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REVIEW

Screening for Type 2 Diabetes Mellitus: A Systematic Review for the U.S. Preventive Services Task Force

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Background: Screening for type 2 diabetes mellitus could lead to earlier identification and treatment of asymptomatic diabetes, impaired fasting glucose (IFG), or impaired glucose tolerance (IGT), potentially resulting in improved outcomes.

Purpose: To update the 2008 U.S. Preventive Services Task Force review on diabetes screening in adults.

Data Sources: Cochrane databases and MEDLINE (2007 through October 2014) and relevant studies from previous Task Force reviews.

Study Selection: Randomized, controlled trials; controlled, observational studies; and systematic reviews.

Data Extraction: Data were abstracted by 1 investigator and checked by a second; 2 investigators independently assessed study quality.

Data Synthesis: In 2 trials, screening for diabetes was associated with no 10-year mortality benefit versus no screening (hazard ratio, 1.06 [95% CI, 0.90 to 1.25]). Sixteen trials consistently found that treatment of IFG or IGT was associated with delayed progression to diabetes. Most trials of treatment of IFG or IGT found no effects on all-cause or cardiovascular mortality, although lifestyle modification was associated with decreased risk for both outcomes after 23 years in 1 trial. For screen-detected diabetes, 1 trial found no effect of an intensive multifactorial intervention on risk for all-cause or cardiovascular mortality versus standard control. In diabetes that was not specifically screen-detected, 9 systematic reviews found that intensive glucose control did not reduce risk for all-cause or cardiovascular mortality and results for intensive blood pressure control were inconsistent.

Limitation: The review was restricted to English-language articles, and few studies were conducted in screen-detected populations.

Conclusion: Screening for diabetes did not improve mortality rates after 10 years of follow-up. More evidence is needed to determine the effectiveness of treatments for screen-detected diabetes. Treatment of IFG or IGT was associated with delayed progression to diabetes.

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In the United States, approximately 21 million persons received diabetes diagnoses in 2010, and an estimated 8 million cases were undiagnosed; roughly 90% to 95% of them have type 2 diabetes mellitus (1, 2). Prevalence of diabetes among U.S. adults has increased, from approximately 5% in 1995 to 8% in 2010 (3). Diabetes is the leading cause of kidney failure, nontraumatic lower-limb amputations, and blindness; a major cause of heart disease and stroke; and the seventh-leading cause of death in the United States (1).

Risk factors for diabetes include obesity, physical inactivity, smoking, and older age (1). Diabetes is more common among certain ethnic and racial minorities (1, 3). Type 2 diabetes is caused by insulin resistance and relative insulin deficiency, resulting in the inability to maintain normoglycemia. Diabetes typically develops slowly (4, 5), although microvascular disease, such as retinopathy and neuropathy, may be present at the time of diagnosis due to vascular damage during the subclinical phase (4, 6).

Screening asymptomatic persons (those without signs or symptoms of hyperglycemia and no clinical sequelae) may lead to earlier identification and earlier or more-intensive treatments, potentially improving health outcomes (2). Strategies for screening include routine screening or targeted screening based on the presence of risk factors, such as obesity or hypertension. In 2008, the U.S. Preventive Services Task Force (USPSTF) recommended diabetes screening in asymptomatic adults with sustained blood pressure (BP) (treated or untreated) greater than 135/80 mm Hg (B recommendation). Although direct evidence on benefits and harms of screening was not available, the recommendation was based on the ability of screening to identify persons with diabetes and evidence that more-intensive BP treatment was associated with reduced risk for cardiovascular events, including cardiovascular mortality, in patients with diabetes and hypertension. The USPSTF found insufficient evidence to assess the balance of benefits and harms of screening in adults without elevated BP (I statement). It also found that lifestyle and drug interventions for impaired fasting glucose (IFG) or impaired glucose tolerance (IGT), defined as a hemoglobin A_{1c} level of 5.7% to 6.4% or a fasting blood glucose level between 5.55 and 6.94 mmol/L (100 and 125 mg/dL) (2), were associated with reduced risk for progression to diabetes (7–14). Other groups also recommend screening persons with risk factors (15–20).

This article updates previous USPSTF reviews (21–23) on diabetes screening in nonpregnant adults.

Methods

Scope of the Review

We developed a review protocol and analytic framework (Appendix Figure 1, available at www.annals.org) that included the following key questions:

1. Is there direct evidence that screening for type 2 diabetes, IFG, or IGT among asymptomatic adults improves health outcomes?

2. What are the harms of screening for type 2 diabetes, IFG, or IGT?

3. Do interventions for screen-detected or early diabetes, IFG, or IGT provide an incremental benefit in health outcomes compared with no interventions or initiating interventions after clinical diagnosis?

4. What are the harms of interventions for screen-detected or early diabetes, IFG, or IGT?

5. Is there evidence that more-intensive glucose, BP, or lipid control interventions improve health outcomes in adults with type 2 diabetes, IFG, or IGT compared with traditional control? Is there evidence that aspirin use improves health outcomes in these populations compared with nonuse?

6. What are the harms of more-intensive interventions compared with traditional control in adults with type 2 diabetes, IFG, or IGT?

7. Do interventions for IFG or IGT delay or prevent the progression to type 2 diabetes?

The full report (24), on which this article is based, provides detailed methods and data for the review, including search strategies, evidence tables, and quality ratings of individual studies (available at www.uspreventiveservicestaskforce.org). The full report includes an additional key question on whether the effects of screening or interventions for screen-detected or early diabetes, IFG, or IGT vary by subgroups; effects of treatments on microvascular outcomes; and evidence on effects of more- versus less-intensive lipid control and aspirin use (24).

Data Sources and Searches

A research librarian searched the Cochrane Central Register of Controlled Trials and the Cochrane Database of Systematic Reviews and MEDLINE (2007 to October 2014). We supplemented electronic searches by reviewing previous USPSTF reports and reference lists of relevant articles.

Study Selection

At least 2 reviewers independently evaluated each study to determine inclusion eligibility using predefined inclusion and exclusion criteria (**Appendix Figure 2**, available at www.annals.org). Because of the limited evidence on treatment of screen-detected diabetes (key question 5), we also included studies of treatment of early diabetes (defined as a pharmacologically untreated hemoglobin A_{1c} level <8.5% or diabetes diagnosis in the past year) that was not specifically screen-detected. **Appendix Figure 3** (available at www.annals.org) summarizes the selection of literature.

Data Abstraction and Quality Rating

One investigator abstracted details about the study design, patient population, setting, screening method, interventions, analysis, follow-up, and results. A second investigator reviewed data abstraction for accuracy. Two investigators independently applied criteria developed by the USPSTF (25) to rate the quality of each study as good, fair, or poor. Discrepancies were resolved through a consensus process.

Data Synthesis and Analysis

We conducted meta-analyses to calculate risk ratios (RRs) on effects of interventions with the DerSimonian–Laird random-effects model using Stata, version 12 (StataCorp). Statistical heterogeneity was assessed using the I^2 statistic (26). When statistical heterogeneity was present, we performed sensitivity analyses using the profile likelihood method because the DerSimonian–Laird model results in overly narrow 95% CIs (27). Two studies (28–30) that used a 2 × 2 factorial design reported no interaction between treatments and were analyzed as a 2-group parallel group trial for the comparison of interest. When studies evaluated several lifestyle strategies, we combined the lifestyle groups. We included all studies in meta-analyses, regardless of event rates. For rare events (incidence <1%), we calculated the Peto odds ratio (31). We stratified results by drug class or lifestyle intervention and performed additional sensitivity analyses based on study quality and presence of outlier trials. We assessed the aggregate internal validity (quality) of the body of evidence for each key question (good, fair, or poor) using methods developed by the USPSTF, based on the quality of studies, precision of estimates, consistency of results, and directness of evidence (25).

Role of the Funding Source

This research was funded by the Agency for Healthcare Research and Quality (AHRQ) under a contract to support the work of the USPSTF. Investigators worked with USPSTF members and AHRQ staff to develop and refine the scope, analytic framework, and key questions; resolve issues arising during the project; and finalize the report. The AHRQ had no role in study selection, quality assessment, synthesis, or development of conclusions. The AHRQ provided project oversight; reviewed the draft report; and distributed the draft for peer review, including to representatives of professional societies and federal agencies. It also performed a final review of the manuscript to ensure that the analysis met methodological standards. The investigators are solely responsible for the content and the decision to submit the manuscript for publication.

RESULTS

Benefits of Screening

Two randomized, controlled trials (ADDITION [Anglo-Danish-Dutch Study of Intensive Treatment in People With Screen Detected Diabetes in Primary Care]–Cambridge [Cambridge, United Kingdom] trial [*n* = 19 226] [32], rated good-quality, and a trial conducted in Ely, United Kingdom [*n* = 4936] [33], rated fair-quality) evaluated effects of diabetes screening versus no screening on mortality (**Appendix Table 1**, available at www.annals.org). The ongoing ADDITION trial includes sites in Cambridge, the Netherlands, and Denmark on intensive versus standard treatment of screen-detected diabetes; however, only the Cambridge site

had a no-screening component (34). Mean age ranged from 51 to 58 years, 36% to 54% of participants were women, and follow-up was 10 years in both studies (32, 33). In ADDITION-Cambridge, persons at high risk for diabetes, based on known risk factors, were randomly assigned in clusters by clinic site to screening or no screening (32). The Ely study randomly enrolled participants (not selected based on high risk for diabetes) to screening or no screening from a single practice site (33). Seventy-eight percent of participants (11 737 of 15 089) invited to screening had screening in the ADDITION trial (32); 68% of participants in the Ely study were screened (33). Methodological shortcomings in the Ely study included unclear randomization and allocation concealment methods, with baseline differences between groups.

Screening was not superior to no screening in reducing risk for all-cause mortality in either the ADDITION (hazard ratio [HR], 1.06 [95% CI, 0.90 to 1.25]) (32) or Ely (unadjusted HR, 0.96 [CI, 0.77 to 1.20]; adjusted HR, 0.79 [CI, 0.63 to 1.00]) (33) trial, with point estimates close to 1. The ADDITION trial also found that screening was not associated with reduced risk for cardiovascular mortality (HR, 1.02 [CI, 0.75 to 1.38]), cancer-related mortality (HR, 1.08 [CI, 0.90 to 1.30]), or diabetes-related mortality (HR, 1.26 [CI, 0.75 to 2.10]) (32). Neither study reported nonmortality health outcomes.

Harms of Screening

A fair-quality pilot study of 116 persons invited for screening in the ADDITION trial found that a new diagnosis of diabetes was associated with increased short-term anxiety 6 weeks after screening, compared with no new diagnosis, based on short-form Spielberger State-Trait Anxiety Inventory scores (46.7 vs. 37.0; P = 0.031) (35). Studies lasting longer than the ADDITION and Ely trials (≥1 year) found no negative psychological effects associated with invitation to screening or notification of positive diabetes status (36, 37). We identified no studies estimating the rate of false-positive test results, psychological effects, or other harms associated with a diagnosis of IFG or IGT.

Benefits of Treating Screen-Detected or Early diabetes, IFG, or IGT

A randomized trial conducted in Da Qing, China, of overweight (mean body mass index [BMI], 25.8 kg/m^2) persons with IGT found that, versus usual care, a 6-year lifestyle intervention was associated with reduced risk for all-cause (HR, 0.71 [CI, 0.51 to 0.99]) and cardiovascular (HR, 0.59 [CI, 0.36 to 0.96]) mortality after 23 years of follow-up (38). The trial was rated fair-quality because of unclear randomization and allocation concealment methods. This study had previously reported no difference in these outcomes after 20-year follow-up (39). Other trials of lifestyle interventions in persons with IFG or IGT and elevated BMI (40, 41) or newly diagnosed diabetes (42–44) with shorter follow-up also reported no beneficial effects on all-cause or cardiovascular mortality (**Appendix Table 2**, available at www.annals.org).

Trials of pharmacologic interventions (alone [28–30, 45–49] or in combination with lifestyle modification [50] vs. placebo or usual care) for early diabetes, IFG, or IGT found few differences in health outcomes, including all-cause and cardiovascular mortality (**Appendix Table 2**). Mean age ranged from 45 to 64 years, and studies enrolled persons who were overweight (BMI >25.0 kg/m^2) or obese (BMI >30.0 kg/m^2). Five studies were rated good-quality and 3 were rated fair-quality; common methodological shortcomings in the fair-quality studies included unclear randomization and allocation concealment methods. Although individual studies were generally underpowered to detect these outcomes and few events were reported in most studies, pooled estimates were close to 1. Based on 8 studies (10, 28, 45–48, 51, 52) of glucose-lowering agents, including 3 (10, 51, 52) from the previous USPSTF review (22), the pooled odds ratio for all-cause mortality was 1.01 (CI, 0.87 to 1.18; I^2 = 28%) (**Appendix Figure 4**, available at www.annals.org). For cardiovascular mortality, the pooled odds ratio was 1.06 (CI, 0.84 to 1.35; I^2 = 7%) based on 5 studies (28, 48, 52–54) of glucose-lowering agents, including 3 studies (52–54) involved in the previous USPSTF review (22) (**Appendix Figure 5**, available at www.annals.org).

Harms of Treating Screen-Detected or Early diabetes, IFG, or IGT

Of 4 good-quality and 5 fair-quality trials that reported harms associated with interventions (28–30, 40, 43–49), 1 study was conducted in persons with screen-detected or early diabetes and the others enrolled persons with IFG or IGT. No study was specifically designed to assess harms. There were few differences between medications or lifestyle modification versus placebo or usual care in risk for harms (**Appendix Table 2**). One trial found that, compared with placebo, acarbose was associated with greater risk for withdrawal because of adverse events (47). Rosiglitazone was associated with increased congestive heart failure in 1 trial, although the estimate was imprecise (HR, 7.04 [CI, 1.60 to 31]) (30). One study found that nateglinide was associated with increased risk for hypoglycemia versus placebo (RR, 1.73 [CI, 1.57 to 1.92]), and valsartan was associated with increased risk for hypotension-related adverse events (RR, 1.16 [CI, 1.11 to 1.23]) (28, 29).

Benefits of More Intensive Treatment Versus Standard Treatment

The treatment phase of the ADDITION-Europe trial evaluated effects of more-intensive multifactorial treatment of screen-detected diabetes (55–57). It was rated fair-quality because of unclear methods of randomization and allocation concealment. The mean hemoglobin A_{1c} level was 6.5%, approximately one fourth of participants were smokers, mean BMI was 31.5 kg/m^2, and 6% to 7% of participants had a previous myocardial infarction (MI). Participants were randomly assigned to a multifactorial intervention that included use of intensive glucose-, BP-, and lipid-lowering targets (hemoglobin A_{1c} level <7.0%, BP <135/85 mm Hg, and total cholesterol level ≤4.5 to 5.0 mmol/L [≤173.7 to 193.1 mg/

dL]) plus a lifestyle education component (n = 1678) versus treatment to standard targets according to local guidelines (n = 1379). Participants were followed for 5 years or until their first cardiovascular event (cardiovascular mortality, nonfatal MI or stroke, revascularization, or [nontraumatic] amputation) (55).

After adjustment for country, intensive treatment was not associated with reduced risk for first cardiovascular event (HR, 0.83 [CI, 0.65 to 1.05]) (55), all-cause (HR, 0.83 [CI, 0.65 to 1.05]) or cardiovascular (HR, 0.88 [CI, 0.51 to 1.51]) mortality, stroke (HR, 0.98 [CI, 0.57 to 1.71]), MI (HR, 0.70 [CI, 0.41 to 1.21]), or revascularization (HR, 0.79 [CI, 0.52 to 1.18]), although most estimates favored intensive therapy. Mortality and cardiovascular event rates were lower than anticipated, with little difference between groups in final hemoglobin A_{1c} and total cholesterol levels and BP (55). There was also no difference in self-reported measures of general and diabetes-specific quality of life (57).

In persons with diabetes that was not specifically screen-detected, 9 good-quality systematic reviews found consistent evidence that intensive glucose lowering to a target hemoglobin A_{1c} level less than 6.0% to 7.5% was not associated with decreased risk for all-cause or cardiovascular mortality compared with less-intensive therapy (**Appendix Table 3**, available at www.annals.org) (58–66). One of the largest and most recent reviews (60) analyzed evidence from 14 trials (n = 28 614), including several large, good-quality trials (67–69) published since the previous USPSTF report. Intensive glucose-lowering therapy was consistently associated with reduced risk for nonfatal MI in 6 reviews (RR range, 0.83 to 0.87) (58, 60, 61, 63, 64, 66).

