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Screening for Prediabetes and Type 2 Diabetes Mellitus in Children and Adolescents: An Evidence Review for the U.S. Preventive Services Task Force

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Structured Abstract

Purpose: To review the evidence on benefits and harms of (1) screening children and adolescents for prediabetes and type 2 diabetes and (2) interventions for prediabetes or type 2 diabetes that was screen detected or recently diagnosed for populations and settings relevant to primary care in the United States.

Data Sources: PubMed/MEDLINE, the Cochrane Library, and trial registries through May 3, 2021; reference lists of retrieved articles; outside experts; and reviewers, with surveillance of the literature through July 22, 2022.

Study Selection: English-language controlled studies evaluating screening for prediabetes or type 2 diabetes or evaluating interventions for prediabetes or type 2 diabetes that was screen detected or recently diagnosed.

Data Extraction: One investigator extracted data and a second checked accuracy. Two reviewers independently rated quality for all included studies using predefined criteria.

Data Synthesis: This review included eight publications (856 participants). Of those, six 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 included randomized, controlled trial (RCT) (TODAY, n=699 adolescents who were obese) reported that two youths with recently diagnosed type 2 diabetes developed renal impairment (0 vs. 1 vs. 1, p=1.00) and 11 developed diabetic ketoacidosis (5 vs. 3 vs. 3, p=0.70), finding no significant difference between metformin, metformin plus rosiglitazone, and metformin plus lifestyle, respectively. One trial of 75 adolescents who were obese with prediabetes compared an intensive lifestyle intervention versus standard care and reported that no participants in either group developed diabetes, although followup was only 6 months. Regarding harms of interventions, two RCTs assessing different comparisons enrolled youths with recently diagnosed diabetes. Major hypoglycemic events were reported by less than 1 percent 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. In one study, gastrointestinal adverse events were more commonly reported by those taking metformin than by those taking placebo.

Limitations: The included trials generally focused on intermediate outcomes (e.g., glycemic control, body mass index) rather than health outcomes of interest. Duration of followup was too short to assess health outcomes in most studies. Evidence was limited by imprecision, unknown consistency (single study for most key questions), and risk of bias (with a single good-quality study).

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 followup likely insufficient to assess health outcomes. Limited data showed that the combination of rosiglitazone plus metformin was associated with hypoglycemic events (compared with metformin alone or metformin plus lifestyle) and that

metformin was associated with gastrointestinal adverse events, consistent with studies conducted in adults.

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Chapter 1. Introduction

Scope and Purpose

This evidence review will be used by the United States Preventive Services Task Force (USPSTF) to make a recommendation on screening asymptomatic children and adolescents for prediabetes and type 2 diabetes. The USPSTF does not have a previous recommendation on this topic for children and adolescents. The USPSTF recommends screening for prediabetes and type 2 diabetes in adults ages 35 to 70 years who are overweight or who have obesity (B recommendation). The USPSTF states that clinicians should offer or refer patients with prediabetes to effective preventive interventions. The USPSTF has I statements for screening for high blood pressure in children and adolescents and for screening for lipid disorders in children and adolescents. The USPSTF recommends that clinicians screen for obesity in children and adolescents age 6 years or older and offer or refer them to comprehensive, intensive behavioral interventions to promote improvements in weight status (B recommendation).

Condition Definition

Diabetes mellitus (DM) refers to a range of metabolic disorders characterized by hyperglycemia. **Table 1** shows general categories and definitions of DM used by the American Diabetes Association (ADA).[1] The ADA guidelines emphasize that type 1 and type 2 diabetes are heterogeneous diseases in which clinical presentation and disease progression may vary considerably. Both type 1 and type 2 diabetes may present in children or adults.[1] The focus of this review is on screening for asymptomatic type 2 diabetes, which is characterized by insulin resistance and relative insulin deficiency.

Definitions of prediabetes and diabetes in children and adolescents are the same as in adults. Three tests can be used to identify prediabetes and type 2 diabetes: hemoglobin A1c, fasting plasma glucose, or an oral glucose tolerance test (OGTT) (**Table 2**). Prediabetes is the term used for individuals whose blood glucose levels are considered higher than normal but do not meet criteria for diabetes. Individuals diagnosed with prediabetes include those who meet criteria for impaired fasting glucose (IFG), meet criteria for impaired glucose tolerance (IGT), and have a glycated hemoglobin (A1c) from 5.7 to 6.4 percent.

Etiology and Natural History

Type 2 diabetes in youth is characterized by insulin resistance combined with relative insulin deficiency.[2, 3] At diagnosis or in the following years, some youth have lost approximately 80 percent of their pancreatic beta cell function, resulting in an inability to compensate for increased insulin resistance.[3-5] This pancreatic dysfunction does not appear to be mediated by antibodies against the pancreatic islet cells (as occurs in type 1 diabetes).[6] Although the progression through obesity, insulin resistance, glucose intolerance, and type 2 diabetes is not fully understood in youth, the timing of this progression appears to be shorter and less predictable compared with adults.[6, 7]

The major acute complications of type 2 diabetes in youth are diabetic ketoacidosis (DKA) and hyperglycemic hyperosmolar state (HHS), which can both result in death if left untreated.[8] Rates of DKA have been decreasing over time with the most recent estimates from 2008 to 2014 indicating that 6 percent to 11 percent of youths with type 2 diabetes had DKA at presentation.[6, 9-11] Higher prevalence of DKA has been associated with younger age at diagnosis, minority race/ethnicity, male gender, and lower family income and parental education.[6, 10] Although less frequent than DKA, the incidence of HHS in youth is increasing.[12, 13] A 2016 study found HHS in 2 percent of youth at diagnosis of diabetes.[9] HHS also appears to be more frequent in non-Hispanic black youths and Hispanic youths than in non-Hispanic white youths.[6]

Youth with type 2 diabetes have an increased prevalence of associated chronic comorbidities, including hypertension, dyslipidemia, and nonalcoholic fatty liver disease. Development of type 2 diabetes during childhood or adolescence results in a longer duration of exposure to a dysfunctional metabolic milieu over the lifetime. This may result in an increased risk of chronic microvascular complications including retinopathy, nephropathy, and neuropathy compared with those who develop type 2 diabetes in adulthood. The impacts on macrovascular complications such as cardiovascular and renal disease and long-term mortality have not been well studied in youth. However, in a study of Pima Indian youth, those with onset of type 2 diabetes before 20 years of age had mortality rates at aged 20 to 54 years that were 2.1 times higher than among persons with diabetes onset at or after age 20 years and 3.1 times higher than nondiabetic persons.[14]

Relatively few data are available to ascertain the natural history of prediabetes in youth. Placebo arms of randomized, controlled trials (RCTs) have found that anywhere from 22 percent to 52 percent of children and adolescents with prediabetes returned to normal glycemia or normal glucose tolerance without intervention over 6 months to 2 years (Contextual Question [CQ] 1 in **Appendix A**).

Risk Factors

Obesity and excess adipose tissue (especially when centrally distributed) are the most important risk factors for type 2 diabetes in youth.[15-17] The SEARCH for Diabetes in Youth study (SEARCH) reported that between 2001 and 2004 nearly 80 percent of youth with type 2 diabetes were obese and that an additional 10 percent were overweight.[16] Family history is a strong risk factor, with estimates that 50 to 75 percent of youth with type 2 diabetes have at least one parent with type 2 diabetes and nearly 90 percent may have a positive family history if grandparents are also included.[18-21]

The vast majority of pediatric cases occur after age 10, with the peak age for presentation occurring at mid-puberty (approximately age 14 years).[22, 23] This timing is likely related to the physiologic, but transient, pubertal insulin resistance that can aggravate the preexisting metabolic challenges of obesity.[17, 24, 25] Some studies indicate that adolescent girls are 1.3 to 1.7 times more likely than boys to be diagnosed with type 2 diabetes, although the reasons are not well understood.[15, 19, 26, 27] Research suggests that maternal obesity and gestational diabetes contribute to obesity and type 2 diabetes in youth.[6, 17] For example, in the Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) cohort, one third of youth with type 2 diabetes had

been born after a pregnancy complicated by preexisting diabetes or gestational diabetes mellitus.[17]

A review summarizing differences in the frequencies of type 2 diabetes by race, ethnicity, socioeconomic position, area of residence, and environmental toxins noted that the causes of differences (e.g., between different racial and ethnic groups) are not well understood.[28] Compared with the type 2 diabetes rate in non-Hispanic white youth, the rate in Native American, African American, and Hispanic youth has been shown to be 8, 5, and 4 times higher, respectively.[26] The relative contributions of various factors to racial/ethnic differences are largely unknown.[28] As with many other health disparities,[29-31] structural factors that disproportionately affect nonwhite populations (e.g., toxic stress, structural and interpersonal racism, economic inequities) may contribute significantly to differences by race/ethnicity. Other potential contributing factors include metabolic characteristics, cultural/environmental influences, and quality of and access to healthcare.[17]

CQ 5 (**Appendix A**) summarizes risk assessment tools that are feasible for use in primary care settings, accurately predict the risk of prediabetes or type 2 diabetes for children and adolescents, and have been externally validated in U.S. populations. Briefly, two such tools were identified: one using an automated computer system based on ADA guidelines and one that adapted the Tool for Assessing Glucose ImpairmenT (TAG-IT) adult risk assessment tool for pediatrics.

Prevalence and Burden

The 2017–2018 National Health Interview Survey from the Centers for Disease Control and Prevention (CDC) estimated that 210,000 children and adolescents younger than age 20 years (or 2.5 per 1,000 U.S. youths) had been diagnosed with diabetes, of which approximately 23,000 had type 2 diabetes.[32]

Most prevalence and incidence data on type 2 diabetes in children come from a limited number of subjects from the SEARCH for Diabetes in Youth Study, a population-based study of children under age 20 years in several geographic regions (county-based from 4 states, insurance-based from 1 state, and from select Native American reservations from 2 additional states) that the CDC and National Institutes of Health have funded since 2000. It found that of 3.5 million children under age 20 years in 2009, 837 (or 0.24 per 1,000) had type 2 diabetes. Based on these data, an estimated 20,262 youth under age 20 years had type 2 diabetes in the United States at that time.[33] This same dataset found that the prevalence of type 2 diabetes was highest in American Indian/American Native (0.63/1,000), black (0.56/1,000), and Hispanic (0.40/1,000) youth and lowest in Asian/Pacific Islander (0.19/1,000) and non-Hispanic white (0.09/1,000) youth.[33] The generalizability of this demographics data is uncertain. It is limited by its small sample size (fewer than 900 people contributing to the data) and selection from particular geographic regions, insurance coverage, and/or specific reservations with low numbers in each.

Data indicate that the prevalence and incidence of type 2 diabetes are rising; in 2001, the overall prevalence of type 2 diabetes in children ages 10 to 19 years was 0.34 per 1,000 and in 2009 was 0.46 per 1,000.[26] SEARCH found that 5,758 children and adolescents ages 10 to 19 years were diagnosed with type 2 diabetes from 2014 to 2015, and the overall incidence of type 2 diabetes in

10- to 19-year-olds has increased significantly from an incidence rate of 0.09 per 1,000 in 2002 to 2003 to 0.14 per 1,000 in 2014 to 2015.[34]

Most of that increase in the incidence rate is in nonwhite and non-Asian children and adolescents. The incidence rate in non-Hispanic white children remained stable between 0.04 and 0.05 children per 1,000 between 2002 and 2015 and for Asian/Pacific Islander children between 0.11 and 0.12 per 1,000 between 2002 and 2015. During the same time period, the incidence rate in non-Hispanic black children increased from 0.20 to 0.38 per 1,000, in Hispanic children the rate increased from 0.13 to 0.21 per 1,000, and in American Indian children (from primarily one southwestern tribe) the rate increased from 0.23 to 0.33 per 1,000.[34]

Children who are obese and overweight are more likely to develop type 2 diabetes than peers who are underweight or who are at a healthy weight. This association between weight and diabetes is stronger in children than in adults.[15] SEARCH data from 2001 to 2004 showed that about 80 percent of 400 children with type 2 diabetes were obese and 10 percent were overweight (compared with 17% of children without diabetes being obese).[16]

Type 2 diabetes is more common in older than younger children, often presenting at the onset of puberty.[27] It is estimated that, based on 2009 SEARCH data, 74 percent of pediatric type 2 diabetes cases are in youths ages 15 to 19 years, 23 percent are in those ages 10 to 14 years, and only 2 percent are in those ages 5 to 9 years.[33]

In terms of burden of disease, diabetes (both type 1 and type 2) is the third most common chronic disease in childhood.[35] In all age groups (not limited to children and adolescents), diabetes was estimated to be the seventh leading cause of overall death in the United States in 2015 based on the Underlying Cause of Death database.[36] Approximately 3 percent of deaths (79,535 of 2,712,630 total deaths) were attributed to diabetes based on death certifications for U.S. residents. Cause of death was based on International Classification of Diseases, Tenth Revision codes, and estimates do not differentiate between type of diabetes. Morbidity from type 2 diabetes is due to both macrovascular disease (atherosclerosis) and microvascular disease (retinopathy, nephropathy, and neuropathy). Complications may begin in childhood or later in adulthood. Among those with type 2 diabetes diagnosed during childhood and adolescence, an estimated 19.9 percent, 9.1 percent, and 17.7 percent had complications of kidney disease, retinopathy, and peripheral neuropathy, respectively, during teenage years and young adulthood.[37] Diabetes is the leading cause of kidney failure, lower-limb amputations other than those caused by injury, and new cases of blindness among adults of all age groups in the United States.[38] Estimates based on results of the Global Burden of Disease Study indicate that diabetes was the third leading cause of years lived with disability in 2016, which is an approximate 30 percent increase from 1990 (when it ranked eighth).[39] In terms of causes of disability-adjusted life-years in the United States, diabetes ranked fourth in 2016, an increase from the sixth leading cause in 1990 (an approximate 11% change).[39]

Rationale for Screening and Screening Strategies

Screening asymptomatic at-risk children and adolescents for prediabetes and type 2 diabetes may allow earlier detection, diagnosis, and interventions for both conditions, with the goal of improving health outcomes by preventing serious complications from type 2 diabetes. In children

and adolescents, earlier detection of prediabetes may lead to interventions to prevent or delay progression to type 2 diabetes.[40] Early diagnosis of type 2 diabetes could potentially lead to earlier treatment to prevent diabetic complications.[41-44] Early diagnosis also may enable clinicians to treat patients with diabetes more effectively without requiring insulin. Strategies for screening for prediabetes and type 2 diabetes generally involve targeted screening of children who are overweight or obese for the presence of one or more risk factors (e.g., type 2 diabetes in a first- or second-degree relative, member of a high-risk racial/ethnic group, maternal history of diabetes or gestational diabetes) followed by fasting glucose, hemoglobin A1c, or OGTT.[1, 45, 46]

Treatment Approaches

Reducing Progression From Prediabetes to Diabetes

Lifestyle interventions to achieve weight loss and increase physical activity are the first-line therapies for preventing progression of prediabetes to diabetes. ADA guidance underlines the value healthy nutrition plays in preventing diabetes, with particular emphasis on the avoidance of sugar-sweetened beverages and sugary snacks.[47] The U.S. Food and Drug Administration (FDA) has not approved any medications to prevent progression of prediabetes to diabetes for any age group, nor has the Canadian Medicare System.[48, 49] Some studies in children and adolescents have shown that metformin can improve metabolic parameters such as body mass index (BMI), fasting glucose, and insulin resistance index.[50]

Management of Diabetes in Children

Goals for HbA1c and fasting glucose levels are the same for children as for adults.[47] Lifestyle interventions are included in first-line therapies for children and adolescents diagnosed with diabetes. Modifications to lifestyle choices, such as increased exercise and improved nutrition, are recommended by the ADA, CDC, and National Institute for Health and Care Excellence.[51, 52] It is recommended that these programs be accompanied by extensive education campaigns on promoting awareness and self-management skills, including establishing individualized regimes for self-monitoring of glycemic targets. Formal programs to improve diet and increase exercise are often paired with pharmacotherapy as first-line therapy.[47, 53]

The FDA has approved three drugs for treatment of type 2 diabetes in children: metformin, insulin, and liraglutide. Metformin is the initial preferred pharmacological treatment for mild to moderate hyperglycemia (HbA1c<8.5%) without metabolic complications. The ADA recommends starting with both basal insulin and metformin if there is marked hyperglycemia (but no ketosis) and insulin alone for those with ketosis. Insulin can be tapered and metformin used as a single therapy if glycemic targets are met.[54] The ADA recommends considering liraglutide therapy if glycemic targets are no longer met with metformin (with or without basal insulin) for children age 10 years or older if they have no past medical history or family history of medullary thyroid carcinoma or multiple endocrine neoplasia type 2.[47] It also notes that the use of medications not approved by the FDA for youth with type 2 diabetes is not recommended outside of research trials.[47] These non-FDA-approved medications include thiazolidinediones (rosiglitazone, pioglitazone), sulfonylureas (glyburide, glimepiride), dipeptidyl peptidase 4 inhibitors (saxagliptin, alogliptin, linagliptin), alpha glucosidase inhibitors (acarbose, miglitol), sodium-glucose cotransporter-2 (SGLT2) inhibitors (canagliflozin, dapagliflozin, empagliflozin),

glucagon-like peptide-1 (GLP1) receptor agonists other than liraglutide (exenatide, dulaglutide, semaglutide, lixisenatide), and meglitinides and have been assessed for type 2 diabetes treatment in children in a number of small pilot studies and case reports. Some professionals recommend anti-obesity drugs (orlistat) and bariatric surgery to treat some children and adolescents who are obese who also have diabetes.[52, 55]

Other Treatments to Reduce Cardiovascular Disease Risk and Complications

Complications of diabetes include nephropathy, neuropathy, retinopathy, and cardiovascular disease. To detect the presence of comorbidities, the ADA recommends blood pressure measurement, a fasting lipid panel, assessment of random urine albumin-to-creatinine ratio, and a dilated eye examination at the time of the diabetes diagnosis.[54] Treatments to decrease cardiovascular risk can include antihypertensive medications. Management to decrease microvascular complications includes routine eye exams for retinopathy, urinary albumin excretion for nephropathy, and foot exams for neuropathy. The ADA encourages the cessation or abstinence of smoking and substance use in children and young adults with type 2 diabetes because it may increase their risk of cardiovascular and blood glucose control problems.

Clinical Practice in the United States and Recommendations of Other Organizations

In recent years, several U.S. and international professional organizations have issued recommendations for screening asymptomatic at-risk children and adolescents for prediabetes and type 2 diabetes (**Appendix A Table 1**). In 2020, the ADA published a position statement on managing youth-onset type 2 diabetes.[47] The ADA recommends risk-based screening for type 2 diabetes in children after onset of puberty or age 10 years who are overweight (BMI ≥85th percentile) or obese (BMI ≥95th percentile) and have one or more additional risk factors for diabetes. Such additional risk factors include maternal history of diabetes or gestational diabetes mellitus during the child's gestation; family history of type 2 diabetes in first- or second-degree relative; being a member of a high-risk racial/ethnic group, including Native American, African American, Latino, Asian American, and Pacific Islander; or signs of insulin resistance or conditions associated with insulin resistance, including acanthosis nigricans, hypertension, dyslipidemia, polycystic ovary syndrome, or small-for-gestational-age birth weight.[17] In terms of screening frequency, the ADA recommends screening to be repeated every 3 years if tests are normal or more frequently if BMI increases.[47] The ADA recommends testing with fasting plasma glucose, 2-h plasma glucose (PG) after 75-g OGTT, or an A1c. Further, the ADA recommends that children and adolescents who are overweight or obese for whom the diagnosis of type 2 diabetes is being considered have a panel of pancreatic autoantibodies tested to exclude the possibility of autoimmune type 1 diabetes.

Chapter 2. Methods

Key Questions and Analytic Framework

The scope and key questions (KQs) were developed by the Evidence-based Practice Center (EPC) investigators, USPSTF members, and Agency for Healthcare Research and Quality (AHRQ) Medical Officers. The analytic framework and KQs that guided the review are shown in **Figure 1**. Six KQs were developed for this review:

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?

In addition to addressing the KQs, this review also looked for evidence related to five CQs that focused on progression from prediabetes to diabetes, whether screening or interventions change intermediate outcomes, agreement among screening tests, and risk assessment tools. These CQs were not a part of this systematic review. They are intended to provide additional background information. Literature addressing the CQs is summarized in **Appendix A**.

Data Sources and Searches

PubMed/MEDLINE and the Cochrane Library were searched for English-language articles published through May 3, 2021. Medical Subject Headings were used as search terms when available and keywords when appropriate, focusing on terms to describe relevant populations, tests, interventions, outcomes, and study designs. Complete search terms and limits are listed in

Appendix B. Targeted searches for unpublished literature were conducted by searching ClinicalTrials.gov. To supplement electronic searches, the reference lists of pertinent review articles and studies that met the inclusion criteria were reviewed. Studies suggested by peer reviewers or public comment respondents were reviewed and, if appropriate, incorporated into the final review. Since May 3, 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, and did not identify any additional studies that would affect the conclusions. All literature search results were managed using EndNote™ version 9.2 (Thomson Reuters, New York, NY).

Study Selection

Inclusion and exclusion criteria for populations, interventions, comparators, outcomes, timing, settings, and study designs were developed with input from the USPSTF (**Appendix B**). English-language studies of asymptomatic, nonpregnant people younger than age 18 conducted in countries categorized as very high on the 2019 Human Development Index were included. For all KQs, controlled clinical trials were eligible. Controlled prospective cohort studies were also eligible for KQs on harms (KQs 2 and 4) and the change in health outcomes after reduction in type 2 diabetes incidence (KQ 6); case-control studies were eligible for KQs on harms (KQs 2 and 4). For KQs 1 and 2 (direct evidence of benefits and harms of screening), studies that compared screening with A1c, fasting glucose, or OGTT with no screening or alternative screening strategies were eligible. For KQs 3 through 6 (benefits and harms of interventions), studies were eligible that evaluated primary care–relevant behavioral counseling interventions or pharmacologic interventions for glycemic control for prediabetes or type 2 diabetes.

Titles and abstracts were independently reviewed by two investigators; those marked for potential inclusion by either reviewer were retrieved for evaluation of the full text. The full texts were then independently reviewed by two investigators to determine final inclusion or exclusion. Disagreements were resolved by discussion and consensus.

Quality Assessment and Data Abstraction

We assessed the quality of studies as good, fair, or poor, using predefined criteria developed by the USPSTF and adapted for this topic (**Appendix B**). Two independent investigators assigned quality ratings for each study. Disagreements were resolved by discussion. Only studies rated as having good or fair quality were included.

For each included study, one investigator extracted pertinent information about the methods, populations, interventions, comparators, outcomes, timing, settings, and study designs. All data extractions were checked by a second investigator for completeness and accuracy.

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 EPC program).[56] Additionally, the applicability of the findings to U.S. primary care populations and settings was assessed. Discrepancies were resolved through consensus discussion.

To determine whether meta-analyses were appropriate, the clinical and methodological heterogeneity of the studies was assessed according to established guidance.[57] 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.

