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REVIEW ARTICLE

Diabetic retinopathy and cognitive dysfunction: a systematic review and meta-analysis

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Abstract

Background This study aims to determine the relationship between diabetic retinopathy (DR) and cognitive dysfunction as well as explores the effects of DR on different cognitive domains.

Methods A systematic search of PubMed, Embase, Web of Science, Wanfang data, CBM, CNKI, and VIP databases from their inception to October 2021. The pooled odds ratio (ORs), hazard ratio (HRs), and 95% confidence interval (CIs) were calculated.

Results Twenty-two studies met the inclusion criteria and meta-analysis included 15 studies. The presence of DR reflects a higher risk of cognitive dysfunction (OR = 2.45; 95% CI: 1.76–3.41; HR = 1.34 95% CI: 1.10–1.62). Cohort study combined risk was 2.62 (95% CI: 1.93–3.56), in cross-sectional study was 2.07 (95% CI: 1.11–3.88). The pooled OR was 2.38 (95% CI: 1.83–3.10) and 3.11 (95% CI: 1.15–8.40) in Asia and Oceania. No such association was found in North America (OR = 2.22; 95% CI: 0.77–6.38). The pooled risk was 2.47 (95% CI: 1.76–3.48) in patients with T2DM, while did not identify an association between these two conditions in T1DM. The combined unadjusted and adjusted ORs were 2.72 (95% CI: 1.99–3.73) and 2.06 (95% CI: 1.49–2.85). DR severity and the risk of cognitive impairment showed a positive correlation and mainly impaired the speeds of psychomotor and information processing.

Conclusions DR can help to identify people at high risk of cognitive dysfunction. Further studies are indispensable for exploring the relationship between DR and cognitive impairment in the patients for different age, gender and race, as well as to assess the risk of cognitive impairment in different populations.

Keywords Diabetic retinopathy · Cognitive dysfunction · Mild cognitive impairment · Cognitive domain · Systematic review

Introduction

The cognitive functions include memory, attention, language fluency, visual space construction, reasoning and judgment, executive function, and other domains [1]. Cognitive dysfunction refers to the degree of cognitive impairment between normal aging and dementia [2]. According to the Alzheimer's disease International (ADI), dementia is predicted to affect about 75.6 million people by 2030 and about 115 million by 2050 worldwide [3], incurring a total expenditure of about $2.54 trillion to $9.12 trillion in disease management [4]. To date, there is no effective treatment for dementia, and the cost of long-term treatment and care imposes a heavy economic burden not only on the affected individuals and their families but also on society.

Mei Wu and Fan Mei have contributed equally to this work and share first authorship.

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Diabetic retinopathy (DR), a typical specific microvascular complication of diabetes, is the major cause of preventable blindness in working-age people [5]. DR has a current global average prevalence of 34.6%, compared to nearly 40.3% in the developed countries [6]. According to a study by the World Trade Organization (WHO) [7], globally there will be more than 500 million diabetics by 2025 and DR will occur in about one-third of these patients.

An increasing number of studies have associated DR with cognitive decline [8–10]. A study [11] has reported microvascular dysfunction as one of the key potential mechanisms leading to cognitive decline in diabetes patients. The microvasculature is involved in regulating many cerebral processes that when damaged, predispose to stroke, depression, and cognitive impairment. Studies suggested that there is a strong relationship between retinopathy and cerebral microvascular injury owing to significant similarities between the retina and cerebral microvasculature in terms of embryological origin, structures, and common physiological characteristics [12]. Since it is difficult to clinically evaluate cerebral microvessels directly, the retinal blood vessels are directly visualized by non-invasive means such as retinography. Therefore, retinography provides a window for observing cerebral microvascular lesions, serving as a possible predictor of cognitive decline [13]. However, due to the differences in the age of the patients, severe microvascular complications, and the prevalence of cardiovascular disease in different countries and regions, the correlation between DR and cognitive decline remains elusive [14–16]. Although Crosby-Nwaobi R et al. [1] systematically evaluated the relationship between DR and cognitive impairment based on type 2 diabetes mellitus (T2DM), only three original studies (two cross-sectional studies and one cohort study) were included in the evaluation. Among them, the cohort study [17] involved diabetic patients undergoing coronary artery bypass surgery limiting the applicability of the outcome, and the data were updated only till 2011. Hence, the more precise relationship between DR and cognitive impairment remains yet to be explored.

Therefore, a systematic review and meta-analysis were performed to ascertain the association of DR and cognitive dysfunction as well as to explore the effects of DR on the cognitive domains.

Methods

This review was performed according to the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guideline [18].

Data sources and searches

Two researchers (MW and FM) conducted supplementary searching of the Pubmed, Embase, Web of Science, Wanfang data, CBM, CNKI, and VIP databases from the inception to October 2021, independently using the terms "Diabetic Retinopathy," "Diabetic Retinopathies," "DR," "PDR," "NPDR," "Cognitive Dysfunction," "Cognitive Dysfunctions," "cognitive Impairment," "cognitive decline," "cognitive defect," "dementia," "Alzheimer's disease." The search strategy is enlisted in detail in Supplementary Table 1. The references and previously published systematic reviews were searched manually for a supplement.

Eligibility criteria

The inclusion criteria were as follows: (a) Observational studies or longitudinal studies based on randomized controlled trials (RCTs); (b) T1DM and T2DM regardless of age, region, and race; (c) DR has a definite and reliable diagnostic method (e.g., retinal photography) and the severity of DR was defined based on a fully validated scale or system [e.g., the modified Airlie House Classification of DR [19] or a system for the DR assessment [20]]; and (d) Primary outcome: cognitive dysfunction events including mild cognitive impairment (MCI), dementia, Alzheimer's disease (AD) and cognitive decline. The changes in the cognitive domains were represented as the secondary outcome.

Exclusion criteria: (a) participants with known dementia or cognitive impairment at the inception of the study; (b) studies published in non-Chinese and non-English; c. Republished literature.

Study selection

All search results were imported to the EndNote X9 software. Two investigators (MW and ZW) evaluated titles and abstracts independently to confirm the inclusion. Before the formal screening, 15% of the samples were randomly selected to evaluate the consistency of the two researchers and the Kappa was calculated, such that if the Kappa $\geq$ 0.75, the consistency was satisfied [21]. Two investigators (MW and ZW) reviewed the full text of potentially qualified and uncertain studies independently to reach a final decision on inclusion and exclusion. Any disagreements in the screening process were resolved through discussion and consultation with a third researcher (BM).

Data extraction

The data were systematically extracted by two researchers (MW and LF) using Microsoft Excel 2010 according to a preset data collection table. Data extraction mainly included the following contents: (a) basic characteristics of the study: name and country of the first author, published year, region of the institute, type of research design, sample capacity, and follow-up period; (b) sample characteristics at baseline: age, sex, type of diabetes; (c) measurement of exposure; (d) measurement of cognitive dysfunction; (e) adjusted factors.

