**EFFICACY AND EFFECTIVENESS OF SCREEN-AND-TREAT POLICIES IN THE PREVENTION OF TYPE TWO DIABETES.**

**SYSTEMATIC REVIEW AND META-ANALYSIS OF SCREENING TESTS AND INTERVENTIONS.**

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**Abstract**

**Objectives**

In the context of high and rising prevalence of type 2 diabetes, to assess:

1. Diagnostic accuracy of screening tests for pre-diabetes.
2. Efficacy of interventions (lifestyle or metformin) in preventing onset of type 2 diabetes in people with pre-diabetes.

**Design**

Systematic review and meta-analysis.

**Data sources and method**

Medline, PreMedline and Embase search. Study protocols and seminal papers were citation-tracked in Google Scholar to identify definitive trials and additional publications. Data on study design, methods and findings were extracted onto Excel spreadsheets; a 20% sample was checked by a second researcher. Data extracted for screening tests included diagnostic accuracy and population prevalence. Two meta-analyses were performed, one summarising accuracy of screening tests (using the oral glucose tolerance test as the gold standard) in identifying pre-diabetes, and the other assessing relative risk of progression to type 2 diabetes following either lifestyle intervention or treatment with metformin.

**Eligibility criteria**

In any language:

1. Empirical studies evaluating test accuracy for identifying pre-diabetes.

2. Interventions (randomised trials and interventional studies) with a control group in people identified through screening.

**Results**

2873 titles were scanned and 148 papers reviewed in full. In the final analysis, 49 studies of screening tests (five of which were prevalence studies) and 50 intervention trials were included. In identifying pre-diabetes, HbA1c had a mean sensitivity of 0.50 (95% confidence interval (CI) 0.41-0.58) and specificity of 0.80 (95%CI 0.74-0.84), though different studies used different cut-off values. Fasting plasma glucose had a mean sensitivity of 0.23 (95% CI 0.17-0.31) and specificity of 0.95 (95% 0.93-0.96). Different measures of glycaemic abnormality identified different sub-populations (e.g. 47% of people with abnormal HbA1c had no other glycaemic abnormality). Lifestyle interventions were associated with a mean 36% (95% CI 28-43%) relative risk reduction in incidence of type 2 diabetes over 6month-6 years, attenuating to 20% (95% CI 8-31%) at follow-up.

**Conclusions**

HbA1c is neither sensitive nor specific for detecting pre-diabetes; fasting glucose is specific but not sensitive. Interventions in people classified through screening as having pre-diabetes have some efficacy in preventing or delaying onset of type 2 diabetes in trial populations. But since screening is inaccurate, many people will be incorrectly diagnosed and referred on for interventions whilst others will be falsely reassured and not offered the intervention. Our findings suggest that ‘screen and treat’ policies alone are unlikely to have substantial impact on the worsening epidemic of type 2 diabetes.

**What this study adds**

What is already known on the subject

* Type 2 diabetes is increasingly common; its prevention is an international health priority.
* There is no agreement on how best to define or detect ‘pre-diabetes’ (i.e. high risk of developing type 2 diabetes in the future).
* Trials in people with pre-diabetes have shown that the onset of type 2 diabetes can be delayed or prevented with lifestyle measures or metformin.

What this study adds

* This is the first systematic review to assess both the diagnostic accuracy of screening tests for pre-diabetes and the efficacy of interventions in those detected by screening.
* Different tests for pre-diabetes define vastly different populations, so depending on the test used, large numbers of people will be unnecessarily treated or falsely reassured.
* ‘Screen and treat’ policies will benefit some but not all people at high risk of developing diabetes; they may need to be complemented by population-wide approaches for effective diabetes prevention.

DEFINITION OF TERMS

* Oral glucose tolerance test
  + Two-part blood test.
  + Part one: fasting plasma glucose (FPG). Blood test taken following overnight fast. If abnormal diagnosed as impaired fasting glucose (IFG).
  + Part two: 2hour glucose tolerance test (2hrGTT). Blood test taken two hours after ingestion of a sugary drink. If abnormal diagnosed as impaired glucose tolerance (IGT)
  + Both tests can be performed independently of each other
* HbA1c
  + Glycated haemoglobin measurement which reflects glucose level over two-three months. Accuracy impaired by haemoglobinopathies.
* Pre-diabetes
  + Arbitrary category to encompass either IFG or IGT or abnormal HbA1c.
* American Diabetes Association (ADA) Diagnostic Criteria
  + Impaired fasting glucose- 5.6-6.9 mmol/L
  + Impaired glucose tolerance 7-11.1 mmol/L
  + HbA1c ‘at risk’ range 5.7-6.4%
* World Health Organisation (WHO) Diagnostic Criteria
  + Impaired fasting glucose- 6.0-6.9 mmol/L
  + Impaired glucose tolerance 7-11.1 mmol/L
  + HbA1c ‘at risk’ range 6.0-6.4%
* International Expert Committee (IEC) Diagnostic Criteria
  + HbA1c ‘at risk’ range 6.0-6.4%

**Introduction**

The prevalence of type 2 diabetes is rising globally; 422 million adults are living with diabetes 1, and the number expected to die from its complications is predicted to double between 2005 and 2030 1. In the UK approximately 3.2 million people have type 2 diabetes and by 2025 it is predicted that this will increase to 5 million people 2. This places considerable financial burden on the NHS. The healthcare cost of diabetes is estimated to be £23.7 billion, a figure expected to rise to £39.8 billion by 2035/36 2. Preventing or delaying type 2 diabetes has become an international priority.

There are two approaches to diabetes prevention: screen and treat, in which a sub-population is identified as ‘high risk’ and offered individual intervention; and a population-wide approach in which everyone is targeted via public health policies on environmental moderators 3 (sociocultural influences, socio-economic influences, transport, green spaces). Finland 4 is taking a multi-level approach to diabetes prevention by using both strategies. In contrast, the UK’s National Diabetes Prevention Programme5,6 follows Australia7 and the United States 8 in placing the emphasis on a screen and treat approach.

