UK National Screening Committee

Screening for Type 2 Diabetes in adults

External review against programme appraisal criteria for the UK National Screening Committee

Version: FINAL

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The UK National Screening Committee secretariat is hosted by Public Health England.

About the UK National Screening Committee (UK NSC)

The UK NSC advises ministers and the NHS in the 4 UK countries about all aspects of population screening and supports implementation of screening programmes. Conditions are reviewed against evidence review criteria according to the UK NSC's evidence review process.

Read a complete list of UK NSC recommendations.

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List of abbreviations

ADA	American Diabetes Association
BMI	Body mass index
CI	Confidence interval
DPP	Diabetes prevention programme
FPG	Fasting plasma glucose
GCT	Glucose challenge test
HDL	High-density lipoproteins
HR	Hazard ratio
IFG	Impaired fasting glucose
IGT	Impaired glucose tolerance
LDL	Low-density lipoproteins
NDH	Non-diabetic hyperglycaemia
NHS	National Health Service
NSC	National Screening Committee
OGTT	Oral glucose tolerance test
OR	Odds ratio
PG	Plasma glucose
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
QUIPS	Quality in prognosis studies
RCT	Randomised controlled trial
REA	Rapid evidence assessment
RR	Relative risk/risk ratio
T2DM	Type 2 diabetes mellitus
USPSTF	United States Preventative Services Task Force
WHO	World Health Organisation
2-hour PG	2-hour post-load plasma glucose test

Plain English summary

Type 2 diabetes (T2DM) is a condition that causes a person's blood sugar levels to be too high. In the short-term, people with diabetes might feel thirsty all the time, be very tired, and need to use the toilet a lot. In the long-term, diabetes can cause serious problems with the eyes, kidneys, nerves, and heart. The main treatments for T2DM are a healthy diet, regular exercise, and specific medications. Pre-diabetes (or non-diabetic hyperglycaemia) is the name given when a person has a higher than usual blood sugar level but they do not have diabetes.

Screening might help to find people who have pre-diabetes or T2DM. By finding people with these conditions, they can get treatment sooner. This might stop the long-term problems that diabetes causes. It might also stop diabetes from occurring in the first place.

Screening and current UK NSC recommendations

The last UK National Screening Committee review was published in 2013. It concluded that the NHS should not screen for T2DM. Key reasons included that there was no randomised controlled trial evidence that screening would lead to better outcomes for people than standard care, and that primary prevention should be considered as T2DM is caused by obesity.

The current review looked at the evidence on:

- The proportion of people with pre-diabetes who go on to develop T2DM;
- Which of the current screening tests best predicts who will develop T2DM-related health problems;
- Whether diet and exercise are useful treatments for pre-diabetes;
- Whether randomised controlled trials have shown that screening for T2DM is beneficial.

The review found that:

- Between 12 and 31% of people with pre-diabetes go on to develop T2DM over the short-to-medium term (3–10 years);
- Extra health problems such as having high blood pressure, or a family history of diabetes might make it more likely to go from pre-diabetes to T2DM;

- People with higher blood glucose (especially in the T2DM range) might be at greater risk of health problems such as retinopathy than those with lower levels of blood glucose, but no single test is better at predicting these
- People are less likely to develop T2DM if they take part in diet and exercise programmes

Recommendations

Consistent with the previous NSC review, the current review does not recommend screening for T2DM in adults. Searching for, and caring for people with pre-diabetes and T2DM already happens through current NHS programmes for diabetes, namely, the NHS Health Check and the NHS Diabetes Prevention Programme. These programmes are currently being evaluated.

The review recommends more research to understand:

- Which people with pre-diabetes go on to develop T2DM,
- Which test is best for predicting problems related to T2DM, and
- Whether screening for T2DM in the general population is beneficial.

Executive summary

Purpose of the review

The purpose of the review was to examine (1) the proportion of people who have non-diabetic hyperglycaemia who go on to develop type 2 diabetes, (2) the accuracy of screening tests for predicting future vascular complications of type 2 diabetes, (3) whether lifestyle interventions are effective for treating people who have non-diabetic hyperglycaemia, and (4) whether screening for type 2 diabetes is beneficial.

Background

Type 2 diabetes mellitus (T2DM) is a chronic metabolic condition that is caused by an inability to produce or use insulin. This prevents glucose being converted into energy and leads to high blood glucose (sugar). Common symptoms of T2DM include fatigue, excessive thirst, and frequent urination. Over time, it can cause serious health problems, such as retinopathy, neuropathy, nephropathy, and cardiovascular disease. Elevated blood glucose that is below the diabetic threshold is often referred to as non-diabetic hyperglycaemia (NDH), although other terms are also used in the literature such as pre-diabetes, impaired glucose tolerance, impaired fasting glucose, or intermediate hyperglycaemia. As part of its 3-year review cycle, the UK NSC needs to review the evidence on whether population screening for T2DM should be recommended in the UK. Because non-diabetic hyperglycaemia can progress to diabetes and it is often an incidental finding of any screening for T2DM (regardless of the type of test and cut-off used), this review will attempt to shed more light on the association between NDH and T2DM and on the effectiveness of the interventions used to manage people with non-diabetic hyperglycaemia.

Focus of the review

This review aims to examine 4 key questions relating to the effectiveness and appropriateness of screening for T2DM. The questions (and associated NSC criteria) are as follows:

1. What proportion of people with untreated non-diabetic hyperglycaemia develop T2DM?
   (UK NSC criterion 1: The condition should be an important health problem as judged by its frequency and/or severity. The epidemiology, incidence, prevalence and natural history of the condition should be understood, including development from

latent to declared disease and/or there should be robust evidence about the association between the risk or disease marker and serious or treatable disease).

2. What is the accuracy of haemoglobin A1c (HbA1c), the oral glucose tolerance test (OGTT), and fasting plasma glucose (FPG) as screening tools for microvascular and macrovascular complications of T2DM?
   (UK NSC criterion 4: There should be a simple, safe, precise and validated screening test).
3. What is the reported effectiveness of lifestyle interventions for people with non-diabetic hyperglycaemia?
   (UK NSC criterion 9: There should be an effective intervention for patients identified through screening, with evidence that intervention at a pre-symptomatic phase leads to better outcomes for the screened individual compared with usual care. Evidence relating to wider benefits of screening, for example those relating to family members, should be taken into account where available. However, where there is no prospect of benefit for the individual screened then the screening programme should not be further considered).
4. Have randomised controlled trials (RCTs) demonstrated the benefit of screening for T2DM?
   (UK NSC criterion 11: There should be evidence from high quality randomised controlled trials that the screening programme is effective in reducing mortality or morbidity. Where screening is aimed solely at providing information to allow the person being screened to make an "informed choice" (such as Down's syndrome or cystic fibrosis carrier screening), there must be evidence from high quality trials that the test accurately measures risk. The information that is provided about the test and its outcome must be of value and readily understood by the individual being screened).

Recommendation under review

The current UK NSC recommendation is not to screen for type 2 diabetes. This is based on the most recent UK NSC review from 2013 which concluded that key UK NSC criteria were not met, e.g. a lack of RCT evidence that screening would be beneficial, limitations in the current screening tests, and evidence that earlier treatment might not be more effective than usual care.[1]

Findings and gaps in the evidence of this review

Key question 1: What proportion of people with untreated non-diabetic hyperglycaemia develop T2DM?

Sub-questions: How long does the progression from non-diabetic hyperglycaemia to T2DM take?

What risk factors are associated with the progression from non-diabetic hyperglycaemia to T2DM?

In a recent Cochrane systematic review, 103 prospective cohort studies were identified that examined the development of T2DM in people who had non-diabetic hyperglycaemia and did not receive interventions as part of the study.[2] The authors reported that the incidence of T2DM increased with length of follow up, although not linearly. This occurred for all tests. For example, when non-diabetic hyperglycaemia was defined as impaired fasting glucose (FPG 6.1 mmol/L), T2DM incidence was 11% in studies that followed up participants for 2 years, and 31% for studies that followed up participants for 12 years. When non-diabetic hyperglycaemia was defined as impaired glucose tolerance (2-hour PG 7.8–11.1 mmol/L), T2DM incidence was 16% in studies that followed up participants for 2 years, and 70% in studies that followed up participants for 12 years. The proportion of people who regressed from non-diabetic hyperglycaemia to normoglycaemia appeared to decrease over time, e.g. 33–59% of participants in studies that followed up participants for 1–5 years, and 17–42% in studies that followed up participants 6–11 years. The pattern of decreasing regression was not consistent over time when comparing studies, for example the proportion of participants regressing from non-diabetic hyperglycaemia to normoglycaemia was 34% in studies that followed up participants for 5 years, 23% in studies that followed up participants for 6 years, and 41% in studies that followed up participants for 7 years. Nevertheless, glycaemic status was predictive of later T2DM (hazard ratios [HR] ranged from 3.6 to 10.1). Two UK studies were identified in the Cochrane review, reporting cumulative incidence of T2DM of 7% over 3 years and 10% over 4.4 years.

In the current review, 2 studies (one from Korea and one from Spain), reported in 4 papers, were identified which followed up people with non-diabetic hyperglycaemia for 3[3 4] and 5[5 6] years. They indicated that between 12 and 31% of people with non-diabetic hyperglycaemia developed T2DM by the end of the study period. There was some evidence that high blood glucose level, high blood pressure, family history of disease, liver function, and obesity were associated with an increased risk of developing type 2 diabetes.[3-6] There were no UK studies addressing this question in the current review.

UK NSC criterion 1:
Natural history of NDH (association with T2DM only): **met**
Frequency, severity, epidemiology, incidence, prevalence: **not considered**

In this review, criterion 1 was partially assessed for the natural history of the incidental finding of NDH in terms of progression, regression and risk factors. No other elements of the criterion were examined, and the criterion was not assessed at all for the target condition T2DM. There is a large body of evidence indicating an association between non-diabetic hyperglycaemia and future T2DM. However, this is against a background of evidence uncertainties. Namely, not all people with non-diabetic hyperglycaemia will go on to develop T2DM, and many people with non-diabetic hyperglycaemia will regress to normoglycaemia. Currently, it is unclear exactly which of the people with blood glucose or HbA1c in the non-diabetic hyperglycaemia range will go on to develop T2DM, who will regress to normoglycaemia, and who will remain in the intermediate blood glucose range, but common risk factors associated with these outcomes are known.

Key question 2: What is the accuracy of type 2 diabetes tests to detect concurrent and predict future diabetes complications?

Seventeen papers were identified that compared micro- and macrovascular complications of T2DM according to blood glucose (FPG and 2-hour postload plasma glucose [2-hour PG]) and HbA1c levels. There was evidence that FPG, 2-hour PG and HbA1c levels were associated with all-cause mortality and micro- and macrovascular complications of diabetes such as retinopathy and nephropathy. There was no consistent evidence that any one glycaemic marker (FPG, 2-hour PG, HbA1c) was better at predicting these outcomes. There was considerable variability between the included studies (e.g sample characteristics, the blood glucose thresholds that were examined); all of the studies were at high risk of bias, and the majority (12/17) had applicability concerns that limit their generalisability to the UK screening setting.

UK NSC criterion 4:
Comparative validity of HBa1c, FPG and OGTT: **Not met** (no clear evidence of superior test accuracy of one test over others)
Overall validity: **not considered**
Simplicity, safety, precision: **not considered**

In this review, criterion 4 was partially assessed for the comparative validity of the screening tests. The simplicity, safety or precision of the tests were not addressed. While there was consistent evidence for an association between higher blood glucose levels and some of the complications of diabetes (i.e. mortality, retinopathy, and nephropathy) for all 3 tests, the reviewers found no evidence that any one test was a better predictor of these complications. As the reviewers were investigating which is the best test, they only included direct comparisons of all 3 tests in the same population. Therefore, studies investigating

validity of a single test alone were not included, and so the question of whether the tests are valid was not directly addressed.

Key question 3: What is the reported effectiveness of lifestyle interventions for people with non-diabetic hyperglycaemia?

In a recent Cochrane systematic review from 2017, 12 randomised controlled trials were identified that compared lifestyle interventions (diet and/or exercise) to standard treatment or no treatment.[7] The authors reported a 43% risk reduction of T2DM amongst participants taking part in lifestyle interventions compared to those receiving standard care/no treatment [relative risk (RR) 0.57 (95% CI, 0.50–0.64)]. There were no statistically significant between-group differences in any other reported outcome, i.e. all-cause mortality, cardiovascular mortality, non-fatal heart attack/stroke, serious adverse events, and health-related quality of life.

In the current review, 2 trials (one from Iran and one from the USA), reported in 3 papers, were identified which compared either diet plus exercise[8 9] or diet alone[10] to standard care. They indicated that fewer people in the diet plus exercise group (21.3%)[9] and the high-monounsaturated fat diet (9.3%)[10] groups developed T2DM than people in the standard care groups (38.6% and 18.3%). Blood glucose levels returned to normal in a greater proportion of people in the diet plus exercise group (64%) compared to those in the standard care group (27.9%).[9] There was some evidence that lifestyle intervention also led to reductions in blood pressure, cholesterol and triglycerides, but it was not clear if these reductions were clinically significant.

UK NSC criterion 9:
Effectiveness of lifestyle interventions to reduce progression from NDH to T2DM: **Met**
Effectiveness of lifestyle interventions to improve health outcomes such as cardiovascular events: **not considered**
Effectiveness of lifestyle interventions for T2DM: **not considered**
Benefit of earlier intervention in pre-symptomatic phase: **not considered**
Evidence relating to the wider benefits of screening: **not considered**

In this review criterion 9 was assessed in relation to the effectiveness of lifestyle interventions to reduce the progression from NDH to T2DM. Overall, the body of evidence from this review and the recent Cochrane systematic review suggest a benefit of diet plus exercise on reducing the risk of T2DM amongst individuals who have NDH. However, the reviewers did not assess the whole criterion as follows. They did not assess (1) the impact of these interventions on health outcomes such as cardiovascular events or mortality, only

the intermediate outcome of T2DM diagnosis, (2) the benefits of earlier treatment for T2DM following screen detection, only NDH, (3) whether pre-symptomatic detection and treatment of NDH or T2DM is beneficial compared to later treatment initiation following symptomatic detection, or (4) the wider benefits of screening, such as to family members.

Key question 4: Have RCTs demonstrated the benefit of screening for T2DM?

In a 2015 systematic review performed for the U.S. Preventive Services Task Force (USPSTF),[11] 2 randomised controlled trials were identified that examined the effect of screening for T2DM. There was no significant difference in risk of mortality between the screening and no screening groups in either of the studies: HR 1.06 (95% CI, 0.90–1.25) in the ADDITION-Cambridge trial,[12] HR 0.79 (95% CI, 0.63–1.00) in the Ely study.[13]

One UK paper was identified which examined the impact of screening for T2DM.[14] This paper followed up a sub-sample of participants from the ADDITION-Cambridge trial.[15] No statistically significant differences were observed between screened and unscreened participants in relation to self-reported cardiovascular events (OR 0.90, 95% CI 0.71–1.15), hypertension (OR 0.90, 95% CI 0.75–1.08), or quality of life (physical health: β –0.33, 95% CI –1.80 to 1.14; mental health: β –0.38, 95% CI –1.33 to 0.57), 7 years after initial randomisation. The proportion of people reporting dyslipidaemia was lower in the screened group (odds ratio [OR] 0.75, 95% CI, 0.64–0.88) in comparison to the unscreened group.

UK NSC criterion 11: Not met

Recommendations on screening

While there is evidence that diet and exercise interventions reduce the risk of people with non-diabetic hyperglycaemia developing T2DM, the direction of evidence in the present rapid review and recent Cochrane systematic review suggest that the majority of people with non-diabetic hyperglycaemia who did not receive interventions as part of the study did not go on to develop T2DM in the short-to-midterm, and that screening for T2DM does not appear to lead to better outcomes. Higher blood glucose (as measured by FPG, 2-hour PG, and HbA1c), particularly in the T2DM range, might be predictive of complications of T2DM such as retinopathy, but this is based on evidence that is at high risk of bias and that does not represent the population of adults in the UK who would be eligible for screening. Further, there is no clear evidence about which of the 3 tests is the best at identifiying complications of T2DM. On this basis, the reviewers found no reason to change the conclusion of the previous review, that systematic population screening for T2DM should

not be recommended. Further research could explore the predictors of T2DM amongst people who have NDH. Limitations in the 2 trials of screening for T2DM might justify a larger randomised controlled trial that more accurately reflects screening as it would occur in practice.

Limitations

Question 1, 3, and 4 used a rapid evidence assessment approach. This approach is, by its nature, less comprehensive (e.g. English language only, restricted search dates, restricted outcomes) and more prone to errors (i.e. 80% of literature screening, data extraction and quality appraisal dependent on a single reviewer; quality appraisal tools not adjusted). While question 2 used a systematic review approach, it had its own limitations. For example, the search required all 3 tests to be mentioned in the title and abstract.

Evidence uncertainties

There is considerable uncertainty regarding the progression from non-diabetic hyperglycaemia to T2DM. Even without intervention such as improved diet or participation in physical activity, a large proportion of the people who meet the criteria for NDH return to normal glucose regulation. This may indicate that NDH is a transient condition that is inappropriately medicalised, risking overdiagnosis, or it might also reflect that the approach to diagnosis is inadequate. It is currently unclear which of the 3 tests that could be used in a screening programme (FPG, 2-hour PG, HbA1c) is the most useful for identifying the complications of T2DM. However, it is important to note that this review found evidence that interventions delivered while individuals have non-diabetic hyperglycaemia reduce the risk that they will develop T2DM in the future. Further research is warranted.

Introduction and approach

Background

Type 2 diabetes mellitus (T2DM) is a metabolic disorder characterised by abnormally high blood sugar (glucose) levels (hyperglycaemia). It is estimated that in England there are over 3.4 million adults living with T2DM, with over 800,000 of them undiagnosed.[16] T2DM is a chronic condition that occurs when either the pancreas does not produce enough insulin (a hormone that regulates blood glucose) or when the body cannot use the insulin it produces effectively.[17 18] Common symptoms include fatigue, excessive thirst, and frequent urination.[19] Long-term complications of T2DM include retinopathy, nephropathy, neuropathy, and cardiovascular disease.[20] Management of T2DM focusses on control of blood glucose levels. Predominantly this is through lifestyle interventions such as improved diet and exercise, and medications such as metformin.

A potentially high-risk category of elevated blood glucose is non-diabetic hyperglycaemia (NDH), also known as pre-diabetes, impaired glucose tolerance (IGT), impaired fasting glucose (IFG), or intermediate hyperglycaemia. Non-diabetic hyperglycaemia refers to an elevated blood glucose level that is below the diabetic range.[17 18] Various blood glucose thresholds have been proposed to indicate NDH status.[21 22] There is debate about the validity of this diagnosis, particularly in relation to whether NDH is a risk factor for T2DM and cardiovascular disease rather than a distinct clinical diagnosis,[23 2 24] Treatments for NDH are broadly the same as for T2DM, namely diet, exercise, and medication.[25] In England, there are 2 NHS programmes to detect people who are at high-risk of T2DM: NHS Health Check, and the NHS Diabetes Prevention Programme.

Current policy context and previous reviews

Type 2 diabetes is a major public health issue, and its prevalence is predicted to rise to nearly 4.5 million adults in England by 2035.[16] The current UK NSC recommendation is not to screen for T2DM. This is based on the most recent UK NSC review published in 2013.[1] At that time, the review authors concluded that key UK NSC criteria were not met because of a lack of RCT evidence that screening would be beneficial, and because of limitations in the current screening tests. It was recommended that a further review should be undertaken in 2017/2018.

Objectives

As part of its 3-year review cycle, the UK NSC needs to review the evidence on whether population screening for T2DM should be recommended in the UK. Because NDH can progress to diabetes and it is often an incidental finding of any screening for T2DM (regardless of the type of test and cut-off used), this review will attempt to shed more light on the association between NDH and T2DM and on the effectiveness of the interventions used to manage people with non-diabetic hyperglycaemia. The review examines 4 key questions regarding (1) the progression of non-diabetic hyperglycaemia to T2DM, (2) the accuracy of screening tests to predict future vascular events, (3) the effectiveness of lifestyle interventions for adults with non-diabetic hyperglycaemia, and (4) the effectiveness of screening for T2DM. The key questions for this review, the criteria they address, and the number of studies included per question are provided in Table 1.

Table 1. Key questions for the evidence summary, and relationship to UK NSC screening criteria

	Criterion	Key questions	Studies Included
	THE CONDITION		
1	The condition should be an important health problem as judged by its frequency and/or severity. The epidemiology, incidence, prevalence and natural history of the condition should be understood, including development from latent to declared disease and/or there should be robust evidence about the association between the risk or disease marker and serious or treatable disease.	Question 1. What proportion of people with untreated non-diabetic hyperglycaemia develop T2DM? Sub-questions: How long does the progression from non-diabetic hyperglycaemia to T2DM take? What are the risk factors associated with the progression from non-diabetic hyperglycaemia to T2DM?	N = 4[3-6]
	THE TEST		
4	There should be a simple, safe, precise and validated screening test.	What is the accuracy of HbA1c, the oral glucose tolerance test (OGTT), fasting plasma glucose (FPG), and the 50g glucose challenge test (50g GCT) as screening tools for microvascular	N = 17[26-42]

	Criterion	Key questions	Studies Included
		and macrovascular complications of T2DM?	
	THE INTERVENTION		
9	There should be an effective intervention for patients identified through screening, with evidence that intervention at a pre-symptomatic phase leads to better outcomes for the screened individual compared with usual care. Evidence relating to wider benefits of screening, for example those relating to family members, should be taken into account where available. However, where there is no prospect of benefit for the individual screened then the screening programme shouldn't be further considered.	What is the reported effectiveness of lifestyle interventions for people with non-diabetic hyperglycaemia?	N = 3[8-10]
	THE SCREENING PROGRAMME		
11	There should be evidence from high quality randomised controlled trials that the screening programme is effective in reducing mortality or morbidity. Where screening is aimed solely at providing information to allow the person being screened to make an "informed choice" (eg. Down's syndrome, cystic fibrosis carrier screening), there must be evidence from high quality trials that the test accurately measures risk. The information that is provided about the test and its outcome must be of value and readily understood by the individual being screened.	Have RCTs demonstrated the benefit of screening for T2DM?	N = 1[14]

Methods

The current review was conducted by the University of Warwick, using the UK National Screening Committee evidence review process. Database searches were conducted on 22 November 2018 (question 1), 20 December 2018 (question 2, FPG, 2-hour PG, HbA1c searches), 19 March 2019 (question 2, 50g GCT search), 29 November 2018 (question 3), and 7 December 2018 (question 4) to identify studies relevant to the questions detailed in Table 1. Questions 1, 3, and 4 have been subject to recent systematic reviews. These served as a baseline for the current reviews.[2 7 11] Therefore, the authors of this evidence summary used the search strategies employed in these prior systematic reviews and searched for literature published since their cut-off dates.

Eligibility for inclusion in the review

The following review process was followed:

1. For questions 1, 3, and 4 one reviewer screened the titles and abstracts of all records identified by the search against the inclusion/exclusion criteria. A random 20% were screened independently by a second reviewer. For question 2, 2 reviewers independently screened titles and abstracts. Any disagreements were resolved by discussion until a consensus was reached, or with the involvement of a third reviewer. Where there was insufficient information available in the title/abstract on which to decide, the article was retained.
2. Full-text articles required for the full-text review stage were acquired.
3. For questions 1, 3, and 4 each article was assessed against the inclusion/exclusion criteria by one reviewer. A second reviewer independently assessed a random 20% of the articles. For question 2, 2 reviewers independently assessed full texts against the inclusion/exclusion criteria. Any disagreements were resolved by discussion until a consensus was reached, or with the involvement of a third reviewer.
4. For question 2, data from figures were extracted using DigitizeIt (https://www.digitizeit.de/).

Eligibility criteria for each question are presented in **Error! Reference source not found.** below.

Table 2. Inclusion and exclusion criteria for the key questions

Key question	Inclusion criteria								Exclusion criteria
	Population	**Target condition**	**Intervention/Prognostic Factors**	**Reference Standard**	**Comparator**	**Outcome**	**Study type**	**Timing**	
1. What proportion of people with untreated non-diabetic hyperglycaemia develop T2DM?	Adults with NDH	T2DM	N/A	Fasting plasma glucose, 2-h plasma glucose, or HbA1c according to WHO or ADA criteria.	N/A	T2DM	Prospective cohort	At least one year	Study designs other than prospective cohort, people with comorbidities at baseline, missing data, follow up period not specified, T2DM evaluated by documents or self-report, inpatient populations, papers published before 2017, non-human studies, conference abstracts, letters, editorials, and

										communications and grey literature. Papers with no extractable data or written in non-English language.
2.	**What is the accuracy of HbA1c, oral glucose tolerance test (OGTT), fasting plasma glucose (FPG), 1-hour glucose challenge test (50g GCT) as screening tools for microvascular and macrovascular complications of T2DM?**	Adults with NDH	T2DM	OGTT (2hr only), FPG, HbA1c, 50g GCT (1hr, non-fasted only)	N/A	OGTT (2hr only), FPG, HbA1c, 50g GCT (1hr, non-fasted only)	Mortality, cardiovascular morbidity, chronic kidney disease, lower extremity amputations, foot ulcers, visual impairment, retinopathy, periodontitis, peripheral sensory neuropathy, health related quality of life, erectile dysfunction	Head-to-head test comparisons (any prospective or retrospective study design as long as 3 tests were compared in the same study population	N/A	Children, adolescents, pregnant women, any subpopulations (i.e. where a whole study population has a particular disease, syndrome, or condition), Type 1 diabetes, gestational diabetes, postprandial glucose tolerance test, 1-hour glucose tolerance test, random glucose test, non-human studies, letters, editorials, communications, conference abstracts, any

										other grey literature, case studies, papers with no extractable data, or written in non-English language.
3.	**What is the reported effectiveness of lifestyle interventions for people with nondiabetic hyperglycaemia?**	Adults with NDH	T2DM	Diet or physical activity or both (including studies with other non-pharmacological components where diet or physical activity are the main intervention)	N/A	Standard treatment, no intervention, or placebos	Prevention of progression to T2DM, reduction of the risk of cardiovascular disease, including lower blood pressure, lower cholesterol levels, lower BMI, reduced mortality	RCT	Trials with a minimum duration of intervention of 2 years	Study designs other than RCTs, intervention duration less than 2 years, studies where the intervention or comparator include pharmacotherapies, participants with 'metabolic syndrome', studies limited to single foods or supplements, studies with identical interventions delivered through different mediums (e.g. group vs individual exercise),

										studies of children, papers published before 2017 or in languages other than English.
4.	**Have RCTs demonstrated the benefit of screening for T2DM?**	Adults, not pregnant	T2DM	Any screening (targeted or universal) for T2DM	N/A	No screening or routine clinical diagnosis	Diabetes diagnosis, NDH diagnosis, reduction of blood glucose levels, reduction of the risk of cardiovascular disease, including decreased blood pressure, lower cholesterol levels and lower BMI, reduction of the risk of retinopathy	RCT	N/A	Study designs other than RCTs, studies focussing on children or pregnant women or individuals who have symptoms of T2DM, papers published before 2015. Non-human studies, conference abstracts, letters, editorials, and communications and grey literature. Papers with no extractable data or written in non-English language. Studies about

					general health checks.

Appraisal for quality/risk of bias tool

The following tools were used to assess the quality and risk of bias of each study included in the review:

- Question 1. Quality in Prognosis Studies (QUIPS) tool.[43]
- Question 2. Modified Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool.[44]
- Questions 3 and 4. Cochrane Collaboration's Risk of Bias Tool.[45]

For questions 1, 3, and 4 risk of bias was undertaken by one reviewer, with a random 20% checked by a second reviewer. For question 2, risk of bias was assessed independently by 2 reviewers. Disagreements were resolved by consensus or through discussion with a third reviewer.

Databases/sources searched

Separate searches were conducted for each review question. For question 1, a search was conducted for literature published after the most recent Cochrane review from 2017.[2] Searches were undertaken in MEDLINE, Embase, ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform Search Portal. For question 2, 2 searches were conducted. The first search was for articles about FPG, 2-hour PG, and HbA1c. These searches were conducted in Medline, Pre-Medline (Daily Update, EPub Ahead of Print, In-Process and Other Non-Indexed Citations), and Embase. The second search was for articles about the 50g GCT. This search was conducted in Medline, PreMedline, Embase, Web of Science, and the Cochrane Library. There were no date limits to either of the question 2 searches. For question 3, a search was conducted for literature published after the most recent Cochrane review from 2017.[7] Searches were undertaken in MEDLINE, Pre-Medline, Embase, the Cochrane library, the WHO International Clinical Trials Registry Platform Search Portal, and ClinicalTrials.gov for literature published from 2017. For question 4, a search was conducted for literature published after the most recent United States Preventative Services Task Force (USPSTF) review from 2015.[11] Searches were undertaken in Medline (OVID), Embase, PreMedline, and the Cochrane Library (Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials) for literature published from 2015. Reference lists of all included articles were screened. The search strategies are presented in Appendix 1.

Question level synthesis

Criterion 1 — What proportion of people with untreated non-diabetic hyperglycaemia develop T2DM?

The condition should be an important health problem as judged by its frequency and/or severity. The epidemiology, incidence, prevalence and natural history of the condition should be understood, including development from latent to declared disease and/or there should be robust evidence about the association between the risk or disease marker and serious or treatable disease.

Question 1 – What proportion of people with untreated non-diabetic hyperglycaemia develop T2DM?

Sub-questions: How long does the progression from non-diabetic hyperglycaemia to T2DM take?

What risk factors are associated with the progression from non-diabetic hyperglycaemia to T2DM?

These questions were not addressed in the last review for the UK NSC.[1] The most recent, high quality systematic review on the topic was a Cochrane review published in 2018.[2] The Cochrane group conducted searches up to December 2016 (updating Medline only in February 2018). They identified 103 prospective cohort studies (93 that evaluated progression from non-diabetic hyperglycaemia (NDH) to T2DM, and 52 that examined glycaemia status as a predictor of T2DM). The studies were conducted in Asia (n = 42), Europe (n = 29), North America (n = 12), Latin America (n = 7), Middle East (n = 7), Australia (n = 3), Africa (n = 1), and Pacific/Indian Ocean islands (n = 2). The studies included over 250,000 participants at baseline and followed people for between one and 24 years. Non-diabetic hyperglycaemia was diagnosed according to American Diabetes Association (ADA) or World Health Organisation (WHO) criteria, and T2DM was diagnosed on the basis of ADA or WHO criteria, use of antidiabetic medication, physician diagnosis or self-report. The authors reported an apparent increase in the incidence of T2DM with length of follow up. This occurred for all tests and all thresholds used to diagnose NDH. For example, when NDH was defined as impaired fasting glucose (FPG 6.1 mmol/L), T2DM incidence was 11% at 2-year follow up and 31% at 12-year follow up. When NDH was defined as impaired glucose tolerance (2-hour PG 7.8 – 11.1 mmol/L), T2DM incidence was 16% at 2-year follow up and 70% at 12-year follow up. There was an apparent decrease in the proportion of people who returned from NDH to normoglycaemia over time, e.g. 33–59% in studies that followed up participants for 1 to 5 years, 17–42% in studies that

followed up participants for 6 to 11 years. Glycaemia status was predictive of T2DM for all tests and thresholds compared to normoglycaemia, with hazard ratios ranging from 3.61 (95% CI, 2.31 to 5.64 – non-diabetic hyperglycaemia defined as IGT) to 10.10 (95% CI, 3.59 to 28.43 – non-diabetic hyperglycaemia defined as HbA1c at 6.0% (7.0 mmol/L) threshold). The current rapid review updates literature published after this review.

Eligibility for inclusion in the review

Articles were included in this question if they reported the results of prospective cohort studies comprised of people with NDH according to ADA or WHO criteria that were conducted over at least one year. The outcome of interest was new onset T2DM. Only papers in English were included. Papers were excluded: if they employed any study design other than prospective cohort, if the sample had comorbidities at baseline or was an inpatient population, if data on transition from NDH to T2DM were missing, if T2DM was evaluated by documents (e.g. hospital records) or self-reported, or if papers were published before 2017. Papers including non-human studies, conference abstracts, letters, editorials, communications and grey literature were also excluded.

Description of the evidence

Full details regarding the numbers of studies included and excluded at each stage of the review are provided in Appendix 2, Figure 9. A total of 2,273 unique records were identified. After screening titles and abstracts, 33 records were retained. Assessment of full texts against inclusion/exclusion criteria resulted in 4 papers (reporting on 2 studies: one Spanish,[3 4] one Korean[5 6]) included in the review (see Appendix 2, Table 29), and the identification of one potentially relevant ongoing trial (see Appendix 2, Table 30).[46] A list of excluded studies (with reasons) is given in Appendix 2, Table 32.

Discussion of findings

Characteristics of included studies

The 2 included studies (reported in 4 articles) are summarised in Appendix 3, Table 37. The articles reported on one study from Korea[5 6] and one study from Spain[3 4]. Final sample sizes ranged from 1,142[3] to 2,830[5]. Participants were followed up for 3[3 4] and 10 years.[5 6] Both studies employed ADA criteria to diagnose non-diabetic hyperglycaemia and T2DM. The method of assessing NDH varied between studies. The Spanish study defined non-

diabetic hyperglycaemia as fasting plasma glucose levels between 100–125 mg/dL (5.6–6.9 mmol/L) and/or HbA1c levels of 5.7–6.4% (6.5–7.6 mmol/L) in the prior 6 months,[3 4] the Korean study defined non-diabetic hyperglycaemia as 2-hour postload glucose levels (after 75g OGTT) between 140–199 mg/dL (7.8–11.1 mmol/L) or fasting plasma glucose levels between 100–125 mg/dL (5.6–6.9 mmol/L),[6] or as HbA1c levels of 5.7–6.4% (6.5–7.6 mmol/L).[5] In the Spanish cohort study, T2DM was defined as fasting plasma glucose ≥ 126 mg/dL (≥7.0 mmol/L) on 2 consecutive occasions, HbA1c ≥ 6.5% (≥ 7.8 mmol/L) on 2 consecutive occasions, or the 2 of them on a single occasion.[3 4] The Korean study defined T2DM as fasting glucose level ≥126 mg/dL (≥7.0 mmol/L), HbA1c ≥ 6.5% (≥ 7.8 mmol/L), 2h-plasma glucose (2-hour PG) level of OGTT ≥200 mg/dL (≥11.1 mmol/L) and history of diagnosed T2DM.[5 6] The primary outcome of interest in each study was new cases of T2DM.

Quality appraisal of included studies

Risk of bias (QUIPS)[43] of the included studies is summarised in Figure 1, with further details provided in Appendix 3, Table 41. None of the studies was at high risk of bias. Risk of bias was moderate in 3 domains for one cohort,[3 4] and in 4 domains in the other cohort.[5 6] No study was at low risk of bias in all domains. The key risks of bias were the reliability of data collection using questionnaires (prognostic factor measurement), and lack of published protocol which made it impossible to assess selective reporting of outcomes (statistical analysis and report).

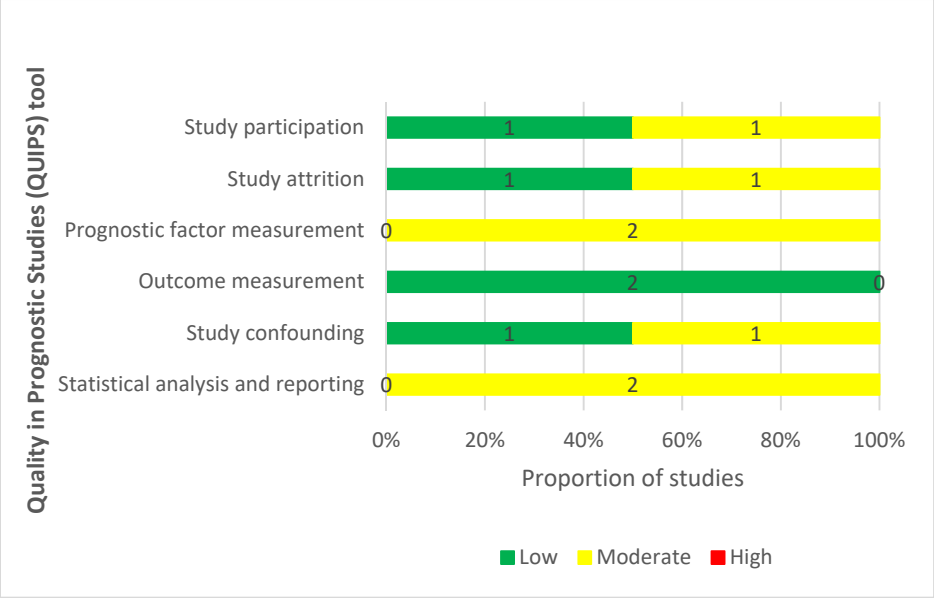


Figure 1. Risk of bias graph: review authors' judgements about each domain presented as percentages across included studies

Applicability of included studies

Applicability is not addressed within the QUIPS tool. Nevertheless, there is an applicability concern of the included studies as neither was carried out in the UK. A particular applicability concern is that the papers by Park and Jung were conducted in Korean participants.[5 6] There is some evidence that Asian populations might be at greater risk of diabetes than European populations, with various causes proposed (e.g. higher visceral and body fat content, younger age of onset, dysfunctional pancreatic insulin secretory function).[47] Non-diabetic hyperglycaemia is less common in Korea than the UK (25% of adults compared to 35.5% of adults), but that T2DM is more common in Korea (11.1% of adults compared to 5.32% of adults).[48-50]

Analysis of the evidence

Main question: What proportion of people with untreated nondiabetic hyperglycaemia develop T2DM?

Between the 2 studies, 4,014 adults with NDH were followed up and tested for T2DM. Using data from the larger analysis for each study (Korean study: Jung et al. n = 2,830,[5] Spanish study: Giraldez-Garcia et al. n = 1,184[4]), there were 881 (31%) new cases of T2DM in the Korean study (an incidence rate of 4.32 per 100 person-years),[5] and 143 (12%) new cases of T2DM in the Spanish study (an incidence rate of 4.25 per 100 person-years).[4]

The recent Cochrane systematic review indicated that, generally, over time there was an increase in the proportion of people with non-diabetic hyperglycaemia who developed T2DM, and a decrease in the proportion of people who regressed from NDH to normoglycaemia.[2] Though proportions were variable between studies that were conducted over different lengths of time. For example, the cumulative incidence of T2DM was 26% in studies that followed up participants for 5 years, 37% in studies that followed up participants for 6 years, and 15% in studies that followed up participants for 7 years. For regression from non-diabetic hyperglycaemia to normoglycaemia, the proportion of participants returning to normoglycaemia was 34% in studies that followed up participants for 5 years, 23% in studies that followed up participants for 6 years, and 41% in studies that followed up participants for 7 years.

Sub-question: How long does the progression from non-diabetic hyperglycaemia to T2DM take?