Expert Review and Public Comment

A draft research plan for this topic was posted on the USPSTF website for public comment from July 30, 2020 to August 26, 2020. In response to comments, the USPSTF changed the title to include prediabetes, added socioeconomic status to the list of prespecified specific populations, clarified the eligibility of school-based health centers and community settings, and added more intermediate outcomes to the CQs. The final version of the research plan was posted on the USPSTF website on November 12, 2020. A draft evidence review was reviewed by content experts, representatives of Federal partners, USPSTF members, and AHRQ Medical Officers. Reviewer comments were presented to the USPSTF during its deliberations and addressed in revisions of this evidence review when appropriate. Revisions included clarifications to the introduction and edits to use person-first language. The draft evidence review was posted for public comment from December 14, 2021, through January 18, 2022; one article was added to CQ 1 based on public comments.

USPSTF and AHRQ Involvement

AHRQ staff and members of the USPSTF participated in developing the scope of work (including the analytic framework and KQs) and reviewed draft reports, but the authors are solely responsible for the content. AHRQ staff provided oversight for the project and assisted in an external review of the draft evidence synthesis.

Chapter 3. Results

Literature Search

We identified 4,335 unique records and assessed 524 full-text articles for eligibility (**Figure 2**). We excluded 516 articles for various reasons, detailed in **Appendix C**, and included eight articles representing three studies. Details of quality assessments of included studies are in **Appendix D Tables 1** through **2**.

Results by Key Question

KQ 1. Is There Direct Evidence That Screening for Type 2 Diabetes and Prediabetes in Asymptomatic Children and Adolescents Improves Health Outcomes?

We found no eligible studies that addressed this question.

KQ 2. What Are the Harms of Screening for Type 2 Diabetes and Prediabetes in Asymptomatic Children and Adolescents?

We found no eligible studies that addressed this question.

KQ 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?

We found no eligible studies that addressed this question.

KQ 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?

We found no eligible studies that addressed this question.

KQ 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, one included RCT (699 participants) that focused on intermediate outcomes reported that two youths with type 2 diabetes developed renal impairment and 11 developed DKA, finding no significant difference between treatments (metformin, metformin rosiglitazone,

and metformin plus a lifestyle intervention). One smaller trial reported that one person in the placebo control group developed DKA. No eligible studies reported on other health outcomes.

Characteristics of Included Studies

We included two RCTs (described in 7 articles) (**Table 3**).[53, 58-63] One was rated as good quality and one was rated as fair quality. The one good-quality RCT (described in 6 articles) enrolled 699 participants and evaluated interventions for recently diagnosed type 2 diabetes.[53, 58-62] The Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) study was a 15-site multicenter trial conducted in the United States. The trial randomized adolescents who were obese (BMI ≥85th percentile for age and sex) with recently diagnosed type 2 diabetes to 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 1,000 mg twice daily, attaining glycemic control with metformin alone (A1c<8.0%), providing standard diabetes education and ensuring the participants' mastery of the material, and confirming adherence. The mean age of participants was 14; mean BMI was 35 kg/m^2; mean baseline A1c values were 7.0 to 7.3 percent across the three study groups; 65 percent were female; 79 percent were nonwhite, 32.5 percent were non-Hispanic black, 39.7 percent were Hispanic, and 20.3 percent were non-Hispanic white. The duration of followup 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 three 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 HbA1c level of at least 8 percent for 6 months or sustained metabolic decompensation requiring insulin (described in CQ 2), and the study focused largely on intermediate outcomes (e.g., glycemic control, BMI) rather than on health outcomes.

The second trial[63] compared metformin and placebo in 82 treatment-naïve adolescents ages 10 to 16 years with previous or newly diagnosed type 2 diabetes.[63] It was a 16-week double-blind placebo-controlled trial of 82 adolescents recruited from 44 sites in multiple countries, including the United States, Russia, Belarus, Ukraine, and Poland. Most participants were from the U.S. sites. The intervention group received up to 2,000 mg daily of metformin for 16 weeks. The mean age of participants was 14; mean BMI was 34 kg/m^2; mean baseline A1c values were 8.3 to 9.0 percent across the study groups; 69 percent were female; and 63 percent were nonwhite. The primary outcome was change in fasting PG from baseline (described in CQ 2).

Renal Impairment

The TODAY study reported two cases of renal impairment (**Table 4**). One case was in the metformin plus rosiglitazone group, and one was in the metformin plus lifestyle intervention group (p=1.00). Renal impairment was defined as an estimated creatinine clearance of less than 70 ml per minute or a serum creatinine of more than 1.5 mg/dl.

Diabetic Ketoacidosis

The TODAY study reported that 11 participants developed DKA. There was no statistically significant difference across treatment groups (5 [2.1%] vs. 3 [1.3%] vs. 3 [1.3%], p=0.70, for metformin monotherapy vs. metformin plus rosiglitazone vs. metformin plus lifestyle, respectively). The smaller trial reported that zero participants in the metformin group developed DKA and that one person in the control group developed DKA.

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.

KQ 4. What Are the Harms of Interventions for Prediabetes, Screen-Detected Type 2 Diabetes, or Recently Diagnosed Type 2 Diabetes?

Overall, two RCTs that enrolled youths with recently diagnosed type 2 diabetes were eligible. The two trials assessed different comparisons. Major hypoglycemic events were reported by less than 1 percent 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. In one study, gastrointestinal (GI) adverse events were more commonly reported by those taking metformin than by those taking placebo. GI 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 3**).[53, 58-63] The TODAY trial is described above in KQ 3; it compared metformin monotherapy, metformin plus rosiglitazone, or metformin plus a lifestyle intervention. The second trial[63] was also described in KQ 3; it reported on harms related to metformin (up to 2,000 mg daily) compared with placebo in treatment-naïve adolescents ages 10 to 16 years with previous or newly diagnosed type 2 diabetes.[63] The duration of followup ranged from 16 weeks[63] 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 5**). 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 zero deaths during the trial.

Hypoglycemic Events

Serious hypoglycemic events requiring medical attention were reported in both trials and were rare (**Table 5**). The TODAY study reported that four youths had severe hypoglycemia (1 [0.4%] vs. 1 [0.4%] vs. 2 [0.8%] for metformin monotherapy vs. metformin plus rosiglitazone vs.

metformin plus lifestyle, respectively, p=1.00). It also reported that more youths had repeated mild hypoglycemia in the group that received metformin plus rosiglitazone (10 [4.3%] vs. 19 [8.2%] vs. 8 [3.4%] for metformin monotherapy vs. metformin plus rosiglitazone vs. metformin plus lifestyle, respectively, p=0.05). The 16-week trial[63] comparing metformin monotherapy with placebo reported zero hypoglycemic events requiring medical attention in either study group.

Gastrointestinal Adverse Events

GI adverse events were common in both studies. The TODAY study reported lower rates of GI symptoms in the metformin plus rosiglitazone group than in the metformin monotherapy or metformin plus lifestyle intervention groups (129 [55.6%] vs. 100 [42.9%] vs. 136 [58.1%], for metformin monotherapy vs. metformin plus rosiglitazone vs. metformin plus lifestyle, respectively, p=0.002). The 16-week trial[63] reported that more youths treated with metformin than with placebo had abdominal pain (25% vs. 12%, p not reported) and nausea or vomiting (17% vs. 10%, p 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 5**). The TODAY study found higher rates of infection (p=0.005) and muscle ache or pain (p=0.05) 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 difference between groups. The TODAY study reported that one participant in the metformin plus rosiglitazone group developed heart failure and one participant in the metformin monotherapy group developed lactic acidosis. The 16-week trial[63] reported that few participants had serious adverse events, all deemed unrelated to the study drug.

KQ 5. Do Interventions for Prediabetes Delay or Prevent Progression to Type 2 Diabetes?

In summary, the one included study reported no evidence that lifestyle interventions were associated with a reduction in the incidence of diabetes, although followup was only 6 months and the study had zero participants progress to type 2 diabetes in either group. No eligible studies that evaluated pharmacologic interventions were identified.

Study Characteristics

We included one fair-quality RCT (75 participants) that compared the Bright Bodies Healthy Lifestyle Program with standard care for adolescents who were obese (BMI>95th percentile) ages 10 to 16 years with prediabetes (**Table 3**).[64] The trial was conducted in the United States in a pediatric obesity clinic starting in September 2009. Regarding prediabetes ascertainment, the trial focused on IGT for participant eligibility, defined as an elevated 2-h OGTT (after a glucose load of 1.75 g/kg, maximum 75 g) result between 130 and 199 mg/dL (using a range that was slightly wider than the current prediabetes criteria of 140 to 199 mg/dL). The mean age of participants was 13, mean BMI was 33 kg/m^2, mean baseline A1c was 5.6 to 5.7 across the

groups, 64 percent were female, and 31 percent were nonwhite. The duration of followup 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 one-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, for returning their weekly exercise log. The trial was rated as fair quality mainly because of the overall attrition (of 23%) and having some participants withdrawn because of starting metformin (**Appendix D**).

The primary outcome of the trial was the 6-month change in PG 2 hours after OGTT (intermediate outcomes are described in CQs 2 and 3). The trial reported that zero participants developed diabetes during the trial (**Table 4**).

KQ 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?

We found no eligible studies that addressed this question.

Chapter 4. Discussion

Summary of Evidence

Table 6 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.

Evidence for Benefit and Harms of Screening

This review found no eligible studies that directly addressed the overarching question (i.e., no studies evaluated screening for prediabetes or type 2 diabetes among asymptomatic youths compared with no screening or alternative screening strategies). Therefore, the strength of evidence was graded as insufficient for KQs 1 and 2.

Benefits of Interventions for Screen-Detected or Recently Diagnosed Diabetes

For screen-detected diabetes, this review found no eligible studies. For recently diagnosed diabetes, two eligible trials were identified. Evidence from one RCT (TODAY) designed to evaluate intermediate outcomes reported very few health outcomes, finding no difference between groups for renal impairment in adolescents who were obese treated with metformin only versus metformin plus rosiglitazone versus metformin plus a lifestyle intervention, and finding no difference for DKA. The other trial reported that one adolescent with diabetes in the placebo group developed DKA compared with zero in the metformin group. The strength of evidence was graded as insufficient because of unknown consistency, substantial imprecision, and a duration of followup likely insufficient to assess health outcomes.

CQs 2 and 3 (**Appendix A**) address whether interventions for children and adolescents with screen-detected or recently diagnosed type 2 diabetes or prediabetes change intermediate outcomes. In summary, CQ 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 impact of pharmacological interventions on other intermediate outcomes (microalbuminuria, subclinical retinopathy, subclinical neuropathy). CQ 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,[18, 53, 65, 66] but another study reported that metformin was not associated with significant changes when compared with control.[63]

Benefits of Interventions for Prediabetes

This review found one 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 followup was only 6 months, results were imprecise (with zero events in either group), consistency is unknown (single study), and the study had high attrition. Among

adults who were obese 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 followup ranging from less than 1 year to 30 years (pooled relative risk, 0.78 [95% confidence interval {CI}, 0.69 to 0.88], 23 trials, 12,915 participants).[67]

CQs 2 and 3 (**Appendix A**) address whether interventions for children and adolescents with screen-detected or recently diagnosed type 2 diabetes or prediabetes change intermediate outcomes. In summary, CQ 2 found that, among those with prediabetes, lifestyle interventions improved 2-h glucose (after OGTT), but not fasting glucose or A1c in one trial, and data on rosiglitazone were inconclusive because of early trial discontinuation. CQ 3 found that lifestyle interventions for children and adolescents with prediabetes improved weight and BMI compared with controls in one study[64] and that prediabetes identification was associated with decreases in BMI in adolescents who were obese and overweight, although evidence was from a retrospective cohort study with many limitations and a medium to high risk of bias.[68]

Harms of Interventions for Prediabetes or Type 2 Diabetes

Low strength of evidence from the two 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; GI adverse effects were commonly associated with metformin; and GI adverse events, infections, and muscle aches and pains were more common among youths treated with metformin and metformin plus a lifestyle intervention than with metformin plus rosiglitazone. The strength of evidence was downgraded to low because of imprecision, unknown consistency (studies assessed different comparisons), and one study was rated as medium risk of bias.

Limitations

This review has limitations. The limitations of the included studies are discussed above in Results and Discussion. Here we focus on limitations of this review. We excluded non-English-language articles. This review was limited to asymptomatic children and focused on the overarching question of screening for prediabetes or type 2 diabetes. This review 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. This review excluded studies limited to or predominately comprising adults or pregnant women and children and adolescents with symptomatic diabetes (e.g., weight loss, polyuria, blurred vision, headache). For studies of recently diagnosed diabetes, this review excluded studies of children and adolescents who had diabetes for more than 1 year or with more advanced diabetes, aiming to identify the studies with good applicability to a screen-detected population.

Future Research Needs

Screening trials of sufficient duration and sample size that focus on health outcomes are needed, as are eligible studies evaluating interventions for prediabetes and screen-detected type 2 diabetes among children and adolescents.

Conclusion

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 followup likely insufficient to assess health outcomes. Limited data showed that the combination of rosiglitazone plus metformin was associated with hypoglycemic events (compared with metformin alone or metformin plus lifestyle) and that metformin was associated with gastrointestinal adverse events, consistent with studies conducted in adults.

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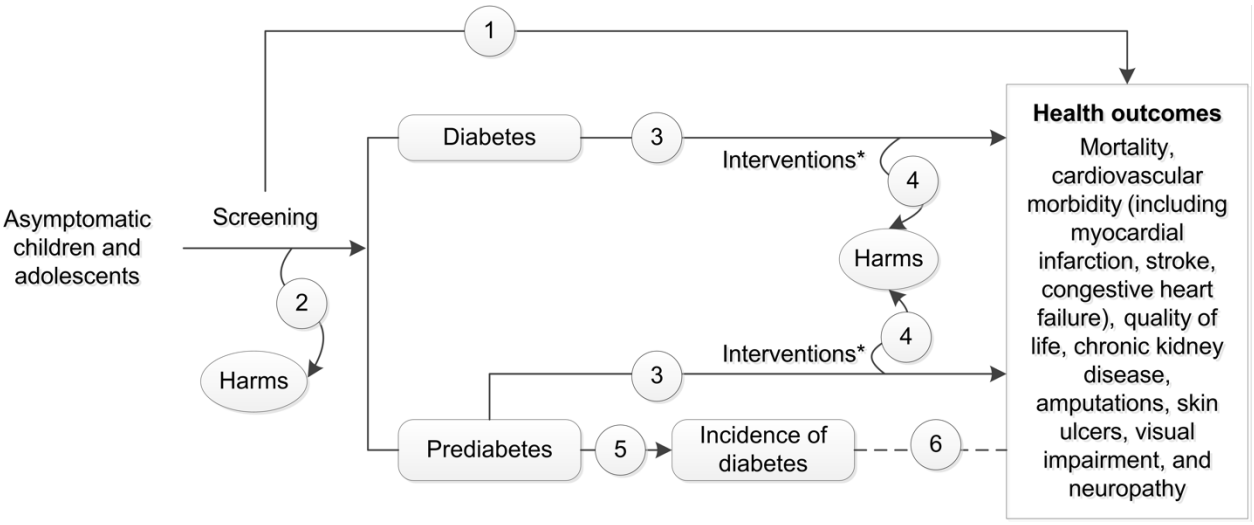
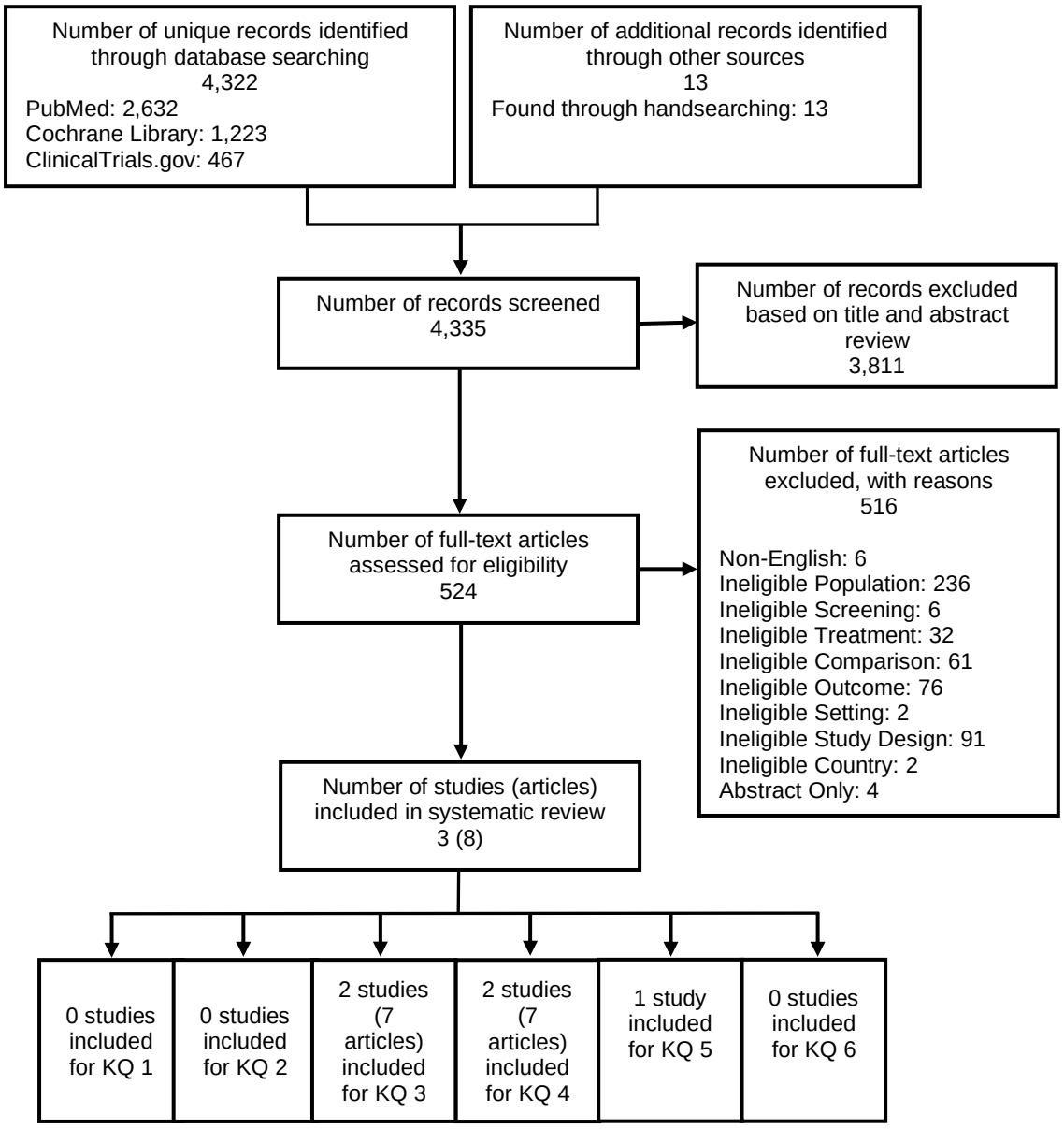
Figure 1. Analytic Framework



* Eligible interventions include pharmacotherapy and primary care–relevant counseling focused on healthy diet and nutrition, physical activity, or both.

Figure 2. Summary of Evidence Search and Selection



Note: The sum of the number of studies per KQ exceeds the total number of studies because some studies were applicable to multiple KQs.

Abbreviations: KQ=key question.

Table 1. Classification of Diabetes (Adapted From ADA Guidelines)[1]

Category	Definition/Etiology
Type 1 diabetes	Diabetes due to autoimmune β-cell destruction, usually leading to absolute insulin deficiency
Type 2 diabetes	Diabetes due to a progressive loss of β-cell insulin secretion frequently on the background of insulin resistance
Gestational diabetes mellitus	Diabetes diagnosed in the second or third trimester of pregnancy that was not clearly overt diabetes before gestation
Diabetes due to other causes	Includes specific types of diabetes attributable to the following: monogenic diabetes syndromes (e.g., maturity-onset diabetes of the young), diseases of the exocrine pancreas (e.g., pancreatitis), and drug- or chemical-induced diabetes (e.g., glucocorticoid use, in the treatment of HIV/AIDS, or after organ transplantation)

Abbreviations: ADA=American Diabetes Association; HIV/AIDS=human immunodeficiency virus/acquired immunodeficiency syndrome.

Table 2. Criteria for the Diagnosis of Type 2 Diabetes and Prediabetes (Adapted From ADA Guidelines)[1]

Diagnosis	A1c*	Fasting† Plasma Glucose	OGTT‡,§	Other
Type 2 diabetes	≥6.5% (48.0 mmol/mol)‡	≥126 mg/dL (7.0 mmol/L)	≥200 mg/dL (11.1 mmol/L)	Random PG ≥200 mg/dL (11.1 mmol/L) in a patient with classic symptoms of hyperglycemia or hyperglycemia crisis
Prediabetes‖	5.7% to 6.4% (39–47.9 mmol/mol)	IFG: 100 to 125 mg/dL (5.6–6.9 mmol/L)	IGT: 140 to 199 mg/dL (7.8–11.0 mmol/L)	NA

* The ADA guidelines note this test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.
† Fasting is defined as no caloric intake for at least 8 hours.
‡ Refers to values measured 2 hours post-load 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-gram anhydrous glucose dissolved in water.
§ The ADA guidelines note this test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.
‖ ADA guidelines note that for all three tests the risk is continuous, extending below the lower limit of the range and becoming disproportionately greater at higher ends of the range.

Abbreviations: A1c=glycated hemoglobin; ADA=American Diabetes Association; DCCT=Diabetes Control and Complications Trial; IFG=impaired fasting glucose; IGT=impaired glucose tolerance; NA=not applicable; NGSP=National Glycohemoglobin Standardization Program; OGTT=oral glucose tolerance test.

Table 3. Characteristics of Included Randomized Trials of Children and Adolescents With Prediabetes or Type 2 Diabetes (KQs 3, 4, and 5)

First Author, Year	Participants	Groups, No.	Duration of Followup	Duration of Diabetes, Mean (Range or SD), Months	Age, Mean (Range or SD), y	No. (%) F	No. (%) Nonwhite	HbA1C Mean (%)(SD)	BMI, Mean (SD) (kg/m^2)	Quality
Jones, 2002[63]	Children (10–16 y) with previous or new diagnosis of type 2 diabetes, BMI >50th percentile for age; 44 sites in multiple countries*	G1: Metformin (titrated up to maximum 2,000 mg/day†), 42 G2: Placebo, 40	16 weeks	NR	G1: 13.9 (1.8) G2: 13.6 (1.8)	G1: 30 (71.4) G2: 27 (67.5)	G1: 25 (59.5) G2: 27 (67.5)	G1: 8.3 (1.3) G2: 9.0 (1.4)	G1: 34.2 (10.6) G2: 33.9 (12.7)	Fair
TODAY Study Group, 2007, 2010, 2012, 2013, 2015, 2016[53, 58-62]	Adolescents who were obese (10–17 y) with type 2 diabetes for <2 years, BMI ≥85th percentile for age and sex at 15 clinical centers in the United States	After a run-in of 2 to 6 months‡ G1: Metformin, 232 G2: Metformin + rosiglitazone 4 mg twice daily, 233 G3: Metformin + lifestyle program, 234	Mean, 3.8 y (range, 2–6.5 y)	G1: 7.8 (6.0) G2: 8.0 (5.7) G3: 7.6 (5.8)	G1: 14.1 (1.9) G2: 14.1 (2.1) G3: 13.8 (2.0)	G1: NR (63.1) G2: NR (65.7) G3: NR (66.0)	G1: 183 (78.9) G2: 186 (79.8) G3: 188 (80.3)	G1: 7.3 (2.2) G2: 7.0 (2.3) G3: 7.1 (2.2)	G1: 35.8 (8.1) G2: 35.0 (7.7) G3: 34.1 (7.1)	Good
Savoye, 2014[64]	Adolescents who were obese (10–16 y) with BMI >95th percentile and prediabetes (elevated OGTT, 2-h 130–199 mg/dL) from the Yale Pediatric Obesity Clinic	G1: Bright Bodies Healthy Lifestyle Program,§ 38 G2: standard care, 37	6 months	NA	G1: 12.7 (1.9) G2: 13.2 (1.8)	G1: 26 (68.4) G2: 23 (62.2)	G1: 11 (29.0) G2: 12 (32.4)	G1: 5.7 (0.4) G2: 5.6 (0.4)	G1: 32.1 (5.2) G2: 34.6 (6.8)	Fair

* Subjects were from the United States (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]).

