PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Analysis of factors related to diabetic retinopathy in newly diagnosed type 2 diabetic patients: a cross-sectional study.
AUTHORS	Hao, Zhaohu; Huang, Xiao; Qin, Yongzhang; Li, Huanming; Tian, Fengshi; Xu, Rong; Chang, Baocheng; Shao, Hailin

VERSION 1 – REVIEW

REVIEWER	Ki-Ho Song The Catholic Univ. of Korea, Korea
REVIEW RETURNED	21-Jun-2019

GENERAL COMMENTS	The authors demonstrated that heavy smoking is an independent risk factor for DR in patients with newly diagnosed type 2 diabetes. However, this was a cross-sectional study, and other variables such as blood pressure, lipid profiles, or medicatioins were not considered for the association of DR presence.

REVIEWER	Valmore Bermúdez-Pirela Universidad Simón Bolívar, Facultad de Ciencias de la Salud, Barranquilla, Colombia
REVIEW RETURNED	14-Jul-2019

GENERAL COMMENTS	The authors aimed to investigate the related factors of Diabetic Retinopathy and to explore the correlation between smoking and DR in patients with newly diagnosed type 2 diabetes in a hospital setting in China. This is a well-designed study with a good number of newly diagnosed patients with Type 2 Diabetes; nevertheless, there are some points to be taken into account to improve the quality of this work: 1. The paper must be checked by an English-native investigator or by a specialised English grammar editing service to enhance stylishly and grammar mistakes. 2. Some suggestions regarding material and methods are depicted in the pdf attached to this review. However, I must emphasise that a better description of the sampling type and process need to be deeply described. For example, the patients were selected from electronic or analogic medical records (database) from the hospital? Did you include ALL patients with this new diagnostic or you took a sample from the total patients with T2D diagnosis? 3. Please, Included the following references in the discussion: https://diabetes.diabetesjournals.org/content/68/2/241.abstract

	https://journals.sagepub.com/doi/full/10.1177/1479164119845904 https://link.springer.com/chapter/10.1007/978-3-030-11815-0_40 https://bjo.bmj.com/content/early/2019/02/02/bjophthalmol-2018-313282.abstract https://link.springer.com/article/10.1007/s13340-018-0357-z Finally, I suggest using a reference manager like Zotero, End NOte or Mendeley, because I noticed some mixing in the referencing styles, including, missing years in some of the references.

REVIEWER	Suhad Bahijri Faculty of Medicine- King Abdulaziz University- Jeddah- Saudi Arabia
REVIEW RETURNED	20-Aug-2019

GENERAL COMMENTS	The manuscript requires complete language editing as there are many mistakes. In abstract diabetic retinopathy (DR) should be written in full when first mentioned. In the introduction, "We" should not be used. Instead use third person. In methods, estimation of HbA1C was not explained adequately. Statistical analysis require rewriting, and adjustment for BMI should be carried out instead of what was done. Results are poorly presented. No need to mention data presented in tables. Table 1 needs redesign to make it more understandable. (Using Statistical value as a heading for the third column is incorrect). The discussion should be reorganized to start with aim, importance, and findings, then go on to compare to previous studies and possible explanations for findings, finally conclusions and detailed limitations.

REVIEWER	Martin Muddu Makerere University Joint AIDS Program (MJAP)
REVIEW RETURNED	21-Aug-2019

GENERAL COMMENTS	The study addresses an important research area of diabetic retinopathy and its relation with smoking and BMI. However, the methods have gaps that need to be addressed. Additionally, the paper is not written in good English. There are many sentences written in wrong English that should be corrected. Please receive specific comments below: In the title: the study design is not reflected, please make the necessary revision. There are many abbreviations which are not defined e.g. DR: Please define all abbreviations the first time you use them. This should be done throughout the manuscript. There ae many sentences which are not written in correct tenses eg line 7 on page 2, line 16 on page 3. Use correct tenses and grammar through the manuscript. On page 3 line 19, you need to mention the patient population in which the diabetic retinopathy is 35.4%. It is not clearly stated. You need to put a reference to the sentence: Line 33 and 34 on page 3 The exclusion criteria was very wide with many conditions excluded. Please confirm that this did not affect the generalizability of the results. Evaluation of Clinical variables How was diabetes mellitus diagnosed? How was type 2 DM distinguished from other types of DM? It is unethical to document patients' names. How did you ensure confidentiality and human subject protection? Please provide an