None of the included studies reported on the time taken for study participants to progress from NDH to T2DM. However, the 2 cohorts were followed up for different time periods. The Spanish cohort was followed for 3 years (12% progressed to T2DM)[4] and the Korean cohort was followed for 10 years (31% progressed to T2DM).[5]

The recent Cochrane systematic review indicated that the incidence of T2DM generally increased with the length of study follow up.[2] For example, when non-diabetic hyperglycaemia was defined as FPG of 5.6–6.0 mmol/L, the incidence of T2DM was 2% (studies with 2 years' follow up), 17% (studies with 3 years' follow up), 17% (studies with 4 years' follow up), 18% (studies with 5 years' follow up), 22% (studies with 6 years' follow up), 18% (studies with 7 years' follow up), 34% (studies with 8 years' follow up), 28% (studies with 9 years' years follow up), 23% (studies with 10 years' follow up) and 31% (studies with 12 years' follow up). When NDH was defined as 2-hour PG of 7.8–11.1 mmol/L, the incidence of T2DM was 13% (studies with 1 year follow up), 16% (studies with 2 years' follow up), 22% (studies with 3 years' follow up), 22% (studies with 4 years' follow up), 39% (studies with 5 years' follow up), 29% (studies with 6 years' follow up), 19% (studies with 7 years' follow up), 43% (studies with 8 years' follow up), 53% (studies with 9 years' follow up), 26% (studies with 10 years' follow up), 46% (studies with 11 years' follow up), 41% (studies with 11 years' follow up), and 60% (studies with 20 years' follow up). When NDH was defined as HbA1c of 6.0–6.4%, the incidence of T2DM were 7% (studies with 3 years' follow up), 44% (studies with 4 years' follow up), 38 (studies with 5 years' follow up), and 29% (studies with 15 years' follow up).

Sub-question: What are the risk factors associated with the progression from non-diabetic hyperglycaemia to T2DM?

A range of risk factors were reported. Park et al. examined the incidental risk of T2DM according to 2-hour PG level stratified by 3 categories within the non-diabetic hyperglycaemia range (140–159 mg/dL, 160–179 mg/dL, and 180–199 mg/dL).[6] Hazard ratios (HR) adjusted for age, sex, study area, hypertension, regular exercise, body mass index (BMI), smoking, total cholesterol, high-density lipoproteins (HDL) cholesterol, serum creatinine and alcohol intake, indicated that participants with NDH had a higher risk of T2DM than those with normal glucose tolerance: 2-hour PG level 140–159 mg/dL, HR 3.07 (95% CI, 2.67–3.54), 2-hour PG level 160–179 mg/dL, HR 5.44 (95% CI, 4.66–6.34), 2-hour PG level 180–199 mg/dL, HR 7.91 (95% CI, 6.53–9.59). An elevated risk of T2DM was also observed when data were stratified by participant sex and their degree of impaired fasting glucose. An association between 2-hour PG level and risk of T2DM would be expected, as the former is used to define T2DM.

In the same cohort, Jung et al. examined the risk of T2DM according to blood pressure, HbA1c levels, and insulin resistance.[5] Compared to those with normal blood pressure (see Park et al. above for adjustments), there was a statistically significant higher risk of developing T2DM amongst participants with either hypertension (HR 1.61, 95% CI 1.35–1.92), prehypertension (HR 1.32, 95% CI 1.10–1.59), systolic blood pressure levels ≥ 130 mmHg (HR 1.39, 95% CI 1.15–1.71) or diastolic blood pressure levels of at least 80 mmHg (HR 1.30, 95% CI 1.07–1.58). Individuals with higher HbA1c levels (6.0–6.4%) had a greater risk of T2DM than those with lower HbA1c levels (5.7–5.9%) (HR 2.30, 95% CI 2.01–2.64). All combinations of elevated blood pressure with either low or high HbA1c were associated with greater risk of T2DM. Finally, adjusted HR indicated that insulin resistance was associated with a higher risk of T2DM in combination with high HbA1c levels (see Appendix 3, Table 37).

Franch-Nadal et al. assessed the predictive value of a broad range of clinical and sociodemographic variables on T2DM in 1,142 adults with NDH.[3] Bivariate analysis of individual variables indicated a significantly higher risk of T2DM amongst people with a family history of diabetes (HR 1.58, 95% CI 1.13–2.21), a BMI ≥ 30 kg/m^2 (HR 1.80, 95% CI 1.29–2.51), an abdominal circumference of ≥ 88 cm (women)/≥ 102 cm (men) (HR 2.21, 95% CI 1.44–3.38), blood pressure ≥ 140/90 mmHg (HR 1.58, 95% CI 1.13–2.20), aspartate transaminase levels > 35 U/L (HR 2.18, 95% CI 1.39–3.41), alanine transaminase levels > 35 U/L (HR 1.93, 95% CI, 1.34–2.76), gamma glutamyl transpeptidase levels > 40 U/L (HR 1.66, 95% CI 1.18–2.35), the presence of metabolic syndrome (HR 3.02, 95% CI 2.14–4.26), and a fatty liver index (a combined measure of triglycerides, gamma glutamyl transpeptidase, waist circumference and BMI) of 30 or greater (HR 2.22, 95% CI 0.97–5.11). Lower risk of T2DM was reported for participants who consumed fruit daily (HR 0.57, 95% CI 0.40–0.81). Participants' age, sex, education level, smoking status, consumption of vegetables or breakfast, exercise, and cholesterol were not associated with risk of T2DM. Using Cox regression models adjusted for age, sex, educational level, family history of diabetes, lifestyles, hypertension, lipid profile and transaminases, fatty liver index ≥ 30 was associated with a greater risk of T2DM (HR 3.21, 95% CI 1.45–7.09).

In the same cohort, Giraldez-Garcia et al. examined the effect of age (dichotomised into 30–59, and 60–74 years) and adiposity (measured as BMI, waist circumference, and waist to hip ratio) on incident T2DM.[4] Hazard ratio (adjusted for a range of sociodemographic, lifestyle, and metabolic variables) indicated a significantly greater risk of T2DM in people with a larger waist circumference (men ≥ 102 cm, women ≥ 88cm) than those with a smaller waist circumference for those aged 30–59 years (HR 2.65, 95% CI 1.24–5.65) but not for those age 60–74 years, or for either age category based on BMI or waist to hip ratio (low vs high). Hazard ratios for a 1 SD increase (where standardised values were used rather than

the underlying values from the anthropometric measures) were significant for waist circumference (30–59 years: HR 1.89, 95% CI 1.38–2.60; 60-74 years: HR 1.44, 95% CI 1.11–1.87) and waist to hip ratio (30–59 years: HR 1.84, 95% CI 1.29–2.26; 60–74 years: HR 1.47, 95% CI 1.13–1.89), but not BMI.

The recent Cochrane systematic review did not investigate risk factors associated with the progression from non-diabetic hyperglycaemia to T2DM (except blood glucose level, discussed above).[2]

Summary of Findings Relevant to Criterion 1:

Natural history of NDH (association with T2DM only): **met**
Frequency, severity, epidemiology, incidence, prevalence: **not considered**

Main question: What proportion of people with untreated non-diabetic hyperglycaemia develop T2DM?
Cochrane systematic review: 93 studies were identified that examined the proportion of people with NDH who develop T2DM. The incidence of T2DM and regression from NDH to normoglycaemia varied over time and between studies. The evidence was generally at low risk of bias, but with uncertainty around study attrition (e.g. lack of information about participant drop out over time).

Current review: 2 studies, reported in 4 papers, were identified that examined the proportion of adults with NDH who develop T2DM.[3-6] They indicated that 12% of adults with NDH were diagnosed with T2DM at 3 year follow up, and 31% were diagnosed with T2DM at 10 year follow up. This evidence was at low-to-moderate risk of bias, with concerns regarding the applicability of the studies to a UK population.

Sub-question: How long does the progression from non-diabetic hyperglycaemia to T2DM take?
Cochrane systematic review: The Cochrane systematic review indicated that the cumulative incidence of T2DM generally increased over time.[2] For example, when NDH was defined as FPG of 5.6–6.0 mmol/L, the incidence of T2DM were 2% (2 years), 17% (3 years), 17% (4 years), 18% (5 years), 22% (6 years), 18% (7 years), 34% (8 years), 28% (9 years), 23% (10 years) and 31% (12 years). The proportion of people who regressed from NDH to normoglycaemia decreased over time, e.g. 33–59% of participants after 1 to 5 years follow up, 17–42% of participants after 6 to 11 years' follow up. The evidence was generally at low risk of bias, but with uncertainty around study attrition.

Current review: None of the 2 studies included in this update review reported on the period of time between NDH and development of T2DM, although the T2DM incidence rate was higher in the cohort with 10 year follow up (31%)[5 6] than the cohort with 3 year follow up.[3 4] This evidence was at low-to-moderate risk of bias.

Sub-question: What are the risk factors associated with the progression from non-diabetic hyperglycaemia to T2DM?
Cochrane systematic review: This review did not investigate risk factors associated with the progression from NDH to T2DM.

Current review: Data from 2 studies indicated that progression from NDH to T2DM is associated with higher levels of 2-hour PG and HbA1c, high blood pressure, greater adiposity, insulin resistance, a family history of T2DM, and a high fatty liver index.[3-6] These results come from studies with moderate risks of bias relating to prognostic factors.

In this review criterion 1 was partially assessed for the natural history of the incidental finding of NDH in terms of progression to T2DM, regression and risk factors. No other elements of the criterion were examined, and the criterion was not assessed at all for the target condition T2DM. There is a body of evidence, from this review and the Cochrane systematic review which suggests that people with NDH are at an increased risk of developing T2DM. However, a large proportion of people with NDH spontaneously regress to normoglycemia, and so are at risk of overdiagnosis. Whilst there is some evidence identifying risk factors which predict who may progress, the reviewers did not investigate the accuracy of combining these into risk prediction models to identify those with NDH who would progress and those who may regress.

Criterion 4 — Predicting vascular complications of diabetes

There should be a simple, safe, precise and validated screening test

Question 2 – What is the accuracy of HbA1c, oral glucose tolerance test (OGTT), fasting plasma glucose (FPG), and the 50-g Glucose Challenge Test (GCT) to detect current and predict future microvascular and macrovascular complications of diabetes?

This question was partially examined in the last review for the NSC.[1] Waugh and colleagues searched for literature on whether different screening tests identify groups at different cardiovascular risk. Results for OGTT, FPG, and HbA1c were mixed. For example, in a longitudinal study of 11,057 followed up for 14.1 years, HbA1c in the NDH range (6.0–6.4%, 7.0–7.6 mmol/L) at baseline was associated with an increased risk of heart failure (adjusted HR 1.40, 95% CI 1.09–1.79) compared to HbA1c in the non-diabetic range (5.0–5.4%, 5.4–6.0 mmol/L). For FPG, there was no significant difference in risk of heart failure in those whose baseline blood glucose levels that were in the non-diabetic (FPG 5.0–5.5 mmol/L) compared to NDH ranges (FPG 5.6-6.0 mmol/L, adjusted HR 1.00, 95% CI 0.84–1.20; FPG 6.1–6.9 mmol/L, adjusted HR 1.11, 95% CI 0.90–1.35).[51 52] In contrast, results from the Strong Heart Study, which followed 4,549 Native Americans for a median of 15 years, found that neither HbA1c nor FPG in the NDH range at baseline was significantly associated with subsequent cardiovascular morbidity (CVD). However, HbA1c in the diabetic range (≥6.5%, 7.8 mmol/L), but not FPG (≥ 7.0 mmol/L), was associated with an increased risk of CVD (adjusted HR 1.40, 95% CI 1.02–1.93). [53] Waugh and colleagues proposed that the 1-hour 50g glucose challenge test (50g GCT) carried out in non-fasted people may be a useful alternative to HbA1c, OGTT, and FPG.

While informative to the present review, the review by Waugh et al. is not directly comparable as it included the predictive value of FPG, 2-hour PG, and HbA1c for surrogate markers of disease (e.g. cardiovascular risk scores, carotid intima-media thickness) rather than disease outcomes, it examined the predictive value of tests for identifying T2DM, and it made comparisons between studies (i.e. different studies using different tests) which may limit the interpretability of the findings due to differences between study populations influencing results.

The current review builds on the work on Waugh and colleagues. Diabetes tests (HbA1c, 2-hour PG, FPG; the combined 2-hour PG and FPG tests are referred to as the Oral Glucose Tolerance Test) are a core part of the diagnosis of diabetes, and therefore there is no independent reference standard at the point of screening. While some have simply used OGTT as the reference standard,[54] the authors of this evidence summary consider this to be inappropriate as these tests might give misleading results.[55] Instead, it is important to

ascertain which screening test is most accurate at identifying people who would go on to have microvascular or macrovascular complications of T2DM, and in whom such complications could be prevented, and/or life extended. The proposed mechanism by which screening improves health outcomes is the early identification of people who are at high risk of adverse health outcomes, to initiate effective treatment to prevent such outcomes. The ideal test identifies those at greatest risk of adverse outcomes, and who will respond to treatment. In the absence of a definitive reference standard diagnosis (which would allow a classic comparative review of test accuracy, comparing the results of 2-hour PG, FPG and HbA1c with the true disease state), the aim of this review was to determine which of the tests (2-hour PG, FPG, HbA1c, or 1-hour 50g GCT) detects the most clinically significant disease. The primary analysis aimed to estimate pooled ability to predict the presence or development of diabetic complications according to test results.

Eligibility for inclusion in the review

Articles were included in this question if they reported the results of direct comparison studies that included (1) OGTT (75g 2-hour version only), fasting plasma glucose, and HbA1c in non-pregnant adults from the general population, or (2) the 50g (non-fasting 1 hour version only) and 2 of OGTT, FPG, or HbA1c in non-pregnant adults from the general population. The outcomes of interest were mortality, cardiovascular morbidity (CVD), chronic kidney disease, lower extremity amputations, skin foot ulcers, visual impairment, retinopathy, periodontitis (including tooth loss), peripheral sensory neuropathy, health related quality of life, and erectile dysfunction. Only papers in English were included. Papers were excluded if they included pregnant women, children or adolescents, or the whole study sample had a particular disease, syndrome, or condition. Papers including non-human studies, conference abstracts, letters, editorials, communications, grey literature, in languages other than English, or where complete data for all glycaemic markers could not be extracted for at least one relevant outcome were also excluded.

Description of the evidence

Full details of the number of studies included and excluded at each stage of the review are provided in Appendix 2, Figures 10 and 11.

FPG, 2-hour PG, HbA1c search

A total of 2,433 unique records were identified. After screening titles and abstracts, 180 records were retained. Assessment of full texts against the inclusion/exclusion criteria identified 17 relevant papers that were included in the review (see Appendix 2, Table 29). A list of excluded studies (with reasons) is given in Appendix 2, Table 33.

50g GCT search

A total of 2,257 unique records were identified. After screening titles and abstracts, 29 records were retained. Assessment of full texts against the inclusion/exclusion criteria resulted in 0 papers being included in the review. A list of excluded studies (with reasons) is given in Appendix 2, Table 34. Although no study was included for this part of the review, 3 studies that met all but 1 of the inclusion criteria (no comparator test) are briefly discussed after the 'analysis of evidence' section for FPG, 2-hour PG and HbA1c, as they were the closest match to the review question.[56-58]

Discussion of findings

Characteristics of included studies

FPG, 2-hour PG, HbA1c

Direct comparisons of the ability of HbA1c, 2-hour PG and FPG levels to detect current or predict future microvascular and macrovascular complications of diabetes and non-diabetic hyperglycaemia from 14 population-based studies were reported in 17 papers. A study-level summary of data extracted from each included publication is presented in Appendix 3, Table 38).

Two articles reported on sub-studies performed as part of the Australian AusDiab (Australian Diabetes, Obesity and Lifestyle) Study.[26 38] Two articles covered follow up analyses of the German KORA (Cooperative Health Research in the Augsburg Region) S4 study,[27 32] and 2 articles referred to sub-studies performed as part of the Japanese Hisayama study.[35 36] The remaining 11 articles reported on studies performed in China (3 studies),[39 41 42] USA (2 studies),[31 33] Finland (1 study),[28] Netherlands (1 study),[29] Egypt (1 study),[30] New Zealand (1 study),[34] Denmark (1 study),[37] and the UK (1 study).[40]

Nine cross-sectional examinations assessed the association between the 3 glycaemic markers and micro- and macrovascular complications present at the time of testing.[27 30 35-39 41 42] Seven longitudinal analyses assessed the prediction of mortality and other future complications by test result,[26 28 29 31 32 34 40] while the remaining study examined both current and future complications.[33]

Three cross-sectional analyses were performed between 1989 and 1998,[30 33 35] and five between 1999 and 2008.[27 36-39] The 2 most recent cross-sectional studies were performed in China in 2011-2012[41] and 2012-2013[42]. The baseline period for the 8 longitudinal analyses was between 1982 and 1998 in 4 studies,[28 33 29 31] and between 1999 and 2002 in 3 studies.[26 32 34] The most recent analysis comes from a London-based study (Whitehall II

study) with glycaemic markers measured between 2002-2004 or 2007-2009 and a median follow up time of 11.5 (IQR 8.9–12.1) years.[40] The follow up time in the remaining 7 longitudinal analyses was median 4 years,[34] mean 4.5 (range 1.4–8.3) years,[33] median 6 years,[26] median 7.2 years,[31] 8 years,[29] up to 10 years,[32] and mean 9.7 years.[28]

The future outcomes assessed were all-cause mortality,[26 29 32 34] CVD mortality,[26 29] CVD,[28 34 40] CVD or mortality,[40] coronary heart disease,[34] heart failure,[31] retinopathy,[33 34] nephropathy/(micro)albuminuria,[33 34] and neuropathy.[34] The assessed current complications comprised retinopathy,[30 33 35-38 41 42] nephropathy/(micro)albuminuria,[33 38 39] and neuropathy.[27]

The number of participants included in the analyses ranged from 516[28] to 31,148[34]. Four papers covered analyses including fewer than 1,000 participants,[27 28 33 37] 10 papers reported on analyses including between 1,000-3,200 participants,[29-32 35 36 38 39 41 42] while the remaining 3 papers referred to analyses including 5,427,[40] 10,026, [26] and 31,148 participants.[34]

Six studies excluded participants with known diabetes from the study, [26 31 33 34 39 40] 7 studies excluded participants with known diabetes from the relevant analyses,[27-29 37 38 42 59] 2 studies performed analyses with and without excluding people receiving hypoglycaemic medication,[30 41] while one study included people with known diabetes in the analyses.[35] The reporting in the remaining paper is unclear but the analyses seem to include people on hypoglycaemic medications.[36] Removing people with diagnosed diabetes introduces bias because diagnoses are more often made on the results of OGTT, so those with higher OGTT results may be systematically removed.

Quality appraisal of included studies

FPG, 2-hour PG, HbA1c

The methodological quality of the included studies assessed by a modified QUADAS-2 tool is summarised in Figure 2, Figure 3, and Table 42 (Appendix 3). These illustrate the risk of bias regarding the 4 assessed domains (patient selection, index tests, reference standard, and flow and timing). Concerns regarding the applicability of the included studies to the current screening review topic in terms of study participants, index test and reference standard were also assessed.

Risk of bias

A study was considered to be at low risk of bias regarding patient selection if a consecutive or random sample of patients was enrolled, a case-control design was avoided, and the study avoided inappropriate exclusions (e.g. people with existing diabetes, people with

lower or higher risk of diabetes). A study was considered to be at low risk of bias regarding the index test if the thresholds were pre-specified or the study reports quantiles results for consecutive thresholds without choosing only one.

The risk of bias regarding the reference standard was considered to be low if the assessment of complications was rigorous (use of a reliable and validated tool and by an independent assessor), reference standard results were interpreted without knowledge of the index test results, and if, for outcomes measured in the future, length of follow up was adequate to ensure that most complications were picked up.

In the fourth domain, relating to flow and timing, a study was considered to be at low risk of bias if: there was an appropriate interval (<1 month) between the index tests (within-person comparisons), there was an appropriate interval between the index tests and reference standard(s) (for studies measuring complications concurrent with testing), all participants received the same reference standard, and all participants (defined as ≥95%, with reasons for exclusion stated and not likely to introduce significant bias) were included in the analysis.

Risk of bias was high in all 17 included studies with 12 studies considered at high risk of bias in 2 or more domains,[26 27 30 31 33 34 36-38 40-42] and 5 studies in one domain.[28 29 32 35 39] Figure 2 shows that the study flow and timing domain and the patient selection domain presented the areas with the greatest risk of bias with 10 and 13 studies, respectively, being classified as high risk of bias.

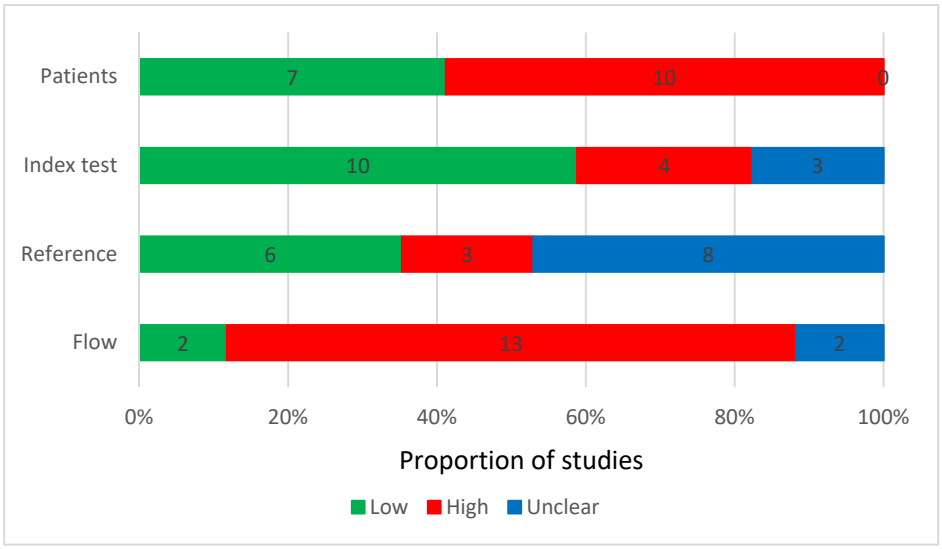


Figure 2. Number (%) of studies with low, high and unclear risk of bias (4 domains assessed)

Applicability of included studies to the UK screening setting

All 17 studies were judged to be of high concern regarding their potential generalisability to the UK screening setting (Figure 3) as the study participants were not from a comparable prevalence setting,[26-42] and/or symptomatic or known diabetes cases were included in all[35] or some [30 41] of the analyses and/or a selected group of the general population (e.g. occupational cohort) was used. [39 40]

Applicability concerns regarding the used index tests were high in 6 studies as one or more of the index tests were not performed according to the review's pre-defined criteria (e.g. samples were frozen and stored) [26 28 33] or the used cut-off was not reported or not all quantile thresholds were reported (e.g. missing 'tails').[27 37 38] The applicability of the remaining 11 studies could not be determined (unclear) due to missing information on: how the index tests were applied, whether patients were classified on the basis of a single test (no re-testing, to reflect the use of these tests for screening as opposed to diagnosis), or whether the test interpretation was carried out by an experienced examiner. [29-32 34-36 39-42] No study was rated at low risk of bias regarding the index tests.

Applicability concerns regarding the used reference standard(s) were rated as low in 5/17 studies. [26 30 39 41 42] Applicability concerns were classed as high in 3 studies as the target condition as defined by the reference standard did not match the review's definition. [27 33 37] The majority of studies (n = 9) did not report the experience of the individual rating the presence of complications (outcome assessor), and so were classified as unclear.[26-35]

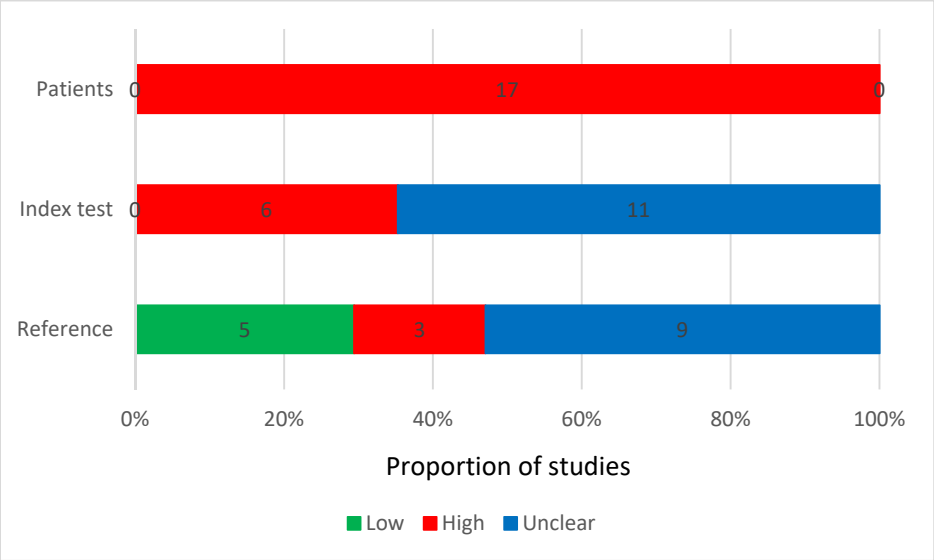


Figure 3. Number (%) of studies with low, high and unclear applicability concerns (3 domains assessed)

Analysis of the evidence

Studies followed 2 approaches to correlate the prevalence of diabetes–related complications with test result, either reporting a complication's prevalence for the presence and absence of T2DM or non-diabetic hyperglycaemia as determined by the WHO and/or ADA diagnostic thresholds, or more commonly by retrospectively dividing study participants into percentile groups according test measurement values, and reporting the prevalence of complications in each group.

FPG, 2-hour PG, HbA1c

Meta-analysis was not possible due to heterogeneity in study characteristics, especially in terms of the blood glucose thresholds that were reported. Therefore, a narrative synthesis of results is provided.

Mortality

All-cause mortality (future)

All-cause mortality was examined in 4 studies.[26 29 32 34] Each study reported rates by different thresholds of blood glucose. Data for the 3 studies that reported mortality percentages (or where these could be calculated) by thresholds are presented in figures 4, 5, and 6.[26 29 32] In 2 of the studies, as blood glucose levels increased so too did the rate of all-cause mortality.[26 29] This pattern was evident for all 3 index tests. However, this was not observed in the third study in which all-cause mortality rates were broadly consistent between glucose thresholds.[34] Overall, all-cause mortality rates were highest in the longest study (8 years)[29] and lowest in the shortest study (4 years)[34]. In the fourth study, crude mortality rates per 1,000 person years were highest in the uppermost category of blood glucose (per 1,000 person years: FPG = 23.22, 2-hour PG = 30.80, HbA1c = 21.39), with no consistent pattern in mortality rates in the first 5 categories of blood glucose.[32]

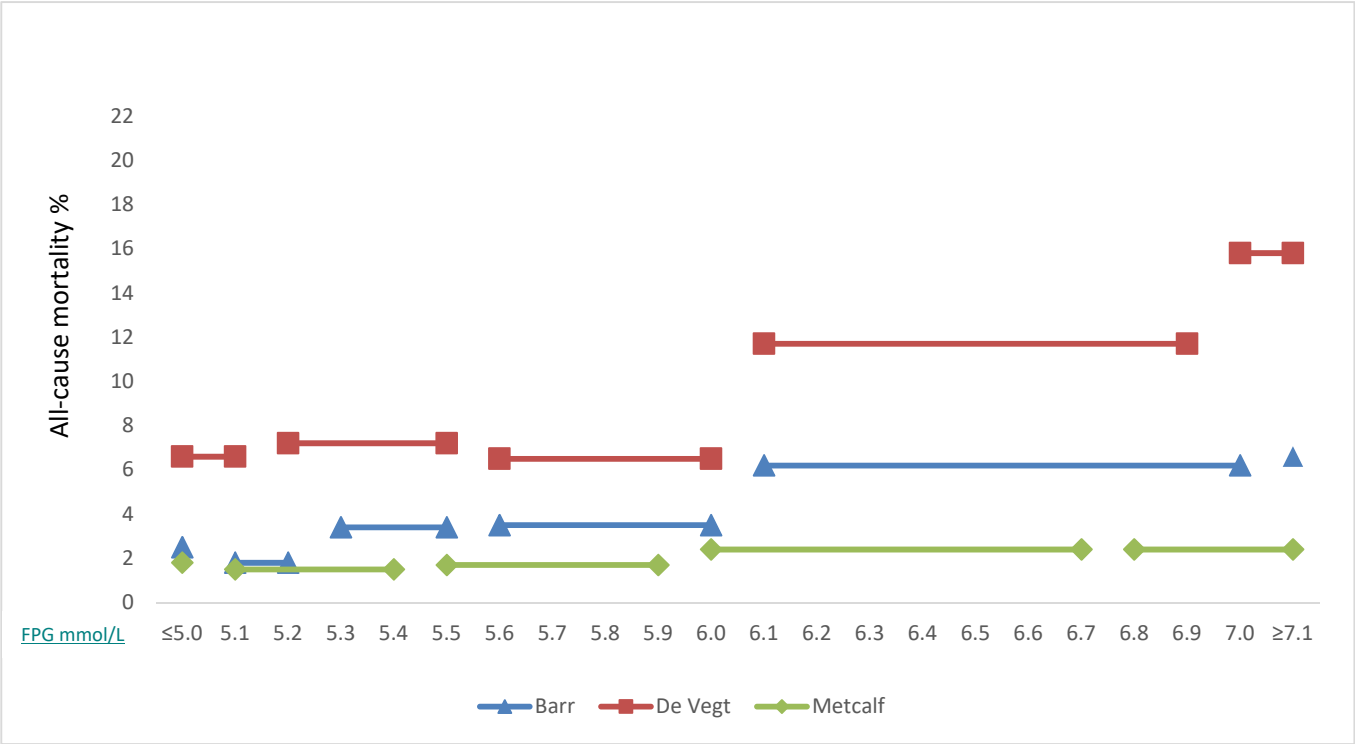


Figure 4. All-cause mortality by FPG

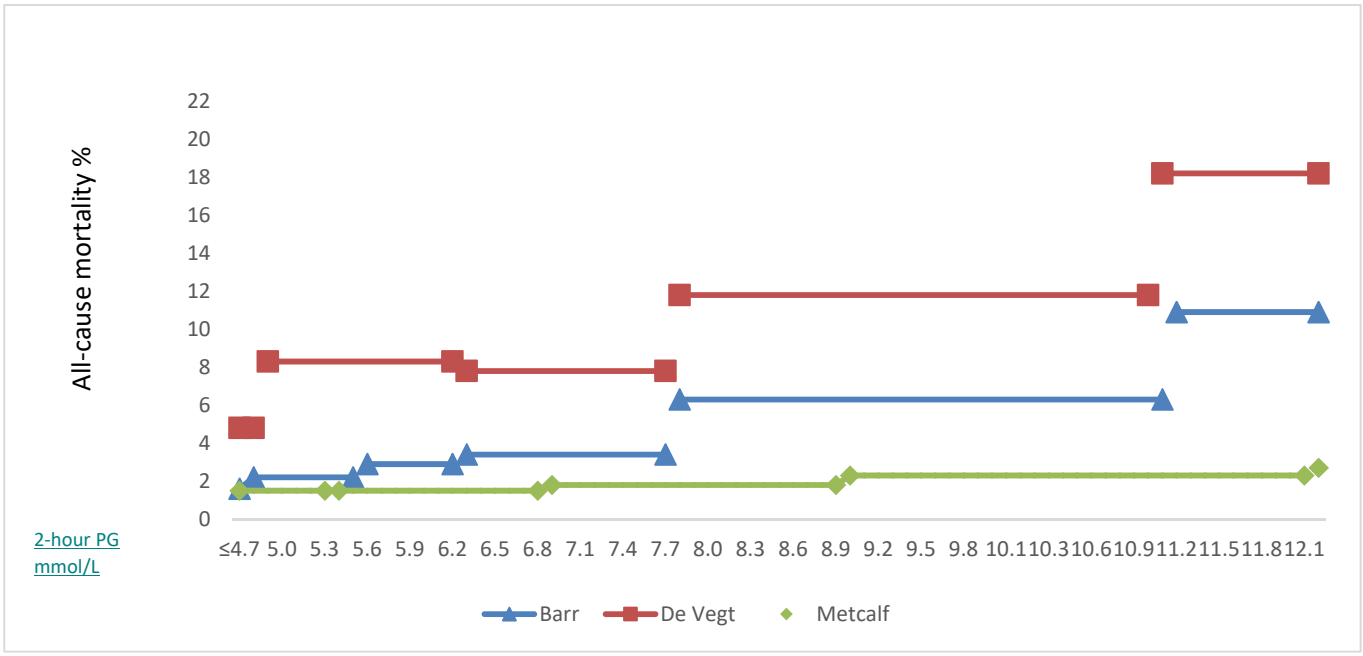


Figure 5. All-cause mortality by 2-hour PG

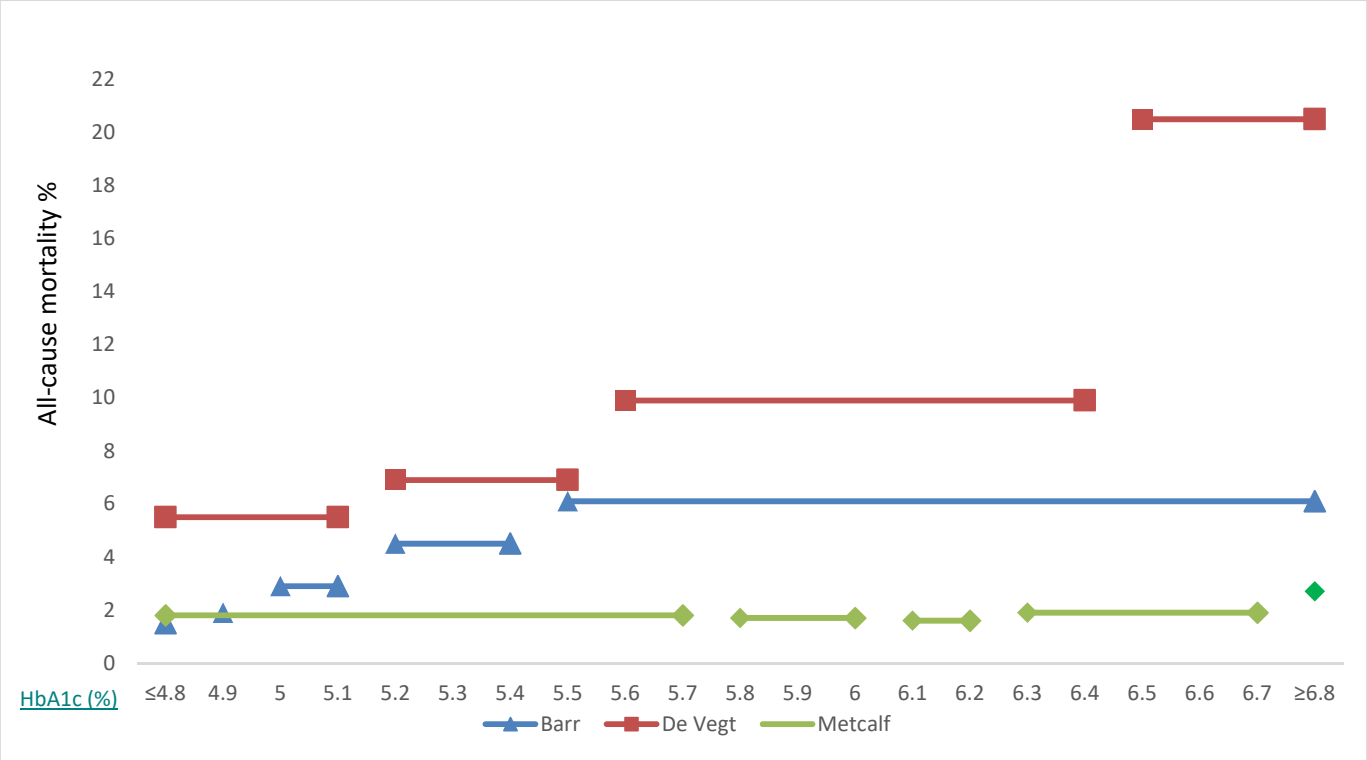


Figure 6. All-cause mortality by HbA1c

Cardiovascular mortality (future)

Cardiovascular mortality was examined in 2 studies, with each study reporting rates according to different thresholds of blood glucose.[26 29] The studies showed a trend towards increasing CVD-mortality with increasing blood glucose, followed by a steeper increase in the uppermost category (which typically reflected the T2DM range according to WHO criteria[60]). Overall rates of CVD-mortality were higher in the longer de Vegt et study[29] (8 years' follow up) than the study by Barr et al.[26] (6.2 years' follow up).

Mortality OR cardiovascular event (future)

These outcomes were examined in one study.[40] The unadjusted risk of a CVD event or mortality was greater for individuals in the NDH range compared to the normoglycaemia range for all 3 tests according to WHO/International Expert Committee (IEC) thresholds: FPG RR 1.27 (95% CI 1.01–1.60), 2-hour PG RR 1.44 (95% CI 1.19–1.75), and HbA1c (RR 1.99 (95% 1.55–2.53). Using ADA criteria, participants in the NDH range were at greater risk of a CVD event or mortality than those in the normoglycaemia range according to 2-hour PG (RR 1.44, 95% CI 1.19–1.75) and HbA1c (RR 1.89, 95% CI 1.62–2.22) thresholds, but not according to the FPG threshold (RR 1.08, 95% CI 0.94–1.25).

Test accuracy metrics for the 10-year risk of mortality or cardiovascular events indicated that sensitivity was higher when using ADA criteria than WHO criteria for both FPG (ADA: 29% [95% CI 26–33%] vs WHO: 10%, [95% CI 7–12%]) and HbA1c (ADA: 27% [95% CI 23–30%] vs WHO: 10% [95% CI 7–12%]). Specificity was higher when using WHO/IEC criteria than ADA criteria for both FPG (ADA: 74% [95% CI 73–75%] vs IEC: 93% [95% CI 92–94%]) and HbA1c (ADA: 84% [95% CI 83–85%] vs IEC: 95% [95% CI 95–96%]). There were no differences in positive (ADA: 13–22%; WHO: 15–22%) or negative (ADA: 88–89%; WHO: 88–89%) predictive values between ADA and WHO/IEC criteria. ADA and WHO criteria for NDH based on 2-hour PG levels are identical so no differences in test accuracy can be observed (sensitivity 20% [95% CI 16–23%], specificity 86% [95% CI 85–87%], PPV 15% [95% CI 12–18%], and NPV 90% [95% CI 89–91%].

Cardiovascular disease (future)

The occurrence of future cardiovascular disease (CVD) was examined in 3 studies, according to WHO/ADA equivalent criteria for T2DM, NDH and normoglycaemia, [28] WHO/IEC/ADA criteria for NDH and normoglycaemia,[40] and quintiles.[34] The results were inconsistent. Vistisen et al. reported increased risk of CVD amongst those with NDH compared to those in the normoglycaemia range,[40] while Cederberg et al. found an increased risk of CVD amongst women with NDH (2-hour PG only) or T2DM (2-hour PG, HbA1c) compared to those in the normoglycaemia range, but no difference in risk for men using any of the tests. [28] No consistent pattern of CVD by threshold was observed in the final paper.[34]

Coronary heart disease (future)

Incident coronary heart disease was examined in one study, with FPG, 2-hour PG, and HbA1c results divided into quintiles.[34] There was no consistent pattern between levels of blood glucose and rates of cornonary heart disease, and the proportion of people with cornonary heart disease by quintiles was similar between the 3 tests.

Retinopathy (current)

Current retinopathy was examined in 7 studies.[30 35-38 41 42] In the cross-sectional analyses by Engelgau et al., the Hisayama study (Miyazaki et al., reporting data from 1998 and Mukai et al. reporting data from 2007/2008), Xin et al., and Zhang et al. the diagnostic performance of FPG, 2-hour PG, and HbA1c for detecting current retinopathy were compared using the area under the receiver operator characteristic curve.[30 35 36 41 42] A summary of area under the curve (AUC) metrics is provided in Table 3. The AUC was 72.5–94.5% for HbA1c, 68.7–96.6% for 2-hour PG, and 76–90.8% for FPG. In all but one case,

there were no significant differences between the AUC of the 3 tests. The exception being the study by Engelgau et al in which the AUC for HbA1c was significantly smaller than for both FPG and 2-hour PG ($p < 0.01$).[30] In all cases, the thresholds were derived retrospectively by examining retinopathy rates and selecting the threshold that would have identified the highest proportion of people with and without retinopathy. Therefore, the estimates of accuracy are likely to overestimate accuracy outside the study.

