Prevalence and clinical characteristics of depression, and effects of screening interventions for depression among people with diabetes mellitus in Low and Middle Income Countries: A Systematic Review Protocol.

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ABBREVIATIONS

AMSTAR - A Measurement Tool to Assess Systematic Reviews
CES-D - Centre for Epidemiological Studies for Depression
DALY - Disability Adjusted Life Years
DM - Diabetes Mellitus
EPOC - Effectiveness of Practice and Organization of Care Cochrane group
GRADE - Grading of Recommendations, Assessment, Development & Evaluation
HSCL - Hopkin's Symptom Check List
ICD-10 - International Classification of Diseases & Related Health Problems
LMIC - Low and Middle Income Country
MINI - Mini International Neuropsychiatric Inventory
MADRAS - Montgomery Asberg Depression Rating Scale
MOOSE - Meta-analysis of Observational Studies in Epidemiology
PHQ-9 - Patient Health Questionnaire 9
PICOS - Participant/Population, Intervention, Comparator, Outcome, Study Design
PRISMA - Preferred Reporting Items for Systematic Reviews and Meta-analyses
QUADAS - Quality Assessment for Diagnostic Accuracy Studies
RevMan - Review Manager open-access software by the Cochrane Collaboration
SCID - Structured Clinical Interview for DSM-IV
SSA - Sub-Saharan Africa
WHO - World Health Organization

ABSTRACT

Diabetes Mellitus and Depression are diseases of high burden globally, and the low and middle income countries are disproportionately affected. Research evidence suggests the two diseases potentiate each other. In particular, persons with diabetes mellitus are likely to be depressed for various reasons including the chronicity of the disease and its treatment. Previous reviews have documented the burden of Depression in Diabetes Mellitus in high or middle income settings with hardly any focus on sub-Saharan Africa or with methodological shortcomings. It could be that the research has not yet been conducted but certainly, the rising burden of non-communicable diseases in sub-Saharan Africa is exponential and will likely stretch the already meagre health resources.

Indeed, early screening and diagnosis is the port of entry for future public health prevention and management of chronic diseases like depression and diabetes. Our review aims to assess two aspects of this problem: First, we will summarize the evidence describing the prevalence and clinical characteristics of depression among people with diabetes mellitus in Low and Middle Income Countries. Secondly, we will assess the evidence about the effects of screening interventions for depression among people with diabetes mellitus in Low and Middle Income Countries. In conducting this review we will employ standard methods as recommended by the Cochrane Collaboration, the GRADE framework of assessing quality of evidence and publish our report using the PRISMA guidelines.

Findings from this review will be employed in guiding decision making in health and advocating for the allocation of the necessary resources for mental health care integration in DM clinics.

BACKGROUND AND RATIONALE:

Burden of depression in Low and Middle Income Countries:

Depression is a mood disorder characterized by changes in ones feelings (e.g. sadness, hopelessness, guilt, irritability); physical status (e.g. body aches, loss of energy, digestive problems); thought process (e.g. poor concentration, memory loss, difficulty with decision making) and behavior (e.g. eating disorders, suicide). Persons with depression will commonly lose interest in life activities, including economic production, [1, 2].

In the Global Burden of Diseases study, Major Depressive Disorder increased by 37% over a 20 year period, and shifted ranks from 15th in 1990 to 11th by 2010 in causing Disability Adjusted Life Years [3]. Field studies have reported the prevalence of depression in the general population of Low and Middle Income Countries to be as high as 10% [4], and the HIV epidemic in sub-Sahara Africa (SSA) has increased this burden of depression [5-7]. Research evidence suggests that depression is associated with chronic disease conditions and decrements in health states[8]. It is reasonable to argue that, with the epidemic of non-communicable diseases in Low and Middle Income Countries (LMICs) [9], depression is likely to increase exponentially.

