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Meta-Analysis

Diabetic Retinopathy May Be a Predictor of Stroke in Patients With Diabetes Mellitus

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Abstract

Background: It is unclear whether diabetic retinopathy (DR) can be a predictor of stroke. In this research context, the objective of our study was to investigate whether there is a significant association between DR and stroke in diabetic patients by meta-analysis.

Methods: After a systematic search of studies in electronic databases, we screened all studies reporting the risk of DR status and stroke incidence and calculated their odds ratios (ORs) and hazard ratios (HRs). The effects of type of diabetes and severity of DR were also considered for subgroup analysis.

Results: We included 19 studies involving 45 495 patients. A pooled HR = 1.62 (1.28-2.06) were found for the risk of DR and stroke in diabetic patients. In a subgroup analysis performed on the type of diabetes, the results showed a significant association between stroke incidence and DR status in patients with type 2 diabetes (T2D) (OR: 1.78; 95% CI, 1.53-2.08), but this association was not conclusive in type 1 diabetes (T1D) (OR: 1.77; 95% CI, 0.48-6.61). The results of the subgroup analysis with diabetes severity showed that both mild and moderate nonproliferative diabetic retinopathy (NPDR) status and severe NPDR and worse status significantly increased the risk of stroke with HRs of 2.01 (1.45-2.78) and 2.27 (1.52-3.39), respectively.

Conclusion: DR status in diabetic patients is associated with an increased risk of stroke. This correlation was robust in patients with T2D, but uncertain in T1D. Based on this result, we have perhaps found the new factor for stroke management, so we analyzed the necessity and advantages of considering DR as a factor for stroke screening and risk management in our studies.

Key Words: diabetic retinopathy, stroke, meta-analysis

Abbreviations: CVD, cardiovascular events; DR, diabetic retinopathy; HR, hazard ratio; OR, odds ratio; NPDR, nonproliferative diabetic retinopathy; T2D, type 2 diabetes mellitus;

Diabetic retinopathy (DR), one of the most common microvascular complications of diabetes, is diagnosed in one-third of diabetic patients and is the leading cause of blindness in people of working age [1, 2]. In addition, the incidence and development of DR is associated with numerous systemic diseases, including stroke, which is the second leading cause of death of the world's population according to epidemiological research [3], especially in low-income and middle-income countries, where the number of stroke patients is increasing by about 2 million per year due to the aging of the population and the growth of the population base [3-5].

To overcome this critical situation, the prediction of risk factors and the related management for stroke is becoming the one of the most important directions of current treatment. Previous studies [6-8] have mostly correlated the risk of stroke with cardiovascular events (CVD); however, as more and more clinical studies and statistical reviews have been conducted, CVD no longer seems to be a strong explanation and predictor of the development of stroke.

For this reason, the studies on the correlation between stroke and diabetes have received a lot of attention in recent years. It is known that diabetes can be an important risk factor for stroke, and the incidence of stroke is 2 to 4 times higher in people with diabetes than in those without diabetes [9]. However, diabetes is also a very important and widespread disease, and the process of microvascular and macrovascular damage that it causes also contributes to the risk of stroke [10, 11]. Therefore, secondary prevention of stroke from a diabetic perspective is now the key to risk management.

DR has now received increasing attention and focus. According to epidemiological and evidence-based surveys [4, 12], the prevalence of DR among diabetic patients worldwide is 34.6%.

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Owing to the comprehensive use and development of ophthalmic examinations, combined with its convenient operation and low cost, DR can be included in the routine screening for chronic complications of diabetes, thus providing the potential for early diagnosis of DR and its use as a stroke screening test. On the one hand, it is increasingly recognized that microvascular disease plays an important role in stroke research [13], and DR as a diabetic microvascular complication naturally falls into this range. On the other hand, although clinical studies on DR and stroke have been conducted in recent years [10, 14, 15], the results have been inconsistent and there is a lack of high-level evidence-based studies.

In such a research background, the objective of our study was to investigate whether there is a significant association between DR and stroke in diabetic patients by meta-analysis. We also briefly analyze the progress of those relevant studies, besides the mechanisms of DR-stroke interaction and the prospects of DR screening, concluding that it is necessary and advantageous to include DR as an independent factor in stroke risk management.

