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REVIEW ARTICLE

Physical activity and risk of diabetic retinopathy: a systematic review and meta-analysis

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Abstract

Aims Diabetic retinopathy (DR) is an important microvascular complication of diabetes mellitus (DM) and a leading cause of visual impairment and blindness among people of working age. Physical activity (PA) or exercise is critical and beneficial for DM patients, whereas studies evaluating the relationship between PA and DR have yielded inconsistent and inconclusive results. The American Diabetes Association's "Standards of Medical Care in Diabetes" has also pointed out the indeterminate roles of PA in DR prevention. The purpose of this systematic review and meta-analysis was to explore the association between PA and DR risk.

Methods Medline (accessed by PubMed), EmBase, and Cochrane Library were systematically searched for studies up to June 2018, and the reference lists of the published articles were searched manually. The association between PA and DR risk was assessed using random-effect meta-analysis.

Results Twenty-two studies were included in this meta-analysis. PA was found to have a protective association with DR [risk ratio (RR) = 0.94, 95% confidence interval (95% CI) 0.90–0.98, $p = 0.005$] in diabetic patients, and the impact was more pronounced on vision-threatening DR (RR = 0.89, 95% CI 0.80–0.98, $p = 0.02$). Sedentary behavior could increase the risk of DR (RR = 1.18, 95% CI 1.01–1.37, $p = 0.04$). Moderate-intensity PA was likely to have a slight protective effect (RR = 0.76, 95% CI 0.58–1.00, $p = 0.05$).

Conclusion PA is associated with lower DR risk, and more studies should focus on the causality between them.

Keywords Physical activity · Diabetic retinopathy · Sedentary behavior · Meta-analysis

Introduction

Diabetic retinopathy (DR), a complication of diabetes mellitus (DM), is a leading cause of visual impairment and blindness among people of working age without sexual difference, seriously affecting people's health and life quality worldwide [1, 2]. DR occurs in both type 1 and type 2 DM, and approximately one in three diabetic patients is affected by some degree of DR and one in ten will develop vision-threatening DR (VTDR) [3], which includes severe non-proliferative DR, proliferative DR (PDR) and clinical significant macular edema (CSME). The number of DR prevalence is projected to increase within the next decade as the number of diabetes is also increasing, particularly in Asian countries such as Indonesia, India, and China [4–7].

Besides controlling primary disease, the most effective way to reduce visual impairment relating to DR is to identify and mitigate related risk factors. A growing body of epidemiological studies has identified several factors associated with the incidence or progression of DR, such as glycemic control, duration of diabetes, systolic and diastolic blood pressure, high cholesterol and hyperlipidemia, obesity, urinary albumin, etc. [8–10], which are the risk factors of DM, as well.

Physical activity (PA) is a critical component of lifestyle intervention in diabetes management and is recommended by the American Diabetes Association's (ADA's) "Standards of Medical Care in Diabetes" [11] for patients with DM. Evidence for the benefits of PA in diabetic patients has been reviewed by the ADA position statement "Physical

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Activity/Exercise and Diabetes" [12]. However, the ADA's standards for diabetes [11] also pointed out that PA's role in the prevention of diabetes complications, such as DR, is still not clear enough [13]. Many studies have worked on this problem, but the results varied from each other. Both inverse [14, 15] and positive [16] association between PA and DR has been reported, while some studies suggested no significant association between them [17–20]. In addition, adverse events due to exercise, such as retinal hemorrhage, were also reported in DR patients [21].

Hence, based on the various evidences above, we conducted a systematic review and meta-analysis of available literature to further assess the association between PA and DR, which may be helpful in DR management.

Methods

Search strategy

This meta-analysis was conducted following the guidance of PRISMA [22]. We searched three electronic databases covering the period up to June 2018: Medline (accessed by PubMed), EmBase, and Cochrane Library. The search terms and strategies for PubMed were (Exercise, Physical Exercise, Physical activity, Exercise Therapy, Exercise Movement Techniques, Resistance Training, Muscle Stretching Exercises, Exercise Isometric, Isometric Exercises, Isometric Exercise, Exercise Aerobic, Aerobic Exercises, Aerobic Exercise, Pilates Exercise, Pilates Training, Training Resistance, Strength Training, Weight Lifting, Strengthening Program, Weight Bearing, Warm Up Exercise, Exercise Therapies, Strength Training, Strengthening Programs, Weight Lifting Exercise Program, Weight Bearing Strengthening Program, Weight Bearing Exercise Program, Motion Therapy, Continuous Passive, and Plyometric Exercise), and (diabetic retinopathy, diabetes mellitus retinopathy, diabetes retinopathy, diabetic retinitis, diabetic retinopathy, and retinopathia diabetica). We also manually searched for additional studies concerning PA and DR in the reference lists of the identified trials or reviews, but not included in the literature search result. We applied no restrictions of language.

Inclusion and exclusion criteria

After the duplicates removed, all the titles and abstracts of the articles identified through both database searching and other sources were screened, and then, full-text articles were reviewed by Chi Ren and Weiming Liu and included in meta-analysis basing on the pre-defined criteria, namely: (1) investigated on human beings other than experimental animals; (2) included physical activity as a study risk factor or variable; (3) reported outcome of DR; and (4) presented odds ratio (OR), risk ratio (RR), or hazard ratio (HR), or original data which allowed the calculation of OR/RR/HR values.

Studies were excluded if any of the following criteria were identified: (1) case reports or case series; (2) not conducted in human; (3) concerned drug effects or specific conditions (e.g., eye surgery, hypertension, or combined other lifestyle intervention); and (4) the data in the study were obviously paradoxical or not presented clearly enough.