Table 3. Discriminative ability of HbA1c, 2-hour plasma glucose, and fasting plasma glucose for detecting diabetic retinopathy (area under the curve)

	AUC		
Study	**HbA1c**	**2-hour PG**	**FPG**
Engelgau	Cut-off: 6.7% 82% (CI not reported) Sensitivity: 60% Specificity: 99.6%	Cut-off: 11.5 mmol/L 86% (CI not reported) Sensitivity: 90% Specificity: 99.5%	Cut-off: 7.2 mmol/L 85% (CI not reported) Sensitivity: 84% Specificity: 99.7%
Miyazaki	Cut-off: 5.7% 94.5% (95% CI 91.6 – 97.5) Sensitivity: 86.5% Specificity: 90.1%	Cut-off: 11.1 mmol/L 96.1% (95% CI 94.4 – 97.7) Sensitivity: 86.5% Specificity: 89.6%	Cut-off: 6.4 mmol/L 90.0% (95% CI 83.8 – 96.7) Sensitivity: 86.5% Specificity: 87.3%
Mukai	Cut-off: 6.1% 91.9% (95% CI 0.88 - 0.96) Sensitivity: 86.5% Specificity: 88.8%	Cut-off: 11.5 mmol/L 94.7% (95% CI 0.92 - 0.97 Sensitivity: 90.4% Specificity: 89.3%	Cut-off: 6.5 mmol/L 90.8% (95% CI 0.87 - 0.95) Sensitivity: 82.7% Specificity: 86.6%
Munch	Not reported	Not reported	Not reported
Tapp	Not reported	Not reported	Not reported
Xin (including people taking antihyperglycemics)	Cut-off: 6.8% 86.4% (95% CI 80.8 – 92.0) Sensitivity: 85.1% Specificity: 88.0%	Cut-off: 15.0 mmol/L 86.9% (95% CI 82.2 – 91.7) Sensitivity: 74.3% Specificity: 90.6%	Cut-off: 7.8 mmol/L 85.4% (95% CI 80.0 – 90.7) Sensitivity: 75.7% Specificity: 87.9%
Xin (excluding people taking antihyperglycemics)	Cut-off: 6.9% 72.5% (95% CI 59.7 – 85.2) Sensitivity: 60.7% Specificity: 93.6%	Cut-off: 10.6 mmol/L 77.6% (95% CI 67.0 – 88.1) Sensitivity: 60.7% Specificity: 86.7%	Cut-off: 6.7 mmol/L 76.8% (95% CI 65.8 – 87.8) Sensitivity: 67.8% Specificity: 80.1%

Zhang	Cut-off: 5.9% 72.7% (95% CI 58.6 86.9) Sensitivity: 77.5% Specificity: 78.4%	Cut-off: not reported 68.7% (95% CI 54.1 - 83.4) Sensitivity: not reported Specificity: not reported	Cut-off: 6.5 mmol/L 76% (95% CI 63.6 - 88.4) Sensitivity: 75.0% Specificity: 85.8%

In the remaining 2 studies, glucose results were divided in deciles[38] and 4 categories: one NDH category and 3 levels of normoglycaemia.[37] In the study by Tapp et al, the highest prevalence of retinopathy for each of the 3 measures of glucose occurred in the top decile: FPG 9.0%, 2-hour PG 10.9%, HbA1c 11.0%. Below this, no clear and consistent pattern of variation was observed.[38] While Munch et al. found little variation in the prevalence of retinopathy by glycaemic markers when measured concurrently.[37]

Retinopathy (future)

Future retinopathy was examined in 2 studies.[33 34] In the study by McCance et al., cut-offs were obtained by plotting frequency distributions of the 3 tests. This identified bimodal distributions. Cut-offs were selected as the test values that divided the distributions with the least overlap (FPG cut-off ≥9.3 mmol/L; 2-hour PG cut-off: ≥12.6 mmol/L; HbA1c cut-off: ≥7.8%, ≥ 9.8 mmol/L). Sensitivity was higher for 2-hour PG (100%, 95% CI 85.0–100%) than FPG (62.1%, 95% CI 42.4–78.7%) and HbA1c (67.9%, 95% CI 47.6–83.4%). Specificity was lower for 2-hour PG (85.5%, 95% CI 83.0–87.7%) than FPG (90.3%, 95% CI 88.1–92.1%) and HbA1c (92.7%, 95% CI 90.7–94.2%). NPV was higher for 2-hour PG (100.0%, 95% CI 99.4–100.0%) than FPG (98.7%, 95% CI 97.5–99.3%). There were no differences in PPV between the 3 tests. In the study by Metcalf et al, FPG, 2-hour PG, and HbA1c results were divided into quintiles.[34] The rates of retinopathy were similar between the 3 tests and, in general, increased in line with increases in blood glucose levels, from 0.2–0.7 in the lowest quintiles to 4.9–5.5% in the highest quintiles.

Nephropathy (current)

Current nephropathy was examined in 3 studies. [33 38 39] In the study by Toulis and colleagues, FPG, 2-hour PG, and HbA1c were significantly associated with albuminuria: FPG OR 1.23 (95% CI 1.08–1.40), 2-hour PG OR 1.26 (95% CI 1.10–1.44), HbA1c OR 1.23 (95% CI 1.08–1.40).[39] In both the paper by Toulis and the paper by Tapp (excluding people who were currently taking medication for diabetes), there were gradual increases in the prevalence of micro/macroalbuminuria with increasing level of HbA1c, followed by more sudden increases for the top 2 category of HbA1c.[38 39] There were less consistents patterns for 2-hour PG and FPG, in which the prevalence of micro/macroalbuminuria sometimes increased and sometimes decreased with increasing glucose levels. Nevertheless, the

prevalence of micro/macroalbuminuria was highest for the highest categories of glucose. In the study by McCance, test accuracy metrics (calculated by the reviewers) for measures of blood glucose (cut-offs as future retinopathy, above) for the detection of current nephropathy indicated that specificity was higher for HbA1c (86.6%, 95% CI 84.2-88.8%) and FPG (86.6%, 95% CI 84.2-88.8%) than for 2-hour PG (78.6%, 95% CI 75.8-81.2%).[33] There were no significant differences in sensitivity, PPV, or NPV between the 3 tests.

Nephropathy (future)

Future nephropathy was examined in 2 studies.[33 34] In the study by Metcalf et al, FPG, 2-hour PG, and HbA1c results were divided into quintiles. [34] The rates of nephropathy were similar between the 3 tests and, in general, increased in line with increases in blood glucose levels, from 0.3–0.6 in the lowest quintiles to 3.8–3.9% in the highest quintiles. In the study by McCance, test accuracy metrics (calculated by the reviewers) for measures of blood glucose (cut-offs as in future retinopathy, above) for the detection of future nephropathy indicated that specificity was higher for HbA1c (89.9%, 95% CI 87.8–91.8%) and FPG (87.9%, 95% CI 85.6–89.9%) than 2-hour PG (82.0%, 95% CI 79.3–84.4%).[33] There were no differences in sensitivity, PPV, or NPV between the 3 tests.

Neuropathy (current)

Current neuropathy was examined in one study, with FPG, 2-hour PG and HbA1c results divided into quartiles.[27] There was no consistent pattern of neuropathy by blood glucose levels for the 3 tests. However, neuropathy was more common in the highest quartile (19.6%) compared to other quartiles (10.2–14.1%) for HbA1c, and more common in the top 2 quartiles (15.5–15.9%) than the 2 lowest quartiles (7.1–11.3%) for FPG and 2-hour PG.

Neuropathy (future)

Future neuropathy was examined as an outcome in one study, with FPG, 2-hour PG, and HbA1c divided into quintiles.[34] In general, rates of neuropathy increased with increasing levels of blood glucose, from 0.1% in the lowest quintile to 0.8–1.0% in the highest quintile. Rates of neuropathy by quintiles were similar between the 3 tests.

<u>50g GCT</u>

No study compared the results of the 1-hour 50g GCT with FPG, 2-hour PG, or HbA1c results. Three studies examined associations between baseline blood glucose (as measured by the 1-hour 50g GCT in non-fasting individuals) and future complications of diabetes.[56-58] All 3 studies used data from the Chicago Heart Association Detection Project

in Industry, which screened men and women from 84 Chicago businesses and organisations between 1967 and 1973 to examine risk factors for CVD and mortality.[63] Lowe et al. included 12,220 men, Levine et al. included 20,112 men and women, and Gapstur et al. included 20,433 men. All 3 studies examined the association between baseline blood glucose levels and future mortality.

Mortality

Cardiovascular mortality (future)

Lowe and colleagues divided 50g GCT results into 3 categories: ≥11.1 mmol/L (diabetic range according to criteria from the Chicago Heart Association Detection Project in Industry study[63]), 8.9–11.0 mmol/L (top 25% of the non-diabetic, non-asymptomatic hyperglycaemic distribution of glucose in white men and the top 15% in black men), and ≤ 8.8mmol/L.[56] After an average of 22 years' follow up, unadjusted CVD mortality rates were 9.8% (n = 778/7,975, ≤8.9 mmol/L), 13.3% (n = 326/2,449, 8.9–11.0 mmol/L), and 17.9% (n = 241/1,343, ≥11.1 mmol/L).

Cancer mortality (future)

Levine and colleagues divided 50g GCT results into 6 categories of mg/dl (approximate mmol/L to 2 decimal places calculated by reviewers): <105 mg/dl (<5.83 mmol/L), 105–129 mg/dl (5.83–7.16 mmol/L), 130–154 mg/dl (7.21 = 8.55 mmol/L), 155–179 mg/dl (8.60–9.93), 180–204 mg/dl (9.99–11.32 mmol/L) ≥ 205 mg/dl (≥ 11.38 mmol/L). No rationale was provided for these cut-offs.[58] After an average of 12 years' follow up, unadjusted cancer mortality rates were 2.0% (n = 70/3,535, <105 mg/dl), 1.9% (100/5,274, 105–129 mg/dl), 2.6% (n = 114/4,422, 130–154 mg/dl), 2.3% (n = 70/3,077, 155–179 mg/dl), 2.9% (n = 56/1,914, 180–204 mg/dl), and 3.9% (n = 74/1,890, ≥ 205 mg/dl).

Prostate cancer mortality (future)

Gapstur and colleagues divided 50g GCT results into 4 categories: ≥11.1 mmol/L (diabetic range[63]) , 8.9–11.0 mmol/L (1 standard deviation (2.2 mmol/L) lower than the diabetic cut-off), 6.7–8.8 mmol/L (2 standard deviations (4.4 mmol/L) lower than the diabetic cut-off), and ≤ 6.6 mmol/L. [64]After an average of 27 years' follow up, unadjusted prostate cancer mortality rates were 0.4% (n = 39/8835, ≤ 6.6 mmol/L), 1.1% (n = 75/6,823, 6.7–8.8 mmol/L), 1.2% (38/3,173, 8.9–11.0 mmol/L), and 1.5% (24/1,602, ≥11.1 mmol/L).

Summary of Findings Relevant to Criterion 4:

Comparative validity of HBa1c, FPG and OGTT: **Not met** (no clear evidence of superior test accuracy of one test over others)
Overall validity: **not considered**
Simplicity, safety, precision: **not considered**

No studies were found that examined the predictive value of 50g GCT compared to FPG, 2-hour PG, or HbA1c. Seventeen studies examined the predictive values of FPG, 2-hour PG, and HbA1c on mortality or micro- and macrovascular complications associated with T2DM. The papers examined mortality (all-cause, cardiovascular), cardiovascular disease (including coronary heart disease), retinopathy, nephropathy, and neuropathy. The most frequently investigated outcomes were retinopathy (9 studies), mortality (6 studies), and nephropathy (4 studies).

In the majority of studies (3/4) there was evidence from longitudinal studies that higher mortality rates were associated with higher baseline blood glucose. The AUC was 72.5–94.5% for HbA1c, 68.7–96.6% for 2-hour PG, and 76–90.8% for FPG. In both cross-sectional (n = 2) and longitudinal studies (n = 3), rates of CVD increased with increasing levels of blood glucose. For retinopathy, cross-sectional (n = 5) and longitudinal studies (n = 2) indicated that all 3 tests were good predictors of retinopathy (albeit using different thresholds of blood glucose). There was consistent evidence from cross-sectional (n = 3) and longitudinal studies (n = 2) that the prevalence of nephropathy was highest amongst those with higher blood glucose levels (particularly in the T2DM range). The evidence about the predictive value of the 3 glycaemic markers and neuropathy was mixed. There was no clear evidence that any one tests (FPG, 2-hour PG, or HbA1c) was better at predicting any of the included complication of T2DM.

The evidence in this review is based on studies that are all at high risk of bias. The majority of studies (12/17) had applicability concerns that limit the generalisability of results to the UK screening setting. Only 1 study was conducted in the UK.[40] This was conducted in a sample of people who would not be representative of the target screening population (35–55 year old British civil servants, with baseline data collected from 2002–2004).

In this review, the simplicity, safety or precision of the tests (NSC criterion 4) were not addressed, nor was the overall validity of each test (only which of the tests was superior). The reviewers found evidence that FPG, 2-hour PG, and HbA1c were predictive of mortality, and micro- and macrovascular complications of T2DM, such as retinopathy and

nephropathy. The reviewers did not find clear evidence that any single test (FPG, 2-hour PG, or HbA1c) was better at predicting complications of T2DM. While all 3 tests appear to be suitable candidates for use in a screening programme, further work is required to (1) identify which tests is most appropriate, (2) identify a suitable cut-off for detecting future complications of T2DM, (3) examine the other elements of the NSC criterion that were not assessed in this review (simplicity, safety, and precision), and (4) explore the acceptability of each tests to a screening population.

Criterion 9 — Effectiveness of lifestyle interventions for treating people who have non-diabetic hyperglycaemia

There should be an effective intervention for patients identified through screening, with evidence that intervention at a pre-symptomatic phase leads to better outcomes for the screened individual compared with usual care. Evidence relating to wider benefits of screening, for example those relating to family members, should be taken into account where available. However, where there is no prospect of benefit for the individual screened then the screening programme should not be further considered.

Question 3 – What is the reported effectiveness of lifestyle interventions for people with non-diabetic hyperglycaemia?

This question was not addressed in the last review for the UK NSC.[1] The most recent, high quality systematic review on the topic was a Cochrane review published in 2017.[7] The Cochrane group conducted searches up to January 2017 (updating Medline until September 2017). They identified 12 RCTs. The studies were conducted in Europe (n = 6), Asia (n = 4), and North America (n = 2), included 5,238 people in total, and had intervention durations of 2 to 6 years. Non-diabetic hyperglycaemia and T2DM were typically diagnosed according to ADA or WHO criteria, use of antidiabetic medication, or physician-reported T2DM (n = 10). A small number of studies employed their own criteria (n = 2). Eleven RCTs compared diet plus physical activity against standard treatment or no treatment, and one RCT compared diet only, physical activity only, diet plus physical activity, and standard treatment. The results indicated that participants in the diet plus physical activity groups had a decreased risk of T2DM compared to those receiving standard care (T2DM incidence: 14.8% versus 25.7% respectively), RR 0.57 (95% CI, 0.50–0.64). There were no significant differences in risk for any of the other outcomes examined (mortality, cardiovascular mortality, non-fatal heart attack/stroke, and health-related quality of life). However, length of follow up might have been too short for some of these outcomes (study follow up ranged from 4 to 23 years).

Eligibility for inclusion in the review

Articles were included in this question if they reported the results of RCTs comparing dietary, physical activity, or combined dietary and physical activity interventions (including studies with other non-pharmacological components where diet or physical activity were the main intervention) against standard treatment, no intervention, or placebos. For inclusion, the minimum duration of intervention was 2 years. Participants must have been diagnosed as having NDH (or any other variant of this term) according to ADA or WHO criteria. The outcomes of interest were: prevention of progression to T2DM, reduction of the risk of

cardiovascular disease, including lower blood pressure, total cholesterol, low-density lipoprotein cholesterol (LDL-chol) or triglyceride levels, increased high-density lipoprotein cholesterol (HDL-chol) levels, lower BMI, reduced mortality. Only papers in English were included. Papers were excluded if they employed study designs other than RCTs, RCTs with an intervention duration of less than 2 years, studies where the intervention or comparator included pharmacotherapies, participants with 'metabolic syndrome', studies limited to single foods or supplements, studies with identical interventions delivered through different mediums (e.g. group vs individual exercise), studies of children, or papers published before 2017, written in non-English language. Papers including non-human studies, conference abstracts, letters, editorials, communications and grey literature were also excluded.

Description of the evidence

Full details regarding the numbers of studies included and excluded at each stage of the review are provided in Appendix 2, Figure 12. A total of 3,270 unique records were identified. After screening titles and abstracts, 21 records were retained. Assessment of full texts against inclusion/exclusion criteria resulted in 3 papers (reporting on 2 trials: one American,[8 9] one Iranian[10]) included in the review (see Appendix 2, Table 29), and the identification of 6 potentially relevant ongoing trials (see Appendix 2, Table 31).[65-70] A list of excluded studies (with reasons) is given in Appendix 2, Table 35.

Discussion of findings

Characteristics of included studies

The included studies are summarised in Appendix 3, Table 39. The 3 articles reported on 2 studies, one from America and one from Iran. Results from the American trial used data from the National Institute of Diabetes and Digestive and Kidney Diseases – Diabetes Prevention Programme (DPP), and was reported in 2 papers.[8 9] One paper analysed data only from participants who were adherent to the treatments,[8] the other paper reported analyses on the basis of both adherence data and intention-to-treat.[9] Results from the Iranian trial were reported in a single paper.[10] The duration of intervention and follow up ranged from 2 years[10] to 3.2 years[8]. Sample sizes ranged from 322[10] to 2,203 (1,988 for adherence only analysis)[9]. The American study compared (1) an intensive lifestyle (diet and physical activity) intervention, (2) standard advice about diet and physical activity plus placebo, and (3) metformin (pharmacotherapies were an exclusion criterion, as this review was concerned with lifestyle interventions, therefore the results of the metformin trial arm

are not discussed further).[8 9] The Iranian study compared 2 dietary interventions (a high-monounsaturated fat diet or a normal fat diet with a diet regimen tailored to each participant by a dietician) to a control group receiving standard dietary advice to follow the United States Department of Agriculture Food Guide Pyramid and to reduce fat intake to less than 30% and saturated fat intake to less than 10% of the total energy consumption.[10] Non-diabetic hyperglycaemia and T2DM were diagnosed according to ADA criteria.[71] The reported outcomes of interest were incidence of T2DM,[8 10] and changes to blood pressure,[9 10] blood cholesterol levels,[10] weight,[10] waist circumference,[10] and blood triglyceride levels.[9 10]

Quality appraisal of included studies

Risk of Bias (Cochrane Risk of Bias tool)[45] of the included trials (2 RCTs published in 3 articles) is shown in Figure 7 and in Appendix 3 Table 43. Both trials were considered to be at unclear risk of bias in 2 domains (allocation concealment, selective outcome reporting).[8-10] This was due insufficient information on which to make an assessment. The remaining applicable domains were judged to be at low risk of bias.

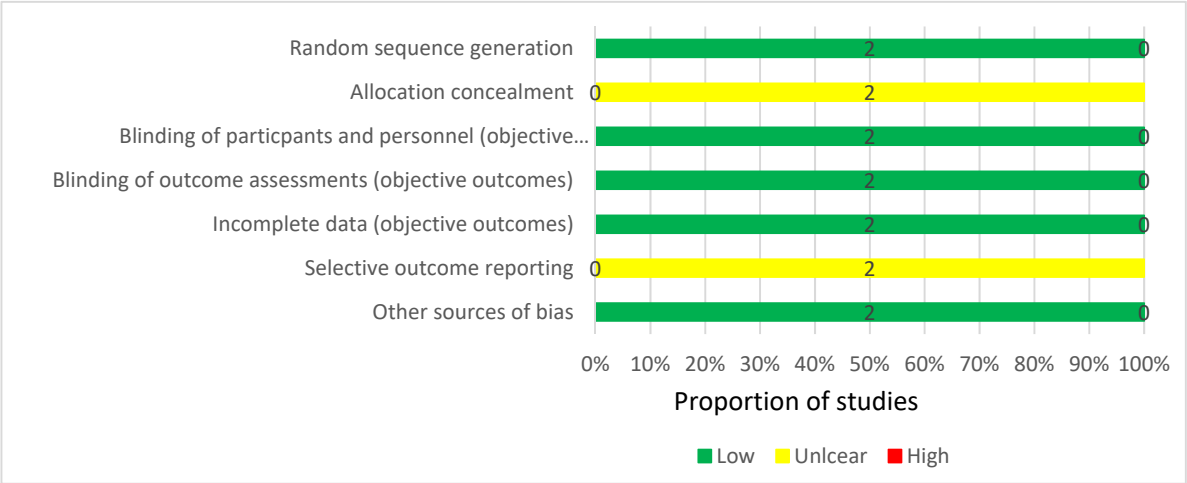


Figure 7. Risk of bias graph: review authors' judgements about each domain presented as percentages across included studies

Applicability of included studies

Applicability is not addressed within the Cochrane Risk of Bias tool. Nevertheless, there is an applicability concern of the included studies as neither was carried out in the UK: there are considerable difference in the demographics of the UK, Iran, and the United States, and

the prevalence of T2DM is approximately twice as high in Iran and the United States than in the UK.

Analysis of the evidence

T2DM

Incidence of T2DM was assessed in both trials.[8-10] In the American DPP trial comparing diet plus exercise to standard care, a per-protocol analysis of only the adherent participants indicated that the risk of developing T2DM was lower in the intervention arm.[9] A total of 141/661 (21.3%, but reported as 14% in the paper) adherent participants developed T2DM in the lifestyle intervention group compared to 296/766 (38.6%, but reported as 28% in the paper) adherent participants in the standard advice group, RR 0.55 (95% CI, 0.47–0.66). The probability of regressing to normal glucose regulation (NGR) was higher in the intervention arm. A total of 423/661 (64% but reported as 40% in the paper) adherent participants regressed to NGR in the lifestyle intervention group compared to 214/766 (27.9% but reported as 20% in the paper) adherent participants in the standard advice group, RR 2.29 (95% CI, 2.02–2.60).

In the Iranian trial comparing high-monounsaturated fat diet, normal fat diet, and standard dietary advice, Cox regression analysis (adjusted for BMI, sex, age, cigarette, alcohol) indicated a lower cumulative incidence of T2DM during the 24-month study in the group following a high-monounsaturated fat diet (10/107, 9.3%) than in the standard dietary advice group (20/109, 18.3%), RR 0.43 (95% CI, 0.1–0.9, p = 0.03).[10]

The Cochrane systematic review indicated that interventions comprising both diet and exercise reduced or delayed the incidence of T2DM amongst people who have NDH.[7]

Blood pressure

The effect of lifestyle interventions on blood pressure was reported in both trials. In the American DPP trial, the estimated net effect of the diet plus exercise intervention versus standard dietary advice in the intention-to-treat analysis showed a greater reduction of systolic blood pressure by 2.39 mmHg (95% CI, -3.44 to -1.35) per year and diastolic blood pressure by 1.99 mmHg (95% CI, -3.63 to -1.35) per year.[8] In the Iranian trial, the observed changes from baseline after 2 years of follow up in systolic blood pressure were similar in the high-monounsaturated fat diet (-2.2 ± 13.6 mmHg), normal fat diet (-1.4 ± 11.8 mmHg), and control (-0.5 ± 9.8 mmHg) groups (p = 0.5, analysis of variance [ANOVA]). Changes from baseline in diastolic blood pressure were also similar between high-monounsaturated fat (-0.4 ± 5.7 mmHg), normal fat (-0.5 ± 4.1 mmHg), and control groups (0.1 ± 3.5 mmHg) (p = 0.4, ANOVA).[10] It was not reported if the reductions in blood pressure were clinically significant.

The Cochrane systematic review did not report on blood pressure.

Blood lipids

Both trials reported the effect of the interventions on blood lipids. In the American DPP trial, blood lipids were reported in terms of total cholesterol, HDL cholesterol, and triglycerides.[8] The net effect of the diet plus exercise intervention versus standard dietary advice in the intention-to-treat analysis was 2.02 mg/dL (95% CI, 1.05 to 2.99) per year on HDL cholesterol levels and -15.74 mg/dL (95% CI, -22.60 to -8.90) per year on plasma triglyceride levels. The estimated net effect of the diet plus exercise intervention versus standard dietary advice on total cholesterol was -2.19 mg/dL (95% CI, -4.96 to 0.56) per year. In the Iranian trial, blood lipids were reported in terms of plasma HDL cholesterol, plasma LDL cholesterol, and plasma triglyceride levels.[10] The changes from baseline in LDL cholesterol levels were significantly different in the high-monounsaturated fat (-2.5 ± 7 mg/dL) and normal fat diet (-2.9 ± 10.7 mg/dL) groups compared to the changes in the control group (1.4 ± 8.6 mg/dL). Changes from baseline in plasma triglycerides were also significantly different in the high-monounsaturated fat (-12.8 ± 22.1 mg/dL) and normal fat (-10.2 ± 21.7 mg/dL) diet groups compared to changes in the control group (0.7 ± 17.5 mg/dL). There was no significant difference in HDL cholesterol changes from baseline between high-monounsaturated fat (1.1 ± 3.3 mg/dL), normal fat (1.0 ± 3 mg/dL), and control (-0.06 ± 5.6 mg/dL) groups (p = 0.06, ANOVA). It is unclear if the observed changes from baseline in blood lipids in each of the groups are clinically significant.

The Cochrane systematic review did not report on blood lipids.

Weight loss – weight (kilograms)/waist circumference (centimetres)

The Iranian trial reported on the effect of dietary interventions on weight loss.[10] In this study, changes in kilogram (kg) body weight from baseline until the end of the 2-year study period were similar between the high-monounsaturated fat diet (-0.1 ± 0.7 kg), normal fat diet (-0.09 ± 0.6 kg), and control (0.2 ± 2.1 kg) groups (p = 0.07, ANOVA). Despite a non-significant ANOVA, pairwise analyses were conducted. These indicated that changes in centimetre (cm) waist circumference from baseline were significantly different in the high-monounsaturated fat (-0.6 cm ± 4.2) and normal fat (-0.5 cm ± 3.8) diet groups compared to the changes in the control group (0.4 cm ± 3.7). It is unclear if the reductions in waist circumference are clinically significant.

The Cochrane systematic review did not report on weight loss.

Summary of Findings Relevant to Criterion 9:

Effectiveness of lifestyle interventions to reduce progression from NDH to T2DM: **Met**
Effectiveness of lifestyle interventions to improve health outcomes such as cardiovascular events: **not considered**
Effectiveness of lifestyle interventions for T2DM: **not considered**
Benefit of earlier intervention in pre-symptomatic phase: **not considered**
Evidence relating to the wider benefits of screening: **not considered**

Cochrane systematic review: 12 RCTs were identified that compared lifestyle interventions to standard treatment/no treatment.[7] This indicated that participants receiving lifestyle interventions (diet plus physical activity) had a decreased risk of developing T2DM compared to those receiving standard care/no treatment, RR 0.57 (95% CI, 0.50–0.64). No between-group differences were observed for any of the other outcomes examined (mortality, cardiovascular mortality, non-fatal heart attack/stroke, serious adverse events, and health-related quality of life). Risk of bias was very variable across the included studies.

Current review: 2 trials reported on the effects of lifestyle interventions (diet, or diet plus physical activity), one American and one Iranian.[8-10] The trials reported lower rates of T2DM amongst individuals taking part in a diet and exercise intervention compared to those receiving standard care (21.3% vs 38.6%, respectively)[9] or amongst those taking part in a high-monounsaturated diet intervention compared to standard dietary advice (9.3% vs 18.3%, respectively).[10] Data from the American trial were reported only on participants who were adherent to treatments. This is likely to overestimate the effect of the diet and exercise intervention.

There was evidence of a beneficial effect of diet plus exercise on blood pressure, HDL cholesterol, and triglycerides from one of the trials.[8] There were mixed results on the impact of a high-monounsaturated diet on weight loss:[10] data in relation to this are sparse and it is unclear if the statistically significant differences are clinically significant, as these are risk factors (which might be transient) rather than clinical outcomes.

The 2 trials were generally at low risk of bias, but with some uncertainty around allocation concealment and selective reporting.

In this review criterion 9 was assessed only in relation to the effectiveness of lifestyle interventions to reduce the progression from non-diabetic hyperglycaemia to T2DM. Overall, the body of evidence from this review and the recent Cochrane systematic review suggest a benefit of diet plus exercise on reducing the risk of T2DM amongst

individuals who have NDH. However, the reviewers did not assess the whole criterion as follows. They did not assess (1) the impact of these interventions on health outcomes such as cardiovascular events or mortality, (2) the benefits of earlier treatment for T2DM following screen detection, only NDH, (3) whether pre-symptomatic detection and treatment of NDH or T2DM is beneficial compared to later treatment initiation following symptomatic detection, or (4) the wider benefits of screening, such as to family members.

Criterion 11 — Benefits of screening for type 2 diabetes

There should be evidence from high quality randomised controlled trials that the screening programme is effective in reducing mortality or morbidity. The information that is provided about the test and its outcome must be of value and readily understood by the individual being screened.

Question 4 – Have RCTs demonstrated the benefit of screening for T2DM?

This question was addressed in the last review for the UK NSC undertaken by Waugh et al. in 2013.[1] A more recent systematic review was conducted by the U.S. Preventive Services Task Force (USPSTF), and published in 2015.[11] The same 2 trials were identified by each review.[12 13] The 2 trials were conducted in the UK. The Ely trial included 4,936 participants, with follow up conducted over 13 years, and participants invited to screening at 5 year intervals.[13 72 73] The ADDITION-Cambridge study included 19,226 participants at high risk of diabetes (i.e. with a risk score ≥0.17[74]) and was conducted over 10 years, with individuals screened once.[12] T2DM was diagnosed according to WHO criteria in both studies.

In the Ely trial, there were no statistically significant differences between invitation to screening and no invitation to screening in terms of all-cause mortality (adjusted HR 0.79, 95% CI 0.63–1.00), self-reported myocardial infarction (RR 0.57, 95% CI 0.22–1.49), self-reported stroke (RR 0.39, 95% CI 0.10–1.58), ischemic heart disease (RR 0.70, 95% CI 0.47–1.04), nephropathy (RR 2.61, 95% CI 0.30–22.78), peripheral neuropathy (RR 0.79, 95% CI 0.57–1.11), peripheral vascular disease (RR 1.63, 95% CI 0.33–8.13), Short Form Health Survey physical function score (67.2 [SD 29.4] vs. 69.6 [SD 30.7]; p=0.64), or Short Form Health Survey mental health score (77.8 [SD 16.5] vs. 79.7 [SD 16.1]; p=0.47)[13 72 73] In the ADDITION-Cambridge trial, there were no significant differences between invitation to screening and no invitation to screening in terms of all-cause mortality (HR 1.06, 95% CI 0.90–1.25), cardiovascular mortality (HR 1.02, 95% CI 0.75–1.38), cancer mortality (HR 1.08, 95% CI 0.90–1.30), diabetes-related mortality (HR 1.26, 95% CI 0.75–2.10), or other mortality (HR 1.10, 95% CI 0.87–1.39).[12]

There are limitations in the applicability of these 2 trials to the present review. The Ely study was not sufficiently powered to detect differences in mortality between the screened and unscreened groups, and there were baseline differences between the groups (age, sex, deprivation) which might indicate issues with randomisation.[13 72 73] The ADDITION-Cambridge trial only included individuals at high risk of T2DM, not a general population who are likely to be the target of a screening programme, also participants were only screened once in this trial.[12] These limit the generalisability of the study results.

Eligibility for inclusion in the review

Articles were included for this question if they reported the results of RCTs which included targeted or universal screening for T2DM. For this question, this review updated the USPSTF review[11] so searches were limited to English language papers published since 2015. Papers including non-human studies, conference abstracts, letters, editorials, communications, grey literature, or in languages other than English were excluded. Similarly, papers with no extractable data or studies about general health checks were also excluded.

Description of the evidence

Appendix 2 contains a full PRISMA flow diagram (Figure 13) along with a table of the included publications and details of which questions these publications were identified as being relevant to (Table 29). All the publications excluded after review of full-text articles for question 4 are listed in Table 36 along with reasons for exclusion. A total of 2,592 unique records were identified. After screening titles and abstracts, 9 records were retained. Assessment of full texts against inclusion/exclusion criteria resulted in one paper being included in the review.[14] No further articles were identified through hand searching reference lists of relevant systematic reviews or included studies, or via information from experts.

Discussion of findings

Characteristics of included studies

A study-level summary of data extracted from the included publication is presented in Appendix 3, Table 40.

The included study was a follow up paper of the ADDITION trial, reported in the 2013 UK NSC and USPSTF reviews.[1 11] The study reported here included a sub-group of 32 GP practices and analysed survey results from 1,945 people.[14] The paper reports on a randomly selected subgroup of 1,373 people (15%) of the screened group and 572 people (40%) from the no-screening control group on long-term self-reported outcomes 7 years after trial randomisation. Non-diabetic hyperglycaemia and T2DM were diagnosed according to WHO criteria.[17]

Quality appraisal of included studies

Risk of bias (Cochrane Risk of Bias tool)[45] of the one included study is shown in Figure 8, and Appendix 3, Table 44. The study was at high risk of bias in 3 domains: blinding of participants and personnel, blinding of outcome assessments, and sampling bias. The study was single blinded, with participants aware of being screened and, if at risk, they were sent further information and an invitation for additional testing. Likewise, all outcome assessments were self-reported, which is subjective and could be prone to response bias. The sample chosen was not completely random. GPs excluded participants with a terminal illness, a major psychiatric disorder or any other condition which might invalidate their consent or ability to complete the questionnaire. Moreover, people who had previously participated in another sub-study of the ADDITION-Cambridge trial were excluded (participants were responders from the whole ADDITION-Cambridge sample). Incomplete reporting was noted for method of allocation concealment and details of incomplete outcome data.

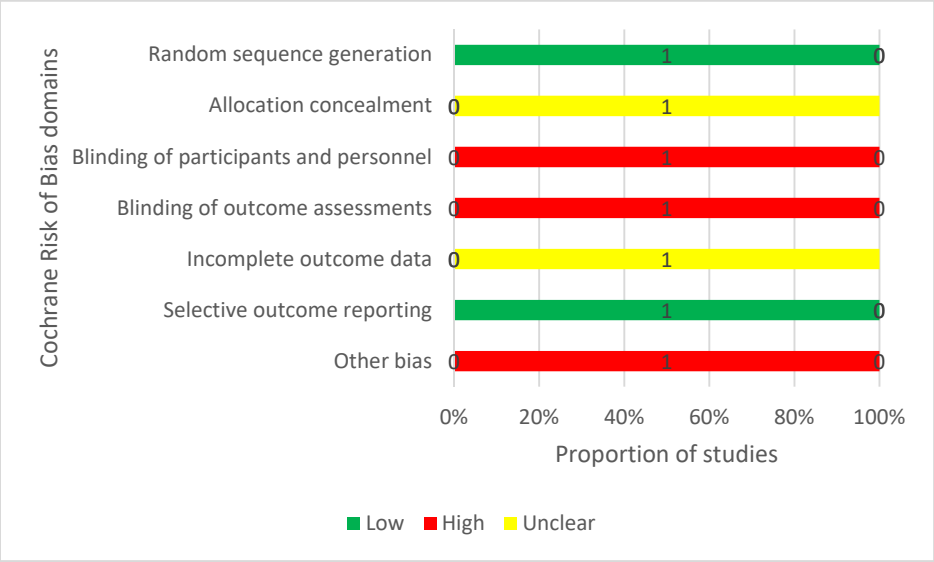


Figure 8. Risk of bias graph: review authors' judgements about each domain of the included study

Analysis of the evidence

Full study details on the outcomes of screened and unscreened groups can be found in Appendix 3, Table 40. Many outcomes were reported in the study, however the only outcomes of interest to this report were reduction of the risk of cardiovascular disease and quality of life. Diagnosis of diabetes was not reported by group, 466 people (2.9% of those eligible for screening) received a diagnosis.

Cardiovascular morbidity

Cardiovascular morbidity was reported using 3 domains – self-reported cardiovascular events (defined as myocardial infarction or stroke), self-reported hypertension and self-reported dyslipidaemia. There were no statistically significant differences in self-reported cardiovascular events (OR 0.90, 95% CI 0.71–1.15) or hypertension (OR 0.90, 95% CI 0.75–1.08) between screened and unscreened people. However, a lower proportion of participants in the screened group reported dyslipidaemia than in the unscreened group (OR 0.75, 95% CI 0.64–0.88).

The recent USPSTF systematic review indicated that there were no statistically significant differences in risk of self-reported myocardial infarction (RR 0.57, 95% CI 0.22–1.49), self-reported stroke (RR 0.39, 95% CI 0.10–1.58), ischemic heart disease (RR 0.70, 95% CI 0.47–1.04), or peripheral vascular disease (RR 1.63, 95% CI 0.33–8.13) in the Ely trial.[11]

Quality of life

The study reported self-rated health status using 4 tools, the Short Form Health Survey-8 physical health summary score, Short Form Health Survey-8 mental health summary score, EQ-5D score and EuroQol visual acuity score. There were no between-group differences on any of these measures: Short Form Health Survey-8 physical health β –0.33 (95% CI –1.80 to 1.14), Short Form Health Survey-8 mental health β –0.38 (95% CI –1.33 to 0.57), EQ-5D 0.002 (95% CI -0.02 to 0.02), EuroQol visual acuity 0.80 (95% CI -1.28 to 2.87).

The USPSTF systematic review identified no significant difference between screened and unscreened groups in terms of Short Form Health Survey physical function score (67.2 (SD 29.4) vs. 69.6 (SD 30.7); p=0.64), or Short Form Health Survey mental health score (77.8 (SD 16.5) vs. 79.7 (SD 16.1); p=0.47).[11]

Summary of Findings Relevant to Criterion 11: not met

Cochrane systematic review: 2 RCTs of screening for T2DM were identified, which reported results in multiple papers.[13 72 73] They indicated no statistically significant differences between screened and unscreened groups for all-cause mortality, cardiovascular mortality, cancer mortality, diabetes-related mortality, other mortality, or self-reported stroke, ischemic heart disease, nephropathy, peripheral neuropathy, peripheral vascular disease, physical function, or mental health.

Current review: one study was found since the previous NSC review.[14] This was a follow up to the ADDITION-Cambridge trial. The paper showed no significant differences between screened and unscreened groups in self-reported cardiovascular events, hypertension, physical health, mental health, or quality of life. However, the proportion of participants with dyslipidaemia was significantly lower in the screened group compared to the unscreened group.

Assessment of the available evidence supports the conclusion of the prior UK NSC review on screening for T2DM, that there is currently a lack of evidence of a benefit of screening. Data for this conclusion are drawn from 2 RCTs, and each of these has limitations: the Ely trial was not powered to detect differences in mortality between screened and unscreened participants, and the ADDITION-Cambridge trial only included people at known high risk of diabetes, with screening occurring at a single point in time.

Overall, based on the quantity and quality of the available evidence, this criterion is not met.