There is international inconsistency on how to identify individuals at high risk of diabetes, to the extent that ‘a transatlantic trip may cure or cause diabetes simply as a result of small but important differences in diagnostic criteria’ 9. In the United States, the American Diabetes Association criteria are recommending a pre-diabetes diagnosis with a fasting plasma glucose (FPG) between 5.6-6.9mmol/L or HbA1c between 5.7%-6.4%. The World Health Organisation and International Expert Committee recommend a fasting plasma glucose cut off of 6-6.9mmol/L and HbA1c of 6-6.4%. The term pre-diabetes is used to encapsulate these ranges and implies that if individuals do not take action they will develop diabetes, (although in reality this is not always the case). Since the recognition of pre-disease states (impaired glucose tolerance, impaired fasting glucose, and elevated HbA1c), trials of lifestyle interventions have been associated with reduced or delayed onset of type 2 diabetes10. However, studies of screening and intervention programmes in real world settings are sparse 11. Women with a history of gestational diabetes have a 7-fold increased risk of developing diabetes post-partum12. These women may not be captured by the pre-diabetes umbrella term, as many have normal glycaemic markers at the six week postpartum review and then fail to attend annual review thereafter 13-17. Gestational diabetes is common in certain minority ethnic groups 18, and in deprived multi-ethnic areas a history of this condition may identify a significant proportion of individuals who could benefit from preventive interventions.

We sought to inform national and local policymaking on prevention of type 2 diabetes by asking two questions: [a] which (if any) screening test should be used to identify people at risk of developing type 2 diabetes? and [b] what is the efficacy of preventive interventions (lifestyle and/or metformin) in those identified as high risk by screening?

**Method**

**Search strategy**

We sought to identify all diagnostic accuracy and prevalence studies focusing on laboratory-assessed HbA1c and fasting plasma glucose (as recommended by the UK National Institute for Health and Care Excellence 19) as screening tools. Capillary glucose and HbA1c point of care testing were excluded due to the lower reliability of these tests. For intervention studies we included trials whose participants were aged ≥18 years and had been identified as one of the ‘at risk’ groups (impaired glucose tolerance, impaired fasting glucose, elevated HbA1c or a history of gestational diabetes (GDM)). We studied two kinds of intervention: lifestyle programmes and metformin, compared to a control, in any setting, and which included weight change, change in glycaemic index or diabetes incidence as an outcome measure. Exclusion criteria included animal studies, molecular biology studies, studies related to children, surgical interventions, and interventions related to medication other than metformin.

The study was undertaken between December 2014 and June 2016. It was commissioned by policymakers in a London borough with high prevalence of type 2 diabetes, so concerns about applicability to a real-world setting helped shape the review questions. With assistance from a specialist librarian, three searches were undertaken: one for screening tests for pre-diabetes, another for intervention trials and a third to identify studies relating to the prevention of type 2 diabetes in women with a history of gestational diabetes. The full search strategy is appended; search terms (MESH and free text) included test, screening, pre-diabetes, impaired glucose tolerance, impaired fasting glucose, gestational diabetes, post-partum, ethnic groups, metformin and lifestyle. EB manually extracted relevant titles from this dataset and reviewed abstracts to identify papers for full review. SR checked a random sample of 750 abstracts (20%). Disagreements were resolved by discussion. Bilingual colleagues translated non-English papers and extracted data with guidance from the research team.

**Diagnostic accuracy meta-analysis**

Diagnostic accuracy studies were tabulated by index and reference test. Raw data for the meta-analysis on true positives, false positives, true negatives and false negatives were extracted directly or calculated using the sensitivity and specificity information given in the paper. Additional data were extracted on population demographics, ethnicity, and diagnostic criteria used. Studies were pooled where HbA1c was the index test and oral glucose tolerance test was the reference standard. We presented these data separately for studies using the World Health Organisation criteria and studies not using these criteria (notably, some studies used the more stringent American Diabetes Association criteria to define pre-diabetes). We also pooled studies with the fasting plasma glucose as the index test and 2hour glucose tolerance test as the reference test. Again we examined the data as a whole as well as separately by diagnostic criteria.

A bivariate diagnostic random-effects meta-analysis 20 was undertaken to pool study-level estimates of diagnostic accuracy using the *reitsma* function from the R 21 package *mada* 22*.* In each case, we reported the pooled sensitivity, false positive rate and false negative rate and 95% confidence intervals. We plotted the bivariate summary receiver operating curve (sROC) over points representing study estimates of sensitivity and false positive rate, weighted by study size, and summarised the discriminative ability of each test using the area under ROC curve (AUROC) and the partial AUROC (which restricts the area to the observed false positive rates). Statistical heterogeneity was described using the I squared statistic for bivariate meta-analysis 23.

**Defining the at-risk population**

To compare differences in the at-risk population identified by each test, we undertook a prevalence analysis. Using euler*APE v3* 24 raw data were analysed from prevalence studies to assess the degree of overlap in the population identified as abnormal by each test. This analysis highlights the differing number of people eligible for interventions, depending on which test and criteria are used. Venn diagrams were created with the area of each ellipse proportional to the prevalence.

**Intervention trial review and meta-analysis**

Data extracted into Excel files from intervention trials included participant demographics, type of intervention, intervention length, primary and secondary outcomes. A second Excel sheet was used to tabulate results, including a clinically significant reduction in BMI (1Kg/m2) or weight (2Kg), clinically significant improvement in glycaemic markers (normoglycaemia, or reduction in fasting plasma glucose by 0.5mmol/l, 2hr glucose tolerance by >1mmol/l, HbA1c to <6), differences in diabetes incidence between groups and whether this was statistically significant 25. Any trial that collected data on diabetes incidence was included in the meta-analysis. Data were extracted directly from the publications and processed using RevMan software. Owing to the heterogeneity of the data we used a random-effects model to create forest plots showing relative risk of developing type 2 diabetes following lifestyle interventions and metformin compared to usual care or no additional intervention.

**Assessment of study quality, applicability, bias and patient involvement**

Quality and applicability of the test papers was assessed using the validated QUADAS-2 tool, designed for the evaluation of diagnostic accuracy papers 26. Following the refinement steps as recommended by the creators the tool was piloted, adapted and refined by EB and SR before being applied to all the papers used in the meta-analysis (full details available from authors). The limitations of the intervention trials were assessed using the Cochrane Risk of Bias tool 27, and the CONSORT checklist (see appendix). The overall quality of the evidence at outcome level was assessed by RN using the GRADE principles 27. An additional assessment was conducted to examine the extent to which participants were involved in the design of the intervention, if feedback was sought, if non-enrolment reasons were given and if interventions could be adapted to meet the individual’s needs.

