

Screening for Type 2 Diabetes in Adults

Diana Sherifali

McMaster Evidence Review and Synthesis Centre

Donna Fitzpatrick-Lewis, Leslea Peirson, Donna Ciliska

McMaster University

Hamilton Ontario Canada

April 16, 2012

CTFPHC Leads:

Kevin Pottie

PHAC Scientific Officer:

Lesley Dunfield/Alejandra Jaramillo

Working Group Members:

Neil Bell, Paula Brauer, James Dickinson, Gabriela Lewin, Patricia Parkin, Marcello Tonelli

Abstract

Background: Clinical guidelines, review questions and the methods used to synthesize evidence of benefits and harms and develop recommendations for screening for type 2 diabetes have varied substantially over the past 10 years. The 2003 US Preventive Services Task Force (USPSTF) determined there was insufficient evidence to screen asymptomatic adults for type 2 diabetes, impaired glucose tolerance (IGT) or impaired fasting glucose (IFG). The 2005 Canadian Task Force for Preventive Health Care (CTFPHC) recommendations suggested there was fair evidence for screening adults with hypertension and/or hyperlipidemia for type 2 diabetes. The revised 2008 USPSTF recommendations suggested screening for type 2 diabetes in asymptomatic adults with sustained blood pressure greater than 135/80 mm/Hg. In light of revisions to the CTFPHC methodology, and the need to update the 2005 CTFPHC recommendations, a systematic review was undertaken to determine the benefits and harms of screening for type 2 diabetes.

Purpose: This review was conducted to determine the clinical benefit of screening for type 2 diabetes using fasting plasma glucose (FPG), oral glucose tolerance test (OGTT), or a glycated hemoglobin (A1c) in asymptomatic adults, 18 years of age or older, at high risk or at average risk of diabetes complications; and to determine the harms associated with screening for type 2 diabetes using FPG, OGTT, or A1c in the same population. Additional contextual questions considered the costs associated with screening; patient values and preferences regarding screening for type 2 diabetes; and risk factors that could guide screening for type 2 diabetes. Other contextual questions included the evidence for screening specific populations; the clinical benefits and harms of early treatment of patients with IGT, IFG and type 2 diabetes; the effective risk assessment scores, diagnostic tests for detecting diabetes and the process and outcome performance measures, or indicators that are identified in the literature to measure and monitor the impact of screening for type 2 diabetes.

Methods: The search strategy from a previous (2008) high quality systematic review on type 2 diabetes screening was updated for key questions pertaining to effects of diabetes screening on average and high risk populations. MEDLINE® and the Cochrane Database of Systematic Reviews were searched from July 2007 to February 2012 for studies in English and French. Clinical Trials.gov was also searched for relevant trials. Systematic reviews and randomized controlled trials with evidence for the clinical benefit or potential harms of FPG, OGTT or A1c for type 2 diabetes were included. Similarly, systematic reviews, randomized controlled trials, and observational studies were used to answer contextual questions.

Data Abstraction: Relevant articles were abstracted. Study quality was assessed using the GRADE System, which classifies quality of evidence on the risk of bias due to limitations in design, inconsistency of findings, indirectness, imprecision and publication bias. Contextual questions were reported in a narrative format.

Results: Previous results showing benefit of screening among those with high blood pressure were confirmed. No new or old trials were found regarding the effect of screening for type 2 diabetes on the incidence of diabetes or morbidity and mortality outcomes. An observational study was found, demonstrating a marginal benefit in mortality in the first cohort invited for type 2 diabetes screening (1990-1992), (HR 0.79; 95% CI 0.63, 1.00). This was not replicated in the second cohort invited for screening (2000-2003). Two studies that used mathematical models to simulate the consequences and costs of population-based screening for diabetes reported that screening high-risk individuals

(using age and hypertension as risk factors) might increase quality adjusted life years as this is simply a mathematical projection and no *real* individual experienced an increase in quality adjusted life years. These studies also reported that population based screening of high-risk populations was cost-effective. Two new randomized controlled trials were identified that assessed the harms of screening for type 2 diabetes; both trials noted that screening was associated with higher levels of short-term anxiety and worry in those with screen detected diabetes, but had limited overall psychological impact. A meta-analysis was not possible due to significant heterogeneity. Evidence related to the contextual questions determined that screening for type 2 diabetes was most cost effective in older adults ≥ 50 years of age with hypertension and obesity, by offsetting long term health care costs. Patients did not find screening bothersome, but wanted physicians to convey the risk of type 2 diabetes. Risk factors that were associated with an increased risk for developing diabetes included: family history of diabetes (1st degree relative), metabolic syndrome; weight related factors; schizophrenia; membership in a high risk population group (i.e., Aboriginal, Hispanic, South Asian, Asian and African); women with a history of gestational diabetes; and individuals over ≥ 65 years of age. There was no new evidence for the clinical benefits and harms of early treatment of type 2 diabetes.

Modeling studies that included screening for diabetes suggest that population based screening beginning at age 45 every three to five years is cost-effective. FINSRISC is a risk assessment tool that has been well validated internally (Finland) as well as externally including studies summarized in this review in populations in Bulgaria and Greece. CANRISK is a recently developed risk assessment questionnaire that can be used to identify risk of diabetes with the diverse ethnic Canadian population. A1c is an effective diagnostic test that is relatively easy to administer and is cost effective.

Limitations: A search for the key questions was updated based on the USPSTF review; therefore EMBASE was not searched, and only articles in English and French are included. The searches for contextual questions such as cost effectiveness, patient values and preferences related to screening and special populations were focused and not based on a full systematic review.

Conclusions: This review found no new or previously completed controlled studies of the effectiveness of screening for type 2 diabetes, but did find one observational study following 4,936 individuals screened for type 2 diabetes on mortality. The 2005 CTFPHC provide a Grade B Level recommendation, based on fair quality evidence, for screening adults with cardiovascular risk factors (hypertension and hyperlipidemia) for type 2 diabetes. Evidence for the harms associated with screening for type 2 diabetes showed minimal clinical significance on anxiety. Recent evidence does indicate a benefit to initiating lifestyle modification and some oral antidiabetic agents for the prevention of type 2 diabetes. Differences between current and previous evidence can be attributed to the new CTFPHC methodology that integrates the GRADE approach, which was not used to develop the previous USPSTF or CTFPHC recommendations.

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Chapter 1: Introduction

Background and Purpose

Clinical guidelines and the methods used to synthesize evidence and develop recommendations for screening for type 2 diabetes have varied substantially over the past 10 years. The 2003 US Preventive Services Task Force (USPSTF) determined there was insufficient evidence to screen asymptomatic adults for type 2 diabetes, impaired glucose tolerance (IGT) or impaired fasting glucose (IFG).¹ The 2005 Canadian Task Force for Preventive Health Care (CTFPHC) recommendations suggested there was fair evidence for screening adults with hypertension and/or hyperlipidemia for type 2 diabetes.² The revised 2008 USPSTF recommendations suggested screening for type 2 diabetes in asymptomatic adults with sustained blood pressure greater than 135/80 mm/Hg.³ In light of revisions to the CTFPHC methodology, and the need to update the 2005 CTFPHC recommendations, a systematic review was undertaken to determine the benefits and harms of screening for type 2 diabetes.

The purpose of this review was to update the 2005 CTFPHC recommendations on screening for type 2 diabetes to prevent vascular complications.² Specifically, the review was conducted to determine the clinical benefit of screening for type 2 diabetes using fasting plasma glucose (FPG), oral glucose tolerance test (OGTT), or a glycated hemoglobin (A1c) in asymptomatic adults, 18 years of age or older, at high risk or at average risk of diabetes complications; and to determine the harms associated with screening for type 2 diabetes using FPG, OGTT, or A1c in the same population.

The USPSTF updated their 2003 guidelines in 2008.⁴ The absence of recent Canadian recommendations was the basis for selecting this topic for an update by the revitalized Canadian Task Force in 2010.

Condition Background

Definition

Type 2 diabetes mellitus represents a cluster of chronic metabolic diseases characterized by hyperglycemia as a result of defective insulin secretion, defective insulin action, or both. Persistent hyperglycemia is associated with consequences resulting in injury or failure of the micro or macrovasculature, such as the nerves, kidneys, eyes, blood vessels and heart.⁵

Previously known as adult-onset diabetes or non-insulin dependent diabetes, the impetus for changing the name reflects the detection of type 2 diabetes in children and adolescents and the proliferate use of insulin in its management. Type 2 diabetes comprises the majority of diabetes cases nationally and globally, and is often asymptomatic in early stages, remaining undiagnosed for long periods of time.⁶

Type 2 diabetes is a heterogeneous metabolic disorder with both genetic and environmental determinants. Predominant insulin resistance with relative insulin deficiency and/or predominant secretory defects with insulin resistance are characteristics of type 2 diabetes.⁷ Optimal management of type 2 diabetes requires early and ongoing lifestyle modification; including physical activity and nutrition, self-management training and pharmacotherapy.⁸⁻¹⁰

Prevalence and Burden of Disease

In 2008/09, almost 2.4 million Canadians (6.8%) were living with diabetes with more than 200,000 Canadians were newly diagnosed with diabetes (6.3 cases per 1,000 individuals).¹¹ This figure may be underestimated as previous research identified the prevalence rate for adults in Ontario at 8.8% in 2005.¹² The Canadian Diabetes Association (CDA) using modeling data estimates that 2.8 million Canadians currently live with diabetes (approximately 8%) and that number will increase to 3.7 million by 2020.¹³

After adjusting for age distributions across Canada, the age-standardized prevalence of diagnosed diabetes was found to be higher in Newfoundland and Labrador, Nova Scotia, Manitoba, and New Brunswick, ranging from 5.6% to 5.9%.¹⁴ Diabetes prevalence was lower and ranged from 4.7-5.1% in the western provinces of Alberta, British Columbia and Saskatchewan.¹⁴ The prevalence for Ontario was higher than the national average (5.6% vs. 5.2%); and the prevalence for Québec was lower than the national average (4.7% vs. 5.2%).¹⁴

The prevalence of type 2 diabetes is greater in high risk populations, including Aboriginal, Hispanic, Asian, South Asian and African groups. The age-adjusted prevalence for Aboriginals in Canada is 2.5 to 5 times higher than that of the general population.¹⁵ Additionally, some ethnic groups having an age-adjusted prevalence as high as 26%.¹⁵ Immigrants from high risk populations face greater risks for diabetes than the general population. Immigrants from South Asia have an approximate four-fold increase in the risk of diabetes, those from Latin America and the Caribbean have a two-fold increase in the risk of diabetes, and individuals from sub-Saharan Africa also have a two-fold increase in the risk of diabetes.¹⁶ Furthermore, age, socioeconomic status, and obesity are associated with increased prevalence rates.¹⁷⁻¹⁹ The prevalence of diabetes rises steadily with age, with Canadian prevalence percentages steadily climbing from about 40-45 years of age at 5.3%, and peaking at approximately 75-79 years of age at 23%.^{14,18,19}

Results from the Canadian Community Health Survey (CCHS) found that of those Canadians diagnosed with type 2 diabetes before the age of 50, 63% were South Asian, 57% were Aboriginal, 50% were Chinese, and 35% were self-described as White.¹⁸ Low socioeconomic status has also been associated with an increase in diabetes prevalence, with estimates at 2.8% among people in the highest income group compared to 3.9% in the lowest income group.¹⁹ Finally, weight and obesity also increases the risk of diabetes, with the prevalence at 2.7% among underweight or normal weight individuals, 5.7% in those considered overweight, and 12.1% in those considered obese.¹⁸

According to the Public Health Agency of Canada's (PHAC) National Diabetes Surveillance System (NDSS), among adults 20 years and older, mortality rates of individuals with diabetes were twice as high, compared to individuals without diabetes.¹⁴ Recognizing that the NDSS does not differentiate between the types of diabetes, most cases (90 to 95%) are representative of type 2 diabetes.¹⁴ Diagnosed diabetes significantly shortens life expectancy for all ages.¹⁴ In 2006-2007, compared to adults without diabetes, adults with diagnosed diabetes were diagnosed three times more often with hypertension (n=1,307,188) and were hospitalized: a) three times more often with overall cardiovascular disease including, heart failure (n=49,665), heart attack (n=26,895), ischaemic heart disease (n=93,691), and stroke (n=23,912); b) seven times more often with chronic kidney disease (n=40,341); and c) 19 times more often with lower limb amputations (n=3,001).¹⁴ Moreover, as the diagnosis of diabetes is often delayed, 20-50% of people with type 2 diabetes present with microvascular and/or macrovascular complications at the time of diagnosis.²⁰⁻²²

Etiology and Natural History

The development of type 2 diabetes is attributed to beta cell dysfunction (insulin secretion and/or insulin deficiency), and insulin resistance. Pancreatic beta cells initially manage elevated glucose levels by secreting additional insulin. However, insulin secretion eventually fails, leading to impaired glucose tolerance, or prediabetes, and eventually clinical diabetes.^{23,24} With the exception of rare forms of type 2 diabetes (e.g., maturity-onset diabetes of the young and diabetes-deafness syndrome) which account for <1% of all cases of diabetes, most cases of diabetes are related to genetics and/or the environment.^{14,25}

Type 2 diabetes is often diagnosed as part a routine physical examination or during treatment for other conditions. A US National Health Interview Survey found that only one-half of the people with type 2 diabetes had symptoms at the time of their diagnosis.²⁶ Although the classic symptoms of hyperglycemia and indicators of diabetes may include polydipsia, polyuria and polyphagia, other symptoms common with type 2 diabetes include fatigue, blurred vision, infection, recent weight loss, and/or neurologic symptoms in the feet.

Although having a strong inheritable link, type 2 diabetes is also associated with a myriad of other factors, including body mass index, waist circumference, diet and activity level.²⁷⁻²⁹ Evidence for the environment as a determinant of diabetes is also apparent in studies of recent immigrants from a developing country to Canada. Research shows that immigrants to Canada of South Asian background have a three to four fold increased risk for diabetes than immigrants from Western Europe or North America.^{12,16}

Consequences if Left Untreated

Short term consequences of type 2 diabetes, if left untreated, include diabetic ketoacidosis (DKA) and hyperosmolar nonketotic state (HNKS). Both acute consequences are rare in type 2 diabetes, but may occur with prolonged hyperglycemia, as a result of a concurrent illness or infection. DKA, typically a consequence of type 1 diabetes, may also be the first manifestation of type 2 diabetes.²⁵ HNKS may occur with severe hyperglycemia, which leads to hyperosmolality and volume contraction. This life threatening acute complication typically presents in the elderly and despite treatment, has a mortality rate of up to 50%.²⁵

Long term consequences of type 2 diabetes are often described as microvascular (retinopathy, nephropathy, neuropathy) and macrovascular (cardiovascular disease) complications. Retinopathy, including proliferative retinopathy and macular edema is found in approximately 40% of the US adult diabetes population.³⁰ Intensive glucose and blood pressure therapy has been proven to prevent the onset and progression of retinopathy.^{21,22} Nephropathy, including chronic kidney disease (CKD) and end-stage renal disease (ESRD) are common and potentially devastating complications of diabetes. It is estimated that 34% of people with diabetes have some form of chronic kidney disease.³¹ The course of nephropathy is a stepwise progression; it begins as a subclinical disease, which moves onto early development of nephropathy characterized by microalbuminuria (30-300 mg/24 hours), and eventually onto overt nephropathy (>300 mg/24 hours).³² To that end, epidemiological data suggest that 10-20% of individuals with diabetes develop ESRD.³³ Individuals with diabetes and ESRD are among those at highest risk for cardiovascular mortality, with a life expectancy of three years after diagnosis.³⁴

Neuropathy is a likely complication that will develop in 40-50% of individuals within the first 10 years after the onset of diabetes, and is associated with sensory loss, pain and weakness.³⁵ Among the various forms of neuropathy, polyneuropathy, damage to a diffuse set of peripheral nerves, particularly in the feet and legs, is the most common form.³⁶ Neuropathy may lead to foot ulcers and infections, which may result in lower limb amputation. The onset and progression of neuropathy can be lessened with intensified glycemic control for persons with diabetes.³⁶

It is estimated that 65-80% of people with diabetes will die of a cardiovascular event, of which a high proportion will occur without prior signs or symptoms of cardiovascular disease (CVD).^{37,38} A meta-analysis of data from over 698,000 individuals found that people with no history of diabetes, and a fasting glucose between 5.6 and 6.1 mmol/L and between 6.1 and 7.0 mmol/L had an increased risk of coronary heart disease of 11% and 17% respectively.³⁹ Previous evidence, particularly from secondary analyses of cardiovascular trials suggests a modest reduction in CVD, specifically myocardial infarction (but not in all-cause mortality) with more intensive hypertension control and glycemic management in people with type 2 diabetes. The modest effect with glucose intensification, and the lack of effect on mortality, suggests a wider approach to diabetes management; targeting blood pressure and lipid management is also required.⁴⁰⁻⁴²

Factors Associated with Type 2 Diabetes

The factors most associated with type 2 diabetes are impaired glucose tolerance and/or impaired fasting glucose, collectively known as prediabetes. In these conditions glucose levels are above normal targets, but they are not high enough to diagnose diabetes (Appendix 1).⁴³ Gestational diabetes or the delivery of a macrosomic infant (>9 lbs) are additional risks associated with diabetes for women. Hypertension, dyslipidemia, abdominal obesity and being overweight are modifiable factors for diabetes, but often present in combinations or patterns of associated factors, such as metabolic syndrome (Appendix 2).⁴⁴ Vascular disease, including coronary, cerebral and peripheral, are also factors associated with type 2 diabetes.⁴³

Non-modifiable risk factors for type 2 diabetes include age (≥ 40 years), having a first-degree relative with type 2 diabetes, being a member of a high-risk population (e.g., people of Aboriginal, Hispanic, South Asian, Asian or African descent), or a diagnosis of schizophrenia. Finally, women with polycystic ovary syndrome are also considered high risk for diabetes.⁴³ A list of risk factors associated with type 2 diabetes is included in Appendix 3.

Rationale for Screening

Diabetes is a disease that meets several criteria which suggests screening might be beneficial: a) diabetes represents an important health problem; b) the natural history of diabetes is understood; c) there is a recognizable asymptomatic period in which diabetes can be diagnosed; d) tests are available that can detect the pre-symptomatic stage of diabetes; and e) treatment after early detection might yield greater benefits than experienced by patients with delayed treatment.⁴⁵ Furthermore, prediabetes is predictive of type 2 diabetes in approximately 50-70% of cases.⁴⁶ It is important to distinguish between screening and diagnosing. Screening involves attempts to detect asymptomatic disease and may also differentiate those at high risk of having a diagnosis of diabetes from those at low risk. Screening methods may include simple, noninvasive/invasive and/or

stepwise approaches.⁴⁷⁻⁵⁰ In contrast, tests undertaken in individuals who present with symptoms in a clinical setting are for diagnostic purposes and do not represent disease screening.

Screening and Diagnosis Strategies

Historically, screening for type 2 diabetes required fasting plasma glucose (FPG) and/or an oral glucose tolerance test (OGTT), which uses both a fasting and a 2-hour post glucose load plasma glucose value (see Appendix 1 for diagnostic criteria). A growing body of literature demonstrates that A1c, OGTT and FPG are equivalent predictors of retinopathy and nephropathy development, thus suggesting that A1c, OGTT and FPG may all be appropriate screening tools for diabetes.⁵¹⁻⁵⁴ The FPG test (defined as no caloric intake for at least eight hours) is also a component of diagnostic testing and is often preferred because it is faster to perform and more convenient for the patient. With a laboratory cost of approximately 6-10 dollars (Cdn), the FPG test yields a sensitivity of 40-60% with a specificity of 76% for identifying individuals with diabetes.^{45,46} A FPG result of ≥ 7 mmol/L requires a second confirmatory glucose test on another day to diagnose diabetes.^{7,43} Similarly, a casual plasma glucose (PG) of ≥ 11.1 mmol/L plus symptoms may also be used to diagnose diabetes. A casual PG may be done any time of the day, without concern for the timing of the last meal; however, without the presence of symptoms of hyperglycemia, a casual PG should be repeated to confirm the diagnosis.⁵²

The OGTT considered the gold standard test for screening and diagnosis, uses both a fasting and 2-hour plasma glucose level following a 75g glucose load. It is indicated when the FPG is not elevated enough to diagnose diabetes (less than 7 mmol/L), but it is above FPG levels (5.6 mmol/L or more).^{43,55-57} The 2-hour plasma glucose test in an OGTT provides a sensitivity of 97%, with a specificity of 100%.⁵⁵ The cost of an OGTT is approximately 36-48 dollars (Cdn).⁵⁷ To diagnose diabetes "a confirmatory laboratory glucose test (either an FPG, a casual PG or a 2hPG in a 75-g OGTT) must be done on another day in all cases in the absence of unequivocal hyperglycemia accompanied by acute metabolic decompensation".⁴³ Repeat confirmatory testing on another day should be considered in the absence of symptoms.⁵² However, the OGTT is difficult to reproduce and taxing on the individual (i.e. time, consuming the glucose load drink).

The A1c test provides a retrospective average of glycemic control for the previous three months, by measuring the binding glucose to hemoglobin during the life span of red blood cells.⁵⁸ In a recent analysis of three ethnically varied US databases, the proposed American Diabetes Association (ADA) diagnostic criteria for diabetes (A1c $\geq 6.5\%$) failed to detect 70% of individuals with diabetes, 71–84% with dysglycemia, and 82–94% with prediabetes, but resulted in more normal diagnoses than the OGTT.⁵¹ It is relatively easy to collect, as the A1c test does not require individuals to fast and has a laboratory cost of approximately 6-19 dollars (Cdn).⁴⁶ The A1c test has traditionally been used to monitor long-term glycemic control, adjust therapy and assess risk for the development and progression of complications. Similarly to the ADA, the CDA has recommended the A1c test for diagnosing type 2 diabetes.^{43,52} However, the ADA recommends that the A1c test be used to screen for diabetes and/or assess the risk of future diabetes where appropriate, provided the A1c test is administered according to the National Glycohemoglobin Standardized Program (NGSP) and traceable to the Diabetes Control and Complications Trial (DCCT) reference assay. An A1c result of 6.5% or higher would lead to a diagnosis of diabetes.⁵⁰ More recently, the World Health Organization (WHO) conducted a systematic review of 11 studies of varying methodologic designs and concluded the following: a) A1c could be used as a diagnostic test, provided that

quality assurance tests were in place to ensure accurate measurements; and b) a cut off of 6.5% or greater was indicative of diabetes.⁵³ However, there is no mention in the WHO report for the use of the A1c test for screening purposes.⁵⁴

The impact of diabetes screening needs to be put into context of costs to the individual, as well as to the health care system. In Canada, a diagnosis of diabetes incurs individual financial costs ranging from 1,000-15,000 dollars annually, as a result of medication use, glucose monitoring, supplies, and complication prevention and management.¹³ Individuals also bear an emotional cost as a result of the diagnosis; one of anxiety and altered self-perception. Insurability is also an issue for individuals following a diagnosis of diabetes. Although there is limited research examining the adverse effects of screening for diabetes, a decrease in quality of life was not associated with screening.⁵⁹ The health care costs of diabetes management are tremendous; by 2020, it is estimated that diabetes will cost the Canadian healthcare system 16.9 billion dollars annually.¹³

Interventions/Treatments

The 2008 USPSTF recommended that individuals with a prediabetes diagnosis be strongly encouraged to undertake lifestyle modifications that include increasing physical activity, altering diet, and weight loss.⁴ It is estimated that a 5% reduction in initial body weight can reduce the risk of progression from prediabetes to type 2 diabetes by approximately 60%.²⁸ The initiation of pharmaceutical agents such as an alpha glucosidase inhibitor, biguanide or thiazolidinedione, independent of lifestyle modification may also prevent progression to type 2 diabetes by 30-60%.⁴³

Current Recommendations of Other Diabetes Stakeholders

The CDA's clinical practice guidelines recommend that all individuals be evaluated annually for type 2 diabetes on the basis of demographic and clinical history, such as risk factors for diabetes (Grade D recommendation, consensus).⁴³ However, screening for type 2 diabetes using a FPG test should be performed every three years in adults 40 years of age or older (Grade D recommendation, consensus). More frequent FPG testing or the use of an OGTT should be considered in high risk individuals (Grade D recommendation, consensus). Finally, testing with an OGTT should be considered in individuals with FPG levels suggestive of prediabetes (5.6-6.9 mmol/L) (Grade D recommendation, consensus).⁴³

A study using administrative health data examined diabetes screening patterns using laboratory tests (FPG, A1c and OGTT) in Ontario, Canada between 1995 and 2005. It was determined that in 2005, 37% of Ontario adults without diabetes were screened with a FPG test, 6% were screened using an A1c test and less than 1% underwent OGTT testing in any year between 1995–2005.⁶⁰ The authors conclude that despite the absence of the A1c test in the CDA's diabetes screening recommendations, A1c testing among individuals without diabetes was increasing rapidly, and OGTT, which is recommended, was rarely performed.⁶⁰

The ADA and the CDA recommend screening for type 2 diabetes in individuals ≥ 45 years and ≥ 40 years of age respectively, every three years, using a fasting plasma glucose test.^{43,50} Adults at high risk for type 2 diabetes should be considered for screening at any age.⁵⁰ Although the effectiveness of early identification of diabetes through mass screening compared with no screening has yet to be clearly shown, there is fair evidence to identify those at risk for future diabetes, and to identify, and if required, treat other CVD risk factors.⁵⁰

Previous Recommendations

Other Diabetes Stakeholders

In 1992, although the Expert Committee of the Canadian Diabetes Advisory Board (ECCDAB) did not provide recommendations for type 2 diabetes screening, they did recommend that adults with a FPG test of ≥ 7.8 mmol/L on at least two occasions should be diagnosed with diabetes.⁶¹ In 1998, the clinical practice guidelines were updated and provided clear recommendations concerning screening for type 2 diabetes, including testing for diabetes using FPG every three years in adults 45 years and older.⁶² Those at high risk were recommended for earlier and more frequent testing (Grade D recommendation, consensus).⁶² In 2003, the CDA's clinical practice expert committee updated the guidelines to include screening for diabetes in adults 40 years and older every three years with a FPG test.⁷

Previous Task Force Recommendations

In 2003, the USPSTF made the following recommendations regarding screening for type 2 diabetes:

- The evidence is insufficient to recommend for or against routinely screening asymptomatic adults for type 2 diabetes, impaired glucose tolerance, or impaired fasting glucose (Grade I statement); and
- Screening for type 2 diabetes in adults with hypertension or hyperlipidemia is recommended. (Grade B recommendation).^{1(p215)}

In 2008, the USPSTF updated and revised the recommendations to the following:

- Screening for type 2 diabetes in asymptomatic adults with sustained blood pressure (either treated or untreated) greater than 135/80 mm Hg is recommended (Grade B recommendation).
- The current evidence is insufficient to assess the balance of benefits and harms of screening for type 2 diabetes in asymptomatic adults with blood pressure of 135/80 mm Hg or lower. (Grade I statement).^{3(p846)}

In 2005, the CTFPHC published a guideline for the screening of type 2 diabetes mellitus to prevent vascular complications.^{2(p177)} The following recommendations were made:

- There is fair evidence to recommend screening adults with hypertension for type 2 diabetes to reduce the incidence of cardiovascular (CV) events and mortality (Grade B recommendation).
- There is fair evidence to recommend screening adults with hyperlipidemia for type 2 diabetes to reduce the incidence of CV events and mortality (Grade B recommendation).
- There is good evidence to recommend treatment of overweight* individuals with impaired glucose tolerance (IGT) with lifestyle interventions to reduce the incidence of diabetes progression (Grade B recommendation).
- There is insufficient evidence to recommend treatment of overweight* individuals with IGT with metformin or acarbose to reduce the incidence of diabetes progression (Grade I recommendation).
- There is fair evidence to recommend treatment of overweight* individuals with IGT with acarbose to prevent cardiovascular outcomes and hypertension (Grade B recommendation).

