Screening for Prediabetes and Type 2 Diabetes
Updated Evidence Report and Systematic Review for the US Preventive Services Task Force

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IMPORTANCE Type 2 diabetes is common and is a leading cause of morbidity and disability.

OBJECTIVE To review the evidence on screening for prediabetes and diabetes to inform the US Preventive Services Task Force (USPSTF).

DATA SOURCES PubMed/MEDLINE, Cochrane Library, and trial registries through September 2019; references; and experts; literature surveillance through May 21, 2021.

STUDY SELECTION English-language controlled studies evaluating screening or interventions for prediabetes or diabetes that was screen detected or recently diagnosed.

DATA EXTRACTION AND SYNTHESIS Dual review of abstracts, full-text articles, and study quality; qualitative synthesis of findings; meta-analyses conducted when at least 3 similar studies were available.

MAIN OUTCOMES AND MEASURES Mortality, cardiovascular morbidity, diabetes-related morbidity, development of diabetes, quality of life, and harms.

RESULTS The review included 89 publications (N = 68 882). Two randomized clinical trials (RCTs) (25 120 participants) found no significant difference between screening and control groups for all-cause or cause-specific mortality at 10 years. For harms (eg, anxiety or worry), the trials reported no significant differences between screening and control groups. For recently diagnosed (not screen-detected) diabetes, 5 RCTs (5138 participants) were included. In the UK Prospective Diabetes Study, health outcomes were improved with intensive glucose control with sulfonylureas or insulin. For example, for all-cause mortality the relative risk (RR) was 0.87 (95% CI, 0.79 to 0.96) over 20 years (10-year posttrial assessment). For overweight persons, intensive glucose control with metformin improved health outcomes at the 10-year follow-up (eg, all-cause mortality: RR, 0.64 [95% CI, 0.45 to 0.91]), and benefits were maintained longer term. Lifestyle interventions (most involving >360 minutes) for obese or overweight persons with prediabetes were associated with reductions in the incidence of diabetes (23 RCTs; pooled RR, 0.78 [95% CI, 0.69 to 0.88]). Lifestyle interventions were also associated with improved intermediate outcomes, such as reduced weight, body mass index, systolic blood pressure, and diastolic blood pressure (pooled weighted mean difference, −1.7 mm Hg [95% CI, −2.6 to −0.8] and −1.2 mm Hg [95% CI, −2.0 to −0.4], respectively). Metformin was associated with a significant reduction in diabetes incidence (pooled RR, 0.73 [95% CI, 0.64 to 0.83]) and reduction in weight and body mass index.

CONCLUSIONS AND RELEVANCE Trials of screening for diabetes found no significant mortality benefit but had insufficient data to assess other health outcomes; evidence on harms of screening was limited. For persons with recently diagnosed (not screen-detected) diabetes, interventions improved health outcomes; for obese or overweight persons with prediabetes, interventions were associated with reduced incidence of diabetes and improvement in other intermediate outcomes.

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Prediabetes and type 2 diabetes are common, estimated to affect about 34% and 13% of all US adults in 2018, respectively.[1] Prevalence of diabetes increased with age and was higher among American Indian/Alaska Native, Hispanic, non-Hispanic Asian, and non-Hispanic Black persons than among non-Hispanic White persons.[1] Diabetes was estimated to be the third leading cause of years lived with disability in 2016 and the seventh leading cause of death in the US in 2017, accounting for more than 80 000 deaths per year.[2,3] Morbidity from diabetes is due to macrovascular disease (atherosclerosis), microvascular disease (retinopathy, nephropathy, and neuropathy), and acute complications of hyperglycemia or hypoglycemia. Diabetes was the leading cause of kidney failure, lower-limb amputations, and new cases of blindness among US adults.[1,4] Risk factors associated with development of diabetes in adults include older age, family history, overweight and obesity, dietary and lifestyle factors, environmental exposures, and others.[5] Three tests can be used to identify diabetes or prediabetes: hemoglobin A_{1c} (HbA_{1c}) concentration, fasting plasma glucose level, or oral glucose tolerance test[6] (**Table 1**).

In 2015, the US Preventive Services Task Force (USPSTF) recommended screening for abnormal blood glucose levels as part of cardiovascular risk assessment in adults aged 40 to 70 years who are overweight or obese. In addition, it recommended that clinicians offer or refer patients with abnormal blood glucose levels to intensive behavioral counseling interventions to promote a healthful diet and physical activity (B recommendation). This updated review evaluates the current evidence on screening for prediabetes and diabetes for populations and settings relevant to primary care in the US to inform an updated recommendation by the USPSTF.

Methods

Scope of Review

Figure 1 shows the analytic framework and key questions (KQs) that guided the review. Detailed methods are available in the full evidence review.[8] In addition to addressing the KQs, the full evidence report also looked for evidence related to 14 contextual and supplemental questions that focused on risk assessment tools, agreement among screening tests, screening tests' prediction of future adverse health outcomes, yield of rescreening at different intervals in adults with an initial normal screening test result, and recently published modeling studies that assess screening (vs no screening) and examine health outcomes, metformin for prediabetes, the natural history of prediabetes, overdiagnosis and overtreatment, disutilities, patient-reported health status measures, uptake, and adherence.

Data Sources and Searches

PubMed/MEDLINE and the Cochrane Library were searched for English-language articles published through September 2019. Search strategies are listed in the eMethods in the Supplement. Clinical trial registries were searched for unpublished studies. To supplement electronic searches, investigators reviewed reference lists of pertinent articles, studies suggested by reviewers, and comments received during public commenting periods. Since September 2019, ongoing surveillance was conducted through article alerts and targeted searches of journals to identify major studies published in the interim that may affect the conclusions or understanding of the evidence and the related USPSTF recommendation. The last surveillance was conducted on May 21, 2021.

Study Selection

Two investigators independently reviewed titles, abstracts, and full-text articles to determine eligibility using prespecified criteria (eTable 1 in the Supplement). Disagreements were resolved by discussion and consensus. English-language studies of asymptomatic, nonpregnant adults 18 years or older conducted in countries categorized as medium or higher on the Human Development Index[9] and rated as fair or good quality were included. For all KQs, randomized clinical trials and nonrandomized controlled intervention studies were eligible. Controlled prospective cohort studies and case-control studies were also eligible for KQs on harms (KQ2 and KQ6).

Data Extraction and Quality Assessment

For each included study, 1 investigator extracted pertinent information about the populations, tests or treatments, comparators, outcomes, settings, and designs, and a second investigator reviewed this information for completeness and accuracy. Two independent investigators assessed the quality of studies as good, fair, or poor, using predefined criteria (eTables 2-6 in the Supplement) developed by the USPSTF and adapted for this topic.[7] Disagreements were resolved by discussion.

Data Synthesis and Analysis

Findings for each KQ were summarized in tabular and narrative format. The overall strength of the evidence for each KQ was assessed as high, moderate, low, or insufficient based on the overall quality of the studies, consistency of results between studies, precision of findings, risk of reporting bias, and limitations of the body of evidence, using methods developed for the USPSTF (and the Evidence-based Practice Center program).[7] Additionally, the applicability of the findings to US primary care populations and settings was assessed. Discrepancies were resolved through consensus discussion. Assessments of clinical importance were based on minimal clinically important differences, when available.