Data extraction and assessment of study quality

From eligible studies to be included in the review, two authors (Chi Ren and Jianqing Li) independently extracted the following information: name of the first author, publication year, location where the study was performed, study design, follow-up period, number of case/cohort, age range, type of DM, DR evaluation, measurements for PA, variables adjusted for in the analysis, and OR/RR/HR value with a 95% confidence interval (95% CI). To avoid the possibility of double counting of patients included in more than one report by the same authors or research groups, the recruitment periods of each study were evaluated. Disagreements were resolved through discussion between two reviewers (Chi Ren and Jianqing Li) or adjudication by a senior author (Peirong Lu).

Quality assessment

Since there was no assessment method suitable for various study type (i.e., cross-sectional study and cohort study), we designed an assessment scale with 11 items based on Newcastle Ottawa Scale (NOS) [23], recommendation of Agency for Healthcare Research and Quality (AHRQ) [24], and STROBE statement [25]. Each item in the scale should be answered with 'yes', 'no', or 'unclear', and an item would be scored '1' when the answer was 'yes'; otherwise, the item would be scored '0'. Quality of the included studies was assessed by two reviewers (Chi Ren and Weiming Liu) independently; disagreements were resolved by a senior author (Peirong Lu). A study with eight or more scores would be defined as high quality.

Statistical analysis

For meta-analysis, under the assumption that RRs were accurate approximations of ORs and HRs, RRs with 95% CI were assessed to determine the strength of association between PA and DR risk. To reduce the potential variation due to different PA measurements between studies or more than two categories defined in a single study, participants were ranked as sedentary if they fell in the lowest activity category in a specific study, and as active otherwise. If

a study reported results separately by subgroups, but not combined, we used a fixed-effects model (FEM) to obtain an overall estimate for the main analysis. If both of adjusted and unadjusted data were reported in the same article, adjusted data were used for assessment. The results were summarized into a single RR with 95% CI if they were provided by gender or other categories in an article.

Pooled-analysis results were calculated as the inverse variance weighted mean of the logarithm of RR with 95% CI to assess the strength of association between PA and risk of DR. We also conducted subgroup analyses by study characteristics (e.g., study design, geographic location, adjustments, or matched for other variables) and by patient characteristics (e.g., gender and type of DM).

The Cochran's Q test was used to assess heterogeneity of the studies, with a threshold p value of 0.10 for significance [26]. We also used the I^2 test for heterogeneity evaluation. The FEM was used as the pooling method if $p_Q \geq 0.10$ or moderate or lower heterogeneity ($I^2 < 50\%$) was found; otherwise, the random-effects model (REM) was adopted ($p_Q < 0.10$ or $I^2 \geq 50\%$).

Moreover, a sensitivity analysis was performed by removing one study at a time to assess whether the results could be affected markedly by a single study [27]. Potential publication bias was evaluated by Egger's regression test [28] and Begg's rank correlation test [29], and presented visually by a funnel plot.

Statistical analyses were carried out using the STATA software package (version 12.0; STATA Corp., College Station, TX). Statistical significance was taken as $p < 0.05$.

Results

Literature search and study selection

Figure 1 demonstrates the details of study selection in this meta-analysis. In brief, we initially identified 1432 articles in total. 85 articles were identified potentially relevant studies concerning PA and DR, and three [30–32] of them were manually identified through other sources. 63 studies were excluded after full-text screening, among which 35 studies included no relevant outcome or exposure, 18 studies contained insufficient data, 3 studies combined PA with other interventions, 6 studies were duplicate reports from the same study population as other studies, and 1 study contained paradoxical data. The remaining 22 studies [14–20, 30, 33–46] were finally included in this meta-analysis.

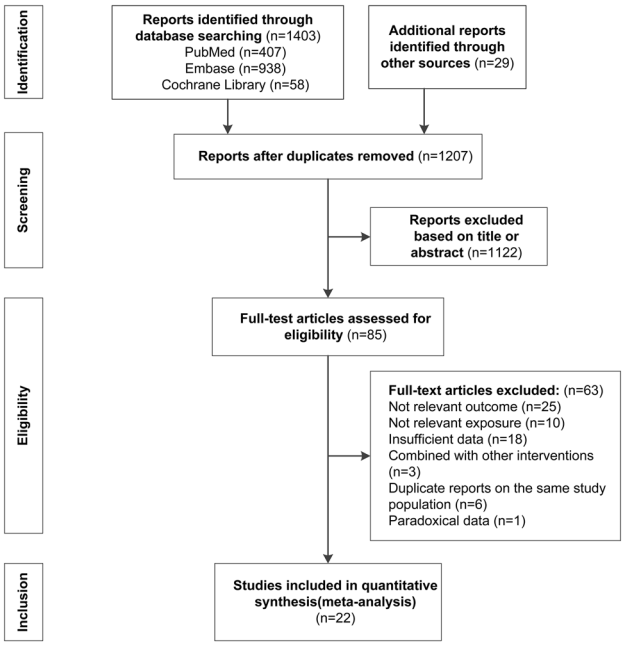

Fig. 1 Flowchart showing the process of literature search and study selection. Additional reports identified through other sources: any potentially relevant studies concerning physical activity and diabetic retinopathy in the reference lists of the identified trials or reviews but not included in the literature search result

Study characteristics and quality assessment

Table 1 shows the detailed characteristics of these studies. A total of 63,936 individuals from America [15, 18–20, 39, 45, 46], Europe [14, 30, 36, 42], Asia [16, 17, 33–35, 37, 38, 40, 41, 44] and Australia [43] were included. In all, it was possible to identify 15 cross-sectional studies [14, 15, 17, 19, 30, 34–38, 40–43, 46], six cohort studies [16, 20, 33, 39, 44, 45] and one longitudinal study [18]. The longest study period was 15 years [44], and the study periods were different among the included studies. Adjustments differed between the studies, including sex, age, BMI, HbA1c level, diabetes duration, race, educational level, smoking status, drinking status, etc.

