Author's response to reviews

Title: Prevalence and progression of visual impairment in patients newly diagnosed with clinical type 2 diabetes: a 6-year follow up study

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Version: 2 Date: 18 November 2010

Author's response to reviews: see over
Submission of the manuscript “Prevalence and progression of visual impairment in patients newly diagnosed with clinical type 2 diabetes: a 6-year follow up study”

Thank you for inviting us to resubmit our manuscript to BMC Public Health.

Below please find our reply in New Times Roman and blue. Additions to the manuscript are in italics.

The changes can be identified in the attached marked copy of the manuscript.

We are looking forward to your reply.

Sincerely yours,

Niels Olivarius

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Reviewer's report
Title: Prevalence and progression of visual impairment in patients newly diagnosed with clinical type 2 diabetes: a 6-year follow up study
Version: 1 Date: 5 September 2010
Reviewer: lars loumann L Knudsen

Reviewer's report:
The present paper is a prospective large scale study following a group of newly diagnoses diabetic subjects, including their visual acuity and several ocular manifestations in the study period. The study gives a broader understanding of visual impairment in elder diabetic subjects and is worth publishing. However a number of points given below should be considered and discussed.

1. In Denmark glaucoma is on of the most frequently occuring causes to visual impairment and blindness. It is still under debate if glaucoma is more frequently occuring in diabetic subjects than in non diabetic subjects. It is a weakness that the study gives no indications of the frequency of glaucoma in the study
population. Would it be possible to give some information about glaucoma in the study group, i.e. glaucoma medication? This would strengthen the study.

In the present study we have no information about pharmacological treatment for glaucoma, but we have information from the ophthalmologists about the diagnosis of glaucoma in each patient. This information was given in answers to open-ended questions about retinal pathologies and reasons for impaired vision as well as to questions about eye operations. As this way of collecting information about glaucoma may underestimate the true prevalence of glaucoma in our patients, we have not yet used these prevalence figures in the manuscript:

- At diagnosis the eye doctors reported glaucoma in the best seeing eye in 18 (1.5%) of 1241 patients. 13 had normal visual acuity and 5 had impaired vision.
- At 6-year follow-up glaucoma was found in the best seeing eye in 14 (1.7%) of 807 patients. 11 had normal visual acuity, 1 had impaired vision, and 2 were blind.

We have, however, access to data on eye pressure. In Table 5 eye pressure is a borderline-significant predictor of deterioration of visual acuity ($p=0.031$, unadjusted and $p=0.045$, age and sex adjusted). We have made a new analysis with eye pressure in two categories: $<20/>\geq20$ mmHg. In this analysis the $p$-values corresponding to those above are $p=0.009$ and $p=0.016$. Given the chosen significance level, this is not a statistically significant result but it is an indication of the significance of eye pressure for the change in eye sight over 6 years.

As a consequence of these considerations, we have added these sentences:

In Methods:

“In open-ended questions information about other retinal pathologies, glaucoma, and eye operations was given, and the presence of cataract was indicated in a closed question. Information about glaucoma was also given as answers to open-ended questions about reasons for impaired vision.”

In Results:

“At diagnosis the eye doctors reported glaucoma in the best seeing eye in 18 (1.5%) of 1241 patients. 13 had normal visual acuity and 5 had impaired vision.”

In Discussion:

“As our way of collecting information about glaucoma may underestimate the true prevalence of glaucoma in our patients, we were not able to analyse the predictive effect of glaucoma for visual loss. The possible importance of eye pressure for the change in eye sight over 6 years is, however, indicated by the non-significant tendency reported in Table 5.”

2.

It is well documented that ophthalmologists can assess retinal disorders with some variability. Studies comprising many ophthalmologists therefore benefit from a pre-study certification of the examining eye doctors. Alternatively a reading center for assessing retinal protographic recordings are beneficial. Was there any thoughts about the quality of the gives ophthalmic examinations?

