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# Diagnosis and Management of Prediabetes
## A Review

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**IMPORTANCE** Prediabetes, an intermediate stage between normal glucose regulation and diabetes, affects 1 in 3 adults in the US and approximately 720 million individuals worldwide.

**OBSERVATIONS** Prediabetes is defined by a fasting glucose level of 100 to 125 mg/dL, a glucose level of 140 to 199 mg/dL measured 2 hours after a 75-g oral glucose load, or glycated hemoglobin level ($HbA_{1C}$) of 5.7% to 6.4% or 6.0% to 6.4%. In the US, approximately 10% of people with prediabetes progress to having diabetes each year. A meta-analysis found that prediabetes at baseline was associated with increased mortality and increased cardiovascular event rates (excess absolute risk, 7.36 per 10 000 person-years for mortality and 8.75 per 10 000 person-years for cardiovascular disease during 6.6 years). Intensive lifestyle modification, consisting of calorie restriction, increased physical activity (≥150 min/wk), self-monitoring, and motivational support, decreased the incidence of diabetes by 6.2 cases per 100 person-years during a 3-year period. Metformin decreased the risk of diabetes among individuals with prediabetes by 3.2 cases per 100 person-years during 3 years. Metformin is most effective for women with prior gestational diabetes and for individuals younger than 60 years with body mass index of 35 or greater, fasting plasma glucose level of 110 mg/dL or higher, or $HbA_{1c}$ level of 6.0% or higher.

**CONCLUSIONS AND RELEVANCE** Prediabetes is associated with increased risk of diabetes, cardiovascular events, and mortality. First-line therapy for prediabetes is lifestyle modification that includes weight loss and exercise or metformin. Lifestyle modification is associated with a larger benefit than metformin.

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Prediabetes, an intermediate stage of glucose dysregulation that may precede type 2 diabetes, affected approximately 720 million individuals worldwide in 2021 and will affect an estimated 1 billion people by 2045.[1] In the US, approximately 10% of people with prediabetes progress to having diabetes each year. This Review summarizes the epidemiology, diagnostic criteria, clinical outcomes, and management of prediabetes.

## Methods

We searched PubMed for English-language articles published between January 1, 1990, and July 31, 2022. The search was updated on November 5, 2022, and February 2, 2023 (eAppendix in the Supplement). We supplemented our searches by searching the Cochrane database, especially for meta-analyses, and identifying additional articles from references of selected ones. Furthermore, we reviewed relevant current practice guidelines. We focused on high-quality prospective cohort studies, randomized trials, systematic reviews, and meta-analyses, and we used nationally representative surveys to obtain estimates of disease frequency. Because outcomes vary according to the case definition of prediabetes, we reported outcomes associated with cases defined by fasting plasma glucose level, 2-hour plasma glucose level after a 75-g oral glucose challenge (2hPG), or glycosylated hemoglobin ($HbA_{1c}$) level. A total of 680 reports were identified, of which 110 were included, consisting of 20 randomized clinical trials, 9 systematic reviews and meta-analyses, 7 guidelines, 3 diagnosis studies, 58 cohort studies, and results of 13 nationally representative surveys.

### Units of Measure

Throughout, laboratory values are reported primarily in conventional units. To convert glucose from mg/dL to mmol/L, multiply values by 0.0555. To convert $HbA_{1c}$ to mmol/mol, use the equation $(10.93 \times HbA_{1c}) - 23.50$.

## Diagnosis of Prediabetes

Slightly different diagnostic criteria for prediabetes have been proposed by the American Diabetes Association,[2] World Health Organization,[3] and the International Expert Committee[4] (**Table 1**). These criteria include impaired fasting glucose, which is based on a fasting glucose level, and impaired glucose tolerance, which is based on a 2hPG. The American Diabetes Association impaired fasting glucose criterion is specified by fasting glucose level of 100 to 125 mg/dL (5.5-6.9 mmol/L). The impaired glucose tolerance criterion is met by a 2hPG of 140 to 199 mg/dL (7.8-11.0 mmol/L)

Table 1. Diagnostic Criteria for Prediabetes

| Criteria | American Diabetes Association (2023) | World Health Organization (2006) | International Expert Committee (2009) |
|---|---|---|---|
| Fasting plasma glucose, mg/dL | 100-125 | 110-125 | NA |
| 2-h Postload plasma glucose (75-g oral glucose tolerance test), mg/dL | 140-199 | 140-199 | NA |
| Hemoglobin $A_{1c}$, % | 5.7-6.4 | NA | 6.0-6.4 |

Abbreviation: NA, not applicable.

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

(Table 1).[2] Prediabetes is also defined with an $HbA_{1c}$ level of 5.7% to 6.4% by the American Diabetes Association[2] or an $HbA_{1c}$ level of 6.0% to 6.4% by the International Expert Committee.[4] As a test for the initial diagnosis of diabetes or prediabetes, $HbA_{1c}$ has the advantage of convenience (no fasting required) compared with fasting plasma glucose level or 2hPG. However, $HbA_{1c}$ may be unreliable as a measure of time-averaged blood glucose levels under certain conditions (eg, hemolytic anemia, iron deficiency, hemoglobinopathies, pregnancy, uremia).[5] Moreover, ethnic differences in $HbA_{1c}$ independent of blood glucose have been reported.[6] In the US Diabetes Prevention Program (DPP), Black individuals had similar fasting plasma glucose and 2hPG values but higher $HbA_{1c}$ values compared with White individuals.[7] A systematic review of various studies documented greater risk of false-positive diagnosis of prediabetes in people who were Black compared with people who were White when $HbA_{1c}$ was used.[8] Corroboration with blood glucose measurement is advisable in people with medical conditions that may affect the validity of $HbA_{1c}$ results.