Depression is treatable and the port of entry in LMICs is routine screening in Primary Health Care settings [10]. Screening (and diagnosis) for depression is feasible and optimizes standardized and adopted symptom-based instruments including: the Patient Health Questionnaire (PHQ), Centre for Epidemiological Studies for Depression (CES-D), Mini International Neuropsychiatric Inventory (MINI), Montgomery Asberg Depression Rating Scale (MADRAS) and the Hopkin's Symptom Check List (HSCL) [10, 11].

Burden of Diabetes Mellitus in Low and Middle Income Countries:

Diabetes is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action or both. Insulin is a hormone that helps glucose get into body cells to give them energy. Without insulin, high blood glucose can lead to serious problems with the heart, eyes, kidneys, nerves, and gums and teeth [1, 12].

Diabetes mellitus is a global health concern due to its increasing prevalence; worldwide, 347 million people are affected [13]. In Sub Saharan Africa, the prevalence varies from 0.6% in rural Uganda [14] to 12% in urban Kenya [15]. More than 80% of diabetes deaths occur in low and middle income countries (LMIC) [13]. In Uganda, 2 million people suffer from the disease, an increase of 27% in the period of 2004-2009 [16]. A population survey done recently in rural eastern Uganda shows a prevalence of 7.4% (95%CI 6.1-8.8) and 8.6% (95%CI 7.3-10.2) using WHO criteria for diabetes and pre-diabetes respectively [17]. The incidence of diabetes is increasing in Uganda, and many LMIC due to the unhealthy diets, physical inactivity and aging with a high overall public health cost [18, 19].

Diabetes is a treatable disease. The current criteria for diagnosis of diabetes includes a hemoglobin A1C ≥ 6.5% or fasting plasma glucose (FPG) ≥ 126 mg/dl (7

mmol/L) or two-hour plasma glucose ≥ 200 mg/dl (11.1 mmol/L) during an oral glucose tolerance test (OGTT) or in a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥ 200 mg/dL (11.1 mmol/L). Symptoms of hyperglycemia include polyuria, polydipsia, weight loss, occasional polyphagia and blurred vision [12].

Dual burden of depression and diabetes mellitus in Low and Middle Income Countries:

Literature on causation suggests a bi-directional relationship between depression and DM, with recent advances implicating hyperactivity of the hypothalamus-Pituitary axis, neurotopins and inflammatory mediators in the development of DM. Similarly, studies have documented that the dysregulation of immunological function, sympatho-medullary activation in depressed individuals can be a risk factor in the development of depression [20, 21]. In addition, chronic diseases like DM have been associated with depression [22].

The prevalence of co-morbid depression and diabetes mellitus (DM) among clinic attendees is on the rise the world over; both disease entities are associated with unfavorable outcomes including poor adherence to medications, early death, and a poor quality of life [5, 23-25]. The presence of co-morbid depression in DM patients has also been associated with poor glycemic control [26]. One can infer that adverse effects 'traditionally' associated with depression such as suicide, loss of productivity, increased health care expenditure are likely to be severe in persons with DM.

Existing literature about the burden of co-morbid depression and DM has often yielded varying results, with prevalence figures in the range of 11% - 31%. The variations in prevalence figures could be attributed to demographic, biological and socioeconomic heterogeneity as well as differences in instruments used to assess for depression in diabetic patients.

A number of countries in LMIC, and especially SSA, continue to grapple with huge patient numbers and severe medical staff shortages at their health facilities [27]. Mental health services are almost non-existent, or poorly integrated in primary health care facilities within LMIC. While some research has examined the integration of mental health in HIV-clinics within SSA [28], little is being done to routinely identify and manage mental illnesses in the setting of non-communicable diseases such as DM.

The diversity in existing literature about the prevalence of and risk factors for depression in DM patients, and the lack of clarity about existing depression screening in primary health care within LMIC call for the synthesis of existing evidence.

Rationale: why update a systematic review on depression among persons with diabetes mellitus in LMICs?

