progression of IGT to diabetes with troglitazone. (12.3% per year in control group compared to 5.4% in treatment group) 8 months after end of trial preventive effects still present.</td>
</tr>
<tr>
<td>XENDOS (Hansson 1999)</td>
<td>3300</td>
<td>4</td>
<td>Orlistat</td>
<td>BMI range 30-43 kg/m²</td>
<td>Every 2 weeks for 6 months, then monthly</td>
<td>Weight loss</td>
<td>37% decrease in new cases diabetes with IGT compared to control group. Intervention group lost 6.9 kg. Control group lost 4.1 kg.</td>
</tr>
<tr>
<td>Indian DPP (Ramachandran 2006)</td>
<td>531</td>
<td>2½</td>
<td>Lifestyle changes and metformin</td>
<td>46 years 25.8 kg/m²</td>
<td>Monthly telephone calls, 6/12 visits</td>
<td>30 minutes exercise/day, decreased calorie and fat and increase fibre intake</td>
<td>Relative risk reduction of diabetes of 28.5% with lifestyle changes, 26.4% with metformin, 28.2% with lifestyle changes + metformin</td>
</tr>
</tbody>
</table>
Studies involving therapeutic agents that do not lower Glucose

Studies involving therapeutic agents that did not specifically target glucose have reported benefits in preventing or delaying the onset of type 2 diabetes. (Table 2.8 and 2.9) However, the diagnosis of diabetes was not a prespecified primary end point and in the studies the diagnosis of diabetes was based on self-reporting, on the new prescription of hypoglycaemic agents or just on a fasting blood glucose values. The pharmacology agents studied include ACE-inhibitors, angiotensin-II receptor blockers (ARBs), calcium-channel blockers and statins and are now being combined with known glucose lowering treatments in an attempt to improve outcomes further. (table 2.10) ACE-inhibitors exert direct effects on the renin-angiotensin system and may prevent diabetes through effects on B-cells and vascular and metabolic effects on muscle, partially mediated by nitric oxide, that enhance the effect of insulin. The effect of ACE-inhibitors on insulin sensitivity appears to be indirect. Inflammation may contribute to the development of diabetes and statins have been shown to decrease the C-reactive protein levels. (Albert 2001) Trials involving ACE inhibitors and ARBs have shown consistently results, whereas trials of statin treatments have been inconsistent in their effect on the prevention of type 2 diabetes.
Table 2.8 Studies involving angiotensin-converting enzyme inhibitors or angiotensin receptor blockers for the prevention of type 2 diabetes

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Therapeutic agent</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart Outcomes Prevention Evaluation Trial (HOPE) (Yusuf 2002)</td>
<td>5720</td>
<td>Ramipril</td>
<td>3.6% of patients on Ramipril developed diabetes compared to 5.4% on placebo. 33% risk reduction</td>
</tr>
<tr>
<td>Captopril Prevention Project (CAPPP) (Hansson 1999)</td>
<td>10 985</td>
<td>Captopril</td>
<td>13% risk reduction in incidence of diabetes compared to conventional antihypertensive treatment</td>
</tr>
<tr>
<td>Studies of Left Ventricular Dysfunction Trial (SOLVD) (Vermes 2003)</td>
<td>291</td>
<td>Enalapril</td>
<td>16.5% absolute risk reduction in new onset diabetes in Enalapril group. 45% in Enalapril treated subgroup with IFG at baseline</td>
</tr>
<tr>
<td>Losartan Intervention for Endpoint Reduction Study (LIFE) (Lindholm 2002)</td>
<td>9193</td>
<td>Losartan</td>
<td>patients on Losartan based treatment had a lower risk of developing diabetes than those on Atenolol based treatment (13.0 per 1000 vs. 17.5 per 1000 person years of treatment)</td>
</tr>
<tr>
<td>Valsartan antihypertensive Long-term Use Evaluation (VALUE) trial (Julius 2004)</td>
<td>10 419</td>
<td>Valsartan</td>
<td>Valsartan based treatment associated with decrease in incidence of diabetes from 16 to 13% compared to Amlodipine based treatment</td>
</tr>
<tr>
<td>International Verapamil-Trandolapril Study (INVEST) (Pepine 2003)</td>
<td>16176</td>
<td>Trandolapril</td>
<td>Verapamil based treatment associated with a decrease in incidence of diabetes from 8.2% to 7% compared with Atenolol based treatment.</td>
</tr>
</tbody>
</table>
Table 2.9 Studies involving HMG-CoA inhibitors (statins) for the prevention of type 2 diabetes

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Therapeutic agent</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>The West of Scotland Coronary Prevention Study (WOSCOPS) (Freeman 2001)</td>
<td>6000 males</td>
<td>Pravastatin 40mg</td>
<td>30% decreased risk of developing diabetes compared to placebo.</td>
</tr>
<tr>
<td>Heart Protection Study (HPS 2003)</td>
<td>14573</td>
<td>Simvastatin 40mg</td>
<td>4.6% of Simvastatin treated patients developed diabetes versus 4.0% in placebo arm</td>
</tr>
<tr>
<td>Long-term Intervention with Pravastatin in Ischaemic Disease (LIPID) study (Keech 2003)</td>
<td>6997</td>
<td>Pravastatin 40mg</td>
<td>4.0% of pravastatin treated patients developed new diabetes compared to 4.5% in the placebo group</td>
</tr>
<tr>
<td>Anglo-Scandinavian Cardiac Outcomes Trial –Lipid lowering arm (ASCOT-LLA) (Sever 2003)</td>
<td>7773</td>
<td>Atorvastatin 10mg</td>
<td>3.0% incidence of diabetes in atorvastatin arm and 2.6% in placebo group</td>
</tr>
</tbody>
</table>

A meta-analysis of twelve randomized controlled clinical trials of ACE inhibitors or ARBs (Abuissa 2005) found that ACE inhibitors or ARB’s were associated with reductions in the incidence of newly diagnosed diabetes by 27% and 23% respectively, and by 25% in the pooled analysis. Although these studies show promising results they were not designed to examine the prevention of type 2 diabetes and therefore need to be interpreted with caution. There are ongoing prospective trials, shown in table 2.10, with these and other drugs to see if these findings can be reproduced in a randomised controlled trial.
Table 2.10 Ongoing prospective trials looking at progression of prediabetes to diabetes

<table>
<thead>
<tr>
<th>Study</th>
<th>Therapeutic agent</th>
<th>comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>DREAM study (DREAM 2004)</td>
<td>Ramipril and Rosiglitazone</td>
<td>5269 individuals with IFG or IGT randomised in a 2x2 factorial design. Powered to examine new cases diabetes and atherosclerosis</td>
</tr>
<tr>
<td>NAVIGATOR study (NAVIGATOR 2002)</td>
<td>Nateglinide and Valsartan</td>
<td>Over 9000 patients, in a 2x2 factorial design, powered to show a reduction in progression of diabetes and cardiovascular disease. Individuals will receive lifestyle advice</td>
</tr>
<tr>
<td>ORIGIN trial (Aventis 2004)</td>
<td>Insulin glargine and PUFA</td>
<td>To determine if insulin mediated normoglycaemia can reduce cardiovascular mortality in individuals with prediabetes or early diabetes (2x2 factorial design)</td>
</tr>
<tr>
<td>CANOE (Canadian Diabetes Association website 2006)</td>
<td>Rosiglitazone and metformin</td>
<td>To determine if combination of glucose lowering treatment and a healthy lifestyle can prevent diabetes in people who are at high risk for diabetes.</td>
</tr>
<tr>
<td>PIPOD (USC 2006)</td>
<td>Pioglitazone</td>
<td>Follow on from TRIPOD – females with gestational diabetes. Pioglitazone continues to show a reduction in new cases of diabetes</td>
</tr>
<tr>
<td>ACT NOW (clinical trials 2006)</td>
<td>Pioglitazone</td>
<td>To determine if Pioglitazone can reduce the conversion of IGT to Diabetes</td>
</tr>
</tbody>
</table>
Summary of preventing the progression of prediabetes

Prevention or delaying progression from IGT to diabetes is feasible. Successful lifestyle interventions, including weight loss and increased physical activity, have been shown to be effective in preventing or delaying the onset of diabetes in people with IGT. Studies that did not include exercise and dietary interventions, or did not maintain them throughout the study, did not achieve such good results. (Jarrett 1977, Swinburn 2001, Chiasson 2002)

The lifestyle interventions that have been shown to be effective are:

- 30 minutes physical activity five times a week. This is now recommended by the Department of Health. (Department of Health 2004) Exercise should make the person’s heart rate increase and make them slightly sweaty.
- Lifestyle interventions leading to weight loss have produced the most benefit. (DPPRG 2002, Tuomilehto 2001) Weight loss of 5-10% of body weight has been shown to be beneficial.
- One-to-one dietary and education sessions on at least seven occasions over 12 months, and then either individual or group sessions every three months (Tuomilehto 2001)
- Weight maintenance programmes involving low-energy diets, increased physical activity and behavioural therapy may need to be instituted after any achievement of weight loss in order to maintain the benefit.

In the DPS none of the individuals who achieved four out of five of their lifestyle change targets progressed from IGT to diabetes (table 2.11). (Tuomilehto 2001).
Table 2.11 Lifestyle change targets in the Finnish DPS

<table>
<thead>
<tr>
<th>Targets in Finnish DPS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduction in body weight of at least 5%</td>
</tr>
<tr>
<td>Decrease total fat intake to less than 30% of energy</td>
</tr>
<tr>
<td>consumed</td>
</tr>
<tr>
<td>Decrease saturated fat intake to less than 10% of energy</td>
</tr>
<tr>
<td>consumed</td>
</tr>
<tr>
<td>Increased fibre intake to at least 15g per 1000 kcal</td>
</tr>
<tr>
<td>Moderate exercise of at least 30 minutes per day</td>
</tr>
</tbody>
</table>

In the Da Qing study, there were significant reductions in the incidence of diabetes in individuals with IGT. In those individuals who did not develop diabetes, the weight changes varied from an increase of 0.93kg to a decrease of 1.77kg. Given this modest change, in this study it seems that exercise is a major contributing factor. (Pan 1997) The beneficial influence of physical activity on the risk of diabetes may be through an increase in insulin-mediated glucose disposal within the skeletal muscle and therefore an improvement in insulin resistance or through an indirect effect on obesity in general, or central obesity in particular. (Burchfield 1995) In both the UK and US male populations, increasing physical activity decreases the risk of diabetes regardless of age and weight. Exercise does seem to need to be taken regularly to achieve a preventive effect. In the Physicians Health study the age-adjusted relative risk for diabetes fell from 0.77 in men who exercised only once a week to 0.58 in men who exercised five or more times per week. (Manson 1992, Burchfield 1995, Perry 1995, Wei 1999) This has also been shown in women, in the Nurses Health study it was found that women who reported that they engaged in vigorous activity at least once a week had a reduced age-adjusted relative risk of diabetes of 0.67 compared with women who did not exercise. (Manson 1991)

Although the benefit is greatest for intensive lifestyle intervention, individuals who are unable to make the necessary changes may benefit from pharmacological intervention. There is evidence showing metformin, orlistat, acarbose and thiazolidinediones can delay the progression of IGT. There is retrospective data showing that ACE-inhibitors, angiotensin-II receptor blockers and statins can
contribute to the prevention of IGT progression. These drugs are being studied in ongoing prospective studies. (table 2.8, 2.9 and 2.10)

Benefits of Lifestyle intervention:

- They have been shown to be effective
- Have few side effects
- Can reverse central obesity, physical inactivity, high fat and high energy diets associated with diabetes
- Promote good health in general by decreasing blood pressure and lipids
- Can empower individuals be making them less reliant on medication
- Can improve quality of life (Tuomilehto 2001)

2.15 Which tests should we use to screen for prediabetes?
Given that the evidence that interventions can delay the onset of diabetes is now available we need to be able to identify those individuals with IGT.

Biochemical tests
To identify those who may benefit from being targeted is a mammoth task. The Da Qing study screened more than 110,000 patients, with a 2-hr post breakfast glucose test, to enter 577 patients into the study. (Pan 1997) Measurement of FPG and 2 hr post-challenge glucose will not identify all those within a population at future risk of developing diabetes. In screening for diabetes the ADA recommend a FPG cut-off of 6.1 mmol/L. At this level only 29% of patients with IGT would be identified. The DECODE group showed that using the WHO diabetes screening FPG cut-off of 5.5 mmol/L, further testing, would be required by 46% of people and many people with IGT would still not be detected.

In a study from Mauritius the fasting glucose value was only predictive in 26% of subjects that progressed to diabetes over a 5-year period. However consideration of the 2-hour OGTT values identified a further 35%. (Shaw 1999)
A FPG or OGTT can be performed to determine whether a patient has IFG or IGT in a similar way to its use in screening for diabetes, it is just that the cut-off points for biochemical tests need to be lower. This decreases the specificity of each test and increases the overall costs. Screening for prediabetes by IFG criteria alone (< 5.6 or 6.1 mmol/l depending on whether the ADA or WHO definition used) (WHO 1999, ADA 2005) would identify fewer individuals who subsequently progress to type 2 diabetes than would the OGTT. Most individuals with IGT have FPG values within the normal range, and therefore if only FPG was used to classify hyperglycaemia sensitivity would decrease. From the population perspective, the lower sensitivity of IFG indicates that far fewer cases of diabetes would be prevented by targeting preventive measures on subjects with IFG than could be prevented by targeting IGT subjects. Therefore if only FPG is used as a screening tool for prediabetes then the threshold for proceeding to an OGTT has to be much lower in order that individuals with normal FPG but elevated 2-hour glucose values would be identified. It may be that blood tests are not the optimal method of screening patients for prediabetes. So are there any other screening tools that could be utilised?

Risk assessment tools

There is increasing interest in the use of risk scores or questionnaires to identify individuals at high risk of prediabetes who would benefit from further screening and diagnostic testing or from lifestyle intervention programmes. The efficiency of such preliminary screening tools varies between populations and geographical areas. At present these tools have been used to screen for diabetes and may need modification to make them applicable for detection of IGT risk. In Denmark the use of a risk questionnaire in a population-based diabetes screening approach was ineffective due to the low response rate to the postal invitations. (Christensen 2004). If the same approach was used for prediabetes screening a similar low response rate would also make screening for prediabetes ineffective. In order to prevent low response rates from being an issue, data from primary care records can be used to complete a risk score, which does not involve individuals completing any forms. This has been done in the UK to detect undiagnosed hyperglycaemia, using the Cambridge risk score, and was seen to be an effective strategy in both Caucasians and South Asians. The criteria for undiagnosed hyperglycaemia was based on finding a FPG ≥ 7.0 mmol/l or a
HbA1c ≥ 6.5% and in South Asians sensitivity 69% and specificity 64%, this compares to White Europeans in whom the sensitivity is reported as 77% and specificity 72%. (Sijaikerman 2004). There are no published results of this score being used to detect prediabetes. However the FDRS has been used to identify those who are at higher risk of developing diabetes, and it is likely that a significant proportion would have prediabetes if the glucose values had been measured. (Lindstrom 2003)

2.16 Summary of screening for prediabetes
The identification of prediabetes is important because it can identify those individuals who have an increased risk of progression to type 2 diabetes but also because of its own association with an increased risk of macrovascular complications (Jarrett 1979, Keen 1982, Fuller 1983). Prevention or delaying progression from IGT to diabetes is feasible. Recent trial data shows that diabetes can certainly be delayed or even prevented by up to 58% with intensive lifestyle changes, acarbose and metformin. IFG also progresses to diabetes but at a slower rate than IGT does. Studies looking at delaying the progression of IFG to diabetes are ongoing. (Table 2.10)

However identifying affected individuals in order they can take advantage of the benefits of primary prevention with lifestyle changes is difficult. The diagnosis of IGT is essentially based on a post-challenge glucose level, and this is time consuming and inconvenient to measure. A large study from Australia looked at the presence of risk factors in combination with either of both of FPG and HbA1c at different cut-off values. Reported sensitivities with different combinations ranged from 33 to 61%. (Colagiuru 2004) These are all too low for an effective screening program. Screening tools such as risk scores and risk questionnaires may have a role in identifying those with prediabetes. There needs to be further studies to determine if the findings in diabetes are reproducible for prediabetes, particularly across ethnic groups. The best method of screening for prediabetes remains unclear.
2.17 Prevention of Diabetes in the United Kingdom

There are many reasons that may make the implementation of the latest evidence challenging in the UK environment outside of a clinical trial setting. Successful trials have targeted those populations with IGT who appear to be enriched with patients at higher risk based on their ethnicity, age, having IFG or heart disease. Intervention with both lifestyle and pharmacological agents which have been successful in other countries have as yet not been shown to be successful in the UK as demonstrated by the Whitehall, Bedford and the Fasting Hyperglycaemia Studies. (Keen 1982, Fuller 1983, Dyson 1997)

Another difficulty is health care professionals’ knowledge and understanding. A study of 34 general practitioners (GP’s) in five primary care groups in the north east of England found that all GP’s had knowledge of IGT as a clinical entity, but they had little awareness of its clinical significance and were uncertain about managing and following up patients with IGT. (Wylie 2002) Some GP’s felt strongly that screening for IGT and subsequent lifestyle intervention medicalised an essentially social problem and that a health educational approach, involving schools and the media should be adopted instead. Only a minority expressed a positive attitude towards a pharmacological approach. The authors concluded that increased awareness of IGT is necessary and guidelines for its management are needed. GP’s appear to remain to be convinced that they have a role in attempting to reduce the incidence of type 2 diabetes by targeting interventions at patient with IGT. (Wylie 2002)

The attitude of patients also makes a difference. A survey in 1995 in European countries looked at attitudes towards physical activity, body weight and health and found that 71% of participants agreed with the statement ‘I do not need to make any changes to the food I eat, as it is already healthy enough’ (Kearney 1997). When questioned, 3% of people in Finland said they did no physical exercise compared with 25% of people in the UK (Zunft 1999). As part of the Coventry Diabetes Study individuals were asked about their knowledge of diabetes symptoms and complications. Most of those without diabetes were unable to name either a complication (Europeans 66%, Asians 89%) or a single symptom (66% and 83% respectively). The knowledge level was highest in Europeans, increased with
increasing educational achievement and was lowest in non-diabetic subjects with out a family history of diabetes. Even those with diabetes had a low level of knowledge. (Simmons 1991) These studies reveal the need for greater awareness of diabetes, dietary education and advice on increasing physical activity. If these could be implemented then the potential for success of any screening and intervention programme increases. Many hours of health care professionals’ expertise per individual would be needed to bring these benefits of education and lifestyle changes in to the UK population. Commitment to long-term dietary and physical activity sessions from individuals to achieve and maintain a weight loss that will influence their progression from IGT to diabetes will be required.

Another challenge we may face when trying to replicate study findings is the difference in progression of IGT to diabetes in the UK population when compared to other populations. The Ely study showed the annual progression to diabetes from IGT with IFG was 2.8%. This is in marked contrast to other populations including the Hoorn study from Holland with an annual progression rate of 10.4% and in Pima Indians of 8.2% (table 2.6) (Unwin 2002)

Challenges that need to be addressed in the design and implementation of successful prevention strategies in the UK.

- Slower progression of IGT to diabetes
- Trials not yet been successful in UK population
- Health care professional’s knowledge and understanding of prediabetes and its’ prevention
- Beliefs, attitude and knowledge of patients

2.18 Conclusion

Type 2 diabetes is increasing in prevalence and many individuals remain undiagnosed. The National Screening Committee has reviewed the topic of screening for diabetes and noted that although type 2 diabetes fulfils many of the criteria needed for screening the optimal methods of screening, cut-off points for tests and screening frequency, particularly in ethnic populations, are unknown.
Based on current evidence and expert opinion, recommendations are for the use of a targeted screening approach, however identifying which groups to target needs further consideration. When screening a targeted population for diabetes guidelines vary between the use of risk scores and questionnaires or a FPG followed by an OGTT in patients with a FPG of 5.5–6.9 mmol/l. There is little data on screening for diabetes in ethnic minority groups, and there are no recommendations for screening or early identification strategies of prediabetes in any population.

After screening for diabetes if patients are found to have IGT or IFG, then they should receive advice on weight loss and increased physical activity. Regular follow up is important for successful lifestyle interventions. Repeated screening for diabetes at an unknown interval and intensive treatment of risk factors is important. Drug therapy should not routinely be used to prevent diabetes.

The physical, psychological and social effects of screening for abnormal glucose tolerance and early diagnosis of diabetes remain unclear. Prospective randomised controlled trials are in progress that may provide the evidence we need. Clinicians still need to be vigilant in recognising clinical situations suggestive of diabetes that warrant diagnostic testing.

In this thesis the risk factors, biochemical investigations, questionnaires and risk scores used in screening will all be studied in patients from a multi-ethnic population, to determine which components have the greatest impact in the early identification of abnormal glucose tolerance. The optimal method for detecting abnormal glucose tolerance early in a mixed ethnic at-risk population will be presented and will be able to inform a modern NHS on how to develop strategies for the early identification and earlier management of diabetes in the primary care setting.
Chapter 3

Methodology of The Screening Those At Risk Study

3.1 Introduction

The Screening Those At Risk (STAR) study is a multi-method, multi-disciplinary approach to address some of the key research questions around the utility of different strategies of screening. In addition the study will determine the prevalence of prediabetes (impaird glucose tolerance (IGT), impaired fasting glucose (IFG) or both) and undiagnosed diabetes in a multi-ethnic community in the United Kingdom.

As discussed in chapter 2 most authorities agree that targeted screening is the best approach. (Herman 1985, ADA 2003, Diabetes UK 2002, WHO 2003) However there is disagreement on who should be targeted and there is no universal accepted method of screening. The National Screening Committee highlighted a number of methods, which could be used for screening. (UK National Screening Committee 2006) These include a fasting glucose, two-hour post challenge glucose, HbA1c, urinalysis for glycosuria, random glucose and risk factor questionnaire or scoring system. The characteristics of some of the possible screening methods are known, yet thresholds for positive tests have not been agreed and the screening tests have not been validated in different populations with varying levels of risk of diabetes, such as ethnic minority populations in the United Kingdom.

3.2 Ethical Approval

Local Research Ethics committee approval and UHL Trust Approval and where appropriate PCT approval was obtained for the study. The study had both ethical approval and indemnity cover.

3.3 Staffing and management of screening programme

The STAR Steering Group met regularly and consisted of the research fellow (myself) as well as the principal investigators, Professor Melanie Davies and Dr Kamlesh
Khunti, co-investigator Dr Azhar Farooqi, and members of the research team. Recruitment commenced in February 2002 and continued until July 2004.

3.4 Inclusion criteria

The inclusion criteria for the study were White Europeans aged between 40 and 75 years, and individuals of other ethnic origin aged between 25 and 75 years, if they had at least one of the following risk factors:

- Known coronary heart disease (CHD)
- Known to be at risk of CHD and on a CHD register (i.e. those with a predicted CHD risk of at least 30% over 10 years)
- Documented history of hypertension or receiving medication for hypertension
- Known high cholesterol
- Known cerebrovascular disease and/or peripheral vascular disease
- Known to have previous diagnosis of IGT or IFG
- Women with polycystic ovary syndrome who are obese (BMI >25kg/m² or >23kg/m² in South Asians)
- BMI > 30kg/m² or > 25kg/m² if sedentary lifestyle
- Women with history of gestational diabetes
- First degree relative with type 2 diabetes
- Current cigarette smokers or those who have stopped within the last 12 months

In two practices all the individuals within this age range were invited regardless of the presence of risk factors. Some of the practices did not hold computerized records for all the inclusion criteria and only information that was documented on the computer at the time of the original visit was obtained.

3.5 Exclusion criteria

Individuals were excluded if they were housebound, had a terminal illness or had previously been diagnosed with diabetes mellitus.
3.6 Methods of recruitment

Two main strategies were used for recruitment that covered primary care and community screening.

3.6.1 Primary Care

In primary care, volunteer practices and Trent Research Network practices were invited to participate. Approval was obtained from both Eastern Leicester and Leicester City West Primary Care Trust Boards before practices within those trusts were approached. Letters were sent to all general practitioners in the Primary Care Trusts inviting them to take part. Primary Care Trusts already have registers of patients with CHD, hypertension, heart failure and diabetes. The GP practices within Leicester are now computerised which provides the opportunity to easily target patients from at-risk categories, as this data is available from the computer databases. A member of the STAR research team arranged with the practice managers to review the patient lists using EMIS, the computerized note system. All patients within the age range 25 to 75 years with at least one of the risk factors recorded were identified. These lists were printed off within each practice. The project manager reviewed these lists and those patients under the age of 40 who had surnames typically European in nature were not invited. The lists were cross checked with practice records to exclude individuals who were already diagnosed with diabetes or who had a terminal illness.

All eligible individuals were then mailed a letter and a pre-screening questionnaire, on practice headed notepaper, signed by their GP and the investigators of the study (Prof M Davies, Dr K Khunti and Dr A Farooqi) (Appendix A) with an information sheet. (Appendix B)

The production of lists, identification of eligible patients and mailings were all completed by the STAR screening team. This took place within the GP practice surgery. For confidentiality the lists of patients were not taken from the surgeries. These lists were then shredded in line with ethical recommendations. The identified patients were sent a letter with an information pack in English and another information letter in four major South Asian languages (Hindi, Gujarati, Urdu and Punjabi) informing the patients that they could get an information pack in their own language. The letter included the list of risk factors that had led them to be identified,
but not which risk factor they personally had. Participants were asked to return the pre-screening questionaire in the pre-paid envelope if they were interested in participating in the study. Participants were given a dedicated study phone number to contact if they required further information.

In fifteen practices individuals within the age range who had at least one risk factor were invited. In two practices all patients within the age range were invited regardless of the presence of risk factors. This was to determine the prevalence of risk factors in the population and to see how screening a population simply by age differed from targeting only those individuals within an age range who had an additional risk factor. With the exception of cigarette smoking, these risk factors are internationally accepted as risk factors for diabetes. They have been identified in the Diabetes UK position statement ‘Early identification of people with type 2 diabetes’ and in the Australian national evidence based guidelines for screening for diabetes and by the American Diabetes Association. (Diabetes UK 2000, Colagiuri 2004, American Diabetes Association 2003) Including cigarette smoking as a risk factor was in order to contribute to the current conflicting evidence on whether cigarette smoking is an independent risk factor for diabetes. Risk factors were identified from GP computerised records, so if risk factors had not been entered into the computer then these patients would not be identified. Whether an individual leads a sedentary life is not recorded on the practise databases. Individuals could only meet this criterion if they were identified through the awareness campaign, after speaking to a member of the screening team, having their body mass index calculated and being asked about lifestyle.

Patients were then given a date to attend for screening either at the hospital closest to them or on the mobile screening unit if that could be located more conveniently for the patients. (Appendix C) Individuals were asked to fast for at least 8 hours prior to attending for screening and to bring a urine sample and list of any prescribed medications with them.

Leaflets and posters, in English and some Asian Languages, were left in participating practices and there was a media campaign in local newspapers and radio stations to
increase awareness of the screening programme. Individuals who did not respond to the first mailing from their GP were sent a further mailing.

3.6.2 Self-invitation and Community Screening

The importance of screening for diabetes and awareness of the study was increased through different methods. There were posters and flyers at GP surgeries, around the hospitals and in community centres, to give patients the opportunity to telephone with any enquiries about the study. Local road shows were organized to target different areas of the community. Outreach days were held in the main city shopping centre, in the main city high street, in a garden centre, in community halls within predominantly Hindu residential areas, locality halls adjacent to Mosques, an awareness stand and a float at the Caribbean carnival and through local radio and newspaper reports. In addition there were fundraising events throughout the period of the study to increase awareness and promote interest in the importance of diagnosing diabetes. When individuals enquired either in person at one of these events or by telephone they were asked a series of questions to determine any risk factors they might have and if eligible they were given an information pack. At some events blood pressure, random blood glucose and cholesterol levels were checked and the results of these discussed on an individual basis with each person.

3.7 The screening visit procedure

The screening visits were performed by the STAR research team. Screening was held at primary care practices, on the mobile screening unit or at the diabetes centres within the Royal Infirmary or the General Hospital – two of the hospitals within the University Hospitals of Leicester NHS Trust. Screening venues were offered to facilitate patients’ attendance by providing locations either near to their place of residence or work. The mobile screening unit was a specially converted former London double-decker bus. (Appendix C)

When patients returned their pre-screening questionnaire their eligibility was confirmed and a date and location for the diabetes screening was arranged. The
appointments were all in the morning, to commence between 08.00 and 09.30 and patients were advised that the visit would last about 2 ½ hours. They were all asked to attend after fasting for at least 8 hours, to bring their medication and a specimen of their first early morning urine.

There were standard operating procedures that were followed for all screening visits, such that patients followed the same procedure in all screening locations. All patients received the patient information sheet at least 24 hours before taking part. Written informed consent was obtained by one of the research nurses or doctors. Interpreters were available to help with the understanding of the information sheet and to be present during the screening procedure if any individual wanted this.

On attending the screening individuals gave their written informed consent for the study and fasting blood samples were taken. Thereafter, individuals were asked to drink a 75g glucose load, in the form of Lucozade (394mls), over a maximum of five minutes, with subsequent blood samples being taken after 120 minutes. During this time the questionnaire booklets were completed, (appendix D) and physical and anthropometric measurements were taken and medical data was collected. (Appendix E)

3.7.1 Biochemical tests

The 20 ml baseline fasting blood samples were collected in appropriate specimen bottles to be sent for lipid profile, urea, creatinine and electrolytes, HbA1c and glucose. Two further samples were taken and saved for future research. At the end of the glucose tolerance test a further 2 mls of venous blood was taken for glucose. Samples were labelled with patient name, date of birth, unique study number and the date and time that each sample was taken. The specimens that were taken to the laboratory with a completed laboratory form included:

- Fasting and 2 hour plasma glucose
- Lipid profile including total cholesterol and HDL cholesterol
- Triglyceride concentration
- Urea, Creatinine and Electrolytes
- HbA1c
• Urine Dipstick for glycosuria
• Urinary Microalbumin:Creatinine ratio

All the samples were measured within the same laboratory using stable methodology standardised to external quality assurance reference values. HbA1c was analysed using the BIO-rad Variant II HPLC system which is DCCT aligned. Glucose [using the hexokinase method (NADPH production at 340 nm)] urea and electrolytes, total and HDL cholesterol and triglycerides were all measured on the Abbott Aeroset clinical chemistry analyser. The LDL cholesterol was calculated using the Friedewald equation. (Friedewald 1972) The Olympus OSR6167 Microalbumin Analyser with a sensitivity of 0.46mg/l was used. Microalbumin:creatinine ratios equal to or greater than 2.5mg/mmol in males and 3.5mg/mmol in females were taken to indicate microalbuminuria.

