

## PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	Prevalence and risk factors for diabetic retinopathy in a cross-sectional population-based study from rural southern China: Dongguan Eye Study
<b>AUTHORS</b>	Cui, Ying; Zhang, Min; Zhang, Liang; Zhang, Lixin; Kuang, Jian; Zhang, Guanrong; Liu, Qingyang; Guo, Haike; Meng, Qianli

### VERSION 1 - REVIEW

<b>REVIEWER</b>	Mayuri Bhargava National University Hospital, Singapore
<b>REVIEW RETURNED</b>	20-Jun-2018

<b>GENERAL COMMENTS</b>	The study aims to investigate the DR prevalence and risk factors in rural population. Though the sample size is large, the study lacks novelty. Also, the study design seems flawed with regards to grading of DR. I wonder why the authors have not used the standardized ETDRS classification. Also the DR grading needs to be explained in detail. The grading scales used are not consistent throughout the paper and this leads erroneous results. Ghe rationale for using CSME as well as DME needs to be explained. definition of VTDR is not clear as well. Limitations of the study need to be mentioned.
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<b>REVIEWER</b>	DR. B.S.GURUPRASAD ASSOC. PROF. OF OPHTHALMOLOGY ESI MEDICAL COLLEGE & POST GRADUATE INSTITUTE OF MEDICAL SCIENCES & RESEARCH, BENGALURU. KARNATAKA STATE. INDIA.
<b>REVIEW RETURNED</b>	02-Jul-2018

<b>GENERAL COMMENTS</b>	Overall a good comprehensive study assessing the prevalence along with risk factors. A few comments: It would have been a complete paper, if the authors were to give a brief overview of key points in the methodology, even though it had been published separately. the questionnaire used for the study needs to be accompanied. since blood tests involved parameters indicating renal function, a brief analysis of nephropathy and its association with retinopathy would have been useful.
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	Finally, the paper should have recommended broad guidelines for creating awareness and treating DR among the population.
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<b>REVIEWER</b>	Mahmoud Ibrahim EDC Center for Diabetes Education , Atlanta , USA
<b>REVIEW RETURNED</b>	02-Nov-2018

<b>GENERAL COMMENTS</b>	<p>November 2nd 2018</p> <p>Reviewer's report: Thank you very much for giving me the chance to review the paper entitled "Prevalence and risk factors for diabetic retinopathy in rural southern China: Dongguan Eye Study. " by Ying CuiEtal</p> <p>A. Summary: The aim of this study was to investigate the prevalence of diabetic retinopathy (DR) and risk factors in residents 40 years and older conducted in Dongguan, rural southern China, it was a population-based study recruited 8952 Han Chinese , Participants received hematological, physical, ophthalmic examinations and completed a questionnaire regarding life styles and systemic medical conditions , prevalence of DR was 18.2% for all patients with diabetes, 32.8% for the patients with previously diagnosed diabetes, and 12.6% for newly diagnosed DM patients. The prevalence of DR in males was significantly higher than that in females . it concluded that lower prevalence of DR was found among the participants with type 2 DM in residents 40 years and older from rural southern China</p> <p>B. Strengths: 1 – The point of research is worthy of investigation considering importance and high prevalence of diabetic retinopathy 2 – The sample size was big and the statistical analysis was good and reflecting the actual results 3 – The Demographic characteristics of participants were simple yet very informative</p> <p>C. Weaknesses: 1- The population-based cross-sectional study examines the relationship between disease (diabetes) and other variables of interest as they exist in a defined population at a single point in time or over a short period of time , however since there is no dimension of time, it cannot support conclusions on the risk of diabetes, nor on causal relationships. It may also exhibit recall bias, because diabetes may influence subjects' responses to questionnaires...etc 2- The references related to the diabetes prevalence were old and should be updated ( see major compulsory revisions ) 3- Ethnic variability and local issues in the Chinese community were not addressed adequately 4- I went through the reference # 4 carefully and found that it was not cited properly in the text of this paper</p>
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	<p>5- The discussion section was good , however the differences between north and south rural areas in China ( gender difference and lifestyle ) were not justified enough</p> <p>Major Compulsory Revisions</p> <ul style="list-style-type: none"> <li>• Reference # 2 , 3 should be updated considering the latest IDF Atlas ( November 2017 )</li> <li>• Proper citation of reference # 4 is needed</li> <li>• Some details about the ethnic differences focusing on the Chinese community is needed</li> </ul> <p>Level of interest: An article whose findings are important to those with closely related research interests</p> <p>Quality of written English: I guess it was ok</p> <p>Statistical review: the manuscript does not need to be seen by a statistician.</p> <p>Declaration of competing interests: 'I declare that I have no competing interests'</p>
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### VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Mayuri Bhargava

Institution and Country: National University Hospital, Singapore

1. The study aims to investigate the DR prevalence and risk factors in rural population. Though the sample size is large, the study lacks novelty. Also, the study design seems flawed with regards to grading of DR. I wonder why the authors have not used the standardized ETDRS classification. Also the DR grading needs to be explained in detail. The grading scales used are not consistent throughout the paper and this leads erroneous results. Ghe rationale for using CSME as well as DME needs to be explained. definition of VTDR is not clear as well. Limitations of the study need to be mentioned.