*Body mass index (BMI, kg/m²) >25 or >22 in individuals of Asian descent

The absence of current Canadian guidelines and the differences between the 2003 and 2008 USPSTF recommendations were the basis for selecting this topic for an update by the revitalized Canadian Task Force in 2010.

Chapter 2: Methods

Analytic Framework and Key Questions

The USPSTF questions and analytic framework were used to guide Key Questions 1 and 2 for the CTFPHC 2011 update (Figure 1).⁴ The population of interest for this review includes asymptomatic adults 18 years of age or older who are at average and moderate risk or high risk (Appendix 3) for type 2 diabetes complications. Non-insulin dependent diabetes will be presumed to be type 2 diabetes. The USPSTF review included adults over the age of 20 years. The search was not redone for studies that included participants between the ages of 18 and 20 years for 2001 to July 2007; however, any new reports since July 2007 that studied people 18 years and over were included.

Key questions:

1. What is the evidence for the clinical benefit of screening for type 2 diabetes using fasting plasma glucose, oral glucose tolerance test, or A1c in asymptomatic adults 18 years of age or older at high risk or at average and moderate risk for diabetes complications to improve intermediate and final health outcomes?
2. What is the evidence for the harm of screening for type 2 diabetes using fasting plasma glucose, oral glucose tolerance test, or A1c in asymptomatic adults 18 years of age or older at high risk or average and moderate risk for diabetes complications?

Additional contextual questions include:

1. What is the cost effectiveness of screening asymptomatic adults 18 years or older for type 2 diabetes from the perspective of the system and the patients?
2. What are the patient values and preferences related to screening for type 2 diabetes?
3. What risk factors could guide screening for type 2 diabetes [e.g., age, hypertension, hyperlipidemia (cholesterol), waist circumference, ethnicity]
4. What is the evidence that screening for diabetes in Aboriginal people, rural/remote, women and elderly improve health outcomes and/or mortality?
5. What are the clinical benefits and harms of early treatment (less than 12 months) of patients with type 2 diabetes compared with later treatment of patients for improvement of intermediate or final health outcomes?
6. What are the clinical benefits and harms of treatment of patients with impaired fasting glucose and impaired glucose tolerance compared with no treatment for improvement of intermediate or final health outcomes?
7. What process and outcome performance measures or indicators have been identified in the literature to measure and monitor the impact of screening for type 2 diabetes?
8. What are the most effective (accurate and reliable), risk assessment tools or questionnaires to predict type 2 diabetes?
 - 8.1 What risk assessment tools or questionnaires to predict type 2 diabetes have been validated in Canada?
9. What is the yield (accuracy, reliability, prevalence, and feasibility) of screening for type 2 diabetes with FBG, OGTT, and hemoglobin A1c in adult patients?

Search Strategies

The USPSTF searched MEDLINE® and the Cochrane Library for relevant English language systematic reviews, randomized controlled trials and observational studies published between March 2001 and July 2007, related to the questions regarding diabetes screening, and potential adverse effects. Clinical Trials.gov was also searched for relevant trials. To answer Key Questions 1 and 2 the same search strategy was implemented, and all searches were updated from 2007 to February 2012. EMBASE was not searched, as it was not searched in the original USPSTF review.

Additional searches were conducted to answer the contextual questions; examining cost effectiveness of screening, patient values and preferences, risk factors to guide screening, screening in subgroups and populations, clinical benefits and harms of early treatment of type 2 diabetes, clinical benefits and harms of treatment for prediabetes, process and outcome performance measures and indicators, risk assessment tools and diagnostic tests. The same databases were searched from 2005 to February 2011. For risk assessment tools and diagnostic tests databases were searched from January 2001 to November 2011. A specific search of the grey literature (non-published or indexed literature) was also completed to find relevant Canadian data using the search terms “diabetes AND screening,” “diabetes screening AND Canada,” and “diabetes screening AND costs.” Reference lists of key articles were also reviewed. A separate search was conducted to search for modeling studies. Detailed search strategies are listed in Appendices 4-6.

Study Selection

Eligible studies included asymptomatic adults 18 years or older at average or high risk for type 2 diabetes complications. Study designs for effectiveness of screening fasting plasma glucose, oral glucose tolerance test, or A1c included randomized controlled trials or systematic reviews and meta-analyses and observational studies with a comparison group and intermediate (incidence of type 2 diabetes, differences in A1c levels and frequency of type 2 diabetes diagnosis) or final outcomes (all-cause mortality, cardiovascular mortality, myocardial infarction, stroke, angina, blindness, end stage renal disease, severe retinopathy). For harms, observational studies, randomized controlled trials, systematic reviews and meta-analyses were included if they reported on anxiety and/or depression related to screening. For both effectiveness and harms the included studies had to have a non-screen comparison group.

For Contextual Question 1, examining the cost effectiveness of screening, no systematic reviews or randomized controlled trials were identified in the search; available observational and simulation modeling studies were included. Observational studies relevant to Contextual Questions 2 to 7, (examining patient values and preferences, risk factors to guide screening, screening in subgroups and populations, clinical benefits and harms of early treatment for type 2 diabetes, clinical benefits and harms of treatment of prediabetes, and process and outcome performance measures or indicators) were included if there were no data available from systematic reviews and/or randomized controlled trials. To address Contextual Questions 8 and 9, we identified high quality systematic reviews; appraised with AMSTAR (a measurement tool for *assessment of multiple systematic reviews*),⁶³ and included relevant primary studies published after the end of the search used in the systematic review to November 2011.

External Review

Before beginning the review, the protocol was internally reviewed by the Diabetes Screening Working Group which includes members of the CTFPHC as well as Public Health Agency of Canada staff. The protocol was sent to two external reviewers with review methodology and/or diabetes content expertise; feedback was received from both reviewers (Appendix 8) and revisions were made. The revised protocol was sent to three reviewers (Appendix 9) and subsequent revisions were made. A draft of the evidence review went to the Diabetes Screening Working Group, and then the revised review went to a panel of external experts (Appendix 10) not affiliated with the CTFPHC.

Quality Assessment, Data Extraction and Analysis

The titles and abstracts were reviewed in duplicate by members of the synthesis team; any article marked for inclusion by either team member went on to full text rating. Full text inclusion, quality assessment and data extraction were done by two people. All disagreements were resolved through discussions rather than relying on a particular level of kappa score to indicate when discussions were no longer necessary. The inclusion results were reviewed by a third person. Data were abstracted by two people using a standard format. The exception to this process was studies related to the contextual questions, for which extraction was done by one person.

The strength of evidence was determined based on the GRADE system of rating quality of evidence using GRADEPro software.^{64,65} This system of grading evidence has been widely used and has been endorsed by over 40 major organizations including the World Health Organization, Centers for Disease Control and Prevention, and the Agency for Healthcare Research and Quality.⁶⁴ The GRADE system classifies quality of evidence according to one of four levels: high, moderate, low and very low. The final grade is based on the risk of bias due to limitations in design, inconsistency of findings, indirectness, imprecision and publication bias.

The Diabetes Screening Working Group rated each of the outcomes and potential harms of screening using the GRADE Process.⁶⁶ GRADE suggests a nine point scale (1-9) to judge the importance of the outcomes and harms. The upper end of the scale, rankings of 7-9, identifies outcomes of critical importance for clinical decision making. Rankings of 4-6 represent outcomes that are important but not critical, while rankings of 1-3 are items that are deemed to be of limited importance to decision making or to patients. This process identified the following important final outcomes: all-cause mortality; cardiovascular mortality; myocardial infarction; stroke; angina; blindness; end stage renal disease; and severe retinopathy. The outcomes of harms associated with diabetes screening resulted in the rankings presented in Table 1.

The GRADE process was also used to assess risk of bias for individual studies addressing Key Questions 1 and 2. This was then used with the summary of findings to assess the overall quality of the evidence. In addition to those required data, we abstracted data about the patient population, the study design, analysis and results for each study.

Information to determine the quality of evidence was abstracted in duplicate from the primary methodology paper from each study. Those abstracting the data were blind to each other's ratings. In cases of disagreement, final decisions were determined by consensus after consultation with a third reviewer. All outcomes of interest for Key Questions 1 and 2 are presented separately in the GRADE Evidence Profiles (Tables 4 and 7). Inconsistency and publication bias were rated as "no" and "unlikely" given that the assessments were based on single studies.

Chapter 3: Results

Summary of the Literature Search

To update the 2005 CTFPHC Screening for Type 2 Diabetes, the literature search for this review replicated and updated the search conducted by the USPSTF review in 2008.⁴ Our search located 11,456 potentially relevant citations (Figure 2). At title and abstract screening, 8,947 were excluded. A total of 2,340 papers were retrieved and were assessed on inclusion criteria. A total of 2,206 papers were excluded at this level because they did not relate to Key Questions 1 or 2. Of the 134 studies that were quality appraised only three studies addressed the key questions. For Key Question 1, one new cohort study was found (see Table 2 for details of this study), and for Key Question 2 two new studies were found (see Table 3 for details of these two studies). The remaining 131 papers were available for consideration in answering the Contextual Questions.

The 2008 USPSTF review included 11 studies of varying methodological designs answering questions pertaining to overall effect of screening on final outcomes⁶⁷⁻⁶⁹ (mortality, quality of life, cardiovascular morbidity, lower-extremity amputations, non-healing ulcers, severe visual impairment, stage IV and V chronic kidney disease and symptomatic neuropathy) and adverse effects of screening.^{59,70-76}

Results for Key Questions

Key Question 1: What is the evidence for the clinical benefit of screening for type 2 diabetes using fasting plasma glucose, oral glucose tolerance test, or A1c in asymptomatic adults 18 years of age or older at high risk or at average and moderate risk for diabetes complications to improve intermediate and final health outcomes?

Summary of findings

No new studies were identified in the literature review examining the effect of screening for type 2 diabetes in a randomized controlled trial or systematic review, in asymptomatic adults 18 years of age or older at high or average risk for diabetes complications (all-cause mortality, cardiovascular mortality, myocardial infarction, stroke, angina, blindness, end stage renal disease or severe retinopathy) since the 2008 USPSTF Recommendation Statement for the Screening of Type 2 Diabetes. The Anglo-Danish-Dutch Study of Intensive Treatment in People with Screen Detected Diabetes in Primary Care (ADDITION) study does not compare screening for diabetes against a comparison arm (no screening or any other form of screening), but rather compares conventional diabetes treatment to intensive multifactorial treatment, and therefore was excluded.⁷⁷ To our knowledge, the effectiveness of a screening intervention via FPG, OGTT or A1c for type 2 diabetes has not been tested to date in a randomized controlled trial.

However, a United Kingdom population-based cohort study by Simmons et al.⁷⁸ was identified in the evidence, which examined the impact of screening for type 2 diabetes using a 75 g OGTT and related cardiovascular (CV) risk factors on population mortality. Men and women between the ages of 40-65 were invited to participate in diabetes screening in three different cohorts: a) cohort one – 1,705 participants were randomly selected to receive an invitation to screen for diabetes and related

cardiovascular risk factors between 1990-1992; b) cohort two – 1,577) participants were randomly selected for screening between 2000-2003; and c) cohort three – 1, 526 were not invited to screening at all.⁷⁸ Mortality was assessed for both screened cohorts; a median of 4 years (initial) and 10 years (rescreening) (cohort one) and 8 years (cohort two). Study characteristics are further summarized in Table 2. Individuals invited for screening between 1990-1992 had a 21% lower all-cause mortality than the cohort not invited for screening at all (HR 0.79; 95% CI 0.63-1.00). In the 1990-1992 cohort, mortality was lower in those that participated in screening for diabetes (HR 0.54; 95% CI 0.40-0.74) than those that did not attend.⁷⁸ Similarly, in the 2000-2003 cohort, mortality was lower in those that participated in screening for diabetes (HR 0.52; 95% CI 0.35-0.78) than those that did not attend.⁷⁸ There was a non-significant reduction in mortality as a result of screening for follow-up period between 1990-1999, which was replicated with the second cohort for follow-up period 2000-2008. The authors conclude that it is unlikely that the early identification of diabetes was the explanation for a few deaths identified as diabetes related (8%) in this population cohort; rather the screening process and information on CV disease may have heightened the awareness of practitioners and patients, thus resulting in greater attention to risk factor modification and management.⁷⁸ The risk of bias was assessed for this study (Table 4) and a GRADE evidence profile and a summary of findings table (Table 5) were generated.

Other relevant study details

The 2008 USPSTF review for screening for type 2 diabetes identified three studies of varying methodological rigour, examining the effect of screening on microvascular outcomes.⁶⁷⁻⁶⁹ A case-control study from the United States examined 303 cases of type 2 diabetes with one or more symptomatic, microvascular, diabetes complications and then matched 1:1 to control subjects (with or without type 2 diabetes, but no signs of complications).⁶⁷ The odds ratio for a history of screening at least once over a 10-year period compared to no screening, was 0.87 (95% CI 0.38-1.98), after adjusting for BMI, number of medical visits, family history of diabetes and the presence of hypertension, hyperlipidemia and coronary artery disease.⁶⁷ The study concludes that screening did not significantly reduce the risk of certain microvascular diabetic complications. The study finding was not statistically significant due to the wide 95% confidence interval.

The Swedish community of Laxå was the setting for a cross-sectional survey to determine the visual acuity in a community that has been routinely screened for diabetes since 1983. Using a national registry, individuals with type 2 diabetes (n=274) were matched by sex and age to a control group without type 2 diabetes (n=256).⁶⁸ Best corrected visual acuity and rates of blindness were compared in both groups. There were no significant differences between the type 2 diabetes and matched control groups.⁶⁸ However, it is unclear how many of the type 2 diabetes group members were screen detected versus clinically diagnosed. Furthermore, considering the diligence of screening for diabetes since 1983 and a Swedish national diabetes registry, it may be difficult to generalize these findings to a Canadian context.

Finally, a cross-sectional survey compared the rates of diabetic retinopathy in individuals newly diagnosed via general practice with type 2 diabetes (n=128; Group 1) to those newly diagnosed with type 2 diabetes via screening programs (n=173; Group 2) in rural and urban India's Tamil Nadu region.⁶⁹ Screening for diabetes involved a two-step process: step one – random plasma glucose (RBG) measured with a glucometer (Accutrend), using a capillary method; and step two – for individuals with a RBG >200 mg/dl or 11 mmol/L, referrals to general physicians or diabetologists were made to further evaluate their diabetes status.⁶⁹ Diabetic retinopathy was detected in 6.4%

(95% CI 2.5-9.5) of individuals in Group 1 and 11.7% (95% CI 5.6-16.4) of individuals in Group 2. Sight threatening diabetic retinopathy was observed in 4.6% of the individuals in Group 1 and 7.8% in Group 2. Baseline characteristics such as age, sex, BMI, physical activity, smoking status, alcohol status and BP influenced diabetic retinopathy in Group 1. However, systolic BP >140 mm/Hg was associated with a higher occurrence of diabetic retinopathy in Group 2.⁶⁹ It is also difficult to determine whether this study sample is representative of other settings in India or whether the study findings are generalizable to the Canadian context.

Inclusion of Modeling Studies

The methods manual of the CTFPHC allows for the use modeling studies when there is insufficient evidence to answer some or all of the key questions.⁷⁹ The Diabetes Screening Working Group reviewed the available evidence and determined that there was insufficient evidence to adequately answer components of the effectiveness question particularly ages to begin or end screening; screening intervals and screening high risk groups. The ERSC were tasked to run a separate search for modeling studies and follow a stepped approach to critically appraise the citations. The full process is outlined in the CTFPHC procedure manual at <http://www.ualberta.ca/~mtonelli/manual.pdf> (see Appendix XI within the manual). Step one determines the applicability of the study to the question asked. Those studies that were applicable were then assessed using a tool adapted from Drummond.⁸⁰ Step three provides an overall analysis of the methodological quality of the modeling studies. Once this was completed the recommended studies were sent to an independent expert of modeling for further analysis (Steps 4 and 5). A total of six studies related to cost effectiveness of screening for type 2 diabetes were found since the previous 2005 CTFPHC recommendations.⁵⁻⁸ However after review through the five step evaluation process only two studies were included for further consideration. The expert results are reported below.

Costs to the health care system

Waugh et al. conducted a high quality model based study using the Sheffield Diabetes model.⁸¹ The model combines the UKPDS risk equations with other microvascular complications risk equations to estimate the incidence and costs associated with most major micro and macrovascular complications. The model incorporates published data on A1c values at screen detection compared to values at clinical detection along with data on the progression of A1c to estimate time to clinical detection for those detected through screening. Analysis concluded that screening for type 2 diabetes appeared to be cost effective for the 40-70 year age cohort. Screening was more effective for hypertensive and obese individuals, as the costs of screening were offset by lower future treatment costs. However, the authors note that the cost effectiveness of screening is determined by the assumptions given to the degree of glucose control and future treatment protocols.⁸¹

A 2010 study by Kahn et al. used a representative sample of the US population to simulate a population of 325,000 people aged 30 years of age and older and tested eight screening strategies compared with a no screening control group.⁵⁵ Those strategies included: a) screen the entire population ≥ 30 years of age (repeat every three years); b) screen entire population ≥ 45 years of age (repeat every year); c) screen entire population ≥ 45 years of age (repeat every three years); d) screen entire population ≥ 45 years of age (repeat every five years); e) screen entire population ≥ 60 years of age (repeat every three years); f) screen anyone when BP is >140/90 mm/Hg (repeat every year); g) screen anyone when BP is >135/80 mm/Hg (repeat every five years); h) screen entire population ≥ 30 years of age (repeat every six months).⁵⁵ All strategies were effective in that they

increased quality adjusted life years (QALYs) when compared to no screening, with screening strategy h) adding the most undiscounted QALYs at 194, and screening strategy e) adding the least QALYs at 93.⁵⁵ Based on an incremental analysis, strategy a) would be the optimal strategy assuming a decision maker was willing to pay at least \$12,961 per QALY. The authors conclude that starting screening every 3-5 years beginning at age 30 is cost effective.⁵⁵

Key Question 2: What is the evidence for the harm of screening for type 2 diabetes using, fasting plasma glucose, oral glucose tolerance test, or A1c in asymptomatic adults 18 years of age or older at high risk or average and moderate risk for diabetes complications?

Summary of findings

The updated search identified two randomized controlled trials, one of which was included in the 2008 USPSTF report.⁴ Both trials were completed in the United Kingdom as part of the ADDITION trial and both reported on the adverse effects of screening for type 2 diabetes, specifically at the primary care or general practitioner level^{76,82} (see Table 3 for a summary of the studies' characteristics). One study reported no significant long term effects of screening for type 2 diabetes,⁷⁶ whereas the other trial reported short term adverse effects on anxiety levels following screening for type 2 diabetes.⁸²

The first trial by Eborall and colleagues was embedded in the ADDITION study and sought to quantify the psychological impact of stepwise type 2 diabetes screening at the primary care level.⁷⁶ Participants were recruited from 15 general practices (10 screening and 5 control) in Cambridge, United Kingdom. A total of 7,380 adults ranging from 40-69 years of age participated in the trial. Those randomized to the intervention group (n=6,416) were invited to participate in a screening protocol at a practitioner's office, whereas the control group (n=964) did not receive any invitation to attend a screening opportunity for type 2 diabetes. The intervention group followed a stepwise screening program which included: a) a random capillary glucose test; b) a fasting capillary glucose test if their random test was ≥ 5.5 mmol/L; and c) an oral glucose tolerance test (75g) if their fasting capillary glucose test was ≥ 6.1 mmol/L.⁷⁶ The diagnosis of type 2 diabetes was subsequently confirmed according to World Health Organization criteria. Outcome measures for anxiety and depression were collected using the Spielberger State Anxiety Inventory (STAI) and the Hospital Anxiety and Depression Scale (HADS). Diabetes specific worry was measured using an adapted version of the Lerman Cancer Worry Scale (LCWS). Of those invited to attend initial screening in the intervention group, only 68% were screened. At baseline, 3-6 months and 12-15 months, no significant differences were found between the intervention (screened) and control (not screened) groups, on any of the outcomes.⁷⁶ Overall, the authors note that screening for type 2 diabetes had a limited psychological impact.

The second trial by Park et al., was a pilot study for the ADDITION trial and tested: a) the feasibility of a stepwise approach to screening for diabetes; b) the uptake of the screening program; and c) the effects of the program on participants' anxiety, self-reported health and illness perceptions of diabetes.⁸² This trial included participants from two general practices in the Cambridge area of the United Kingdom and randomized them in 2:1 to either the intervention group (invited for type 2 diabetes screening; n=116) or control (not invited for type 2 diabetes screening; n=238). The intervention group then followed a stepwise screening program similar to that of

Eborall et al.'s study.^{76,82} Outcome measures included the Spielberger State Anxiety Inventory (STAI) and the Illness Perception Questionnaire (IPQ). No significant differences were noted at baseline between the two groups. Six weeks after participating, the screen invited participants reported being more anxious than those not invited (mean STAI score: 37.6 vs. 34.1, $p=0.015$) and those diagnosed with diabetes were more anxious than those determined not to have type 2 diabetes (mean STAI score: 46.7 vs. 37.0, $p=0.031$).⁸² The data from this trial suggest that screening for type 2 diabetes in the primary care setting is feasible but may be associated with higher levels of short-term anxiety in screen invited participants. The risk of bias was assessed (Table 6) and a GRADE evidence profile (Table 7) was created for the two studies^{76,82} that considered adverse effects of screening for type 2 diabetes.

Other relevant study details

The 2008 USPSTF identified eight studies that assessed the adverse effects of screening high risk individuals for type 2 diabetes. As discussed previously, a trial by Eborall et al.⁷⁶ randomized participants to a screening program versus no screening and assessed the adverse effects, specifically anxiety and depression. An additional seven studies were identified, including cohort and cross sectional survey studies. Three of the studies were from the Hoorn Screening Study group, which reported no significant changes in anxiety, well-being or diabetes symptoms at 2 weeks, 6 months or 1 year following diabetes screening.⁷⁰⁻⁷² The four additional studies reported similar findings at the time of screening and at one year, concluding that health related quality of life and anxiety levels did not change as a result of screening at a population or primary care level or from the subsequent diagnosis of type 2 diabetes.^{59,73-75,78}

Results for Contextual Questions

Contextual Question 1: What is the cost effectiveness of screening asymptomatic adults 18 years or older for type 2 diabetes from the perspective of the system and the patients?

Summary of findings

A total of six papers related to cost effectiveness of screening for type 2 diabetes were found since the previous 2005 CTFPHC recommendations. One study was a systematic review of the literature⁸¹ and five studies were based on various modeling approaches.^{55,83-86} Costs to individuals were not identified in the updated literature review.

