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Impact of Retinal Vein Occlusion on Stroke Incidence: A Meta-Analysis

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***Background*—**Considerable controversy exists on the association between retinal vein occlusion (RVO) and stroke risk. Therefore, we conducted a meta-analysis to assess the relationship between RVO and stroke risk.

***Methods and Results*—**PubMed, EMBASE, and the Cochrane library databases were searched for cohort studies with data on RVO and stroke risk. Studies that reported adjusted relative risks (RRs) with 95% CIs of stroke associated with RVO were included. Stratified analyses were conducted according to key characteristics. A total of 5 articles including results from 6 prospective cohort studies with 431 cases of stroke and 37 471 participants were included in the meta-analysis. Overall, after adjustment for established cardiovascular risk factors, participants with RVO at baseline were considerably more associated with a greater incidence of stroke risk (combined RR: 1.50, 95% CI: 1.19–1.90), compared to participants without RVO. The results were more pronounced for stroke (RR: 1.72, 95% CI: 1.24–2.37) in the stratified with a stroke history. The risk of stroke was nonsignificant in male subjects (RR: 1.20, 95% CI: 0.96–1.49) and in female subjects (RR: 0.93, 95% CI: 0.64–1.34). The presence of both central RVO (RR: 1.90, 95% CI: 1.46–2.48) and branch RVO (RR: 1.79, 95% CI: 1.18–2.72) was associated with increased risk of stroke. Stratifying by age, the associations between RVO and risk of stroke were similar between the age range in the cohorts that ranged from 50 to 59 years and 60 to 69 years.

***Conclusions*—**Exposure to RVO was associated with an increased risk of stroke, especially in subjects aged between 50 and 69 years. Future studies on the effect of RVO treatment and modifiable risk factor reduction on stroke risk in RVO patients are warranted. **(*J Am Heart Assoc*. 2016;5:e004703 doi: 10.1161/JAHA.116.004703)**

Key Words: meta-analysis • renal infarction • stroke

Retinal vein occlusion (RVO) is the second most frequently occurring retinal vascular disease and is a frequent cause of painless visual loss in middle-aged and elderly individuals.[1–3] The incidence of RVO is greater than 48 per 0.1 million person-years in the general population and 136.09 per 0.1 million person-years in those aged 50 years and older.[4] With the aging of the population, the incidence and associated burden of RVO are likely to rapidly increase globally. However, the effectiveness of the management of systemic risks associated with RVO and its impact on cerebrovascular disease in patients with RVO remains unknown.[4,5]

Retinal vasculature has recently gained attention, because traditional risk factors of cardiovascular and cerebrovascular diseases such as old age,[3] cigarette smoking,[6] high activated factor VII,[7] and high blood viscosity[8] are insufficient to fully explain the occurrence of arterial thromboembolic events.[9] During the past decade, epidemiologic studies have shown that RVO is associated with an increased risk of cardiovascular disease, especially hypertension,[10] diabetes mellitus,[11] and coronary artery disease.[12] However, the results of cohort studies that examined the association between RVO and the risk of stroke are inconsistent.[12–16] A recent longitudinal, population-based study revealed that RVO was significantly associated with stroke development after adjusting for potential confounders.[16] Nevertheless, a retrospective nationwide population-based study in China concluded that there was no overall association of RVO with stroke except in the 60- to 69-year subgroup.[14] Furthermore, central RVO and branch RVO may affect the risk of stroke independently. A registry-based cohort study revealed that central RVO was

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Accompanying Data S1, Tables S1 through S3 and Figure S1 are available at http://jaha.ahajournals.org/content/5/12/e004703/DC1/embed/inline-supplementary-material-1.pdf

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associated with an increased risk of stroke.[15] However, this new information should be carefully managed because this was a small-scale investigation, and RVO subtypes have long been known to be associated with different risk factors.

Given these inconsistent results, to obtain a more comprehensive estimate of the putative influence of RVO on stroke, we conducted a meta-analysis of cohort studies to assess the association between RVO and the risk of stroke.