Our response: We appreciate the referee’s comments. This article used International Clinical Diabetic Retinopathy Disease Severity Scales, which is a grading standard designed according to WESDR and ETDRS (Ref. 1-2).

Although it is considered the "gold standard" for grading the severity of diabetic retinopathy in clinical trials, its use in everyday clinical practice is not simple or practical (Ref 2). The most important reason is that Dongguan ophthalmology research is conducted in rural areas, where doctors in primary hospitals can use the simple classification of DR (International Clinical Diabetic Retinopathy Disease Severity Scales) to track these patients and provide eye care.

Macular edema (ME) is defined as the presence or absence of clinically significant macular edema (CSME). In other words, the ME is defined by the presence of a hard exudate in the presence of a microaneurysm and a spotted hemorrhage within one disk diameter from the center of the fovea or a

focal photocoagulation scar in the macular area. CSME will be considered to exist when the ME is in the range of 500 µm of the center of the fovea, or if there is a focal photocoagulation scar in the macular area. Vision-threatening retinopathy (VTDR) is defined as the presence of severe NPDR, proliferative retinopathy or CSME. The definition will be included in the revised manuscript. Definition of DR, ME, CSME and VTDR in the Method section.

References:

1. World J Diabetes. 2013 Dec 15; 4(6): 290–294.
2. Ophthalmology. 2003 Sep;110(9):1677-82.

Reviewer: 2

Reviewer Name: DR. Bettadapura S. GURUPRASAD

Institution and Country: ASSOC. PROF. OF OPHTHALMOLOGY, ESI MEDICAL COLLEGE & POST GRADUATE INSTITUTE OF MEDICAL SCIENCES & RESEARCH, BENGALURU. KARNATAKA STATE. INDIA.

1. Overall a good comprehensive study assessing the prevalence along with risk factors. A few comments: It would have been a complete paper, if the authors were to give a brief overview of key points in the methodology, even though it had been published separately. the questionnaire used for the study needs to be accompanied. since blood tests involved parameters indicating renal function, a brief analysis of nephropathy and its association with retinopathy would have been useful. Finally, the paper should have recommended broad guidelines for creating awareness and treating DR among the population.

Our response: We appreciate the referee's valuable comments. We have included the brief overview of key points in the methodology and cited relative references. In addition, the questionnaire used in this study was also included as supplementary file in the revised manuscript. As to the blood tests, we agreed that blood tests contain information for renal function. Thus, we analyzed the renal function (BUN and Scr) and DR. However, the result of our univariate analysis showed that there was no statistical significance, thus we did not include renal function in multivariate regression analysis. Please see Table 5 in the revised manuscript.

Thus, based on this study, we recommend an ophthalmic exam, especially for individuals with DM and DR risk factors. There is a need to raise awareness and education in DM and DR, especially in subjects with DR risk factors to reduce the incidence of DR and macular edema. We have included the recommended broad guideline in the conclusion section of the revised manuscript. Finally, we would like to express our sincerely thankfulness to the referee for giving us valuable comments on improving this study.

Reviewer: 3

Reviewer Name: Mahmoud Ibrahim

Institution and Country: EDC Center for Diabetes Education , Atlanta , USA

The aim of this study was to investigate the prevalence of diabetic retinopathy (DR) and risk factors in residents 40 years and older conducted in Dongguan, rural southern China, it was a population-based study recruited 8952 Han Chinese , Participants received hematological, physical, ophthalmic examinations and completed a questionnaire regarding life styles and systemic medical conditions , prevalence of DR was 18.2% for all patients with diabetes, 32.8% for the patients with previously diagnosed diabetes, and 12.6% for newly diagnosed DM patients. The prevalence of DR in males was significantly higher than that in females. it concluded that lower prevalence of DR was found among the participants with type 2 DM in residents 40 years and older from rural southern China

#### B. Strengths:

- 1 – The point of research is worthy of investigation considering importance and high prevalence of diabetic retinopathy
- 2 – The sample size was big and the statistical analysis was good and reflecting the actual results
- 3 – The Demographic characteristics of participants were simple yet very informative

#### C. Weaknesses:

1. The population-based cross-sectional study examines the relationship between disease (diabetes) and other variables of interest as they exist in a defined population at a single point in time or over a short period of time, however since there is no dimension of time, it cannot support conclusions on the risk of diabetes, nor on causal relationships. It may also exhibit recall bias, because diabetes may influence subjects' responses to questionnaires...etc

Our response: Thanks for the referee's valuable comments. We agree that time dimension is a limitation of this population-based cross-sectional study because it may influence the risk of diabetes, causal relationship, recall bias etc. Thus, we have included the limitation and strength in the Discussion section of revised manuscript.