To determine whether meta-analyses were appropriate, the clinical and methodological heterogeneity of the studies was assessed according to established guidance.[10] For KQ7 and KQ9, when at least 3 similar studies were available, quantitative synthesis was conducted with random-effects models using the inverse-variance weighted method (DerSimonian and Laird) to estimate pooled effects.[11] For binary outcomes (eg, progression to diabetes), relative risks (RRs) and 95% CIs were calculated. Statistical significance was assumed when 95% CIs of pooled results did not cross the null. All testing was 2-sided. For continuous outcomes (eg, blood pressure), the weighted mean difference (WMD) between intervention and control was calculated. Whenever possible, the number of all randomized patients was used as the denominator to reflect a true intention-to-treat approach to analysis. For all quantitative syntheses, the I^2 statistic was calculated to assess statistical heterogeneity in effects between studies.[12,13] An I^2 from 0% to 40% might not be important, from 30% to 60% may represent moderate heterogeneity, from 50% to 90% may represent substantial heterogeneity, and 75% or greater represents considerable heterogeneity.[14] Additional analyses were conducted to explore

Table 1. Criteria for the Diagnosis of Type 2 Diabetes and Prediabetes[a]

Diagnosis	HbA_{1c}[b]	Fasting plasma glucose, mg/dL[c]	OGTT, mg/dL[b,d]	Other
Diabetes	≥6.5% (48 mmol/mol)[d]	≥126	≥200	Random plasma glucose ≥200 mg/dL in a patient with classic symptoms of hyperglycemia or hyperglycemia crisis
Prediabetes[e]	5.7% to 6.4% (39-47 mmol/mol)	IFG: 100-125	IGT: 140-199	NA

Abbreviations: HbA_{1c}, hemoglobin A_{1c}; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; NA, not applicable; OGTT, oral glucose tolerance test.

SI conversion factor: To convert glucose values to mmol/L, multiply by 0.0555.

[a] Adapted from American Diabetes Association (ADA) standards.[6] A second test is required for confirmation unless there is a clear clinical diagnosis (eg, patient in hyperglycemic crisis).

[b] The guidelines note this test should be performed in a laboratory using a method that is National Glycohemoglobin Standardization Program–certified and standardized to the Diabetes Control and Complications Trial assay.

[c] Fasting is defined as no caloric intake for at least 8 hours.

[d] Refers to values measured 2 hours postload on the 75-g OGTT. Per the ADA recommendations, the test should be performed as described by the World Health Organization, using a glucose load containing the equivalent of 75 g of anhydrous glucose dissolved in water.

[e] Prediabetes is the term used for individuals potentially at increased risk for diabetes whose glucose levels are considered higher than normal but do not meet criteria for diabetes. ADA guidelines note that for all 3 tests the risk is continuous, extending below the lower limit of the range and becoming disproportionately greater at higher ends of the range.

heterogeneity or robustness of findings, stratifying by duration of follow-up (ie, timing of outcome assessment), lifestyle intervention contact time (ie, dose), and baseline body mass index (BMI) of study participants. The total hours of interventionist contact time (ie, dose) was estimated based on the planned number and length of contacts. An intervention was characterized as low-dose if the number of minutes was estimated to be 30 or less, medium-dose if the number of minutes was 31 to 360, and high-dose if the number of minutes was greater than 360. For KQ7, the number needed to treat to prevent 1 person from developing diabetes was calculated for interventions with moderate or high strength of evidence (for benefit), using the pooled RRs and the control group event rate from the Diabetes Prevention Program (DPP) (over 3 years) and the DPP Outcomes Study (DPPOS) (over 15 years). When studies reported raw numbers of events but did not report hazard ratios (HRs), RRs, or odds ratios, RRs were calculated.

Quantitative analyses were conducted using Comprehensive Meta-Analysis version 3.3 (Biostat Inc) and Stata version 14 (StataCorp).

Results

A total of 89 publications were included (**Figure 2**).[15-103] Two randomized clinical trials (RCTs) addressed whether screening for diabetes improves health outcomes.[36,38,49-51] This review found no trials that assessed screening for prediabetes and no trials that assessed KQ3. Most articles assessed interventions for prediabetes. Results for KQ8 are reported in the eResults in the Supplement. Individual study quality ratings are reported in eTables 2-6 in the Supplement.

Benefits of Screening

Key Question 1a. Is there direct evidence that screening for type 2 diabetes and prediabetes in asymptomatic adults improves health outcomes?

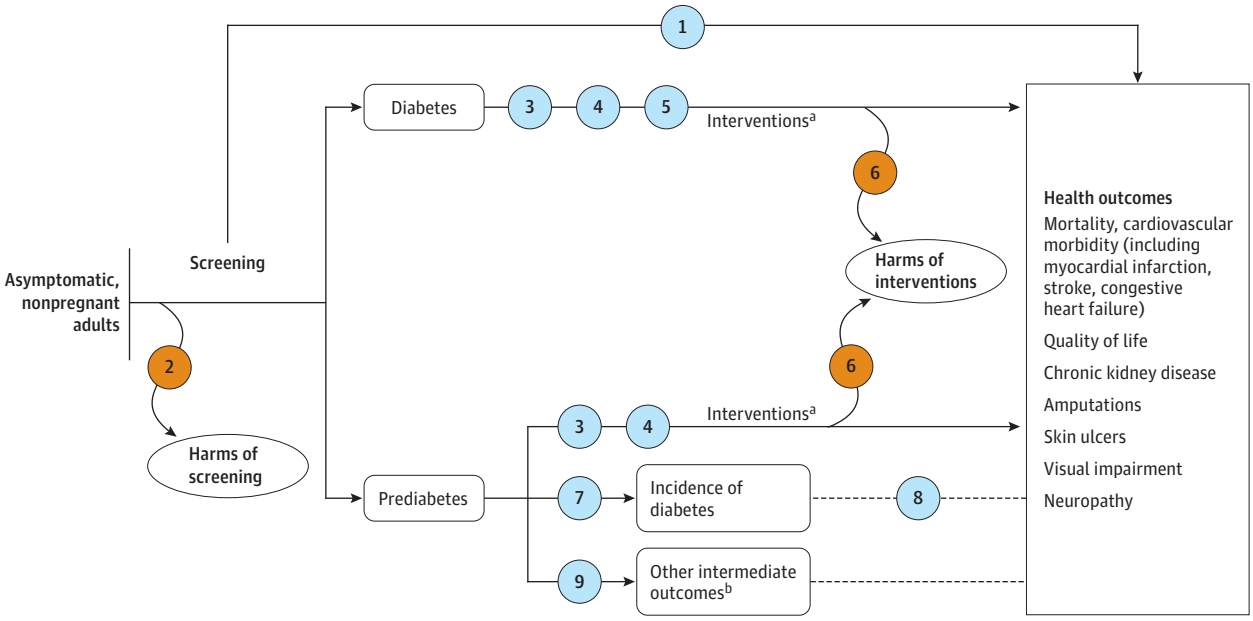
Key Question 1b. Does the effectiveness of screening differ for subgroups defined by age, sex, race and ethnicity, socioeconomic status, or BMI?

Two RCTs (described in 5 articles) conducted in the UK evaluated invitations to screening for diabetes: the Anglo-Danish-Dutch Study of Intensive Treatment In People With Screen Detected Diabetes in Primary Care (ADDITION)–Cambridge (n = 20 184 participants)[36,49] and the Ely study (n = 4936 participants) (eTable 7 in the Supplement).[38,50,51] The trials began screening in 1990 (Ely) and 2002 (ADDITION-Cambridge). Duration of follow-up ranged from 7 to 13 years for the outcomes reported.

ADDITION-Cambridge was a cluster RCT of 33 general practices that evaluated a stepwise screening approach starting with the result of a random capillary blood glucose measurement. ADDITION-Cambridge was a screening and intervention study that randomized practices 1:3:3 to no screening, screening invitations followed by intensive treatment of screen-detected diabetes (HbA_{1c} target <7.0%, blood pressure target ≤135/85 mm Hg, cholesterol targets, and low-dose aspirin use unless contraindicated), or screening followed by routine care of screen-detected diabetes; analyses combined the screening groups (comparing 5 control practices with 27 screening practices). Participants were aged 40 to 69 years (mean, 58) without known diabetes and at high risk of diabetes (based on a risk score of ≥1.7 on a diabetes risk score that included age, sex, BMI, steroid and antihypertensive medication, family and smoking history).[104] Mean BMI was 30.5 (calculated as weight in kilograms divided by height in meters squared). Of those invited, 78% were screened (11 737/15 089) and 466 of those (4% of those screened, 3% of those invited) were diagnosed with diabetes based on 1999 World Health Organization criteria. Number diagnosed with diabetes was not reported for the control group.