Methods

Literature Search

The search was conducted according to the recommendations of the Meta-analysis Of Observational Studies in Epidemiology Group (MOOSE).[17] A systematic search of PubMed, EMBASE, and the Cochrane library databases was performed up to March 2016. The following terms were used: "retinal vein occlusion," "retinal vein obstruction," and "stroke," "cerebrovascular disease," "cerebrovascular disorders," "cerebral infarct," "ischemic stroke," "intracranial hemorrhage," "intracranial artery disease," "cardiovascular disease," "myocardial ischemia," "myocardial infarct," "ischemic heart disease," "coronary heart disease," and "longitudinal studies," "cohort studies," "follow-up studies." The search strategy is given (details in Data S1). We restricted the search to human studies. There were no language restrictions. In addition, we reviewed the reference lists of the obtained articles and contacted the authors to identify additional relevant studies and information. When the same or a similar patient cohort was included in these publications, only the most recent or complete report was selected for analysis.

Study Selection

Studies were selected when the following entry criteria were met: (1) the study of adult patients had a cohort design; (2) the exposure of interest was RVO at baseline; (3) the outcome of interest was stroke, including all types of stroke (fatal, nonfatal, ischemic, and hemorrhagic stroke); (4) quantitative estimates of the multivariate-adjusted relative risk (RR) and 95% CI for stroke associated with RVO were reported; and (5) a follow-up period longer than 1 year was used. Studies were excluded if (1) the study had a cross-sectional case-control design; (2) unadjusted or only age- or sex-adjusted RR were reported; (3) 95% CI was not reported; (4) the study was duplicated; and (5) the follow-up period of the study was less than 1 year.

Data Extraction

Data were extracted into a Microsoft Access database with redefined fields that captured aspects of the study quality, as well as individual results, including the first author's last name, publication year, location, number of cases and size of the cohort, participants' age, follow-up years, assessment of RVO and stroke, number of cases, and adjusted covariates. All data were independently abstracted in duplicate by two investigators (Y.T. and B.Y.). Discrepancies were resolved by consensus. When necessary, the original authors were contacted for supplementary information.

Assessment of Study Quality

The quality of all articles that met the selection criteria was assessed. The Newcastle–Ottawa Scale was used to assess the quality of the studies.[18] The quality of the cohort studies was evaluated by the following 3 major components: selection of the study group (up to 4 stars), quality of the adjustment for confounding (up to 2 stars), and assessment of outcome in the cohorts (up to 3 stars). A higher score represented a better methodological quality. The full score was 9 stars. In our analysis, the quality of studies was graded as "good" if they had $\geq$7 awarded stars.

Statistical Analysis

Multivariate-adjusted outcome data were used for analysis, and hazard ratios were considered equivalent to RRs. These values were converted in each study using natural logarithms, and the standard errors were calculated from these logarithmic numbers and the corresponding 95% CIs. The RR of stroke in patients with RVO was analyzed, and the values of this indicator were compared with those of individuals without RVO. We combined these estimates using a random-effects model, which takes into account both within-study and between-study variabilities.[19] Heterogeneity was quantified using tau^2 and the amount of between-study variance attributable to heterogeneity, which was defined by I^2. $P<0.5$ was considered statistically significant at the level, as determined by Cochran's Q statistical test.[20] If there was evidence of heterogeneity, stratified syntheses and sensitivity analyses were employed to explain what contributed to the heterogeneity. We performed predefined stratified analyses according to sex (females versus males), RVO type (central RVO versus branch RVO), history of stroke (yes versus no), and mean age (5 levels of age categories). We calculated linear P for trend and P for interaction for stratified analyses. Potential publication bias was assessed by the Egger's test and the symmetry of the funnel plot.[21–23] In case of publication bias, the "nonparametric trim-and-fill" method was used to compute for risk estimates corrected for this bias.[24] If the pooled RR of stroke for RVO was statistically significant, population attributable risk, which expresses the proportion of events attributable to exposure, was

determined. The formula for population attributable risk calculation was as follows: population attributable risk%=(P_e)(RR−1)/([P_e] [RR−1]+1)×100%, where P_e indicates the proportion of participants exposed to the risk factor, and RR denotes the estimated relative risk.[25,26] The level of statistical significance for the 2-tailed test of each hypothesis was 0.05. All statistical analyses were conducted with the Review Manager version 5.3 (The Cochrane Collaboration, Software Update, Oxford, UK) and Stata version 11 (Stata Corporation, College Station, TX).

