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Richter, Bernd; Hemmingsen, Bianca; Metzendorf, Maria Inti; Takwoingi, Yemisi

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Intermediate hyperglycaemia as a predictor for the development of type 2 diabetes: prognostic factor exemplar review (Protocol)

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[Prognosis Protocol]

Intermediate hyperglycaemia as a predictor for the development of type 2 diabetes: prognostic factor exemplar review

Bernd Richter¹, Bianca Hemmingsen², Maria-Inti Metzendorf¹, Yemisi Takwoingi³

¹Cochrane Metabolic and Endocrine Disorders Group, Institute of General Practice, Medical Faculty of the Heinrich-Heine-University Düsseldorf, Düsseldorf, Germany. ²Department of Internal Medicine, Herlev University Hospital, Herlev, Denmark. ³Institute of Applied Health Research, University of Birmingham, Birmingham, UK

Contact address: Bernd Richter, Cochrane Metabolic and Endocrine Disorders Group, Institute of General Practice, Medical Faculty of the Heinrich-Heine-University Düsseldorf, PO Box 101007, Düsseldorf, 40001, Germany. richterb@uni-duesseldorf.de.

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ABSTRACT

This is a protocol for a Cochrane Review (Prognosis). The objectives are as follows:

To assess whether intermediate hyperglycaemia is a predictor for the development of type 2 diabetes mellitus (T2DM).

BACKGROUND

'Prediabetes', 'borderline diabetes', the 'prediabetic stage', 'high risk of diabetes', 'dysglycaemia' or 'intermediate hyperglycaemia' are often characterised by various measurements of elevated blood glucose concentrations, such as (isolated) impaired fasting glucose (IFG), (isolated) impaired glucose tolerance (IGT), (isolated) elevated glycosylated haemoglobin A1c (HbA1c) or combinations of these conditions (WHO/IDF 2006). Elevated blood glucose levels that indicate hyperglycaemia are too high to be considered normal, but are below the diagnostic threshold for type 2 diabetes mellitus (T2DM). Therefore, due to the continuous glycaemic spectrum from the normal to the diabetic stage, a sound evidence base is needed to define glycaemic thresholds for people at high risk of T2DM, especially because dysglycaemia is commonly an asymptomatic condition, and naturally often remains

'undiagnosed' (CDC 2015). The various terms used to describe the diverse stages of hyperglycaemia may cause people to have marked emotional reactions. For example, the term 'prediabetes' may imply (at least for non-experts) that the disease diabetes is unavoidable, whereas (high) risk of diabetes has the positive connotation of possibly being able to avoid the disease altogether. In addition to the disputable construct of intermediate health states termed 'prediseases' (Viera 2011), many people may associate the label 'prediabetes' with dire consequences. Alternatively, any diagnosis of 'prediabetes' may be an opportunity to review, for example, eating habits and physical activity levels, thus enabling 'affected' individuals to actively change their way of life.

Several institutional bodies like the American Diabetes Association (ADA) and the World Health Organization (WHO) established commonly-used criteria to define people who are at a high risk of

developing T2DM.

- In 1979, the National Diabetes Data Group (NDDG) described glucose intolerance as a concept of a metabolic state intermediate between normoglycaemia and diabetes (NDDG 1979). NDDG defined this IGT by an elevated two-hour plasma glucose concentration (7.8 mmol/L to 11.1 mmol/L or 140 mg/dL to 199 mg/dL) two hours after a 75 g glucose load on the oral glucose tolerance test (OGTT).

- In 1997, the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus and later the WHO defined two intermediate states of glucose regulation existing between regular glucose homeostasis and diabetes: IGT was diagnosed two hours after a 75 g OGTT by a plasma glucose level of 7.8 mmol/L to 11.1 mmol/L (140 mg/dL to 199 mg/dL) or by the concept of IFG (ADA 1997; WHO 1999). The initial definition of IFG was a fasting plasma glucose (FPG) level of 6.1 mmol/L to 6.9 mmol/L (110 mg/dL to 125 mg/dL). In 2003, the ADA reduced the lower threshold to 5.6 mmol/L (100 mg/dL) (ADA 2003). However, the WHO did not endorse this lower cut-off point for IFG (WHO/IDF 2006).

- More recently, an elevated HbA1c has been introduced to identify people at high risk of developing T2DM. In 2009, the International Expert Committee (IEC) suggested HbA1c measurements of 6.0% to 6.4% (42 mmol/mol to 46 mmol/mol) to identify people at a high risk of T2DM (IEC 2009). In 2010, the ADA re-defined this HbA1c level as 5.7% to 6.4% (39 mmol/mol to 46 mmol/mol) (ADA 2010), a decision not endorsed by WHO, IEC or other organisations.