The Ely study was a parallel-group RCT at a single practice that evaluated screening every 5 years with an oral glucose tolerance test along with screening for cardiovascular disease (CVD) risk factors (cholesterol and blood pressure). The study had no protocol for standard interventions for those with screen-detected diabetes. The risk of bias for the trial was rated as medium because of unclear methods of randomization, unclear allocation concealment, and baseline differences between groups. Participants were aged 40 to 65 years (mean, 51 years) and required to be free from known diabetes (not selected based on risk). In the initial 10-year phase, 68% of those invited were screened (1157/1705) and 116 (10% of those screened, 7% of those invited) were diagnosed with diabetes. Among a subset of participants who were diagnosed with diabetes and attended a health assessment after 12 years (n = 152 persons), diabetes cases were identified a mean of 3.3 years earlier for those in the screening group (n = 92) than in the control group (n = 60).[50]

Figure 1. Analytic Framework: Screening for Prediabetes and Type 2 Diabetes



Key questions

1. a. Is there direct evidence that screening for type 2 diabetes and prediabetes in asymptomatic adults improves health outcomes?
   b. Does the effectiveness of screening differ for subgroups defined by age, sex, race and ethnicity, socioeconomic status, or BMI?
2. a. What are the harms of screening for type 2 diabetes and prediabetes in asymptomatic adults?
   b. Do the harms of screening differ for subgroups defined by age, sex, race and ethnicity, socioeconomic status, or BMI?
3. a. Do interventions for screen-detected type 2 diabetes and prediabetes provide an incremental benefit in health outcomes when delivered at the time of detection compared with initiating interventions later, after clinical diagnosis?
   b. Does the effectiveness of these interventions differ for subgroups defined by age, sex, race and ethnicity, socioeconomic status, or BMI?
4. a. Do interventions for screen-detected type 2 diabetes and prediabetes improve health outcomes compared with no intervention, usual care, or interventions with different treatment targets?
   b. Does the effectiveness of these interventions differ for subgroups defined by age, sex, race and ethnicity, socioeconomic status, or BMI?
5. a. Do interventions for recently diagnosed type 2 diabetes improve health outcomes compared with no intervention, usual care, or interventions with different treatment targets?
   b. Does the effectiveness of these interventions differ for subgroups defined by age, sex, race and ethnicity, socioeconomic status, or BMI?
6. What are the harms of interventions for prediabetes, screen-detected type 2 diabetes, or recently diagnosed type 2 diabetes?
7. a. Do interventions for prediabetes delay or prevent progression to type 2 diabetes?
   b. Does the effectiveness of these interventions differ for subgroups defined by age, sex, race and ethnicity, socioeconomic status, or BMI?
8. After interventions for prediabetes are provided, what is the magnitude of change in health outcomes that results from the reduction in type 2 diabetes incidence?
9. Do interventions for prediabetes improve other intermediate outcomes (blood pressure, lipid levels, BMI, weight, and calculated 10-year cardiovascular disease risk)?

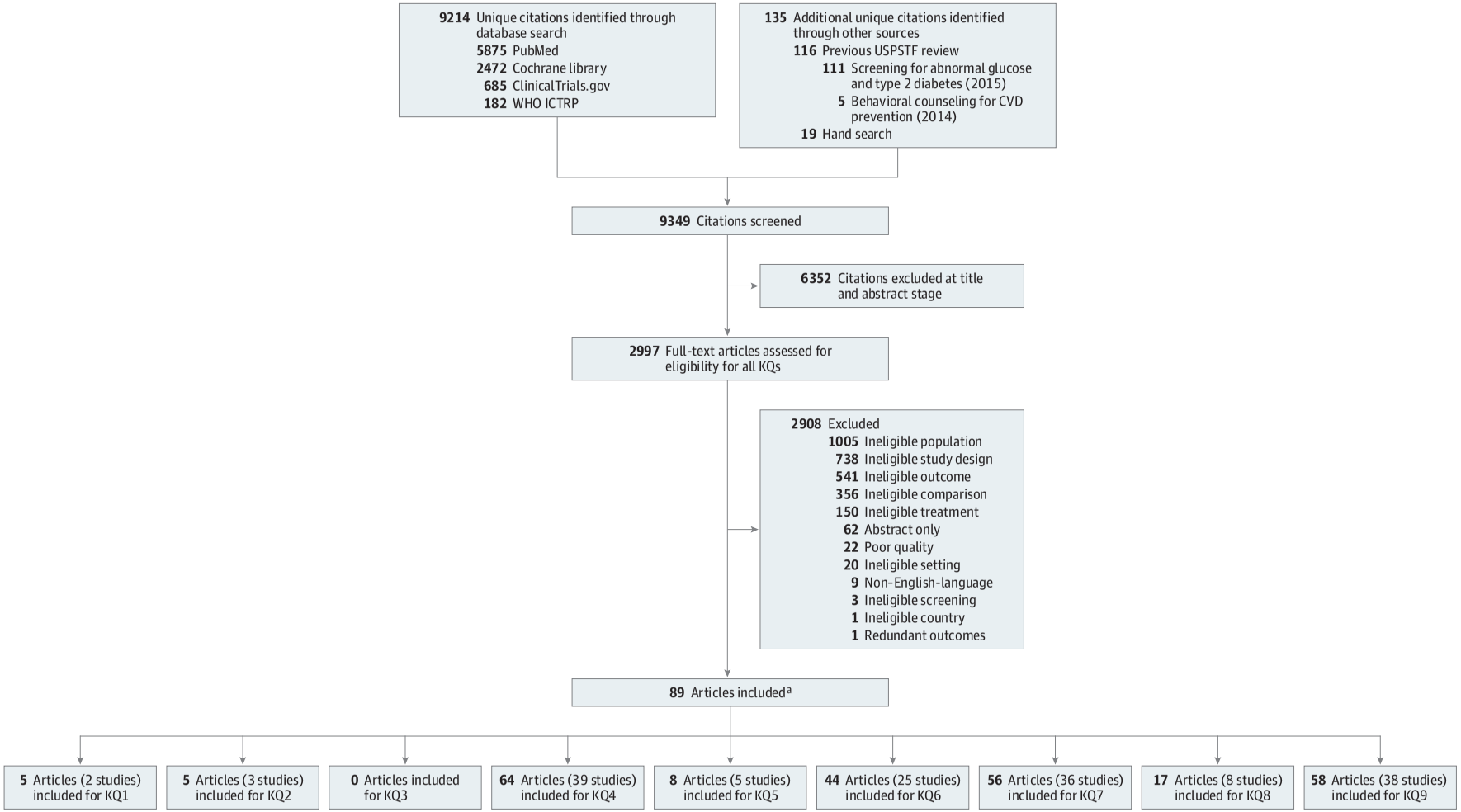
Evidence reviews for the US Preventive Services Task Force (USPSTF) use an analytic framework to visually display the key questions that the review will address to allow the USPSTF to evaluate the effectiveness and safety of a preventive service. The questions are depicted by linkages that relate interventions and outcomes. For additional information see the USPSTF Procedure Manual.[7] BMI indicates body mass index.

[a] Eligible interventions included pharmacotherapy and primary care–relevant behavioral counseling focused on healthy diet and nutrition, physical activity, or both.

[b] Other intermediate outcomes included blood pressure, lipid levels, BMI, weight, and calculated 10-year cardiovascular disease risk.

Neither trial found a reduction in all-cause or type-specific mortality for screening compared with no screening over about 10 years of follow-up (all-cause mortality in ADDITION-Cambridge: HR, 1.06 [95% CI, 0.90 to 1.25]; Ely study: unadjusted HR, 0.96 [95% CI, 0.77

Figure 2. Literature Search Flow Diagram: Screening for Prediabetes and Type 2 Diabetes



CVD indicates cardiovascular disease; KQ, key question; USPSTF, US Preventive Services Task Force; WHO ICTRP, World Health Organization International Clinical Trials Registry Platform.