The scale used in quality assessment is demonstrated by Table 2 and the results are shown in Table 1. In general, quality of evidence was high for the association between PA and DR (20 of 22).

Pooled-analysis results

We first analyzed the overall association between PA and DR, and obtained the RR of 0.94 (95% CI 0.90–0.98, $p = 0.005$, $I^2 = 78.9\%$, $p_{\text{heterogeneity}} < 0.001$) (Fig. 2), indicating a slight but effective reduction in the risk of DR

Table 1 Characteristics of eligible studies

First author (publication year)	Country	Age range/year	No. of case/cohort	DM Type	DR evaluation	Measurement of PA	Adjustment/matched	RR (95% CI)	Quality score
Cross-sectional studies									
Dharmastuti (2018) [17]	Indonesia	> 30	1116	T2DM	Fundus photography	Walking distances per day	Sex, age, DM duration, SBP, the occurrence of heart disease, foot ulcer, gangrene, sedentary activity per day	0.99 (0.61–1.62)	10
She (2017) [34]	China	NA	747	NA	Fundus photography	Exercise intensity in the past 7 days	None	1.47 (0.73–2.97)	7
Praidou (2017) [14]	Greece	49–67	320	NA	OCT and FFA	Hours of PA per week	HbA1c, BMI	0.73 (0.66–0.80)	10
Loprinzi (2016) [19]	USA	NA	282	NA	Fundus photography	Accelerometer	Sex, age, race/ethnicity, comorbid illness, smoking status, visual acuity, mean arterial pressure, serum cholesterol level, HbA1c level, homocysteine level, functional disability	1.00 (0.99–1.01)	9
Yan (2016) [35]	China	30–85	1100	T2DM	Fundus photography	Any routine walking exercise	Sex, age	0.71 (0.13–3.87)	10
Bohn (2015) [36]	Germany	18–80	18,028	T1DM	Medical documents	Frequency of PA per week	Sex, age, DM duration	1.01 (0.95–1.08)	8
Li (2015) [37]	China	NA	517	T2DM	FFA	MET h /week	BMI, smoking status, daily amount of smoking, ethanol intake, income pressure	0.87 (0.64–1.19)	9
Wang (2014) [38]	China	20–90	2699	T2DM	Clinical DR Disease Severity Scale	Any regular PA	None	1.03 (0.85–1.24)	8
Yang (2013) [41]	Korea	≥ 19	10,345	NA	Fundus photography	Whether ≥ 5 times of exercise/week	Sex, age	1.02 (1.01–1.03)	8
Li (2013) [40]	China	NA	1100	T2DM	Fundus photography	Time of PA per week	None	0.72 (0.51–1.05)	8

Table 1 (continued)

First author (publication year)	Country	Age range/year	No. of case/cohort	DM Type	DR evaluation	Measurement of PA	Adjustment/matched	RR (95% CI)	Quality score
Janevic (2013) [15]	USA	≥51	2003	T1DM	Self-reports	Whether meet PA guideline	Sex, age, educational level, marital status, race, wealth	0.54 (0.36–0.81)	8
Carral (2013) [42]	Spain	18–60	130	T1DM	FUNDUS photography	Minutes per week	DM duration, smoking, BMI, HBP, insulin doses, number of hypoglycemia in the previous month	0.71 (0.43–1.18)	8
Tikellis (2010) [43]	Australia	45–64	15,792	NA	Fundus photography	Activity index	SEX, age, race, post secondary education, BMI, DM, current drinker, current smoker, HDL, MABP	0.80 (0.69–0.93)	9
Wad' en (2008) [30]	Finland	10–81	1945	T1DM	Medical records	MET h /week	None	0.85 (0.67–1.06)	9
Kriska (1991) [46]	USA	8–48	628	T1DM	FUNDUS photography	Hours of PA per week in aldulthood	None	0.78 (0.46–1.33)	7
Cohort studies									
Kuwata (2017) [33]	Japan	20–64	1814	T2DM	Fundus photography	MET h /week	Age, sex, BMI, duration of DM, SBP, DBP, HR, HbA1c, HDL, LDL, triglyceride, eGFR, diabetes therapy and history of CVD, BMI	0.71 (0.57–0.89)	11
Bener (2014) [16]	Qatar	≥20	1633	T2DM	Questionaire	Any PA habits	HBP, family history of DM, consanguinity	1.91 (1.30–2.82)	9
Makura (2013) [39]	USA	13–39	1441	T1DM	Fundus photography	MET h /week	DM duration, BMI, baseline HbA1c, triglycerides, cholesterol, SBP, DBP, smoking status	1.12 (0.86–1.46)	11

Table 1 (continued)

First author (publication year)	Country	Age range/year	No. of case/cohort	DM Type	DR evaluation	Measurement of PA	Adjustment/matched	RR (95% CI)	Quality score
Ahmed (2011) [44]	Bangladesh	45–64	977	T2DM	Fundus photography	Medical records	Sex, age, HbA1c, SBP, BMI, area of residence, fasting blood glucose, triglyceride, total cholesterol, serum creatinine	1.10 (0.80–1.30)	11
Cruickshanks (1995) [20]	USA	< 30	606	T1DM	Fundus photography	SELF-rated activity	Sex, age, DM duration, complications, retinopathy level	0.68 (0.27–1.73)	11
Laporte (1986) [45]	USA	21–55	671	T1DM	NA	Whether participated in team sports	Year of DM onset, age at DM onset, smoking status, education, drinking status, hypertension, renal disease	0.76 (0.53–1.09)	10
Longitudinal study									
Chen (2015) [18]	USA	> 65	1142	NA	Self-reports	Whether meet PA guideline	Sex, age, race, marital status, years of schooling completed, household income, BMI, total illness burden index score, low cognition, whether use insulin, and whether use oral diabetes medications	0.78 (0.39–1.56)	9

