JAMA | US Preventive Services Task Force | EVIDENCE REPORT

Screening for Prediabetes and Type 2 Diabetes in Children and Adolescents

Evidence Report and Systematic Review for the US Preventive Services Task Force

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IMPORTANCE Of youths diagnosed with type 2 diabetes, many develop microvascular complications by young adulthood.

OBJECTIVE To review the evidence on benefits and harms of screening children and adolescents for prediabetes and type 2 diabetes to inform the US Preventive Services Task Force (USPSTF).

DATA SOURCES PubMed/MEDLINE, Cochrane Library, and trial registries through May 3, 2021; references; experts; literature surveillance through July 22, 2022.

STUDY SELECTION English-language controlled studies evaluating screening or interventions for prediabetes or type 2 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.

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

RESULTS This review included 8 publications (856 participants; mean age, 14 years [range, 10-17 years]). Of those, 6 were from the Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) study. No eligible studies directly evaluated the benefits or harms of screening. One randomized clinical trial (RCT) (TODAY; n = 699 adolescents with obesity; mean age, 14 years) comparing metformin, metformin plus rosiglitazone, and metformin plus lifestyle intervention reported that 2 youths with recently diagnosed diabetes developed kidney impairment (0 vs 1 vs 1, respectively; $P > .99$) and 11 developed diabetic ketoacidosis (5 vs 3 vs 3, respectively; $P = .70$). One RCT of 75 adolescents (mean age, 13 years) with obesity with prediabetes compared an intensive lifestyle intervention with standard care and reported that no participants in either group developed diabetes, although follow-up was only 6 months. Regarding harms of interventions, 2 RCTs assessing different comparisons enrolled youths with recently diagnosed diabetes. Major hypoglycemic events were reported by less than 1% of participants. Minor hypoglycemic events were more common among youths treated with metformin plus rosiglitazone than among those treated with metformin or metformin plus lifestyle intervention in TODAY (8.2% vs 4.3% vs 3.4%, $P = .05$). In 1 study, gastrointestinal adverse events were more commonly reported by those taking metformin than by those taking placebo (abdominal pain: 25% vs 12%; nausea/vomiting: 17% vs 10%; *P* not reported).

CONCLUSIONS AND RELEVANCE No eligible studies directly evaluated the benefits or harms of screening for prediabetes and type 2 diabetes in children and adolescents. For youths with prediabetes or recently diagnosed (not screen-detected) diabetes, the only eligible trials reported few health outcomes and found no difference between groups, although evidence was limited by substantial imprecision and a duration of follow-up likely insufficient to assess health outcomes.

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An estimated 210 000 US children and adolescents (2.5 per 1000) had diabetes in 2018, of whom approximately 23 000 had type 2 diabetes (0.24 per 1000).[1] Prevalence estimates for prediabetes from 2005 to 2016 indicated that almost 20% of those aged 12 to 18 years had prediabetes.[2] Data indicate that the prevalence and incidence of type 2 diabetes are increasing.[3,4] Risk factors include overweight and obesity, age (most pediatric cases occur after age 10 years, with the peak occurring at midpuberty), and family history.[5] Prevalence estimates are highest in American Indian/Alaska Native, Black, and Hispanic youth.[6] Differences in the frequencies of type 2 diabetes by socioeconomic position, area of residence, and environmental factors have also been described; the relative contributions of various factors to racial and ethnic differences are largely unknown, but structural factors that disproportionately affect racial and ethnic minority populations (eg, quality of and access to health care, toxic stress, structural racism) may contribute significantly.[7,8]

The major acute complications of type 2 diabetes in youth are diabetic ketoacidosis and hyperglycemic hyperosmolar state.[9] Long-term morbidity is due to both macrovascular disease (atherosclerosis) and microvascular disease (retinopathy, nephropathy, and neuropathy). Among those with type 2 diabetes diagnosed during childhood and adolescence, many develop complications of kidney disease, retinopathy, and peripheral neuropathy during teenage years and young adulthood.[10,11]

In 2021, the US Preventive Services Task Force (USPSTF) recommended screening for prediabetes and type 2 diabetes in adults aged 35 to 70 years with overweight or obesity (B recommendation). The USPSTF has not previously issued a recommendation on this topic for children and adolescents. This review evaluated the evidence on screening children and adolescents for prediabetes and type 2 diabetes for populations and settings relevant to primary care in the US to inform an updated recommendation by the USPSTF.

Methods

Scope of Review

Detailed methods are available in the full evidence review.[5] **Figure 1** shows the analytic framework, the key questions (KQs) that guided the systematic review, and the contextual questions intended to provide additional background information. In addition to addressing the KQs, this review looked for evidence related to 5 contextual questions that focused on progression from prediabetes to diabetes (natural history of prediabetes), whether screening or interventions change intermediate outcomes, agreement among screening tests, and risk assessment tools.

eTable 1 in the Supplement shows general categories and definitions of diabetes.[13] Three tests can be used to identify prediabetes and type 2 diabetes: hemoglobin A_{1c} (HbA_{1c}) level, fasting plasma glucose level, or an oral glucose tolerance test (OGTT) (eTable 2 in the Supplement).

Data Sources and Searches

PubMed/MEDLINE and the Cochrane Library were searched for English-language articles published through May 3, 2021. 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 May 2021, 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 July 22, 2022.

Study Selection

Two investigators independently reviewed titles, abstracts, and full-text articles to determine eligibility using prespecified criteria (eTable 3 in the Supplement). Disagreements were resolved by discussion and consensus. English-language studies of asymptomatic, nonpregnant persons younger than 18 years conducted in countries categorized as very high on the Human Development Index[14] and rated as fair or good quality were included. For all KQs, randomized clinical trials (RCTs) and nonrandomized controlled intervention studies were eligible. Controlled prospective cohort studies were also eligible for KQs on harms (KQ2 and KQ4) and the change in health outcomes after reduction in type 2 diabetes incidence (KQ6); case-control studies were eligible for KQs on harms (KQ2 and KQ4). For KQ1 and KQ2 (direct evidence of benefits and harms of screening), studies that compared screening with HbA_{1c}, fasting glucose, or OGTT with no screening or alternative screening strategies were eligible. For KQs 3 through 6 (benefits and harms of interventions), studies that evaluated primary care–relevant behavioral counseling interventions or pharmacologic interventions for glycemic control for prediabetes or diabetes were eligible.

