Diabetes mellitus as a risk factor for retinal vein occlusion

A meta-analysis

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Abstract

Retinal vein occlusion (RVO) is the second most common etiology for vision loss. There is contrasting evidence on the association between diabetes mellitus (DM) and the risk of RVO. We performed a meta-analysis of published articles before October 31, 2019, to estimate a pooled odds ratio for the association between DM and RVO, including central and branch RVO by a fixed or random effects model. We identified 37 publications from 38 studies (1 publication was from 2 studies), published between 1985 and 2019. In total, 148,654 cases and 23,768,820 controls were included in this meta-analysis. The results of pooled analysis for all 37 publications (or 38 studies) showed a significant association between DM and the risk of RVO (OR = 1.68, 95% CI: 1.43–1.99). Subgroup analysis indicated that DM was significantly associated with CRVO (OR = 1.98, 95% CI: 1.29–3.03, I^2 = 67.9%), but not significantly associated with BRVO (OR = 1.22, 95% CI: 0.95–1.56, I^2 = 64.1%). In conclusion, the result of present meta-analysis suggested that DM is a risk factor for RVO. More well-designed studies on the relationship between RVO and DM should be undertaken in the future.

Abbreviations: BRVO = branch retinal vein occlusions, CRVO = central retinal vein occlusion, DM = diabetes mellitus, HTN = hypertension, I^2 = I-squared, OR = odds ratio, RVO = retinal vein occlusion.

Keywords: diabetes mellitus, meta-analysis, retinal vein occlusion

1. Introduction

Retinal vein occlusion (RVO) is the second most common etiology for vision loss resulting from retinal vascular disorder.[1] RVO exists as 2 subtypes: central retinal vein occlusion (CRVO) and branch retinal vein occlusion (BRVO). A recent analysis revealed that approximately 16 million people worldwide are affected by BRVO.[2] BRVO may result from compression of a branch retinal vein by an adjacent arteriosclerosis retinal artery. Although CRVO shows low prevalence compared to BRVO, it is associated with a worse visual prognosis. CRVO is typically caused by thrombus formation near the lamina cribrosa[1,3] and frequently leads to devastating complications such as neovascular glaucoma.[4]

Systemic condition such as hypertension (HTN), dyslipidemia, diabetes mellitus (DM), and heart diseases increase the risk for endothelial damage or abnormal blood flow; thus, they are associated with RVO.[5] DM, with a prevalence of 2.8% in 2000 and estimated prevalence rate of 4.4% in 2030,[6] is an increasingly severe epidemic health problem globally related with serious acute and chronic complications, resulting from the changing lifestyle and aging population.[7]

Components of metabolic syndrome as risk factors for RVO have been controversial with only some prior studies showing an association between DM and RVO.[8–14] Therefore, this meta-analysis was could determine DM as a possible risk factor.

2. Materials and methods

The present study involved reviewing of issued studies under the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) guidelines, and thus, ethical approval was not required.

2.1. Search strategy and study selection

The systematic review was performed by searching databases of PubMed, Web of Science, Scopus, and Cochrane Library to identify relevant studies with the following keywords DM and RVO, and the last search was updated on October 31, 2019. Both Medical Subject Headings and free text terms for key words were used. Detailed search strategies are presented in Supplementary Table 1, http://links.lww.com/MD/D859. The reference lists of papers of interest, and published review articles were also explored to retrieve potentially additional studies. Duplicate publications were included only once. Inclusion criteria of the studies were as follows:

(1) clear information of RVO confirmation and of included patients and controls;
(2) control groups without RVO; and
(3) the number of individuals with DM in RVO cases and controls.

Exclusion criteria were as follows:

(1) case reports, laboratory studies, letters, reviews, or expert opinions;
(2) studies with overlapping or duplicate data; and
(3) lack of enough cases (less than 10) with any form of RVO.