Assessment of the risk of bias

Two researchers (MW and FM) using the Newcastle–Ottawa Scale (NOS) [22] evaluated the risk of bias independently. The full mark was 9. Studies with a score of more than 7 indicated a lower risk of bias, scores of 5–7 indicated a moderate risk of bias, while scores less than 5 indicated a high risk of bias.

Statistical analysis

The summary ORs, HRs, and 95% CIs of DR and cognitive dysfunction were calculated using STATA15.0 software for meta-analysis. The statistical heterogeneity was analyzed by the χ^2 test and I^2 method. If $P > 0.10$ and $I^2 \leq 50\%$, the fixed-effect model was used for the combined analysis. If $P \leq 0.10$ and $I^2 > 50\%$, the random-effect model was adopted. The studies that did not report effects size (OR/HR) were explained by descriptive analysis.

To explore the potential sources of heterogeneity and obtain further information, the subgroup analyses were planned using the following factors: type of studies [Cross-sectional study vs. cohort study vs. case–control study], type of diabetes [T1DM vs. T2DM)], region [Asia vs. North America vs. Oceania], age [0–17 years old vs. 18–65 years old vs. ≥ 66 years old], gender [male vs. female], race [White vs. Black], DR severity [mild vs. moderate or severe vs. proliferative]. The publication bias was evaluated by making funnel plots and Egger's tests. If necessary, the sensitivity analysis was conducted by excluding the studies with a high risk of bias and studies with small sample size.

Results

After supplementary searching the articles published before October, 2021, 5340 results were identified. A supplementary search conducted led to the identification of nine additional potentially relevant studies. After screening the titles and abstracts, 54 articles were considered potentially relevant. Finally, 22 studies [9, 10, 13–17, 23–37] were included in our systematic review by reading through the full text based on the eligibility criteria, and 15 studies [9, 13, 14, 16, 17, 26, 28–31, 33–37] were included in the primary meta-analysis (Fig. 1).

Study characteristics

The basic characteristics of the 22 studies are shown in Table 1, including eight cross-sectional studies [14, 16, 23, 24, 26, 27, 34, 37], eleven cohort studies [9, 13, 15, 17, 28–31, 33, 35, 36], and one case–control study [25]. Also, there were two longitudinal studies [10, 32] based on RCTs. These studies were performed in Asia [14, 17, 25, 26, 31, 35, 37], North America [9, 10, 13, 16, 28, 29, 32–34, 36], Europe [15, 23, 24, 27] and Oceania [30].

In total, 1,962,068 patients with diabetes were enrolled comprising eight studies [9, 10, 15, 17, 23, 25, 30, 35] including only T2DM patients, six studies [24, 27, 29, 32, 33, 36] comprised only T1DM, and the remaining eight studies [13, 14, 16, 26, 28, 31, 34, 37] included patients with both types of diabetes. The average age of the participants considered in this study was 26.4–70.6 yrs old, the proportion of males ranged from 41.7–77.8% and the average follow-up duration was between 0.5 and 27 yrs.

All the included studies used four different DR diagnostic methods. Thirteen studies [13, 15–17, 23, 26, 27, 31–34, 36, 37] performed retinal photography, two studies were [14, 25] assessed by ophthalmologic examination (fundoscopic examination), three were [10, 24, 30] identified by retinal imaging and eye examinations and four studies were diagnosed [9, 28, 29, 35] based on the medical records.

Risk of bias

The risk of bias was assessed in all the 22 trials (Fig. 2) and the scores ranged between 5 and 9. The overall risk of bias was found to be low in thirteen studies [9, 10, 13, 16, 23, 26, 28, 29, 31, 32, 34–36], moderate in 9 [14, 15, 17, 24, 25, 27, 30, 33, 37] studies. Five studies [15, 17, 24, 25, 27] were considered controversial in terms of sample representation. Four studies [15, 24, 25, 27] had relatively small ($n < 100$) sample size and one study [17] was not population-based. Comparing the groups, most of the studies were based on age, gender, education level, etc., while four studies [17, 30, 33, 37] did not report the adjustment factors. In terms of outcomes, eight studies [9, 10, 15, 17, 29, 31, 33, 35] had a relatively short follow-up time (< 8 yr).