The various glycaemic tests do not identify the same people at risk, as there is an imperfect overlap among the glycaemic modalities available to define intermediate hyperglycaemia (Cheng 2006; Gosmanov 2014; Morris 2013; Selvin 2011). Unlike IFG and IGT, HbA1c reflects longer-term glycaemic control, i.e. how a person's blood glucose concentrations have been during the preceding two to three months (Inzucchi 2012). Compared with IFG and IGT measurements, HbA1c assessments have less intrapersonal variability when repeated. However, haemoglobin variants, genetic haemoglobinopathies, thalassemias and iron deficiency anaemia substantially influence HbA1c measurements (Mostafa 2011). The FPG thresholds of defining IFG and the question whether HbA1c is an adequate tool to diagnose intermediate hyperglycaemia are still debated (Buysschaert 2011; Buysschaert 2016). In studies investigating the risk of intermediate hyperglycaemia the effects are probably underestimated if time-dependent effects are not taken into account (Lind 2009). On the other hand, it is questioned whether HbA1c is the right outcome for studies of diabetes at all (Lipska 2017).

Also, IFG and IGT differ in their age and sex distribution and both increase with advancing age (Nathan 2007), as glucose tolerance

deteriorates with age (Gale 2013). Ethnicity and geography are additional important features: the prevalence of an elevated HbA1c in non-Hispanic black people is twice as high as in non-Hispanic white people and the opposite is true for IGT (Selvin 2011; Ziemer 2010). The number of people identified in South Asian compared with European cohorts and the associated cardiovascular disease (CVD) risk associated with intermediate hyperglycaemia depends on how 'prediabetes' is diagnosed (Eastwood 2016).

The increase in T2DM results from an interaction between genetic and environmental factors reflecting behavioural changes over time such as decreased physical activity levels and increased body weight (DeFronzo 2011; Nathan 2007). Both IFG and IGT are insulin-resistant states and insulin resistance is thought to be the core defect in T2DM: people with (isolated) IFG predominantly have β -cell dysfunction with impaired insulin secretion (DeFronzo 1989), moderate hepatic insulin resistance, but near-normal muscle insulin sensitivity. The consequence is an excessive fasting hepatic glucose production followed by an elevated FPG. During an OGTT the early insulin response (0 to 30/60 min) is impaired, resulting in an excessive early rise in post-load glucose (PG). The late insulin response (60 to 120 min) appears intact and the two-hour PG returns to its approximately starting FPG level (DeFronzo 2011; Nathan 2007). People with (isolated) IGT have normal to slightly reduced hepatic insulin sensitivity and moderate to severe muscle insulin resistance (Abdul-Ghani 2006; Jensen 2002). During an OGTT the early *and* the late insulin response are impaired. Hyperglycaemia is progressive and prolonged after the glucose load, the two-hour PG remains above its starting FPG level (DeFronzo 2011; Nathan 2007).

There are some known risk indicators for the development of T2DM, e.g. a positive family history, gestational diabetes mellitus, obesity, ethnicity, polycystic ovarian syndrome, impaired insulin secretion and insulin resistance, abnormal coagulation factors and endothelial dysfunction. However, the evidence base for the weight of a single risk indicator and the interplay of various factors is still under investigation. Type 2 diabetes mellitus is a rather complex metabolic state and could be described as an asymptomatic risk factor for a future disease (Yudkin 2016), and hence prediabetes a risk factor for another risk factor (Nathan 2007).

Diabetes is a category, whereas IFG and IGT reflect a continuous variable with more or less arbitrarily chosen cut-off points (Yudkin 1990; Yudkin 2014). The reduced lower threshold of 5.6 mmol/L (100 mg/dL) to define IFG by ADA 2003 substantially increased the prevalence of IFG with potential significant impact on public health and socioeconomic issues (Davidson 2003; Yudkin 2014; Yudkin 2016). Others argue that even if it was only possible to delay the onset of diabetes by detecting and treating 'prediabetes', substantial benefits might ensue (Cefalu 2016). Interestingly, some people with intermediate hyperglycaemia will not develop T2DM, and some people will return or 'regress' to normoglycaemia. In the Diabetes Prevention Program (DPP) the hazard ratio (HR)

of developing T2DM was 0.44 (95% confidence interval (CI) 0.37 to 0.55) in people having at least one normal OGTT during the DPP compared with people who never regressed to normoglycaemia during the DPP (Perreault 2012; Perreault 2014). The ADA associated regression with remission and defined it as a partial or complete diabetes remission of glycaemic measurements for at least one year without pharmacological or surgical interventions (Buse 2009). This could have significant impact on “the therapeutic strategy from diabetes prevention and lifelong glucose-lowering treatment to induction of regression and monitoring for relapse” (Yakubovich 2012).

OBJECTIVES

To assess whether intermediate hyperglycaemia is a predictor for the development of type 2 diabetes mellitus (T2DM).

METHODS

Criteria for considering studies for this review

Study design

To investigate intermediate hyperglycaemia as a possible predictor (exposition) for the development of T2DM, the adequate study design to investigate the long-term transition between ‘prediabetes’ and T2DM is a prospective cohort study. Prognostic studies are studies investigating variables which are predictive of future events as well as studies of aetiological factors (Altman 2001), which is why this review is called a prognostic factor exemplar review.