3.7.2 The standardised health assessment
A specially-trained nurse or research assistant confirmed the method of recruitment and completed the standardised health assessment interview, (Appendix E) which included:

• Previous medical history including history of myocardial infarction and stroke
• Current and previous medication
• Information about other disease particularly hypertension and CHD
• Current and past smoking habits
• Family history of diabetes and CHD (defined as the use of GTN, having had a previous medical or hospital diagnosis of myocardial infarction)
3.7.3 Anthropometric measures

- Height - measured on fixed scales, to the nearest 0.5cm
- Weight - with light indoor clothing measured to the nearest 0.1 kg.
- Body mass index (BMI) was calculated from height and weight
- Blood pressure – The right arm was used after the patient had been sitting for at least five minutes. Three measurements were taken using an automated sphygmomanometer and appropriate sized cuff. The cuff should encircle at least 80% of the arm, but not more than 100%. (British Hypertension Society 2006) The average of the last two readings was calculated and used for analysis.
- Hip and waist circumference – Measurements were taken with a soft tape while individuals were standing. Waist circumference was measured mid-way between the lowest rib and the iliac crest. Hip circumference was measured over the widest part of the gluteal region
- Waist-to-hip ratio was calculated from the hip and waist measurements.
- 12-lead ECG

3.7.4 Questionnaires

Individuals were asked to complete the study questionnaire booklet. Individuals were asked to return the questionnaire booklet if they were not able to read or complete the questionnaire unaided. These questionnaires would determine the impact of screening on anxiety levels and would explore a number of psychological issues around screening for diabetes. These questionnaires are outlined in detail below, summarized in table 3.4 and copies are included in Appendix D.

Psychological well-being

This included overall well being. The WHO five-item questionnaire is short screening instrument for the detection of depression in the general population. This study has been evaluated positively in the elderly population. (Bonsignore 2001)
Anxiety was assessed using the Spielberger State Anxiety Scale Short Form. This is a
well validated, six-item, four-option response questionnaire. It refers to emotional reactions characterized by subjective feelings of tension, apprehension, nervousness and worry. It is well validated and has been used in many studies. (Marteau 1992, Spielberger 1983)

Depression and diabetes related symptoms
This questionnaire looked in more detail at how many people experienced each of 34 symptoms that could be related to elevated glucose levels and whether there was any correlation between symptoms and glucose results. In addition the Centre for Epidemiology Studies (CESD) twenty-item depression scale was included to assess the frequency and severity with which symptoms of depression are experienced. This questionnaire explores individuals’ experience of positive and negative moods and thoughts over the previous seven days. (Boey 1999, Radloff 1977)

Beliefs about diabetes.
Illness Beliefs were assessed using three scales from the Diabetes Illness Representations Questionnaire (Skinner 2003), which is a slightly revised version of the Illness Perceptions Questionnaire (Weinman 1996). Beliefs about the cause of, duration of, and the consequences of diabetes were assessed. The seriousness of the threat of diabetes to health and the perceived impact of diabetes on day to day functioning were part of the consequences of diabetes. For all three scales a five-option response format from “strongly agree” to “strongly disagree” was used. The instructions were also revised to ask participants what they generally thought about type 2 diabetes.

Basic information about health (SF-12)
This is a single-page health survey which is useful in monitoring outcomes in general and in specific populations, it was to determine individuals’ views on their own health and whether this had any impact on their usual activities. (Ware 1996)
Personality and Emotional stability
The Big Five Personality Inventory 44 questionnaire measures personality and emotional stability. It is a well-validated, 44-item, five-option response format instrument which measures agreeableness, conscientiousness, emotional stability, extroversion and openness to experience. Individuals indicate how applicable the descriptive statements are to themselves. (John 1991)

Social class questionnaire
This questionnaire is from the Office of National Statistics and was used in the 2001 Census. It is self-completed by individuals for the person in their household with the highest income. Students were asked to complete this based on their highest earning parent. The NS-SEC self-coded matrix derivation table was used to code social class. (Department of Health 2001)

Physical activity questionnaire
This questionnaire is the short version of the International Physical Activity Questionnaire. (IPAQ) It was developed in 1996 and was designed to obtain internationally comparable data on health-related activity and comprises of seven questions. It has been validated and can determine an individual’s level of physical activity. (International Physical Activity Questionnaire 2002)

Ethnicity Classification
This was based on the census classification

3.7.5 Risk Scores and Questionnaires
The Griffin or Cambridge Diabetes Risk score, (CDRS) which includes age, gender, BMI, steroid and anti-hypertensive use, family and smoking history, and was developed in Cambridge to identify those individuals at risk of diabetes was completed for all individuals. (Park 2002) The Finnish Diabetes Risk Score (FDRS) was developed in Finland and is a similar system of producing a score for each
individual indicating their risk of diabetes was also completed. (Lindstrom 2003) The aim was to validate each of these scores in our population, which included individuals from black, minority and ethnic groups. Results from these scores and questionnaires are discussed in chapter 5.

3.8 Metabolic Syndrome

An International Diabetes Federation (IDF) consensus document was published in 2005 with new criteria for the metabolic syndrome that provides a single universally accepted diagnostic tool to identify patients with the metabolic syndrome within the clinical setting more easily. In the new definition central obesity is an essential criterion and two further criteria are required from: raised triglycerides, decreased HDL cholesterol, hypertension and elevated FPG. Central obesity is measured by waist circumference and there are gender and ethnic specific cut-off values. (IDF 2005) Prior to the IDF definition, the World Health Organization (WHO) and National Cholesterol Education Expert Panel on Detection, Evaluation, and Treatment of high Blood Cholesterol in Adults (NCEP) had separate definitions for the metabolic syndrome. (WHO 2003, Executive Summary 2001) These definitions, along with the new IDF definition for the metabolic syndrome are shown in table 3.1.

The prevalence of the metabolic syndrome in our screened cohort was determined from anthropometric and biochemical investigations. The prevalence was calculated in each of the glucose tolerance groups – normal, IFG, IGT and diabetes. The prevalence of the different definitions of the metabolic syndrome was calculated for males and female in each ethnic group. (WHO 2003, Executive Summary 2001, IDF 2005)
Table 3.1 Definitions for the Metabolic Syndrome

<table>
<thead>
<tr>
<th>WHO definition</th>
<th>Glucose</th>
<th>Blood pressure</th>
<th>Lipids (1)</th>
<th>Lipids (2)</th>
<th>Central obesity</th>
<th>Albumin:creatinine ratio</th>
<th>Insulin resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes, IGT or IFG and 2 or more of:</td>
<td>Essential requirement to have diabetes, IGT or IFG</td>
<td>≥ 140/90 or on treatment</td>
<td>Triglycerides ≥ 1.7 mmol/l or HDL &lt; 0.9 mmol/l men or &lt; 1.0 mmol/l women</td>
<td>WHR &gt; 0.9 men &gt; 0.85 women or BMI &gt; 30 kg/m²</td>
<td>Men: &gt; 2.5 mg/mmol Women: &gt; 3.5 mg/mmol</td>
<td>glucose uptake &lt; lowest 25% for background population</td>
<td></td>
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<tr>
<td>ATP/NCEP III definition</td>
<td>3 or more of:</td>
<td>Fasting glucose ≥ 6.1 mmol/l</td>
<td>≥ 130 / ≥ 85 mmHg or on treatment</td>
<td>Triglycerides &gt; 1.7 mmol/l or on fibrates</td>
<td>HDL Cholesterol &lt; 1.03 mmol/l men. &lt; 1.29 mmol/l women</td>
<td>waist circumference &gt; 102 cm men &gt; 88 cm women</td>
<td></td>
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<tr>
<td>IDF definition</td>
<td>Central obesity and 2 or more of:</td>
<td>Fasting glucose ≥ 5.6 mmol/l or previously diagnosed diabetes</td>
<td>≥ 130 / ≥ 85 mmHg or on treatment</td>
<td>Triglycerides &gt; 1.7 mmol/l or on treatment</td>
<td>HDL cholesterol &lt; 0.9 mmol/l males and &lt; 1.1 mmol/l in females or on treatment</td>
<td>Essential requirement waist circumference ≥ 94 cm for Europid men, ≥ 90 cm for South Asian men and ≥ 80 cm for both Europid and South Asian women.</td>
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3.9 Database management
Patients were all given a unique study number that was used on all their documentation and investigations. Numbers were serial and commenced at one for those screened at the Royal Infirmary, at 5000 for those screened on the mobile screening unit, at 6000 for those screened at the General Hospital and any individuals who were not eligible for inclusion in the study were given numbers commencing at 10000. Data from the case report form and laboratory investigation results sheets were entered onto the database manually. The database was password protected. The password was known to a minimum number of authorised users. The main database had no patient names on it, and a separate password protected database of names and identifying numbers was maintained. All data entries were verified by a separate member of staff and a random 10% of all entries were cross checked by a member of the STAR steering group. Once the data entry was complete, had been verified and randomly checked, the database was locked.

3.10 Subsequent management
Individuals and their general practitioners were all informed by letter of the results of their tests, within 2 weeks. Subsequent management of patients found to have abnormal glucose tolerance had been discussed and agreed with individual practices in advance.

3.10.1 Diagnosis and Management of subjects with newly diagnosed prediabetes
Prediabetes is the presence of impaired fasting glucose (IFG), impaired glucose tolerance (IGT) or both IFG and IGT. IGT was defined as a venous FPG of < 7.0 mmol/l and a level of between 7.8 and 11.1 mmol/l two hours after a 75-gram oral glucose load (WHO 2003). IFG is defined as a FPG between 6.1 to 6.9 mmol/l with a 2-hour plasma glucose of less than 7.8 mmol/l. (WHO 2003) The ADA have lowered their definition of IFG to a FPG value of ≥ 5.6 mmol/l, however this has not been accepted internationally. (ADA 2005) In this study the WHO definition is used with a FPG of 6.1-6.9 mmol/l.
Individuals who were found to have prediabetes were advised they would be invited for a re-screen after 12 months. All individuals were given an IGT booklet which explained what prediabetes is and included details on the progression of prediabetes to diabetes and contained information on how to decrease the risk of this occurring by keeping physically active, following a healthy diet and if their BMI was greater than 25kg/m² to lose weight. All eligible patients were invited to take part in either the NAVIGATOR or DREAM trials which targeted individuals with prediabetes in an attempt to delay the progression to diabetes. (NAVIGATOR 2002, DREAM 2004)

3.10.2 Management of subjects with newly diagnosed type 2 diabetes
Those patients identified as having diabetes were recalled for a repeat OGTT to confirm the diagnosis, if they had no active symptoms of diabetes, in accordance with WHO guidelines on the diagnosis of diabetes. (Alberti 1998) With prior agreement from the GP’s, after the diagnosis of diabetes had been confirmed, patients were offered an outpatient appointment at the Leicester Royal Infirmary. All patients were seen by myself and their baseline physical and biochemical characteristics were documented. Patients were reviewed every 3 months for the first 12 months and then every 6 months. Cardiovascular risk factors were addressed and hyperglycaemia treated according to local guidelines. (www.leicestershirediabetes.co.uk) These guidelines are based on national and international evidence based guidelines. (NICE 2002, Joint British Societies 2005) The presence of microvascular and macrovascular complications was determined. Individuals were all offered fundal photography through dilated pupils, a microalbumin/creatinine ratio and examination of their feet to determine the presence of peripheral neuropathy and peripheral vascular disease. These are the same investigations that would usually be offered to newly diagnosed patients. The inability to detect at least 3 out of 5 stimuli from a 10-g monofilament the sole of either foot was recorded as peripheral neuropathy. PVD was assessed by palpation of pedal pulses. The absence of at least two pulses was taken as abnormal. Group education sessions were offered to the patients who attended clinic prior to August 2003. All patients who did not attend the group education sessions were offered individual appointments with the diabetes specialist nurses and dietician. Patients received education and advice on both short and long term management and
on how to achieve their targets, which included non-pharmacological measures of smoking cessation and increased physical activity. Exercise on prescription was offered to all individuals. Some patients chose to have their follow-up care provided by their primary care team.

3.11 Practice Profiles

General practices within Eastern Leicester Primary Care Trust (PCT) and Leicester City West PCT were approached by invitation mailer to participate in the study. For those practices who did not respond to the initial mailing, a follow-up mailer was sent after 2 months. A total of 29 practices within Leicester City West PCT and 32 practices within Eastern Leicester PCT were approached. Nine practices from Eastern Leicester and 8 practices for the Leicester City West PCTs were initiated and participated in the screening study.

Table 3.2 shows the number of whole time equivalent general practitioners and the size of each of the practices. There were six single-handed general practices, three practices with two GPs and the remaining seven practices had up to six GPs in their surgeries. In total 52 different GPs were employed in these practices. All the Practices were within City of Leicester Local Authority. Practice A consists of two surgeries on two sites which are run as one practice; the second surgery falls into the Charnwood District Local Authority.
Table 3.2 Characteristics of Practices Involved in Screening

<table>
<thead>
<tr>
<th>Practice</th>
<th>A</th>
<th>B</th>
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<th>O</th>
<th>P</th>
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<tr>
<td>Population screening</td>
<td>Targeted screening</td>
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<tr>
<td>Number of GP's</td>
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<td>6</td>
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<td>LCW</td>
<td>EL</td>
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<tr>
<td>Female life expectancy</td>
<td>78.2 / 82.3 years</td>
<td>79.3 years</td>
<td>77.4 years</td>
<td>80.3 years</td>
<td>75.9 years</td>
<td>79.3 years</td>
<td>79.9 years</td>
<td>76.4 years</td>
<td>79.9 years</td>
<td>79.4 years</td>
<td>79.4 years</td>
<td>78.1 years</td>
<td>81.5 years</td>
<td>79.3 years</td>
<td>75.9 years</td>
<td>79.3 years</td>
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<tr>
<td>Male life expectancy</td>
<td>73.9 / 75.3 years</td>
<td>73.7 years</td>
<td>74.7 years</td>
<td>72.2 years</td>
<td>68.3 years</td>
<td>73.7 years</td>
<td>74.2 years</td>
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<td>74.2 years</td>
<td>74.0 years</td>
<td>74.0 years</td>
<td>71.4 years</td>
<td>74.5 years</td>
<td>73.7 years</td>
<td>68.3 years</td>
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<td>9773</td>
<td>13054</td>
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<td>13736</td>
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<td>1742</td>
<td>7257</td>
<td>6962</td>
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<td>6789</td>
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<tr>
<td>Prevalence of known diabetes</td>
<td>6.4%</td>
<td>5.8%</td>
<td>3.3%</td>
<td>4.5%</td>
<td>3.8%</td>
<td>0.5%</td>
<td>6.3%</td>
<td>3.5%</td>
<td>4.1%</td>
<td>3.0%</td>
<td>7.6%</td>
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<td>n=224</td>
<td>n=147</td>
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</table>

* Leicester City West Primary Care Trust = LCW. Eastern Leicester Primary Care Trust = EL
The practices can be characterized in many different ways including deprivation, life expectancy, list size and ethnicity. One of the most powerful determinants of health is deprivation, with most health indicators being adversely affected by poverty. (Acheson 1998) Two of the commonest indicators of deprivation are the Townsend Material Deprivation Score and Jarman Underprivileged Area Score. The Jarman score was originally developed as measure of General Practice workload and has been used primarily as a weighting indicator for additional ‘deprivation’ payments to General Practitioners. (EMPHO 2005)

The Jarman Score was developed during the 1981 census and contains eight variables which include:

- Unemployment: number of residents unemployed as a percentage of those economically active
- Overcrowding: % of households with more than one person per room
- Lone parents: % of residents in ‘lone parent’ households
- Under 5’s: % of residents aged under 5 years
- Elderly living alone: % of elderly living alone
- Ethnicity: % of households headed by a person born outside the UK
- Low social class: % of households headed by an unskilled person (social class V)
- Residential mobility: % of residents who changed address in the previous year

The Townsend Score was developed to measure socio-economic deprivation and is used as an indicator of material deprivation. (EMPHO 2005) It is based on four census variables, selected to represent material deprivation.

- Unemployment: % of economically active residents who are unemployed
- Car ownership: % of private households who do not possess a car
- Home ownership: % of private households not owner occupied
- Overcrowding: % of private households with more than one person per room.

The Townsend Material deprivation score for the City Of Leicester Local Authority is 6.27 which is ranked 25th, and the Jarman score is 37.2 which is ranked 11th highest. There are 410 local authorities in England and Wales, and both of these commonly
used markers of deprivation show that our screening study in Leicester was performed in areas with levels of deprivation among the worst 10% in the country.

The census also provides information on ethnicity. In the City of Leicester Local Authority there are 29.9% of people who class themselves as belonging to Indian, Pakistani or Bangladeshi ethnic groups. The national average is 2.6%. Within the City of Leicester there are variations in this percentage. The Eastern Leicester Primary Care Trust, which includes nine of our practices, has an ethnic minority population of 51%, compared to 13.5% in Leicester City West Primary Care Trust, where the remaining eight practices were recruited from.

The average life expectancy at birth in the East Midlands is 80.3 years in females and 75.9 years in males. The life expectancy for each practice is shown in table one, these figures are from the 2001 Census information and are determined by geographical areas based on Electoral Wards. All the females in this study have a lower life expectancy than the average for the East Midlands and in fourteen out of the seventeen general practices involved there is a lower than average life expectancy for males. (Census 2001) Deaths before the average age of death are sometimes referred to as premature and are of public health interest in that they are often linked to illnesses which could be seen as preventable.

### 3.12 Response rates

Table 3.3 shows the calculated numbers of individuals invited for screening and the response rate for each practice to those invitations. The calculated response rates varied from 2.1% to 30%. We believe the two practices with response rates recorded of under 5% (practice D and F) and two further practices with response rates between 5 and 8% (practice B and O) are due to difficulties in obtaining accurate figures of the numbers of invitations sent out. For confidentiality reasons the lists generated of patients eligible to be invited were not allowed to be taken out of the GP premises and no record was taken of the number of invitations mailed. In order to have an idea of the response rates for each practice, lists of patients within the age range and with at least one eligible risk factor were generated again at the end of study. These
calculations are unlikely to be an accurate reflection of the original number of invitations mailed. There are a number of reasons that may contribute to this. Since 2004, under the new GMS contact, practices are paid to record information including smoking status, the presence of CHD, stroke and TIA, hypertension and diabetes. Payment is also available to record blood pressure of patients aged over 45 years. (DOH 2004) The financial incentives involved in having accurately recorded information may have led to a greater number of individuals being identified from the EMIS computer searches at the end of study than would have been identified at the start of the study.

The practices which were involved in the study all had high deprivation scores and a greater proportion of individuals from ethnic minority populations. These are both likely to have had a negative impact on the response rates to a screening study for health related activities.

The amount of information now required to be included in the patient information sheets (PIS) is likely to be a further deterrent to individuals agreeing to take part in the study. The PIS comprised six sides of A4 paper. (Appendix B) The volume of information that ethics committees now require to be provided to individuals prior to attending for any research study may have contributed to low response rate for screening. Individuals who heard about the screening study through the outreach and awareness events were well motivated and not concerned about the volume of information provided, but informal feedback from practice nurses and GP’s was that the PIS was a deterrent due to the amount of detail included.

A previous screening study in Leicester found a response rate after a single-invitation for self-testing of post-prandial glycosuria of 34.4 % in South Asians and 54% in Caucasian (Davies 1999). In the Coventry Diabetes Study, which was more labour intensive with fieldworkers making house visits and testing capillary blood for glucose, the response rate of those found be more at risk of having diabetes, who then attended for an OGTT was 64.2% in Asian and 57.5% in Caucasian individuals. (Simmons 1989) In a study by Lawrence et al where fasting blood glucose levels were used to screen for diabetes the response rate was 35%. (Lawrence 2001)
In the Diabetes, Heart Disease and Stroke (DHDS) pilot prevention project 24 general practices were involved in screening for diabetes. Screening protocols varied between practices but all practices used a random capillary glucose > 6.0 mmol/l as the cut-off for diagnostic testing. 61% of individuals invited for screening had a random capillary glucose taken. In some practices screening was opportunistic, which did not necessitate extra visits for screening, no patient information sheets or ethics forms were submitted and only verbal consent was taken. All of these reasons will have contributed to the initial response rate of 61%, which is higher than in the STAR study. However more than 30% of those with a glucose above the cut-off level did not attend for a diagnostic glucose test, and only 20% completed an OGTT. (Diabetes, Heart Disease and Stroke Prevention Project 2006)

In the STAR study the four practices with calculated response rates of less than 8% are probably due to significant changes in the recording of the presence of risk factors (and therefore data collection) at a practice level. The remaining practices have rates of up to 30%. These are still under the response levels found in earlier studies. This is disappointing and may reflect changes in recording of risk factors by the practices, the complexity of the patient information sheets, the inclusion of an OGTT as part of screening process and therefore a greater time commitment from individuals’ and the greater prevalence of patients from ethnic minorities who have previously been shown to have lower response rates than Caucasians. (Davies 1999). In the STAR study there was local publicity and individually addressed invitation letters were sent from their own general practitioner, but no home visits were made, which may partly account for our lower response rates. The location of screening may have deterred some individuals from attending screening. The likelihood of this was decreased by using the mobile screening unit, which travelled to some general practice surgeries, but this was only available for 20% of those screened and the remainder of the individuals were invited for screening at one of the local hospitals.
Table 3.3 Calculated Response Rates to Screening Invitations

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<td>200</td>
<td>634</td>
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<td>24.7%</td>
<td>2.5%</td>
<td>11.0%</td>
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<td>10.6%</td>
<td>11.5%</td>
<td>22.5%</td>
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3.13 Summary
The STAR study was designed to address some of the research questions around different methods of screening for abnormal glucose tolerance, particularly in ethnic populations where there have been only a few studies performed. The diverse ethnic population of Leicester provided the opportunity for a definitive study to determine the optimum method of screening an at risk multiethnic population. As all patients received an oral glucose tolerance test, the gold standard test to diagnose diabetes and prediabetes, the performance of other screening methods can be reliably described. This study looked at the baseline characteristics of those identified with abnormal glucose tolerance. The role of FPG, HbA1c, risk factors, risk scores and questionnaires as screening tools for previously undiagnosed abnormal glucose tolerance will be determined and discussed. The prevalence of metabolic syndrome according to each of the three definitions in each of the categories of abnormal glucose tolerance will be presented. The impact of screening on anxiety will be presented. This study will increase the evidence currently available in the ongoing debate on how to screen, whether to screen and the impact of screening for abnormal glucose tolerance. The different methodologies can be compared to see which methods are more applicable to different populations and circumstances.
Chapter 4

Prevalence and clinical characteristics of White European and South Asian adults with screen-detected type 2 diabetes

4.1 Introduction
It is well known that patients with diabetes often have complications at the time of diagnosis. (UKPDS 6 1990, Thompson 1996, Hillier 2001, Davies 1996) Much of this data arises from patients with diabetes diagnosed conventionally when they present with symptoms or when diabetes is diagnosed incidentally during investigations for other pathology. A few studies have reported the characteristics of patients with screen-detected diabetes, (Davies 1996, Wens 2002, Edelman 2003, Spijkerman 2003, Meyer 1994) however, studies in South Asians are lacking. In the UKPDS patients had conventionally diagnosed diabetes and South Asians were on average 5 years younger and less obese than Caucasian subjects although the prevalence of microvascular complications was similar. (UKPDS 6 1990, Meyer 1994) The aim of this study was to determine the prevalence and describe the characteristics of patients diagnosed as having diabetes through a screening programme and to compare the characteristics of White European and South Asian people.

4.2 Methods
The Screening Those At Risk (STAR) study was designed to identify the prevalence of undiagnosed diabetes. This screening study was conducted in Leicestershire with a population of over 950,000, approximately one third of whom are resident in the city. South Asians make up 24% of the population. All individuals aged 40-75 years, and 25-75 years if not of White European origin, who had at least one recognised risk factor for diabetes (identified from general practice computer records) from fifteen general practices were invited to attend screening. All patients within the age ranges were invited from a further two general practices. The patients were sent a letter and information pack in English and a flyer in four languages advising patients how to get details in their own language. Non-responders were sent a second letter. There were leaflets for participating practices and a local media campaign.
Risk factors included a known history of coronary heart disease, hypertension, dyslipidaemia, cerebrovascular disease, peripheral vascular disease (PVD), impaired glucose tolerance (IGT) or impaired fasting glycaemia, (IFG) gestational diabetes or polycystic ovary syndrome in those with a BMI>25kg/m². Other risk factors included a first-degree relative with type 2 diabetes or BMI>25kg/m² if leading a sedentary life, otherwise >30kg/m². Exclusion criteria were patients who were housebound, had a terminal illness or were already known to have diabetes. All patients provided written consent. The screening was conducted within the general practice, on a mobile screening unit or at one of the teaching hospitals, between February 2002 and July 2004. Ethical approval was obtained from the local ethics committee.

All patients attended after at least an eight-hour fast, and venous blood samples were taken for glucose, HbA1c, lipids and renal function. A 75-g oral glucose load (394mls Lucozade) was given and a venous blood sample taken after 120 minutes. All samples were analysed in the same laboratory using stable methodology standardised to external quality assurance reference values. Further assessment included blood pressure, height and weight. BMI was calculated. Maximum waist measurements were taken. Early morning urinary albumin and creatinine levels were measured and the albumin:creatinine ratio (ACR) calculated. Microalbuminuria was defined as an ACR >2.5mg/mmol in males and 3.5mg/mmol in females. A twelve-lead electrocardiograph was performed and classified according to the Minnesota classification. (Rose 1982) All patients were asked to self-complete an ethnicity (Census classification).

Individuals found to have glucose results within the diabetes range, using the WHO 1998 criteria, were invited for a repeat OGTT. (WHO 1999) Patients found to have diabetes were invited for a full clinical assessment and were seen by the same physician. Respiratory, cardiovascular, peripheral vascular and retinal examinations (single field digital photograph through dilated fundi) were included. PVD was assessed by palpation of pedal pulses. The absence of at least two pulses was taken as abnormal. The baseline characteristics of all patients are included. Physical examination findings are only included for those patients attending the hospital.
Data on the prevalence of retinopathy is from those patients who had retinal photographs taken or were reviewed by an Ophthalmologist.

Patients were considered to have hypertension if the systolic blood pressure was ≥140/90 mmHg or if the patients were taking anti-hypertensive medication. Dyslipidaemia was diagnosed if total cholesterol was >5.0 mmol/l, triglycerides >2.3 mmol/l or if the patient was receiving lipid-lowering medication. Definitions for being overweight and obese were a BMI ≥25kg/m² and 30kg/m² in White Europeans and 23kg/m² and 27.5 kg/m² in South Asians. Definitions for central obesity of abdominal circumference ≥94cm in Caucasian males, ≥80 cm in Caucasian and South Asian females and ≥90 cm in South Asian males. (IDF 2005)

The different definitions for the metabolic syndrome are presented in table 3.1. The prevalence of the metabolic syndrome in each of the population groups and for each glucose category was determined.

4.3 Statistical Analysis
The characteristics of South Asians aged 25-39 years are described, but only the patients in the age range 40-75 years were compared. All analyses comparing the two ethnic groups were age adjusted. For the comparison of continuous variables multiple regression models were fitted and for the categorical variables, logistic regression models were used. For all models, except when age itself was being assessed, age was fitted as a covariate. Due to the difference in age between the ethnic groups, prevalence of diabetes was reported as an overall prevalence for the study for each group, and stratified by age. A p-value<0.05 was considered significant. Results are presented as mean (SD) or as a percent, with 95% CI given where appropriate. Only individuals who underwent a retinopathy assessment (49%) or PVD assessment (51%) were used in the calculation of the prevalence for these two complications. As there were no reasons for those undergoing the tests to differ in any way from the rest of the study population, the calculated prevalences should be unbiased estimates. McNemars (non-parametric) test for related samples and the Mann Whitney U (non-parametric) test for non-related samples were used in analysis of the metabolic syndrome data.
4.4 Results

4.4.1 Baseline characteristics

3515 patients were screened, of whom 92.2% (n=3241) were aged between 40-75 years and 7.8% (274) of patients were aged 25-39 years. White Europeans accounted for 58.6% (105) of those with screen-detected diabetes and included those of White British, Irish or European origin. South Asians were 36.5% (65) of those with screen-detected diabetes with the majority being of Indian origin (95.6%). Of those aged 40-75 years, 92.7% (3005) had at least one risk factor for diabetes compared to 77.4% (212) in those aged 25-39 years. Nineteen (10.9%) individuals had a history of a myocardial infarction, 4.9% (n=9) had angina and 2.2% (n=4) had a history of a cerebrovascular accident.

The overall prevalence of diabetes was 5.1% (179/3515) (95% CI: 4.3-5.9). In those patients in the age range 40-75 years the prevalence was 5.3% (172/3241) (95% CI: 4.1 to 5.6), compared to 2.6 % (7/274)(95% CI: 1.0 to 5.2) in the younger age range (South Asians, 25-39 years).

When only those patients with at least one risk factor are analysed the prevalence was similar in those aged 40-75 years at 5.4% (163/3005)(95% CI: 4.6 to 6.3) and slightly greater in those aged 25-39 years at 3.3% (7/212)(95% CI: 1.3 to 6.7) than when all patients are included in the analysis.

When the ethnic groups are compared the prevalence of diabetes in those aged 40-75 years was greater at 6.5% (58/899) (95% CI: 4.9 to 8.3) in South Asians compared to 4.7 % (105/2236) (95% CI: 3.8 to 5.7) in White Europeans.

