Annals of Internal Medicine | Clinical Guidelines

Screening Adults for Type 2 Diabetes: A Review of the Evidence for the U.S. Preventive Services Task Force

Susan L. Norris, MD, MPH; Devan Kansagara, MD; Christina Bougatsos, BS; and Rongwei Fu, PhD

Background: More than 19 million Americans are affected by type 2 diabetes mellitus, which is undiagnosed in one third of these persons. In addition, it is estimated that more than 54 million adults have prediabetes. Debate continues over the benefits and harms of screening and then treating adults who have asymptomatic diabetes or prediabetes.

Purpose: To update the 2003 U.S. Preventive Services Task Force review on the evidence for potential benefits and harms of screening adults for type 2 diabetes and prediabetes in primary care settings.

Data Sources: MEDLINE and the Cochrane Library for relevant studies and systematic reviews published in English between March 2001 and July 2007.

Study Selection: Trials and observational studies that directly addressed the effectiveness and adverse effects of screening interventions were included. Randomized, controlled trials were used to assess the effectiveness of diabetes and prediabetes treatments. For diabetes interventions, trials of patients with disease for 1 year or less were included, as well as trials comparing outcomes among diabetic and nondiabetic patients.

Data Extraction: Relevant data were abstracted in duplicate into a standardized template.

Data Synthesis: Data were synthesized in a qualitative manner, and a random-effects meta-analysis of the effects of interventions in prediabetes on the incidence of diabetes was performed.

Limitations: Most of the data on diabetes treatment were not from primary trial data but from subgroup analyses. Participants in intensive lifestyle interventions for prediabetes may not be representative of general prediabetic populations.

Conclusion: Direct evidence is lacking on the health benefits of detecting type 2 diabetes by either targeted or mass screening, and indirect evidence also fails to demonstrate health benefits for screening general populations. Persons with hypertension probably benefit from screening, because blood pressure targets for persons with diabetes are lower than those for persons without diabetes. Intensive lifestyle and pharmacotherapeutic interventions reduce the progression of prediabetes to diabetes, but few data examine the effect of these interventions on long-term health outcomes.

Ann Intern Med. 2008;148:855-868. www.annals.org
For author affiliations, see end of text.

The 2002 National Health and Nutrition Examination Survey estimated that 19.3 million U.S. adults (9.3% of the total U.S. population) had diabetes mellitus, one third of whom had undiagnosed diabetes (1). In addition, 26.0% had impaired fasting glucose and impaired glucose tolerance was even more prevalent (2). The prevalence of diagnosed diabetes is increasing, particularly among obese individuals (1, 3). The risk for death among persons with diabetes is about twice that of persons without diabetes, and cardiovascular events account for more than three fourths of these deaths (4).

Type 2 diabetes often goes undiagnosed for many years because hyperglycemia develops gradually and may not produce symptoms (3, 5). Persons with diabetes are at increased risk for microvascular and macrovascular complications, and duration of diabetes and degree of hyperglycemia are associated with an increased risk for microvascular complications (6–9). The prevalence of macrovascular complications is elevated in persons with prediabetes (defined as impaired fasting glucose, impaired glucose tolerance, or both) and in persons with newly diagnosed diabetes (10–18). A substantial proportion of persons presenting with a new cardiovascular event have undiagnosed diabetes or prediabetes (10, 19–23). Several recent observational studies and a meta-analysis suggest an association between chronic hyperglycemia and cardiovascular disease and stroke (24–27).

Diabetes has a long preclinical phase, estimated at 10 to 12 years on the basis of the progression of microvascular complications (28), and valid and reliable tests can detect type 2 diabetes during this asymptomatic period (29). The previous evidence review for the U.S. Preventive Services Task Force (USPSTF) (29, 30) suggested that screening is justified if the ensuing treatments offer incremental net benefits compared with treatment at the time of clinical presentation. In 2003, the USPSTF concluded that the evidence was insufficient to recommend for or against routinely screening asymptomatic adults for type 2 diabetes or

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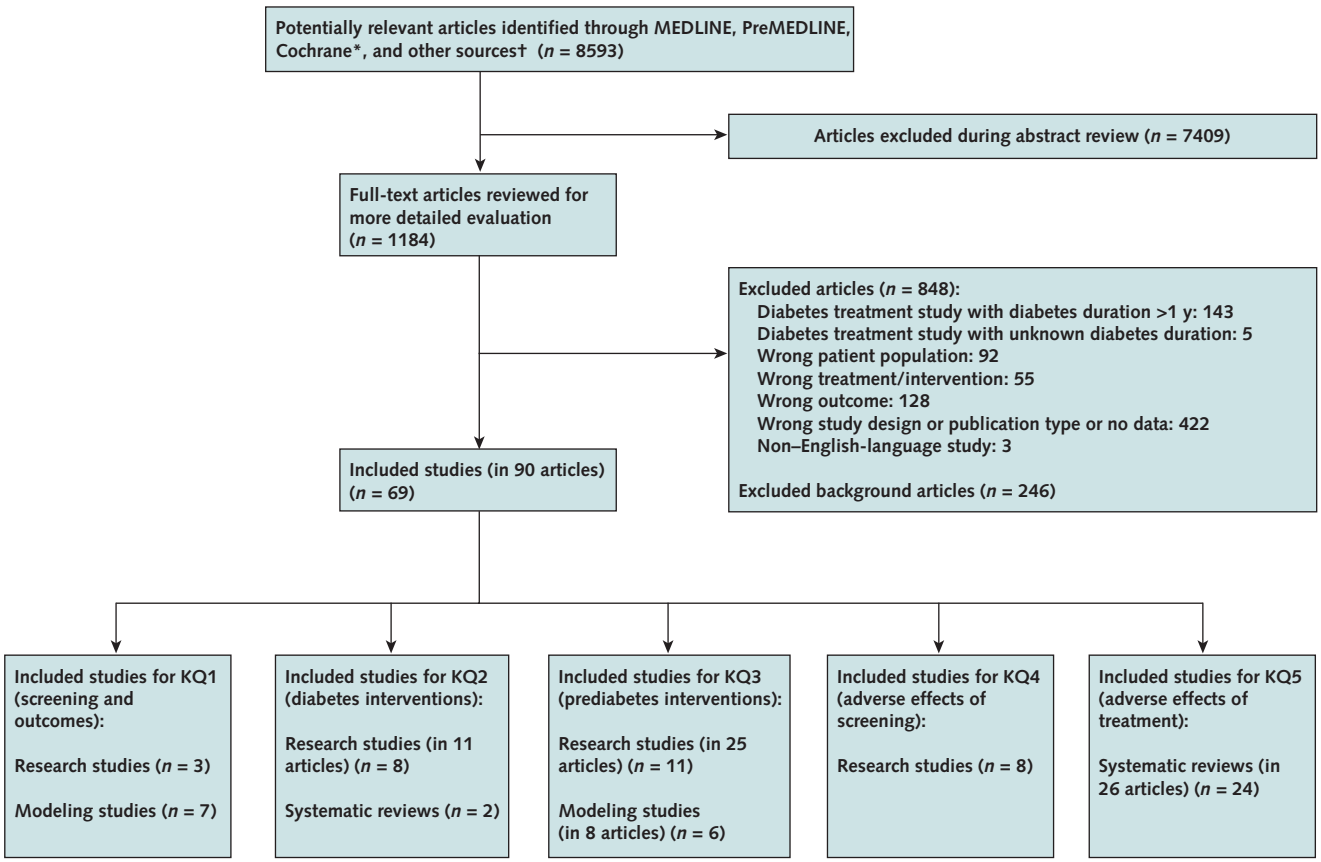
Figure. **Study flow diagram.**



KQ = key question. *Cochrane databases were the Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and Database of Abstracts of Reviews of Effects. †Other sources were reference lists and expert referrals.

prediabetes, but it did recommend screening for adults with hypertension or hyperlipidemia (31).

This review summarizes evidence that has become available since the previous report to inform an update of the 2003 USPSTF recommendations on screening for type 2 diabetes and prediabetes.