† Mean final dose of metformin was 1,798 mg/day.

‡ The run-in involved weaning from nonstudy diabetes medications, initiating metformin at a dose of up to 1,000 mg twice daily, attaining glycemic control with metformin alone (A1c <8.0%), providing standard diabetes education and ensuring the participants' mastery of the material, and confirming adherence.

§ The program consisted of two 50-minute exercise sessions per week, one 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, for returning their weekly exercise log.

Abbreviations: BMI=body mass index; G=group; HbA1c=glycated hemoglobin; KQ=key question; NA=not applicable; NR=not reported; OGTT=oral glucose tolerance test; SD=standard deviation; TODAY=Treatment Options for Type 2 Diabetes in Adolescents and Youth.

Table 4. Results of Trials of Children and Adolescents With Prediabetes or Type 2 Diabetes Reporting Health Outcomes (KQ 3) or Progression From Prediabetes to Type 2 Diabetes (KQ 5)

First Author, Year	G1 (N) G2 (N)	Progression to Diabetes	Mortality G1 vs. G2; HR (95% CI)	CVD Events G1 vs. G2; HR (95% CI)	Diabetic Ketoacidosis	Chronic Kidney Disease G1 N (%) G2 N (%) HR (95% CI)	Amputations G1 N (%) G2 N (%) HR (95% CI)	Skin Ulcers G1 N (%) G2 N (%) HR (95% CI)	Visual Impairment G1 N (%) G2 N (%) HR (95% CI)	Neuropathy G1 N (%) G2 N (%) HR (95% CI)
Jones, 2002[63]	G1: 42 G2: 40	NA	NR	NR	G1: 0 G2: 1 (2.5%)	NR	NR	NR	NR	NR
TODAY Study Group, 2007, 2010, 2012, 2013, 2015, 2016[53, 58-62]	G1: 232 G2: 233 G3: 234	NA	G1: 0 G2: 0 G3: 0	NR	G1: 5 (2.1) G2: 3 (1.3) G3: 3 (1.3) p=0.70	**Renal impairment**: G1: 0 G2: 1 (0.4) G3: 1 (0.4) p=1.00	NR	NR	NR	NR
Savoye, 2014[64]	G1: 38 G2: 37	G1: 0 G2: 0	NR	NR	NR	NR	NR	NR	NR	NR

Abbreviations: CI=confidence interval; CVD=cardiovascular disease; G=group; HR=hazard ratio; N=number; NA=not applicable; NR=not reported; TODAY=Treatment Options for Type 2 Diabetes in Adolescents and Youth; vs.=versus.

Table 5. Results of Included Trials of Children and Adolescents With Type 2 Diabetes Reporting Harms/Adverse Events Due to Treatment (KQ 4)

First Author, Year	CV Adverse Events G1 N (%) G2 N (%) HR (95% CI)	Hypoglycemic Events G1 N (%) G2 N (%) HR (95% CI)	All-Cause Withdrawals G1 N (%) G2 N (%) HR (95% CI)	Gastrointestinal Adverse Events G1 N (%) G2 N (%) HR (95% CI)	Lactic Acidosis G1 N (%) G2 N (%) HR (95% CI)	Other Adverse Events G1 N (%) G2 N (%) HR (95% CI)
Jones, 2002[63]	NR	**Hypoglycemic events requiring medical attention:** G1: 0 G2: 0	G1: 6 (14.3) G2: 4 (10.0)	**Abdominal pain** G1: NR (25) G2: NR (12) **Nausea/vomiting** G1: NR (17) G2: NR (10)	G1: 0 G2: 0	Other adverse events, as reported by the authors (all deemed unrelated to the study drug) G1: 2 (4.7%) (one person became seropositive for hepatitis B and one had severe abdominal pain and diarrhea due to a viral infection) G2: 2 (5.4%) (one had hyperglycemia and one experienced problems associated with diabetes and increased liver function enzymes; a third participant had diabetic ketoacidosis) (covered in **Table 4**)
TODAY Study Group, 2007, 2010, 2012, 2013, 2015, 2016[53, 58-62]	**Heart failure** Before primary outcome G1: 0 G2: 0 G3: 0 After primary outcome (out of 319 participants who had the primary outcome of treatment failure) G1: 0 G2: 1 (1.1) G3: 0	**Severe hypoglycemia:** G1: 1 (0.4) G2: 1 (0.4) G3: 2 (0.8) p=1.00 **Mild hypoglycemia:** G1: 10 (4.3) G2: 19 (8.2) G3: 8 (3.4) p=0.05 **Repeated mild hypoglycemia** Before primary outcome (out of all 699 participants) G1: 5 (2.1) G2: 16 (6.9) G3: 6 (2.6) p=0.094 After primary outcome (out of 319 participants) G1: 4 (3.3) G2: 3 (3.3) G3: 1 (0.9) p=0.029	G1: 15 (6.4) G2: 20 (8.6) G3: 15 (6.4)	**GI symptoms** Full sample: G1: 129 (55.6) G2: 100 (42.9) G3: 136 (58.1) p=0.002	G1: 1 (0.4) G2: 0 G3: 0 p=0.33	**Rash** G1: 108 (46.5) G2: 101 (43.3) G3: 95 (40.6) p=0.43 **Infection** G1: 149 (64.2) G2: 120 (51.5) G3: 151 (64.5) p=0.005 **Sprain or fracture** G1: 66 (28.4) G2: 53 (22.7) G3: 64 (27.4) p=0.33 **Muscle ache or pain** G1: 68 (29.3) G2: 53 (22.7) G3: 77 (32.9) p=0.05 **Anemia** G1: 71 (30.6) G2: 58 (24.8) G3: 52 (22.2) p=0.11 **Edema** G1: 17 (7.3) G2: 17 (7.3) G3: 17 (7.3) p=1.00

Abbreviations: CI=confidence interval; CV=cardiovascular; G=group; HR=hazard ratio; KQ=key question; N=number; NR=not reported; TODAY=Treatment Options for Type 2 Diabetes in Adolescents and Youth.

Table 6. Summary of Evidence on Screening for Prediabetes and Type 2 Diabetes in Children and Adolescents

Key Question and Topic	No. of Studies (k), No. of Participants (n)	Summary of Findings	Consistency and Precision	Study Quality	Limitations (Including Reporting Bias)	Overall Strength of Evidence	Applicability
KQ 1. Benefits of screening	0, 0	No eligible studies	NA	NA	NA	Insufficient	NA
KQ 2. Harms of screening	0, 0	No eligible studies	NA	NA	NA	Insufficient	NA
KQ 3. Benefits of interventions for screen-detected or recently diagnosed type 2 diabetes and prediabetes	2 RCTs (7 publications), 781 participants	The TODAY study (n=699) reported no significant difference between groups for renal impairment in youths treated with metformin only vs. metformin plus rosiglitazone vs. metformin plus a lifestyle intervention (0 vs. 1 vs. 1, p=1.00) and no difference for DKA (5 vs. 3 vs. 3, p=0.70, respectively). One smaller trial (n=82) reported that one adolescent with diabetes in the placebo group developed DKA compared with zero 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 followup 3.8 years in TODAY (range 2–6.5 y) likely insufficient to assess health outcomes; followup of 16 weeks in the smaller trial; reporting bias not detected	Insufficient	The TODAY trial enrolled adolescents who were obese (age 10–17 y) with previous or newly diagnosed type 2 diabetes; predominantly nonwhite participants from U.S.; during run-in and prior to randomization, participants had to achieve glycemic control (HbA1c <8%), achieve mastery of diabetes education material, and confirm adherence.
KQ 4. Harms of interventions for type 2 diabetes	2 RCTs (7 publications), 781 participants	**Hypoglycemic events:** More youths treated with metformin plus rosiglitazone had repeated mild hypoglycemia than those treated with metformin or metformin plus lifestyle (8.2% vs. 4.3% vs. 3.4%), p=0.05. **Gastrointestinal adverse events**: Higher rates with metformin alone and metformin plus lifestyle intervention than with metformin plus rosiglitazone (55.6% vs. 58.1% vs. 42.9%, p=0.002). Higher rates of abdominal pain (25% vs. 12%, P NR) and nausea or vomiting (17% vs. 10%, P NR) for youths treated with metformin for 16 weeks than with placebo. **Infection:** Lower rates with metformin plus rosiglitazone than with metformin alone or metformin plus a lifestyle intervention (p=0.005). **Muscle aches or pains:** Lower rates with metformin plus rosiglitazone than with metformin alone or metformin plus a lifestyle intervention (p=0.05). **Heart failure:** One participant treated with metformin plus 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 who were obese (ages 10–17 y) with previous or newly diagnosed type 2 diabetes; predominantly nonwhite participants from the U.S.
KQ 4. Harms of interventions for prediabetes	0, 0	No eligible studies	NA	NA	NA	Insufficient	NA

Table 6. Summary of Evidence on Screening for Prediabetes and Type 2 Diabetes in Children and Adolescents

Key Question and Topic	No. of Studies (k), No. of Participants (n)	Summary of Findings	Consistency and Precision	Study Quality	Limitations (Including Reporting Bias)	Overall Strength of Evidence	Applicability
KQ 5. 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 months.	Consistency unknown (single study); imprecise	Fair	Followup duration of 6 months; high attrition; some participants were withdrawn for being started on metformin (n=5); reporting bias not detected	Insufficient	Children ages 10–16 years with BMI >95th percentile and prediabetes (elevated OGTT, 2-h 130–199 mg/dL) seen in a pediatric obesity clinic; high-contact lifestyle intervention with both diet/nutrition and physical activity/exercise components.
KQ 6. 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; KQ=key question; NA=not applicable; NR=not reported; OGTT=oral glucose tolerance test; RCT=randomized, controlled trial; TODAY=Treatment Options for Type 2 Diabetes in Adolescents and Youth.

Contextual Questions (CQs)

CQ 1. 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 prediabetes range (without intervention), and over what time frame?
c. How does this differ by baseline hemoglobin (Hb) glycated hemoglobin (A1c) level, fasting glucose level, or glucose tolerance?

Overall, current available studies are limited but suggest that many children and adolescents with prediabetes (22% to 52%) return to normal glycemia or glucose tolerance without intervention over 6 months to 2 years.

A limited number of randomized, controlled trials (RCTs) of prediabetes had control groups that received no intervention, allowing an opportunity to follow those subjects over the course of the study to assess natural history. These studies suggested that a large portion of children and adolescents with prediabetes will remain with prediabetes or revert to normoglycemia over a 2-year period; this pattern appears similar regardless of the method of measuring glycemia or glucose tolerance. The largest of these was the HEALTHY study. This study randomized 21 schools to the control arm, collected baseline metabolic health data on 6th graders, and then collected the same data again 2 years later. Of those with prediabetes at baseline (n=128, HgA1C 5.7-6.4), the 2-year followup assessments revealed that 51 (39.8%) had a normal HgA1c, 76 (59.4%) persisted with prediabetes, and 1 (0.8%) progressed to diabetes. By comparison, of those with A1c <5.7 at baseline (n=3,852), 3,761 (97.6%) remained <5.7 at the 2-year followup, 88 (2.3%) progressed to prediabetes, and 3 (0.1%) progressed to diabetes. Of those with an elevated fasting plasma glucose (FPG) at baseline (100-125 mg/dL, n=635), 330 (52%) regressed to <100 mg/dL at followup, 298 (46.9%) remained between 100-125 mg/dL and 7 (1.1%) progressed to FPG greater than or equal to 126 mg/dL. By comparison, of those with baseline FPG <100 mg/dL (n=3,345), 2,774 (82.9%) remained <100 mg/dL at followup, 567 (17%) progressed to 100-125 mg/dL, and 4 (0.1%) progressed to FPG ≥ 126 mg/dL at followup.[72] The placebo arm of a small trial of adolescents ages 10 to 16 years who were obese found that the 22 percent (6 of 21) who had oral glucose tolerance test (OGTT) 2-hour blood glucose greater than or equal to 130 at baseline converted to less than 130 at the 6-month followup without intervention.[64]

No identified prospective cohort studies have followed children with prediabetes or diabetes over time to determine what proportion return to normoglycemia without intervention. Two cohort studies followed youth with prediabetes for 2 years and found that 8 percent to 24 percent progressed to type 2 diabetes, while 45 to 65 percent reverted to normal glucose tolerance, but both studies involved some lifestyle intervention for participants.[7, 73] One of the cohort studies was conducted in an obesity clinic and followed children with prediabetes over 2 years. It provided dietary counseling and evaluation every 5 to 6 months, but it did not have a group who received no intervention. Of 162 adolescents with prediabetes at baseline, 102 (65%) reverted to normal glucose tolerance at 2 years, 44 (27%) had persistent prediabetes, and 13 (8%) progressed to type 2 diabetes.[73] A similar smaller cohort study in the same obesity clinic followed a subset

of children and adolescents with prediabetes over 18 to 24 months, providing biannual nutrition and physical activity counseling. It found that of 33 children and adolescents with prediabetes at baseline, 15 (45.5%) reverted to normal glucose tolerance at followup, 10 (30.3%) maintained prediabetes, and 8 (24.2%) progressed to type 2 diabetes.[7]

One additional cohort study followed American Indian children and adolescents from the southwestern United States from 1965 to 2007.[74] Of 2,095 children and adolescents ages 10 to 19 years, they identified 62 with prediabetes (HgA1c 5.7-6.4) at baseline and followed them through age 39 years. It is unclear (in the article) whether the children and adolescents received any interventions for obesity or prediabetes during the followup period. The study did not report how many of the 62 children and adolescents with prediabetes went on to develop diabetes, but it did include bar graphs with incidence rates for diabetes cases per 1,000 person-years and bar graphs with rate ratios. Male children with prediabetes (n=13) had a fourfold higher incidence rate of diabetes at followup compared with those with baseline HgA1c of 5.3 or less (n=831), while female children with prediabetes at baseline (n=49) had a sevenfold higher incidence of diabetes than female children with baseline HgA1c of 5.3 or less (n=964). Median time from diagnosis of prediabetes to diabetes or last examination before diabetes developed was 5.2 years. Results were similar for prediabetes as defined by FPG or 2-h postprandial blood glucose.

CQ 2. a. Does screening for prediabetes or type 2 diabetes change the intermediate outcomes of HbA1c level, FPG level, 2-hour glucose tolerance test results, subclinical retinopathy, microalbuminuria, or subclinical neuropathy for children and adolescents?

This review identified no studies for CQ 2a.

b. Do interventions for children and adolescents with screen-detected or recently diagnosed type 2 diabetes or prediabetes change the intermediate outcomes of HbA1c level, FPG level, 2-hour glucose tolerance test results, subclinical retinopathy, microalbuminuria, or subclinical neuropathy?

Summary

Among those recently diagnosed with type 2 diabetes, metformin improved glycemia, including A1c and FPG levels, compared with placebo in one trial; rosiglitazone combined with metformin improved glycemic control, as measured by A1c <8 percent and/or need for rescue insulin, compared with metformin alone or metformin and lifestyle in one trial, but only while rosiglitazone was being used (i.e., there was no long-term protective effect from prior use); liraglutide combined with metformin resulted in improved glycemia, as measured by A1c and FPG, compared with metformin and placebo in one trial. Among those with prediabetes, lifestyle improved 2-h glucose, but not fasting glucose or A1c, compared with usual care in one trial; data on rosiglitazone were inconclusive because of early trial discontinuation. There was no evidence that metformin combined with rosiglitazone or combined with lifestyle affected microalbuminuria compared with metformin alone in one trial. We found no trials (absence of evidence) demonstrating that interventions for children and adolescents with recently diagnosed type 2 diabetes or prediabetes change subclinical retinopathy or subclinical neuropathy.

Impact of Interventions on Glycemia in Children/Adolescents With Recently Diagnosed Type 2 Diabetes

Three studies (4 articles) examined the glycemic impact of treating recently diagnosed type 2 diabetes.[53, 63, 75, 76] A double-blind RCT (also included in KQ 4) conducted across 44 sites in the United States, Russia, Ukraine, Belarus, and Poland examined whether screening for type 2 diabetes changed the intermediate outcomes of A1c and FPG.[63] In that trial, Jones et al examined the impact of metformin (titrated up to 2,000 mg/day as tolerated [mean final dose of metformin=1,798 mg]) versus placebo in 82 children ages 10 to 16 years who were previously or newly diagnosed with type 2 diabetes. Some participants may have had a previous diagnosis of type 2 diabetes and taken oral glucose-lowering medication previously (but at least 28 days before trial start). The independent Data and Safety Monitoring Board recommended an end to the double-blind period (all participants were switched to open-label metformin) based on 8-week data showing that 70.0 percent of the placebo subjects had required rescue medication for exceeding the predetermined glycemic threshold compared with 15.8 percent of metformin subjects. At the end of double-blind treatment, the adjusted mean FPG had significantly decreased in the metformin group but increased in the placebo group (-2.4 mmol/l [-42.9 mg/dl] vs. +1.2 mmol/l [+21.4 mg/dl]; $p<0.001$). The mean adjusted HbA1c level at the end of the double-blind period was also significantly lower in the metformin group compared with the placebo group (7.5 vs. 8.6%, respectively; $p<0.001$). The proportion of subjects who met at least one of the American Diabetes Association (ADA) glycemic treatment target levels (FPG <7.0 mmol/l [<126 mg/dl] or HbA1c <7.0%) by their last double-blind treatment visit was 84 percent for the metformin group compared with 22 percent for the placebo group.

In the TODAY trial (described in KQs 3 and 4),[53] 699 adolescents who were obese, ages 10 to 17 years, and with recent onset of type 2 diabetes (mean duration of diagnosed type 2 diabetes=7.8 months) were randomized to metformin, metformin plus rosiglitazone, or metformin plus lifestyle program. The primary outcome was loss of glycemic control, defined as a glycated hemoglobin level of at least 8 percent for 6 months or sustained metabolic decompensation requiring insulin. The authors reported that 51.7 percent (95% CI, 45.3 to 58.2), 38.6 percent (95% CI, 32.4 to 44.9), and 46.6 percent (95% CI, 40.2 to 53.0) of participants experienced loss of glycemic control in the metformin, metformin plus rosiglitazone, and metformin plus lifestyle interventions, respectively. Metformin plus rosiglitazone was associated with a 25.3 percent decrease in the occurrence of the loss of glycemic control compared with metformin alone ($p=0.006$); the glycemic impact of metformin plus lifestyle intervention did not differ significantly from that of metformin alone or metformin plus rosiglitazone. In TODAY2,[76] a followup study of 572 TODAY participants, rosiglitazone was permanently discontinued in those who had been assigned to that arm. All participants continued receiving metformin monotherapy at the same dose they were taking at the end of TODAY, and add-on insulin therapy was continued or started in participants who had metabolic decompensation during followup. After 36 months, the rate of glycemic failure did not differ among participants who were previously randomized to any of the three TODAY treatment arms (metformin, metformin plus rosiglitazone, or metformin plus lifestyle program). By the end of the 96 months' total observation period (including TODAY and TODAY2), 173 participants (25.6% of the original cohort) remained free of glycemic failure. There were no statistically significant differences by sex or race/ethnicity.

The third study was a double-blind multicenter (25 countries) RCT examining the glycemic impact of metformin plus liraglutide (up to 1.8 mg per day) vs metformin plus placebo in 134 participants aged 10 to 17 years with type 2 diabetes (mean duration 1.9 years).[75] All participants were encouraged to follow a diet and exercise regimen. The authors reported that 23 percent and 15 percent of liraglutide-metformin and metformin only participants, respectively, were also taking basal insulin at baseline; their insulin dosage was reduced by 20 percent at the time of randomization but could be increased back up to the baseline dose (but no higher) after completion of the dose-escalation period. The primary end point was the change from baseline in the A1c level, and secondary end points included change in FPG level. Mean A1c levels at week 26 were reduced from baseline by 0.64 percentage points in the liraglutide group, whereas the levels increased by 0.42 percentage points in the placebo group (estimated treatment difference, -1.06 percentage points [95% CI, -1.65 to -0.46]; p<0.001). Moreover, 63.7 percent of the patients in the liraglutide group, as compared with 36.5 percent in the placebo group, attained A1c levels of less than 7.0 percent (p<0.001). Liraglutide was also superior to placebo in reducing FPG levels by 26 weeks (-1.08 mmol/L vs. 0.80 mmol/L).

Impact of Interventions on Other Intermediate Outcomes in Children/Adolescents With Recently Diagnosed Type 2 Diabetes

The TODAY trial examined the development of microalbuminuria (albumin:creatinine ratio of 30 or more, with albumin measured in milligrams per deciliter and creatinine in grams per deciliter).[77] The prevalence of microalbuminuria increased from 6.3 to 16.6 percent by the end of the study, but the incidence of new cases of microalbuminuria did not differ across treatment arms.

No studies examined subclinical retinopathy or subclinical nephropathy and reported results that were eligible for this report. The TODAY study reported on the prevalence of retinopathy among study participants using retinal images that were taken during the last year of the study, but it did not report data separated by the three study groups nor did it collect baseline data to enable reporting of changes in or incidence of retinopathy.[78]

Impact of Interventions on Glycemia in Children/Adolescents With Prediabetes

Lifestyle: An RCT (described in KQ 5) compared a lifestyle program (Bright Bodies [BB]) with standard clinical care (CC) among 75 racially/ethnically diverse adolescents who were obese (ages 10-16 years) with prediabetes as defined by an elevated OGTT 2-h blood glucose (130-199 mg/dL; using a range that was slightly wider than the current prediabetes criteria of 140 to 199 mg/dL).[64] The BB intervention was family based, tailored for inner-city minority children and their families, and consisted of two 50-min exercise sessions per week, one weekly weigh-in, and a 40-min nutrition/behavior modification class. Participants were encouraged to exercise 3 additional days per week and given guidance on making healthy food choices including low-fat foods of moderate portions. The primary outcomes were change in 2-h blood glucose level and percentage conversion from elevated to nonelevated 2-h blood glucose level (<130 mg/dL) at the 6-month followup. The BB group experienced a greater decrease in 2-h glucose compared with CC (27.2 vs. 10.1 mg/dL; difference=17.1 [95% CI -29.0 to -5.1]; p=0.005). In addition, more participants in the BB experienced conversion to normal 2-h glucose (<130 mg/dL) compared with CC (p=0.003). Fasting glucose and A1c did not differ between groups at 6 months.