**Patient involvement**

The review was conceptualized by a patient participation group led by the project lead SV. Patients and clinicians raised questions on how best to identify those at risk of diabetes and explore how the Clinical Commissioning Group can support people in Newham to minimize their risk. In this way, patient and citizen involvement shaped the research question and methodology of this review. The authors attended regular project meetings, reporting back the results of the review to the rest of the team which included GP leads from the practices piloting interventions as well as the area lead for diabetes.

Figure 1- Flow diagram

**Results**

**Search results**

Figure 1 shows the review flowchart. 148 publications underwent full paper review, (83 relating to diagnostic accuracy testing and 65 relating to intervention trials). Data from 46 papers were extracted and used to construct the diagnostic accuracy meta-analysis. 50 unique intervention trials were reviewed in full as well as publications related to these (protocol designs, sub-analyses).

**Diagnostic accuracy of tests for pre-diabetes**

Table 1 lists the studies included in the diagnostic accuracy meta-analysis, showing country of origin, population demographics, and QUADAS-2 assessment for bias and applicability. Figures 2 & 3 show the ROC curves constructed from data extracted from these trials. The pooled sensitivity of the HbA1c at identifying abnormalities as defined by the oral glucose tolerance test was 0.49 (95% CI 0.40 to 0.58); its specificity was 0.79 (95%CI 0.73 to 0.84). Data were extracted from studies using both World Health Organisation and American Diabetes Association criteria, as well as studies which determined the optimal diagnostic cut offs using the optimal sensitivity and specificity assessed from their own populations. AUROC are used to estimate the overall diagnostic accuracy of a test with a value of 1 equating to the perfect test. The calculated AUROC of the HbA1c was 0.71. However, a low sensitivity leads to a high number of false negative results (i.e. people incorrectly identified normal). When this is taken into account (with the partial AUROC calculation) the accuracy reduces to 0.59. A sub-analysis using the International Expert Committee / World Health Organisation criteria for HbA1c did not alter the sensitivity of this test.