Materials and Methods

Data Retrieval and Study Screening

Two researchers (Z.W. and K.Z.) independently searched relevant studies in common databases such as PubMed, Web of Science, Embase, and Cochrane Library. The range was set to studies from all countries during 1976 o 2022, the language of publication was English, and the key words and subject terms (medical subject headings; MeSH) were "stroke," "cerebrovascular events," "cerebrovascular accidents," "cerebrovascular accidents," "cerebral palsy," "diabetic retinopathy," "non-proliferative diabetic retinopathy," and "proliferative diabetic retinopathy." Also, to identify potential additional studies, we searched Google Scholar, relevant reviews, and references cited in studies that met the criteria. The eligibility criteria related to study characteristics were population-based retrospective studies, cohort studies, or randomized controlled trials reporting on the association between DR in any state and all types of stroke events. Our supplemental search strategy was consistent the aforementioned criteria, with a last search date of June 1, 2022.

All search results were exported to EndNote X8 (Bld 10063) software for subsequent screening. Two researchers (Z.W. and K.Z.) separated the studies into odds ratio (OR) and hazard ratio (HR) groups according to the type of findings; articles with OR as a outcome were identified with a specific sample size (n) for the DR or stroke group for subsequent analysis. Those articles that did not mention sample size (n) in the full text were treated as follows: (i) the specific sample size was calculated for each group using the given baseline data or outcome event data; and (ii) the corresponding author of the article was contacted to obtain the required data. Studies for which data could not be obtained by the aforementioned methods were excluded.

In addition, the exclusion criteria included (i) studies in which the diagnostic methods for stroke and DR were not described in the text or were considered inappropriate by the researchers; (ii) for different studies of patients in the same region (community, hospital, or medical center), we included only articles with higher-quality assessment results the Newcastle-Ottawa Scale (NOS), and if the quality scores were the same, we included the most recently published one; (iii) studies with a specific coverage and propensity to observe participants. The review of articles and data was performed independently by 2 reviewers (J.Y. and X.Z.), who reviewed and cross-checked the articles before analysis. In case of any disagreement, discussion or consultation with the supervising researcher (D.C.) determined a final decision.

Assessment of Study Quality and Risk of Bias

Two reviewers (Y.C. and R.C.) evaluated study quality and risk of bias for the included studies using the Newcastle-Ottawa Scale. The quality parameters rated include selection (4 points), comparability (2 points), and exposure (3 points) assessment. The two reviewers appropriately adjusted the scoring details before scoring (Table 1 shows the specific entries and scoring details). Studies scoring more than 7 after adding up their quality parameters were considered high-quality studies with a low risk of bias, scores of 5 to 7 indicated moderate-quality studies with a moderate risk of bias, and scores of less than 5 indicated lower-quality studies with a high risk of bias. Any disagreement between the 2 reviewers on this assessment were resolved through discussion with the supervising investigator (D.C.). Publication bias was assessed using funnel plots, completing the symmetry assessment with the Begg test.

Statistical Analysis

After including studies with "no DR" and "with DR" as effects, we examined pooled risk estimates of HRs, ORs, and their 95% CIs calculated from the included studies or from the extracted data to summarize the stroke events associated with DR. In the OR group, statistical heterogeneity was assessed by forest plots and tested using χ^2 and I^2 methods. If there was no statistical heterogeneity between outcomes ($P > .10$ and $I^2 < 50\%$), meta-analysis was performed using Mantel-Haenszel statistical methods and fixed-effects models. If there was statistical heterogeneity between the results ($P < .10$ and $I^2 > 50\%$), a meta-analysis was performed using the Mantel-Haenszel statistical method with a random-effects model. For the HR group, we used the statistical method of "inverse variance" to analyze those results with low heterogeneity and "random (I-V heterogeneity)" as an effect model for the meta-analysis. We planned to conduct subgroup analyses using the following factors: type of diabetes (type 1 [T1D] vs type 2 [T2D]), and severity of DR (mild and moderate nonproliferative diabetic retinopathy [NPDR] vs severe NPDR and worse). In addition, we performed sensitivity analyses by excluding studies that were assessed as being of insufficient quality.

All statistical analyses for this study were completed using StataSEWin32 (version 419.12.0.866) and Microsoft Excel for Microsoft 365 MSO (16.0.14026.20202) 64-bit.

