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# Can type 2 diabetes and its associated complications be prevented or delayed in people with intermediate hyperglycaemia?

Stinton, Chris; Herath, Deshani; Parr, Janette; Mansbridge, Alice; Williams, Hannah; Rotar, Oxana; Grove, Amy; Al-Khudairy, Lena; Kudrna, Laura; Johnson, Samantha A; Oyebode, Oyinlola; Taylor-Phillips, Sian

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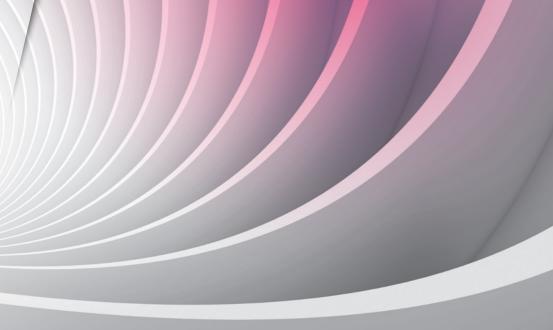
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#### WHO HEALTH EVIDENCE NETWORK SYNTHESIS REPORT, 80

Can type 2 diabetes and its associated complications be prevented or delayed in people with intermediate hyperglycaemia?

Chris Stinton | Deshani Herath | Janette Parr | Alice Mansbridge | Hannah Williams | Oxana Rotar | Amy Grove | Lena Al-Khudairy | Laura Kudrna | Samantha A. Johnson | Oyinlola Oyebode | Sian Taylor-Phillips





#### The Health Evidence Network

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#### WHO Health Evidence Network synthesis report, 80

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#### **Abstract**

Diabetes affects one in 11 adults in the WHO European Region. It is a key risk factor for cardiovascular diseases, kidney failure, vision loss and nerve damage. Intermediate hyperglycaemia is a state in which blood glucose levels are above the normal range but below the threshold for diabetes. It is associated with an increased risk for type 2 diabetes, obesity, cardiovascular diseases and mortality. This review assessed the effects of interventions for people with intermediate hyperglycaemia. Results from randomized controlled trials indicate that the risk of developing type 2 diabetes in people with intermediate hyperglycaemia is reduced by lifestyle and (some) pharmacological interventions. Most of the available evidence did not find a difference in mortality or other serious health outcomes for either pharmacological or lifestyle interventions. However, the follow-up periods may have been too short for health outcomes to have emerged. The current evidence suggests that the risk of developing type 2 diabetes is reduced through intervention at the point of intermediate hyperglycaemia, but that the effects of these interventions on long-term health outcomes are unclear.

#### Keywords

 ${\tt SYSTEMATIC REVIEW, DIABETES MELLITUS\, TYPE\, 2/PREVENTION\, \&\, CONTROL, POPULATION, PUBLIC HEALTH PRACTICE, RANDOMIZED\, CONTROL\, TRIAL$ 

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## **CONTENTS**

• Abbreviations	iv
Acknowledgements	v
Screening terminology	viii
Summary	x
▶ 1. Introduction  ▶ 1.1 Background  ▶ 1.2 Methodology	1
Results      2.1 Study characteristics      2.2 Q1a. Do interventions for people with intermediate	
<ul> <li>hyperglycaemia delay or prevent the development of T2DM?</li> <li>2.3 Q1b. Do interventions for people with intermediate hyperglycaemia affect mortality or serious health outcomes?</li> <li>2.4 Q2. What proportion of people with intermediate hyperglycaemia return to normoglycaemic levels</li> </ul>	10
without intervention?  > 2.5 Q3. What are the harms of intervention for intermediate hyperglycaemia?	
3. Discussion	16
<ul><li>3.1 Strengths and limitations of this review</li><li>3.2 Summary of results</li></ul>	
▶ 3.3 Comparison with previous reviews	
<ul> <li>▶ 3.4 Intermediate hyperglycaemia in the WHO European Region</li> <li>▶ 3.5 Future research</li> </ul>	
3.6 Policy considerations	
▶ 4. Conclusions	23
Annex 1. Search strategy	24
Annex 2. Studies excluded after full-text review	36
Annex 3. Included studies	165
N Deferences	

## **ABBREVIATIONS**

CI confidence interval HbA1c haemoglobin A1c

RCT randomized controlled trial

T2DM type 2 diabetes mellitus

USPSTF United States Preventive Services Task Force

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#### SCREENING TERMINOLOGY

The following definitions of technical terms on screening are those used in the guide (1–5), while recognizing that they may not always align with definitions that appear in other texts.

Case-finding. This activity is conducted in daily clinical practice and involves finding cases by assessing patients who are indicated to be at risk of a condition when they seek help from the health system. It is an integral part of the health system (not an organized, systematic programme) and does not involve health authorities actively inviting people to participate.

Opportunistic screening. This is non-systematic screening that occurs when a screening test is offered to an individual (i) during service user–service provider interactions or (ii) on demand or on an ad hoc basis, or (iii) to individuals outside the eligible group. In practice, it is used when patients are in contact with the health system for a reason other than experiencing symptoms for the disease being screened for (if they are symptomatic, it is not screening) or if they request the screening test.

**Population-level screening programme.** An organized, systematic public health programme to reduce the burden of disease in society by identifying and managing preclinical disease or the risk factors of disease among asymptomatic people. A predefined eligible population (based on age and/or sex) is actively invited to participate in a quality-assured screening pathway that includes diagnosis and treatment.

Targeted screening. An organized, systematic screening programme that aims to improve health outcomes in people with the condition being screened for, among people identified as being at high risk of a specific condition (because of lifestyle factors, genetic variants or having another health condition). This is a form of population-level screening (see the definition above) and, similarly, involves actively inviting a predefined eligible population to participate in a quality-assured screening pathway that includes diagnosis and treatment. The difference is that targeted screening aims to identify groups of people with a higher risk of a specific condition beyond demographic factors such as age or sex. Examples include lung cancer screening for individuals who smoke or retinopathy screening for people with diabetes.

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<sup>1.</sup> All references were accessed on 5 February 2024.

#### **SUMMARY**

#### The issue

Diabetes mellitus (referred to as diabetes in this report) is a chronic health condition that affects one in 11 adults in the WHO European Region. Lesser degrees of hyperglycaemia that do not reach the threshold for diagnosis of diabetes (referred to as intermediate hyperglycaemia) can be associated with an increased risk of developing diabetes. In general, the risk of developing diabetes increases with time but risk will vary depending on how intermediate hyperglycaemia is defined. Intermediate hyperglycaemia is additionally linked to a heightened susceptibility to cardiovascular diseases and mortality. However, this risk too varies depending on how intermediate hyperglycaemia is defined. Treatment of intermediate hyperglycaemia may be important for preventing type 2 diabetes mellitus (T2DM) and its complications. The effectiveness of interventions in individuals with intermediate hyperglycaemia was explored in this report.

#### The synthesis question

The overall objective of this report was to evaluate the benefits and harms of interventions for people who have intermediate hyperglycaemia detected through any method.

#### Types of evidence

This report builds on a broad review published in 2021 that covered questions relating to screening, available interventions and the natural history of T2DM and intermediate hyperglycaemia. Four questions from this review were updated using a rapid review approach and a selected grey literature search. Searches were carried out in English and Russian between June and September 2022 for randomized controlled trials (RCTs) of interventions for intermediate hyperglycaemia. A total of 72 papers, reporting on 51 trials, were identified: 12 examined pharmacological interventions, 34 examined lifestyle interventions and five examined both. Thirty-four trials were identified in the previous review, and an additional 17 new trials were found in the updated search carried out for the present review.

#### Results

Meta-analyses indicated that, compared with a control group, the incidence of T2DM was lower among participants taking some pharmacological interventions (e.g. metformin vs placebo or standard care; thiazolidinediones vs placebo with/ without diabetes education/lifestyle modification, alpha glucosidase inhibitors vs placebo or lifestyle modification). Meta-analyses of results from lifestyle interventions indicated that such interventions are associated with a lower risk of T2DM than comparators such as no intervention, standard care or general advice about healthy living. Most of the available evidence did not find a difference in mortality or other serious health outcomes for either pharmacological or lifestyle interventions. However, the duration of studies may have been too short for such longer-term outcomes to have emerged (range: 0.9–6 years).

The control arms of five RCTs in which participants received no active intervention indicated that 3–32% of people with intermediate hyperglycaemia returned to normoglycaemia during follow-up. The intervention arms of 19 RCTs reported some harms/adverse events that may be associated with interventions for intermediate hyperglycaemia in adults. Types of adverse event varied widely across studies and were not necessarily attributed to the study intervention.

#### **Policy considerations**

Based on the review findings, Member States of the WHO European Region could:

- exercise caution when specifically targeting people with intermediate hyperglycaemia using lifestyle interventions to reduce or delay the risk of T2DM given the uncertainty of the available evidence and fluctuations from intermediate hyperglycaemia to normoglycaemia and T2DM that can occur over time;
- exercise caution in promoting pharmacological interventions to reduce or delay T2DM for people with intermediate hyperglycaemia given the limitations in the evidence and the finding that pharmacological interventions did not reduce negative health outcomes;

- ensure that data are collected to support evaluation of the long-term impacts of any interventions that are planned or in place to reduce or delay T2DM for people with intermediate hyperglycaemia; and
- consider alternative approaches to delaying or reducing the risk of T2DM in the general population, such as primary prevention strategies and efforts to reduce sugar intake and obesity and to increase physical activity across the population that do not rely on the identification of intermediate hyperglycaemia in order to initiate action for the prevention of T2DM.

#### 1. INTRODUCTION

## 1.1 Background

#### 1.1.1 Intermediate hyperglycaemia and T2DM

Diabetes mellitus (referred to as diabetes in this report) is a chronic disorder of glucose metabolism caused by insufficient production of insulin or an inability of cells to respond adequately to insulin. It is a key risk factor for cardiovascular diseases, kidney failure, vision loss and nerve damage, and it can lead to amputations. Other consequences may include cancer, infections and liver disease (1). There are three main types of diabetes: type 1, type 2 (T2DM) and gestational diabetes.

Impaired glucose tolerance and impaired fasting glucose are not clinical entities but denote a state in which blood glucose levels are above the normal range while remaining below the diagnostic threshold for T2DM. This state is sometimes called intermediate hyperglycaemia or prediabetes (2). In general, the risk of developing diabetes for those with blood glucose levels above the normal range increases with time but varies with the definition used to define intermediate hyperglycaemia (i.e. the cut-off points used) (3–5). Diabetes and intermediate hyperglycaemia are detected by measuring plasma glucose during a fasting state (fasting plasma glucose), glucose tolerance (2 hours after a 75-g oral load of glucose has been consumed) or glycated haemoglobin (haemoglobin A1c; HbA1c). Fasting plasma glucose and the glucose tolerance test reflect blood glucose at the time of testing. while HbA1c reflects average blood glucose values over the previous 2-3 months. According to WHO and the International Diabetes Federation, a definition of impaired glucose tolerance requires both fasting plasma glucose of <7 mmol/L and 2-hour plasma glucose of 7.8-11.0 mmol/L detected through an oral glucose tolerance test (2). For a definition of impaired fasting glucose, WHO and the International Diabetes Federation use 6.1–6.9 mmol/L. while the American Diabetes Association uses a broader range of 5.6–6.9 mmol/L (6). The incidence of T2DM generally increases over time among people with intermediate hyperglycaemia, albeit with considerable variability in estimates (5). In addition to being associated with an increased risk for developing T2DM, intermediate hyperglycaemia is also associated with obesity and an increased risk for cardiovascular diseases and for mortality (7). Therefore, a question arises of whether early detection and treatment of intermediate hyperglycaemia may be considered important for preventing T2DM and its complications.

1

## 1.1.2 Intermediate hyperglycaemia and T2DM in the WHO European Region

There are an estimated 61 million people living with diabetes in the WHO European Region, and the number is expected to reach around 67 million by 2030 and 69 million by 2045 (8). Rates of intermediate hyperglycaemia are reported to be increasing (9), but accurate data are lacking (10). More than 70% of people with intermediate hyperglycaemia are reported to live in low- and middle-income countries: the lowest rates of intermediate hyperglycaemia are seen in the International Diabetes Federation's Europe Region (11).

#### 1.1.3 WHO previous work on intermediate hyperglycaemia

There is limited prior WHO work specifically on intermediate hyperglycaemia. WHO has published guidelines for the diagnosis and classification of diabetes since 1965 (2,12–16), with thresholds for determining intermediate hyperglycaemia according to fasting plasma glucose (6.1–6.9 mmol/L) and glucose tolerance (7.8–11.0 mmol/L) being added in 2006 (2). A more recent WHO publication considered the value of HbA1c in the diagnosis of T2DM (12). It concluded that a threshold of 38.9 mmol/mol could be used as a cut-off to diagnose T2DM, but that no recommendation could be made on how to interpret HbA1c levels below 48 mmol/mol (6.5%) (12).

Although explicit guidance on the management of intermediate hyperglycaemia has not yet been produced by WHO, it is considered indirectly in documents concerning the prevention of noncommunicable diseases. For example, resolutions have been made regarding the prevention and control of T2DM and the implementation of policies and strategies to target the key risk factors for T2DM (17). Most Member States of the WHO European Region have national policies in place regarding T2DM, and surveys of national capacity to prevent noncommunicable diseases (including but not limited to diabetes) indicate that most of these Member States (90%) have a national policy to address diet and physical activity, of which around 80% are operational (18). The impact of these on intermediate hyperglycaemia is not currently known.

#### 1.1.4 Context of this review

Several recent reviews have considered the effectiveness of interventions for intermediate hyperglycaemia (19–21). The present report builds on the most comprehensive of these, conducted by the United States Preventive Services Task Force (USPSTF) (21). The USPSTF review covered 23 questions relating to T2DM and intermediate hyperglycaemia, including the benefits and harms of interventions

for intermediate hyperglycaemia. It is the most comprehensive review to date on the topic. Searches were conducted up to September 2019 (with ongoing targeted surveillance up to May 2021) for studies that were conducted in countries with medium or higher values on the Human Development Index (22). Only studies that were published in English and were rated as being of fair or good quality were included in the review.

This report expands and updates three of the key questions from the USPSTF review on intermediate hyperglycaemia (regardless of its method of detection) to ensure that data relevant to the WHO European Region were captured. The current report incorporated evidence published after the formal USPSTF search was completed (September 2019), adding evidence from any country regardless of Human Development Index category (22) and not excluding evidence because of study quality.

This report focuses on the effectiveness of interventions for intermediate hyperglycaemia detected through any means. A companion Health Evidence Network synthesis report examines the evidence on population screening of asymptomatic adults for T2DM and intermediate hyperglycaemia (23).

#### 1.1.5 Objectives of this report

The overall objective of this report was to evaluate the evidence on the effectiveness of interventions for intermediate hyperglycaemia by examining the following questions:

- Q1. Do interventions for people with intermediate hyperglycaemia:
  - (a) delay or prevent development of T2DM, or
  - (b) affect mortality or serious health outcomes?
- Q2. What proportion of people with intermediate hyperglycaemia will return to normoglycaemic levels without intervention?
- Q3. What are the harms of intervention for intermediate hyperglycaemia?

## 1.2 Methodology

An enhanced rapid evidence assessment (24) was conducted between June and September 2022 in English and Russian. A systematic literature search was undertaken in the PubMed and Cochrane (reviews, trials and protocol) databases,

using terms relating to diabetes and intermediate hyperglycaemia, interventions for these conditions and population screening. The search was limited to RCTs and systematic reviews of RCTs. A start date of 2019 was applied to the search for RCTs to identify additional studies published since the USPSTF review (21). No date limit was applied to the systematic review search. References of included studies and relevant systematic reviews were assessed for additional trials. It was assumed that all information in the USPSTF review was correct and none of the studies in that review was reassessed for accuracy. Q1 was examined using data from RCTs. Q2 and Q3 were examined using data from the control arm (Q2) and intervention arm (Q3) of studies that were included in Q1. Full details of the search strategies, review methods and eligibility criteria can be found in Annex 1.

The search retrieved 2879 records in English after removal of duplicates and 185 records in Russian after removal of inappropriate records. Of these, 828 (819 in English and nine in Russian) articles were selected for full-text assessment. In total, 18 RCTs (reported in 19 papers) fulfilled the inclusion criteria. Data were also included from 34 trials (reported in 50 papers) identified in the USPSTF review (21) and three trials identified through scrutiny of prior systematic reviews. Annex 2 provides details of the studies excluded after full-text appraisal and Annex 3 of the data abstracted from the included references (25–96).

#### 2. RESULTS

Section 2.1 presents the characteristics of the studies included in this review. Section 2.2 presents the evidence on whether interventions for people who have intermediate hyperglycaemia prevent or delay T2DM and section 2.3 presents the evidence regarding the effect of such interventions on serious health outcomes or mortality. Section 2.4 presents the evidence on the proportion of people with intermediate hyperglycaemia whose blood glucose levels return to normal without intervention. Section 2.5 presents the data on the harms of interventions for intermediate hyperglycaemia. Meta-analyses were conducted where it was meaningful to pool data: that is, where at least three similar studies assessed the same outcome and there was minimal clinical and methodological heterogeneity. Most results are presented in narrative form.

## 2.1 Study characteristics

Fifty-one trials (reported in 72 relevant papers) assessed interventions for people with intermediate hyperglycaemia: 12 examined pharmacological interventions, 34 examined lifestyle interventions and five examined both. The USPSTF review identified 34 trials and an additional 17 new trials were found in the updated search. For some trials, the same outcomes were presented in multiple papers. In such cases, data were reported from the paper with the longest follow-up.

The trials were conducted in Australia (69), Bangladesh (41), Canada (30), China (31,33–37,60,68,91,92,95), China, Hong Kong SAR (89,90), Denmark (64), Finland (54–56), India (38,39,61,62), Japan (63,65,88,94), the Netherlands (Kingdom of the) (32,82), the Russian Federation (52), Saudi Arabia (28), Spain (40), Sweden (58,59,67,75), Thailand (27), the United Kingdom (England (53,66,76,77,79,93), Scotland (29)), the United States of America (25,26,42–48,57,70,78,80,86,87) and across multiple countries (49–51,71–74,81,83–85). Most trials enrolled participants with a mean (or median) age between 50 and 60 years and included both men and women.

In the trials examining lifestyle interventions, the majority (34/39) included diet and physical activity components, such as education or advice on T2DM, diet and exercise; motivational interviewing to increase physical activity and reduce calorie intake; advice on diet and exercise with supervised exercise classes; and one trial involved a residential course in which participants' meals were made for them. The remaining five trials focused on physical activity alone (e.g. exercise classes or advice

to increase physical activity) (31,59,70,93) or diet alone (e.g. nutritional education) (40). The content and delivery of the lifestyle interventions varied widely between studies. For example, 31 studies were high contact (i.e. more than 360 minutes of contact time with the deliverer of interventions); three were medium contact (31–360 minutes of contact time with the deliverer of interventions); three were low contact (30 minutes or less of contact time with the deliverer of interventions) (41,71,89,90) and two had an unclear amount of contact (91,95). The interventions were delivered in group settings in 13 studies (26,27,31,38,41,57,59,64,66,76,78,79,93), individually in 14 studies (42,43,54,60,65,68–71,77,82,91,94,95), both individually and in groups in seven studies (28,33–37,40,53,63,86,87), through texts/e-mails in three studies (41,89,90,96), with family members in one study (29), or were not specified (61,67). A range of health-care professionals were involved in delivering the interventions, including nurses, dietitians, nutritionists, physiotherapists, physicians and life coaches. The study duration of trials of lifestyle interventions ranged from 6 months to 10 years, with a median duration of 2 years.

In the trials of pharmacological interventions, the following medications were assessed: metformin alone (39,45,52,61,78,80), insulin followed by metformin (80), acarbose (32,52,84,85), glimepiride (75), liraglutide alone (81), liraglutide with metformin (80), nateglinide (72), pioglitazone (25,61,68), ramipril (49–51), rosiglitazone (30,49–51), semaglutide (83), valsartan (73) and voglibose (88). The duration of pharmacological intervention studies ranged from 6 months to 15 years, with a median duration of 3 years.

# 2.2 Q1a. Do interventions for people with intermediate hyperglycaemia delay or prevent the development of T2DM?

This section deals with the effects of pharmacological or lifestyle interventions for progression to T2DM. Risks of bias were present in the majority of studies (Annex 3, Table A3.1).

#### 2.2.1 Pharmacological interventions

Results for progression to T2DM among people with intermediate hyperglycaemia who received pharmacological interventions are shown in Table 1 and include meta-analyses of studies of metformin, thiazolidinediones and alpha glucosidase inhibitors.

Table 1. Progression to T2DM in trials of pharmacological interventions among people with intermediate hyperglycaemia

Pharmacological	No.	Percentage with T2DM		. RR (95% CI) <sup>a</sup>
intervention trials		Intervention	Control	(95% CI)
Metformin (47,52,61,78,80)	5	43.1	50.0	Pooled RR: 0.82 (0.70-0.96), <i>l</i> ² = 20%
Thiazolidinediones (25,50,62,68)	4	11.7	23.4	Pooled RR: 0.59 (0.35-0.99), <i>l</i> <sup>2</sup> = 93%
Alpha glucosidase inhibitors (32,52,84,85,88)	4	17.2	25.0	Pooled RR: 0.63 (0.44–0.92), <i>l</i> * = 66%
Glimepiride (75)	1	30.1	39.9	0.76 (0.55–1.05)
Liraglutide (81)	1	1.7	6.1	0.28 (0.18-0.45)
Metformin + lifestyle (39)	1	26.0	35.0	0.79 (0.60–1.32)
Nateglinide (72)	1	36.0	33.9	1.06 (1.01–1.12)
Ramipril (49)	1	17.1	18.5	0.93 (0.83–1.04)
Rosiglitazone + metformin (30)	1	13.6	39.4	0.35 (0.20-0.59)
Semaglutide (83)	1	0	4.0	0.20 (0.01–4.66)
Valsartan (73)	1	33.1	36.8	0.90 (0.85–0.95)

CI: confidence interval; RR: relative risk.

Meta-analyses indicate that, compared with controls, the incidence of T2DM was lower among participants prescribed metformin (45,52,61,78,80), thiazolidinediones (either pioglitazone or rosiglitazone) (25,50,62,68) or alpha glucosidase inhibitors (either acarbose or voglibose) (32,52,84,85,88). There was substantial heterogeneity in the pooled estimates for thiazolidinediones and alpha glucosidase inhibitors. Evidence for pharmacological interventions with data only available from single trials suggested that the incidence of T2DM is lower than in controls for people prescribed liraglutide (81), valsartan (73), rosiglitazone combined with metformin (30)

<sup>&</sup>lt;sup>a</sup> Statistically significant results in bold.

or metformin combined with lifestyle intervention (39). Conversely, the risk of T2DM was higher among people taking nateglinide than in those taking a placebo (72). No difference in risk of T2DM was observed for single trials of ramipril (49), glimepiride (75) or semaglutide (83).

#### 2.2.2 Lifestyle interventions

Meta-analysis of 38 RCTs indicated that lifestyle interventions (overall) were associated with a lower risk of T2DM than comparators such as no intervention, standard care or general advice about healthy living (Table 2). There was substantial heterogeneity, however, so this should be interpreted with caution.

Table 2. Progression to T2DM in trials of lifestyle interventions among people with intermediate hyperglycaemia

Lifestyle intervention	No. trials	Percentage with T2DM		Pooled RR
		Intervention	Control	(95% CI) <sup>a</sup>
All lifestyle	38	16.7	19.3	0.73 (0.65–0.83), <i>I</i> ° = 67%
Level of contact				
High (26–29, 31,33,38,41,42,52,54,57,59, 61,63–69,76–79,82,86,87,93)	30	13.9	16.5	0.73 (0.63–0.84), <i>I</i> ° = 71%
Medium (60,70,93,96)	4	4.1	11.7	0.42 (0.19-0.90), I <sup>2</sup> = 53%
Low (41,71,90)	3	19.9	21.0	0.95 (0.83–1.08), $J^2 = 0\%$
Study duration				
<1 year (69,93,95)	3	5.6	7.3	0.29 (0.02–3.71), $J^2 = 81\%$
1–2 years (26– 28,31,38,40,41,60,64,70,71,76– 78,86,87,91,96)	18	11.3	13.9	0.68 (0.54-0.86), <i>P</i> = 62%

Table 2, contd

Lifestyle intervention	No. trials	Percentage with T2DM		Pooled RR
		Intervention	Control	(95% CI) <sup>a</sup>
>2 years (29,33,42,54,57,59,61,63, 65–68,81,82,90,94)	17	17.5	19.6	0.76 (0.65–0.89), I <sup>2</sup> = 73%
Method of intervention del	ivery			
Group (26,27,31,38,41,57,59,6 4,66,76,78,79,93)	13	10.5	11.8	0.76 (0.61–0.96), l² = 60%
Individual (43,54,60,65,68,6 9,70,77,82,91,94,95)	12	11.4	19.6	0.69 (0.52–0.91), l² = 72%
Baseline body mass index (kg/m²)				
<25.0 (41,60,63,65,95,96)	6	9.7	12.3	0.52 (0.33–0.82), l² = 78%
25.0–25.9 (26,33,38,40,61, 68,69,71,79,82,90,91,93,94)	14	17.7	17.5	0.88 (0.76–1.01), $I^2 = 50\%$
≥30.0 (26,28,29,42,53,54,57,5 9,64,66,67,70,76,78,86,87)	16	12.3	19.7	0.68 (0.56-0.82), l² = 40%

CI: confidence interval; RR: relative risk.