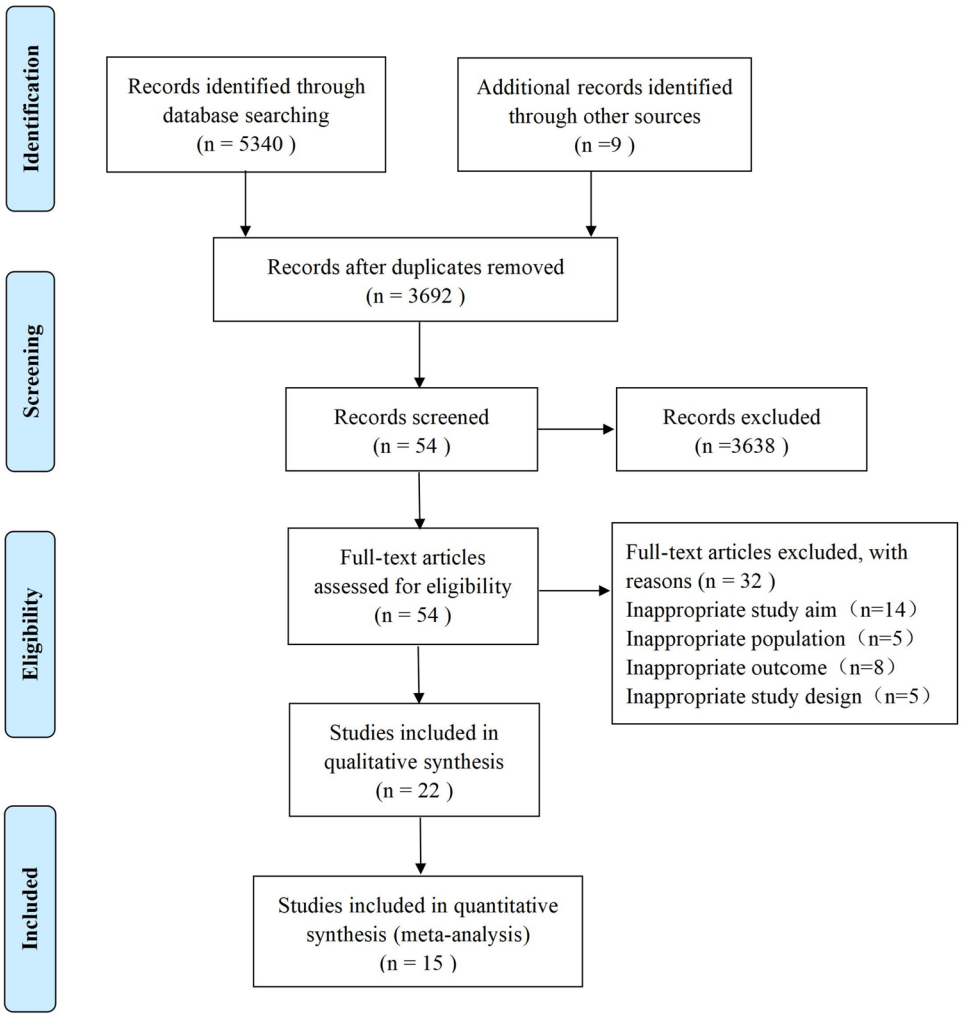

Fig. 1 Flowchart of literature selection

Primary outcomes

DR and risk of cognitive dysfunction

A total of 15 studies [9, 13, 14, 16, 17, 26, 28–31, 33–37] reported the effect size of the association between DR and cognitive dysfunction and were included in the meta-analysis. Ten studies included comprehensive analyses involving OR as an effect measure [14, 16, 17, 26, 30, 31, 33, 34, 36, 37], The median follow-up duration for 4803 patients among the ten studies was 6.5 years, and the data were appropriately adjusted for six of these studies. Since heterogeneity was low ($I^2 = 40.3\%$), the fixed-effects model was employed. The pooled OR found DR to be significantly associated with the cognitive dysfunction event (OR: 2.45; 95% CI: 1.76–3.41; Fig. 3). The comprehensive analysis with HRs and 95% CIs as the effect size included five studies [9, 13, 28, 29, 35] where all the data were appropriately adjusted. The median follow-up duration of 1,953,931 patients in the five studies was 6.6 yrs. Since the heterogeneity ($I^2 = 86.6\%$) was significant, the random effect model was used for analysis. The meta-analysis showed that DR was associated with cognitive impairment in patients with diabetes (HR: 1.34; 95% CI: 1.10–1.62; Fig. 3).

ORs and 95% CIs were reported in five cross-sectional studies [14, 16, 26, 34, 37] and cohort studies [17, 30, 31, 33, 36]. The heterogeneity among these studies was high ($I^2 = 60.1\%$); the random effect model was adopted for analysis. The subgroup analysis for the type of research pooled OR of 2.62 (95% CI: 1.93–3.56; Fig. 4) among the cohort studies and in cross-sectional studies was 2.07 (95% CI: 1.11–3.88; Fig. 4).

The subgroup analysis was performed based on different regions (Asia, North America, and Oceania). Of the ten studies that reported ORs and 95% CI [14, 16, 17, 26, 30, 31, 33, 34, 36, 37], five studies [14, 17, 26, 31, 37] were from Asia, four [16, 33, 34, 36] were from North America and the last one [30] was from Oceania. Since the high heterogeneity among the included studies ($I^2 = 72.7\%$) was high, the random effect model was used for analysis. DR was found

Table 1 Characteristics of the studies included in the review

Study	Year	Country	Study design	Diabetes type	Sample size (% males)	Follow-up period, years	Age, years	DR identification	Cognitive measurements	Adjustment factors
Umegaki [14]	2008	Japan	①	Both	907	NR	≥65	Fundoscopic examination	MMSE	Age
Ong [26]	2012	Singapore	①	Both	365	NR	≥60	Retinal photographs	AMT	Age, gender, education level, income category, type of housing, cataract, AMD, DR, glaucoma
Baker [16]	2007	US	①	Both	289	NR	≥65	Retinal photographs	MMSE 3MSE, DSST	Age, gender, race, field center, education level, internal carotid intima-media thickness, weight, hypertension, diabetes status, cigarette smoking status
Gupta [31]	2019	Singapore	②	Both	682 (55.6)	6	67.3±5.2	Retinal photographs	AMT	Age, gender, race, education, income, spherical equivalent, HbA1c, diabetes duration, hypertension, CVD and presence of eye conditions, better eye presenting visual acuity
Wong [34]	2002	US	①	Both	770 (48.1)	NR	NR	Retinal photographs	DWR, DSST, WFT	Age, gender, race, field center, education, occupation, diabetes, fasting glucose, hypertension, mean arterial blood pressure averaged over visits 1 through 3, carotid IMT, cigarette smoking, alcohol consumption, fasting total and HDL cholesterol levels, triglyceride levels
Bruce [30]	2014	Australia	②	T2DM	335 (50.7)	14.7±1.1	57.5±9.2	Ophthalmoscopy, Retinal photographs	MMSE, CDR	Unadjusted
Kadoi [17]	2005	Japan	②	T2DM	180 (77.8)	0.5	64.0±11	Retinal photographs	MMSE, RAVLT, TMT, DSF, GPT	Unadjusted
Exalto [9]	2014	US	②	T2DM	29,961 (54)	6.6	70.6±6.8	Medical record	Medical record	Age, gender, race, education, vascular factors
Lee [28]	2019	US	②	Both	621	>8	≥65	Medical record	CASI	Age, gender, race, education, APOEε4 alleles, smoking status

Table 1 (continued)

Study	Year	Country	Study design	Diabetes type	Sample size (% males)	Follow-up period, years	Age, years	DR identification	Cognitive measurements	Adjustment factors
Rodill [29]	2018	US	②	T1DM	3742 (52.6)	6.2 ± 5.3	56.1 ± 8.5	Medical record	Medical record	Age, gender, race, severe glycemic events, glycosylated hemoglobin, vascular comorbidities
Ryan [33]	2003	US	②	T1DM	103 (41.7)	7	40.4 ± 6.2	Retinal photographs	VPALT, SDLT, 4WSTM, RCFMT, TPT, WAIS-R, WCST, DVT, DSST, GPT, TMT	Unadjusted
Oğuz TEKİN [25]	2009	Turkey	③	T2DM	75 (46.7)	NR	57 ± 8.1	Ophthalmologic examination	MMSE	Age, education level, length of disease
Ding [23]	2010	UK	①	T2DM	NO DR: 705 (49.2) Mild DR: 292 (55.1) Moderate-to-severe DR: 47 (57.4)	NR	NO DR: 67.3 ± 4.2 Mild DR: 67.4 ± 4.2 Moderate-to-severe DR: 67.1 ± 4.2	Retinal photographs	FACES, LM, MR, LNS, DST, VFT, TMTB, MHVS, MMSE	Age, gender, education level, vascular risk factors, macrovascular disease, depression
Jacobson [32]	2011	US	④	T1DM	1144 (53)	18.5	27.0 ± 6.9	Retinal photographs	WAIS-R, HRB, WMS, DVT, GPT, VFT, 4WSTM, SDLT, EFT	Gender, baseline age, duration of follow-up, education level, the number of interval cognitive tests taken, presence of painful neuropathy, and visual acuity at EDIC year 12
Hugenschmidt [10]	2014	US	④	T2DM	1862 (56.1)	3	62.3 ± 5.7	Standardized eye examination, Retinal photographs	MMSE, DSST, RAVLT, Stroop test	Age, gender, ethnicity, education, smoking, and geographic region, duration of diabetes, HbA1c, HDL, triglycerides, systolic blood pressure, use of antihypertensive medication, depression, alcohol use, presence of neuropathy, and visual acuity

Table 1 (continued)