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 4-6 in the Supplement) developed by the USPSTF and adapted for this topic.[12] 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).[12] Additionally, the applicability of the findings to US primary care populations and settings was assessed. Discrepancies were resolved through consensus discussion.

The appropriateness of meta-analyses was determined using established guidance to assess the clinical and methodological heterogeneity of the studies.[15] The populations, tests, treatments, comparators, outcomes, and study designs were assessed qualitatively, looking for similarities and differences. Because of the limited number of similar studies for each KQ, meta-analyses were not conducted.

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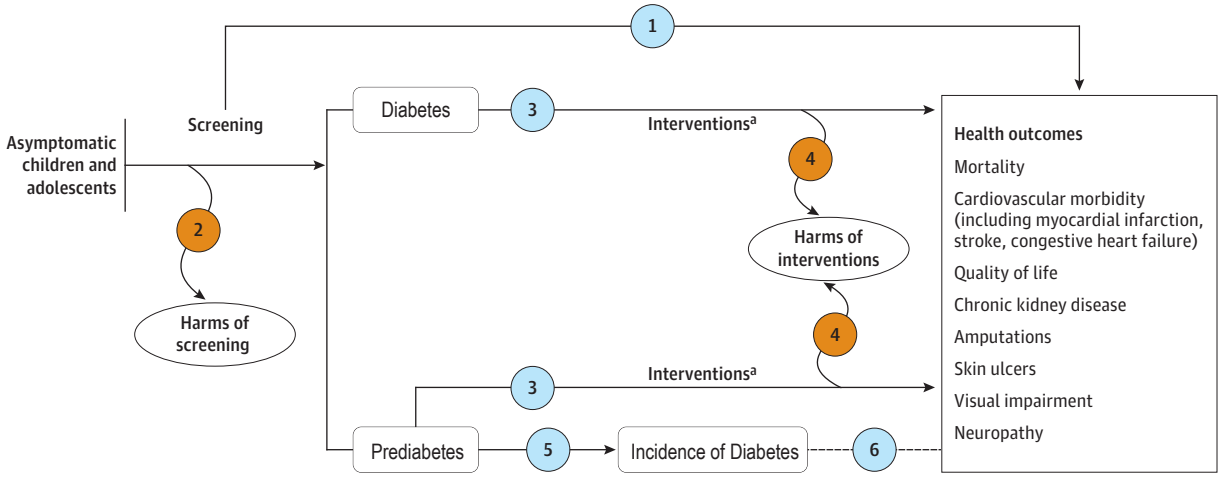
Figure 1. Analytic Framework: Screening for Prediabetes and Type 2 Diabetes in Children and Adolescents



Key questions

1. Is there direct evidence that screening for type 2 diabetes and prediabetes in asymptomatic children and adolescents improves health outcomes?
2. What are the harms of screening for type 2 diabetes and prediabetes in asymptomatic children and adolescents?
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. 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?
   c. Do interventions for recently diagnosed type 2 diabetes improve health outcomes compared with no intervention, usual care, or interventions with different treatment targets?
4. What are the harms of interventions for prediabetes, screen-detected type 2 diabetes, or recently diagnosed type 2 diabetes?
5. Do interventions for prediabetes delay or prevent progression to type 2 diabetes?
6. 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?

Contextual questions

- CQ1 a. What percentage of children and adolescents with prediabetes progress to type 2 diabetes, remain prediabetic, or return to normal glycemia or glucose tolerance (without intervention), and over what time frame?
  b. What percentage of children and adolescents with type 2 diabetes return to normal glycemia or glucose tolerance or to the prediabetic range (without intervention), and over what time frame?
  c. How does this differ by baseline hemoglobin HbA_{1c} level, fasting glucose level, or glucose tolerance?
- CQ2 a. Does screening for prediabetes or type 2 diabetes change the intermediate outcomes of HbA_{1c} level, FPG level, 2-hour glucose tolerance test results, subclinical retinopathy, microalbuminuria, or subclinical neuropathy for children and adolescents?
  b. Do interventions for children and adolescents with screen-detected or recently diagnosed type 2 diabetes or prediabetes change the intermediate outcomes of HbA_{1c} level, FPG level, 2-hour glucose tolerance test results, subclinical retinopathy, microalbuminuria, or subclinical neuropathy?
- CQ3 a. Do interventions for (or does knowledge of) prediabetes change BMI, weight, or healthy behaviors?
  b. Do interventions for (or does knowledge of) type 2 diabetes change BMI, weight, or healthy behaviors?
- CQ4 What is the frequency of agreement among screening tests (HbA_{1c} level, FPG level, and 2-hour glucose tolerance test) for prediabetes and type 2 diabetes?
- CQ5 Are there risk assessment tools that are feasible for use in primary care settings, that accurately predict the risk of prediabetes or type 2 diabetes for children and adolescents, and have been externally validated in US populations?

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. A dashed line indicates a health outcome that immediately follows an intermediate outcome. The contextual questions (CQs) are also listed; they were not a part of this systematic review. They are intended to provide additional background information. For additional information, see the USPSTF Procedure Manual.[12] BMI indicates body mass index; FPG, fasting plasma glucose; HbA_{1c}, hemoglobin A_{1c}.

