

Is central obesity associated with diabetic retinopathy in Chinese individuals? An exploratory study

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Abstract

Objective: To our knowledge, the independent association between central obesity, defined by waist circumference (WC) or waist-to-hip ratio (WHR), and diabetic retinopathy (DR) remains unknown in Chinese individuals.

Method: The study was conducted in two stages. First, the relationship between WC or WHR and DR was estimated in a case-control set (DR vs. non-DR) for the whole population before and after propensity score matching. Subsequently, a systematic review and meta-analysis was performed on evidence from the literature to validate the relationship.

Results: Of 511 eligible patients, DR (N = 156) and non-DR (N = 156) patients with similar propensity scores were included in the propensity score matching analyses. Central obesity (defined by WC) was associated with risk of DR (odds ratio [OR] 1.07, 95% confidence interval [95% CI] (1.03–1.10)). The meta-analysis showed that central obesity significantly increased the risk of DR by 12% (OR 1.12, 95% CI 1.02–1.22). Analysis of data from 18 studies showed a significant association between continuous body mass index and risk of proliferative DR (OR 0.95, 95% CI 0.93–0.98; $I^2 = 50\%$).

Conclusion: Central obesity, particularly as defined by WC, is associated with the risk of DR in the Chinese population.

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Keywords

Waist circumference, waist-to-hip ratio, body mass index, central obesity, diabetic retinopathy, China, propensity score matching, case control

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Introduction

It is widely accepted that diabetic retinopathy (DR) is a major risk factor for vision-threatening retinopathy in adults.^{1,2} However, in contrast to the more complete understanding of hazards associated with DR, risk factors related to DR remain inadequately elucidated.

The central role of diabetes duration and hyperglycaemia in the development and progression of DR is well known.^{3,4} Our previous study provided evidence for the role of blood pressure in the development of DR.⁵ Although the maintenance of normoglycaemia cannot stop the development of DR, other DR risk factors are important to its development.

Research suggests that obesity is associated with DR; however, the association between body mass index (BMI), an indicator of generalized obesity, and DR is inconsistent, possibly because of ethnic differences and the obesity paradox.^{6,7} Recent research indicates that central obesity, defined by waist-to-hip ratio (WHR), may be more associated with DR in the Singaporean population than is BMI.⁸ However, waist circumference (WC), another index of central obesity, is more closely related to central obesity in Chinese individuals than are BMI or WHR.⁹ There have been few studies on the relationship between WC and DR risk in China.

In response to this evidence gap, the present study recruited patients with DR at the Beijing Tongren Hospital (Beijing, China).

Covariant factors, such as diabetic duration, haemoglobin A1c (HbA1c), glomerular filter rate, blood pressure and lipid profiles, were matched using propensity score matching to elucidate the association between WC and DR. Subsequently, an up-to-date review of previous studies was conducted to determine the relationship between central obesity and risk of DR.

Methods

This was a hospital-based case-control study. Participants were hospital inpatients selected during January 2015 and December 2017 in Beijing, China. Only patients with comprehensive data on DR and anthropometric parameters were included in the analysis. The data that support these study findings are available from the corresponding author upon reasonable request. WC, a direct indicator of central obesity, was measured at the middle point between the last floating rib and the iliac crest (cm). Results were compared against recommended values: <94 cm (men) and <80 cm (women).¹⁰ As an index of body fat distribution, WHR was determined by dividing WC and hip circumference. Hip circumference (cm) was measured with a measuring tape around the femoral trochanters. According to the World Health Organization (WHO), central obesity is defined as a WC ≥ 102 cm for men and ≥ 88 cm for women or a WHR > 1.0 for men and > 0.9 for women. We used WC as a measure of central obesity. BMI was

calculated by dividing weight and height squared (kg/m^2). Weight was measured using a balance-beam scale and height was measured using a wall-mounted stadiometer with patients in their underwear and without shoes. BMI was categorized into underweight (<18.5), normal ($18.5\text{--}24.9$), overweight ($25\text{--}29.9$) and obese (≥ 30), according to WHO-defined international BMI cut points. However, owing to the small number of individuals who were underweight ($n=3$), the underweight and normal weight categories were combined.

