

## 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>	Association of Different Kinds of Obesity with Diabetic Retinopathy in Patients with Type 2 Diabetes
<b>AUTHORS</b>	Li, Wangting; Gong, Xia; Wang, Wei; Xiong, Kun; Meng, Jie; Li, Yuting; Wang, Lanhua; Liang, Xiaoling; Jin, Ling; Huang, Wenyong

### VERSION 1 – REVIEW

<b>REVIEWER</b>	Zi-lin Sun Southeast Univ, Department of Endocrinology
<b>REVIEW RETURNED</b>	09-Oct-2021

<b>GENERAL COMMENTS</b>	<p>Though the authors have got many results, the interpretation and explanation of the results are very average. In addition, almost all of these have been done and published. Overall, there is insufficient novelty or significance to meet publication criteria. Even though, there are some questions should be noted.</p> <p>(1) For Chinese, is it appropriate to choose 25 kg/m<sup>2</sup> as the cut-off point of BMI for obesity?</p> <p>(2) In regression analysis, the directions of OR are inconsistent in different stratifications, and the 95% CI of some stratifications are too large (indicating that the sample size of this stratification is insufficient), indicating that there may be some problems in the quality of data.</p> <p>Therefore, I cannot support its publication in BMJ Open in its present form.</p>
-------------------------	---

<b>REVIEWER</b>	Kiran Shah Diabetes & Thyroid Care Center
<b>REVIEW RETURNED</b>	01-Dec-2021

<b>GENERAL COMMENTS</b>	<p>Though multiple research have revealed both positive and negative associations between diabetic retinopathy and obesity, the use of four obesity associated tools BMI, WHR, WhtR, and BAI for DR, DME, and VTDR in diabetic patients and the associated outcomes revealed in the study are intriguing. The findings of the prospective studies are something I'm looking forward to seeing.</p>
-------------------------	--

<b>REVIEWER</b>	Simon George Regional Institute of Ophthalmology, Ophthalmology
<b>REVIEW RETURNED</b>	15-Dec-2021

<b>GENERAL COMMENTS</b>	<p>After going through the article, I would like to suggest the following changes</p> <p>1) The primary outcomes mentioned in this article are DR ( mild, moderate and severe NPDR ,PDR ) , DME and VTDR ( DME and PDR ). Was PDR patients included in both the DR and VTDR groups</p>
-------------------------	--

	<p>? Were the patients with history of treatment for DR excluded from the study ? Some of the DR patients will also have DME . Were such patients included in DR group or DME group or both ? In my opinion, the primary outcomes should be modified as no DR +/- DME , mild DR +/- DME , moderate DR +/- DME , severe NPDR +/- DME ,PDR +/- DME. The association of the obesity related indexes should be analyzed with these outcomes .</p> <p>2) 483 consecutive participants underwent hip circumference measurement and 1484 consecutive participants underwent waist circumference measurement. How many participants were subjected to both hip circumference and waist circumference measurements ? The obesity related indexes should be calculated in the group participants with both measurements taken. Will this number meet the sample size required for the study ?</p> <p>3)The univariate and multivariate model results in this study should be reviewed by a specialist statistician.</p>
--	---

<b>REVIEWER</b>	Mahmoud Ashraf Ibrahim EDC , Center for Diabetes Education, Diabetes
<b>REVIEW RETURNED</b>	16-Dec-2021

<b>GENERAL COMMENTS</b>	<p>December 16th 2021</p> <p>Reviewer's report: Thank you very much for giving me the chance to review the paper entitled Association of Different Kinds of Obesity with Diabetic Retinopathy in Patients with Type 2 Diabetes. "By Huang, et al</p> <p>A. Summary:</p> <p>This study aimed to investigate the prevalence of obesity, and analyze the association of four obesity-related indexes, the authors recruited 2305 diabetic patients to investigate the prevalence and the association of different types of obesity with Diabetic Retinopathy using obesity-related indexes like BMI, WHR...etc. they found that The prevalence of DR, DME and VTDR was higher in patients with higher BMI/WHR or lower WHtR/BAI.</p> <p>B. Strengths:</p> <p>1 – The point of research is worthy of investigation. I am not aware of a large number of studies looked at this possible association, especially the correlation between BAI and Diabetic Retinopathy. Even though I am not sure if it is the first study to look at this association as was mentioned in the text, I suggest removing the word (first)</p> <p>2 – The sample size was good, though not sure about the proper representation of the community there, was the sample examined by an epidemiologist?</p> <p>3- The statistical analysis was good and reflecting the results, also the tables and the figures were informative.</p> <p>C. Weaknesses:</p> <p>1- In line 14, they put the title (Article summary: Strengths and</p>
-------------------------	--