The diagnosis of diabetes was unconfirmed in 7.2% (13/179) of patients, who did not attend for a re-screen. Retinal photographs and peripheral vascular assessments were offered to the 77.7% (139/179) of patients attending hospital follow up. A small group of patients [8.4% (15/179)] chose to be followed up in primary care and 14.0% (25/179) did not attend for follow-up.
The clinical characteristics of people with screen-detected diabetes in the age range 40-75 years are shown in Table 4.1. Compared to White Europeans, South Asians with screen-detected diabetes were diagnosed at a younger age, with similar FPG and HbA1c levels. All South Asian people under the age of 40 with screen-detected diabetes were overweight and 85.7% were obese. (Table 4.3) The HbA1c in South Asians was 7.6 (1.7) % compared to 7.0 (1.7) % in White Europeans. Although this did not reach statistical significance this difference of 0.6 % is clinically significant. The 2-hour glucose values again did not reach statistical significance after adjusting for age but there was a trend for South Asians to have greater values: 14.4 (4.4)mmol/l vs. 12.8 (4.3)mmol/l in White Europeans. South Asians with diabetes had a lower BMI and waist circumference compared to White Europeans. The prevalence of abnormal body weight and central obesity were similar in the two groups. (Table 4.2) A minority of patients were of normal weight.
Table 4.1 Clinical Characteristics at diagnosis of patients aged 40-75 years with screen detected type 2 diabetes

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<th>All patients</th>
<th>White Europeans</th>
<th>South Asians</th>
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<tr>
<td>N</td>
<td>163</td>
<td>105</td>
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<td>Age – years</td>
<td>59.9 (9.7)</td>
<td>63.2 (8.7)</td>
<td>54.1 (8.6)</td>
<td>&lt;0.001*</td>
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<td>HbA1c - %</td>
<td>7.2 (1.7)</td>
<td>7.0 (1.7)</td>
<td>7.6 (1.7)</td>
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<td>FPG – mmol/l</td>
<td>7.7 (2.5)</td>
<td>7.7 (2.5)</td>
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<td>2-hg – mmol/l</td>
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<td>Total Chol – mmol/l</td>
<td>5.3 (1.0)</td>
<td>5.3 (1.0)</td>
<td>5.3 (0.9)</td>
<td>0.334</td>
</tr>
<tr>
<td>HDL – mmol/l</td>
<td>1.2 (0.4)</td>
<td>1.2 (0.3)</td>
<td>1.2 (0.5)</td>
<td>0.817</td>
</tr>
<tr>
<td>LDL – mmol/l</td>
<td>3.2 (0.9)</td>
<td>3.2 (0.9)</td>
<td>3.2 (0.8)</td>
<td>0.965</td>
</tr>
<tr>
<td>Trig – mmol/l</td>
<td>2.1 (1.5)</td>
<td>2.2 (1.6)</td>
<td>2.1 (1.4)</td>
<td>0.110</td>
</tr>
<tr>
<td>Weight – kg</td>
<td>83.2 (15.8)</td>
<td>87.0 (14.1)</td>
<td>76.4 (16.6)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Height – m</td>
<td>1.65 (0.10)</td>
<td>1.67 (0.09)</td>
<td>1.62 (0.11)</td>
<td>0.001*</td>
</tr>
<tr>
<td>BMI – kg/m²</td>
<td>30.2 (5.1)</td>
<td>30.9 (4.5)</td>
<td>28.9 (5.8)</td>
<td>0.004*</td>
</tr>
<tr>
<td>Waist circumference – cm</td>
<td>102.5 (12.7)</td>
<td>104.1 (12.9)</td>
<td>99.5 (11.9)</td>
<td>0.027*</td>
</tr>
<tr>
<td>Waist hip ratio</td>
<td>0.94 (0.09)</td>
<td>0.94 (0.10)</td>
<td>0.94 (0.09)</td>
<td>0.815</td>
</tr>
<tr>
<td>Systolic BP – mmHg</td>
<td>143 (22)</td>
<td>145 (22)</td>
<td>141 (23)</td>
<td>0.678</td>
</tr>
<tr>
<td>Diastolic BP – mmHg</td>
<td>83 (12)</td>
<td>82 (12)</td>
<td>85 (11)</td>
<td>0.280</td>
</tr>
</tbody>
</table>

Results are mean ± 1SD.  P values reported are age adjusted where appropriate
* Indicates a significant (p<0.05) result
4.4.2 Glycaemia, Hypertension and Dyslipidaemia

There was no difference in the FPG, 7.9 (SD 2.6) vs. 7.7 (2.5) mmol/l, 2-hour plasma glucose, 14.4 (4.4) vs. 12.8 (4.3) mmol/l, and HbA1c values 7.6 (1.7)% vs. 7.0 (1.7)% between South Asians and White Europeans respectively. However the prevalence of patients with an elevated HbA1c (>6.5%) was 78.2% (n=43) in South Asians and 47.0% (n=47) in White Europeans (p=0.002).

There was no difference in blood pressure values 141/85 (23/11) mmHg in South Asians vs. 145/82 (22/12) mmHg in White Europeans, and no difference in the prevalence of hypertension; 64.9% vs. 84.5%. Of those found to be hypertensive there was no difference in the prescriptions for anti-hypertensive treatment 65.0% (n=24) South Asians and 75.9% (n=66) of White Europeans (p=0.885). There was no difference in the type of antihypertensive treatment: 34% diuretic, 45.5% beta-blocker, 29.3% calcium-channel antagonist and 23.6% ACE-inhibitor.

There were no ethnic differences in the lipid values: overall mean total cholesterol was 5.3 (1.0)mmol/l, HDL 1.2 (0.4)mmol/l and triglyceride concentration 2.1 (1.5)mmol/l. However the prevalence of dyslipidaemia was greater in White Europeans (80.8%, n=84) than in South Asians (66.7%, n=38) p=0.048, as more White Europeans were receiving lipid-lowering medication to achieve the same lipid values (21% vs. 9.2%).

4.4.3 Complications

Table 4.2 compares the prevalence of complications with that reported in the UKPDS. (UKPDS 6 1990) The prevalence of microalbuminuria was 16.5% (95% CI:11.0 to 23.2) and renal impairment (serum creatinine>120μmol/l) was 4.3% (95% CI:1.7 to 8.6). Neither of these varied between the populations. Of those patients who had retinal assessments the prevalence of at least one microaneurysm was 2.5% (95% CI: 0.3 to 8.7). There were no cases of proliferative retinopathy. In this study 14.8% (n=22) of patients were found to have an electrocardiogram with definite ischaemic changes. Of those found to have screen-detected diabetes 26.8% (n=48) had at least one complication (from microalbuminuria, retinopathy, abnormal electrocardiograph, PVD and elevated plasma creatinine) and 6.7% (n=12) had at least two complications.
<table>
<thead>
<tr>
<th>Complication</th>
<th>All patients</th>
<th>All WE</th>
<th>All SA</th>
<th>P value</th>
<th>UKPDS prevalence of complications</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% (n) (95% CI)</td>
<td>% (n) (95% CI)</td>
<td>% (n) (95% CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>HbA1c &gt;6.5%</strong></td>
<td>58.1 (90) (49.9 to 65.9)</td>
<td>47.0 (47) (36.9 to 57.2)</td>
<td>78.2 (43) (65.0 to 88.1)</td>
<td>0.002*</td>
<td>Not reported</td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td>77.5 (124) (70.2 to 83.7)</td>
<td>84.5 (87) (76.0 to 90.9)</td>
<td>64.9 (37) (51.1 to 77.1)</td>
<td>0.208</td>
<td>35% (but definition of hypertension &gt;160/95)</td>
</tr>
<tr>
<td>(BP ≥ 140/90 mmHg or on antihypertensive treatment)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Dyslipidaemia</strong></td>
<td>75.8 (122) (68.4 to 82.2)</td>
<td>80.8 (84) (71.9 to 87.8)</td>
<td>66.7 (38) (52.9 to 78.6)</td>
<td>0.048*</td>
<td>Not reported</td>
</tr>
<tr>
<td>(Cholesterol &gt;5.0mmol/l or triglycerides &gt;2.3 mmol/l or on lipid lowering treatment)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Overweight</strong></td>
<td>92.5 (148) (87.3 to 96.1)</td>
<td>93.2 (96) (86.5 to 97.2)</td>
<td>91.2 (52) (80.1 to 97.1)</td>
<td>0.624</td>
<td>Not reported</td>
</tr>
<tr>
<td>(BMI ≥ 25 kg/m² in WE or 23 kg/m² in SA)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Obesity</strong></td>
<td>56.9 (91) (48.8 to 64.7)</td>
<td>59.2 (61) (49.1 to 68.8)</td>
<td>52.6 (30) (39.0 to 66.0)</td>
<td>0.125</td>
<td>Different criteria used</td>
</tr>
<tr>
<td>(BMI ≥ 30 kg/m² in WE or 27.5 kg/m² in SA)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Prevalence of central obesity</strong></td>
<td>90.8 (148) (85.2 to 94.8)</td>
<td>91.4 (96) (84.4 to 96.0)</td>
<td>89.7 (52) (78.8 to 96.1)</td>
<td>0.857</td>
<td>Not reported</td>
</tr>
<tr>
<td>(Waist circumference ≥94cm in Caucasian males, ≥80 cm in Caucasian and South Asian females and ≥ 90 cm in South Asian males)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Retinopathy</strong></td>
<td>2.5 (2) (0.3 to 8.7)</td>
<td>3.6 (2) (0.4 to 12.5)</td>
<td>0 (0) (0 to 13.7)</td>
<td>0.922</td>
<td>21%</td>
</tr>
<tr>
<td>(On retinal photograph or by review by Ophthalmologist)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Abnormal ECG</strong></td>
<td>14.8 (22) (9.4 to 21.5)</td>
<td>18.4 (18) (11.3 to 27.5)</td>
<td>7.8 (4) (2.2 to 18.9)</td>
<td>0.245</td>
<td>18%</td>
</tr>
<tr>
<td>(Probable ischaemia as per Minnesota coding)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Microalbuminuria</strong></td>
<td>16.5 (26) (11.0 to 23.2)</td>
<td>16.7 (17) (10.0 to 25.3)</td>
<td>16.1 (9) (7.6 to 28.3)</td>
<td>0.802</td>
<td>Not reported</td>
</tr>
<tr>
<td>(Microalbuminuria ≥ 2.5 in males and ≥ 3.5 mg/mmol in females)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Renal impairment</strong></td>
<td>4.3 (7) (1.7 to 8.6)</td>
<td>5.8 (6) (2.2 to 12.2)</td>
<td>1.8 (1) (0.04 to 9.6)</td>
<td>0.960</td>
<td>3%</td>
</tr>
<tr>
<td>(Creatinine &gt; 120 μmol/l)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Peripheral vascular disease</strong></td>
<td>9.6 (8) (4.3 to 18.1)</td>
<td>10.2 (6) (3.8 to 20.8)</td>
<td>8.3 (2) (1.0 to 27.0)</td>
<td>0.550</td>
<td>13%</td>
</tr>
<tr>
<td>(absence of at least 2 foot pulses on palpation)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

p-values are adjusted for age, * indicates a significant (p<0.05) result
Table 4.3 The prevalence of metabolic abnormalities in White Europeans and South Asians in different age ranges

<table>
<thead>
<tr>
<th></th>
<th>Age &lt; 40 years *</th>
<th>Age ≥ 40 and &lt; 60 years</th>
<th>Age ≥ 60 and ≤ 75 years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>White Europeans</td>
<td>South Asians</td>
<td>White Europeans</td>
</tr>
<tr>
<td>HbA1c &gt;6.5%</td>
<td>none</td>
<td>57.1%</td>
<td>53.3%</td>
</tr>
<tr>
<td>Prevalence of BP &gt; 140/90 mmHg</td>
<td>None</td>
<td>42.9%</td>
<td>70.0%</td>
</tr>
<tr>
<td>or on antihypertensive</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prevalence of cholesterol</td>
<td>none</td>
<td>42.9%</td>
<td>83.3%</td>
</tr>
<tr>
<td>&gt;5.0mmol/l or triglycerides &gt; 2.3 mmol/l or on lipid lowering treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prevalence of BMI ≥ 25 kg/m² in WE or 23 kg² in SA</td>
<td>none</td>
<td>100.0%</td>
<td>93.3%</td>
</tr>
<tr>
<td>Prevalence of BMI ≥ 30 kg/m² in WE or 27.5 kg/m² in SA</td>
<td>none</td>
<td>85.7%</td>
<td>70.0%</td>
</tr>
<tr>
<td>Prevalence of central obesity (IDF definition) waist circumference</td>
<td>none</td>
<td>85.7%</td>
<td>96.7%</td>
</tr>
</tbody>
</table>

(* only 7 individual in this group)
4.4.4 Metabolic syndrome
The prevalence of the metabolic syndrome according to the different definitions and glucose tolerance groups is shown in table 4.4. The WHO criteria for the metabolic syndrome is such that a patient has to have abnormal glucose tolerance to meet this definition. Whereas to meet the IDF criteria ethnically defined central obesity is an essential component. The NCEP definition needs 3 out of 5 abnormalities, of which abnormal glucose tolerance and central obesity are two of the criteria – but neither is essential.

Using the WHO definition for the metabolic syndrome would not allow those people with normal glucose tolerance to be identified. Both the NCEP and IDF can identify individuals with normal glucose tolerance who also have the metabolic syndrome.

Over 75% of patients with type 2 diabetes meet the criteria for metabolic syndrome and over 50% of those patients with prediabetes also meet the criteria. However there are statistical differences in the ability of the definitions to identify the metabolic syndrome.

The prevalence of the metabolic syndrome within populations
The WHO and IDF criteria identifies a greater percentage of patients with the metabolic syndrome, compared to the NCEP diagnosis due to the higher BP and lower glucose and obesity targets. In White Europeans with diabetes the WHO definition identifies a greater number of individuals than the NCEP criteria for the metabolic syndrome. (p=0.049) Whereas South Asians with diabetes have the same prevalence of the metabolic syndrome with each definition.

In individuals with pre-diabetes the WHO definition identifies more individuals with the metabolic syndrome than the other two definitions (p<0.001), and in White Europeans the IDF definition identifies more individuals with the metabolic syndrome that the NCEP definition.
In individuals with normal glucose tolerance each definition has a statistically different prevalence in both populations. The WHO definition identifies no-one and the NCEP definition identifies fewer than the IDF definition. (p<0.001)

In individuals with diabetes the different definitions have most agreement, and in those with normal glucose tolerance there is least agreement between the definitions.

**Table 4.4**
Prevalence of the metabolic syndrome, according to the different definitions, glucose tolerance status and population groups

<table>
<thead>
<tr>
<th></th>
<th>WHO definition</th>
<th>NCEP definition</th>
<th>IDF definition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>type 2 diabetes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>82.7 %</td>
<td>75.4 %</td>
<td>83.8 %</td>
</tr>
<tr>
<td>South Asian</td>
<td>75.4 % *</td>
<td>72.3 %</td>
<td>78.5 %</td>
</tr>
<tr>
<td>White European</td>
<td>87.6 % * +</td>
<td>79.0 % +</td>
<td>85.7 %</td>
</tr>
<tr>
<td><strong>IGT and / or IFG</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>69.6 %</td>
<td>51.8 %</td>
<td>57.7 %</td>
</tr>
<tr>
<td>South Asian</td>
<td>66.8 % +</td>
<td>48.4 % +</td>
<td>54.2 % +</td>
</tr>
<tr>
<td>White European</td>
<td>72.1 % +</td>
<td>54.7 % +</td>
<td>59.9 % +</td>
</tr>
<tr>
<td><strong>normal glucose tolerance</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>0 %</td>
<td>20.4 %</td>
<td>24.2 %</td>
</tr>
<tr>
<td>South Asian</td>
<td>0 % +</td>
<td>17.0 % * +</td>
<td>20.7 % * +</td>
</tr>
<tr>
<td>White European</td>
<td>0 % +</td>
<td>22.3 % * +</td>
<td>26.2 % * +</td>
</tr>
</tbody>
</table>

*= statistically significant difference between population groups
+= statistically significant difference between the definitions of metabolic syndrome

**The prevalence of the metabolic syndrome within glucose categories**
There are also differences in the ability of the definitions to diagnose the metabolic syndrome within glucose categories. Within those individuals found to have
diabetes the WHO definition is more likely to diagnose White Europeans as having metabolic syndrome than South Asians. (p = 0.04) There is no statistical difference in individuals with prediabetes. Whereas in those with normal glucose tolerance the NCEP and IDF definitions are more likely to diagnose White Europeans as having the metabolic syndrome than South Asians. (p=0.001 and p=0.002 respectively) This is even after having South Asian specific cut-off values for central obesity in the IDF definition.

4.5 Discussion
In this population-based screening study, we found a higher prevalence of undiagnosed diabetes in South Asians and White Europeans (6.5% and 4.7% respectively). People of South Asian origin with screen-detected diabetes are diagnosed at a younger age with a lower BMI and with a greater proportion having an elevated HbA1c (>6.5%).

4.5.1 Comparison with other studies
The prevalence of diabetes in the South Asian population in Leicester is 1.4-fold greater than in White Europeans. Other studies have previously found a greater difference. (Mather 1985, Bhopal 1999) In Newcastle this was 6.7-fold greater in Bangladeshian males, 5.5-fold greater in Pakistani males and 3.8-fold greater in Indian males than European males. There are several reasons why our difference in prevalence may be lower. In this cohort 95.6% of the South Asians were of Indian descent; this group has been found to have a lower prevalence of diabetes than other ethnic minorities. In addition, this was a screening study for undiagnosed diabetes and individuals were excluded if they were known to have diabetes. Furthermore, there has been a high awareness of diabetes and the need for earlier detection in South Asians in Leicester for a number of years.

In South Asians there was a trend for elevated 2-hour glucose values, which reached statistical significance before adjusting for age, after adjustment there was a greater proportion of South Asians with an elevated HbA1c. The DECODE study found that excess macrovascular risk in patients with diabetes was attributable to post-prandial hyperglycaemia, and not FPG. (DECODE 1999) The trend for greater 2-
hour glucose values 14.4(4.4) vs. 12.8(4.3) mmol/l) in South Asians may help explain why South Asians with diabetes have previously been found to have a greater prevalence of macrovascular complications. (McKeigue 1988, Burden 1992)

4.5.2 Hypertension and Hyperlipidaemia
Our cohort had a lower mean blood pressure (143/83 mmHg) and a higher proportion (75%) of those with hypertension were already on treatment compared to previous studies (Hillier 2001, Davies 1996, Burden 1992). This suggests patients are now being identified and treated more aggressively, reflecting the recommendations of recent evidence based guidelines. (Williams 2004). Lipid profiles of our cohort were also more favourable compared to previous studies. This may reflect the national trend of increased awareness of hyperlipidaemia and the greater use of lipid lowering treatment.

4.5.3 Glycaemia
The average FPG of UKPDS patients (Colagiuri 2002) was 11.8 mmol/l compared to 7.7 mmol/l in this study. The lower level of glycaemia in our cohort is consistent with patients being identified earlier. (Colagiuri 2002). Follow up will contribute to determining the value of detecting diabetes early.

4.5.4 Microvascular Complications
An early sign of nephropathy in diabetes is microalbuminuria. In this cohort 16.5% had microalbuminuria at diagnosis. This is similar to other studies: 18.2% in Finland, (Niskanen 1996), 17.2% in a screen-detected cohort in Holland (Spijkerman 2003) and 26.7% in non-screen detected patients from Holland. (Spijkerman 2003). However, 21% of patients in UKPDS had more than one microaneurysm at diagnosis (UKPDS 6 1990) compared to our prevalence of 2.5%. This may be an underestimation as our patients received single field photography compared to the four-fields in UKPDS.

4.5.5 Macrovascular Complications
The prevalence of an abnormal electrocardiograph in our cohort was lower than in UKPDS (UKPDS 6 1990) (14.8% vs. 18%). In a study of Newcastle residents, of
whom only 11% were known to have diabetes, the prevalence of abnormal electrocardiographs was 5% in South Asians and 1% in White Europeans. (Bhopal 1999) The prevalence of renovascular disease was higher in our cohort (4.3%) than was found in UKPDS (3%). (UKPDS 6 1990, Adler 2003) These patients were previously unknown to have renal impairment. Through identifying this abnormality early investigation and treatment to slow down progression of renal impairment can be implemented.

4.5.6 The Metabolic Syndrome
The metabolic syndrome can provide us with a useful reminder of the clustering of certain cardiovascular risk factors. After identification, components of the metabolic syndrome can be managed appropriately to prevent or delay progression of associated cardiovascular risk factors. In individuals with diabetes other risk factors such as dyslipidaemia, hypertension and central obesity, that contribute to the metabolic syndrome, will be addressed as part of good clinical practice.

The WHO definition may need an OGTT to diagnose metabolic syndrome, whereas the other 2 definitions can be diagnosed on a fasting blood sample. The IDF and NCEP definitions are more likely therefore to be useful in a clinical setting. The ultimate role of metabolic syndrome in practice may depend on showing the predictive value for cardiovascular disease or progression to diabetes in individuals with prediabetes or normal glucose tolerance. There may be differences between ethnic groups in the predictive ability of the metabolic syndrome.

4.5.7 Strengths and Limitations of the study
We acknowledge the limitations of this study. Over a quarter of patients had complications at diagnosis, but small numbers make differences between ethnic groups difficult to identify. The majority of patients were selected on the basis of having one recognised risk factor, this does follow international recommendations but may have resulted in a higher prevalence of diabetes compared to a true unselected population-screening programme. (Diabetes UK 2005, US Preventive Service Task Force 2003) Furthermore, as our patients had one risk factor, the prevalence of complications might also be higher. The strengths of this study
include using both FPG and 2-hour glucose values, and repeating these on a separate day, to confirm the diagnosis of diabetes. This has a greater sensitivity than screening with risk scores, questionnaires or FPG alone. (Wolfgang 2005) This was a large cohort of patients and included a significant proportion of South Asians. Although there is some heterogeneity among the South Asian population in Leicester, 95.6% of the Asian people found to have screen-detected diabetes screened were of Indian origin.

4.5.8 Interpretation of findings

Systematic screening of patients with one risk factor for diabetes identifies people with diabetes with a high prevalence of microvascular and macrovascular complications. Through screening, patients are identified earlier in the diabetes disease process, as reflected by the lower FPG at diagnosis, compared to conventionally diagnosed patients. Improving glycaemic control has been shown to be effective in reducing microvascular complications (Adler 2003, Ohkubo 1995) and may protect against macrovascular disease. Treatment of hypertension and dyslipidaemia has been shown to improve cardiovascular outcomes, which are the major cause of morbidity and mortality. (Stratton 2000) In these screen-detected patients 73.2% (n=131) of patients would have benefited from the addition of at least one pharmacological intervention with antihypertensive, lipid-lowering or glucose-lowering medication, using evidence-based guidelines.

Having identified this cohort of screen-detected patients, follow up will be important to determine whether detecting diabetes early and treating risk factors will influence the progression of diabetes and the development of complications. South Asians have the same baseline characteristics as White Europeans but at a younger age. The UKPDS found that South Asians with conventionally diagnosed diabetes were about 5 years younger than Whites. (UKPDS 6 1990) We have found that South Asians with screen-detected diabetes are 11 years younger at diagnosis; this provides us with further opportunities to improve outcomes in these patients. South Asians are known to have greater cardiovascular morbidity and mortality than White Europeans with diabetes, this does not seem to be due to differences in conventional measures, including blood pressure, lipids, abdominal circumference and body mass index. There may be a role for measuring and finding treatments to
modify novel markers of cardiovascular disease including high-sensitivity C-reactive protein, tumour necrosis factor and lipoproteins.

4.6 Summary
Screening patients with a known risk factor identifies a substantial number of patients with undiagnosed diabetes in primary care. Over 70% of these people would benefit from pharmacological intervention. The prevalence of complications is also high in this population. South Asians are diagnosed 11 years earlier and have a greater prevalence of elevated HbA1c levels than White Europeans. Screening for diabetes in people with a risk factor in primary care is an effective way of identifying undiagnosed diabetes and to prevent long-term complications.
Chapter 5

The use of risk factors, risk scores and questionnaires in screening for diabetes in a mixed ethnic population

5.1. Risk factors

THE DIABETES UK POSITION STATEMENT ON SCREENING FOR DIABETES RECOMMENDS THAT INDIVIDUALS WHO ARE OVER 40 YEARS AND OF WHITE ORIGIN, OR OVER 25 YEARS OF AGE IF FROM BLACK, ASIAN AND MINORITY ETHNIC GROUPS, SHOULD BE SCREENED IF THEY HAVE ONE RISK FACTOR. THEY ALSO RECOMMEND THAT INDIVIDUALS, OF ANY AGE, WITH TWO OR MORE RISK FACTORS SHOULD BE SCREENED FOR DIABETES. (TABLE 5.1) (DIABETES UK 2002)
Table 5.1 Risk factors for type 2 diabetes identified by Diabetes UK

<table>
<thead>
<tr>
<th>Risk Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>First degree relative with diabetes</td>
</tr>
<tr>
<td>BMI ≥ 25kg/m² and have a sedentary lifestyle</td>
</tr>
<tr>
<td>Ischaemic heart disease</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
</tr>
<tr>
<td>Hypertension.</td>
</tr>
<tr>
<td>Gestational diabetes</td>
</tr>
<tr>
<td>Polycystic ovary syndrome (if BMI ≥ 30 kg/m²)</td>
</tr>
<tr>
<td>History of impaired glucose tolerance or impaired fasting glycaemia</td>
</tr>
</tbody>
</table>

The American Diabetes Association (ADA) position statement (ADA 2004) on screening describes eleven risk factors for type 2 diabetes: (table 5.2) The risk factors are similar to those suggested by Diabetes UK but they include the additional risk factors of delivery of a baby weighing more than 9lbs and dyslipidaemia. The guidelines differ also in that being over 45 years and of a minority ethnic origin does not meet the Diabetes UK guidelines, without the presence of an additional risk factor.

Table 5.2 Risk factors for type 2 diabetes identified by the ADA

<table>
<thead>
<tr>
<th>Risk Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 45 years of age</td>
</tr>
<tr>
<td>BMI ≥ 25kg/m²</td>
</tr>
<tr>
<td>First degree relative with diabetes</td>
</tr>
<tr>
<td>Habitual physical inactivity</td>
</tr>
<tr>
<td>Race/ethnicity</td>
</tr>
<tr>
<td>Previously identified IFG or IGT</td>
</tr>
<tr>
<td>History of gestational diabetes or delivery of baby weighing more than 9 lbs</td>
</tr>
<tr>
<td>Hypertension: &gt;140/90 mmHg</td>
</tr>
<tr>
<td>Dyslipidaemia: HDL &lt; 0.9 mmol/l and/or triglycerides &gt; 2.82 mmol/l</td>
</tr>
<tr>
<td>Polycystic ovary syndrome</td>
</tr>
<tr>
<td>History of vascular disease</td>
</tr>
</tbody>
</table>
5.1.1 Cigarette Smoking

Cigarette smoking is not one of the ADA or Diabetes UK recognised risk factors. The evidence for cigarette smoking being an independent risk factor for diabetes is variable. Cigarette smokers were found to be at highest risk of developing diabetes over 25 years of follow up in the Zutphen study. (Feskens 1989) The Health Professionals’ follow-up study from the United States, of over 51 000 men aged 40 to 75 years, found the age and BMI adjusted relative risk of newly diagnosed diabetes, after a mean follow-up of 6 years, was 2.38 in men smoking 15-24 cigarettes per day and 1.94 for men smoking more than 25 cigarettes per day compared with those individuals who had never smoked. (Rimm 1995) However, the British Regional Heart Study of over 7700 men aged 40-59, across 24 towns in Britain, followed individuals for a mean follow-up of 12.8 years and found no evidence that cigarette smoking was an independent risk factor for diabetes. (Perry 1995) This study did find that current smoking was associated with a 50% increase in the risk of diabetes relative to those who had never smoked, after adjustment for age and BMI. This effect was decreased after adjustment was made for physical activity. Former smokers were at similar risk of diabetes as men who had never smoked. (Perry 1995) A 5-year prospective study of 10 000 males in Israel and a review of the Framingham data found no association between cigarette smoking and the development of diabetes. (Medalie 1979, Wilson 1986)

As a potential risk factor, cigarette smoking, is difficult to separate from associated lifestyles, including lack of physical activity, lower BMI but increased central adiposity and a higher level of dietary fat intake. (Eisen 1999, Will 2001) Any increased risk found in smokers may not be as a result of the smoking itself, but be related to the dietary and activity changes. Cigarette smoking has been shown to lead to insulin resistance (Facchini 1992) and insulin resistance precedes diabetes. (Lillioja 1993) Whether cigarette smoking is actually an independent risk factor for diabetes has yet to be determined. Cigarette smoking was included as a risk factor for screening in the STAR study to increase the evidence in this area.
5.2 Risk scores and Questionnaires
The likelihood of an individual having diabetes is increased by the presence of one or more risk factors. (ADA 2004, Diabetes UK 2002, Australian EWG 2001) In our study, individuals with no identified risk factors, other than being within the study age range, had a prevalence of 3.0% of diabetes detected through screening. Whereas individuals with one or more risk factors had a greater prevalence of diabetes of 7.6%. (p=0.21) Using a scoring method, which assesses the combination of risk factors in each individual, could contribute towards identifying individuals who would benefit from targeted screening. (Griffin 2000, Lindstrom 2003) This information should ideally be easily identifiable and could come from data available routinely in primary care or by individuals completing a questionnaire. A risk score based on questions about phenotypical characteristics for type 2 diabetes will not achieve 100% sensitivity because some individuals with type 2 diabetes will have a phenotype more like individuals with type 1 diabetes. (Tuomi 1999) However using a risk score as the first test for screening for diabetes is attractive because it allows more targeted screening by decreasing the number of people who will need more invasive, costly and time consuming tests. (Griffin 2000, Glumer 2004)

5.2.1 Cambridge Diabetes Risk Score
A risk factor score was developed for use as a screening tool by Griffin et al (Griffin 2000) and is known as the Cambridge Diabetes Risk Score (CDRS). The score was produced using from the Wessex study, on cases of clinically diagnosed type 2 diabetes (Kinmouth 1996), and from the Ely study of prevalent cases of screen-detected diabetes. (Williams 1995). The score is calculated to produce a value between 0 and 1 to give the probability of having type 2 diabetes. The higher the score, the higher the chance of having undiagnosed diabetes. The score can be calculated using the logistic model below and is based on the sum of each of the variables included.
Cambridge Diabetes Risk Score = \[ \frac{1}{1 + e^{-(\alpha + \beta_1x_1 + \beta_2x_2 + \beta_3x_3 + \beta_4x_4 + \beta_5x_5 + \beta_6x_6 + \beta_7x_7)}} \]

where \[ \alpha = -0.6322 \]

\[ \beta_1x_1 = -0.879 \text{ if female and 0 if male} \]
\[ \beta_2x_2 = 1.222 \text{ if prescribed antihypertensive medication and 0 if not} \]
\[ \beta_3x_3 = 2.191 \text{ if prescribed steroids and 0 if not} \]
\[ \beta_4x_4 = 0.063 \text{ multiplied by age in years} \]
\[ \beta_5x_5 = 0 \text{ if BMI < 25 kg/m}^2, 0.699 \text{ if BMI} \geq 25 \text{ kg/m}^2 < 27.5 \text{ kg/m}^2, 1.97 \text{ if BMI} \geq 27.5 \text{ kg/m}^2 \text{ and} < 30 \text{ kg/m}^2, \text{ and 2.518 if BMI} \geq 30 \text{ kg/m}^2 \]
\[ \beta_6x_6 = 0 \text{ if no first degree relative with diabetes, 0.728 if there is a parent or sibling with diabetes and 0.753 if there is both a parent and sibling with diabetes} \]
\[ \beta_7x_7 = 0 \text{ for non-smokers, -0.218 for ex-smokers and 0.855 for current smokers}. \]

The performance of the CDRS, in detecting diabetes, was evaluated in an independent, randomly selected, population-based sample from the Ely study. When the risk score was used to determine the probability of having undiagnosed diabetes the sensitivity was 77%, specificity 72% and area under receiver operating characteristic (ROC) curve was 80% (95% confidence intervals 68 to 91%). (Griffin 2000) When the score was used to predict undiagnosed hyperglycaemia (HbA1c >7.0%) in the Health Survey of England 1999 population, which included people from ethnic minorities, (using the same cut-point of 0.199) there was decreased sensitivity of 53%, with 78% specificity. (Park 2002) The performance of the CDRS in detecting diabetes was not presented as this data was unavailable in the Health Survey. (Spijkerman 2004)

This CDRS does include BMI and requires the presence of other risk factors to have been entered onto the computer database. It is a difficult formula to use because it involves complex arithmetical calculations, and although computer software is available to perform the calculations, this may be a deterrent to its use. With the CDRS there is no necessity for translation of questions or instruction sheets for non-
English speaking individuals as it can be completed by computer. The CDRS was developed and validated in a population aged 40 to 64 years, and then tested in a population aged 39 to 78 years. (Park 2002). In our cohort all those individuals within this age range who had no missing variables had their score calculated. If there are any missing variables then this may affect the performance of the CDRS. The authors of the CDRS did find that the risk score performed well in Caucasians, even in the absence of information on family history of diabetes. (Park 2002) However this may not be the same with other variables or in black, minority and ethnic populations where family history is more prevalent.

