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Glycosylated Haemoglobin as a Predictor of Cardiovascular Events and Mortality: A Protocol for a Systematic Review and Meta-Analysis

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Glycosylated Haemoglobin as a Predictor of Cardiovascular Events and Mortality: A Protocol for a Systematic Review and Meta-Analysis

Systematic review registration: PROSPERO CRD42015032552

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ABSTRACT

Introduction: The glycosylated haemoglobin level (HbA1c) is an indicator of the average blood glucose concentrations over the preceding 2-3 months, which is used as a convenient and well-known biomarker in clinical practice. Currently, epidemiological evidence suggests that the HbA1c level is an independent risk factor for cardiovascular events such as myocardial infarction, stroke, coronary heart disease, and heart failure. This protocol aim to conduct systematic review and meta-analysis to determine the relationships between the HbA1c levels with cardiovascular outcomes and cause of death; and to analyse the range of HbA1c that is a predictor of cardiovascular disease and/or mortality based on data from published observational studies.

Methods and analysis: The search will be conducted using the MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and Web of Science databases from their inception. Observational studies written in Portuguese, Spanish or English will be included. The Quality In Prognosis Studies tool will be used to assess the risk of bias for the studies included in the systematic review or meta-analysis. The hazard ratios for the cardiovascular outcomes and causes of death with 95% confidence intervals will be determined as the primary outcomes. Subgroup analyses will be performed based on the cardiovascular outcomes, the cause of death studied, or the type of population included in the studies.

Ethics and dissemination: This systematic review will synthesise evidence regarding the potential of using the HbA1c level as a prognostic marker for cardiovascular disease outcomes and/or mortality. The results will be disseminated by the publication of a manuscript in a peer-reviewed journal. Ethical approval will not be needed because the data used for this systematic review will be obtained from published studies and there will not be any concerns about privacy.

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Strengths and limitations of this study

- This review of evidence will be useful to improve future research on HbA1c level as a prognostic marker for cardiovascular disease outcomes and/or mortality.

- Study selection, data extraction and quality assessment will be performed independently by two researchers.
- Limitations and strengths will be discussed in our review, and the results will be put into context with other studies in the field.
- Different population-based studies can be a source of variable quality and heterogeneity between studies and may limit the quality of the evidence of this meta-analysis and systematic review.

INTRODUCTION

Cardiovascular disease (CVD) is a chronic disorder that develops insidiously throughout an individual's life and usually has progressed to an advanced stage by the time-symptoms occur[1]. The percentage of all deaths due to CVD before the age of 75 years in Europe represents 42% in women and 38% in men[2]. Cardiovascular disease, especially coronary heart disease, is the leading cause of premature death worldwide.[3]

In 2007 was developed The Reynolds Risk Score for predicting CVD risk, which incorporates information on glycosylated haemoglobin (HbA1c), but this score was only used in people with known diabetes[4]. In 2010, the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines considered the HbA1c level as an appropriate index for CVD risk assessment in asymptomatic adults without a diagnosis of diabetes[5]. Finally, the Canadian Cardiovascular Society proposed that the CVD risk could be stratified by measuring the levels of fasting plasma glucose, HbA1c, or both[6].

The HbA1c level is an indicator of the average blood glucose concentrations over the preceding two to three months, which is used as a convenient and well-known biomarker in clinical practice[7-8]. Epidemiological evidence suggests that the HbA1c level is an independent risk factor for cardiovascular events[9]. There is also evidence that the association between the HbA1C level with mortality from all-causes and CVD could be found at lower levels than the diabetic threshold[10]. A recent meta-analysis showed that HbA1c level was an independent predictor of mortality in coronary artery disease patients without but not in patients with established diabetes[11].

Currently, the association between chronic hyperglycaemia and cardiovascular complications is not well defined. Several observational studies have demonstrated that

a higher HbA1c level was associated with increased risks of CVD and death[9, 12-13]. Thus, an elevated HbA1c level might contribute to the development of CVD, but the association between the HbA1c level with the risk of CVD and mortality in the general population remains unclear. Therefore, this protocol aims to present a clear and transparent procedure for systematically review, evaluate and summarize the existing information on the relationship between the HbA1c levels and CVD and death, which could guide clinical decision making for further treatment strategies and also could inform and facilitate future intervention research.

