BMJ Open

Continuous Glucose Monitoring Metrics for Earlier Identification of Prediabetes: Protocol for a Systematic Review and Meta-Analysis

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2022-061756
Article Type:	Protocol
Date Submitted by the Author:	07-Feb-2022
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Keywords:	PREVENTIVE MEDICINE, PRIMARY CARE, Physiology < NATURAL SCIENCE DISCIPLINES

TITLE Continuous Glucose Monitoring Metrics for Earlier Identification of Prediabetes: Protocol for a Systematic Review and Meta-Analysis

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Key words:
Continuous glucose monitoring
Glucose variability
Prediabetes

Word Count: 3666

ABSTRACT

Introduction: Glycaemic variability is not well characterized in nondiabetic subjects. More comprehensive sampling as obtained with continuous glucose monitoring (CGM) may improve diagnostic accuracy of the transition from health to prediabetes. Our goal is to investigate the glycaemic system as it shifts from health to predisease in nondiabetic patients utilizing CGM metrics. New insights may offer therapeutic promise for reversing dysglycaemia more successfully with dietary, nutritional, and lifestyle change before progression occurs to prediabetes and diabetes.

Methods and analysis: This systematic review will include comprehensive searches of the PubMed, Scopus, Cochrane Library, and ClinicalTrials.gov databases, with restrictions set to studies published in the last 10 years in English. Reference lists of studies that meet eligibility criteria in the screening process will subsequently be screened for the potential inclusion of additional studies. We will include studies that examine CGM use and report diagnostic criteria such as fasting glucose and/or haemoglobin A1C (HbA1c) such that we can assess correlation between CGM metrics and established diagnostic criteria and describe how CGM metrics are altered in the transition from health to prediabetes. The screening and data extraction will be conducted by two independent reviewers using Covidence. All included papers will also be evaluated for quality and publication bias using Cochrane Collaboration risk of bias tools. If there are two or more studies with quantitative estimates that can be combined, we will conduct a meta-analysis after assessing heterogeneity.

Ethics and dissemination: The systematic review methodology does not require formal ethical review due to the nature of the study design. Study findings will be publicly available and published in a peer-reviewed journal.

Prospero registration number: submitted on 2/1/22, CRD pending

STRENGTHS AND LIMITATIONS OF THIS STUDY

- To our knowledge, this will be the first systematic review and meta-analysis to compare continuous glucose monitoring metrics with the gold standard for diagnosis of health or prediabetes in a nondiabetic population.
- The evidence is determined through a systematic search in four biomedical databases and targeted searching of the grey literature in relevant conference proceedings.
- The Covidence systematic review software will be used for blinded screening, conflict resolving, data extraction, and quality assessment by three independent reviewers.
- The Cochrane Collaboration risk of bias tools will be used for evaluating quality and risk of bias.
- Limitations include a bias for studies published in English in the past 10 years.

INTRODUCTION

Rates of prediabetes and diabetes continue to increase in prevalence. Prediabetes affects 88 million adults, more than 1 in 3 US adults.[1] However, most people with prediabetes are undiagnosed or unaware. Prediabetes is thought to be an intermediate state of hyperglycaemia with glycemic parameters above normal but below the diabetes threshold. Further, the gold standard of blood sugar measurement from the American Diabetes Association—fasting glucose,

glycosylated haemoglobin (Haemoglobin A1C or HbA1c), and oral glucose tolerance testing in response to a 75-gram glucose load[2]—are limited because they diagnose dysglycaemia late in the pathophysiological process when it may be more difficult to reverse. Prediabetes represents worsening fasting glucose and/or impaired glucose tolerance, but definitions vary, leading to significant practice disparity and low guideline adherence.[3] Additionally, there are racial and gender disparities in prediabetes screening.[4]

Glycaemic variability is not well characterized in nondiabetic subjects. Normal glucose (euglycaaemia) variability on a moment-to-moment basis has yet to be elucidated. Most standards of euglycaemia rely on targets from epidemiologic studies of episodic measurement, which document clinical labs measured annually rather than a more comprehensive characterization of the individual's glycaemic status. People with similar HbA1C and mean glucose show extremely different daily glucose excursions and variability, leading to debate and lack of consensus about pathophysiological pathways in the gradient from health to disease.[5] Indeed, standard measurements like HbA1C are limited because several conditions affect reliability, including patient ethnicity; conditions that impair erythrocyte production or alter the normal process of glycation; and even normal aging.[6, 7] Moreover, fasting glucose of 100 mg/dL may not be sufficient to separate normoglycemic from prediabetic individuals. Subjects with fasting glucose less than 100 mg/dL show impaired glucose tolerance when monitored continuously for at least 24 hours.[8] Subjects who are morbidly obese who are euglycaemic have higher glycemic variability compared with normal weight, nondiabetic subjects.[9] Some investigators use a fasting plasma glucose level ≤5.4 mmol/l (97 mg/dl) after an overnight fast because it has greater sensitivity to exclude diabetes in the absences of an Oral Glucose Tolerance Test (OGTT).[10] Evidence supports increased insulin resistance and up to a three-fold greater risk of diabetes when fasting glucose exceeds 90 mg/dl.[11]