Inclusion criteria

Our outcome of primary interest is the diagnosis of newly developed T2DM (T2DM incidence) in individuals with intermediate hyperglycaemia, defined by impaired fasting glucose (IFG), impaired glucose tolerance (IGT), elevated HbA1c or any combination of these.

- T2DM incidence should be diagnosed by blood glucose measurements such as fasting plasma glucose (FPG), two-hour post-load glucose (PG) or HbA1c. Diagnosis may be combined with self-reported diabetes, physician-diagnosed diabetes or use of antidiabetic medications such as oral hypoglycaemic drugs or insulin are possible.

- Standard definitions of intermediate hyperglycaemia, i.e. cut-off values for IFG, IGT or elevated HbA1c as defined by ADA or WHO (ADA 1997; ADA 2003; ADA 2010; ICH 1997; IEC 2009; WHO 1998; WHO/IDF 2006).

Exclusion criteria

- Intervention trials and study designs other than prospective cohort studies.
- Predefined unhealthy cohort at baseline or substantial comorbidities at baseline (e.g. IFG in individuals with hypertension or persons with coronary heart disease and IGT).
- Missing data on transition from intermediate hyperglycaemia to T2DM.
- Follow-up period after baseline assessment not specified.
- Type 2 diabetes incidence evaluated by documents (e.g. hospital records, retrospective use of databases) or self-report only.
- Conference abstracts.

Search methods for identification of studies

We will search the following sources from inception of each database to the specified date.

- Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present.
- Embase 1974 to 2016 Week 50.
- ClinicalTrials.gov.
- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) Search Portal (<http://apps.who.int/trialsearch/>).

The search strategy will consist of two modules.

- Strategy A: ‘Prediabetes’ as predictor for cardiovascular disease (CVD), mortality, stroke, cancer, micro/macrovacular complications (population block (prediabetes + prognosis filter)) OR prediabetes risk factors/diagnostic criteria (IFG, IGT, HbA1c adjacent prognosis terms) AND outcomes (diabetes complications, micro/macro vascular, mortality)
- Strategy B: ‘Prediabetes’ as predictor for diabetes incidence (population block (prediabetes + prognosis filter)) OR prediabetes risk factors/diagnostic criteria (IFG, IGT, HbA1c adjacent prognosis terms) AND outcomes (diabetes incidence).

We will combine both strategies because it is likely that search results for ‘prediabetes’ as a predictor for complications may also contain data on diabetes incidence. The search strategy has been developed using analytical text mining of 21 relevant diabetes complications studies and 22 relevant diabetes incidence studies already known and selected by review author BR. We used the tools PubReMiner, TerMine and AntConc and applied the prognosis filters by the Hedges Team, McMaster University, Canada. Additionally, we extracted studies from 16 identified meta-analyses (Echouffo-Tcheugui 2016; Erqou 2013; Ford 2010; Hope 2016; Huang 2014; Huang 2014a; Huang 2016; Lee 2012; Morris 2013; Santos-Oliveira 2011; Sarwar 2010; Schottker 2016; Twito 2015; Xu 2015; Zhang 2012; Zhong 2016).

The fundamental problem with this type of review is the difficulty to define the population of interest, i.e. people with intermediate

hyperglycaemia. We expect a great number of terms describing this population, such as people with prediabetes, mentioning of IFG, IGT or HbA1c somewhere in the title or abstract, and terms like risk factors, predictors, prevalence, incidence or several other concepts which cannot be foreseen by the development of a regular search strategy. One way to address this problem is to formulate very sensitive search strategies with the consequence of being faced with tens of thousands database hits, which is currently unfeasible but may be addressed in the future with advanced data-mining technologies. Instead, we decided to establish a more specific search, augmented by thorough identification of systematic reviews addressing our review question and checking of reference lists.

We will continuously apply a MEDLINE (via Ovid SP) email alert service established by the Cochrane Metabolic and Endocrine Disorders (CMED) Group to identify newly published studies using the same search strategy as described for MEDLINE (for details on search strategies, see [Appendix 1](#)). If we identify new trials for inclusion, we will evaluate these, and incorporate the findings into our review ([Beller 2013](#)).

If we detect additional key words of relevance during any of the electronic or other searches, we will modify the electronic search strategies to incorporate these terms.

Selection of studies

Two review authors (BR and BH) will independently scan the abstract, title, or both, of every record we will retrieve in the literature searches, to determine which trials to be assessed further. We will investigate the full text of all potentially relevant articles. We will resolve discrepancies through consensus or by recourse to a third review author (MIM). We will prepare a flow diagram of the number of studies identified and excluded at each stage in accordance with the PRISMA (Preferred reporting items for systematic reviews and meta-analyses) flow diagram of trial selection ([Liberati 2009](#)).

