# 3. Prevention or Delay of Diabetes and Associated Comorbidities: *Standards of Care in Diabetes—2024*

*American Diabetes Association Professional Practice Committee**

*Diabetes Care 2024;47(Suppl. 1):S43–S51 | https://doi.org/10.2337/dc24-S003*





**The American Diabetes Association (ADA) "Standards of Care in Diabetes" includes the ADA's current clinical practice recommendations and is intended to provide the components of diabetes care, general treatment goals and guidelines, and tools to evaluate quality of care. Members of the ADA Professional Practice Committee, an interprofessional expert committee, are responsible for updating the Standards of Care annually, or more frequently as warranted. For a detailed description of ADA standards, statements, and reports, as well as the evidence-grading system for ADA's clinical practice recommendations and a full list of Professional Practice Committee members, please refer to Introduction and Methodology. Readers who wish to comment on the Standards of Care are invited to do so at professional.diabetes.org/SOC.**

*For guidelines related to screening for increased risk for type 2 diabetes (prediabetes), please refer to Section 2, "Diagnosis and Classification and of Diabetes." For guidelines related to screening, diagnosis, and management of type 2 diabetes in youth, please refer to Section 14, "Children and Adolescents."*

***Recommendations***

**3.1** In people with prediabetes, monitor for the development of type 2 diabetes at least annually; modify based on individual risk assessment. **E**

**3.2** In people with preclinical type 1 diabetes, monitor for disease progression using A1C approximately every 6 months and 75-g oral glucose tolerance test (i.e., fasting and 2-h plasma glucose) annually; modify frequency of monitoring based on individual risk assessment based on age, number and type of autoantibodies, and glycemic metrics. **E**

Screening for prediabetes and type 2 diabetes risk through an assessment of risk factors (**Table 2.5**) or with an assessment tool, such as the American Diabetes Association risk test (**Fig. 2.2**), is recommended to guide whether to perform a diagnostic test for prediabetes (**Table 2.2**) and type 2 diabetes (**Table 2.1**) (see Section 2, "Diagnosis and Classification of Diabetes"). Testing high-risk adults for prediabetes is warranted because the laboratory assessment is safe and reasonable in cost, substantial time exists before the development of type 2 diabetes and its complications during which one can intervene, and there are effective approaches delaying type 2 diabetes in those with prediabetes with an A1C 5.7–6.4% (39–47 mmol/mol), impaired glucose tolerance (IGT), or impaired fasting glucose (IFG). The utility of screening with A1C for prediabetes

**A complete list of members of the American Diabetes Association Professional Practice Committee can be found at https://doi.org/10.2337/dc24-SINT.*

*Duality of interest information for each author is available at https://doi.org/10.2337/dc24-SDIS.*

*Suggested citation: American Diabetes Association Professional Practice Committee. 3. Prevention or delay of diabetes and associated comorbidities:* Standards of Care in Diabetes—2024. *Diabetes Care 2024;47(Suppl. 1):S43–S51*

and diabetes may be limited in the presence of hemoglobinopathies and conditions that affect red blood cell turnover. See Section 2, "Diagnosis and Classification of Diabetes," and Section 6, "Glycemic Goals and Hypoglycemia," for additional details on the appropriate use and limitations of A1C testing.

Three distinct stages of type 1 diabetes have been defined, with symptomatic type 1 diabetes being stage 3 (**Table 2.3**). In individuals at risk for development of clinical type 1 diabetes, younger age of seroconversion (particularly under age 3 years), the total number of diabetes related autoantibodies (1), and the development of autoantibodies against islet antigen 2 (IA-2) have all been associated with more rapid progression to clinical type 1 diabetes. While continuous glucose monitoring can predict progression to overt diabetes in children with autoantibodies (2), oral glucose tolerance testing–based metrics are superior in predicting progression compared with continuous glucose monitoring (3). The decision to perform an oral glucose tolerance test may depend on such factors as eligibility and interest for stage-specific treatments, participation in clinical research, and availability and burden of testing.

## LIFESTYLE BEHAVIOR CHANGE FOR DIABETES PREVENTION

***Recommendations***

**3.3** Refer adults with overweight or obesity at high risk of type 2 diabetes, as seen in the Diabetes Prevention Program (DPP), to an intensive lifestyle behavior change program to achieve and maintain a weight reduction of at least 7% of initial body weight through healthy reduced-calorie diet and ≥150 min/week of moderate-intensity physical activity. **A**

**3.4** A variety of eating patterns can be considered to prevent type 2 diabetes in individuals with prediabetes. **B**

**3.5** Given the cost-effectiveness of lifestyle behavior modification programs for diabetes prevention, such diabetes prevention programs should be offered to adults at high risk of type 2 diabetes. **A** Diabetes prevention programs should be covered by third-party payers, and inconsistencies in access should be addressed. **E**

**3.6** Based on individual preference, certified technology-assisted diabetes prevention programs may be effective in preventing type 2 diabetes and should be considered. **B**

### The Diabetes Prevention Program

Several major randomized controlled trials, including the Diabetes Prevention Program (DPP) trial (4), the Finnish Diabetes Prevention Study (DPS) (5), and the Da Qing Diabetes Prevention Study (Da Qing study) (6), demonstrate that lifestyle/behavioral intervention with an individualized reduced-calorie meal plan is highly effective in preventing or delaying type 2 diabetes and improving other cardiometabolic risk factors (such as blood pressure, lipids, and inflammation) (7). The strongest evidence for diabetes prevention in the U.S. comes from the DPP trial (4). The DPP demonstrated that intensive lifestyle intervention could reduce the risk of incident type 2 diabetes by 58% over 3 years. Follow-up of three large trials of lifestyle intervention for diabetes prevention showed sustained reduction in the risk of progression to type 2 diabetes: 39% reduction at 30 years in the Da Qing study (8), 43% reduction at 7 years in the Finnish DPS (5), and 34% reduction at 10 years (9) and 27% reduction at 15 years (10) in the U.S. Diabetes Prevention Program Outcomes Study (DPPOS).

The DPP lifestyle intervention was a goal-based intervention. All participants were given the same weight loss and physical activity goals, but individualization was permitted in the specific methods used to achieve the goals (11). The two major goals of the DPP intensive lifestyle intervention were to achieve and maintain a minimum of 7% weight loss and 150 min of moderate-intensity physical activity per week, such as brisk walking. Although weight loss was the most important factor in reducing the risk of incident diabetes, achieving the behavioral goal of at least 150 min of physical activity per week, even without achieving the weight loss goal, reduced the incidence of type 2 diabetes by 44% (12).

The 7% weight loss goal was selected because it was feasible to achieve and maintain and likely to lessen the risk of developing diabetes (as well as improve other cardiometabolic risk factors). Participants were encouraged to achieve the ≥7% weight loss during the first 6 months of the intervention. Further analysis suggests higher benefit for prevention of diabetes with at least 7–10% weight loss with lifestyle interventions (12). The recommended pace of weight loss was 1–2 lb/week. Calorie goals were calculated by estimating the daily calories needed to maintain the participant's initial weight and subtracting 500–1,000 calories/day (depending on initial body weight). The initial focus of the dietary intervention was on reducing total fat rather than calories. After several weeks, the concept of calorie balance and the need to restrict calories and fat was introduced (11).