Intensive BP-lowering was associated with reduced risk for all-cause mortality (RR, 0.90 [CI, 0.82 to 0.98]; I^2 = 0%) and stroke (RR, 0.83 [CI, 0.73 to 0.95]; I^2 = 27%) in 1 good-quality systematic review (70), but individual trials defined intensive BP control differently and some trials showed inconsistent effects (**Appendix Table 4**, available at www.annals.org). One recent large trial (n = 4732) (71) found no difference between a systolic BP target of 140 mm Hg and 120 mm Hg in risk for all-cause (RR, 1.11 [CI, 0.89 to 1.38]) or cardiovascular (RR, 1.04 [CI, 0.73 to 1.48]) mortality, whereas another (n = 11 140) (72, 73) found that, compared with placebo, the addition of an angiotensin-converting enzyme inhibitor plus a diuretic was associated with decreased risk for all-cause (RR, 0.87 [CI, 0.76 to 0.98]) and cardiovascular (RR, 0.33 [CI, 0.15 to 0.74]) mortality. Results from older studies (22) were also mixed and characterized by variability in antihypertensive treatments and baseline, target, and achieved BP levels (74–79).

Harms of More Intensive Treatment Versus Standard Treatment

The ADDITION-Netherlands study found no difference between intensive multifactorial treatment versus standard treatment in risk for severe hypoglycemia after 1 year of follow-up, but the event rate was low and the estimate was imprecise (0.4% vs. 0.0%; RR, 2.86 [CI, 0.12 to 70]) (80).

In persons with diabetes not specifically screen-detected, intensive glucose control was associated with increased risk for severe hypoglycemia and serious nonhypoglycemia adverse events requiring medical intervention (**Appendix Table 3**) (59, 60, 63, 65). Harms of other interventions, including intensive BP-lowering and intensive multifactorial interventions, were mixed (71, 72, 81, 82).

Benefits of Treatment in IFG or IGT on the Delay or Prevention of Progression to Diabetes

We identified 14 randomized, controlled trials (28, 29, 38–40, 45–47, 49, 83–89), 1 quasi-randomized trial (48), and 1 cohort study (90) on the effects of interventions for IFG or IGT on risk for progression to diabetes (**Appendix Table 5**, available at www.annals.org) (28, 29, 38–40, 45–49, 83–90). Three trials were rated good-quality (28, 29, 46, 49), and the remainder were fair-quality. Methodological shortcomings in the fair-quality studies included unclear randomization and allocation concealment methods, unblinded design, and lack of intention-to-treat analysis. The studies assessed lifestyle interventions (6 studies) (38, 40, 84, 86–88), pharmacologic interventions (8 studies in 9 publications) (28, 29, 45–49, 89, 90), and multifactorial interventions (2 studies) (83, 85). Treatment duration ranged from 6 months to 6 years, with follow-up extending up to 23 years. Mean age ranged from 45 to 65 years. In all but 1 study (86), participants were overweight or obese. Mean total cholesterol levels ranged from 4.3 to 5.9 mmol/L (166 to 228 mg/dL) (**Appendix Table 5**).

Lifestyle Interventions

Lifestyle interventions were associated with decreased risk for progression to diabetes, based on 6 studies (38, 40, 84, 86–88), including 4 (7–10) that were in the previous USPSTF review (22) (pooled RR, 0.55 [CI, 0.43 to 0.70]; I^2 = 77%; profile likelihood estimate, 0.57 [CI, 0.43 to 0.70]) (**Appendix Figure 6**, available at www.annals.org). After exclusion of the Da Qing trial, an outlier study with very long (23-year) follow-up (38), we found similar results (pooled RR, 0.53 [CI, 0.44 to 0.63]; I^2 = 25%).

Pharmacologic Interventions

Eight studies published since the previous USPSTF review assessed the effect of pharmacologic interventions (28, 45–49, 89, 90). Thiazolinediones were associated with decreased risk for progression to diabetes (3 studies; pooled RR, 0.50 [CI, 0.28 to 0.92]; I^2 = 92%) (**Appendix Figure 7**, available at www.annals.org) (45, 48, 52). Statistical heterogeneity was substantial, and the estimate was no longer statistically significant using the profile likelihood method (RR, 0.51 [CI, 0.23 to 1.06]). Excluding the Indian Diabetes Prevential Programme-2 trial (48), which was conducted in India among mostly male participants, eliminated much of the heterogeneity (RR, 0.42 [CI, 0.37 to 0.47]; I^2 = 36%).

Table. Summary of Evidence

Main Findings From Previous USPSTF Report	Number and Type of Studies Identified for Update*	Limitations	Consistency	Applicability	Summary of Findings	Overall Quality†
KQ 1. Is there direct evidence that screening for type 2 diabetes, IFG, or IGT among asymptomatic adults improves health outcomes?						
No RCTs on the effects of screening for diabetes on clinical outcomes 1 case–control study found no association between screening and improvement in microvascular outcomes	2 RCTs	Mortality outcomes limited to 10 y	Consistent	Both trials in the United Kingdom; ADDITION in high-risk population; Ely trial in average-risk population	2 RCTs found no effect on all-cause or CV mortality with screening vs. no screening after 10 y	Fair
KQ 2. What are the harms of screening for type 2 diabetes, IFG, or IGT?						
No evidence on serious psychological or other adverse effects associated with a new diagnosis of diabetes	3 RCTs	Small sample size in study showing that short-term anxiety was associated with invitation to screening	Consistent	All trials in the United Kingdom; 2 studies in high-risk population; 1 study in average-risk population	In the short term, being invited to screening increased anxiety vs. not being invited; in longer-term follow-up (>1 y), anxiety or depression did not differ between persons with negative screening results for diabetes and those unscreened or in those with positive screening results for diabetes vs. those with negative screening results	Fair
KQ 3. Do interventions for screen-detected or early type 2 diabetes, IFG, or IGT provide an incremental benefit in health outcomes compared with no interventions or initiating interventions after clinical diagnosis?						
No clear evidence on the benefit of treatment in the screen-detected diabetes population or comparing treatment effects in persons with screen- and clinically detected diabetes, although 1 trial found that acarbose was associated with reduced risk for MI	13 RCTs (16 publications)	Most studies underpowered to evaluate mortality and other CV outcomes and were limited to 3-y follow-up with few events; evidence often limited to a single study per drug	Consistent	Few studies in a nonwhite population; some studies required patients to have CVD or risk factors for diabetes or CVD; others excluded patients with CVD	Most studies found no benefit on all-cause or CV mortality with glucose-lowering or antihypertensive medications or with lifestyle modification, although 1 study of lifestyle modification found reduced risk for all-cause and CV mortality after 23-y follow-up	Fair

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Main Findings From Previous USPSTF Report	Number and Type of Studies Identified for Update*	Limitations	Consistency	Applicability	Summary of Findings	Overall Quality†
KQ 4. What are the harms of interventions for screen-detected or early type 2 diabetes, IFG, or IGT?						
No studies reported serious harms No studies done in persons with screen-detected diabetes reported harms Studies done in persons with IFG or IGT included in the previous report found no differences in withdrawal rates between lifestyle or pharmacologic interventions and control	9 RCTs (11 publications)	Few studies in screen-detected or early diabetes, IFG, or IGT populations; studies not designed to evaluate harms	Consistent	Few studies in a nonwhite population; some studies required patients to have CVD or risk factors for diabetes or CVD; others excluded patients with CVD	Little difference between active medication or lifestyle modification vs. placebo or usual care in risk for harms Acarbose was associated with greater withdrawal rates; single-study evidence was available for increased risk for any adverse event with pioglitazone and voglibose, increased hypoglycemia with nateglinide, and increased hypotension with valsartan	Fair
KQ 5. Is there evidence that more intensive glucose, BP, or lipid control interventions improve health outcomes in adults with type 2 diabetes, IFG, or IGT compared with traditional control? Is there evidence that aspirin use improves health outcomes in these populations compared with nonuse?						
No evidence in a screen-detected diabetes population Studies that enrolled persons with established diabetes found no clear evidence of a differential effect on individual health outcomes with intensive BP or lipid lowering or with aspirin for primary prevention of CVD	Persons with screen-detected diabetes: 1 RCT (3 publications) Persons with diabetes not specifically screen-detected: 9 systematic reviews and 2 RCTs (3 publications)	Some studies were underpowered because event rates were lower than anticipated Limited evidence in persons with IFG, IGT, and screen-detected diabetes	Persons with screen-detected diabetes: Consistent Persons with diabetes not specifically screen-detected: Glucose control: Consistent BP control: Inconsistent	Only 1 fair-quality trial enrolled persons with screen-detected diabetes; other studies enrolled persons with established diabetes	Persons with screen-detected diabetes: Use of an intensive multifactorial glucose-, BP-, and lipid-lowering intervention did not significantly reduce risk for all-cause or CV mortality, MI, stroke, or revascularization after 5-y follow-up Persons with diabetes not specifically screen-detected: Intensive glucose-lowering did not significantly decrease risk for all-cause or CV mortality but was associated with a significant reduction in risk for nonfatal MI in systematic reviews Intensive BP lowering reduced risk for all-cause mortality and stroke in a good-quality systematic review; however, results from recently published trials were mixed on the effect on health outcomes, although different interventions and BP targets were used in these studies	Good

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Main Findings From Previous USPSTF Report	Number and Type of Studies Identified for Update*	Limitations	Consistency	Applicability	Summary of Findings	Overall Quality†
KQ 6. What are the harms of more intensive interventions compared with traditional control in adults with type 2 diabetes, IFG, or IGT?						
Not assessed	4 systematic reviews and 6 RCTs	Trials generally not designed to assess harms; interventions and targets varied	Consistent for effects of glucose-lowering therapy; inconsistent for BP-lowering therapy	Unclear; no evidence in screen-detected population	No clear differences in harms of intensive multifactorial intervention compared with standard care in persons with screen-detected diabetes In persons with diabetes not specifically screen-detected, intensive glucose lowering was consistently associated with increased risk for severe hypoglycemia; evidence on harms of intensive BP lowering was mixed	Fair
KQ 7. Do interventions for IFG or IGT delay or prevent the progression to type 2 diabetes?						
6 studies of lifestyle interventions and 8 studies of pharmacologic interventions found some evidence that intervention delays or prevents progression	Lifestyle interventions: 6 RCTs Pharmacologic interventions: 8 RCTs (9 publications) Multifactorial interventions: 2 RCTs	Some studies underpowered; lack of blinding in many studies; content of interventions varied widely	Lifestyle interventions: Consistent Pharmacologic interventions: Consistent Multifactorial interventions: Consistent	Few studies reported race/ethnicity, but effects were largely consistent among studies in various countries	6 studies of lifestyle interventions found significantly reduced progression to diabetes compared with usual care when pooled with 4 older studies Pharmacologic interventions reduced progression to diabetes on the basis of pooled results of 3 studies of thiazolidinediones and 4 studies of α-glucosidase inhibitors; other studies found that valsartan and a combination of low-dose metformin and rosiglitazone but not nateglinide or glimepiride reduced progression to diabetes 2 studies of multifactorial interventions found no effect on risk for progression to diabetes, although the estimate of 1 study was imprecise	Good

ADDITION = Anglo-Danish-Dutch Study of Intensive Treatment in People With Screen Detected Diabetes in Primary Care; BP = blood pressure; CV = cardiovascular; CVD = CV disease; IFG = impaired fasting glucose; IGT = impaired glucose tolerance; KQ = key question; MI = myocardial infarction; RCT = randomized, controlled trial; USPSTF = U.S. Preventive Services Task Force.
* Additional studies, including an additional KQ on subgroups, may be found in the full version of the report (24).
† Based on new evidence identified for this update plus previously reviewed evidence.

A similar effect was found in 4 studies of α-glucosidase inhibitors (RR, 0.64 [CI, 0.45 to 0.90]; I^2 = 67%; profile likelihood method, 0.65 [CI, 0.44 to 0.91]) (**Appendix Figure 8**, available at www.annals.org) (46, 47, 51, 91). Other studies found that valsartan (29) and a combination of low-dose metformin and rosiglitazone (49), but not nateglinide (28) or glimepiride (89), was associated with reduced risk for progression to diabetes.

Multifactorial Interventions

Two trials examined the multifactorial interventions consisting of intensive glucose, BP, and lipid control, in addition to lifestyle counseling and aspirin (83, 85). The ADDITION-Denmark trial (n = 1510) found that the multifactorial intervention was associated with a decreased risk for progression to diabetes that was nearly statistically significant (RR, 0.89 [CI, 0.78 to 1.02]) (85). Effects were greater in the subgroup that also received motivational interviewing (RR, 0.83 [CI, 0.68 to 1.00]) than in those that did not (RR, 0.95 [CI, 0.80 to 1.14]). A smaller (n = 181) Chinese study reported a lower incidence of progression to diabetes in the intervention than the control group, but the estimate was imprecise (0.0% vs. 5.8%; RR, 0.08 [CI, 0.00 to 1.42]) (83).

DISCUSSION

The **Table** summarizes the evidence reviewed for this update. In 2 trials, 1 of which focused on persons at greater risk for diabetes, screening was not associated with decreased risk for mortality versus no screening after 10 years of follow-up (32, 33). Point estimates from both trials were close to 1 and did not indicate a trend toward benefit in the good-quality trial, although the CIs encompass potentially meaningful effects (for example, 10% and 37% reduction in risk for all-cause mortality). Possible explanations for the lack of a mortality effect include limited screening uptake, increased mortality among nonattendees invited to screening (potentially attenuating estimates based on intention-to-treat analyses), increased diabetes screening across groups outside of the study protocol, improved management of cardiovascular disease risk factors and diabetes contributing to decreased mortality, and inadequate length of follow-up to adequately assess mortality. In addition, screening trials did not report nonmortality clinical outcomes, which may require less lengthy follow-up to detect clinically relevant effects. Evidence on harms associated with screening is sparse, although limited evidence showed no clear long-term negative effects on psychological measures (35–37).

Lifestyle and pharmacologic interventions both seem to be effective in delaying or preventing progression from IFG or IGT to diabetes in persons with high BMI (7–10, 39, 40, 45–47, 51, 52, 84, 86, 88, 89, 91). Effects of interventions on long-term clinical outcomes are less clear. The study with the longest follow-up (23 years) found that lifestyle modification for 6 years for early diabetes, IFG, or IGT was associated with a mortality benefit (38). Studies with shorter duration of follow-up found no beneficial effects of treatment on mortality, although evidence for improvement in microvascular outcomes was limited, as discussed in more detail in the full report (24).

Pharmacologic treatment of screen-detected or early diabetes, IFG, or IGT was associated with increased risk for withdrawal because of adverse events versus placebo in 1 study (47), with no clear increased risk for serious adverse events. In general, trials were not designed or powered to specifically assess the risk for serious but uncommon or rare adverse events, although studies not restricted to persons with screen-detected or early diabetes did not show a clear increase in risk for such events, such as lactic acidosis with metformin (92).

Since the previous USPSTF review, there is now evidence from a large, good-quality trial that an intensive multifactorial intervention for screen-detected diabetes aimed at decreasing glucose and lipid levels and BP was not associated with a statistically significant reduction in risk for all-cause or cardiovascular mortality or morbidity versus standard treatment, although estimates favored intensive treatment (56). For diabetes not specifically identified by screening, systematic reviews consistently found no association between intensive versus less-intensive glucose-lowering therapy and reduced risk for all-cause or cardiovascular mortality (58–66). Intensive glucose-lowering therapy was associated with reduced risk for nonfatal MI but increased risk for severe hypoglycemia. Other outcomes, such as retinopathy and neuropathy (discussed in the full report [24]), were found less frequently in these reviews, and pooled risk estimates were inconsistent, precluding reliable conclusions.

The 2008 USPSTF review (22) found that effects of intensive BP control were greater in persons with diabetes versus those without it, based on subgroup analyses from trials that were generally less successful at achieving lower BP than recent studies (71, 72). Since then, there is more evidence on the benefits of more effective, intensive BP control versus standard therapy, specifically in persons with diabetes. Although a good-quality systematic review found that intensive BP control in persons with diabetes was associated with reduced risk for all-cause mortality versus less-intensive BP control (70), results from individual studies, including those from the recent, large, well-conducted trials (71, 72), were inconsistent.

Our review has limitations. We only included English-language articles, although a recent review found that this limitation did not introduce bias into systematic review findings (93). We identified only 2 screening studies, and only 1 treatment study was conducted in a screen-detected population. We included evidence on intensive treatment from studies of persons with early diabetes that was not specifically screen-detected because studies in screen-detected populations were lacking, which could limit applicability to screening settings.

We identified many important research gaps. Screening studies in U.S. populations, in which the

prevalence of undiagnosed diabetes (and IFG or IGT) is likely to be greater than the 3% identified in the ADDITION-Cambridge and Ely studies, would be more applicable for informing U.S. screening decisions. As detailed in the full report, there is also little evidence on the effect of screening on ethnic and racial minorities, in whom the prevalence of diabetes is greater than in persons of white, European ancestry (24). Longer-term follow-up of the treatment phase of the ADDITION trial is needed to determine whether beneficial trends become statistically significant as more events occur (56). Studies of the effect of interventions for early diabetes, IFG, or IGT, particularly studies of lifestyle interventions with long-term (>20 years) follow-up, are needed to confirm the findings of the Da Qing study (38).