Diabetic retinopathy screening

The presence of DR was diagnosed using digital retinal photographs (2 eyes \times 7 fields), taken using a TRC-NW7SF (Topcon Co., Tokyo, Japan) non-mydratic camera at 45° . These photographs were subsequently examined independently by two qualified retinal photography graders following quality assurance protocols. The severity of DR was graded based on the international clinical DR and diabetic macular oedema disease severity scales.¹¹

Ethics statement

The study was conducted with approval from the ethics committee of Beijing Tongren Hospital, Capital Medical University, and adhered to the tenets of the Declaration of Helsinki. Additionally, written informed consent was obtained from each participant.

Systematic review and meta-analysis

A meta-analysis was performed following the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) guidelines.¹² No ethical approval was warranted, as this was a meta-analysis of available studies.

PubMed, EMBASE and the Cochrane Library databases were searched for studies carried out up to September 2018 using the following terms: ('waist circumference' or 'WC' or 'WHR' or 'waist hip ratio' or 'visceral fat' or 'BMI' or 'body mass index' or 'body mass' or 'body weight' or 'obesity' or 'overweight' or 'adiposity') and ('diabetic retinopathy' or 'diabetic ocular' or 'diabetic ophthalmic'). To be included, study results had to be presented as odds ratios (OR) together with 95% confidence intervals (CI), or to provide enough data to perform these calculations, and to be published in English. Figure 1 shows the results of the literature search.

Statistics

Descriptive statistics were summarized using means for continuous variables and proportions for categorical variables. Demographics and disease risk factors were compared between DR and non-DR groups using the chi square test for categorical variables and the independent *t*-test for continuous variables.

To control for differences between participant characteristics in the two groups (Table 1), propensity score matching was performed to identify individuals with similar characteristics and to explore the effect of obesity indicators on DR.¹³ Pre-match imbalance and post-match balance were assessed for all the included covariates before and after matching by estimating standardized differences. Imbalance was defined as an absolute value higher than 0.2 for a given covariate.¹⁴ Proportional regression models were used to obtain the risk ratios and associated 95% CIs after propensity score matching.

The results of the original studies from the multivariable models were used. The inverse variance weighted method was used to obtain overall ORs and 95% CIs for an increase in risk of obesity.

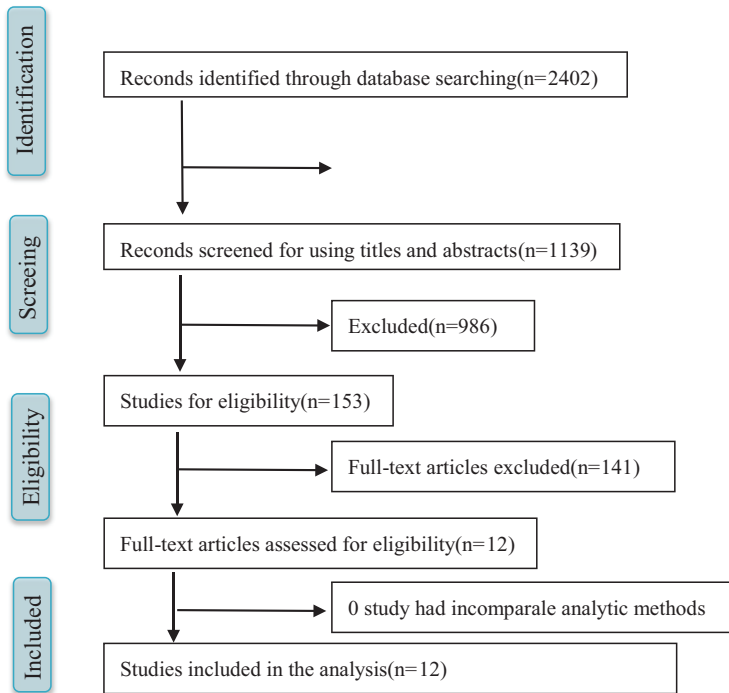


Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow chart.

A significant Q-statistic ($P < 0.10$) indicated heterogeneity across studies. Heterogeneity was quantified using the I^2 metric in the meta-analysis.¹⁵ The pooled OR was estimated using fixed effects (Mantel and Haenszel) and random effects (DerSimonian and Laird) models. When heterogeneity between studies was detected, the random effects model was estimated.¹⁶ The analyses were performed using STATA version 13.0 (StataCorp LP, College Station, TX, USA).