First, there is rising burden of non-communicable diseases in LMICs with the potential of stretching the already scarce resources available for infectious diseases. Co-morbid depression and diabetes mellitus presents unprecedented clinical, public health and socioeconomic challenges, as already stated in our section examining the disease burden.

Although we found a number of reviews addressing different aspects about this same subject [20, 23-26, 29-41], these hardly focused on LMICs and in particular sub-Sahara Africa. One recent systematic review by Roy and colleagues [42] had methodological limitations with a low average AMSTAR score of 2.5 out of 11, when assessed by 2 reviewers with an agreement kappa of 0.74 [43]. Key methodological gaps included non-reporting of use of *a priori* protocol; English language limitations with the potential of excluding studies from say Francophone LMICs; not assessing methodological quality of included studies; non-mention of supplementary search for studies beyond electronic means (gray literature) all of which may contribute to the various biases. Not least, in the same review the literature search was as far back as August 2011, presenting an opportunity to update it for over 30 months.

Although reviews may not conform to the PRISMA [44] reporting guidelines, this does not necessarily imply methodological inferiority. However, in light of advancements in systematic review methodology including reporting in the recent past, coupled with more available open access journal space, and the opportunity for supplementary information to be uploaded on the world-wide-web; it is reasonable to categorize what was not reported in the review in the review as having been left out by the reviewers and represent a methodological flaw.

A systematic review of the literature about the extent of depression in DM patients, and the nature of screening interventions to address depression in diabetes clinics can inform theory, practice and policy. Such findings can be used in guiding and advocating for the allocation of the necessary resources for mental health care integration in DM clinics.

AIMS:

Aim 1. To summarize the evidence describing the prevalence and clinical characteristics of depression among people with diabetes mellitus in Low and Middle Income Countries.
Aim 2. To summarize the evidence about effects of screening interventions for depression among people with diabetes mellitus in Low and Middle Income Countries.

SYSTEMATIC REVIEW METHODS:

Protocol development and registration:

This systematic review protocol will be registered in the open access online registry, PROSPERO, University of York, York, United Kingdom, http://www.crd.york.ac.uk/PROSPERO/ [45]. Briefly, we will use standard systematic methods that limit bias, by duplicate searching, identifying and selecting studies, as well as abstracting data, [46]. We will refer to the following recommendations: the MOOSE statement (Meta-Analysis of Observational Studies in Epidemiology) [47], to assess the first question about prevalence of depression in diabetes mellitus; the Cochrane Handbook with specific attention to diagnostic strategy studies, for the question of depression screening effects [48]. Finally, we will report our results in line with the PRISMA guidelines (Preferred Reporting Items for Systematic Reviews and Meta-analyses).

Review questions:

The first question of burden of depression in persons with diabetes mellitus, in LMICs will provide an appropriate context for assessing the effects of screening interventions. The second part will assess the effects of interventions to screen for depression among diabetics. In the second part, the following elements will be assessed;
Population: Persons suffering from depression or DM or both disease conditions.
Intervention: Screening or diagnosis strategy for depression among DM patients; screening or diagnosis strategy for DM among depressed patients.
Comparator: No routine screening or diagnosis for depression in DM patients, or vice versa in depression patients.
Outcome: Diagnosis of depression; diagnosis of DM
Study design: (a) Randomized Controlled Trials (b) Quasi Experimental designs: controlled before and after studies; and interrupted time series design (c) Observational studies: cross-sectional and cohort designs.
Setting: Primary Health Care service delivery in Low and Middle Income Countries as defined by the World Bank criteria. Priority will be given to Low Income Countries and sub-Saharan Africa.

