Screening for Type 2 Diabetes

D. Sherifali
McMaster Evidence Review and Synthesis Centre
Project Staff: M. Gauld, D. Fitzpatrick-Lewis, M. Rice
McMaster University
Hamilton Ontario Canada

CFTPC
N. Bell, P. Brauer, J. Dickinson, G. Lewin, P. Parkin, K. Pottie

PHAC:
L. Dunfield

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Work Plan

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1. Purpose and Background

Purpose

The purpose of this review is to provide an update of the 2005 Canadian Task Force recommendations on screening for type 2 diabetes to prevent vascular complications (Feig, Palda, & Lipscombe, with the Canadian Task Force on Preventive Health Care (CTFPHC), 2005). The goal of this update is to determine the effectiveness of screening for type 2 diabetes, and for impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT), in adults over the age of 18 years for the prevention of diabetes progression and vascular complications.

The US Preventive Service Task Force (USPSTF) updated their 2003 guidelines in 2008 (Norris, Kansagara, Bougatsos & Fu, 2008). 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

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 (Gerstein & Haynes, 2001).

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 (Cowie, Rust, Byrd-Holt, 2006).

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 (Ur, 2008). Optimal management of type 2 diabetes requires early and ongoing lifestyle modification; including physical activity and nutrition, self-management training and pharmacotherapy (Vermeire, Wens, VanRoyen, Biot, Hearnshaw, Lindenmeyer, et al., 2005; Ismail, Winkley & Rabe-Hesketh, 2004; Goudswaard, Stolk & Zuithoff, et al., 2004).

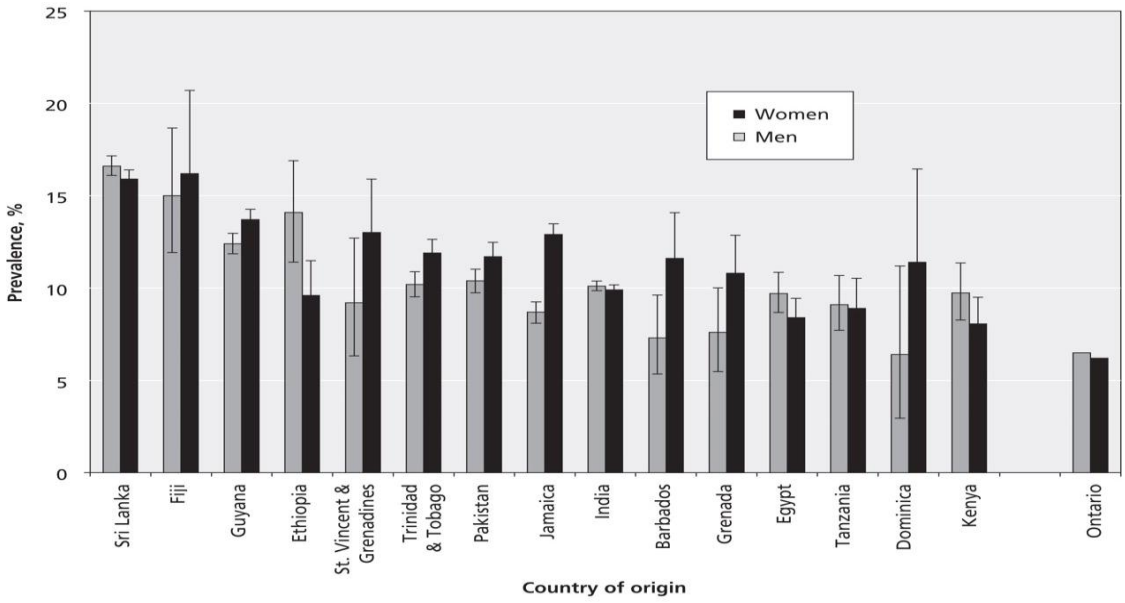
Prevalence and burden of disease

In Canada in 2006-2007, there were an estimated 199,471 new cases of diabetes diagnosed, with a prevalence of diagnosed diabetes for the whole population at 6.2% (Public Health Agency of Canada (PHAC), 2009a). This may be underestimated as further research identified the prevalence rate for adults in Ontario to be at 8.8% in 2005 (Lipscombe & Hux, 2007). The Canadian Diabetes Association (CDA) estimates that 2.8 million Canadians currently live with diabetes and that number will increase to 3.7 million by 2020 (CDA, 2010).