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

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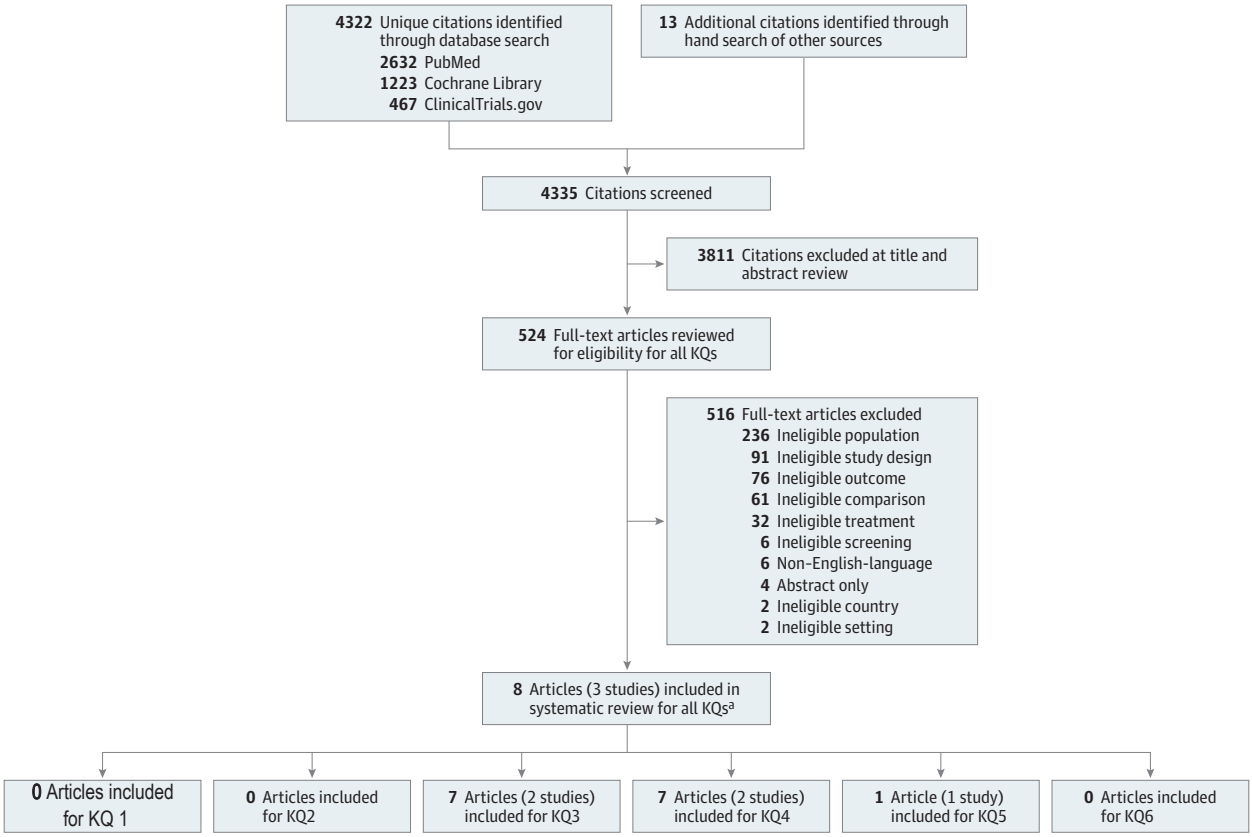
Figure 2. Literature Search Flow Diagram: Screening for Prediabetes and Type 2 Diabetes in Children and Adolescents



KQ indicates key question.

[a] Number of studies per KQ sums to more than the total number of studies because some studies were applicable to multiple KQs.

Results

A total of 8 publications were included (**Figure 2**). Individual study quality ratings are reported in eTables 4-6 in the Supplement. The 8 publications reported on 3 RCTs and included a total of 856 participants with a mean age of 14 years (range, 10-17 years).

Benefits of Screening

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

No eligible studies addressed this question.

Harms of Screening

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

No eligible studies addressed this question.

Benefits of Interventions

Key Question 3a. 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?

Key Question 3b. 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 3c. Do interventions for recently diagnosed type 2 diabetes improve health outcomes compared with no intervention, usual care, or interventions with different treatment targets?

In summary, no eligible studies addressed KQ3a or KQ3b; 2 RCTs were eligible for KQ3c.

Characteristics of Included Studies

The review included 2 RCTs (described in 7 articles) (**Table 1**).[16-22] One was rated as good quality and 1 was rated as fair quality. The 1 good-quality RCT (described in 6 articles), the Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) study, enrolled 699 participants and evaluated interventions for recently diagnosed diabetes.[17-22] The TODAY study was a 15-site multicenter trial conducted in the US. The trial randomized adolescents with obesity (body mass index [BMI] ≥85th percentile for age and sex) and recently diagnosed diabetes to receive metformin monotherapy, metformin plus rosiglitazone, or metformin plus a lifestyle intervention. Prior to randomization, all participants completed a run-in of 2 to 6 months that involved weaning from nonstudy diabetes medications, initiating metformin at a dose of up to 1000 mg twice daily,

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Table 1. Characteristics of Included Randomized Trials of Children and Adolescents With Prediabetes or Type 2 Diabetes (KQ3, KQ4, KQ5)

