Screening Strategies for Adults with Type 2 Diabetes Mellitus

by

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MRNHEL002

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Declaration:

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Abstract

There are insufficient randomized controlled trials to address whether screening for type 2 diabetes mellitus (T2DM) improves health outcomes. This systematic review sought to cast a wider net and synthesise evidence from non-randomised intervention studies to assess the effectiveness of T2DM screening in adults for reducing mortality and T2DM-associated morbidity. We searched PubMed/MEDLINE, Scopus, Web of Science, CINAHL, Academic Search Premier and Health Source Nursing Academic (inception onwards; last search July 2021). We included non-randomised intervention studies that assessed T2DM screening compared to no screening, in adults without known T2DM. Screening was performed independently by two reviewers. Data was abstracted by one reviewer and checked by a second, as was risk of bias (ROBINS-I) and certainty of evidence (GRADE). A narrative summary was performed. We screened 10,892 records, retrieving 67 for full-text screening with one record meeting inclusion criteria. The study was a prospective cohort comparing T2DM screening versus no screening. It included adults, 40 - 65 years, with no known T2DM from a single community practice in Ely, England (N = 4,936) and evaluated outcomes at two time periods. The study was assessed as having moderate risk of bias. There may be little or no difference in mortality between those who were invited to screening versus those who were not invited (1990-1999: adjusted hazard ratio (aHR) 0.79 [95% confidence interval (CI) 0.63 – 1.00], n = 4,936, low certainty evidence and 2000 - 2008: aHR 1.18 [95% CI 0.93 - 1.51], n = 3,002, low certainty evidence). We found only one study reporting the effectiveness of screening for T2DM in adults. Therefore, despite ongoing T2DM screening in clinical care, this review highlights an important research gap in understanding the true health benefits of screening.

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Part A: A systematic review protocol.

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Abstract:

Background**:**

There is limited evidence on whether screening for type 2 diabetes mellitus affects health outcomes. A recent systematic review of randomised clinical trials found only one trial met their inclusion criteria, therefore current guidelines for screening interventions for type 2 diabetes mellitus are based on expert opinions and best practice rather than synthesised evidence. This systematic review seeks to collate evidence from non-randomised studies to investigate the effect of screening for adults with type 2 diabetes on outcomes including diabetes related morbidity, mortality (all-cause and diabetes-related) and harms.

Methods**:**

This systematic review will follow Effective Practice and Organisation of Care (EPOC) guidelines for the synthesis of non-randomised studies. We will search PubMed/MEDLINE, Scopus, Web of Science, CINAHL, Academic Search Premier and Health Source Nursing Academic (from inception onwards). We will include non-randomised trials, controlled before-after studies, interrupted time-series studies, repeated measures studies and concurrently controlled prospective cohort studies. The primary outcome will be diabetes-related morbidity (microvascular complications of diabetic retinopathy, nephropathy or neuropathy or macrovascular complications of non-fatal myocardial infarction, peripheral arterial disease, or non-fatal stroke). The secondary outcomes will be mortality (all-cause and diabetes-related) and harms of screening strategies to patients (including psychological harms or adverse events following treatments) or to health care system (including resource allocation for false-positives or overdiagnosis). Two reviewers will independently screen all citations and full-text articles. Data will be abstracted by one reviewer and checked by a second. The risk of bias of individual studies will be appraised using the ROBINS-I tool. GRADE will be used to determine the quality of the scientific evidence. If feasible, we will conduct random effects meta-analysis where appropriate. If necessary, analyses will be conducted to explore the potential sources of heterogeneity (e.g., age, sex, socio-economic status, rural versus urban or low-middle income versus high income country). We will disseminate the findings via publications and through relevant networks.

Discussion:

The protocol outlines the methods for systematically reviewing and synthesising evidence of screening strategies for type 2 diabetes mellitus and their effect on health outcomes associated with the disease. The potential impact of this systematic review is improved evidence-informed decision-making for policies and practice for screening of type-2 diabetes.

Systematic review registration:

PROSPERO CRD42020147439

Keywords

Screening, mass screening, targeted, opportunistic, type 2 diabetes mellitus

Background

Description of the condition

Diabetes mellitus is a disease of increasing global concern. The global prevalence of diabetes was approximately 425 million people in 2017, approximately 8.5% of the adult population, and is expected to double by 2045 (1). In high income countries, type 2 diabetes mellitus accounts for approximately 90% of diabetes cases; there is insufficient data to estimate the ratio of type 2 diabetes mellitus in low- and middle-income countries but it is assumed to be similar (1, 2). Clinical diabetes is diagnosed through the detection of elevated levels of glucose in the blood (hyperglycaemia) (3), however it is estimated that half of the people who have diabetes are not diagnosed (1).

In addition to those individuals who have clinical diabetes, another 352 million, approximately 7.3% of the adult population, have intermediate blood glucose levels that are considered in between normal and clinically diagnosed diabetes (1, 3). These intermediate blood glucose levels perform as a risk score, where increasing values are associated with an increasing likelihood of progression to diabetes, cardiovascular disease as well as all-cause mortality (2, 4). Patients who present with intermediate levels of blood glucose are described using several terminologies including mild glucose intolerance, non-diabetic hyperglycaemia, and prediabetes. The terminology promoted by the World Health Organization (WHO) is impaired glucose tolerance (IGT), impaired fasting glucose (IFG) and intermediate hyperglycaemia (3, 5). The term prediabetes is gaining in popularity even though the WHO has warned its use may lead to disease stigma and detract from the significant cardiovascular risk of this population (5). About a third of people with IGT and IFG are young, aged between 20-39 years, meaning they will spend many years at risk of developing diabetes (1). Other risk factors, apart from intermediate glucose levels, for the development of diabetes is increasing age of more than 45 years as well as obesity (2).

Type 2 diabetes mellitus arises due to defective insulin activity in body tissues, defective insulin secretion from pancreas, or a combination of the two (2). Type 2 diabetes mellitus usually occurs in older adults but with a change in lifestyle factors, such as inactivity and obesity, the condition is increasingly being detected in children,

adolescents, and young adults (1, 2). Current management of type 2 diabetes mellitus involves lifestyle modification: increasing physical activity, improving diet, reaching a healthy body weight and stopping smoking, all monitored by regular screening (2). If lifestyle modification does not result in sufficiently decreased blood glucose levels, medication may be prescribed, of which there are a range of treatment options available (2). The complication with type 2 diabetes mellitus is the long latency period, often lasting several years, during which time the individual is often asymptomatic and unaware of their condition (1, 2). This prolonged asymptomatic state results in long term damage to the body's organs that leads to negative health outcomes including pregnancy complications, oral health problems, disabilities such as blindness, reduced wound healing, foot disease that may require amputation, stroke, heart and kidney disease and death (1-3).

Description of the intervention

There are many types of screening interventions and strategies that may be used to detect disease in a population often classified as mass, opportunistic and targeted strategies - as presented in Table 1 (2, 6). This systematic review will use these classifications, but if additional strategies are noted, these too will be included.

Table 1: Screening strategies applied to detect diabetes

Mass	Screening of an entire apparently healthy population regardless of risk factors.
Opportunistic	Screening of individuals, who may or may not be considered at-risk for diabetes, when presenting for any reason to the health system or other opportunistic interaction (e.g., HIV testing drive).
Targeted	Seeking out and screening individuals from a population who are considered at-risk of developing diabetes (e.g., obese, older age).

The biochemical tests commonly used are fasting plasma glucose (FPG), oral glucose tolerance test (OGTT) and detection of glycated haemoglobin A1C (HbA1c) although there are also urine glucose tests available or random blood glucose tests (2, 6). In addition, there are a number of risk scores (7, 8), including the Finnish Diabetes Risk Score (FINDRISC) (9) and the American Diabetes Association's risk test (10), however, these are not commonly used as a stand-alone screening tools. Classification of patients post testing can be termed as in the normal range or as

having diabetes, impaired glucose tolerance (IGT) or impaired fasting glucose (IFG) (as presented in Table 2) (1, 3).

Table 2: WHO recommended ranges used to classify patients according to blood glucose levels (3).

Diabetes	
Fasting plasma glucose	≥ 7.0 mmol/L (126 mg/dl) OR
2-h plasma glucose*	≥ 11.1 mmol/L (200 mg/dl) OR
HbA1c	≥ 6.5%
Impaired glucose tolerance (IGT)	
Fasting plasma glucose	< 7.0 mmol/L (126 mg/dl) AND
2-h plasma glucose*	≥ 7.8 and < 11.1 mmol/L (140 mg/dl and 200 mg/dl)
Impaired fasting glucose (IFG)	
Fasting plasma glucose	6.1 to 6.9 mmol/L (110 mg/dl to 125 mg/dl) AND (if measured)
2-h plasma glucose*	< 7.8 mmol/L (140 mg/dl)

* Venous plasma glucose 2 hours after ingestion of 75 g oral glucose load

How the intervention might work

The theory behind screening for type 2 diabetes mellitus is to identify either disease or associated risk factors to initiate preventative measures that can halt, slow, or improve the course of disease (11). Therefore, the earlier the disease is detected, especially where there is high risk of disease, theoretically, the better the expected outcomes. The logic model in Figure 1 describes a complex system in which the intervention interacts with participants, context, implementation and how these affect the outcomes and the impact of this research (12).

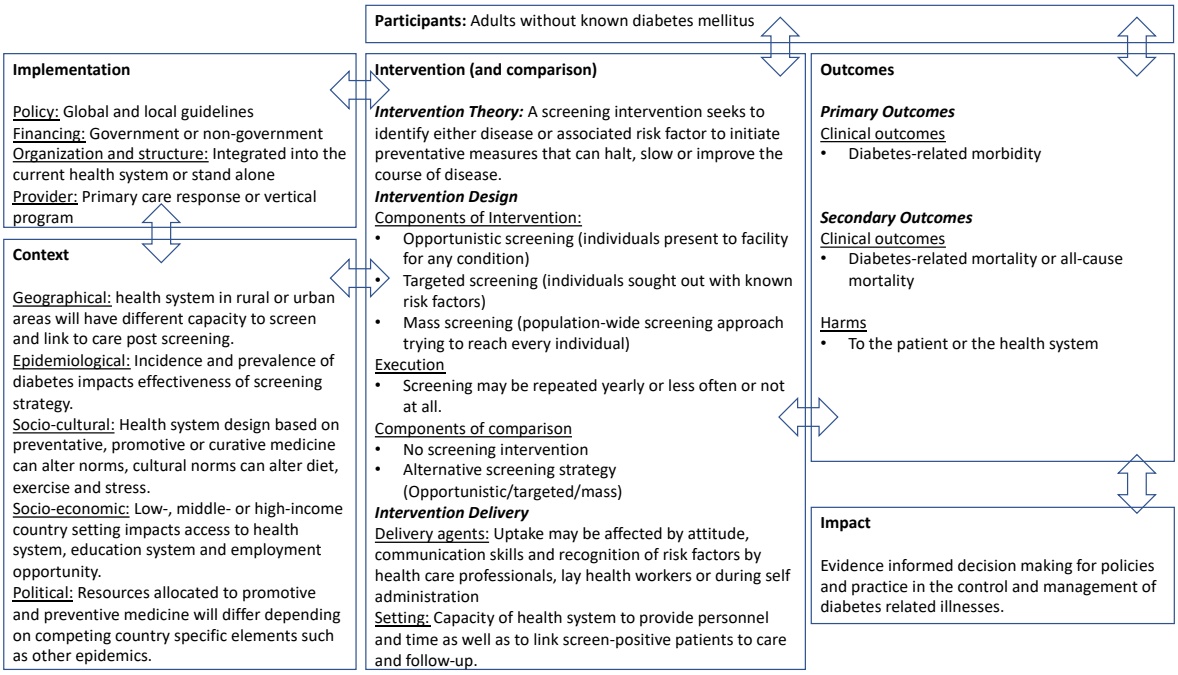

Figure 1: Logic model describing the interactions between screening for diabetes, implementation, context, participants, outcomes, and impact.

Why it is important to do this review

Guidelines for screening interventions for type 2 diabetes mellitus, such as those released by the UK National Screening Committee (13), the American Diabetes Association (2) or the Society for Endocrinology, Metabolism and Diabetes of South Africa (14), are based on expert opinion and local practice rather than synthesised evidence. This is because there is limited information to provide evidence about best practice for screening interventions for type 2 diabetes mellitus and even less evidence in low- and middle-income countries (15). A recently published Cochrane review assessed the effects of any type of screening compared with no screening for type 2 diabetes (16) and found only one trial, the ADDITION-Cambridge trial (17), met their inclusion criteria. The ADDITION-Cambridge trial consisted of 20,184 participants aged 40 - 69 years from general practices in England who were at risk for diabetes but had no known diabetes. These participants were randomised to screening versus no screening arms and followed up for a median of 9.6 years (November 2001 to November 2011). The review found moderate certainty evidence that screening for diabetes probably makes little or no difference to all-cause mortality and low certainty evidence that it may make little or no difference to diabetes-related mortality. However,

because the review only included one trial, firm conclusions about early diabetes screening on health outcomes cannot be drawn. In consultation with the authors of the unpublished Cochrane review and considering the public health importance of screening and the potential impact on large populations, we propose to assess evidence from non-randomised intervention study designs. The questions for the systematic review will include: Does screening for type 2 diabetes mellitus reduce morbidity and/ or mortality? Does a particular screening strategy result in a greater reduction of morbidity and/ or mortality as compared to another screening strategy? Does screening for type 2 diabetes mellitus result in harms to participants or the health system?

Objectives

Primary Objective:

To assess the effectiveness of targeted, opportunistic, or mass screening for type 2 diabetes mellitus on reduction of diabetes-associated morbidity in adults.

Secondary Objectives:

To assess the effectiveness of targeted, opportunistic, or mass screening for type 2 diabetes mellitus on reduction of mortality (all cause as well as diabetes-associated) in adults.

To assess the harms of targeted, opportunistic, or mass screening for type 2 diabetes mellitus in adults.

Methods

The present protocol has been registered within the PROSPERO database (CRD42020147439). This manuscript is being reported in accordance with the reporting guidance provided in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) statement (18) (see checklist in Additional file 1).

As existing reviews have found limited randomised evidence addressing this question (15, 19, 20), we will focus on non-randomised intervention studies (NRIS). We will employ the Cochrane EPOC criteria (21) and NRIS of interest will include non-randomised trials, controlled before-after studies, interrupted time-series study, repeated measures study and concurrently controlled prospective cohort study. The difficulty associated with labelling NRIS is well-documented in the literature; several of these designs, for example, have been used interchangeably, we will make use of the EPOC definitions and flow diagram to assist in study design identification (Appendix 1):

- Non-randomised trial (NRT): is a study design in which individual participants, or clusters of participants, are allocated to intervention or comparator in a quasi-random or non-random manner. If there is an allocation rule it is often by, for example, alternation, day of the week, odd/even hospital, or identification number.
- Controlled before-after (CBA): is a study design that estimates intervention effectiveness by comparing pre- and post-intervention outcomes in individuals or clusters that receive the intervention and those that do not.
- Interrupted time series (ITS) studies: design which uses multiple observations from individuals or clusters pre-intervention to establish the pre-existing outcome trend; intervention effectiveness is then estimated by measuring post-intervention changes in the expected outcome trend associated with the introduction of an intervention (the 'interruption'). An ITS study can identify both immediate and long-term changes associated with the intervention. The interrupted time-series studies will be required to have a clearly defined point in time when the intervention occurred and a minimum of 3 time points before and 3 time points after the intervention (21).
- A repeated measures (RM) study is an interrupted time-series study but where the outcomes of interest are measured in the same participants at each point in time.
- Concurrently controlled prospective cohort study (PCS): is where subjects are identified prospectively as having received an intervention or comparator and

are then followed over time. The allocation rule is often in relation to organizational factors such as ward, clinic, doctor, or provider organization. Control arms should be contemporaneous, we will not include retrospective control arms.

'PICO' eligibility

Types of participants

We will include adults aged 18 years and older without documented diabetes mellitus or pregnancy.