RR risk ratio, *CI* confidence interval, *PA* physical activity, *DR* diabetic retinopathy, *DM* diabetes mellitus, *T1DM* type 1 diabetes mellitus, *T2DM* type 2 diabetes mellitus, *OCT* optical coherence tomography, *FFA* fundus fluorescein angiography, *MET* metabolic equivalent of task, *BMI* body mass index, *HbA1c* hemoglobin A1c, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *MABP* mean arterial blood pressure, *HR* heart rate, *CVD* cardiovascular disease, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *eGFR* estimated glomerular filtration rate, *NA* not available

Table 2 Quality assessment scale

Items	Answer[a]	Score[b]
1. Was the study a cohort study?		
2. Was the spectrum of participants' representative?		
3. Were the inclusion and exclusion criteria clearly described?		
4. Were the source of data and recruitment period clearly described?		
5. Were all of the statistical analysis methods in the study clearly described?		
6. Were exposure and unexposure groups matched in the design or cofounders adjusted for analysis?		
7. Were there multiple ratings for PA for different categories of exposure?		
8. Was the DR case definition adequate?		
9. Was the PA definition adequate?		
10. Did all of the included population participated in or responded to the study? If not, was the withdrawals reported or discussed ?[c]		
11. Whether the study discussed the limitation and potential bias of the study?		
Total score		

[a]Each item in the scale should be answered with 'yes', 'no', or 'unclear'

[b]An item would be scored '1' when the answer was 'yes'; otherwise, the item would be scored '0'

[c]The answer to the item would be 'yes' if either of the two questions is answered with 'yes'

for individuals who were physically active compared to inactive ones.

Association between PA of different intensity and DR

Seven studies [17, 20, 30, 34, 37, 40, 42] divided PA into several categories according to intensity level (Fig. 3). Activities of moderate intensity [17, 20, 37, 40, 42] were more likely to exert a salubrious impact on DR (RR = 0.76, 95% CI 0.58–1.00, $p = 0.05$) than low intensity [30, 37] and high [17, 20, 34, 37, 42] intensity.

Association between PA and vision-threatening DR

Seven studies [17, 18, 20, 30, 45–47] provided risk estimates of PA in relation to vision-threatening DR (VTDR) (RR = 0.89, 95% CI 0.80–0.98, $p = 0.02$) (Fig. 4). This result highlighted the importance of being physically active for VTDR.

Association between sedentary behavior and DR

Eight studies [16, 17, 19, 30, 36, 38, 40, 42] reported on sedentary behavior in relation to DR, and the pooled analysis revealed that sedentary lifestyle would significantly increase the probability of having DR in DM patients (RR = 1.18, 95% CI 1.01–1.37, $p = 0.04$) (Fig. 5). This result further supported the assumption that PA lowered risks of DR.

Subgroup analyses results

A series of subgroup analyses were also conducted (Table 3). Pooled RR of 15 cross-sectional studies [14, 15, 17, 19, 30, 34–38, 40–43, 46] indicated the protective effect of PA on DR, while the pooled RR of six cohort studies [16, 20, 33, 39, 44, 45] did not. Adjusted estimates from 17 studies [14–20, 33, 35–37, 39, 41–45] favored PA, while unadjusted estimates from five studies [30, 34, 38, 40, 46] showed no significant result. Two studies [47, 48] were excluded from overall analysis due to duplicated population, but some data from these two studies were used in the gender subgroup analysis, instead of the two studies previously included in the overall analysis [19, 20] which lacked enough detailed data. PA's influence on risk of DR showed almost no sexual difference. In addition, our subgroup analyses revealed that none of study design, adjustments, geographic location, or type of DM could influence heterogeneity.

Publication bias and sensitivity assessment

Neither Egger's regression test ($p = 0.06$) nor Begg's rank correlation test ($p = 0.46$) indicated any publication bias (Fig. 6). In the sensitivity analysis, removal of one study [14] could materially alter the results, which could be the source of heterogeneity (Fig. 7).