Costs to the health care system

Waugh et al. reviewed five studies that assessed the aims of screening for undiagnosed diabetes and whether screening should be considered for other forms of abnormal glucose metabolism (e.g., impaired fasting glucose, impaired glucose tolerance and metabolic syndrome).⁸¹ In their systematic review of the literature, it was determined that screening and detection of impaired glucose tolerance is worthwhile as the risk of cardiovascular disease and diabetes can be prevented through established lifestyle and pharmacological interventions. Screening for type 2 diabetes was less concise according to Waugh et al.⁸¹ Screening would require a two-step process, starting with a systematic approach targeting high risk individuals. The second step was not clearly defined in the review, as the authors concluded that the choice of test (FPG, OGTT or A1c) was dependent on

cost, convenience and reproducibility, and that there is no perfect test. Modeling analyses concluded that screening for type 2 diabetes appeared to be cost effective for the 40-70 year age cohort. Screening was more effective for hypertensive and obese individuals, as the costs of screening were offset by lower future treatment costs. However, the authors note that the cost effectiveness of screening is determined by the assumptions given to the degree of glucose control and future treatment protocols.⁸¹

A study by Glümer et al. aimed to address deficiencies in cost effective modeling studies for type 2 diabetes screening, by taking into account the degree of uncertainty regarding treatment combinations, compliance and baseline risk for coronary heart disease (CHD).⁸³ Using population data from the Danish Inter99 study and the United Kingdom Prospective Diabetes Study coronary heart disease risk engine, simulations were determined in a theoretical population of 1,000,000 individuals, assuming a 75% screening attendance rate.⁸³ Treatment combinations were set at targets based on BMI ($>25 \text{ kg/m}^2$) and systolic ($\geq 140 \text{ mm/Hg}$) and diastolic ($\geq 85 \text{ mm/Hg}$) blood pressure. Compared with a no screening strategy, the most cost effective approach was to target all individuals 50 years of age and older with a BMI over 30, which resulted in an estimated incremental cost effectiveness ratio (ICER) of £46,597 per CHD event prevented. The second most effective strategy included screening all European men 45 years and older with a BMI over 25 and all non-European men and women 50 years of age and older with a BMI over 30. This strategy resulted in an ICER of £46,661 per CHD event prevented.⁸⁴ Overall, the authors note that their modeling approach reflects a great deal of uncertainty with respect to screening for diabetes and its subsequent treatment combinations, which is therefore reflected in the overall costs associated with screening.⁸³ Furthermore, it is uncertain to what extent this modeling population (mostly Scandinavian) would apply to Canada's heterogeneous population.

Another modeling study using data from the United Kingdom compared four different screening strategies and subsequent interventions to determine the most cost effective approach in adults.⁸⁴ The four strategies included: a) screening for type 2 diabetes to enable early detection and treatment; b) screening for type 2 diabetes and IGT, and intervening with lifestyle modification in those with IGT to prevent or delay type 2 diabetes; c) same as b) but with pharmacotherapy intervention instead of lifestyle modification; and d) no screening at all.⁸⁴ Discounting for 3.5% per year for both costs and benefits and using a hypothetical population of 45 years of age or older with above average risk, the modeling simulated the long term effects (50 years) of each screening strategy. The estimated costs for each quality adjusted life year (QALY) gained with type 2 diabetes screening alone was £14,150; £6,242 for screening for diabetes and IGT, followed by lifestyle interventions; and £7,023 for screening for diabetes and IGT, followed by a pharmacotherapy intervention.⁸⁴ At a theoretical 'willingness-to-pay' level of £20,000, the probability of the intervention being cost effective was 49%, 93% and 85% for each of the screening strategies. Although the authors note that screening for type 2 diabetes in a high risk population aged over 45 years, and intervening if IGT is detected is cost effective, the cost effectiveness of screening for type 2 diabetes alone remains uncertain.⁸⁴ The findings from this UK cost effectiveness modeling study may be generalizable to Canada's heterogeneous population and similar health care system.

A study from Germany, using statutory health insurance statistics also considered the cost effectiveness of screening for type 2 diabetes.⁸⁵ The study sought to compare the costs of screening versus current practice, which includes the diagnosis of type 2 diabetes in routine clinical care or after the manifestation of a clinical symptom. The model readily allowed for detailed subgroup analysis accounting for the different characteristics of the German population and assessed

endpoints such as quality of life, lifetime costs, age at diabetes diagnosis, and incidence and age at occurrence of diabetes-related complications such as myocardial infarction (MI), stroke, renal failure and blindness.⁸⁵ The modeling simulation determined that those with screen detected type 2 diabetes lived on average 0.8 years longer than those receiving current practice, but overall average time of illness in the screening group was markedly longer than current practice. The authors conclude that screening for type 2 diabetes was cost effective in the general population; €562.54 per QALY for lifestyle intervention and €325.44 per QALY for prevention with metformin (2006 values).⁸⁵ However, the authors caution that the current German health insurance system is lacking long-term incentives to support preventive screening programmes.⁸⁵

A Mexican study examined the potential savings from a screening and prevention program for early diabetes and hypertension, known as the Prevention in Mexican Institute of Social Security.⁸⁶ The program was established to address the high prevalence of type 2 diabetes among beneficiaries of the social security program (prevalence rate of 14.8%).⁸⁶ The results of this study conclude that for each US dollar invested in screening and prevention of type 2 diabetes, 84 to 323 US dollars were saved over a 25 year period, and that older adults (age 60 and older) and adult women (age 30-59) benefited the most from the screening program. Interestingly, the authors note that despite the cost savings accrued with the current screening and prevention program, screening via plasma glucose samples was not being used widely enough or was insufficiently targeting those at greater risk.⁸⁶

Finally, a 2010 study by Kahn et al. used a representative sample of the US population to simulate a population of 325,000 people aged 30 years of age and older and tested eight screening strategies compared with a no screening control group.⁵⁵ Those strategies included: a) screen the entire population ≥ 30 years of age (repeat every three years); b) screen entire population ≥ 45 years of age (repeat every year); c) screen entire population ≥ 45 years of age (repeat every three years); d) screen entire population ≥ 45 years of age (repeat every five years); e) screen entire population ≥ 60 years of age (repeat every three years); f) screen anyone when BP is $>140/90$ mm/Hg (repeat every year); g) screen anyone when BP is $>135/80$ mm/Hg (repeat every five years); h) screen entire population ≥ 30 years of age (repeat every six months).⁵⁵ All simulated models contributed to QALYs, with screening strategy a) adding the most undiscounted QALYs at 171, and screening strategy e) adding the least QALYs at 93.⁵⁵ The most cost effective screening strategies per QALY included: screening strategy c) (9,731 US\$/QALY); and screening strategy d) (9,786 US\$/QALY).⁵⁵ Therefore, the authors note that the most cost effective range to start screening is at approximately 30 years of age and to repeat screening every 3 to 5 years.⁵⁵

Contextual Question 2: What are patient values and preferences related to screening for type 2 diabetes?

Summary of findings

There were 11 primary studies identified as relevant to the issue of patient values and preferences related to screening for type 2 diabetes. Patient perceptions and preferences, preferences for patient/provider involvement and communication, and other factors are included in this summary. Some of the original studies were included in the discussion of Key Question 2. Otherwise, studies of qualitative and quantitative designs will be summarized narratively according to their findings.

Patient perceptions and preferences

Patient perceptions of screening were generally identified as positive in the literature, particularly at the initial invitational screening stage.^{87,88} The authors note that this may be a result of the focus on population screening and benefits, and not on individual advantages, thus the potential for adverse effects are not discussed or mentioned. Furthermore, type 2 diabetes may be regarded as a less *severe* disease than cancers, thus it may not be perceived by patients as a major concern or worry at the time of screening. Patients were also positive towards the screening experience when they were informed that their screening was part of a health check. Patients found their health check to be a positive experience, and not negatively associated with a disease.⁸³

In a qualitative study of 15 patients with screen-detected prediabetes from the United Kingdom, many felt *uncertainty* regarding the seriousness of type 2 diabetes as they proceeded through the screening process.⁸⁹ As patients proceeded through the lengthy screening, testing and confirmation stages, many expressed that a pending diagnosis of type 2 diabetes was viewed as less severe and urgent in nature as more time elapsed.⁸⁹ In another qualitative study of 40 Dutch participants who proceeded through the Hoorn stepwise type 2 diabetes screening project, many found the screening process positive, earnest, and not burdensome.⁹⁰

Patients also expressed their acceptability and satisfaction with point of care screening for type 2 diabetes, as measured by an on-site A1c capillary test method.⁹¹ One hundred and eighty four patients from eight general practitioner offices were offered point of care testing in comparison to usual stepwise screening.⁹¹ Point of care testing for A1c was perceived as time saving and provided an immediate opportunity for discussion with their physician. The intervention and control group had similar diabetes clinic satisfaction scores at the conclusion of the study ($p = 0.507$).⁹¹ However, the authors note that patients were limited in their understanding of A1c levels and that overall, the adoption of point of care screening with a blood test could not be recommended without further evidence.

Preferences for patient/physician involvement and communication

A common theme identified in the literature was a lack of awareness of the risks for type 2 diabetes and the lack of labeling as diagnosed with type 2 diabetes that occurred throughout the screening process.^{59,91-94} Several qualitative and descriptive studies discussed the importance of increasing awareness of the risks and complications associated with type 2 diabetes.^{59,90-94} Researchers note that: a) patients should be made aware of their risk factors that led to a screening invitation and that a negative screen test does not exclude them from continuing to be at risk for type 2 diabetes; b) that a diagnosis should not be normalized by emphasizing the commonness of type 2 diabetes; and c)

although type 2 diabetes may be managed, patients should be aware of the risks and consequences of the disease and the risk factors that deemed them to be at high risk (e.g., hyperlipidemia, hypertension, obesity).^{59,91-94}

As Eborall and colleagues note, the challenge for physicians is balancing the right amount of information to convey and to engage patients in making lifestyle changes without raising anxiety levels to the point of disengagement.⁸⁷ Other studies note that the potential for giving too much information and/or labeling with a diagnosis of type 2 diabetes is often short term and should not be a barrier to diabetes screening.⁷³ Adriaanse et al. note that the previously held assumption that receiving a diagnosis of type 2 diabetes can be distressing and debilitating is being challenged in the current literature.^{90,94} To that end, research suggests that recognizing the diagnosis and labeling are critical components of the therapeutic process.⁹¹⁻⁹⁴

Other factors

Framing of the invitation message and conveying the importance of screening for type 2 diabetes has also been examined with respect to patient preferences and effects of screening adherence.⁹⁵⁻⁹⁷ A trial from the United Kingdom embedded in the ADDITION study, randomized 106 high risk patients to receive either positive message (gain) or negative message (loss) type 2 diabetes screening invitations to determine the effects on screening uptake, anxiety and self-rated health.⁹⁵ No significant differences between the gain and loss messaging groups were detected in attendance ($p=0.88$), anxiety ($p=0.1$) or self-rated health ($p=0.77$), noting that framing of information related to diabetes screening did not influence uptake or psychological factors.⁹⁵ These conclusions were supported by another trial (DICISION study group) from the United Kingdom that examined the effect of informed choice ($n=633$) versus standard screening invitations ($n=639$) on uptake; concluding that invitations that promoted informed choice did not impact screening adherence ($p=0.51$).⁹⁷

Contextual Question 3: What risk factors could guide screening for type 2 diabetes (e.g., age, hypertension, cholesterol, waist circumference, ethnicity)?

Summary of the findings

A total of four reviews^{81,98-100} and five studies^{14,102-106} related to risk factors that could guide screening for type 2 diabetes were found since the previous 2005 CTFPHC recommendations. The risk factors that will be summarized include: metabolic syndrome (hypertension, hyperlipidemia and/or glucose irregularities); weight related factors (BMI, waist/hip ratio, waist circumference and adiponectin); age and ethnicity. Other risk factors will also be discussed.

Metabolic syndrome (MetS)

A meta-analysis of 16 prospective cohort studies was conducted to derive estimates of relative risk of diabetes, using various definitions of MetS.⁹⁸ Using random-effects modeling, relative risks ranged from 3.53 (95% CI 2.84-4.39) using the 2001 National Cholesterol Education Program (NCEP) definition, to a high of 5.17 (95% CI 3.99-6.69) using the 1999 World Health Organization definition.⁹⁹ The investigators note that regardless of the MetS definition, once four or more criteria were met, the relative risk increased to a range of 10.9-24.4.⁹⁸

Two studies were also reviewed that provided secondary analyses of large trials to determine risk factors associated with type 2 diabetes.^{101,102} A secondary analysis of 1,368 patients from the multinational STOP-NIDDM trial also concluded that having at least three of the five MetS traits (see Appendix 2), as defined by the 2001 NCEP Third Adult Treatment Panel (ATP 111) definition derived a hazard ratio (HR) of 1.61 (95% CI 1.32-1.95; $p < 0.0001$).¹⁰¹ With respect to individual traits from the NCEP-ATP III MetS definition, impaired fasting glucose was the strongest predictor of conversion to type 2 diabetes (HR 1.51; 95% CI 1.26-1.81; $p < 0.0001$), followed by high triglyceridemia (HR 1.38; 95% CI 1.14-1.68; $p < 0.0009$), low high density lipids (HR 1.31; 95% CI 1.08-1.59; $p < 0.0062$) and high blood pressure ($\geq 130/85$ mm/Hg) (HR 1.24; 95% CI 1.03-1.49; $p < 0.0208$).¹⁰¹ An additional secondary analysis study of the Diabscreen trial data ($n = 3,474$) also demonstrated the association of elevated blood pressure and the odds of undiagnosed type 2 diabetes.¹⁰³ An elevated blood pressure ($>135/80$ mm/Hg) yielded an odds ratio (OR) of 2.5 (95% CI 1.6-3.8; $p < 0.001$), suggesting the odds of having undiagnosed type 2 diabetes were significantly higher in individuals with even mildly elevated blood pressure.¹⁰²

Weight related factors

Weight related indicators are known to be risk factors for type 2 diabetes. Specifically, BMI, waist circumference and waist/hip ratio are highly correlated and should yield similar relative risks for type 2 diabetes.¹⁰⁰ In a meta-analysis of 32 studies (cohort or nested case-control designs), the pooled relative risks for incidence of diabetes were: 1.87 (95% CI 1.67-2.10) per Standard Deviation (SD) of BMI; 1.87 (95% CI 1.58-2.20) for SD of waist circumference; and 1.88 (95% CI 1.61-2.19) per SD of waist/hip ratio.¹⁰⁰ However, the authors caution the clinical utility of focusing on central obesity alone as a risk factor for type 2 diabetes. In the secondary analysis study of the Diabscreen trial data ($n = 3,474$), having a BMI over 27 kg/m^2 was significantly associated with undiagnosed diabetes (OR 3.2; 95% CI 2.0-5.2; $p < 0.001$).¹⁰² Interestingly, the STOP-NIDDM secondary analysis did not demonstrate a significant relationship between large waist circumference (≥ 102 cm for males, ≥ 88 for females) and type 2 diabetes (HR 1.19; 95% CI 0.97-1.46; $p = 0.09$).¹⁰²

The association of weight related factors, specifically obesity and type 2 diabetes is further explored in the literature through adiponectin levels. Adiponectin, a hormone that adapts a number of metabolic processes including glucose regulation, is inversely correlated with body fat percentage in adults.¹⁰⁴ In a meta-analysis of 13 studies of 14,598 individuals, including 2,623 cases of type 2 diabetes, the relative risk for type 2 diabetes with a higher adiponectin level was 0.72 (95% CI 0.67-0.78; $p < 0.001$) per every 1-log microg/mL increment in adiponectin levels, irrespective of ethnicity, adiponectin assay, method of diabetes diagnosis or sex.⁹⁹ The reviewers note that adiponectin levels in addition to other established risk factors for type 2 diabetes should be further evaluated.

Other risk factors

Schizophrenia and its association with type 2 diabetes is well documented; however the use of antipsychotic medications may be responsible for this observed relationship.⁴³ In a small cross sectional study from Ireland, 120 individuals (38 drug-naïve patients with schizophrenia; 38 matched controls without schizophrenia and 44 unaffected parents of the patients) were administered oral glucose tolerance tests to determine the frequency of type 2 diabetes.¹⁰³ The frequency of impaired glucose tolerance was 10.5% in patients with schizophrenia, 18.2% in unaffected relatives and 0% in the matched controls without schizophrenia ($p < 0.05$). Although this

study sample was small, it does demonstrate an independent relationship between schizophrenia and impaired glucose, as well as familial association (genetic and/or environmental) between schizophrenia patients and their family.¹⁰³

The prevalence of diabetes is greater in high risk populations, including people of Hispanic, South Asian and African origins.¹⁶ In a population based study using administrative health data, 1,122,771 immigrants to Ontario were compared to long term residents (n= 7,503,085) to determine prevalence rates of type 2 diabetes in various ethnic groups.¹⁶ Immigrants from South Asia had an approximate four-fold increase in the risk of diabetes (OR 4.01; 95% CI 3.82-4.21 for men; OR 3.22; 95% CI 3.07-3.37 for women), those from Latin America and the Caribbean had a two-fold increase in the risk of diabetes (OR 2.18; 95% CI 2.08-2.30 for men; OR 2.40; 95% CI 2.29-2.52 for women), and individuals from sub-Sahara Africa also had a two-fold increase in the risk of diabetes (OR 2.31; 95% CI 2.17-2.45 for men; OR 1.83; 95% CI 1.72-1.95 for women).¹⁶ The researchers note that in these particularly high risk ethnic groups, the risk of diabetes becomes evident at an earlier age, at approximately 35-49 years.¹⁶

Contextual Question 4: What is the evidence that screening for diabetes in Aboriginal people, rural/remote, women and elderly improves health outcomes and/or mortality?

Summary of findings

No new evidence was found to demonstrate that screening for type 2 diabetes in various populations (e.g., Aboriginal people, rural/remote, women and the elderly) improved health outcomes and/or mortality. However, a total of nine studies^{6,15,16,89,92,97,105-107} and one grey literature document¹⁴ discussed risk factors and/or screening for type 2 diabetes in subgroups, specifically Aboriginal people, women and the elderly. Socioeconomic status (SES) was also evident as a risk factor for type 2 diabetes. No evidence was located for rural/remote dwelling as a risk factor for type 2 diabetes.

Aboriginal community

In a population based study of Aboriginal Canadians (n=8,275) and non-Aboriginal people (n=82,306), researchers established an age adjusted prevalence for Aboriginal people in Canada to be 2.5 to 5 times higher than that of the general population, with some individual communities having an age-adjusted prevalence as high as 26%.¹⁵ Overall, Aboriginal women were among those at greatest risk, with a four-fold increase in type 2 diabetes compared to non-Aboriginal women. Aboriginal men had a 2.5 times higher prevalence rate when compared to non-Aboriginal men. The researchers note that the greatest incidence (32/1,000 people) of type 2 diabetes in Aboriginal people was between the ages of 40-49 years.¹⁵

A secondary analysis from a cohort study determined the predictive association of MetS and its components of type 2 diabetes incidence in an Aboriginal community.¹⁰⁶ Regardless of using the NCEP ATP III definition of MetS or the International Diabetes Federation (IDF) criteria, the ORs were 2.03 (95% CI 1.10-3.75) for NCEP ATP III and 2.14 (95% CI 1.29-3.55) for IDF criteria.¹⁰⁶ Of the individual criteria defining MetS, hypertension had the strongest association with type 2 diabetes (OR 2.59; 95% CI 1.43-4.70), followed by elevated fasting glucose (OR 2.3; 95% CI 1.40-3.77) and elevated triglycerides (OR 2.07; 95% CI 1.46-2.93).¹⁰⁶ The authors note that MetS may be useful in identifying Aboriginal people at risk for type 2 diabetes.

Finally, a Canadian study of 418 Aboriginal people sought to determine whether previously screened individuals followed up on recommendations, based upon their screening results.¹⁰⁵ The authors note that various diabetes stakeholder groups have previously recommended against screening in rural or community settings due to lack of beneficial evidence and adherence to screening recommendations. Oster et al. found that of individuals who were told they had prediabetes, 59% followed up with a physician, and of those who were told they had ‘probable’ type 2 diabetes, 66% followed up with a physician.¹⁰⁵ The screening strategies deployed in the remote communities included portable diagnostic equipment to capture FPG and A1c. The authors note that this type of opportunistic screening is advantageous, particularly among Aboriginal groups that may otherwise not seek conventional health care.¹⁰⁵

Women

In a large population based cohort study from Ontario, 659,164 pregnant women with no history of pre-existing diabetes were followed for a total of nine years.¹⁰⁷ Of these women, 21,823 (3.3%) went on to develop gestational diabetes. The probability of women developing type 2 diabetes after having gestational diabetes was 3.7% at nine months after delivery and 18.9% nine years after delivery. After controlling for age, SES, hypertension and other health care utilization factors, the risk of developing type 2 diabetes was significant (HR 37.28; 95% CI 34.5-40.9; $p < 0.001$).¹⁰⁷ The authors note that gestational diabetes poses a significant risk for type 2 diabetes and that clinicians should assist in counseling women following delivery to decrease their risk of developing type 2 diabetes.¹⁰⁷

Elderly

According to the Public Health Agency of Canada’s 2009 National Diabetes Surveillance System, age is a risk factor for type 2 diabetes, particularly as the prevalence percentage climbs steadily between the ages of 40-69, with the prevalence percentage at approximately 20% at age 65.¹⁴ This prevalence percentage was also confirmed in a US cohort, using the National Health and Nutrition Examination Survey (NHANES). In a cohort from 1999-2002, the prevalence percentage was 21.6% in those aged 65 years and older.⁶ Interestingly, in a secondary analysis of a large Dutch cohort ($n=3,474$), age was not associated with undiagnosed type 2 diabetes (OR 1.3; 95% CI 0.8-1.9; $p=0.26$).¹⁰²

Socioeconomic status (SES)

In two randomized controlled trials assessing the effect of stepwise screening programs for type 2 diabetes, SES variables contributed to attendance and uptake of screening behaviours. In a United Kingdom trial of 1,272 participants at risk, attendance was lower in the most deprived group ($p < 0.001$), where most deprived was defined as an index, derived from lower economic, social, and housing standing.⁹⁷ Conversely, a Dutch trial of 4,603 high risk individuals from the ADDITION study found that those most likely to participate in the screening process were unemployed.⁸⁸ However, the authors note that there were no significant differences in education or income levels among the attenders and non-attenders.⁸⁸

Contextual Question 5: What are the clinical benefits and harms of early treatment (less than 12 months) of patients with type 2 diabetes compared with later treatment of patients for improvement of intermediate or final health outcomes?

Summary of findings

No new evidence was identified in the literature review examining the clinical benefits and harms of early treatments of patients with type 2 diabetes compared with later treatment of patients for improvement of intermediate or final health outcomes since the 2005 CTFPHC's screening for type 2 diabetes recommendations.² The ADDITION trial does not compare early versus late treatment, but rather compares conventional diabetes treatment to intensive multifactorial treatment, and therefore was excluded.¹⁰⁸ To our knowledge, the effectiveness of early versus late treatment for type 2 diabetes has not been tested to date in a randomized controlled trial.

Contextual Question 6: What are the clinical benefits and harms of treatment of patients with impaired fasting glucose and impaired glucose tolerance compared with no treatment for improvement of intermediate or final health outcomes?

Summary of findings

A total of nine studies¹⁰⁹⁻¹¹⁷ related to the clinical benefits and harms of treatment of patients with IFG or IGT compared with no treatment for improvement of intermediate or final health outcomes were found. Treatments include lifestyle^{109,110} and pharmacotherapy interventions.¹¹¹⁻¹¹⁷

Lifestyle interventions

A trial in the United Kingdom randomized 78 individuals with IGT to either a 24-month lifestyle intervention or to a control group.¹⁰⁹ The control group received results from their clinical assessment, whereas the intervention group received dietary and physical activity advice, as well as regular review appointments. After 24 months, the mean weight gain in the control group was 1.5 kg and the intervention group lost a mean of 1.8 kg ($p=0.008$).¹⁰⁹ However, improvements in fasting plasma glucose or 2-hour glucose levels were not significant in either group after 24 months.¹⁰⁹ Although the study concludes with similar findings to that of previous lifestyle trials, follow up at 24 months was only 75% in the control group and 81% in the intervention group.

A larger trial completed in Italy randomized 335 individuals with MetS (specifically IFG, as defined by 2001 NCEP ATP III) to either a control group or the intervention group.¹¹⁰ Initially, both groups received standard practice counseling regarding lifestyle modifications; however, the intervention group then continued with regular and individualized lifestyle counseling for one year. At the end of the study, the lifestyle intervention group significantly reduced components of MetS (IFG, hypertension, hypertriglyceridemia and/or hyperlipidemia), as well as the incidence of MetS (OR 0.28; 95% CI 0.18-0.44).¹¹⁰ The intervention group also noted reductions in the incidence of type 2 diabetes (OR 0.23; 95% CI 0.06-0.85)¹¹⁰, thus illustrating how a lifestyle intervention based on general recommendations was effective in the primary care setting.