**Table 1: Diagnostic Accuracy Data for the detection of Pre-Diabetes and QUADAS Analysis**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  |  |  |  |  |  |  |  | | **QUADAS Bias** | | | | | **QUADAS Applicability** | | |
|  | Country | Reference test criteria | Population information | Positive Predictive Value | Negative Predictive Value | Index Sensitivity | Index Specificity |  | | Bias | | Index test | Reference test | Test Timing | Patient selection | Index test | Reference test |
| **OGTT reference test (FPG+/-IGT), HbA1c index test** | | | | | | | | | | | | | | | | | |
| Incani 201528 | Italy | ADA | One risk factor | 0.81 | 0.37 | 0.53 | 0.7 | |  | | U | L | L | L | L | L | L |
| Guo 201429 | US | ADA | national survey | 0.71 | 0.57 | 0.35 | 0.86 | |  | | L | U | U | U | L | L | L |
| Wu 201330 | China | WHO | Rural Chinese | 0.75 | 0.57 | 0.72 | 0.61 | |  | | H | H | L | L | U | L | L |
| Lee 201331 | Korean | ADA | Korean | 0.73 | 0.39 | 0.49 | 0.66 | |  | | H | H | L | L | H | L | L |
| Bhowmik 201232 | India (Bangladesh) | WHO | Rural | 0.18 | 0.96 | 0.64 | 0.73 | |  | | L | H | L | L | U | L | L |
| Ma 201333 | China | WHO&ADA | Urban | 0.34 | 0.76 | 0.45 | 0.67 | |  | | U | H | L | L | U | L | L |
| Vlaar 201334 | Netherlands | ADA | South Asian | 0.35 | 0.88 | 0.66 | 0.68 | |  | | L | L | L | L | U | L | L |
| Bhansali 201235 | North India | WHO/IEC | South Asian | 0.43 | 0.85 | 0.36 | 0.9 | |  | | L | L | L | L | U | L | L |
| Tankova 201236 | Bulgaria | WHO | One risk factor | 0.47 | 0.43 | 0.71 | 0.64 | |  | | H | H | L | L | L | H | L |
| Pinelli 201137 | US | ADA | Arabic ethnicity | 0.57 | 0.55 | 0.14 | 0.91 | |  | | L | L | L | L | U | L | L |
| Mostafa 2010 38 | UK | WHO | 23% South Asian | 0.30 | 0.89 | 0.40 | 0.84 | |  | | L | L | L | L | L | L | L |
| Hu 2010 39 | China | WHO | Chinese | 0.52 | 0.65 | 0.66 | 0.51 | |  | | L | H | L | L | U | L | L |
| Lorenzo 201040 | US | ADA | Mixed | 0.63 | 0.51 | 0.24 | 0.85 | |  | | U | U | L | H | L | L | L |
| Mohan 201041 | South India | ADA&WHO | Indian | 0.20 | 0.93 | 0.66 | 0.62 | |  | | L | H | L | U | L | L | L |
| Zhou 200942 | China | WHO | Chinese | 0.62 | 0.79 | 0.25 | 0.95 | |  | | L | H | L | L | U | L | L |
| Tanaka 201143 | Japan | WHO | Japanese | 0.80 | 0.73 | 0.76 | 0.77 | |  | | U | H | L | L | U | L | L |
| Yoshinaga 199644 | Japan | WHO | Japanese | 0.43 | 0.65 | 0.43 | 0.65 | |  | | L | H | H | L | U | L | L |
| Lin 201445 | China | WHO | Chinese | 0.39 | 0.86 | 0.647 | 0.828 | |  | | H | H | H | L | U | L | L |
| Yang 201246 | China | WHO | One risk factor | 0.63 | 0.94 | 0.70 | 0.87 | |  | | U | H | L | L | L | L | L |
| Tay 201147 | China | WHO | elevated BMI | 0.72 | 0.50 | 0.81 | 0.39 | |  | | U | L | L | L | U | L | L |
| Gingras 201348 | Canada | ADA | GDM,raised WC | 0.89 | 0.33 | 0.76 | 0.62 | |  | | L | L | L | L | L | L | L |
| Katreddy 201349 | Ireland | WHO | GDM | 0.19 | 0.88 | 0.28 | 0.80 | |  | | L | L | L | L | L | L | L |
| Picon 201250 | Spain | ADA | GDM | 0.55 | 0.56 | 0.23 | 0.84 | |  | | H | L | L | L | U | L | L |
| **FPG reference, HbA1c index test** | | | | | | | | | | | | | | | | | |
| Du 201351 | China | ADA | One risk factor | 0.55 | 0.78 | 0.47 | 0.83 | |  | | L | L | L | L | U | L | L |
| Kumaravel 201252 | UK | ADA | One risk factor | 0.63 | 0.88 | 0.21 | 0.98 | |  | | L | L | L | U | U | L | L |
| Kim 201153 | US | ADA | GDM | 0.75 | 0.62 | 0.39 | 0.81 | |  | | H | L | L | L | L | L | L |
| Sun 201354 | China | ADA | Metabolic syndrome | 0.31 | 0.92 | 0.6 | 0.76 | |  | | L | L | L | L | U | L | L |
| **HbA1c +FPG combined index, IGT reference test** | | | | | | | | | | | | | | | | | |
| Hu (repeat)39 |  |  |  | 0.59 | 0.70 | 0.42 | 0.82 | |  | |  |  |  |  |  |  |  |
| Tanaka (repeat)43 |  |  |  | 0.97 | 0.68 | 0.62 | 0.98 | |  | |  |  |  |  |  |  |  |
| Modan 198455 | Israel | ADA | National data set | 0.16 | 0.99 | 0.92 | 0.45 | |  | | L | H | L | L | U | L | L |
| Noctor 201256 57 | Ireland | ADA | GDM | 0.56 | 0.97 | 0.9 | 0.84 | |  | | U | U | L | U | U | L | L |
| **FPG index, IGT reference** | |  |  |  |  |  |  |  | |  | |  |  |  |  |  |  |
| Hu (repeat)39 |  |  |  | 0.62 | 0.69 | 0.82 | 0.81 | |  | |  |  |  |  |  |  |  |
| Picon (repeat)50 |  |  |  | 1 | 0.87 | 0.83 | 1 | |  | |  |  |  |  |  |  |  |
| Ihsan 200458 | Oman | WHO | unclear | 0.27 | 0.75 | 0.3 | 0.9 | |  | | U | L | L | U | U | L | L |
| Myers 201459 | UK | WHO | GDM | 0.32 | 0.96 | 0.61 | 0.93 | |  | | H | L | L | L | L | L | L |
| Mehmet 201060 | UK | WHO | GDM | 0.63 | 0.84 | 0.86 | 0.88 | |  | | U | L | L | L | l | L | L |
| Holt 200361 | UK | WHO | GDM | 0.43 | 1 | 1 | 0.94 | |  | | U | L | L | L | l | L | L |
| McClean 201062 | UK | WHO | GDM | 0.51 | 0.92 | 0.73 | 0.94 | |  | | U | L | L | L | L | L | L |
| Kwong 200963 | Canada | WHO | GDM | 0.2 | 0.87 | 0.05 | 97 | |  | | H | L | L | L | U | L | L |
| Reinblatt 200664 | Canada | WHO | GDM | 0.84 | 0.61 | 0.14 | 0.98 | |  | | H | L | L | L | U | L | L |
| Agarwal 200365 | UAE | WHO | GDM | 0.33 | 0.85 | 0.18 | 0.92 | |  | | U | L | L | L | U | L | L |
| Costa 200066 | Spain | WHO | GDM Caucasian | 0.25 | 0.89 | 0.08 | 0.97 | |  | | U | L | L | L | U | L | L |
| Conway 199967 | US | ADA | GDM | 0.45 | 0.88 | 0.36 | 0.92 | |  | | H | L | L | L | L | L | L |
| Mudalige 201468 | UK | WHO | GDM | 0.48 | 0.92 | 0.35 | 0.95 | |  | | U | L | L | L | L | L | L |
| Venkataraman 201469 | UK | WHO | GDM | 0.22 | 0.93 | 0.14 | 0.96 | |  | | U | L | L | L | L | L | L |
| Russell 201370 | UK | WHO | GDM | 0.13 | 0.96 | 0.2 | 0.93 | |  | | H | L | L | L | L | L | L |
| Joseph 201371 | UK | WHO | GDM | 0.38 | 0.87 | 0.45 | 0.93 | |  | | H | L | L | L | L | L | L |
| Ko 200172 | China | WHO | unclear | 0.63 | 0.92 | 0.17 | 0.99 | |  | | L | U | U | U | U | L | L |
| Kakad 201073 | UK | WHO | GDM | 0.36 | 0.86 | 0.21 | 0.93 | |  | | H | L | L | L | L | L | L |
| Cypryk 200474 | Poland | WHO | GDM | 0.75 | 0.83 | 0.12 | 0.99 | |  | | U | L | L | L | U | L | L |

Analysis of studies using the fasting plasma glucose as the index test found that this test had a sensitivity of 0.25 (0.19 to 0.32) and specificity of 0.95 (95% 0.92 to 0.96) at identifying impaired glucose tolerance. The analysis calculated an AUROC of 0.72 with a partial AUROC of 0.42. A sub analysis of studies using the criteria implemented in the UK did not change the results seen.

Figure 2 - Studies using HbA1c as index test and OGTT as reference standard

[INSERT HERE]

|  |  |  |
| --- | --- | --- |
|  | All studies (n = 23) | Excluding high risk of bias studies (n=18) |
| Pooled Sensitivity | 0.49 (0.40 to 0.58) | 0.47 (0.37 to 0.58) |
| Pooled false positive rate | 0.21 (0.16 to 0.27) | 0.19 (0.14 to 0.26) |
| AUC | 0.71 | 0.71 |
| Partial AUC (restricted to observed fpr’s) | 0.59 | 0.60 |
| Specificity | 0.79 (0.73 to 0.84) | 0.81 (0.74 to 0.86) |
| False negative rate | 0.51 (0.42 to 0.60) | 0.53 (0.42 to 0.63) |
| I squared | 80% | 76% |

Figure 3 Studies using FPG as index test and IGT as reference standard.

