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Prediction of risk of diabetic retinopathy for all-cause mortality, stroke and heart failure
Evidence from epidemiological observational studies

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Abstract

To examine and quantify the potential relation between diabetic retinopathy (DR) and risk of all-cause mortality, stroke and heart failure (HF).

The resources of meta-analysis of epidemiological observational studies were from Pub-med, EMBASE, CINAHL, Cochrane Library, conference, and proceedings.

Random/fixed effects models were used to calculate pooled subgroup analysis stratified by different grades of DR was performed to explore the potential source of heterogeneity. Statistical manipulations were undertaken using program STATA.

Of the included 25 studies, comprising 142,625 participants, 19 studies were concluded to find the relation of DR to all-cause mortality, 5 for stroke, and 3 for HF. Risk ratio (RR) for all-cause mortality with the presence of DR was 2.33 (95% CI 1.92–2.81) compared with diabetic individuals without DR. Evidences showed a higher risk of all-cause mortality associated with DR in patients with T2D or T1D (RR 2.25, 95% CI 1.91–2.65. RR 2.68, 95% CI 1.34–5.36). According to different grades of DR in patients with T2D, RR for all-cause mortality varied, the risk of nonproliferative diabetic retinopathy (NPDR) was 1.38 (1.11–1.70), while the risk of proliferative diabetic retinopathy (PDR) was 2.32 (1.75–3.06). There was no evidence of significant heterogeneity (Cochran Q test $P = 0.29$ vs 0.26, $I^2 = 19.6\%$ vs 22.6%, respectively). Data from 5 studies in relation to DR and the risk of stroke showed that DR was significantly associated with increased risk of stroke (RR = 1.74, 95%CI: 1.35–2.24), compared with patients without DR. Furthermore, DR (as compared with individuals without DR) was associated with a marginal increased risk of HF in patients with diabetes mellitus (DM) (n = 3 studies; RR 2.24, 95% CI 0.98–5.14, $P = 0.056$).

Our results showed that DR increased the risk of all-cause mortality, regardless of the different stages, compared with the diabetic individuals without DR. DR predicted increased risk of stroke and HF. Although only 3 studies about HF were available, the association between DR and HF should be careful.

Abbreviations: CI = confidence interval, DM = diabetes mellitus, DR = diabetic retinopathy, HF = heart failure, NPDR = nonproliferative diabetic retinopathy, PDR = proliferative diabetic retinopathy, RR = risk ratio.

Keywords: all-cause mortality, diabetic retinopathy, heart failure, stroke

1. Introduction

It has been proposed that the impact of diabetic retinopathy (DR) on vision is well known. There are more than 93 million patients with DR out of which 17 million have proliferative diabetic retinopathy (PDR).[1] In China, an estimated 40% (8% for vision-threatening retinopathy) of people with type 2 diabetes (T2D) and 86% (42%) with type 1 diabetes (T1D) have DR.[2] DR has been associated with an increased cardiovascular(CV) events risk in both T2D and T1D.[3,4]

Evidence from cohort studies of DR and risk of stroke and heart failure (HF) are controversial.[5–10] The mechanism by which DR might play a role in the physiology of stroke and HF in diabetes remains to be elucidated. Additionally, the association between DR and all-cause mortality in most studies has been examined by categorizing DR into dichotomous variable. There exists much uncertainty about relationship between different stages of DR and the risk of all-cause mortality.

Therefore, our study addresses an important gap in the published data. The aim of our study is to evaluate the risk of different stages of DR to the all-cause mortality, and to assess the association between DR and risk of all-cause mortality, stroke, and HF, by conducting an accumulated evidence of cohort studies.

2. Methods

Our research was performed in accordance with the recommendations of the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) and the Meta-analysis of Observational Studies in Epidemiology (MOOSE) statements.[11,12] And the ethical approval was not necessary because our meta-analysis was based on data from previously published studies.

2.1. Search strategy and selection criteria

PubMed, EMBASE, and the Cochrane Library were searched for researches to April, 2016, using the terms: "diabetic retinopathy" in combination with the following terms – "survival, mortality, heart failure, stroke, and cereo-vascular events." Further, complementary searches in the reference lists of selected articles were added. The supplementary strategy was implemented in addition to a manual search of proceedings of relevant conferences.

