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Association of obesity and risk of diabetic retinopathy in diabetes patients
A meta-analysis of prospective cohort studies

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Abstract

Background: Diabetic retinopathy (DR) was considered to be a common complication of diabetes. The purpose of the current study was to investigate the potential association between obesity and DR risk by conducting a meta-analysis of prospective studies.

Methods: A consummate literature search of PubMed, EMBASE, and web of science was conducted until July 2016. A total of 13 prospective cohort studies were included in this meta-analysis.

Results: On meta-analysis of all the studies assessing DR risk, obesity was associated with a significant increase in DR incidence (relative risk [RR], 1.20; 95% confidence interval [CI], 1.01–1.43; $I^2 = 59.6\%$). When only proliferative DR (PDR) was considered, no significant association between obesity and risk of PDR was detected. Significant harmful effect was detected in type 2 diabetes mellitus (T2DM) group (RR, 1.40; 95% CI, 1.05–1.87; $I^2 = 67.6\%$) but not mixed group (RR, 1.04; 95% CI, 0.97–1.18; $I^2 = 0.00\%$). No significant publication bias was detected in the selected 13 studies.

Conclusion: Obesity was a risk factor for non-proliferative DR. However additional well-designed and well-conducted epidemiologic studies were required to deepen our understanding of the relation between obesity and DR.

Abbreviations: BMI = body mass index, CI = confidence intervals, DR = diabetic retinopathy, MOOSE = Meta-analysis of Observational Studies in Epidemiology, NOS = Newcastle-Ottawa Scale, OR = odds ratios, PDR = proliferative diabetic retinopathy, PRISMA = preferred reporting items for systematic reviews and meta-analyses, RR = relative risk, T1DM = type 1 diabetes mellitus, T2DM = type 2 diabetes mellitus, WHR = waist-to-hip ratio.

Keywords: body mass index, diabetic retinopathy, meta-analysis, obesity, risk factor

1. Introduction

Both type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM) were considered as important burdens on public health system.[1] Diabetic retinopathy (DR), which was a common complication of diabetes, remained to be one of the leading preventable causes of visual impairment in the whole world.[2] Through intense glucose control, retinal laser photoco-

agulation and vitrectomy, the incidence of blindness caused by DR was significantly reduced. However, visual disability caused by DR would continue to be important issue in coming decades. To gain the most effective management of DR, early diagnosis and careful management would provide fundamental contribution. The detection of modifiable risk factors of DR had an important value on public health and clinical management. Epidemiological study could provide better knowledge on risk factors of DR and previous national population-based studies reported common risk factors for DR.[3] Longer diabetes duration, worse glucose control, hypertension, and tobacco smoking were considered generally established risk factors for DR.[4] Early management and intense treatment for patients with higher DR risks would provide better prognoses.

The impacts of obesity on carcinomas, cardiovascular, and metabolic systems disorders have been widespread and obese was regarded as a harmful factor in most diseases.[5,6] Considering that there was significant relation between obesity and diabetes risk, it was natural to consider the potential effect of obesity on the incidence of DR. Through a population-based study involving 6499 individuals with a follow-up of 11.1 years, it was found that obesity was associated with an increased risk of diabetes.[7] Besides, obesity was an established risk factor for several systemic diseases including hypertension, stroke, dyslipidemia, and sleep apnea,[8] and these diseases were reported as potential risk factors of DR.[9,10] The association between obesity and DR risk was reported in several previous observational studies, however, no accordant conclusions were obtained. Data of a hospital-based study with 156 diabetic persons showed that obesity may be considered as a risk factor for DR in T2DM patients.[11] While in

a cross-sectional study using clinical data in Saudi National Diabetes Registry data with a cohort of 50,464 Saudi patients, overweight and obesity were reported to be associated with an inversed risk of DR after adjustments of age and sex.[12] Besides, a database analyses in UK demonstrated the body mass index (BMI) was not associated with retinopathy status in T2DM patients through multivariate logistic regression.[13] Meta-analysis is a useful statistical tool to gain a more powerful conclusion through pooling consubstantiate but independent studies together.[14] The purpose of this current meta-analysis was to investigate the relationship between obesity and DR risk of prospective cohorts. Besides, detailed analyses in this study would also provide certain suggestions for improvement of following study designs.