Source	Participants	Duration of follow-up	Study group (No. of participants)	Mean (SD)		No. (%)		Mean (SD)		Quality
				Duration of diabetes, mo	Age, y	Female	Racial or ethnic minority	HbA_{1c}, %	BMI[a]	
Jones et al,[16] 2002	Children (10-16 y) with previous or new diagnosis of type 2 diabetes, BMI >50th percentile for age; 44 sites in multiple countries[b]	16 wk	Metformin (titrated up to maximum 2000 mg/d) (42)[c]	NR	13.9 (1.8)	30 (71.4)	25 (59.5)	8.3 (1.3)	34.2 (10.6)	Fair
			Placebo (40)	NR	13.6 (1.8)	27 (67.5)	27 (67.5)	9.0 (1.4)	33.9 (12.7)	
TODAY Zeitler et al,[17] 2012 TODAY Study Group,[18] 2013 TODAY Study Group,[19] 2010 Levitt Katz et al,[20] 2015 Zeitler et al,[21] 2007 Kelsey et al,[22] 2016	Adolescents with obesity (10-17 y) with type 2 diabetes for <2 y, BMI ≥85th percentile for age and sex at 15 clinical centers in the US	Mean, 3.8 y (range, 2-6.5 y)	Metformin (232)[d]	7.8 (6.0)	14.1 (1.9)	NR (63.1)	183 (78.9)	7.3 (2.2)	35.8 (8.1)	Good
			Metformin + rosiglitazone, 4 mg twice daily (233)[d]	8.0 (5.7)	14.1 (2.1)	NR (65.7)	186 (79.8)	7.0 (2.3)	35.0 (7.7)	
			Metformin + lifestyle intervention (234)[d]	7.6 (5.8)	13.8 (2.0)	NR (66.0)	188 (80.3)	7.1 (2.2)	34.1 (7.1)	
Savoye et al,[23] 2014	Adolescents with obesity (10-16 y) with BMI >95th percentile and prediabetes (elevated OGTT, 2-h 130-199 mg/dL) from the Yale Pediatric Obesity Clinic	6 mo	Bright Bodies Healthy Lifestyle Program (38)[e]	NA	12.7 (1.9)	26 (68.4)	11 (29.0)	5.7 (0.4)	32.1 (5.2)	Fair
			Standard care (37)	NA	13.2 (1.8)	23 (62.2)	12 (32.4)	5.6 (0.4)	34.6 (6.8)	

Abbreviations: BMI, body mass index; HbA_{1c}, hemoglobin A_{1c}; KQ, key question; NA, not applicable; NR, not reported; OGTT, oral glucose tolerance test; TODAY, Treatment Options for Type 2 Diabetes in Adolescents and Youth.

[a] Calculated as weight in kilograms divided by height in meters squared.

[b] Participants were from the US (25 sites [n = 62]), Russia (6 sites [n = 13]), Ukraine (1 site [n = 4]), Belarus (1 site [n = 2]), and Poland (1 site [n = 1]).

[c] Mean final dose of metformin was 1798 mg/d.

[d] The run-in involved weaning from nonstudy diabetes medications, initiating metformin at a dose of up to 1000 mg twice daily, attaining glycemic control with metformin alone (HbA_{1c} <8.0%), providing standard diabetes education and ensuring the participants' mastery of the material, and confirming adherence.

[e] The program consisted of two 50-minute exercise sessions per week, 1 weekly weigh-in, and a 40-minute nutrition/behavior modification class. Participants were encouraged to exercise 3 additional days per week and record the duration and type of exercise. The study used raffle tickets for gift cards to motivate participants; tickets could be earned if weight stayed the same or decreased and, in some cases, if participants returned their weekly exercise log.

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attaining glycemic control with metformin alone (HbA_{1c} <8.0%), providing standard diabetes education and ensuring the participants' mastery of the material, and confirming adherence. The mean age of participants was 14 years; mean BMI was 35 (calculated as weight in kilograms divided by height in meters squared); mean baseline HbA_{1c} values were 7.0% to 7.3% across the 3 study groups; 65.0% were female; 32.5% were non-Hispanic Black, 39.7% were Hispanic, and 20.3% were non-Hispanic White. The duration of follow-up ranged from 2 to 6.5 years (mean, 3.8 years). The lifestyle intervention focused on diet/nutrition, physical activity, and family support. The program included 3 phases of in-person contacts: once weekly for the first 6 to 8 months, twice weekly for months 6 to 8 through months 12 to 16, and then once monthly until the end of the study. The primary outcome of the trial was loss of glycemic control, defined as an HbA_{1c} level of at least 8% for 6 months or sustained metabolic decompensation requiring insulin, and the study focused largely on intermediate outcomes (eg, glycemic control, BMI) rather than on health outcomes.

The second trial[16] compared metformin and placebo in 82 treatment-naive adolescents aged 10 to 16 years with previous or newly diagnosed diabetes.[16] It was a 16-week double-blind placebo-controlled trial of 82 adolescents recruited from 44 sites in multiple countries, including the US, Russia, Belarus, Ukraine, and Poland. Most participants were from the US sites. The intervention group received up to 2000 mg daily of metformin for 16 weeks. The mean age of participants was 14 years; mean BMI was 34; mean baseline HbA_{1c} values were 8.3% to 9.0% across the study groups; 69.0% were female; and 37.0% were White. The primary outcome was change in fasting plasma glucose level from baseline.

Kidney Impairment

The TODAY study reported 2 cases of kidney impairment, defined as an estimated creatinine clearance of less than 70 mL/min/1.73 m^2 (1.17 mL/s/m^2) or a serum creatinine level of more than 1.5 mg/dL (132.6 µmol/L) (**Table 2**). One case was in the metformin plus rosiglitazone group, and 1 was in the metformin plus lifestyle intervention group ($P > .99$).

Diabetic Ketoacidosis

The TODAY study reported that 11 participants developed diabetic ketoacidosis. There was no statistically significant difference across treatment groups (5 [2.1%] for metformin monotherapy vs 3 [1.3%] for metformin plus rosiglitazone vs 3 [1.3%] for metformin plus lifestyle intervention, $P = .70$). The smaller trial reported that 0 participants in the metformin group and 1 person in the control group developed diabetic ketoacidosis.

Other Health Outcomes

No eligible studies reported other health outcomes, including mortality, cardiovascular morbidity (including myocardial infarction, stroke, congestive heart failure), amputation, skin ulcers, visual impairment (including blindness), neuropathy, and quality of life.

Harms of Interventions

Key Question 4. What are the harms of interventions for prediabetes, screen-detected type 2 diabetes, or recently diagnosed type 2 diabetes?

