BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-023684
Article Type:	Protocol
Date Submitted by the Author:	25-Apr-2018
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Keywords:	Type 2 diabetes, Gestational diabetes, Multi-morbidity, Integrated care, Africa

Integrated management of type 2 diabetes and gestational diabetes within multi-morbidity conditions in Africa: A systematic review protocol

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Abstract

Introduction: Multi-morbidity, defined as the co-existence of more than one chronic condition in one person, has been increasing due to comorbid non-communicable and infectious chronic diseases (CNCICDs). Type 2 diabetes (T2D) and gestational diabetes mellitus (GDM) incidences within the CNCICDs conditions are increasing and overwhelming already weak and under-resourced health care systems in Africa. There is then an urgent need for the integrated management of CNCICDs. We aim to review the integrated management of T2D and GDM within multi-morbidity conditions in Africa.

Methods: Studies that have assessed the integrated management of T2D and GDM within multi-morbidity conditions in Africa will be considered based on the PICO method: Population (adult diagnosed with T2D and GDM, who also have other diseases, non-communicable diseases (NCDs) and infectious, in public primary and secondary health care facilities in Africa); Intervention (integrated management of T2D and GDM, also suffering from other diseases in Africa), Comparator (Unintegrated management of T2D and GDM in Africa) and Outcomes (integrated management of T2D and GDM in Africa). The following databases Cochrane Library, MEDLINE, PubMed and SCOUPS, the WHO International Clinical trials Registry Platform, among others will be searched. Two reviewers (JCM, MW) will independently screen, select eligible studies, and extract data. Discrepancies will be resolved by consensus or by discussion with the third author (AR). Quality of included studies will be assessed using the Effective Public Health Practice Project (EPHPP). Narrative synthesis of extracted data and meta-analysis, if

necessary will be conducted and then reported according to the preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P).

Ethics consideration and dissemination: By only using the published data, there is no ethics approval required for this study. This systematic review will be included in JCM's PhD thesis and its findings will also be disseminated through peer-reviewed publication and conference presentation.

Systematic review registration: PROSPERO CRD42016046630

Keywords: Type 2 diabetes, gestational diabetes, multi-morbidity, integrated care, Africa.

1. Introduction

The World Health Organisation (WHO) global report in 2016 estimated that 415-422 million adults worldwide had diabetes in 2014-2015 and that diabetes caused 5 million deaths in 2015, with an estimated 673 billions USA dollars of total global health expenditure in diabetes care (1,2). In the Africa region there were and estimated 14.2 million people with diabetes in 2015 increasing to 34.2 million in 2040 (1,3). With the expected rural depopulation causing increased exposure to urban environments and diabetogenic lifestyles such as inactivity, obesity, depression, smoking among others, diabetes cases are expected to increase by 54% to 642 million worldwide by 2040 (3–5).

Globally, the burden of non-communicable diseases (NCDs) is rising. Low and middle-income countries (LMICs) are most affected by changes in patterns of population age distributions, fertility, life expectancy, morbidity and mortality, known as the "epidemiological transition" (6). In Africa, especially in sub-Saharan Africa, this is occurring against a background of continuing infectious disease epidemics (i.e., HIV and tuberculosis), increasingly becoming a coinfection epidemic that requires an integrated response (7). Consequently, multi-morbidity defined as the co-existence of more than one chronic condition in one person, has been increasing due to comorbid non-communicable and infectious chronic diseases (CNCICDs) (8). Given the risk factors and complex care needs of multi-morbidity, there is a need to integrate health care systems, particularly between primary and secondary health care.

The current approaches to surveillance, prevention and treatment of CNCICDs appear to be insufficient to provide for the long-term health needs of this convergence especially in the context of human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS) era, antiretroviral therapy (ART) linked concomitant metabolic complications and HIV/AIDS allied opportunistic infectious diseases (9). To address this, the WHO developed the Innovative Care for Chronic Conditions (ICCC) Framework to provide a health care systems roadmap that would meet the increasing needs of chronic disease care within this growing multi-morbidity context. This framework incorporates community, patient, healthcare and policy environment perspectives, and has been adapted by different health care systems. However, it does not clearly include the infectious diseases within the context of multi-morbidity (8) and it is then necessary to reorganise health care services and systems to tackle this growing public health problem (8,9).

The 2016 global diabetes report (1) emphasizes the need to reach better outcomes of diabetes management through an integrated management, especially with NCDs such as cardiovascular diseases as well as tuberculosis and/or HIV/AIDS. This is especially important where the prevalence of these diseases is high. Despite calls for a shift in approach from disease-specific interventions to the integrated delivery model (10), health care systems in Africa are weak and under-resourced to provide care for the increasing number of patients with multi-morbidities including diabetes, especially compared to high-income settings (11).

Two types of diabetes commonly identified during adulthood are type 2 diabetes (T2D), that is insulin resistance linked diabetes, and gestational diabetes (GDM), known as a

glucose intolerance with onset or first recognition during pregnancy. T2D can be prevented or delayed for women with previous GDM (12–16). The established connection between T2D and GDM (9) does not determine how GMD is managed. It can either be managed alone in diabetic clinic or preferably within integrated care at ANC and postnatal clinics, which is a right approach for increasing multi-morbidity (17,18).

The treatment pathway for women with GDM is through accessing antenatal care (ANC) at the nearest health facility for their pregnancy follow-up and delivery. In contrast, only a small proportion of women with recent GDM return for postpartum oral glucose tolerance test, assessment and management (19–23). The main challenge is that GDM women must navigate fragmented health systems for their care and care of their babies and this situation supports calls for integrated health systems and services that are easy for patients to navigate (24).

Disease-specific or vertical programmes can be used to manage specific diseases and health problems while strengthening fragmented health systems in Africa (25). However, disease specific or stand-alone interventions are criticized for not promoting equity and sustainability of their outcomes (26), and therefore integrated programmes to address various NCDs such diabetes in comorbid conditions are recommended (9,27).

Integrated care is "*combining parts so that they work to form a whole (i.e., integration) in order to optimise care and treatment to people where fragmentations in care have led to a negative impact on their care experiences and outcomes*" (28). It describes a range of organizational arrangements with variable nature and intensity and comprises two main

concepts: a) an organizational structure focused on economic benefits (cost effectiveness), or b) a way of organizing service delivery (29,30). We conceptualized integration based on dynamic interactions in which formal governance is arranged, responsibilities are shared and resources are pooled (31,32), regardless of many other existing integration level models such integrated care typologies used in a recent systematic review that studied integration of cardiovascular diseases, hypertension and diabetes with HIV services (33).

The analysis of interactions in health systems enables us to understand the levels of integration. They include **partial** integration initiatives ranging from (1) the **linkage** or unstructured interactions, (2) the **coordination** with a committee to oversee their goal-oriented works but keeping the separated structures, and **full integration** in which two programmes are merged in their structures (funds, human resources, informational system) and functional elements (strategic planning, resources allocution, interventions delivery) (31,34).

Integrated health care systems have advantages such as being associated with more accessibility of care, improved quality and safety of care, health care cost reductions and economic benefits for both providers and families (35,36). This integrated management approach including partial and full integration initiatives, will play a key in responding and providing the appropriate health care services to the increasing cases of multiple conditions (33).

We aim to provide a systematic review on integrated management of T2D and GDM within the CNCICDs conditions in Africa. The ultimate goal is to describe the emerging practices and lessons learned from integrated management of GDM and T2D within comorbidity conditions in Africa and the different research gaps to GDM and T2D integration within management of other non-communicable and infectious chronic diseases.

This systematic review aims to answer the following research questions: 1) What are the existing integrated interventions and services delivery models to managing T2D including GDM within multi-morbidity conditions in Africa? 2) What are the successes and challenges of the existing integrated management of T2D including GDM within multi-morbidity conditions?

2. Methods

The Cochrane Handbook (37) and systematic review study protocol published by the Cochrane Collaboration Methods Groups provide the methodological framework in designing and conducting this systematic review to enable critical appraisal and replication.

Criteria for considering studies for this review

Search strategy, inclusion criteria and quality of studies: Studies that have assessed the integrated management of T2D and GDM within multi-morbidity conditions in Africa

will be considered, including randomised controlled trials (RCTs), non-randomised controlled trials, quasi-randomised controlled trials (QCTs) and observational studies.

Our search for articles will be based on the following Population, Intervention, Comparator and Outcome (PICO) method (38) describing population, intervention, comparator and outcome (see the table below).

PICO description table

Population	Intervention	Comparator	Outcomes
Adults diagnosed with T2D and women diagnosed with GDM, who have other diseases in public primary and secondary health care facilities in Africa	Partial or full Integrated management of T2D in adults and GDM in pregnant women who have other diseases in Africa	Unintegrated management of T2D and GDM in public primary and secondary health care facilities in Africa.	Utilisation and effectiveness of Integrated management of T2D and GDM in public primary and secondary health care facilities within multi-morbidity conditions in Africa

Studies will all kinds of interventions with different targeted participants from all ethnicities, genders, socioeconomic, educational backgrounds and in all countries in Africa who were diagnosed with T2D and GDM as one disease of the multi-morbidity using standard diagnostic criteria will be eligible for inclusion. The patients who had T2D

including GDM before and after occurrence of other diseases and the interventions to handle both diseases will be included in this review. Interventions carried out or facilitated by health care providers including community health workers in public health facilities will also be included, providing that the focus of the intervention is to treat diseases in which one is diabetes, specifically T2D and GDM. Studies that separately evaluated interventions or assessing vertical programmes of T2D, GDM and other diseases, will be excluded.

Types of outcome measures

Studies reporting at least one of the following outcomes will be included:

- **Primary outcomes**

Two primary outcomes will be considered: 1) Integrated care outcome and 2) cost-effectiveness outcome. For the integrated care outcome, the focus will be on patients screened and/or treated for both T2D and GDM in the course of treatment of other major diseases (e.g. HIV, tuberculosis, cardio-vascular diseases, etc.) in what is known as multi-morbidity conditions. For cost-effectiveness outcome, the focus will be on approach to integrated diagnosis and treatment of T2D and GDM within comorbidity conditions, which simplifies the workload and saves means of depleted health systems in Africa and helps the patients to do not navigate different levels of health systems for their comorbidities that positively impacts the family economies.

- **Secondary outcomes**

We will also consider early diagnosis through the integrated management of other diseases as this improves clinical outcomes and strengthens health systems for the long-term results of the integrated management of T2D diabetes including GDM within comorbidity conditions.

Search methods for identification of studies

Study design and database

We did register this protocol online on PROSPERO, the International prospective register of systematic reviews, found at (https://www.crd.york.ac.uk/prospero/, registration no. CRD42016046630).

Our search strategy will use the controlled terms (MeSH: Medical subject heading) and free texts. The following databases Cochrane Library, MEDLINE, PubMed and SCOUPS. Other database resources such as the WHO International Clinical trials Registry Platform, Clinicaltrials.gov, Pan African Clinical Trials Registry (PACTR) and HINARI (Health InterNetwork Access to Research Initiative) will be searched. Additional search will be conducted in Google scholar. Our research will focus on articles published and gray literature in English and French languages. Upon the extraction of interesting articles in other languages without any English or French abstracts, we will then include them or get assisted by a researcher who is fluent in those languages. Since there were not many articles regarding our review topic in our preliminary search, there will be no time limits in our search but our focus will be limited to all fifty-four African countries. Search Strategy will be validated with the assistance of a Librarian.