After adjusting for age distributions between provinces and territories, the age-standardized prevalence of diagnosed diabetes was found to be higher in Newfoundland and Labrador, Nova Scotia, Manitoba, and New Brunswick. Prevalence was lower in the west; Alberta, British Columbia, and Saskatchewan. The prevalence for Ontario was higher than the national average; and for Quebec, the prevalence was lower than the national average (PHAC, 2009a).

The prevalence of diabetes is greater in high risk populations, including Aboriginal, Hispanic, Asian, South Asian and African communities. The age adjusted prevalence for Aboriginals in Canada is 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% (Dyck, Osgood, Lin, Gao & Stang, 2010). Additionally immigrants from high risk populations face increased risks for diabetes than that of the general population, as depicted in Figure 1. 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-Sahara Africa also have a two-fold increase in the risk of diabetes (Creatore, Moineddin, Booth, Manuel, DesMeules, McDermott, et al., 2010).

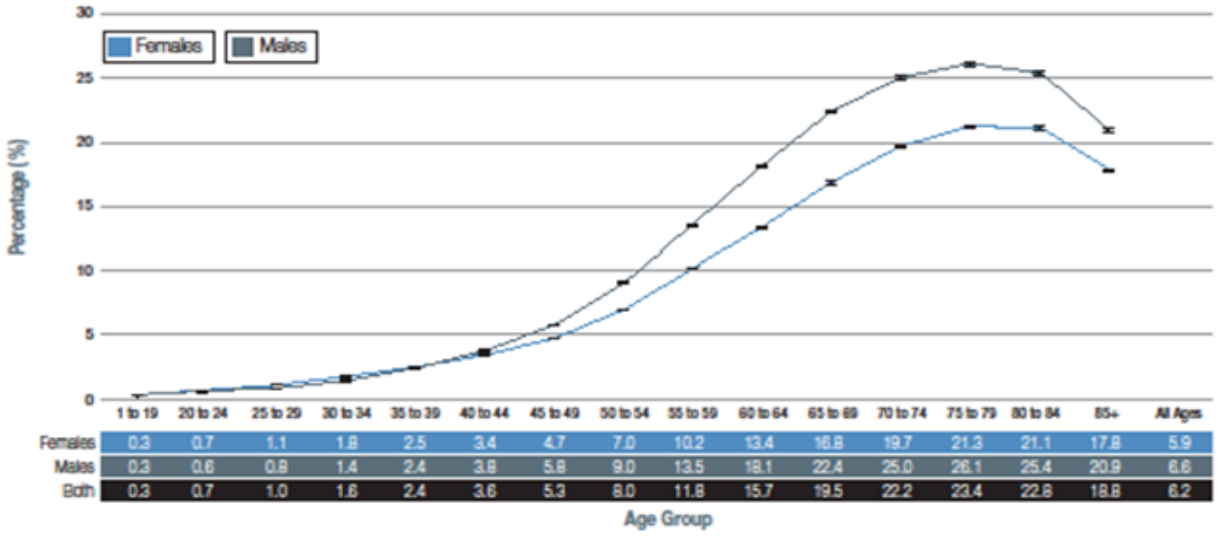
Figure 1: Age-adjusted, sex-specific prevalence of diabetes (with 95% confidence intervals) in 2005 among recent immigrants to Ontario from the 15 countries of origin with the highest prevalence.



Adapted from Creatore et al. CMAJ 2010; 182:781-789.

Furthermore, age, socioeconomic status, and obesity are associated with increased prevalence rates (Sanmartin & Gilmore, 2008; Statistics Canada, 2003; CDA, 2008). The incidence of diabetes rises steadily with age, as shown in Figure 2 (CDA, 2003; PHAC, 2009a; Statistics Canada, 2008).

Figure 2. Incidence percentages of diagnosed diabetes among people aged 1 year or older by age group and sex, in Canada between 2006-2007.



Adapted from the PHAC's National Diabetes Surveillance Survey, 2009.