Table 2. Results of Trials of Children and Adolescents With Prediabetes or Type 2 Diabetes Reporting Health Outcomes (KQ3) or Progression From Prediabetes to Type 2 Diabetes (KQ5)

Source	Study group (No. of participants)	No. (%)									
		Progression to diabetes	Mortality	CVD events	Diabetic ketoacidosis	Chronic kidney disease	Amputations	Skin ulcers	Visual impairment	Neuropathy
Jones et al,[16] 2002	Metformin (titrated up to maximum 2000 mg/d) (42)	NA	NR	NR	0	NR	NR	NR	NR	NR
	Placebo (40)	NA	NR	NR	1 (2.5)	NR	NR	NR	NR	NR
TODAY	Metformin (232)	NA	0	NR	5 (2.1)[a]	0[b]	NR	NR	NR	NR
Zeitler et al,[17] 2012 TODAY Study Group,[18] 2013	Metformin + rosiglitazone, 4 mg twice daily (233)	NA	0	NR	3 (1.3)[a]	1 (0.4)[b]	NR	NR	NR	NR
TODAY Study Group,[19] 2010 Levitt Katz et al,[20] 2015 Zeitler et al,[21] 2007 Kelsey et al,[22] 2016	Metformin + lifestyle intervention (234)	NA	0	NR	3 (1.3)[a]	1 (0.4)[b]	NR	NR	NR	NR
Savoye et al,[23] 2014	Bright Bodies Healthy Lifestyle Program (38)	0	NR	NR	NR	NR	NR	NR	NR	NR
	Standard care (37)	0	NR	NR	NR	NR	NR	NR	NR	NR

Abbreviations: CVD, cardiovascular disease; KQ, key question; NA, not applicable; NR, not reported; TODAY, Treatment Options for Type 2 Diabetes in Adolescents and Youth.

[a] $P = .70$ for comparison of the 3 interventions.

[b] Chronic kidney disease defined as kidney impairment. $P > .99$ for comparison of the 3 interventions.

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Overall, 2 RCTs (described in 7 articles) that enrolled a total of 781 youths (mean age, 14 years) with recently diagnosed type 2 diabetes were eligible.[16-22] The 2 trials assessed different comparisons. Major hypoglycemic events were reported by less than 1% of participants. Minor hypoglycemic events were more common among youths treated with metformin plus rosiglitazone than among those treated with metformin or metformin plus lifestyle intervention. In 1 study, gastrointestinal adverse events were more commonly reported by those taking metformin than by those taking placebo. Gastrointestinal adverse events, infections, and muscle aches and pains were less common among youths treated with metformin plus rosiglitazone than with metformin alone or metformin plus a lifestyle intervention. No eligible studies assessed harms for youths with screen-detected diabetes or prediabetes, and no eligible studies reported on harms of lifestyle interventions provided without pharmacotherapy.

Harms of Interventions for Recently Diagnosed Type 2 Diabetes

Two RCTs (described in 7 articles) reported on harms of interventions for recently diagnosed type 2 diabetes (Table 1).[16-22] The TODAY trial was described above in KQ3; it compared metformin monotherapy, metformin plus rosiglitazone, or metformin plus a lifestyle intervention. The second trial[16] was also described in KQ3; it reported on harms related to metformin (up to 2000 mg daily) compared with placebo in treatment-naive adolescents aged 10 to 16 years with previous or newly diagnosed type 2 diabetes.[16] The duration of follow-up ranged from 16 weeks[16] to a mean of 3.8 years (TODAY). Both studies reported on withdrawals, hypoglycemic events requiring medical attention, gastrointestinal adverse events, and lactic acidosis (**Table 3**). The TODAY study reported on other adverse events, including rash, infection, sprain or fracture, muscle ache or pain, anemia, and edema. The TODAY study reported 0 deaths during the trial.

Hypoglycemic Events

Serious hypoglycemic events requiring medical attention were reported in both trials and were rare (Table 3). The TODAY study reported that 4 youths had severe hypoglycemia (1 [0.4%] for metformin monotherapy vs 1 [0.4%] for metformin plus rosiglitazone vs 2 [0.8%] for metformin plus lifestyle intervention, $P > .99$). It also reported that more youths had repeated mild hypoglycemia in the group that received metformin plus rosiglitazone (10 [4.3%] for metformin monotherapy vs 19 [8.2%] for metformin plus rosiglitazone vs 8 [3.4%] for metformin plus lifestyle intervention, $P = .05$). The 16-week trial[16] comparing metformin monotherapy with placebo reported 0 hypoglycemic events requiring medical attention in either study group.

Gastrointestinal Adverse Events

Gastrointestinal adverse events were common in both studies. The TODAY study reported lower rates of gastrointestinal symptoms in the metformin plus rosiglitazone group (100 [42.9%]) than in the metformin monotherapy (129 [55.6%]) or metformin plus lifestyle intervention (136 [58.1%]) groups ($P = .002$). The 16-week trial[16] reported that more youths treated with metformin than with placebo had abdominal pain (25% vs 12%, *P* value not reported) and nausea or vomiting (17% vs 10%, *P* value not reported).

Other Adverse Events

Both studies reported other adverse events; types of events reported (and definitions) varied, and most found no difference between groups or reported that no adverse events were attributed to study interventions (Table 3). The TODAY study found higher rates of infection (64.2% vs 64.5% vs 51.5%, $P = .005$) and muscle ache or pain (29.3% vs 32.9% vs 22.7%, $P = .05$) in the metformin monotherapy and metformin plus lifestyle intervention groups than in the metformin plus rosiglitazone group. The TODAY study reported on rash, sprain or fracture, anemia, and edema but found no statistically significant differences between groups. The TODAY study reported that 1 participant in the metformin plus rosiglitazone group developed heart failure and 1 participant in the metformin monotherapy group developed lactic acidosis. The 16-week trial[16] reported that few participants had serious adverse events, all deemed unrelated to the study drug.

Prediabetes Interventions and Progression to Diabetes

Key Question 5. Do interventions for prediabetes delay or prevent progression to type 2 diabetes?