Results

Patient characteristics before and after matching

Prior to matching, 511 individuals with type 2 diabetes mellitus were identified.

The clinical characteristics of the non-DR (NDR) and DR (DR) groups were compared. Prior to matching, there were significant differences in patient demographics and clinical characteristics for DM duration ($P < 0.001$), GFR ($P < 0.001$), WC ($P = 0.006$), fasting plasma glucose ($P < 0.001$), systolic blood pressure ($P < 0.001$), HbA1c ($P < 0.001$), urine albumin excretion ($P < 0.001$) and fasting C-peptide ($P < 0.001$) (Table 1). A total of 348 NDR and 163 DR individuals were selected for investigation. No significant differences were found in sex, blood pressure, BMI, glomerular filtration rate (GFR), triglycerides (TG), high-density lipoprotein (HDL), total cholesterol (TC) and body fat (%). There were significant differences between the DR and NDR groups in diabetic duration, fasting

Table 1. Demographics and clinical characteristics of diabetic retinopathy and non-diabetic retinopathy groups prior to propensity score matching.

	Before matching			After matching		
	DR	NDR	P-value	DR	NDR	P-value
No.	163	348		156	156	
Sex (male/female)	84/79	199/149	NS	81/75	89/67	NS
Age (years)	57.8 ± 11.0	59.1 ± 11.4	NS	58.27 ± 11.02	58.44 ± 10.60	0.863
Duration of DM	14.4 ± 10.2	10.3 ± 8.1	<0.001	12.43 ± 9.3	11.87 ± 8.9	0.937
BMI (kg/m ²)	25.2 ± 2.60	25.0 ± 2.72	NS	25.22 ± 2.62	24.84 ± 2.66	0.201
GFR (mL/min/1.73m ²)	87.3 ± 17.8	91.7 ± 18.24	<0.001	89.61 ± 18.21	90.35 ± 17.85	0.483
SCr (mmol/l)	62.76 ± 16.66	65.48 ± 14.48	0.06	62.94 ± 16.70	63.85 ± 14.18	0.700
WC	92.2 ± 7.91	90.2 ± 7.89	0.006	92.5 ± 7.93	89.9 ± 7.40	0.004
FBG (mmol/l)	8.31 ± 2.78	7.34 ± 2.25	<0.001	8.21 ± 2.82	7.95 ± 2.28	0.183
TG (mmol/l)	1.80 ± 1.23	1.71 ± 1.23	NS	1.74 ± 1.25	1.63 ± 1.14	0.336
TC (mmol/l)	4.56 ± 1.03	4.43 ± 0.95	NS	4.51 ± 1.11	4.55 ± 0.91	0.841
HDL (mmol/l)	1.07 ± 0.27	1.17 ± 0.27	NS	1.08 ± 0.27	1.13 ± 0.28	0.101
LDL-c (mmol/l)	2.72 ± 0.90	2.63 ± 0.80	NS	2.69 ± 0.92	2.72 ± 0.75	0.766
SBP (mmHg)	134.64 ± 12.46	130.97 ± 12.11	<0.001	134.27 ± 12.55	134.96 ± 12.49	0.693
DBP (mmHg)	74.39 ± 8.87	75.29 ± 8.31	NS	74.40 ± 9.01	75.75 ± 8.74	0.131
HbA1c (%)	9.3 ± 1.80	8.5 ± 1.77	<0.001	9.15 ± 1.72	9.07 ± 1.67	0.706
UAER (mg/24 h)	239.66 ± 926.30	27.76 ± 103.74	<0.001	237.93 ± 942.35	28.33 ± 80.55	0.006
Fasting C-peptide (nmol/l)	1.54 ± 0.73	1.96 ± 0.92	<0.001	1.54 ± 0.72	1.56 ± 0.74	0.849
Waist-to-hip ratio	0.94 ± 0.06	0.92 ± 0.06	0.08	0.94 ± 0.06	0.93 ± 0.06	0.06
Hip circumference	98.09 ± 5.56	97.25 ± 6.26	NS	98.15 ± 5.63	97.18 ± 5.47	0.28
Body fat	31.87 ± 6.97	31.46 ± 6.80	NS	31.91 ± 7.10	31.14 ± 6.98	0.325

NS: non-significant; DR: diabetic retinopathy; NDR: non-diabetic retinopathy; DM: diabetes mellitus; BMI: body mass index; GFR: glomerular filtration rate; SCr: serum creatinine; WC: waist circumference; FBG: fasting plasma glucose; TG: triglycerides; TC: total cholesterol; HDL: high-density lipoprotein; LDL: low-density lipoprotein; SBP: systolic blood pressure; DBP: diastolic blood pressure; HbA1c: haemoglobin A1c; UAER: urine albumin excretion.