Data extraction and management

For studies that fulfil our inclusion criteria, one review author (BR) will extract key study characteristics, inclusion and exclusion criteria of study participants, stated aim of the study, definitions of exposure and outcome (normoglycaemia, intermediate glycaemia and type 2 diabetes incidence), baseline characteristics of study participants, data on transition from intermediate hyperglycaemia (as defined by IFG, IGT, elevated HbA1c or combinations thereof) to T2DM and assess risk of bias. Another author (MIM) will check these data extractions and we will resolve any disagreements by discussion or, if required, by consultation with a third review author (BH)

Dealing with companion publications

In the event of companion documents or multiple reports of a prospective cohort study because of different time points investigated, we will focus on the analysis of the publication describing the longest follow-up from baseline and extract data from shorter follow-ups in case some expositions were not reported in the publication on the longest follow-up (e.g. the most recent paper might describe the association between elevated HbA1c and T2DM incidence, but an older publication might describe the association between IGT and T2DM incidence). Companion documents or multiple reports of a primary study will be listed as secondary references under the primary reference of the included, ongoing or excluded study.

Assessment of risk of bias in included studies

One review author (BR) will assess the risk of bias of each included study and another review author (MIM) will check on accuracy of this assessment. We will resolve any disagreements by consensus, or by consultation with a third review author (BH). We will use a tailored version of the Quality In Prognosis Studies (QUIPS) tool ([Dretzke 2014](#); [Hayden 2013](#)) for assessing risk of bias in studies of prognostic factors, see [Appendix 2](#). We will investigate the influence of low risk of bias studies (low risk of bias in all domains, i.e. study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding, statistical analysis and reporting) versus unclear/high risk of bias studies (unclear or high risk of bias in at least one of these domains).

Data synthesis

Our primary aim is to provide a transparent overview of the whole data matrix describing a wide variety of possible associations between various isolated and combined definitions of intermediate hyperglycaemia and incident diabetes in dissimilar populations covering diverse time periods.

First, we will group studies on similar exposure variables, i.e. (isolated) IFG 5.6 mmol/L, (isolated) IFG 6.1 mmol/L, (isolated) IGT, IFG and IGT, HbA1c 6.0% to 6.4% and HbA1c 5.7% to 6.4%. Then we will subgroup different ethnicities under these exposure variables at comparable follow-up periods.

We expect the following outcome measures.

- Cases (cumulative incidence at follow-up; e.g. 20 new diabetes cases of 400 people with IFG at baseline (5%)).
- Cumulative incidence rates (cases per 1000 person-years).
- Odds ratios (ORs), rate ratios (RsR), hazard ratios (HRs).

We therefore plan to perform random-effects meta-analyses on proportions, incidence rate differences ([Spittal 2015](#)), incidence RRs, ORs, relative risks and time-to-event data (HRs).

For incidence rates where reported, we will try to calculate the person-time exposed from the number of cases occurring in the exposed ('prediabetic') group and non-exposed (normoglycaemic)

group. We will then establish a matrix of exposed cases and person-time as well as non-exposed cases and person time and perform an incidence rate ratio and/or an incidence rate difference random-effects meta-analysis.

In case publications report HRs with associated 95% CIs we will obtain standard errors from these CIs as described in chapter 7.7.7.3 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) and establish a meta-analysis by means of the generic inverse-variance method (RevMan 2014). When possible, we will report both adjusted and unadjusted HRs, but will primarily use adjusted HRs of multivariate models of studies incorporating similar covariates (Dretzke 2014).

Assessment of heterogeneity

We expect substantial clinical heterogeneity within the included prospective cohort studies because of geographical, ethnical and methodological diversity. We do not intend to address statistical heterogeneity (inconsistency) by means of the I^2 statistic because this statistic does not tell us how much the effect size varies, which is what people are interested in when asking about the implications of heterogeneity (Borenstein 2017). Also, the I^2 statistic is problematic in the context of prognostic studies because individual studies often have large sample sizes resulting in narrow CIs which can result in high I^2 values even if inconsistency between studies is moderate (Iorio 2015). Instead, we will report the range of the effects of the random-effects meta-analyses by means of prediction intervals (Borenstein 2017; Higgins 2009; IntHout 2016; Riley 2015). In a random-effects model meta-analysis the prediction interval reflects the whole distribution of effects across study populations including what effect is to be expected in a future study (IntHout 2016; Riley 2015).

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Sensitivity analysis

We plan to perform sensitivity analyses to explore the influence of the following factors (when applicable) on effect sizes by restricting analysis to the following.

- Taking into account risk of bias, as specified in the assessment of risk of bias in the included studies section.
- Very long or large studies to establish the extent to which they dominate the results.