The present study was necessarily nationwide, as we had to include almost 500 general practitioners in order to obtain a large enough sample of newly diagnosed diabetic patients. Therefore, we had to rely on the cooperation of all practicing ophthalmologists in Denmark as it was impossible to send all patients to the nearest ophthalmological department because of travel distances of up to 150 km. In 1988, when this study was organized, very few practicing ophthalmologists used retinal photography, as this service was not reimbursed by the National Health Service in Denmark. These circumstances made it impossible to use retinal photographs and a reading center.
The logistical challenges of the study design were immense. We had to rely on the cooperation of the many ophthalmologists without inviting them to participate in the study beforehand, as the general practitioners were spread out over the whole country, and we could not identify the ophthalmologists who were working near the general practitioners participating in the study. This meant that we were unable to gather the ophthalmologists for pre-study certification activities as suggested by the reviewer. In the end almost all practicing ophthalmologists in Denmark participated.

We have discussed these limitations of the study in the Discussion section, where we conclude that given our research question and the epidemiological methods that we use, these limitations does not jeopardize our analyses and main results:

“Strengths and limitations of the study
[...]
Almost all Danish ophthalmologists contributed to the study increasing the inter-rater variability, and their screening by funduscopy may have overlooked 10-40% of sight-threatening eye disease [1]. Such measurement errors in the predictor variables will tend to reduce a true association between e.g. an eye pathology and the outcome, i.e. visual acuity, but it does not invalidate the associations that we actually find. It can be assumed that the detection rate for eye disease was higher in patients with low visual acuity. This may have biased the cross-sectional associations between eye disease and visual acuity in Table 1 and 4, but it does not to the same extent compromise the estimation of the predictive power of the eye pathologies at diagnosis for the change in visual acuity during the following 6 years. Therefore, our non-standardized estimation of eye pathologies at diabetes diagnosis only diminishes our ability to detect an effect of these variables on changes in visual acuity.”

3.
The statistics comprised the best seeing eye. Since ocular pathology often varies in the two eyes this setup gives a possible underestimation of the ocular pathologies. I would have preferred a setup selection all right eyes or alternatively a randomization procedure. What was the argument for the present setup?

It is true that we are underestimating retinal pathologies as we report only from the best seeing eye in these patients. However, our purpose is not to give a detailed description of eye pathologies, but to analyze change in visual acuity over 6 years and its predictors. As a person’s ability to see depends on the visual acuity of the best seeing eye, at least according to the definition we use, it seems appropriate to concentrate on the best seeing eye. We would be able to repeat the analyses using the other eye, if the editor thinks that this is relevant, but from the patient’s point of view we believe that the analyses of the best seeing eye are more relevant than analyses using a randomly selected eye or the right eye or the worst seeing eye.

We have added a sentence to the discussion in order to clarify this:
“By presenting results from the best seeing eye only, we are underestimating the prevalence of eye pathologies in this patient group. This is because our main purpose is to estimate the change in visual acuity and its predictors, and eye pathologies are important in this study only insofar they are predictors of visual loss. In most studies the main pathology in the better eye is considered the cause of visual impairment [2,3]. We analysed predictors of vision impairment prospectively. Furthermore, to improve statistical strength we chose to analyse visual acuity as a continuous outcome.”
I suggest the others consider the above given point. I still find the paper worth publishing since such large scale studies are very difficult to perform and timeconsuming.

**Level of interest:** An article of importance in its field  
**Quality of written English:** Acceptable  
**Statistical review:** No, the manuscript does not need to be seen by a statistician.  
**Declaration of competing interests:**  
I declare that I have no competing interests below

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**Reviewer's report**

**Title:** Prevalence and progression of visual impairment in patients newly diagnosed with clinical type 2 diabetes: a 6-year follow up study  
**Version:** 1  
**Date:** 20 September 2010  
**Reviewer:** Kåre I. Birkeland

**Reviewer's report:**  
In the present study, 807 of originally included 1,241 persons with newly diagnosed type 2 diabetes aged ≥40 years were followed up for 6 years with respect to ophtalmological status. The abstract states that blindness rose from 0.9% to 2.4% and the prevalence of moderate visual impairment rose from 5.4% to 6.7%. Baseline predictors of level of visual acuity and speed of continued visual loss were identified.

The manuscript contains potential important information, but it is difficult at least for this reviewer to follow the numbers through the text and tables, and the authors should try to simplify the presentation.

The manuscript quite rightly contains 5 tables and 2 figures, but we believe that by limiting the presentation to the best seeing eye, we have made an important, and relevant, step towards simplification. We present data on

- visual acuity at diagnosis (Table 1),  
- changes in VA from baseline until 6-y. follow up (Table 2),  
- concomitants (in the shape of retinopathy) of VA at 6-year follow up (Table 4), and  
- an analysis of predictors of 6-y. visual change in mixed models (Table 5).

