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Title Page

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

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Abstract

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

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

Research Design and Methods A total of 1562(67.8%) participants were overweight or obese. The prevalence of DR, DME and VTDR was higher in patients with higher BMI/WHR or lower WHtR/BAI. In the univariate regression model, WHR correlated positively with DR, while WHtR and BAI correlated negatively with DR, DME and VTDR. The association remained independent of age, sex and lipid metabolism parameters. In the multivariate model, obese presented as a protective factor for DME and VTDR, while the second quarter of WHtR(Q2-WHtR) presented as a risk factor. However, the association was significant only in female patients, but not male patients.

Conclusions As high as 67.8% diabetic patients were overweight or obese. Obese presented as a significant protective factor of VTDR, while Q2-WHtR presented as a significant risk factor. Therefore,

more attention should be paid to centripetal obesity as well as general obesity. Further research is also needed to focus on the improvement of sex-specific weight management in diabetic patients.

Keywords Diabetes mellitus, diabetic retinopathy, obesity, BMI, WHR, WHtR, BAI

Article summary: (Strengths and limitations of this study)

- This study is a combined study that analyzed the association of four obesity-related indexes (BMI, WHR, WHtR, and BAI) with the presence and the severity of diabetic retinopathy.
- The data enrolled 2305 type 2 diabetes mellites (T2DM) patients who participated in the Guangzhou Diabetic Eye Study in China.
- Any diabetic retinopathy, diabetic macular edema (DME), and vision-threatening diabetic retinopathy (VTDR) were selected as primary outcomes.
- It is the first study to analyze the association between BAI and DR.
- We are collecting follow-up data to further prospectively analyze the relationship between obesity and diabetic retinopathy.

Introduction

Diabetic retinopathy (DR) is one of the most common complications of diabetes mellitus and is a leading cause of vision loss and blindness throughout the world[1]. It severely affects the life quality of diabetic patients and increases the economic burden of treatment without timely management[1]. Although obesity is one of the established risk factors that correlated positively with diabetes mellitus[2,3], the relationship between obesity and DR varies in different studies. For instance, in a cross-sectional study that enrolled 50,464 Saudi diabetic patients, overweight and obesity presented as a protective factor for DR[4]. However, in a meta-analysis of prospective cohort studies, obesity correlated with a significant increase in DR incidence[5]. The methods to improve the weight management of diabetic patients to decrease the presence and severity of DR have become a major public health problem.

Body mass index (BMI) has been commonly used to assess weight level in the previous study[4,6,7], but it could not distinguish whether a patient is general obese or abdominal obese. To solve the problem, waist to hip ratio (WHR) and waist to height ratio (WHtR) are developed to assess centripetal obesity, while body adiposity index (BAI) is established and has a significant linear relationship with body fat rate[8]. However, combined or separate studies about association of WHR, WHtR, and BAI with DR are still limited. Studies to explore the relationship between obesity and DR among Chinese people are also limited.

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

BAI) with the presence and the severity of DR.

Methods

Study design and participants

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

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

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

Demographic information, medical history, and biometric parameter assessment

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

Assessment of BMI, WHR, WHtR, and BAI

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

BMI was calculated as weight divided by height squared and was categorized into normal weight (18.5-22.9 kg/m2), overweight (23.0-25.0 kg/m2), and obese (>25.0 kg/m2), according to Asia-Pacific BMI cutoff points[9-11]. Sixty underweight participants (BMI <18.5 kg/m2) were not included because of the small sample size. WHR was calculated as waist circumference divided by hip circumference, while WHtR was calculated by dividing waist circumference by height. BAI was calculated as hip circumference divided by $(\text{height})^{1.5}$ minus 18. Because of

the lack of standardized classifications, WHR, WHtR, and BAI were categorized in quarters.

Assessment of DR, DME, and VTDR

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

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

Statistical analysis

All analyses were performed using STATA statistical software (Stata version 14.0, Stata Corp., College Station, TX). BMI, WHR, WHtR, and BAI classifications were used as both continuous variables and categorical variables. To compare the differences in characteristics of participants with or without DR, DME, and VTDR, the Mann-Whitney U test was used for continuous variables, and the Chi-square test was used for categorical variables.