Review summary

Conclusions and implications for policy

This review examined 4 key questions relating to the effectiveness and appropriateness of screening for T2DM:

1. What proportion of people with untreated non-diabetic hyperglycaemia develop T2DM? (UK NSC criterion 1)
2. What is the accuracy of haemoglobin A1c (HbA1c), 2-hour 75g oral glucose tolerance test (2-hour PG), fasting plasma glucose (FPG), and the 50g glucose challenge test (GCT) as screening tools for microvascular and macrovascular complications of T2DM? (UK NSC criterion 4).
3. What is the reported effectiveness of lifestyle interventions for people with non-diabetic hyperglycaemia? (UK NSC criterion 9)
4. Have RCTs demonstrated the benefit of screening for T2DM? (UK NSC criterion 11)

The results indicate that there is consistent evidence that interventions to improve diet and physical activity reduce the risk that people with NDH will develop T2DM, and that people with higher blood glucose levels appear to be at greater risk of micro- and macrovascular complications of T2DM such as retinopathy, nephropathy, and early mortality than those with lower blood glucose levels. However, the evidence from this review, and prior systematic reviews, does not support screening for T2DM overall. This is driven by uncertainty regarding which people with blood glucose in the non-diabetic hyperglycaemia range will progress to T2DM (although the common risk factors for T2DM are well known) and which will revert to normoglycaemia, by the lack of clear evidence about which of the 3 potential screening markers is the most appropriate for screening, and by the fact that RCTs have not found that screening improved outcomes in comparison to standard care. Furthermore, there are applicability concerns of the evidence in relation to the UK setting. For example, (1) the majority of data are derived from studies that employed ADA criteria (which uses lower thresholds for NDH and T2DM than WHO criteria), and (2) the study participants were not from comparable prevalence settings, included people who were symptomatic or had known T2DM, or were from selected group of the general population (e.g. occupational cohort).

A critical gap in the evidence is that there have been no large RCTs that accurately reflect screening practice. Data on the potential benefits of screening are derived from 2 trials, one of which was not powered to detected differences in risk of mortality between screened and unscreened participants,[13 72 73] and one which only included people who were known to be

at high risk of T2DM.[12] Therefore it is not possible to know (from the available evidence) what, if any, difference screening for T2DM would make. A trial that is adequately powered and that accurately represents screening practice would be required to understand this. There is also uncertainty regarding the progression from NDH to T2DM. While individuals with non-diabetic hyperglycaemia appear to be at increased risk for T2DM, in the short-to-midterm the majority do not become diabetic (even in the absence of formal intervention) and a significant proportion will return to normal glucose function.

Limitations

The key limitation of this review is that the reviewers used a rapid evidence approach to identifying and evaluating evidence for questions 1, 3, and 4. The rapid evidence approach is, by its nature, less systematic and comprehensive than the more frequently used systematic review approach to evidence synthesis. For example, the rapid evidence approach searched only for English language publications and for a restricted number of outcomes. Relevant studies in other languages or those that examined other outcomes might be available. The approach may also be more prone to producing errors. For example, a single reviewer searched titles and abstracts, and conducted full text assessment, quality appraisal, and data extraction, with a second reviewer carrying out independent assessment (sifting titles and abstracts, full text assessment) or checking (quality appraisal and data extraction) of only 20% of each of these tasks. Therefore, the majority of the review process was carried out with no quality assurance. It is possible that errors made by the first reviewer remain undetected. Question 2 used systematic review methods (i.e. 2 reviewers conducting each part of the process), but had its own limitations. First, the searches required all 3 index tests to be mentioned in the study title or abstract. It is possible that relevant studies were missed because they did not include this information. There may also be useful information in studies that only compared pairs of the tests. Second, the reviewers did not perform meta-analysis due to heterogeneity between studies (e.g. the thresholds used, charateristics of study participants and underlying prevalence of T2DM), so our summary of the data is narrative.

Acknowledgements
We would like to thank Dr Jacoby Patterson for her assistance with sifting and sorting papers for question 2 (50-g Glucose Challenge Test)

Appendix 1 — Search strategy

Electronic databases

Separate searches were conducted for each question. The search strategy included searches of the databases shown in Tables 4–8.

Table 4. Summary of electronic database searches and dates for key question 1

Database	Platform	Searched on date	Date range of search
MEDLINE (MEDLINE, MEDLINE In-Process Process and Other Non-Indexed Citations, MEDLINE Daily Update, Medline, Epub Ahead of Print)	Ovid SP	19.11.2018	2017 to November Week 2 2018
Embase	Ovid SP	19.11.2018	2017 to 2018 Week 47
WHO International Clinical Trials Registry Platform	WHO International Clinical Trials Registry Platform	19.11.2018	2017 to 22.11.2018
Clinicaltrials.gov	Clinicaltrials.gov	19.11.2018	01.01.2017 to 22.11.18.

Table 5. Summary of electronic database searches and dates for key question 2 (FPG, 2-hour PG, HbA1c search)

Database	Platform	Searched on date	Date range of search
MEDLINE, MEDLINE In-Process, MEDLINE Daily, Epub Ahead of Print	Ovid SP	20.03.19	1946 to December Week 2 2018
Embase	Ovid SP	20.03.19	1947 to 2018 Week 51

Table 6. Summary of electronic database searches and dates for key question 2 (50g GCT)

Database	Platform	Searched on date	Date range of search
MEDLINE (MEDLINE, MEDLINE In-Process Process and Other Non-Indexed Citations, MEDLINE Daily Update, Medline, Epub Ahead of Print)	Ovid SP	19.03.19	1946 to March 18, 2019
Embase Classic+Embase	Ovid SP	19.03.19	1947 to 2019 Week 11
Web of Science		19.03.19	All years
The Cochrane Library, including: - Cochrane Database of Systematic Reviews - Cochrane Central Register of Controlled Trials	Wiley Online	19.03.19	All to 19.03.2019

- Cochrane Protocols
- Cochrane Clinical Answers

Table 7. Summary of electronic database searches and dates for key question 3

Database	Platform	Searched on date	Date range of search
MEDLINE, Pre-MEDLINE	Ovid SP	26.11.2018	2017 to November Week 3 2018
Embase	Ovid SP	26.11.2018	2017 to 2018 Week 47
The Cochrane Library, including: - Cochrane Database of Systematic Reviews (CDSR) - Cochrane Central Register of Controlled Trials (CENTRAL)	Wiley Online	26.11.2018	All to 29.11.2018
WHO International Clinical Trials Registry Platform	WHO International Clinical Trials Registry Platform	26.11.2018	No date limit to search
Clinicaltrials.gov	Clinicaltrials.gov	29.11.2018	No date limit to search

Table 8. Summary of electronic database searches and dates for key question 4

Database	Platform	Searched on date	Date range of search
MEDLINE, Pre-MEDLINE	Ovid SP	07.12.2018	2015 to November Week 5 2018
Embase	Ovid SP	07.12.2018	2015 to Week 49 2018
The Cochrane Library, including: - Cochrane Database of Systematic Reviews (CDSR) - Cochrane Central Register of Controlled Trials (CENTRAL)	Wiley Online	07.12.2018	2015 to 07.12.2018

Search Terms (question 1)

Search terms included combinations of free text and subject headings (Medical Subject Headings [MeSH] for MEDLINE, and Emtree terms for Embase), grouped into the following categories:

- disease area: **type 2 diabetes, nondiabetic hyperglycaemia**
- other term group: **predictors, outcomes**
- exclusions: **exclusions terms**

Search terms for MEDLINE, are shown in **Error! Reference source not found.**, search terms for EMBASE are shown in Table 10, search terms for ClinicalTrial.gov are shown in Table 11, and search terms for the ICTRP are shown in **Error! Reference source not found.**.

Table 9. Search strategy for MEDLINE

Term Group	#	Search terms	Results

Disease area	1	Prediabetic State/	5830
Disease area	2	(prediabet* or pre diabet*).tw.	8089
Disease area	3	intermediate hyperglyc?emi*.tw.	52
Disease area	4	or/1-3	10356
Other	5	(incidence.sh. or exp mortality/ or follow-up studies.sh. or prognos*.tw. or predict*.tw. or course*.tw.)	3127718
Other	6	prognosis/ or diagnosed.tw. or cohort*.mp. or predictor*.tw. or death.tw. or exp models, statistical/	2405248
Other	7	or/5-6	4496547
	8	4 and 7	3618
Disease area	9	((impaired fasting adj2 glucose) or IFG or (impaired adj FPG)).tw.	5114
Disease area	10	(impaired glucose tolerance or IGT).tw.	11558
Disease area	11	("HbA(1c)" or HbA1 or HbA1c or "HbA 1c" or ((glycosylated or glycated) adj h?emoglobin)).tw.	43522
Other	12	or/9-11	57261
Other	13	(predict* or associa* or prognos*).tw.	5170572
Other	14	((prognostic or predict*) adj2 model?).tw	79604
Other	15	predictive value?.tw.	96355
Other	16	(risk adj (predict* or factor? or score)).tw.	526654
Other	17	or/13-16	5367291
Disease area	18	(((impaired fasting adj2 glucose) or IFG or "impaired FPG" or impaired glucose tolerance or IGT or "HbA(1c)" or HbA1 or HbA1c or "HbA 1c" or ((glycosylated or glycated) adj h?emoglobin)) adj3 (predict* or associa* or	4480

		prognos* or ((prognostic or predict*) adj2 model?) or predictive value? or (risk adj (predict* or factor? or score))))).tw.	
Other	19	8 or 18	7862
Other	20	complication?.tw.	812168
Other	21	mortality.tw.	663061
Other	22	(CHD or CVD).tw.	50803
Other	23	(coronary adj2 disease).tw.	131928
Other	24	(coronar* adj (event? or syndrome?)).tw.	33004
Other	25	(heart adj (failure or disease? or attack? or infarct*)).tw.	291208
Other	26	(myocardial adj (infarct* or isch?emi*)).tw.	202641
Other	27	cardiac failure.tw.	11394
Other	28	angina.tw.	50200
Other	29	revasculari*.tw.	54053
Other	30	(stroke or strokes).tw.	216643
Other	31	cerebrovascular.tw.	48571
Other	32	((brain* or cerebr*) adj (infarct* or isch?emi*)).tw.	49546
Other	33	apoplexy.tw.	2871
	34	((vascular or peripheral arter*) adj disease?).tw.	50383
Other	35	cardiovascular.tw.	386967
Other	36	(neuropath or polyneuropath*).tw.	13234
Other	37	(retinopath* or maculopath*).tw.	43126
Other	38	(nephropath* or nephrotic or proteinuri* or albuminuri*).tw.	98817
Other	39	((kidney or renal) adj (disease? or failure or transplant*)).tw.	246106
Other	40	((chronic or endstage or end stage) adj (renal or kidney)).tw.	101476
Other	41	(crd or crf or ckf or ckd or eskd or eskf or esrd or esrf).tw.	53538

Other	42	(microvascular or macrovascular or ((micro or macro) adj vascular)).tw.	56135
Other	43	(cancer or carcino* or neoplas* or tumo?r?).tw.	2805644
Other	44	(amputation? or ulcer* or foot or feet or wound*).tw.	475910
Other	45	or/20-44	5460048
Other	46	19 and 45	3274
Other	47	((diabet* or type 2 or type II or t2d*) adj4 (progress* or inciden* or conversion or develop* or future)).tw.	53152
Other	48	19 and 47	1687
Other	49	46 or 48	4311
Exclusions	50	exp animals/ not humans/	4515931
Other	51	49 not 50	4219
Exclusions	52	(gestational or PCOS).tw.	110126
Other	53	51 not 52	4057
Exclusions	54	(comment or letter or editorial).pt.	1672278
Other	55	53 not 54	4011
Exclusions	56	remove duplicates from 55	4006
Exclusions	57	limit 56 to yr="2017 - Current"	806

Table 10. Search strategy for EMBASE (searched via the Wiley Online platform)

Term Group	#	Search terms	Results
Disease area	1	(prediabet* or pre diabet*).tw.	12751
Disease area	2	intermediate hyperglyc?emi*.tw.	87
Disease area	3	or/1-2	12818
	4	exp disease course/ or risk.mp. or diagnos*.mp. or follow-up.mp. or ep.fs. or outcome.tw.	11059362
Other	5	follow-up.mp. or prognos*.tw. or ep.fs.	3194951
Other	6	or/4-5	11123327
Other	7	3 and 6	9203
Disease area	8	8 ((impaired fasting adj2 glucose) or IFG or (impaired adj FPG)).tw.	8318

Disease area	9	(impaired glucose tolerance or IGT).tw.	17697
Disease area	10	("HbA(1c)" or HbA1 or HbA1c or "HbA 1c" or ((glycosylated or glycated) adj h?emoglobin)).tw.	79495
Disease area	11	11 or/8-10 (99909)	
Other	12	(predict* or associa* or prognos*).tw.	6880099
Other	13	((prognostic or predict*) adj2 model?).tw.	103811
Other	14	predictive value?.tw.	141603
Other	15	(risk adj (predict* or factor? or score)).tw.	772823
Other	16	or/12-15	7158173
Disease area	17	(((impaired fasting adj2 glucose) or IFG or "impaired FPG" or impaired glucose tolerance or IGT or "HbA(1c)" or HbA1 or HbA1c or "HbA 1c" or ((glycosylated or glycated) adj h?emoglobin)) adj3 (predict* or associa* or prognos* or ((prognostic or predict*) adj2 model?) or predictive value? or (risk adj (predict* or factor? or score)))).tw.	7355
Other	18	7 or 17	16076
Other	19	complication?.tw.	1159725
Other	20	mortality.tw.	951685
Other	21	(CHD or CVD).tw.	78778
Other	22	(coronary adj2 disease).tw.	190698
Other	23	(coronar* adj (event? or syndrome?)).tw.	56162
Other	24	(heart adj (failure or disease? or attack? or infarct*)).tw.	429319
Other	25	(myocardial adj (infarct* or isch?emi*)).tw.	279978
Other	26	cardiac failure.tw.	15806
Other	27	angina.tw.	68130
Other	28	revasculari*.tw.	82079
Other	29	(stroke or strokes).tw.	339959

Other	30	cerebrovascular.tw.	69137
Other	31	((brain* or cerebr*) adj (infarct* or isch?emi*)).tw.	67600
Other	32	apoplexy.tw.	2796
Other	33	((vascular or peripheral arter*) adj disease?).tw.	70462
Other	34	cardiovascular.tw.	562176
Other	35	(neuropath or polyneuropath*).tw.	19780
Other	36	(retinopath* or maculopath*).tw.	56308
Other	37	(nephropath* or nephrotic or proteinuri* or albuminuri*).tw.	131574
Other	38	((kidney or renal) adj (disease? or failure or transplant*)).tw.	349782
Other	39	((chronic or endstage or end stage) adj (renal or kidney)).tw.	145864
Other	40	(crd or crf or ckf or ckd or eskd or eskf or esrd or esrf).tw.	84465
Other	41	(microvascular or macrovascular or ((micro or macro) adj vascular)).tw.	78998
Other	42	(cancer or carcino* or neoplas* or tumo?r?).tw.	3626220
Other	43	(amputation? or ulcer* or foot or feet or wound*).tw.	594300
Other	44	or/19-43	7194122
Other	45	18 and 44	7372
Disease area	46	((diabet* or type 2 or type II or t2d*) adj4 (progress* or inciden* or conversion or develop* or future)).tw.	77942
Other	47	18 and 46	3804
Other	48	45 or 47	9559
Exclusions	49	exp animals/ or exp invertebrate/ or animal experiment/ or animal model/ or animal tissue/ or animal cell/ or nonhuman/	25090860
Exclusions	50	human/ or normal human.mp. or human cell/ [mp=title, abstract, heading	19097385

		word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	
Exclusions	51	49 and 50	19042986
Exclusions	52	49 not 51	6047874
Exclusions	53	48 not 52	9199
Exclusions	54	(gestational or PCOS).tw	9199
Exclusions	55	53 not 54	8799
Exclusions	56	(comment or letter or editorial).pt.	1629771
Exclusions	57	55 not 56	8749
Exclusions	58	limit 57 to yr="2017 - Current"	1685

Table 11. Search strategy for Clinical Trials (Searched via clinicaltrials.gov)

Term Group	#	Search terms	Results
Disease are	1	prediabetes OR prediabetic OR “pre diabetes” OR “pre diabetic” OR “intermediate hyperglycemia” OR “intermediate hyperglycaemia” OR “intermediate hyperglycemic” OR “intermediate hyperglycaemic” OR “impaired glucose tolerance” OR “impaired fasting glucose”	
Other	2	complication OR complications OR mortality OR CHD OR CVD OR coronary OR heart OR myocardial OR infarct OR infarction OR infarcts OR infarctions OR ischemia OR ischemic OR ischaemia OR ischaemic OR failure OR angina OR	

		revascularization OR revascularisation OR revascularizations OR revascularisations OR stroke OR strokes OR cerebrovascular OR apoplexy OR vascular or peripheral OR cardiovascular OR neuropathy OR neuropathies OR polyneuropathy OR polyneuropathies OR retinopathy OR retinopathies OR maculopathy OR maculopathies OR nephropathy OR nephropathies OR nephrotic OR proteinuria OR proteinuric OR albuminuria OR kidney OR renal OR CRD OR CRF OR CKF OR CRF OR CKD OR ESKD OR ESKF OR ESRD OR ESRF OR microvascular OR macrovascular OR “micro vascular” OR “macro vascular” OR cancer OR carcinoma OR neoplasm OR neoplasms OR tumor OR tumors OR tumour OR tumours OR amputation OR amputations OR ulcer OR foot OR feet OR wounds OR (diabetes OR diabetic OR “type 2” OR “type II” OR T2D OR T2DM)
Other	3	(progress OR progression OR progressed OR incident OR incidence OR conversion OR developed OR development OR future)

	4	#1 AND #2 AND #3	340

Table 12. Search strategy for the International Clinical Trials Registry Platform (Searched via the ICTRP search portal)

Term Group	#	Search terms	Results
Disease area	1	prediabet* AND prognos* OR	1
Disease area	2	prediabet* AND predict* OR	5
Disease area	3	prediabet* AND inciden* OR	4
Disease area	4	prediabet* AND mortality OR	0
Disease area	5	prediabet* AND prevent* OR	85
Disease area	6	prediabet* AND progress* OR	15
Disease area	7	prediabet* AND develop* OR	39
Disease area	8	pre diabet* AND prognos* OR	1
Disease area	9	pre diabet* AND predict* OR	11
Disease area	10	pre diabet* AND inciden* OR	5
Disease area	11	pre diabet* AND mortality OR	0
Disease area	12	pre diabet* AND prevent* OR	132
Disease area	13	pre diabet* AND progress* OR	27
Disease area	14	pre diabet* AND develop* OR	35
Disease area	15	impaired glucose tolerance AND prognos* OR	1
Disease area	16	impaired glucose tolerance AND predict* OR	3
Disease area	17	impaired glucose tolerance AND inciden* OR	7
Disease area	18	impaired glucose tolerance AND mortality OR	4
Disease area	19	impaired glucose tolerance AND prevent* OR	49

Disease area	20	impaired glucose tolerance AND progress* OR	14
Disease area	21	impaired glucose tolerance AND develop* OR	29
Disease area	22	impaired fasting glucose AND prognos* OR	0
Disease area	23	impaired fasting glucose AND predict* OR	0
Disease area	24	impaired fasting glucose AND inciden* OR	1
Disease area	25	impaired fasting glucose AND mortality OR	1
Disease area	26	impaired fasting glucose AND prevent* OR	13
Disease area	27	impaired fasting glucose AND progress* OR	6
Disease area	28	impaired fasting glucose AND develop* OR	9
Disease area	29	HbA* AND prognos* OR	3
Disease area	30	HbA* AND predict* OR	15
Disease area	31	HbA* AND inciden* OR	7
Disease area	32	HbA* AND mortality OR	5
Disease area	33	HbA* AND prevent* OR	35
Disease area	34	HbA* AND progress* OR	23
Disease area	35	HbA* AND develop*	42
	36	#1 - #35 (AND)	340

Search Terms (question 2 – FPG, 2-hour PG, HbA1c)

Search terms included combinations of free text and subject headings (Medical Subject Headings [MeSH] for MEDLINE, and Emtree terms for Embase), grouped into the following categories:

- disease area: **type 2 diabetes, nondiabetic hyperglycaemia**
- study design: **RCTs**
- other term group: **interventions, outcomes**
- exclusions: **exclusion terms**

Search terms for MEDLINE are shown in Table 13, search terms for pre-MEDLINE are shown in Table 14, and search terms for Embase are shown in Table 15

Table 13. Search strategy for MEDLINE

Term Group	#	Search terms	Results
Disease area	1	exp Prediabetic State/	5849

Disease area	2	exp Glucose intolerance/	7988
Disease area	3	(prediabet* or pre diabet* or pre-diabet*).tw.	6734
Disease area	4	borderline diabet*.mp.	107
Disease area	5	intermediate hyperglyc?emi*.tw.	41
Disease area	6	(hyperglyc?emi* and (non diabet* or non-diabet*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	1849
Disease area	7	((impaired fasting adj2 glucose) or IFG or (impaired adj FPG)).tw.	4427
Disease area	8	(fasting glucose adj3 impair*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	3196
Disease area	9	glucose intolerance.tw.	8398
Disease area	10	((impaired glucose adj (tolerance or metabolism)) or IGT).tw.	11360
Disease area	11	(glucose intolerance adj3 impair*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	252

Disease area	12	exp Diabetes Mellitus, Type 2/ or diabetes mellitus/	224492
Disease area	13	type II diabet*.mp.	7899
Disease area	14	type 2 diabet*.mp.	95888
Disease area	15	(t2d or t2dm or niddm).mp.	24271
Disease area	16	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 14 or 15	263213
Disease area	17	exp Glycated Hemoglobin A/	31487
Disease area	18	(hba1c or Hba1 or "Hba(1c)" or "hba 1c" or a1c).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	37505
Disease area	19	((glycosylated or glycated) adj H?emoglobin).tw.	15437
Disease area	20	17 or 18 or 19	51780
Disease area	21	ogtt.mp. or exp Glucose Tolerance Test/	35370
Disease area	22	(oral glucose tolerance or oral glucose tolerance test* or glucose tolerance test*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	40734
Disease area	23	((two hour* or two-hour* or 2h or 2-h or 2 h or 2 hour* or 2-hour* or 2hour*) adj4 glucose).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol	5928

		supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	
Disease area	24	2hpg.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	200
Disease area	25	21 or 22 or 23 or 24	44034
Disease area	26	(fpg or fasting plasma glucose or fasting blood glucose or fasting glucose).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	31182
Disease area	27	20 and 25 and 26	1952
Disease area	28	27 and 16	1696
Exclusions	29	(child* or infant* or infancy or adolescen* or teenage*).ti.	899109
Exclusions	30	(genetic* or gene*).ti.	954911
Exclusions	31	*Prediabetic State/ge [Genetics]	112
Other	32	29 or 30 or 31	1838084
Other	33	28 not 32	1595

Table 14. Search strategy for Pre-MEDLINE

Term Group	#	Search terms	Results
Disease area	1	exp Prediabetic State/ ()	14
Disease area	2	exp Glucose intolerance/	20
Disease area	3	(prediabet* or pre diabet* or pre-diabet*).tw.	1394
Disease area	4	borderline diabet*.mp.	7

Disease area	5	5 intermediate hyperglyc?emi*.tw. ()	13
Disease area	6	(hyperglyc?emi* and (non diabet* or non-diabet*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	216
Disease area	7	((impaired fasting adj2 glucose) or IFG or (impaired adj FPG)).tw.	709
Disease area	8	(fasting glucose adj3 impair*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	420
Disease area	9	glucose intolerance.tw.	920
Disease area	10	((impaired glucose adj (tolerance or metabolism)) or IGT).tw.	1169
Disease area	11	(glucose intolerance adj3 impair*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	26
Disease area	12	exp Diabetes Mellitus, Type 2/ or diabetes mellitus/	297
Disease area	13	type II diabet*.mp.	1100
Disease area	14	type 2 diabet*.mp.	19600

Disease area	15	(t2d or t2dm or niddm).mp.	6061
Disease area	16	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 14 or 15	22916
Disease area	17	exp Glycated Hemoglobin A/	69
Disease area	18	(hba1c or Hba1 or "Hba(1c)" or "hba 1c" or a1c).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	6916
Disease area	19	((glycosylated or glycated) adj H?emoglobin).tw.	3132
Disease area	20	17 or 18 or 19	8088
Disease area	21	ogtt.mp. or exp Glucose Tolerance Test/	930
Disease area	22	(oral glucose tolerance or oral glucose tolerance test* or glucose tolerance test*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	2109
Disease area	23	((two hour* or two-hour* or 2h or 2-h or 2 h or 2 hour* or 2-hour* or 2hour*) adj4 glucose).mp.	669
Disease area	24	2hpg.mp.	34
Disease area	25	21 or 22 or 23 or 24	2634
Disease area	26	(fpg or fasting plasma glucose or fasting blood glucose or fasting glucose).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword	5198

		heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	
Disease area	27	20 and 25 and 26	288
Disease area	28	27 and 16	203
Exclusions	29	(child* or infant* or infancy or adolescen* or teenage*).ti.	92766
Exclusions	30	(genetic* or gene*).ti.	120885
Exclusions	31	*Prediabetic State/ge [Genetics]	2)
Exclusions	32	29 or 30 or 31	211691
Exclusions	33	28 not 32	191

Table 15. Search strategy for Embase

Term Group	#	Search terms	Results
Disease area	1	prediabetic state.mp. or exp impaired glucose tolerance/	28843
Disease area	2	exp glucose intolerance/	16916
Disease area	3	(prediabet* or pre diabet* or pre-diabet*).tw.	13862
Disease area	4	borderline diabet*.mp.	195
Disease area	5	intermediate hyperglyc?emi*.tw.	89
Disease area	6	(hyperglyc?emi* and (non-diabet* or non diabet*)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	3756
Disease area	7	((impaired fasting adj2 glucose) or IFG or (impaired adj FPG)).tw.	8392
Disease area	8	(fasting glucose adj3 impair*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating	5987

		subheading word, candidate term word]	
Disease area	9	glucose intolerance.tw.	13837
Disease area	10	((impaired glucose adj (tolerance or matabolism)) or IGT).tw.	17956
Disease area	11	(glucose intolerance adj3 impair*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	440
Disease area	12	exp non insulin dependent diabetes mellitus/	223739
Disease area	13	diabetes mellitus/	542108
Disease area	14	type 2 diabet*.mp.	180300
Disease area	15	type II diabet*.mp.	14050
Disease area	16	(t2d or t2dm or niddm).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	53524
Disease area	17	or/1-16	780304
Disease area	18	exp hemoglobin A1c/	90259
Disease area	19	(hba1c or hba1 or "hba(1c)" or "hba 1c" or a1c).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] ()	110238
Disease area	20	((Glycosylated or glycated) adj h?emoglobin).tw.	24925
Disease area	21	18 or 19 or 20	119382
Disease area	22	ogtt.mp. or exp oral glucose tolerance test/	32680
Disease area	23	(oral glucose tolerance or oral glucose tolerance test* or	64058

		glucose tolerance test*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	
Disease area	24	((two hour* or two-hour*or 2h or 2-h or 2 h or 2 hour* or 2-hour* or 2hour*) adj4 glucose).mp.	8848
Disease area	25	2hpg.mp. ()	444
Disease area	26	22 or 23 or 24 or 25	70208
Disease area	27	(fpg or fasting plasma glucose or fasting blood glucose or fasting glucose).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	61142
Disease area	28	21 and 26 and 27	4166
Disease area	29	28 and 17	3709
Exclusions	30	(child* or infant* or infancy or adolescen* or teenage*).ti.	1237670
Exclusions	31	(genetic* or gene*).ti.	1261875
Exclusions	32	30 or 31	2476154
Disease area	33	29 not 32	3458
Other		limit 33 to (article or article in press or "review")	2136

Search Terms (question 2 – 50g GCT)

Search terms included combinations of free text and subject headings (Medical Subject Headings [MeSH] for MEDLINE, and Emtree terms for Embase), grouped into the following categories:

- disease area: **type 2 diabetes, nondiabetic hyperglycaemia**
- study design: **RCTs**
- other term group: **interventions, outcomes**

- exclusions: **exclusion terms**

Search terms for MEDLINE and pre-MEDLINE are shown in Table 16, search terms for Embase are shown in Table 17, search terms for Web of Science are shown in Table 18, and search terms for the Cochrane library are shown in Table 19.

Table 16. Search strategy for MEDLINE and pre-MEDLINE

Term Group	#	Search terms	Results
Disease area	1	((50g or 50 g or 50-g) adj3 glucose).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	1119

Table 17. Search strategy for Embase

Term Group	#	Search terms	Results
Disease area	1	((50g or 50 g or 50-g) adj3 glucose).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	1817

Table 18. Search strategy for Web of Science

Term Group	#	Search terms	Results
Disease area	1	TOPIC: ((50g or 50-g or "50 g") NEAR/3 (glucose)) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years	874

Table 19. Search strategy for Cochrane library (reviews, trials, protocols, clinical answers)

Term Group	#	Search terms	Results
Disease area	1	(50g or "50 g") NEAR/3 (glucose)	247

Search Terms (question 3)

Search terms included combinations of free text and subject headings (Medical Subject Headings [MeSH] for MEDLINE, and Emtree terms for Embase), grouped into the following categories:

- disease area: **type 2 diabetes, nondiabetic hyperglycaemia**
- study design: **RCTs**
- other term group: **interventions, outcomes**
- exclusions: **exclusion terms**

Search terms for MEDLINE and pre-MEDLINE are shown in Table 20, search terms for Embase are shown in Table 21, search terms for the Cochrane Library databases are shown in **Error! Reference source not found.**22, search terms for the ICTPR are shown in Table 23, and search terms for Clinicaltrials.gov are shown in Table 24.

Table 20. Search strategy for MEDLINE and pre-MEDLINE

Term Group	#	Search terms	Results
Disease area	1	Prediabetic State/	5835
Disease area	2	Glucose intolerance/	7974
Disease area	3	(prediabet* or pre diabet*).tw.	8100
Disease area	4	intermediate hyperglyc?emi*.tw.	52
Disease area	5	((impaired fasting adj2 glucose) or IFG or (impaired adj FPG)).tw.	5124
Disease area	6	glucose intolerance.tw.	9293
Disease area	7	((impaired glucose adj (tolerance or metabolism)) or IGT).tw.	12519
Disease area	8	("HbA(1c)" or HbA1 or HbA1c or "HbA 1c" or ((glycosylated or glycated) adj h?emoglobin)).tw.	43566
Disease area	9	(risk adj3 ("type 2" or "type II" or diabetes or T2D* or NIDDM)).tw.	26931
Disease area	10	*Diabetes mellitus/pc	2272
Disease area	11	*diabetes mellitus, Type 2/pc	3766

Disease area	12	or/1-11	100373
Other	13	Life Style/	52724
Other	14	exp Exercise/	171833
Other	15	exp Exercise Therapy/	44456
Other	16	ext Diet/	0
Other	17	exp Diet therapy/	50421
Other	18	((lifestyle or life style) adj3 (intervention? or change* or modif* or program or programme)).tw.	23801
Other	19	diet*.tw.	507872
Other	20	(nutrition* adj3 (intervention? or change* or modif* or program or programme)).tw.	14977
Other	21	exercis*.tw.	265142
Other	22	physical activit*.tw.	94519
Other	23	resistance training.tw.	6264
Other	24	or/13-23	955627
	25	12 and 24	20509
Other	26	(diabetes prevention adj (program* or stud* or trial?)).tw.	1208
Other	27	25 or 26	21039
Other	28	complication?.tw.	812623
Other	29	mortality.tw.	663574
Other	30	(CHD or CVD).tw.	50854
Other	31	(coronary adj2 disease).tw.	131970
Other	32	(coronar* adj (event? or syndrome?)).tw.	33023
Other	33	(heart adj (failure or disease? or attack? or infarct*)).tw.	33023
Other	34	(myocardial adj (infarct* or isch?emi*)).tw.	202678
Other	35	cardiac failure.tw.	11398
Other	36	angina.tw.	50207
Other	37	revasculari*.tw.	54054
Other	38	(stroke or strokes).tw.	216788
Other	39	cerebrovascular.tw.	48591
Other	40	((brain* or cerebr*) adj (infarct* or isch?emi*)).tw.	49570
Other	41	apoplexy.tw.	2873
Other	42	((vascular or peripheral arter*) adj disease?).tw.	50413
Other	43	cardiovascular.tw.	387198
Other	44	(neuropath or polyneuropath*).tw.	13239

Other	45	(retinopath* or maculopath*).tw.	43171
Other	46	(nephropath* or nephrotic or proteinuri* or albuminuri*).tw.	98853
Other	47	((kidney or renal) adj (disease? or failure or transplant*)).tw.	246227
Other	48	((chronic or endstage or end stage) adj (renal or kidney)).tw.	101546
Other	49	(crd or crf or ckf or ckd or eskd or eskf or esrd or esrf).tw.	53582
Other	50	(microvascular or macrovascular or ((micro or macro) adj vascular)).tw.	56180
Other	51	(cancer or carcino* or neoplas* or tumo?r?).tw.	2807430
Other	52	(amputation? or ulcer* or foot or feet or wound*).tw.	476104
Other	53	((risk or progress* or prevent* or inciden* or conversion or develop* or delay*) adj4 (diabetes or T2D* or NIDDM or "type 2" or "type II")).tw.	75394
Other	54	or/28-53	5503099
	55	27 and 54	13279
Study design	56	randomized controlled trial.pt.	471716
Study design	57	controlled clinical trial.pt.	92759
Study design	58	randomi?ed.ab.	510925
Study design	59	placebo.ab.	193370
Study design	60	clinical trials as topic/	185321
Study design	61	randomly.ab.	300636
Study design	62	trial.ti.	190304
Study design	63	or/56-62	1214898
Exclusions	64	exp animals/ not humans/	4517568
Exclusions	65	63 not 64	4517568
Other	66	55 and 65	2952
Study design	67	cochrane database of systematic reviews.jn. or search*.tw. or meta analysis.pt. or medline.tw. or systematic review.tw.	478476
Study design	68	55 and 67	714
Study design	69	66 or 68	3387
Exclusions	70	(2017* or 2018* or 2019*).dt.	2360527
Other	71	69 and 70	553
Exclusions	72	remove duplicates from 71	549

Table 21. Search strategy for Embase

Term Group	#	Search terms	Results
Disease area	1	(prediabet* or pre diabet*).tw.	13714
Disease area	2	intermediate hyperglyc?emi*.tw.	87
Disease area	3	((impaired fasting adj2 glucose) or IFG or (impaired adj FPG)).tw.	8337
Disease area	4	glucose intolerance.tw.	13742
Disease area	5	((impaired glucose adj (tolerance or metabolism)) or IGT).tw.	19335
Disease area	6	("HbA(1c)" or HbA1 or HbA1c or "HbA 1c" or ((glycosylated or glycated) adj h?emoglobin)).tw.	79511
Other	7	(risk adj3 ("type 2" or "type II" or diabetes or T2D* or NIDDM)).tw.	41268
Other	8	or/1-7	153883
Other	9	(lifestyle of life style adj3 (intervention? or change* or modif* or program or programme)).tw.	0
Other	10	diet*.tw.	690389
Other	11	(nutrition* adj3 (intervention? or change* or modif* or program or programme)).tw.	20801
Other	12	exercis*.tw.	368618
Other	13	physical activit*.tw.	129432
Other	14	resistance training.tw.	7553
Other	15	or/9-14	1116246
Other	16	8 and 15	26614
Other	17	(diabetes prevention adj (program* or stud* or trial?)).tw.	1744
Other	18	16 or 17	27880
Other	19	complication?.tw.	1229455
Other	20	mortality.tw.	995117
Other	21	(CHD or CVD).tw.	79028
Other	22	(coronary adj2 disease).tw.	197800
Other	23	(coronar* adj (event? or syndrome?)).tw.	56299
Other	24	(heart adj (failure or disease? or attack? or infarct*)).tw.	456124

Other	25	(myocardial adj (infarct* or isch?emi*)).tw.	298208
Other	26	cardiac failure.tw.	18828
Other	27	angina.tw.	74777
Other	28	revasculari*.tw.	84147
Other	29	(stroke or strokes).tw.	345877
Other	30	cerebrovascular.tw.	73070
Other	31	((brain* or cerebr*) adj (infarct* or isch?emi*)).tw.	69356
Other	32	apoplexy.tw.	4041
Other	33	((vascular or peripheral arter*) adj disease?).tw.	75895
Other	34	cardiovascular.tw.	580138
Other	35	(neuropath or polyneuropath*).tw.	20551
Other	36	(retinopath* or maculopath*).tw.	60316
Other	37	(nephropath* or nephrotic or proteinuri* or albuminuri*).tw.	142613
Other	38	((kidney or renal) adj (disease? or failure or transplant*)).tw.	366452
Other	39	((chronic or endstage or end stage) adj (renal or kidney)).tw.	149386
Other	40	(crd or crf or ckf or ckd or eskd or eskf or esrd or esrf).tw.	84803
Other	41	(microvascular or macrovascular or ((micro or macro) adj vascular)).tw.	79483
Other	42	(cancer or carcino* or neoplas* or tumo?r?).tw.	3908159
Other	43	(amputation? or ulcer* or foot or feet or wound*).tw.	683462
Other	44	((risk or progress* or prevent* or inciden* or conversion or develop* or delay*) adj4 (diabetes or T2D* or NIDDM or "type 2" or "type II")).tw.	115026
Other	45	or/19-44	7798944
Other	46	8 and 45	17446
Study design	47	random*.tw. or clinical trial*.mp. or exp treatment outcome/	3553394
Other	48	46 and 47	5421
Exclusions	49	exp animals/ or exp invertebrate/ or animal experiment/ or animal model/	27208302

		or animal tissue/ or animal cell/ or nonhuman/	
Exclusions	50	human/ or normal human/ or human cell/ [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	20417220
Exclusions	51	49 and 50	20365135
Exclusions	52	49 not 51	6843167
Exclusions	53	48 not 52	5231
Exclusions	54	conference.pt.	3973591
Exclusions	55	53 not 54	3628
Exclusions	56	(2017* or 2018* or 2019*).dc.	3395937
Other	57	55 and 56	644