[a] The sum of the number of articles per KQ exceeds the total number of articles because some articles were applicable to multiple KQs.

to 1.20] and adjusted HR, 0.79 [95% CI, 0.63 to 1.00]). Neither trial found statistically significant differences between screening and control groups for cardiovascular events, quality of life, nephropathy, or neuropathy, but data collection was limited to a minority of participants from the trials who completed follow-up surveys at 7 years (ADDITION-Cambridge) or attended a health assessment at 12 to 13 years (Ely), and results were imprecise (eTable 8 in the Supplement).[36,50,51]

Harms of Screening

Key Question 2a. What are the harms of screening for type 2 diabetes and prediabetes in asymptomatic adults?

Key Question 2b. Do the harms of screening differ for subgroups defined by age, sex, race and ethnicity, socioeconomic status, or BMI?

Five articles that evaluated participants in the ADDITION-Cambridge pilot phase, ADDITION-Cambridge trial, or Ely trial were included (eTable 7 in the Supplement).[39,50-53] All 3 trials reported some information on anxiety from screening, 2 reported on depression, 2 reported on self-reported health, and 1 reported on worry about diabetes (eTable 9 in the Supplement). No 2 studies used the same outcome measures at similar time points. None of the trials reported on labeling, harms from false-positive results, burden, inconvenience, or unnecessary testing and treatment. Overall, results of the 3 trials did not find clinically important differences between the screening and control groups in measures of anxiety, depression, worry, or self-reported health, but the results suggest possible short-term increases in anxiety (at 6 weeks) among persons screened and diagnosed with diabetes compared with those screened and not diagnosed with diabetes (eResults and eTable 9 in the Supplement).

Benefits of Interventions for Type 2 Diabetes and Prediabetes

Key Question 4a. Do interventions for screen-detected type 2 diabetes and prediabetes improve health outcomes compared with no intervention, usual care, or interventions with different treatment targets?

Key Question 4b. Does the effectiveness of these interventions differ for subgroups defined by age, sex, race and ethnicity, socioeconomic status, or BMI?

One cluster RCT (ADDITION-Europe, described in 8 articles[15,75-80,103]) that evaluated interventions for individuals with screen-detected diabetes and 38 RCTs (described in 56 articles[16-25,27-35,40-48,56-74,85-92,98]) that evaluated interventions for individuals with prediabetes were included (eResults and eTables 10 and 11 in the Supplement).[15,75-80,103] For persons with diabetes, low strength of evidence from 1 cluster RCT (described in 8 articles) found no significant difference over a mean of 5.3 years of follow-up between an intensive multifactorial intervention aimed at controlling glucose, blood pressure, and cholesterol levels and routine care in the risk of all-cause mortality, cardiovascular-related mortality, and the occurrence of a first cardiovascular event (myocardial infarction, stroke, revascularization, or amputation).[15,75-80,103] Differences remained nonsignificant at the 10-year follow-up. There was also no significant difference between groups in the risk of outcomes related to chronic kidney disease, visual impairment, and neuropathy. Of the 4 sites (Denmark, the Netherlands, UK-Cambridge, UK-Leicester), all but 1 (UK-Leicester) found no difference between groups across a range of quality-of-life outcomes.

For trials of interventions for people with prediabetes, the duration of follow-up in most trials was insufficient to assess for effects on mortality, CVD events, and other health outcomes (eResults in the Supplement). Most trials reporting mortality or CVD events over a follow-up duration of 6 years or less had few events with no significant difference between groups. In the 2 trials reporting outcomes beyond 6 years, 1 (the Finnish DPP) found no statistically significant difference for all-cause mortality (2.2 vs 3.8 deaths per 1000 person-years; HR, 0.57 [95% CI, 0.21 to 1.58]) or composite CVD events (22.9 vs 22.0 events per 1000 person-years; HR, 1.04 [95% CI, 0.72 to 1.51]) over 10 years of follow-up.[40] The second trial (the China Da Qing Diabetes Prevention Outcomes Study) found lower all-cause mortality (28.1% vs 38.4%; HR, 0.71 [95% CI, 0.51 to 0.99]) and CVD-related mortality (11.9% vs 19.6%; HR, 0.59 [95% CI, 0.36 to 0.96]) for a 6-year combined lifestyle intervention group compared with controls at 23 years but not at earlier follow-ups; differences remained at the 30-year follow-up.[34,98] The trial was rated as having at least medium risk of bias mainly because of unclear randomization and allocation concealment methods and baseline differences for smoking that could bias results in favor of intervention. Five trials reporting quality of life found either no difference between groups,[43,44] mixed results (improvements on some domains but not others),[63] or small improvements in scores that are not likely clinically important (eResults in the Supplement).[16,22] The DPPOS study found no difference in an aggregate microvascular outcome (nephropathy, retinopathy, and neuropathy) at 15 years (placebo, 12.4%; metformin, 13.0%; intensive lifestyle, 11.3%).[30]

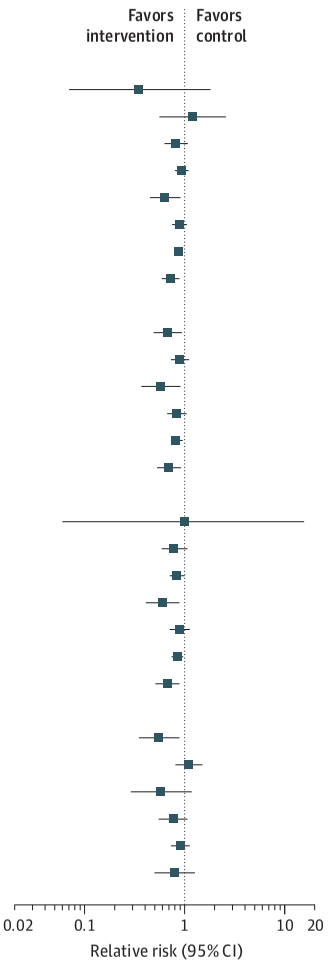
Key Question 5a. Do interventions for recently diagnosed type 2 diabetes improve health outcomes compared with no intervention, usual care, or interventions with different treatment targets?

Key Question 5b. Does the effectiveness of these interventions differ for subgroups defined by age, sex, race and ethnicity, socioeconomic status, or BMI?

This review included 5 RCTs (described in 8 articles) evaluating interventions for recently diagnosed diabetes (eResults and eTable 12 in the Supplement).[54,55,81-84,93,94] Three were related to the UK Prospective Diabetes Study (UKPDS), which was a randomized multicenter trial that ran for 20 years (from 1977 to 1997) in 23 sites across the UK. Moderate strength of evidence from the 5 RCTs found no statistically significant difference in all-cause mortality, diabetes-related mortality, and cardiovascular outcomes between intensive glucose control with sulfonylureas or insulin and conventional care at 10 years' or shorter follow-up (**Figure 3**).[54,55,81-84,93,94] However, over longer-term follow-up (20 years after randomization), intensive glucose control with sulfonylureas or insulin decreased the risk for all-cause mortality (RR, 0.87 [95% CI, 0.79 to 0.96]), diabetes-related mortality (RR, 0.83 [95% CI, 0.73 to 0.96]), and myocardial infarction (RR, 0.85 [95% CI, 0.74 to 0.97]) (Figure 3; eResults in the Supplement). Tighter control of blood pressure compared with less tight control (<150/85 vs <180/105) resulted in a reduced risk of diabetes-related mortality and stroke after 9 years of follow-up, but there was no difference between groups at longer-term follow-up (10 years posttrial) (Figure 3; eResults in the Supplement). Intensive glucose control with metformin compared with conventional care

Figure 3. All-Cause Mortality, Diabetes-Related Mortality, Myocardial Infarction, and Stroke Outcomes in Trials of Interventions for Persons With Recently Diagnosed Diabetes (KQ5)