	<p>limitations of this study), however no limitations were mentioned under!</p> <p>2- I am not sure why waist circumference and hip circumference was not measured on some participants? this should be justified in the discussion section</p> <p>3- I went through references [18, 19] concerning the possible obesity paradox, I did not find a direct correlation with retinopathy, even though both references are relatively old, I am afraid this may address a mixed message related to the possible protective aspects of obesity!!</p> <p>Major Compulsory Revisions</p> <p>None.</p> <p>Level of interest: An article whose findings are important to those with closely one related research interests</p> <p>Quality of written English: I guess it was ok</p> <p>Statistical review: the manuscript may not need to be seen by a statistician.</p> <p>Declaration of competing interests: 'I declare that I have no competing interests'</p>
--	--

<b>REVIEWER</b>	Gebiso Roba Debele Mettu University, Public health
<b>REVIEW RETURNED</b>	24-Dec-2021

<b>GENERAL COMMENTS</b>	<p>I thank you for your invitation to review this interesting concept – DM complication specifically diabetic retinopathy.</p> <p>Thanks to the authors for their great effort. The paper contributes to a great understanding of the “Association of Different Kinds of Obesity with Diabetic Retinopathy in Patients with Type 2 Diabetes”. While I find this contribution is novel, the paper needs some revision and I will enumerate below the comments that need to be addressed.</p> <p>Comments</p> <p>Abstract</p> <p>On page 2 line 22 you wrote “We aimed to investigate the prevalence of obesity, and analyze the association.....”. This statement seems like as your primary outcome is obesity, while your primary outcome is different types of DR. Is that your primary outcome is DR or obesity?</p> <p>Line 31, better to change ‘Research Design and Methods’ to Results because what was wrote under this subtitle was the result parts.</p> <p>line 35-37 says that, ‘In the multivariate model, obese presented as a protective factor for DME and VTDR, while the second quarter of WHtR(Q2-WHtR) presented as a risk factor. However, the association was significant only in female patients, but not male patients. From this finding we are going to recommend as being obese is good to prevent or reduce DR. Do you think this finding is due really obese is a proactive factor for DME and VTDR or due to majority of the selected subjects who have obesity did not developed DR? In the discussion parts the reason why those factors were significant only in female should be clarified and discussed with evidence.</p> <p>“A total of 1562(67.8%) participants were overweight or obese”. Better to write the % for overweight and obese separately. And you put this result in the descriptive parts of your study. Since your</p>
-------------------------	--

	<p>primary outcome is DR, I prefer to say a total of ____, ____, and ____ developed DR, DME and VTDR respectively. The prevalence was higher among patients with higher BMI/WHR or lower WHtR/BAI.</p> <p><b>Introduction</b>  On line 56-58, "To solve the problem, .....is established and has a significant linear relationship with body fat rate". The result of your study is not expected to be written in the introduction parts.  At the end of your introduction, I prefer to write, Therefore, this study assessed the association of obesity-related indexes with DR, diabetic macular edema (DME), and vision-threatening diabetic retinopathy (VTDR) among T2DM patients using the data of Guangzhou Diabetic Eye Study in China.</p> <p><b>Methods</b>  <b>Statistical Analysis</b>  Why you used Mann-Whitney U test? Why not independent t-test if your outcome is normally distributed?  On line 138 you said "Patients and the public were not involved in the development of this research cohort." If no patients were not involved in this specific study, from where do you get the informed consent to conduct the research? Because you have obtained a Written informed consent from all participants.</p> <p><b>Results and discussion</b>  "In general, 336 (14.58%) participants developed DR, including 76 (3.30%) patients with mild NPDR, 197 (8.55%) patients with moderate NPDR, 45 (1.95%) patients with severe NPDR, 17 (0.74%) patients with PDR, and 93 (4.03%) patients with DME. (4.25%) patients developed VTDR." This statement is the statement that needs to be included in the results part of the abstract. Because those outcomes were your primary outcome.  As I tried to understand from the results of your analysis you fitted different logistic regression for all obesity indices. Because all obesity indices were not taken from all individuals in the study. There, you have included this information in the analysis part of the methods. Focus on the comments given on the abstract to be included in the discussion part.</p>
--	---