2.2. Data extraction and quality assessment

Two investigators conducted the systematic search and extracted data independently by the name of the first author, year of publication, country/region, races, study period, study design, total number of RVO patients and control subjects, RVO type, DM patients, age (mean or median) of RVO patients and control cases. The quality of the included studies was evaluated by using the Newcastle–Ottawa Scale (NOS).[15] The NOS has a minimum score of zero and a maximum score of nine. All included studies were regarded as low, moderate, and high quality based on NOS scores of 0 to 3, 4 to 6, and 7 to 9, respectively.[16] Any discrepancy was resolved by consensus, and if needed, by consultation with the third author.

2.3. Statistical analysis

The results were evaluated as odds ratios (ORs) for each included study. ORs and 95% confidence intervals (CIs) were obtained directly or calculated from each publication. The heterogeneity of pooled OR was estimated by Higgins I-squared (I^2) statistic. If heterogeneity existed (I^2 greater than 50%), a random-effects model was applied; otherwise, a fixed-effects model was conducted.[17,18] Egger linear regression and Begg funnel plot test were applied to evaluate publication bias and a $P < .05$ was considered significant. Leave-one-out sensitivity analysis was applied to confirm the outcomes' credibility of this meta-analysis. All statistical analyses were performed by STATA software version 12.0 (STATA Corporation, College Station, TX) and all P values were 2-sided.

3. Results

3.1. Study characteristics

The process of detailed screening is shown in Figure 1. We identified 37 publications[8–12,14,19–48] from 38 studies (1 publication[49] was from 2 studies: Beaver Dam Eye Study and
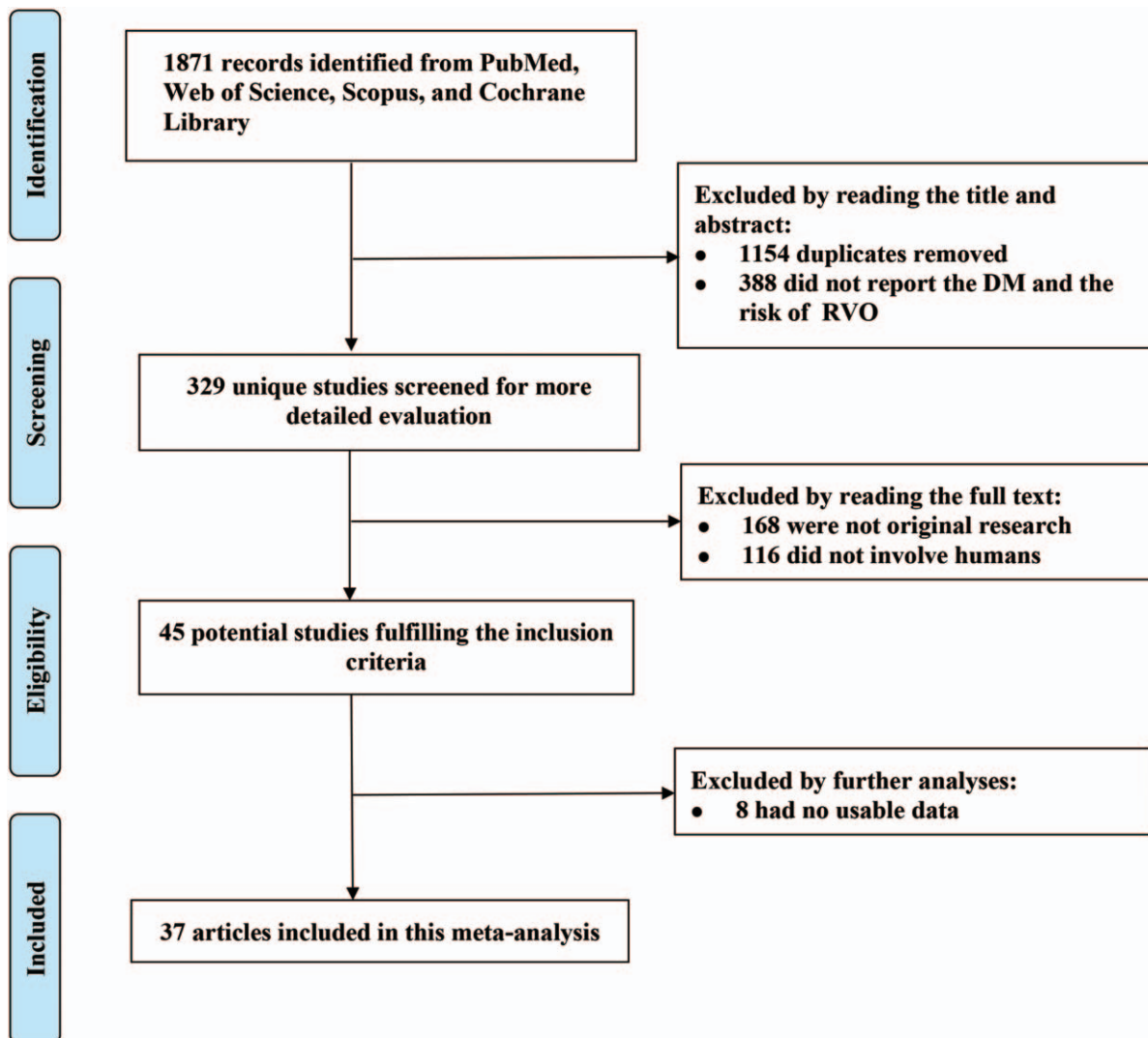