Two reviewers (JCM and MW) will proceed with the articles selection at the same time based on the above described inclusion criteria into two steps: 1) examining the title and abstract, and then, 2) reviewing the full texts. The inclusion of an article will be made by consensus. In case the two (JCM and MW) fail to reach consensus, the decision from a third person who is experienced in clinical and public health publications (AR) will be required. The quality of articles selected will be assessed using the tool "Effective Public Health Practice Project (EPHPP)" and this tool will be appropriate and enough to this study instead of using the newly developed tool, "the Cochrane Collaboration Risk of Bias Tool (CCRBT)" (39).

Reference lists

Manual-search by (MJC and MW) lists of references of included studies, tables of contents of relevant journals and conference abstracts for relevant material will be conducted. A grey literature search strategy by (JCM and MW) will be developed to conduct web-based searches to obtain key unpublished sources in our stated search languages.

Selection of studies

Full copies of articles identified by the search, and considered to meet the inclusion criteria, based on the title and abstract will be obtained for data synthesis. Initially, studies will be screened using predefined inclusion and exclusion criteria. Two reviewers (JCM and MW) will apply the criteria independently to the results of the searches, based first on titles and abstracts only. At least two reviewers (JCM and MW) will proceed with the articles selection at the same time based on our described inclusion criteria into two

steps: 1) examining the title and abstract, and then, 2) reviewing the full texts. The inclusion of an article will be made by consensus. In case the two (JCM and MW) fail to reach consensus, the decision from a third person (AR) will be required. All studies which initially appear to meet inclusion criteria but on closer inspection do not meet the inclusion criteria will be detailed in the table "characteristics of excluded studies". A flow chart will be produced to facilitate transparency of the process (40).

Data extraction and management

JCM and MW will extract data on: author's name, country, year, type of paper/report, form of publication, study design, comorbidity, description of the intervention (including process, cost-effectiveness and outcomes), context of integrated intervention (i.e. PHC, hospitals), details about participants (including number in each group, baseline health information, demographic characteristics), length of intervention and follow-up.

Quality assessment

As above said, the quality of articles selected will be assessed using the EPHPP, a Quality Assessment Tool for Quantitative Studies (41). The EPHPP is a standardized tool relevant to evaluate quality of quantitative observational studies (41). This quality assessment tool does encompass the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist and has acceptable content and construct validity, along with excellent inter-rater reliability compared to the CCRBT (41,42). Two reviewers (JCM and MW) will independently assess the risk of bias in the included studies and cross-checked by third reviewer (AR).

The following individual quality elements recommended in the modified Cochrane Collaboration tool to assess risk of bias for randomized controlled trials bias (high, low, or unclear) as a judgment for individual elements from five domains (selection, performance, attrition, reporting, and other) (43), will be assessed.

Any disagreements over bias between two reviewers will be settled by involving the third review author and each bias in these domains for each study will be separately presented in a table in the final review publication.

Statistical analysis and data synthesis

We will first undertake a narrative synthesis to summarize and discuss findings of included studies. We will then present findings by primary and secondary outcomes. We will used tabular summary to synthetize individual studies characteristics and results (intervention effects). The data synthesis will be conducted through the measurements of effect for continuous outcomes of the included studies. Studies reporting multiple outcomes and outcome measures will be categories according to definitions outline in section types of outcome measure above.

A predetermined order of preference for extracting multiple outcome measures will be used where data is available in several formats. For RCTs preference will be to extract data that requires the least manipulation by authors or inference by review authors. Raw values (e.g. Means and standard deviations) rather than calculated effect size will be extracted. For studies reporting both final values and changes from baseline for outcomes, preference will be to extract the former. In case of cluster-RCTs, the

preference will be (i) extract adjusted estimates reported by the study, or (ii) use raw data and inflated the standard error (SE) data using weighting.

In case of missing data in some eligible studies, efforts will be made to contact corresponding authors to request for clarification all relevant information. For ongoing studies trial authors will be contacted for further information and updates.

Statistical analysis and subgroup analysis and investigation of heterogeneity

Heterogeneity between studies will then be assessed using both x^2 and I^2 and Q statistics where appropriate. The I^2 statistic estimates the percentage of total variation across studies due to a true difference rather than chance. In general, I^2 values greater than 60–70% indicate the presence of substantial heterogeneity. We will explore sources of heterogeneity by comparing the pooled study estimates between subgroups defined by study-level characteristics. Subgroup analysis will be performed where heterogeneity is statistically significant. Sensitivity analyses will be conducted to determine the potential sources of heterogeneity. Two additional sensitivity analyses will be conducted to: (i) evaluate the effect of excluding studies unable to meet each quality criterion affect the overall estimate, and (ii) evaluate the change in the results if only high-quality studies where included.

In case the identified studies are of substantial heterogeneity and where statistical pooling is impossible, the findings will be summarizing in a narrative form by tables and figures to facilitate in effective data presentations. Two reviewers will write the narratives independently and later checked by other reviewers. Decisions on any disagreements will be resolved through discussions and consensus by all reviewers in the team. We will assess the presence of publication bias by using a funnel plot and the Egger test of bias

(44). Subgroup and sensitivity analyses will be conducted to look at the effects of certain factors on for example: geographic region, age and gender and diabetes type of participating patients.

Reporting of this review

This systematic review will be reported according to PRISMA-P (preferred reporting items for systematic review and meta-analysis protocols 2015 checklist; see online supplementary table S1).

Patient and public involvement

There will be no patient and/or public involvement in this study.

Ethics and dissemination

Given that this is a protocol for a systematic review only using the published data, there is no ethics approval required for this study. This systematic review will be included in JCM's PhD thesis, a research supervised by Christina Zarowsky (CZ) and Helen Trottier (HT). Its findings will also be disseminated through peer-reviewed publications and conference presentations.

Abbreviations

AIDS: Acquired Immunodeficiency Syndrome

ANC: Antenatal Care

ART: Antiretroviral Therapy

CCRBT: Cochrane Collaboration Risk of Bias Tool

CNCICDs: Comorbid Non-Communicable and Infectious Chronic Diseases

EPHPP: Effective Public Health Practice Project

GDM: Gestational Diabetes Mellitus

HINARI: Health InterNetwork Access to Research Initiative

HIV: Human Immunodeficiency Virus

ICCC: Innovative Care for Chronic Conditions

LMICs: Low and Middle Income Countries

MeSH: Medical subject heading

NCDs: Non-Communicable Diseases

PACTR: Pan African Clinical Trials Registry

PICO: Population, Intervention, Comparator and Outcome

PRISMA-P: Preferred Reporting Items for Systematic review and Meta-Analysis Protocols

QCTs: Quasi-randomised Controlled Trials

RCTs: Randomised Controlled Trial

SE: Standard Error

STROBE: Strengthening the Reporting of Observational Studies in Epidemiology

T2D: Type 2 Diabetes

Acknowledgements

We would like to thank Sylvie Fontaine, the librarian at paramedical library, Université de Montréal, Canada, for her valuable contribution to search strategy development.

Funding

No funding has been received for the review protocol or the review. JCM holds a PhD scholarship of her supervisor Christina Zarowsky from the Canadian Institutes of Health Research (CIHR) under the "Team Grant – Implementation Research in the Prevention

and Treatment of Type II Diabetes in Low and Middle Income Countries" competition. This funding is for the following randomized trial: integrated health system intervention aimed at reducing type 2 diabetes risk in women after gestational diabetes in South Africa (IINDIAGO). Helen Trottier holds a salary award (chercheur-boursier) from the "Fond de la recherche en santé- du Québec (FRQ-S) and a salary award (New Investigator Salary Award) from Canadian Institutes of Health Research (CIHR).

Availability of data and materials

Not applicable.

Author contributions

MJC, and MW designed the study. MJC wrote the first manuscript of the review. MJC, MW, AR, EM, KM, SN, HT, CZ and NL critically revised the review. All authors read and approved the final manuscript.

Authors' information

MJC is a MHA, MSc, MA, MPhil and PhD candidate in Public Health-Global Health. MW is a MD, MPH and PhD candidate in Public Health. AR is a MPH and PhD in Health care and Epidemiology-Global Health. EM is a MBBS and Fellow of West African College of Physicians (FWACP) in Internal Medicine-Endocrinology. KM is a BA, HDE, PGDip. in Health Promotion and PhD in Public Health. HT is a M.Sc and PhD in Epidemiology. CZ is a MD, MPH and PhD in Medical Anthropology. NL is MBChB,

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Competing interests

MJC, MW, AR, EM, KM, SN, HT, CZ and NL declare no competing interests.

Consent for publication

Not applicable.

Ethics approval and consent to participate

Not applicable.

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Reporting checklist for protocol of a systematic review.

Based on the PRISMA-P guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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In your methods section, say that you used the PRISMA-P reporting guidelines, and cite them as:

Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1.

		Reporting Item	Page Number
Identification	#1a	Identify the report as a protocol of a systematic review	1
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	n/a
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	3
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1, 18
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	17
	#4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list	n/a

		changes; otherwise, state plan for documenting important protocol amendments	
Sources	#5a	Indicate sources of financial or other support for the review	17
Sponsor	#5b	Provide name for the review funder and / or sponsor	17
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	n/a
Rationale	#6	Describe the rationale for the review in the context of what is already known	4
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	7
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	8
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	10
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	8
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	12
Study records - 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)	12
Study records - 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	13

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	9
Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	10
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	13
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	13
	#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 I2, Kendall's τ)	14
	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	15
	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	15
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	15
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	15

BMJ Open

Integrated management of type 2 diabetes and gestational diabetes within multi-morbidity conditions in Africa: A systematic review protocol

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-023684.R1
Article Type:	Protocol
Date Submitted by the Author:	27-Sep-2018
Complete List of Authors:	MUTABAZI, Jean Claude; École de Santé Publique, Université de Montréal, Département de Médecine Sociale et Préventive - Santé Mondiale; Centre de Recherche du Centre Hospitalier Universitaire de Montréal (CRCHUM), Werfalli, Mahmoud; University of Cape Town, Chronic Disease Initiative for Africa, Department of Medicine, Faculty of Health Science Rawat , Angeli; The School of Population and Public Health, University of British Colombia Musa, Ezekiel; University of Cape Town, Chronic Disease Initiative for Africa, Department of Medicine, Faculty of Health Science; University of Cape Town, Integrated Intervention for DIAbetes risks after GestatiOnal diabetes (IINDIAGO), Department of Medicine, Faculty of Health Science Norris, Shane; University of Witwatersrand, Paediatrics and Child Health; University of Cape Town, Integrated Intervention for DIAbetes risks after GestatiOnal diabetes (IINDIAGO), Department of Medicine, Faculty of Health Science Murphy, Katherine; University of Cape Town, Chronic Disease Initiative for Africa, Department of Medicine, Faculty of Health Science; University of Cape Town, Integrated Intervention for DIAbetes risks after GestatiOnal diabetes (IINDIAGO), Department of Medicine, Faculty of Health Science Trottier, Helen; École de Santé Publique, Université de Montréal, Médecine Sociale et Préventive; Centre de Recherche du Centre Hospitalier Universitaire Sainte Justine Levitt, Naomi; University of Cape Town, Chronic Disease Initiative for Africa, Department of Medicine, Faculty of Health Science; University of Cape Town, Integrated Intervention for DIAbetes risks after GestatiOnal diabetes (IINDIAGO), Department of Medicine, Faculty of Health Science Zarowsky, Christina; École de Santé Publique, Université de Montréal , Médecine Sociale et Préventive; Centre de Recherche du Centre Hospitalier de l'Université de Montréal (CRCHUM)
Primary Subject Heading:	Health services research
Secondary Subject Heading:	Diabetes and endocrinology
Keywords:	Type 2 diabetes, Gestational diabetes, Multi-morbidity, Integrated care, Global health, Africa

Integrated management of type 2 diabetes and gestational diabetes within multi-morbidity conditions in Africa: A systematic review protocol

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Abstract

Introduction: Multi-morbidity, defined as the co-existence of more than one chronic condition in one person, has been increasing due to comorbid non-communicable and infectious chronic diseases (CNCICDs). Type 2 diabetes (T2D) and gestational diabetes mellitus (GDM) incidences within the CNCICDs conditions are increasing and overwhelming already weak and under-resourced health care systems in Africa. There is then an urgent need for the integrated management of CNCICDs. We aim to review the integrated management of T2D and GDM within multi-morbidity conditions in Africa.