	explanation. In line 51 page 4, patients were divided into 2 groups rather than “two cases”. Please make the correction. Please define what you mean by Non-Diabetic Retinopathy. Is it another form of Retinopathy? Line 4 page 5 Results section Your study is not a clinical trial. The statement should be revised in line 29 page 5. The English Grammar should be edited. How was type 2 DM diagnosed in patients aged less than 40 years of age? You had defined the smoking index earlier. You do not need to define it again. Line 53 page 5. You need to interpret the association of BMI with DR to show that patients with BMI>28 were less likely to have DR, rather than “BMI (≥28kg/m2) is a related factor for DR in Newly diagnosed diabetic patients (OR=0.634, p=0.012)”. You need to provide a reference for this statement. Line 12 page 6. What do you mean by PDR in table 1? Please define all abbreviations at first use. You need to be specific on what you meant by drinking history in your table 1. The percentage is not correct as it does not add up to 100% with its corresponding figure in NDR, in Line 25 of table 2. Discussion Provide a summary of your findings and discuss focusing on your results not the available literature. You need to mention the limitations of your study. One of which is the cross sectional nature of the study. In addition, lack of a non-diabetic control limits the internal validity. Hypertension was highly prevalent in the patient population, could it have confounded the results on retinopathy? The exclusion criteria was too wide. It negatively affects external validity. Conclusion In your cross sectional study you are unable to conclude that smoking is a risk factor. It is an associated factor. Please make the necessary correction.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

The authors demonstrated that heavy smoking is an independent risk factor for DR in patients with newly diagnosed type 2 diabetes. However, this was a cross-sectional study, and other variables such as blood pressure, lipid profiles, or medicatioins were not considered for the association of DR presence.

Reply : Thank you for your advice. The study is a cross-sectional study. Since the subjects were newly diagnosed type 2 diabetes mellitus and smoking occurred before the diagnosis of diabetes, so we came to the conclusion that it was a risk factor. It was not rigorous to draw the conclusion at that time. Blood pressure was investigated among the related factors. We didn't take into account the effect of blood lipids, and this is our design error. The subjects were newly diagnosed diabetes mellitus patients who did not start taking hypoglycemic drugs regularly at the time of entering this study. We will take all these factors into account the next time we do this kind of research.Thank you again.

Reviewer: 2

The authors aimed to investigate the related factors of Diabetic Retinopathy and to explore the correlation between smoking and DR in patients with newly diagnosed type 2 diabetes in a hospital setting in China.This is a well-designed study with a good number of newly diagnosed patients with Type 2 Diabetes; nevertheless, there are some points to be taken into account to improve the quality of this work:

The paper must be checked by an English-native investigator or by a specialised English grammar editing service to enhance stylishly and grammar mistakes.

Reply : The revised manuscript was checked by an English-native investigator. Thank you.

Some suggestions regarding material and methods are depicted in the pdf attached to this review. However, I must emphasise that a better description of the sampling type and process need to be deeply described. For example, the patients were selected from electronic or analogic medical records (database) from the hospital? Did you include ALL patients with this new diagnostic or you took a sample from the total patients with T2D diagnosis?

Reply : Thank you for your valuable suggestions for revision.The subjects were all newly diagnosed type 2 diabetes patients who had undergone fundus examination in our hospital during this period. The patients came from an electronic database of newly diagnosed type 2 diabetics at the hospital's diabetes identification center.All the patients who underwent fundus examination were screened in this study. The sampling type and process was described in the revised manuscript. Modifications were made in accordance with suggestions in the pdf attached to this review. Thank you for your careful guidance.

Please, Included the following references in the discussion:

https://diabetes.diabetesjournals.org/content/68/2/241.abstract

https://journals.sagepub.com/doi/full/10.1177/1479164119845904

https://link.springer.com/chapter/10.1007/978-3-030-11815-0_40

https://bjo.bmj.com/content/early/2019/02/02/bjophthalmol-2018-313282.abstract

https://link.springer.com/article/10.1007/s13340-018-0357-z

Reply: The references you recommend above is relatively new and relevant. I have benefited a lot from learning these papers.Thank you for your suggestion. The discussion section of the revised version adds relevant content.