Subgroup analyses suggested some differences in the efficacy of lifestyle interventions (Table 2). For example, the risk of T2DM was significantly lower in intervention groups than control groups in studies that were conducted over 1 year or longer but not in groups analysed at less than one1 year; in studies of people with a baseline body mass index of < 25.0 or  $\geq$ 30.0 kg/m² but not among people with baseline body mass index of 25.0–25.9 kg/m²; and in studies in which participants had medium or high contact with study deliverers but not low levels of contact. Both individual and group delivery of lifestyle interventions appeared to reduce the risk of T2DM compared with control groups. Caution is warranted in the interpretation of these results as heterogeneity was moderate to substantial across all subgroup analyses.

<sup>&</sup>lt;sup>a</sup> Statistically significant results in bold.

# 2.3 Q1b. Do interventions for people with intermediate hyperglycaemia affect mortality or serious health outcomes?

Summary results of the review and meta-analyses for mortality and serious health outcomes are shown in Table 3. Detailed results are reported in Table A3.2 (Annex 3). Risks of bias were present in the majority of studies (Annex 3, Table A3.1).

Table 3. Mortality and serious health outcomes in trials of interventions among people with intermediate hyperglycaemia

Health outcome	Significant effect in favour of the intervention was observed <sup>a</sup>	No significant effect of the intervention was observed
All-cause mortality	Lifestyle (37)	Acarbose (32), glimepiride (75), liraglutide (81), metformin (61), metformin + lifestyle (39,42,61), nateglinide + lifestyle (72), pioglitazone (62), ramipril (49), rosiglitazone (50), valsartan + lifestyle (73), voglibose (88), lifestyle (42,55,59,61,64,70,94)
Cardiovascular mortality	Lifestyle (37)	Glimepiride (75), liraglutide (81), metformin + standard lifestyle (44), nateglinide + lifestyle (72), ramipril (51), rosiglitazone (51), valsartan + lifestyle (73)
Non-fatal stroke	None	Liraglutide (81)
Non-fatal myocardial infarction	None	Liraglutide (81), pioglitazone (25)
End-stage renal disease	None	Valsartan (74)
Amputation	None	Nateglinide (72), valsartan (74)
Revascularization	None	Nateglinide (72), valsartan (73)

#### Table 3. contd

Health outcome	Significant effect in favour of the intervention was observed <sup>a</sup>	No significant effect of the intervention was observed
Retinopathy	None	Lifestyle (37)
Nephropathy	None	Lifestyle (37)
Neuropathy	None	Lifestyle (37)

None: no trial with this outcome showed a significant result.

#### 2.3.1 Pharmacological interventions

The available evidence did not show a statistically significant difference in all-cause mortality (32,39,42,49,50,61,62,72,73,75,81,88), cardiovascular mortality (44,51,72,73,75,81), non-fatal stroke (81), non-fatal myocardial infarction (25,81), end-stage renal disease (74), amputations (72,74) or revascularization (72,73) between pharmacological intervention and control groups (no drug trial has looked at retinopathy, nephropathy, neuropathy). In general for each medication, data were only available from a single trial, the outcomes were rare and the duration of studies may have been too short for longer-term clinical outcomes to have emerged (range: 0.9–6.0 years). These limit the extent to which reliable conclusions can be drawn.

#### 2.3.2 Lifestyle interventions

In most trials (six out of seven), the follow-up period was too short (median: 3 years) to allow differences to develop in all-cause mortality, and no association was found between lifestyle intervention and a reduction in all-cause mortality (55,59,61,64,70,94). While the general approach to intervention was similar across the studies (i.e. to increase physical activity and/or reduce calorie intake), the precise content varied (e.g. advice and encouragement to increase physical activity (61), advice on health promotion (64), advice to reduce calories and increase physical activity (55,94), a home-based exercise programme (70) and taught group exercises (59)). A significantly lower incidence of all-cause mortality was observed in the much longer Da Qing trial (30 years), which included taught exercises, a calorie-controlled diet, and group

<sup>1.</sup> Full title: Da Qing Diabetes Prevention Outcome Study.

and individual counselling conducted over 6 years (37). Caution is required in the interpretation of this trial because of risks of bias (such as unclear randomization and differences in baseline characteristics between the groups) and lack of information on whether the lifestyle recommendations were continued after the initial 6-year period. Long-term follow-up of the DPP trial² found no difference (14.5% vs 13.2%) in all-cause mortality at a median of 21 years between participants in the intensive lifestyle intervention arm (which included access to a lifestyle coach for each participant, supervised physical activity sessions, taught sessions on behavioural management and frequent contact) and those in the standard care arm (advice about preventing T2DM) (47). However, randomization was not maintained during the follow-up period as all participants were offered the lifestyle intervention. No between-group differences were observed in incidence of retinopathy, nephropathy or neuropathy at 30-year follow-up in the Da Qing study (37).

# 2.4 Q2. What proportion of people with intermediate hyperglycaemia return to normoglycaemic levels without intervention?

The control arms of five RCTs in which participants received no active intervention (waiting list, placebo or no intervention) indicated that 3–32% of people with intermediate hyperglycaemia returned to normoglycaemia at follow-up. In the DPP trial, 24% of participants in the placebo arm experienced at least one episode of return to normal glucose tolerance at 3 years, although the study did not report how long this was maintained (21). In the STEP 6 trial, 32% of participants (8/25) in the placebo arm were normoglycaemic at 68 weeks (83). In the Healthy Living Course trial, 26% of people in the waiting list arm were normoglycaemic at 6-month follow-up (69). Zhou (2011) reported that 3% of participants (2/58) in the control arm (no intervention) were normoglycaemic at 6 months (95). Finally, Oldroyd et al. (2006) reported that 13% of participants who received no intervention (4/32) were normoglycaemic at 2 years (77). No information was provided about the characteristics of those who returned to normoglycaemia without intervention in any of the five trials.

Full title: Diabetes Prevention Program (long-term follow-up is Diabetes Prevention Program Outcomes Study).

<sup>3.</sup> Full title: Semaglutide Treatment Effect in People with Obesity.

## 2.5 Q3. What are the harms of intervention for intermediate hyperglycaemia?

The intervention arm of 14 RCTs (20 papers) reported some harms/adverse events. The types of adverse event varied widely across studies and were not necessarily attributed to the study intervention.

#### 2.5.1 Musculoskeletal events

The majority of lifestyle interventions reported musculoskeletal events such as sprains requiring medical attention (4.3 events/100 patient-years) (45), arthritis in knee causing pain in walking (1/83; 1.2%) (29), overall musculoskeletal symptoms (24.1 events/100 patient-years over 15 years of follow-up) (45), knee pain and musculoskeletal injury to lower back and leg (1/450; 0.22%) (57) and overall musculoskeletal problems (4/1333; 0.3%) (96).

#### 2.5.2 Hypoglycaemic events

One study with a lifestyle intervention arm reported hypoglycaemic symptoms among four participants (0.8%) that might be related to the intervention (68).

Three RCTs of pharmacotherapy (72–74) (nateglinide or valsartan) and four trials of a combination of pharmacotherapy (liraglutide, pioglitazone, rosiglitazone and metformin) and a lifestyle intervention delivered in the same drug arm (30,48,68,81) reported hypoglycaemic events. Forms of hypoglycaemia varied across studies. Trials reported the severity of events as "serious" (0/1073 participants taking metformin (48)), "nonserious" (7/1073 participants taking metformin (48)), "mild" (676/4645 participants taking nateglinide (72)), "moderate" (214/4645 participants taking nateglinide (72)), "severe" (no participants taking liraglutide (81) and 21/4645 participants taking nateglinide (72)). Other studies reported any hypoglycaemic event with no further definitions/cut-offs (30,72–74).

#### 2.5.3 Gastrointestinal adverse events

In studies of pharmacological interventions, gastrointestinal events were reported for 10 trials as follows:

- valsartan (diarrhoea in 612 (13.2%) participants) (73);
- nateglinide (diarrhoea in 593 (13%) participants) (72);

- liraglutide (nausea in 614 (41%) participants, diarrhoea in 379 (41%) participants and pancreatitis in 10 (0.6%) participants) (81);
- pioglitazone (unspecified digestive system events in 13 (4.3%) participants (25) and abdominal pain in 0–1 (0.2%) participants (68));
- acarbose (any gastrointestinal event in 597 (83%) participants (84), flatulence in 486 (68%) participants (84) and 15.9% of participants (number not specified) (33), diarrhoea in 229 (32%) participants (84) and 9.5% of participants (number not specified) (33), and enlarged abdomen in 13.5% of participants (number not specified) (33)); and
- metformin plus rosiglitazone (any gastrointestinal event in 37 (35.9%) participants (30), diarrhoea in 16 (16%) participants (30)), metformin (any gastrointestinal event in 29 (8%) participants (78) and gastrointestinal symptoms in the past year in 259 (28%) participants (48)).

#### 2.5.4 Drug-related study withdrawals

Withdrawals from trials due to drug-specific adverse events were reported in three trials: one participant (3.4%) withdrew due to metformin side-effects (78), 46 participants (5%) withdrew due to voglibose side-effects (88) and four participants (2%) withdrew due to rosiglitazone side-effects (30).

#### 2.5.5 Adverse event study withdrawals

A higher dose of acarbose (100 mg three times a day) was discontinued by 136 participants (19%) due to adverse events (84,85). A lower dose of acarbose (50 mg three times a day) was discontinued due to adverse events by 22 participants (36.7%) (32) and by two participants (1.6%) (33). Discontinuation due to adverse events was reported for 62 participants (7%) taking voglibose (88), 199 participants (13%) taking liraglutide (81), 520 participants (11.2%) taking nateglinide (72) and 556 participants (12.0%) taking valsartan (73). Unspecified adverse events were reported in 14 participants (17.1%) taking part in the HELP PD trial (57).4

#### 2.5.6 Withdrawals due to weight gain

Nine participants (3%) randomized to pioglitazone withdrew due to weight gain (25), and 50 participants (1.9%) randomized to rosiglitazone (49–51) withdrew due to weight gain.

<sup>4.</sup> Full title: Healthy Living Partnerships to Prevent Diabetes.

#### 2.5.7 Other reasons for withdrawals

Other reasons for study withdrawals were given in the DREAM<sup>5</sup> trial for participants receiving ramipril over 3 years; the most common reason for discontinuation of ramipril was patient's decision in 456 participants (17.4%), cough in 255 participants (9.7%), physician advice in 61 participants (2.3%), and peripheral oedema in 25 participants (1%) and angiooedema in three (0.1%) (49). In participants taking rosiglitazone, withdrawal due to oedema was reported in 439 participants (4.8%), physician advice in 50 participants (1.9%) and patient refusal in 503 participants (18.9%) (50).

 $<sup>{\</sup>bf 5.} \ \ {\sf Diabetes} \ {\sf REduction} \ {\sf Assessment} \ {\sf with} \ {\sf ramipril} \ {\sf and} \ {\sf rosiglitazone} \ {\sf Medication}.$ 

#### 3. DISCUSSION

## 3.1 Strengths and limitations of this review

An important strength of this review is that, first, it builds on the most comprehensive review to date on the benefits and harms of screening for T2DM and intermediate hyperglycaemia (16). Therefore, the evidence presented here is both appropriately broad and up to date. Secondly, the focus was on clinical outcomes, rather than intermediate outcomes. While there are more papers on intermediate outcomes such as blood pressure, weight loss and body mass index, a focus on these could lead to erroneous conclusions being drawn about the benefits of interventions on health outcomes. Thirdly, searches were conducted in both English and Russian, languages that are widely used in the WHO European Region.

This review has several limitations. First, it employed rapid evidence synthesis methods (24). While this approach is frequently used by policy-makers across the world to make decisions, it places the burden of assessment onto a single reviewer. While the first reviewer conducts all elements of the review, the second reviewer only reviews 20% of studies. Therefore, any mistakes relating to the 80% of tasks not reviewed by the second reviewer would go undetected. Secondly, not all possible clinical outcomes that were reported in the included papers were assessed, such as composite cardiovascular events, mixed fatal/non-fatal stroke or ischaemic heart disease. Thirdly, searches were limited to publications in English or Russian. A small number of studies in other languages were identified because their abstracts were in English, but relevant papers in other languages may exist but were not identified. Fourthly, the papers in languages other than English or Russian that were identified were translated using an online translation tool, and so the accuracy of these translations cannot be confirmed. Fifthly, there was substantial heterogeneity in the meta-analyses of the effect of thiazolidinediones, alpha glucosidase inhibitors and lifestyle interventions on T2DM. Therefore, caution is needed in the interpretation of these results. This is particularly important as a prior review of interventions (diet/physical activity) for intermediate hyperglycaemia reported the overall quality of the evidence to be "very low" (for mortality) and "very low" to "moderate" (for T2DM) using the GRADE (Grading of Recommendations, Assessment, Development and Evaluations) system, suggesting that the true effect of interventions may be different to the effects estimated in the trials (97).

## 3.2 Summary of results

The results of this review suggest that the risk of developing T2DM is reduced or delayed for people with intermediate hyperglycaemia who are assigned to interventions with metformin, thiazolidinediones, alpha glucosidase inhibitors, liraglutide or valsartan. No effect on T2DM was observed in trials of glimepiride, nateglinide, ramipril or semaglutide. Most evidence came from single trials of interventions. In relation to health outcomes, none of the included trials found evidence that pharmacological interventions reduce all-cause mortality, cardiovascular mortality, non-fatal stroke, non-fatal myocardial infarction, end-stage renal disease, amputations or revascularization. However, sample sizes may have been too small to detect statistically significant differences between intervention and control groups, and follow-up periods may not have been long enough for these types of outcome to have emerged.

There is also evidence that participating in a range of lifestyle interventions, such as those that include education or advice on T2DM, diet and exercise (with or without structured exercise classes) or motivational interviewing to increase physical activity and reduce calorie intake, is beneficial in delaying or reducing the risk of T2DM. Evidence of this effect was observed in studies conducted over 1 year or longer, but not in those covering less than 1 year); for individuals with a body mass index of more than 30 kg/m<sup>2</sup>; or where there is at least a medium level of contact (31 minutes or more) between participants and deliverers of interventions. Delivery of these interventions appears to be helpful whether via groups or to individuals. However, due to the high level of heterogeneity, there is some uncertainty in these results. Participation in lifestyle interventions (education on diet and physical activity, with a high level of contact with deliverers of interventions and conducted over 2.8 years or more) was found to reduce cardiovascular mortality in one RCT (37). No effect was observed on retinopathy, nephropathy or neuropathy. In relation to all-cause mortality, most trials (five out of seven) found no effect but may have had insufficient follow-up (55,59,61,64,70); one trial found no effect but had contamination during follow-up (47), and one trial over a longer time period but at high risk of bias found a reduction in all-cause mortality (37).

Caution is warranted in extrapolating the results of the trials to real-world settings due to the definitions and methods used in the studies to determine intermediate hyperglycaemia. Most of the studies included people with impaired glucose tolerance (detected using the oral glucose tolerance test). This raises two main issues. First, in clinical practice, most people with intermediate hyperglycaemia would be detected

using a fasting plasma glucose or HbA1c test rather than the oral glucose tolerance test, so it is less likely that impaired glucose tolerance would be found. Secondly, as the risk of developing T2DM varied by how intermediate hyperglycaemia was defined in the studies, it is not clear if the effects observed in the trials of people with largely impaired glucose tolerance would be observed in people with intermediate hyperglycaemia of a different definition. Thirdly, people in RCTs may have blood glucose testing more often than those in the real-world setting.

Data from the intervention arms of RCTs included in  $Q_1$  indicated a range of harms, including musculoskeletal problems (e.g. sprains, knee pain), symptoms of hypoglycaemia or gastrointestinal problems (e.g. diarrhoea, nausea). Data from the control arm of five RCTs included in  $Q_1$  indicated that 3–32% (median: 24) of study participants returned to normoglycaemia without intervention over relatively short periods (study follow-up periods were 6 months to 3 years).

## 3.3 Comparison with previous reviews

Although somewhat different eligibility criteria were employed across the reviews, the results of the present review are broadly comparable to those of prior reviews (19-21,98,99). In terms of T2DM diagnosis, the reviews indicate that rates of T2DM are lower among people with intermediate hyperglycaemia who are allocated to treatment with metformin (19-21,98), alpha glucosidase inhibitors (acarbose, voglibose) (20,21,99), thiazolidinediones (pioglitazone, rosiglitazone) (20,21), liraglutide (21) or valsartan (21,100), and in those who participate in lifestyle interventions (diet plus exercise) (19–21) compared with those who do not. Mixed evidence has been found for metformin combined with lifestyle interventions (98). The current and previous reviews agree that there is no evidence that ramipril (20,21) or glimepiride (20,21) reduces progression to T2DM. A review by the Cochrane Collaboration concluded that there is currently insufficient evidence on whether insulin secretagogues (including but not limited to glimepiride) reduce the risk of developing T2DM, compared with placebo (100). Another Cochrane review reported no firm evidence regarding the risk of T2DM and dipeptidyl-peptidase-4 inhibitors or glucagon-like peptide-1 analogues (101).

In relation to other health outcomes, the present review is consistent with other reviews in that there was some evidence for a benefit of lifestyle interventions on cardiovascular mortality (21). However, there was little evidence that pharmacological or lifestyle interventions are associated with a reduction in health outcomes such as non-fatal stroke or myocardial infarction, end-stage renal disease, retinopathy

or neuropathy (21,97,99). Most studies had insufficient follow-up to properly evaluate health outcomes

The types and frequencies of harms in the present review were similar to those reported in the USPSTF review (21). However, while the present review only looked at harms in the intervention arms, the USPSTF review included a comparison of harms between intervention and controls arms in 21 trials. It found no significant group differences for hypoglycaemia (sitagliptin, metformin, nateglinide, and rosiglitazone plus metformin), few differences for musculoskeletal problems (lifestyle interventions) and mixed results for gastrointestinal problems (no difference for pioglitazone, sitagliptin, nateglinide or valsartan; significantly greater in intervention groups for metformin, acarbose or liraglutide) and withdrawals due to adverse events (no difference for metformin, sitagliptin, nateglinide, valsartan, or rosiglitazone plus metformin; significantly greater in intervention groups for pioglitazone, ramipril, rosiglitazone, voglibose or liraglutide; and inconsistent results for acarbose).

The proportion of people who returned to normoglycaemia without intervention (3–32%; median: 24) was somewhat lower than the rates reported in a more comprehensive systematic review of cohort studies by the Cochrane Collaboration (5). In that review, the proportion of people who transitioned from intermediate hyperglycaemia to normoglycaemia was 33–59% in studies with 1–5 years of follow-up and 17–42% in studies with 6–11 years of follow-up. The differences in results may derive from the differing approaches of the two reviews; evidence in the Cochrane review was taken from prospective cohort studies that in general had longer follow-up, while evidence in the present review came from the control arms of RCTs that in general had shorter follow-up.

As indicated in section 1.1.4, a complementary review has been conducted in parallel to the present work (23). That review examined the effectiveness of population screening for T2DM and intermediate hyperglycaemia, using direct and indirect evidence. Whereas direct evidence refers to studies in which an applicable population is randomized to an offer of screening or no offer of screening and are followed up for health outcomes, indirect evidence refers to studies that have assessed different parts of the screening pathway that are combined to estimate what direct evidence might show. That review found no evidence (either direct or indirect) on population screening for intermediate hyperglycaemia, and no direct evidence of benefit of population screening for T2DM (from a single, biased and underpowered study) (23).

The results of the present review suggest that some types of lifestyle intervention (e.g. education on diet and exercise with or without structured exercises, with at least a medium level of contact with deliverers of interventions and conducted over at least 1 year) and pharmacological intervention (metformin, alpha glucosidase inhibitors or thiazolidinediones) may be effective in reducing progression to T<sub>2</sub>DM in people who have intermediate hyperglycaemia, with uncertainty on their long-term effects. However, this does not mean that a screening programme to identify and treat people with intermediate hyperglycaemia would be effective in reducing mortality or micro- and macrovascular health outcomes. This is because the effectiveness of screening is not determined by the presence of an effective intervention alone. It also relies on other factors, for example the availability of treatment, the accuracy of the screening test and an understanding of the natural history of a disease (102). The natural history of intermediate hyperglycaemia is not well understood, with up to 42% of people returning to normal glycaemic levels over 6–11 years of follow-up without any formal intervention taking place. Further, the applicability of studies of interventions for intermediate hyperglycaemia to real life is unclear. Finally, the spectrum of intermediate hyperglycaemia that would be detected by screening is not known, nor if the effects of interventions observed in people with screen-detected intermediate hyperglycaemia would be the same as those observed in the study cohorts who were not detected via screening.

## 3.4 Intermediate hyperglycaemia in the WHO European Region

Many of the single-country studies included in this review were conducted in settings within the WHO European Region, including Denmark, Finland, the Netherlands (Kingdom of the), the Russian Federation, Spain, Sweden and the United Kingdom. Of the multicountry studies included in the review, all but one used populations from within the WHO European Region. This means that the findings are likely to be applicable to high-income and upper-middle-income countries of the WHO European Region. However, it is less clear about the transferability of the evidence to low- or lower-middle-income countries in the Region.

The complementary review (23) examined country-level screening for intermediate hyperglycaemia and T2DM in the WHO European Region (23), where current practice regarding intermediate hyperglycaemia varied. Some countries are currently recommending or implementing approaches for detecting intermediate hyperglycaemia (e.g. assessment of blood glucose in general health checks or

through walk-in services, as well as case-finding among people at high risk of T2DM), while others do not have a strategy for detecting intermediate hyperglycaemia. Those people who are identified as having intermediate hyperglycaemia may be recommended or referred for behavioural intervention, in line with the European Association for the Study of Diabetes Guidelines (103) and the guidelines of the European Society of Cardiology (104). It is not clear whether or, if so, where pharmacological treatment is being offered routinely for those with intermediate hyperglycaemia within the WHO European Region.

### 3.5 Future research

First, most evidence reported outcomes after relatively short follow-up periods. Complications associated with T2DM (such as micro- and macrovascular problems) may take many years to emerge, beyond the duration of the study periods. Studies with longer follow-up are required to improve our understanding of the potential benefits and harms of interventions for people who have intermediate hyperglycaemia. Secondly, studies on lifestyle interventions in this review were conducted in many different ways. For example, some were conducted via groups, others with individuals; some lifestyle interventions involved a lot of contact or input with the intervention deliverers, other involved only a small amount of contact (or no direct contact); and some interventions focused on diet, some on exercise and some on both. Future research could be conducted to find out what the important parts of these interventions are. Thirdly, given that the most common definition of intermediate hyperglycaemia in the trials was impaired glucose tolerance, further research is required to clarify the impact of interventions for people with impaired fasting glucose and moderately elevated HbA1c. Fourthly, the natural history of intermediate hyperglycaemia is not well understood. While there is evidence that some people who have intermediate hyperglycaemia will return to normoglycaemia without intervention, it is not clear which people or why. Research on the characteristics of people who return to normoglycaemia from intermediate hyperglycaemia without intervention is required to understand this. Fifthly, the available evidence is derived from a relatively small number of high-income and upper-middle-income European countries (with only Denmark, Finland, the Netherlands (Kingdom of), the Russian Federation, Spain, Sweden and the United Kingdom represented). Therefore, results might not generalize to low- or lower-middle-income countries within the WHO European Region. or to those with different population demographics, prevalence of intermediate hyperglycaemia or health systems. Studies conducted in other Member States of the Region are required to understand if and/or how these differences affect the

benefits and harms of interventions in intermediate hyperglycaemia. Finally, a review based on searches in languages other than English or Russian might identify evidence from a broader range of countries.

# 3.6 Policy considerations

Based on the review findings, Member States of the WHO European Region could:

- exercise caution when specifically targeting people with intermediate hyperglycaemia using lifestyle interventions to reduce or delay the risk of T2DM given the uncertainty of the available evidence and fluctuations from intermediate hyperglycaemia to normoglycaemia and T2DM that can occur over time;
- exercise caution in promoting pharmacological interventions to reduce or delay T2DM for people with intermediate hyperglycaemia given the limitations in the evidence and the finding that pharmacological interventions did not reduce negative health outcomes;
- ensure that data are collected to support evaluation of the long-term impacts
  of any interventions that are planned or in place to reduce or delay T2DM for
  people with intermediate hyperglycaemia; and
- consider alternative approaches to delaying or reducing the risk of T2DM in the general population, such as primary prevention strategies and efforts to reduce sugar intake, obesity and to increase physical activity across the population that do not rely on the identification of intermediate hyperglycaemia in order to initiate action for the prevention of T2DM.

# 4. CONCLUSIONS

Intermediate hyperglycaemia is associated with an increased risk for developing T2DM, cardiovascular diseases and mortality. Nonetheless, the risk fluctuates based on the definition of intermediate hyperglycaemia applied. The present review assessed the RCT evidence on whether interventions for intermediate hyperglycaemia reduce these risks, and considered the harms of these interventions and the proportion of people who return to normoglycaemia without intervention. The results suggest that metformin, thiazolidinediones, alpha glucosidase inhibitors, liraglutide, valsartan and lifestyle interventions are associated with a reduced risk of developing T2DM. The impact of interventions on long-term health outcomes is unclear. There was some evidence of an association between lifestyle interventions and reduced risk of cardiovascular mortality, but no significant benefit of intervention was observed for other health outcomes, although follow-up periods may not have been long enough for these to become apparent. A range of harms were reported for pharmacological and lifestyle interventions, including musculoskeletal problems, hypoglycaemia and gastrointestinal problems. Between 3% and 32% of study participants returned to normoglycaemia without intervention. Further research is needed to establish the long-term benefits and harms of interventions for people who have intermediate hyperglycaemia.

# **ANNEX 1. SEARCH STRATEGY**

One systematic literature search was undertaken to cover all review questions. The search was adapted from that used in the USPSTF review (21) and used terms relating to diabetes and intermediate hyperglycaemia, interventions for these conditions and population screening. The search was limited to RCTs and systematic reviews of RCTs. A data limit of 2019 was applied to the search for RCTs to identify studies published since the USPSTF review (21). No date limit was applied to the search for systematic reviews. The search was conducted in the MEDLINE and Cochrane (reviews, trials and protocol) databases.