Results

Literature Search and Characteristics

The results of the literature research and selection are presented in Figure 1. The literature review identified 88 full articles for detailed assessment, of which 69 were excluded for duplicate records and reporting of findings of studies that did not fulfill our inclusion criteria. Hence, 19 articles remained for analysis, among which 14 articles were excluded for one of the following reasons: lack of available data (6 articles), absence of stroke estimates included (6 articles), and lack of cohort design (2 articles). Furthermore, 1 article pooled data from 2 population-based cohort studies.[13] Finally, the present meta-analysis included results from 6 independent cohort studies (published in 5 articles).[12–16] Table 1 and Tables S1 through S3 present the characteristics of the included studies, which involved a total of 37 471 participants. The cumulative incidence of RVO in these participants was 17.1%. In addition, among the patients with RVO, 431 (6.7%) patients had claims for stroke. These studies were published between 2007 and 2015.[12–16] Out of them, 1 study was conducted primarily in the United States,[12] 1 in Korea,[16] 1 in China,[14] 1 in Denmark,[15] and 1 study contained data from 2 countries (the United States and Australia).[13] The number of participants ranged from 2450 (in the study conducted by Ho et al[14]) to 18 000 (in the study conducted by Werther et al[12]). Furthermore, the follow-up duration ranged from 1.5 to 12 years,[12,13] with a median of 5.7 years. All included studies reported the proportion of RVO in the study's participants (range from 1.2%[13] to 25.0%[12]). Population attributable risk for the association of stroke with RVO was ≈11.2%. All investigations provided adjusted risk estimates (eg, age, sex, body mass index, hypertension, diabetes, etc) and were graded as good quality according to the Newcastle–Ottawa Quality Assessment Scale.

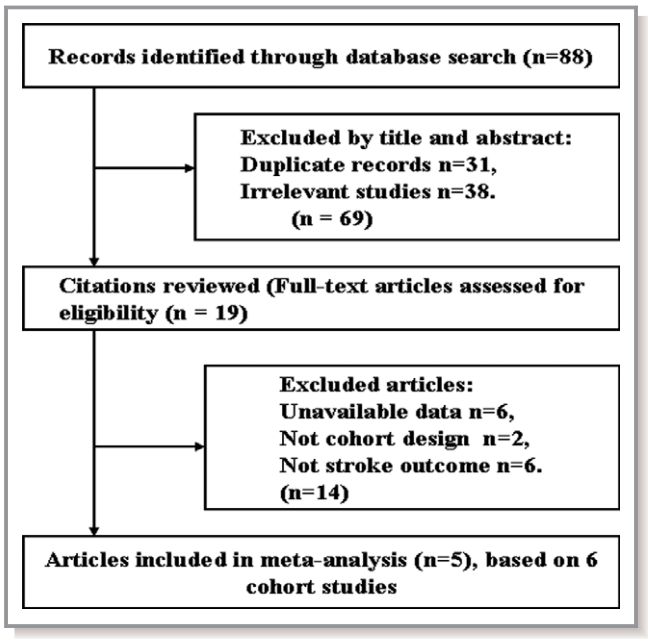

Figure 1. Process of literature search and study selection.

Association Between RVO and the Risk of Stroke

The multivariable adjusted RRs of stroke in relation to RVO from individual studies and the combined RR are presented in Figure 2.[12–16] Among the 5 studies, 3 revealed that RVO was associated with an increased risk of stroke.[12,15,16] Overall, after adjustment for established cardiovascular risk factors, participants with RVO at baseline exhibited a greater incidence of stroke risk (combined RR: 1.50, 95% CI: 1.19–1.90, Figure 2), compared to participants who did not have RVO at baseline.[12–16] There was evidence of significant heterogeneity in the magnitude of the association across studies (P for heterogeneity=0.05, I^2=57%). There was no evidence of publication bias by inspection of the funnel plot and formal statistical tests (Egger test, P=0.578, Figure S1).

Stratified Analysis

The stratified analyses are shown in Table 2. Stratified by sex, no association between RVO and the risk of stroke was observed in male (RR: 1.20, 95% CI: 0.96–1.49, n=3) or female (RR: 0.93, 95% CI: 0.64–1.34, n=3) subjects. Central RVOs were reported in 2 studies and were calculated using the random-effects model for analyses (P for heterogeneity=0.32, I^2=0%). Central RVO significantly increased the risk of stroke (RR: 1.90, 95% CI: 1.46–2.48, n=2). A similar result was obtained in the branch RVO group. After stratification by history of stroke, RVO was observed to significantly elevate the risk of recurrent stroke (RR: 1.72, 95% CI: 1.24–2.37; n=3), but not of the first stroke (RR: 1.29, 95% CI: 0.90–1.85, n=2). Previous studies have shown that age was one of the RVO risk factors. Thus, we pooled the logarithm of RR for comparable categories of age levels. As shown in Table 2, RVO was associated with an increased risk of subsequent