Results from the Canadian Community Health Survey (CCHS) found that of those Canadians diagnosed with diabetes before the age of 50 years, 63% were South Asians, 57% were Aboriginal, 50% were Chinese, and 35% were self-described as White (Statistics Canada, 2003). 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 those in the lowest income group (Rabi, Edwards, Southern, Svenson, Sargious, Norton, et al., 2006). Finally, weight and obesity also increases the risk of diabetes, with the prevalence among underweight or normal weight individuals at 2.7%, 5.7% in those considered overweight, and 12.1% in those considered obese (Statistics Canada, 2003).

According to PHAC's National Diabetes Surveillance System (NDSS), among adults aged 20 years and older, mortality rates of individuals with diabetes were twice as high, compared to individuals without diabetes (PHAC, 2009a). Diagnosed diabetes significantly shortened life expectancy for all ages. Women and men with diagnosed diabetes in the 25 to 39 year age groups had about an 8-year reduction in life expectancy (PHAC, 2009a). In 2005-2006, adults with diagnosed diabetes were hospitalized: a) three times more often with overall cardiovascular disease including, hypertensive disease (1,397,188), heart failure (49,665), heart attack (93,691), ischaemic heart disease (26,895), and stroke (23,912); b) seven times more often with chronic kidney disease (40,341); and c) 23 times more often with lower limb amputations, than adults without diabetes (3,001) (PHAC, 2009a). 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 (Klein, Klein, Moss, et al., 1984; UK Prospective Diabetes Study (UKPDS) Group; 1998).

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 (Warren, Martin, Kroleswski, et al., 1990; Hamman, 1992). 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 genes, the environment or both (Capes & Anand, 2001).

Type 2 diabetes is often diagnosed 'by chance', usually part of 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 (Harris, Flegal, Cowie, et al., 1998). The classic symptoms of diabetes include polydipsia, polyuria and polyphagia. However, other symptoms common with type 2 diabetes include fatigue, blurred vision, infection, recent weight loss, and/or neurologic symptoms in the feet.

The previous notion that type 2 diabetes was exclusively a result of poor lifestyle choices and not an inheritable metabolic disorder was proven otherwise with evidence from monozygotic twins, demonstrating a strong link in heritability, approximately 34-80%, particularly in certain ethnic groups and parents with diabetes (Rewers & Hamman, 1995). Type 2 diabetes is also

determined by a myriad of other lifestyle factors, including body mass index, waist circumference, diet and activity level (Knowler, Barrett-Connor, Fowler, et al., 2002; Orozco, Buchleitner, Gimenez-Perez, Roque i Figuls, Richter & Mauricio, 2008). 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 3-4 fold increase risk for diabetes than immigrants from Western Europe or North America (Creatore, et al., 2010; Lipscombe & Hux, 2007).

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 in type 1 diabetes, may also be the first manifestation of type 2 diabetes, leading to a diagnosis. The mortality rate of DKA with appropriate management is < 3% (Capes & Anand, 2001). 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% (Capes & Anand, 2001).

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 U.S. adult diabetes population (Kempen, O'Colmain, Leske, et al., 2004). Intensive glucose and blood pressure therapy has been proven to prevent the onset and progression of retinopathy (UK Prospective Diabetes Study Group, 1998). Nephropathy, including chronic kidney disease (CKD) and end-stage renal disease (ESRD) are common and potentially devastating complications of diabetes. It is estimated that 50% of people with diabetes have some form of chronic kidney disease (CIHI, 2001). The course of nephropathy is a step-wise progression, which begins as a subclinical disease, to the early developing of nephropathy, characterized by microalbuminuria (30-300 mg/24 hours), to eventually overt nephropathy (> 300 mg/24 hours) (Steele, 2001). To that end, epidemiological data suggests that 10-20% of individuals with diabetes develop ESRD (Ritz & Stefanski, 1996). Individuals with ESRD are among those at the highest risk for cardiovascular mortality, with a life expectancy of three years after diagnosis (Gerstein, Mann, Yi, et al., 2001).

Neuropathy is a likely complication that will develop in 40-50% of individuals within the first 10 years of the onset of diabetes, and is associated with sensory loss, pain and weakness (Dyck, Kratz, Karnes, et al., 1993). 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 (Bril & Perkins, 2008). Neuropathy may then 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 (Bril & Perkins, 2008).