Finally, the Diabetes Prevention Program (DPP)¹¹⁸ study followed up with 2766 of the original 3150 active participants for an average of 5.7 years, to investigate whether the persistence of

lifestyle interventions remained long-term, specifically the prevention of type 2 diabetes. Participants were followed in their original randomized group (910 participants were from the lifestyle, 924 from the metformin, and 932 were from the original placebo groups). Diabetes incidence rates during the active phase DPP were similar to the follow-up study: a) active intensive lifestyle group - 4.8 cases per 100 person-years (95% CI 4.1-5.7), follow up intensive lifestyle group - 5.9 cases per 100 person-years (95% CI 5.1-6.8); b) active metformin group - 7.8 cases per 100 person-years (95% CI 6.8-8.8), follow-up metformin group 4.9 cases per 100 person-years (95% CI 4.2-5.7); and c) active placebo group - 11.0 cases per 100 person-years (95% CI 9.8-12.3), follow-up placebo group 5.6 cases per 100 person years (95% CI 4.8-6.5). The follow-up study concluded that diabetes incidence was reduced over 10 years by 34% in the lifestyle group and 18% in the metformin group, when compared to placebo.

Pharmacotherapy interventions

A Dutch trial assessed the effect of acarbose versus placebo in reducing the incidence of type 2 diabetes in 118 individuals with IGT.¹¹¹ The absolute risk reduction for type 2 diabetes after three years was 6% (95% CI 9-21). However, the number of participants dropping out of the study was greater in the acarbose group (36.7%) than the placebo group (13.8%), mainly due to gastrointestinal side effects (abdominal pain, diarrhea, flatulence), which were not documented as serious adverse events.¹¹¹

A large multinational trial (NAVIGATOR – Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research) randomized 9,306 individuals with IGT to either nateglinide (up to 60 mg TID) or placebo, or valsartan or placebo.^{112,113} Subjects were followed for a median of 5 years with an 80% follow up rate in both the nateglinide and placebo arms. At the completion of the trial, nateglinide did not significantly reduce the incidence of diabetes compared to placebo (HR 1.07; 95% CI 1.0-1.15; p=0.05).¹¹² Furthermore, nateglinide did not decrease the incidence of the extended composite cardiovascular outcome (death from a cardiovascular cause, nonfatal myocardial infarction, nonfatal stroke, hospitalization for heart failure, arterial revascularization or hospitalization for unstable angina) (HR 0.93; 95% CI 0.93-1.03; p=0.16).¹¹² To that end, nateglinide did not reduce the incidence of intermediate (diabetes) or long term (cardiovascular) outcomes.¹¹² The incidence of diabetes was reduced in the valsartan group as compared to the placebo group (HR 0.86; 95% CI 0.80-0.92; p<0.001) and did not significantly decrease the incidence of the extended cardiovascular outcome (HR 0.96; 95% CI 0.86-1.07; p=0.43).¹¹³

The Diabetes Reduction Assessment with ramipril and rosiglitazone Medication (DREAM) trial randomized 5,269 individuals with IFG or IGT to either ramipril versus placebo or rosiglitazone 8 mg once a day versus placebo.¹¹⁴⁻¹¹⁶ The drug adherence rates were 88.4% for the placebo group, 74% for the rosiglitazone group and 75.4% for the ramipril group.^{114,115} At the end of the three year follow up period, rosiglitazone significantly reduced the risk of diabetes by 60% (HR 0.40; 95% CI 0.35-0.45; p<0.0001) and 51% in the rosiglitazone group became normoglycemic (HR 1.71; 95% CI 1.57-1.87; p<0.0001).¹¹⁴ Although cardiovascular event rates were the same in each group, more individuals in the rosiglitazone group developed heart failure compared with the placebo group (p=0.01).¹¹⁵ Furthermore, the incidence of type 2 diabetes did not differ significantly between the placebo and ramipril groups (HR 0.91; 95% CI 0.81-1.03; p=0.015).¹¹⁵ Finally, neither ramipril (HR 0.98; 95% CI 0.84-1.13; p=0.75) nor rosiglitazone (HR 0.87; 95% CI 0.75-1.01; p=0.07) reduced the risk of the composite cardiorenal outcomes (cardiac and renal outcomes combined).¹¹⁶

Finally, the Canadian Normoglycemia Outcomes Evaluation (CANOE) trial recruited 207 patients with IGT and randomized them to either placebo, or a combination of rosiglitazone (2 mg twice a day) and metformin (500 mg twice a day).¹¹⁷ At study completion (median follow up of 3.9 years), fewer individuals in the intervention group developed diabetes than in the placebo group ($p<0.001$). The relative risk reduction was 66% (95% CI 41-80) and the absolute risk reduction was 26% (95% CI 14-37).¹¹⁹ Adverse events documented during the trial included an increase in diarrhea in the rosiglitazone/metformin group (16% vs. 6%; $p=0.025$).¹¹⁷

Contextual Question 7: What process and outcome performance measures or indicator have been identified in the literature to measure and monitor the impact of screening for type 2 diabetes?

A) COVERAGE

Proportion of at-risk people who are aware of the need for screening¹²⁰

Practices that use culturally appropriate awareness materials for informing people about screening

PARTICIPATION RATE [Adapted from AIHW¹²⁰]

Average Risk people over the age of 40 years

The proportion of people at risk of Type 2 diabetes being screened, and the proportion of these undergoing appropriate screening (as defined by evidence-based guidelines).

Special Populations: Aboriginal men and women; rural and remote, women, elderly (Populations identified in by our protocol)

Retention Rate¹²¹

Percentage of MDs who utilize a risk questionnaire such as CANRISK

Percentage of MDs who order screening test (OGTT, A1c) [Adapted based on our review]

B) Follow-up¹²¹

Abnormal rate

Follow-up rate

Loss to follow-up

Screening Interval

Frequency of screening

Number of practices with a recall system

C) Quality of Screening¹²²

Screening test used

A1c levels reported

D) System capacity indicators/resource utilization

Percentage of Canadians tested per fiscal year⁶⁰

Percentage of Canadians over age 40 tested over one to five years⁶⁰

The proportion of health care providers who have a diabetes screening system in place including flags for screening individuals at high risk for diabetes or diabetes complications

Does it follow evidence-based guidelines?

Is there a register/recall system?

Is it culturally appropriate?

Are primary care practices accredited?¹²⁰

E) Detection

Pre-diabetes detection

Type 2 diabetes detection

Detection rates in subpopulations (Aboriginal, rural/remote dwellers, women, elderly)

[Adapted from AIHW¹²⁰]

F) Disease extent at diagnosis¹²¹

G) Incidence¹²⁰

Prediabetes

Diabetes¹²⁰

Incidence rates in subpopulations (Aboriginal, rural/remote dwellers, women, elderly)

[Adapted from AIHW¹²⁰]

Contextual Question 8: What are the most effective (accurate and reliable), risk assessment tools or questionnaires to predict type 2 diabetes?

Summary of findings

Our search located one recent systematic review¹²³ that examine the most accurate and reliable risk assessment tools or questionnaires to predict type 2 diabetes. The review was quality appraised using AMSTAR⁶³ (Appendix 11) from which it scored ten out of a possible eleven. Based on methodological quality of this review we accepted their findings and undertook a subsequent search of the literature (February 2011- November 2011) to update evidence for the risk assessment tools and models Noble et al. identified as being suitable for clinical use. That search located 2 papers externally validating FINDRISC.^{124,125} Through contact with a key informant we became aware of an 'accepted for publication' paper validating CANRISK.¹²⁶

Noble et al. conducted a systematic review that evaluated current risk models and scores for type 2 diabetes using both standard systematic review methodology as well as realist (most qualitative) methodology (Appendix 12).¹²³ Their sample included 43 studies which described 145 risk models or scores, of which 94 were selected for full data extraction. From those, seven validated risk scores or models were judged to be appropriate for use in clinical or public health setting. Those are

FINDRISC, ARIC (Atherosclerosis Risk in Communities), Ausdrisk (Australia), Cambridge risk score, Framingham Offspring Study, San Antonio risk score and QD Score. The AUROCs in the 7 recommended tools range from 0.74 to 0.85 for internal validations and from 0.72 to 0.84 in external validations. Six out of the seven recommended tools have been validated internally and externally; the only one that hasn't been validated externally is Ausdrisk but it has been studied as part of an intervention to improve patient important outcomes. FINDRISC is the tool that has been validated in more countries (Finland, Holland, Denmark, Sweden, UK, Australia).

One study from the Noble review report preliminary data that FINDRISC plus educational interventions appears to reduce incidence of diabetes after 12 months.¹²⁷ As well, this study demonstrates that FIN-2D2 (using FINRISC and repeat consultation in primary health-care, the FINNAIR project (a workplace-targeted intervention involving airline employees) and the GOAL programme (good aging in Lahti region – a community-based prevention program) have shown that screening for type 2 diabetes risk with FINDRISC and implementing large-scale lifestyle interventions in primary care are feasible.

FINDRISC was first validated in Finland as an effective method to identify risk of diabetes especially in persons age 45-64.¹²⁸ Important variables in this model include age; body mass index (BMI); waist circumference; physical activity; dietary consumption of fruits, vegetables and berries; use of antihypertensive medications; history of high blood glucose; and family history of diabetes.¹²⁹ In 2011 FINDRISC was externally validated in populations in Bulgaria¹²⁴ and Greece.¹²⁵ Tankova et al. sought to validate FINDRISK for the prediction of type 2 diabetes and pre-diabetes in a high risk Bulgarian population. The sample included 2169 subjects (879 males and 1290 females), mean age 50.3± 14.4 years and mean BMI 29.6±6.1 kg/m², having at least one of the main risk factors for diabetes. A FINDRISC score of greater or equal 12, measured sensitivity 0.78 (95% CI 0.73, 0.85) and specificity 0.62 (0.58, 0.68). For cut point of FINDRISC ≥10, sensitivity measured 0.84 (95% CI 0.71, 0.90) and specificity 0.61 (0.54, 0.71). FINDRISC was also validated in a Greek population. A total of 869 people residing in or around Athens participated (379 males with a mean age of 56.2±10.8 years. The optimal cut point for detecting unknown diabetes was a FINDRISC score of greater or equal 15. At this point the sensitivity was 81.1% and specificity was 59.8%. The AUROC curve for detecting unknown diabetes was 0.724 (95% CI: 0.699, 0.770).

Sub-question: 8.1 What risk assessment tools or questionnaires to predict type 2 diabetes have been validated in Canada?

In Canada, adults from seven provinces were recruited between 2007 and 2011 to participate in a cross sectional study to validate the CANRISK questionnaire for the detection of diabetes and pre-diabetes (N=6475).¹²⁶ CANRISK was adapted from FINRISC to account for the diverse ethnic composition of the Canadian population. The variables added were ethnicity, sex, education and macrosomia. Selected screening thresholds are reported as pCANRISK score (paper version of the tool) 21 slightly elevated, 29 moderate, 32 balanced, 33 high and 43 very high. The balanced score has a sensitivity of 70%, specificity of 67%, PPV of 35% and NPV of 90%.

Contextual Question 9 What is the yield (accuracy, reliability, prevalence, and feasibility) of screening for type 2 diabetes with FPG, OGTT, and A1c in adult patients?

Our search located one recent systematic review⁵³ that examined the most accurate and reliable tests to diagnose type 2 diabetes that were linked to patient important outcomes. The review was quality appraised using AMSTAR⁶³ from which it scored ten out of a possible eleven. The WHO systematic review included 11 papers that met their inclusion criteria. Their analysis of the evidence indicated a range of A1c levels between 5.8-7.3% associated with retinopathy. An A1c of $\geq 6.5\%$ had a Positive Predictive Value (PPV) of 15.9%, a Negative Predictive Value (NPV) of 97%, sensitivity of 7.9% and specificity of 97% for the 10 year incidence of diabetes related retinopathy. The results were summarized using GRADE⁶⁶ and the recommendations were based on the quality of evidence assessed by GRADE. The WHO report recommended

A1c can be used as a diagnostic test for diabetes providing that stringent quality assurance tests are in place and assays are standardized to criteria aligned to the international reference values, and there are no conditions present which preclude its accurate measurement.

An A1c of 6.5% is recommended as the cut point for diagnosing diabetes. A value of less than 6.5% does not exclude diabetes diagnosed using glucose tests.

Quality of evidence assessed by GRADE: moderate

Strength of recommendation based on GRADE criteria: conditional⁵⁴

Based on methodological quality of this review we accepted their findings and undertook a subsequent search of the literature (September 2010-November 2011) to update evidence for the effective tests for diagnosing diabetes. The search located 12 papers that compared A1C with FGT for the detection of diabetes.^{119,130-139} It should be noted that those 12 papers do not report outcomes beyond the diagnosis of diabetes. Of the 12, we focused on the results of papers in which A1c was compared with FPG or OGTT and provided information on the sensitivity, specificity, PPV/NPV and AUROC measures of A1c $\geq 6.5\%$ for the detection of type 2 diabetes. Four studies met that inclusion criteria. Those studies report a range of sensitivity 24-56.9; specificity 98.4-99; PPV 50-84; NPV 96.6-98.8 and AUROC .078-892.^{131,135,137,140} It should be noted that the included papers did not provide similar statistical analysis for FPG or OGTT as reported above for the A1c.

Discussion

Since the publication of the 2005 CTFPHC² and the 2008 USPSTF⁴ report for screening for type 2 diabetes recommendations, there has been one new cohort study publication to contribute to the discussion about the effectiveness of screening for type 2 diabetes. The population-based study demonstrated that screening had a non-significant reduction on mortality; however, no new evidence was found regarding the effectiveness of screening for type 2 diabetes on intermediate outcomes such as incidence of type 2 diabetes, differences in A1c levels, and frequency of diagnosis. To that end, the previous CTFPHC recommendations for screening adults with cardiovascular risk factors (hypertension and hyperlipidemia) for type 2 diabetes should remain.

With respect to screening strategies, the literature did not examine the effect of screening via different, or in comparison to other clinical screening measures (e.g., fasting plasma glucose, oral glucose tolerance test or A1c). The literature does remain controversial with respect to the best choice of clinical test to screen individuals for type 2 diabetes. Of note, the oral glucose tolerance test is often cited as the gold standard, as it includes a fasting plasma glucose and a 2-hour post prandial glucose level. However, this test is costly, difficult to reproduce and is inconvenient to patients.^{112,113} Interestingly, since the last CTFPHC and USPSTF recommendations for screening for type 2 diabetes, the A1c test has been considered as a possible screening test, particularly as it has been added as a diagnostic test for type 2 diabetes by the American Diabetes Association and the WHO.^{50,53,54} However, two recent epidemiological studies challenge the sensitivity of the A1c test in predicting and diagnosing type 2 diabetes.^{141,142} Both studies suggest that the sensitivity of the A1c $\geq 6.5\%$ ranges from 20.9% to 47%.^{141,142} Nevertheless, the A1c test may be useful for screening glucose irregularities and not just for diagnosing type 2 diabetes.

The HOORN⁷⁰⁻⁷² and ADDITION^{76,82} study groups, as well as other studies provided evidence that the risk of harm associated with screening is negligible. The harms associated with screening for type 2 diabetes were minimal, with little effect on anxiety levels, self-rated health status and quality of life.

Cost effectiveness studies varied in their conclusions, particularly due to the various modeling techniques and in the assumptions of glucose control requirements, multifactorial interventions for diabetes management (e.g., hypertension and hyperlipidemia) and future treatment protocols. To that end, it is difficult to generate conclusions based on the variability between the studies.

Patient preferences reflect the importance of *communication* as it relates to screening and potentially diagnosing, and the *process* of screening for type 2 diabetes. Framing the screening invitation in a positive (gain) or negative (loss) manner did not alter adherence rates to screening protocols. Regardless of the messaging style, patients attended if it was important to them. To that end, studies suggest that patients want physicians to label their risk factors and/or diabetes and stress the importance of managing risk factors (if screening is negative) or managing diabetes to prevent complications (if screening is positive). This may present a challenge for physicians in trying to provide enough information to engage their patients without overwhelming or alarming them. With respect to the process of screening, there was some discussion that stepwise screening approaches give patients an impression that type 2 diabetes is not an urgent or pressing issue, particularly as time elapses during the screening, confirmation and diagnosing processes. Finally, the evidence did suggest that presenting the screening process as part of a health check – a value added program, did improve adherence by providing a positive experience for individuals.

With respect to risk factors to guide screening or identifying high risk populations, the literature appears to be consistent with previous recommendations and does not necessarily provide new evidence to suggest additional risk factors for type 2 diabetes. Metabolic syndrome, specifically impaired glucose tolerance and/or impaired fasting glucose, hypertension and hyperlipidemia continue to be critical risk factors. Weight related risk factors including adiponectin are also reflected in the literature as associated with type 2 diabetes. According to a small observational study, schizophrenia, independent of medication use, appears to be associated with type 2 diabetes. Finally, ethnicity (Aboriginal and South Asian), women with previous gestational diabetes, and age all are important risk factors for type 2 diabetes and may highlight the need to screen for type 2 diabetes when they present alongside other known risk factors.

FINDRISC is a risk assessment tool that has been well validated internally (Finland) as well as externally including studies summarized in this review in populations in Bulgaria and Greece. CANRISK is a recently developed risk assessment questionnaire that can be used to identify risk of diabetes with the diverse ethnic Canadian population. A1c is an effective diagnostic test that is relatively easy to administer and is cost effective.

Finally, lifestyle interventions for prediabetes (IGT/IFG) have demonstrated efficacy in the literature, as well as the use of various oral medications for type 2 diabetes. Interestingly, the literature reflects more pharmacotherapy interventions in combination with lifestyle interventions. This may be for two reasons: a) most standards of care require lifestyle counseling upon the detection of prediabetes, therefore mitigating the amount of lifestyle trials using a ‘no counseling’ control group; and b) the growing belief that patients may obtain cardio and renal protection with some oral antidiabetic agents or as a result of normoglycemia.

Limitations

There are several limitations associated with this review. The search was limited to only those databases searched in the USPSTF review; only English language papers were included in the USPSTF search and only English and French were included in this update; only MEDLINE® and Cochrane databases were searched. EMBASE would be a logical database for searching for this question, but this was not done for the current review as the USPSTF review search strategy was the initial framework for this update. We found no new trials that examined the effectiveness of screening for type 2 diabetes. The studies found for the harms (anxiety) of screening were too heterogeneous for a meta-analysis.

The search for information about patient values and preferences, and special populations was focused and limited by a short timeframe and few databases. A systematic review process was not undertaken for these questions; rather it was a rapid review.¹⁴³

Future Research

The effectiveness of a screening intervention for type 2 diabetes has not been adequately tested to date in a randomized controlled trial. Screening interventions may include the actual screening test (questionnaire, blood test) or the process (stepwise approach versus an alternative approach). Also, to determine the impact of screening for type 2 diabetes versus no screening on final outcomes such as cardiovascular endpoints, long term follow up would be required in a large sample. This would be very costly and of course controversial as there remain inconsistencies across various key diabetes stakeholder associations and interest groups around the criteria to diagnose diabetes. Finally, early treatment of diabetes as a result of screen detection versus later treatment of diabetes presents a growing challenge. Many guidelines and standards of care endorse immediate lifestyle intervention if not pharmacotherapy upon the diagnosis of type 2 diabetes. Thus, withholding treatment presents an ethical and moral dilemma. Perhaps the best alternative would be a case control study examining final outcomes and reviewing historically ‘when’ type 2 diabetes was diagnosed and how (screened versus case-finding) may shed some light on the association of screen detected type 2 diabetes and early treatment versus usual care. Unfortunately, this method cannot demonstrate cause and effect, but it might demonstrate strong associations that may reflect a need to change practice. To that end, further research is required to determine the effect of screening for type 2 diabetes, the best approach to screening (detection, minimizes harm and is cost effective) and the best treatment once prediabetes or type 2 diabetes is diagnosed.

Conclusion

This review found one new observational study of limited benefit regarding the effectiveness of screening for type 2 diabetes on mortality. Specifically, no controlled trial evidence exists showing that screening for type 2 diabetes improves intermediate or long term health outcomes. However, the evidence indicates that the harms associated with screening for type 2 diabetes are minimal, with little effect on anxiety levels, self-rated health status and quality of life. New evidence does suggest a benefit to initiating lifestyle modification and some oral antidiabetic agents such as rosiglitazone and/or metformin for the prevention of type 2 diabetes. However, the risk of adverse effects associated with some oral antidiabetic agents need to be carefully weighed against the benefit of type 2 diabetes prevention. Modeling data indicate that screening high risk individuals is cost effective. Risk assessment tools with internal and external validity can be effective at identifying individuals who are at high risk of being diagnosed with diabetes. Screening with tests A1c, FPG or OGTT provide similar diagnostic outcomes, however A1c is easiest to administer and is cost effective.

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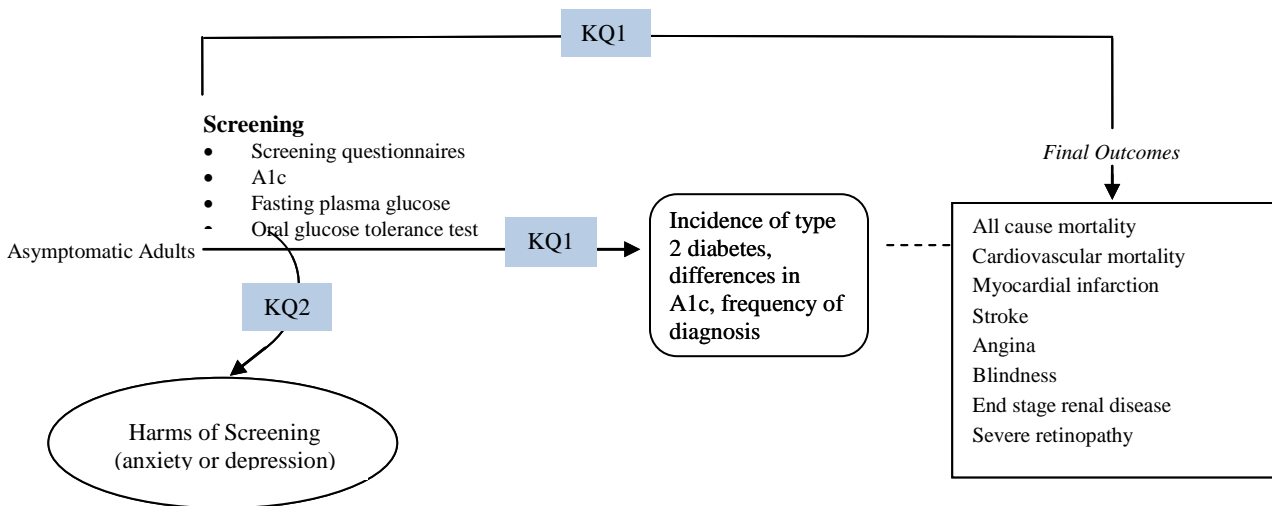
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Figure 1: Analytic Framework and Research Questions (Based on Norris et al.⁴)



Abbreviation: KQ=Key Question

Key Questions

1. What is the evidence for the clinical benefit of screening for type 2 diabetes using questionnaires, fasting plasma glucose, oral glucose tolerance test, or A1c in asymptomatic adults 18 years of age or older at high risk or at average risk for diabetes complications to improve intermediate and final health outcomes?
2. What is the evidence for the harm of screening for type 2 diabetes using questionnaires, plasma fasting plasma glucose, oral glucose tolerance test, or A1c in asymptomatic adults 18 years of age or older at high risk or average risk for diabetes complications?

Contextual Questions:

1. What is the cost effectiveness of screening asymptomatic adults 18 years or older for type 2 diabetes? Costs to the system and to patients will be included if found.
2. What are the patient values and preferences related to screening for type 2 diabetes?
3. What risk factors could guide screening for type 2 diabetes (e.g. age, hypertension, cholesterol, waist circumference, or ethnicity)?
4. What is the evidence that screening for diabetes in Aboriginal people, rural/remote, women and elderly improve health outcomes and/or mortality?
5. What are the clinical benefits and harms of early treatment (less than 12 months) of patients with type 2 diabetes compared with later treatment of patients for improvement of intermediate or final health outcomes?
6. What are the clinical benefits and harms of treatment of patients with impaired fasting glucose and impaired glucose tolerance compared with no treatment for improvement of intermediate or final health outcomes?
7. What process and outcome performance measures or indicators have been identified in the literature to measure and monitor the impact of screening for type 2 diabetes?
8. What are the most effective (accurate and reliable), risk assessment tools or questionnaires to predict type 2 diabetes?
 - 8.1 What risk assessment tools or questionnaires to predict type 2 diabetes have been validated in Canada?
9. What is the yield (accuracy, reliability, prevalence, and feasibility) of screening for type 2 diabetes with FBG, OGTT, and hemoglobin A1c in adult patients?