Results

Search and Assessment

First, we identified 6149 studies in a search of the databases. A supplementary search June 1, 2022, identified an additional 1120 relevant studies that fulfilled the requirements. The study selection process is shown in Fig. 1. We ultimately identified 19 studies [10, 13, 16-28] that included a total of 45 495 patients for analysis (Table 2). Of these studies, 4 involved T1D

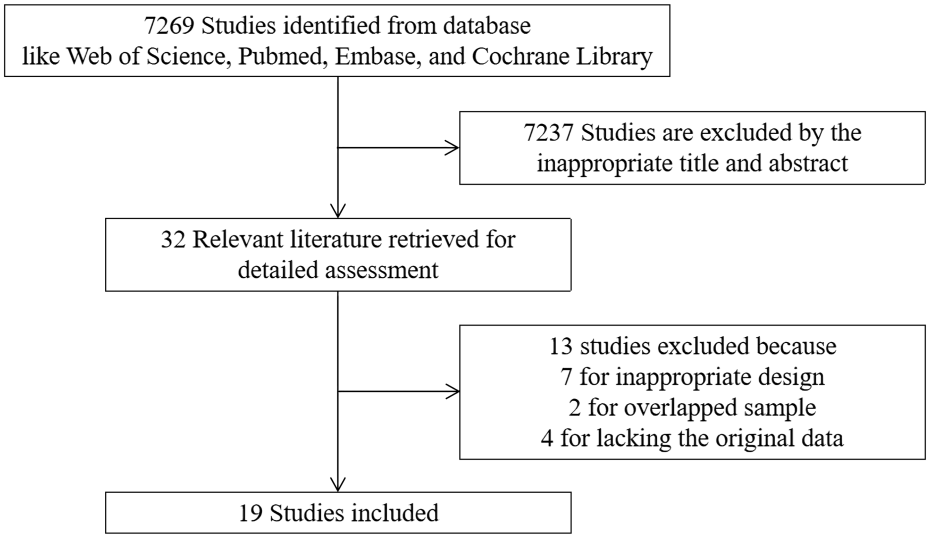

Figure 1. Screening process for published studies and reasons for exclusion.

(sample size n_1: 6762; mean follow-up M_1: 10.53 years) and 16 involved T2D (n_2: 38 733; M_2: 6.69 years).

The results of the quality assessment showed that 10 (52.63%) of the included studies were considered to be of high quality, 9 (47.37%) were considered to be of moderate quality, and there were no studies of low quality according to the results of the Newcastle-Ottawa Scale scores (Table 2). This means that all included studies were basically eligible for our study. As for publication bias (Fig. 2), the results of the funnel plot and Begg test showed that there was no significant publication bias or publication bias did not significantly affect the results in the studies of the association between DR and incident stroke in patients with diabetes.

Subgroup Analysis

A comprehensive analysis involving patients with T2D included 13 studies (Fig. 3). The presence of DR status was found to be significantly associated with stroke events (OR: 1.78; 95% CI, 1.53-2.08). Thirteen studies included 34 208 patients with a mean follow-up of 6.87 years, which represented 76.33% of all patients, and a fixed-effects model was used because of low heterogeneity (I^2: 21.9%; P = .228). Only 4 studies [15, 22, 26, 29] did not have such an association.

Similarly, the analysis involving patients with T1D included 4 studies (see Fig. 3). The presence of DR was found to be not significantly associated with stroke events (OR: 1.77; 95% CI, 0.48-6.61). A total of 6762 individuals were included in the 4 studies with a mean follow-up of 10.52 years, and a random-effects model was used because of the high heterogeneity (I^2: 96.9%; P = .000). No such association was found in any of 3 studies [17, 18, 28].

In addition, a comprehensive analysis involving the HR as an effect measure included 10 studies (Fig. 4A). The pooled HR for any DR was found to be significantly associated with HR for stroke events (HR: 1.62; 95% CI, 1.28-2.06). A total of 6762 patients were included in the 10 studies with a mean follow-up of 7.63 years, and a random-effects model was employed because of significant heterogeneity between studies (I^2: 76.2%; P = .000).

In a pooled analysis of DR severity as a subgroup, the results included 8 studies (Fig. 4B). HR for mild and moderate NPDR was found to be significantly associated with HR for stroke events (HR: 2.01; 95% CI, 1.45-2.78); DR for severe NPDR and worse states was also significantly associated with HR for stroke events (HR: 2.27; 95% CI, 1.52-3.39).

