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OPEN PEER REVIEW

Assessing the Effectiveness of Type 2 Diabetes Screening in the Republic of Uzbekistan

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Contents

1 Original submission 2
2 Revision 1 Davood Khalili 3
Authors' reply to reviewers 4
Reviewer and editor comments 9
3 Revision 2 Davood Khalili 10
Authors' reply to reviewers 11
Reviewer and editor comments 13
4 Revision 3 Davood Khalili 14
Authors' reply to reviewers 15
Reviewer and editor comments 16

1 Original submission

0 comments

No public comments in this round.

2

Revision 1

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

Reviewer 1:
Dear EIC

The manuscript entitled "Assessment of the Effectiveness of Type 2 Diabetes Mellitus Screening in the Republic of Uzbekistan" is based upon the pilot study of adult diabetes mellitus screening in 2 urban and 2 rural health centers in the Republic of Uzbekistan. The current paper desires to examine and explain the effectiveness of type 2 diabetes mellitus screening in the country, but it is not successful. Below there are some major issues to address:
• The methods are not well-described and clear in detailed (sampling, lab method and apparatus, definitions…)
• The discussion has improper writing style with several irrelevant points.
• The result section has numerous and unsuitable tables and figures, without sufficient explanation and footnotes, and also has some technical errors.

Dear Reviewer,

Thank you for the valuable comments! We hope the revised manuscript will leave a more favorable impression. Regarding your comments:

- We have added some information about the methods used during the study;
- We have also revised and re-written the discussion part;
- We have added the additional information clarifying the data.

Reviewer 2:
I read with great interest the manuscript entitled "Assessment of the Effectiveness of Type 2 Diabetes Mellitus Screening in the Republic of Uzbekistan". It is a very important issue in a country in a region with a high prevalence of diabetes that merits more attention. It seems that the study is relatively well designed, but the reporting and its scientific writing have many inadequacies. The main point of the method is that, If there is no intervention (i.e more testing or treatment) after the detection of a diabetic patient using different criteria in different arms, all lab measurements and criteria could be applied to just one group. In this way, the prevalence of diabetes based on different criteria would be more comparable. Nonetheless, I have some concerns as follows…

Dear Reviewer,

Thank you for the valuable comments! We have revised the manuscript and hope it now looks more consistent. Regarding your comments:

Major comments
- The introduction is well written and convincing but a little long for a scientific paper.
We tried to shorten the Introduction part without losing the meaning.

- The method should begin with a Study Population section in more detail. Setting (population-based, clinic-based or other settings), sampling, the sample size required, inclusion and exclusion criteria especially age range, the number invited, and finally the numbers accepted and recruited in the study should be explained. A flowchart for the study population is needed.
We should note that **all** patients who applied to polyclinics for **any** reason, met the inclusion criteria, and signed the consent form were included in the study as we tried to conduct a study as close as possible to the real clinical practice. We planned to recruit approximately 2500 patients (the actual number was 2430). Regarding a flowchart, the figures 2-4 are representing the number of

patients who applied to GPs, were tested, and the share of those who have abnormal glycemia. We tried to clarify the information regarding these figures in text.

- The method of randomization is confusing. What is the cluster? How many clusters were randomized? If there is cluster randomization, why people in Gijduvan and Namangan were assigned only to one arm and people in Bukhara and Turakurgan to the other 3 arms of the screening program.

- The consort statement for cluster randomized trials should be followed for reporting this trial. Reference: Campbell MK, Piaggio G, Elbourne DR, Altman DG; for the CONSORT Group. Consort 2010 statement: extension to cluster randomised trials. BMJ. 2012 Sep 4;345:e5661. And also:
http://www.consort-statement.org/extensions?ContentWidgetId=554

A cluster is a location of GP in the outpatient department (village or town) selected for this research (in our trial Gijduvan, Turakurgan, Namangan, Bukhara). To conduct the study, we randomly fixed the type of screening for certain localities.

We are combining this cluster randomization scheme with the factorial design to have an option to analyze data from two points of view - The number of screening criteria & Screening scenario. Both of them are the answer to the same question: how we can simplify screening and make it cheaper.