### VERSION 1 – AUTHOR RESPONSE

**Reviewer #1**

Though the authors have got many results, the interpretation and explanation of the results are very average. In addition, almost all of these have been done and published. Overall, there is insufficient novelty or significance to meet publication criteria. Even though, there are some questions that should be noted.

(1) For Chinese, is it appropriate to choose 25 kg/m<sup>2</sup> as the cut-off point of BMI for obesity?

**Response:**

We thank the reviewer for your comments and suggestions. However, after we had reviewed the articles and found different BMI cut points, we finally decided to adopt the BMI cut points according to the researches of Hills et al<sup>8</sup>, which was proved to be more efficient in Asian people<sup>9-10</sup>. (Page 6-7 Line 124-126)

**Reference :**

8 Hills, A. P. et al., Epidemiology and determinants of type 2 diabetes in south Asia. The Lancet Diabetes & Endocrinology 6 966 (2018).

9 Forthun, I. et al., Maternal Prepregnancy BMI and Risk of Cerebral Palsy in Offspring. PEDIATRICS 138 e20160874 (2016).

10 Morisaki, N. et al., Pre-pregnancy BMI-specific optimal gestational weight gain for women in Japan. J EPIDEMIOLOG 27 492 (2017).

(2) In regression analysis, the directions of OR are inconsistent in different stratifications, and the 95% CI of some stratifications are too large (indicating that the sample size of this stratification is insufficient), indicating that there may be some problems in the quality of data.

Response:

Thank you for the comments. The two problem (inconsistent OR and the large 95% CI), which referred to the association of obesity index and diabetic retinopathy (Table 3-2 and 3-3), may be a result influenced by the small number of patients in some of the categories after they were grouped by sex (there were "no observation" categories in Table S3-1 and Table S3-2). Therefore, we included the table into the supplementary materials and revised the discussion (Page 18 Line 268-271). We have also deleted the referred result in the Abstract for the less-convincing evidence. However, the problem did not occur in the full model concerning all the participants (Table 3), since eventually 483 patients have undergone all the measurement including height, weight, waist circumference and hip circumference (Page 18 Line 272-276). This may demonstrate our results with strong confidence.

Therefore, I cannot support its publication in BMJ Open in its present form.

Response:

Thank you for the comments and suggestions. We have reorganized and rewrote the Results and Discussion part for better understanding, hoping it will come to your satisfaction.

Reviewer: 2

Though multiple research have revealed both positive and negative associations between diabetic retinopathy and obesity, the use of four obesity associated tools BMI, WHR, WhtR, and BAI for DR, DME, and VTDR in diabetic patients and the associated outcomes revealed in the study are intriguing. The findings of the prospective studies are something I'm looking forward to seeing.

Response:

We thank the reviewer for your warm comments.

Reviewer: 3

After going through the article, I would like to suggest the following changes

1) The primary outcomes mentioned in this article are DR (mild, moderate and severe NPDR, PDR), DME and VTDR (DME and PDR). Was PDR patients included in both the DR and VTDR groups? Were the patients with history of treatment for DR excluded from the study? Some of the DR patients will also have DME. Were such patients included in DR group or DME group or both? In my opinion, the primary outcomes should be modified as no DR +/- DME, mild DR +/- DME, moderate DR +/- DME, severe NPDR +/- DME, PDR +/- DME. The association of the obesity related indexes should be analyzed with these outcomes.