5.2.2 Finnish Diabetes Risk Score
The Finnish Diabetes Risk Score (FDRS) was developed in Finland, by Tuomilehto, to characterize individuals according to both their future risk of developing and current risk of having type 2 diabetes. (Lindstrom 2003) The score was developed and validated in a population aged between 35 and 64 years old. It is based on the risk factors - age, BMI, waist circumference, use of blood pressure medication, history of high blood glucose, physical activity, and daily consumption of vegetables, fruit or berries. The FDRS was derived from the coefficients of logistic regression, which were then used to formulate the score, which can be calculated by adding up the score for each variable as shown in table 5.3. The Finnish DRS does not need clinical data to be collected from an individual by a health care professional. Individuals are instructed to measure their own waist circumference. The risk score is a simple and quick questionnaire completed by the individual.
Table 5.3 Variables and scoring methods for Finnish DRS
(* only included in modified FDRS)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Score for each variable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
</tr>
<tr>
<td>45-54</td>
<td>2</td>
</tr>
<tr>
<td>55-64</td>
<td>3</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td></td>
</tr>
<tr>
<td>&gt; 25 to 30</td>
<td>1</td>
</tr>
<tr>
<td>&gt; 30</td>
<td>3</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td></td>
</tr>
<tr>
<td>Men ≥ 94 and &lt; 102; women ≥ 80 and &lt; 88</td>
<td>3</td>
</tr>
<tr>
<td>Men ≥ 102; women ≥ 88</td>
<td>4</td>
</tr>
<tr>
<td>Use of blood pressure medication</td>
<td>2</td>
</tr>
<tr>
<td>History of high blood glucose</td>
<td>5</td>
</tr>
<tr>
<td>Physical activity less than 4 hours per week</td>
<td>2</td>
</tr>
<tr>
<td>Daily consumption of vegetables, fruits or berries</td>
<td>1</td>
</tr>
<tr>
<td>* First degree relative with diabetes</td>
<td>* 5</td>
</tr>
</tbody>
</table>

The score ranges from 0 to 20, and the authors found a cut-point of nine identifies individuals at the greatest risk of developing type 2 diabetes, with a sensitivity of 81% and a specificity of 77%. For the detection of undiagnosed diabetes, the sensitivity of the FDRS was 77% and the specificity 67% with a positive predictive value (PPV) of 12% and a negative predictive value (NPV) of 99%. (Lindstrom 2003) Since the publication of the FDRS, the authors have suggested a modification which includes family history. The presence of a positive family history in a first degree relative contributes five points and increases the possible total score to 25. (unpublished personal communication)

The FDRS and modified FDRS (including family history) was calculated for all the individuals in our cohort who had completed the questionnaire, and the performance of the score in detecting undiagnosed diabetes in South Asians and White Europeans was determined.
5.3 The STAR Study

Inclusion criteria for the STAR study were risk factors that could be systematically identified from general practice databases and are being recorded as part of the new GMS contract for GPs. (DoH 2004) Through the screening procedure other factors that may not be routinely included on practice databases unless there is an additional intervention from a health care professional, such as waist and hip measurements, blood glucose or lipid levels, have also been studied.

One of the study aims was to compare risk factors for diabetes in the South Asian and White European populations, and to determine which factors are the most important. A further aim was to calculate the Cambridge Diabetes Risk Score (DRS) and the Finnish Diabetes Risk Score (DRS) values, to see if the performance of the scores in detecting diabetes and prediabetes varies and to see whether there should be different cut-points in South Asians and White Europeans for each score. From the results it was determined if risk scores perform better than risk factors used alone or risk factors used in combination. A further aim was to develop a screening strategy for diabetes that could be easily applicable throughout the country.

**Inclusion and Exclusion Criteria**

Eligible risk factors included a known history of coronary heart disease (CHD), hypertension, dyslipidaemia, cerebro-vascular disease (CVD), peripheral vascular disease (PVD), impaired glucose tolerance (IGT) or impaired fasting glycaemia (IFG). Other risk factors included having a first-degree relative with type 2 diabetes and a BMI greater than 30 kg/m². Further risk factors for females included history of gestational diabetes or polycystic ovary syndrome (PCOS) in those with a BMI greater than 25 kg/m² or 23 kg/m² in South Asians. Current cigarette smokers or those who had stopped smoking within the last 12 months were also eligible for screening. Exclusion criteria included being housebound, diagnosis with a terminal illness or a previous diagnosis of diabetes.

Table 5.4 shows the percentage of each practice that met the inclusion criteria. In practices A and B, where being within the age range was the only inclusion criteria, 60.5% and 61.0% of each practice were invited respectively. The remaining patients did not meet the age criteria. In practices C to Q the percentage of people
identified as having a risk factor and therefore invited varies from 5.0% to 37.8%. The presence of risk factors is unlikely to be this varied, with the exception of the Practice that serves the University of Leicester – where the patients are predominantly undergraduate students. This variation may reflect the recording of and retrieval of risk factor information from the computer. Table 5.5 shows the prevalence of each of the inclusion criteria risk factors in the whole cohort and in South Asians and White Europeans.

Table 5.4 Percentage of each practice meeting inclusion criteria

<table>
<thead>
<tr>
<th>Practice</th>
<th>Practice list size</th>
<th>% of practice meeting inclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>13504</td>
<td>60.5% *</td>
</tr>
<tr>
<td>B</td>
<td>2936</td>
<td>61.0% *</td>
</tr>
<tr>
<td>C</td>
<td>9773</td>
<td>13.9%</td>
</tr>
<tr>
<td>D</td>
<td>16054</td>
<td>35.0%</td>
</tr>
<tr>
<td>E</td>
<td>5844</td>
<td>12.3%</td>
</tr>
<tr>
<td>F</td>
<td>13736</td>
<td>5.8%</td>
</tr>
<tr>
<td>G</td>
<td>3923</td>
<td>5.0%</td>
</tr>
<tr>
<td>H</td>
<td>2535</td>
<td>28.6%</td>
</tr>
<tr>
<td>I</td>
<td>7121</td>
<td>18.7%</td>
</tr>
<tr>
<td>J</td>
<td>2765</td>
<td>10.4%</td>
</tr>
<tr>
<td>K</td>
<td>3611</td>
<td>20.4%</td>
</tr>
<tr>
<td>L</td>
<td>2516</td>
<td>11.0%</td>
</tr>
<tr>
<td>M</td>
<td>1742</td>
<td>37.8%</td>
</tr>
<tr>
<td>N</td>
<td>7257</td>
<td>12.1%</td>
</tr>
<tr>
<td>O</td>
<td>6962</td>
<td>5.4%</td>
</tr>
<tr>
<td>P</td>
<td>5300</td>
<td>12.7%</td>
</tr>
<tr>
<td>Q</td>
<td>6789</td>
<td>8.6%</td>
</tr>
</tbody>
</table>

* number of people within the practice meeting the age criteria, as these practices were population screened
Table 5.5
Prevalence of each risk factor in the population screened

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>All cohort screened % (n)</th>
<th>South Asians (age ≥25 and &lt; 40 years) % (n)</th>
<th>South Asians (age ≥ 40 and ≤75 years) % (n)</th>
<th>White Europeans (age ≥ 40 and ≤ 75 years) % (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI ≥ 30 kg/m²</td>
<td>29.3 (1030)</td>
<td>13.7 (34)</td>
<td>23.1 (208)</td>
<td>33.1 (741)</td>
</tr>
<tr>
<td>Current cigarette smokers</td>
<td>22.8 (803)</td>
<td>17.7 (44)</td>
<td>8.5 (76)</td>
<td>28.8 (644)</td>
</tr>
<tr>
<td>Known cerebro-vascular or peripheral vascular disease</td>
<td>2.6 (91)</td>
<td>0 (0)</td>
<td>1.4 (13)</td>
<td>3.4 (75)</td>
</tr>
<tr>
<td>Known dyslipidaemia</td>
<td>12.6 (443)</td>
<td>0.4 (1)</td>
<td>9.9 (89)</td>
<td>15.6 (348)</td>
</tr>
<tr>
<td>First-degree relative with type 2 diabetes</td>
<td>41.2 (1448)</td>
<td>60.9 (151)</td>
<td>57.7 (519)</td>
<td>31.9 (714)</td>
</tr>
<tr>
<td>History of gestational diabetes</td>
<td>16.5 (58)</td>
<td>2.0 (5)</td>
<td>1.6 (14)</td>
<td>1.7 (38)</td>
</tr>
<tr>
<td>Known hypertension</td>
<td>36.5 (1282)</td>
<td>2.4 (6)</td>
<td>30.8 (277)</td>
<td>42.7 (954)</td>
</tr>
<tr>
<td>History of IGT or IFG</td>
<td>1.3 (46)</td>
<td>0 (0)</td>
<td>1.6 (14)</td>
<td>1.4 (32)</td>
</tr>
<tr>
<td>History of coronary heart disease</td>
<td>11.7 (413)</td>
<td>0.4 (1)</td>
<td>9.1 (82)</td>
<td>14.5 (324)</td>
</tr>
</tbody>
</table>
5.4 Statistical analysis

The odds ratios (OR) and 95% confidence intervals (CI) for each risk factor were calculated using univariate analysis. Chi-squared tests were used to test for significant differences. The sensitivity, specificity and predictive values of the Cambridge DRS and Finnish DRS for both White Europeans and South Asian population were calculated. The positive predictive value (PPV) was calculated as the proportion of individuals with a positive test who had type 2 diabetes, and the negative predictive value (NPV) as the proportion of individuals with a negative test without type 2 diabetes. In addition the proportion of individuals who needed subsequent testing was compared. Confidence intervals were calculated and are reported at 95%.

The performance of the Cambridge DRS and Finnish DRS were evaluated using the area under the curve (AUC) of a receiver operating characteristics (ROC) curve, where the sensitivity of each score was plotted against the false-positive rate (1-specificity). The AUC quantifies how well the score correctly distinguishes an individual with diabetes from an individual without diabetes. The larger the AUC, the better the performance of the test. (Lang 1997)

5.5 Results

5.5.1 Prevalence of abnormal glucose tolerance and risk factors

A total of 3135 patients aged between 40 and 75 years received a 75-gram oral glucose tolerance test. (28.7% [n=899] South Asian and 71.3% [n=2235] White European) Of those who attended for screening 53.6% were female and 50.2% (n = 1573) were from the fifteen practices where individuals with at least one risk factor were invited. A further 31.3% (n = 976) were from the two practices where all individuals within the age range invited and 18.7% (n=586) of patients referred themselves for screening. Of those patients attending from the practices where the presence of a risk factor was not an inclusion criteria 76.6% (n=748) had at least one risk factor and 99.3% (n=582) of those who self-referred also had at least one risk factor.
As discussed in chapter 4 the prevalence of diabetes, in those aged 40 to 75 years, was greater in South Asians; 6.5% (58/899, 95% CI: 4.9 to 8.3) compared to White Europeans 4.7% (105/2238, CI: 3.8 to 5.7). The prevalence of prediabetes is greater and showed a similar pattern with a greater prevalence in South Asians [19.9% (179/899, CI: 17.3-22.7)] in South Asians and in White Europeans [15.4% (344/2238, CI: 13.9-16.9)]. The prevalence of undiagnosed abnormal glucose tolerance increases as the number of recognised risk factors increases (table 5.6) and is greater in South Asians than in White Europeans.

Table 5.6 Number of risk factors and prevalence of abnormal glucose tolerance in those aged 40 to 75 years

| Number of risk factors | South Asians | | | White Europeans | | |
|------------------------|--------------|------------------|------------------|------------------|------------------|
|                        | Number of patients with each risk factor | Prevalence of prediabetes with each number of risk factors (N) | Prevalence of diabetes with each number of risk factors | Number of patients with each risk factor | Prevalence of prediabetes with each number of risk factors | Prevalence of diabetes with each number of risk factors |
| 0                      | 122          | 9.8% (12)        | 3.3% (4)         | 110              | 5.5% (6)         | 3.6% (4)         |
| 1                      | 375          | 18.4% (69)       | 5.3% (20)        | 738              | 10.6% (78)       | 1.8% (13)        |
| 2                      | 250          | 18.8% (47)       | 8.0% (20)        | 711              | 15.5% (110)      | 4.5% (32)        |
| 3                      | 94           | 36.2% (34)       | 7.4% (7)         | 395              | 20.3% (80)       | 6.1% (24)        |
| 4+                     | 56           | 30.4% (17)       | 12.5% (7)        | 281              | 24.9% (70)       | 10.7% (30)       |
| Overall                | 899          | 19.9% (179)      | 6.5% (58)        | 2235             | 15.4% (344)      | 4.7% (105)       |

The odds ratios and 95% confidence intervals (CI) for each risk factor in those aged 40 to 75 years of age in the whole cohort are shown in table 5.7 for diabetes and in table 5.8 for prediabetes. For the risk factor polycystic ovarian syndrome we were unable to calculate an odds ratio for diabetes as none of those females had diabetes.
The risk factors with a significant impact on the presence of diabetes, within the whole cohort, were:

- Coronary heart disease
- Hypertension
- Dyslipidaemia
- IGT or IFG
- First degree relative with diabetes
- BMI > 30kg/m²

When South Asians and White Europeans were studied separately, in White Europeans cerebrovascular disease or peripheral vascular disease and gestational diabetes remained non-significant. Whereas in those individuals who were cigarette smokers the odds ratio for diabetes decreased to 0.40 (0.23-0.69), suggesting a decreased risk of diabetes. The only risk factors in the South Asians that remained significant when South Asians were analysed as a separate group were obesity (BMI > 30 kg/m²) and hypertension.

Significant risk factors in White Europeans for diabetes:

- Coronary heart disease
- Hypertension
- Dyslipidaemia
- IGT or IFG
- First degree relative with diabetes
- BMI > 30kg/m²
- BMI > 25 kg/m² with a sedentary lifestyle,

Significant risk factors in South Asians for diabetes:

- Hypertension
- BMI > 30kg/m²
<table>
<thead>
<tr>
<th>Risk factor</th>
<th>All individuals (N=3135)</th>
<th></th>
<th>White Europeans (N=2236)</th>
<th></th>
<th>South Asians (N=899)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds ratio</td>
<td>p-value</td>
<td>Odds ratio</td>
<td>p-value</td>
<td>Odds ratio</td>
<td>p-value</td>
</tr>
<tr>
<td></td>
<td>(95% CI)</td>
<td></td>
<td>(95% CI)</td>
<td></td>
<td>(95% CI)</td>
<td></td>
</tr>
<tr>
<td>BMI $&gt;$ 25 kg/m$^2$ and sedentary</td>
<td>1.12</td>
<td>0.763</td>
<td>1.66</td>
<td>0.484</td>
<td>1.89</td>
<td>0.199</td>
</tr>
<tr>
<td></td>
<td>(0.53, 2.33)</td>
<td></td>
<td>(0.20, 2.12)</td>
<td></td>
<td>(0.72, 4.99)</td>
<td></td>
</tr>
<tr>
<td>BMI $&gt;$ 30 kg/m$^2$</td>
<td>2.33</td>
<td>&lt;0.001</td>
<td>2.84</td>
<td>&lt;0.001</td>
<td>1.83</td>
<td>0.036</td>
</tr>
<tr>
<td></td>
<td>(1.69, 3.20)</td>
<td></td>
<td>(1.90, 4.22)</td>
<td></td>
<td>(1.03, 3.22)</td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>0.43</td>
<td>0.427</td>
<td>0.40</td>
<td>0.001</td>
<td>0.79</td>
<td>0.660</td>
</tr>
<tr>
<td></td>
<td>(0.26, 0.70)</td>
<td></td>
<td>(0.23, 0.69)</td>
<td></td>
<td>(0.27, 2.25)</td>
<td></td>
</tr>
<tr>
<td>Cerebrovascular disease or Peripheral vascular disease</td>
<td>1.87</td>
<td>0.101</td>
<td>2.17</td>
<td>0.059</td>
<td>1.21</td>
<td>0.855</td>
</tr>
<tr>
<td></td>
<td>(0.88, 3.93)</td>
<td></td>
<td>(0.97, 4.84)</td>
<td></td>
<td>(0.15, 9.49)</td>
<td></td>
</tr>
<tr>
<td>Dyslipidaemia</td>
<td>1.55</td>
<td>0.032</td>
<td>1.65</td>
<td>0.036</td>
<td>1.50</td>
<td>0.308</td>
</tr>
<tr>
<td></td>
<td>(1.03, 2.31)</td>
<td></td>
<td>(1.03, 2.65)</td>
<td></td>
<td>(0.68, 3.28)</td>
<td></td>
</tr>
<tr>
<td>First degree relative</td>
<td>1.30</td>
<td>&lt;0.001</td>
<td>1.85</td>
<td>&lt;0.001</td>
<td>1.04</td>
<td>0.887</td>
</tr>
<tr>
<td></td>
<td>(1.16, 2.20)</td>
<td></td>
<td>(1.24, 2.75)</td>
<td></td>
<td>(0.60, 1.79)</td>
<td></td>
</tr>
<tr>
<td>Gestational diabetes</td>
<td>1.53</td>
<td>0.418</td>
<td>1.13</td>
<td>0.868</td>
<td>2.47</td>
<td>0.245</td>
</tr>
<tr>
<td></td>
<td>(0.54, 4.30)</td>
<td></td>
<td>(0.26, 4.76)</td>
<td></td>
<td>(0.54, 11.30)</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.88</td>
<td>&lt;0.001</td>
<td>2.00</td>
<td>0.001</td>
<td>1.91</td>
<td>0.018</td>
</tr>
<tr>
<td></td>
<td>(1.36, 2.58)</td>
<td></td>
<td>(1.34, 2.98)</td>
<td></td>
<td>(1.11, 3.27)</td>
<td></td>
</tr>
<tr>
<td>IGT or IFG</td>
<td>3.38</td>
<td>0.004</td>
<td>4.91</td>
<td>0.001</td>
<td>1.11</td>
<td>0.916</td>
</tr>
<tr>
<td></td>
<td>(1.48, 7.67)</td>
<td></td>
<td>(1.97, 12.19)</td>
<td></td>
<td>(0.14, 8.69)</td>
<td></td>
</tr>
<tr>
<td>Known CHD</td>
<td>1.70</td>
<td>0.010</td>
<td>1.71</td>
<td>0.029</td>
<td>1.93</td>
<td>0.085</td>
</tr>
<tr>
<td></td>
<td>(1.13, 2.54)</td>
<td></td>
<td>(1.05, 2.75)</td>
<td></td>
<td>(0.91, 4.09)</td>
<td></td>
</tr>
</tbody>
</table>

Table 5.7 Risk factor analysis for diabetes for individuals, aged 40 to 75 years
Table 5.8 Risk factor analysis for pre-diabetes for individuals, aged 40 to 75 years

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>All individuals (N=3135)</th>
<th>White Europeans (N=2236)</th>
<th>South Asians (N=899)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds ratio (95% CI)</td>
<td>p-value</td>
<td>Odds ratio (95% CI)</td>
</tr>
<tr>
<td>BMI&gt;25 kg/m² and sedentary</td>
<td>1.1 (0.72-1.72)</td>
<td>0.64</td>
<td>0.96 (0.54-1.72)</td>
</tr>
<tr>
<td>BMI&gt;30 kg/m²</td>
<td>1.67 (1.38-2.02)</td>
<td>&lt;0.005</td>
<td>1.88 (1.45-2.38)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>0.63 (0.50-0.80)</td>
<td>&lt;0.005</td>
<td>0.65 (0.49-0.86)</td>
</tr>
<tr>
<td>Cerebrovascular disease or Peripheral vascular disease</td>
<td>1.07 (0.62-0.85)</td>
<td>0.805</td>
<td>0.94 (0.49-1.81)</td>
</tr>
<tr>
<td>Dyslipidaemia</td>
<td>1.57 (1.23-2.01)</td>
<td>&lt;0.005</td>
<td>1.69 (1.27-2.25)</td>
</tr>
<tr>
<td>First degree relative</td>
<td>1.27 (1.05-1.53)</td>
<td>0.013</td>
<td>1.19 (0.93-1.51)</td>
</tr>
<tr>
<td>Gestational diabetes</td>
<td>0.53 (0.21-1.34)</td>
<td>0.171</td>
<td>0.30 (0.07-1.26)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.89 (1.57-2.28)</td>
<td>&lt;0.005</td>
<td>2.04 (1.62-2.58)</td>
</tr>
<tr>
<td>IGT or IFG</td>
<td>1.79 (0.92-3.48)</td>
<td>0.083</td>
<td>2.18 (1.00-4.76)</td>
</tr>
<tr>
<td>Known CHD</td>
<td>1.56 (1.21-2.00)</td>
<td>0.001</td>
<td>1.69 (1.26-2.26)</td>
</tr>
</tbody>
</table>
The risk factors with a significant impact on the presence of prediabetes, within the whole cohort, were:
- Coronary heart disease
- Hypertension
- Dyslipidaemia
- First degree relative with diabetes
- BMI > 30kg/m²

When South Asians and White Europeans were studied separately, in White Europeans cerebrovascular disease or peripheral vascular disease, gestational diabetes and BMI > 25kg/m² remained non-significant. Whereas in those White Europeans who were cigarette smokers the odds ratio for prediabetes decreased to 0.65 (0.49-0.86), suggesting a decreased risk. The only risk factor for prediabetes in the South Asians that remained significant when South Asians were analysed as a separate group was hypertension.

Significant risk factors in White Europeans for prediabetes:
- Coronary heart disease
- Hypertension
- Dyslipidaemia
- IGT or IFG
- BMI > 30kg/m²

Significant risk factors in South Asians for prediabetes:
- Hypertension

5.5.2 Cumulative effect of risk factors

Table 5.9 shows the effect of multiple risk factors on the increased risk of diabetes. The presence of two risk factors increased the odds ratio of diabetes being present in all combinations from at least the individual risk factor with the lower odds ratio. In White Europeans hypertension and obesity accounted for 92.4% (97/105) of all those found to have diabetes. Whereas in South Asians these two risk factors were present in only 64.6% (42/65).
Table 5.9 Risk factor analysis for diabetes in the presence of two risk factors in those aged 40 to 75 years

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>White Europeans</th>
<th>South Asians</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds ratios</td>
<td>95% Confidence intervals</td>
</tr>
<tr>
<td>BMI&gt;30kg/m² and CVD/PVD</td>
<td>2.29</td>
<td>0.52–9.97</td>
</tr>
<tr>
<td>BMI&gt;30kg/m² and CHD</td>
<td>1.88</td>
<td>0.96–3.72</td>
</tr>
<tr>
<td>BMI&gt;30kg/m² and 1° relative</td>
<td>3.12</td>
<td>1.98–4.91</td>
</tr>
<tr>
<td>BMI&gt;30kg/m² and IGT/IFG</td>
<td>7.06</td>
<td>2.52–19.8</td>
</tr>
<tr>
<td>BMI&gt;30kg/m² and hypertension</td>
<td>2.73</td>
<td>1.8–4.17</td>
</tr>
<tr>
<td>CVD/PVD and 1° relative</td>
<td>5.20</td>
<td>1.44–8.71</td>
</tr>
<tr>
<td>CVD/PVD and hypertension</td>
<td>2.88</td>
<td>1.19–6.91</td>
</tr>
<tr>
<td>1° relative and hypertension</td>
<td>3.12</td>
<td>1.97–4.94</td>
</tr>
<tr>
<td>1° relative and IGT/IFG</td>
<td>3.41</td>
<td>0.41–28.6</td>
</tr>
<tr>
<td>Hypertension and IGT/ IFG</td>
<td>15.2</td>
<td>4.74–8.69</td>
</tr>
<tr>
<td>Hypertension and CHD</td>
<td>1.95</td>
<td>1.15–3.32</td>
</tr>
</tbody>
</table>

* CVP/PVD = Cerebrovascular disease or Peripheral vascular disease

**Summary of risk factor screening**

This study looked at ten risk factors for diabetes in South Asians and in White Europeans, that are easily measureable, readily identifiable and could be recorded on GP databases. However, as seen in table 5.4, the prevalence of one of these risk factors, according to the general practice databases, varies from 5.0 to 37.8%. Since the new GMS contract was introduced in 2004, practices are paid to record information for patients across a number of clinical indicators. (DOH 2004) These include smoking status, coronary heart disease, stroke and TIA, hypertension and hyperlipidaemia. Payment is also offered for recording BMI in patients known to have diabetes and those whom have had an acute coronary event. If the data is recorded in at least 55% of patients GP’s achieve the target, and if 75% of patients have the data recorded then a higher target is achieved and there is a greater financial reward. (DoH 2004) Practices are also paid to check cholesterol levels for patients on the coronary heart disease and TIA or stroke registers. It is common clinical practice to carry out a blood glucose level at the same time. Most practices perform the lipid blood test on a fasting sample and therefore most patients have a fasting glucose as well. In selecting which risk factors to include for a diabetes
screening study it would be sensible to ensure the risk factors are those which are already, or could easily be, recorded, such as hypertension and BMI, rather than PCOS, IFG or IGT.

In White Europeans the risk factors with the greatest contribution to diabetes are obesity (BMI>30kg/m$^2$) and a previous diagnosis of IGT or IFG. However, the prevalence of IGT or IFG was only 1.3%, so the usefulness of this risk factor in a screening programme is limited. The sensitivity of using either obesity or hypertension as the first screening tool in White Europeans is 85.7%, with a specificity of 39.8%.

In South Asians hypertension and a BMI $\geq$ 30 kg/m$^2$ were significantly associated with diabetes. These two risk factors accounted for only 60.3% (35/58) of individuals with diabetes. If BMI is to be used in for screening South Asians the cut-off value will need to be different. The sensitivity of either BMI $\geq$ 25 kg/m$^2$ or hypertension being present is 86.2%, with a specificity of 23.3%.

This study found that a past history of vascular disease, (either cardiac, cerebral or peripheral) IGT or IFG and family history of diabetes are major risk factors for diabetes in White Europeans but not in South Asians. As the number of risk factors increases, South Asians have a greater prevalence of diabetes, compared to White Europeans. In White Europeans the presence of some risk factors (BMI>25kg/m$^2$, cerebrovascular disease or peripheral vascular disease and gestational diabetes) leads to no increased risk of diabetes. Whereas in South Asians there are more risk factors that in isolation confer no increased risk of diabetes. These include BMI>25kg/m$^2$, current cigarette smoker, cerebrovascular disease or peripheral vascular disease, dyslipidaemia, first degree relative with diabetes, gestational diabetes, IGT or IFG, and CHD.

This reveals some of the differences in risk factors for screen-detected type 2 diabetes between South Asian and White European population. This information could be used in a screening programme for diabetes to target those individuals most at risk. Using risk factors identifiable from databases has advantages in its simplicity and the ability to identify those who would benefit from further testing.
This would decrease those individuals who would need a subsequent test. Targeting individuals with an elevated BMI ($\geq 30 \text{ kg/m}^2$ in White Europeans and $\geq 25 \text{ kg/m}^2$ in South Asians) or with hypertension would have a sensitivity of over 85%.

Unfortunately using a similar method in prediabetes is less successful. In South Asians it is only hypertension that is significantly associated with prediabetes and only 40% of South Asians with prediabetes had hypertension. In White Europeans there are more significant risk factors, but each one is present in less 58% of individuals. (Coronary heart disease 20.6%; Hypertension 58%; BMI $> 30\text{kg/m}^2$ 45.6%; hypercholesterolaemia 22.1%) The sensitivity of using risk factors as screening tools on their own for prediabetes is too low for a successful programme.

5.5.3 Waist Circumference

Waist circumference is increasingly being recognised as a more sensitive marker of central obesity than BMI. Central or abdominal obesity is an independent and powerful predictor of adverse cardiovascular outcomes. Abdominal obesity is caused by intra-abdominal adiposity. Waist circumference is a surrogate measure of intra-abdominal fat and particularly of visceral fat. The Nurses’ Health Study of over 44 000 women found the risk of developing type 2 diabetes increased linearly with an increasing waist circumference. (Carey 1997) The INTERHEART study of over 30 000 patients with a myocardial infarction found that increasing waist circumference was strongly associated with the risk of myocardial infarction even after adjustment for known cardiovascular risk factors. (Yusuf 2005) The link between abdominal obesity and adverse cardiovascular outcomes through cardiometabolic risk factors is established.