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)

(Booth, Kapral, Fung, et al., 2006; Poirier, 2008). A meta analysis of over 698 000 individual data found that individuals 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 by about 11% and 17% respectively (Emerging Risk Factors Collaboration, 2010). The NDSS estimates that Canadians with diabetes were three times more likely to be hospitalized for ischemic heart disease and myocardial infarctions, than Canadians without diabetes (PHAC, 2009a). The research evidence thus far demonstrates a modest reduction in CVD, specifically myocardial infarction with glucose intensification in people with type 2 diabetes. The modest effect with glucose intensification suggests a wider approach to diabetes management, targeting blood pressure and lipid management is also required (The ADVANCE Collaborative Group, 2008; The ACCORD Study Group, 2008; Gerstein, 2010).

Risk factors

The most important risk factors for type 2 diabetes are impaired glucose tolerance and/or impaired fasting glucose, or collectively known as prediabetes; in which case glucose levels are above normal targets, but not high enough to diagnosis as diabetes (Ur, Chiasson, Ransom & Rowe, 2008). Gestational diabetes or the delivery of a macrosomic infant (> 9 lbs) are additional risk factors for women. Hypertension, dyslipidemia, abdominal obesity and being overweight are modifiable risk factors for diabetes. Vascular disease, including coronary, cerebral and peripheral, are also risk factors for type 2 diabetes (Ur et al., 2008).

Non-modifiable risk factors include age ($\geq$ 40 years of age), 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 are considered risk factors for type 2 diabetes. Finally, women with polycystic ovary syndrome are also considered high risk for diabetes (Ur, et al., 2008). A list of risk factors for type 2 diabetes is included in Appendix 1.

Rationale for screening

Diabetes is a disease that meets several disease screening principles: 1) diabetes represents an important health problem; 2) the natural history of diabetes is understood; 3) there is a recognizable asymptomatic period in which diabetes can be diagnosed; 4) tests are available that can detect the pre-symptomatic stage of diabetes; 5) screening is ongoing and not an isolated event; and 6) treatment after early detection yields greater benefits than in those with delayed treatment. (Engelgau, Narayan & Herman, 2000). Furthermore, prediabetes is predictive of type 2 diabetes in approximately 50-70% of cases (Canadian Agency for Drugs and Technologies in Health (CADTH), 2009). However, it is important to distinguish between screening and diagnosing. Screening involves attempts to detect asymptomatic disease and screening tests differentiate those at high risk from those at low risk. Screening methods may include simple, noninvasive/invasive and/or stepwise approaches (Calman, 1994; Morrison, 1992; Wilson & Jungner, 1968). In contrast, tests undertaken in individuals with symptoms presenting in a clinical setting are for diagnostic purposes and do not represent disease screening.

The American Diabetes Association (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 (Ur, et al., 2008; ADA, 2010). Adults at high risk for type 2 diabetes should be considered for screening at any age (ADA, 2010). 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, identify, and if required, treat other CVD risk factors (ADA, 2010).

Screening strategies

Historically, screening for type 2 diabetes required fasting blood glucose (FBG) and/or an oral glucose tolerance test (OGTT), which uses both a fasting and a 2 hour post glucose load blood glucose value (Appendix 2). A growing body of literature demonstrates that glycated hemoglobin (A1C), OGTT and FBG are equivalent as predictors of retinopathy and nephropathy development, thus suggesting that A1C, OGTT and FBG may all be valid screening tools for diabetes (Bennett, Guo & Dharmage, 2007). The screening strategies considered in this review are FBG, OGTT, and A1C. The FBG 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. At a laboratory cost of approximately 6-10 dollars (Cdn), the FBG test yields a sensitivity of 40-60% with a specificity of 76% for identifying individuals with diabetes (Kahn, Alperin, Eddy, Borch-Johnson, Buse, Feigelman, et al., 2010; Engelgau, et al., 2000 ; Harris, 1993; CADTH, 2009). A FBG result of ≥ of 7 mmol/L requires a second confirmatory glucose test on another day to diagnosis diabetes (Ur, et al., 2008).