Search strategy and preliminary results:

Our comprehensive search strategy consists of, (a) electronic search, (b) search for gray literature (conference proceedings, clinical trial registers), (c) contacting experts in the field of depression or DM (physicians, diabetologists, psychiatrists, psychologists, counsellors, public mental health specialists et cetera), and (d) using the reference bibliography of index full text articles to identify potentially relevant studies. The electronic search strategy will follow the PICOS approach (Population, Intervention, Comparator, Outcome and Study design), and conducted in at least two major data bases including PubMed/Medline, EMBASE and Psych-info. We will use Google Scholar to identify relevant citations. The electronic search terms will include various combinations of Medical Subject Headings (MESH) and plain language words to capture the elements of PICOS described in the review question section. Thus far we have developed the electronic search strategy and preliminary results are shown below, (Table 1).

Table 1: Yield of literature on depression in diabetes mellitus and diabetes mellitus in depression in LMICs.

Search number **(Data base)**	**Search terms**	**Number of hits*** **(Relevant)**
#1 (PubMed)	((((("depressive disorder"[MeSH Terms] OR "depression"[MeSH Terms] OR depression[Text Word]) AND ("diabetes mellitus"[MeSH Terms] OR "diabetes insipidus"[MeSH Terms] OR diabetes[Text Word])) AND ("epidemiology"[Subheading] OR "burden of"[All Fields] OR "prevalence"[MeSH Terms] OR prevalence[Text Word])) AND "screening"[All Fields] OR "interventions"[All Fields]) AND "developing countries"[All Fields]	4062

**Number of articles as at 17.01.2014*

Limitations of the search terms: The search will be initially limited to the most recent 10 years, and subsequently incrementally by 5 year bands retrospectively with accrual of studies. We will not employ language limitations. This will permit assessment of the more recent and relevant evidence whilst catering for feasibility to deliver a quality review paper.

Study selection and eligibility:

Two or more independent reviewers will screen the titles and assess the articles for eligibility. Full text articles will be further assessed for inclusion in parallel, and agreement will be estimated by Cohen's Kappa. Consensus and a third reviewer will be applied to arbitrate in the event of disagreement.

Inclusion criteria: The types of studies (designs) to be included have been described in the review question section, but will generally follow the criteria described by the Effectiveness of Practice and Organization of Care Cochrane group (EPOC). Studies that have assessed for the prevalence of depression by means of a gold standard instrument (MINI, ICD-10, SCID), through a routinely used screening scale (PHQ-9, CES-D, MADRAS, HSCL), or through an interview by a trained mental health worker. Studies that have documented the routine depression screening in DM patients. All studies in which a gold standard instrument (ICD-10, MINI, SCID) or a detailed psychiatric interview by a trained mental health worker was used to diagnose depression. All studies where there exists a routine depression screening protocol. Similarly for DM, we will include studies which used the standard of screening and diagnosis of the setting.

Exclusion criteria: Studies in which a rating scale was used to diagnose depression. And studies

Data abstraction:

Data will be abstracted into a spread sheet, in duplicate and independently by any two reviewers including DA and EO.

Exposure variables: This spreadsheet will be piloted and adjusted to suit capture of the required including: study administrative information, setting, patient population demographic characteristics, screening strategy (intervention), reference standard/diagnostic criteria used to confirm a depressive disorder.

Outcome measures: These will include: (a) Outcomes for disease burden measured as the absolute number, or proportion (prevalence) or rate (incidence) of depression among diabetics; (b) Clinical characteristics of patients with depression and diabetes mellitus; (c) The effects of depression screening strategies among diabetics (e.g. yield of depression among diabetics, time-to-diagnosis, treatment of depression, prevalence of complications of DM, and economic measures like quality of life). These effects will be defined as the yield of the screening intervention which may be reported as: absolute number or proportion of depressed patients among diabetics; absolute or relative binary measures of effects including odds ratios, relative risk, and absolute risk difference. In the event of survival analysis data, Hazard Ratios will be used. We will standardize these measures by re-computing the relative risk and absolute risk. Relative risk are more consistent across studies but absolute risk measures provide better interpretation[49]. Missing data will be designated as not reported (NR).