Study	Year	Country	Study design	Diabetes type	Sample size (% males)	Follow-up period, years	Age, years	DR identification	Cognitive measurements	Adjustment factors
Wessels [27]	2007	Netherlands	①	T1DM	25 (30)	NR	NO DR: 42.1 ± 4.5 DR: 42.3 ± 5.3	Retinal photographs	WAIS-R, RCFMT, RCFMT, 15WT, TMT, SCWT, D2 Test, GIT sorting, WCST, CWF	Age, education level, depression
de Bresser [15]	2010	Netherlands	②	T2DM	68 (47)	4	65 ± 5.6	Retinal photographs	TMT, SCWT, BSAT, Animal naming, WAIS-3, CBT, RAVLT, LLT, TCF, RAPM	Age, gender, IQ
Ferguson [24]	2003	UK	①	T1DM	71 (56)	NR	NO DR: 26.4 ± 4.6 DR: 31.5 ± 6	Retinal photographs, ophthalmoscopy	WAIS-R, NART, IT, CRT, VFT, PASAT	Gender, retinopathy status, Severe hypoglycemia, premorbid cognitive ability, Duration of diabetes
Nunley [36]	2015	US	②	T1DM	97 (49)	27	49.1 ± 6.6	Retinal photographs	NAART, DSST, GPT, TMT, VFT, animal naming, FACES, SCWT, LNS, RAVLT, 4WSTM, ROCF	Education
Oğure [37]	2015	Turkey	①	Both	120 (53)	NR	NO DR: 62.83 ± 7.81 Mild DR: 60.83 ± 5.23 Moderate DR: 65.00 ± 8.00 PDR: 66.63 ± 7.65	Retinal photographs	MoCA	Unadjusted
Yu [35]	2020	Korea	②	T2DM	1,917,702 (58)	5.1	≥ 40	Medical record	Medical record	Age, gender, smoking, alcohol intake, exercise, income, plasma glucose concentration, duration of diabetes, BMI, dyslipidemia, hypertension, diabetic retinopathy, CKD, stroke, IHD, depression, number of OHAs, and treatment with insulin

Table 1 (continued)

Study	Year	Country	Study design	Diabetes type	Sample size (% males)	Follow-up period, years	Age, years	DR identification	Cognitive measurements	Adjustment factors
Deal [13]	2019	US	②	Both	1905	16	50–73	Retinal photographs	CDR medical record	Age, education, gender, race center interaction, BMI, drinking status, smoking status, diabetes, hypertensive status, CHD, and history of stroke

(1) Country: the USA, the United States of America; the UK, the United Kingdom; (2) Study design: ① Cross-sectional study; ② Cohort study ③ Case–control study; ④ longitudinal studies based on randomized controlled trial;

(3) Diabetes type: T2DM, type 2 diabetes mellitus; T1DM, type 1 diabetes mellitus; (4) DR, diabetic retinopathy;

(5) Cognitive measurements: 1. MMSE: Mini-mental state examination 2. AMT: The abbreviated mental test 3. 3MSE: Modified mini-mental state examination 4. DSST: Digit-symbol substitution test 5. DWR: The delayed word recall test

6. WFT: The word fluency test 7. CDR: the clinical dementia rating 8. DSF: Digit span forward 9. GPT: Grooved pegboard test 10. CASI: The cognitive abilities screening instrument

11. WAIS-R: The Wechsler adult intelligence Scale-revised 12. NART: The national adult reading test 13. IT: Inspection time 14. CRT: Choice reaction time 15. VFT: Borkowski verbal fluency test

16. PASAT: Paced auditory serial addition task 17. FACES: Faces and family pictures subtest 18. LM: Logical memory I 19. MR: Matrix reasoning 20. LNS: Letter-number sequencing 21. DST: Digit symbol test

22. TMT: Trail making test 23. MHVS: A synonyms of the mill hill vocabulary scale 24. HRB: the Halstead–Reitan neuropsychological battery 25. WMS: the Wechsler memory scale 26. DVT: the digit vigilance test

27. GPT: the grooved pegboard test 28. 4WSTM: The four-word short term memory test 29. SDLT: The symbol-digit learning test 30. EFT: The embedded figures test 31. VPALT: the verbal paired-associate learning test 32. RCFMT: the Rey complex figure memory test 33. TPT: the tactual performance test 34. WCST: The Wisconsin card sorting test 35. 15WT: The 15 words text

36. SCWT: The Stroop color word test 37. CWF: The category word fluency task 38. BSAT: Brixton spatial anticipation test 39. CBT: Corsi block-tapping task 40. LLT: Location learning test 41. TCF: Taylor complex figure 42. RAPM: Raven advanced progressive matrices 43. NAART: North American adult reading test; 44. RAVLT: Rey auditory verbal learning tests; 45. ROCF: Rey–Osterrieth complex figure; 46. MocA: Montreal cognitive assessment (5) Adjustment factors: 1. AMD: Age-related macular degeneration 2. CVD: Cardiovascular disease 3. OHAs: Oral hypoglycemic agents 4. IMT: Intima-media wall thickness 5. HDL: High-density lipoprotein 6. EDIC: Epidemiology of diabetes interventions and complications 7. CKD: Chronic kidney disease 8. BMI: Body mass index 9. IHD: Ischemic heart diseases 10. CHD: Coronary heart disease