The OGTT, considered to be the gold standard test for screening, uses both a fasting and 2-hour blood glucose level following a 75 gram glucose load. It is indicated when the FBG is not elevated enough to diagnose as diabetes (< 7 mmol/L), but yet above fasting blood glucose levels (≥ 5.6 mmol/L) (Ur, et al., 2008). The 2-hour blood glucose test in an OGTT provides a sensitivity of 97%, with a specificity of 100% (Harris, 1993). The cost of an OGTT is approximately 25-30 dollars (Cdn) (personal communication, Laboratory Services, Hamilton Health Sciences (HHS), September 15, 2009). If the FBG and 2-hour blood glucose levels are elevated (≥ 7 mmol/L and ≥ 11.1 mmol/L), then a diagnosis of diabetes can be made (Ur, et al., 2008).

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 (Garlick et al., 1983). The A1C has a sensitivity ranging from 78-81% and a specificity of 79-84% (Bennett et al., 2007). It is relatively easy to collect, as the A1C test does not require fasting and has a laboratory cost of approximately 6-19 dollars (Cdn) (CADTH, 2009). 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. In Canada, the A1C test is currently not recommended for screening type 2 diabetes (Ur, et al., 2008). 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 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% would lead to a diagnosis of diabetes (ADA, 2010).

An additional type 2 diabetes screening tool that is currently being piloted is the CANRISK questionnaire; a 16 item survey designed to predict an individual's ten year risk of developing type 2 diabetes (CADTH, 2009). The CANRISK is modeled on the validated Finnish questionnaire, (FINDRISC) and includes questions about family history, body weight, lifestyle and other factors (PHAC, 2009b). Participants aged 40-75 years are currently piloting this step wise screening approach which does not require laboratory testing, unless an individual is identified as high risk for type 2 diabetes. Currently the CANRISK method is detecting 5% new cases of undiagnosed diabetes and 15% new prediabetes cases, which would otherwise not be detected through FBG tests (PHAC, 2009b). However, the CANRISK questionnaire is currently being tested for validity across Canada.

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 to 15,000 dollars annually, as a result of medication use, glucose monitoring, supplies, and complication prevention and management (CDA, 2010). 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 (Edelman, Olsen, Dudley, Harris & Oddone, 2002). The health care costs of diabetes management are tremendous, as by 2020, it is estimated that diabetes will cost the Canadian healthcare system 16.9 billion dollars annually (CDA, 2010).

A recent review determined that the A1C test may be the most cost effective screening test for diabetes, as it is convenient and it also reflects post prandial glucose excursions (Waugh, Scotland, McNamee, Gillett, Brennan, Williams, et al., 2007). The OGTT was deemed too expensive and inconvenient, and the FBG test was incapable of detecting individuals with impaired glucose tolerance (Waugh, et al., 2007). The authors also conclude that screening for diabetes appears to be cost-effective for the 40-70-year age group, but even in the 40-49-year age group, the incremental cost-effectiveness ratio for screening versus no screening was 10,216 pounds or approximately 15,630 (Cdn) dollars per quality-adjusted life-year. However, the authors caution that the cost-effectiveness of screening for type 2 diabetes is determined as much by, if not more than, the degree of glycemic control and future treatment, than by assumptions related to the screening process (Waugh, et al., 2007).

Interventions/treatments

Individuals with a prediabetes diagnosis are strongly encouraged to undertake lifestyle modifications that include increasing physical activity, altering one's diet and weight loss. 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% (Knowler et al., 2002). The initiation of pharmaceutical agents such as an alpha glucosidase inhibitor, biguanide or thiazolidinedione may also prevent the progress to type 2 diabetes by 30-60% respectively (Ur, et al., 2008).

The goals of treatment for type 2 diabetes are similar to prediabetes treatment, in that lifestyle modification is a cornerstone of management. Pharmacotherapy plays a more integral part in the

treatment of type 2 diabetes, with the initiation of oral medications if glucose targets are not obtained after 3 months of lifestyle management (Harper, Hanna, Woo, Dawson, Yale, MacCallum, et al., 2008). For individuals with marked hyperglycemia at the time of diagnosis, as evidenced by an A1C $\geq$ 9%, multiple oral agents may be considered, along with insulin (Harper, et al., 2008). The nature of type 2 diabetes is one that is progressive and dynamic and requires ongoing evaluation of management every three to six months. The goals of type 2 diabetes management are to ultimately achieve euglycemia or near normal glycemic targets, while minimizing adverse events (e.g. hypoglycemia), and preventing short and long term complications.

Current clinical practice.