Rosiglitazone. In a pilot randomized, double-blind, placebo-controlled study, 21 adolescents who were obese (between ages 13 and 18 years) with impaired glucose tolerance (diagnosed via OGTT) received either rosiglitazone (8 mg daily) or placebo over 4 months.[79] Nutritional and exercise recommendations were given to both groups. The study was stopped early because recruitment became difficult due to concerns that had emerged from the literature regarding cardiac complications associated with rosiglitazone. Fifty-eight percent (n=7) in the rosiglitazone group vs. 44 percent (n=4) in the placebo group converted from impaired glucose tolerance (IGT) to normal glucose tolerance (p=0.53). Fasting glucose and A1c were collected during the study but not reported.

CQ 3. a. Do interventions for (or does knowledge of) prediabetes change body mass index (BMI), weight, or healthy behaviors?

In summary, three studies were identified that addressed whether interventions for prediabetes or if knowledge of prediabetes was associated with changes in BMI and weight.[64, 68, 79] No studies were identified that examined changes in healthy behaviors. Included studies compared lifestyle with standard care[64] and rosiglitazone with placebo,[79] and assessed the association of prediabetes identification with BMI.[68] All three studies reported on BMI,[64, 68, 79] and two studies reported on weight.[64, 79] Two of the included studies were RCTs, and one was a cohort study. All three studies were conducted in the United States and included racially diverse samples. Overall, studies reported that lifestyle interventions for children and adolescents with prediabetes improved the intermediate outcomes of weight and BMI compared with controls, rosiglitazone did not reduce weight or BMI compared with placebo, and prediabetes identification was associated with decreases in BMI in adolescents who were obese and overweight.

Two RCTs of prediabetes interventions reported on changes in BMI and weight.[64, 79] One study (described in KQ 5) recruited adolescents from an obesity clinic (n=75) and compared the lifestyle invention BB with standard care.[64] Participating adolescents (ages 10-16 years) were required to have an elevated OGTT 2-h glucose (130-199 mg/dl), a BMI greater than 95th percentile, and a Tanner stage of greater than 2. The final sample included mostly nonwhite (66%) females (70%). At 6 months, participation in BB was associated with a significant decrease in weight (-3.1 kg [95% CI, -5.3 to -0.9]) and BMI (-1.05 kg/m2 [95% CI, -1.78 to -0.32]; z-score, -0.09 [95% CI, -0.14 to -0.04]) compared with standard care. The second included trial (n=23) compared rosiglitazone with placebo and recruited participants from the same obesity clinic as in the BB study.[79] Participants were between the ages of 13 and 18 years, had IGT or impaired fasting glucose (IFG)-IGT, and were in Tanner stage II-IV with a BMI z-score greater than 2 for age and sex. In the sample of mostly nonwhite (76%) females (57%), the study reported no significant differences in BMI (0.07 vs. -0.016, p=0.757) or weight changes (1.81 vs. 0.61, p=0.541) when comparing rosiglitazone with placebo at posttreatment.

A U.S.-based retrospective cohort study (n=4,184) using data from the Children's Hospital of Philadelphia examined the association between prediabetes identification and BMI.[68] In a sample of children (ages 10 to 18 years) who were overweight or obese (BMI z-score $\geq$1.04), the study compared differences in BMI z-score before and after available HbA1c tests. Median followup was 9.7 years. Youth were categorized as "screened" if at least one HbA1c result was available. Prediabetes was defined as 5.7 percent to 6.4 percent, 39 to 46 mmol/mol, and normal was defined as less than 5.7 percent, less than 39 mmol/mol. Using an adjusted model (adjusting for BMI z-score at HbA1c, age at HbA1c, sex, race, ethnicity, and insurance type), the study

reported that children who had an HbA1c in the prediabetes range had a greater decrease in BMI z-score slope than children with a normal HbA1c (pre/post difference of -0.050/y [prediabetes] vs. -0.027 [normal], difference in difference: -0.023/year [95% CI, -0.042 to -0.004]). Children who had an HbA1c in the prediabetes range also had a greater decrease in BMI z-score slope than age-matched "unscreened" children who were obese (difference in difference: -0.031/year [95% CI, -0.042 to -0.021]) adjusting for BMI z-score at HbA1c (or matched age), age, sex, race, ethnicity, and insurance type. Limitations of the study include a lack of any information about whether or how prediabetes diagnosis was conveyed to patients, whether patients were provided counseling or interventions, whether patients changed behaviors as a result of HbA1c testing or prediabetes diagnosis, and reasons for testing (e.g., testing may be more likely for children who were obese who were initiating interventions for their obesity).

CQ 3. b. Do interventions for (or does knowledge of) type 2 diabetes change BMI, weight, or healthy behaviors?

Two RCTs were identified that examined the association between diabetes interventions and changes in BMI, weight, and healthy behaviors.[18, 53, 63, 65, 66, 80] No studies were identified that examined if knowledge of diabetes was associated with BMI, weight, or healthy behaviors. The two identified trials examined metformin,[18, 53, 63, 65, 66, 80] metformin plus rosiglitazone,[18, 53, 65, 66, 80] and lifestyle intervention.[18, 53, 65, 66, 80] One trial (TODAY) was conducted in the United States,[18, 53, 65, 66, 80] and one trial included sites within multiple countries.[63] Both trials included racially diverse samples. Overall, studies reported that interventions including metformin (e.g., metformin alone, metformin plus lifestyle intervention) were associated with decreases in BMI and weight when compared with active comparisons (e.g., metformin plus rosiglitazone); one study reported that metformin was not associated with significant changes compared with control. Studies comparing metformin with metformin plus lifestyle reported significant differences in BMI change and average weight change at shorter followups (e.g., 6 months). Differences between metformin and metformin plus lifestyle were not found for meaningful reductions in weight or when average weight change was examined at longer followups (e.g., 24 months). Studies also reported that interventions that included rosiglitazone (e.g., metformin plus rosiglitazone) were associated with increases in BMI when compared with other active comparators (e.g., metformin alone, metformin plus lifestyle). The findings of the two included trials were mixed. In addition, the TODAY study reported that the combination of metformin plus lifestyle was associated with improved health behaviors compared with metformin plus rosiglitazone for males at 6 months, although data were missing for many participants. Significant differences in health behaviors were not found between other intervention groups (e.g., metformin alone vs. metformin plus lifestyle, metformin alone vs. metformin plus rosiglitazone) among males, and no significant differences were found between groups among females.

One trial[63] conducted in multiple countries included children between the ages 8-16 years with a previous or new diabetes diagnosis. In the sample of mostly nonwhite (63%) females (70%), no significant differences were reported in the mean changes for BMI or weight when comparing metformin with placebo (-0.5 kg/m^2 vs. -0.4 kg/m^2 and -1.5 kg vs. -0.9 kg, respectively) at 16 weeks posttreatment.[63]

The second identified trial was the TODAY study (described in KQ 3).[18, 53, 65, 66, 80] At 6 months, the combination of metformin plus lifestyle was associated with significant decreases in BMI compared with metformin alone (-0.21 vs. 0.35, p=0.0201) or in comparison with metformin plus rosiglitazone (-0.21 vs. 0.70, p=0.0002). At 24 months, significant differences in BMI were reported between metformin plus rosiglitazone compared with metformin alone (2.93 vs. 1.57; p<0.0001) and when comparing metformin plus rosiglitazone with metformin plus lifestyle (2.93 vs. 1.52, p<0.001).

For average change in percentage overweight (defined as BMI minus BMI at the 50th percentile for age and sex, divided by BMI at the 50th percentile), the TODAY study reported that both metformin alone (-1.42 percentage points) and metformin plus lifestyle (-3.64 percentage points) were associated with significant decreases. The study also reported that metformin plus rosiglitazone was associated with a significant increase in percentage overweight (0.81 percentage points). The overall comparison and the comparison across all three groups were significant for this outcome at 6 months (p<0.001). At 24 months, differences between metformin plus rosiglitazone compared with metformin alone (0.89 percentage points vs. -4.42 percentage points), and metformin plus rosiglitazone compared with metformin plus lifestyle (0.89 percentage points vs. -5.02 percentage points) remained statistically significant (p<0.001). The differences between metformin and metformin and lifestyle were no longer significant at 24 months.[18, 53, 65, 66, 80]

The TODAY study also reported on the proportion of children with a meaningful reduction ($\geq$7 percentage points) in percentage overweight posttreatment. A higher proportion of children in the metformin plus lifestyle group had a meaningful reduction in overweight participants compared with metformin plus rosiglitazone (31.2% vs. 16.7%, p<0.001) at 6 months. The study did not report any significant differences when comparing metformin plus lifestyle versus metformin alone (31.2% vs. 24.3%, p=NS).[18, 53, 65, 66, 80]

In addition, the TODAY study reported on the association between interventions and health behaviors.[80] However, the results for these outcomes may have a high risk of bias because of missing data (with data missing for 36 percent to 41 percent of participants, depending on the time point). At 6 months, males in the metformin plus lifestyle group were more likely to improve their eating habits and sedentary lifestyles compared with males in the metformin plus rosiglitazone group (50% vs. 26%, p=0.01). No significant differences were found between metformin plus lifestyle and metformin plus rosiglitazone at 24 months. Also, no significant differences were found between metformin plus lifestyle and metformin alone or between metformin alone and metformin plus rosiglitazone at 6 or 24 months. No significant differences in health behaviors were reported for females at 6 or 24 months across the three intervention groups.[80]

CQ 4. What is the frequency of agreement among screening tests (HbA1c level, FPG level, and 2-hour glucose tolerance test) for prediabetes and type 2 diabetes?

We focused on studies from very high HDI countries with at least 100 participants that reported relevant outcomes and used (at least some) data collected within the past 10 years. Studies were required to report frequency of agreement between at least two of the relevant tests and to use current criteria for diagnosis of prediabetes or type 2 diabetes (based on the ADA guidelines); we

excluded studies that used older criteria. We included eight articles (**Appendix A Table 2**). Of those eight, one compared A1c and OGTT,[81] two compared A1c and FPG,[72, 82] and five compared the results of all three tests (A1c, FPG, and OGTT).[83-87] Sample sizes ranged from 117 to 3,980. Five of the studies were conducted in the United States. The studies typically enrolled youths who were obese and overweight. Many of the studies reported relatively large differences in the proportion of youths diagnosed with prediabetes or diabetes when using different tests.[72, 81, 82, 85, 87] For example, a study of 902 predominantly black youths conducted in the United States reported that prediabetes prevalence was 54.3 percent based on A1c compared with only 5.6 percent when using OGTT, and a study of 149 predominately Hispanic youths reported a diabetes or prediabetes (combined) prevalence of 48 percent based on A1c compared with 12 percent based on FPG and 16 percent based on OGTT.[81, 87]

These findings are consistent with evidence in adults. Further, elevations in A1c, FPG, and OGTT results may represent somewhat different metabolic states. The 2021 evidence review for the USPSTF on screening for prediabetes and diabetes in adults summarized a systematic review on the prevalence of prediabetes that would be identified by various screening tests.[88] The review identified five studies (with a total of 17,108 adults) that showed generally low agreement between HbA1c, fasting plasma glucose, and 2-hour glucose tolerance test.[88] For example, using ADA criteria, the prevalence of prediabetes by any test was 54 percent.[88] Of those, 25 percent had isolated IFG, 6 percent isolated IGT, 22 percent isolated HbA1c criteria, 7 percent IFG and IGT, 27 percent IFG and HbA1c criteria, 4 percent IGT and HBA1c criteria, and 9 percent had all three.[88]

CQ 5. Are there risk assessment tools that are feasible for use in primary care settings, accurately predict the risk of prediabetes or type 2 diabetes for children and adolescents, and have been externally validated in U.S. populations?

We found two risk assessment tools for predicting risk of type 2 diabetes or prediabetes that have been validated in U.S. children or adolescents. Hannon and colleagues conducted a cluster-randomized clinical trial (published in 2017) to study the feasibility and effectiveness of a computerized clinical decision support system called Child Health Improvement Through Computer Automation (CHICA).[89-94] The risk assessment tool compiled relevant inputs from the parent section of a previsit questionnaire (family history, race/ethnicity), the clinic staff prescreening form (patient height and weight), and a physician worksheet (signs and symptoms of insulin resistance or conditions associated with insulin resistance). CHICA analyzes these inputs and identifies those at "high risk for type 2 diabetes" using the ADA guidelines from 2000 (i.e., if they had BMI $\geq 85^{th}$ percentile and two or more of the following risk factors: a family history of type 2 diabetes in a first- or second-degree relative, black race, Hispanic ethnicity, maternal history of diabetes or gestational diabetes, and signs of or conditions associated with insulin resistance) (the article did not provide additional details about what signs or conditions were considered as associated with insulin resistance). If high risk, it recommended screening for type 2 diabetes using FPG and HbA1c where prediabetes was defined as FPG 95 to 125 mg/dL and HbA1c 5.7 to 6.5 percent, and diabetes as FPG greater than125 mg/dL and HbA1c greater than 6.5 percent. Children age 10 years or older (n=1,369) attending four primary care clinics in Indiana were included. The primary outcome was the percentage of youths identified with documented risk factors for type 2 diabetes. The authors found that the screening rate was significantly higher after using the tool, but the authors noted that using the tool did not lead to

more patients being diagnosed with prediabetes or type 2 diabetes (although the study was not designed or powered for that outcome). The authors found that when using FPG, 33.3 percent of control patients screened and 22.2 percent of intervention patients had FPG in the prediabetes range, and none were in the diabetes range. When using HbA1c, 31.2 percent of control patients and 20.6 percent of intervention patients had levels in the prediabetes range, and only one patient in the intervention group was diagnosed with diabetes.

DuBose and colleagues developed an adapted version of the adult risk assessment tool called Tool for Assessing Glucose ImpairmenT (TAG-IT) for an adolescent population (published in 2012) and named it Tool for Assessing Glucose ImpairmenT among Adolescents (TAG-IT-A).[95, 96] They used data from a national U.S. sample from the Centers for Disease Control and Prevention's National Health and Nutrition Examination Survey (NHANES) from 1999 to 2008. To develop TAG-IT-A, the authors followed the development process of TAG-IT. They used multiple regression to calculate the association of individual patient factors (age, race, sex, BMI, resting heart rate, hypertension diagnosis [measured resting blood pressure or physician diagnosis]) and fasting blood glucose and FPG greater than or equal to 100 mg/dL, defined as IFG. They then used regression to calculate the association of the group of significant factors with FPG level and calculated weighted scores for each factor to create a TAG-IT-A scoring system. The scoring system involves each predictive factor being given a score, modeled after the Charlson Comorbidity Index.[97] Odds ratios (ORs) from 1.0 to 1.19 were assigned 0 points, ORs from 1.2 to 1.49 were assigned 1 point, ORs from 1.5 to 2.49 were assigned 2 points, etc. The score from each factor is added together to create a final score, and as scores increased from 3 or higher, the authors reported that sensitivity of TAG-IT-A improved. The authors found that there was a positive and significant relationship between FPG and age (ages 12-14 years), sex (male), BMI (obese), and resting heart rate (≥70 beats per minute), which are the four components that create the TAG-IT-A score. TAG-IT-A score was predictive of IFG with an area under the receiver operating curve (AUC)=0.61 (confidence interval not reported), indicating inadequate discrimination. Although the AUC was lower than it was found for the original TAG-IT tool, it was thought that TAG-IT-A may not be as predictive in adolescents because other variables that are not captured may be important, such as aerobic fitness, pubertal development, and physical activity levels.

We identified one additional tool that has not been studied in the United States but was studied in a European pediatric population. Gray and colleagues conducted an accuracy evaluation (published in 2019) of a previously developed risk prediction tool called PRESTARt, comparing it with a reference standard of clinician assessment of whether the participant was high or low risk of developing type 2 diabetes in their lifetime.[98] Aside from stating that two clinicians independently judged each participant, with a third adjudicating if needed, no additional details are provided about how lifetime risk status was established. The authors recruited 636 adolescents age 12 to 14 years from five European countries (Germany, Greece, Portugal, Spain, and the United Kingdom). They found that participants were high risk if they were overweight/obese and had at least one other risk factor from among the following: high waist circumference, family history of diabetes, parental obesity, not breast fed, high sugar intake, high screen time, low physical activity, and low fruit and vegetable intake. The AUC when comparing PRESTARt and clinician assessment was 0.74 (95% CI, 0.71 to 0.78).

Appendix A Table 1. Screening Recommendations of Other Groups

Organization, Year	Screening Recommendation	Risk Factors Considered	Frequency of Screening
American Diabetes Association, 2020[47]	Screen children after onset of puberty or age 10 years who are overweight or obese and have one or more additional risk factors with FPG or 2-h PG after 75-g OGTT, or an A1c	Puberty; age (after 10 years); overweight (BMI ≥85th percentile) or obese (BMI ≥95th percentile); additional risk factors include maternal history of diabetes or GDM during the child's gestation, family history of type 2 diabetes in first- or second-degree relative, race/ethnicity (Native American, African American, Latino, Asian American, Pacific Islander), or signs of insulin resistance or conditions associated with insulin resistance (acanthosis nigricans, hypertension, dyslipidemia, polycystic ovary syndrome, or small-for-gestational-age birth weight)	Repeat screening every 3 years or more frequently if BMI is increasing
Diabetes Canada, 2018[69]	Screen nonpubertal children with at least three risk factors and pubertal children with at least two risk factors with a combination of A1c and a FPG test or a random PG test	Obesity (BMI >95th percentile for age and gender), member of a high-risk ethnic group (e.g., aboriginal, African, Asian, Hispanic, or South Asian descent), family history of type 2 diabetes or exposure to hyperglycemia in utero and symptoms of insulin resistance (including acanthosis nigricans, hypertension, dyslipidemia, NAFLD)	Repeat screening every 2 years in nonpubertal children with ≥3 risk factors and in pubertal children with ≥2 risk factors, in children with IFG or impaired glucose tolerance, in children with use of atypical antipsychotic medications, and in children with PCOS
International Society for Pediatric and Adolescent Diabetes, 2014[70]	Screen children and adolescents using American Diabetes Association criteria including using a FPG test, a 2-h postchallenge glucose test, or a hemoglobin A1c	NR	Does not specify, but supporting the American Diabetes Association criteria implies every 3 years or more frequent if BMI is increasing
National Institute for Health and Care Excellence (NICE), 2015[52]	Does not have a true screening recommendation, but it states to "think about the possibility of type 2 diabetes in children and young people with suspected diabetes"	Family history of type 2 diabetes, obese at presentation, are of black or Asian family origin, have no insulin requirement or an insulin requirement of <0.5 units/kg body weight/day after the partial remission phase, and demonstrate evidence of insulin resistance	NR
Pediatric Endocrine Society (PES) Drugs and Therapeutics Committee, 2012[71]	Screen children who are asymptomatic or minimally symptomatic and at risk with HbA1c test	HbA1c is unreliable in those with sickle-cell carrier status	NR

Abbreviations: BMI=body mass index; FPG=fasting plasma glucose; GDM=gestational diabetes mellitus; HbA1c=glycated hemoglobin; IFG=impaired fasting glucose; NAFLD=non-alcoholic fatty liver disease; NICE=National Institute for Health and Care Excellence; NR=not reported; OGTT=oral glucose tolerance test; PCOS=polycystic ovary syndrome; PES=Pediatric Endocrine Society; PG=2-h plasma glucose.

Appendix A Table 2. Studies That Compared Agreement Among Screening Tests, by Comparison

Author, Year	Comparison	N	Age, Mean (Range)	Country	Race and Ethnicity	Main Results
Hitt et al, 2016[81]	A1c and OGTT	902	11.6 (2 to 18 y)	U.S.	70% Black	Diabetes prevalence: based on A1c was 2.9% (n=26) vs. 1.7% (n=15) based on OGTT Prediabetes prevalence: based on A1c was 54.3% (n=491) vs. 5.6% (n=51) based on OGTT
Buse et al, 2013[72] HEALTHY	A1c and FPG	3,980	11 (10 to 14 y)	U.S.	91.5% White	3.2% had A1c of 5.7%-6.4%; 16.0% had IFG. Of those with A1c of 5.7% to 6.4% (128 participants), 63.3% had normal fasting glucose (<100) and 36.7% had IFG. Of those with normal A1c (<5.7%) (3,852 participants), 84.7% had normal fasting glucose and 15.3% had IFG
Tester et al, 2013[82]	A1c and FPG	1,356	11 (2 to 19 y)	U.S.	14% Black 49% Hispanic	Prediabetes prevalence was 20.7% based on A1c vs. 7.8% based on IFG
Kim et al, 2019[83]	A1c, FPG, and OGTT	190	12.6 (NR)	South Korea	NR	Diabetes prevalence: based on A1c was 22.1% (n=42) vs. 21.1% (n=40) based on OGTT Prediabetes prevalence: based on A1c was 21.6% (n=41) vs. 17.4% (n=33) based on OGTT Diagnostic sensitivity (for diabetes) was lower for FPG (63.8%) than for A1c (89.4%) or OGTT (85.1%)
Yoon et al, 2018[84]	A1c, FPG, and OGTT	236	10.4 (NR)	South Korea	NR	Diabetes prevalence: 17% (n=39) based on OGTT. Prediabetes prevalence: 22% (n=52) based on OGTT. Using ADA cutoffs, A1c had sensitivity of 87.2% and specificity of 98.5% for detecting diabetes and FPG had 66.7% and 99.0%, respectively (compared with OGTT reference standard)
Chan et al, 2016[85]	A1c, FPG, and OGTT	117	14.1 (10 to 18 y)	U.S.	22% White 17% Black 59% Hispanic	About half of the participants met criteria for prediabetes or diabetes based on either OGTT (40.2%) or HbA1c (51.3%), but only 9% met FPG criteria for prediabetes or diabetes
Galhardo and Shield, 2015[86]	A1c, FPG, and OGTT	266	12.3 (8.9 to 17.6 y)	Portugal	90% White	Diabetes prevalence: 1 (0.4%) based on A1c vs 0 (0%) based on OGTT Prediabetes prevalence: 32 (12%) based on A1c vs. 13 (4.9%) based on OGTT A1c had AUC of 0.59 (95% CI, 0.40 to 0.78) and FPG had AUC of 0.76 (95% CI, 0.66 to 0.87) using OGTT as the reference standard
Brar et al, 2014[87]	A1c, FPG, and OGTT	149	13.0 to 13.8 (NR)	U.S.	71% Hispanic	Prediabetes or type 2 diabetes prevalence: 71 (48%) based on A1c vs. 18 (12%) based on FPG vs. 24 (16%) based on OGTT

Abbreviations: ADA=American Diabetes Association; AUC=area under the curve; CI=confidence interval; FPG=fasting plasma glucose; IFG=impaired fasting glucose; NR=not reported; OGTT=oral glucose tolerance test.