Methods

The methods of the USPSTF evidence reviews are fully detailed elsewhere (32). The analytic framework (**Appendix Figure 1**, available at www.annals.org) focuses on decreasing the risk for complications from type 2 diabetes as a result of screening for diabetes. We did not consider secondary prevention studies that exclusively enrolled persons with known cardiovascular disease, because we considered those persons to have a potential preexisting diabetes complication.

We searched MEDLINE and the Cochrane Library for relevant English-language systematic reviews and studies published between March 2001 (6 months before the end date of the previous search) and July 2007 related to 5 key questions. We also examined the reference lists of included studies and ClinicalTrials.gov for relevant trials. We evaluated all studies included in relevant systematic reviews for potential inclusion. We included randomized, controlled trials (RCTs) and observational studies that examined the effectiveness or adverse effects of screening and diagnosis of type 2 diabetes. We used RCTs to assess the effectiveness of diabetes and prediabetes treatments. For diabetes interventions, we included trials with patients who had disease for 1 year or less, as well as trials comparing outcomes among diabetic and nondiabetic populations. We used good-quality systematic reviews to assess the adverse effects of treatment. Search strategies are available in the full evidence report, which can be found at www.ahrq.gov/clinic/uspstf/uspstopics.htm.

An investigator screened titles and abstracts, and a random sample of 1500 titles and abstracts was dual reviewed. Two reviewers examined the full text of potentially relevant articles to achieve consensus on inclusion (**Figure**). Data were abstracted by one investigator and checked by another. We assessed internal validity of individual trials by examining factors that might introduce bias: adequate randomization, allocation concealment, baseline comparabil-

ity of participants, blinding, and loss to follow-up. We rated studies as good, fair, or poor quality by using standard USPSTF criteria (32). We rated systematic reviews on the basis of established criteria, and we included only good-quality reviews (33, 34). We assessed potential applicability of individual studies to primary care practice on the basis of the methods of participant recruitment and selection.

We identified studies that modeled screening interventions from our main search, as well as from a recent, good-quality systematic review of screening for type 2 diabetes by the National Health Service Research and Development Health Technology Assessment Programme (35). We independently abstracted the relevant studies included in that report and relied on their extensive assessments of model quality.

We performed a qualitative synthesis of abstracted data that were generally too heterogeneous for quantitative pooling, except for estimates of the effect of pharmacotherapeutic or lifestyle interventions on diabetes incidence in prediabetic populations. We calculated these pooled estimates by using a hazard ratio and its SE from Cox regression; either a rate ratio or a risk ratio was calculated when a hazard ratio was not reported (36–38). We tested for statistical heterogeneity with the standard chi-square test and obtained the overall estimates of relative risk by using a random-effects model (39).

Role of the Funding Source

This study was funded by the Agency for Healthcare Research and Quality (AHRQ) under a contract to support the work of the USPSTF. Agency staff and USPSTF members participated in the initial scope of this work and reviewed interim analyses and the final report. A draft version was distributed to content experts for review. Agency approval was required before this manuscript could be submitted for publication, but the authors are solely responsible for the content and the decision to submit it for publication.

RESULTS

Key Question 1

Is there direct evidence that systematic screening for type 2 diabetes, impaired fasting glucose, or impaired glucose tolerance among asymptomatic adults improves health outcomes?

We identified no RCTs examining the effectiveness of a screening program for type 2 diabetes. A small, good-quality, case–control study did not find benefit from screening when microvascular complications were considered (40). Limited data from 2 cross-sectional studies did not provide good-quality, direct evidence of the effectiveness of screening for type 2 diabetes in either targeted or general populations (41, 42).

Of modeling studies identified (35, 43–48), 2 recent high-quality studies suggested that targeted screening for type 2 diabetes among persons with hypertension may be relatively cost-effective when macrovascular benefits of optimal blood pressure control are considered (35, 47), older persons benefitted more than younger persons (35, 47), and screening obese persons was more cost-effective than mass screening (35).

The ADDITION (Anglo-Danish-Dutch Study of Intensive Treatment in People with Screen Detected Diabetes in Primary Care) study (49), currently in progress, may shed light on differences in baseline characteristics and long-term health outcomes between persons with screening-detected diabetes and those who present with symptoms.

Key Question 2

Does beginning treatment of type 2 diabetes early as a result of screening provide an incremental benefit in health outcomes compared with initiating treatment after clinical diagnosis?

We identified no studies that directly explored this question by comparing treatment effects between persons with screening-detected versus clinically detected diabetes, nor did we identify new studies reporting treatment effects in an exclusively screening-detected or recently diagnosed diabetes cohort. Because of the lack of direct evidence, we examined intervention studies comparing treatment effects in diabetic versus nondiabetic populations (50–61) to address the question: "Would early knowledge of a diabetes diagnosis prompt a change in clinical management?"

Tight Glycemic Control

No new, completed studies have examined the effect of glycemic control strategies in persons with newly diagnosed type 2 diabetes since the previous USPSTF review (29). The UKPDS (United Kingdom Prospective Diabetes Study) (62) remains the largest and most influential trial of intensive glycemic control in persons with newly diagnosed, mainly clinically detected, type 2 diabetes. In the UKPDS, persons assigned to intensive glycemic control had a 25% reduction (95% CI, 7% to 40%) in microvascular complications, mostly due to a reduced need for retinal photocoagulation, as well as a nonsignificant 16% relative risk reduction (CI, 71% to 100%) of myocardial infarction (62). The UKPDS investigators estimated that 19.6 persons (CI, 10 to 500 persons) would need to be intensively treated for 10 years to prevent 1 person from developing any single clinical end point (62). A recent meta-analysis combined results from the UKPDS and other older trials examined in the last USPSTF review, and it concluded that tight glycemic control resulted in a modest reduction of macrovascular events, particularly peripheral vascular and cerebrovascular events, in persons with type 2 diabetes (combined incidence rate ratio for any macrovascular event, 0.81 [CI, 0.73 to 0.91]) (27). Examination of the individual trials, however, showed largely nonsignificant results, and it was unclear how overlapping populations from the UKPDS were accounted for in the meta-analysis.

It is unlikely that good-quality trial evidence of the final health benefits of early glycemic control in a screening-detected population will ever be available because withholding treatment from persons with known diabetes is unethical and the length of follow-up required might be prohibitive. The ADDITION study (49) should provide valuable information, although it will be assessing the incremental benefit of very aggressive glycemic control over current standards for glycemic control in a screened population.

Specific Antihypertensive Treatment

There is no clear evidence that persons with diabetes detected by screening would respond differently to specific antihypertensive regimens compared with persons without diabetes. We found no new studies involving antihypertensive agents in screening-detected individuals; however, we identified 2 new trials comparing the effect of different antihypertensive regimens in persons with and those without diabetes (**Appendix Table 1**, available at www.annals.org) (51, 52). The ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial) (51) was an effectiveness trial showing no demonstrable advantage of either a calcium-channel blocker or an angiotensin-converting enzyme inhibitor over a thiazide diuretic in reducing deaths or cardiovascular events in both the diabetes and nondiabetes subgroups. A second study compared verapamil with either a β-blocker or a thiazide diuretic and found no evidence of a differential effect on cardiovascular outcomes between those with and those without diabetes (52). However, neither trial was originally powered to detect differences between the diabetes and nondiabetes subgroups. A third trial (included in the previous USPSTF review [29]) examined persons with hypertension and left ventricular hypertrophy. It showed that persons with diabetes had lower cardiovascular mortality with losartan compared with atenolol, and those without diabetes experienced a reduction in stroke with losartan (53, 54).

We identified 1 meta-analysis of antihypertensive trials that compared outcomes between persons with and those without diabetes (63). Angiotensin-receptor blockers provided significantly greater protection against congestive heart failure for those with diabetes than for those without diabetes. All of the studies of angiotensin-converting enzyme inhibitors compared with placebo were secondary prevention trials, except for the HOPE (Heart Outcomes Prevention Evaluation) trial, which was a combination of primary and secondary prevention (64, 65) and was included in the previous USPSTF review (29). The HOPE trial showed that persons with type 2 diabetes and at least moderate cardiovascular risk (age >55 years and 1 additional cardiovascular risk factor) experienced a 25% relative risk reduction (CI, 12% to 36%) in cardiovascular events, cardiovascular deaths, and stroke with ramipril treatment—a similar benefit to that achieved in persons with a history of ischemic heart disease and no diabetes (64, 65).