#### Search terms

#### English

Search terms and combinations in English were used for a search carried out on 21 June 2022 in MEDLINE (Ovid MEDLINE ALL <1946 to 20 June 2022>) (Table A1.1) and in the Cochrane Library (Table A1.2). The search strategy also included scrutiny of the references in the included RCTs and relevant systematic reviews.

Table A1.1. English search terms and combinations for the search in MEDLINE

ID	Search term	Hits
1	exp Diabetes Mellitus, Type 2/	158 870
2	glucose tolerance.af.	64 060
3	impaired glucose tolerance.af.	11 875
4	igt.af.	5 405
5	impaired fasting glucose.af.	4 281
6	ifg.af.	4 556
7	exp Glucose Intolerance/	9 594
8	glucose intolerance.af.	17 743
9	exp Prediabetic State/	8 358
10	prediabetic state.af.	8 630

ID	Search term	Hits
11	prediabet*.af.	13 274
12	"pre diabetes".af.	2 248
13	diabetes mellitus type 2.af.	160 452
14	type 2 diabetes mellitus.af.	55 823
15	or/1–14	246 031
16	exp Blood Glucose/	177 790
17	blood glucose.ti,ab.	80 054
18	exp Glucose Tolerance Test/	36 624
19	ogtt.ti,ab.	9 515
20	glucose tolerance test.ti.	1 978
21	exp Glycated Hemoglobin A/	40 345
22	hemoglobin A1c.af.	22 106
23	hbaıc.af.	41 793
24	fasting plasma glucose.ti,ab.	14 196
25	or/16–24	276 179
26	"hba(1c)".ti,ab.	4 599
27	hba1.ti,ab.	1 880
28	hbaɪc.ti,ab.	41 326
29	"hba ıc".ti,ab.	4 599
30	((glycosylated or glycated) and hemoglobin). ti,ab.	19 047
31	or/26–30	57 316
32	25 or 31	281 200

ID	Search term	Hits
33	15 and 32	107 707
34	exp Mass Screening/	140 749
35	screen*.ti,ab.	883 679
36	34 or 35	927 040
37	33 and 36	7 135
38	exp Pregnancy/ or gestation*.mp.	1 059 973
39	37 not 38	5 325
40	limit 39 to English language	4 933
41	limit 40 to "all adult (19 plus years)"	3 138
42	exp animals/ not humans.sh.	5 019 716
43	41 not 42	3 138
44	((randomised or randomized) and controlled and trial).ti,ab.	215 411
45	(controlled and trial).ti,ab.	245 439
46	controlled clinical trial.pt.	94 915
47	randomized controlled trial.pt.	571 201
48	exp Single-Blind Method/	32 010
49	exp Double-Blind Method/	172 183
50	exp Random Allocation/	106 855
51	or/44-50	869 286
52	43 and 51	446
53	limit 52 to yr="2019-Current"	99
54	review.pt. and systematic.ti,ab.	163 778

ID	Search term	Hits
55	systematic review.af.	261 880
56	exp "Review Literature as Topic"/ and systematic.ti,ab.	12 001
57	meta-analysis.pt.	162 528
58	exp Meta-Analysis as Topic/	25 161
59	meta-analysis.af.	247 257
60	meta synthesis.ti.	859
61	systematic literature review.ti.	5 416
62	this systematic review.tw.	43 346
63	"cochrane database of systematic reviews".jn.	15 888
64	or/54-63	425 781
65	51 and 64	27 791
66	43 and 65	13
67	53 or 66	105

# Table A1.2. English search terms and combinations for the search in Cochrane Library

ID	Search	Hits
#1	MeSH descriptor: [Diabetes Mellitus, Type 2] explode all trees	19 976
#2	("glucose tolerance"):ti,ab,kw	9 474
#3	("impaired glucose tolerance"):ti,ab,kw	3 292
#4	("IGT"):ti,ab,kw	1 069
#5	(impaired fasting glucose):ti,ab,kw	2 407

ID	Search	Hits
#6	(ifg):ti,ab,kw	592
#7	MeSH descriptor: [Glucose Intolerance] explode all trees	1 239
#8	("glucose intolerance"):ti,ab,kw	2 100
#9	MeSH descriptor: [Prediabetic State] explode all trees	1 244
#10	("prediabetic state"):ti,ab,kw	1 303
#11	(prediabet*):ti,ab,kw	3 138
#12	("pre-diabetes"):ti,ab,kw	743
#13	("diabetes mellitus type 2"):ti,ab,kw	21 319
#14	("type 2 diabetes mellitus"):ti,ab,kw	13 385
#15	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14	38 882
#16	MeSH descriptor: [Blood Glucose] explode all trees	17 430
#17	"blood glucose":ti,ab	18 835
#18	MeSH descriptor: [Glucose Tolerance Test] explode all trees	2 127
#19	ogtt:ti,ab	2 525
#20	"glucose tolerance test":ti	158
#21	MeSH descriptor: [Glycated Hemoglobin A] explode all trees	6 401
#22	("hemoglobin Aıc"):ti,ab,kw	8 045
#23	("HbA1c"):ti,ab,kw	19 903
#24	"fasting plasma glucose":ti,ab	5 345
#25	#16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24	50 718
#26	(hba(1c)):ti,ab	2 644

ID	Search	Hits
#27	hban:ti,ab	325
#28	hbarc:ti,ab	19 903
#29	"hba าc":ti,ab	1 506
#30	((Glycosylated or glycated) and hemoglobin):ti,ab	7 190
#31	#26 or #27 or #28 or #29 or #30	25 695
#32	#25 or #31	53 097
#33	#15 and #32	21 604
#34	MeSH descriptor: [Mass Screening] explode all trees	4 112
#35	screen*:ti,ab	80 956
#36	#34 or #35	81 872
#37	#33 and #36	1 943
#38	(gestation*):ti,ab,kw	27 874
#39	MeSH descriptor: [Pregnancy] explode all trees	24 542
#40	#38 or #39	45 537
#41	#37 not #40	1 753
#42	(adult*):ti,ab,kw	736 012
#43	#41 and #42	744
#44	MeSH descriptor: [Humans] explode all trees	647 921
#45	#43 and #44	324
#46	MeSH descriptor: [Animals] explode all trees	647 954
#47	#43 not #46	420
#48	#45 or #47	744

#### Russian

The following search terms and combinations in Russian were used for a search carried out from May to July 2023: диспансеризация, ежегодные профилактические осмотры, скрининг, популяционный скрининг, сахарный диабет, глюкоза сыворотки, глюкоза плазмы, промежуточная гипергликемия, ранние нарушения углеводного обмена, преддиабет, гипергликемия натощак, нарушенная толерантность к глюкозе, гликированный гемоглобин, гликозилированный гемоглобин, школа пациентов.

## Study selection

#### Inclusion criteria

Studies that satisfied the criteria outlined under the patient/population, intervention, comparison and outcomes model with a duration of at least 6 months of followup were included (Table A1.3).

Table A1.3. Study inclusion criteria using the patient/population, intervention, comparison and outcomes model

Component	Criteria
Population	All questions: adults diagnosed with intermediate hyperglycaemia according to WHO (16) or American Diabetes Association (6) criteria Where data permit, subgroup analyses conducted according to the method of detection of intermediate hyperglycaemia (e.g. screen detection, clinical detection)
Intervention	Q1: any physical, dietary, pharmacological or psychological intervention Q2: no intervention Q3: any physical, dietary, pharmacological or psychological intervention
Comparators	Q1: no intervention, placebo, usual care or interventions with different treatment targets Q2: not applicable Q3: not applicable

#### Table A1.3. contd

Component	Criteria
Outcomes	Q1: T2DM, mortality, cardiovascular mortality, non-fatal myocardial infarction, non-fatal stroke, non-traumatic amputation, revascularization, nephropathy (chronic kidney disease), neuropathy (peripheral, autonomic, proximal, mononeuropathy), retinopathy (moderate/severe non-proliferative diabetic retinopathy, proliferative diabetic retinopathy), macular oedema, reduced visual acuity, blindness, foot ulcers  Q2: normoglycaemia according to WHO (16) or American Diabetes Association (6) criteria  Q3: harms of interventions
Study type	Q1: RCT Q2: control arm population of RCTs from Q1 Q3: intervention arm population of RCTs from Q1

#### Exclusion criteria

The following exclusion criteria were used:

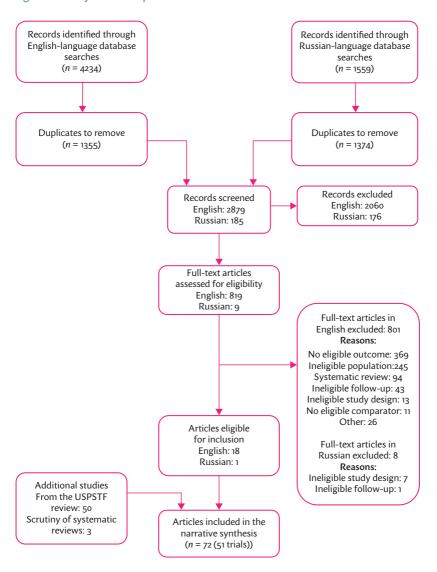
- studies on people:
  - younger than 18 years;
  - with T2DM;
  - who are pregnant;
  - with a recent hospitalization or myocardial infarction;
  - with known cardiovascular diseases or severe chronic kidney disease;
  - taking antipsychotic drugs or glucocorticoids;
  - living in an institution; and
  - with medical conditions limiting their applicability to primary-care-based populations (e.g. those with acute illness);
- studies where intermediate hyperglycaemia is self-reported or diagnosed according to methods other than HbA1c, fasting plasma glucose or oral glucose tolerance test;

- qualitative studies, modelling studies, case series, case reports, uncontrolled observational studies, retrospective cohort studies, any other non-RCT design;
- comparative effectiveness (head-to-head) trials of medications or behavioural counselling without another eligible control group;
- studies not generalizable to primary care (e.g. inpatient hospital, emergency departments, nursing homes, other institutional settings, school-based programmes or occupational settings);
- studies in which more than 10% of the sample do not meet the inclusion criteria; and
- letters, editorials, communications, conference abstracts and publications that contain no numerical outcomes data.

#### Selection process

An enhanced rapid evidence assessment approach was taken. Titles and abstracts of records identified by the searches were screened by one reviewer. A second reviewer then independently assessed a random 20% sample of the titles/abstracts. The search retrieved 2879 records in English after removal of duplicates and 185 records in Russian after removal of inappropriate records. The full publications of those papers considered potentially relevant by either reviewer (819 English and nine Russian) were then sourced, although outcomes were not considered at this stage. The full text of these articles was then assessed against the inclusion/exclusion criteria by one reviewer, with a random 20% sample assessed independently by a second reviewer. Disagreements were resolved by consensus or through discussion with a third reviewer. In total, 18 RCTs (reported in 19 papers) fulfilled the inclusion criteria. Data were also included from 34 trials (reported in 50 papers) identified in the USPSTF review (Fig. A1.1) (21) and three trials (reported in three papers) identified through the scrutiny of other systematic reviews. In total, data were available from 51 RCTs. Annex 2 lists the studies that were excluded following full-text screening with the reasons for exclusion.

Fig. A1.1. Study selection process



#### Quality appraisal

Risk of bias was assessed using the Cochrane Risk of Bias tool 2, which considers the risk of bias across five domains: (i) the randomization process, (ii) deviation from the intended intervention, (iii) missing outcome data, (iv) measurement of outcomes, and (v) selection of the reported results (105). Quality appraisal was conducted by one reviewer, with a random 20% assessed independently by a second reviewer. Disagreements were resolved by consensus or through discussion with a third reviewer. Annex 3 contains results from the risk of bias assessment.

#### Data extraction

The following data were extracted from all included studies: design; setting; country; duration; age and sex of participants; condition (type of intermediate hyperglycaemia: impaired fasting glucose or impaired glucose tolerance); diagnostic test used and criteria; number of participants screened, randomized and included in the analysis; and intervention and numbers in the intervention and control arm. The following data were extracted from the study results for both the intervention and control arm, recording the absolute numbers and hazard ratios and confidence intervals (CIs) for the data: number of people with T2DM and intermediate hyperglycaemia, all-cause mortality, cardiovascular mortality, non-fatal myocardial infarction, non-fatal stroke, non-traumatic amputation, revascularization, nephropathy (chronic kidney disease), neuropathy (general), neuropathy (specific subtypes: peripheral, autonomic, proximal, mononeuropathy), vision (moderate/severe non-proliferative diabetic retinopathy, proliferative diabetic retinopathy, macular oedema, reduced visual acuity), foot ulcers and harms (any).

Data were extracted by one reviewer, with a random 20% checked by a second reviewer. All data extracted were entered into a piloted electronic data collection form. Any disagreements were resolved by consensus or discussion with a third reviewer.

#### Methods of analysis and synthesis

Findings of studies were summarized in text and tables. As all outcomes were binary (did occur/did not occur), relative risks (with 95% CI values) were calculated using the numbers available in the papers, with the baseline number as denominator. Where multiple papers reported the same outcome, the one with the longest follow-up period was included. Where studies had multiple intervention arms, these were combined where it was reasonable to do so (e.g. they were more- or less-intensive versions of the same type of intervention). Meta-analyses were conducted using

Revman (106) where at least three similar studies were available. Random-effects models using the inverse-variance weighted method (DerSimonian and Laird method) were used to estimate pooled effects (107). A narrative summary was provided for all studies that could not be meta-analysed. Subgroup analyses were conducted in line with those of the USPSTF review and the same definitions for categorizing participants into subgroups was employed.

# ANNEX 2. STUDIES EXCLUDED AFTER FULL-TEXT REVIEW

Table A2.1 lists the 801 articles that were excluded after full-text review in the English language searches and Table A2.2 the eight Russian language articles.

Table A2.1. Articles in the English language search that were excluded after full-text review

Reference	Reason for exclusion
Abbasnezhad A, Falahi E, Gonzalez MJ, Kavehi P, Fouladvand F, Choghakhori R. Effect of different dietary approaches compared with a regular diet on systolic and diastolic blood pressure in patients with type 2 diabetes: a systematic review and meta-analysis. Diabetes Res Clin Pract. 2020;163:108108. doi: 10.1016/j. diabres.2020.108108.	Systematic review
Abdelgani S, Puckett C, Adams J, Triplitt C, DeFronzo RA, Abdul-Ghani M. Insulin secretion is a strong predictor for need of insulin therapy in patients with new-onset diabetes and HbA1c of more than 10%: a post hoc analysis of the EDICT study. Diabetes Obes Metab. 2021;23(7):1631–9. doi: 10.1111/dom.14383.	No eligible outcome
Abdelgani S, Puckett C, Adams J, Triplitt C, DeFronzo RA, Abdul-Ghani M. Insulin secretion predicts the response to antidiabetic therapy in patients with new-onset diabetes. J Clin Endocrinol Metab. 2021;106(12):3497–504. doi: 10.1210/clinem/dgab403.	No eligible outcome
Abdul-Ghani M, Puckett C, Adams J, Khattab A, Baskoy G, Cersosimo E et al. Durability of triple combination therapy versus stepwise addition therapy in patients with newonset T2DM: 3-year follow-up of EDICT. Diabetes Care. 2021;44(2):433–9. doi: 10.2337/dc20-0978.	No eligible comparator
Abdul-Ghani M, Migahid O, Megahed A, DeFronzo RA, Al-Ozairi E, Jayyousi A. Combination therapy with pioglitazone/exenatide improves beta-cell function and produces superior glycaemic control compared with basal/bolus insulin in poorly controlled type 2 diabetes: a 3-year follow-up of the Qatar study. Diabetes Obes Metab. 2020;22(12):2287–94. doi: 10.1111/dom.14153.	Ineligible population

Reference	Reason for exclusion
Abdullah F, Sattar A, Shaukat K, Ahmad S, Nawaz S, Maryam B. To compare the efficacy of dapagliflozin and metformin vs sitagliptin and metformin in newly diagnosed type 2 diabetic patients. Pak J Med Health Sci. 2021;15(1):85–6.	No eligible outcome
Abildgaard J, Johansen MY, Skov-Jeppesen K, Andersen LB, Karstoft K, Hansen KB et al. Effects of a lifestyle intervention on bone turnover in persons with type 2 diabetes: a post hoc analysis of the U-TURN Trial. Med Sci Sports Exerc. 2022;54(1):38–46. doi: 10.1249/MSS.0000000000002776.	No eligible outcome
Abreu M, Tumyan A, Elhassan A, Peicher K, Papacostea O, Dimachkie P et al. A randomized trial comparing the efficacy and safety of treating patients with type 2 diabetes and highly elevated HbA1c levels with basalbolus insulin or a glucagon-like peptide-1 receptor agonist plus basal insulin: the SIMPLE study. Diabetes Obes Metab. 2019;21(9):2133–41. doi: 10.1111/dom.13794.	No eligible outcome
Abu-Saad K, Murad H, Barid R, Olmer L, Ziv A, Younis-Zeidan N et al. Development and efficacy of an electronic, culturally adapted lifestyle counseling tool for improving diabetes-related dietary knowledge: randomized controlled trial among ethnic minority adults with type 2 diabetes mellitus. J Med Internet Res. 2019;21(10):e13674. doi: 10.2196/13674.	No eligible outcome
Adam TC, Drummen M, Macdonald I, Jalo E, Siig-Vestentoft P, Martínez JA et al. Association of psychobehavioral variables with HOMA-IR and BMI differs for men and women with prediabetes in the PREVIEW lifestyle intervention. Diabetes Care. 2021;44(7):1491–8. doi: 10.2337/dc21-0059.	No eligible outcome
Aekplakorn W, Tantayotai V, Numsangkul S, Tatsato N, Luckanajantachote P, Himathongkam T. Evaluation of a community-based diabetes prevention program in Thailand: a cluster randomized controlled trial. J Prim Care Community Health. 2019;10:2150132719847374. doi: 10.1177/2150132719847374.	Already included in USPSTF review

Reference	Reason for exclusion
Agarwal P, Mukerji G, Desveaux L, Ivers NM, Bhattacharyya O, Hensel JM et al. Mobile app for improved self-management of type 2 diabetes: multicenter pragmatic randomized controlled trial. JMIR Mhealth Uhealth. 2019;7(1):e10321. doi: 10.2196/10321.	No eligible outcome
Agbaje OF, Coleman RL, Hattersley AT, Jones AG, Pearson ER, Shields BM et al. Predicting post one-year durability of glucose-lowering monotherapies in patients with newly-diagnosed type 2 diabetes mellitus: a MASTERMIND precision medicine approach (UKPDS 87). Diabetes Res Clin Pract. 2020;166:108333. doi: 10.1016/j.diabres.2020.108333.	No eligible outcome
Ahern AL, Griffin SJ, Wheeler GM, Sharp SJ, Aveyard P, Boyland EJ et al. The effect of referral to an open-group behavioural weight-management programme on the relative risk of normoglycaemia, non-diabetic hyperglycaemia and type 2 diabetes: secondary analysis of the WRAP trial. Diabetes Obes Metab. 2020;22(11):2069–76. doi: 10.1111/dom.14123.	No eligible comparator
Åkerblom A, Oldgren J, Latva-Rasku A, Johansson L, Lisovskaja V, Karlsson C et al. Effects of DAPAgliflozin on CARDiac substrate uptake, myocardial efficiency, and myocardial contractile work in type 2 diabetes patients: a description of the DAPACARD study. Ups J Med Sci. 2019;124(1):59–64. doi: 10.1080/03009734.2018.1515281.	No eligible outcome
Al-Aubaidy HA, Dayan A, Deseo MA, Itsiopoulos C, Jamil D, Hadi NR et al. Twelve-week Mediterranean diet intervention increases citrus bioflavonoid levels and reduces inflammation in people with type 2 diabetes mellitus. Nutrients. 2021;13(4):1133. doi: 10.3390/nu13041133.	No eligible outcome
Alfawaz H, Naeef AF, Wani K, Khattak MNK, Sabico S, Alnaami AM et al. Improvements in glycemic, micronutrient, and mineral indices in Arab adults with pre-diabetes post-lifestyle modification program. Nutrients. 2019;11(11)2775. doi: 10.3390/nu11112775.	No eligible outcome

Reference	Reason for exclusion
Al-Ghafri TS, Al-Harthi S, Al-Farsi Y, Craigie AM, Bannerman E, Anderson AS. Changes in self-efficacy and social support after an intervention to increase physical activity among adults with type 2 diabetes in Oman: a 12-month follow-up of the MOVEdiabetes trial. Sultan Qaboos Univ Med J. 2021;21(1):e42–9. doi: 10.18295/squmj.2021.21.01.006.	No eligible outcome
Al-Hamdan R, Avery A, Salter A, Al-Disi D, Al-Daghri NM, McCullough F. Identification of education models to improve health outcomes in Arab women with prediabetes. Nutrients. 2019;11(5):1113. doi: 10.3390/nu11051113.	No eligible outcome
Al-Hamdan R, Avery A, Al-Disi D, Sabico S, Al-Daghri NM, McCullough F. Efficacy of lifestyle intervention program for Arab women with prediabetes using social media as an alternative platform of delivery. J Diabetes Investig. 2021;12(10):1872–80. doi: 10.1111/jdi.13531.	No eligible outcome
Alison C, Anselm S. The effectiveness of diabetes medication therapy adherence clinic to improve glycaemic control among patients with type 2 diabetes mellitus: a randomised controlled trial. Med J Malaysia. 2020;75(3):246–53. PMID: 32467540.	No eligible outcome
Alonso-Dominguez R, García-Ortiz L, Patino-Alonso MC, Sánchez-Aguadero N, Gomez-Marcos MA, Recio-Rodriguez JI. Effectiveness of a multifactorial intervention in increasing adherence to the Mediterranean diet among patients with diabetes mellitus type 2: a controlled and randomized study (EMID study). Nutrients. 2019;11(1):162. doi: 10.3390/nu11010162.	No eligible outcome
Alonso-Dominguez R, Patino-Alonso MC, Sánchez-Aguadero N, García-Ortiz L, Recio-Rodriguez JI, Gomez-Marcos MA. Effect of a multifactorial intervention on the increase in physical activity in subjects with type 2 diabetes mellitus: a randomized clinical trial (EMID study). Eur J Cardiovasc Nurs. 2019;18(5):399–409. doi: 10.1177/1474515119835048.	No eligible outcome

Tuble 72.1. conta		
Reference	Reason for exclusion	
Alshehri MM, Alenazi AM, Alothman SA, Rucker JL, Phadnis MA, Miles JM et al. Using cognitive behavioral therapy for insomnia in people with type 2 diabetes, pilot RCT Part I: sleep and concomitant symptom. Behav Sleep Med. 2021;19(5):652–71. doi: 10.1080/15402002.2020.1831501.	No eligible outcome	
Álvarez C, Ramirez-Campillo R, Lucia A, Ramirez-Velez R, Izquierdo M. Concurrent exercise training on hyperglycemia and comorbidities associated: non-responders using clinical cutoff points. Scand J Med Sci Sports. 2019;29(7):952–67. doi: 10.1111/sms.13413.	No eligible outcome	
Álvarez-Canales MFL, Salazar-López SS, Farfán-Vázquez D, Martínez-López YE, Gonzalez- Mena JN, Jiménez-Ceja LM et al. Effect of linagliptin on glucose metabolism and pancreatic beta cell function in patients with persistent prediabetes after metformin and lifestyle. Sci Rep. 2021;11(1):8750. doi: 10.1038/s41598-021-88108-8.	Ineligible population	
Andreadis P, Karagiannis T, Malandris K, Avgerinos I, Liakos A, Manolopoulos A et al. Semaglutide for type 2 diabetes mellitus: a systematic review and meta- analysis. Diabetes Obes Metab. 2018;20(9):2255–63. doi: 10.1111/dom.13361.	Systematic review	
Andreae SJ, Andreae LJ, Cherrington AL, Richman JS, Johnson E, Clark D et al. Peer coach delivered storytelling program improved diabetes medication adherence: a cluster randomized trial. Contemp Clin Trials. 2021;104:106358. doi: 10.1016/j.cct.2021.106358.	No eligible outcome	
Ang L, Kidwell KM, Dillon B, Reiss J, Fang F, Leone V et al. Dapagliflozin and measures of cardiovascular autonomic function in patients with type 2 diabetes (T2D). J Diabetes Complications. 2021;35(8):107949. doi: 10.1016/j.jdiacomp.2021.107949.	No eligible outcome	
Angellotti E, D'Alessio D, Dawson-Hughes B, Chu Y, Nelson J, Hu P et al. Effect of vitamin D supplementation on cardiovascular risk in type 2 diabetes. Clin Nutr. 2019;38(5):2449–53. doi: 10.1016/j.clnu.2018.10.003.	No eligible outcome	

