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Body mass index and risk of diabetic retinopathy

A meta-analysis and systematic review

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Abstract

Diabetic retinopathy (DR) is a frequent cause of acquired blindness worldwide. Various studies have reported the effects of body mass index (BMI) on the risk of DR, but the results remain controversial. Therefore, a meta-analysis was performed to evaluate the relationship between BMI and the risk of DR.

A systematic search was performed using the Cochrane Library, PubMed, and Embase databases to obtain articles published through December 2016. Articles regarding the association between BMI and the risk of DR were retrieved. The adjusted odds ratios (ORs) and their 95% confidence intervals (CIs) were included and then pooled with a random effects model.

A total of 27 articles were included in this meta-analysis. When BMI was analyzed as a categorical variable, neither being overweight (OR = 0.89, 95% CI 0.75–1.07; $P = .21$; $I^2 = 65\%$) nor obesity (OR = 0.97, 95% CI 0.73–1.30; $P = .86$) were associated with an increased risk of DR when compared with normal weight. When BMI was analyzed as a continuous variable, a higher BMI was not associated with an increased risk of DR (OR = 0.99, 95% CI 0.97–1.01; $P = .25$; I2 = 79%). The pooled results did not significantly change after the sensitivity analysis.

Based on the current publications, neither being overweight nor obesity is associated with an increased risk of DR. Further studies should confirm these findings.

Abbreviations: BMI = body mass index, CI = confidence interval, DR = diabetic retinopathy, HbA1c = glycated hemoglobin, HDL-C = high-density lipoprotein cholesterol, NOS = Newcastle–Ottawa scale, OR = odds ratio, WC = waist circumference, WHO = World Health Organization, WHR = waist-to-hip ratio.

Keywords: body mass index, diabetic retinopathy, risk factor

1. Introduction

Diabetic retinopathy (DR), the most common visual complication of diabetes, is a frequent cause of acquired blindness. In 2010, it was reported that nearly 285 million people worldwide had been plagued with diabetes, of which over one-third had signs of DR.[1] Recent epidemiological studies have identified that the duration of diabetes, blood pressure, and glycemic control are several key risk factors for the development of DR.[2] However, evidence from the Action to Control Cardiovascular Risk in Diabetes (ACCORD-Eye) and Action in Diabetes and Vascular Disease (ADVANCE) revealed that limited effects had been obtained despite better glucose and blood pressure control.[3,4] Thus, exploring modifiable risk factors has become increasingly important.

Body mass index (BMI), the most commonly used index of body mass, is calculated by dividing the weight in kilograms by the square of the height in meters.[5] According to the World Health Organization BMI classification system, BMI is categorized into the following four grades: underweight ($<18.5\,kg/m^2$), normal weight ($18.5\,kg/m^2$–$24.9\,kg/m^2$), overweight ($25.0\,kg/m^2$–$29.9\,kg/m^2$), and obese ($\geq 30.0\,kg/m^2$). It has been shown that being overweight and obesity are 2 risk factors for diabetes mellitus.[6] Thus, overweight and obese people are more vulnerable to DR. However, the results from previous studies were equivocal, with some studies[7–9] observing a decreased incidence of DR in higher BMI individuals, while other studies[10–13] detected a null association between high BMI and the incidence of DR. Moreover, other studies[14,15] demonstrated that a significant decrease in glycated hemoglobin (HbA1c) and a significant increase in high-density lipoprotein cholesterol (HDL-C) and blood pressure were observed in higher BMI individuals, all of which are the risk factors for DR. Motivated by these equivocal results, we conducted a meta-analysis to assess the association between BMI and the risk of DR.

2. Methods

In performing this meta-analysis, we adhered to the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) guidelines.[16] No ethical approval was warranted since it was a meta-analysis of available studies.