The goal for physical activity was selected to approximate at least 700 kcal/week expenditure from physical activity. For ease of translation, this goal was described as at least 150 min of moderate-intensity physical activity per week, similar in intensity to brisk walking. Participants were encouraged to distribute their activity throughout the week with a minimum frequency of three times per week and at least 10 min per session. A maximum of 75 min of strength training could be applied toward the total 150 min/week physical activity goal (11).

To implement the weight loss and physical activity goals, the DPP used an individual model of treatment rather than a group-based approach. This choice was based on a desire to intervene before participants had the possibility of developing diabetes or losing interest in the program. The individual approach also allowed for the tailoring of interventions to reflect the diversity of the population (11).

The DPP intervention was administered as a structured core curriculum followed by a flexible maintenance program of individual counseling, group sessions, motivational campaigns, and restart opportunities. The 16-session core curriculum was completed within the first 24 weeks of the program. It included sessions on lowering calories, increasing physical activity, self-monitoring, maintaining healthy lifestyle behaviors (such as how to choose healthy food options when eating out), and guidance on managing psychological, social, and motivational challenges. Further details are available regarding the core curriculum sessions (11).

### Nutrition

Nutrition counseling for weight loss in the DPP lifestyle intervention arm included a

reduction of total dietary fat and calories (4,11,12). However, evidence suggests that there is not an ideal percentage of calories from carbohydrate, protein, and fat for all people to prevent diabetes; therefore, macronutrient distribution should be based on an individualized assessment of current eating patterns, preferences, and metabolic goals (13). Based on other trials, a variety of eating patterns (13,14) may also be appropriate for individuals with prediabetes (13), including Mediterranean-style and low-carbohydrate eating plans (15–18). Observational studies have also shown that vegetarian, plant-based (may include some animal products), and Dietary Approaches to Stop Hypertension (DASH) eating patterns are associated with a lower risk of developing type 2 diabetes (19–22). Evidence suggests that the overall quality of food consumed (as measured by the Healthy Eating Index, Alternative Healthy Eating Index, and DASH score), with an emphasis on whole grains, legumes, nuts, fruits, and vegetables and minimal refined and processed foods, is also associated with a lower risk of type 2 diabetes (21,23–25). As is the case for those with diabetes, individualized medical nutrition therapy (see Section 5, "Facilitating Positive Health Behaviors and Well-being to Improve Health Outcomes," for more detailed information) is effective in lowering A1C in individuals diagnosed with prediabetes (26).

### Physical Activity

Moderate-intensity physical activity, such as brisk walking for 150 min/week, has shown beneficial effects in those with prediabetes (4). Similarly, moderate-intensity physical activity has been shown to improve insulin sensitivity and reduce abdominal fat in children and young adults (27,28). Health care professionals are encouraged to promote a DPP-style program to all individuals who have been identified to be at an increased risk of type 2 diabetes. In addition to aerobic activity, a physical activity plan designed to prevent diabetes may include resistance training (11,29,30). Breaking up prolonged sedentary time may also be encouraged, as it is associated with moderately lower postprandial glucose levels (31,32). The effects of physical activity appear to extend to the prevention of gestational diabetes mellitus (GDM) (33).

### Delivery and Dissemination of Lifestyle Behavior Change for Diabetes Prevention

Because the intensive lifestyle intervention in the DPP was effective in preventing type 2 diabetes among those at high risk for the disease and lifestyle behavior change programs for diabetes prevention were shown to be cost-effective, broader efforts to disseminate scalable lifestyle behavior change programs for diabetes prevention with coverage by third-party payers ensued (34–38). Group delivery of DPP content in community or primary care settings has demonstrated the potential to reduce overall program costs while still producing weight loss and diabetes risk reduction (39–43).

The Centers for Disease Control and Prevention (CDC) developed the National Diabetes Prevention Program (National DPP), a resource designed to bring such evidence-based lifestyle change programs for preventing type 2 diabetes to communities (cdc.gov/diabetes/prevention/index.htm). This online resource includes locations of CDC-recognized diabetes prevention lifestyle change programs (cdc.gov/diabetes/prevention/find-a-program.html). To be eligible for this program, individuals must have a BMI in the overweight range and be at risk for diabetes based on laboratory testing, a previous diagnosis of GDM, or a positive risk test (cdc.gov/prediabetes/takethetest/). During the first 4 years of implementation of the CDC's National DPP, 36% achieved the 5% weight loss goal (44). The CDC has also developed the Diabetes Prevention Impact Tool Kit (nccd.cdc.gov/toolkit/diabetesimpact) to help organizations assess the economics of providing or covering the National DPP (45). To expand preventive services using a cost-effective model, the Centers for Medicare & Medicaid Services expanded Medicare reimbursement coverage for the National DPP to organizations recognized by the CDC that become Medicare suppliers for this service (innovation.cms.gov/innovation-models/medicare-diabetes-prevention-program). The locations of Medicare DPPs are available online at innovation.cms.gov/innovation-models/medicare-diabetes-prevention-program/mdpp-map. To qualify for Medicare coverage, individuals must have BMI $>25$ kg/m$^2$ (or BMI $>23$ kg/m$^2$ if self-identified as Asian) and glycemic testing consistent with prediabetes in the last year. Medicaid coverage of the National DPP is also expanding on a state-by-state basis.

While CDC-recognized behavioral counseling programs, including Medicare DPP services, have met minimum quality standards and are reimbursed by many payers, lower retention rates have been reported for younger adults and racial and ethnic minority populations (46). Therefore, other programs and modalities of behavioral counseling for diabetes prevention may also be appropriate and efficacious based on individual preferences and availability. The use of community health workers to support DPP-like interventions has been shown to be effective and cost-effective (47,48) (see Section 1, "Improving Care and Promoting Health in Populations," for more information). The use of community health workers may facilitate the adoption of behavior changes for diabetes prevention while bridging barriers related to social determinants of health. However, coverage by third-party payers remains limited. Counseling by a registered dietitian nutritionist (RDN) has been shown to help individuals with prediabetes improve eating habits, increase physical activity, and achieve 7–10% weight loss (13,49–51). Individualized medical nutrition therapy (see Section 5, "Facilitating Positive Health Behaviors and Well-being to Improve Health Outcomes," for more detailed information) is also effective in improving glycemia in individuals diagnosed with prediabetes (26,49). Furthermore, trials involving medical nutrition therapy for adults with prediabetes found significant reductions in weight, waist circumference, and glycemia. Individuals with prediabetes can benefit from referral to an RDN for individualized medical nutrition therapy upon diagnosis and at regular intervals throughout their treatment plan (50,52). Other health care professionals, such as pharmacists and diabetes care and education specialists, may be considered for diabetes prevention efforts (53,54).

Technology-assisted programs may effectively deliver a DPP-like intervention (55–60). A digital diabetes prevention program improved cardiovascular risk at 4 months but not at 12 months (61). Such technology-assisted programs may deliver content through smartphones, web-based applications, and telehealth and may be an acceptable and efficacious option to bridge barriers, particularly for individuals with low income and people in rural locations; however, not

all technology-assisted programs are effective (55,62–64). The CDC Diabetes Prevention Recognition Program (DPRP) (cdc.gov/diabetes/prevention/requirements-recognition.htm) certifies technology-assisted modalities as effective vehicles for DPP-based interventions; such programs must use an approved curriculum, include interaction with a coach, and attain the DPP outcomes of participation, physical activity reporting, and weight loss. Health care professionals should consider referring adults with prediabetes to certified technology-assisted programs.