Routinely waist circumference has not been measured in clinical practice, but could easily be measured. Waist circumference was included in the anthropometric measures performed for the STAR study. The ability of waist circumference to identify those individuals at risk of prevalent diabetes and prediabetes was tested using ROC curves. Figure 5.1 shows the ROC curves for waist circumference and BMI when used for screening South Asians and White Europeans for diabetes (Figure 5.1a - 5.1d) and for prediabetes. (figure 5.1e - 5.1h)
Figure 5.1
ROC curves for screening for diabetes with waist circumference and BMI in

5.1a. South Asian females
Waist Circumference AUC = 0.68
BMI AUC = 0.64

5.1b. South Asian males
Waist Circumference AUC = 0.71
BMI AUC = 0.67
5.1c. White European females
Waist Circumference AUC = 0.73
BMI AUC = 0.69

5.1d. White European males
Waist Circumference AUC = 0.69
BMI AUC = 0.67
ROC curve for screening for prediabetes or diabetes with waist circumference and BMI in

5.1e. South Asian females
Waist Circumference AUC=0.69
BMI AUC = 0.69

5.1f. South Asian males
Waist Circumference AUC = 0.65
BMI AUC = 0.61
5.1g. White European males
Waist Circumference AUC= 0.63
BMI AUC = 0.63

5.1h. White European females
Waist Circumference AUC= 0.68
BMI AUC = 0.65
When waist circumference is used as a screening tool for diabetes it performs better than BMI in both South Asians and White Europeans, as shown by a greater area under the curve (AUC).

When the waist circumference is used as a screening tool for prediabetes or diabetes it is less effective than when used for diabetes. The waist circumference has similar performance to the BMI when used in South Asian females and White European males. Whereas when screening for prediabetes or diabetes both South Asian males and White European females the waist circumference performs better than the BMI.

In a screening programme for diabetes if waist circumference was used as the first screening method the specificities, sensitivities and cut-off values are given in table 5.10a. Table 5.10b show the same values for prediabetes or diabetes screening. These are low specificities, but as a test it is non invasive, is non-expensive and can be performed by non-trained health care professionals.

Table 5.10a The performance of waist circumference when screening for diabetes

<table>
<thead>
<tr>
<th>Ethnic group</th>
<th>Age (years)*</th>
<th>Sex</th>
<th>Sensitivity %</th>
<th>Specificity %</th>
<th>Cut-off for waist circumference (cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>South Asian</td>
<td>≥ 25 and &lt; 40</td>
<td>Female</td>
<td>100</td>
<td>82.1</td>
<td>96</td>
</tr>
<tr>
<td></td>
<td>≥ 40 and &lt; 75</td>
<td>Female</td>
<td>88.8</td>
<td>29.0</td>
<td>84</td>
</tr>
<tr>
<td></td>
<td>≥ 25 and &lt; 40</td>
<td>Male</td>
<td>88.5</td>
<td>53.1</td>
<td>91</td>
</tr>
<tr>
<td></td>
<td>≥ 40 and &lt; 75</td>
<td>Male</td>
<td>90.4</td>
<td>16.1</td>
<td>86</td>
</tr>
<tr>
<td>White European</td>
<td>≥ 40 and &lt; 75</td>
<td>Female</td>
<td>89.9</td>
<td>34.6</td>
<td>86</td>
</tr>
<tr>
<td></td>
<td>≥ 40 and &lt; 75</td>
<td>Male</td>
<td>89.1</td>
<td>35.1</td>
<td>94.5</td>
</tr>
</tbody>
</table>

(* numbers small in age range ≥ 25 and < 40 years)
Table 5.10b The performance of waist circumference when screening for prediabetes or diabetes

<table>
<thead>
<tr>
<th>Ethnic group</th>
<th>Age (years)*</th>
<th>Sex</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Cut-off for waist circumference (cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>South Asian</td>
<td>≥ 25 and &lt; 40</td>
<td>Female</td>
<td>91.0</td>
<td>67.1</td>
<td>86.0</td>
</tr>
<tr>
<td></td>
<td>≥ 40 and ≤ 75</td>
<td>Female</td>
<td>90.0</td>
<td>33.8</td>
<td>82.5</td>
</tr>
<tr>
<td></td>
<td>≥ 25 and &lt; 40</td>
<td>Male</td>
<td>90.9</td>
<td>41.9</td>
<td>88.5</td>
</tr>
<tr>
<td></td>
<td>≥ 40 and ≤ 75</td>
<td>Male</td>
<td>90.8</td>
<td>20.0</td>
<td>85.5</td>
</tr>
<tr>
<td>White European</td>
<td>≥ 40 and ≤ 75</td>
<td>Female</td>
<td>91.6</td>
<td>17.2</td>
<td>82.5</td>
</tr>
<tr>
<td></td>
<td>≥ 40 and ≤ 75</td>
<td>Male</td>
<td>90.9</td>
<td>20.2</td>
<td>89.5</td>
</tr>
</tbody>
</table>

(* numbers small in age range ≥ 25 and < 40 years)

There may be a role in using waist circumference as the initial non-invasive test in a screening programme for diabetes or in a programme for screening for prediabetes and diabetes. This would involve an additional measurement than is usually made in patients in primary care, but is simple and could either be done by the individual themselves or by a member of the health care professional team at the practice.

5.5.4 Cambridge Diabetes Risk Score

The Cambridge DRS was determined for 3095 individuals, 28.7% (888/3095) were South Asian and 71.3% (2207/3095) were White European. In those who had the CDRS calculated the prevalence of screen-detected diabetes was 6.4% (57/888) in South Asians and 4.7% (103/2207) in White Europeans. The prevalence of prediabetes was 19.3% (171/888) in South Asians and 14.8% (326/2207) in White Europeans. Figure 5.2 shows the ROC curves for diabetes and prediabetes in both ethnic groups.
Figure 5.2

5.2a. ROC curves for Cambridge DRS for diabetes in South Asians
AUC = 0.63

5.2b. ROC curves for Cambridge DRS for diabetes White Europeans
AUC = 0.68
5.2c. ROC curves for Cambridge DRS for prediabetes in South Asians
AUC = 0.61

5.2d. ROC curves for Cambridge DRS for prediabetes in White Europeans
AUC = 0.63
Figures 5.3 and 5.4 show the ROC curves for South Asians and White Europeans respectively in different age groups. In White Europeans there is very little variation across the ages, whereas in South Asians the AUC decreases as the age increases. In those South Asians over 60 years, the AUC is low at 0.56. Table 5.11 shows how the Cambridge DRS cut-points need to vary to produce the same sensitivity values for each ethnic group. As the score performs differently across the ages in South Asians separate age bands are shown.

Figure 5.3 ROC curve for Cambridge DRS for diabetes in South Asians

5.3a. > 40 and < 50 years
AUC = 0.68
5.3b. \(\geq 50 \text{ and } < 60 \text{ years} \)
AUC = 0.59

\[ \text{ROC Curve} \]

- Sensitivity
- Specificity

Diagonal segments are produced by ties.

5.3c. \(\geq 60 \text{ and } \leq 75 \text{ years} \)
AUC = 0.56

\[ \text{ROC Curve} \]

- Sensitivity
- Specificity

Diagonal segments are produced by ties.
ROC curve for Cambridge DRS for prediabetes in South Asians

5.3d. $\geq 40$ and $< 50$ years
AUC = 0.58

5.3e. $\geq 50$ and $< 60$ years
AUC = 0.62
5.3f. $\geq 60$ and $\leq 75$ years
AUC $= 0.57$

![ROC Curve](image)

Diagonal segments are produced by ties.

Figure 5.4
ROC curve for Cambridge DRS for diabetes in White Europeans

5.4a. $\geq 40$ and $< 50$ years
AUC $= 0.64$

![ROC Curve](image)

Diagonal segments are produced by ties.
5.4b. $\geq 50$ and $< 60$ years

AUC = 0.63

ROC Curve

5.4c. $\geq 60$ and $\leq 75$ years

AUC = 0.66

ROC Curve
ROC Curve for Cambridge DRS for prediabetes in White Europeans

5.4d. ≥ 40 and < 50 years
AUC = 0.54

![ROC Curve](image)

Diagonal segments are produced by ties.

5.4e. ≥ 50 and < 60 years
AUC = 0.65

![ROC Curve](image)

Diagonal segments are produced by ties.
5.4f. ≥ 60 and ≤ 75 years
AUC = 0.57

Table 5.11a
Cambridge DRS for White Europeans and South Asians, aged 39 to 75 years, for identifying type 2 diabetes

<table>
<thead>
<tr>
<th>Sensitivity</th>
<th>White Europeans</th>
<th>South Asians ≥39 and &lt;50 years</th>
<th>South Asians ≥50 and &lt;60 years</th>
<th>South Asians ≥60 years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CDRS cut-off</td>
<td>Specificity %</td>
<td>CDRS cut-off</td>
<td>Specificity %</td>
</tr>
<tr>
<td>95%</td>
<td>0.135</td>
<td>23.7</td>
<td>0.050</td>
<td>8.1</td>
</tr>
<tr>
<td>90%</td>
<td>0.175</td>
<td>30.2</td>
<td>0.090</td>
<td>20.3</td>
</tr>
<tr>
<td>85%</td>
<td>0.270</td>
<td>42.0</td>
<td>0.130</td>
<td>29.1</td>
</tr>
<tr>
<td>80%</td>
<td>0.330</td>
<td>47.1</td>
<td>0.175</td>
<td>35.2</td>
</tr>
<tr>
<td>75%</td>
<td>0.420</td>
<td>54.8</td>
<td>0.185</td>
<td>37.3</td>
</tr>
<tr>
<td>70%</td>
<td>0.480</td>
<td>59.9</td>
<td>0.225</td>
<td>43.4</td>
</tr>
<tr>
<td>65%</td>
<td>0.525</td>
<td>64.3</td>
<td>0.270</td>
<td>49.9</td>
</tr>
<tr>
<td>60%</td>
<td>0.600</td>
<td>70.2</td>
<td>0.320</td>
<td>54.8</td>
</tr>
</tbody>
</table>
Table 5.11b
Cambridge DRS for White Europeans and South Asians, aged 39 to 75 years, for identifying prediabetes

<table>
<thead>
<tr>
<th>Sensitivity</th>
<th>White Europeans</th>
<th>South Asians</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CRS cut-off</td>
<td>Specificity</td>
</tr>
<tr>
<td>95%</td>
<td>0.075</td>
<td>13.7</td>
</tr>
<tr>
<td>90%</td>
<td>0.115</td>
<td>20.7</td>
</tr>
<tr>
<td>85%</td>
<td>0.185</td>
<td>32.9</td>
</tr>
<tr>
<td>80%</td>
<td>0.235</td>
<td>38.6</td>
</tr>
<tr>
<td>75%</td>
<td>0.285</td>
<td>43.8</td>
</tr>
<tr>
<td>70%</td>
<td>0.325</td>
<td>48.2</td>
</tr>
<tr>
<td>65%</td>
<td>0.385</td>
<td>53.9</td>
</tr>
<tr>
<td>60%</td>
<td>0.435</td>
<td>58.0</td>
</tr>
</tbody>
</table>

The authors suggest a cut-point of 0.199 in the Cambridge DRS when screening for diabetes. If we used this level in White Europeans the sensitivity is reasonable at 89.4%, but the specificity decreases to 32.8%. Alternative cut-points could be selected from Table 5.11a, depending on the desired sensitivity and specificity values required from the CDRS. There is a large difference in the performance of the score in different ages. (table 5.12) The Cambridge DRS has greater sensitivities in the older age group than in the younger groups. In South Asians the overall sensitivity for the cohort is 71.9%. Again there is variation in the sensitivity depending on the age group. There is a higher sensitivity in those over 60 years, than those under 60 years old. Age is one of the variables included in the CDRS; the older the individual the greater the score. This does appear to have an adverse effect on the overall performance of the CDRS. If the CDRS was adapted to enable South Asians to achieve a higher score than White Europeans of the same age, then the performance of the score in South Asians may improve.
Table 5.12
Performance of the Cambridge DRS using authors’ recommended cut-point of 0.199 in detecting type 2 diabetes

<table>
<thead>
<tr>
<th>Ethnic group</th>
<th>Age group</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>South Asian</td>
<td>≥ 40 and &lt; 50 years</td>
<td>70.0%</td>
<td>59.9%</td>
</tr>
<tr>
<td></td>
<td>≥ 50 and &lt; 60 years</td>
<td>61.9%</td>
<td>48.3%</td>
</tr>
<tr>
<td></td>
<td>≥ 60 and &lt; 75 years</td>
<td>87.5%</td>
<td>24.6%</td>
</tr>
<tr>
<td></td>
<td>≥ 40 and ≤ 75 years</td>
<td>71.9%</td>
<td>49.5%</td>
</tr>
<tr>
<td>White Europeans</td>
<td>≥ 40 and &lt; 50 years</td>
<td>63.6%</td>
<td>60.3%</td>
</tr>
<tr>
<td></td>
<td>≥ 50 and &lt; 60 years</td>
<td>78.9%</td>
<td>23.2%</td>
</tr>
<tr>
<td></td>
<td>≥ 60 and &lt; 75 years</td>
<td>95.9%</td>
<td>20.6%</td>
</tr>
<tr>
<td></td>
<td>≥ 40 and ≤ 75 years</td>
<td>89.4%</td>
<td>32.8%</td>
</tr>
<tr>
<td>Original cohort from Ely</td>
<td>40-64 years</td>
<td>77%</td>
<td>72%</td>
</tr>
</tbody>
</table>

Summary of Cambridge Diabetes Risk Score
The team who developed the Cambridge DRS recommended a cut-off of 0.199 for detecting type 2 diabetes, and reported a sensitivity of 77% and specificity of 72%. We were unable to reproduce this performance. We found the maximal sensitivity and specificity of the Cambridge DRS score to be a cut-point of 0.27 in South Asians (sensitivity 60%, specificity 60%) and 0.35 (sensitivity 78%, specificity 49%) in White Europeans. To achieve 90% sensitivity a cut-off of 0.090 in South Asians under the age of 50 years (specificity 20.3%) and 0.065 in South Asians over the age of 50 years (specificity 17.5%) and 0.175 in White Europeans, irrespective of age, (specificity 30.2%) would be needed. These specificities are low. Table 5.11a shows the sensitivities and specificities for different CDRS cut-offs.
When the CDRS is used to screen for patients with prediabetes the performance is poor. The AUC varies from 0.54 to 0.65, depending on the age and ethnic group of the patients. It was only individuals aged 50 - 60 years where the DRS had an AUC over 0.60.

The CDRS, is based on readily available information from primary care databases, and can identify 90% of South Asians and White Europeans with previously undiagnosed type 2 diabetes with specificities of 17.5 to 30.2%. If the same cut-off point is used in all ages and ethnic groups then the specificity is lower. The CDRS has only a limited role as a stand alone screening tool for prediabetes.

However if the CDRS were combined with other screening methods, as the first of two or more steps in a screening programme, the CDRS would be more useful than as a screening tool. Each individuals’ risk score could be calculated. After the calculation of the risk score, subsequent testing would be restricted to those at a greater risk of diabetes. There would be no impact from potential low response rates as the CDRS is calculated from data routinely available from primary care databases. There is no necessity for translations of questions or instruction sheets for non-English speaking individuals.

5.5.5 Finnish Diabetes Risk Score

The Finnish Diabetes Risk Score (FDRS) questionnaire was completed by 2382 individuals, of whom 36.6% (869/2382) were South Asian and 59.9% (1422/2382) were White European. The prevalence of diabetes in those completing the questionnaire was 6.9% overall; 10.5% (91/869) in South Asians and 4.9% (69/1422) in White Europeans. The AUC for the FDRS in detecting diabetes was 0.48 in South Asians and 0.43 for White Europeans.
Figure 5.5

5.5a. ROC curve for Finnish DRS in South Asians, ≥ 25 and < 75 years
AUC = 0.48

[Graph of ROC curve for Finnish DRS in South Asians]

5.5b. ROC curve for Finnish DRS in White Europeans, ≥ 40 and < 75 years
AUC = 0.43

[Graph of ROC curve for Finnish DRS in White Europeans]
When the population is divided into different age bands, then the AUC remains low regardless of the age range being studied, as shown in figures 5.6 and 5.7. The FDRS does not perform well South Asians or White Europeans in this study.

The Finnish DRS score was developed and validated in a Finnish population aged between 35 and 64 years old. When the FDRS is applied only to individuals within that age range, in this study population, the AUC for South Asians is 0.45 and in White Europeans is 0.42. At these values, the FDRS score has no ability to discriminate between the presence and absence of diabetes. Extending the age range above that in which the Finnish DRS was created does not change the performance of the score.

Figure 5.6
ROC curves for Finnish DRS in South Asians

5.6a. ≥ 25 and < 45 years
AUC = 0.49
5.6b. \( \geq 45 \) and \(< 65 \) years
AUC = 0.48

![ROC Curve](image1)

Diagonal segments are produced by ties.

5.6c. \( \geq 65 \) and \(< 75 \) years
AUC = 0.49

![ROC Curve](image2)

Diagonal segments are produced by ties.
5.6d. $\geq 35$ and $< 64$ years  
AUC = 0.45

Figure 5.7  
ROC curve for Finnish DRS in White Europeans

5.7a. $\geq 40$ and $< 45$ years  
AUC = 0.27
5.7b. > 45 and < 65 years
AUC = 0.44

![ROC Curve for 5.7b.](image)

Diagonal segments are produced by ties.

5.7c. ≥ 65 and < 75 years
AUC = 0.43

![ROC Curve for 5.7c.](image)

Diagonal segments are produced by ties.
5.7d. ≥ 35 and < 64 years
AUC = 0.42

Table 5.13 shows the sensitivities and specificities at different cut-points for South Asians and White Europeans. As the cut-point increases, the sensitivity decreases and specificity increases. At every cut-point the sensitivity is lower in South Asians. The authors of the Finnish DRS suggested a cut-point of nine, as the threshold at which there was no need for further screening. (Sensitivity 81.0% and specificity 76.0%) We were unable to reproduce that sensitivity at that cut-point in our cohort. Using that cut-point in White Europeans there is 39.1% sensitivity and 53.5% specificity. Whereas in South Asians the sensitivity would be 28.6% and specificity is 70.6%. The sensitivity of the FDRS is too low to use as a screening test for diabetes.
Table 5.13  Finnish DRS cut off values for predicting type 2 diabetes

<table>
<thead>
<tr>
<th>Cut-off value</th>
<th></th>
<th>White Europeans</th>
<th></th>
<th>South Asians</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Age ≥ 40 and &lt; 75 years</td>
<td></td>
<td>Age ≥ 25 and &lt; 75 years</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sensitivity %</td>
<td>Specificity %</td>
<td>Sensitivity %</td>
<td>Specificity %</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>95.7</td>
<td>2.7</td>
<td>91.2</td>
<td>8.7</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>85.5</td>
<td>5.4</td>
<td>83.5</td>
<td>16.5</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>78.3</td>
<td>11.3</td>
<td>70.3</td>
<td>26.2</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>71.0</td>
<td>18.9</td>
<td>62.6</td>
<td>35.2</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>69.6</td>
<td>24.7</td>
<td>54.9</td>
<td>41.9</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>59.4</td>
<td>32.0</td>
<td>45.1</td>
<td>51.2</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>49.3</td>
<td>42.3</td>
<td>34.1</td>
<td>61.9</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>39.1</td>
<td>53.5</td>
<td>28.6</td>
<td>70.6</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>23.2</td>
<td>66.6</td>
<td>11.0</td>
<td>82.3</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>13.0</td>
<td>78.0</td>
<td>6.6</td>
<td>91.4</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>7.2</td>
<td>88.6</td>
<td>1.1</td>
<td>95.8</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>0</td>
<td>94.1</td>
<td>0</td>
<td>98.3</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>0</td>
<td>99.0</td>
<td>0</td>
<td>99.6</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>0</td>
<td>99.9</td>
<td>0</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>0</td>
<td>100</td>
<td>0</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>0</td>
<td>100</td>
<td>0</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>0</td>
<td>100</td>
<td>0</td>
<td>100</td>
<td></td>
</tr>
</tbody>
</table>
Table 5.14 Sensitivity and specificity using the authors recommended cut-point of 9 in Finnish DRS

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>Age (years)</th>
<th>Sensitivity %</th>
<th>Specificity %</th>
</tr>
</thead>
<tbody>
<tr>
<td>South Asians</td>
<td>≥ 25 and &lt; 45</td>
<td>7.3</td>
<td>90.6</td>
</tr>
<tr>
<td></td>
<td>≥ 45 and &lt; 65</td>
<td>39.0</td>
<td>59.5</td>
</tr>
<tr>
<td></td>
<td>≥ 65 and ≤ 75</td>
<td>77.8</td>
<td>43.3</td>
</tr>
<tr>
<td></td>
<td>Overall: ≥34 to &lt; 64</td>
<td>24.7</td>
<td>68.9</td>
</tr>
<tr>
<td>White Europeans</td>
<td>≥ 40 and &lt; 45</td>
<td>0.0</td>
<td>84.5</td>
</tr>
<tr>
<td></td>
<td>≥ 45 and &lt; 65</td>
<td>46.2</td>
<td>49.2</td>
</tr>
<tr>
<td></td>
<td>≥ 65 and ≤ 75</td>
<td>42.9</td>
<td>48.4</td>
</tr>
<tr>
<td></td>
<td>Overall: ≥40 and &lt; 64</td>
<td>37.8</td>
<td>56.3</td>
</tr>
</tbody>
</table>

5.5.5.1 Finnish Diabetes Risk Score and Prediabetes

The prevalence of prediabetes in those completing the questionnaire was 15.8% (136/861) in South Asians and 16.1% (227/1416) in White Europeans. If the FDRS was used to identify those individuals with prediabetes or diabetes, similar results are found as to when it is used to detect diabetes. The AUC for South Asians is 0.45 and in White Europeans is 0.48. The specificities are too low for it to be useful. (figure 5.8)
Figure 5.8

5.8a. ROC curve for Finnish DRS in South Asians to detect prediabetes or diabetes, \( \geq 25 \) and \( < 75 \) years
AUC = 0.46

5.8b. ROC curve for Finnish DRS in White Europeans to detect prediabetes or diabetes, \( \geq 40 \) and \( < 75 \) years
AUC = 0.48
Summary of Finnish Diabetes Risk Score

Ideally any stand alone screening tool should have a sensitivity of around 90%, in order to minimise false negatives. When the FDRS is used either to screen for diabetes or for prediabetes and diabetes the sensitivity and the specificities are too low. There is not a major role for the FDRS in screening in the United Kingdom for diabetes or prediabetes. The authors of the FDRS have modified the score to improve sensitivity. (Personal communication) Figure 5.9 shows the percentage and frequency of the modified FDRS in each ethnic group and in those with and without diabetes. The mean modified FDRS in South Asians with diabetes is 8.1 (SD 3.95) and in those without diabetes 9.01 (SD 4.06). In White Europeans with diabetes the mean modified FDRS is 7.9 (SD 3.72) and in those without diabetes 9.29 (SD 3.89). Hence the score has no ability to discriminate between those with and without diabetes. ROC curves analysis shows similar AUC between the FDRS and modified FDRS. In our UK population the modified FDRS does not perform better than FDRS.

Figure 5.9
Histograms of the Modified FDRS
5.9a. in South Asians with diabetes
5.9b. in South Asians without diabetes

5.9c. in White Europeans with diabetes
5.6 Discussion

The ability of the Cambridge DRS, Finnish DRS, the risk factors which were found to be most significant and waist circumference in screening for diabetes or screening for prediabetes or diabetes are compared in table 5.15a and b respectively. A sensitivity of around 90% has been used to compare the specificities of each test.
Table 5.15a
Summary of the performance of different methods to screen for diabetes

<table>
<thead>
<tr>
<th>Ethnic group</th>
<th>Age group (Years)</th>
<th>Cut-point</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Finnish DRS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>South Asian</td>
<td>≥ 25 and &lt; 40</td>
<td>1</td>
<td>90.5%</td>
<td>16.5%</td>
</tr>
<tr>
<td>White European</td>
<td>≥ 40 and &lt; 75</td>
<td>3</td>
<td>90.0%</td>
<td>9.2%</td>
</tr>
<tr>
<td><strong>Cambridge DRS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>South Asian</td>
<td>≥ 40 and &lt; 75</td>
<td>0.07</td>
<td>91.2%</td>
<td>21.7%</td>
</tr>
<tr>
<td>White European</td>
<td>≥ 40 and &lt; 75</td>
<td>0.175</td>
<td>90%</td>
<td>30.2%</td>
</tr>
<tr>
<td><strong>Waist circumference</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>South Asian males</td>
<td>≥ 25 and &lt; 40</td>
<td>90.5 cm</td>
<td>87.5%</td>
<td>54.2%</td>
</tr>
<tr>
<td></td>
<td>≥ 40 and &lt; 75</td>
<td>86 cm</td>
<td>90.4%</td>
<td>15.6%</td>
</tr>
<tr>
<td>South Asian females</td>
<td>≥ 25 and &lt; 40</td>
<td>96 cm</td>
<td>90%</td>
<td>82.8%</td>
</tr>
<tr>
<td></td>
<td>≥ 40 and &lt; 75</td>
<td>84 cm</td>
<td>88.8%</td>
<td>29.3%</td>
</tr>
<tr>
<td>White European males</td>
<td>≥ 40 and &lt; 75</td>
<td>94.5 cm</td>
<td>89.1%</td>
<td>35.1%</td>
</tr>
<tr>
<td>White European females</td>
<td>≥ 40 and &lt; 75</td>
<td>85.9 cm</td>
<td>90.3%</td>
<td>34.8%</td>
</tr>
<tr>
<td><strong>Hypertension or elevated BMI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>South Asian</td>
<td>≥ 25 and &lt; 40</td>
<td>≥140/90 mmHg or on treatment or ≥25 kg/m²</td>
<td>100%</td>
<td>48.1%</td>
</tr>
<tr>
<td></td>
<td>≥ 40 and &lt; 75</td>
<td>≥140/90 mmHg or on treatment or ≥25 kg/m²</td>
<td>86.2%</td>
<td>23.3%</td>
</tr>
<tr>
<td>White European</td>
<td>≥ 40 and &lt; 75</td>
<td>≥140/90 mmHg or on treatment or ≥30 kg/m²</td>
<td>85.7%</td>
<td>39.8%</td>
</tr>
</tbody>
</table>

(* numbers small in age range ≥ 25 and < 40 years)
Table 5.15b
Summary of the performance of different methods of screening for prediabetes or diabetes

<table>
<thead>
<tr>
<th>Method</th>
<th>Ethnic group</th>
<th>Age group (Years)</th>
<th>Cut-point</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Finnish DRS</td>
<td>South Asian</td>
<td>≥ 25 and &lt; 40</td>
<td>1</td>
<td>84.3</td>
<td>15.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥ 40 and ≤ 75</td>
<td>3</td>
<td>86.9</td>
<td>7.9</td>
</tr>
<tr>
<td></td>
<td>White European</td>
<td>≥ 40 and ≤ 75</td>
<td>3</td>
<td>92.9</td>
<td>5.5</td>
</tr>
<tr>
<td>Cambridge DRS</td>
<td>South Asian</td>
<td>≥ 40 and ≤ 75</td>
<td>0.075</td>
<td>90.0</td>
<td>27.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>White European</td>
<td>≥ 40 and ≤ 75</td>
<td>0.115</td>
<td>90.0</td>
<td>20.7</td>
</tr>
<tr>
<td>Waist circumference</td>
<td>South Asian</td>
<td>≥ 25 and &lt; 40</td>
<td>88.5 cm</td>
<td>90.9</td>
<td>41.9</td>
</tr>
<tr>
<td>males</td>
<td></td>
<td>≥ 40 and ≤ 75</td>
<td>85.5 cm</td>
<td>90.8</td>
<td>20.0</td>
</tr>
<tr>
<td>South Asian</td>
<td>females</td>
<td>≥ 25 and &lt; 40</td>
<td>86.0 cm</td>
<td>91.0</td>
<td>67.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥ 40 and ≤ 75</td>
<td>82.5 cm</td>
<td>90.0</td>
<td>33.8</td>
</tr>
<tr>
<td>White European</td>
<td>males</td>
<td>≥ 40 and ≤ 75</td>
<td>89.5 cm</td>
<td>90.9</td>
<td>20.2</td>
</tr>
<tr>
<td></td>
<td>females</td>
<td>≥ 40 and ≤ 75</td>
<td>82.5 cm</td>
<td>91.6</td>
<td>17.2</td>
</tr>
<tr>
<td>Hypertension or elevated BMI</td>
<td>South Asian</td>
<td>≥ 25 and &lt; 40</td>
<td>≥140/90 mmHg or on treatment or ≥ 25 kg/m²</td>
<td>94.4</td>
<td>50.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥ 40 and ≤ 75</td>
<td>≥140/90 mmHg or on treatment or ≥ 25 kg/m²</td>
<td>89.9</td>
<td>27.2</td>
</tr>
<tr>
<td></td>
<td>White European</td>
<td>≥ 40 and ≤ 75</td>
<td>≥140/90 mmHg or on treatment or ≥ 30 kg/m²</td>
<td>78.0</td>
<td>42.8</td>
</tr>
</tbody>
</table>

(* numbers small in age range ≥ 25 and < 40 years)
5.6.1 Risk factors

This study determined the risk factors for screen detected diabetes that are readily identifiable and could be recorded on GP databases. In White Europeans the risk factors with the greatest contribution to screen detected diabetes are obesity (BMI>30kg/m²) and a previous diagnosis of IGT or IFG. However, only a small proportion of individuals have a diagnosis of IGT or IFG, so the usefulness of this risk factor in a screening programme is limited due to its low prevalence. We found that 85.7% of White Europeans who were diagnosed with diabetes were known to have either obesity or hypertension. If BMI is to be used in screening for type 2 diabetes in South Asians the cut-off value will need to be lower than in White Europeans. Over 86% of South Asians with diabetes had either hypertension or a BMI > 25 kg/m². Therefore targeting individuals with either of these two risk factors would identify over 86% of those with undiagnosed diabetes. (specificities 39.8% and 23% respectively)

Waist circumference is not usually measured but is non-invasive, simple and has reasonable performance when gender specific cut-off values are used to screen for diabetes. (table 5.15a) When the sensitivity of waist circumference is fixed at around 90% then, in South Asians, aged 25-40 years, the specificities are 53.1% in males and 82.1% in females. In South Asians, aged 40-75 years, the specificities are lower, at 16.1% in males and 29.3% for females. In White Europeans the specificities are similar in males and females at 31.1% and 34.6% respectively. In those South Asians under 40 waist circumference is at least as effective as the combination of hypertension and an elevated BMI in detecting diabetes. In South Asians sensitivity is 86.2% and specificity 23.3% and in White Europeans sensitivity 87.6% and specificity 37.2%.