In Canada, the CDA's clinical practice guidelines recommends that all individuals should be evaluated annually for type 2 diabetes on the basis of demographic and clinical criteria (Grade D recommendation, consensus) (Ur, et al., 2008). However, screening for type 2 diabetes using a FBG test should be performed every three years in adults $\geq$ 40 years of age (Grade D recommendation, consensus). More frequent FBG 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 FBG levels suggestive of prediabetes (5.6-6.9 mmol/L) (Grade D recommendation, consensus) (Ur, et al., 2008).

A study using administrative health data examined diabetes screening patterns using laboratory tests (FBG, 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 FBG test, 6.0% were screened using an A1C test and less than 1% of Ontarians underwent OGTT testing in any year between 1995–2005 (Wilson, Lipscombe, Rosella & Manuel, 2009). 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 (Wilson, et al., 2009).

2. Previous Reviews and CTFPHC Recommendations

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 FBG test of $\geq$ 7.8 mmol/L on at least two occasions should be diagnosed with diabetes (ECCDAB, 1992). In 1998, the clinical practice guidelines were updated and provided clear recommendations for the screening of type 2 diabetes, including testing for diabetes using a FBG every three years in adults $\geq$ 45 years of age. Those at high risk were recommended to be tested earlier and more often (Grade D recommendation, consensus) (Meltzer, Leiter, Daneman, Gerstein, Lau, Ludwig, et al., 1998). In 2003, the CDA's clinical practice expert committee updated the guidelines to include screening for diabetes in adults $\geq$ 40 years of age, every three years with a FBG test (CDA, 2003).

In 2005, the CTFPHC published a guideline for the screening of type 2 diabetes mellitus to prevent vascular complications (Feig, et al., 2005). 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

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) (Harris, Donahue, Rathore, Frame, Woolf & Lohr, 2003).

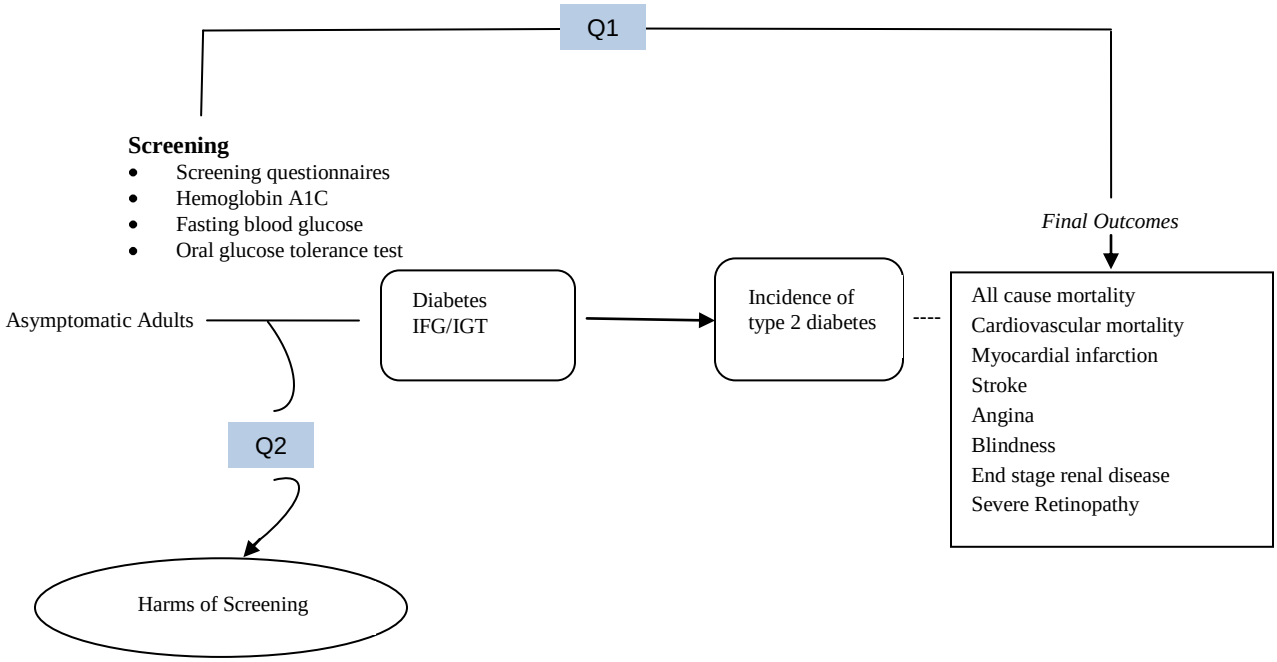
In 2008, the USPSTF group updated and revised the recommendations to the following:

- 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) (Norris, et al., 2008).