2.1. Literature search and study selection

We electronically searched the Cochrane Library, PubMed, and Embase databases up to December 2016 for articles evaluating the effects of BMI on DR in patients with type 1 or type 2

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diabetes. The key words related to body mass ("body mass index" or "body mass" or "BMI" or "body weight" or "obesity" or "overweight'" or "adiposity") and "diabetic retinopathy" were used to search for the relevant articles published in English. Moreover, reference lists and conference abstracts were also examined to retrieve potential relevant studies.

Studies were included if they fulfilled the following criteria: (a) observational study type; (b) participants with type 1 or 2 diabetes or both; (c) outcomes included DR; and (d) BMI was analyzed as a categorical or continuous variable. The categorical levels of BMI were assessed according to the WHO-recommended BMI classifications.[17] BMI levels within $2\,kg/m^2$ of standard categories were also considered to be acceptable in case losing studies were available. The exclusion criteria were as follows: (a) the adjusted risk estimates were unavailable; (b) certain publication types (*e.g.,* reviews, letters, case reports, comments, conference abstracts, and editorials); and (c) studies with duplicate or insufficient data.

2.2. Data extraction and quality assessment

Two reviewers (Z-Y and Z-YZ) independently screened all the identified articles, and any disagreements were resolved through discussion or through a consultation with the senior researcher (W-CY). For the included studies, the basic characteristics including the first author, publication year, study location, age range, design of study, sample size, diagnostic basis, grading standard, and the outcome were extracted. Additionally, if one study had several risk estimates (e.g., different periods of follow-up or different multivariate statistical analysis models), the risk estimate with the longest follow-up or the estimate that was most completely adjusted was extracted.

The Newcastle–Ottawa scale (NOS) score was used to evaluate the quality of the observational studies,[18,19] which gave with a maximum score of 9 for the cohort or case-control study, and 8 for the cross-sectional study. NOS scores of 0–3, 4–6, and ≥7 were defined as low, moderate, and high quality, respectively.

2.3. Statistical analysis

All the statistical analyses were completed with the Revman Manager 5.3 (the Nordic Cochrane Center, Rigshospitalet, Denmark; http://ims.cochrane.org/revman). We assessed the association between BMI and the risk of DR when BMI was analyzed as a categorical or continuous variable. For each study, the adjusted odds ratio (OR) and its 95% confidence interval (CI) were regarded as the common risk estimate and pooled by the random-effects model with inverse variance weighting. The random-effects model was more conservative and could provide better estimates with wider confidence intervals than the fixed-effect model for any heterogeneity.[20] The consistency of included studies was evaluated using the Cochrane Q test complemented with I^2 values, where I^2 values $<25\%$ indicated no heterogeneity, $25\% \le I^2 < 50\%$ indicated low heterogeneity, $50\% \le I^2 < 75\%$ indicated moderate heterogeneity, and $I^2 \ge 75\%$ indicated high heterogeneity. In view of the heterogeneity among the included studies, we performed a sensitivity analysis by removing the included articles one by one. A funnel plot was used to assess the publication bias when more than 10 studies were included. In the presence of potential publication bias, visual asymmetry would be observed in the funnel plot.

3. Results

3.1. Study selection

As shown in Fig. 1, a total of 1544 articles were initially identified the Cochrane Library (n=34), PubMed (n=572), and Embase (n=938) databases, of which 836 duplicate articles were removed. Among the remaining 708 articles, we excluded another 672 articles after screening the titles and abstracts. The potential 36 relevant articles thoroughly assessed for eligibility, and 9 of them were excluded for different reasons. Two articles[10,12] calculated the total effect of overweight and obesity together instead of their separate effects. A case-control study[13] only reported the unadjusted ORs at a 95% CI. Two studies[21,22] treated the nonobese group as the control. Four studies[23–25,57] did not adhere to the BMI classification we adopted. Finally, 27 articles[7,26–51] were included in this meta-analysis. All of the basic characteristics and the reporting qualities of the included studies are shown in Table 1.