Types of interventions

We will include studies comparing one of the screening strategies, targeted, opportunistic or mass screening interventions for the detection of type 2 diabetes mellitus, against no screening or another of the screening strategies (Table 1). There will be a 6-month minimum follow up time required for the primary clinical outcome of morbidity.

Types of outcome measures

Primary outcomes

Clinical outcomes

- Diabetes-related morbidity: defined as study reported microvascular complications (diabetic retinopathy, diabetic nephropathy, diabetic neuropathy) or macrovascular complications (non-fatal myocardial infarction, peripheral arterial disease, non-fatal stroke) and measured from 6-months after screening.

Secondary outcomes

Clinical outcomes

- Mortality (all-cause and diabetes-related) defined as death due to any-cause including diabetes or other cardiovascular causes (including acute myocardial infarction, ischemic heart disease, stroke or any cardiovascular disorder that lead to death) and measured at any time after screening.

Harms of diabetes screening:

Harms to patients. Defined as event/s reported in the study at any time after screening.

- psychological harms such as anxiety or stigma that impacts on quality of life due to a false-positive test.

- Number of days of work lost.
- Side-effects from treatment
- Loss of health insurance benefits

Harms to health care system. Defined as event/s reported in the study at any time after screening.

- False-positive test resulting in human, physical and financial resource allocation to patients who are not in need
- Overdiagnosis may lead to over-extension of human, physical and financial resources for patients who end up in prolonged treatment and engagement with the health system even if they never develop disease

The rationale for prioritisation of outcomes: Primary outcome serves to inform whether screening alters the course of disease as assumed per screening theory (11) and depicted Figure 1. Secondary outcome of mortality contributes to the current data outlining no reduction in mortality following screening intervention (19) while also assessing harms that may arise from screening intervention (3) and therefore contribute to evidence to substantiate policy and practice recommendations.

Search methods for identification of studies

Electronic searches

The University of Cape Town Health Sciences Reference Librarian (MS) assisted the first author (HM) in developing the search strategy and will provide advice and guidance in conducting the searches for the review.

Electronic Database Search (from inception onwards):

- PubMed (MEDLINE)
- Scopus (Includes majority of EMBASE contents)
- Web of Science Platform (Web of Science Core Collection, Biological Abstracts, SciELO Citation Index)
- Academic Search Premier (on the EBSCOhost platform)
- CINAHL (on the EBSCOhost platform)
- Health Source Nursing Academic (on the EBSCOhost platform)

A draft search strategy for PubMed/MEDLINE, based off the original search strategy utilized by the Cochrane Review team and revised by an information specialist, is provided in Appendix 2 (see Appendix 2). We will include all studies regardless of publication status however we will only include English language studies. We are aware that this decision may lead to language bias (22), but due to capacity and resource limitation of the systematic review team, we are restricted to English only. We will search all databases from inception to the date of search. The search syntax will first be tested and optimised in PubMed. We will thereafter replicate the searches in the other databases adapting search syntax as necessary for those databases.

Grey Literature search:

We will conduct a grey literature search to identify studies not indexed in the databases listed above.

- OpenGrey (Multidisciplinary European database, covering science, technology, biomedical science, economics, social science and humanities)
- Conference abstracts from The American Diabetes Association (ADA), the European Association for the Study of Diabetes (EASD) meeting and Diabetologia will be used to track down full text articles.
- National Institute for Health Research Economic Evaluation Database (NHS EED).
- Cost-Effectiveness Analysis Registry (CEA) (www.healtheconomics).

We will search key references, such as systematic reviews, by cross-checking reference lists for additional potentially eligible primary studies (23). We will also contact experts in the field to check if we have missed any relevant studies. We may contact authors of included studies to clarify reported published information and to seek unpublished data.

Methods for screening search results

Screening methods

We will collate and transfer search results to Rayyan screening software (24) and remove duplicate records. At least two review authors will independently screen titles and abstracts of every record retrieved. Outcome measures will not be used to exclude studies during title and abstract screening. The potentially eligible records will be retrieved for full text screening. The two review authors will independently review full text records for compliance of studies with eligibility criteria of the review. A decision tree based on the eligibility criteria will be used to assist in decision making for exclusion of studies (See Appendix 3). Two review authors will resolve any disagreements through discussion or, if required, will consult a third review author. A study must meet all inclusion criteria to be included. We will list excluded studies at the full text screening stage in the 'Characteristics of excluded studies' table. We will collate multiple reports of the same study so that each study rather than each report is the unit of interest in the review. We will provide any information we can obtain about ongoing studies. We will record the selection process in sufficient detail to complete a PRISMA flow diagram (25).

Data collection and analysis

Data extraction

We will use a standard data extraction form in Microsoft Excel to capture study characteristics and outcome data (22, 26); we will pilot the form on at least one eligible study. One review author will extract the following study characteristics from the included studies and an independent review author will check the extraction:

1. Source: study ID (created by review author), review author ID (created by review author), citation and contact details.
2. Eligibility: confirm eligibility for review, reason for exclusion
3. Methods: study design, number of study centres and location, study setting, withdrawals, date of study, follow-up, confounding factors considered, and the methods used to control for confounding, aspects of risk of bias specific for

NRIS (see “Assessment of risk of bias in included studies” below), how missing data was handled.

4. Participants: number, mean/ median age, age range, gender, severity of condition, diagnostic criteria, inclusion criteria, exclusion criteria, screening criteria, diagnostic criteria, presence of known risk factors for type 2 diabetes mellitus (obesity, family history), co-morbidity (hypertension, dyslipidaemia), socio-demographics
5. Interventions: intervention components, comparison, fidelity assessment using the Template for Intervention Description and Replication (TIDieR) as a guide (27).
6. Outcomes: primary and secondary outcomes specified above in the section “Types of outcome measures”.
7. Miscellaneous: funding source, notable conflicts of interest of study authors, ethical approval, key conclusions of the study authors, miscellaneous comments from the study authors, references to other relevant studies, correspondence required, miscellaneous comments by the review authors.

One review author will extract outcome data from included studies and an independent review author will check extracted data. We will note in the 'Characteristics of included studies' table if outcome data were reported in an unusable way. We will resolve disagreements by consensus or by involving a third review author.

Assessment of risk of bias in included studies

Two review authors will independently assess risk of bias for each study using the ROBINS-I tool (28). Any disagreement will be resolved by discussion or by involving a third review author.

We will assess the risk of bias according to the following domains:

1. Pre-intervention: Bias due to confounding
2. Pre-intervention: Bias in selection of participants into the study
3. At intervention: Bias in classification of interventions
4. Post-intervention: Bias due to deviations from intended interventions
5. Post-intervention: Bias due to missing data
6. Post-intervention: Bias in measurement of outcomes
7. Post-intervention: Bias in selection of the reported result

We will judge each potential source of bias as low risk, moderate risk, serious risk, critical risk of bias or no information. We will summarise the 'Risk of bias' judgements across different studies for each of the domains listed. We will consider blinding separately for different key outcomes where necessary (e.g. for unblinded outcome assessment, risk of bias for all-cause mortality may be very different than for a patient reported pain scale). Where information on risk of bias relates to unpublished data or correspondence with a trialist, we will note this in the 'Risk of bias' table. We will not exclude studies on the grounds of their risk of bias but will clearly report the risk of bias when presenting the results of the studies. When considering treatment effects, we will consider the risk of bias for the studies that contribute to that outcome. We will conduct the review according to this published protocol and report any deviations from it in the 'Differences between protocol and review' section of the systematic review.

Dealing with missing data

Authors will be contacted, and missing data will be requested. If only returned in part and data can be logically imputed, such as standard errors, this will occur. All missing data will be clearly reported in the data extraction forms and risk of bias table and as such be assessed in the sensitivity analysis.

Data management

EndNote X9 and Microsoft Excel will be used for data management. If there is a conflict between data reported across multiple sources for a single study (e.g., between a published article and a trial registry record), we will report the data from the first peer-reviewed published article.

Data synthesis

Preparation for Data Synthesis

In preparation for synthesis (either meta-analyses or synthesis without meta-analysis) we will assess how much data are available for each of our objectives by creating a table to compare the PICO elements and the study design features as well as the extracted numerical data for the compilation of a meta-analysis.

Measures of treatment effect

We will estimate the effect of the intervention using risk ratio for dichotomous data, and mean difference or standardised mean difference for continuous data. Time to

event outcomes will be reported as hazard ratios. If other effect estimates are provided, we will convert between estimates where possible. Measures of precision will be 95% confidence intervals. We will ensure that an increase in scores for continuous outcomes can be interpreted in the same way for each outcome, explain the direction to the reader, and report where the directions were reversed if this was necessary. Interrupted time series data will be analysed and, if required, a statistical comparison of time trends before and after the intervention will be performed. For ITS studies, the guideline as outlined in Analysis in EPOC reviews will be followed with assistance of a statistician to ensure integrity of analysis (29).

Unit of analysis issues

To avoid unit of analysis errors we will consider the unit used to cluster the intervention (such as a ward, clinic, doctor, or provider organization) or in the case of repeated measures that there will be multiple observations for the same outcome. For instance, multiple screening intervention events per participant may occur over time that may cause a unit-of-analysis error. In order to calculate the confidence intervals the participants per treatment group rather than the number of intervention attempts will be used (22). Multiple intervention groups could create unit-of-analysis issues especially if different screening interventions are compared against no screening intervention and use the same participants with no screening intervention in both comparisons (22). If there is more than one comparison in the study design, we will combine groups into a single pairwise comparison. If there is a unit of analysis error in the reported analysis for a study and there is insufficient information to reanalyse the results, the study authors will be contacted to obtain necessary data. If these data are not available, we will not report confidence intervals or p-values for which there is a unit of analysis error (30).

Quantitative synthesis

We will undertake meta-analyses only where this is meaningful i.e., if the interventions, participants, and the underlying clinical question are similar enough for pooling to make sense. If feasible and appropriate, outcome data from primary studies will be used to perform random effects meta-analyses. Since heterogeneity is expected a priori, we will estimate the pooled treatment effect estimates and its 95% confidence interval using the random effects model. The random effects model assumes the effect

estimates follow a normal distribution, considering both within-study and between-study variation.

Assessment of heterogeneity

Forest plots will be used to visualise the extent of heterogeneity among studies. We will quantify statistical heterogeneity by estimating the variance between studies using I^2 statistic. The I^2 is the proportion of variation in effect estimates that is due to genuine variation rather than sampling (random) error. I^2 ranges between 0% and 100% (with values of 0–25% and 75–100% taken to indicate low and considerable heterogeneity, respectively) (22). We will also calculate the chi-squared test where a p-value < 0.1 indicates statistically significant heterogeneity.

Assessment of publication bias

If we include more than 10 studies investigating a particular outcome, we will use a funnel plot to explore possible publication bias, interpreting the results with caution (31).

Subgroup analysis and investigation of heterogeneity

We expect the following population characteristics may introduce clinical heterogeneity: Age, sex, socio-economic status (6).

We expect the following contexts may introduce health system heterogeneity: Study setting of rural or urban or in a low-middle income country or a high income country (as defined by the World Bank) (6).

We will use the following outcomes in subgroup analysis.

1. Diabetes-associated morbidity
2. Mortality (all-cause and diabetes-associated)
3. Harms

Sensitivity analysis

We may conduct a sensitivity analysis to explore the influence of various factors on the effect size of the primary outcomes of the review only. We will stratify studies according to:

1. Restricting the analysis to published studies.

2. Restricting the analysis to studies with a low risk of bias, as specified in “Assessment of risk of bias in included studies”
3. Imputing missing data.

Any *post hoc* sensitivity analyses that may arise during the review process will be justified in the final report.

Assessment of certainty of evidence using the GRADE approach

Two review authors will independently assess the certainty of the evidence (high, moderate, low, and very low) for each outcome using the five GRADE considerations for downgrading the certainty of evidence (risk of bias, consistency of effect, imprecision, indirectness, and publication bias) and the three criteria for upgrading the certainty of evidence (large effect, dose response and residual confounding opposing the observed effect) (32). We will use GRADEpro software GDT (33) to create the 'Summary of findings' tables for the main intervention comparisons and include the following outcomes: diabetes-associated morbidity, mortality (all-cause and diabetes-associated); harms (See Appendix 4 for SoF). We will resolve disagreements on certainty ratings by discussion and provide justification for decisions to down- or upgrade the ratings using footnotes in the SoF table and make comments to aid readers' understanding of the review where necessary. We will use plain language statements to report these findings in the review (34). The SoF tables will be used to draw conclusions about the certainty of the evidence within the text of the review. If during the review process, we become aware of an important outcome that we failed to list in our planned 'SoF' tables, we will include the relevant outcome and explain the reasons for this is the section 'Differences between protocol and review'.

Discussion

Systematic reviews of screening for type 2 diabetes have found no evidence that this intervention saves lives (15, 19, 20), therefore this review will primarily focus on the impact of screening on the reduction of diabetes-associated morbidities. The impact of this review is synthesised data for the provision of evidence-based decision-making for informing policy and practice around screening strategies for type 2 diabetes mellitus. Important protocol amendments will be documented and noted in the discussion.

Limitations

The potential limitations of this review at a study (outcome) level include: The potential finding of insufficient studies of similar study design and clinical question to synthesise abstracted study data. The overall completeness and applicability of evidence and quality of evidence especially due to the limitation to non-randomized studies due to the lack of randomized studies and therefore the lower quality of evidence. The limitation to English studies only and therefore the potential to miss published research. The limitation of not being able to discern between all-cause mortality and diabetes-related mortality and therefore combining this outcome under one mortality outcome. The potential limitation of this review at a systematic review process level include: The potential biases in the review process such as post-hoc analysis and focus of outcome objectives.

Acknowledgements

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- The authors of an unpublished Cochrane systematic review titled “Screening for type 2 diabetes mellitus”: Nasheeta Peer and Solange Durao, South African Medical Research Council for providing their protocol to form the basis of this protocol, as well as a summary of their findings to form the rationale of the protocol and a quote to summarise the findings of their unpublished review.
- Information specialist Maria-Inti Metzendorf, Cochrane Metabolic and Endocrine Disorders Group: Provided search strategy for the unpublished Cochrane review by Peer and Durao upon which the current search strategy is based.
- CEBHA+ Methodological Support Group Jake Burns and Peter Philipsborn, Ludwig-Maximillians Universitat Munchen: are internal reviewers for CEBHA+ which funds this review and assisted by providing critical review of the draft protocol.
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Contributions of authors

Conceiving the protocol: [BS, TK]

Designing the protocol: [HM, BS]

Co-ordinating the protocol: [HM]

Designing search strategies: [MS, HM]

Writing the protocol: [HM]

Providing general advice on the protocol and approving the final version: [PKO, MS, BK, TK, BS]

Securing funding for the protocol: [BS, TK]

Performing previous work that was the foundation of the current study: [NP, SD]

Guarantor of the review: [BS]

Competing interests

The authors declare that they have no competing interests.