Table 22. Search strategy for the Cochrane Library Databases

Term Group	#	Search terms	Results
Disease area	1	MeSH descriptor: [Prediabetic State] this term only	
Disease area	2	MeSH descriptor: [Glucose Intolerance] this term only	
Disease area	3	((prediabet* or pre diabet*)):ti,ab,kw (Word variations have been searched)	
Disease area	4	((intermediate hyperglyc?emi*)):ti,ab,kw (Word variations have been searched)	
Disease area	5	(((impaired fasting NEAR/2 glucose) or IFG or impaired IFG)):ti,ab,kw (Word variations have been searched)	
Disease area	6	(glucose intolerance):ti,ab,kw (Word variations have been searched)	
Disease area	7	(((impaired glucose NEAR (tolerance or metabolism)) or IGT)):ti,ab,kw (Word variations have been searched)	
Disease area	8	(("HbA(1c)" or HbA1 or HbA1c or "Hba 1c" or ((glycosylated or glycated) NEAR	

		h?emoglobin))):ti,ab,kw (Word variations have been searched)
Disease area	9	((risk NEAR/3 ("type2" or "type II" or diabetes or T2D* or NIDDM))):ti,ab,kw (Word variations have been searched)
Disease area	10	MeSH descriptor: [Diabetes Mellitus] this term only and with qualifier(s): [prevention & control - PC]
Disease area	11	MeSH descriptor: [Diabetes Mellitus, Type 2] this term only and with qualifier(s): [prevention & control - PC]
Disease area	12	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11
Other	13	MeSH descriptor: [Life Style] this term only
Other	14	MeSH descriptor: [Exercise] explode all trees
Other	15	MeSH descriptor: [Exercise Therapy] explode all trees
Other	16	MeSH descriptor: [Diet] explode all trees
Other	17	MeSH descriptor: [Diet Therapy] explode all trees
Other	18	(((lifestyle or life style) NEAR/3 (intervention? or change* or modif* or program or programme))):ti,ab,kw (Word variations have been searched)
Other	19	(diet*):ti,ab,kw (Word variations have been searched)
Other	20	((nutrition* NEAR/3 (intervention? or change* or modif* or program or programme))):ti,ab,kw (Word variations have been searched)
Other	21	(exercis*):ti,ab,kw (Word variations have been searched)
Other	22	(physical activit*):ti,ab,kw (Word variations have been searched)
Other	23	(resistance training):ti,ab,kw (Word variations have been searched)
Other	24	#13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23
Other	25	#12 and #24
Other	26	((diabetes prevention NEAR (program* or stud* or

		trial?))):ti,ab,kw (Word variations have been searched)
Other	27	#25 or #26
Other	28	(complication?):ti,ab,kw (Word variations have been searched)
Other	29	(mortality):ti,ab,kw (Word variations have been searched)
Other	30	((CHD or CVD)):ti,ab,kw (Word variations have been searched)
Other	31	((coronary NEAR/2 disease)):ti,ab,kw (Word variations have been searched)
Other	32	((coronar* NEAR (event? or syndrome?))):ti,ab,kw (Word variations have been searched)
Other	33	((heart NEAR (failure or disease? or attack? or infarct*))):ti,ab,kw (Word variations have been searched)
Other	34	((myocardial NEAR (infarc* or isch?emi*))):ti,ab,kw (Word variations have been searched)
Other	35	(cardiac failure):ti,ab,kw (Word variations have been searched)
Other	36	(angina):ti,ab,kw (Word variations have been searched)
Other	37	(revasculari*):ti,ab,kw (Word variations have been searched)
Other	38	((stroke or strokes)):ti,ab,kw (Word variations have been searched)
Other	39	(cerebrovascular):ti,ab,kw (Word variations have been searched)
Other	40	(((brain* or cerebr*) NEAR (infarct* or isch?emi*))):ti,ab,kw (Word variations have been searched)
Other	41	(apoplexy):ti,ab,kw (Word variations have been searched)
Other	42	(((vascular or peripheral arter*) NEAR disease?)):ti,ab,kw (Word variations have been searched)
Other	43	(cardiovascular):ti,ab,kw (Word variations have been searched)
Other	44	(neuropath* or polyneuropath*):ti,ab,kw (Word variations have been searched)
Other	45	(retinopath* or maculopath*):ti,ab,kw (Word variations have been searched)

Other	46	(nephropath* or nephrotic or proteinuri* or albuminuri*):ti,ab,kw (Word variations have been searched)
Other	47	(((chronic or endstage or end stage) NEAR (renal or kidney))):ti,ab,kw (Word variations have been searched)
Other	48	(crd or crf or ckf or ckd or eskd or eskf or esrd or esrf):ti,ab,kw (Word variations have been searched)
Other	49	((microvascular or macrovascular or ((micro or macro) NEAR vascular))):ti,ab,kw (Word variations have been searched)
Other	50	((cancer or carcino* or neoplas* or tumo?r?)):ti,ab,kw (Word variations have been searched)
Other	51	(amputation? or ulcer* or foot or feet or wound*):ti,ab,kw (Word variations have been searched)
Other	52	((kidney or renal) NEAR (disease? or failure or transplant*)):ti,ab,kw
Other	53	(((risk or progress* or prevent* or inciden* or conversion or develop* or delay*) NEAR/4 (diabetes or T2D* or NIDDM or "type 2" or "type II"))):ti,ab,kw (Word variations have been searched)
Other	54	#28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46 or #47 or #48 or #49 or #50 or #51 or #52 or #53
Other	55	#27 and #54

Table 23. Search strategy for the International Clinical Trials Registry Platform (Searched via the ICTRP search portal)

Term Group	#	Search terms	Results
Disease area/other	1	prediabet* AND lifestyle OR	66
Disease area/other	2	prediabet* AND style OR	11

Disease area/other	3	prediabet* AND exercis* OR prediabet* AND activity OR	45
Disease area/other	4	prediabet* AND diet* OR	45
Disease area/other	5	diabet* AND prevent* AND lifestyle OR	80
Disease area/other	6	diabet* AND prevent* AND style OR	235
Disease area/other	7	diabet* AND prevent* AND exercis* OR	28
Disease area/other	8	diabet* AND prevent* AND activity OR	146
Disease area/other	9	diabet* AND prevent* AND diet* OR	170
Disease area/other	10	diabet* AND incidence AND lifestyle OR	200
Disease area/other	11	diabet* AND incidence AND style OR	7
Disease area/other	12	diabet* AND incidence AND exercis* OR	8
Disease area/other	13	diabet* AND incidence AND activity OR	12
Disease area/other	14	diabet* AND incidence AND diet*	17

Table 24. Clinical Trials (Expert Search run by Clinical Trials)

Term Group	#	Search terms	Results
Disease area + other	1	EXACT "Interventional" [STUDY-TYPES] AND (prediabetes OR prediabetic OR "pre diabetes" OR "pre diabetic" OR hyperglycemia OR hyperglycaemia OR hyperglycemic OR hyperglycaemic OR "impaired glucose tolerance" OR "impaired fasting glucose" OR "glucose intolerance" OR IGT OR IFG OR "HbA(1c)" OR HbA1 OR HbA1c OR "HbA 1c" or glycosylated	76

		hemoglobin OR glycosylated haemoglobin OR glycated hemoglobin OR glycated haemoglobin OR "risk for diabetes" OR "risk of diabetes" OR "risk for type 2" OR "risk for type II" OR "risk of type 2" OR "risk of type II") [DISEASE] AND (exercise OR exercises OR training OR lifestyle OR "life style" OR activity OR activities OR physical OR diet OR dietary OR diets OR nutrition OR nutritional OR "diabetes prevention" OR "diabetes mellitus prevention" OR "type 2 prevention" OR "type II prevention") [TREATMENT] AND (complication OR complications OR mortality OR coronary OR heart OR myocardial OR infarct OR infarction OR infarcts OR infarctions OR ischemia OR ischemic OR ischaemia OR ischaemic OR failure OR angina OR revascularization OR revascularisation OR revascularizations OR revascularisations OR stroke OR strokes OR cerebrovascular OR apoplexy OR vascular or peripheral OR cardiovascular OR neuropathy OR neuropathies OR polyneuropathy OR polyneuropathies OR retinopathy OR retinopathies OR

		maculopathy OR maculopathies OR nephropathy OR nephropathies OR nephrotic OR proteinuria OR proteinuric OR albuminuria OR kidney OR renal OR microvascular OR macrovascular OR "micro vascular" OR "macro vascular" OR cancer OR carcinoma OR neoplasm OR neoplasms OR tumor OR tumors OR tumour OR tumours OR amputation OR amputations OR ulcer OR foot OR feet OR wounds OR ((diabetes OR "type 2" OR "type II" OR T2D OR T2DM) AND (risk OR progress OR progression OR progressed OR incident OR incidence OR conversion OR developed OR development OR develop OR delay OR delayed OR prevention OR prevent OR prevented))) [OUTCOME]	

Search Terms (question 4)

Search terms included combinations of free text and subject headings (Medical Subject Headings [MeSH] for MEDLINE, and Emtree terms for Embase), grouped into the following categories:

- disease area: **type 2 diabetes, nondiabetic hyperglycaemia**
- study design: **RCTs**
- other term group: **interventions, outcomes**
- exclusions: **exclusion terms**

Search terms for MEDLINE are shown in Table 25, search terms for Embase are shown in Table 26, search terms for pre-MEDLINE are shown in Table 27, and search terms for the Cochrane Library databases are shown in **Error! Reference source not found.**28.

Table 25. Search strategy for MEDLINE (searched via OVID)

Term Group	#	Search terms	Results
Disease area	1	exp Diabetes Mellitus, Type 2/	118291
Disease area	2	Diabetes Mellitus/	110119
Disease area	3	((type 2 or type II) and diabetes).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	148857
Disease area	4	(t2d or t2dm).mp.	17525
Disease area	5	niddm.mp.	6734
Disease area	6	1 or 2 or 3 or 4 or 5	251818
Other	7	exp Mass Screening/	118414
Other	8	screen*.mp.	639805
Other	9	early diagnosis/	23412
Other	10	(early adj4 (diagnos* or detect*)).mp.	180356
Other	11	7 or 8 or 9 or 10	791725
Study design	12	randomized controlled trial.pt.	471779
Study design	13	controlled clinical trial.pt.	92751
Study design	14	randomi?ed.ab.	446282
Study design	15	placebo.ab.	176049
Study design	16	Clinical Trials as Topic/	185394
Study design	17	randomly.ab.	258409
Study design	18	trial.ti.	164494
Study design	19	12 or 13 or 14 or 15 or 16 or 17 or 18	1100905
Other	20	6 and 11 and 19	1352
Exclusions	21	limit 20 to yr="2015 -Current"	352
Exclusions	22	limit 21 to (english language and humans)	340

Table 26. Search strategy for Embase (searched via OVID)

Term Group	#	Search terms	Results
Disease area	1	exp non insulin dependent diabetes mellitus/	222888

Disease area	2	diabetes mellitus/	540714
Disease area	3	((type 2 or type II) and diabetes).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	205942
Disease area	4	(t2d or t2dm).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	45079
Disease area	5	5 niddm.mp. (8173)	
Disease area	6	1 or 2 or 3 or 4 or 5	754805
Other	7	exp mass screening/ or exp screening/ or exp screening test/	653674
Other	8	screen*.mp.	1200560
Other	9	exp early diagnosis/	105295
Other	10	(early and (diagnos* or detect*)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	795622
Other	11	7 or 8 or 9 or 10	1906295
Study design	12	(random* or factorial* or crossover* or cross over* or cross-over* or placebo* or assign* or allocat* or volunteer*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating	2340665

		subheading word, candidate term word]	
Study design	13	((doubl* adj blind*) or (singl* adj blind*)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	283414
Study design	14	crossover procedure/	57850
Study design	15	double blind procedure/	158454
Study design	16	randomized controlled trial/	528439
Study design	17	17 single blind procedure/ (33272)	
Study design	18	12 or 13 or 14 or 15 or 16 or 17	2369420
Other	19	6 and 11 and 18	8601
Exclusions	20	limit 19 to yr="2015 -Current"	2783
Exclusions	21	limit 20 to (human and english language)	2637
Exclusions	22	limit 21 to (article or article in press or "review")	1607

Table 27. Search strategy for pre-MEDLINE (searched via OVID)

Term Group	#	Search terms	Results
Disease area	1	exp Diabetes Mellitus, Type 2/	0
Disease area	2	Diabetes Mellitus/	1
Disease area	3	((type 2 or type II) and diabetes).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	21141
Disease area	4	(t2d or t2dm).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword	5908

		heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	
Disease area	5	niddm.mp.	178
Disease area	6	1 or 2 or 3 or 4 or 5	21518
Other	7	exp Mass Screening/	0
Other	8	screen*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	90787
Other	9	(early adj4 (diagnos* or detect*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	25781
Other	10	7 or 8 or 9	112347
Study design	11	randomized controlled trial.pt.	278
Study design	12	controlled clinical trial.pt.	20
Study design	13	randomi?ed.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	73809
Study design	14	placebo.ab.	17665
Study design	15	clinical trials as topic.mp. [mp=title, abstract, original title, name of substance word,	51

		subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	
Study design	16	randomly.ab.	43059
Study design	17	17 trial.ti. (26485)	
Study design	18	11 or 12 or 13 or 14 or 15 or 16 or 17	118685
Other	19	6 and 10 and 18	138
Exclusions	20	limit 19 to yr="2015 -Current"	107
Exclusions	21	limit 20 to english language	105

Table 28. Search strategy for the Cochrane Library Databases

Term Group	#	Search terms	Results
Disease area	1	MeSH descriptor: [Diabetes Mellitus, Type 2] explode all trees	
Disease area	2	MeSH descriptor: [Diabetes Mellitus] this term only	
Disease area	3	((type 2 or type II) and diabetes):ti,ab,kw (Word variations have been searched)	
Disease area	4	(t2d or t2dm):ti,ab,kw	
Disease area	5	(niddm):ti,ab,kw	
Disease area	6	#1 or #2 or #3 or #4 or #5	
Other	7	MeSH descriptor: [Mass Screening] explode all trees	
Other	8	(screen*):ti,ab,kw	
Other	9	MeSH descriptor: [Early Diagnosis] this term only	
Other	10	(early and (diagnos* or detect*)):ti,ab,kw	
Other	11	#7 or #8 or #9 or #10	
Study design	12	(randomized controlled trial):pt	
Study design	13	("controlled clinical trial"):pt	
Study design	14	(randomi?ed):ab	
Study design	15	(placebo):ab	
Study design	16	MeSH descriptor: [Clinical Trials as Topic] this term only	
Study design	17	(randomly):ab	
Study design	18	(trial):ti	

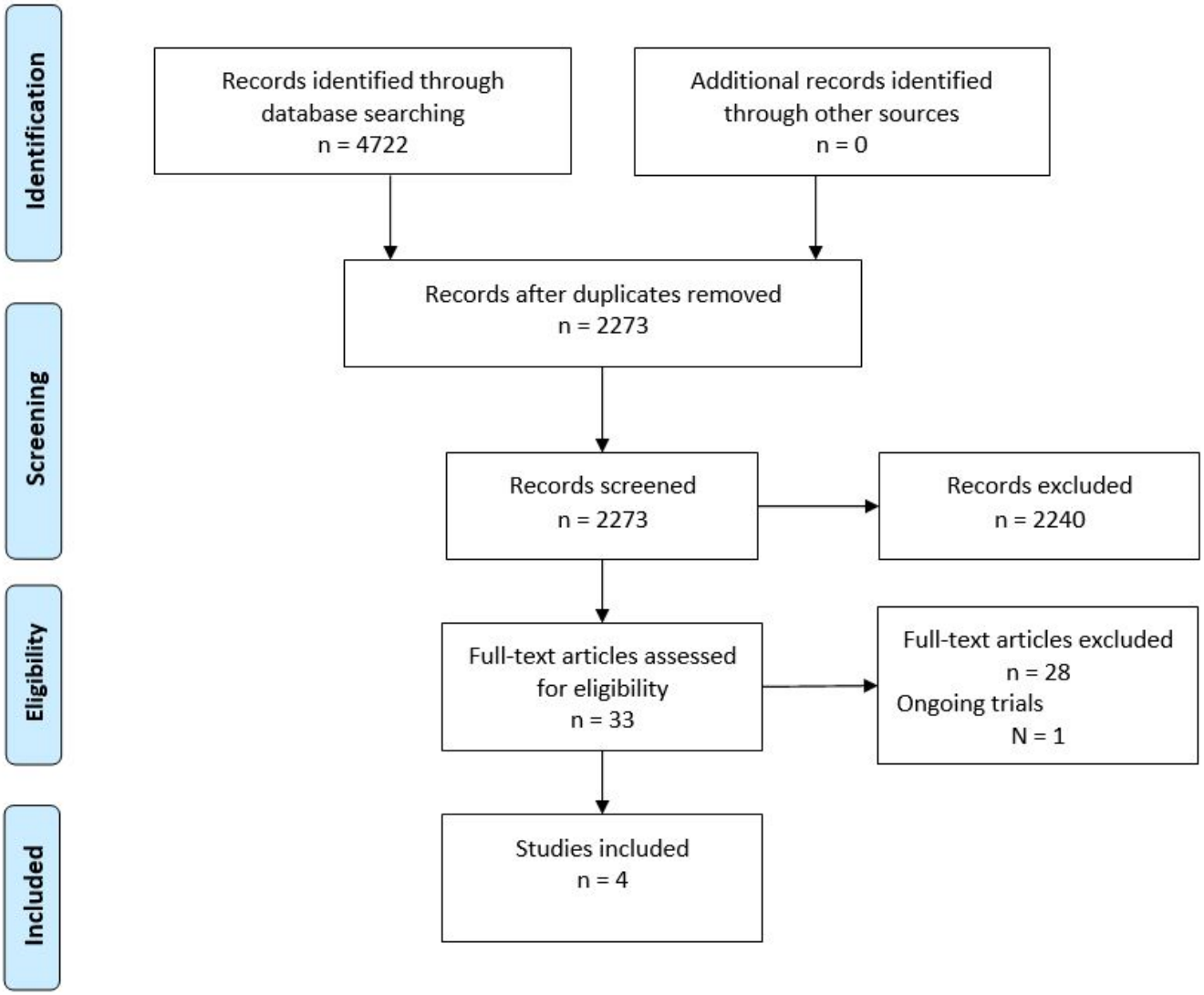
Study design	19	#12 or #13 or #14 or #15 or #16 or #17 or #18	
Other	20	#6 and #11 and #19	

Results were imported into EndNote and de-duplicated.

Appendix 2 — Included and excluded studies

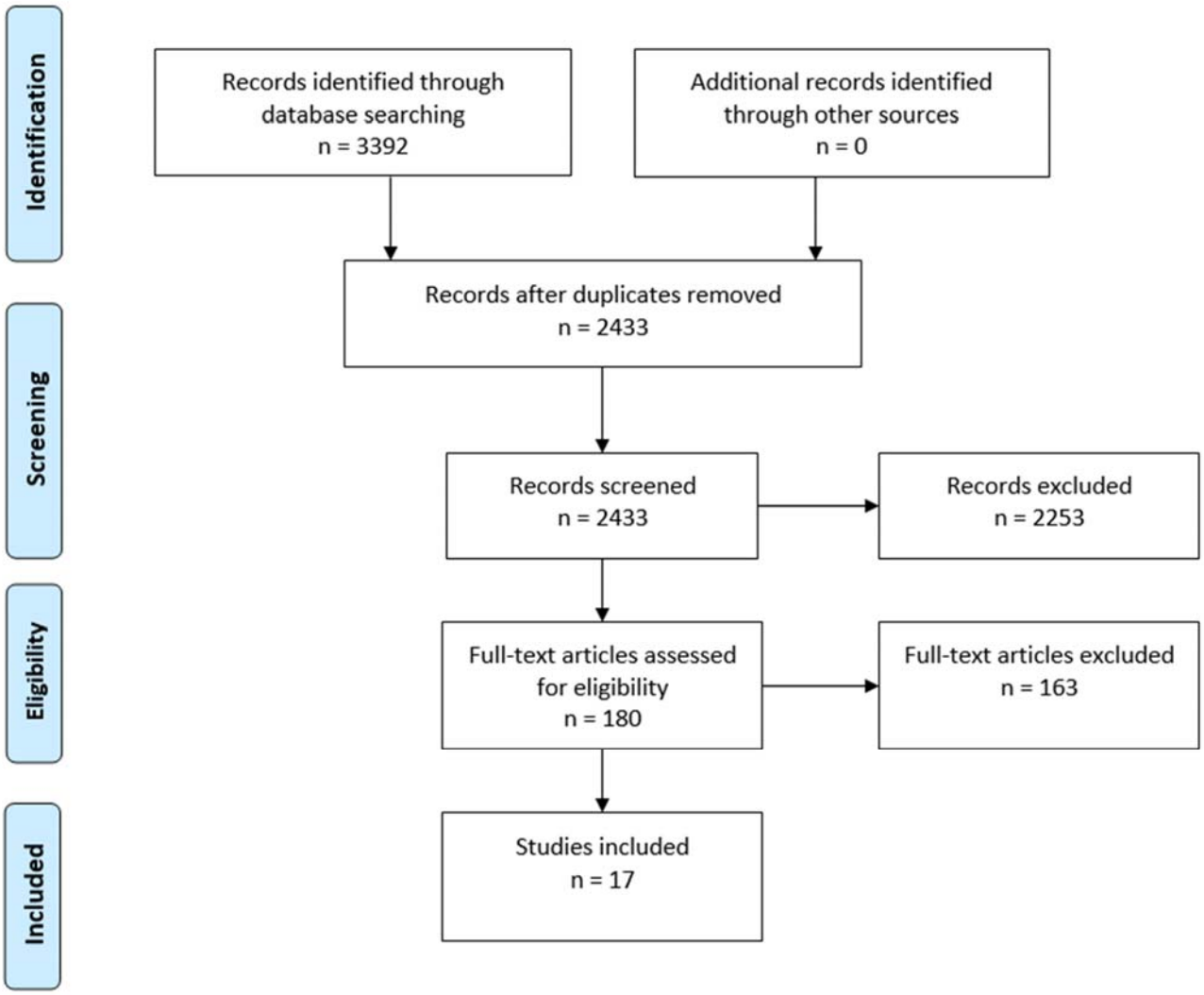
Error! Not a valid bookmark self-reference. summarises the volume of publications included and excluded at each stage of the review. Four publications were ultimately judged to be relevant and were considered for extraction. Publications that were included or excluded after the review of full-text articles are detailed below.

Figure 9. Summary of publications included and excluded at each stage of the review (question 1)



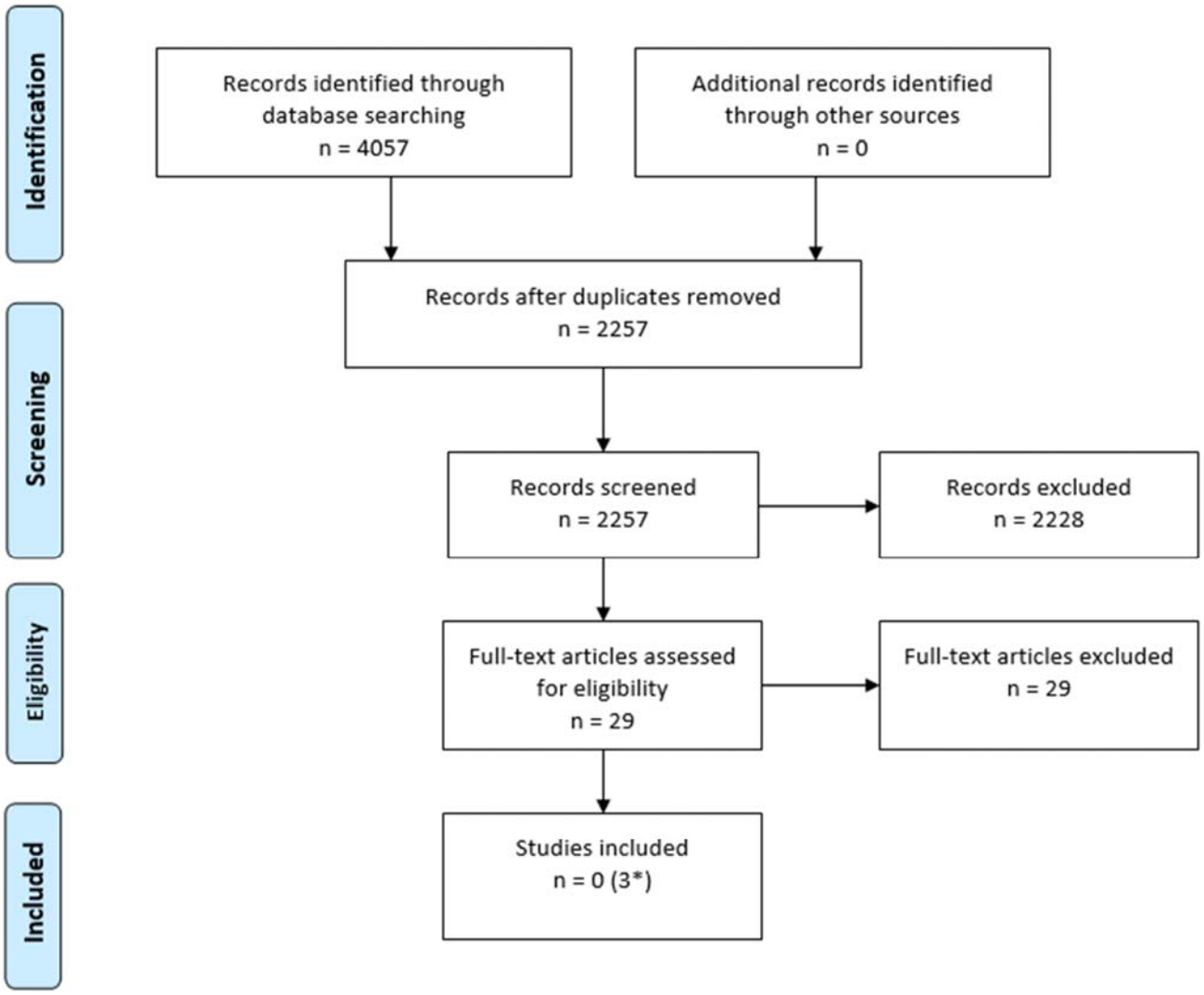
Error! Not a valid bookmark self-reference. summarises the volume of publications included and excluded at each stage of the review. Seventeen publications were ultimately judged to be relevant and were considered for extraction. Publications that were included or excluded after the review of full-text articles are detailed below.

Figure 10. Summary of publications included and excluded at each stage of the review (question 2 – FPG, 2-hour PG, and HbA1c)



Error! Not a valid bookmark self-reference. summarises the volume of publications included and excluded at each stage of the review. No publications were ultimately judged to be relevant and thus considered for extraction. Publications that were included or excluded after the review of full-text articles are detailed below.

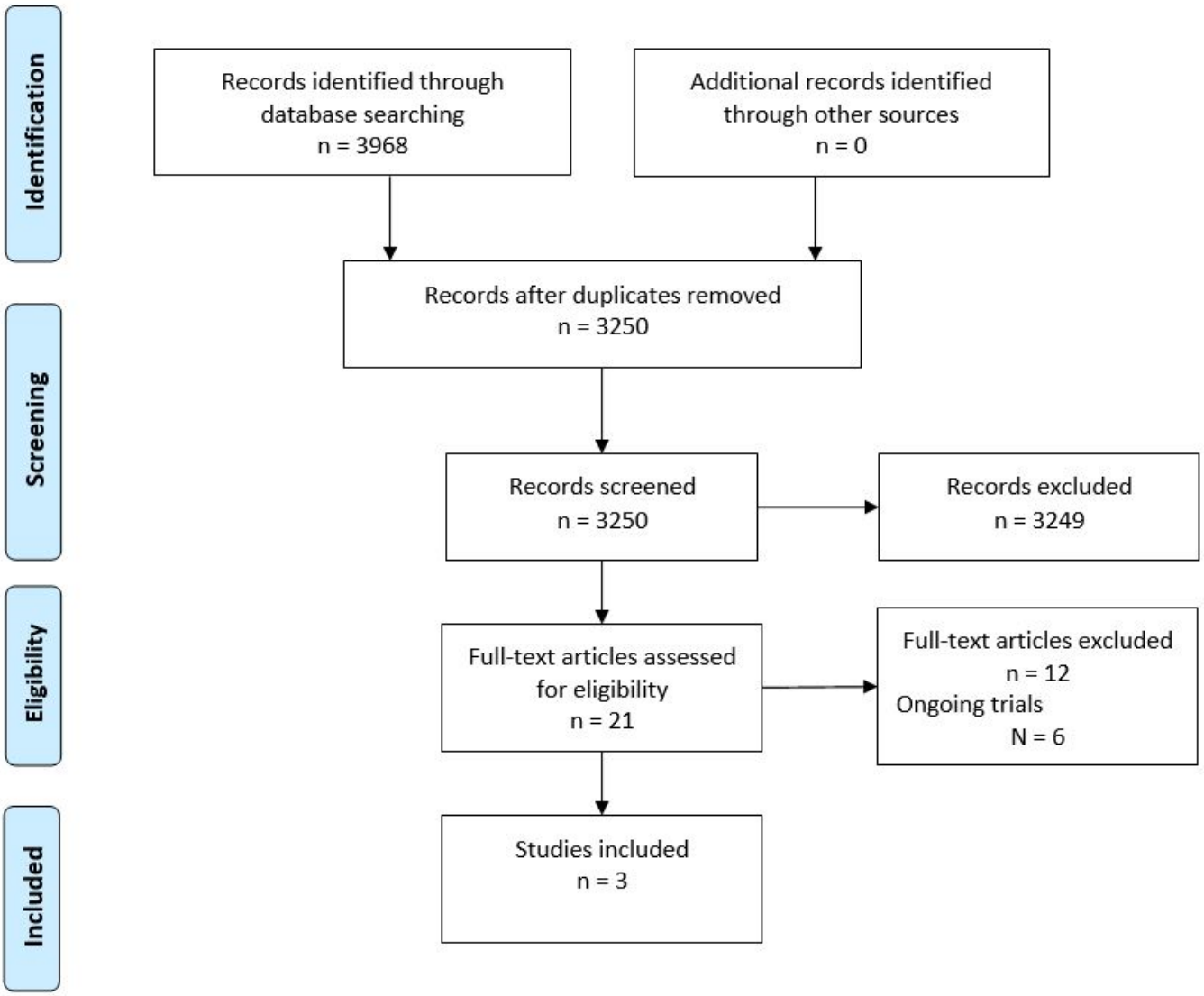
Figure 11. Summary of publications included and excluded at each stage of the review (question 2 – 50g GCT)



* 3 studies did not meet the inclusion criteria, but are discussed as the closest match to the review question

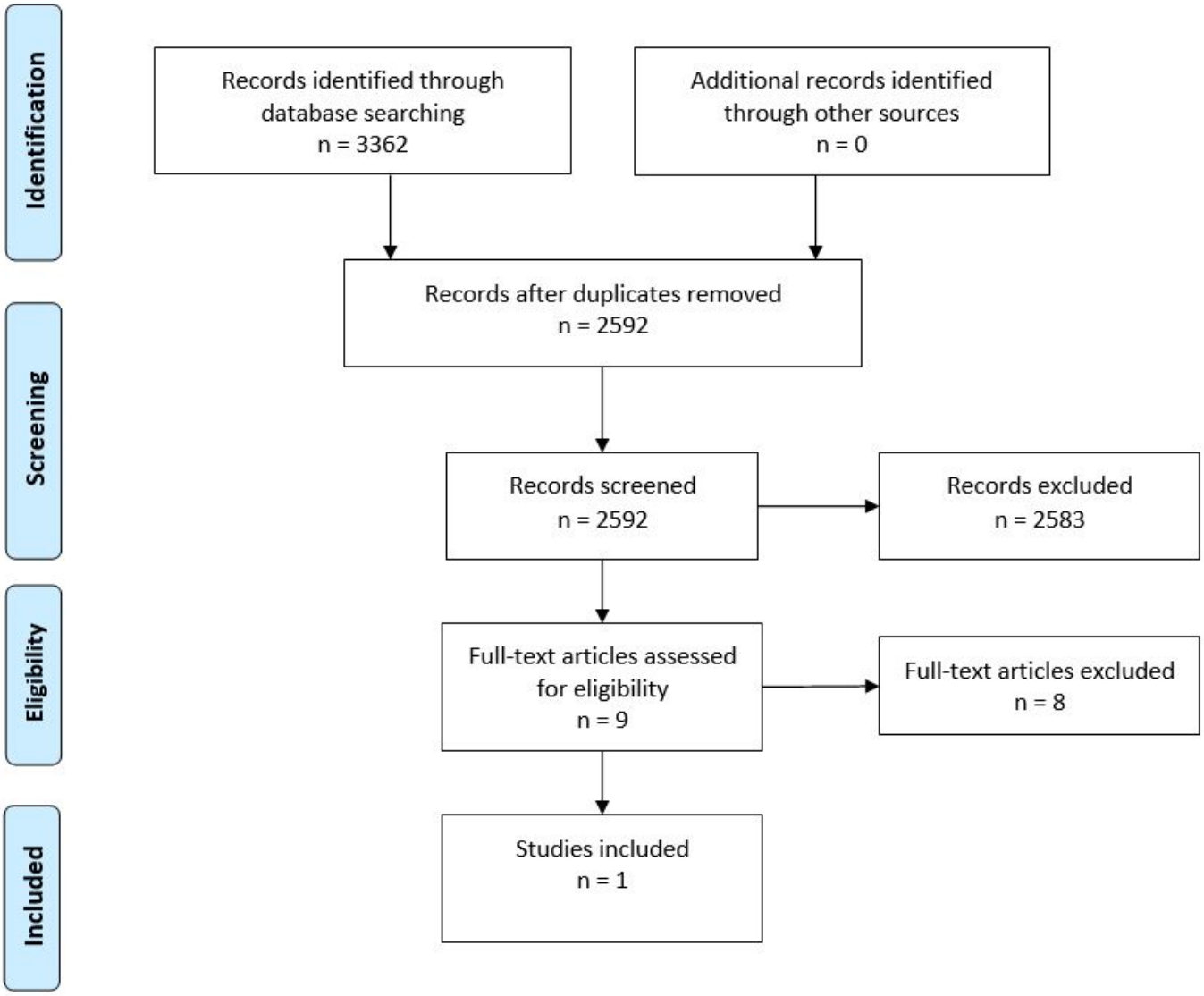
Error! Not a valid bookmark self-reference. summarises the volume of publications included and excluded at each stage of the review. Three publications were ultimately judged to be relevant and were considered for extraction. Publications that were included or excluded after the review of full-text articles are detailed below.

Figure 12. Summary of publications included and excluded at each stage of the review (question 3)



Error! Not a valid bookmark self-reference.3 summarises the volume of publications included and excluded at each stage of the review. One publication was ultimately judged to be relevant and were considered for extraction. Publications that were included or excluded after the review of full-text articles are detailed below.

Figure 13. Summary of publications included and excluded at each stage of the review (question 4)



Publications included after review of full-text articles

The 25 publications included after review of full-texts are summarised in **Error! Reference source not found.** below. Ongoing trials are identified in Tables 30–31.
Publications not selected for extraction and data synthesis are detailed in Tables 32–36 below.

Table 29. Summary of publications included after review of full-text articles, and the question(s) each publication was identified as being relevant to

Study	Q1	Q2	Q3	Q4
Barr	-	Y	-	-
Bongaerts	-	Y	-	-
Cederberg	-	Y	-	-
de Vegt	-	Y	-	-
Echouffo-Tcheugui	-	-	-	Y
Engelgau	-	Y	-	-
Franch-Nadal	Y	-	-	-
Giraldez-Garcia	Y	-	-	-
Herman	-	-	Y	-
Jung	Y	-	-	-
Kalogeropoulos	-	Y	-	-
Kowall	-	Y	-	-
McCance	-	Y	-	-
Metcalf	-	Y	-	-
Miyazaki	-	Y	-	-
Mukai	-	Y	-	-
Munch	-	Y	-	-
Park	Y	-	-	-
Salimi	-	-	Y	-
Shahbazi	-	-	Y	-
Tapp	-	Y	-	-
Toulis	-	Y	-	-
Vistisen	-	Y	-	-
Xin	-	Y	-	-
Zhang	-	Y	-	-

Table 30. Ongoing trials (question 1)

Trial name	Progression from Impaired Fasting Glucose to Diabetes Mellitus among Chinese (NCT03617757)
Starting date	October 1, 2017
Estimated completion date	June 2019
Contact information	Dr. Esther YT Yu, Ap Lei Chau General Out-patient Clinic Hong Kong, ytyu@hku.hk

Table 31. Ongoing trials (question 3)

Trial name	Hospital-based Diabetes Prevention Study in Korea
Starting date	November 2016
Estimated completion date	November 2010
Contact information	Jeong-Taek Woo, Kyunghee University Medical Center Seoul, South Korea, jtwoomd@khmc.or.kr

Trial name	Effect of Diet and Physical Activity on Incidence of Type 2 Diabetes (PREVIEW)
Starting date	June 2013
Estimated completion date	December 2018
Contact information	Professor Anne Raben, Department of Nutrition, Exercise and Sports (NEXS), Faculty of SCIENCE, University of Copenhagen, Denmark, ara@nexs.ku.dk

Trial name	Effect of Diet and Physical Activity on Incidence of Type 2 Diabetes (PREVIEW)
Starting date	June 2013
Estimated completion date	December 2018

Contact information	Professor Anne Raben, Department of Nutrition, Exercise and Sports (NEXS), Faculty of SCIENCE, University of Copenhagen, Denmark, ara@nexs.ku.dk

Trial name	Diabetes Prevention for Mexican Americans
Starting date	15th September 2017
Estimated completion date	March 2022
Contact information	Heather E Cuevas, University of Texas, USA, hcuevas@nursing.utexas.edu

Trial name	Diabetes Prevention Using SMS Technology
Starting date	3rd June 2013
Estimated completion date	30th November 2017
Contact information	Desmond Johnston, Imperial College London, UK, d.johnston@imperial.ac.uk

Trial name	The Norfolk Diabetes Prevention Study
Starting date	April 2011
Estimated completion date	July 2018
Contact information	Melanie Pascale, University of East Anglia, UK, melanie.pascale@nnuh.nhs.uk

Publications excluded after review of full-text articles

Publications excluded from the review (along with reasons for exclusion, are listed in **Error! Reference source not found.**32–36.