Source	Treatment	Follow-up duration, y	Intervention group		Control group		Relative risk (95% CI)
			With event, No.	Without event, No.	With event, No.	Without event, No.	
All-cause mortality							
Davies et al,[54] 2008	Group education[a]	1	2	435	5	382	0.35 (0.07-1.82)
Khunti et al,[55] 2012	Group education[a]	3	15	422	11	376	1.21 (0.56-2.60)
Holman et al,[83] 2008	BP control[b]	9	134	624	83	307	0.82 (0.63-1.08)
UKPDS,[84] 1998	Glucose control[c]	10	489	2240	213	925	0.94 (0.80-1.10)
UKPDS,[94] 1998	Weight control[d]	10	50	292	89	322	0.64 (0.45-0.91)
Holman et al,[83] 2008	BP control[b]	10 posttrial	373	385	211	179	0.89 (0.75-1.06)
Holman et al,[82] 2008	Glucose control[c]	10 posttrial	1162	1567	537	601	0.87 (0.79-0.96)
Holman et al,[82] 2008	Weight control[d]	10 posttrial	152	190	217	294	0.73 (0.59-0.89)
Diabetes specific mortality							
Holman et al,[83] 2008	BP control[b]	9	82	676	62	328	0.68 (0.49-0.94)
UKPDS,[84] 1998	Glucose control[c]	10	285	2444	129	1009	0.90 (0.73-1.11)
UKPDS,[94] 1998	Weight control[d]	10	28	314	55	356	0.58 (0.37-0.91)
Holman et al,[83] 2008	BP control[b]	10 posttrial	203	555	122	268	0.84 (0.67-1.05)
Holman et al,[82] 2008	Glucose control[c]	10 posttrial	618	2111	297	841	0.83 (0.73-0.96)
Holman et al,[82] 2008	Weight control[d]	10 posttrial	81	261	120	291	0.70 (0.53-0.92)
Myocardial infarction							
Yang et al,[93] 2013	Multifactorial[e]	7	1	74	1	74	1.00 (0.06-15.7)
Holman et al,[81] 2008	BP control[b]	9	107	651	69	321	0.79 (0.59-1.07)
UKPDS,[84] 1998	Glucose control[c]	10	387	2342	186	952	0.84 (0.71-1.00)
UKPDS,[94] 1998	Weight control[d]	10	39	303	73	338	0.61 (0.41-0.89)
Holman et al,[83] 2008	BP control[b]	10 posttrial	205	553	115	275	0.90 (0.71-1.13)
Holman et al,[82] 2008	Glucose control[c]	10 posttrial	678	2051	319	819	0.85 (0.74-0.97)
Holman et al,[82] 2008	Weight control[d]	10 posttrial	81	261	126	285	0.67 (0.51-0.89)
Stroke							
Holman et al,[81] 2008	BP control[b]	9	38	720	34	356	0.56 (0.35-0.89)
UKPDS,[84] 1998	Glucose control[c]	10	148	2581	55	1083	1.11 (0.81-1.51)
UKPDS,[94] 1998	Weight control[d]	10	12	330	23	388	0.59 (0.29-1.18)
Holman et al,[83] 2008	BP control[b]	10 posttrial	90	668	58	332	0.77 (0.55-1.07)
Holman et al,[82] 2008	Glucose control[c]	10 posttrial	260	2469	116	1022	0.91 (0.73-1.13)
Holman et al,[82] 2008	Weight control[d]	10 posttrial	34	308	42	369	0.80 (0.50-1.27)



BP indicates blood pressure; KQ, key question; UKPDS, UK Prospective Diabetes Study.

[a] Group education in the DESMOND trial.

[b] Tighter blood pressure control (<150/85 vs <180/105) in the hypertension in diabetes study embedded in UKPDS.

[c] Intensive therapy with sulfonylureas or insulin in UKPDS.

[d] Metformin for overweight substudy UKPDS group.

[e] Multifactorial intensive therapy.

in overweight persons reduced the risk of all-cause mortality, diabetes-related mortality, and myocardial infarction at both 10 and 20 years after randomization (Figure 3; eResults in the Supplement).

Harms of Interventions

Key Question 6. What are the harms of interventions for prediabetes, screen-detected type 2 diabetes, or recently diagnosed type 2 diabetes?

Harms of interventions for diabetes were sparsely reported, rare, and (when reported) not significantly different between intervention and control groups across trials (eResults in the Supplement). Four RCTs (described in 6 articles) reported on harms of interventions for screen-detected or recently diagnosed diabetes.[37,54,55,79,80,84] None were specifically designed to investigate harms.

Twenty-one trials reported on harms associated with interventions for prediabetes (8 assessing a lifestyle intervention[17,18,21,29-31,48,69,73,74,91,92] and 13 assessing a pharmacologic intervention[22,23,25,32,41,42,56,58,59,64,66-68,70,71,90]) (eResults in the Supplement). Categories and definitions used for adverse events were heterogenous across studies, and few trials (3 trials) reported adverse events beyond 5 years of follow-up.[65,66,74] Five trials reported rates of hypoglycemia (using various definitions), each comparing a different medication with placebo (liraglutide, sitagliptin, metformin, nateglinide, and rosiglitazone plus metformin); event rates were low, and no trial found a significant difference between groups over follow-up durations ranging from 8 weeks to 5 years.[22,32,66,70,74]

Twelve studies reported withdrawals due to adverse events associated with a pharmacotherapy intervention. Six trials (2 assessing metformin[21,41] and 1 each assessing sitagliptin,[32] nateglinide,[66] valsartan,[67] acarbose,[90] and rosiglitazone plus metformin[70]) found no increased risk of withdrawals among the intervention group compared with placebo or control, and 6 found higher rates of withdrawals due to adverse effects associated with the pharmacologic intervention than the placebo, including 2 studies of acarbose[68,71] and 1 study each assessing pioglitazone,[56] ramipril,[58] rosiglitazone,[59] voglibose,[64] and liraglutide.[22]

Nine studies of pharmacologic interventions reported on gastrointestinal adverse events; compared with placebo or control, higher rates were seen in studies assessing metformin (3 studies),[21,70,73] acarbose (2 studies), and liraglutide (1 study),[22] and rates were similar among groups in 1 study each assessing pioglitazone, sitagliptin, nateglinide, and valsartan.[32,56,66,67] Seventeen studies reported other adverse events; types of events reported (and definitions) were heterogeneous and most found no difference between groups. Four studies of lifestyle interventions reported on musculoskeletal-related adverse events, 2 found no significant difference between groups,[17,29] and 1 (the DPP) found higher rates of musculoskeletal symptoms per 100 person-years in the intensive lifestyle intervention group compared with the control group (24.1 vs 21.1 events per 100 person-years; $P < .02$) at 2.3 years[73] but no difference between groups for sprains or fractures needing medical attention at 15 years after randomization.[30]

Benefits of Interventions for Prediabetes

Key Question 7a. Do interventions for prediabetes delay or prevent progression to type 2 diabetes?

Key Question 7b. Does the effectiveness of these interventions differ for subgroups defined by age, sex, race and ethnicity, socioeconomic status, or BMI?

Twenty-three trials (described in 33 articles[16-18,20,21,26,28-31,33,34,40,44,46-48,60-62,65,69,73,74,86-89,92,96,98,101,102]) compared lifestyle interventions with controls for delaying or preventing the onset of diabetes, and 15 trials (reported in 23 articles[21,22,24,25,30,41,42,56,58,59,61,62,64,66-68,70,71,73,91,92,95]) evaluated pharmacologic interventions to delay or prevent diabetes (eResults in the Supplement). Lifestyle interventions were significantly associated with a reduction in the incidence of diabetes (pooled RR, 0.78 [95% CI, 0.69 to 0.88]; 23 trials; 12 915 participants) (**Figure 4**). Most trials assessed high-contact lifestyle interventions. Pooled RRs were 0.63 (95% CI, 0.50 to 0.81) for follow-up less than 1 year, 0.58 (95% CI, 0.41 to 0.82) for follow-up 1 to 2 years, and 0.81 (95% CI, 0.73 to 0.89) for follow-up greater than 2 years. For medications, metformin, thiazolidinediones , and α-glucosidase inhibitors were all significantly associated with a reduction in diabetes (pooled RR, 0.73 [95% CI, 0.64 to 0.83] for metformin; 0.50 [95% CI, 0.28 to 0.92] for thiazolidinediones; and 0.64 [95% CI, 0.43 to 0.96] for α-glucosidase inhibitors) (Figure 4), although results for thiazolidinediones and α-glucosidase inhibitors were limited by imprecision, inconsistency, and risk of bias (for trials of α-glucosidase inhibitors).