The binary and ordinal logistic regression model was used to assess the association of BMI, WHR, WHtR, and BAI with the presence of any DR and VTDR. In special, the outcome of the ordinal logistic regression model of DR was set as no DR, mild NPDR, moderate NPDR, and VTDR

(including PDR and DME). In the multivariate logistic model, the association was adjusted for potential confounding factors established in previous research. These factors 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). P values less than 0.05 were considered statistically significant.

Patient and public involvement statement

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

Results

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

Compared with participants who did not have DR, participants with DR had a younger age, a lower level of education, a longer duration of diabetes, and a higher proportion of males, smoking history, drinking history, and insulin use (Table 1). They also had a higher level of Hba1c, creatinine, microalbuminuria, and systolic blood pressure, but shorter axis length (all p <0.05). Moreover, their BMI, WHR, WHtR, and BAI were higher. According to Asia-Pacific BMI cutoff points, as high as 947 participants (41.1%) were obese, and 615 (26.7%) were overweight, while only 683 participants (29.6%) were normal weight.

Association of BMI with any DR, DME and VTDR

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

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)

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

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

In the full model that further adjusted for continuous variables (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 (sex, smoking history, drinking history, education, duration of diabetes, and insulin use), the association of BMI became significant with both DME and VTDR (for DME, p for trend = 0.031; for VTDR, p for trend = 0.016, Table 3-1). Obesity was inversely associated with DME and VTDR with a decreased OR (for DME, or=0.40, [95%CI, 0.16-0.96]; for VTDR, or=0.37, [95%CI, 0.16-0.87], Table 3-1). However, the association was only significant in female patients (for DME, p for trend =0.021, or of obesity =0.10, [95%CI, 0.01-0.77]; for VTDR, p for trend =0.015, or of obesity =0.09, [95%CI, 0.01-0.76], Table 3-2), but not in male patients (Table 3-3).

Association of WHR with any DR and severe DR

The prevalence of DR, DME and VTDR was the highest in the fourth quarter of WHR (Q4-WHR) (Figure 2, Table 2). In the univariable logistic regression model, Q4-WHR 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/m2 (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	v14.29	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 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)	0.82(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

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

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

Association of WHtR with any DR and severe DR

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

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

Association of BAI with any DR and severe DR

The prevalence of DR and severe VTDR showed a downward trend with the increase of

BAI (Figure 2, Table 2). However, in the univariate logistic regression model, increased BAI was associated with a decreased risk of DR (Table 4). After adjusted for sex and age, the association became less significant, while in the full model, the association with either any DR, DME or VTDR was not significant.

Discussion

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

Previous studies recognized obesity as a critical component of metabolic syndrome, which induces insulin resistance and advances the development of type 2 diabetes[2,3]. Therefore, weight control is usually recommended in the management of diabetes and several systemic diseases to reduce the prevalence of complications[3,12,13]. However, in this study, three obesity-related indexes, BMI, WHtR, and BAI, were all negatively associated with DR. The result presented as an "obesity paradox", which was also presented in several previous studies[14-16]. Moreover, it was more significant in the association with VTDR. The first possible reason would be that

VTDR, presented and DME or PDR, was more likely to appear in the patients with advanced diabetes. Advanced diabetes would manifest as weight loss as one of the metabolic complications, contributing to the inverse association of obesity with DR. Second, BMI could hardly differentiate general obesity and centripetal obesity, which may play a different role in the progress of diabetes. Third, all the participants were from the community. They were diagnosed with diabetes in the hospital before the enrollment. The patients who had severe complications, low willingness to seek doctor's help or mobility problems, would be limited, contributing to the selection bias in the study.

Although obesity was recognized as one of the important biomarkers inducing insulin resistance[17], the obesity paradox has prevented scientists from making recommendations on weight management for diabetic patients. Several studies have revealed a positive association between centripetal obesity and chronic inflammation[18,19], which may contribute to the positive correlation between centripetal obesity (presented as higher WHR) and diabetic progression[20]. However, in our study, as the indicator of centripetal obesity, Q2-WHtR associated positively with DR, and WHtR generally shows an opposite trend, indicating a nonlinear relationship between centripetal obesity. It also demonstrated WHtR as a more critical factor of DR as well as the traditional index BMI.

