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

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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.


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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/uspostopics.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 comparability.
type 2 diabetes among persons with hypertension may be high-quality studies suggested that targeted screening for general populations (41, 42).

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 Diabetest 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).

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

<table>
<thead>
<tr>
<th>Prevalence of Undiagnosed Disease</th>
<th>Patient Population</th>
<th>Tight Glycemic Control to Prevent 1 Case of Blindness in 1 Eye (Screening 1000 People with Given Prevalence)</th>
<th>Tight Blood Pressure Control to Prevent 1 CVD Event (Screening 1000 Hypertensive People with Given Prevalence)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Increase in Persons with Tight Glycemic Control, %</td>
<td>Cases of Blindness Averted, n</td>
</tr>
<tr>
<td>2.8%</td>
<td>Standardized prevalence in U.S.:‡</td>
<td>50</td>
<td>0.06</td>
</tr>
<tr>
<td></td>
<td>90</td>
<td>0.11</td>
<td>9122</td>
</tr>
<tr>
<td>3.6%</td>
<td>Standardized prevalence in U.S. non-Hispanic black persons†</td>
<td>50</td>
<td>0.08</td>
</tr>
<tr>
<td></td>
<td>90</td>
<td>0.14</td>
<td>7095</td>
</tr>
<tr>
<td>6.0%</td>
<td>Prevalence estimated for previous review</td>
<td>50</td>
<td>0.13</td>
</tr>
<tr>
<td></td>
<td>90</td>
<td>0.23</td>
<td>4257</td>
</tr>
</tbody>
</table>

* 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).

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

<table>
<thead>
<tr>
<th>Prevalence of IGT or IFG</th>
<th>Patient Population</th>
<th>Lifestyle Intervention to Prevent 1 Case of Diabetes (Screening 1000 People with Given Prevalence)†</th>
<th>Metformin to Prevent 1 Case of Diabetes (Screening 1000 People with Given Prevalence)‡</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Increase in Persons Adhering to Intervention, %</td>
<td>Cases of Diabetes Delayed, n</td>
</tr>
<tr>
<td>15.0%</td>
<td>IGT only, total U.S. population§</td>
<td>50</td>
<td>4.79</td>
</tr>
<tr>
<td></td>
<td>90</td>
<td>8.61</td>
<td>116</td>
</tr>
<tr>
<td>26.0%</td>
<td>IFG only, total U.S. population¶</td>
<td>50</td>
<td>8.29</td>
</tr>
<tr>
<td></td>
<td>90</td>
<td>14.93</td>
<td>67</td>
</tr>
<tr>
<td>40.0%</td>
<td>Estimate IFG and/or IGT¶</td>
<td>50</td>
<td>12.76</td>
</tr>
<tr>
<td></td>
<td>90</td>
<td>22.97</td>
<td>44</td>
</tr>
</tbody>
</table>

* 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).
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 long-standing 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 post-randomization 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.

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Elevated risk of cardiovascular disease prior to clinical diagnosis of type 2 diabetes.

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Appendix Figure 1. Analytic framework.

KQ = key question.
Appendix Figure 2. Diabetes incidence in lifestyle trials.

<table>
<thead>
<tr>
<th>Study, Year (Reference)</th>
<th>Follow-up, y</th>
<th>Participants, n</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pan et al., 1997 (80)</td>
<td>6</td>
<td>133 (Control)</td>
<td>397 (Intervention)</td>
</tr>
<tr>
<td>Tuomilehto et al., 2001 (76)</td>
<td>3.2</td>
<td>257 (Control)</td>
<td>265 (Intervention)</td>
</tr>
<tr>
<td>DPP, 2002 (36)</td>
<td>2.8</td>
<td>1082 (Control)</td>
<td>1079 (Intervention)</td>
</tr>
<tr>
<td>Kosaka et al., 2005 (38)</td>
<td>4</td>
<td>356 (Control)</td>
<td>102 (Intervention)</td>
</tr>
<tr>
<td>Ramachandran et al., 2006 (77)</td>
<td>3</td>
<td>136 (Control)</td>
<td>133 (Intervention)</td>
</tr>
<tr>
<td>All studies combined</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Test for heterogeneity: $Q = 6.104; P = 0.192$

DPP = Diabetes Prevention Program.