In conclusion, screening for diabetes did not improve mortality rates after 10 years of follow-up in 2 trials (32, 33) but was found to decrease mortality rates in a lifestyle intervention study with 23 years of follow-up (38). More evidence is needed to determine the effectiveness of treatments for screen-detected diabetes. Treatment of IFG or IGT was associated with delayed progression to diabetes.

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References

1. **Centers for Disease Control and Prevention.** National Diabetes Statistics Report: Estimates of Diabetes and Its Burden in the United States, 2014. Atlanta, GA: U.S. Department of Health and Human Services; 2014. Accessed at www.cdc.gov/diabetes/pubs/factsheet11.htm on 20 August 2014.

2. **American Diabetes Association.** Diagnosis and classification of diabetes mellitus. Diabetes Care. 2013;36 Suppl 1:S67-74. [PMID: 23264425] doi:10.2337/dc13-S067

3. **Centers for Disease Control and Prevention (CDC).** Increasing prevalence of diagnosed diabetes–United States and Puerto Rico, 1995-2010. MMWR Morb Mortal Wkly Rep. 2012;61:918-21. [PMID: 23151951]

4. **Harris MI, Eastman RC.** Early detection of undiagnosed diabetes mellitus: a U.S. perspective. Diabetes Metab Res Rev. 2000;16:230-6. [PMID: 10934451]

5. **Harris MI, Klein R, Welborn TA, Knuiman MW.** Onset of NIDDM occurs at least 4–7 yr before clinical diagnosis. Diabetes Care. 1992;15:815-9. [PMID: 1516497]

6. **American Diabetes Association.** Standards of medical care in diabetes–2014. Diabetes Care. 2014;37 Suppl 1:S14-80. [PMID: 24357209] doi:10.2337/dc14-S014

7. **Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, et al; Diabetes Prevention Program Research Group.** Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med. 2002;346:393-403. [PMID: 11832527]

8. **Kosaka K, Noda M, Kuzuya T.** Prevention of type 2 diabetes by lifestyle intervention: a Japanese trial in IGT males. Diabetes Res Clin Pract. 2005;67:152-62. [PMID: 15649575]

9. **Tuomilehto J, Lindström J, Eriksson JG, Valle TT, Hämäläinen H, Ilanne-Parikka P, et al; Finnish Diabetes Prevention Study Group.** Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. N Engl J Med. 2001;344:1343-50. [PMID: 11333990]

10. **Ramachandran A, Snehalatha C, Mary S, Mukesh B, Bhaskar AD, Vijay V; Indian Diabetes Prevention Programme (IDPP).** The Indian Diabetes Prevention Programme shows that lifestyle modification and metformin prevent type 2 diabetes in Asian Indian subjects with impaired glucose tolerance (IDPP-1). Diabetologia. 2006;49:289-97. [PMID: 16391903]

11. **Watanabe M, Yamaoka K, Yokotsuka M, Tango T.** Randomized controlled trial of a new dietary education program to prevent type 2 diabetes in a high-risk group of Japanese male workers. Diabetes Care. 2003;26:3209-14. [PMID: 14633803]

12. **Swinburn BA, Metcalf PA, Ley SJ.** Long-term (5-year) effects of a reduced-fat diet intervention in individuals with glucose intolerance. Diabetes Care. 2001;24:619-24. [PMID: 11315819]

13. **Pan XR, Li GW, Hu YH, Wang JX, Yang WY, An ZX, et al.** Effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerance. The Da Qing IGT and Diabetes Study. Diabetes Care. 1997;20:537-44. [PMID: 9096977]

14. **Dyson PA, Hammersley MS, Morris RJ, Holman RR, Turner RC.** The Fasting Hyperglycaemia Study: II. Randomized controlled trial of reinforced healthy-living advice in subjects with increased but not diabetic fasting plasma glucose. Metabolism. 1997;46:50-5. [PMID: 9439560]

15. **American Diabetes Association.** Standards of medical care in diabetes–2015. Diabetes Care. 2015;38 Suppl 1:S1-94.

16. **Handelsman Y, Mechanick JI, Blonde L, Grunberger G, Bloomgarden ZT, Bray GA, et al; AACE Task Force for Developing Diabetes Comprehensive Care Plan.** American Association of Clinical Endocrinologists Medical Guidelines for Clinical Practice for developing a diabetes mellitus comprehensive care plan. Endocr Pract. 2011;17 Suppl 2:1-53. [PMID: 21474420]

17. **American Academy of Family Physicians.** Summary of Recommendations for Clinical Preventive Services. Leawood, KS: American Acad Family Physicians; 2012:19.

18. **Colagiuri S, Davies D, Girgis S, Colagiuri R.** National Evidence Based Guideline for Case Detection and Diagnosis of Type 2 Diabetes. Canberra, Australia: National Health and Medical Research Council; 2009. Accessed at www.nhmrc.gov.au/_files_nhmrc/file/publications/synopses/di17-diabetes-detection-diagnosis.pdf on 28 October 2014.

19. **Diabetes UK.** Position statement. 2012 Accessed at www.diabetes.org.uk/Documents/About%20Us/What%20we%20say/diabetes-uk-postition-statement-early-identification-type-2-0914.pdf on 28 October 2014.

20. **Pottie K, Jaramillo A, Lewin G, Dickinson J, Bell N, Brauer P, et al; Canadian Task Force on Preventive Health Care.** Recommendations on screening for type 2 diabetes in adults. CMAJ. 2012;184:1687-96. [PMID: 23073674] doi:10.1503/cmaj.120732

21. **Harris R, Donahue K, Rathore SS, Frame P, Woolf SH, Lohr KN.** Screening adults for type 2 diabetes: a review of the evidence for the U.S. Preventive Services Task Force. Ann Intern Med. 2003;138:215-29. [PMID: 12558362]
22. **Norris SL, Kansagara D, Bougatsos C, Nygren P, Fu R.** Screening for Type 2 Diabetes: Update of 2003 Systematic Evidence Review for the U.S. Preventive Services Task Force. Evidence synthesis no. 61. AHRQ publication no. 08-05116-EF-1. Rockville, MD: Agency for Healthcare Research and Quality; 2008.
23. **Norris SL, Kansagara D, Bougatsos C, Fu R; U.S. Preventive Services Task Force.** Screening adults for type 2 diabetes: a review of the evidence for the U.S. Preventive Services Task Force. Ann Intern Med. 2008;148:855-68. [PMID: 18519931]
24. **Selph S, Dana T, Blazina I, Bougatsos C, Patel H, Chou R.** Screening for Type 2 Diabetes Mellitus: Systematic Review to Update the 2008 U.S. Preventive Services Task Force Recommendation. Evidence synthesis no. 117. AHRQ publication no. 3-05190-EF-1. Rockville, MD: Agency for Healthcare Research and Quality; 2014.
25. **U.S. Preventive Services Task Force.** U.S. Preventive Services Task Force Procedure Manual. AHRQ publication no. 08-05118-EF. Rockville, MD: Agency for Healthcare Research and Quality; 2008. Accessed at www.uspreventiveservicestaskforce.org/uspstf08/methods/procmanual.htm on 28 October 2014.
26. **Higgins JP, Thompson SG, Deeks JJ, Altman DG.** Measuring inconsistency in meta-analyses. BMJ. 2003;327:557-60. [PMID: 12958120]
27. **Cornell JE, Mulrow CD, Localio R, Stack CB, Meibohm AR, Guallar E, et al.** Random-effects meta-analysis of inconsistent effects: a time for change. Ann Intern Med. 2014;160:267-70. [PMID: 24727843]
28. **Holman RR, Haffner SM, McMurray JJ, Bethel MA, Holzhauer B, Hua TA, et al; NAVIGATOR Study Group.** Effect of nateglinide on the incidence of diabetes and cardiovascular events. N Engl J Med. 2010;362:1463-76. [PMID: 20228402] doi:10.1056/NEJMoa1001122
29. **McMurray JJ, Holman RR, Haffner SM, Bethel MA, Holzhauer B, Hua TA, et al; NAVIGATOR Study Group.** Effect of valsartan on the incidence of diabetes and cardiovascular events. N Engl J Med. 2010;362:1477-90. [PMID: 20228403] doi:10.1056/NEJMoa1001121
30. **Dagenais GR, Gerstein HC, Holman R, Budaj A, Escalante A, Hedner T, et al; DREAM Trial Investigators.** Effects of ramipril and rosiglitazone on cardiovascular and renal outcomes in people with impaired glucose tolerance or impaired fasting glucose: results of the Diabetes REduction Assessment with ramipril and rosiglitazone Medication (DREAM) trial. Diabetes Care. 2008;31:1007-14. [PMID: 18268075] doi:10.2337/dc07-1868
31. **Fu R, Gartlehner G, Grant M, Shamliyan T, Sedrakyan A, Wilt TJ, et al.** Conducting quantitative synthesis when comparing medical interventions: AHRQ and the Effective Health Care Program. J Clin Epidemiol. 2011;64:1187-97. [PMID: 21477993] doi:10.1016/j.jclinepi.2010.08.010
32. **Simmons RK, Echouffo-Tcheugui JB, Sharp SJ, Sargeant LA, Williams KM, Prevost AT, et al.** Screening for type 2 diabetes and population mortality over 10 years (ADDITION-Cambridge): a cluster-randomised controlled trial. Lancet. 2012;380:1741-8. [PMID: 23040422] doi:10.1016/S0140-6736(12)61422-6
33. **Simmons RK, Rahman M, Jakes RW, Yuyun MF, Niggebrugge AR, Hennings SH, et al.** Effect of population screening for type 2 diabetes on mortality: long-term follow-up of the Ely cohort. Diabetologia. 2011;54:312-9. [PMID: 20978739] doi:10.1007/s00125-010-1949-8
34. **Lauritzen T, Griffin S, Borch-Johnsen K, Wareham NJ, Wolffenbuttel BH, Rutten G; Anglo-Danish-Dutch Study of Intensive Treatment in People with Screen Detected Diabetes in Primary Care.** The ADDITION study: proposed trial of the cost-effectiveness of an intensive multifactorial intervention on morbidity and mortality among people with type 2 diabetes detected by screening. Int J Obes Relat Metab Disord. 2000;24 Suppl 3:S6-11. [PMID: 11063279]
35. **Park P, Simmons RK, Prevost AT, Griffin SJ.** Screening for type 2 diabetes is feasible, acceptable, but associated with increased short-term anxiety: a randomised controlled trial in British general practice. BMC Public Health. 2008;8:350. [PMID: 18840266] doi:10.1186/1471-2458-8-350
36. **Rahman M, Simmons RK, Hennings SH, Wareham NJ, Griffin SJ.** Effect of screening for type 2 diabetes on population-level self-rated health outcomes and measures of cardiovascular risk: 13-year follow-up of the Ely cohort. Diabet Med. 2012;29:886-92. [PMID: 22283392] doi:10.1111/j.1464-5491.2012.03570.x
37. **Paddison CA, Eborall HC, French DP, Kinmonth AL, Prevost AT, Griffin SJ, et al.** Predictors of anxiety and depression among people attending diabetes screening: a prospective cohort study embedded in the ADDITION (Cambridge) randomized control trial. Br J Health Psychol. 2011;16:213-26. [PMID: 21226792] doi:10.1348/135910710X495366
38. **Li G, Zhang P, Wang J, An Y, Gong Q, Gregg EW, et al.** Cardiovascular mortality, all-cause mortality, and diabetes incidence after lifestyle intervention for people with impaired glucose tolerance in the Da Qing Diabetes Prevention Study: a 23-year follow-up study. Lancet Diabetes Endocrinol. 2014;2:474-80. [PMID: 24731674] doi:10.1016/S2213-8587(14)70057-9
39. **Li G, Zhang P, Wang J, Gregg EW, Yang W, Gong Q, et al.** The long-term effect of lifestyle interventions to prevent diabetes in the China Da Qing Diabetes Prevention Study: a 20-year follow-up study. Lancet. 2008;371:1783-9. [PMID: 18502303] doi:10.1016/S0140-6736(08)60766-7
40. **Saito T, Watanabe M, Nishida J, Izumi T, Omura M, Takagi T, et al; Zensharen Study for Prevention of Lifestyle Diseases Group.** Lifestyle modification and prevention of type 2 diabetes in overweight Japanese with impaired fasting glucose levels: a randomized controlled trial. Arch Intern Med. 2011;171:1352-60. [PMID: 21824948] doi:10.1001/archinternmed.2011.275
41. **Uusitupa M, Peltonen M, Lindström J, Aunola S, Ilanne-Parikka P, Keinänen-Kiukaanniemi S, et al; Finnish Diabetes Prevention Study Group.** Ten-year mortality and cardiovascular morbidity in the Finnish Diabetes Prevention Study–secondary analysis of the randomized trial. PLoS One. 2009;4:e5656. [PMID: 19479072] doi:10.1371/journal.pone.0005656
42. **Andrews RC, Cooper AR, Montgomery AA, Norcross AJ, Peters TJ, Sharp DJ, et al.** Diet or diet plus physical activity versus usual care in patients with newly diagnosed type 2 diabetes: the Early ACTID randomised controlled trial. Lancet. 2011;378:129-39. [PMID: 21705068] doi:10.1016/S0140-6736(11)60442-X
43. **Davies MJ, Heller S, Skinner TC, Campbell MJ, Carey ME, Cradock S, et al; Diabetes Education and Self Management for Ongoing and Newly Diagnosed Collaborative.** Effectiveness of the diabetes education and self management for ongoing and newly diagnosed (DESMOND) programme for people with newly diagnosed type 2 diabetes: cluster randomised controlled trial. BMJ. 2008;336:491-5. [PMID: 18276664] doi:10.1136/bmj.39474.922025.BE
44. **Khunti K, Gray LJ, Skinner T, Carey ME, Realf K, Dallosso H, et al.** Effectiveness of a diabetes education and self management programme (DESMOND) for people with newly diagnosed type 2 diabetes mellitus: three year follow-up of a cluster randomised controlled trial in primary care. BMJ. 2012;344:e2333. [PMID: 22539172] doi:10.1136/bmj.e2333
45. **DeFronzo RA, Tripathy D, Schwenke DC, Banerji M, Bray GA, Buchanan TA, et al; ACT NOW Study.** Pioglitazone for diabetes prevention in impaired glucose tolerance. N Engl J Med. 2011;364:1104-15. [PMID: 21428766] doi:10.1056/NEJMoa1010949
46. **Kawamori R, Tajima N, Iwamoto Y, Kashiwagi A, Shimamoto K, Kaku K; Voglibose Ph-3 Study Group.** Voglibose for prevention of type 2 diabetes mellitus: a randomised, double-blind trial in Japanese individuals with impaired glucose tolerance. Lancet. 2009;373:1607-14. [PMID: 19395079] doi:10.1016/S0140-6736(09)60222-1
47. **Nijpels G, Boorsma W, Dekker JM, Kostense PJ, Bouter LM, Heine RJ.** A study of the effects of acarbose on glucose metabolism in patients predisposed to developing diabetes: the Dutch acarbose intervention study in persons with impaired glucose tolerance (DAISI). Diabetes Metab Res Rev. 2008;24:611-6. [PMID: 18756586] doi:10.1002/dmrr.839