Our study also found that the associations between obesity-related index (both BMI and WHR) and VTDR were only significant in female patients, indicating that female patients would have a higher risk with the increase of centripetal obesity. The sex-specific obesity-diabetes association has been reported in several studies, but the association between obesity-related indexes (including BMI, WHR, WHtR, BAI) and diabetic retinopathy was seldom

reported. We furthered analyzed the sex-specific distribution regarding different obesity-related indexes (Figure 3). Male patients have a significantly higher WHR, lower WHtR and lower BAI. Therefore, weight control management and standard weight range should be made regarding different sex in diabetic patients.

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

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

Contributors

W Huang and W Wei conceived and designed the study. W Li, W Wei, X Gong, L Wang, J Meng, Y Li, and K Xiong collected and interpreted the data. W Li and W Wei carried out the statistical analysis. W Li wrote the manuscript. W Huang, W Wang, and X Gong reviewed and edited the manuscript. All authors have seen the final version of the manuscript and approved it for publication.

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Declaration of Interests

The authors declare no competing financial interests.

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Figure Legend

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

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: • >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: • 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: • 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.

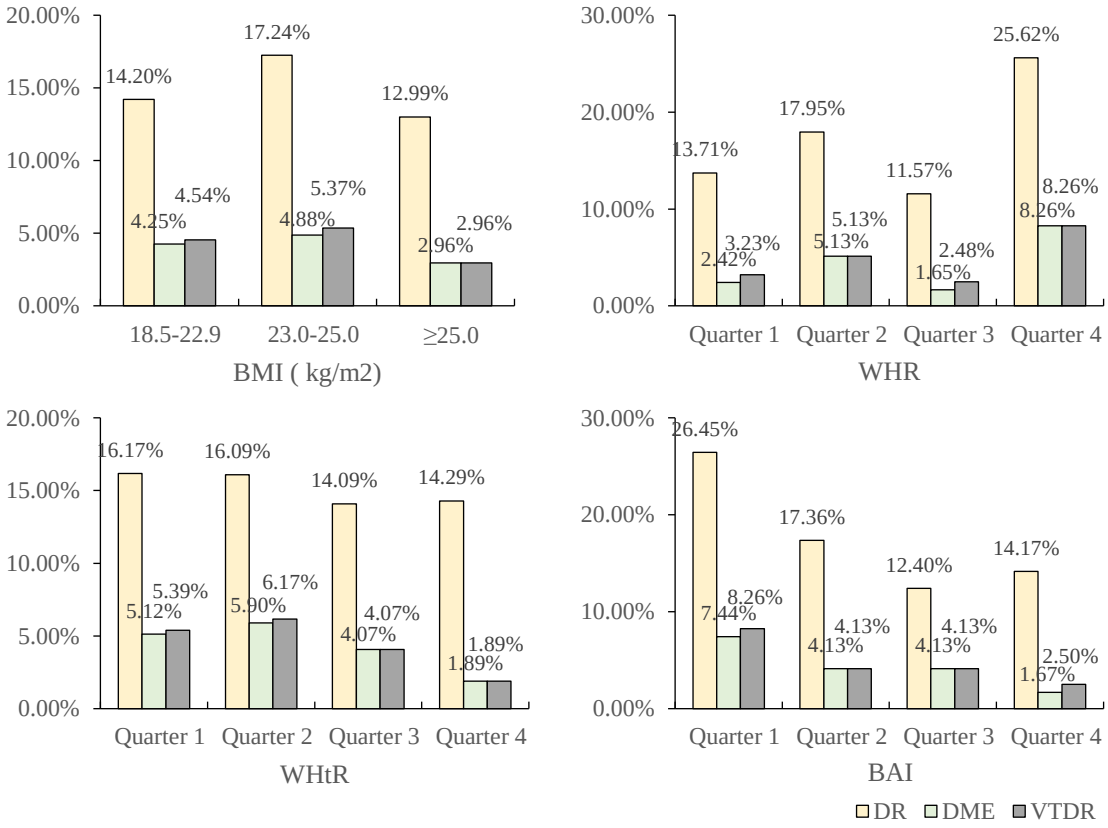

Figure 2. The prevalence of diabetic retinopathy (DR) and severe DR (diabetic retinopathy, DME, and vision threatening diabetic retinopathy, VTDR) in different groups of the obesity-related indexes. Footnotes: BMI: Body mass index. WHR: Waist to hip ratio. WHtR: waist to height ratio. BAI: Body adiposity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