Studies were eligible to be included in the meta-analyses if they met the following criteria: a cohort study on the association between diabetic retinopathy or DR and risk of all-cause mortality, HF, and stroke. To be included, study results were presented as a risk ratio (RR) or hazard risk (HR) together with 95% confidence interval (CI), or enough data to perform their calculations, language of articles was limited to English.

2.2. Data synthesis and analysis

We used the results of the original studies from multivariable models with the most complete adjustment for potential confounders. We used the inverse variance weighted method to obtain overall hazard ratios and 95% CIs for an increase in risk of DR. A significant Q-statistic ($P < 0.10$) indicated heterogeneity across studies. Heterogeneity was quantified with the I^2 metric, which is independent of the number of studies in the systematic review.[13] The pooled RR was estimated using fixed effects (FEs, Mantel and Haenszel) and random effects (REs, DerSimonian and Laird) models. When there is heterogeneity between studies, the pooled RR was estimated using the random effects model.[14] Statistical manipulations were undertaken using program STATA (version 13.0, StataCorp LP, TX).

3. Results

3.1. Characteristics of the included studies

Of the 25 studies included (Fig. 1), comprising 142,625 participants, 19 studies were concluded to find the relation between DR to all-cause mortality (n=19,813, Table 1), and 5 studies about stroke (n=7727, Table 2), 3 studies about HF (n=117,451, Table 3).

3.2. DR and the risk of all-cause mortality

Analysis of 19 studies showed that the RR for all-cause mortality with the presence of DR was 2.33 (95% CI 1.92–2.81) compared with patients without DR in patients of diabetes mellitus (DM) (Fig. 2). This analysis was associated with significant heterogeneity (Cochran Q test $P = 0.001$, $I^2 = 69\%$). To explore the contribution of age, Hba1c at baseline to relation between DR and overall mortality, meta-regression showed a nonsignificance of age and Hba1c to DR ($P = 0.395$, $P = 0.907$).

Evidences of 14 observational studies were pooled to evaluate the risk of all-cause mortality associated with DR in patients with T2D, which demonstrated a higher risk of all-cause mortality (RR 2.25, 95% CI 1.91–2.65). There was marginal significance of heterogeneity (Cochran Q test $P = 0.041$, $I^2 = 43.7\%$).

DR was associated with a significant increase in the RR of all-cause mortality in patients with T1D based on meta-analysis of observational studies (n=5 studies; RR 2.68, 95% CI 1.34–5.36). The results were inconsistent across studies (Cochran Q test $P = 0.001$, $I^2 = 78.7\%$). In T1D studies, because of lack in data of the different stages of DR, DR is not categorized as nonproliferative diabetic retinopathy (NPDR) and PDR to assess risk for all-cause mortality.

According to different grades of DR in patients with T2D, RR for all-cause mortality varied as well, the risk of NPDR was 1.38 (1.11–1.70), PDR was 2.32 (1.75–3.06). There was no evidence of significant heterogeneity (Cochran Q test $P = 0.29$ vs 0.26, $I^2 = 19.6\%$ vs 22.6%, respectively).

3.3. DR and the risk of stroke

Data from 5 studies on DR and the risk of stroke were pooled. DR was associated with a significantly increased risk of stroke (RR=1.74, 95%CI 1.35–2.24), compared with patients without DR. The results were consistent across studies (Cochran Q test $P = 0.78$, $I^2 = 0\%$, Table 4).

3.4. DR and the risk of HF

DR (as compared with patients without DR) was marginally associated with a significant increase in the risk of HF in patients with DM (n=3 studies; RR 2.24, 95% CI 0.98–5.14, $P = 0.056$) (Fig. 3). There was a significant heterogeneity (Cochran Q test $P = 0.01$, $I^2 = 85.6\%$, Table 4).
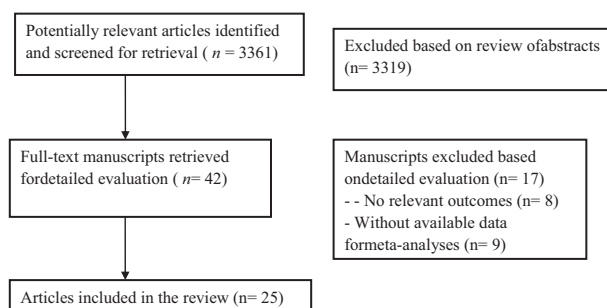


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Figure 1. Flow chart demonstrated those studies that were processed for inclusion in our meta-analysis.