Figure 1. Methodological flow diagram of the meta-analysis.

Table 1

Characteristics of all the included studies.

Author	Country/region	Year	Race	Study period	Study design	Type of RVO	Case group			Control group			NOS score
							Total RVO patients	Number of DM	Age	Total controls	Number of DM	Age	
Johnston	US	1985	White/Black/Other	1977–1982	Case control	BRVO	225	47 (20.89%)	70	100	14 (14%)	69	7
Appiah	US	1987	NA	1983–1984	Case control	RVO	68	11 (16.18%)	62	50	16 (32%)	58.6	6
Elman	US	1990	White/Black	1980–1986	Case control	CRVO	191	26 (13.61%)	65.2	191	25 (13.09%)	NA	7
Rath	US	1990	NA	1985–1990	Case control	RVO	87	28 (32.18%)	68.4	85	18 (21.18%)	66.7	6
Sekimoto	Japan	1992	NA	1986–1989	Case control	RVO	63	19 (30.16%)	61.6	50	12 (24%)	62.3	6
The EDCc Study Group	US	1996	White/Other	1986–1990	Case control	CRVO	258	43 (16.67%)	NA	1142	102 (8.93%)	NA	7
Timmerman	Netherlands	1997	NA	1991–1993	Case control	BRVO	24	8 (33.33%)	63	24	8 (33.33%)	66	7
Simons	US	1997	White/Black/Hispanic	NA	Case control	BRVO	36	5 (13.89%)	67.2	36	10 (27.78%)	67.1	7
Salomon	Israel	1998	NA	1996	Case control	RVO	102	17 (16.67%)	62.7	105	16 (15.24%)	57.8	7
Marcucci	Italy	2001	NA	1998–1999	Case control	CRVO	100	12 (12%)	59	100	0 (0%)	56	6
Kadayifcilar	Turkey	2001	NA	1999	Case control	RVO	54	6 (11.11%)	59.7	12	2 (16.67%)	62.4	7
Yaghoubi	Iran	2004	NA	2002	Case control	RVO	24	4 (16.67%)	60.5	24	1 (4.17%)	61.7	7
Yildirim	Turkey	2004	NA	2001–2002	Case control	RVO	33	5 (15.15%)	61	25	3 (12%)	58	7
Weger	Austria	2005	Caucasian	NA	Case control	BRVO	294	28 (9.52%)	67	294	41 (13.95%)	67.1	7
Gumus	Turkey	2006	NA	2003–2004	Case control	CRVO	26	2 (7.69%)	57.7	78	7 (8.97%)	57.4	7
						BRVO	56	4 (7.14%)		78	7 (8.97%)		
Pinna	Italy	2007	Sardinian ancestry	1996–2005	Case control	CRVO	194	29 (14.95%)	65.2	896	134 (14.96%)	65	7
						BRVO	254	31 (12.2%)	64.9				
Leoncini	Italy	2007	NA	NA	Case control	RVO	38	4 (10.53%)	67.3	40	0 (0%)	63.3	6
Cugati	Australia	2007	Beaver Dam-white	1988–1990	cohort study	RVO	38	7 (18.42%)	70.1	4784	426 (8.9%)	61.8	7
			Blue Mountains-white	1922–1994		RVO	58	5 (8.62%)	71.6	3498	269 (7.69%)	65.9	
Koizumi	Italy	2007	NA	2005–2006	Case control	CRVO	144	23 (15.97%)	69.6	144	12 (8.33%)	68.9	7
Mirko	Italy	2010	NA	1999–2005	Case control	RVO	117	21 (17.95%)	54	202	16 (7.92%)	52	8
Bertelsen	Denmark	2012	NA	1976–2010	Case control	BRVO	1020	52 (5.1%)	NA	106357	2976 (2.8%)	NA	6