Sensitivity Analysis

After including high-quality studies only (NOS ≥ 7), the results showed some changes. On the one hand, the analysis involving patients with T2D included 8 studies (Fig. 5A) and found that the presence of DR status remained significantly associated with stroke events (OR: 1.79; 95% CI, 1.52-2.09). The analysis involving patients with T1D included 3 studies and showed that the presence of DR was found to be not significantly associated with stroke events (OR: 0.84; 95% CI, 0.64-1.08) and, moreover, its heterogeneity became insignificant as inappropriate articles were removed (I^2: 22.3%; P = .276). On the other hand, the pooled analysis involving HR as an effect measure included 4 studies (Fig. 5B) and the pooled HR for any DR was significantly associated with HR for stroke events (HR: 1.77; 95% CI, 1.49-2.11). The comprehensive analysis with DR severity as a subgroup also included 4 studies (see Fig. 5B) and HR for mild and moderate NPDR was significantly associated with HR for stroke events (HR: 1.96; 95% CI, 0.97-3.94); DR for severe NPDR and worse states was also significantly associated with HR for stroke events (HR: 2.39; 95% CI, 1.58-3.63).

Discussion

The meta-analysis performed, which included 45 495 patients in 19 studies, showed that the presence of DR was associated with an increased risk of stroke events in patients with diabetes—an association that was robust in patients with T2D but inconclusive in patients with T1D. When the severity of DR was considered, both mild and moderate NPDR and severe NPDR and worse were found to significantly increase the risk of stroke, and in addition, we found a trend toward increased stroke risk with increasing DR stage and DR lesion severity.

The results we have gained are interesting and worthy of further discussion. First, from the perspective of the literature

Table 1. Characteristics of inclusion study

First author	Publication y	Country and region	Findings type	Sample size	Type of diabetes	Mean follow-up y	End points	Diagnosis of DR
Cheung [19]	2006	Australia	OR and HR	1617	T2D	7.8	Ischemic stroke	Retinal photographs
Hitman [20]	2007	UK	OR and HR	2838	T2D	3.9	Stroke	Any retinopathy in DM
Bello [26]	2007	USA	OR	4038	T2D	2.4	Stroke	Medical records
Fuller [17]	2001	UK	OR	3742	T1D and T2D	12	Fatal or nonfatal stroke	Medical records
Hankey [24]	2012	Australia	OR and HR	9795	T2D	5	Ischemic and hemorrhagic stroke	ETDRS
Cohen [13]	2003	USA	OR	1689	T2D	5.3	Stroke	ETDRS
Hjelmgren [29]	2018	Sweden	OR and HR	445	T2D	3.1	Stroke/TIA	Fundus photography
Ono [18]	2002	Japan	OR	223	T1D	11.6	Stroke	Fundus photography
Drinkwater [15]	2020	Australia	OR and HR	1521	T2D	9.0	Stroke	ETDRS
Hägg [23]	2013	Finland	OR and HR	4083	T1D	9.0	Stroke	Laser treatment
Kawasaki [25]	2013	Japan	OR	1620	T2D	8	Stroke	ETDRS
Gerstein [22]	2012	Canada	OR and HR	3433	T2D	4.7	Fatal or nonfatal stroke	ETDRS
Barlovic [28]	2018	Slovenia	OR	1689	T1D	9.5	Ischemic and hemorrhagic stroke	Laser treatment
Wong [14]	2020	USA	OR	2828	DM (T2D)	5.4	Stroke	ETDRS
Lip [27]	2015	France	OR	1409	DM (T2D)	2.6	Stroke/TE	Medical records
Landers [30]	2018	Australia	HR	737	DM (T2D)	8.7	Stroke	Fundus photography
Chou [10]	2016	Taiwan	HR	1311	DM (T2D)	15	Stroke/TIA	Medical records
Protopsaltis [21]	2008	Greece	HR	599	DM (T2D)	10.1	Ischemic stroke	NA
Klein [16]	1999	USA	HR	1878	DM (T2D)	4	Stroke	Fundus photography

Abbreviations: DM, diabetes mellitus; DR, diabetic retinopathy; ETDRS, Early Treatment Diabetic Retinopathy Study; HR, hazard ratio; NA, not available; OR, odds ratio; T2D, type 2 diabetes mellitus; TE, thromboembolism; TIA, transient ischemic attack; UK, United Kingdom; USA, United States of America.

