## PEER REVIEW HISTORY



## ARTICLE DETAILS

| | |
|---|---|
| **TITLE (PROVISIONAL)** | Randomized controlled trials on prevention, diagnosis, and treatment of diabetes in African countries - a systematic review |
| **AUTHORS** | Sandholzer-Yilmaz, Angelika; Kroeber, Eric; Ayele, Wondimu; Frese, T; Kantelhardt, Eva; Unverzagt, Susanne |

## VERSION 1 – REVIEW

| | |
|---|---|
| **REVIEWER** | David Flood<br>University of Michigan |
| **REVIEW RETURNED** | 29-Sep-2021 |

| | |
|---|---|
| **GENERAL COMMENTS** | This study is a systematic review and meta-analysis of randomized clinical trials of interventions to prevent, diagnose, and treat diabetes in the African region.<br><br>I think that this topic is of high clinical and policy relevance and that the authors have generally conducted a methodologically rigorous review. I congratulate them on the tremendous work this paper must have required. I think the paper would generally be a good fit for BMJ Open, though I do have some reservations as I note below.<br><br>Major comment:<br><br>My main critique in reading this manuscript is to ponder whether the framing of the review is optimal for the intended objective of the study ("to collect the best locally generated evidence on DM interventions, identify knowledge gaps, and determine underexplored research areas"). This objective to me seems very reasonable and important, though the scope is extremely broad given the focus on all forms of diabetes (type 1, type 2, and gestational), in all domains of care (prevention, diagnosis, treatment), in all countries in Africa (an extremely populous and diverse continent). The review carefully identifies many studies meeting eligibility, before concluding: "The identified studies offer a variety of effective approaches as a basis for local guidelines in the different fields of action in DM care adjusted to regional circumstances."<br><br>My interpretation of this study's findings differs from that of the authors. Unfortunately, I do not think it is reasonable to apply the data in this review as the basis for any guidelines -- the data is too sparse, too biased, too heterogeneous. The authors have opted to restrict the studies in this review to randomized trials, which I think is fine if the purpose of the study is more of a mapping exercise than an evidence-generation exercise. But, given the underwhelming quality of studies identified, one wonders if the "best locally generated evidence on DM interventions" should also include |

| | |
|---|---|
| | carefully done non-randomized, observational, and even qualitative research. These are forms of evidence too.<br><br>Thus, my suggestion -- which the authors may take of leave -- would be to emphasize the astonishing knowledge gaps and underexplored research areas. I see at least five key findings. In my view, (1) the paucity of RCTs for all forms of diabetes across the entire continent of Africa is truly scandalous. Along this line, (2) the level of bias in the trials was very high. You also found that (3) there is near-absence of trials conducted in rural areas and at the primary care level. Another pattern that I observed though this is not specifically stated is that (4) there were very limited rigorous implementation research studies assessing the delivery of known evidence-based care in the health system. Finally, there were very substantial country-level geographic disparities in where research has been conducted (i.e., a disproportionate number trials from Egypt); (5) it may be worth remarking on how the geographic distribution of the trials likely does not correspond with the absolute burden of diabetes across the continent. The authors could also likely demonstrate that less research has emerged from poorer countries.<br><br>Minor comments:<br><br>- It is difficult to follow the PRISMA flow diagram, and I cannot get the arithmetic to work out. This should be revised or clarified. How many duplicates were there? Why does screened (n=3,584) minus excluded (n=3,551) not equal full-text articles assessed (n=185)?<br><br>- The discussion is extremely long and, to me, reads too much as reciting the findings rather than adding an interpretative lens to the findings. I would suggest distilling it down considerably by focusing on the most salient, high-impact points the authors wish to emphasize.<br><br>- Notably absent is a discussion about how the findings build on or relate to recommendations of the 2017 Lancet Commission on Diabetes in sub-Saharan Africa.<br><br>- Note on English language requirement: The text states that no study was restricted due to English language criteria, but were the searches themselves conducted in English? If so, it could be true that records could have been missed, and thus the statement would not be accurate.<br><br>- I think it would be useful for the reader for the authors to assess an overall risk of bias using the Cochrane approach. If the authors view this as not necessary, I would be interested in their justification as to why not. When looking through the risk of bias table, it would seem to me that nearly all the studies would be judged as high risk of bias in an overall assessment; this seems like a noteworthy finding. This approach could also make the "potential biases" section much more concise.<br><br>- An important limitation in this study is that interventions assessing the cardiovascular risk factors of diabetes are not explored (i.e., hypertension, smoking, dyslipidemia/statin use). There is increasing recognition that addressing the population-level burden of diabetes in LMICs will require more focus on these cardiovascular risk factors rather than scaling-up diabetes diagnosis or improving glycemic |