Study Characteristics

The review included 1 fair-quality RCT (75 participants) that compared the Bright Bodies Healthy Lifestyle Program with standard care for adolescents with obesity (BMI >95th percentile) aged 10 to 16 years with prediabetes (Table 1).[23] The trial was conducted in the US in a pediatric obesity clinic starting in September 2009. Regarding prediabetes ascertainment, the trial focused on impaired glucose tolerance for participant eligibility, defined as an elevated 2-hour OGTT (after a glucose load of 1.75 g/kg [maximum, 75 g]) result between 130 and 199 mg/dL (7.21-11.04 mmol/L) (using a range that was slightly wider than the current prediabetes criterion of 140 to 199 mg/dL [7.77-11.04 mmol/L]). The mean age of participants was 13 years, mean BMI was 33, mean baseline HbA_{1c} level was 5.6% to 5.7% across the groups, 64% were female, and 69% were White. The duration of follow-up was 6 months. The lifestyle program focused on both diet/nutrition and physical activity. The high-contact program included twice-weekly 50-minute exercise classes, a once-weekly weigh-in, and a 1-time 40-minute nutrition/behavior modification class (all administered in group settings). Participants were encouraged to exercise 3 additional days per week and record the duration and type of exercise. The study used raffle tickets for gift cards to motivate participants; tickets could be earned if weight stayed the same or decreased and, in some cases, if participants returned their weekly exercise log. The trial was rated as fair quality mainly because of the overall attrition (of 23%) and because some participants withdrew because they started metformin.

The primary outcome of the trial was the 6-month change in plasma glucose level 2 hours after OGTT (intermediate outcomes are described in the Contextual Questions [Supplement]). The trial reported that 0 participants developed diabetes during the trial.

Change in Health Outcomes After Prediabetes Interventions

Key Question 6. 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?

No eligible studies addressed this question.

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Table 3. Results of Included Trials of Children and Adolescents With Type 2 Diabetes Reporting Harms/Adverse Events Due to Treatment (KQ4)

Source	Study group (No. of participants)	No. (%)					
		Cardiovascular adverse events	Hypoglycemic events	All-cause withdrawals	Gastrointestinal adverse events	Lactic acidosis	Other adverse events
Jones et al,[16] 2002	Metformin (titrated up to maximum 2000 mg/d) (42) Placebo (40)	NR	Hypoglycemic events requiring medical attention Metformin: 0 Placebo: 0	Metformin: 6 (14.3) Placebo: 4 (10.0)	Abdominal pain Metformin: NR (25) Placebo: NR (12) Nausea/vomiting Metformin: NR (17) Placebo: NR (10)	Metformin: 0 Placebo: 0	Other adverse events, as reported by the authors (all deemed unrelated to the study drug) Metformin: 2 (4.7%) (1 person became seropositive for hepatitis B and 1 had severe abdominal pain and diarrhea due to a viral infection) Placebo: 2 (5.4%) (1 had hyperglycemia and 1 experienced problems associated with diabetes and increased liver function enzyme levels); a third participant had diabetic ketoacidosis (reported in Table 2)
TODAY Zeitler et al,[17] 2012 TODAY Study Group,[18] 2013 TODAY Study Group,[19] 2010 Levitt Katz et al,[20] 2015 Zeitler et al,[21] 2007 Kelsey et al,[22] 2016	Metformin (232) Metformin + rosiglitazone, 4 mg twice daily (233) Metformin + lifestyle intervention (234)	Heart failure before primary outcome[a] Metformin: 0 Metformin + rosiglitazone: 0 Metformin + lifestyle intervention: 0 After primary outcome[a] (of 319 participants who had the primary outcome of treatment failure) Metformin: 0 Metformin + rosiglitazone: 1 (1.1) Metformin + lifestyle intervention: 0	Severe hypoglycemia[b] Metformin: 1 (0.4) Metformin + rosiglitazone: 1 (0.4) Metformin + lifestyle intervention: 2 (0.8) Mild hypoglycemia[c] Metformin: 10 (4.3) Metformin + rosiglitazone: 19 (8.2) Metformin + lifestyle intervention: 8 (3.4) Repeated mild hypoglycemia before primary outcome (of all 699 participants)[a,d] Metformin: 5 (2.1) Metformin + rosiglitazone: 16 (6.9) Metformin + lifestyle intervention: 6 (2.6) After primary outcome (of 319 participants)[a,e] Metformin: 4 (3.3) Metformin + rosiglitazone: 3 (3.3) Metformin + lifestyle intervention: 1 (0.9)	Metformin: 15 (6.4) Metformin + rosiglitazone: 20 (8.6) Metformin + lifestyle intervention: 15 (6.4)	Gastrointestinal symptoms, full sample[f] Metformin: 129 (55.6) Metformin + rosiglitazone: 100 (42.9) Metformin + lifestyle intervention: 136 (58.1) *P* = .002	Metformin: 1 (0.4)[g] Metformin + rosiglitazone: 0[g] Metformin + lifestyle intervention: 0[g]	Rash[h] Metformin: 108 (46.5) Metformin + rosiglitazone: 101 (43.3) Metformin + lifestyle intervention: 95 (40.6) Infection[i] Metformin: 149 (64.2) Metformin + rosiglitazone: 120 (51.5) Metformin + lifestyle intervention: 151 (64.5) Sprain or fracture[g] Metformin: 66 (28.4) Metformin + rosiglitazone: 53 (22.7) Metformin + lifestyle intervention: 64 (27.4) Muscle ache or pain[c] Metformin: 68 (29.3) Metformin + rosiglitazone: 53 (22.7) Metformin + lifestyle intervention: 77 (32.9) Anemia[j] Metformin: 71 (30.6) Metformin + rosiglitazone: 58 (24.8) Metformin + lifestyle intervention: 52 (22.2) Edema[b] Metformin: 17 (7.3) Metformin + rosiglitazone: 17 (7.3) Metformin + lifestyle intervention: 17 (7.3)

Abbreviations: KQ, key question; NR, not reported; TODAY, Treatment Options for Type 2 Diabetes in Adolescents and Youth.

[a] The primary outcome of the trial was loss of glycemic control, defined as a hemoglobin A_{1c} level of at least 8% for 6 months or sustained metabolic decompensation requiring insulin.

[b] *P* > .99 for comparison of the 3 interventions.

[c] *P* = .05 for comparison of the 3 interventions.