## Screening for Prediabetes

The US Preventive Services Task Force recommends screening for prediabetes every 3 years in adults aged 35 to 70 years who have overweight or obesity.[9] The American Diabetes Association recommends universal screening every 3 years for prediabetes among all adults aged 35 years or older regardless of risk factors.[2] Both the US Preventive Services Task Force and American Diabetes Association recommend using fasting plasma glucose, $HbA_{1c}$, or 2hPG as a screening test.[2,9] In a nationally representative cross-sectional study of the US population, fasting plasma glucose identified 28.3% of individuals as having prediabetes compared with 21.7% using $HbA_{1c}$ and 13.3% using 2hPG.[10] The same study reported a concordance rate for prediabetes diagnosis among all 3 tests (fasting plasma glucose, $HbA_{1c}$, and 2hPG) of 4.1%.[10] The US Preventive Services Task Force and American Diabetes Association recommend annual monitoring for progression to diabetes among individuals with prediabetes. For diagnosing diabetes, the American Diabetes Association recommends reliance on 2 abnormal screening test results either from the same sample or 2 separate test samples. If 2 separate test samples are used, the second test, which may either be a repeat of the initial test or a different test, should be performed without delay.[2] However, there are no similar guidelines regarding repeated testing for confirming the diagnosis of prediabetes. The low concordance among the 3 screening tests, which is in part due to the instability of prediabetes states such as impaired fasting glucose, increases the likelihood of false-positive results when screening with a single test.

## Pathophysiology of Prediabetes

Compared with individuals with normal glucose regulation, those with prediabetes who have impaired fasting glucose tend to have higher or "inappropriate" endogenous glucose production because of hepatic insulin resistance, reduced hepatic glucose clearance, and lower ability of glucose to stimulate its own uptake and suppress its own production. Individuals with impaired fasting glucose also have impaired beta cell function.[11,12] Impaired glucose tolerance is predominantly characterized by skeletal muscle resistance that causes delayed glucose uptake, and by beta cell dysfunction.[11,12] People with prediabetes, identified as having impaired fasting glucose, impaired glucose tolerance, or both, exhibit various degrees of insulin resistance and beta cell dysfunction,[13,14] with near-maximal insulin resistance and a beta cell function loss of 80% or greater in impaired glucose tolerance.[15] Because $HbA_{1c}$ quantifies the mean glucose level during the past 2 to 3 months, patients with prediabetes defined by an elevated $HbA_{1c}$ level may have worsening impaired fasting glucose, impaired glucose tolerance, or both.[12]

## Epidemiology of Prediabetes

Longitudinal studies that observed adults with normal glucose regulation reported annual rates of incident prediabetes of 6.2% among predominantly White participants in the Baltimore Longitudinal Study on Aging,[16] 7.8% among people who were Pima Indian,[17] and 11% among Black or White adults with parental history of type 2 diabetes.[18] Those prospective studies showed that progression from normal glucose regulation to prediabetes was associated with increased body weight and insulin resistance, combined with a decline in endogenous insulin secretion in response to glucose (beta cell dysfunction),[19-21] demonstrating that insulin resistance and beta cell failure evolve simultaneously rather than sequentially. People who maintained normal glucose regulation despite weight gain and insulin resistance had a well-functioning endogenous insulin secretory response to glucose load.[19-21] These findings are congruent with those from a postmortem investigation showing an approximately 40% relative decrease in pancreatic beta cell volume among individuals with prediabetes compared with those with normal fasting plasma glucose levels.[22]

The major risk factors for prediabetes include overweight or obesity (defined by the World Health Organization as a body mass index [BMI; calculated as weight in kilograms divided by height in meters squared] of 25.0 to 29.9 for overweight and ≥30 for obesity),[23] older age, physical inactivity, unhealthy diet, and

Commonly Asked Questions About Prediabetes

**How often do patients with prediabetes progress to diabetes?**
Randomized clinical trials reported annual rates of progression from prediabetes to diabetes that ranged from 5.8% to 18.3%, during an average follow-up period of approximately 3 years, among untreated participants assigned to control groups. In the US Diabetes Prevention Program (DPP), the incidence (cases per 100 person-years) of diabetes was 11.0 (95% CI, 9.8-12.3) during 2.8 years of randomized treatment. During 30-year follow-up in the China Da Qing study, the cumulative diabetes incidence was 95.9% among participants enrolled with prediabetes and assigned to the control group. A meta-analysis (including >250 000 participants followed for up to 24 years) reported a cumulative incidence of diabetes of 31% to 41% over a median follow-up of 12 years.