2. Methods

This systematic review and meta-analysis was conducted according to the Meta-analysis of Observational Studies in Epidemiology (MOOSE)[15] and reported following preferred reporting items for systematic reviews and meta-analyses (PRISMA)[16] guidelines. No ethics committee or institutional review board approvement was required in this study.

2.1. Search strategy

PubMed, EMBASE, and web of science were searched using selected key words regarding obesity and DR (last search update July 206). The key word group for obesity was composed by obesity, overweight, adiposity, body mass index, BMI, metabolic syndrome, intra-abdominal fat, waist–hip ratio, and waist circumference. No restrictions of language or publication data in literature search were applied. Besides, the reference lists of the selected articles were reviewed to identify additional eligible publications. When supplemental data were required, the contacts with corresponding authors of related studies were conducted if necessary.

2.2. Inclusion and exclusion criteria

For inclusion, the studies would be included if they met the following criteria: the association between obesity and DR was evaluated; a prospective cohort study design was adopted; the odds ratios (OR), relative risk (RR) with 95% confidence intervals (CI) or sufficient data to calculate them were reported. The exclusion criteria included: not cohort design was adopted; no available data in suitable format was reported.

2.3. Data extraction and quality scale

Two investigators (WZ and YW) extracted the data from each included publication independently. The extracted data included first author of each publication, country, age of participants, study period, publication year, diagnosis and deification of DR, exposure definition, adjustments or matched factors, RR value in each study. If both adjusted and non-adjusted data were provided, only the adjusted value was used. When stratified data were provided in the original article, only the highest/lowest group data were extracted and used in the calculation. If only OR was provided, the following formula was used to the calculate RR:

$$\text{Relative risk} = \frac{\text{odds ratio}}{[(1-\text{Po}) + (\text{Po} \times \text{odds ratio})]}$$

In the formula, Po was the incidence rate of DR in the nonexposed group. If only the primary data were reported, we converted it into RR value.

Considering the only prospective cohort studies were included in this study, Newcastle-Ottawa Scale (NOS) was obtained in the quality scale for each included study.[17] NOS was a quality assessment scale of methodological quality for both case-control and cohort studies. In this study, the selection, comparability, and exposure of each study were scored and the studies with NOS score over 6 stars were considered as relatively high quality. Any disagreements in data extraction, data reforming, and quality scale were resolved by discussion with the third reviewer (YFM).

3. Statistical analysis

Considering the observational design nature of the included studies, a random-effects model was used for the quantitative synthesis. As all the included studies were prospective cohort study, RR values were used to evaluate the associations between obesity and the risk of DR.

The test of heterogeneity in quantitative calculation across studies was carried out using both χ^2 and I^2 test. Because tests for heterogeneity lack power, an I^2 value $>50\%$ or $P < .1$ in χ^2 test was considered to show substantial heterogeneity. In this current meta-analysis, subgroup analyses by stratifying study characteristics (such as DM type, study site, and adjusting status) were conducted to detect the sources of heterogeneity. Potential publication bias would be detected by both the funnel plot analysis and Egger test.[18,19] All the statistical analyses were performed using STATA Version 12 (StataCorp Stata Statistical Software: release 12.0, College Station, TX).

4. Results

4.1. Literature search

A total of 4172 articles were detected from the 3 databases (1631 in PubMed, 2669 in EMBASE, and 412 in web of science). Besides, 22 additional records were detected through reviewing the reference lists of relevant articles. After the exclusion of 3707 articles with unrelated topics, the abstracts of 937 publications were reviewed for potential inclusion. Of the 937 remaining articles, 710 papers were excluded because they were case reports, reviews, and overlapped articles. Besides, the papers in which DR was not involved were also dropped through screening the abstracts. After reviewing the full text of the 227 remaining articles, a total of 13 prospective cohort studies were included in the final quantitative synthesis. Among the 214 excluded studies, 44 studies didn't reported study designs equivocally, 166 studies didn't report outcomes of interest with raw data, and 4 cohort studies were previously reported. In total, 13 publications between 1993 and 2016 were included in this current meta-analysis.[20–32] The flow diagram for the literature search identifying the relevant studies was present in Fig. 1.