HM: None known

PKO: None known

MS: None known

BMK: None known

TK: None known

BS: None known

Ethics approval and consent to participate

Ethics approval is not required for a systematic review of secondary data.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

List of abbreviations

ADA	American Diabetes Association
CBA	controlled before-after
CEA	Cost-Effectiveness Analysis Registry
CEBHA+	Collaboration for Evidence-Based Healthcare and Public Health in Africa
EASD	European Association for the Study of Diabetes
EPOC	Effective Practice and Organisation of Care
FPG	fasting plasma glucose
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HbA1c	detection of glycated haemoglobin A1C
ITS	interrupted time series
NHS EED	NHS Economic Evaluation Database
NRT	non-randomised trial
NRIS	non-randomised intervention studies
OGTT	oral glucose tolerance test
PCS	prospective cohort study
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RM	repeated measures
SoF	Summary of findings
TIDieR	Template for Intervention Description and Replication

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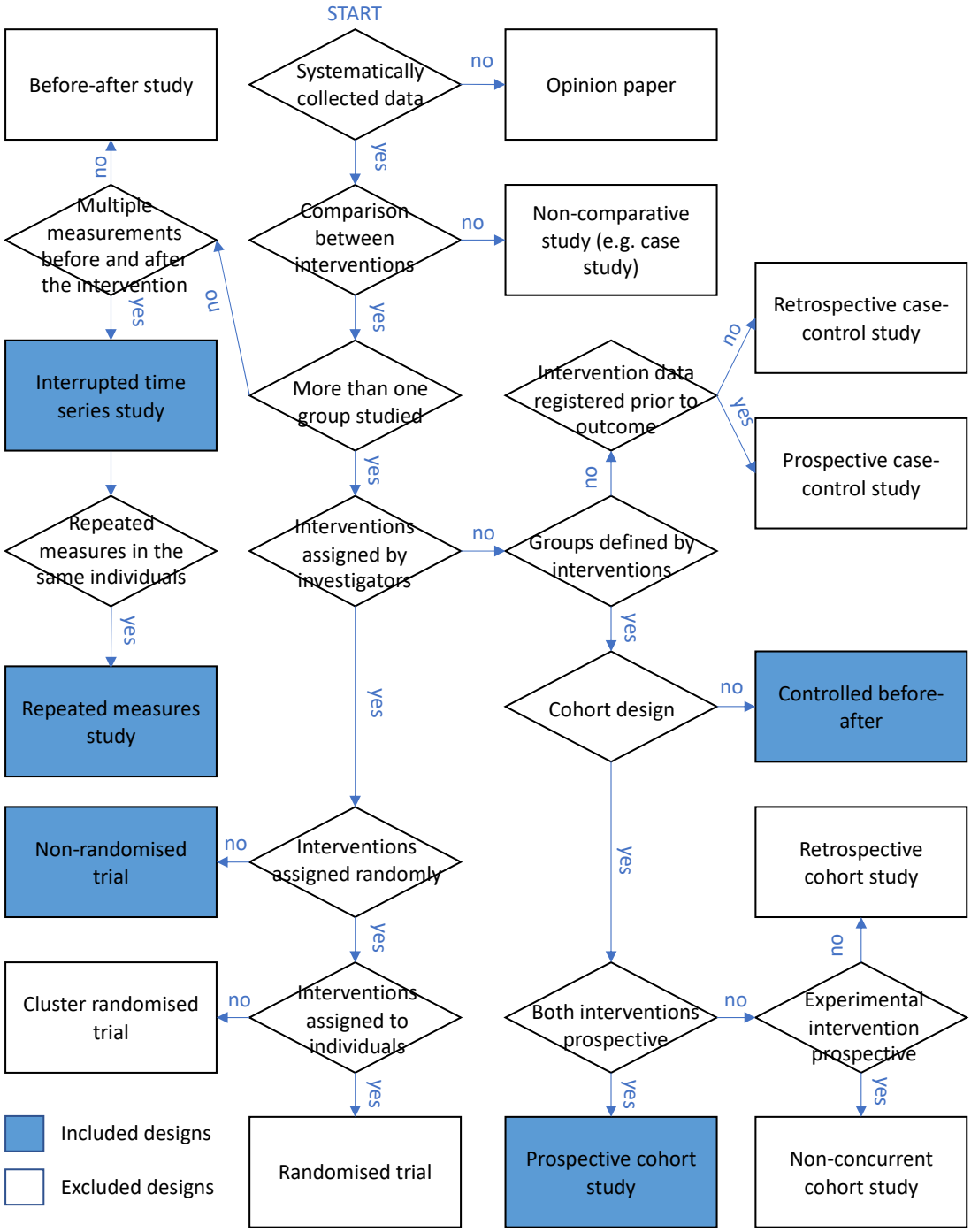
Protocol Appendix

Appendix 1 Flow diagram to assist with identifying the type of study (modified from (34))



Appendix 2 Search Strategy for PubMed:

Set 1:

Diabetes Mellitus, Type 2 [MeSH] OR [Text Word field:] Adult onset diabetes OR late onset diabetes OR latent diabetes OR mature onset diabetes OR MODY OR NIDDM OR noninsulin-dependent diabetes OR slow onset diabetes OR stable onset diabetes OR type 2 diabetes OR type II diabetes OR T2DM OR T2D

Set 2:

Diabetes Insipidus [MeSH] OR [Text Word field:] diabetes insipidus

Set 3:

1 NOT 2

Set 4:

Mass screening [MeSH] OR [Text Word field:] screening

Set 5:

3 AND 4

Set 6:

Animals [MeSH] NOT Humans [MeSH]

Set 7:

5 NOT 6

Set 8:

[All fields:] Trial OR trials OR before-and-after study OR before-and-after studies OR cohort OR comparative study OR comparative studies OR Controlled OR evaluation study OR evaluation studies OR follow-up study OR follow-up studies OR interrupted time series OR longitudinal study OR longitudinal studies OR non-randomised OR non-randomized OR nonrandomised OR nonrandomized OR non randomised OR non randomized OR program evaluation OR programme evaluation OR prospective study OR prospective studies OR quantitative study OR quantitative studies OR quasi experimental OR repeated measures

Set 9:

7 AND 8

Appendix 3 Provisional Eligibility Decision Tree for Full Text Exclusion

Hierarchy	Exclusion reason	Explanation of reason
1	Duplicate	Record is a duplicate of another study already included in the review
2	Animal study	Study conducted in non-human population
3	Study withdrawn	Study was withdrawn before results became available
4	Ongoing study	Study is ongoing; No study results have been published. Study will be described in 'Ongoing studies' section of the review.
5	Wrong intervention	Study does not include screening for type 2 diabetes mellitus
6	Wrong study design	Study is not eligible as per Appendix 1 study designs.
7	Wrong population	Study intervention/ outcomes involve individuals who have type 2 diabetes mellitus or are pregnant
8	Research question is inappropriate	Study is not eligible due to inappropriate research question or objectives that do not address systematic review objectives.
9	Wrong Outcomes	Study does not report outcomes that align with primary or secondary outcome measures.

Appendix 4 Provisional Summary of Findings Table

<table>
<tr><td colspan="7">Targeted, opportunistic or mass screening for type 2 diabetes mellitus compared to each other or no screening in children, adolescents and adults.</td></tr>
<tr><td>Patients or population</td><td colspan="6">children, adolescents, and adults without documented diabetes mellitus or pregnancy.</td></tr>
<tr><td>Intervention</td><td colspan="6">targeted, opportunistic or mass screening for type 2 diabetes mellitus.</td></tr>
<tr><td>Comparison</td><td colspan="6">Other screening (targeted, opportunistic, or mass) or no screening for type 2 diabetes mellitus.</td></tr>
<tr><td rowspan="3">Outcomes</td><td colspan="2">Illustrative comparative risks (95% CI)</td><td rowspan="3">Relative effect (95% CI)</td><td rowspan="3">Number of participants (studies)</td><td rowspan="3">Quality of evidence (GRADE)</td><td rowspan="3">Comments</td></tr>
<tr><td>Assumed risk</td><td>Corresponding risk</td></tr>
<tr><td>With targeted, opportunistic, or mass screening</td><td>With other screening or without screening</td></tr>
<tr><td>Diabetes-related morbidity</td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Mortality (all-cause and diabetes-related)</td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Harms</td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
</table>

Part B: A systematic review.

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Part B has been submitted to BMC Systematic Reviews.

Abstract:

Background: There are insufficient randomized controlled trials to address whether screening for type 2 diabetes mellitus (T2DM) improves health outcomes. This systematic review sought to cast a wider net and synthesise evidence from non-randomised intervention studies.

Objectives: To assess the effectiveness of T2DM screening in adults for reducing mortality and T2DM-associated morbidity.

Search methods**:** We searched PubMed/MEDLINE, Scopus, Web of Science, CINAHL, Academic Search Premier and Health Source Nursing Academic (inception onwards; last search July 2021).

Selection criteria: We included non-randomised intervention studies that assessed T2DM screening compared to no screening, in adults without known T2DM

Data collection and analysis: Screening was performed independently by two reviewers. Data was abstracted by one reviewer and checked by a second, as was risk of bias (ROBINS-I) and certainty of evidence (GRADE). A narrative summary was performed.

Main results: We screened 10,892 records, retrieving 67 for full-text screening with one record meeting inclusion criteria. The study was a prospective cohort comparing T2DM screening versus no screening. It included adults, 40 - 65 years, with no known T2DM from a single community practice in Ely, England (N = 4,936) and evaluated outcomes at two time periods. The study was assessed as having moderate risk of bias. There may be little or no difference in mortality between those who were invited to screening versus those who were not invited (1990-1999: adjusted hazard ratio (aHR) 0.79 [95% confidence interval (CI) 0.63 – 1.00], n = 4,936, low certainty evidence and 2000 - 2008: aHR 1.18 [95% CI 0.93 - 1.51], n = 3,002, low certainty evidence).

Author's conclusions: We found only one study reporting the effectiveness of screening for T2DM in adults. Therefore, despite ongoing T2DM screening in clinical care, this review highlights an important research gap in understanding the true health benefits of screening.

Funding: Collaboration for Evidence-Based Healthcare and Public Health in Africa (CEBHA+)

Systematic review protocol:
doi: 10.1186/s13643-020-01417-3

Keywords
Screening, mass screening, targeted, opportunistic, type 2 diabetes mellitus

Plain language summary

Screening versus no screening for diabetes in adults.

A systematic review was performed searching for studies that compared two groups of adults, those who were screened for type 2 diabetes with those who were not screened. Only one study was included. The study was conducted in England and included 4,936 people aged 40-65 years from a single community primary health care practice. While the study reported no change in risk of dying for those who were invited to screening compared to those who were not invited to screening, it did report a reduction in risk of dying for those who attended the screening. When assessing the quality of the evidence we found it to be low quality, this means that further research is needed to understand the true effect of screening for diabetes mellitus. The key take home of this review is the important lack of knowledge and the need for more research around screening for type 2 diabetes mellitus to ensure best practice for patients.

Background

Description of the condition

Type 2 diabetes mellitus (T2DM) is a chronic health condition that typically affects adults but is also found in children and adolescents (3, 35). Chronic uncontrolled T2DM leads to poor health outcomes including death, microvascular complications (diabetic retinopathy, diabetic nephropathy, diabetic neuropathy) and macrovascular complications (non-fatal myocardial infarction, peripheral arterial disease, non-fatal stroke) (3). Acute T2DM can result in complications such as abnormally high blood sugar and diabetic ketoacidosis or abnormally low blood sugar and seizures or loss of consciousness either of these extremes of blood sugar levels can lead to death (3). The global prevalence of T2DM is increasing and with this increase the burden of T2DM- associated morbidity and mortality (1, 3).

T2DM is diagnosed through the detection of high levels of glucose in the blood with exact tests and cut-off levels varying between countries but generally a fasting plasma

glucose ≥ 7.0 mmol/L (126 mg/dl) or a 2- hour plasma glucose test of ≥ 11.1 mmol/L (200 mg/dl) or an HbA1c value ≥ 6.5% (3). Complication arise as these cut-off levels are not exact, individuals with elevated blood glucose levels are associated with poor health outcomes therefore an expert committee on T2DM recommended that individuals who do not meet diagnostic criteria should be considered at lower risk for T2DM rather than at no risk for T2DM (36). However a controversy is at play between the members of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD), the International Diabetes Federation (IDF) and the World Health Organisation (WHO) with the introduction of a term: prediabetes (37). This term is rejected by EASD, IDF and the WHO; they use the terms 'impaired glucose tolerance' or 'impaired fasting glucose'. The dispute arises due to the lack of evidence to support prediabetes as a diagnostic term for the development of T2DM (38). The use of prediabetes may lead to misleading information for health care workers and patients as well as overuse of exposure to unnecessary harms from pharmaceutical interventions and a waste of resources aimed at behavioural interventions for individuals who will not necessarily go onto develop T2DM (37).

Description of the intervention

Screening for T2DM usually fall into one of three approaches, mass, targeted or opportunistic (39). Mass screening is a strategy where all individuals in the population are offered screening. Targeted screening is a strategy where individuals who are considered at high risk of developing disease are offered screening. Opportunistic screening is a strategy where individuals are screened if it is convenient for the programme such as individuals who present to their general practitioners for a consult may then be offered screening. Targeted and opportunistic strategies may occur together such as targeting high risk individuals who present to primary health care centres. The comparator to screening for T2DM would be no screening for T2DM.

The logistics of screening differs due to a multitude of factors including the location where the screening occurs, the type of screening test employed, who administers the screening, whether the screening is aimed only at T2DM or at multiple conditions and what intervention/s are implemented following screening. The WHO current recommendation for screening for T2DM promotes local specific policies drawn up by health authorities and professional organisations (39). The WHO promotes screening in areas where there is a high prevalence of undiagnosed T2DM and a high prevalence

of complications and cardiovascular disease in individuals living with T2DM (39). The WHO highlights the lack of direct evidence for screening and the need for local authorities to balance the capacity of the health system to perform screening and appropriate clinical and psycho-social follow up with other local health priorities (39).

How the intervention might work

Screening theory (11) serves as the rationale for screening for T2DM whereby the goal is to detect those individuals who are living with T2DM but are unaware of it and to intervene to either halt the progression of the disease or slow the progression of the disease and therefore to improve the quality of life for the individual and reduce the burden on the health system and society over the longer term.

Why it is important to do this review

Screening for T2DM can require substantial financial and human resources. Knowing whether screening for T2DM makes an impact on health outcomes is important to understand. A recently conducted systematic review looking at this research area found only one study met their inclusion criteria (16). Therefore, there are insufficient randomized controlled trials to inform our understanding of whether screening for T2DM improves health outcomes or results in harms (16, 39). Therefore, this systematic review sought to cast a wider net and synthesise evidence from non-randomised intervention studies.

Objectives

The primary objective was to assess the effectiveness of targeted, opportunistic, or mass screening versus no screening for type 2 diabetes mellitus on the reduction of all-cause mortality and T2DM-associated morbidity in adults. The secondary objective was to assess the harms of targeted, opportunistic, or mass screening versus no screening for type 2 diabetes mellitus in adults.

Any differences between protocol and review were noted in the section “Differences between protocol and review” after the discussion. The manuscript followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) (40).

Criteria for considering studies for this review

Types of studies

Non-randomised intervention study (NRIS) designs (21) including non-randomised trial, controlled before-after, interrupted time series, repeated measures and concurrently controlled prospective cohort study with both an intervention and a comparator arm that were prospective were eligible for inclusion.

Types of participants

Adults aged 18 years and older without documented T2DM or pregnancy were eligible for inclusion.

Types of interventions

Studies that compared screening for the detection of T2DM, as compared to no screening or another of the screening strategies were eligible for inclusion.

Types of outcome measures

Primary outcomes

All- cause mortality was defined as death due to any-cause including diabetes or other cardiovascular causes (including acute myocardial infarction, ischemic heart disease, stroke or any cardiovascular disorder that led to death) and measured at any time after screening.

T2DM-related morbidity was defined as study reported microvascular complications (diabetic retinopathy, diabetic nephropathy, diabetic neuropathy) or macrovascular complications (non-fatal myocardial infarction, peripheral arterial disease, non-fatal stroke) and measured from 6-months after screening.

Secondary outcomes

Harms of T2DM screening were defined as event/s reported in the study at any time after screening. Possible harms to patients included for instance psychological harms such as anxiety or stigma that impacted on quality of life due to a false-positive test, number of days of work lost, side-effects from treatment and loss of health insurance benefits. Possible harms to the health care system included a false-positive test resulting in human, physical and financial resource allocation to patients who were not

in need or overdiagnosis that lead to over-extension of human, physical and financial resources for patients who ended up in prolonged treatment and engagement with the health system even if they never developed disease.

Exclusion criteria: Studies which were not in English

Search methods for identification of studies

Search strategies were provided in the supplementary information.

Electronic searches

The following databases were searched from inception to the date indicated: PubMed (9 July 2021), Scopus (16 July 2021), Academic Search Premier (21 July 2021), CINAHL (21 July 2021), Health Source Nursing Academic (21 July 2021), Web of Science Core Collection (21 July 2021), Biological Abstracts (21 July 2021), SciELO Citation Index (21 July 2021).

