**Author’s response to reviews**

**Title:** The prevalence of and major risk factors associated with diabetic retinopathy in Gegharkunik province of Armenia: Cross-sectional study

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**Author’s response to reviews:**

Dear Editorial Team,

Thank you for the review of our manuscript entitled “The prevalence of and major risk factors associated with diabetic retinopathy in Gegharkunik province of Armenia: Cross-sectional study” and the constructive feedback from the reviewers.

On behalf of the authors’ team, I am pleased to re-submit the manuscript entitled “The prevalence of and major risk factors associated with diabetic retinopathy in Gegharkunik province of Armenia: Cross-sectional study”. This version addresses the comments of both reviewers. Please find the description of our response to each reviewer’s comments bellow.

Responses to the reviewers’ comments:

Reviewer 1

MAJOR COMPULSORY REVISIONS

1. Methods/Analysis: The authors must provide details on how multivariate analyses were performed, in the Methods/Analysis sub-section rather than in the Results section.

We have addressed the comment and now provide the details on how we performed the analyses in the Analysis subsection of the Methods (see page 8 in the revised manuscript).

2. It seems that the authors entered only the variables that were significantly associated with diabetic retinopathy in the bivariate analysis into multivariate logistic regression model. By doing that, they may have failed to control potential confounders that were not significantly associated with diabetic retinopathy (p-value > 0.05) but may have an effect on the occurrence of diabetic nephropathy (though non-significant). I suggest the authors to extend the threshold for inclusion into multivariate logistic regression model to a pre-defined p-value greater than 0.05 (such as 0.10, 0.15, 0.20). The authors should also use the epidemiological relevance of the variables as criteria for variable selection in
the model.

We have performed bivariate analysis and all the variables with the significance level at 0.25 and lower have been included in our final model. After addressing the reviewer’s comment our multivariate model now includes additional variables recommended by the literature (see page 21, Table 2).

3. The authors should present results of both univariate and multivariate logistic regression analyses.

Table 2 now presents the results of both adjusted and unadjusted logistic regression analyses (see p.21).

MINOR ESSENTIAL REVISIONS

1. Methods: the authors state that “Use of diabetes medication was assessed by asking whether the patient took pills for diabetes in the past week and use of blood pressure medication was assessed by asking whether the patient took pills to control high blood pressure in the past week.” So, if a diabetic treated patient has stopped taking his anti-diabetic treatment two weeks ago, for example because of financial limitations, does it mean that this patient does not use diabetic medication?

We agree with the reviewer’s concern that those patients who stopped taking medication two weeks before the survey could have been misclassified as not using diabetes medication in our study. However, since 96% of participants in our sample reported using medication, we consider the possible effect of misclassification as not a significant problem for the study.

2. Methods: the authors should not present BMI as continuous variable, but rather categorize it according to range as normal weight (BMI: 18.5-24.9), overweight (BMI: 25.0-29.9), mild or class I obesity (BMI: 30.0-34.9), moderate or class II obesity (BMI: 35.0-39.9) and severe or class III obesity (BMI: # 40). Presenting BMI by the mean with standard deviation of the general sample is not informative enough.

We categorized BMI based on the reviewer’s suggestion. We explained the details in the Study variables subsection and rerun the analysis with BMI as a categorical variable (see page 6 and Table 2).

3. Results: please provide standard deviation for mean.

We added the standard deviations for mean age and diabetes duration in the text (see page 9, first and third paragraphs and Table 1).

4. Results: please define in the Methods section what is considered as “diabetic angiopathy” in the Results section.

We added the details about diabetic angiopathy under the subtitle of “eye screening procedure” in the Methods section (see page 8, first paragraph).
5. Results: How do the authors explained that up to 62.9% of the patients did not know about the type of diabetes they had.

Indeed our study showed that many patients did not know about the type of diabetes they had. Our study did not look into the reasons for this phenomenon. Further studies that would examine the quality of counseling provided to diabetes patients by healthcare providers in Armenia and the overall awareness about the disease among diabetes patients could help to answer this question.

6. Results: the authors present data on obesity, thus they should provide the classification of obesity used (see comment 2).

We added BMI classification in the Results (see page 9 and Tables 1&2).

7. Results: The authors state that “High cholesterol level was reported by 22.0%”. How was lipid profile assessed?

Our study used self reported information about cholesterol level. We discuss the reasons for relying on self-reported information, and associated limitations in the discussion session (see page 13, second paragraph).