If the editor thinks that this is appropriate to refer Table 3, which does not contain any data on VA, to an electronic appendix, we will be happy to do so.

**Major comments**  
1. The data are 10-20 yrs old, which reduces their relevance for today's practice. Hence, the statement in the Discussion part that “Our patients are likely to be representative of Danish patients with newly diagnosed...diabetes” may be modified. Even though the subjects is commented on by the authors later in the Discussion part, the former paragraph is misleading as rather big changes in diabetes care have taken place during the last 20 yrs.
It is correct that the patient sample was established many years ago. Nowadays diabetic patients are increasingly diagnosed by screening and therefore diagnosed at an earlier stage in the natural history of diabetes than our patients. It is however to be expected that a diabetic patient diagnosed by screening after a few years will be on a track in the natural history of diabetes similar to the patients in our sample. The crucial characteristic of our sample is that it is population-based. We assume that our patient sample is the largest population-based patient sample in the world when it comes to patients newly diagnosed with clinical type 2 diabetes. In e.g. UKPDS the investigators did not aim at obtaining a population-based sample, as the patients were to be randomized anyway ([4] and R Holman, personal communication). When you publish epidemiological analyses from RCTs, however, patient selection becomes important, and this is why we write: “Our patients are likely to be representative of Danish patients with newly diagnosed, clinical, often symptomatic diabetes in this age group because of […]”

In 1989-92 patients were diagnosed primarily because of symptoms, and more than 90% of our patients had one or more symptom at diagnosis [5]. We made an effort to underline the difference between our patients and “modern” patients diagnosed by screening through labelling the diabetes of our patients as “clinical”, and we have now added the term “, often symptomatic” to “clinical type 2 diabetes” in the Abstract, in the Discussion section, and in the Conclusion.

We are aware of the possible influence of the age of our patient sample on the results, and in the next paragraph in “Strengths and limitations” we write “Our patient sample was established in the early 90’s and since then both surgical treatment of eye pathologies and pharmacological treatment of hyperglycaemia, hypertension and dyslipidaemia have been intensified, as has screening for diabetes. These initiatives to improve diabetes care and to identify patients earlier in the natural history of diabetes have probably decreased the variability of measures of treatment quality, so if a similar follow up study were to be made today, the associations between variables would perhaps be harder to identify. There is, however, no reason to suppose that the causal patterns underlying the associations that we have identified would be substantially different.”

If these reservations do not cover the critique of the reviewer, please let us know.

2. It is stated in the abstract that the prevalence of moderate visual impairment rose from 5.4% to 6.7%. This must be a misleading expression, the correct is probably that prevalence was 6.7% after 6 yrs in those with normal vision at baseline. But than n is not 807.

The crude prevalence of visual impairment actually rose from 5.4% (67 of 1,241, see Table 1) to 6.7% (54 of 807, see Table 2). In order to clarify to the reader that these prevalences emerge from different total numbers, we have added the following sentence to the abstract: “After 6 years, 807 patients were followed up”, and added the numbers to the percentages in the abstract: “Over 6 years, the prevalence of blindness (visual acuity of best seeing eye ≤0.1) rose from 0.9% (11/1,241) to 2.4% (19/807) and the prevalence of moderate visual impairment (>0.1; <0.5) rose from 5.4% (67/1,241) to 6.7% (54/807).”

These figures are influenced by the over-mortality of patients with impaired vision, and we have discussed this question in the Discussion section: “In studies of patients with known type 2 diabetes, which are to some extent population-based, the prevalence of 7-11% for moderate visual impairment [6-9] is similar to the 6.7% observed 6 years after diagnosis in the present study. Of the 54 patients with moderate visual impairment at this
point, however, 48 had normal vision at diagnosis, but the prevalence rate increased only modestly because of the over-mortality of patients with low vision [10].”

3. Diagnosis of diabetes was made “Based on hyperglycaemic symptoms and/or raised blood glucose values measured in general practice, the diagnosis was established by a single whole blood or plasma glucose concentration ≥ 7.0/8.0 mmol/l…”

a. What is the impact of including subjects with only symptoms of hyperglycaemia? Of only a single glucose measurement?