Finally, I suggest using a reference manager like Zotero, End NOte or Mendeley, because I noticed some mixing in the referencing styles, including, missing years in some of the references.

Reply: Thank you for your specific and careful Suggestions. We have carefully checked the format of references in the revised draft.

Reviewer: 3

The manuscript requires complete language editing as there are many mistakes. In abstract diabetic retinopathy (DR) should be written in full when first mentioned. In the introduction, "We" should not be used. Instead use third person. In methods, estimation of HbA1C was not explained adequately.

Statistical analysis require rewriting, and adjustment for BMI should be carried out instead of what was done. Results are poorly presented. No need to mention data presented in tables. Table 1 needs redesign to make it more understandable. (Using Statistical value as a heading for the third column is incorrect). The discussion should be reorganized to start with aim, importance, and findings, then go on to compare to previous studies and possible explanations for findings, finally conclusions and detailed limitations.

Reply： Thank you for your suggestions and comments.The revised manuscript was checked by an English-native investigator. In abstract diabetic retinopathy (DR) was written in full when first mentioned in the revised draft. In the introduction, we replace "We" with "the present study". Venous blood samples were collected by EDTA tubes in fasting state in the morning. The level of HbA1c was determined by affinity chromatography in hospital standard laboratory.We removed the duplicate description of the result section.We used statistical description as a heading for the third column in the revised draft. We reorganized the discussion、conclusion and limitations. Thank you for the sincere advice.

Reviewer: 4

The paper is not written in good English. There are many sentences written in wrong English that should be corrected. Please receive specific comments below:

In the title: the study design is not reflected, please make the necessary revision.

Reply: After consulting with the authors, we changed the title as "**Analysis of related factors of diabetic retinopathy in newly diagnosed type 2 diabetic patients: a cross-sectional study".**

There are many abbreviations which are not defined e.g. DR: Please define all abbreviations the first time you use them. This should be done throughout the manuscript.

Reply: In the revised manuscript, we explained the BMI, DR, HbA1c, T2DM, etc. which appeared for the first time.

There ae many sentences which are not written in correct tenses eg line 7 on page 2, line 16 on page 3. Use correct tenses and grammar through the manuscript.

Reply： The revised manuscript was checked by an English-native investigator.

On page 3 line 19, you need to mention the patient population in which the diabetic retinopathy is 35.4%. It is not clearly stated.

Reply： In the revised manuscript, we added"the incidence of diabetic retinopathy in the total diabetic population was 35.4%".

You need to put a reference to the sentence: Line 33 and 34 on page 3

Reply: In the revised manuscript,we put a reference to the sentence.

The exclusion criteria was very wide with many conditions excluded. Please confirm that this did not affect the generalizability of the results.

Reply： This survey was mainly aimed diagnosed newly diagnosed type 2 diabetes patients, so other types of diabetes were excluded. Since the fundus screening and questionnaire filling were completed in the outpatient department, the exclusion criteria included patients with severe communication difficulties and who could not cooperate with the examination.

The exclusion criteria are not clearly stated. In the revised manuscript, we changed “mental illness” to “severe mental illness” and “anemia” to “severe anemia” in light of the actual situation.

We confirm that this did not affect the generalizability of the results.

How was diabetes mellitus diagnosed? How was type 2 DM distinguished from other types of DM?

(1)How was diabetes mellitus diagnosed?

Reply: Our hospital is a diabetes identification center in Tianjin, and all newly diagnosed diabetes patients in the region are diagnosed by our hospital. According to the Chinese guidelines for the prevention and treatment of diabetes, all patients with diabetes in our hospital need to be diagnosed by oral glucose tolerance test. The diagnostic criteria during execution are as follows:(1)Fasting plasma glucose(FPG)≥ 7.0mmol/l. Fasting is defined as no caloric intake for at least 8h; Or(2)2-h plasma glucose ≥11.1mmol/l during an oral glucose tolerance test(OGTT). The test should be performed as described by the World Health Organization, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in the water. HbA1c test is not standardized in China, so it cannot be used as a diagnostic standard.