### Lifestyle and Type 1 Diabetes Progression

Observational studies suggest that in those with islet autoantibodies, factors that may increase β-cell demand including less physical activity (65), higher dietary glycemic index (66), and total sugar intake (67) are associated with progression to clinical diabetes. Similar associations have not been seen in the development of autoantibodies. In The Environmental Determinants of Diabetes in the Young (TEDDY) longitudinal study, daily minutes spent in moderate to vigorous physical activity were associated with a reduced risk of progression to type 1 diabetes in children 5 to 15 years of age with multiple islet autoantibodies (hazard ratio [HR] 0.92 [95% CI 0.86–0.99] per 10-min increase; $P = 0.021$) (65). In the Diabetes Autoimmunity Study in the Young (DAISY), in children with islet autoantibodies, progression to type 1 diabetes was associated with higher dietary glycemic index (HR 2.20 [95% CI 1.17–4.15]) and total sugar intake (HR 1.75 [95% CI 1.07–2.85]) (66,67). In nonobese diabetic mice, an animal model for the development of type 1 diabetes, sustained high glucose drinking significantly aggravated islet inflammation and accelerated the onset of type 1 diabetes (68). Lifestyle interventions focusing on such factors in those with stage 1 or stage 2 type 1 diabetes have not yet been reported.

## PHARMACOLOGIC INTERVENTIONS

***Recommendations***

**3.7** Metformin for the prevention of type 2 diabetes should be considered in adults at high risk of type 2 diabetes, as typified by the DPP, especially those aged 25–59 years with BMI ≥35 kg/m$^2$, higher fasting plasma glucose (e.g., ≥110 mg/dL [≥6 mmol/L]), and higher A1C (e.g., ≥6.0% [≥42 mmol/mol]), and in individuals with prior gestational diabetes mellitus. **A**

**3.8** Long-term use of metformin may be associated with vitamin B12 deficiency; consider periodic assessment of vitamin B12 level in metformin-treated individuals, especially in those with anemia or peripheral neuropathy. **B**

Because weight loss through behavior changes in diet and physical activity can be difficult to maintain long term (9), people at high risk of type 2 diabetes may benefit from additional support and pharmacotherapeutic options, if needed. Various pharmacologic agents used to treat diabetes have been evaluated for diabetes prevention. Metformin, α-glucosidase inhibitors, incretin receptor agonists (e.g., liraglutide and semaglutide), thiazolidinediones, and insulin have been shown to lower the incidence of diabetes in specific populations (69–74), whereas diabetes prevention was not seen with nateglinide (75).

In the DPP, weight loss was an important factor in reducing the risk of progression, with every kilogram of weight loss conferring a 16% reduction in risk of progression over 3.2 years (12). In individuals with previous history of GDM, the risk of type 2 diabetes increased by 18% for every 1 unit BMI above the preconception baseline (76). Several medications evaluated for weight loss (e.g., orlistat, phentermine/topiramate, liraglutide, semaglutide, and tirzepatide) have been shown to decrease the incidence of type 2 diabetes in those with prediabetes (74,77–79).

Studies of other pharmacologic agents have shown some efficacy in diabetes prevention with valsartan or testosterone (80,81), but no efficacy in preventing diabetes with ramipril or anti-inflammatory drugs (81–84). Although the Vitamin D and Type 2 Diabetes (D2d) prospective randomized controlled trial showed no significant benefit of vitamin D versus placebo on the progression to type 2 diabetes in individuals at high risk (85), post hoc analyses and meta-analyses suggest a potential benefit in specific populations (85–89). Further research is needed to define characteristics and clinical indicators where vitamin D supplementation may be of benefit (80).

No pharmacologic agent has been approved by the U.S. Food and Drug Administration for prevention of type 2 diabetes. The risk versus benefit of each medication in support of person-centered goals must be weighed in addition to cost and burden of administration.

Metformin has the most safety data as a pharmacologic therapy for diabetes prevention (90). Metformin was overall less effective than lifestyle modification in the DPP, though group differences attenuated over time in the DPPOS (10), and metformin may be cost-saving over a 10-year period (36). In the DPP, metformin was as effective as lifestyle modification in participants with BMI ≥35 kg/m$^2$ and in younger participants aged 25–44 years (4). In individuals with a history of GDM in the DPP, metformin and intensive lifestyle modification led to an equivalent 50% reduction in diabetes risk (91). Both interventions remained highly effective during a 10-year follow-up period (92). By the time of the 15-year follow-up (DPPOS), exploratory analyses demonstrated that participants with a higher baseline fasting glucose (≥110 mg/dL [≥6 mmol/L] vs. 95–109 mg/dL [5.3–5.9 mmol/L]), those with a higher A1C (6.0–6.4% [42–46 mmol/mol] vs. <6.0% [<42 mmol/mol]), and individuals with a history of GDM (vs. individuals without a history of GDM) experienced higher risk reductions with metformin, identifying subgroups of participants that may benefit the most from metformin (93). In the Indian Diabetes Prevention Program (IDPP-1), metformin and lifestyle intervention reduced diabetes risk similarly at 30 months; however, the lifestyle intervention in IDPP-1 was less intensive than that in the DPP (94). Based on findings from the DPP, metformin should be recommended as an option for high-risk individuals (e.g., younger individuals, those with history of GDM, or those with BMI ≥35 kg/m$^2$). A recent Chinese open-label randomized controlled trial showed that metformin combined with standard lifestyle intervention further reduced the risk of developing diabetes than lifestyle intervention alone by ∼17% over 2 years (95). Periodic assessment of vitamin B12 level in those taking metformin chronically should be considered to check for possible deficiency, especially in those with anemia or peripheral neuropathy (96,97) (see Section 9, "Pharmacologic Approaches to

Glycemic Treatment," for more details). The effect of metformin on vitamin B12 increases with time (98), with a higher risk for vitamin B12 deficiency (<150 pmol/L) noted at 4–5 years. A person who has been on metformin for more than 4 years or is at risk for vitamin B12 deficiency for other reasons (e.g., vegan, previous gastric/small bowel surgery) should be monitored for vitamin B12 deficiency annually (99).

## PREVENTION OF VASCULAR DISEASE AND MORTALITY

***Recommendations***

**3.9** Prediabetes is associated with heightened cardiovascular risk; therefore, screening for and treatment of modifiable risk factors for cardiovascular disease are suggested. **B**

**3.10** Statin therapy may increase the risk of type 2 diabetes in people at high risk of developing type 2 diabetes. In such individuals, glucose status should be monitored regularly and diabetes prevention approaches reinforced. It is not recommended that statins be discontinued for this adverse effect. **B**

**3.11** In people with a history of stroke and evidence of insulin resistance and prediabetes, pioglitazone may be considered to lower the risk of stroke or myocardial infarction. However, this benefit needs to be balanced with the increased risk of weight gain, edema, and fractures. **A** Lower doses may mitigate the risk of adverse effects but may be less effective. **C**