Excess glycaemic variability, especially postprandial, triggers increased oxidative stress that can damage tissues, such as blood vessels.[12, 13, 14] Glycaemic variability within the gold standard of "normal" may raise cardiovascular risk and precede an increase in HbA1c.[15] Glycaemic variability may modulate cardiovascular risk even when fasting glucose and A1C are normal.[16] While most of the data on downstream damage from excess glucose excursions are derived from diabetic patients, the scientific literature increasingly indicates that micro- and macro-vascular complications may occur in nondiabetic subjects.[17, 18, 19] Risk may be higher in women at lower glucose levels compared to men.[20, 21] Evidence shows that characterizing dysglycaemia with greater precision uncovers higher cardiometabolic risk associated with specific glucose derangements such as postprandial hyperglycaemia,[22, 23] acute glucose spikes,[24, 25] and perhaps nocturnal hypoglycaemia.[26, 27, 28, 29] From a systems biology perspective, the convention of single or limited series measurement of glucose testing may be inadequate to detect downstream dysfunction, setting the stage for more dense sampling and real-world evidence as obtained with continuous glucose monitoring (CGM) and potentially better diagnostic accuracy.[30]

Our goal is to interrogate the glycemic system as it shifts from health to predisease in nondiabetic patients utilizing CGM metrics. New insights may offer therapeutic promise for reversing dysglycaemia more successfully with dietary, nutritional, and lifestyle change before progression occurs to prediabetes and diabetes.

Objectives

This systematic review aims to answer the questions:

1. How do continuous glucose monitoring metrics differ between euglycaemia and prediabetes?
2. What is the relation (correlation) between CGM dynamic metrics and established diagnostic criteria?
3. What is the diagnostic power of CGM dynamic metrics?

METHODS AND ANALYSIS

The protocol for the present systematic review and meta-analysis follows the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) guidelines,[31] and the Cochrane Handbook of Systematic Reviews of Interventions.[32]

The protocol has been submitted for registration with the National Institute for Health Research (NIHR) International Prospective Register of Systematic Reviews (CRD pending).

Eligibility criteria

A summary of the participants, interventions, comparators and outcomes considered, as well as the type of studies included according to PICOS strategy,[33] is provided below.

Population

The target population is adults (> 18 years old) who are diagnosed with prediabetes (fasting glucose 100-125 mg/dL after a minimum 8-hour fast, and/or hemoglobin A1C 5.7-6.4%, and/or 2-hour oral glucose tolerance test with glucose 140-199 mg/dL) as defined by the American Diabetes Association (ADA), https://www.diabetes.org/a1c/diagnosis, accessed January 24, 2022. We will use the criteria of fasting glucose 100-125 mg/dL or hemoglobin A1C of 5.7-6.4% since the 2-hour oral glucose tolerance test is less commonly used in clinical practice, but we will extract the data if available. Studies that include only participants above the age of 65 or diagnosed with Type 1 and/or Type 2 diabetes will be excluded. Studies will also be excluded if focused on subjects with acute illness or systemic chronic disease (e.g., liver, kidney, stroke, coronary artery disease).

Intervention

We will evaluate primary studies that report outcomes of the use of CGM in patients with prediabetes and/or healthy subjects.

Comparison

Potentially relevant CGM biomarkers are identified by comparing prediabetes values to values for healthy controls (fasting glucose < 100 mg/dL, and/or hemoglobin A1C < 5.7%, and/or 2-hour oral glucose tolerance test with glucose <140 mg/dL).
CGM biomarkers are then compared to standard diagnostics for prediabetes.

Outcomes

In order to explore and define novel CGM biomarkers to predict transition from normal to prediabetic phenotype, the following outcomes are considered:

- CGM metrics (e.g., SD, CV, CONGA, MAGE, MAG, M-value, HBGI, LBGI, J-index, L-index, GRADE, % Time in range, % Time below range, % Time above range)
- Pearson correlation coefficient and results of error grid analysis between the CGM system metrics and established glucose monitoring methods (fasting glucose, hemoglobin A1C, 2-hour oral glucose tolerance test).
- CGM metrics diagnostic power (e.g., sensitivity, specificity, area under the curve, diagnostic odds ratio).

Study design

This review includes observational (e.g., case report, case series, cross-sectional, case–control, cohort) and interventional (e.g., quasi-experimental studies, randomized controlled trials, community trials, field trials) primary, peer-review studies in which CGM is the only intervention under investigation. We will exclude reviews, editorials, commentaries, letters, opinions, meta-analysis, case reports, conference abstracts, comments, preclinical (in-vitro; animal model) studies, and clinical trials involving additional interventions. Studies will be restricted to the English language and published in the last 10 years.

Search methods for identifying studies

Sources of studies

We will conduct systematic searches of the PubMed, Scopus, Cochrane Library, and ClinicalTrials.gov databases. Searches will be limited to studies published in English within 10 years of the time of conducting the search. We will additionally search for unpublished studies in grey literature, by reviewing abstracts from a targeted group of conference proceedings for potential inclusion of additional studies. When available, the proceedings of these conferences from 2012 to 2022 will be searched: Precision Nutrition and Metabolism Conference; Harvard Precision Medicine Annual Conference; International Precision Medicine Conference; and Precision Medicine World Conference.