Intensity of Antihypertensive Treatment

As discussed in the previous USPSTF review (29), 1 trial (the HOT [Hypertension Optimal Treatment] trial [66]) provided evidence that aggressive blood pressure control in persons with diabetes reduces cardiovascular morbidity. In that trial, the diabetes subgroup experienced a 51% relative risk reduction in cardiovascular events from more aggressive blood pressure control, a greater benefit than that observed in nondiabetic patients (29, 66). We did not identify new trials comparing intensive and less intensive blood pressure treatment targets in persons with and without diabetes. A recent meta-analysis presented limited evidence that higher-intensity antihypertensive treatment reduces the risk for major cardiovascular events in persons with diabetes (relative risk, 0.64 [CI, 0.46 to 0.89]) but not in those without diabetes (63); the differential effect on cardiovascular mortality was less clear. The ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial, currently in progress, will examine the relative benefits of very intensive blood pressure control compared with more moderate standards (target systolic blood pressure <120 mm Hg vs. <140 mm Hg) (67).

Initiation of Lipid-Lowering Treatment

Studies of intensive lipid-lowering treatment suggest that persons with diabetes benefit to a similar extent as those without diabetes. For this update, we identified 4 trials (**Appendix Table 2**, available at www.annals.org) (50, 55, 57, 58) and 1 meta-analysis (68) examining the effects of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors on primary prevention of cardiovascular events and deaths in persons with and without diabetes. In 1 trial, neither the diabetes group nor the nondiabetes subgroup benefited from statin treatment in reducing mortality or cardiovascular event rates, but the rate of nonstudy statin use was high in the control group and the differential reduction in low-density lipoprotein cholesterol between study groups was relatively small (50). In 2 fair-quality trials, statin therapy did not significantly reduce the primary end point (coronary events in 1 trial and coronary and/or stroke events in the other) in the diabetes subgroup, but it did benefit the nondiabetes subgroup (55, 58). Comparisons between persons with and those without diabetes were hampered by a relatively low absolute number of events in the diabetes subgroup.

The Heart Protection Study (57) was a large, good-quality RCT examining the efficacy of an HMG-CoA reductase inhibitor in primary and secondary prevention of cardiovascular events and death. Persons with diabetes had a similar reduction in cardiovascular events (relative risk reduction, 27% [CI, 7% to 40%]) as did persons without diabetes who had known vascular disease, and the benefit

was independent of initial low-density lipoprotein cholesterol levels. Many in the diabetes subgroup had additional cardiovascular risk factors, including smoking, hypertension, dyslipidemia (high triglyceride and low high-density lipoprotein cholesterol levels), or a combination of these. Although persons with shorter diabetes duration seemed to benefit to a similar extent as those with much longer-duration diabetes, power was insufficient to determine whether participants with newly diagnosed diabetes (that is, ≤1 year) benefited to a significant extent.

A recent meta-analysis of 6 primary prevention trials—the 4 just discussed, an older trial using a fibric acid derivative, and an older statin trial—reported that lipid-lowering drug treatment seemed to be equally efficacious in persons with and those without diabetes (68).

Aspirin for Primary Prevention

The previous USPSTF review (29) included several trials of aspirin for primary prevention of cardiovascular disease. The Antithrombotic Trialists' Collaborative meta-analysis showed a nonsignificant 7% relative risk reduction in the incidence of vascular events in the high-risk diabetic population (69), a result mainly driven by the results of the ETDRS (Early Treatment Diabetic Retinopathy Study), in which the incidence of fatal and nonfatal coronary events decreased in the treatment group (relative risk, 0.83 [CI, 0.66 to 1.04]) (70). In the Physicians' Health Study (71), aspirin was associated with significant cardiovascular risk reduction in persons with diabetes, and the benefit seemed greater in those with diabetes than in those without.

We identified 2 new studies of low-dose aspirin for primary prevention of cardiovascular events in persons with and without diabetes (59, 60). In the Primary Prevention Project (59), the subgroup with diabetes did not experience any benefit, whereas the subgroup without diabetes experienced a reduction in the incidence of major cardiovascular and cerebrovascular events (relative risk, 0.59 [CI, 0.37 to 0.94]). This fair-quality study was stopped early, with a resultant low event rate in both groups. Given the small size of the group with diabetes, the trial was probably underpowered to detect a difference in this subgroup. The Women's Health Study (60), a large, good-quality trial, showed that aspirin reduced the incidence of ischemic stroke (relative risk, 0.42 [CI, 0.22 to 0.82]), but not cardiovascular events, in women with diabetes. There was no evidence that the effect of aspirin was significantly more pronounced in women with diabetes than in those without. The difference in results between the Primary Prevention Project (59) and the Women's Health Study (60) may be due to differences in the populations considered or to the differential risks for stroke versus those for myocardial infarction (the rate of stroke was higher than that of myocardial infarction in the Women's Health Study).

Key Question 3

Does beginning treatment of impaired fasting glucose or impaired glucose tolerance early as a result of screening provide an incremental benefit in final health outcomes compared with initiating treatment after clinical diagnosis of type 2 diabetes?

Three studies reported cardiovascular outcomes with intensive lifestyle interventions in persons with prediabetes (36, 72, 73). In the DPP (Diabetes Prevention Program) (36), neither the cumulative incidence of cardiovascular disease nor the event rate differed among treatment groups; however, the study was not adequately powered to examine these outcomes (74). The STOP-NIDDM (Study to Prevent Non–Insulin-Dependent Diabetes Mellitus) trial (72), in which patients with impaired glucose tolerance were randomly assigned to placebo or acarbose, showed a reduction in cardiovascular events of any type (hazard ratio, 0.51 [CI, 0.28 to 0.95]; absolute risk reduction, 2.5%). However, this study was limited by an attrition rate of 24% overall, with a much higher rate in the treatment group. In the DREAM (Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication) trial (73, 75), the incidence rate of the primary composite outcome of cardiovascular events did not significantly differ between the rosiglitazone and placebo groups (hazard ratio, 1.37 [CI, 0.97 to 1.94]) (75) (**Appendix Table 3**, available at www.annals.org).

Many studies have examined the effect of lifestyle interventions on the incidence of type 2 diabetes among persons with prediabetes (36, 38, 76–81), several of which (36, 76, 80, 81) were included in the previous review (29). In the DPP (36), the incidence of diabetes was reduced at 3-year follow-up with an intensive lifestyle intervention (reduction in incidence, 58% [CI, 48% to 66%]) and with treatment with metformin (reduction in incidence, 31% [CI, 17% to 43%]), both compared with placebo. The Finnish Diabetes Prevention study (76) examined a lifestyle intervention, and the incidence rate of diabetes was significantly reduced at mean follow-up of 3.2 years (hazard ratio, 0.4 [CI, 0.3 to 0.7]). This was maintained 3 years after completion of the intervention (hazard ratio, 0.57 [CI, 0.43 to 0.76]) (82). A Chinese study also reported a significant decrease in the incidence of type 2 diabetes at 6-year follow-up with an intensive lifestyle intervention (80). Two smaller, more recent trials examined the effect of lifestyle interventions on incidence rates of diabetes among persons with prediabetes and found a significant decrease in incidence compared with usual care (38, 77).