People with prediabetes often have other cardiovascular risk factors, including hypertension and dyslipidemia (100), and are at increased risk for cardiovascular disease (101,102). Evaluation for tobacco use and referral for tobacco cessation should be part of routine care for those at risk for diabetes. Of note, the years immediately following smoking cessation may represent a time of increased risk for diabetes (103–105), and individuals should be monitored for diabetes development and receive evidence-based lifestyle behavior change for diabetes prevention described in this section. See Section 5, "Facilitating Positive Health Behaviors and Well-being to Improve Health Outcomes," for more detailed information. The lifestyle interventions for weight loss in study populations at risk for type 2 diabetes have shown a reduction in cardiovascular risk factors and the need for medications used to treat these cardiovascular risk factors (106,107). The lifestyle intervention in the Da Qing study was associated with lowering cardiovascular disease and mortality at 23 and 30 years of observational follow-up (6,8). Treatment goals and therapies for hypertension and dyslipidemia in the primary and secondary prevention of cardiovascular disease for people with prediabetes should be based on their level of cardiovascular risk. Increased vigilance is warranted to identify and treat these and other cardiovascular diseases risk factors (108). Statin use increases risk of diabetes (109–113). In the DPP, statin use was associated with greater diabetes risk irrespective of the treatment group (pooled HR [95% CI] for incident diabetes 1.36 [1.17–1.58]) (111). In trials of primary and secondary prevention of cardiovascular disease, cardiovascular and mortality benefits of statin therapy exceed the risk of diabetes (114,115), suggesting a favorable benefit-to-harm balance with statin therapy. Hence, discontinuation of statins is not recommended in this population due to concerns of diabetes risk.

Cardiovascular outcome trials in people without diabetes also inform risk reduction potential in people without diabetes at increased cardiometabolic risk (see Section 10, "Cardiovascular Disease and Risk Management," for more details). The IRIS (Insulin Resistance Intervention after Stroke) trial of people with a recent (<6 months) stroke or transient ischemic attack, without diabetes but with insulin resistance (as defined by a HOMA of insulin resistance index of ≥3.0), evaluated pioglitazone (target dose of 45 mg daily) compared with placebo. At 4.8 years, the risk of stroke or myocardial infarction, as well as the risk of diabetes, was lower in the pioglitazone group than with placebo; weight gain, edema, and fractures were higher in the pioglitazone treatment group (116–119). Lower doses may mitigate the adverse effects but may also be less effective (120).

## PERSON-CENTERED CARE GOALS

***Recommendations***

**3.12** In adults with overweight or obesity at high risk of type 2 diabetes, care goals should include weight loss and maintenance, minimizing the progression of hyperglycemia, and attention to cardiovascular risk. **B**

**3.13** Pharmacotherapy (e.g., for weight management, minimizing the progression of hyperglycemia, and cardiovascular risk reduction) may be considered to support person-centered care goals. **B**

**3.14** More intensive preventive approaches should be considered in individuals who are at particularly high risk of progression to diabetes, including individuals with BMI ≥35 kg/m$^2$, those at higher glucose levels (e.g., fasting plasma glucose 110–125 mg/dL [6.1–6.9 mmol/L], 2–h postchallenge glucose 173–199 mg/dL [9.6–11.0 mmol/L], and A1C ≥6.0% [≥42 mmol/mol]), and individuals with a history of gestational diabetes mellitus. **A**

Individualized risk-to-benefit ratio should be considered in screening, intervention, and monitoring to lower the risk of type 2 diabetes and associated comorbidities. Multiple factors, including age, BMI, and other comorbidities, may influence the risk of progression to diabetes and lifetime risk of complications (121,122). Prediabetes is associated with increased cardiovascular disease and mortality (102), which emphasizes the importance of attending to cardiovascular risk in this population.

In the DPP, which enrolled high-risk individuals with IGT, elevated fasting glucose, and elevated BMI, the crude incidence of diabetes within the placebo group was 11 cases per 100 person-years, with a cumulative 3-year incidence of diabetes of 29% (4). Characteristics of individuals in the DPP/DPPOS who were at particularly high risk of progression to diabetes (crude incidence of diabetes 14–22 cases per 100 person-years) included BMI ≥35 kg/m$^2$, higher glucose levels (e.g., fasting plasma glucose 110–125 mg/dL [6–6.9 mmol/L], 2–h postchallenge glucose 173–199 mg/dL [9.6–11.0 mmol/L], and A1C ≥6.0% [≥42 mmol/mol]), and a history of GDM (4,91,92). In contrast, in the community-based Atherosclerosis Risk in Communities (ARIC) study, observational follow-up of adults with mean age 75 years with laboratory evidence of prediabetes (based on A1C 5.7–6.4% [39–47 mmol/mol] and/or fasting glucose 100–125 mg/dL [5.6–6.9 mmol/L]), but not meeting specific BMI criteria, found lower progression to

diabetes over 6 years: 9% of those with A1C-defined prediabetes, 8% with IFG (122).

Thus, it is important to individualize the risk-to-benefit ratio of intervention and consider person-centered goals. Risk models have generally found higher benefit of the intervention in those at highest risk (12). Diabetes prevention trials and observational studies highlight key principles that may guide person-centered goals. In the DPP, which enrolled a high-risk population meeting criteria for overweight or obesity, weight loss was an important mediator of diabetes prevention or delay, with greater metabolic benefit seen with greater weight loss (12,123). In the DPP/DPPOS, progression to diabetes, duration of diabetes, and mean level of glycemia were important determinants of the development of microvascular complications (10). Achieving normal glucose regulation, even once, during the DPP was associated with a lower risk of diabetes and lower risk of microvascular complications (124). Observational follow-up of the Da Qing study also showed that regression from IGT to normal glucose tolerance or remaining with IGT rather than progressing to type 2 diabetes at the end of the 6-year intervention trial resulted in significantly lower risk of cardiovascular disease and microvascular disease over 30 years (125).

Pharmacotherapy for weight management (see Section 8, "Obesity and Weight Management for the Prevention and Treatment of Type 2 Diabetes," for more details), minimizing the progression of hyperglycemia (see Section 9, "Pharmacologic Approaches to Glycemic Treatment," for more details), and cardiovascular risk reduction (see Section 10, "Cardiovascular Disease and Risk Management," for more details) can be considered to support individualized person-centered goals, with more intensive preventive approaches considered in individuals at high risk of progression.

## PHARMACOLOGIC INTERVENTIONS TO DELAY SYMPTOMATIC TYPE 1 DIABETES

***Recommendation***

**3.15** Teplizumab-mzwv infusion to delay the onset of symptomatic type 1 diabetes (stage 3) should be considered in selected individuals aged ≥8 years with stage 2 type 1 diabetes. Management should be in a specialized setting with appropriately trained personnel. **B**

Teplizumab has been approved to delay the onset of stage 3 type 1 diabetes in people 8 years of age and older with stage 2 type 1 diabetes based in part on the results of a single trial in relatives of people with type 1 diabetes (126). In this study, 44 individuals were randomized to a 14-day course of teplizumab and 32 to placebo. The median time to stage 3 type 1 diabetes diagnosis was 48.4 months in the teplizumab group and 24.4 months in the placebo group. Type 1 diabetes was diagnosed in 19 (43%) of participants who received teplizumab and 23 (72%) of those who received placebo (HR 0.41 [95% CI 0.22–0.78]). In prespecified analyses, the presence of HLA-DR4, absence of HLA-DR3, and absence of anti–zinc transporter 8 antibody predicted response to teplizumab (HR 0.20 [95% CI 0.09–0.45], 0.18 [0.07–0.45], and [0.07 [0.02 to 0.26], respectively). The most common adverse reactions were transient lymphopenia (73%) followed by rash (36%).