Methods: Studies that have assessed the integrated management of T2D and GDM within multi-morbidity conditions in Africa will be considered based on the PICO method: Population (adult diagnosed with T2D and GDM, who also have other diseases, non-communicable diseases (NCDs) and infectious, in public primary and secondary health care facilities in Africa); Intervention (integrated management of T2D and GDM, also suffering from other diseases in Africa), Comparator (Unintegrated management of T2D and GDM in Africa) and Outcomes (integrated management of T2D and GDM in Africa). The following databases Cochrane Library, MEDLINE, PubMed and SCOPUS, the WHO International Clinical Trials Registry Platform, among others will be searched. Two reviewers (JCM, MW) will independently screen, select eligible studies, and extract data. Discrepancies will be resolved by consensus or by a discussion with the third author (AR). Quality of included studies will be assessed using both the newly developed tool, "the Cochrane Collaboration Risk of Bias Tool (CCRBT)" and "Risk Of Bias In Non-randomized Studies - of Interventions (ROBINS-I)". A narrative synthesis of extracted

data and meta-analysis, if necessary will be conducted and then reported according to the preferred reporting items for systematic review and meta-analysis (PRISMA).

Ethics consideration and dissemination: By only using the published data, there is no ethics approval required for this study. This systematic review will be included in JCM's PhD thesis and its findings will also be disseminated through peer-reviewed publication and conference presentation.

Systematic review registration: PROSPERO CRD42016046630

Keywords: Type 2 diabetes, gestational diabetes, multi-morbidity, integrated care, Africa.

Strengths and limitations of this study

- √ Substantial search strategy to identify relevant studies will be adopted, a large number of online databases will be searched, public health websites will be manually searched and credible experts will be consulted.
- √ Study results will be assessed and reported in accordance with relevant guidelines for quality assessment of systematic reviews.
- √ Scarcity of eligible studies for selection and inclusion is expected.
- √ Reviewers will not be blinded during data extraction and quality assessment stages.

1. Introduction

The World Health Organisation (WHO) global report in 2016 estimated that 415-422 million adults worldwide had diabetes in 2014-2015 and that diabetes caused 5 million deaths in 2015, with an estimated 673 billion USA dollars of total global health expenditure in diabetes care [1, 2]. In the Africa region there were an estimated 14.2 million people with diabetes in 2015 increasing to 34.2 million in 2040 [1, 3]. With the expected rural depopulation causing increased exposure to urban environments and diabetogenic lifestyles such as inactivity, obesity, depression, smoking among others, diabetes cases are expected to increase by 54% to 642 million worldwide by 2040 [3-5].

Globally, the burden of non-communicable diseases (NCDs) is rising. Low and middle-income countries (LMICs) are most affected by changes in patterns of population age distributions, fertility, life expectancy, morbidity and mortality, known as the "epidemiological transition" [6]. In Africa, especially in sub-Saharan Africa, this is occurring against a background of continuing infectious disease epidemics (i.e., HIV and tuberculosis), increasingly becoming a coinfection epidemic that requires an integrated response [7]. Consequently, multi-morbidity defined as the co-existence of more than one chronic condition in one person, has been increasing due to comorbid non-communicable and infectious chronic diseases (CNCICDs) [8]. Given the risk factors and complex care needs of multi-morbidity, there is a need to integrate healthcare systems, particularly between primary and secondary health care.

The current approaches to surveillance, prevention and treatment of CNCICDs appear to be insufficient to provide for the long-term health needs of this convergence especially in the context of human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS) era, antiretroviral therapy (ART) linked concomitant metabolic complications and HIV/AIDS allied opportunistic infectious diseases [9]. To address this, the WHO developed the Innovative Care for Chronic Conditions (ICCC) Framework to provide a healthcare systems roadmap that would meet the increasing needs of chronic disease care within this growing multi-morbidity context. This framework incorporates community, patient, healthcare and policy environment perspectives, and has been adopted by different healthcare systems. However, it does not clearly include the infectious diseases within the context of multi-morbidity [8] and it is then necessary to reorganise health care services and systems to tackle this growing public health problem [8, 9].

The 2016 global diabetes report [1] emphasizes the need to reach better outcomes of diabetes management through an integrated management, especially with NCDs such as cardiovascular diseases as well as tuberculosis and/or HIV/AIDS. This is especially important where the prevalence of these diseases is high. Despite calls for a shift in approach from disease-specific interventions to the integrated delivery model [10], health care systems in Africa are weak and under-resourced to provide care for the increasing number of patients with multi-morbidities including diabetes, especially compared to high-income settings [11].

Two types of diabetes commonly identified during adulthood are type 2 diabetes (T2D), that is insulin resistance linked diabetes, and gestational diabetes (GDM), known as a

glucose intolerance with onset or first recognition during pregnancy. T2D can be prevented or delayed for women with previous GDM [12-16]. The established connection between T2D and GDM [9] does not determine how GMD is managed. It can either be managed alone in a diabetic clinic or preferably within integrated care at ANC and postnatal clinics, which is a right approach for increasing multi-morbidity [17, 18].

The treatment pathway for women with GDM is through accessing antenatal care (ANC) at the nearest health facility for their pregnancy follow-up and delivery. In contrast, only a small proportion of women with recent GDM return for postpartum oral glucose tolerance test, assessment and management [19-23]. The main challenge is that GDM women must navigate fragmented health systems for their care and care of their babies and this situation supports calls for integrated health systems and services that are easy for patients to navigate [24].

Disease-specific or vertical programmes can be used to manage specific diseases and health problems while strengthening fragmented health systems in Africa [25]. However, disease-specific or stand-alone interventions are criticized for not promoting equity and sustainability of their outcomes [26], and therefore integrated programmes to address various NCDs such diabetes in comorbid conditions are recommended [9, 27].

Integrated care is "*combining parts so that they work to form a whole (i.e., integration) in order to optimise care and treatment to people where fragmentations in care have led to a negative impact on their care experiences and outcomes*" [28]. It describes a range of organizational arrangements with variable nature and intensity and comprises two main concepts: a) an organizational structure focused on economic benefits (cost-

effectiveness), or b) a way of organizing service delivery [29, 30]. We conceptualized integration based on dynamic interactions in which formal governance is arranged, responsibilities are shared and resources are pooled [29, 31], regardless of many other existing integration level models such integrated care typologies used in a recent systematic review that studied the integration of cardiovascular diseases, hypertension and diabetes with HIV services [32].

The analysis of interactions in health systems enables us to understand the levels of integration. They include partial integration initiatives ranging from (1) the linkage or unstructured interactions, (2) the coordination with a committee to oversee their goal-oriented works but keeping the separated structures, and full integration in which two programmes are merged in their structures (funds, human resources, informational system) and functional elements (strategic planning, resources allocation, interventions delivery) [29, 33].

Integrated health care systems have advantages such as being associated with more accessibility of care, improved quality and safety of care, health care cost reductions and economic benefits for both providers and families [34, 35]. This integrated management approach including partial and full integration initiatives, will play a key in responding and providing the appropriate health care services to the increasing cases of multiple conditions [32].

We aim to provide a systematic review on integrated management of T2D and GDM within the CNCICDs conditions in Africa. The ultimate goal is to describe the emerging practices and lessons learned from integrated management of GDM and T2D within comorbidity conditions in Africa and the different research gaps to GDM and T2D

integration within management of other non-communicable and infectious chronic diseases.

This systematic review aims to answer the following research questions: 1) What are the existing integrated interventions and services delivery models for managing T2D including GDM within multi-morbidity conditions in Africa? 2) What are the successes and challenges of the existing integrated management of T2D including GDM within multi-morbidity conditions?

2. Methods

The Cochrane Handbook and systematic review study protocol [36] published by the Cochrane Collaboration Methods Groups that provides the methodological framework in designing and conducting this systematic review to enable critical appraisal and replication. We did register this protocol online on PROSPERO, the International prospective register of systematic reviews, found at (https://www.crd.york.ac.uk/prospero/, registration no. CRD42016046630).

Study design

This systematic review will only include studies of good quality based on the developed inclusion and exclusion criteria.

Patient and public involvement

There will be no patient and/or public involvement in this study.

Search strategy for the identification of relevant studies

Our search strategy will use the controlled terms (MeSH: Medical subject heading) and free texts. The following databases Cochrane Library, MEDLINE, PubMed and

SCOPUS. Other database resources such as the WHO International Clinical Trials Registry Platform, Clinicaltrials.gov, Pan African Clinical Trials Registry (PACTR) and HINARI (Health InterNetwork Access to Research Initiative) will be searched. Additional search will be conducted in Google scholar. Our research will focus on articles published and gray literature in English and French languages. Upon the extraction of interesting articles in other languages without any English or French abstracts, we will then include them or get assisted by a researcher who is fluent in those languages. Since there were not many articles regarding our review topic in our preliminary search, there will be no time limits in our search but our focus will be limited to all fifty-four African countries. The search will be conducted from the start of each database until the present date to include all relevant studies. Search Strategy will be validated with the assistance of a Librarian.

Our search for articles will be based on the following Population, Intervention, Comparator and Outcome (PICO) method [37] describing the population, intervention, comparator and outcome (see the table 1 below).

PICO description table

Population	**Intervention**	**Comparator**	**Outcomes**
Adults diagnosed with T2D and women diagnosed with GDM, who have other diseases in public primary and secondary health care facilities in Africa	Partial or full Integrated management of T2D in adults and GDM in pregnant women who have other diseases in Africa	Unintegrated management of T2D and GDM in public primary and secondary healthcare facilities in Africa.	Utilisation and effectiveness of Integrated management of T2D and GDM in public primary and secondary healthcare facilities within multi-

			morbidity conditions in Africa

Criteria for considering studies for this review

Studies that have assessed the integrated management of T2D and GDM within multi-morbidity conditions in Africa will be considered, including randomised controlled trials (RCTs), non-RCTs, quasi-randomised controlled trials (QCTs) and observational studies. Studies will be all kinds of interventions with different targeted participants from all ethnicities, genders, socioeconomic, educational backgrounds and in all countries in Africa who were diagnosed with T2D and GDM as one disease of the multi-morbidity using standard diagnostic criteria will be eligible for inclusion. The patients who had T2D including GDM before and after the occurrence of other diseases and the interventions to handle both diseases will be included in this review. Interventions carried out or facilitated by healthcare providers including community health workers in public health facilities will also be included, providing that the focus of the intervention is to treat diseases in which one is diabetes, specifically T2D and GDM. Studies that separately evaluated interventions or assessing vertical programmes of T2D, GDM and other diseases, will be excluded.

Reference lists

Manual-search by (MJC and MW) lists of references of included studies, tables of contents of relevant journals and conference abstracts for the relevant material will be conducted. A grey literature search strategy by (JCM and MW) will be developed to conduct web-based searches to obtain key unpublished sources in our stated search languages.