[d] *P* = .09 for comparison of the 3 interventions.

[e] *P* = .03 for comparison of the 3 interventions.

[f] *P* = .002 for comparison of the 3 interventions.

[g] *P* = .33 for comparison of the 3 interventions.

[h] *P* = .43 for comparison of the 3 interventions.

[i] *P* = .005 for comparison of the 3 interventions.

[j] *P* = .11 for comparison of the 3 interventions.

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Table 4. Summary of Evidence on Screening for Prediabetes and Type 2 Diabetes in Children and Adolescents

No. of studies	No. of participants	Summary of findings	Consistency and precision	Study quality	Limitations (including reporting bias)	Overall strength of evidence	Applicability
KQ1: Benefits of screening							
0	0	No eligible studies	NA	NA	NA	Insufficient	NA
KQ2: Harms of screening							
0	0	No eligible studies	NA	NA	NA	Insufficient	NA
KQ3: Benefits of interventions for screen-detected or recently diagnosed type 2 diabetes and prediabetes							
2 RCTs (7 publications)	781	TODAY (n = 699) reported no significant difference between groups for kidney impairment in youths treated with metformin only vs metformin + rosiglitazone vs metformin + a lifestyle intervention (0 vs 1 vs 1, *P* > .99) and no difference for DKA (5 vs 3 vs 3, *P* = .70, respectively) One smaller trial (n = 82) reported that 1 adolescent with diabetes in the placebo group developed DKA compared with 0 in the metformin group No eligible studies reported other health outcomes	Consistency unknown (no 2 studies assessed the same comparisons); imprecise	Good: 1 Fair: 1	Mean follow-up 3.8 y in TODAY (range, 2-6.5 y) likely insufficient to assess health outcomes; follow-up of 16 wk in the smaller trial; reporting bias not detected	Insufficient	TODAY enrolled adolescents with obesity (aged 10-17 y) with previous or newly diagnosed type 2 diabetes; racially and ethnically diverse participants from the US; during run-in and prior to randomization, participants had to achieve glycemic control (HbA_{1c} <8%), achieve mastery of diabetes education material, and confirm adherence
KQ4: Harms of interventions							
Interventions for type 2 diabetes: 2 RCTs (7 publications)	781 participants	Hypoglycemic events: More youths treated with metformin + rosiglitazone had repeated mild hypoglycemia than those treated with metformin or metformin + lifestyle intervention (8.2% vs 4.3% vs 3.4%, *P* = .05) Gastrointestinal adverse events: Higher rates with metformin alone and metformin + lifestyle intervention than with metformin + rosiglitazone (55.6% vs 58.1% vs 42.9%, *P* = .002) Higher rates of abdominal pain (25% vs 12%, *P* value NR) and nausea or vomiting (17% vs 10%, *P* value NR) for youths treated with metformin for 16 wk than with placebo Infection: Lower rates with metformin + rosiglitazone than with metformin alone or metformin + lifestyle intervention (*P* = .005) Muscle aches or pains: Lower rates with metformin + rosiglitazone than with metformin alone or metformin + lifestyle intervention (*P* = .05) Heart failure: One participant treated with metformin + rosiglitazone developed heart failure	Consistency unknown (no 2 studies used similar measures at similar time points for the same comparison); imprecise	Good: 1 Fair: 1	Included studies assessed different comparisons; reporting bias not detected	Low	Youths with obesity aged 10-17 y with previous or newly diagnosed type 2 diabetes; racially and ethnically diverse participants from the US
Interventions for prediabetes: 0	0	No eligible studies	NA	NA	NA	Insufficient	NA

(continued)

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Table 4. Summary of Evidence on Screening for Prediabetes and Type 2 Diabetes in Children and Adolescents (continued)

No. of studies	No. of participants	Summary of findings	Consistency and precision	Study quality	Limitations (including reporting bias)	Overall strength of evidence	Applicability
KQ5: Interventions for prediabetes to delay or prevent progression to type 2 diabetes							
1 RCT	75 participants	No participants in the high-contact healthy lifestyle intervention group or the control group developed diabetes over 6 mo	Consistency unknown (single study); imprecise	Fair	Follow-up duration, 6 mo; high attrition; some participants were withdrawn for having started metformin (n = 5); reporting bias not detected	Insufficient	Children aged 10-16 y with BMI >95th percentile and prediabetes (elevated 2-h OGTT, 130-199 mg/dL) seen in a pediatric obesity clinic; high-contact lifestyle intervention with both diet/nutrition and physical activity/exercise components
KQ6: Change in health outcomes that results from reduction in diabetes after interventions for prediabetes							
0	0	No eligible studies	NA	NA	NA	Insufficient	NA

Abbreviations: BMI, body mass index; DKA, diabetic ketoacidosis; HbA_{1c}, hemoglobin A_{1c}; KQ, key question; NA, not applicable; NR, not reported; OGTT, oral glucose tolerance test; RCT, randomized clinical trial; TODAY, Treatment Options for Type 2 Diabetes in Adolescents and Youth.

Contextual Questions

The details for the Contextual Questions are reported in the Supplement. In summary, Contextual Question 1 focuses on the natural history of prediabetes and found that 22% to 52% of children and adolescents with prediabetes returned to normal glycemia or normal glucose tolerance without intervention over 6 months to 2 years.