Appendix Figure 3. Diabetes incidence in drug trials.

<table>
<thead>
<tr>
<th>Study, Year (Reference)</th>
<th>Drug</th>
<th>Follow-up, y</th>
<th>Participants, n</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heymsfield et al., 2000 (37)</td>
<td>Orlistat</td>
<td>2</td>
<td>53 (Control)</td>
<td>67 (Intervention)</td>
</tr>
<tr>
<td>Chiasson et al., 2002 (72)</td>
<td>Acarbose</td>
<td>3.3</td>
<td>715 (Control)</td>
<td>714 (Intervention)</td>
</tr>
<tr>
<td>DPP, 2002 (36)</td>
<td>Metformin</td>
<td>2.8</td>
<td>1082 (Control)</td>
<td>1073 (Intervention)</td>
</tr>
<tr>
<td>Torgerson et al., 2004 (83)</td>
<td>Orlistat</td>
<td>4</td>
<td>1637 (Control)</td>
<td>1640 (Intervention)</td>
</tr>
<tr>
<td>DREAM, 2006 (75)</td>
<td>Rosiglitazone</td>
<td>3</td>
<td>2635 (Control)</td>
<td>2634 (Intervention)</td>
</tr>
<tr>
<td>DREAM, 2006 (73)</td>
<td>Ramipril</td>
<td>3</td>
<td>2646 (Control)</td>
<td>2623 (Intervention)</td>
</tr>
<tr>
<td>Ramachandran et al., 2006 (77)</td>
<td>Metformin</td>
<td>3</td>
<td>136 (Control)</td>
<td>133 (Intervention)</td>
</tr>
<tr>
<td>All studies combined</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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*

<table>
<thead>
<tr>
<th>Study, Year (Reference)</th>
<th>Intervention</th>
<th>Sample Size (Diabetes Subgroup/Total), n/n</th>
<th>Baseline Cardiovascular Risk Factors†</th>
<th>Achieved Blood Pressure, mm Hg</th>
<th>Outcome: Relative Risk (95% CI)</th>
<th>Quality Rating</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALLHAT, 2002 (50), 2005 (51), 2001 (155)</td>
<td>Chlorthalidone vs. lisinopril vs. amlodipine‡</td>
<td>13 103/31 512</td>
<td>History of CVD: 36%/62%</td>
<td>Mean SBP (SD) in DM subgroup: Chlorthalidone: 136.9 (15.5); Amlodipine: 137.8 (11.8); Lisinopril: 137.0 (11.6)</td>
<td>Fatal CVD or nonfatal MI in the DM subgroup:</td>
<td>Fair</td>
<td>Significantly higher rate of attrition in the lisinopril group</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Smoking: 13%/28%</td>
<td>Mean SBP (SD) in normoglycemia subgroup: Chlorthalidone: 132.4 (11.3); Amlodipine: 132.5 (11.2); Lisinopril: 133.1 (11.4)</td>
<td>Lisinopril–chlorthalidone: 0.97 (0.85–1.10); P = 0.64</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Hyperlipidemia: NR</td>
<td>Mean SBP (SD) in total study sample (DM subgroup NR):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Established vascular disease: 18.7%</td>
<td>Verapamil: 136.5/79.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Stroke: 4.6%</td>
<td>Atenolol or HCTZ: 136.6/79.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CONVINCE, 2003 (52)</td>
<td>Verapamil vs. amlodipine or HCTZ</td>
<td>3236/16 476</td>
<td>Hyperlipidemia: 31.2%</td>
<td>Mean SBP (SD) in DM subgroup: Chlorthalidone: 136.5/79.0</td>
<td>Fatal CVD, stroke, or MI:</td>
<td>Fair</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Previous MI: 7.6%</td>
<td>Atenolol or HCTZ: 136.6/79.5</td>
<td>DM subgroup: 0.86 (0.66–1.12); P = NR</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Stroke: 4.6%</td>
<td>Atenolol or HCTZ: 136.6/79.5</td>
<td>Normoglycemia subgroup: 1.10 (0.92–1.31); P = NR</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Established vascular disease: 18.7%</td>
<td>Verapamil: 136.5/79.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Stroke: 4.6%</td>
<td>Atenolol or HCTZ: 136.6/79.5</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*ALLHAT = Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; CONVINCE = Controlled Oral 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.
§Doxazosin treatment was prematurely discontinued because of an excess of heart failure events.
¶P < 0.5 compared with chlorthalidone.