Response:

We thank the reviewer for your comments and suggestions, and sorry for causing misunderstanding. We have drawn Figure 1 for better understanding (see below). Therefore, PDR patients were included in both the DR and VTDR groups. We have also revised the referred part of exclusion criteria (Page 5 Line 87-97) as below:

Patients with any evidence of the following conditions were excluded: (I) best corrected visual acuity (BCVA) worse than 20/200, axial length > 30 mm or unmeasurable, spherical equivalent (SphE) ≤ -

12.0 degrees, astigmatism > 4 degrees, or intraocular pressure (IOP) > 21 mmHg in the right eye; (II) except DR, other combined eye diseases that could affect retinal thickness in the right eye, such as glaucoma, age-related macular degeneration, and retinal detachment; (III) surgery or invasive treatment or laser treatment history on the right eye; (IV) severe systemic diseases, such as uncontrolled hypertension, severe cardiovascular and cerebrovascular disease, malignant tumors, and nephritis; (V) general surgery history, such as heart bypass, thrombolysis, and kidney transplantation; (VI) cognitive disorders or mental illness that would hinder the patient's cooperation with tests; and (VII) inability to obtain clear fundus or SS-OCT images because of refractive media opacity or non-cooperation. Therefore, the patients with history of treatment for DR were excluded from the study.

We have also tried to reclassified the patients with outcomes following your comments. However, the small number in some specific classification (for example, only one participants with DR-&DME+, and only five participants with PDR+&DME-) would lead to bias of the statistical results. The reason would be that all the participants were from the community, and the diabetic participants with severe condition (e.g. very poor eye sight, past DR treatment history, occurred with other combined eye diseases that could affect retinal thickness, etc.) were excluded. Therefore, the participants usually had a less severe condition, which may affect the generalizability of the results. Since DR and DME referred to different pathological process, and that VTDR would concentrate more on patient visual function, we decided to use DR, DME and VTDR as our primary outcomes.

Table R1. The number of patients with DR and DMR outcome.

DME		DR outcome	
outcome	No DME	DME	Total
No DR	1,969	1	1,970
Mild NPDR	67	9	76
Moderate NPDR	155	42	197
Severe NPDR	16	29	45
PDR	5	12	17
Total	2,212	93	2,305

2) 483 consecutive participants underwent hip circumference measurement and 1484 consecutive participants underwent waist circumference measurement. How many participants were subjected to both hip circumference and waist circumference measurements? The obesity related indexes should be calculated in the group participants with both measurements taken. Will this number meet the sample size required for the study?

Response:

Thank you for the comments, and sorry for causing misunderstanding. A total of 483 participants were subjected to both hip circumference and waist circumference measurements. Therefore, the full model concerning all the measurement including height, weight, waist circumference and hip circumference (the results about WHR, WHtR and BAI in Table 3) eventually enrolled 483 patients, while the results about BMI (Table 3) enrolled the data of 2305 patients. The inconsistency in measurement was due to the reduction of the examination time and to improve the compliance of participants, so the measurement of waist circumference and hip circumference was not performed on every participant. We have revised the discussion part for better understanding (Page 18 Line 272-276). The sample size meets the requirement of the analysis.

3)The univariate and multivariate model results in this study should be reviewed by a specialist statistician.

Response:

Thank you for the suggestion. Our statistical methods and results were performed under the direction of Dr. Wei Wang and Ling Jin, who are the authors of the paper. Both of them has sufficient experience in the field of ophthalmic epidemiology and statistical analysis.

Reviewer: 4

Thank you very much for giving me the chance to review the paper entitled "Association of Different Kinds of Obesity with Diabetic Retinopathy in Patients with Type 2 Diabetes" by Huang, et al

A. Summary:

This study aimed to investigate the prevalence of obesity, and analyze the association of four obesity-related indexes, the authors recruited 2305 diabetic patients to investigate the prevalence and the association of different types of obesity with Diabetic Retinopathy using obesity-related indexes like BMI, WHR...etc. they found that The prevalence of DR, DME and VTDR was higher in patients with higher BMI/WHR or lower WHtR/BAI.