5.6.2 Cigarette smoking

The odds ratios for diabetes in White Europeans is 0.4 (0.23-0.69) for current cigarette smoking and in South Asians is 0.79 (0.27-2.25), this suggests that cigarette smoking is not an independent risk factor for diabetes in this cohort of patients. Indeed, White Europeans who are cigarette smokers, without other risk factors, are less likely to have screen detected diabetes than those who are non-smokers.
5.6.3 Cambridge Diabetes Risk Score

We were unable to reproduce the published performance of the CDRS. Table 5.14 shows the cut-off values needed to achieve a sensitivity of 90%. Although it may be simpler to have a single cut-off point for all populations, to maintain reasonable sensitivity and specificity of the CDRS, different values are needed.

The CDRS, which is based on readily available information from primary care databases can identify 90% of South Asians and White Europeans with previously undiagnosed type 2 diabetes with specificities of 21.7 to 30.2%. If 80% sensitivity was sufficient then greater specificities, of around 30%, can be achieved.

Completion of the CDRS could be computerized from information already on a database. Once the CDRS had been calculated subsequent testing could be restricted to those found to be at a greater risk of diabetes, by having a greater score.

When the Cambridge DRS was applied to the 1958 British birth cohort, the authors reported that the Cambridge DRS did not provide any additional advantage to the identification of diabetes risk than using BMI on its own. (Thomas 2005) In that study the diabetes risk was determined as the presence of an elevated HbA1c (6.0-6.99%). We have confirmed this finding that the Cambridge DRS does not have any further advantage over the BMI.

5.6.4 Finnish Diabetes Risk Score

As expected the Finnish DRS also performs differently in South Asians when compared to White Europeans. For every cut-point there is lower sensitivity in the South Asians. Age, waist circumference and BMI all contribute numerically to the score and this study has shown that South Asians have diabetes at a younger age, with a lower BMI and with smaller waist circumference. Therefore lower cut-points are needed to achieve same sensitivities. However to achieve around 90% sensitivity the specificities are all under 20%. Using the FDRS in individuals to screen for diabetes cannot be recommended: the AUC is under 0.5 in both White Europeans and South Asians and therefore does not distinguish those with normal glucose tolerance and those with diabetes.
The characteristics of South Asians and White Europeans found to have diabetes are different and therefore the Finnish DRS could be adjusted for South Asians. This might make it more useful. Table 5.16 shows the Finnish DRS with appropriate adjustments made for South Asians using internationally recognised ethnic BMI and waist circumference measurements. (IDF 2005) In addition, as shown in chapter 4, South Asians are diagnosed with diabetes on an average 9 years earlier and the score for age has also been changed. The ethnic adjusted modified FDRS (includes family history) still does not perform well. The AUC is 0.45. The reason for the poor performance is that the individuals with diabetes have a mean FDRS of 10.45 (SD 3.90) and those without diabetes a mean of 11.17 (SD 4.09). The FDRS even when modified to include family history and adjusted for ethnic age, BMI and waist circumference still does not perform well as a screening test in our population.

Other studies have looked at the performance of the FDRS in independent population samples. The KORA survey from Germany found that the FDRS performed less well when applied to the local population than when compared to original data. The difference was attributed to population variance of risk factors including age, BMI, antihypertensive medication and smoking. (Rathmann 2005) The IGLOO study from Italy also looked at the performance of the FDRS in their local population. (Franciosi 2005) The FDRS was used opportunistically by general practitioners when individuals, with one or more cardiovascular risk factors, attended their offices. They found that with a cut-off value of 9 the sensitivity of the FDRS was 77% with a specificity of 45%. (AUC = 0.67) These findings were not replicated in our study. This may be due to the difference in population characteristics; 17.4% of the Italian study population had undiagnosed type 2 diabetes, whereas in this study the rate was 6.8% in South Asians and 4.7% in White Europeans. (Franciosi 2005) The performance of any screening test for diabetes will decrease as prevalence of the diabetes in the population being studied decreases.
Table 5.16 Variables and scoring methods for Finnish DRS adjusted for South Asians
(* only included in modified FDRS)

<table>
<thead>
<tr>
<th>Finnish DRS</th>
<th>Cut-off values adjusted for South Asians</th>
<th>Score for each variable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>45 - 54</td>
<td>35 - 44</td>
<td>2</td>
</tr>
<tr>
<td>≥ 55</td>
<td>≥ 45</td>
<td>3</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 25 to 30</td>
<td>&gt; 23.5</td>
<td>1</td>
</tr>
<tr>
<td>&gt; 30</td>
<td>&gt; 27.5</td>
<td>3</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men ≥ 94 and &lt; 102; women ≥ 80 and &lt; 88</td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>Men ≥ 102; women ≥ 88</td>
<td>Men ≥ 90; Women ≥ 80</td>
<td>4</td>
</tr>
<tr>
<td>Use of blood pressure medication</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>History of high blood glucose</td>
<td></td>
<td>5</td>
</tr>
<tr>
<td>Physical activity less than 4 hours per week</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Daily consumption of vegetables, fruits or berries</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>* First degree relative with diabetes</td>
<td></td>
<td>* 5</td>
</tr>
</tbody>
</table>

5.6.5 Computer completed DRS vs. patient completed DRS

There are benefits to using both computer completed and patient completed risk scores. Trade-offs between response rates, cost-effectiveness, sensitivity and specificity of the two methods need considering. In the UK there are well-established computerized patient medical records, which are comprehensive and increasingly complex. However these do depend on the data being present on the computer. Since the implementation of the new GMS contract for general practitioners, the documentation and recording of ischaemic heart disease, TIA or cerebrovascular events, smoking status, blood pressure, and cholesterol are much more likely to be present and complete. Screening methods that involve parameters already recorded on databases are going to be more effective than measures that are not uniformly recorded.
Education of risk factors and awareness of diabetes can be delivered through patient completed questionnaires, but their effectiveness in screening would be decreased if response rates are low. The majority of individuals diagnosed with diabetes through screening will be asymptomatic, which may adversely affect the completion rate of questionnaires, (such as FDRS) which are likely to be lower than the CDRS, which is completed from databases by computer. However, individuals who are asymptomatic may not attend their GP surgery and the database may be incomplete, which would decrease the performance of a computer completed score. Any method that is non-invasive will have some benefits over an initial invasive test, such as blood testing, where the response rate and acceptability are likely to be even lower than for a questionnaire. Questionnaires completed by individuals may be a useful method of increasing awareness of lifestyle options. Information about the benefits of increasing physical activity and changing to a more healthy diet could be included.

The calculation of risk scores, either following a questionnaire or computer database search, is much less labour intensive than oral glucose tolerance testing (OGTT) or fasting glucose testing and therefore may be preferable as the initial screening test. Computer calculated risk scores can provide better population coverage, and by varying the cut-point, at-risk patients can be targeted. The sensitivity could be improved if all the variables were recorded on the database, including BMI, which is often under-recorded. With the implementation of the new GMS contract there are some variables which attract financial incentives and therefore are more likely to be recorded.

Questionnaire methods, such as the FDRS, can be labour intensive, due to the large number of patients who need identifying and mailing, collating the data into a database, and then calculating risk factor scores from different formulae, which may be inconvenient and a deterrent to their use.
5.6.6 Strengths and weaknesses of the STAR study

The strengths of this study include using both fasting glucose and 2-hour glucose values, and repeating these on a separate day, to confirm the diagnosis of diabetes. We were therefore able to compare the outcome of screening with risk factors, risk scores, questionnaires and blood tests, against the gold standard diagnostic tool, providing an unrivalled opportunity of comparing different screening methods.

This was a large cohort of patients and included a significant proportion of South Asians. Although there is some heterogeneity among the South Asian population in Leicester, 95.6% of the Asian people found to have screen-detected diabetes screened in our population are of Indian origin. However this data is likely to be applicable to people of Indian origin living in other geographical areas.

Community screening, or screening after self referral has in the past been shown to be poorly targeted, in that it can fail to reach the groups that are most at risk and inappropriately test those at low risk who may be more receptive to such opportunities. In this cohort 99.4% of those who were screened after self-referral to the programme had at least one risk factor. The promotional literature distributed and the information available on newspapers, radio and television broadcasts did emphasise the importance of testing those who were at risk – and this study did target those individuals successfully.

There are also some weaknesses to this study. Participation relied on individuals being pro-active in responding to an invitation letter from their GP, or responding to local media awareness activities. This cohort may therefore not be representative of the local population. The low response rates are discussed in section 3.12. For ethical reasons we are unable to study the characteristics of non-responders, to determine if this is an important issue. The limitations around the method of selection of individuals for screening and the number of individuals found to have diabetes are discussed in section 4.5.7. There were only seven South Asians found to have diabetes and eleven with pre-diabetes in the age range 25 to 40 years. Therefore data about screening this group of individuals has to be interpreted with caution and recommendations about screening this age range have not be made from this data and further work needs to be done.
5.7 Conclusion
The National Screening Committee recommended that researchers established the feasibility and practicality of identifying people at risk; response rates to an invitation for screening; and the health benefits and potential negative effects of being tested and diagnosed. They also recommended investigation of the utility of different screening tests, and of optimum screening intervals. (Department of Health 2001)

From those risk factors for diabetes which are currently recorded by general practitioners we have identified the most important in White Europeans to be a previous diagnosis of IFG or IGT, having a first degree relative with diabetes, a BMI $\geqslant 30$kg/m$^2$ and known cerebrovascular or peripheral vascular disease. In South Asians the significant risk factors for undiagnosed type 2 diabetes are hypertension and having a BMI $\geqslant 25$kg/m$^2$. As the number of risk factors an individual has increases, the greater the risk for abnormal glucose tolerance. Waist circumference is not routinely measured at present but we have found that individuals with an elevated waist circumference are also at a significantly greater risk of being diagnosed with diabetes or prediabetes.

Having tested different screening methods for diabetes we have found that the presence of either hypertension or increased BMI performs as well as the more complex Cambridge DRS and the self-assessment tool, the Finnish DRS. The BMI cut-points are BMI $\geqslant 30$kg/m$^2$ in White Europeans and BMI $\geqslant 25$ kg/m$^2$ in South Asians. If a practice were able to measure waist circumference then this could be used to screen for diabetes. An elevated waist circumference is as effective at targeting those individuals, at high risk of diabetes, as either the CDRS or the presence of hypertension or an elevated BMI.

A suggested algorithm for identifying those individuals who would benefit from proceeding to further testing is shown in figure 5.10. If a practice chose to use its current data base then the presence of either an elevated BMI or hypertension could be used to screen for diabetes. An alternative first step in screening could be to identify individuals with an elevated waist circumference. Whilst there are some logistical issues around how and who should measure waist circumference, this does
provide an alternative method of identifying individuals who would benefit from further testing, without those individuals necessarily having to be seen by a healthcare professional. Individuals identified with an elevated BMI, hypertension or elevated waist circumference could proceed to a more invasive test to diagnose diabetes. These tests are discussed in chapter 6. The combination of the initial screening procedure followed by a more invasive blood test is described in chapter 8.

The sensitivity of risk scores, risk questionnaires and risk factors are too low to be useful as stand alone screening tools for prediabetes. Further work in this area would be useful to determine the optimal method of screening for prediabetes.
Figure 5.10

Screening algorithm to identify individuals at high risk of diabetes who would benefit from proceeding to further tests

South Asians

Age: ≥ 40 and ≤ 75 years

Known to have one of:
- BP ≥ 140/90 mmHg or on treatment
- BMI > 25 kg/m² or
- waist circumference > 84 cm females
  > 86 cm males

Proceed to invasive blood test.
Discussed in chapter 6 and 8

White Europeans

Age: ≥ 40 and ≤ 75 years

Known to have one of:
- BP ≥ 140/90 mmHg or on treatment
- BMI > 30 kg/m² or
- waist circumference > 86 cm in females
  > 93.5 cm in males
Chapter 6

The Effectiveness of Fasting Plasma Glucose and Haemoglobin\textsubscript{A}1c in Screening for Abnormal Glucose Tolerance in South Asians and White Europeans

6.1 Introduction

Although screening for type 2 diabetes has been recommended in some countries there remains uncertainty in the United Kingdom over some important issues, including who and how to screen and the practicality and performance of different screening methods in different populations.

As the incidence of diabetes rises, the prevalence of associated microvascular and macrovascular complications are likely to increase and it is becoming increasingly important that people with abnormal glucose tolerance are identified at an early stage in order to reduce the impact on individuals and on health care resources. The positive predictive value of screening tests would be greater in a population with a higher prevalence of abnormal glucose tolerance. Therefore tests that have been validated in a predominantly Caucasian population may not have the same performance in a South Asian population. There are as yet no internationally accepted cut-off points to define a positive screening test for abnormal glucose tolerance and it is possible that cut-off levels may vary between ethnic populations.

The oral glucose tolerance test is the gold standard for diagnosing type 2 diabetes. It has limited used for mass screening due to the need for fasting, the time-consuming nature of the test and the poor reproducibility of the results. (Peters 1996, McCance 1994) Alternative approaches to screening include the use of FPG or HbA1c. The FPG is a relatively simple and inexpensive test, and can provide consistent results. The only limiting factor is that the patient has to attend fasting. HbA1c is a marker of long-term blood glucose control and is used as a measure of an individual’s glycaemic control over the previous three months. It requires no patient preparation, can be taken at any time of the day, is not affected by recent meals and has been shown to be directly related to microvascular and macrovascular complications. (UKPDS 33 1998, Khaw 2004) It is more costly than FPG in laboratory terms but this should be balanced against health care professional time
and patient convenience. Most laboratories now have DCCT/UKPDS aligned assays for measurement of HbA1c.

The aim of this study was to compare the performance of FPG and HbA1c to detect unrecognised prediabetes and diabetes in at risk patients of South Asian and White European origin living in the United Kingdom.

6.2 Research Design and Methods

The Screening Those At Risk (STAR) study was designed to identify the prevalence of undiagnosed abnormal glucose tolerance and determine the performance of different screening tests. All individuals aged 40 to 75 years, and aged 25 to 39 years if not of White European origin, who had at least one recognised risk factor for diabetes (identified from GP computer records) from fifteen General Practices were invited to attend screening. In addition all patients within the age ranges for the ethnic groups were invited from two General Practices, irrespective of the presence of risk factors.

Risk factors included a known history of coronary heart disease, hypertension, hyperlipidaemia, cerebrovascular disease, peripheral vascular disease, and a past record in the notes of impaired glucose tolerance (IGT) or impaired fasting glycaemia (IFG). Other risk factors included a first-degree relative with type 2 diabetes and a body mass index greater than 30 kg/m². Further risk factors for females included history of gestational diabetes or polycystic ovary syndrome in those with a body mass index greater than 25 kg/m². Exclusion criteria were individuals who were housebound, had a terminal illness or were already known to have diabetes mellitus. The screening was conducted within the general practice, on a mobile screening unit or at one of the local hospitals over an 18 month period. Ethical approval was obtained from the local ethics committee and all patients gave written informed consent.

Individuals attended after fasting for at least eight hours, and venous blood samples were taken for glucose, HbA1c, lipid fractions and renal function. A 75-g oral glucose load (394mls Lucozade) was given and a venous blood sample taken after
120 minutes. All samples were analysed in the same laboratory using stable methodologies that are standardised to outside reference values. All patients were asked to self-complete an ethnicity (Census classification) and general health questionnaire.

Individuals found to have glucose results within the diabetes range, using the WHO 1999 criteria, were invited for a repeat oral glucose tolerance test to confirm the diagnosis. (fasting plasma glucose ≥7.0 mmol/l or 2-hour post glucose challenge glucose ≥11.1 mmol/l) (WHO 1999) Individuals with fasting plasma glucose ≥6.1 but < 7.0 mmol/l are defined as having IFG. Individuals with the 2-hour post glucose challenge glucose ≥7.8 and <11.1 mmol/l are classified as having IGT. (WHO 1999) In those in whom abnormal glucose tolerance was confirmed the glucose values from the first oral glucose tolerance test are reported.

6.3 Statistical Analysis

SPSS version 12 was used to calculate prevalence, confidence intervals and to construct the receiver-operator characteristic (ROC) curves. These ROC curves were used to compare the performance of FPG and HbA1c in determining the presence of diabetes or prediabetes. A ROC curve is used to describe the performance of a test over a range of cut-off points and can demonstrate the trade-off between sensitivity and specificity. The curve is constructed by plotting the sensitivity or true-positive rate against 1-specificity or the false positive rate. The overall performance of the test can be quantified by the area under the ROC curve (AUC); the larger the area the better the performance. (Lang 1997) Technically, the optimal threshold in ROC curves is when there is maximum sensitivity and specificity. (Lang 1997) However, in a screening programme for diabetes this may not be the optimal cut-off for a test, as at the ‘optimal’ cut-off the sensitivity may be too low, and too many people who may benefit from further testing would not be given the opportunity to do so.
6.4 Results

3515 individuals were screened. Of those 63.8% (2242) were White European and 32.7% (1149) were of South Asian origin. The mean age of those screened was 55.0 years and 46.4% (1631) were male. The prevalence of risk factors, in those screened, identified from searching the general practice databases was 11.7% (411) for coronary heart disease, 36.5% (1282) hypertension, 12.6% (443) hyperlipidaemia, 2.6% (91) cerebrovascular or peripheral vascular disease, 1.3% (46) past history of IGT or IFG, 41.2% (1448) first degree relative with diabetes, 29.3% (1030) known to have body mass index >30kg/m², 1.7% (58) gestational diabetes and 0.2% (7) polycystic ovarian syndrome. (table 5.5)

The prevalence of screen-detected type 2 diabetes in people aged 40 to 75 years was 6.5% (58/899, 95% CI: 4.8-8.1) in South Asians and 4.7% (105/2238, 95% CI: 1.0-5.2) in White Europeans. The prevalence of prediabetes (IFG, IGT or both) in the same age range was 19.9% (179/899, CI: 17.3-22.7) in South Asians and was 15.4% (344/2238, CI: 13.9-16.9) in White Europeans. In the South Asians aged 25 to 39 years the prevalence of diabetes was 2.6% (n=7/248, CI: 1.14-5.73) and of prediabetes was 4.4% (11/248, CI: 2.23-7.80).

The ROC curves for FPG and HbA1c screening tests are shown in figures 6.1 and 6.2. When screening for diabetes in the 40 to 75 year age range in White Europeans the area under the curve (AUC) is 0.95 (CI: 0.92-0.98) for FPG and 0.88 (CI: 0.84–0.92) for HbA1c. In South Asians the AUC is 0.93 (CI: 0.89–0.97) for FPG and 0.94 (CI: 0.91–0.97) for HbA1c. When these tests are used to screen for prediabetes the AUC’s were lower; White Europeans FPG is 0.78 (CI: 0.76-0.81) and HbA1c is 0.69 (CI: 0.66-0.72) and in South Asians FPG 0.77 (CI: 0.73-0.81) and HbA1c 0.73 (CI: 0.69-0.77). The AUC for diabetes in South Asians in the younger age group (25 to 39 years) using FPG was 0.99 (CI: 0.98-1.00) and for HbA1c is 0.98 (CI: 0.96-1.00) and for prediabetes the AUC is 0.92 (CI: 0.86-0.98) and 0.78 (CI: 0.63-0.93) for FPG and HbA1c respectively.
Figure 6.1
Receiver-operating characteristic curve using FPG and HbA1c in White Europeans aged 40-75 years

6.1a. for diagnosing previously unrecognised type 2 diabetes

6.1b. for diagnosing previously unrecognised prediabetes
Figure 6.2
Receiver-operating characteristic curve using FPG and HbA1c in South Asians aged 40-75 years
6.2a. for diagnosing previously unrecognised type 2 diabetes

6.2b. for diagnosing previously unrecognised prediabetes
In those aged 40-75 years, to achieve 90% sensitivity in the diagnosis of previously undetected diabetes, in South Asians the FPG cut-off level was $\geq 5.4\text{mmol/l}$ (specificity 70%) and HbA1c $\geq 6.2\%$ (specificity 82%). In the White Europeans FPG was $\geq 6.0\text{mmol/l}$ (specificity 91%) and HbA1c $\geq 5.8\%$ (specificity 70%) (Table 6.1). When using these tests to screen for prediabetes, in South Asians the FPG level was $\geq 4.9\ \text{mmol/l}$ (specificity 38%) and HbA1c $\geq 5.6\%$ (specificity 41.1%). In the White Europeans, the FPG was $\geq 4.9\ \text{mmol/l}$ (specificity 40%) and HbA1c $\geq 5.3\%$ with a specificity of 25%.

6.5 Discussion

6.5.1 General discussion

This is a large screening study for diabetes and prediabetes in the United Kingdom that includes a significant proportion of South Asian individuals (32.7%) that uses the gold standard diagnostic test (75-g OGTT) to diagnose the presence of abnormal glucose tolerance. (WHO 1999) This screening programme demonstrates that the FPG and HbA1c could be used with 90% sensitivity and specificities of at least 70% as screening tests for diabetes in both South Asians and White Europeans. The ROC curves demonstrate that the tests perform as well in both population groups but to achieve 90% sensitivity then the cut-off values need to vary between the groups. When screening for prediabetes, at 90% sensitivity, FPG and HbA1c have lower specificities (25% to 40%), making these tests unsuitable as stand alone screening tools for prediabetes, as many individuals would require subsequent OGTT testing to determine if they have prediabetes.

For diabetes screening, in the age range 40 to 75 years, for 90% sensitivity the FPG cut-off value is lower in South Asians than in White Europeans, whereas HbA1c cut-off levels are greater. (Table 6.1) In White Europeans the AUC for the ROC curves is greater for the FPG (0.95: CI: 0.92-0.98) than for the HbA1c (0.88: CI: 0.85-0.92), implying that the FPG is a more useful test than HbA1c. This is confirmed by the number of individuals who would need to proceed to a further test; 12.4% for FPG and 39.6% for HbA1c values. Whereas in South Asians the AUC are similar for both FPG and HbA1c implying the tests have a similar performance. In the younger South Asians (25 to 40 years) FPG and HbA1c do perform better as
screening tests for diabetes when compared to those in age range 40 to 74 years. Fewer individuals need to proceed with further OGTT to determine previously undiagnosed type 2 diabetes. In South Asians under 40 years of age there were only 7 individuals with diabetes and 11 with prediabetes so data from this group is not robust.

Table 6.1 How to screen for diabetes and prediabetes with 90% sensitivity

<table>
<thead>
<tr>
<th>Ethnic group</th>
<th>South Asian</th>
<th>White European</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of patient</td>
<td>≥ 25 and &lt; 40 years *</td>
<td>≥ 40 and ≤ 75 years</td>
</tr>
<tr>
<td>FPG cut-off value</td>
<td>5.9 mmol/l</td>
<td>5.4 mmol/l</td>
</tr>
<tr>
<td>HbA1c cut-off value</td>
<td>-</td>
<td>6.1 %</td>
</tr>
<tr>
<td>% of individuals needing further tests</td>
<td>6.5 %</td>
<td>10.1 %</td>
</tr>
<tr>
<td>Specificity of test</td>
<td>96 %</td>
<td>93 %</td>
</tr>
<tr>
<td>FPG Area Under ROC Curve (95% CI)</td>
<td>0.99 (0.98-1.00)</td>
<td>-</td>
</tr>
<tr>
<td>HbA1c Area Under ROC curve (95% CI)</td>
<td>-</td>
<td>0.98 (0.96-1.00)</td>
</tr>
</tbody>
</table>

| Prediabetes | | |
| FPG cut-off value | 5.2 mmol/l | - | 4.9 mmol/l | - | 4.9 mmol/l | - |
| HbA1c cut-off value | - | 5.2 % | - | 5.6 % | - | 5.5 % |
| % of individuals needing further tests | 32.3 % | 82.3 % | 71.7 % | 67.7 % | 68.7 % | 76 % |
| Specificity of test | 69.7 % | 16.0 % | 38.0 % | 41.1 % | 40 % | 25 % |
| FPG Area Under ROC Curve (95% CI) | 0.92 (0.85-0.98) | - | 0.77 (0.73-0.81) | - | 0.78 (0.76-0.81) | - |
| HbA1c Area Under ROC curve (95% CI) | - | 0.78 (0.63-0.93) | - | 0.73 (0.69-0.77) | - | 0.69 (0.66-0.73) |

(* numbers small in age range ≥ 25 and < 40 years)
Data from the DPP suggests that those individuals with IGT would benefit from lifestyle interventions with about 58% reduction in the risk of developing diabetes. (DPPRG 2002) Therefore identifying those individuals with prediabetes is necessary so that they can be targeted with lifestyle intervention advice and recommendations. In this study when screening for prediabetes, with a sensitivity of 90%, the cut-off value for FPG in both ethnic groups is 4.9 mmol/l, but the HbA1c cut-off value in South Asians was higher (5.6% vs. 5.4%). When using blood tests to screen for prediabetes, the AUCs were much lower. Therefore to maintain 90% sensitivity a greater number of people would need to proceed to a further test. This is between 66% and 76% depending on ethnic group and blood test. When screening for prediabetes in younger South Asians a similar pattern is seen to those in older age range, with lower AUC corresponding to a greater number of individuals who would need to proceed to further tests. The prevalence of IFG in this study was based on the WHO 1999 criteria with a FPG of ≥ 6.1mmol/l, however the ADA recently recommended a lower definition for IFG with a FPG ≥5.6mmol/l. (WHO 1999, ADA 2005) This lower value would make the screening tests even less specific. It is likely that a two-step screening procedure would perform better, with a less expensive initial test, such as a questionnaire or risk score (Griffin 2000, Lindstrom 2003) which could then be followed by a more invasive procedure, such as a blood test, if a certain score was reached. This approach which has been adopted by the Finnish for identifying individuals at high risk of diabetes (Lindstrom 2003) needs validation for detection of prediabetes in a UK population before it can be recommended.

6.5.2 Why is there a difference in cut-off values for screening

South Asians in the United Kingdom have a substantially increased risk of diabetes and cardiovascular disease than Caucasians. (McKeigue 1991) This greater prevalence of disease is not completely explained. Several different factors contribute including greater insulin resistance, low birth weight and genetic susceptibility. In this study when screening for abnormal glucose tolerance South Asians would require lower fasting glucose and greater HbA1c cut-off values than White Europeans. Previous studies have shown that IFG and IGT are not analogous groups, indeed the concordance varies between 20 and 40%. (Harris 1998, Larsson 1998, Davies 2000, Unwin 2002) Individuals with IFG are characterized by beta
cell dysfunction, whereas those with IGT and a relatively normal fasting glucose concentration have features of the insulin resistance syndrome. Those with both IFG and IGT are likely to have both beta cell dysfunction and insulin resistance. (Davies 2000) HbA1c is more related to the 2-hour glucose than the fasting glucose. (Davies 2000) The findings of this study therefore suggest that South Asians have relatively less beta cell dysfunction and more insulin resistance which are consistent with previous findings. (McKeigue 1991)

6.5.3 Current Screening Guidelines

The World Health Organization position statement on screening states that below a FPG of 5.5mmol/l the diagnosis of diabetes is unlikely and above this value it would be sensible to proceed to an OGTT. (WHO 1994) The ADA recommends a FPG of 6.1 mmol/l as the threshold at which the patient does not proceed to an OGTT. (ADA 2000) Neither the ADA, WHO or Diabetes UK recommend different cut-off values for ethnic populations. (WHO 1994, Diabetes UK 2002, ADA 2000)

If we were to apply the WHO 5.5 mmol/l threshold value to our population, the sensitivity will increase but at the expense of specificity: in White Europeans sensitivity increases to 94.3% (specificity 75.7%) and in South Asians increases to 92.9% (specificity 74%). Using the WHO value of 5.5 mmol/l would also increase the number of White Europeans needing further investigation to 32.3%.

Using the greater ADA FPG threshold of 6.1 mmol/l the specificities increase but at the expense of sensitivity. The sensitivity is 79.4% (specificity 93%) in White Europeans and 84% (specificity 91.8%) in South Asians. The consequences of this are that 20.6% of White Europeans and 16.0% of South Asians with diabetes would be missed. HbA1c is not currently recommended as a screening test by the WHO, ADA or Diabetes UK. (WHO 1994, Diabetes UK 2002, ADA 2000)
6.6 Summary

Limitations of screening for diabetes have previously included the lack of practical screening tests that are both sufficiently specific and sensitive. This study has shown that FPG and HbA1c can be used, in individuals at risk of diabetes, with 90% sensitivity and reasonable specificities with different cut-off points in different ethnic groups to identify those individuals who would benefit from proceeding to an OGTT in order to diagnose diabetes. To optimise the performance of these screening tests and minimize the number of individuals requiring further investigation we would recommend in White Europeans aged 40 to 75 years, a FPG value of $\geq 6.0$ mmol/l (specificity 91%, sensitivity 90%) and in South Asians 40-75 years a HBA1C $\geq 6.2\%$ (specificity 82% and sensitivity 90%).

We recommend screening for diabetes in individuals with at least one recognised risk factor. The screening algorithm is demonstrated in figure 6.3.

When screening for prediabetes FPG and HbA1c have low specificities and are not suitable methods to identifying abnormal glucose at an early stage, further work is needed to determine the optimal method of identifying those with prediabetes.
Figure 6.3
Algorithm for screening individuals with at least one risk factor for diabetes with 90% sensitivity

South Asian

40-75 years

HbA1c

<6.2%  ≥ 6.2%

Address risk factor(s) that made person eligible for screening

White European

40 – 75 years

FPG

< 6.0 mmol/l  ≥ 6.0 mmol/l

Proceed to a 75g OGTT

Recognised risk factors include:
• history of CHD, hypertension, hyperlipidaemia, cerebrovascular disease, PVD, IGT, IFG or gestational diabetes
• first-degree relative with type 2 diabetes
• body mass index ≥ 30 kg/m²
• Polycystic ovary syndrome

Number of people needing to proceed to OGTT:
South Asians  24.1%
White Europeans  12.4%
Chapter 7

Anxiety beliefs and diabetes screening

7.1 Introduction
An important part of any screening programme is to ensure that individuals participating do not come to any harm. There have been concerns expressed over the psychological consequences of screening. These concerns include anticipatory anxiety, negative feelings after a positive result, annoyance, false reassurance leading to worsening of risk, and the effects of ‘labelling’ such as increased absenteeism from work. (Engelgau 2000) The limited published research on these issues provides little evidence for a negative impact on individual’s current emotional well-being. (Farmer 2001, Adriansee 2002, Ludvigson 2002)

The low levels of distress reported in screening studies to date may be a consequence of the time delay in measurement. Adriansee and colleagues reported the results of interviews with individuals who were found to have an elevated risk of diabetes two weeks after screening and with those diagnosed with diabetes 2 months after the screening was complete. (Adriansee 2003) However this does not address the question of whether the anxiety was alleviated as a consequence of receiving feedback on the results, thereby reducing uncertainty. A more recent study by Farmer and colleagues reported only slightly elevated levels of anxiety in individuals (relatives of diagnosed patients) being screened for type 2 diabetes. (Farmer 2003)

This lack of increased anxiety may reflect the fact that individuals do not perceive themselves to be at risk of developing diabetes. (Pierce 2001) Forty one percent of offspring of people with diabetes reported that either they were at low risk of developing diabetes even after receiving education about their risks or that diabetes is not perceived as a serious condition. (Pierce 2000) The studies that have explored these issues have used single-item questions. However single-item questions do have some inherent psychometric limitations. (Hampson 1997, Pierce 2000 and 2001, Adriansee 2002, Ludvigson 2002, Farmer 2003.) Therefore, this issue needs to be explored further using more psychometrically robust assessments
of individuals’ beliefs about type 2 diabetes, which is addressed in this study by using a measure derived from the Illness Representation literature.