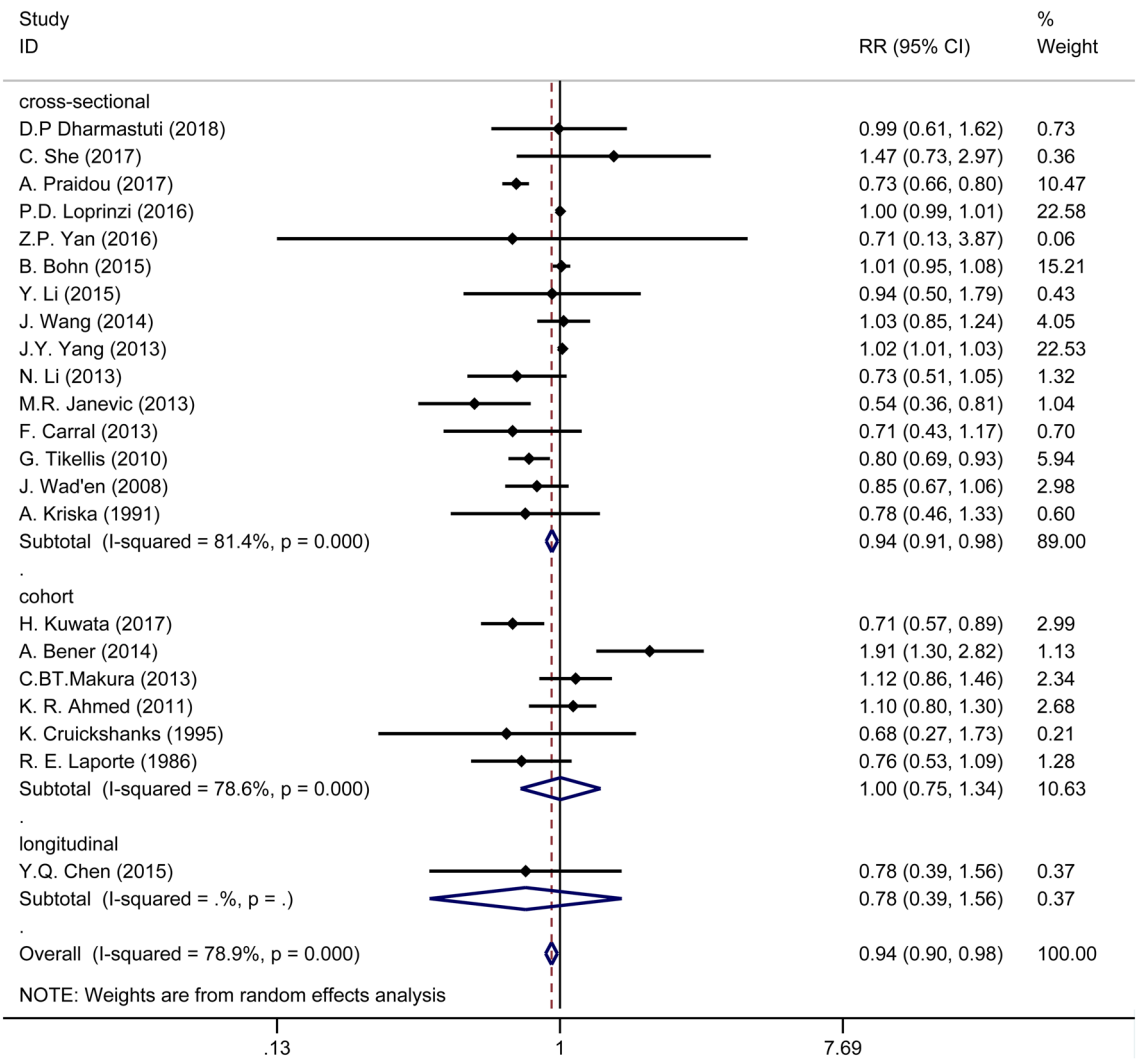

Fig. 2 Forest plot summarizing the association between physical activity and diabetic retinopathy using the random-effects model. Significance test for overall effect: $p = 0.005$. Dashed line indicates overall estimate. Bars indicate 95% confidence interval (CI). *RR* risk ratio

Discussion

To our knowledge, this meta-analysis is the first to assess the relationship between PA and DR risk. Our analysis revealed that staying more physically active was associated with lower DR risk, and the impact was more pronounced for VTDR. Moreover, activities of moderate intensity were beneficial, while sedentary behavior could significantly increase DR risk. These results were in line with the general conception of PA as a protective factor of DR, sending out a public message of diabetic patients being physically active to maintain ocular health.

Association between PA and DR

Our results revealed the linkage of PA to DR risk (RR = 0.94, 95% CI 0.90–0.98, $p = 0.005$). Since PA is recommended by authoritative guidelines for diabetes in different parts of the world [11, 49–51], PA would benefit not only diabetes but also its complications such as DR.

Although PA is widely recommended and appealed for, the level of PA is still low in many places around the world [52]. It has been well established that physical inactivity is associated with higher risk of diabetes, and may be the principal cause for approximately one-fourth cases of the disease [53]. Ample evidence has suggested the contribution that inactivity made to diabetic complications [16, 30, 54, 55]. In this study, we highlighted higher risk of DR in diabetic patients who were more sedentary. The negative impact of sedentary behavior on DR seemed even more significant than the positive impact of PA.

Evidence for the effects of low-, moderate-, and high-intensity activities was still insufficient in our assessment. While moderate-intensity activities [17, 20, 37, 40, 42]