	Number of screening criteria	
Screening scenario	1 screening criteria	3 screening criteria
Glu -> Glu	Gijduvan	Turakurgan
Glu -> HbA1c	Namangan	Bukhara

- If there is no gold standard (e.g. repeating glucose tests and diagnosis based on ADA criteria) and the final outcome is just the percent of diabetes diagnosis in each arm of the study, what is the role of the endocrinologist or GP? If there were objective criteria for diagnosis of diabetes in each arm, what was the difference of diagnosis by endocrinologist or GP? Just a trained physician can report the results of the lab measurements based on the criteria in each arm.

The problem of Uzbekistan as a low-income country is the limited resources, including human resources. The country is lacking endocrinologists, and GPs are not always qualified enough to redirect the patient to an endocrinologist in time. For instance, even in our study, trained GPs did not follow the protocol strictly which led to the inclusion of patients under 45 years of age in the study for an additional analysis. In this regard, it seems rational to implement educational programs for GPs, however, the final diagnosis in any case should be established by an endocrinologist.

- What is the rationale for considering high BMI and high blood pressure for eligibility for screening? Why other factors like history of cardiovascular disease, family history of type 2 diabetes, history of gestational diabetes mellitus, or delivery of a baby weighing above 4 kg (as ADA recommended) have not been considered?

We used BMI and BP as criteria because of their simplicity. Not all patients are aware of the family history of diabetes, moreover, in conditions of Uzbekistan where T2DM is extremely underdiagnosed this strategy may be not a good choice. And the second reason is the extremely low knowledge level of diabetes through the GP in Uzbekistan, in real settings, outside of the capital.

- What is the definition of prediabetes in this study? Is it based on glucose or HbA1c or both?

We used both definitions.

- Based on table 1, there are many differences between different arms (study groups). So the random allocation using cluster randomization is questionable.
The differences between these groups are related to such parameters as SBP, weight, BMI, WC, obesity frequency which can be explained by the criteria used: the group of 3 inclusion criteria was established in that way it should have more obese patients with higher blood pressure as obesity and blood pressure were among these inclusion criteria.
HbA1c, glucose
Difference in Hba1c, glucose is important finding, here is we completely agree with you. But this is not just a finding, this is one of the study results. So, with 3 screening criteria we can find more cases with T2D -> HbA1c, glucose higher.

- Figure 1 is confusing and not easy to understand and should be reorganized.
- Figures 2, 3, and 4 are confusing as well. Nothing is mentioned about them in the methods; nothing about the first and second visit; what is the "double glucose scenario" or "glucose–HbA1c" scenario? It seems that these results are not directly related to the aims of this paper and can be omitted.
We have added some additional information to the Methods part as well as the notes for Figures and hope this could clarify the paper.

- In table 4, the 95% CIs are too wide to be reliable. No conclusion can be reached from these wide CIs.
Thank you, this is important question. Calculation of this split by the age requested by our authority. They are looking for the option to target nationwide screening program to the specific age group. So, we did this split by this request. But as you clearly found CI is too wide to make any conclusions. Explanation is simple – the sample size is not enough to detect any difference in those subpopulations. If you want, we can delete this table from the article.

- The discussion was not written scientifically. It is a more detailed description of the issue, is too long, and has not focused on the results of this study. The results have not been compared with the same studies from other countries especially developed countries and countries in the region. The strengths and limitations of the study should be mentioned before the conclusion.
Thank you for the valuable comment. We have rewritten the Discussion part and hope it will leave a more favorable impression. However, as we noted, the comparing our study with the same studies from developed countries can be counterproductive as Uzbekistan is a low-income country with very limited resources. Regarding the comparing our results with the results of the same studies that were conducted in the countries of our region, we could only use the data from Russia as it has the most established T2DM database. The limitation of this comparison is that Russia is a middle-income country with a different ethnic composition which also differs in the European & the Asian parts of the country. However, we tried to collect all the available up-to-date information about the state of affairs in the region.