Table 1. Study Characteristics

First Author, Publication (Year)	Country	Participants (% Male)	Age Range or Mean (Years)	Follow-Up Duration (Years)	Adjustment for Covariates	Pre-Stroke Excluded	Study Quality
Cugati S et al[13] (2007)	USA, Australia	8282 (44)	43 to 86	12	Age, sex, BMI, current smoking, hypertension, DM, glaucoma, and study site	No	Good
Ho JD et al[14] (2009)	China	2450 (53.4)	≥18	5	Age, sex, geographic region, hypertension, DM, hyperlipidemia, and renal disease	Yes	Good
Werther W et al[12] (2011)	USA	18 000 (49.8)	18 to 89	1.5	Age, sex, angina, cardiac arrhythmia, Charlson score, CHF, DM, heart disease, history of ATEs, hyperlipidemia, hypertension, and other CVA	No	Good
Bertelsen M et al[15] (2014)	Denmark	2634 (52.4)	≥18	5.7	Age, sex, hypertension, peripheral vascular disease, Charlson Comorbidity Index, IHD, MI, CHF, CVA, and DM	No	Good
Rim TH et al[16] (2015)	Korea	6105 (44.7)	≥18	8	Age, sex, residential area, household income, hypertension, DM, and CKD	Yes	Good

ATEs indicates arterial thromboembolic events; BMI, body mass index; CHF, congestive heart failure; CKD, chronic kidney disease; CVA, cerebrovascular accident; DM, diabetes mellitus; IHD, ischemic heart disease; MI, myocardial infarction.

stroke in the 2 subgroups (50–59 and 60–69 years) when the estimates were stratified by age category.

Sensitivity Analysis

The robustness of our results was evaluated by sensitivity analysis. When studies included in the meta-analysis were deleted 1 at a time, the results of the meta-analysis remained largely unchanged, indicating that the results of the present meta-analysis were stable (data not shown). A sensitivity analysis was also performed by omitting a pooled study, which was combined with 2 studies, in which the patients were from different counties. It was found that the risk of stroke in RVO patients remained significant (RR: 1.56, 95% CI: 1.23–1.97) compared to patients without RVO. Furthermore, we excluded another study from the United States that included a sample size that was larger than those of the other cohorts and revealed that the association between RVO and the risk of stroke was almost significant (RR: 1.42, 95% CI: 1.04–1.94).

Discussion

In this meta-analysis of 6 cohort studies involving 431 cases of stroke and 37 471 participants, we found that RVO was associated with increased risk of stroke. These results were particularly pronounced in participants with a history of stroke, aged 50–69 years with RVO.

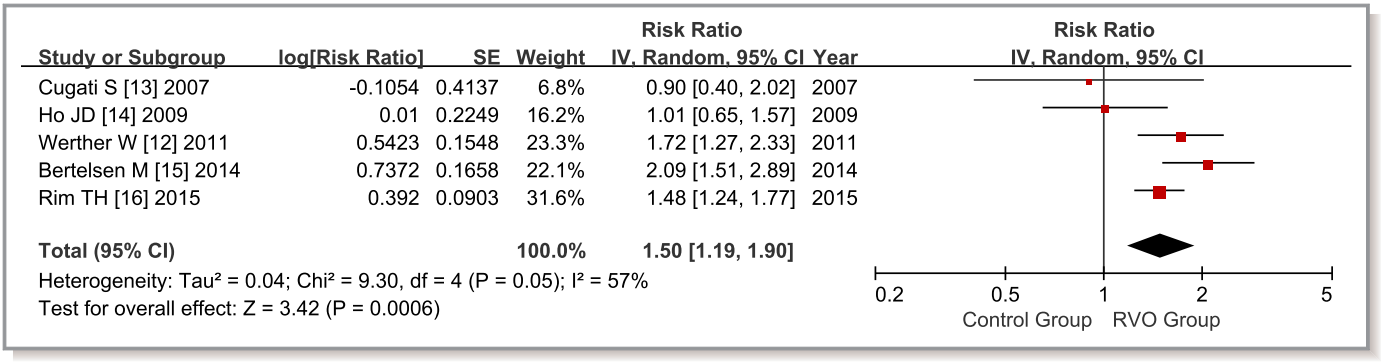

Figure 2. Random effects analysis of fully adjusted studies for the association between retinal vein occlusion and stroke risk. The square box in the graph portrays the weight that each study contributed to the analysis. IV indicates inverse variance; RVO, retinal vein occlusion.