(6) NR: No report

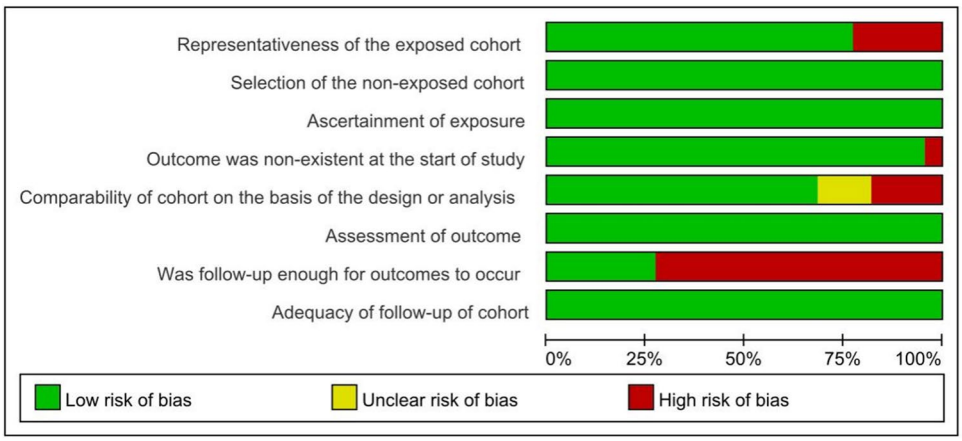

Fig. 2 Quality assessment and risk of bias assessment

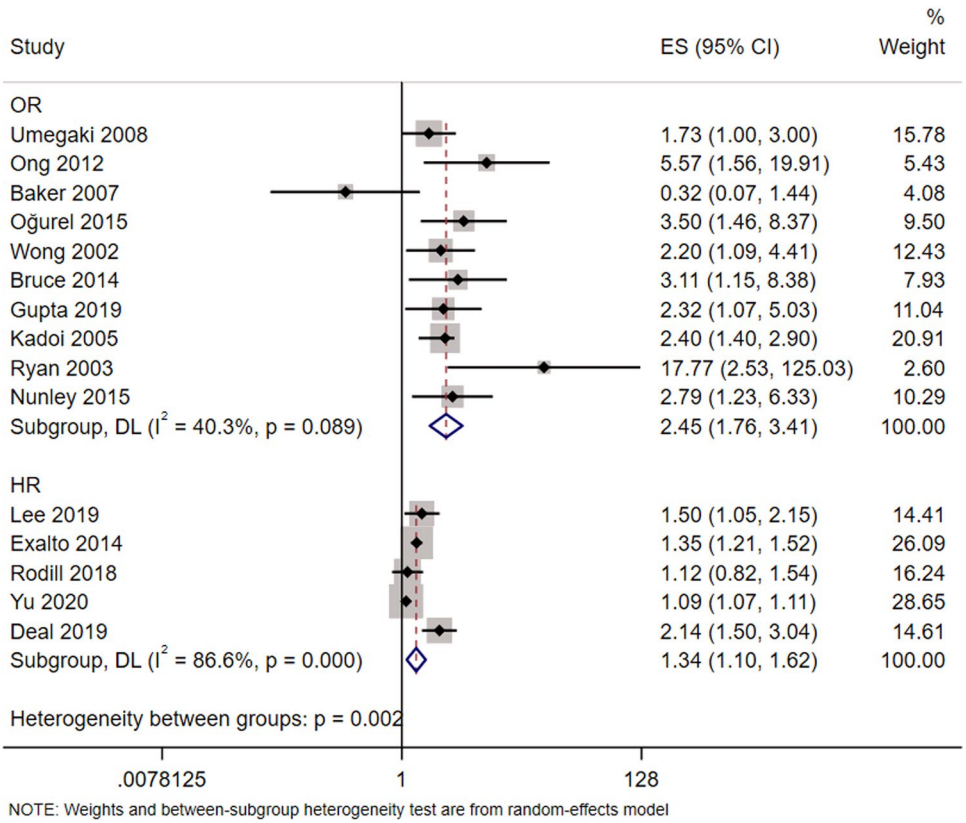

Fig. 3 Pooled odds ratio/hazard ratio (OR/HR) associating DR with cognitive impairment

to be significantly associated with cognitive impairment in Asia (OR: 2.38; 95% CI: 1.83–3.10; Fig. 5) and Oceania (OR: 3.11; 95% CI: 1.15–8.40; Fig. 5), but there was no statistically significant association in North America (OR: 2.22; 95% CI: 0.77–6.38; Fig. 5).

Five studies [26, 31, 33, 36, 37] reported the effects of different severities of DR on cognitive impairment events. The assessments were made based on the severity of DR using the modified Airlie House Classification system and Wisconsin Epidemiologic Study of DR Classification and Grading System. Subgroup analysis showed that the higher the severity of DR, the higher would be the risk of cognitive impairment. Combined risk was 2.02 (95%CI: 1.05–3.91; Fig. 6) in Minimal or mild DR patients, the pooled OR was 4.17 (95% CI: 2.09–8.30; Fig. 6) and 4.27 (95% CI: 2.23–8.18; Fig. 6) in people with moderate or severe and proliferative DR.

Subgroup analysis for the diabetes subtypes yielded pooled OR of 2.47 (95% CI: 1.76–3.48; Fig. 7) among T2DM patients, while no significant association was found in the patients with T1DM (OR: 5.65; 95% CI: 0.97–32.91; Fig. 7). In addition, we also performed subgroup analysis

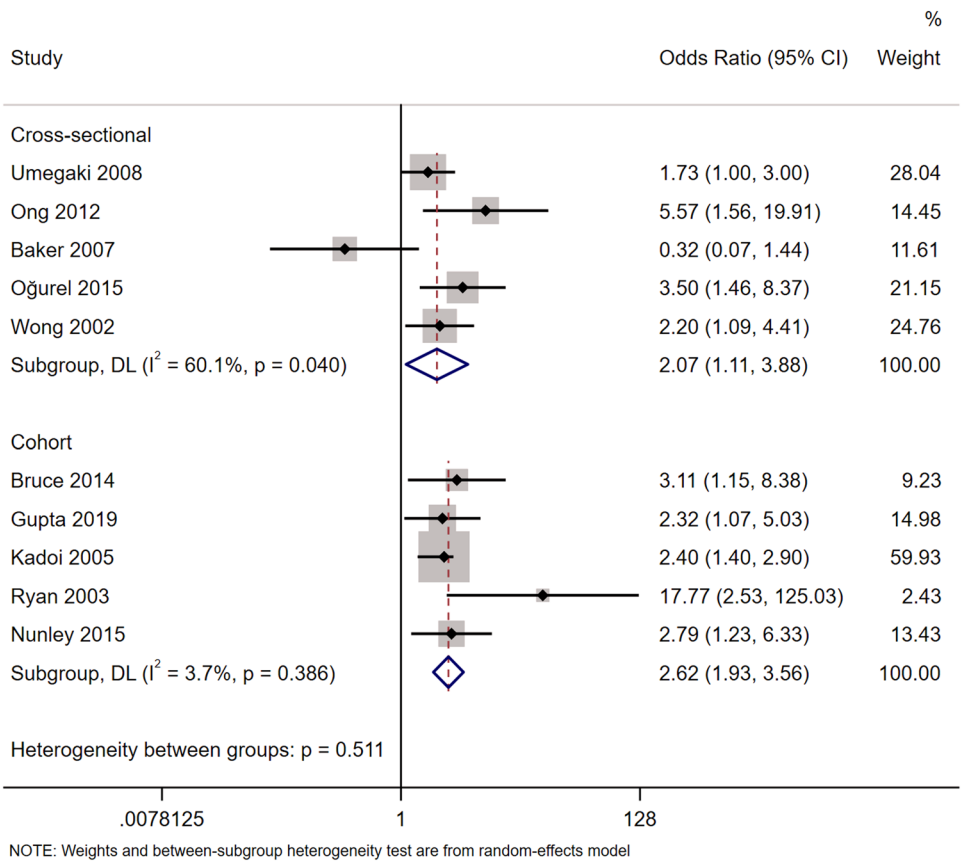

Fig. 4 Pooled OR for associating DR with cognitive impairment in different types of studies

based on unadjusted and adjusted ORs. Because of the low heterogeneity among these studies ($I^2 = 45.7\%$), the fixed model was adopted and the combined ORs were 2.72 (95% CI: 1.99–3.73; Fig. 8) and 2.06 (95% CI: 1.49–2.85; Fig. 8).

Secondary outcome

We examined six cognitive domains: memory, psychomotor speed, executive functioning, attention, information processing speed, and spatial ability. The included studies showed great heterogeneity in the methods of measurement for cognitive function, even with multiple assessment tools within the same cognitive domain (Supplementary Table 2). Accordingly, the descriptive analysis was performed for the secondary outcome.