C-peptide and WC ($P < 0.05$, Table 1). Age, low-density lipoprotein (LDL) and WHR showed a marginally significant difference.

After propensity score matching, 312 patients were included in the analysis (NDR = 156, DR = 156). Table 1 summarizes patient demographics and disease characteristics post-matching. In the propensity score-matched individuals, sex, BMI, HDL, LDL, blood pressure, GFR, age, fasting C-peptide, TG and TC were comparable between the groups; WC and WHR were not (Table 1). The logistic regression analysis indicated an association between WC and risk of DR (OR 1.07, 95% CI 1.03–1.10). There was no significant

association between body fat (OR 1.02, 95% CI 0.98–1.05), WHR (OR 1.35, 95% CI 0.97–1.92) or BMI (OR 1.05, 0.97–1.14) and DR.

Meta-analysis

Central obesity and DR. Data on the effect of central obesity on DR were available from four trials plus our previous study.^{17–20} An increased DR risk was associated with central obesity (OR 1.12, 95% CI 1.02–1.22) (Figure 2). There was no evidence of heterogeneity ($I^2 = 80\%$; $P = 0.001$). Further analysis using the different measures of central obesity (WC and WHR) showed that WHR

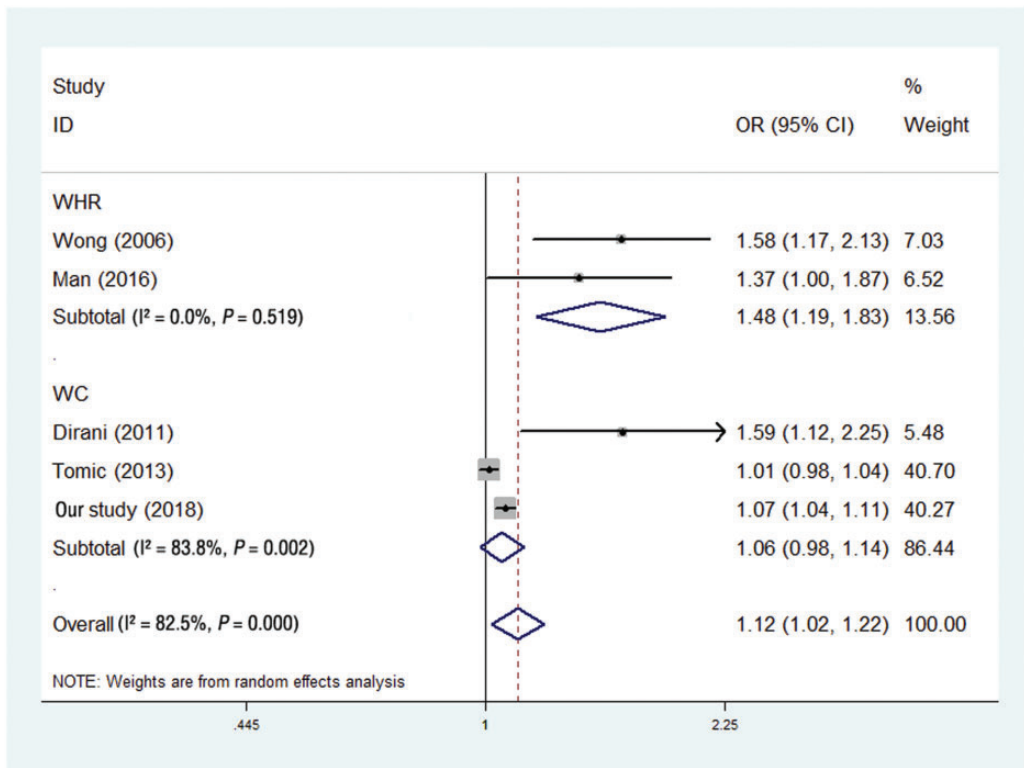


Figure 2. Association between central obesity and diabetic retinopathy risk in patients with type 2 diabetes mellitus: data from five observational studies.