The DPP compared an intensive lifestyle modification program with metformin and placebo, finding a greater reduction in diabetes incidence over about 3 years with a lifestyle program than with metformin, as compared with placebo (58% vs 31% reduction in diabetes incidence).[73] The authors estimated that about 7 persons would need to be treated with the lifestyle intervention or about 14 with metformin to prevent 1 case of diabetes over about 3 years.[73] Longer follow-up over a mean of 15 years reported by the DPPOS also found greater reduction for persons in the lifestyle program than for those taking metformin, although it found a decline in between-group difference (27% vs 18% reduction in diabetes incidence).[30]

Key Question 9. Do interventions for prediabetes improve other intermediate outcomes (blood pressure, lipid levels, BMI, weight, and calculated 10-year CVD risk)?

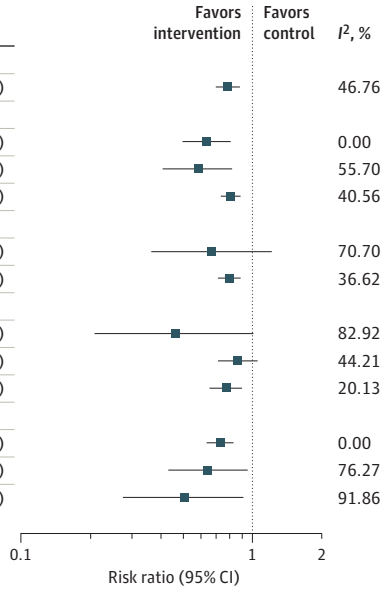
Thirty-eight RCTs (described in 58 articles) were included (eResults in the Supplement).[16-31,33,35,40-48,56-60,62,63,65-74,86-89,91,92,96-102] Lifestyle interventions were significantly associated with reduced systolic and diastolic blood pressure (pooled WMD, −1.7 mm hg [95% CI, −2.6 to −0.8] for systolic and −1.2 mm hg [95% CI, −2.0 to −0.4] for diastolic), weight (pooled WMD, −1.15 kg [95% CI, −1.56 to −0.74]), and BMI (pooled WMD, −0.54 [95% CI, −0.76 to −0.33]) (eFigures 2, 3, and 4 in the Supplement). Most trials evaluating hypoglycemic agents found no statistically significant association with changes in blood pressure or lipids. Trials of some hypoglycemic agents (metformin, acarbose, or liraglutide) reported reductions in weight and BMI, whereas meta-analysis of trials evaluating thiazolidinediones found a significant association with weight gain (pooled WMD, 1.9 kg [95% CI, 0.8 to 3.1]) (eResults in the Supplement).

Discussion

This evidence review evaluated benefits and harms of screening for prediabetes and diabetes and of interventions for prediabetes

Figure 4. Delaying or Preventing Progression to Diabetes: Results of Meta-analyses of Trials Evaluating Interventions for Persons With Prediabetes (KQ7)

Category	No. of studies	Total No.	Risk ratio (95% CI)	I^2, %
Lifestyle intervention				
All (longest follow-up)	23	12 915	0.78 (0.69-0.88)	46.76
Time point, mo				
<12	4	3518	0.63 (0.50-0.81)	0.00
12-24	15	5946	0.58 (0.41-0.82)	55.70
>24	13	8947	0.81 (0.73-0.89)	40.56
Contact dose				
Medium	5	3579	0.67 (0.37-1.22)	70.70
High	18	9303	0.79 (0.71-0.89)	36.62
BMI				
<25	4	3803	0.46 (0.21-1.02)	82.92
25-29.5	6	3575	0.86 (0.71-1.05)	44.21
≥30	13	5503	0.77 (0.65-0.91)	20.13
Pharmacological intervention				
Metformin	3	2181	0.73 (0.64-0.83)	0.00
Acarbose or voglibose	3	3264	0.64 (0.43-0.96)	76.27
Pioglitazone or rosiglitazone	3	6238	0.50 (0.28-0.92)	91.86



BMI indicates body mass index (calculated as weight in kilograms divided by height in meters squared); KQ, key question.

or diabetes that was screen detected or recently diagnosed for populations and settings relevant to US primary care; a summary of the evidence is provided in **Table 2**. For benefits of screening, the strength of evidence from 2 trials (25 120 total participants) was low (for no benefit) for mortality and was insufficient for all other outcomes. The data for outcomes other than mortality were limited, because data were missing for most participants, and the duration of follow-up in trials may have been too short to detect benefits for health outcomes. Neither trial assessed screening for prediabetes, and neither assessed initial screening with HbA_{1c} or fasting glucose. For harms of screening, the strength of evidence was low from 2 trials that reported no significant differences between screening and control groups for anxiety, depression, worry, or self-reported health, but 1 reported short-term increases in anxiety (at 6 weeks) among persons screened and diagnosed with diabetes vs those not diagnosed with diabetes. No included studies reported on labeling, harms from false-positive results, burden, inconvenience, or unnecessary testing and treatment.

For screen-detected diabetes, the strength of evidence from the ADDITION-Europe trial (3057 participants) was low (for no benefit). Follow-up may have been too short to detect benefits for health outcomes, and results were imprecise. For recently diagnosed (not screen-detected) diabetes, the strength of evidence from 5 trials (5138 participants) was moderate for improved long-term health outcomes. Regarding applicability, it is uncertain whether results from trials of persons with recently diagnosed diabetes are applicable to those with screen-detected diabetes. Recently diagnosed diabetes was generally clinically detected (eg, because of symptoms) and may represent a different subset of the diabetes spectrum, possibly with greater condition severity. The evidence of benefits for persons with recently diagnosed (not screen-detected) diabetes comes primarily from the UKPDS, conducted among predominantly White participants from 1977 through 1997, when routine care for CVD prevention would not have included treatments now considered to be current standard medical therapy (eg, statins, lower blood pressure targets). The comparison used in the hypertension in diabetes study embedded in UKPDS exemplifies differences from current standard therapy because it compared tighter control of blood pressure by targeting pressures less than 150/85 mm Hg vs less tight control targeting pressures less than 180/105 mm Hg.

For prediabetes, most trials had insufficient duration of follow-up for long-term health outcomes, reported few events, and found no differences between groups. One trial of a 6-year lifestyle intervention for persons with impaired glucose tolerance conducted in China (Da Qing, n = 576) reported lower all-cause mortality and CVD-related mortality at 23 years and at 30 years but not at earlier follow-up. The trial was limited by at least medium risk of bias, and the original trial was designed to assess diabetes incidence and not long-term health outcomes. Regarding applicability, the trial began in 1986, when (like UKPDS) routine care for CVD prevention would not have included treatments now considered to be current standard medical therapy. Participants had impaired glucose tolerance, and mean baseline BMI was 25.7; applicability to other categories of prediabetes, US populations, and those in different BMI categories is uncertain.

High strength of evidence from meta-analyses found that lifestyle interventions for obese or overweight persons with prediabetes were significantly associated with a reduction in the incidence of diabetes in trials ranging from 1 year of follow-up to 30 years of follow-up (including 13 trials with at least 3 years of follow-up). Lifestyle interventions were also significantly associated with reduced blood pressure, weight, and BMI. The clinical importance of the small mean reductions is somewhat uncertain. For blood pressure, for example, some guidelines suggest that reductions of 2 to 3 mm Hg could result in significant improvement in cardiovascular outcomes.[105] Regarding applicability, the findings are applicable to overweight and obese adults, and most trials evaluated high-contact interventions (>360 minutes). For example, the intensive