Appendix B1. Original Literature Search Strategies

PubMed Screening, 8/3/2020

Search Number	Query	Filters	Results
1	"Diabetes Mellitus, Type 2"[Mesh] OR "Glucose Tolerance"[Mesh] OR "glucose tolerance"[All Fields] OR "impaired glucose tolerance"[All Fields] OR dysglycemia[tiab] OR IGT OR "impaired fasting glucose" OR IFG OR "Glucose Intolerance"[MeSH] OR "glucose intolerance"[All Fields] OR "Prediabetic State"[MeSH] OR "prediabetic state"[All Fields] OR prediabet* OR "pre diabetes"[All Fields] OR "diabetes mellitus type 2"[All Fields] OR "type 2 diabetes mellitus"[All Fields]		213,359
2	"Blood Glucose"[Mesh] OR "blood glucose"[tiab] OR "Glucose Tolerance Test"[Mesh] OR OGTT[tiab] OR "glucose tolerance test"[ti] OR "Glycated Hemoglobin A"[Mesh] OR "hemoglobin A1c" OR HbA1c OR "fasting plasma glucose"[tiab] OR "oral glucose tolerance"[tiab]		253,967
3	#1 AND #2		97,474
4	"Mass Screening"[Mesh] OR screen*[tiab]		796,716
5	#3 AND #4		6,429
6	#5 NOT (gestation* OR Pregnancy[Mesh])		4,708
7	#5 NOT (gestation* OR Pregnancy[Mesh])	English	4,331
8	#5 NOT (gestation* OR Pregnancy[Mesh])	English, Child: birth-18 years	698
9	adolescen*[tiab] OR boys[tiab] OR child*[tiab] OR children[tiab] OR girls[tiab] OR pediatric[tiab] OR paediatric*[tiab] OR teen[tiab] OR teens[tiab] OR teenage[tiab] OR teenaged[tiab] OR teenager*[tiab] OR toddler*[tiab]		1,766,063
10	#7 AND #9		345
11	#8 OR #10		759
12	(#11 AND humans[mesh:noexp]) OR (#11 NOT animals[mesh:noexp])		758
13	("review"[Publication Type] AND "systematic"[tiab]) OR "systematic review"[All Fields] OR ("review literature as topic"[MeSH] AND "systematic"[tiab]) OR "meta-analysis"[Publication Type] OR "meta-analysis as topic"[MeSH Terms] OR "meta-analysis"[All Fields] OR "meta synthesis"[ti] OR "systematic literature review"[ti] OR "this systematic review"[tw] OR "cochrane database syst rev"[ta]		323,325
14	#12 AND #13		**11**
15	"controlled clinical trial"[publication type] OR "Randomized Controlled Trial"[Publication Type] OR "Single-Blind Method"[MeSH] OR "Double-Blind Method"[MeSH] OR "Random Allocation"[MeSH] OR (controlled[tiab] AND trial[tiab]) OR groups [tiab] OR placebo [tiab] OR randomised [tiab] OR randomized [tiab] OR randomly [tiab] OR trial [tiab]		3,141,667
16	#12 AND #15		**206**
17	#12 AND "Case-Control Studies"[MeSH]		74
18	"Cohort Studies"Mesh] OR "Epidemiologic Studies"[Mesh] OR "Follow-up Studies"[Mesh] OR "prospective cohort" OR "prospective studies"[MeSH] OR (prospective*[All Fields] AND cohort[All Fields] AND (study[All Fields] OR studies[All Fields]))		2,550,540
19	#12 AND #18		284
20	"Evaluation Study"[pt] OR "Comparative Study"[pt]		2,062,504
21	#12 AND #20		70
22	#17 OR #19 OR #21		**324**

Appendix B1. Original Literature Search Strategies

PubMed Interventions, 8/3/2020

Search Number	Query	Filters	Results
1	"Diabetes Mellitus, Type 2"[Mesh] OR "Glucose Tolerance"[Mesh] OR "glucose tolerance"[All Fields] OR "impaired glucose tolerance"[All Fields] OR dysglycemia[tiab] OR IGT OR "impaired fasting glucose" OR IFG OR "Glucose Intolerance"[MeSH] OR "glucose intolerance"[All Fields] OR "Prediabetic State"[MeSH] OR "prediabetic state"[All Fields] OR prediabet* OR "pre diabetes"[All Fields] OR "diabetes mellitus type 2"[All Fields] OR "type 2 diabetes mellitus"[All Fields]		213,359
2	Actos[tiab] OR Albiglutide[tiab] OR Amaryl[tiab] OR Biguanides[Mesh] OR Biguanides[tiab] OR Bydureon[tiab] OR Byetta[tiab] OR DiaBeta[tiab] OR "Dipeptidyl-Peptidase IV Inhibitors"[Mesh] OR "Dipeptidyl-Peptidase IV Inhibitors"[Pharmacological Action] OR "Dipeptidyl peptidase IV inhibitor"[tiab] OR "Dipeptidyl peptidase IV inhibitors"[tiab] OR dulaglutide[Supplementary Concept] OR dulaglutide[tiab] OR exenatide[Supplementary Concept] OR Exenatide[tiab] OR Fortamet[tiab] OR Gliclazide[Mesh] OR Gliclazide[tiab] OR glimepiride[tiab] OR Glipizide[Mesh] OR glipizide[tiab] OR "GLP-1 receptor agonist"[tiab] OR "GLP-1 receptor agonists"[tiab] OR "Glucagon-like peptide-1 receptor agonist"[tiab] OR "Glucagon-like peptide-1 receptor agonists"[tiab] OR Glucophage[tiab] OR Glucotrol[tiab] OR "Glucotrol XL"[tiab] OR Glumetza[tiab] OR Glyburide[Mesh] OR glyburide[tiab] OR "Glynase PresTab"[tiab] OR Linagliptin[Mesh] OR Linagliptin[tiab] OR Liraglutide[Mesh] OR liraglutide[tiab] OR lixisenatide[Supplementary Concept] OR lixisenatide[tiab] OR Lyxumia[tiab] OR Meglitinides[tiab] OR Metformin[Mesh] OR Metformin[tiab] OR Micronase[tiab] OR nateglinide[Supplementary Concept] OR Nateglinide[tiab] OR Ozempic[tiab] OR pioglitazone[Supplementary Concept] OR Pioglitazone[tiab] OR Prandin[tiab] OR Repaglinide[tiab] OR rosiglitazone[Supplementary Concept] OR Rosiglitazone[tiab] OR Saxagliptin[tiab] OR semaglutide[Supplementary Concept] OR semaglutide[tiab] OR Sitagliptin[tiab] OR "Sitagliptin Phosphate"[Mesh] OR "Sitagliptin Phosphate, Metformin Hydrochloride Drug Combination"[Mesh] OR "Sulfonylurea Compounds"[Mesh] OR Starlix[tiab] OR Sulfonylureas[tiab] OR Tanzeum[tiab] OR Thiazolidinediones[Mesh] OR Thiazolidinediones[tiab] OR Tolazamide[Mesh] OR Tolazamide[tiab] OR Tolbutamide[Mesh] OR tolbutamide[tiab] OR Trulicity[tiab] OR TZDs[tiab] OR Victoza[tiab] OR vildagliptin[Supplementary Concept] OR vildagliptin[tiab]		78,684
3	#1 AND #2		23,456

Appendix B1. Original Literature Search Strategies

Search Number	Query	Filters	Results
4	advice[tiab] OR "Behavior Therapy"[Mesh] OR "behavior therapy"[tiab] OR (behavior*[tiab] AND therap*[tiab]) OR (behavior*[tiab] AND chang*[tiab]) OR (behavior*[tiab] AND modification*[tiab]) OR "Caloric Restriction"[Mesh] OR ((child*[tiab] AND parent*[tiab]) and therap*[tiab]) OR Counseling[Mesh] OR counsel*[tiab] OR "cognitive behavior"[tiab] OR "cognitive behavioral"[tiab] OR "cognitive therap*"[tiab] OR CBT[ti] OR "Diabetes Prevention Program"[tiab] OR "Diabetes Prevention Programme"[tiab] OR DPP[tiab] OR ("Diabetes Prevention"[tiab] AND (program*[tiab] OR stud*[tiab] OR trial*[tiab])) OR diet[ti] OR "Diet, Carbohydrate-Restricted"[Mesh] OR "Diet, Fat-Restricted"[Mesh] OR "Diet, Mediterranean"[Mesh] OR "Diet, Reducing"[Mesh] OR "Diet Therapy"[Mesh] OR dietary[ti] OR "Directive Counseling"[Mesh] OR Exercise[Mesh] OR exercise[ti] OR "Exercise Therapy"[Mesh] OR "family intervention*"[tiab] OR "family therap*"[tiab] OR "Feedback, Psychological"[Mesh] OR "group therap*"[tiab] OR "Health Behavior"[Majr] OR "health behavior"[tiab] OR "health behaviors"[tiab] OR "health behavioral"[tiab] "health behaviours"[tiab] OR "health behaviour"[tiab] OR "Health Education"[Mesh] OR "Health Education as Topic"[Mesh] OR "health education"[tiab] OR "Health Promotion"[Majr] OR "health promotion"[tiab] OR "Life Style"[Mesh] OR lifestyle[tiab] OR "life style"[tiab] OR "Lifestyle Intervention"[Mesh] OR "Motivational Interviewing"[Mesh] OR "motivational interviewing"[tiab] OR "non pharmacologic intervention"[tiab] OR "nonpharmacologic intervention"[tiab] OR "parent* intervention*"[tiab] OR "Patient Education as Topic"[Mesh] OR "patient education"[tiab] OR "physical activity"[ti] OR "physically active"[ti] OR "psychological feedback"[tiab] OR "Risk Reduction Behavior"[Mesh] OR "Risk Reduction Behavior"[tiab] OR "Weight Loss"[Mesh] OR "Weight Reduction Programs"[Mesh]		507,576
5	#1 AND #4		19,500
6	#3 OR #5		41,039
7	(#6 AND Humans[Mesh:NOEXP]) OR (#6 NOT Animals[Mesh:NOEXP])		38,332
8	(#6 AND Humans[Mesh:NOEXP]) OR (#6 NOT Animals[Mesh:NOEXP])	English	34,717
9	(#6 AND Humans[Mesh:NOEXP]) OR (#6 NOT Animals[Mesh:NOEXP])	English, Child: birth-18 years	2,985
10	adolescen*[tiab] OR boys[tiab] OR child*[tiab] OR children[tiab] OR girls[tiab] OR pediatric[tiab] OR paediatric*[tiab] OR teen[tiab] OR teens[tiab] OR teenage[tiab] OR teenaged[tiab] OR teenager*[tiab] OR toddler*[tiab]		1,766,063
11	#8 AND #10		1,507
12	#9 OR #11		3,429
13	address[pt] OR "autobiography"[pt] OR "bibliography"[pt] OR "biography"[pt] OR "case report"[tw] OR "case reports"[tw] OR "case series"[tw] OR "comment"[pt] OR "comment on"[All Fields] OR congress[pt] OR "cross-sectional"[tw] OR "dictionary"[pt] OR "directory"[pt] OR "editorial"[pt] OR "festschrift"[pt] OR "historical article"[pt] OR "interview"[pt] OR lecture[pt] OR "legal case"[pt] OR "legislation"[pt] OR letter[pt] OR "news"[pt] OR "newspaper article"[pt] OR "patient education handout"[pt] OR "periodical index"[pt] OR "retrospective cohort"[tw] OR ("Animals"[Mesh] NOT "Humans"[Mesh]) OR rats[tw] OR cow[tw] OR cows[tw] OR chicken[tw] OR chickens[tw] OR horse[tw] OR horses[tw] OR mice[tw] OR mouse[tw] OR bovine[tw] OR sheep OR ovine OR murine OR murinae		10,840,629
14	#12 NOT #13		2,846

Appendix B1. Original Literature Search Strategies

Search Number	Query	Filters	Results
15	#14 NOT (gestation* OR Pregnancy[Mesh])		2,500
16	"controlled clinical trial"[publication type] OR "Randomized Controlled Trial"[Publication Type] OR "Single-Blind Method"[MeSH] OR "Double-Blind Method"[MeSH] OR "Random Allocation"[MeSH] OR (controlled[tiab] AND trial[tiab]) OR groups [tiab] OR placebo [tiab] OR randomised [tiab] OR randomized [tiab] OR randomly [tiab] OR trial [tiab]		3,141,667
17	#15 AND #16		**999**
18	("review"[Publication Type] AND "systematic"[tiab]) OR "systematic review"[All Fields] OR ("review literature as topic"[MeSH] AND "systematic"[tiab]) OR "meta-analysis"[Publication Type] OR "meta-analysis as topic"[MeSH Terms] OR "meta-analysis"[All Fields] OR "meta synthesis"[ti] OR "systematic literature review"[ti] OR "this systematic review"[tw] OR "cochrane database syst rev"[ta]		323,325
19	#15 AND #18		**76**
20	#15 AND "Case-Control Studies"[MeSH]		**188**
21	#15 AND ("Cohort Studies"[Mesh:NOEXP] OR "Epidemiologic Studies"[Mesh] OR "Follow-up Studies"[Mesh] OR "prospective cohort" OR "prospective studies"[MeSH] OR (prospective*[All Fields] AND cohort[All Fields] AND (study[All Fields] OR studies[All Fields])))		**519**
22	#15 AND ("Evaluation Study"[pt] OR "Comparative Study"[pt])		**252**

Cochrane Library Screening, 8/3/2020

ID	Search	Hits
#1	[mh "Diabetes Mellitus, Type 2"] OR [mh "Glucose Tolerance"] OR "glucose tolerance" OR "impaired glucose tolerance" OR dysglycemia:ti,ab OR IGT OR "impaired fasting glucose" OR IFG OR [mh "Glucose Intolerance"] OR "glucose intolerance" OR [mh "Prediabetic State"] OR "prediabetic state" OR prediabet* OR "pre diabetes" OR "diabetes mellitus type 2" OR "type 2 diabetes mellitus"	34233
#2	[mh "Blood Glucose"] OR "blood glucose":ti,ab OR [mh "Glucose Tolerance Test"] OR OGTT:ti,ab OR "glucose tolerance test":ti OR [mh "Glycated Hemoglobin A"] OR "hemoglobin A1c" OR HbA1c OR "fasting plasma glucose":ti,ab OR "oral glucose tolerance":ti,ab	45778
#3	#1 AND #2	19244
#4	[mh "Mass Screening"] OR screen*:ti,ab	67390
#5	#3 AND #4	1702
#6	#5 NOT (gestation* OR [mh Pregnancy])	1521
#7	adolescen*:ti,ab,kw OR boys:ti,ab,kw OR child*:ti,ab,kw OR children:ti,ab,kw OR girls:ti,ab,kw OR pediatric:ti,ab,kw OR paediatric*:ti,ab,kw OR teen:ti,ab,kw OR teens:ti,ab,kw OR teenage:ti,ab,kw OR teenaged:ti,ab,kw OR teenager*:ti,ab,kw OR toddler*:ti,ab,kw	248461
#8	#6 AND #7	**197**

Appendix B1. Original Literature Search Strategies

Cochrane Library Interventions, 8/3/2020

ID	Search	Hits
#1	[mh "Diabetes Mellitus, Type 2"] OR [mh "Glucose Tolerance"] OR "glucose tolerance" OR "impaired glucose tolerance" OR dysglycemia:ti,ab OR IGT OR "impaired fasting glucose" OR IFG OR [mh "Glucose Intolerance"] OR "glucose intolerance" OR [mh "Prediabetic State"] OR "prediabetic state" OR prediabet* OR "pre diabetes" OR "diabetes mellitus type 2" OR "type 2 diabetes mellitus"	34233
#2	Actos:ti,ab OR Albiglutide:ti,ab OR Amaryl:ti,ab OR [mh Biguanides] OR Biguanides:ti,ab OR Bydureon:ti,ab OR Byetta:ti,ab OR DiaBeta:ti,ab OR [mh "Dipeptidyl-Peptidase IV Inhibitors"] OR "Dipeptidyl peptidase IV inhibitor":ti,ab OR "Dipeptidyl peptidase IV inhibitors":ti,ab OR dulaglutide:ti,ab OR Exenatide:ti,ab OR Fortamet:ti,ab OR [mh Gliclazide] OR Gliclazide:ti,ab OR glimepiride:ti,ab OR [mh Glipizide] OR glipizide:ti,ab OR "GLP-1 receptor agonist":ti,ab OR "GLP-1 receptor agonists":ti,ab OR "Glucagon-like peptide-1 receptor agonist":ti,ab OR "Glucagon-like peptide-1 receptor agonists":ti,ab OR Glucophage:ti,ab OR Glucotrol:ti,ab OR "Glucotrol XL":ti,ab OR Glumetza:ti,ab OR [mh Glyburide] OR glyburide:ti,ab OR "Glynase PresTab":ti,ab OR [mh Linagliptin] OR Linagliptin:ti,ab OR [mh Liraglutide] OR liraglutide:ti,ab OR lixisenatide:ti,ab OR Lyxumia:ti,ab OR Meglitinides:ti,ab OR [mh Metformin] OR Metformin:ti,ab OR Micronase:ti,ab OR Nateglinide:ti,ab OR Ozempic:ti,ab OR Pioglitazone:ti,ab OR Prandin:ti,ab OR Repaglinide:ti,ab OR Rosiglitazone:ti,ab OR Saxagliptin:ti,ab OR semaglutide:ti,ab OR Sitagliptin:ti,ab OR [mh "Sitagliptin Phosphate"] OR [mh "Sitagliptin Phosphate, Metformin Hydrochloride Drug Combination"] OR [mh "Sulfonylurea Compounds"] OR Starlix:ti,ab OR Sulfonylureas:ti,ab OR Tanzeum:ti,ab OR [mh Thiazolidinediones] OR Thiazolidinediones:ti,ab OR [mh Tolazamide] OR Tolazamide:ti,ab OR [mh Tolbutamide] OR tolbutamide:ti,ab OR Trulicity:ti,ab OR TZDs:ti,ab OR Victoza:ti,ab OR vildagliptin:ti,ab	21765
#3	#1 AND #2	9227
#4	advice:ti,ab OR [mh "Behavior Therapy"] OR "behavior therapy":ti,ab OR (behavior*:ti,ab AND therap*:ti,ab) OR (behavior*:ti,ab AND chang*:ti,ab) OR (behavior*:ti,ab AND modification*:ti,ab) OR [mh "Caloric Restriction"] OR ((child*:ti,ab AND parent*:ti,ab) and therap*:ti,ab) OR [mh Counseling] OR counsel*:ti,ab OR "cognitive behavior":ti,ab OR "cognitive behavioral":ti,ab OR "cognitive therap*":ti,ab OR CBT:ti OR "Diabetes Prevention Program":ti,ab OR "Diabetes Prevention Programme":ti,ab OR DPP:ti,ab OR ("Diabetes Prevention":ti,ab AND (program*:ti,ab OR stud*:ti,ab OR trial*:ti,ab)) OR diet:ti OR [mh "Diet, Carbohydrate-Restricted"] OR [mh "Diet, Fat-Restricted"] OR [mh "Diet, Mediterranean"] OR [mh "Diet, Reducing"] OR [mh "Diet Therapy"] OR dietary:ti OR [mh "Directive Counseling"] OR [mh Exercise] OR exercise:ti OR [mh "Exercise Therapy"] OR "family intervention*":ti,ab OR "family therap*":ti,ab OR [mh "Feedback, Psychological"] OR "group therap*":ti,ab OR [mh ^"Health Behavior"] OR "health behavior":ti,ab OR "health behaviors":ti,ab OR "health behavioral":ti,ab "health behaviours":ti,ab OR "health behaviour":ti,ab OR [mh "Health Education"] OR [mh "Health Education as Topic"] OR "health education":ti,ab OR [mh ^"Health Promotion"] OR "health promotion":ti,ab OR [mh "Life Style"] OR lifestyle:ti,ab OR "life style":ti,ab OR [mh "Lifestyle Intervention"] OR [mh "Motivational Interviewing"] OR "motivational interviewing":ti,ab OR "non pharmacologic intervention":ti,ab OR "nonpharmacologic intervention":ti,ab OR "parent* intervention*":ti,ab OR [mh "Patient Education as Topic"] OR "patient education":ti,ab OR "physical activity":ti OR "physically active":ti OR "psychological feedback":ti,ab OR [mh "Risk Reduction Behavior"] OR "Risk Reduction Behavior":ti,ab OR [mh "Weight Loss"] OR [mh "Weight Reduction Programs"]	181889
#5	#1 AND #4	8940
#6	#3 OR #5	16313
#7	#6 NOT ([mh animals] NOT [mh humans])	16313
#8	adolescen*:ti,ab,kw OR boys:ti,ab,kw OR child*:ti,ab,kw OR children:ti,ab,kw OR girls:ti,ab,kw OR pediatric:ti,ab,kw OR paediatric*:ti,ab,kw OR teen:ti,ab,kw OR teens:ti,ab,kw OR teenage:ti,ab,kw OR teenaged:ti,ab,kw OR teenager*:ti,ab,kw OR toddler*:ti,ab,kw	248461
#9	#7 AND #8	1360
#10	#9 NOT (gestation* OR [mh Pregnancy])	**1162**

Appendix B1. Original Literature Search Strategies

PubMed Interventions Addendum #1, 8/4/2020

Search Number	Query	Filters	Results
1	"Diabetes Mellitus, Type 2"[Mesh] OR "Glucose Tolerance"[Mesh] OR "glucose tolerance"[All Fields] OR "impaired glucose tolerance"[All Fields] OR dysglycemia[tiab] OR IGT OR "impaired fasting glucose" OR IFG OR "Glucose Intolerance"[MeSH] OR "glucose intolerance"[All Fields] OR "Prediabetic State"[MeSH] OR "prediabetic state"[All Fields] OR prediabet* OR "pre diabetes"[All Fields] OR "diabetes mellitus type 2"[All Fields] OR "type 2 diabetes mellitus"[All Fields]		213,453
2	advice[tiab] OR "Behavior Therapy"[Mesh] OR "behavior therapy"[tiab] OR (behavior*[tiab] AND therap*[tiab]) OR (behavior*[tiab] AND chang*[tiab]) OR (behavior*[tiab] AND modification*[tiab]) OR "Caloric Restriction"[Mesh] OR ((child*[tiab] AND parent*[tiab]) and therap*[tiab]) OR Counseling[Mesh] OR counsel*[tiab] OR "cognitive behavior"[tiab] OR "cognitive behavioral"[tiab] OR "cognitive therap*"[tiab] OR CBT[ti] OR "Diabetes Prevention Program"[tiab] OR "Diabetes Prevention Programme"[tiab] OR DPP[tiab] OR ("Diabetes Prevention"[tiab] AND (program*[tiab] OR stud*[tiab] OR trial*[tiab])) OR diet[ti] OR "Diet, Carbohydrate-Restricted"[Mesh] OR "Diet, Fat-Restricted"[Mesh] OR "Diet, Mediterranean"[Mesh] OR "Diet, Reducing"[Mesh] OR "Diet Therapy"[Mesh] OR dietary[ti] OR "Directive Counseling"[Mesh] OR Exercise[Mesh] OR exercise[ti] OR "Exercise Therapy"[Mesh] OR "family intervention*"[tiab] OR "family therap*"[tiab] OR "Feedback, Psychological"[Mesh] OR "group therap*"[tiab] OR "Health Behavior"[Majr] OR "health behavior"[tiab] OR "health behaviors"[tiab] OR "health behavioral"[tiab] OR "health behaviours"[tiab] OR "health behaviour"[tiab] OR "Health Education"[Mesh] OR "Health Education as Topic"[Mesh] OR "health education"[tiab] OR "Health Promotion"[Majr] OR "health promotion"[tiab] OR "Life Style"[Mesh] OR lifestyle[tiab] OR "life style"[tiab] OR "Lifestyle Intervention"[Mesh] OR "Motivational Interviewing"[Mesh] OR "motivational interviewing"[tiab] OR "non pharmacologic intervention"[tiab] OR "nonpharmacologic intervention"[tiab] OR "parent* intervention*"[tiab] OR "Patient Education as Topic"[Mesh] OR "patient education"[tiab] OR "physical activity"[ti] OR "physically active"[ti] OR "psychological feedback"[tiab] OR "Risk Reduction Behavior"[Mesh] OR "Risk Reduction Behavior"[tiab] OR "Weight Loss"[Mesh] OR "Weight Reduction Programs"[Mesh]		1,475,119
3	#1 AND #2		37,820
4	(#3 AND Humans[Mesh:NOEXP]) OR (#3 NOT Animals[Mesh:NOEXP])		33,767
5	(#3 AND Humans[Mesh:NOEXP]) OR (#3 NOT Animals[Mesh:NOEXP])	English	31,056
6	(#3 AND Humans[Mesh:NOEXP]) OR (#3 NOT Animals[Mesh:NOEXP])	English, Child: birth-18 years	3,077
7	adolescen*[tiab] OR boys[tiab] OR child*[tiab] OR children[tiab] OR girls[tiab] OR pediatric[tiab] OR paediatric*[tiab] OR teen[tiab] OR teens[tiab] OR teenage[tiab] OR teenaged[tiab] OR teenager*[tiab] OR toddler*[tiab]		1,766,520
8	#5 AND #7		1,778
9	#6 OR #8		3,617
10	address[pt] OR "autobiography"[pt] OR "bibliography"[pt] OR "biography"[pt] OR "case report"[tw] OR "case reports"[tw] OR "case series"[tw] OR "comment"[pt] OR "comment on"[All Fields] OR congress[pt] OR "cross-sectional"[tw] OR "dictionary"[pt] OR "directory"[pt] OR "editorial"[pt] OR "festschrift"[pt] OR "historical article"[pt] OR "interview"[pt] OR lecture[pt] OR "legal case"[pt] OR "legislation"[pt] OR letter[pt] OR "news"[pt] OR "newspaper article"[pt] OR "patient education handout"[pt] OR "periodical index"[pt] OR "retrospective cohort"[tw] OR ("Animals"[Mesh] NOT "Humans"[Mesh]) OR rats[tw] OR cow[tw] OR cows[tw] OR chicken[tw] OR chickens[tw] OR horse[tw] OR horses[tw] OR mice[tw] OR mouse[tw] OR bovine[tw] OR sheep OR ovine OR murine OR murinae		10,842,788