48. **Ramachandran A, Snehalatha C, Mary S, Selvam S, Kumar CK, Seeli AC, et al.** Pioglitazone does not enhance the effectiveness of lifestyle modification in preventing conversion of impaired glucose tolerance to diabetes in Asian Indians: results of the Indian Diabetes Prevention Programme-2 (IDPP-2). Diabetologia. 2009;52:1019-26. [PMID: 19277602] doi:10.1007/s00125-009-1315-x
49. **Zinman B, Harris SB, Neuman J, Gerstein HC, Retnakaran RR, Raboud J, et al.** Low-dose combination therapy with rosiglitazone and metformin to prevent type 2 diabetes mellitus (CANOE trial): a double-blind randomised controlled study. Lancet. 2010;376:103-11. [PMID: 20605202] doi:10.1016/S0140-6736(10)60746-5
50. **Florez H, Pan Q, Ackermann RT, Marrero DG, Barrett-Connor E, Delahanty L, et al; Diabetes Prevention Program Research Group.** Impact of lifestyle intervention and metformin on health-related quality of life: the diabetes prevention program randomized trial. J Gen Intern Med. 2012;27:1594-601. [PMID: 22692637] doi:10.1007/s11606-012-2122-5
51. **Chiasson JL, Josse RG, Gomis R, Hanefeld M, Karasik A, Laakso M; STOP-NIDDM Trial Research Group.** Acarbose for prevention of type 2 diabetes mellitus: the STOP-NIDDM randomised trial. Lancet. 2002;359:2072-7. [PMID: 12086760]
52. **Gerstein HC, Yusuf S, Bosch J, Pogue J, Sheridan P, Dinccag N, et al; DREAM (Diabetes REduction Assessment with ramipril and rosiglitazone Medication) Trial Investigators.** Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomised controlled trial. Lancet. 2006;368:1096-105. [PMID: 16997664]
53. **Chiasson JL, Josse RG, Gomis R, Hanefeld M, Karasik A, Laakso M; STOP-NIDDM Trial Research Group.** Acarbose treatment and the risk of cardiovascular disease and hypertension in patients with impaired glucose tolerance: the STOP-NIDDM trial. JAMA. 2003;290:486-94. [PMID: 12876091]
54. **Ratner R, Goldberg R, Haffner S, Marcovina S, Orchard T, Fowler S, et al; Diabetes Prevention Program Research Group.** Impact of intensive lifestyle and metformin therapy on cardiovascular disease risk factors in the diabetes prevention program. Diabetes Care. 2005;28:888-94. [PMID: 15793191]
55. **Griffin SJ, Borch-Johnsen K, Davies MJ, Khunti K, Rutten GE, Sandbæk A, et al.** Effect of early intensive multifactorial therapy on 5-year cardiovascular outcomes in individuals with type 2 diabetes detected by screening (ADDITION-Europe): a cluster-randomised trial. Lancet. 2011;378:156-67. [PMID: 21705063] doi:10.1016/S0140-6736(11)60698-3
56. **Simmons RK, Sharp SJ, Sandbæk A, Borch-Johnsen K, Davies MJ, Khunti K, et al.** Does early intensive multifactorial treatment reduce total cardiovascular burden in individuals with screen-detected diabetes? Findings from the ADDITION-Europe cluster-randomized trial. Diabet Med. 2012;29:e409-16. [PMID: 22823477] doi:10.1111/j.1464-5491.2012.03759.x
57. **Van den Donk M, Griffin SJ, Stellato RK, Simmons RK, Sandbæk A, Lauritzen T, et al.** Effect of early intensive multifactorial therapy compared with routine care on self-reported health status, general well-being, diabetes-specific quality of life and treatment satisfaction in screen-detected type 2 diabetes mellitus patients (ADDITION-Europe): a cluster-randomised trial. Diabetologia. 2013. [PMID: 23959571]
58. **Buehler AM, Cavalcanti AB, Berwanger O, Figueiro M, Laranjeira LN, Zazula AD, et al.** Effect of tight blood glucose control versus conventional control in patients with type 2 diabetes mellitus: a systematic review with meta-analysis of randomized controlled trials. Cardiovasc Ther. 2013;31:147-60. [PMID: 22212499] doi:10.1111/j.1755-5922.2011.00308.x
59. **Hemmingsen B, Lund SS, Gluud C, Vaag A, Almdal TP, Hemmingsen C, et al.** Targeting intensive glycaemic control versus targeting conventional glycaemic control for type 2 diabetes mellitus. Cochrane Database Syst Rev. 2013;11:CD008143. [PMID: 24214280] doi:10.1002/14651858.CD008143.pub3
60. **Hemmingsen B, Lund SS, Gluud C, Vaag A, Almdal T, Hemmingsen C, et al.** Intensive glycaemic control for patients with type 2 diabetes: systematic review with meta-analysis and trial sequential analysis of randomised clinical trials. BMJ. 2011;343:d6898. [PMID: 22115901] doi:10.1136/bmj.d6898
61. **Boussageon R, Bejan-Angoulvant T, Saadatian-Elahi M, Lafont S, Bergeonneau C, Kassaï B, et al.** Effect of intensive glucose lowering treatment on all-cause mortality, cardiovascular death, and microvascular events in type 2 diabetes: meta-analysis of randomised controlled trials. BMJ. 2011;343:d4169. [PMID: 21791495] doi:10.1136/bmj.d4169
62. **Wu H, Xu MJ, Zou DJ, Han QJ, Hu X.** Intensive glycemic control and macrovascular events in type 2 diabetes mellitus: a meta-analysis of randomized controlled trials. Chin Med J (Engl). 2010;123:2908-13. [PMID: 21034605]
63. **Kelly TN, Bazzano LA, Fonseca VA, Thethi TK, Reynolds K, He J.** Systematic review: glucose control and cardiovascular disease in type 2 diabetes. Ann Intern Med. 2009;151:394-403. [PMID: 19620144]
64. **Ray KK, Seshasai SR, Wijesuriya S, Sivakumaran R, Nethercott S, Preiss D, et al.** Effect of intensive control of glucose on cardiovascular outcomes and death in patients with diabetes mellitus: a meta-analysis of randomised controlled trials. Lancet. 2009;373:1765-72. [PMID: 19465231] doi:10.1016/S0140-6736(09)60697-8
65. **Ma J, Yang W, Fang N, Zhu W, Wei M.** The association between intensive glycemic control and vascular complications in type 2 diabetes mellitus: a meta-analysis. Nutr Metab Cardiovasc Dis. 2009;19:596-603. [PMID: 19819121] doi:10.1016/j.numecd.2009.07.004
66. **Mannucci E, Monami M, Lamanna C, Gori F, Marchionni N.** Prevention of cardiovascular disease through glycemic control in type 2 diabetes: a meta-analysis of randomized clinical trials. Nutr Metab Cardiovasc Dis. 2009;19:604-12. [PMID: 19427768] doi:10.1016/j.numecd.2009.03.021
67. **Gerstein HC, Miller ME, Byington RP, Goff DC Jr, Bigger JT, Buse JB, et al; Action to Control Cardiovascular Risk in Diabetes Study Group.** Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med. 2008;358:2545-59. [PMID: 18539917] doi:10.1056/NEJMoa0802743
68. **Zoungas S, de Galan BE, Ninomiya T, Grobbee D, Hamet P, Heller S, et al; ADVANCE Collaborative Group.** Combined effects of routine blood pressure lowering and intensive glucose control on macrovascular and microvascular outcomes in patients with type 2 diabetes: new results from the ADVANCE trial. Diabetes Care. 2009;32:2068-74. [PMID: 19651921] doi:10.2337/dc09-0959
69. **Duckworth W, Abraira C, Moritz T, Reda D, Emanuele N, Reaven PD, et al; VADT Investigators.** Glucose control and vascular complications in veterans with type 2 diabetes. N Engl J Med. 2009;360:129-39. [PMID: 19092145] doi:10.1056/NEJMoa0808431
70. **Bangalore S, Kumar S, Lobach I, Messerli FH.** Blood pressure targets in subjects with type 2 diabetes mellitus/impaired fasting glucose: observations from traditional and Bayesian random-effects meta-analyses of randomized trials. Circulation. 2011;123:2799-810. [PMID: 21632497] doi:10.1161/CIRCULATIONAHA.110.016337
71. **Cushman WC, Evans GW, Byington RP, Goff DC Jr, Grimm RH Jr, Cutler JA, et al; ACCORD Study Group.** Effects of intensive blood-pressure control in type 2 diabetes mellitus. N Engl J Med. 2010;362:1575-85. [PMID: 20228401] doi:10.1056/NEJMoa1001286
72. **Patel A, MacMahon S, Chalmers J, Neal B, Woodward M, Billot L, et al; ADVANCE Collaborative Group.** Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): a randomised controlled trial. Lancet. 2007;370:829-40. [PMID: 17765963]
73. **Poulter NR.** Blood pressure and glucose control in subjects with diabetes: new analyses from ADVANCE. J Hypertens Suppl. 2009;27:S3-8. [PMID: 19483505] doi:10.1097/01.hjh.0000354417.70192.be
74. **Hansson L, Zanchetti A, Carruthers SG, Dahlöf B, Elmfeldt D, Julius S, et al.** Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. HOT Study Group. Lancet. 1998;351:1755-62. [PMID: 9635947]
75. **UK Prospective Diabetes Study Group.** Tight blood pressure control and risk of macrovascular and microvascular complications

in type 2 diabetes: UKPDS 38. BMJ. 1998;317:703-13. [PMID: 9732337]
76. **Holman RR, Paul SK, Bethel MA, Neil HA, Matthews DR.** Long-term follow-up after tight control of blood pressure in type 2 diabetes. N Engl J Med. 2008;359:1565-76. [PMID: 18784091] doi:10.1056/NEJMoa0806359
77. **Estacio RO, Jeffers BW, Hiatt WR, Biggerstaff SL, Gifford N, Schrier RW.** The effect of nisoldipine as compared with enalapril on cardiovascular outcomes in patients with non–insulin-dependent diabetes and hypertension. N Engl J Med. 1998;338:645-52. [PMID: 9486993]
78. **Schrier RW, Estacio RO, Esler A, Mehler P.** Effects of aggressive blood pressure control in normotensive type 2 diabetic patients on albuminuria, retinopathy and strokes. Kidney Int. 2002;61:1086-97. [PMID: 11849464]
79. **Schrier RW, Estacio RO, Mehler PS, Hiatt WR.** Appropriate blood pressure control in hypertensive and normotensive type 2 diabetes mellitus: a summary of the ABCD trial. Nat Clin Pract Nephrol. 2007;3:428-38. [PMID: 17653121]
80. **Janssen PG, Gorter KJ, Stolk RP, Rutten GE.** Randomised controlled trial of intensive multifactorial treatment for cardiovascular risk in patients with screen-detected type 2 diabetes: 1-year data from the ADDITION-Netherlands study. Br J Gen Pract. 2009;59:43-8. [PMID: 19105915] doi:10.3399/bjgp09X394851
81. **Howard BV, Roman MJ, Devereux RB, Fleg JL, Galloway JM, Henderson JA, et al.** Effect of lower targets for blood pressure and LDL cholesterol on atherosclerosis in diabetes: the SANDS randomized trial. JAMA. 2008;299:1678-89. [PMID: 18398080] doi:10.1001/jama.299.14.1678
82. **Gaede P, Lund-Andersen H, Parving HH, Pedersen O.** Effect of a multifactorial intervention on mortality in type 2 diabetes. N Engl J Med. 2008;358:580-91. [PMID: 18256393] doi:10.1056/NEJMoa0706245
83. **Lu YH, Lu JM, Wang SY, Li CL, Zheng RP, Tian H, et al.** Outcome of intensive integrated intervention in participants with impaired glucose regulation in China. Adv Ther. 2011;28:511-9. [PMID: 21533568] doi:10.1007/s12325-011-0022-4
84. **Penn L, White M, Oldroyd J, Walker M, Alberti KG, Mathers JC.** Prevention of type 2 diabetes in adults with impaired glucose tolerance: the European Diabetes Prevention RCT in Newcastle upon Tyne, UK. BMC Public Health. 2009;9:342. [PMID: 19758428] doi:10.1186/1471-2458-9-342
85. **Rasmussen SS, Glümer C, Sandbaek A, Lauritzen T, Borch-Johnsen K.** General effect on high-risk persons when general practitioners are trained in intensive treatment of type 2 diabetes. Scand J Prim Health Care. 2008;26:166-73. [PMID: 18677673] doi:10.1080/02813430802264624
86. **Sakane N, Sato J, Tsushita K, Tsujii S, Kotani K, Tsuzaki K, et al; Japan Diabetes Prevention Program (JDPP) Research Group.** Prevention of type 2 diabetes in a primary healthcare setting: three-year results of lifestyle intervention in Japanese subjects with impaired glucose tolerance. BMC Public Health. 2011;11:40. [PMID: 21235825] doi:10.1186/1471-2458-11-40
87. **Lindahl B, Nilsson TK, Borch-Johnsen K, Røder ME, Söderberg S, Widman L, et al.** A randomized lifestyle intervention with 5-year follow-up in subjects with impaired glucose tolerance: pronounced short-term impact but long-term adherence problems. Scand J Public Health. 2009;37:434-42. [PMID: 19181821] doi:10.1177/1403494808101373
88. **Katula JA, Vitolins MZ, Morgan TM, Lawlor MS, Blackwell CS, Isom SP, et al.** The Healthy Living Partnerships to Prevent Diabetes study: 2-year outcomes of a randomized controlled trial. Am J Prev Med. 2013;44:S324-32. [PMID: 23498294] doi:10.1016/j.amepre.2012.12.015
89. **Lindblad U, Lindberg G, Månsson NO, Ranstam J, Tyrberg M, Jansson S, et al.** Can sulphonylurea addition to lifestyle changes help to delay diabetes development in subjects with impaired fasting glucose? The Nepi ANtidiabetes StudY (NANSY) [Letter]. Diabetes Obes Metab. 2011;13:185-8. [PMID: 21199271] doi:10.1111/j.1463-1326.2010.01331.x
90. **Armato J, DeFronzo RA, Abdul-Ghani M, Ruby R.** Successful treatment of prediabetes in clinical practice: targeting insulin resistance and β-cell dysfunction. Endocr Pract. 2012;18:342-50. [PMID: 22068250] doi:10.4158/EP11194.OR
91. **Pan CY, Gao Y, Chen JW, Luo BY, Fu ZZ, Lu JM, et al.** Efficacy of acarbose in Chinese subjects with impaired glucose tolerance. Diabetes Res Clin Pract. 2003;61:183-90. [PMID: 12965108]
92. **Salpeter SR, Greyber E, Pasternak GA, Salpeter EE.** Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus. Cochrane Database Syst Rev. 2010:CD002967. [PMID: 20393934] doi:10.1002/14651858.CD002967.pub4
93. **Morrison A, Polisena J, Husereau D, Moulton K, Clark M, Fiander M, et al.** The effect of English-language restriction on systematic review-based meta-analyses: a systematic review of empirical studies. Int J Technol Assess Health Care. 2012;28:138-44. [PMID: 22559755] doi:10.1017/S0266462312000086

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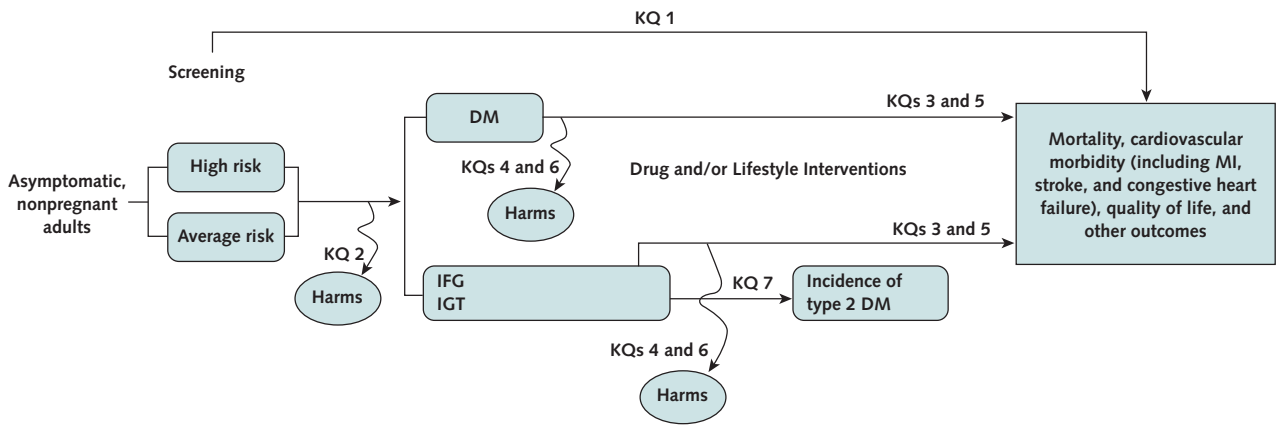
Appendix Figure 1. Analytic framework.