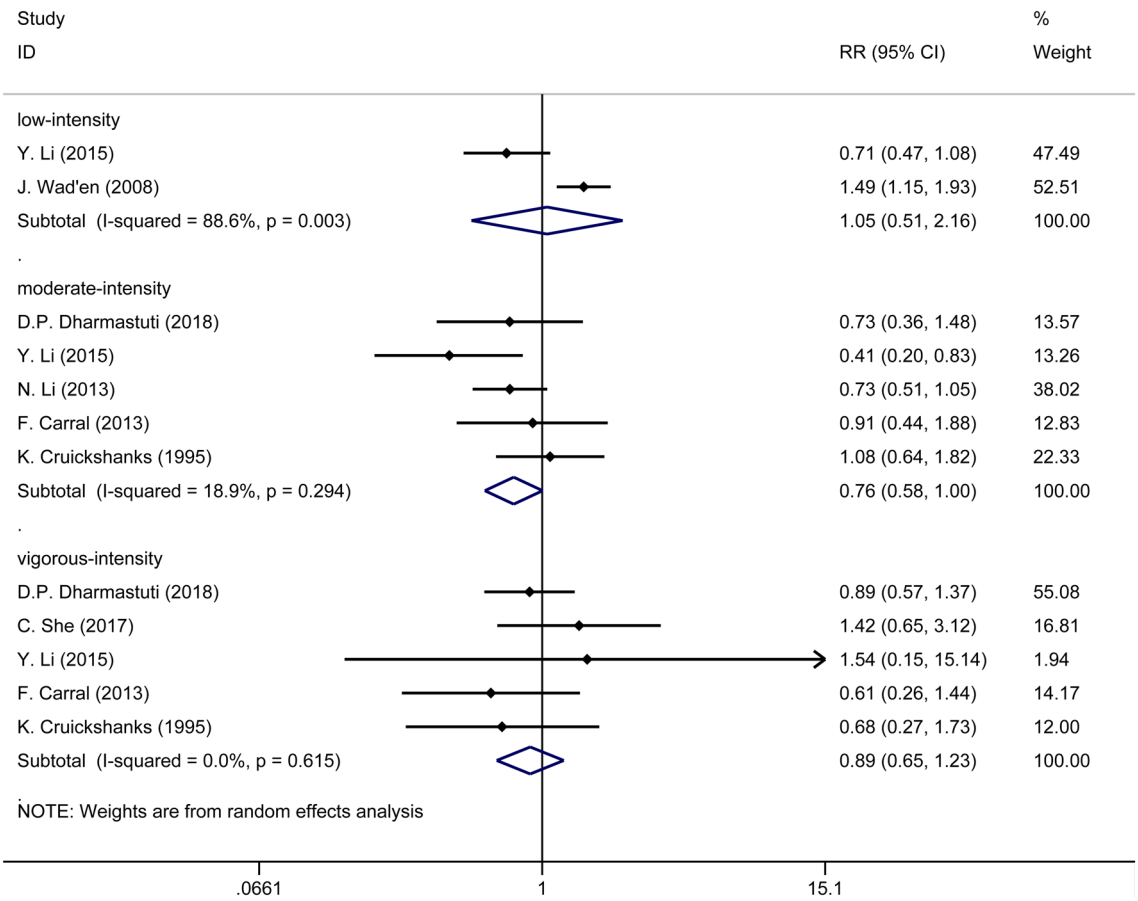

Fig. 3 Forest plot showing the association between physical activity and diabetic retinopathy across different activity intensities using the random-effects model. Significance test for subgroup estimates: low intensity, $p=0.90$; moderate intensity, $p=0.05$; vigorous intensity, $p=0.48$. Bars indicate 95% confidence interval (CI). *RR* risk ratio

seemed to have a salubrious positive effect. Another finding in our study was the remarkable protective effect of PA on VTDR. It appears worth mentioning that if VTDR is present, then vigorous-intensity aerobic or resistance exercise should be avoided to reduce the risk of triggering vitreous hemorrhage or retinal detachment [21, 56]. Besides, exaggerated blood pressure responses to exercise were found in PDR patients [57]. Vigorous exercise-related Valsalva-type maneuvers may induce the occurrence of hemodynamic process, which elevate systolic blood pressure, subsequently rising the likelihood of ocular hemorrhage [58, 59] and leading to worse prognosis [60]. Moreover, vigorous exercises generally involve anaerobic metabolism which has different effects from aerobic activity, and could be harmful [58].

High heterogeneity existed among studies and was not influenced by study design, adjustments, geographic location, or type of DM. This might be due to the diversity in population stratification, inclusion and exclusion criteria, ways for measurement of PA and lengths of follow-up, etc. Sensitivity analysis revealed that the removal of one study [14] significantly altered the result of overall analysis, which might contribute to the heterogeneity. The possible causes could be as follows: First, the number of participants was smaller than other studies as only 320. Second, the age range of participants was narrow (46–67 years) and relatively older than others, and no adjustment was made to it. Third, the inclusion criteria made restrictions to visual acuity and duration of DM, while the others did not. Fourth, in this study, DR was diagnosed with optical coherence tomography (OCT) and fundus fluorescence angiography (FFA), while, in others, diagnosis was mostly performed using fundus photography.

Underlying mechanisms of PA's effects on DR

DR is a disease characterized by morphological lesions, secondary to retinal auto-regulation disorder, which is assumed related to disturbances in retinal blood flow [61–64]. Dilation of retinal arteriolar is related to the development of DR and may predict the early retinopathy in individuals with diabetes [65–69]. Earlier studies demonstrated a significant correlation between PA and retinal microvascular signs,

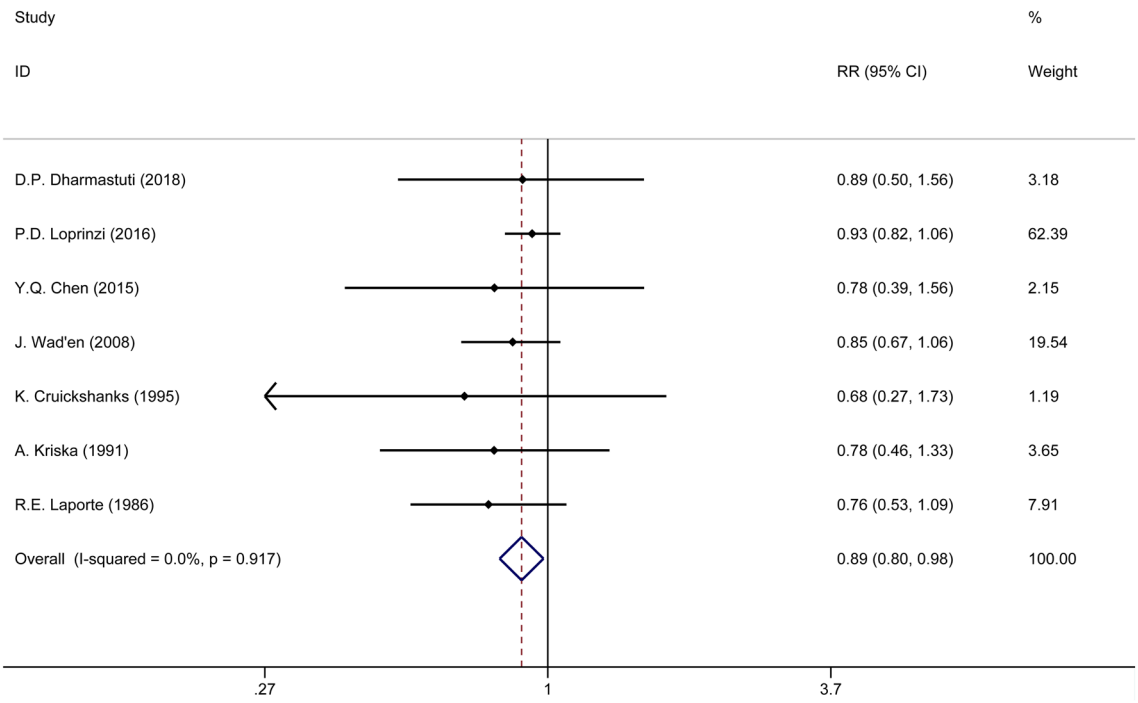

Fig. 4 Forest plot summarizing the association between physical activity and vision-threatening diabetic retinopathy using the fixed-effects model. Significance test for estimate: $p=0.02$. Bars indicate 95% confidence interval (CI). *RR* risk ratio