Appendix B1. Original Literature Search Strategies

Search Number	Query	Filters	Results
11	#9 NOT #10		2,978
12	#11 NOT (gestation* OR Pregnancy[Mesh])		2,547
13	("review"[Publication Type] AND "systematic"[tiab]) OR "systematic review"[All Fields] OR ("review literature as topic"[MeSH] AND "systematic"[tiab]) OR "meta-analysis"[Publication Type] OR "meta-analysis as topic"[MeSH Terms] OR "meta-analysis"[All Fields] OR "meta synthesis"[ti] OR "systematic literature review"[ti] OR "this systematic review"[tw] OR "cochrane database syst rev"[ta]		323,538
14	#12 AND #13		**88**
15	"controlled clinical trial"[publication type] OR "Randomized Controlled Trial"[Publication Type] OR "Single-Blind Method"[MeSH] OR "Double-Blind Method"[MeSH] OR "Random Allocation"[MeSH] OR (controlled[tiab] AND trial[tiab]) OR groups [tiab] OR placebo [tiab] OR randomised [tiab] OR randomized [tiab] OR randomly [tiab] OR trial [tiab]		3,142,672
16	#12 AND #15		**918**
17	#12 AND "Case-Control Studies"[MeSH]		**165**
18	#12 AND ("Cohort Studies"[Mesh:NOEXP] OR "Epidemiologic Studies"[Mesh] OR "Follow-up Studies"[Mesh] OR "prospective cohort" OR "prospective studies"[MeSH] OR (prospective*[All Fields] AND cohort[All Fields] AND (study[All Fields] OR studies[All Fields])))		**496**
19	#12 AND ("Evaluation Study"[pt] OR "Comparative Study"[pt])		**224**

Appendix B1. Original Literature Search Strategies

Cochrane Library Interventions Addendum #1, 8/4/2020

ID	Search	Hits
#1	[mh “Diabetes Mellitus, Type 2”] OR [mh “Glucose Tolerance”] OR “glucose tolerance” OR “impaired glucose tolerance” OR dysglycemia:ti,ab OR IGT OR “impaired fasting glucose” OR IFG OR [mh “Glucose Intolerance”] OR “glucose intolerance” OR [mh “Prediabetic State”] OR “prediabetic state” OR prediabet* OR “pre diabetes” OR “diabetes mellitus type 2” OR “type 2 diabetes mellitus”	34233
#2	advice:ti,ab OR [mh “Behavior Therapy”] OR “behavior therapy”:ti,ab OR (behavior*:ti,ab AND therap*:ti,ab) OR (behavior*:ti,ab AND chang*:ti,ab) OR (behavior*:ti,ab AND modification*:ti,ab) OR [mh “Caloric Restriction”] OR ((child*:ti,ab AND parent*:ti,ab) and therap*:ti,ab) OR [mh Counseling] OR counsel*:ti,ab OR “cognitive behavior”:ti,ab OR “cognitive behavioral”:ti,ab OR “cognitive therap*”:ti,ab OR CBT:ti OR “Diabetes Prevention Program”:ti,ab OR “Diabetes Prevention Programme”:ti,ab OR DPP:ti,ab OR (“Diabetes Prevention”:ti,ab AND (program*:ti,ab OR stud*:ti,ab OR trial*:ti,ab)) OR diet:ti OR [mh “Diet, Carbohydrate-Restricted”] OR [mh “Diet, Fat-Restricted”] OR [mh “Diet, Mediterranean”] OR [mh “Diet, Reducing”] OR [mh “Diet Therapy”] OR dietary:ti OR [mh “Directive Counseling”] OR [mh Exercise] OR exercise:ti OR [mh “Exercise Therapy”] OR “family intervention*”:ti,ab OR “family therap*”:ti,ab OR [mh “Feedback, Psychological”] OR “group therap*”:ti,ab OR [mh ^”Health Behavior”] OR “health behavior”:ti,ab OR “health behaviors”:ti,ab OR “health behavioral”:ti,ab OR “health behaviours”:ti,ab OR “health behaviour”:ti,ab OR [mh “Health Education”] OR [mh “Health Education as Topic”] OR “health education”:ti,ab OR [mh ^”Health Promotion”] OR “health promotion”:ti,ab OR [mh “Life Style”] OR lifestyle:ti,ab OR “life style”:ti,ab OR [mh “Lifestyle Intervention”] OR [mh “Motivational Interviewing”] OR “motivational interviewing”:ti,ab OR “non pharmacologic intervention”:ti,ab OR “nonpharmacologic intervention”:ti,ab OR “parent* intervention*”:ti,ab OR [mh “Patient Education as Topic”] OR “patient education”:ti,ab OR “physical activity”:ti OR “physically active”:ti OR “psychological feedback”:ti,ab OR [mh “Risk Reduction Behavior”] OR “Risk Reduction Behavior”:ti,ab OR [mh “Weight Loss”] OR [mh “Weight Reduction Programs”]	181924
#3	#1 AND #2	8941
#4	#3 NOT ([mh animals] NOT [mh humans])	8941
#5	adolescen*:ti,ab,kw OR boys:ti,ab,kw OR child*:ti,ab,kw OR children:ti,ab,kw OR girls:ti,ab,kw OR pediatric:ti,ab,kw OR paediatric*:ti,ab,kw OR teen:ti,ab,kw OR teens:ti,ab,kw OR teenage:ti,ab,kw OR teenaged:ti,ab,kw OR teenager*:ti,ab,kw OR toddler*:ti,ab,kw	248464
#6	#4 AND #5	844
#7	#6 NOT (gestation* OR [mh Pregnancy])	**700**

Appendix B1. Original Literature Search Strategies

PubMed Interventions Addendum #2, 8/19/2020

Search Number	Query	Filters	Results
1	"Diabetes Mellitus, Type 2"[Mesh] OR "Glucose Tolerance"[Mesh] OR "Glucose Intolerance"[MeSH] OR "Prediabetic State"[MeSH]		143,540
2	("diabetes mellitus type 2"[All Fields] OR dysglycemia[tiab] OR "glucose tolerance"[All Fields] OR "glucose intolerance"[All Fields] OR IGT OR "impaired fasting glucose" OR IFG OR "impaired glucose tolerance"[All Fields] OR "prediabetic state"[All Fields] OR prediabet* OR "pre diabetes"[All Fields] OR "type 2 diabetes mellitus"[All Fields]) NOT (Medline[sb])		17,008
3	#1 OR #2		160,548
5	#3 NOT ("Diabetes Mellitus, Type 1"[Mesh] OR "diabetes mellitus type 1" OR "type 1 diabetes")		143,845
6	(hypoglycemic agents[mh] OR "Hypoglycemic Agents" [Pharmacological Action]) OR ("hypoglycemic agent*"[tiab] NOT Medline[sb])		259,681
7	#5 AND #6		41,304
8	(Insulin[Mesh] OR "Insulin, Long-Acting"[Mesh] OR "Insulin, Isophane"[Mesh] OR "Insulin Glargine"[Mesh]) OR (insulin[tiab] NOT medline[sb])		219,909
9	#5 AND #8		28,029
10	#7 OR #9		47,259
11	(#10 AND Humans[Mesh:NOEXP]) OR (#10 NOT Animals[Mesh:NOEXP])		42,806
12	(#10 AND Humans[Mesh:NOEXP]) OR (#10 NOT Animals[Mesh:NOEXP])	English	39,189
13	(#10 AND Humans[Mesh:NOEXP]) OR (#10 NOT Animals[Mesh:NOEXP])	English, Child: birth-18 years	1,942
14	(adolescen*[tiab] OR boys[tiab] OR child*[tiab] OR children[tiab] OR girls[tiab] OR pediatric[tiab] OR paediatric*[tiab] OR teen[tiab] OR teens[tiab] OR teenage[tiab] OR teenaged[tiab] OR teenager*[tiab] OR toddler*[tiab]) NOT Medline[sb]		203,552
15	#12 AND #14		305
16	#13 OR #15		2,247
17	address[pt] OR "autobiography"[pt] OR "bibliography"[pt] OR "biography"[pt] OR "case report"[tw] OR "case reports"[tw] OR "case series"[tw] OR "comment"[pt] OR "comment on"[All Fields] OR congress[pt] OR "cross-sectional"[tw] OR "dictionary"[pt] OR "directory"[pt] OR "editorial"[pt] OR "festschrift"[pt] OR "historical article"[pt] OR "interview"[pt] OR lecture[pt] OR "legal case"[pt] OR "legislation"[pt] OR letter[pt] OR "news"[pt] OR "newspaper article"[pt] OR "patient education handout"[pt] OR "periodical index"[pt] OR "retrospective cohort"[tw] OR ("Animals"[Mesh] NOT "Humans"[Mesh]) OR rats[tw] OR cow[tw] OR cows[tw] OR chicken[tw] OR chickens[tw] OR horse[tw] OR horses[tw] OR mice[tw] OR mouse[tw] OR bovine[tw] OR sheep OR ovine OR murine OR murinae		10,860,747
18	#16 NOT #17		1,767
19	#15 NOT (gestation* OR Pregnancy[Mesh])		265
20	"controlled clinical trial"[publication type] OR "Randomized Controlled Trial"[Publication Type] OR "Single-Blind Method"[MeSH] OR "Double-Blind Method"[MeSH] OR "Random Allocation"[MeSH] OR (controlled[tiab] AND trial[tiab]) OR groups [tiab] OR placebo [tiab] OR randomised [tiab] OR randomized [tiab] OR randomly [tiab] OR trial [tiab]		3,151,828
21	#19 AND #20		**77**

Appendix B1. Original Literature Search Strategies

Search Number	Query	Filters	Results
22	("review"[Publication Type] AND "systematic"[tiab]) OR "systematic review"[All Fields] OR ("review literature as topic"[MeSH] AND "systematic"[tiab]) OR "meta-analysis"[Publication Type] OR "meta-analysis as topic"[MeSH Terms] OR "meta-analysis"[All Fields] OR "meta synthesis"[ti] OR "systematic literature review"[ti] OR "this systematic review"[tw] OR "cochrane database syst rev"[ta]		325,513
23	#19 AND #22		**10**
24	#19 AND "Case-Control Studies"[MeSH]		0
25	#19 AND ("Cohort Studies"[Mesh:NOEXP] OR "Epidemiologic Studies"[Mesh] OR "Follow-up Studies"[Mesh] OR "prospective cohort" OR "prospective studies"[MeSH] OR (prospective*[All Fields] AND cohort[All Fields] AND (study[All Fields] OR studies[All Fields])))		**7**
26	#19 AND ("Evaluation Study"[pt] OR "Comparative Study"[pt])		0

Cochrane Library Interventions Addendum #2, 8/20/2020

ID	Search	Hits
#1	[mh "Diabetes Mellitus, Type 2"] OR [mh "Glucose Tolerance"] OR "glucose tolerance" OR "impaired glucose tolerance" OR dysglycemia:ti,ab OR IGT OR "impaired fasting glucose" OR IFG OR [mh "Glucose Intolerance"] OR "glucose intolerance" OR [mh "Prediabetic State"] OR "prediabetic state" OR prediabet* OR "pre diabetes" OR "diabetes mellitus type 2" OR "type 2 diabetes mellitus"	34234
#2	#1 NOT ([mh "Diabetes Mellitus, Type 1"] OR "diabetes mellitus type 1":ti,ab,kw OR "type 1 diabetes":ti,ab,kw)	33099
#3	[mh "hypoglycemic agents"] OR "hypoglycemic agent*":ti,ab,kw	8175
#4	#2 AND #3	5220
#5	[mh Insulin] OR [mh "Insulin, Long-Acting"] OR [mh "Insulin, Isophane"] OR [mh "Insulin Glargine"] OR insulin:ti,ab,kw	58978
#6	#2 AND #5	18697
#7	#4 OR #6	20183
#8	adolescen*:ti,ab,kw OR boys:ti,ab,kw OR child*:ti,ab,kw OR children:ti,ab,kw OR girls:ti,ab,kw OR pediatric:ti,ab,kw OR paediatric*:ti,ab,kw OR teen:ti,ab,kw OR teens:ti,ab,kw OR teenage:ti,ab,kw OR teenaged:ti,ab,kw OR teenager*:ti,ab,kw OR toddler*:ti,ab,kw	248470
#9	#7 AND #8	1492
#10	#9 NOT (gestation* OR [mh Pregnancy])	**1322**

PubMed Interventions Addendum #3, 5/3/2021

Search Number	Query	Filters	Results
1	"Diabetes Mellitus, Type 2"[Mesh] OR "Glucose Intolerance"[MeSH] OR "Prediabetic State"[MeSH]		150,744
2	("diabetes mellitus type 2"[All Fields] OR dysglycemia[tiab] OR "glucose tolerance"[All Fields] OR "glucose intolerance"[All Fields] OR IGT OR "impaired fasting glucose" OR IFG OR "impaired glucose tolerance"[All Fields] OR "prediabetic state"[All Fields] OR prediabet* OR "pre diabetes"[All Fields] OR "type 2 diabetes mellitus"[All Fields]) NOT (Medline[sb])		18,860
3	#1 OR #2		169,604
4	#3 NOT ("Diabetes Mellitus, Type 1"[Mesh] OR "diabetes mellitus type 1" OR "type 1 diabetes")		152,347
5	(hypoglycemic agents[mh] OR "Hypoglycemic Agents" [Pharmacological Action]) OR ("hypoglycemic agent*"[tiab] NOT Medline[sb])		266,210
6	#4 AND #5		43,303
7	(Insulin[Mesh] OR "Insulin, Long-Acting"[Mesh] OR "Insulin, Isophane"[Mesh] OR "Insulin Glargine"[Mesh]) OR (insulin[tiab] NOT medline[sb])		225,745

Appendix B1. Original Literature Search Strategies

Search Number	Query	Filters	Results
8	#4 AND #7		29,218
9	#6 OR #8		49,756
10	(#9 AND Humans[Mesh:NOEXP]) OR (#9 NOT Animals[Mesh:NOEXP])		45,102
11	(#9 AND Humans[Mesh:NOEXP]) OR (#9 NOT Animals[Mesh:NOEXP])	English	41,438
12	(#9 AND Humans[Mesh:NOEXP]) OR (#9 NOT Animals[Mesh:NOEXP])	English, Child: birth-18 years	2,019
13	#11 AND ((adolescen*[tiab] OR boys[tiab] OR child*[tiab] OR children[tiab] OR girls[tiab] OR pediatric[tiab] OR paediatric*[tiab] OR teen[tiab] OR teens[tiab] OR teenage[tiab] OR teenaged[tiab] OR teenager*[tiab] OR toddler*[tiab]) NOT Medline[sb])		316
14	#12 NOT #13		2,019
15	address[pt] OR "autobiography"[pt] OR "bibliography"[pt] OR "biography"[pt] OR "case report"[tw] OR "case reports"[tw] OR "case series"[tw] OR "comment"[pt] OR "comment on"[All Fields] OR congress[pt] OR "cross-sectional"[tw] OR "dictionary"[pt] OR "directory"[pt] OR "editorial"[pt] OR "festschrift"[pt] OR "historical article"[pt] OR "interview"[pt] OR lecture[pt] OR "legal case"[pt] OR "legislation"[pt] OR letter[pt] OR "news"[pt] OR "newspaper article"[pt] OR "patient education handout"[pt] OR "periodical index"[pt] OR "retrospective cohort"[tw] OR ("Animals"[Mesh] NOT "Humans"[Mesh]) OR rats[tw] OR cow[tw] OR cows[tw] OR chicken[tw] OR chickens[tw] OR horse[tw] OR horses[tw] OR mice[tw] OR mouse[tw] OR bovine[tw] OR sheep OR ovine OR murine OR murinae		11,199,555
16	#14 NOT #15		1,608
17	#16 NOT (gestation* OR Pregnancy[Mesh])		1,461
18	"controlled clinical trial"[publication type] OR "Randomized Controlled Trial"[Publication Type] OR "Single-Blind Method"[MeSH] OR "Double-Blind Method"[MeSH] OR "Random Allocation"[MeSH] OR (controlled[tiab] AND trial[tiab]) OR groups [tiab] OR placebo [tiab] OR randomised [tiab] OR randomized [tiab] OR randomly [tiab] OR trial [tiab]		3,313,682
19	#17 AND #18		712
20	("review"[Publication Type] AND "systematic"[tiab]) OR "systematic review"[All Fields] OR ("review literature as topic"[MeSH] AND "systematic"[tiab]) OR "meta-analysis"[Publication Type] OR "meta-analysis as topic"[MeSH Terms] OR "meta-analysis"[All Fields] OR "meta synthesis"[ti] OR "systematic literature review"[ti] OR "this systematic review"[tw] OR "cochrane database syst rev"[ta]		362,198
21	#17 AND #20		32
22	#17 AND "Case-Control Studies"[MeSH]		176
23	#17 AND ("Cohort Studies"[Mesh:NOEXP] OR "Epidemiologic Studies"[Mesh] OR "Follow-up Studies"[Mesh] OR "prospective cohort" OR "prospective studies"[MeSH] OR (prospective*[All Fields] AND cohort[All Fields] AND (study[All Fields] OR studies[All Fields])))		397
24	#17 AND ("Evaluation Study"[pt] OR "Comparative Study"[pt])		198

Appendix B1. Original Literature Search Strategies

PubMed Screening, 5/3/2021

Search Number	Query	Filters	Results
1	"Diabetes Mellitus, Type 2"[Mesh] OR "glucose tolerance"[All Fields] OR "impaired glucose tolerance"[All Fields] OR dysglycemia[tiab] OR IGT OR "impaired fasting glucose" OR IFG OR "Glucose Intolerance"[MeSH] OR "glucose intolerance"[All Fields] OR "Prediabetic State"[MeSH] OR "prediabetic state"[All Fields] OR prediabet* OR "pre diabetes"[All Fields] OR "diabetes mellitus type 2"[All Fields] OR "type 2 diabetes mellitus"[All Fields]		224,878
2	"Blood Glucose"[Mesh] OR "blood glucose"[tiab] OR "Glucose Tolerance Test"[Mesh] OR OGTT[tiab] OR "glucose tolerance test"[ti] OR "Glycated Hemoglobin A"[Mesh] OR "hemoglobin A1c" OR HbA1c OR "fasting plasma glucose"[tiab] OR "oral glucose tolerance"[tiab]		264,030
3	#1 AND #2		101,723
4	#3 NOT ("Diabetes Mellitus, Type 1"[Mesh] OR "diabetes mellitus type 1" OR "type 1 diabetes")		94,239
5	#4 AND ("Mass Screening"[Mesh] OR screen*[tiab])		6,345
6	#5 NOT (gestation* OR Pregnancy[Mesh])		4,617
7	#5 NOT (gestation* OR Pregnancy[Mesh])	English	4,272
8	#5 NOT (gestation* OR Pregnancy[Mesh])	English, Child: birth-18 years	605
9	adolescen*[tiab] OR boys[tiab] OR child*[tiab] OR children[tiab] OR girls[tiab] OR pediatric[tiab] OR paediatric*[tiab] OR teen[tiab] OR teens[tiab] OR teenage[tiab] OR teenaged[tiab] OR teenager*[tiab] OR toddler*[tiab]		1,850,962
10	#7 AND #9		301
11	#8 OR #10		665
12	(#11 AND Humans[mesh:noexp]) OR (#11 NOT Animals[mesh:noexp])		664
13	(#11 AND Humans[mesh:noexp]) OR (#11 NOT Animals[mesh:noexp])	from 2019/8/3 - 3000/12/12	60
14	("review"[Publication Type] AND "systematic"[tiab]) OR "systematic review"[All Fields] OR ("review literature as topic"[MeSH] AND "systematic"[tiab]) OR "meta-analysis"[Publication Type] OR "meta-analysis as topic"[MeSH Terms] OR "meta-analysis"[All Fields] OR "meta synthesis"[ti] OR "systematic literature review"[ti] OR "this systematic review"[tw] OR "cochrane database syst rev"[ta]		362,198
15	#13 AND #14		2
16	"controlled clinical trial"[publication type] OR "Randomized Controlled Trial"[Publication Type] OR "Single-Blind Method"[MeSH] OR "Double-Blind Method"[MeSH] OR "Random Allocation"[MeSH] OR (controlled[tiab] AND trial[tiab]) OR groups [tiab] OR placebo [tiab] OR randomised [tiab] OR randomized [tiab] OR randomly [tiab] OR trial [tiab]		3,313,682
17	#13 AND #16		19
18	#13 AND "Case-Control Studies"[MeSH]		5
19	"Cohort Studies"[Mesh] OR "Epidemiologic Studies"[Mesh] OR "Follow-up Studies"[Mesh] OR "prospective cohort" OR "prospective studies"[MeSH] OR (prospective*[All Fields] AND cohort[All Fields] AND (study[All Fields] OR studies[All Fields]))		2,694,511
20	#13 AND #19		21
21	"Evaluation Study"[pt] OR "Comparative Study"[pt]		2,087,906
22	#13 AND #21		0

