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Association of Different Kinds of Obesity with Diabetic Retinopathy in Patients with Type 2 Diabetes

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4 1 **Title Page**

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6 2 **Association of Different Kinds of Obesity with Diabetic Retinopathy in Patients**
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9 3 **with Type 2 Diabetes**

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4 **19 Abstract**

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6 **20 Introduction** Although obesity is one of the established risk factors of diabetes mellitus, the

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9 21 relationship between obesity and diabetic retinopathy (DR) remains unclear in different studies. We

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11 22 aimed to investigate the prevalence of obesity, and analyze the association of four obesity-related

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14 23 indexes, including body mass index(BMI), waist to hip ratio(WHR), waist to height ratio(WHtR) and

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17 24 body adiposity index(BAI), with diabetic retinopathy (DR) in diabetic patients.

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20 25 **Research Design and Methods** We prospectively enrolled 2305 diabetic patients (2305 eyes) in

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22 26 Guangzhou Diabetic Eye Study (GDES) between Nov2017 and Dec 2019 to investigate the prevalence

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25 27 and the association of different types of obesity with DR using BMI, WHR, WHtR and BAI. DR,

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28 28 diabetic macular edema (DME) and vision-threatening diabetic retinopathy(VTDR) were selected as

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30 29 primary outcomes. BMI was categorized as normal (18.5-22.9kg/m²), overweight(23.0-25.0kg/m²), and

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33 30 obese(>25.0kg/m²); WHR, WHtR and BAI were categorized into quarters.

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36 31 **Research Design and Methods** A total of 1562(67.8%) participants were overweight or obese. The

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38 32 prevalence of DR, DME and VTDR was higher in patients with higher BMI/WHR or lower WHtR/BAI.

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41 33 In the univariate regression model, WHR correlated positively with DR, while WHtR and BAI

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44 34 correlated negatively with DR, DME and VTDR. The association remained independent of age, sex and

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47 35 lipid metabolism parameters. In the multivariate model, obese presented as a protective factor for DME

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50 36 and VTDR, while the second quarter of WHtR(Q2-WHtR) presented as a risk factor. However, the

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53 37 association was significant only in female patients, but not male patients.

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56 38 **Conclusions** As high as 67.8% diabetic patients were overweight or obese. Obese presented as a

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59 39 significant protective factor of VTDR, while Q2-WHtR presented as a significant risk factor. Therefore,

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4 40 more attention should be paid to centripetal obesity as well as general obesity. Further research is also
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7 41 needed to focus on the improvement of sex-specific weight management in diabetic patients.
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9 42 **Keywords** Diabetes mellitus, diabetic retinopathy, obesity, BMI, WHR, WHtR, BAI
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14 **Article summary: (Strengths and limitations of this study)**
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17 • This study is a combined study that analyzed the association of four obesity-related
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19 indexes (BMI, WHR, WHtR, and BAI) with the presence and the severity of diabetic
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21 retinopathy.
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25 • The data enrolled 2305 type 2 diabetes mellites (T2DM) patients who participated in the
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27 Guangzhou Diabetic Eye Study in China.
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31 • Any diabetic retinopathy, diabetic macular edema (DME), and vision-threatening diabetic
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33 retinopathy (VTDR) were selected as primary outcomes.
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37 • It is the first study to analyze the association between BAI and DR.
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41 • We are collecting follow-up data to further prospectively analyze the relationship between
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43 obesity and diabetic retinopathy.
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43 **Introduction**

44 Diabetic retinopathy (DR) is one of the most common complications of diabetes mellitus
45 and is a leading cause of vision loss and blindness throughout the world¹. It severely affects the
46 life quality of diabetic patients and increases the economic burden of treatment without timely
47 management¹. Although obesity is one of the established risk factors that correlated positively
48 with diabetes mellitus^{2,3}, the relationship between obesity and DR varies in different studies.
49 For instance, in a cross-sectional study that enrolled 50,464 Saudi diabetic patients, overweight
50 and obesity presented as a protective factor for DR⁴. However, in a meta-analysis of prospective
51 cohort studies, obesity correlated with a significant increase in DR incidence⁵. The methods to
52 improve the weight management of diabetic patients to decrease the presence and severity of
53 DR have become a major public health problem.

54 Body mass index (BMI) has been commonly used to assess weight level in the previous
55 study^{4,6,7}, but it could not distinguish whether a patient is general obese or abdominal obese. To
56 solve the problem, waist to hip ratio (WHR) and waist to height ratio (WHtR) are developed to
57 assess centripetal obesity, while body adiposity index (BAI) is established and has a significant
58 linear relationship with body fat rate⁸. However, combined or separate studies about association
59 of WHR, WHtR, and BAI with DR are still limited. Studies to explore the relationship between
60 obesity and DR among Chinese people are also limited.

61 Therefore, in this study, any DR, diabetic macular edema (DME), and vision-threatening
62 diabetic retinopathy (VTDR) were selected as primary outcomes. We used the data of 2305
63 type 2 diabetes mellites (T2DM) patients who participated in the Guangzhou Diabetic Eye
64 Study, and analyzed the association of four obesity-related indexes (BMI, WHR, WHtR, and

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4 65 BAI) with the presence and the severity of DR.
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9 67 **Methods**

10 11 68 **Study design and participants**

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14 69 The Guangzhou Diabetic Eye Study (GDES) is an ongoing prospective study that enrolled
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17 70 diabetes patients from communities in Guangzhou. Before enrollment, the participants were
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20 71 diagnosed with diabetes in the general hospitals, and were registered and followed up in the
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23 72 community health centers. They were referred to Zhongshan Ophthalmic Center and underwent
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25 73 ophthalmic examinations and physical examinations at the baseline visit, one-year visit, and
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27 74 two-year visit. Demographic information and medical history were also collected at the same
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30 75 time. All the participants were free from cognitive impairments. They were able to conduct
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33 76 normal conservations and lived independently in the community.

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35 77 A total of 2372 diabetic patients participated and completed the examinations between
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38 78 Nov 2017 and Dec 2019. Sixty-seven participants with ungradable fundus images were
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41 79 excluded, and 2305 participants were finally included. The baseline data of demographic
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44 80 information, medical history, ophthalmic examinations, and physical examinations were
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47 81 extracted in the analysis. There was no missing data in the study.

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49 82 This study followed the tenets of the Declaration of Helsinki and was approved by the
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52 83 Institutional Review Board of Zhongshan Ophthalmic Center (IRB-ZOC), Guangzhou, China.
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55 84 Written informed consent was obtained from all participants. Patient records and information
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58 85 were anonymized and de-identified before analysis.

59 86 **Demographic information, medical history, and biometric parameter assessment**

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4 87 Demographic information and medical history (e.g., age, sex, education, smoking and
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6 88 drinking history, duration of diabetes, and insulin use) were collected using a standardized
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9 89 questionnaire. The previous medical records would be checked and confirmed by the doctors.
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11 90 The physical examination, including a blood pressure test, blood test, biochemical test, and
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14 91 urine test, was carried out by a certified nurse.

17 92 **Assessment of BMI, WHR, WHtR, and BAI**

19 93 The participants' weight (in kilograms), height (in meters), waist circumference (in
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22 94 centimeters), and hip circumference were measured by certified nurses. Participants were
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25 95 required to remove their shoes and the heavy object (e.g., mobile phones, keys, and wallets) on
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28 96 them. Weight was measured using a weight scale. Height was measured using a measuring stick
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31 97 on the weight scale. Waist and hip circumferences were assessed using a nonstretchable medical
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34 98 tape. Waist circumference was taken at the smallest horizontal girth between the costal margins
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37 99 and the iliac crests at the end of tidal expiration. Hip circumference was taken at the maximal
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40 100 protuberance of the buttocks. Every participant underwent the weight and height measurement,
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43 101 while 483 consecutive participants underwent hip circumference measurement, and 1484
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46 102 consecutive participants underwent waist circumference measurement.

47 103 BMI was calculated as weight divided by height squared and was categorized into normal
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49 104 weight (18.5-22.9 kg/m²), overweight (23.0-25.0 kg/m²), and obese (>25.0 kg/m²), according
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51 105 to Asia-Pacific BMI cutoff points⁹⁻¹¹. Sixty underweight participants (BMI <18.5 kg/m²) were
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54 106 not included because of the small sample size. WHR was calculated as waist circumference
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57 107 divided by hip circumference, while WHtR was calculated by dividing waist circumference by
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59 108 height. BAI was calculated as hip circumference divided by (height)^{1.5} minus 18. Because of
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4 109 the lack of standardized classifications, WHR, WHtR, and BAI were categorized in quarters.
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7 **110 Assessment of DR, DME, and VTDR**
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9 111 All the participants underwent ophthalmic examinations including vision test, intraocular
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11 112 pressure test, anterior segment examination, intraocular lens (IOL) master test, mydriatic
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13 113 fundus photography, and optical coherence tomography examination, by trained
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15 114 ophthalmologists.
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19 115 DR and DME were diagnosed and graded according to the International Clinical Severity
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21 116 Scale of Diabetic Retinopathy and Diabetic Macular Edema (Figure 1), using 7-position fundus
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23 117 photos of participants. Any DR, DME, and VTDR were selected as primary outcomes. Any DR
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25 118 was defined as the presence of mild non-proliferative diabetic retinopathy (NPDR), moderate
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27 119 NPDR, severe NPDR, or PDR. VTDR was defined as the presence of DME or PDR. For each
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29 120 participant, only the data of the worse eye would be used. If the DR grades of both eyes were
30
31 121 consistent, then the right eye would be selected for analysis.
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38 **122 Statistical analysis**
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40 123 All analyses were performed using STATA statistical software (Stata version 14.0, Stata
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42 124 Corp., College Station, TX). BMI, WHR, WHtR, and BAI classifications were used as both
43
44 125 continuous variables and categorical variables. To compare the differences in characteristics of
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46 126 participants with or without DR, DME, and VTDR, the Mann-Whitney U test was used for
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48 127 continuous variables, and the Chi-square test was used for categorical variables.
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53 128 The binary and ordinal logistic regression model was used to assess the association of BMI,
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55 129 WHR, WHtR, and BAI with the presence of any DR and VTDR. In special, the outcome of the
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57 130 ordinal logistic regression model of DR was set as no DR, mild NPDR, moderate NPDR, and VTDR
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4 131 (including PDR and DME). In the multivariate logistic model, the association was adjusted for
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7 132 potential confounding factors established in previous research. These factors included continuous
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9 133 variables (e.g., age, systolic blood pressure, HbA1c, c-reaction protein, total cholesterol, triglycerides,
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11 134 low-density cholesterol, high-density cholesterol, creatinine, microalbuminuria, uric acid, and axial
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14 135 length) and categorical variables (e.g., sex, smoking history, drinking history, education, duration of
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17 136 diabetes, and insulin use). P values less than 0.05 were considered statistically significant.

137 **Patient and public involvement statement**

138 Patients and the public were not involved in the development of this research cohort.

139 **Results**

140 In general, 336 (14.58%) participants developed DR, including 76 (3.30%) patients with
141 mild NPDR, 197 (8.55%) patients with moderate NPDR, 45 (1.95%) patients with severe
142 NPDR, 17 (0.74%) patients with PDR, and 93 (4.03%) patients with DME. 98 (4.25%) patients
143 developed VTDR.

144 Compared with participants who did not have DR, participants with DR had a younger
145 age, a lower level of education, a longer duration of diabetes, and a higher proportion of males,
146 smoking history, drinking history, and insulin use (Table 1). They also had a higher level of
147 HbA1c, creatinine, microalbuminuria, and systolic blood pressure, but shorter axis length (all p
148 <0.05). Moreover, their BMI, WHR, WHtR, and BAI were higher. According to Asia-Pacific
149 BMI cutoff points, as high as 947 participants (41.1%) were obese, and 615 (26.7%) were
150 overweight, while only 683 participants (29.6%) were normal weight.

151 **Association of BMI with any DR, DME and VTDR**

152 The prevalence of any DR, DME and VTDR in overweight diabetic patients was higher

Table 1. The characteristics of participants with or without diabetic retinopathy (DR), diabetic macular edema (DME) and vision threatening diabetic retinopathy (VTDR). Footnotes: BMI: Body mass index. WHR: Waist to hip ratio. WHtR: waist to height ratio. BAI: Body adiposity index.