B. Strengths:

1 – The point of research is worthy of investigation. I am not aware of a large number of studies looked at this possible association, especially the correlation between BAI and Diabetic Retinopathy. Even though I am not sure if it is the first study to look at this association as was mentioned in the text, I suggest removing the word (first)

Response:

We thank the reviewer for your comments and suggestions. In the new version, we reorganized and rewrote the 'Strengths and limitations' section (Page 3 Line 44-57) as:

Article summary: (Strengths and limitations of this study)

1. This study is a combined study that analyzed the association of four obesity-related indexes (BMI, WHR, WHtR, and BAI) with the presence and the severity of diabetic retinopathy.
2. Any diabetic retinopathy, diabetic macular edema (DME), and vision-threatening diabetic retinopathy (VTDR) were selected as primary outcomes.
3. DR and DME were diagnosed and graded according to the International Clinical Severity Scale of Diabetic Retinopathy and Diabetic Macular Edema (Figure 1), using 7-position fundus photos of participants.
4. To reduce the examination time and improve the compliance of participants, the measurement of waist circumference and hip circumference was not performed on every participant, while eventually 483 patients have undergone all the measurements.
5. The diabetic participants with severe conditions (e.g. very poor eyesight, past DR treatment history, occurred with other combined eye diseases that could affect the retinal thickness, etc.) were excluded from our study.

We also revised the referred part in Discussion as "Third, we found a significant negative association between BAI and DR in the univariate logistic regression model, while the association became less significant in the multivariable model."

2 – The sample size was good, though not sure about the proper representation of the community there, was the sample examined by an epidemiologist?

Response:

Thank you for the comments. As a cohort study, participants are included as much as possible. In this study, the sample size has also met the requirement of the analysis.

3- The statistical analysis was good and reflecting the results, also the tables and the figures were informative.

Response:

Thank you for the comments.

C. Weaknesses:

1- In line 14, they put the title (Article summary: Strengths and limitations of this study), however no limitations were mentioned under!

Response:

Thank you for the comments. We have reorganized the "Strengths and limitations of this study" (Page 3 Line 44-57), which was already presented above.

2- I am not sure why waist circumference and hip circumference was not measured on some participants? this should be justified in the discussion section

Response:

Thank you for the comments. and sorry for causing misunderstanding. The inconsistency in measurement was due to the reduction of the examination time and to improve the compliance of participants, so the measurement of waist circumference and hip circumference was not performed on every participant. Still, a total of 483 participants were subjected to both hip circumference and waist circumference measurements. Therefore, the full model concerning all the measurement including height, weight, waist circumference and hip circumference (the results about WHR, WHtR and BAI in Table 3) eventually enrolled 483 patients, while the results about BMI (Table 3) enrolled the data of 2305 patients. We have revised the Discussion part and included this point as one of the limitation for better understanding (Page 18 Line 272-276) for better understanding.

3- I went through references [18, 19] concerning the possible obesity paradox, I did not find a direct correlation with retinopathy, even though both references are relatively old, I am afraid this may address a mixed message related to the possible protective aspects of obesity!!

Response:

Thank you for the comments. In the new version, we revised the paragraph focusing on the relationship of centripetal obesity (presented as higher WHR) and diabetic progression. The references have been modified as well. The paragraph was revised as:

Although obesity was recognized as one of the important biomarkers inducing insulin resistance<sup>16</sup>, the obesity paradox has prevented scientists from making recommendations on weight management for diabetic patients. The positive correlation between centripetal obesity (presented as higher WHR) and diabetic progression has shed light on this problem. <sup>17</sup> In study of Tien Yin Wong et al, WHR was regarded to assess centripetal obesity, and BAI is established and has a significant linear relationship with body fat rate.<sup>18</sup> They demonstrated that abdominal obesity may be a more critical factor of DR than the generalized obesity. However, in our study, as the indicator of centripetal obesity, Q2-WHtR associated positively with DR, and WHtR generally shows an opposite trend, indicating a nonlinear relationship between centripetal obesity. Therefore, we are collecting follow-up data to further prospectively analyze the relationship between obesity and diabetic retinopathy. (Page 17-18 Line 250-260)