Table 32. Publications excluded after review of full-text articles question 1

	Reference	Reason for exclusion
1	Barber SR, Dhalwani NN, Davies MJ, et al. External national validation of the Leicester Self-Assessment score for Type 2 diabetes using data from the English Longitudinal Study of Ageing. Diabet Med 2017;34(11):1575-83.	Self-reported diabetes diagnosis
2	Bracco PA, Duncan BB, Barreto SM, et al. Progression of prediabetes to diabetes in Brazilian adults: Elsabrasil. Diabetes 2017;66 (Supplement 1):A425.	Conference abstract
3	Cahn A, Shoshan A, Sagiv T, et al. Use of a machine learning algorithm improves prediction of progression to diabetes. Diabetes 2018;67 (Supplement 1):A345.	Conference abstract
4	Davis J, Liu M, Alemi F, et al. Elevated HbA1c in united states veterans and risk of incident diabetes and all-cause mortality. Journal of General Internal Medicine 2017;32 (2 Supplement 1):S179.	Conference abstract
5	DeJesus RS, Breitkopf CR, Rutten LJ, et al. Incidence Rate of Prediabetes Progression to Diabetes: Modeling an Optimum Target Group for Intervention. Popul Health Manag 2017;20(3):216-23.	Retrospective cohort
6	Fazli GS. Prediabetes to type 2 diabetes among recent immigrants and long-term residents in canada. Diabetes 2017;66 (Supplement 1):A454-A55.	Conference abstract
7	Glauber H, Vollmer WM, Nichols GA. A Simple Model for Predicting Two-Year Risk of Diabetes Development in Individuals with Prediabetes. Perm 2018;22.	Diagnoses from medical records only
8	Golan R, Comaneshter DS, Vinker S, et al. Conversion to Diabetes 5 Years Post Bariatric Surgery in Individuals with Obesity and Pre-Diabetes. Surgery for Obesity and Related Diseases 2018;14 (11 Supplement):S99.	Conference abstract
9	He F. Diets with a low glycaemic load have favourable effects on prediabetes progression and regression: a prospective cohort study. J Hum Nutr Diet 2018;31(3):292-300.	Proportion of self-reported diabetes unclear. No reply from author
10	He FY, Chen CG, Lin DZ, et al. A greater glycemic load reduction was associated with a lower diabetes risk in pre-diabetic patients who consume a high glycemic load diet. Nutrition Research 2018;53:77-84.	Proportion of self-reported diabetes unclear. No reply from author
11	Hirata A, Sugiyama D, Kuwabara K, et al. Fatty liver index predicts incident diabetes in a Japanese general population with and without impaired fasting glucose. Hepatol 2018;48(9):708-16.	General health checks, not specifically diabetes

12	Iranfar N, Smith TC. When Should "Pre" Carry as Much Weight in the Diabetes Comorbidity Debate? Insights From a Population-Based Survey. Prev Chronic Dis 2018;15:E36.	Self-reported diabetes diagnosis
13	Johnson ES, Keast EM, Yang X, et al. A pragmatic model to predict diabetes among patients with elevated hemoglobin A1c values: A cohort study. Pharmacoepidemiology and Drug Safety 2017;26 (Supplement 2):77-78.	Conference abstract
14	Kim CW, Chang Y, Sung E, et al. Sleep duration and progression to diabetes in people with prediabetes defined by HbA_{1c} concentration. Diabet Med 2017;34(11):1591-98.	General health checks, not specifically diabetes
15	Krabbe CEM, Schipf S, Ittermann T, et al. Comparison of traditional diabetes risk scores and HbA1c to predict type 2 diabetes mellitus in a population based cohort study. J Diabetes Complications 2017;31(11):1602-07.	Diabetes diagnosis via self-report, use of antidiabetic medication, or random plasma glucose. No separation of data by method.
16	Lee DY, Park SK, Kim HJ, et al. The influence of prehypertension, hypertension and HbA1c on the development of type 2 diabetes mellitus in prediabetes: The Korean genome and epidemiology study (KOGES). Journal of Hypertension 2018;36 (Supplement 1):e83.	Conference abstract
17	Leong A, Daya N, Porneala B, et al. Type 2 diabetes (T2D) prediction by hemoglobin A1C in real-world scenarios. Diabetes 2017;66 (Supplement 1):A418-A19.	Conference abstract
18	Liu L, Guan X, Yuan Z, et al. Different contributions of lipid profiles and BMI to the natural history of type 2 diabetes: A 3-year cohort study in China. Diabetes/Metabolism Research and Reviews Conference: 21st Scientific Meeting of the Chinese Diabetes Society China 2017;33(Supplement 1).	Conference abstract
19	Mahtab N, Farzad H, Mohsen B, et al. The 10-year trend of adult diabetes, prediabetes and associated risk factors in Tehran: Phases 1 and 4 of Tehran Lipid and Glucose Study. Diabetes Metab Syndr 2017;11(3):183-87.	Not prospective cohort (cross-sectional)
20	Mansourian M, Yazdani A, Faghihimani E, et al. Factors associated with progression to pre-diabetes: a recurrent events analysis. Eat Weight Disord 2018;22:22.	Participants do not have NDH at baseline
21	Pasquel FJ, Loop MS, Menke A, et al. Progression from prediabetes to diabetes in hispanics/latinos. Results from the hispanic community health study/study of latinos (HCHS/SOL). Circulation Conference: American Heart Association's Epidemiology and Prevention/Lifestyle and Cardiometabolic Health 2018;137(Supplement 1).	Conference abstract
22	Quan J, Li TK, Pang H, et al. Diabetes incidence and prevalence in Hong Kong, China during 2006-2014. Diabet Med 2017;34(7):902-08.	Not prospective cohort (cross-sectional)
23	Roncero-Ramos I, Jimenez-Lucena R, Alcala-Diaz JF, et al. Alpha cell function interacts with diet to modulate prediabetes and Type 2 diabetes. Journal of Nutritional Biochemistry 2018;62:247-56.	Not prospective cohort (intervention)

24	Shang Y, Fratiglioni L, Marsegilia A, et al. Incidence and evolution of prediabetes among older adults-a population-based cohort study. Diabetes 2018;67 (Supplement 1):LB49.	Conference abstract
25	Ustulin M, Rhee SY, Chon S, et al. Importance of family history of diabetes in computing a diabetes risk score in Korean prediabetic population. Sci 2018;8(1):15958.	Not prospective cohort (retrospective)
26	Voortman T, Chen Z, Franco OH. Protein intake and risk of prediabetes and type 2 diabetes. FASEB Journal Conference: Experimental Biology 2017;31(1 Supplement 1).	Conference abstract
27	Warren B, Pankow JS, Matsushita K, et al. Comparative prognostic performance of definitions of prediabetes: a prospective cohort analysis of the Atherosclerosis Risk in Communities (ARIC) study. Lancet Diabetes Endocrinol 2017;5(1):34-42.	Diabetes diagnosis via self-report of physician or glucose-lowering medication only
28	Wu J, Ward E, Threatt T, et al. Progression to Type 2 Diabetes and Its Effect on Health Care Costs in Low-Income and Insured Patients with Prediabetes: A Retrospective Study Using Medicaid Claims Data. J Manag Care Spec Pharm 2017;23(3):309-16.	Not prospective cohort (retrospective)

Table 33. Publications excluded after review of full-text articles question 2 (FPG, 2-hour PG, HbA1c)

	Reference	Reason for exclusion
1	Lind M, Tuomilehto J, Uusitupa M, Nerman O, Eriksson J, Ilanne-Parikka P, et al. The association between HbA1c, fasting glucose, 1-hour glucose and 2-hour glucose during an oral glucose tolerance test and cardiovascular disease in individuals with elevated risk for diabetes. PLoS ONE. 2014;9(10):e109506.	Subpopulation
2	AbuShady MM, Mohamady Y, Enany B, Nammas W. Prevalence of prediabetes in patients with acute coronary syndrome: impact on in-hospital outcomes. Intern Med J. 2015;45(2):183-8.	Subpopulation
3	Akha O, Makhlough A, Khoddad T, Kharazm P. Evaluation of microalbuminuria and its related risk factors in patients with type II diabetes referred to endocrinology clinics in Sari, 2003-2009. [Persian]. Journal of Mazandaran University of Medical Sciences. 2013;23(107):11-8.	Not in English
4	Alattar A, Al-Majed H, Almuaili T, Almutairi O, Shaghouli A, Altorah W. Prevalence of impaired glucose regulation in asymptomatic Kuwaiti young adults. Med Princ Pract. 2012;21(1):51-5.	No eligible health outcome
5	Almeida-Junior JL, Gil-Santana L, Oliveira CA, Castro S, Cafezeiro AS, Daltro C, et al. Glucose Metabolism Disorder Is Associated with Pulmonary Tuberculosis in Individuals with Respiratory Symptoms from Brazil. PLoS ONE. 2016;11(4):e0153590.	Subpopulation
6	Altin C, Sade LE, Gezmis E, Ozen N, Duzceker O, Bozbas H, et al. Assessment of Subclinical Atherosclerosis by Carotid Intima-Media Thickness and Epicardial Adipose Tissue Thickness in Prediabetes. Angiology. 2016;67(10):961-9.	No eligible health outcome
7	Amini M, Horri N, Zare M, Haghighi S, Hosseini SM, Aminorroaya A, et al. People with impaired glucose tolerance and impaired fasting glucose are similarly susceptible to cardiovascular disease: a study in first-degree relatives of type 2 diabetic patients. Ann Nutr Metab. 2010;56(4):267-72.	No eligible health outcome

8	Araki A, Ito H, Hattori A, Inoue J, Sato T, Shiraki M, et al. Risk factors for development of retinopathy in elderly Japanese patients with diabetes mellitus. Diabetes Care. 1993;16(8):1184-6.	Subpopulation
9	Arora S, Gordon MB. High incidence of impaired glucose regulation in patients with no known history of diabetes mellitus but with hyperglycemia after undergoing a cardiac surgical procedure. Endocr Pract. 2009;15(5):425-30.	No eligible health outcome
10	Aviles-Santa ML, Perez CM, Schneiderman N, Savage PJ, Kaplan RC, Teng Y, et al. Detecting prediabetes among Hispanics/Latinos from diverse heritage groups: Does the test matter? Findings from the Hispanic Community Health Study/Study of Latinos. Prev Med. 2017;95:110-8.	No eligible health outcome
11	Aviles-Santa ML, Schneiderman N, Savage PJ, Kaplan RC, Teng Y, Perez CM, et al. Identifying Probable Diabetes Mellitus among Hispanics/Latinos from Four U.S. Cities: Findings from the Hispanic Community Health Study/Study of Latinos. Endocr Pract. 2016;22(10):1151-60.	No eligible health outcome
12	Badings EA, Dyal L, Schoterman L, Lok DJ, Stoel I, Gerding MN, et al. Strategies to detect abnormal glucose metabolism in people at high risk of cardiovascular disease from the ORIGIN (Outcome Reduction with Initial Glargine Intervention) trial population. J Diabetes. 2011;3(3):232-7.	No eligible health outcome
13	Bahar A, Makhlough A, Yousefi A, Kashi Z, Abediankenari S. Correlation between prediabetes conditions and microalbuminuria. Nephro-Urology Monthly. 2013;5(2):741-4.	Outcome not reported for all three tests
14	Benaiges D, Chillaron JJ, Pedro-Botet J, Mas A, Puig de Dou J, Sagarra E, et al. Role of A1c in the postpartum screening of women with gestational diabetes. Gynecol Endocrinol. 2013;29(7):687-90.	Ineligible population
15	Bergman M, Chetrit A, Roth J, Dankner R. Dysglycemia and long-term mortality: observations from the Israel study of glucose intolerance, obesity and hypertension. Diabetes Metab Res Rev. 2015;31(4):368-75.	Ineligible index test
16	Bethel MA, Chacra AR, Deedwania P, Fulcher GR, Holman RR, Jenssen T, et al. A novel risk classification paradigm for patients with impaired glucose tolerance and high cardiovascular risk. Am J Cardiol. 2013;112(2):231-7.	No eligible health outcome
17	Bhowmik B, Binte Munir S, Ara Hossain I, Siddiquee T, Diep LM, Mahmood S, et al. Prevalence of type 2 diabetes and impaired glucose regulation with associated cardiometabolic risk factors and depression in an urbanizing rural community in bangladesh: a population-based cross-sectional study. Diabetes Metab J. 2012;36(6):422-32.	No eligible health outcome
18	Bjarnason TA, Hafthorsson SO, Kristinsdottir LB, Oskarsdottir ES, Aspelund T, Sigurdsson S, et al. Oral glucose tolerance test predicts increased carotid plaque burden in patients with acute coronary syndrome. PLoS ONE. 2017;12(8):e0183839.	Subpopulation
19	Bjarnason TA, Kristinsdottir LB, Oskarsdottir ES, Hafthorsson SO, Olafsson I, Lund SH, et al. Editor's Choice- Diagnosis of type 2 diabetes and prediabetes among patients with acute coronary syndromes. Europ Heart J Acute Cardiovasc Care. 2017;6(8):744-9.	Subpopulation
20	Bonora E, Kiechl S, Willeit J, Oberhollenzer F, Egger G, Bonadonna R, et al. Plasma glucose within the normal range is not associated with carotid atherosclerosis: prospective results in subjects with normal glucose tolerance from the Bruneck Study. Diabetes Care. 1999;22(8):1339-46.	No eligible health outcome
21	Boronat M, Saavedra P, Lopez-Rios L, Riano M, Wagner AM, Novoa FJ. Differences in cardiovascular risk profile of diabetic subjects discordantly classified by diagnostic criteria based on glycated hemoglobin and oral glucose tolerance test. Diabetes Care. 2010;33(12):2671-3.	No eligible health outcome
22	Braatvedt G, Gamble G, Kyle C. Metabolic characteristics of patients with apparently normal fasting plasma glucose. N Z Med J. 2006;119(1240):U2123.	No eligible health outcome
23	Bur A, Herkner H, Woisetschlager C, Vlcek M, Derhaschnig U, Hirschl MM. Is fasting blood glucose a reliable parameter for screening for diabetes in hypertension? Am J Hypertens. 2003;16(4):297-301.	Subpopulation

24	Cederholm J, Ronquist G, Wibell L. Comparison of glycosylated hemoglobin with the oral glucose tolerance test; a study in subjects with normoglycemia, glucose intolerance and non-insulin-dependent diabetes mellitus. Diabete et Metabolisme. 1984;10(4):224-9.	No eligible health outcome
25	Chen YX, Fang CF, Wang X, Nie RQ, Li G, Tang L, et al. Glucometabolic state of in-hospital primary hypertension patients with normal fasting blood glucose in a sub-population of China. Diabetes Metab Res Rev. 2009;25(4):357-62.	Subpopulation
26	Colomo N, Linares F, Rubio-Martin E, Moreno MJ, de Mora M, Garcia AM, et al. Stress hyperglycaemia in hospitalized patients with coronary artery disease and type 2 diabetes risk. Eur J Clin Invest. 2013;43(10):1060-8.	Subpopulation
27	Davies MJ, Raymond NT, Day JL, Hales CN, Burden AC. Impaired glucose tolerance and fasting hyperglycaemia have different characteristics. Diabet Med. 2000;17(6):433-40.	No eligible health outcome
28	De La Hera JM, Vegas JM, Hernandez E, Lozano I, Garcia-Ruiz JM, Fernandez-Cimadevilla OC, et al. Performance of glycated hemoglobin and a risk model for detection of unknown diabetes in coronary patients. [Spanish]. Revista Espanola de Cardiologia. 2011;64(9):759-65.	Subpopulation
29	de Mulder M, Oemrawsingh RM, Stam F, Boersma E, Umans VA. Comparison of diagnostic criteria to detect undiagnosed diabetes in hyperglycaemic patients with acute coronary syndrome. Heart. 2012;98(1):37-41.	Subpopulation
30	De Pergola G, Nardecchia A, Cirillo M, Boninfante B, Sciaraffia M, Giagulli VA, et al. Higher Waist Circumference, Fasting Hyperinsulinemia And Insulin Resistance Characterize Hypertensive Patients With Impaired Glucose Metabolism. Endocr Metab Immune Disord Drug Targets. 2015;15(4):297-301.	Subpopulation
31	De Rekeneire N, Peila R, Ding J, Colbert LH, Visser M, Shorr RI, et al. Diabetes, hyperglycemia, and inflammation in older individuals: The Health, Aging and Body Composition study. Diabetes Care. 2006;29(8):1902-8.	Outcome not reported for all three tests
32	Del Olmo MI, Merino-Torres JF, Argente M, Ramos A, Navas MS, Campos V, et al. Detection of glucose abnormalities in patients with acute coronary heart disease: study of reliable tools in clinical practice. J Endocrinol Invest. 2012;35(1):71-6.	Subpopulation
33	Demmer RT, Allison MA, Cai J, Kaplan RC, Desai AA, Hurwitz BE, et al. Association of Impaired Glucose Regulation and Insulin Resistance With Cardiac Structure and Function: Results From ECHO-SOL (Echocardiographic Study of Latinos). Circ Cardiovasc Imaging. 2016;9(10).	Outcome not reported for all three tests
34	Di Pino A, Mangiafico S, Urbano F, Scicali R, Scandura S, D'Agate V, et al. HbA1c Identifies Subjects With Prediabetes and Subclinical Left Ventricular Diastolic Dysfunction. J Clin Endocrinol Metab. 2017;102(10):3756-64.	Outcome not reported for all three tests
35	Diamantopoulos EJ, Andreadis EA, Tsourous GI, Katsanou PM, Georgiopoulos DX, Dimitriadis GD, et al. Intermediate postchallenge hyperglycemia in overweight and obese subjects: a new marker of impaired glucose regulation? Angiology. 2006;57(6):709-16.	Outcome not reported for all three tests
36	Dimova R, Tankova T, Guergueltcheva V, Tournev I, Chakarova N, Grozeva G, et al. Risk factors for autonomic and somatic nerve dysfunction in different stages of glucose tolerance. J Diabetes Complications. 2017;31(3):537-43.	Outcome not reported for all three tests
37	Ding C, Hsu SH, Wu YJ, Su TC. Additive effects of postchallenge hyperglycemia and low-density lipoprotein particles on the risk of arterial stiffness in healthy adults. Lipids health dis. 2014;13:179.	No eligible health outcome
38	Doerr R, Hoffmann U, Otter W, Heinemann L, Hunger-Battefeld W, Kulzer B, et al. Oral glucose tolerance test and HbA1c for diagnosis of diabetes in patients undergoing coronary angiography: [corrected] the Silent Diabetes Study.[Erratum appears in Diabetologia. 2011 Nov;54(11):2968]. Diabetologia. 2011;54(11):2923-30.	Subpopulation

39	Dyck PJ, Clark VM, Overland CJ, Davies JL, Pach JM, Dyck PJB, et al. Impaired glycemia and diabetic polyneuropathy: The OC IG survey. Diabetes Care. 2012;35(3):584-91.	Outcome not reported for all three tests
40	Faerch K, Johansen NB, Witte DR, Lauritzen T, Jorgensen ME, Vistisen D. Relationship between insulin resistance and s-cell dysfunction in subphenotypes of prediabetes and type 2 diabetes. Translational Endocrinology and Metabolism. 2015;100(2):707-16.	Subpopulation
41	Faerch K, Witte DR, Tabak AG, Perreault L, Herder C, Brunner EJ, et al. Trajectories of cardiometabolic risk factors before diagnosis of three subtypes of type 2 diabetes: a post-hoc analysis of the longitudinal Whitehall II cohort study. Lancet Diabetes Endocrinol. 2013;1(1):43-51.	No eligible health outcome
42	Faghihi-Kashani S, Bonnet F, Hafezi-Nejad N, Heidari B, Aghajani Nargesi A, Sheikhbahaei S, et al. Fasting hyperinsulinaemia and 2-h glycaemia predict coronary heart disease in patients with type 2 diabetes. Diabetes Metab. 2016;42(1):55-61.	Subpopulation
43	Farhan S, Jarai R, Tentzeris I, Kautzky-Willer A, Samaha E, Smetana P, et al. Comparison of HbA1c and oral glucose tolerance test for diagnosis of diabetes in patients with coronary artery disease. Clin. 2012;101(8):625-30.	Subpopulation
44	Feringa HH, Vidakovic R, Karagiannis SE, Dunkelgrun M, Elhendy A, Boersma E, et al. Impaired glucose regulation, elevated glycated haemoglobin and cardiac ischaemic events in vascular surgery patients. Diabet Med. 2008;25(3):314-9.	Subpopulation
45	Fonville S, Zandbergen AA, Vermeer SE, Dippel DW, Koudstaal PJ, den Hertog HM. Prevalence of prediabetes and newly diagnosed diabetes in patients with a transient ischemic attack or stroke. Cerebrovasc Dis. 2013;36(4):283-9.	Subpopulation
46	Gianchandani RY, Saberi S, Patil P, Prager RL, Pop-Busui R. Prevalence and Determinants of Glycemic Abnormalities in Cardiac Surgery Patients without a History of Diabetes: A Prospective Study. Front Endocrinol (Lausanne). 2015;6:125.	Subpopulation
47	Gianchandani RY, Saberi S, Zrull CA, Patil PV, Jha L, Kling-Colson SC, et al. Evaluation of hemoglobin A1c criteria to assess preoperative diabetes risk in cardiac surgery patients. Diabetes Technol Ther. 2011;13(12):1249-54.	Subpopulation
48	Giblin LJ, Boyd LD, Rainchuso L, Chadbourne D. Short-term effects of non-surgical periodontal therapy on clinical measures of impaired glucose tolerance in people with prediabetes and chronic periodontitis. J Dent Hyg. 2014;88 Suppl 1:23-30.	Subpopulation
49	Gui MH, Qin GY, Ning G, Hong J, Li XY, Lu AK, et al. The comparison of coronary angiographic profiles between diabetic and nondiabetic patients with coronary artery disease in a Chinese population. Diabetes Research and Clinical Practice. 2009;85(2):213-9.	Subpopulation
50	Gyberg V, De Bacquer D, Kotseva K, De Backer G, Schnell O, Sundvall J, et al. Screening for dysglycaemia in patients with coronary artery disease as reflected by fasting glucose, oral glucose tolerance test, and HbA1c: A report from EUROASPIRE IV - A survey from the European Society of Cardiology. European Heart Journal. 2015;36(19):1171-7c.	Subpopulation
51	Gyberg V, De Bacquer D, Kotseva K, De Backer G, Schnell O, Tuomilehto J, et al. Time-saving screening for diabetes in patients with coronary artery disease: a report from EUROASPIRE IV. BMJ Open. 2016;6(12):e013835.	Subpopulation
52	Hage C, Lundman P, Ryden L, Mellbin L. Fasting glucose, HbA1c, or oral glucose tolerance testing for the detection of glucose abnormalities in patients with acute coronary syndromes. Eur J Prev Cardiolog. 2013;20(4):549-54.	Subpopulation
53	Han JY, Ma XY, Yu LJ, Shao Y, Wang QY. Correlation between serum YKL-40 levels and albuminuria in type 2 diabetes. Genet Mol Res. 2015;14(4):18596-603.	Subpopulation
54	Han XY, Ji LN, Zhou XH. Cross-sectional study of the pathophysiologic and clinical features in the first-degree relatives of type 2 diabetic patients. [Chinese]. Beijing da xue xue bao. 2005;Yi xue ban = Journal of Peking University. Health sciences. 37(2):159-62.	Not in English

55	Hanefeld M, Koehler C, Henkel E, Fuecker K, Schaper F, Temelkova-Kurktschiev T. Post-challenge hyperglycaemia relates more strongly than fasting hyperglycaemia with carotid intima-media thickness: the RIAD Study. Risk Factors in Impaired Glucose Tolerance for Atherosclerosis and Diabetes. Diabet Med. 2000;17(12):835-40.	Outcome not reported for all three tests
56	Hanefeld M, Temelkova-Kurktschiev T, Schaper F, Henkel E, Siegert G, Koehler C. Impaired fasting glucose is not a risk factor for atherosclerosis. Diabet Med. 1999;16(3):212-8.	Outcome not reported for all three tests
57	Hashimoto K, Ikewaki K, Yagi H, Nagasawa H, Imamoto S, Shibata T, et al. Glucose intolerance is common in Japanese patients with acute coronary syndrome who were not previously diagnosed with diabetes. Diabetes Care. 2005;28(5):1182-6.	Subpopulation
58	Henninger J, Hammarstedt A, Rawshani A, Eliasson B. Metabolic predictors of impaired glucose tolerance and type 2 diabetes in a predisposed population--A prospective cohort study. BMC Endocr Disord. 2015;15:51.	No eligible health outcome
59	Hjellestad ID, Astor MC, Nilsen RM, Softeland E, Jonung T. HbA1c versus oral glucose tolerance test as a method to diagnose diabetes mellitus in vascular surgery patients.[Erratum appears in Cardiovasc Diabetol. 2018 Mar 22;17 (1):42; PMID: 29566676]. Cardiovasc. 2013;12:79.	Subpopulation
60	Hjellestad ID, Softeland E, Husebye ES, Jonung T. HbA1c predicts long-term postoperative mortality in patients with unknown glycemic status at admission for vascular surgery: An exploratory study. J Diabetes. 2018;27:27.	Subpopulation
61	Holzmann M, Olsson A, Johansson J, Jensen-Urstad M. Left ventricular diastolic function is related to glucose in a middle-aged population. Journal of Internal Medicine. 2002;251(5):415-20.	No eligible health outcome
62	Huang X, Zhou Y, Xu B, Sun W, Lin L, Sun J, et al. Glycated haemoglobin A1c is associated with low-grade albuminuria in Chinese adults. BMJ Open. 2015;5(8):e007429.	No extractable data
63	Hutchinson MS, Joakimsen RM, Njolstad I, Schirmer H, Figenschau Y, Svartberg J, et al. Effects of age and sex on estimated diabetes prevalence using different diagnostic criteria: The tromso OGTT study. International Journal of Endocrinology. 2013;2013 (no pagination)(613475).	No eligible health outcome
64	Iraj B, Taheri N, Amini M, Amini P, Aminorroaya A. Should the first degree relatives of type 2 diabetic patients with isolated impaired fasting glucose be considered for a diabetes primary prevention program? J. 2010;15(5):264-9.	No eligible health outcome
65	Ito C. Evidence for diabetes mellitus criteria in 2010 using HbA1c. Diabetology International. 2013;4(1):9-15.	Outcome not reported for all three tests
66	Jing J, Pan Y, Zhao X, Zheng H, Jia Q, Li H, et al. Prognosis of Ischemic Stroke with Newly Diagnosed Diabetes Mellitus According to Hemoglobin A1c Criteria in Chinese Population. Stroke. 2016;47(8):2038-44.	Subpopulation
67	Joshipura KJ, Munoz-Torres FJ, Dye BA, Leroux BG, Ramirez-Vick M, Perez CM. Longitudinal association between periodontitis and development of diabetes. Diabetes Res Clin Pract. 2018;141:284-93.	Outcome not reported for all three tests
68	Kalogeropoulos A, Georgiopoulou V, Harris TB, Kritchevsky SB, Bauer DC, Smith AL, et al. Glycemic status and incident heart failure in elderly without history of diabetes mellitus: the health, aging, and body composition study. J Card Fail. 2009;15(7):593-9.	Ineligible population
69	Karatas M, Sahin M, Ertugrul D, Kulaksizoglu M, Dogruk A, Gokcel A, et al. High prevalence of neuropathy in patients with impaired 60-minute oral glucose tolerance test but normal fasting and 120-minute glucose levels. Minerva Endocrinologica. 2008;33(4):289-96.	Outcome not reported for all three tests
70	Kim HJ, Ahn CW, Kang ES, Myoung SM, Cha BS, Won YJ, et al. The level of 2-h post-challenge glucose is an independent risk factor of carotid intima-media thickness progression in Korean type 2 diabetic patients. J Diabetes Complications. 2007;21(1):7-12.	Subpopulation

71	Knudsen EC, Seljeflot I, Abdelnoor M, Eritsland J, Mangschau A, Arnesen H, et al. Abnormal glucose regulation in patients with acute ST- elevation myocardial infarction-a cohort study on 224 patients. Cardiovasc. 2009;8:6.	Subpopulation
72	Kowall B, Ebert N, Then C, Thiery J, Koenig W, Meisinger C, et al. Associations between blood glucose and carotid intima-media thickness disappear after adjustment for shared risk factors: the KORA F4 study. PLoS ONE. 2012;7(12):e52590.	No extractable data
73	Ku YH, Choi SH, Lim S, Cho YM, Park YJ, Park KS, et al. Carotid intimal-medial thickness is not increased in women with previous gestational diabetes mellitus. Diabetes Metab J. 2011;35(5):497-503.	Ineligible population
74	Kuramitsu S, Yokoi H, Domei T, Nomura A, Watanabe H, Yamaji K, et al. Impact of post-challenge hyperglycemia on clinical outcomes in Japanese patients with stable angina undergoing percutaneous coronary intervention. Cardiovasc. 2013;12:74.	Subpopulation
75	Lauritzen T, Sandbaek A, Skriver MV, Borch-Johnsen K. HbA1c and cardiovascular risk score identify people who may benefit from preventive interventions: a 7 year follow-up of a high-risk screening programme for diabetes in primary care (ADDITION), Denmark. Diabetologia. 2011;54(6):1318-26.	Subpopulation
76	Li HY, Lin MS, Shih SR, Hua CH, Liu YL, Chuang LM, et al. The performance of risk scores and hemoglobin A1c to find undiagnosed diabetes with isolated postload hyperglycemia. Endocr J. 2011;58(6):441-8.	No eligible health outcome
77	Liang KW, Sheu WHH, Lee WJ, Lee WL, Pan HC, Lee IT, et al. Post-challenge insulin concentration is useful for differentiating between coronary artery disease and cardiac syndrome X in subjects without known diabetes mellitus. Diabetology and Metabolic Syndrome. 2017;9 (1) (no pagination)(10).	Subpopulation
78	Lin Y, Xu Y, Chen G, Huang B, Chen Z, Yao L, et al. Glycated hemoglobin, diabetes mellitus, and cardiovascular risk in a cross-sectional study among She Chinese population. J Endocrinol Invest. 2012;35(1):35-41.	No eligible health outcome
79	Lin YC, Chen HS. Longer time to peak glucose during the oral glucose tolerance test increases cardiovascular risk score and diabetes prevalence. PLoS ONE. 2017;12(12):e0189047.	No eligible health outcome
80	Lonati C, Morganti A, Comarella L, Mancia G, Zanchetti A, Group IS. Prevalence of type 2 diabetes among patients with hypertension under the care of 30 Italian clinics of hypertension: results of the (Iper)tensione and (dia)bete study. J Hypertens. 2008;26(9):1801-8.	Subpopulation
81	Lopez Lopez R, Fuentes Garcia R, Gonzalez-Villalpando M-E, Gonzalez-Villalpando C. Diabetic by HbA1c, Normal by OGTT: A Frequent Finding in the Mexico City Diabetes Study. Journal of the Endocrine Society. 2017;1(10):1247-58.	No eligible health outcome
82	Lu W, Resnick HE, Jain AK, Adams-Campbell LL, Jablonski KA, Gottlieb AM, et al. Effects of isolated post-challenge hyperglycemia on mortality in American Indians: the Strong Heart Study. Ann Epidemiol. 2003;13(3):182-8.	Outcome not reported for all three tests
83	Luders S, Hammersen F, Kulschewski A, Venneklaas U, Zuchner C, Gansz A, et al. Diagnosis of impaired glucose tolerance in hypertensive patients in daily clinical practice. Int J Clin Pract. 2005;59(6):632-8.	Subpopulation
84	Magliano DJ, Barr EL, Zimmet PZ, Cameron AJ, Dunstan DW, Colagiuri S, et al. Glucose indices, health behaviors, and incidence of diabetes in Australia: the Australian Diabetes, Obesity and Lifestyle Study. Diabetes Care. 2008;31(2):267-72.	No eligible health outcome
85	Marini MA, Succurro E, Castaldo E, Cufone S, Arturi F, Sciacqua A, et al. Cardiometabolic risk profiles and carotid atherosclerosis in individuals with prediabetes identified by fasting glucose, postchallenge glucose, and hemoglobin A<inf>1c</inf> criteria. Diabetes Care. 2012;35(5):1144-9.	No eligible health outcome
86	Menke A, Rust KF, Cowie CC. Diabetes based on 2-h plasma glucose among those classified as having prediabetes based on fasting plasma glucose or A1c. Diab Vasc Dis Res. 2018;15(1):46-54.	Outcome not reported for all three tests
87	Miyakoshi T, Oka R, Nakasone Y, Sato Y, Yamauchi K, Hashikura R, et al. Development of new diabetes risk scores on the basis of the current definition of diabetes in Japanese subjects [Rapid Communication]. Endocr J. 2016;63(9):857-65.	No eligible health outcome

88	Modan M, Harris MI, Halkin H. Evaluation of WHO and NDDG criteria for impaired glucose tolerance. Results from two national samples. Diabetes. 1989;38(12):1630-5.	No eligible health outcome
89	Modan M, Meytes D, Rozeman P, Yosef SB, Sehayek E, Yosef NB, et al. Significance of high HbA1 levels in normal glucose tolerance. Diabetes Care. 1988;11(5):422-8.	Ineligible index test
90	Mohieldein AH, Hasan M, Al-Harbi KK, Alodailah SS, Azahrani RM, Al-Mushawwah SA. Dyslipidemia and reduced total antioxidant status in young adult Saudis with prediabetes. Diabetes Metab Syndr. 2015;9(4):287-91.	No eligible health outcome
91	Mokta J, Kumar S, Ganju N, Mokta K, Panda PK, Gupta S. High incidence of abnormal glucose metabolism in acute coronary syndrome patients at a moderate altitude: A sub-Himalayan study. Indian J Endocrinol Metab. 2017;21(1):142-7.	Subpopulation
92	Mostaza JM, Lahoz C, Salinero-Fort MA, de Burgos-Lunar C, Laguna F, Estirado E, et al. Carotid atherosclerosis severity in relation to glycemic status: a cross-sectional population study. Atherosclerosis. 2015;242(2):377-82.	No eligible health outcome
93	Mukai N, Ninomiya T, Hata J, Hirakawa Y, Ikeda F, Fukuhara M, et al. Association of hemoglobin A1c and glycated albumin with carotid atherosclerosis in community-dwelling Japanese subjects: the Hisayama Study. Cardiovasc. 2015;14:84.	No eligible health outcome
94	Munch-Andersen T, Olsen DB, Sondergaard H, Daugaard JR, Bysted A, Christensen DL, et al. Metabolic profile in two physically active Inuit groups consuming either a western or a traditional Inuit diet. Int J Circumpolar Health. 2012;71:17342.	No eligible health outcome
95	Nagi DK, Pettitt DJ, Bennett PH, Klein R, Knowler WC. Diabetic retinopathy assessed by fundus photography in Pima Indians with impaired glucose tolerance and NIDDM. Diabet Med. 1997;14(6):449-56.	Outcome not reported for all three tests
96	Nakagami T, Tominaga M, Nishimura R, Yoshiike N, Daimon M, Oizumi T, et al. Is the measurement of glycated hemoglobin A1c alone an efficient screening test for undiagnosed diabetes? Japan National Diabetes Survey. Diabetes Res Clin Pract. 2007;76(2):251-6.	No eligible health outcome
97	Nemeth N, Putz Z, Istenes I, Korei AE, Vagi OE, Kempler M, et al. Is there a connection between postprandial hyperglycemia and IGT related sensory nerve dysfunction? Nutr Metab Cardiovasc Dis. 2017;27(7):609-14.	No eligible health outcome
98	Ohkura T, Taniguchi SI, Inoue K, Yamamoto N, Matsuzawa K, Fujioka Y, et al. Screening criteria of diabetes mellitus and impaired glucose tolerance of the Japanese population in a rural area of Japan: The Tottori-Kofu study. Yonago Acta Medica. 2009;52(3):105-14.	No eligible health outcome
99	Olos R, Knazeje M, Migra M, Dragula M, Farkas A, Kovar F, et al. Prevalence of abnormal glucose regulation and its optimal screening in patients with acute STEMI. Cardiology Letters. 2011;20(6):476-80.	Not in English
100	Ouchi M, Suzuki T, Hashimoto M, Motoyama M, Ohara M, Suzuki K, et al. Urinary N-acetyl-beta-D-glucosaminidase levels are positively correlated with 2-hr plasma glucose levels during oral glucose tolerance testing in prediabetes. J Clin Lab Anal. 2012;26(6):473-80.	No eligible health outcome
101	Owens DR, Volund A, Jones D, Shannon AG, Jones IR, Birtwell AJ, et al. Retinopathy in newly presenting non-insulin-dependent (type 2) diabetic patients. Diabetes Res. 1988;9(2):59-65.	Subpopulation
102	Pang C, Jia L, Jiang S, Liu W, Hou X, Zuo Y, et al. Determination of diabetic retinopathy prevalence and associated risk factors in Chinese diabetic and pre-diabetic subjects: Shanghai diabetic complications study. Diabetes/Metabolism Research Reviews. 2012;28(3):276-83.	Subpopulation
103	Peng G, Lin M, Zhang K, Chen J, Wang Y, Yang Y, et al. Hemoglobin A1c can identify more cardiovascular and metabolic risk profile in OGTT-negative Chinese population. International Journal of Medical Sciences. 2013;10(8):1028-34.	No eligible health outcome
104	Pradeepa R, Anitha B, Mohan V, Ganesan A, Rema M. Risk factors for diabetic retinopathy in a South Indian Type 2 diabetic population--the Chennai Urban Rural Epidemiology Study (CURES) Eye Study 4. Diabet Med. 2008;25(5):536-42.	Ineligible index test

105	Pramodkumar TA, Priya M, Jebarani S, Anjana RM, Mohan V, Pradeepa R. Metabolic profile of normal glucose-tolerant subjects with elevated 1-h plasma glucose values. Indian J Endocrinol Metab. 2016;20(5):612-8.	No eligible health outcome
106	Qiao Q, Dekker JM, de Vegt F, Nijpels G, Nissinen A, Stehouwer CD, et al. Two prospective studies found that elevated 2-hr glucose predicted male mortality independent of fasting glucose and HbA1c. J Clin Epidemiol. 2004;57(6):590-6.	No extractable data
107	Quatraro A, Giugliano D, De Rosa N, Minei A, Ettorre M, Donzella C, et al. Is a family history of diabetes associated with an increased level of cardiovascular risk factors? Studies in healthy people and in subjects with different degree of glucose intolerance. Diabete et Metabolisme. 1993;19(2):230-8.	No eligible health outcome
108	Qvist R, Ismail IS, Chinna K, Muniandy S. Use of glycated hemoglobin (HbA(1C)) and impaired glucose tolerance in the screening of undiagnosed diabetes in the Malaysian population. Indian J. 2008;23(3):246-9.	No eligible health outcome
109	Rajput R, Dangi A, Singh H. Prevalence of glucose intolerance in rheumatoid arthritis patients at a tertiary care centre in Haryana. Diabetes Metab Syndr. 2017;11 Suppl 2:S1013-S6.	Subpopulation
110	Ramachandran A, Chamukuttan S, Immaneni S, Shanmugam RM, Vishnu N, Viswanathan V, et al. High incidence of glucose intolerance in Asian-Indian subjects with acute coronary syndrome. Diabetes Care. 2005;28(10):2492-6.	Subpopulation
111	Rasmussen SS, Glumer C, Sandbaek A, Lauritzen T, Borch-Johnsen K. Determinants of progression from impaired fasting glucose and impaired glucose tolerance to diabetes in a high-risk screened population: 3 year follow-up in the ADDITION study, Denmark. Diabetologia. 2008;51(2):249-57.	No eligible health outcome
112	Rathmann W, Strassburger K, Heier M, Holle R, Thorand B, Giani G, et al. Incidence of Type 2 diabetes in the elderly German population and the effect of clinical and lifestyle risk factors: KORA S4/F4 cohort study. Diabet Med. 2009;26(12):1212-9.	No eligible health outcome
113	Resnick HE, Harris MI, Brock DB, Harris TB. American Diabetes Association diabetes diagnostic criteria, advancing age, and cardiovascular disease risk profiles: results from the Third National Health and Nutrition Examination Survey. Diabetes Care. 2000;23(2):176-80.	No eligible health outcome
114	Rha SW, Choi BG, Seo HS, Park SH, Park JY, Chen KY, et al. Impact of Statin Use on Development of New-Onset Diabetes Mellitus in Asian Population. Am J Cardiol. 2016;117(3):382-7.	Outcome not reported for all three tests
115	Rizza S, Copetti M, Cardellini M, Porzio O, Luzi A, Pecchioli C, et al. Atherosclerosis severity but not undiagnosed diabetes predicts new cardiovascular events of subjects in secondary cardiovascular prevention. Atherosclerosis. 2012;223(2):448-53.	Subpopulation
116	Rogala B, Bozek A, Gluck J, Rymarczyk B, Jarzab J, Maurer M. Coexistence of angioedema alone with impaired glucose tolerance. Int Arch Allergy Immunol. 2014;165(4):265-9.	Subpopulation
117	Saadi H, Carruthers SG, Nagelkerke N, Al-Maskari F, Afandi B, Reed R, et al. Prevalence of diabetes mellitus and its complications in a population-based sample in Al Ain, United Arab Emirates. Diabetes Res Clin Pract. 2007;78(3):369-77.	Outcome not reported for all three tests
118	Schneider MP, Ott C, Ritt M, Raff U, Schlaich MP, Schmieder RE. Postchallenge hyperglycemia is closely related with early vascular damage in overweight and obese patients. J Hypertens. 2012;30(1):147-52.	No eligible health outcome
119	Shahim B, De Bacquer D, De Backer G, Gyberg V, Kotseva K, Mellbin L, et al. The Prognostic Value of Fasting Plasma Glucose, Two-Hour Postload Glucose, and HbA_{1c} in Patients With Coronary Artery Disease: A Report From EUROASPIRE IV: A Survey From the European Society of Cardiology. Diabetes Care. 2017;40(9):1233-40.	Subpopulation
120	Shahim B, Gyberg V, De Bacquer D, Kotseva K, De Backer G, Schnell O, et al. Undetected dysglycaemia common in primary care patients treated for hypertension and/or dyslipidaemia: on the need for a screening strategy in clinical practice. A report from EUROASPIRE IV a registry from the EuroObservational Research Programme of the European Society of Cardiology. Cardiovasc. 2018;17(1):21.	Subpopulation