Selection of studies

Full copies of articles identified by the search, and considered to meet the inclusion criteria, based on the title and abstract will be obtained for data synthesis. Initially, studies will be screened using predefined inclusion and exclusion criteria. Two reviewers (JCM and MW) will apply the criteria independently to the results of the searches, based first on titles and abstracts only. At least two reviewers (JCM and MW) will proceed independently with the articles selection at the same time based on our described inclusion criteria into two steps: 1) examining the title and abstract, and then, 2) reviewing the full texts. Study authors of eligible articles for which the full text copies are not freely accessible will be contacted to obtain their access and additional information about them will also be requested if required. The inclusion of an article will be made by consensus. In case the two (JCM and MW) do not reach consensus, the decision from a third person (AR) will be required and reasons for exclusion will be recorded. All studies which initially appear to meet inclusion criteria but on closer inspection do not meet the inclusion criteria will also be detailed in the table of "characteristics of excluded studies". The preferred reporting items for systematic review and meta-analysis (PRISMA) flow chart will be produced to facilitate transparency of the process (See Fig. 1) [38, 39].

Types of outcome measures

Studies reporting at least one of the following outcomes will be included:

Primary outcomes

Two primary outcomes will be considered: 1) Integrated care outcome and 2) cost-effectiveness outcome. For the integrated care outcome, the focus will be on patients screened and/or treated for both T2D and GDM in the course of treatment of other major

diseases (e.g. HIV, tuberculosis, cardiovascular diseases, etc.) in what is known as multi-morbidity conditions. For cost-effectiveness outcome, the focus will be on approach to integrated diagnosis and treatment of T2D and GDM within comorbidity conditions, which simplifies the workload and saves means of depleted health systems in Africa and helps the patients to do not navigate different levels of health systems for their comorbidities that positively impacts the family economies.

Secondary outcomes

We will also consider early diagnosis through the integrated management of other diseases as this improves clinical outcomes and strengthens health systems for the long-term results of the integrated management of T2D diabetes including GDM within comorbidity conditions.

Quality assessment

The quality of articles selected will be assessed using the newly developed tool, "the Cochrane Collaboration Risk of Bias Tool (CCRBT)" and "Risk Of Bias In Non-randomized Studies - of Interventions (ROBINS-I)" [40, 41]. The CCRBT is an appropriate quality assessment tool for or RCTs & QCTs [41, 42]. Since the quick preliminary search shows that there are few RCTs and QCTs to be included in this study, this single tool will not be enough and the ROBINS-I will be used to assess the quality of non-RCTs and observational studies [41]. These quality assessment tools encompass all aspects needed to appraise the quality of any studies that will be selected for inclusion.

Two reviewers (JCM and MW) will independently assess the risk of bias in the included studies and cross-checked by a third reviewer (AR).

The following individual quality elements recommended in the modified Cochrane Collaboration tool to assess the risk of bias for RCTs (high, low, or unclear) as a judgment for individual elements from six domains (selection, performance, attrition, reporting, and other) [40], will be assessed for RCTs and QCTs. Likewise, the elements recommended in the ROBINS-I to assess risk of bias for non-RCTs and observational studies (low, moderate, serious and critical) as a judgement for individual categories from six domains of bias (bias due to confounding, bias in selection of participants into the study, bias in classification of interventions, bias due to deviations from intended interventions, bias due to missing data, bias in measurement of outcomes and bias in selection of the reported result) [41] will also be assessed.

Any disagreements over bias between two reviewers will be settled by involving the third review author and each bias in these domains for each study will be separately presented in a table in the final review publication.

Data extraction and management

As above discussed, the selected citation titles and abstracts will be exported from the search engines to Endnote X8.2 and duplicates will be removed automatically and a search will be conducted manually to check any missed duplicates. Eligible citations will be retrieved after the screening of titles and abstracts and full texts be sought and imported.

JCM and MW will extract data on: study ID, author's name, country, year, type of paper/report, form of publication, study design, comorbidity, description of the intervention (including process, cost-effectiveness and outcomes), context of integrated intervention (i.e. PHC, hospitals), details about participants (including number in each

group, baseline health information, demographic characteristics), length of intervention and follow-up.

Data analysis and synthesis

We will first undertake a narrative synthesis to summarize and discuss the findings of the included studies. We will then present findings through primary and secondary outcomes. We will use tabular summary to synthesize individual studies characteristics and results (intervention effects). The data synthesis will be conducted through the measurements of effect for continuous outcomes of the included studies. Studies reporting multiple outcomes and outcome measures will be categories according to definitions outline in section types of outcome measure above.

A predetermined order of preference for extracting multiple outcome measures will be used where data is available in several formats. For RCTs preference will be to extract data that requires the least manipulation by authors or inference by review authors. Raw values (e.g. Means and standard deviations) rather than calculated effect size will be extracted. For studies reporting both final values and changes from baseline for outcomes, preference will be to extract the former. In the case of cluster-RCTs, the preference will be (i) extract adjusted estimates reported by the study, or (ii) use raw data and inflated the standard error (SE) data using weighting.

In case of missing data in some eligible studies, efforts will be made to contact corresponding authors to request for clarification of all relevant information. For ongoing studies trial authors will be contacted for further information and updates.

Statistical analysis and subgroup analysis and investigation of heterogeneity

Heterogeneity between studies will then be assessed using both x^2 and I^2 and Q statistics where appropriate. The I^2 statistic estimates the percentage of total variation across studies due to a true difference rather than chance. In general, I^2 values greater than 60–70% indicate the presence of substantial heterogeneity. We will explore sources of heterogeneity by comparing the pooled study estimates between subgroups defined by study-level characteristics. Subgroup analysis will be performed where heterogeneity is statistically significant. Sensitivity analyses will be conducted to determine the potential sources of heterogeneity. Two additional sensitivity analyses will be conducted to: (i) evaluate the effect of excluding studies unable to meet each quality criterion affect the overall estimate, and (ii) evaluate the change in the results if only high-quality studies where included.

In case the identified studies are of substantial heterogeneity and where statistical pooling is impossible, the findings will be summarizing in a narrative form by tables and figures to facilitate in effective data presentations. Two reviewers will write the narratives independently and later checked by other reviewers. Decisions on any disagreements will be resolved through discussions and consensus by all reviewers in the team. We will assess the presence of publication bias by using a funnel plot and the Egger test of bias [43]. Subgroup and sensitivity analyses will be conducted to look at the effects of certain factors on for example: geographic region, age and gender and diabetes type of participating patients.

Reporting of this review

This systematic review results will be reported according to preferred reporting items for systematic review and meta-analysis (PRISMA) (see Table. 2) [39].

Ethics and dissemination

Given that this is a protocol for a systematic review only using the published data, there is no ethics approval required for this study. This systematic review will be included in JCM's PhD thesis, a research supervised by Christina Zarowsky (CZ) and Helen Trottier (HT). Its findings will also be disseminated through peer-reviewed publications and conference presentations.

Figure and table legends

Figure 1: The preferred reporting items for systematic review and meta-analysis (PRISMA) flow chart

Table 2: The 27 checklist items pertain to the content of a systematic review and meta-analysis.

Abbreviations

AIDS: Acquired Immunodeficiency Syndrome

ANC: Antenatal Care

ART: Antiretroviral Therapy

CCRBT: Cochrane Collaboration Risk of Bias Tool

CNCICDs: Comorbid Non-Communicable and Infectious Chronic Diseases

EPHPP: Effective Public Health Practice Project

GDM: Gestational Diabetes Mellitus

HINARI: Health InterNetwork Access to Research Initiative

HIV: Human Immunodeficiency Virus

ICCC: Innovative Care for Chronic Conditions

LMICs: Low and Middle-Income Countries

MeSH: Medical subject heading

NCDs: Non-Communicable Diseases

PACTR: Pan African Clinical Trials Registry

PICO: Population, Intervention, Comparator and Outcome

PRISMA: Preferred Reporting Items for Systematic review and Meta-Analysis

QCTs: Quasi-randomised Controlled Trials

RCTs: Randomised Controlled Trial

ROBINS-I: Risk Of Bias In Non-randomized Studies - of Interventions

SE: Standard Error

T2D: Type 2 Diabetes.

Acknowledgments

We would like to thank Sylvie Fontaine, the librarian at the paramedical library, Université de Montréal, Canada, for her valuable contribution to search strategy development and the the reviewers of the manuscript for their constructive inputs.

Funding

No funder.

Availability of data and materials

Not applicable.

Author contributions

MJC, and MW designed the study. MJC wrote the first manuscript of the review. MJC, MW, AR, EM, KM, SN, HT, NL and CZ critically revised the review. All authors read and approved the final manuscript.

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Competing interests

MJC, MW, AR, EM, KM, SN, HT, NL and CZ declare no competing interests.

Consent for publication

Not applicable.

Ethics approval and consent to participate

Not applicable.

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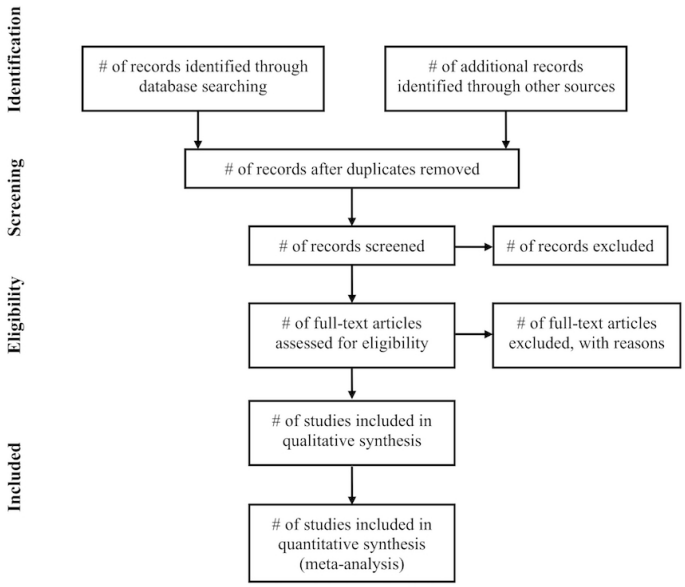

Fig. 1-PRISMA flowchart for systematic review

90x127mm (300 x 300 DPI)

BMJ Open

Integrated management of type 2 diabetes and gestational diabetes within multi-morbidity conditions in Africa: A systematic review protocol

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-023684.R2
Article Type:	Protocol
Date Submitted by the Author:	12-Jan-2019
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Primary Subject Heading:	Health services research
Secondary Subject Heading:	Diabetes and endocrinology
Keywords:	Type 2 diabetes, Gestational diabetes, Multi-morbidity, Integrated care, Global health, Africa

Integrated management of type 2 diabetes and gestational diabetes within multi-morbidity conditions in Africa: A systematic review protocol

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Abstract

Introduction: Multi-morbidity, defined as the co-existence of more than one chronic condition in one person, has been increasing due to comorbid non-communicable and infectious chronic diseases (CNCICDs). Type 2 diabetes (T2D) and gestational diabetes mellitus (GDM) incidences within the CNCICDs conditions are increasing and overwhelming already weak and under-resourced health care systems in Africa. There is then an urgent need for the integrated management of CNCICDs. We aim to review the integrated management of T2D and GDM within multi-morbidity conditions in Africa.