| | |
|---|---|
| | control:<br>https://www.thelancet.com/journals/langlo/article/PIIS2214-109X(21)00340-5/fulltext |

| | |
|---|---|
| **REVIEWER** | Jiaqiong Xu<br>Houston Methodist Research Institute |
| **REVIEW RETURNED** | 01-Oct-2021 |

| | |
|---|---|
| **GENERAL COMMENTS** | This is a well-written manuscript, which was a comprehensive systematic review. The statistical methods are appropriate. I have a couple comments:<br>1. The outcomes listed were all-cause mortality, glycemic control, complications, quality of life, hospital admission, treatment adherence and costs. But only overall effect of HbA1c levels was presented. How about others, especially the primary outcome, all-cause mortality?<br>2. The authors stated that “Statistically significant results on HbA1c with MDs over 0.25 % for HbA1c were considered clinically relevant” Is there any reference for using MDs over 0.25%? |

**VERSION 1 – AUTHOR RESPONSE**

Reviewer: 1
Dr. David Flood, University of Michigan

Comments to the Author:

This study is a systematic review and meta-analysis of randomized clinical trials of interventions to prevent, diagnose, and treat diabetes in the African region.

I think that this topic is of high clinical and policy relevance and that the authors have generally conducted a methodologically rigorous review. I congratulate them on the tremendous work this paper must have required. I think the paper would generally be a good fit for BMJ Open, though I do have some reservations as I note below.

**Major comment:**

**My main critique in reading this manuscript is to ponder whether the framing of the review is optimal for the intended objective of the study ("to collect the best locally generated evidence on DM interventions, identify knowledge gaps, and determine underexplored research areas"). This objective to me seems very reasonable and important, though the scope is extremely broad given the focus on all forms of diabetes (type 1, type 2, and gestational), in all domains of care (prevention, diagnosis, treatment), in all countries in Africa (an extremely populous and diverse continent). The review carefully identifies many studies meeting eligibility, before concluding: "The identified studies offer a variety of effective approaches as a basis for local guidelines in the different fields of action in DM care adjusted to regional circumstances."**

**My interpretation of this study's findings differs from that of the authors. Unfortunately, I do not think it is reasonable to apply the data in this review as the basis for any guidelines -- the data is too sparse, too biased, too heterogeneous. The authors have opted to restrict the studies in this review to randomized trials, which I think is fine if the purpose of the study is more of a mapping exercise than an evidence-generation exercise. But, given the underwhelming quality of studies identified, one wonders if the "best locally generated evidence on DM interventions" should also include carefully done non-randomized, observational, and even qualitative research. These are forms of evidence too.**

**Thus, my suggestion -- which the authors may take of leave -- would be to emphasize the astonishing knowledge gaps and underexplored research areas. I see at least five key findings. In my view, (1) the paucity of RCTs for all forms of diabetes across the entire continent of Africa is truly scandalous. Along this line, (2) the level of bias in the trials was very high. You also found that (3) there is near-absence of trials conducted in rural areas and at the primary care level. Another pattern that I observed though this is not specifically stated is that (4) there were very limited rigorous implementation research studies assessing the delivery of known evidence-based care in the health system. Finally, there were very substantial country-level geographic disparities in where research has been conducted (i.e., a disproportionate number trials from Egypt); (5) it may be worth remarking on how the geographic distribution of the trials likely does not correspond with the absolute burden of diabetes across the continent. The authors could also likely demonstrate that less research has emerged from poorer countries.**

Authors response:

Thank you very much for your comprehensive and insightful comments on the reviews frame and discussion content. We believe that the five statements you've carved out are well assessed. Despite the implementation research aspect being new, we've highlighted these thoughts throughout the discussion, making the text more concise and readable. Nevertheless, we've shortened but kept large parts of the contextualizations of our finding since we believe that the actual interventions that were successfully trialed should also be put in a focus to inform clinicians, researchers and policy makers to find tanglible and specific interventions that might be applicable to their respective situation.