Reference	Reason for exclusion
Angwin C, Jenkinson C, Jones A, Jennison C, Henley W, Farmer A et al. TriMaster: randomised double-blind crossover study of a DPP4 inhibitor, SGLT2 inhibitor and thiazolidinedione as second-line or third-line therapy in patients with type 2 diabetes who have suboptimal glycaemic control on metformin treatment with or without a sulfonylurea – A MASTERMIND study protocol. BMJ Open. 2020;10(12):e042784. doi: 10.1136/bmjopen-2020-042784.	No eligible outcome
Anirban M, Soumyabrata RC, Debmalya S, Bhattacharjee K. Liraglutide: Indian experience. Indian J Endocrinol Metab. 2019;22(6):818–26. doi: 10.4103/ijem. IJEM_187_18.	Systematic review
Apolzan JW, Venditti EM, Edelstein SL, Knowler WC, Dabelea D, Boyko EJ et al. Long-term weight loss with metformin or lifestyle intervention in the Diabetes Prevention Program Outcomes Study. Ann Intern Med. 2019;170(10):682–90. doi: 10.7326/M18-1605.	Already included in USPSTF review
Araki E, Yamashita S, Arai H, Yokote K, Satoh J, Inoguchi T et al. Efficacy and safety of pemafibrate in people with type 2 diabetes and elevated triglyceride levels: 52-week data from the PROVIDE study. Diabetes Obes Metab. 2019;21(7):1737–44. doi: 10.1111/dom.13686.	Ineligible population
Araki E, Terauchi Y, Watada H, Deenadayalan S, Christiansen E, Horio H et al. Efficacy and safety of oral semaglutide in Japanese patients with type 2 diabetes: a post hoc subgroup analysis of the PIONEER 1, 3, 4 and 8 trials. Diabetes Obes Metab. 2021;23(12):2785–94. doi: 10.1111/dom.14536.	Ineligible population
Arguedas JA, Leiva V, Wright JM. Blood pressure targets for hypertension in people with diabetes mellitus. Cochrane Database Syst Rev. 2013;(10):CD008277. doi: 10.1002/14651858.CD008277.pub2.	Systematic review

Reference	Reason for exclusion
Aroda VR, Christophi CA, Edelstein SL, Perreault L, Kim C, Golden SH et al. Circulating sex hormone binding globulin levels are modified with intensive lifestyle intervention, but their changes did not independently predict diabetes risk in the Diabetes Prevention Program. BMJ Open Diabetes Res Care. 2020;8(2):e001841. doi: 10.1136/bmjdrc-2020-001841.	No eligible outcome
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Reference	Reason for exclusion
Bacha F, El Ghormli L, Arslanian S, Zeitler P, Laffel LM, Levitt Katz LE et al. Predictors of response to insulin therapy in youth with poorly-controlled type 2 diabetes in the TODAY trial. Pediatr Diabetes. 2019;20(7):871–9. doi: 10.1111/pedi.12906.	No eligible outcome
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Reference	Reason for exclusion
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Reference	Reason for exclusion
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Reason for exclusion  No eligible outcome
No eligible outcome
Ineligible population
Ineligible population
No eligible outcome
Ineligible population
No eligible outcome

Reference	Reason for exclusion
Bessell E, Fuller NR, Markovic TP, Lau NS, Burk J, Hendy C et al. Effects of alpha-cyclodextrin on cholesterol control and hydrolyzed ginseng extract on glycemic control in people with prediabetes: a randomized clinical trial. JAMA Netw Open. 2020;3(11):e2023491. doi: 10.1001/jamanetworkopen.2020.23491.	No eligible comparator
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	Reference	Reason for exclusion
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	Bizino MB, Jazet IM, de Heer P, van Eyk HJ, Dekkers IA, Rensen PCN et al. Placebo-controlled randomised trial with liraglutide on magnetic resonance endpoints in individuals with type 2 diabetes: a pre-specified secondary study on ectopic fat accumulation. Diabetologia. 2020;63(1):65–74. doi: 10.1007/s00125-019-05021-6.	No eligible outcome
	Blonde L, Fainberg U, Kaltoft MS, Mosenzon O, Ramesh C, Rea R. Efficacy of liraglutide added to sodium-glucose cotransporter-2 inhibitors in type 2 diabetes, stratified by baseline characteristics: post-hoc analysis of LIRA-ADD2SGLT2i. Diabetes Obes Metab. 2021;23(10):2234–41. doi: 10.1111/dom.14464.	No eligible outcome
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S ER till SES ER S C a 2 ES t A N E C h fi	Rizino MB, Jazet IM, de Heer P, van Eyk HJ, Dekkers IA, Rensen PCN et al. Placebo-controlled randomised rial with liraglutide on magnetic resonance endpoints in individuals with type 2 diabetes: a pre-specified secondary study on ectopic fat accumulation. Diabetologia. 2020;63(1):65–74. doi: 10.1007/100125-019-05021-6.  Blonde L, Fainberg U, Kaltoft MS, Mosenzon O, Ramesh C, Rea R. Efficacy of liraglutide added to sodium-glucose cotransporter-2 inhibitors in type 2 diabetes, stratified by baseline characteristics: post-hoc snalysis of LIRA-ADD2SGLT2i. Diabetes Obes Metab. 1021;23(10):2234–41. doi: 10.1111/dom.14464.  Bock BC, Thind H, Fava JL, Dunsiger S, Guthrie KM, Stroud L et al. Feasibility of yoga as a complementary herapy for patients with type 2 diabetes: the Healthy Active and in Control (HA1C) study. Complement Therefore Med. 2019;42:125–31. doi: 10.1016/j.ctim.2018.09.019.	No eligible outcome  No eligible outcome

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Reference	Reason for exclusion
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Bonora E, Frías JP, Tinahones FJ, Van J, Malik RE, Yu Z et al. Effect of dulaglutide 3.0 and 4.5 mg on weight in patients with type 2 diabetes: exploratory analyses of AWARD-11. Diabetes Obes Metab. 2021;23(10):2242–50. doi: 10.1111/dom.14465.	No eligible outcome
Boonthongkaew C, Tong-Un T, Kanpetta Y, Chaungchot N, Leelayuwat C, Leelayuwat N. Vitamin C supplementation improves blood pressure and oxidative stress after acute exercise in patients with poorly controlled type 2 diabetes mellitus: a randomized, placebo-controlled, cross-over study. Chin J Physiol. 2021;64(1):16–23. doi: 10.4103/cjp.cjp_95_20.	No eligible outcome
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Reference	Reason for exclusion
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Buse JB, Bode BW, Mertens A, Cho YM, Christiansen E, Hertz CL et al. Long-term efficacy and safety of oral semaglutide and the effect of switching from sitagliptin to oral semaglutide in patients with type 2 diabetes: a 52-week, randomized, open-label extension of the PIONEER 7 trial. BMJ Open Diabetes Res Care. 2020;8(2):e001649. doi: 10.1136/bmjdrc-2020-001649.	Ineligible population
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Reference	Reason for exclusion
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Cardona A, O'Brien A, Bernier MC, Somogyi A, Wysocki VH, Smart S et al. Trimethylamine N-oxide and incident atherosclerotic events in highrisk individuals with diabetes: an ACCORD trial post hoc analysis. BMJ Open Diabetes Res Care. 2019;7(1):e000718. doi: 10.1136/bmjdrc-2019-000718.	Ineligible population
Cardenas A, Hivert MF, Gold DR, Hauser R, Kleinman KP, Lin PD et al. Associations of perfluoroalkyl and polyfluoroalkyl substances with incident diabetes and microvascular disease. Diabetes Care. 2019;42(9):1824–32. doi: 10.2337/dc18-2254.	No new data from this paper (study included)
Carlson AL, Mullen DM, Mazze R, Strock E, Richter S, Bergenstal RM. Evaluation of insulin glargine and exenatide alone and in combination: a randomized clinical trial with continuous glucose monitoring and ambulatory glucose profile analysis. Endocr Pract. 2019;25(4):306–14. doi: 10.4158/EP-2018-0177.	No eligible outcome
Carmichael OT, Neiberg RH, Dutton GR, Hayden KM, Horton E, Pi-Sunyer FX et al. Long-term change in physiological markers and cognitive performance in type 2 diabetes: the Look AHEAD study. J Clin Endocrinol Metab. 2020;105(12):e4778–91. doi: 10.1210/clinem/dgaa591.	No eligible outcome

Reference	Reason for exclusion
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Castillo-Hernandez KG, Laviada-Molina H, Hernandez-Escalante VM, Molina-Segui F, Mena-Macossay L, Caballero AE. Peer support added to diabetes education improves metabolic control and quality of life in Mayan adults living with type 2 diabetes: a randomized controlled trial. Can J Diabetes. 2021;45(3):206–13. doi: 10.1016/j.jcjd.2020.08.107.	No eligible outcome
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Reference	Reason for exclusion
Chen S, Burstrom B, Sparring V, Qian D, Burstrom K. Differential impact of an education-based intervention for patients with type 2 diabetes mellitus in rural China. Int J Environ Res Public Health. 2019;16(15):2676. doi: 10.3390/ijerph16152676.	No eligible outcome
Chen S, Qian D, Burstrom K, Burstrom B. Impact of an educational intervention in primary care on fasting blood glucose levels and diabetes knowledge among patients with type 2 diabetes mellitus in rural China. Patient Educ Couns. 2020;103(9):1767–73. doi: 10.1016/j.pec.2020.03.010.	No eligible outcome
Chen X, Xu Y, Zhang J, Shao S, Duan Y, Liu P et al. Exenatide twice daily plus glargine versus aspart 70/30 twice daily in patients with type 2 diabetes with inadequate glycemic control on premixed human insulin and metformin. Endocr Pract. 2021;27(8):790–7. doi: 10.1016/j.eprac.2021.03.015.	Ineligible population
Chen ZZ, Liu J, Morningstar J, Heckman-Stoddard BM, Lee CG, Dagogo-Jack S et al. Metabolite profiles of incident diabetes and heterogeneity of treatment effect in the Diabetes Prevention Program. Diabetes. 2019;68(12):2337–49. doi: 10.2337/db19-0236.	No eligible outcome
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Reference	Reason for exclusion
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Chihara A, Tanaka A, Morimoto T, Sakuma M, Shimabukuro M, Nomiyama T et al. Differences in lipid metabolism between anagliptin and sitagliptin in patients with type 2 diabetes on statin therapy: a secondary analysis of the REASON trial. Cardiovasc Diabetol. 2019;18(1):158. doi: 10.1186/s12933-019-0965-3.	No eligible outcome
Chilcott J, Tappenden P, Jones ML, Wight JP. A systematic review of the clinical effectiveness of pioglitazone in the treatment of type 2 diabetes mellitus. Clin Ther. 2001;23(11):1792–823. doi: 10.1016/s0149-2918(00)80078-8.	Systematic review
Cho KY, Nomoto H, Nakamura A, Kawata S, Sugawara H, Takeuchi J et al. Improved time in range and postprandial hyperglycemia with canagliflozin in combination with teneligliptin: secondary analyses of the CALMER study. J Diabetes Investig. 2021;12(8): 1417–24. doi: 10.1111/jdi.13498.	No eligible outcome
Cho YM, Deerochanawong C, Seekaew S, Suraamornkul S, Benjachareonwong S, Sattanon S et al. Efficacy and safety of gemigliptin as add-on therapy to insulin, with or without metformin, in patients with type 2 diabetes mellitus (ZEUS II study). Diabetes Obes Metab. 2020;22(1):123–7. doi: 10.1111/dom.13873.	Ineligible population

Reference	Reason for exclusion
Choomai A, Wattanapisit A, Tiangtam O. Effects of an actual insulin injection demonstration on insulin acceptance among patients with T2DM: a pragmatic randomized controlled trial. Rom J Intern Med. 2021;59(2):151–8. doi: 10.2478/rjim-2020-0040.	No eligible outcome
Cintra RMR, Soares AAS, Breder I, Munhoz DB, Barreto J, Kimura-Medorima ST et al. Assessment of dapagliflozin effect on diabetic endothelial dysfunction of brachial artery (ADDENDA-BHS2 trial): rationale, design, and baseline characteristics of a randomized controlled trial. Diabetol Metab Syndr. 2019;11(1):62. doi: 10.1186/S13098-019-0457-3.	No follow-up (baseline data only)
Clements JN, Isaacs D, Hartman RE, Gambill K. Pharmacokinetics and clinical implications of oral semaglutide for type 2 diabetes mellitus. Clin Pharmacokinet. 2021;60(2):153–63. doi: 10.1007/s40262-020-00951-6.	Systematic review
Clemmensen KKB, Blond MB, Amadid H, Bruhn L, Vistisen D, Karstoft K et al. No effects of dapagliflozin, metformin or exercise on plasma glucagon concentrations in individuals with prediabetes: a post hoc analysis from the randomized controlled PRE-D trial. Diabetes Obes Metab. 2021;23(2):530–9. doi: 10.1111/dom.14246.	No eligible outcome
Cojic M, Kocic R, Klisic A, Cvejanov-Kezunovic L, Kavaric N, Kocic G. A novel mechanism of vitamin D anti-inflammatory/antioxidative potential in type 2 diabetic patients on metformin therapy. Arch Med Sci. 2020;16(5):1004–12. doi: 10.5114/aoms.2020.92832.	No eligible outcome
Colhoun HM, Leiter LA, Muller-Wieland D, Cariou B, Ray KK, Tinahones FJ et al. Effect of alirocumab on individuals with type 2 diabetes, high triglycerides, and low high-density lipoprotein cholesterol. Cardiovasc Diabetol. 2020;19(1):14. doi: 10.1186/s12933-020-0991-1.	Ineligible population

Table A2.1. Contd	
Reference	Reason for exclusion
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Cox DJ, Banton T, Moncrief M, Conaway M, Diamond A, Holmes V et al. Glycemic excursion minimization in the management of type 2 diabetes: a novel intervention tested in a randomized clinical trial. BMJ Open Diabetes Res Care. 2020;8(2):e001795. doi: 10.1136/bmjdrc-2020-001795.	No eligible outcome
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Faerch K, Blond MB, Bruhn L, Amadid H, Vistisen D, Clemmensen KKB et al. The effects of dapagliflozin, metformin or exercise on glycaemic variability in overweight or obese individuals with prediabetes (the PRE-D Trial): a multi-arm, randomised, controlled trial. Diabetologia. 2021;64(1):42–55. doi: 10.1007/s00125-020-05306-1.	No eligible outcome
Fajriansyah, Iskandarsyah A, Puspitasari IM, Lestari K. Impact of pharmacist counseling on health-related quality of life of patients with type 2 diabetes mellitus: a cluster randomized controlled study. J Diabetes Metab Disord. 2020;19(2):675–82. doi: 10.1007/s40200-020-00528-x.	No eligible outcome
Fang H, Xu F, Du J, Liang L, Li W, Shen L et al. Impact of baseline characteristics on glycemic effects of add-on saxagliptin or acarbose to metformin therapy: subgroup analysis of the SMART study in Chinese patients with type 2 diabetes mellitus. J Diabetes Investig. 2020;11(4):896–905. doi: 10.1111/jdi.13224.	Ineligible population

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Fayfman M, Galindo RJ, Rubin DJ, Mize DL, Anzola I, Urrutia MA et al. A randomized controlled trial on the safety and efficacy of exenatide therapy for the inpatient management of general medicine and surgery patients with type 2 diabetes. Diabetes Care. 2019;42(3):450–6. doi: 10.2337/dc18-1760.	Ineligible population
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Fournier M, Germe M, Theobald K, Scholz GH, Lehmacher W. Indirect comparison of lixisenatide versus neutral protamine Hagedorn insulin as add-on to metformin and sulphonylurea in patients with type 2 diabetes mellitus. Ger Med Sci. 2014;12:Doc14. doi: 10.3205/000199.	Systematic review
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Francis SL, Simmering JE, Polgreen LA, Evans NJ, Hosteng KR, Carr LJ et al. Gamifying accelerometer use increases physical activity levels of individuals pre-disposed to type II diabetes. Prev Med Rep. 2021;23:101426. doi: 10.1016/j.pmedr.2021.101426.	No eligible outcome
Frías JP, Bonora E, Cox DA, Bethel MA, Kwan AYM, Raha S et al. Glycaemic efficacy of an expanded dose range of dulaglutide according to baseline glycated haemoglobin (HbA1c) subgroup: post hoc analysis of AWARD-11. Diabetes Obes Metab. 2021;23(12):2819–24. doi: 10.1111/dom.14533.	No eligible outcome
Frías JP, Bonora E, Nevarez Ruiz L, Li YG, Yu Z, Milicevic Z et al. Efficacy and safety of dulaglutide 3.0 mg and 4.5 mg versus dulaglutide 1.5 mg in metformin-treated patients with type 2 diabetes in a randomized controlled trial (AWARD-11). Diabetes Care. 2021;44(3):765–73. doi: 10.2337/dc20-1473.	Ineligible population

Reference	Reason for exclusion
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Frías JP, Zimmer Z, Lam RLH, Amorin G, Ntabadde C, Iredale C et al. Double-blind, randomized clinical trial assessing the efficacy and safety of early initiation of sitagliptin during metformin uptitration in the treatment of patients with type 2 diabetes: the CompoSIT-M study. Diabetes Obes Metab. 2019;21(5):1128–35. doi: 10.1111/dom.13626.	Ineligible population
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Frydenberg M, Maindal HT, Fletcher A, Juul L. Is patient activation a mediator of the effect of a health promoting intervention in adults at high risk of type 2 diabetes? A longitudinal path model analysis within a randomised trial. BMC Public Health. 2022;22(1):439. doi: 10.1186/s12889-022-12864-z.	No eligible outcome
Fu J, Liu J, Xu Y, Yang N, Yang W, Wang G. Comparison of therapeutic effects of acarbose and metformin under different beta-cell function status in Chinese patients with type 2 diabetes. Endocr J. 2019;66(5):443–50. doi: 10.1507/endocrj.EJ18-0466.	No eligible outcome

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Fuchigami A, Shigiyama F, Kitazawa T, Okada Y, Ichijo T, Higa M et al. Efficacy of dapagliflozin versus sitagliptin on cardiometabolic risk factors in Japanese patients with type 2 diabetes: a prospective, randomized study (DIVERSITY-CVR). Cardiovasc Diabetol. 2020;19(1):1. doi: 10.1186/s12933-019-0977-z.	No eligible outcome
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Fullerton B, Siebenhofer A, Jeitler K, Horvath K, Semlitsch T, Berghold A et al. Short-acting insulin analogues versus regular human insulin for adult, non-pregnant persons with type 2 diabetes mellitus. Cochrane Database Syst Rev. 2018;(12):CD013228. doi: 10.1002/14651858.CD013228.	Systematic review
Furuhashi M, Sakuma I, Morimoto T, Higashiura Y, Sakai A, Matsumoto M et al. Treatment with anagliptin, a DPP-4 inhibitor, decreases FABP4 concentration in patients with type 2 diabetes mellitus at a high risk for cardiovascular disease who are receiving statin therapy. Cardiovasc Diabetol. 2020;19(1):89. doi: 10.1186/s12933-020-01061-0.	No eligible outcome
Furuhashi M, Sakuma I, Morimoto T, Higashiura Y, Sakai A, Matsumoto M et al. Differential effects of DPP-4 inhibitors, anagliptin and sitagliptin, on PCSK9 levels in patients with type 2 diabetes mellitus who are receiving statin therapy. J Atheroscler Thromb. 2022;29(1):24–37. doi: 10.5551/jat.58396.	No eligible outcome
Gaitán JM, Eichner NZM, Gilbertson NM, Heiston EM, Weltman A, Malin SK. Two weeks of interval training enhances fat oxidation during exercise in obese adults with prediabetes. J Sports Sci Med. 2019;18(4):636–44. PMID: 31827347.	Ineligible follow-up duration

Reference	Reason for exclusion
Gamboa Moreno E, Mateo-Abad M, Ochoa de Retana García L, Vrotsou K, Del Campo Pena E, Sánchez Perez Á et al. Efficacy of a self-management education programme on patients with type 2 diabetes in primary care: a randomised controlled trial. Prim Care Diabetes. 2019;13(2):122–33. doi: 10.1016/j.pcd.2018.10.001.	No eligible outcome
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Reason for exclusion
No eligible outcome
Ineligible population
Ineligible population
Ineligible follow-up duration
Ineligible population
Ineligible population
No eligible outcome

Reference	Reason for exclusion
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Reference	Reason for exclusion
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Reference	Reason for exclusion
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Reference	Reason for exclusion
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Reference	Reason for exclusion
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Reference	Reason for exclusion
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Reference	Reason for exclusion
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Reference	Reason for exclusion
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Reference	Reason for exclusion
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Reason for exclusion
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No eligible outcome
No eligible outcome
Ineligible population
No eligible outcome
No eligible outcome

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Reason for exclusion
No eligible outcome
No eligible outcome
Ineligible population
Ineligible population
Ineligible population
No eligible outcome

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Knowler WC, Liao E et al. Effect of vitamin D supplementation on kidney function in adults with prediabetes: a secondary analysis of a randomized trial. Clin J Am Soc Nephrol. 2021;16(8):1201–9. doi: 10.2215/CJN.00420121.  Kim SH, Kim Y, Choi S, Jeon B. Evaluation of nurse-led social media intervention for diabetes self-management: a mixed-method study. J Nurs Scholarsh. 2022;54(5):569–77. doi: 10.1111/jnu.12770.  Kim Y, Lee H, Seo JM. Integrated diabetes self-management program using smartphone application: a randomized controlled trial. West J Nurs Res. 2022;44(4):383–94. doi: 10.1177/0193945921994912.  Kinduryte Schorling O, Clark D, Zwiener I, Kaspers S, Lee J, Iliev H. Pooled safety and tolerability analysis of empagliflozin in patients with type 2 diabetes mellitus. Adv Ther. 2020;37(8):3463–84. doi: 10.1007/s12325-020-01329-7.  Kitazawa T, Seino H, Ohashi H, Inazawa T, Inoue M, Ai M et al. Comparison of tofogliflozin versus glimepiride as the third oral agent added to metformin plus a dipeptidyl peptidase-4 inhibitor in Japanese patients with type 2 diabetes: a randomized, 24-week, open-label, controlled trial (STOP-OB). Diabetes Obes	Kumar A, Kalra B et al. Effect of the glucagon-like peptide-1 analogue liraglutide versus placebo treatment on circulating proglucagon-derived peptides that mediate improvements in body weight, insulin secretion and action: a randomized controlled trial. Diabetes Obes	No eligible outcome
social media intervention for diabetes self-management: a mixed-method study. J Nurs Scholarsh. 2022;54(5):569–77. doi: 10.1111/jnu.12770.  Kim Y, Lee H, Seo JM. Integrated diabetes self-management program using smartphone application: a randomized controlled trial. West J Nurs Res. 2022;44(4):383–94. doi: 10.1177/0193945921994912.  Kinduryte Schorling O, Clark D, Zwiener I, Kaspers S, Lee J, Iliev H. Pooled safety and tolerability analysis of empagliflozin in patients with type 2 diabetes mellitus. Adv Ther. 2020;37(8):3463–84. doi: 10.1007/s12325-020-01329-7.  Kitazawa T, Seino H, Ohashi H, Inazawa T, Inoue M, Ai M et al. Comparison of tofogliflozin versus glimepiride as the third oral agent added to metformin plus a dipeptidyl peptidase-4 inhibitor in Japanese patients with type 2 diabetes: a randomized, 24-week, open-label, controlled trial (STOP-OB). Diabetes Obes	Knowler WC, Liao E et al. Effect of vitamin D supplementation on kidney function in adults with prediabetes: a secondary analysis of a randomized trial. Clin J Am Soc Nephrol. 2021;16(8):1201–9.	Ineligible intervention
management program using smartphone application: a randomized controlled trial. West J Nurs Res. 2022;44(4):383–94. doi: 10.1177/0193945921994912.  Kinduryte Schorling O, Clark D, Zwiener I, Kaspers S, Lee J, Iliev H. Pooled safety and tolerability analysis of empagliflozin in patients with type 2 diabetes mellitus. Adv Ther. 2020;37(8):3463–84. doi: 10.1007/S12325-020-01329-7.  Kitazawa T, Seino H, Ohashi H, Inazawa T, Inoue M, Ai M et al. Comparison of tofogliflozin versus glimepiride as the third oral agent added to metformin plus a dipeptidyl peptidase-4 inhibitor in Japanese patients with type 2 diabetes: a randomized, 24-week, open-label, controlled trial (STOP-OB). Diabetes Obes	social media intervention for diabetes self-management: a mixed-method study. J Nurs Scholarsh. 2022;54(5):569–77.	Ineligible population
Lee J, Iliev H. Pooled safety and tolerability analysis of empagliflozin in patients with type 2 diabetes mellitus. Adv Ther. 2020;37(8):3463–84. doi: 10.1007/s12325-020-01329-7.  Kitazawa T, Seino H, Ohashi H, Inazawa T, Inoue M, Ai M et al. Comparison of tofogliflozin versus glimepiride as the third oral agent added to metformin plus a dipeptidyl peptidase-4 inhibitor in Japanese patients with type 2 diabetes: a randomized, 24-week, open-label, controlled trial (STOP-OB). Diabetes Obes	management program using smartphone application: a randomized controlled trial. West   Nurs Res.	Ineligible population
Ai M et al. Comparison of tofogliflozin versus glimepiride as the third oral agent added to metformin plus a dipeptidyl peptidase-4 inhibitor in Japanese patients with type 2 diabetes: a randomized, 24-week, open-label, controlled trial (STOP-OB). Diabetes Obes	Lee J, Iliev H. Pooled safety and tolerability analysis of empagliflozin in patients with type 2 diabetes mellitus. Adv	Ineligible population
, 6, 6, 6	Ai M et al. Comparison of tofogliflozin versus glimepiride as the third oral agent added to metformin plus a dipeptidyl peptidase-4 inhibitor in Japanese patients with type 2 diabetes: a randomized, 24-week, open-label, controlled trial (STOP-OB). Diabetes Obes	No eligible outcome

Reference	Reason for exclusion
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Reason for exclusion
No eligible outcome
No eligible outcome
Ineligible population
Ineligible population
No eligible outcome
No new data from this paper (study included)