Capua	Italy	2012	NA	1998–2007	Case control	RVO	45	5 (11.11%)	54.1	145	7 (4.83%)	53.8	6
Giannaki	Greece	2013	NA	2007–2011	Case control	RVO	51	13 (25.49%)	NA	51	3 (5.88%)	NA	6
Newman-Casey	US	2014	White/Black/Latino/Asian-American/Other/Missing	2001–2009	Cohort study	BRVO	2283	886 (38.81%)	69.2	490205	155600 (31.74%)	65.6	6
Fernández-Vega	Spain	2019	Spanish	NA	Case control	RVO	183	25 (13.66%)	62.49	176	19 (10.8%)	64.25	7
Aikaterini	Greece	2019	NA	NA	Case control	BRVO	24	4 (16.67%)	71.9	82	2 (2.44%)	71.3	6
						CRVO	45	11 (24.44%)	71.5	82	2 (2.44%)	71.3	
Kim	Korea	2019	Korean population	2009–2015	Cohort study	RVO	117639	25422 (21.61%)	60.4	23031764	2112579 (9.17%)	47.6	6
Chen	Taiwan	2019	NA	1995–2013	Cohort study	RVO	22919	8635 (37.68%)	61.8	114595	14468 (12.63%)	43.2	6
Christiansen	Denmark	2019	Danish	1997–2011	cohort study	RVO	529	50 (9.45%)	73.4	6840	368 (5.38%)	71.4	6
Schwaber	USA	2019	White/Black/African American/Others	2012–2015	Case control	RVO	214	110 (51.4%)	NA	856	248 (28.97%)	NA	6
Thapa	Nepal	2017	NA	2007–2010	Cohort study	RVO	55	4 (7.27%)	NA	1805	164 (9.09%)	NA	8
Szigeti	Hungary	2016	Caucasians	2010–2013	Case control	RVO	130	25 (19.23%)	69	125	31 (24.8%)	68	7
Demir	Turkey	2015	NA	NA	Case control	BRVO	133	32 (24.06%)	64.3	167	23 (13.77%)	62.9	7
						CRVO	54	15 (27.78%)	63.3	167	23 (13.77%)		
Kutluturk	Turkey	2014	NA	2008–2011	Case control	RVO	80	31 (38.75%)	60.2	80	12 (15%)	59	7
Weger	Austria	2013	Caucasian	NA	Case control	BRVO	285	46 (16.14%)	66.9	333	21 (6.31%)	69.1	7
						CRVO	401	26 (6.48%)	66.5				
Ortak	Turkey	2013	NA	NA	Case control	RVO	162	25 (15.43%)	64.2	174	12 (6.9%)	64.6	6
Chan	Singapore	2013	Singapore Indians	2007–2009	Cohort study	BRVO	18	7 (38.89%)	65.3	3185	1051 (33%)	57.5	7

BRVO = branch retinal vein occlusions, CRVO = central retinal vein occlusion, DM = diabetes mellitus, NOS = Newcastle–Ottawa Scale, RVO = retinal vein occlusion.

Blue Mountains Eye Study), published between 1985 and 2019, according to the inclusion and exclusion criteria. The characteristics of all the included studies and their quality based on the NOS score are demonstrated in Table 1. In total, 148,654 cases and 23,768,820 controls were included in this meta-analysis. Among them, 1123 cases were CRVO, 4842 cases were BRVO, and 142,689 cases were RVO.