Search strategy

A medical librarian on the review team developed a comprehensive search strategy encompassing the aims of the systematic review. The strategy combines four sets of terms with Boolean operators: 1) terms related to prediabetes; 2) terms related to continuous glucose monitoring; 3) terms related to diagnostic criteria for prediabetes; and 4) terms related to diagnostic accuracy and the prediction of transition. Each set of terms includes both keywords searched in the title/abstract field and database-specific subject headings. Terms within each set are combined with the operator OR. The four sets of terms are then combined with the operator AND, yielding studies that include at least one term from each set. The initial search strategy was developed in PubMed (see online supplementary file 1). The strategy will be translated into the other included databases, using appropriate subject headings for each database.

Study selection

All records identified in the database search will be uploaded to Covidence systematic review software (https://www.covidence.org) for automatic deduplication and blinded screening, conflict resolving, study selection and data extraction. Two authors will independently perform the initial primary article screening based on the information contained in their titles and abstracts, and categorize them into three groups: relevant, irrelevant and unsure. In case of disagreement, the article will be re-evaluated and, if the disagreement persist, a third reviewer will make a final decision. Full-paper screening will then be conducted by the same independent investigators and a list of articles to be included in the review is compiled. Reference lists of articles that meet eligibility criteria in the screening process will subsequently be screened for potential inclusion of additional studies.

Data extraction

Two independent authors will extract data from the final studies identified as eligible to be included in the review using a predesigned pilot-tested data collection form using the Covidence extraction module. Eventual discrepancies will be addressed with a third reviewer and discussed until consensus is reached.

The data to be extracted will include:

1. Publication details: authors, title, journal, year of publication, country in which the study was conducted and funding source(s).
2. Study design: type of study, inclusion and exclusion criteria, method of recruitment of participants, limitations and mitigation strategies.
3. Participant details: sample size, demographic information (e.g. age, gender, comorbidities).
4. Intervention characteristics: CGM device, aim of intervention.
5. Study outcomes: CGM metrics, correlation between CGM metrics and established diagnostic criteria.

In cases of missing, incomplete, or unclear data in the included studies, we will attempt to contact study authors for further information.

Risk of Bias

The Cochrane Collaboration risk of bias tools will be used to assess the risk of bias in the studies that meet inclusion criteria.[34, 35, 36] This will be assessed independently by two reviewers, with conflicts resolved by a third reviewer.

Data synthesis and analysis

Data will be entered into a custom database and a narrative synthesis will summarize the findings of the review by organizing data into a systematic narrative review, tables, and figures of data extraction. For continuous outcomes analysis will be performed using standardized mean differences (SMD) or mean differences (MD) with its respective 95% CIs. Binary outcomes will be analyzed and reported using risk ratio (RR) or odds ratio (OR) with its respective 95% CIs. Studies with similar characteristics and outcomes will be grouped and, where suitable data and homogeneity exist, a meta-analysis will be performed using random effects models. A combined Pearson correlation coefficient between CGM metrics and established diagnostic criteria (i.e., fasting plasma glucose, hemoglobin A1C, 2-hour oral glucose tolerance test) and according 95% CI will also be calculated. If sufficient data are available, subgroup analysis will be carried out to

explore CGM metrics estimates for prediabetes stratified by age, sex, race and ethnicity, and body mass index.

Patient and Public Involvement
As this research will be based on previously published data, there will be no patient and members of the public involvement in the design, interpretation or dissemination of the findings.

DISCUSSION

This systematic review will provide important information about the benefits of adding CGM to standard diagnostic measures in the diagnosis of euglycaemia versus prediabetes. Currently, there are many challenges that exist with the diagnosis of prediabetes.[37] The technology, emerging algorithms, and more comprehensive data set have shown promise distinguishing euglycemic from prediabetic subjects at an earlier stage, and likely before standard measures such as HbA1C show abnormalities. Previously, Hall et al. discovered that in individuals considered to be euglycemic by single or episodic measurement, CGM identifies an additional 15% of patients with prediabetes and 2% with diabetes, suggesting that dysglycaemia is more prevalent than previously understood and that CGM metrics may be a more sensitive indicator of dysglycaemia.[38] The findings will inform further work that will aim to more fully characterize the stages in the transition from health to prediabetes, potentially providing a mechanism for patients to be more involved and empowered to reverse dysglycaemia in response to food and lifestyle factors. There are two clear limitations to the current review protocol. The review will be restricted to published studies in the last 10 years, which introduces publication bias. Secondly, only studies written in English language will be included, introducing language bias.

Ethics and dissemination
Owing to the study design of systematic reviews and meta-analyses, ethics approval is not necessary. The systematic review will be published in a peer-reviewed journal and presented at appropriate conferences. This protocol will be adapted for the analysis of other classes of biomarkers for prediabetes.

Authors' contributions
SG was involved with conceptualization, methodology, preliminary systematic review, formal analysis, writing the protocol manuscript, study supervision, and project administration; LP was involved in project conception and development, methodology, preliminary systematic review, formal analysis, study supervision, acquisition of data, data analysis and writing the protocol; AN was involved in conceptualization, study supervision and writing the manuscript; GL was involved in systematic review search strategy development, registration of the protocol in Prospero, and writing of the protocol manuscript; DM was involved in project conception and development, and writing the protocol manuscript. All authors read and approved the final manuscript.

Funding statement
This work is supported by a restricted gift from Levels Health.