3.2. Meta-analysis of BMI and DR

When BMI was analyzed as a categorical variable, 6 studies compared the risk of DR between 'overweight or obese BMI' and 'normal BMI.' As shown in Fig. 2, neither being overweight (OR=0.89, 95% CI 0.75–1.07; $P=.21$; $I^2=65\%$) nor obesity (OR=0.97, 95% CI 0.73–1.30; $P=.86$; $I^2=72\%$) were associated with an increased risk of DR when compared with normal weight. When BMI was analyzed as a continuous variable, 23 studies reported an association between BMI and the risk of DR. As shown in Fig. 3, a higher BMI was not associated with an increased risk of DR (OR=0.99, 95% CI 0.97–1.01; $P=.25$; $I^2=79\%$). In view of the heterogeneity among the included studies, we performed a sensitivity analysis to explore the source of heterogeneity. After we removed the included articles one by one, the I^2 values were still more than 50%, which indicated moderate-high heterogeneity. However, the sensitivity analysis demonstrated that the stability of the overall treatment effects was good.

3.3. Publication bias

As shown in Fig. 4, the largest studies plotted near the average and the smaller studies were spread evenly on both sides of the average, indicating that a possible absence of publication bias was observed when the BMI was analyzed as a continuous variable. However, when BMI was analyzed as a categorical variable, only 6 studies were included. We therefore did not display the funnel plot in this part, as the analyses are likely underpowered.

4. Discussion

As shown in a systematic analysis,[52] obesity has become a major global health challenge because of the increasing prevalence of obesity worldwide. From 1980 to 2013, the proportion of overweight and obese people increased to 36.9% for men and 38.0% for women. Consequently, increased morbidity and decreased life expectancy were also observed in the obese.[53] Obesity has also been observed to have detrimental effects on multiple eye diseases such as glaucoma,[54] late age-related maculopathy,[55] and cataracts.[56] However, although an increasing number of epidemiologic studies have been performed to analyze the association between BMI and DR, the results are

