Progression to diabetes: 5 year follow-up of the Northland Diabetes Screening and Cardiovascular risk assessment pilot

A thesis presented to fulfil requirements for the degree of

Master

of

Public Health

at Massey University, Wellington, New Zealand.

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2013

Abstract

Aim: The primary aim was to determine the effect the *Northland Diabetes Screening and Cardiovascular risk assessment pilot* had on the progression from a normal glucose test (NGT) at baseline to diabetes.

Method: Patients from a single practice (Maori = 1509, Non-Maori = 619) who were invited onto the pilot with NGT at baseline were retrospectively followed up for 7 years. Results for Pilot (PG) (Maori = 336, Non-Maori 255) and Non-Pilot (NPG) groups (Maori = 537, Non-Maori = 204) were compared on progression to diabetes, impaired glucose tolerance (IGT), all-cause mortality.

Results for Maori: There were 10 incidence cases of diabetes, 20 IGT and 18 deaths from any-cause during a median duration of follow-up of 6.4 years in the PG compared with 22 incidence cases of diabetes, 23 IGT and 30 deaths from any-cause in the NPG followed for a median duration of 4.3 years. Participation in the pilot was associated with a statistically significant protective effect on progression to diabetes (Age-adjusted rate ratio 0.44(95% CI 0.2156, 0.912) and all-cause mortality (Age-adjusted rate ratio 0.49 (95% CI 0.2771, 0.8626).

Results for Non-Maori: There were 12 incidence cases of diabetes, 13 IGT diagnoses and 19 deaths from any-cause during a median duration of follow-up of 6.2 years in the PG compared with 9/204 diabetes incidence cases, 11 IGT and 13 deaths from any-cause in the NPG followed for a median duration of 4.7 years. There was no statistically significant association with participation in the pilot on progression to diabetes, IGT or all-cause mortality.

Conclusion: The protective effect for Maori patients in the pilot on progression to diabetes was either because they had inherently lower risk than the non-pilot group or potentially because their baseline results were interpreted in the context of their CVD risk. The effectiveness of CVDRA programmes on reducing incidence diabetes should be formally assessed. Research focusing on risk reduction for Maori aged 35-49 years is recommended.

Acknowledgements

Setting the aims and objectives for this project involved discussions with the pilot's stakeholders and health officials in particular Dr Shane Cross, Chris Farelly, Kim Tito, Dr Nick Chamberlain, and Dr Sandy Dawson; as well as the researchers two supervisors Dr Christine Van Dalen and Associate Professor Barry Borman, both of the Centre for Public Health Research, Massey University. From these discussions along with guidance from the researcher's two supervisors, the study design and the aims and objectives were set.

Staff at the general practice provided advice and support during data extraction. The data management, analyses, interpretation, and selection of topics have all been done by the researcher.

Dr Christine Van Dalen and Associate Professor Barry Borman have provided advice and constructive feedback and edits through earlier versions and this report, particularly aimed at improving communication of ideas and information as well as the overall flow of the report.

This research is a follow-up study on the *Northland Diabetes Screening and Cardiovascular Risk Assessment Pilot* (2004-2007). Acknowledgement of previous work related to the pilot design and implementation goes to a team of Northland authorities led by Dr Nick Chamberlain.

Research presented from the pilot evaluation based on the work of the researcher, Bronwyn White, has been previously credited to meet research requirements for a Post-Graduate Diploma in Public Health at Massey University in 2008.

There was no formal funding for this follow-up study however the former Tihewa Mauriora PHO assisted by funding two return flights for the researcher (based in Nelson) to visit Northland and practice staff provided much appreciated hospitality and transport for the researcher within Northland during the visits.

Ethical approval was granted for this study by the Northern Y Regional Ethics Committee on August 2011 Reference NTY/11EXP/006 for this study.

I'd like thank all the people who have contributed to this follow-up study. A very special thank-you goes to Shane and Alyson Cross, Nick Chamberlain, Christine Van Dalen and Barry Borman.

I'd also like to thank all my family and friends for your ongoing support and tireless patience with me. I especially wish to thank Anna and Mary Hansen for always believing in me.

Bronwyn White

Table of Contents

List of Tables

List of Figures

Chapter 1 Introduction

1.1 Background

Diabetes is a chronic disease that occurs when the body cannot produce enough of the hormone insulin or, it cannot effectively use the insulin it produces (World Health Organisation (WHO), 2011). Insulin is required to absorb glucose from the blood into the body's cells. When insulin levels are low, or when the cells do not respond appropriately to insulin, blood glucose levels rise. Prolonged raised blood glucose – or hyperglycaemia – is damaging to tissues over time and can lead to life threatening health issues of the heart, blood vessels, eyes, kidneys, and nerves (International Diabetes Federation (IDF), 2011).

There are three main types of diabetes: type 1 diabetes, type 2 diabetes, and gestational diabetes. Type 1 diabetes usually occurs in children and younger adults. Glucose builds up in the blood because the body does not produce enough insulin. Symptoms of type 1 diabetes are excessive excretion of urine, thirst, constant hunger, weight loss, vision changes and fatigue and these symptoms usually occur acutely. This sudden onset of symptoms leads to a rapid diagnosis (IDF, 2011).

Type 2 diabetes is the most common type of diabetes, estimated to account for 90 to 95% of all diabetes (Gonzalez, Johansson, Wallander, & Rodriguez, 2009; American Diabetes Association (ADA), 2010), and is associated with increasing age and obesity (Ministry of Health (MoH), 2012a). Type 2 diabetes is different to Type 1 diabetes in that glucose builds up in the blood not because it does not produce enough insulin, as in Type 1 diabetes, but because the body cannot effectively use the insulin it produces (IDF, 2011).

Hyperglycaemia (raised blood sugar) develops gradually and is often not severe enough for the person to notice any of the classic symptoms (ADA, 2010). People with type 2 diabetes may only complain of tiredness and lethargy, symptoms that can just as easily be explained by the stresses of everyday life (National Health Priority Action Council (NHPAC), 2006). This lack of specific and acute symptoms partly explains why a person may not be

diagnosed for several years after the onset of the disease (WHO, 2011) during which time the effects of prolonged hyperglycaemia begin to make a silent and sinister attack on vulnerable tissues in the body.

Gestational diabetes is the type of diabetes that occurs during pregnancy. The body is unable to make or use insulin the body needs for pregnancy. This form of diabetes usually, but not always, goes away after the baby is born (MoH, 2012a). Gestational diabetes is a risk factor for developing type 2 diabetes (IDF, 2011).

Prevention of type 2 diabetes is the broad theme of this research. The main causes of susceptibility to type 2 diabetes are not fully understood but fall into two main interacting categories – genetic and environmental (Nolan, Damm & Prentki, 2011; Echouffo-Tcheugui, Ali, Griffen, & Narayan, 2011; Coppell et al, 2009) over an individual's life-course (IDF, 2011; Mayer-Davis, Dabelea, Lawrence, Meigs, & Teff, 2011). While increasing age and family history are non-modifiable risk factors for diabetes, the presence of genetic susceptibility does not make diabetes inevitable (Mayer-Davis et al.,2011; Uusitupa et al., 2011). There are risk factors that can be modified to prevent diabetes.

The key modifiable risk factors for type 2 diabetes are generated by having a greater fuel intake (or over-nutrition) than fuel output (such as low levels of physical activity). When the body is functioning normally, people who have a greater fuel intake than fuel output store excess fuel in subcutaneous adipose tissue. The body can maintain a normal blood glucose range and skeletal muscle, the liver and heart are not damaged. By comparison, in a person susceptible to type 2 diabetes, the excess fuel is stored in visceral adipose tissue. Visceral adipose storage means the excess fuel is stored in the heart, skeletal muscle, liver, and islet β-cells in the pancreas causing nutrient-induced damage to these tissues (Nolan et al., 2011) leading increased liver glucose production, insulin resistance and subsequently chronic hyperglycaemia (Echouffo-Tcheugui et al., 2011).

Chronic hyperglycaemia leads to cardiovascular disease, stroke, kidney disease, lower limb ulcers and retinal damage, with an estimated 70% of people with type 2 diabetes dying from cardiovascular causes (Laasko, 2001).

Preceding a clear diagnosis of diabetes are states where glucose levels are abnormal but have not reached the threshold for diabetes. These are impaired fasting glucose or impaired glucose tolerance, commonly collectively referred to as "pre-diabetes" (Fonseca, 2009).

Evidence that progression to type 2 diabetes can be delayed or prevented with lifestyle interventions in those with pre-diabetes (Pan et al., 1997; Tuomilehto, et al., 2001; Knowler, et al., 2002; Kosaka et al., 2005; Ramachandran et al., 2006) is now universally accepted (ADA, NID, AKD, 2003; Echouffo-Tcheugui et al., 2011). Applying this evidence into practice requires a method to identify individuals that have pre-diabetes.

Screening is a public health tool that essentially identifies those who are unlikely to develop the disease from those most likely to either have the disease, or, have an early indicator of elevated risk of progressing to the disease (National Screening Unit (NSU), 2012). An intervention is then offered to those who either have the disease, or an early predictor of disease.

In New Zealand blood glucose assessments are included in cardiovascular disease risk assessments (CVDRA) and CVDRAs are recommended for people with a high risk of progressing to diabetes. Detection and recording of diabetes and implementing CVRDAs programmes have been progressively encouraged and formalised since 2001 to the current day (PriceWaterhouse Coopers (PWC), 2001; MoH, 2003; MoH, 2007, MoH, 2012b). The main benefit of cardiovascular disease risk assessments (CVDRA) for patients is to enable lifestyle choices and for treatment options to be established early (BPAC NZ, 2012). Healthy lifestyle choices reduce modifiable risk factors for cardiovascular disease such as over nutrition and reduced physical activity and these are also risk factors for Type 2 diabetes.

This thesis explores the effect of participating in the *Northland Diabetes Screening and Cardiovascular risk assessment pilot* that was implemented from 2004 to 2007. The researcher expected that participating in the pilot would have an effect on progression to diabetes because when people were identified with increased risk of diabetes and cardiovascular disease (CVD) there would be an increase in primary care discussions on lifestyle behaviours in the

context of their total CVD risk. Those screened for diabetes independently of the pilot were unlikely to have had their glucose results interpreted in the context of their CVD risk until a later date (July 1st , 2008) when the formal CVDRA programmes were rolled out (Te Tai Tokerau PHO, 2011). It was hypothesised that for those whose baseline blood glucose test was normal, progression to diabetes, impaired glucose tolerance, and all-cause mortality would be different for pilot participants compared with non-pilot participants.

The key research questions were:

1. Did participating in the *Northland Diabetes Screening and Cardiovascular risk assessment pilot* affect progression to diabetes?
2. Is data from general practice information systems suitable to measure diabetes incidence rates and other useful health planning and monitoring measures?

There are two main reasons why these questions were asked.

First, since the role out of CVDRA programmes there has been little evidence showing whether this commitment to reducing risk has had any impact on slowing or preventing progression to diabetes - beyond describing a general increase in practice diabetes prevalence (Waldron and Horsburg, 2009). "Prevalence" is the term to measure the number of people with the disease in a defined population at a point or period in time.

Prevalence estimates are needed to plan and resource services appropriately, monitor performance of interventions and inform quality of care programmes (Thornley et al., 2011; Dannaei et al., 2011). However, prevalence of diabetes can increase because the population is ageing and because of improvements in earlier detection and quality of care for people living with diabetes. For example, changes from higher mortality and higher fertility to lower mortality and lower fertility have led to populations transitioning in age structure. Statistics New Zealand (2006) has estimated that the proportion of people aged 65 years and over would make up about 25% of New Zealand's population by the late 2030's compared with 12% in 2005. Older people have a higher prevalence of diabetes therefore increases to the proportion of the population that is older would contribute to increasing prevalence of diabetes (Magliano et al., 2009). Also, increasing awareness of the importance for early detection

of diabetes is likely to bring forward the date that people are diagnosed with diabetes (Rahman, Simmons, Hennings, Wareham & Griffin, 2012). Magliano et al., (2009) also stated that improvements in risk reduction – especially cardiovascular risk reductions should mean people live longer with diabetes. The combination of earlier diagnoses of diabetes and reductions in mortality in those with diagnosed diabetes would contribute to increasing diabetes prevalence estimates. Therefore diabetes prevalence may not give a fair account of whether existing resources aimed to reduce risk have had an effect on preventing type 2 diabetes.

Second, general practice should hold repeated measures of blood glucose assessments and recorded diabetes diagnoses in their general practice information systems. The frequency which rescreening should occur is outlined in the NZ Clinical Guidelines and is determined by the result of these assessments (New Zealand Guidelines Group (NZGG), 2012). The New Zealand government expects improvements in detecting diabetes and recording and management of other important cardiovascular risk factors from District Heath Boards, Primary Health Organisations, and Primary Care providers (MoH, 2012b). Because CVDRA and diabetes screening is recommended for people with higher risk of diabetes compared to the general adult population, general practice data could be a potentially viable source of routinely collected blood glucose levels of high-risk, non-diabetic individuals from which to estimate progression to diabetes.

By using routinely collected data in general practice this paper can explore whether this source could be used to determine if participating in the *Northland Diabetes Screening and Cardiovascular risk assessment pilot* has had an effect on progression to type 2 diabetes. However measuring progression using this data source potentially poses challenges which will be explored in this thesis.

The layout of this report closely follows that of a scientific report. Following the introduction (Chapter 1), Chapter 2, the literature review, covers a range of topics beginning with key terms that will be encountered throughout the

thesis. The key terms purposefully focus on methodological issues and are illustrated with examples of published literature.

The literature review then introduces Diabetes in a New Zealand context followed by a specific section on research into estimating diabetes prevalence and incidence. A brief section discusses the cost of diabetes followed by an explanation of disease control that demonstrates where diabetes screening fits in the broader strategies. The final section of the literature review takes a closer look at the limitations of screening studies and measuring diabetes incidence.

Chapter 3 describes the context for the current research is set and presents the aims and objectives and the full methods.

In chapter 4 the results are presented broadly in three parts. The first describes the characteristics of the study participants and their baseline results. The second section focuses on a subgroup analyses specifically on progression to diabetes, impaired glucose tolerance (IGT) and all-cause mortality and rescreening. The third section gives the analyses of the pooled data which presents age specific rates and estimates numbers need to screen and undiagnosed diabetes.

In chapter 5 the results are discussed with respect to comparisons with other published data and the impact of bias on the results. The potential implications of the study for Maori, measuring diabetes incidence from general practice data and resource allocation are put forward. Recommendations are also made for future action on reducing the incidence of type 2 diabetes that health authorities could consider.

Chapter 2 Literature review

2.1 Defining the terms

2.1.1 Diagnostic criteria

About 100 years ago methods were developed to measure glucose in the blood and this became the method by which a diagnosis of diabetes was made (Sacks, 2011). Since 1965 the definitions and diagnostic criteria have been regularly revised as new information has become available. Fasting glucose tests (Fasting plasma glucose and Oral Glucose Tolerance tests) have been the main diagnostic tool (see WHO 2006 diagnostic criteria in Appendix 1).

The appropriate choice of test for patients is an important consideration not only because of barriers associated with the inconvenience of the fasting requirement for the test and the difficulty in having the test done in the morning. It is also because of the range of biological, pre-analytical, or analytical factors which lead to variation in results (Sacks, 2011). For example, notice in the most current NZ diagnostic criteria in Table 1 that the use of the oral glucose tolerance test (OGTT) was no longer routinely recommended however NZGG state that:

"An oral glucose tolerance test (OGTT) should be used where there is uncertainty about the validity of HbA1c measures in specific patients (e.g. in the presence of haemoglobinopathy or abnormal red cell turnover) or where there are special clinical reasons."

(NZGG, 2012 pg. 48)

Each of the three main glucose tests (the fasting plasma glucose (FPG), the oral glucose tolerance test (OGTT) and the glycated haemoglobin (HbA1c)) that are recommended to diagnose diabetes in New Zealand (NZGG, 2012) also have different abilities to detect or rule out diabetes. The term "sensitivity" of a blood glucose test is the proportion of people who have the diabetes to test positive. A highly sensitive test is unlikely misclassify a person with diabetes as negative. The term "specificity" of a blood glucose test is the proportion of people who do not have diabetes to test negative on the screening test. A test with a high specificity is unlikely to classify a person who does not have diabetes as positive (WHO, 2003).

Table 1. Interpreting screening tests for type 2 diabetes (NZGG, 2012)

RESULT	ACTION	WHY
Symptomatic		
HbA1c ≥50 mmol/mol and, if measured Fasting plasma glucose ≥7.0 mmol/L Or Random plasma glucose ≥11.1 mmol/L	No further tests required	Diabetes is confirmed
Asymptomatic		
HbA1c ≥50 mmol/mol and, if measured Fasting plasma glucose ≥7.0 mmol/L Or Random plasma glucose ≥11.1 mmol/L	Repeat HbA1c or a fasting plasma glucose	Two results above the diagnostic cut-offs, on separate occasions are required for the diagnosis of diabetes*
HbA1c 41–49 mmol/Mol and, if measured Fasting plasma glucose 6.1–6.9 mmol/L	Advise on diet and lifestyle modification. If over 35 years, a full cardiovascular risk assessment and appropriate management is indicated Repeat the test after 6–12 months	Results indicate 'prediabetes' or impaired fasting glucose*
HbA1c ≤40 mmol/mol and, if measured Fasting plasma glucose ≤6.0 mmol/L	Retest at the next cardiovascular risk reassessment interval	This result is normal
* When HbA1c and fasting plasma glucose are discordant with regard to diagnosis of diabetes, repeat testing at an interval of 3–6 months is recommended. The test that is above the diagnostic cut point should be repeated – if the second test remains above the diagnostic threshold then diabetes is confirmed. If the second result is discordant with the first, then subsequent repeat testing at intervals of 3–6 months is recommended. Patients with discordant results are likely to have test results near the diagnostic threshold.		

The less than 100 % concordance between Fasting Plasma Glucose, Oral Glucose Tolerance, and the HbA1c tests (Sacks, 2011; Echouffo-Tcheugui et al., 2011) means that diabetes can be classified by one criteria and not another. The OGTT has long been held has "the gold standard test" for a diagnosis of diabetes due it its ability to detect a postprandial (post meal) glucose concentration before FPG increases (Sacks, 2011). Criteria for diagnosing diabetes are frequently revised and clinicians' choice of tests will be influenced by a range of factors such as pre-existing conditions and the presence or absence of symptoms.

2.1.2 Screening

The National Health Committee (NHC) (2003) defines screening as:

"a health service in which members of a defined population, who do not necessarily perceive they are at risk of, or are already affected by, a disease or its complications, are asked a question or offered a test to identify those individuals who are more likely to be helped than harmed by further tests or treatments to reduce the risk of disease or its complications."

(NHC, 2003)

Screening can be re-occurring or a once only event. It can be a formal programme with a defined, co-ordinated and monitored pathway or an informal process where the various components of a programme are not connected in a formalised way (NSU, 2012).

Opportunistic screening can be used to detect those that either have the disease or, have an early indicator of elevated risk of progressing to the disease. Evans, Langley and Gray (2008), refer to opportunistic screening as "clinical opportunistic screening" and defines this as:

"…a clinical process in which a health professional uses a consultation with a patient to consider the possibility of the patient having a condition other than that for which the advice was sought"

(Evans et al., 2008, p 379)

There are three main biases associated with screening studies: selection bias, length-time bias, and lead-time bias. This section will define length-time bias and lead-time bias as selection bias will be described in 2.1.8.4.

2.1.3 Length-time bias

Length-time bias refers to over-estimated effects of screening in favour of individuals with a less aggressive form of a disease.

2.1.4 Lead-time bias

Lead-time is the interval between the time of detection by screening and the time the disease would have been diagnosed in the absence of screening. The duration of the complication free period of disease is extended by diagnosing by screening compared with diagnosis in the absence of screening (WHO, 2003; Duffy et al., 2008). When lead-time bias occurs, survival or important health outcomes appears to be longer or better in cases diagnosed by screening compared with those clinically diagnosed when in fact, there may be no difference at all.

2.1.5 Incidence

Incidence is the number of new cases of a disease or condition (numerator) in a specified population (denominator) in a specified time period. There are three main measures for measuring new cases of disease occurrence – the incidence rate, the incidence proportion and the incidence odds. These measures differ due to the denominator used but they all use the same numerator (see Table 2).

In Table 2 each rate has a corresponding relative measure of effect**:** the rate ratio, the risk ratio, and the incidence odds ratio. When there has been substantial loss to follow-up then it is more appropriate to use person-time measures as this allows for a more precise effect measure which controls for the variation in the amount of time contributed to a study (Pearce, 2003; Riegelman, 2005).

Table 2. Measures of disease occurrence and measures of effect

Measure of disease occurrence	Corresponding measure of effect
Incidence rate = number of cases/ person-years at risk	Rate ratio = incidence rate in exposed/incidence rate in unexposed
Incidence proportion = number of cases/total number of people at risk	Risk ratio = incidence proportion of exposed/incidence proportion in unexposed
Incidence odds = number of people who developed the disease/number of people who did not develop the disease	Incidence odds ratio = incidence odds in the exposed group/incidence odds in the unexposed group

Once a measure of effect has been calculated, a researcher must then decide on the likelihood that these results occurred by chance or the probability that the results are true. To do this, a researcher takes their study hypothesis and turns it into a null hypothesis. For example instead of stating that there will be differences between the groups, the researcher's null hypothesis will be that there is no difference (Reigelman, 2005).

Statistical significance testing is used to determine the probability, usually signified with a p value, that there is no difference between the groups, i.e. that the result could have been due to 'chance'. The researcher must decide what level of probability will be used to reject the null hypothesis. The most frequently used level of probability is 5%. If the result is under 5% then the researchers can reject the null hypothesis that there is no difference (Reigelman, 2005).

Confidence intervals combine the strength of the association along with the effect of chance on the likelihood of the results. The 95% confidence interval is most commonly used. The 95% confidence interval allows the researcher and reader to observe where the difference or association lies within the confidence interval. When used for incidence rate ratios the value of 1 equals the null hypothesis. Therefore if the interval includes 1 then any difference is likely to be due to chance.

To summarise, statistical tests such as the confidence interval and p value are commonly used to estimate the likelihood that the results of the study (the measures of effect or point estimate) occurred by chance. Pearce (2003) stresses that these statistical methods i.e. the confidence interval and p value, assume that no systematic error is present.

2.1.6 Prevalence

Prevalence is the number of people with the disease in a defined population at a point or period in time. Measures of prevalence follow those presented above on incidence except the numerator is the total number of cases of the disease of interest – i.e. new and existing diabetes.

2.1.7 Random Error

Random error (lack of precision) occurs in any type of study and random error does not tend to favour either the exposed or unexposed group (Weisberg, 2010). There will always be random differences in risk distributed among the groups that we do not know about. What this means is that the results (the association between the exposure and the outcome) could occur by chance due to these unknown differences in risk.