Competing interests

None

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(((((("diabetes prevention" [title/abstract] OR "diabetes risk*" [title/abstract] OR "diabetes susceptibility" [title/abstract] OR "prediabet*" [title/abstract] OR "pre-diabet*" [title/abstract] OR "prediabetic state" [mesh]) AND ("blood glucose self-monitoring" [mesh] OR "blood sugar self monitor*" [title/abstract] OR "blood sugar self-monitor*" [title/abstract] OR "CGM" [title/abstract] OR "CGMS" [title/abstract] OR "glucose monitor*" [title/abstract] OR "glucose self monitor*" [title/abstract] OR "glucose self-monitor*" [title/abstract] OR "monitoring, ambulatory" [mesh] OR "monitoring, physiologic/instrumentation" [mesh] OR "monitoring, physiologic/methods" [mesh] OR "personalized medicine" [title/abstract] OR "precision medicine" [mesh] OR "precision medicine" [title/abstract] OR "RT-CGM" [title/abstract])) AND ("biomarker*" [title/abstract] OR "biomarkers/analysis" [mesh] OR "biomarkers/blood" [mesh] OR "blood chemical analys*" [title/abstract] OR "blood chemical analysis" [mesh] OR "blood glucose self-monitoring/statistics and numerical data" [mesh] OR "blood glucose/analysis" [mesh] OR "criteria" [title/abstract] OR "deviation*" [title/abstract] OR "dysglycemia" [title/abstract] OR “euglycemi*” [title/abstract] OR “euglycaemi*” [title/abstract] OR "fluctuation*" [title/abstract] OR "glucose tolerance test" [mesh] OR "glucose" [title/abstract] OR "glucotype*" [title/abstract] OR "glycaemic" [title/abstract] OR "glycated hemoglobin A/analysis" [mesh] OR "glycated hemoglobin A/statistics and numerical data" [mesh] OR "glycemic" [title/abstract] OR "HbA1c" [title/abstract] OR "hemoglobin A1c" [title/abstract] OR "hyperglycemia" [mesh] OR "hyperglycemia" [title/abstract] OR "metric*" [title/abstract] OR "normal*" [title/abstract] OR "normoglycemic*" [title/abstract] OR "phenotyp*" [title/abstract] OR "prediabetic state/analysis" [mesh] OR "prediabetic state/blood" [mesh] OR "prediabetic state/blood" [mesh] OR "prediabetic state/statistics and numerical data" [mesh] OR "reference values" [mesh] OR "reference*" [title/abstract] OR "screening*" [title/abstract] OR "standard*" [title/abstract] OR "test*" [title/abstract] OR "variability" [title/abstract] OR "variation*" [title/abstract])) AND ("detect*" [title/abstract] OR "diagnos*" [title/abstract] OR "disease progression" [mesh] OR "early diagnosis" [mesh] OR "early medical intervention" [mesh] OR "identif*" [title/abstract] OR "prediabet*" [title/abstract] OR "pre-diabet*" [title/abstract] OR "prediabetic state/classification" [mesh] OR "prediabetic state/diagnosis" [mesh] OR "prediabetic state/prevention and control" [mesh] OR "prediabetic*" [title/abstract] OR "pre-diabetic*" [title/abstract] OR "predict*" [title/abstract] OR "predictive value of tests" [mesh] OR "prevent*" [title/abstract] OR "progression*" [mesh] OR "risk assessment" [mesh] OR "risk factors" [mesh] OR "risk*" [title/abstract] OR "transition*" [title/abstract])) AND ((english[Filter]))) AND ((y_10[Filter]))

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Page 1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Page 1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Page 2
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Page 3
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Page 3, 4
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Pages 1, 4
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Page 4, supplement
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Page 4
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Page 4, 5
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Page 3, 4, 5
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Page 3,,4, 7
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Page 1, 5
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Page 3, 4, 5
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	N/A
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	N/A
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	N/A
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	N/A
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	N/A

	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	N/A
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	N/A
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Page 1

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	N/A
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	N/A
Study characteristics	17	Cite each included study and present its characteristics.	N/A
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	N/A
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	N/A
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	N/A
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	N/A
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	N/A
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	N/A
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	N/A
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	N/A
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Page 6
	23b	Discuss any limitations of the evidence included in the review.	Page 1, 6
	23c	Discuss any limitations of the review processes used.	
	23d	Discuss implications of the results for practice, policy, and future research.	
OTHER INFORMATION			
	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Page 1

Registration and protocol	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Page 1
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	N/A
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Page 7
Competing interests	26	Declare any competing interests of review authors.	Page 7
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	N/A

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

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BMJ Open

Continuous Glucose Monitoring Metrics for Earlier Identification of Prediabetes: Protocol for a Systematic Review and Meta-Analysis

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2022-061756.R1
Article Type:	Protocol
Date Submitted by the Author:	13-Jul-2022
Complete List of Authors:	Gottfried, Sara; Thomas Jefferson University Hospitals, Department of Integrative Medicine and Nutritional Sciences Pontiggia, Laura; Thomas Jefferson University Hospitals, Institute of Emerging Health Professions (IEHP), College of Health Professions Newberg, Andrew; Thomas Jefferson University Hospitals, Department of Integrative Medicine and Nutritional Sciences Laynor, Gregory; Thomas Jefferson University, Information Services, Scott Memorial Library Monti, Daniel; Thomas Jefferson University Hospitals, Department of Integrative Medicine and Nutritional Sciences
Primary Subject Heading:	Nutrition and metabolism
Secondary Subject Heading:	Patient-centred medicine, Diabetes and endocrinology
Keywords:	PREVENTIVE MEDICINE, PRIMARY CARE, Physiology < NATURAL SCIENCE DISCIPLINES, GENERAL MEDICINE (see Internal Medicine), Health informatics < BIOTECHNOLOGY & BIOINFORMATICS