3.2. Meta-analysis

The results of pooled analysis for all 37 publications showed a significant association between DM and the risk of RVO (OR = 1.68, 95% CI: 1.43–1.99) (Fig. 2) with significant heterogeneity across the studies ($I^2 = 96.6\%$). In the subgroup analysis by type of RVO, the results indicated that DM was a risk factor for the

CRVO group (OR = 1.98, 95% CI: 1.29–3.03, $I^2 = 67.9\%$) and mix group (OR = 1.94, CI: 1.59–2.38, $I^2 = 96.8\%$), but not significantly associated with BRVO group (OR = 1.22, 95% CI: 0.95–1.56, $I^2 = 64.1\%$). However, in subgroup analysis by study design, DM was associated with increased risk of RVO in both case-control studies (OR = 1.58, 95% CI: 1.27–1.96, $I^2 = 63.9\%$) and cohort studies (OR = 2.01, 95% CI: 1.49–2.71, $I^2 = 99.2\%$). Subgroup analysis by country showed association between DM and the risk of RVO in US (OR = 1.4, 95% CI: 1.01–1.94, $I^2 = 78.4\%$), Turkey (OR = 2.09, 95% CI: 1.48–2.93, $I^2 = 29.3\%$), and Italy (OR = 2.16, 95% CI: 1.22–3.83, $I^2 = 56.8\%$). On the basis of sample size (studies with less than 1000 subjects were classified as "Small", studies between 1000 and 10,000 subjects as "Middle", and with more than 10,000 subjects as "Large"), DM was a risk factor in the Small group (OR = 1.52, 95% CI:
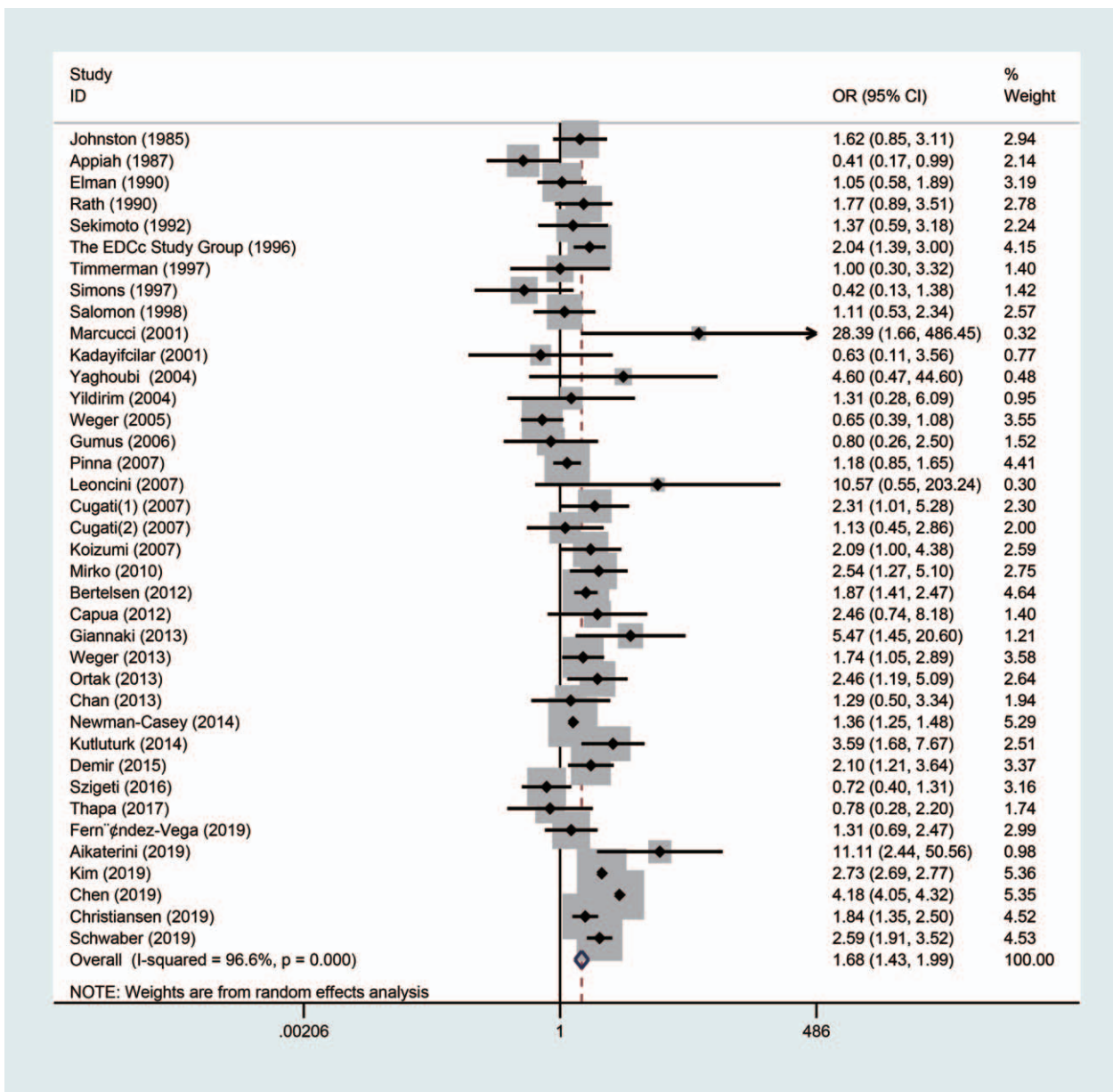