Table 1

Characteristics of studies included in meta-analysis of associations of DR with risk of all-cause mortality.

Characteristics of study	First author	Publication year	Country	Numbers	Type of Diabetes	Mean follow-up, years	Endpoints	Diagnosis of DR
Cohort study	Ono [15]	2002	Japanese	223	T2D	11.6	All-cause mortality	Ophthalmologic records
Cohort study	Klein [16]	1999	Americans	1370	Older-onset diabetes	8.5	All-cause mortality	Fundus photography
Cohort study	van Leiden [17]	2003	Caucasian population	631	T2D	10.7	Cardiovascular; All-cause mortality	Fundus photography
Cohort study	Liew [18]	2009	Australian	199	T2D	12	CHD death	Fundus photography
Cohort study	Cheung[5]	2007	Americans	1456	T2D	7.8	Fatal CHD event	Fundus photography
Cohort study	Juutilainen [19]	2007	Finnish	828	T2D	18	All-cause mortality; CVD mortality; CHD mortality	Fundus photography
Cohort study	Sasaki [20]	1997	Japanese	1939	T1D	14.9	All-cause mortality	Not mentioned
Cohort study	Lovestam-Adrian [21]	2007	Swedish	363	T2D	10	Cardiovascular morbidity; all-cause mortality	Fundus photography
Cohort study	Sasaki [22]	1989	Japanese	1636	T2D	9.4	All-cause mortality	Not mentioned
Cohort study	Tong [23]	2007	Chinese	3261	T2D	3.4	All-cause mortality	Fundus photography
Cohort study	Kim [24]	2002		365	T2D		Death; myocardial infarction, cerebrovascular event	Direct ophthalmoscopy
Cohort study	Hanis [25]	1993	Americans	321	T1D	8	All-cause mortality	Direct ophthalmoscopy and fundus photography
Cohort study	Forsblom [26]	1998	European	134	T2D	9	All-cause mortality	Direct ophthalmoscopy and fluorescein angiography
Cohort study	Mottl [27]	2014	American	3210	T2D	4	Cardiovascular death	Fundus photography
Cohort study	Gimeno Orna [28]	2006	Spanish	458	T2D	8	Total mortality.	Direct ophthalmoscopy
Cohort study	Soedamah-Muthu [29]	2008	European	2787	T1D		All-cause mortality	Fundus photography
Cohort study	Klein[7]	2004	Americans	996	T1D	20	All-cause mortality	Fundus photography
Cohort study	Weis [30]	2001	Australians	147	T1D		All-cause mortality	Direct ophthalmoscopy
Cohort study	Torffvit [31]	2005	Swedish	462	T1D	12	Myocardial infarction angina, heart failure, death	Fundus photography
Cohort study	van Hecke [32]	2005	European	2237	T1D	7.5	All-cause mortality	Fundus photography

CHD = coronary heart disease, CVD = cardiovascular disease, DR = diabetic retinopathy, T1D = type 1 diabetes, T2D = type 2 diabetes.

Table 2

Characteristics of studies included in meta-analysis of associations of DR with risk of stroke.

Characteristics of Study	First author	Publication year	Country	Numbers	Type of diabetes	Mean follow-up, years	Endpoints	Diagnosis of DR
Cohort study	Cheung [5]	2007	Singapore	1617	T2D	7.8 (mean)	Stroke	Fundus photography
Cohort study	Kawasaki [6]	2013	Japanese	1620	T2D	8	Stroke	Direct ophthalmoscopy; fundus photography; fluorescein angiography
Cohort study	Petitti [33]	1995	Americans	2124	Diabetes	6	Stroke	Ophthalmologic records
Cohort study	Klein [7]	2004	Americans	996	T1D	20	Stroke	Fundus photography
Cohort study	Klein [16]	1999	Americans	1370	Older-onset diabetes	8.5	Stroke	Fundus photography

DR = diabetic retinopathy, T1D = type 1 diabetes, T2D = type 2 diabetes.

Characteristics of studies included in meta-analysis of associations of DR with risk of HF.