Appendix B1. Original Literature Search Strategies

PubMed Interventions, 5/3/2021

Search Number	Query	Filters	Results
1	"Diabetes Mellitus, Type 2"[Mesh] OR "Glucose Intolerance"[MeSH] OR "Prediabetic State"[MeSH]		150,744
2	("diabetes mellitus type 2"[All Fields] OR dysglycemia[tiab] OR "glucose tolerance"[All Fields] OR "glucose intolerance"[All Fields] OR IGT OR "impaired fasting glucose" OR IFG OR "impaired glucose tolerance"[All Fields] OR "prediabetic state"[All Fields] OR prediabet* OR "pre diabetes"[All Fields] OR "type 2 diabetes mellitus"[All Fields]) NOT (Medline[sb])		18,860
3	#1 OR #2		169,604
4	#3 NOT ("Diabetes Mellitus, Type 1"[Mesh] OR "diabetes mellitus type 1" OR "type 1 diabetes")		152,347
5	(hypoglycemic agents[mh] OR "Hypoglycemic Agents" [Pharmacological Action]) OR ("hypoglycemic agent*"[tiab] NOT Medline[sb])		266,210
6	#4 AND #5		43,303
7	(Insulin[Mesh] OR "Insulin, Long-Acting"[Mesh] OR "Insulin, Isophane"[Mesh] OR "Insulin Glargine"[Mesh]) OR (insulin[tiab] NOT medline[sb])		225,745
8	#4 AND #7		29,218
9	Actos[tiab] OR Albiglutide[tiab] OR Amaryl[tiab] OR Biguanides[Mesh] OR Biguanides[tiab] OR Bydureon[tiab] OR Byetta[tiab] OR DiaBeta[tiab] OR "Dipeptidyl-Peptidase IV Inhibitors"[Mesh] OR "Dipeptidyl-Peptidase IV Inhibitors"[Pharmacological Action] OR "Dipeptidyl peptidase IV inhibitor"[tiab] OR "Dipeptidyl peptidase IV inhibitors"[tiab] OR dulaglutide[Supplementary Concept] OR dulaglutide[tiab] OR exenatide[Supplementary Concept] OR Exenatide[tiab] OR Fortamet[tiab] OR Gliclazide[Mesh] OR Gliclazide[tiab] OR glimepiride[tiab] OR Glipizide[Mesh] OR glipizide[tiab] OR "GLP-1 receptor agonist"[tiab] OR "GLP-1 receptor agonists"[tiab] OR "Glucagon-like peptide-1 receptor agonist"[tiab] OR "Glucagon-like peptide-1 receptor agonists"[tiab] OR Glucophage[tiab] OR Glucotrol[tiab] OR "Glucotrol XL"[tiab] OR Glumetza[tiab] OR Glyburide[Mesh] OR glyburide[tiab] OR "Glynase PresTab"[tiab] OR Linagliptin[Mesh] OR Linagliptin[tiab] OR Liraglutide[Mesh] OR liraglutide[tiab] OR lixisenatide[Supplementary Concept] OR lixisenatide[tiab] OR Lyxumia[tiab] OR Meglitinides[tiab] OR Metformin[Mesh] OR Metformin[tiab] OR Micronase[tiab] OR nateglinide[Supplementary Concept] OR Nateglinide[tiab] OR Ozempic[tiab] OR pioglitazone[Supplementary Concept] OR Pioglitazone[tiab] OR Prandin[tiab] OR Repaglinide[tiab] OR rosiglitazone[Supplementary Concept] OR Rosiglitazone[tiab] OR Saxagliptin[tiab] OR semaglutide[Supplementary Concept] OR semaglutide[tiab] OR Sitagliptin[tiab] OR "Sitagliptin Phosphate"[Mesh] OR "Sitagliptin Phosphate, Metformin Hydrochloride Drug Combination"[Mesh] OR "Sulfonylurea Compounds"[Mesh] OR Starlix[tiab] OR Sulfonylureas[tiab] OR Tanzeum[tiab] OR Thiazolidinediones[Mesh] OR Thiazolidinediones[tiab] OR Tolazamide[Mesh] OR Tolazamide[tiab] OR Tolbutamide[Mesh] OR tolbutamide[tiab] OR Trulicity[tiab] OR TZDs[tiab] OR Victoza[tiab] OR vildagliptin[Supplementary Concept] OR vildagliptin[tiab]		82,627
10	#4 AND #9		20,543

Appendix B1. Original Literature Search Strategies

Search Number	Query	Filters	Results
11	advice[tiab] OR "Behavior Therapy"[Mesh] OR "behavior therapy"[tiab] OR (behavior*[tiab] AND therap*[tiab]) OR (behavior*[tiab] AND chang*[tiab]) OR (behavior*[tiab] AND modification*[tiab]) OR "Caloric Restriction"[Mesh] OR ((child*[tiab] AND parent*[tiab]) and therap*[tiab]) OR Counseling[Mesh] OR counsel*[tiab] OR "cognitive behavior"[tiab] OR "cognitive behavioral"[tiab] OR "cognitive therap*"[tiab] OR CBT[ti] OR "Diabetes Prevention Program"[tiab] OR "Diabetes Prevention Programme"[tiab] OR DPP[tiab] OR ("Diabetes Prevention"[tiab] AND (program*[tiab] OR stud*[tiab] OR trial*[tiab])) OR diet[ti] OR "Diet, Carbohydrate-Restricted"[Mesh] OR "Diet, Fat-Restricted"[Mesh] OR "Diet, Mediterranean"[Mesh] OR "Diet, Reducing"[Mesh] OR "Diet Therapy"[Mesh] OR dietary[ti] OR "Directive Counseling"[Mesh] OR Exercise[Mesh] OR exercise[ti] OR "Exercise Therapy"[Mesh] OR "family intervention*"[tiab] OR "family therap*"[tiab] OR "Feedback, Psychological"[Mesh] OR "group therap*"[tiab] OR "Health Behavior"[Majr] OR "health behavior"[tiab] OR "health behaviors"[tiab] OR "health behavioral"[tiab] OR "health behaviours"[tiab] OR "health behaviour"[tiab] OR "Health Education"[Mesh] OR "health education"[tiab] OR "Health Promotion"[Majr] OR "health promotion"[tiab] OR "Life Style"[Mesh] OR lifestyle[tiab] OR "life style"[tiab] OR "Motivational Interviewing"[Mesh] OR "motivational interviewing"[tiab] OR "non pharmacologic intervention"[tiab] OR "nonpharmacologic intervention"[tiab] OR "parent* intervention*"[tiab] OR "Patient Education as Topic"[Mesh] OR "patient education"[tiab] OR "physical activity"[ti] OR "physically active"[ti] OR "psychological feedback"[tiab] OR "Risk Reduction Behavior"[Mesh] OR "Risk Reduction Behavior"[tiab] OR "Weight Loss"[Mesh] OR "Weight Reduction Programs"[Mesh]		1,544,095
12	#4 AND #11		30,288
13	#6 OR #8 OR #10 OR #12		72,197
14	(#13 AND Humans[Mesh:NOEXP]) OR (#13 NOT Animals[Mesh:NOEXP])		66,506
15	(#13 AND Humans[Mesh:NOEXP]) OR (#13 NOT Animals[Mesh:NOEXP])	English	61,430
16	(#13 AND Humans[Mesh:NOEXP]) OR (#13 NOT Animals[Mesh:NOEXP])	Child: birth-18 years	3,828
17	(adolescen*[tiab] OR boys[tiab] OR child*[tiab] OR children[tiab] OR girls[tiab] OR pediatric[tiab] OR paediatric*[tiab] OR teen[tiab] OR teens[tiab] OR teenage[tiab] OR teenaged[tiab] OR teenager*[tiab] OR toddler*[tiab]) NOT Medline[sb]		225,420
18	#14 AND #17		436
19	#16 OR #18		4,264
20	address[pt] OR "autobiography"[pt] OR "bibliography"[pt] OR "biography"[pt] OR "case report"[tw] OR "case reports"[tw] OR "case series"[tw] OR "comment"[pt] OR "comment on"[All Fields] OR congress[pt] OR "cross-sectional"[tw] OR "dictionary"[pt] OR "directory"[pt] OR "editorial"[pt] OR "festschrift"[pt] OR "historical article"[pt] OR "interview"[pt] OR lecture[pt] OR "legal case"[pt] OR "legislation"[pt] OR letter[pt] OR "news"[pt] OR "newspaper article"[pt] OR "patient education handout"[pt] OR "periodical index"[pt] OR "retrospective cohort"[tw] OR ("Animals"[Mesh] NOT "Humans"[Mesh]) OR rats[tw] OR cow[tw] OR cows[tw] OR chicken[tw] OR chickens[tw] OR horse[tw] OR horses[tw] OR mice[tw] OR mouse[tw] OR bovine[tw] OR sheep OR ovine OR murine OR murinae		11,199,555
21	#19 NOT #20		3,636
22	#21 NOT (gestation* OR Pregnancy[Mesh])		3,009
23	#21 NOT (gestation* OR Pregnancy[Mesh])	from 2019/8/3 - 3000/12/12	316

Appendix B1. Original Literature Search Strategies

Search Number	Query	Filters	Results
24	"controlled clinical trial"[publication type] OR "Randomized Controlled Trial"[Publication Type] OR "Single-Blind Method"[MeSH] OR "Double-Blind Method"[MeSH] OR "Random Allocation"[MeSH] OR (controlled[tiab] AND trial[tiab]) OR groups [tiab] OR placeb o [tiab] OR randomised [tiab] OR randomized [tiab] OR randomly [tiab] OR trial [tiab]		3,313,682
25	#23 AND #24		139
26	("review"[Publication Type] AND "systematic"[tiab]) OR "systematic review"[All Fields] OR ("review literature as topic"[MeSH] AND "systematic"[tiab]) OR "meta-analysis"[Publication Type] OR "meta-analysis as topic"[MeSH Terms] OR "meta-analysis"[All Fields] OR "meta synthesis"[ti] OR "systematic literature review"[ti] OR "this systematic review"[tw] OR "cochrane database syst rev"[ta]		362,198
27	#23 AND #26		16
28	#23 AND "Case-Control Studies"[MeSH]		24
29	#23 AND ("Cohort Studies"[Mesh:NOEXP] OR "Epidemiologic Studies"[Mesh] OR "Follow-up Studies"[Mesh] OR "prospective cohort" OR "prospective studies"[MeSH] OR (prospective*[All Fields] AND cohort[All Fields] AND (study[All Fields] OR studies[All Fields])))		71
30	#23 AND ("Evaluation Study"[pt] OR "Comparative Study"[pt])		11

Cochrane Library Screening, 5/3/2021

ID	Search	Hits
#1	[mh "Diabetes Mellitus, Type 2"] OR "glucose tolerance" OR "impaired glucose tolerance" OR dysglycemia:ti,ab OR IGT OR "impaired fasting glucose" OR IFG OR [mh "Glucose Intolerance"] OR "glucose intolerance" OR [mh "Prediabetic State"] OR "prediabetic state" OR prediabet* OR "pre diabetes" OR "diabetes mellitus type 2" OR "type 2 diabetes mellitus"	36248
#2	[mh "Blood Glucose"] OR "blood glucose":ti,ab OR [mh "Glucose Tolerance Test"] OR OGTT:ti,ab OR "glucose tolerance test":ti OR [mh "Glycated Hemoglobin A"] OR "hemoglobin A1c" OR HbA1c OR "fasting plasma glucose":ti,ab OR "oral glucose tolerance":ti,ab	48756
#3	#1 AND #2	20381
#4	[mh "Mass Screening"] OR screen*:ti,ab	73937
#5	#3 AND #4	1840
#6	#5 NOT (gestation* OR [mh Pregnancy])	1645
#7	adolescen*:ti,ab,kw OR boys:ti,ab,kw OR child*:ti,ab,kw OR children:ti,ab,kw OR girls:ti,ab,kw OR infant*:ti,ab,kw OR pediatric:ti,ab,kw OR paediatric*:ti,ab,kw OR teen:ti,ab,kw OR teens:ti,ab,kw OR teenage:ti,ab,kw OR teenaged:ti,ab,kw OR teenager*:ti,ab,kw OR toddler*:ti,ab,kw	289615
#8	#6 AND #7	213
#9	#8 with Cochrane Library publication date Between Aug 2019 and Dec 2021	41
#10	#9 NOT ([mh "Diabetes Mellitus, Type 1"] OR "diabetes mellitus type 1":ti,ab,kw OR "type 1 diabetes":ti,ab,kw)	38

Appendix B1. Original Literature Search Strategies

Cochrane Library Interventions, 5/3/2021

ID	Search	Hits
#1	[mh "Diabetes Mellitus, Type 2"] OR "glucose tolerance" OR "impaired glucose tolerance" OR dysglycemia:ti,ab OR IGT OR "impaired fasting glucose" OR IFG OR [mh "Glucose Intolerance"] OR "glucose intolerance" OR [mh "Prediabetic State"] OR "prediabetic state" OR prediabet* OR "pre diabetes" OR "diabetes mellitus type 2" OR "type 2 diabetes mellitus"	36248
#2	#1 NOT ([mh "Diabetes Mellitus, Type 1"] OR "diabetes mellitus type 1":ti,ab,kw OR "type 1 diabetes":ti,ab,kw)	35092
#3	Actos:ti,ab OR Albiglutide:ti,ab OR Amaryl:ti,ab OR [mh Biguanides] OR Biguanides:ti,ab OR Bydureon:ti,ab OR Byetta:ti,ab OR DiaBeta:ti,ab OR [mh "Dipeptidyl-Peptidase IV Inhibitors"] OR "Dipeptidyl peptidase IV inhibitor":ti,ab OR "Dipeptidyl peptidase IV inhibitors":ti,ab OR dulaglutide:ti,ab OR Exenatide:ti,ab OR Fortamet:ti,ab OR [mh Gliclazide] OR Gliclazide:ti,ab OR glimepiride:ti,ab OR [mh Glipizide] OR glipizide:ti,ab OR "GLP-1 receptor agonist":ti,ab OR "GLP-1 receptor agonists":ti,ab OR "Glucagon-like peptide-1 receptor agonist":ti,ab OR "Glucagon-like peptide-1 receptor agonists":ti,ab OR Glucophage:ti,ab OR Glucotrol:ti,ab OR "Glucotrol XL":ti,ab OR Glumetza:ti,ab OR [mh Glyburide] OR glyburide:ti,ab OR "Glynase PresTab":ti,ab OR [mh Linagliptin] OR Linagliptin:ti,ab OR [mh Liraglutide] OR liraglutide:ti,ab OR lixisenatide:ti,ab OR Lyxumia:ti,ab OR Meglitinides:ti,ab OR [mh Metformin] OR Metformin:ti,ab OR Micronase:ti,ab OR Nateglinide:ti,ab OR Ozempic:ti,ab OR Pioglitazone:ti,ab OR Prandin:ti,ab OR Repaglinide:ti,ab OR Rosiglitazone:ti,ab OR Saxagliptin:ti,ab OR semaglutide:ti,ab OR Sitagliptin:ti,ab OR [mh "Sitagliptin Phosphate"] OR [mh "Sitagliptin Phosphate, Metformin Hydrochloride Drug Combination"] OR [mh "Sulfonylurea Compounds"] OR Starlix:ti,ab OR Sulfonylureas:ti,ab OR Tanzeum:ti,ab OR [mh Thiazolidinediones] OR Thiazolidinediones:ti,ab OR [mh Tolazamide] OR Tolazamide:ti,ab OR [mh Tolbutamide] OR tolbutamide:ti,ab OR Trulicity:ti,ab OR TZDs:ti,ab OR Victoza:ti,ab OR vildagliptin:ti,ab	22966
#4	#2 AND #3	9584
#5	#2 AND ([mh "hypoglycemic agents"] OR "hypoglycemic agent*":ti,ab,kw)	5438
#6	#2 AND ([mh Insulin] OR [mh "Insulin, Long-Acting"] OR [mh "Insulin, Isophane"] OR [mh "Insulin Glargine"] OR insulin:ti,ab,kw)	19860
#7	#4 OR #5 OR #6	23813
#8	advice:ti,ab OR [mh "Behavior Therapy"] OR "behavior therapy":ti,ab OR (behavior*:ti,ab AND therap*:ti,ab) OR (behavior*:ti,ab AND chang*:ti,ab) OR (behavior*:ti,ab AND modification*:ti,ab) OR [mh "Caloric Restriction"] OR ((child*:ti,ab AND parent*:ti,ab) and therap*:ti,ab) OR [mh Counseling] OR counsel*:ti,ab OR "cognitive behavior":ti,ab OR "cognitive behavioral":ti,ab OR "cognitive therap*":ti,ab OR CBT:ti OR "Diabetes Prevention Program":ti,ab OR "Diabetes Prevention Programme":ti,ab OR DPP:ti,ab OR ("Diabetes Prevention":ti,ab AND (program*:ti,ab OR stud*:ti,ab OR trial*:ti,ab)) OR diet:ti OR [mh "Diet, Carbohydrate-Restricted"] OR [mh "Diet, Fat-Restricted"] OR [mh "Diet, Mediterranean"] OR [mh "Diet, Reducing"] OR [mh "Diet Therapy"] OR dietary:ti OR [mh "Directive Counseling"] OR [mh Exercise] OR exercise:ti OR [mh "Exercise Therapy"] OR "family intervention*":ti,ab OR "family therap*":ti,ab OR [mh "Feedback, Psychological"] OR "group therap*":ti,ab OR [mh ^"Health Behavior"] OR "health behavior":ti,ab OR "health behaviors":ti,ab OR "health behavioral":ti,ab OR "health behaviours":ti,ab OR "health behaviour":ti,ab OR [mh "Health Education"] OR "health education":ti,ab OR [mh ^"Health Promotion"] OR "health promotion":ti,ab OR [mh "Life Style"] OR lifestyle:ti,ab OR "life style":ti,ab OR [mh "Motivational Interviewing"] OR "motivational interviewing":ti,ab OR "non pharmacologic intervention":ti,ab OR "nonpharmacologic intervention":ti,ab OR "parent* intervention*":ti,ab OR [mh "Patient Education as Topic"] OR "patient education":ti,ab OR "physical activity":ti OR "physically active":ti OR "psychological feedback":ti,ab OR [mh "Risk Reduction Behavior"] OR "Risk Reduction Behavior":ti,ab OR [mh "Weight Loss"] OR [mh "Weight Reduction Programs"]	195053
#9	#1 AND #8	9525
#10	#7 OR #9	27598
#11	#10 NOT (gestation* OR [mh Pregnancy])	26684
#12	#11 NOT ([mh animals] NOT [mh humans])	26684
#13	adolescen*:ti,ab,kw OR boys:ti,ab,kw OR child*:ti,ab,kw OR children:ti,ab,kw OR girls:ti,ab,kw OR infant*:ti,ab,kw OR pediatric:ti,ab,kw OR paediatric*:ti,ab,kw OR teen:ti,ab,kw OR teens:ti,ab,kw OR teenage:ti,ab,kw OR teenaged:ti,ab,kw OR teenager*:ti,ab,kw OR toddler*:ti,ab,kw	289615
#14	#12 AND #13	1771
#15	#14 with Cochrane Library publication date from Aug 2019 to Dec 2021	267 (3 are reviews)
#16	#15 with Publication Year from 2019 to 2021, in Trials	182

ClinicalTrials.gov, 5/3/2021

Screening (**40** results)

Condition box: ("Diabetes Mellitus, Type 2" OR "Glucose Tolerance" OR "impaired glucose tolerance" OR IGT OR "impaired fasting glucose" OR IFG OR "Glucose Intolerance" OR "Prediabetic State" OR prediabet* OR "pre diabetes" OR "diabetes mellitus type 2" OR "type 2 diabetes mellitus")

AND

Other terms box: ("blood glucose" OR OGTT OR "glucose tolerance test" OR "Glycated Hemoglobin A" OR "hemoglobin A1c" OR HbA1c OR "fasting plasma glucose" OR "HbA(1c)" OR HbA1 OR HbA1c OR "HbA 1c" OR "glycosylated hemoglobin" OR "glycated hemoglobin" OR "oral glucose tolerance") AND (screen* OR screening)

Used child limits Age Group Child (birth-17)

Expert search: (("blood glucose" OR OGTT OR "glucose tolerance test" OR "Glycated Hemoglobin A" OR "hemoglobin A1c" OR HbA1c OR "fasting plasma glucose" OR "HbA(1c)" OR HbA1 OR HbA1c OR "HbA 1c" OR "glycosylated hemoglobin" OR "glycated hemoglobin" OR "oral glucose tolerance") AND (screen* OR screening)) AND AREA[ConditionSearch] ("Diabetes Mellitus, Type 2" OR "Glucose Tolerance" OR "impaired glucose tolerance" OR IGT OR "impaired fasting glucose" OR IFG OR "Glucose Intolerance" OR "Prediabetic State" OR prediabet* OR "pre diabetes" OR "diabetes mellitus type 2" OR "type 2 diabetes mellitus") AND AREA[StdAge] EXPAND[Term] COVER[FullMatch] "Child"

Interventions (integrates terms for hypoglycemic agents and insulin)
A. Pharmacologic Interventions (**322** results)

Condition box: ("Diabetes Mellitus, Type 2" OR "Glucose Tolerance" OR "impaired glucose tolerance" OR IGT OR "impaired fasting glucose" OR IFG OR "glucose Intolerance" OR "Prediabetic State" OR prediabet* OR "pre diabetes" OR "diabetes mellitus type 2" OR "type 2 diabetes mellitus")

AND

Intervention/treatment box: (Actos OR Albiglutide OR Amaryl OR Biguanides OR Bydureon OR Byetta OR DiaBeta OR "Dipeptidyl-Peptidase IV Inhibitors" OR "Dipeptidyl peptidase IV inhibitor" OR dulaglutide OR Exenatide OR Fortamet OR Gliclazide OR glimepiride OR Glipizide OR "GLP-1 receptor agonist" OR "GLP-1 receptor agonists" OR "Glucagon-like peptide-1 receptor agonist" OR "Glucagon-like peptide-1 receptor agonists" OR Glucophage OR Glucotrol OR Glumetza OR Glyburide OR "Glynase PresTab" hypoglycemic agent* OR "hypoglycemic agents" OR insulin OR Linagliptin OR Liraglutide OR lixisenatide OR Lyxumia OR Meglitinides OR Metformin OR Micronase OR Ozempic OR Pioglitazone OR Prandin OR Repaglinide OR Rosiglitazone OR Saxagliptin OR semaglutide OR Sitagliptin OR "Sulfonylurea

Compounds" OR Starlix OR Sulfonylureas OR Tanzeum OR Thiazolidinediones OR Tolazamide OR Tolbutamide OR Trulicity OR TZDs OR Victoza OR vildagliptin)

Used child limits Age Group Child (birth-17)

In Expert Search box: AREA[ConditionSearch] ("Diabetes Mellitus, Type 2" OR "Glucose Tolerance" OR "impaired glucose tolerance" OR IGT OR "impaired fasting glucose" OR IFG OR "glucose Intolerance" OR "Prediabetic State" OR prediabet* OR "pre diabetes" OR "diabetes mellitus type 2" OR "type 2 diabetes mellitus") AND AREA[InterventionSearch] (Actos OR Albiglutide OR Amaryl OR Biguanides OR Bydureon OR Byetta OR DiaBeta OR "Dipeptidyl-Peptidase IV Inhibitors" OR "Dipeptidyl peptidase IV inhibitor" OR dulaglutide OR Exenatide OR Fortamet OR Gliclazide OR glimepiride OR Glipizide OR "GLP-1 receptor agonist" OR "GLP-1 receptor agonists" OR "Glucagon-like peptide-1 receptor agonist" OR "Glucagon-like peptide-1 receptor agonists" OR Glucophage OR Glucotrol OR Glumetza OR Glyburide OR "Glynase PresTab" hypoglycemic agent* OR "hypoglycemic agents" OR insulin OR Linagliptin OR Liraglutide OR lixisenatide OR Lyxumia OR Meglitinides OR Metformin OR Micronase OR Ozempic OR Pioglitazone OR Prandin OR Repaglinide OR Rosiglitazone OR Saxagliptin OR semaglutide OR Sitagliptin OR "Sulfonylurea Compounds" OR Starlix OR Sulfonylureas OR Tanzeum OR Thiazolidinediones OR Tolazamide OR Tolbutamide OR Trulicity OR TZDs OR Victoza OR vildagliptin) AND AREA[StdAge] EXPAND[Term] COVER[FullMatch] "Child"