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

<table>
<thead>
<tr>
<th>Study, Year (Reference)</th>
<th>Intervention</th>
<th>Sample Size (Diabetes Subgroup/Total), n/n</th>
<th>Baseline Cardiovascular Risk Factors</th>
<th>Mean Achieved LDL-C Level (SD), mg/dL</th>
<th>Outcome: Relative Risk (95%CI)</th>
<th>Quality Rating</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALLHAT, 2002 (50)</td>
<td>Pravastatin titrated to achieve 25% reduction in LDL-C vs. usual care</td>
<td>3835/10 355†</td>
<td>Total group (DM subgroup information NR): HTN: 100%; History of CVD: 14.2%; Smoking: 23.6%; Mean LDL-C: 145.6 mg/dL (SD: 21.4)</td>
<td>Pravastatin: 104.0 (29.1); Usual care: 121.2 (34.6)</td>
<td>All-cause mortality, pravastatin vs. usual care: DM subgroup: 1.63 (0.86–2.22); P = NR; Non-DM subgroup: 0.98 (0.84–1.11); P = NR; CHD death or nonfatal MI: DM subgroup: 0.88 (0.71–1.03); P = NR; Non-DM: 0.82 (0.76–1.18); P = NR; Difference between DM and normoglycemia subgroups: P = NR</td>
<td>Fair</td>
<td>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</td>
</tr>
<tr>
<td>ASCOT, 2003 (55), 2005 (56)</td>
<td>Atorvastatin, 10 mg vs. placebo</td>
<td>2532/10 305</td>
<td>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</td>
<td>Atorvastatin: 83.9 (26.5); Placebo: 117.8 (30.4)</td>
<td>Nonfatal MI or fatal CHD‡: DM subgroup: 0.84 (0.53–1.29); P = NR; Non-DM subgroup: 0.56 (0.41–0.77); P = NR; Total CVD events and procedures: DM subgroup: 0.73 (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</td>
<td>Fair</td>
<td>Study stopped early; relatively low number of total events in DM subgroup</td>
</tr>
<tr>
<td>Heart Protection Study, 2003 (57)</td>
<td>Simvastatin, 40 mg vs. placebo</td>
<td>5963/20 536</td>
<td>DM/total group: 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)</td>
<td>Simvastatin: 89.7; Placebo: 128.7</td>
<td>Nonfatal MI or fatal CVD‡: DM subgroup: 0.73 (0.62–0.85); P &lt; 0.001; Non-DM subgroup: 0.73 (0.66–0.81); P &lt; 0.001; Stroke: DM subgroup: 0.76 (0.61–0.96); P = 0.01; Non-DM subgroup: 0.74 (0.64–0.86); P &lt; 0.001; Difference between DM and normoglycemia subgroups: P = 0.10</td>
<td>Good (for overall trial)</td>
<td>Baseline characteristics differed significantly between DM and normoglycemic subgroups</td>
</tr>
<tr>
<td>PROSPER, 2002 (58)</td>
<td>Pravastatin, 40 mg vs. placebo</td>
<td>623/5804</td>
<td>Total group (DM subgroup information NR): Previous angina: 26.5%; Previous MI: 13.4%; Coronary artery disease: 21.2%; Vascular disease: 44.2%; DM: 148.1 mg/dL (SD: 31.2); Hypertension: 61.9%; Smoking: 28.8%</td>
<td>Mean LDL at 3 months: pravastatin, 96.7; placebo, 146.6</td>
<td>Nonfatal MI, fatal CVD, nonfatal and fatal stroke: DM subgroup: 1.27 (0.90–1.80); P = NR; Non-DM: 0.76 (0.58–0.93); P = NR; Difference between DM and normoglycemia subgroups: P = 0.015</td>
<td>Fair</td>
<td>Little diabetes-specific information and relatively few persons with diabetes limit conclusions</td>
</tr>
</tbody>
</table>