Subgroup analysis

Because we are stratifying analyses by exposure variables and ethnicity, which we think are the main features creating heterogeneity, we do not plan to perform subgroup analyses. In case we are able to extract a meaningful number of studies (at least 10 studies) specifying diabetes incidence data, we plan to carry out subgroup analyses with investigation of interactions for the subgroups:

- age, depending on data;
- gender.

Should we be able to extract T2DM incidence data for children and adolescents, we will separately report results for this group of study participants.

Quality of evidence

We will create a 'Summary of findings' table using Review Manager 5 (RevMan 5.3) table editor (RevMan 2014). We will use an adapted version of the GRADE framework of prognostic factor research (Huguet 2013) for describing the influence of our exposition variables IFG, IGT, elevated HbA1c and IFG/IGT on the development of T2DM. We will justify all decisions to downgrade the quality of trials using footnotes and we will make comments to aid the reader's understanding of the Cochrane review where necessary.

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* Indicates the major publication for the study

APPENDICES

Appendix I. Search strategies

MEDLINE (Ovid SP)

Whole strategy (combining strategy A: 'prediabetes' as predictor for cardiovascular disease, mortality, stroke, cancer, micro/macrovascular complications and strategy B: 'prediabetes' as predictor for diabetes incidence)

1. Prediabetic state/
2. (prediabet* or pre diabet*).tw.
3. intermediate hyperglyc?emi*.tw.
4. or/1-3
5. incidence.sh. or exp mortality/ or follow-up studies.sh. or prognos*.tw. or predict*.tw. or course*.tw. [prognosis filter sensmax]
6. prognosis/ or diagnosed.tw. or cohort*.mp. or predictor*.tw. or death.tw. or exp models, statistical/ [prognosis filter bestbalance]
7. or/5-6
8. 4 and 7 [Population block (Prediabetes + Prognosis filter)]
9. ((impaired fasting adj2 glucose) or IFG or (impaired adj FPG)).tw
10. (impaired glucose tolerance or IGT).tw.
11. ("HbA(1c)" or HbA1 or HbA1c or "HbA 1c" or ((glycosylated or glycated) adj h?emoglobin)).tw
12. or/9-11
13. (predict* or associa* or prognos*).tw.
14. ((prognostic or predict*) adj2 model?).tw.
15. predictive value?.tw.
16. (risk adj (predict* or factor? or score)).tw.
17. or/13-16
18. (((impaired fasting adj2 glucose) or IFG or "impaired FPG" or impaired glucose tolerance or IGT or "HbA(1c)" or HbA1 or HbA1c or "HbA 1c" or ((glycosylated or glycated) adj h?emoglobin)) adj3 (predict* or associa* or prognos* or ((prognostic or predict*) adj2 model?) or predictive value? or (risk adj (predict* or factor? or score))))).tw. [12 adj3 17 // risk factor block]
19. 8 or 18 [Block 1 or block 2]
20. complication?.tw.
21. mortality.tw.
22. (CHD or CVD).tw.
23. (coronary adj2 disease).tw.
24. (coronar* adj (event? or syndrome?)).tw.
25. (heart adj (failure or disease? or attack? or infarct*)).tw
26. (myocardial adj (infarct* or isch?emi*)).tw.
27. cardiac failure.tw.
28. angina.tw.
29. revasculari*.tw.
30. (stroke or strokes).tw.
31. cerebrovascular.tw.
32. ((brain* or cerebr*) adj (infarct* or isch?emi*)).tw.
33. apoplexy.tw.
34. ((vascular or peripheral arter*) adj disease?).tw.
35. cardiovascular.tw.
36. (neuropath* or polyneuropath*).tw.
37. (retinopath* or maculopath*).tw.
38. (nephropath* or nephrotic or proteinuri* or albuminuri*).tw
39. ((kidney or renal) adj (disease? or failure or transplant*)).tw

(Continued)

40. ((chronic or endstage or end stage) adj (renal or kidney)).tw
41. (CRD or CRF or CKF or CRF or CKD or ESKD or ESKF or ESRD or ESRF).tw
42. (microvascular or macrovascular or ((micro or macro) adj vascular)).tw
43. (cancer or carcino* or neoplas* or tumo?r?).tw.
44. (amputation? or ulcer* or foot or feet or wound*).tw.
45. or/20-44 [3rd block: outcomes]
46. 19 and 45
47. ((diabet* or type 2 or type II or T2D*) adj4 (progress* or inciden* or conversion or develop* or future)).tw. [strategy B]
48. 19 and 47
49. 46 or 48
50. exp animals/ not humans/
51. 49 not 50
52. (gestational or PCOS).tw.
53. 51 not 52
54. (comment or letter or editorial).pt.
55. 53 not 54
56. remove duplicates from 55

Embase (Ovid SP)

Whole strategy (combining strategy A: 'prediabetes' as predictor for cardiovascular disease, mortality, stroke, cancer, micro/macrovascular complications and strategy B: 'prediabetes' as predictor for diabetes incidence)