DR and memory

Memory was the most frequently tested parameter for all the included studies. There were seven studies [10, 15, 23, 27, 32–34] using a total of 16 cognitive evaluation methods for measuring the memory function in patients with DR, among which only Wong et al. [34] found DR to be associated with lower memory performance.

DR and psychomotor speed

The effect of DR on psychomotor speed was measured in six studies [10, 23, 24, 32–34], using five different cognitive assessment tools. Five studies [10, 23, 24, 32, 33] showed that there was a significant deterioration in the domain of psychomotor speed in the patients with DR.

DR and executive functioning

The executive function was examined through six studies [10, 15, 23, 24, 27, 32] in patients with DR. According to Ding et al. [23], out of the seven different cognitive measurements used, the executive function scores decreased in the male DR patients.

DR and attention

The relationship between DR and the field of attention was reported in three studies [15, 24, 27], using four methods for assessing cognitive function. Ferguson et al. [24] found that the DR patients demonstrate a poor ability to maintain concentration.

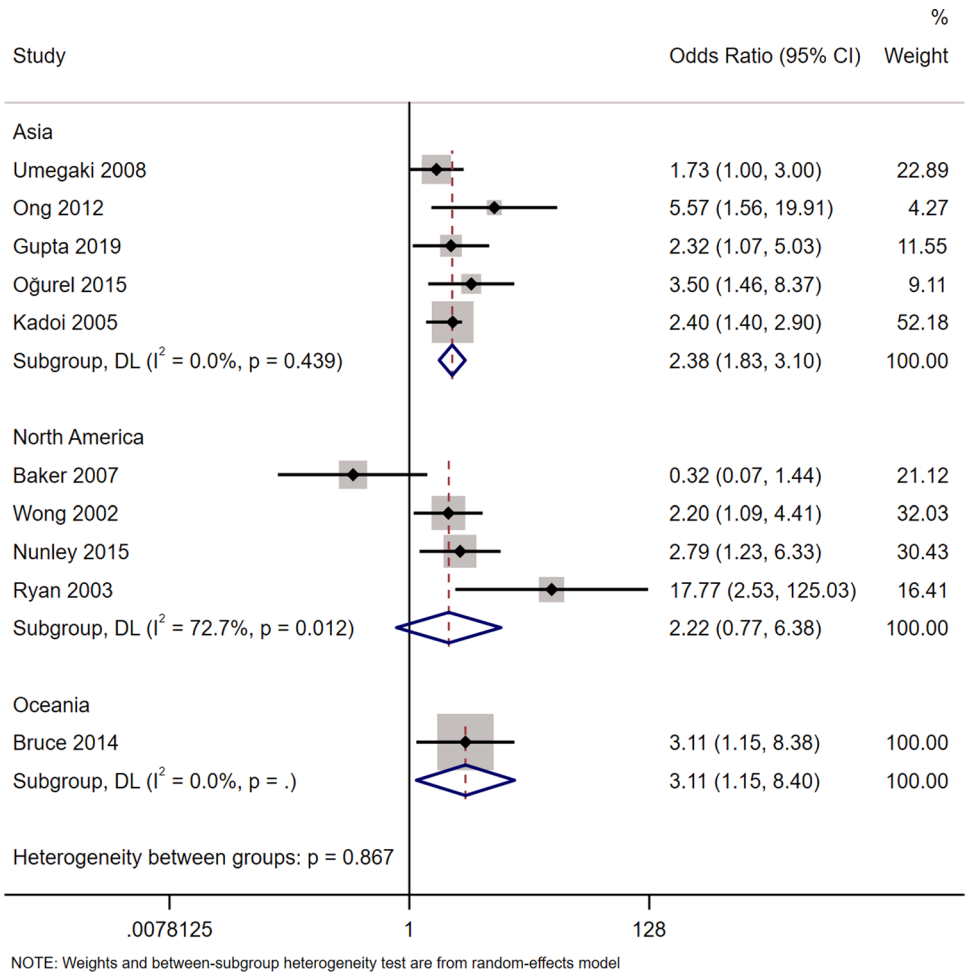

Fig. 5 Pooled OR for associating DR with cognitive impairment in different regions

DR and information processing speed

The information processing speed of patients with DR was assessed in four studies [15, 23, 24, 27] using five cognitive assessment tools, out of which three studies showed that the processing speed was worsened in the DR patients.

DR and spatial ability

The spatial ability of DR patients was measured through three studies [24, 32, 33] using four different cognitive measurements. Ferguson et al. [24] reported that DR was associated with poor spatial ability.

Publication bias

The publication bias for the studies was assessed using funnel plots and Egger's regression tests (Supplementary Fig. 1). The funnel plots demonstrated the distribution on both sides to be asymmetrical. Further evaluation by Egger's test with relatively high sensitivity and accuracy showed that there was a significant publication bias was present in the included studies ($P = 0.01$). We proved the stability of our results using the trim-and-fill method and the results showed that four studies were missing, since there was no significant difference with or without adjustment (1.575 [95% CI, 1.290–1.923] [$P < 0.001$] vs. 1.75 [95% CI, 1.428–2.165] [$P < 0.001$]), thereby ruling out large publication bias effects (Supplementary Fig. 2).

Discussion

This study comprehensively investigated the association between DR and cognitive dysfunction through a detailed evaluation of the included studies to determine the credibility of the evidence. The meta-analysis included 1,962,068 participants across 15 studies, providing medium to high-quality evidence substantiating significant association between DR and an increased risk of cognitive dysfunction in diabetes patients. The existence of DR was mostly related to the decrease in the psychomotor and information processing speeds.