Table 2. Stratified Analyses of RVO and Stroke Risk

Group	No. of Studies	Test of Association		Heterogeneity Test			*P** for Interaction
		RR (95% CI)	*P* Value	χ^2	*P* Value	I^2, %	
All studies	5	1.50 (1.19–1.90)	0.0006	9.30	0.05	57	
RVO type							<0.00001
CRVO	2	1.90 (1.46–2.48)	<0.00001	0.99	0.32	0	
BRVO	1	1.79 (1.18–2.72)	0.006	—	—	—	
Baseline stroke excluded							0.0006
Yes	2	1.29 (0.90–1.85)	0.16	2.48	0.11	60	
No	3	1.72 (1.24–2.37)	0.0010	3.70	0.16	46	
Sex							0.49
Males	3	1.20 (0.96–1.49)	0.10	3.54	0.17	44	
Females	3	0.93 (0.64–1.34)	0.70	7.66	0.02	74	
Mean age, y							<0.00001
<50	2	2.26 (0.59–8.65)	0.23	2.29	0.13	56	
50 to 59	3	2.23 (1.22–4.09)	0.009	3.74	0.15	47	
60 to 69	3	4.0 (1.36–11.79)	0.01	22.47	<0.0001	91	
70 to 79	4	3.30 (0.92–11.9)	0.07	65.65	<0.00001	95	
≥80	2	5.51 (0.21–142.3)	0.30	20.19	<0.00001	95	

BRVO indicates branch retinal vein occlusion; CRVO, central retinal vein occlusion; RR, relative risk; RVO, retinal vein occlusion.
**P* for interaction was utilized to assess the stratified differences.

RVO is classified into central RVO and branch RVO, and is a common cause of severe visual impairment.[27] In recent decades, overwhelming evidence has indicated that RVO is associated with well-known risk factors for cardiovascular disease.[3,6,10,11] There is also some information that RVO may have a direct role in the development of cardiovascular disease (eg, coronary heart disease, stroke, etc).[12–16] However, the exact mechanism of the effect by which RVO may have a direct or indirect role in the development of stroke remains ambiguous. Several mechanisms may be involved in the association between RVO and the risk of stroke. First, RVO is associated with certain cardiovascular risk factors, such as hypertension,[10] diabetes mellitus,[11] dyslipidemia,[28] smoking habits,[6] high body mass index,[29] and age,[3] which are also known as risk factors for stroke. Second, a long-term impairment of retinal microvasculature could lead directly to cerebral small-vessel disease and is characterized by lacunar infarcts and white matter lesions.[30–32] Moreover, some retinal vascular changes, including retinal arteriolar narrowing and retinal venular widening, have been reported to be associated with the lacunar stroke subtype.[30–32] These retinal vascular changes are also typical findings observed in individuals with RVO. Third, the risk factors for RVO that were established in previous epidemiologic studies include venous thromboembolic events,[33] deficiencies of anticoagulant proteins,[34] coronary artery disease,[12] and kidney disease,[35] all of which are also important risk factors for stroke.

Over the past decades, although previous clinical studies have investigated the role of RVO in either cardiovascular disease or cerebrovascular diseases, it remains unclear whether the association between RVO and the risk of stroke is causal.[12–16] Three studies suggested that RVO is associated with an increased risk of stroke,[12,15,16] while 2 studies failed to find such an association.[13,14] An earlier systematic review of retinal microvascular abnormalities and the risk of stroke revealed that the presence of retinal microvascular abnormalities was positively associated with stroke incidence.[36] This systematic review included 4 papers that investigated the association between RVO and the incidence and/or prevalence of stroke. Among these papers, 2 papers assessed the connection between RVO and the incidence stroke, and found no association,[13,37] whereas the other 2 papers indicated that RVO was associated with prevalent stroke.[38] In the present meta-analysis, we found that the risk of stroke was higher in patients with RVO and a history of stroke. This result is consistent with the registry-based cohort study conducted by Bertelsen et al,[15] while no association was noted in the Beaver Dam Eye Study and Blue Mountains Eye Study.[13] Previous investigations have established that coronary artery disease was one of the risk factors for RVO, especially for the central subtype.[15,16] Moreover, individuals with central RVO had a higher overall comorbidity index than branch RVO patients dominated by systemic vascular