Numerous clinical studies are being conducted to test methods for preventing or delaying the onset of stage 3 type 1 diabetes in those with evidence of autoimmunity without symptoms or for delaying loss of insulin secretory capacity after onset of stage 3, some with promising results (see ClinicalTrials.gov and TrialNet.org).

## References


1. Ziegler AG, Rewers M, Simell O, et al. Seroconversion to multiple islet autoantibodies and risk of progression to diabetes in children. JAMA 2013;309:2473–2479
2. Steck A, Dong F, Taki I, et al. Continuous glucose monitoring predicts progression to diabetes in autoantibody-positive children. J Clin Endocrinol Metab 2019;104:3337–3344
3. Ylescupidez A, Speake C, Pietropaolo SL, et al. OGTT metrics surpass continuous glucose monitoring data for T1D prediction in multiple-autoantibody-positive individuals [published correction appears in J Clin Endocrinol Metab 2023;dgad574]. J Clin Endocrinol Metab 2023;dgad472
4. Knowler WC, Barrett-Connor E, Fowler SE, et al.; Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 2002;346:393–403
5. Lindström J, Ilanne-Parikka P, Peltonen M, et al.; Finnish Diabetes Prevention Study Group. Sustained reduction in the incidence of type 2 diabetes by lifestyle intervention: follow-up of the Finnish Diabetes Prevention Study. Lancet 2006;368:1673–1679
6. Li G, Zhang P, Wang J, et al. Cardiovascular mortality, all-cause mortality, and diabetes incidence after lifestyle intervention for people with impaired glucose tolerance in the Da Qing Diabetes Prevention Study: a 23-year follow-up study. Lancet Diabetes Endocrinol 2014;2:474–480
7. Nathan DM, Bennett PH, Crandall JP, et al.; DPP Research Group. Does diabetes prevention translate into reduced long-term vascular complications of diabetes? Diabetologia 2019;62:1319–1328
8. Gong Q, Zhang P, Wang J, et al.; Da Qing Diabetes Prevention Study Group. Morbidity and mortality after lifestyle intervention for people with impaired glucose tolerance: 30-year results of the Da Qing Diabetes Prevention Outcome Study. Lancet Diabetes Endocrinol 2019;7:452–461
9. Knowler WC, Fowler SE, Hamman RF, et al.; Diabetes Prevention Program Research Group. 10-year follow-up of diabetes incidence and weight loss in the Diabetes Prevention Program Outcomes Study. Lancet 2009;374:1677–1686
10. Diabetes Prevention Program Research Group. Long-term effects of lifestyle intervention or metformin on diabetes development and microvascular complications over 15-year follow-up: the Diabetes Prevention Program Outcomes Study. Lancet Diabetes Endocrinol 2015;3:866–875
11. Diabetes Prevention Program (DPP) Research Group. The Diabetes Prevention Program (DPP): description of lifestyle intervention. Diabetes Care 2002;25:2165–2171
12. Hamman RF, Wing RR, Edelstein SL, et al. Effect of weight loss with lifestyle intervention on risk of diabetes. Diabetes Care 2006;29:2102–2107
13. Evert AB, Dennison M, Gardner CD, et al. Nutrition therapy for adults with diabetes or prediabetes: a consensus report. Diabetes Care 2019;42:731–754
14. U.S.Department of Health and Human Servicesand U.S. Department of Agriculture. *2015–2020 Dietary Guidelines for Americans*. 8th Ed. Accessed 7 October 2023. Available from https://health.gov/sites/default/files/2019-09/2015-2020_Dietary_Guidelines.pdf
15. Salas-Salvadó J, Guasch-Ferré M, Lee CH, Estruch R, Clish CB, Ros E. Protective effects of the Mediterranean diet on type 2 diabetes and metabolic syndrome. J Nutr 2015;146:920S–927S
16. Bloomfield HE, Koeller E, Greer N, MacDonald R, Kane R, Wilt TJ. Effects on health outcomes of a Mediterranean diet with no restriction on fat intake: a systematic review and meta-analysis. Ann Intern Med 2016;165:491–500
17. Estruch R, Ros E, Salas-Salvadó J, et al.; PREDIMED Study Investigators. Primary prevention of cardiovascular disease with a Mediterranean diet supplemented with extra-virgin olive oil or nuts. N Engl J Med 2018;378:e34
18. Stentz FB, Brewer A, Wan J, et al. Remission of pre-diabetes to normal glucose tolerance in obese adults with high protein versus high carbohydrate diet: randomized control trial. BMJ Open Diabetes Res Care 2016;4:e000258
19. Chiu THT, Pan WH, Lin MN, Lin CL. Vegetarian diet, change in dietary patterns, and diabetes risk: a prospective study. Nutr Diabetes 2018;8:12
20. Lee Y, Park K. Adherence to a vegetarian diet and diabetes risk: a systematic review and meta-analysis of observational studies. Nutrients 2017;9:603