2. The references related to the diabetes prevalence were old and should be updated (see major compulsory revisions)

Our response: We have replaced the old references with latest IDF Atlas, including Ogurtsova et al. (2017) 128: 40-50 and IDF Diabetes Atlas 8th Edition. Thanks for the referee's valuable suggestion.

3. Ethnic variability and local issues in the Chinese community were not addressed adequately

Our response: This is an interesting question. Ethnic is widely considered to be a complex, independent risk factor associated with diabetic retinopathy, and it is generally accepted that the observations of the certain ethnic population cannot fully infer other ethnic groups. All ethnic variability may be affected by risk factors for diabetic retinopathy, such as severity of hyperglycemia, hypertension and hyperlipidemia. However, other ethnic-associated risk factors may also play important roles, such as torso obesity, urbanization, insulin resistance, local health care systems, genetic susceptibility and epigenetics. Thus, ethnic variability and local issues in the Chinese community may also be associated with the diabetic retinopathy. However, this study aims to investigate the prevalence of diabetic retinopathy and risk factors among residents over 40 years old in the rural area of Dongguan, southern China. Our population-based study concluded that male, higher education level, longer duration of DM, higher SBP and HbA1c were independent risk factors for the development of diabetic retinopathy in patients with diabetes. Thus, our current analysis cannot provide solid evidence for connecting ethnic variability, local issues in the Chinese community, and diabetic retinopathy

4. I went through the reference # 4 carefully and found that it was not cited properly in the text of this paper

Our response: Thanks to the referee for pointing out the mistake. In the previous manuscript, we cited the wrong reference #4 to describe the diabetes burden in Chinese population. We apologize for the error and we have fixed this mistake in the revised manuscript.

5. The discussion section was good, however the differences between north and south rural areas in China (gender difference and lifestyle) were not justified enough

Our response: After carefully consideration, we agree the referee's comments. Currently, the limited information is insufficient to discuss the differences between north and south rural areas in China. Thus, we removed this part of discussion in the revised manuscript.

6. Major Compulsory Revisions

- Reference # 2 , 3 should be updated considering the latest IDF Atlas ( November 2017 )
- Proper citation of reference # 4 is needed
- Some details about the ethnic differences focusing on the Chinese community is needed

Our response: Thanks for the valuable comments. We have replaced the old references with latest IDF Atlas, including Ogurtsova et al. (2017) 128: 40-50 and IDF Diabetes Atlas 8th Edition. In addition to reference #4, we have included 2 additional references in the revised manuscript to describe the geographic and ethnic variability in the prevalence of DR. For example, the reference of Singapore Epidemiology of Eye Disease (SEED) study showed that Chinese had a lower prevalence of any DR (26.2%) than that of Indian (30.7%) and of Malays (25.5%). Since ethnic difference on the Chinese community are not the focus of this study (please see the response of question 3), we will try to design a research program to answer this question in the next study.

7. Level of interest: An article whose findings are important to those with closely related research interests  
 Quality of written English: I guess it was ok  
 Statistical review: the manuscript does not need to be seen by a statistician.

Our response: Thanks for the referee's comment. The entire revised manuscript has been scientifically edited, and English has been improved by a native English speaker to enable reader to understand the study.

**VERSION 2 – REVIEW**

<b>REVIEWER</b>	Mahmoud Ibrahim EDC Center for Diabetes Education , Atlanta
<b>REVIEW RETURNED</b>	30-Apr-2019