Searching other resources:

The following grey literature was searched from inception until data indicated: OpenGrey (10 December 2019), European Association for the Study of Diabetes meeting (11 December 2019), National Institute for Health Research Economic Evaluation Database (12 December 2019), Cost-Effectiveness Analysis Registry (12 December 2019). In addition, we cross-checked reference lists from all full-text articles included at screening as well as the Cochrane systematic review on this topic (16) to be certain we had not missed any potentially eligible primary studies.

Data collection and analysis

Selection of studies

At least two review authors (HM, BS, NB, PO, MS) independently screened titles and abstracts of every record retrieved. Any potentially eligible records were retrieved for full text screening and two review authors (HM, BS) independently reviewed these with final agreement resolved with advisory group (TK, BK, YB). All articles excluded at full text screening stage were described in the 'Characteristics of excluded studies' table. The selection process was presented as a PRISMA flow diagram (40).

Data collection and management

We used a standard data extraction form in Microsoft Excel to capture details about the study design, participants, interventions and outcome data (22, 26). One review author extracted the data (HM) while a second review author checked it (BS). No study authors or sponsors were contacted, and no conversion of extracted data was necessary.

Assessment of risk of bias in included studies

Two review authors (HS, BS) independently assessed risk of bias for each study. The ROBINS-I tool (28) was used with each potential source of bias judged as low risk, moderate risk, serious risk, critical risk of bias or no information and an overall summary risk was presented for each study. The following domains were assessed:

1. Pre-intervention: Bias due to confounding
2. Pre-intervention: Bias in selection of participants into the study
3. At intervention: Bias in classification of interventions
4. Post-intervention: Bias due to deviations from intended interventions
5. Post-intervention: Bias due to missing data
6. Post-intervention: Bias in measurement of outcomes
7. Post-intervention: Bias in selection of the reported result

Dealing with missing data

There was no apparent missing data in the study included.

Assessment of reporting biases

There was only one study included therefore we did not assess reporting bias.

Data Synthesis

Preparation for data synthesis

In preparation for synthesis without meta-analysis, we assessed how much data were available for each of our objectives by creating a table to compare the PICO elements and the study design features.

Measures of treatment effect

The effect measures presented were adjusted hazard ratio (aHR) with 95% confidence interval (CI) in the included study.

Unit of analysis issues

There was only one study included therefore we did not address unit of analysis issues.

Quantitative synthesis

There was only one study included therefore we did not perform quantitative synthesis but rather a narrative synthesis.

Assessment of certainty of evidence using the GRADE approach

Two review authors (HM, TK) independently assessed the certainty of the evidence (high, moderate, low, and very low) for each outcome using the five GRADE considerations for downgrading the certainty of evidence (risk of bias, consistency of effect, imprecision, indirectness, and publication bias) and the three criteria for upgrading the certainty of evidence (large effect, dose response and residual confounding opposing the observed effect) (32). We used GRADEpro software GDT (33) to create the 'Summary of findings' tables for the main intervention comparisons and include the following outcomes: all-cause mortality, T2DM-associated morbidity and harms. We resolved disagreements on certainty ratings by discussion and provided justification for decisions to down- or upgrade the ratings using footnotes in the SoF table and made comments to aid readers' understanding of the review process where necessary. We used plain language statements to report these findings in the review and to draw conclusions on the certainty of evidence (34).

Results

Description of studies

Results of the search

Searching electronic databases and other sources identified 15,456 records of which 10,892 were title and abstract screened and 67 full text articles were retrieved and only 1 was found to meet the inclusion criteria (Figure 1).

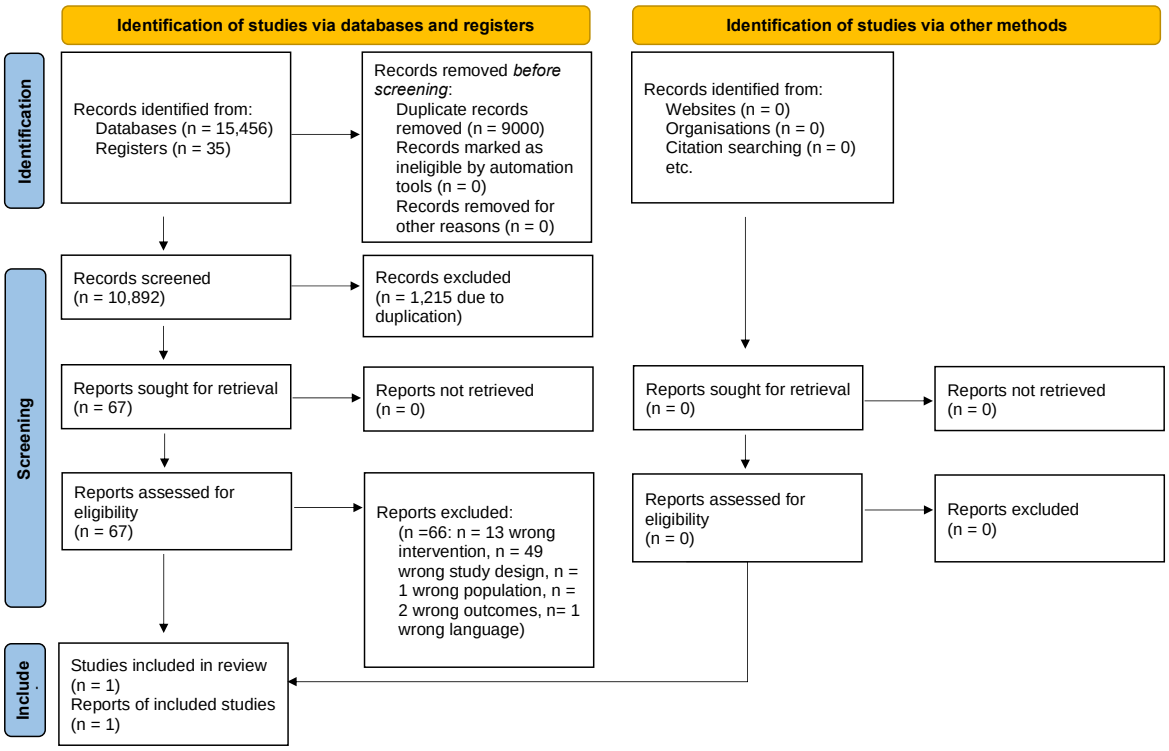

Figure 1: Study flow diagram

Included studies

Only one report from the Ely cohort study met the inclusion criteria (41) (Table 1: Overview of Study Population and Supplementary Table 1: Characteristics of Included Studies). The following is a brief overview of the included Ely study (41):

Study objective: "The aim of the study was to assess the impact of invitation to screening for type 2 diabetes and related cardiovascular risk factors on population mortality" (41).

Study setting: Sampling frame consisted of a single primary health care practice in Ely, Cambridgeshire, the United Kingdom (n = 15,920).

Study participants: Men and women aged 40-65 years without known T2DM and who were not housebound were eligible (n= 4,936).

Study design: A prospective controlled cohort study split into two consecutive time periods that were independently analysed. The first period started in 1990 where one-third of the eligible population were randomly selected and invited to screening while the remaining two-thirds of the eligible population were not invited to screening, these individuals were followed till 1999. The second period started in 2000 where approximately half of those who had not been invited to screening previously were now randomly selected and invited to screening. The other half were never invited to screening. These individuals were followed till 2008. Those involved in each period were followed up for a median of either 10 years for the earlier arm or 8 years for the later arm.

Study intervention: The study intervention was a postal invitation to participate in screening for T2DM and the comparator was no invitation to participate in screening. At screening, an oral glucose tolerance test was performed, and cardiovascular disease risk factors were assessed.

Study outcomes: The outcome of interest in the follow-up was mortality data which was obtained from the Office of National Statistics.

Table 1: Overview of Study Populations Table

Study ID (Study design and setting)	Intervention (I) and comparator (C)	Description of power and sample size calculation	Screened/ eligible (N)	Included (n)	Analysed (primary outcome)	Time period of study and Follow-up duration
Ely, 2011 Prospectively controlled cohort study	I: mass screening: Individuals aged 40-65 years C: not invited to screening: Individuals aged 40-65 years	No justification given however they do note "Finally, the moderate sample size means that we may have been underpowered to detect possible differences in mortality between screened and unscreened groups."	15,920	4,936	Not reported	Time period: 1990-2008 Follow-up: median 10 and 8.1 years respectively
First cohort 1990-1999 (n= 4,936): I: invited 1,705; attended 1,157 (68%), deaths 116 C: not invited 3,231; deaths 229 345 deaths between 1991 and 1999 in a median of 10 years or 47,854 person years of risk. Second cohort 2000-2008 (n = 3,002) *: I: invited 1,577; attended 714 (45%); deaths 165 C: not invited 1,425; deaths 126 291 deaths between 2000-2008 in a median of 8.1 years or 23,144 person-years of risk * Comprised of comparator group of the first cohort however 229 eligible participants died prior to initiation of the second cohort screening						

Excluded studies

The remaining 66 articles that were retrieved for full text were excluded as detailed in the Supplementary Table 2: Characteristics of Excluded Studies. Of note, two reports

tagged onto the end of the Ely study were excluded due to the retrospective nature of their study design (42, 43). Three additional studies, Diabscreen (44), Laxa (45) and the VIP (46) studies appeared to meet the inclusion criteria however they were later excluded due to their study design which included a prospective intervention but a retrospective comparator arm (non-concurrent cohort study; see Supplementary Figure 1 for study design decision tree (34)). These studies are reported on in the discussion.

Risk of bias in included studies

Details of risk of bias is included in Supplementary Table 1: Characteristics of Included Studies and a graphical overview is presented in Figure 2. The overall risk of bias of the single study that met the inclusion criteria was considered moderate.

Pre-intervention: The study was assigned a moderate risk of bias due to confounding. Confounding is expected due to non-randomisation however the predetermined confounding factors of age, comorbidities, and socioeconomic status of participants in the intervention and comparator groups were measured and controlled for. The study was assigned a low risk of bias for selection of participants into the study. Assessing factors internal to the study design where selection of participants is related to both intervention (invitation to screening) and outcome (mortality). There was no relation in the selection of participants to both intervention (invitation to screening) and outcome (mortality) as participants were randomly selected from the sampling frame of the primary practice of Ely.

At intervention: The study was assigned low risk of bias in the classification of interventions as the researchers assigned into groups those who would receive the intervention and those who would not receive the intervention.

Post-intervention: The study was assigned moderate risk of bias due to deviations from intended interventions as even though this study was an invitation to screening study the post-intervention treatment package was not defined and could have impacted on participants' outcomes. The study was assigned low risk of bias in the "due to missing data" category as data were determined to be reasonably complete and similar across groups. The study was assigned low risk of bias in the measurement of outcomes as

mortality was extracted from a standardised nationwide database with two researchers independently assessing these data and reaching consensus. The study was assigned moderate risk of bias in the selection of the reported result due to a lack of reference to a study protocol or statistical analysis plan.

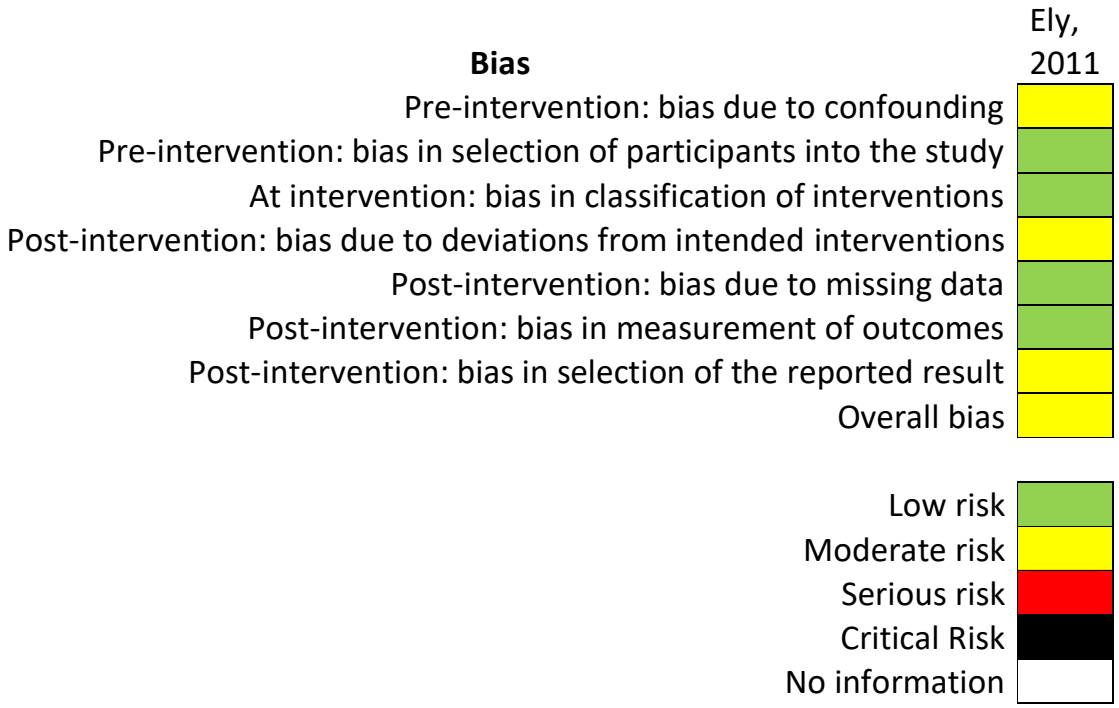

Figure 2: Risk of bias graph indicating review author's judgements about each risk of bias item for the included study.

Effects of interventions

For a brief snapshot see the Summary of Findings Table.

Baseline characteristics

All 4,936 individuals were identified as eligible for enrolment and a baseline characteristics table was presented for the first cohort 1990-1999 but not the second cohort that occurred consecutively after 2000-2008 (See the Overview of Study Populations Table). There was a reported statistical difference but not a large effect size difference at baseline in the age, gender, and social deprivation score for those in the invited as compared to uninvited group even though these groups were

randomly selected (See Supplementary Table 3: Baseline Characteristics). The social deprivation score was derived from a composite measure of four factors, unemployment, overcrowding, car ownership and home ownership, which were presented as relative to the mean deprivation in England and Wales. Attendance following an invitation to screening was 68% in cohort 1 and 45% in cohort 2, those who attended versus those who did not attend were reported as younger and living in areas which were better off in terms of their social deprivation score.

Primary outcomes

All-cause Mortality

Mortality data was obtained by checking for death certification of the entire cohort enrolled at 1990 and following up till 31 January 2008 with the Office of National Statistics (ONS). Ely, 2011 reported in both the first cohort (followed from 1990-1999) and the second cohort (followed from 2000-2008) there may be little or no effect on all-cause mortality in those invited to screening as compared to those who were not invited to screening (Cohort 1: adjusted hazard ratio (aHR) 0.79 [95% confidence interval (CI) 0.63 – 1.00], n = 4,936, low certainty of evidence and Cohort 2: aHR 1.18 [95% CI 0.93 - 1.51], n = 3,002, low certainty of evidence). However, when the study authors did what appears to be post hoc analysis of a selected sample, comparing those in the intervention group who were invited and who attended the screening as compared to those not invited to screening, they found there was a reduction in all-cause mortality (Cohort 1: aHR 0.54 [95% CI 0.40 – 0.74], n = 4,388, very low certainty of evidence and Cohort 2: aHR 0.52 [95% 0.35 – 0.78], n = 2,139, very low certainty of evidence). The hazard ratios reported were adjusted for age, male sex, and deprivation. The total number of deaths reported in cohort 1 was 345 of 4,936 with 116 of these in the intervention group and a median follow-up 10 years in this cohort. The total number of deaths reported in cohort 2 was 291 of 3,002 with 165 of these in the intervention group and a median follow-up of 8.1 years in this cohort.

T2DM related morbidity

This outcome was not reported.

Secondary outcomes

Harms of T2DM screening

This outcome was not reported.