[INSERT HERE]

|  |  |  |
| --- | --- | --- |
|  | All studies (n= 19) | Excluding studies at high risk of bias (n = 11) |
| Pooled Sensitivity | 0.25 (0.19 to 0.32) | 0.24 (0.17 to 0.32) |
| Pooled false positive rate | 0.06 (0.04 to 0.08) | 0.05 (0.03 to 0.07) |
| AUC | 0.72 | 0.73 |
| Partial AUC (restricted to observed fpr’s) | 0.422 | 0.27 |
| Specificity | 0.94 (0.92 to 0.96) | 0.95 (0.93 to 0.97) |
| FNR | 0.75 (0.68 to 0.81) | 0.76 (0.86 to 0.83) |
| I squared | 99% | 99% |

The main source of potential bias from these studies was selection bias. In many studies, the sampling strategy was unclear or participants self-selected to attend for screening (for example by answering an invitation or advertisement) rather than using a true population sample (random or consecutive). This was a particular concern in studies of follow-up after gestational diabetes, which usually defined their population as women who had attended for the oral glucose tolerance tests, with no information on those who did not attend. Most diagnostic accuracy studies scored well on the QUADAS scale for applicability, indicating that the patient populations were similar to those tested in primary care settings and the use of diagnostic tests and their interpretation was in keeping with our review question. These analyses demonstrated a high level of heterogeneity, indicating that the test performs differently depending on population and setting. These are important considerations when assessing the diagnostic accuracy of the tests with specified populations. The results of the QUADAS tool were used to undertake a sensitivity analyses. Excluding studies at high risk or bias and outlying studies did not significantly alter the results (see Appendix).

**Agreement between different diagnostic tests for pre-diabetes**

Only five studies (table 2) gave a pre-diabetes prevalence comparison of all three tests (HbA1c, fasting plasma glucose, 2hr glucose tolerance test). Using current International Expert Committee and World Health Organisation guidelines 27% of the populations studied were identified as ‘pre-diabetic’ by one of the tests (of which 48% had an elevated HbA1c alone); if American Diabetes Association criteria are applied to the same cohort, this figure was 49% (of which 71% had an elevated HbA1c alone). There was low agreement between the three tests on which individuals were classified as having pre-diabetes. Figure 4 illustrates this limited overlap. Substituting the American Diabetes Association criteria for both the oral glucose tolerance test and HbA1c increases the degree of overlap between the test results but in doing this doubles the estimated prevalence of pre-diabetes (Figure 5).

**Table 2 Prevalence Analysis**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Author** | **Country** | **Population Demographics** | **Diagnostic Criteria for HbA1c** | **Diagnostic Criteria for OGTT** | **Total Population tested** | **% Tested Population 'pre-diabetic'** | **% pre-diabetic population with abnormal HbA1c alone** |
| Incani28 | Italy | BMI>35 or DM risk factors | ADA | ADA | 1054 | 49% | 17% |
| James75 | USA | Mixed ethnicity. NHANES Survey | ADA | ADA | 3627 | 37% | 8% |
| Zhang76 | China | Chinese. GHS population survey | ADA | ADA | 3590 | 66% | 29% |
| Benaiges77 | Spain | Mixed ethnicity. GDM | ADA | ADA | 141 | 42% | 25% |
| Mostafa38 | UK | WE and SA ethnicity | IEC | WHO | 8696 | 27% | 48% |

Figure 4: Prevalence of Pre-Diabetes by Diagnostic Test using IEC and WHO Criteria

Pre-diabetes prevalence 27%.

Of those with an abnormal result:

1. 4.7% Isolated IFG
2. 24.4% Isolated IGT
3. 47.8% Isolated HbA1c

ab- 2.9% IFG+IGT

ac- 4.1% IFG +HbA1c

bc- 12.2% IGT +HbA1c

abc- 3.9% IGT+IFG+Hba1c

1. area outside ellipse normal result 72%

[INSERT HERE]

Figure 5: Prevalence of Pre-Diabetes by Diagnostic Test using ADA criteria for all tests.

[INSERT HERE]

Pre-diabetes prevalence 54%. Of those with an abnormal result:

1. Isolated IFG (25.4%)
2. Isolated IGT (6.0%)
3. Isolated HbA1c (22.4%)

ab- IFG+IGT (7.2%)

ac- IFG +HbA1c (26.7%)

bc- IGT +HbA1c (3.6%)

abc- IGT+IFG+Hba1c (8.7%)

1. Area outside ellipse normal result 46%

**Interventions to prevent diabetes in screen-detected pre-diabetes**

50 trials met our eligibility criteria10, 78-126 tables 3 to 6 (see online publication) summarise the methods and results of these studies. Only 25 of the trials (21 of lifestyle interventions alone, 2 of metformin alone and 2 assessed both) had the necessary information available to be included in the meta-analysis. All trials were performed in adults identified at risk of developing diabetes defined by the oral glucose tolerance test or had a history of gestational diabetes. There was heterogeneity in the number of participants in each trial (ranging from hundreds to thousands), length of interventions (4 weeks- 6 years), intensity of intervention (frequency of contacts) and delivery method. Inter-rater agreement on data extraction was 100%, with the exception of a single paper in which the authors did not distinguish between primary and secondary outcomes. 19 of the 49 trials used the development of diabetes as a primary outcome measure. Some trials had begun with this outcome but during the trial substituted it for weight reduction and/or change in glycaemic markers because of low recruitment 78. Many studies showed differences in weight and change in glycaemic markers between groups that were statistically but not clinically significant. At the end of the intervention, 20 of the 49 trials showed a clinically significant reduction in weight between the groups, 15 showed a clinically significant improvement in glycaemic markers, 23 showed some difference in favour of the intervention arm in the number of people developing diabetes, but this difference was only statistically significant in 7 of those trials (see tables 5 and 6).