Table 2. The Newcastle-Ottawa Scale

Study	Selection[a]				Comparability[b]		Outcome[c]			Quality score
	Representative of treat group	Representative of refer group	Assignment for treatment	Outcome in baseline	For normal baseline	For special baseline	Assessment of outcome	Adequate follow-time	Adequate follow-up	
Cheung [19]	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	9
Hitman [20]	No	No	Yes	No	No	Yes	Yes	Yes	No	5
Bello [26]	Yes	Yes	Yes	No	No	No	Yes	Yes	No	6
Fuller [17]	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes	7
Hankey [24]	Yes	Yes	Yes	No	No	No	Yes	Yes	No	6
Cohen [13]	Yes	Yes	Yes	No	No	Yes	Yes	Yes	No	7
Hjelmgren [29]	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	7
Ono [18]	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	9
Drinkwater [15]	Yes	Yes	Yes	No	No	Yes	Yes	Yes	No	7
Hägg [23]	No	No	Yes	No	Yes	No	Yes	Yes	No	5
Kawasaki [25]	Yes	Yes	Yes	No	Yes	No	Yes	Yes	No	7
Gerstein [22]	Yes	Yes	Yes	No	No	No	Yes	Yes	No	6
Barlovic [28]	Yes	Yes	Yes	No	No	No	Yes	Yes	No	6
Wong [14]	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	9
Lip [27]	No	No	Yes	No	No	No	Yes	Yes	Yes	5
Landers [30]	Yes	Yes	Yes	No	NA	NA	Yes	Yes	Yes	7
Chou [10]	No	No	Yes	No	No	No	Yes	Yes	Yes	5
Protopsaltis [21]	Yes	Yes	Yes	No	No	No	No	Yes	Yes	6
Klein [16]	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes	7

[a]Representative if the study is countrywide, not if it is a province/city/continent.
[b]General baseline: sex/body mass index/vital signs, etc; special baseline: high-density lipoprotein/glycated hemoglobin A_{1c}, etc; comparable if 1 item or less is significant, not if 2 items or more are significant.
[c]Score if follow-up time has been 5 years or more, and score for missed follow-up rate is less than or equal to 5%.
[d]If the relevant scoring item is not mentioned, this item will be treated as 0.5 points; and all decimal places will be discarded when the score is counted.

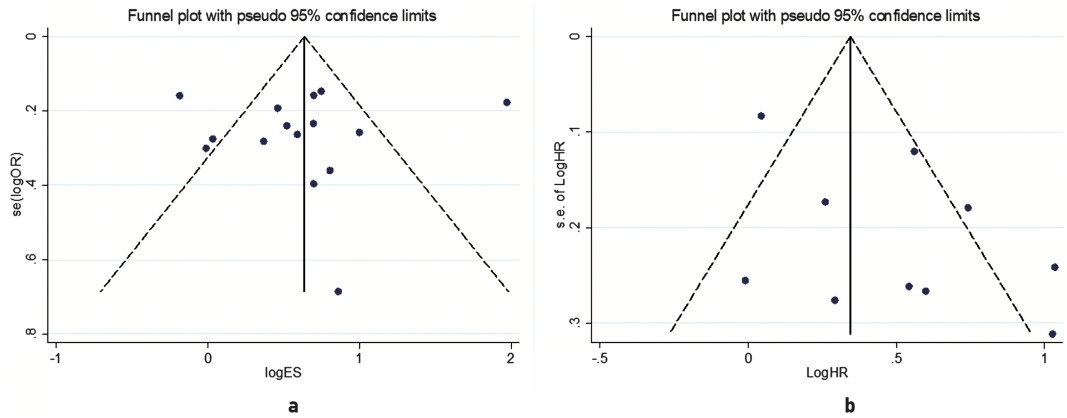

Figure 2. Funnel plot of included studies, which shows that there was no significant asymmetry in the 15 included studies in the A, odds ratio group, or the 10 studies in the B, hazard ratio group, suggesting no significant publication bias.