Random error is most effectively reduced by increasing the size of the study. This leads to a more precise measurement of effect (Pearce, 2003) by reducing the variability of the distribution of random differences in risk. If the size of the study increased Pearce (2003) would caution that in observational studies, even if size were increased there is no guarantee that the random differences in risk would even out.

2.1.8 Systematic Error

Systematic error or lack of internal validity is also referred to as bias (Pearce, 2003; Weisberg, 2010). Weisberg (2010) proposed that biases could be considered as "methodological biases" because they have been generated from the methods used to carry out the research. In contrast to random error, systematic error or bias is considered as non-random. Non-random bias implies that differences in distributions of a variable occur in in one group more than another. This can lead to finding a difference where there may none, or conversely reporting no difference when there may in fact be one.

While there are many types of error, this review will discuss the three main types of systematic error and techniques to control this type of error. The types of systematic error are: 1. confounding, 2. selection bias, and 3. information bias. Following this, screening specific biases will be discussed.

2.1.8.1 Confounding

The word "confounding" originates from the Latin word "confundere" which means to 'pour together, mix up' (Oxford Dictionaries, 2013). A potential confounder must fulfil three conditions:

"*1. The confounder is known to be predictive of the disease in the absence of the exposure being studied*

2. The confounder is associated with the exposure under study

3. The confounder is not on the causal pathway"

(Pearce, 2003)

Confounding creates the appearance that a relationship or association exists between an exposure and an outcome when it is more likely that other factors could explain the difference (Weisberg, 2010). Age, gender, ethnicity, smoking status, and socioeconomic status are frequently confounders in many epidemiological studies. Controlling for the potential effect of confounding can be carried out in the study design stage and in the analytical stage.

2.1.8.2 Control of confounding: Study Design stage

Study design methods to control for confounding include randomisation, restriction, and matching.

The main purpose of randomisation is to ensure that the allocation to the intervention group is random and does not occur due to the influence of some other unknown factors or prejudices (Kane & Radosevich, 2011). However, confounding can occur in any type of study as even randomisation may result in the groups having different characteristics by chance (Pearce, 2003; Riegelman, 2005). For example, a New Zealand randomised controlled trial on the composition of the diet on body fat found that the randomisation did not result in comparable groups. Investigators had to apply statistical methods to take these differences into account (Brooking, Williams & Mann, 2012)

Restriction can control confounding by excluding participants with the confounder from the study. Which confounding variables are restricted will

depend on the research question and the investigators prior knowledge of confounders.

Matching involves selecting the population of interest and then selecting comparison group(s) by matching on potential confounders such as age, sex, ethnicity, and socioeconomic status as the population of interest. This method should mean that the distributions of selected confounders are similar.

Selecting the variables to match is important. If matching is done on a factor associated with the exposure of interest but not the disease of interest then it could reduce the precision rather than improve it. This is called overmatching. For example, if a non-diabetic control group was matched by body weight with a sample of diabetes adults and studied to determine risk factors for diabetes, it would not be surprising that the two groups would consume the same number of calories. It could then be concluded that the number of calories consumed was not associated with developing diabetes, however this only occurred because the groups were matched for weight (Riegleman, 2005). If however groups are matched on a strong risk factor it usually improves the precision of the effect estimates (Pearce, 2003).

2.1.8.3 Control of confounding: Analytical methods

Epidemiological studies aim to measure the effect between an exposure and an outcome (Tripepi, Jagar, Dekker, Wanner, & Zoccali, 2007; Pearce, 2003). When confounding and other biases such as selection bias (discussed below) cannot be removed then other strategies can be used to determine how much the identified variables affect the estimate and in what direction the estimate may be biased. Assessing how much the estimate changes when the factor is controlled indicates the strength and direction of the effect of the confounding variable or variables (Pearce, 2003; Normand, et al., 2005). The main analytic methods are stratification and the use of multivariate techniques.

Stratification separates the study and comparison groups into strata defined by specific factors that are thought to be confounding such as age and ethnicity. In each subgroup an estimate is calculated and then combined into an adjusted estimate that takes into account the effects of the confounding variable (Riegelman, 2005).

Multivariate methods allow for control of a number of potential confounders in the relationship between an exposure and outcome. Regression estimates how confounders are related to the outcome and results in an adjusted estimate of the effect. Regressions models include: linear regression, logistic regression, and cox proportional hazards regression, a type of survival analysis depending on the type of outcome measure being used. For example, if the outcome is binary then a logistic regression model would be used. If the outcome is the time to an event then a proportional hazard would be used (Normand, et al., 2005). Linear regression would be used with continuous variables.

A study by Rasmussen, Glumer, Sandbaek, Lauritzen, and Borch-Johnsen, (2006) has been used to illustrate identifying and controlling for confounding variables

Summary of the study: Rasmussen et al., (2006) estimated the one-year progression rates from Impaired fasting Glucose and Impaired Glucose Tolerance to diabetes in a Danish population who had been identified through diabetes screening. There were 1160 individuals at baseline and 811 at one

year of follow-up (70%). From this, the incidence of diabetes was 17.6 per 100 person-years in those with impaired fasting glucose and 18.8 per 100 person-years in those with impaired glucose tolerance at baseline. Because of the high risk of progressing to diabetes in 1 year, authors recommended intensive follow-up and intervention strategies for people with IFG and OGT.

Comments: This study illustrates the way in which Rasmussen et al., (2006) had considered factors that could confound the results given that in their study there were 1160 individuals at baseline and 811 at follow-up (70%). The authors first assessed the distribution of known confounders at baseline between groups and tested for statistical differences. They determined that there were no statistical differences between attenders and non-attenders with regards baseline factors; however they did find that non-attendees had lower 2 hour blood glucose results than attendees. The authors suggested this may indicate that those with higher risk attended for follow-up which could mean an overestimation of progression rates.

2.1.8.4 Selection bias

The main causes of bias in cohort studies result from the way patients are selected and from loss to follow-up (Normand et al., 2005). The main difference between selection bias and confounding is that selection bias occurs due to the *way* in which participants were selected from the source population (Pearce, 2003; Weisberg, 2010) rather than biases *inherent* in the source population (Pearce, 2003). For example, people who self-select to participate in a screening programme tend to more health-conscious and therefore have less risk of disease and complications (Raffle, 2011). This is often referred to as "the healthy participant" effect. When this group is compared with those who do not participate (often referred to as "non-responders") in screening programmes, the screened group is more likely to have better outcomes even in the absence of screening due to differences in baseline risk (WHO & IDF, 2003).

One way to confirm the presence of the healthy participant effect for evaluations of screening interventions is to include all-cause mortality as an outcome measure for both participants and non-participants. All-cause

mortality is the term that refers to death from any cause. When there are statistically significant differences in rates of all-cause mortality between comparison groups the only plausible explanation is that the groups have inherently different risk of disease or injury (Raffle, 2011).

The groups may also differ in other important characteristics that are known to affect the risk of disease. For example, age is a frequent confounding variable because the risk/rate of many health outcomes is age dependent. When the way in which groups are selected, invited, and assigned to the intervention results in a greater distribution of older people in one group compared to the other, then this could bias the results. Once any differences between the groups due to selection bias and loss to follow-up are identified, they can be minimised using the same techniques of control as used for confounders (Pearce, 2003) described earlier.

A study by Simmons et al. (2012) has been used to selection bias applied to selection of general practices.

Summary of study: Simmons et al., (2012), assessed the effect of a population-based stepwise diabetes screening programme on mortality over 10 years (ADDITION-Cambridge study). This was a study in which the intervention was applied after a diagnosis of diabetes was made. In this study 138 practices were invited to participate. Sixty-three agreed to participate; however of these, three practices did pilot work, 5 were randomly assigned to a no-screen control arm and six practices withdrew. This left 49 practices in the study.

Comments: Selection bias also applies to participating practices. Authors of this paper stated that the practices that participated served less deprived areas than the average general practice in England and estimated that risk of disease would likely be higher in areas with more deprivation than this study sample, assuming attendance rates and data collection systems were similar (Simmons, et al., 2012). However, an early paper based on the same ADDITION-Cambridge study in 2010 the authors stated that "*there was no difference between those practices that participated and those that declined with respect to average*

practice size, prevalence of known diabetes, and deprivation score" (Sargeant et al., 2010).

What may be concluded from these two contrasting statements is that Cambridge as a whole may be less deprived than England as a whole. Therefore these results may not be able to be generalised to the rest of the English population outside of Cambridge. The authors had stated that criteria for participating required practices to set up practice-based screening and could provide data on age, sex, body mass index, and prescribed steroid and antihypertensive medication for 70% of their patients aged 40-69 years. Reasons for practices dropping out ranged from other commitments or unforeseen difficulties setting up the screening programme (Simmons et al., 2012).

They also considered the impact on the ability to generalise their results to the rest of England based on differences in ethnic composition of their study population which was predominantly white. However, it was noted that the authors did not report how different the 6 practices that withdrew were compared with regard to practice size, prevalence of diabetes, and deprivation to the practices that remained in the study.

2.1.8.5 Loss to follow-up

Loss to follow-up is major problem for cohort studies. This occurs when participants have stopped contributing to the study, for example due to moving away from the area in which the study is being conducted, death, or simply dropping out of the study. When this occurs, the groups being compared may have differences in completeness of follow-up data. For this reason, loss to follow-up is similar to selection bias in that if loss to follow-up is more or less likely in one group, then there are likely to be differences in calculated estimates of risk of developing the outcome of interest.

2.1.8.6 Information bias

Information bias occurs when people who have had the intervention (or exposure) are classified into the group without the intervention. Conversely, information bias should be considered when there is likelihood that people who have the disease or outcome of interest have been classified as not having

the disease or outcome of interest. Information bias is often referred to as misclassification bias and there are two types of misclassification: non-differential misclassification and differential misclassification.

Non-differential misclassification occurs when both the exposed and unexposed groups have the same chance of being misclassified with the disease or exposure. Non-differential misclassification tends to make the resulting estimate of the exposure appear to have less or no effect on the outcome compared to the other group. However this only occurs when the misclassification error is independent of other errors (Pearce, 2003).

Differential misclassification occurs when the chance of being misclassified only occurs in one group and can bias the effect measure in either direction. Defining the exposure being measured is a critical requirement to assigning people correctly into comparison groups however this can still be inaccurate if the data source used to ascertain the exposure is incomplete or inaccurate.

2.2 Diabetes in New Zealand

Type 2 diabetes is a priority health issue in New Zealand (MoH, 2012b), with both a high and rapid increase in the number of people with diabetes. In 2001, the New Zealand Ministry of Health estimated 125,000 people were diagnosed with type 2 diabetes. Officials predicted that this number would increase to 180,000 people by 2011 (MoH, 2007). However, in 2011 the total number of people with diabetes in New Zealand was estimated to be over 200,000 people, the majority diagnosed with type 2 diabetes (MoH, 2012b). Initiatives to improve diabetes detection may partly explain why the number of people with diabetes is greater than predicted. Yet, despite these improvements, health officials estimated around 100,000 more people with diabetes remain undiagnosed (MoH, 2012b). Increases in the number of people with type 2 diabetes is followed by increases in the number of people with cardiovascular disease, stroke, kidney disease, lower limb ulcers and retinal damage thus increasing health-sector costs in primary and secondary care (Jackson et al., 2009).

Estimating the impact of diabetes on mortality has proven to be challenging. Chen, Florkowski, Dever, and Beaven, (2004) found that diabetes was under-

reported on more than 50% of death certificates which potentially questions the reliability of death certificates. Coppell, McBride, and Williams (2004) also found that diabetes was under-reported on death certificates and concluded if the impact of the diabetes epidemic on mortality is to be monitored appropriately then improvements to completion of diabetes on death certificates is necessary. Joshy, Colonne, Dunn, Simmons, and Lawrenson (2010) noted that diabetes was more likely to be reported on NZHIS coding for Maori than Europeans. Several studies have found Maori with diabetes to have higher excess mortality compared to other ethnic groups (Jeffreys, Wright, 'T Mannetje, Huang, & Pearce, 2005; Kerr, Gamble, Doughty, R.N., Simmons, & Baker, 2006; Joshy et al., 2010).

Diabetes prevalence has been estimated to be around three times higher in Maori and Pacific people and diagnosis occurs at younger ages compared with the rest of New Zealand population (MoH, 2007; Joshy & Simmons, 2006). Further adding to the burden of disease for Maori and Pacific people is the increased risk of developing complications including renal failure, lower limb amputations, eye problems and heart disease (Robson and Harris, 2007). This could be explained by the younger ages at which Maori and Pacific people develop diabetes with poorer control of diabetes related to increasing length of time with diabetes (Lawrenson, Gibbons, Joshy & Choi, 2009), and improvements in survival (Fonesca, 2009 ; Zhao, Condon, Guthridge & You, 2010).

2.2.1 Estimating diabetes prevalence

Estimating diabetes prevalence requires knowing the number of people with known diabetes and new diabetes. Joshy & Simmons (2006b) carried out a review of the burden of diabetes which described a comprehensive range of New Zealand diabetes research published between 1982 and 2004. Prevalence was described as either prevalence of known diabetes or prevalence of undiagnosed diabetes.

Diabetes prevalence has been estimated in a number of ways. For example, estimating diagnosed diabetes can be based on self-reported diabetes such as that used in the New Zealand Health Surveys (MoH, 2013). Prevalence of diabetes is reported in studies which use purposely collected oral glucose

tolerance test results to identify people with diabetes in a community setting such as Ngati & Healthy (Tipene-Leach et al., 2004; Coppell et al., 2009), Te Wai o Rona (Simmons, Rush & Crook, 2009) and the DHAH survey (Sundborn et al., 2007). Routinely collected data sources such as audits of cardiovascular risk assessments data such as PREDICT tm, diabetes registers, primary care read codes, drug dispensing and hospitalisations data, and "Get Checked"[1] data can be combined to calculate a derived estimates validated against individual data sources such as primary care diagnoses (Thornley et a., 2011; Joshy et al., 2009) or epidemiological surveys (Smith et al., 2010).

All sources and methods to calculate diagnosed diabetes prevalence have limitations. How best to measure diagnosed diabetes prevalence was the topic of a National Diabetes Epidemiology Workshop held in Wellington in 2007. From this day a number of limitations were noted. Low response rates introduce selection bias and were identified as a major limitation for surveys especially those using oral glucose tolerance tests to diagnose diabetes. Self-reported data in surveys may not be accurate. For example, Sundborn et al., (2007), noted that self-reported surveys are likely to be under-reported and will miss those whose diabetes is yet to be diagnosed. Get checked data depended on patients attending for their annual review so could also introduce a selection bias and could misclassify those with pre-diabetes with diabetes. Most data sources cannot be used to estimate undiagnosed diabetes or pre-diabetes states (Coppell, 2007).

Primary care read codes have been assessed to determine their reliability. In a review of care provided in New Zealand General practice for people with diabetes, Lawrenson et al., (2009) applied a range of methods to validate diabetes diagnostic codes from general practice records. They found overall that diabetes diagnostic read codes had a sensitivity of 98.0% and a sensitivity of 99.9%. A New Zealand study compared the diagnoses of diabetes in primary care was compared to other methods of estimating diabetes prevalence. The recording of diabetes in primary care was concluded as a

[1] Note that in July 2012 this diabetes management programme was replaced with the Diabetes Care Improvement Package (MoH, 2012) http://www.health.govt.nz/our-work/diseases-and-conditions/diabetes/diabetes-care-improvement-package

reliable source of data to validate other sources used to estimate diabetes prevalence (Thornley et al, 2011).

Since the review by Joshy & Simmons (2006), literature reporting newly diagnosed diabetes and undiagnosed diabetes have been noted in a number of studies including an audit of cardiovascular risk assessment programmes (Faatoese, 2011), diabetes screening (White & Chamberlain, 2009) an epidemiological survey (Sundborn et al., 2007) and community-wide diabetes prevention research (Simmons, Rush & Crook, 2009; Tipene-Leach et al., 2004; Coppell, 2009). Each of these studies has taken a "slice" of time in accordance with cross-sectional study design. For example, Coppell et al., (2009), compared results from two cross-sectional studies taken from two points in time (baseline and follow-up) from which to assess the impact of a community wide lifestyle intervention – Ngati and Healthy - on insulin resistance prevalence (the primary outcome measure) and other variables including new and known diabetes, and impaired glucose tolerance diabetes (Tipene-Leach et al., 2004; Coppell, 2009).

New diabetes cases reported in cross-sectional studies could be new disease occurrence (incidence cases) or part of the true diabetes prevalence which has gone undiagnosed. An alternative way to learn more about duration of diabetes in newly diagnosed patients was demonstrated by Simmons, Rush & Crook (2009), who followed up those identified with undiagnosed diabetes for the presence of retinopathy on the premise that retinopathy prevalence in newly diagnosed individuals is a measure of the duration that individuals have been undiagnosed (Harris, Klein, Welbourn & Knuiman, 1992). What they observed was a low prevalence of retinopathy at diagnosis and they suggested this indicated greater uptake to diabetes screening therefore earlier detection was occurring in their area of study (Simmons, Rush, & Crook, 2009).

A point of difference between these studies was the tests used to estimate diabetes. Faatoese et al., (2011) determined the levels of cardiovascular disease (CVD), diagnosed and undiagnosed risk factors (which includes diabetes) and clinical management of CVD. Their study was set in the Wairoa district on the

east coast of the North Island and was limited to a Maori cohort aged between 20 and 64 years. They reported that 2% of their cohort had single fasting blood glucose test greater than 6.9mmol/L. At the time of publication confirmation of type 2 diabetes was not available.

White & Chamberlain (2009) reported the general practice results of the Northland Diabetes Screening and Cardiovascular Risk Assessment pilot. Of the 668/752 (88.8%) Maori who completed the screening pathway (FPG, if over 5.5mmol/L then OGTT), 24/668 (3.6%) were diagnosed with diabetes and 24/668 (3.6%) were diagnosed with IGT. Of the 451/499 (90.2%) Non-Maori who completed the screening pathway, 9/451 (2.0%) were diagnosed with diabetes and 10/451 (2.2%) were identified with IGT.

Simmons, Rush & Crook (2009), Sundborn et al., (2007), Tipene-Leach et al., (2004) and Coppell, (2009) all used a single OGT to identify new or undiagnosed diabetes. The study by Simmons, Rush & Crook (2009) was set in Waikato and Lakes District Health Board regions and was based on a sample of Maori residents aged 28 years and over. Of the 3623 people who had an OGT test, 207 (5.7%) were newly diagnosed with diabetes, 365 (10.1%) with IGT and 153 (4.2%) with IFT.

Ngati and Healthy is a collaborative community intervention aimed to reduce the incidence of insulin resistance in a predominantly Maori rural community in the short term (2 years) (Coppell et al., 2009). In the baseline cross-sectional study by Tipene-Leach et al., (2004) a sample of Maori 25 years of age and over who were registered on the Ngati Porou Hauora East Coast enrolled patient register were randomly selected to be invited to participate in the study. The response rate was 48.7%. The age-standardised prevalence (standardised to the WHO world population) and 95% confidence interval of known diabetes was 7.1% (4.0-10.2%) and new diabetes was 3.6 % (1.4-5.3%).

The second of the interrupted time series cross-sectional studies reporting the 2 year results, reported the baseline results without age-standardisation. Known diabetes at baseline in 2003 was 8.4% (24/286) and 7.6 (18/236) at the follow-up in 2006. New diabetes was 4.2% (12/286) at baseline in 2003 and at the 2006 follow-up it was 3.0 (7/236) giving a total prevalence of 12.6%

(36/286) at baseline and 10.6% (25/236) at follow-up in 2006. Pre-diabetes (IFG and IGT) proportions were 4.2% (12/286) in 2003 and 13.6% (32/236) in 2006. Insulin resistance was 35.5% (93/286) in 2003 and 25.4% (60/236) in 2006, suggesting the short term goal of reducing insulin resistance was achieved (Coppell et al., 2009).

The Diabetes Heart and Health Survey (DHAH) was a cross-sectional study to estimate the prevalence of new and known diabetes, impaired glucose tolerance and impaired fasting glucose. Participants were of Maori, Pacific, and European ethnicity and selected from two sampling frames covering the Auckland area. Response rates were 61.3% and 65.0% for the two sampling frames used. Age sex adjusted diabetes prevalence were reported for each ethnic group. Known diabetes prevalence was 12.0% for Maori, 19.5% for Pacific people and 3.9% for European. Prevalence of new diabetes was 3.8 % for Maori, 4.0% for Pacific people and 1.8% for European. These results suggest the total diabetes prevalence in this sample was 15.8% for Maori, 23.5% for Pacific people and 5.7% for European. The age- standardised rates of Impaired Fasting Glucose and Impaired Glucose tolerance respectively for Maori were 3.0% and 7.3%, for Pacific people were 4.1% and 7.9%, and for European were 2.2% and 6.7% (Sundborn et al., 2007).

2.2.2 Estimating diabetes incidence

There is less New Zealand published literature specifically on diabetes incidence. A few studies on type 1 and type 2 diabetes have reported diabetes incidence in children (Campbell-Stokes & Taylor, 2005; Miller, et al., 2011). The studies presented on diabetes prevalence have all used cross-sectional designs. To determine the incidence or progression to a disease over time would involve a length of time required to follow-up, resources to collect the relevant data, and a reliable source to identify incident cases (Pearce, 2003). These reasons may explain the lack of studies which use incidence diabetes as an outcome measure.

As with diabetes prevalence studies, if a routinely collected source of data such as repeated blood glucose levels in a non-diabetic population was available and a source of diagnosed diabetes was reliable, then the costs involved with monitoring diabetes incidence could be reduced, thus making it feasible.

2.3 Cost of diabetes

The direct costs of health care for people with diabetes in New Zealand was estimated to increase to around 15% of Vote Health ($1,600-1,800 million per annum) by 2020 compared with 3% of the 2006 Vote Health proportion (PWC, 2007). Based on 2003 figures direct costs of renal replacement therapy was estimated to be NZ$90million per annum and diabetic nephropathy was estimated to account for $36million in direct annual healthcare costs (Endre, Beaven, & Buttimore, 2006). Sheerin (2009) estimated the annual expenditure by a District Health Board on hospital admissions for treating diabetes related complications. This relied on reliable recording of diabetes as a primary or secondary diagnosis and therefore is likely to be an underestimate. Sheerin, (2009) estimated the costs in 2005/6 was $10.1million and totalled 9511 days stay in hospital. Indirect costs, thought to be mainly attributed to the impact of diabetes on workforce participation and productivity (Vijan, Hayward & Langa, 2004.; Dall et al. 2008), are also of major concern and are considered to be even greater than the direct costs of health care (Vijan et al, 2004).

In the book "Sick Societies" Stuckler and Suhrcke (2011) ask the question: who suffers from the costs of chronic diseases such as diabetes? The answer is everyone. Like those in developing countries, for Maori and Pacific people the onset of diabetes is during the productive younger years and is in increasing numbers. This brings negative socioeconomic consequences for individuals, families, communities, and nations (WHO, 2005).