Please find the changes throughout the discussion part including two new subheadings (Rural vs. urban, primary vs. secondary care and geographic disparities, Scarcity of randomized DM trials in African countries) and the conclusions.

**Minor comments:**

**- It is difficult to follow the PRISMA flow diagram, and I cannot get the arithmetic to work out. This should be revised or clarified. How many duplicates were there? Why does screened (n=3,584) minus excluded (n=3,551) not equal full-text articles assessed (n=185)?**

Authors response: Thanks for this advice. We screened titles and abstracts of 3584 references, excluded 3399 references and ordered and read a total of 185 full-text articles. We corrected figure 1.

**- The discussion is extremely long and, to me, reads too much as reciting the findings rather than adding an interpretative lens to the findings. I would suggest distilling it down considerably by focusing on the most salient, high-impact points the authors wish to emphasize.**

Authors response:

Thank you very much for the comment, we've condensed the discussion, reordered several parts and shortened the parts that are taking up the findings. Nevertheless we considering an inclusion of a discussion of successful interventions important.

- **Notably absent is a discussion about how the findings build on or relate to recommendations of the 2017 Lancet Commission on Diabetes in sub-Saharan Africa.**

Authors response:

- Thank you for this very interesting publication.

One of the key messages stated in this publication is the lack of reliable data conducted in this area. Evidence from high income countries is not always transmittable to low-income countries and therefore local interventions which likely are to be integrated and affordable in those countries are needed. Cost-effectiveness of interventions needs to be guranteed due to the limited resourcess. It is urgent to invest in the prevention of diabetes and its complications as this must be more cost effective than the treatment once complications occure. We found a couple of effective interventions on educational strategies. They can relate to the recommendations of the 2017 Lancet Commision on Diabetes in sub-Saharan Africa where education at different levels (personal, community and health care provider levels) is essential for management of the burden of diabetes.

All those major points had been discussed in our manuskript, but we added a little discussion under “educational strateges for patients and health care provides” and cited this publication.

**- Note on English language requirement: The text states that no study was restricted due to English language criteria, but were the searches themselves conducted in English? If so, it could be true that records could have been missed, and thus the statement would not be accurate.**

Authors response:
We discussed your comment and agree that we might have missed studies from journals not listened in MEDLINE or CENTRAL. Therefore, we have added a search in regional electronic databases (African Journals Online and African Index Medicus).
To our knowledge, studies listened in these databases are indexed, cataloged, compiled and integrated databases by librarians to controlled vocabulary and related terms from the Unified Medical Language System (UMLS) into English language.
According to a library service (https://library.svhm.org.au/literature_searching/medline), non-English records from the 1980s and 1990s might have been missed. Therefore, we do not think, that we might have missed a relevant number of references on the basis of our English search terms.
Summarizing these facts, we added under the subchapter Strength and limitations: “Eventually, we did not exclude any study due to the publication language, but we might have missed studies from journals that are not listened in searched databases. “

**- I think it would be useful for the reader for the authors to assess an overall risk of bias using the Cochrane approach. If the authors view this as not necessary, I would be interested in their justification as to why not. When looking through the risk of bias table, it would seem to me that nearly all the studies would be judged as high risk of bias in an overall assessment; this seems like a noteworthy finding. This approach could also make the "potential biases" section much more concise.**

Authors response:

We judged risk of bias on the basis of the Cochrane risk of bias tool Higgins JPT, Thormas J, Chandler J, et al. Cochrane handbook for systematic reviews of interventions version 5.1. 0 [updated March 2011].) This tool does not recommend to judge an overall risk of bias. Therefore, we described “None of the included studies was categorized as low risk of bias in all seven domains only (see Table 6: Judgement on risk of bias available in the supplements).”

**- An important limitation in this study is that interventions assessing the cardiovascular risk factors of diabetes are not explored (i.e., hypertension, smoking, dyslipidemia/statin use).**

**There is increasing recognition that addressing the population-level burden of diabetes in LMICs will require more focus on these cardiovascular risk factors rather than scaling-up diabetes diagnosis or improving glycemic control:**

**https://www.thelancet.com/journals/langlo/article/PIIS2214-109X(21)00340-5/fulltext**

Authors response:

Thanks for this very interesting publication. Due to the very broad scope of our systematic review, we concentrated on interventions to prevent, diagnose and treat diabetes by the improvement of glycaemic control. We did not include interventions to reduce cardiovascular risk factors. But we added the following sentence as a limitation of our review: "Next, this review does not include non-randomized study types including prospective cohort trials or qualitative research, probable not taking into account the evidence that has been accumulated. Nevertheless, our aim was to search for randomized trials, since these study types, if conducted well, have a high evidence quality, allowing to minimize biases. Moreover, many of the studies included had a high risk of bias."