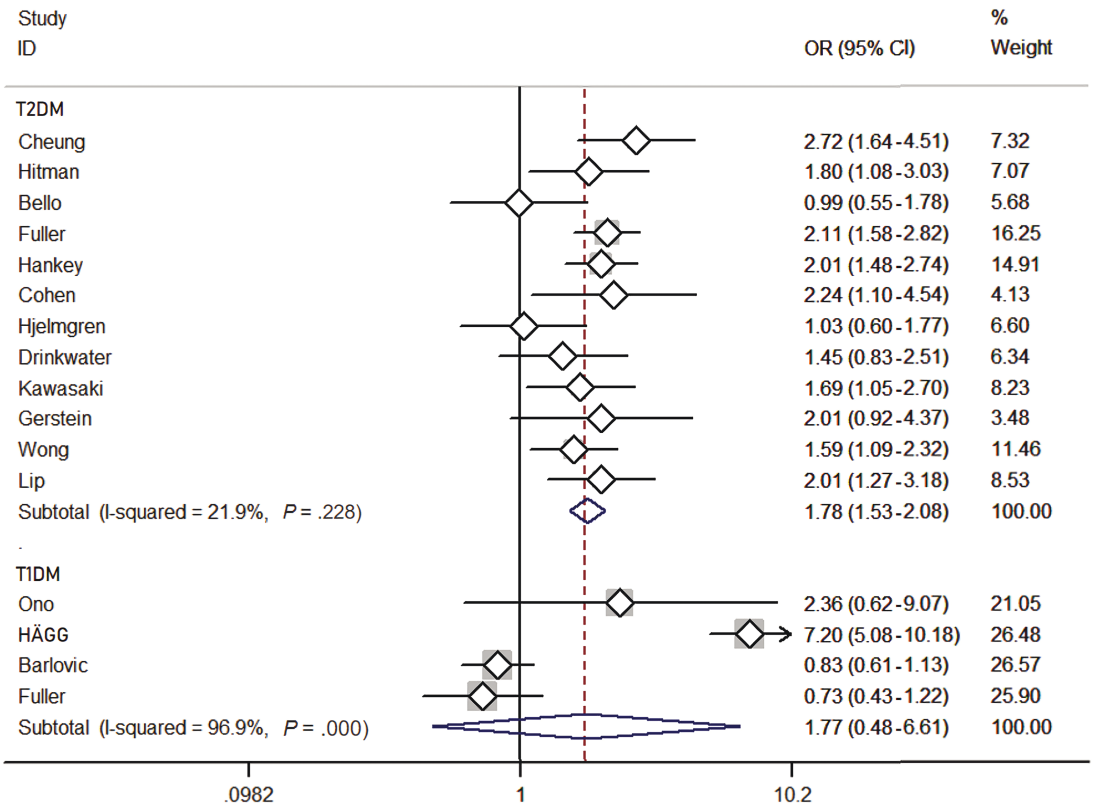

Figure 3. Forest plot of included studies, with 12 studies of type 2 diabetes and 4 studies of type 1 diabetes included, respectively. The *P* values represent the heterogeneity of the subgroups and the whole studies; and the diamonds in the figure represent the results of the meta-analysis of the different studies that accounted for different weights.

search, most articles were of high quality, not only with some new studies published in the last 5 to 3 years, but also with high representation, large sample size, and long follow-up periods. In addition, the funnel plot and Begg test showed no significantly publication bias, which proved that our analytical work is convincing in terms of data collection.

It has to be mentioned that the results of the subgroup analysis and sensitivity analysis in the T1D were inconsistent and significantly heterogeneous. Although the results still support a significant increase in stroke risk with DR after inclusion of T1D and T2D studies, we were still unsure whether DR is associated with stroke in T1D. Furthermore, this trend seemed to be detectable in the analysis of DR on stroke for different processes—as DR progresses, the risk of stroke also increases. However, this trend could not be supported by high-quality evidence, which may be caused by the different classification criteria for DR progression in different studies, resulting in only 3 studies that could be included.

Some limitations exist in our study, although the relevant analytical work has been refined as much as possible. (i) It is possible that the researchers of the original data used different diagnostic criteria, disease definitions, and statistical methods when conducting their respective clinical studies, leading to changes in the study results. (ii) The inconsistency