Meta-analysis (figure 6) showed that lifestyle interventions reduced the relative risk of developing diabetes by 31% (95% CI 15-44%) if the intervention lasted 6 months-2 years. This translates to 69 (95% CI 56 to 85) out of 1000 people in the lifestyle intervention group developing diabetes compared to 100 out of 1000 without the intervention, or a number needed to treat (NNT) of 33 (95% CIs 23 to 67). Lifestyle interventions lasting 3-6 years showed a 37% (95% CIs 28 to 46%) relative risk reduction, equating to 151 (95% CI 129 to 172) out of 1000 people in the lifestyle intervention group developing diabetes compared to 239 of 1000 in the control group (NNT 12 (95% CIs 10 to 15)). Due to the small number of follow-up studies it is difficult to assess diabetes risk reduction following the completion of lifestyle interventions. Our estimates show that relative risk reduction of developing diabetes attenuates to 20% (95% CIs 8 to 31%))84, 96, 110, 127-129 in the post-trial period.

Figure 6: Relative risk reduction at the end of lifestyle trials

[INSERT HERE]

**Risk of Bias Legend**

A – Random sequence generation (selection bias)

B – Allocation concealment (selection bias)

C – Blinding of outcome assessment (detection bias)

D – Incomplete outcome data (attrition bias)

E – Selective reporting (reporting bias)

**Figure 7: Relative risk reduction at follow up post intervention**

[INSERT HERE]

**Risk of Bias Legend**

A – Random sequence generation (selection bias)

B – Allocation concealment (selection bias)

C – Blinding of outcome assessment (detection bias)

D – Incomplete outcome data (attrition bias)

E – Selective reporting (reporting bias)

**Figure 8: Relative risk reduction at the end of metformin trial**

[INSERT HERE]

**Risk of Bias Legend**

A – Random sequence generation (selection bias)

B – Allocation concealment (selection bias)

C – Blinding of outcome assessment (detection bias)

D – Incomplete outcome data (attrition bias)

E – Selective reporting (reporting bias)

Meta-analysis evaluating the impact of metformin (figure 8) showed a relative risk reduction of 26% (95% CIs 16 to 35%) whilst participants were on this medication, translating to 218 (95% CI 192 to 248) out of 1000 developing diabetes on metformin compared to 295 of 1000 not receiving this medication (NNT 14 (95% CIs 10 to 22)). The benefits of metformin were assessed at the end of the trial periods once the participants have been on the medication for a pre-specified length of time. There were no follow up studies examining for persistence of benefit once metformin had been discontinued, but the US DPP study did show some improvements in diabetes incidence reduction with long-term metformin use. 130

The main sources of potential bias (as estimated by Cochrane risk of bias tool) were selection bias (lack of allocation concealment) and attrition bias (where authors used per-protocol analysis instead of an intention to treat analysis to assess changes in outcome measures), potentially leading to over estimation of the benefits of the intervention. In order to provide the most comprehensive synthesis of relevant studies we did not pre-specify a minimum methodological quality threshold for included studies. However, we performed a sensitivity analysis removing the studies at high risk of bias to test whether the exclusions of some trials changed the overall findings. Omitting these did not significantly change the overall results (for example removal of Ramachandran 2006 did not significantly alter the relative risk reduction).

Using the GRADE approach, we assessed the evidence to be of moderate quality for progression to type 2 diabetes with metformin versus control, low quality for lifestyle interventions of 1-2 years and 3-6 years’ duration versus control and very low quality for progression to diabetes at post-trial follow up for lifestyle interventions versus control. This means that the true risk reductions from interventions may be substantially different from the meta-analysis estimates. All outcomes were downgraded for indirectness as the study populations may not be representative of those who would receive the intervention in a real-life setting and the measure used to identify those at most risk (oral glucose tolerance test) is not widely used in practice. A further downgrade was due to the statistical heterogeneity in two out of the four outcomes (lifestyle interventions with a 3-6 year follow up (I2=45%; downgraded once) and post intervention follow up (I2=82%; downgraded twice)). This high degree of heterogeneity is likely due to differences in sample size, length and intensity of interventions included in this analysis, but the small number of trials contributing to the post intervention follow up analysis limited our ability to explore this using subgroup analysis. Seven papers 10, 95, 101, 105, 106, 116, 126 described at least one element of patient and participant involvement. The majority of interventions were inflexible with a one-size-fits-all approach.

**Gestational diabetes**

Nine trials assessed lifestyle interventions in women with a history of gestational diabetes (see tables 4 and 6). These focused on diet, exercise and increasing breast-feeding uptake. None showed a statistically significant reduction in diabetes incidence between the intervention and control groups. Attrition rates were high in these trials. Only three trials had sufficient data to be included in the meta-analysis.

**Withdrawal and attrition rates**

15 papers78, 96, 118 10, 81, 92, 97, 101, 103, 105-107, 109, 110, 116, 126 had the necessary data available to assess withdrawal and attrition rates. Of the pre-diabetic population identified, only 27% went on to complete the trial (the rest of the pre-diabetic population were either not eligible, declined to participate or withdrew from the intervention (figure 9)). Therefore, relative risk reductions calculated from intervention trials reflect risk improvements seen in a limited proportion of the total pre-diabetic population.

**Figure 9: Attrition rate from at-risk population to trial completion**

**[INSERT HERE]**

Data from research studies suggest high attrition and withdrawal rates in screen and treat programmes. Overall, only 27% of people in an eligible pre-diabetic population completed a trial of a preventive intervention

**Discussion**

**Principal Findings**

This systematic review, commissioned by local policymakers who wished to identify an effective ‘screen and treat’ strategy for type 2 diabetes prevention in an area of high prevalence, has included 99 studies and produced three main findings. First, the diagnostic accuracy of tests used to detect pre-diabetes in screening programmes is low. The most commonly used test (HbA1c) is neither sensitive nor specific; the fasting glucose test is specific but not sensitive. Low sensitivity results in a high number of false negatives, resulting in a large number of people being falsely reassured. Second, the diagnostic tests identify different pre-diabetic population groups with limited overlap. If the American Diabetes Association criteria are used instead of World Health Organisation ones, the prevalence of those diagnosed with pre-diabetes doubles. Third, both individually-targeted lifestyle interventions and metformin have some efficacy in preventing or delaying the onset of type 2 diabetes, though the protective effect of the former is greatest in longer interventions (3-6 years) and attenuates with time from intervention. However, we only have moderate to very low confidence in these estimates because study quality was often low. Fourth, in women with a history of gestational diabetes, the evidence base for lifestyle interventions in preventing progression to type 2 diabetes is currently weak.