4.2. Study characteristics

The main characteristics of all the included studies in this present analysis were showed in Table 1. In the all the included studies, a total of 14,575 participants were included in this meta-analysis. The range of publication date was between 1993 and 2016. When the diabetes type was considered, both T2DM and mixed types were included in the analysis. The follow-up duration among all the studies ranged from 1 year to 20 years. The sites
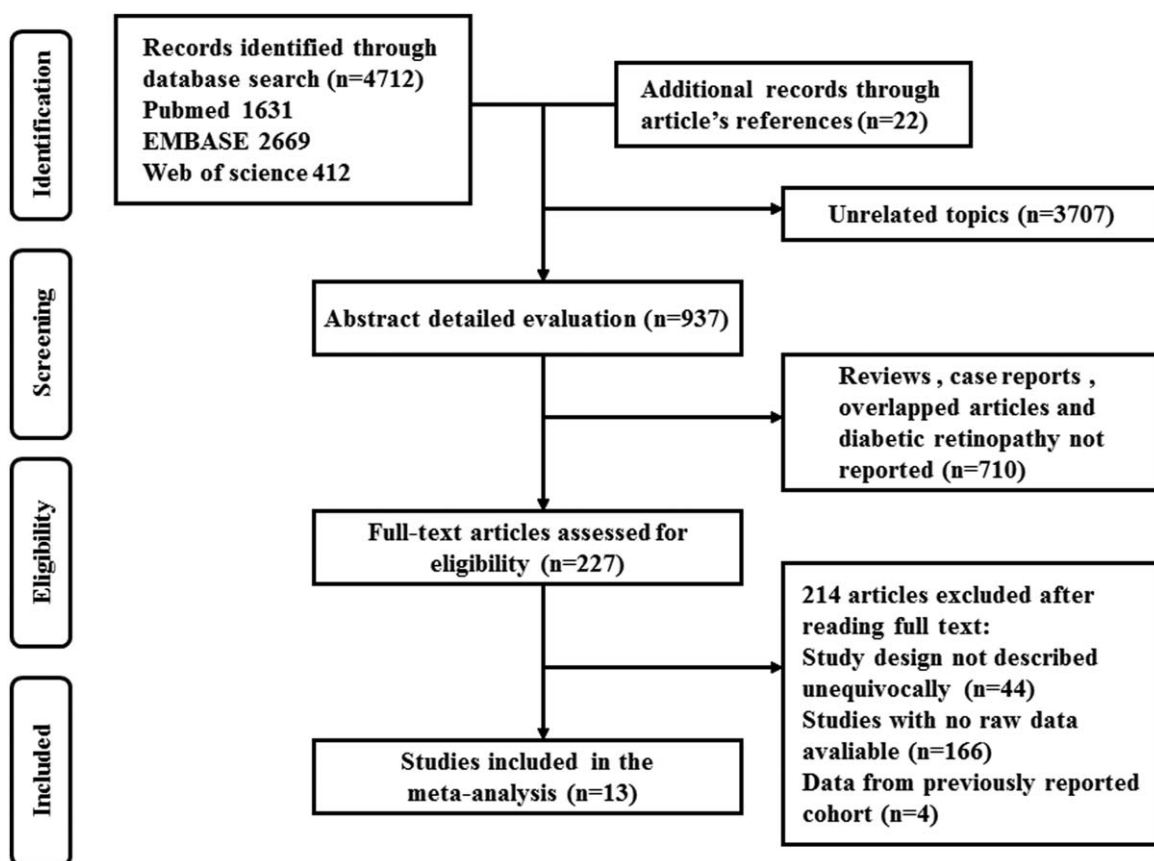
Figure 1. PRISMA diagram for identification of relevant studies. PRISMA = preferred reporting items for systematic reviews and meta-analyses.

where the studies had been carried out were as follows: 7 in Asia, 5 in Europe, and 1 in Americas. The methodological quality of each included study was assessed by NOS. NOS was designed for the quality assessment of observational studies and the maximum was 9 stars. The NOS scales for all the included studies ranged from 5 to 8 and the average score was 7.15 stars. The rate of high-quality (>6 stars) were present in most included studies (12 in 13).

4.3. Obesity and the risk of DR

Figure 2 demonstrated the effect of obesity on DR risk through pooling all the included studies in this meta-analysis. The analyses of the 13 included studies showed that obesity was a risk factor for the incidence of DR (RR, 1.20; 95% CI, 1.01–1.43; $I^2 = 59.6\%$).