Figure 2: Search Results

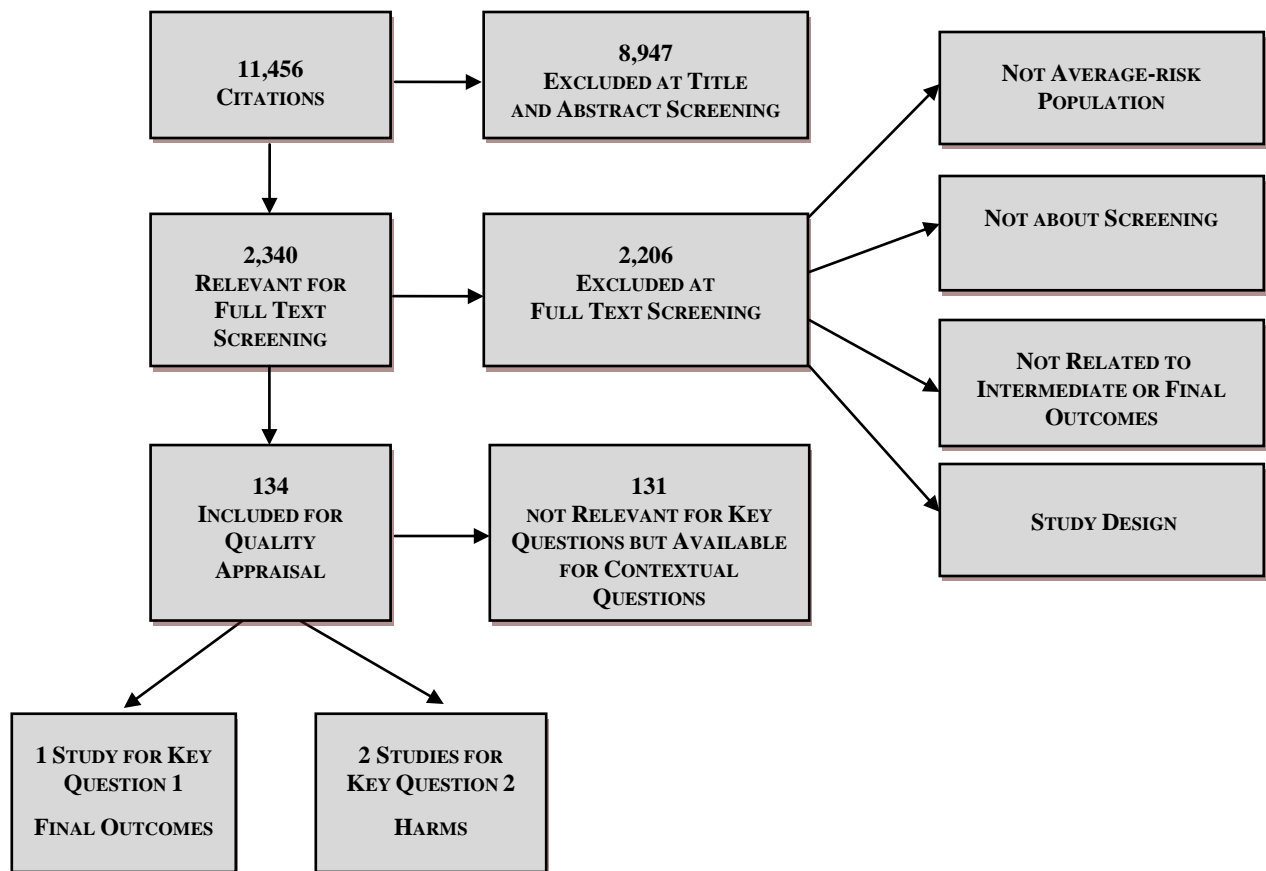


Table 1: Harms of Screening: Ranking of Importance to Decision Making

| Harm | Importance | Ranking |
|---|--------------|---------|
| Anxiety/Depression Related to Screening | Important | 6 |
| Insurability | Not Relevant | 5 |
| Embarrassment | Not Relevant | 3 |

The Diabetes Screening Working Group rated each of the outcomes and potential harms of screening using the GRADE Process.⁶⁶ GRADE suggests a nine point scale (1-9) to judge the importance of the outcomes and harms. The upper end of the scale, rankings of 7-9, identifies outcomes of critical importance for clinical decision making. Rankings of 4-6 represent outcomes that are important but not critical, while rankings of 1-3 are items that are deemed to be of limited importance to decision making or to patients.

Table 2: Characteristics of Included Study for Key Question 1: Clinical Benefits of Screening for Type 2 Diabetes

| | |
|-----------------------|--|
| First Author | Simmons, RK ⁷⁸ |
| Country | UK |
| Title of Study | Effect of population screening for type 2 diabetes on mortality: long-term follow-up of the Ely cohort |
| Objective | To assess the impact of invitation to screening for type 2 diabetes and related cardiovascular risk factors on population mortality |
| Methods | <p>Design: Parallel-group population-based cohort</p> <p>Selection: All adult patients, aged 40-65, free of known diabetes, registered with a single practice in Ely, UK (n=4,936)</p> <p>Blinding: N/A</p> |
| Participants | <p>Sample: 1990-92: 1,705 randomly invited for screening; 1,157 (68%) attended screening; 3,231 not invited for screening</p> <p>2000-03: (of those not invited in 1990-92) 1,577 randomly invited for screening; 714 (45%) attended; 1,425 never invited</p> <p>Characteristics (of invited and not invited screening groups in 1990):</p> <p>Sex: 45.1% male (invited); 50.7% male (not invited)</p> <p>Mean Age at Entry: 52.8 years (male and female invited); 50.9 years (male not invited) and 51.2 (female not invited)</p> <p>Withdrawals/Drop-outs: N/A</p> <p>Study Recruitment Years: 1990-1992</p> <p>Follow Up: up to 18 years</p> |
| Intervention | Invited for screening for type 2 diabetes or not invited; additional comparison of screening attenders versus non-attenders |
| Outcomes | <p>Population mortality was assessed by flagging all individuals in the original sampling frame, including those not invited for screening, for death certification at the Office of National Statistics. Vital status was obtained for the entire cohort and results for follow-up to January 31, 2008 are reported. There were 345 deaths between 1990 and 1999 (median 10 year follow up). Adjusting for age, sex and deprivation, individuals invited to the 1990-1992 screening had a non-significant, 21% lower, all-cause mortality (HR 0.79; 95% CI 0.63-1.00; p. 05). There were 291 deaths between 2000-2008 (median 8 year follow-up), with no significant difference in mortality between participants who were invited and not invited to the 2000-2003 screening.</p> <p>Compared with the non-invited group, those who attended screening at any point had a significantly lower mortality and those who did not attend had a significantly higher mortality.</p> |

Table 3: Characteristics of Included Studies for Key Question 2: Harms Related to Screening for Type 2 Diabetes

| | |
|-----------------------|--|
| First Author | Eborall, HC ⁷⁶ |
| Country | United Kingdom |
| Title of Study | Psychological impact of screening for type 2 diabetes: controlled trial and comparative study embedded in the ADDITION (Cambridge) randomized controlled trial |
| Objective | To quantify the psychological impact of primary care-based stepwise screening for type 2 diabetes. |
| Methods | <p>Design: Randomized controlled clinical trial</p> <p>Selection: Participants recruited from clinical settings that did not have diagnosed type 2 diabetes.</p> <p>Blinding: Unclear</p> |
| Participants | <p>Sample: Invited for Screening (n=6,416); Screened (n=4,370); Control (n=964)</p> <p>Characteristics:</p> <p>Sex: 35% female (screened) and 36% female (control)</p> <p>Mean Age: 58 years (screened) and 59 years (control)</p> <p>Withdrawals/Drop-outs: N/A</p> <p>Study Recruitment Years: N/A</p> <p>Follow Up: up to 15 months</p> |
| Intervention | Invited for screening for type 2 diabetes or not invited (controls); comparative study of subgroups of screening attendees |
| Outcomes | <p>Anxiety was measured using the Spielberger State Anxiety Inventory (STAI) (short form); anxiety and depression were measured using the Hospital Anxiety and Depression Scale (HADS); diabetes-specific worry was measured using the adapted Lerman Cancer Worry Scale (LCWS).</p> <p>No significant differences at baseline, 3-6 months and 12-15 months between the type 2 diabetes screened group (random plasma glucose screening) and the controls in any outcomes.</p> <p>Screening had a limited psychological impact on patients, with some negligible negative psychological impact with subsequent clinical investigations following a positive screen test for type 2 diabetes.</p> |

Table 3 (cont'd): Characteristics of Included Studies for Key Question 2: Harms Related to Screening for Type 2 Diabetes

| | |
|-----------------------|---|
| First Author | Park, P ⁸² |
| Country | United Kingdom |
| Title of Study | Screening for type 2 diabetes is feasible, acceptable, but associated with increased short-term anxiety: A randomized controlled trial in British general practice |
| Objective | To examine: a) the feasibility of a stepwise screening program in general practice; b) the uptake of the screening program; and c) the effects of the program on participants' anxiety, self-rated health and illness perceptions of diabetes. A pilot study for the ADDITION Cambridge study. |
| Methods | <p>Design: Randomized controlled trial, randomized 2:1.</p> <p>Selection: High risk participants were recruited from two general practices into a stepwise screening program to confirm the presence or absence of diabetes.</p> <p>Blinding: Unclear</p> |
| Participants | <p>Sample: Invited for Screening: Intervention (n=116) Not Invited for Screening: Control (n=238)</p> <p>Characteristics:</p> <p>Sex: 34% female (intervention); 37% female (control)</p> <p>Mean Age: 58 years (intervention); 59 years (control)</p> <p>Withdrawals/Drop-outs: 95 (82%) people attended the random capillary glucose test of the 116 that were invited.</p> <p>Follow Up: 6 weeks</p> |
| Intervention | <p>Intervention: a letter invitation to attend screening for type 2 diabetes at their local general practitioner.</p> <p>Control: no invitation to attend.</p> |
| Outcomes | <p>Anxiety was measured using the Spielberger State Anxiety Inventory (STAI) and illness perceptions were assessed using the 50-item diabetes Illness Perception Questionnaire (IPQ).</p> <p>The intervention group followed a stepwise screening program including: a) a random capillary glucose test; b) a fasting capillary glucose test if their random glucose test was ≥ 5.5 mmol/L; c) an oral glucose tolerance test if their fasting capillary glucose test was between 5.5-12 mmol/L. If participants had a 2-hour capillary glucose level ≥ 11.0 mmol/L, they were informed they had type 2 diabetes.</p> <p>Six weeks after participating, screen invited participants reported being more anxious than those not invited (mean STAI score: 37.6 vs. 34.1, $p=0.015$) and those diagnosed with diabetes were more anxious than those determined to not have type 2 diabetes (mean STAI score: 46.7 vs. 37.0, $p=0.031$).</p> <p>Screening for type 2 diabetes in the primary care setting is feasible but may be associated with higher levels of short-term anxiety in the screen invited participants.</p> |

Table 4: Risk of Bias Table for Study Included for Key Question 1:
Clinical Benefits of Screening for Type 2 Diabetes

Included Study: Simmons et al.⁷⁸

| Item | Judgement | Description |
|------------------------------------|-----------|---|
| Adequate sequence generation? | No | Observational (Parallel Cohort) Study. Participants were randomly selected (in two cohorts, 1997-99 and 2000-03) for invitation to screening from a single practice population. The authors do not describe how patients were randomly selected to receive a screening invitation. |
| Allocation concealment? | No | Observational (Parallel Cohort) Study. No information about allocation concealment, probably not done. |
| Blinding? | No | Observational (Parallel Cohort) Study. The authors do not discuss issues related to blinding. Blinding of participants would not be possible in this study. The authors do not discuss blinding of outcome assessors. Two researchers independently coded cause of death. If these researchers were aware of a patient's status (screening versus no screening) it is possible this information might influence their classification of cause of death. However, the mortality outcome would not be affected by a lack of blinding. |
| Incomplete outcome data addressed? | Yes | Outcome (death) reported for all patients in sampling frame including those who were invited to screening and attended, those who were invited and did not attend, and those who were not invited |
| Free of selective reporting? | Yes | All outcomes of interest were reported on in the results. |
| Free of other bias? | Yes | No other biases were observed. |

Table 5: GRADE Evidence Profile and Summary of Findings Table for Study Included for Key Question 1: Clinical Benefits of Screening for Type 2 Diabetes

Included Study: Simmons et al.⁷⁸

| Quality Assessment | | | | | | | Summary of Findings | | | | Importance | |
|---|---------------------|-------------------------------------|---------------------------------------|-------------------------|------------------------|----------------------|-------------------------------|--------------------------------|---------------------------------------|---|------------|----------|
| | | | | | | | No of patients | | Effect | | | Quality |
| No of Studies | Design | Limitations | Inconsistency | Indirectness | Imprecision | Other Considerations | Screening | Control | Relative (95% CI) | Absolute | | |
| Overall Mortality (1990-1992 Cohort) (Follow-up Median 10 Years ¹ ; Death Certificate at Office of National Statistics) | | | | | | | | | | | | |
| 1 ^a | observational study | no serious limitations ² | no serious inconsistency ³ | no serious indirectness | no serious imprecision | none ³ | 116/1,705 (6.8%) ⁴ | 229/3,231 (7.08%) ⁵ | HR 0.79 (0.63 to 1) ^{6,7} | 14,455 fewer per 1,000,000 (from 25,619 fewer to 0 more) | ⊕⊕⊕⊖ LOW | CRITICAL |
| Overall Mortality (2000-2003 Cohort) (Follow-up Median 8.1 Years ⁸ ; Death Certificate at Office of National Statistics) | | | | | | | | | | | | |
| 1 ^a | observational study | no serious limitations ² | no serious inconsistency ³ | no serious indirectness | no serious imprecision | none ³ | 165/1,577 (10.46%) | 126/1,425 (8.84%) | HR 1.18 (0.93 to 1.51) ^{6,9} | 15,065 more per 1,000,000 (from 5,927 fewer to 42,039 more) | ⊕⊕⊕⊖ LOW | CRITICAL |

¹ 1991 to 1999 (47,854 person-years of risk)

² The authors report potential selection bias: "despite random selection of participants into invitation groups, participants who were offered screening were older at baseline, lived in more deprived areas and included a smaller proportion of men." However, we did not downgrade this criterion since in the analysis the researchers adjusted for age, sex and deprivation.

³ Single study

⁴ 52 (45%) of deaths were recorded as cancer-related, 41 (35%) were due to cardiovascular causes and 23 (20%) were coded as 'other'

⁵ 107 (47%) were cancer deaths, 74 (32%) were cardiovascular deaths and 48 (21%) were coded as 'other'

⁶ p=0.05; adjusted for age, sex and deprivation

⁷ For 22 individuals (6%) among the total deceased (1991-1999), diabetes was included as the underlying cause on the death certificate

⁸ 2000 to 2008 (23,144 person-years of risk)

⁹ For 22 individuals (8%) among the total deceased (2000-2008) diabetes as included as the underlying cause on the death certificate

Included Study: Simmons et al.⁷⁸

| Summary of Findings Table for KQ1: Clinical Benefits of Screening for Type 2 Diabetes | | | | | |
|---|--|--|---|------------------------------|-----------------------------------|
| Outcomes | Illustrative Comparative Risks* (95% CI) | | Relative Effect (95% CI) | No of Participants (Studies) | Quality of the Evidence (GRADE) |
| | Assumed Risk | Corresponding Risk | | | |
| | Control | Screening | | | |
| Overall Mortality (1990-1992 Cohort) Death Certificate at Office of National Statistics Follow-up: median 10 years ¹ | 70,876 per 1,000,000² | 56,521 per 1,000,000 (45,337 to 71,000) ³ | HR 0.79 (0.63 to 1) ^{4,5} | 4,936 (1 study) | ⊕⊕⊖⊖ low ^{6,7} |
| Overall Mortality (2000-2003 Cohort) Death Certificate at Office of National Statistics Follow-up: median 8.1 years ⁸ | 88,421 per 1,000,000 | 102,997 per 1,000,000 (82,100 to 129,854) | HR 1.18 (0.93 to 1.51) ^{4,9} | 3,002 (1 study) | ⊕⊕⊖⊖ low ⁷ |
| *The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: Confidence interval; HR: Hazard ratio; | | | | | |
| GRADE Working Group grades of evidence | | | | | |
| High quality: Further research is very unlikely to change our confidence in the estimate of effect. | | | | | |
| Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. | | | | | |
| Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. | | | | | |
| Very low quality: We are very uncertain about the estimate. | | | | | |
| ¹ 1991 to 1999 (47,854 person-years of risk) | | | | | |
| ² 107 (47%) were cancer deaths, 74 (32%) were cardiovascular deaths and 48 (21%) were coded as 'other' | | | | | |
| ³ 52 (45%) of deaths were recorded as cancer-related, 41 (35%) were due to cardiovascular causes and 23 (20%) were coded as 'other' | | | | | |
| ⁴ p=0.05; adjusted for age, sex and deprivation | | | | | |
| ⁵ For 22 individuals (6%) among the total deceased (1991-1999), diabetes was included as the underlying cause on the death certificate | | | | | |
| ⁶ The authors report potential selection bias: "despite random selection of participants into invitation groups, participants who were offered screening were older at baseline, lived in more deprived areas and included a smaller proportion of men." However, we did not downgrade this criterion since in the analysis the researchers adjusted for age, sex and deprivation. | | | | | |
| ⁷ Single study | | | | | |
| ⁸ 2000 to 2008 (23,144 person-years of risk) | | | | | |
| ⁹ For 22 individuals (8%) among the total deceased (2000-2008) diabetes as included as the underlying cause on the death certificate | | | | | |

Table 6: Risk of Bias Tables for Studies Included for Key Question 2: Harms of Screening for Type 2 Diabetes
Eborall et al. 2007⁷⁶

| Item | Judgement | Description |
|------------------------------------|-----------|--|
| Adequate sequence generation? | No | In the ADDITION (Cambridge) trial practices were randomly allocated to screening or control arms. In this sub-study on the psychological impact of screening it was not possible to randomly select practices for screening because it started later than the main trial and many practices had already finished screening. Furthermore, three of the 10 screening sites included in this sub-study had already started the screening process. Therefore, randomization was not deemed adequate for the sub-study. |
| Allocation concealment? | No | The authors do not discuss concealment of allocation. There was no randomized selection of practices for this study within the screening sites in the main ADDITION trial. |
| Blinding? | Unclear | The authors do not discuss issues related to blinding. Blinding of practices and participants would not possible in this study. The authors do not discuss blinding of outcome assessors. |
| Incomplete outcome data addressed? | No | There was loss to follow up among the invited to screening non-attenders. An analysis was done to assess the impact if these non-responders had similar outcome measures at baseline. Non-response rates were similar across the three main groups from the initial test to 3-6 months (roughly 7%). |
| Free of selective reporting? | Yes | All outcomes of interest were reported on in the results. |
| Free of other bias? | Yes | No other biases were observed. |

Park et al. 2008⁸²

| Item | Judgement | Description |
|------------------------------------|------------------|--|
| Adequate sequence generation? | Yes | The investigators indicate they used SPSS (v.9.0.1) to individually randomize participants into invited and non-invited groups. |
| Allocation concealment? | Unclear | The authors do not discuss concealment of allocation. |
| Blinding? | Unclear | The authors do not discuss issues related to blinding. |
| Incomplete outcome data addressed? | Yes | An available case analysis was performed. All data for participants who completed the questionnaires (intervention n=77, control n=168) were included in the analysis. |
| Free of selective reporting? | Yes | All outcomes of interest were reported on in the results. |
| Free of other bias? | Yes | No other biases were observed. |

Table 7: GRADE Evidence Profile for Key Question 2: Harms Related to Screening for Type 2 Diabetes

| Outcomes | No. of Studies No. of Patients | Mean Score (SD) | | Absolute Effect (95% CI), P value ¹ | Quality Rating |
|---|-----------------------------------|---|------------------------|---|---|
| ANXIETY | | | | | |
| Spielberger State Anxiety Inventory (STAI) Park et al. 2008 ⁸² | 1 RCT 355 patients | 6 Weeks After Last Contact ² | | The mean STAI score in the intervention group was 3.5 higher (0.22-6.78), 0.04 | ⊕⊕⊕⊖ MODERATE due to design limitations ^{3,4,5} |
| | | 34.1 (12.1) n=168 | 37.6 (12.2) n=77 | | |
| Spielberger State Anxiety Inventory (STAI) Eborall et al. 2007 ⁷⁶ | 1 RCT 7,380 patients | Initial Time Point ⁶ | | The mean STAI score in the intervention group was 0.53 lower (-2.60-1.54), 0.62 | ⊕⊕⊕⊖ LOW due to design limitations ^{3,4,5,7,8} |
| | | 32.7 (11.5) n=199 | 32.7 (11.6) n=2,468 | | |
| | | 3-6 Months After Initial Time Point | | The mean STAI score in the intervention group was 1.51 higher (-0.17-3.20), 0.10 | |
| | | 31.8 (11.4) n=358 | 33.5 (12.0) n=2,504 | | |
| | | 12-15 Months After Initial Time Point | | The mean STAI score in the intervention group was 0.57 higher (-1.11-2.24), 0.52 | |
| | | 32.8 (11.8) n=304 | 35.5 (12.2) n=2,377 | | |
| Hospital Anxiety and Depression Scale (HADS): Anxiety Subscale Eborall et al. 2007 ⁷⁶ | 1 RCT 7,380 patients | Initial Time Point ⁶ | | The mean HADS Anxiety score in the intervention group was 0.46 lower (-0.99-0.07), 0.12 | ⊕⊕⊕⊖ LOW due to design limitations ^{3,4,5,7,8} |
| | | 6.42 (4.39) n=255 | 6.04 (3.79) n=3,140 | | |
| | | 3-6 Months After Initial Time Point | | The mean HADS Anxiety score in the intervention group was 0.12 lower (-0.55-0.32), 0.61 | |
| | | 5.97 (3.86) n=442 | 5.91 (3.89) n=3,159 | | |
| | | 12-15 Months After Initial Time Point | | The mean HADS Anxiety score in the intervention group was 0.01 lower (-0.47-0.45), 0.98 | |
| | | 5.81 (3.87) n=377 | 5.85 (3.87) n=3,034 | | |

| DEPRESSION | | | | | |
|--|-------------------------|---------------------------------------|------------------------|---|--|
| Hospital Anxiety and Depression Scale (HADS): Depression Subscale Eborall et al. 2007 ⁷⁶ | 1 RCT 7,380 patients | Initial Time Point ⁶ | | The mean HADS Depression score in the intervention group was 0.37 lower (-0.93-0.18), 0.21 | ⊕⊕⊕⊖ LOW due to design limitations ^{3,4,5,7,8} |
| | | 4.52 (3.48) n=256 | 4.24 (3.31) n=3,161 | | |
| | | 3-6 Months After Initial Time Point | | The mean HADS Depression score in the intervention group was 0.01 higher (-0.51-0.54), 0.96 | |
| | | 4.18 (3.38) n=444 | 4.24 (3.40) n=3,177 | | |
| | | 12-15 Months After Initial Time Point | | The mean HADS Depression score in the intervention group was 0.22 higher (-0.31-0.74), 0.44 | |
| | | 4.03 (3.35) n=378 | 4.28 (3.40) n=3,049 | | |

1. Eborall *et al* used adjusted mean differences for age and comorbidity (use of antihypertensives) to compute absolute effect
2. Questionnaires were sent 6 weeks after last contact, either test or invitation
3. Unclear allocation concealment
4. No information regarding blinding
5. Quality rating is for a single study, thus imprecision and publication bias criteria were rated as “no” and “unlikely”
6. Questionnaires given to participants after initial test or non-attendance (screening group) and to a sub-group of controls; data for screening attenders included in analysis only if questionnaire completed/returned before results of test received
7. A non-randomized sample of screening practices was used
8. Large loss to follow up (for the 3-6 and 12-15 month follow-up period)

Appendices

Appendix 1: Diagnostic Criteria for Impaired Fasting Glucose,
Impaired Glucose Tolerance and Type 2 Diabetes

Appendix 2: Definitions of Metabolic Syndrome

Appendix 3: Risk Factors Associated with Type 2 Diabetes

Appendix 4: Diabetes Screening Literature Search Strategies

Appendix 5: Grey Literature Search

Appendix 6: Search Strategy Modeling

Appendix 7: Search Strategy Diagnostic Risk Assessment

Appendix 8: List External Reviewers – Original Protocol

Appendix 9: List of External Reviewers – Revised Protocol

Appendix 10: List of External Reviewers – Evidence Synthesis

Appendix 11: AMSTAR Criteria Applied Reviews

Appendix 12: Components of Risk Assessment Tools

Appendix 13: WHO Evidence Sets

Appendix 14: Characteristics of A1c Tests

Appendix 1: Diagnostic Criteria for Impaired Fasting Glucose, Impaired Glucose Tolerance and Type 2 Diabetes

| | | 1992 | 1998 | 2003 | 2008 |
|--------------------|--------------|-------------|-------------|-------------|-------------|
| Prediabetes | IFG | n/a | 6.1-6.9 | 6.1-6.9 | 6.1-6.9 |
| | IGT (2 hour) | n/a | 7.8-11.0 | 7.8-11.0 | 7.8-11.0 |
| Diabetes | Fasting | >7.8 | ≥7.0 | ≥7.0 | ≥7.0 |
| | 2 hour | >11.1 | ≥11.1 | ≥11.1 | ≥11.1 |
| | A1C | n/a | n/a | n/a | ≥6.5% |

IFG: impaired fasting glucose; IGT: impaired glucose tolerance, A1C glycated hemoglobin. All laboratory values expressed as mmol/L. A result indicative of diabetes should be repeated to rule out laboratory error, unless the diagnostic criteria are supported by clinical symptoms. Adapted from the Canadian Diabetes Association's recommendations and guidelines for the management of diabetes.^{7,43,52,62}

Appendix 2: Definitions of Metabolic Syndrome

| | WHO | NCEP ATP III | IDF | Harmonized Metabolic Syndrome (IDF, NHLBI, AHA, WHF, IAS & IASO) |
|---|--|---|--|---|
| Diagnostic Criteria | Diabetes, IFG, IGT or insulin resistance PLUS ≥ 2 other risk determinants are present. | ≥ 3 risk determinants are present. | Central obesity (using ethnic-specific values) PLUS ≥ 2 other risk determinants are present. | Presence of 3 of the 5 risk factors |
| Plasma Glucose | Diabetes, IFG, IGT or insulin resistance | FPG ≥ 5.6 mmol/L | FPG ≥ 5.6 mmol/L (or previously diagnosed type 2 diabetes) | FPG > 5.6 mmol/L |
| Blood Pressure | $\geq 140/90$ mm/Hg | $\geq 130/85$ mm/Hg | $\geq 130/85$ mm/Hg (or previously diagnosed hypertension) | <u>$>130/85$ mm/Hg</u> |
| Triglycerides | ≥ 1.7 mmol/L | ≥ 1.7 mmol/L | ≥ 1.7 mmol/L (or receiving treatment) | <u>>1.7 mmol/L</u> |
| High Density Lipoprotein (HDL) Cholesterol | <0.9 mmol/L (men) <1.0 mmol/L (women) | <1.0 mmol/L (men) <1.3 mmol/L (women) | <1.0 mmol/L (men) <1.3 mmol/L (women) (or receiving treatment) | < 1.0 mmol/L (men) < 1.3 mmol/L (women) |
| Abdominal Obesity | Waist to Hip Ratio: >0.90 (men) >0.85 (women) | Waist Circumference: >102 cm (men) >88 cm (women) | South Asian, Malaysian, Asian, Indian, Chinese, Japanese, Ethnic South and Central American populations: Waist Circumference: ≥ 90 cm (men) ≥ 80 cm (women) All other populations: Waist Circumference: ≥ 94 cm (men) ≥ 80 cm (women) | <u>≥ 94 cm – males</u> <u>>80 cm – females</u> |

| | | | | |
|------------------------|---|-----|-----|-----|
| Kidney Function | Urinary albumin excretion rate: > 20 micrograms/min OR ACR \geq 30 mg/g | N/A | N/A | N/A |
|------------------------|---|-----|-----|-----|

WHO – World Health Organization; NCEP ATP III – National Cholesterol Education Program Adult Treatment Panel III; IDF – International Diabetes Federation; NHLBI – National Heart, Lung and Blood Institute; AHA – American Heart Association; World Heart Federation; IAS – International Atherosclerosis Society; IASO – International Association for the Study of Obesity; IFG – impaired fasting glucose; IGT – impaired glucose tolerance; N/A – not applicable.