**What is an effective lifestyle intervention for prediabetes?**
Effective lifestyle interventions in randomized clinical trials consisted of calorie restriction, increased physical activity, self-monitoring of food intake and exercise behavior, along with support for managing psychological, social, and motivational obstacles. The American Diabetes Association recommends at least 7% weight loss through healthy diet and approximately 150 min/wk of moderate-intensity physical activity in people with prediabetes.

**Should medications be prescribed to slow progression of prediabetes to diabetes?**
Randomized clinical trials of several medications (including metformin, pioglitazone, and acarbose) have demonstrated efficacy over placebo in delaying progression to diabetes. However, no medication has been approved by the US Food and Drug Administration for diabetes prevention, and drugs tend to lose their effect on progression to diabetes when discontinued. Lifestyle modification is the mainstay of diabetes prevention. However, the American Diabetes Association recommends that metformin treatment should be considered for people with prediabetes, particularly those aged <60 years with body mass index ≥35, fasting plasma glucose ≥110 mg/dL, and $HbA_{1c}$ ≥6.0%, and for women with prior gestational diabetes.

genetic predisposition. In the 2017-2020 National Health and Nutrition Examination Survey (NHANES), prediabetes (defined with fasting plasma glucose, 2hPG, or $HbA_{1c}$) was more prevalent in the group aged 65 years or older compared with the one aged 18 to 44 years (48.8% vs 27.8%).[24] In a national US sample, more than 80% of individuals with prediabetes were overweight or had obesity (BMI ≥25).[25] A meta-analysis of 4 cohort studies from Germany of subjects of European origin showed that a history of diabetes in at least 1 first-degree relative was associated with increased odds of having prediabetes, defined as impaired fasting glucose, impaired glucose tolerance, or both (odds ratio, 1.40; 95% CI, 1.27-1.54).[26] However, in a US study the incidence rate of prediabetes was similar (≈11% per year) among offspring of parents with type 2 diabetes during a 5-year follow-up period whether they were Black or White individuals.[18]

National surveys of US adults aged 18 years or older conducted between 2017 and 2020 showed a prediabetes prevalence of 38% in the overall population.[24] In 2021, the International Diabetes Federation estimated the global impaired glucose tolerance prevalence at 10.2%,[1] corresponding to 541 million adults aged 20 to 79 years,[1] with a lower estimated prevalence of 5.7% when prediabetes was defined by an elevated impaired fasting glucose level.[1] An analysis of race- and ethnicity-specific data from the 2017-2020 NHANES showed no significant differences in the prevalence of prediabetes for persons who were non-Hispanic Asian (prevalence, 37.3%; 95% CI, 32.6%-42.3%), non-Hispanic Black (prevalence, 39.2%; 95% CI, 35.8%-42.6%), Hispanic (prevalence, 35.4%; 95% CI, 31.3%-37.7%), or non-Hispanic White (prevalence, 38.7%; 95% CI, 35.5%-41.9%).[24] During the past 3 decades in the United States, the prevalence of prediabetes increased steadily across all racial, ethnic, and age groups.[27-29] The International Diabetes Federation projected that by 2045, the number of adults with impaired glucose tolerance will be 730 million, or 11.2% of the world's adult population.[1] The equivalent estimate based on impaired fasting glucose is 441 million adults, or 6.2% of the global adult population.[1] The increasing prevalence of obesity among children and adolescents,[30] and the likely resultant increase in the prevalence of prediabetes,[31] may further increase the prevalence of prediabetes.

## Complications in Persons With Prediabetes

### Progression to Diabetes

In the observational Baltimore Longitudinal Study of Aging, 102 of 265 participants with prediabetes progressed to diabetes during 10 years of follow-up.[16] The study enrolled predominantly White people (96%), which is not representative of the US population. The randomized clinical trials of diabetes prevention in Asia, Europe, and the United States reported annual rates of progression from prediabetes to diabetes in their control group, which ranged from 5.8% to 18.3%.[32-35] In the DPP, which enrolled a diverse cross section of the US population, the incidence of diabetes in the placebo group was 11.0 per 100 person-years (95% CI, 9.8-12.3) during the first 2.8 years of the study.[34]

During a 30-year follow-up period in the Chinese Da Qing study, the cumulative diabetes incidence was 95.9% among participants with prediabetes and assigned to the control group.[36] A meta-analysis (103 prospective cohort studies with up to 24 years of follow-up) reported a cumulative incidence of diabetes of 31% for impaired fasting glucose during 12 years (relative risk, 4.32), 41% for impaired glucose tolerance during 12 years (relative risk, 3.61), and 31% for individuals with prediabetes defined by an $HbA_{1c}$ level of 5.7% to 6.4% during 10 years (relative risk, 5.5).[37] For individuals with both impaired fasting glucose and impaired glucose tolerance, the relative risk was 6.90. The highest relative risk for diabetes was for individuals with the highest $HbA_{1c}$ level (relative risk of 10 for those with $HbA_{1c}$ 6.0%-6.4%).[37]

Age of prediabetes onset may influence the rate of progression to diabetes; older individuals (>60 years) with prediabetes appear to develop diabetes at a lower rate than middle-aged individuals with prediabetes (cumulative diabetes incidence rate was ≈9% during a 6.5-year period among individuals aged 75 years on average).[38] The primary results of the US DPP showed that individuals from the major US racial and ethnic groups progressed from impaired glucose tolerance to type 2 diabetes at similar rates, without evidence of significant ethnic differences.[34] In the DPP control group, the crude incidence rates of diabetes (per 100 person-years) were 10.3, 12.4, 11.7, 12.9, and 12.1 among persons who were