To deepen the understanding on the relationship between obesity and DR, the subgroup analyses by study characters and adjusting status were conducted (Table 2). When only proliferative DR (PDR) was considered, no significant association between obesity and risk of PDR was detected (RR, 1.15; 95% CI, 0.89–1.48; $I^2 = 32.5\%$). Considering that different subtypes of diabetes demonstrated diverse clinical manifestations, significant harmful effect was detected in T2DM group (RR, 1.40; 95% CI, 1.05–1.87; $I^2 = 67.6\%$) but not mix group (RR, 1.04; 95% CI, 0.97–1.18; $I^2 = 0.00\%$). Subgroup analysis by study sites showed that the studies in Asia demonstrated significant relationship between obesity and DR risk (RR, 1.22; 95% CI, 1.04–1.44; $I^2 = 33.8\%$). However, the studies conducted in neither Europe nor America demonstrated statistically significant association. Besides, it was in longer follow-up

group (>8 years) but not shorter follow-up group (<8 years) demonstrated significant association. When the adjustment status was considered and no significant association was detected in subgroup meta-analysis by the adjustments of age, sex, diabetes duration, and HAb1c.

4.4. Sensitivity analysis and publication bias

To assess the robustness of the conclusion in this study, we conducted a sensitivity analyses through dropping the studies with lower methodological quality (<6 stars in NOS). After excluding 1 study from the meta-analysis and it was found that obesity was a significant harmful factor for DR (RR, 1.22; 95% CI, 1.00–1.47; $I^2 = 62.9\%$).

To assess the publication bias, both visual inspection of funnel plots and Egger test were used. No significant publication bias was found in the selected 13 studies (Begg test, $P = .180$; Eegg test, $P = .377$). The funnel plot was symmetrical and presented in Fig. 3.

5. Discussion

This meta-analysis of 13 prospective cohort studies on obesity for DR risk demonstrated the existence of a significant harmful effect for DR incidence. In general the conclusion was robust and no publication bias was detected. However, advanced analyses by study designs or adjusting statuses demonstrated no significant associations.

Obesity, which was a major public health problem, was reported to be associated with development of different diseases[33,34] and

Table 1

Characteristics of studies of obesity and diabetic retinopathy risk included in the final analysis (n = 13).

Author, publication year	Country	Age, y	Study period, y	DR diagnosis	DR definition	No. of case/cohort	Diabetes type	Adjustment/matched	Exposure definition (BMI, kg/m²)	NOS scale
Yoshida et al, 2001[22]	Japan	54	7	Direct and indirect ophthalmoscopy	Background retinopathy or more	132/787	T2DM	Gender, diastolic blood, age at first visit, BMI at first visit, total cholesterol, systolic blood pressure	<20.6, <22.1, 23.7 ≥23.7	6
Tanaka et al, 2016[23]	Japan	58.3±6.9	8	NR	International diabetic retinopathy and diabetic macular edema disease scales	318/1141	T2DM	Age at baseline, HbA1C, years after diagnosis, log-albumin-to-creatinine ratio, waist-to-hip ratio and log triglycerides	Current obesity, past obesity	7
Janghorbani et al, 2001[25]	UK	49.5±7.5	4.6	Direct ophthalmoscopy	3 types	928/4352	T1DM and T2DM	Gender, age, age at diagnosis, duration of DM, HbA1, blood pressure, casual blood, glucose, smoking	<27, 27–33 ≥34	8
van Leiden et al, 2003[26]	Netherlands	63.2±6.5	9.4	Retinal photographs	EURODIAB scale	27/233	T1DM and T2DM	Age, sex, HbA1c level, and hypertension	<25.16, <27.62 ≥27.62;	9
Lamparter et al, 2014[27]	Germany	60.0±9.1	5	Retinal photographs	Early treatment diabetic retinopathy study	75/722	T2DM	Sex, age, family history of myocardial infarction, hypertension, dyslipidemia, smoking, stroke, chronic heart failure, chronic obstructive pulmonary disease, myocardial infarction, coronary artery disease, peripheral artery disease	<27, ≥30	7
Klein et al, 1997[28]	USA	66.6±11.3	4/10	Retinal photographs	13 levels of severity	540/1370	T2DM	Systolic blood pressure, glycosylated hemoglobin A	Normal, underweight, overweight, obese	8
Haupt et al, 1999[29]	Germany	54.5±6.9	NA	Ophthalmoscopy	3 types	184/698	T2DM	Sex duration of disease, age on diagnose, age on admission, cholesterol, LDL, Creatinine Albumin	<25, 25–30, 30–35, ≥35	6
Bener et al, 2014[30]	Qatar	45.3±15.0	20	Questionnaire	NA	204/1633	T1DM and T2DM	Age, tyoe of DM, gender, Nationality, level of education, physical activity	<25, ≥25	7
Ahmed et al, 2011[31]	Bangladesh	45–60	15	Direct and indirect ophthalmoscopy	2 stages	229/977	T2DM	Age, sex, area, physical activity, fasting blood glucose, HbA1C, TC, TG, creatinine, SBP	18.5–24.9, <18.5 25–30, >30	8
Ozmen and Boyvada , 2003[21]	Turkey	58.07±9.13	1	Direct ophthalmoscopy	Early treatment diabetic retinopathy study	127/267	T2DM	NA	<25, 25.1–29.9 30–39.9, >40	7
Tanaka et al, 2013[20]	Japan	62.1±8.6	7.2 y	Ophthalmoscopy	International diabetic retinopathy and diabetic macular edema disease scales	1748	T2DM	Age, HbA1c, years after diagnosis, ACR	<18.5, <25, ≥25	7
Araki et al, 1993[32]	Japan	69.2±5.5	7.9±2.6	Ophthalmoscopy	NA	49/110	T1DM and T2DM	Age, age at onset, sex, diabetes duration, FPG plasma glucose, HbA1	<25, ≥25	5
Janghorbani et al, 2003[24]	Iran	45.7±9.3	5.1±2.1	Fundus photography	NA	249/549	T1DM and T2DM	Age	<27 27–33 ≥34	7