Methods: Studies that have assessed the integrated management of T2D and GDM within multi-morbidity conditions in Africa will be considered based on the PICO method: Population (adult diagnosed with T2D and GDM, who also have other diseases, non-communicable diseases (NCDs) and infectious, in public primary and secondary health care facilities in Africa); Intervention (integrated management of T2D and GDM, also suffering from other diseases in Africa), Comparator (Unintegrated management of T2D and GDM in Africa) and Outcomes (integrated management of T2D and GDM in Africa). The following databases Cochrane Library, MEDLINE, PubMed and SCOPUS, the WHO International Clinical Trials Registry Platform, among others will be searched. Two reviewers (JCM, MW) will independently screen, select eligible studies, and extract data. Discrepancies will be resolved by consensus or by a discussion with the third author (AR). Quality of included studies will be assessed using both the newly developed tool, "the Cochrane Collaboration Risk of Bias Tool (CCRBT)" and "Risk Of Bias In Non-randomized Studies - of Interventions (ROBINS-I)". A narrative synthesis of extracted data

and meta-analysis, if necessary will be conducted and then reported according to the preferred reporting items for systematic review and meta-analysis (PRISMA).

Ethics consideration and dissemination: By only using the published data, there is no ethics approval required for this study. This systematic review will be included in JCM's PhD thesis and its findings will also be disseminated through peer-reviewed publication and conference presentation.

Systematic review registration: PROSPERO CRD42016046630

Keywords: Type 2 diabetes, gestational diabetes, multi-morbidity, integrated care, Africa.

Strengths and limitations of this study

- √ Substantial search strategy to identify relevant studies will be adopted, a large number of online databases will be searched, public health websites will be manually searched and credible experts will be consulted.
- √ Study results will be assessed and reported in accordance with relevant guidelines for quality assessment of systematic reviews.
- √ Scarcity of eligible studies for selection and inclusion is expected.
- √ Reviewers will not be blinded during data extraction and quality assessment stages.

1. Introduction

The World Health Organisation (WHO) global report in 2016 estimated that 415-422 million adults worldwide had diabetes in 2014-2015 and that diabetes caused 5 million deaths in 2015, with an estimated 673 billion USA dollars of total global health expenditure in diabetes care [1, 2]. In the Africa region there were an estimated 14.2 million people with diabetes in 2015 increasing to 34.2 million in 2040 [1, 3]. With the expected rural depopulation causing increased exposure to urban environments and diabetogenic lifestyles such as inactivity, obesity, depression, smoking among others, diabetes cases are expected to increase by 54% to 642 million worldwide by 2040 [3-5].

Globally, the burden of non-communicable diseases (NCDs) is rising. Low and middle-income countries (LMICs) are most affected by changes in patterns of population age distributions, fertility, life expectancy, morbidity and mortality, known as the "epidemiological transition" [6]. In Africa, especially in sub-Saharan Africa, this is occurring against a background of continuing infectious disease epidemics (i.e., HIV and tuberculosis), increasingly becoming a coinfection epidemic that requires an integrated response [7]. Consequently, multi-morbidity defined as the co-existence of more than one chronic condition in one person, has been increasing due to comorbid non-communicable and infectious chronic diseases (CNCICDs) [8]. Given the risk factors and complex care needs of multi-morbidity, there is a need to integrate healthcare systems, particularly between primary and secondary health care.

The current approaches to surveillance, prevention and treatment of CNCICDs appear to be insufficient to provide for the long-term health needs of this convergence especially in

the context of human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS) era, antiretroviral therapy (ART) linked concomitant metabolic complications and HIV/AIDS allied opportunistic infectious diseases [9]. To address this, the WHO developed the Innovative Care for Chronic Conditions (ICCC) Framework to provide a healthcare systems roadmap that would meet the increasing needs of chronic disease care within this growing multi-morbidity context. This framework incorporates community, patient, healthcare and policy environment perspectives, and has been adopted by different healthcare systems. However, it does not clearly include the infectious diseases within the context of multi-morbidity [8] and it is then necessary to reorganise health care services and systems to tackle this growing public health problem [8, 9].

The 2016 global diabetes report [1] emphasizes the need to reach better outcomes of diabetes management through an integrated management, especially with NCDs such as cardiovascular diseases as well as tuberculosis and/or HIV/AIDS. This is especially important where the prevalence of these diseases is high. Despite calls for a shift in approach from disease-specific interventions to the integrated delivery model [10], health care systems in Africa are weak and under-resourced to provide care for the increasing number of patients with multi-morbidities including diabetes, especially compared to high-income settings [11].

Two types of diabetes commonly identified during adulthood are type 2 diabetes (T2D), that is insulin resistance linked diabetes, and gestational diabetes (GDM), known as a glucose intolerance with onset or first recognition during pregnancy. T2D can be prevented or delayed for women with previous GDM [12-16]. The established connection between T2D and GDM [9] does not determine how GMD is managed. It can either be managed

alone in a diabetic clinic or preferably within integrated care at ANC and postnatal clinics, which is a right approach for increasing multi-morbidity [17, 18].

The treatment pathway for women with GDM is through accessing antenatal care (ANC) at the nearest health facility for their pregnancy follow-up and delivery. In contrast, only a small proportion of women with recent GDM return for postpartum oral glucose tolerance test, assessment and management [19-23]. The main challenge is that GDM women must navigate fragmented health systems for their care and care of their babies and this situation supports calls for integrated health systems and services that are easy for patients to navigate [24].

Disease-specific or vertical programmes can be used to manage specific diseases and health problems while strengthening fragmented health systems in Africa [25]. However, disease-specific or stand-alone interventions are criticized for not promoting equity and sustainability of their outcomes [26], and therefore integrated programmes to address various NCDs such diabetes in comorbid conditions are recommended [9, 27].

Integrated care is "*combining parts so that they work to form a whole (i.e., integration) in order to optimise care and treatment to people where fragmentations in care have led to a negative impact on their care experiences and outcomes*" [28]. It describes a range of organizational arrangements with variable nature and intensity and comprises two main concepts: a) an organizational structure focused on economic benefits (cost-effectiveness), or b) a way of organizing service delivery [29, 30]. We conceptualized integration based on dynamic interactions in which formal governance is arranged, responsibilities are shared and resources are pooled [29, 31], regardless of many other existing integration level

models such integrated care typologies used in a recent systematic review that studied the integration of cardiovascular diseases, hypertension and diabetes with HIV services [32].

The analysis of interactions in health systems enables us to understand the levels of integration. They include partial integration initiatives ranging from (1) the linkage or unstructured interactions, (2) the coordination with a committee to oversee their goal-oriented works but keeping the separated structures, and full integration in which two programmes are merged in their structures (funds, human resources, informational system) and functional elements (strategic planning, resources allocation, interventions delivery) [29, 33].

Integrated health care systems have advantages such as being associated with more accessibility of care, improved quality and safety of care, health care cost reductions and economic benefits for both providers and families [34, 35]. This integrated management approach including partial and full integration initiatives, will play a key in responding and providing the appropriate health care services to the increasing cases of multiple conditions [32].

We aim to provide a systematic review on integrated management of T2D and GDM within the CNCICDs conditions in Africa. The ultimate goal is to describe the emerging practices and lessons learned from integrated management of GDM and T2D within comorbidity conditions in Africa and the different research gaps to GDM and T2D integration within management of other non-communicable and infectious chronic diseases.

This systematic review aims to answer the following research questions: 1) What are the existing integrated interventions and services delivery models for managing T2D including GDM within multi-morbidity conditions in Africa? 2) What are the successes and

challenges of the existing integrated management of T2D including GDM within multi-morbidity conditions?

2. Methods

The Cochrane Handbook and systematic review study protocol [36] published by the Cochrane Collaboration Methods Groups provides the methodological framework in designing and conducting this systematic review to enable critical appraisal and replication. We did register this protocol online on PROSPERO, the International prospective register of systematic reviews, found at (https://www.crd.york.ac.uk/prospero/, registration no. CRD42016046630).

Study design

This systematic review will only include studies of good quality based on the developed inclusion and exclusion criteria.

Patient and public involvement

There will be no patient and/or public involvement in this study.

Search strategy for the identification of relevant studies

Our search strategy will use the controlled terms (MeSH: Medical subject heading) and free texts. The following databases will be searched: Cochrane Library, MEDLINE, PubMed and SCOPUS. Other database resources such as the WHO International Clinical Trials Registry Platform, Clinicaltrials.gov, Pan African Clinical Trials Registry (PACTR) and HINARI (Health InterNetwork Access to Research Initiative) will also be searched. Additional search will be conducted in Google scholar. Our research will focus on articles published and gray literature in English and French languages. Upon the extraction of

interesting articles in other languages without any English or French abstracts, we will then include them or get assisted by a researcher who is fluent in those languages. Since there were not many articles regarding our review topic in our preliminary search, there will be no starting time limits in our search but our focus will be limited to all fifty-four African countries. However, the search will be conducted from the start of each database until the 31st December to include as many relevant studies as possible. Search Strategy will be validated with the assistance of a Librarian.

Our search for articles will be based on the following Population, Intervention, Comparator and Outcome (PICO) method [37] (see the table 1 below).

Table 1: PICO description table

Population	Intervention	Comparator	Outcomes
Adults diagnosed with T2D and women diagnosed with GDM, who have other diseases in public primary and secondary health care facilities in Africa	Partial or full Integrated management of T2D in adults and GDM in pregnant women who have other diseases in Africa	Unintegrated management of T2D and GDM in public primary and secondary healthcare facilities in Africa.	Utilisation and effectiveness of Integrated management of T2D and GDM in public primary and secondary healthcare facilities within multi-morbidity conditions in Africa

Criteria for considering studies for this review

Studies that have assessed the integrated management of T2D and GDM within multi-morbidity conditions in Africa will be considered, including randomised controlled trials (RCTs), non-RCTs, quasi-randomised controlled trials (QCTs) and observational studies.

Studies will be all kinds of interventions with different targeted participants from all ethnicities, genders, socioeconomic, educational backgrounds and in all countries in Africa who were diagnosed with T2D and GDM as one disease of the multi-morbidity using standard diagnostic criteria will be eligible for inclusion. The patients who had T2D including GDM before and after the occurrence of other diseases and the interventions to handle both diseases will be included in this review. Interventions carried out or facilitated by healthcare providers including community health workers in public health facilities will also be included, providing that the focus of the intervention is to treat diseases in which one is diabetes, specifically T2D and GDM. Studies that separately evaluated interventions or assessing vertical programmes of T2D, GDM and other diseases, will be excluded.

Reference lists

Manual-search by (MJC and MW) lists of references of included studies, tables of contents of relevant journals and conference abstracts for the relevant material will be conducted. A grey literature search strategy by (JCM and MW) will be developed to conduct web-based searches to obtain key unpublished sources in our stated search languages.

Selection of studies

Full copies of articles identified by the search, and considered to meet the inclusion criteria, based on the title and abstract will be obtained for data synthesis. Initially, studies will be screened using predefined inclusion and exclusion criteria. Two reviewers (JCM and MW) will apply the criteria independently to the results of the searches, based first on titles and abstracts only. At least two reviewers (JCM and MW) will proceed independently with the articles selection at the same time based on our described inclusion criteria into two steps: 1) examining the title and abstract, and then, 2) reviewing the full texts. Study authors of

eligible articles for which the full text copies are not freely accessible will be contacted to obtain their access and additional information about them will also be requested if required. The inclusion of an article will be made by consensus. In case the two (JCM and MW) do not reach consensus, the decision from a third person (AR) will be required and reasons for exclusion will be recorded. All studies which initially appear to meet inclusion criteria but on closer inspection do not meet the inclusion criteria will also be detailed in the table of "characteristics of excluded studies". The preferred reporting items for systematic review and meta-analysis (PRISMA) flow chart will be produced to facilitate transparency of the process (See Fig. 1) [38, 39].