Asides from societal costs of health care and loss of productivity, chronic diseases such as diabetes put households at risk of poverty. As health begins to decline and the number of appointments and procedures increase, the ability to carry out the day to day responsibilities of parenting and employment lessens. Family dynamics can change as the need for care and support increases. Employment may eventually be lost reducing income and increasing the pressure on other family members to work (Stuckler and Suhrcke, 2011).

Metcalfe et al., (2009) found that having previously diagnosed diabetes may have an adverse impact on the individuals earning power. Passey et al., (2009) studied the personal individual economic outcomes that could be gained from the benefits of lifestyle interventions for Australian individuals aged 45 -64 years with pre-diabetes. They found that on average males could earn an additional AUS$44,600 per year and females AUS$31,800 per year. In addition to the benefits on health and wellbeing, Passey et al., (2009), concluded that there would be considerable benefits for individuals through additional working years and personal income. It follows that prevention of diabetes would go a long way to reducing the number of children growing up in relative poverty, particularly Maori and Pacific people.

Type 2 diabetes is a major public health issue and impacts at every level of society, throughout the lifecourse, and across generations. The United Nations acknowledged that non-communicable diseases are a global problem (IDF, 2011). Type 2 diabetes is one of the non-communicable diseases which the United Nations recognise as a costly and debilitating disease (United Nations Assembly, 2006) and threatens survival and economic prosperity for

communities around the world (IDF, 2011). Communities therefore benefit from disease control solutions specifically for diabetes.

2.4 Disease control

Disease control falls mainly into three categories – control of causes, control of spread of disease, and early detection. Since the focus of this thesis falls into the early detection category, a greater emphasis will be placed on this section compared with the control of causes and control of spread of disease.

2.4.1 Control of causes- individual's risk

An individual's risk of chronic disease can be attributed to a few common modifiable risk factors that lead to obesity, specifically nutrition and physical activity. Lifestyle interventions which address nutritional intake and levels of physical activity have been found to delay or prevent diabetes in those with impaired glucose tolerance (Pan et al., 1997; Tuomilehto, et al., 2001; Knowler, et al., 2002; Kosaka et al., 2005; Ramachandran et al., 2006) and cardiovascular disease (Nolan et al., 2011). The summary of the main studies which assessed the effect of lifestyle interventions on progression to diabetes in individuals who have Impaired Glucose Tolerance are presented below.

The Finnish Diabetes Prevention Study: This study outlines the benefits of intensive intervention in reducing the risk of developing diabetes. Participants were 40-64 years of age with Impaired Glucose Tolerance (IGT) and BMI >25kg/m^2. They were then randomly assigned to the control group (general advice about healthy lifestyle and annual testing) or the intensive intervention group (multiple individual sessions with a nutritionist and supervised individually tailored circuit-type resistance training sessions.) After the median follow-up time of three years, cumulative incidence of diabetes was 11% (95 % CI 6-15%) in the intervention group and 23 %(95 % CI 17-25%) in the control group. The reduction in incidence was observed in both males and females (Lindström et al., 2003). At the extended follow-up time of 10 years, the reduced cumulative incidence in the intervention group was sustained (Lindström et al., 2006). After 10 years of follow-up, which included a comparison with a population-based cohort, there was no statistically significant difference in all-cause mortality and cardiovascular mortality rates between the intervention and control group, however compared with a

population based cohort, there were statistically significant differences in all-cause mortality and cardiovascular mortality (Uusitupa et al., 2009).

The Diabetes Prevention Program: This study, set in the United States of America, demonstrates the benefits of intensive life style interventions compared with standard lifestyle interventions with or without or treatment with metformin in reducing the risk of developing type 2 diabetes. Participants were those detected with IGT and were randomly assigned into 3 groups. These groups were; a control group (standard lifestyle recommendations); an intensive lifestyle intervention group (16 session core curriculum followed by individual sessions with "case manager" every two months); and a third group receiving the standard lifestyle recommendations plus metformin. The intensive lifestyle intervention group where found to have a reduction in risk of developing type 2 diabetes of 58% compared with the control group. This reduction in risk was superior to the reduction of 31% observed in the standard lifestyle plus metformin group compared with the control group (Diabetes Prevention Programme Group, 2002; Orchard et al., 2005). After 10 years of follow-up the cumulative incidence was reduced by 34 % in the lifestyle group and 18% in the metformin group compared with the control group. Thus prevention or delay of diabetes using lifestyle or metformin interventions can be sustained for 10 years (Diabetes Prevention Group, 2009).

Indian Diabetes Prevention Program: Participants with IGT and a mean age of 46 years and BMI 25.8kg/m² were randomised into four groups. The groups were: a control group, a lifestyle modification group, a metformin group, and a combined lifestyle medication and metformin group. Median follow-up was 30 months. Compared with the control group the relative risk reduction was higher for the lifestyle modification group than the metformin group (28.5% versus 26.4%). The combined lifestyle medication and metformin group risk reduction of 28.2% was similar to that of lifestyle intervention alone suggesting that the addition of metformin did not add any further reduction in risk (Ramacahndran et al., 2006; Ramacahndran et al., 2007).

Japanese Prevention trial: In this study, males only with IGT were randomly assigned to either intensive lifestyle intervention or standard intervention. Cumulative incidence of diabetes after 4 years was 3.0% in the intervention group and 9.3% in the control group (Kosaka et al., 2005).

New Zealand researchers have aimed to determine intensive lifestyle interventions that could be offered to people with newly diagnosed diabetes. Interventions focussing on nutritional advice have reported reductions in weight loss. Coppell, et al., (2010) found that intensive dietary advice can potentially improve glycaemic control by reducing HBA1c levels and reduce weight for people with type 2 diabetes who have unsatisfactory glycaemic control despite optimised drug treatment over 6 months. Krebs et al., (2012) randomly allocated a sample of overweight people with type 2 diabetes into a low-fat high-protein diet or low-fat high carbohydrate diet group and compared groups on weight loss. They reported that the losses were modest and similar between both groups over two years. Sukala et al., (2011) evaluated the effectiveness of resistance training or aerobic training for improving HbA1c in a sample of Pacific people with type 2 diabetes over 16 weeks. Although they did not find resistance or aerobic training improved HbA1c over 16 weeks, they did observe that participants who attend 75% or more training sessions had reduced waist circumferences.

Brooking, Williams, and Mann, (2012) compared a fibre rich carbohydrate and a fat reduction diet with a high protein diet and a control group in a sample of Maori at risk of type 2 diabetes over 24 weeks. They found that weight loss was similar in both intervention groups, however analyses of dietary records showed that adherence to the high protein diet tended to be continued even after the intensive nutritional support had been withdrawn.

(Applying evidence from these studies to practice is discussed further under the heading of early detection.)

2.4.2 Control of causes- causes of causes

Health is largely determined by societal factors outside of healthcare (Stuckler & Suhrcke, 2011). Rose put forward the challenge for public health to address not only the causes of an individual's poor health but also "the causes of the

causes" (Rose, 2001). Some of the drivers leading to the increase in the prevalence of diabetes are: 1. increases in the adult ageing population, 2. people living longer with diabetes, and 3. changes in behaviour associated with urbanisation, resulting in increases in obesity.

Increasing age is a risk factor for developing diabetes (IDF, 2011) and was described in the background introduction to this thesis. Briefly, increases to the proportion of the population that is older would contribute to increasing prevalence of diabetes (Magliano et al., 2009).

People are now living longer with diagnosed diabetes. The combination of earlier diagnosis and reductions in mortality means that the total number of people with new or existing diabetes would contribute to increasing diabetes prevalence.

Nolan et al., (2011) identified that urbanisation, westernised diet, and modern day technological advances create environments that have impacted on the way in which people live their lives. These advances make it easy to reduce energy expenditure and increase over nutrition, thereby promoting obesity and increasing the risk of developing diabetes.

Community-wide diabetes prevention plans incorporate what is referred to as "structural interventions". New Zealand examples of these are Ngati and Healthy, and Let's Bet Diabetes. These aim to create environments where choosing being smokefree, being free from alcohol related harm, being physically active, and eating a healthy diet are easy (Coppell et al, 2009; Barron & Orr-Walker, 2010). Feeling unsafe is also a major contributor to population levels of reduced physical activity and may reduce an individual's confidence to be physically active. Prevention strategies should include addressing fear of crime and perceptions of safety (Harrison, Gemmell & Heller, 2007; Bennett et al., 2007).

2.4.3 Control of spread of disease

Type 2 diabetes is a non-communicable disease therefore strategies to limit person to person spread such as those used for communicable diseases are not applicable. However, it could be argued that spread of type 2 diabetes does transfer from person to person through learned behaviours. Our family,

friends and colleagues play a role in the choices we make through our idea of what is socially normal (referred to as social norms). For example, if it is normal to eat buckets of Kentucky Fried Chicken (KFC) with your friends at your house on a regular basis after a session at the pub, this normalises a diet with a high caloric intake. If you grew up in a family with this lifestyle and all your friends and/or work mates now do this, then this way of living will "spread" by way of being a "socially normal" choice. Clearly to break away from this way of living will impose major challenges for the individual and their relationships with people in their family and wider social networks.

Mother to child spread can also occur through an epigenetic effect. Epigenetics is the field which studies changes in function of the genome. Changes occur because of factors which activate chemical switches that regulate the gene expression. Examples of factors which can switch on or off parts of the genome are stress, diet, behaviour, and toxins. A hyperglycaemic environment is also an example of an environment which can switch parts of the genome on or off (University of Utah, 2012). Vrachnis et al., (2012) reviewed the impact of maternal diabetes on epigenetic changes. They concluded that diabetes that occurs in off-spring is mainly a result of exposure to a diabetic intrauterine environment, along with genetic susceptibility.

On the basis that "spread" of type 2 diabetes is due to learned behaviours, accepted social norms, and epigenetic changes, good health during pregnancy and support of families, particularly during the early childhood when behaviours are being learned, should be included as part of a strategy to prevent diabetes (Nolan et al., 2011)

2.4.4 Early detection

Early detection is the category of disease control where the potential benefits occur when individuals are detected early in the disease or the development of disease, and then offered interventions proven to result in improved health outcomes. When early detection strategies are considered for defined populations, this comes under the heading of "screening".

2.4.5 Screening for diabetes

Undiagnosed diabetes is associated with worse outcomes than diagnosed diabetes with respect to diabetes complications and cardiovascular risk factors (Gaede, Johansson, Wallander & Rodriguez, 2008; Li, Zhang, Barker, Chowdhury &Zhang, 2010; Williams, Van Gaal, & Lucioni, 2002). The rationale behind screening for diabetes to detect those with diabetes is to offer early management of high blood glucose levels and thereby to reduce the impact of diabetes complications and preserve β-cell functioning for as long as possible (Lindstrom et al., 2003).

An example of a diabetes screening study which aimed to detect diabetes early and offer interventions to reduce the impact of diabetes is the ADDiTION study (Anglo-Danish-Dutch Study of Intensive Treatment In PeOple With screeN Detected Diabetes in Primary Care). This study involved 334 general practices in Denmark, United Kingdom (Cambridge) and the Netherlands. These practices were randomised into two groups. Both groups screened for diabetes, however the control group offered routine care for those diagnosed with diabetes according to national guidelines, whereas the intervention group offered those diagnosed with diabetes a multifactorial treatment (Clinical Trials Register, 2012). A 10 year follow-up of patients in the Cambridge arm was carried out to assess the effect of the intervention on mortality from any cause, cardiovascular disease or diabetes-related mortality. They found that screening for diabetes was not associated with a reduction in all-cause mortality, cardiovascular or diabetes-related mortality (Simmons et al., 2012).

Screening for diabetes also has the potential to identify those with pre-diabetes, an early predictor of diabetes. Interventions that address the contribution of nutrition and physical activity to developing diabetes can be offered to those identified with pre-diabetes.

The Diabetes in Europe – Prevention using Lifestyle, Physical Activity and Nutritional intervention programme in Catalonia (DE-PLAN_CAT), is an example of a programme where the purpose of diabetes screening is to identify individuals in the high risk, pre-diabetes stage of the disease. The DE-PLAN –CAT was a prospective cohort study set in Catalonia, Spain where 2054 White-Europeans aged 45-75 years were screened using the Finnish

Diabetes Risk Score (FINDRISC) followed by an oral glucose tolerance test. Those with a FINDRISC score greater than 14 or pre-diabetes defined by WHO criteria were assigned by the participating primary care centre into the standard care or intensive group. Patients who were assigned to the intensive group were given the choice of either an individual intensive session or a group session. However some later chose to swap from either the group to the individual choice or from the individual to the group. The primary outcome measure was the development of diabetes and patients were followed for 4 years. A highly statistically significant (p=0.005) relative risk reduction of 36.5% , (p = 0.005) was observed for the intensive group as a whole. The absolute incidence of diabetes was 7.2/100 person-years in the standard care group and 4.6/100 person-years in the intensive group. The cumulative 4 year incidence for the intensive group was 18.3% (95 % CI 14.3, 22.9) compared with 28.8% (95 % CI 22.9, 35.3) in the standard group, resulting in a Hazard ratio of 0.64 (95 % CI 0.47, 0.87) (Costa et al., 2012).

In New Zealand, screening for diabetes occurs predominantly through cardiovascular risk screening implemented in primary care. The New Zealand government expects improvements in detecting diabetes and recording and management of other important cardiovascular risk factors from District Heath Boards, Primary Health Organisations, and Primary Care providers.

The debate about whether formal diabetes screening programmes should be implemented is frequently revisited. The promise of lifestyle interventions to prevent diabetes for those with pre-diabetes has led a number of translational programmes in primary care outside of New Zealand. In the process of screening for diabetes to identify those with pre-diabetes, people with new or undiagnosed diabetes will also be detected therefore the two are inseparable in approach (Echouffo-Tcheugui et al., 2011). However these approaches differ with regards to the key outcome measure the intervention is aiming to prevent. In this case of lifestyle interventions for those without diabetes, the key outcome measure is a diagnosis of diabetes.

2.4.6 Numbers needed to screen

Numbers needed to screen (NNS) is a useful concept to gain information about how efficient screening is. Wilson, Rosella, Lipscombe and Manual

(2010) investigated the efficiency and effectiveness of diabetes screening in a population resident in Ontario, Canada, aged 20 years and over, and over a five year period. Their study highlighted the potential for assessing current screening practices using administrative general practice sources. The methods used specific information to calculate coverage (total screened/total population expected to be screened), efficiency (represented by the NNS) and effectiveness (determined by the proportion with undiagnosed diabetes). NNS was calculated by taking the number of people who had had at least one blood glucose test in a defined period of time and dividing it by the number of incident diabetes cases the study detected. NNS was then also used to calculate undiagnosed diabetes, by taking the number of people not screened for diabetes and dividing it by the NNS. Overall results was coverage was 66.1% for Males from which 4.7% were diagnosed with diabetes making NNS = 14 males and the proportion of undiagnosed diabetes 2.4%. For females coverage was 80.6 % from which 3.7% were diagnosed with diabetes making NNS =22 and the proportion of undiagnosed diabetes was 0.9% (Wilson et al., 2012).

Gray, Evans, Wright and Langley (2012), used NNS in the broader context of reporting cost of clinical opportunistic screening in a single general practice in the United Kingdom. Data on blood glucose testing was retrieved from the practice's electronic management system for all non-pregnant adults defined as 16 years of age and above over a three year period. Number need to screen (NNS) was calculated using the same method as Wilson et al., (2010) (the total number screened divided by the number of diabetes detected). Overall coverage was 22.7% from which 2.0% were diagnosed with diabetes making a NNS of 51.

Methods used by Wilson et al., (2010) were applied to other studies that did not report NNS. In the White and Chamberlain (2009) paper, coverage could only be based on those who had completed the screening pathway over a period of 3 years. From this 54.0% of Maori completed the screening pathway of which 3.6% were diagnosed with diabetes making the NNS = 28 for Maori. For Non-Maori 51.5% completed the screening pathway of which 2.0% were diagnosed making the NNS = 50 for Non-Maori.

By contrast, applying the results based on a single OGT test in a community-wide diabetes prevention programme the baseline coverage (response rate) in 2003 was 48.5% from which 4.2% were newly diagnosed with diabetes making NNS = 24 (286/12). In the two year follow-up results in 2006, coverage was 47.7% from which 3.0% were newly diagnosed with diabetes making a NNS of 34 (Coppell et al., 2009).

These studies differ in criteria and tests used to define diabetes, the prevalence of underlying risk factors in the populations studied, methods used to recruit the participants, and variation in knowledge of completeness of follow-up testing. All of these factors contributed to the variation of NNS presented here.

2.5 Limitations of screening studies

Earlier in this literature review the main biases encountered in any research were presented. This section takes a closer look at the implications and what others have found when assessing screening for diabetes.

2.5.1 Uptake to screening

Uptake to screening is more likely to occur in populations with inherently lower risk (Raffle, 2011; WHO & IDF, 2003). Many studies have noted certain population groups which have lower uptake to screening and potentially higher risk of the disease or outcome of interest. For example, Dunstan et al., (2002), found that younger age responders were under-represented and middle-age and older age groups over represented at examinations involving tests requiring blood tests. Simmons et al., (2012) found that non-attenders for screening were more likely to be young, more obese, to be men, less likely to be taking antihypertensive drugs and had higher all-cause mortality (Hazard Ratio =2.01 (95%CI =1.74, 2.32). Social deprivation has also been found to be associated with lower uptake to screening (Sargeant et al., 2010; Wilson et al., 2010). Coppell et al., (2009) found that younger Maori males did not participant in the community diabetes prevention programme – Ngati and Healthy - compared with younger Maori females.

The implication for assessing the outcomes for screening participants compared with a control group is that if those that do not uptake have a different distribution and severity of risk factors for developing the disease of

interest a range of potential biases, such as selection bias –particularly the healthy participant effect, and potentially also lead-time bias, may be introduced. Both of these biases can therefore lead to results which suggest a benefit due to screening when in fact there maybe none.

There can also be implications for translating evidence into practice with the same degree of efficacy as randomised control trials. For example, after four year follow-up of the DE-PLAN study, Costa et al., (2012) reported a lower risk reduction for progression to diabetes from pre-diabetic state in a real life setting compared with intervention trials such as the *Finnish Diabetes Prevention Study* and the *Diabetes Prevention Program*. The authors had mentioned that in general the differences in methods and intensity of interventions applied could easily explain why the reductions maybe more modest than lower and in particular discussed the effect of non-randomisation and high discontinuation rates on interpreting the results.

There are also New Zealand specific implications if uptake to screening is lower for Maori. Under the Crown obligation established by the Treaty of Waitangi Maori should enjoy a health status at least as good as Non-Maori (MoH, 2012d). Maori and Pacific people are 2-3 times more likely to develop diabetes (MoH, 2007). Maori are also overrepresented in areas of higher deprivation. Correlations between deprivation and increased diabetes prevalence and undiagnosed diabetes have also been reported consistently, however in 2009 Joshy et al., (2009) questioned whether this was true for Maori. They found that the prevalence of diabetes was as high in the least deprived as in the most deprived Maori and proposed a possible explanation was that least deprived Maori are more likely to be detected due to more frequent visits to the doctor. However, rates of doctor visits were found to increase with socioeconomic deprivation among Maori and Europeans in New Zealand (Health Utilisation Research Alliance, 2006). Faatoese et al., (2011) found that in rural New Zealand Maori population high levels of undiagnosed and diagnosed hypertension, dyslipidaemia, and diabetes; despite observing that 69% of the study cohort had visited their doctor within the last six months and 85% had visited within the last year. More frequent visits may not necessarily translate into increased testing.

Opportunistic screening offers a mechanism to increase uptake to screening. Faatoese et al., (2012) recommended that opportunities to conduct CVD screening while patients are attending for other reasons should be taken, given the frequency of attendance to primary care. Engelgau, Narayan and Herman (2000) proposed that opportunistic screening is the most cost-effective way to detect individuals at risk of progressing to diabetes. However, opportunistic screening entails extra work and costs for doctors and also depends on general practitioners awareness of the disease, the patient's emotional state, doctors' time pressures, and the patient visiting the doctor in the first place (Gray, Evans, Wright, & Langley, 2012). Wilson, Rosella, Lipscombe, and Manual (2010), found that clinical screening behaviour increases as the proportion of the population increases in risk. In a high risk population such as that in Northland, this could mean that those who were invited to the pilot but did not participate would be more likely to be screened as part of usual clinical practice compared with other practices.

Opportunistic screening may also occur at a later stage of disease progression compared with those screened via systematic recall. Tipene-Leach et al., (2004) had identified that young men were less likely to participate in their study. In their study's setting, the forestry industry employed a high proportion of young men. The authors had postulated that the forestry workers may be less likely to seek time away from work to attend non-acute health appointments and thus explain the lower participation. In this scenario, the predominantly young male forestry workforce could then be offered screening opportunistically as a strategy to ensure uptake in this demographic group. However screening may be more infrequent with opportunistic screening and the timeliness of testing is more likely to occur at a later point in time compared with systematic recall. If comparing outcomes with those screened in response to systematic recall, it is most likely to flag the likelihood that lead-time bias may be present.

2.5.2 Loss to follow-up

Loss to follow-up can have a similar effect on the results as selection bias. That is, there may be characteristics about those lost to follow-up that are different to those who have continued contributing time to the study (see example

below). Migration may be one reason why people may be lost to follow-up. According to Statistics New Zealand, Maori have becoming increasingly mobile. Around 47% of Maori had moved within New Zealand in the previous 5 years in 1986. By 2006 internal migration had increased to around 60%. The greatest increases in mobility were observed in those aged 35 years and over. Explanations for increasing mobility are economic and employment opportunities and increase inter-ethnic, inter-regional, and inter-iwi partnering (Statistics New Zealand, 2012). The New Zealand population as a whole has become increasingly mobile. The implication of this increasing mobility for assessing progression to diabetes overtime is that people may be lost to follow-up due to migration.

How much bias results from loss to follow-up depends on whether participants are lost randomly in both exposure groups or not. Kristman, Manno, and Côté (2004), tested the validity of the recommended acceptable loss to follow-up of 60-80% without severely biasing the results. They tested three possible scenarios which they defined as "completely missing at random", "missing at random", and "missing not at random". They found that when loss to follow up was random there was no important bias, however when loss was non-random, the bias was serious even with relatively low levels of loss to follow-up. Since loss to follow-up in cohort (follow-up) studies is considered non-random, they recommended that researchers make every effort to control for loss to follow-up (Kristman et al., 2004).

The following study by Engberg, Visten, Lau, Glumer, Jorgensen, Pedersen, and Borch-Johnsen, (2009) is an how the authors made adjustments for loss to follow-up and the effect of these adjustments on the study.