ACR = albumin/creatinine ratio, BMI = body mass index, DR = diabetic retinopathy, LDL = low-density lipoprotein, NA = not available, NOS = Newcastle-Ottawa Scale, NR = not reported, T1DM = type 1 diabetes mellitus, T2DM = type 2 diabetes mellitus.
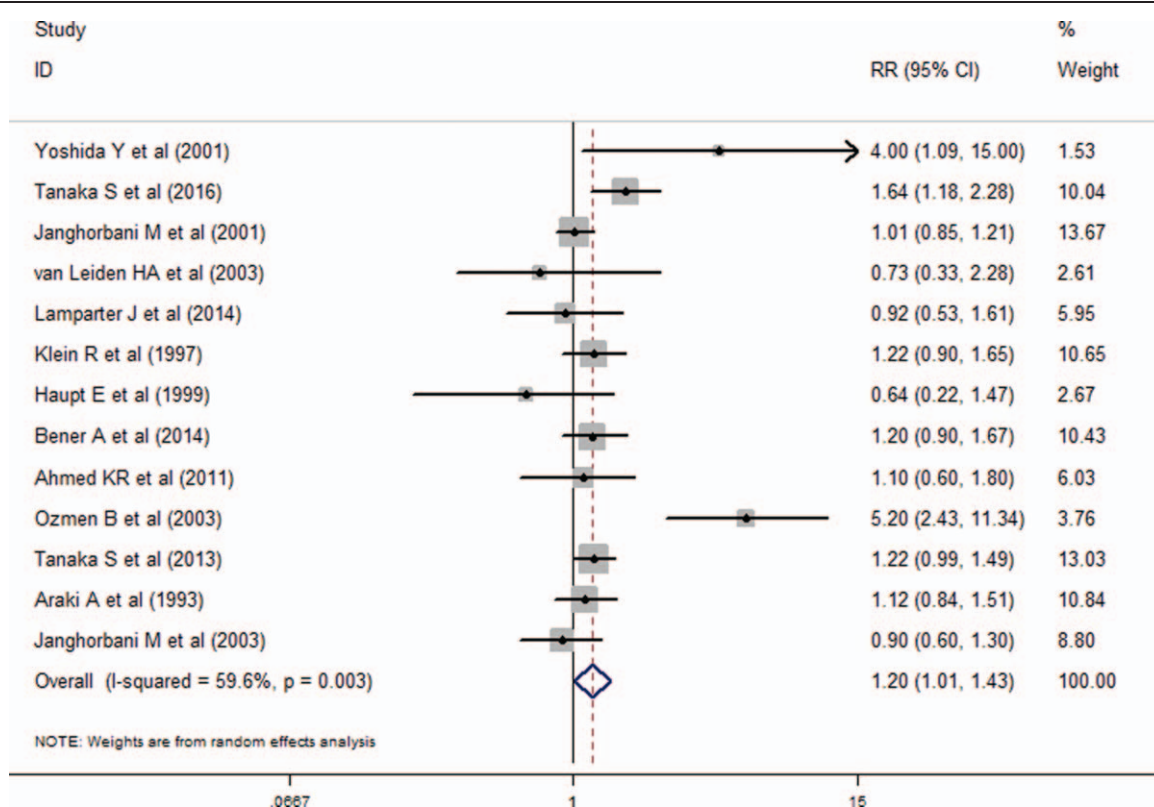
Figure 2. Forest plot for the association between obesity and DR risk. DR = diabetic retinopathy.