* 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.
<table>
<thead>
<tr>
<th>Study, Year (Reference)</th>
<th>Country</th>
<th>Quality Rating</th>
<th>Total Sample Size, n</th>
<th>Mean Length of Follow-up</th>
<th>Sample Characteristics†</th>
<th>Intervention</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>DPP, 2000 (156, 157), 2002 (36), 2005 (74, 145)</td>
<td>United States</td>
<td>Good</td>
<td>3234</td>
<td>2.8 y; 3.2 y for CVD outcomes</td>
<td>Age, 51 y (10.7); 32.3% men</td>
<td>Intensive lifestyle vs. metformin vs. placebo</td>
<td>Cumulative incidence of T2DM: metformin, 18% lower (95% CI, 48%-66%); lifestyle, 31% lower (95% CI, 17%-43%) than placebo Cumulative incidence of CVD and CVD event rate; NSD among groups, but underpowered for this outcome</td>
</tr>
<tr>
<td>DREAM trial, 2004 (158), 2006 (73, 75)</td>
<td>International; multicenter</td>
<td>Good</td>
<td>5269</td>
<td>Median, 3.0 y</td>
<td>Age, 51 y (10.9); 40.8% men; BMI, 30.9 kg/m² (5.6)</td>
<td>Rosiglitazone vs. placebo; ramipril vs. placebo</td>
<td>Rosiglitazone: Death: HR, 0.93 (95% CI, 0.52–1.54); P = 0.7 T2DM incidence: HR, 0.35 (95% CI, 0.20–0.59); P &lt; 0.001 Composite CVD outcome: HR, 0.45 (95% CI, 0.35–0.61); P = 0.01 Ramipril: Death: HR, 0.88 (95% CI, 0.60–1.29); P = 0.60 T2DM incidence: HR, 0.90 (95% CI, 0.63–1.13); P = 0.55 Composite CVD outcome: HR, 0.91 (95% CI, 0.81–1.03); P = 0.68</td>
</tr>
<tr>
<td>Finnish Diabetes Prevention Study, 1999 (161), 2001 (76), 2003 (141), 2005 (159), 2006 (82)</td>
<td>Finland</td>
<td>Fair</td>
<td>522</td>
<td>3.2 y for postintervention outcomes; median total follow-up, 7 y</td>
<td>Age, 55 y (7); 32.9% men</td>
<td>Lifestyle vs. usual care</td>
<td>Cumulative incidence of T2DM: At 3.2 y: HR, 0.84 (95% CI, 0.67–1.06); P = 0.001 At 7 y: HR, 0.87 (95% CI, 0.62–1.23); P = 0.001</td>
</tr>
<tr>
<td>Indian Diabetes Prevention Programme, 2006 (77)</td>
<td>India</td>
<td>Fair</td>
<td>531</td>
<td>Median, 2.5 y</td>
<td>Age, 54.9 y (5.7); 79.0% men</td>
<td>Lifestyle and metformin vs. lifestyle vs. metformin</td>
<td>Relative risk reduction in incidence of T2DM at year 3: Lifestyle, 28.5% (95% CI, 20.5–37.0%); Metformin: 26.4% (95% CI, 19.1–35.1%); Lifestyle and metformin: 24.2% (95% CI, 20.3–37.0%)</td>
</tr>
<tr>
<td>Watanabe et al., 2003 (78)</td>
<td>Japan</td>
<td>Fair</td>
<td>173</td>
<td>2.0 y</td>
<td>Age, 55.1 y (7.1); 100% men</td>
<td>Dietary counseling vs. usual care</td>
<td>T2DM incidence: NSD between groups (data not provided)</td>