Table 2 Summary of findings:

Invitation to screening compared to no invitation to screening for type 2 diabetes mellitus in adults

Patient or population: type 2 diabetes mellitus in adults
Setting: global
Intervention: invitation to screening
Comparison: no invitation to screening

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with no invitation to screening	**Risk with invitation to screening**				
all-cause mortality (1990-1999) assessed with: death certificate follow up: median 10 years	71 per 1,000	**56 per 1,000** (45 to 71)	**aHR 0.79** (0.63 to 1.00)	4936 (1 observational study)	⨁⨁◯◯ LOW [a,b]	Invitation to screening may result in little to no difference in all-cause mortality.
all-cause mortality (2000-2008) assessed with: death certificate follow up: median 8.1 years	88 per 1,000	**103 per 1,000** (82 to 130)	**aHR 1.18** (0.93 to 1.51)	3002 (1 observational study)	⨁⨁◯◯ LOW [a,b]	Invitation to screening may result in little to no difference in all-cause mortality.
morbidity - not reported	-	-	-	-	-	
harms - not reported	-	-	-	-	-	

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; a**HR:** Adjusted Hazard Ratio

Table 2 Summary of findings:

Invitation to screening compared to no invitation to screening for type 2 diabetes mellitus in adults

Patient or population: type 2 diabetes mellitus in adults
Setting: global
Intervention: invitation to screening
Comparison: no invitation to screening

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with no invitation to screening	**Risk with invitation to screening**				

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations
a. Downgraded by one level for indirectness: Ely, 2011 does not include a global population representation and therefore is downgraded as it is not directly applicable to answer the PICO of the systematic review.
b. Downgraded by one level for imprecision: The point estimate of the two cohorts would result in different clinical actions therefore indicating imprecision in the finding. The authors recognise their sample size may be underpowered to detect possible differences in mortality between screened and unscreened groups.

Table 3 Summary of findings:

Attendance to screening compared to no invitation to screening for type 2 diabetes mellitus in adults

Patient or population: type 2 diabetes mellitus in adults
Setting: global
Intervention: attendance to screening
Comparison: no invitation to screening

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with no invitation to screening	**Risk with attendance to screening**				
all-cause mortality (1990-1999) assessed with: death certificate follow up: median 10 years	0 per 1,000	**NaN per 1,000** (-- to --)	**aHR 0.54** (0.40 to 0.74)	4388 (1 observational study)	⨁◯◯◯ VERY LOW [a,b,c]	Attendance to screening may reduce all-cause mortality.
all-cause mortality (2000-2008) assessed with: death certificate follow up: median 8.1 years	0 per 1,000	**NaN per 1,000** (-- to --)	**aHR 0.52** (0.35 to 0.78)	2139 (1 observational study)	⨁◯◯◯ VERY LOW [a,b,c]	Attendance to screening may reduce all-cause mortality.
morbidity - not reported	-	-	-	-	-	
harms - not reported	-	-	-	-	-	

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; a**HR:** Adjusted Hazard Ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. This analysis was post-hoc.
b. Ely, 2011 does not include a global population representation and therefore is downgraded as it is not directly applicable to answer the PICO of the systematic review.
c. The authors recognize their sample size may be underpowered to detect possible differences in mortality between screened and unscreened groups, this exploratory analysis decreases this sample size to a portion of 45 - 68% of those individuals in the intervention.

Discussion

Summary of main results

We report a dearth in published non-randomised intervention studies investigating screening for T2DM in adults. We found only one study (41) that met our inclusion criteria, and one outcome of interest was reported (all-cause mortality). From the available evidence, we report that invitation to screening for T2DM was shown to have little or no effect over the course of a decade on all-cause mortality of these individuals. Further evidence may impact the effect size in either direction. However, there may be a slight decrease in all-cause mortality in those individuals who took up the invitation to screening as compared to those who did not receive an invitation. There were no studies that met our inclusion criteria that reported on the impact of screening for T2DM and T2DM-related morbidities or on any potential harms associated with screening.

Overall completeness and applicability of evidence

The evidence from this review for the outcomes studied is limited in its applicability to other populations and screening strategies and therefore the context of the study reported and the context in which screening is to take place should be considered when planning to implement screening. The only outcome reported is all-cause mortality with no reporting of T2DM-related morbidity or screening associated harms, therefore we do not have a complete picture of desirable and undesirable effects. The population represented are over 40 years old and located in a single area with the United Kingdom, therefore may not be applicable to many settings globally. The intervention is a mass screening intervention where invitations were posted to those who were eligible. The postal system in many countries is barely functional and seldomly utilised as a reliable form of communication, therefore this approach would have limited applicability. In addition, many countries implement opportunistic

screening strategies rather than mass strategies again limiting the wider applicability of these findings. Therefore, there is limited external validity of this review simply due to the limitation of only one study meeting our inclusion criteria and that study being limited in geographic location as well as in intervention style and outcomes reported.

Quality of the evidence

The quality of the body of evidence is limited due to only one study, from one setting, meeting the inclusion criteria (n=4,936 participants). The outcome of all-cause mortality was considered as low quality of evidence by GRADE. This was downgraded to low evidence due to several factors. Firstly, the evidence was downgraded by one level for serious indirectness as the included study was not broadly representative of different populations, including those living in LMICs which the systematic review aimed to address. Secondly it was downgraded for imprecision as the consecutive cohorts reported point estimates in opposite directions therefore requiring different clinical courses of action.

Potential biases in the review process

Language being restricted to English may have missed studies. A key limitation that may introduce bias is the review question's narrow focus on the effect of a screening intervention and then on health outcomes that occur many years later (often 10 years or more). The period between screening intervention and outcomes is where behaviour and/ pharmacological interventions are typically aimed to alter the course of disease. This treatment phase is likely to impact the outcomes and needs to be accounted for and reported on in any future systematic reviews as well as study designs investigating screening.

Agreements and disagreements with other studies or reviews

The findings of this review are similar to those of the recent Cochrane systematic review of randomized control trials of screening for T2DM (16) which found a single study fit their inclusion criteria and demonstrated no effect of screening for T2DM on all-cause mortality within a 10-year period. Two reports from the Ely study were

excluded due to the retrospective nature of the study design, these articles utilised self-reported health status over more than a decade and showed that there was no difference between those who were screened or not screened (42, 43). Three additional studies that appeared to meet the inclusion criteria but were later excluded were the Diabscreen (44), the Laxa (45) and the VIP (46) studies. Diabscreen (44) was an opportunistic targeted screening strategy of 45–75-year-olds with T2DM risk factors based in the Netherlands who visited their primary health care provider. The study had a 10 year follow up and outcomes of interest were CVD-related mortality and morbidity of microvascular and macrovascular complications related to T2DM in those who were diagnosed with T2DM following screening as compared to those who were clinically diagnosed. This study also found no apparent differences between those who were screened and those who were not screened. Laxa (45) was an opportunistic screening strategy based in a county of Sweden and aimed at people aged 35-79 years who visited their primary health care provider. The individuals were followed for an average of 10 years for outcomes of interest that were all-cause mortality and macrovascular morbidity in those who were diagnosed with T2DM following screening as compared to those who were clinically diagnosed. The study also found no apparent differences between those who were screened and those who were not screened. The VIP (46) study was a mass screening program for diabetes within a health promotion program for decreasing cardiovascular risk mortality and morbidity for all adults over 30 years of ages based in a county of Sweden. The outcomes of all-cause mortality, T2DM-related macrovascular and microvascular morbidity were investigated for more than 10 years in individuals who had screen detected T2DM as compared to those who had clinically detected T2DM. In contrast to our findings, this study found that in individuals with screen detected diabetes as compared to clinically detected diabetes had lower rates of all-cause mortality as well as T2DM-associated morbidities. Of note was the diabetes screening intervention within a health promotion intervention employed in this study as compared to a diabetes screening intervention alone.

Author's conclusions

Implications for practice

From this review, there is insufficient English written evidence to recommend either for or against screening for T2DM. Additionally, there is insufficient English written evidence to suggest there are harms associated with screening for T2DM. Lastly, current practice guidelines promoting screening are based on screening theory shown to be effective in other diseases. Screening theory states that the early detection of asymptomatic T2DM allows for behaviour and pharmaceutical interventions to alter the course of disease improving a patient's health status by preventing or delaying morbidity and mortality associated with the disease. This review did find that screening for T2DM may reduce mortality although this evidence was uncertain and the effect on other efficacy and safety outcomes remain unknown. A recent systematic review on cost-effectiveness of screening for T2DM found screening to be cost-effective (47). Therefore, the implication for practice is for health care workers to continue to screen for T2DM according to relevant global or local policies.

Implications for research

This systematic review highlights the scarcity of knowledge available in English to answer the study query. The limitation of this study being limited to English language publications only, can be addressed by a similar study with no language limitations to capture any missed publications. Another option to address the knowledge base in this area is through other forms of non-comparative data that may provide additional contextual evidence about the value of screening e.g., costs, acceptability, equity, and local prevalence of diseases. In sum, the lack of easily accessible high-quality studies in this area highlights the need to prioritise the research topic: Is screening theory applicable to people living with T2DM?

Firstly, there is a requirement for high quality studies to generate direct evidence on whether screening for T2DM affects T2DM associated health outcomes. The inclusion of an implementation science approach to these studies would assist with speeding up the transition from clinical to implementation and therefore ultimately improve our public health outcomes. There are subtopics within this which require further investigation including but not limited to: Which screening strategy should be employed; mass, targeted or opportunistic? Where should screening be conducted and by whom? What are barriers and enablers of screening? What tests should be used for screening?

Secondly, there is a critical need for these studies and for pragmatic studies within clinical practice to include a predetermined component that investigates potential harms that may be inflicted to either the patient or the health system during screening.

Thirdly, there is a need to investigate the effectiveness of interventions for individuals who are identified while asymptomatic during the screening process and the impact these interventions on the course of their disease to inform clinicians on best practice for treatment decisions for these individuals.

Other Information

The review was registered with PROSPERO CRD42020147439, and the protocol is published (doi: 10.1186/s13643-020-01417-3) (48).

Differences between protocol and review:

Methods:

1. Updated PRISMA reporting from 2009 to 2020 version.
2. The outcome mortality was determined to be a primary outcome as opposed to a secondary outcome. However, outcomes in a systematic review should be ranked according to their clinical impact, therefore mortality was incorrectly classified in the protocol.
3. Due to the inclusion of only one study, we did not perform quantitative analysis, assessment of heterogeneity, subgroup analysis or sensitivity analysis.

Declarations:

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Contributions of authors

Conceiving the review: [BS, TK]

Data extraction and analysis: [HM, BS]

Developing and writing the review: [HM]

Co-ordinating the review: [HM]

Designing search strategies: [MS, HM]

Providing general advice on the review and approving the final version: [BK, TK, BS]

Securing funding for the review: [BS, TK]

Performing previous work that was the foundation of the current study: [NP, SD]

Guarantor of the review: [BS]

Competing interests

The authors declare that they have no competing interests.

HM: None known

BMK: None known

TK: None known

BS: None known

Ethics approval and consent to participate

Ethics approval is not required for a systematic review of secondary data.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

List of abbreviations

CEBHA+	Collaboration for Evidence-Based Healthcare and Public Health in Africa
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HbA1c	detection of glycated haemoglobin A1C
NRIS	non-randomised intervention studies
PCS	prospective cohort study
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
SoF	Summary of findings

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42. Rahman M, Simmons RK, Hennings SH, Wareham NJ, Griffin SJ. How much does screening bring forward the diagnosis of type 2 diabetes and reduce complications? Twelve year follow-up of the Ely cohort. Diabetologia. 2012;55(6):1651-9.
43. Rahman M, Simmons RK, Hennings SH, Wareham NJ, Griffin SJ. Effect of screening for Type 2 diabetes on population-level self-rated health outcomes and measures of cardiovascular risk: 13-year follow-up of the Ely cohort. Diabet Med. 2012;29(7):886-92.
44. Klein Woolthuis EP, de Grauw WJC, van Keeken SM, Akkermans RP, van de Lisdonk EH, Metsemakers JFM, et al. Vascular outcomes in patients with screen-detected or clinically diagnosed type 2 diabetes: Diabscreen study follow-up. Annals of Family Medicine. 2013;11(1):20-7.
45. Jansson SP, Andersson DK, Svardsudd K. Mortality and cardiovascular disease outcomes among 740 patients with new-onset Type 2 diabetes detected by screening or clinically diagnosed in general practice. Diabet Med. 2016;33(3):324-31.
46. Feldman AL, Griffin SJ, Fharm E, Norberg M, Wennberg P, Weinehall L, et al. Screening for type 2 diabetes: do screen-detected cases fare better? Diabetologia. 2017;60(11):2200-9.
47. Najafi B, Farzadfar F, Ghaderi H, Hadian M. Cost effectiveness of type 2 diabetes screening: A systematic review. Med J Islam Repub Iran. 2016;30:326-.

48. Mearns H, Otiku PK, Shelton M, Kredo T, Kagina BM, Schmidt BM. Screening strategies for adults with type 2 diabetes mellitus: a systematic review protocol. Syst Rev. 2020;9(1):156.

Supplementary Table 1: Characteristics of Included Studies (n=1)

Ely, 2011	
Study Characteristics	
Methods	**Study Design**: concurrently controlled prospective cohort study (PCS).
Participants	**Inclusion criteria**: all men and women aged 40–65 years were randomly selected from a sampling frame of adults free of known diabetes registered with a single practice serving the city of Ely, United Kingdom. **Exclusion criteria**: Housebound individuals were excluded prior to invitation.
Interventions	mass screening **Description:** Two rounds of screening occurred one in 1990-1992 where one-third of the sampling frame were randomly invited for screening while the remainder were not. Followed by a second round of screening in 2000-2003 where half of those who were not invited were now randomly invited for screening while the other half were never invited for screening. Each cohort was reported on separately with a median follow up of 10 and 8.1 years respectively. **Comparator:** The adults who formed part of the sampling frame and who were not invited for screening were the comparator. **Screening:** fasting plasma glucose test (75 g OGTT) and related cardiovascular disease (CVD) risk factors. **Diagnosis:** not reported **Treatment**: "No standard intervention package was specified for people found to have type 2 diabetes or elevated CVD risk factors following screening. GPs were informed of the results and advised to take whatever action they thought necessary." **Number of study centres**: 1 Intervention and 1 comparator sites (these are the same site).
Outcomes	Reported as adjusted hazard ratio for mortality of those invited for screening compared to those not invited for screening. **Morbidity; microvascular complications:** not reported **Morbidity; macrovascular complications:** not reported **Mortality:** all-cause death **Harms:** not reported
Study Details	
Publication details	**Language of publication**: English **Funding**: "The Ely study was supported by the Medical Research Council and NHS Research and Development (R&D). M. Rahman was funded by an NHS R&D training fellowship." **Publication status**: peer-reviewed journal
Stated aim of study	**Quote**: "The aim of this study was to assess the impact of invitation to screening for type 2 diabetes and related cardiovascular risk factors on population mortality."
Notes	
Risk of bias (low risk, moderate risk, serious risk, critical risk of bias or no information)	