Figure 2. Forest plot of the risk estimates of the association between diabetes mellitus and retinal vein occlusion in the overall analysis.
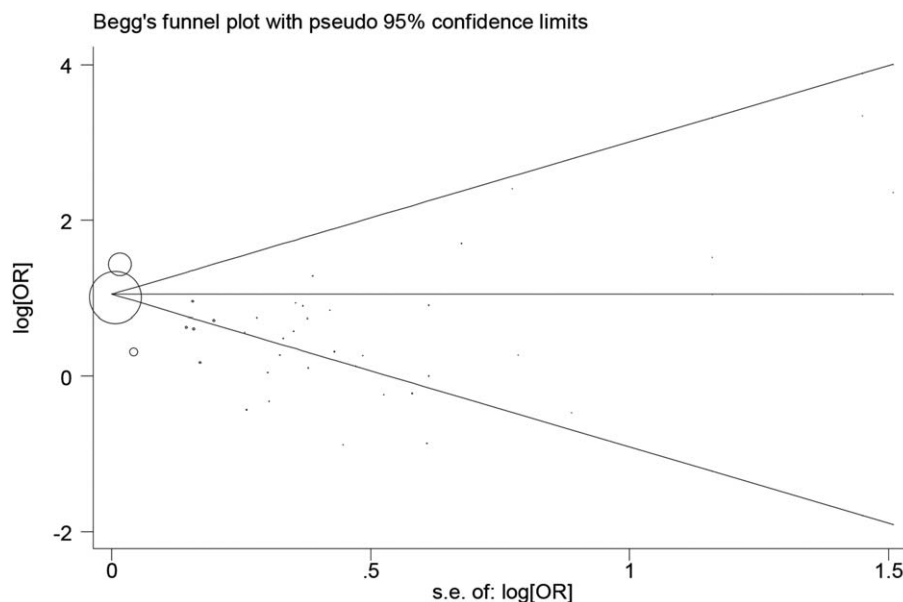
Figure 3. Funnel plot evaluating the association between diabetes mellitus and retinal vein occlusion in the overall analysis.

1.14–2.03, $I^2 = 61.8\%$), Middle group (OR = 1.72, 95% CI: 1.35–2.17, $I^2 = 50.7\%$), and Large group (OR = 2.35, 95% CI: 1.66–3.32, $I^2 = 99.7\%$). As per the publication year, the analysis showed that DM was not a risk factor in studies published before 2000 (OR = 1.18, 95% CI: 0.83–1.69, $I^2 = 53.8\%$) as well as published between 2000 and 2010 (OR = 1.47, 95% CI: 0.99–2.19, $I^2 = 53.6\%$), however, DM is associated with the risk of RVO in studies published after 2010 (OR = 2.07, 95% CI: 1.67–2.58 $I^2 = 98.3\%$). Subgroup analysis based on NOS score showed a significant association between DM and increased risk of RVO

in the moderate quality (OR = 2.13, 95% CI: 1.68–2.72, $I^2 = 98.5\%$) and high-quality groups (OR = 1.4, 95% CI: 1.12–1.74, $I^2 = 51.8\%$).