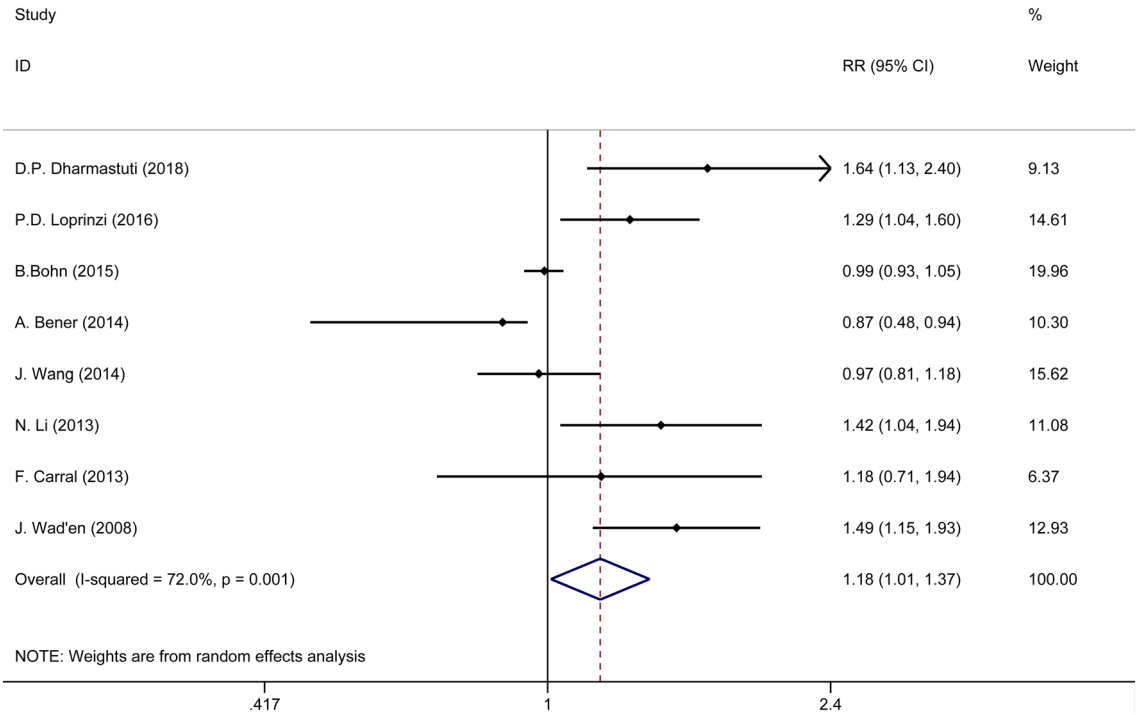

Fig. 5 Forest plot summarizing the association between sedentary behavior and diabetic retinopathy using the random-effects model. Significance test for estimate: $p=0.04$. Bars indicate 95% confidence interval (CI). *RR* risk ratio

Table 3 Results of subgroup analysis between PA and DR with pooled RR

	No. studies	RR (95% CI)	*p* value	I-square (%)	Test for heterogeneity within subgroup (*p* value)
Study design					
Cross-sectional	15	0.94 (0.91–0.98)	< 0.01	81.4	< 0.01
Cohort	6	1.00 (0.75–1.34)	0.98	78.6	< 0.01
Longitudinal	1	0.78 (0.39–1.56)	0.49	NA	NA
Adjustments					
Yes	17	0.94 (0.90–0.99)	0.01	82.7	< 0.01
No	5	0.91 (0.77–1.07)	0.26	26.5	0.24
Geographic location					
America	7	0.86 (0.71–1.04)	0.12	56.5	0.03
Europe	4	0.84 (0.67–1.05)	0.12	90.8	< 0.01
Asia	10	1.01 (0.87–1.16)	0.93	63.4	0.06
Australia	1	0.80 (0.69–0.93)	< 0.01	NA	NA
Gender					
Male	4	0.99 (0.95–1.01)	0.35	21	0.28
Female	4	0.96 (0.91–1.01)	0.22	46	0.14
Type of DM					
T1DM	8	0.86 (0.73–1.01)	0.06	58.0	0.02
T2DM	8	0.99 (0.79–1.24)	0.94	69.3	< 0.01

RR risk ratio, *CI* confidence interval, *PA* physical activity, *DR* diabetic retinopathy, *DM* diabetes mellitus, *T1DM* type 1 diabetes mellitus, *T2DM* type 2 diabetes mellitus, *NA* not applicable