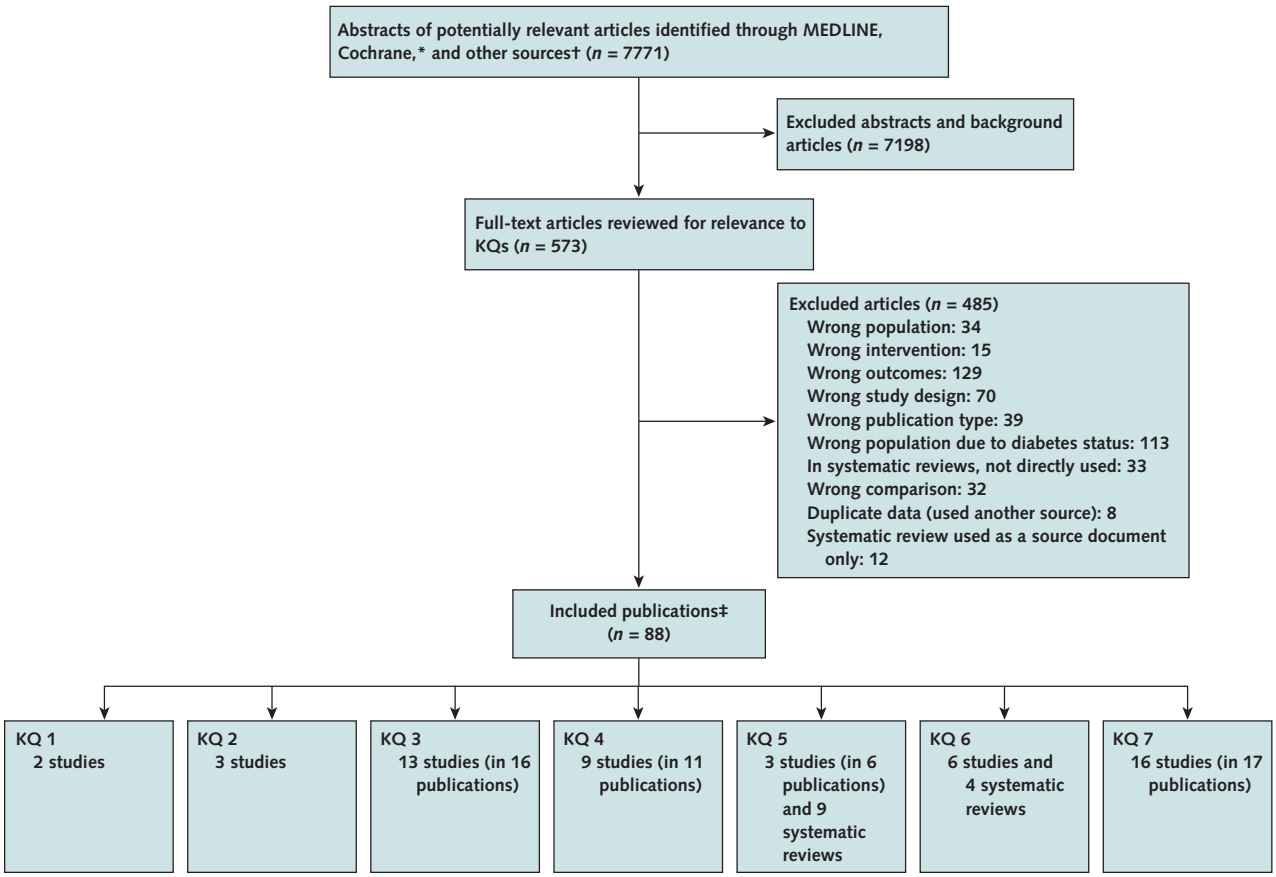
DM = diabetes mellitus; IGF = impaired fasting glucose; IGT = impaired glucose tolerance; KQ = key question; MI = myocardial infarction.

Appendix Figure 2. Inclusion and exclusion criteria per KQ.

	Include	Exclude
Populations	KQs 1 and 2: Asymptomatic, nonpregnant adults KQs 3 and 4: Asymptomatic, nonpregnant adults with screen-detected or mild type 2 DM (based on untreated A_{1c} levels), IFG, or IGT KQ 5: Asymptomatic, nonpregnant adults with screen-detected or mild type 2 DM (based on untreated A_{1c} levels), IFG, or IGT, as well as abnormal BP and/or lipid levels KQ 6: Asymptomatic, nonpregnant adults with IFG or IGT KQ 7: All of the above	KQs 1–7: Children, adolescents, and pregnant women and persons with symptomatic type 2 DM, IFG, or IGT
Interventions	KQs 1 and 2: Screening (targeted or universal) for IFG, IGT, or DM KQs 3, 4, and 6: Any intervention for glycemic control; lifestyle modification KQ 5: Any intervention for more stringent BP or lipid control or aspirin; more intensive lifestyle modification KQ 7: All of the above	
Comparison	KQ 1: No screening or alternative screening strategies KQs 3 and 4: No intervention/usual care or interventions in persons with advanced DM KQ 5: Conventional intervention KQ 6: No intervention or usual care KQ 7: All of the above	
Outcomes	KQs 1, 3, and 5: Mortality, cardiovascular morbidity (including MI, stroke, and congestive heart failure), chronic kidney disease, amputations, skin ulcers, visual impairment (including blindness), periodontitis (including tooth loss), moderate to severe neuropathy, and quality of life KQ 2: Labeling, anxiety, and false-positive results KQ 4: Serious side effects from treatments, including death, heart attack, stroke, cancer, and hypoglycemic events requiring medical attention KQ 6: Development of type 2 DM KQ 7: All of the above	
Settings	KQs 1–7: Applicable to primary care	
Study designs	KQs 1, 3, 5, and 6: Randomized, controlled trials and controlled observational studies, systematic reviews KQ 2: Any KQ 4: Randomized, controlled trials and controlled observational studies, systematic reviews, and large longitudinal studies KQ 7: All of the above	

BP = blood pressure; DM = diabetes mellitus; IGF = impaired fasting glucose; IGT = impaired glucose tolerance; KQ = key question; MI = myocardial infarction.

Appendix Figure 3. Summary of evidence search and selection.



KQ = key question.
* Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews.
‡ Other sources include previous reports, reference lists of relevant articles, and systematic reviews. An additional 27 publications are included in the full report (23).
§ Some studies have several publications and some are included for more than 1 KQ.

Appendix Table 1. Effect of Screening for Diabetes on Health Outcomes

Author, Year Study Name Quality	Study Design Setting Country	Interventions	Population	Duration of Follow-up	Results
Simmons 2012[32] ADDITION-Cambridge Good	Cluster RCT 33 general practices United Kingdom	A. Invited to stepwise screening of high-risk participants with random capillary blood glucose and HbA1c (n=15,089; 27 sites) A1. Invited to and attended screening (n=11,737/15,089; 78%) A2. Did not attend screening (n=3,352/15,089; 22%) B. No screening (n=4,137; 5 sites)	A vs. B Mean age 58 vs. 58 years 64% vs. 64% male Race not reported Mean BMI 30.6 vs. 30.5 kg/m^2 Median diabetes risk score 0.34 vs. 0.35* Index of Multiple Deprivation score: 12.9 (SD 7.7) vs. 16.1 (SD 9.0)†	10 years	A vs. B All-cause mortality: HR 1.06 (95% CI 0.90 to 1.25) Cardiovascular mortality: HR 1.02 (95% CI 0.75 to 1.38) Cancer mortality: HR 1.08 (95% CI 0.90 to 1.30) DM-related mortality: HR 1.26 (95% CI 0.75 to 2.10) Other mortality: HR 1.10 (95% CI 0.87 to 1.39) A1 vs. A2 All-cause mortality: HR 2.01 (95% CI 1.74 to 2.32)
Simmons 2011[33] Ely cohort Fair	RCT 1 general practice United Kingdom	Phase 1 (1990 to 1999) A. Invited to screening with OGTT; rescreening at 5 and 10 years (n=1,705) A1. Attended screening (n=1,157/1,705; 68%) A2. Did not attend screening (n=548/1,705; 32%) B. No screening (n=3,231)	Phase 1 A vs. B Mean age 53 vs. 51 years 45% vs. 51% male Race not reported Townsend Index of Deprivation Score −1.3 vs. −1.5‡	Phase 1 10 years	Phase 1 A vs. B All-cause mortality: HR 0.96 (95% CI 0.77 to 1.20); aHR§ 0.79 (95% CI 0.63 to 1.00) A1 vs. B All-cause mortality: HR 0.64 (95% CI 0.47 to 0.86); aHR 0.54 (95% CI 0.40 to 0.74) A2 vs. B All-cause mortality: HR 1.68 (95% CI 1.27 to 2.22); aHR 1.36 (95% CI 1.01 to 1.82)

ADDITION = Anglo-Danish-Dutch Study of Intensive Treatment in People With Screen Detected Diabetes in Primary Care; aHR = adjusted HR; BMI = body mass index; DM = diabetes mellitus; HbA1c = hemoglobin A1c; HR = hazard ratio; OGTT = oral glucose tolerance test; RCT = randomized, controlled trial.

* Risk score determined using a previously validated model incorporating age, sex, BMI, use of steroids or antihypertensives, family history, and smoking history.[67] A risk score of 0.35 was estimated to have 41% sensitivity, 86% specificity, 12% positive predictive value, and 96% negative predictive value.

† Higher score=higher level of deprivation.

‡ Score >0=greater deprivation than the mean, <0=less deprivation than the mean.

§ Adjusted for age, sex, and Index of Deprivation Score.

Appendix Table 2. Health Outcomes in Studies of Interventions for Screen-Detected/Early DM, IFG, or IGT

Author, Year Country Study Design Study Name Treatment Duration Follow-up	Intervention and Comparison	Population	Health Outcomes	Quality
Lifestyle interventions				
Andrews, 2011[42] 217 sites + community recruitment in the United Kingdom RCT Early ACTID Treatment duration and follow-up: 1 year	A. Intensive dietary advice and exercise (n=246) B. Intensive dietary advice (n=248) C. Usual care (n=99)	Patients with newly diagnosed DM A vs. B vs. C Mean age: 60 vs. 60 vs. 60 years Female sex: 36% vs. 34% vs. 37% Race: 94% vs. 96% vs. 97% white; other races NR Mean HbA1c: 6.7% vs. 6.6% vs. 6.7% Mean BMI: 31.6 vs. 31.5 vs. 32.3 kg/m^2 Mean BP: NR; >180/100 mm Hg at baseline excluded Mean total cholesterol: 4.3 vs. 4.3 vs. 4.4 mmol/L Proportion of smokers: 7% vs. 10% vs. 8%	A vs. B vs. C All-cause mortality: 0% (0/246) vs. 0% (0/248) vs. 1% (1/99); A vs. C: RR 0.14 (95% CI 0.01 to 3.31); B vs. C: RR 0.14 (95% CI 0.01 to 3.29)	Good
Davies, 2008[43] and Khunti, 2012[44] 13 sites in the United Kingdom Cluster RCT DESMOND Treatment duration: One 6-hour education session Follow-up: 3 years	A. Single, 6-hour group education session focusing on lifestyle, food, physical activity, and CV risk factors + standard clinical management (n=437) B. Usual care (n=387)	Patients with newly diagnosed DM A vs. B Mean age: 60 vs. 60 years Female sex: 47% vs. 43% (p<0.05) Race: 94% vs. 94% white; other races NR Mean HbA1c: 8.3% vs. 7.9% (p<0.05) Mean BMI: 32.3 vs. 32.4 kg/m^2 Mean BP: 141/82 vs. 140/81 mm Hg Mean total cholesterol: 5.4 vs. 5.4 mmol/L Proportion of smokers: 14% vs. 16%	A vs. B Quality of life, WHOQOL-BREF* Overall satisfaction with quality of life: 4.0 vs. 4.0; p=0.48 Overall satisfaction with health: 4.0 vs. 4.0; p=0.94	Fair
Li, 2008[39] and Li, 2014[38] 33 centers China Cluster RCT Da Qing DPS Treatment duration: 6 years Follow-up: 23 years	A. Interventions: Combined lifestyle, diet, or lifestyle + diet Diet intervention: Increase vegetable intake and lose weight by decreasing calories from sugar and alcohol; increase leisure time physical activity (n=438) B. Control (n=138)	Patients with IGT A vs. B Mean age: 45 vs. 47 years Female sex: 47% vs. 43% Race: NR Mean fasting glucose: 5.6 vs. 5.5 mmol/L Mean BMI: 25.7 vs. 26.2 kg/m^2 Mean BP: 132/87 vs. 134/89 mm Hg Mean total cholesterol: 5.2 vs. 5.3 mmol/L Proportion of smokers: NR	A vs. B: 20-year results All-cause mortality: 25% vs. 29%; HR, 0.96 (95% CI 0.65 to 1.41) CV mortality: 12% vs. 17%; HR 0.83 (95% CI 0.48 to 1.40) CV events: 41% vs. 44%; HR 0.98 (95% CI 0.71 to 1.37) A vs. B: 23-year results All-cause mortality: 28% (121/430) vs. 38% (53/138); HR 0.71 (95% CI 0.51 to 0.99) CV mortality: 12% (51/430) vs. 20% (27/138); HR 0.59 (95% CI 0.36 to 0.96)	Fair
Saito, 2011[40] 38 centers in Japan RCT Treatment duration: 3 years Follow-up: 3 years	A. Individual lifestyle counseling session aimed at decreasing body weight and increasing physical activity with follow-up at 1, 3, 6, 12, 18, 24, 30, and 36 months (n=330) B. Usual care (n=311)	Patients with IFG A vs. B Mean age: 50 vs. 48 years Female sex: 28% vs. 29% Race: NR Mean HbA1c: 5.4% vs. 5.4% Mean BMI: 26.9 vs. 27.1 kg/m^2 Mean BP: 130/81 vs. 131/81 mm Hg Mean total cholesterol: 5.5 vs. 5.5 mmol/L Proportion of smokers: 25% vs. 28%	A vs. B All-cause mortality: 0.3% (1/311) vs. 0% (0/330); RR 3.18 (95% CI 0.13 to 78)	Fair
Uusitupa, 2009[41] Finnish DPS 5 centers in Finland RCT Mean follow-up: 11 to 14 years (varied by intervention group)	A. Intensive diet and counseling group (n=257) B. Control group (n=248)	Patients with IGT and BMI >25 kg/m^2 A vs. B Mean age: 55 vs. 55 years Female sex: 66% vs. 68% Race: NR Mean fasting glucose: 6.1 vs. 6.2 mmol/L Mean BMI: 31.4 vs. 31.2 kg/m^2 Mean BP: 140/88 vs. 136/86 mm Hg Mean total cholesterol: 5.6 vs. 5.6 mmol/L Proportion of smokers: 7% vs. 7%	A vs. B All-cause mortality: 2.2 vs. 3.8 events/1,000 person-years; HR 0.57 (95% CI 0.21 to 1.58) CV events: 22.9 vs. 22.0 events/1,000 person-years; HR 1.04 (95% CI 0.72 to 1.51)	Fair
Pharmacologic interventions				
DeFronzo, 2011[45] 8 centers in United States RCT Median follow-up: 2.4 years	A. Pioglitazone 30 mg/day for 1 month, increased to 45 mg/day (n=303) B. Placebo (n=299)	Patients with IGT, BMI >25, and ≥1 other DM risk factor A vs. B Mean age: 53 vs. 52 years Female sex: 58% vs. 58% Race: 51% vs. 57% white; 26% vs. 25% Hispanic; 19% vs. 15% black; 3% vs. 3% other Mean HbA1c: 5.5% vs. 5.5% Mean BMI: 33.0 vs. 34.5 kg/m^2 Mean BP: 127/74 vs. 128/74 mm Hg Mean total cholesterol: 4.3 vs. 4.5 mmol/L Proportion of smokers: NR	A vs. B All-cause mortality: 1% (3/303) vs. 0.3% (1/299); OR 2.96 (95% CI 0.31 to 28.62) CV events: 9% (26/303) vs. 8% (23/299); RR 1.11 (95% CI 0.65 to 1.91)	Fair
DREAM Trial Investigators, 2008[30] 191 centers in 21 countries RCT Mean follow-up: 3 years	A. Ramipril 15 mg/day (n=2,623) B. Placebo (n=2,646) C. Rosiglitazone 0.8 mg/day (n=2,635) D. Placebo (n=2,634) Patients randomized twice, to ramipril or placebo and rosiglitazone or placebo	Patients with IFG or IGT A vs. B and C vs. D Mean age: 55 vs. 55 years and 55 vs. 55 years Female sex: 60% vs. 59% and 58% vs. 60% Race: NR Median fasting plasma glucose: 5.9 vs. 5.9 and 5.8 vs. 5.8 mmol/L Mean BMI: 30.9 vs. 30.9 and 30.8 vs. 31.0 kg/m^2 Mean BP: 136/83 vs. 136/83 and 136/83 vs. 136/84 mm Hg Mean total cholesterol: NR; A vs. B: 36% and 35% history of dyslipidemia; C vs. D: 15% vs. 15% statin or fibrate use Proportion of current or former smokers: 44% vs. 45% and 44% vs. 45%	A vs. B Total mortality: 1% (31/2623) vs. 1% (32/2646); HR 0.98 (95% CI 0.60 to 1.61) CV mortality: 0.5% (12/2623) vs. 0.4% (10/2646); HR 1.21 (95% CI 0.52 to 2.80) CV events: 3% (69/2623) vs. 2% (64/2646); HR 1.09 (95% CI 0.78 to 1.53) C vs. D Total mortality: 1% (30/2635) vs. 1% (33/2634); OR 0.91 (95% CI 0.56 to 1.49) CV mortality: 0.5% (12/2635) vs. 0.4% (10/2634); OR 1.20 (95% CI 0.52 to 2.78) CV events: 3% (77/2635) vs. 2% (56/2634); HR 1.38 (95% CI 0.98 to 1.95)	Good