disorders (such as coronary artery disease and cerebrovascular disease).[33,39] This could be explained in part by the higher stroke risk among RVO patients with a prior stroke. It has been shown that RVO is more prevalent in males than in females, and its occurrence is more frequent in older age.[33] In addition, as highlighted in previous reports, the differences in the impact of major cardiovascular risk factors were greater in males than in females. Historically, males have been more frequently subjected to the negative influence of smoking, drinking, and other unhealthy behaviors. These unfavorable habits may explain why male RVO patients appear to have a higher risk of stroke than female patients. To our knowledge, this meta-analysis is the first to reveal the potential relationship between RVO and the risk of stroke. Stroke is a heterogeneous disorder with 2 main pathophysiological divisions: hemorrhagic and ischemic stroke. Furthermore, while stroke subtypes share many vascular risk factors, their underlying pathophysiology varies, reflecting different disease processes. In general, any study that aims to understand the pathophysiology of stroke, or even assess any novel risk factors for stroke, should subdivide stroke into ischemic and hemorrhagic. This categorization requires a careful clinical assessment and appropriate brain imaging. However, in our examination, only 1 study further analyzed the data according to the stroke subtype. Rim et al analyzed data from the National Registry database with 8 years of follow-up. They found that patients with RVO exhibited a significantly higher risk of both ischemic and hemorrhagic stroke, although this result was not significant for hemorrhagic stroke. Moreover, other risk factors that contributed to RVO occurrence, such as health and behavioral risk factors, could not be evaluated. The influence of these missing data was likely to bias the true association among these individual studies.

Furthermore, in this meta-analysis, heterogeneity between studies was found that was not altered much in the sensitivity analysis. Heterogeneity might have come from several sources, among which, sex differences and the status of having or not having a prior stroke were the greatest. In the present meta-analysis, the sample size of each study was different, causing divergent power; thus, heterogeneity could vary immensely. Relatively small sample sizes, incomplete matching, and insufficient representative samples generated from a single center constitute the limitations that might have caused heterogeneity. Certainly, the observed heterogeneity could be attributable to differences in behavioral factors, country of origin, and methodological factors concerning the design. As mentioned earlier, the presence of heterogeneity calls for caution in interpreting these present meta-analysis findings.

In interpreting these results, some limitations of the current meta-analysis should be acknowledged. First, 1 limitation of any meta-analysis of observational studies is that residual confounding (multiple morbidities/comorbidities) or confounding by unmeasured factors (such as unhealthy behaviors) might have affected the strength of the association between RVO and stroke risk. Second, the assessment standards of RVO in the included studies were different. We cannot exclude the possibility of recall bias in the assessments of RVO based on the International Classification of Disease codes rather than using standardized grading of retinal photographs. Third, the number of available studies of different outcomes of RVO that could be included in this meta-analysis was moderate. Therefore, the results could have been influenced by factors, such as random error, publication bias, etc. In addition, the number of studies included in the subgroup of RVO was small; hence, there was a lack of sufficient reliability to confirm or refute a relationship in a definitive manner. Fourth, it would be interesting to determine whether the RVO-stroke association differed by stroke subtypes; however, few data were available for a stratified analysis. Among the 5 articles, 3 articles reported on total stroke cases (any type of stroke), 1 article defined stroke as ischemic or hemorrhagic, and the data in the remaining article were examined by the type of stroke. Finally, another possible limitation could be because of language bias. We attempted to minimize this bias by searching 3 major electronic databases with no language restriction. However, some articles published in Chinese or other non-English languages might not appear in international journal databases and could have been missed by our searches.[40]

In conclusion, the results from this meta-analysis provide new evidence that after the adjustment of traditional cardiovascular risk factors, the incidence of RVO in patients may indicate an increased risk of stroke. Future studies on the effect of RVO treatment and modifiable risk factor reduction on stroke risk in RVO patients are warranted.

Author Contributions

Li and Tang conceived and designed the study. Hu and Huang searched the databases and checked these according to the eligible criteria and exclusion criteria. Tang helped develop search strategies. Tan and Yang extracted the quantitative data. Huang and Tan analyzed the data. Li wrote the draft of the paper. All authors contributed in writing, reviewing, or revising the paper. Li and Tang were the guarantors.

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Disclosures

None.