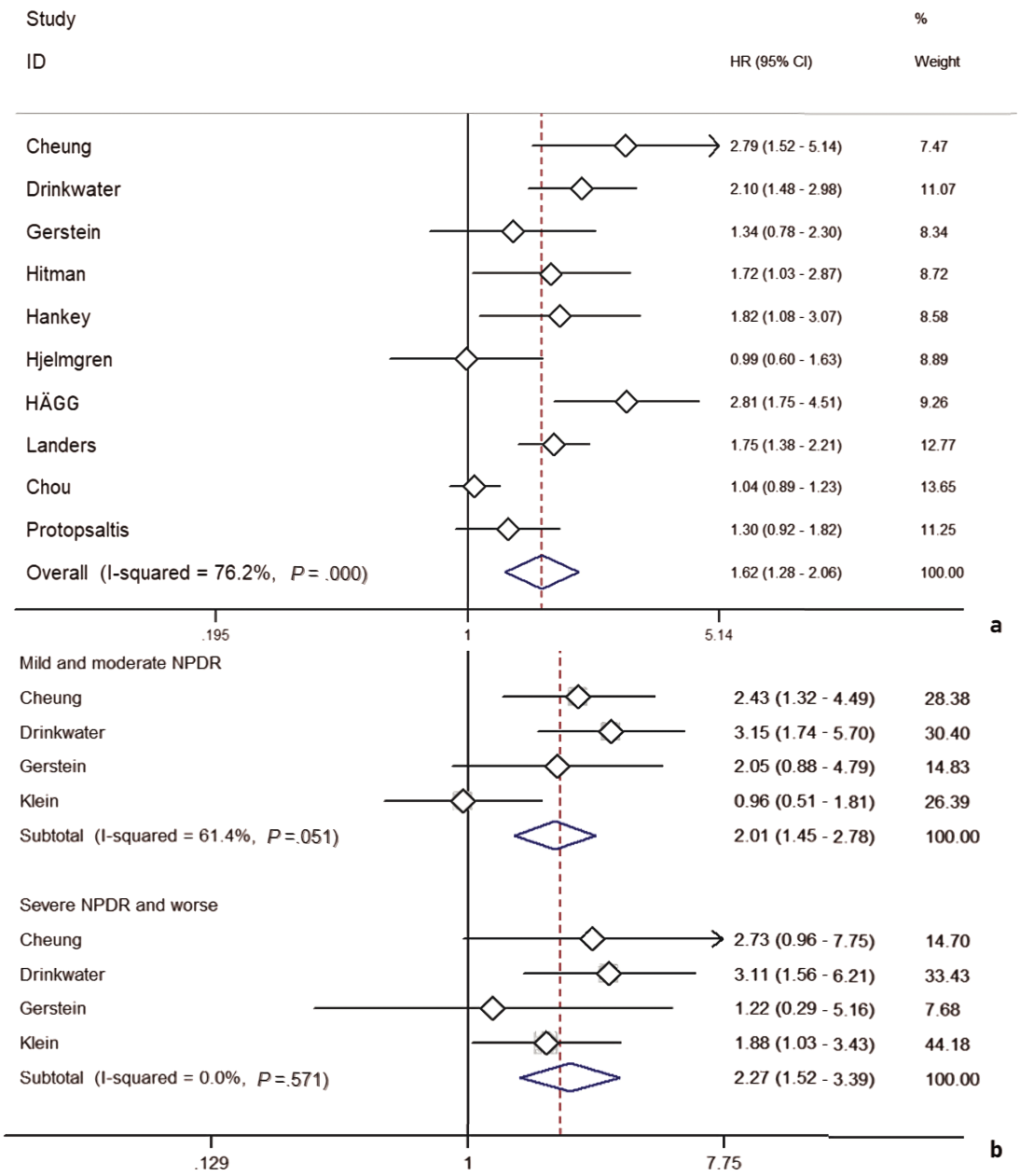

Figure 4. Ten studies with hazard ratio as a finding are shown in A, while subgroup analyses of 4 studies with "mild and moderate NPDR" and "severe NPDR and worse" as representative groups of diabetic retinopathy (DR) progression are shown in B.

of the results might be due to the different treatments for the disease. There were different diagnostic criteria and treatments in different regions or at different times in the same region for DR, and even for diabetes itself, and the choice or change of these methods might affect the statistics of clinical results. (iii) Stroke was mostly counted as an outcome of CVD in studies, which often resulted in less comprehensive final data for secondary use. (iv) Few studies included treatment of DR as a baseline variable (like antivascular endothelial growth factor therapy); however, there were many prior studies showing that local treatment of DR as a baseline variable has the potential to have a significant influence on stroke outcome.

Some researches [31] have included 5 studies on DR in stroke risk when exploring the potential relationship between DR and the risk of all-cause mortality, stroke and heart failure, which revealed that DR was significantly associated with an increased risk of stroke compared with patients without DR [RR (Risk Ratio): 1.74; 95% CI, 1.35-2.24]. In a meta-analysis of 18 cohort studies, researchers [32] also concluded that the presence of DR was associated with an increased risk of stroke in patients with diabetes, with an RR of 2.29 (95% CI, 1.77-2.96; $P < .0001$), while no definitive results were obtained in patients with T1D.