121	Silbernagel G, Sourij H, Grammer TB, Kleber ME, Hartaigh BO, Winkelmann BR, et al. Isolated post-challenge hyperglycaemia predicts increased cardiovascular mortality. Atherosclerosis. 2012;225(1):194-9.	Subpopulation
122	Singleton JR, Smith AG, Bromberg MB. Increased prevalence of impaired glucose tolerance in patients with painful sensory neuropathy. Diabetes Care. 2001;24(8):1448-53.	Subpopulation
123	Singleton JR, Smith AG, Bromberg MB. Painful sensory polyneuropathy associated with impaired glucose tolerance. Muscle Nerve. 2001;24(9):1225-8.	Subpopulation
124	Soma P, Rheeder P. Unsuspected glucose abnormalities in patients with coronary artery disease. Samj, S. 2006;96(3):216-20.	Subpopulation
125	Stevens AL, Hansen D, Vandoren V, Westerlaken R, Creemers A, Eijnde BO, et al. Mandatory oral glucose tolerance tests identify more diabetics in stable patients with chronic heart failure: a prospective observational study. Diabetol Metab Syndr. 2014;6(1):44.	Subpopulation
126	Strojek K, Raz I, Jermendy G, Gitt AK, Liu R, Zhang Q, et al. Factors Associated With Cardiovascular Events in Patients With Type 2 Diabetes and Acute Myocardial Infarction. J Clin Endocrinol Metab. 2016;101(1):243-53.	Subpopulation
127	Sun ZJ, Yang YC, Wu JS, Wang MC, Chang CJ, Lu FH. Increased risk of glomerular hyperfiltration in subjects with impaired glucose tolerance and newly diagnosed diabetes. Nephrol Dial Transplant. 2016;31(8):1295-301.	No eligible health outcome
128	Suntsov YI, Bolotskaya LL, Rudakova OG, Andrianova EA, Tolkacheva AA, Kon IL. Prevalence of type 2 diabetes mellitus and its complications among the population of Moscow Region - A cross-sectional epidemiological study. [Russian]. Diabetes Mellitus. 2013;16(4):6-10.	Not in English
129	Tahrani AA, Geen J, Hanna FW, Jones PW, Cassidy D, Bates D, et al. Predicting dysglycaemia in patients under investigation for acute coronary syndrome. Qjm. 2011;104(3):231-6.	Subpopulation
130	Tanaka K, Kanazawa I, Yamaguchi T, Sugimoto T. One-hour post-load hyperglycemia by 75g oral glucose tolerance test as a novel risk factor of atherosclerosis. Endocr J. 2014;61(4):329-34.	No extractable data
131	Tapp RJ, Shaw JE, Harper CA, de Courten MP, Balkau B, McCarty DJ, et al. The prevalence of and factors associated with diabetic retinopathy in the Australian population. Diabetes Care. 2003;26(6):1731-7.	Outcome not reported for all three tests
132	Tekumit H, Cenal AR, Polat A, Uzun K, Tataroglu C, Akinci E. Diagnostic value of hemoglobin A1c and fasting plasma glucose levels in coronary artery bypass grafting patients with undiagnosed diabetes mellitus. Ann Thorac Surg. 2010;89(5):1482-7.	Subpopulation
133	Temelkova-Kurktschiev TS, Koehler C, Henkel E, Leonhardt W, Fuecker K, Hanefeld M. Postchallenge plasma glucose and glycemic spikes are more strongly associated with atherosclerosis than fasting glucose or HbA1c level. Diabetes Care. 2000;23(12):1830-4.	No eligible health outcome
134	Temelkova-Kurktschiev TS, Koehler C, Leonhardt W, Schaper F, Henkel E, Siegert G, et al. Increased intimal-medial thickness in newly detected type 2 diabetes: risk factors. Diabetes Care. 1999;22(2):333-8.	No eligible health outcome
135	Tenerz A, Nilsson G, Forberg R, Ohrvik J, Malmberg K, Berne C, et al. Basal glucometabolic status has an impact on long-term prognosis following an acute myocardial infarction in non-diabetic patients. Journal of Internal Medicine. 2003;254(5):494-503.	Subpopulation
136	Tenerz A, Norhammar A, Silveira A, Hamsten A, Nilsson G, Ryden L, et al. Diabetes, insulin resistance, and the metabolic syndrome in patients with acute myocardial infarction without previously known diabetes. Diabetes Care. 2003;26(10):2770-6.	Subpopulation
137	Tsang ML, Chan PF, Lai LKP, Chow KL, Luk MMH, Wong S, et al. Impaired fasting glucose (IFG) among Chinese hypertensive patients in two Hong Kong primary care clinics: Use the ADA criteria or WHO criteria? Hong Kong Practitioner. 2017;39(1):2-12.	Subpopulation
138	Tzeng TF, Hsiao PJ, Hsieh MC, Shin SJ. Association of nephropathy and retinopathy, blood pressure, age in newly diagnosed type 2 diabetes mellitus. Kaohsiung J Med Sci. 2001;17(6):294-301.	Subpopulation

139	Veyhe AS, Andreassen J, Halling J, Grandjean P, Petersen MS, Weihe P. Prevalence of type 2 diabetes and prediabetes in the Faroe Islands. Diabetes Res Clin Pract. 2018;140:162-73.	No eligible health outcome
140	Vyssoulis GP, Liakos CI, Karpanou EA, Triantafyllou AI, Michaelides AP, Tzamou VE, et al. Impaired glucose homeostasis in non-diabetic Greek hypertensives with diabetes family history. Effect of the obesity status. J Am Soc Hypertens. 2013;7(4):294-304.	Subpopulation
141	Wang C, Song J, Ma Z, Yang W, Li C, Zhang X, et al. Fluctuation between fasting and 2-H postload glucose state is associated with chronic kidney disease in previously diagnosed type 2 diabetes patients with HbA1c >= 7%. PLoS ONE. 2014;9(7):e102941.	Subpopulation
142	Wang JS, Lee IT, Lee WJ, Lin SY, Fu CP, Lee WL, et al. Comparing HbA1c, fasting and 2-h plasma glucose for screening for abnormal glucose regulation in patients undergoing coronary angiography. Clin Chem Lab Med. 2015;53(9):1441-9.	Subpopulation
143	Wang JS, Lee IT, Lee WJ, Lin SY, Fu CP, Ting CT, et al. Performance of HbA1c and fasting plasma glucose in screening for diabetes in patients undergoing coronary angiography. Diabetes Care. 2013;36(5):1138-40.	Subpopulation
144	Wang ST, Zhang CY, Zhang CM, Rong W. The plasma osteoprotegerin level and osteoprotegerin expression in renal biopsy tissue are increased in type 2 diabetes with nephropathy. Exp Clin Endocrinol Diabetes. 2015;123(2):106-11.	Subpopulation
145	Warren B, Pankow JS, Matsushita K, Punjabi NM, Daya NR, Grams M, et al. Comparative prognostic performance of definitions of prediabetes: a prospective cohort analysis of the Atherosclerosis Risk in Communities (ARIC) study. Lancet Diabetes Endocrinol. 2017;5(1):34-42.	Index tests not conducted at the same time
146	Wierusz-Wysocka B, Zozulinska D, Knast B, Pisarczyk-Wiza D. Appearance of undiagnosed diabetes mellitus in the population of professionally active people in the urban areas. [Polish]. Polskie archiwum medycyny wewntrznej. 2001;106(3):815-21.	Not in English
147	Wilmot EG, Edwardson CL, Biddle SJ, Gorely T, Henson J, Khunti K, et al. Prevalence of diabetes and impaired glucose metabolism in younger 'at risk' UK adults: insights from the STAND programme of research. Diabet Med. 2013;30(6):671-5.	No eligible health outcome
148	Woo J, Cockram CS, Lau E, Chan A, Swaminathan R. Association between insulin and blood pressure in a community population with normal glucose tolerance. J Hum Hypertens. 1992;6(5):343-7.	No eligible health outcome
149	Woo J, Lam CW, Kay R, Wong AH, Teoh R, Nicholls MG. The influence of hyperglycemia and diabetes mellitus on immediate and 3-month morbidity and mortality after acute stroke. Arch Neurol. 1990;47(11):1174-7.	Subpopulation
150	Woo YC, Cheung BM, Yeung CY, Lee CH, Hui EY, Fong CH, et al. Cardiometabolic risk profile of participants with prediabetes diagnosed by HbA1c criteria in an urban Hong Kong Chinese population over 40 years of age. Diabet Med. 2015;32(9):1207-11.	No eligible health outcome
151	Wu S, Shi Y, Pan Y, Li J, Jia Q, Zhang N, et al. Glycated hemoglobin independently or in combination with fasting plasma glucose versus oral glucose tolerance test to detect abnormal glycometabolism in acute ischemic stroke: a Chinese cross-sectional study. BMC Neurol. 2014;14:177.	Subpopulation
152	Xiang GD, Pu JH, Zhao LS, Sun HL, Hou J, Yue L. Association between plasma osteoprotegerin concentrations and urinary albumin excretion in Type 2 diabetes. Diabet Med. 2009;26(4):397-403.	Subpopulation
153	Xu Y, Zhao W, Wang W, Bi Y, Li J, Mi S, et al. Plasma glucose and hemoglobin A1c for the detection of diabetes in Chinese adults. J Diabetes. 2016;8(3):378-86.	No eligible health outcome
154	Yan LH, Mu B, Guan Y, Liu X, Zhao N, Pan D, et al. Assessment of the relationship between non-alcoholic fatty liver disease and diabetic complications. Journal of Diabetes Investigation. 2016;7(6):889-94.	Subpopulation
155	Yu Y, Ouyang XJ, Lou QL, Gu LB, Mo YZ, Ko GT, et al. Validity of glycated hemoglobin in screening and diagnosing type 2 diabetes mellitus in Chinese subjects. Korean J Intern Med. 2012;27(1):41-6.	No eligible health outcome
156	Yubero-Serrano EM, Delgado-Lista J, Alcala-Diaz JF, Garcia-Rios A, Perez-Caballero AI, Blanco-Rojo R, et al. A dysregulation of glucose metabolism control is associated with carotid atherosclerosis in patients with coronary heart disease (CORDIOPREV-DIAB study). Atherosclerosis. 2016;253:178-85.	Subpopulation

157	Yun J-S, Ko S-H, Kim J-H, Moon K-W, Park Y-M, Yoo K-D, et al. Diabetic retinopathy and endothelial dysfunction in patients with type 2 diabetes mellitus.[Erratum appears in Diabetes Metab J. 2013 Dec;37(6):488 Note: Moon, Kun-Woong [corrected to Moon, Keon-Woong]]. Diabetes Metab J. 2013;37(4):262-9.	Subpopulation
158	Zagami RM, Di Pino A, Urbano F, Piro S, Purrello F, Rabuazzo AM. Low circulating vitamin D levels are associated with increased arterial stiffness in prediabetic subjects identified according to HbA1c. Atherosclerosis. 2015;243(2):395-401.	Outcome not reported for all three tests
159	Zhang N, Hu X, Zhang Q, Bai P, Cai M, Zeng TS, et al. Non-high-density lipoprotein cholesterol: High-density lipoprotein cholesterol ratio is an independent risk factor for diabetes mellitus: Results from a population-based cohort study. J Diabetes. 2018;10(9):708-14.	No eligible health outcome
160	Zhang R, Dong SY, Wang F, Ma C, Zhao XL, Zeng Q, et al. Associations between Body Composition Indices and Metabolic Disorders in Chinese Adults: A Cross-Sectional Observational Study. Chin Med J. 2018;131(4):379-88.	Ineligible index test
161	Zhang X, Shi Q, Zheng H, Jia Q, Zhao X, Liu L, et al. Prevalence of Abnormal Glucose Regulation according to Different Diagnostic Criteria in Ischaemic Stroke without a History of Diabetes. Biomed Res Int. 2018;2018:8358724.	Subpopulation
162	Zhang YH, Ma WJ, Thomas GN, Xu YJ, Lao XQ, Xu XJ, et al. Diabetes and pre-diabetes as determined by glycated haemoglobin A1c and glucose levels in a developing southern Chinese population. PLoS ONE. 2012;7(5):e37260.	No eligible health outcome
163	Zivkovic M, Tonjes A, Baber R, Wirkner K, Loeffler M, Engel C. Prevalence of moderately increased albuminuria among individuals with normal HbA1c level but impaired glucose tolerance: Results from the LIFE-Adult-Study. Endocrinology, Diabetes and Metabolism. 2018;1 (4) (no pagination)(e00030).	Outcome not reported for all three tests

Table 34. Publications excluded after review of full-text articles question 2 (50g GCT)

	Reference	Reason for exclusion
1	Adachi H, Hirai Y, Tsuruta M, Fujiura Y, Imaizuml T. Is insulin resistance or diabetes mellitus associated with stroke? An 18-year follow-up study. Diabetes Res Clin Pract. 2001;51(3):215-23.	No comparator
2	Batty GD, Kivimaki M, Smith GD, Marmot MG, Shipley MJ. Post-challenge blood glucose concentration and stroke mortality rates in non-diabetic men in London: 38-year follow-up of the original Whitehall prospective cohort study. Diabetologia. 2008;51(7):1123-6.	Ineligible test
3	Beaven DW, Arcus AC, Bell JP, Smith JR. Epidemiology of diabetes mellitus. N Z Med J. 1974;80(525):291-9.	Review
4	Brunner EJ, Shipley MJ, Witte DR, Fuller JH, Marmot MG. Relation between blood glucose and coronary mortality over 33 years in the Whitehall Study. Diabetes Care. 2006;29(1):26-31.	Ineligible test
5	Crombie DL, Pike LA, Malins JM. Ten year follow up report on Birmingham Diabetes Survey of 1961. British Medical Journal. 1976;2(6026):35-7.	Ineligible test
6	Crombie DL, Pike LA, Pinsent RJFH, Fitzgerald MG, Malins JM. Five-year follow-up report on the Birmingham diabetes survey of 1962. Report by the Birmingham Diabetes Survey Working Party. British Medical Journal. 1970;3(5718):301-5.	Ineligible test
7	Fuller JH, McCartney P, Jarrett RJ, Keen H, Rose G, Shipley MJ, et al. Hyperglycaemia and coronary heart disease: The Whitehall study. Journal of Chronic Diseases. 1979;32(11-12):721-8.	Ineligible test
8	Fuller JH, Shipley MJ, Rose G, Jarrett RJ, Keen H. Coronary-heart-disease risk and impaired glucose tolerance. The Whitehall study. Lancet (London, England). 1980;1(8183):1373-6.	Ineligible test

9	Gapstur SM, Gann PH, Colangelo LA, Barron-Simpson R, Kopp P, Dyer A, et al. Postload plasma glucose concentration and 27-year prostate cancer mortality (United States). Cancer Causes Control. 2001;12(8):763-72.	No comparator
10	Geddes M, Maltoni G. Critical evaluation of several years' activity aimed at the diagnosis of asymptomatic diabetes in the Province of Florence. Revision of method. Acta Diabetol Lat. 1977;14(1-2):38-50.	No eligible outcomes
11	Jarrett RJ, Keen H. Hyperglycaemia and diabetes mellitus. Lancet (London, England). 1976;2(7993):1009-12.	Review
12	Jarrett RJ, Keen H, Boyns DR. The concomitants of raised blood sugar: studies in newly detected hyperglycamics. I. A comparative assessment of neurological functions in blood sugar groups. Guys Hosp. 1969;J. Rep. 118(2):237-46.	Ineligible test
13	Jarrett RJ, Keen H, McCartney M, Fuller JH, Hamilton PJ, Reid DD, et al. Glucose tolerance and blood pressure in two population samples: their relation to diabetes mellitus and hypertension. Int J Epidemiol. 1978;7(1):15-24.	No eligible outcomes
14	Kawate R, Miyanishi M, Nishimoto Y. Prevalence and mortality of diabetes mellitus in Japanese in Hawaii and Japan, DIABETES MELLITUS IN ASIA. EXCERPTA MEDICA,AMSTERDAM,ICS No. 1976;390:82-90.	No eligible outcomes
15	Keen H, Chlouverakis C, Fuller J, Jarrett RJ. The concomitants of raised blood sugar: studies in newly detected hyperglycaemics. II. Urinary albumin excretion, blood pressure and their relation to blood sugar levels. Guys Hospital Reports. 1969;118(2):247-54.	Ineligible test
16	Keen H, Jarrett RJ, Chlouverakis C, Boyns DR. The effect of treatment of moderate hyperglycaemia on the incidence of arterial disease. Postgraduate Medical Journal. 1968;44(518 S):960-5.	No comparator
17	Keen H, Rose G, Pyke DA, Boyns D, Chlouverakis C, Mistry S. Blood-sugar and arterial disease. Lancet (London, England). 1965;2(7411):505-8.	Ineligible test
18	Kings Bury KJ. The relation between glucose tolerance and atherosclerotic vascular disease. Lancet (London, England). 1966;2(7478):103-9.	Subpopulation
19	Laws A, Marcus EB, Grove JS, Curb JD. Lipids and lipoproteins as risk factors for coronary heart disease in men with abnormal glucose tolerance: the Honolulu Heart Program. Journal of Internal Medicine. 1993;234(5):471-8.	No comparator
20	Levine W, Dyer AR, Shekelle RB, Schoenberger JA, Stamler J. Post-load plasma glucose and cancer mortality in middle-aged men and women. 12-year follow-up findings of the Chicago Heart Association Detection Project in Industry. Am J Epidemiol. 1990;131(2):254-62.	No comparator
21	Lowe LP, Liu K, Greenland P, Metzger BE, Dyer AR, Stamler J. Diabetes, asymptomatic hyperglycemia, and 22-year mortality in black and white men. The Chicago Heart Association Detection Project in Industry Study. Diabetes Care. 1997;20(2):163-9.	No comparator
22	Michael C, Edelstein I, Whisson A. Prevalence of diabetes, glycosuria and related variables among a Cape coloured population. South African medical journal. 1971;45(29):795-801.	No comparator
23	Ohneda A, Kobayashi T, Nihei J. Evaluation of new criteria for diagnosis of diabetes mellitus based on follow-up study of borderline diabetes. Tohoku J Exp Med. 1982;137(4):437-44.	Ineligible test
24	Rodriguez BL, Lau N, Burchfiel CM, Abbott RD, Sharp DS, Yano K, et al. Glucose intolerance and 23-year risk of coronary heart disease and total mortality: the Honolulu Heart Program. Diabetes Care. 1999;22(8):1262-5.	No extractable data
25	Sasaki A. Assessment of the new criteria for diabetes mellitus according to 10-year relative survival rates. Diabetologia. 1981;20(3):195-8.	Ineligible test
26	Sasaki A, Suzuki T, Horiuchi N. Development of diabetes in Japanese subjects with impaired glucose tolerance: a seven year follow-up study. Diabetologia. 1982;22(3):154-7.	Ineligible test
27	Sayegh HA, Jarrett RJ. Oral glucose-tolerance tests and the diagnosis of diabetes: results of a prospective study based on the Whitehall survey. Lancet (London, England). 1979;2(8140):431-3.	Ineligible test

28	Sigurdsson G, Gottskalksson G, Thorsteinsson T, Davidsson D, Olafsson O, Samuelsson S, et al. Community screening for glucose intolerance in middle-aged Icelandic men. Deterioration to diabetes over a period of 71/2 years. Acta Med Scand. 1981;210(1-2):21-6.	No eligible outcomes
29	Verrillo A, de Teresa A, Nunziata G, Rucco E. Epidemiology of diabetes mellitus in an Italian rural community. Diabete et Metabolisme. 1983;9(1):9-13.	No eligible outcomes

Table 35. Publications excluded after review of full-text articles question 3

	Reference	Reason for exclusion
1	Cardenas A, Hauser R, Gold DR, et al. Association of Perfluoroalkyl and Polyfluoroalkyl Substances With Adiposity. JAMA Netw Open. 2018;1(4):e181493.	Cohort study
2	Davies MJ, Gray LJ, Ahrabian D, et al. A community-based primary prevention programme for type 2 diabetes mellitus integrating identification and lifestyle intervention for prevention: a cluster randomised controlled trial. NIHR Journals Library 2017;01:01.	Abridged version of paper captured in previous review
3	DeBoer MD, Filipp SL, Gurka MJ. Use of a Metabolic Syndrome Severity Z Score to Track Risk During Treatment of Prediabetes: An Analysis of the Diabetes Prevention Program. Diabetes Care. 2018 Nov;41(11):2421-2430.	Cohort study
4	Diabetes Prevention Program Research Group. Protocol for the Diabetes Prevention Program (DPP). https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01602051/full	Pre-2017
5	Diabetes Prevention Program Research Group. Protocol for the Diabetes Prevention Program (DPP). https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01602050/full	Pre-2017
6	Goodman C, Man B, Xia Y, et al. Diabetes incidence by bmi category in the diabetes prevention program. Journal of general internal medicine Conference: 41st annual meeting of the society of general internal medicine, SGIM 2018 United states 2018;33(2 Supplement 1):158.	Conference abstract
7	Luchsinger JA, Ma Y, Christophi CA, Florez H, Golden SH, Hazuda H, Crandall J, Venditti E, Watson K, Jeffries S, Manly JJ, Pi-Sunyer FX; Diabetes Prevention Program Research Group. Metformin, Lifestyle Intervention, and Cognition in the Diabetes Prevention Program Outcomes Study. Diabetes Care. 2017 Jul;40(7):958-965. oi: 10.2337/dc16-2376.	Cohort study
8	NCT. Diabetes Prevention Programme. Clinicaltrials.gov/ct2/show/nct00004992	Pre-2017
9	NCT. Prevention of Type 2 Diabetes Mellitus by Changes in Diet. clinicaltrialsgov/show/nct02250066 2014	Pre-2017
10	Perreault L, Pan Q, Aroda VR, et al. Exploring residual risk for diabetes and microvascular disease in the Diabetes Prevention Program Outcomes Study (DPPOS). Diabet Med 2017;34(12):1747-55.	Cohort study
11	Schwartz AV, Pan Q, Hazuda HP, et al. Long-term effects of lifestyle intervention and metformin during DPP on appendicular lean mass. Diabetes Conference: 78th scientific sessions of the american diabetes association, ADA 2018 United states 2018;67(Supplement 1):A394.	Conference abstract
12	Shen X, Zhang P, Wang J, An Y, Gregg EW, Zhang B, Li H, Gong Q, Chen Y, Shuai Y, Engelgau MM, Hu Y, Bennett PH, Li G. Influence of improvement or worsening of glucose tolerance on risk of stroke in persons with impaired glucose tolerance. Int J Stroke. 2018 Dec;13(9):941-948.	No between-group comparisons

Table 36. Publications excluded after review of full-text articles question 4

	Reference	Reason for exclusion
1	Feldman AL, Griffin SJ, Fhärm E, Norberg M, Wennberg P, Weinehall L, Rolandsson O. Screening for type 2 diabetes: do screen-detected cases fare better? Diabetologia. 2017 Nov;60(11):2200-2209.	Not an RCT
2	Krass I, Carter R, Mitchell B, Mohebbi M, Shih STF, Trinder P, Versace VL, Wilson F, Namara KM. Pharmacy Diabetes Screening Trial: protocol for a pragmatic cluster-randomised controlled trial to compare three screening methods for undiagnosed type 2 diabetes in Australian community pharmacy. BMJ Open. 2017 Dec 27;7(12):e017725.	No unscreened group
3	Lau CJ, Pisinger C, Husemoen LLN, Jacobsen RK, Linneberg A, Jørgensen T, Glümer C. Effect of general health screening and lifestyle counselling on incidence of diabetes in general population: Inter99 randomised trial. Prev Med. 2016 Oct;91:172-179.	General health checks, not specifically diabetes
4	Lindholt JS, Søgaard R. Population screening and intervention for vascular disease in Danish men (VIVA): a randomised controlled trial. Lancet. 2017 Nov 18; 390(10109):2256-2265.	Not screening for diabetes
5	Simmons RK, Griffin SJ, Lauritzen T, Sandbæk A. Effect of screening for type 2 diabetes on risk of cardiovascular disease and mortality: a controlled trial among 139,075 individuals diagnosed with diabetes in Denmark between 2001 and 2009. Diabetologia. 2017 Nov;60(11):2192-2199.	Not an RCT
6	Simmons RK, Griffin SJ, Witte DR, Borch-Johnsen K, Lauritzen T, Sandbæk A. Effect of population screening for type 2 diabetes and cardiovascular risk factors on mortality rate and cardiovascular events: a controlled trial among 1,912,392 Danish adults. Diabetologia. 2017 Nov;60(11):2183-2191.	Not an RCT
7	Skaaby T, Jorgensen T, Linneberg A. A randomized general population study of the effects of repeated health checks on incident diabetes. Endocrine 2018;60(1):122-28.	General health checks, not specifically diabetes
8	Wagner J, Naranjo D, Khun T, Seng S, Horn IS, Suttiratana SC, Keuky L. Diabetes and cardiometabolic risk factors in Cambodia: Results from two screening studies. J Diabetes. 2018 Feb;10(2):148-157.	Not an RCT

Appendix 3 — Summary and appraisal of individual studies

Data Extraction

Table 37. Studies relevant to criterion 1 (question 1)

Study reference	Study design, country	Participants	Follow up	Main findings
Jung[5]	Prospective cohort, Korea	2,830 participants with prediabetes, according to ADA criteria	10 years	881/2,830 (31%) **Blood pressure, adjust* HR (95% CI)** Normal blood pressure: Reference (1.00) Prehypertension: 1.32 (1.10–1.59) Hypertension: 1.61 (1.35–1.92) **HbA1c group, adjust* HR (95% CI)** Low HbA1c: Reference (1.00) High HbA1c: 2.30 (2.01–2.64) **HbA1c with blood pressure subgroup, adjust* HR (95% CI)** Normal BP + low HbA1c: Reference (1.00) Prehypertension + low HbA1c: 1.38 (1.08–1.77) Hypertension + low HbA1c: 1.68 (1.32–2.12) Normal BP + high HbA1c: 2.41 (1.86–3.12) Prehypertension + high HbA1c: 3.18 (2.45–4.12) Hypertension + high HbA1c: 3.82 (3.00–4.87)

				Systolic blood pressure, adjust* HR (95% CI) <120 mmHg: Reference (1.00) 120–129 mmHg: 1.15 (0.96–1.38) 130–139 mmHg: 1.39 (1.15–1.71) 140–149 mmHg: 1.47 (1.15–1.87) ≥150 mmHg: 1.87 (1.48–2.37) **Diastolic blood pressure, adjust* HR (95% CI)** <80 mmHg: Reference (1.00) 80–84 mmHg: 1.30 (1.07–1.58) 85–89 mmHg: 1.32 (1.08–1.62) 90–99 mmHg: 1.35 (1.12–1.63) ≥100 mmHg: 1.50 (1.14–1.99) * age, sex, study area (Ansan or Ansung), BMI, regular exercise, smoking, Triglyceride, HDL Cholesterol, HOMA-IR, hsCRP and alcohol intake
Park[6]	Prospective cohort, Korea	1,506 participants with prediabetes, according to ADA criteria	10 years	**Adjusted* hazard ratios (HRs) and 95% confidence intervals (CI)** **Incidence of type 2 diabetes mellitus according to the 2-h plasma glucose level.** *All participants* <140 mg/dL: Reference (1.00) 140–159 mg/dL: 3.07 (2.67–3.54) 160–179 mg/dL: 5.44 (4.66–6.34) 180–199 mg/dL 7.91 (6.53–9.59) *Male participants* <140 mg/dL: Reference (1.00) 140–159 mg/dL: 3.05 (2.47–3.76)

				160–179 mg/dL: 5.95 (4.78–7.40) 180–199 mg/dL: 8.61 (6.63–11.19) *Female participants* <140 mg/dL: Reference (1.00) 140–159 mg/dL: 3.07 (2.54–3.72) 160–179 mg/dL: 5.14 (4.13–6.40) 180–199 mg/dL: 7.17 (5.38–9.54) **Normal blood pressure** Low HbA1c without IR: Reference (1.00) Low HbA1c with IR: 1.51 (0.93–2.44) High HbA1c without IR: 2.34 (1.73–3.18) High HbA1c with IR: 4.07 (2.51–6.60) **Prehypertension** Low HbA1c without IR: Reference (1.00) Low HbA1c with IR: 1.05 (0.63–1.77) High HbA1c without IR: 2.20 (1.65–2.95) High HbA1c with IR: 2.85 (1.69–4.80) **Hypertension** Low HbA1c without IR: Reference (1.00) Low HbA1c with IR: 1.38 (0.91–2.09) High HbA1c without IR: 2.13 (1.66–2.72) High HbA1c with IR: 3.96 (2.66–5.90) ***** age, sex, study area (Ansan or Ansung), BMI, regular exercise, smoking, Triglyceride, HDL Cholesterol, HOMA-IR, hsCRP and alcohol intake

Franch-Nadal[3]	Prospective cohort, Spain	1,142 participants with prediabetes, according to ADA criteria	3 years	T2DM 107/1,142 (9.4%) **Gender, HR (95% CI)** Men: 1.00 Women: 1.01 (0.73±1.41) **Age, HR (95% CI)** 30±49 years: 1,00 50±64 years: 0.93 (0.58±1.47) 65±74 years: 0.94 (0.58±1.54) **Educational level, HR (95% CI)** Less than secondary: 1.00 Secondary or higher: 0.88 (0.62±1.25) **Family history of diabetes, HR (95% CI)** No: 1.00 Yes: 1.58 (1.13±2.21) **Tobacco consumption, HR (95% CI)** Smoker: 1.00 Ex-smoker: 1.49 (0.89±2.48) Never smoker: 1.16 (0.69±1.95) **Alcohol consumption, HR (95% CI)** None: 1.00 Low risk: 0.74 (0.52±1.07)

				High risk or harmful: 0.85 (0.51±1.43) **Daily consumption of fruits, HR (95% CI)** No: 1.00 Yes: 0.57 (0.40±0.81) **Daily consumption of vegetables, HR (95% CI)** No: 1.00 Yes: 1.04 (0.75±1.46) **Complete breakfast, HR (95% CI)** No: 1.00 Yes: 0.71 (0.46±1.09) **Regular physical activity, HR (95% CI)** No: 1.00 Yes: 0.74 (0.53±1.03) **BMI (kg/m^2), HR (95% CI)** <30: 1.00 30: 1.80 (1.29±2.51) **Abdominal circumference (cm), HR (95% CI)** <88 cm (women)/ <102 cm (men): 1.00 88 cm (women)/ 102 cm (men): 2.21 (1.44±3.38) **Blood pressure (mmHg), HR (95% CI)** <140/90: 1.00

				140/90: 1.58 (1.13±2.20) **Liver enzymes (U/L), HR (95% CI)** AST 35: 1.00 AST >35: 2.18 (1.39±3.41) ALT 35: 1.00 ALT >35: 1.93 (1.34±2.76) GGT 40: 1.00 GGT >40: 1.66 (1.18±2.35) **Lipid profile (mg/dL), HR (95% CI)** Total cholesterol <250: 1.00 Total cholesterol 250: 0.85 (0.51±1.42) HDL cholesterol <40 (men)/ <50 (women): 1.00 HDL cholesterol 40 (men)/ 50 (women): 0.58 (0.41±0.82) LDL cholesterol <100: 1.00 LDL cholesterol 100:: 0.87 (0.58±1.30) Triglycerides <150 1.00 Triglycerides 150: 1.63 (1.16±2.30) **Metabolic syndrome, HR (95% CI)** No 1.00 Yes 3.02 (2.14±4.26) **Fatty liver index, HR (95% CI)** <30 1.00 30 – 60 2.22 (0.97±5.11) ≥ 60: 4.52 (2.10±9.72)

				Incident T2D; unadjusted, HR (95% CI) FLI < 30: 1.00 FLI 30 – 59: 2.22 (0.97±5.11) FLI ≥ 60: 52 (2.10±9.72) **Base model: Incident T2D adjusted for age, sex and educational level, HR (95% CI)** FLI < 30: 1.00 FLI 30 – 59: 2.40 (1.03±5.55) FLI ≥ 60: 4.97 (2.28±10.80) **Base model adjusted for family history of T2D, HR (95% CI)** FLI < 30: 1.00 FLI 30 – 59: 2.31 (1.00±5.36) FLI ≥ 60: 4.82 (2.22±10.48) **Base model adjusted for lifestyle, HR (95% CI)** FLI < 30: 1.00 FLI 30 – 59: 2.26 (0.97±5.24) FLI ≥ 60: 4.63 (2.12±10.10) **Base model adjusted for hypertension, HR (95% CI)** FLI < 30: 1.00 FLI 30 – 59: 2.30 (0.99±5.34) FLI ≥ 60: 4.59 (2.10±10.03) **Base model adjusted for lipids (total and HDL cholesterol), HR (95% CI)** FLI < 30 :1.00

				FLI 30 – 59: 2.35 (1.01±5.44) FLI ≥ 60: 4.58 (2.09±10.01) **Base model adjusted for transaminases (AST, ALT) , HR (95% CI)** FLI 30: 1.00 FLI 30 – 59: 2.22 (0.96±5.14) FLI ≥ 60: 4.13 (1.88±9.04) **Base model adjusted for family history of T2D, lifestyle hypertension, lipids and transaminases, HR (95% CI)** All FLI 30: 1.00 FLI 30 – 59: 1.96 (0.85±4.54) FLI ≥ 60: 3.21 (1.45±7.09) Men FLI 30: 1.00 FLI 30 – 59: 1.53 (0.43±5.40) FLI ≥ 60: 1.70 (0.50±5.74) Women FLI 30: 1.00 FLI 30 – 59: 1.73 (0.53±5.59) FLI ≥ 60: 4.95 (1.73±14.29)
Giraldez-Garcia[4]	Prospective cohort, Spain	1,184 participants with prediabetes, according to ADA criteria	3 years	T2DM 143/1,184 (12%) **BMI**

				Clinical cut-off (≥ 102 cm and ≥ 88 cm vs. < 102 cm and < 88 cm in males and females respectively) 30 – 59 years HR 0.73 (95% CI 0.40-1.32) 60 – 74 years HR 1.26 (95% CI 0.75-2.11) *1 standard deviation increase* 30 – 59 years HR 1.25 (95% CI 0.92-1.69) 60 – 74 years HR 1.29 (95% CI 0.99-1.68) **Waist circumference** *Clinical cut-off (≥ 102 cm and ≥ 88 cm vs. < 102 cm and < 88 cm in males and females respectively* 30 – 59 years HR 2.65 (95% CI 1.24-5.65) 60 – 74 years HR 1.33 (95% CI 0.68-2.59) *1 standard deviation increase* 30 – 59 years HR 1.89 (95% CI 1.38-2.60) 60 – 74 years HR 1.44 (95% CI 1.11-1.87) **Waist to height ratio** *Clinical cut-off (≥ 0.55 vs. < 0.55)* 30-59 years HR 2.34 (95% CI 0.88-6.21) 60-74 years HR 0.94 (95% CI 0.40-2.19) *1 standard deviation increase* 30-59 years HR 1.84 (95% CI 1.29-2.26) 60-74 years HR 1.47 (95% CI 1.13-1.89)

Table 38. Studies relevant to criterion 4 (question 2)

Study reference	Study design, country	Participants	Follow up	Main findings
Barr[26]	Prospective cohort, Australia	10,026	Median 6 years	**All-cause mortality** HbA1c % <4.9: 32/2,096 (1.5%) 4.9-: 38/2,043 (1.9%) 5.0-: 56/1,954 (2.9%) 5.2-: 98/2,155 (4.5%) >5.4: 108/1,778 (6.1%) 2-hour PG Mmol/L <4.8: 34/2,178 (1.6%) 4.8-: 47/2,089 (2.2%) 5.6-: 51/1,785 (2.9%) 6.3-: 77/2,271 (3.4%) 7.8-: 87/1,372 (6.3%) >11.1: 36/331 (10.9%) FPG Mmol/L <5.1: 66/2,614 (2.5%) 5.1-: 28/1,569 (1.8%) 5.3-: 80/2,339 (3.4%) 5.6-: 80/2,265 (3.5%) 6.1-: 63/1,013 (6.2%) >7.0: 15/226 (6.6%) **CVD mortality** HbA1c % <4.9: 10/2,096 (0.5%) 4.9-: 8/2,043 (0.4%) 5.0-: 14/1,954 (0.7%) 5.2-: 25/2,155 (1.2%) >5.4: 31/1,778 (1.7%) 2-hour PG Mmol/L <4.8: 8/2,178 (0.4%) 4.8-: 10/2,089 (0.5%) 5.6-: 14/1,785 (0.8%) 6.3-: 22/2,271 (1.0%) 7.8-: 21/1,372 (1.5%) >11.1: 13/331 (3.9%) FPG Mmol/L <5.1: 20/2,614 (0.8%) 5.1-: 5/1,569 (0.3%) 5.3-: 13/2,339 (0.6%) 5.6-: 23/2,265 (1.0%) 6.1-: 20/1,013 (2.0%) >7.0: 7/226 (3.1%)
Bongaerts[27]	Cross-sectional, Germany	1,100	NA	**Distal sensorimotor polyneuropathy** HbA1c % 4.7-5.4: 32/313 (10.2%) 5.5-5.7: 48/340 (14.1%) 5.8-5.9: 21/177 (11.9%) 6.0-12.1: 53/270 (19.6%) 2-hour PG mg/dL 49-99: 27/239 (11.3%) 100-119: 16/224 (7.1%) 120-149: 36/233 (15.5%) 150-275: 36/227 (15.9%) FPG mg/dL 66-91: 31/253 (12.3%) 92-97: 29/224 (12.9%) 98-104: 27/218 (12.4%) 105-168: 28/228 (12.3%)
Cederberg[28]	Prospective cohort, Finland	593	Mean 9.7 years	**CVD incidence** HbA1c Women % ≤5.6%: 33.5% 5.7-6.4%: 32% ≥6.5%: 100% 2-hour PG Women Mmol/L ≤7.7: 28.8% 7.8-11.0: 47.5% ≥11.1: 58.3% FPG Women Mmol/L ≤5.5: 32.5% 5.6-6.0: 45.5% ≥6.1: 47.1%

				Men % ≤5.6%: 40.4% 5.7-6.4%: 47.1% ≥6.5%: 25%	Men Mmol/L ≤7.7: 41.8% 7.8-11.0: 43.2% ≥11.1: 25%	Men Mmol/L ≤5.5: 42.8% 5.6-6.0: 26.1% ≥6.1: 53.3%
de Vegt[29]	Prospective cohort, Netherlands	2,484	8 years	**All-cause mortality** HbA1c % <5.2%: 41/752 (5.5%) 5.2-5.5%: 55/798 (6.9%) 5.6-6.4%: 72/730 (9.9%) ≥6.5%: 17/83 (20.5%) **CVD mortality** HbA1c % <5.2: 16/752 (2.1%) 5.2-5.5: 32/798 (4.0%) 5.6-6.4: 39/730 (5.3%) ≥6.5: 11/83 (13.3%)	2-hour PG Mmol/L <4.9: 39/811 (4.8%) 4.9-6.2: 62/749 (8.3%) 6.3-7.7: 34/438 (7.8%) 7.8-11.0: 30/255 (11.8%) ≥11.1: 20/110 (18.2%) 2-hour PG Mmol/L <4.9: 18/811 (2.2%) 4.9-6.2: 36/749 (4.8%) 6.3-7.7: 18/438 (4.1%) 7.8-11.0: 15/255 (5.9%) ≥11.1: 11/110 (10%)	FPG Mmol/L <5.2: 47/712 (6.6%) 5.2-5.5: 49/682 (7.2%) 5.6-6.0: 37/567 (6.5%) 6.1-6.9: 33/282 (11.7%) ≥7.0: 19/120 (15.8%) FPG Mmol/L <5.2: 26/712 (3.7%) 5.2-5.5: 25/682 (3.7%) 5.6-6.0: 17/567 (3.0%) 6.1-6.9: 19/282 (6.7%) ≥7.0: 11/120 (9.2%)
Engelgau[30]	Cross-sectional, Egypt	2,021	NA	**Retinopathy** *Whole sample* HbA1c: 0.82 2-hour PG: 0.86 FPG: 0.85 *No antihyperglycemic* HbA1c: 0.72 2-hour PG: 0.76 FPG: 0.79		
Kalogeropoulos[31]	Prospective cohort, USA	2,386	Median 7.2 years	**Incident heart failure (hazard ratio per SD)** HbA1c: HR 1.26 (95% CI 1.13-1.41), Wald 17.07, P<0.001 2-hour PF: HR 1.22 (95% CI 1.07-1.39), Wald 9.09, P=0.02 FPG: HR 1.22 (95% CI 1.10-1.35), Wald 14.32, P<0.001		