In the revised draft, we added the diagnostic criteria to the inclusion criteria.

(2)How was type 2 DM distinguished from other types of DM?

Reply : For new cases of young onset, significant weight loss, and ketosis onset, the hospital's diabetes identification center identifies type 1 and type 2 diabetes by examining antibodies to insulin, glutamate decarboxylase and islet cells. Because of government funding, it is not possible to make this differential diagnosis for all patients.It must be noted that a small number of patients with other types of diabetes may be missed.

It is unethical to document patients’ names. How did you ensure confidentiality and human subject protection? Please provide an explanation.

Reply : Thank you for your friendly reminder.

As a public service department, we must register the patient's name, gender, id number, mobile phone number, address and other information when working. We hide sensitive personal data from our research. In the study, we use computer system to generate a sequence number to replace these private information.

In line 51 page 4, patients were divided into 2 groups rather than “two cases”. Please make the correction.

Reply : Thank you. In the revised manuscript， I corrected the error statement.

Please define what you mean by Non-Diabetic Retinopathy. Is it another form of Retinopathy? Line 4 page 5.

Reply： Non-diabetic retinopathy here includes normal and other retinopathy that may be caused by other causes such as fundus arteriosclerosis and so on. In the revised manuscript，I defined this.

11、Your study is not a clinical trial. The statement should be revised in line 29 page 5. The English Grammar should be edited.

Reply： Thank you. The study is not a clinical trial. More precisely, this figure 1 is the structural map of this cross-sectional study. In the revised draft, I revised this.

How was type 2 DM diagnosed in patients aged less than 40 years of age?

Reply： Many studies now show that the risk of complications varies with the age of onset of diabetes. The younger the age of diabetes, the greater the risk of complications over the same course of disease. In many studies patients diagnosed before 40 years old are referred to as early-onset diabetes patients.

You had defined the smoking index earlier. You do not need to define it again. Line 53 page 5.

Reply: Thank you for your advice. We removed duplicate descriptions in the revised draft.

You need to interpret the association of BMI with DR to show that patients with BMI>28 were less likely to have DR, rather than “BMI (≥28kg/m2) is a related factor for DR in Newly diagnosed diabetic patients (OR=0.634, p=0.012)”.

Reply： In the revised draft, we describe the result as “patients with BMI≥28kg/m^2 were less likely to have DR”.

You need to provide a reference for this statement. Line 12 page 6.

Reply:I provided references in the revised draft for this statement. Thank you.

What do you mean by PDR in table 1? Please define all abbreviations at first use.

Reply：Thank you. By revising these questions, I learned a lot and thought more carefully. Abbreviations：DR,diabetic retinopathy; PDR,proliferative diabetic retinopathy.

You need to be specific on what you meant by drinking history in your table 1.

Reply: Thank you. I described the history of drinking like this” Drinking history(n,%)” in table 1.

The percentage is not correct as it does not add up to 100% with its corresponding figure in NDR, in Line 25 of table 2.

Reply: Thank you. There is a mistake. 144（219.1%）should be 144(19.1%).Thank you.

Provide a summary of your findings and discuss focusing on your results not the available literature.

Reply: Some revisions have been made in the discussion section of the revised draft. Thank you.

You need to mention the limitations of your study. One of which is the cross sectional nature of the study. In addition, lack of a non-diabetic control limits the internal validity. Hypertension was highly prevalent in the patient population, could it have confounded the results on retinopathy? The exclusion criteria was too wide. It negatively affects external validity.

Reply: We supplement the limitations of the study. Diabetes mellitus is characteristic of fundus changes, which are different from those caused by other diseases such as hypertension.

In your cross sectional study you are unable to conclude that smoking is a risk factor. It is an associated factor. Please make the necessary correction.

Reply: We have made the correction in the revised manuscript. Thank you.

5、Other changes

The address of the hospital “Tianjin Metabolic Diseases Hospital” has changed, so the address of 1 has changed in the revised manuscript.