Bias	Outcome	Author's judgement	Support for judgement
Pre-intervention: bias due to confounding	mortality	moderate risk	**Quote**: "Data were available on age at baseline, sex and postal address code. Missing postcodes from the original 1990 address data were updated by a Royal Mail recommended company (www.dataprocessing.co.uk, accessed 22 June 2010). Postcodes were available for 90% of participants and were linked to enumeration districts to calculate the Townsend Index... Cox proportional HRs were calculated for the association between baseline characteristics and mortality." **Comment**: Confounding is expected but important clinical and context domains were measured and controlled for and reliability and validity of the measurement was sufficient.
Pre-intervention: bias in selection of participants into the study	mortality	low risk	**Comment**: Selection into the study was not based on the intervention or outcome but to the individual's registration at the primary health care facility. All individuals that formed part of the sampling frame were eligible unless housebound and therefore unable to respond to the invitation for screening.
At intervention: bias in classification of interventions	mortality	low risk	**Quote**: "In brief, approximately one-third (n= 1,705) of all men and women aged 40–65 years old was randomly selected from a sampling frame of adults free of known diabetes registered with a single practice serving Ely (n=4,936). Housebound individuals were excluded prior to invitation. Selected individuals were invited between 1990 and 1992 for screening for type 2 diabetes with a 75 g OGTT and related CVD risk factors." **Comment**: Sampling frame consisted of all registered individuals in the area. Therefore, unlikely to classify those with intervention or comparator incorrectly as intervention status is well defined and status is based on information collected at the time of the intervention.
Post-intervention: bias due to deviations from	mortality	moderate risk	**Quote:** "No standard intervention package was specified for people found to have type 2 diabetes or elevated CVD risk factors following screening. GPs were

intended interventions			informed of the results and advised to take whatever action they thought necessary." **Comment:** The intervention investigated is invitation to screening however the co-intervention is treatment post screening as this will affect the outcome of mortality. As the treatment was not standardized across groups we do not know if there were imbalances here and cannot determine what action GPs may have taken and if this action was imbalanced if diabetes was detected via screening or via standard clinical practice.
Post-intervention: bias due to missing data	mortality	low risk	**Quote:** "At baseline 90% of participant's data were available for participant characteristics and at follow-up attendance rate is clearly noted at each visit and baseline demographics were compared and found to be similar between those who attended and those who did not attend." **Comment**: Data were reasonably complete and similar across groups.
Post-intervention: bias in measurement of outcomes	mortality	Low risk	**Quote:** "In order to assess the impact of invitation to screening on population mortality, all individuals in the original sampling frame, including those who were not invited for screening, were flagged for death certification at the Office of National Statistics (ONS). Vital status has been obtained for the entire cohort and we report results for follow-up to 31 January 2008. Deaths were coded into three groups (cardiovascular, cancer and other) based on the primary cause of death using the international Classification of Diseases, 10th edition (ICD-10; www.who.int/classifications/icd/en/). Two researchers independently coded the deaths with 94% agreement. Consensus was reached after discussion with a third researcher. Cardiovascular death was defined as an ICD-10 code in the range I00–I99 and cancers deaths as C00–D48. It was also noted whether diabetes was included as the underlying cause of death on each certificate."
Post-intervention: bias in	mortality	moderate risk	**Comment**: As there is no reference to a registered protocol or statistical analysis plan there is no clear evidence that results correspond to intended outcomes. The

selection of the reported result			outcome measurements are clearly defined and consistent with no indication of selection of the reported analysis from among multiple analyses and no indication of selection of the cohort or subgroups for analysis and reporting based on the results.
Overall bias	mortality	moderate risk	**Comment**: The study provides sound evidence for a non-randomized study but cannot be considered comparable to a well-performed randomized trial.

Supplementary Table 2: Characteristics of Excluded Studies (n=66)

	Citation	Reason for Exclusion	Comment
1	Diabetes screening works - at a cost. Pulse 2006; 66(34): 4-.	Wrong study design	Commentary in a newspaper on the ADDITION Cambridge study results
2	Diabetes screening ramps up workload. Pulse 2007; 67(27): 4-.	Wrong study design	Commentary in a newspaper on the ADDITION Cambridge study results
3	INTERVENTION EFFECTIVENESS IN THE COMMUNITY. Diabetes 2008; 57: A74-A7.	Wrong study design	No PDF available The Abstract reads as “The article presents abstracts of medical studies including "Effect of Screening for Type 2 Diabetes on Population Mortality: A Randomised Trial," by Justin B. Echouffo, "Long-Term Impact of Lifestyle Interventions to Prevent Diabetes: 20-Year Follow-Up of Da Qing Diabetes Prevention Study," by Peter H. Bennett et al, and "Antidiabetic Therapies and Cancer Mortality in Type 2 Diabetes: Assessing Time-Varying Exposure," by Samantha L. Bowker et al.”
4	Type 2 diabetes screening has limited psychological impact. Australian Journal of Pharmacy 2009; 90(1): 78.	Wrong study design	AJP publishes commentaries on research findings so unlikely to be a primary study. No PDF available.
5	Diabetes screening works as part of annual review. Pulse 2011; 71(34): 14-.	Wrong study design	Commentary in a newspaper on the ADDITION Cambridge study results
6	Abdel-Rahman MY. Not All Patients Initially Screened for Diabetes. Fertility Weekly 2012: 8-9.	Wrong study design	Commentary on a web-based survey
7	Abdel-Rahman MY, Jackson LW, Rodewald KJ, Abdellah MA, Ismail SA, Hurd WW. Polycystic ovary syndrome and diabetes screening: A survey of gynecologists and reproductive endocrinologists.	Wrong intervention	Measuring screening rates rather than screening strategies

	European Journal of Obstetrics and Gynecology and Reproductive Biology 2012; 162(2): 178-81.		
8	Abdul-Ghani MA, Sabah M, Minuchin O, Vardi P, Raz I, Wainstein J. Primary prevention of type 2 diabetes: How do we do it? Israel Medical Association Journal 2004; 6(5): 305-7.	Wrong study design	Narrative review
9	Acosta T, Fernandez A, Sanchez M, et al. Successful implementation of a community program of screening and three year primary prevention of type 2 diabetes with lifestyle modifications: DE-PLAN study. Diabetologia 2011; 54: S136-S.	Wrong intervention	Measuring screening tool rather than screening strategy
10	Adams SR, Wiley DM, Fargeix A, George V, Neugebauer RS, Schmittdiel JA. Employer-Based Screening for Diabetes and Prediabetes in an Integrated Health Care Delivery System: A Natural Experiment for Translation in Diabetes (NEXT-D) Study. J Occup Environ Med 2015; 57(11): 1147-53.	Wrong outcomes	No reported outcome of morbidity, mortality or harms.
11	Adriaanse M, Dekker J, Spijkerman A, et al. Diabetes-related symptoms and negative mood in	Wrong study design	Based on The Hoorn Screening Study that has no control group in its study design.

	participants of a targeted population-screening program for type 2 diabetes: The Hoorn Screening Study. Quality of Life Research 2005; 14(6): 1501-9.		
12	Adriaanse MC, Dekker JM, Spijkerman AMW, et al. Health-related quality of life in the first year following diagnosis of Type 2 diabetes: Newly diagnosed patients in general practice compared with screening-detected patients. The Hoorn screening study. Diabetic Medicine 2004; 21(10): 1075-81.	Wrong study design	Based on The Hoorn Screening Study that has no control group in its study design.
13	Adriaanse MC, Pouwer F. Screening for type 2 diabetes does not reduce mortality over 10 years. Evidence-Based Medicine 2013; 18(5).	Wrong study design	Cluster randomized controlled trial
14	Adriaanse MC, Snoek FJ. The psychological impact of screening for type 2 diabetes. Diabetes/Metabolism Research and Reviews 2006; 22(1): 20-5.	Wrong study design	Retrospective qualitative study on patients who tested positive versus negative from the Hoorn Study
15	Adriaanse MC, Snoek FJ, Dekker JM, et al. No substantial psychological impact of the diagnosis of Type 2 diabetes following targeted population screening:	Wrong study design	Hoorn study is not controlled.

	The Hoorn Screening Study. Diabetic Medicine 2004; 21(9): 992-8.		
16	Adriaanse M, Snoek F, Dekker J, van der Ploeg H, Heine R. Screening for Type 2 diabetes: an exploration of subjects' perceptions regarding diagnosis and procedure. Diabet Med 2002; 19(5): 406-11.	Wrong study design	Explorative interview study
17	Ahmad M, Javed N, Marral AI. SCREENING FOR DIABETES AND HYPERTENSION IN WORKPLACE ENVIRONMENTS. Indo American Journal of Pharmaceutical Sciences 2018; 5(9): 9499-504.	Wrong study design	Descriptive epidemiological study - no control group
18	Alssema M, Vistisen D, Heymans MW, et al. The Evaluation of Screening and Early Detection Strategies for Type 2 Diabetes and Impaired Glucose Tolerance (DETECT-2) update of the Finnish diabetes risk score for prediction of incident type 2 diabetes. Diabetologia 2011; 54(5): 1004-12.	Wrong intervention	Measuring screening tool rather than screening strategy
19	Amini M, Timori A, Aminorroaya A. Quality of care for first-degree relatives of type 2 diabetes patients diagnosed with diabetes at a screening program	wrong intervention	Evaluation of the quality of care for newly diagnosed diabetic patients

	one year after diagnosis. Rev Diabet Stud 2008; 5(1): 52-8.		
20	Aoun S, Johnson L. Men's health promotion by general practitioners in a workplace setting. Aust J Rural Health 2002; 10(6): 268-72.	wrong study design	No control group
21	Azizi F, Gouya MM, Vazirian P, Dolatshahi P, Habibian S. Screening for type 2 diabetes in the Iranian national programme: A preliminary report. Eastern Mediterranean Health Journal 2003; 9(5): 1122-7.	Wrong study design	No control group
22	Bali V, Yermilov I, Koyama A, Legorreta AP. Secondary prevention of diabetes through workplace health screening. Occupational Medicine 2018; 68(9): 610-6.	Wrong study design	No control group
23	Barengo NC, Acosta T, Arrieta A, Ricaurte C, Mayor D, Tuomilehto J. Screening for people with glucose metabolism disorders within the framework of the Demojuan project in Barranquilla, Colombia; 2013.	Wrong intervention	Looking at feasibility of using the FINRISC score as a screening tool
24	Barkoudah E, Weinrauch LA. Screening for abnormal blood glucose and type 2	Wrong study design	Letter to the editor commentary on U.S. Preventive Services Task Force's recommendation

	diabetes mellitus. Annals of Internal Medicine 2016; 165(3): 225.		
25	Barry HC. Screening for type 2 diabetes mellitus: 10-year mortality not improved. American Family Physician 2013; 87(7): 512.	Wrong study design	A point- of-care clinical decision support system commentary on ADDITION-Cambridge
26	Bartram S, Rigby D. Diabetes screening as part of a vascular disease risk management programme. Community Pract 2012; 85(10): 24-7.	Wrong intervention	Measuring screening tool rather than screening strategy
27	Bromley L, Bharaj HS. Screening for diabetes and cardiovascular disease outcomes in people of South Asian ethnicity in Bolton. Diabetes and Primary Care 2016; 18(6): 279-82.	Wrong study design	No comparator group
28	Burnside N, Bell P, McIllwaine C, McCartney R. The sweet sound of screening? Ulster Med J 2011; 80(3): 165.	Wrong study design	Cost effectiveness and uptake pilot of targeted screening with no control group
29	Chang HJ, Kuo HS, Tung TH, Chou P, Chen TH. Evaluation of a population-based screening for type 2 diabetes: a community-based screening project in Puli, Taiwan. *Prev Med.* 2000;31(4):396-402.	Wrong study design	This study inputs data from a community-based cross-sectional study into a Markov model. This is not primary data.
30	Dhippayom T, Fuangchan A, Tunpichart S, Chaiyakunapruk N.	Wrong intervention	Measuring screening tool rather than screening strategy

	Opportunistic screening and health promotion for type 2 diabetes: An expanding public health role for the community pharmacist. Journal of Public Health (United Kingdom) 2013; 35(2): 262-9.		
31	Eborall HC, Griffin SJ, Prevost AT, Kinmonth AL, French DP, Sutton S. Psychological impact of screening for type 2 diabetes: controlled trial and comparative study embedded in the ADDITION (Cambridge) randomised controlled trial. BMJ 2007; 335(7618): 486.	Wrong study design	RCT (ADDITION-Cambridge)
32	Engstrom S, Berne C, Gahnberg L, Svardsudd K. Effectiveness of screening for diabetes mellitus in dental health care. Diabet Med 2013; 30(2): 239-45.	Wrong outcomes	No reported outcome of morbidity, mortality, or harms - cannot access PDF but can see this from abstract
33	Evans P, Langley P, Gray DP. Diagnosing type 2 diabetes before patients complain of diabetic symptoms--clinical opportunistic screening in a single general practice. Fam Pract 2008; 25(5): 376-81.	Wrong study design	Retrospective cohort study
34	Farmer AJ, Doll H, Levy JC, Salkovskis PM. The impact of screening for Type 2 diabetes in siblings of	Wrong study design	Cohort with no comparator group.

	patients with established diabetes. Diabet Med 2003; 20(12): 996-1004.		
35	Feldman AL, Griffin SJ, Fharm E, et al. Screening for type 2 diabetes: do screen-detected cases fare better? *Diabetologia.* 2017;60(11):2200-2209.	Wrong study design	Retrospective comparator arm
36	Fisher BG, Ang YL, Goodhart C, Simmons RK. Record-based, stepwise screening for type 2 diabetes integrated into an annual cardiovascular care review system: Findings from a UK general practice. Prim Care Diabetes 2011; 5(4): 265-9.	Wrong study design	No control group
37	Hoebaus C, Herz CT, Pesau G, Zierfuss B, Koppensteiner R, Schernthaner GH. Screening for diabetes and early treatment reduces mortality in peripheral arterial disease over seven years. Diabetologia 2018; 61: S48-S9.	Wrong study design	No control group
38	Hofer TP, Vijan S, Hayward RA. Estimating the microvascular benefits of screening for type 2 diabetes mellitus. Int J Technol Assess Health Care 2000; 16(3): 822-33.	Wrong study design	Modelled data not primary data
39	Iqbal MT. An opportunistic pre-diabetes screening	Wrong study design	Commentary

	program offered with existing hypertension screening. J Prev Med Hyg 2013; 54(1): 14-6.		
40	Jansson SP, Andersson DK, Svardsudd K. Mortality and cardiovascular disease outcomes among 740 patients with new-onset Type 2 diabetes detected by screening or clinically diagnosed in general practice. *Diabet Med.* 2016;33(3):324-331.	Wrong study design	Retrospective comparator arm
41	Klein Woolthuis EP, de Grauw WJ, van Gerwen WH, et al. Yield of opportunistic targeted screening for type 2 diabetes in primary care: the diabscreen study. Ann Fam Med 2009; 7(5): 422-30.	Wrong study design	No control group
42	Klein Woolthuis EP, de Grauw WJC, van Keeken SM, et al. Vascular outcomes in patients with screen-detected or clinically diagnosed type 2 diabetes: Diabscreen study follow-up. *Annals of Family Medicine.* 2013;11(1):20-27.	Wrong study design	Retrospective comparator arm
43	Lawrenson RA, Dunn PJ, Jury D, Sceats J. Discover diabetes: screening for diabetes mellitus in the Waikato. N Z Med J 1993; 106(969): 522-4.	Wrong intervention	Looking at whether screening tool detects diabetes not at screening strategy. "Free screening for diabetes mellitus was offered, in three rural communities as part of an initiative of the Waikato Area Health Board to improve the detection and management of type 2 diabetes."