21. Qian F, Liu G, Hu FB, Bhupathiraju SN, Sun Q. Association between plant-based dietary patterns and risk of type 2 diabetes: a systematic review and meta-analysis. JAMA Intern Med 2019;179:1335–1344
22. Esposito K, Chiodini P, Maiorino MI, Bellastella G, Panagiotakos D, Giugliano D. Which diet for prevention of type 2 diabetes? A meta-analysis of prospective studies. Endocrine 2014;47:107–116
23. Ley SH, Hamdy O, Mohan V, Hu FB. Prevention and management of type 2 diabetes: dietary components and nutritional strategies. Lancet 2014;383:1999–2007
24. Jacobs S, Harmon BE, Boushey CJ, et al. A priori-defined diet quality indexes and risk of type 2 diabetes: the Multiethnic Cohort. Diabetologia 2015;58:98–112
25. Chiuve SE, Fung TT, Rimm EB, et al. Alternative dietary indices both strongly predict risk of chronic disease. J Nutr 2012;142:1009–1018
26. Parker AR, Byham-Gray L, Denmark R, Winkle PJ. The effect of medical nutrition therapy by a registered dietitian nutritionist in patients with prediabetes participating in a randomized controlled clinical research trial. J Acad Nutr Diet 2014;114:1739–1748
27. Fedewa MV, Gist NH, Evans EM, Dishman RK. Exercise and insulin resistance in youth: a meta-analysis. Pediatrics 2014;133:e163–e174
28. Davis CL, Pollock NK, Waller JL, et al. Exercise dose and diabetes risk in overweight and obese children: a randomized controlled trial. JAMA 2012;308:1103–1112
29. Sigal RJ, Alberga AS, Goldfield GS, et al. Effects of aerobic training, resistance training, or both on percentage body fat and cardiometabolic risk markers in obese adolescents: the healthy eating aerobic and resistance training in youth randomized clinical trial. JAMA Pediatr 2014;168:1006–1014
30. Dai X, Zhai L, Chen Q, et al. Two-year-supervised resistance training prevented diabetes incidence in people with prediabetes: a randomised control trial. Diabetes Metab Res Rev 2019;35:e3143
31. Thorp AA, Kingwell BA, Sethi P, Hammond L, Owen N, Dunstan DW. Alternating bouts of sitting and standing attenuate postprandial glucose responses. Med Sci Sports Exerc 2014;46:2053–2061
32. Healy GN, Dunstan DW, Salmon J, et al. Breaks in sedentary time: beneficial associations with metabolic risk. Diabetes Care 2008;31:661–666
33. Russo LM, Nobles C, Ertel KA, Chasan-Taber L, Whitcomb BW. Physical activity interventions in pregnancy and risk of gestational diabetes mellitus: a systematic review and meta-analysis. Obstet Gynecol 2015;125:576–582
34. Herman WH, Hoerger TJ, Brandle M, et al.; Diabetes Prevention Program Research Group. The cost-effectiveness of lifestyle modification or metformin in preventing type 2 diabetes in adults with impaired glucose tolerance. Ann Intern Med 2005;142:323–332
35. Chen F, Su W, Becker SH, et al. Clinical and economic impact of a digital, remotely-delivered intensive behavioral counseling program on medicare beneficiaries at risk for diabetes and cardiovascular disease. PLoS One 2016;11:e0163627
36. Diabetes Prevention Program Research Group. The 10-year cost-effectiveness of lifestyle intervention or metformin for diabetes prevention: an intent-to-treat analysis of the DPP/DPPOS. Diabetes Care 2012;35:723–730
37. Alva ML, Hoerger TJ, Jeyaraman R, Amico P, Rojas-Smith L. Impact of the YMCA of the USA Diabetes Prevention Program on Medicare spending and utilization. Health Aff (Millwood) 2017;36:417–424
38. Zhou X, Siegel KR, Ng BP, et al. Cost-effectiveness of diabetes prevention interventions targeting high-risk individuals and whole populations: a systematic review. Diabetes Care 2020;43:1593–1616
39. Ackermann RT, Finch EA, Brizendine E, Zhou H, Marrero DG. Translating the Diabetes Prevention Program into the community. The DEPLOY pilot study. Am J Prev Med 2008;35:357–363
40. Balk EM, Earley A, Raman G, Avendano EA, Pittas AG, Remington PL. Combined diet and physical activity promotion programs to prevent type 2 diabetes among persons at increased risk: a systematic review for the Community Preventive Services Task Force. Ann Intern Med 2015;163:437–451
41. Li R, Qu S, Zhang P, et al. Economic evaluation of combined diet and physical activity promotion programs to prevent type 2 diabetes among persons at increased risk: a systematic review for the Community Preventive Services Task Force. Ann Intern Med 2015;163:452–460
42. Gilmer T, O'Connor PJ, Schiff JS, et al. Cost-effectiveness of a community-based diabetes prevention program with participation incentives for medicaid beneficiaries. Health Serv Res 2018;53:4704–4724
43. Ackermann RT, Kang R, Cooper AJ, et al. Effect on health care expenditures during nationwide implementation of the Diabetes Prevention Program as a health insurance benefit. Diabetes Care 2019;42:1776–1783
44. Ely EK, Gruss SM, Luman ET, et al. A national effort to prevent type 2 diabetes: participant-level evaluation of CDC's National Diabetes Prevention Program. Diabetes Care 2017;40:1331–1341
45. Lanza A, Soler R, Smith B, Hoerger T, Neuwahl S, Zhang P. The Diabetes Prevention Impact Tool Kit: an online tool kit to assess the cost-effectiveness of preventing type 2 diabetes. J Public Health Manag Pract 2019;25:E1–E5
46. Cannon MJ, Masalovich S, Ng BP, et al. Retention among participants in the National Diabetes Prevention Program lifestyle change program, 2012-2017. Diabetes Care 2020;43:2042–2049
47. The Community Guide. Diabetes prevention: interventions engaging community health workers, 2016. Accessed 7 October 2023. Available from https://www.thecommunityguide.org/findings/diabetes-prevention-interventions-engaging-community-health-workers
48. Jacob V, Chattopadhyay SK, Hopkins DP, et al. Economics of community health workers for chronic disease: findings from Community Guide systematic reviews. Am J Prev Med 2019;56:e95–e106
49. Raynor HA, Davidson PG, Burns H, et al. Medical nutrition therapy and weight loss questions for the Evidence Analysis Library prevention of type 2 diabetes project: systematic reviews. J Acad Nutr Diet 2017;117:1578–1611
50. Sun Y, You W, Almeida F, Estabrooks P, Davy B. The effectiveness and cost of lifestyle interventions including nutrition education for diabetes prevention: a systematic review and meta-analysis. J Acad Nutr Diet 2017;117:404–421.e36
51. Briggs Early K, Stanley K. Position of the Academy of Nutrition and Dietetics: the role of medical nutrition therapy and registered dietitian nutritionists in the prevention and treatment of prediabetes and type 2 diabetes. J Acad Nutr Diet 2018;118:343–353
52. Powers MA, Bardsley JK, Cypress M, et al. Diabetes self-management education and support in adults with type 2 diabetes: a consensus report of the American Diabetes Association, the Association of Diabetes Care & Education Specialists, the Academy of Nutrition and Dietetics, the American Academy of Family Physicians, the American Academy of PAs, the American Association of Nurse Practitioners, and the American Pharmacists Association. Diabetes Care 2020;43:1636–1649
53. Hudspeth BD. Power of prevention: the pharmacist's role in prediabetes management. Diabetes Spectr 2018;31:320–323
54. Butcher MK, Vanderwood KK, Hall TO, Gohdes D, Helgerson SD, Harwell TS. Capacity of diabetes education programs to provide both diabetes self-management education and to implement diabetes prevention services. J Public Health Manag Pract 2011;17:242–247
55. Grock S, Ku JH, Kim J, Moin T. A review of technology-assisted interventions for diabetes prevention. Curr Diab Rep 2017;17:107
56. Sepah SC, Jiang L, Peters AL. Translating the Diabetes Prevention Program into an online social network: validation against CDC standards. Diabetes Educ 2014;40:435–443
57. Bian RR, Piatt GA, Sen A, et al. The effect of technology-mediated diabetes prevention interventions on weight: a meta-analysis. J Med Internet Res 2017;19:e76
58. Sepah SC, Jiang L, Peters AL. Long-term outcomes of a Web-based diabetes prevention program: 2-year results of a single-arm longitudinal study. J Med Internet Res 2015;17:e92
59. Moin T, Damschroder LJ, AuYoung M, et al. Results from a trial of an online Diabetes Prevention Program intervention. Am J Prev Med 2018;55:583–591
60. Michaelides A, Major J, Pienkosz E Jr, Wood M, Kim Y, Toro-Ramos T. Usefulness of a novel mobile Diabetes Prevention Program delivery platform with human coaching: 65-week observational follow-up. JMIR Mhealth Uhealth 2018;6:e93
61. Michaud TL, Almeida FA, Porter GC, et al. Effects of a digital diabetes prevention program on cardiovascular risk among individuals with prediabetes. Prim Care Diabetes 2023;17:148–154
62. Kim SE, Castro Sweet CM, Cho E, Tsai J, Cousineau MR. Evaluation of a digital diabetes prevention program adapted for low-income patients, 2016-2018. Prev Chronic Dis 2019;16:E155
63. Vadheim LM, Patch K, Brokaw SM, et al. Telehealth delivery of the Diabetes Prevention