Minor comments
- By "carbohydrate metabolism disorders" you mean dysglycemia I think. Replacing it is recommended.
Thank you for the comment, we have replaced it.

- By "inclusion criteria" you mean "eligibility criteria" for screening. Inclusion and exclusion criteria are usually used for sampling at the beginning of the study.

Agree, corrected

- It is not a cost-effective analysis and any conclusion about the cost-effectiveness of the screening methods should be removed. No effect of different scenarios has been studied and just the prevalences have been reported. However, the cost of different scenarios can still be compared and discussed.

Agree, corrected

- Although screening tools like FINDRISK have not been validated for the central Asian population, these tools have been validated for Iranian populations who are racially very close to the Uzbek population. The authors can refer to the references below:
"Non-invasive Risk Prediction Models in Identifying Undiagnosed Type 2 Diabetes or Predicting Future Incident Cases in the Iranian Population. Archives of Iranian Medicine (AIM). 2019 Mar 1;22(3)."
"The external validity and performance of the no-laboratory American Diabetes Association screening tool for identifying undiagnosed type 2 diabetes among the Iranian population. Primary care diabetes. 2020 Dec 1;14(6):672-7."
"Performance of stepwise screening methods in identifying individuals at high risk of type 2 diabetes in an Iranian population. International journal of health policy and management. 2021"
Thank you for the valuable comment. We should note that Iran and the Central Asian region have different ethnic compositions, so we can not extrapolate the results for the Iranian population to the Uzbek population. According to the open resources, more than a half of the population in Iran are Persians, followed by Azerbaijanis, Kurds, and other ethnicities. The population of Uzbekistan may be similar to that of Iran, but only partly, since Uzbekistan is located in the Central Asia and neighbors with states predominantly populated by Turkic peoples.

- The setting of the study is clinics, not the general population, so the prevalences may be overestimated. It is a limitation of the study and should be mentioned as a limitation in the discussion.

Sure, agree, this statement is added to the manuscript.

- Some results for the prevalences have been reported without saying the criteria. For example in lines 193-196, which criteria the prevalences in men and women are based on?
An analysis of sex and age characteristics among all patients revealed that the prevalence of T2DM detected by screening was 15.2% among men and 11.6% among women. At the same time, T2DM was diagnosed in 8.0% of the patients under 50 years of age and in 12.8% of the patients 50–59 years of age.

- In lines 190-191, it is mentioned that "The use of HbA1c as an additional diagnostic method allowed 14.1 % of prediabetes cases to be detected, and repeat glycemic determination allowed 20.2 % of cases to be detected." Nothing mentioned about adding HbA1c or repeating glucose measurement for diagnosis of diabetes in the Method section.
We have added more information in the Methods part of the paper, so we hope the study design will seem more consistent.

- The numbers of different groups are different in table 1 and table 5.
Thank you, this is misprint, corrected. The right data is:

Method of screening		Number of eligibility criteria	
HbA1c	Glucose	3 factors	1 factor
1,195	1,225	1,215	1,205

- *Citations in the Reference section are not in a standard and unique manner.*
We used a reference manager with an official style of a journal. Thank you for the comment, we will double check this part of the manuscript.

2 Revision 1

1 comment · 20 Jul 2022

Davood Khalili Reviewer

MAJOR REVISION 20 Jul 2022

I reviewed the revised manuscript of "Assessment of the Effectiveness of Type 2 Diabetes Mellitus Screening in the Republic of Uzbekistan". Thanks to the authors for the revision; however, although the authors have addressed some of my comments, the manuscript has not been improved adequately, and the methods and results are still confusing.