This study assessed the impact of screening for diabetes on anxiety levels in an ethnically mixed population in the UK, and explores whether health beliefs about type 2 diabetes account for an increase in anxiety levels.

7.2 Methods
Individuals participating in this study were asked to complete a questionnaire booklet that explored a number of psychological issues around screening for diabetes. The questionnaire booklet was only available in English and individuals were asked to complete it unaided. A copy is included in appendix D.

7.2.1 Measures
Anxiety was assessed using the short form of the Spielberger State-Trait Anxiety Scale Short. (Marteau 1992) This is a six item, four-option response questionnaire with scale scores adjusted to fall between 20 and 80. Previous studies have identified a normative score of 25, and a clinically significant score of 42. (Marteau 1992) It refers to emotional reactions characterized by subjective feelings of tension, apprehension, nervousness and worry. It is well validated and has been used in many studies. (Marteau 1992, Spielberger 1983)

The Big Five Personality Inventory 44 questionnaire was used to measure personality and emotional stability. (John 1991) It is a well-validated, 44-item, five-option response format instrument which measures agreeableness, conscientiousness, emotional stability, extroversion and openness to experience. Individuals indicate how applicable the descriptive statements are to themselves. (John 1991) There is no clinically relevant cut-offs as it is an individual difference measure.

Illness beliefs were assessed using three scales from the Diabetes Illness Representations Questionnaire (Skinner 2003) which is a slightly revised version of the Illness Perceptions Questionnaire. (Weinman 1996) Beliefs about the cause of diabetes were assessed using the 10-item cause scale. Beliefs about the duration of
diabetes were assessed using the four-item timeline scale. Beliefs about the consequences of diabetes were assessed along two dimensions: seriousness or threat of diabetes to health which consisted of four items, and the perceived impact of diabetes on day-to-day functioning which consisted of six items. For all three scales, a five-option response format from ‘strongly agree’ to ‘strongly disagree’ was used. The instructions were also revised to ask individuals what they generally thought about type 2 diabetes.

7.3 Analysis
Questionnaire data was entered manually into a database. The standardized health interview data was entered into a separate database and the two databases were then merged. Because of problems with recording the individuals’ study number on the questionnaires, a number of questionnaires could not be linked to the results of the standardized health assessment. Therefore where data are reported that combines data from the health assessment and the questionnaire, the number of individuals in the analysis is substantially reduced. Gender differences, differences between ethnic groups and family history were tested using an independent t-test. Correlations were assessed using the Pearson’s product moment coefficient, with missing data excluded pair wise. For categorical variables, comparison was conducted using the chi-squared test. Because of the large sample size and number of tests being performed, the criteria for significance was increased to $p<0.001$ for two tailed tests.

7.4 Results
7.4.1 Sample characteristics
Questionnaires were given to 1339 individuals, of which 30 were returned unanswered, 40 had no identification numbers, and 40 had duplicated identification numbers (excluding 80 booklets). Therefore 150 questionnaires could not be linked with the standardized health assessments. Thus 1189 questionnaires were linked to data from the standardized health assessments.
7.4.2 Anxiety
Table 7.1 shows the anxiety scores separated into ethnic and gender groups. Individuals reported little to moderate amounts of anxiety at screening (mean 35.2; SD = 11.6) with females reporting slightly more anxiety than males (females 35.8, SD = 12.0; males 32.8, SD = 11.2; t = 2.96; p<0.001) However this effect was not significant when controlled for emotional stability (which was correlated with state anxiety r = -0.45; n = 930; p<0.001), with females describing themselves as less emotionally stable than males (t = 4.49; Degrees of freedom [dof] = 577; p<0.001). There was no significant effect of family history of diabetes, ethnic group or recruitment method on anxiety.
Table 7.1 Demographics and levels of anxiety in individuals completing the questionnaires

<table>
<thead>
<tr>
<th></th>
<th>Linked samples</th>
<th>Male (54%)</th>
<th>Female (46%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>75%</td>
<td>71%</td>
</tr>
<tr>
<td>Anxiety</td>
<td>34.9 ± 12.4</td>
<td>34.0 ± 11.8</td>
<td>35.6 ± 13.0</td>
</tr>
<tr>
<td>Age (Years)</td>
<td>60.5 ± 9.9</td>
<td>61.8 ± 9.7</td>
<td>59.6 ± 9.9</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>28.5 ± 5.6</td>
<td>28.3 ± 4.4</td>
<td>28.7 ± 6.4</td>
</tr>
<tr>
<td>BP (mmHg)</td>
<td>134 ± 25 / 80 + 11</td>
<td>139 ± 21 / 83 + 12</td>
<td>131 ± 23 / 78 + 12</td>
</tr>
<tr>
<td>Total cholesterol (mmol/l)</td>
<td>5.4 ± 1.2</td>
<td>5.3 ± 1.2</td>
<td>5.5 ± 1.2</td>
</tr>
<tr>
<td>HDL (mmol/l)</td>
<td>1.4 ± 0.5</td>
<td>1.3 ± 1.6</td>
<td>1.5 ± 0.5</td>
</tr>
<tr>
<td>Relative with diabetes (%)</td>
<td>37</td>
<td>31</td>
<td>42</td>
</tr>
</tbody>
</table>

White European

|                      |                | 21%        | 27%          | 18%          |
|                      |                |            |              |              |
| Anxiety              | 36.4 ± 13.9    | 38.6 ± 15.8| 33.8 ± 11.2  |
| Age (Years)          | 51.2 ± 11.2    | 52.8 ± 11.8| 48.9 ± 10.1  |
| BMI (kg/m²)          | 26.9 ± 4.4     | 26.4 ± 3.3 | 27.6 ± 5.4   |
| BP (mmHg)            | 128 ± 21 / 80 + 11 | 133 ± 19 / 83 + 11 | 124 ± 21 / 77 + 11 |
| Total cholesterol (mmol/l) | 5.1 ± 0.9 | 5.0 ± 0.9  | 5.1 ± 0.9  |
| HDL (mmol/l)         | 1.2 ± 0.4      | 1.1 ± 0.3  | 1.4 ± 0.4   |
| Relative with diabetes (%) | 70          | 66         | 74          |

South Asian

(any discrepancies are due to missing data)
7.4.3 Illness beliefs

Table 7.2 shows the responses for the 10 causal items, the four serious items, and items with scale scores for the duration and impact scales. These were combined into three categories (‘strongly agree’ and ‘agree’ combined into ‘agree’ and ‘strongly disagree’ and disagree’ combined into ‘disagree’). Over 60% agreed that diabetes was caused by a person’s diet and was hereditary, but a substantial number of individuals (23% and 26% respectively) did not agree that these factors caused diabetes. There was a significant correlation between the number of first-degree relatives with diabetes and the level of agreement that diabetes was hereditary ($r = 0.22, p<0.001$)

Males were more likely to agree that germs ($t = 4.41$, dof 586; $p<0.001$), pollution ($t = 3.41$, dof 5.87, $p<0.001$) and their own behaviour ($t = 3.49$, dof 588, $p<0.001$) caused diabetes, compared with females.

South Asian individuals were more likely than White Europeans to agree that diabetes was hereditary ($t = 3.59$, $p<0.001$), caused by poor medical care ($t = 4.11$, $p< 0.001$) and that a person's state of mind was a major factor in causing diabetes ($t = 3.691$, $p<0.001$). Those who had a first-degree relative with diabetes, were more likely to agree that diabetes was hereditary ($t = 3.22$, $p<0.001$). There was no significant association between individuals’ causal beliefs, their anxiety levels or emotional stability.

When looking at beliefs about the duration of diabetes, 21% did not agree that diabetes was a permanent chronic condition you had for the rest of your life. White Europeans were more likely than South Asians to agree that diabetes was chronic condition ($t = 3.38$, $p<0.001$). Those individuals who had both a sibling and a parent with diabetes were more likely to agree that diabetes was a permanent condition ($t = 3.10$, $p< 0.001$). Belief that diabetes was a chronic condition was not significantly correlated with anxiety or emotional stability.
Table 7.2 Percentage of individuals agreeing with cause, duration and consequences belief items

<table>
<thead>
<tr>
<th>Illness belief item</th>
<th>% agree</th>
<th>% uncertain</th>
<th>% disagree</th>
<th>% no response</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Caused by</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Germ or virus</td>
<td>10</td>
<td>23</td>
<td>53</td>
<td>14</td>
</tr>
<tr>
<td>Diet plays a major part</td>
<td>64</td>
<td>15</td>
<td>8</td>
<td>13</td>
</tr>
<tr>
<td>Pollution of the environment</td>
<td>9</td>
<td>29</td>
<td>47</td>
<td>15</td>
</tr>
<tr>
<td>Hereditary (runs in families)</td>
<td>61</td>
<td>19</td>
<td>7</td>
<td>13</td>
</tr>
<tr>
<td>Just by chance</td>
<td>21</td>
<td>33</td>
<td>33</td>
<td>15</td>
</tr>
<tr>
<td>Stress is a major factor</td>
<td>30</td>
<td>38</td>
<td>17</td>
<td>15</td>
</tr>
<tr>
<td>Largely as a result of own behaviour</td>
<td>23</td>
<td>35</td>
<td>29</td>
<td>14</td>
</tr>
<tr>
<td>Other people played a large role</td>
<td>7</td>
<td>26</td>
<td>53</td>
<td>14</td>
</tr>
<tr>
<td>Poor medical care</td>
<td>11</td>
<td>26</td>
<td>49</td>
<td>15</td>
</tr>
<tr>
<td>Person’s state of mind plays a major part</td>
<td>14</td>
<td>32</td>
<td>40</td>
<td>14</td>
</tr>
<tr>
<td><strong>Duration</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>You have diabetes for the rest of your life</td>
<td>*52</td>
<td>*24</td>
<td>*9</td>
<td>18%</td>
</tr>
<tr>
<td>* the mean item response of the scale was calculated, then converted into three categories to generate percentage</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Impact</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes has a major impact</td>
<td>*52</td>
<td>*19</td>
<td>*14</td>
<td>15</td>
</tr>
<tr>
<td>Diabetes is a serious threat to a person’s health</td>
<td>59</td>
<td>16</td>
<td>10</td>
<td>15</td>
</tr>
<tr>
<td>A person with diabetes has a shorter life</td>
<td>19</td>
<td>34</td>
<td>32</td>
<td>15</td>
</tr>
<tr>
<td>Type 2 diabetes is only a minor problem</td>
<td>15</td>
<td>26</td>
<td>47</td>
<td>15</td>
</tr>
<tr>
<td>People with type 2 diabetes usually get complications</td>
<td>31</td>
<td>40</td>
<td>13</td>
<td>16</td>
</tr>
</tbody>
</table>
The impact scale score indicated that only 38% agreed that diabetes would have negative impact on their life, with 30% actively disagreeing that diabetes would have a negative impact on their life. Males reported that diabetes would have a greater impact than females. (t = 3.47, dof 567, p< 0.001). Beliefs about the impact of diabetes were not related to ethnicity, recruitment method, age, family history of diabetes, anxiety at screening or emotional stability.

The seriousness scale had very poor internal consistency so the items were analysed separately. Although 59% of the sample agreed that diabetes was serious and 47% disagreed it was a minor problem, 31% agreed that people with diabetes usually developed complications and only 19% agreed that it would shorten their life. Males were more likely to agree that diabetes would shorten their life compared with females. (t = 4.15, p< 0.001) There were no significant associations with effects of ethnicity, age, recruitment method, family history of diabetes, state anxiety or emotional stability.

The 12% (n = 155) of individuals who agreed with these three items

- diabetes was serious
- diabetes can shorten life and
- diabetes can cause complications

were more anxious than those who did not agree with these items. (t = 1.7, dof 947, p< 0.05) However, when this, along with demographic variables, family history of diabetes and personality was entered into a stepwise multiple regression, emotional stability was the only significant predictor of anxiety at screening accounting for 25% of the variance in anxiety. (t = 9.98, p<0.001).
7.5 Discussion

One of the major concerns that has needed addressing around screening for type 2 diabetes is the possible potential for negative psychological consequences of screening. Previous work has indicated that anxiety levels shortly after screening were low, but suggested they may be slightly elevated at the time of screening. (Adriansee 2002, Ludvigsson 2002, Farmer 2003). This same work also reported only very slightly elevated anxiety with a mean of 35.2. Given that previous studies have identified a normative score of 25, and a clinically significant score of 42 (Marteau 1992), the data reported here indicates a slight increase in anxiety, that does not reach clinical relevance.

Farmer (Farmer 2003) also found equivalent rates of anxiety of 34.5 (95% CI 33.4 - 35.6) to those in this study, indicating the robustness of these results. Furthermore, the mean levels of reported anxiety symptoms in this population are lower than the mean reported by individuals attending for a standard health check at their general practitioner. (mean anxiety 36.4; 95% CI 32.9-39.9) (Qureshi 2001)

This indicates that there appears to be little, if any, impact of screening for type 2 diabetes on the anxiety level of an individual. Low levels of anxiety seen in earlier studies are not explained by recovery of mood post-screening, rather this is the ongoing level of patient anxiety.

The low levels of anxiety found in this and previous studies would seem surprising given the concern over the negative impact of screening. One factor that may explain these findings is the discrepancy between health-care professionals’ beliefs about diabetes and those of the general population. Previous studies have documented the fact that many offspring of people with diabetes do not perceive themselves to be at risk of developing diabetes. (Pierce 2001) Even following an education programme, 41% of offspring of people with diabetes felt their risk of developing diabetes was low. (Pierce 2000)

In this study, although over 60% agreed that diabetes was serious, only half agreed that you had it for the rest of your life and less than 20% agreed that it would shorten their life. This compares with data from the offspring of people with
diabetes, where 35% were aware of a link between diabetes and hardening and narrowing of the arteries. (Pierce 2001)

In this study, beliefs did not seem to differ across gender, ethnic background or whether there was a family history of diabetes. In contrast data from the Netherlands reported that screen-detected patients who had a family history of diabetes reported it to be more serious than those without a family history. However, this Dutch study may simply reflect an information-seeking response to having been given a diagnosis of diabetes. (Adriaanse 2003)

The lack of a difference between people who have familial exposure to diabetes and those who have not, is in line with previous studies showing that significant numbers of young people with diabetes and their parents, do not agree that it is a serious or chronic condition. (John 1991, Skinner 2003) This would suggest that people may not display anxiety as they do not feel there is something to be worried about.

The lack of association between emotional stability and illness beliefs is more interesting as, in individuals with an illness, this dimension is usually associated with more negative views about their condition (Skinner 2002). In this study the result could be due to the method of recruitment. Individuals either self-referred to attend for screening, or responded to a letter from their GP. There was a strong association between emotional stability and reported anxiety in the sample. It may be that personality dimensions may only work to influence illness beliefs once a diagnosis is made. It has already been suggested that there may be differences in the way conscientiousness acts to influence health behaviour when looking at illness-prevention behaviour vs. illness-management behaviour. (Skinner 2002) Therefore, it may be possible that emotional stability will influence illness specific beliefs only once a diagnosis has been made and the issue has greater importance to the individual.

There are some weaknesses to this study. Participation relied on individuals being pro-active in responding to an invitation letter from their GP, or responding to local media awareness activities. This population may therefore not be representative of
the local population. For example, we cannot be sure if people with more negative beliefs about diabetes, or more anxious individuals, would be more likely to attend for screening to address their fear, or whether they would act to avoid confronting these worries by not participating.

There is also the problem of the reliance of self-report questionnaire data, presented only in English, for this ethnically diverse population. The decision to only use English versions was based from experience of the team in previous research, that individuals are very unlikely to be able to read text in their native language if they cannot read English. The option to provide a translator to verbally administer the questionnaires was also discounted because of the cost, and the need to consider how differential administration would affect results. Therefore individuals were asked not to respond to any questions they felt they did not understand. This process did not allow for any effect that different cultural contexts would put on the interpretation of questions.

The result of this study, which was in an ethnically mixed population, replicated that of previous studies, indicating that screening for diabetes does not seem to induce any significant anxiety. Although bivariate analysis did indicate that those individuals who perceived diabetes to be serious, life shortening and resulted in complications had higher anxiety scores, the personality trait of emotional stability was the strongest predictor of anxiety.
Chapter 8

Final Strategy on how to screen for diabetes

8.1 Introduction
This study was designed to compare different methods of screening for type 2 diabetes. Overall 3515 individuals, aged 25-75 years, of South Asian or White European origin, were screened for abnormal glucose tolerance using different methods, including the gold standard diagnostic OGTT. The performance of other screening methods can be accurately determined. These different methods have been compared and a strategy on how to screen for diabetes has been devised.

8.2 Diabetes Risk Scores
Diabetes Risk Scores (DRS) have been advocated as non-invasive tools in screening for type 2 diabetes. (Griffin 2000, Lindstrom 2003) We have tested two diabetes risk scores (Cambridge DRS and Finnish DRS).

8.2.1 Cambridge DRS
The Cambridge DRS involves seven risk factors entered into a mathematical model. (Griffin 2000) We were unable to reproduce the published performance of the Cambridge DRS in detecting diabetes. This was calculated for 3095 individuals screened in the STAR study. In White Europeans sensitivity was 89.4% but specificity was only 32.8%. In South Asians to achieve a sensitivity close to 90% the specificity decreases to under 20%.

8.2.2 Finnish DRS
The Finnish DRS is also based on seven risk factors. (Lindstrom 2003) These differ to those used in the Cambridge DRS; age, BMI, waist circumference, use of blood pressure medication, history of high blood glucose, physical activity, and daily consumption of vegetables, fruit or berries.

The Finnish DRS questionnaire was completed by 2382 individuals, of whom 36.6% (869/2382) were South Asian and 59.9% (1422/2382) were White European. The prevalence of diabetes in those completing the questionnaire was 6.9% overall;
10.5% (91/869) in South Asians and 4.9% (69/1422) in White Europeans. The AUC for the Finnish DRS was 0.48 in South Asians and 0.43 for White Europeans.

The authors of the Finnish DRS suggested a cut-point of nine, as the threshold at which there was no need for further screening. We have been unable to reproduce this performance, even after modifying the FDRS (to include family history) and adjusting the age, waist circumference and BMI for ethnicity. The AUC in South Asians and White Europeans indicate the Finnish DRS does not have a major role in strategies used to identify people with diabetes. The FDRS cannot be recommended as it will not distinguish those who do and those who do not have diabetes.

8.3 Risk Factors

In White Europeans the risk factors with the greatest contribution to diabetes are obesity (BMI ≥ 30kg/m²) and a previous diagnosis of IGT or IFG. However due to the low prevalence (1.3%) of previously diagnosed IGT or IFG, the usefulness of this particular risk factor is limited. The sensitivity of either obesity or hypertension as the first screening tool is 85.7% with a specificity of 39.8%. However because of the high odds ratio of developing diabetes with a previous diagnosis of IGT or IFG, this could be included in a screening strategy.

In South Asians a BMI ≥ 25kg/m² or hypertension are significantly associated with diabetes and the sensitivity of either of these being present in 86.2%, with a specificity of 23.3%.

This study found that waist circumference does perform well as a screening tool. However waist circumference is not routinely measured and is not included in the current GMS contract. Waist circumference, which is simple and inexpensive to measure, was included as part of this study, to determine its effectiveness as a screening tool. It could be determined by sending tape measures via the post with clear instructions for individuals to measure their own waist circumference.

The presence of an elevated waist circumference was found to be useful as the first step in a screening programme for diabetes. When the sensitivity is set at 90% then the specificities are at least 31% in White Europeans and range from 16% to 82% in
South Asians. In those aged 40-75 years the cut-off value in White European males is $\geq 93.5\text{cm}$ (31.1% specific) and in females $\geq 86 \text{cm}$. (34.6% specific) The cut-off values in South Asians within the same age range are lower, in males $\geq 86.0 \text{cm}$ and in females $\geq 84 \text{cm}$. When South Asians in the lower age range 25-40 years were studied the specificities are much greater and waist circumference greater. In females a waist circumference of $\geq 96 \text{cm}$ has 82% specificity and in males $\geq 91\text{cm}$ has 53.1% specificity.

When selecting a test to use as the first step in a screening programme, the presence of hypertension or an elevated BMI perform at least as well as the Cambridge DRS, and are much easier to obtain. The waist circumference performs well in the White Europeans and slightly less well in South Asians. However waist circumference is simple and potentially could be used to screen more individuals as it inexpensive and does not need to involve individuals attending the practice or a screening centre. The choice of the first step in a screening strategy would depend on how the practice, primary care trust or organization wanted to proceed.

8.4 Invasive blood tests

Having used a first step to target the invasive blood tests to a smaller cohort of individuals, the optimal choice of blood test varies between ethnic groups. ROC curves were used to test the performance of different blood tests.

This study found that tests perform differently in South Asians and in White Europeans, and therefore cut-points of tests should be different in South Asians to maintain sensitivity and specificity.
8.5 Recommended Strategy

A simple stepwise strategy for screening for diabetes can be recommended. In this study only 7 South Asians in the age range 25-40 years were found to have diabetes. A screening strategy based on 7 individuals would not be robust. The individual steps in the screening process have been described in previous chapters but for the overall recommended strategy only individuals aged 40–75 years have been included.

Algorithm one would be appropriate if a practice chose to use current registers and databases. Whereas, algorithm two could be followed if a practice wanted to screen all individuals (rather than just those who had a risk factor recorded on the computer). A simple 3 step procedure can identify the majority of undiagnosed diabetes.

Algorithms 3 and 4 have the same first step as algorithms 1 and 2 but have just one option for blood testing, that of a FPG. This simplifies the screening process.
Algorithm 1 – Screening individuals aged 40-75 years for diabetes using risk factors

White European

- BP ≥ 140/90 mmHg or on treatment
- or BMI ≥ 30 kg/m²
- or previous diagnosis of IGT or IFG

- FPG ≥ 6.0 mmol/l

  Yes

  OGGT

  - Meets diabetes criteria

    Yes

    Diabetes

  No

  Address risk factors that caused individual to be eligible to be screened

South Asian

- BP ≥ 140/90 mmHg or on treatment
- or BMI ≥ 25 kg/m²
- or previous diagnosis of IGT or IFG

- HbA1c ≥ 6.2%

  Yes

  Meets diabetes criteria

  Yes

  Diabetes

  No
Figure 8.2
Algorithm 2 – Screening individuals aged 40-75 years for diabetes using waist circumference

White European

Males ≥ 94.5 cm
Females ≥ 85.9 cm

FPG ≥ 6.0 mmol/l

OGTT

Meets diabetes criteria

Yes

diabetes

No

South Asian

Males ≥ 86 cm
Females ≥ 84 cm

HbA1c ≥ 6.2%

Yes

No

Address risk factors that caused individual to be eligible to be screened
Figure 8.3
Algorithm 3 – Screening individuals aged 40–75 years for diabetes using risk factors and fasting plasma glucose

White European

BP ≥ 140/90 mmHg or on treatment
or
BMI ≥ 30 kg/m²
or
previous diagnosis of IGT or IFG

South Asian

BP ≥ 140/90 mmHg or on treatment
or
BMI ≥ 25 kg/m²
or
previous diagnosis of IGT or IFG

FPG ≥ 6.0 mmol/l

Yes

OGTT

Meets diabetes criteria

Yes

Diabetes

No

Address risk factors that caused individual to be eligible to be screened

No
Figure 8.4
Algorithm 4 – Screening individuals aged 40-75 years for diabetes using waist circumference and fasting plasma glucose

White European

Males ≥ 94.5 cm
Females ≥ 85.9 cm

South Asian

Males ≥ 86 cm
Females ≥ 84 cm

FPG ≥ 6.0 mmol/l

Yes

No

OGTT

Meets diabetes criteria

Yes

No

Diabetes

Address risk factors that caused individual to be eligible to be screened
8.6 Sensitivity and specificity of screening

Sensitivity and specificity are both important in any screening programme. The overall sensitivity of algorithm 1 is around 76%. The sensitivity of each step is shown in table 8.1.

The overall sensitivity of algorithm 2 is around 80% and is shown in table 8.2. Table 8.3 shows the sensitivity and specificity of the simpler algorithm 3, where risk factor screening is followed by FPG. In South Asians the sensitivity decreases to 70.7% but the specificity increase to 20.5%. The performance of the screening strategy for White Europeans is unchanged as the strategy is the same. However, if the cut-off value for FPG is decreased to 5.4 mmol/l the sensitivity of the strategy increases to over 80% but at the expense of decreasing the specificity.

Table 8.4 demonstrates similar findings for algorithm 4 where waist circumference measurements are followed only by a FPG. South Asians have decreased sensitivity but increased specificity compared to algorithm 2. These figures are altered further if the cut-off value for FPG is decreased to 5.4 mmol/l.

Table 8.1 Sensitivity of algorithm 1

<table>
<thead>
<tr>
<th>Age 40-75 (years)</th>
<th>Risk factor screening</th>
<th>Blood tests</th>
<th>Overall strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sex</td>
<td>Sensitivity %</td>
<td>Specificity %</td>
</tr>
<tr>
<td>White European</td>
<td>Male and female</td>
<td>85.7</td>
<td>66.3</td>
</tr>
<tr>
<td>South Asian</td>
<td>Male and female</td>
<td>86.2</td>
<td>23.3</td>
</tr>
</tbody>
</table>
Table 8.2 Sensitivity of algorithm 2

<table>
<thead>
<tr>
<th>Age 40-75 (Years)</th>
<th>Sex</th>
<th>Waist circumference</th>
<th>Blood tests</th>
<th>Overall strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Sensitivity %</td>
<td>Specificity %</td>
<td>Sensitivity %</td>
</tr>
<tr>
<td>White European</td>
<td>Male</td>
<td>89.1</td>
<td>35.6</td>
<td>90.0</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>89.9</td>
<td>33.1</td>
<td>90.0</td>
</tr>
<tr>
<td>South Asian</td>
<td>Male</td>
<td>90.4</td>
<td>14.6</td>
<td>90.0</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>88.8</td>
<td>28.7</td>
<td>90.0</td>
</tr>
</tbody>
</table>

Table 8.3 Sensitivity of algorithm 3

<table>
<thead>
<tr>
<th>Age 40-75 (years)</th>
<th>Risk factor screening</th>
<th>Blood tests If cut off FPG&gt;6.0</th>
<th>Overall strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sensitivity %</td>
<td>Specificity %</td>
<td>Sensitivity %</td>
</tr>
<tr>
<td>White European</td>
<td>85.7</td>
<td>66.3</td>
<td>90</td>
</tr>
<tr>
<td>South Asian</td>
<td>86.2</td>
<td>23.3</td>
<td>82.0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>White European</th>
<th>Blood tests if cut off FPG&gt;5.4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sensitivity %</td>
</tr>
<tr>
<td>South Asian</td>
<td>86.2</td>
</tr>
</tbody>
</table>
Table 8.4 Sensitivity of algorithm 4

<table>
<thead>
<tr>
<th>Age 40-75 (Years)</th>
<th>Sex</th>
<th>waist circumference</th>
<th>blood tests if cut off FPG&gt;6.0</th>
<th>Overall strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Sensitivity %</td>
<td>Specificity %</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Sensitivity %</td>
<td>Specificity %</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Sensitivity %</td>
<td>Specificity %</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Sensitivity %</td>
<td>Specificity %</td>
</tr>
<tr>
<td>White European</td>
<td>Male</td>
<td>87.5</td>
<td>35.6</td>
<td>93.9</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>89.8</td>
<td>33.1</td>
<td>90.5</td>
</tr>
<tr>
<td>South Asian</td>
<td>Male</td>
<td>90.6</td>
<td>14.6</td>
<td>86.2</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>96.2</td>
<td>28.7</td>
<td>80.0</td>
</tr>
</tbody>
</table>

| White European    | Male| 87.5                | 35.6                          | 95.9             | 57.7             | 83.9 | 20.5 |
|                   | Female| 89.8             | 33.1                          | 95.5             | 71.7             | 85.8 | 23.7 |
| South Asian       | Male| 90.6                | 14.6                          | 93.1             | 57.6             | 84.3 | 8.4  |
|                   | Female| 96.2              | 28.7                          | 96.0             | 71.3             | 92.4 | 20.5 |
The specificity of each step in any screening programme is also important, as this will influence the number of people involved at each step and therefore the cost of screening. We found that just over 61% of patients from the general practices were within the age range 40-75 years. Table 8.5 shows the percentage of individuals needing to proceed to blood tests.

In algorithm 1 61.3% of White Europeans within the age range had one of the risk factors (hypertension, a BMI $\geq 30$ kg/m$^2$ or a previous diagnosis of IGT or IFG) and therefore would need to proceed to have a FPG sample. 10.1% met the cut-off value for FPG and therefore would proceed to an OGTT. In South Asians aged 40-75 years 77.3% have one of the risk factors (hypertension, a BMI $\geq 25$ kg/m$^2$ or a previous diagnosis of IGT or IFG) and need to proceed to a HbA1c. 13.1% meet the cut-off value and would need to proceed to an OGTT.

Table 8.6 shows the implications of numbers of tests that would be required for a typical single handed practice, a typical group practice and in 1000 patients, with different proportions of ethnic patients if algorithm 1 were to be used. The percentage of individuals with risk factors are based on the findings in this study.