Reference	Reason for exclusion
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Reference	Reason for exclusion
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Reason for exclusion
No eligible outcome
No eligible outcome
No eligible outcome
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Reference	Reason for exclusion
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Systematic review
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Arniella G, Negron R et al. Outcomes of a weight loss intervention to prevent diabetes among low-income residents of East Harlem, New York. Health Educ Behav. 2019;46(6):1073–82. doi: 10.1177/1090198119868232.  McBain H, Mulligan K, Haddad M, Flood C, Jones J, Simpson A. Self management interventions for type 2 diabetes in adult people with severe mental illness. Cochrane Database Syst Rev. 2016;(4):CD011361. doi: 10.1002/14651858.CD011361.pub2.  McCrimmon RJ, Catarig A-M, Frías JP, Lausvig NL, le Roux CW, Thielke D et al. Effects of once-weekly semaglutide vs once-daily canagliflozin on body composition in type 2 diabetes: a substudy of the SUSTAIN 8 randomised controlled clinical trial. Diabetologia. 2020;63(3):473–85. doi: 10.1007/s00125-019-05065-8.  McInnes N, Hall S, Hramiak I, Sigal RJ, Goldenberg R, Gupta N et al. Remission of type 2 diabetes following a short-term intensive intervention with insulin glargine, sitagliptin, and metformin: results of an open-label randomized parallel-design trial. Diabetes Care. 2022;45(1):178–85. doi: 10.2337/dc21-0278.  Mehrzadi S, Mirzaei R, Heydari M, Sasani M, Yaqoobvand B, Huseini HF. Efficacy and safety of a traditional herbal combination in patients with type II diabetes mellitus: a randomized controlled trial. J Diet	Stumvoll M, Del Prato S. Glycaemic durability of an early combination therapy with vildagliptin and metformin versus sequential metformin monotherapy in newly diagnosed type 2 diabetes (VERIFY): a 5-year, multicentre, randomised, double-blind trial. Lancet.	No eligible outcome
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le Roux CW, Thielke D et al. Effects of once-weekly semaglutide vs once-daily canagliflozin on body composition in type 2 diabetes: a substudy of the SUSTAIN 8 randomised controlled clinical trial. Diabetologia. 2020;63(3):473–85. doi: 10.1007/s00125-019-05065-8.  McInnes N, Hall S, Hramiak I, Sigal RJ, Goldenberg R, Gupta N et al. Remission of type 2 diabetes following a short-term intensive intervention with insulin glargine, sitagliptin, and metformin: results of an open-label randomized parallel-design trial. Diabetes Care. 2022;45(1):178–85. doi: 10.2337/dc21-0278.  Mehrzadi S, Mirzaei R, Heydari M, Sasani M, Yaqoobvand B, Huseini HF. Efficacy and safety of a traditional herbal combination in patients with type II diabetes mellitus: a randomized controlled trial. J Diet	Simpson A. Self management interventions for type 2 diabetes in adult people with severe mental illness. Cochrane Database Syst Rev. 2016;(4):CD011361.	Systematic review
Gupta N et al. Remission of type 2 diabetes following a short-term intensive intervention with insulin glargine, sitagliptin, and metformin: results of an open-label randomized parallel-design trial. Diabetes Care. 2022;45(1):178–85. doi: 10.2337/dc21-0278.  Mehrzadi S, Mirzaei R, Heydari M, Sasani M, Yaqoobvand B, Huseini HF. Efficacy and safety of a traditional herbal combination in patients with type II diabetes mellitus: a randomized controlled trial. J Diet	le Roux CW, Thielke D et al. Effects of once-weekly semaglutide vs once-daily canagliflozin on body composition in type 2 diabetes: a substudy of the SUSTAIN 8 randomised controlled clinical trial. Diabetologia. 2020;63(3):473–85. doi: 10.1007/	No eligible outcome
Yaqoobvand B, Huseini HF. Efficacy and safety of a traditional herbal combination in patients with type II diabetes mellitus: a randomized controlled trial. J Diet	Gupta N et al. Remission of type 2 diabetes following a short-term intensive intervention with insulin glargine, sitagliptin, and metformin: results of an open-label randomized parallel-design trial. Diabetes Care.	Ineligible population
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Molavynejad S, Miladinia M, Jahangiri M. A randomized trial of comparing video telecare education vs inperson education on dietary regimen compliance in patients with type 2 diabetes mellitus: a support for clinical telehealth providers. BMC Endocr Disord. 2022;22(1):116. doi: 10.1186/s12902-022-01032-4.	No eligible outcome
Mollentze WF, Joubert G, Prins A, van der Linde S, Marx GM, Tsie KG. The safety and efficacy of a lowenergy diet to induce weight loss, improve metabolic health, and induce diabetes remission in insulin-treated obese men with type 2 diabetes: a pilot RCT. Int J Diabetes Dev Ctries. 2019;39(4):618–25. doi: 10.1007/s13410-019-00734-1	Ineligible population

Reference	Reason for exclusion
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Mora-Rodriguez R, Ortega JF, Ramirez-Jiménez M, Moreno-Cabañas A, Morales-Palomo F. Insulin sensitivity improvement with exercise training is mediated by body weight loss in subjects with metabolic syndrome. Diabetes Metab. 2020;46(3):210–18. doi: 10.1016/j.diabet.2019.05.004.	Ineligible follow-up duration
Moravcova K, Karbanova M, Bretschneider MP, Sovova M, Ozana J, Sovova E. Comparing digital therapeutic intervention with an intensive obesity management program: randomized controlled trial. Nutrients. 2022;14(10):2005. doi: 10.3390/nu14102005.	No eligible outcome
Morieri ML, Shah HS, Sjaarda J, Lenzini PA, Campbell H, Motsinger-Reif AA et al. <i>PPARA</i> polymorphism influences the cardiovascular benefit of fenofibrate in type 2 diabetes: findings from ACCORD-Lipid. Diabetes. 2020;69(4):771–83. doi: 10.2337/db19-0973.	Ineligible population
Mosenzon O, Bain SC, Heerspink HJL, Idorn T, Mann JFE, Persson F et al. Cardiovascular and renal outcomes by baseline albuminuria status and renal function: results from the LEADER randomized trial. Diabetes Obes Metab. 2020;22(11):2077–88. doi: 10.1111/dom.14126.	Ineligible population
Mostafa TM, Hegazy SK, Elnaidany SS, Shehabeldin WA, Sawan ES. <i>Nigella sativa</i> as a promising intervention for metabolic and inflammatory disorders in obese prediabetic subjects: a comparative study of <i>Nigella sativa</i> versus both lifestyle modification and metformin. J Diabetes Complications. 2021;35(7):107947. doi: 10.1016/j.jdiacomp.2021.107947.	No eligible outcome
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Reference	Reason for exclusion
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Table A2.1. contu		
Reference	Reason for exclusion	
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Nelson LA, Greevy RA, Spieker A, Wallston KA, Elasy TA, Kripalani S et al. Effects of a tailored text messaging intervention among diverse adults with type 2 diabetes: evidence from the 15-month REACH randomized controlled trial. Diabetes Care. 2021;44(1):26–34. doi: 10.2337/dc20-0961.	No eligible outcome	
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Nicolucci A, Haxhi J, D'Errico V, Sacchetti M, Orlando G, Cardelli P et al. Effect of a behavioural intervention for adoption and maintenance of a physically active lifestyle on psychological well-being and quality of life in patients with type 2 diabetes: the IDES_2 randomized clinical trial. Sports Med. 2022;52(3):643–54. doi: 10.1007/s40279-021-01556-0.	No eligible outcome	
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Reference	Reason for exclusion
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Quast DR, Schenker N, Menge BA, Nauck MA, Kapitza C, Meier JJ. Effects of lixisenatide versus liraglutide (short- and long-acting GLP-1 receptor agonists) on esophageal and gastric function in patients with type 2 diabetes. Diabetes Care. 2020;43(9):2137–45. doi: 10.2337/dc20-0720.	Ineligible follow-up duration
Quezada-Fernandez P, Trujillo-Quiros J, Pascoe-Gonzalez S, Trujillo-Rangel WA, Cardona-Muller D, Ramos-Becerra CG et al. Effect of green tea extract on arterial stiffness, lipid profile and sRAGE in patients with type 2 diabetes mellitus: a randomised, doubleblind, placebo-controlled trial. Int J Food Sci Nutr. 2019;70(8):977–85. doi: 10.1080/09637486.2019.1589430.	Ineligible follow-up duration
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Reference	Reason for exclusion
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Reference	Reason for exclusion
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Reference	Reason for exclusion
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Rezki A, Cosson E, Fysekidis M, Chiheb S, Vicaut E, Valensi P. Acute and long-term effects of saxagliptin on a set of cardiovascular targets measured at fasting and post-prandially in obese patients with impaired glucose tolerance: a placebo-controlled study. Nutr Metab Cardiovasc Dis. 2021;31(10):2945–58. doi: 10.1016/j.numecd.2021.06.017.	Ineligible follow-up duration
Rezki A, Fysekidis M, Chiheb S, Vicaut E, Cosson E, Valensi P. Acute and long-term effects of saxagliptin on post-prandial glycemic response in obese patients with impaired glucose tolerance. Nutr Metab Cardiovasc Dis. 2021;31(4):1257–66. doi: 10.1016/j.numecd.2020.12.025.	Ineligible follow-up duration

Reference	Reason for exclusion
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Reason for exclusion
Ineligible population
No eligible outcome
Systematic review
Ineligible follow-up duration
Ineligible population
No eligible outcome

Reference	Reason for exclusion
Rodbard HW, Rosenstock J, Canani LH, Deerochanawong C, Gumprecht J, Lindberg SO et al. Oral semaglutide versus empagliflozin in patients with type 2 diabetes uncontrolled on metformin: the PIONEER 2 trial. Diabetes Care. 2019;42(12):2272–81. doi: 10.2337/dc19-0883.	Ineligible population
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Romera I, Conget I, Vázquez LA, Gentilella R, Lebrec J, Jódar E, Reviriego J. Once-weekly dulaglutide versus insulin glargine in the early control of fasting serum glucose and HbA1c. J Diabetes Complications. 2020;34(7):107575. doi: 10.1016/j.jdiacomp.2020.107575.	Ineligible population
Roncero-Ramos I, Gutierrez-Mariscal FM, Gomez-Delgado F, Villasanta-Gonzalez A, Torres-Pena JD, Cruz-Ares SDL et al. Beta cell functionality and hepatic insulin resistance are major contributors to type 2 diabetes remission and starting pharmacological therapy: from CORDIOPREV randomized controlled trial. Transl Res. 2021;238:12–24. doi: 10.1016/j.trsl.2021.07.001.	Ineligible population
Roncero-Ramos I, Alcala-Diaz JF, Rangel-Zuniga OA, Gomez-Delgado F, Jiménez-Lucena R, García-Rios A et al. Prediabetes diagnosis criteria, type 2 diabetes risk and dietary modulation: the CORDIOPREV study. Clin Nutr. 2020;39(2):492–500. doi: 10.1016/j.clnu.2019.02.027.	Ineligible population
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Rosenstock J, Nino A, Soffer J, Erskine L, Acusta A, Dole J et al. Impact of a weekly glucagon-like peptide 1 receptor agonist, albiglutide, on glycemic control and on reducing prandial insulin use in type 2 diabetes inadequately controlled on multiple insulin therapy: a randomized trial. Diabetes Care. 2020;43(10):2509–18. doi: 10.2337/dc19-2316.	Ineligible population
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Reference	Reason for exclusion
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Rosenstock J, Wysham C, Frías JP, Kaneko S, Lee CJ, Fernandez Lando L et al. Efficacy and safety of a novel dual GIP and GLP-1 receptor agonist tirzepatide in patients with type 2 diabetes (SURPASS-1): a double-blind, randomised, phase 3 trial. Lancet. 2021;398(10295):143–55. doi: 10.1016/S0140-6736(21)01324-6.	Ineligible population
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Rossen J, Larsson K, Hagstromer M, Yngve A, Brismar K, Ainsworth B et al. Effects of a three-armed randomised controlled trial using self-monitoring of daily steps with and without counselling in prediabetes and type 2 diabetes: the Sophia Step study. Int J Behav Nutr Phys Act. 2021;18(1):121. doi: 10.1186/s12966-021-01193-w.	No eligible outcome
Roussel R, Duran-García S, Zhang Y, Shah S, Darmiento C, Shankar RR et al. Double-blind, randomized clinical trial comparing the efficacy and safety of continuing or discontinuing the dipeptidyl peptidase-4 inhibitor sitagliptin when initiating insulin glargine therapy in patients with type 2 diabetes: the CompoSIT-I study. Diabetes Obes Metab. 2019;21(4):781–90. doi: 10.1111/dom.13574.	Ineligible population
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Safarpour P, Daneshi-Maskooni M, Vafa M, Nourbakhsh M, Janani L, Maddah M et al. Vitamin D supplementation improves SIRT1, irisin, and glucose indices in overweight or obese type 2 diabetic patients: a double-blind randomized placebo-controlled clinical trial. BMC Fam Pract. 2020;21(1):26. doi: 10.1186/S12875-020-1096-3.	Ineligible population

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Sakane N, Kotani K, Suganuma A, Takahashi K, Sato J, Suzuki S et al. Effects of obesity, metabolic syndrome, and non-alcoholic or alcoholic elevated liver enzymes on incidence of diabetes following lifestyle intervention: a subanalysis of the J-DOIT1. J Occup Health. 2020;62(1):e12109. doi: 10.1002/1348-9585.	No new data from this paper (study included)
Sakane N, Kotani K, Suganuma A, Takahashi K, Sato J, Suzuki S et al. Prevention of metabolic syndrome by telephone-delivered lifestyle intervention in a real-world setting: sub-analysis of a cluster-randomized trial. Metab Syndr Relat Disord. 2019;17(7):355–61. doi: 10.1089/met.2018.0130.	No eligible outcome
Sakane N, Oshima Y, Kotani K, Suganuma A, Nirengi S, Takahashi K et al. Self-weighing frequency and the incidence of type 2 diabetes: post hoc analysis of a cluster-randomized controlled trial. BMC Res Notes. 2020;13(1):375. doi: 10.1186/s13104-020-05215-x.	Ineligible population
Sakane N, Oshima Y, Kotani K, Suganuma A, Takahashi K, Sato J et al. Impact of telephone support programme using telemonitoring on stage of change towards healthy eating and active exercise in people with prediabetes. J Telemed Telecare. 2021;27(5):307–13. doi: 10.1177/1357633X211010981.	No new data from this paper (study included)
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Reference	Reason for exclusion
Sampson M, Clark A, Bachmann M, Garner N, Irvine L, Howe A et al. Effects of the Norfolk diabetes prevention lifestyle intervention (NDPS) on glycaemic control in screen-detected type 2 diabetes: a randomised controlled trial. BMC Med. 2021;19(1):183. doi: 10.1186/s12916-021-02053-x.	No eligible outcome
Sanaeinasab H, Saffari M, Yazdanparast D, Karimi Zarchi A, Al-Zaben F, Koenig HG et al. Effects of a health education program to promote healthy lifestyle and glycemic control in patients with type 2 diabetes: a randomized controlled trial. Prim Care Diabetes. 2021;15(2):275–82. doi: 10.1016/j.pcd.2020.09.007.	Ineligible follow-up duration
Sanatkar S, Baldwin P, Clarke J, Fletcher S, Gunn J, Wilhelm K et al. The influence of personality on trajectories of distress, health and functioning in mild-to-moderately depressed adults with type 2 diabetes. Psychol Health Med. 2020;25(3):296–308. doi: 10.1080/13548506.2019.1668567.	Ineligible study design
Sánchez A, Pablo S, García-Álvarez A, Dominguez S, Grandes G, for the PREDIAPS Group. Effectiveness of two procedures for deploying a facilitated collaborative modeling implementation strategy-the PVS-PREDIAPS strategy-to optimize type 2 diabetes prevention in primary care: the PREDIAPS cluster randomized hybrid type II implementation trial. Implement Sci. 2021;16(1):58. doi: 10.1186/S13012-021-01127-x.	No eligible outcome
Sarid O, Berger R, Guez J. Reduced HbA1c levels in type 2 diabetes patients: an interaction between a pedagogical format for students and psychoeducational intervention for patients. Diabetes Metab Syndr. 2019;13(3):2280–4. doi: 10.1016/j.dsx.2019.05.021.	No eligible outcome
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Sasako T, Ueki K, Miyake K, Okazaki Y, Takeuchi Y, Ohashi Y et al. Effect of a multifactorial intervention on fracture in patients with type 2 diabetes: subanalysis of the J-DOIT3 study. J Clin Endocrinol Metab. 2021;106(5):e2116–28. doi: 10.1210/clinem/dgab013.	No eligible outcome
Sato S, Tajiri Y, Shimono D, Sumiyoshi S, Futata T. Changes in psychological behavior accompanied by the short-term usage of flash glucose monitoring for newly diagnosed type 2 diabetes mellitus. Ther Res. 2020;41(7):577–86.	No eligible outcome
Schafer GL, Songer TJ, Arena VC, Kramer MK, Miller RG, Kriska AM. Participant food and activity costs in a translational Diabetes Prevention Program. Transl Behav Med. 2021;11(2):351–8. doi: 10.1093/tbm/ibaao31.	No eligible outcome
Schlicker S, Weisel KK, Buntrock C, Berking M, Nobis S, Lehr D et al. Do nonsuicidal severely depressed individuals with diabetes profit from internet-based guided self-help? Secondary analyses of a pragmatic randomized trial. J Diabetes Res. 2019;2019:2634094. doi: 10.1155/2019/2634094.	No eligible outcome
Schmiedel K, Mayr A, Fießler C, Schlager H, Friedland K. [Quality of life and satisfaction during the diabetes prevention program GLICEMIA: a cluster-randomized, controlled trial.] Gesundheitswesen. 2020;82(11):844–51. doi: 10.1055/a-0883-4888 (in German).	Ineligible population
Schulte EM, Tuerk PW, Wadden TA, Garvey WT, Weiss D, Hermayer KL et al. Changes in weight control behaviors and hedonic hunger in a commercial weight management program adapted for individuals with type 2 diabetes. Int J Obes (Lond). 2020;44(5):990–8. doi: 10.1038/s41366-020-0530-x.	No eligible outcome

Reference	Reason for exclusion
Schwartz AV, Pan Q, Aroda VR, Crandall JP, Kriska A, Diabetes Prevention Program Research Group. Longterm effects of lifestyle and metformin interventions in DPP on bone density. Osteoporos Int. 2021;32(11):2279–87. doi: 10.1007/s00198-021-05989-1.	No new data from this paper (study included)
Schwingshackl L, Missbach B, Konig J, Hoffmann G. Adherence to a Mediterranean diet and risk of diabetes: a systematic review and meta-analysis. Public Health Nutr. 2015;18(7):1292–9. doi: 10.1017/S1368980014001542.	Systematic review
Selcuk-Tosun A, Zincir H. The effect of a transtheoretical model-based motivational interview on self-efficacy, metabolic control, and health behaviour in adults with type 2 diabetes mellitus: a randomized controlled trial. Int J Nurs Pract. 2019;25(4):e12742. doi: 10.1111/ijn.12742.	No eligible outcome
Selph S, Dana T, Blazina I, Bougatsos C, Patel H, Chou R. Screening for type 2 diabetes mellitus: a systematic review for the US Preventive Services Task Force. Ann Intern Med. 2015;162(11):765–76. doi: 10.7326/M14-2221.	Systematic review
Selvin E, Wang D, McEvoy JW, Juraschek SP, Lazo M, Hamet P et al. Response of 1,5-anhydroglucitol level to intensive glucose- and blood-pressure-lowering interventions, and its associations with clinical outcomes in the ADVANCE trial. Diabetes Obes Metab. 2019;21(8):2017–23. doi: 10.1111/dom.13755.	No eligible outcome
Semlitsch T, Engler J, Siebenhofer A, Jeitler K, Berghold A, Horvath K. (Ultra-)long-acting insulin analogues versus NPH insulin (human isophane insulin) for adults with type 2 diabetes mellitus. Cochrane Database Syst Rev. 2020;(11):CD005613. doi: 10.1002/14651858.CD005613.pub4.	Systematic review
Sesti G, Bardtrum L, Dagdelen S, Halladin N, Haluzík M, Őrsy P et al. A greater proportion of participants with type 2 diabetes achieve treatment targets with insulin degludec/liraglutide versus insulin glargine 100 units/mL at 26 weeks: DUAL VIII, a randomized trial designed to resemble clinical practice. Diabetes Obes Metab. 2020;22(5):873–8. doi: 10.1111/dom.13957.	Ineligible population

Reference	Reason for exclusion
Shaddinger BC, Soffer J, Vlasakakis G, Shabbout M, Weston C, Nino A. Efficacy and safety of an albiglutide liquid formulation compared with the lyophilized formulation: a 26-week randomized, double-blind, repeat-dose study in patients with type 2 diabetes mellitus. Diabetes Res Clin Pract. 2019;152:125–34. doi: 10.1016/j.diabres.2019.04.018.	Ineligible population
Shailaja K, Thomas AA, Mathaikutty JR, Abraham N, John RL. Impact of patient counselling among type 2 diabetes mellitus patients in a tertiary care hospital. Int J Pharma Bio Sci. 2020;11(2):33–9. doi: 10.22376/ijpbs.2020.11.2.p33-39.	No eligible outcome
Shaman AM, Bain SC, Bakris GL, Buse JB, Idorn T, Mahaffey KW et al. Effect of the glucagon-like peptide-1 receptor agonists semaglutide and liraglutide on kidney outcomes in patients with type 2 diabetes: pooled analysis of SUSTAIN 6 and LEADER. Circulation. 2022;145(8):575–85. doi: 10.1161/CIRCULATIONAHA.121.055459.	Ineligible population
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Shearer J, Kalyani M, Mangelis A, de Silva D, de Silva P, Wijesuriya M et al. Cost-effectiveness of peer-educator-delivered lifestyle modification for type 2 diabetes prevention in a young healthy population in Sri Lanka: a trial-based economic evaluation and economic model. Pharmacoecon Open. 2021;5(4):693–700. doi: 10.1007/s41669-021-00284-5.	Ineligible population
Shen B, Ji XY. Study on the efficacy and mechanism of Jiangzhi Ligan decoction in the treatment of T2DM with NAFLD based on NLRP3 inflammasome. Chin J Pharm Biotech. 2022;29(1):39–44. doi: 10.19526/j.cnki.1005-8915.20220107.	No eligible outcome

Reference	Reason for exclusion
Shen XX, Wang JP, Chen YY, An YL, Gong QH, Zhang B et al. [Subjects with impaired glucose tolerance returned to normal glucose status for six years had lower long-term risk of diabetes: 20 years follow up of Daqing Diabetes Prevention Study]. Zhonghua Nei Ke Za Zhi. 2019;58(5):372–6. doi:10.3760/cma.j.is sn.0578-1426.2019.05.008 (in Chinese).	Ineligible language
Shen Y, Yang X, Han X, Xi W, Jiang L, Wang S et al. Influence of GLP-1 receptor agonist on insulin dosage and blood glucose control of patients with type 2 diabetes mellitus. Am J Transl Res. 2021;13(10):11814–23. PMID: 34786110.	No eligible outcome
Sheng CS, Miao Y, Ding L, Cheng Y, Wang D, Yang Y et al. Prognostic significance of visit-to-visit variability, and maximum and minimum LDL cholesterol in diabetes mellitus. Lipids Health Dis. 2022;21(1):19. doi: 10.1186/s12944-022-01628-8.	Ineligible population
Shi C, Fang X, Yang Y, Bai R, Yu S, Sun G et al. Intensive multifactorial intervention improved renal impairment in short-duration type 2 diabetes: a randomized, controlled, 7-year follow-up trial. J Diabetes Complications. 2020;34(1):107468. doi: 10.1016/j.jdiacomp.2019.107468.	No eligible outcome
Shi LX, Liu XM, Shi YQ, Li QM, Ma JH, Li YB et al. Efficacy and safety of dulaglutide monotherapy compared with glimepiride in Chinese patients with type 2 diabetes: post-hoc analyses of a randomized, double-blind, phase III study. J Diabetes Investig. 2020;11(1):142–50. doi: 10.1111/jdi.13075.	Ineligible population
Shi S, Gouskova N, Najafzadeh M, Wei LJ, Kim DH. Intensive versus standard blood pressure control in type 2 diabetes: a restricted mean survival time analysis of a randomised controlled trial. BMJ Open. 2021;11(9):e050335. doi: 10.1136/bmjopen-2021-050335.	Ineligible population
Shin NR, Gu N, Choi HS, Kim H. Combined effects of <i>Scutellaria baicalensis</i> with metformin on glucose tolerance of patients with type 2 diabetes via gut microbiota modulation. Am J Physiol Endocrinol Metab. 2020;318(1):E52–61. doi: 10.1152/ajpendo.00221.2019.	No eligible outcome

Reference	Reason for exclusion
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Reason for exclusion
No eligible outcome
Ineligible population
Ineligible population
Ineligible follow-up duration
Ineligible follow-up duration
No eligible outcome

Reference	Reason for exclusion
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Reason for exclusion
Ineligible population
Ineligible population
No eligible outcome
No new data from this paper (study included)
Ineligible population
Ineligible population