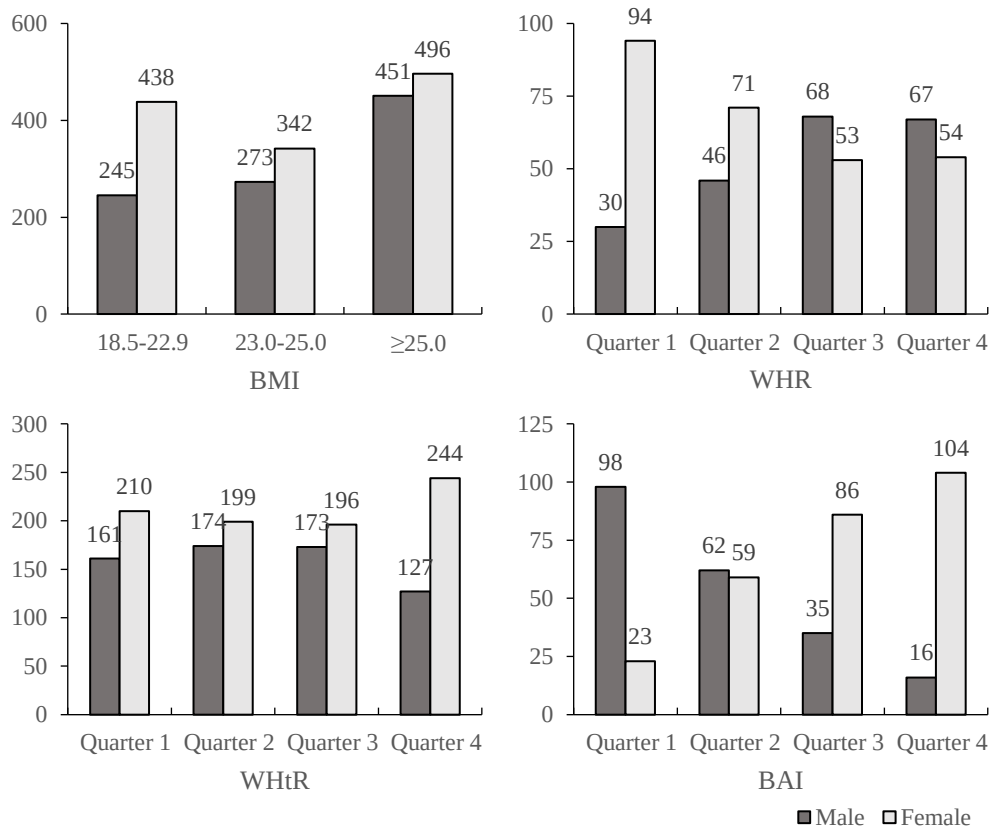

Figure 3. The number of male and female patients in different groups of the obesity-related indexes.

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 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)	1.24(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		

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.

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Title Page

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

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Abstract

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

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

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

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

Keywords Diabetes mellitus, diabetic retinopathy, obesity, BMI, WHR, WHtR, BAI

Article summary: (Strengths and limitations of this study)

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

Introduction

Diabetic retinopathy (DR) is one of the most common complications of diabetes mellitus and is a leading cause of vision loss and blindness throughout the world[1]. It severely affects the life quality of diabetic patients and increases the economic burden of treatment without timely management[1]. Although obesity is one of the established risk factors that correlated positively with diabetes mellitus[2,3], the relationship between obesity and DR varies in different studies. For instance, in a cross-sectional study that enrolled 50,464 Saudi diabetic patients, overweight and obesity presented as a protective factor for DR[4]. However, in a meta-analysis of prospective cohort studies, obesity correlated with a significant increase in DR incidence[5]. The methods to improve the weight management of diabetic patients to decrease the presence and severity of DR have become a major public health problem.

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

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

Methods

Study design and participants

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

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

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

Demographic information, medical history, and biometric parameter assessment

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

Assessment of BMI, WHR, WHtR, and BAI

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

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

weight (18.5-22.9 kg/m2), overweight (23.0-25.0 kg/m2), and obese (>25.0 kg/m2), according to Asia-Pacific BMI cutoff points[8-10]. Sixty underweight participants (BMI <18.5 kg/m2) were not included because of the small sample size. WHR was calculated as waist circumference divided by hip circumference, while WHtR was calculated by dividing waist circumference by height. BAI was calculated as hip circumference divided by (height)$^{1.5}$ minus 18. Because of the lack of standardized classifications, WHR, WHtR, and BAI were categorized in quarters.