3.3. Publication bias and sensitivity analysis

Begg funnel plot and Egger linear regression test were evaluated for publication bias. In all included studies, the results did not indicate any evidence of bias ($P = .085$) (Fig. 3, Table 2). However, there was publication bias in the Italy group analysis

Table 2

The results of meta-analysis.

subgroup	No. of trials	Model	OR	95%CI	I^2 (%)	Bias-*P* value
All	38	Random	1.68	1.43–1.99	96.60	.079
Type of RVO						
BRVO	12	Random	1.22	0.95–1.56	64.1	.514
CRVO	9	Random	1.98	1.29–3.03	67.9	.216
Mix	22	Random	1.94	1.59–2.38	96.80	.585
Study design						
case control	30	Random	1.58	1.27–1.96	63.9	.973
cohort study	8	Random	2.01	1.49–2.710	99.2	.725
NOS score						
moderate quality	15	Random	2.13	1.68–2.72	98.5	.65
high quality	23	Random	1.4	1.12–1.74	51.8	.709
Country						
US	9	Random	1.4	1.01–1.94	78.4	.97
Turkey	6	Fixed	2.09	1.48–2.93	29.3	.138
Italy	6	Random	2.16	1.22–3.83	56.8	.006
Sample size						
≤1000	25	Random	1.52	1.14–2.03	61.8	.109
1000–10,000	9	Random	1.72	1.35–2.17	50.7	.31
>10,000	4	Random	2.35	1.66–3.32	99.7	.89
Publication year						
Before 2000	9	Random	1.18	0.83–1.69	53.80	.021
2000–2010	12	Random	1.47	0.99–2.19	53.6	.129
After 2010	17	Random	2.07	1.67–2.58	98.3	.535

BRVO = branch retinal vein occlusions, CRVO = central retinal vein occlusion, RVO = retinal vein occlusion.
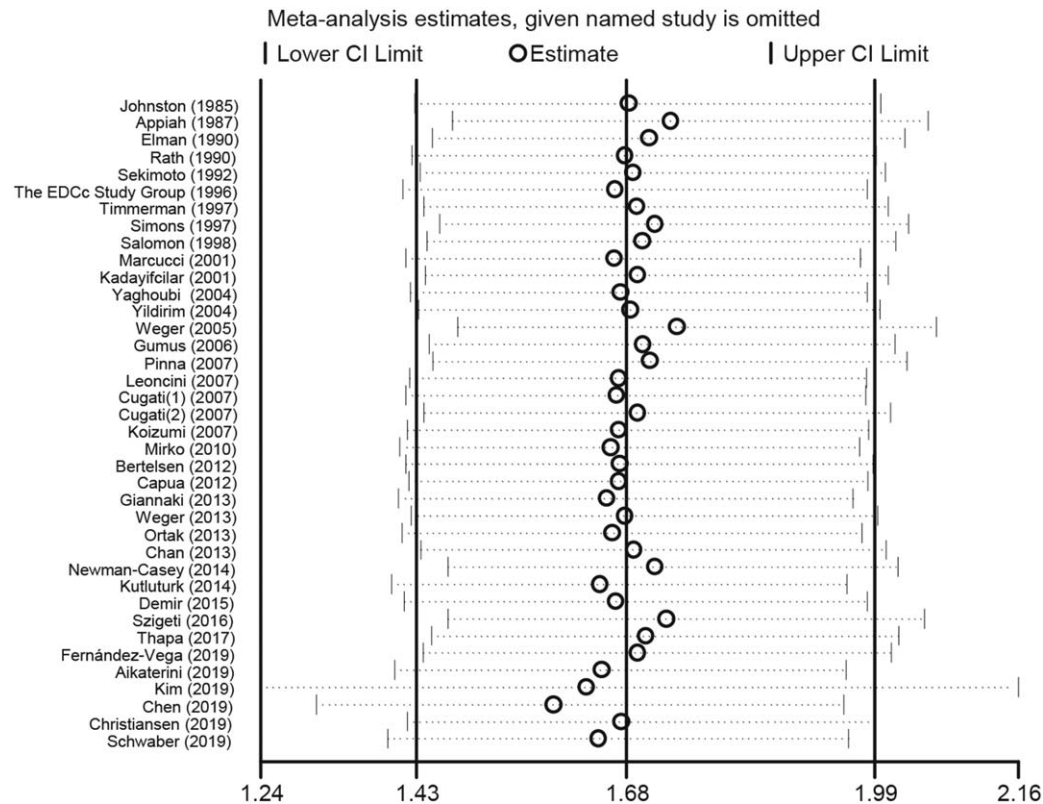
Figure 4. Leave-one-out sensitivity analyses estimating the association between diabetes mellitus and retinal vein occlusion in the overall analysis.