	DR n=336	No DR n=1970	DME n=93	No DME n=2212	VTDR n=98	No VTDR n=2207
Medical history						
Age, median (IQR), year	64.0(10.0)	65.0(10.0)	62.0(9.0)	65.0(10.0)	61.5(9.0)	65.0(10.0)
Sex, %						
Female	49.4	58.35	43.01	57.64	42.86	57.68
Male	50.6	41.65	56.99	42.36	57.14	42.32
Smoking history, %						
No	81.88	86.29	83.12	85.76	82.5	85.79
Yes	18.12	13.71	16.88	14.24	17.5	14.21
Drinking history, %						
No	88.04	91.18	89.61	90.78	87.5	90.87
Yes	11.96	8.82	10.39	9.22	12.5	9.13
Education, %						
Educated	16.42	11.26	16	11.83	15.09	11.85
Not educated	83.58	88.74	84	88.17	84.91	88.15
Diabetes duration, %, year						
<5	18.15	39.21	21.51	36.75	20.41	36.84
5-9	20.24	26.16	17.2	25.63	17.35	25.65
10-19	40.48	27.37	45.16	28.62	44.9	28.59
≥20	21.13	7.26	16.13	9	17.35	8.93
Taking insulin, %						
No	52.38	82.73	51.61	79.43	51.02	79.52

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Yes	47.62	17.27	48.39	20.57	48.98	20.48
Examination and laboratory tests, median (IQR)						
Systolic blood pressure, mmHg	136.00(26.00)	133.00(24.00)	133.00(28.00)	134.00(24.00)	132.50(27.50)	134.00(24.00)
bmi	23.97(3.52)	24.40(4.06)	23.72(3.09)	24.38(3.99)	23.59(2.67)	24.39(4.02)
whr	0.91(0.09)	0.90(0.07)	0.93(0.07)	0.90(0.08)	0.91(0.08)	0.90(0.08)
whtr	0.53(0.07)	0.54(0.07)	0.52(0.06)	0.54(0.07)	0.52(0.06)	0.54(0.07)
BAI	27.48(5.13)	28.86(5.12)	26.89(3.70)	28.74(5.28)	26.89(3.99)	28.74(5.27)
Hba1c, %	7.80(2.20)	6.60(1.30)	8.00(2.40)	6.60(1.40)	8.00(2.50)	6.60(1.40)
C-reaction protein	1.35(2.03)	1.47(2.00)	1.19(1.68)	1.45(2.02)	1.17(1.69)	1.46(2.02)
Total cholesterol	4.73(1.37)	4.78(1.40)	4.91(1.55)	4.77(1.38)	4.90(1.56)	4.77(1.38)
Triglycerides	1.90(1.60)	1.91(1.58)	1.96(1.50)	1.90(1.58)	1.99(1.49)	1.90(1.58)
Low-density cholesterol	2.97(1.16)	3.00(1.28)	3.16(1.24)	2.98(1.25)	3.15(1.23)	2.98(1.25)
High-density cholesterol	1.22(0.47)	1.22(0.51)	1.21(0.50)	1.22(0.50)	1.21(0.50)	1.22(0.50)
Creatinine	76.00(28.00)	69.00(25.00)	79.00(26.00)	70.00(25.00)	80.00(27.00)	70.00(25.00)
Microalbuminuria	1.96(8.22)	0.85(2.29)	2.54(9.62)	0.91(2.48)	2.54(9.89)	0.91(2.48)
Uric acid	374.00(123.00)	368.00(128.00)	357.00(144.00)	369.00(128.00)	355.50(132.00)	369.00(128.00)
Axial length, mm	23.25(1.20)	23.44(1.19)	23.19(1.15)	23.43(1.20)	23.16(1.17)	23.43(1.20)

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4 153 than that in patients who were normal weight or obese (Figure 2, Table 2). However, there was
5
6 154 no significance in the association of BMI with any DR in the univariate binary or ordinal logistic
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9 155 model.

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11 156 After adjusted for gender and age, obesity presented as a protective factor for VTDR (odds
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14 157 ratio [or]=0.57, [95%CI, 0.33-0.96], p for trend = 0.028, Supplementary Table S1). The
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17 158 association remained after the regression model was additionally adjusted for lipid metabolism
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20 159 parameter (Supplementary Table S2).

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22 160 In the full model that further adjusted for continuous variables (age, systolic blood pressure,
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25 161 HbA1c, c-reaction protein, total cholesterol, triglycerides, low-density cholesterol, high-density
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28 162 cholesterol, creatinine, microalbuminuria, uric acid, and axial length) and categorical variables
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31 163 (sex, smoking history, drinking history, education, duration of diabetes, and insulin use), the
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34 164 association of BMI became significant with both DME and VTDR (for DME, p for trend =
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37 165 0.031; for VTDR, p for trend = 0.016, Table 3-1). Obesity was inversely associated with DME
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40 166 and VTDR with a decreased OR (for DME, or=0.40, [95%CI, 0.16-0.96]; for VTDR, or=0.37,
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42
43 167 [95%CI, 0.16-0.87], Table 3-1). However, the association was only significant in female
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46 168 patients (for DME, p for trend =0.021, or of obesity =0.10, [95%CI, 0.01-0.77]; for VTDR, p
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48
49 169 for trend =0.015, or of obesity =0.09, [95%CI, 0.01-0.76], Table 3-2), but not in male patients
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51
52 170 (Table 3-3).

171 **Association of WHR with any DR and severe DR**

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54 172 The prevalence of DR, DME and VTDR was the highest in the fourth quarter of WHR
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57 173 (Q4-WHR) (Figure 2, Table 2). In the univariable logistic regression model, Q4-WHR
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59
60 174 presented as a risk factor for DR (in the binary model, or=2.17, [95%CI, 1.13-4.17]; in the

Table 2. The prevalence of DR, DME and VTDR in different groups of the obesity-related indexes.

	No. of patients	DR prevalence, %	DME prevalence, %	VTDR prevalence, %
BMI, kg/m ² (n=2245)				
18.5-22.9 (normal weight)	683	14.20	4.25	4.54
23.0-25.0 (over weight)	615	17.24	4.88	5.37
≥25.0 (obese)	947	12.99	2.96	2.96
WHR, (n=483)				
Quarter 1	124	13.71	2.42	3.23
Quarter 2	117	17.95	5.13	5.13
Quarter 3	121	11.57	1.65	2.48
Quarter 4	121	25.62	8.26	8.26
WHtR, (n=1484)				
Quarter 1	371	16.17	5.12	5.39
Quarter 2	373	16.09	5.90	6.17
Quarter 3	369	14.09	4.07	4.07
Quarter 4	371	14.29	1.89	1.89
BAI, (n=483)				
Quarter 1	121	26.45	7.44	8.26
Quarter 2	121	17.36	4.13	4.13
Quarter 3	121	12.40	4.13	4.13
Quarter 4	120	14.17	1.67	2.50

Table 3-1 The OR of BMI, WHR, WHtR, and BAI in the binary logistic regression model additionally adjusted for other variables in all patients.

Footnotes: These variables included continuous variables (e.g., age, systolic blood pressure, HbA1c, c-reaction protein, total cholesterol, triglycerides, low-density cholesterol, high-density cholesterol, creatinine, microalbuminuria, uric acid, and axial length) and categorical variables (e.g., sex, smoking history, drinking history, education, duration of diabetes, and insulin use). DR, DME and VTDR were set as outcomes of the regression model, respectively.

	DR		DME		VTDR	
	Odds ratio (95%CI)	P value	Odds ratio (95%CI)	P value	Odds ratio (95%CI)	P value
BMI, kg/m²						
18.5-22.9 (normal weight)	Ref.		Ref.		Ref.	
23.0-25.0 (overweight)	0.82(0.52, 1.29)	0.393	1.01(0.43, 2.37)	0.989	1.03(0.46, 2.32)	0.946
≥25.0 (obese)	0.72(0.47, 1.10)	0.131	0.40(0.16, 0.96)	0.041	0.37(0.16, 0.87)	0.023
P for trend		0.134		0.031		0.016
WHR						
Quarter 1	Ref.		Ref.		Ref.	
Quarter 2	0.94(0.39, 2.29)	0.900	2.77(0.30, 25.73)	0.370	1.56(0.22, 10.86)	0.655
Quarter 3	0.49(0.19, 1.25)	0.136	0.79(0.09, 6.96)	0.830	0.62(0.11, 3.35)	0.579
Quarter 4	1.06(0.46, 2.45)	0.893	3.21(0.42, 24.78)	0.263	1.98(0.34, 11.61)	0.450
P for trend		0.834		0.459		0.645
WHtR						
Quarter 1	Ref.		Ref.		Ref.	
Quarter 2	1.07(0.61, 1.87)	0.820	3.04(1.04, 8.85)	0.041	2.74(1.01, 7.43)	0.048
Quarter 3	0.64(0.35, 1.16)	0.142	1.13(0.31, 4.03)	0.856	0.93(0.28, 3.07)	0.906
Quarter 4	0.81(0.44, 1.48)	0.494	0.57(0.13, 2.59)	0.468	0.48(0.11, 2.09)	0.330
P for trend		0.234		0.252		0.133
BAI						
Quarter 1	Ref.		Ref.		Ref.	
Quarter 2	0.77(0.35, 1.69)	0.512	1.15(0.29, 4.52)	0.845	1.05(0.29, 3.74)	0.943
Quarter 3	0.60(0.26, 1.37)	0.226	0.89(0.19, 4.13)	0.879	0.77(0.19, 3.08)	0.706
Quarter 4	0.57(0.23, 1.39)	0.216	0.63(0.11, 3.55)	0.605	0.92(0.22, 3.77)	0.909
P for trend		0.191		0.610		0.769

Table 3-2 The OR of BMI, WHR, WHtR, and BAI in the binary logistic regression model additionally adjusted for other variables in female patients.

Footnotes: DR, DME and VTDR were set as outcomes of the regression model, respectively.

	DR		DME		VTDR	
	Odds ratio (95%CI)	P valve	Odds ratio (95%CI)	P valve	Odds ratio (95%CI)	P valve
BMI, kg/m2						
18.5-22.9 (normal weight)	Ref.		Ref.		Ref.	
23.0-25.0 (overweight)	0.89(0.49, 1.62)	0.708	0.68(0.17, 2.68)	0.582	0.57(0.15, 2.17)	0.412
≥25.0 (obese)	0.77(0.43, 1.39)	0.392	0.10(0.01, 0.77)	0.027	0.09(0.01, 0.76)	0.027
P for trend		0.392		0.021		0.015
WHR						
Quarter 1	Ref.		Ref.		Ref.	
Quarter 2	1.31(0.46, 3.75)	0.610	1.42(0.02, 81.66)	0.866	0.78(0.02, 29.41)	0.894
Quarter 3	0.25(0.04, 1.34)	0.106	*	*	*	*
Quarter 4	1.20(0.40, 3.55)	0.748	3.52(0.20, 61.43)	0.389	2.21(0.26, 18.92)	0.470
P for trend		0.617		0.459		0.786
WHtR						
Quarter 1	Ref.		Ref.		Ref.	
Quarter 2	1.36(0.60, 3.09)	0.466	6.79(1.19, 38.57)	0.031	7.38(1.48, 36.77)	0.015
Quarter 3	0.70(0.30, 1.67)	0.421	*	*	*	*
Quarter 4	1.10(0.47, 2.56)	0.828	0.41(0.06, 2.63)	0.347	0.40(0.06, 2.73)	0.351
P for trend		0.884		0.065		0.049
BAI						
Quarter 1	Ref.		Ref.		Ref.	
Quarter 2	1.11(0.26, 4.78)	0.889	0.31(0.01, 12.27)	0.534	0.30(0.01, 8.98)	0.487
Quarter 3	0.66(0.15, 2.93)	0.582	0.83(0.04, 15.46)	0.898	0.80(0.11, 5.86)	0.822
Quarter 4	0.73(0.17, 3.11)	0.673	0.26(0.01, 6.94)	0.425	0.76(0.14, 4.26)	0.758
P for trend		0.512		0.653		0.857

* No observation.

Table 3-3 The OR of BMI, WHR, WHtR, and BAI in the binary logistic regression model additionally adjusted for other variables in male patients.

Footnotes: DR, DME and VTDR were set as outcomes of the regression model, respectively.

	DR		DME		VTDR	
	Odds ratio (95%CI)	P valve	Odds ratio (95%CI)	P valve	Odds ratio (95%CI)	P valve
BMI, kg/m²						
18.5-22.9 (normal weight)	Ref.		Ref.		Ref.	
23.0-25.0 (overweight)	0.61(0.29, 1.27)	0.182	1.63(0.46, 5.74)	0.448	1.84(0.54, 6.22)	0.328
≥25.0 (obese)	0.59(0.29, 1.19)	0.144	0.73(0.23, 2.38)	0.605	0.71(0.22, 2.27)	0.565
P for trend		0.183		0.411		0.326
WHR						
Quarter 1	Ref.		*	*	*	*
Quarter 2	0.64(0.12, 3.39)	0.602	Ref.		Ref.	
Quarter 3	0.61(0.14, 2.73)	0.514	0.40(0.06, 2.78)	0.354	0.53(0.09, 3.02)	0.472
Quarter 4	1.07(0.27, 4.29)	0.919	1.35(0.18, 9.92)	0.771	1.55(0.21, 11.45)	0.669
P for trend		0.777		0.190		0.136
WHtR						
Quarter 1	Ref.		Ref.		Ref.	
Quarter 2	0.75(0.33, 1.70)	0.494	1.85(0.53, 6.52)	0.337	1.43(0.44, 4.66)	0.557
Quarter 3	0.48(0.19, 1.18)	0.109	1.39(0.35, 5.56)	0.643	1.06(0.29, 3.88)	0.927
Quarter 4	0.56(0.21, 1.50)	0.248	0.68(0.09, 5.40)	0.718	0.57(0.07, 4.64)	0.601
P for trend		0.124		0.714		0.567
BAI						
Quarter 1	Ref.		Ref.		Ref.	
Quarter 2	0.57(0.19, 1.75)	0.327	1.61(0.36, 7.12)	0.530	1.55(0.38, 6.33)	0.544
Quarter 3	0.60(0.22, 1.67)	0.330	0.41(0.04, 3.90)	0.438	0.35(0.04, 3.04)	0.339
Quarter 4	0.46(0.08, 2.80)	0.403	*	*	*	*
P for trend		0.243		0.464		0.399

* No observation.

Table 4. The odds ratio (OR) of BMI, WHR, WHtR, and BAI in the univariate logistic regression model. Footnotes: DR, DME and VTDR were set as outcomes of the regression model, respectively.