Table 2. Summary of Evidence on Screening for Prediabetes and Type 2 Diabetes

Topic	No. of studies (No. of publications; No. of participants)	Summary of findings	Consistency and precision	Study quality	Limitations (including reporting bias)	Overall strength of evidence	Applicability
KQ1: Benefits of screening							
	2 RCTs (5 publications; n = 25 120)	For invitations to screening with a stepwise approach (starting with random glucose measurement) or OGTT every 5 y compared with controls, no significant difference between groups for all-cause or cause-specific mortality at 10 y, or self-reported CVD events or quality of life at 7-13 y	Consistency unknown (the 2 trials evaluated different screening approaches); imprecise	1 Good 1 Fair	Duration of follow-up may be too short; for outcomes other than mortality, missing data from most participants; reporting bias not detected	Low for no benefit for mortality Insufficient for all other outcomes	Asymptomatic adults aged 40-69 y; trials evaluated invitations to screening for diabetes; neither assessed screening for prediabetes or focused on fasting glucose or HbA_{1c} as the initial test; neither reported race and ethnicity; mean BMI was 30-31 (NR in 1 trial)
KQ2: Harms of screening							
	3 RCTs (5 publications; n = 9328)[a]	No significant differences between screening and control groups for anxiety, depression, worry, or self-reported health Possible short-term increases in anxiety (at 6 wk) among persons screened and diagnosed with diabetes vs those not diagnosed with diabetes (STAI scores, 46.7 vs 37.0; *P* = .03) No trials reported on labeling, harms from false-positive results, burden, inconvenience, or unnecessary testing and treatment	Consistency unknown (no 2 studies used similar measures at similar time points); imprecise	Fair (at least medium risk of bias)	Missing data from many participants; heterogeneity of measures used and timing of assessments; reporting bias not detected	Low for anxiety, depression, worry, or self-reported health Insufficient for other outcomes[b]	Asymptomatic adults aged 40-69 y at high risk of diabetes
KQ3: Intervening at time of screen detection vs later							
	No eligible studies	NA	NA	NA	NA	Insufficient	NA
KQ4: Benefits of interventions							
Benefits of interventions for screen-detected diabetes	1 RCT (8 publications; n = 3057)	ADDITION-Europe found no difference over 5 to 10 y between an intensive multifactorial intervention aimed at controlling glucose, blood pressure, and cholesterol levels and routine care in the risk of all-cause mortality, cardiovascular-related mortality, cardiovascular events, quality of life, nephropathy, retinopathy, or neuropathy	Consistency unknown (single study); imprecise	Fair	Follow-up may have been too short; decisions about medication choices were made by individual physicians and patients; reporting bias not detected	Low for no benefit	Adults aged 40-69 y with screen-detected diabetes; mean baseline HbA_{1c}, 7.0% (median, 6.5%); mean BMI, 31.5; participants were predominantly White; screening risk questionnaire followed by random glucose measurement or invitation to have OGTT

(continued)

Table 2. Summary of Evidence on Screening for Prediabetes and Type 2 Diabetes (continued)

Topic	No. of studies (No. of publications; No. of participants)	Summary of findings	Consistency and precision	Study quality	Limitations (including reporting bias)	Overall strength of evidence	Applicability
Benefits of interventions for prediabetes	38 studies (56 publications; n = 36 393)	Most trials reported mortality or CVD events after ≤6 y and reported few events with no difference between groups Two trials had ≥10 y of follow-up: Finnish DPP (n = 505) found no statistically significant difference between groups for mortality or composite CVD events over 10 y,[c] and Da Qing (n = 576) found no statistically significant difference between lifestyle and control groups at 20 y,[d] but rates were lower in the combined intervention groups at 23 y for all-cause mortality (28.1% vs 38.4%; HR, 0.71 [95% CI, 0.51 to 0.99]) and CVD-related mortality (11.9% vs 19.6%; HR, 0.59 [95% CI, 0.36 to 0.96]); rates remained lower at 30-y follow-up For QOL, 5 trials suggested no clinically meaningful benefit	Reasonably consistent for CVD events, mortality, and QOL; consistency unknown for aggregate microvascular outcome (single study); imprecise	Fair	Follow-up duration too short in most studies; at least medium risk of bias in the Da Qing trial,[e] and relatively few participants; heterogeneity of measures used to assess QOL; reporting bias not detected	Low for long-term mortality benefit after 20 y	Adults with prediabetes; the trial reporting reduction in CVD events associated with acarbose included a population at high risk of CVD; the Da Qing trial, showing long-term mortality benefit associated with a lifestyle intervention, was conducted in China and used a 6-y lifestyle intervention
KQ5: Benefits of interventions for recently diagnosed diabetes							
	5 RCTs[f] (8 publications; n = 5138)	Intensive glucose control with sulfonylureas or insulin decreased the risk for all-cause mortality (RR, 0.87 [95% CI, 0.79 to 0.96]), diabetes-related mortality (RR, 0.83 [95% CI, 0.73 to 0.96]), and myocardial infarction (RR, 0.85 [95% CI, 0.74 to 0.97]) over 20 y (10-y posttrial assessment) but not at shorter follow-up For overweight persons, intensive glucose control with metformin decreased the risk for all-cause mortality (RR, 0.64 [95% CI, 0.45 to 0.91]), diabetes-related mortality (RR, 0.58 [95% CI, 0.37 to 0.91]), and myocardial infarction (RR, 0.61 [95% CI, 0.41 to 0.89]) at 10-y follow-up, and benefits were maintained longer term[g]	Consistency unknown;[h] precise for mortality and CVD outcomes; imprecise for other outcomes	Good	The longer-term results presented were from 10-y posttrial monitoring Only 1 lifestyle intervention was included with follow-up for only 3 y and few clinical events Reporting bias was not detected Duration of diabetes at baseline was NR in the UKPDS	Moderate for improved long-term health outcomes	Most of the data are from UKPDS, conducted from 1977-1997; 4 of the included studies were from the UK; participants were predominantly White
KQ6: Harms of interventions							
Harms of interventions for diabetes	4 RCTs (6 publications; n = 5402)	Overall, harms were generally sparsely reported, rare, and (when reported) not significantly different between groups UKPDS reported major hypoglycemic events in 1% to 1.8% of participants receiving sulfonylureas or insulin (vs 0.7% in the conventional care group)	Unknown consistency; imprecise	Fair	Included studies all assessed different interventions; reporting bias not detected	Low	Screen-detected or newly diagnosed diabetes

(continued)

Table 2. Summary of Evidence on Screening for Prediabetes and Type 2 Diabetes (continued)

Topic	No. of studies (No. of publications; No. of participants)	Summary of findings	Consistency and precision	Study quality	Limitations (including reporting bias)	Overall strength of evidence	Applicability
Harms of interventions for prediabetes	21 RCTs (38 publications; n = 32 468)	Lifestyle interventions: 2 studies found no or few musculoskeletal adverse events; DPP found higher rates of musculoskeletal symptoms among the intensive lifestyle intervention group Medications: no increased risk of hypoglycemic events vs placebo in 5 trials assessing 5 different medications (liraglutide, sitagliptin, metformin, nateglinide, and rosiglitazone + metformin) Six pharmacologic trials found higher rates of GI adverse events vs controls: metformin (3 trials), acarbose (2 trials), and liraglutide (1 trial)	Lifestyle interventions: inconsistent, imprecise Pharmacologic interventions: reasonably consistent; imprecise	Fair	Sparse reporting of harms (of 38 studies of interventions for prediabetes, 21 reported on harms)	Low	Adults with screen-detected or newly diagnosed prediabetes; most studies reporting harms assessed pharmacologic interventions
KQ7: Interventions for prediabetes to delay or prevent progression to diabetes							
	Lifestyle: 23 RCTs (33 publications; n = 12 915) Pharmacologic: 15 RCTs (23 publications; n = 24 295)	Lifestyle interventions associated with reduction in diabetes (23 trials; pooled RR, 0.78 [95% CI, 0.69 to 0.88])[i] Follow-up <1 y: pooled RR, 0.63 (95% CI, 0.50 to 0.81) Follow-up 1-2 y: pooled RR, 0.58 (95% CI, 0.41 to 0.82) Follow-up >2 y: pooled RR, 0.81 (95% CI, 0.73 to 0.89) For medications, metformin, thiazolidinediones, and AGIs were all associated with a reduction in diabetes (metformin pooled RR, 0.73 [95% CI, 0.64 to 0.83]; thiazolidinediones pooled RR, 0.50 [95% CI, 0.28 to 0.92]; AGIs pooled RR, 0.64 [95% CI, 0.43 to 0.96])[j]	Reasonably consistent (except for thiazolidinediones and AGIs); precise for lifestyle interventions and metformin, imprecise for thiazolidinediones and AGIs	Good: 6 Fair: 30	Heterogeneity in approaches to defining prediabetes; higher rates of dropout or nonadherence in studies of AGIs; reporting bias not detected	High for lifestyle interventions and metformin (for benefit) Low for other medications[k] (for benefit)	Asymptomatic adults aged 40-60 y; most trials evaluated high-contact lifestyle interventions; mean baseline BMI ranged from 24 to 39
KQ8: Change in health outcomes that results from reduction in diabetes incidence after interventions for prediabetes							
	8 Studies (17 publications; n = 23 489)	Two trials had >5 y of follow-up; 1 had >10 y of follow-up One trial (Da Qing, n = 576) reported reduction in both diabetes incidence and long-term adverse health outcomes with more than the 5-y follow-up, finding that a 6-y lifestyle intervention yielded an absolute decrease in diabetes incidence of 24% (over 6 y) and was associated with 10% fewer deaths and 8% fewer cardiovascular deaths over 30 y	Consistency unknown (single study with adequate long-term follow-up); imprecise	Fair	Most trials had insufficient follow-up to assess long-term health outcomes; at least medium risk of bias in the Da Qing trial;[l] and relatively few participants	Low	Trials in the US and other highly developed countries had insufficient follow-up; Da Qing trial was conducted in China