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Table 2–Continued

Author, Year Country Study Design Study Name Treatment Duration Follow-up	Intervention and Comparison	Population	Health Outcomes	Quality
Kawamori, 2009[46] 103 centers in Japan RCT Treatment duration: 5 years Mean follow-up: 3 years	A. Voglibose, 0.2 mg/day (n=897) B. Placebo (n=881)	Patients with IFG A vs. B Mean age: 56 vs. 56 years Female sex: 40% vs. 40% Race: NR Mean fasting plasma glucose: 5.8 vs. 5.9 mmol/L Mean BMI: 25.8 vs. 25.9 kg/m^2 Mean BP: NR; 59% vs. 58% history of hypertension Mean total cholesterol: NR; 77% vs. 76% history of dyslipidemia Proportion of smokers: NR	A vs. B All-cause mortality: 0.7% (6/897) vs. 0% (0/881); OR 12.77 (95% CI 0.72 to 226.99)	Good
NAVIGATOR, 2010[28] 806 centers in 40 countries RCT Median follow-up: 5 years	A. Nateglinide 60 mg/3 times daily (n=4,645) B. Placebo (n=4,661) Patients also randomized in 2x2 factorial design to receive valsartan or placebo	Patients with IGT and at least 1 CV risk factor or known CVD A vs. B Mean age: 64 vs. 64 years Female sex: 51% vs. 50% Race: 83% vs. 83% white; 3% vs. 3% black; 7% vs. 8% Asian; 8% vs. 8% other Mean HbA1c: 5.8% vs. 5.8% Mean BMI: 30.5 vs. 30.5 kg/m^2 Mean BP: 140/83 vs. 140/83 mm Hg Mean total cholesterol: 5.4 vs. 5.4 mmol/L Proportion of smokers: 11% vs. 11%	A vs. B All-cause mortality: 7% (310/4645) vs. 7% (312/4661); OR 1.00 (95% CI 0.85 to 1.17) CV mortality: 3% (126/4645) vs. 4% (118/4661); OR 1.07 (95% CI 0.83 to 1.38) Stroke: 4% (111/4645) vs. 3% (126/4661); HR 0.89 (95% CI 0.69 to 1.15)	Good
NAVIGATOR, 2010[29] 806 centers in 40 countries RCT Median follow-up: 5 years	A. Valsartan 160 mg/once daily (n=4,631) B. Placebo (n=4,675) Patients also randomized in 2x2 factorial design to receive nateglinide or placebo	Patients with IGT and at least one CV risk factor or known CVD A vs. B Mean age: 64 vs. 64 years Female sex: 50% vs. 51% Race: 83% vs. 83% white; 2% vs. 3% black; 6% vs. 7% Asian; 8% vs. 8% other Mean HbA1c: 5.8% vs. 5.8% Mean BMI: 30.4 vs. 30.6 kg/m^2 Mean BP: 139/83 vs. 140/83 mm Hg Mean total cholesterol: 5.4 vs. 5.4 mmol/L Proportion of smokers: 11% vs. 11%	A vs. B All-cause mortality: 6% (295/4631) vs. 12% (327/4675); OR 1.00 (95% CI 0.85 to 1.17) CV mortality: 3% (128/4631) vs. 3% (116/4675); OR 1.07 (95% CI 0.83 to 1.38) MI: 3% (138/4631) vs. 3% (140/4675); HR 0.97 (95% CI 0.77 to 1.23) Heart failure requiring hospitalization: 2% (91/4631) vs. 2% (94/4675); HR 0.97 (95% CI 0.72 to 1.29) Stroke: 2% (105/4631) vs. 3% (132/4675); HR 0.79 (95% CI 0.61 to 1.02)	Good
Nijpels, 2008[47] 1 center in the Netherlands RCT DAISI Treatment duration: 3 years	A. Acarbose 50 mg/3 times daily (n=60) B. Placebo (n=58)	Patients with IGT A vs. B Mean age: 59 vs. 57 years Female sex: 49% vs. 50% Race: NR Mean HbA1c: 5.9% vs. 5.6% Mean BMI: 28.4 vs. 29.5 kg/m^2 Mean BP: NR Mean total cholesterol: NR Proportion of smokers: 25% vs. 23%	A vs. B All-cause mortality: 2% (1/60) vs. 5% (3/58); OR 0.32 (95% CI 0.03 to 3.19)	Fair
Ramachandran, 2009[48] India RCT IDPP-2 Mean follow-up: 3 years	A. Pioglitazone (n=181) B. Placebo (n=186)	Patients with IGT A vs. B Mean age: 45.1 vs. 45.5 years Female sex: 13% vs. 14% Race: NR Mean HbA1c: 5.8% vs. 5.8% Mean BMI: 26.0 vs. 26.2 kg/m^2 Mean BP: 118/75 vs. 118/76 mm Hg Mean total cholesterol: 5.2 vs. 5.3 mmol/L Proportion of smokers: 37% vs. 47%	A vs. B All-cause mortality: 1% (2/203) vs. 0.5% (1/203); OR 2.00 (95% CI 0.18 to 22.23) CV mortality: 0.9% (2/204) vs. 0% (0/203); OR 4.98 (95% CI 0.24 to 104.28)	Fair
Zinman, 2010[49] 2 centers in Canada RCT CANOE Treatment duration: NR Median follow-up: 3.9 years	A. Metformin 500 mg plus rosiglitazone 2 mg/twice daily as a fixed-dose combination (n=103) B. Placebo (n=104)	Patients with IGT and/or IFG and ≥1 risk factor for DM A vs. B Mean age: 50 vs. 55 years Female sex: 65% vs. 68% Race: 75% vs. 74% white; 8% vs. 7% South Asian; 7% vs. 7% Latino; 11% vs. 13% other Mean fasting glucose: 5.4 vs. 5.4 mmol/L Mean BMI: 31.3 vs. 32.0 kg/m^2 Mean BP: 130/80 vs. 128/82 mm Hg Mean total cholesterol: 4.9 vs. 5.4 mmol/L Proportion of smokers: NR	A vs. B MI: 0% (0/103) vs. 1% (1/104); RR 0.34 (95% CI 0.01 to 8.17) Congestive heart failure: 0% (0/103) vs. 1% (1/104); RR 0.34 (95% CI 0.01 to 8.17)	Good

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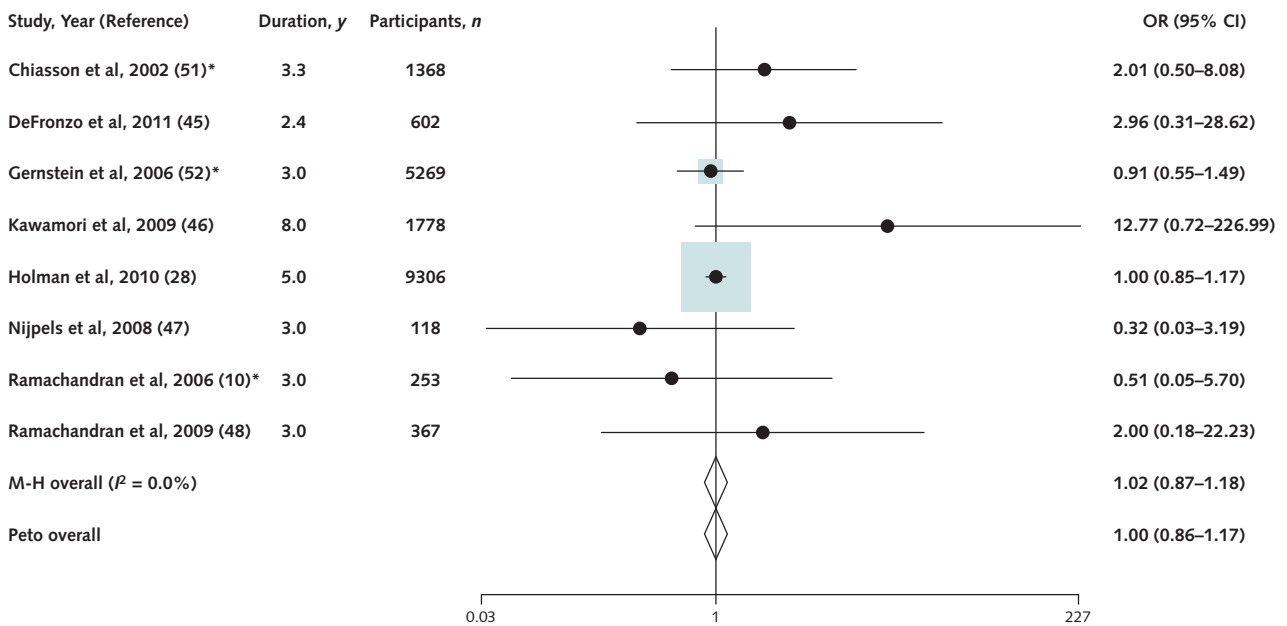
Table 2–Continued

Author, Year Country Study Design Study Name Treatment Duration Follow-up	Intervention and Comparison	Population	Health Outcomes	Quality
Lifestyle and pharmacologic interventions				
Florez 2012[50] 27 centers in the United States RCT Diabetes Prevention Program Treatment duration: 3 years Median follow-up: 5 years	A. Intensive lifestyle intervention, including diet and exercise to achieve modest weight reduction (n=1,048) B. Metformin 850 mg/twice daily (n=1,043) C. Placebo (n=1,041)	Patients with IGT and BMI ≥24 kg/m^2 (≥22 kg/m^2 in Asian Americans) A vs. B vs. C Mean age: 51 vs. 51 vs. 50 years Female sex: 68% vs. 66% vs. 69% Race: 54% vs. 56% vs. 54% white; 19% vs. 21% vs. 20% black; 17% vs. 15% vs. 16% Hispanic; 9% vs. 8% vs. 10% other Mean HbA1c: 5.9% vs. 5.9% vs. 5.9% Mean BMI: 33.9 vs. 33.9 vs. 34.2 kg/m^2 Mean blood pressure: NR Mean total cholesterol: NR Proportion of smokers: NR	A vs. C Quality of life, SF-36 score* changes from baseline, mean between-group difference: SF-6D: 0.0084 (SD 0.0041; p<0.05) PCS: 1.57 (SD 0.30; p<0.01) MCS: −0.29 (SD 0.32; p=NS) Physical function: 3.58 (SD 0.66; p<0.01) Body pain: 1.93 (SD 0.78; p<0.01) General health: 3.23 (SD 0.66; p<0.01) Vitality: 2.05 (SD 0.77; p<0.01) B vs. C Quality of life, SF-36 score* changes from baseline, mean between-group difference: SF-6D: 0.0019 (SD 0.0041; p=NS) PCS: 0.15 (SD 0.30; p=NS) MCS: 0.22 (SD 0.32; p=NS) Physical function: 0.13 (SD 0.71; p=NS) Body pain: 0.50 (SD 0.78; p=NS) General health: 0.06 (SD 0.66; p=NS) Vitality: 0.09 (SD 0.76; p=NS)	Good

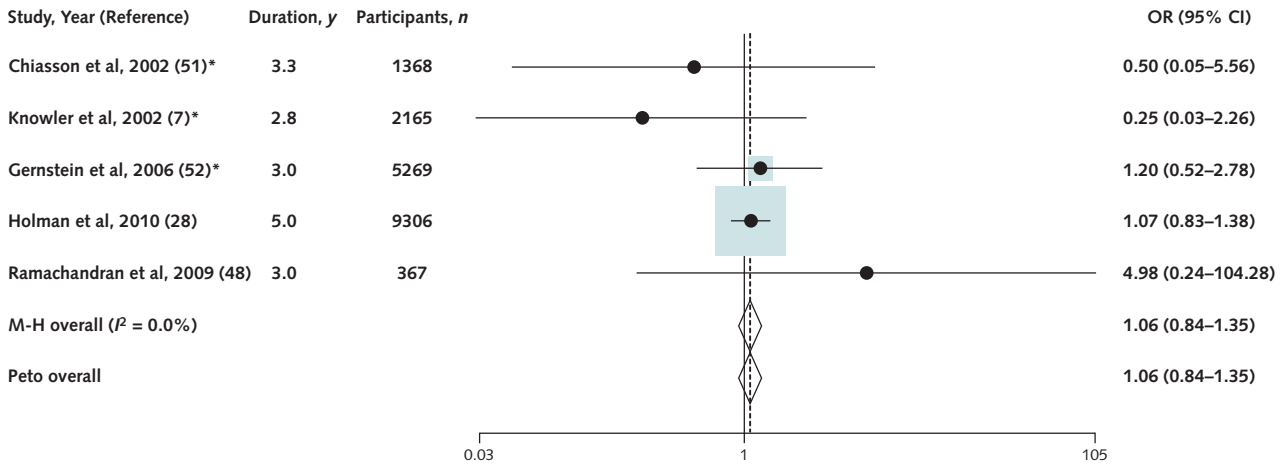
ACTID = Activity in Diabetes; BMI = body mass index; BP = blood pressure; CANOE = Canadian Normoglycemia Outcomes Evaluation; CV = cardiovascular; CVD = CV disease; DAISI = Dutch Acarbose Intervention Study in Persons With Impaired Glucose Tolerance; DESMOND = Diabetes Education and Self Management for Ongoing and Newly Diagnosed; DM = diabetes mellitus; DPS = Diabetes Prevention Study; DREAM = Diabetes Reduction Assessment With Ramipril and Rosiglitazone Medication; HbA1c = hemoglobin A1c; HR = hazard ratio; IDPP-2 = Indian Diabetes Prevention Program-2; IFG = impaired fasting glucose; IGT = impaired glucose tolerance; MCS = SF-36 Mental Health Component Summary; MI = myocardial infarction; NAVIGATOR = Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research; NR = not reported; NS = not significant; OR = odds ratio; PCS = SF-36 Physical Component Summary; RCT = randomized, controlled trial; RR = relative risk; SF = short form; WHOQOL-BREF = World Health Organization Quality of Life Assessment, short version.
* Scale 1 to 5 for each domain; higher score = higher quality of life.

Appendix Figure 4. Meta-analysis of the effect of pharmacologic interventions on all-cause mortality.



M-H = Mantel–Haenszel fixed-effects model; OR = odds ratio.
* Included in the 2008 report (22).

Appendix Figure 5. Meta-analysis of the effect of pharmacologic interventions on cardiovascular mortality.



M-H = Mantel–Haenszel fixed-effects model; OR = odds ratio.
* Included in the 2008 report (22).

Appendix Table 3. Good-Quality Systematic Reviews of Intensive vs. Standard Glucose Control in People With DM Reporting Health Outcomes and Harms

Author, Year	Intensive vs. Standard Control Number of Studies; RR, 95% CI; I^2 (If Reported)*				
	All-Cause Mortality	**CV Mortality**	**Stroke**	**MI**	**Harms**
Buehler, 2013[58]	6 studies; 1.03, 0.90 to 1.17; I^2=50%	6 studies; 1.04, 0.83 to 1.29; I^2=60%	Nonfatal stroke: 5 studies; 1.02, 0.88 to 1.17; I^2=0%	Nonfatal MI: 5 studies; 0.85, 0.76 to 0.95; I^2=0%	Severe hypoglycemia: 5 studies; 2.39, 1.79 to 3.18; I^2=62%
Hemmingsen, 2013[59]	18 studies; 1.01, 0.9 to 1.13; I^2=40%	18 studies; 1.06, 0.9 to 1.26; I^2=37%	Nonfatal stroke: 11 studies; 0.96, 0.80 to 1.16; 1^2=20%	Nonfatal MI: 12 studies; 0.87, 0.76 to 1.00; I^2=28%	Severe hypoglycemia: 12 studies; 1.76, 1.46 to 2.13; I^2=95%
Boussageon, 2011[61]	9 studies; 1.04, 0.91 to 1.19; I^2=42%	10 studies; 1.11, 0.86 to 1.43; I^2=61%	Fatal or nonfatal stroke: 8 studies; 0.96, 0.83 to 1.13; I^2=0%	Nonfatal MI: 8 studies; 0.85, 0.74 to 0.96; I^2=0% Fatal or nonfatal MI: 8 studies; 0.90, 0.81 to 1.01; I^2=0%	–
Hemmingsen, 2011[60]	12 studies; 1.02, 0.91 to 1.13; I^2=30%	12 studies; 1.11, 0.92 to 1.35; I^2=46%	–	Nonfatal MI: 8 studies; 0.85, 0.76 to 0.95; I^2=0%	Severe hypoglycemia: 9 studies; 2.39, 1.71 to 3.34; I^2=73%
Wu, 2010[62]	6 studies; 0.95, 0.80 to 1.12	5 studies; 1.10, 0.79 to 1.53	–	–	–
Kelly, 2009[63]	5 studies; 0.98, 0.84 to 1.15; I^2=72%	5 studies; 0.97, 0.76 to 1.24; I^2=76%	Fatal or nonfatal stroke: 5 studies; 0.98, 0.86 to 1.11 Nonfatal stroke: 5 studies; 0.98, 0.82 to 1.17 Fatal stroke: 5 studies; 0.87, 0.63 to 1.20	Nonfatal MI: 5 studies; 0.84, 0.75 to 0.94 Fatal MI: 5 studies; 0.94, −0.75 to 1.18	Severe hypoglycemia: 5 studies; 2.03, 1.46 to 2.81; I^2=85%
Ma, 2009[65]	3 studies; 1.02, 0.98 to 1.07	–	3 studies; 0.97, 0.84 to 1.12	–	Severe hypoglycemia: 2 studies; 2.34, 1.64 to 3.35; I^2=89%
Mannucci, 2009[66]	5 studies; OR 1.01, 0.88 to 1.15	5 studies; OR 1.01, 0.82 to 1.26	Fatal or nonfatal stroke: 5 studies; OR 0.94, 0.83 to 1.06	Fatal or nonfatal MI: 5 studies; OR 0.85, 0.78 to 0.93	–
Ray, 2009[64]	5 studies; OR 1.02, 0.87 to 1.19	5 studies; OR 1.01, 0.82 to 1.26	–	Nonfatal MI: 5 studies; OR 0.83, 0.75 to 0.93	–