White, Black, Hispanic, American Indian, or Asian, respectively.[34] Similarly, a prospective cohort study of 15 080 adults for 5 years reported that self-identified race or ethnicity was not a significant predictor of incident diabetes (odds ratio for Black vs White individuals, 0.98; 95% CI, 0.69-1.40; odds ratio for other races vs White individuals, 1.09; 95% CI, 0.59-2.02).[39]

### Microvascular and Macrovascular Complications

Individuals with prediabetes have more cardiovascular disease risk factors than people without prediabetes,[40] and they have increased rates of cardiovascular events. A meta-analysis of prospective studies (129 studies; 10 069 955 individuals; median follow-up duration, 9.8 years [range, 2.0-26]) showed that prediabetes at baseline (defined by impaired glucose tolerance or impaired fasting glucose) was associated with increased rates of cardiovascular disease (incidence rate per 10 000 person-years, 58.3 in those with normal glucose regulation vs 67.0 among those with prediabetes) and all-cause mortality (incidence rate per 10 000 person-years, 73.6 in those with normal glucose regulation vs 81 among those with prediabetes).[41] The absolute risk difference in people with prediabetes vs people with normoglycemia was 7.36 per 10 000 person-years (95% CI, 9.59-12.51) for all-cause mortality and 8.75 per 10 000 person-years (95% CI, 6.41-10.49) for composite cardiovascular disease.[41] Numerous cohort studies have described a high mortality risk among individuals with prediabetes (impaired fasting glucose, impaired glucose tolerance, or $HbA_{1c}$-based prediabetes) compared with those with normoglycemia.[42-49] Prediabetes is associated with higher rates of hospitalization.[50]

Microvascular complications, including retinopathy,[51] neuropathy,[52] and nephropathy,[53] are frequent among individuals with prediabetes. Up to 7.9% of individuals with prediabetes had retinopathy at baseline in the US DPP.[51] The proportion of individuals with prediabetes who had peripheral neuropathy was 7.5% to 16% in the 2009-2014 NHANES survey.[52] The prevalence of chronic kidney disease, based on estimated glomerular filtration rate, among individuals with prediabetes was 9.7% in the 2017-2020 NHANES survey.[54] In prospective studies, the risk of chronic kidney disease associated with prediabetes has been shown to be higher than that associated with normoglycemia (relative risk for chronic kidney disease was 1.10 to 1.50, depending on the definition of prediabetes; absolute rates not reported).[55,56] Prediabetes has also been linked to a higher frequency of impaired cognition and structural brain alterations compared with normal glucose regulation.[57,58] No professional organization formally recommends regular screening for microvascular or macrovascular complications among individuals with prediabetes because there is a lack of data on its effectiveness and cost-effectiveness.

## Spontaneous Remission of Prediabetes

A meta-analysis that included 12 257 adults from 47 cohort studies (composed mainly of subjects with abnormal impaired fasting glucose, impaired glucose tolerance, or both, and less often by an elevated $HbA_{1c}$ level) evaluated resolution of prediabetes to sustained normoglycemia during a follow-up period of 1 to 11 years.[37] Resolution of prediabetes occurred in 33% to 59% of individuals within 1 to 5 years of follow-up and in 17% to 42% of individuals during 6 to 11 years of follow-up. These rates of resolution decreased with longer follow-up.[37]

## Treatment for Prediabetes

### Lifestyle Modifications

Among people with prediabetes, diabetes can be prevented with intensive lifestyle modification, such as diet and exercise (Figure; **Table 2**).[32-35] None of the diabetes prevention trials enrolled participants by using $HbA_{1c}$ criteria for prediabetes. In the US DPP, people with impaired glucose tolerance were randomized to a lifestyle modification program, metformin, or placebo. Partners from the public and private sector provided services to participants with prediabetes to decrease the risk of overt diabetes through lifestyle-change interventions that include eating healthier and increasing physical activity as part of a daily routine. The lifestyle intervention consisted of 16 individual core sessions taught by case managers (trained nutritionists, exercise physiologists, or behavioral psychologists) during the first 6 months of the intervention.[61] These sessions were followed by twice-monthly in-person "maintenance" sessions, with telephone contact between sessions.[61] In the US DPP trial, diabetes incidence rate during a 3-year period was 10.8 cases per 100 person-years in the control group vs 4.8 cases per 100 person-years with the lifestyle intervention.[34] Lifestyle intervention was well tolerated, without major adverse events. The rate of hospitalization for any reason was 16.1% in the placebo group compared with 15.9% in the metformin group and 15.6% in the lifestyle intervention group.[35] However, more people in the lifestyle group vs placebo reported musculoskeletal symptoms (24.1% vs 21.1%). Death rate per 100 person-years was 0.16% in the placebo group and 0.10% in the lifestyle intervention group. No deaths were attributable to participation in the DPP.[35]