We did not limit our inclusion of subjects to those who had symptoms. Patients could also be considered for inclusion solely on the basis of “raised blood glucose values measured in general practice” as indicated above. The general practitioners were prompted to include all newly diagnosed patients on their patient list with newly diagnosed diabetes during the well-defined period. Patients who were hospitalized at the time of diagnosis were also considered for inclusion [11]. Most patients had symptoms, but in a quite large number of cases (approx. 1/3) the diabetes was diagnosed as “an unexpected finding by a routine examination”. All patients, with or without symptoms, usually had their blood glucose measured by their general practitioner with a bedside glucometer. To avoid giving the diagnosis diabetes to non-diabetic subjects, all patients had to have their raised blood glucose level confirmed at a major (often hospital) laboratory. As indicated in Fig. 1 this confirmation was not possible in 47 cases, and this shows that our procedure was necessary. None of these 47 patients have been included in any of the papers from this study.

b. Why were these limits used – at variance with international guidelines?

The main reason why we used these relatively high diagnostic limits was that we wanted to ensure that we did not include any non-diabetic patients. Our study doctors made use of almost 100 different clinical chemical departments from all over Denmark, and although glucose is very simple to measure in blood or plasma, the variability between laboratories was considerable. We wanted to overrule these measuring problems by increasing the diagnostic level. It may seem strange nowadays, but we also did so for ethical reasons, in order not to label anyone with the diagnosis diabetes who had not a conclusive diagnostic measurement.

Minor comments

1. The expression “For the health practitioner visual acuity is a ubiquitous and handy measure of visual function” is of course correct, but it needs to be stated that it is a crude measure and is not enough for follow-up of patients with diabetes, as prevention mostly is too late when visual impairment is present.

This is quite correct. The sentence is quite imprecise and we have added a sentence to the sentence above in line with the suggestions by the reviewer:

[...]but visual acuity is not a suitable measure of future visual loss as the sight-threatening eye pathologies often are present for many years before vision begins to decline as a result of these pathologies.

2. The discrepancies in numbers in the following should be corrected or commented: “At 6-year follow up, the 159 noncensored patients without information about visual acuity (Fig. 1) did not differ from the 807 re-examined patients with regard to age (p=0.23), sex (p=0.82), diagnostic plasma glucose (p=0.43), prevalence of DR at diagnosis (3.2% (5/158) vs. 4.4% (35/800)
These discrepancies are explained fully by the fact that for some patients, i.e. one and 7, respectively, of the 159 and 807 patients information about diabetic retinopathy was missing.

3. Of the 25 subjects that were moderately impaired at baseline, more than half had normal visual acuity at 6-year follow-up. Please comment?

Of the 25 patients with moderate visual impairment at baseline, 14 had normal visual acuity 6 years later. Of these 14 patients 7 had had a cataract operation since the baseline examination and one had had a retinal laser treatment. This may explain the improvement in 8 patients. In the remaining 6 patients the improvement may have been minor but enough to move the patients across the discriminatory limit of 0.5 in decimal acuity. To help the reader to interpret these findings we have added this sentence to the Results section:

“Of the 25 patients in Table 2 with moderate visual impairment at baseline, 14 had normal visual acuity 6 years later. Of these 14 patients, 7 had had a cataract operation since the baseline examination and one had had a retinal laser treatment.”

4. The major reasons for visual impairment in this population seem to be AMD and cataract; both not directly related to diabetes and metabolic control. May be this should have some more emphasis?

We have been reluctant to give this observation more emphasis because we don’t want to over-interpret our finding of no association between HbA1c (and other common risk factors) and change in visual acuity. As indicated below (paragraph 5), this finding may be caused by our patient sample being examined very close to the day of diagnosis. It gives, however, as indicated by the reviewer, food for thought that AMD and cataract are so much more prevalent than other eye pathologies. According to the suggestion by the reviewer, we have added the following sentence to the first sentences in the Discussion section:

“In a population-based cohort of patients newly diagnosed with clinical, often symptomatic type 2 diabetes, 6.3% were visually impaired. Among those patients with reduced sight, 76% had cataract and 58% retinopathy, usually AMD, although many of these eye pathologies are not closely related to diabetes and metabolic control. During the first 6 years after diabetes diagnosis [...]”