</tr>
<tr>
<td>Pan et al., 2003 (84)</td>
<td>China</td>
<td>Fair</td>
<td>261</td>
<td>16 wk</td>
<td>Age, 54.5 y (8.5); 40.0% men</td>
<td>Acarbose vs. placebo</td>
<td>T2DM incidence: acarbose, 5.6%; placebo, 9.5%; P = 0.245</td>
</tr>
<tr>
<td>Kosaka et al., 2005 (38)</td>
<td>Japan</td>
<td>Fair</td>
<td>458</td>
<td>4.0 y</td>
<td>Age, NR: 100% men</td>
<td>Lifestyle vs. usual care</td>
<td>Cumulative incidence T2DM over 4 yr: Lifestyle, 3%; control, 9.3%; P = 0.043 between groups</td>
</tr>
<tr>
<td>Heymsfield et al., 2006 (37)</td>
<td>United States</td>
<td>Fair to poor</td>
<td>675</td>
<td>2.5 y</td>
<td>Age, 43.9 y (11.5% men</td>
<td>O-ribitol vs. placebo; both received lifestyle intervention</td>
<td>IGT at baseline and at follow-up: Normoglycemia: orlistat, 71.6%; placebo, 49.1%; IGT: orlistat, 25.4%; placebo, 43.4%; T2DM: orlistat: 2.9%; placebo, 7.8%; P = 0.04 between groups</td>
</tr>
<tr>
<td>STDP-NIDDM trial, 1998 (163), 2002 (72), 2003 (162)</td>
<td>International; multicenter</td>
<td>Fair</td>
<td>1429</td>
<td>3.3 y</td>
<td>Age, 54.5 y (7.9); 49.4% men</td>
<td>Acarbose vs. placebo; both received lifestyle intervention</td>
<td>Cumulative incidence of T2DM: OR, 0.76 (95% CI, 0.57–1.02); P = 0.015 Any CVD event: OR, 0.31 (95% CI, 0.18–0.55); P = 0.02 MI: OR, 0.09 (95% CI, 0.03–0.27); P = 0.02</td>
</tr>
<tr>
<td>Swinburn et al., 2001 (79)</td>
<td>New Zealand</td>
<td>Fair to poor</td>
<td>136</td>
<td>5.0 y</td>
<td>Age, 52.2 y (6.5); 50.7% men</td>
<td>Reduced-fat diet vs. usual diet</td>
<td>Intervention was associated with a lower proportion of persons with T2DM or IGT at 3 y (P &lt; 0.05); NSD at 2, 3, or 5 y among those with no change in BMI. Total population: 94% had IGT at recruitment, but only 32% had prediabetes with repeated testing at randomization; results are for all included participants</td>
</tr>
<tr>
<td>XENDOS study, 2001 (164), 2004 (83)</td>
<td>Sweden</td>
<td>Fair to poor</td>
<td>3305 total (694 with IGT)</td>
<td>4.0 y</td>
<td>Age, 43.8 y (15.0); 44.8% men; BMI, 37.7 kg/m² (4.3)</td>
<td>O-ribitol vs. placebo; both received lifestyle intervention</td>
<td>Cumulative incidence of T2DM in IGT subgroup after 4 yr: OR, 0.551; P = 0.0024</td>
</tr>
</tbody>
</table>

* 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 NIDDM; T2DM = type 2 diabetes mellitus; XENDOS = XENical in the Prevention of Diabetes in Obese Subjects.† Data are reported as means (SDs), unless otherwise noted.