1. (prediabet* or pre diabet*).tw.
2. intermediate hyperglyc?emi*.tw.
3. or/1-2
4. exp disease course or risk*.mp. or diagnos*.mp. or follow-up.mp. or ep.fs. or outcome.tw. [prognosis filter sensmax]
5. follow-up.mp. or prognos*.tw. or ep.fs. [prognosis filter bestbalance]
6. or/4-5
7. 3 and 6 [Population block (Prediabetes + Prognosis filter)]
8. ((impaired fasting adj2 glucose) or IFG or (impaired adj FPG)).tw
9. (impaired glucose tolerance or IGT).tw.
10. ("HbA(1c)" or HbA1 or HbA1c or "HbA 1c" or ((glycosylated or glyated) adj h?emoglobin)).tw
11. or/8-10
12. (predict* or associa* or prognos*).tw.
13. ((prognostic or predict*) adj2 model?).tw.
14. predictive value?.tw.
15. (risk adj (predict* or factor? or score)).tw.
16. or/12-15
17. (((impaired fasting adj2 glucose) or IFG or "impaired FPG" or impaired glucose tolerance or IGT or "HbA(1c)" or HbA1 or HbA1c or "HbA 1c" or ((glycosylated or glyated) adj h?emoglobin) adj3 (predict* or associa* or prognos* or ((prognostic or predict*) adj2 model?) or predictive value? or (risk adj (predict* or factor? or score))))).tw. [12 adj3 17 // risk factor block]
18. 7 or 17 [block 1 or block 2]
19. complication?.tw.
20. mortality.tw.
21. (CHD or CVD).tw.
22. (coronary adj2 disease).tw.
23. (coronar* adj (event? or syndrome?)).tw.
24. (heart adj (failure or disease? or attack? or infarct?)).tw
25. (myocardial adj (infarct* or isch?emi?)).tw.

(Continued)

26. cardiac failure.tw
27. angina.tw
28. revasculari*.tw
29. (stroke or strokes).tw
30. cerebrovascular.tw
31. ((brain* or cerebr*) adj (infarct* or isch?emi*)).tw
32. apoplexy.tw
33. ((vascular or peripheral arter*) adj disease?).tw
34. cardiovascular.tw
35. (neuropath* or polyneuropath*).tw
36. (retinopath* or maculopath*).tw
37. (nephropath* or nephrotic or proteinuri* or albuminuri*).tw
38. ((kidney or renal) adj (disease? or failure or transplant*)).tw
39. ((chronic or endstage or end stage) adj (renal or kidney)).tw
40. (CRD or CRF or CKF or CRF or CKD or ESKD or ESKF or ESRD or ESRF).tw
41. (microvascular or macrovascular or ((micro or macro) adj vascular)).tw
42. (cancer or carcino* or neoplas* or tumo:r?).tw
43. (amputation? or ulcer* or foot or feet or wound*).tw
44. or/19-43 [3rd block: outcomes]
45. 18 and 44
46. ((diabet* or type 2 or type II or T2D*) adj4 (progress* or inciden* or conversion or develop* or future)).tw. [strategy B]
47. 18 and 46
48. 45 or 47
49. exp animals/ or exp invertebrate/ or animal experiment/ or animal model/ or animal tissue/ or animal cell/ or nonhuman/ [TSC
Portal filter for exclusion of animal references]
50. human/ or normal human/ or human cell/
51. 49 and 50
52. 49 not 51
53. 48 not 52
54. (gestational or PCOS).tw
55. 53 not 54
56. (comment or letter or editorial or conference).pt.
57. 55 not 56
58. remove duplicates from 57

ClinicalTrials.gov (Expert search)

(prediabetes OR prediabetic OR “pre diabetes” OR “pre diabetic” OR “intermediate hyperglycemia” OR “intermediate hyperglycaemia” OR “intermediate hyperglycemic” OR “intermediate hyperglycaemic” OR “impaired glucose tolerance” OR “impaired fasting glucose”) AND (complication OR complications OR mortality OR CHD OR CVD OR coronary OR heart OR myocardial OR infarct OR infarction OR infarcts OR infarctions OR ischemia OR ischemic OR ischaemia OR ischaemic OR failure OR angina OR revascularization OR revascularisation OR revascularizations OR revascularisations OR stroke OR strokes OR cerebrovascular OR apoplexy OR vascular or peripheral OR cardiovascular OR neuropathy OR neuropathies OR polyneuropathy OR polyneuropathies OR retinopathy OR retinopathies OR maculopathy OR maculopathies OR nephropathy OR nephropathies OR nephrotic OR proteinuria OR proteinuric OR albuminuria OR kidney OR renal OR CRD OR CRF OR CKF OR CRF OR CKD OR ESKD OR ESKF OR ESRD OR ESRF OR microvascular OR macrovascular OR “micro vascular” OR “macro vascular” OR cancer OR carcinoma OR neoplasm OR neoplasms OR tumor OR tumors OR tumour OR tumours OR amputation OR amputations OR ulcer OR foot OR feet OR wounds OR (diabetes OR diabetic OR “type 2” OR “type II” OR T2D OR T2DM) AND (progress OR progression OR progressed OR incident OR incidence OR conversion OR developed OR development OR future)) [OUTCOME]