Several recent studies examined the effect of pharmacotherapeutic interventions on diabetes incidence. In the DREAM trial (73, 75), rosiglitazone reduced the incidence of diabetes among persons with prediabetes when it was administered for a median of 3.0 years (hazard ratio, 0.38 [CI, 0.33 to 0.44]) (75), whereas ramipril was not effective in reducing the incidence of diabetes (73). In the STOP-NIDDM trial (72), the incidence rate of type 2 diabetes

Table 1. **Summary of Evidence***

Variable	Design	Limitations	Consistency
Key question 1: overall effect of screening on final outcomes			
3 studies	Case–control and cross-sectional studies (40–42)	Data were limited; studies considered microvascular complications only.	Studies were consistent.
Key question 2: diabetes treatment			
8 studies	RCTs with diabetes vs. nondiabetes (subgroup analyses); RCTs with duration of T2DM ≤1 y (50–52, 55, 57–61)	Several studies were probably underpowered for the diabetes subgroup. Baseline characteristics differed between the diabetes and nondiabetes subgroups.	Studies generally showed no evidence of a significant differential effect between diabetes and nondiabetes subgroups.
Key question 3: prediabetes treatment			
11 studies	RCTs (36–38, 72, 75–79, 83, 84)	Mean follow-up, approximately 3 years; longest follow-up, 7 years; only 3 studies examined long-term health outcomes.	Lifestyle and drug interventions consistently produced a decrease in incidence of T2DM.
Key question 4: adverse effects of screening			
8 studies	Cohort and cross-sectional studies (98–100, 103–105, 107, 109)	All observational studies; predominantly white; study samples composed of volunteers; short follow-up.	It is difficult to compare results across studies because of heterogeneous outcome measures and comparison groups; however, no serious adverse effects were noted.
Key question 5: adverse effects of treatment			
24 studies	Systematic reviews (111–113, 115–124, 126–136)	Reviews were almost entirely based on trials of short to moderate duration; long-term data were lacking.	Not applicable; different drugs were examined in each review.

* ACE-I = angiotensin-converting enzyme inhibitor; BP = blood pressure; CVD = cardiovascular disease; NSD = no significant difference; RCT = randomized, controlled trial; T2DM = type 2 diabetes mellitus.

was reduced significantly in the acarbose treatment group over the 3.3-year intervention (hazard ratio, 0.75 [CI, 0.63 to 0.90]).

In the XENDOS (XENical in the Prevention of Diabetes in Obese Subjects) study (83), which was rated fair-to-poor quality because of high attrition, orlistat reduced the incidence of type 2 diabetes over 4 years in patients with impaired glucose tolerance (hazard ratio, 0.55 [CI not reported]) (83). A meta-analysis of 3 other studies of orlistat produced similar results (37). Acarbose (84) and metformin (77) also decreased diabetes incidence at up to 3-year follow-up. Two studies of interventions in persons with prediabetes are in progress, and published results are not yet available (85, 86).

Results from our meta-analyses showed that the incidence of type 2 diabetes was decreased with lifestyle interventions (pooled hazard ratio, 0.48 [CI, 0.40 to 0.58]) (**Appendix Figures 2** and **3**, available at www.annals.org). Pharmacotherapeutic interventions also reduced diabetes incidence (pooled hazard ratio, 0.65 [CI, 0.51 to 0.83]), although the data were statistically heterogeneous largely due to the effect of the rosiglitazone group of the DREAM trial (73).

We did not identify any data to address the question of whether there should be different treatment targets for lipid levels and blood pressure for persons with prediabetes compared with normoglycemic persons.

We identified only 1 study examining the comparative effectiveness of different medications for treating hyperlipidemia, hypertension, and cardiovascular disease among

Table 1—**Continued**

Primary Care Applicability	Overall Quality Rating	Summary of Findings
Case–control study was representative of a primary care population, but results did not represent population-level results from a screening program. Fair-quality cross-sectional study was a non-U.S. population in an area of high screening rates and national registries; however, an unknown percentage was clinically detected.	Poor	Both fair-quality studies demonstrated no benefit for screening: Case–control study: Patients with ≥1 glucose screening event in 10 years had a 13% reduction in risk for severe microvascular T2DM complications. Cross-sectional study: No significant differences between T2DM population and general Swedish population (where there is a high level of screening for T2DM) in most measures of visual acuity. One poor-quality study showed NSD.
Studies were representative of a primary care population, but results did not represent population-level results from a screening program.	Fair	Persons with T2DM without known CVD seem to benefit from aggressive lipid-lowering treatment as much as persons without T2DM with known CVD. There is little strong evidence that specific antihypertensive drugs benefit persons with T2DM more than those without. Persons with T2DM seem to benefit from a lower BP target than persons without. Fair evidence suggests a marginal benefit of aspirin for primary prevention of CVD, although no clear evidence suggests that those with diabetes benefit more than other subgroups at high risk for CVD.
Trials consisted of highly selected participants.	Fair	Intensive lifestyle and pharmacotherapeutic interventions reduce the progression of prediabetes to T2DM at follow-up up to 7 years. Few data exist on the effect of these interventions on cardiovascular events, death, or other long-term health outcomes.
Studies included persons at high risk for T2DM, so results may not be applicable to primary care populations.	Fair to poor	Data were sparse on the psychological effects of screening for T2DM, and no available data suggested significant adverse effects at up to 1-year follow-up. No study reported serious, long-term, adverse effects of a new diagnosis of T2DM.
Included studies were largely trials of selected populations with limited applicability to real-world, primary care populations.	Fair	Acarbose: NSD in death from placebo; gastrointestinal side effects common. Metformin: NSD in death, hypoglycemia, lactic acidosis vs. placebo or diet. ACE-I: significant increase in cough vs. placebo. β-Blockers: increase in withdrawals secondary to adverse events vs. placebo; NSD in total deaths. Rosiglitazone: new data on potential for increased risk for cardiac events and heart failure.

persons with prediabetes versus those with normoglycemia. The ALLHAT (51) examined various antihypertensive therapies among persons with diabetes, impaired fasting glucose, and normoglycemia and failed to demonstrate superiority for an angiotensin-converting enzyme inhibitor or a calcium-channel blocker compared with a thiazide-type diuretic across the 3 glycemic strata for the composite outcome of coronary heart disease death and nonfatal myocardial infarction.

Modeling studies have been used to examine the treatment of prediabetes (35, 87–94). The health technology assessment by Waugh and colleagues (35) recommended screening for glucose intolerance because strategies for reducing cholesterol and blood pressure are effective and because type 2 diabetes can be prevented. Waugh and colleagues seem to assume that the effects of treating persons with screening-detected diabetes are the same as those of treating persons with clinically detected diabetes and that there are proven linkages between treating dysglycemia and final health outcomes. They also systematically reviewed published economic models and noted that, despite the variable quality, structure, and assumptions of the models, all predicted that delaying the onset of diabetes would substantially reduce the incidence of vascular complications, improve quality of life, and avoid future medical costs. They concluded that if a screening program was implemented to target persons at risk for diabetes, subsequent treatment for persons with impaired glucose tolerance with lifestyle or pharmacologic interventions was a good use of resources.

Herman and associates (90) examined the lifetime utility and cost-effectiveness of the DPP lifestyle intervention (36) and found the intervention to be relatively cost-effective (cost per quality-adjusted life-year, $8800 [from a so-

cietal perspective]), with a 0.5-year gain in life expectancy and 20% decrease in diabetes incidence. Results were somewhat less marked with metformin, which was still relatively cost-effective.

Eddy and colleagues (87, 88) examined the DPP interventions and also predicted large absolute reductions in the proportion of persons developing type 2 diabetes and a delay of 7 to 8 years in onset of diabetes, as well as that the DPP lifestyle intervention will lead to fewer complications and improved quality-adjusted life-years (95). They, however, estimated much higher marginal cost-effectiveness ratios than did Herman and associates (96).

Several other models recently evaluated primary prevention of type 2 diabetes among persons with impaired glucose tolerance (91, 92, 94, 97), and all demonstrated relative cost-effectiveness of lifestyle interventions. Two models examined metformin and found it to be cost-saving under many conditions (92, 97).

Key Question 4

What adverse effects result from screening a person for type 2 diabetes, impaired fasting glucose, or impaired glucose tolerance?

Data are sparse on the psychological effects of screening for type 2 diabetes, and none of the data that we identified suggested significant adverse effects at up to 1-year follow-up (98–110). In the ADDITION study (103), stepwise screening had limited effects on anxiety levels at up to 1-year follow-up. In a cross-sectional study, Skinner and colleagues (109) did not find that screening high-risk patients for type 2 diabetes with an oral glucose tolerance test was associated with significant anxiety. Other included studies also did not report any serious psychological effects of a new diagnosis of type 2 diabetes (98–104, 107, 108, 110).