Risk of Bias Assessment:

The methodological quality of the individual studies will be independently assessed for each of the outcomes, by DA, PK, LR and EO using the REVMAN 5.2 software. The following methodological items will be considered: For the question on burden of disease, (a) sampling strategy; (b) measurement errors, or misclassification;

c) measure of uncertainty. In part two on effects, where applicable sequence generation, allocation concealment, blinding. Additional criteria of sample size, losses to follow up, and borrowing features specific to screening and diagnosis studies elaborated in QUADAS-1 (Quality Assessment in Diagnostic Accuracy Studies) will be employed [50, 51]. Any ambiguity will be resolved by consensus and RO will be the arbiter.

Assessment of overall quality of evidence:

We will employ the GRADE criteria to assess for confidence in the evidence for a particular outcome (Grading, Recommendations, Assessment, Development and Evaluation) [52, 53]. This will include developing summary of findings tables for each outcome. Noteworthy, although GRADE criteria for observational studies and screening or diagnostic studies are still under development, we will assume a perspective of diagnostic strategy. In this regard we will still apply expert opinion to downgrade or upgrade the quality of evidence.

Data Synthesis:

This will follow methods proposed in the PRISMA [54], Cochrane [48] and MOOSE [47]publications. Included studies will be reported using descriptive statistics. *Narrative synthesis*: Structured synthesis of data will be done and precede any meta-analyses. This will employ majorly descriptive statistics and if appropriate Forest plots. A funnel plot, Begg's and Egger's test will be employed to explore publication bias. *Meta-analysis*: Prevalence data will be transformed using appropriate statistical methods to facilitate meta-analysis. Data on effects of screening will be standardized. Biological, methodological and statistical heterogeneity will be assessed using the Cochran's Q and the I-squared statistics. In the absence of statistically significant heterogeneity, we will use RevMan v.5.2 [55]and Stata v.11.2, to pool and analyze the data using the random effects model or network meta-analysis in the event of multiple interventions, multiple outcomes or making decision assumptions for missing data. In order to explore the robustness of the results of the primary outcome, sensitivity analyses will be conducted. Potential factors to be explored in this sensitivity analyses are: study quality and patient related heterogeneity.

REPORTING AND DISCUSSION OF RESULTS:

Findings from this review will be reported according to the PRISMA statement [44], and PRISMA extension for equity considerations [54]. The discussion section will draw on findings from the synthesis. Policy relevant aspects of applicability, relevance, equity, costs and monitoring and evaluation will be addressed here. We will hold bi-monthly synthesis meetings on a rolling basis as data accumulates.

POTENTIAL LIMITATIONS OF REVIEW METHODS:

This review may be limited by:
Language and time bias: We propose to include French literature, which we will screen using Google Scholar. We will then contact The Centre for the Development of Best Practices in Health (CDBPH), University of Yaoundé 1, Yaoundé, Cameroon; for analysis of full text articles written in French. In terms of time bias, we will include all

studies since 1990 as recommended by the Cochrane EPOC group. However, in the event of very few studies, we will search earlier years in blocks of five years.
Evidence types: It is possible to identify poorly designed observational designs which provide lower quality evidence of effects, for quantitative outcomes. Rather than exclude weaker study designs which are largely observational, we will employ the Risk of Bias criteria for different study designs, elaborated in the protocol and recommended by the Cochrane EPOC group in assessing the quality of included primary studies and employing these quality features in sensitivity analyses; followed by the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) framework in assessing the overall quality of evidence for specific quantitative outcomes. Here, we will develop summary of findings tables, and assess the confidence in the effect estimates, and strength of recommendations basing on the quality of evidence. Indeed, with low quality or absence of evidence, we will identify areas for further research.
Synthesis & reporting: (a) Due to the different study designs, interventions and varying contexts, synthesis will be a challenge. We will employ multi-stage structured synthesis, followed by meta-analysis where feasible.

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ANNEXES:

Annex 1: Electronic search strategy
Annex 2: Draft data abstraction form