Other trials conducted during 3- to 6-year periods in China,[32] Finland,[33] Japan,[59] and India[35] showed that lifestyle interventions consisting of dietary changes and increased physical activity were associated with a decreased incidence of diabetes compared with placebo or usual care (Table 2). In most randomized clinical trials,[35] the effects of lifestyle modification were primarily mediated by weight loss.[62] Two trials, the Chinese Da Qing study and the Indian DPP, were exceptions to these findings and did not demonstrate that the effects of lifestyle modification were primarily mediated by weight loss. The results of these latter studies may be explained by a lower BMI among participants at enrollment (mean [SD] BMI of 26 [3.8] in the Da Qing study and 25.8 [3.5] in the Indian DPP study) compared with that in other prevention studies such as the US DPP (mean [SD] BMI at enrollment, 34 [6.7]) or the Finnish prevention study (mean [SD] BMI at enrollment, 31 [4.6]).[63]

In most of the diabetes prevention clinical trials, the effects of lifestyle modification on diabetes incidence persisted after discontinuation of the intervention. During the extended follow-up of the Finnish Diabetes Prevention Study (13-year incidence rate per 100 person-years, 4.5 in the intervention group and 7.2 in the control group), Chinese Da Qing study (30-year diabetes incidence rate per 1000 person-years, 117.5 in the control group and 70.7 in the intervention group), and US DPP (15-year cumulative incidence of diabetes, 55% in the lifestyle group and 62% in the placebo

Table 2. Efficacy of Lifestyle Intervention From Randomized Trials to Prevent Type 2 Diabetes

| Source | Country | Study duration | Prediabetes definition | Age, y/BMI, mean (SD) | Study groups (No.) | Weight target | Mean follow-up, y | Intervention vs control | | Reversal of prediabetes, % | Years of follow-up after active intervention |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | Relative risk reduction for diabetes, % | Absolute risk reduction for diabetes | | |
| Da Qing[32] | China | 1986-1992 | IGT | 45 (9)/25.8 (3.8) | Diet (130)<br>Exercise (141)<br>Diet and exercise (126)<br>Control (133) | No specific target | 6 | Diet, 31.5<br>Exercise, 46<br>Diet and exercise, 42 | Cumulative incidence: 65.9% in control vs 47.1% in diet, 44.2% in exercise, and 44.6% in diet and exercise groups | NR | 30 |
| Finnish DPS[33] | Finland | 1993-2001 | IGT | 55 (7)/31 (4.5) | Diet and exercise (265)<br>Control (257) | >5% Weight loss | 4 | Diet and exercise, 58 | Incidence rate per 1000 person-years: 32 cases in diet and exercise group vs 78 in control group | NR | 13 |
| DPP[34] | US | 1996-2001 | IGT (+ IFG in some) | 51 (10.7)/34 (6.7) | Diet and exercise (1079)<br>Metformin (1073)<br>Control (1082) | 7% Weight loss | 2.8 | Diet and exercise, 58<br>Metformin, 31 | Incidence rate per 100 person-years: 10.8 in placebo vs 7.8 in metformin groups and 4.8 in lifestyle (diet and exercise) intervention groups | Lifestyle, 40<br>Metformin, 20 | 15 |
| Japanese trial[59] | Japan | 1984-2003 | IGT (men only) | NR/24 (2.2) | Diet and exercise (102)<br>Control (356) | No specific target | 4 | Diet and exercise, 67.4 | Cumulative incidence: 9.3% in control group vs 3.0% in intervention group (diet and exercise) | Lifestyle, 53.8 | NR |
| Indian DPP-1[35] | India | 2003-2005 | IGT | 46 (5.7)/25.8 (3.5) | Diet and exercise (133)<br>Metformin (133)<br>Diet, exercise, and metformin (136)<br>Control (136) | No specific target | 3 | Diet and exercise, 28.5<br>Metformin, 26.4<br>Diet, exercise, and metformin, 28.2 | Cumulative incidence: 55.0% in control group vs 39.3% in diet and exercise, 40.5% in metformin, 39.5% in diet, exercise, and metformin groups | NR | NR |
| Indian DPP-2[60] | India | 2003-2005 | IGT | 45 (6.2)/26 (3.3) | Diet and exercise (203)<br>Diet, exercise, and pioglitazone (204) | No specific target | 3 | Diet, exercise, and pioglitazone (vs diet and exercise), 1.8 | Cumulative incidence: 31.6% in diet and exercise group vs 29.8% in pioglitazone group | Lifestyle, 32.3<br>Pioglitazone, 40.9 | NR |

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); DPP, Diabetes Prevention Program; DPS, Finnish Diabetes Prevention Study; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; NR, not reported.