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SUPPLEMENTAL MATERIAL

Data S1. Search strategy

The following terms were used to search the database for cohort studies of retinal vein occlusion and stroke:

PubMed:

#1: ("Retinal vein occlusion"[Mesh]) OR ((retinal vein occlusion[Text Word]) OR retinal vein obstruction[Text Word])

#2: (((((((("Stroke"[Mesh]) OR "Coronary Disease"[Mesh]) OR "Coronary Artery Disease"[Mesh]) OR "Myocardial Infarction"[Mesh]) OR "Myocardial Ischemia"[Mesh]) OR "Cerebrovascular Disorders"[Mesh]) OR "Cardiovascular Diseases"[Mesh]) OR "Heart Failure"[Mesh]) OR "Coronary Thrombosis"[Mesh]) OR (((((((((stroke[Text Word]) OR coronary heart disease[Text Word]) OR coronary artery disease[Text Word]) OR myocardial infarction[Text Word]) OR myocardial ischemia[Text Word]) OR cerebrovascular disorders[Text Word]) OR cardiovascular disease[Text Word]) OR heart failure[Text Word]) OR coronary thrombosis[Text Word])

#3: ((("Cohort Studies"[Mesh]) OR "Longitudinal Studies"[Mesh]) OR "Follow-Up Studies"[Mesh]) OR (((Cohort Studies[Text Word]) OR Longitudinal Studies[Text Word]) OR Follow-Up Studies[Text Word])

#4 : #1 AND #2 AND #3

Embase:

#1: 'Retinal vein occlusion' OR 'retinal vein obstruction'

#2: 'stroke' OR 'coronary heart disease' OR 'coronary artery disease' OR 'myocardial infarction' OR 'myocardial ischemia' OR 'cerebrovascular disorders' OR 'cardiovascular disease' OR 'heart failure' OR 'coronary thrombosis'

#3: 'Cohort Studies' OR 'Longitudinal Studies' OR 'Follow-Up Studies'

#4: #1 AND #2 AND #3

Cochrane Library:

#1: stroke:ti,ab,kw or coronary heart disease:ti,ab,kw or coronary artery disease:ti,ab,kw or myocardial infarction:ti,ab,kw or myocardial ischemia:ti,ab,kw or cerebrovascular disorders:ti,ab,kw or cardiovascular disease:ti,ab,kw or heart failure:ti,ab,kw or coronary thrombosis:ti,ab,kw or [Coronary Thrombosis] explode all trees or [Heart Failure] explode all trees or [Cardiovascular Diseases] explode all trees or [Cerebrovascular Disorders] explode all trees or [Myocardial Ischemia] explode all trees or [Myocardial Infarction] explode all trees or [Coronary Artery Disease] explode all trees or [Coronary Disease] explode all trees or [Stroke] explode all trees

#2: Retinal vein occlusion:ti,ab,kw or retinal vein obstruction:ti,ab,kw or [Retinal Vein Occlusion] explode all trees

#3: Cohort Studies:ti,ab,kw or "longitudinal studies":ti,ab,kw or Follow-Up Studies:ti,ab,kw or [Follow-Up Studies] explode all trees or [Longitudinal Studies] explode all trees or [Cohort Studies] explode all trees

#4: #1 AND #2 AND #3

Table S1. Characteristics of participants in the 5 articles of RVO

First author, publication (year)	Study design	Stroke subtypes	RVO assessment	Stroke ascertainment
Cugati S et al.[1] (2007)	RC	Any type of stroke	Photographs and retinal specialists	National Death Index data and death certificates (ICD-9-CM code 430.0-438.9 and ICD-10-CM code I60.0-I69.9)
Ho JD et al.[2] (2009)	RC	Any type of stroke	Visited ambulatory care physicians (ICD-9-CM codes 362.35 or 362.36)	Visited ambulatory care index (ICD-9-CM codes 430-438), death certificate data
Werehter W et al.[3] (2011)	RC	IS or HS	Two claims on separate days (ICD-9-CM code 362.35 or code 362.36)	Received inpatient or health care category (ICD-9-CM codes 431-434, and 436)
Bertelsen M et al.[4] (2014)	RC	Any type of stroke	Fundus photographs, fluorescein angiograms, and written records (ICD-10 code H.348 and ICD-8 codes 37703, 37708 and 37709)	Hospital discharge diagnoses (ICD-8 or ICD-10)
Rim TH et al.[5] (2015)	PC	IS: 1.51 (1.24-1.84), HS: 1.30 (0.83-2.05)	Received inpatient and outpatient care (ICD-9-CM codes 362.35 or 362.36)	Visited ambulatory and inpatient care index (ICD-9-CM codes 430-438)

Abbreviations: RC = retrospective cohort; PC = prospective cohort; IS = ischemic stroke; HS = hemorrhagic stroke; RVO = retinal vein occlusion; ICD = International Classification of Diseases.