Most intervention trials included in this study used the oral glucose tolerance test to identify their study population. However, in practice this test is not widely used. It is time consuming, requires fasting, ingestion of a sugary drink (which many people find unpleasant) and because of intra-individual variability needs to be done twice. HbA1c is estimated on a single non-fasting blood test, but varies by ethnicity, leading to over- and under-estimation of the result 131-133 and may be inaccurate in the presence of haemoglobinopathy. The fasting plasma glucose test is a single blood test but requires the person to have fasted for several hours so is impractical for mass screening.

Accuracy of tests depends on cut-off points. Using the International Expert Committee and World Health Organisation criteria for defining pre-diabetes, HbA1c correctly identifies only half the individuals with an abnormal oral glucose tolerance test but also assigns the pre-diabetes label to large numbers of individuals with a normal oral glucose tolerance test. Different diagnostic criteria result in a different estimate of the prevalence of pre-diabetes; this will have implications for which (and how many) individuals are eligible for lifestyle interventions. Furthermore, people identified using HbA1c may not have the same glycaemic abnormality as those entered into trials on the basis of an oral glucose tolerance test and may respond differently to interventions.

Systematic reviews assessing progression from at-risk states to diabetes have shown those at most risk of developing diabetes had both impaired fasting glucose and impaired glucose tolerance; HbA1c showed a lower progression rate, similar to impaired fasting glucose alone 134-136. Those with a history of gestational diabetes have the highest progression rates to diabetes with a sevenfold increased risk following the first diagnosis12 and a 70% cumulative incidence at 10 years 137.

Of the 50 intervention trials included in this review, 34 used surrogate endpoints (most commonly, weight loss) as their primary outcome. Whilst most demonstrated statistically significant changes in these endpoints, authors rarely commented critically on the sustainability or clinical significance of these. Weight reduction has been shown to correlate poorly with diabetes incidence reduction in some populations 106. The trials in our sample that did show a statistically significant reduction in the definitive endpoint of diabetes incidence lasted between 3 and 6 years and were intensive in nature with individuals closely monitored.

Whilst reduced diabetes incidence is possible if the interventions are intensive, the relative risk reductions seen in trials apply only to those who enrol and adhere to the intervention. Given the number of people who will not meet eligibility criteria or who decline or do not complete the intervention (Figure 9), there is no scientific basis for extrapolating percentage risk reductions seen in trials to an equivalent reduction in diabetes incidence nationally. Poor enrolment and completion of lifestyle interventions will limit the impact national prevention programmes will have on the overall burden of disease.

**Comparison to other Systematic Reviews**

This systematic review is the first to combine the analysis of diagnostic accuracy with efficacy of interventions to give an overall estimate of how screen and treat policies may play out in populations, focusing on the end-point of progression to type 2 diabetes. Edwardson et al 138 reviewed the effectiveness of risk scores and lifestyle interventions but did not assess their accuracy and the implications of their use. Other systematic reviewers performed a more in-depth analysis of improvement in surrogate endpoints such as weight loss and improvements in glycaemic markers 11, 139-142. However, a review carried out by the Institute for Clinical and Economic Review raised concerns regarding the clinical importance and sustainability of improvements of these surrogate markers 143

Similar relative risk reductions in diabetes incidence with lifestyle interventions and metformin in study populations were found in other systematic reviews 142. Previous meta-analyses 144, 145 showed a higher relative risk reduction when they included only the most tightly controlled trials with stringent population enrolment criteria. In contrast, Public Health England’s meta-analysis of translational studies identified a lower relative risk reduction due to the inclusion of pragmatic trials and observational studies146, and showed high levels of statistical heterogeneity between primary studies. One systematic review assessed UK based community and national interventions whose participants were the most deprived, vulnerable and socially excluded (groups often omitted from clinical trials) 147. They found that the effects of the interventions were small in these groups, with no evidence of long-term reduction in diabetes incidence.

Labelling people as having ‘pre-diabetes’ has significant personal implications (medicalisation, intrusive testing and stigma) for people who may never go on to develop diabetes. Other scholars have voiced similar concerns to those raised in this systematic review with regards to the danger of inaccurate classification and/or overdiagnosis with tests for pre-diabetes 148, effectiveness of lifestyle interventions in the real world 149 and the limited impact of screen and treat policies in the absence of a complementary population-based approach 150.

Whether these interventions reduce longer-term cardiovascular morbidity and mortality remains unclear. A meta-analysis and systematic review undertaken by Hopper et al 151 agreed with our findings that lifestyle interventions can reduce the relative risk of developing diabetes. Whilst these interventions did result in a reduction in incidence of cardiovascular events, this did not translate into a significant reduction in all-cause or cardiovascular mortality. Long-term follow-up studies undertaken by the Chinese Da Qinq study and the Finnish Diabetes Prevention Study found that there was no significant difference between intervention and control groups in first cardiovascular events 127 or cardiovascular morbidity 152, though the study was not powered to detect such a difference.

**Meaning and implications for policy makers, clinicians and academics**

This review was requested by a local clinical commissioning group in an inner London borough where the local diabetes prevention programme has largely consisted of a community prescription initiative offered to people classified as having pre-diabetes with a BMI of 27 or above, a history of gestational diabetes or a QRISK>20%. Intensive interventions lasting years, such as those included in this systematic review, are not an option given its cash-limited budget.

Our findings indicate that in settings such as this, screen and treat policies for pre-diabetes will benefit individuals who are ‘true positives’, have sufficient personal, family and community resources to enable them to attend and comply with preventative interventions. Incentivised diabetes prevention programmes programmes will also pick up people with undiagnosed diabetes (an estimated 2 to 10% of those screened38, 78, 81, 116, 126) who can be offered timely management. However, a significant proportion of people at high risk of developing type 2 diabetes will go on to develop the condition despite such programmes. These include people who test ‘false negative’ and those who, despite testing positive and being offered a lifestyle intervention, lack the personal resources and social connections to support and sustain lifestyle change.