TITLE Continuous Glucose Monitoring Metrics for Earlier Identification of Prediabetes: Protocol for a Systematic Review and Meta-Analysis

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Key words:
Continuous glucose monitoring
Glucose variability
Prediabetes

Word Count: 3877

ABSTRACT

Introduction: Glycaemic variability and other metrics are not well characterized in nondiabetic subjects. More comprehensive sampling as obtained with continuous glucose monitoring (CGM) may improve diagnostic accuracy of the transition from health to prediabetes. Our goal is to investigate the glycaemic system as it shifts from health to predisease in nondiabetic adult patients utilizing CGM metrics. New insights may offer therapeutic promise for reversing dysglycaemia more successfully with dietary, nutritional, and lifestyle change before progression occurs to prediabetes and diabetes.

Methods and analysis: This systematic review will include comprehensive searches of the PubMed, Scopus, Cochrane Library, and ClinicalTrials.gov databases, with restrictions set to studies published in the last 10 years in English and planned search date March 10, 2022. Reference lists of studies that meet eligibility criteria in the screening process will subsequently be screened for the potential inclusion of additional studies. We will include studies that examine CGM use and report diagnostic criteria such as fasting glucose and/or haemoglobin A1C (HbA1c) such that we can assess correlation between CGM metrics and established diagnostic criteria and describe how CGM metrics are altered in the transition from health to prediabetes. The screening and data extraction will be conducted by two independent reviewers using Covidence. All included papers will also be evaluated for quality and publication bias using Cochrane Collaboration risk of bias tools. If there are two or more studies with quantitative estimates that can be combined, we will conduct a meta-analysis after assessing heterogeneity.

Ethics and dissemination: The systematic review methodology does not require formal ethical review due to the nature of the study design. Study findings will be publicly available and published in a peer-reviewed journal.

Prospero registration number: CRD42022308222

STRENGTHS AND LIMITATIONS OF THIS STUDY

- To our knowledge, this will be the first systematic review and meta-analysis to compare continuous glucose monitoring metrics with the gold standard for diagnosis of health or prediabetes in a nondiabetic population.
- The evidence is determined through a systematic search in four biomedical databases and targeted searching of the grey literature in relevant conference proceedings.
- The Covidence systematic review software will be used for blinded screening, conflict resolving, data extraction, and quality assessment by three independent reviewers.
- The Cochrane Collaboration risk of bias tools will be used for evaluating quality and risk of bias.
- Limitations include a bias for studies published in English in the past 10 years, with adult subjects in age range from 18 to 65 years.

INTRODUCTION

Rates of prediabetes and diabetes continue to increase in prevalence. Prediabetes affects 88 million adults, more than 1 in 3 US adults.[1] However, most people with prediabetes are undiagnosed or unaware. Prediabetes is thought to be an intermediate state of hyperglycaemia

with glycemic parameters above normal but below the diabetes threshold. Further, the gold standard of blood sugar measurement from the American Diabetes Association—fasting glucose, glycosylated haemoglobin (Haemoglobin A1C or HbA1c), and oral glucose tolerance testing in response to a 75-gram glucose load[2]—are limited because they diagnose dysglycaemia late in the pathophysiological process when it may be more difficult to reverse. Prediabetes represents worsening fasting glucose and/or impaired glucose tolerance, but definitions vary, leading to significant practice disparity and low guideline adherence.[3] Additionally, there are racial and gender disparities in prediabetes screening.[4]

Glycaemic variability and other CGM metrics are not well characterized in nondiabetic subjects. Normal glucose (euglycaaemia) variability on a moment-to-moment basis has yet to be elucidated. Most standards of euglycaemia rely on targets from epidemiologic studies of episodic measurement, which document clinical labs measured annually rather than a more comprehensive characterization of the individual's glycaemic status. People with similar HbA1C and mean glucose show extremely different daily glucose excursions and variability, leading to debate and lack of consensus about pathophysiological pathways in the gradient from health to disease.[5] Indeed, standard measurements like HbA1C are limited because several conditions affect reliability, including patient ethnicity; conditions that impair erythrocyte production or alter the normal process of glycation; and even normal aging.[6, 7] Moreover, fasting glucose of 100 mg/dL may not be sufficient to separate normoglycemic from prediabetic individuals. Subjects with fasting glucose less than 100 mg/dL show impaired glucose tolerance when monitored continuously for at least 24 hours.[8] Subjects who are morbidly obese who are euglycaemic have higher glycemic variability compared with normal weight, nondiabetic subjects.[9] Some investigators use a fasting plasma glucose level ≤5.4 mmol/l (97 mg/dl) after an overnight fast because it has greater sensitivity to exclude diabetes in the absences of an Oral Glucose Tolerance Test (OGTT).[10] Evidence supports increased insulin resistance and up to a three-fold greater risk of diabetes when fasting glucose exceeds 90 mg/dl.[11]