Summary of the study: The investigators studied the progression rates to impaired glucose regulation and diabetes in a Danish population that had been part of the Inter99 study. They did this by comparing progression rates from baseline to 5 years of follow-up for the whole population and the high risk population. In this cohort the rates from normal glucose tolerance to

diabetes were 0.3 (95% CI 0.2-0.3) per 100 person-years in the whole group and 0.4 (95% CI 0.3-0.6) for the high risk group.

Comments: Loss to follow-up was potentially a major issue for the investigators. They controlled for the possible effect by applying restrictions in the study design – that is, they included only individuals with the relevant follow-up data at the various follow-up intervals. This also eliminated the potential to misclassify participants incorrectly into an outcome measure due to missing fasting plasma glucose tests or oral glucose tolerance tests.

Selection bias was also a major issue for this study given that baseline participation in the study was relatively low (52.5%) and that more males, older individuals, more Danish Nationals and less individuals with high risk were examined at follow-up compared with individuals lost to follow-up. This suggests that this study was affected by the healthy participant effect. This is further compounded by those lost to follow-up having higher risk. These investigators applied restrictions for those without complete follow-up data and along with the low participation rate, this lead to results that were based on a population not typical of the source population. The investigators had to trade off having a complete dataset and increased precision of the study results with study results that cannot be confidently generalised to the Danish population.

2.5.3 Progression to diabetes from a negative screening test

Weir and Bonner-Weir (2004) described progression to diabetes into definable stages that are marked by changes in metabolic and β-cell function. The stages are compensation, stable adaptation, unstable early decompensation, stable decompensation, and severe decompensation and are described in Table 3.

Researchers must decide on the potential that length time and lead time biases may have on their results. For example, the transition from normal glycaemia to diabetes had been thought to be either a moderate change in glucose over time or a rapid change (Mason, Hanson & Knowler, 2007). This thinking was reflected in the report of a World Health Organisation (WHO) and International Diabetes Federation (IDF) meeting in 2003 where the following statement was made with regards to length time bias:

"This relates to the fact that individuals with rapid metabolic deterioration will tend to develop symptoms that prompt them to contact their health services. Thus only people with slowly progressing and milder disease remain to be identified by screening. These people are likely to have a better clinical outcome than rapidly progressing cases, regardless of the treatment"

(WHO, 2003)

However since then, more has been learnt about progression to diabetes. Longitudinal studies have confirmed the theory of two distinct phases of glucose levels change leading up to the threshold of diabetes. The first phase occurs over a long period of time with a moderately linear increase in blood glucose followed by the second phase, a rapid increase (Mason et al., 2007; Ferrannini et al., 2004). Based on a sample of Pima Indians, Mason et al., (2007) estimated that glucose levels can change from negative to positive for diabetes in less than 4.5 years. This time of rapid increase in glucose levels was identified as an important period for preventing the development of diabetes.

Table 3. The stages of progression to diabetes

Stage	Description
1. Compensation	Insulin resistance increases due to obesity, physical inactivity, and genetic predisposition and is accompanied by an overall increase in insulin secretion to maintain normal blood glucose levels.
2 Stable Adaptation	Fasting Glucose levels rise (approx. 5.0-7.3 mmol/L). Change from compensation as normal glucose levels are no longer maintained stable on the basis that many individuals in this stage can remain so for years without progressing to diabetes.
3 Unstable early decompensation	While people may remain in a state of stable adaptation for many years, when β-cell mass is no longer adequate during this stage glucose levels rise over a relatively short period of time. There may not be any noticeable clinical symptoms during this stage and could be regarded as a transient stage.
4 Stable decompensation	People in this stage still have enough insulin secretion to remain in this stage without progressing to ketoacidosis. People with 2DM can stay in this stage for relatively long periods
5 Severe decompensation	Loss of β-cells so severe that people require insulin for survival

Adapted from Weir and Bonner-Weir, 2004

Given this revised information length time bias may be less of an issue than previously thought for type 2 diabetes screening. The bias that would be more likely to occur is lead-time bias due to differences in when screening occurred in the progression to diabetes, rather than whether the individuals had fast or slow progressing disease.

Lead time bias is more difficult to ascertain. Gray et al., (2012), Simmons, Rush, & Crook (2009), and Rahman et al., (2012) have suggested that the presence or absence of symptoms or retinopathy at diagnosis is one way to ascertain the stage of disease progression those detected with diabetes maybe.

The following study by Rahman et al., (2012) is used to illustrate how authors applied restriction methods and controlled for selection bias and misclassification bias.

Summary of the study: This study, based on a Dutch population, aimed to estimate how much screening for type 2 diabetes brings forward diagnosis and whether this has any benefits on health outcomes. They found that the screened population had significantly longer duration of diabetes compared with the unscreened population (5.0 years compared with 1.7 years) and no differences in health outcomes were measured. Authors concluded that on average screening brings forward a diagnosis of diabetes 3.3 years early with no apparent impact on health outcomes compared with the unscreened population.

Comments: Restriction techniques were applied to control for confounding by age (40- 65 years) and pre-existing diabetes. Both the screening group and no screening group were invited to a health assessment. The investigators assessed the distributions by age, sex, and social deprivation in the screened and unscreened group, and tested for any statistically significant differences (of which there were none) in those who attended and did not attend the health assessment to rule out selection bias. The investigators were therefore able to infer that their results were generally applicable.

The final selection of study participants was from the group of attenders to the health assessment. Only those diagnosed with diabetes were used to compare

outcomes between the screening group and no screening group. The screening group was very slightly older than the no screening group and these differences just reached significance at (p=0.048). However, investigators did not report adjusting for age.

The potential for misclassification in the screening and no-screening group existed because of factors external to the study design. Examples include the effect of opportunistic screening and improvements in the detection and management of cardiovascular risk in the wider Dutch general practice population. This could potentially mean improvements in health outcomes being measured in the comparison group without exposure to the intervention being measured. Because this affected only the unscreened group and not both groups, this is an example of differential misclassification that can bias the estimate in either direction. The investigators of this study suggested that the effect of screening on outcomes may have been diluted due to the comparison group having been exposed to early diagnosis and treatment. Therefore researchers should also consider the effect of other risk reduction activities their comparison groups may be exposed to during their studies.

2.5.4 Rates of progression to diabetes from a normal glucose test

Most studies which evaluate the effect of a diabetes screening intervention on progression to diabetes are based on people whose glucose levels have reached the "pre-diabetes" levels e.g. the Diabetes Prevention Program Outcomes study, The DE-PLAN programme (Catalonia), or those who have been screen detected with diabetes (e.g. ADDITION, ACCORD). Kenealy et al., (2004) estimated that 5% of a high risk population with a negative blood glucose test would progress to diabetes in 3 years. The Kenealy et al., (2004) article was the only New Zealand published article which estimated progression to diabetes from a negative blood glucose test, defined as a fasting plasma gluyce (FPG) test < 6.1mmol/L.

The World Health Organisation had estimated from available data that annual progression from a normal glucose test was somewhere between 0.6% - 1.2%, depending on the demographics of the population studied (WHO, 2003). Only

a limited number of international studies were identified which measured progression from a negative screening test to a diagnosis of diabetes. Rates of progression are as follows:

- Progression from NGT (defined as <6.1mmol/L) to diabetes in a Dutch Study (*the HOORN study*) from1989 to 1998 was 0.7 per 100 person-years (de Vegt et al, 2001).
- *The Ely study* which ran from 1990 until 10 years after baseline test in Cambridgeshire, England, reported a rate of 2.4/1000 person-years (95% CI 1.2-4.8) in the group with normal fasting glucose at baseline (NGT defined as <5.6 in this study) (Rahman et al., 2012).
- Engberg et al.,(2009) reported rates based on a mainly European Danish population from 1999 until 5 years after their baseline assessment that were included in the *Inter99 Study*. The rates were 0.3 (95% CI 0.2-0.3) per 100 person-years in the whole group and 0.4 (95% CI 0.3-0.6) for the high risk group.
- Based on a small sample included in the *ADDITION – Netherlands* study, 6/142 people (4.2%) in the Normal Glucose tolerance group progressed to diabetes in three years (Janssen et al., 2008). Taking the person-years for this group of 420.4 this equates to a rate of 1.4 (95% CI 0.58 – 2.97) per 100 person-years.

In the Inter99 study, high risk was defined fairly similarly to the Northland Diabetes and Cardiovascular risk assessment pilot. They defined high risk as individuals with an Ischemic heart disease score in the upper quintile for their age and sex strata (Engberg et al., 2009), or individuals with a range of risk factors most of which were the same as those used in the Northland pilot (see table 4). Engberg et al., (2009) also recognised that the rates in their study were not likely to reflect progression rates in Denmark because of the effect of the intervention. They also acknowledged the difficulties of comparing with other "high-risk" groups because of the different criteria for defining high risk.

Each of these studies presented above were based on different age groups, populations and countries with different baseline risk over different periods of time, with some using slightly different cut-off criteria for a negative baseline

glucose test. This leads to problems in comparability between studies. In addition, differences in age ranges, inclusion exclusion criteria, methods of handle missing data, urban versus rural and different time periods all create comparison difficulties for researchers estimating the prevalence of diabetes (James et al., 2011) and the global impact of diabetes (Danaei et al., 2011).

2.6 Literature review summary

Diabetes is a major health issue for New Zealand. Maori and Pacific people have a higher burden of diabetes compared with Europeans. The New Zealand health sector and researchers have made progress to improve the detection and recording of type 2 diabetes. Researchers and government authorities have also shown a commitment to the quality of diabetes prevalence methodology.

Much less research using diabetes incidence as an outcome measure has been carried out in New Zealand compared with internationally. Diabetes cases detected in cross-sectional study designs are most frequently described as "new diabetes", "newly diagnosed diabetes" or "undiagnosed diabetes" in research that has taken place over relatively short time frames. A number of promising intensive lifestyle trials have been carried out using weight loss, or reductions in HbA1c as the primary outcome measures. A promising community-wide intervention programme has also shown reductions in the primary outcome measure of insulin resistance prevalence over short periods of time.

Diabetes screening has potential to identify both new diabetes and IFG or IGT cases that would benefit from intensive lifestyle interventions. Screening follow-up studies are most prone to selection bias, lead time bias, and biases associated with loss to follow-up.

Several important observations were made from the research reviewed in this literature review. The first was that all-cause mortality is a useful measure to use for screening studies to assist with identifying the potential of the healthy participant effect on the results. Second was that including cases who have died from any cause is likely to result in incomplete follow-up data, introducing a form of selection bias if those who have died have a different

risk from those who remain in the study. Third was that researchers' trade-off having a complete set of data with results unlikely to be obtained in real-world practice. Fourth, diabetes screening research used different definitions e.g. high-risk, and exclusion and inclusion criteria, making comparability with other studies problematic.

No New Zealand studies were found which assessed the effect of diabetes screening as part of cardiovascular risk assessments on progression to diabetes. Continued expectations of CVDRA will result in a routinely collected source of repeated blood glucose levels in a high risk non-diabetic population. Primary care Read Codes for type 2 diabetes have been regarded as a reliable source of diagnosed diabetes. Potentially this source of data could be used to monitor the effect of prevention efforts to reduce the risk of progression to diabetes.

Chapter 3 Methods

3.1 The setting: Northland, New Zealand

Northland's population was estimated to be 159,160 in 2012 which is approximately 3.6% of New Zealand's population (Northland District Health Board (NDHB), 2012). Around 30% of Northland's population is Maori compared with 14% for New Zealand as a whole (Statistics New Zealand, 2006). Northland also has one of the most deprived populations in the country (NDHB, 2012).

Figure 3 shows that 50% of Northlands population live in the Whangarei District Council with Whangarei City being by far the greatest urban area in Northland. The other main centres are towns of approximately 5000 people. The remainder of the population is spread over the rural areas (Statistics New Zealand, 2006; NDHB, 2012).

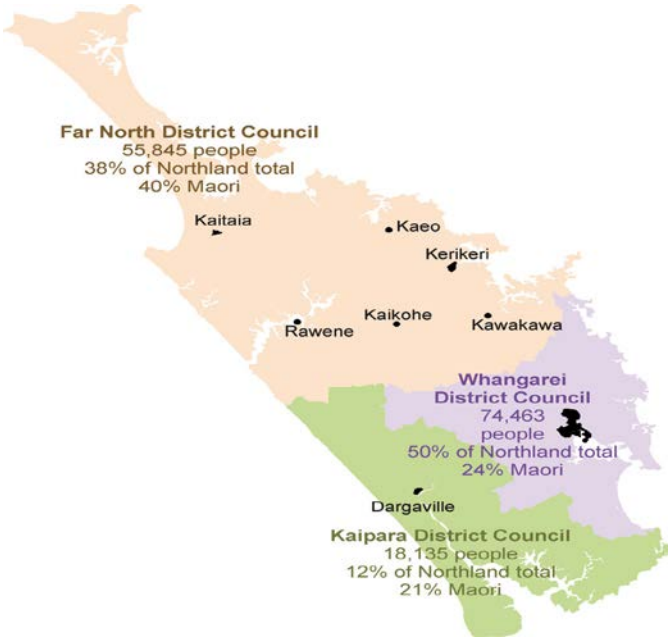

Figure 1. Northland's population distribution by Local Authority and proportion of Maori

Source: Northland District Health Board, Northland Health Services Plan 2012-2017

3.2 Type 2 Diabetes in Northland

Type 2 Diabetes is a major health issue in Northland. In 2009 6.9% (approximately 8140 people) of the adult population (> 15 years) were

estimated to have diabetes. This number is projected to increase to 14560 people by 2026, an increase of 72%, attributed mainly to increasing levels of obesity (NDHB, 2012).

Given that diabetes prevalence is around three times higher in Maori and Pacific people at younger ages compared with the rest of the New Zealand population (MoH, 2007), the implications of diabetes on a population with a high proportion of Maori are significant and pose a high societal cost. Zhang et al., (2010) found that local health departments were more likely to conduct diabetes screening programmes if the burden of diabetes was high. Simmons et al., (2012) recognised that that the benefits of screening could be greater in areas where the population risk is greater –that is in areas with greater deprivation compared with areas less deprived, if a good level of uptake could be achieved. The *Northland Diabetes Screening and Cardiovascular risk assessment pilot* was one such initiative.

3.3 The pilot study

3.3.1 Background

The *Northland Diabetes Screening and Cardiovascular risk assessment pilot* was developed by staff at Northland District Health Board led by Dr Nick Chamberlain and funded by the Ministry of Health, in 2004. The rationale for developing the pilot was the Ministry of Health's interest in promoting initiatives encouraged by the World Health Organisation (WHO) to improve early detection of diabetes (WHO, 2003; PWC, 2001). However, there was also interest in assessing the prevalence of undiagnosed diabetes in this population and testing the efficacy of practice recall systems. The pilot involved four general practices, an Iwi Provider, Northland Pathology Ltd and Northland District Health Board.

Near the completion of the pilot study in 2006, Dr Chamberlain approached Massey University's Centre for Public Health Research (CPHR) to commission an evaluation of the pilot. The researcher (BW) became involved only when the evaluation of the pilot was commissioned at the end of the pilot.

3.3.2 Evaluation methods

There were four general practices, serving a mixture of urban and rural populations, with a total registered population of 28,000, included in the pilot study. The evaluation design included an assessment of the screening and diagnostic pathway for diabetes detection, cardiovascular risk assessment results, and a provider survey.

The pilot study had a cross-sectional study design. Results of the pilot were described as the observed prevalence of screening detected diabetes in a population with no known diabetes over a period of time defined as 2004-2006.

General practice staff were required to identify who to screen based on the criteria shown in Table 4. Note that the inclusion criteria were similar to New Zealand Guidelines with the exception that these were not delineated by gender. Exclusion criteria were; known history of diabetes, and fasting plasma glucose result < 5.5mmol/L in the previous year (White, 2008).

3.3.3 Study size

Due to funding constraints of the pilot, each practice was given a quota of patients to include in the pilot. The priority was to screen Maori and Pacific People and the quota was determined based on the number of Maori and Pacific Island people identified from the practices' age-sex registers with no known diabetes. For all four general practices this totalled 1800 people. As funding was available for 2200 people, screening of Non-Maori was available for 400 Non-Maori (White, 2008).

Table 4. Inclusion criteria for the Northland Diabetes and Cardiovascular Risk Assessment pilot 2004

Criteria for Maori and Pacific Island people and people of Asian decent	Criteria for European
All Maori and Pacific Island people >35 years of age, or: 10 years younger if in combination with one or more of the following risk factors: BMI>30 (kg/m2), 1st-degree relative with Type 2 type 2 diabetes, hypertension, triglycerides >2.8 mmol/L, low HDL cholesterol, polycystic ovary syndrome, or a history of CVD	European>50 years of age, or: 10 years younger if in combination with one or more of the following risk factors: BMI>30 (kg/m2), 1st-degree relative with Type 2 type 2 diabetes, hypertension, triglycerides >2.8 mmol/L, low HDL cholesterol, polycystic ovary syndrome, or a history of CVD

3.3.4 Recruitment

Patients that were identified from practice systems were then sent an invitation letter which explained the purpose of the study and included fasting instructions, a laboratory form and an informed consent form. Patients who did not have a recent fasting lipids test result were sent an additional laboratory form for fasting lipid testing to be taken at the same time as the tests on the other laboratory form (White & Chamberlain, 2009).

According to the pilot protocol, practices were also able to recruit using an opportunistic approach. That is, as patients attended for unrelated appointments, they could be formally invited onto the pilot programme. Patients invited using this approach were given the invitation letter, informed consent form, and laboratory forms (White & Chamberlain, 2009).

All patients screened for diabetes as part of the pilot protocol were also required to have a cardiovascular risk score calculated. Results of blood glucose tests greater than 5.5mmol/L were required to be followed up with an oral glucose tolerance test. The cardiovascular risk score determined the level of appropriate follow-up for prevention and management of cardiovascular

risk factors according to the 2003 New Zealand Guidelines (White & Chamberlain, 2009). For those who did not elect to participate in the pilot programme, routine care was provided following the 2003 New Zealand Guidelines (NZGG, 2003)

3.3.5 Data collection

Northland Pathology Ltd. designed and maintained an Excel spread sheet of the following data: Patient details, ethnicity, primary care doctor, FPG results, CVD risk score, method of recruitment, and follow-up OGT result.

3.3.6 Data analysis

Data was analysed in two groups: Maori and Non-Maori. Completeness of the screening pathway was assessed. A complete pathway was defined as those with 5.5- 11.0mmol/l and a recorded Oral Glucose tolerance test (OGT), or a FPG test < 5.5mmol/L. Prevalence of IGT and diabetes was calculated using WHO criteria (2006) of all participants with completed screens using crude detection rates stratified by age (White & Chamberlain, 2009).

3.3.7 Key results

A total of 1251 people were screened of which 60% were Maori (752/1251). From the 89% (668/752) of Maori with a completed pathway, 3.6% (24/668) were diagnosed with diabetes and 3.6% (24/668) with IGT. From the 90% (451/499) of Non-Maori with completed screens, 2.0% (9/451) were diagnosed with diabetes and 2.2% (10/451) with IGT. However, only around 50% of those who should have had a follow-up OGT, had the test done. The proportion of completed CVDRAs was statistically significantly (p=0.0001) lower in Maori (76.6%, 576/752) compared with Non-Maori (85.4%, 426/499).

3.3.8 Provider survey

Key stakeholders (Ministry of Health, Northland District Health Board authorities, participating general practices and Iwi provider, and Northland Pathology Ltd) were invited to contribute to the design of the provider survey. This was done by meeting with each of the key stakeholders where each was asked; "What would make the evaluation useful to you?" From the autonomous discussions occurring between the evaluator (BW) and the stakeholders, themes were drawn out and these themes were used to develop the survey objectives. The survey objectives covered aspects of systems and

methods to recruit for the pilot, follow-up of FPGs >5.5mmol/L with an OGT, CVD risk calculations and general views on the benefits of and methods for screening for diabetes, resources to improve outcomes, and pilot process views - see Appendix 2.

There were 12/17 completed surveys from a multidisciplinary sample (general practitioner n = 5, registered nurse n = 3, practice manager n = 3, and receptionist n= 1). The key findings from the pilot evaluation's provider survey indicated that not all service providers had a system for identifying who to screen, or who to follow-up for non-response. There were concerns about the capacity and resources of primary care to cope with the increase in numbers of patients being tested, and managing those detected with diabetes and high cardiovascular risk. Ninety-eight percent of those surveyed agreed with the approach of systematic recall to screen for diabetes as part of CVD risk assessment.

3.3.9 Evaluation conclusions

It was clear that there was a need for better practice management systems to ease the burden on practice staff to identify those requiring follow-up testing and re-screening for cardiovascular risk factors and diabetes detection. Without improvements in these areas the success of future recall programmes would be compromised (White, 2008).

The OGT test posed a barrier to effective diagnosis of diabetes. The inconvenience of fasting tests for patients with high risk, particularly the OGT, suggested that a test such as the HbA1c, which does not require the patient to be fasting, could increase the effectiveness of diabetes screening to detect diabetes. White and Chamberlain (2009), recommended further investigation into the use of HbA1c for screening or diagnosing diabetes for high risk groups.

The pilot focussed on screening for diabetes accompanied by a CVDRA. The completeness of CVDRAs for Maori was statistically significant ($p<0.001$) lower than Non-Maori. If CVDRA programmes were used as the sole mechanism to screen for diabetes, this could potentially result in fewer Maori screened for diabetes thus leading to asymptomatic diabetes being

undiagnosed in Maori populations. White and Chamberlain (2009) cautioned against the reliance on CVDRA programmes as the sole mechanism to identify Maori with diabetes or IGT.

3.3.10 Pilot outcomes

Around the same time as the pilot, there had been a number of studies investigating the feasibility of using recall systems particularly in the area of cardiovascular risk assessments (Sheerin, Hamilton, Humphrey & Scragg, 2007; Sinclair & Kerr, 2006; Rafter et al., 2008). The findings of these studies along with the pilot evaluation provided authorities with a consistent message on the need for improvements to information systems, specifically recall and follow-up capabilities, to ensure improved service delivery and population health.

Following this outcome, Northland and Wanganui Health authorities joined together in support of the development and implementation of Patient Dashboard. The Patient Dashboard is a Medtech practice management extension tool which allows practice staff to see the patient "at a glance". This pops up whenever they select the patient they are about to see and provides a traffic light system to highlight any missing data or activities that are either overdue or require action (McMenamin, Nicholson & Leech, 2011).

This study also contributed to early discussions on the use of HbA1c for screening or diagnosing diabetes. The provisional findings of the study were presented at a National Diabetes Epidemiology Workshop hosted by the Ministry of Health in 2007. The barriers of the OGT test and the potential for the use of HBA1c to screen or diagnose type 2 diabetes were discussed. The recommendation for the use of HBA1c for screening and diagnosing diabetes was also published in the paper presenting the pilot results (White & Chamberlain, 2009).