Several studies compared persons with screening-detected diabetes with persons without diabetes. Using Hoorn observational data, Adriaanse and colleagues (100) found no significant differences in well-being and health-related quality of life between patients with newly diagnosed diabetes and those at high risk but without diabetes at 2-week and 1-year follow-ups. Poorer quality-of-life scores at 6-month follow-up in the group with diabetes may suggest a temporary effect. Similar results were found in several other studies (98, 104, 107). In the ADDITION study (102, 103, 110), persons with screening-detected diabetes generally reported low emotional distress, with some differences in distress and self-efficacy noted between groups treated intensively compared with usual care.

We identified no studies that addressed the effects of a false-positive result from any of the tests used to screen for dysglycemia. We identified no studies that directly addressed labeling of persons with screening-detected diabetes and no studies that examined the effect of a diagnosis of prediabetes.

Key Question 5

What adverse effects result from treating a person with type 2 diabetes, impaired fasting glucose, or impaired glucose tolerance detected by screening?

Recent systematic reviews of the adverse effects of drugs used in treating type 2 diabetes and prediabetes (111–136) reveal some important new data related to the safety to thiazolidinediones. An association between rosiglitazone and increased risk for myocardial infarction (134, 137) and heart failure (134) was noted recently. For other drugs examined in the studies included in this review, we identified no new data on severe adverse effects compared with data available at the time of the previous USPSTF review (29). Intensive glucose control in the UKPDS was not associated with high rates of hypoglycemia (0.55% annual incidence of major hypoglycemia) (138). Relatively common side effects, such as cough with angiotensin-converting enzyme inhibitors and gastrointestinal effects with acarbose, should be considered when prescribing these drugs, but they are not associated with increased deaths or adverse cardiovascular outcomes.

Discussion

No direct evidence clearly determines whether screening asymptomatic individuals for diabetes or prediabetes alters health outcomes (**Table 1**). Evidence shows that persons with diabetes benefit from control of blood pressure and lipid levels, but studies have not included persons with screening-detected diabetes. Persons with hypertension and type 2 diabetes benefit from lower blood pressure targets than persons with hypertension but without diabetes (66). Persons with newly diagnosed, largely clinically detected, diabetes benefit from intensive glycemic control, largely because of a reduction in microvascular events (62). Evidence shows that intensive lifestyle modification in persons with prediabetes—an implicitly screening-detected population—delays the progression to clinical diabetes, but whether treatment alters final health outcomes is unknown because studies were not powered for those outcomes or were not of sufficient duration.

Tables 2 and **3** show the numbers needed to screen to prevent an outcome of interest in different theoretical populations. These outcomes have not changed from the estimates of the previous USPSTF review (29) because we identified no new data on the effectiveness of these interventions. As noted elsewhere (29), interventions that target cardiovascular events produce greater effects than those that target microvascular complications occurring later in the disease process.

On the basis of the DPP (36) and the Finnish Diabetes Prevention Study (76), screening 1000 persons with prediabetes will delay 44 cases of type 2 diabetes over 3.0 years. Pharmacotherapy with metformin (on the basis of DPP data [36]) produced a somewhat less favorable number needed to screen. Many important assumptions under-

Table 2. **Number Needed to Screen for Type 2 Diabetes to Prevent 1 Adverse Event after 5 Years of Additional Treatment***

Prevalence of Undiagnosed Disease	Patient Population	Tight Glycemic Control to Prevent 1 Case of Blindness in 1 Eye (Screening 1000 People with Given Prevalence)			Tight Blood Pressure Control to Prevent 1 CVD Event (Screening 1000 Hypertensive People with Given Prevalence)		
		Increase in Persons with Tight Glycemic Control, %	Cases of Blindness Averted, *n*†	NNS	Increase in Persons with Tight Blood Pressure Control, %	CVD Events Averted, *n*‡	NNS
2.8%	Standardized prevalence in U.S.‡	50	0.06	16 420	50	0.53	1905
		90	0.11	9122	90	0.95	1058
3.6%	Standardized prevalence in U.S. non-Hispanic black persons‡	50	0.08	12 771	50	0.68	1481
		90	0.14	7095	90	1.22	823
6.0%	Prevalence estimated for previous review	50	0.13	7663	50	1.13	889
		90	0.23	4257	90	2.03	494

* CVD = cardiovascular disease; NNS = number needed to screen.
† Relative risk reduction, 0.29 over 5 years; rate of blindness in no-treatment group, 1.5% over 5 years. Data on incidence of retinal photocoagulation in 1 eye from the United Kingdom Prospective Diabetes Study (62).
‡ Relative risk reduction of 0.50 over 5 years; 5-year incidence in usual treatment group, 7.5%. Data from the Hypertension Optimal Treatment trial (66).

lying number-needed-to-screen estimates remain, including length of the asymptomatic period, prevalence of undiagnosed diabetes or prediabetes, incidence rates of diabetes complications, and treatment effect.

Screening targeted to populations at risk for diabetes would probably increase the yield and economic efficiency of screening, and risk scores have been developed to identify those at high risk for diabetes (139–144). In the DPP, older age and higher body mass index increased the yield of screening across ethnic groups (145). On the other hand, the prevalence of diagnosed diabetes in certain high-risk groups, such as non-Hispanic black persons and Mexican-American persons, has increased, whereas the proportion of persons with undiagnosed disease in those groups has decreased, suggesting that opportunistic screening targeted to populations at high risk may already be occurring. This trend reduces the prevalence of undiagnosed diabetes and increases the number needed to screen to prevent adverse events in the remaining unscreened group (1).

A diabetes population of significant interest to a screening program would be individuals who would benefit from aggressive interventions to reduce macrovascular complications in persons who would not have been otherwise identified through recommended hypertension and hyperlipidemia screening (31). Many persons with diabetes are hypertensive or have additional cardiovascular disease risk factors, and those with the highest cardiovascular risk profiles are likely to benefit most from treatment (57, 62, 146–148). As shown in the Heart Protection Study (63), elevated low-density lipoprotein cholesterol levels alone

Table 3. **Number Needed to Screen for Prediabetes to Prevent 1 Case of Diabetes after 3 Years***

Prevalence of IGT or IFG	Patient Population	Lifestyle Intervention to Prevent 1 Case of Diabetes (Screening 1000 People with Given Prevalence)†			Metformin to Prevent 1 Case of Diabetes (Screening 1000 People with Given Prevalence)‡		
		Increase in Persons Adhering to Intervention, %	Cases of Diabetes Delayed, *n*	NNS	Increase in Persons Adhering to Intervention, %	Cases of Diabetes Delayed, *n*	NNS
15.0%	IGT only, total U.S. population§	50	4.79	209	50	2.56	391
		90	8.61	116	90	4.60	217
26.0%	IFG only, total U.S. population‖	50	8.29	121	50	4.43	226
		90	14.93	67	90	7.98	125
40.0%	Estimate IFG and/or IGT¶	50	12.76	78	50	6.82	147
		90	22.97	44	90	12.28	81

* IFG = impaired fasting glucose; IGT = impaired glucose tolerance; NNS = number needed to screen.
† Relative risk reduction, 58%; 38% achieved weight loss goal of 7% at end of 3-year follow-up (intention-to-treat analysis); control rate, 11%. Data from the Diabetes Prevention Program (36).
‡ Relative risk reduction, 31% with adherence rates (≥80% of medications taken); 77% in control group; 72% in intervention group. Data from the Diabetes Prevention Program (36).
§ Based on National Health and Nutrition Examination Survey, 1994 data (2).
‖ Prevalence data from National Health and Nutrition Examination Survey, 2002 (1): IFG, 5.5–6.93 mmol/L (100–126 mg/dL).
¶ From National Institute of Diabetes and Digestive and Kidney Diseases, 1994 data (http://diabetes.niddk.nih.gov/dm/pubs/statistics).

may not identify many persons with diabetes and dyslipidemia who might benefit from lipid-lowering treatment, but this population had higher-than-average cardiovascular risk profiles. The benefit of identifying and treating asymptomatic diabetes in normotensive, nondyslipidemic persons at average cardiovascular risk is unclear.