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Wei L, Wang J, Li Z, Zhang Y, Gao Y. Design and implementation of an Omaha System-based integrated nursing management model for patients with newly-diagnosed diabetes. Prim Care Diabetes. 2019;13(2): 142–9. doi: 10.1016/j.pcd.2018.11.001.	Ineligible study design
Wei S, Brejnrod AD, Trivedi U, Mortensen MS, Johansen MY, Karstoft IK et al. Impact of intensive lifestyle intervention on gut microbiota composition in type 2 diabetes: a post-hoc analysis of a randomized clinical trial. Gut Microbes. 2022;14(1):2005407. doi: 10.1080/19490976.2021.2005407.	No eligible outcome
Wei X, Zhang Z, Chong MKC, Hicks JP, Gong W, Zou G et al. Evaluation of a package of risk-based pharmaceutical and lifestyle interventions in patients with hypertension and/or diabetes in rural China: a pragmatic cluster randomised controlled trial. PLOS Med. 2021;18(7):e1003694. doi: 10.1371/journal. pmed.1003694.	Ineligible population
Wei Y, Chen Y, Zhao Y, Rothman R, Ming J, Wang L et al. Health literacy and exercise interventions on clinical outcomes in Chinese patients with diabetes: a propensity score-matched comparison. BMJ Open Diabetes Res Care. 2020;8(1):e001179. doi: 10.1136/bmjdrc-2020-001179.	Ineligible study design
Wen Q, Hu M, Lai M, Li J, Hu Z, Quan K et al. Effect of acupuncture and metformin on insulin sensitivity in women with polycystic ovary syndrome and insulin resistance: a three-armed randomized controlled trial. Hum Reprod. 2022;37(3):542–52. doi: 10.1093/humrep/deab272.	No eligible outcome
implementation of an Omaha System-based integrated nursing management model for patients with newly-diagnosed diabetes. Prim Care Diabetes. 2019;13(2): 142–9. doi: 10.1016/j.pcd.2018.11.001.  Wei S, Brejnrod AD, Trivedi U, Mortensen MS, Johansen MY, Karstoft IK et al. Impact of intensive lifestyle intervention on gut microbiota composition in type 2 diabetes: a post-hoc analysis of a randomized clinical trial. Gut Microbes. 2022;14(1):2005407. doi: 10.1080/19490976.2021.2005407.  Wei X, Zhang Z, Chong MKC, Hicks JP, Gong W, Zou G et al. Evaluation of a package of risk-based pharmaceutical and lifestyle interventions in patients with hypertension and/or diabetes in rural China: a pragmatic cluster randomised controlled trial. PLOS Med. 2021;18(7):e1003694. doi: 10.1371/journal. pmed.1003694.  Wei Y, Chen Y, Zhao Y, Rothman R, Ming J, Wang L et al. Health literacy and exercise interventions on clinical outcomes in Chinese patients with diabetes: a propensity score-matched comparison. BMJ Open Diabetes Res Care. 2020;8(1):e001179. doi: 10.1136/bmjdrc-2020-001179.  Wen Q, Hu M, Lai M, Li J, Hu Z, Quan K et al. Effect of acupuncture and metformin on insulin sensitivity in women with polycystic ovary syndrome and insulin resistance: a three-armed randomized controlled trial. Hum Reprod. 2022;37(3):542–52. doi: 10.1093/humrep/	No eligible outcome  Ineligible population  Ineligible study design

Reference	Reason for exclusion
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E, Helbig C, Loscher S et al. Patient-centered communication and shared decision making to reduce HbArc levels of patients with poorly controlled type 2 diabetes mellitus: results of the cluster-randomized controlled DEBATE trial. BMC Fam Pract. 2019;20(1):87. doi: 10.1186/s12875-019-0977-9.  Woodard L, Amspoker AB, Hundt NE, Gordon HS, Hertz B, Odom E et al. Comparison of collaborative goal setting with enhanced education for managing diabetes-associated distress and hemoglobin A1c levels: a randomized clinical trial. JAMA Netw Open. 2022;5(5):e229975. doi: 10.1001/jamanetworkopen.2022.9975.  Woods-Giscombe CL, Gaylord SA, Li Y, Brintz CE, Bangdiwala SI, Buse JB et al. A mixed-methods, randomized clinical trial to examine feasibility of a mindfulness-based stress management and diabetes risk reduction intervention for African Americans with prediabetes. Evid Based Complement Alternat Med. 2019;2019:3962623. doi: 10.1155/2019/3962623.  Wysham CH, Rosenstock J, Vetter ML, Wang H, Hardy E, Iqbal N. Further improvement in glycemic control after switching from exenatide two times per day to exenatide once-weekly autoinjected suspension in patients with type 2 diabetes: 52-week results from the DURATION-NEO-1 study. BMJ Open Diabetes Res	Yeap BB, Handelsman DJ et al. Testosterone treatment to prevent or revert type 2 diabetes in men enrolled in a lifestyle programme (T4DM): a randomised, doubleblind, placebo-controlled, 2-year, phase 3b trial. Lancet Diabetes Endocrinol. 2021;9(1):32–45. doi: 10.1016/	Ineligible population
Hertz B, Odom E et al. Comparison of collaborative goal setting with enhanced education for managing diabetes-associated distress and hemoglobin A1c levels: a randomized clinical trial. JAMA Netw Open. 2022;5(5):e229975. doi: 10.1001/jamanetworkopen.2022.9975.  Woods-Giscombe CL, Gaylord SA, Li Y, Brintz CE, Bangdiwala SI, Buse JB et al. A mixed-methods, randomized clinical trial to examine feasibility of a mindfulness-based stress management and diabetes risk reduction intervention for African Americans with prediabetes. Evid Based Complement Alternat Med. 2019;2019;3962623. doi: 10.1155/2019/3962623.  Wysham CH, Rosenstock J, Vetter ML, Wang H, Hardy E, Iqbal N. Further improvement in glycemic control after switching from exenatide two times per day to exenatide once-weekly autoinjected suspension in patients with type 2 diabetes:52-week results from the DURATION-NEO-1 study. BMJ Open Diabetes Res	E, Helbig C, Loscher S et al. Patient-centered communication and shared decision making to reduce HbA1c levels of patients with poorly controlled type 2 diabetes mellitus: results of the cluster-randomized controlled DEBATE trial. BMC Fam Pract. 2019;20(1):87.	No eligible outcome
Bangdiwala SI, Buse JB et al. A mixed-methods, randomized clinical trial to examine feasibility of a mindfulness-based stress management and diabetes risk reduction intervention for African Americans with prediabetes. Evid Based Complement Alternat Med. 2019;2019:3962623. doi: 10.1155/2019/3962623.  Wysham CH, Rosenstock J, Vetter ML, Wang H, Hardy E, Iqbal N. Further improvement in glycemic control after switching from exenatide two times per day to exenatide once-weekly autoinjected suspension in patients with type 2 diabetes:52-week results from the DURATION-NEO-1 study. BMJ Open Diabetes Res	Hertz B, Odom E et al. Comparison of collaborative goal setting with enhanced education for managing diabetes-associated distress and hemoglobin A1c levels: a randomized clinical trial. JAMA Netw Open. 2022;5(5):e229975. doi: 10.1001/	Ineligible population
Hardy E, Iqbal N. Further improvement in glycemic control after switching from exenatide two times per day to exenatide once-weekly autoinjected suspension in patients with type 2 diabetes:52-week results from the DURATION-NEO-1 study. BMJ Open Diabetes Res	Bangdiwala SI, Buse JB et al. A mixed-methods, randomized clinical trial to examine feasibility of a mindfulness-based stress management and diabetes risk reduction intervention for African Americans with prediabetes. Evid Based Complement Alternat Med.	No eligible outcome
	Hardy E, Iqbal N. Further improvement in glycemic control after switching from exenatide two times per day to exenatide once-weekly autoinjected suspension in patients with type 2 diabetes:52-week results from the DURATION-NEO-1 study. BMJ Open Diabetes Res	Ineligible population

Reference	Reason for exclusion
Xiao X, Wang C, Lai X, Zhang B, Gu L, Hou J et al. Achieving the composite end-point of glycated hemoglobin < 7.0% without weight gain or hypoglycemia with once-weekly dulaglutide in Chinese patients with type 2 diabetes: a post-hoc analysis. J Diabetes Investig. 2020;11(3):647–52. doi: 10.1111/jdi.13187.	Ineligible population
Xu C, Dong Z, Zhang P, Chang G, Xiang Q, Zhang M et al. Effect of group cognitive behavioural therapy on psychological stress and blood glucose in people with type 2 diabetes mellitus: a community-based cluster randomized controlled trial in China. Diabet Med. 2021;38(2):e14491. doi: 10.1111/dme.14491.	No eligible outcome
Xu Z, Geng J, Zhang S, Zhang K, Yang L, Li J et al. A mobile-based intervention for dietary behavior and physical activity change in individuals at high risk for type 2 diabetes mellitus: randomized controlled trial. JMIR Mhealth Uhealth. 2020;8(11):e19869. doi: 10.2196/19869.	Ineligible population
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Reference	Reason for exclusion
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Yancy WS Jr, Crowley MJ, Dar MS, Coffman CJ, Jeffreys AS, Maciejewski ML et al. Comparison of group medical visits combined with intensive weight management vs group medical visits alone for glycemia in patients with type 2 diabetes: a noninferiority randomized clinical trial. JAMA Intern Med. 2020;180(1):70–9. doi: 10.1001/jamainternmed.2019.4802.	No eligible outcome
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Reference	Reason for exclusion
Yang W, Xu X, Lei T, Ma J, Li L, Shen J et al. Efficacy and safety of linagliptin as add-on therapy to insulin in Chinese patients with type 2 diabetes mellitus: a randomized, double-blind, placebo-controlled trial. Diabetes Obes Metab. 2021;23(2):642–7. doi: 10.1111/dom.14231.	Ineligible follow-up duration
Yao WY, Han MG, De Vito G, Fang H, Xia Q, Chen Y et al. Physical activity and glycemic control status in Chinese patients with type 2 diabetes: a secondary analysis of a randomized controlled trial. Int J Environ Res Public Health. 2021;18(8):4292. doi: 10.3390/ijerph18084292.	No eligible outcome
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Reference	Reason for exclusion
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Yu HM, Park KS, Hong JH, Park KY, Lee JM, Ku BJ et al. Comparison of the efficacy and safety of insulin detemir administered once daily according to two titration algorithms (3–0–3 and 2–4–6–8) in patients with type 2 diabetes mellitus. Endocrinol Metab (Seoul). 2020;35(1):142–48. doi: 10.3803/EnM.2020.35.1.142.	Ineligible follow-up duration
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Zarnigar SK, Khan S. The effect of <i>Bergenia ligulata</i> WALL in prediabetes: a randomized single-blind placebo-controlled study. Int J Pharm Res. 2022;14(1): 161–4. doi: 10.31838/ijpr/2022.14.01.024.	Ineligible follow-up duration
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Zhang Y, Xie H, Tian Y, Zhou L, Yan R, Xie C. Efficacy of Shenqi compound particle on blood glucose and oxidative stress compared with metformin for patients with newly diagnosed type 2 diabetes mellitus: randomized clinical trial. Int J Clin Exp Med. 2019;12(7):8271–80.	Ineligible follow-up duration
Zhao X, Yu X, Zhang X. The role of peer support education model in management of glucose and lipid levels in patients with type 2 diabetes mellitus in Chinese adults. J Diabetes Res. 2019;2019:5634030. doi: 10.1155/2019/5634030.	No eligible outcome
Zheng F, Liu S, Liu Y, Deng L. Effects of an outpatient diabetes self-management education on patients with type 2 diabetes in China: a randomized controlled trial. J Diabetes Res. 2019;2019:1073131. doi: 10.1155/2019/1073131.	Ineligible follow-up duration
Zhou L, Cai X, Luo Y, Zhang F, Ji L. Baseline triglyceride level affected the efficacy of vildagliptin in treating type 2 diabetes: a post hoc analysis of the VISION study. J Diabetes Res. 2019;2019:9347132. doi: 10.1155/2019/9347132.	Ineligible population
Zhu R, Fogelholm M, Poppitt SD, Silvestre MP, Moller G, Huttunen-Lenz M et al. Adherence to a plant-based diet and consumption of specific plant foods-associations with 3-year weight-loss maintenance and cardiometabolic risk factors: a secondary analysis of the PREVIEW intervention study. Nutrients. 2021;13(11):3916. doi: 10.3390/nu13113916.	No eligible outcome

Reference	Reason for exclusion
Zhu R, Larsen TM, Fogelholm M, Poppitt SD, Vestentoft PS, Silvestre MP et al. Dose-dependent associations of dietary glycemic index, glycemic load, and fiber with 3-year weight loss maintenance and glycemic status in a high-risk population: a secondary analysis of the Diabetes Prevention Study PREVIEW. Diabetes Care. 2021;44(7):1672–81. doi: 10.2337/dc20-3092.	Ineligible study design
Zhyzhneuskaya SV, Al-Mrabeh A, Peters C, Barnes A, Aribisala B, Hollingsworth KG et al. Time course of normalization of functional $\beta$ -cell capacity in the Diabetes Remission Clinical Trial after weight loss in type 2 diabetes. Diabetes Care. 2020;43(4):813–20. doi: 10.2337/dc19-0371.	Ineligible population
Zobel EH, Ripa RS, von Scholten BJ, Rotbain Curovic V, Kjaer A, Hansen TW et al. Effect of liraglutide on expression of inflammatory genes in type 2 diabetes. Sci Rep. 2021;11(1):18522. doi: 10.1038/s41598-021-97967-0.	No eligible outcome
Zurbau A, Smircic Duvnjak L, Magas S, Jovanovski E, Miocic J, Jenkins AL et al. Co-administration of viscous fiber, Salba-chia and ginseng on glycemic management in type 2 diabetes: a double-blind randomized controlled trial. Eur J Nutr. 2021;60(6):3071–83. doi: 10.1007/s00394-020-02434-7.	Ineligible follow-up duration

Table A2.2. Articles in the Russian language search that were excluded after full-text review

ull-text review	
Reference	Reason for exclusion
Боева, Валентина Владимировна, and А. Н. Завьялов. Медикаментозная профилактика сахарного диабета 2-го типа у пациентов с ранними нарушениями углеводного обмена: эффективность и клинические исходы при длительном наблюдении. [Boeva VV, Zavyalov AN. Preventive pharmacotherapy of type 2 diabetes mellitus in patients with early carbohydrate metabolism disorders: long-term efficacy and clinical outcomes]. Вестник Российского государственного медицинского университета 2 (2020): 74–80. doi: 10.24075/brsmu.2020.014.	Ineligible study design
Демидова ИЮ, Боева ВВ, Завьялов АН. Отдаленные результаты медикаментозной коррекции предиабета. [Demidova IYu, Boeva VV, Zavyalov AN. Long-term results of pharmacological correction of prediabetes]. Endocrinol News Opin Train. 2020;1(30):27–34.	Ineligible study design
Демидова ИЮ, Боева ВВ. Ранняя диагностика и лечение начальных стадий нарушений углеводного обмена [Demidova IYu, Boyeva VV. Early diagnosis and treatment of initial stages of carbohydrate metabolism disorders]. Bull RSMU. 2013;1:9–13.	Ineligible study design
Dreval' AV, Misnikova IV, Barsukov IA, Dzebisashvili GG. [Risk of type 2 diabetes mellitus and acute cardiovascular disorders in patients with early disturbances of carbohydrate metabolism.] Klin Med (Mosk). 2012;90(11):30–4. PMID: 23516850.	Ineligible study design
Кушунина ДВ, Калинина АМ, Горный БЕ, Дубовой ИИ, Антонов КА Драпкина ОМ. Динамика частоты гиперхолестеринемии и гипергликемии у пациентов разного возраста, регулярно проходящих диспансеризацию [Kushunina DV, Kalinina AM, Gorny BE, Dubovoy II, Antonov KA, Drapkina OM. Dynamics of the frequency of hypercholesterolemia and hyperglycemia in patients of different ages regularly undergoing medical examination]. Profil Med. 2021; 24(3):51–7. doi: 10.17116/profmed20212406151 (in Russian).	Ineligible study design

Reference	Reason for exclusion
Романенко ИА, Маврычева НВ, Полятыкина ТС, Романенко АВ, Гринштейн ВБ. К вопросу профилактики сахарного диабета 2-го типа у лиц с нарушенной толерантностью к глюкозе. [Romanenko IA, Mavrycheva NV, Polyatykina TS, Romanenko AV, Grinshtein VB. To the issue of prophylaxis of type 2 diabetes mellitus in individuals with impaired glucose tolerance]. Med Almanac. 2014;5(35):115–17.	Ineligible study design
Romanenko LA, Polyatykina TS, Mavrycheva NV, Budnikova NV, Grinshtein VB. [Dynamics of metabolic characteristics, markers of oxidative stress and vascular wall damage during treatment of obese prediabetic patients.] Klin Med (Mosk). 2016;94(3):221–4. PMID: 27522729.	Ineligible study design
Шишкова ВН, Мамедов МН, Анциферов МБ, Оганов РГ. Эффективность и безопасность антигипергликемической терапии у пациентов с метаболическим синдромом и предиабетом [Shishkova V, Mamedov Antsiferov MM, Oganov R. Efficacy and safety of antiglycemic therapy in patients with metabolic syndrome and prediabetes]. Doctor. 2008;3:2–5.	Ineligible follow up

# **ANNEX 3. INCLUDED STUDIES**

Table A<sub>3.1</sub> outlines the data extracted from the included studies. Table A<sub>3.2</sub> gives the detailed health outcomes with pharmacological interventions and Table A<sub>3.3</sub> gives the detailed health outcomes with lifestyle interventions.

Table A<sub>3.1</sub>. Characteristics of included studies

Study: reference by first author and publication year	Data category	Description
ACT NOW Study: DeFronzo, 2011 (25)	Study design	RCT
	Setting	8 clinical centres, United States
	Age of participants (mean years (SD))	52.3 (0.5)
	IHG diagnosis	IGT (plasma glucose 7.8–11.0 mmol/L at 2 h during single OGTT)
	Intervention	G1: pioglitazone 30 mg/day for 1 month, increased to 45 mg/day
	Comparator	G2: placebo
	Total study duration	Median: 2.4 years; mean: 2.2 years
	Participants in each arm	G1: 303 G2: 299
	Relevant outcomes	T2DM (plasma glucose ≥ 11.1 mmol/L 2 h after oral glucose load), non-fatal myocardial infarction
	Study quality	Fair <sup>a</sup>
Ackermann, 2015	Study design	RCT
(26)	Setting	Primary care clinics, United States
	IHG diagnosis	FPG 5.6–7.0 mmol/L, IGT 7.8–11.0 mmol/L 2 h after ingestion of oral glucose load, or HbA1c 5.7–6.9%
	Intervention	G1: group-based YMCA (youth organization) adaptation of the DPP, lifestyle intervention

Study: reference by first author and publication year	Data category	Description
	Comparator	G2: usual care plus brief counselling and information on community resources
	Total study duration	ı year
	Participants in each arm	G1: 257 G2: 252
	Relevant outcomes	T2DM (method and criteria not reported)
	Study quality	Good <sup>a</sup>
Aekplakorn, 2019	Study design	RCT
(27)	Setting	68 primary care units in 8 provinces, Thailand
	IHG diagnosis	IGT (plasma glucose ≥ 7.8 mmol/L and < 11.1 mmol/L 2 h after ingestion of 75-g oral glucose load)
	Intervention	G1: lifestyle intervention
	Comparator	G2: usual care with one-time educational programme
	Total study duration	24 months
	Participants in each arm	G1: 1030 G2: 873
	Relevant outcomes	T2DM (FPG ≥ 7.0 mmol/L, or a plasma glucose ≥ 11.1 mmol/L 2-h after 75-g oral glucose load)
	Study quality	Good <sup>a</sup>
Amer, 2020 (28)	Study design	Parallel RCT
	Setting	Hospital patients, Saudi Arabia
	IHG diagnosis	Impaired fasting glucose (2017 ADA criteria (108)): 5.6–6.9 mmol/L

Study: reference by first author and publication year	Data category	Description
	Intervention	G1: intensive lifestyle intervention, including strict lifestyle modification with tailored counselling for improving diet and exercise behaviours
	Comparator	G2: general advice for lifestyle modifications
	Total study duration	18 months
	Participants in each arm	G1: 73 G2: 85
	Relevant outcomes	T2DM (method and criteria not reported)
	Study quality	High risk of bias <sup>b</sup>
Bhopal, 2014 (29)	Study design	Non-blinded family cluster RCT
	Setting	National Health Service Lothian and Greater Glasgow and Clyde Health Board, Scotland (United Kingdom)
	IHG diagnosis	IGT or impaired fasting glucose according to WHO 1999 criteria (16)
	Intervention	G1: 15 visits from a dietitian over 3 years
	Comparator	G2: control with 4 visits over 3 years
	Total study duration	3 years
	Participants in each arm	G1: 85 G2: 86
	Relevant outcomes	T2DM (method and criteria not reported)
	Study quality	Fair <sup>a</sup>
CANOE Trial: Zinman, 2010 (30)	Study design	RCT
	Setting	Clinics in Ontario, Canada

Study: reference by first author and publication year	Data category	Description
	Age of participants (median (IQR))	G1: 50.0 (44.0–61.0) G2: 55.0 (46.0–61.0)
	IHG diagnosis	IGT (FPG $\geq$ 7.0 mmol/L and plasma glucose 7.8–11.0 mmol/L 2 h after 75-g oral glucose load)
	Intervention	G1: rosiglitazone 2 mg and metformin 500 mg twice daily and lifestyle intervention
	Comparator	G2: placebo and lifestyle intervention
	Total study duration	median 3.9 years (IQR: 3.0-4.6)
	Participants in each arm	G1: 103 G2: 104
	Relevant outcomes	T2DM (FPG ≥ 7.0 mmol/L or plasma glucose > 11.0 mmol/L at 2 h during
		OGTT)
	Study quality	Good <sup>a</sup>
Dai, 2019 (31); Yan, 2019 (92)	Study quality Study design	,
		Good <sup>a</sup>
	Study design	Good <sup>a</sup> Parallel RCT
	Study design  Setting  Age of participants	Good <sup>a</sup> Parallel RCT  Health service centres, China
	Study design  Setting  Age of participants (mean years)	Good <sup>a</sup> Parallel RCT  Health service centres, China 59.0  "Prediabetes" (2018 ADA criteria (6)): FPG 5.6–7.0 mmol/L and/or plasma glucose 7.8–11.1 mmol/L at 2 h after oral glucose load and/or HbA1c
	Study design  Setting  Age of participants (mean years)  IHG diagnosis	Gooda  Parallel RCT  Health service centres, China 59.0  "Prediabetes" (2018 ADA criteria (6)): FPG 5.6–7.0 mmol/L and/or plasma glucose 7.8–11.1 mmol/L at 2 h after oral glucose load and/or HbA1c 5.7–6.4%  G1: aerobic training G2: resistance training
	Study design  Setting  Age of participants (mean years)  IHG diagnosis  Intervention	Gooda  Parallel RCT  Health service centres, China 59.0  "Prediabetes" (2018 ADA criteria (6)): FPG 5.6–7.0 mmol/L and/or plasma glucose 7.8–11.1 mmol/L at 2 h after oral glucose load and/or HbA1c 5.7–6.4%  G1: aerobic training G2: resistance training G3: aerobic and resistance training

Study: reference by first author and publication year	Data category	Description
	Participants in each arm	G1: 34 G2: 31 G3: 37 G4: 35
	Relevant outcomes	T2DM (2018 ADA criteria (6)): FPG $\geq$ 7.0 mmol/L and/or FPG $\geq$ 11.1 mmol/L at 2 h during OGTT and/or HbA1c $\geq$ 6.5% (48 mmol/mol)
	Study quality	High risk of bias <sup>b</sup>
DAISI Trial: Nijpels, 2008 (32)	Study design	RCT
	Setting	Invited subjects invited from population register in Hoorn, Netherlands (Kingdom of the)
	Age of participants (mean years (SD))	G1: 58.5 (7.9) G2: 56.5 (7.0)
	IHG diagnosis	FPG 7.8 mmol/L, plasma glucose 8.6–11.1 mmol/L 2 h after oral glucose load, HbA1c ≤ 7.0%
	Intervention	G1: acarbose 50 mg 3 times a day
	Comparator	G2: placebo
	Total study duration	3 years
	Participants in each arm	G1: 60 G2: 58
	Relevant outcomes	T2DM: FPG (≥ 7.8 mmol/L and/or plasma glucose ≥ 11.1 mmol/L 2 h after oral glucose load) and IGT (FPG < 7.8 mmol/L and/or plasma glucose ≥ 7.8 to < 11.1 mmol/L 2 h after oral glucose load)
	Study quality	Faira

3		
Study: reference by first author and publication year	Data category	Description
Da Qing Study Group: Pan 1997 (33); Li 2008, 2014 (34,35); Gong, 2019, 2021 (36,37)	Study design	RCT
	Setting	33 primary care clinics in Da Qing, China
	Age of participants (median years (SE))	Baseline FPG < 5.6 mmol/L G1: 44.6 (0.7) G2: 47.2 (1.1) Baseline FPG ≥ 5.6 mmol/L G3: 44.8 (0.6) G4: 46.0 (1.1)
	IHG diagnosis	IGT 7.8–11.1 mmol/L at 2 h during 75 g OGTT
	Intervention	G1: one of 3 lifestyle interventions for 6 years: diet, exercise or diet plus exercise
	Comparator	G2: standard medical care
	Total study duration	6-year study and 30-year follow-up
	Participants in each arm	576 overall Baseline FPG $<$ 5.6 mmol/L G1: 214 G2 73 Baseline FPG $\ge$ 5.6 mmol/L G3: 224 G4: 65
	Relevant outcomes	T2DM (IGT ≥ 11.1 mmol/L at 2 h during a 75-g OGTT), all-cause mortality, cardiovascular mortality, retinopathy, nephropathy, neuropathy
	Study quality	Fair <sup>a</sup>

Study: reference by first author and publication year	Data category	Description
Diabetes	Study design	RCT
Community Lifestyle Improvement	Setting	Community-based recruitment in Chennai, India
Program: Weber, 2016 (39); Ford, 2019 (38)	Age of participants (mean years (SD))	G1: 44.8 (9.0) G2: 44.0 (9.5)
(30)	IHG diagnosis	IFG (FPG 5.6–6.9 mmol/L), and/or IGT (plasma glucose 7.8–11.0 mmol/L 2 h after oral glucose load)
	Intervention	G1: stepwise intervention of adapted DPP lifestyle classes plus metformin 500 mg twice daily at 4 months if at high risk of developing diabetes
	Comparator	G2: standard of care
	Total study duration	3 years (mean: 2.54; range: 4–48 months)
	Participants in each arm	G1: 283 G2: 295
	Relevant outcomes	T2DM (FPG $\geq$ 7.0 mmol/L or plasma glucose $\geq$ 11.1 mmol/L 2 h after oral glucose load)
	Study quality	Fair <sup>a</sup>
Díaz-Rizzolo, 2021 (40)	Study design	Parallel RCT
	Setting	Primary care, Spain
	Age of participants (mean years)	71.2
	IHG diagnosis	IFG 5.6–7.0 mmol/L
	Intervention	G1: nutritional advice + sardines (source of taurine)
	Comparator	G2: nutritional advice
	Total study duration	ı year