3.4 The Northland Diabetes Screening and Cardiovascular risk assessment pilot: 5 year follow-up study

3.4.1 Introduction

To date there has been no assessment of whether the pilot study contributed to improved health outcomes for those who participated nor whether CVDRA programmes have prevented or delayed progression to diabetes.

This follow-up project arose out of discussions with key pilot stakeholders informing the pilot evaluation design (see 3.3.8). It was proposed then that it would be useful to learn what the longer-term implications of the pilot on progression to diabetes. It was determined that this was outside of the scope of the pilot evaluation brief, mainly because not enough time had progressed. This follow-up study forms the investigative section of this thesis.

3.4.2 Aims and Objectives

Primary aim

To determine if participation in the pilot had an effect on progression to diabetes, impaired glucose tolerance, and death from any cause from a normal baseline blood glucose test, compared with non-participation.

Secondary aim

To determine the suitability of general practice information systems to measure diabetes incidence rates.

Objectives

1. To describe the methodology used to carry out the follow-up study.

2. To analyse the data using:

- Exploratory data analyses
- Comparison of main groups by primary and secondary outcomes with rate ratios and mean progression time
    - Overall incidence rates, numbers needed to screen (NNS), and undiagnosed diabetes, by 5 year age bands and gender stratified by ethnic group

3) To evaluate:

- The results in the context of other literature and assessment of bias
- How well the study meet the primary and secondary aims

4) To make recommendations for future research and action

3.4.3 Methods

3.4.3.1 Study Design

People invited to participate in the *Northland Type 2 diabetes Screening and Cardiovascular risk assessment pilot* were self-selecting into groups with no randomisation used. Follow-up was to observe what had occurred in real-life. This meant that the observational study design options were either: case-control, cross-sectional, or cohort/follow-up designs.

A retrospective follow-up study design was selected over case-control and cross-sectional study designs for several reasons;

Firstly, the aim of this study was to determine the effect of participation in the pilot study on progression to diabetes. This meant that the study design needed to be able to determine changes over time in the same group of people. As cross-sectional studies take a "slice" of time and make comparisons between the variables of interest, the cross-sectional design was not suitable to answer the research aim.

Secondly, in a case-control design, comparison groups are determined by the outcome rather than the exposure (Pearce, 2003; Reigelman, 2005). This would be a less useful way to determine the effect of the pilot programme on progression to diabetes for health services planning. It is mainly for this reason that a follow-up study (cohort) design was selected – that is, to follow-up based on exposure not outcome. The cohort being followed up all had one thing in common – they had all been invited to participate in the *Northland Diabetes Screening and Cardiovascular Risk Assessment pilot.*

In a prospective follow-up study design, data is routinely collected and stored as it occurs in real-life. This is considered prospective data collection. Had the data in this follow-up study been collected and stored in the practice management system specifically for the purpose of this study, a prospective follow-up study design could have been used. However, the data was

retrieved from the practice management system at the end of the study period dating back to the beginning of the pilot study. Data was collected for the purposes of administration and clinical investigation or management, not specifically for the purpose of this study. Therefore this study is a retrospective study design.

The advantage in using a retrospective study design is that rescreening and the outcomes can be observed as they occur in real life. Also, it would be unlikely that practice staff would have biased the results to favour those in the pilot group over those that did not participate in the pilot.

3.4.3.2. Sample selection

While the *Northland Diabetes Screening and Cardiovascular risk assessment* pilot had four participating general practices and an Iwi Provider, the follow-up study was conducted in only one general practice. The reasons for this are explained below.

1. This practice screened the majority of the patients

Selecting one general practice instead of four would reduce the study size. However this practice screened the majority of the total number of general practice patients in the pilot. The selected practice screened 63.4% (477/752) of the total number of Maori screened by general practices and 71.3% (356/499) of Non-Maori

2. The practice held the original systematic recall list on Medtech

This reason was critical for being able to conduct this study. Without this list, it would not be possible to identify the whole sample that was invited to participate in the pilot. In section 3.3.2 the inclusion and exclusion criteria of the pilot were presented. In statistical terms the exclusion inclusion criteria defines what the "target population" was for the pilot. The job of identifying patients applying these criteria was up to each practice. In statistical terms the original systematic recall list was considered "the frame" from which the pilot sample was selected. This recall list can also be used to retrieve the data from

the practice management system. In statistical terms, the recall list becomes the "data collection tool" for this follow-up study.

3. Eliminating bias created by different service provider systems and processes

From the pilot evaluation it was identified that each practice differed in their capacity, practices and process towards screening for diabetes. These differences could create unnecessary bias. For example, different standing orders for diabetes screening could mean that screening is less or more frequent, the population who should be screened could be different, different tests could be used for screening and diagnosis, and systems to identify those whose tests results require follow-up could be different. All these differences would mean that a patient could be diagnosed in one practice and not another. By restricting the sample to one practice, the results would not be able to be confounded by differences in general practice systems and processes.

4. Majority of the population are Maori and live in areas with the highest levels of deprivation

There was strong interest in assessing the implications of screening for type 2 diabetes in a population where the majority of the population was Maori (~60%) and lived in very deprived circumstances (~70% NZ Dep quintile of 5). While this generated a non-representative sample of Northland overall and affected generalizability of the results, this was in-keeping with the intent of the pilot which was to prioritise for Maori and those less advantaged.

3.4.3.3 Setting

The chosen practice is based in a service town in the Far North of Northland. This independent urban area services its residents and those in the surrounding rural area.

The average deprivation of the areas where the practice is set is 9 and 10. This means that on average people who live in these areas have the highest levels of deprivation in the New Zealand population (University of Otago, 2007).

Using Census 2006 data, the distribution of Maori in the total population was compared across three age categories for all of New Zealand, Northland, and

the practice setting. Table 6 shows how different this distribution is even comparing the practice population with Northland as a whole. Half of the total population aged 30-69 years that live in the areas where the practice is located are Maori (Statistics New Zealand, 2006).

Table 5. Comparisons of distribution (in percent) of Maori by setting and age category

	Age category			
	<30	30-69	70+	All ages
Region	%	%	%	%
New Zealand	20.2	10.7	3.7	14.0
Northland	42.4	22.8	10.5	29.3
Practice setting	70.0	50.7	33.6	58.7

3.4.3.4 Study size

Previously, it was described how each practice was assigned a quota for the pilot study. The quota for the selected practice in this follow-up was 800. The frame, that is the systematic recall list, which was used to select the pilot participants, was based on the age sex ethnicity register of the chosen general practice. This list was generated by practice staff. For this follow-up study, the study size was determined by the number of people on this list. Because of this no study power calculations were carried out.

3.4.3.5 Participants

The number of people selected by the practice from the practice register based on age and ethnicity that were invited onto the pilot programme came to 2320 once duplicates were removed. By ethnic category there were 1645 Maori (70.9%) and 675 Non-Maori (29.1%). Patients were then examined for eligibility for this study according to inclusion and exclusion criteria.

3.4.3.6 Inclusion criteria

All Maori patients that were aged 35 years and over OR all Non-Maori patients that were aged 50 years of over AND on the systematic recall list generated by the chosen general practice, were included in this follow-up study.

3.4.3.7 Exclusion criteria

A diagnosis of type 2 diabetes before the commencement of the pilot OR before the baseline assessment date OR age < 35 years if Maori or < 50 years if Non-Maori OR no National Health Index (NHI) OR no ethnicity code, lead to exclusion from the study.

This resulted in 136 Maori and 56 Non-Maori being excluded from this study leaving a total of 2128 people eligible of which 1509 (70.9%) were Maori and 619 (29.1%) were Non-Maori. The reasons for exclusions are shown in Table 6. The total remaining is referred to in the remainder of this report as the "source population".

Table 6. Number and percentage of exclusions from the study by reason and ethnic group

	Maori		**Non-Maori**		**Total**	
Total invited	1645	%	675	%	2320	%
Reason for exclusion						
No NHI	13	0.8	3	0.4	16	0.7
Casual patient	37	2.2	27	4.0	64	2.8
Dx exclusions*	3	0.2	4	0.6	7	0.3
Age exclusions	83	5.0	22	3.3	105	4.5
Total exclusions	***136***	***8.3***	***56***	***8.3***	***192***	***8.3***
Total remaining	**1509**	**91.7**	**619**	**91.7**	**2128**	**91.7**

*Dx exclusions refers to exclusions because the diagnosis date of diabetes was before the implementation of the pilot programme.

3.5.4 Assignment into groups

All participants were sorted into two groups: Pilot and Non-Pilot groups. Pilot status was determined by comparing NHIs with baseline data in the pilot data file. Validation of pilot participation was carried out by randomly citing the scanned signed informed consent forms stored in the electronic patient records and thereby confirming participation.

A further assessment of status was determined by the presence of a corresponding fasting blood glucose measurement in the follow-up study datafile extracted from the medical records for all identified pilot participants. The baseline pilot study data held eight entries which used an unidentifiable or scrambled identifier. This may have led to those eight people being incorrectly assigned to one of the non-pilot groups. Validation of pilot

participation by randomly checking the scanned copy of the signed informed consent form was 100% for those checked. A further 15 pilot participants had no matching blood glucose result recorded in the extracted blood measurement data for the entire duration being studied (1/9/2004-31/8/2011). This brought about a total of 23 people who participated in the pilot programme according to the pilot baseline data that were potentially misclassified into another group or excluded from the from the study. In total 671 pilot participants were identified by NHI from the baseline data and assigned to the "Pilot" group.

It was anticipated that the practice would still screen those invited to participate in the pilot for type 2 diabetes according to NZGG clinical guidelines (NZGG, 2003) even if the patients decided not to formally participate in the pilot. It was likely therefore that the Non-Pilot group would consist of two groups; a screened non-pilot group and an unscreened non-pilot group.

3.5.5 Method of follow-up

The dataset used in this study was extracted from the General Practice's electronic patient management system – (Medtech). The General Practice management system holds a range of data collected for administrative, medical management, and diagnostic testing purposes. All patients' glucose measurements results were electronically transferred from the laboratory and stored in Medtech.

For the follow-up study, data that had been stored in the practice management system was extracted retrospectively at the end of the follow-up time period. The collection tool was the original query build used to generate the systematic recall list. Personal contact fields were removed from the query build while date of birth and NHI was maintained. Additional fields were added to the query build to extract the specific data required for the variables of interest shown in Table 7 below.

Table 7. Complete list of data extracted from Medtech

Variable description	Data extracted
Identifier	NHI
Age	Date of birth
All-cause mortality	Date of death
Deprivation index	Quintile
Sex	Gender
Ethnicity	Ethnicity code
Blood Glucose measurements	All forms of glucose measurements (Gluc, HbA1c, OGTT) Result Date of test
Type 2 diabetes diagnosis	Type 2 diabetes classification codes used Date of diagnosis
Date of transfer from practice	Not able to extract via query build
Pilot participant	Not able to extract via query build

The data extracted was stored on two Excel 2010 files. The first file contained everything except for the blood glucose measurements. The second file contained the blood glucose measurements, date taken, and the result by NHI.

The first file was used to build the Master file. The steps taken to do this are described below. The operational definitions will be presented in the following section of this chapter. The steps were:

1. Data cleaning involved removing duplicates and assessing completeness of information. In a small number of cases an NHI was not available and patients were dropped from the study (refer to Table 7).

2. Next, a tracker code field was created and each NHI was given a unique Tracker code. The tracker code was applied to the corresponding NHI in this file also. The tracker codes were checked twice for accuracy.

3. All patients were assigned into two groups – participants and non-participants. The methods of assignment were described in the previous section.

4. Once assignment was completed a word document was created which contained the NHI and corresponding Tracker code for each patient and stored, after which all NHIs in all files (Master file, Blood glucose

measurement file, and the baseline pilot programme dataset) were permanently removed.

5. The first recorded glucose result during the time period was entered along with the date, and type of test, into the masterfile into new fields created for this purpose. These results were classified as normal or abnormal (see definitions in 3.5.6).

6. At the same time, the initial series of tests were compared with the diagnosis date and if a diagnosis occurred within 16 weeks of the first date, then the patient was classified as "baseline diabetes".

7. Repeat blood glucose series were counted up until the point of censor (defined 3.5.6 under the heading of 'person-years') and categorised into numbers of rescreens, as defined in the operational definitions (3.5.6).

8. Patients identified with Impaired Glucose Tolerance (IGT) from the file containing glucose measurements were assigned as IGT in a new field along with the date of the relevant laboratory test.

9. Other variables such as age and person-years were calculated and added as separate fields to the master file.

3.5.6 Definition of Variables

Type 2 diabetes diagnoses: The earliest date of diabetes diagnosis extracted from the practice management system according to classification terms provided by practice staff was used to determine who would be classified with diabetes.

Impaired Glucose Tolerance: Detection of Impaired Glucose Tolerance (IGT) was defined as the secondary outcome. IGT was determined by selecting all Oral Glucose Tolerance test results within the range of 7.8 mmol/L and 11.0 mmol/L

Baseline screening type 2 diabetes: Those who received a diagnosis within 16 weeks of the baseline test were categorised as "baseline diabetes".

Time from baseline to diagnosis: Time from the baseline result to the diagnosis date was used as a categorical variable and a continuous variable.

As a categorical variable, time was categorised into time periods. Diagnosis date was determined by the diagnosis date in the practice management system. The time periods were between; 17 – 52 weeks, >1<=2years, >2<=3 years, >3<=4 years, >4<=5 years, >5<=6 years, >6<=7 years.

As a continuous variable, the number of days between the baseline test and the diagnosis date was calculated for each patient. For diabetes, the diagnosis date was determined by the diagnosis date in the practice management system. The date of diagnosis of IGT was the date of the Oral Glucose Tolerance test result. Days were converted into months.

Ethnicity: Ethnicity was analysed in two groups, Maori and Non-Maori. From the data extracted from the practice management system ethnicity was determined by the ethnicity codes. The ethnicity code for Maori was "21". Therefore, all Ethnicity codes which equalled 21 were classified as Maori and all other codes were classified as "Non-Maori".

Age: Age was calculated using Excel 2010 by calculating the number of days from the individual's date of birth and the date of the commencement of the pilot programme (September, 1st, 2004). The number of days was then converted into age in years up to the number of decimal points used by Excel and then rounded up or down to the nearest year by Excel.

Age was also calculated to determine mean age and standard deviation of each group at the time of a diagnosis of diabetes, IGT or when death occurred. Excel 2010 was used to calculate the number of days from the date of birth to the date of diagnosis or death recorded in the practice management system for each patient. Days were then converted into years, as mentioned above. .

NZ Deprivation Index by Quintile: NZ Deprivation 2006 scores were calculated from the 2006 census for each meshblock. Statistics New Zealand (2012b) defines a meshblock as the smallest geographical unit from which data is collected and analysed. The census information on income, education, transport, support, home ownership, living space, and employment data is used to calculate the relative deprivation for each meshblock (Salmond, Crampton, and Atkinson, 2007).

The New Zealand population is divided into tenths. A value of 1 means the person lives in a meshblock in the least deprived 10 per cent of New Zealand areas. A value of 10 means the person lives in a meshblock in the most deprived 10 per cent of New Zealand areas. Quintiles are deprivation values categorised into 5 groups. A quintile of 1 combines deprivation values 1 and 2, a quintile with a value of 2 combines deprivation values of 3 and 4, and so on. A person with a quintile value of 5 indicates that they live in an area with 20 percent of New Zealand's greatest deprivation (Salmond, Crampton, and Atkinson, 2007). This follow-up study used the New Zealand Deprivation 2006 quintiles recorded on the practice management system for each patient. The values were used to represent the level of deprivation in which the individual lives, not the level of deprivation of the individual (Salmond, Crampton, and Atkinson, 2007).

The classification of the area unit was based on the patient's address. Inaccurate addresses due to high internal migration that were recorded in the practice management system were not likely to impact greatly on the misclassification of average area unit deprivation. This reasoning was based on findings by Morrison and Nissen, who compared area unit of origin to area unit destination between those who moved between the 2001 and 2006 census. They found that people who live in relatively more deprived areas are more likely to move to areas which have either the same or similar levels of deprivation (Morrison & Nissen, 2010).

Person-years: Person-years were calculated by taking the time in years from the start date of the pilot implementation until the time of censure. Censure date was either: 1) the date of classification with type 2 diabetes 2) the date of death, or 3) the end date of the follow up period (31 August, 2011), whichever occurred first.

The values were summed for each group. The rounding up or down of decimal points only occurred after the incidence rates were calculated.

Rescreening: After the initial baseline test the subsequent blood glucose measurements were assessed for each patient. A rescreen of a single blood glucose test would be counted as one rescreen. The exception to this rule was

when a series of tests had occurred within a short time frame (1 day to 3 weeks) because the patient had a result in the equivocal range. This series would be counted as one rescreen.

Normal Glucose Test: During the pilot a blood glucose cutoff of 5.5mmol/L cutoff was used to determine the appropriate course of follow-up action. For this follow-up study the cutoff used to estimate primary and secondary outcomes from a normal glucose test result will be 6.1mmol/L. This level was chosen to increase the ability to compare future New Zealand studies on progression to diabetes with results of this study. This was because in 2012 the New Zealand Guidelines for screening and diagnosing diabetes was reviewed and follow-up diagnostic testing of blood glucose tests in the 5.5-6.0mmol/L range was no longer recommended. The comparability with studies set in other countries applying WHO criteria would also be increased. The World Health Organisation (2006) recommended that a FPG result less than 6.1mmol/L was associated with a low risk of developing diabetes and cardiovascular disease.

Comparisons of the proportion of pilot and non-pilot participants that had an abnormal test were made using the cutoff value of 5.5mmol/L for the pilot study and 6.1mmol/L for the follow-up study.

3.5.7 Analyses

3.5.7.1 Exploratory analysis

The distributions of person characteristics were analysed following an exploratory analytical approach. The purpose of this was to identify any differences between characteristics that could explain any differences found in the results of the measures of effect. Also, identifying differences of person characteristics has implications for health service utilisation i.e. who uptakes to a formal invitation versus usual care (referred to throughout this report as opportunistic screening). The population who did not have any blood glucose assessment during the entire study time would be described as much as possible.

3.5.7.2 Measures of effect

The primary outcome measure of interest were; 1. to measure the progression to type 2 diabetes or impaired glucose tolerance, and all-cause mortality for each group, and 2. the comparisons of these measures between groups.

The incidence rate was calculated with the number of cases diagnosed with type 2 diabetes as the numerator and the total sum of person-years calculated specifically for each stratum as the denominator. The product was then multiplied by 1000 to generate the incident rate per 1000 person-years.

All data was presented separately by ethnic group. Stratification was used to control for identified confounding variables. When the numbers of the outcome event were too small, stratification was calculated for one confounding variable at a time.

Mean time and standard deviations were calculated using Excel 2010.

3.5.7.3 Statistical testing

The Mantel-Haenszel method was used to calculate both crude and adjusted rate ratios using Open Epi version 2.3.1. Statistical significance was determined by the range of the confidence interval. An interval crossing 1 would indicate that there was no statistically significant difference between the groups.

For categorical and continuous variables, statistical differences between groups were calculated by using chi square contingency for categorical variables and t-tests for continuous variables. All calculations were made using Open Epi version 2.3.1. The level of significance was set at $p<0.05$. http://www.openepi.com/OE2.3/Menu/OpenEpiMenu.htm .

3.5.7.4 Other analyses using pooled data

3.5.7.4.1 Incidence proportion

The data of all patients with a fasting blood glucose test less than 6.1mmol/L was pooled. The incidence proportion was used in order to compare with the estimate proposed by Kenealy et al., 2002. To calculate this, the number of incidence cases was divided by the total number of people screened, stratified by Maori and Non-Maori.

3.5.7.4.2 Incidence rates, efficiency of screening and undiagnosed diabetes

The data of all patients with one or more fasting blood glucose tests, regardless of baseline tests, were pooled. Using this data, incidence rates/1000 person-years were calculated separately for Maori and Non-Māori and stratified by 5 year age bands and gender.

Number needed to screen (NNS) and undiagnosed diabetes was calculated by following the methods described by Wilson et al., (2010). NNS was calculated by taking the number of people who had had at least one blood glucose test in a five year period and dividing it by the number of incident diabetes cases.

Undiagnosed diabetes was calculated by taking the number of individuals not tested and dividing it by the number needed to screen. This would give an estimate of how many additional cases of diabetes could have been detected in a 100% screening scenario.

Chapter 4 Results

4.1 Baseline characteristics

4.1.1 Baseline characteristics-Maori

Of the 1509 Maori included in this study, 385 (25.5%) self-selected onto the pilot programme (hereafter referred to as the "Pilot group") i.e. 48.1% of the pilot quota (385/800). Of the remaining 1124, 691 underwent diabetes screening at some point during the study period i.e. 45.8% of total number of Maori (691/1509). This group is referred to as the "Non-Pilot group". There were 433 people with no glucose screening result recorded for the entire study period (28.7%, 433/1509). These are referred to from this point on as the "Unscreened group".

Table 8. Baseline person characteristics for Maori

Total N ***(%)***	**Source** **1509 (100)**		**Pilot** **385 (25.5)**		**Non-Pilot** **691 (45.8)**		**Unscreened** **433 (28.7)**	
	n	***%***	n	*%*	n	*%*	n	*%*
age category								
35-39	**310**	***20.5***	28*	*7.3*	133	*19.2*	149	*34.4*
40-44	**346**	***22.9***	61*	*15.8*	159	*23.0*	126	*29.1*
45-49	**318**	***21.1***	87	*22.6*	152	*22.0*	79	*18.2*
50-54	**212**	***14.0***	65†	*16.9*	110	*15.9*	37	*8.5*
55-59	**112**	***7.4***	42*	*10.9*	52	*7.5*	18	*4.2*
60-64	**71**	***4.7***	35*	*9.1*	28	*4.1*	8	*1.8*
65-69	**53**	***3.5***	27*	*7.0*	19	*2.7*	7	*1.6*
70-74	**51**	***3.4***	28*	*7.3*	18	*2.6*	5	*1.2*
75+	**36**	***2.4***	12†	*3.1*	20	*2.9*	4	*0.9*
gender								
Female	**818**	***54.2***	222	*57.7*	365	*52.8*	231	*53.3*
Male	**691**	***45.8***	163	*42.3*	326	*47.2*	202	*46.7*
Quintile								
1	**19**	***1.3***	4	*1.0*	11	*1.6*	4	*0.9*
2	**24**	***1.6***	4	*1.0*	12	*1.7*	8	*1.8*
3	**75**	***5.0***	15	*3.9*	40	*5.8*	20	*4.6*
4	**134**	***8.9***	33	*8.6*	63	*9.1*	38	*8.8*
5	**1164**	***77.1***	304	*79.0*	536	*77.6*	324	*74.8*
NA	**93**	***6.2***	25	*6.5*	29	*4.2*	39	*9.0*

* Pilot group is significantly different ($p<0.05$)from the Non-Pilot group and Unscreened group

† Pilot group is significantly different ($p<0.05$) from Unscreened group only

In Table 8, the baseline person characteristics are shown for each of the three groups. The Non-Pilot group had a remarkably similar distribution of age

compared with the source population. There were also more males in the non-pilot group compared to the source population and pilot group (p = 0.06), but similar to the unscreened group distribution (p= 0.11).