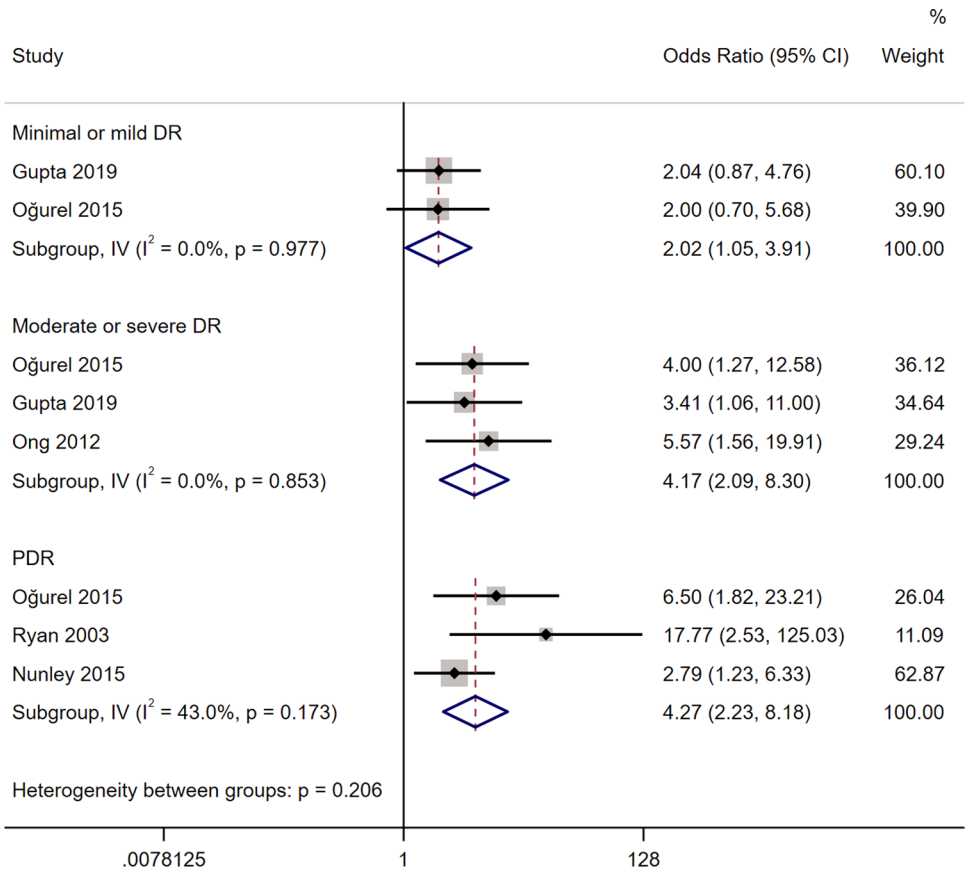

Fig. 6 Pooled OR for associating different severities of DR with cognitive impairment

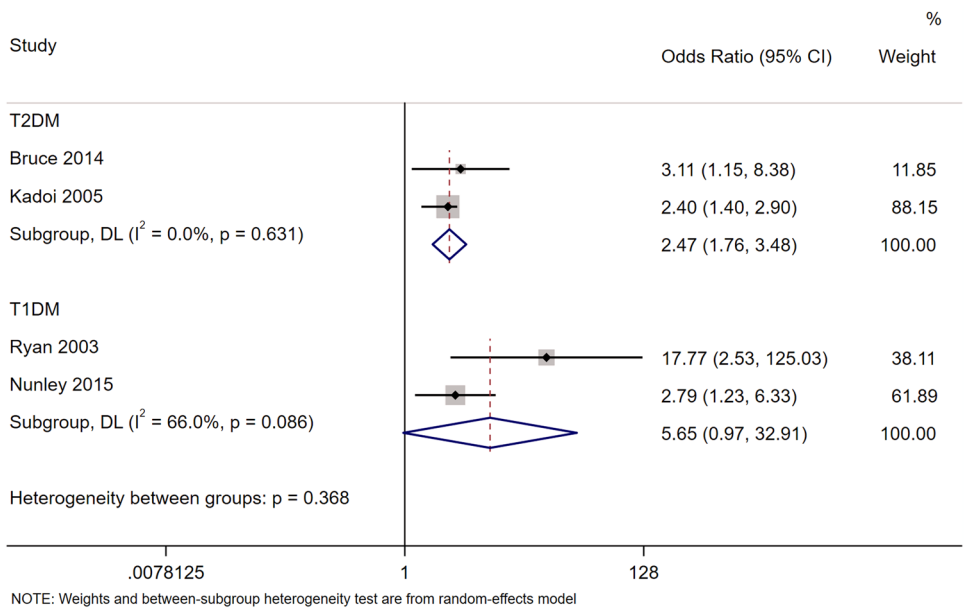

Fig. 7 Pooled OR for associating DR with cognitive impairment in different diabetes subtypes

The existence of DR is associated with cognitive dysfunction

DR can help to identify people at high risk of cognitive dysfunction. To date, the mechanism of DR and cognitive impairment is elusive which could be explained by the following possible mechanisms. Firstly, the blood-retinal barrier is closely related to the blood–brain barrier (BBB) due to the similar embryological origin, structure, and physiological characteristics between the retina and the cerebral microvessels

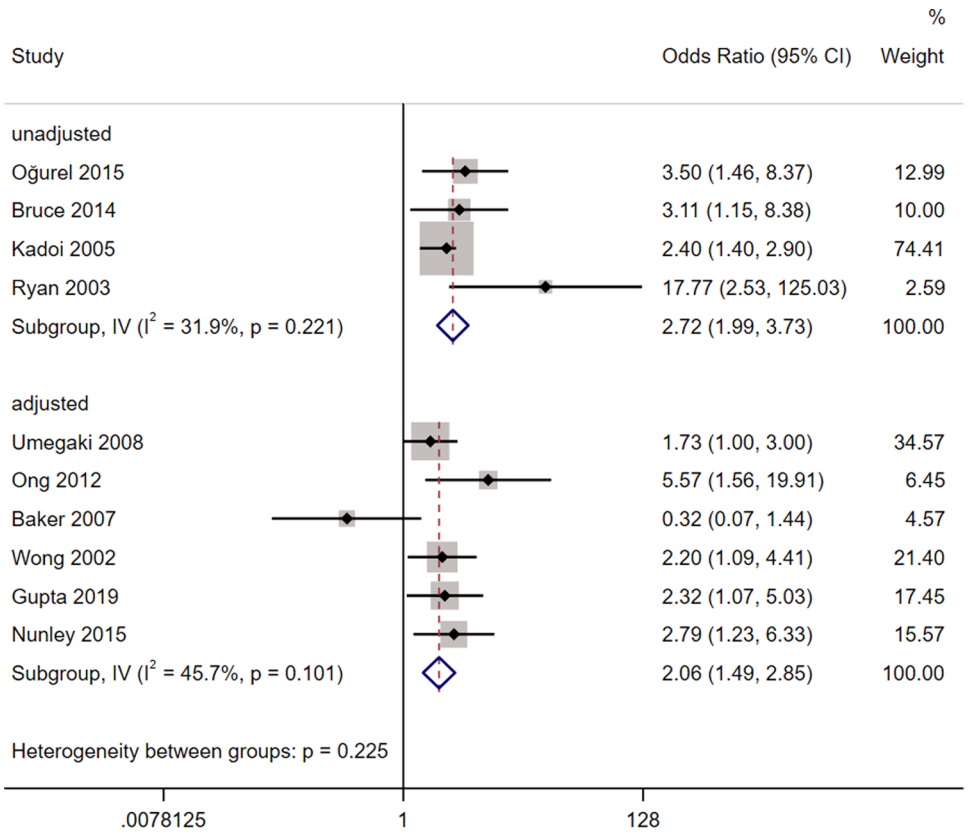

Fig. 8 Pooled OR stratified by whether confounding factors had been adjusted

[12]. The increased permeability of the blood-retinal barrier in the DR patients is possibly the reflection of similar damage in the BBB, leading to the decline in cognition [38]. Secondly, in diabetes, hyperglycemia and insulin resistance may damage the microvessels through endothelial dysfunction, developing complications in diabetic microvascular complications (e.g., DR), possibly affecting the occurrence and progression of cerebral microvascular diseases, associated with cognitive impairment [39]. In addition, another potential mechanism is accounted to the manifestation of common risk factors for DR and cognitive decline like hypertension [40]. Therefore, the occurrence of cognitive dysfunction and dementia can be delayed by positive and effective measures such as screening diabetic patients for retinal microvascular complications and identifying the groups with the risk of cognitive decline.