OBJECTIVE

The aim of this protocol study is to establish a transparent and clear methodology to conduct a systematic review and meta-analysis aimed to: i) determine the relationship between the HbA1c levels with the cause of death and cardiovascular outcomes based on data from observational studies, and ii) analyse what level of HbA1c is a predictor of CVD and/or mortality.

METHODS AND ANALYSIS

Review design

This protocol was developed based on the Preferred Reporting Items for Systematic Review and Meta-analysis Protocols (PRISMA-P)[14] and was registered with PROSPERO (Registration number: CRD42015032552). The MOOSE[15] (Meta-analysis of observational studies in epidemiology: a proposal for reporting), PRISMA[16] (Preferred Reporting Items for Systematic Reviews) and Cochrane Collaboration Handbook[17] will be used to guide the review methods.

Literature review

The literature search will be conducted using the MEDLINE (via PubMed), EMBASE, the Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews, and the Web of Science databases from their inception.

The following search terms will be combined using Boolean operators: glycosylated hemoglobin, HbA1c, hemoglobin levels, glycated hemoglobin, hemoglobin A1c,

cardiovascular, cardiovascular disease, coronary heart disease, heart failure, stroke, peripheral arterial disease, cardiovascular events, coronary artery disease, myocardial infarction, cardiovascular outcomes, mortality, all-cause mortality, cardiovascular mortality, cause-specific mortality, death, cardiovascular death, observational study, cohort study and population-based (Table 1).

Previous systematic reviews and meta-analysis, and relevant references included in the selected studies will be screened as supplemental sources.

Inclusion/exclusion criteria for study selection

Studies regarding on the HbA1c level and cardiovascular outcomes retrieved in the literature search that meet the following criteria will be included: i) prospective or retrospective observational studies; ii) studies that observed the following cardiovascular outcomes: myocardial infarction, stroke, major adverse cardiovascular events (MACE), coronary heart disease, and heart failure; iii) reports of all-cause mortality and/or cardiovascular mortality; iv) outcomes measured using univariate and multivariable Cox proportional hazards models; v) population of adults aged 18 or older with any restriction on the race, gender or diabetic status; and vi) studies published in Portuguese, Spanish or English.

The process; of identifying, screening of studies and inclusion or exclusion of those studies; is shown in the PRISMA flow chart (Figure 1).

Study selection and data extraction

Two reviewers will independently check titles and abstracts to identify eligible studies according to the inclusion criteria. Then, the full manuscripts of the identified studies will be examined. Finally, two reviewers will check the included and excluded studies and verify the reasons why they were included/excluded. Any discrepancies will be resolved by discussion, a third reviewer will be asked on case of disagreement.

Two authors will independently extract the data regarding the author information, year of publication, design of the study, country, study project name and year of data collection, number, age of participants, methods used for HbA1c test certified by National Glycohemoglobin Standardization Program (NGSP), number of cardiovascular events, level of HbA1c used as the reference, and the hazard ratio (HR) for each HbA1c level (Table 2)

Any disagreement will be resolved by discussion to reach a consensus. When necessary, authors of the potential included studies will be contacted to obtain any missing information.

Assessment of the risk of bias in the included studies

After blinding the included studies by author, title and year of publication, two independent researchers to assess the methodological quality will by the Quality in Prognosis Studies tool (QUIPS)[18]. Any disagreement in the assessment of the risk of bias will be discussed to reach a consensus. A third reviewer will make the final decision if a consensus is not reached. The QUIPS tool involves the use of 6 domains for the risk of bias: study participation (sampling bias), study attrition (attrition bias), prognostic factor measurement, outcome measurement (ascertainment bias), confounding measurement and accounting, and analysis and reporting. Studies will be considered to have a low, moderate or high risk of bias, satisfied by scores of 5 to 6, 3 to 4, or 1 to 2 for the 6 bias domains, respectively.