VERSION 2 – REVIEW

REVIEWER	Prof. Suhad Bahijri Faculty of Medicine- King Abdulaziz University- Jeddah- Saudi Arabia
REVIEW RETURNED	12-Sep-2019

GENERAL COMMENTS	Comments2 Even though a lot of effort was made to revise the manuscript, there remain some points that need further revision. Moreover, the manuscript requires further language editing as there are still some mistakes. Abstract: diabetic retinopathy (DR) should be written in full when first mentioned. This was not amended in the revised version Introduction: The sentence " It is well-known that smoking may cause an increase in proteinuria" needs a reference The sentence "Everyone speculates that smoking has a adjunct effect on DR, but there is no direct clinical epidemiological evidence supporting the suggestion that there is a direct link between smoking and DR in newly diagnosed patients" should be reformulated, and a proper reference given. The used reference is irrelevant The rational for the study should be emphasized more Methods: "We" should not be used. Instead use third person. There is a lot of repetition. Requires reorganization. A reference should be provided for the sentence "BMI (≥28kg/m2)

	met obesity criteria according to Chinese standards" Reference 11 is irrelevant, and should be replaced by more appropriate one A reference should be given to " WHO (1984) smoking survey method" Statistical analysis: adjustment for Age and BMI should be carried out instead of what was done. Results: are poorly presented. "We" should not be used. Instead use third person. No need to mention data presented in tables. Table 1 still needs redesign to make it more understandable. (Using Statistical description as a heading for the third column is incorrect).

REVIEWER	Martin Muddu Makerere University Joint AIDS Program (MJAP)
REVIEW RETURNED	17-Sep-2019

GENERAL COMMENTS	The paper brings out an association between DR, BMI and Smoking in the diabetes population. Being a cross sectional study in one center, limits its ability to conclude that smoking or a high BMI is a risk factor for DR. The information generated is limited.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 3
Reviewer Name
Prof. Suhad Bahijri
Institution and Country
Faculty of Medicine- King Abdulaziz University- Jeddah- Saudi Arabia
Comments2
(1)Even though a lot of effort was made to revise the manuscript, there remain some points that need further revision. Moreover, the manuscript requires further language editing as there are still some mistakes.
Answer：We fixed some mistakes. There may remain some more points that need further revision.Thank you.
(2)Abstract: diabetic retinopathy (DR) should be written in full when first mentioned. This was not amended in the revised version
Answer：I have revised the abstract. Full write of DR is added. Thank you.
(3)Introduction:The sentence " It is well-known that smoking may cause an increase in proteinuria" needs a reference。
Answer：Thank you. I added a reference. ”Ohkuma T , Nakamura U , Iwase M , et al. Effects of smoking and its cessation on creatinine- and cystatin C-based estimated glomerular filtration rates and albuminuria in male patients with type 2 diabetes mellitus: the Fukuoka Diabetes Registry[J]. Hypertension Research, 2016.”
(4)Introduction:The sentence "Everyone speculates that smoking has a adjunct effect on DR, but there is no direct clinical epidemiological evidence supporting the suggestion that there is a direct link between smoking and DR in newly diagnosed patients" should be reformulated, and a proper reference given. The used reference is irrelevant. The rational for the study should be emphasized more.
Answer: I reorganized the presentation.I added relevant references.
However, many studies show that smoking has no significant correlation with DR（Mose SE,Klein R,Klein BE. Cigarette smoking and ten-year progression of diabetic retinopathy[J].Ophthalmology,1996,103(3):1438-1442.）. Even some studies in China have shown