Table 3. Randomized Clinical Trials of Medications for Prevention of Type 2 Diabetes

| Source | Country/year of publication | Prediabetes phenotype | BMI at entry, mean (SD) | Study groups | Study size, No. | Mean follow-up, y | Relative risk reduction for intervention vs placebo (95% CI), % | Absolute risk reduction related to intervention |
|---|---|---|---|---|---|---|---|---|
| TRIPOD[78] | US/2002 | IGT (women with a history of gestational diabetes) | 30 (5.7) | Troglitazone vs placebo | 266 | 2.5 | 55 (17 to 75) | Annual diabetes incidence rate: 12.1% in placebo group vs 5.4% in troglitazone group |
| STOP-NIDDM[79] | International/ 2002 | IGT and IFG | 31 (4.2) | Acarbose vs placebo | 1429 | 3.3 | 25 (10 to 37) | Cumulative incidence: 42% in the placebo group vs 32% in the acarbose group |
| DPP[34] | US/2002 | IGT and IFG | 34 (6.7) | Metformin vs placebo | 3234 | 2.8 | 31 (17 to 43) | Incidence rate per 100 person-years: 11.0 in the placebo group vs 7.8 in the metformin group |
| DPP[80] | US/2005 | IGT | NR | Troglitazone vs placebo | 585 | 0.9 | 75 (NR) | Incidence rate per 100 person-years: 3.0 in the troglitazone group vs 12.0 in the placebo group |
| XENDOS[81] | International/ 2006 | Normal glucose regulation and IGT | 37 (4.4) | Orlistat vs placebo | 3305 | 4 | 37 (14 to 54) | Cumulative incidence: 9% in the placebo group vs 6.2% in the orlistat group |
| Indian DPP-1[35] | India/2006 | IGT | 25.8 (3.5) | Metformin vs placebo | 531 | 2.5 | 26.4 (19.1 to 35.1) | Cumulative incidence: 55.0% in the placebo group vs 40.5% in the metformin group |
| Indian DPP-2[97] | India/2006 | IGT | 25.9 (3.3) | Pioglitazone vs placebo | 407 | 3 | 2 (−44 to 33) | Cumulative incidence: 31.6% in the placebo group vs 29.8% in the pioglitazone group |
| DREAM[82] | International/ 2006 | IGT and IFG | 30.9 (5.6) | Rosiglitazone vs placebo | 5269 | 3 | 62 (56 to 67) | Cumulative incidence: 25.0% in the placebo group vs 10.6% in the rosiglitazone group |
| DREAM[83] | International/ 2006 | IGT and IFG | 30.9 (5.6) | Ramipril vs placebo | 5269 | 3 | 9 (−3 to 20) | Cumulative incidence: 19.5% in the placebo group vs 18.1% in the ramipril group |
| Voglibose trial[84] | Japan/2006 | IGT | 25.8 (3.8) | Voglibose vs placebo | 1780 | 0.9 | 40 (18 to 57) | Cumulative incidence: 17% in the placebo group vs 8% in the voglibose group |
| NAVIGATOR[85] | International/ 2010 | IGT and IFG | 30.5 (5.4) | Nateglinide vs placebo | 9306 | 5 | −7 (−15 to 0)[a] (Favors placebo) | Cumulative incidence: 34% in the placebo group vs 34% in the nateglinide group |
| NAVIGATOR[86] | International/ 2010 | IGT and IFG | 30.5 (5.4) | Valsartan vs placebo | 9306 | 5 | 14 (8 to 20) | Cumulative incidence: 36.8% in the placebo group vs 33.1% in the valsartan group |
| ACT NOW[87] | US/2010 | IGT | 33.7 (SE, 0.4) | Pioglitazone vs placebo | 602 | 2.4 | 72 (51 to 84) | Incidence rate per 100 person-years: 7.6 in the placebo group vs 2.1 in the pioglitazone group |
| CANOE[88] | Canada/2010 | IGT | 31.7 (27.1-36.8) | Metformin and rosiglitazone vs placebo | 207 | 3.9 | 66 (41 to 80) | Cumulative incidence: 39% in the placebo group vs 14% in the treatment group |
| SCALE[89,90] | International/ 2010 | IGT and IFG | 38.9 (6.4) | Liraglutide vs placebo | 2254 | 3 | 79 (66 to 87) | Cumulative incidence: 6% in the placebo group vs 2% in the liraglutide group |
| ACE[91] | China and Hong Kong/ 2010 | IGT | 24.5 (3.1) | Acarbose vs placebo | 6522 | 5 | 18 (6 to 29) | Incidence rate per 100 person-years: 3.8 in the placebo group vs 3.2 in the acarbose group |

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); DPP, Diabetes Prevention Program; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; NR, not reported.