Reviewer: 2

Dr. Jiaqiong Xu, Houston Methodist Research Institute

Comments to the Author:

This is a well-written manuscript, which was a comprehensive systematic review. The statistical methods are appropriate. I have a couple comments:

1. **The outcomes listed were all-cause mortality, glycemic control, complications, quality of life, hospital admission, treatment adherence and costs. But only overall effect of HbA1c levels was presented. How about others, especially the primary outcome, all-cause mortality?**

Authors response:

We planned all-cause-mortality as primary outcome. This most important outcome was used in several Cochrane reviews (e.g. Jones et al. 2019. Techniques of monitoring blood glucose during pregnancy for women with pre-existing diabetes, Shyanddan et al. 2011. Glucagon-like peptide analogues for type 2 diabetes mellitus, Lo et al. 2018. Insulin and glucose-lowering agents for treating people with diabetes and chronic kidney disease), but we did not identify a study reporting this endpoint. We describe this fact under Strength and limitations: "Our pre-planned primary outcome was mortality which was not reported in any of the included studies. Since DM is a chronic disease with a slow progression and long-term development of organ damage, the survival time is higher than the follow-up time of most of the studies. The included studies looked at long-term treatment strategies rather than treatment for acute hypo- or hyperglycemic events that can lead to acutely fatal events."

2. **The authors stated that "Statistically significant results on HbA1c with MDs over 0.25 % for HbA1c were considered clinically relevant" Is there any reference for using MDs over 0.25%?**

Authors response:

J Diabetes Sci Technol. 2017 Mar; 11(2): 315–323.

Published online 2017 Mar 1. doi: 10.1177/1932296816662048

PMCID: PMC5478016

PMID: 27510441

**Description of a New Predictive Modeling Approach That Correlates the Risk and Associated Cost of Well-Defined Diabetes-Related Complications With Changes in Glycated Hemoglobin (HbA1c)**

Kurt Fortwaengler, PMP,[1] Christopher G. Parkin, MS,[2] Kurt Neeser, PhD, MPH,[3] Monika Neumann, ISp,[3] and Oliver Mast, MSc[4]

The association of HbA1c level to DM2 complications is described in the model derived by Fortwaengler et al., MDs smaller than 0.25% (absolute) are, based on this model, likely to cause a drop in the frequency of complications of less then 5%. Therefore we considered a MD of less than 0.25% as not clinically relevant. However, it is hard to decide about the clinical relevance of a certain MD due to uncertainties in many models. In the end we feel that there is no objective definition of a clinically significant difference. We assume that our approach did not lead to an underestimation of potentially existing evidence.

## VERSION 2 – REVIEW

| | |
|---|---|
| **REVIEWER** | David Flood<br>University of Michigan |
| **REVIEW RETURNED** | 30-Jan-2022 |

| | |
|---|---|
| **GENERAL COMMENTS** | The authors have adequately addressed my comments. |

| | |
|---|---|
| **REVIEWER** | Jiaqiong Xu<br>Houston Methodist Research Institute |
| **REVIEW RETURNED** | 26-Jan-2022 |

| | |
|---|---|
| **GENERAL COMMENTS** | I gave the review on 10/1/2021 with the following comments:<br>1. The outcomes listed were all-cause mortality, glycemic control, complications, quality of life, hospital admission, treatment adherence and costs. But only overall effect of HbA1c levels was presented. How about others, especially the primary outcome, all-cause mortality?<br>2. The authors stated that “Statistically significant results on HbA1c with MDs over 0.25 % for HbA1c were considered clinically relevant” Is there any reference for using MDs over 0.25%?<br><br>But I didn't see the reply to these comments or the changes in the manuscript. Did I miss something here? |

## VERSION 2 – AUTHOR RESPONSE

Reviewer: 2
Dr. Jiaqiong Xu, Houston Methodist Research Institute
Comments to the Author:
I gave the review on 10/1/2021 with the following comments:

1. The outcomes listed were all-cause mortality, glycemic control, complications, quality of life, hospital admission, treatment adherence and costs. But only overall effect of HbA1c levels was presented. How about others, especially the primary outcome, all-cause mortality?