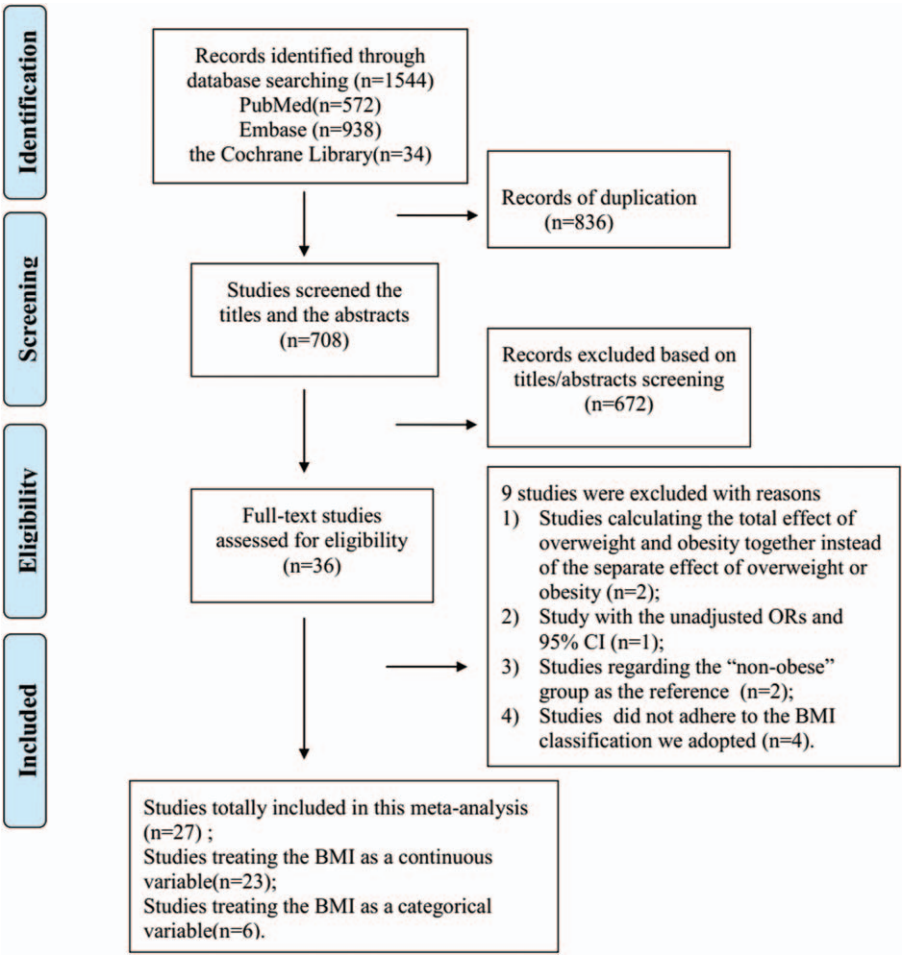

Figure 1. Overview of the research strategy. BMI = body mass index, OR = odds ratio.

still inclusive. To our knowledge, this was the first meta-analysis to evaluate the association between BMI and DR. In our meta-analysis, neither being overweight nor obesity conferred an increased risk of DR. This was consistent with the previous studies[57] where BMI was analyzed as a continuous variable. Notably, significant heterogeneity was observed in our analysis, which may be attributed to differences in study design, participant characteristics, and race or ethnicity, suggesting that our results should be treated with great caution.

To date, very few mechanisms have accounted for the neutral association between BMI and DR. Perhaps obesity has both protective and adverse effects on the risk of DR. Elevated BMI may confer a protective effect on DR through many ways. First, increased C-peptide levels were found in higher BMI individuals,[58] which could reduce the risk of DR.[59] Moreover, a higher BMI may be a reflection of better glycemic control or shorter diabetes duration. Obese individuals were also more vulnerable to suffer from comorbid conditions; consequently, aggressive treatments have been taken, and reduced the development of DR. In contrast, a higher BMI may have adverse effects on DR. First, an elevated BMI is often correlated with hypertension and dyslipidemia, both of which are risk factors for DR.[1] Additionally, hyperleptinemia in obese individuals[60] may increase blood pressure and oxidative stress levels, which may partly be responsible for the development of DR. Moreover, higher vascular endothelial growth factor levels were observed in obese individuals,[61] which has been shown to be involved in the pathogenesis of proliferative DR.[62] We hypothesize that the neutral effects of BMI on DR may counteract its adverse and protective effects.

In contrast to BMI, which is an index for measuring generalized obesity, WHR is used to assess abdominal obesity. There may be some differences in the associations between WHR or BMI and DR. A study[27] evaluating the risk of DR in an obese population based on BMI and WHR showed an increased risk in the abdominal obesity group but not in the generalized obesity group. The mechanisms underlying the detrimental WHR-DR association were not defined; however, the high levels of inflammation[63] and insulin resistance[64] in the abdominal area of obese people may be responsible for the development of DR.

4.1. Limitations

There were several limitations in our meta-analysis, so the results should be interpreted with great caution. First, most of the studies we included were cross-sectional; thus, a causal relationship could not be conferred. Second, BMI is not an accurate parameter to reflect body adiposity since it also includes bone mass and muscle. For example, low BMI individuals may have a higher WC or metabolically obese normal weight.[65] Third, significant heterogeneity existed between the studies. Regretfully, we failed to explore the source of heterogeneity because of the limited

Table 1

Characteristics of the 27 included studies in this meta-analysis.

Study	Region	Design of study	Sample size	Age, years	Male ratio, %	BMI (categorical variable/ continuous variable)	Outcome	Quality assessment
Man et al[26]	Singapore	Cross-sectional	420	57.8±7.5	67.9	Categorical/continuous	T2DM with DR	High
Ahmed et al[30]	Bangladesh	Cohort	977	45-60	47.9	Categorical	T2DM with DR	Moderate
Rooney et al[27]	Singapore.	Cross-sectional	2278	61.9±9.6	49.8	Categorical	T2DM with DR T1DM with DR	High
Dirani et al[29]	Australia	Cross-sectional	492	Median 65	66.1	categorical/continuous	T2DM with DR T1DM with DR	High
Lu et al[28]	China	Cross-sectional	2533	Mean 57.3	58.9	Categorical	T2DM with DR	High
Martín-Merino et al[31]	United Kingdom	Case-control	17,130	63±11.7	55.9	Categorical	T2DM with DR	High
Webb et al [32]	South Africa	Cross-sectional	397	NA	NA	Continuous	T2DM with DR T1DM with DR	Moderate
Azizi-Soleiman et al[33]	Iran	Cross-sectional	1872	Mean 50.3	32.7	Continuous		High
Kajiwara et al[34]	Japan	Cohort	383	59.4±11.0	36.0	Continuous	T2DM with DR	High
Tomic et al[35]	Croatia	Cross-sectional	107	66.74±8.01	62.6	Continuous	T2DM with DR	High
Okumura et al[43]	Japan	Cross-sectional	230	60.9±6.3	68.3	Continuous	T2DM with DR	High
Li and Wang[37]	China	Cohort	2194	Mean 72.5	76.9	Continuous	DM with DR	High
Collins et al[42]	Samoa	Cross-sectional	248	25-74	NA	Continuous	T2DM with DR	High
Yoshida et al[40]	Japan	Cohort	787	Mean 54	NA	Continuous	T2DM with DR	Moderate
Mitchell et al[41]	Australia	Cross-sectional	253	≥49	NA	Continuous	T2DM with DR T1DM with DR	High
Lim 2010[7]	Singapore	Cross-sectional	718	62.5±9.4	43	Continuous	DM with DR	High
Zheng et al[38]	Singapore	Cross-sectional	3400	≥40	NA	Continuous	T2DM with DR T1DM with DR	High
Garberg et al[46]	Sweden	Cohort	773	≤70	NA	Continuous	T2DM with DR	High
Sekioka et al[44]	Japan	Cross-sectional	674	64.7±13.9	66.2	Continuous	T2DM with DR	Moderate
Jee et al[47]	Korean	Cross-sectional	1678	>40	50	Continuous	T2DM with DR T1DM with DR	Moderate
Xu et al[48]	China	Cross-sectional	2007	64.1±9.0	40	Continuous	T2DM with DR	High
Loprinzi[45]	United States	Cross-sectional	223	Mean 62	46.3	Continuous	DM with DR	Moderate
Wong et al[49]	Singapore	Cross-sectional	3261	58.7±11.01	51.9	Continuous	DM with DR	High
Fujisawa et al[50]	Japan	Cross-sectional	294	60.2±10.5	48.3	Continuous	T2DM with DR	High
Rema et al[51]	India	Cross-sectional	6792	55.0±10.0	NA	Continuous	T2DM with DR	Moderate
Lim et al[36]	Korea	Cross-sectional	2164	50.1±10.5	56.4	Continuous	T2DM with DR	High
Kawasaki et al[39]	Japan	Cohort	1221	58.2±6.9	55	Continuous	T2DM with DR	High

BMI = body mass index, HbA1c = glycated hemoglobin, HDL-C = high-density lipoprotein cholesterol, SBP = systolic blood pressure, T1DM with DR = type 1 diabetes mellitus with diabetic retinopathy, T2DM with DR = type 2 diabetes mellitus with diabetic retinopathy, TG = triglyceride, WHR = waist to hip ratio.

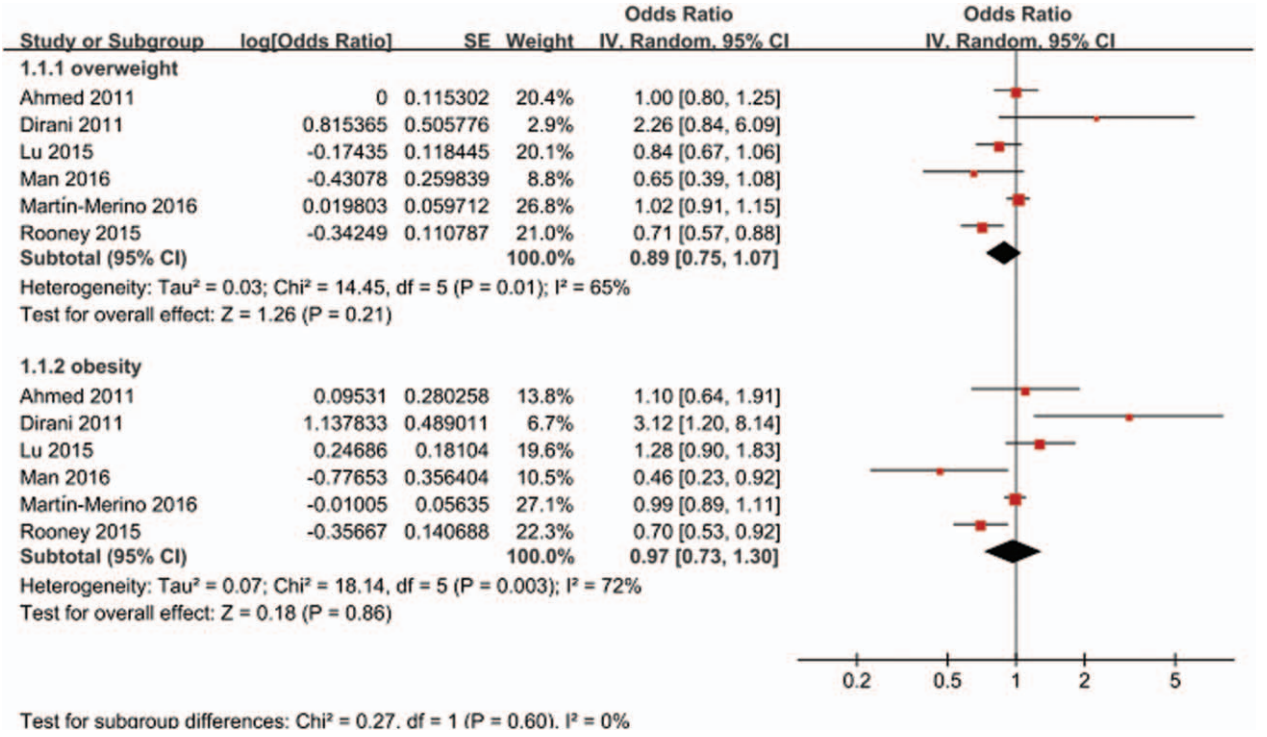

Figure 2. Forest plot for the association between BMI and the risk of DR when BMI was analyzed as a categorical variable. BMI = body mass index, CI = confidence interval, DR = diabetic retinopathy, SE = standard error.

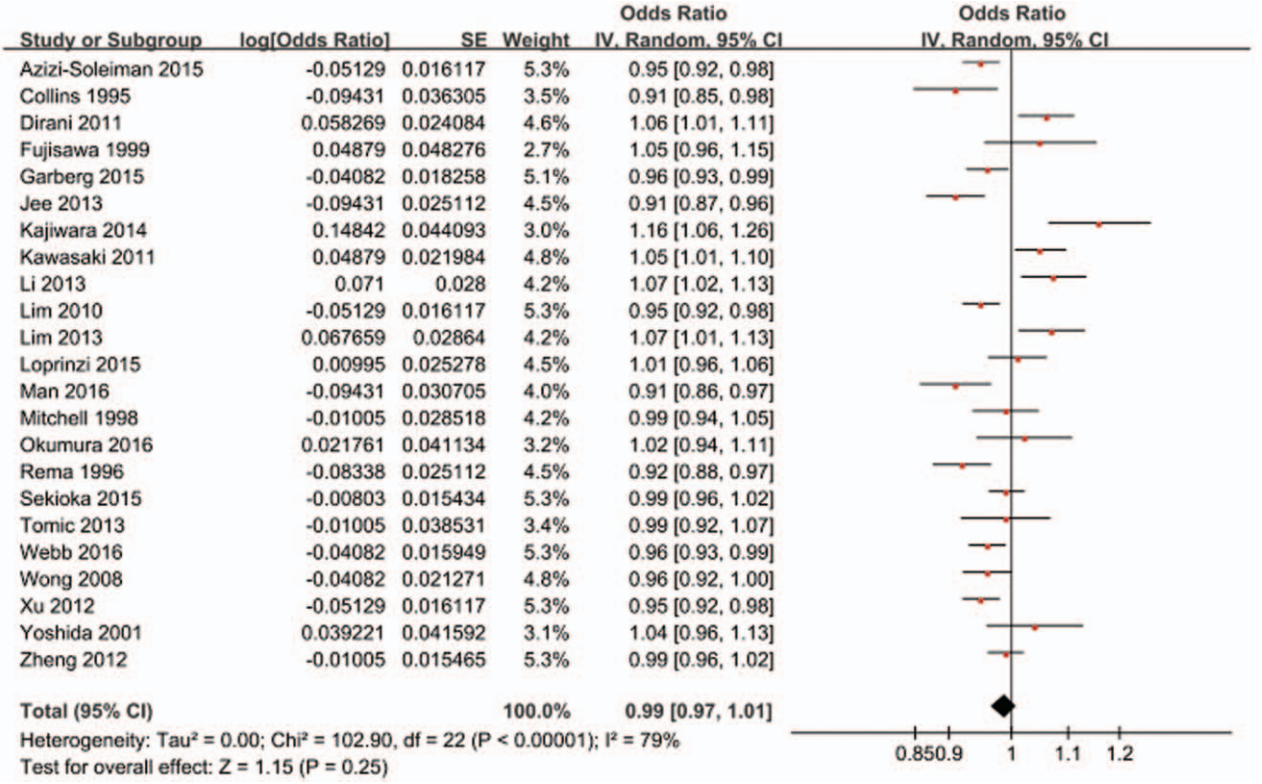

Figure 3. Forest plot for the association between BMI and the risk of DR when BMI was analyzed as a continuous variable. BMI = body mass index, DR = diabetic retinopathy, SE = standard error, CI = confidence interval.

number of included studies. Fourth, several studies included in this meta-analysis evaluated the association between BMI and DR without differentiating the types of diabetes; therefore, we could not separately evaluate the effects of BMI on DR in patients with type 1 or type 2 diabetes.

5. Conclusions

Our meta-analysis demonstrated that elevated BMI did not increase the risk of DR. However, since being overweight and obesity are risk factors for multiple diseases, it is still imperative to maintain a healthy weight. Notably, since BMI is an index to assess generalized obesity, other anthropometric measurement indexes (e.g., WHR and WC) should also be used to explore the association between obesity and DR. Furthermore, longitudinal studies based on different anthropometric measurement indexes are warranted to determine the association between being overweight or obese and DR.

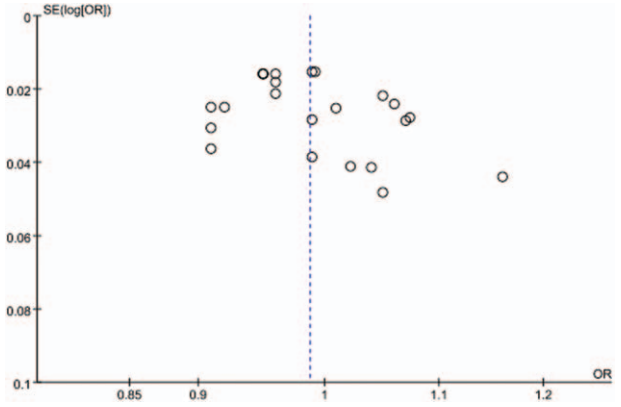

Figure 4. Funnel plot of all the included studies for the bias analysis when BMI was analyzed as a continuous variable. BMI = body mass index, SE = standard error.

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