Adapted from Ur⁷ and Albertie et al.⁴⁴

Appendix 3: Risk Factors Associated with Type 2 Diabetes

- Age ≥ 40 years
- First-degree relative with type 2 diabetes
- Member of high-risk population (e.g., people of Aboriginal, Hispanic, South Asian, Asian or African descent)
- History of impaired glucose tolerance or impaired fasting glucose*
- Presence of complications associated with diabetes
- Vascular disease (coronary, cerebrovascular or peripheral)*
- History of gestational diabetes mellitus
- History of delivery of a macrosomic infant
- Hypertension*
- Dyslipidemia*
- Overweight*
- Abdominal obesity*
- Polycystic ovary syndrome*
- Acanthosis nigricans*
- Schizophrenia
- Metabolic syndrome (see Appendix 2)

*Associated with insulin resistance

Adapted from Ur et al.⁴³

Appendix 4: Diabetes Screening Literature Search Strategies

Adverse Effects - Overall

Database: EBM Reviews - Cochrane Central Register of Controlled Trials

Search Strategy:

- 1 ((fasting glucose or glucose tolerance) adj3 impair\$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
- 2 (prediabet\$ or pre-diabet\$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
- 3 ((type 2 or type II or non-insulin dependent) adj3 diabet\$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
- 4 1 or 2 or 3
- 5 (screen\$ or diagnos\$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
- 6 4 and 5
- 7 (adverse effect\$ or harm or harmed or harming or harms or iatrogen\$ or nosocom\$ or drug interaction\$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
- 8 ((Diagnos\$ adj5 (Error\$ or mistak\$)) or (false\$ adj3 (positiv\$ or negativ\$)) or (observer\$ adj variation\$)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
- 9 (prejudic\$ or bias\$ or stigma\$ or discriminat\$ or unfair\$ or illegal\$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
- 10 ((Stress\$ or tension\$) adj5 (Psychologic\$ or emotion\$ or mental\$ or family or families or interpersonal\$)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
- 11 (((Life or living) adj3 (Chang\$ or style\$)) or lifestyle\$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
- 12 7 or 8 or 9 or 10 or 11
- 13 4 and 12

Database: EBM Reviews - Cochrane Database of Systematic Reviews

Search Strategy:

- 1 ((fasting glucose or glucose tolerance) adj3 impair\$).mp. [mp=title, abstract, full text, keywords, caption text]
- 2 (prediabet\$ or pre-diabet\$).mp. [mp=title, abstract, full text, keywords, caption text]
- 3 ((type 2 or type II or non-insulin dependent) adj3 diabet\$).mp. [mp=title, abstract, full text, keywords, caption text]
- 4 1 or 2 or 3
- 5 (screen\$ or diagnos\$).mp. [mp=title, abstract, full text, keywords, caption text]
- 6 4 and 5

- 7 (adverse effect\$ or harm or harmed or harming or harms or iatrogen\$ or nosocom\$ or drug interaction\$).mp. [mp=title, abstract, full text, keywords, caption text]
- 8 ((Diagnos\$ adj5 (Error\$ or mistak\$)) or (false\$ adj3 (positiv\$ or negativ\$)) or (observer\$ adj variation\$)).mp. [mp=title, abstract, full text, keywords, caption text]
- 9 (prejudic\$ or bias\$ or stigma\$ or discriminat\$ or unfair\$ or illegal\$).mp. [mp=title, abstract, full text, keywords, caption text]
- 10 ((Stress\$ or tension\$) adj5 (Psychologic\$ or emotion\$ or mental\$ or family or families or interpersonal\$)).mp. [mp=title, abstract, full text, keywords, caption text]
- 11 (((Life or living) adj3 (Chang\$ or style\$)) or lifestyle\$).mp. [mp=title, abstract, full text, keywords, caption text]
- 12 7 or 8 or 9 or 10 or 11
- 13 4 and 12

Database: EBM Reviews - Database of Abstracts of Reviews of Effects

Search Strategy:

- 1 ((fasting glucose or glucose tolerance) adj3 impair\$).mp. [mp=title, full text, keywords]
- 2 (prediabet\$ or pre-diabet\$).mp. [mp=title, full text, keywords]
- 3 ((type 2 or type II or non-insulin dependent) adj3 diabet\$).mp. [mp=title, full text, keywords]
- 4 1 or 2 or 3
- 5 (screen\$ or diagnos\$).mp. [mp=title, full text, keywords]
- 6 4 and 5
- 7 (adverse effect\$ or harm or harmed or harming or harms or iatrogen\$ or nosocom\$ or drug interaction\$).mp. [mp=title, full text, keywords]
- 8 ((Diagnos\$ adj5 (Error\$ or mistak\$)) or (false\$ adj3 (positiv\$ or negativ\$)) or (observer\$ adj variation\$)).mp. [mp=title, full text, keywords]
- 9 (prejudic\$ or bias\$ or stigma\$ or discriminat\$ or unfair\$ or illegal\$).mp. [mp=title, full text, keywords]
- 10 ((Stress\$ or tension\$) adj5 (Psychologic\$ or emotion\$ or mental\$ or family or families or interpersonal\$)).mp. [mp=title, full text, keywords]
- 11 (((Life or living) adj3 (Chang\$ or style\$)) or lifestyle\$).mp. [mp=title, full text, keywords]
- 12 7 or 8 or 9 or 10 or 11
- 13 4 and 12

Database: Ovid MEDLINE(R)

Search Strategy:

- 1 exp Diabetes Mellitus, Type 2/

- 2 ((fasting glucose or glucose tolerance) adj3 impair\$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
- 3 (prediabet\$ or pre-diabet\$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
- 4 ((type 2 or type II or non-insulin dependent) adj3 diabet\$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
- 5 1 or 2 or 3 or 4
- 6 (screen\$ or diagnos\$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
- 7 5 and 6
- 8 (200109\$ or 20011\$ or 2002\$ or 2003\$ or 2004\$ or 2005\$ or 2006\$ or 2007\$).ed.
- 9 7 and 8
- 10 limit 9 to (humans and english language
- 11 (adverse effect\$ or harm or iatrogen\$ or nosocom\$ or drug interaction\$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
- 12 exp Diagnostic Errors/
- 13 (prejudic\$ or stigma\$ or discriminat\$ or unfair\$ or illegal\$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
- 14 exp Stress, Psychological/
- 15 exp Life Change Events/
- 16 11 or 12 or 13 or 14 or 15
- 17 5 and 16
- 18 8 and 17
- 19 limit 18 to english language
- 20 limit 19 to humans

Adverse Effects of Treatment – Systematic Reviews

Database: Ovid MEDLINE(R)

Search Strategy:

- 1 exp Hypoglycemic Agents/ae, po, ct, to [Adverse Effects, Poisoning, Contraindications, Toxicity]
- 2 exp Sulfonyleurea Compounds/ae, po, ct, to [Adverse Effects, Poisoning, Contraindications, Toxicity]
- 3 exp Angiotensin-Converting Enzyme Inhibitors/ae, po, ct, to [Adverse Effects, Poisoning, Contraindications, Toxicity]
- 4 exp Receptors, Angiotensin/ai [Antagonists & Inhibitors]
- 5 (ae or po or to or ct).fs.
- 6 (adverse effect\$ or poison\$ or toxic\$ or contraindicat\$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
- 7 5 or 6

8 4 and 7
 9 exp Angiotensin II Type 1 Receptor Blockers/ae, po, ct, to
 10 8 or 9
 11 exp Calcium Channel Blockers/ae, po, ct, to [Adverse Effects, Poisoning,
 Contraindications, Toxicity]
 12 exp Thiazides/ae, ct [Adverse Effects, Contraindications]
 13 exp Hydroxymethylglutaryl-CoA Reductase Inhibitors/ae, po, ct, to [Adverse
 Effects, Poisoning, Contraindications,
 Toxicity]
 14 orlistat.mp.
 15 7 and 14
 16 exp Insulin/ae, po, ct, to [Adverse Effects, Poisoning, Contraindications, Toxicity]
 17 exp Aspirin/ae, po, ct, to [Adverse Effects, Poisoning, Contraindications, Toxicity]
 18 1 or 2 or 3 or 10 or 11 or 12 or 13 or 15 or 16 or 17
 19 (systematic\$ adj review\$).mp. [mp=title, original title, abstract, name of substance
 word, subject heading word]
 20 (data adj synthesis).tw.
 21 (published adj studies).ab.
 22 (data adj extraction).ab.
 23 meta-analysis/
 24 (meta-analy\$ or metaanaly\$).mp. [mp=title, original title, abstract, name of
 substance word, subject heading word]
 25 19 or 20 or 21 or 22 or 23 or 24
 26 comment.pt.
 27 letter.pt.
 28 editorial.pt.
 29 Animals/
 30 Humans/
 31 29 not (29 and 30)
 32 18 not 31
 33 32 and (19 or 20 or 21 or 22 or 23 or 24)
 34 limit 33 to yr="2001 - 2007"

Hemoglobin A1c

Database: EBM Reviews - Cochrane Central Register of Controlled Trials

Search Strategy:

1 ((Diabet\$ adj3 (type II or type 2 or non-insulin depend\$)) or NIDDM or MODY).mp.
 [mp=title, original title, abstract,
 mesh headings, heading words, keyword]
 2 (impair\$ adj3 (fasting glucose or glucose tolerance)).mp. [mp=title, original title,
 abstract, mesh headings, heading
 words, keyword]
 3 (prediabet\$ or pre-diabet\$).mp. [mp=title, original title, abstract, mesh headings,
 heading words, keyword]

4 1 or 2 or 3
 5 exp Hemoglobin A, Glycosylated/
 6 (hba 1c or a 1c or a1c).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
 7 ((glycat\$ or glycosyl\$) adj7 (hemoglobin\$ or hgb or red blood cell\$ or rbc\$)).mp.
 [mp=title, original title, abstract, mesh headings, heading words, keyword]
 8 5 or 6 or 7
 9 4 and 8
 10 ((Diagnos\$ adj5 (Error\$ or mistake\$)) or (false\$ adj3 (positiv\$ or negativ\$)) or (observer\$ adj3 variation\$)).mp.
 [mp=title, original title, abstract, mesh headings, heading words, keyword]
 11 (sensitivity adj2 specificity).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
 12 (Reproduc\$ adj5 (Result\$ or outcome\$ or reading\$ or value\$)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
 13 (accura\$ or reliab\$ or prevalen\$ or yield\$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
 14 10 or 11 or 12 or 13
 15 exp Mass Screening/
 16 (screen\$ or diagnos\$ or test\$ or detect\$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
 17 15 or 16
 18 9 and 17

Database: EBM Reviews - Cochrane Database of Systematic Reviews

Search Strategy:

1 ((Diabet\$ adj3 (type II or type 2 or non-insulin depend\$)) or NIDDM or MODY).mp.
 [mp=title, abstract, full text, keywords, caption text]
 2 (impair\$ adj3 (fasting glucose or glucose tolerance)).mp. [mp=title, abstract, full text, keywords, caption text]
 3 (prediabet\$ or pre-diabet\$).mp. [mp=title, abstract, full text, keywords, caption text]
 4 1 or 2 or 3
 5 [exp Hemoglobin A, Glycosylated/
 6 (hba 1c or a 1c or a1c).mp. [mp=title, abstract, full text, keywords, caption text]
 7 ((glycat\$ or glycosyl\$) adj7 (hemoglobin\$ or hgb or red blood cell\$ or rbc\$)).mp.
 [mp=title, abstract, full text, keywords, caption text]
 8 5 or 6 or 7
 9 4 and 8
 10 ((Diagnos\$ adj5 (Error\$ or mistake\$)) or (false\$ adj3 (positiv\$ or negativ\$)) or (observer\$ adj3 variation\$)).mp.
 [mp=title, abstract, full text, keywords, caption text]

- 11 (sensitivity adj2 specificity).mp. [mp=title, abstract, full text, keywords, caption text]
- 12 (Reproduc\$ adj5 (Result\$ or outcome\$ or reading\$ or value\$)).mp. [mp=title, abstract, full text, keywords, caption text]
- 13 (accura\$ or reliab\$ or prevalen\$ or yield\$).mp. [mp=title, abstract, full text, keywords, caption text]
- 14 10 or 11 or 12 or 13
- 15 [exp Mass Screening/]
- 16 (screen\$ or diagnos\$ or test\$ or detect\$).mp. [mp=title, abstract, full text, keywords, caption text]
- 17 15 or 16
- 18 9 and 17

Database: Ovid MEDLINE(R)

Search Strategy:

- 1 exp Diabetes Mellitus, type II/
- 2 (impair\$ adj3 (fasting glucose or glucose tolerance)).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
- 3 (prediabet\$ or pre-diabet\$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
- 4 1 or 2 or 3
- 5 exp Hemoglobin A, Glycosylated/
- 6 a1c.mp.
- 7 (glycosyl\$ adj7 (hemoglobin\$ or hgb or red blood cell\$ or rbc\$)).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
- 8 5 or 6 or 7
- 9 4 and 8
- 10 (systematic adj review\$).tw.
- 11 (data adj synthesis).tw.
- 12 (published adj studies).ab.
- 13 (data adj extraction).ab.
- 14 meta-analysis/
- 15 comment.pt.
- 16 letter.pt.
- 17 editorial.pt.
- 18 animal/
- 19 human/
- 20 18 not (18 and 19)
- 21 9 not (15 or 16 or 17 or 20)
- 22 21 and (10 or 11 or 12 or 13 or 14)
- 23 (200109\$ or 2002\$ or 2003\$ or 2004\$ or 2005\$ or 2006\$ or 2007\$).ed.
- 24 22 and 23

Screening

Database: EBM Reviews - Cochrane Central Register of Controlled Trials

Search Strategy:

- 1 ((fasting glucose or glucose tolerance) adj3 impair\$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
- 2 (prediabet\$ or pre-diabet\$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
- 3 ((type 2 or type II or non-insulin dependent) adj3 diabet\$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
- 4 1 or 2 or 3
- 5 (screen\$ or diagnos\$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
- 6 4 and 5

Database: EBM Reviews - Cochrane Database of Systematic Reviews

Search Strategy:

- 1 ((fasting glucose or glucose tolerance) adj3 impair\$).mp. [mp=title, abstract, full text, keywords, caption text]
- 2 (prediabet\$ or pre-diabet\$).mp. [mp=title, abstract, full text, keywords, caption text]
- 3 ((type 2 or type II or non-insulin dependent) adj3 diabet\$).mp. [mp=title, abstract, full text, keywords, caption text]
- 4 1 or 2 or 3
- 5 (screen\$ or diagnos\$).mp. [mp=title, abstract, full text, keywords, caption text]
- 6 4 and 5

Database: EBM Reviews - Database of Abstracts of Reviews of Effects

Search Strategy:

- 1 ((fasting glucose or glucose tolerance) adj3 impair\$).mp. [mp=title, full text, keywords]
- 2 (prediabet\$ or pre-diabet\$).mp. [mp=title, full text, keywords] (0)
- 3 ((type 2 or type II or non-insulin dependent) adj3 diabet\$).mp. [mp=title, full text, keywords]
- 4 1 or 2 or 3
- 5 (screen\$ or diagnos\$).mp. [mp=title, full text, keywords]
- 6 4 and 5

Database: Ovid MEDLINE(R)

Search Strategy:

- 1 exp Diabetes Mellitus, Type 2/
- 2 ((fasting glucose or glucose tolerance) adj3 impair\$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]

- 3 (prediabet\$ or pre-diabet\$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
- 4 ((type 2 or type II or non-insulin dependent) adj3 diabet\$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
- 5 1 or 2 or 3 or 4
- 6 (screen\$ or diagnos\$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
- 7 5 and 6
- 8 (200109\$ or 20011\$ or 2002\$ or 2003\$ or 2004\$ or 2005\$ or 2006\$).ed.
- 9 7 and 8
- 10 limit 9 to (humans and english language)
- 11 limit 10 to yr="2004 - 2007"
- 12 (200109\$ or 20011\$ or 2002\$ or 2003\$).ed.
- 13 9 and 12

Database: Ovid MEDLINE(R)

Search Strategy:

- 1 exp Diabetes Mellitus, Type 2/
- 2 ((fasting glucose or glucose tolerance) adj3 impair\$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
- 3 (prediabet\$ or pre-diabet\$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
- 4 ((type 2 or type II or non-insulin dependent) adj3 diabet\$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
- 5 1 or 2 or 3 or 4
- 6 (screen\$ or diagnos\$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
- 7 5 and 6
- 8 (200109\$ or 20011\$ or 2002\$ or 2003\$ or 2004\$ or 2005\$ or 2006\$).ed.
- 9 7 and 8
- 10 limit 9 to (humans and english language)
- 11 limit 10 to yr="2004 - 2007"

Treatment

Database: EBM Reviews - Cochrane Central Register of Controlled Trials

Search Strategy:

- 1 ((Diabet\$ adj3 (type II or type 2 or non-insulin depend\$)) or MODY or NIDDM).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
- 2 (impair\$ adj3 (fasting glucose or glucose tolerance)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]

3 (prediabet\$ or pre-diabet\$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
4 1 or 2 or 3
5 Hypoglycemic Agent\$.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
6 Glipizide.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
7 Glyburide.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
8 Glimepiride.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
9 Metformin.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
10 Rosiglitazone.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
11 Pioglitazone.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
12 Repaglinide.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
13 Nateglinide.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
14 Acarbose.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
15 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14
16 5 or 15
17 4 and 16
18 (Angiotensin Converting Enzyme Inhibitor\$ or ace inhibitor\$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
19 (Angiotensin adj3 (block\$ or antagon\$ or receptor\$)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
20 (Calcium Channel\$ adj3 (antagon\$ or Block\$)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
21 (antihypertensi\$ or anti-hypertensi\$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
22 18 or 19 or 20 or 21
23 4 and 22
24 Hydroxymethylglutaryl CoA Reductase\$.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
25 Lovastatin.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
26 Pravastatin.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]

27 Fluvastatin.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]

28 Atorvastatin.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]

29 Rosuvastatin.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]

30 25 or 26 or 27 or 28 or 29

31 24 or 30

32 4 and 31

33 Antilipemic\$.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]

34 Gemfibrozil.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]

35 Fenofibrate.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]

36 Nicotinic Acid.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]

37 Cholestyramine.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword])

38 Colestipol.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]

39 Colesevelam.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]

40 Ezetimibe.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]

41 34 or 35 or 36 or 37 or 38 or 39 or 40

42 33 or 41

43 4 and 42

44 Aspirin.mp.

45 4 and 44

46 (Life Style\$ or lifestyle\$ or ((living or live or lived) adj5 style\$)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]

47 4 and 46

48 Exercis\$.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]

49 (tai chi or tai ji or relaxation or walk\$ or yoga or jog or jogging).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]

50 (Physical\$ adj3 (Fitness or fit)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]

51 48 or 49 or 50

52 4 and 51

53 ((Gastric or stomach) adj3 Bypass\$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]

54 gastroplast\$.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
 55 ((obese or obesity) adj3 (surger\$ or surgic\$)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
 56 53 or 54 or 55
 57 4 and 56
 58 anti-obesity agent\$.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
 59 ((obese or obesity) adj3 (drug\$ or pharmaco\$)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
 60 orlistat.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
 61 sibutramine.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
 62 fluoxetine.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
 63 58 or 59 or 60 or 61 or 62
 64 4 and 63
 65 Counsel\$.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
 66 4 and 65
 67 (Patient\$ adj3 (Educate\$ or inform\$)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
 68 4 and 67
 69 footcare.mp.
 70 ((foot or feet or toe or toes or heel or plantar) adj5 (care or cares or caring or cared)).mp.
 71 ((foot or feet or toe or toes or heel or plantar) adj5 (disease\$ or ulcer\$ or sore\$)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
 72 69 or 70 or 71
 73 4 and 72
 74 17 or 23 or 32 or 43 or 45 or 47 or 52 or 57 or 64 or 66 or 68 or 73
 75 limit 74 to yr="2001 - 2007"

Database: EBM Reviews - Cochrane Central Register of Controlled Trials

Search Strategy:

1 ((Diabet\$ adj3 (type II or type 2 or non-insulin depend\$)) or MODY or NIDDM).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
 2 (impair\$ adj3 (fasting glucose or glucose tolerance)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]

3 (prediabet\$ or pre-diabet\$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
4 1 or 2 or 3
5 Hypoglycemic Agent\$.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
6 Glipizide.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
7 Glyburide.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
8 Glimepiride.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
9 Metformin.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
10 Rosiglitazone.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
11 Pioglitazone.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
12 Repaglinide.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
13 Nateglinide.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
14 Acarbose.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
15 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14
16 5 or 15
17 4 and 16
18 (Angiotensin Converting Enzyme Inhibitor\$ or ace inhibitor\$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
19 (Angiotensin adj3 (block\$ or antagon\$ or receptor\$)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
20 (Calcium Channel\$ adj3 (antagon\$ or Block\$)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
21 (antihypertensi\$ or anti-hypertensi\$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
22 18 or 19 or 20 or 21
23 4 and 22
24 Hydroxymethylglutaryl CoA Reductase\$.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
25 Lovastatin.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
26 Pravastatin.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]

27 Fluvastatin.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]

28 Atorvastatin.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]

29 Rosuvastatin.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]

30 25 or 26 or 27 or 28 or 29

31 24 or 30

32 4 and 31

33 Antilipemic\$.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]

34 Gemfibrozil.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]

35 Fenofibrate.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]

36 Nicotinic Acid.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]

37 Cholestyramine.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]

38 Colestipol.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]

39 Colesevelam.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]

40 Ezetimibe.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]

41 34 or 35 or 36 or 37 or 38 or 39 or 40

42 33 or 41

43 4 and 42

44 Aspirin.mp.

45 4 and 44

46 (Life Style\$ or lifestyle\$ or ((living or live or lived) adj5 style\$)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]

47 4 and 46

48 Exercis\$.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]

49 (tai chi or tai ji or relaxation or walk\$ or yoga or jog or jogging).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]

50 (Physical\$ adj3 (Fitness or fit)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]

51 48 or 49 or 50

52 4 and 51

53 ((Gastric or stomach) adj3 Bypass\$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]

54 gastroplast\$.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
 55 ((obese or obesity) adj3 (surger\$ or surgic\$)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
 56 53 or 54 or 55
 57 4 and 56
 58 anti-obesity agent\$.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
 59 ((obese or obesity) adj3 (drug\$ or pharmaco\$)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
 60 orlistat.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
 61 sibutramine.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
 62 fluoxetine.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
 63 58 or 59 or 60 or 61 or 62
 64 4 and 63
 65 Counsel\$.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
 66 4 and 65
 67 (Patient\$ adj3 (Educate\$ or inform\$)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
 68 4 and 67
 69 footcare.mp.
 70 ((foot or feet or toe or toes or heel or plantar) adj5 (care or cares or caring or cared)).mp.
 71 ((foot or feet or toe or toes or heel or plantar) adj5 (disease\$ or ulcer\$ or sore\$)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
 72 69 or 70 or 71
 73 4 and 72
 74 17 or 23 or 32 or 43 or 45 or 47 or 52 or 57 or 64 or 66 or 68 or 73
 75 limit 74 to yr="2001 - 2007"