important cause of mortality in the whole world.[6,35] It also indicated that the relation between obesity and diabetes risk was significant.[36] However, inconsistent conclusions on the association between obesity and DR were detected in previous epidemiological studies. In a cross-sectional study including 501 adults with T1DM, it was found that obesity (BMI > 30 kg/m^2) was the predominant risk factor for retinopathy.[37] While through

multinomial logistic regression analyses in a cross-sectional clinic-based study, it was found that BMI was inversely associated with mild-moderate and severe DR. Thus, a higher BMI appeared to confer a protective effect on DR risk in Asian patients with T2DM.[38] Insignificant association between BMI and DR was also reported in previous cross-sectional studies.[39,40] Besides, case control studies were also conducted to detect the effect of obesity

Table 2

Summary relative risk (RR) and 95% confidence interval (CI) for subgroup meta-analysis by study designs and adjusting status.

	Subgroups	No. of studies	Summary effect RR (95% CI)	P value	I^2, %	P value
DR stage	PDR	4	1.146 (0.889–1.477)	.65	32.5	.218
	Any DR	13	1.202 (1.014–1.427)	.385	59.6	.003
Site	Asia	7	1.221 (1.036–1.439)	.017	33.8	.17
	Europe	5	1.188 (0.670–2.107)	.556	78.4	.001
	Americas	1	1.220 (0.901–1.652)	.198	–	–
DM type	T2DM	8	1.397 (1.045–1.868)	.187	67.6	.003
	Mixed	5	1.041 (0.917–1.183)	.942	0.0	.693
Follow-up	<8 years	9	1.205 (0.946–1.535)	.131	66.9	.002
	≥8 years	5	1.207 (1.023–1.424)	.005	0.0	.403
Adjustments						
Age	Yes	8	1.140 (0.961–1.353)	.133	66.5	.067
	No	5	1.374 (0.894–2.111)	.147	33.5	.004
Gender adjusted	Yes	6	1.066 (0.898–1.266)	.462	11.7	.34
	No	7	1.299 (1.001–1.685)	.049	71.4	.002
DM duration	Yes	5	1.169 (0.972–1.404)	.096	51.9	.081
	No	8	1.287 (0.934–1.773)	.122	67.1	.003
HAb1c	Yes	5	1.173 (0.983–1.399)	.076	48.2	.102
	No	8	1.276 (0.923–1.765)	.141	68.0	.003

CI = confidence interval, DR = diabetic retinopathy, PDR = proliferative diabetic retinopathy, RR = relative risk, T1DM = type 1 diabetes mellitus, T2DM = type 2 diabetes mellitus.
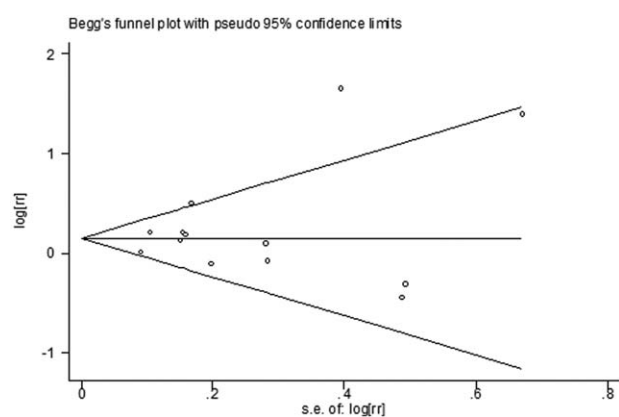
Figure 3. Funnel plot for assessment of publication bias.

on DR. However, previous case-control studies also indicated inconsistent conclusions.[41,42] Cohort study design demonstrated stronger power in the detection of the risk factors. Besides, meta-analysis was a useful tool in epidemiological study. In this current meta-analysis, only prospective cohort studies were included and robust conclusion was gained. Through pooling 13 independent studies together, slight but significant harmful effect of obesity on the DR incidence was detected. Thus, the results in this study provided high level of evidence for the existence of the relationship between obesity and DR.