There were more people living in quintile 5 (the most deprived) in the Pilot group compared with the source population and Non-Pilot group (p=0.30) and Unscreened group (p = 0.08).

Table 8 also shows that there were more people in the older age groups over 50 years of age and there were statistically significant differences for both the pilot and unscreened groups compared with the Non-Pilot group. There was a statistically significantly lower number of younger Maori aged 35-39 years of age in the Pilot group compared with the Unscreened group (28/385 v 149/433, p = <0.001) and the Non-Pilot group (28/385 v 133/691, p =<0.001). There were also a statistically significantly lower number of Maori in the 40-44 year old age group in the Pilot group compared with the Unscreened group (61/385 v 126/433 p = <0.001) and the Non-Pilot group (61/385 v 159 /691, p = 0.003). The differences and similarities in age distribution between groups are shown in Figure 2.

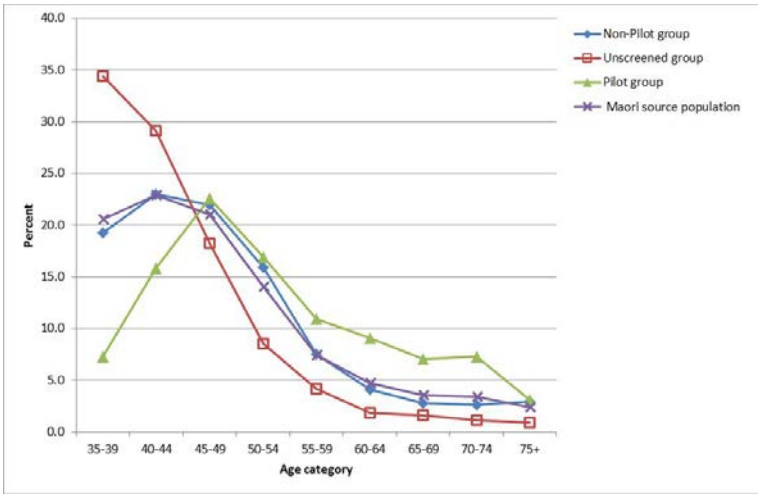

Figure 2. Comparisons of distribution of age with groups for Maori

4.1.2 Baseline characteristics – Non-Maori

The composition of the Non-Maori group was as follows: Pacific people (1.8%), Asian (0.6%), Other (0.5%), and European (97.1%). Table 9 shows the

distribution of the source population with the remaining person variables included in this study for Non-Maori. In total there were 619 Non-Maori people included in this study of which 44.1% (273/619) were in the Pilot group , 38.5% (238/619) in the Non-Pilot group, and 17.4% (108/619) in the Unscreened group.

There was a greater distribution of females in the pilot group (45.1%) compared to the non-pilot group (35.7%) and the unscreened group (42.6%). The differences in gender distribution between the pilot and non-pilot groups were statistically significant (p = 0.016).

Table 9. Baseline characteristics for Non-Maori

Total (%)	**Source 619 (100)**		**Pilot 273 (44.1)**		**Non-Pilot 238 (38.5)**		**Unscreened 108 (17.4)**	
	n	**%**	n	%	n	%	n	%
age category								
50-54	**143**	***23.1***	55	*20.1*	63	*26.5*	25	*23.1*
55-59	**156**	***25.2***	68	*24.9*	58	*24.4*	30	*27.8*
60-64	**112**	***18.1***	56	*20.5*	40	*16.8*	16	*14.8*
65-69	**67**	***10.8***	31	*11.4*	25	*10.5*	11	*10.2*
70-74	**51**	***8.2***	21	*7.7*	22	*9.2*	8	*7.4*
75+	**90**	***14.5***	42	*15.4*	30	*12.6*	18	*16.7*
gender								
Female	**254**	***41.0***	123*	*45.1*	85	*35.7*	46	*42.6*
Male	**365**	***59.0***	150*	*54.9*	153	*64.3*	62	*57.4*
quintile								
1	**37**	***6.0***	20	*7.3*	14	*5.9*	3	*2.8*
2	**20**	***3.2***	8	*2.9*	9	*3.8*	3	*2.8*
3	**67**	***10.8***	32	*11.7*	27	*11.3*	8	*7.4*
4	**73**	***11.8***	33	*12.1*	24	*10.1*	16	*14.8*
5	**389**	***62.8***	167	*61.2*	157	*66.0*	65	*60.2*
NA	**33**	***5.3***	13†	*4.8*	7	*2.9*	13	*12.0*

* Pilot group is statistically significantly different (p<0.5) from the Non-Pilot group
† Pilot group is statistically significantly different (p<0.5) from the Unscreened group

There was very little variation in the distributions of gender, and deprivation in the Unscreened Non-Maori group compared with the source population. There was also little difference between groups by age (Figure 3).

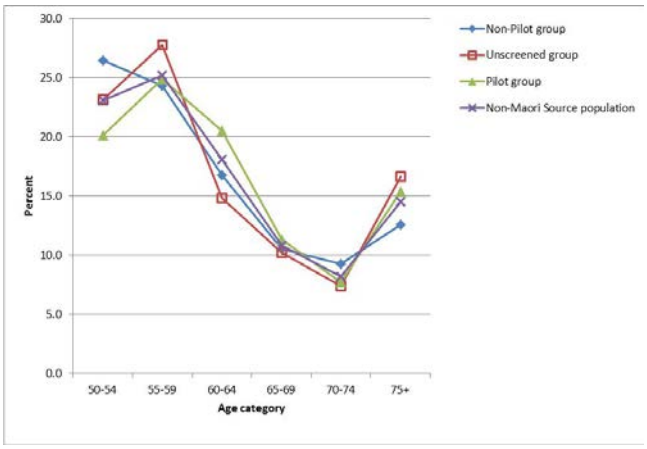

Figure 3. The distribution of age categories for Non-Maori by screening group compared with source population

4.1.3 Overall summary of screening activity

The overall uptake to the pilot programme and description of screening activity is shown in figure 4. For Maori the actual uptake was 25.5 % (385/1509) and for Non-Maori the uptake was 44.1% (273/619).

Figure 4 breaks down the amount of screening that occurred according to the defined time periods of this study. Almost as many Maori in the Non-Pilot group were screened during the pilot period as those who participated in the pilot programme (Non-Pilot group was 21.7% (328/1509) versus the Pilot group, 25.5% (385/1509)). An additional 24.1 % (363/1509) of the Non-Pilot group had a screening test during the follow-up period.

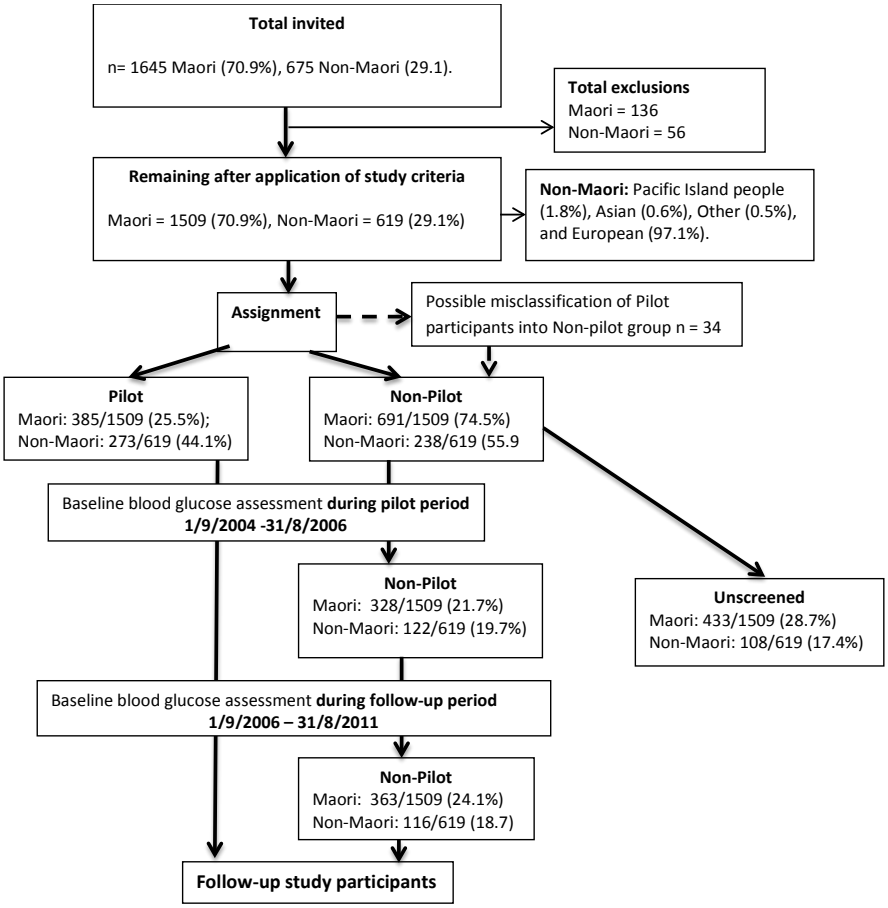

Figure 4. Summary of baseline screening activity

For Non Maori, in addition to the 44.1% (273/619) of patients in the Pilot group, there was also an additional 19.7% (122/619) screened during the pilot period and 18.7% (116/619) screened during the follow-up period. Out of all of the people invited to participate in the *Northland Diabetes and Cardiovascular risk assessment pilot* 71.3% of Maori (1076/1509) and 82.7% (511/619) of Non-Maori had had at least one blood glucose assessment between September 2004 and August 2011.

4.2 Baseline results

4.2.1 Baseline results for Maori

The proportion of Maori with abnormal screening tests was calculated and compared between the Pilot and Non-Pilot group using two cut-off criteria. The lower cut-off of 5.5mmol/L was the cut-off for diagnostic testing and part of the pilot protocol, whereas the cut-off of 6.1mmol/L was the revised cut-off in 2012. It was noted that for both criteria the proportion of Maori in the Non-pilot group whose baseline screening results were abnormal was much greater

compared with the pilot group and these differences were highly statistically significant (5.5 cut-off p<0.001; 6.1 cut-off p <0.001**).**

Table 10 shows the difference in the number of screening tests using the two cutoff values that would have required follow-up testing to rule in or out a diagnosis of diabetes in this population. Overall using the higher cut-off would have reduced the number of follow-up tests from 362 to 203.

Table 10. Proportion of abnormal screening test results for Maori using two cut-off points

Cut-off		Pilot	Non-Pilot	Total
5.5mmol/L				
<5.5	n	283	431	714
	%	*73.5*	*62.4*	*66.4*
≥5.5	n	102*	260	362
	%	*26.5*	*37.6*	*33.6*
6.1mmol/L				
<6.1	n	336	537	873
	%	*87.3*	*77.7*	*81.1*
≥6.1	n	49**	154	203
	%	*12.7*	*22.3*	*18.9*

* Pilot group significantly different from Non-Pilot group, p <0.001
**Pilot group significantly different from Non-Pilot group, p <0.001

Table 11 shows the person characteristics according to baseline glucose status with the 6.1 cut-off criteria applied. From all Maori screened in the pilot 10/385 (2.6%) were diagnosed with diabetes within 16 weeks of their baseline screening test which was similar to the Non-Pilot group (2.5%, 17/691). In the pilot group, 10.4% (40/385) Maori had glucose results in the pre-diabetes range (6.1-6.9mmol/L) compared with 19.8% (137/691) in the non-pilot group.

The distribution of person characteristics in the Pilot and Non-Pilot groups, whose baseline tests were < 6.1mmol/L (referred to here on as the Normal Glucose Tolerance (NGT)), were compared. The differences of distribution of age in the NGT groups were highly statistically significant (all p = <0.001), however the differences in proportion of males and people living in the most deprived areas was not statistically different between the NGT groups.

Table 11. Characteristics of Maori patients categorised by baseline blood glucose result

	NGT‡				6.1-6.9				Baseline diabetes			
	Pilot		Non-Pilot		Pilot		Non-Pilot		Pilot		Non-Pilot	
	n	***%****	**n**	***%****	**n**	***%****	**n**	***%****	**n**	***%****	**n**	***%****
Age 35-49	154†	*40.0*	358	*51.8*	18	*4.7*	77	*11.1*	4	*1.0*	9	*1.3*
50-64	123†	*31.9*	141	*20.4*	15	*3.9*	43	*6.2*	2	*0.5*	6	*0.9*
65+	58†	*15.1*	38	*5.5*	7	*1.8*	17	*2.5*	3	*0.8*	2	*0.3*
Male	140	*36.4*	245	*35.5*	18	*4.7*	74	*10.7*	5	*1.3*	7	*1.0*
DepQ5	266	*69.1*	412	*59.6*	30	*7.8*	112	*19.8*	8	*2.1*	12	*1.7*
Totals	**335**	***87.0***	**537**	***77.7***	**40**	***10.4***	**137**	***19.8***	**10**	***2.6***	**17**	***2.5***

‡ NGT is used to refer those with Normal Glucose Tolerance at baseline defined as a FPG test result <6.1mmol/L
*The total Maori in the pilot group (385) and non-pilot group (691) was used to calculate percentages
† NGT Pilot group statistically significantly different (p<0.5) to NGT Non-Pilot group
DepQ5 = Deprivation quintile 5, the most deprived residential areas

4.2.2 Baseline results for Non-Maori

As described for Maori, the proportion of abnormal tests (shown in Table 12) for Non-Maori in the Non-Pilot group regardless of criteria was statistically significantly higher than in the Pilot group (5.5 cutoff p= 0.02; 6.1 cutoff p= 0.002).

Table 12. Proportion of abnormal screening test results for Non-Maori using two cut-off points

Cut-off		Pilot n=253	Non-Pilot n=238	Total n=511
5.5mmol/L				
<5.5	n	223	177	400
	%	*81.7*	*74.4*	*78.3*
≥5.5	n	50*	61	111
	%	*18.3*	*25.6*	*21.7*
6.1mmol/L				
<6.1	n	255	204	459
	%	*93.4*	*85.7*	*89.8*
≥6.1	n	18**	34	52
	%	*6.6*	*14.3*	*10.2*

*Pilot group significantly different from Non-Pilot group, p= 0.02
**Pilot group significantly different from Non-Pilot group, p = 0.002

Table 13 shows the distribution of person characteristics according to baseline glucose status with the 6.1 cut-off criteria applied. From all Non-Maori screened in the pilot, 0.7% (2/273) were diagnosed with diabetes within 16 weeks of their baseline screening test. In the Non-Pilot group, 1.3% (3/238)

were diagnosed with diabetes within 16 weeks of their baseline test. In the pilot group 6.2% (17/273) Non-Maori had glucose results in the pre-diabetes range (6.1-6.9mmol/L) compared with 13.0% (31/238) in the non-pilot group.

Table 13 Characteristics of Non-Maori patients categorised by baseline blood glucose result

	NGT				6.1-6.9				Diabetes			
	Pilot		Non-Pilot		Pilot		Non-Pilot		Pilot		Non-Pilot	
	n	***%****	**n**	***%****	**n**	***%****	**n**	***%****	**n**	***%****	**n**	***%****
Age 50-64	166	*60.8*	145	*60.9*	12	*4.4*	14	*5.9*	1	*0.4*	2	*0.8*
65+	88	*32.2*	59	*24.8*	5	*1.8*	17	*7.1*	1	*0.4*	1	*0.4*
Male	139†	*50.9*	129	*54.2*	10	*3.7*	22	*9.2*	1	*0.4*	2	*0.8*
Dep Q 5	154	*56.4*	138	*58.0*	11	*4.0*	7	*2.9*	2	*0.7*	2	*0.8*
Total	**254**	***93.0***	**204**	***85.7***	**17**	***6.2***	**31**	***13.0***	**2**	***0.7***	**3**	***1.3***

‡ NGT is used to refer those with Normal Glucose Tolerance at baseline defined as a FPG test result <6.1mmol/L
*The total Non-Maori in the pilot group (273) and non-pilot group (238) was used to calculate percentages
† NGT Pilot group statistically significantly different (p<0.5) to NGT Non-Pilot group
DepQ5 = Deprivation quintile 5, the most deprived residential areas

The difference in distribution of males with NGT between the pilot and non-pilot groups were statistically significant (p = 0.03), however, the differences in the distribution of age or people living in the most deprived areas in the NGT groups were not statistically different.

4.3 Progression to diabetes, IGT, and all-cause mortality from normal baseline test

4.3.1 Results for Maori

4.3.1.1 Progression to diabetes

There were 3.0% (10/385) Maori who had progressed to diabetes in the pilot group compared with 4.1% (22/537) in the non-pilot group (p=0.196) (Table 14). The incidence rate in the pilot group was 4.9 (95%CI 2.35-9.028)/1000 person-years and was 10.1 (95%CI 6.519, 15.11)/1000 person-years in the non-pilot group. The difference between the crude (0.48 (95%CI 0.2292-1.022) and age-adjusted 0.44 (95%CI 0.2156, 0.912) rate ratio indicated that the differences in age distribution between the groups only slightly confounded the results and the protective association for pilot participants on progression to diabetes can be considered as statistically significant. The range of the 95% confidence interval indicated the protective effect would range from moderate to weakly protective 95% of the time.

The average time (in months) from the negative baseline test to a diagnosis of diabetes was longer in the Pilot group (42.8 months, SD = 19.9) compared with the Non-pilot group (38.5 months, SD = 18.8). This difference in mean time to progression to a diagnosis of diabetes was statistically significant (p = 0.001).

The average age at diagnosis was 4 years younger in the pilot group compared with the non-pilot group (53 years, SD = 8 v 57 years, SD = 9) and these differences were highly statistically significant, p <0.001).

4.3.1.2 Progression to IGT

Twenty (6.0%) of Maori in the Pilot group progressed to IGT of which two (0.5%) also went onto a diagnosis of diabetes. In the Non-pilot group there were 23 people (4.3%) who progressed to IGT of which three (0.6%) also went onto a diagnosis of diabetes (Table 14).

Table 14. Outcome results for Maori from a normal baseline test

	Pilot	Non-Pilot	p value*
Total number	336	537	
Person-years total	2036.9	2168.8	
Average follow-up (years) (Mean/Median)	6.1, 6.4	4.0, 4.3	
Progression to diabetes			
n, %	10, 3.0	22, 4.1	0.196
Months, (mean,SD)	42.8, 19.9	38.5, 18.8	0.001
Age at diagnosis, (mean,SD)	53, 6	57, 9	<0.001
Incidence rate (95% CI)	4.909 (2.35, 9.029)	10.14 (6.355, 15.36)	
Rate ratio, crude (95%CI)	0.48 (0.2292, 1.022)		
Age -adjusted rate ratio	0.44 (0.2156, 0.912)		
Progression to IGT			
n, %	20, 6	23, 4.3	0.134
Months, (mean,SD)	64.1, 12.8	39.5, 20.4	<0.001
Age at diagnosis, (mean,SD)	61, 9	58, 9	<0.001
Incidence rate (95% CI)	9.819 (5.995, 15.16)	10.6 (6.721, 15.91)	
RR, crude	0.93 (0.5085, 1.686)		
Age -adjusted rate ratio	0.79 (0.4232, 1.47)		
All-cause mortality			
n, %	18, 5.4	30, 5.6	0.443
Age at death (mean,SD)	64, 13	65, 15	0.298
Rate	8.837 (5.235, 13.97)	13.83 (9.331, 19.75)	
Rate ratio, crude	0.64 (0.3561, 1.146)		
Age -adjusted rate ratio	0.49 (0.2771, 0.8626)		

***** Chi square used for categories, T-test used for continuous variables, statistically significant values in bold.

The incidence rate of progression to IGT was 9.819 (95%CI 5.995- 15.16)/1000 person-years in the pilot group and 10.14 (6.355, 15.36)/1000 person-years in the non-pilot group. The crude rate ratio was 0.93 (95%CI 0.5085, 1.686), however the age-adjusted rate ratio was 0.79 (95%CI 0.4232, 1.47). This change in rate ratio confirmed the presence of confounding due to age and that the direction of confounding was towards the null value. The 95% confidence interval of the age-adjusted rate rates indicated that there was no statistical difference between the groups.

The average time (in months) from the negative baseline test to a diagnosis of IGT was longer in the Pilot group (64.1 months, SD = 12.8) compared with the Non-pilot group (39.5 months, SD = 20.4). The difference in mean time to progression to a diagnosis of IGT between the pilot and non-pilot group was highly statistically significant ($p < 0.001$).

The average age at diagnosis was 3 years younger in the pilot group compared with the non-pilot group (61 years, SD = 9 v 58 years, SD = 9) and these differences were highly significant ($p < 0.001$).

4.3.1.3 All-cause mortality

Table 14 also shows that in the pilot group (5.4%) 18/385 people died from any cause compared with (5.6%) 30/537 in the non-pilot group and the difference was not statistically different. The average age at death was 64 years (SD = 13) in the pilot group compared with 65 years (SD = 15) in the non-pilot group, also not statistically different.

The all-cause mortality rate in the pilot group (8.837 (95%CI 5.235, 13.97)/1000 person-years) was lower compared with the non-pilot group (13.83 (9.331, 19.75)/1000 person-years). The difference between the crude (0.64 (95%CI 0.3561, 1.146)/1000 person-years) and age-adjusted rate ratio (0.49 (95%C 0.2771, 0.8626)/1000 person-years) indicated that the differences in age between the pilot and non-pilot groups had confounded the results towards the null value. The 95% confidence interval of the age-adjusted rate ratio did not cross one which showed that the lower rate of mortality from any cause in the pilot group was statistically significant 95% of the time.

4.3.2 Results for Non-Maori

4.3.2.1 Progression to diabetes

Table 15 shows that in the 255 Non-Maori in the Pilot group, 12 (4.7%) progressed to diabetes compared to 4.4% (9/204) in the Non-Pilot group (p=0.441). For the Non-Maori pilot group the incident rate was 7.9 (95%CI 4.282, 13.44)/1000 person-years and 10.4 (95%CI 5.053, 19.01) /1000 person-years in the non-pilot group.

The difference between the crude (0.76 (95%CI 0.3215, 1.81) and age-adjusted rate ratios (0.74 (95%CI 0.312, 1.746) suggested that the presence of bias due to confounding by age was small. There was a stronger presence of bias due to confounding because of the differences in the distribution of gender between the groups (crude rate ratio = 0.76 (95%CI 0.3215, 1.81) versus 0.81 (95%CI 0.3441, 1.9) compared with age (crude rate ratio = 0.76 (0.3215, 1.81) = 0.74 (0.312, 1.746). The direction of the bias due to age pulled the estimate away from the null value whereas the direction of bias due confounding by sex moved the estimate closer to the null value. After adjusting for sex the confidence interval crossed 1 which meant that the differences between the pilot and non-pilot groups on progression to diabetes were not statistically significant.