Statistical analysis

The researchers will create tables to summarize the characteristics of the included studies and any important questions related to the aim of this systematic review. The reviewers will determine whether a meta-analysis is possible after the data have been extracted. At least, five observations addressing HR for cardiovascular outcomes and mortality will be required to conduct a meta-analysis. If it is possible to carry out a meta-analysis, the STATA 14 software will be used to combine the extracted HR with 95% CIs using an inverse variance model. We will compare adjusted and unadjusted estimates separately for each outcome. A fixed-effects model will be used if there is no evidence of heterogeneity; otherwise, a random-effects model will be used[19]. For the HbA1c levels, we will group studies by similar cut-off points to obtain meta-analysis results for each cut-off point whenever possible. We will used generalized least squares regression models to assess the pooled dose-response relation between HbA1c and CVD outcomes across prospective cohort studies that have heterogeneous categorizations of HbA1c[20]. Each meta-analysis will be summarized by the pooled HR and 95% confidence intervals. Studies providing insufficient data to perform the analyses will be omitted from the data synthesis. The heterogeneity of the studies will be assessed with an I^2 statistic. Usually, I^2 values of <25, 25-50, and >50% are considered to represent

small, medium, and large amounts of heterogeneity, respectively[21]. If a meta-analysis is not possible, we will undertake a narrative synthesis. Finally, publication bias was visually evaluated using a funnel plot, as well as with the method proposed by Egger[22]. The strength of the body evidence will be evaluated by Grading of Recommendations Assessment, Development and Evaluation tool (GRADE)[23].

Subgroup analyses and meta-regression

Subgroup analyses and meta-regression will be performed based on the cardiovascular outcomes (myocardial infarction, stroke, MACE, coronary heart disease, heart failure), cause of death studied (all causes of mortality or cardiovascular mortality), or on the type of population included in the studies (diabetic, prediabetic or non-diabetic), because these may be major factors causing heterogeneity. Furthermore, the age of the study participants, design of the study, and QUIPS score will be considered for additional subgroup analyses.

Sensitivity analysis

Excluding the included studies from the analysis one by one and comparing the results will perform sensitivity analyses.

DISCUSSION

The utility of the HbA1c level as a prognostic marker for CVD outcomes and/or mortality is currently a source of controversy in the medical literature. Therefore, we will conduct a systematic review to identify what HbA1c level might be able to predict the CVD outcomes and mortality.

There is currently no consensus on what percentages should be used to determine the level of heterogeneity in categorical terms. Therefore, in this study, we will use the definition suggested by Higgins et al. to indicate that there is heterogeneity when the I^2 value is greater than 50%[21].

Possible limitations that can be found in this research are: publication bias, information bias, poor statistical analyses, and inadequate reporting of methods and findings of the primary studies[24]. However, it is important to summarize the information available on this issue. To overcome these limitations, we will follow the recommendations included in the MOOSE, PRISMA and Cochrane Collaboration Handbook. According to the

Cochrane Prognosis Methods Group, we will use the QUIPS tool to assess the quality of the included studies[18].

There have already been numerous studies on the use of the HbA1c level as a prognostic marker for CVD outcomes and mortality, but the individual studies have been controversial, so there is uncertainty regarding its use. This makes it necessary to conduct this systematic review to provide a global overview of the current literature and to improve future research on this topic. It is therefore this protocol provide a clear and structured procedure for maximizing the extraction of relevant information and provide summarized information regarding the importance of HbA1c levels for controlling the risk of CVD outcomes and mortality.

Authors' contributions: VMV and ICR designed the study. VMV was the principal investigator and guarantor. ICR and VMV were the main coordinators of the study. BP, CAB, FRA, and VMV conducted the study. ICR, BP and FRA gave statistical and epidemiological support. ICR wrote the article with the support of CAB and ICR. All authors revised and approved the final version of the manuscript.

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Competing interests: None declared

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Table 1. Search strategy for MEDLINE

"glycosylated haemoglobin" OR "HbA1c" OR "hemoglobin levels" OR "glycated haemoglobin" OR "hemoglobin A1c"	AND	cardiovascular OR "cardiovascular disease" OR "coronary heart disease" OR "heart failure" OR Stroke OR "peripheral arterial disease" OR "cardiovascular events" OR "coronary artery disease" OR "myocardial infarction" OR "cardiovascular outcomes" OR mortality OR "all-cause mortality" OR "cardiovascular mortality" OR "cause-specific mortality" OR death OR "cardiovascular death"	AND	"observational study" OR "cohort study" OR "population-based

Table 2. Characteristics of studies included in the systematic review and/or meta-analysis.