	Binary regression model of DR		Ordinal regression model of DR		Binary regression model of DME		Binary regression model of VTDR	
	OR (95%CI)	P valve	OR (95%CI)	P valve	OR (95%CI)	P valve	Odds ratio (95%CI)	P valve
BMI, kg/m2								
18.5-22.9 (normal weight)	Ref.		Ref.		Ref.		Ref.	
23.0-25.0 (overweight)	1.26(0.93, 1.70)	0.133	1.28(0.95, 1.72)	0.109	1.16(0.69, 1.95)	0.585	1.19(0.72, 1.97)	0.492
≥25.0 (obese)	0.90(0.68, 1.20)	0.479	0.89(0.67, 1.18)	0.425	0.69(0.40, 1.17)	0.164	0.64(0.38, 1.08)	0.094
P for trend		0.381		0.329		0.147		0.083
WHR								
Quarter 1	Ref.		Ref.		Ref.		Ref.	
Quarter 2	1.38(0.69, 2.76)	0.368	1.39(0.69, 2.77)	0.355	2.18(0.53, 8.93)	0.279	1.62(0.45, 5.90)	0.463
Quarter 3	0.82(0.39, 1.75)	0.615	0.85(0.40, 1.80)	0.669	0.68(0.11, 4.13)	0.673	0.76(0.17, 3.48)	0.727
Quarter 4	2.17(1.13, 4.17)	0.021	2.25(1.18, 4.32)	0.014	3.63(0.97, 13.54)	0.055	2.70(0.82, 8.87)	0.101
P for trend		0.056		0.040		0.093		0.152
WHtR								
Quarter 1	Ref.		Ref.		Ref.		Ref.	
Quarter 2	0.99(0.67, 1.47)	0.974	0.99(0.67, 1.46)	0.962	1.16(0.62, 2.18)	0.643	1.15(0.62, 2.14)	0.651
Quarter 3	0.85(0.57, 1.27)	0.430	0.86(0.57, 1.28)	0.457	0.79(0.39, 1.57)	0.494	0.74(0.37, 1.48)	0.397
Quarter 4	0.86(0.58, 1.29)	0.475	0.86(0.57, 1.28)	0.444	0.36(0.15, 0.86)	0.021	0.34(0.14, 0.81)	0.015
P for trend		0.358		0.344		0.015		0.009
BAI								
Quarter 1	Ref.		Ref.		Ref.		Ref.	
Quarter 2	0.64(0.34, 1.19)	0.158	0.61(0.33, 1.13)	0.117	0.54(0.17, 1.65)	0.277	0.48(0.16, 1.44)	0.191
Quarter 3	0.43(0.22, 0.85)	0.015	0.43(0.22, 0.84)	0.014	0.54(0.17, 1.65)	0.277	0.48(0.16, 1.44)	0.191
Quarter 4	0.50(0.26, 0.97)	0.039	0.49(0.25, 0.94)	0.031	0.21(0.04, 1.00)	0.05	0.28(0.08, 1.06)	0.061
P for trend		0.017		0.015		0.042		0.051

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4 175 ordinal model, $or=2.25$, [95%CI, 1.18-4.32], Table 4). When DME and VTDR were set as the
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7 176 outcome of the model, WHR presented a similar trend, although it was not significant.

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9 177 After the logistic regression model was adjusted for sex and age, Q4-WHR remained a risk
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12 178 factor for DR ($or=2.02$, [95% CI, 1.03-3.98], Supplementary Table S1). The association
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15 179 remained independent of the lipid metabolism parameter (Supplementary Table S2). However,
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17 180 in the full model, the association of WHR with DR and severe DR presented a similar trend,
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20 181 but was not significant (Table 3-1).

21 22 182 **Association of WHtR with any DR and severe DR**

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25 183 The prevalence of DR decreased slightly with the growth of WHtR, while the prevalence
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28 184 of DME and VTDR was the highest in the Q2-WHtR, and then decreased (Table 2). In the
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31 185 univariate regression model, Q4-WHtR presented as a significant protective factor for DME
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33 186 ($or=0.36$, [95%CI, 0.15-0.86], Table 4) and VTDR, ($or=0.34$, [95%CI, 0.14-0.81]).

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35 187 In the logistic regression model adjusted for sex and age, Q4-WHtR remained as a
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38 188 protective factor of VTDR ($or=0.40$, [95% CI, 0.16-0.96], Supplementary Table S1),
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41 189 independent of lipid metabolism parameter (Supplementary Table S2). In the full model, Q2-
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44 190 WHtR presented as a significant risk factor of DME ($or=3.04$, [95 %CI, 1.04-8.85], Table 3-1)
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47 191 and VTDR ($or=2.74$, [95%CI, 1.01-7.43]). The association was also more significant in female
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50 192 patients (for DME, p for trend =0.065, or of Q2-WHtR =6.79, [95%CI, 1.19-38.57]; for VTDR,
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53 193 p for trend =0.049, or of Q2-WHtR =7.38, [95%CI, 1.48-36.77], Table 3-2), but not in male
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56 194 patients either (Table 3-2).

57 58 195 **Association of BAI with any DR and severe DR**

59 196 The prevalence of DR and severe VTDR showed a downward trend with the increase of
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4 197 BAI (Figure 2, Table 2). However, in the univariate logistic regression model, increased BAI
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6 198 was associated with a decreased risk of DR (Table 4). After adjusted for sex and age, the
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9 199 association became less significant, while in the full model, the association with either any DR,
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12 200 DME or VTDR was not significant.

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17 202 **Discussion**

19 203 In this study, we enrolled 2,305 participants and analyzed the association of obesity with
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22 204 any DR, DME and VTDR. There are three main findings in our study. First, only 29.6% of
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25 205 diabetic patients had normal weight, while as high as 67.8% of diabetic patients were
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27 206 overweight or obese. Second, obesity (BMI>25.0kg/m²) presented as a significant protective
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30 207 factor of VTDR, while Q2-WHtR presented as a significant risk factor. However, both of the
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33 208 associations were only significant in female patients, but not in male patients. Third, as the first
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35 209 study analyzing the association between BAI and DR, we found a significant negative
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38 210 association in the univariate logistic regression model, while the association became less
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41 211 significant in the multivariable model.

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43 212 Previous studies recognized obesity as a critical component of metabolic syndrome, which
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45 213 induces insulin resistance and advances the development of type 2 diabetes^{2,3}. Therefore, weight
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48 214 control is usually recommended in the management of diabetes and several systemic diseases
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51 215 to reduce the prevalence of complications^{3,12,13}. However, in this study, three obesity-related
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53 216 indexes, BMI, WHtR, and BAI, were all negatively associated with DR. The result presented
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56 217 as an "obesity paradox", which was also presented in several previous studies¹⁴⁻¹⁶. Moreover, it
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59 218 was more significant in the association with VTDR. The first possible reason would be that
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4 219 VTDR, presented and DME or PDR, was more likely to appear in the patients with advanced
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6 220 diabetes. Advanced diabetes would manifest as weight loss as one of the metabolic
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9 221 complications, contributing to the inverse association of obesity with DR. Second, BMI could
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11 222 hardly differentiate general obesity and centripetal obesity, which may play a different role in
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14 223 the progress of diabetes. Third, all the participants were from the community. They were
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17 224 diagnosed with diabetes in the hospital before the enrollment. The patients who had severe
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19 225 complications, low willingness to seek doctor's help or mobility problems, would be limited,
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22 226 contributing to the selection bias in the study.

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25 227 Although obesity was recognized as one of the important biomarkers inducing insulin
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27 228 resistance¹⁷, the obesity paradox has prevented scientists from making recommendations on
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30 229 weight management for diabetic patients. Several studies have revealed a positive association
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32 230 between centripetal obesity and chronic inflammation^{18,19}, which may contribute to the positive
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35 231 correlation between centripetal obesity (presented as higher WHR) and diabetic progression²⁰.
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38 232 However, in our study, as the indicator of centripetal obesity, Q2-WHtR associated positively
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40 233 with DR, and WHtR generally shows an opposite trend, indicating a nonlinear relationship
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43 234 between centripetal obesity. It also demonstrated WHtR as a more critical factor of DR as well
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45 235 as the traditional index BMI.

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48 236 Our study also found that the associations between obesity-related index (both BMI and
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50 237 WHR) and VTDR were only significant in female patients, indicating that female patients
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53 238 would have a higher risk with the increase of centripetal obesity. The sex-specific obesity-
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56 239 diabetes association has been reported in several studies, but the association between obesity-
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58 240 related indexes (including BMI, WHR, WHtR, BAI) and diabetic retinopathy was seldom
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4 241 reported. We furthered analyzed the sex-specific distribution regarding different obesity-related
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6 242 indexes (Figure 3). Male patients have a significantly higher WHR, lower WHtR and lower
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9 243 BAI. Therefore, weight control management and standard weight range should be made
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12 244 regarding different sex in diabetic patients.

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14 245 There are some other limitations in this study. First, the measurement of waist
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16 246 circumference and hip circumference was not performed on every participant. Therefore, we
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19 247 are unable to put BMI, WHR, WHtR, and BAI in the full model at the same time. In the sex-
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22 248 specific regression model, there was no positive observation in several groups (Q3-WHR and
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24 249 Q3-WHtR in female patients, Q-1-WHR and Q4-BAI in male patients). Second, although we
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27 250 used robust regression to make the odds ratio more robust, we did not exclude the influence of
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30 251 collinearity in the full model, which may contribute to the variation of the association of factors
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33 252 such as BAI with DR. Third, the participants with diabetes in our study were free from cognitive
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35 253 impairments and were referred to Zhongshan Ophthalmic Center from the community health
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38 254 centers. These patients usually had a less severe condition than the patients who were less
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40 255 willing to undertake routine examination in the community health centers because of mobility
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43 256 problems or less attention on their health problems, affecting the generalizability of the results.

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45 257 In summary, this study provides medical data of 2,305 participants, and analyzed the
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48 258 relationship between obesity and DR. The results presented general obesity and centripetal
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51 259 obesity as a protective factor in the development of DR, which was more significant in female
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54 260 patients. Because the interactions between obesity and DR is not completely clear, further
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57 261 researches are needed to focus on the improvement of sex-specific weight management in
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59 262 diabetic patients regarding different sex.

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4 263 **Contributors**

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6 264 W Huang and W Wei conceived and designed the study. W Li, W Wei, X Gong, L Wang,
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9 265 J Meng, Y Li, and K Xiong collected and interpreted the data. W Li and W Wei carried out the
10
11 266 statistical analysis. W Li wrote the manuscript. W Huang, W Wang, and X Gong reviewed and
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14 267 edited the manuscript. All authors have seen the final version of the manuscript and approved
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17 268 it for publication.
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26
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34
35 275 study; collection, management, analysis and interpretation of the data; preparation, review or
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38 276 approval of the manuscript; and decision to submit the manuscript for publication.
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43 278 **Declaration of Interests**

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45 279 The authors declare no competing financial interests.
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3 **Figure Legend**
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7 **Figure 1. International Clinical Severity Scale of Diabetic Retinopathy and Diabetic**
8 **Macular Edema.** Footnotes: DR: diabetic retinopathy; NPDR: non-proliferative diabetic
9 retinopathy; PDR: proliferative diabetic retinopathy; IRMA: intraretinal microvascular
10 abnormalities; DME: diabetic macular edema.
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16 **Figure 2. The prevalence of diabetic retinopathy (DR) and severe DR (diabetic**
17 **retinopathy, DME, and vision threatening diabetic retinopathy, VTDR) in different**
18 **groups of the obesity-related indexes.** Footnotes: BMI: Body mass index. WHR: Waist to
19 hip ratio. WHtR: waist to height ratio. BAI: Body adiposity index.
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26 **Figure 3. The number of male and female patients in different groups of the obesity-**
27 **related indexes**
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Severity level	Findings after pupil dilation	Any DR	DME	VTDR
DR scale				
No DR	No abnormalities			
Mild NPDR	Microaneurysms only			
Moderate NPDR	More than just microaneurysms but less than Severe NPDR			
Severe NPDR	Any of the following: <ul style="list-style-type: none"> • >20 intraretinal hemorrhages in each of 4 quadrants; • Definite venous beading in 2+ quadrants; • Prominent IRMA in 1+ quadrant And no signs of proliferative retinopathy			
PDR	One or more of the following: <ul style="list-style-type: none"> • Neovascularization; • Vitreous/preretinal hemorrhage 			
DME scale				
No DME	No apparent retinal thickening or hard exudates in posterior pole			
DME	Some retinal thickening or hard exudates in posterior pole: <ul style="list-style-type: none"> • Mild: some retinal thickening or hard exudates in posterior pole but distant from the center of the macular; • Moderate: retinal thickening or hard exudates approaching the center of the macula but not involving the center; • Severe: Retinal thickening or hard exudates involving the center of the macular. 			

Figure 1. International Clinical Severity Scale of Diabetic Retinopathy and Diabetic Macular Edema. Footnotes: DR: diabetic retinopathy; NPDR: non-proliferative diabetic retinopathy; PDR: proliferative diabetic retinopathy; IRMA: intraretinal microvascular abnormalities; DME: diabetic macular edema.