Assessment of DR, DME, and VTDR

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

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

Statistical analysis

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

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

The binary and ordinal logistic regression model was used to assess the association of BMI, WHR, WHtR, and BAI with the presence of any DR and VTDR. In special, the outcome of the ordinal logistic regression model of DR was set as no DR, mild NPDR, moderate NPDR, and VTDR (including PDR and DME). In the multivariate logistic model, the association was adjusted for potential confounding factors established in previous research. These factors 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). P values less than 0.05 were considered statistically significant.

Patient and public involvement statement

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

Results

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

developed VTDR.

Compared with participants who did not have DR, participants with DR had a younger age, a lower level of education, a longer duration of diabetes, and a higher proportion of males, smoking history, drinking history, and insulin use (Table 1). They also had a higher level of Hba1c, creatinine, microalbuminuria, and systolic blood pressure, but shorter axis length (all p <0.05). Moreover, their BMI, WHR, WHtR, and BAI were higher. According to Asia-Pacific BMI cutoff points, as high as 947 participants (41.1%) were obese, and 615 (26.7%) were overweight, while only 683 participants (29.6%) were normal weight.

Association of BMI with any DR, DME and VTDR

The prevalence of any DR, DME and VTDR in overweight diabetic patients was higher than that in patients who were normal weight or obese (Figure 2, Table 2). However, there was no significance in the association of BMI with any DR in the univariate binary or ordinal logistic model.

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

In the full model that further adjusted for continuous variables (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 (sex, smoking history, drinking history, education, duration of diabetes, and insulin use), the association of BMI became significant with both DME and VTDR (for DME, p for trend =

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)						

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)

0.031; for VTDR, p for trend = 0.016, Table 3). Obesity was inversely associated with DME and VTDR with a decreased OR (for DME, or=0.40, [95%CI, 0.16-0.96]; for VTDR, or=0.37, [95%CI, 0.16-0.87], Table 3). However, the association was only significant in female patients (for DME, p for trend =0.021, or of obesity =0.10, [95%CI, 0.01-0.77]; for VTDR, p for trend =0.015, or of obesity =0.09, [95%CI, 0.01-0.76], Table S3-1), but not in male patients (Table S3-2).

Association of WHR with any DR and severe DR

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

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

Association of WHtR with any DR and severe DR

The prevalence of DR decreased slightly with the growth of WHtR, while the prevalence of DME and VTDR was the highest in the Q2-WHtR, and then decreased (Table 2). In the univariate regression model, Q4-WHtR presented as a significant protective factor for DME (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/m2 (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	v14.29	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 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)	0.82(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

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

Association of BAI with any DR and severe DR

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

Discussion

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

while the association became less significant in the multivariable model.

Previous studies recognized obesity as a critical component of metabolic syndrome, which induces insulin resistance and advances the development of type 2 diabetes[2,3]. Therefore, weight control is usually recommended in the management of diabetes and several systemic diseases to reduce the prevalence of complications[3,11,12]. However, in this study, three obesity-related indexes, BMI, WHtR, and BAI, were all negatively associated with DR. The result presented as an "obesity paradox", which was also presented in several previous studies[13-15]. Moreover, it was more significant in the association with VTDR. The first possible reason would be that VTDR, presented and DME or PDR, was more likely to appear in the patients with advanced diabetes. Advanced diabetes would manifest as weight loss as one of the metabolic complications, contributing to the inverse association of obesity with DR. Second, BMI could hardly differentiate general obesity and centripetal obesity, which may play a different role in the progress of diabetes. Third, all the participants were from the community. They were diagnosed with diabetes in the hospital before the enrollment. The patients who had severe complications, low willingness to seek doctor's help or mobility problems, would be limited, contributing to the selection bias in the study.

Although obesity was recognized as one of the important biomarkers inducing insulin resistance[16], the obesity paradox has prevented scientists from making recommendations on weight management for diabetic patients. The positive correlation between centripetal obesity (presented as higher WHR) and diabetic progression has shed light on this problem. [17] In study of Tien Yin Wong *etal*, WHR was regarded to assess centripetal obesity, and BAI is established and has a significant linear relationship with body fat rate.[18] They demonstrated that abdominal

obesity may be a more critical factor of DR than the generalized obesity. However, in our study, as the indicator of centripetal obesity, Q2-WHtR associated positively with DR, and WHtR generally shows an opposite trend, indicating a nonlinear relationship between centripetal obesity. Therefore, we are collecting follow-up data to further prospectively analyze the relationship between obesity and diabetic retinopathy.