The potential yield of diabetes and prediabetes screening must be weighed carefully against the potential harms of screening and diagnosis. We did not identify evidence suggesting serious adverse effects of screening for type 2 diabetes. The literature does, however, have important limitations. Included studies examined persons at high risk for diabetes, and thus the results may not be applicable to mass screening programs that are not targeted (98–100). Theoretical concerns include the effects of labeling (149) on anxiety and insurability, but available evidence is insufficient to support or refute these concerns.

Several limitations deserve mention. First, we restricted our review of diabetes treatment to studies with mean diabetes duration of 1 year or less, because we felt that these patient populations would most closely resemble screening-detected populations. Individuals with longstanding type 2 diabetes will likely show greater benefits from treatment, so focusing on treatment of early disease, in the absence of trials with extended follow-up, may underestimate the effectiveness of treatment and therefore screening interventions. For studies comparing a given treatment among persons with and persons without type 2 diabetes, we included studies of any duration of disease, and the applicability of these data to populations with screening-detected disease is uncertain. Second, attempts to divide patients with diagnosed diabetes into those with a "clinical diagnosis" based on symptoms and those deemed to be "screened" because of alleged asymptomatic status does not truly compare "not screened" with "screened" patients. Third, participants with prediabetes in studies of intensive lifestyle interventions may not be representative of general prediabetic populations. For example, the level of physical inactivity in the DPP cohort was less than that reported in the Third National Health and Nutrition Examination Survey (150). Fourth, most of the data on diabetes treatment were from prespecified subgroup analyses of large trials that included both diabetic and nondiabetic populations. The diabetes and nondiabetes subgroups had important differences, and subgroup analyses were often underpowered to demonstrate significant changes in primary outcomes. Prevention trials among persons with prediabetes were powered to examine the primary outcome of new cases of diabetes and not to examine long-term health outcomes, such as cardiovascular events.

Models rely on data from trials and observational studies and are only as good as the data and assumptions underlying them. All 7 models that we identified that examined the effect of screening interventions (35, 43–48) lack transparency to some degree, and all have had 1 or more of their important underlying assumptions criticized (35).

Further research is needed to define the benefits and harms of screening average-risk individuals for type 2 diabetes. We must learn whether early, aggressive glycemic control in persons with diabetes produces improvements in clinical outcomes after many years of follow-up (151). An extension of the largest study of an initial strategy of sustained tight glycemic control in type 1 diabetes (152) suggested that participants originally randomly assigned to tight glycemic control had a significant reduction in cardiovascular events at long-term follow-up despite similar glycemic control in the control group during the postrandomization period (153). To date, similar data are unavailable for type 2 diabetes. We also need studies to define the duration of the prediabetes phase and identify measurable risk factors for progression to diabetes and its complications, particularly cardiovascular disease.

The cost-effectiveness of diabetes screening programs is considered to be mainly determined by the long-term health benefits rather than the cost of detection and treatment of diabetes (154). Thus, intervention research needs to continue focusing on long-term, sustainable interventions that affect health outcomes in real-world settings. Further work is also needed to examine the effect of screening and diagnosis on patient self-efficacy, motivation for lifestyle change, and the potential psychological effects of labeling.

Direct evidence is lacking on the health benefits of detecting type 2 diabetes by either targeted or mass screening, and indirect evidence also fails to demonstrate health benefits for screening general populations or persons at high risk for diabetes complications without hypertension. Persons with hypertension do benefit from knowing their diagnosis of diabetes, because blood pressure targets are lower than for nondiabetic persons. Although intensive lifestyle interventions delay or prevent diabetes onset in persons with prediabetes, positive effects of this delay on long-term health outcomes have not been adequately demonstrated.

From the Oregon Evidence-based Practice Center of the Oregon Health & Science University and Portland Veterans Administration Medical Center, Portland, Oregon.

Acknowledgment: The following people provided valuable guidance and insights: Mark Helfand, MD, MPH, Evelyn Whitlock, MD, MPH, and Peggy Nygren, MA, of the Oregon Evidence-based Practice Center; Tracy Wolff, MD, MPH, and Mary Barton, MD, MPP, at the Agency for Healthcare Research and Quality; and the U.S. Preventive Services Task Force members Ned Calonge, MD, Russ Harris, MD, MPH, George Isham, MD, MS, and Virginia Moyer, MD, MPH. The authors thank Andrew Hamilton, MLS, MS, for assistance in developing and running search strategies; Peggy Nygren, MA, and Tracy Dana, MLS, for assistance with data abstraction; and Sarah Baird, MS, for technical assistance.

Grant Support: This report was conducted by the Oregon Evidence-based Practice Center under contract to the Agency for Healthcare Research and Quality (contract no. 290-02-0024, Task Order no. 2 for the U.S. Preventive Services Task Force).

Potential Financial Conflicts of Interest: None disclosed.

Requests for Single Reprints: Susan L. Norris, MD, MPH, Department of Medical Informatics and Clinical Epidemiology, Oregon Health & Science University, 3181 SW Sam Jackson Park Road, Mail Stop B1CC, Portland, OR 97239.

Current author addresses are available at www.annals.org.

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Current Author Addresses: Drs. Norris and Fu and Ms. Bougatsos: Department of Medical Informatics and Clinical Epidemiology, Oregon Health & Science University, 3181 SW Sam Jackson Park Road, Mail Stop BICC, Portland, OR 97239.

Dr. Kansagara: Portland Veterans Administration Medical Center, 3710 SW US Veterans Hospital Road, Portland, OR 97239.

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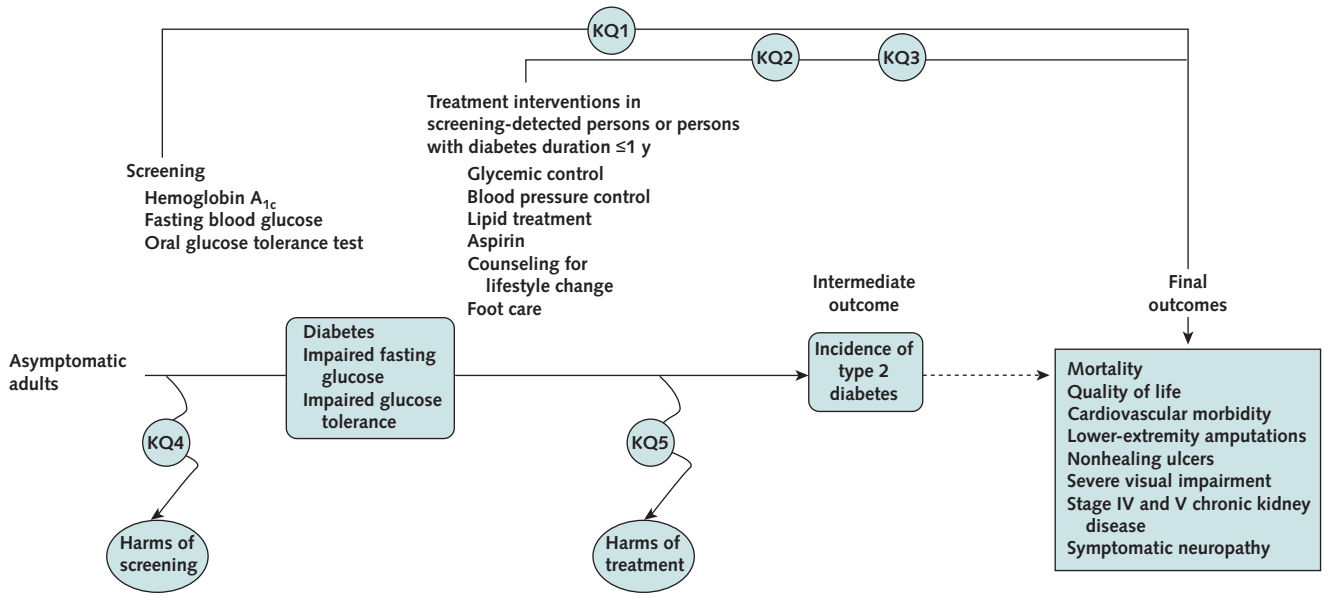
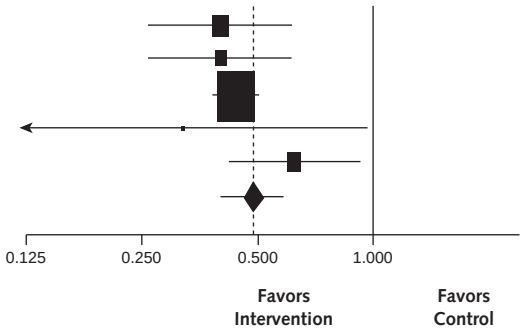
Appendix Figure 1. **Analytic framework.**



KQ = key question.