The average time from the negative baseline test to a diagnosis of diabetes was longer in the Pilot group (43.1 months, SD = 23.7) compared with the Non-pilot group (39.8 months, SD = 26.2). The difference in mean time to progression to a diagnosis of diabetes between the pilot and non-pilot group was not statistically significant (p=0.158).

The average age at diagnosis was 1 year younger in the pilot group compared with the non-pilot group (67 years, SD = 7 v 68 years, SD = 8) and these differences were highly statistically significant (p <0.001).

Table 15. Outcome results for Non-Maori from a normal baseline test

	Pilot	Non-Pilot	p value*
Total	255	204	
Person-years	1518.3	868.7	
Average follow-up (years) (Mean/Median)	6.0, 6.2	4.3, 4.7	
Progression to diabetes			
n, %	12, 4.7	9, 4.4	0.441
Months, mean/SD	43.1, 23.7	39.8, 26.2	0.158
Age at diagnosis	67, 7	68, 8	0.161
Incidence rate (95% CI)	7.9 (4.282, 13.44)	10.4 (5.053, 19.01)	
Rate ratio, crude (95%CI)	0.76 (0.3215, 1.81)		
Age -adjusted rate ratio (95%CI)	0.74 (0.312, 1.746)		
Sex-adjusted rate ratio (95%CI)	0.81 (0.3441, 1.9)		
Progression to IGT			
n, %	13, 5.1	11, 5.4	0.444
Months, mean/SD	57.7, 16.9	39.8, 26.2	**<0.001**
Age at diagnosis (mean/SD)	70, 10	68, 9	**0.027**
Incidence rate (95% CI)	8.6 (4.762, 14.27)	12.7 (6.659, 22.01)	
Rate ratio, crude (95%CI)	0.68 (0.303, 1.509)		
Age -adjusted rate ratio (95%CI)	0.66 (0.2971, 1.479)		
Sex-adjusted rate ratio (95%CI)	0.72 (0.3155, 1.638)		
All-cause mortality			
n, %	19 7.5	13 6.4	0.326
Age at death (mean/SD)	74 13	81 9	**<0.001**
Rate (95%CI)	12.5 (7.758, 19.18)	15.0 (8.23, 24.95)	
Rate ratio, crude (95%CI)	0.84 (0.413, 1.693)		
Age -adjusted rate ratio (95%CI)	0.73 (0.3647, 1.468)		
Sex-adjusted rate ratio (95%CI)	0.89 (0.4404, 1.786)		

* Chi square used for categories, T-test used for continuous variables, statistically significant values in bold.

4.3.2.2 Progression to IGT

Table 15 shows that 13 Non-Maori in the pilot group (5.1%) progressed to IGT of which two (0.8%) also went onto a diagnosis of diabetes. In the Non-pilot group there were 11 people who progressed to IGT (5.4%) of which one (0.5%) also went onto a diagnosis of diabetes.

The incidence rate of progression to IGT was 8.6 (4.762, 14.27) /1000 person-years in the pilot group and 12.7 (6.659, 22.01)/1000 person-years in the non-pilot group. The crude rate ratio was 0.68 (0.303, 1.509), however the age-adjusted rate ratio was 0.66 (0.2971, 1.479) and the sex-adjusted rate ratio was 0.72 (0.3155, 1.638). This suggested that the presence of bias due to

confounding by sex was slightly greater than confounding by age. After adjusting for sex the confidence interval indicated that the differences between the pilot and non-pilot groups on progression to IGT were not statistically significant.

The average time from the negative baseline test to a diagnosis of IGT was longer in the Pilot group (57.7 months, SD = 16.9) compared with the Non-pilot group (39.8 months, SD = 26.2). The difference in mean time to progression to a diagnosis of IGT between the pilot and non-pilot group was highly statistically significant ($p < 0.001$).

The average age at diagnosis was two years younger in the pilot group compared with the non-pilot group (70 years, SD = 10 v 68 years, SD = 9) and this difference was statistically significant p=0.027).

4.3.2.3 All-cause mortality

Table 15 also shows that in the pilot group 19/255 (7.5%) people died from any cause compared with 13/204 (6.4%) in the non-pilot group (p = 0.326). The average age at death was 74 years (SD = 13) in the pilot group compared with 81 years (SD = 9) in the non-pilot group. The differences in mean age at death between the pilot and non-pilot groups was statistically significant ($p < 0.001$).

The all-cause mortality rate was lower in the pilot group compared with the non-pilot group (12.5 (95%CI 7.758, 19.18)/1000 person-years versus 15.0 (95%CI 8.23, 24.95)/1000 person-years). The crude rate ratio was 0.84 (95%CI 0.413, 1.693), however the age-adjusted rate ratio was 0.73 (95%CI 0.3647, 1.468) and the sex-adjusted rate ratio was 0.89 (95%CI 0.4404, 1.786). This suggested that the presence of bias due to confounding by age was greater than confounding by sex. After adjusting for sex and age, the lower mortality rate observed in the pilot group was not statistically significant 95% of the time.

4.3.3 Rescreening

As expected, the frequency of rescreening was statistically different between groups due to differences in follow-up time. Overall, for Maori in the pilot group only 16.6% (56/336) had no repeat screening result recorded compared

with 35.4 % (190/537) in the non-pilot group (p<0.001). However, when rescreening behaviour was assessed comparing only those screened during the pilot period (September, 2004-Augst 2006), the significant difference disappeared (non-pilot 51/243, p= 0.0934). Figure 5 depicts the closing of the difference between the pilot group and the whole non-pilot sample and then the non-pilot sample screened during the same time period as pilot participants.

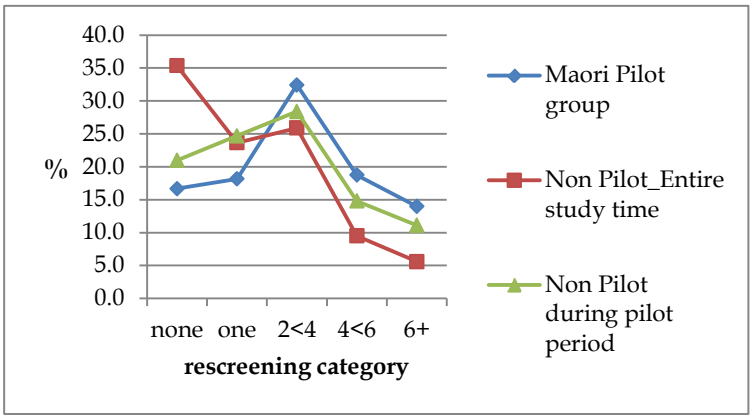

Figure 5. Distribution of rescreening for Maori comparing baseline time periods perhaps include the periods

There was a statistically significant difference for Non-Maori, 17.6% (45/255) of the pilot group had no repeat screening result recorded compared with 32.4 % (66/204) in the non-pilot group (p<0.001). However, when rescreening behaviour was assessed from those screened during the pilot period only, again the statistically significant difference disappeared (p= 0.1103) (Figure 6)

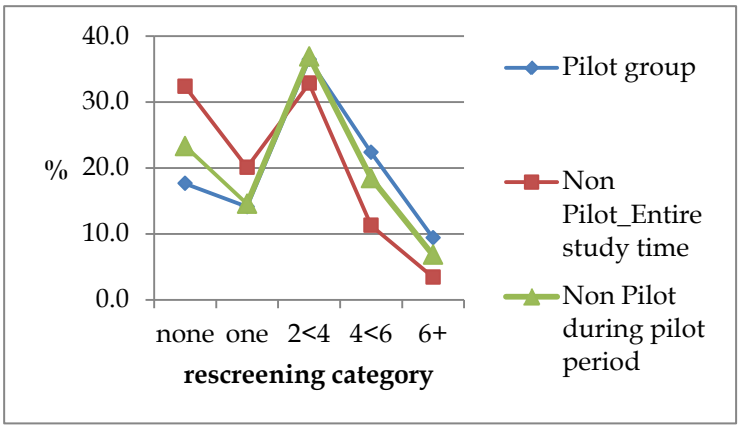

Figure 6. Distribution of rescreening for Non-Maori comparing baseline time periods

4.4 Additional analyses- Pooled data

4.4.1 Incidence proportion

The incidence proportion that had progressed to diabetes within 3 years from a negative baseline result using the 6.1mmol/L cutoff was 1.7% (15/873) for Maori and 1.3% (6/459) for Non-Maori. Using the 5.5mmol/L cutoff the incidence proportion was 1.4% (10/714) for Maori and 0.5% for Non-Maori (2/400) within three years of the baseline test.

4.4.2 Incidence rates, efficiency and undiagnosed diabetes

The overall diabetes incidence rate for all Maori (pilot and non-pilot groups combined) was 21.5 (17.7, 25.9)/1000 person-years and for Non-Maori it was 13.5 (9.6, 18.6)/1000 person-years (Table 16). Overall 10 Maori (1076/106) and 15 (511/35) Non-Maori need to be screened to detect one new case. In a 100% screening scenario over 7 years an additional 43 Maori would have been detected with diabetes and 7 Non-Maori.

The proportion of Maori aged 50 years and over who had one or more blood glucose test ranged from 82.5 – 90.2%. This level of diabetes screening was similar to the sample of Non-Maori patients aged 50 years and over (range 80.0-85.7%) (Table 16).

For all Maori the lowest incidence rates were observed in those aged 35-39 and 40-44 years of age at baseline (14.3 (7, 26.3)/1000 person-years and 13.3 (7.4, 22.1)/1000 person-years, respectively). These age groups were also found to have lowest uptake to a blood glucose testing during the entire study period (51.9% in the 35-30 year old age group and 63.6% in the 40-44 year old age group) and the highest number needed to screen (NNS), (18 and 17 respectively).

For all Maori with a diagnosis of diabetes, 70.8% (75/106) were aged between 40 – 59 years at baseline. The potential for undiagnosed diabetes was highest in the age groups with the lower screening proportions, specifically Maori who were aged 35 -49 years at baseline.

Table 16. Effectiveness and efficiency of diabetes screening using pooled data†

Totals	Source n	Total n	%	Diabetes n	Person-Years n	Diabetes incidence rate/1000 (95%CI)	NNS * n	UnDx ** n
Maori	1509	1076	71.3	106	4926.3	21.5 (17.7, 25.9)	10	43
Non-Maori	619	511	82.6	35	2587.1	13.5 (9.6, 18.6)	15	7
Total	2128	1587	74.6	141	7513.4	18.8 (15.9, 22.1)	11	48
Age at baseline								
Maori								
35-39	310	161	51.9	9	628.0	14.3 (7, 26.3)	18	8
40-44	346	220	63.6	13	979.0	13.3 (7.4, 22.1)	17	7
45-49	318	239	75.2	26	1160.9	22.4 (14.9, 32.4)	9	9
50-54	212	175	82.5	21	828.3	25.4 (16.1, 38.1)	8	4
55-59	112	94	83.9	15	450.0	33.3 (19.4, 53.7)	6	3
60-64	71	63	88.7	8	313.8	25.5 (11.8, 48.4)	8	1
65-69	53	46	86.8	5	231.7	21.6 (7.9, 47.8)	9	1
70-74	51	46	90.2	4	231.6	17.3 (5.5, 41.7)	12	0
75+	36	32	88.9	5	102.9	48.6 (17.8, 107.7)	6	1
Non-Maori								
50-54	143	118	82.5	6	633.6	9.5 (3.8, 19.7)	20	1
55-59	156	126	80.8	8	643.1	12.4 (5.8, 23.6)	16	2
60-64	112	96	85.7	6	502.8	11.9 (4.8, 24.8)	16	1
65-69	67	56	83.6	5	281.8	17.7 (6.5, 39.3)	11	1
70-74	51	43	84.3	7	196.5	35.6 (15.6, 70.5)	6	1
75+	90	72	80	3	329.3	9.1 (2.3, 24.8)	24	1
Gender								
Maori								
Female	818	587	71.8	54	2725.1	19.8 (15.03, 5.66)	11	21
Male	691	489	70.8	52	2201.2	23.6 (17.83, 0.74)	9	21
Non-Maori								
Female	254	208	81.9	12	1098.2	10.9 (5.92, 18.58)	17	3
Male	365	303	83	23	1488.9	15.4 (10.03,22.81)	13	5

* NNS refers to Number Needed to Screen to detect on new case

** Undx refers to undiagnosed diabetes. This estimated the number of additional cases that would have been detected in a 100% screening scenario. Numbers presented in the stratified levels have been rounded up or down and therefore may equal the numbers presented in the totals.

† Pooled data includes all patients who had one or more blood glucose test during the entire study period, regardless of baseline result.

Chapter 5 Discussion

5.1 Summary of main findings

This study found a protective effect for pilot participants on progression to diabetes, IGT, and all-cause mortality and that progression time to diabetes and IGT was longer compared with non-pilot participants. For Maori, the differences between pilot and non-pilot groups were statistically different for progression to diabetes, all-cause mortality, mean time to diabetes and IGT, and mean age at diagnosis of diabetes and IGT. For Non-Maori, mean progression time to IGT and age at death were the only parameters which reached statistical significance.

Assessing screening coverage rates, it was observed that the process of self-selection based on a formal invitation onto the pilot programme resulted in 25.5% of Maori and 44.5% of Non-Maori participating in the pilot. The selection of a general practice proactive in screening for diabetes meant that an additional 24.1% of Maori and 18.7% of Non-Maori were screened opportunistically simultaneous to the pilot. Over the seven years in total, 71.3% of Maori and 82.6% of Non-Maori had at least one screening test.

The key finding from the pooled data analyses was that the proportion of individuals that had progressed to diabetes from a negative baseline test (< 6.1mmol/L) within three years was 1.7% for Maori and 1.3% for Non-Maori.

The pooled analyses of data regardless of baseline test result identified that 10 Maori (1076/106) and 15 (511/35) Non-Maori needed to be screened to detect one new case. In a 100% screening scenario, over 7 years an additional 43 Maori and 7 Non-Maori with undiagnosed diabetes could have been detected. For Maori, the greatest number of undiagnosed diabetes was observed in the younger age groups (35-49). Diabetes incidence rates, regardless of baseline test result, were highest in the 45-54 (19.1/1000 person-years) and 55-64 (22.3/1000 person-years) age categories for Maori and the 70 years and over age category for Non-Maori (15.2/1000 person-years). The incidence rates of those aged 35-44 at baseline were the lowest for all Maori; however, this was also the age group with the lowest proportion of glucose tests.

5.2 Comparisons with other studies

5.2.1 Progression to diabetes

This is the first New Zealand study known to the researcher that reports the effect of participation in a diabetes and cardiovascular risk assessment programme on progression to diabetes from a negative glucose test. Therefore no comparisons with New Zealand studies could be made.

The incidence rates reported in this study were generally much higher compared with the incidence rates reported in the Hoorn study, the Ely study, the pooled data of Inter99 study and the *ADDITION – Netherlands* study, (de Vegt et al, 2001; Rahman et al., 2012; Engberg et al.,2009; Janssen et al., 2008). This could be expected when comparing incidence rates of a population with a high proportion of Maori and those living with the high deprivation with studies set in Europe based predominantly on white middle class Europeans. However, comparability with other studies is also problematic due to the differences in the inclusion and exclusion criteria they use, for example, when defining "high risk". The study with the most similar criteria to the *Northland Diabetes and Cardiovascular risk assessment pilot (*see Table 4) was the high risk group in the pooled Inter99 data by Engberg et al., (2009). Their study also observed similar incidence rates for progression to diabetes from a negative test in their high risk group (0.4/100 person-years (95% CI 0.3-0.6) compared with the Maori pilot group (4.909/1000 person-years (95% CI 2.35 – 9.029). These two rates if expressed in per 100 person-years are lower than the estimated range of annual progression of 0.6%-1.2% per year presented by the World Health Organisation (WHO, 2003).

The proportion that was expected to progress to diabetes from a negative test if CVDRA were having no effect on progression to diabetes was 5%. This parameter was based on pre CVDRA estimates presented by Keneally et al., (2002) who had estimated that 5% of a high risk population with a negative fasting test (<6.1mmol/L) would progress to diabetes within three years. From the pooled analyses, this study observed that 1.7% (15/873) of Maori and 1.3% (6/459) had progressed to diabetes from a negative test, defined as 6.1mmol/L, within a three year period from their baseline test. At face value these findings suggest that CVDRAs may have reduced the proportion

progressing to diabetes. However, it is more likely that these findings confirm the limitations of using proportions when time contributions have not been factored into the denominator, making the denominator larger and thus resulting in a lower estimate. Using person-years improves the precision; however this method also has limitations which will be discussed further in section 5.4.

For all groups in this study, progression to diabetes from a negative test occurred on average between 38.5 and 43.1 months (3.2 – 3.5 years) from the baseline test. This is consistent with natural history of disease where a moderately linear increase in blood glucose levels is followed by a rapid increase in glucose levels, with glucose results changing from negative to positive for diabetes in less than 4.5 years (Mason et al., 2007; Ferrannini et al., 2004).

5.2.2 Uptake to screening

The uptake to formal screening was much lower in the younger age groups, particularly for Maori, and in males, particularly for Non-Maori males. These findings were consistent with other studies (Tipene-Leach et al.,2004; Faatoese et al., 2011; Wilson et al., 2010; Sargeant et al., 2010). Caution should be taken interpreting the low uptake to the pilot by Maori (25.5%) compared with Non-Maori (44.5%). The lower uptake by Maori compared with Non-Maori could be partly explained by the differences in age criteria. Around 65 % (974/1509) of the Maori source population was aged less than 50 years and the younger age groups had very low uptake to the pilot. Also the quota for this practice was capped at 800 people for the pilot programme. Even if all 800 people screened were Maori, the maximum uptake to screening in this pilot could have reached was 53.0% (800/1509).

What this study was able to demonstrate was the value that opportunistic screening can have on improving uptake to screening. Simultaneous to the pilot implementation an additional 24.1% of Maori and 18.7% of Non-Maori were screened opportunistically. Perhaps even more importantly, while younger Maori people and males were less likely to be screened in the pilot, they were more likely to be screened opportunistically thereby increasing the overall coverage in these groups. These findings validate the call by Faatoese

et al., (2012) for incorporating opportunistic approaches to increase recording of risk factors for CVD such as diagnosing diabetes. However, even with opportunistic screening and the implementation of the formal CVDRA programmes in July 2008, this study found that the lowest uptake for screening overall (shown in Table 16) was observed in younger Maori aged 35-49 years at baseline and these were also the age groups with the highest estimated number of undiagnosed in a 100% screening scenario.

5.2.3 Baseline diabetes

Of Maori screened in the pilot group, 2.6% (10/385) were diagnosed with diabetes within 16 weeks of their baseline screening test. This was similar to the Non-Pilot group (17/691, 2.5%). Together Maori demonstrated a combined total of 2.5% (27/1076) diagnosed with diabetes. Overall, 1.0% (5/511) of Non-Maori were diagnosed with diabetes within 16 weeks of the baseline test. Of these 3 were from the Non-Pilot group (1.3%, 3/238) and 2 were from the Pilot group (0.7%, 2/273).

These results were lower compared with other New Zealand studies reporting new diabetes, newly diagnosed diabetes or undiagnosed diabetes (Coppell, 2009; Sundborn et al., 2007; Simmons, Rush & Crook, 2009). This included the published results of the Northland Diabetes and CVDRA pilot that were based on the four general practices where 3.6 % of Maori and 2.0% of Non-Maori were diagnosed with diabetes (White & Chamberlain, 2009). The lower baseline diabetes proportions found in this study could be explained by the methods used to calculate them. For example, in the White and Chamberlain (2009) paper, the proportions were calculated using only those that had completed the screening pathway. In this study, all those with a baseline screening test were included in the denominator irrespective of follow-up testing which means the denominator was larger than it may have been if only those with follow-up testing were used to calculate the proportion.

In section 5.2.1 the challenge of comparing studies with different definitions of inclusion and exclusion criteria was discussed and illustrated with the only study with a similar result also having the closest criteria for “high risk” to the pilot study. Comparing studies which use different glucose tests could also be

expected to show different results and this will be discussed further in relation to pre-diabetes.

5.2.4 Pre-diabetes

Pre-diabetes was defined in this study as a FPG result between 6.-6.9mmol/L. The proportion of Maori in the pilot group with a baseline test in the pre-diabetes was 10.4%. This was lower than the rate reported by Simmons et al, derived from the baseline results of the Te Wai o Rona study (14.3%) (Simmons, Rush & Crook, (2009), and also lower than the two year results of the Ngati and Healthy programme (13.6%) (Coppell et al., 2009). By comparison, the proportion of Maori in the non-pilot group with a baseline test in the pre-diabetes range was much higher at 19.8%.

Fasting Plasma Glucose, Oral Glucose Tolerance, and the HbA1c tests vary due to differences in the range of biological, pre-analytical, or analytical factors to the point where concordance between them is less than 100% (Sacks, 2011). The OGTT has long been held as the gold standard and the test most frequently used by New Zealand epidemiological surveys to determine diabetes, impaired glucose tolerance and impaired fasting glucose prevalence (Coppell, 2009; Sundborn et al., 2007; Simmons, Rush & Crook, 2009). That this study resulted in a lower proportion compared with Te Rona Wai, Diabetes Heart and Health Study and Ngati and healthy could also be explained by their predominant use of OGT tests which have better ability to predict diabetes or rule out diabetes (sensitivity and sensitivity) compared with this study which used diabetes read codes based on FPG tests that may be followed by an OGTT, or repeated FPG. However, this does not explain why the proportion of Maori in the non-pilot group was much higher. It is most likely that this finding demonstrates the advantages of using a less cumbersome test than the OGT to define pre-diabetes because a greater number of people may have had the test this way.

Progression times to diabetes or IGT was longer for Maori in the pilot group compared with those in the non-pilot groups. Potentially interventions aimed to reduce progression to diabetes from a pre-diabetic state could be followed by an increase in the prevalence of pre-diabetes. For example, Coppell et al., (2009) found a higher prevalence of IFG and IGT in the two year follow-up of

the Ngati and Healthy programme. These authors proposed that progression to diabetes from IFG and IGT may have been reduced by participating in the study and thus increasing the prevalence of these pre-diabetic states. Costa et al., (2012) found that intensive lifestyle programmes targeted at people with pre-diabetes that were implemented in a Catalonia primary care setting over 4 years achieved a 36.5% risk reduction (p=0.005) for the intensive group compared with the standard care. If the proportion of people progressing from normal to pre-diabetes remains at a constant state, and interventions which aim to reduce progression to diabetes have an effect, then the number of people with pre-diabetes could be expected to increase.