Our study also found that the associations between obesity-related index (both BMI and WHR) and VTDR were only significant in female patients, indicating that female patients would have a higher risk with the increase of centripetal obesity. The sex-specific obesity-diabetes association has been reported in several studies, but the association between obesity-related indexes (including BMI, WHR, WHtR, BAI) and diabetic retinopathy was seldom reported. We furthered analyzed the sex-specific distribution regarding different obesity-related indexes (Figure 3). Male patients have a significantly higher WHR, lower WHtR and lower BAI. However, the results may be influenced by the small number of patients in some of the categories after they were grouped by sex (there were "no observation" categories in Table S3-1 and Table S3-2). Therefore, more studies should be designed to investigate the weight control management and standard weight range regarding different sex in diabetic patients.

There are some other limitations in this study. First, in order to reduce the examination time and improve the compliance of participants, the measurement of waist circumference and hip circumference was not performed on every participant, while eventually 483 patients have undergone all the measurement including height, weight, waist circumference and hip circumference. Therefore, we are unable to put BMI, WHR, WHtR, and BAI in the full model with 2,305 patients at the same time. Second, although we used robust regression to make the

odds ratio more robust, we did not exclude the influence of collinearity in the full model, which may contribute to the variation of the association of factors such as BAI with DR. Third, the diabetic participants with severe condition (e.g. very poor eye sight, past DR treatment history, occurred with other combined eye diseases that could affect retinal thickness, etc.) were excluded. On contrary, the participants usually had a less severe condition, which may affect the generalizability of the results.

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

Contributors

W Huang and W Wei conceived and designed the study. W Li, W Wei, X Gong, L Wang, J Meng, Y Li, and K Xiong collected and interpreted the data. W Li, W Wei and L Jin carried out the statistical analysis. W Li wrote the manuscript. W Huang, W Wang, X Gong, and X Liang reviewed and edited the manuscript. All authors have seen the final version of the manuscript and approved it for publication.

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Declaration of Interests

The authors declare no competing financial interests.

Data availability statement

All data relevant to the study are included in the article or uploaded as supplementary information

Ethical Approval Statement

This study was approved by the Institutional Review Board of Zhongshan Ophthalmic Center (2017KYPJ094).

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Figure Legend

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

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: • >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: • 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: • 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.