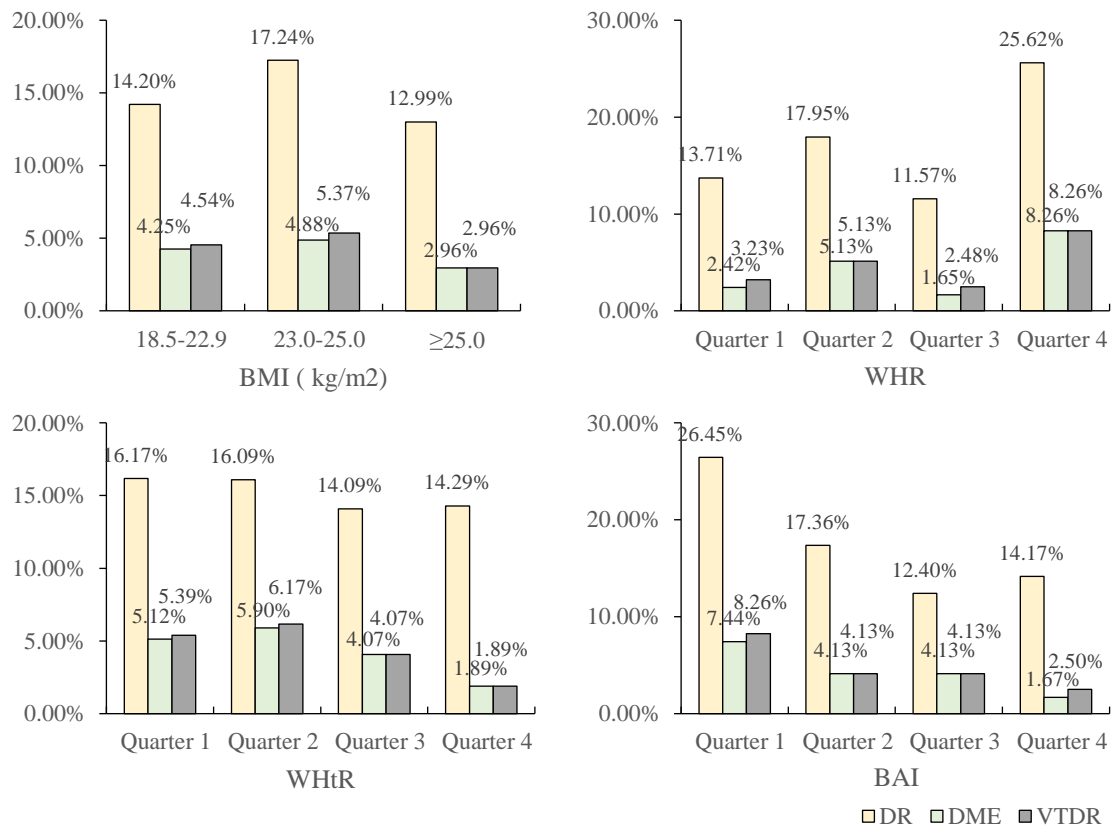


Figure 2. The prevalence of diabetic retinopathy (DR) and severe DR (diabetic retinopathy, DME, and vision threatening diabetic retinopathy, VTDR) in different groups of the obesity-related indexes. Footnotes: BMI: Body mass index. WHR: Waist to hip ratio. WHtR: waist to height ratio. BAI: Body adiposity index.

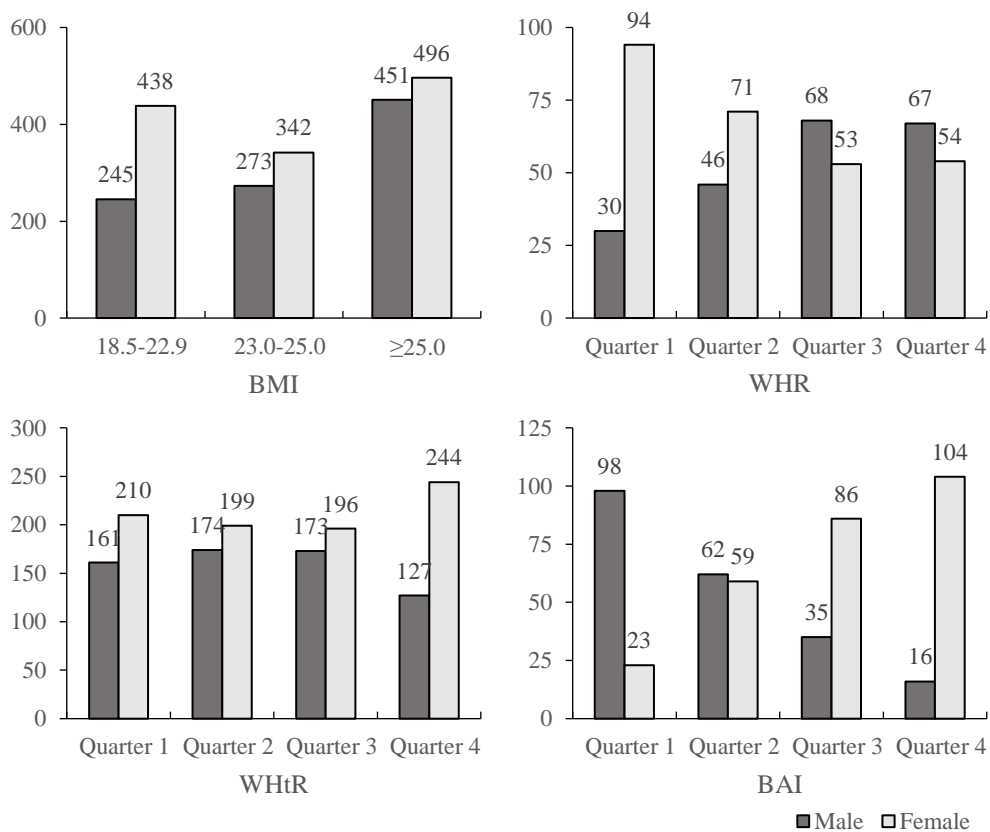


Figure 3. The number of male and female patients in different groups of the obesity-related indexes.

Supplementary Materials

Table S1 The odds ratio (OR) of Body mass index (BMI), Waist to hip ratio (WHR), waist to height ratio (WHtR), and Body adiposity index (BAI) in the binary logistic regression model adjusted for age and sex. Footnotes: diabetic retinopathy (DR), diabetic macular edema (DME) and vision threatening diabetic retinopathy (VTDR) were set as outcomes of the regression model, respectively.

	DR		DME		VTDR	
	Odds ratio (95%CI)	P valve	Odds ratio (95%CI)	P valve	Odds ratio (95%CI)	P valve
BMI, kg/m²						
18.5-22.9 (normal weight)	Ref.		Ref.		Ref.	
23.0-25.0 (overweight)	1.22(0.90, 1.65)	0.200	1.09(0.64, 1.84)	0.758	1.12(0.67, 1.86)	0.660
≥25.0 (obese)	0.85(0.64, 1.14)	0.275	0.61(0.35, 1.04)	0.067	0.57(0.33, 0.96)	0.034
P for trend		0.204		0.056		0.028
WHR						
Quarter 1	Ref.		Ref.		Ref.	
Quarter 2	1.32(0.66, 2.67)	0.434	2.18(0.52, 9.10)	0.283	1.60(0.43, 5.93)	0.478
Quarter 3	0.77(0.35, 1.67)	0.503	0.68(0.11, 4.30)	0.682	0.76(0.16, 3.59)	0.725
Quarter 4	2.02(1.03, 3.98)	0.041	3.61(0.92, 14.16)	0.065	2.65(0.77, 9.12)	0.123
P for trend		0.089		0.101		0.169
WHtR						
Quarter 1	Ref.		Ref.		Ref.	
Quarter 2	1.00(0.68, 1.48)	0.991	1.21(0.64, 2.28)	0.558	1.20(0.64, 2.23)	0.567
Quarter 3	0.87(0.58, 1.30)	0.495	0.84(0.42, 1.68)	0.620	0.79(0.40, 1.58)	0.509
Quarter 4	0.95(0.63, 1.42)	0.785	0.42(0.17, 1.02)	0.055	0.40(0.16, 0.96)	0.039
P for trend		0.627		0.046		0.029
BAI						
Quarter 1	Ref.		Ref.		Ref.	
Quarter 2	0.64(0.34, 1.23)	0.182	0.57(0.18, 1.84)	0.344	0.51(0.16, 1.60)	0.247
Quarter 3	0.44(0.21, 0.93)	0.031	0.62(0.18, 2.18)	0.456	0.55(0.16, 1.90)	0.348
Quarter 4	0.52(0.24, 1.13)	0.098	0.27(0.05, 1.56)	0.144	0.37(0.08, 1.69)	0.199
P for trend		0.060		0.166		0.201

Table S2 The OR of BMI, WHR, WHtR, and BAI in the binary logistic regression model adjusted for age, sex, and lipid metabolism parameter (total cholesterol, triglycerides, low-density cholesterol, and high-density cholesterol). Footnotes: DR, DME and VTDR were set as outcomes of the regression model, respectively.

	DR		DME		VTDR	
	Odds ratio (95%CI)	P value	Odds ratio (95%CI)	P value	Odds ratio (95%CI)	P value
BMI, kg/m²						
18.5-22.9 (normal weight)	Ref.		Ref.		Ref.	
23.0-25.0 (overweight)	1.24(0.91, 1.68)	0.175	1.10(0.64, 1.88)	0.729	1.13(0.67, 1.89)	0.649
≥25.0 (obese)	0.87(0.64, 1.17)	0.343	0.61(0.35, 1.06)	0.079	0.56(0.33, 0.97)	0.039
P for trend		0.251		0.065		0.030
WHR						
Quarter 1	Ref.		Ref.		Ref.	
Quarter 2	1.37(0.67, 2.78)	0.387	2.38(0.56, 10.10)	0.241	1.68(0.45, 6.35)	0.441
Quarter 3	0.81(0.36, 1.80)	0.604	0.78(0.12, 5.15)	0.795	0.79(0.16, 3.95)	0.776
Quarter 4	2.22(1.08, 4.55)	0.030	4.37(1.02, 18.80)	0.048	2.85(0.76, 10.69)	0.121
P for trend		0.066		0.074		0.165
WHtR						
Quarter 1	Ref.		Ref.		Ref.	
Quarter 2	0.97(0.65, 1.45)	0.874	1.26(0.65, 2.43)	0.492	1.22(0.64, 2.32)	0.537
Quarter 3	0.84(0.55, 1.28)	0.413	0.88(0.42, 1.81)	0.720	0.81(0.39, 1.65)	0.559
Quarter 4	0.90(0.59, 1.38)	0.639	0.43(0.17, 1.08)	0.072	0.40(0.16, 0.98)	0.046
P for trend		0.511		0.060		0.033
BAI						
Quarter 1	Ref.	Ref.	Ref.		Ref.	
Quarter 2	0.64(0.33, 1.23)	0.177	0.60(0.18, 1.96)	0.396	0.53(0.17, 1.72)	0.293
Quarter 3	0.43(0.20, 0.92)	0.030	0.64(0.18, 2.27)	0.486	0.55(0.16, 1.91)	0.348
Quarter 4	0.51(0.23, 1.12)	0.095	0.28(0.05, 1.65)	0.161	0.37(0.08, 1.72)	0.202
P for trend		0.059		0.186		0.200

STROBE Statement—checklist of items that should be included in reports of observational studies

Section/item	Item No	Recommendation	Reported on Page Number/Line Number	Reported on Section/Paragraph
Title and abstract	1	(a) Indicate the study’s design with a commonly used term in the title or the abstract		
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found		
Introduction				
Background/ rationale	2	Explain the scientific background and rationale for the investigation being reported		
Objectives	3	State specific objectives, including any prespecified hypotheses		
Methods				
Study design	4	Present key elements of study design early in the paper		
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection		
Participants	6	(a) Cohort study —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up Case-control study —Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls Cross-sectional study —Give the eligibility criteria, and the sources and methods of selection of participants		
		(b) Cohort study —For matched studies, give matching criteria and number of exposed and unexposed Case-control study —For matched studies, give matching criteria and the number of controls per case		
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable		
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group		
Bias	9	Describe any efforts to address potential sources of bias		
Study size	10	Explain how the study size was arrived at		
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why		

Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding		
		(b) Describe any methods used to examine subgroups and interactions		
		(c) Explain how missing data were addressed		
		(d) Cohort study —If applicable, explain how loss to follow-up was addressed Case-control study —If applicable, explain how matching of cases and controls was addressed Cross-sectional study —If applicable, describe analytical methods taking account of sampling strategy		
		(e) Describe any sensitivity analyses		
Results				
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed		
		(b) Give reasons for non-participation at each stage		
		(c) Consider use of a flow diagram		
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders		
		(b) Indicate number of participants with missing data for each variable of interest		
		(c) Cohort study —Summarise follow-up time (eg, average and total amount)		
Outcome data	15*	Cohort study —Report numbers of outcome events or summary measures over time		
		Case-control study —Report numbers in each exposure category, or summary measures of exposure		
		Cross-sectional study —Report numbers of outcome events or summary measures		
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included		
		(b) Report category boundaries when continuous variables were categorized		
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period		
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses		
Discussion				
Key results	18	Summarise key results with reference to study objectives		
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias		

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Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence		
Generalisability	21	Discuss the generalisability (external validity) of the study results		
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based		

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Association of Different Kinds of Obesity with Diabetic Retinopathy in Patients with Type 2 Diabetes

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4 **1 Title Page**

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6 **2 Association of Different Kinds of Obesity with Diabetic Retinopathy in Patients**
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9 **3 with Type 2 Diabetes**

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4 **19 Abstract**

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6 **20 Introduction** Although obesity is one of the established risk factors of diabetes mellitus, the
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21 relationship between obesity and diabetic retinopathy (DR) remains unclear in different studies. This
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23 study aimed to investigate the association of diabetic retinopathy (DR) with four obesity-related
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25 indexes, including body mass index (BMI), waist to hip ratio (WHR), waist to height ratio (WHtR) and
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27 body adiposity index (BAI) in diabetic patients.