(Continued)

ICTRP Search Portal (Standard search)

prediabet* AND prognos* OR
prediabet* AND predict* OR
prediabet* AND inciden* OR
prediabet* AND mortality OR
prediabet* AND prevent* OR
prediabet* AND progress* OR
prediabet* AND develop* OR
pre diabet* AND prognos* OR
pre diabet* AND predict* OR
pre diabet* AND inciden* OR
pre diabet* AND mortality OR
pre diabet* AND prevent* OR
pre diabet* AND progress* OR
pre diabet* AND develop* OR
impaired glucose tolerance AND prognos* OR
impaired glucose tolerance AND predict* OR
impaired glucose tolerance AND inciden* OR
impaired glucose tolerance AND mortality OR
impaired glucose tolerance AND prevent* OR
impaired glucose tolerance AND progress* OR
impaired glucose tolerance AND develop* OR
impaired fasting glucose AND prognos* OR
impaired fasting glucose AND predict* OR
impaired fasting glucose AND inciden* OR
impaired fasting glucose AND mortality OR
impaired fasting glucose AND prevent* OR
impaired fasting glucose AND progress* OR
impaired fasting glucose AND develop* OR
HbA* AND prognos* OR
HbA* AND predict* OR
HbA* AND inciden* OR
HbA* AND mortality OR
HbA* AND prevent* OR
HbA* AND progress* OR
HbA* AND develop*

Appendix 2. QUIPS tool signalling questions

Trial ID	Trial ID
Signalling question	Authors' judgement for 'yes'
Study participation (STP) - yes/no^a/unclear^b/NA^c	
a. Adequate participation in the study by eligible persons	NA: usually participants with intermediate hyperglycaemia or with no diabetes at baseline are selected from a greater cohort on another research question (e.g. cardiovascular risk factors in elderly people)
b. Description of the source population or population of interest	Source population for cohort with intermediate hyperglycaemia is clearly described
c. Description of the baseline study sample	Number of people with intermediate hyperglycaemia at baseline is clearly described
d. Adequate description of the sampling frame and recruitment	Way of how the source population was established, selection criteria and key characteristics of the source population clearly described
e. Adequate description of the period and place of recruitment	Time period and place of recruitment for both baseline and follow-up examinations are clearly described
f. Adequate description of inclusion and exclusion criteria	Definition of people with normoglycaemia, intermediate hyperglycaemia or diabetes mellitus and description of other in- and exclusion criteria
STP risk of bias rating (high/low/unclear)	High: majority of items is answered with 'no'; Low: all items answered with 'yes'; Unclear: majority of items is answered with 'unclear' Note: potentially a single item may introduce a high risk of bias, depending on study specifics
Study attrition (STA) - yes/no/unclear	
a. Adequate response rate for study participants	NA: usually participants with intermediate hyperglycaemia or with no diabetes at baseline are selected from a greater cohort (e.g. all obese people)
b. Description of attempts to collect information on participants who dropped out	Attempts to collect information on participants who dropped out are described (e.g. telephone contact, mail, registers)
c. Reasons for loss to follow-up are provided	Reasons on participants who dropped out are available (e.g. deceased participants between baseline and follow-up, participants moving to another location)
d. Adequate description of participants lost to follow-up	Key elements of participants lost to follow-up are described (age, sex, glucose status at baseline, body mass index)

(Continued)

e. There are no important differences between participants who completed the study and those who did not	Study authors describe differences between participants completing the study and those who did not as not important or information provided to judge the differences
STA risk of bias rating (high/low/unclear)	High: majority of items is answered with 'no'; Low: all items answered with 'yes'; Unclear: majority of items is answered with 'unclear' Note: potentially a single item may introduce a high risk of bias, depending on study specifics

Prognostic factor measurement (PFM) - yes/no/unclear/NA

Prognostic factor

a. A clear definition or description of the PF is provided	Measurements for intermediate hyperglycaemia are provided (e. g. IFG, IGT, elevated HbA1c)
b. Method of PF measurement is adequately valid and reliable	Ideally measurements for intermediate hyperglycaemia are repeated to ensure diagnosis, single measurements are accepted as well; technique for glucose measurement or HbA1c measurement described
c. Continuous variables are reported or appropriate cut points are used	Standard categories for intermediate hyperglycaemia (FPG 5.6-6.9 mmol/L (IFG5.6), FPG 6.1-6.9 mmol/L (IFG6.1), 2-hr PG 7.8-<11.0 mmol/L (IGT), HbA1c 6.0-6.4% (HbA1c6.0), HbA1c 5.7-6.4% (HbA1c5.7))
d. The method and setting of measurement of PF is the same for all study participants	Measurements of intermediate hyperglycaemia are the same for all study participants
e. Adequate proportion of the study sample has complete data for the PF	NA: usually participants with intermediate hyperglycaemia or with no diabetes at baseline are selected from a greater cohort (e. g. proportion 100% because study focused on IGT-subcohort)
f. Appropriate methods of imputation are used for missing PF data	NA: missing laboratory measurements for intermediate hyperglycaemia cannot be reliably imputed