Reference :

16 Arkan, M. C. et al., IKK-beta links inflammation to obesity-induced insulin resistance. NAT MED 11 191 (2005).



17 Man, R. E. K. et al., Differential Association of Generalized and Abdominal Obesity With Diabetic Retinopathy in Asian Patients With Type 2 Diabetes. JAMA OPHTHALMOL 134 251 (2016).  
18 Bergman, R. N. et al., A Better Index of Body Adiposity. OBESITY 19 1083 (2011).

Major Compulsory Revisions: None.

Level of interest: An article whose findings are important to those with closely one.

Quality of written English: I guess it was ok

Statistical review: The manuscript may not need to be seen by a statistician.

Declaration of competing interests: I declare that I have no competing interests

Response:

Thank you again for your review and comments.

Reviewer: 5

I thank you for your invitation to review this interesting concept – DM complication specifically diabetic retinopathy.

Thanks to the authors for their great effort. The paper contributes to a great understanding of the “Association of Different Kinds of Obesity with Diabetic Retinopathy in Patients with Type 2 Diabetes”. While I find this contribution is novel, the paper needs some revision and I will enumerate below the comments that need to be addressed.

Comments:

Abstract

On page 2 line 22 you wrote “We aimed to investigate the prevalence of obesity, and analyze the association.....”. This statement seems like as your primary outcome is obesity, while your primary outcome is different types of DR. Is that your primary outcome is DR or obesity?

Response:

We thank the reviewer for your detailed comments and suggestions. In the new version, we revised the sentence as “This study aimed to investigate the association of diabetic retinopathy (DR) with four obesity-related indexes, including body mass index (BMI), waist to hip ratio (WHR), waist to height ratio (WHtR) and body adiposity index (BAI) in diabetic patients” (Page 2 Line 21-23) for better understanding.

Line 31, better to change ‘Research Design and Methods’ to Results because what was wrote under this subtitle was the result parts.

Response:

Thank you for the comments. We have changed ‘Research Design and Methods’ to Results accordingly (Page 2 Line 31).

line 35-37 says that, ‘In the multivariate model, obese presented as a protective factor for DME and VTDR, while the second quarter of WHtR(Q2-WHtR) presented as a risk factor. However, the association was significant only in female patients, but not male patients. From this finding we are going to recommend as being obese is good to prevent or reduce DR. Do you think this finding is due really obese is a proactive factor for DME and VTDR or due to majority of the selected subjects who have obesity did not developed DR? In the discussion parts the reason why those factors were significant only in female should be clarified and discussed with evidence.

Response:

Thank you for the review and comments. Although some previous studies have similar findings, 17 we suggested the result be influenced by the small number of patients in some of the categories after

they were grouped by sex (there were “no observation” categories in Table S3-1 and Table S3-2). Therefore, we included the table into the supplementary materials and revised the discussion (Page 18 Line 268-271). We have also deleted the referred result in the Abstract for the less-convinced evidence. However, the problem did not occur in the full model concerning all the participants (Table 3), since eventually 483 patients have undergone all the measurement including height, weight, waist circumference and hip circumference (Page 18 Line 272-276).

Reference :

17 Man, R. E. K. et al., Differential Association of Generalized and Abdominal Obesity With Diabetic Retinopathy in Asian Patients With Type 2 Diabetes. JAMA OPHTHALMOL 134 251 (2016).

“A total of 1562(67.8%) participants were overweight or obese”. Better to write the % for overweight and obese separately. And you put this result in the descriptive parts of your study. Since your primary outcome is DR, I prefer to say a total of \_\_\_\_, \_\_\_\_, and \_\_\_\_ developed DR, DME and VTDR respectively. The prevalence was higher among patients with higher BMI/WHR or lower WHtR/BAI.