Excess glycaemic variability, especially postprandial, triggers increased oxidative stress that can damage tissues, such as blood vessels.[12, 13, 14] Glycaemic variability within the gold standard of "normal" may raise cardiovascular risk and precede an increase in HbA1c.[15] Glycaemic variability may modulate cardiovascular risk even when fasting glucose and A1C are normal.[16] While most of the data on downstream damage from excess glucose excursions are derived from diabetic patients, the scientific literature increasingly indicates that micro- and macro-vascular complications may occur in nondiabetic subjects.[17, 18, 19] Risk may be higher in women at lower glucose levels compared to men.[20, 21] Evidence shows that characterizing dysglycaemia with greater precision uncovers higher cardiometabolic risk associated with specific glucose derangements such as postprandial hyperglycaemia,[22, 23] acute glucose spikes,[24, 25] and perhaps nocturnal hypoglycaemia.[26, 27, 28, 29] From a systems biology perspective, the convention of single or limited series measurement of glucose testing may be inadequate to detect downstream dysfunction, setting the stage for more dense sampling and real-world evidence as obtained with continuous glucose monitoring (CGM) and potentially better diagnostic accuracy.[30]

Our goal is to interrogate the glycemic system as it shifts from health to predisease in nondiabetic patients utilizing CGM metrics. New insights may offer therapeutic promise for

reversing dysglycaemia more successfully with dietary, nutritional, and lifestyle change before progression occurs to prediabetes and diabetes.

Objectives

This systematic review aims to answer the questions:

1. How do continuous glucose monitoring metrics differ between euglycaemia and prediabetes?
2. What is the relation (correlation) between CGM dynamic metrics and established diagnostic criteria?
3. What is the diagnostic power of CGM dynamic metrics?

METHODS AND ANALYSIS

The protocol for the present systematic review and meta-analysis follows the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) guidelines,[31] and the Cochrane Handbook of Systematic Reviews of Interventions.[32]

The protocol has been submitted for registration with the National Institute for Health Research (NIHR) International Prospective Register of Systematic Reviews (CRD pending).

Eligibility criteria

A summary of the participants, interventions, comparators, and outcomes considered, as well as the type of studies included according to PICOS strategy,[33] is provided below.

Population

The target population is adults (> 18 years old) who are diagnosed with prediabetes (fasting glucose 100-125 mg/dL after a minimum 8-hour fast, and/or hemoglobin A1C 5.7-6.4%, and/or 2-hour oral glucose tolerance test with glucose 140-199 mg/dL) as defined by the American Diabetes Association (ADA), https://www.diabetes.org/a1c/diagnosis, accessed January 24, 2022. We will use the criteria of fasting glucose 100-125 mg/dL or hemoglobin A1C of 5.7-6.4% since the 2-hour oral glucose tolerance test is less commonly used in clinical practice, but we will extract the data if available. In order to create the most homogenous pool of studies to address our research questions in nondiabetic adults, studies that include only participants under the age of 18, above the age of 65, or diagnosed with Type 1 and/or Type 2 diabetes will be excluded. Studies will also be excluded if focused on subjects with acute illness or systemic chronic disease (e.g., liver, kidney, stroke, coronary artery disease).

Intervention

We will evaluate primary studies that report outcomes of the use of CGM in patients with prediabetes and/or healthy subjects.

Comparison

Potentially relevant CGM biomarkers are identified by comparing prediabetes values to values for healthy controls (fasting glucose < 100 mg/dL, and/or hemoglobin A1C < 5.7%, and/or 2-hour oral glucose tolerance test with glucose <140 mg/dL).
CGM biomarkers are then compared to standard diagnostics for prediabetes.

Outcomes

In order to explore and define novel CGM biomarkers to predict transition from normal to prediabetic phenotype, the following outcomes are considered:

- CGM metrics include mean, SD, CV, CONGA, MAGE, MAG, M-value, HBGI, LBGI, J-index, L-index, GRADE, % Time in range, % Time below range, % Time above range). (Note that the definition of time in range may vary by author, which will be addressed in the systematic review.)
- Pearson correlation coefficient and results of error grid analysis between the CGM system metrics and established glucose monitoring methods (fasting glucose, hemoglobin A1C, 2-hour oral glucose tolerance test).
- CGM metrics diagnostic power (e.g., sensitivity, specificity, area under the curve, diagnostic odds ratio).

Study design

This review includes observational (e.g., case report, case series, cross-sectional, case–control, cohort) and interventional (e.g., quasi-experimental studies, randomized controlled trials, community trials, field trials) primary, peer-review studies in which CGM is the only intervention under investigation. We will exclude reviews, editorials, commentaries, letters, opinions, meta-analysis, case reports, conference abstracts, comments, preclinical (in-vitro; animal model) studies, and clinical trials involving additional interventions. Studies will be restricted to the English language and published in the last 10 years, since for technologies that evolve and improve rapidly, like CGM, the more recent studies (using the technology closer to the current one) are majorly relevant.

Search methods for identifying studies

Sources of studies

We will conduct systematic searches of the PubMed, Scopus, Cochrane Library, and ClinicalTrials.gov databases. Searches will be limited to studies published in English within 10 years of the time of conducting the search. We will additionally search for unpublished studies in grey literature, by reviewing abstracts from a targeted group of conference proceedings for potential inclusion of additional studies. When available, the proceedings of these conferences from 2012 to 2022 will be searched: Precision Nutrition and Metabolism Conference; Harvard Precision Medicine Annual Conference; International Precision Medicine Conference; and Precision Medicine World Conference.