Characteristics of study	First author	Publication year	Country	Numbers	Type of diabetes	Mean follow-up, years	Endpoints	Diagnosis of DR
Cohort study	Cheung[8]	2008	Singapore	1021	T2D	8.9	HF	Fundus photography
Cohort study	Wong[9]	2005	Americans	627	Diabetes	6.2	HF	Fundus photography
Cohort study	Bertoni[10]	2004	Americans	115,803	Diabetes	5	HF	Not mentioned

DR = diabetic retinopathy, HF = heart failure, T2D = type 2 diabetes.
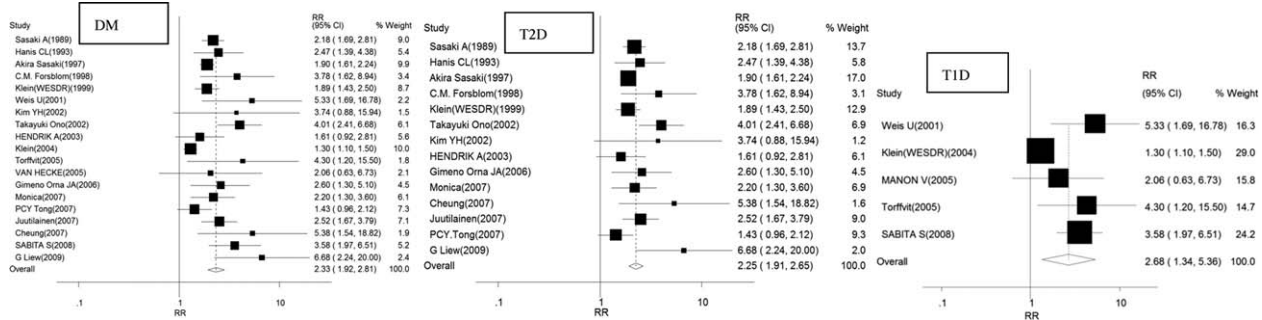

Figure 2. Risk ratios of all-cause mortality for DR in nineteen cohorts. 95% CI ■ (for each group) and ◇ (for all studies combined). Broken vertical line represents summary RR of the total pooled data. CI = confidence interval, DR = diabetic retinopathy, RR = risk ratio.

3.5. Publication bias

Funnel plots and the Egger regression test suggested a borderline significant asymmetry in the analysis of T2D ($P = 0.10$). However, the trim-and-fill computation revealed that there were no missing trials, indicating that the publication bias did not interfere with the interpretation of the results. There were no publication biases in analysis of T1D in both tests ($P = 0.21$).

The potential presence of publication bias was evaluated by a funnel plot of the estimate of log-RR. The Begger funnel plots

appeared symmetric. And there was no evidence of bias using the Egger method ($\tau = 1.94$, $P = 0.15$), as well as using the Begg test ($z = 1.85$, $P = 0.18$), suggesting that no publication bias was observed in this meta-analysis.

4. Discussions

There are limited prospective data on the relationship between DR and all-cause mortality, HF, or stroke. We conducted meta-analysis to evaluate the risk of DR in association with these

Meta-analysis of DR and risk of all-cause mortality, stroke, and HF.

Comparison	No of studies	Participants (N)	Pooled HR	Heterogeneity (I^2)
All-cause mortality	15 + 5	16,394 + 6629[*]	2.33 (1.92–2.81)	69.1%
Stroke	5	7727	1.74 (1.35–2.24)	0
HF	3	117,674	2.24 (0.98–5.14)	86.5%

DR = diabetic retinopathy, HF = heart failure, HR = hazard risk.
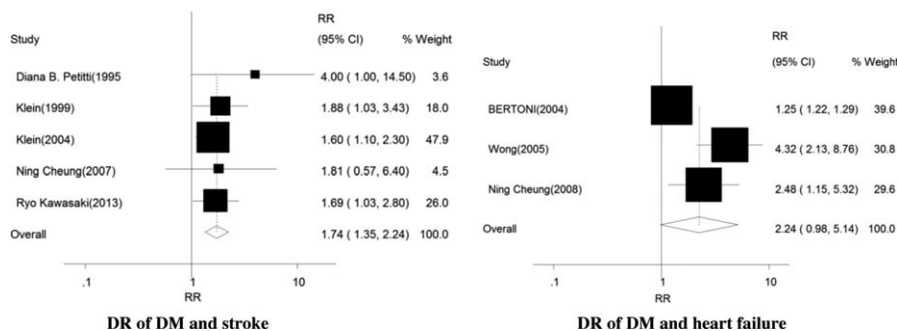[*] Indicated T2D + T1D.