CV = cardiovascular; DM = diabetes mellitus; MI = myocardial infarction; OR = odds ratio; RR = relative risk.
* Results for other outcomes are summarized in the full report.[24]

Appendix Table 4. Trials of Variably Defined Intensive vs. Standard BP Control in People With DM

Study n Duration of Follow-up	Interventions	BP: Baseline; Target; Achieved (mm Hg)	Intensive vs. Standard BP Lowering, RR (95% CI)				
			All-Cause Mortality	CV Mortality	Stroke	Myocardial Infarction	Other Outcomes
ABCD (H)* [79] n=470 5 years	Intensive: Nisoldipine or enalapril, plus open-label antihypertensives to achieve target DBP Standard: Nisoldipine or enalapril	Baseline Intensive: 156/98 Standard: 154/98 Target Intensive: DBP ≤75 Standard: DBP 80 to 89 Achieved Intensive: 132/78 Standard: 138/86	6% (13/237) vs. 10% (25/233); 0.51 (0.27 to 0.97)	–	–	7% (16/237) vs. 6% (14/233); 1.12 (0.56 to 2.25)	Nephropathy: 7% (16/237) vs. 10% (23/233); 0.68 (0.37 to 1.26)
ABCD (N)* [78] n=480 5 years	Intensive: Nisoldipine 10 to 60 mg/day or enalapril 5 to 40 mg/day Standard: Placebo	Baseline Intensive: 136/84 Standard: 137/84 Target Intensive: DBP decrease of ≥10 Standard: No DBP decrease (DBP 80 to 89) Achieved Intensive: 128/75 Standard: 137/81	8% (18/237) vs. 8% (20/243); 0.92 (0.50 to 1.70)	5% (13/237) vs. 4% (9/243); 1.48 (0.65 to 3.40)	2% (4/237) vs. 5% (13/243); 0.32 (0.10 to 0.95)	8% (19/237) vs. 6% (15/243); 1.30 (0.68 to 2.50)	Congestive heart failure: 5% (12/237) vs. 5% (11/243); 1.12 (0.50 to 2.49)
ACCORD [71] n=4,732 5 years	Intensive: Use of antihypertensives necessary to reach target according to a prespecified treatment algorithm Standard: Usual care	Baseline Intensive:139/76 Standard: 139/76 Target Intensive: SBP <120 Standard: SBP <140 Achieved Intensive: 119/64 Standard: 134/71	6% (150/2,363) vs. 6% (144/2,371); 1.11 (0.89 to 1.38)	3% (60/2,363) vs. 2% (58/2,372); 1.04 (0.73 to 1.48)	2% (36/2,363) vs. 3% (62/2,371); 0.58 (0.39 to 0.88)	5% (126/2,362) vs. 6% (146/2,371); 0.87 (0.69 to 1.09)	Fatal or nonfatal heart failure: 4% (83/2,363) vs. 4% (90/2,371); 0.93 (0.69 to 1.24) Loss of visual acuity: 35% (819/2,339) vs. 36% (849/2,352); 0.97 (0.90 to 1.05) Score >2 on Michigan Neuropathy Screening Instrument: 53% (722/1,353) vs. 56% (781/1,388); 0.95 (0.89 to 1.02)
ADVANCE [72] n=11,140 4 years	Intensive: Addition to existing BP regimen of fixed-dose combination of perindopril-indapamide; no target set Standard: Existing BP regimen with addition of placebo	Baseline Intensive: 145/81 Standard: 145/81 Target Intensive: No target Standard: No target Achieved Intensive: 136/73 Standard: 140/73	7% (408/5,569) vs. 9% (471/5,571); 0.87 (0.76 to 0.98)	4% (211/5,569) vs. 5% (257/5,571); 0.82 (0.69 to 0.98)	–	–	Renal events: 22% (1,243/5,569) vs. 27% (1,500/5,571); 0.83 (0.78 to 0.89) New or worsening retinopathy: 5% (289/5,569) vs. 5% (286/5,571); 1.01 (0.86 to 1.19) New or worsening nephropathy: 3% (181/5,569) vs. 4% (216/5,571); 0.84 (0.69 to 1.02)
HOT* [74] n=1,501 with DM 4 years	Intensive: Felodipine + others added incrementally if needed to reach target Standard: Felodipine	Baseline Intensive: 170/105 Standard: 170/105 Target Intensive: DBP ≤80 Standard: DBP ≤85 or 90 Achieved Intensive: 140/81 Standard: 143/84	3% (17/499) vs. 6% (59/1,002); 0.58 (0.34 to 0.94)	1% (7/499) vs. 4% (42/1,002); 0.33 (0.15 to 0.74)	2% (12/499) vs. 3% (30/1,002); 0.80 (0.41 to 1.56)	3% (15/499) vs. 3% (34/1,002); 0.89 (0.49 to 1.61)	–
UKPDS* [75] n=1,148 8 years	Intensive: Captopril or atenolol + others added incrementally if needed to reach target Standard: No use of ACE inhibitors or β-blockers	Baseline Intensive: 160/93 Standard: 160/93 Target Intensive: <150/85 Standard: <180/105 Achieved Intensive: 143/79 Standard: 152/22	18% (134/758) vs. 21% (83/390); 0.83 (0.65 to 1.06)	–	5% (38/758) vs. 9% (34/390); 0.58 (0.37 to 0.90)	14% (107/758) vs. 18% (69/390); 0.80 (0.60 to 1.05)	DM-related death: 11% (82/758) vs. 16% (62/390); 0.68 (0.50 to 0.92)
UKPDS [76] n=1,148 16 years (8 years on trial + 8 years post-trial monitoring)	Intensive: Captopril or atenolol + others added incrementally if needed to reach target Standard: No use of ACE inhibitors or β-blockers	Baseline Intensive: 160/93 Standard: 160/93 Target Intensive: Standard: Achieved Intensive: 143/79 Standard: 152/22	49% (373/758) vs. 54% (211/390); 0.89 (0.75 to 1.06)	–	12% (90/758) vs. 15% (58/390); 0.77 (0.55 to 1.07)	27% (205/758) vs. 29% (115/390); 0.90 (0.71 to 1.13)	DM-related death: 27% (203/758) vs. 31% (122/390); 0.84 (0.67 to 1.05)

ABCD = Appropriate Blood Pressure Control in Diabetes; ACCORD = Action to Control Cardiovascular Risk in Diabetes; ACE = angiotensin-converting enzyme; ADVANCE = Action in Diabetes and Vascular Disease; BP = blood pressure; CV = cardiovascular; DBP = diastolic blood pressure; DM = diabetes mellitus; H = hypertensive subgroup; HOT = Hypertensive Optimal Treatment; N = nonhypertensive subgroup; RR = relative risk; SBP = systolic blood pressure; UKPDS = U.K. Prospective Diabetes Study.

* Included in the prior U.S. Preventive Services Task Force report [22].

Appendix Table 5. Studies of Interventions to Prevent or Delay Progression to DM

Author, Year Country Study Design Study Name Treatment Duration Follow-up	Intervention and Comparison	Population	Progression to DM	Quality
Lifestyle interventions				
Katula, 2013[88] Community setting, United States RCT Treatment duration: 2 years	A. Intensive lifestyle intervention (n=151) B. Usual care (n=150)	Overweight or obese patients with IFG A vs. B Mean age: 57.3 vs. 58.5 years Female sex: 58% vs. 57% Race: 73.5% white, 25.8% black, 0.7% other vs. 74% white, 23.3% black, 2.7% other Mean fasting glucose: 5.9 vs. 5.9 mmol/L Mean BMI: 32.8 vs. 32.6 Mean blood pressure: Not reported Mean total cholesterol: Not reported Proportion of smokers: Not reported	A vs. B Incidence: 2.6% (4/151) vs. 7.3% (11/150); RR 0.36, 95% CI 0.12 to 1.11	Fair
Li, 2014[38] and Li, 2008[39] 33 centers, China Cluster RCT Da Qing DPS Treatment duration: 6 years Follow-up: 20 years (mean 9.4 years)	A. Interventions: Combined lifestyle, diet, or lifestyle + diet; diet intervention: increase vegetable intake and lose weight by decreasing calories from sugar and alcohol; increase leisure time physical activity (n=438) B. Control (n=138)	Patients with IGT A vs. B Mean age: 45 vs. 47 years Female sex: 47% vs. 43% Race: Not reported Mean fasting glucose: 5.6 vs. 5.5 mmol/L Mean BMI: 25.7 vs. 26.2 kg/m^2 Mean blood pressure: 132/87 vs. 134/89 mm Hg Mean total cholesterol: 5.21 vs. 5.26 mmol/L Proportion of smokers: Not reported	A vs. B: 20-year results Incidence: 6.9 vs. 11.3 cases/100 person-years per year Cumulative incidence: 79.7% vs. 92.8% Adjusted HR: 0.57, 95% CI 0.41 to 0.81 NNT: 6 A vs. B: 23-year results Incidence: 7.3 vs. 12.3 cases/100 person-years per year Cumulative incidence: 73% (312/430) vs. 90% (124/138); RR 0.86, 95% CI 0.80 to 0.92 Adjusted HR: 0.55, 95% CI 0.40 to 0.76	Fair
Lindahl, 2009[87] Single center, Sweden Vasterbotten Intervention Programme Treatment duration: 1 year Follow-up: 5 years	A. Intensive lifestyle intervention, including a month-long stay in a wellness center and 4-day follow-up 1 year later (n=83) B. Usual care (n=85)	Patients with IGT and BMI >27 A vs. B Mean age: 52 vs. 54 years Female sex: 70% vs. 61% Race: Not reported Mean fasting glucose: 5.8 vs. 6.2 mmol//L Mean BMI: 31.2 vs. 30.2 Mean blood pressure: 141/84 vs. 141/86 Mean total cholesterol: 5.6 vs. 5.6 mmol/L Proportion of (ever) smokers: 42% vs. 34%	A vs. B Incidence at 1 year (end of intervention): 6% (5/83) vs. 23.5% (20/85); RR 0.26, 95% CI 0.10 to 0.65 Incidence at 3 years: 14.5% (12/83) vs. 23.5% (20/85); RR 0.61, 95% CI 0.32 to 1.18 Incidence at 5 years: 20% (17/83) vs. 27% (23/85); RR 0.75, 95% CI 0.44 to 1.31	Fair
Penn, 2009[84] United Kingdom RCT EDIPS Treatment duration: Up to 5 years Median follow-up: 3.1 years	A. Biweekly sessions for 1 month and monthly for 3 months and every 3 months for up to 5 years; motivational interview from dietician and physiotherapist with quarterly newsletter and advice to target >50% energy from carbohydrates (n=51) B. 1 session of health promotion advice (n=51)	Patients with IGT and BMI >25 A vs. B Mean age: 57 vs. 57 years Female sex: 59% vs. 61% Race: Not reported Mean fasting glucose: 5.7 vs. 5.8 mmol/L Mean BMI: 34.1 vs. 33.5 kg/m^2 Mean blood pressure: Not reported Mean total cholesterol: Not reported Proportion of smokers: Not reported	A vs. B Incidence: 9.8% (5/51) vs. 21.6% (11/51); RR 0.45, 95% CI 0.17 to 1.22 Incidence rate per 1,000 persons: 32.7 vs. 67.1	Fair
Saito, 2011[40] 38 centers in Japan RCT Zensharen Study for Prevention of Lifestyle Diseases Treatment duration: 5 years and 3 months Mean follow-up: 2.7 years	A. Individual session and goal to decrease weight by 5% with follow up at 1, 3, 6, 12, 18, 24, 30, and 36 months (n=330) B. 1 session of advice to reduce weight by 5% (n=311)	Patients with IGT and BMI >24 A vs. B Mean age: 50 vs.48 years Female sex: 28% vs. 29% Race: Not reported Mean HbA1c: 5.4% vs. 5.4% Mean BMI: 26.9 vs. 27.1 kg/m^2 Mean blood pressure: 130/81 vs. 131/81 mm Hg Mean total cholesterol: 5.5 vs. 5.5 mmol/L Proportion of smokers: 25% vs. 28%	A vs. B Cumulative incidence: 10.6% (35/330) vs. 16.4% (51/311); RR 0.65, 95% CI 0.43 to 0.97	Fair
Sakane, 2011[86] 32 community clinics in Japan RCT JDPP Treatment duration: 6 years Follow-up: 3 years	A. Individual and group sessions (4 group session lasting 2 to 3 hours, biannual individual session lasting 20 to 40 minutes) (n=146) B. 1 group session (n=150)	Patients with IGT A vs. B Mean age: 51 vs. 51 years Female sex: 50% vs. 49% Race: Not reported Mean fasting glucose: 5.9 vs. 6.1 mmol/L Mean BMI: 24.8 vs. 24.5 kg/m^2 Mean blood pressure: Not reported Mean total cholesterol: Not reported Proportion of smokers: Not reported	A vs. B Incidence: 6.1% (9/146) vs. 12% (18/150); RR 0.51, 95% CI 0.24 to 1.11	Fair
Pharmacologic interventions				
Armato, 2012[90] United States Prospective cohort Mean follow-up: 6.9 vs. 5.5 vs. 8.9 months	A. Pioglitazone 15 mg/day and metformin 850 mg/day (n=40) B. Pioglitazone 15 mg/day, metformin 850 mg/day, and exenatide 10 mcg/twice daily (n=47) C. Lifestyle counseling, including weight loss 7% over 3 months, diet information, walking 30 minutes per day 7 days per week (n=18)	Patients with IFG or IGT A vs. B vs. C Mean age: 62 vs. 56 vs. 61 years; p=0.03 Female sex: 28% vs. 43% vs. 39% Race: 82.5% white, 2.5% black, 15% other vs. 83% white, 2.1% black, 14.9% other vs. 100% white Mean HbA1c: 5.8% vs. 5.7% vs. 5.6% Mean BMI: 27.0 vs. 29.7 vs. 27.5 kg/m^2 Mean blood pressure: Not reported Mean total cholesterol: Not reported Proportion of smokers: Not reported	A vs. B vs. C Incidence: 0 vs. 0 vs. 5.6% (1/18); A vs. C, RR 0.15, 95% CI 0.01 to 3.62; B vs. C, RR 0.13, 95% CI 0.01 to 3.10	Fair