Program to rural communities. Transl Behav Med 2017;7:286–291
64. Fischer HH, Durfee MJ, Raghunath SG, Ritchie ND. Short message service text message support for weight loss in patients with prediabetes: pragmatic trial. JMIR Diabetes 2019;4:e12985
65. Liu X, Johnson SB, Lynch KF, et al.; TEDDY Study Group. Physical activity and the development of islet autoimmunity and type 1 diabetes in 5- to 15-year-old children followed in the TEDDY study. Diabetes Care 2023;46:1409–1416
66. Lamb MM, Yin X, Barriga K, et al. Dietary glycemic index, development of islet autoimmunity, and subsequent progression to type 1 diabetes in young children. J Clin Endocrinol Metab 2008; 93:3936–3942
67. Lamb MM, Frederiksen B, Seifert JA, Kroehl M, Rewers M, Norris JM. Sugar intake is associated with progression from islet autoimmunity to type 1 diabetes: the Diabetes Autoimmunity Study in the Young. Diabetologia 2015;58:2027–2034
68. Li X, Wang L, Meng G, et al. Sustained high glucose intake accelerates type 1 diabetes in NOD mice. Front Endocrinol (Lausanne) 2022;13: 1037822
69. Gerstein HC, Bosch J, Dagenais GR, et al.; ORIGIN Trial Investigators. Basal insulin and cardiovascular and other outcomes in dysglycemia. N Engl J Med 2012;367:319–328
70. DeFronzo RA, Tripathy D, Schwenke DC, et al.; ACT NOW Study. Pioglitazone for diabetes prevention in impaired glucose tolerance. N Engl J Med 2011;364:1104–1115
71. Gerstein HC, Yusuf S, Bosch J, et al.; DREAM (Diabetes REduction Assessment with ramipril and rosiglitazone Medication) Trial Investigators. Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomised controlled trial. Lancet 2006;368:1096–1105
72. le Roux CW, Astrup A, Fujioka K, et al.; SCALE Obesity Prediabetes NN8022-1839 Study Group. 3 years of liraglutide versus placebo for type 2 diabetes risk reduction and weight management in individuals with prediabetes: a randomised, double-blind trial. Lancet 2017;389:1399–1409
73. Chiasson JL, Josse RG, Gomis R, Hanefeld M, Karasik A; STOP-NIDDM Trail Research Group. Acarbose for prevention of type 2 diabetes mellitus: the STOP-NIDDM randomised trial. Lancet 2002;359:2072–2077
74. Wilding JPH, Batterham RL, Calanna S, et al.; STEP 1 Study Group. Once-weekly semaglutide in adults with overweight or obesity. N Engl J Med 2021;384:989–1002
75. Holman RR, Haffner SM, McMurray JJ, et al.; NAVIGATOR Study Group. Effect of nateglinide on the incidence of diabetes and cardiovascular events. N Engl J Med 2010;362:1463–1476
76. Dennison RA, Chen ES, Green ME, et al. The absolute and relative risk of type 2 diabetes after gestational diabetes: a systematic review and meta-analysis of 129 studies. Diabetes Res Clin Pract 2021;171:108625
77. Torgerson JS, Hauptman J, Boldrin MN, Sjöström L. XENical in the prevention of diabetes in obese subjects (XENDOS) study: a randomized study of orlistat as an adjunct to lifestyle changes for the prevention of type 2 diabetes in obese patients. Diabetes Care 2004;27:155–161
78. Garvey WT, Ryan DH, Henry R, et al. Prevention of type 2 diabetes in subjects with prediabetes and metabolic syndrome treated with phentermine and topiramate extended release. Diabetes Care 2014;37:912–921
79. Jastreboff AM, Aronne LJ, Ahmad NN, et al.; SURMOUNT-1 Investigators. Tirzepatide once weekly for the treatment of obesity. N Engl J Med 2022;387:205–216
80. Wittert G, Bracken K, Robledo KP, et al. Testosterone treatment to prevent or revert type 2 diabetes in men enrolled in a lifestyle programme (T4DM): a randomised, double-blind, placebo-controlled, 2-year, phase 3b trial. Lancet Diabetes Endocrinol 2021;9:32–45
81. McMurray JJ, Holman RR, Haffner SM, et al.; NAVIGATOR Study Group. Effect of valsartan on the incidence of diabetes and cardiovascular events. N Engl J Med 2010;362:1477–1490
82. Bosch J, Yusuf S, Gerstein HC, et al.; DREAM Trial Investigators. Effect of ramipril on the incidence of diabetes. N Engl J Med 2006;355: 1551–1562
83. Ray KK, Colhoun HM, Szarek M, et al.; ODYSSEY OUTCOMES Committees and Investigators. Effects of alirocumab on cardiovascular and metabolic outcomes after acute coronary syndrome in patients with or without diabetes: a prespecified analysis of the ODYSSEY OUTCOMES randomised controlled trial. Lancet Diabetes Endocrinol 2019;7:618–628
84. Everett BM, Donath MY, Pradhan AD, et al. Anti-inflammatory therapy with canakinumab for the prevention and management of diabetes. J Am Coll Cardiol 2018;71:2392–2401
85. Pittas AG, Dawson-Hughes B, Sheehan P, et al.; D2d Research Group. Vitamin D supplementation and prevention of type 2 diabetes. N Engl J Med 2019;381:520–530
86. Dawson-Hughes B, Staten MA, Knowler WC, et al.; D2d Research Group. Intratrial exposure to vitamin D and New-onset diabetes among adults with prediabetes: a secondary analysis from the vitamin D and type 2 diabetes (D2d) study. Diabetes Care 2020;43:2916–2922
87. Zhang Y, Tan H, Tang J, et al. Effects of vitamin D supplementation on prevention of type 2 diabetes in patients with prediabetes: a systematic review and meta-analysis. Diabetes Care 2020;43:1650–1658
88. Barbarawi M, Zayed Y, Barbarawi O, et al. Effect of vitamin D supplementation on the incidence of diabetes mellitus. J Clin Endocrinol Metab 2020;105:dgaa335
89. Pittas AG, Kawahara T, Jorde R, et al. Vitamin D and risk for type 2 diabetes in people with prediabetes: a systematic review and meta-analysis of individual participant data from 3 randomized clinical trials. Ann Intern Med 2023;176:355–363
90. Diabetes Prevention Program Research Group. Long-term safety, tolerability, and weight loss associated with metformin in the Diabetes Prevention Program Outcomes Study. Diabetes Care 2012;35:731–737
91. Ratner RE, Christophi CA, Metzger BE, et al.; Diabetes Prevention Program Research Group. Prevention of diabetes in women with a history of gestational diabetes: effects of metformin and lifestyle interventions. J Clin Endocrinol Metab 2008;93:4774–4779
92. Aroda VR, Christophi CA, Edelstein SL, et al.; Diabetes Prevention Program Research Group. The effect of lifestyle intervention and metformin on preventing or delaying diabetes among women with and without gestational diabetes: the Diabetes Prevention Program Outcomes Study 10-year follow-up. J Clin Endocrinol Metab 2015; 100:1646–1653
93. Diabetes Prevention Program Research Group. Long-term effects of metformin on diabetes prevention: identification of subgroups that benefited most in the Diabetes Prevention Program and Diabetes Prevention Program Outcomes Study. Diabetes Care 2019;42:601–608
94. Ramachandran A, Snehalatha C, Mary S, Mukesh B, Bhaskar AD; Indian Diabetes Prevention Programme (IDPP). The Indian Diabetes Prevention Programme shows that lifestyle modification and metformin prevent type 2 diabetes in Asian Indian subjects with impaired glucose tolerance (IDPP-1). Diabetologia 2006;49:289–297
95. Zhang L, Zhang Y, Shen S, et al.; China Diabetes Prevention Program Study Group. Safety and effectiveness of metformin plus lifestyle intervention compared with lifestyle intervention alone in preventing progression to diabetes in a Chinese population with impaired glucose regulation: a multicentre, open-label, randomised controlled trial. Lancet Diabetes Endocrinol 2023;11:567–577
96. Griffin SJ, Bethel MA, Holman RR, et al. Metformin in non-diabetic hyperglycaemia: the GLINT feasibility RCT. Health Technol Assess 2018; 22:1–64
97. Aroda VR, Edelstein SL, Goldberg RB, et al.; Diabetes Prevention Program Research Group. Long-term metformin use and vitamin B12 deficiency in the Diabetes Prevention Program Outcomes Study. J Clin Endocrinol Metab 2016; 101:1754–1761
98. de Jager J, Kooy A, Lehert P, et al. Long term treatment with metformin in patients with type 2 diabetes and risk of vitamin B-12 deficiency: randomised placebo controlled trial. BMJ 2010; 340:c2181
99. Kidney Disease: Improving Global Outcomes (KDIGO) Diabetes Work Group. KDIGO 2020 clinical practice guideline for diabetes management in chronic kidney disease. Kidney Int 2020;98(4S): S1–S115
100. Ali MK, Bullard KM, Saydah S, Imperatore G, Gregg EW. Cardiovascular and renal burdens of prediabetes in the USA: analysis of data from serial cross-sectional surveys, 1988-2014. Lancet Diabetes Endocrinol 2018;6:392–403
101. Pan Y, Chen W, Wang Y. Prediabetes and outcome of ischemic stroke or transient ischemic attack: a systematic review and meta-analysis. J Stroke Cerebrovasc Dis 2019;28:683–692
102. Huang Y, Cai X, Mai W, Li M, Hu Y. Association between prediabetes and risk of cardiovascular disease and all cause mortality: systematic review and meta-analysis. BMJ 2016; 355:i5953
103. Yeh HC, Duncan BB, Schmidt MI, Wang NY, Brancati FL. Smoking, smoking cessation, and risk for type 2 diabetes mellitus: a cohort study. Ann Intern Med 2010;152:10–17
104. Oba S, Noda M, Waki K, et al.; Japan Public Health Center-Based Prospective Study Group. Smoking cessation increases short-term risk of type 2 diabetes irrespective of weight gain: the Japan Public Health Center-Based Prospective Study. PLoS One 2012;7:e17061