Reference	Design	Country	Study/Year data collection	Age	n	n cardiovascular events	HbA1c method	HbA1c reference level	HR for Hba1c levels
Author information and year of publication	*Design of the study*	*Country*	*Study project name and year of data collection*	*Age of participants*	*Number of participants*	*Number of cardiovascular events*	*Methods used for HbA1c test certified by NGSP*	*Level of HbA1c used as the reference*	*HR for each HbA1c level*

Hba1c: glycosilated haemoglobin; NGSP: National Glycohemoglobin Standardization Program; HR: Hazard ratio

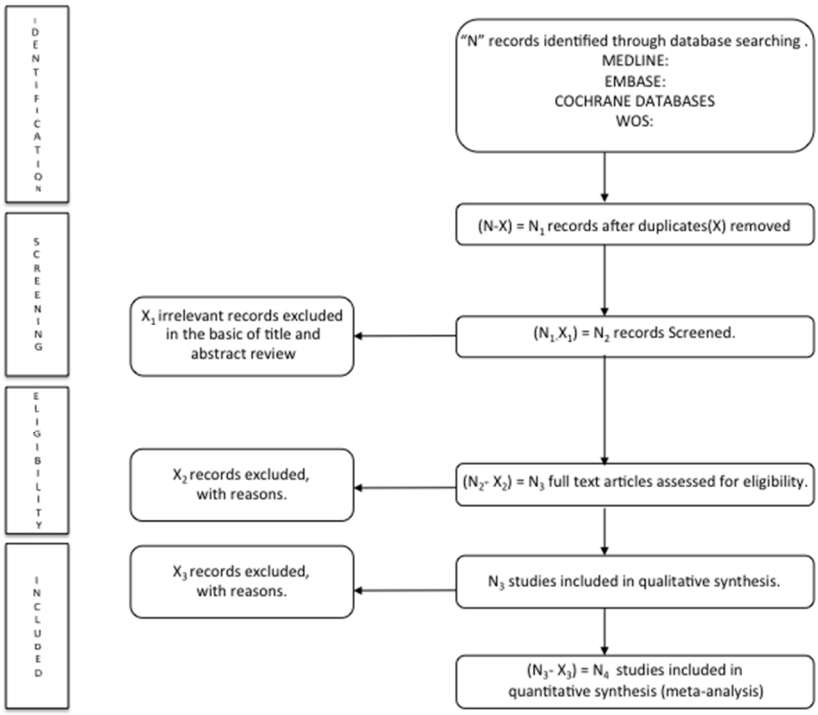

Figure 1. Literature search PRISMA consort diagram.
254x190mm (72 x 72 DPI)

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Page number
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	Page 1; line 1-2
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	NA
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	Page1; line 3
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	Page 1; line 4-11
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	Page 8; line 217-221
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	NA
Support:			
Sources	5a	Indicate sources of financial or other support for the review	Page 8; line 222-223
Sponsor	5b	Provide name for the review funder and/or sponsor	NA
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	NA
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	Page 3-4; line 63-94
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	Page 4; line 96-101
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	Page 5; line 124-136
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other	Page 4-5; line

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		grey literature sources) with planned dates of coverage	111-123 Figure 1
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Table 1
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	Page 5-6; line 136-150
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	Page 5-6; line 136-150
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	Page 5-6; line 136-150
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	Page 5-6; line 136-150 Table 2
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	Table 2
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	Page 6; line 151-161
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	Page 6-7; line 162-182
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	Page 6-7; line 162-182
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	Page 7; line 183-193
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	Page 6; line 163-167
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	Page 7; line 181-182
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	Page 7; line 183-184

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

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a higher HbA1c level was associated with increased risks of CVD and death[9, 12-13]. Thus, an elevated HbA1c level might contribute to the development of CVD, but the association between the HbA1c level with the risk of CVD and mortality in the general population remains unclear. Therefore, this protocol aims to present a clear and transparent procedure for systematically review, evaluate and summarize the existing information on the relationship between the HbA1c levels and CVD and death, which could guide clinical decision making for further treatment strategies and also could inform and facilitate future intervention research.