PFM risk of bias rating (high/low/unclear)	High: majority of items is answered with 'no'; Low: all items answered with 'yes'; Unclear: majority of items is answered with 'unclear' Note: potentially a single item may introduce a high risk of bias, depending on study specifics
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Outcome measurement (OM) - yes/no/unclear/NA

Outcome measurement

a. A clear definition of the outcome is provided	Measurement of type 2 diabetes mellitus has to be defined
b. Method of outcome measurement used is adequately valid and reliable	Measurement of type 2 diabetes mellitus: a glucose (FPG, PG) or HbA1c measurement has to be a part of the diagnosis (self-reported diabetes alone will not be accepted)

(Continued)

c. The method and setting of outcome measurement is the same for all study participants	Measurements of type 2 diabetes mellitus are the same for all study participants
OM rating (high/low/unclear)	High: majority of items is answered with 'no'; Low: all items answered with 'yes'; Unclear: majority of items is answered with 'unclear' Note: potentially a single item may introduce a high risk of bias, depending on study specifics

Study confounding (SC) - yes/no/unclear/NA		Study confounding
a. All important confounders are measured	Important confounders are: age, sex, family history of diabetes, ethnicity, body mass index, blood pressure and hypertension, smoking and drinking status, socioeconomic status, comedications and comorbidities, physical activity	
b. Clear definitions of the important confounders measured are provided	Measurement of confounders has to be clearly described	
c. Measurement of all important confounders is adequately valid and reliable	Measurement of confounders is valid and reliable	
d. The method and setting of confounding measurement are the same for all study participants	Measurements of confounders are the same for all study participants	
e. Appropriate methods are used if imputation is used for missing confounder data	Strategy to impute missing confounder data is described	
f. Important potential confounders are accounted for in the study design	Methods section of the publication describes strategy to account for confounders	
g. Important potential confounders are accounted for in the analysis	Important confounders are accounted for in multivariate logistic regression and Cox proportional hazards models	
SC risk of bias rating (high/low/unclear)	High: majority of items is answered with 'no'; Low: all items answered with 'yes'; Unclear: majority of items is answered with 'unclear' Note: potentially a single item may introduce a high risk of bias, depending on study specifics	

Statistical analysis and reporting (SAR) - yes/no/unclear/NA		Statistical analysis
a. Sufficient presentation of data to assess the adequacy of the analytic strategy	Mean or median values, including confidence intervals or standard errors or standard deviations	
b. Strategy for model building is appropriate and is based on a conceptual framework or model	NA: we do not anticipate conceptual frameworks or explicit model building strategies for this type of research question (focusing on one prognostic factor only)	

(Continued)

c. The selected statistical model is adequate for the design of the study	Mainly incidence rates, uni- and multivariate logistic regression, Cox proportional hazard model
d. There is no selective reporting of results	NA: development of type 2 diabetes mellitus and potentially regression to normoglycaemia from intermediate hyperglycaemia are the only outcomes; if missing the study will be excluded
SAR risk of bias rating (high/low/unclear)	High: majority of items is answered with 'no'; Low: all items answered with 'yes'; Unclear: majority of items is answered with 'unclear' Note: potentially a single item may introduce a high risk of bias, depending on study specifics

^a**No:** no or no relevant information to answer the signalling question

^b**Unclear:** not enough information to answer signalling question with yes or no

^c**NA** (not applicable): signalling question not appropriate for this type of prognostic review

FPG: fasting plasma glucose; HbA1c: glycosylated haemoglobin A1c; IFG: impaired fasting glucose; IGT: impaired glucose tolerance;

PG: post-load glucose (after an oral glucose tolerance test (OGTT))

^a**No:** no or no rel

^b**Unclear:** not e

with yes or no

^c**NA** (not applic

type of prognost

FPG: fasting pl

A1c; IFG: impair

PG: post-load gl

CONTRIBUTIONS OF AUTHORS

All review authors read and approved the final protocol draft.

Bernd Richter (BR): protocol and review draft, search strategy development, acquisition of trial reports, trial selection, data extraction of all trials, data analysis, data interpretation and writing of drafts.

Maria-Inti Metzendorf (MIM): search strategy development, trial selection, check of data extraction, review of drafts.

Bianca Hemmingsen (BH): protocol and review draft, trial selection, data interpretation and review of drafts.

Yemisi Takwoingi (YT): protocol and review draft, data analysis, data interpretation and review of drafts

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BR: this review is funded by the World Health Organization (WHO).

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