Appendix Figure 2. **Diabetes incidence in lifestyle trials.**

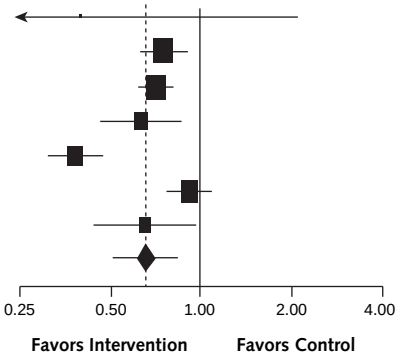
Study, Year (Reference)	Follow-up, *y*	Participants, *n*		Relative Risk (95% CI)
		Control Group	Intervention Group	
Pan et al., 1997 (80)	6	133	397	0.60 (0.43–0.83)
Tuomilehto et al., 2001 (76)	3.2	257	265	0.40 (0.26–0.61)
DPP, 2002 (36)	2.8	1082	1079	0.44 (0.38–0.50)
Kosaka et al., 2005 (38)	4	356	102	0.32 (0.11–0.96)
Ramachandran et al., 2006 (77)	3	136	133	0.62 (0.42–0.92)
All studies combined				0.48 (0.40–0.58)
Test for heterogeneity: $Q = 6.104$; $P = 0.192$				



DPP = Diabetes Prevention Program.

Appendix Figure 3. **Diabetes incidence in drug trials.**

Study, Year (Reference)	Drug	Follow-up, *y*	Participants, *n*		Relative Risk (95% CI)
			Control Group	Intervention Group	
Heymsfield et al., 2000 (37)	Orlistat	2	53	67	0.40 (0.08–2.08)
Chiasson et al., 2002 (72)	Acarbose	3.3	715	714	0.75 (0.63–0.90)
DPP, 2002 (36)	Metformin	2.8	1082	1073	0.71 (0.62–0.81)
Torgerson et al., 2004 (83)	Orlistat	4	1637	1640	0.63 (0.46–0.86)
DREAM, 2006 (75)	Rosiglitazone	3	2635	2634	0.38 (0.31–0.47)
DREAM, 2006 (73)	Ramipril	3	2646	2623	0.91 (0.77–1.08)
Ramachandran et al., 2006 (77)	Metformin	3	136	133	0.65 (0.44–0.96)
All studies combined					0.65 (0.51–0.83)
Test for heterogeneity: $Q = 23.466$; $P = 0.001$					



DPP = Diabetes Prevention Program; DREAM = Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication.

Appendix Table 1. **Randomized, Controlled Trials of Hypertension Treatment in Diabetic Populations***

Study, Year (Reference)	Intervention	Sample Size (Diabetes Subgroup/ Total), *n/n*	Baseline Cardiovascular Risk Factors†	Achieved Blood Pressure, *mm Hg*	Outcome: Relative Risk (95% CI)	Quality Rating	Comment
ALLHAT, 2002 (50), 2005 (51), 2001 (155)	Chlorthalidone vs. lisinopril vs. amlodipine‡	13 101/31 512	HTN: 100/100 History of CVD: 36%/62% Smoking: 13%/28% Hyperlipidemia: NR	Mean SBP (SD) in DM subgroup: Chlorthalidone: 135.0 (15.6) Amlodipine: 136.3 (15.9)§ Lisinopril: 137.9 (19.0)§ Mean SBP (SD) in normoglycemia subgroup: Chlorthalidone: 133.4 (14.9) Amlodipine: 133.5 (14.1) Lisinopril: 134.8 (17.3)	Fatal CVD or nonfatal MI in the DM subgroup: Amlodipine–chlorthalidone: 0.97 (0.86–1.10); $P = 0.64$ Lisinopril–chlorthalidone: 0.97 (0.85–1.10); $P = 0.59$ Fatal CVD or nonfatal MI in the normoglycemia subgroup: Amlodipine–chlorthalidone: 0.94 (0.82–1.07); $P = 0.36$ Lisinopril–chlorthalidone: 1.02 (0.89–1.16); $P = 0.79$ Difference between DM and normoglycemia subgroups: $P =$ NR‖	Fair	Significantly higher rate of attrition in the lisinopril group
CONVINCE, 2003 (52)	Verapamil vs. atenolol or HCTZ	3239/16 476	HTN: 100% Hyperlipidemia: 31.2% Previous MI: 7.6% Established vascular disease: 16.7% Stroke: 4.6%	Mean SBP/DBP in total study sample (DM subgroup NR): Verapamil: 136.5/79.0 Atenolol or HCTZ: 136.6/79.5	Fatal CVD, stroke, or MI: DM subgroup: 0.86 (0.66–1.12); $P =$NR Normoglycemia subgroup: 1.10 (0.92–1.31); $P =$ NR Difference between DM and normoglycemia subgroups: $P = 0.16$‖	Fair	–

* ALLHAT = Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; CONVINCE = Controlled Onset Verapamil Investigation of Cardiovascular End Points; CVD = cardiovascular disease; DBP = diastolic blood pressure; DM = diabetes mellitus; HCTZ = hydrochlorothiazide; HTN = hypertension; MI = myocardial infarction; NR = not reported; SBP = systolic blood pressure.
† Data reported as percentages for the DM/non-DM groups in ALLHAT and for the total study sample for the CONVINCE study (data for the DM subgroup alone NR).
‡ Doxazosin treatment was prematurely discontinued because of an excess of heart failure events.
§ $P < 0.5$ compared with chlorthalidone.
‖ *P* value for interaction between DM and normoglycemia subgroups for primary outcome.

Appendix Table 2. **Randomized, Controlled Trials of Lipid Interventions in Diabetic and Nondiabetic Populations***

Study, Year (Reference)	Intervention	Sample Size (Diabetes Subgroup/ Total), *n/n*	Baseline Cardiovascular Risk Factors	Mean Achieved LDL-C Level (SD), *mg/dL*	Outcome: Relative Risk (95% CI)	Quality Rating	Comment
ALLHAT, 2002 (50)	Pravastatin titrated to achieve 25% reduction in LDL-C vs. usual care	3635/10 355†	Total group (DM subgroup information NR): HTN: 100% History of CVD: 14.2% Smoking: 23.1% Mean LDL-C: 145.6 mg/dL (SD, 21.4)	Pravastatin: 104.0 (29.1) Usual care: 121.2 (34.6)	All-cause mortality, pravastatin vs. usual care‡: DM subgroup: 1.03 (0.86–1.22); P = NR Non-DM subgroup: 0.96 (0.84–1.1); P = NR CHD death or nonfatal MI: DM subgroup: 0.89 (0.71–1.10); P = NR Non-DM: 0.92 (0.76–1.10); P = NR Difference between DM and normoglycemia subgroups: P = NR§	Fair	Relatively small difference in LDL-C between intervention and usual care groups because of withdrawals in intervention group and off-protocol statin use in usual care group
ASCOT, 2003 (55), 2005 (56)	Atorvastatin, 10 mg, vs. placebo	2532/10 305	DM/total group: HTN: 100%/100% Mean LDL-C: 28.7 mg/dL (SD, 27.3)/124.8 mg/dL (SD, 27.3) Smoking: 20.3%/32.2% Cerebrovascular disease: 7.5%/9.7% Peripheral vascular disease: 5.3%/5.0% Mean number of CVD risk factors: 4.1/3.7	Atorvastatin: 83.9 (26.5) Placebo: 117.8 (30.4)	Nonfatal MI or fatal CHD‡: DM subgroup: 0.84 (0.55–1.29); P = NR Non-DM subgroup: 0.56 (0.41–0.77); P = NR Total CVD events and procedures: DM subgroup: 0.77 (0.61–0.98); P = NR Non-DM subgroup: 0.80 (0.68–0.94); P = NR Difference between DM and normoglycemia subgroups: P = 0.82§	Fair	Study stopped early; relatively low number of total events in DM subgroup
Heart Protection Study, 2003 (57)	Simvastatin, 40 mg, vs. placebo	5963/20 536	DM/non-DM: Previous MI: 19%/51% Other history of CVD: 14%/28% Smoking: 67%/78% Blood pressure: 148/82 mm Hg/143/81 mm Hg Mean LDL-C: 124.8 mg/dL (SD, 32.0)/132.6 mg/dL (SD, 32.0)	Simvastatin: 89.7 Placebo: 128.7	Nonfatal MI or fatal CVD‡: DM subgroup: 0.73 (0.62–0.85); $P < 0.001$ Non-DM subgroup: 0.73 (0.66–0.81); $P < 0.001$ Stroke: DM subgroup: 0.76 (0.61–0.94); P = 0.01 Non-DM subgroup: 0.74 (0.64–0.86); $P < 0.001$ Difference between DM and normoglycemia subgroups: P = 0.10§	Good (for overall trial)	Baseline characteristics differed significantly between DM and normoglycemic subgroups
PROSPER, 2002 (58)	Pravastatin, 40 mg, vs. placebo	623/5804	Total group (DM subgroup information NR): Previous angina: 26.9% Previous MI: 13.4% Cerebrovascular disease: 11.2% Vascular disease: 44.2% Mean LDL-C: 148.2 mg/dL (SD, 31.2) Hypertension: 61.9% Smoking: 26.8%	Mean LDL at 3 months: pravastatin, 96.7; placebo, 146.6	Nonfatal MI, fatal CVD, nonfatal and fatal stroke‡: DM subgroup: 1.27 (0.90–1.80); P = NR Non-DM subgroup: 0.79 (0.69–0.91); P = NR Difference between DM and normoglycemia subgroups: P = 0.015§	Fair	Little diabetes-specific information and relatively few persons with diabetes limit conclusions