5. “Fraction of haemoglobin A1c was determined by ion-exchange, high-performance liquid chromatography (reference interval: 5.4-7.4%).” Please use either the expression “HbA1c” or “fraction of glycosylated haemoglobin” and state which method that was used, or was it different methods? With same reference interval? What was the coefficient of variation? This is important information, especially because HbA1c did not turn out to predict progression of retinopathy, at variance with other studies.

Please note, that we used the same method and reference interval for HbA1c throughout the study. We have extended the Methods section with the requested information about the quality control of HbA1c:

“Throughout the study, HbA1c was determined by the same ion-exchange, high-performance liquid chromatography method (HPLC, reference interval: 5.4-7.4%) at Odense University Hospital. Samples from 100 blood donors (age 20-80 years, 33 men, 67 women) were analysed, and the reference interval (mean ± 2SD) was calculated to be 5.4-7.4%. Quality assurance was obtained with commercial control preparations from Bio-Rad. In October-December 1995, the mean (SD) of low (N = 24) and high (N = 29) control samples were 6.7 (0.31)% and 10.4 (0.63)%, respectively, resulting in coefficients of variation (CV = SD x 100/mean) of 4.6% and 6.0%.”
We have discussed the “missing” association between several known predictors of visual loss, like plasma glucose and HbA1c in the discussion section in the following way:

“In UKPDS the incidence of visual impairment was slightly lower in the tight vs. the less tight blood pressure control group [9]. Similarly, blood pressure, HbA1c and proteinuria have been shown to be indicative of visual loss in follow up studies [12-14], but none of these non-ocular patient variables was associated with visual loss in the present study. This could be due to measurement error and above all regression dilution bias [15], which is particularly relevant for biochemical and clinical variables in the dysmetabolic state of newly diagnosed clinical diabetes. In studies including patients with known diabetes [12-14], the measured risk factor levels are supposedly closer to an average steady state level, a kind of set point which is typical for the patient in question.”

6. Urinary albumin concentration was an important predictor of baseline eye disease and also significant for progression in the unadjusted analysis. This is important information to the practitioner that only is found in the on-line table; please include in the result section.

We agree that Table 5 contains the main results of the study and will include it in the results section, but in the present manuscript it is an attached file because of its size and landscape format.

7. Median diagnostic plasma glucose was 13.7 (10.7-17.0) mmol/l. Was that the fasting level?

Yes, these blood samples were drawn in the fasting state, and this level is approximately 2 mmol/l higher than the diagnostic fasting level in UKPDS (11.3 mmol/l) reflecting the difference between the two studies in diagnostic limit as well as the primary exclusions in UKPDS of patients with high blood glucose levels after the 3 month run-in period [4].

Level of interest: An article whose findings are important to those with closely related research interests
Quality of written English: Acceptable
Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.
Declaration of competing interests: I declare that I have no competing interests

Reviewer’s report
Title: Prevalence and progression of visual impairment in patients newly diagnosed with clinical type 2 diabetes: a 6-year follow up study
Version: 1 Date: 15 October 2010
Reviewer: Stian Lydersen
Reviewer’s report:
General comment:
The authors have used appropriate statistical methods.
Major comment:
1.
Page 7-8:
You excluded the 5.8% (72/1241) patient who had an eye operation on their best seeing eye during follow-up. It seems realistic that many, maybe most, of these would have developed impaired visual acuity had they not been operated. In a sense this implies that you underestimate the cumulative incidence of visual impairment. Please comment on this and the possibly induced bias. Perhaps it is interesting to carry out a secondary analysis (sensitivity analysis) considering these, or some of these, to have impaired vision?

Our aim in relation to change in visual acuity was two-fold:

1) We aimed at describing the observed change in visual acuity. These data are presented in Table 2 and 4. In these analyses data from all patients with a measurement of visual acuity are shown (except that a few patients are missing in Table 4 because of missing information about retinopathy). I.e. patients who had an eye operation during the 6 years are retained in the analyses, and the levels of visual acuity are possibly positively affected by (successful) eye operations. Hence these tables present the levels of visual impairment experienced by the patient, but probably underestimate the incidence of visual impairment in the way described by the reviewer.