44	Li C, Lumey LH. Impact of disease screening on awareness and management of hypertension and diabetes between 2011 and 2015: results from the China health and retirement longitudinal study. BMC Public Health 2019; 19(1): 421.	Wrong study design	No control group
45	Macedo SKAM, De Paula FV, Lopes ACCC, et al. Screening for diabetes in pharmaceutical professionals in the State of Mato Grosso do Sul. Mundo da Saude 2019; 43(2): 456-71.	Wrong Language	Not in English
46	Mahon J. 2012 - A single screening for type 2 diabetes in high-risk adults did not reduce mortality over 10 years. ACP Journal Club 2013; 158(2): 1-.	Wrong study design	Journal club on ADDITION-Cambridge trial
47	Man B, Turyk ME, Kominiarek MA, Xia Y, Gerber BS. Diabetes screening in US women with a history of gestational diabetes, national health and nutrition examination survey, 2007-2012. Preventing Chronic Disease 2016; 13(9).	Wrong study design	Cross-sectional survey
48	Nwaneri C, Bowen-Jones D, Cooper H. Screening for type 2 diabetes and population mortality over 10 years. The	Wrong study design	Commentary

	Lancet 2013; 381(9870): 901-2.		
49	O'Brien MJ, Lee JY, Carnethon MR, et al. Detecting Dysglycemia Using the 2015 United States Preventive Services Task Force Screening Criteria: A Cohort Analysis of Community Health Center Patients. PLoS Medicine 2016; 13(7): 1-18.	Wrong study design	Retrospective analysis of electronic health record
50	Patel M. Screening for type 2 diabetes in primary care: is it feasible? Diabetes & Primary Care 2005; 7(3): 139-44.	Wrong study design	No control group
51	Rahman M, Simmons RK, Hennings SH, Wareham NJ, Griffin SJ. Effect of screening for Type 2 diabetes on population-level self-rated health outcomes and measures of cardiovascular risk: 13-year follow-up of the Ely cohort. *Diabet Med.* 2012;29(7):886-892.	Wrong study design	Retrospective comparator arm
52	Rahman M, Simmons RK, Hennings SH, Wareham NJ, Griffin SJ. How much does screening bring forward the diagnosis of type 2 diabetes and reduce complications? Twelve year follow-up of the Ely cohort. *Diabetologia.*	Wrong study design	Retrospective comparator arm

	2012;55(6):1651-1659.		
53	Simmons RK, Griffin SJ, Lauritzen T, Sandbaek 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; 60(11): 2192-9.	Wrong study design	Post-hoc analysis of a controlled trial using a retrospectively constructed comparator group with a prospectively followed intervention group comparing mortality rate and cardiovascular outcomes in individuals with incident diabetes in the screened group with those from the unscreened group.
54	Simmons RK, Griffin SJ, Witte DR, Borch-Johnsen K, Lauritzen T, Sandbaek 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; 60(11): 2183-91.	Wrong study design	Retrospective concurrently controlled cohort study
55	Skinner TC, Davies MJ, Farooqi AM, Jarvis J, Tringham JR, Khunti K. Diabetes screening anxiety and beliefs. Diabetic Medicine 2005; 22(11): 1497-502.	Wrong study design	Cross-sectional study (no control)
56	Snella KA, Canales AE, Irons BK, et al. Pharmacy- and community-based screenings for diabetes and cardiovascular	Wrong intervention	Measuring screening tool rather than screening strategy

	conditions in high-risk individuals. J Am Pharm Assoc (2003) 2006; 46(3): 370-7.		
57	Sohler N, Matti-Orozco B, Young E, et al. OPPORTUNISTIC SCREENING FOR DIABETES AND PREDIABETES USING HEMOGLOBIN A1C IN AN URBAN PRIMARY CARE SETTING. Endocr Pract 2016; 22(2): 143-50.	Wrong study design	Retrospective analyses (cannot obtain full text)
58	Sortso C, Komkova A, Sandbaek A, et al. Effect of screening for type 2 diabetes on healthcare costs: a register-based study among 139,075 individuals diagnosed with diabetes in Denmark between 2001 and 2009. Diabetologia 2018; 61(6): 1306-14.	Wrong study design	retrospective concurrently controlled cohort study -> additionally no outcomes as specified in protocol.
59	Spijkerman AMW, Dekker JM, Nijpels G, et al. Microvascular complications at time of diagnosis of type 2 diabetes are similar among diabetic patients detected by targeted screening and patients newly diagnosed in general practice: The Hoorn Screening Study. Diabetes Care 2003; 26(9): 2604-8.	Wrong study design	No control group
60	Spijkerman AMW, Dekker JM, Nijpels G, et al. Impact of	Wrong population	Participants were type 2 diabetic subjects (n = 174) of a population-based cohort study.

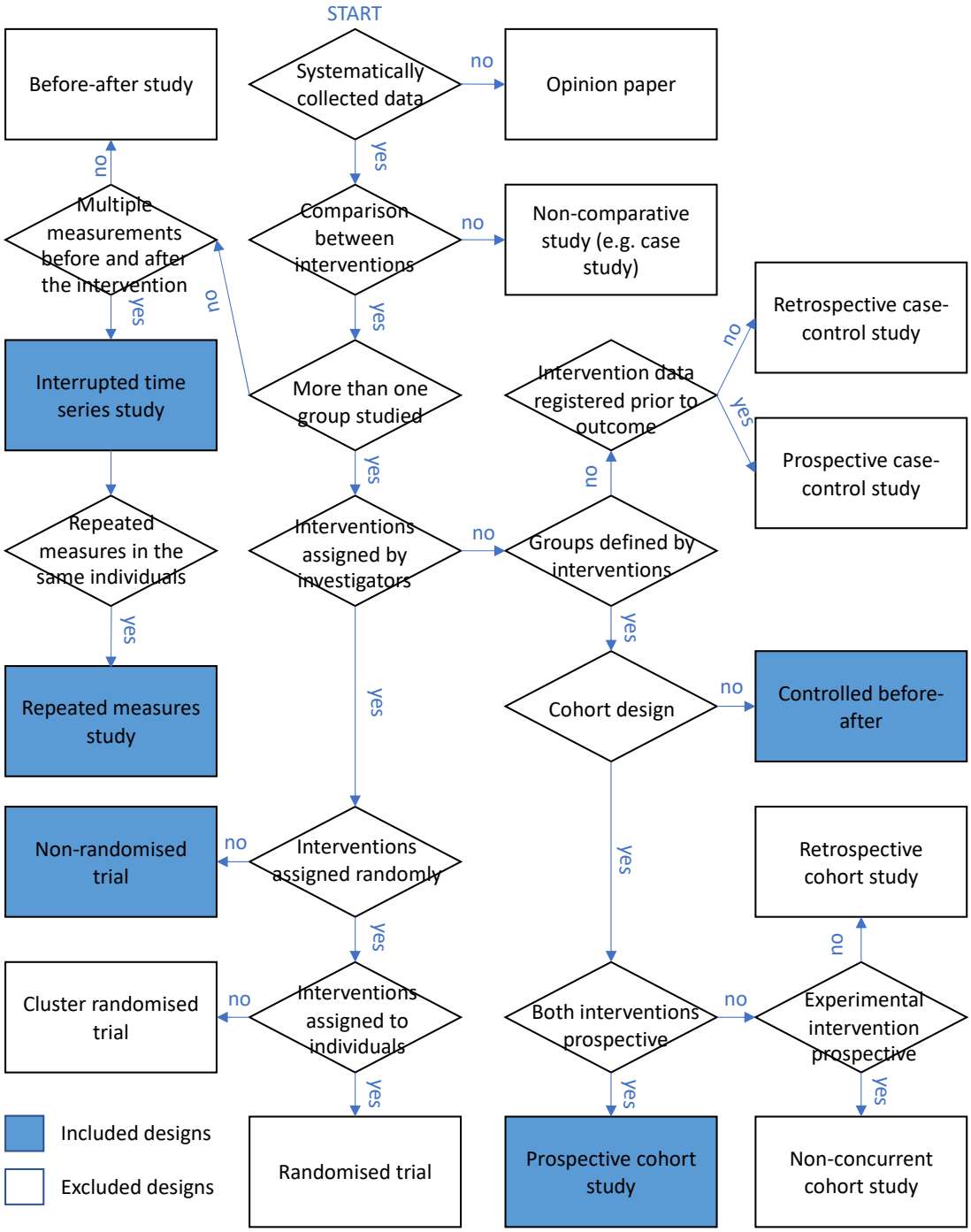
	diabetes duration and cardiovascular risk factors on mortality in type 2 diabetes: The Hoorn Study. European Journal of Clinical Investigation 2002; 32(12): 924-30.		
61	Tarride J-E, Smofsky A, Nykoliation P, et al. Effectiveness of a Type 2 Diabetes Screening Intervention in the Canadian Workplace. Canadian Journal of Diabetes 2018; 42(5): 493-.	Wrong intervention	Evaluating screening tool rather than screening strategy
62	Vita P, Cardona-Morrell M, Bauman A, et al. Type 2 diabetes prevention in the community: 12-Month outcomes from the Sydney Diabetes Prevention Program. Diabetes Res Clin Pract 2016; 112: 13-9.	Wrong intervention	A 12-month lifestyle modification program targeting people aged 50–65 years at high-risk of developing type 2 diabetes conducted in the greater Sydney area
63	White B, Chamberlain N. Screening for diabetes, impaired glucose tolerance, and cardiovascular risk in primary care: a Northland, New Zealand pilot study. N Z Med J 2009; 122(1295): 28-37.	Wrong study design	No control group
64	Willems JI, Otto SJ, Klijs B, de Koning HJ. Screening for type 2 diabetes in a high-risk population: effects of a negative screening test after 4 years follow-up. Ann	Wrong study design	No control group

	Behav Med 2014; 47(1): 102-10.		
65	Willis A, Roshan M, Patel N, et al. A community faith centre based screening and educational intervention to reduce the risk of type 2 diabetes: A feasibility study. Diabetes Res Clin Pract 2016; 120: 73-80.	Wrong intervention	Evaluating screening tool rather than screening strategy "We conducted a study to assess the feasibility of delivering a faith centre-based pathway for screening and referral to group education for high-risk individuals to increase screening uptake and reduce diabetes risk."
66	Zhang Y, Ning F, Sun J, et al. Impact of a diabetes screening program on a rural Chinese population: a 3-year follow-up study. BMC Public Health 2015; 15: 198.	Wrong intervention	Screening for pre-diabetes. Wrong study design -> no comparator group.

Supplementary Table 3: Baseline Characteristics

Study ID	Intervention (I) and comparator (C); n (%)	Description of participants	Country and setting	Sex male n (%)	Age in years (SD)	Townsend Index of Deprivation
Ely, 2011	Cohort 1 1990-1999 I: mass screening 1,705 (34.5) C: not invited to screening 3,231 (65.5)	Men and women aged 40-65 years who were registered with a single primary practice in Ely. Individuals who had known diabetes or who were housebound were excluded.	A single primary health care centre in Ely, Cambridgeshire, United Kingdom	I: 769 (45.1) C: 1,639 (50.7)	I: Female 52.8 (7.8) Male: 52.8 (7.9) C: Female 51.2 (7.3) Male 50.9 (7.3)	I: −1.3 (2.0) C: −1.5 (1.7)
Ely, 2011	Cohort 2 2000-2008 I: mass screening 1,577 (52.5) C: not invited to screening 1,425 (47.5)	Individuals who were part of the comparator group for cohort 1.	As above	Not reported	Not reported	Not reported

Supplementary Figure 1: Flow diagram to assist with identifying the type of study (modified from (34))



Supplementary Search Strategy for PubMed:

Set 1

Diabetes Mellitus, Type 2 [MeSH] OR [Text Word field:] Adult onset diabetes OR late onset diabetes OR latent diabetes OR mature onset diabetes OR MODY OR NIDDM OR noninsulin-dependent diabetes OR slow onset diabetes OR stable onset diabetes OR type 2 diabetes OR type II diabetes OR T2DM OR T2D

Set 2

Diabetes Insipidus [MeSH] OR [Text Word field:] diabetes insipidus

Set 3

1 NOT 2

Set 4

Mass screening [MeSH] OR [Text Word field:] screening

Set 5

3 AND 4

Set 6

Animals [MeSH] NOT Humans [MeSH]

Set 7

5 NOT 6

Set 8

[All fields:] Trial OR trials OR before-and-after study OR before-and-after studies OR cohort OR comparative study OR comparative studies OR Controlled OR evaluation study OR evaluation studies OR follow-up study OR follow-up studies OR interrupted time series OR longitudinal study OR longitudinal studies OR non-randomised OR non-randomized OR nonrandomised OR nonrandomized OR non randomised OR non randomized OR program evaluation OR programme evaluation OR prospective study OR prospective studies OR quantitative study OR quantitative studies OR quasi experimental OR repeated measures

Set 9

7 AND 8

Supplementary Search Strategy for Scopus:

Set 1

[Title/abstract/keyword fields]: “Adult onset diabetes” OR “late onset diabetes” OR “latent diabetes” OR “mature onset diabetes” OR MODY OR NIDDM OR “noninsulin-

dependent diabetes” OR “slow onset diabetes” OR “stable onset diabetes” OR “type 2 diabetes” OR “type II diabetes” OR T2DM OR T2D

Set 2

[Title/abstract/keyword fields]: “diabetes insipidus”

Set 3

1 AND NOT 2

Set 4

[Title/abstract/keyword fields]: screening

Set 5

3 AND 4

Set 6

[IndexTerms]: (Animal* AND NOT human*)

Set 7

5 AND NOT 6

Set 8

[All fields:] Trial* OR “before-and-after stud*” OR cohort OR “comparative stud*” OR Controlled OR “evaluation stud*” OR “follow-up stud*” OR “interrupted time series” OR “longitudinal stud*” OR non-randomi?ed OR “program* evaluation” OR “prospective stud*” OR “quantitative stud*” OR “quasi experimental” OR “repeated measure*”

Set 9

7 AND 8

LIMIT TO: English

Supplementary Search Strategy for Web of Science Platform (Web of Science Core Collection):

Set 1

TS=(“Adult onset diabetes” OR “late onset diabetes” OR “latent diabetes” OR “mature onset diabetes” OR MODY OR NIDDM OR “noninsulin-dependent diabetes” OR “slow onset diabetes” OR “stable onset diabetes” OR “type 2 diabetes” OR “type II diabetes” OR T2DM OR T2D)

Set 2

TS=(Diabetes NEAR/0 insipidus)

Set 3

#1 NOT #2

Set 4

TS=(screening)

Set 5

#3 AND #4

Set 6

TS=(Trial* OR “before-and-after stud*” OR cohort OR “comparative stud*” OR Controlled OR “evaluation stud*” OR “follow-up stud*” OR “interrupted time series” OR “longitudinal stud*” OR non-randomi?ed OR “program* evaluation” OR “prospective stud*” OR “quantitative stud*” OR “quasi experimental” OR “repeated measure*”)

Set 7

#5 AND #6

Exclude Medline

Refine: Web of Science Core Collection

Refine English

Supplementary Search Strategy for Web of Science Platform (Biological Abstracts):

Set 1

TS=(“Adult onset diabetes” OR “late onset diabetes” OR “latent diabetes” OR “mature onset diabetes” OR MODY OR NIDDM OR “noninsulin-dependent diabetes” OR “slow onset diabetes” OR “stable onset diabetes” OR “type 2 diabetes” OR “type II diabetes” OR T2DM OR T2D)

Set 2

TS=(Diabetes NEAR/0 insipidus)

Set 3

#1 NOT #2

Set 4

TS=(screening)

Set 5

#3 AND #4

Set 6

TS=(Trial* OR “before-and-after stud*” OR cohort OR “comparative stud*” OR Controlled OR “evaluation stud*” OR “follow-up stud*” OR “interrupted time series” OR “longitudinal stud*” OR non-randomi?ed OR “program* evaluation” OR “prospective stud*” OR “quantitative stud*” OR “quasi experimental” OR “repeated measure*”)

Set 7

#5 AND #6

Exclude Medline

Refine: Biological Abstract

Refine English

Supplementary Search Strategy for Web of Science Platform (SciELO Citation Index):

Set 1

TS=("Adult onset diabetes" OR "late onset diabetes" OR "latent diabetes" OR "mature onset diabetes" OR MODY OR NIDDM OR "noninsulin-dependent diabetes" OR "slow onset diabetes" OR "stable onset diabetes" OR "type 2 diabetes" OR "type II diabetes" OR T2DM OR T2D)

Set 2

TS=(Diabetes NEAR/0 insipidus)

Set 3

#1 NOT #2

Set 4

TS=(screening)

Set 5

#3 AND #4

Set 6

TS=(Trial* OR "before-and-after stud*" OR cohort OR "comparative stud*" OR Controlled OR "evaluation stud*" OR "follow-up stud*" OR "interrupted time series" OR "longitudinal stud*" OR non-randomi?ed OR "program* evaluation" OR "prospective stud*" OR "quantitative stud*" OR "quasi experimental" OR "repeated measure*")

Set 7

#5 AND #6

Exclude Medline

Refine: SciELO

Refine English

Supplementary Search Strategy for EBSCOhost platform (Academic Search Premier)

Set 1

SU: Non-insulin-dependent diabetes

OR

[Title field:] Adult onset diabetes OR late onset diabetes OR latent diabetes OR mature onset diabetes OR MODY OR NIDDM OR noninsulin-dependent diabetes OR slow

onset diabetes OR stable onset diabetes OR type 2 diabetes OR type II diabetes OR T2DM OR T2D

OR

[Abstract field:] Adult onset diabetes OR late onset diabetes OR latent diabetes OR mature onset diabetes OR MODY OR NIDDM OR noninsulin-dependent diabetes OR slow onset diabetes OR stable onset diabetes OR type 2 diabetes OR type II diabetes OR T2DM OR T2D

Set 2

SU: Diabetes Insipidus

OR

[Title field:] diabetes insipidus

OR

[Abstract field:] diabetes insipidus

Set 3

S1 NOT S2

Set 4

SU: Medical screening

OR

[Title field:] screening

OR

[Abstract field:] screening

Set 5

3 AND 4

Set 6

SU: Animals

Set 7

S5 NOT S6

Set 8

TX: Trial* OR before-and-after stud* OR cohort OR comparative stud* OR controlled OR evaluation stud* OR follow-up stud* OR interrupted time series OR longitudinal stud* OR non-randomised OR non-randomized OR nonrandomised OR nonrandomized OR “non randomised” OR “non randomized” OR program* evaluation OR prospective stud* OR quantitative stud* OR quasi experimental OR repeated measures

Set 9

S7 AND S8

Limit to Language: English

Supplementary Search Strategy for EBSCOhost platform (CINAHL)

Set 1

MM: Diabetes, Mellitus, Type 2

OR

[Title field:] Adult onset diabetes OR late onset diabetes OR latent diabetes OR mature onset diabetes OR MODY OR NIDDM OR noninsulin-dependent diabetes OR slow onset diabetes OR stable onset diabetes OR type 2 diabetes OR type II diabetes OR T2DM OR T2D

OR

[Abstract field:] Adult onset diabetes OR late onset diabetes OR latent diabetes OR mature onset diabetes OR MODY OR NIDDM OR noninsulin-dependent diabetes OR slow onset diabetes OR stable onset diabetes OR type 2 diabetes OR type II diabetes OR T2DM OR T2D

Set 2

MH: Diabetes Insipidus

OR

[Title field:] diabetes insipidus

OR

[Abstract field:] diabetes insipidus

Set 3

S1 NOT S2

Set 4

MH: Health screening

OR

[Title field:] screening

OR

[Abstract field:] screening

Set 5

3 AND 4

Set 6

MH: Animals

Set 7

5 NOT 6

Set 8

[TX]: Trial* OR before-and-after stud* OR cohort OR comparative stud* OR controlled OR evaluation stud* OR follow-up stud* OR interrupted time series OR longitudinal stud* OR non-randomised OR non-randomized OR nonrandomised OR nonrandomized OR "non randomised" OR " non randomized" OR program* evaluation OR prospective stud* OR quantitative stud* OR quasi experimental OR repeated measures

Set 9

7 AND 8

Limit to English

Supplementary Search Strategy for EBSCOhost platform (Health Source: Nursing/Academic Edition)

Set 1

DE "non-insulin-dependent diabetes"

OR

[Title field:] Adult onset diabetes OR late onset diabetes OR latent diabetes OR mature onset diabetes OR MODY OR NIDDM OR noninsulin-dependent diabetes OR slow onset diabetes OR stable onset diabetes OR type 2 diabetes OR type II diabetes OR T2DM OR T2D

OR

[Abstract field:] Adult onset diabetes OR late onset diabetes OR latent diabetes OR mature onset diabetes OR MODY OR NIDDM OR noninsulin-dependent diabetes OR slow onset diabetes OR stable onset diabetes OR type 2 diabetes OR type II diabetes OR T2DM OR T2D

Set 2

DE "diabetes Insipidus"

OR

[Title field:] diabetes insipidus

OR

[Abstract field:] diabetes insipidus

Set 3

1 NOT 2

Set 4

DE "MEDICAL screening"

OR

[Title field:] screening

OR

[Abstract field:] screening

Set 5

3 AND 4

Set 6

DE “Animals”

Set 7

5 NOT 6

Set 8

[TX]: Trial* OR before-and-after stud* OR cohort OR comparative stud* OR controlled OR evaluation stud* OR follow-up stud* OR interrupted time series OR longitudinal stud* OR non-randomised OR non-randomized OR nonrandomised OR nonrandomized OR “non randomised” OR “non randomized” OR program* evaluation OR prospective stud* OR quantitative stud* OR quasi experimental OR repeated measures

Set 9

7 AND 8

Limit to English

Supplementary Search Strategy for OpenGrey

diabetes mellitus AND screening

Refine to English Language

Supplementary Search Strategy for Conference abstracts from the European Association for the Study of Diabetes (EASD) meeting

screening

Filter by Abstract

Filter by Keyword: Prevention of type 2 diabetes

Supplementary Search Strategy for National Institute for Health Research Economic Evaluation Database (NHS EED)

Title (Diabetes mellitus AND screening)

Supplementary Search Strategy for Cost-Effectiveness Analysis Registry (CEA)

Title (Diabetes AND screening)

Appendix

Appendix 1: BMC Systematic Reviews Instructions to Authors

As per mini dissertation instructions the following have been directly copied from https://bmcpublichealth.biomedcentral.com/submission-guidelines/preparing-your-manuscript/research-article

Research article

Criteria

Research articles should report on original primary research or new experimental or computational methods, tests or procedures. Manuscripts reporting results of a clinical trial must conform to CONSORT 2010 guidelines. Authors of randomized controlled trials should submit a complete CONSORT checklist alongside their manuscript, available at www.consort-statement.org. Research articles may also report on systematic reviews of published research provided they adhere to the appropriate reporting guidelines which are detailed in our editorial policies. Please note that non-commissioned pooled analyses of selected published research and bibliometric analyses will not be considered. Studies reporting descriptive results from a single institution will only be considered if analogous data have not been previously published in a peer reviewed journal and the conclusions provide distinct insights that are of relevance to a regional or international audience.

Authors can receive free advice on how and where to share their research data, according to their specific research community, from a team of research data editors by contacting our Research Data Helpdesk.

Preparing your manuscript

The information below details the section headings that you should include in your manuscript and what information should be within each section.

Please note that your manuscript must include a 'Declarations' section including all of the subheadings (please see below for more information).

Title page

The title page should:

- present a title that includes, if appropriate, the study design e.g.:

    - "A versus B in the treatment of C: a randomized controlled trial", "X is a risk factor for Y: a case control study", "What is the impact of factor X on subject Y: A systematic review"
    - or for non-clinical or non-research studies a description of what the article reports
- list the full names and institutional addresses for all authors
    - if a collaboration group should be listed as an author, please list the Group name as an author. If you would like the names of the individual members of the Group to be searchable through their individual PubMed records, please include this information in the “Acknowledgements” section in accordance with the instructions below
- indicate the corresponding author

Abstract

The Abstract should not exceed 350 words. Please minimize the use of abbreviations and do not cite references in the abstract. Reports of randomized controlled trials should follow the CONSORT extension for abstracts. The abstract must include the following separate sections:

- **Background:** the context and purpose of the study
- **Methods:** how the study was performed and statistical tests used
- **Results:** the main findings
- **Conclusions:** brief summary and potential implications
- **Trial registration:** If your article reports the results of a health care intervention on human participants, it must be registered in an appropriate registry and the registration number and date of registration should be in stated in this section. If it was not registered prospectively (before enrollment of the first participant), you should include the words 'retrospectively registered'. See our editorial policies for more information on trial registration

Keywords

Three to ten keywords representing the main content of the article.

Background

The Background section should explain the background to the study, its aims, a summary of the existing literature and why this study was necessary or its contribution to the field.

Methods

The methods section should include:

- the aim, design and setting of the study
- the characteristics of participants or description of materials
- a clear description of all processes, interventions and comparisons. Generic drug names should generally be used. When proprietary brands are used in research, include the brand names in parentheses
- the type of statistical analysis used, including a power calculation if appropriate

Results

This should include the findings of the study including, if appropriate, results of statistical analysis which must be included either in the text or as tables and figures.

Discussion

This section should discuss the implications of the findings in context of existing research and highlight limitations of the study.

Conclusions

This should state clearly the main conclusions and provide an explanation of the importance and relevance of the study reported.

List of abbreviations

If abbreviations are used in the text they should be defined in the text at first use, and a list of abbreviations should be provided.

Declarations

All manuscripts must contain the following sections under the heading 'Declarations':

- Ethics approval and consent to participate
- Consent for publication
- Availability of data and materials
- Competing interests
- Funding
- Authors' contributions
- Acknowledgements
- Authors' information (optional)

Please see below for details on the information to be included in these sections.

If any of the sections are not relevant to your manuscript, please include the heading and write 'Not applicable' for that section.

Ethics approval and consent to participate

Manuscripts reporting studies involving human participants, human data or human tissue must:

- include a statement on ethics approval and consent (even where the need for approval was waived)
- include the name of the ethics committee that approved the study and the committee's reference number if appropriate

Studies involving animals must include a statement on ethics approval and for experimental studies involving client-owned animals, authors must also include a statement on informed consent from the client or owner.

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If your manuscript does not report on or involve the use of any animal or human data or tissue, please state "Not applicable" in this section.

Consent for publication

If your manuscript contains any individual person's data in any form (including any individual details, images or videos), consent for publication must be obtained from that person, or in the case of children, their parent or legal guardian. All presentations of case reports must have consent for publication.

You can use your institutional consent form or our consent form if you prefer. You should not send the form to us on submission, but we may request to see a copy at any stage (including after publication).

See our editorial policies for more information on consent for publication.

If your manuscript does not contain data from any individual person, please state "Not applicable" in this section.

Availability of data and materials

All manuscripts must include an 'Availability of data and materials' statement. Data availability statements should include information on where data supporting the results reported in the article can be found including, where applicable, hyperlinks to publicly archived datasets analysed or generated during the study. By data we mean the minimal dataset that would be necessary to interpret, replicate and build upon the findings reported in the article. We recognise it is not always possible to share research data publicly, for instance when individual privacy could be compromised, and in such instances data availability should still be stated in the manuscript along with any conditions for access.

Data availability statements can take one of the following forms (or a combination of more than one if required for multiple datasets):

- The datasets generated and/or analysed during the current study are available in the [NAME] repository, [PERSISTENT WEB LINK TO DATASETS]
- The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.
- All data generated or analysed during this study are included in this published article [and its supplementary information files].
- The datasets generated and/or analysed during the current study are not publicly available due [REASON WHY DATA ARE NOT PUBLIC] but are available from the corresponding author on reasonable request.
- Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.
- The data that support the findings of this study are available from [third party name] but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of [third party name].
- Not applicable. If your manuscript does not contain any data, please state 'Not applicable' in this section.

More examples of template data availability statements, which include examples of openly available and restricted access datasets, are available here.

BioMed Central also requires that authors cite any publicly available data on which the conclusions of the paper rely in the manuscript. Data citations should include a persistent identifier (such as a DOI) and should ideally be included in the reference list. Citations of datasets, when they appear in the reference list, should include the minimum information recommended by DataCite and follow journal style. Dataset identifiers including DOIs should be expressed as full URLs.

For example:

Hao Z, AghaKouchak A, Nakhjiri N, Farahmand A. Global integrated drought monitoring and prediction system (GIDMaPS) data sets. figshare. 2014. http://dx.doi.org/10.6084/m9.figshare.853801

With the corresponding text in the Availability of data and materials statement:

The datasets generated during and/or analysed during the current study are available in the [NAME] repository, [PERSISTENT WEB LINK TO DATASETS].[Reference number]

If you wish to co-submit a data note describing your data to be published in *BMC Research Notes*, you can do so by visiting our submission portal. Data notes support open data and help authors to comply with funder policies on data sharing. Co-published data notes will be linked to the research article the data support (example).

Competing interests

All financial and non-financial competing interests must be declared in this section.

See our editorial policies for a full explanation of competing interests. If you are unsure whether you or any of your co-authors have a competing interest please contact the editorial office.

Please use the authors initials to refer to each authors' competing interests in this section.

If you do not have any competing interests, please state "The authors declare that they have no competing interests" in this section.

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Authors' contributions

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Please use initials to refer to each author's contribution in this section, for example: "FC analyzed and interpreted the patient data regarding the hematological disease and the transplant. RH performed the histological examination of the kidney, and was a major contributor in writing the manuscript. All authors read and approved the final manuscript."

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Please acknowledge anyone who contributed towards the article who does not meet the criteria for authorship including anyone who provided professional writing services or materials.

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Footnotes can be used to give additional information, which may include the citation of a reference included in the reference list. They should not consist solely of a reference citation, and they should never include the bibliographic details of a reference. They should also not contain any figures or tables.

Footnotes to the text are numbered consecutively; those to tables should be indicated by superscript lower-case letters (or asterisks for significance values and other statistical data). Footnotes to the title or the authors of the article are not given reference symbols.

Always use footnotes instead of endnotes.

References

Examples of the Vancouver reference style are shown below.

See our editorial policies for author guidance on good citation practice

Web links and URLs: All web links and URLs, including links to the authors' own websites, should be given a reference number and included in the reference list rather than within the text of the manuscript. They should be provided in full, including both the title of the site and the URL, as well as the date the site was accessed, in the following format: The Mouse Tumor Biology Database. http://tumor.informatics.jax.org/mtbwi/index.do. Accessed 20 May 2013. If an author or group of authors can clearly be associated with a web link, such as for weblogs, then they should be included in the reference.

Example reference style:

Article within a journal

Smith JJ. The world of science. Am J Sci. 1999;36:234-5.

Article within a journal (no page numbers)

Rohrmann S, Overvad K, Bueno-de-Mesquita HB, Jakobsen MU, Egeberg R, Tjønneland A, et al. Meat consumption and mortality - results from the European Prospective Investigation into Cancer and Nutrition. BMC Medicine. 2013;11:63.

Article within a journal by DOI

Slifka MK, Whitton JL. Clinical implications of dysregulated cytokine production. Dig J Mol Med. 2000; doi:10.1007/s801090000086.

Article within a journal supplement

Frumin AM, Nussbaum J, Esposito M. Functional asplenia: demonstration of splenic activity by bone marrow scan. Blood 1979;59 Suppl 1:26-32.

Book chapter, or an article within a book

Wyllie AH, Kerr JFR, Currie AR. Cell death: the significance of apoptosis. In: Bourne GH, Danielli JF, Jeon KW, editors. International review of cytology. London: Academic; 1980. p. 251-306.

OnlineFirst chapter in a series (without a volume designation but with a DOI)

Saito Y, Hyuga H. Rate equation approaches to amplification of enantiomeric excess and chiral symmetry breaking. Top Curr Chem. 2007. doi:10.1007/128_2006_108.

Complete book, authored

Blenkinsopp A, Paxton P. Symptoms in the pharmacy: a guide to the management of common illness. 3rd ed. Oxford: Blackwell Science; 1998.

Online document

Doe J. Title of subordinate document. In: The dictionary of substances and their effects. Royal Society of Chemistry. 1999. http://www.rsc.org/dose/title of subordinate document. Accessed 15 Jan 1999.

Online database

Healthwise Knowledgebase. US Pharmacopeia, Rockville. 1998. http://www.healthwise.org. Accessed 21 Sept 1998.

Supplementary material/private homepage

Doe J. Title of supplementary material. 2000. http://www.privatehomepage.com. Accessed 22 Feb 2000.

University site

Doe, J: Title of preprint. http://www.uni-heidelberg.de/mydata.html (1999). Accessed 25 Dec 1999.

FTP site

Doe, J: Trivial HTTP, RFC2169. ftp://ftp.isi.edu/in-notes/rfc2169.txt (1999). Accessed 12 Nov 1999.

Organization site

ISSN International Centre: The ISSN register. http://www.issn.org (2006). Accessed 20 Feb 2007.

Dataset with persistent identifier

Zheng L-Y, Guo X-S, He B, Sun L-J, Peng Y, Dong S-S, et al. Genome data from sweet and grain sorghum (Sorghum bicolor). GigaScience Database. 2011. http://dx.doi.org/10.5524/100012.

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