Database: EBM Reviews - Cochrane Database of Systematic Reviews

Search Strategy:

1 ((Diabet\$ adj3 (type II or type 2 or non-insulin depend\$)) or MODY or NIDDM).mp. [mp=title, abstract, full text, keywords, caption text]
 2 (impair\$ adj3 (fasting glucose or glucose tolerance)).mp. [mp=title, abstract, full text, keywords, caption text]
 3 (prediabet\$ or pre-diabet\$).mp. [mp=title, abstract, full text, keywords, caption text]
 4 1 or 2 or 3

5 Hypoglycemic Agent\$.mp. [mp=title, abstract, full text, keywords, caption text]
 6 Glipizide.mp. [mp=title, abstract, full text, keywords, caption text]
 7 Glyburide.mp. [mp=title, abstract, full text, keywords, caption text]
 8 Glimepiride.mp. [mp=title, abstract, full text, keywords, caption text]
 9 Metformin.mp. [mp=title, abstract, full text, keywords, caption text]
 10 Rosiglitazone.mp. [mp=title, abstract, full text, keywords, caption text]
 11 Pioglitazone.mp. [mp=title, abstract, full text, keywords, caption text]
 12 Repaglinide.mp. [mp=title, abstract, full text, keywords, caption text]
 13 Nateglinide.mp. [mp=title, abstract, full text, keywords, caption text]
 14 Acarbose.mp. [mp=title, abstract, full text, keywords, caption text]
 15 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14
 16 5 or 15
 17 4 and 16
 18 (Angiotensin Converting Enzyme Inhibitor\$ or ace inhibitor\$).mp. [mp=title, abstract, full text, keywords, caption text]
 19 (Angiotensin adj3 (block\$ or antagonist\$ or receptor\$)).mp. [mp=title, abstract, full text, keywords, caption text]
 20 (Calcium Channel\$ adj3 (antagon\$ or Block\$)).mp. [mp=title, abstract, full text, keywords, caption text]
 21 (antihypertensi\$ or anti-hypertensi\$).mp. [mp=title, abstract, full text, keywords, caption text]
 22 18 or 19 or 20 or 21
 23 4 and 22
 24 Hydroxymethylglutaryl CoA Reductase\$.mp. [mp=title, abstract, full text, keywords, caption text]
 25 Lovastatin.mp. [mp=title, abstract, full text, keywords, caption text]
 26 Pravastatin.mp. [mp=title, abstract, full text, keywords, caption text]
 27 Fluvastatin.mp. [mp=title, abstract, full text, keywords, caption text]
 28 Atorvastatin.mp. [mp=title, abstract, full text, keywords, caption text]
 29 Rosuvastatin.mp. [mp=title, abstract, full text, keywords, caption text]
 30 25 or 26 or 27 or 28 or 29
 31 24 or 30
 32 4 and 31
 33 Antilipemic\$.mp. [mp=title, abstract, full text, keywords, caption text]
 34 Gemfibrozil.mp. [mp=title, abstract, full text, keywords, caption text]
 35 Fenofibrate.mp. [mp=title, abstract, full text, keywords, caption text]
 36 Nicotinic Acid.mp. [mp=title, abstract, full text, keywords, caption text]
 37 Cholestyramine.mp. [mp=title, abstract, full text, keywords, caption text]
 38 Colestipol.mp. [mp=title, abstract, full text, keywords, caption text]
 39 Colesevelam.mp. [mp=title, abstract, full text, keywords, caption text]
 40 Ezetimibe.mp. [mp=title, abstract, full text, keywords, caption text]
 41 34 or 35 or 36 or 37 or 38 or 39 or 40
 42 33 or 41
 43 4 and 42
 44 Aspirin.mp.
 45 4 and 44

- 46 (Life Style\$ or lifestyle\$ or ((living or live or lived) adj5 style\$)).mp. [mp=title, abstract, full text, keywords, caption text]
- 47 4 and 46
- 48 Exercis\$.mp. [mp=title, abstract, full text, keywords, caption text]
- 49 (tai chi or tai ji or relaxation or walk\$ or yoga or jog or jogging).mp. [mp=title, abstract, full text, keywords, caption text]
- 50 (Physical\$ adj3 (Fitness or fit)).mp. [mp=title, abstract, full text, keywords, caption text]
- 51 48 or 49 or 50
- 52 4 and 51
- 53 ((Gastric or stomach) adj3 Bypass\$).mp. [mp=title, abstract, full text, keywords, caption text]
- 54 gastroplast\$.mp. [mp=title, abstract, full text, keywords, caption text]
- 55 ((obese or obesity) adj3 (surger\$ or surgic\$)).mp. [mp=title, abstract, full text, keywords, caption text]
- 56 53 or 54 or 55
- 57 4 and 56
- 58 anti-obesity agent\$.mp. [mp=title, abstract, full text, keywords, caption text]
- 59 ((obese or obesity) adj3 (drug\$ or pharmaco\$)).mp. [mp=title, abstract, full text, keywords, caption text]
- 60 orlistat.mp. [mp=title, abstract, full text, keywords, caption text]
- 61 sibutramine.mp. [mp=title, abstract, full text, keywords, caption text]
- 62 fluoxetine.mp. [mp=title, abstract, full text, keywords, caption text]
- 63 58 or 59 or 60 or 61 or 62
- 64 4 and 63
- 65 Counsel\$.mp. [mp=title, abstract, full text, keywords, caption text]
- 66 4 and 65
- 67 (Patient\$ adj3 (Educate\$ or inform\$)).mp. [mp=title, abstract, full text, keywords, caption text]
- 68 4 and 67
- 69 footcare.mp.
- 70 ((foot or feet or toe or toes or heel or plantar) adj5 (care or cares or caring or cared)).mp.
- 71 ((foot or feet or toe or toes or heel or plantar) adj5 (disease\$ or ulcer\$ or sore\$)).mp. [mp=title, abstract, full text, keywords, caption text]
- 72 69 or 70 or 71
- 73 4 and 72
- 74 17 or 23 or 32 or 43 or 45 or 47 or 52 or 57 or 64 or 66 or 68 or 73

Database: EBM Reviews - Database of Abstracts of Reviews of Effects

Search Strategy:

- 1 ((Diabet\$ adj3 (type II or type 2 or non-insulin depend\$)) or MODY or NIDDM).mp. [mp=title, full text, keywords]

- 2 (impair\$ adj3 (fasting glucose or glucose tolerance)).mp. [mp=title, full text, keywords]
- 3 (prediabet\$ or pre-diabet\$).mp. [mp=title, full text, keywords]
- 4 1 or 2 or 3
- 5 Hypoglycemic Agent\$.mp. [mp=title, full text, keywords]
- 6 Glipizide.mp. [mp=title, full text, keywords]
- 7 Glyburide.mp. [mp=title, full text, keywords]
- 8 Glimepiride.mp. [mp=title, full text, keywords]
- 9 Metformin.mp. [mp=title, full text, keywords]
- 10 Rosiglitazone.mp. [mp=title, full text, keywords]
- 11 Pioglitazone.mp. [mp=title, full text, keywords]
- 12 Repaglinide.mp. [mp=title, full text, keywords]
- 13 Nateglinide.mp. [mp=title, full text, keywords]
- 14 Acarbose.mp. [mp=title, full text, keywords]
- 15 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14
- 16 5 or 15
- 17 4 and 16
- 18 (Angiotensin Converting Enzyme Inhibitor\$ or ace inhibitor\$).mp. [mp=title, full text, keywords]
- 19 (Angiotensin adj3 (block\$ or antagon\$ or receptor\$)).mp. [mp=title, full text, keywords]
- 20 (Calcium Channel\$ adj3 (antagon\$ or Block\$)).mp. [mp=title, full text, keywords]
- 21 (antihypertensi\$ or anti-hypertensi\$).mp. [mp=title, full text, keywords]
- 22 18 or 19 or 20 or 21
- 23 4 and 22
- 24 Hydroxymethylglutaryl CoA Reductase\$.mp. [mp=title, full text, keywords]
- 25 Lovastatin.mp. [mp=title, full text, keywords]
- 26 Pravastatin.mp. [mp=title, full text, keywords]
- 27 Fluvastatin.mp. [mp=title, full text, keywords]
- 28 Atorvastatin.mp. [mp=title, full text, keywords]
- 29 Rosuvastatin.mp. [mp=title, full text, keywords]
- 30 25 or 26 or 27 or 28 or 29
- 31 24 or 30
- 32 4 and 31
- 33 Antilipemic\$.mp. [mp=title, full text, keywords]
- 34 Gemfibrozil.mp. [mp=title, full text, keywords]
- 35 Fenofibrate.mp. [mp=title, full text, keywords]
- 36 Nicotinic Acid.mp. [mp=title, full text, keywords]
- 37 Cholestyramine.mp. [mp=title, full text, keywords]
- 38 Colestipol.mp. [mp=title, full text, keywords]
- 39 Colesevelam.mp. [mp=title, full text, keywords]
- 40 Ezetimibe.mp. [mp=title, full text, keywords]
- 41 34 or 35 or 36 or 37 or 38 or 39 or 40
- 42 33 or 41
- 43 4 and 42
- 44 Aspirin.mp.

45 4 and 44
 46 (Life Style\$ or lifestyle\$ or ((living or live or lived) adj5 style\$)).mp. [mp=title, full text, keywords]
 47 4 and 46
 48 Exercis\$.mp. [mp=title, full text, keywords]
 49 (tai chi or tai ji or relaxation or walk\$ or yoga or jog or jogging).mp. [mp=title, full text, keywords]
 50 (Physical\$ adj3 (Fitness or fit)).mp. [mp=title, full text, keywords]
 51 48 or 49 or 50
 52 4 and 51
 53 ((Gastric or stomach) adj3 Bypass\$).mp. [mp=title, full text, keywords]
 54 gastroplast\$.mp. [mp=title, full text, keywords]
 55 ((obese or obesity) adj3 (surger\$ or surgic\$)).mp. [mp=title, full text, keywords]
 56 53 or 54 or 55
 57 4 and 56
 58 anti-obesity agent\$.mp. [mp=title, full text, keywords]
 59 ((obese or obesity) adj3 (drug\$ or pharmaco\$)).mp. [mp=title, full text, keywords]
 60 orlistat.mp. [mp=title, full text, keywords]
 61 sibutramine.mp. [mp=title, full text, keywords]
 62 fluoxetine.mp. [mp=title, full text, keywords]
 63 58 or 59 or 60 or 61 or 62
 64 4 and 63
 65 Counsel\$.mp. [mp=title, full text, keywords]
 66 4 and 65
 67 (Patient\$ adj3 (Educat\$ or inform\$)).mp. [mp=title, full text, keywords]
 68 4 and 67
 69 footcare.mp.
 70 ((foot or feet or toe or toes or heel or plantar) adj5 (care or cares or caring or cared)).mp.
 71 ((foot or feet or toe or toes or heel or plantar) adj5 (disease\$ or ulcer\$ or sore\$)).mp. [mp=title, full text, keywords]
 72 69 or 70 or 71
 73 4 and 72
 74 17 or 23 or 32 or 43 or 45 or 47 or 52 or 57 or 64 or 66 or 68 or 73

Database: Ovid MEDLINE(R)

Search Strategy:

1 exp Diabetes Mellitus, type II/
 2 (impair\$ adj3 (fasting glucose or glucose tolerance)).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
 3 (prediabet\$ or pre-diabet\$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
 4 1 or 2 or 3
 5 exp Hypoglycemic Agents/

- 6 Glipizide.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
- 7 Glyburide.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
- 8 Glimepiride.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
- 9 Metformin.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
- 10 Rosiglitazone.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
- 11 Pioglitazone.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
- 12 Repaglinide.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
- 13 Nateglinide.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
- 14 Acarbose.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
- 15 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14
- 16 5 or 15
- 17 4 and 16
- 18 exp Angiotensin-Converting Enzyme Inhibitors/
- 19 exp Angiotensin II/
- 20 exp Receptors, Angiotensin/ai [Antagonists & Inhibitors]
- 21 19 and 20
- 22 exp Angiotensin II Type 1 Receptor Block
- 23 21 or 22
- 24 exp Calcium Channel Blockers/
- 25 exp antihypertensive agents/
- 26 18 or 23 or 24 or 25
- 27 4 and 26
- 28 exp Hydroxymethylglutaryl CoA Reductases/
- 29 Lovastatin.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
- 30 Pravastatin.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
- 31 Fluvastatin.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
- 32 Atorvastatin.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
- 33 Rosuvastatin.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
- 34 29 or 30 or 31 or 32 or 33
- 35 28 or 34
- 36 4 and 35
- 37 exp Antilipemic Agents/

38 Gemfibrozil.mp. [mp=title, original title, abstract, name of substance word, subject heading word]

39 Fenofibrate.mp. [mp=title, original title, abstract, name of substance word, subject heading word]

40 Nicotinic Acid.mp. [mp=title, original title, abstract, name of substance word, subject heading word]

41 Cholestyramine.mp. [mp=title, original title, abstract, name of substance word, subject heading word]

42 Colestipol.mp. [mp=title, original title, abstract, name of substance word, subject heading word]

43 Colesevelam.mp. [mp=title, original title, abstract, name of substance word, subject heading word]

44 Ezetimibe.mp. [mp=title, original title, abstract, name of substance word, subject heading word]

45 38 or 39 or 40 or 41 or 42 or 43 or 44

46 37 or 45

47 4 and 46

48 exp Aspirin/

49 4 and 48

50 exp Life Style/

51 4 and 50

52 exp Exercise/ or exp Exercise Movement Techniques/

53 exp Physical Fitness/

54 52 or 53

55 4 and 54

56 exp Gastric Bypass/

57 exp gastroplasty/

58 exp obesity/su

59 56 or 57 or 58

60 4 and 59

61 exp anti-obesity agents/

62 exp obesity/dt

63 orlistat.mp. [mp=title, original title, abstract, name of substance word, subject heading word]

64 sibutramine.mp. [mp=title, original title, abstract, name of substance word, subject heading word]

65 fluoxetine.mp. [mp=title, original title, abstract, name of substance word, subject heading word]

66 61 or 62 or 63 or 64 or 65

67 4 and 66

68 exp Counseling/

69 4 and 68

70 exp Patient Education/

71 4 and 70

72 exp Foot Diseases/nu, pc, dh, dt, rh, su, tu [Nursing, Prevention & Control, Diet Therapy, Drug Therapy, Rehabilitation,

Surgery, Therapeutic Use]

73 footcare.mp.

74 ((foot or feet or toe or toes or heel or plantar) adj5 (care or cares or caring or cared)).mp.

75 72 or 73 or 74

76 4 and 75

77 (200109\$ or 20011\$ or 2002\$ or 2003\$ or 2004\$ or 2005\$ or 2006\$).ed.

78 17 and 77

79 27 and 77

80 36 and 77

81 47 not 36

82 77 and 81

83 49 and 77

84 51 and 77

85 55 and 77

86 60 and 77

87 67 and 77

88 69 and 77

89 71 and 77

90 76 and 77

91 randomized controlled trial.pt.

92 controlled clinical trial.pt.

93 randomized controlled trials/

94 random allocation/

95 double-blind method/

96 single blind method/

97 91 or 92 or 93 or 94 or 95 or 96

98 animal/ not human/

99 97 not 98

100 clinical trial.pt.

101 (clinic\$ adj25 trial\$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]

102 exp Clinical Trials/

103 ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj (mask\$ or blind\$)).mp. [mp=title, original title, abstract, name of substance word, subject heading word]

104 exp Placebos/

105 placebo\$.mp.)

106 random\$.mp.

107 Research Design/

108 (latin adj square).mp. [mp=title, original title, abstract, name of substance word, subject heading word]

109 100 or 101 or 102 or 103 or 104 or 105 or 106 or 107 or 108

110 109 not 98

111 110 not 99

112 99 or 111

113 78 and 112
 114 79 and 112
 115 80 and 112
 116 82 and 112
 117 83 and 112
 118 84 and 112
 119 85 and 112
 120 86 and 112
 121 87 and 112
 122 88 and 112
 123 89 and 112
 124 90 and 112
 125 113 or 114 or 115 or 116 or 117 or 118 or 119 or 120 or 121 or 122 or 123 or 124
 126 limit 125 to english language
 127 limit 125 to abstracts
 128 126 or 127
 129 limit 128 to yr="2001 - 2007"

Database: Ovid MEDLINE(R)

Search Strategy:

1 exp Diabetes Mellitus, type II/
 2 (impair\$ adj3 (fasting glucose or glucose tolerance)).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
 3 (prediabet\$ or pre-diabet\$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
 4 1 or 2 or 3
 5 exp Hypoglycemic Agents/
 6 Glipizide.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
 7 Glyburide.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
 8 Glimepiride.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
 9 Metformin.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
 10 Rosiglitazone.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
 11 Pioglitazone.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
 12 Repaglinide.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
 13 Nateglinide.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
 14 Acarbose.mp. [mp=title, original title, abstract, name of substance word, subject heading word]

15 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14
 16 5 or 15
 17 4 and 16
 18 exp Angiotensin-Converting Enzyme Inhibitors/
 19 exp Angiotensin II/
 20 exp Receptors, Angiotensin/ai [Antagonists & Inhibitors]
 21 19 and 20
 22 exp Angiotensin II Type 1 Receptor Blockers/
 23 21 or 22
 24 exp Calcium Channel Blockers/
 25 exp antihypertensive agents/
 26 18 or 23 or 24 or 25
 27 4 and 26
 28 exp Hydroxymethylglutaryl CoA Reductases/
 29 Lovastatin.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
 30 Pravastatin.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
 31 Fluvastatin.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
 32 Atorvastatin.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
 33 Rosuvastatin.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
 34 29 or 30 or 31 or 32 or 33
 35 28 or 34
 36 4 and 35
 37 exp Antilipemic Agents/
 38 Gemfibrozil.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
 39 Fenofibrate.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
 40 Nicotinic Acid.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
 41 Cholestyramine.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
 42 Colestipol.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
 43 Colesevelam.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
 44 Ezetimibe.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
 45 38 or 39 or 40 or 41 or 42 or 43 or 44
 46 37 or 45
 47 4 and 46
 48 exp Aspirin/

49 4 and 48
 50 exp Life Style/
 51 4 and 50
 52 exp Exercise/ or exp Exercise Movement Techniques/
 53 exp Physical Fitness/
 54 52 or 53
 55 4 and 54
 56 exp Gastric Bypass/
 57 exp gastroplasty/
 58 exp obesity/su
 59 56 or 57 or 58
 60 4 and 59
 61 exp anti-obesity agents/
 62 exp obesity/dt
 63 orlistat.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
 64 sibutramine.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
 65 fluoxetine.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
 66 61 or 62 or 63 or 64 or 65
 67 4 and 66
 68 exp Counseling/
 69 4 and 68
 70 exp Patient Education/
 71 4 and 70
 72 exp Foot Diseases/nu, pc, dh, dt, rh, su, tu [Nursing, Prevention & Control, Diet Therapy, Drug Therapy, Rehabilitation, Surgery, Therapeutic Use]
 73 footcare.mp.
 74 ((foot or feet or toe or toes or heel or plantar) adj5 (care or cares or caring or cared)).mp.
 75 72 or 73 or 74
 76 4 and 75
 77 (200109\$ or 20011\$ or 2002\$ or 2003\$ or 2004\$ or 2005\$ or 2006\$).ed.
 78 17 and 77
 79 27 and 77
 80 36 and 77
 81 47 not 36
 82 77 and 81
 83 49 and 77
 84 51 and 77
 85 55 and 77
 86 60 and 77
 87 67 and 77
 88 69 and 77

89 71 and 77
 90 76 and 77
 91 randomized controlled trial.pt.
 92 controlled clinical trial.pt.
 93 randomized controlled trials/
 94 random allocation/
 95 double-blind method/
 96 single blind method/
 97 91 or 92 or 93 or 94 or 95 or 96
 98 animal/ not human/
 99 97 not 98
 100 clinical trial.pt.
 101 (clinic\$ adj25 trial\$).mp. [mp=title, original title, abstract, name of substance
 word, subject heading word]
 102 exp Clinical Trials/
 103 ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj (mask\$ or blind\$)).mp. [mp=title,
 original title, abstract, name of substance
 word, subject heading word])
 104 exp Placebos/
 105 placebo\$.mp.
 106 random\$.mp.
 107 Research Design/
 108 (latin adj square).mp. [mp=title, original title, abstract, name of substance word,
 subject heading word]
 109 100 or 101 or 102 or 103 or 104 or 105 or 106 or 107 or 108
 110 109 not 98
 111 110 not 99
 112 99 or 111
 113 78 and 112
 114 79 and 112
 115 80 and 112
 116 82 and 112
 117 83 and 112
 118 84 and 112
 119 85 and 112
 120 86 and 112
 121 87 and 112
 122 88 and 112
 123 89 and 112
 124 90 and 112
 125 113 or 114 or 115 or 116 or 117 or 118 or 119 or 120 or 121 or 122 or 123 or 124
 126 limit 125 to english language
 127 limit 125 to abstracts
 128 126 or 127
 129 limit 128 to yr="2001 - 2003"
 130 limit 128 to yr="2004 - 2007"

Database: Ovid MEDLINE(R)

Search Strategy:

- 1 exp Diabetes Mellitus, type II/
- 2 (impair\$ adj3 (fasting glucose or glucose tolerance)).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
- 3 (prediabet\$ or pre-diabet\$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
- 4 1 or 2 or 3
- 5 exp Hypoglycemic Agents/
- 6 Glipizide.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
- 7 Glyburide.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
- 8 Glimepiride.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
- 9 Metformin.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
- 10 Rosiglitazone.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
- 11 Pioglitazone.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
- 12 Repaglinide.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
- 13 Nateglinide.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
- 14 Acarbose.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
- 15 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14
- 16 5 or 15
- 17 4 and 16
- 18 exp Angiotensin-Converting Enzyme Inhibitors/
- 19 exp Angiotensin II/
- 20 exp Receptors, Angiotensin/ai [Antagonists & Inhibitors]
- 21 19 and 20
- 22 exp Angiotensin II Type 1 Receptor Blockers/
- 23 21 or 22
- 24 exp Calcium Channel Blockers/
- 25 exp antihypertensive agents/
- 26 18 or 23 or 24 or 25
- 27 4 and 26
- 28 exp Hydroxymethylglutaryl CoA Reductases/
- 29 Lovastatin.mp. [mp=title, original title, abstract, name of substance word, subject heading word]

30 Pravastatin.mp. [mp=title, original title, abstract, name of substance word, subject heading word]

31 Fluvastatin.mp. [mp=title, original title, abstract, name of substance word, subject heading word]

32 Atorvastatin.mp. [mp=title, original title, abstract, name of substance word, subject heading word]

33 Rosuvastatin.mp. [mp=title, original title, abstract, name of substance word, subject heading word]

34 29 or 30 or 31 or 32 or 33

35 28 or 34

36 4 and 35

37 exp Antilipemic Agents/

38 Gemfibrozil.mp. [mp=title, original title, abstract, name of substance word, subject heading word]

39 Fenofibrate.mp. [mp=title, original title, abstract, name of substance word, subject heading word] (

40 Nicotinic Acid.mp. [mp=title, original title, abstract, name of substance word, subject heading word]

41 Cholestyramine.mp. [mp=title, original title, abstract, name of substance word, subject heading word]

42 Colestipol.mp. [mp=title, original title, abstract, name of substance word, subject heading word]

43 Colesevelam.mp. [mp=title, original title, abstract, name of substance word, subject heading word]

44 Ezetimibe.mp. [mp=title, original title, abstract, name of substance word, subject heading word]

45 38 or 39 or 40 or 41 or 42 or 43 or 44

46 37 or 45

47 4 and 46

48 exp Aspirin/

49 4 and 48

50 exp Life Style/

51 4 and 50

52 exp Exercise/ or exp Exercise Movement Techniques/

53 exp Physical Fitness/

54 52 or 53

55 4 and 54

56 exp Gastric Bypass/

57 exp gastroplasty/

58 exp obesity/su

59 56 or 57 or 58

60 4 and 59

61 exp anti-obesity agents/

62 exp obesity/dt

63 orlistat.mp. [mp=title, original title, abstract, name of substance word, subject heading word]

64 sibutramine.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
 65 fluoxetine.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
 66 61 or 62 or 63 or 64 or 65
 67 4 and 66
 68 exp Counseling/
 69 4 and 68
 70 exp Patient Education/
 71 4 and 70
 72 exp Foot Diseases/nu, pc, dh, dt, rh, su, tu [Nursing, Prevention & Control, Diet Therapy, Drug Therapy, Rehabilitation, Surgery, Therapeutic Use]
 73 footcare.mp.
 74 ((foot or feet or toe or toes or heel or plantar) adj5 (care or cares or caring or cared)).mp.
 75 72 or 73 or 74
 76 4 and 75
 77 (200109\$ or 20011\$ or 2002\$ or 2003\$ or 2004\$ or 2005\$ or 2006\$).ed.
 78 17 and 77
 79 27 and 77
 80 36 and 77
 81 47 not 36
 82 77 and 81
 83 49 and 77
 84 51 and 77
 85 55 and 77
 86 60 and 77
 87 67 and 77
 88 69 and 77
 89 71 and 77
 90 76 and 77
 91 randomized controlled trial.pt.
 92 controlled clinical trial.pt.
 93 randomized controlled trials/
 94 random allocation/
 95 double-blind method/
 96 single blind method/
 97 91 or 92 or 93 or 94 or 95 or 96
 98 animal/ not human/
 99 97 not 98
 100 clinical trial.pt.
 101 (clinic\$ adj25 trial\$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
 102 exp Clinical Trials/

103 ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj (mask\$ or blind\$)).mp. [mp=title,
 original title, abstract, name of substance
 word, subject heading word]
 104 exp Placebos/
 105 placebo\$.mp.
 106 random\$.mp.
 107 Research Design/
 108 (latin adj square).mp. [mp=title, original title, abstract, name of substance word,
 subject heading word]
 109 100 or 101 or 102 or 103 or 104 or 105 or 106 or 107 or 10
 110 109 not 98
 111 110 not 99
 112 99 or 111
 113 78 and 112
 114 79 and 112
 115 80 and 112
 116 82 and 112
 117 83 and 112
 118 84 and 112
 119 85 and 112
 120 86 and 112
 121 87 and 112
 122 88 and 112
 123 89 and 112
 124 90 and 112
 125 113 or 114 or 115 or 116 or 117 or 118 or 119 or 120 or 121 or 122 or 123 or 124
 126 limit 125 to english language
 127 limit 125 to abstracts
 128 126 or 127
 130 limit 128 to yr="2004 - 2007"
 131 128 not (129 or 130)

Appendix 5: Grey Literature Search

Google search limited to Canada

- “diabetes screening AND harms”
- “diabetes screening AND Canada”
- “diabetes screening AND costs”

Specific Sites Search: search terms included “diabetes screening” OR “diabetic AND screening” OR “diabetes mellitus”

Agence d'évaluation des technologies et des modes d'intervention en santé (AETMIS), Québec <http://www.aetmis.gouv.qc.ca/>

Canadian Agency for Drugs and Technologies in Health (CADTH) <http://www.cadth.ca>
<http://www.cadth.ca/index.php/en/hta/reports-publications>.