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25 Research Design and Methods We prospectively enrolled 2305 diabetic patients (2305 eyes) in the
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27 Guangzhou Diabetic Eye Study (GDES) between Nov2017 and Dec 2019 to investigate the prevalence
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29 and the association of different types of obesity with DR using BMI, WHR, WHtR and BAI. DR,
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31 diabetic macular edema (DME) and vision-threatening diabetic retinopathy(VTDR) were selected as
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33 primary outcomes. BMI was categorized as normal (18.5-22.9kg/m²), overweight(23.0-25.0kg/m²), and
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35 obese(>25.0kg/m²); WHR, WHtR and BAI were categorized into quarters.

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31 Results A total of 336 (14.58%), 93 (4.03%) and 98 (4.25%) developed DR, DME and VTDR
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33 respectively. The prevalence of DR, DME and VTDR was higher in patients with higher BMI/WHR or
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35 lower WHtR/BAI. In the univariate regression model, WHR correlated positively with DR, while WHtR
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37 and BAI correlated negatively with DR, DME and VTDR. The association remained independent of
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39 age, sex and lipid metabolism parameters. In the multivariate model, obese presented as a protective
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41 factor for DME and VTDR, while the second quarter of WHtR(Q2-WHtR) presented as a risk factor.

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37 Conclusions As high as 67.8% of diabetic patients were overweight or obese. Obese presented as a
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39 significant protective factor of VTDR, while Q2-WHtR presented as a significant risk factor. Therefore,
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41 more attention should be paid to centripetal obesity as well as general obesity. Further research is also
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43 needed to focus on the improvement of sex-specific weight management in diabetic patients.

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6 42 **Keywords** Diabetes mellitus, diabetic retinopathy, obesity, BMI, WHR, WHtR, BAI

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11 44 **Article summary: (Strengths and limitations of this study)**

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14 45 1. This study is a combined study that analyzed the association of four obesity-related indexes

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17 46 (BMI, WHR, WHtR, and BAI) with the presence and the severity of diabetic retinopathy.

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20 47 2. Any diabetic retinopathy, diabetic macular edema (DME), and vision-threatening diabetic

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22 48 retinopathy (VTDR) were selected as primary outcomes.

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25 49 3. DR and DME were diagnosed and graded according to the International Clinical Severity

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27 50 Scale of Diabetic Retinopathy and Diabetic Macular Edema (Figure 1), using 7-position fundus

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30 51 photos of participants.

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32 52 4. To reduce the examination time and improve the compliance of participants, the

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35 53 measurement of waist circumference and hip circumference was not performed on every

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38 54 participant, while eventually 483 patients have undergone all the measurements.

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40 55 5. The diabetic participants with severe conditions (e.g. very poor eyesight, past DR treatment

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43 56 history, occurred with other combined eye diseases that could affect the retinal thickness, etc.)

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46 57 were excluded from our study.

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59 **Introduction**

60 Diabetic retinopathy (DR) is one of the most common complications of diabetes mellitus
61 and is a leading cause of vision loss and blindness throughout the world¹. It severely affects the
62 life quality of diabetic patients and increases the economic burden of treatment without timely
63 management¹. Although obesity is one of the established risk factors that correlated positively
64 with diabetes mellitus^{2,3}, the relationship between obesity and DR varies in different studies.
65 For instance, in a cross-sectional study that enrolled 50,464 Saudi diabetic patients, overweight
66 and obesity presented as a protective factor for DR⁴. However, in a meta-analysis of prospective
67 cohort studies, obesity correlated with a significant increase in DR incidence⁵. The methods to
68 improve the weight management of diabetic patients to decrease the presence and severity of
69 DR have become a major public health problem.

70 Body mass index (BMI) has been commonly used to assess weight level in the previous
71 study^{4,6,7}, but it could not distinguish whether a patient is general obese or abdominal obese.
72 Moreover, combined or separate studies about the association of waist to hip ratio (WHR), waist
73 to height ratio (WHtR), and body adiposity index (BAI) with DR are still limited. Studies to
74 explore the relationship between obesity and DR among Chinese people are also limited.

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

79 **Methods**

80 **Study design and participants**

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4 81 The Guangzhou Diabetic Eye Study (GDES) is an ongoing prospective study that enrolled
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6 82 diabetes patients from communities in Guangzhou. Before enrollment, the participants were
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9 83 diagnosed with diabetes in the general hospitals, and were registered and followed up in the
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11 84 community health centers. They were referred to Zhongshan Ophthalmic Center and underwent
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14 85 ophthalmic examinations and physical examinations at the baseline visit, one-year visit, and
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17 86 two-year visit. Demographic information and medical history were also collected at the same
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19 87 time. However, patients with any evidence of the following conditions were excluded: (I) best
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22 88 corrected visual acuity (BCVA) worse than 20/200, axial length > 30 mm or unmeasurable,
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25 89 spherical equivalent (SphE) \leq -12.0 degrees, astigmatism > 4 degrees, or intraocular pressure
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27 90 (IOP) > 21 mmHg in the right eye; (II) except DR, other combined eye diseases that could
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30 91 affect retinal thickness in the right eye, such as glaucoma, age-related macular degeneration,
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33 92 and retinal detachment; (III) surgery or invasive treatment or laser treatment history on the right
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36 93 eye; (IV) severe systemic diseases, such as uncontrolled hypertension, severe cardiovascular
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39 94 and cerebrovascular disease, malignant tumors, and nephritis; (V) general surgery history, such
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42 95 as heart bypass, thrombolysis, and kidney transplantation; (VI) cognitive disorders or mental
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45 96 illness that would hinder the patient's cooperation with tests; and (VII) inability to obtain clear
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48 97 fundus or SS-OCT images because of refractive media opacity or non-cooperation.

48 98 A total of 2372 diabetic patients participated and completed the examinations between
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51 99 Nov 2017 and Dec 2019. Sixty-seven participants with ungradable fundus images were
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54 100 excluded, and 2305 participants were finally included. The baseline data of demographic
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57 101 information, medical history, ophthalmic examinations, and physical examinations were
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60 102 extracted in the analysis. There was no missing data in the study.

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4 103 This study followed the tenets of the Declaration of Helsinki and was approved by the
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6 104 Institutional Review Board of Zhongshan Ophthalmic Center (2017KYPJ094), Guangzhou,
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9 105 China. Written informed consent was obtained from all participants. Patient records and
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12 106 information were anonymized and de-identified before analysis.

107 **Demographic information, medical history, and biometric parameter assessment**

108 Demographic information and medical history (e.g., age, sex, education, smoking and
109 drinking history, duration of diabetes, and insulin use) were collected using a standardized
110 questionnaire. The previous medical records would be checked and confirmed by the doctors.
111 The physical examination, including a blood pressure test, blood test, biochemical test, and
112 urine test, was carried out by a certified nurse.

113 **Assessment of BMI, WHR, WHtR, and BAI**

114 The participants' weight (in kilograms), height (in meters), waist circumference (in
115 centimeters), and hip circumference were measured by certified nurses. Participants were
116 required to remove their shoes and the heavy object (e.g., mobile phones, keys, and wallets) on
117 them. Weight was measured using a weight scale. Height was measured using a measuring stick
118 on the weight scale. Waist and hip circumferences were assessed using a nonstretchable medical
119 tape. Waist circumference was taken at the smallest horizontal girth between the costal margins
120 and the iliac crests at the end of tidal expiration. Hip circumference was taken at the maximal
121 protuberance of the buttocks. Every participant underwent the weight and height measurement,
122 while 483 consecutive participants underwent hip circumference measurement, and 1484
123 consecutive participants underwent waist circumference measurement.

124 BMI was calculated as weight divided by height squared and was categorized into normal

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4 125 weight (18.5-22.9 kg/m²), overweight (23.0-25.0 kg/m²), and obese (>25.0 kg/m²), according
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6 126 to Asia-Pacific BMI cutoff points⁸⁻¹⁰. Sixty underweight participants (BMI <18.5 kg/m²) were
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9 127 not included because of the small sample size. WHR was calculated as waist circumference
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11 128 divided by hip circumference, while WHtR was calculated by dividing waist circumference by
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14 129 height. BAI was calculated as hip circumference divided by (height)^{1.5} minus 18. Because of
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17 130 the lack of standardized classifications, WHR, WHtR, and BAI were categorized in quarters.

131 **Assessment of DR, DME, and VTDR**

132 All the participants underwent ophthalmic examinations including vision test, intraocular
133 pressure test, anterior segment examination, intraocular lens (IOL) master test, mydriatic
134 fundus photography, and optical coherence tomography examination, by trained
135 ophthalmologists.

136 DR and DME were diagnosed and graded according to the International Clinical Severity
137 Scale of Diabetic Retinopathy and Diabetic Macular Edema (Figure 1), using 7-position fundus
138 photos of participants. Any DR, DME, and VTDR were selected as primary outcomes. Any DR
139 was defined as the presence of mild non-proliferative diabetic retinopathy (NPDR), moderate
140 NPDR, severe NPDR, or PDR. VTDR was defined as the presence of DME or PDR. For each
141 participant, only the data of the worse eye would be used. If the DR grades of both eyes were
142 consistent, then the right eye would be selected for analysis.

143 **Statistical analysis**

144 All analyses were performed using STATA statistical software (Stata version 14.0, Stata
145 Corp., College Station, TX). BMI, WHR, WHtR, and BAI classifications were used as both
146 continuous variables and categorical variables. To compare the differences in characteristics of

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4 147 participants with or without DR, DME, and VTDR, the Student t-test was used for continuous
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6 148 variables that were normally distributed, the Mann-Whitney U test was used for other
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9 149 continuous variables (creatinine and microalbuminuria), and the Chi-square test was used for
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12 150 categorical variables.

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14 151 The binary and ordinal logistic regression model was used to assess the association of BMI,
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16 152 WHR, WHtR, and BAI with the presence of any DR and VTDR. In special, the outcome of the
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19 153 ordinal logistic regression model of DR was set as no DR, mild NPDR, moderate NPDR, and VTDR
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22 154 (including PDR and DME). In the multivariate logistic model, the association was adjusted for
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25 155 potential confounding factors established in previous research. These factors included continuous
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27 156 variables (e.g., age, systolic blood pressure, HbA1c, c-reaction protein, total cholesterol, triglycerides,
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30 157 low-density cholesterol, high-density cholesterol, creatinine, microalbuminuria, uric acid, and axial
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32
33 158 length) and categorical variables (e.g., sex, smoking history, drinking history, education, duration of
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35 159 diabetes, and insulin use). P values less than 0.05 were considered statistically significant.

36 37 38 160 **Patient and public involvement statement**

39
40 161 Patients and/or the public were not involved in the design, or conduct, or reporting, or
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43 162 dissemination plans of this research.

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47 48 49 50 164 **Results**

51
52 165 In general, 336 (14.58%) participants developed DR, including 76 (3.30%) patients with
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55 166 mild NPDR, 197 (8.55%) patients with moderate NPDR, 45 (1.95%) patients with severe
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58 167 NPDR, 17 (0.74%) patients with PDR, and 93 (4.03%) patients with DME. 98 (4.25%) patients
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4 168 developed VTDR.
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6 169 Compared with participants who did not have DR, participants with DR had a younger
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8
9 170 age, a lower level of education, a longer duration of diabetes, and a higher proportion of males,
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11 171 smoking history, drinking history, and insulin use (Table 1). They also had a higher level of
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13 172 HbA1c, creatinine, microalbuminuria, and systolic blood pressure, but shorter axis length (all p
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15 173 <0.05). Moreover, their BMI, WHR, WHtR, and BAI were higher. According to Asia-Pacific
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17 174 BMI cutoff points, as high as 947 participants (41.1%) were obese, and 615 (26.7%) were
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19 175 overweight, while only 683 participants (29.6%) were normal weight.
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25 176 **Association of BMI with any DR, DME and VTDR**

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27 177 The prevalence of any DR, DME and VTDR in overweight diabetic patients was higher
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29 178 than that in patients who were normal weight or obese (Figure 2, Table 2). However, there was
30
31 179 no significance in the association of BMI with any DR in the univariate binary or ordinal logistic
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33 180 model.
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38 181 After adjusted for sex and age, obesity presented as a protective factor for VTDR (odds
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40 182 ratio [or]=0.57, [95%CI, 0.33-0.96], p for trend = 0.028, Supplementary Table S1). The
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42 183 association remained after the regression model was additionally adjusted for lipid metabolism
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44 184 parameter (Supplementary Table S2).
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48 185 In the full model that further adjusted for continuous variables (age, systolic blood pressure,
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50 186 HbA1c, c-reaction protein, total cholesterol, triglycerides, low-density cholesterol, high-density
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52 187 cholesterol, creatinine, microalbuminuria, uric acid, and axial length) and categorical variables
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54 188 (sex, smoking history, drinking history, education, duration of diabetes, and insulin use), the
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56 189 association of BMI became significant with both DME and VTDR (for DME, p for trend =
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Table 1. The characteristics of participants with or without diabetic retinopathy (DR), diabetic macular edema (DME) and vision threatening diabetic retinopathy (VTDR). Footnotes: BMI: Body mass index. WHR: Waist to hip ratio. WHtR: waist to height ratio. BAI: Body adiposity index.