Search strategy

A medical librarian on the review team developed a comprehensive search strategy encompassing the aims of the systematic review. The strategy combines four sets of terms with Boolean operators: 1) terms related to prediabetes; 2) terms related to continuous glucose monitoring; 3) terms related to diagnostic criteria for prediabetes; and 4) terms related to

diagnostic accuracy and the prediction of transition. Each set of terms includes both keywords searched in the title/abstract field and database-specific subject headings. Terms within each set are combined with the operator OR. The four sets of terms are then combined with the operator AND, yielding studies that include at least one term from each set. The initial search strategy was developed in PubMed (see online supplementary file 1). The strategy will be translated into the other included databases, using appropriate subject headings for each database.

Study selection

All records identified in the database search will be uploaded to Covidence systematic review software (https://www.covidence.org) for automatic deduplication and blinded screening, conflict resolving, study selection and data extraction. Two authors will independently perform the initial primary article screening based on the information contained in their titles and abstracts, and categorize them into three groups: relevant, irrelevant and unsure. In case of disagreement, the article will be re-evaluated and, if the disagreement persist, a third reviewer will make a final decision. Full-paper screening will then be conducted by the same independent investigators and a list of articles to be included in the review is compiled. Reference lists of articles that meet eligibility criteria in the screening process will subsequently be screened for potential inclusion of additional studies.

Data extraction

Two independent authors will extract data from the final studies identified as eligible to be included in the review using a predesigned pilot-tested data collection form using the Covidence extraction module. Eventual discrepancies will be addressed with a third reviewer and discussed until consensus is reached.

The data to be extracted will include:

1. Publication details: authors, title, journal, year of publication, country in which the study was conducted and funding source(s).
2. Study design: type of study, inclusion and exclusion criteria, method of recruitment of participants, limitations and mitigation strategies.
3. Participant details: sample size, demographic information (e.g. age, gender, comorbidities).
4. Intervention characteristics: CGM device brand and model, CGM duration, aim of intervention.
5. Study outcomes: CGM metrics, correlation between CGM metrics and established diagnostic criteria.

In cases of missing, incomplete, or unclear data in the included studies, we will attempt to contact study authors for further information.

Risk of Bias

The Cochrane Collaboration risk of bias tools will be used to assess the risk of bias in the studies that meet inclusion criteria.[34, 35, 36] This will be assessed independently by two reviewers, with conflicts resolved by a third reviewer.

Data synthesis and analysis

Data will be entered into a custom database and a narrative synthesis will summarize the findings of the review by organizing data into a systematic narrative review, tables, and figures of data extraction. For continuous outcomes analysis will be performed using standardized mean differences (SMD) or mean differences (MD) with its respective 95% CIs. Binary outcomes will be analyzed and reported using risk ratio (RR) or odds ratio (OR) with its respective 95% CIs. Studies with similar characteristics and outcomes will be grouped and, where suitable data and homogeneity exist, a meta-analysis will be performed using random effects models. A combined Pearson correlation coefficient between CGM metrics and established diagnostic criteria (i.e., fasting plasma glucose, hemoglobin A1C, 2-hour oral glucose tolerance test) and according 95% CI will also be calculated. If sufficient data are available, subgroup analysis will be carried out to explore CGM metrics estimates for prediabetes stratified by age, sex, race and ethnicity, type of CGM device, and body mass index.

Patient and Public Involvement

As this research will be based on previously published data, there will be no patient and members of the public involvement in the design, interpretation or dissemination of the findings.

DISCUSSION

This systematic review will provide important information about the benefits of adding CGM to standard diagnostic measures in the diagnosis of euglycaemia versus prediabetes. Currently, there are many challenges that exist with the diagnosis of prediabetes.[37] The technology, emerging algorithms, and more comprehensive data set have shown promise distinguishing euglycemic from prediabetic subjects at an earlier stage, and likely before standard measures such as HbA1C show abnormalities. Previously, Hall et al. discovered that in individuals considered to be euglycemic by single or episodic measurement, CGM identifies an additional 15% of patients with prediabetes and 2% with diabetes, suggesting that dysglycaemia is more prevalent than previously understood and that CGM metrics may be a more sensitive indicator of dysglycaemia, though the cost is certainly higher[38] The findings will inform further work that will aim to more fully characterize the stages in the transition from health to prediabetes, potentially providing a mechanism for patients to be more involved and empowered to reverse dysglycaemia in response to food and lifestyle factors. There are several limitations to the current review protocol. The review will be restricted to published studies in the last 10 years, which introduces publication bias. Secondly, only studies written in English language will be included, introducing language bias. Thirdly, we acknowledge that CGM values in nondiabetic subjects are not linked with hard outcomes like retinopathy or nephropathy, so that the clinical relevance of our findings will remain associative only. Finally, we note that CGMs have not been validated by any health agency for any form of diabetes or nondiabetes and that the identified CGM metrics are exploratory.

Ethics and dissemination

Owing to the study design of systematic reviews and meta-analyses, ethics approval is not necessary. The systematic review will be published in a peer-reviewed journal and presented at appropriate conferences. This protocol will be adapted for the analysis of other classes of biomarkers for prediabetes.