Types of outcome measures

Studies reporting at least one of the following outcomes will be included:

Primary outcomes

Two primary outcomes will be considered: 1) Integrated care outcome and 2) cost-effectiveness outcome. For the integrated care outcome, the focus will be on patients screened and/or treated for both T2D and GDM in the course of treatment of other major diseases (e.g. HIV, tuberculosis, cardiovascular diseases, etc.) in what is known as multi-morbidity conditions. For cost-effectiveness outcome, the focus will be on approach to integrated diagnosis and treatment of T2D and GDM within comorbidity conditions, which simplifies the workload and saves means of depleted health systems in Africa and helps the patients to do not navigate different levels of health systems for their comorbidities that positively impacts the family economies.

Secondary outcomes

We will also consider early diagnosis through the integrated management of other diseases as this improves clinical outcomes and strengthens health systems for the long-term results of the integrated management of T2D diabetes including GDM within comorbidity conditions.

Quality assessment

The quality of articles selected will be assessed using the newly developed tool, "the Cochrane Collaboration Risk of Bias Tool (CCRBT)" and "Risk Of Bias In Non-randomized Studies - of Interventions (ROBINS-I)" [40, 41]. The CCRBT is an appropriate quality assessment tool for or RCTs & QCTs [41, 42]. Since the quick preliminary search shows that there are few RCTs and QCTs to be included in this study, this single tool will not be enough and the ROBINS-I will be used to assess the quality of non-RCTs and observational studies [41]. These quality assessment tools encompass all aspects needed to appraise the quality of any studies that will be selected for inclusion.

Two reviewers (JCM and MW) will independently assess the risk of bias in the included studies and cross-checked by a third reviewer (AR).

The following individual quality elements recommended in the modified Cochrane Collaboration tool to assess the risk of bias for RCTs (high, low, or unclear) as a judgment for individual elements from six domains (selection, performance, attrition, reporting, and other) [40], will be assessed for RCTs and QCTs. Likewise, the elements recommended in the ROBINS-I to assess risk of bias for non-RCTs and observational studies (low, moderate, serious and critical) as a judgement for individual categories from six domains of bias (bias due to confounding, bias in selection of participants into the study, bias in classification of interventions, bias due to deviations from intended interventions, bias due

to missing data, bias in measurement of outcomes and bias in selection of the reported result) [41] will also be assessed.

Any disagreements over bias between two reviewers will be settled by involving the third review author and each bias in these domains for each study will be separately presented in a table in the final review publication.

Data extraction and management

As above discussed, the selected citation titles and abstracts will be exported from the search engines to Endnote X8.2 and duplicates will be removed automatically and a search will be conducted manually to check any missed duplicates. Eligible citations will be retrieved after the screening of titles and abstracts and full texts be sought and imported.

JCM and MW will extract data on: study ID, author's name, country, year, type of paper/report, form of publication, study design, comorbidity, description of the intervention (including process, cost-effectiveness and outcomes), context of integrated intervention (i.e. PHC, hospitals), details about participants (including number in each group, baseline health information, demographic characteristics), length of intervention and follow-up.

Data analysis and synthesis

We will first undertake a narrative synthesis to summarize and discuss the findings of the included studies. We will then present findings through primary and secondary outcomes. We will use tabular summary to synthesize individual studies characteristics and results (intervention effects). The data synthesis will be conducted through the measurements of effect for continuous outcomes of the included studies. Studies reporting multiple

outcomes and outcome measures will be categories according to definitions outline in section types of outcome measure above.

A predetermined order of preference for extracting multiple outcome measures will be used where data is available in several formats. For RCTs preference will be to extract data that requires the least manipulation by authors or inference by review authors. Raw values (e.g. Means and standard deviations) rather than calculated effect size will be extracted. For studies reporting both final values and changes from baseline for outcomes, preference will be to extract the former. In the case of cluster-RCTs, the preference will be (i) extract adjusted estimates reported by the study, or (ii) use raw data and inflated the standard error (SE) data using weighting.

In case of missing data in some eligible studies, efforts will be made to contact corresponding authors to request for clarification of all relevant information. For ongoing studies trial authors will be contacted for further information and updates.

Statistical analysis and subgroup analysis and investigation of heterogeneity

Heterogeneity between studies will then be assessed using both x^2 and I^2 and Q statistics where appropriate. The I^2 statistic estimates the percentage of total variation across studies due to a true difference rather than chance. In general, I^2 values greater than 60–70% indicate the presence of substantial heterogeneity. We will explore sources of heterogeneity by comparing the pooled study estimates between subgroups defined by study-level characteristics. Subgroup analysis will be performed where heterogeneity is statistically significant. Sensitivity analyses will be conducted to determine the potential sources of heterogeneity. Two additional sensitivity analyses will be conducted to: (i) evaluate the

effect of excluding studies unable to meet each quality criterion affect the overall estimate, and (ii) evaluate the change in the results if only high-quality studies where included.

In case the identified studies are of substantial heterogeneity and where statistical pooling is impossible, the findings will be summarizing in a narrative form by tables and figures to facilitate in effective data presentations. Two reviewers will write the narratives independently and later checked by other reviewers. Decisions on any disagreements will be resolved through discussions and consensus by all reviewers in the team. We will assess the presence of publication bias by using a funnel plot and the Egger test of bias [43]. Subgroup and sensitivity analyses will be conducted to look at the effects of certain factors on for example: geographic region, age and gender and diabetes type of participating patients.

Reporting of this review

This systematic review results will be reported according to preferred reporting items for systematic review and meta-analysis (PRISMA) (see Table 2) [39].

Ethics and dissemination

Given that this is a protocol for a systematic review only using the published data, there is no ethics approval required for this study. This systematic review will be included in JCM's PhD thesis, a research supervised by Christina Zarowsky (CZ) and Helen Trottier (HT). Its findings will also be disseminated through peer-reviewed publications and conference presentations.

Table 2: The 27 checklist items pertain to the content of a systematic review and meta-analysis.

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	

RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	

Figure and table legends

Figure 1: The preferred reporting items for systematic review and meta-analysis (PRISMA) flow chart

Table 1: PICO description table

Table 2: The 27 checklist items pertain to the content of a systematic review and meta-analysis.

Abbreviations

AIDS: Acquired Immunodeficiency Syndrome

ANC: Antenatal Care

ART: Antiretroviral Therapy

CCRBT: Cochrane Collaboration Risk of Bias Tool

CNCICDs: Comorbid Non-Communicable and Infectious Chronic Diseases

EPHPP: Effective Public Health Practice Project

GDM: Gestational Diabetes Mellitus

HINARI: Health InterNetwork Access to Research Initiative

HIV: Human Immunodeficiency Virus

ICCC: Innovative Care for Chronic Conditions

LMICs: Low and Middle-Income Countries

MeSH: Medical subject heading

NCDs: Non-Communicable Diseases

PACTR: Pan African Clinical Trials Registry

PICO: Population, Intervention, Comparator and Outcome

PRISMA: Preferred Reporting Items for Systematic review and Meta-Analysis

QCTs: Quasi-randomised Controlled Trials

RCTs: Randomised Controlled Trial

ROBINS-I: Risk Of Bias In Non-randomized Studies - of Interventions

SE: Standard Error

T2D: Type 2 Diabetes.

Acknowledgments

We would like to thank Sylvie Fontaine, the librarian at the paramedical library, Université de Montréal, Canada, for her valuable contribution to search strategy development and the the reviewers of the manuscript for their constructive inputs.

Funding

No funder.

Availability of data and materials

Not applicable.

Author contributions

MJC, and MW designed the study. MJC wrote the first manuscript of the review. MJC, MW, AR, EM, KM, SN, HT, NL and CZ critically revised the review. All authors read and approved the final manuscript.

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Competing interests

MJC, MW, AR, EM, KM, SN, HT, NL and CZ declare no competing interests.

Consent for publication

Not applicable.

Ethics approval and consent to participate

Not applicable.

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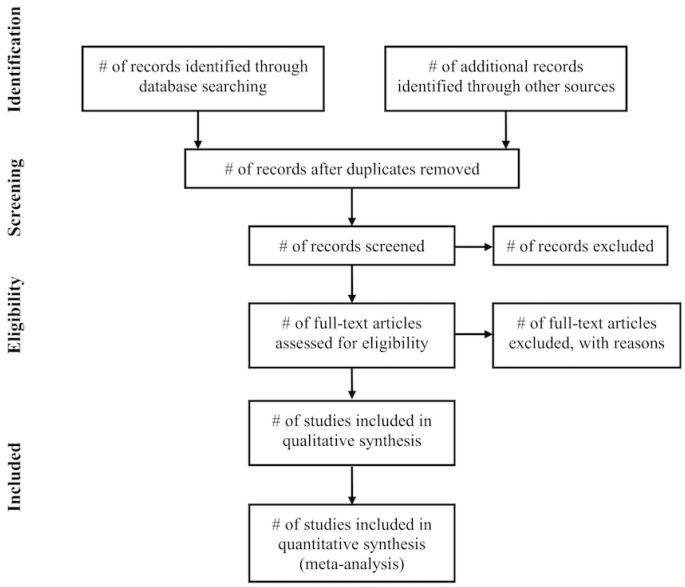

Fig. 1-PRISMA flowchart for systematic review

90x127mm (300 x 300 DPI)

BMJ Open

Integrated management of type 2 diabetes and gestational diabetes within multi-morbidity conditions in Africa: A systematic review protocol

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-023684.R3
Article Type:	Protocol
Date Submitted by the Author:	24-Jan-2019
Complete List of Authors:	MUTABAZI, Jean Claude; École de Santé Publique, Université de Montréal, Département de Médecine Sociale et Préventive - Santé Mondiale; Institut de Recherche en Santé Publique de l'Université de Montréal (IRSPUM) , École de santé publique, Université de Montréal Werfalli, Mahmoud; University of Cape Town, Chronic Disease Initiative for Africa, Department of Medicine, Faculty of Health Science Rawat , Angeli; The School of Population and Public Health, University of British Colombia Musa, Ezekiel; University of Cape Town, Chronic Disease Initiative for Africa, Department of Medicine, Faculty of Health Science; University of Cape Town, Integrated Intervention for DIAbetes risks after GestatiOnal diabetes (IINDIAGO), Department of Medicine, Faculty of Health Science Norris, Shane; University of Witwatersrand, Paediatrics and Child Health; University of Cape Town, Integrated Intervention for DIAbetes risks after GestatiOnal diabetes (IINDIAGO), Department of Medicine, Faculty of Health Science Murphy, Katherine; University of Cape Town, Chronic Disease Initiative for Africa, Department of Medicine, Faculty of Health Science; University of Cape Town, Integrated Intervention for DIAbetes risks after GestatiOnal diabetes (IINDIAGO), Department of Medicine, Faculty of Health Science Trottier, Helen; École de Santé Publique, Université de Montréal, Médecine Sociale et Préventive; Centre de Recherche du Centre Hospitalier Universitaire Sainte Justine Levitt, Naomi; University of Cape Town, Chronic Disease Initiative for Africa, Department of Medicine, Faculty of Health Science; University of Cape Town, Integrated Intervention for DIAbetes risks after GestatiOnal diabetes (IINDIAGO), Department of Medicine, Faculty of Health Science Zarowsky, Christina; École de Santé Publique, Université de Montréal , Médecine Sociale et Préventive; Institut de Recherche en Santé Publique de l'Université de Montréal (IRSPUM) , École de santé publique, Université de Montréal
Primary Subject Heading:	Health services research
Secondary Subject Heading:	Diabetes and endocrinology
Keywords:	Type 2 diabetes, Gestational diabetes, Multi-morbidity, Integrated care, Global health, Africa

Integrated management of type 2 diabetes and gestational diabetes within multi-morbidity conditions in Africa: A systematic review protocol

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Abstract

Introduction: Multi-morbidity, defined as the co-existence of more than one chronic condition in one person, has been increasing due to comorbid non-communicable and infectious chronic diseases (CNCICDs). Type 2 diabetes (T2D) and gestational diabetes mellitus (GDM) incidences within the CNCICDs conditions are increasing and overwhelming already weak and under-resourced health care systems in Africa. There is then an urgent need for the integrated management of CNCICDs. We aim to review the integrated management of T2D and GDM within multi-morbidity conditions in Africa.