- There is no description in the text of the steps and the first and second visits (as shown in figure 1).
- What are the 3 eligibility criteria exactly? Is it Age>=45 OR Hypertension OR obesity? Or is it Age>=45 AND Hypertension AND Obesity? Or is it Age>=45 AND "Hypertension OR Obesity"?
- Cluster randomization with just 4 villages or towns is questionable. Many differences between areas may result in differences in prevalences. It is the main limitation of the study and should be discussed in the discussion.
- Supplementary figures 1 and 2 are helpful but contain some mistakes. In figure 1, the boxes related to fasting and non-fasting subjects have been switched, I think. The cutoffs for blood glucose levels are not inserted correctly (7.8 and 11.1 in the right box do not seem correct). The last box on the right side is missing. In figure 2, subjects with high glucose levels at the first visit should be referred to an endocrinologist, as I understood. All numbers and definitions in these figures should be reassessed.
- Table 1 is still confusing. It should present the baseline characteristics of all participants before screening, not those of screened subjects at the second step. In the optimal situation, there should be no difference between the two arms regarding the baseline characteristics.

Before these points are clarified, I cannot consider other parts of the manuscript and make a decision.

3

Revision 2

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

- There is no description in the text regarding steps and first and second visits (as shown in figure 1)
- What are the 3 eligibility criteria exactly? Is it Age>=45 OR Hypertension OR obesity? Or it is Age>=45 AND Hypertension AND Obesity? Or it is Age>=45 AND "Hypertension OR Obesity"?
- Cluster randomization with just 4 villages or towns is questionable. Many differences between areas may result in differences in prevalences. It is the main limitation of the study and should be discussed in the discussion.
- Supplementary figures 1 and 2 are helpful but with some mistakes. In figure 1, the boxes related to Fasting and Non-fasting subjects are replaced, I think. The cutoffs of blood glucose levels are not inserted correctly (7.8 and 11.1 in the right box do not seem correct). The last box on the right side is missing. In figure 2, the high glucose levels in the first visit should be referred to an endocrinologist, as I understood. All numbers and definitions in these figures should be re-assessed.
- Table 1 is still confusing. It should be about baseline characteristics devoted to all participants at the baseline before the screening, not to screened subjects at the second step. At the optimum situation, there should be no difference between the two arms regarding the baseline characteristics.

Dear Reviewer,

Thank you for the valuable comments! We hope the revised manuscript will leave a more favorable impression. Regarding your comments:

- There is no description in the text regarding steps and first and second visits (as shown in figure 1)

We added the information regarding the steps to the Materials and Methods section.

In step 1, one screening criterion was used in Gijduvan and Namangan, and 3 screening criteria were used in Bukhara and Turakurgan. The screening was performed by pretrained medical personnel: general practitioners (GPs) and district nurses. The training was conducted once, before the start of the pilot, in the form of a 2-hour workshop. In case of hyperglycemia detection, patients were invited for the second visit (Step 2) with regard to the scenario (Figure 1).

Glycemia was determined with test strips using a OneTouch glucometer in capillary blood plasma:

- fasting glycemia < 6.1 mmol/L — normal (recommendations given),
  - ≥ 7.1 mmol/L — referral to an endocrinologist,
  - intermediate value — repeated checkup for confirmation (Step 2).
- incidental glycemia
  - < 7.8 mmol/L — normal (recommendations given),
  - ≥ 11.1 mmol/L — referral to an endocrinologist,
  - intermediate value — repeated checkup for confirmation (Step 2).

- What are the 3 eligibility criteria exactly? Is it Age>=45 OR Hypertension OR obesity? Or it is Age>=45 AND Hypertension AND Obesity? Or it is Age>=45 AND "Hypertension OR Obesity"?

Agree, corrected.

1. Depending on the number of eligibility criteria: 1 (≥ 45 years) or 3 eligibility criteria (≥ 45 years of age & BP ≥ 140/80 mm Hg OR taking antihypertensive medications & obesity (BMI ≥ 30 kg/m^2, WC ≥ 80 cm in women and ≥ 90 cm in men))

- Cluster randomization with just 4 villages or towns is questionable. Many differences between areas may result in differences in prevalences. It is the main limitation of the study and should be discussed in the discussion.

Agree, corrected.

Another limitation is the methodology of cluster randomization with only 4 villages & cities, since the prevalence may differ in other parts of the country. However, it should be noted that the current article reflects the results of a pilot study.