8. Results: the authors state that “Most of the patients (58.4%) described their overall health status as “satisfactory”, 26.4% described it as “bad”, 14.3% as “good”, 0.6% as “excellent”, and 0.3% as “very good”.” How was health status evaluated?

The participants reported on their health status using a question about their health in general from the SF-36 questionnaire.1 The question asks “In general, how would you assess your health currently? The response options include 1) Excellent 2) Very good 3) Good, 4) Fair and 5) Poor.

9. Table 1: BMI should be categorized (see comment 2).

We have categorized BMI (see pages 6, 9 and Tables 1&2).

DISCRETIONARY REVISIONS
1. Analysis: Please provide information on the manufacturer, town and country of the statistical software (SPSS version 17).

We added the reference about SPSS 17.0 (see ref. 34).

2. Results: “Ninety percent of the patients with DR had non-proliferative DR…” Correct to “ninety point two percent”.

We have addressed the reviewer’s comment (see page 9, second paragraph).

Reviewer 2
1. Abstract. Minor Essential Revisions: Background, the sentence “Diabetic retinopathy (DR) is the leading cause of vision loss in adults…” should be modified. DR is one of the leading causes of blindness in adults not the leading
cause.

We have modified the first sentence of the background section in the Abstract to address the reviewer’s comment.

2. Background. Major Compulsory Revisions: The sentence “Age-related blindness is increasing throughout the world, as is blindness due to uncontrolled diabetes” is not given in the Ref 2. Ref 2 says AMD, cataract and glaucoma are the leading causes of blindness in the US and “aging” is the main reason of increasing blindness in the next 20 years. DR is very important and prevalent but it is necessary to be accurate in selecting and interpreting the proper citations.

We changed the citation (see reference 2).

3. Major Compulsory Revisions: Please include more details about the sampling frame, sampling method, date and duration of data collection phase. It is not clear how many urban and rural PHC units are located in the survey area? how many of them where included in this study? What is the coverage rate of DM registry in these units? etc.,...

We added the requested information to address the reviewer’s comment (see page 5, data collection section).

4. Do endocrinologists work at PHC level in this province? Usually mid-/ low-level staffs work at PHC level. Please clarify

In Armenia, including in Gegharkunik province, PHC is provided by polyclinics that also have endocrinologists working there. The endocrinologists working in PHC facilities are responsible for providing consultation and care to patients with diabetes.2 We clarified this in the paper and provided needed references (see page 5, third paragraph).

5. The response rate is very low (47%) and only known and registered subjects with DM were recruited; therefore, it seems occurring selection-bias has been very probable in this study. I recommend including a paragraph in the discussion and explaining about this limitation and its effect on the results.

We include a paragraph about the low response rate and associated limitations in the discussion section (see page13, last paragraph).

6. Major Compulsory Revisions: Page 5, last Para: Please include the instrument or give an accessible reference. I could not find the instrument.

We have provided the reference for the instrument we have used.3

7. Major Compulsory Revisions: Variables, Page 6: In sentence “The blood glucose level was estimated based on the patients’ recall of the latest result of their blood glucose level.”, please consider it as the study limitation because it may be a source for information bias in this study because even a documented blood sample (BS or FBS) is not a good indicator for managing blood sugar.
Instead, HA1c is a more reliable indicator.

We have a discussion about self-reported data, including self-reported blood glucose levels, and related limitations in the Discussion (see page 14, second paragraph).

8. Major Compulsory Revisions: Behavioral Risk Factors Surveillance System Questionnaire: Page 6, last Para: Please include the instrument or give an accessible link.

We changed the link for the reference of Behavioral Risk Factors Surveillance System Questionnaire (see reference # 27).

9. Major Compulsory Revisions: The grading of DR is usually based on EDTRS, ICO or Scottish classification not WHO. Therefore, it can limit the comparability of your results with other studies. I would recommend to reanalysis your results considering the ICO (International Council of Ophthalmology) classification for DR grading.

We acknowledge that WHO classification of diabetic retinopathy may limit the comparability of our study results with other studies using alternative classifications. Yet the WHO classification that we employed in our study is often used and internationally accepted. 4–6 Unfortunately, we cannot change the classification at this stage because we relied on clinical examinations to identify cases with diabetic retinopathy, whereas it has limited capacity to differentiate between multiple subtypes of diabetic retinopathy recognized by ICO.