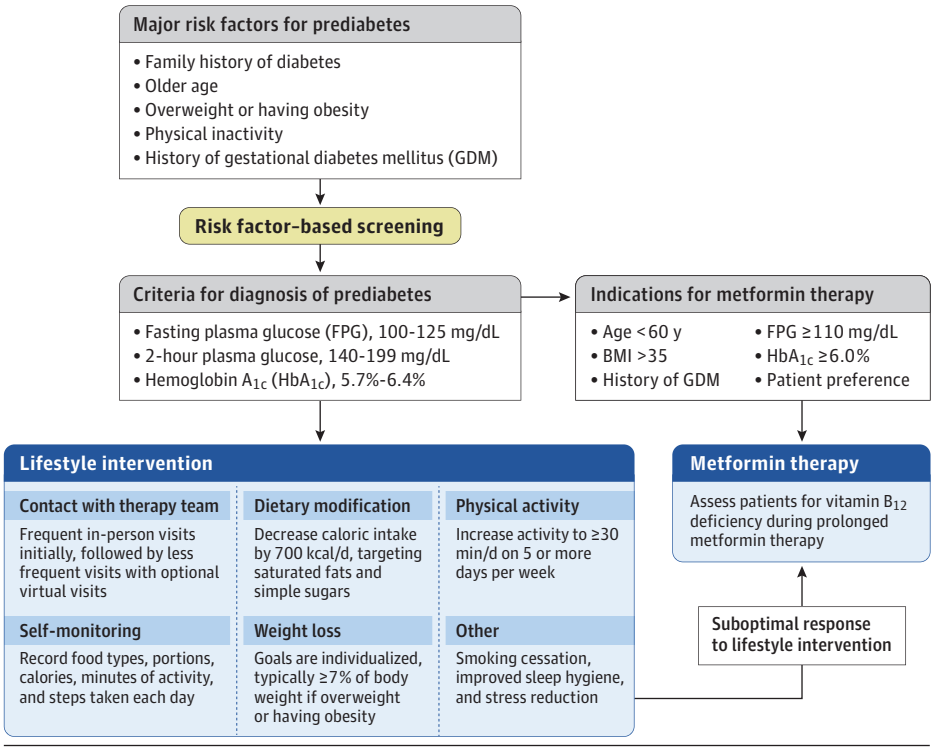
[a] Denotes a lack of risk reduction.

group),[36,64-69] there were persistently lower incidence rates of diabetes in the intervention groups.

In the DPP trial, despite improvements in cardiovascular disease risk factors (systolic blood pressure, low-density lipoprotein cholesterol levels, and triglyceride levels),[70] the lifestyle intervention delivered during the first 2.8 years of the study did not significantly reduce the risks of nephropathy, retinopathy, or neuropathy after 15 years of follow-up (prevalence of complications, 11.3% in the lifestyle group vs 12.4% in the placebo group).[68] Subclinical atherosclerosis as assessed in the DPP by coronary artery calcium level after 14 years was 75% in the lifestyle group vs 84% in the placebo group,[71] whereas cardiovascular events during 21 years showed a crude incidence rate per 1000 person-years of 5.28 in the placebo group vs 6.10 in the lifestyle group.[72]

In the Da Qing study, lifestyle modification was associated with a significant reduction in diabetes during the 6-year active trial period[32] and in the posttrial period.[36,65,67,73] The Da Qing study showed more favorable long-term results after the lifestyle intervention for cardiovascular and microvascular outcomes. In the study's 30-year follow-up report, prior lifestyle modification was associated with significant reductions in cardiovascular death (cumulative incidence, 45.7% in the intervention group vs 56.3% in the

Figure. Approach to Screening, Diagnosis, and Management of Prediabetes




Lifestyle modification is the preferred initial approach after a diagnosis of prediabetes. BMI is calculated as weight in kilograms divided by height in meters squared. This specific algorithm has not been tested in randomized clinical trials.

control group) and cardiovascular disease events (cumulative incidence, 52.9% in the intervention group vs 66.5% in the control group) after 30 years of follow-up.[36] The Da Qing study showed a reduction in the combined burden of microvascular complications (retinopathy, nephropathy, and neuropathy) after 30 years of follow-up (cumulative incidence, 25.1% in the intervention group vs 34.0% in the control group).[36]

Individuals with persistent prediabetes who do not progress to diabetes may still face increased risks of complications.[37-54] After 3 years of follow-up during the active phase of DPP, 40% of participants in the intensive lifestyle modification group achieved normal glucose tolerance vs 20% in the metformin or placebo group.[34,74] Among the DPP participants, the factors associated with a high likelihood of reversal to normal glucose regulation included lower baseline fasting plasma glucose level and 2hPG, younger age, higher insulin response to a glucose load, and weight loss.[74] A post hoc analysis from the DPP Outcomes Study also demonstrated a lower risk of diabetes 10 years from randomization among individuals who were able to achieve normal glucose regulation during the 6 years after the DPP active intervention (6-year cumulative incidence of diabetes, 2.6% in participants achieving normal glucose regulation vs 3.2% among those who remained with prediabetes).[75] In the DPP, the long-term benefits of normal glucose regulation included decreased risk of diabetes, a lower prevalence of microvascular disease, and decreased macrovascular risk.[74,76] A meta-analysis of 47 randomized trials (n = 26 460 participants) showed strong evidence for lifestyle modification, and moderate evidence for drugs, in achieving normoglycemia among people with prediabetes.[77]

## Drug Therapies

Several randomized clinical trials have demonstrated that, compared with placebo, metformin reduced the incidence of diabetes among people with prediabetes (**Table 3**). Metformin was tested in the DPP (3-year crude diabetes incidence rates per 100 person-years were 11.0 and 7.8 in the placebo and metformin groups, respectively)[34] and the Indian DPP (3-year cumulative incidence of diabetes was 55.0% and 40.5% in the placebo and metformin groups, respectively).[35] Although metformin was less effective than lifestyle modification in preventing progression to diabetes in the DPP, it had an effect similar to that of lifestyle modification among individuals with BMI 35 or greater (3-year crude diabetes incidence rates per 100 person-years were 14.3, 7.0, and 7.3 in the placebo, metformin, and lifestyle groups, respectively).[34] In women with a history of gestational diabetes, metformin and intensive lifestyle modification similarly prevented progression from prediabetes to diabetes (10-year age-adjusted diabetes incidence rates per 100 person-years were 11.4, 6.7, and 7.6 in the placebo, metformin, and lifestyle groups, respectively).[92,93] After 15 years of follow-up in the DPP Outcomes Study, metformin (vs placebo) had a greater effect on diabetes incidence in women with a history of gestational diabetes (15-year absolute diabetes incidence rate difference vs the placebo group was −4.57 cases per 100 person-years) than in parous women without a history of gestational diabetes (absolute diabetes incidence rate difference vs the placebo group was −0.38 cases per 100 person-years).[94] However, metformin was not associated with lower risk of diabetes for all age groups. It was less effective than placebo in lowering the 2.8-year incidence of diabetes among DPP participants aged 60 years or older (absolute diabetes incidence rate