5.3 Limitations

5.3.1 Selection Bias

5.3.1.1 Identified confounders

In an ideal study, the comparison group should be as identical to the intervention group as possible except that the comparison group does not receive the intervention (Weisberg, 2010). In this study, this was not the case. The way in which patients of this practice were invited to be screened (i.e. the formal invitation by letter versus the opportunistic approach) led to a significant difference in distributions of age categories between the Pilot and Non-Pilot groups for Maori and a significant difference in the distribution of gender for Non-Maori. In both Maori and Non-Maori ethnic groups, any differences in outcome results could be explained by differences in these two characteristics thus potentially leading to bias in the results.

The presence of confounding due to age was confirmed in the Maori Pilot group compared with the Non-pilot group. Age confounded the results to show there was no difference on progression to diabetes when in fact there was a moderate to weak protective effect for the pilot group that was statistically significant, once age was adjusted for. Age also confounded the results for all-cause mortality and the extent of confounding was even greater.

For Non-Maori, because of the very small numbers, adjusting for age and sex was calculated separately. The effect of the differences between the distribution of males and females between the groups had a greater degree of

confounding than the effect of age. However, even after adjusting for age and sex there was no statistically significant difference between groups.

In conclusion, selection bias was evident in the differences of distribution by age for Maori and gender for Non-Maori because of the way in which patients were invited to participate. The adjusted rate ratios should be used to interpret the results for Maori and Non-Maori. However, while the way in which patients were assigned to groups meant that selection bias had to be controlled for in the analyses, it was learnt that younger Maori and males of either ethnic groups were more likely to be screened if testing was offered while attending for another reason.

5.3.1.2 Unknown differences in risk - Healthy participant effect?

The healthy participant effect is an alternative explanation for the protective effect of participating in the pilot group. As mentioned in the literature review, people who self-select to participate in research tend to be more health conscious and may have different baseline risk compared to those who do not (Raffle, 2010). In terms of error, the healthy participant effect is a form of selection bias, particularly if this favours one group more than the other.

There were two differences between the groups that signalled that the healthy participant effect could have biased the results. First, the proportion of abnormal baseline results was greater in the both ethnic groups in the Non-Pilot groups compared with the Pilot groups and these differences were statistically significant. This finding suggests that the Non-pilot group may have had a higher risk of diabetes. Second, all-cause mortality was higher in the Non-Pilot groups compared to the Pilot groups, and this was statistically significant for Maori. This finding suggests that the Non-pilot group may have had a generally higher risk for a range of factors and behaviours.

However, the healthy participant effect may in turn mask a true protective effect for Maori pilot participants. During the time of the pilot, CVDRA were in the very early phases of development (PREDICT versions 1 and 2). Practice systems were being tested to determine what was needed to implement nation-wide systematic recall programmes to assess CVD risk. The pilot protocol included a simultaneous CVDRA, and based on the evaluation of the

whole pilot sample across the four general practices, 76.6% of Maori and 85.4% of Non-Maori had a completed CVDRA score (White & Chamberlain, 2009). Pilot participants would have had their glucose results interpreted in the context of other CVD risk factors and depending on their total risk, interventions would be intensified and prioritised for those with the greatest CVD risk. Non-pilot participants would not have necessarily benefited from CVDRAs until the later role out of the programmes. Given that the five leading causes of death for Maori living in New Zealand independent urban and rural areas between 2004-08 were ischaemic heart disease, accidents, lung cancer, diabetes, and chronic obstructive pulmonary disease (MoH, 2012), interventions to reduce CVD risk factors offered to the pilot group sooner than the non-pilot group, may have had a true protective effect on all-cause mortality for Maori.

It is plausible that a protective effect of CVDRAs could be observed at a population level in a short period of time. New Zealand studies have shown that reductions in important diabetes risk factors can be achieved in relatively short periods of time, i.e. between 24 weeks and two years. For example, the Ngati and Healthy programme, demonstrated reductions in insulin resistance (Coppell et al., 2009), and intensive lifestyle interventions have shown reductions in weight loss (Krebs et al., 2012; Coppell et al., 2010; Brooking, Williams & Mann, 2012) and HbA1c (Coppell et a., 2010).

Had information on obesity, family history, smoking, hypertension, hyperlipidaemia and other risk factors, been obtained for this study, it may have been possible to assess whether the effects were due to risk reductions from early exposure to CVDRA or due to the healthy participant effect. The main reason why this was not obtained was because this study primarily aimed to determine whether there was an effect on participating in the pilot and whether general practice data could be used in this way, before conducting a larger studying including a wider range of risk factors.

With the limited information available on other variables the healthy participant phenomena is a leading explanation for the differences between Maori pilot and non-pilot participants. The possibility that earlier exposure to

CVDRAs could have contributed to the protective effect cannot be entirely ruled out.

5.3.3 Lead time bias

The higher proportion of abnormal baseline tests in the non-pilot groups could also be indicative lead time bias, instead of the healthy participant effect. The prevalence of obesity, reduced physical activity, and smoking has been found to be higher in more deprived areas (Metcalfe et al., 2008). For Maori, the pilot group had a higher, although not statistically significant different, proportion of people living with the most deprivation. Because of this, the researcher did not expect that the Maori pilot group would have had less baseline risk. An alternative explanation could be that a greater proportion of those in the pilot group had their baseline test at an earlier point in the natural history of progression to diabetes. This is an example of lead-time bias.

To explain this further in the context of stages of progression to diabetes presented in the literature review, when the physiological responses move from the compensation stage to the stable adaptation stage, fasting glucose levels begin to rise to around 5.0-7.3 mmol/L. While this stage can be maintained and tightly regulated for many years, it is followed by a relatively rapid increase in glucose levels (Weir & Bonner-Weir, 2004; Tabak et al., 2012). Given that a greater proportion of non-pilot patients had an abnormal test compared with pilot patients at baseline, pilot patients had a greater length of mean time from baseline test to progression to IGT compared with non-pilot groups. This fits with the natural progression to diabetes, giving lead-time bias merit as an explanation for the protective effect of the pilot on progression to diabetes, particularly for Maori.

5.4.4 Misclassification

5.4.4.1 Exposure status (Pilot versus Non-Pilot)

It was not possible to identify pilot participants from the practice management system without individually searching scanned documents for the scanned copy of the signed informed consent on the list of the source population. Instead, the baseline data from the Pilot study was used to identify and assign patients into the Pilot and Non-Pilot groups. Working across two data sources,

data extracted from Medtech and the baseline pilot programme dataset created and maintained by Northland Pathology Ltd, could have introduced misclassification bias because of differences in NHIs (i.e the use of scrambled NHIs) or conflicting information of blood glucose results. This occurred for 23 pilot participants only, therefore misclassification bias was differential misclassification. When this occurred these patients were either excluded from the study or assigned into the unscreened group. In either situation, this would have had little effect on the results presented in this study.

5.4.4.2 Diabetes detection

There was variation in the way that random and fasting glucose results were named in the practice management system. It could not be assumed that the corresponding results were based on fasting tests unless they were specifically labelled as such. Every effort was made to retrieve all blood glucose results by using all known field names, which created an unexpected and significant demand on the researcher's time resource to prepare the data for analysis. Because of time constraints created by this additional work, an audit comparing diagnoses with laboratory results was not carried out.

The practice had a standing order that discouraged the use of random glucose tests, therefore the results used to determine the baseline reading were assumed to be fasting plasma glucose results. This may have misclassified those with a normal result of a random glucose test, where the range of normal is higher than in a fasting sample, into the abnormal baseline test results, and thus excluding these patients from the analyses estimating progression to diabetes. Because of the pilot protocol that stipulated a FPG followed by OGTT, misclassification could have occurred more frequently in the non-pilot group for the baseline tests. This type of misclassification bias is called differential misclassification bias and can bias the results in either direction. While this could also explain the reason why the proportion of non-pilot abnormal tests were much greater compared with the pilot study, the practice standing orders for FPG's for diabetes screening should have minimised the likelihood that random glucose tests were a frequent occurrence.

5.4.4.3 Completeness of follow-up data

The pilot and non-pilot groups screened during the pilot period had very similar degrees of rescreening done. Given all people in these groups would not be expected to have their next blood glucose assessment for three years (according to NZGG guidelines) unless they had a cardiovascular risk that warranted more frequent assessments, there was a high number of people who had had at least one rescreen. This means that lower rates of detection of diabetes is unlikely to explain the differences between the groups.

Incomplete follow-up data due to transfer to another medical centre was difficult to determine. According to practice staff, it was not unusual for a patient to transfer to another practice, remaining as a casual patient in the original practice, then transfer back some time later. In this scenario it would be expected that testing and any diagnoses made would be transferred back, and their results retrieved for this study. The only information that may indicate how many this may be at any one point in time was based on the proportion of casual patients when data was extracted (see Table 6). The proportion was lower for Maori (2.2%) compared with Non-Maori (4.0%). However those who were known casual patients at the end of the follow-up period were excluded from this study.

Incomplete data due to migration was also difficult to determine. Migration would also be likely to affect the reliability of the residential area and subsequently classification of unit area deprivation if patients' addresses were not up-to-date. In 2006, 60% of Maori were believed to move to another part of New Zealand within the previous 5 years (Statistics New Zealand, 2012). In this scenario it would be expected that internal migration would occur in both groups. The challenge of retrieving date of transfer meant that all people with a baseline test contributed time to this study until there was a diagnosis of diabetes, death, or the follow-up period finished. The effect on the denominator was that it was larger than it may have been if the relevant information was available and the resulting estimate would have been an underestimate by an unknown magnitude. However, this was likely to occur in both pilot and non-pilot group's and is another example of non-differential

misclassification bias which tends to either underestimate or have no effect on the results.

5.4 Implications

5.4.1 Implications for Maori

Maori who participated in the *Northland Diabetes Screening and Cardiovascular risk Assessment pilot* in this practice, who had a normal baseline test, were less likely to progress to diabetes and die from any cause compared to those in the non-pilot group. Whether this was because pilot participants had inherently lower risk, were screened earlier in the disease progression, or because of early exposure to their blood glucose results being interpreted in the context of their CVD risk, was not able to be determined in this study.

Diabetes prevalence has been estimated to be around three times higher in Maori and Pacific people and diagnosis occurs at younger ages compared with the rest of New Zealand population (MoH, 2007; Joshy & Simmons, 2006). A family history diabetes, suggestive of a genetic susceptibility does not make diabetes inevitable (Mayer-Davis et al.,2011; Uusitupa et al., 2011). Pilot participants themselves could potentially have the greatest impact on reducing the incidence of diabetes in their community. How this is most likely to occur is through their influence within their families, friends and colleagues. They can influence others by strengthening social norms that have a protective effect against developing diabetes and premature death. Sharing the results of this study to this Maori community is therefore vital.

Beyond this population, the distribution of demographics in this study population was different to many other parts of Northland and most other parts of New Zealand. How then could these results apply to Maori living in other areas of New Zealand? When Joshy et al., (2009) considered this for the results of their study, they put forward the view that because rates of obesity, lifestyle and other risk factors are likely to be similar for Maori in other parts of New Zealand, it is reasonable to generalise the results for Maori living in areas with the most deprivation.

There are a couple of considerations that need to be made before applying the same view to these results. Firstly, there may be differences in underlying risk

factors between those living in urban areas compared to the people in this study which were predominantly residents of an independent settlement or the surrounding rural areas. Secondly, in places where the proportion of Maori in the population is much less than 70% and the burden of diabetes is less evident, general practices may not have the same awareness of screening for diabetes as demonstrated in this practice.

Even with a total of 71% people screened for diabetes, Maori aged 35-49 were less likely to be screened at all and were estimated to be most likely to have undiagnosed diabetes. The low uptake to screening coupled with the lower likelihood of being detected with diabetes either through a formal or opportunistic approach suggested that this age group may have barriers beyond general practice service delivery such as work and other time commitments and stresses competing for priority. Further investigation is needed to look at the issues occurring for the 35-49 year old age group as this study shows that this is potentially an important age to direct interventions to reduce future diabetes and death from any cause.

5.4.2 Measuring diabetes incidence

Researchers and government authorities have shown a commitment to improve the quality of diabetes prevalence methodology. However, much less is reported on the rates of diabetes incidence, even with all the resources that has gone into risk reduction.

This study showed that most of the relevant information was available to calculate diabetes incidence rates following a population that had a fasting glucose test less than 6.1mmol/L at baseline. General practice data could also be used to determine the number of screenings and the length of time between diabetes screenings. Compared with other methods to calculate diabetes prevalence, diabetes diagnoses based on primary care Read Codes in a high-risk population predominantly from Auckland and Northland regions were considered a reliable source of diagnosed diabetes (Thornley et al., 2011). Therefore Read Codes could be used to identify incidence cases of diabetes.

As yet CVDRA has not included the increased risk of CVD in those with non-diabetic hyperglycaemia. This has the potential to underestimate an

individual's risk, as even high levels of blood glucose are associated with increased risk for CVD if other CVD risk factors are present (Chamnan et al., 2011). Chamnan et al., (2011) supported the view that cardiovascular risk calculations should include non-diabetic hyperglycaemia as a continuous risk factor. If this were to occur, blood glucose results stored in either general practice records or in a system such as PREDICT $_{TM}$, could be used to monitor the effect of prevention efforts to reduce the risk of progression to diabetes. However, given the difficulties experienced by the researcher when extracting the data from general practice records, this may be an information system challenge.

In New Zealand, a lot of resource has gone into cardiovascular risk assessments. Measuring the effect of diabetes screening on reducing diabetes incidence in the context of cardiovascular risk assessment programmes may become more important as promising intensive lifestyle interventions become more integrated into best practice. This study gives some indication of incidence rates in the context of early and later exposure to CVDRAs and may be able to be used to compare the effect of future interventions in high risk populations.

5.5 Conclusion

This study found a protective effect for pilot participants on progression to diabetes, IGT, and all-cause mortality and that progression time to diabetes and IGT was longer compared with non-pilot participants. Whether this was because pilot participants had inherently lower risk, were screened earlier in the disease progression, or because of early exposure to their results being interpreted in the context of their CVD risk, was not able to be determined in this study. The distribution of factors such as family history, BMI, hypertension, smoking etc., was not available for this study. Inclusion of these factors would have improved the ability of this study to explain the reason for the protective effect.

The value of opportunistic screening on improving uptake to screening was demonstrated by this practice's results. Younger people and males were more likely to be screened opportunistically than in response to a formal invitation to participate in a pilot. Even so, Maori aged 35-49 were less likely to be

screened at all and were estimated to be most likely to have undiagnosed diabetes. Migration and family and work commitments could offer possible explanations for this.

The major implication of this research for Maori is that diabetes and premature death were less likely outcomes for Maori pilot participants. Potentially, the pilot participants themselves could have the greatest impact on reducing the incidence of diabetes in their community. How this is most likely to occur is through their influence on their families, friends and colleagues, by strengthening social norms that have a protective effect against developing diabetes and premature death.

A high level of repeated glucose measures were available for this cohort based on data from this general practice. Administrative data such as this could be used to estimate the coverage of screening, efficiency and effectiveness and proportion of undiagnosed diabetes as well as progression to diabetes, IGT and all-cause mortality. However, the limitations of this source of data included: problems with time intensiveness of extraction of glucose measures, and the lack of ability to obtain the date of transfer or migration and therefore provide accurate measures of person-time contribution. If these issues could be overcome, it may be possible to make monitoring diabetes incidence in a high risk non-diabetic population feasible.

5.6 Recommendations

Northland Health and Maori authorities could investigate whether Maori aged 35-49 could be a priority population group for intensive diabetes prevention and other disease or injury prevention activities, taking into account competing work and family commitments.

The effectiveness of CVDRA programmes in patients with normal glucose levels or non-diabetic hyperglycaemia on reducing incidence diabetes should be formally assessed in a range of New Zealand populations.

Information technology specialists' working with Northland health authorities, primary care providers and researchers could assess the practicalities of overcoming the issues associated with storing and retrieving blood glucose results and the date of transfer or migration in general practice systems, to improve future monitoring of incidence diabetes.

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Appendix 1 World Health Organisation Diagnostic Criteria for Diabetes

Diabetes	
• Fasting plasma glucose • 2–h plasma glucose*	≥7.0mmol/l (126mg/dl) or ≥11.1mmol/l (200mg/dl)
Impaired Glucose Tolerance (IGT)	
• Fasting plasma glucose • 2–h plasma glucose*	<7.0mmol/l (126mg/dl) and ≥7.8 and <11.1mmol/l (140mg/dl and 200mg/dl)
Impaired Fasting Glucose (IFG)	
• Fasting plasma glucose • 2–h plasma glucose*	6.1 to 6.9mmol/l (110mg/dl to 125mg/dl) and (if measured) <7.8mmol/l (140mg/dl)

* Venous plasma glucose 2–h after ingestion of 75g oral glucose load
* If 2–h plasma glucose is not measured, status is uncertain as diabetes or IGT cannot be excluded

Adapted from: World Health Organisation (WHO). (2006). *Definition and diagnosis of diabetes mellitus and intermediate hyperglycemia*. Geneva: World Health Organisation

Appendix 2 Pilot provider questionnaire

NORTHLAND DIABETES AND CARDIOVASCULAR RISK SCREENING PILOT

(2004-2007)

The following questionnaire should take you no longer than 10 minutes, but if you wish to take your time that is also fine. Please answer all questions. If the question is *not* relevant to your role in the pilot please tick the box "**n/a**".

If you have any problems with the questionnaire, please feel welcome to contact Bronwyn White on (03) 546 1265 or email: bronwyn.white@nmdhb.govt.nz

Diabetes and Cardiovascular risk Screening Pilot in General Practice

Your professional role is?

☐ General practitioner ☐ Practice nurse

☐ Reception staff ☐ Practice manager

The following questions relate to *before* the pilot began in 2004.

Q1. Prior to beginning the pilot, did you have a system for routinely recalling patients to screen for diabetes?

☐ Yes
☐ No
☐ N/a

Q2. Prior to the beginning of the pilot, did you routinely calculate and record Cardiovascular (CVD) risk?

☐ Yes
☐ No
☐ Sometimes
☐ N/a

The next set of questions relate to identifying patients and inviting them onto the screening pilot

Q3. When identifying patients to **include** in the screening pilot, how easy was it to identify those with a greater than 5% risk of developing Diabetes?

☐ Easy

☐ Not very easy

☐ Not at all easy

☐ N/a

Q4. When identifying patients to **exclude** in the screening pilot, how easy was it to identify those patients by a recent negative screen?

☐ Easy

☐ Not very easy

☐ Not at all easy

☐ N/a

Questions 5-9 refer to the *first* invitation to screening pilot patients identified from your practice register.

Q5. Which method did you use most of the time for the **first** invitation to patients onto the pilot?

☐ Letter

☐ Telephone

☐ Other

☐ N/a

Q6. Did you stagger the first invitations?

☐ Yes

☐ No

☐ N/a

Q7. If YES, please describe how you staggered the invitations.

_____

_____

Q8. Over which approximate timeframe were all the first invitations issued?

☐ < 6 months

☐ < 12 months

☐ <18 months

☐ >18 months

☐ don't know

The next section relates to patients once they were on the screening pathway

Q9. At ANY time in the pilot, did you have difficulty calculating CVD risk?

☐ Yes

☐ No

☐ N/a

Q10. If YES, was this because of; [*Tick as many boxes as you need to answer*]

☐ Server was down

☐ Difficulties using Predict Version 1

☐ Difficulties using Predict Version 2

☐ Waiting for FPG result

☐ No recent fasting lipids

☐ Need to recall patient for further information

☐ Other, please comment _____

Q11. How likely was it that someone with **known** cardiovascular disease was CVD risk assessed for this pilot?

☐ Very likely
☐ Likely
☐ Not very likely
☐ Not at all likely
☐ N/a

Q12. Do you agree with requesting a GTT for a patient with a FPG between 5.5 and <7 mmol/L?

☐ Yes
☐ No
☐ Other, please comment_____
☐ N/a

The next questions are about those who did not respond to the first invitation and are referred to from this point on as "non-responders"

Q13. Which point of reference was most likely to prompt the identification of non-responders?

☐ Lab results
☐ Pilot feedback reports
☐ Claiming for funding
☐ No point of reference
☐ Other, please specify_____
☐ N/a

Q14. Did you make a **second** attempt to contact non-responders?

☐ Yes
☐ No

☐ N/a

Q15. If YES, which method did you use most of the time to contact non-responders?

☐ Second letter
☐ Telephone
☐ Home visit
☐ Other, please specify_____

Q16. Did you refer patients to the outreach provider?

☐ Yes
☐ No
☐ Sometimes
☐ N/a

Q17. **If NO, please indicate why**

_____
_____
_____
_____

Q18. Did you receive lab results for patients from your practice screened via the outreach provider?

☐ Yes
☐ No
☐ N/a

Q19. If YES, how likely were you to:

Q19.1 Attempt to recall patients with FPG >5.5 mmol/L

☐ Very likely
☐ Likely
☐ Not very likely

☐ Not at all likely

☐ N/a

Q19.2 Complete CVD risk assessment

☐ Very likely

☐ Likely

☐ Not very likely

☐ Not at all likely

☐ N/a

Q19.3 Re-refer to outreach to assist with further tests and information

☐ Very likely

☐ Likely

☐ Not very likely

☐ Not at all likely

☐ N/a

Q20. How useful were the feedback reports from Northland DHB?

☐ Very useful

☐ Useful

☐ Not very useful

☐ N/a

Q21. In your professional role in the pilot, did you provide patients who tested negative for Diabetes with healthy lifestyle education?

☐ Yes

☐ No

☐ Sometimes

☐ N/a

Q22. Thinking of the opportunistic approach, what were the advantages of screening for Diabetes and CVD risk this way?

_____

_____

_____

Q23. Since completing the pilot, do you now routinely calculate and record CVD risk?

☐ Yes
☐ No
☐ Sometimes
☐ N/a

The final section: overall what do you think?

Q24. Thinking of screening for diabetes, please indicate on a scale of 1-5 whether you disagree or agree with the following statements.

Disagree Agree				
1 5	2	3	4	Screening for diabetes in the general population
1 5	2	3	4	Community based screening in high risk populations
1 5	2	3	4	Systematic recall of high risk patients to screen for diabetes in General Practice
1 5	2	3	4	Systematic recall of high risk patients to screen for diabetes as part of CVD risk assessment

Q25. Was the funding realistic?

☐ Yes
☐ No
☐ N/a

Comments_____

_____

_____

_____

_____

_____

Q26. Did you feel adequately resourced to improve health outcomes for patients identified from the pilot with;

Q26.1 Diabetes?

☐ Yes

☐ No

☐ N/a

Q26.2. Impaired Glucose Tolerance?

☐ Yes

☐ No

☐ N/a

Q26.3 Impaired Fasting Glucose?

☐ Yes

☐ No

☐ N/a

Q26.4 Raised CVD risk?

☐ Yes

☐ No

☐ N/a

Thank you for completing the questionnaire.
Please return to Bronwyn White in the reply paid envelope provided.