	DR n=336	No DR n=1970	DME n=93	No DME n=2212	VTDR n=98	No VTDR n=2207
Medical history						
Age, median (IQR), year	64.0(10.0)	65.0(10.0)	62.0(9.0)	65.0(10.0)	61.5(9.0)	65.0(10.0)
Sex, %						
Female	49.4	58.35	43.01	57.64	42.86	57.68
Male	50.6	41.65	56.99	42.36	57.14	42.32
Smoking history, %						
No	81.88	86.29	83.12	85.76	82.5	85.79
Yes	18.12	13.71	16.88	14.24	17.5	14.21
Drinking history, %						
No	88.04	91.18	89.61	90.78	87.5	90.87
Yes	11.96	8.82	10.39	9.22	12.5	9.13
Education, %						
Educated	16.42	11.26	16	11.83	15.09	11.85
Not educated	83.58	88.74	84	88.17	84.91	88.15
Diabetes duration, %, year						
<5	18.15	39.21	21.51	36.75	20.41	36.84
5-9	20.24	26.16	17.2	25.63	17.35	25.65
10-19	40.48	27.37	45.16	28.62	44.9	28.59
≥20	21.13	7.26	16.13	9	17.35	8.93
Taking insulin, %						
No	52.38	82.73	51.61	79.43	51.02	79.52
Yes	47.62	17.27	48.39	20.57	48.98	20.48
Examination and laboratory tests, median (IQR)						

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5	Systolic blood pressure, mmHg	136.00(26.00)	133.00(24.00)	133.00(28.00)	134.00(24.00)	132.50(27.50)	134.00(24.00)
6	bmi	23.97(3.52)	24.40(4.06)	23.72(3.09)	24.38(3.99)	23.59(2.67)	24.39(4.02)
7	whr	0.91(0.09)	0.90(0.07)	0.93(0.07)	0.90(0.08)	0.91(0.08)	0.90(0.08)
8	whtr	0.53(0.07)	0.54(0.07)	0.52(0.06)	0.54(0.07)	0.52(0.06)	0.54(0.07)
9	BAI	27.48(5.13)	28.86(5.12)	26.89(3.70)	28.74(5.28)	26.89(3.99)	28.74(5.27)
10	Hba1c, %	7.80(2.20)	6.60(1.30)	8.00(2.40)	6.60(1.40)	8.00(2.50)	6.60(1.40)
11	C-reaction protein	1.35(2.03)	1.47(2.00)	1.19(1.68)	1.45(2.02)	1.17(1.69)	1.46(2.02)
12	Total cholesterol	4.73(1.37)	4.78(1.40)	4.91(1.55)	4.77(1.38)	4.90(1.56)	4.77(1.38)
13	Triglycerides	1.90(1.60)	1.91(1.58)	1.96(1.50)	1.90(1.58)	1.99(1.49)	1.90(1.58)
14	Low-density cholesterol	2.97(1.16)	3.00(1.28)	3.16(1.24)	2.98(1.25)	3.15(1.23)	2.98(1.25)
15	High-density cholesterol	1.22(0.47)	1.22(0.51)	1.21(0.50)	1.22(0.50)	1.21(0.50)	1.22(0.50)
16	Creatinine	76.00(28.00)	69.00(25.00)	79.00(26.00)	70.00(25.00)	80.00(27.00)	70.00(25.00)
17	Microalbuminuria	1.96(8.22)	0.85(2.29)	2.54(9.62)	0.91(2.48)	2.54(9.89)	0.91(2.48)
18	Uric acid	374.00(123.00)	368.00(128.00)	357.00(144.00)	369.00(128.00)	355.50(132.00)	369.00(128.00)
19	Axial length, mm	23.25(1.20)	23.44(1.19)	23.19(1.15)	23.43(1.20)	23.16(1.17)	23.43(1.20)
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4 190 0.031; for VTDR, p for trend = 0.016, Table 3). Obesity was inversely associated with DME
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6 191 and VTDR with a decreased OR (for DME, $or=0.40$, [95%CI, 0.16-0.96]; for VTDR, $or=0.37$,
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9 192 [95%CI, 0.16-0.87], Table 3). However, the association was only significant in female patients
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11 193 (for DME, p for trend =0.021, or of obesity =0.10, [95%CI, 0.01-0.77]; for VTDR, p for trend
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14 194 =0.015, or of obesity =0.09, [95%CI, 0.01-0.76], Table S3-1), but not in male patients (Table
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17 195 S3-2).

196 **Association of WHR with any DR and severe DR**

197 The prevalence of DR, DME and VTDR was the highest in the fourth quarter of WHR
198 (Q4-WHR) (Figure 2, Table 2). In the univariable logistic regression model, Q4-WHR
199 presented as a risk factor for DR (in the binary model, $or=2.17$, [95%CI, 1.13-4.17]; in the
200 ordinal model, $or=2.25$, [95%CI, 1.18-4.32], Table 4). When DME and VTDR were set as the
201 outcome of the model, WHR presented a similar trend, although it was not significant.

202 After the logistic regression model was adjusted for sex and age, Q4-WHR remained a risk
203 factor for DR ($or=2.02$, [95% CI, 1.03-3.98], Supplementary Table S1). The association
204 remained independent of the lipid metabolism parameter (Supplementary Table S2). However,
205 in the full model, the association of WHR with DR and severe DR presented a similar trend,
206 but was not significant (Table 3).

207 **Association of WHtR with any DR and severe DR**

208 The prevalence of DR decreased slightly with the growth of WHtR, while the prevalence
209 of DME and VTDR was the highest in the Q2-WHtR, and then decreased (Table 2). In the
210 univariate regression model, Q4-WHtR presented as a significant protective factor for DME
211 ($or=0.36$, [95%CI, 0.15-0.86], Table 4) and VTDR, ($or=0.34$, [95%CI, 0.14-0.81]).

Table 2. The prevalence of DR, DME and VTDR in different groups of the obesity-related indexes.

	No. of patients	DR prevalence, %	DME prevalence, %	VTDR prevalence, %
BMI, kg/m ² (n=2245)				
18.5-22.9 (normal weight)	683	14.20	4.25	4.54
23.0-25.0 (over weight)	615	17.24	4.88	5.37
≥25.0 (obese)	947	12.99	2.96	2.96
WHR, (n=483)				
Quarter 1	124	13.71	2.42	3.23
Quarter 2	117	17.95	5.13	5.13
Quarter 3	121	11.57	1.65	2.48
Quarter 4	121	25.62	8.26	8.26
WHtR, (n=1484)				
Quarter 1	371	16.17	5.12	5.39
Quarter 2	373	16.09	5.90	6.17
Quarter 3	369	14.09	4.07	4.07
Quarter 4	371	14.29	1.89	1.89
BAI, (n=483)				
Quarter 1	121	26.45	7.44	8.26
Quarter 2	121	17.36	4.13	4.13
Quarter 3	121	12.40	4.13	4.13
Quarter 4	120	14.17	1.67	2.50

Table 3 The OR of BMI, WHR, WHtR, and BAI in the binary logistic regression model additionally adjusted for other variables in all patients.

Footnotes: These variables included continuous variables (e.g., age, systolic blood pressure, HbA1c, c-reaction protein, total cholesterol, triglycerides, low-density cholesterol, high-density cholesterol, creatinine, microalbuminuria, uric acid, and axial length) and categorical variables (e.g., sex, smoking history, drinking history, education, duration of diabetes, and insulin use). DR, DME and VTDR were set as outcomes of the regression model, respectively.

	DR		DME		VTDR	
	Odds ratio (95%CI)	P value	Odds ratio (95%CI)	P value	Odds ratio (95%CI)	P value
BMI, kg/m²						
18.5-22.9 (normal weight)	Ref.		Ref.		Ref.	
23.0-25.0 (overweight)	0.82(0.52, 1.29)	0.393	1.01(0.43, 2.37)	0.989	1.03(0.46, 2.32)	0.946
≥25.0 (obese)	0.72(0.47, 1.10)	0.131	0.40(0.16, 0.96)	0.041	0.37(0.16, 0.87)	0.023
P for trend		0.134		0.031		0.016
WHR						
Quarter 1	Ref.		Ref.		Ref.	
Quarter 2	0.94(0.39, 2.29)	0.900	2.77(0.30, 25.73)	0.370	1.56(0.22, 10.86)	0.655
Quarter 3	0.49(0.19, 1.25)	0.136	0.79(0.09, 6.96)	0.830	0.62(0.11, 3.35)	0.579
Quarter 4	1.06(0.46, 2.45)	0.893	3.21(0.42, 24.78)	0.263	1.98(0.34, 11.61)	0.450
P for trend		0.834		0.459		0.645
WHtR						
Quarter 1	Ref.		Ref.		Ref.	
Quarter 2	1.07(0.61, 1.87)	0.820	3.04(1.04, 8.85)	0.041	2.74(1.01, 7.43)	0.048
Quarter 3	0.64(0.35, 1.16)	0.142	1.13(0.31, 4.03)	0.856	0.93(0.28, 3.07)	0.906
Quarter 4	0.81(0.44, 1.48)	0.494	0.57(0.13, 2.59)	0.468	0.48(0.11, 2.09)	0.330
P for trend		0.234		0.252		0.133
BAI						
Quarter 1	Ref.		Ref.		Ref.	
Quarter 2	0.77(0.35, 1.69)	0.512	1.15(0.29, 4.52)	0.845	1.05(0.29, 3.74)	0.943
Quarter 3	0.60(0.26, 1.37)	0.226	0.89(0.19, 4.13)	0.879	0.77(0.19, 3.08)	0.706
Quarter 4	0.57(0.23, 1.39)	0.216	0.63(0.11, 3.55)	0.605	0.92(0.22, 3.77)	0.909
P for trend		0.191		0.610		0.769

Table 4. The odds ratio (OR) of BMI, WHR, WHtR, and BAI in the univariate logistic regression model. Footnotes: DR, DME and VTDR were set as outcomes of the regression model, respectively.

	Binary regression model of DR		Ordinal regression model of DR		Binary regression model of DME		Binary regression model of VTDR	
	OR (95%CI)	P valve	OR (95%CI)	P valve	OR (95%CI)	P valve	Odds ratio (95%CI)	P valve
BMI, kg/m²								
18.5-22.9 (normal weight)	Ref.		Ref.		Ref.		Ref.	
23.0-25.0 (overweight)	1.26(0.93, 1.70)	0.133	1.28(0.95, 1.72)	0.109	1.16(0.69, 1.95)	0.585	1.19(0.72, 1.97)	0.492
≥25.0 (obese)	0.90(0.68, 1.20)	0.479	0.89(0.67, 1.18)	0.425	0.69(0.40, 1.17)	0.164	0.64(0.38, 1.08)	0.094
P for trend		0.381		0.329		0.147		0.083
WHR								
Quarter 1	Ref.		Ref.		Ref.		Ref.	
Quarter 2	1.38(0.69, 2.76)	0.368	1.39(0.69, 2.77)	0.355	2.18(0.53, 8.93)	0.279	1.62(0.45, 5.90)	0.463
Quarter 3	0.82(0.39, 1.75)	0.615	0.85(0.40, 1.80)	0.669	0.68(0.11, 4.13)	0.673	0.76(0.17, 3.48)	0.727
Quarter 4	2.17(1.13, 4.17)	0.021	2.25(1.18, 4.32)	0.014	3.63(0.97, 13.54)	0.055	2.70(0.82, 8.87)	0.101
P for trend		0.056		0.040		0.093		0.152
WHtR								
Quarter 1	Ref.		Ref.		Ref.		Ref.	
Quarter 2	0.99(0.67, 1.47)	0.974	0.99(0.67, 1.46)	0.962	1.16(0.62, 2.18)	0.643	1.15(0.62, 2.14)	0.651
Quarter 3	0.85(0.57, 1.27)	0.430	0.86(0.57, 1.28)	0.457	0.79(0.39, 1.57)	0.494	0.74(0.37, 1.48)	0.397
Quarter 4	0.86(0.58, 1.29)	0.475	0.86(0.57, 1.28)	0.444	0.36(0.15, 0.86)	0.021	0.34(0.14, 0.81)	0.015
P for trend		0.358		0.344		0.015		0.009
BAI								
Quarter 1	Ref.		Ref.		Ref.		Ref.	
Quarter 2	0.64(0.34, 1.19)	0.158	0.61(0.33, 1.13)	0.117	0.54(0.17, 1.65)	0.277	0.48(0.16, 1.44)	0.191
Quarter 3	0.43(0.22, 0.85)	0.015	0.43(0.22, 0.84)	0.014	0.54(0.17, 1.65)	0.277	0.48(0.16, 1.44)	0.191
Quarter 4	0.50(0.26, 0.97)	0.039	0.49(0.25, 0.94)	0.031	0.21(0.04, 1.00)	0.05	0.28(0.08, 1.06)	0.061
P for trend		0.017		0.015		0.042		0.051

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4 213 In the logistic regression model adjusted for sex and age, Q4-WHtR remained as a
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6 214 protective factor of VTDR (or=0.40, [95% CI, 0.16-0.96], Supplementary Table S1),
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9 215 independent of lipid metabolism parameter (Supplementary Table S2). In the full model, Q2-
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11 216 WHtR presented as a significant risk factor of DME (or=3.04, [95 %CI, 1.04-8.85], Table 3)
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14 217 and VTDR (or=2.74, [95%CI, 1.01-7.43]). The association was also more significant in female
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17 218 patients (for DME, p for trend =0.065, or of Q2-WHtR =6.79, [95%CI, 1.19-38.57]; for VTDR,
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19 219 p for trend =0.049, or of Q2-WHtR =7.38, [95%CI, 1.48-36.77], Table S3-1), but not in male
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22 220 patients either (Table S3-2).