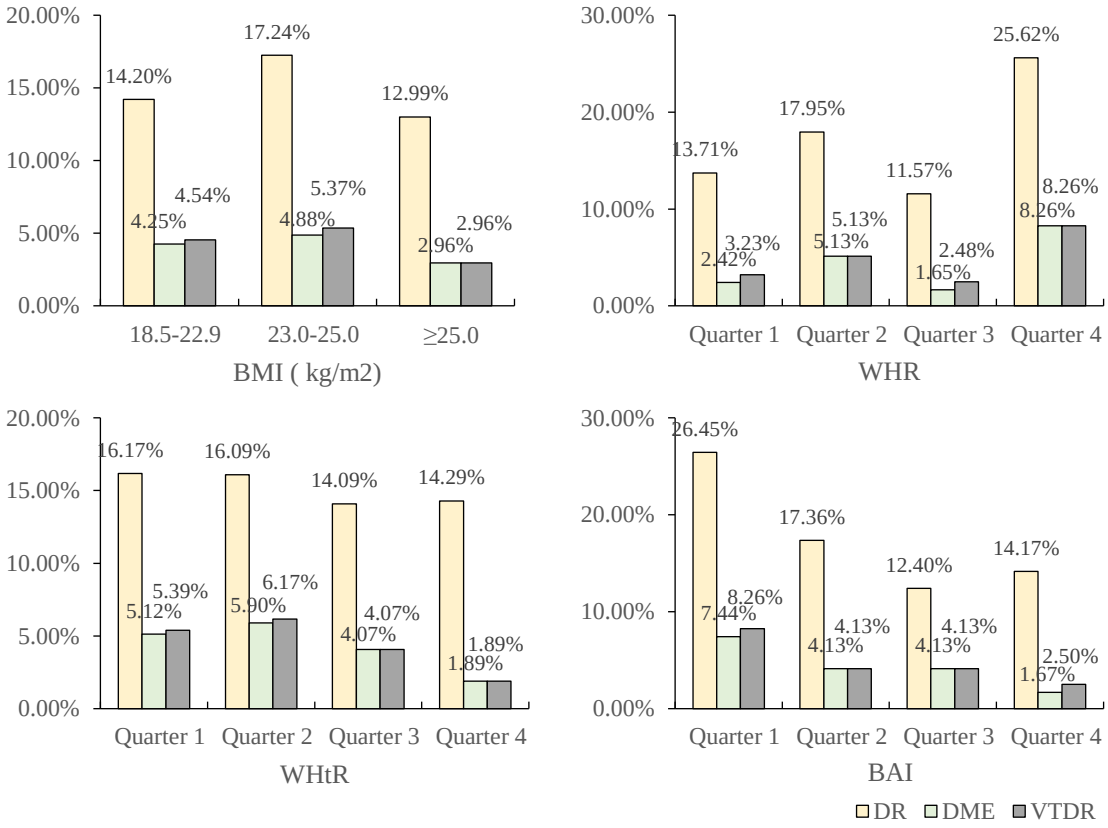

Figure 2. The prevalence of diabetic retinopathy (DR) and severe DR (diabetic retinopathy, DME, and vision threatening diabetic retinopathy, VTDR) in different groups of the obesity-related indexes. Footnotes: BMI: Body mass index. WHR: Waist to hip ratio. WHtR: waist to height ratio. BAI: Body adiposity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

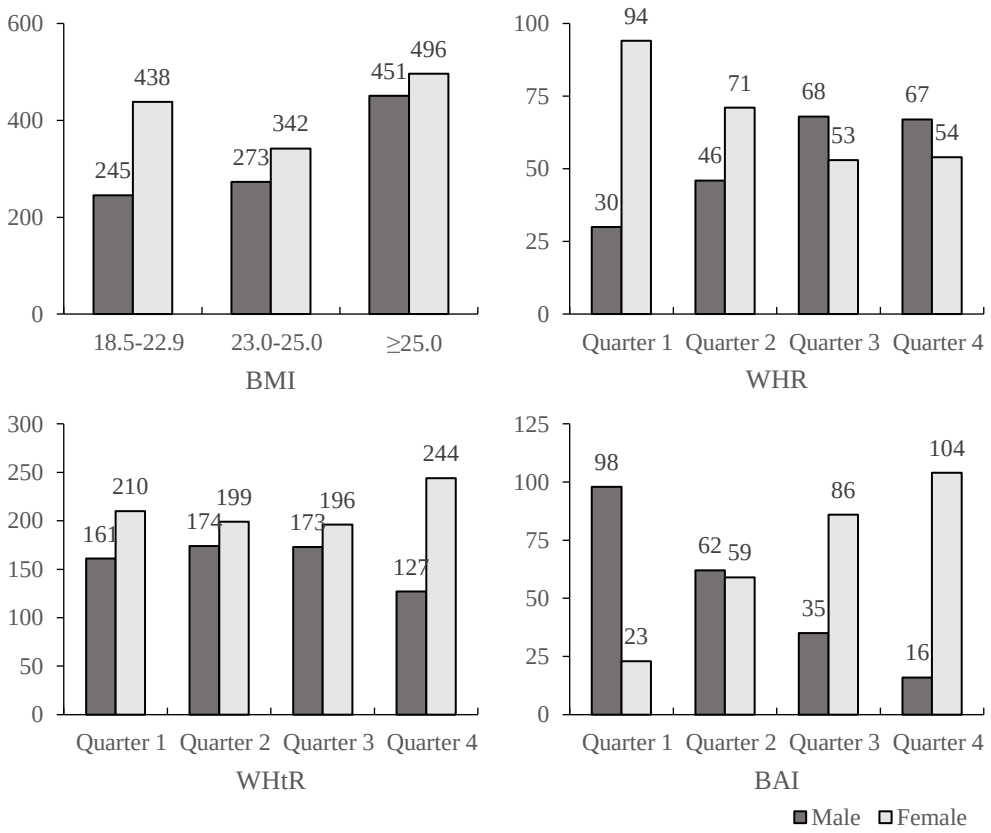

Figure 3. The number of male and female patients in different groups of the obesity-related indexes.

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 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)	1.24(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 valve	DME Odds ratio (95%CI)	P valve	VTDR 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 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		

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.