($P = .006$, Table 2) and studies published before 2000 ($P = .021$, Table 2). We used the sequential omission of each individual study to check if any single study impacted the results. Figure 4 shows that the result was not affected by each individual study and this indicated the stability of the results in the overall analysis.

4. Discussion

RVO is the second most common retinal vascular disorder and a relatively common and frequent cause of visual loss, mainly in elderly patients, resulting from macularedema and retinal ischemia.[50] Although it was first recognized over a century ago, the exact pathogenesis remains unclear. The risk factor for RVO is further connected with systemic conditions such as HTN, arteriosclerosis, DM, hyperlipidemia (HLD), vascular cerebral stroke, blood hyperviscosity, and thrombophilia.[51] Early in 2008, O'Mahoney et al[52] concluded that DM is a risk factor for RVO in adults based on the analysis of 2877 RVO cases and 13,225 controls from 20 studies. Since then, more studies about the relationship between RVO and DM were issued that may significantly change their conclusion. Thus, new analysis was necessary.

This meta-analysis involving 148,654 cases with RVO and 23,768,820 controls supported that individuals with DM were positively related with an increased risk of RVO. Compared with the previous meta-analysis,[52] the number of included studies was more than one-fold in this study with multi-fold cases and controls. In addition, we conducted subgroup analyses based on several factors (such as country and NOS

score), which were not conducted by O'Mahoney et al. Thus, this study provides more accuracy about the relationship between DM and RVO.

In the subgroup analysis by type of RVO, we found no association between DM and the risk of BRVO, but DM was a risk factor for the CRVO group and mix group. Previously, Pinna et al[28] found that the prevalence rate of DM was lower in the BRVO group (12.2%) than in the control group (15%). However, Demir et al[44] and Christodoulou et al[37] indicated that the prevalence rate of DM was higher in the BRVO group (24% and 16.7%, respectively) than in the control group (14% and 2.4%, respectively). This meta-analysis included more studies, which can strengthen the statistical power. Notably, the present study missed several BRVO data because 22 included studies (mix group) only included RVO data. Thus, we should be cautioned about the relationship between DM and BRVO, with more future studies suggested. Studies published after 2010 that showed association between DM and risk of RVO might have used more accurate methods and thus provided a more representative case-control study.

Significant heterogeneity was found in the overall analysis. When data were pooled into subgroup analyses, the heterogeneity decreased in some groups. Further analysis showed 2 studies[38,39] affected heterogeneity. Both studies were population based cohort studies including 137,541 samples and 23,149,403 samples, respectively. After excluding both studies, the I^2 decreased to 61.7% and results did not change. Moreover, we used the sequential omission of each individual study and the result was not affected by each individual study, thus indicating the stability of the results.

Our study has several concerning limitations. First, the studies included in this meta-analysis were all published in English, the language bias being inevitable. Second, we could not conduct subgroup analysis based on other contributing clinical factors (such as HTN and HLD) because of insufficient data. Finally yet importantly, only published studies with available data were included, and the unpublished data mat thus influence the conclusions.

In conclusion, the result of present meta-analysis suggested that DM is a risk factor for RVO. Considering these limitations listed above, more well-designed studies on the relationship between RVO and DM should be undertaken in the future.

Author contributions

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