Centre for Evaluation of Medicines (Father Sean O'Sullivan Research Centre; St. Joseph's Healthcare Hamilton; and McMaster University, Faculty of Health Sciences, Hamilton, Ontario) <http://www.thecem.net/http://www.thecem.net/>

Centre for Health Services and Policy Research, University of British Columbia
<http://www.chspr.ubc.ca/cgi-bin/pub>

Health Quality Council, Saskatchewan
<http://www.hqc.sk.ca/>

Institute for Clinical Evaluative Sciences (ICES), Ontario
<http://www.ices.on.ca/>

IHE Institute of Health Economics, HTA Unit, Alberta
<http://www.ihe.ca/publications/library/>

Manitoba Centre for Health Policy (MCHP)
<http://umanitoba.ca/medicine/units/mchp/>

Ontario Health Technology Advisory Committee Analyses and Recommendations
http://www.health.gov.on.ca/english/providers/program/ohtac/tech/recommend/rec_mn.html

Technology Assessment Unit of the McGill University Health Centre
<http://www.mcgill.ca/tau/publications/>

Centre for Health Economics and Policy Analysis (CHEPA), McMaster University
<http://www.chepa.org/>

Institute of Health Economics (IHE)

<http://www.ihe.ca>

Canadian Institute for Health Information (CIHI)

<http://www.cihi.ca/CIHI-ext-portal/internet/EN/Home/home/cihi000001>

Health Canada

<http://www.hc-sc.gc.ca/english/>

Public Health Agency of Canada

<http://www.phac-aspc.gc.ca/index-eng.php>

Statistics Canada

<http://www.statcan.gc.ca/start-debut-eng.html>

Canadian Diabetes Association

<http://www.diabetes.ca>

Canadian Journal of Diabetes

<http://www.diabetes.ca/publications/cjd>

Diabetes Voice

<http://www.diabetesvoice.org>

National Aboriginal Diabetes Association

<http://www.nada.ca/>

Diabetes Research & Treatment Centre

<http://www.drhc.ca>

Appendix 6: Search Strategy Modeling

Search Strategy Modeling-Frequency/Interval June 16, 2011

Database: Ovid MEDLINE(R) <1948 to June Week 2 2011>

Search Strategy:

-
- 1 exp Diabetes Mellitus, Type 2/ (65715)
 - 2 ((fasting glucose or glucose tolerance) adj3 impair*).mp. (8107)
 - 3 (prediabet* or pre-diabet*).mp. (4672)
 - 4 ((type 2 or type II or non-insulin dependent) adj3 diabet*).mp. (81625)
 - 5 or/1-4 (89666)
 - 6 (simulation or model or modelling or modeling).ti. (227784)
 - 7 models, theoretical/ or exp models, statistical/ (278145)
 - 8 6 or 7 (475435)
 - 9 5 and 8 (4103)
 - 10 mass screening/ or screen*.tw. (368275)
 - 11 9 and 10 (254)
 - 12 ((screen* or testing) adj4 (frequency or interval)).tw. (2744)
 - 13 5 and 12 (51)
 - 14 11 or 13 (296)
 - 15 animals/ not humans/ (3519133)
 - 16 (animal or mouse or rat).ti. (589099)
 - 17 15 or 16 (3604864)
 - 18 14 not 17 (283)
 - 19 limit 18 to (english or french) (274)
 - 20 limit 19 to yr="2005 -Current" (169)

Appendix 7: Search Strategy Diagnostic Risk Assessment

Database: Ovid MEDLINE(R) <1948 to November Week 3 2011>

Search Strategy:

```
-----
1  75g.ti. (14)
2  *Mass Screening/ (37901)
3  risk prediction tools.mp. (44)
4  *risk assessment/ (15593)
5  (risk assessment or risk stratification or risk prediction).tw. (33010)
6  (risk adj3 (predication or tool or score or scale)).tw. (7754)
7  or/2-6 (87939)
8  di.fs. (1788864)
9  predict*.tw. (701300)
10 predictability.tw. (6287)
11 8 or 9 or 10 (2383534)
12 Blood Glucose/du [Diagnostic Use] (5)
13 *Hemoglobin A, Glycosylated/an, du [Analysis, Diagnostic Use] (2846)
14 *blood glucose/ (34171)
15 *fasting/ (7421)
16 14 and 15 (723)
17 (HbA1c or HbA 1c or hemoglobin A1c or A1c).ti. (1660)
18 *diabetes mellitus/ or exp *diabetes mellitus, type 2/ (111887)
19 (diabetes or diabetic).ti. (189415)
20 exp *diabetes mellitus, type 1/ not diabetes mellitus, type 2/ (38579)
21 (18 or 19) not 20 (183220)
22 12 or 13 or 16 or 17 (4277)
23 21 and 22 (2169)
24 7 and 21 (2100)
25 23 or 24 (4230)
26 *Glucose Tolerance Test/ (4716)
27 21 and 26 (1641)
28 25 or 27 (5715)
29 specificity.tw. (272462)
30 21 and 29 (1512)
31 28 or 30 (6884)
32 limit 31 to (english or french) (5805)
33 animals/ not humans/ (3630436)
34 32 not 33 (5649)
35 limit 34 to (case reports or comment or editorial or in vitro or letter or news or
newspaper article or video-audio media or webcasts) (624)
36 34 not 35 (5025)
37 limit 36 to yr="2001 -Current" (3017)
38 (pediatr* or paediatr*).jn. (155789)
39 37 not 38 (3000)
```

Appendix 8: List of External Reviewers – Original Protocol

| | |
|-----------------------|---|
| Dr. Hertzell Gerstein | Professor of Medicine, Director, Endocrinology and Metabolism, McMaster University. |
| Dr. Kara Nerenberg | General Internist, Assistant Professor, Department of Medicine, University of Alberta |

Appendix 9: List of External Reviewers – Revised Protocol

| | |
|--------------------|---|
| Dr. Kara Nerenberg | General Internist, Assistant Professor, Department of Medicine, University of Alberta |
| Dr. Gina Agarwal | Physician, Assistant Professor, Department of Family Medicine, McMaster University |
| Dr. Dale Clayton | Medical Director, CDHA Diabetes Center, Assistant Professor of Medicine and School of Health & Human Performance, Dalhousie University |

Appendix 10: List of External Reviewers – Evidence Synthesis

1. Lisa Ashley (lashley@cna-aiic.ca)
2. Barbara Foster (Barbara.foster@hc-sc.gc.ca)
3. Verna Mai (verna.mai@partnershipagainstcancer.ca)
4. Dr. Alice Cheng (ChengA@smh.ca)
5. Dr. Ronald Goldenberg (ronaldgoldenberg@gmail.com)
6. Jayne Thirsk (Jayne.thirsk@dietitians.ca)
7. Howard Morrison (howard.morrison@phac-aspc.gc.ca)
8. Chris Robinson (Chris.Robinson@phac-aspc.gc.ca)
9. Jay Onysko (Jay.onysko@phac-aspc.gc.ca)
10. Paul Belanger (paul.belanger@cihr-irsc.gc.ca)
11. Pamela Bradley (pamela.bradley@hc-sc.gc.ca)
12. Gilles Plourde (Gilles_plourde@hc-sc.gc.ca)
13. Kara Nerenberg (kara.nerenberg@albertahealthservices.ca)
14. Hertzell Gerstein (gerstein@mcmaster.ca)
15. Agarwal Gina (agarg@mcmaster.ca)
16. Janusz Kaczorowski (janusz.kaczorowski@familymed.ubc.ca)
17. Sumit Majumdar (Me2.majumdar@ualberta.ca)
18. Bob Goldstein (gold@jdrf.ca)

Appendix 11: AMSTAR Criteria Applied Reviews

| | Noble ¹²³ | WHO ⁵³ |
|--|----------------------|-------------------|
| ‘A priori’ design | Y | Y |
| Duplicate study selection and Data extraction | Y | Y |
| Comprehensive literature search | Y | Y |
| Status of publication use as an inclusion criterion | Y | Y |
| List of included/excluded studies | Y | Y |
| Characteristics of individual studies (aggregate) | Y | Y |
| Scientific quality of the included studies assessed and documented | Y | Y |
| Scientific quality of the included studies used appropriately in formatting conclusions | Y | Y |
| Appropriate methods to combine studies | Y | Y |
| Publication bias charted | N | N |
| Conflict of interest stated | Y | Y |

Legend: Y= Yes; N=No; P= Partial; C=Can’t Answer; NA=Not Applicable

Appendix 12: Components of Risk Assessment Tools

| Study, country | Risk Factors included in score | Sensitivity/Specificity | PPV/NPV | AUROC | Calibration |
|--|--|---|---|--|-----------------------|
| Makrilakis (2011) ¹²⁵ Greece | Age, BMI, waist circumference, use of antihypertensive medication, history of high blood glucose, physical inactivity, daily consumption of vegetables, fruits and berries | Cutoff value for detecting unknown diabetes of FINDRISC ≥ 15 81.1% /59.8%. FINDRISC ≥ 10 96.7% / 29.5%. FINDRISC ≥ 7 100%/ 10.7%. | 19.3/96.4 | 0.724 (95% CI: 0.677–0.770) | NR* |
| Tankova (2011) ¹²⁴ Bulgaria | Age, BMI, waist circumference, use of antihypertensive medication, history of high blood glucose, physical inactivity, daily consumption of vegetables, fruits and berries | FINDRISC ≥ 12 0.78/ 0.62 FINDRISC ≥ 10 , 0.84 /0.61 | NR | 0.7 | NR |
| Robinson (2011) ¹²⁶ Canada | Age, BMI, waist circumference, use of antihypertensive medication, history of high blood glucose, physical inactivity, daily consumption of vegetables, fruits and berries, ethnicity, education | Threshold score of 21 (slightly elevated risk) - 95/28; threshold score of 29 (moderate) - 80/55; threshold score of 32 (balanced) - 70/67; threshold score of 33 (high) - 66/70; threshold score of 43 (very high) - 30/94 | Threshold score of 21 - 25/96; threshold score of 29 - 31/92; threshold score of 32 - 35/90; threshold score of 33 - 36/89; threshold score of 43 - 55/84 | electronic and paper-based CANRISK scores were 0.75 (95% CI: 0.73–0.78) and 0.75 (95% CI: 0.73–0.78) | Hosmer-Lemeshow 0.002 |

*NR – nor reported

Appendix 13: A1c and prevalent microvascular complications – study characteristics⁵³

| Author, year and country | Subject no and gender (M/F) | Age (years) | Prevalence of diabetes (%) | Inclusion/ exclusion criteria | A1c test method | Glucose method | Diabetes diagnostic criteria | Blood sample |
|---|-----------------------------|----------------|--|---|--|------------------------|------------------------------|-----------------------------------|
| Colagiuri et al. (in press, Diabetes Care), International | 47,364 22,127/ 25,237 | 20-79 | 14.3 | Age 20-79 years with gradable retinal photographs and data for at least one measure of glycaemia (FPG, 2h PG or A1c) | Varies by study | Varies by study | WHO 1999 | Varies by study |
| Engelgau et al. (1997), Egypt | 1,018 417/601 | Mean: 45 | 35.6 | ≥ 20 years old, Egyptian (note: includes people with known diabetes, many of whom were receiving anti-hyperglycaemic treatment) | Affinity chromatography (Pierce Scientific) CV: 6.0% | Glucose oxidase | WHO 1980 | Capillary blood and Serum glucose |
| Expert Committee (1997), US | 2,821 NR | 40-74 | NR | NR | NR | NR | NR | NR |
| Ito et al. (2000a), Japan | 12,208 6,440/5,768 | 58.6 ± 11.6 | NR | Japanese atomic bomb survivors | HPLC | Glucose oxidase | WHO 1999 | Venous plasma |
| McCance et al. (1994), US – Pima Indian | 960 384/576 | ≥ 25 | 14-26 depending on measurement and cut-point (26.3 for 2-h PG ≥ 11.1 mmol/L) | Pima Indian subjects ≥ 25 years of age not receiving insulin or oral hypoglycaemic treatment at baseline | HPLC | Potassium ferricyanide | WHO 1985 | Venous plasma |
| Miyazaki et al. (2004), Japan | 1,637 | 40-79 | 21-23 depending on measurement (21 for 2-h PG ≥ 11.1 mmol/L) | Age 40-79 years, not receiving insulin treatment (note: includes people receiving oral anti- hyperglycaemic treatment) | HPLC | Glucose oxidase | WHO 1999 | Venous plasma |
| Tapp et al. (2006), Australia | 2,476 1,114/1,362 | Mean: 59 | 34.5 | Age ≥ 25 years | Boronate affinity HPLC (Bio-Rad Variant Haemoglobin Testing System) CV: < 2% | Olympus AU600 analyser | WHO 1999 | Venous plasma |

2-h PG = 2 hour plasma glucose; ADA = American Diabetes Association; BMI = body mass index; CV = coefficient of variation; HPLC = high-performance liquid chromatography; NR = not reported; WHO = World Health Organization.

Appendix 13: A1c, FPG and 2-h PG cut-points associated with prevalent microvascular complications⁵³

| Study | Complication | A1c | | | | FPG | | | | 2-h PG | | | |
|--|--|-----------------------|------|-----------------|-----------------|----------------------------|-------|-----------------|-----------------|----------------------------|-------|-----------------|-----------------|
| | | Optimum cut-point (%) | AROC | Sensitivity (%) | Specificity (%) | Optimum cut-point (mmol/L) | AROC | Sensitivity (%) | Specificity (%) | Optimum cut-point (mmol/L) | AROC | Sensitivity (%) | Specificity (%) |
| Colagiuri et al. (in press, Diabetes Care) | Retinopathy (ROC curve analysis) | ≥6.3 | 0.90 | 86 | 86 | ≥6.5 | 0.87 | 82 | 81 | ≥12.4 | 0.89 | 83 | 83 |
| | Retinopathy (visual inspection of decile distribution) | 6.4-6.8 | NR | NR | NR | 6.4-6.8 | NR | NR | NR | 9.8-10.6 | NR | NR | NR |
| Engelgau et al. (1997) | Bi-modal: - Entire population | ≥6.7 | NR | 68 | 100 | ≥7.2 | NR | 84 | 100 | ≥11.5 | NR | 90 | 100 |
| | Retinopathy#: - Entire population | ≥7.6 | 0.82 | NR | NR | ≥6.6 | 0.85* | NR | NR | ≥14.4 | 0.86* | NR | NR |
| Expert Committee, (1997) | Retinopathy | ≥6.2 | NR | NR | NR | ≥6.7 | NR | NR | NR | ≥10.8 | NR | NR | NR |
| Ito et al. (2000a) | Retinopathy | ≥7.3 | NR | NR | NR | ≥7.0 | NR | NR | NR | ≥11.0 | NR | NR | NR |
| McCance et al. (1994) | Retinopathy | ≥7.0 | NR | 78 | 85 | ≥7.2 | NR | 81 | 80 | ≥13.0 | NR | 88 | 81 |
| | WHO equivalent | ≥6.1 | NR | 81 | 77 | ≥6.8 | NR | 81 | 77 | ≥11.1 | NR | 88 | 76 |
| | ROC curve analysis | ≥5.7 | 0.95 | 87 | 90 | ≥6.4 | 0.96 | 87 | 87 | ≥11.1 | 0.90 | 87 | 90 |
| Miyazaki et al. (2004) | Retinopathy | ≥5.8 | NR | NR | NR | ≥6.5 | NR | NR | NR | ≥11.0 | NR | NR | NR |
| Tapp et al. (2006) | Retinopathy | ≥6.1 | NR | NR | NR | ≥7.1 | NR | NR | NR | ≥13.1 | NR | NR | NR |
| | Microalbuminuria | ≥6.1 | NR | NR | NR | ≥7.2 | NR | NR | NR | NR | NR | NR | NR |
| | Retinopathy§ | ≥6.0 | NR | NR | NR | ≥8.5 | NR | NR | NR | NR | NR | NR | NR |
| | Microalbuminuria | NIL | - | - | - | NIL | - | - | - | NR | NR | NR | NR |

* Significantly different from A1c (p < 0.01); # Median decile value; § By change point analysis. 2-h PG = 2 hour plasma glucose; AROC = Area under the receiver operator characteristic curve; FPG = fasting plasma glucose; NR = Not reported; ROC = receiver operator characteristic; WHO = World Health Organization.

Appendix 13: A1c and incident microvascular complications – study characteristics⁵³

| Author, year and country | Subject no and gender (M/F) | Age (years) | Follow-up (years) | Incidence of diabetes (%) | Inclusion/ exclusion criteria | A1c test method | Glucose method | Diabetes diagnostic criteria | Blood sample |
|--|-----------------------------|-------------|-------------------|----------------------------|---|--|-----------------------|------------------------------|---------------|
| Massin et al. (in press, Archives of Ophthalmol, France | 700 504/196 | 30-65 | 10 | NR Retinopathy: 6.3 | Aged 30-65 years. Excluded if uninterpretable retinal photographs | HPLC (Hitachi/Merck-VWR) or DCA 2000 automated immunoassay system (Bayer Diagnostics) | Glucose oxidase | NR | Venous plasma |
| Van Leiden et al. (2003), Netherlands | 233 124/109 | 50-74 | 9.4 | NR Retinopathy: 11.6 | Aged 50-74 years from Hoorn, Netherlands. | HPLC (Modular Diabetes Monitoring system; Bio-Rad) Normal range: 4.3-6.1% | Glucose Dehydrogenase | WHO 1999 | Venous plasma |

HPLC = high-performance liquid chromatography; NR = not reported; WHO = World Health Organization.

Appendix 13: GRADE table for A1c and detection of prevalent microvascular complications⁵³

| Outcome | No. of studies | Study design | Factors that may decrease quality of evidence | | | | | Final quality | Effect per 1000 ¹ | Importance |
|---|--|---------------|---|------------|---------------|-------------|----------------|---------------|---|--------------|
| | | | Limitations | Indirectne | Inconsistency | Imprecision | Reporting bias | | | |
| True positives (patients with prevalent complications) | 3 studies ² (31,797 patients) | Observational | None ³ | None | None | None | Unlikely | ⊕⊕⊕ moderate | Prev 80%: 672 Prev 40%: 336 Prev 10%: 84 | IMPORTANT |
| True negatives (patients without prevalent complications) | 3 (31,797 patients) | Observational | None ³ | None | None | None | Unlikely | ⊕⊕⊕O moderate | Prev 80%: 172 Prev 40%: 516 Prev 10%: 774 | IMPORTANT |
| False positives (patients incorrectly classified as having prevalent complications) | 3 (31,797 patients) | Observational | None ³ | None | None | None | Unlikely | ⊕⊕⊕O moderate | Prev 80%: 28 Prev 40%: 84 Prev 10%: 126 | IMPORTANT |
| False negatives (patients incorrectly classified as not having prevalent complications) | 3 (31,797 patients) | Observational | None ³ | None | None | None | Unlikely | ⊕⊕⊕O moderate | Prev 80%: 128 Prev 40%: 64 Prev 10%: 16 | IMPORTANT |
| Inconclusive ⁴ | 4 studies (19,142 patients) | Observational | – | – | – | – | – | – | – | IMPORTANT |
| Cost | Not reported | – | – | – | – | – | – | – | – | NOT RELEVANT |

¹ Based on combined sensitivity of 84% and specificity of 86%

² One study contained pooled data from 8 studies with 29,819 participants

³ Although not a serious limitation, one study oversampled people with known diabetes

⁴ These 4 studies did not report information on sensitivity and specificity of A1c for predicting prevalent microvascular complications

Appendix 13: GRADE table for A1c and incident microvascular complications⁵³

| Outcome | No. of studies | Study design | Factors that may decrease quality of evidence | | | | | Final quality | Effect per 1000 ² | Importance |
|--|------------------------|---------------|---|--------------|------------------|-----------------------------|----------------|---------------|---|--------------|
| | | | Limitations | Indirectness | Inconsistency | Imprecision | Reporting bias | | | |
| True positives (patients with incident complications) | 1 study (700 patients) | Observational | None | None | N/A ² | Not assessable ³ | Unlikely | ⊕⊕⊕⊕ low | Prev 80%: 128 Prev 40%: 64 Prev 10%: 16 | IMPORTANT |
| True negatives (patients without incident complications) | 1 (700 patients) | Observational | None | None | N/A ² | Not assessable ³ | Unlikely | ⊕⊕⊕⊕ low | Prev 80%: 194 Prev 40%: 582 Prev 10%: 873 | IMPORTANT |
| False positives (patients incorrectly classified as having incident complications) | 1 (700 patients) | Observational | None | None | N/A ² | Not assessable ³ | Unlikely | ⊕⊕⊕⊕ low | Prev 80%: 6 Prev 40%: 18 Prev 10%: 27 | IMPORTANT |
| False negatives (patients incorrectly classified as not having incident complications) | 1 (700 patients) | Observational | None | None | N/A ² | Not assessable ³ | Unlikely | ⊕⊕⊕⊕ low | Prev 80%: 672 Prev 40%: 336 Prev 10%: 84 | IMPORTANT |
| Inconclusive ⁴ | 1 study (233 patients) | Observational | – | – | – | – | – | – | – | IMPORTANT |
| Cost | Not reported | – | – | – | – | – | – | – | – | NOT RELEVANT |

²Based on combined sensitivity of 16% and specificity of 97%

²Imprecision could not be assessed as confidence intervals were not reported

³Inconsistency is not applicable with data from only one study

⁴This study did not report information on sensitivity and specificity of A1c for predicting incident microvascular complications

Appendix 14: Characteristics of A1c Tests

| Study | Characteristics | Sensitivity/Specificity% | PPV/NPV% | AUROC |
|---|---|--------------------------------------|----------|---------------------|
| Peter (2011) ¹³¹ Country: Germany | N=2,036 at increased risk of DM Age: 40.3 (Mean) Gender: 35% Male BMI: 30.8 Race: Caucasian | 46.8/98.7 | 84/96.6 | NR* |
| Selvin (2011) ¹⁴⁰ Country: USA | N: 12,385 without DM Age: 56.8 (mean) Gender: 44.5% (M), 55.5% (F) BMI: 27.5+-5.1 Race: 20.9% African American, 79.1% White | 47/98 – single test | NR | .892 (95%CI)** |
| | | 67/97 – repeat tests (3 years apart) | NR | .936 (95%CI)** |
| Lipska (2010) ¹³⁵ Country: USA | N: 1,865 without DM Age: 76.5+/-2.9 yrs. Gender: 48.4% (M) Race: 41.6% African American | 56.9/98.4 | 50/98.8 | .078 (P<0.001) |
| van 't Riet (2010) ¹³⁷ Country: Netherlands | N: 2,753 Age: 53.5+-6.7 Gender: 46.9% (M) BMI: 26.3+-4.0 Race: 89.2% Dutch born | 24/99 | 93/97 | .895 (0.861, 0.930) |

*NR – not reported

**Confidence range not reported in study

Note: The included papers did not provide similar statistical analysis for FPG or OGTT as reported above for the HB1Ac