105. Hu Y, Zong G, Liu G, et al. Smoking cessation, weight change, type 2 diabetes, and mortality. N Engl J Med 2018;379:623–632
106. Orchard TJ, Temprosa M, Barrett-Connor E, et al.; Diabetes Prevention Program Outcomes Study Research Group. Long-term effects of the Diabetes Prevention Program interventions on cardiovascular risk factors: a report from the DPP Outcomes Study. Diabet Med 2013;30:46–55
107. Salas-Salvadó J, Díaz-López A, Ruiz-Canela M, et al.; PREDIMED-Plus investigators. Effect of a lifestyle intervention program with energy-restricted mediterranean diet and exercise on weight loss and cardiovascular risk factors: one-year results of the PREDIMED-Plus trial. Diabetes Care 2019;42:777–788
108. Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation 2019;140:e596–e646
109. Thakker D, Nair S, Pagada A, Jamdade V, Malik A. Statin use and the risk of developing diabetes: a network meta-analysis. Pharmacoepidemiol Drug Saf 2016;25:1131–1149
110. Macedo AF, Douglas I, Smeeth L, Forbes H, Ebrahim S. Statins and the risk of type 2 diabetes mellitus: cohort study using the UK clinical practice pesearch datalink. BMC Cardiovasc Disord 2014;14:85
111. Crandall JP, Mather K, Rajpathak SN, et al. Statin use and risk of developing diabetes: results from the Diabetes Prevention Program. BMJ Open Diabetes Res Care 2017;5:e000438
112. Preiss D, Seshasai SR, Welsh P, et al. Risk of incident diabetes with intensive-dose compared with moderate-dose statin therapy: a meta-analysis. JAMA 2011;305:2556–2564
113. Mansi IA, Chansard M, Lingvay I, Zhang S, Halm EA, Alvarez CA. Association of statin therapy initiation with diabetes progression: a retrospective matched-cohort study. JAMA Intern Med 2021;181:1562–1574
114. Ridker PM, Pradhan A, MacFadyen JG, Libby P, Glynn RJ. Cardiovascular benefits and diabetes risks of statin therapy in primary prevention: an analysis from the JUPITER trial. Lancet 2012;380:565–571
115. Cai T, Abel L, Langford O, et al. Associations between statins and adverse events in primary prevention of cardiovascular disease: systematic review with pairwise, network, and dose-response meta-analyses. BMJ 2021;374:n1537
116. Kernan WN, Viscoli CM, Furie KL, et al.; IRIS Trial Investigators. Pioglitazone after ischemic stroke or transient ischemic attack. N Engl J Med 2016;374:1321–1331
117. Inzucchi SE, Viscoli CM, Young LH, et al.; IRIS Trial Investigators. Pioglitazone prevents diabetes in patients with insulin resistance and cerebrovascular disease. Diabetes Care 2016;39:1684–1692
118. Spence JD, Viscoli CM, Inzucchi SE, et al.; IRIS Investigators. Pioglitazone therapy in patients with stroke and prediabetes: a post hoc analysis of the IRIS randomized clinical trial. JAMA Neurol 2019;76:526–535
119. Saremi A, Schwenke DC, Buchanan TA, et al. Pioglitazone slows progression of atherosclerosis in prediabetes independent of changes in cardiovascular risk factors [published correction appears in Arterioscler Thromb Vasc Biol 2013;35:e114]. Arterioscler Thromb Vasc Biol 2013;33:393–399
120. Spence JD, Viscoli C, Kernan WN, et al. Efficacy of lower doses of pioglitazone after stroke or transient ischaemic attack in patients with insulin resistance. Diabetes Obes Metab 2022;24:1150–1158
121. Nadeau KJ, Anderson BJ, Berg EG, et al. Youth-onset type 2 diabetes consensus report: current status, challenges, and priorities. Diabetes Care 2016;39:1635–1642
122. Rooney MR, Rawlings AM, Pankow JS, et al. Risk of progression to diabetes among older adults with prediabetes. JAMA Intern Med 2021;181:511–519
123. Lachin JM, Christophi CA, Edelstein SL, et al.; DDK Research Group. Factors associated with diabetes onset during metformin versus placebo therapy in the diabetes prevention program. Diabetes 2007;56:1153–1159
124. Perreault L, Pan Q, Schroeder EB, et al.; Diabetes Prevention Program Research Group. Regression from prediabetes to normal glucose regulation and prevalence of microvascular disease in the Diabetes Prevention Program Outcomes Study (DPPOS). Diabetes Care 2019;42:1809–1815
125. Chen Y, Zhang P, Wang J, et al. Associations of progression to diabetes and regression to normal glucose tolerance with development of cardiovascular and microvascular disease among people with impaired glucose tolerance: a secondary analysis of the 30 year Da Qing Diabetes Prevention Outcome Study. Diabetologia 2021;64:1279–1287
126. Herold KC, Bundy BN, Long SA, et al.; Type 1 Diabetes TrialNet Study Group. An anti-CD3 antibody, teplizumab, in relatives at risk for type 1 diabetes. N Engl J Med 2019;381:603–613