Table S2. Characteristics of the 5 articles of RVO

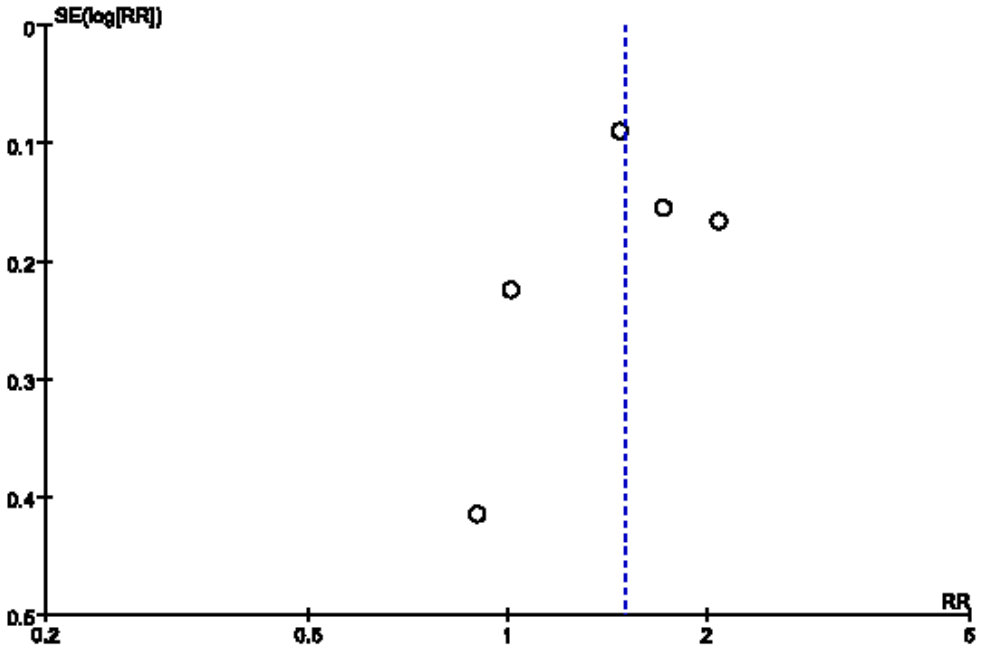
First author, publication (year)	Country	Participants (% male)	No. of RVO cases	Percent of RVO	No[a]. of stroke cases
Cugati S et al.[1] (2007)	USA, Australia	8282 (44)	96 (Males: 38, Females: 58)	1.2	7
Ho JD et al.[2] (2009)	China	2450 (53.4)	350 (Males: 187, Females: 163)	14.3	123
Werehter W et al.[3] (2011)	USA	18000 (49.8)	4500 (Males: 2239, Females: 2261; CRVO: 1670, BRVO: 2830)	25.0	78
Bertelsen M et al.[4] (2014)	Denmark	2634 (52.4)	439 (CRVO) (Males: 230, Females: 209)	16.7	50
Rim TH et al.[5] (2015)	Korea	6105 (44.7)	1031 (Males: 459, Females: 572)	16.9	173 (IS: 145, HS: 28)

Abbreviations: RVO = retinal vein occlusion; CRVO = central retinal vein occlusion; BRVO = branch retinal vein occlusion; IS = ischemic stroke; HS = hemorrhagic stroke; [a] = the number of stroke cases among those with RVO.

Table S3. Quality assessment of included studies by Newcastle-Ottawa Scale.

	Selection				Comparability		Outcome			
First author, publication (year)	Representativeness of exposed cohort	Selection of non-exposed cohort	Exposure Ascertainment	Outcome not present at start of study	Study controls for age	Study controls for any additional important factor	Assessment of Outcome	Length of follow-up	Adequacy of follow-up	Score
Cugati S *et al.*[1] (2007)	★	★	★		★	★	★	★	★	8
Ho JD *et al.*[2] (2009)	★	★	★	★	★	★	★	★	★	9
Werther W *et al.*[3] (2011)	★	★	★		★	★	★		★	7
Bertelsen M *et al.*[4] (2014)	★	★	★		★	★	★	★	★	8
Rim TH *et al.*[5] (2015)	★	★	★	★	★	★	★	★	★	9

Figure S1. Funnel plot of retinal vein occlusion and relative risk of stroke.



Supplemental References:

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