Filled squares: 95% confidence intervals (CIs) for each group; open diamond: 95% CIs for all studies combined. The broken vertical line represents summary ORs of the total pooled data. WHR: waist-to-hip ratio; WC: waist circumference.

was associated with risk of DR (OR 1.48, 95% CI 1.19–1.83), but the association between WC and DR was only marginally significant (OR 1.06, 95% CI 0.98–1.14).

Body mass index and proliferative DR. Data from 18 studies were included to analyse the relationship between BMI and risk of DR.^{10,17–19,21–34} The results showed a marginally significant association between continuous BMI and DR risk (OR 0.97, 95% CI 0.95–0.99; $P=0.01$; $I^2=69\%$). Subgroup

analysis by ethnicity retained significance for Asian individuals (OR 0.97, 95% CI 0.94–0.99) but not for White individuals (OR 0.99, 95% CI 0.95 to 1.03) (Figure 3).

Data from five observational studies were pooled to evaluate the association between risk of proliferative DR and continuous BMI in patients with type 2 diabetes mellitus.^{19,24,25,28} There was a significant association between BMI and risk of DR (OR 0.95, 95% CI 0.93–0.98; $P=0.002$; $I^2=50\%$, Figure 4).

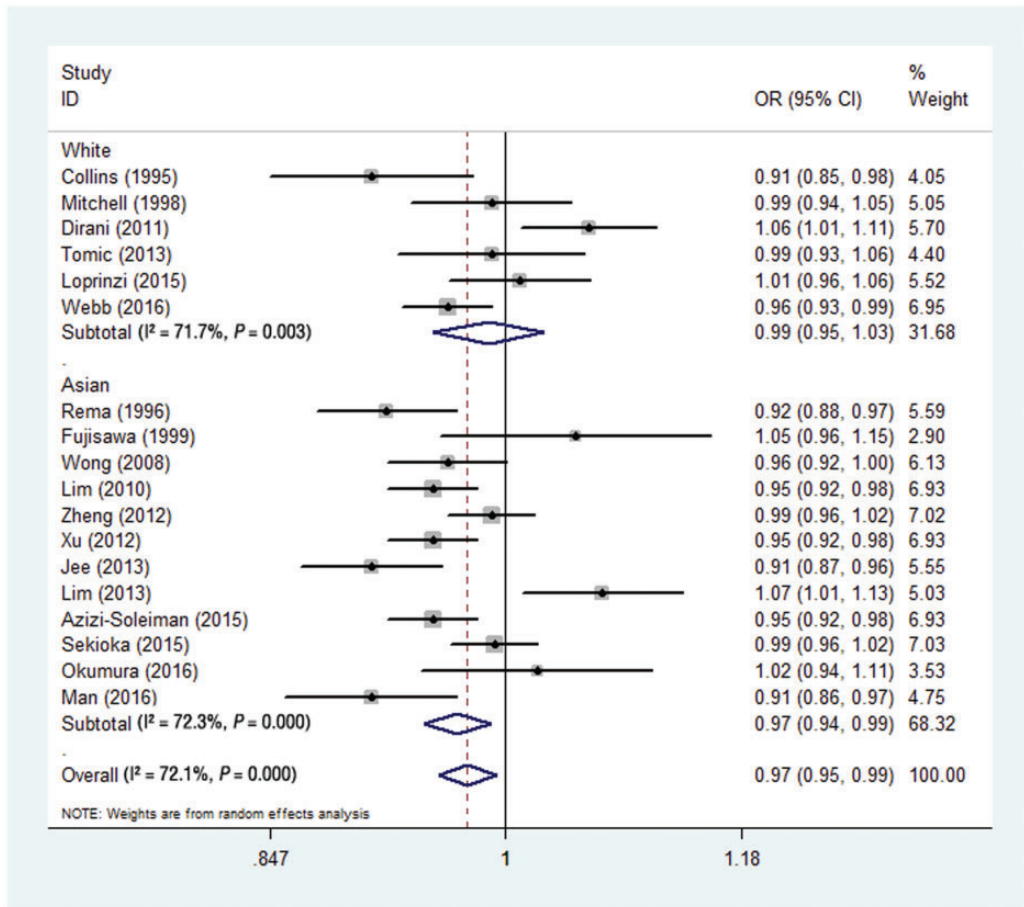


Figure 3. The relationship of body mass index to risk of diabetic retinopathy. Filled squares: 95% confidence intervals (CIs) for each group; open diamond: 95% CIs for all studies combined. The broken vertical line represents summary ORs of the total pooled data.