(continued)

Table 2. Summary of Evidence on Screening for Prediabetes and Type 2 Diabetes (continued)

Topic	No. of studies (No. of publications; No. of participants)	Summary of findings	Consistency and precision	Study quality	Limitations (including reporting bias)	Overall strength of evidence	Applicability
KQ9: Interventions for prediabetes and other intermediate outcomes							
	Lifestyle: 28 studies (41 publications; n = 14 671) Pharmacologic: 13 studies (25 publications; n = 26 619)	Lifestyle interventions: associated with reduced SBP (pooled WMD, −1.7 mm Hg [95% CI, −2.6 to −0.8]) and DBP (pooled WMD, −1.2 mm Hg [95% CI, −2.0 to −0.4]), weight (pooled WMD, −1.2 kg [95% CI−1.6 to −0.7)], and BMI (pooled WMD, −0.54 [95% CI, −0.76 to −0.33]) Medications: most trials found no statistically significant association between hypoglycemic agents and changes in blood pressure or lipid levels[m] but found reduction in weight and BMI[n] (except thiazolidinediones were associated with weight gain (pooled WMD, 1.9 kg [95% CI, 0.8 to 3.1])	Lifestyle: reasonably consistent; precise Hypoglycemic medications: inconsistent or consistency unknown (depending on the medication); imprecise	Good: 5 Fair: 33	Outcomes were often among many secondary outcomes and not the primary focus of trials; substantial or considerable statistical heterogeneity in some meta-analyses for weight, BMI, and lipids; reporting bias not detected	Lifestyle: high for benefit[o] Medications: low for no benefit for blood pressure and lipids; moderate for weight loss with metformin and weight gain with thiazolidinediones	Asymptomatic adults aged 40-60 y; most trials evaluated high-contact lifestyle interventions; mean baseline BMI ranged from 24 to 39 (and was >30 in most)

Abbreviations: ADDITION, Anglo-Danish-Dutch Study of Intensive Treatment In People With Screen Detected Diabetes in Primary Care; AGI, α-glucosidase inhibitor; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CVD, cardiovascular disease; DBP, systolic blood pressure; DPP, Diabetes Prevention Program; GI, gastrointestinal; $HbA_{1C,}$ hemoglobin A_{1c}; HR, hazard ratio; KQ, key question; NA, not applicable; NR, not reported; OGTT, oral glucose tolerance test; QOL, quality of life; RCT, randomized clinical trial; RR, relative risk; SBP, systolic blood pressure; STAI, State-Trait Anxiety Inventory; UKPDS, United Kingdom Prospective Diabetes Study; WMD, weighted mean difference.

[a] Comprising 7380 participants surveyed from all 5 control practices and 10 intervention practices in ADDITION-Cambridge (although the number responding for any given time point and outcome measure ranged from 2667 to 3654), 1594 from the Ely study (1442 without and 152 with diabetes), and 354 from the ADDITION-Cambridge pilot.

[b] Including labeling, harms from false-positive results, burden, inconvenience, or unnecessary testing and treatment.

[c] The Finnish DPP (n = 505) found no statistically significant difference between groups for all-cause mortality (2.2 vs 3.8 deaths per 1000 person-years; HR, 0.57 [95% CI, 0.21-1.58]) or composite CVD events (incident fatal and nonfatal acute coronary events, coronary heart disease, stroke, and hypertensive disease) (22.9 vs 22.0 events per 1000 person-years; HR, 1.04 [95% CI, 0.72-1.51]) over 10 years of follow-up.[4O]

[d] Da Qing trial found no significant difference between lifestyle groups and control for all-cause mortality (25.0% vs 29.3%; HR, 0.96 [95% CI, 0.65-1.41]) or CVD-related mortality (12% vs 17%; HR, 0.83 [95% CI, 0.48-1.40]) at 20 years, but rates were significantly lower in the combined intervention group at 23 years for all-cause mortality (28.1% vs 38.4%; HR, 0.71 [95% CI, 0.51-0.99]) and CVD-related mortality (11.9% vs 19.6%; HR, 0.59 [95% CI, 0.36-0.96]), and differences remained significant at 30 years.

[e] Unclear randomization and allocation concealment methods; baseline differences for smoking that bias results in favor of intervention.

[f] Three of the trials were related to the UKPDS, which was a randomized multicenter trial that ran for 20 years (from 1977 to 1997) in 23 sites across the UK.

[g] Tighter control of BP vs less tight control (<150/85 vs <180/105) decreased the risk of diabetes-related mortality (RR, 0.68 [95% CI, 0.49-0.94]) and stroke (RR, 0.56 [95% CI, 0.35-0.89]) at 9 years' follow-up, but the benefits were not maintained over longer term follow-up.

[h] Single study for each intervention and outcome, with most evidence of benefit coming from UKPDS trials.

[i] Estimated number needed to treat, 9 over 15 years.

[j] Estimated numbers needed to treat were 13 over 3 years and 8 over 15 years for metformin.

[k] Downgrading for imprecision and inconsistency for thiazolidinediones and AGIs and for risk of bias for AGIs.

[l] Unclear randomization and allocation concealment methods; baseline differences for smoking that bias results in favor of intervention.

[m] For some medications (rosiglitazone, acarbose), a single trial reported a statistically significant reduction in BP, but the finding has not been replicated.

[n] Trials reporting reduction in weight or BMI assessed metformin, acarbose, or liraglutide.

[o] Presence of dose response increased the strength of evidence for some outcomes (ie, greater improvement with high-contact interventions).

lifestyle modification program evaluated in the DPP comprised a 16-lesson curriculum covering diet, exercise, and behavior modification that was taught one-on-one by case managers. The goals of the lifestyle intervention were to achieve and maintain at least a 7% weight reduction through a low-calorie, low-fat diet and moderate-intensity physical activity for at least 150 minutes per week.

This review found high strength of evidence that using metformin for prediabetes was significantly associated with a reduction in diabetes incidence (defined in the trials by fasting glucose, oral glucose tolerance test result, or HbA_{1c} level), although head-to-head trial data demonstrated that lifestyle interventions were superior to metformin.[30,73]

Limitations

This review has several limitations. First, non–English-language articles were excluded. Second, for studies of recently diagnosed diabetes, studies of persons who had diabetes for more than 1 year or with more advanced diabetes were excluded, aiming to identify the studies with good applicability to a screen-detected population. Third, the review did not evaluate studies of weight loss medications or bariatric surgery to treat diabetes.

Conclusions

Trials of screening for diabetes found no mortality benefit but had insufficient data to assess other health outcomes; evidence on harms of screening was limited. For persons with recently diagnosed (not screen-detected) diabetes, interventions improved health outcomes; for obese or overweight persons with prediabetes, interventions were associated with reduced incidence of diabetes and improvement in other intermediate outcomes.

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