In algorithm 2, where the first step involves waist circumference, then 79.3% of South Asians aged 40-75 years and 66.8% of White Europeans would need to progress to blood tests. Only 20.9% of South Asians 40-75 years and 10.5% of White Europeans would need to proceed to an OGTT.
Table 8.5 Percentage of individuals needing to proceed to blood tests for each algorithm when screening for diabetes

<table>
<thead>
<tr>
<th>Algorithm</th>
<th>1 + 3</th>
<th>2 + 4</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40-75 years</td>
<td>% needing to have first blood test</td>
<td>% needing to have OGTT (with different blood tests in ethnic groups)</td>
<td>% needing to have OGTT (with single cut-off FPG ≥ 6.0 mmol/l)</td>
<td>% needing to have OGTT (with single cut-off FPG ≥ 5.4 mmol/l)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White Europeans</td>
<td>61.3</td>
<td>66.8</td>
<td>10.1</td>
<td>10.5</td>
<td>10.1</td>
<td>10.5</td>
<td>23.8</td>
<td>25.5</td>
</tr>
<tr>
<td>South Asians</td>
<td>77.3</td>
<td>79.3</td>
<td>13.1</td>
<td>20.9</td>
<td>13.1</td>
<td>13.3</td>
<td>32.6</td>
<td>32.3</td>
</tr>
</tbody>
</table>
Table 8.6 Expected number of individuals and cost of consumables for each step in a single handed practice, group practice and per 1000 population using algorithm 1.

<table>
<thead>
<tr>
<th></th>
<th>Number of patients</th>
<th>Number within age range</th>
<th>Number with hypertension or elevated BMI and therefore needing blood test</th>
<th>Number needing OGTT</th>
<th>Cost of consumables (£)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single handed practice (30% South Asian)</td>
<td>2500</td>
<td>1525</td>
<td>985</td>
<td>332 need HbA1c</td>
<td>192</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>653 need FPG</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2500</td>
<td>1525</td>
<td>940</td>
<td>33 need HbA1c</td>
<td>158</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>907 need FPG</td>
<td></td>
</tr>
<tr>
<td>Group practice with 5 partners (30% South Asian)</td>
<td>12500</td>
<td>7625</td>
<td>4925</td>
<td>1660 need HbA1c</td>
<td>960</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3265 need FPG</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4925 need HbA1c</td>
<td>790</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4535 need FPG</td>
<td></td>
</tr>
<tr>
<td>Per 1000 White European population</td>
<td>1000</td>
<td>610</td>
<td>373</td>
<td>373 need FPG</td>
<td>62</td>
</tr>
<tr>
<td>Per 1000 South Asian population</td>
<td>1000</td>
<td>610</td>
<td>471</td>
<td>471 need HbA1c</td>
<td>111</td>
</tr>
</tbody>
</table>
8.7 Expected costs of algorithms

Time and expertise would be needed to complete the data base search required to identify all individuals within age range with a documented risk factor. With appropriate software in place this does not need to be difficult or time consuming and could be part of an existing staff members’ job description. No extra cost would necessarily be involved.

For this study, (February 2002-August 2004) the cost of blood tests to be analysed at the laboratory was £2.39 for HbA1c, £2.14 for both FPG and the 2-hour glucose. (unpublished personal communication) These costs do not include the health care professional time involved in taking the extra blood samples or the cost of the 75-g of glucose required for the OGTT. This could be in the form of Lucozade which can be obtained at £0.12 per 100ml. (www.tesco.com) This is under £0.50 per individual OGTT. There are cheaper methods of providing 75-g of glucose, but Lucozade is the simplest and involves least health care professional time. Powdered glucose could be provided and then mixed with water to be ready to consume.

8.8 Implications at a practice level
In an average single handed general practice of 2500 patients just over 60% of patients would fall within age range 40 to 75 years of age. Table 8.6 shows the expected number of individuals who would need each step doing in a typical single handed practice, group practice and per 1000 population, if algorithm one was used.

8.9 Which algorithm is best
Which algorithm is chosen for screening for diabetes could be decided at a practice level and depends on the efficiency of the database already in use. If the data base was accurate and risk factors of blood pressure and BMI were reliably recorded then algorithm 1 may be preferable. However if the database is not robust or data is incomplete then algorithm 2 may be preferable where patients could measure their own waist circumference or opportunistic measurements could be taken when patients attend the surgery. Either algorithm could be used on an opportunistic basis, such that individuals attending the surgery for any reason could have either waist circumference, BMI or BP measured to identify at risk individuals who would
benefit from proceeding to blood tests for diabetes screening. Algorithm 3 and 4 have the same beginning as algorithm 1 and 2, but use only one blood test (FPG) to simplify the strategy.

The cut-off values for blood tests or waist circumference or BMI could be altered at a practice level to achieve different sensitivities and specificities. Tables 8.4 and 8.5 show the difference in sensitivity, specificity and the number of people needing to proceed to an OGTT that decreasing the FPG cut-off would make in.

**8.10 Summary**

This study has tested different screening strategies and found that it is practical, feasible and effective to implement a screening programme for diabetes. Different approaches can be taken in each practice depending on current systems in place in each practice and the desired levels of specificity and sensitivity.
Conclusion

At the beginning of this thesis I outlined the increasing prevalence of type 2 diabetes and the opportunity provided by the time between the onset of the decline of glucose tolerance and the diagnosis of diabetes to identify glucose intolerance early and the potential to intervene to improve long term outcomes. At present there is no national screening programme for diabetes in the United Kingdom and there is controversy and debate with regard to who and how to screen for diabetes.

The literature on different screening methods for diabetes, including how, who and when to screen was reviewed. Although type 2 diabetes does fulfil many of the criteria needed for screening, the optimal methods of screening, cut-off points for tests and screening frequency, particularly in different populations is not clear. The evidence on preventing the progression of prediabetes to diabetes and delaying the onset of complications of diabetes was reviewed. The current best evidence is for interventions that target those individuals at highest risk. Patients at highest risk include those with IGT, targeting them with lifestyle changes including physical activity and dietary factors have been shown to be effective in the Chinese, North American and Finnish populations. Some pharmacological agents have also been shown to be effective. There is no international agreement on the optimal method for screening for prediabetes and diabetes, this is important so that the methods that have been found to be effective in slowing the progression to diabetes and the onset of complications can be targeted to those individual who would benefit most.

In the STAR study individuals with at least one risk factor recorded on the GP database were invited to attend for screening. A standardised health assessment, anthropometric measures and questionnaires were completed. The risk factors, biochemical investigations, questionnaires and risk scores that could potentially be used in screening were studied in both South Asian and White European populations, to determine which methods have the greatest impact when screening for abnormal glucose tolerance.
In the STAR study 3515 individuals attended for screening. The prevalence of diabetes in those aged 40-75 years was 6.5% in South Asians and 4.7% in White Europeans. In the younger South Asians, aged 25-40 years, the prevalence of diabetes was 2.6%. The prevalence of prediabetes is greater and showed a similar pattern with a greater prevalence in South Asians (19.9%) than in White Europeans (15.4%). The STAR study found that systematic screening of patients with at least one risk factor for diabetes identifies people with diabetes with a high prevalence of microvascular and macrovascular complications. South Asians have the same baseline characteristics as White Europeans but at a younger age. Through screening patients are identified earlier in the diabetes disease process, as reflected by a lower FPG at diagnosis compared to conventionally diagnosed patients. In the patients with screen-detected diabetes 73.2% would have benefited from the addition of at least one pharmacological intervention with antihypertensive, lipid lowering or glucose lowering medication using evidence based guidelines.

One of the major concerns that has needed addressing around screening for type 2 diabetes is the potential for negative psychological consequences of screening. This study found that there appears to be little, if any, impact of screening for type 2 diabetes on the anxiety levels of an individual. The reason for this may be that people are not anxious as they do not feel there is something to be worried about. Although over 60% agreed that diabetes was serious, only half agreed that you had it for the rest of your life and less than 20% agreed that it would shorten their life.

From those risk factors for diabetes which are currently recorded by general practitioners we have identified the most important in White Europeans to be a previous diagnosis of IFG or IGT, having a first degree relative with diabetes, a BMI ≥ 30kg/m² and known cerebrovascular or peripheral vascular disease. In South Asians the significant risk factors for undiagnosed type 2 diabetes are hypertension and having a BMI ≥ 25kg/m². As the number of risk factors an individual has increases, the greater the risk for abnormal glucose tolerance. Waist circumference is not routinely measured at present but we have found that individuals with an elevated waist circumference are also at a significantly greater risk of being diagnosed with diabetes or prediabetes.
Having tested different screening methods for diabetes this study found that the presence of either hypertension or increased BMI performs as well as the more complex Cambridge DRS and the self-assessment tool, the Finnish DRS. The BMI cut-points are $\geq 30\text{kg/m}^2$ in White Europeans and $\geq 25\text{kg/m}^2$ in South Asians. If a practice measured waist circumference then this could be used to screen for diabetes. An elevated waist circumference is as effective at targeting those individuals, at high risk of diabetes, as either the Cambridge DRS or the presence of hypertension or an elevated BMI.

A suggested algorithm for identifying those individuals, aged between 40 and 75 years, who would benefit from proceeding to further testing was developed. If a practice chose to use its current data base then the presence of either an elevated BMI or hypertension could be used to screen for diabetes. An alternative first step in screening could be to identify individuals with an elevated waist circumference. Those individuals with an elevated BMI, hypertension or elevated waist circumference could proceed to a more invasive test to diagnose diabetes. The STAR study found that FPG and HbA1c could be used in individuals at risk of diabetes, with different cut-off points in South Asians and White Europeans, to identify those individuals who would benefit from proceeding to an OGTT in order to diagnose diabetes.

The sensitivity of risk scores, risk questionnaires and risk factors are too low to be useful as stand alone screening tools for prediabetes. Whereas it is the specificities of FPG and HbA1c that are too low to make them useful methods in screening for prediabetes. Further work is needed to determine the optimal method of identifying those with prediabetes.

The STAR study has tested different screening strategies and found that is practical, feasible and effective to screen for diabetes. Different approaches can be taken in each practice or primary care trust depending on current systems in place and the desired levels of specificity and sensitivity. The simple and effective stepwise strategies described in this thesis detail the options for screening an at risk multi-ethnic population for diabetes in the United Kingdom in an effective and efficient method.
Appendices

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Case Report Form (includes ethnicity questionnaire, Cambridge DRS, Finnish DRS and standardised health questionnaire) 206
I would like to invite you to participate in a research study that is being conducted across Leicestershire with GP practices and the diabetes team at the Leicester Royal Infirmary. This study is called STAR. Screening Those targeted At Risk.

To be suitable for joining this study you need to have at least one of the following risk factors:

- Known Heart Disease (heart attack/angina) or on Coronary Heart Disease Register
- Hypertension (high blood pressure)
- Current/previous cigarette smoker (last 12 months) (10 cigarettes per day for at least 5 years)
- Suffered from a stroke
- A woman diagnosed with diabetes during pregnancy
- Previous diagnosis of Impaired Glucose Tolerance
- Be overweight
- Father, Mother, Brother or Sister with diabetes

If you would like to take part in this study the team at the Leicester Royal Infirmary will need to do a glucose tolerance test on you. You will also get a general health screen.

I have enclosed an information sheet about the study, which details what would be involved if you take part.

If you would like to take part in the STAR study, please complete and sign the enclosed form and send it back in the pre-paid envelope to the Diabetes Research Team at the Leicester Royal Infirmary.

Many thanks for taking the time to read this information sheet.

Kind Regards

Name of General Practitioner
Screening Targeted to those At Risk

Name: ........................................................................

Address: ....................................................................

........................................................................

........................................................................

Telephone Number: .................................................

Name of GP: ...........................................................

Address of GP Surgery: ............................................

........................................................................

........................................................................

I would / would not like to take part in the STAR study.

Signed: .................................................................
Date: .................................................................

I would prefer to be screened at *Leicester Royal Infirmary/ Leicester General Hospital
*Please delete as necessary

If you are taking part in the STAR Study, please complete the following section and return this form to us in the prepaid envelope provided.
# Volunteer Screening Form

## Ethnic Origin

<table>
<thead>
<tr>
<th>Ethnic Origin</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>White European – Aged 40-75</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indo Asian – Aged 25-75</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Afro-Carribean or Chinese – Aged 25-75</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

## Do you have diabetes?  
- [ ] Yes  
- [ ] No

## Known difficulty taking blood
- [ ] Yes  
- [ ] No

## Known Coronary Heart Disease
- [ ] Yes

## Hypertension (high blood pressure)
- If yes, what is the name of the medication you are taking: 

  _____________________________________________

- [ ] Yes

## High Cholesterol
- [ ] Yes

## Current/previous cigarette smoker (last 12 months)
- (10 cigarettes per day for at least 5 years)
- [ ] Yes

## Suffered from a stroke or heart disease
- [ ] Yes

## Previous diagnosis of Impaired Glucose Tolerance (IGT) or impaired fasting glucose
- [ ] Yes

## Women who were diagnosed with diabetes during pregnancy
- [ ] Yes

## Weight

## Height

## Mother, Father, Brother or Sister with diabetes
- [ ] Yes
Screening Targeted to those At Risk

Early Identification of Diabetes Mellitus

PATIENT INFORMATION SHEET

Version 10. 22nd December 2003

Principle Investigator: Dr Melanie Davies, Consultant Physician,
Diabetes and Endocrinology

You are being invited to take part in a project being undertaken at the
Leicester Royal Infirmary, to screen for early signs of Diabetes. This study is
called STAR. (Screening Those At Risk). Before you decide to take part, it is
important for you to understand what the screening will involve, so please
take time to read this information sheet carefully. If there is any part of this
leaflet that you do not understand or you require further information on
please let us know.
What is the purpose of the screening?

Type 2 diabetes (also known as non-insulin dependent diabetes) is a disease where blood sugar levels (glucose) in the body become uncontrolled due to the pancreas not producing enough insulin and the body not responding to the insulin effectively. Patients who are diagnosed with type 2 diabetes are at risk of suffering with problems associated with the feet, eyes, heart, circulation and kidneys. Past research has shown that a lot of people have type 2 diabetes without knowing that they have the disease. Whilst type 2 diabetes is untreated damage is being caused to the, eyes, heart and feet and other organs. Some people may develop a condition called ‘pre diabetes before they develop type 2 diabetes. This is when the body cannot deal with the sugar (glucose) in the blood correctly but diabetes has NOT yet developed. Research has shown that some people with pre-diabetes go on to develop diabetes. Because of this the health care agencies are looking at the prevention and early detection of type 2 diabetes and pre-diabetes in certain groups of people, who are at risk of developing the disease.

The aim of screening people for pre-diabetes and diabetes is to pick up early signs of type 2 diabetes mellitus and therefore help control the condition to avoid some of the conditions which can arise from having the condition. You have been asked to take part in this study because you are at increased risk of developing both pre-diabetes and type 2 diabetes. Some people are at higher risk than others for developing diabetes because of certain risk factors such as being over weight, a family history of diabetes, history of heart disease, diabetes during pregnancy, high cholesterol, smoking and high blood pressure. You have been asked to join this study because you are above a certain age and have one of the risk factors for diabetes. In some G.P practices we will invite everyone for screening over a certain age even if they don’t have a risk factor. This is so we can find out which people we should be screening in the future, for example those with a risk factor or everyone over a certain age.
What will happen to me if I take part?

If you take part in the study we will ask you to attend either the Leicester Royal Infirmary, your GP surgery, the Leicester General Hospital or the Diabetes Mobile Clinic for a Glucose Tolerance Test (GTT) and other blood tests which help identify related conditions such as high cholesterol. This will take around 2 ½ hours to do and will be in the morning. On the day before your visit, you will need to fast overnight, for at least 8 hours (i.e., no food and only water to drink after midnight) before the next morning.

What is a Glucose Tolerance Test?

A GTT involves drinking a sugary drink (Lucozade) after fasting from midnight and then having your blood sugar levels measured to see how well your body is dealing with the sugar intake. Before you drink the Lucozade drink we will take blood samples from you to check your blood sugar levels, your insulin levels and the level of fats in your blood (cholesterol). Once you have had the Lucozade drink we will take a second blood sample from you after 2 hours. In total we will take about 50 mls of blood (about 10 teaspoons) over 2 hours. These 3 blood samples will be taken from your arm using a syringe and a needle.

24 mls of blood (5 teaspoons) will be taken and stored in our freezer so that we can analyse some samples at a later date. Some of these samples will be used to look at the insulin levels in the blood. Some samples may also be used for future research in pre-diabetes and diabetes. We may also want to do studies in the future to look at the different kinds of genes that are involved in people who have attended for screening. We may wish to use your stored sample for these purposes. Any study that we want to do in the future will have approval from the local ethics committee. Samples may be stored for up to 10 years, however you still own the sample and can ask for it to be destroyed at any time. You can opt out of this part of the study if you want, this will mean that we will take less blood from you.
What else will I have to do?

In between waiting for blood samples to be taken, we will give you a general health check. This will include taking your height, weight, blood pressure, waist and hip measurements. We will also check foot pressures in a selection of people who attend for screening. We will also take a urine sample from you to check how well your kidneys are working. We will also do a heart tracing (an electrocardiogram). We will also ask you about your past medical history, medication that you are taking and your smoking habits. We will also ask you about any exercise that you take, your eating habits and if any of your family have diabetes or heart problems.

We will also give you a questionnaire to fill in about how you have found the screening experience. This questionnaire will take about 30 minutes to complete. This can be done in between having blood samples taken. The questionnaire will contain questions about your health, personality and overall well-being. There are also questions about your beliefs of diabetes and the symptoms of diabetes.

What do I need to do?

If you want to take part in the study we will ask you to sign a consent form the day you come for your glucose tolerance test.

Will there be any side effects?

You may suffer slight discomfort while the blood samples are being taken from your arm and some people do experience bruising after blood samples have been taken.
What happens next?

Your GP will be informed of the results of the glucose tolerance test. If the results of the glucose tolerance test show you have diabetes we will invite you back as part of routine care to have a second oral glucose tolerance test. This is because to diagnose diabetes we need two positive tests on two separate occasions. If this second test confirms the diagnosis of diabetes you will be seen in the Diabetes Clinic. If the test reveals that you have pre-diabetes a management plan will be discussed with your GP. You will not be denied any treatment that the results of the tests suggest you should be given.

Some people who are diagnosed with pre-diabetes will be sent a series of questionnaires (the same ones that will completed when you have your OGTT), after they have had their results. These questionnaires will be used to see if people have different views about pre-diabetes, their lifestyle and diabetes after they have been diagnosed with pre-diabetes. These questionnaires will be at 2, 4 and 8 months following the initial OGTT. We will also select a small sample of people with a ‘normal’ result to send these questionnaires to. We will also send out people with pre-diabetes an information booklet. All people with pre-diabetes will also be invited to attend a group education session about pre-diabetes.

20 people with pre-diabetes and 10 people who have had a normal glucose tolerance result will be randomly selected (a bit like tossing a coin) to take part in interviews with a nurse about how they feel about their OGTT results. These interviews will last about 30 minutes and will be conducted in your home or in the hospital setting (whichever you decide). The interviews will be tape-recorded and you will be asked to sign a separate consent form to take part in this part of the study. All the tapes will be destroyed at the end of the study. It is your decision whether or not you want to take part in this area of the STAR study. If you decide not to your future care will not be affected.
All people with pre-diabetes will be invited to have another OGTT after 1 year to see if they have gone on to develop diabetes. When people come to this appointment they will be asked to complete the questionnaire done at their first OGTT.

After we have measured your skin thickness, we will also carry out a “Bioimpedance” measurement. This involves two electrodes being attached to the foot and the wrist. A very low-grade electrical current is passed between the electrodes and this will let us measure the total water and fat percentage in your body. There are no risks with this and the procedure is not painful in any way. You do not have to take part in this Section of the study if you are contacted after receiving your results.

**What if I am harmed by the study?**
Medical research is covered for mishaps in the same way as for patients undergoing treatment in the NHS i.e compensation is only available is negligence occurs.

**Will I benefit from taking part?**
By having the glucose tolerance test we will be able to identify whether or not you have pre-diabetes or type 2 diabetes. If the blood tests show us you have either of these, it means that we can treat your condition earlier which means that you are reducing your chances of developing the complications of diabetes. You will also be helping us to find out which people we should screen for diabetes in the future. If you are found to have pre-diabetes we will call you back every year for another GTT to see if you have gone on to develop diabetes. We may also ask some people who have had a normal glucose tolerance test to come back for another glucose tolerance test in three years to see if they have gone on to develop diabetes.
What happens if I do not wish to participate in this study or wish to withdraw from the study?
If you do not wish to participate in this study or if you wish to withdraw from the study you may do so without justifying your decision and your future treatment will not be affected.

Will information obtained in the study be confidential?
Only your GP and other members of the research team will need to have access to your medical notes. All information will remain completely confidential. The results of the study may be published in a professional journal, but you will not be identified by name. Your GP will be informed of the results of your GTT, electrocardiogram and your general health check up.

Will I be able to claim travelling expenses?
Yes, you can claim your expenses for traveling from the study team.

If you have any problems, concerns or other questions about the study, please contact the STAR team and ask to speak to one of the Research Nurses on 0116 2586798.

If you have any complaints about the way the investigator has carried out the study, you may contact the UHL complaints department, Leicester Royal Infirmary, Tel: (0116) 258 5416.
Patient Identification Number:  
Date:  

STAR Study

Name:  
Home Address:  

Sex:  Male   Female   Date of Birth:  

Contact Telephone Number  
GP Name/Address:  
Referral Method:  

<table>
<thead>
<tr>
<th>Referral Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>SHIRES/ Roadshow</td>
</tr>
<tr>
<td>Newspaper</td>
</tr>
<tr>
<td>Word of Mouth</td>
</tr>
<tr>
<td>GP Practice</td>
</tr>
<tr>
<td>Other (State)</td>
</tr>
</tbody>
</table>

Occupation:  
Social Class Coding:  Ethnic Origin:  

You will need to have the following things done during the morning

- Fasting blood samples
- Blood Pressure
- Health questionnaire
- Height/Weight
- Hip/waist measurements
- ECG
- 2 hour blood samples

This is due at  

206
Inclusion/Exclusion Criteria

Are patients:

- White European – Aged 40-75: Yes
- Indo Asian – Aged 25-75: Yes
- Afro-Carribean or Chinese – Aged 25-75: Yes

Subjects must have one or more of the following:

- Known CHD: Yes
- Known to be at risk of CHD: Yes
- On a CHD register: Yes
- Hypertension: Yes
- Hypercholesterolaemia: Yes
- Current cigarette smoker (includes those stopped within the last 12 months): Yes
- Ex cigarette smoker (those people who have stopped more than 12 months ago): Yes
- Cerebrovascular disease / peripheral vascular disease: Yes
- Previous diagnosis of IGT or impaired fasting glucose: Yes
- Women with polycystic ovary syndrome with a BMI > 23: Yes
- Women with previous history of gestational diabetes: Yes
- BMI > 25 with a sedentary lifestyle: Yes
- BMI > 30: Yes
- Mother, Father, Brother, Sister with diabetes: Yes

Patients must not have any of the following:

- Diabetes: Yes
- Housebound: Yes
- Terminal Illness: Yes
Patient Identification Number: 

Consent taken: □ Yes

394 mls lucozade: □ Yes Time: ________________

Blood Tests (fasting):
Orange: □ Yes
Brown x 2: □ Yes
Yellow: □ Yes
Red 2.5ml EDTA □ Yes

Blood Tests (120 mins) Time taken: ________________
Yellow: □ Yes
Red 10 ml EDTA □ Yes

Urine Dipstick □ Yes

Result: Negative □ Other □ (please specify)

Blood samples spun □ Orange Stored in rack: ____________
Numbers: _____ _____
Brown: Stored in rack: ____________
Numbers: _____ _
Patient Identification Number: 

**Laboratory Sample – Results**

**Fasting Samples**
- Fasting Insulin: Result _____________________________
- Total Cholesterol: Result _____________________________
- LDL Cholesterol: Result _____________________________
- HDL Cholesterol: Result _____________________________
- Total Chol./HDL Ratio: Result _____________________________
- Triglyceride Concentration: Result _____________________________
- Sodium: Result _____________________________
- Potassium: Result _____________________________
- Urea: Result _____________________________
- Creatinine: Result _____________________________
- Ultra sensitive CRP: Result _____________________________
- HbA1c: Result _____________________________
- Glucose: Result _____________________________

**120 minute sample**
- Glucose: Result _____________________________
- Urine albumin: Result _____________________________
- Urine albumin/creatinine: Ratio _____________________________

**Comments:** Normal [ ] IGT [ ] Diabetes [ ]
<table>
<thead>
<tr>
<th>Patient Identification Number: [<strong>] [</strong>] [<strong>] [</strong>] [__]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Height: [<strong>] [</strong>] m²  Weight: [<strong>] [</strong>] [__] kg</td>
</tr>
<tr>
<td>Calculated BMI: [<strong>] [</strong>] [__] kg/m²</td>
</tr>
<tr>
<td>Waist Measurement: [<strong>] [</strong>] cm  Hip Measurement: [<strong>] [</strong>] cm</td>
</tr>
<tr>
<td>Waist/Hip Ratio: [<strong>] / [</strong>]</td>
</tr>
<tr>
<td>Blood pressure 1: [<strong>] / [</strong>] mmHg</td>
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<tr>
<td>Blood pressure 2: [<strong>] / [</strong>] mmHg</td>
</tr>
<tr>
<td>Blood pressure 3: [<strong>] / [</strong>] mmHg</td>
</tr>
<tr>
<td>Average: BP 2 and 3: [<strong>] / [</strong>] mmHg</td>
</tr>
<tr>
<td>Patient Identification Number:</td>
</tr>
<tr>
<td>------------------------------</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>WHITE:</th>
<th>CHINESE:</th>
</tr>
</thead>
<tbody>
<tr>
<td>White British</td>
<td>Chinese</td>
</tr>
<tr>
<td>White Irish</td>
<td>Any other</td>
</tr>
<tr>
<td>Any other white background</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>MIXED:</th>
<th>BLACK OR BLACK BRITISH:</th>
</tr>
</thead>
<tbody>
<tr>
<td>White and Black Caribbean</td>
<td>Caribbean</td>
</tr>
<tr>
<td>White and Black African</td>
<td>African</td>
</tr>
<tr>
<td>White and Asian</td>
<td>Any other black background</td>
</tr>
<tr>
<td>Any other mixed race</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>ASIAN OR ASIAN BRITISH:</th>
</tr>
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<tbody>
<tr>
<td>Indian</td>
</tr>
<tr>
<td>Pakistani</td>
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<tr>
<td>Bangladeshi</td>
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<tr>
<td>Any other Asian background</td>
</tr>
</tbody>
</table>

12 Lead ECG? Yes

Comments:

Health Questionnaire Completed Yes
Cambridge Diabetes Risk Score

BMI < 25: □ Yes
BMI 25 to 27.49 □ Yes
BMI 27.5 to 29.99 □ Yes
BMI > 30 □ Yes

Number of 1st degree relatives with diabetes: □ □

Parent or sibling with diabetes: □ Yes
Parent and sibling with diabetes □ Yes
Non-smoker □ Yes
Ex-smoker (gave up more than 12 months ago) □ Yes

How Many Per Day? ___________

Current smoker (includes those who gave up within past 12 months) □ Yes
How Many Per Day? ___________

Currently prescribed anti-hypertensive medication? □ Yes
Currently prescribed steroids? □ Yes
STANDARD HEALTH QUESTIONNAIRE

Does the patient have a past history of:

<table>
<thead>
<tr>
<th>Condition</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>MI</td>
<td></td>
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<tr>
<td>Angina</td>
<td></td>
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</tr>
<tr>
<td>Stroke</td>
<td></td>
<td></td>
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<tr>
<td>Angioplasty/CABG</td>
<td></td>
<td></td>
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<tr>
<td>Leg Angioplasty/bypass</td>
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</tbody>
</table>

Does the patient currently take any medication?

- Yes [ ]  - No [x]

If ‘yes’, please enter details below:

<table>
<thead>
<tr>
<th>Name of Medication</th>
<th>Dose</th>
<th>Reason for use</th>
<th>Start date</th>
</tr>
</thead>
<tbody>
<tr>
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</table>

Does the patient have any medical conditions, for which he/she is receiving care/medical advice from your GP or a Hospital Consultant?

- Yes [ ]  - No [x]

If ‘yes’, please enter details on other page.
Details of condition: | How long have you had this condition?
---|---

Does the patient have a family history of diabetes?
Yes [ ] No [ ]
If ‘yes’, please provide details below:

__________________________________________________________________

__________________________________________________________________

Does the patient have a family history of cardiovascular disease?
Yes [ ] No [ ]
If ‘yes’, please provide details below:

__________________________________________________________________

__________________________________________________________________
Finnish Diabetes Risk Score

What is your age?

Below 45 years  
45-54 years  
55-64 years  
Above 64 years  

Do you exercise or exert yourself in your spare time or at work at least 30 minutes on most days?

Yes  
No  

How often do you eat vegetables and fruits or berries?

Everyday  
No everyday  

Have you ever used drugs for high blood pressure?

No  
Yes  

Has a physician or other health care provider ever told you that you have high blood glucose (in a medical check-up, during an illness or pregnancy?)

No  
Yes  

Do any of your family members have diabetes?

No  
Yes  Grandparent, uncle, aunt or cousin (but no parent or own child)  
Yes  Biological father, mother, sibling or own child
Publications related to this thesis

Papers


Abstracts


Jarvis J, Davies MJ, Tringham JR, Skinner TC, Farooqi AM, Mandalia P, Patel H, Khunti K. Baseline characteristics of individuals identified with prediabetes (IGT, IFG or both) through a systematic screening programme. Diabetic Medicine 2005; 22(suppl 2):98.

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Cowie CC, Harris MI, Eberhardt MS. Frequency and determinants of screening for diabetes in the US. *Diabetes* 1994; **17**:1158-1163.


Davies M, Day J. Screening for non-insulin dependent diabetes mellitus: how often should it be performed? *J Med Screening* 1994; **1**:78-81.


Ludvigsson J. Gustafsson-Stolt U, Liss PE, Svensson T. Mothers of children in ABIS, a population-based screening for prediabetes, experience few ethical conflicts and have a positive attitude. *Ann NY Acad Sci* 2002; 958:376-381.


NAVIGATOR Trial Steering Committee: Nateglinide and valsartan in impaired glucose tolerance outcomes research: rationale and design of the NAVIGATOR trial. *Diabetes* 2002; 51:A116.


United Kingdom Prospective Study Group (UKPDS). Tight blood pressure control and risk of macrovascular and microvascular outcomes in people with diabetes: UKPDS 38. *BMJ* 1998; **317**:703-713.


West KM, Ahuja MM, Bennett PH, Czyzyk A, De Acosta OM, Fuller JH et al. The role of circulating glucose and triglyceride concentrations and their interactions with other ‘risk factors’ as determinants of arterial disease in nine diabetic population samples from the WHO Multinational Study. *Diabetes Care* 1983; **6**:361-369.