- Supplementary figures 1 and 2 are helpful but with some mistakes. In figure 1, the boxes related to Fasting and Non-fasting subjects are replaced, I think. The cutoffs of blood glucose levels are not inserted correctly (7.8 and 11.1 in the right box do not seem correct). The last box on the right side is missing. In figure 2, the high glucose levels in the first visit should be referred to an endocrinologist, as I understood. All numbers and definitions in these figures should be re-assessed.

Thank you for this valuable comment. We corrected the data and hope that now the results are clearer.

- Table 1 is still confusing. It should be about baseline characteristics devoted to all participants at the baseline before the screening, not to screened subjects at the second step. At the optimum situation, there should be no difference between the two arms regarding the baseline characteristics.

Agreed. We divided Table 1 into two tables. As per the difference between the two arms, there should be differences, because different eligibility criteria were tested for each group.

3 Revision 2

1 comment · 15 Aug 2022

Davood Khalili Reviewer

MINOR REVISION 15 Aug 2022

Thanks to the authors for their response to my questions and comments. Regarding my concern about the 3 eligibility criteria, they responded that the definition of the 3 eligibility criteria is "≥ 45 years of age & BP ≥ 140/80 mm Hg OR taking antihypertensive medications & obesity". In this case, all individuals screened with these criteria should be obese. As table 1 shows, only 47.4% of this group are obese. So it may be "≥ 45 years of age & (BP ≥ 140/80 mm Hg OR taking antihypertensive medications OR obesity)". Because this definition is the main concept of the study, this point should be clear.

On the other hand, the conclusion in the abstract says that "The reasonable strategy is the screening for incidental glycemia in all patients with at least one T2D risk factor." What do you mean by "at least one risk factor"? Is it age>=45 or hypertension or obesity? Or is it only age>=45? It also depends on the definition of the 3 eligibility criteria.

The conclusion in the last paragraph of the discussion should be more detailed, including the appropriate scenario accepted for screening for diabetes in this study (like the conclusion of the abstract).

Supplementary figures and tables were not included in this revision.

4

Revision 3

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

Thanks to the authors for their response to my questions and comments, regarding my concern about the 3 eligibility criteria, they responded that the definition of 3 eligibility criteria is "≥ 45 years of age & BP ≥ 140/80 mm Hg OR taking antihypertensive medications & obesity". In this case, all individuals screened with these criteria should be obese. As table 1 shows, only 47.4% of this group are obese. So it may be "≥ 45 years of age & (BP ≥ 140/80 mm Hg OR taking antihypertensive medications OR obesity)". Because this definition is the main concept of the study, this point should be clear.
On the other hand, the conclusion in the abstract says that "The reasonable strategy is the screening for incidental glycemia in all patients with at least one T2D risk factor." What do you mean by "at least one risk factor". Is it Age>=45 or hypertension or obesity? Or it is only age>=45. It also depends on the definition of 3 eligibility criteria.
The conclusion in the last paragraph of the discussion should be more detailed including the appropriate scenario accepted for screening for diabetes in this study (like the conclusion of the abstract).
Supplementary figures and tables were not included in this revision.

Dear Reviewer,

Thank you for the valuable comments, they are really helpful.

We added the information that patients were enrolled in the study through the advertisements regarding ongoing screening that were posted in general practitioners (GP) offices.

In some of the clusters, patients were invited to the screening if they met the 1 inclusion criterion (≥ 45 years). In another series of clusters, if they had to meet the 3 inclusion criteria. Patients independently decided whether the inclusion criteria met and whether to undergo screening. Pre-specified data analysis (ITT) assumed that the main analysis of the dataset would be performed in a full sample of patients, regardless of whether they correctly identified themselves with the group suitable for screening or not (for example, whether they would correctly calculate their BMI). Additional data analysis (Per Protocol, PP) was carried out on a set of patients who met all the inclusion criteria (we added that in the Supplementary).

4 Revision 3

1 comment · 4 Oct 2022

Davood Khalili Reviewer

ACCEPT 4 Oct 2022

Dear Editor,
I reviewed the authors' response. Although there are some limitations in the methods, reporting both ITT and PP analyses allows the reader to understand the shortcomings.
The manuscript merits publication now.