Kowall[32]	Prospective cohort, Germany	1,653	Median 8.8 years	**All-cause mortality (crude, per 1000 person years)** HbA1c / 2-hour PG / FPG % / Mmol/L / Mmol/L 5.2%: 16.34 (9.52-26.16) / <79: 11.19 (5.78-19.55) / <88: 9.25 (4.23-17.56) 5.2/5.3%: 9.75 (5.33-16.36) / ≥79, <94: 5.64 (2.71-10.38) / ≥88, <93: 5.43 (2.60-9.99) 5.4/5.5%: 7.87 (4.67-12.45) / ≥94, <114: 12.54 (8.64-17.62) / ≥93, <99: 13.81 (9.73-19.04) 5.6/5.7%: 12.46 (8.63-17.41) / ≥114, <140: 12.20 (8.55-16.89) / ≥99, <107: 12.79 (8.91-17.78) 5.8-6.0%: 13.85 (9.53-19.45) / ≥140, <177: 11.53 (6.94-18.00) / ≥107, <116: 14.41 (9.41-21.10) ≥6.1%: 21.39 (14.10-31.12) / ≥177: 30.80 (21.20-43.25) / ≥116: 23.22 (15.17-34.02)
McCance[33]	Cross-sectional and longitudinal, USA	960, but varied by analysis	Mean 4.5 years	**Prevalent retinopathy test accuracy (antimodal)** HbA1c: cut-off ≥7.8%, sensitivity 65.6%, specificity 87.6% 2-hour PG: cut-off ≥12.6 mmol/L, sensitivity 87.5%, specificity 80.2% FPG: cut-off ≥9.3 mmol/L, sensitivity 68.8%, specificity 87.7% **Prevalent retinopathy test accuracy (WHO)** HbA1c: cut-off ≥6.1%, sensitivity 81.3%, specificity 76.8% 2-hour PG: cut-off ≥11.1 mmol/L, sensitivity 87.5%, specificity 75.8% FPG: cut-off ≥6.8 mmol/L, sensitivity 81.2%, specificity 77.1% **Prevalence retinopathy test accuracy (ROC analyses)** HbA1c: cut-off ≥7.0%, sensitivity 78.1%, specificity 84.7% 2-hour PG: cut-off ≥13.0 mmol/L, sensitivity 87.5%, specificity 81.4% FPG: ≥7.2 mmol/L, sensitivity 81.3%, specificity 80.4% **5-year incident retinopathy** HbA1c / 2-hour PG / FPG % / Mmol/L / Mmol/L ≤5.4: 0% / ≤4.6: 0% / ≤4.8: 0% 5.8: 0% / 5.4: 0% / 5.0: 0% 6.0: 3.0% / 5.9: 0% / 5.2: 0% 6.2: 0% / 6.5: 0% / 5.4: 0% 6.4: 1.1% / 7.0: 0% / 5.5: 0% 6.7: 0.9% / 7.8: 0% / 5.8: 0% 6.9: 0% / 9.1: 0% / 6.2: 1.1% 7.4: 2.1% / 11.5: 0% / 6.8: 2.1% 9.1: 1.9% / 18.1: 10.6% / 10.2: 7.2% >9.1: 20.0% / >18.1: 20.0% / >10.2: 20.0% **Prevalent nephropathy test accuracy (antimodal)**

				HbA1c: ≥7.8%, sensitivity 40.0%, specificity 86.6% 2-hour PG: ≥12.6 mmol/L, sensitivity 52.0%, specificity 78.6% FPG: ≥9.3 mol/L, sensitivity 40.0%, specificity 86.6%
Metcalf[34]	Cohort, New Zealand	31,148	Median 4 years	**All-cause mortality** HbA1c / 2-hour PG / FPG Mmol/mol / Mmol/L / Mmol/L < 40 106/5884 (1.8%) / < 5.4 89/6034 (1.5%) / < 5.1 96/5370 (1.8%) 40 - 42 96/(5780 (1.7%) / 5.4 - 6.8 91/6118 (1.5%) / 5.1 - 5.4 82/5654 (1.5%) 43 - 44 85/5214 (1.6%) / 6.9 - 8.9 116/6330 (1.8%) / 5.5 - 5.9 113/6836 (1.7%) 45 - 50 149/7734 (1.9%) / 9.0 - 12.1 146/6423 (2.3%) / 6.0 - 6.7 159/6648 (2.4%) ≥ 51 175/6536 (2.7%) / ≥ 12.2 169/6243 (2.7%) / ≥ 6.8 161/6640 (2.4%) **Cardiovascular disease** HbA1c / 2-hour PG / FPG Mmol/mol / Mmol/L / Mmol/L < 40 419/5884 (7.1%) / < 5.4 304/6034 (5.0%) / < 5.1 343/5370 (6.4%) 40 - 42 414/5780 (7.2%) / 5.4 - 6.8 412/6118 (6.7%) / 5.1 - 5.4 376/5654 (6.7%) 43 - 44 365/5214 (7.0%) / 6.9 - 8.9 509/6330 (8.0%) / 5.5 - 5.9 460/6836 (6.7%) 45 - 50 644/7734 (8.3%) / 9.0 - 12.1 598/6423 (9.3%) / 6.0 - 6.7 611/6648 (9.2%) ≥ 51 538/6536 (8.2%) / ≥ 12.2 557/6243 (8.9%) / ≥ 6.8 590/6640 (8.9%) **Coronary heart disease** HbA1c / 2-hour PG / FPG Mmol/mol / Mmol/L / Mmol/L < 40 199/5884 (3.4%) / < 5.4 171/6034 (2.8%) / < 5.1 170/5370 (3.2%) 40 - 42 235/5780 (4.1%) / 5.4 - 6.8 226/6118 (3.7%) / 5.1 - 5.4 208/5654 (3.7%) 43 - 44 185/5214 (3.5%) / 6.9 - 8.9 254/6330 (4.0%) / 5.5 - 5.9 234/6836 (3.4%) 45 - 50 350/7734 (4.5%) / 9.0 - 12.1 312/6423 (4.9%) / 6.0 - 6.7 338/6648 (5.1%) ≥ 51 281/6536 (4.3%) / ≥ 12.2 287/6243 (4.6%) / ≥ 6.8 300/6640 (4.5%) **Retinopathy** HbA1c / 2-hour PG / FPG Mmol/mol / Mmol/L / Mmol/L < 40 40/5884 (0.7%) / < 5.4 12/6034 (0.2%) / < 5.1 28/5370 (0.5%) 40 - 42 84/5780 (1.5%) / 5.4 - 6.8 35/6118 (0.6%) / 5.1 - 5.4 40/5654 (0.7%)

				43 - 44 56/5214 (1.1%) 6.9 - 8.9 87/6330 (1.4%) 5.5 - 5.9 110/6836 (1.6%) 45 - 50 191/7734 (2.5%) 9.0 - 12.1 228/6423 (3.5%) 6.0 to 6.7 205/6648 (3.1%) ≥ 51 336/6536 (5.1%) ≥ 12.2 345/6243 (5.5%) ≥ 6.- 324/6640 (4.9%) **Nephropathy** HbA1c 2-hour PG FPG Mmol/mol Mmol/L Mmol/L < 40 36/5884 (0.6%) < 5.4 20/6034 (0.3%) < 5.1 32/5370 (0.6%) 40 - 42 59/5780 (1.0%) 5.4 - 6.8 29/6118 (0.5%) 5.1 - 5.4 39/5654 (0.7%) 43 - 44 48/5214 (0.9%) 6.9 - 8.9 81/6330 (1.3%) 5.5 - 5.9 75/6836 (1.1%) 45 - 50 143/7734 (1.8%) 9.0 - 12.1 176/6423 (2.7%) 6.0 - 6.7 136/6648 (2.0%) ≥ 51 257/6536 (3.9%) ≥ 12.2 237/6243 (3.8%) ≥ 6.8 261/6640 (3.9%) **Neuropathy** HbA1c 2-hour PG FPG Mmol/mol Mmol/L Mmol/L < 40 8/5884 (0.1%) < 5.4 6/6034 (0.1%) < 5.1 6/5370 (0.1%) 40 - 42 13/5780 (0.2%) 5.4 - 6.8 8/6118 (0.1%) 5.1 - 5.4 7/5654 (0.1%) 43 - 44 12/5214 (0.2%) 6.9 - 8.9 17/6330 (0.3%) 5.5 - 5.9 14/6836 (0.2%) 45 - 50 39/7734 (0.5%) 9.0 - 12.1 30/6423 (0.5%) 6.0 - 6.7 35/6648 (0.5%) ≥ 51 51/6536 (0.8%) ≥ 12.2 61/6243 (1.0%) ≥ 6.8 61/6640 (0.9%)
Miyazaki[35]	Cross-sectional, Japan	1,950	NA	**Retinopathy test accuracy (maximum of sensitivity and specificity)** HbA1c: cut-off 5.7%, sensitivity 86.5%, specificity 90.1% 2-hour PG: cut-off 11.1 mmol/L, sensitivity 86.5%, specificity 89.6% FPG: cut-off 6.4 mmol/L, sensitivity 86.5%, specificity 87.3% **Retinopathy prevalence AUC** HbA1c: 94.5% (95% CI 91.6–97.5) 2-hour PG: 96.1% (95% CI 94.4 –97.7) FPG: 90.0% (95% CI 83.8–96.7
Mukai[36]	Cross-sectional, Japan	2,957	NA	**Retinopathy prevalence AUC** HbA1c: 0.919 (95% CI 0.878-0.959) 2-hour PG: 0.947 (95% CI 0.922-0.971) FPG: 0.908 (95% CI 0.866-0.949)

<table>
<tr>
<td>Munch[37]</td>
<td>Cross-sectional, Denmark</td>
<td>970</td>
<td>NA</td>
<td>Retinopathy prevalence
<table>
<tr><td>HbA1c</td><td></td><td>2-hour PG</td><td></td><td>FPG</td><td></td></tr>
<tr><td>%</td><td></td><td>%</td><td></td><td>%</td><td></td></tr>
<tr><td><5.5</td><td>10⁄114 (8.8%)</td><td><5.0</td><td>11／164 (6.7%)</td><td><5.0</td><td>6⁄102 (5.9%)</td></tr>
<tr><td>5.5 – 5.9</td><td>28⁄332 (8.4%)</td><td>5.0 – 5.9</td><td>15／153 (9.8%)</td><td>5.0 – 5.5</td><td>21⁄282 (7.5%)</td></tr>
<tr><td>6.0 – 6.4</td><td>15⁄213 (7.0%)</td><td>6.0 – 7.7</td><td>15／180 (8.3%)</td><td>5.6 – 6.0</td><td>18⁄207 (8.7%)</td></tr>
<tr><td>≥6.5</td><td>6/51 (12%)</td><td>7.8 – 11.0</td><td>18／214 (8.4%)</td><td>6.1 – 6.9</td><td>14⁄120 (12%)</td></tr>
</table></td>
</tr>
<tr>
<td>Tapp[38]</td>
<td>Prospective cohort, Australia</td>
<td>2,476</td>
<td>NA</td>
<td>Retinopathy prevalence
No antihyperglycemic
<table>
<tr><td>HbA1c</td><td></td><td>2-hour PG</td><td></td><td>FPG</td><td></td></tr>
<tr><td>%</td><td>%</td><td>Mmol/L</td><td>%</td><td>Mmol/L</td><td>%</td></tr>
<tr><td>3.9-</td><td>8.5</td><td>2.3-</td><td>5.2</td><td>2.5-</td><td>6.8</td></tr>
<tr><td>4.9-</td><td>4.2</td><td>5.5-</td><td>6.4</td><td>5.0-</td><td>7.9</td></tr>
<tr><td>5.0-</td><td>7.1</td><td>6.9-</td><td>4.3</td><td>5.3-</td><td>6.6</td></tr>
<tr><td>5.2-</td><td>4.4</td><td>7.8-</td><td>7.3</td><td>5.5-</td><td>7.2</td></tr>
<tr><td>5.3-</td><td>10.5</td><td>8.3-</td><td>7.2</td><td>5.7-</td><td>5.3</td></tr>
<tr><td>5.4-</td><td>6.6</td><td>8.8-</td><td>7.6</td><td>5.9-</td><td>6.0</td></tr>
<tr><td>5.6-</td><td>6.8</td><td>9.3-</td><td>7.0</td><td>6.2-</td><td>5.8</td></tr>
<tr><td>5.8-</td><td>5.3</td><td>9.9-</td><td>6.6</td><td>6.5-</td><td>6.9</td></tr>
<tr><td>6.1-</td><td>10.1</td><td>11.2-</td><td>6.5</td><td>7.1-</td><td>7.4</td></tr>
<tr><td>7.0-</td><td>11.0</td><td>13.1-</td><td>10.9</td><td>8.6-</td><td>9.0</td></tr>
</table>
Microalbuminuria prevalence
No antihyperglycemic
<table>
<tr><td>HbA1c</td><td></td><td>2-hour PG</td><td></td><td>FPG</td><td></td></tr>
<tr><td>%</td><td>%</td><td>Mmol/L</td><td>%</td><td>Mmol/L</td><td>%</td></tr>
<tr><td>3.8-</td><td>5.8</td><td>2.3-</td><td>3.4</td><td>2.5-</td><td>8.9</td></tr>
<tr><td>4.9-</td><td>9.4</td><td>5.5-</td><td>3.8</td><td>5.0-</td><td>8.8</td></tr>
<tr><td>5.0-</td><td>11.3</td><td>6.9-</td><td>9.4</td><td>5.3-</td><td>7.9</td></tr>
<tr><td>5.2-</td><td>8.9</td><td>7.8-</td><td>11.4</td><td>5.5-</td><td>8.3</td></tr>
<tr><td>5.3-</td><td>9.9</td><td>8.3-</td><td>11.1</td><td>5.7-</td><td>11.9</td></tr>
<tr><td>5.4-</td><td>14.2</td><td>8.8-</td><td>8.2</td><td>5.9-</td><td>11.8</td></tr>
<tr><td>5.6-</td><td>13.1</td><td>9.3-</td><td>9.9</td><td>6.2-</td><td>12.4</td></tr>
<tr><td>5.8-</td><td>11.6</td><td>9.9-</td><td>16.0</td><td>6.5-</td><td>10.2</td></tr>
<tr><td>6.1-</td><td>15.3</td><td>11.2-</td><td>18.2</td><td>7.1-</td><td>19.1</td></tr>
<tr><td>7.0-</td><td>21.2</td><td>13.1-</td><td>19.8</td><td>8.6-</td><td>21.8</td></tr>
</table></td>
</tr>
</table>

Toulis[39]	Cross-sectional, China	1,232	NA	**Albuminuria AUC** HbA1c: 0.54 (95% CI 0.50 to 0.58) 2-hour PG: 0.55 (95% CI 0.51 to 0.59) FPG: 0.54 (95% CI 0.49 to 0.58)
Vistisen[40]	Cohort, UK	5,427	Median 11.5 year	**Mortality or cardiovascular event (fatal or nonfatal) nondiabetic hyperglycaemia vs normoglycaemia** *WHO/IEC criteria* HbA1c: RR 1.99 (95% CI 1.55 - 2.53) 2-hour PG: RR 1.44 (95% CI 1.19 - 1.75) FPG: RR 1.27 (95% CI 1.01 - 1.60) *ADA criteria* HbA1c: RR 1.89 (95% CI 1.62 - 2.22) 2-hour PG: RR 1.44 (95% CI 1.19 - 1.75) FPG: RR 1.08 (95% CI 0.93 - 1.25) **Fatal or non-fatal CVD nondiabetic hyperglycaemia vs normoglycaemia** *ADA criteria* HbA1c: RR 2.03 (95% CI 1.67;2.45) 2-hour PG: RR 1.37 (95% CI 1.08;1.75) FPG: RR 1.09 (95% CI 0.91;1.31)
Xin[41]	Cross-sectional, China	2,592	NA	**Retinopathy test accuracy (joinpoint regression)** *Whole sample* HbA1c: cut-off 6.4%, sensitivity 85.1%, specificity 82.1% 2-hour PG: cut-off 10.7 mmol/L, sensitivity 78.4%, specificity 82.1% FPG: cut-off 7.2 mmol/L, sensitivity 78.4%, specificity 83.0% *No antihyperglycemic* HbA1c: cut-off 6.7%, sensitivity 60.7%, specificity 91.6% 2-hour PG: cut-off 12.0 mmol/L, sensitivity 53.6%, specificity 90.5% FPG: cut-off 6.8 mmol/L, sensitivity 64.3%, specificity 81.4% **Retinopathy test performance (maximum sensitivity plus specificity)** *Whole sample* HbA1c: cut-off 6.8%, sensitivity 85.1%, specificity 88.0% 2-hour PG: cut-off 15.0 mmol/L, sensitivity 74.3%, specificity 90.6% FPG: cut-off 7.8 mmol/L, sensitivity 75.7%, specificity 87.9%

				No antihyperglycemic HbA1c: cut-off 6.9%, sensitivity 60.7%, specificity 93.6% 2-hour PG: cut-off 10.6 mmol/L, sensitivity 60.7%, specificity 86.7% FPG: cut-off 6.7 mmol/L, sensitivity 67.8%, specificity 80.1% **Retinopathy AUC** *Whole sample* HbA1c: 86.4% (95% CI 80.8–92.0) 2-hour PG: 86.9% (95% CI 82.2–91.7) FPG: 85.4% (95% CI 80.0–90.7) *No antihyperglycemic* HbA1c: 72.5% (95% CI 59.7–85.2) 2-hour PG: 77.6% (95% CI 67.0–88.1) FPG: 76.8% (95% CI 65.8–87.8)
Zhang[42]	Cross-sectional, China	3,350	NA	**Retinopathy AUC** HbA1c: 72.7% (95% CI 58.6, 86.9) 2-hour PG: 68.7% (95% CI 54.1, 83.4) FPG: 76% (95% CI 63.6, 88.4)

Table 39. Studies relevant to criterion 9 (question 3)

Study reference	Study design, country	Participants	Description of trial arms	Follow up	Main findings
Herman[9]	RCT, USA	Overweight/obese adults who participated in the National Institute of Diabetes and Digestive and Kidney Diseases – Diabetes Prevention Programme, NDH according to ADA criteria. Total participants randomised in programme n = 3,234 (lifestyle intervention, metformin, or placebo)	Lifestyle: goal to lose 7% of initial body weight and to maintain weight loss, at least 700 kcal/week expenditure from physical activities, individual case manager/coach, frequent contact (n = 661) Control: placebo, plus standard advice about diet and physical activity (n = 766)	Mean = 3.2 years	**Progression to T2DM (adherent only)** Lifestyle: 141/661 (21.3%) Control: 296/766 (38.6%) Risk ratio 0.55 (95% CI 0.47 – 0.66)* **Regression to normoglycaemia (adherent only)** Lifestyle: 423/661 (64%) Control: 214/766 (27.9%) Risk ratio 2.29 (95% CI 2.02 – 2.60)*

		Total available for current study = 3,163 (lifestyle intervention, metformin, or placebo) Total included in current study n = 1,427 (adherent to lifestyle and placebo only) Metformin adherent n = 713			
Salimi[8]	RCT, USA	Overweight/obese adults who participated in the National Institute of Diabetes and Digestive and Kidney Diseases – Diabetes Prevention Programme, NDH according to ADA criteria. Total participants randomised in programme n = 3,234 (lifestyle intervention, metformin, or placebo) Total available for current study = 3,052 (lifestyle intervention, metformin, or placebo) Total included in current study n = 1,988 (lifestyle and placebo only) Metformin n = 985	Lifestyle: goal to lose 7% of initial body weight and to maintain weight loss, at least 700 kcal/week expenditure from physical activities, individual case manager/coach, frequent contact (n = 1,023) Control: placebo, plus standard advice about diet and physical activity (n = 1,014)	Median = 2.74 years	**Blood pressure, difference (95% CI)** *Systolic, mmHg* ITT: -2.39 (-3.44 to -1.35) *Diastolic, mmHg* ITT: -1.99 (-3.63 to -1.35) **Plasma lipids, difference (95% CI)** *Triglyceride* ITT: -15.74 (-22.60 to -8.90) *Cholesterol* ITT: -2.19 (-4.94 to 0.56) *HDL* 2.02 (1.05 to 2.99)
Shahbazi[10]	RCT, Iran	Adults over 20; living in Sarableh City, Iran; diagnosis of NDH according to ADA criteria. Total NDH n = 336 Current study invited n = 3,286 Current study participated n = 322	High-monounsaturated fat: diet regimen written by dietician, 15% protein, 45% fat (25% monounsaturated fatty acid, 10% polyunsaturated fatty acid, 10% saturated fatty acid), 40% carbohydrate (n = 107). Normal-monounsaturated fat: diet regimen written by dietician, 15% protein, 30% fat (10% monounsaturated fatty acid, 10% polyunsaturated fatty acid, 10% saturated fatty acid), 40% carbohydrate (n = 106).	2 years	**Weight (kg), change (sd)** HMD: −0.1 ± 0.7 NFD: −0.09 ± 0.6 Control: 0.2 ± 2.1 Note. No significant between group differences **Waist circumference (cm), change (sd)** HMD: −0.6 ± 4.2 NFD: −0.5 ± 3.8 Control: 0.4 ± 3.7b Note. ANOVA not significant, but carried out pairwise comparisons. HMD/NFD > control

			Control group: encouraged to follow USDA food pyramid, reduce fat to < 30% of calories, and reduce saturated fat to < 10% of calories (n = 109).		**Plasma glucose (mg/dL), change (sd)** *Fasting state* HMD: −1.6 ± 8.2 NFD: −1.4 ± 7.9 Control: 4.3 ± 10.7 Note. HMD/NFD > control *2Hpp* HMD: −3.9 ± 16.5 NFD: −0.6 ± 17.7 Control: 3.3 ± 14.8 Note. HMD/NFD > control **Plasma lipids, change (sd)** *LDL* HMD: −2.5 ± 7 NFD: −2.9 ± 10.7 Control: 1.4 ± 8.6 Note. HMD/NFD > control *HDL* HMD: 1.1 ± 3.3 NFD: 1.0 ± 3 Control: −0.06 ± 5.6 Note. No significant between group differences *Triglycerides* HMD: −12.8 ± 22.1 NFD: −10.2 ± 21.7 Control: 0.7 ± 17.5 Note. HMD/NFD > control **Blood pressure, change (sd)** *Systolic*

					HMD: −2.2 ± 13.6 NFD: −1.4 ± 11.8 Control: −0.5 ± 9.8 Note. No significant between group differences *Diastolic* HMD: −0.4 ± 5.7 NFD: −0.5 ± 4.1 Control: 0.1 ± 3.5 Note. No significant between group differences

Table 40. Studies relevant to criterion 11 (question 4)

Study reference	Study design, country	Participants	Description of trial arms	Main findings
Echouffo-Tcheugu 2015[14]	RCT postal questionnaire, UK	40 – 59 years, high risk of T2DM, patient at eligible GP practice in Eastern England Total RCT N = 20,188 Current study invited n = 3,286 c 1,995	Intervention: Invited to screening, offered intervention (dietician, frequent contact with health care professionals, medication, provision of glucometer for self-monitoring, educational material (n = 1373) Control: No invitation to screening (n = 572)	**Self-reported cardiovascular morbidity, n (%)** *Cardio events:* Screen 142 (12.4) No screen 67 (13.5) OR 0.90 (95% CI 0.71, 1.15) *Hypertension:* Screen 809 (60.9) No screen 352 (13.5) OR 0.90 (95% CI 0.75, 1.08) *Dyslipidemia:* Screen 502 (41.2) No screen 254 (48.3) OR 0.75 (95% CI 0.64, 0.88) **Self-reported prescribed medications, n (%)** *Antihypertensive* Screen 853 (72.5) No screen 369 (74.7)

				OR 0.89 (95% CI 0.73-1.10) *ACE inhibitors* Screen 546 (46.4) No screen 244 (49.4) OR 0.89 (95% CI 0.75-1.06) *Lipid lowering drugs* Screen 507 (43.1) No screen 244 (49.4) OR 0.78 (95% CI 0.63-0.95) *Antiplatelet drugs* Screen 335 (28.5) No screen 185 (37.5) OR 0.67 (95 CI 0.53-0.83) *Glucose lowering drugs* Screen 97 (8.3) No screen 48 (9.7) OR 0.84 (95% CI 0.57-1.21) **Self-rated health status (SF-8), score (SD)** *Mean SF-8 physical health summary score (0 to 100)* Screen 7.4 (9.8) No screen 47.8 (10.3) Mean difference –0.33 (95% CI –1.80 to 1.14) *Mean SF-8 mental health summary score (0 to 100)* Screen 51.8 (8.6) No screen 52.2 (8.1) Mean difference –0.38 (95% CI –1.33 to 0.57) *Mean EQ-5D score (scale -0.3 to 1.0)* Screen 0.87 (0.16) No screen 0.87 (0.15) Mean difference 0.002 (–0.02 to 0.02) *Mean EuroQol visual acuity score (0 to 100)* Screen 74.5 (16.5) No screen 73.7 (17.2) Mean difference 0.80 (95% CI –1.28 to 2.87) **Self-reported health behaviour** *Current smoker, n (%)*

				Screen 143 (10.5) No screen 61 (10.7) OR 0.97 (95% CI 0.72-1.32) *Alcohol consumption (units per week), mean (SD)* Screen 8.2 (11.9) No screen 8.1 (11.1) Mean difference 0.14 (95% CI –1.07 to 1.35) *1 or more portions fresh fruit per day, n (%)* Screen 627 (46.4) No screen 249 (43.8) OR 1.11 (95% CI 0.93-1.33) *1 or more portions green leafy vegetables per day, n (%)* Screen 339 (25.2) No screen 117 (20.7) OR 1.28 (95% CI 0.99-1.66) *1 or more portions other vegetables per day, n (%)* Screen 382 (28.5) No screen 142 (25.1) OR 1.19 (95% CI 0.99-1.43) *5 or more portions oily fish per week, n (%)* Screen 27 (2.1) No screen 10 (1.8) OR 1.14 (95% CI 0.61-2.11) *5 or more portions meat products per week, n (%)* Screen 104 (7.8) No screen 51 (9.1) OR 0.84 (95% CI 0.64-1.11) *1 or more portions whole meal (brown) bread per day, n (%)* Screen 414 (30.8) No screen 167 (29.9) OR 1.04 (95% CI 0.89-1.22) *Total physical activity (METhours per week), mean (SD)* Screen 45.1 (51.3) No screen 44.6 (51.9) Mean difference 0.50 (95% CI –4.08 to 5.07) *Vigorous activity (MET-hours per week), mean (SD)*

				Screen 16.2 (31.7) No screen 15.3 (32.5) Mean difference 0.89 (95% CI –2.09 to 3.86) *Walking activity (MET-hours per week), mean (SD)* Screen 22.6 (21.1) No screen 21.2 (21.0) Mean difference 1.35 (95% CI –1.17 to 3.86) *Sedentary time (hours per day), mean (SD)* Screen 5.3 (2.7) No screen 5.4 (2.8) Mean difference –0.11 (95% CI –0.32 to 0.09) *Number of hospital admissions in past 3 months, mean (SD)* Screen 0.11 (0.37) No screen 0.13 (0.44) Mean difference 0.85 (95% CI 0.58-1.25) *Number of family physician consultations in past 3 months, mean (SD)* Screen 1.1 (1.3) No screen 1.2 (1.5) Mean difference 0.93 (95% CI 0.78-1.12) *Number of nurse consultations in past 3 months, mean (SD)* Screen 0.8 (1.7) No screen 0.8 (1.7) Mean difference 1.04 (95% CI 0.79-1.36)

CI = confidence interval; EQ-5D = EuroQual measure of health outcome; MET = Metabolic equivalents of physical activity; OR = odds ratio; SD = standard deviation; SF-8 = 8-item short form health survey

Appraisal for quality and risk of bias

Risk of bias of the included studies are reported below.

Table 41. Risk of bias of included studies for question 1 using the QUIPS

Study	Risk of bias domains					
	Study participation	Study attrition	Prognostic factor measurement	Outcome measurement	Study confounding	Statistical analysis and reporting
Franch-Nadal/Giraldez-Garcia[3 4]	Low	Low	Moderate	Low	Moderate	Moderate
Jung/Park[5 6]	Moderate	Moderate	Moderate	Low	Low	Moderate

Table 42. Risk of bias of included studies for question 2 using the QUADAS

Study	Risk of bias domains				Applicability concerns		
	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
Barr[26]	high	low	unclear	high	high	high	low
Bongaerts[27]	low	low	high	high	high	high	high
Cederberg[28]	low	low	unclear	high	high	high	unclear
de Vegt[29]	low	low	unclear	high	high	unclear	unclear
Engelgau[30]	high	high	unclear	high	high	unclear	low
Kalogeropoulos[31]	high	unclear	high	low	high	unclear	unclear
Kowall[32]	low	low	unclear	high	high	unclear	unclear
McCance[33]	high	low	high	unclear	high	high	high
Metcalf[34]	high	low	unclear	high	high	unclear	unclear
Miyazaki[35]	low	low	unclear	high	high	unclear	unclear
Mukai[36]	low	high	low	high	high	unclear	unclear
Munch[37]	high	unclear	low	high	high	high	high

Tapp[38]	high	high	low	high	high	high	unclear
Toulis[39]	high	unclear	low	low	high	unclear	low
Vistisen[40]	high	low	unclear	high	low	unclear	unclear
Xin[41]	high	high	low	unclear	high	unclear	low
Zhang[42]	low	low	low	high	high	unclear	low

Table 43. Risk of bias of included studies for question 3 using the Cochrane Collaboration's Risk of Bias Tool

	Risk of bias domains						
Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel (objective outcomes)	Blinding of outcome assessments (objective outcomes)	Incomplete outcome data (objective outcomes)	Selective outcome reporting	Other sources of bias
Herman/Salimi[8 9]	Low	Unclear	Low	Low	Low	Unclear	Low
Shahbazi[10]	Low	Unclear	Low	Low	Low	Unclear	Low

Table 44. Risk of bias of included studies for question 4 using the Cochrane Collaboration's Risk of Bias Tool

	Risk of bias domains						
Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessments	Incomplete outcome data	Selective outcome reporting	Other sources of bias
Echouffo-Tcheugui[14]	Low	Unclear	High	High	Unclear	Low	High

Appendix 4 – UK NSC reporting checklist for evidence summaries

All items on the UK NSC Reporting Checklist for Evidence Summaries have been addressed in this report. A summary of the checklist, along with the page or pages where each item can be found in this report, is presented in Table .

Table 45. UK NSC reporting checklist for evidence summaries

	Section	Item	Page no.
1.	TITLE AND SUMMARIES		
1.1	Title sheet	Identify the review as a UK NSC evidence summary.	Title page
1.2	Plain English summary	Plain English description of the executive summary.	6
1.3	Executive summary	Structured overview of the whole report. To include: the purpose/aim of the review; background; previous recommendations; findings and gaps in the evidence; recommendations on the screening that can or cannot be made on the basis of the review.	8
2.	INTRODUCTION AND APPROACH		
2.1	Background and objectives	Background – Current policy context and rationale for the current review – for example, reference to details of previous reviews, basis for current recommendation, recommendations made, gaps identified, drivers for new reviews	15
		Objectives – What are the questions the current evidence summary intends to answer? – statement of the key questions for the current evidence summary, criteria they address, and number of studies included per question, description of the overall results of the literature search.	16
		Method – briefly outline the rapid review methods used.	18

2.2	Eligibility for inclusion in the review	State all criteria for inclusion and exclusion of studies to the review clearly (PICO, dates, language, study type, publication type, publication status etc.) To be decided *a priori*.	18
2.3	Appraisal for quality/risk of bias tool	Details of tool/checklist used to assess quality, e.g. QUADAS 2, CASP, SIGN, AMSTAR.	24
3.	SEARCH STRATEGY AND STUDY SELECTION (QUESTION 1)		
3.1	Databases/ sources searched	Give details of all databases searched (including platform/interface and coverage dates) and date of final search.	24
3.2	Search strategy and results	Present the full search strategy for at least one database (usually a version of Medline), including limits and search filters if used.	64
		Provide details of the total number of (results from each database searched), number of duplicates removed, and the final number of unique records to consider for inclusion.	101
3.3	Study selection	State the process for selecting studies – inclusion and exclusion criteria, number of studies screened by title/abstract and full text, number of reviewers, any cross checking carried out.	26
3.	SEARCH STRATEGY AND STUDY SELECTION (QUESTION 2)		
3.4	Databases/ sources searched	Give details of all databases searched (including platform/interface and coverage dates) and date of final search.	24
3.6	Search strategy and results	Present the full search strategy for at least one database (usually a version of Medline), including limits and search filters if used.	73/82
		Provide details of the total number of (results from each database searched), number of duplicates removed, and the final number of unique records to consider for inclusion.	102/103
3.7	Study selection	State the process for selecting studies – inclusion and exclusion criteria, number of studies screened by title/abstract and full text, number of reviewers, any cross checking carried out.	34/35
3.	SEARCH STRATEGY AND STUDY SELECTION (QUESTION 3)		
3.8	Databases/ sources searched	Give details of all databases searched (including platform/interface and coverage dates) and date of final search.	24

3.9	Search strategy and results	Present the full search strategy for at least one database (usually a version of Medline), including limits and search filters if used.	83
		Provide details of the total number of (results from each database searched), number of duplicates removed, and the final number of unique records to consider for inclusion.	104
3.10	Study selection	State the process for selecting studies – inclusion and exclusion criteria, number of studies screened by title/abstract and full text, number of reviewers, any cross checking carried out.	49
3.	SEARCH STRATEGY AND STUDY SELECTION (QUESTION 4)		
3.11	Databases/ sources searched	Give details of all databases searched (including platform/interface and coverage dates) and date of final search.	24
3.12	Search strategy and results	Present the full search strategy for at least one database (usually a version of Medline), including limits and search filters if used.	95
		Provide details of the total number of (results from each database searched), number of duplicates removed, and the final number of unique records to consider for inclusion.	105
3.13	Study selection	State the process for selecting studies – inclusion and exclusion criteria, number of studies screened by title/abstract and full text, number of reviewers, any cross checking carried out.	56
4.	STUDY LEVEL REPORTING OF RESULTS (QUESTION 1)		
4.1	Study level reporting, results and risk of bias assessment	For each study, produce a table that includes the full citation and a summary of the data relevant to the question (for example, study size, PICO, follow-up period, outcomes reported, statistical analyses etc.).	125
		Provide a simple summary of key measures, effect estimates and confidence intervals for each study where available.	125
		For each study, present the results of any assessment of quality/risk of bias.	148
4.	STUDY LEVEL REPORTING OF RESULTS (QUESTION 2)		
4.2	Study level reporting, results	For each study, produce a table that includes the full citation and a summary of the data relevant to the question (for example,	134

	and risk of bias assessment	study size, PICO, follow-up period, outcomes reported, statistical analyses etc.).	
		Provide a simple summary of key measures, effect estimates and confidence intervals for each study where available.	134
		For each study, present the results of any assessment of quality/risk of bias.	148
4.	STUDY LEVEL REPORTING OF RESULTS (QUESTION 3)		
4.3	Study level reporting, results and risk of bias assessment	For each study, produce a table that includes the full citation and a summary of the data relevant to the question (for example, study size, PICO, follow-up period, outcomes reported, statistical analyses etc.).	141
		Provide a simple summary of key measures, effect estimates and confidence intervals for each study where available.	141
		For each study, present the results of any assessment of quality/risk of bias.	149
4.	STUDY LEVEL REPORTING OF RESULTS (QUESTION 4)		
4.4	Study level reporting, results and risk of bias assessment	For each study, produce a table that includes the full citation and a summary of the data relevant to the question (for example, study size, PICO, follow-up period, outcomes reported, statistical analyses etc.).	144 144
		Provide a simple summary of key measures, effect estimates and confidence intervals for each study where available.	
		For each study, present the results of any assessment of quality/risk of bias.	149
5.	QUESTION LEVEL SYNTHESIS (QUESTION 1)		
5.1	Description of the evidence	For each question, give numbers of studies screened, assessed for eligibility, and included in the review, with summary reasons for exclusion.	101
5.2	Combining and presenting the findings	Provide a balanced discussion of the body of evidence which avoids over reliance on one study or set of studies. Consideration of four components should inform the reviewer's	28

		judgement on whether the criterion is ‘met’, ‘not met’ or ‘uncertain’: quantity; quality; applicability and consistency.	
5.3	Summary of findings	Provide a description of the evidence reviewed and included for each question, with reference to their eligibility for inclusion. Summarise the main findings including the quality/risk of bias issues for each question. Have the criteria addressed been ‘met’, ‘not met’ or ‘uncertain’?	31
5.	QUESTION LEVEL SYNTHESIS (QUESTION 2)		
5.4	Description of the evidence	For each question, give numbers of studies screened, assessed for eligibility, and included in the review, with summary reasons for exclusion.	102/103
5.5	Combining and presenting the findings	Provide a balanced discussion of the body of evidence which avoids over reliance on one study or set of studies. Consideration of four components should inform the reviewer’s judgement on whether the criterion is ‘met’, ‘not met’ or ‘uncertain’: quantity; quality; applicability and consistency.	39
5.6	Summary of findings	Provide a description of the evidence reviewed and included for each question, with reference to their eligibility for inclusion. Summarise the main findings including the quality/risk of bias issues for each question. Have the criteria addressed been ‘met’, ‘not met’ or ‘uncertain’?	47
5.	QUESTION LEVEL SYNTHESIS (QUESTION 3)		
5.7	Description of the evidence	For each question, give numbers of studies screened, assessed for eligibility, and included in the review, with summary reasons for exclusion.	104
5.8	Combining and presenting the findings	Provide a balanced discussion of the body of evidence which avoids over reliance on one study or set of studies. Consideration of four components should inform the reviewer’s judgement on whether the criterion is ‘met’, ‘not met’ or ‘uncertain’: quantity; quality; applicability and consistency.	51
5.9	Summary of findings	Provide a description of the evidence reviewed and included for each question, with reference to their eligibility for inclusion.	54

		Summarise the main findings including the quality/risk of bias issues for each question. Have the criteria addressed been ‘met’, ‘not met’ or ‘uncertain’?	
5.	QUESTION LEVEL SYNTHESIS (QUESTION 4)		
5.10	Description of the evidence	For each question, give numbers of studies screened, assessed for eligibility, and included in the review, with summary reasons for exclusion.	105
5.12	Combining and presenting the findings	Provide a balanced discussion of the body of evidence which avoids over reliance on one study or set of studies. Consideration of four components should inform the reviewer’s judgement on whether the criterion is ‘met’, ‘not met’ or ‘uncertain’: quantity; quality; applicability and consistency.	57
5.13	Summary of findings	Provide a description of the evidence reviewed and included for each question, with reference to their eligibility for inclusion. Summarise the main findings including the quality/risk of bias issues for each question. Have the criteria addressed been ‘met’, ‘not met’ or ‘uncertain’?	60
6.	REVIEW SUMMARY		
6.1	Conclusions and implications for policy	Do findings indicate whether screening should be recommended? Is further work warranted? Are there gaps in the evidence highlighted by the review?	61
6.2	Limitations	Discuss limitations of the available evidence and of the review methodology if relevant.	62

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