221 **Association of BAI with any DR and severe DR**

222 The prevalence of DR and severe VTDR showed a downward trend with the increase of
223 BAI (Figure 2, Table 2). However, in the univariate logistic regression model, increased BAI
224 was associated with a decreased risk of DR (Table 4). After adjusted for sex and age, the
225 association became less significant, while in the full model, the association with either any DR,
226 DME or VTDR was not significant.

227

228 **Discussion**

229 In this study, we enrolled 2,305 participants and analyzed the association of obesity with
230 any DR, DME and VTDR. There are three main findings in our study. First, only 29.6% of
231 diabetic patients had normal weight, while as high as 67.8% of diabetic patients were
232 overweight or obese. Second, obesity (BMI>25.0kg/m²) presented as a significant protective
233 factor of VTDR, while Q2-WHtR presented as a significant risk factor. Third, we found a
234 significant negative association between BAI and DR in the univariate logistic regression model,

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4 235 while the association became less significant in the multivariable model.
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6 236 Previous studies recognized obesity as a critical component of metabolic syndrome, which
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9 237 induces insulin resistance and advances the development of type 2 diabetes^{2,3}. Therefore, weight
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11 238 control is usually recommended in the management of diabetes and several systemic diseases
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14 239 to reduce the prevalence of complications^{3,11,12}. However, in this study, three obesity-related
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17 240 indexes, BMI, WHtR, and BAI, were all negatively associated with DR. The result presented
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19 241 as an "obesity paradox", which was also presented in several previous studies¹³⁻¹⁵. Moreover, it
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22 242 was more significant in the association with VTDR. The first possible reason would be that
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25 243 VTDR, presented and DME or PDR, was more likely to appear in the patients with advanced
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27 244 diabetes. Advanced diabetes would manifest as weight loss as one of the metabolic
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30 245 complications, contributing to the inverse association of obesity with DR. Second, BMI could
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32 246 hardly differentiate general obesity and centripetal obesity, which may play a different role in
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35 247 the progress of diabetes. Third, all the participants were from the community. They were
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38 248 diagnosed with diabetes in the hospital before the enrollment. The patients who had severe
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41 249 complications, low willingness to seek doctor's help or mobility problems, would be limited,
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43 250 contributing to the selection bias in the study.

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45 251 Although obesity was recognized as one of the important biomarkers inducing insulin
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48 252 resistance¹⁶, the obesity paradox has prevented scientists from making recommendations on
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51 253 weight management for diabetic patients. The positive correlation between centripetal obesity
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53 254 (presented as higher WHR) and diabetic progression has shed light on this problem.¹⁷ In study
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56 255 of Tien Yin Wong *et al*, WHR was regarded to assess centripetal obesity, and BAI is established
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59 256 and has a significant linear relationship with body fat rate.¹⁸ They demonstrated that abdominal
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4 257 obesity may be a more critical factor of DR than the generalized obesity. However, in our study,
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6 258 as the indicator of centripetal obesity, Q2-WHtR associated positively with DR, and WHtR
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9 259 generally shows an opposite trend, indicating a nonlinear relationship between centripetal
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11 260 obesity. Therefore, we are collecting follow-up data to further prospectively analyze the
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14 261 relationship between obesity and diabetic retinopathy.

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17 262 Our study also found that the associations between obesity-related index (both BMI and
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19 263 WHR) and VTDR were only significant in female patients, indicating that female patients
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22 264 would have a higher risk with the increase of centripetal obesity. The sex-specific obesity-
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24 265 diabetes association has been reported in several studies, but the association between obesity-
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27 266 related indexes (including BMI, WHR, WHtR, BAI) and diabetic retinopathy was seldom
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30 267 reported. We furthered analyzed the sex-specific distribution regarding different obesity-related
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32 268 indexes (Figure 3). Male patients have a significantly higher WHR, lower WHtR and lower
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35 269 BAI. However, the results may be influenced by the small number of patients in some of the
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38 270 categories after they were grouped by sex (there were “no observation” categories in Table S3-1
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40 271 and Table S3-2). Therefore, more studies should be designed to investigate the weight control
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43 272 management and standard weight range regarding different sex in diabetic patients.

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45 273 There are some other limitations in this study. First, in order to reduce the examination
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48 274 time and improve the compliance of participants, the measurement of waist circumference and
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51 275 hip circumference was not performed on every participant, while eventually 483 patients have
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53 276 undergone all the measurement including height, weight, waist circumference and hip
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56 277 circumference. Therefore, we are unable to put BMI, WHR, WHtR, and BAI in the full model
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58 278 with 2,305 patients at the same time. Second, although we used robust regression to make the
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4 279 odds ratio more robust, we did not exclude the influence of collinearity in the full model, which
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6 280 may contribute to the variation of the association of factors such as BAI with DR. Third, the
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9 281 diabetic participants with severe condition (e.g. very poor eye sight, past DR treatment history,
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11 282 occurred with other combined eye diseases that could affect retinal thickness, etc.) were
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14 283 excluded. On contrary, the participants usually had a less severe condition, which may affect
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17 284 the generalizability of the results.

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19 285 In summary, this study provides medical data of 2,305 participants, and analyzed the
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22 286 relationship between obesity and DR. The results presented general obesity and centripetal
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25 287 obesity as a protective factor in the development of DR, which was more significant in female
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28 288 patients. Because the interactions between obesity and DR is not completely clear, further
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31 289 researches are needed to focus on the improvement of sex-specific weight management in
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33 290 diabetic patients regarding different sex.
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4 291 **Contributors**

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6 292 W Huang and W Wei conceived and designed the study. W Li, W Wei, X Gong, L Wang,
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9 293 J Meng, Y Li, and K Xiong collected and interpreted the data. W Li, W Wei and L Jin carried
10
11 294 out the statistical analysis. W Li wrote the manuscript. W Huang, W Wang, X Gong, and X
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14 295 Liang reviewed and edited the manuscript. All authors have seen the final version of the
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17 296 manuscript and approved it for publication.
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33
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35 303 study; collection, management, analysis and interpretation of the data; preparation, review or
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38 304 approval of the manuscript; and decision to submit the manuscript for publication.
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43 306 **Declaration of Interests**

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45 307 The authors declare no competing financial interests.
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51 309 **Data availability statement**

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53 310 All data relevant to the study are included in the article or uploaded as supplementary
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56 311 information
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4 **313 Ethical Approval Statement**
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6 314 This study was approved by the Institutional Review Board of Zhongshan Ophthalmic
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9 315 Center (2017KYPJ094).
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3 **Figure Legend**
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7 **Figure 1. International Clinical Severity Scale of Diabetic Retinopathy and Diabetic**
8 **Macular Edema.** Footnotes: DR: diabetic retinopathy; NPDR: non-proliferative diabetic
9 retinopathy; PDR: proliferative diabetic retinopathy; IRMA: intraretinal microvascular
10 abnormalities; DME: diabetic macular edema.
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16 **Figure 2. The prevalence of diabetic retinopathy (DR) and severe DR (diabetic**
17 **retinopathy, DME, and vision threatening diabetic retinopathy, VTDR) in different**
18 **groups of the obesity-related indexes.** Footnotes: BMI: Body mass index. WHR: Waist to
19 hip ratio. WHtR: waist to height ratio. BAI: Body adiposity index.
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26 **Figure 3. The number of male and female patients in different groups of the obesity-**
27 **related indexes**
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Severity level	Findings after pupil dilation	Any DR	DME	VTDR
DR scale				
No DR	No abnormalities			
Mild NPDR	Microaneurysms only			
Moderate NPDR	More than just microaneurysms but less than Severe NPDR			
Severe NPDR	Any of the following: <ul style="list-style-type: none"> • >20 intraretinal hemorrhages in each of 4 quadrants; • Definite venous beading in 2+ quadrants; • Prominent IRMA in 1+ quadrant And no signs of proliferative retinopathy			
PDR	One or more of the following: <ul style="list-style-type: none"> • Neovascularization; • Vitreous/preretinal hemorrhage 			
DME scale				
No DME	No apparent retinal thickening or hard exudates in posterior pole			
DME	Some retinal thickening or hard exudates in posterior pole: <ul style="list-style-type: none"> • Mild: some retinal thickening or hard exudates in posterior pole but distant from the center of the macular; • Moderate: retinal thickening or hard exudates approaching the center of the macula but not involving the center; • Severe: Retinal thickening or hard exudates involving the center of the macular. 			

Figure 1. International Clinical Severity Scale of Diabetic Retinopathy and Diabetic Macular Edema. Footnotes: DR: diabetic retinopathy; NPDR: non-proliferative diabetic retinopathy; PDR: proliferative diabetic retinopathy; IRMA: intraretinal microvascular abnormalities; DME: diabetic macular edema.

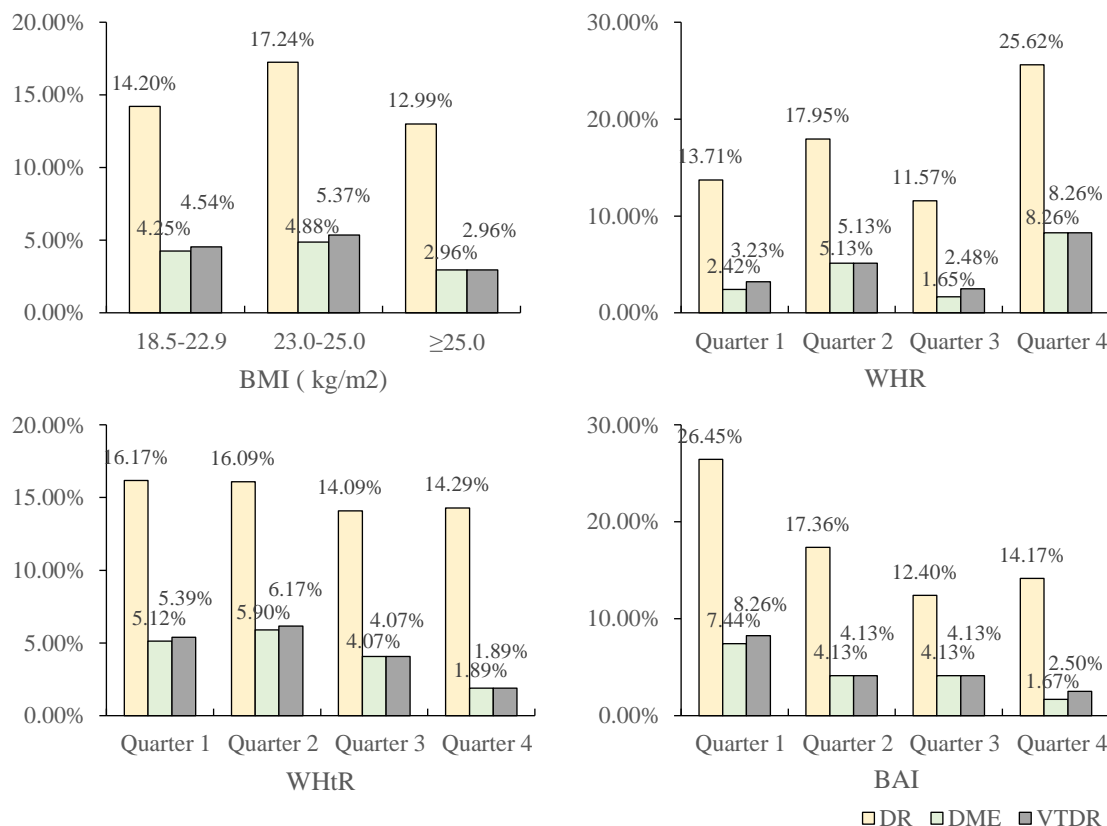


Figure 2. The prevalence of diabetic retinopathy (DR) and severe DR (diabetic retinopathy, DME, and vision threatening diabetic retinopathy, VTDR) in different groups of the obesity-related indexes. Footnotes: BMI: Body mass index. WHR: Waist to hip ratio. WHtR: waist to height ratio. BAI: Body adiposity index.

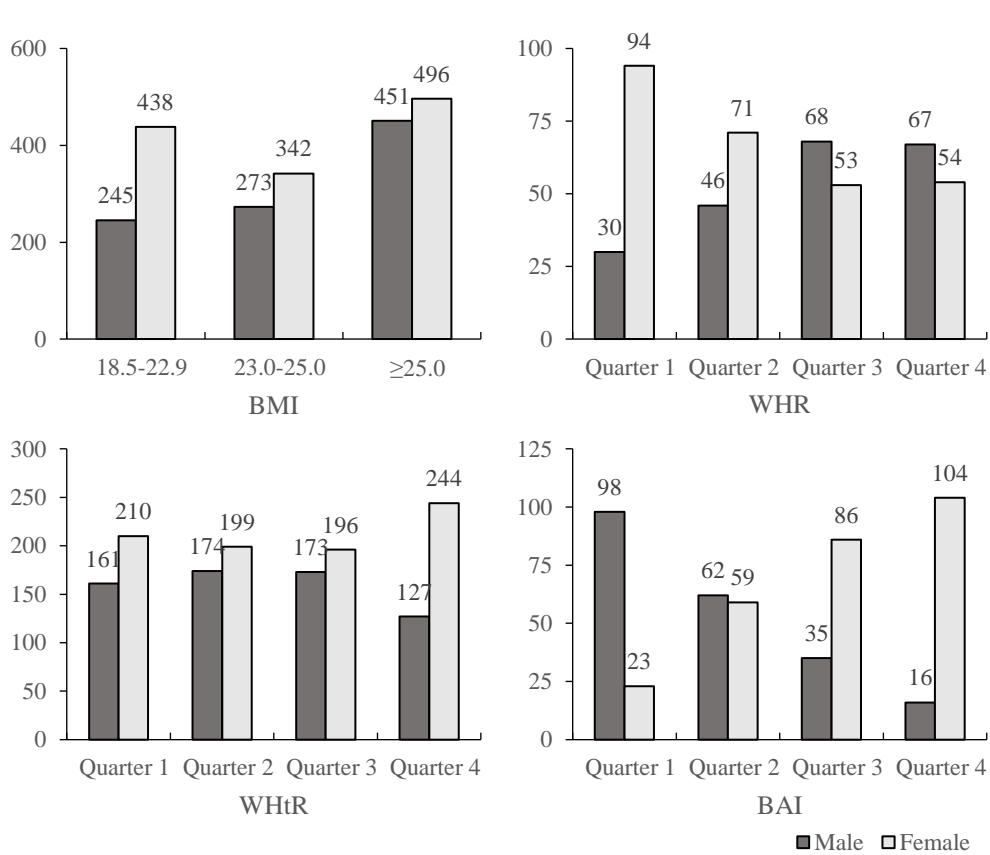


Figure 3. The number of male and female patients in different groups of the obesity-related indexes.