Contextual Questions 2 and 3 in the Supplement address whether interventions change intermediate outcomes for children and adolescents with screen-detected or recently diagnosed type 2 diabetes. In summary, Contextual Question 2 found that, among those recently diagnosed with type 2 diabetes, lifestyle and pharmacological interventions (metformin, rosiglitazone, liraglutide) improved glycemia, but data were limited or lacking about the effect of these interventions on other intermediate outcomes (microalbuminuria, subclinical retinopathy, subclinical neuropathy). Contextual Question 3 found that, for those with diabetes, metformin alone and metformin plus a lifestyle intervention were associated with decreases in BMI and weight when compared with metformin plus rosiglitazone in TODAY,[17,24-26] but another study reported that metformin was not associated with significant changes when compared with control.[16]

Contextual Questions 2 and 3 in the Supplement also address whether interventions change intermediate outcomes for children and adolescents with prediabetes. In summary, Contextual Question 2 found that, among those with prediabetes, lifestyle interventions improved 2-hour glucose level (after OGTT), but not levels of fasting glucose or HbA_{1c}, in 1 trial, and data on rosiglitazone were inconclusive because of early trial discontinuation. Contextual Question 3 found that lifestyle interventions for children and adolescents with prediabetes improved weight and BMI compared with controls in 1 study[23] and that prediabetes identification was associated with decreases in BMI in adolescents with obesity and overweight, although evidence was from a retrospective cohort study with many limitations and a medium to high risk of bias.[27]

Contextual Question 4 in the Supplement summarizes studies reporting on the frequency of agreement among screening tests (eTable 7 in the Supplement). Contextual Question 5 in the Supplement describes 2 risk assessment tools for predicting risk of type 2 diabetes or prediabetes that have been validated in US children or adolescents: 1 using an automated computer system based on American Diabetes Association guidelines and 1 that adapted the Tool for Assessing Glucose Impairment (TAG-IT) adult risk assessment tool for pediatrics.

Discussion

This study reviewed the evidence on benefits and harms of screening for prediabetes and type 2 prediabetes in children and adolescents. **Table 4** provides a summary of the main findings in this evidence review organized by KQ, along with a description of consistency, precision, quality, limitations, strength of evidence, and applicability. Overall, limited data were eligible for this review, and the strength of evidence was graded as insufficient or low for all KQs. No eligible studies directly addressed the overarching question (ie, no studies evaluated screening for prediabetes or type 2 diabetes among asymptomatic youths compared with no screening or

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alternative screening strategies), and none enrolled children and adolescents with screen-detected diabetes.

For youths with recently diagnosed diabetes, the strength of evidence was graded as insufficient because of unknown consistency, substantial imprecision, and a duration of follow-up likely insufficient to assess health outcomes. For youths with prediabetes, this review found 1 eligible trial that assessed whether lifestyle interventions for prediabetes can help prevent progression to type 2 diabetes. However, the strength of evidence was graded as insufficient because follow-up was only 6 months, results were imprecise (with 0 events in either group), consistency is unknown (single study), and the study had high attrition. Among adults with obesity and overweight, recent meta-analyses for the USPSTF found high strength of evidence that lifestyle interventions were associated with reduction in the incidence of diabetes in trials with follow-up ranging from less than 1 year to 30 years (pooled relative risk, 0.78 [95% CI, 0.69-0.88]; 23 trials, 12 915 participants).[28]

For harms of interventions for prediabetes or type 2 diabetes, low strength of evidence from the 2 included trials indicates that minor hypoglycemic events were more common among youths treated with metformin plus rosiglitazone than among those treated with metformin or metformin plus lifestyle intervention; gastrointestinal adverse effects were commonly associated with metformin; and gastrointestinal adverse events, infections, and muscle aches and pains were more common among youths treated with metformin or metformin plus a lifestyle intervention than with metformin plus rosiglitazone. The strength of evidence was downgraded to low because of imprecision and unknown consistency (studies assessed different comparisons), and 1 study was rated as having medium risk of bias.

Limitations

This review has several limitations. First, non–English-language articles were excluded. Second, the review was limited to asymptomatic children and focused on the overarching question of screening for prediabetes or type 2 diabetes. It did not evaluate diagnostic testing of symptomatic children or those with signs of insulin resistance, diagnostic testing of children with conditions associated with insulin resistance, or screening for type 1 diabetes. Third, the review excluded studies limited to or predominately comprising adults or pregnant women and children and adolescents with symptomatic diabetes (eg, weight loss, polyuria, blurred vision, headache). In addition, studies of children and adolescents 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. Fourth, the review did not evaluate accuracy of screening tests because there is not a reference standard available for comparison; instead, studies reporting on the frequency of agreement among screening tests were evaluated in Contextual Question 4.

Conclusions

No eligible studies directly evaluated the benefits or harms of screening for prediabetes and type 2 diabetes in children and adolescents. For youths with prediabetes or recently diagnosed (not screen-detected) diabetes, the only eligible trials reported few health outcomes and found no difference between groups, although evidence was limited by substantial imprecision and a duration of follow-up likely insufficient to assess health outcomes.

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Author Contributions: Dr Jonas had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Jonas, Vander Schaaf, Allison, LeBlanc.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: All authors.
Critical revision of the manuscript for important intellectual content: Jonas, Vander Schaaf, Allison, Ali, LeBlanc.
Statistical analysis: Jonas.
Obtained funding: Jonas.
Administrative, technical, or material support: Jonas, Riley, Middleton, Baker, Voisin.
Supervision: Jonas.

Conflict of Interest Disclosures: Dr Vander Schaaf reported receiving grants from The Duke Endowment to support collaboration to address food insecurity and participating on national committees of the American Academy of Pediatrics, which has position statements on pediatric screening. Dr LeBlanc reported that Dexcom donated continuous glucose monitoring devices for a multicenter National Institutes of Health study on which she is an investigator. No other disclosures were reported.

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Additional Information: A draft version of the full evidence review underwent external peer review from 3 content experts (Callie L. Brown, MD, MPH, Wake Forest University School of Medicine; Sheela N. Magge, MD, MSCE, Johns Hopkins University School of Medicine; Hanna Xu, MD, Cook County Health, Illinois) and 3 federal partner reviewers (Centers for Disease Control and Prevention, Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institute of Diabetes and Digestive and Kidney Diseases). Comments from reviewers were presented to the USPSTF during its deliberation of the evidence and were considered in preparing the final evidence review. USPSTF members and peer reviewers did not receive financial compensation for their contributions.

Editorial Disclaimer: This evidence review is presented as a document in support of the accompanying USPSTF Recommendation Statement. It did not undergo additional peer review after submission to *JAMA*.

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