Study: reference by first author and publication year  Participants in each arm  Participants in each arm  Relevant outcomes  Study quality  DMagic RCT: Fottrell, 2019 (41)  Setting  Age of participants  HG diagnosis  WHO 2006 criteria (2): impaired fasting glucose (FPG > 6.1 mmol/L to < 7.0 mmol/L and plasma glucose < 7.8 mmol/L to < 11.1 mmol/L and plasma glucose > 7.8 mmol/L to < 11.1 mmol/L a hafter 75-g oral glucose load)  Intervention  G1: 75  G2: 77  Relevant outcomes  WHO 2006 criteria (2): impaired fasting glucose (FPG > 6.1 mmol/L to < 7.0 mmol/L and plasma glucose < 7.8 mmol/L to < 11.1 mmol/L and plasma glucose > 7.8 mmol/L to < 11.1 mmol/L a hafter 75-g oral glucose load)  Intervention  G1: m-health (behaviour change via mobile phone messages) G2: participatory and learning  Comparator  G3: treatment as usual 2 years  Participants in each arm G2: 665 G3: 712  Relevant outcomes  T2DM (WHO 2006 criteria (2)): FPG > 7.0 mmol/L or plasma glucose > 11.1 mmol/L a hafter 75-g oral glucose load  Study quality  High risk of bias <sup>b</sup>	3		
arm G2: 77  Relevant outcomes T2DM (method and criteria not reported)  Study quality High risk of bias <sup>b</sup> DMagic RCT: Fottrell, 2019 (41)  Setting General population, Bangladesh Age of participants Not reported  IHG diagnosis WHO 2006 criteria (2): impaired fasting glucose (FPG > 6.1 mmol/L to < 7.0 mmol/L and plasma glucose < 7.8 mmol/L 2 h after 75-g oral glucose load) or impaired FPG < 7.0 mmol/L and plasma glucose > 7.8 mmol/L to < 11.1 mmol/L 2 h after 75-g oral glucose load)  Intervention G1: m-health (behaviour change via mobile phone messages) G2: participatory and learning  Comparator G3: treatment as usual  Total study duration 2 years  Participants in each arm G2: 665 G3: 712  Relevant outcomes T2DM (WHO 2006 criteria (2)): FPG > 7.0 mmol/L or plasma glucose > 11.1 mmol/L 2 h after 75-g oral glucose load	by first author and	Data category	Description
reported)  Study quality High risk of bias <sup>b</sup> DMagic RCT: Fottrell, 2019 (41)  Setting General population, Bangladesh  Age of participants Not reported  IHG diagnosis WHO 2006 criteria (2): impaired fasting glucose (FPG > 6.1 mmol/L to < 7.0 mmol/L and plasma glucose < 7.8 mmol/L 2 h after 75-g oral glucose load) or impaired FPG < 7.0 mmol/L to < 11.1 mmol/L 2 h after 75-g oral glucose load)  Intervention G1: m-health (behaviour change via mobile phone messages) G2: participatory and learning  Comparator G3: treatment as usual  Total study duration 2 years  Participants in each arm G2: 665 G3: 712  Relevant outcomes T2DM (WHO 2006 criteria (2)): FPG > 7.0 mmol/L or plasma glucose > 11.1 mmol/L 2 h after 75-g oral glucose load			
DMagic RCT: Fottrell, 2019 (41)  Setting  Age of participants  IHG diagnosis  WHO 2006 criteria (2): impaired fasting glucose (FPG > 6.1 mmol/L to < 7.0 mmol/L and plasma glucose < 7.8 mmol/L 2 h after 75-g oral glucose load) or impaired FPG < 7.0 mmol/L to < 11.1 mmol/L 2 h after 75-g oral glucose load)  Intervention  G1: m-health (behaviour change via mobile phone messages) G2: participatory and learning  Comparator  Total study duration  Participants in each arm  Participants in each arm  Relevant outcomes  T2DM (WHO 2006 criteria (2)): FPG > 7.0 mmol/L or plasma glucose > 11.1 mmol/L 2 h after 75-g oral glucose load		Relevant outcomes	
Fottrell, 2019 (41)  Setting  Age of participants  IHG diagnosis  WHO 2006 criteria (2): impaired fasting glucose (FPG > 6.1 mmol/L to < 7.0 mmol/L and plasma glucose < 7.8 mmol/L 2 h after 75-g oral glucose load) or impaired FPG < 7.0 mmol/L and plasma glucose > 7.8 mmol/L to < 11.1 mmol/L 2 h after 75-g oral glucose load)  Intervention  G1: m-health (behaviour change via mobile phone messages) G2: participatory and learning  Comparator  G3: treatment as usual  Total study duration Participants in each arm G1: 717 G2: 665 G3: 712  Relevant outcomes  T2DM (WHO 2006 criteria (2)): FPG > 7.0 mmol/L or plasma glucose > 11.1 mmol/L 2 h after 75-g oral glucose load		Study quality	High risk of bias <sup>b</sup>
Age of participants  IHG diagnosis  WHO 2006 criteria (2): impaired fasting glucose (FPG > 6.1 mmol/L to < 7.0 mmol/L and plasma glucose < 7.8 mmol/L 2 h after 75-g oral glucose load) or impaired FPG < 7.0 mmol/L to < 11.1 mmol/L 2 h after 75-g oral glucose load)  Intervention  G1: m-health (behaviour change via mobile phone messages) G2: participatory and learning  Comparator  G3: treatment as usual  Total study duration  Participants in each arm  G1: 717 G2: 665 G3: 712  Relevant outcomes  T2DM (WHO 2006 criteria (2)): FPG > 7.0 mmol/L or plasma glucose > 11.1 mmol/L 2 h after 75-g oral glucose load		Study design	Cluster RCT
IHG diagnosis  WHO 2006 criteria (2): impaired fasting glucose (FPG > 6.1 mmol/L to < 7.0 mmol/L and plasma glucose < 7.8 mmol/L 2 h after 75-g oral glucose load) or impaired FPG < 7.0 mmol/L to < 11.1 mmol/L 2 h after 75-g oral glucose load)  Intervention  G1: m-health (behaviour change via mobile phone messages) G2: participatory and learning  Comparator  G3: treatment as usual  Total study duration  Participants in each arm  G1: 717 G2: 665 G3: 712  Relevant outcomes  T2DM (WHO 2006 criteria (2)): FPG > 7.0 mmol/L or plasma glucose > 11.1 mmol/L 2 h after 75-g oral glucose load	Fottrell, 2019 <b>(41)</b>	Setting	General population, Bangladesh
fasting glucose (FPG > 6.1 mmol/L to < 7.0 mmol/L and plasma glucose < 7.8 mmol/L 2 h after 75-g oral glucose load) or impaired FPG < 7.0 mmol/L to < 11.1 mmol/L 2 h after 75-g oral glucose > 7.8 mmol/L to < 11.1 mmol/L 2 h after 75-g oral glucose load)  Intervention  G1: m-health (behaviour change via mobile phone messages) G2: participatory and learning  Comparator  G3: treatment as usual  Total study duration 2 years  Participants in each arm G2: 665 G3: 712  Relevant outcomes  T2DM (WHO 2006 criteria (2)): FPG > 7.0 mmol/L or plasma glucose > 11.1 mmol/L 2 h after 75-g oral glucose load		Age of participants	Not reported
mobile phone messages) G2: participatory and learning  Comparator G3: treatment as usual  Total study duration 2 years  Participants in each arm G2: 665 G3: 712  Relevant outcomes T2DM (WHO 2006 criteria (2)): FPG > 7.0 mmol/L or plasma glucose > 11.1 mmol/L 2 h after 75-g oral glucose load		IHG diagnosis	fasting glucose (FPG > 6.1 mmol/L to < 7.0 mmol/L and plasma glucose < 7.8 mmol/L 2 h after 75-g oral glucose load) or impaired FPG < 7.0mmol/L and plasma glucose > 7.8 mmol/L to < 11.1 mmol/L 2 h
Total study duration 2 years  Participants in each arm G1: 717 G2: 665 G3: 712  Relevant outcomes T2DM (WHO 2006 criteria (2)): FPG > 7.0 mmol/L or plasma glucose > 11.1 mmol/L 2 h after 75-g oral glucose load		Intervention	mobile phone messages)
Participants in each arm G1: 717 G2: 665 G3: 712  Relevant outcomes T2DM (WHO 2006 criteria (2)): FPG > 7.0 mmol/L or plasma glucose > 11.1 mmol/L 2 h after 75-g oral glucose load		Comparator	G3: treatment as usual
arm  G2: 665 G3: 712  Relevant outcomes  T2DM (WHO 2006 criteria (2)): FPG > 7.0 mmol/L or plasma glucose > 11.1 mmol/L 2 h after 75-g oral glucose load		Total study duration	2 years
> 7.0 mmol/L <i>or</i> plasma glucose > 11.1 mmol/L 2 h after 75-g oral glucose load		'	G2: 665
Study quality High risk of bias <sup>b</sup>		Relevant outcomes	> 7.0 mmol/L <i>or</i> plasma glucose > 11.1 mmol/L 2 h after 75-g oral
		Study quality	High risk of bias <sup>b</sup>

Study: reference by first author and publication year	Data category	Description
DPP 2002–2019:	Study design	RCT
Knowler, 2002, 2009 (42,43); Ratner, 2005	Setting	Clinical centres, United States
(44); DPP Research Group, 2009, 2012, 2015, 2019, 2021	Age of participants (median years (SD))	G1: 50.6 (11.3) G2: 50.9 (10.3) G3: 50.3 (10.4)
(45–48)	IHG diagnosis	FPG 5.2–7.0 mmol/L (≤ 7.0 mmol/L for American Indians), and plasma glucose 7.8–10. mmol/L 2 h after a 75-g oral glucose load
	Intervention	G1: intensive lifestyle intervention G2: standard lifestyle recommendations plus metformin 850 mg twice daily
	Comparator	G3: standard lifestyle recommendation plus placebo twice daily
	Total study duration	2.8 years (DPP), 15 years (DPPOS)
	Participants in each arm	G1: 1079 (910 enrolled in DPPOS) G2: 1073 (924 enrolled in DPPOS) G3: 1082 (932 enrolled in DPPOS)
	Relevant outcomes	T2DM (ADA 1997 criteria (109): FPG ≥ 7.0 mmol/L and ≥ 11.1 mmol/L 2 h after a 75-g oral glucose load), all-cause mortality
	Study quality	Good (DPP), <sup>b</sup> fair (DPPOS) <sup>b</sup>
DREAM Trial Investigators: Bosch, 2006 (49); Gerstein, 2006 (50); Dagenais, 2008 (51)	Study design	RCT
	Setting	Multiple countries

Study: reference by first author and publication year	Data category	Description
	IHG diagnosis	Impaired FPG $\geq$ 6.1 to <7.0 mmol/L and plasma glucose < 11.1 mmol/L at 2 h oral glucose load, or IGT (FPG < 7.0 mmol/L and plasma glucose $\geq$ 7.8 to < 11.1 mmol/L at 2 h after oral glucose load) or isolated impaired FPG ( $\geq$ 6.1 to < 7.0 mmol/L and plasma glucose < 7.8 mmol/L 2 h after 75-g oral glucose load)
	Intervention	G1: ramipril 15 mg/day G2: rosiglitazone o.8 mg/day
	Comparator	G3: placebo (for ramipril) G4: placebo (for rosiglitazone)
	Total study duration	Median: 3 years
	Participants in each arm	G1: 2623 G2: 2635 G3: 2646 G4: 2634
	Relevant outcomes	T2DM (FPG at least 7.0 mmol/L or plasma glucose ≥ 11.1 mmol/L 2 h after oral glucose load), all-cause mortality, cardiovascular mortality
	Study quality	Good <sup>a</sup>
Dreval, 2008 (52)	Study design	RCT
	Setting	Community, Russian Federation
	Age of participants (mean years)	56.4
	IHG diagnosis	IFG (FPG 6.1–6.9 mmol/L) or IGT (7.8–11.1 mmol/ at 2 h during OGTT)
	Intervention	G1: metformin 1700 mg daily with standard lifestyle modification recommendation G2: acarbose 150 mg daily

Study: reference by first author and publication year	Data category	Description
	Comparator	G3: standard lifestyle modification recommendation
	Total study duration	6 months
	Participants in each arm	G1: 15 G2: 10 G3: 10
	Relevant outcomes	T2DM (FPG ≥ 7.0 mmol/L, at 2 h during 75 g OGTT)
	Study quality	Some concern <sup>b</sup>
European Diabetes	Study design	RCT
Prevention RCT: Penn, 2009 (53)	Setting	Hospital clinical research facility Newcastle upon Tyne, United Kingdom
	Age of participants (median years (IQR))	G1: 56.8 (40–72) G2: 57.4 (38–74)
	IHG diagnosis	IGT (plasma glucose 7.8–11.0 mmol/L 2 h after oral glucose load from 2 consecutive standard OGTTs (glucose load 75 g))
	Intervention	G1: individual behavioural intervention
	Comparator	G2: usual care and standard health promotion advice
	Total study duration	Mean follow-up 3.1 years
	Participants in each arm	G1: 51 G2: 51
	Relevant outcomes	T2DM (method and criteria not reported)
	Study quality	Fair <sup>a</sup>

Study: reference by first author and publication year	Data category	Description
Finnish Diabetes	Study design	RCT
Prevention Study: Tuomilehto, 2001	Setting	Not reported, Finland
(54); Uusitupa, 2009 (55); Aro, 2019 (56)	IHG diagnosis	IGT (plasma glucose ≥ 7.8 mmol/L and < 11.1 mmol/L 2 h after ingestion of 75-g oral glucose load)
	Intervention	G1: individual counselling for weight reduction, healthy diet, physical activity
	Comparator	G2: standard care
	Total study duration	Median 4 years of intervention
	Participants in each arm	G1: 265 G2: 257
	Relevant outcomes	All-cause mortality
	Study quality	Fair <sup>a</sup>
HELP PD: Vitolins,		
	Study design	Parallel RCT
HELP PD: Vitolins, 2019 (57)	Study design Setting	Parallel RCT General population, United States
	, 0	
	Setting Age of participants	General population, United States G1: 57.0
	Setting Age of participants (mean years)	General population, United States G1: 57.0 G2: 58.0
	Setting Age of participants (mean years) IHG diagnosis	General population, United States G1: 57.0 G2: 58.0 FPG 5.3–6.9 mmol/L G1: lifestyle maintenance
	Setting Age of participants (mean years) IHG diagnosis Intervention	General population, United States G1: 57.0 G2: 58.0 FPG 5.3–6.9 mmol/L G1: lifestyle maintenance (self-directed, group directed) G2: 2 individual visits with a registered dietitian/nutritionist and monthly newsletters with information on healthy lifestyle
	Setting Age of participants (mean years) IHG diagnosis Intervention Comparator	General population, United States G1: 57.0 G2: 58.0 FPG 5.3–6.9 mmol/L G1: lifestyle maintenance (self-directed, group directed) G2: 2 individual visits with a registered dietitian/nutritionist and monthly newsletters with information on healthy lifestyle behaviours and community resources
	Setting Age of participants (mean years) IHG diagnosis Intervention Comparator  Total study duration Participants in each	General population, United States G1: 57.0 G2: 58.0 FPG 5.3–6.9 mmol/L G1: lifestyle maintenance (self-directed, group directed) G2: 2 individual visits with a registered dietitian/nutritionist and monthly newsletters with information on healthy lifestyle behaviours and community resources 72 months G1: 71

Study: reference by first author and publication year	Data category	Description
Hellgren, 2014, 2021	Study design	RCT
(58,59)	Setting	Primary care, Sweden
	Age of participants (mean years)	71.0
	IHG diagnosis	FPG ( $\geq$ 6.1 to < 7.0 mmol/L with normal glucose tolerance) and/ or IGT (capillary glucose $\geq$ 8.9 to < 12.2 mmol/L at 2 h after oral glucose load with FPG < 7.0 mmol/L)
	Intervention	G1: lifestyle (exercise, 2 versions combined)
	Comparator	G2: treatment as usual
	Total study duration	8 year
	Participants in each arm	G1: 46 G2: 28
	Relevant outcomes	T2DM (method and criteria not reported), all-cause mortality
	Study quality	Fair <sup>a</sup>
Hu, 2017 (60)	Study design	RCT
	Setting	Yiyang City, Hunan Province, China
	Age of participants (mean years)	69.5
	IHG diagnosis	Impaired FPG (6.1–7.0 mmol/L and plasma glucose < 7.8 mmol/L 2 h after oral glucose load), IGT (FPG 6.1 mmol/L and plasma glucose 7.8–11.1 mmol/L 2 h after 75-g oral glucose load)
	Intervention	G1: intensive synthetic intervention (lifestyle education and intervention, self-monitoring blood glucose, support group)
	Comparator	G2: standard health advice

Table A3.1. Conta		
Study: reference by first author and publication year	Data category	Description
	Total study duration	ı year
	Participants in each arm	G1: 214 G2: 220
	Relevant outcomes	T2DM (FPG $\geq$ 7.8 mmol/L and/or plasma glucose $\geq$ 11.1 mmol/L at 2 h during OGTT)
	Study quality	Fair <sup>a</sup>
Indian Diabetes Prevention Programme: Ramachandran, 2006 (61)	Study design	RCT
	Setting	Community, India
	Age of participants (median years (SD))	G1: 46.1 (5.7) G2: 45.9 (5.9) G3: 46.3 (5.7) G4: 45.2 (5.7)
	IHG diagnosis	IGT (FPG < 7.0 mmol/L, plasma glucose ≥ 7.8 to < 11.1 mmol/L at 2 h during OGTT)
	Intervention	G1: lifestyle intervention G2: metformin G3: lifestyle intervention + metformin
	Comparator	G4: standard health-care advice
	Total study duration	3 years
	Participants in each arm	G1: 133 G2: 133 G3:129 G4: 136
	Relevant outcomes	T2DM (FPG $\geq$ 7.0 mmol/L and/or plasma glucose $\geq$ 11.1 mmol/L 2 h after oral glucose load in OGTT)
	Study quality	Fair <sup>a</sup>

Study: reference by first author and publication year	Data category	Description
Indian Diabetes	Study design	RCT
Prevention Programme 2:	Setting	Community, India
Ramachandran, 2009 (62)	Age of participants (median years (SD))	G1: 45.1 (6.1) G2: 45.5 (6.3)
	IHG diagnosis	IGT (plasma glucose ≥ 7.8 to < 11.1 mmol/L at 2 h during OGTT)
	Intervention	G1: pioglitazone 30 mg daily + lifestyle modification
	Comparator	G2: placebo + lifestyle modification
	Total study duration	3 years
	Participants in each arm	G1: 204 G2: 203
	Relevant outcomes	T2DM (FPG ≥ 7.0 mmol/L and/or plasma glucose ≥ 11.1 mmol/L at 2 h by OGTT), normoglycaemia, mortality
	Study quality	Faira
Japan Diabetes Prevention Program: Sakane, 2011 (63)	Study design	RCT
	Setting	32 community health-care institutions and company clinics, Japan
	Age of participants (median years (SD))	G1: 51.0 (7.0) G2: 51.0 (6.0)
	IHG diagnosis	FPG ≥ 5.6–6.9 mmol/L, casual plasma glucose ≥ 7.8 mmol/L but < 11.1 mmol/L when blood drawn within 2 h after a meal, or capillary plasma glucose 6.1–7.8 mmol/L when blood drawn 2 h or more after a meal, or IGT as indicated by a previous OGTT

Study: reference by first author and publication year	Data category	Description
	Intervention	G1: repeated sessions of group and individual lifestyle modification intervention
	Comparator	G2: one group session at baseline on healthy lifestyle and prevention of diabetes
	Total study duration	3 years
	Participants in each arm	G1: 152 G2: 152
	Relevant outcomes	T <sub>2</sub> DM (FPG $\geq$ 7.0 mmol/L by OGTT)
	Study quality	Faira
J-DOIT1: Sakane, 2015 <b>(96)</b>	Study design	RCT
	Setting	17 community/company health-care divisions, Japan
	Age of participants (mean years (SD))	G1: 48.9 (7.8) G2: 48.9 (7.5)
	IHG diagnosis	FPG 5.6-6.9 mmol/L
	Intervention	G1: 1-year telephone-delivered lifestyle support intervention
	Comparator	G2: control (periodic newsletters about diabetes)
	Total study duration	4.2 years (median)
	Participants in each arm	G1: 1240 G2: 1367
	Relevant outcomes	T2DM (FPG $\geq$ 7.0 mmol/L, a diagnosis of diabetes, use of antidiabetic drugs)
	Study quality	Fair

Study: reference by first author and publication year	Data category	Description
Juul, 2016 <b>(64)</b>	Study design	RCT
	Setting	19 general practices in Holstebro, Denmark
	Age of participants (median years)	58.0
	IHG diagnosis	FPG 6.1–6.9 mmol/L and/or HbA1c 6.0% to < 6.5%
	Intervention	G1: 2-h group sessions over 5 weeks plus further session after 1 and 6 months
	Comparator	G2: standard care
	Total study duration	ı year
	Participants in each arm	G1: 63 G2: 64
	Relevant outcomes	All-cause mortality
	Relevant outcomes Study quality	All-cause mortality Fair <sup>a</sup>
Kosaka, 2005 (65)		•
Kosaka, 2005 (65)	Study quality	Faira
Kosaka, 2005 (65)	Study quality Study design	Fair <sup>a</sup> RCT
Kosaka, 2005 (65)	Study quality Study design Setting	Fair <sup>a</sup> RCT  Hospital medical centre, Japan
Kosaka, 2005 (65)	Study quality Study design Setting Age of participants	Fair <sup>a</sup> RCT  Hospital medical centre, Japan  Not reported  IGT (FPG < 7.8 mmol/L and plasma glucose of 8.9–13.1 mmol/L at 2 h
Kosaka, 2005 (65)	Study quality Study design Setting Age of participants IHG diagnosis	Fair <sup>a</sup> RCT  Hospital medical centre, Japan  Not reported  IGT (FPG < 7.8 mmol/L and plasma glucose of 8.9–13.1 mmol/L at 2 h during 100 g OGTT)
Kosaka, 2005 (65)	Study quality Study design Setting Age of participants IHG diagnosis	Faira  RCT  Hospital medical centre, Japan  Not reported  IGT (FPG < 7.8 mmol/L and plasma glucose of 8.9–13.1 mmol/L at 2 h during 100 g OGTT)  G1: lifestyle intervention
Kosaka, 2005 (65)	Study quality Study design Setting Age of participants IHG diagnosis Intervention Comparator	Faira  RCT  Hospital medical centre, Japan  Not reported  IGT (FPG < 7.8 mmol/L and plasma glucose of 8.9–13.1 mmol/L at 2 h during 100 g OGTT)  G1: lifestyle intervention  G2: usual care
Kosaka, 2005 (65)	Study quality Study design Setting Age of participants IHG diagnosis Intervention Comparator Total study duration Participants in each	Faira  RCT  Hospital medical centre, Japan  Not reported  IGT (FPG < 7.8 mmol/L and plasma glucose of 8.9–13.1 mmol/L at 2 h during 100 g OGTT)  G1: lifestyle intervention  G2: usual care  4 years  G1: 356

Study: reference by first author and publication year	Data category	Description
Let's Prevent	Study design	RCT
Diabetes RCT: Davies, 2016 (66)	Setting	44 general practices, England (United Kingdom)
	Age of participants (mean years)	63.9
	IHG diagnosis	IFG (FPG 6.1–6.9 mmol/L) and/or IGT (7.8–11.0 mmol/L at 2 h after oral glucose load)
	Intervention	G1: 6-h group structured education programme with an annual refresher course and regular phone contact
	Comparator	G2: standard care
	Total study duration	Follow-up for 3 years
	Participants in each arm	G1: 447 G2: 433
	Relevant outcomes	T2DM (FPG $\geq$ 7.0 mmol/L and/or plasma glucose $\geq$ 11.1 mmol/L 2 h after oral glucose load)
	Study quality	Faira
Lindahl, 2009 (67)	Study design	RCT
	Setting	Various centres, northern Sweden
	Age of participants (median years (SD))	G1: 52.2 (9.0) G2: 53.5 (8.4)
	IHG diagnosis	Plasma glucose during an OGTT in the range for IGT
	Intervention	G1: intensive lifestyle with 1-month residential stay
	Comparator	G2: usual care
	Total study duration	5 years

Study: reference	Data category	Description
by first author and publication year	Data category	Description
	Participants in each arm	G1: 151 (randomized, but only 100 directly invited; 50 assigned as substitutes) G2: 150 (randomized, but only 100 directly invited; 50 assigned as substitutes)
	Relevant outcomes	T2DM (FPG 7.0 mmol/L)
	Study quality	Faira
Luo, 2022 <b>(68)</b>	Study design	Parallel RCT
	Setting	Outpatient clinic, China
	Age of participants (mean years)	53.0
	IHG diagnosis	FPG ≥ 6.1 to < 7.0 mmol/L and plasma glucose < 7:8 mmol/L 2 h after 75-g oral glucose load, or FPG < 7:0 mmol/L and plasma glucose ≥ 7:8 to < 11.1 mmol/L during a single OGTT
	Intervention	G1: lifestyle (diet and exercise) + placebo G2: pioglitazone 30 mg/day (+ standard education) G3: lifestyle (diet and exercise) + pioglitazone 30 mg/day
	Comparator	G4: treatment as usual (standard education) + placebo
	Total study duration	3 years
	Participants in each arm	G1: 490 G2: 492 G3: 483 G4: 480
	Relevant outcomes	T2DM (method and criteria not reported)
	Study quality	High risk of bias <sup>b</sup>