Supplementary Materials

Table S1 The odds ratio (OR) of Body mass index (BMI), Waist to hip ratio (WHR), waist to height ratio (WHtR), and Body adiposity index (BAI) in the binary logistic regression model adjusted for age and sex. Footnotes: diabetic retinopathy (DR), diabetic macular edema (DME) and vision threatening diabetic retinopathy (VTDR) were set as outcomes of the regression model, respectively.

	DR		DME		VTDR	
	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value
BMI, kg/m²						
18.5-22.9 (normal weight)	Ref.		Ref.		Ref.	
23.0-25.0 (overweight)	1.22(0.90, 1.65)	0.200	1.09(0.64, 1.84)	0.758	1.12(0.67, 1.86)	0.660
≥25.0 (obese)	0.85(0.64, 1.14)	0.275	0.61(0.35, 1.04)	0.067	0.57(0.33, 0.96)	0.034
P for trend		0.204		0.056		0.028
WHR						
Quarter 1	Ref.		Ref.		Ref.	
Quarter 2	1.32(0.66, 2.67)	0.434	2.18(0.52, 9.10)	0.283	1.60(0.43, 5.93)	0.478
Quarter 3	0.77(0.35, 1.67)	0.503	0.68(0.11, 4.30)	0.682	0.76(0.16, 3.59)	0.725
Quarter 4	2.02(1.03, 3.98)	0.041	3.61(0.92, 14.16)	0.065	2.65(0.77, 9.12)	0.123
P for trend		0.089		0.101		0.169
WHtR						
Quarter 1	Ref.		Ref.		Ref.	
Quarter 2	1.00(0.68, 1.48)	0.991	1.21(0.64, 2.28)	0.558	1.20(0.64, 2.23)	0.567
Quarter 3	0.87(0.58, 1.30)	0.495	0.84(0.42, 1.68)	0.620	0.79(0.40, 1.58)	0.509
Quarter 4	0.95(0.63, 1.42)	0.785	0.42(0.17, 1.02)	0.055	0.40(0.16, 0.96)	0.039
P for trend		0.627		0.046		0.029
BAI						
Quarter 1	Ref.		Ref.		Ref.	
Quarter 2	0.64(0.34, 1.23)	0.182	0.57(0.18, 1.84)	0.344	0.51(0.16, 1.60)	0.247
Quarter 3	0.44(0.21, 0.93)	0.031	0.62(0.18, 2.18)	0.456	0.55(0.16, 1.90)	0.348
Quarter 4	0.52(0.24, 1.13)	0.098	0.27(0.05, 1.56)	0.144	0.37(0.08, 1.69)	0.199
P for trend		0.060		0.166		0.201

Table S2 The OR of BMI, WHR, WHtR, and BAI in the binary logistic regression model adjusted for age, sex, and lipid metabolism parameter (total cholesterol, triglycerides, low-density cholesterol, and high-density cholesterol). Footnotes: DR, DME and VTDR were set as outcomes of the regression model, respectively.

	DR		DME		VTDR	
	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value
BMI, kg/m2						
18.5-22.9 (normal weight)	Ref.		Ref.		Ref.	
23.0-25.0 (overweight)	1.24(0.91, 1.68)	0.175	1.10(0.64, 1.88)	0.729	1.13(0.67, 1.89)	0.649
≥25.0 (obese)	0.87(0.64, 1.17)	0.343	0.61(0.35, 1.06)	0.079	0.56(0.33, 0.97)	0.039
P for trend		0.251		0.065		0.030
WHR						
Quarter 1	Ref.		Ref.		Ref.	
Quarter 2	1.37(0.67, 2.78)	0.387	2.38(0.56, 10.10)	0.241	1.68(0.45, 6.35)	0.441
Quarter 3	0.81(0.36, 1.80)	0.604	0.78(0.12, 5.15)	0.795	0.79(0.16, 3.95)	0.776
Quarter 4	2.22(1.08, 4.55)	0.030	4.37(1.02, 18.80)	0.048	2.85(0.76, 10.69)	0.121
P for trend		0.066		0.074		0.165
WHtR						
Quarter 1	Ref.		Ref.		Ref.	
Quarter 2	0.97(0.65, 1.45)	0.874	1.26(0.65, 2.43)	0.492	1.22(0.64, 2.32)	0.537
Quarter 3	0.84(0.55, 1.28)	0.413	0.88(0.42, 1.81)	0.720	0.81(0.39, 1.65)	0.559
Quarter 4	0.90(0.59, 1.38)	0.639	0.43(0.17, 1.08)	0.072	0.40(0.16, 0.98)	0.046
P for trend		0.511		0.060		0.033
BAI						
Quarter 1	Ref.	Ref.	Ref.		Ref.	
Quarter 2	0.64(0.33, 1.23)	0.177	0.60(0.18, 1.96)	0.396	0.53(0.17, 1.72)	0.293
Quarter 3	0.43(0.20, 0.92)	0.030	0.64(0.18, 2.27)	0.486	0.55(0.16, 1.91)	0.348
Quarter 4	0.51(0.23, 1.12)	0.095	0.28(0.05, 1.65)	0.161	0.37(0.08, 1.72)	0.202
P for trend		0.059		0.186		0.200

Table S3-1 The OR of BMI, WHR, WHtR, and BAI in the binary logistic regression model additionally adjusted for variables in female patients.

Footnotes: These variables included continuous variables (e.g., age, systolic blood pressure, HbA1c, c-reaction protein, total cholesterol, triglycerides, low-density cholesterol, high-density cholesterol, creatinine, microalbuminuria, uric acid, and axial length) and categorical variables (e.g., sex, smoking history, drinking history, education, duration of diabetes, and insulin use). DR, DME and VTDR were set as outcomes of the regression model, respectively. DR, DME and VTDR were set as outcomes of the regression model, respectively.

	DR Odds ratio (95%CI)	P value	DME Odds ratio (95%CI)	P value	VTDR Odds ratio (95%CI)	P value
BMI, kg/m²						
18.5-22.9 (normal weight)	Ref.		Ref.		Ref.	
23.0-25.0 (overweight)	0.89(0.49, 1.62)	0.708	0.68(0.17, 2.68)	0.582	0.57(0.15, 2.17)	0.412
≥25.0 (obese)	0.77(0.43, 1.39)	0.392	0.10(0.01, 0.77)	0.027	0.09(0.01, 0.76)	0.027
P for trend		0.392		0.021		0.015
WHR						
Quarter 1	Ref.		Ref.		Ref.	
Quarter 2	1.31(0.46, 3.75)	0.610	1.42(0.02, 81.66)	0.866	0.78(0.02, 29.41)	0.894
Quarter 3	0.25(0.04, 1.34)	0.106	*	*	*	*
Quarter 4	1.20(0.40, 3.55)	0.748	3.52(0.20, 61.43)	0.389	2.21(0.26, 18.92)	0.470
P for trend		0.617		0.459		0.786
WHtR						
Quarter 1	Ref.		Ref.		Ref.	
Quarter 2	1.36(0.60, 3.09)	0.466	6.79(1.19, 38.57)	0.031	7.38(1.48, 36.77)	0.015
Quarter 3	0.70(0.30, 1.67)	0.421	*	*	*	*
Quarter 4	1.10(0.47, 2.56)	0.828	0.41(0.06, 2.63)	0.347	0.40(0.06, 2.73)	0.351
P for trend		0.884		0.065		0.049
BAI						
Quarter 1	Ref.		Ref.		Ref.	
Quarter 2	1.11(0.26, 4.78)	0.889	0.31(0.01, 12.27)	0.534	0.30(0.01, 8.98)	0.487
Quarter 3	0.66(0.15, 2.93)	0.582	0.83(0.04, 15.46)	0.898	0.80(0.11, 5.86)	0.822
Quarter 4	0.73(0.17, 3.11)	0.673	0.26(0.01, 6.94)	0.425	0.76(0.14, 4.26)	0.758
P for trend		0.512		0.653		0.857

* No observation.

Table S3-2 The OR of BMI, WHR, WHtR, and BAI in the binary logistic regression model additionally adjusted for variables in male patients.

	DR		DME		VTDR	
	Odds ratio (95%CI)	P valve	Odds ratio (95%CI)	P valve	Odds ratio (95%CI)	P valve
BMI, kg/m2						
18.5-22.9 (normal weight)	Ref.		Ref.		Ref.	
23.0-25.0 (overweight)	0.61(0.29, 1.27)	0.182	1.63(0.46, 5.74)	0.448	1.84(0.54, 6.22)	0.328
≥25.0 (obese)	0.59(0.29, 1.19)	0.144	0.73(0.23, 2.38)	0.605	0.71(0.22, 2.27)	0.565
P for trend		0.183		0.411		0.326
WHR						
Quarter 1	Ref.		*	*	*	*
Quarter 2	0.64(0.12, 3.39)	0.602	Ref.		Ref.	
Quarter 3	0.61(0.14, 2.73)	0.514	0.40(0.06, 2.78)	0.354	0.53(0.09, 3.02)	0.472
Quarter 4	1.07(0.27, 4.29)	0.919	1.35(0.18, 9.92)	0.771	1.55(0.21, 11.45)	0.669
P for trend		0.777		0.190		0.136
WHtR						
Quarter 1	Ref.		Ref.		Ref.	
Quarter 2	0.75(0.33, 1.70)	0.494	1.85(0.53, 6.52)	0.337	1.43(0.44, 4.66)	0.557
Quarter 3	0.48(0.19, 1.18)	0.109	1.39(0.35, 5.56)	0.643	1.06(0.29, 3.88)	0.927
Quarter 4	0.56(0.21, 1.50)	0.248	0.68(0.09, 5.40)	0.718	0.57(0.07, 4.64)	0.601
P for trend		0.124		0.714		0.567
BAI						
Quarter 1	Ref.		Ref.		Ref.	
Quarter 2	0.57(0.19, 1.75)	0.327	1.61(0.36, 7.12)	0.530	1.55(0.38, 6.33)	0.544
Quarter 3	0.60(0.22, 1.67)	0.330	0.41(0.04, 3.90)	0.438	0.35(0.04, 3.04)	0.339
Quarter 4	0.46(0.08, 2.80)	0.403	*	*	*	*
P for trend		0.243		0.464		0.399

* No observation.

STROBE Statement—checklist of items that should be included in reports of observational studies

Section/item	Item No	Recommendation	Reported on Page Number/Line Number	Reported on Section/Paragraph
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract		
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found		
Introduction				
Background/ rationale	2	Explain the scientific background and rationale for the investigation being reported		
Objectives	3	State specific objectives, including any prespecified hypotheses		
Methods				
Study design	4	Present key elements of study design early in the paper		
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection		
Participants	6	(a) Cohort study —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up Case-control study —Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls Cross-sectional study —Give the eligibility criteria, and the sources and methods of selection of participants		
		(b) Cohort study —For matched studies, give matching criteria and number of exposed and unexposed Case-control study —For matched studies, give matching criteria and the number of controls per case		
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable		
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group		
Bias	9	Describe any efforts to address potential sources of bias		
Study size	10	Explain how the study size was arrived at		
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why		

Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding		
		(b) Describe any methods used to examine subgroups and interactions		
		(c) Explain how missing data were addressed		
		(d) Cohort study —If applicable, explain how loss to follow-up was addressed Case-control study —If applicable, explain how matching of cases and controls was addressed Cross-sectional study —If applicable, describe analytical methods taking account of sampling strategy		
		(e) Describe any sensitivity analyses		
Results				
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed		
		(b) Give reasons for non-participation at each stage		
		(c) Consider use of a flow diagram		
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders		
		(b) Indicate number of participants with missing data for each variable of interest		
		(c) Cohort study —Summarise follow-up time (eg, average and total amount)		
Outcome data	15*	Cohort study —Report numbers of outcome events or summary measures over time		
		Case-control study —Report numbers in each exposure category, or summary measures of exposure		
		Cross-sectional study —Report numbers of outcome events or summary measures		
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included		
		(b) Report category boundaries when continuous variables were categorized		
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period		
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses		
Discussion				
Key results	18	Summarise key results with reference to study objectives		
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias		

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Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence						
Generalisability	21	Discuss the generalisability (external validity) of the study results						
Other information								
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based						

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.