But I didn't see the reply to these comments or the changes in the manuscript. Did I miss something here?

**Answer:**

Thank you for your comment, your concern on outcome reporting, especially on the primary outcome all-cause mortality, has previously been addressed in the strengths and limitations section:

"Our pre-planned primary outcome was mortality which was not reported in any of the included studies. Since DM is a chronic disease with a slow progression and long-term development of organ damage, the survival time is higher than the follow-up time of most of the studies. The included studies looked at long-term treatment strategies rather than treatment for acute hypo- or hyperglycemic events that can lead to acutely fatal events. Nevertheless, long-term glucose control, being represented by the HbA1c value is one of the strongest clinical-outcome indicators of efficient DM management and health outcomes (137). It is easy to measure and serves as a representation of the individual's average blood glucose levels in the previous 3 months (137). Furthermore, it is up to discussion if improvement of glycemic control based on blood glucose measures like HbA1C are necessary the best strategic in LMIC or if diabetes complications are more effectively prevented by targeting blood pressure or blood lipids (138)."

Therefore, we've only done a meta-analysis (displayed in forest plots in figures 3 and 4) to estimate the overall effect on glycemic control by the proxy of HbA1c level changes.

Results on quality of life, hospital admission, costs, complications and treatment adherence are described narratively throughout the results section and in supplementary table 1 to 4. These results were not reported regularly. When reported, the interventions as well the measures were very heterogeneous, and the authorial team arrived with the conclusion that a meta-analysis/pooling is not viable.

Example from results section on hospital admission:

*"Two studies reported fewer admissions to different health-care facilities (hospital or emergency room and clinic visits) (Abaza 2017, Chraibi 2017)."*

From Results/Interventions for patients with DM2/Educational strategies. This information is also included in supplementary table 3.

Example from results section on quality of life:

*“Results on quality of life were reported in two studies with follow-up periods over 12 months and conflicting results. A structured self-care education program by pharmacists and nurses (Adibe 2013) improved quality of life, but no benefit was shown after group education by trained professionals (Mash 2014).”*

From Results/Interventions for patients with DM2/Educational strategies. This information is also included in supplementary table 3.

2. The authors stated that “Statistically significant results on HbA1c with MDs over 0.25 % for HbA1c were considered clinically relevant” Is there any reference for using MDs over 0.25%?

**Answer:**

Thank you for the comment. We chose a HbA1c change of > 0.25% as clinically relevant based on a model by Fortwaengler et al. We forgot to add the reference in the methods section but changed that. Here is the publication including an explanation why the chosen cut-off is usable:

***Description of a New Predictive Modeling Approach That Correlates the Risk and Associated Cost of Well-Defined Diabetes-Related Complications With Changes in Glycated Hemoglobin (HbA1c)***

*Kurt Fortwaengler, PMP,1 Christopher G. Parkin, MS,2 Kurt Neeser, PhD, MPH,3 Monika Neumann, ISp,3 and Oliver Mast, MSc4*

*The association of HbA1c level to DM2 complications is described in the model derived by Fortwaengler et al., MDs smaller than 0.25% (absolute) are, based on this model, likely to cause a drop in the frequency of complications of less then 5%. Therefore, we considered a MD of less than 0.25% as not clinically relevant. However, it is hard to decide about the clinical relevance of a certain MD due to uncertainties in many models. In the end we feel that there is no objective definition of a clinically significant difference. We assume that our approach did not lead to an underestimation of potentially existing evidence.*

Here is the statement from our manuscript from the results section/data synthesis with the new reference (27):

*“Statistically significant results on HbA1c with MDs over 0.25 % for HbA1c were considered clinically relevant (27).”*

Reviewer: 1
Dr. David Flood, University of Michigan
Comments to the Author:
The authors have adequately addressed my comments.

**VERSION 3 – REVIEW**

| | |
|---|---|
| **REVIEWER** | Jiaqiong Xu<br>Houston Methodist Research Institute |
| **REVIEW RETURNED** | 03-Mar-2022 |

| | |
|---|---|
| **GENERAL COMMENTS** | Thanks the authors for addressing my previous comments. I don't have any further questions. |