OBJECTIVE

The aim of this protocol study is to establish a transparent and clear methodology to conduct a systematic review and meta-analysis aimed to: i) determine the relationship between the HbA1c levels with the cause of death and cardiovascular outcomes based on data from observational studies, and ii) analyse what level of HbA1c is a predictor of CVD and/or mortality.

METHODS AND ANALYSIS

Review design

This protocol was developed based on the Preferred Reporting Items for Systematic Review and Meta-analysis Protocols (PRISMA-P)[14] and was registered with PROSPERO (Registration number: CRD42015032552). The MOOSE[15] (Meta-analysis of observational studies in epidemiology: a proposal for reporting), PRISMA[16] (Preferred Reporting Items for Systematic Reviews) and Cochrane Collaboration Handbook[17] will be used to guide the review methods.

Literature review

The literature search will be conducted using the MEDLINE (via PubMed), EMBASE, the Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews, and the Web of Science databases from the date of their inception until August 2016. Study records will be managed by means of the Mendeley reference manager (Mendeley Ltd. 2016, United Kingdom).

The following search terms will be combined using Boolean operators: glycosylated hemoglobin, HbA1c, hemoglobin levels, glycated hemoglobin, hemoglobin A1c, cardiovascular, cardiovascular disease, coronary heart disease, heart failure, stroke, peripheral arterial disease, cardiovascular events, coronary artery disease, myocardial infarction, cardiovascular outcomes, mortality, all-cause mortality, cardiovascular mortality, cause-specific mortality, death, cardiovascular death, observational study, cohort study and population-based (Table 1).

Previous systematic reviews and meta-analysis, and relevant references included in the selected studies will be screened as supplemental sources.

Inclusion/exclusion criteria for study selection

Studies regarding on the HbA1c level and cardiovascular outcomes retrieved in the literature search that meet the following criteria will be included: i) prospective or retrospective observational studies; ii) studies that observed the following cardiovascular outcomes: myocardial infarction, stroke, major adverse cardiovascular events (MACE), coronary heart disease, and heart failure; iii) reports of all-cause mortality and/or cardiovascular mortality; iv) outcomes measured using univariate and multivariable Cox proportional hazards models; v) population of adults aged 18 or older with any restriction on the race, gender or diabetic status; and vi) studies published in Portuguese, Spanish or English.

The process; of identifying, screening of studies and inclusion or exclusion of those studies; is shown in the PRISMA flow chart (Figure 1).

Study selection and data extraction

Two reviewers will independently check titles and abstracts to identify eligible studies according to the inclusion criteria. Then, the full manuscripts of the identified studies will be examined. Finally, two reviewers will check the included and excluded studies and verify the reasons why they were included/excluded. Any discrepancies will be resolved by discussion, a third reviewer will be asked on case of disagreement.

Two authors will independently extract the data regarding the author information, year of publication, design of the study, country, study project name and year of data collection, number, age of participants, population characteristics (diabetic or non-

diabetic), methods used for HbA1c test certified by National Glycohemoglobin Standardization Program (NGSP), number of cardiovascular events, level of HbA1c used as the reference, and the hazard ratio (HR) for each HbA1c level (Table 2)

Any disagreement will be resolved by discussion to reach a consensus. When necessary, authors of the potential included studies will be contacted to obtain any missing information.

Assessment of the risk of bias in the included studies

After blinding the included studies by author, title and year of publication, two independent researchers to assess the methodological quality will by the Quality in Prognosis Studies tool (QUIPS)[18]. Any disagreement in the assessment of the risk of bias will be discussed to reach a consensus. A third reviewer will make the final decision if a consensus is not reached. The QUIPS tool involves the use of 6 domains for the risk of bias: study participation (sampling bias), study attrition (attrition bias), prognostic factor measurement, outcome measurement (ascertainment bias), confounding measurement and accounting, and analysis and reporting. Studies will be considered to have a low, moderate or high risk of bias, satisfied by scores of 5 to 6, 3 to 4, or 1 to 2 for the 6 bias domains, respectively.