In summary, DR status in diabetic patients is associated with an increased risk of stroke. This correlation was robust in patients with T2D, but uncertain in T1D. Therefore, screening for DR should be considered as a routine procedure in the assessment and management of stroke risk, using

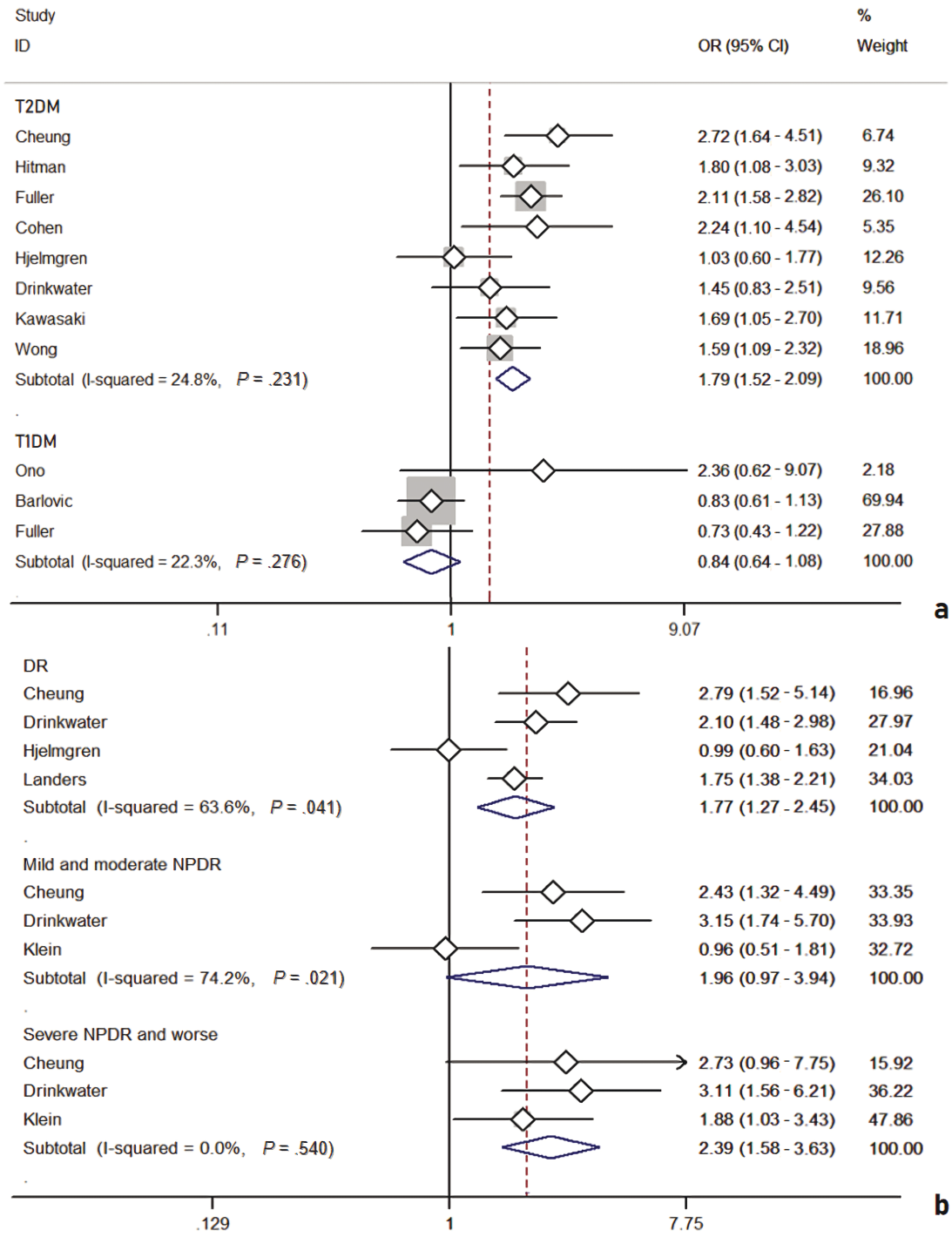

Figure 5. Eight studies with type 2 diabetes mellitus (T2D) and 3 studies with type 1 diabetes mellitus (T1D) in the odds ratio (OR) group after screening are shown in A, and 4 studies with diabetic retinopathy (DR) and 3 studies with different progression of DR in the hazard ratio group are shown in B.

optical coherence tomography, optical coherence tomography angiography, scanning laser ophthalmoscopy, and other ophthalmic examinations.

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Conflict of Interest

We declare that we do not have any commercial or associative interest that represents a conflict of interest in connection with the work submitted.

Data Availability

Some or all data generated or analyzed during this study are included in this published article or in the data repositories listed in "References."

Clinical Trial Information

PROSPERO registration No. CRD42021268540 (registered at 18/08/2021).

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