Response:

Thank you for the comments. We revised the sentence accordingly (Page 2 Line 31-32) as:  
A total of 336 (14.58%), 93 (4.03%) and 98 (4.25%) developed DR, DME and VTDR respectively. The prevalence of DR, DME and VTDR was higher in patients with higher BMI/WHR or lower WHtR/BAI.

Introduction

On line 56-58, “To solve the problem, .....is established and has a significant linear relationship with body fat rate”. The result of your study is not expected to written in the introduction parts.

Response:

Thank you for the suggestion. We deleted it from introduction and discussed with our results in Discussion part accordingly (Page 17-18 Line 250-260).

At the end of your introduction, I prefer to write, Therefore, this study assessed the association of obesity-related indexes with DR, diabetic macular edema (DME), and vision-threatening diabetic retinopathy (VTDR) among T2DM patients using the data of Guangzhou Diabetic Eye Study in China.

Response:

Thank you for the review and comments. We revised the paragraph accordingly (Page 4 Line 75-77) as:

Therefore, this study assessed the association of obesity-related indexes with DR, diabetic macular edema (DME), and vision-threatening diabetic retinopathy (VTDR) among T2DM patients using the data of the Guangzhou Diabetic Eye Study in China.

Methods

Statistical Analysis

Why you used Mann-Whitney U test? Why not independent t-test if your outcome is normally distributed?

Response:

Thank you for the review and comments, and sorry for the mistakes during former revision which caused misunderstanding. Because some of the continuous variables (e.g. creatinine and microalbuminuria) were not normally distributed, both the Student t-test and the Mann-Whitney U test have been used in our study. The Student t-test was used for continuous variables that were normally distributed (age, systolic blood pressure, Hba1c, c-reaction protein, total cholesterol, triglycerides, low-density cholesterol, high-density cholesterol, uric acid, and axial length), while the Mann-Whitney

U test was used for other continuous variables (creatinine and microalbuminuria). We have revised the paragraphs accordingly in the Methods part (Page 8 Line 147-149) for better understanding.

On line 138 you said “Patients and the public were not involved in the development of this research cohort.” If no patients were not involved in this specific study, from where do you get the informed consent to conduct the research? Because you have obtained a Written informed consent from all participants.

Response:

Thank you for the review and comments. We have referred to the previous studies published on BMJ Open, and revised the sentence as (Page 8 Line 160-162):

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Results and discussion

“In general, 336 (14.58%) participants developed DR, including 76 (3.30%) patients with mild NPDR, 197 (8.55%) patients with moderate NPDR, 45 (1.95%) patients with severe NPDR, 17 (0.74%) patients with PDR, and 93 (4.03%) patients with DME. (4.25%) patients developed VTDR.” This statement is the statement that need to included in the results parts of abstract. Because those outcomes were your primary outcome.

Response:

Thank you for the review and comments. As mentioned above, we have included the major information in the Abstract accordingly (Page 2 Line 31-32) as:

A total of 336 (14.58%), 93 (4.03%) and 98 (4.25%) developed DR, DME and VTDR respectively. The prevalence of DR, DME and VTDR was higher in patients with higher BMI/WHR or lower WHtR/BAI.

As I tried to understand from the results of your analysis you fitted different logistic regression for all obesity indices. Because all obesity indices were not taken from all individual in the study. There, you have included this information in the analysis parts of methods.

Focus on the comments given on the abstract to be included in the discussion parts.

Response:

Thank you again for the review and comments. We have revised the Abstract, Introduction, Methods, Results and Discussion accordingly for better understanding.

#### VERSION 2 – REVIEW

<b>REVIEWER</b>	Mahmoud Ashraf Ibrahim EDC , Center for Diabetes Education, Diabetes
<b>REVIEW RETURNED</b>	26-Feb-2022
<b>GENERAL COMMENTS</b>	i think this revised version is good to go
<b>REVIEWER</b>	Gebiso Roba Debele Mettu University, Public health
<b>REVIEW RETURNED</b>	02-Mar-2022
<b>GENERAL COMMENTS</b>	My comments to this aper during my first review of the paper was addressed.