Methods: Studies that have assessed the integrated management of T2D and GDM within multi-morbidity conditions in Africa will be considered based on the PICO method: Population (adult diagnosed with T2D and GDM, who also have other diseases, non-communicable diseases (NCDs) and infectious, in public primary and secondary health care facilities in Africa); Intervention (integrated management of T2D and GDM, also suffering from other diseases in Africa), Comparator (Unintegrated management of T2D and GDM in Africa) and Outcomes (integrated management of T2D and GDM in Africa). The following databases Cochrane Library, MEDLINE, PubMed and SCOPUS, the WHO International Clinical Trials Registry Platform, among others will be searched. Two reviewers (JCM, MW) will independently screen, select eligible studies, and extract data. Discrepancies will be resolved by consensus or by a discussion with the third author (AR). Quality of included studies will be assessed using both the newly developed tool, "the Cochrane Collaboration Risk of Bias Tool (CCRBT)" and "Risk Of Bias In Non-randomized Studies - of Interventions (ROBINS-I)". A narrative synthesis of extracted data

and meta-analysis, if necessary will be conducted and then reported according to the preferred reporting items for systematic review and meta-analysis (PRISMA).

Ethics consideration and dissemination: By only using the published data, there is no ethics approval required for this study. This systematic review will be included in JCM's PhD thesis and its findings will also be disseminated through peer-reviewed publication and conference presentation.

Systematic review registration: PROSPERO CRD42016046630

Keywords: Type 2 diabetes, gestational diabetes, multi-morbidity, integrated care, Africa.

Strengths and limitations of this study

- √ Substantial search strategy to identify relevant studies will be adopted, a large number of online databases will be searched, public health websites will be manually searched and credible experts will be consulted.
- √ Study results will be assessed and reported in accordance with relevant guidelines for quality assessment of systematic reviews.
- √ Scarcity of eligible studies for selection and inclusion is expected.
- √ Reviewers will not be blinded during data extraction and quality assessment stages.

1. Introduction

The World Health Organisation (WHO) global report in 2016 estimated that 415-422 million adults worldwide had diabetes in 2014-2015 and that diabetes caused 5 million deaths in 2015, with an estimated 673 billion USA dollars of total global health expenditure in diabetes care [1, 2]. In the Africa region there were an estimated 14.2 million people with diabetes in 2015 increasing to 34.2 million in 2040 [1, 3]. With the expected rural depopulation causing increased exposure to urban environments and diabetogenic lifestyles such as inactivity, obesity, depression, smoking among others, diabetes cases are expected to increase by 54% to 642 million worldwide by 2040 [3-5].

Globally, the burden of non-communicable diseases (NCDs) is rising. Low and middle-income countries (LMICs) are most affected by changes in patterns of population age distributions, fertility, life expectancy, morbidity and mortality, known as the "epidemiological transition" [6]. In Africa, especially in sub-Saharan Africa, this is occurring against a background of continuing infectious disease epidemics (i.e., HIV and tuberculosis), increasingly becoming a coinfection epidemic that requires an integrated response [7]. Consequently, multi-morbidity defined as the co-existence of more than one chronic condition in one person, has been increasing due to comorbid non-communicable and infectious chronic diseases (CNCICDs) [8]. Given the risk factors and complex care needs of multi-morbidity, there is a need to integrate healthcare systems, particularly between primary and secondary health care.

The current approaches to surveillance, prevention and treatment of CNCICDs appear to be insufficient to provide for the long-term health needs of this convergence especially in

the context of human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS) era, antiretroviral therapy (ART) linked concomitant metabolic complications and HIV/AIDS allied opportunistic infectious diseases [9]. To address this, the WHO developed the Innovative Care for Chronic Conditions (ICCC) Framework to provide a healthcare systems roadmap that would meet the increasing needs of chronic disease care within this growing multi-morbidity context. This framework incorporates community, patient, healthcare and policy environment perspectives, and has been adopted by different healthcare systems. However, it does not clearly include the infectious diseases within the context of multi-morbidity [8] and it is then necessary to reorganise health care services and systems to tackle this growing public health problem [8, 9].

The 2016 global diabetes report [1] emphasizes the need to reach better outcomes of diabetes management through an integrated management, especially with NCDs such as cardiovascular diseases as well as tuberculosis and/or HIV/AIDS. This is especially important where the prevalence of these diseases is high. Despite calls for a shift in approach from disease-specific interventions to the integrated delivery model [10], health care systems in Africa are weak and under-resourced to provide care for the increasing number of patients with multi-morbidities including diabetes, especially compared to high-income settings [11].

Two types of diabetes commonly identified during adulthood are type 2 diabetes (T2D), that is insulin resistance linked diabetes, and gestational diabetes (GDM), known as a glucose intolerance with onset or first recognition during pregnancy. T2D can be prevented or delayed for women with previous GDM [12-16]. The established connection between T2D and GDM [9] does not determine how GMD is managed. It can either be managed

alone in a diabetic clinic or preferably within integrated care at ANC and postnatal clinics, which is a right approach for increasing multi-morbidity [17, 18].

The treatment pathway for women with GDM is through accessing antenatal care (ANC) at the nearest health facility for their pregnancy follow-up and delivery. In contrast, only a small proportion of women with recent GDM return for postpartum oral glucose tolerance test, assessment and management [19-23]. The main challenge is that GDM women must navigate fragmented health systems for their care and care of their babies and this situation supports calls for integrated health systems and services that are easy for patients to navigate [24].

Disease-specific or vertical programmes can be used to manage specific diseases and health problems while strengthening fragmented health systems in Africa [25]. However, disease-specific or stand-alone interventions are criticized for not promoting equity and sustainability of their outcomes [26], and therefore integrated programmes to address various NCDs such diabetes in comorbid conditions are recommended [9, 27].

Integrated care is "*combining parts so that they work to form a whole (i.e., integration) in order to optimise care and treatment to people where fragmentations in care have led to a negative impact on their care experiences and outcomes*" [28]. It describes a range of organizational arrangements with variable nature and intensity and comprises two main concepts: a) an organizational structure focused on economic benefits (cost-effectiveness), or b) a way of organizing service delivery [29, 30]. We conceptualized integration based on dynamic interactions in which formal governance is arranged, responsibilities are shared and resources are pooled [29, 31], regardless of many other existing integration level

models such integrated care typologies used in a recent systematic review that studied the integration of cardiovascular diseases, hypertension and diabetes with HIV services [32].

The analysis of interactions in health systems enables us to understand the levels of integration. They include partial integration initiatives ranging from (1) the linkage or unstructured interactions, (2) the coordination with a committee to oversee their goal-oriented works but keeping the separated structures, and full integration in which two programmes are merged in their structures (funds, human resources, informational system) and functional elements (strategic planning, resources allocation, interventions delivery) [29, 33].

Integrated health care systems have advantages such as being associated with more accessibility of care, improved quality and safety of care, health care cost reductions and economic benefits for both providers and families [34, 35]. This integrated management approach including partial and full integration initiatives, will play a key in responding and providing the appropriate health care services to the increasing cases of multiple conditions [32].

We aim to provide a systematic review on integrated management of T2D and GDM within the CNCICDs conditions in Africa. The ultimate goal is to describe the emerging practices and lessons learned from integrated management of GDM and T2D within comorbidity conditions in Africa and the different research gaps to GDM and T2D integration within management of other non-communicable and infectious chronic diseases.

This systematic review aims to answer the following research questions: 1) What are the existing integrated interventions and services delivery models for managing T2D including GDM within multi-morbidity conditions in Africa? 2) What are the successes and

challenges of the existing integrated management of T2D including GDM within multi-morbidity conditions?

2. Methods

The Cochrane Handbook and systematic review study protocol [36] published by the Cochrane Collaboration Methods Groups provides the methodological framework in designing and conducting this systematic review to enable critical appraisal and replication. We did register this protocol online on PROSPERO, the International prospective register of systematic reviews, found at (https://www.crd.york.ac.uk/prospero/, registration no. CRD42016046630).

Study design

This systematic review will only include studies of good quality based on the developed inclusion and exclusion criteria.

Patient and public involvement

There will be no patient and/or public involvement in this study.

Search strategy for the identification of relevant studies

Our search strategy will use the controlled terms (MeSH: Medical subject heading) and free texts. The following databases will be searched: Cochrane Library, MEDLINE, PubMed and SCOPUS. Other database resources such as the WHO International Clinical Trials Registry Platform, Clinicaltrials.gov, Pan African Clinical Trials Registry (PACTR) and HINARI (Health InterNetwork Access to Research Initiative) will also be searched. Additional search will be conducted in Google scholar. Our research will focus on articles published and gray literature in English and French languages. Upon the extraction of

interesting articles in other languages without any English or French abstracts, we will then include them or get assisted by a researcher who is fluent in those languages. Since there were not many articles regarding our review topic in our preliminary search, there will be no starting time limits in our search but our focus will be limited to all fifty-four African countries. However, the search will be conducted from the start of each database until the 31st December to include as many relevant studies as possible. Search Strategy will be validated with the assistance of a Librarian.

Our search for articles will be based on the following Population, Intervention, Comparator and Outcome (PICO) method [37] (see the table 1 below).

Table 1: PICO description table

Population	Intervention	Comparator	Outcomes
Adults diagnosed with T2D and women diagnosed with GDM, who have other diseases in public primary and secondary health care facilities in Africa	Partial or full Integrated management of T2D in adults and GDM in pregnant women who have other diseases in Africa	Unintegrated management of T2D and GDM in public primary and secondary healthcare facilities in Africa.	Utilisation and effectiveness of Integrated management of T2D and GDM in public primary and secondary healthcare facilities within multi-morbidity conditions in Africa

Criteria for considering studies for this review

Studies that have assessed the integrated management of T2D and GDM within multi-morbidity conditions in Africa will be considered, including randomised controlled trials (RCTs), non-RCTs, quasi-randomised controlled trials (QCTs) and observational studies.

Studies will be all kinds of interventions with different targeted participants from all ethnicities, genders, socioeconomic, educational backgrounds and in all countries in Africa who were diagnosed with T2D and GDM as one disease of the multi-morbidity using standard diagnostic criteria will be eligible for inclusion. The patients who had T2D including GDM before and after the occurrence of other diseases and the interventions to handle both diseases will be included in this review. Interventions carried out or facilitated by healthcare providers including community health workers in public health facilities will also be included, providing that the focus of the intervention is to treat diseases in which one is diabetes, specifically T2D and GDM. Studies that separately evaluated interventions or assessing vertical programmes of T2D, GDM and other diseases, will be excluded.

Reference lists

Manual-search by (MJC and MW) lists of references of included studies, tables of contents of relevant journals and conference abstracts for the relevant material will be conducted. A grey literature search strategy by (JCM and MW) will be developed to conduct web-based searches to obtain key unpublished sources in our stated search languages.

Selection of studies

Full copies of articles identified by the search, and considered to meet the inclusion criteria, based on the title and abstract will be obtained for data synthesis. Initially, studies will be screened using predefined inclusion and exclusion criteria. Two reviewers (JCM and MW) will apply the criteria independently to the results of the searches, based first on titles and abstracts only. At least two reviewers (JCM and MW) will proceed independently with the articles selection at the same time based on our described inclusion criteria into two steps: 1) examining the title and abstract, and then, 2) reviewing the full texts. Study authors of

eligible articles for which the full text copies are not freely accessible will be contacted to obtain their access and additional information about them will also be requested if required. The inclusion of an article will be made by consensus. In case the two (JCM and MW) do not reach consensus, the decision from a third person (AR) will be required and reasons for exclusion will be recorded. All studies which initially appear to meet inclusion criteria but on closer inspection do not meet the inclusion criteria will also be detailed in the table of "characteristics of excluded studies". The preferred reporting items for systematic review and meta-analysis (PRISMA) flow chart will be produced to facilitate transparency of the process (See Fig. 1) [38, 39].

Types of outcome measures

Studies reporting at least one of the following outcomes will be included:

Primary outcomes

Two primary outcomes will be considered: 1) Integrated care outcome and 2) cost-effectiveness outcome. For the integrated care outcome, the focus will be on patients screened and/or treated for both T2D and GDM in the course of treatment of other major diseases (e.g. HIV, tuberculosis, cardiovascular diseases, etc.) in what is known as multi-morbidity conditions. For cost-effectiveness outcome, the focus will be on approach to integrated diagnosis and treatment of T2D and GDM within comorbidity conditions, which simplifies the workload and saves means of depleted health systems in Africa and helps the patients to do not navigate different levels of health systems for their comorbidities that positively impacts the family economies.

Secondary outcomes

We will also consider early diagnosis through the integrated management of other diseases as this improves clinical outcomes and strengthens health systems for the long-term results of the integrated management of T2D diabetes including GDM within comorbidity conditions.

Quality assessment

The quality of articles selected will be assessed using the newly developed tool, "the Cochrane Collaboration Risk of Bias Tool (CCRBT)" and "Risk Of Bias In Non-randomized Studies - of Interventions (ROBINS-I)" [40, 41]. The CCRBT is an appropriate quality assessment tool for or RCTs & QCTs [41, 42]. Since the quick preliminary search shows that there are few RCTs and QCTs to be included in this study, this single tool will not be enough and the ROBINS-I will be used to assess the quality of non-RCTs and observational studies [41]. These quality assessment tools encompass all aspects needed to appraise the quality of any studies that will be selected for inclusion.

Two reviewers (JCM and MW) will independently assess the risk of bias in the included studies and cross-checked by a third reviewer (AR).

The following individual quality elements recommended in the modified Cochrane Collaboration tool to assess the risk of bias for RCTs (high, low, or unclear) as a judgment for individual elements from six domains (selection, performance, attrition, reporting, and other) [40], will be assessed for RCTs and QCTs. Likewise, the elements recommended in the ROBINS-I to assess risk of bias for non-RCTs and observational studies (low, moderate, serious and critical) as a judgement for individual categories from six domains of bias (bias due to confounding, bias in selection of participants into the study, bias in classification of interventions, bias due to deviations from intended interventions, bias due

to missing data, bias in measurement of outcomes and bias in selection of the reported result) [41] will also be assessed.

Any disagreements over bias between two reviewers will be settled by involving the third review author and each bias in these domains for each study will be separately presented in a table in the final review publication.

Data extraction and management

As above discussed, the selected citation titles and abstracts will be exported from the search engines to Endnote X8.2 and duplicates will be removed automatically and a search will be conducted manually to check any missed duplicates. Eligible citations will be retrieved after the screening of titles and abstracts and full texts be sought and imported.

JCM and MW will extract data on: study ID, author's name, country, year, type of paper/report, form of publication, study design, comorbidity, description of the intervention (including process, cost-effectiveness and outcomes), context of integrated intervention (i.e. PHC, hospitals), details about participants (including number in each group, baseline health information, demographic characteristics), length of intervention and follow-up.

Data analysis and synthesis

We will first undertake a narrative synthesis to summarize and discuss the findings of the included studies. We will then present findings through primary and secondary outcomes. We will use tabular summary to synthesize individual studies characteristics and results (intervention effects). The data synthesis will be conducted through the measurements of effect for continuous outcomes of the included studies. Studies reporting multiple

outcomes and outcome measures will be categories according to definitions outline in section types of outcome measure above.

A predetermined order of preference for extracting multiple outcome measures will be used where data is available in several formats. For RCTs preference will be to extract data that requires the least manipulation by authors or inference by review authors. Raw values (e.g. Means and standard deviations) rather than calculated effect size will be extracted. For studies reporting both final values and changes from baseline for outcomes, preference will be to extract the former. In the case of cluster-RCTs, the preference will be (i) extract adjusted estimates reported by the study, or (ii) use raw data and inflated the standard error (SE) data using weighting.

In case of missing data in some eligible studies, efforts will be made to contact corresponding authors to request for clarification of all relevant information. For ongoing studies trial authors will be contacted for further information and updates.

Statistical analysis and subgroup analysis and investigation of heterogeneity

Heterogeneity between studies will then be assessed using both x^2 and I^2 and Q statistics where appropriate. The I^2 statistic estimates the percentage of total variation across studies due to a true difference rather than chance. In general, I^2 values greater than 60–70% indicate the presence of substantial heterogeneity. We will explore sources of heterogeneity by comparing the pooled study estimates between subgroups defined by study-level characteristics. Subgroup analysis will be performed where heterogeneity is statistically significant. Sensitivity analyses will be conducted to determine the potential sources of heterogeneity. Two additional sensitivity analyses will be conducted to: (i) evaluate the

effect of excluding studies unable to meet each quality criterion affect the overall estimate, and (ii) evaluate the change in the results if only high-quality studies where included.

In case the identified studies are of substantial heterogeneity and where statistical pooling is impossible, the findings will be summarizing in a narrative form by tables and figures to facilitate in effective data presentations. Two reviewers will write the narratives independently and later checked by other reviewers. Decisions on any disagreements will be resolved through discussions and consensus by all reviewers in the team. We will assess the presence of publication bias by using a funnel plot and the Egger test of bias [43]. Subgroup and sensitivity analyses will be conducted to look at the effects of certain factors on for example: geographic region, age and gender and diabetes type of participating patients.

Reporting of this review

This protocol complies with the requirements of Preferred Reporting Items for Systematic Reviews and Meta-analyses Protocol (PRISMA-P), which is included as a supplementary file 1. The systematic review results will be reported according to preferred reporting items for systematic review and meta-analysis (PRISMA) [39].

Ethics and dissemination

Given that this is a protocol for a systematic review only using the published data, there is no ethics approval required for this study. This systematic review will be included in JCM's PhD thesis, a research supervised by Christina Zarowsky (CZ) and Helen Trottier (HT). Its findings will also be disseminated through peer-reviewed publications and conference presentations.

Figure and table legends

Figure 1: The preferred reporting items for systematic review and meta-analysis (PRISMA) flow chart

Table 1: PICO description table

Supplementary file 1: PRISMA-P 2015 Checklist. The Preferred Reporting Items for Systematic Reviews and Meta-analyses for Protocols 2015 (PRISMA-P 2015) checklist was used in development of this protocol. Items 1b, 2, 4, 5b, 5c, 15d, 16 and 17 were not applicable.

Abbreviations

AIDS: Acquired Immunodeficiency Syndrome

ANC: Antenatal Care

ART: Antiretroviral Therapy

CCRBT: Cochrane Collaboration Risk of Bias Tool

CNCICDs: Comorbid Non-Communicable and Infectious Chronic Diseases

EPHPP: Effective Public Health Practice Project

GDM: Gestational Diabetes Mellitus

HINARI: Health InterNetwork Access to Research Initiative

HIV: Human Immunodeficiency Virus

ICCC: Innovative Care for Chronic Conditions

LMICs: Low and Middle-Income Countries

MeSH: Medical subject heading

NCDs: Non-Communicable Diseases

PACTR: Pan African Clinical Trials Registry

PICO: Population, Intervention, Comparator and Outcome

PRISMA: Preferred Reporting Items for Systematic review and Meta-Analysis

QCTs: Quasi-randomised Controlled Trials

RCTs: Randomised Controlled Trial

ROBINS-I: Risk Of Bias In Non-randomized Studies - of Interventions

SE: Standard Error

T2D: Type 2 Diabetes.

Acknowledgments

We would like to thank Sylvie Fontaine, the librarian at the paramedical library, Université de Montréal, Canada, for her valuable contribution to search strategy development and the the reviewers of the manuscript for their constructive inputs.

Funding

No funder.

Availability of data and materials

Not applicable.

Author contributions

MJC, and MW designed the study. MJC wrote the first manuscript of the review. MJC, MW, AR, EM, KM, SN, HT, NL and CZ critically revised the review. All authors read and approved the final manuscript.

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Competing interests

MJC, MW, AR, EM, KM, SN, HT, NL and CZ declare no competing interests.

Consent for publication

Not applicable.

Ethics approval and consent to participate

Not applicable.

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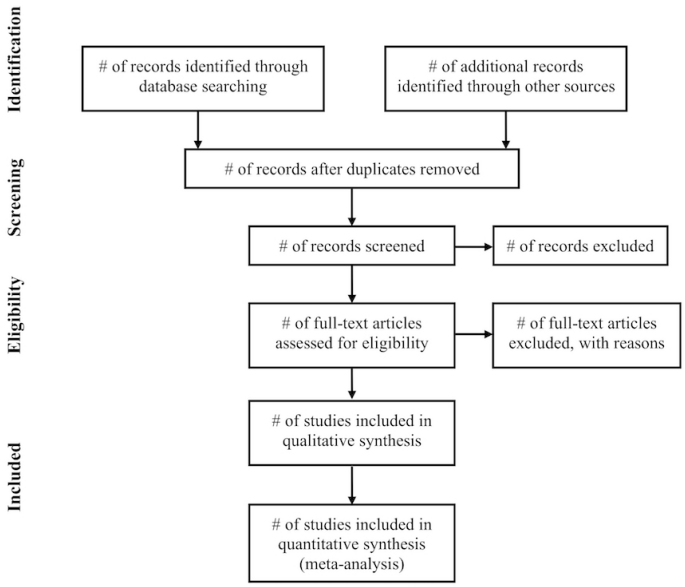

Fig. 1-PRISMA flowchart for systematic review

90x127mm (300 x 300 DPI)

PRISMA-P 2015 Checklist

This checklist has been adapted for use with protocol submissions to *Systematic Reviews* from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 **4**:1

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	☒	☐	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	☐	☐	
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	☒	☐	3, 8
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	☒	☐	1, 17-18
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	☒	☐	17
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	☐	☐	
Support					
Sources	5a	Indicate sources of financial or other support for the review	☒	☐	17 (No funder)
Sponsor	5b	Provide name for the review funder and/or sponsor	☐	☐	
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	☐	☐	
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	☒	☐	4-7
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	☒	☐	7-8

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	☒	☐	9
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	☒	☐	8
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	☒	☐	8-9
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☒	☐	13
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	☒	☐	10
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	☒	☐	9-11
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	☒	☐	9-11
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	☒	☐	11-12
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	☒	☐	12-13
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	☒	☐	13-15
	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 (e.g., I^2, Kendall's tau)	☒	☐	13-15
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	☒	☐	13-15
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☐	☐	

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	☐	☐	
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	☐	☐	