Authors' contributions

SG was involved with conceptualization, methodology, preliminary systematic review, formal analysis, writing the protocol manuscript, study supervision, and project administration; LP was involved in project conception and development, methodology, preliminary systematic review, formal analysis, study supervision, acquisition of data, data analysis and writing the protocol; AN was involved in conceptualization, study supervision and writing the manuscript; GL was involved in systematic review search strategy development, registration of the protocol in Prospero, and writing of the protocol manuscript; DM was involved in project conception and development, and writing the protocol manuscript. All authors read and approved the final manuscript.

Funding statement

This research received no specific grant from any funding agency in the public, commercial or not for profit sector.

Competing interests

None

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(((((("diabetes prevention" [title/abstract] OR "diabetes risk*" [title/abstract] OR "diabetes susceptibility" [title/abstract] OR "prediabet*" [title/abstract] OR "pre-diabet*" [title/abstract] OR "prediabetic state" [mesh]) AND ("blood glucose self-monitoring" [mesh] OR "blood sugar self monitor*" [title/abstract] OR "blood sugar self-monitor*" [title/abstract] OR "CGM" [title/abstract] OR "CGMS" [title/abstract] OR "glucose monitor*" [title/abstract] OR "glucose self monitor*" [title/abstract] OR "glucose self-monitor*" [title/abstract] OR "monitoring, ambulatory" [mesh] OR "monitoring, physiologic/instrumentation" [mesh] OR "monitoring, physiologic/methods" [mesh] OR "personalized medicine" [title/abstract] OR "precision medicine" [mesh] OR "precision medicine" [title/abstract] OR "RT-CGM" [title/abstract])) AND ("biomarker*" [title/abstract] OR "biomarkers/analysis" [mesh] OR "biomarkers/blood" [mesh] OR "blood chemical analys*" [title/abstract] OR "blood chemical analysis" [mesh] OR "blood glucose self-monitoring/statistics and numerical data" [mesh] OR "blood glucose/analysis" [mesh] OR "criteria" [title/abstract] OR "deviation*" [title/abstract] OR "dysglycemia" [title/abstract] OR “euglycemi*” [title/abstract] OR “euglycaemi*” [title/abstract] OR "fluctuation*" [title/abstract] OR "glucose tolerance test" [mesh] OR "glucose" [title/abstract] OR "glucotype*" [title/abstract] OR "glycaemic" [title/abstract] OR "glycated hemoglobin A/analysis" [mesh] OR "glycated hemoglobin A/statistics and numerical data" [mesh] OR "glycemic" [title/abstract] OR "HbA1c" [title/abstract] OR "hemoglobin A1c" [title/abstract] OR "hyperglycemia" [mesh] OR "hyperglycemia" [title/abstract] OR "metric*" [title/abstract] OR "normal*" [title/abstract] OR "normoglycemic*" [title/abstract] OR "phenotyp*" [title/abstract] OR "prediabetic state/analysis" [mesh] OR "prediabetic state/blood" [mesh] OR "prediabetic state/blood" [mesh] OR "prediabetic state/statistics and numerical data" [mesh] OR "reference values" [mesh] OR "reference*" [title/abstract] OR "screening*" [title/abstract] OR "standard*" [title/abstract] OR "test*" [title/abstract] OR "variability" [title/abstract] OR "variation*" [title/abstract])) AND ("detect*" [title/abstract] OR "diagnos*" [title/abstract] OR "disease progression" [mesh] OR "early diagnosis" [mesh] OR "early medical intervention" [mesh] OR "identif*" [title/abstract] OR "prediabet*" [title/abstract] OR "pre-diabet*" [title/abstract] OR "prediabetic state/classification" [mesh] OR "prediabetic state/diagnosis" [mesh] OR "prediabetic state/prevention and control" [mesh] OR "prediabetic*" [title/abstract] OR "pre-diabetic*" [title/abstract] OR "predict*" [title/abstract] OR "predictive value of tests" [mesh] OR "prevent*" [title/abstract] OR "progression*" [mesh] OR "risk assessment" [mesh] OR "risk factors" [mesh] OR "risk*" [title/abstract] OR "transition*" [title/abstract])) AND ((english[Filter]))) AND ((y_10[Filter]))

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
ADMINISTRATIVE INFORMATION		
Title:		
Identification	1a	Identify the report as a protocol of a systematic review Page 1 – Line 2
Update	1b	If the protocol is for an update of a previous systematic review, identify as such N/A
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number Page 2 – Line 57
Authors:		
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author Page 1 – Lines 4-25
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review Page 8 – Lines 305-314
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 N/A
Support:		
Sources	5a	Indicate sources of financial or other support for the review Page 8 – Lines 316-317
Sponsor	5b	Provide name for the review funder and/or sponsor Page 8 – Line 317
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol Page 8 – Line 317
INTRODUCTION		
Rationale	6	Describe the rationale for the review in the context of what is already known Page 3 – Lines 88-121
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO) Pages 3 & 4 – Lines 123-135
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 Pages 4 & 5 – Lines 147-196
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage Page 5 – Lines 200-208
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 Pages 5 & 6 – Lines 210-220
Study records:		
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review Page 6 – Lines 223-225

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 6 – Lines 225-232
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 6 – Lines 234-238
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 6 – Lines 239-251
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale Page 5 – Lines 174-185
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 – Lines 253-256
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised Page 6 – Lines 259-261
	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 7 – Lines 261-270
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression) N/A
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned N/A
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies) Page 6 – Lines 253-256
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE) Page 6 – Lines 253-256

*** 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.**

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.