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.

3. Analytic Framework

Figure 3: Analytic framework for screening for type 2 diabetes.



Abbreviation: Q: Question. (Adapted from Norris, et al., 2008).

4. Key Questions

1. What is the evidence for the clinical benefit of screening for type 2 diabetes using questionnaires, fasting blood 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, fasting blood 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 to improve health outcomes?

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 (IFG) and impaired glucose tolerance (IGT) 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?

5. Literature Search and Review

USPSTF (Norris et al, 2008) 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 five questions regarding diabetes screening, diagnosis and potential adverse effects. Clinical Trials.gov was also searched for relevant trials. There were separate searches for adverse effects, adverse effects of treatment, hemoglobin A1C, screening and treatment. To answer key questions 1 and 2 the same search strategy will be implemented, and all searches will be updated to July 2010. To answer contextual questions 1 - 7, focused searches for systematic reviews and randomized control trials will be done of the same databases from 2005 to the present. For contextual questions 2-4, observational or epidemiological studies may be included, depending on the availability of data from systematic reviews and randomized controlled trials. The search for cost-effectiveness studies will include simulation modeling for cost-effectiveness and cost-benefit analysis.

6. Inclusion/ Exclusion Criteria

The following inclusion criteria will be utilized (Norris, et al., 2008):

Methods:
English language, published randomized controlled trials, observational studies and systematic reviews for the effectiveness or adverse effects of screening and diagnosis of type 2 diabetes will be included.

Population:
Asymptomatic adults 18 years of age or older who are at high risk or average risk for type 2 diabetes complications (Appendix 1) will be included. 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 will not be redone for studies including those between the ages of 18-20 years for

2001-July 2007; however, any new reports since July 2007 that studied people 18 years and over will be included.

Interventions:
Screening methods: Studies using the FBG, OGTT and A1C will be considered for this updated review. Screening questionnaires such as the CANRISK and FINRISK will be included in the search to determine if a two phase screening approach is effective.

Comparators:
The comparator for screening will be no screening or studies that compare the screening tests.

Outcomes:
The outcomes will focus on final health outcomes primarily: all cause mortality; cardiovascular mortality; stroke; myocardial infarction; end stage renal disease; angina; blindness; and severe retinopathy. For prediabetes, the intermediate outcome examined was incidence of type 2 diabetes, as this outcome was the primary outcome for the studies included. Outcomes will be prioritized by the Working Group using the GRADE process.

Harms of screening will also be collected. Harms will be prioritized by the Working Group using the GRADE process.

7. Quality and strength of evidence criteria

The retrieved included studies will be reviewed according to the criteria set out in the CTFPHC Procedure Manual, 2009), Appendices VII and VIII.

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Appendix 1: Risk factors for 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

*Associated with insulin resistance

(Adapted from Ur, E., Chiasson, JL., Ransom, et al., 2008).

Appendix 2: Diagnostic criteria for impaired fasting glucose, impaired glucose tolerance and diabetes since 1992.

		1992	1998	2003	2008
Prediabetes	IFG	n/a	6.1-6.9	6.1-6.9	6.1-6.9
	IGT (2hr)	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 hr	>11.1	≥11.1	≥11.1	≥11.1

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.

Appendix 3: USPSTF 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$)) or lifestyl$).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$)) or lifestyl$).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$)) or lifestyl$).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 Sulfonylurea 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 Alc

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 (Educat$ 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 (Educat$ 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 antagon$ 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$)).mp. [mp=title, abstract, full text, keywords, capti
text]
47 4 and 46
48 Exercis$.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, captio
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 (Educat$ 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
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104 exp Placebos/
105 placebo$.mp.
106 random$.mp.
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108 (latin adj square).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
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111 110 not 99
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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
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129 limit 128 to yr="2001 - 2003"
130 limit 128 to yr="2004 - 2007"

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