* To convert LDL-C units to mmol/L, multiply value by 0.0259. ALLHAT = Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; ASCOT = Anglo-Scandinavian Cardiac Outcomes Trial; CHD = coronary heart disease; CVD = cardiovascular disease; DM = diabetes; HTN = hypertension; LDL-C = low-density lipoprotein cholesterol; MI = myocardial infarction; NR = not reported; PROSPER = Prospective Study of Pravastatin in the Elderly at Risk.
† Including persons in the doxazosin group.
‡ Primary outcome.
§ P value for interaction between DM and normoglycemia subgroups for primary outcome.

Appendix Table 3. **Randomized, Controlled Trials of Interventions in Prediabetes***

Study, Year (Reference)	Country	Quality Rating	Total Sample Size, *n*	Mean Length of Follow-up	Sample Characteristics†	Intervention	Outcomes
DPP, 2000 (156, 157), 2002 (36), 2005 (74, 145)	United States	Good	3234	2.8 y; 3.2 y for CVD outcomes	Age, 51 y (10.7); 32.3% men	Intensive lifestyle vs. metformin vs. placebo	Cumulative incidence of T2DM: metformin, 58% lower (95% CI, 48%–66%); lifestyle, 31% lower (CI, 17%–43%) than placebo Cumulative incidence of CVD and CVD event rate: NSD among groups, but underpowered for this outcome
DREAM trial, 2004 (158), 2006 (73, 75)	International; multicenter	Good	5269	Median, 3.0 y	Age, 5.7 y (10.9); 40.8% men; BMI, 30.9 kg/m^2 (5.6)	Rosiglitazone vs. placebo; ramipril vs. placebo	Rosiglitazone: Death: HR, 0.91 (CI, 0.55–1.49); $P = 0.7$ T2DM incidence: HR, 0.38 (CI, 0.33– 0.44); $P < 0.001$ Composite CVD outcome: HR, 0.40 (CI, 0.35–0.46); $P = 0.08$ Ramipril: Death: HR, 0.98 (CI, 0.60–1.60) T2DM incidence: HR, 0.91 (CI, 0.80– 1.03) Composite CVD outcome: HR, 0.91 (CI, 0.81–1.03); $P = 0.68$
Finnish Diabetes Prevention Study, 1999 (161), 2001 (76), 2003 (141), 2003 (159), 2005 (160), 2006 (82)	Finland	Fair	522	3.2 y for postintervention outcomes; median total follow-up, 7 y	Age, 55 y (7); 32.9% men	Lifestyle vs. usual care	Cumulative incidence of T2DM: At 3.2 y: HR, 0.4 (CI, 0.3–0.7); $P < 0.001$ At 7 y: HR, 0.57 (CI, 0.43–0.76); $P < 0.001$
Indian Diabetes Prevention Programme, 2006 (77)	India	Fair	531	Median, 2.5 y	Age, 54.9 y (5.7); 79.0% men	Lifestyle and metformin vs. lifestyle vs. metformin vs. placebo	Relative risk reduction in incidence of T2DM at year 3: Lifestyle: 28.5% (CI, 20.5%–37.3%) Metformin: 26.4% (CI, 19.1%–35.1%) Lifestyle and metformin: 28.2% (CI, 20.3%–37.0%)
Watanabe et al., 2003 (78)	Japan	Fair	173	1.0 y	Age, 55.1 y (7.1); 100% men	Dietary counseling vs. usual care	T2DM incidence: NSD between groups (data not provided)
Pan et al., 2003 (84)	China	Fair	261	16 wk	Age, 54.5 y (8.5); 40.0% men	Acarbose vs. placebo	T2DM incidence: acarbose, 5.6%; placebo, 9.5%; $P = 0.245$
Kosaka et al., 2005 (38)	Japan	Fair	458	4.0 y	Age, NR; 100% men	Lifestyle vs. usual care	Cumulative incidence T2DM over 4 y: lifestyle, 3%; control, 9.3%; $P = 0.043$ between groups
Heymsfield et al., 2000 (37)	International; multicenter	Fair to poor	675	2.0 y	Age, 43.9 y; 17.5% men	Orlistat vs. placebo; both received lifestyle intervention	IGT at baseline and at follow-up: Normoglycemia: orlistat, 71.6%; placebo, 49.1% IGT: orlistat, 25.4%; placebo, 43.4% T2DM: orlistat, 3.0%; placebo, 7.6% $P = 0.04$ between groups
STOP-NIDDM trial, 1998 (163), 2002 (72), 2003 (162)	International; multicenter	Fair	1429	3.3 y	Age, 54.5 y (7.9); 49% men	Acarbose vs. placebo; both received lifestyle intervention	Cumulative incidence of: T2DM: HR, 0.75 (CI, 0.63–0.90); $P = 0.0015$ Any CVD event: HR, 0.51 (CI, 0.28–0.95); $P = 0.02$ MI: HR, 0.09 (CI, 0.01–0.72); $P = 0.02$
Swinburn et al., 2001 (79)	New Zealand	Fair to poor	136	5.0 y	Age, 52.2 y (6.5); 50.7% men	Reduced-fat diet vs. usual diet	Intervention was associated with a lower proportion of persons with T2DM or IGT at 1 y ($P < 0.05$); NSD at 2, 3, or 5 y Included population all had IGT at recruitment, but only 31% had prediabetes with repeated testing at randomization; results are for all included patients
XENDOS study, 2001 (164), 2004 (83)	Sweden	Fair to poor	3305 total (694 with IGT)	4.0 y	Age, 43.8 y (8.0); 44.8% men; BMI, 37.3 kg/m^2 (4.3)	Orlistat vs. placebo; both received lifestyle intervention	Cumulative incidence of T2DM in IGT subgroup after 4 y: HR, 0.551; $P = 0.0024$

* BMI = body mass index; CVD = cardiovascular disease; DPP = Diabetes Prevention Program; DREAM = Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication; HR = hazard ratio; IGT = impaired glucose tolerance; MI = myocardial infarction; NSD = no significant difference; OGTT = oral glucose tolerance test; STOP-NIDDM = Study to Prevent Non–Insulin-Dependent Diabetes Mellitus; T2DM = type 2 diabetes mellitus; XENDOS = XENical in the Prevention of Diabetes in Obese Subjects.
† Data are reported as means (SDs), unless otherwise noted.