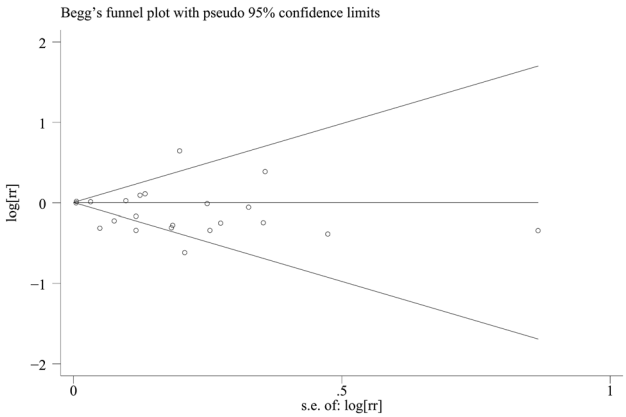

Fig. 6 Funnel plot for physical activity with diabetic retinopathy

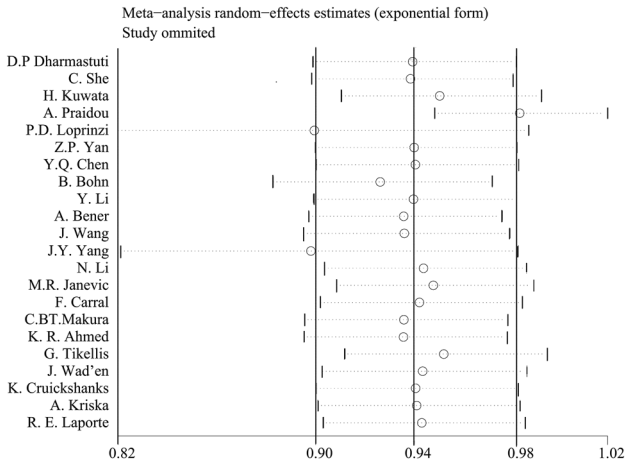

Fig. 7 Sensitivity analysis of the association between physical activity and diabetic retinopathy

such as retinal venules and arteriolar caliber [70, 71]. Wider central retinal venular equivalent (CRVE) was reported in diabetic patients who were less physically active [43, 72], and increased retinal blood flow during exercise was also observed [73, 74]. Retinal production of two major vasodilators, nitric oxide synthase (NOS) and cyclooxygenase (COX), increased in arterial blood and skeletal muscles of diabetic patients after exercise [75, 76]. These results indicated that PA exerted its effects through altering retinal blood flow.

Glycemic control, reflected by HbA1c level, is a fundamental part of diabetes management and strongly related to DR status [77–79]. Meta-analysis by Umpierre et al. [80] concluded that more structured exercise training, meeting ADA's guideline (> 150 min per week), and receiving PA advice alone were associated with more HbA1c decline in T2DM patients. Meta-analysis by Boniol et al. [81] also achieved similar conclusion, suggesting a possible mechanism of PA's impact on DR through improving glycemic control.

Another possible mechanism is alteration of 25-hydroxyvitamin D (25OH-D) level. Ample evidence has showed

that higher PA level is beneficial for 25OH-D status in people of all ages [82–87]. Keech et al. [88] reported lower blood 25OH-D concentration related to a higher odds of macrovascular and microvascular events (including DR) in the FIELD cohort [89–91], and this relationship was further confirmed by meta-analysis (pooled OR = 2.03, 95% CI 1.07–3.86, $p = 0.03$) [92]. Notably, 25OH-D is a metabolite produced by liver, generally used to determine the vitamin D status. Ortlepp JR et al. [93] also reported that PA's effects on fasting glucose levels might depend on vitamin D receptor genotype. All this suggested potential roles of 25OH-D and vitamin D may play in PA's benefits, and further studies are needed to confirm this assumption.

As oxidative stress and inflammation reported to be involved in the pathogenesis of DR [94, 95], antioxidant and anti-inflammatory therapy has showed bright perspectives in DR treatment [96, 97]. Ample evidence has displayed modulation of oxidative stress and inflammation by exercise [98]. Several experiments have demonstrated reduced oxidative stress in mice retina during exercise with progression of DR inhibited [99–102] and a remarkable shift of activated microglia from a pro-inflammatory M1 to an anti-inflammatory M2 phenotype in streptozotocin-induced rat model after treadmill exercise [103]. The evidence above indicated another mechanism of PA's effects.

Several investigations have been conducted into single-nucleotide polymorphisms (SNPs) related to PA, e.g., *SLC30A8* (rs13266634) and near *IRS-1* (rs2943641, rs1522813) [104, 105], which were further found related to DR [106, 107].

Limitations of our study

There were some limitations in this meta-analysis.

Since most of the included studies were cross-sectional studies, although our results showed the correlation of PA to DR, the causality between them was still not clear enough.

Self-reported PA could not precisely reflect actual PA level, especially when PA was divided into several categories, i.e., occupational PA, transportational PA, housework-related PA, or the duration and intensity per session. Definition of PA level varied among studies, as well, which might influence the results.

High heterogeneity was identified in this meta-analysis, and we found out one study [14] which might contribute to this. Beside the factors mentioned in subgroup analyses, many other factors could also influence the heterogeneity and the result of this meta-analysis, such as age range of participants, ways of DR evaluation, and adjustment/matched items. In addition, although many studies adjusted some important cofounding factors, the potential influence of undefined or unmeasured factors on heterogeneity could not be ignored.

Moreover, PA level was likely to reduce due to visual impact caused by DR or presence of other DM complications, and possibly related to other risk factors of DR, so the effects of PA alone might be over-estimated to some extent.

Conclusion

PA is related to lower risk of DR, and the impact is stronger on VTDR. Moderate-intensity PA is more recommended, and sedentary lifestyle should be avoided. Further research should focus on the causality between PA and DR and consider the possible mechanisms. Understanding the systematic factors associated with DR risk may help clinicians and patients in DR management.

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Author contributions CR and PL conceived of the idea and designed the study. CR, WL, and JL collected the data. CR, JX, and YC performed the data analysis. CR, WL, and PL participated in the critical revision of the manuscript. All authors read and approved the final manuscript.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Human and animal rights This article does not contain any studies with human participants or animals performed by any of the authors.

Ethical approval As this was a review study, no ethics approval was required.

Informed consent For this type of study, informed consent was not required.

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