Because of the low accuracy of screening tests and the limited reach of intervention programmes policymakers may wish to consider supplementing screen-and-treat policies with population-based approaches aimed at entire communities. The World Health Organisation, for example, proposes *“multisectoral action that simultaneously addresses different sectors that contribute to the production, distribution and marketing of food, while concurrently shaping an environment that facilitates and promotes adequate levels of physical activity”* (World Health Organisation 2014 page xiv)153.

**Strengths and limitations**

This is the first systematic review to assess both the diagnostic accuracy of screening tests for pre-diabetes and the efficacy of interventions in those classified through screening as having pre-diabetes. Furthermore, it is a comprehensive review synthesising a large volume of international literature, including translations from languages other than English. It was inspired by a question by front-line policymakers and focused on producing a practical answer to that question. As such, and unlike much secondary and primary research, it fulfils the important criterion of ‘usefulness’ 154.

The main limitation of the review was the number of exclusions due to incomplete data available in published studies. Despite efforts to contact authors, we were unable to obtain the data needed to contribute to the meta-analysis in eighteen potentially eligible papers. In the prevalence analysis only five out of 28 papers compared all three diagnostic tests, so these findings should be interpreted with caution. A high proportion of studies that assessed the diagnostic accuracy of the fasting plasma glucose did so in participants with a history of gestational diabetes – a bias that may influence the generalizability of this analysis.

Only half of the intervention studies were included in the meta-analysis because the trial or intervention lengths were too short to be able to capture diabetes incidence. Additionally, the analysis of diabetes risk reduction at follow periods was limited due to the small number of primary studies which performed follow up analyses. We recommend that primary studies of diabetes prevention programmes should be resourced to undertake long-term follow-up to assess for sustained benefits including diabetes incidence, cardiovascular morbidity and mortality.

Intervention studies which used risk scores to identify their population instead of blood tests exist155, but were outside the scope of this systematic review. Further synthesis of interventions using wider population eligibility criteria could provide additional insights into the benefits of these.

**Future work**

On the basis of the findings of this review, we suggest three avenues for further research. The first is pragmatic real-world effectiveness and cost-effectiveness studies of interventions for pre-diabetes that have already been shown to be efficacious in trials.149, 156 Studies of the translational gap between randomised trial evidence and real-world uptake and impact is always important,157 but particularly so when the ‘real world’ appears unlikely to be able to replicate the conditions (e.g. health literacy, language fluency and comorbidities of target population; intensity and duration of intervention; completeness of follow-up) that characterised the most positive trials149, 158. These real-world studies should address the impact on behaviour of individuals who test positive for pre-diabetes (only one-third of whom would be predicted to engage with interventions [figure 9]) and the costs (to both participants and the health service). More specifically, effectiveness and cost-effectiveness studies should explore the implications of screen and treat programmes for both commissioners and providers – including the opportunity costs of spending a limited budget on a programme for which a variable percentage of the pre-diabetic population would be eligible for and engage with depending on locality.

The second avenue for further research is the evaluation of population level and/or health system interventions. Individual lifestyle choices are constructed by sociocultural, political and economic influences, which may be more effectively addressed using population-wide strategies such as protection of green spaces, increased walkability of the environment, affordable leisure activities, improved food labelling, independent regulation of food nutritional standards, regulation on food advertising, affordable fruit and vegetables and school-based programmes. Such systematic structural approaches addressing ‘upstream’ influences on diabetes pathogenesis require well-supported public health teams working alongside local governments to improve the health of communities and may be vital components of a multifaceted long term primary prevention strategy159.

Currently, only a tiny fraction of the literature on diabetes prevention is informed by an appreciation of the social complexity underlying diabetes pathogenesis160 161, 162. The 2014 Foresight Report on Obesity was a model of good practice in teasing out the complex interactions between genetic, physiological, psychological, sociocultural, economic and political determinants of obesity; it provided a strong and consistent message that short-term ‘behaviour change’ interventions were unlikely to succeed in isolation.163 A comparable initiative for type 2 diabetes could add richness to our current understanding of the condition and help inform the design of evidence-based strategies aimed at influencing its ‘upstream’ determinants.

**Conclusion**

As the prevalence of type 2 diabetes rises inexorably in high-, middle- and low-income countries alike, controversy continues to surround the questions of who is ‘at risk’ and what preventive interventions to offer them. A screen and treat policy will only be effective if (a) a test exists that correctly identifies those at high risk (sensitivity) while also excluding those at low risk (specificity); and (b) an intervention exists that is acceptable to, and also efficacious in, those at high risk. This review has shown that of the two screening tests for pre-diabetes that are available and acceptable to patients and clinicians, fasting glucose is specific but not sensitive and HbA1c is neither sensitive but not specific. Trial evidence suggests that lifestyle interventions have a potential role in reducing individual progression to diabetes, and may benefit those high-risk individuals who have the motivation, resources and social support to achieve sustained lifestyle change. However, given that this is likely to be a limited proportion of the identified pre-diabetic population substantial research resources should be directed at the evaluation of upstream interventions aimed at the entire population.

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**Contributors:** EB conceptualized the review assisted with developing the search strategy and ran the search, scanned all titles and abstracts, extracted quantitative data on all the papers, citation checked, performed the prevalence analysis, performed the meta-analysis of the intervention studies, undertook the QUADAS, Risk of Bias and CONSORT assessment and cowrote and revised drafts of the paper. SR conceptualized the review independently reviewed the data extraction process from the search results and methods from the intervention papers, adapted the QUADAS and Risk of Bias tool verifying the methodology and checked a sample of this assessment. JO advised on the analysis of the quantitative data and carried out the diagnostic accuracy bivariate meta-analysis. RN advised on the quality assessment of the literature and undertook the GRADE assessment. RN also reviewed drafts of the paper, assisted with graphically representing the Risk of Bias tool using RevMan. SV conceptualized the study, frame the question and manages the project steering group. TG is the academic supervisor for the project, conceptualized the study, advised on systematic review methodology, co-wrote and revised drafts of the paper. TG acts as guarantor.

All authors, external and internal, had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis. The lead author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained. The systematic review is registered with PROSPERO (registration number is: CRD42016042920).

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