Statistical analysis

The researchers will create tables to summarize the characteristics of the included studies and any important questions related to the aim of this systematic review. The reviewers will determine whether a meta-analysis is possible after the data have been extracted. At least, five observations addressing HR for cardiovascular outcomes and mortality will be required to conduct a meta-analysis. If it is possible to carry out a meta-analysis, the STATA 14 software will be used to combine the extracted HR with 95% CIs using an inverse variance model. We will compare adjusted and unadjusted estimates separately for each outcome. A fixed-effects model will be used if there is no evidence of heterogeneity; otherwise, a random-effects model will be used[19]. For the HbA1c levels, we will group studies by similar cut-off points to obtain meta-analysis results for each cut-off point whenever possible. We will used generalized least squares regression models to assess the pooled dose-response relation between HbA1c and CVD outcomes across prospective cohort studies that have heterogeneous categorizations of HbA1c[20]. Each meta-analysis will be summarized by the pooled HR and 95%

confidence intervals. Studies providing insufficient data to perform the analyses will be omitted from the data synthesis. The heterogeneity of the studies will be assessed with an I^2 statistic. Usually, I^2 values of <25, 25-50, and >50% are considered to represent small, medium, and large amounts of heterogeneity, respectively[21]. If a meta-analysis is not possible, we will undertake a narrative synthesis. Finally, publication bias was visually evaluated using a funnel plot, as well as with the method proposed by Egger[22]. The strength of the body evidence will be evaluated by Grading of Recommendations Assessment, Development and Evaluation tool (GRADE)[23].

Subgroup analyses and meta-regression

Subgroup analyses and meta-regression will be performed based on the cardiovascular outcomes (myocardial infarction, stroke, MACE, coronary heart disease, heart failure), cause of death studied (all causes of mortality or cardiovascular mortality), on the type of population included in the studies (diabetic, pre-diabetic or non-diabetic), or on the age of the study participants (young adults aged 18–35 years, middle-aged adults aged 36–55 years, or older adults aged older than 55 years), because these may be major factors causing heterogeneity. Furthermore, design of the study and QUIPS score will be considered for additional subgroup analyses.

Sensitivity analysis

Excluding the included studies from the analysis one by one and comparing the results will perform sensitivity analyses.

DISCUSSION

The utility of the HbA1c level as a prognostic marker for CVD outcomes and/or mortality is currently a source of controversy in the medical literature. Therefore, we will conduct a systematic review to identify what HbA1c level might be able to predict the CVD outcomes and mortality.

There is currently no consensus on what percentages should be used to determine the level of heterogeneity in categorical terms. Therefore, in this study, we will use the definition suggested by Higgins et al. to indicate that there is heterogeneity when the I^2 value is greater than 50%[21].

Possible limitations that can be found in this research are: publication bias, information bias, poor statistical analyses, and inadequate reporting of methods and findings of the

primary studies[24]. However, it is important to summarize the information available on this issue. To overcome these limitations, we will follow the recommendations included in the MOOSE, PRISMA and Cochrane Collaboration Handbook. According to the Cochrane Prognosis Methods Group, we will use the QUIPS tool to assess the quality of the included studies[18].

There have already been numerous studies on the use of the HbA1c level as a prognostic marker for CVD outcomes and mortality, but the individual studies have been controversial, so there is uncertainty regarding its use. This makes it necessary to conduct this systematic review to provide a global overview of the current literature and to improve future research on this topic. It is therefore this protocol provide a clear and structured procedure for maximizing the extraction of relevant information and provide summarized information regarding the importance of HbA1c levels for controlling the risk of CVD outcomes and mortality.

Authors' contributions: VMV and ICR designed the study. VMV was the principal investigator and guarantor. ICR and VMV were the main coordinators of the study. BP, CAB, FRA, and VMV conducted the study. ICR, BP and FRA gave statistical and epidemiological support. ICR wrote the article with the support of CAB and ICR. All authors revised and approved the final version of the manuscript.