difference vs the placebo group was 1.2 cases per 100 person-years vs −4.9 cases per 100 person-years in those 25-44 years).[34] The American Diabetes Association recommends that metformin be considered in specific subgroups of patients with prediabetes, including those with BMI 35 or greater, those younger than 60 years, women with a history of gestational diabetes, or those with higher fasting plasma glucose level (≥110 mg/dL) or higher $HbA_{1c}$ level (≥6.0%)[95] (**Figure**). In the DPP, metformin treatment compared with placebo was associated with a higher frequency of gastrointestinal symptoms (77.8 vs 30.7 events per 100 person-years).[34] Individuals receiving long-term treatment with metformin may experience malabsorption of vitamin $B_{12}$ and intrinsic factor and should be monitored for vitamin $B_{12}$ deficiency.[95,96]

Thiazolidinediones were evaluated for diabetes prevention in people with prediabetes in 3 clinical trials, including the DPP (1-year diabetes incidence rate per 100 person-years was 3.0 in the troglitazone group vs 12.0 in the placebo group),[80] DREAM (3-year cumulative incidence was 10.6% in the rosiglitazone group vs 25.0% in the placebo group),[82] and ACT NOW (3-year diabetes incidence rate per 100 person-years was 2.1 in the pioglitazone group vs 7.6 in the placebo group).[87] Clinical trials of α-glucosidase inhibitors included the STOP-NIDDM trial (3-year cumulative diabetes incidence was 32% in the acarbose group vs 42% in the placebo group),[79] the ACE study (5-year diabetes incidence rate per 100 person-years was 3.2 in the acarbose group vs 3.8 in the placebo group),[91] and a study of patients in Japan (1-year cumulative diabetes incidence was 8% in the voglibose group vs 17% in the placebo group).[84] The glucagon-like peptide 1 analogues that were studied in individuals with prediabetes included liraglutide (associated with risk reduction, 3-year cumulative diabetes incidence was 2% in the liraglutide group vs 6% in the placebo group[89,90]) and semaglutide (at week 68, type 2 diabetes was observed in 0.5% of participants who had prediabetes at week 0 in the semaglutide group vs 3.0% in the placebo group in the STEP Program[97]). Tirzepatide, a dual glucose-dependent insulinotropic polypeptide and glucagon-like peptide 1 receptor agonist, causes significant weight loss, but to our knowledge data on preventing progression from prediabetes to diabetes have not been reported.[60]

The long-term effect of drugs for preventing diabetes has been generally lower than that of intensive lifestyle modification. In addition, after medication cessation, glycemia typically returns to the original prediabetic range, whereas lifestyle modification has a more sustainable effect.[98,99] Drugs such as metformin or thiazolidinedione do not have permanent effects on insulin resistance and beta cell dysfunction,[100,101] which likely explains the lack of sustained effect. In randomized clinical trials, there was no additive benefit on diabetes risk reduction beyond that observed with lifestyle modification (3-year cumulative diabetes incidence, 31.6% in the placebo group vs 29.8% in the pioglitazone group; 3-year cumulative diabetes incidence, 39.5% in the metformin and lifestyle groups vs 55.0% in the placebo group).[35,102] However, a study that combined metformin and rosiglitazone in people with prediabetes reported greater diabetes risk reduction than each medication alone (3.9-year cumulative diabetes incidence, 14% in the metformin and rosiglitazone group vs 39% in the placebo group).[88]

Although there is limited evidence regarding the ability of medications to reduce cardiovascular microvascular and mortality outcomes, a post hoc analysis from STOP-NIDDM reported beneficial effects of acarbose on cardiovascular events in people with prediabetes (cumulative incidence of events, 4.7% in the placebo group vs 2.2% in the acarbose group).[103]

## Limitations

This review has several limitations. First, the quality of included studies was not formally evaluated. Second, the literature search might have missed some relevant studies. Third, the findings from the randomized clinical trials may not apply to all individuals with prediabetes defined by the various criteria. Fourth, the clinical trials of diabetes prevention had a relatively short intervention duration, followed by time without the intervention before measurement outcomes. Thus, observations made strictly during the extended follow-up period cannot be attributed solely to the effect of prior exposure during the intervention phase of the study.

## Conclusions

Prediabetes is associated with increased risk of diabetes, cardiovascular events, and mortality. First-line therapy for prediabetes is lifestyle modification that includes weight loss and exercise or metformin. Lifestyle modification is associated with a larger benefit than metformin.

ARTICLE INFORMATION

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