However, no significant association was detected in several advanced subgroup analyses and thus more detailed researches were required. When the diabetes types were considered, it was found significant association between obesity and DR in T2DM. While no previous prospective cohort study was conducted to detect the effect of obesity on the incidence of DR in T1DM cases. Even no stratified results on obesity and DR risk were reported, however, the relation between BMI and retinopathy incidence in T1DM cases was reported. A population-based cohort of 727 T1DM patients with 25 years follow-up, it was found that BMI was associated with DR in risk age and sex adjusted multivariate models.[43] A retrospective cohort consisting of 989 T1DM patients who were followed up for a mean of 10.1 years showed that BMI at baseline was not associated with the development of DR.[44] When time-dependent obesity along the follow-up duration was considered, BMI was associated with DR incidence. Besides, the occurrence of DR has been related to high BMI in the T1DM cases in a study in Sweden.[45] When diabetes of both subtypes were considered, it was found that obesity was associated with high risk of DR incidence in this meta-analysis. However, further advanced cohort analyses were required to gain more knowledge in the effect of obesity on the risk of DR.

In this study, the definition of obesity was based on the BMI. A previous cross-sectional clinic-based study showed that BMI was inversely associated with DR incidence while waist-to-hip ratio (WHR) was positively associated with retinopathy risk.[38] The interesting results of that study indicated that more clinical trials were required to determine whether WHR is a more clinically relevant risk marker than BMI for individuals with T2DM. The data from Sankara Nethralaya Diabetic Retinopathy Epidemiology and Molecular Genetics Study (SN-DREAMS-I) reported that increased WHR in women was associated with DR; higher BMI group had a protective role for any DR in the overall group through logistic regression analyses.[46] Among the 13 included prospective study, 2 studies reported the results based WHR

while no significant association was detected (RR, 2.60; 95% CI, 0.332–20.390; $I^2 = 85.9\%$). In the other hand, WHR abnormality was a sign of metabolism syndrome and several previous studies indicated the relationship between metabolism syndrome and DR incidence. A case-control study with 2551 Chinese participants, it was found that metabolism syndrome was a strong and independent indicator of DR even to the same extent as glycemic control.[42] Thus, more advanced study should be conducted to detect the potential association.

The main strength of this study lied in the detailed literature search. Systematical literature strategy and a huge amount of full-text articles (over 200 publications) were reviewed in the literature searching progress. Besides, considering the higher evidence of cohort study design, only prospective cohort studies were included in this meta-analysis and selection bias could be ignored. However, there were also some limitations should be acknowledged in this meta-analysis. First, even a systematical literature was conducted in this study, the number of the included studies was small. The relatively small amount of included study might be influence the strength of the conclusion in this study. First, the conclusion of this study might be influenced by deficient criteria of obesity or different BMI stratifications among the included studies. In the meta-analysis, we adopted the highest versus lowest data in quantitative synthesis. Even no statistical heterogeneity was detected, the variability in the study design might influence the conclusion of this study. Second, we attempted to detect the dose–response relationship between obesity and DR risk. However, even significant association was detected, no sufficient data (including BMI stratification, pervasion-years data, and RR value in each group) could be extracted from most included studies. More well-designed studies with detailed data were required in the future. Third, the pooled risk estimate may be affected by 1 individual study and thus more related studies were required.

6. Conclusions

In conclusion, the findings in this current meta-analysis of prospective cohort studies suggest that obesity was a risk factor for non-proliferative DR. However, the significance could not be detected in several subgroup analysis and thus additional well-designed and well-conducted epidemiologic studies were required to deepen our understanding of the relation between obesity and DR risk. Advanced studies with more data on T1DM cases and different obesity definitions were urgent required.

Author contributions

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Supervision: Yan Wu.
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Writing – original draft: Wei Zhu, Yan Wu, Yi-Fang Meng, Qian Xing, Jian-Jun Tao, Jiong Lu.

Writing – review and editing: Qian Xing.

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