Data category	Description
Study design	Parallel RCT
Setting	Primary care, Australia
Age of participants (mean years)	62.5
IHG diagnosis	Impaired FPG (6.1–7.0 mmol/L), IGT (plasma glucose 7.8–11.0 mmol/L 2 h after oral glucose load) or both IFG and IGT (via OGTT)
Intervention	G1: lifestyle (diet and exercise)
Comparator	G2: waiting list
Total study duration	6 months
Participants in each arm	G1: 183 G2: 91
Relevant outcomes	T2DM (FPG $\geq$ 7.0 mmol and/or IGT $\geq$ 11.0 mmol/L)
Study quality	Poor <sup>a</sup>
Study design	RCT
Setting	Primary care clinics of Durham Veterans Affairs Medical Centre, United States
Age of participants (mean years (SD))	G1: 67.1 (6.3) G2: 67.7 (6.2)
IHG diagnosis	IGT (FPG 5.6-7.0 mmol/L)
Intervention	Gi: home-based multicomponent physical activity counselling programme including one in-person baseline counselling session, regular telephone counselling, physician endorsement in clinic with monthly automated encouragement, and customized mailed materials; all study participants, including controls, received a consultation in a Veterans Affairs weight management programme
	Study design Setting Age of participants (mean years) IHG diagnosis  Intervention Comparator Total study duration Participants in each arm Relevant outcomes Study quality Study design Setting  Age of participants (mean years (SD)) IHG diagnosis

Study: reference by first author and publication year	Data category	Description
	Comparator	G2: usual care
	Total study duration	ı year
	Participants in each arm	G1: 108 G2: 122
	Relevant outcomes	T2DM (method and criteria not reported)
	Study quality	Fair <sup>a</sup>
Nanditha, 2020 (71)	Study design	Parallel RCT
	Setting	Primary care, India and United Kingdom
	Age of participants (mean years)	52.0
	IHG diagnosis	HbA1c 6.0-6.4%
	Intervention	G1: lifestyle (diet and exercise at baseline, followed by motivational texts)
	Comparator	G2: treatment as usual (advice at baseline)
	Total study duration	2 years
	Participants in each arm	G1: 1031 G2: 1031
	Relevant outcomes	T2DM ("international criteria for FPG or HbA1c")
	Study quality	Some concerns <sup>b</sup>
NAVIGATOR Study Group: Holman, 2010 (72); McMurray, 2010 (73); Currie, 2017 (74)	Study design	RCT
	Setting	Clinical centres

Study: reference by first author and publication year	Data category	Description
	Age of participants (mean years)	G1: 63.7 (6.8) G2: 63.8 (6.9) G3: 63.7 (6.8) G4: 63.8 (6.8)
	IHG diagnosis	IGT (plasma glucose $\geq$ 7.8 mmol/L to $<$ 11.1 mmol/L 2 h after a 75-g oral glucose load and FPG $\geq$ 5.3 mmol/L to $<$ 7.0 mmol/L)
	Intervention	G1: nateglinide 60 mg 3 times daily G2: valsartan 160 mg once a day
	Comparator	G3: placebo (for nateglinide) G4: placebo (for valsartan)
	Total study duration	Median: 5 years
	Participants in each arm	G1: 4645 G2: 4631 G3: 4661 G4: 4675
	Relevant outcomes	T2DM (FPG ≥ 7.0 mmol/L or plasma glucose ≥ 11.1 mmol/L 2 h after oral glucose load, confirmed by OGTT), all-cause mortality, cardiovascular mortality, amputations, revascularization, end-stage renal disease
	Study quality	Good <sup>a</sup>
Nepi ANtidiabetes StudY: Lindblad, 2011 <b>(75)</b>	Study design	RCT
	Setting	Primary care, Sweden
	Age of participants (median years (SD))	G1: 60.4 (6.8) G2: 59.6 (6.7)
	IHG diagnosis	IFG (2 consecutive (10-h overnight) FPG ≥ 5.6 mmol/L, with mean 5.6–6.0 mmol/L)
	Intervention	G1: glimepiride 1 mg/daily

Study: reference by first author and publication year	Data category	Description
	Comparator	G2: placebo
	Total study duration	Mean 3.7 years
	Participants in each arm	G1: 136 G2: 138
	Relevant outcomes	T2DM (2 consecutive FPG ≥ 6.1 mmol/L)
	Study quality	Faira
Norfolk Diabetes	Study design	Parallel RCT
Prevention Study: Sampson, 2021 <b>(76)</b>	Setting	Primary care, England (United Kingdom)
	Age of participants (mean years)	G1: 66.5 G2: 66.7 G3: 65.3
	IHG diagnosis	HbA1c 6.0–6.4%, IFG 5.6–7.0 mmol/L
	Intervention	G1: standard lifestyle advice (diet and exercise) G2: enhanced lifestyle advice (diet, exercise, motivational phone calls)
	Comparator	G3: standard care
	Total study duration	3 years 10 months
	Participants in each arm	G1: 424 G2: 426 G3: 178
	Relevant outcomes	T2DM (HbA1c ≥ 6.5%, FPG ≥ 7.0 mmol/L)
	Study quality	High risk of bias <sup>b</sup>
Oldroyd, 2006 (77)	Study design	Parallel RCT
	Setting	General population, England (United Kingdom)
	Age of participants (mean years)	G1: 58.2 G2: 57.5

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Study: reference by first author and publication year	Data category	Description
	IHG diagnosis	FPG (< 7.8 mmol/L), IGT (plasma glucose 7.8–11.0 mmol/L 2 h after oral glucose load)
	Intervention	G1: lifestyle (diet and exercise)
	Comparator	G2: nothing
	Total study duration	2 years
	Participants in each arm	G1: 37 G1: 32
	Relevant outcomes	T2DM (FPG $\geq$ 7.8 mmol/L or plasma glucose $\geq$ 11.1 mmol/L 2 h after oral glucose load)
	Study quality	High risk of bias⁵
PREVENT-DM Trial: O'Brien, 2017 (78)	Study design	RCT
	Setting	Health centre in Philadelphia, United States
	Age of participants (mean years (SD))	G1: 45.5 (12.3) G2: 45.8 (11.7) G3: 44.0 (13.6)
	IHG diagnosis	Impaired fasting glucose (FPG 5.6–7.0 mmol/L), HbA1c 5.7–6.4% or both
	Intervention	G1: intensive group-based adaptation of the DPP lifestyle intervention delivered by <i>promotoras</i> (community health-care workers) G2: metformin 850 mg twice daily
	Comparator	G3: standard care plus written educational materials on diabetes prevention
	Total study duration	ı year
	Comparator	educational materials on diabetes

Study: reference by first author and publication year	Data category	Description
	Participants in each arm	G1: 33 G2: 29 G3: 30
	Relevant outcomes	T2DM (method and criteria not reported)
	Study quality	Fair <sup>a</sup>
PROPELS RCT: Khunti, 2021 <b>(79)</b>	Study design	Stratified RCT
	Setting	Primary care, England (United Kingdom)
	Age of participants (mean years)	G1: 59.4 G2: 59.3 G3: 59.4
	IHG diagnosis	HbA1c 6.0–6.4%, FPG 5.5–6.9 mmol/L, or glucose 7.8–11.0 mmol/L at 2 h after 75-g oral glucose
	Intervention	G1: walkaway (exercise, diabetes knowledge) G2: walkaway + (exercise, diabetes knowledge, text messages)
	Comparator	G3: advice on IHG and exercise
	Total study duration	4 years
	Participants in each arm	G1: 450 G2: 456 G3: 460
	Relevant outcomes	T2DM (HbA1c ≥ 6.5%)
	Study quality	Some concerns <sup>b</sup>
RISE Consortium: Sam, 2021 (80)	Study design	Parallel RCT
	Setting	3 clinical centres, United States
	Age of participants (mean years)	53.9

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Study: reference by first author and publication year	Data category	Description
	IHG diagnosis	FPG 5.3-6.9 mmol/L, plasma glucose $\geq$ 7.8 mmol/L at 2 h in OGTT, and HbA1c $\leq$ 7%
	Intervention	G1: metformin 500 mg titrated to 1000 mg twice daily over 4 weeks (or to tolerated dose) G2: glargine insulin for 3 months (titrated based on daily selfmonitored fasting blood glucose); after 3 months, glargine insulin stopped and metformin initiated and titrated to 1000 mg twice daily (or the maximum tolerated dose) for the remainder of the intervention G3: liraglutide titrated from 0.6 to 1.2 mg then to a final dose of 1.8 mg daily (as tolerated); metformin subsequently added and titrated to 1000 mg twice daily (or the maximum tolerated dose) for the remainder of the intervention period
	Comparator	G4: placebo
	Total study duration	12 months
	Participants in each arm	G1: 65 G2: 67 G3: 68 G4: 67
	Relevant outcomes	T2DM (HbA1c ≥ 6.5% or FPG ≥ 7.0 mmol/L or plasma glucose ≥ 11.0 mmol/L at 2 h during OGTT, or a random plasma glucose ≥ 11.1 mmol/L in patients with classic symptoms of hyperglycaemia or hyperglycaemic crisis)
	Study quality	High risk of bias <sup>b</sup>

Study: reference by first author and publication year	Data category	Description
SCALE Obesity	Study design	RCT
Prediabetes NN8022-1839 Study: le Roux, 2017 (81)	Setting	191 clinical research sites in 27 countries
, , , , ,	Age of participants (median years (SD))	G1: 47.5 (11.7) G2: 47.3 (11.8)
	IHG diagnosis	HbA1c 5.7–6.4%, FPG 5.6–6.9 mmol/L, or plasma glucose 7.8–11.0 mmol/L 2 h after 75-g oral glucose load
	Intervention	G1: liraglutide
	Comparator	G2: placebo
	Total study duration	160 weeks
	Participants in each arm	G1: 1505 G2: 749
	Relevant outcomes	T2DM (HbA1c ≥ 6.5% or FPG ≥ 7.0 mmol/L or plasma glucose ≥ 11.1 mmol/L at 2 h during OGTT) or a random plasma glucose ≥ 11.1 mmol/L in patients with classic symptoms of hyperglycaemia or hyperglycaemic crisis, all-cause mortality, cardiovascular mortality, non-fatal stroke, non-fatal myocardial infarction
	Study quality	Fair <sup>a</sup>
SLIM Study: Roumen, 2008 (82)	Study design	Stratified RCT
	Setting	General population, Netherlands (Kingdom of the)
	Age of participants (mean years)	G1: 54.2 G2: 58.4
	IHG diagnosis	Mean 2-h glucose concentration 7.8–12.5 mmol/L from 2 OGTTs and FPG < 7.8 mmol/L

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Study: reference by first author and publication year	Data category	Description
	Intervention	G1: lifestyle (diet and exercise)
	Comparator	G2: brief advice about diet/exercise
	Total study duration	3 years
	Participants in each arm	G1: 61 G2: 60
	Relevant outcomes	T2DM (FPG $\geq$ 7.0 mmol/L, plasma glucose $\geq$ 11.1 mmol/L 2 h after oral glucose load)
	Study quality	High risk of bias <sup>b</sup>
STEP 6: Kadowaki,	Study design	Stratified RCT
2022 (83)	Setting	General population, Japan and Republic of Korea
	Age of participants	Not reported
	IHG diagnosis	FPG 5.6–6.9 mmol/L, plasma glucose 7.8–11.0 mmol/L at 2 h during OGTT, HbA1c 5.7–6.4%
	Intervention	G1: semaglutide 1.7 mg G2: semaglutide 2.4 mg
	Comparator	G <sub>3</sub> : placebo
	Total study duration	75 weeks
	Participants in each arm	G1: 20 G2: 43 G3: 25
	Relevant outcomes	T2DM (FPG ≥ 7.0 mmol/L; plasma glucose ≥ 11.1 mmol/L at 2 h during OGTT; HbA1c ≥ 6.5%; a random plasma glucose ≥ 11.1 mmol/L in patients with classic symptoms of hyperglycaemia or hyperglycaemic crisis)
	Study quality	Some concerns <sup>b</sup>

Study: reference by first author and publication year	Data category	Description
STOP-NIDDM Trial: Chiasson, 2002, 2003 (84,85)	Setting	Hospitals in Austria, Canada, Denmark, Finland, Germany, Israel, Norway, Sweden, Spain
	Age of participants (mean years (SD))	54.5 (7.9)
	IHG diagnosis	IGT (plasma glucose ≥7.8 mmol/l but < 11.1 mmol/l 2 h after 75-g oral glucose load)
	Intervention	G1: acarbose 3 times a day
	Comparator	G2: placebo
	Total study duration	Mean follow-up 3.3 years (SD: 1.15)
	Participants in each arm	G1: 714 G2: 715
	Relevant outcomes	T2DM (plasma glucose ≥ 7.8 mmol/L and < 11.1 mmol/L 2 h after 75-g oral glucose load based on one OGTT)
	Study quality	Fair <sup>a</sup>
Toro-Ramos, 2020 (86)	Study design	Parallel RCT
	Setting	Primary care, United States
	Age of participants (mean years)	G1: 55.7 G2: 57.5
	IHG diagnosis	IFG (FPG 5.6–6.9 mmol/L) or IGT (plasma glucose 7.8–11.0 mmol/L 2 h after 75-g oral glucose load during OGTT) or HbA1c 5.7–6.4%
	Intervention	G1: lifestyle (delivered via mobile phone)
	Comparator	G2: written advice
	Total study duration	12 months
	Participants in each arm	G1: 103 G2: 99

Study: reference by first author and publication year	Data category	Description
	Relevant outcomes	T2DM (HbA1c ≥ 6.5%)
	Study quality	Some concerns <sup>b</sup>
Van Name, 2016	Study design	Parallel group RCT
(87)	Setting	Urban community, United States
	Age of participants (median years (SD))	G1: 43.8 (10.8) G2: 43 (9.7)
	IHG diagnosis	FPG 5.6–6.9 mmol/L, or plasma glucose 7.8–11.0 mmol/L at 2 h during OGTT
	Intervention	G1: intensive lifestyle intervention (modified DPP: 14 weeks of group sessions focused on food choices, behaviour change, physical activity, weight loss)
	Comparator	G2: usual care
	Total study duration	ı year
	Participants in each arm	G1: 65 G2: 65
	Relevant outcomes	T2DM (method and criteria not reported)
	Study quality	Fair <sup>a</sup>
Voglibose Ph-3 Study Group: Kawamori, 2009 (88)	Study design	RCT
	Setting	Multicentre, Japan
	Age of participants (mean (SD))	G1: 55.7 (9.1) G2: 55.7 (9.2)
	IHG diagnosis	FPG < 6.9 mmol/L, plasma glucose 7.8–11.0 mmol/L at 2 h during OGTT, HbA1c < 6.5% plus at least one risk factor for T2DM

Study: reference by first author and publication year	Data category	Description
	Intervention	G1: voglibose 0.2 mg 3 times a day
	Comparator	G2: placebo
	Total study duration (mean (SD))	48.1 (36.3) G1: 45.0 (34.7) G2: 51.3 (37.6)
	Participants in each arm	G1: 897 G2: 883
	Relevant outcomes	T2DM (HbA1c ≥ 6·5%, and, on 2 separate occasions, at least one of the following: (i) plasma glucose ≥ 11.1 mmol/L at 2 h after oral glucose load, (ii) FPG ≥ 7·0 mmol/L, (iii) random plasma glucose ≥ 11.1 mmol/L)
	Study quality	Gooda
Wong, 2013, 2018 (89,90)	Study design	RCT
	Setting	Community health project, China (Hong Kong SAR)
	Age of participants (median years (SD))	G1: 54.1 (6.1) G2: 55.2 (6.5)
	IHG diagnosis	FPG 5.6–6.9 mmol/L or plasma glucose 7.8–11.0 mmol/L 2 h after a 75-g glucose load
	Intervention	G1: short message service intervention
	Comparator	G2: usual care
	Total study duration	5 years
	Participants in each arm	G1: 54 G2: 50
	Relevant outcomes	T2DM (method and criteria not reported)
	Study quality	Fair <sup>a</sup>

Study: reference by first author and publication year	Data category	Description
Xu, 2013 (91)	Study design	Stratified RCT
	Setting	Primary care, China
	Age of participants (mean years)	G1: 60.4 G2: 56.6
	IHG diagnosis	FPG 5.6–6.9 mmol/L or plasma glucose 7.8–11.0 mmol/L 2 h after a 75-g glucose load
	Intervention	G1: lifestyle (diet and exercise)
	Comparator	G2: general healthy living advice
	Total study duration	9 months
	Participants in each arm	G1: 41 G2: 40
	Relevant outcomes	T2DM (method and criteria not reported)
	Study quality	Some concerns <sup>b</sup>
Yates, 2009 (93)	Study design	RCT
rates, 2009 (93)	oracy acoig	ICT
rates, 2009 (93)	Setting	Leicester, United Kingdom
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14103, 2009 (93)	Setting Age of participants	Leicester, United Kingdom G1: 66 (8) G2: 64 (7)
14103, 2009 (93)	Setting Age of participants (mean years (SD))	Leicester, United Kingdom G1: 66 (8) G2: 64 (7) G3: 65 (10) IGT (FPG < 7.0 mmol/L and plasma glucose 7.8–11.0 mmol/L 2 h after 75-g
14103, 2009 (93)	Setting Age of participants (mean years (SD)) IHG diagnosis	Leicester, United Kingdom G1: 66 (8) G2: 64 (7) G3: 65 (10) IGT (FPG < 7.0 mmol/L and plasma glucose 7.8–11.0 mmol/L 2 h after 75-g oral glucose load during OGTT) G1: physical activity intervention with pedometer use G2: physical activity intervention
rates, 2009 (95)	Setting Age of participants (mean years (SD)) IHG diagnosis Intervention	Leicester, United Kingdom  G1: 66 (8)  G2: 64 (7)  G3: 65 (10)  IGT (FPG < 7.0 mmol/L and plasma glucose 7.8–11.0 mmol/L 2 h after 75-g oral glucose load during OGTT)  G1: physical activity intervention with pedometer use  G2: physical activity intervention without pedometer use

Study: reference by first author and publication year	Data category	Description	
	Participants in each arm	G1: 29 G2: 29 G3: 29	
	Relevant outcomes	T2DM (FPG $\geq$ 7 mmol/L or plasma glucose $\geq$ 11.1 mmol/L 2 h after 75-g oral glucose load in OGTT)	
	Study quality	Fair <sup>a</sup>	
Zensharen Study:	Study design	RCT	
Saito, 2011 <b>(94)</b>	Setting	Hospitals and clinics, Japan	
	Age of participants (median years (IQR))	G1: 50 (44–54) G2: 48 (41–54)	
	IHG diagnosis	FPG 5.6–7.0 mmol/L	
	Intervention	G1: frequent intervention (individual instructions and follow-up support for lifestyle modification 9 times over 36 months)	
	Comparator	G2: control group (individual instructions and follow-up support for lifestyle modification 4 times over 12 months)	
	Total study duration	3 years	
	Participants in each arm	G1: 311 G2: 330	
	Relevant outcomes	T2DM (FPG $\geq$ 7.0 mmol/L, plasma glucose $\geq$ 11.1 mmol/L at 2 h in 75 g OGTT)	
	Study quality	Faira	

Study: reference by first author and publication year	Data category	Description
Zhou, 2011 (95)	Study design	Cluster RCT
	Setting	Urban residents, China
	Age of participants (mean years)	62.1
	IHG diagnosis	Impaired fasting glucose (FPG 5.6–6.9 mmol/L), and/or IGT (plasma glucose 7.8–11.0 mmol/L 2 h after oral glucose load in OGTT)
	Intervention	G1: exercise G2: diet G3: exercise + diet
	Comparator	G4: control, no intervention
	Total study duration	6 months
	Participants in each arm	G1: 58 G2: 57 G3: 59 G4: 58
	Relevant outcomes	T2DM (FPG ≥ 7.0mmol/L or plasma glucose ≥ 11.1mmol/L at 2 h during OGTT)
	Study quality	Some concerns <sup>b</sup>

ADA: American Diabetes Association; DPPOS: Diabetes Prevention Program Outcomes Study; FPG: fasting plasma glucose; IFG: impaired fasting glycaemia; IGT: impaired glucose tolerance; IHG: intermediate hyperglycaemia; IQR: interquartile range; OGTT: oral glucose tolerance test; SD: standard deviation.

<sup>&</sup>lt;sup>a</sup> Rating according to the USPSTF Quality Rating Criteria (21).

<sup>&</sup>lt;sup>b</sup> Rating according to the Cochrane Risk of Bias Tool-2 (105).

Table A<sub>3.2</sub>. Detailed health outcomes with pharmacological interventions

Outcome	Intervention		Proportion with outcome of interest <sup>a</sup>	
		Intervention	Control	CI) <sup>b</sup>
All-cause mortality	Metformin + lifestyle (42)	NR	NR	NR
	Metformin + lifestyle (61)	0.8	0.7	1.05 (0.07–16.68)
	Metformin + lifestyle (39)	0	0	NA
	Metformin (61)	0	0.7	NA
	Ramipril (49)	1.2	1.2	0.98 (0.60-1.60)
	Rosiglitazone (50)	1.1	1.3	0.91 (0.56–1.49)
	Voglibose (88)	0.7	0	NA
	Liraglutide (81)	0.1	0.3	0.50 (0.07–3.35)
	Glimepiride (75)	3.7	1.4	2.54 (0.50–12.85)
	Nateglinide + lifestyle (72)	6.7	6.7	1.00 (0.86–1.16)
	Valsartan + lifestyle (73)	6.4	7.0	0.91 (0.78–1.06)
	Acarbose (32)	1.7	5.2	0.23 (0.03–3.01)
	Pioglitazone (62)	1.0	0.5	1.99 (0.18–21.78)
Cardiovascular mortality	Metformin + standard lifestyle (44)	0.1	0.4	0.25 (0.03–2.25)
	Ramipril (51)	0.5	0.4	1.21 (0.52–2.80)
	Rosiglitazone (51)	0.5	0.4	1.20 (0.52–2.78)
	Liraglutide (81)	0.1	0	NA
	Glimepiride (75)	0.7	1.4	0.51 (0.05–5.53)

Table A<sub>3.2</sub>. contd

Outcome	Intervention	Proportion with outcome of interest <sup>a</sup> Intervention Control		Relative risk (95% CI) <sup>b</sup>
	Nateglinide + lifestyle (72)	2.7	2.5	1.07 (0.84–1.37)
	Valsartan + lifestyle (73)	2.8	2.5	1.11 (0.87–1.43)
Non-fatal stroke	Liraglutide (81)	0.1	0.3	0.50 (0.07–3.35)
Non-fatal myocardial infarction	Liraglutide (81)	0.2	0.1	1.49 (0.16–14.33)
	Pioglitazone (25)	0.7	0.3	1.97 (0.18–21.65)
End-stage renal disease	Valsartan (74)	0.1	0.1	1.01 (0.29–3.48)
Amputation	Nateglinide (72)	0.02	0.1	0.17 (0.02–1.39)
	Valsartan (74)	0.1	0.04	2.52 (0.49–13.00)
Revascularization	Nateglinide (72)	7.1	6.8	1.06 (0.91–1.23)
	Valsartan (73)	6.8	7.1	0.96 (0.83–1.12)

NA: not applicable; NR: not reported.

 $<sup>^{\</sup>rm a}$  Percentage of people randomized to each arm (intervention or control) that had the outcome of interest.

<sup>&</sup>lt;sup>b</sup> No results were statistically significant.

Table A<sub>3.3</sub>. Detailed health outcomes with lifestyle interventions

Outcome	Intervention _		Proportion with outcome of interest <sup>a</sup>	
		Intervention	Control	(95% CI) <sup>b</sup>
All-cause mortality	Clinical trial (59)	10.7	7.7	1.39 (0.40–4.86)
	Community setting (64)	0	0	NA
	Primary care in Durham Veterans Affairs Medical Center (70)	0.7	0.8	1.36 (0.12–14.79)
	Da Qing Diabetes Prevention Outcome Study (37)	46	56	0.82 (0.69–0.98)
	Finnish Diabetes Prevention (55)	2.3	4.0	0.58 (0.21–1.57)
	Indian Diabetes Prevention Programme (61)	0.8	0.7	1.02 (0.06–16.18)
	Zensharen Study (94)	0.3	0	NA
	Diabetes Prevention Programme (42)	NR	NR	NR
Cardiovascular mortality	Diabetes Prevention Programme (44)	0.2	0.1	0.50 (0.09–2.73)
	Da Qing Diabetes Prevention Outcome Study (37)	20.3	29	0.70 (0.51–0.97)
Retinopathy	Da Qing Diabetes Prevention Outcome Study (37)	12.8	18.8	0.68 (0.44–1.04)

## Table A<sub>3.3</sub>. contd

Outcome	Intervention	Proportion with outcome of interest <sup>a</sup>		Relative risk
		Intervention	Control	(95% CI) <sup>b</sup>
Nephropathy	Da Qing Diabetes Prevention Outcome Study (37)	3.7	5.1	0.72 (0.30–1.71)
Neuropathy	Da Qing Diabetes Prevention Outcome Study (37)	9.5	5.1	1.86 (0.78–4.48)

NA: not applicable; NR: not reported.

<sup>&</sup>lt;sup>a</sup> Percentage of people randomized to each arm (intervention or control) that had the outcome of interest.

<sup>&</sup>lt;sup>b</sup> Statistically significant results in bold.

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