B. Non-pharmacologic interventions (**186** results)

Condition box: ("Diabetes Mellitus, Type 2" OR "Glucose Tolerance" OR "impaired glucose tolerance" OR IGT OR "impaired fasting glucose" OR IFG OR "glucose Intolerance" OR "Prediabetic State" OR prediabet* OR "pre diabetes" OR "diabetes mellitus type 2" OR "type 2 diabetes mellitus")

AND

Non-Pharmacological Interventions in Treatment/Interventions box: (advice OR "Behavior Therapy" OR (behavior* AND therap*) OR (behavior* AND chang*) OR (behavior* AND modification*) OR "Caloric Restriction" OR ((child* AND parent*) and therap*) OR counsel* OR "cognitive behavior" OR "cognitive behavioral" OR "cognitive therap*" OR CBT OR "Diabetes Prevention Program" OR "Diabetes Prevention Programme" OR DPP OR ("Diabetes Prevention" AND (program* OR stud* OR trial*)) OR diet OR dietary OR Exercise OR "family intervention*" OR "family therap*" OR "Feedback, Psychological" OR "group therap*" OR "Health Behavior" OR "health behaviors" OR "health behavioral" OR "health behaviours" OR "health behaviour" OR "health behavioural" OR "Health Education" OR "Health Education as Topic" OR "health education" OR "Health Promotion" OR "health promotion" OR "Life Style" OR lifestyle OR "life style" OR "Lifestyle Intervention" OR "Motivational Interviewing" OR "motivational interviewing" OR "non pharmacologic intervention" OR "nonpharmacologic intervention" OR "parent* intervention*" OR "patient education" OR "physical activity" OR "physically active" OR "psychological feedback" OR "Risk Reduction Behavior" OR "Risk Reduction Behavior" OR "Weight Loss" OR "Weight Reduction Programs")

Used child limits Age Group Child (birth-17)

In Expert Search box: AREA[ConditionSearch] ("Diabetes Mellitus, Type 2" OR "Glucose Tolerance" OR "impaired glucose tolerance" OR IGT OR "impaired fasting glucose" OR IFG OR "glucose Intolerance" OR "Prediabetic State" OR prediabet* OR "pre diabetes" OR "diabetes mellitus type 2" OR "type 2 diabetes mellitus") AND AREA[InterventionSearch] (advice OR "Behavior Therapy" OR (behavior* AND therap*) OR (behavior* AND chang*) OR (behavior* AND modification*) OR "Caloric Restriction" OR ((child* AND parent*) and therap*) OR counsel* OR "cognitive behavior" OR "cognitive behavioral" OR "cognitive therap*" OR CBT OR "Diabetes Prevention Program" OR "Diabetes Prevention Programme" OR DPP OR ("Diabetes Prevention" AND (program* OR stud* OR trial*)) OR diet OR dietary OR Exercise OR "family intervention*" OR "family therap*" OR "Feedback, Psychological" OR "group therap*" OR "Health Behavior" OR "health behaviors" OR "health behavioral" OR "health behaviours" OR "health behaviour" OR "health behavioural" OR "Health Education" OR "Health Education as Topic" OR "health education" OR "Health Promotion" OR "health promotion" OR "Life Style" OR lifestyle OR "life style" OR "Lifestyle Intervention" OR "Motivational Interviewing" OR "motivational interviewing" OR "non pharmacologic intervention" OR "nonpharmacologic intervention" OR "parent* intervention*" OR "patient education" OR "physical activity" OR "physically active" OR "psychological feedback" OR "Risk Reduction Behavior" OR "Risk Reduction Behavior" OR "Weight Loss" OR "Weight Reduction Programs") AND AREA[StdAge] EXPAND[Term] COVER[FullMatch] "Child"

Appendix B2. Eligibility Criteria

	Include	Exclude
Populations	**All KQs:** Studies of people younger than age 18; studies of participants without obvious symptoms of diabetes (e.g., for KQ 1, studies of unselected populations that may include some participants with unrecognized symptoms of diabetes such as fatigue); nonpregnant women with a history of gestational diabetes (if they are >1 year postpartum); studies that substantially overlap this age range (e.g., ages 14–65 years) were eligible if results for younger participants were reported separately. At least 50% of the study population must have met the review eligibility criteria or results must have been reported separately for the population eligible for the review. **KQs 1, 2:** Asymptomatic, nonpregnant children and adolescents **KQs 3:** Asymptomatic, nonpregnant children and adolescents with screen-detected prediabetes or type 2 diabetes (3a and 3b) or with recently diagnosed type 2 diabetes (3c); studies of people with Maturity Onset Diabetes of the Young (MODY) were also eligible. **KQ 4:** Asymptomatic, nonpregnant children and adolescents with screen-detected prediabetes or type 2 diabetes; nonpregnant children and adolescents with recently diagnosed type 2 diabetes; studies of people with MODY were also eligible. **KQs 5–6:** Asymptomatic, nonpregnant children and adolescents with screen-detected prediabetes **Specific populations:** Studies that examined whether effectiveness of screening or intervention differed based on age, sex, race/ethnicity, BMI, sexual maturity rating, age of menarche, and socioeconomic status were examined.	**KQs 1–6:** Studies limited to or predominately comprising adults or pregnant women; persons with symptomatic prediabetes or type 2 diabetes (e.g., weight loss, polyuria, blurred vision, headache); persons with a recent hospitalization; persons taking antipsychotics or glucocorticoids; persons with known cardiovascular disease or severe chronic kidney disease; persons living in an institution; other persons with medical conditions limiting their applicability to primary care–based populations (e.g., those with acute illness) **KQ 3c:** Studies limited to or predominately comprising persons who have had diabetes for more than 1 year or with more advanced diabetes (e.g., persons already taking insulin or other medications; persons with proliferative retinopathy, nephropathy)
Screening	**KQs 1, 2:** Screening (targeted or universal) for prediabetes* or diabetes; tests include hemoglobin A1c, FPG, and the OGTT	All other tests, such as genetic testing for the risk of prediabetes or diabetes or testing for autoantibodies, which may be used for further evaluation after a diabetes diagnosis (e.g., to assess for type 1 or type 2 diabetes)
Interventions	**KQs 3–6:** Primary care–relevant behavioral counseling or pharmacotherapy interventions for glycemic control. Behavioral counseling interventions provided alone or as part of a larger multicomponent intervention on diet and nutrition, physical activity, sedentary behavior, or a combination thereof, including but not limited to assessment with feedback, advice, collaborative goal setting, assistance, exercise prescriptions (referral to exercise facility or program), or arrangement of further contacts Interventions delivered via face-to-face contact, telephone, print materials, or technology (e.g., computer based, text messages, remote video feed) and delivered by a number of potential interventionists, including but not limited to clinicians, nurses, exercise specialists, dietitians, nutritionists, and behavioral health specialists Dietary counseling may involve: • Increased consumption of fruits, vegetables, whole grains, fat-free or low-fat dairy, and/or lean proteins	• Counseling interventions aimed at depression • Prenatal or postnatal dietary counseling • Counseling interventions with components that are not feasible for implementation in healthcare settings (e.g., occupational/worksite-, church-, or school-based interventions conducted within existing social networks) • Social marketing (e.g., media campaigns) • Policy (e.g., local or state public/health policy) • Stress management interventions (e.g., meditation, yoga, tai chi) • Use of incentives (e.g., paying persons to lose weight) • Supervised exercise with the goal of assessing effects of exercise

Appendix B2. Eligibility Criteria

	Include	Exclude
	• Limited consumption of sodium, saturated fat, trans fat, and/or sugar-sweetened food and beverages Physical activity counseling may involve: • Aerobic activities that involve repeated use of large muscles, such as walking, cycling, and swimming • Resistance training designed to improve physical strength • Reduction of sedentary behaviors • Optional or access to guided physical activity or exercise classes Limited guided physical activity (i.e., 1 to 2 sessions) or provision of food samples is allowed if intention is to teach or demonstrate healthy lifestyle principles	• Dietary counseling solely focused on increasing intake of specific vitamins, micronutrients, herbal supplements, spices (e.g., ginger, cinnamon), or antioxidants through dietary change or supplementation, or counseling on alcohol • Surgery
Comparisons	**KQs 1, 2:** No screening or alternative screening strategies **KQ 3a:** Comparison based on timing; sooner vs. later intervention (i.e., starting intervention upon detection by screening vs. starting later based on clinical diagnosis); clinical diagnosis refers to any approach based on development of symptoms (e.g., polyuria, polydipsia, paresthesia, vision changes) or monitoring of biomarkers (e.g., increase in hemoglobin A1c above a certain threshold) **KQs 3b, 3c:** No intervention, placebo, usual care (can include minimal intervention), different treatment targets (e.g., glucose or blood pressure targets), wait-list, or attention control (for lifestyle interventions) **KQ 4:** All comparisons eligible for KQ 3 **KQs 5–6:** Sooner vs. later intervention, no intervention, placebo, usual care, wait-list, or attention control (for lifestyle interventions)	Comparative effectiveness (head-to-head) trials of medications or behavioral counseling without another eligible control group
Outcomes	**KQs 1, 3, 6:** Mortality, cardiovascular morbidity (including myocardial infarction, stroke, congestive heart failure), chronic kidney disease, amputation, skin ulcers, visual impairment (including blindness), periodontitis (including tooth loss), moderate to severe neuropathy, and quality of life **KQ 2:** Labeling, anxiety, harms from false-positive results, burden, inconvenience, depression, and unnecessary testing and treatment **KQ 4:** Serious side effects from treatment, including gastrointestinal side effects, mortality, myocardial infarction, stroke, cancer, and hypoglycemic events requiring medical attention; burden and inconvenience **KQ 5:** Development of type 2 diabetes	**KQs 1, 3, 5, 6:** Studies with less than 6 months of followup
Study Designs	**All KQs:** Controlled clinical trials **KQs 2, 4:** Controlled prospective cohort studies and case-control studies are also eligible **KQ 6:** Controlled prospective cohort studies are also eligible	Modeling studies, systematic reviews,† case series, case reports, uncontrolled observational studies, retrospective cohort studies, editorials, and all other study designs not mentioned

Appendix B2. Eligibility Criteria

	Include	Exclude
Settings	Studies conducted in or recruited from primary care settings or settings otherwise applicable to primary care, including school-based health centers and other community settings that provide primary care or are referable from primary care (i.e., screening/interventions that could feasibly be implemented in or referred from primary care)	Settings not generalizable to primary care (e.g., inpatient hospital units, emergency departments, nursing home and other institutional settings, school-based curricula or programs that are not referable from primary care, occupational settings)
Countries	Studies conducted in countries categorized as "Very High" on the Human Development Index in the 2019 Human Development Report (as defined by the United Nations Development Programme)	Studies conducted in countries that are categorized as lower than "Very High" on the Human Development Index in the 2019 Human Development Report
Language	English	Languages other than English
Study Quality	Good or Fair	Poor (according to design-specific USPSTF criteria)

* Prediabetes includes individuals who meet criteria for IFG, IGT, and those with an A1c from 5.7 to 6.4 percent.

† Systematic reviews were excluded from the evidence review. However, separate searches were conducted to identify relevant systematic reviews, and the citations of all studies included in those systematic reviews were reviewed to ensure that the database searches have captured all relevant primary studies.

Abbreviations: A1c=glycated hemoglobin; BMI=body mass index; FPG=fasting plasma glucose; IFG=impaired fasting glucose; IGT=impaired glucose tolerance; KQ=key question; MODY=Maturity Onset Diabetes of the Young; OGTT=oral glucose tolerance test; USPSTF=U.S. Preventive Services Task Force.

Randomized, Controlled Trials and Cohort Studies

Criteria

- Initial assembly of comparable groups
- Randomized, controlled trials (RCTs)—adequate randomization, including concealment and whether potential confounders were distributed equally among groups; cohort studies—consideration of potential confounders with either restriction or measurement for adjustment in the analysis; consideration of inception cohorts
- Maintenance of comparable groups (includes attrition, crossovers, adherence, and contamination)
- Important differential loss to followup or overall high loss to followup
- Measurements that are equal, reliable, and valid (includes masking of outcome assessment)
- Clear definition of interventions
- Important outcomes considered
- Analysis: Adjustment for potential confounders for cohort studies or intention-to-treat analysis for RCTs; for cluster RCTs, correction for correlation coefficient

Definition of Ratings Based on Above Criteria

Good: Meets all criteria: Comparable groups are assembled initially and maintained throughout the study (followup ≥80%); reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; important outcomes are considered; and appropriate attention is given to confounders in analysis. In addition, intention-to-treat analysis is used for RCTs.

Fair: Studies will be graded "fair" if any or all of the following problems occur without the important limitations noted in the "poor" category below: Generally comparable groups are assembled initially, but some question remains on whether some (although not major) differences occurred in followup; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are accounted for. Intention-to-treat analysis is lacking for RCTs.

Poor: Studies will be graded "poor" if any of the following major limitations exist: Groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied equally among groups (including not masking outcome assessment); and key confounders are given little or no attention. Intention-to-treat analysis is lacking for RCTs.

Source: U.S. Preventive Services Task Force. U.S. Preventive Services Task Force, Procedure Manual, Appendix VI. Rockville, MD: U.S. Preventive Services Task Force; 2015[56]

Diagnostic Accuracy Studies

Criteria:

- Screening test relevant, available for primary care, and adequately described
- Credible reference standard, performed regardless of test results
- Reference standard interpreted independently of screening test
- Indeterminate results handled in a reasonable manner
- Spectrum of patients included in study
- Sample size
- Reliable screening test

Definition of Ratings Based on Above Criteria:
Good: Evaluates relevant available screening test; uses a credible reference standard; interprets reference standard independently of screening test; assesses reliability of test; has few or handles indeterminate results in a reasonable manner; includes large number (greater than 100) of broad-spectrum patients with and without disease.

Fair: Evaluates relevant available screening test; uses reasonable although not best standard; interprets reference standard independent of screening test; has moderate sample size (50 to 100 subjects) and a "medium" spectrum of patients.

Poor: Has a fatal flaw, such as uses inappropriate reference standard; improperly administers screening test; biased ascertainment of reference standard; has very small sample size or very narrow selected spectrum of patients.

Source: U.S. Preventive Services Task Force. U.S. Preventive Services Task Force, Procedure Manual, Appendix VI. Rockville, MD: U.S. Preventive Services Task Force; 2015[56]

Appendix C. Excluded Articles

X1: Non-English
X2: Ineligible Population
X3: Ineligible Screening
X4: Ineligible Treatment
X5: Ineligible Comparison
X6: Ineligible Outcome
X7: Ineligible Setting
X8: Ineligible Study Design
X9: Ineligible Country
X10: Abstract Only

1. Metformin: new indication. Useful for some children with type 2 diabetes. *Prescrire Int*. 2007 Apr;16(88):50-2. PMID: 17458042. Exclusion Code: X8.
2. Effects of metformin, metformin plus rosiglitazone, and metformin plus lifestyle on insulin sensitivity and β-cell function in TODAY. *Diabetes Care*. 2013 Jun;36(6):1749-57. doi: 10.2337/dc12-2393. PMID: 23704674. Exclusion Code: X6.
3. Lipid and inflammatory cardiovascular risk worsens over 3 years in youth with type 2 diabetes: the TODAY clinical trial. *Diabetes Care*. 2013 Jun;36(6):1758-64. doi: 10.2337/dc12-2388. PMID: 23704675. Exclusion Code: X6.
4. Restoring Insulin Secretion (RISE): design of studies of β-cell preservation in prediabetes and early type 2 diabetes across the life span. *Diabetes Care*. 2014;37(3):780-8. doi: 10.2337/dc13-1879. PMID: 24194506. Exclusion Code: X6.
5. Effects of a community-based diabetes prevention program for obese latino youth. *Diabetes*. 2017;Conference: 77th Scientific Sessions of the American Diabetes Association, ADA 2017. United States. 66(pp A369)PMID: CN-01471124. Exclusion Code: X2.
6. Impact of insulin and metformin versus metformin alone on β-cell function in youth with impaired glucose tolerance or recently diagnosed type 2 diabetes. *Diabetes Care*. 2018 Aug;41(8):1717-25. doi: 10.2337/dc18-0787. PMID: 29941500. Exclusion Code: X5.
7. Effects of treatment of impaired glucose tolerance or recently diagnosed type 2 diabetes with metformin alone or in combination with insulin glargine on β-cell function: comparison of responses in youth and adults. *Diabetes*. 2019 Aug;68(8):1670-80. doi: 10.2337/db19-0299. PMID: 31178433. Exclusion Code: X6.
8. DIABRISK-SL trial: further consideration of age and impact of imputations. *BMC Med*. 2019;17(1)doi: 10.1186/s12916-019-1361-2. PMID: CN-02002832. Exclusion Code: X8.
9. Reducing the incidence of predictors of cardio-metabolic disease and dysglycaemia with lifestyle modification in at-risk persons-results of further analyses of DIABRISK-SL in those below 18 years of age. *BMC Med*. 2019;17(1)doi: 10.1186/s12916-019-1398-2. PMID: CN-02092627. Exclusion Code: X2.

10. Effects of treatment of impaired glucose tolerance or recently diagnosed type 2 diabetes with metformin alone or in combination with insulin glargine on Î²-cell function: comparison of responses in youth and adults: the RISE consortium. *Diabetes*. 2019;68(8):1670-80. doi: 10.2337/db19-0299. PMID: CN-02011190. Exclusion Code: X5.
11. Abdella K, McReelis KD, Strungaru MH. Diabetic retinopathy screening in a Canadian community pediatric diabetes clinic. *Can J Ophthalmol*. 2019 Feb;54(1):27-32. doi: 10.1016/j.jcjo.2018.03.012. PMID: 30851771. Exclusion Code: X2.
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Appendix D Table 1. Quality Assessment of Randomized, Controlled Clinical Trials (All KQs)

First author, Year Trial name	Was random-ization adequate?	Was allocation concealment adequate?	Were groups similar at baseline?	What was the reported adherence to the intervention?	Did the study have cross-overs or contamination raising concern for bias?	What was the overall attrition? Enter values for both loss to f/u (missing data) and noncompleters	What was the differential attrition?	Did the study have high differential attrition (>10% but think about how it might bias) or overall high attrition (depends on duration and outcome; generally 20%) raising concern for bias?
Kelsey, 2016[62] Zeitler, 2012[53] TODAY Study Group[58] TODAY Study Group[59] Levitt Katz, 2015[60] Zeitler, 2007[61] Treatment Options for type 2 Diabetes in Adolescents and Youth (TODAY) Study	Yes	Yes	Yes	Adherence to the medication regimen before the primary outcome was reached or the study was completed ranged from 84% at month 8 to 57% at month 60 but did not differ significantly across treatments. The rate of attendance at lifestyle program visits during the first 24 months was 75.2%; 53.6% of participants met the preplanned target of attending 75% or more of visits over these 2 years.	No	Combining withdrawing consent and data censored: 6.4% (15/232) vs. 8.6% (20/233) vs. 6.4% (15/234)	2.2%	No
Jones, 2002[63]	Unclear	Unclear	No, placebo had higher FPG and higher A1c and TG. Metformin group had higher C-peptide.	7.5% of placebo (3/40) and 45.2% (19/42) completed metformin	Yes	At 16 weeks: 10/82=12.2% overall	At 16 weeks: Metformin group 6/42=14.3% At 16 weeks: Placebo group 4/40=10% Between-group difference of 4.3%	No
Savoye, 2014[64]	Yes	Yes	Yes	2/38 in the intervention group never attended the intervention visits, and 5 others did not finish the study intervention.	No	23% (6-month followup assessments were missing for 17/75 participants)	8.6% (18.4% [7/38] vs. 27.0% [10/37])	Yes

Appendix D Table 1. Quality Assessment of Randomized, Controlled Clinical Trials (All KQs)

First author, Year Trial name	Were outcome measure-ments equal, valid, and reliable?	Were patients masked?	Were providers masked?	Were outcome assessors masked?	Was the duration of followup adequate to assess the outcome?	What was the method used to handle missing data?	Did the study use an ITT analysis (i.e., analyze people in the groups they were randomized to)?	Quality rating (for benefits)	Comments
Kelsey, 2016[62] Zeitler, 2012[53] TODAY Study Group[58] TODAY Study Group[59] Levitt Katz, 2015[60] Zeitler, 2007[61] Treatment Options for type 2 Diabetes in Adolescents and Youth (TODAY) Study	Yes	Yes	Yes	Yes	Yes	Censored; all randomized participants were included in the time-to-event analysis.	Yes (all participants included in time-to-event analysis)	Good	None
Jones, 2002[63]	Yes	Yes	Unclear	Unclear	Yes	NR	No	Fair	None
Savoye, 2014[64]	Yes	No	No	Yes	Unclear	Multiple imputation	Yes	Fair	None

Abbreviations: FPG=fasting plasma glucose; ITT=intention to treat; KQ=key question; NR=not reported; TG=triglycerides; TODAY=Treatment Options for Type 2 Diabetes in Adolescents and Youth.

Appendix D Table 2. Quality Assessment of Randomized, Controlled Clinical Trials: Additional Questions for Studies Reporting Harms (KQ 2 and KQ 4 only)

First author, Year Trial name	Were harms prespecified and defined?	Were ascertainment techniques for harms adequately described?	Were ascertainment techniques for harms equal, valid, and reliable?	Was duration of followup adequate for harms assessment?	Quality rating (for harms)	Comments
Kelsey, 2016[62] Zeitler, 2012[53] TODAY Study Group[58] TODAY Study Group[59] Levitt Katz, 2015[60] Zeitler, 2007[61] Treatment Options for type 2 Diabetes in Adolescents and Youth (TODAY) Study	Yes	Yes	Yes	Yes	Good	
Jones, 2002[63]	Unclear	No	Unclear	Yes	Fair	Unsure how harms data was measured.

For RCTs and cohorts, definition of ratings based on above criteria:

Good: Meets all criteria: Comparable groups are assembled initially and maintained throughout the study (followup ≥80%); reliable and valid measurement instruments are used and applied equally to all groups; interventions are spelled out clearly; all important outcomes are considered; and appropriate attention to confounders in analysis. In addition, intention-to-treat analysis is used for RCTs.

Fair: Studies are graded "fair" if any or all of the following problems occur, without the fatal flaws noted in the "poor" category below: Generally comparable groups are assembled initially, but some question remains whether some (although not major) differences occurred with followup; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are accounted for. Intention-to-treat analysis is used for RCTs.

Poor: Studies are graded "poor" if any of the following fatal flaws exist: Groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied equally among groups (including not masking outcome assessment); and key confounders are given little or no attention. Intention-to-treat analysis is lacking for RCTs.

Abbreviations: RCT=randomized, controlled trial; TODAY=Treatment Options for Type 2 Diabetes in Adolescents and Youth.