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Table 5–Continued

Author, Year Country Study Design Study Name Treatment Duration Follow-up	Intervention and Comparison	Population	Progression to DM	Quality
DeFronzo, 2011[45] 8 centers in United States RCT Median follow-up: 2.4 years	A. Pioglitazone 30 mg/day for 1 month, increased to 45 mg/day (n=303) B. Placebo (n=299)	Patients with IGT, BMI >25, and ≥1 other risk factor for DM A vs. B Mean age: 53 vs. 52 years Female sex: 58% vs. 58% Race: 51% vs. 57% white; 26 vs. 25% Hispanic; 19% vs.15% black; 3% vs. 3% other Mean HbA1c: 5.5% vs. 5.5% Mean BMI: 33.0 vs. 34.5 kg/m^2 Mean blood pressure: 127/74 vs. 128/74 mm Hg Mean total cholesterol: 4.3 vs. 4.5 mmol/L Proportion of smokers: Not reported	A vs. B Incidence: 5.0% (15/303) vs. 16.7% (50/299); RR 0.30, 95% CI 0.17 to 0.52 Annual average incidence: 2.1% vs. 7.6%; p<0.001 HR: 0.28 (95% CI 0.16 to 0.49) NNT for duration of trial (2.2 years): 8 NNT for 1 year: 18	Fair
Kawamori, 2009[46] 103 centers in Japan RCT Treatment duration: 5 years Mean follow-up: 3 years	A. Voglibose 0.2 mg/day (n=897) B. Placebo (n=881)	Patients with IFG A vs. B Mean age: 56 vs. 56 years Female sex: 40% vs. 40% Race: Not reported Mean fasting plasma glucose: 5.8 vs. 5.9 mmol/L Mean BMI: 25.8 vs. 25.9 kg/m^2 Mean blood pressure: Not reported; 59% vs. 58% history of hypertension Mean total cholesterol: Not reported; 77% vs. 76% history of dyslipidemia Proportion of smokers: Not reported	A vs. B Incidence: 5.5% (50/897) vs. 12% (106/881); RR 0.46, 95% CI 0.34 to 0.64 HR: 0.595	Good
Lindblad, 2011[89] 23 centers in Sweden RCT Median follow-up: 3.7 years	A. Glimepiride 1 mg/day (n=136) B. Placebo (n=138)	Patients with IFG A vs. B Mean age: 60 vs. 60 years Female sex: 35% vs. 46% Race: Not reported Mean HbA1c: 4.9% vs. 4.9% Mean BMI: 29.9 vs. 29.6 kg/m^2 Mean blood pressure: 144/82 vs.141/82 mm Hg Mean total cholesterol: 5.5 vs. 5.4 mmol/L Proportion of smokers: Not reported	A vs. B Incidence: 30.1% (41/136) vs. 39.9% (55/138); RR 0.76, 95% CI 0.55 to 1.05 Incidence, adjusted for baseline HbA1c, proinsulin, and CRP: OR 0.62 (p=0.028)	Fair
NAVIGATOR, 2010[28] (nateglinide results) 806 centers in 40 countries RCT Median follow-up: 5 years	A. Nateglinide 60 mg/3 times daily (n=4,645) B. Placebo (n=4,661) Patients also randomized in 2x2 factorial design to receive valsartan or placebo	Patients with IGT and at least 1 CV risk factor or known CVD A vs. B Mean age: 64 vs. 64 years Female sex: 51% vs. 50% Race: 83% vs. 83% white; 3% vs. 3% black; 7% vs. 8% Asian; 8% vs.8% other Mean HbA1c: 5.8% vs. 5.8% Mean BMI: 30.5 vs. 30.5 kg/m^2 Mean blood pressure: 140/83 vs. 140/83 mm Hg Mean total cholesterol: 5.4 vs. 5.4 mmol/L Proportion of smokers: 11% vs. 11%	A vs. B Incidence: 36.0% (1647/4,645) vs. 33.9% (1580/4,661); RR 1.05, 95% CI 0.99 to 1.11 Absolute hazard difference: 6.18 (95% CI 0.47 to 11.90) HR: 1.07 (95% CI 1.00 to 1.15)	Good
NAVIGATOR, 2010[29] (valsartan results) 806 centers in 40 countries RCT Median follow-up: 5 years	A. Valsartan 160 mg/once daily (n=4,631) B. Placebo (n=4,675) Patients also randomized in 2x2 factorial design to receive nateglinide or placebo	Patients with IGT and at least 1 CV risk factor or known CVD A vs. B Mean age: 64 vs. 64 years Female sex: 50% vs. 51% Race: 83% vs. 83% white; 2% vs. 3% black, 6% vs. 7% Asian, 8% vs. 8% other Mean HbA1c: 5.8% vs. 5.8% Mean BMI: 30.4 vs. 30.6 kg/m^2 Mean blood pressure: 139/83 vs. 140/83 mm Hg Mean total cholesterol: 5.4 vs. 5.4 mmol/L Proportion of smokers: 11% vs. 11%	A vs. B Incidence: 33.1% (1532/4,631) vs. 36.8% (1722/4,675); RR 0.90, 95% CI 0.85 to 0.95 Absolute hazard difference: −12.6 (95% CI −18.4 to −6.9) HR: 0.86 (95% CI 0.80 to 0.92)	Good
Nijpels, 2008[47] 1 center in the Netherlands RCT DAISI Treatment duration: 3 years	A. Acarbose 50 mg/3 times daily (n=60) B. Placebo (n=58)	Patients with IGT A vs. B Mean age: 59 vs. 57 years Female sex: 49% vs. 50% Race: Not reported Mean HbA1c: 5.9% vs. 5.6% Mean BMI: 28.4 vs. 29.5 kg/m^2 Mean blood pressure: Not reported Mean total cholesterol: Not reported Proportion of smokers: 25% vs. 23%	A vs. B Incidence: 18.3% (11/60) vs. 24.1% (14/58); RR 0.76, 95% CI 0.38 to 1.53 Attributable risk: −0.14 (95% CI −0.46 to 0.21) Absolute risk reduction: 6% (95% CI −9% to 21%)	Fair

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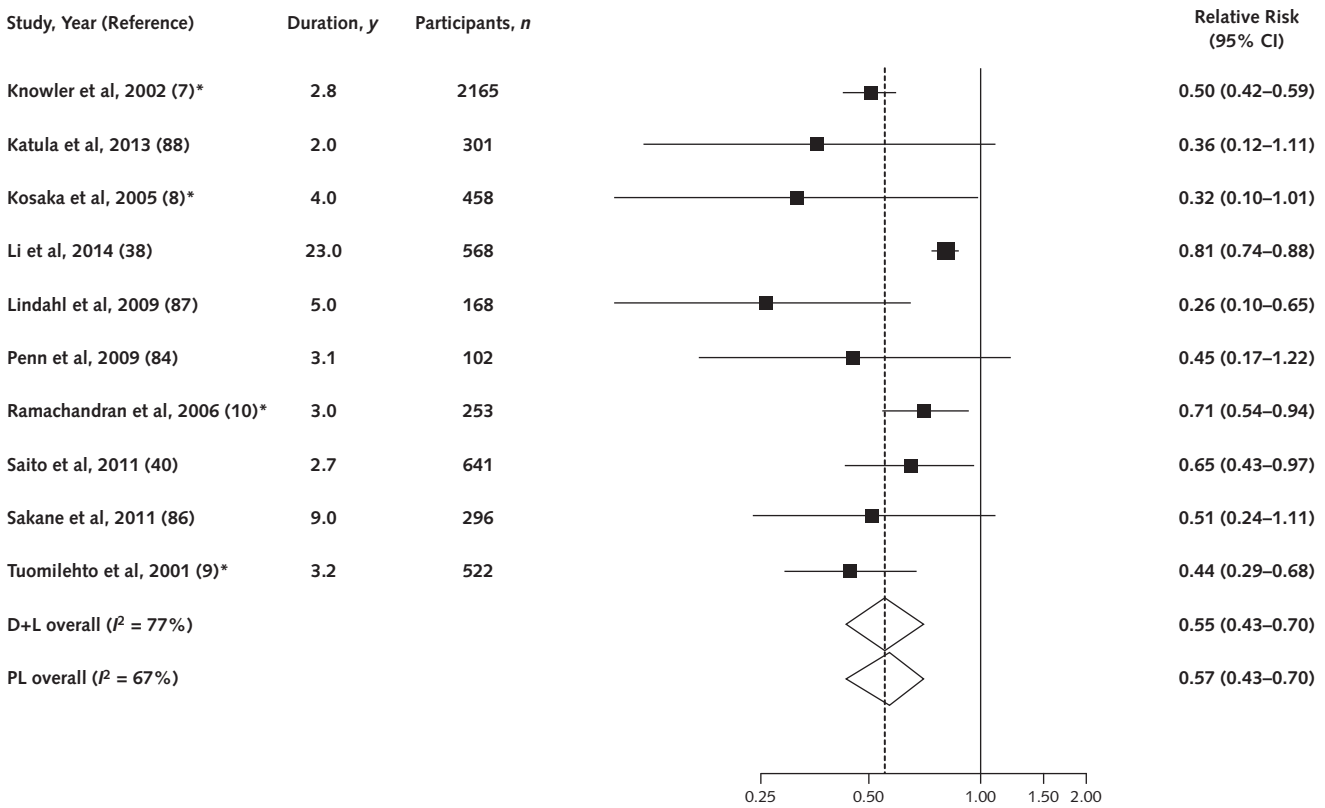
Table 5–Continued

Author, Year Country Study Design Study Name Treatment Duration Follow-up	Intervention and Comparison	Population	Progression to DM	Quality
Ramachandran, 2009[48] India RCT IDPP-2 Mean follow-up: 3 years	A. Pioglitazone (n=181) B. Placebo (n=186)	Patients with IGT A vs. B Mean age 45.1 vs. 45.5 years Female sex: 13% vs. 14% Race: Not reported Mean HbA1c: 5.8% vs. 5.8% Mean BMI: 26.0 vs. 26.2 kg/m^2 Mean blood pressure: 118/75 vs.118/76 mm Hg Mean total cholesterol: 5.2 vs. 5.3 mmol/L Proportion of smokers: 37% vs. 47%	A vs. B Cumulative incidence: 29.8% (54/181) vs. 31.6% (59/186); RR 0.94, 95% CI 0.69 to 1.28	Fair
Zinman, 2010[49] 2 centers in Canada RCT CANOE Treatment duration: Not reported Median follow-up: 3.9 years	A. Metformin 500 mg plus rosiglitazone 2 mg/twice daily as a fixed-dose combination (n=103) B. Placebo (n=104)	Patients with IGT and ≥1 risk factor for DM A vs. B Mean age: 50 vs. 55 years Female sex: 65% vs. 68% Race: 75% vs. 74% white; 8% vs. 7% South Asian; 7% vs. 7% Latino; 11% vs.13% other Mean fasting glucose: 5.4 vs. 5.4 mmol/L Mean BMI: 31.3 vs. 32.0 kg/m^2 Mean blood pressure: 130/80 vs. 128/82 mm Hg Mean total cholesterol: 4.9 vs. 5.4 mmol/L Proportion of smokers: Not reported	A vs. B Incidence: 13.6% (14/103) vs. 39.4% (41/104); RR 0.34, 95% CI 0.20 to 0.59 RR reduction: 66% (95% CI 41 to 80%) Absolute risk reduction: 26% (95% CI 14 to 37%) NNT over 3.9 years: 4 (95% CI 2.7 to 7.1) HR: 0.31 (95% CI 0.17 to 0.58)	Good
Multifactorial interventions				
Lu, 2011[83] 4 communities in China RCT Treatment duration: 2 years	A. IGT: Acarbose 50 mg/3 times daily; IFG or IGT/IFG: Metformin 250 mg/3 times daily; antihypertensives, antidyslipidemia agents, and aspirin (n=95) B. Control: Health/diabetic education once a month (n=86)	Patients with IGT and BMI >19 A vs. B Mean age: 62 vs. 65 years Female sex: 47% vs. 48% Race: Not reported Mean HbA1c: 5.9% vs. 6.0% Mean BMI: 27.1 vs. 26.9 kg/m^2 Mean blood pressure: 130/79 vs. 130/79 mm Hg Mean total cholesterol: 5.1 vs. 5.0 mmol/L Proportion of smokers: Not reported	A vs. B Incidence: 0% vs. 5.8% (5/86); RR 0.08, 95% CI 0.00 to 1.42	Fair
Rasmussen, 2008[85] Multicenter, Denmark Cluster RCT ADDITION-Denmark	A. Intensive management, including lifestyle advice, aspirin, drug treatment of blood glucose, blood pressure, and lipids according to strict targets (n=865); subgroup received motivational interviewing training B. Standard care (n=645)	Patients with IGT or IFG A vs. B IFG Mean age: 60 vs. 60 years Female sex: 43% vs. 43% Race: Not reported Mean BMI: 29.1 vs. 29.1 kg/m^2 Proportion with hypertension: 41% vs. 49% Mean total cholesterol: 5.7 vs. 5.7 mmol/L Proportion of smokers: 26% vs. 27% IGT Mean age: 61 vs. 61 years Female sex: 53% vs. 60% (p=0.037) Race: Not reported Mean BMI: 29.5 vs. 29.8 kg/m^2 Proportion with hypertension: 53% vs. 53% Mean total cholesterol: 5.8 vs. 5.9 mmol/L Proportion of smokers: 28% vs. 21% (p=0.016)	A vs. B Incidence: 14.1 vs. 15.8 cases/100 person-years; RR 0.89, 95% CI 0.78 to 1.02 Subanalyses Motivational interviewing + intensive intervention: RR 0.83, 95% CI 0.68 to 1.00 Intensive treatment alone: RR 0.95, 95% CI 0.80 to 1.14 IFG: RR 0.90, 95% CI 0.73 to 1.12 IGT: RR 0.90, 95% CI 0.77 to 1.07	Fair

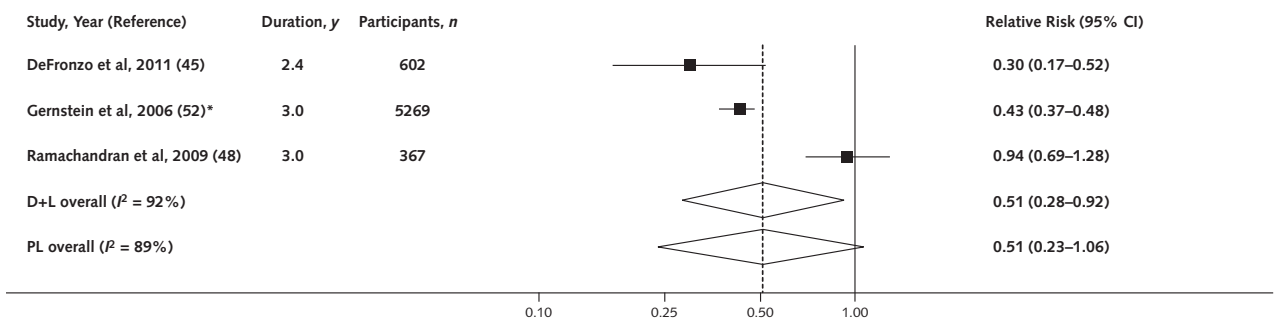
ADDITION = Anglo-Dutch-Danish Study of Intensive Treatment in People With Screen Detected Diabetes in Primary Care; BMI = body mass index; CANOE = Canadian Normoglycemia Outcomes Evaluation; CRP = C-reactive protein; CV = cardiovascular; CVD = CV disease; DAISI = Dutch Acarbose Intervention Study in Persons With Impaired Glucose Tolerance; DM = diabetes mellitus; DPS = Diabetes Prevention Study; EDIPS = European Diabetes Prevention Study; HbA1c = hemoglobin A1c; HR = hazard ratio; IDPP-2 = Indian Diabetes Prevention Program-2; IFG = impaired fasting glucose; IGT = impaired glucose tolerance; JDPP = Japanese Diabetes Prevention Program; NAVIGATOR = Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research; NNT = number needed to treat; OR = odds ratio; RCT = randomized, controlled trial; RR = relative risk.

Appendix Figure 6. Meta-analysis of the effect of lifestyle interventions on incidence of progression to DM.



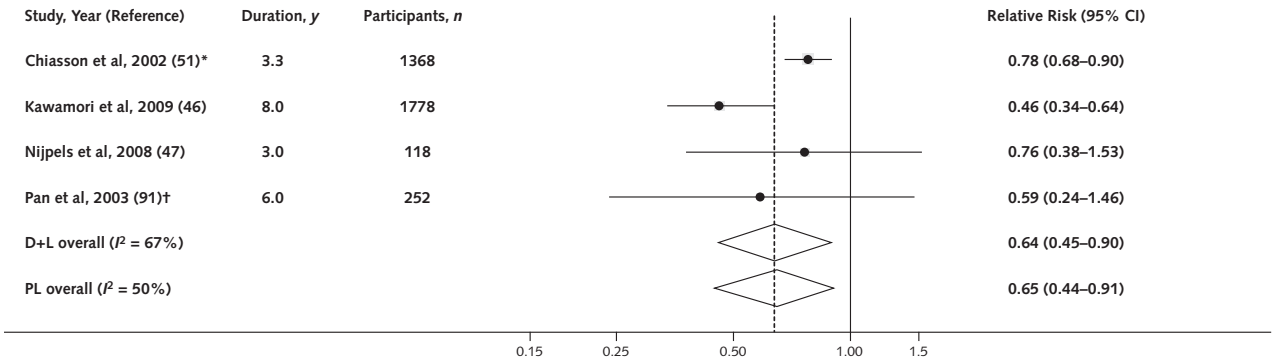
DM = diabetes mellitus; D+L = DerSimonian–Laird random-effects model; PL = profile likelihood model.
* Included in the 2008 report (22).

Appendix Figure 7. Meta-analysis of the effect of thiazolidinediones on incidence of progression to DM.



DM = diabetes mellitus; D+L = DerSimonian–Laird random-effects model; PL = profile likelihood model.
* Included in the 2008 report (22).

Appendix Figure 8. Meta-analysis of the effect of α-glucosidase inhibitors on incidence of progression to DM.



DM = diabetes mellitus; D+L = DerSimonian–Laird random-effects model; PL = profile likelihood model.
* Included in the 2008 report (22).
† Included in the 2003 report (21).