Figure 3. Risk ratios for DR of stroke in 5 cohorts/heart failure in 3 cohorts. 95% CI ■ (for each group) and ◇ (for all studies combined). Broken vertical line represents summary RR of the total pooled data. CI = confidence interval, DR = diabetic retinopathy, RR = risk ratio.

events. Our results show that the different stages of DR were associated with the increase of risk of all-cause mortality in patients with T2D. DR was significantly associated with the rising risk of stroke in individuals with diabetes.

The novelty of our results indicated a graded relation between severity of DR and the risk of all-cause mortality in patients with T2D, which is indicative that PDR individuals have more risk factors than NPDR. Due to scarce data on T1D, analysis could not be performed. The association between DR and all-cause mortality has been noted to be of similar magnitude, regardless of diabetes type,[27,34] which is in accordance to our results in this paper (RR 2.68, 95% CI 1.34–5.36, in T1D; RR 2.25, 95% CI 1.91–2.65, in T2D).

The association between DR and HF was significant in this meta-analysis, although the significance was marginal ($P =$ 0.056). The mechanism by which DR might play a role in the pathophysiology of HF in DM remains to be elucidated. The key evidence is reduced coronary microcirculation leading to chronic myocardial ischemia, which is induced by lack of compensatory angiogenesis in response to myocardial remodeling.[35,36] Evidence indicated that individuals with DR were more likely to have left ventricular concentric remodeling, a precursor for HF (OR 1.72, 95% CI: 1.20–2.47).[37] Reports manifest that DR reflects diastolic cardiac dysfunction, which is indicative of HF.[38–40] Therefore, another explanation was that retinopathy simply lies along a continuum of disease that eventually leads to macrovascular damage and HF.[41]

Up to one-third of symptomatic strokes are major contributor of morbidity and mortality in diabetic individuals, they can be attributed to disease of the small cerebral arteries,[42] especially in folks with diabetes.[43] Due to the paucity of noninvasive tools to explore the cerebral microcirculation, relatively little is known about these arterioles pathologies.[44] Our findings showed that DR was significantly associated with the rising risk of stroke in characters with diabetes (pooled RR = 1.74, 95% CI 1.35–2.24). The feasible mechanism between DR and stroke might be that embryological origin, anatomical features, and physiological properties were shared.[45,46]

Vascular lesions in eyes with DR may mirror similar pathological disease processes in the cerebral microcirculation. Therefore, DR might demonstrate microvascular dysfunction not only in the retina but also in other organs such as heart and brain.[47] Our findings are in accordance with the concept that DR, stroke, and HF may have shared certain pathophysiological mechanisms.[48] Clearly, future studies are needed to verify this hypothesis and to perhaps uncover other noncirculatory backgrounds that could explain the risk of DR.

5. Limitation

The strengths of our meta-analysis are related to our extensive literature search and no evidence of publication bias. The quality of included studies was checked according to the Newcastle scale statement, and most of the included studies fulfilled all criteria. Nevertheless, some limitations should also be noted. First, possible limitation is that our adjusted meta-analyses undertaken were not ideal because the authors of the original studies used different statistical models. Second, we did not conduct different stages of DR for stroke and HF because of scarcity of data to classify DR. Furthermore, we did not perform sensitivity analyses or meta-regression to examine the contribution of participants' baseline characteristics (such as age, HbA1c, and duration of T2D) in assessing relationship between DR and stroke and HF.

Finally, none of the included studies were designed to explore association between DR and "target organ damage." Hence, any conclusions regarding hard outcomes, such as all-cause mortality, stroke, or HF, should be considered with caution.

6. Conclusions

The meta-analysis showed that DR was associated with increased risk for all-cause mortality, regardless of the different stages of DR, compared with the diabetic individuals without DR. DR increased the risk of stroke and HF. Only 3 studies about HF were available, the exact association between DR and HF needs further studies to clarify.

Acknowledgement

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