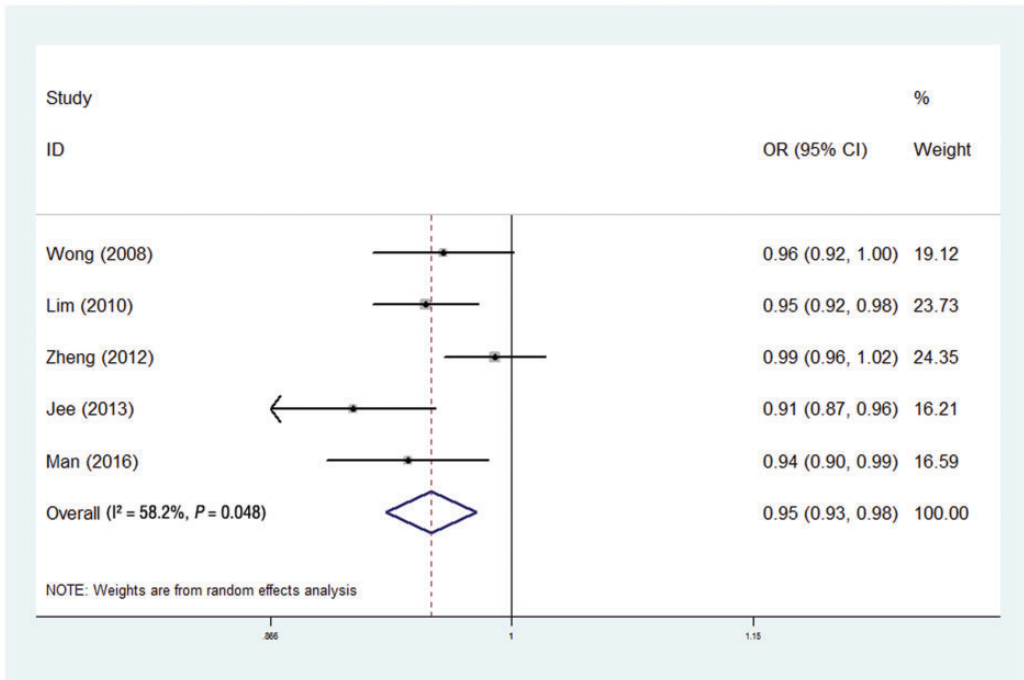


Figure 4. The risk of continuous body mass index with proliferative diabetic retinopathy in patients with type 2 diabetes mellitus: data from five observational studies.

Filled squares: 95% confidence intervals (CIs) for each group; open diamond 95% CIs for all studies combined. The broken vertical line represents summary ORs of the total pooled data.

Publication bias

The potential presence of publication bias was evaluated using a funnel plot of the estimate of log OR. Neither the funnel plot nor the Egger method ($t=1.92$, $P=0.48$) showed any evidence of bias, suggesting that no publication bias was present (Figure 5).

Discussion

The novelty of this study was its exploration of the association between central obesity (defined by WC or WHR) and risk of DR using propensity score matching analysis in a Chinese clinical sample. The relationship between central obesity and DR risk was also evaluated by a systematic review and meta-analysis of published

studies. We also validated the association between BMI and risk of proliferative DR.

Our data suggest that WC, an index of central obesity, is significantly associated with risk of DR, even after propensity score matching (OR 1.07, 95% CI 1.03–1.10). When the confounding factors were balanced (e.g. diabetic duration, HbA1c, fasting C-peptide, blood pressure, lipids and GFR), the association between BMI or WHR with DR disappeared, which seems to indicate a genuine effect of abdominal fat accumulation on DR. Previous research showed that, compared with WHR and BMI, WC has the strongest correlation with central obesity as diagnosed by computed tomography examination.⁹ Although BMI and WHR may be common indicators of obesity, WC,