that smoking is a protective factor for DR(Li Y, Wang J, Qu B, etal.Prevalence and risk factors of diabetic retinopathy in hospital patients[J].Natl Med J China,2018,98(6):440-444(in Chinese).). Thank you.
(5)Methods: "We" should not be used. Instead use third person.
Answer: We changed it to a third person.
(6)There is a lot of repetition. Requires reorganization.
Answer: I removed the repetitive description. If there is any more inappropriate description, please continue to help me. Thank you.
(7)A reference should be provided for the sentence "BMI (≥28kg/m2) met obesity criteria according to Chinese standards" .Reference 11 is irrelevant, and should be replaced by more appropriate one.
Answer: The BMI cut-off point of obesity in China's obesity prevention and control guidelines has always been 28. I added the reference.
(8)A reference should be given to " WHO (1984) smoking survey method"
Answer: The definition of smoking(WHO1984) was translated by Weng Xinzhi and published in the Journal of cardio pulmonary vascular in China. At present, the Chinese version of the magazine has been found, but there was no corresponding English abstract and DOI at that time. For this reason, I found WHO 1997 guidelines and relevant definitions. The difference between the two guidelines is the duration of smoking. The former is more than one year, and the latter is 6 months. In this study, the minimum smoking age of smokers was 2 years, and there was no smoking cessation, so the reference of this department was changed to WHO 1997 standard. I added the reference.Thank you.
(9)Statistical analysis: adjustment for Age and BMI should be carried out instead of what was done.
Answer：First, the related factors of DR were analyzed in the general population. Through the comparison of obese and non obese people, we found that there was a significant difference in patients' age. Then according to the age distribution of patients, the age of diabetes diagnosis was divided into these three situations(< 50,50~60,≥60 years). Finally, adjustment for Age and BMI was carried out. Through this statistical analysis, it is found that there was a negative correlation between DR and the age of diagnosis of diabetes≥60 years. This is not found in the previous analysis.Thank you.
(10)Results are poorly presented. "We" should not be used. Instead use third person. No need to mention data presented in tables. 1 still needs redesign to make it more understandable. (Using Statistical description as a heading for the third column is incorrect).
Answer: I modified the expression of the results. We added tables.Thank you.

Reviewer: 4
Reviewer Name
Martin Muddu
Institution and Country
Makerere University Joint AIDS Program (MJAP)
Please state any competing interests or state ‘None declared’:
None declared
Please leave your comments for the authors below
The paper brings out an association between DR, BMI and Smoking in the diabetes population. Being a cross sectional study in one center, limits its ability to conclude that smoking or a high BMI is a risk factor for DR. The information generated is limited.
Answer: There are obvious limitations in this study. There are few studies on the factors related to newly diagnosed diabetic retinopathy in type 2 diabetes mellitus patients in China. The innovation of this study is to evaluate the severity of smoking by calculating smoking index and to observe the age of diabetes diagnosis. Thank you.I will pay more attention to better research design in the future.

VERSION 3 – REVIEW

REVIEWER	Prof. Suhad Bahijri Faculty of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia
REVIEW RETURNED	30-Nov-2019

GENERAL COMMENTS	There are still many grammatical mistakes. In addition wrong expressions are used. Language editing is needed. I recommended adjustment for age and BMI, and this was not done in the revised version. The results might be different if this was carried out.

VERSION 3 – AUTHOR RESPONSE

Reviewer: 3

Reviewer Name

Prof. Suhad Bahijri

Institution and Country

Faculty of Medicine, King Abdulaziz University,

Jeddah, Saudi Arabia

Please state any competing interests or state 'None declared':

None declared

Please leave your comments for the authors below

There are still many grammatical mistakes. In addition wrong expressions are used. Language editing is needed. I recommended adjustment for age and BMI, and this was not done in the revised version. The results might be different if this was carried out.

Answer：I have asked a native English speaking colleague to improve the quality of the English throughout the manuscript. If there are still many grammatical mistakes and wrong expressions, please remind me. Thank you.

In the proposal, you suggest to adjust the age and BMI. The suggestion is very good. After consulting with the statistical professionals, we adjusted smoking, BMI and age as covariates in the first regression analysis. Patients with BMI≥28kg/m^2 were less likely to have DR in newly diagnosed diabetic patients (OR=0.592, p=0.004). The age of DM diagnosis was also statistically significant in the regression analysis(p=0.047)**.** The incidence of DR in patients over 60 years old diagnosed with diabetes was significantly lower than that in patients under 50 years old(OR=0.596,p=0.024). Since obesity is unlikely to have a protective effect on DR, we conducted a group analysis on obesity or not. Your suggestions are very important. I will pay more attention to these problems in the future work.Thank you.

VERSION 4 – REVIEW

REVIEWER	Prof. Suhad Bahijri Faculty of Medicine- King Abdulaziz University- Jeddah- Saudi Arabia
REVIEW RETURNED	15-Dec-2019

GENERAL COMMENTS	Language editing has been carried out satisfactorily, and results were discussed more clearly.