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Competing interests: None declared

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Table 1. Search strategy for MEDLINE

"glycosylated haemoglobin" OR "HbA1c" OR "hemoglobin levels" OR "glycated haemoglobin" OR "hemoglobin A1c"	AND	cardiovascular OR "cardiovascular disease" OR "coronary heart disease" OR "heart failure" OR Stroke OR "peripheral arterial disease" OR "cardiovascular events" OR "coronary artery disease" OR "myocardial infarction" OR "cardiovascular outcomes" OR mortality OR "all-cause mortality" OR "cardiovascular mortality" OR "cause-specific mortality" OR death OR "cardiovascular death"	AND	"observational study" OR "cohort study" OR "population-based

Table 2. Characteristics of studies included in the systematic review and/or meta-analysis.

Reference	Design	Country	Study/Year data collection	Age	n	n cardiovascular events	HbA1c method	HbA1c reference level	HR for Hba1c levels
Author information and year of publication	*Design of the study*	*Country*	*Study project name and year of data collection*	*Age of participants*	*Number of participants*	*Number of cardiovascular events*	*Methods used for HbA1c test certified by NGSP*	*Level of HbA1c used as the reference*	*HR for each HbA1c level*

Hba1c: glycosilated haemoglobin; NGSP: National Glycohemoglobin Standardization Program; HR: Hazard ratio

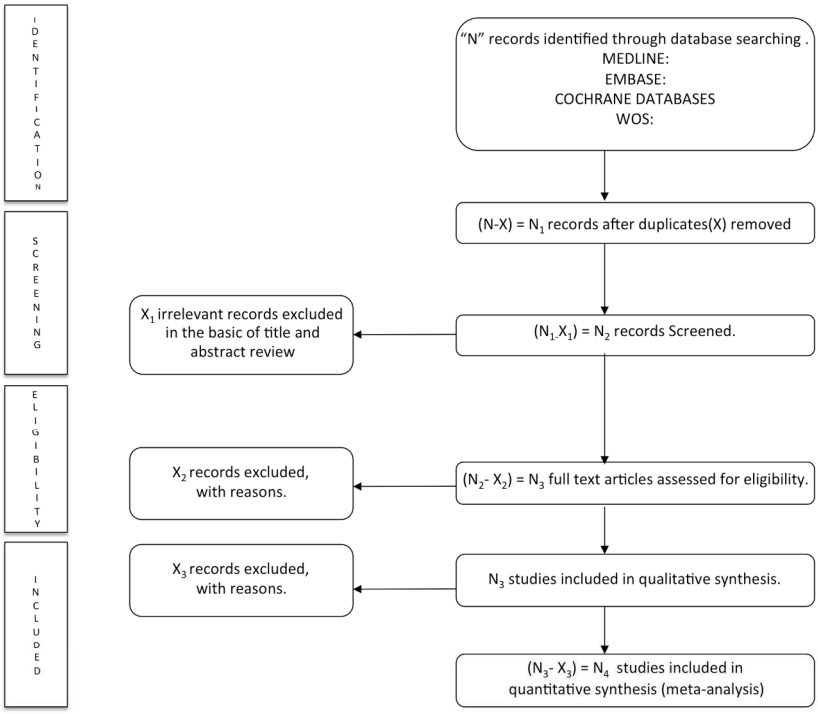

Figure 1. Literature search PRISMA consort diagram.
299x225mm (300 x 300 DPI)

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Page number
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	Page 1; line 1-2
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	NA
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	Page1; line 3
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	Page 1; line 4-11
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	Page 8; line 217-221
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	NA
Support:			
Sources	5a	Indicate sources of financial or other support for the review	Page 8; line 222-223
Sponsor	5b	Provide name for the review funder and/or sponsor	NA
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	NA
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	Page 3-4; line 63-94
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	Page 4; line 96-101
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	Page 5; line 124-136
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other	Page 4-5; line

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

		grey literature sources) with planned dates of coverage	111-123 Figure 1
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Table 1
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	Page 5-6; line 136-150
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	Page 5-6; line 136-150
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	Page 5-6; line 136-150
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	Page 5-6; line 136-150 Table 2
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	Table 2
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	Page 6; line 151-161
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	Page 6-7; line 162-182
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	Page 6-7; line 162-182
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	Page 7; line 183-193
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	Page 6; line 163-167
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	Page 7; line 181-182
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	Page 7; line 183-184

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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