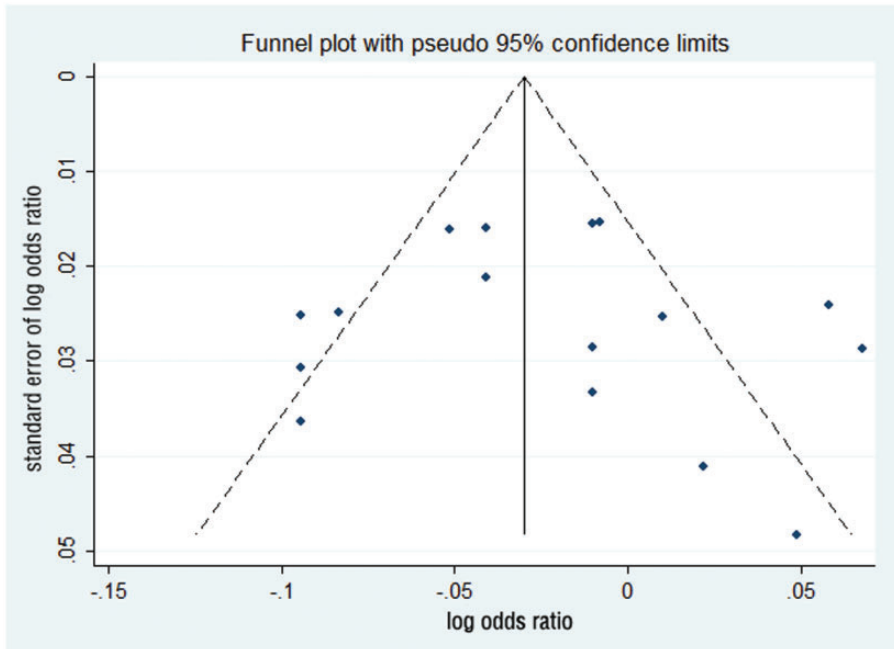


Figure 5. Estimated log of odds ratios indicating publication bias.

an index of visceral fat, seems a better indicator of the risk of vascular complications, particularly DR. A tempting hypothesis from these case-control data is that visceral fat distribution may contribute to the pathogenesis of DR,³⁵ in accordance with the suggestion that BMI may not be the best parameter for measuring the microvascular damage of obesity.⁶

Many explanations and mechanisms have been proposed to account for this association, including increased oxidative stress in persons with central obesity and DR,³⁶ and associations between DR and metabolic syndrome.³⁷ Emerging evidence suggests the beneficial effects of weight reduction. Progression of DR is impeded after bariatric surgery.³⁸ The risk of more severe DR may be reduced by greater physical activity.³⁹ However, it is still unclear whether central obesity or generalized obesity plays the greater role in risk reduction. More research is needed to confirm the

relationship between body fat distribution and DR in Asian groups, and to further understand the mechanisms by which central obesity is related to DR.

Despite the limited research on the relationship between WC and risk of DR, studies on central obesity (defined by either WC or WHR) were reviewed and analysed. The analysis showed that central obesity significantly increased the risk of DR by 12%. Further analysis of central obesity, defined by WHR, was associated with risk of DR (OR 1.48, 95% CI 1.19–1.83). Although large WC seems to play a role in DR, the mean hip circumference does not differ much between individuals with and without DR,⁴⁰ a finding that our results supported. Therefore, the discrepancy in DR risk between different WHRs might be a result of WC, not hip circumference. The marginal significance shown by the meta-analysis of central obesity (defined by WC) studies could be attributed to the scarcity of Asian

studies (OR 1.06, 95% CI 0.98–1.14); Asians typically have a greater propensity for visceral fat deposition at lower BMI than Whites.⁴¹

There are several study limitations. Despite propensity score matching to reduce the role of confounding factors in the model, there may have been effects from additional unknown factors. Second, previous studies indicate that earlier diabetes diagnosis age also increases the risk of DR,⁴² but this could not be measured in this study. Third, the relationship between central obesity and risk of DR severity could not be examined because of the limited sample size. However, the meta-analysis indicated that there is an association between generalized obesity, defined by BMI, and risk of proliferative DR.

Conclusion

Central obesity, as defined by WC, was associated with the risk of DR in this sample. Further research examining causal relationships between central obesity and DR needs to be conducted using longitudinal designs.

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Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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