We included a discussion about limitations introduced by our diagnostic method in the Discussion section (see page14, first paragraph).

10. Major Compulsory Revisions: How macular edema was identified and classified? I think ME should be included in the results because it is very important in patients with DM.

We have information about macular degeneration but not about macular edema. Our diagnostic method did not allow us to identify cases of macular edema.

11. Major Compulsory Revisions: Currently, stereoscopic fundus photography is proposed for DR classification but clinical examination was used in this study. Again it may be a source of misclassification (information bias) in this study and should be included in study limitation.

We included a discussion about limitations introduced by our diagnostic method in the Discussion section (see page14, first paragraph). Also please see our responses to comments 9 and 10.

12. Discretionary Revisions: Oral consent should have been observed by a witness or ideally a written consent should have been taken.

The Institutional Review Board of the American University of Armenia reviewed
and approved the study protocol. The Institutional Review Board (IRB) of the American University of Armenia (AUA) is registered with the National Institute of Health, the United States Department of Health and Human Services. The IRB functions under the guidance of the Office for Human Research Protection (OHRP), which provides regulatory oversight and clarifications on ethical issues in biomedical and social-behavioral research.

13. Major Compulsory Revisions: Age- and sex-standardized prevalence rates are usually reported in an epidemiologic study. Please give adjusted prevalence rates of DR and its grading considering “all registered people with DM in Gegharkunik province” as the sampling in your study.

We have added the age and gender standardized rate of diabetic retinopathy in the paper (see page 9, second paragraph).

14. Major Compulsory Revisions: In terms of descriptive statistics, they should be more precise. Please add 95% CI to all proportions (e.g. DR prevalence,…)

We added 95% CIs for all proportions (see Table 1).

15. Minor Essential Revisions: Please add the response rate.

We added response rate to the Methods section (page 5).

16. Major Compulsory Revisions: Please compare the baseline characteristics of the responders and non-responders. It can help to interpret the generalizability of the results.

We compared baseline characteristics (age and gender) of all registered patients with diabetes in Gegharkunik province with our sample (see page 9, first paragraph).

17. Minor Essential Revisions: Page 9, Para 3, sentence “Roughly half of the patients were physically active …..”: In the result section, the exact amount of each variable should be reported. Please replace “roughly” with a precise figure.

We added the precise number of physically active people to the paragraph (page 10, first paragraph).

18. Major Compulsory Revisions: Page 9, Para 4: “bivariate logistic regression” is used for binary variables. How this model has been used for age or diabetes duration that are continues variables. Please consider revising the model.

Our outcome variable was binary (presence or absence of diabetic retinopathy). Our independent variables included both categorical and continuous variables. We were able to use bivariate and multivariate logistic regression.

19. Discretionary Revisions: Page9, last Para: In addition, it is better not to exclude some main confounding variables like smoking, and physical activity from the multivariate logistic regression model.
We have modified the multivariate logistic regression model and added smoking and physical activity variables (see Table 2).

20. Major Compulsory Revisions: Table 1: please include crude and standardized rates. And please included more details of DR and macular edema grading (e.g. mild NPDR, moderate NPDR, ....Mild DME, CSME,...)

We have calculated the crude and standardized rates of having DR among the diabetic patients. We did not collect information about macular edema. Please see our responses to comments 9 and 10.

21. Minor Essential: Table 1: please add 95%CI to the prevalence rates

We added 95% CI to the prevalence rates in Table 1.

22. Ref 1: Please complete the citation. The CDC of which country is referred to? In addition, I could not access to the document by connecting to the given link.

We added the country of CDC in the reference # 1. We have checked the link, which is http://www.cdc.gov/visionhealth/pdf/improving_nations_vision_health.pdf

23. Ref 23: Again the exact webpage cannot be found. Please give the exact citation. If it is a standard questionnaire or method, it should have been published as a paper or in a textbook.

We changed the link for ref. 23, now ref. 24.

24. Ref 20, 23, 25, 28: Please replace these references with a primary reference. The WHO, the CDC and other organizations usually give their recommendations based on some robust published papers, so please find those citations and cite to the main sources.

Ref. #20, now #22
Ref. #23, now #24, please see our answer to comment #23.
Ref. #25 was replaced by two references #27 & #28.
Ref. #28 was replaced by the reference #31.

References
3. Stanford Patient Education Research Center: Stanford University School of Medicine. Sample questionnaire: Diabetes.; 2012. Available at:

