Systematic Review and Meta-Analysis

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Relationship between retinal vascular occlusions and incident cerebrovascular diseases

A systematic review and meta-analysis

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Abstract

Several studies investigating the role of retinal vascular occlusions, on cerebrovascular diseases (CVD) have been reported, but the results are still inconsistent. We therefore sought to evaluate the relationship between retinal vascular occlusions and CVD.

We systematically searched the Cochrane Library, PubMed, and ScienceDirect databases through January 31, 2016 for studies evaluating the effect of retinal vascular occlusions on the risk of CVD. Data were abstracted using predefined criteria, and then pooled by RevMan 5.3 software.

A total of 9 retrospective studies were included in this meta-analysis. When compared with individuals without retinal vascular occlusions, both individuals with retinal artery occlusion (RAO) (odds ratio [OR] = 2.01, 95% confidence interval [CI]: 1.21–3.34; $P = 0.005$) and individuals with retinal vein occlusion (RVO) (OR = 1.37, 95% CI: 1.24–1.50; $P < 0.00001$) had higher risks of developing CVD. Additionally, both individuals with central retinal artery occlusion (CRAO) (OR = 2.00, 95% CI: 1.12–3.56; $P = 0.02$) and branch retinal artery occlusion (BRAO) (OR = 1.60, 95% CI: 1.03–1.48; $P = 0.04$) were significantly associated with increased risk of CVD.

Published literatures support both RVO and RAO are associated with increased risks of CVD. Further prospective studies are needed to confirm these findings.

Abbreviations: BRAO = branch retinal artery occlusion, BRVO = branch retinal vein occlusion, CI = confidence interval, CRAO = central retinal artery occlusion, CRVO = central retinal vein occlusion, CVD = cerebrovascular diseases, NOS = Newcastle–Ottawa Scale, OR = odds ratio, RAO = retinal artery occlusion, RVO = retinal vein occlusion.

Keywords: cerebrovascular disease, retinal arterial occlusion, retinal vascular occlusions, retinal vein occlusion

1. Introduction

Cerebrovascular diseases (CVD) are a group of illnesses of the blood vessels supplying the brain, which primarily affect the older population. CVD are the leading causes of death, and place an enormous burden on both patients and caregivers. Early identification of high-risk CVD patients and undertaking timely preventive measures are therefore very important. Even though CVD could be prevented to a large extent since there are many modifiable risk factors such as high blood pressure, smoking, alcohol abuse, physical inactivity, and an unhealthy diet,[1,2] the potentially serious disabilities due to CVD still represent a great public health challenge on our society. Recently, retinal conditions, such as hypertensive retinopathy[3] and mild non-proliferative diabetic retinopathy,[4] have been identified as the possible risk factors of CVD. Retinal vascular occlusions, composing of retinal artery occlusion (RAO) and retinal vein occlusion (RVO), are retinal vascular diseases in which retinal veins are occluded by thrombus. A previous meta-analysis by Khan et al[5] indicated that RVO is associated with increased risks of developing cardiovascular diseases, such as stroke and myocardial infarction. Also, studies reporting the association between retinal vascular occlusions and CVD have also been increasingly emerged. However, individual studies have yielded conflicting findings. Some prior studies[6–11] indicated that the occurrence risk of CVD in patients with retinal vascular occlusions was increased, while other studies[12,13] observed no significant association. The quantitative synthetic data to shed light on these contradictory results have not been well established. Therefore, the aim of this work was to explore the evidence on the association between retinal vascular occlusions and the development of CVD.

2. Methods

2.1. Eligibility criteria

In the present meta-analysis, we extracted the data from published studies, and therefore, the ethical approval was not necessary. Studies were included if they met the following criteria: studies that evaluated the effect of retinal vascular occlusions on

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CVD; participants – patients with retinal vascular occlusions composing of RAO and RVO; and type of study – retrospective and/or prospective. The following exclusion criteria were applied: studies that had no control group or had a self-controlled group; certain publication types (i.e., letters, case reports, and comments); and studies with insufficient or duplicate data.

2.2. Literature search strategy

A literature search was performed in the Cochrane Library, PubMed, and ScienceDirect databases until January 31, 2016. We did not apply any language restrictions. Two groups of keywords were combined by the Boolean operator "and" (Supplemental Table 1, http://links.lww.com/MD/B79). The 1st terms were linked to the exposure (retinal vascular occlusions, OR retinal arterial occlusion, OR retinal arterial obstruction, OR retinal artery occlusion, OR retinal artery obstruction OR retinal vein occlusion, OR retinal vein obstruction). The 2nd terms were linked to the outcome (cerebrovascular disease OR cerebrovascular events OR stroke OR transient ischemic attack OR cerebrovascular disorders OR cerebral infarction OR brain infarction OR cerebral hemorrhage). Additional studies were identified by a hand search from reference of original studies on this topic. The retrieved studies were carefully examined to exclude potentially duplicate or overlapping data.

2.3. Data abstraction and quality assessment

Two reviewers (Z-Y and Z-WG) abstracted data independently using the predetermined criteria. Disagreements were resolved by discussion or consensus with the senior researcher (W-CY). For each study, we documented the 1st author, study characteristics (i.e., year of publication, duration, and design), and participant characteristics (i.e., sex, age, and sample size). Newcastle–Ottawa Scale was used for assessing the quality of all studies, involving selection, comparability, and assessment of outcome.[14]

2.4. Risk of bias and consistency test

We used funnel plots to assess the potential risk of publication bias, recommended by the Cochrane collaboration (www.cochrane-handbook.org). A visually significant asymmetry in the funnel plots indicated a major publication bias. The consistency test was evaluated using the Cochrane Q test and I^2 statistic. I^2 values of 25%, 50%, and 75% represent low, moderate, and high heterogeneity, respectively. When I^2 values were $\leq$50%, a fixed-effects model was chosen.

2.5. Statistical analysis

All statistical analyses were performed using Review Manager (RevMan) version 5.3 software (The Nordic Cochrane Center, Rigshospitalet, Denmark; http://ims.cochrane.org/revman). We primarily examined separately the effect of RAO and RVO on the risk of developing CVD. Also, the association between central retinal artery occlusion (CRAO)/branch retinal artery occlusion (BRAO) and CVD was further evaluated. However, because of the limited data, we failed to assess the individual effect of central retinal vein occlusion (CRVO)/branch retinal vein occlusion (BRVO) on CVD. Sensitivity analyses were performed where appropriate. A 2-tailed *P*-value less than 0.05 indicated a significant difference.

3. Results

3.1. Study selection

A total of 3684 articles were initially identified (Fig. 1). Thereinto, 3287 articles were excluded based on title and abstract screening. We then review the full-text of 397 potentially relevant articles, and 375 articles with no enough information between retinal vascular occlusions and CVD were excluded. Thus, 22 articles were assessed for eligibility, and 13 of the 22 studies were excluded for the following reasons: they were: cross-sectional or case–control studies (n = 3); of a certain publication type (e.g., letters, case reports, and comments) (n = 7); and studies with insufficient or duplicate data (n = 3). Finally, 9 retrospective articles[15–23] fulfilled the inclusion criteria (numbers of participants[n] = 324,518). A total of 7 articles[16–19,21–23] evaluated the association between RVO and CVD, while 3 articles[15,20,21] evaluated the role of RAO on the risk of developing CVD. Basic characteristics of these included articles are shown in Table 1. The reporting quality of the included articles was globally acceptable (Table 1). A possible absence of publication bias was observed using funnel plots (Fig. 2).

3.2. RVO and the risk of CVD

When regarding the association between RVO and the risk of CVD, we included 7 studies with 7894 RVO cases and 226,431 control cases in this part. Six[17–19,21–23] of 7 studies indicated that the incidence of CVD in patients with RVO was increased, while the study of Ho et al[16] observed nosignificant association between RVO and CVD. For the primary analysis, a random-effects model was preferred due to moderate heterogeneity (I^2 = 57%). As results, patients with RVO had an increased risk of CVD (odds ratio [OR] = 1.38, 95% confidence interval [CI]: 1.17–1.63; P = 0.0001). In the sensitivity analysis, we found that a selection bias may occur in the hospital-based study by Bertelsen et al[22] because the more symptomatic and initiative patients were more inclined to be enrolled. Also, the control group was sampled from a repository which recorded the vital information of all residents except for their medical information, so the potential patients with CRVO might be grouped into the comparison cohort. Thus, the selection bias may counterbalance the effects of CRVO on developing CVD. After we excluded this study, I^2 values dropped from 57% to 43%, but the OR value in individuals with RVO was not significantly changed (OR = 1.37, 95%CI: 1.24–1.50, $P < 0.00001$, Fig. 3). Therefore, we could reasonably conclude that the study of Bertelsen et al[22] was the main source of heterogeneity.

3.3. RAO and the risk of CVD

A total of 3 studies with 758 RAO cases and 89,435 control cases estimated an association between RAO and CVD. In this section, a random-effects model was preferred due to high heterogeneity (I^2 = 81%). When compared with the control group, the RAO group had nearly 2 times increased risks of CVD (OR = 2.01, 95%CI: 1.21–3.34; P = 0.005, Fig. 4). Additionally, as shown in Fig. 4, both individuals with CRAO (OR = 2.00, 95%CI: 1.12–3.56; P = 0.02) and BRAO (OR = 1.60, 95%CI: 1.03–1.48; P = 0.04) were significantly associated with increased risk of CVD. Given the existence of high heterogeneity, we therefore should interpret the results cautiously.

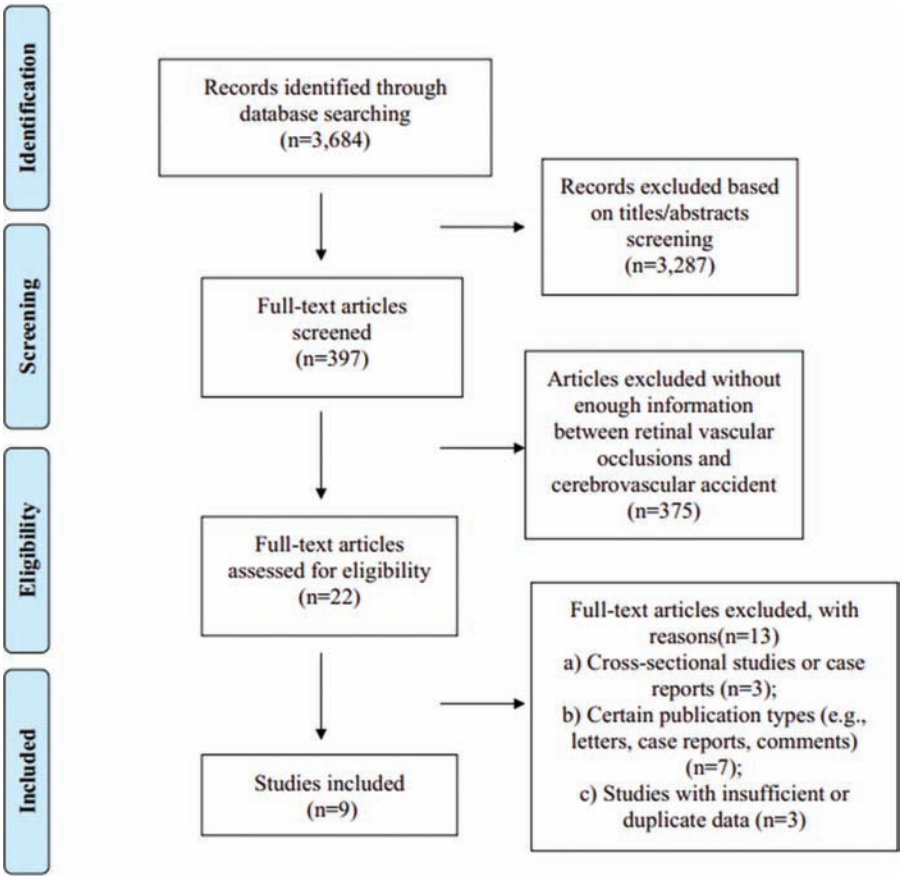

Figure 1. Overview of the research strategy. Note: This was an overview of the number of articles included during each stage of the systematic review process.

Table 1

Basic characteristics of studies included in the systematic review and meta-analysis.

Study (author-year)	Region	Sex, age	Numbers of participants (with/without RVO/RAO)	Outcomes	NOS items	Category of retinal vascular occlusions	Adjustments
Bruno-1995[15]	America	Both, mean 68.8 years	140 (RAO 70/70)	Stroke	7 Stars	With RAO and without RAO	Stroke history, smoking history
Ho-2009[16]	China	Both, NA	2450 (RVO 350/2100)	Stroke	9 Stars	With RVO and without RVO	Age, sex, and the geographic location, hypertension, DM, hyperlipidemia, and renal disease
Werther-2011[17]	America	Both, 64 ±13.3 years	18,000 (RVO 4500/13,500)	CVA	9 Stars	With RVO and without RVO	Angina, cardiac arrhythmia, charlson score, HF, DM, heart disease, hyperlipidemia, hypertension, other cerebrovascular disease
Di Capua-2012[18]	Italy	Both, 54.3 ±13.6 years	190 (RVO 45/145)	Stroke/TIA	8 Stars	With RVO and without RVO	Age, sex, blood pressure level, obesity, DM, hypercholesterolemia, hypertriglyceridemia, renal disease and cigarette smoking habit
Bertelsen-2012[19]	Denmark	Both, ≥40 years	117,968 (RVO 1168/116,800)	CVA	8 Stars	With RVO and without RVO	Sex and index year
Chang-2012[20]	China	Both, 60.2 ±14.7 years	3212 (RAO 464/2748)	Stroke	9 Stars	With RAO and without RAO	Age, sex, hypertension, DM, hyperlipidemia, renal disease
Christiansen-2013[21]	Denmark	Both, NA	87,202 (RVO 361/86,617) and (RVO 224/86,617)	Stroke/ TE/TIA	9 Stars	With RAO/RVO and without RAO/RVO	Age, sex, year of inclusion, concomitant medication, peripheral/ coronary vascular disease
Bertelsen-2014[22]	Denmark	Both, NA	2634 (RVO 439/2195)	CVA	8 Stars	With RVO and without RVO	Sex, age, and index date
Rim-2015[23]	Korea	Both, NA	6105 (RVO 1031/5074)	Stroke	9 Stars	With RVO and without RVO	Age, sex, residential area, household income, hypertension, DM, and CKD

CKD = chronic kidney disease, CVA = cerebrovascular accident, DM = diabetes mellitus, HF = heart failure, NA = not available, NOS = Newcastle–Ottawa Scale, RAO = retinal artery occlusion, RVO = retinal vein occlusion, TE = thromboembolism, TIA = transient ischemic attack.

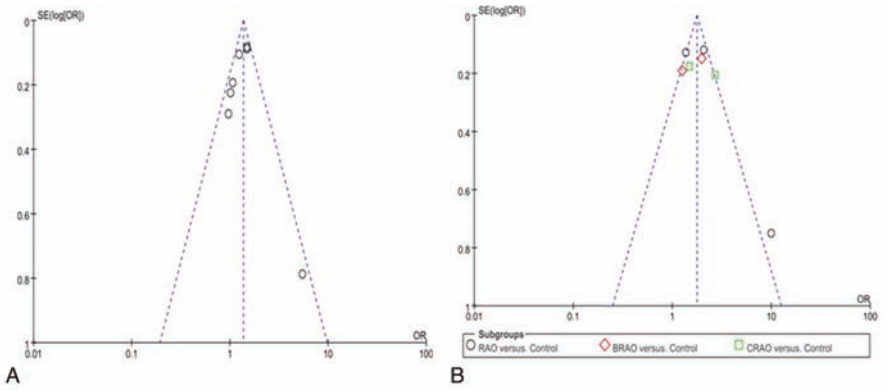

Figure 2. Funnel plots of all included studies for the bias analysis: (A) Funnel plot of the association between RVO and CVD; (B) Funnel plot of the association between RAO and CVD. CVD = cerebrovascular diseases, OR = odds ratio, RVO = retinal vein occlusion, SE = standard error.

4. Discussion

In 2013, Khan et al[5] have indicated that, when compared with the general Canadian population, patients with RVO have a higher risk of developing cardiovascular diseases such as stroke and myocardial infarction. However, whether patients with RVO have similar effects on the development of CVD is still ambiguous. In the present meta-analysis, it revealed that RVO was associated with increased risk of developing CVD. Consistent with our findings, Park et al[24] performed a self-controlled case series study which included 44,603 patients with RVO, and the results showed that the risk of stroke increased during the 1 year before and after RVO occurrence. Hitherto, the pathogenesis of CVD in RVO patients remains unclear but they may be linked by the following aspects. First, anatomically, both the retinal vessels and cerebral vessels stem from internal carotid vascular system, and share common structural characteristics (size and blood–brain/retinal barrier). Thus, changes in the retinal vessels may be a clue of the development of CVD.[25,26] Second, RVO and CVD have shared many common systemic risk factors, such as hypertension, arteriosclerosis, diabetes mellitus, and hyperlipidemia.[27,28] Third, a pooled data from Atherosclerosis Risk in Communities Study and the Cardiovascular Health Study revealed that RVO was associated with carotid artery plaque, which was also a potential risk factor for ischemic stroke.[29]

Similarly, our current meta-analysis also revealed that RAO was associated with increased risk of CVD. In addition, when regarding the type of occlusion, both CRAO and BRAO were significantly associated with increased risk of CVD. In the self-controlled case series study of Park et al,[30] the risk of stroke increased during the 1 year before and after CRAO occurrence. However, given the existence of high heterogeneity, the results should be interpreted cautiously. Although we could not attempt to explore the potential sources of heterogeneity because only 3 studies were included in this part, we speculated the following reasons responsible for the high heterogeneity. First, the study populations were variable, and the sample size and the total numbers of studies were small, which may partly contribute to the heterogeneity. For example, we included the study by Brun et al[15] only with 70 RAO cases and 70 control cases, which may be a potential source of heterogeneity. Second, stroke and transient ischemic attack both belong to the subtypes of CVD. The outcomes of 3 included studies[15,20,21] were the different subtypes of CVD. Third, during the follow-up time, patients with RAO received different medications in different studies, which might somewhat effect the incidence of CVD. Furthermore,

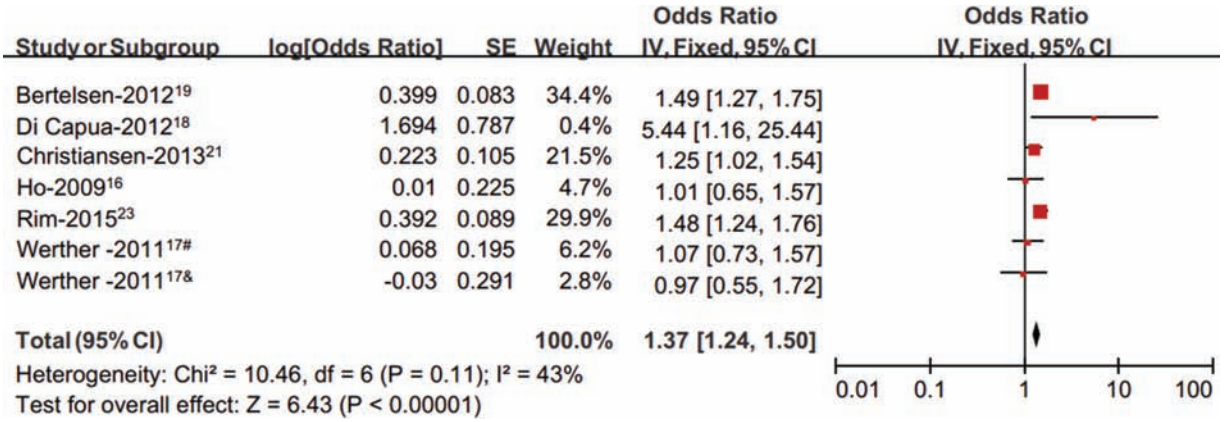

Figure 3. Meta-analysis of the association between RVO and developing CVD. #Estimating the association between BRVO and CVD; &estimating the association between CRVO and CVD. BRVO = branch retinal vein occlusion, CI = confidence interval, CRVO = central retinal vein occlusion, CVD = cerebrovascular diseases, IV = inverse of the variance, RVO = retinal vein occlusion, SE = standard error.

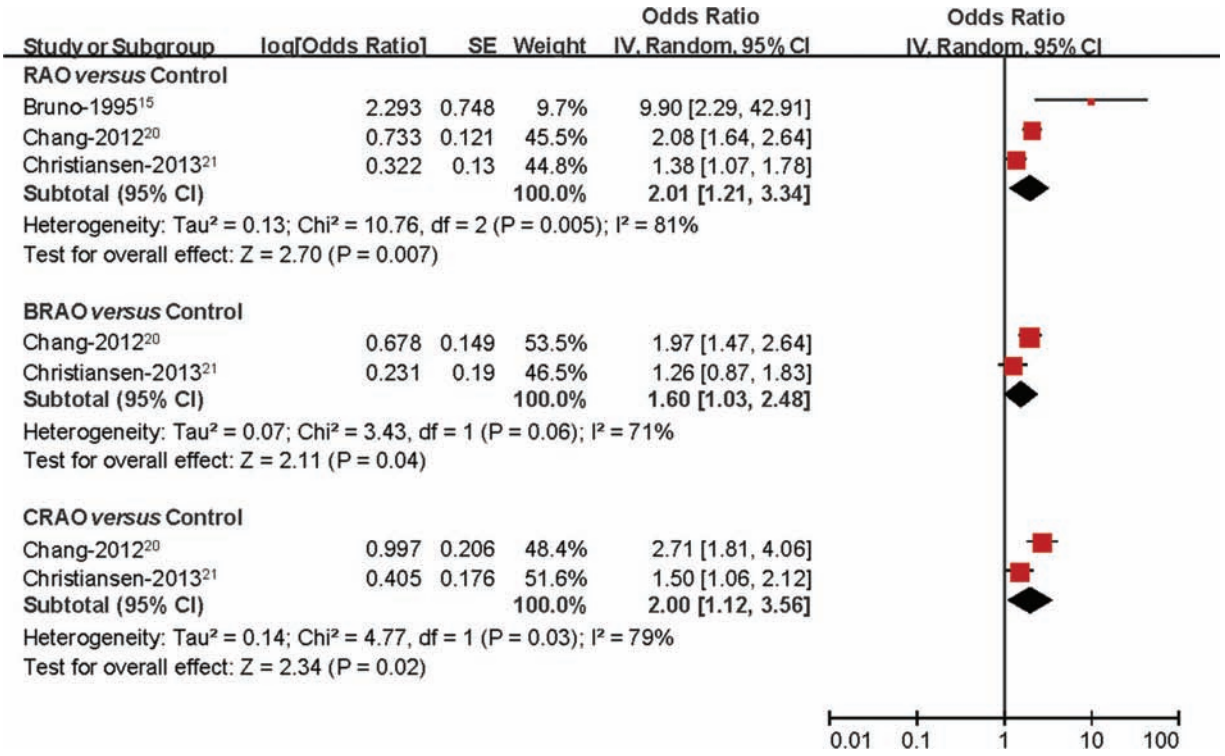

Figure 4. Meta-analysis of the association between RAO and developing CVD. BRVO = branch retinal vein occlusion, CI = confidence interval, CRVO = central retinal vein occlusion, CVD = cerebrovascular diseases, IV = inverse of the variance, RVO = retinal vein occlusion, SE = standard error.

although there was heterogeneity among these included studies, it was noted that all of them had effects in the same direction (Fig. 4), individually indicating that RAO (both CRVO and BRVO) is associated with increased risks of CVD. Surely, further prospective studies are needed to confirm these findings.

A meta-analysis evaluating the association between retinal vascular occlusions and CVD-related mortality was impossible because the total numbers of studies were small. Therefore, we described the association between retinal vascular occlusions and CVD-related mortality. To date, 2 articles[31,32] have revealed that RAO may increase the risk of CVD-related mortality. Conversely, another 3 articles have described CVD-related mortality in the patients with RVO. In 1992, Mansour et al[33] firstly followed 78 patients with CRVO, and found that only 1 patient was CVD related in the 13 deceased patients, which was expected to be 2.6 patients according to the national surveys. However, in this study, statistical data of the national surveys were regarded as the control group, which might induce different confounding factors and further confuse the association between RVO and CVD-related mortality. Tsaloumas et al[34] also followed 558 patients with RVO for an average of about 9 years and observed that RVO did not have a statistically significant increased risk of CVD-related mortality. However, during the follow-up period, the treatment of associated medical conditions such as hypertension, diabetes was proceeding. Since hypertension and diabetes were established risk factors of CVD-related mortality, effective treatment may counterbalance the effects of RVO on CVD-related mortality. Cugati et al[35] also indicated that RVO was not associated with CVD-related mortality. RVO did not increase the CVD related mortality; however, a higher CVD related mortality was observed in the RAO patients. The underlying mechanisms why RVO and RAO had different effects on CVD-related mortality are still unknown, and more studies should further confirm these findings.

5. Limitations

Our study had several potential limitations as follows. First, the design of all the included studies were retrospective, and further study should include the prospective studies to validate the causal effects. Second, the association between CVD and the subtypes of RVO were not evaluated due to the limiting data. Third, when evaluating the association between RAO and the risk of CVD, the high heterogeneity was presented. Further study should explore the potential sources of heterogeneity by subgroup analyses and sensitivity analyses. Fourth, we evaluated the association between retinal vascular occlusions and CVD without differentiating the subtypes of CVD, which could not reveal the association between a certain specific subtype of CVD and retinal vascular occlusions. Finally, because of the limiting data, we could not evaluate the association of the subtypes of RVO (CRVO and BRVO) with CVD.

6. Conclusions

In summary, this meta-analysis suggested both RVO and RAO were associated with increased risks of CVD. More prospective studies would be warranted to provide further insights into the association of retinal vascular occlusions with CVD.

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