<b>GENERAL COMMENTS</b>	<p>January 24th 2019</p> <p>Reviewer's report:          Thank you very much for giving me the chance to review the paper entitled          "Prevalence and risk factors for diabetic retinopathy in rural southern China: Dongguan Eye Study "by Qianli Meng , etal</p> <p>A. Summary:          The aim of this study was to investigate the prevalence of diabetic retinopathy (DR) and risk factors among residents over 40 years old in the rural area of Dongguan, southern China. It was a population-based study, the investigators recruited adult rural population aged 40 years or older. The participants received hematological, physical, ophthalmic examinations and completed a questionnaire regarding lifestyle and systemic medical conditions. They looked at the frequency and risk factors of visual impairment and the major vision-threatening eye diseases. They concluded that a relatively lower prevalence of diabetic retinopathy was found among the participants with type 2 diabetes in residents over 40 years in rural area of the southern China. Thus, an ophthalmic examination is recommended, especially for individuals with DM</p> <p>B. Strengths:</p>
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	<p>1 – The point of research is worthy of investigation. Diabetic retinopathy is by far one of the most common and important complication of diabetes and it could threaten the vision</p> <p>2 – The sample size was huge and included comprehensive demographic characteristics of the participants.</p> <p>3- The statistical analysis, tables and figures were good and reflecting the actual results</p> <p>C. Weaknesses:</p> <p>1 – The cross-sectional study examines the relationship between disease (diabetes) and other variables of interest as they exist in a defined population at a single point in time or over a short period of time , however since there is no dimension of time, it cannot support conclusions on the risk of diabetes, nor on causal relationships. It may also exhibit recall bias, because diabetes may influence subjects' responses to questionnaires...etc</p> <p>2 – Despite the methodology of the study was good, yet it did not provide any new information supported by evidence.</p> <p>3 - I thought it was better to focus on the diabetic retinopathy among people with diabetes rather than doing a big population screening for people with and without diabetes, also the questionnaire included many things not very relevant to diabetic retinopathy.</p> <p>4 Some files were provided with non-English language ( probably Chinese ) , so I was not able to review these files</p> <p>5 I got two different versions ( clean and track changes copies ) , I reviewed the first version ( clean ) only</p> <p>Quality of written English: moderate  Statistical review: the manuscript does not need to be seen by a statistician.  Declaration of competing interests:  'I declare that I have no competing interests'</p>
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## VERSION 2 – AUTHOR RESPONSE

Reviewers' comments:

Reviewer #3

Reviewer Name: Mahmoud Ibrahim

Institution and Country: EDC Center for Diabetes Education, Atlanta

Reviewer's report:

Thank you very much for giving me the chance to review the paper entitled

“Prevalence and risk factors for diabetic retinopathy in rural southern China: Dongguan Eye Study “by Qianli Meng, etal

A. Summary:

The aim of this study was to investigate the prevalence of diabetic retinopathy (DR) and risk factors among residents over 40 years old in the rural area of Dongguan, southern China. It was a population-based study, the investigators recruited adult rural population aged 40 years or older. The participants received hematological, physical, ophthalmic examinations and completed a questionnaire regarding lifestyle and systemic medical conditions. They looked at the frequency and risk factors of visual impairment and the major vision-threatening eye diseases. They concluded that a relatively lower prevalence of diabetic retinopathy was found among the participants with type 2 diabetes in residents over 40 years in rural area of the southern China. Thus, an ophthalmic examination is recommended, especially for individuals with DM

B. Strengths:

- 1 – The point of research is worthy of investigation. Diabetic retinopathy is by far one of the most common and important complication of diabetes and it could threaten the vision
- 2 – The sample size was huge and included comprehensive demographic characteristics of the participants.
- 3- The statistical analysis, tables and figures were good and reflecting the actual results

C. Weaknesses:

1 – The cross-sectional study examines the relationship between disease (diabetes) and other variables of interest as they exist in a defined population at a single point in time or over a short period of time , however since there is no dimension of time, it cannot support conclusions on the risk of diabetes, nor on causal relationships. It may also exhibit recall bias, because diabetes may influence subjects' responses to questionnaires...etc

Our response : We thank the reviewer's comment. We agree that time dimension is a limitation of this population-based cross-sectional study because it may influence the risk of diabetes, causal relationship, recall bias etc. This limitation has been stated and discussed in the Discussion section. (P.21, highlighted in yellow)

2 – Despite the methodology of the study was good, yet it did not provide any new information supported by evidence.

Our response : We have added “The results of this study reinforce the links or findings about DR. We recommended the patients with risk factors should be tracked clinically.” in the discussion section. (P.17-18, highlighted in yellow)

3 – I thought it was better to focus on the diabetic retinopathy among people with diabetes rather than doing a big population screening for people with and without diabetes, also the questionnaire included many things not very relevant to diabetic retinopathy.

Our response : We should have our study focus on the diabetic retinopathy among people with diabetes only and have revised Table 1 (P.29-30) and questionnaire (supplementary file 1)

4 – Some files were provided with non-English language (probably Chinese), so I was not able to review these files

Our response : We thank the reviewer’s comment. The document provided in Chinese language is the Questionnaire used in this study and is designed for people whose native language is Chinese. All the factors assessed in the Questionnaire have been described in supplementary file 2.

5 – I got two different versions (clean and track changes copies), I reviewed the first version (clean) only

Our response : Sorry to make a mistake in sending two versions. There is only one version of manuscript submitted in this present revision.