2) We also aimed at describing predictors of this 6-year change in visual acuity, the incidence of visual impairment on a logMAR scale. These results are presented in Table 5, and in these analyses we use mixed models in which measurements of visual acuity made after an operation were excluded from the analyses. We assumed that an eye operation would influence visual acuity (positively, if the operation was successful and the indication of the operation was correct). We were, however, not interested in the change in visual acuity caused by operation, as we focused the analyses on the predictive power of the baseline variables for change in visual acuity. It is implicit in the mixed models that visual acuity is imputed beyond the time of the eye operation according to the visual change observed in patients who were not operated. Hence, implicitly we assume that the visual acuity continues to deteriorate after a patient’s observations are censored at the time of the eye operation and we avoid the underestimation the reviewer describes.

We have added the following sentence to both the Methods section and the foot notes of Table 5: “[...] from a mixed model using all available measurements of visual acuity which come from the best seeing eye in all cases.”

Minor comments:

2. Page 7 line 6 from bottom:
The terms “multivariate analysis” and “multivariable analysis” are sometimes incorrectly used interchangeably. In the strict sense, multivariate analysis refers to simultaneously predicting multiple outcomes. I suggest you use the more general term multivariable analysis.
We have followed this suggestion.

3. Page 8 line 10:
Did you really use Kruskall-Wallis and chi squared tests? If not, delete (part of) this sentence.
These two tests are used e.g. in the comparison of included and excluded patients in the Methods section/Study population.

4.
Page 8 line 11:
Significance level 0.001 would correspond to a Bonferroni correction if there were 50 =0.05/0.001 tests, which you do not have! This is unnecessarily conservative. I suggest you use a less conservative level, such as 0.005 or 0.01.

The significance level of 0.001 was chosen already when we planned the present analyses on the basis of our earlier publications using similar models with a large number of p-values [16,17]. We decided to be cautious in the interpretation of the p-values as the study is descriptive and the hypotheses about the predictive value of the many baseline variables were created post hoc in our dataset. We did this on the basis of a literature search showing that no other study had addressed this question with a full set of socio-demographic, clinical, biochemical and behavioral characteristics. We realize, however, that our significance level may be too conservative, and we have reconsidered the situation:

Based on the method of Benjamini-Hochberg to account for multiple testing [18] used on the p-values in Table 5, a significance level of 0.0179 is to be used in order to control the false discovery rate at 5%. The method of Benjamini-Hochberg does not assume independence of the tests, so this relatively high significance level relative to the number of tests done may be explained to a considerable extent by dependence between the tests performed in Table 5. On the basis of this calculation and the presence of the other p-values in the manuscript we recognize that the reviewer is right and we have chosen the significance level to be 0.01 instead of 0.001.

In Statistical methods have changed the text as follows:
“To account for multiple statistical testing, we applied the method of Benjamini-Hochberg [18] on the p-values in Table 5, and found that a significance level of 0.0179 was to be used in order to control the false discovery rate at 5%. Accordingly, the nominal level of statistical significance was chosen to be $p < 0.05$, except in the mixed models in Table 5, where it was $p < 0.01$.”

This new significance level has prompted us to make the following changes:
In Abstract (Results):
“Baseline predictors of level of visual acuity (age, age-related macular degeneration (AMD), cataract, living alone, low self-rated health, and sedentary life-style) and speed of continued visual loss (age, AMD, diabetic retinopathy (DR), cataract, living alone, and high fasting triglycerides) were identified.”

In Results:
“All significant effects, except that of self-rated health and triglycerides, are illustrated in Fig. 2.”

In Discussion:
“The baseline predictors of both the level of and speed of progressive visual impairment after diagnosis were AMD, cataract, age at diagnosis, and living alone. The level of visual acuity over 6 years was lower in patients who had a low self-rated health or a sedentary life-style. The rate of the 6-year visual loss increased if the patient had DR or high fasting triglycerides at diabetes diagnosis.”
“Among many candidate predictors we found only relatively high age, living alone and high triglycerides to be associated with worsening of visual acuity over 6 years, while high age, living alone, low self-rated health, and low level of physical activity were associated with a low level of visual acuity. Presumably the three last-mentioned relations are cases of […]”

5.
Page 9 line 7:
Please include the number of cases, like in the preceding sentences.
This sentence has been changed as follows:
“DR (n=52), AMD (154), and cataract (337) were associated with […]”

Level of interest: An article of importance in its field
Quality of written English: Acceptable
 Statistical review: No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests:
I declare that I have no competing interests

Reference List


