Health system interventions to improve clinical and patient-centered outcomes for adults with type 2 diabetes in low- and middle-income countries: A systematic review and meta-analysis

Review protocol
Version: January 3, 2020

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BACKGROUND

Rationale

Type 2 diabetes mellitus (T2DM) conveys a high burden of death and disability globally that disproportionately impacts people in low- and middle-income countries (LMICs). Of the 450 million people worldwide with T2DM, approximately 80% reside in LMICs.[1] From 1980-2014, the absolute number of people and percent of the population with diabetes increased more quickly in LMICs than in high-income countries (HICs).[2] People with diabetes in LMICs experience premature and morbidity and mortality relative to HICs.[3]

The design and implementation of interventions to effectively address the diabetes burden in LMICs is thus a global health priority. However, systematic reviews examining health systems interventions or quality improvement strategies for diabetes have included few studies in LMICs.[4-9] Given differences in health system infrastructure, resources, and population risk factors, it should not be assumed that interventions designed and tested in HICs are generalizable.

Among the few diabetes interventions reported from LMICs, studies have focused on prevention[10,11], regional evidence,[12] or specific interventions such as task shifting,[13,14] deployment of community health workers,[15-17] or lifestyle change.[18,19] Other reviews of cardiovascular disease interventions in LMICs have not emphasized diabetes.[20] To date, no review has synthesized evidence across different types of health system interventions to improve type 2 diabetes outcomes in LMICs.

Therefore, we will examine the impact of health system interventions aiming to improve clinical and patient-centered outcomes for adults with T2DM in LMICs.

METHODS

This systematic review will be conducted based on guidance from the Cochrane Effective Practice and Organisation of Care (EPOC) group, which conducts reviews on health systems interventions.[21] We registered the review in PROSPERO (CRD42018106765) and followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines.[22]

Framework

Our PICO summary and analytic framework is described below and in Figure 1. This framework is based on an example from the literature.[23,24]

- **Population**: Non-pregnant, community-dwelling adults with type 2 diabetes in low- or middle-income countries
- **Interventions**: Health systems interventions aiming to improve clinical and patient-centered outcomes
- **Comparator**: Usual Care
- **Outcomes**:

- Clinical outcomes: Mortality and health-related quality of life (using any standardized instrument)
- Intermediate outcomes: Absolute change in glycemic control indicator (hemoglobin A1c of fasting blood glucose)
- Resource utilization: Cost-effectiveness (using cost-effectiveness or cost-utility analysis)

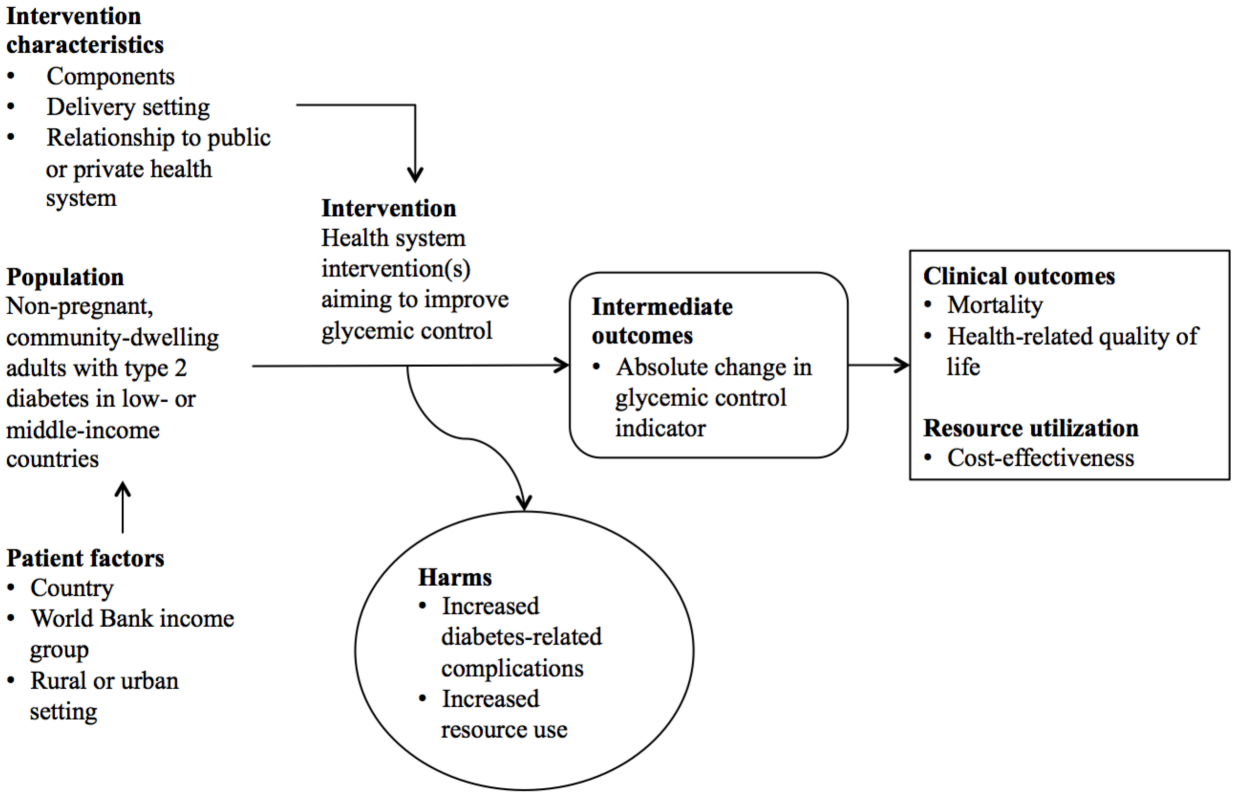

Figure 1: PICO framework.

Search strategy and selection criteria

Our search strategy intersects three concepts: type 2 diabetes, LMICs, and study design.[25,26] (See Figure 2: Schematic of search strategy.) With the assistance of a research librarian (SJB), we will perform serial searches of Ovid MEDLINE, Cochrane Library, EMBASE, African Index Medicus, LILACS, and Global Index Medicus. To identify additional potentially eligible studies, we also manually will review the references of included studies, related systematic reviews, and the websites of major international diabetes organizations. All searches will be developed in Ovid MEDLINE and syntax will be translated to other bibliographic databases. To ensure search quality, a second reference librarian will peer-review the search terms.

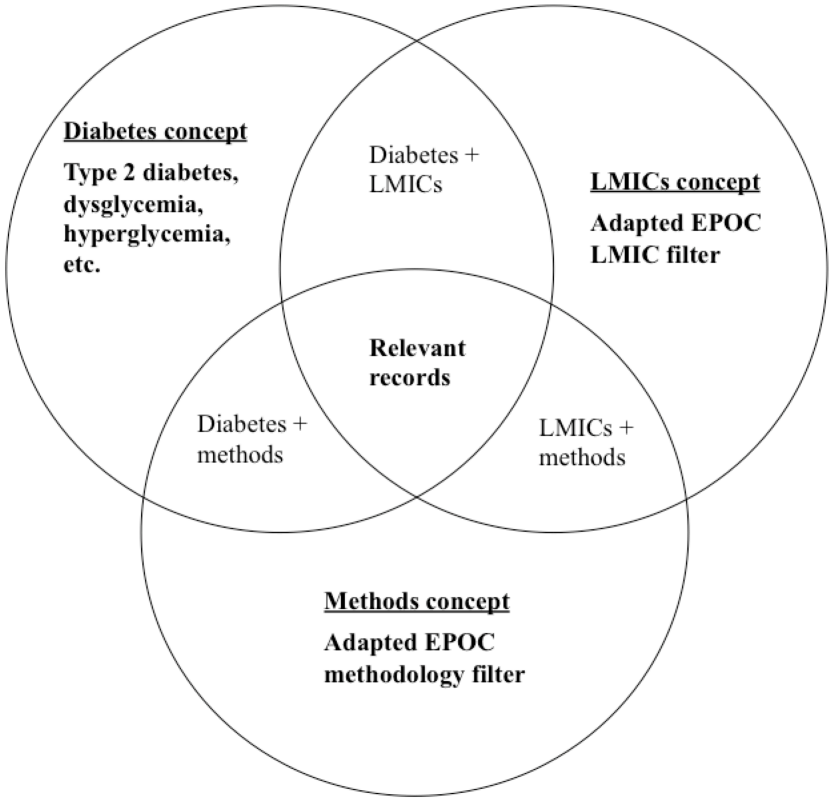

Figure 2: Schematic of search strategy.

We will included randomized controlled trials (RCTs) of health systems interventions conducted in at least one LMIC as defined by 2019 World Bank lending categories.[27] Both individual and cluster RCTs will be eligible. We pre-specified that included studies were published in English, enrolled 100 or more participants for at least 24 weeks, and reported at least one of the following outcomes: glycemic changes, mortality, health-related quality of life, or resource utilization. We will exclude interventions focused on Ramadan, insulin titration, or glucose self-monitoring as nuances related to these unique contexts limit generalizability. No date restrictions were applied.

We will defin a health systems intervention as one "designed to improve professional practice and the delivery of effective health services."[21] Included studies will describe an intervention within the four domains of EPOC health system interventions:[28]

- Delivery arrangements: Changes in how, when and where healthcare is organized and delivered, and who delivers healthcare.
- Financial arrangements: Changes in how funds are collected, insurance schemes, how services are purchased, and the use of targeted financial incentives or disincentives
- Governance arrangements: Rules or processes that affect the way in which powers are exercised, particularly with regard to authority, accountability, openness, participation, and coherence.

- Implementation strategies: Interventions designed to bring about changes in healthcare organizations, the behavior of healthcare professionals, or the use of health services by healthcare recipients.

We will exclude trials of patient behavior change alone if health-care professional behavior is not primarily influenced.[21] We define "health-care professional" broadly to encompass physicians, nurses, pharmacists, and other allied health workers. Thus, an intervention *training* health-care professionals on diabetes education will be included; however, an intervention aiming to improve outcomes solely through individualized diabetes education will be excluded.[21]

Data analysis

A reference librarian (SJB) will download all records to Endnote, remove duplicates, and import records to Covidence ®.[29] Two authors (DF and JG) will independently screen studies by title and abstract and, subsequently, by full-text review. Disagreements will be resolved first by consensus and, if needed, in consultation with a third author (PR). We will aggregate multiple reports of the same intervention for extraction and analysis. We will use the TIDieR checklist and EPOC template to structure extraction.[30,31] One author (DF) will extract summary data into a customized electronic spreadsheet, and a second author (JG) independently verified the extracted data. In addition relevant outcomes, we will extract study elements including country, setting, duration and follow-up, number of participants enrolled, intervention description, and comparator. We will classify each study by one or more taxonomy category from EPOC.[28] Within each category, we will use consensus between two reviewers (DF and JG) to group interventions into similar subcategories. If outcomes are not reported or missing, we will authors twice over four weeks via email to obtain these data. To assess risk of bias, two reviewers (DF and JG) independently will assess studies using the Cochrane EPOC tool.[32] Disagreements will be resolved by discussion between the two reviewers and, if needed, in consultation with a third reviewer (PR). We will summarize findings using EPOC guidance.[33]

Statistical analysis

We will conduct a meta-analysis if we deem studies within similarly categorized groups to have sufficient clinical homogeneity. We likely would conduct a meta-analysis for the glycemic outcome only and limit studies to those not judged as having high risk of bias. We plan to use random-effects meta-analysis models for mean between-group difference of hemoglobin A1c (HbA1c) change in each intervention category. The meta-analysis may be restricted to trials not classified as high risk of bias. Sample sizes for cluster RCTs would be adjusted to account for the design effect using the intracluster correlation coefficient.[34] We would follow the methodology recommended in the Cochrane handbook to derive within-group mean and standard deviation when complete HbA1c results were not reported.[34] Analyses will be performed in Stata (16.0). Heterogeneity will be quantified by calculating I^2 and T^2. We might perform exploratory analyses by excluding trials in which the comparator arm was enhanced usual care and/or constructing meta-regression models with baseline HbA1c as a covariate. Publication bias would be assessed by visual inspection of funnel plots. We would use GRADE and EPOC guidance to prepare a summary of findings table for the outcome of glycemic control.[35,36]

Role of the funding source

There is no funding source for this study. The corresponding author will have full access to all the data in the study and will have final responsibility for the decision to submit for publication.

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