In the subgroup analysis, there were inconsistencies in the relationship between DR and cognitive impairment in different regions. There were few studies in this subgroup that depicted great heterogeneity in the age and type of diabetes, lowering the statistical efficiency. A recent systematic review [41] showed that the incidence of DR varied significantly in different regions, ranging between 2.2 and 12.7%, and the difference was probably related to social economy, eating habits, and lifestyle, while these were also related to the factors of cognitive impairment [42]. Future studies should therefore focus on analyzing the differences between the DR and cognitive impairment in various regions, providing the epidemiological basis for targeted prevention and screening.

Subgroup analysis showed a positive correlation between the DR severity and the risk of cognitive impairment. To increase the severity of DR, there was also a significant increase in trend in the risk of developing cognitive impairment. However, the included studies were based on different DR diagnosis and cognitive measurement methods. Hence, these results should be interpreted with caution. Larger cohort studies based on the same DR diagnosis and grading criteria are warranted to verify the findings.

Furthermore, we only found significant relationship between DR and cognitive dysfunction in T2DM, while patients with T1DM did not find such an association. A systematic review [43] showed that the prevalence of DR in T1DM was higher compared to that in T2DM (54.4% vs. 25.0%). The difference like cognitive impairment in T1DM and T2DM was due to the pathophysiology. In T2DM patients with hyperinsulinemia and insulin resistance, cognitive dysfunction could be explained by a cascade of metabolic, hormonal, and rheological disorders, while other mechanisms could be triggered by cognitive impairment in T1DM [44]. Thus, the risk of cognitive impairment in DR patients with T1DM should continue to be assessed.

The proposed subgroup of age, sex, and race could not be further discussed due to limited data availability. Age is a dependent risk factor for AD. Since brain aging and comorbidities are caused by aging, there was a significant increase in the prevalence of MCI among the elderly population. However, the incidence and prevalence rate stratification based on age have not been determined at present [45]. Therefore, it is necessary to assess the risk of cognitive impairment in DR patients of different age groups. A study [46] found that males are at higher risk of MCI than women. However, Barnes et al. [47] have suggested that women are at higher risk of dementia, Hence, there is an ambiguity in the relationship between gender and cognitive function. Weuve et al. [48] reported that black participants performed worse on the cognitive tests than the white participants and the risk of AD in the black participants was twice that in the whites. The difference in ethnicity was presumably due to the difference in the education level, access to materialistic and social resources, and racial discrimination. More research should focus on the ethnic differences in this regard.

Identifying MCI in the DR patients to prevent dementia

Our secondary outcome concentrated on the effects of DR on the six cognitive domains, and damage in any of these cognitive domains could be a precursor to MCI. The previous study [49] showed that elderly MCI patients are at high risk for developing dementia, especially AD. Significantly, a systematic review by Pandya et al. [50] found that MCI patients have higher rates of recuperation of cognition compared to those who have progressive dementia. Extant studies [51, 52] have reported that the incidence of MCI reversal ranged from 30–50%. Accordingly, if MCI can be prognosed and effective lifestyle interventions can be taken (diet, exercise, and cognitive stimulation) timely, leading to the delay in the disease progression to dementia.

Owing to the present diversity in the diagnostic guidelines for MCI, there is a high chance of underdiagnosis or delayed diagnosis [53], and thus, there is an urgent need for developing reliable tools for screening as well as diagnosis. MMSE is one of the most commonly used dementia screening tools, but studies [54] have shown that because it has highly variable sensitivity and specificity, MMSE might be not reliable enough for the early identification of potential MCI. MoCA is a widely accepted screening tool in clinics, but the long administration time and interference by education levels limited its application as a screening method of MCI in the community [55]. Zhuang et al. [56] suggested that the combination of highly sensitive tool should be used for MCI primary screening as well as two highly specific combinations in secondary screening. Breton et al. [57] recommended that the memory alteration test was the most appropriate for primary care. Further studies should focus on exploring or developing high-sensitive screening tools for MCI in people of different ages and education levels. Screening for cognitive impairment should therefore focus on the elderly, people with microvascular disease, metabolic disease, history of alcoholism, and depression.

Limitations

There are limitations to our systematic review. Firstly, the included studies have significant differences in the age of the population, follow-up period, DR identification method, geographic regions, diagnosis method of cognitive dysfunction, and adjustment factors. More than 30 cognitive measurements were used in the included studies, which not only may lead to greater heterogeneity but also reduce the reliability of our analysis. Secondly, owing to inconsistencies in the cognitive assessment methods and diagnostic criteria among the included studies and limitations of available data, the subgroups for age, sex and ethnicity could not be further analyzed. Some subgroups didn't reduce the heterogeneity and the results need to be interpreted with caution. Thirdly, not all studies were adjusted for confounding factors such as depression, alcohol consumption, medication history, vision, thyroid function, cholesterol, triglyceride, and urinary protein levels, etc., probably affecting the accuracy of our conclusions. Last but not least, although we conducted a comprehensive systematic search, we merely reviewed the published studies in Chinese and English, possibly ignoring the published and unpublished studies in other languages that might lead to a potential language and publication bias.

Future

The systematic review highlighted issues that need to be addressed in future research. First of all, based on this study, the relationship between DR and cognitive impairment in a different age, gender and race, should be further explored to provide individualized early prevention and treatment measures. Secondly, further prospective studies should be based on the same grading criteria and cognitive measurements to further confirm the association between mild, moderate or severe and proliferative DR and cognitive dysfunction. Next, future study designs should fully evaluate the history of alcohol, drug, and substance abuse, vision, depression, etc., in the included population. This would minimize the confounding factors that might interfere with outcomes. Finally, future studies must recommend highly sensitive cognitive assessment methods for different populations and gradually improve the screening guidelines, conducting early

lifestyle intervention for MCI patients to delay the progression of dementia.

Conclusion

The presence of DR reflects a higher risk of cognitive impairment and mainly impairs the psychomotor speed and information processing speed. Screening for DR should be executed effectively in clinical studies and MCI in the DR patients should be identified on time to reduce the risk of cognitive decline and dementia. Additional research is required to explore the relationship between DR and cognitive impairment in patients of different ages, gender, race and TIDM patients, for evaluating the risk of cognitive decline in different populations.

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Author contributions BM, KH, and MW came up with the original design of the research. MW, FM, ZW, and LF completed literature search, screening and data collection. MW, QG, FC, and LZ performed the statistical analysis. The data were analyzed by MW, FM, XL and BM. MW wrote the first draft of the article and all authors participated in the supplement and revision of the research.

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Data availability The data that support the findings of this study are available on request from the corresponding author.

Declarations

Conflict of interest The authors declare no conflict of interest.

Ethical approval Not applicable.

Informed consent Not applicable.

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