Int J Clin Exp Med 2018;11(12):12889-12901
www.ijcem.com /ISSN:1940-5901/IJCEM0067558

Review Article

Anti-diabetic medications and risk of macular edema in patients with type 2 diabetes: a systemic review and meta-analysis

Wei Zhu[1*], Yifang Meng[1*], Yan Wu[2*], Jiong Lu[1]

[1]Department of Ophthalmology, Changshu No.2 People's Hospital, Changshu, China; [2]Department of Ophthalmology, The First Affiliated Hospital to Soochow University, Suzhou, China. [*]Equal contributors.

Received October 19, 2017; Accepted March 1, 2018; Epub December 15, 2018; Published December 30, 2018

Abstract: Several kinds of anti-diabetic medications (ADMs) are recommended for treatment of type 2 diabetes mellitus (T2DM). Association between use of ADMs and risk of macular edema is currently unclear. We reviewed the literature to quantify the effect of ADMs on the incidence of macular edema. A comprehensive search was conducted in MEDLINE, EMBASE, and Web of Science up through May 2016. The data of AMDs use and incidence of macular edema were pooled in a meta-analysis. A total of 13 (8 cohort studies, 4 case-control studies, and 1 randomized-controlled trial) studies were included in this meta-analysis. Among all of the ADMs, insulin use increased macular edema risk (OR = 2.65; 95% CI = 1.70-4.14) whereas oral ADM intake was probably not associated with macular edema incidence (OR = 1.77; 95% CI = 0.93-3.37). The use of thiazolinedione (OR = 2.19; 95% CI = 1.49-3.21) and meglitinide (OR = 2.20; 95% CI = 1.15-4.20) were risk factors for macular edema and the use of sulfonylureas (OR = 0.83; 95% CI = 0.69-0.99) might be a protective factor while metformin (OR = 0.94; 95% CI = 0.79-1.13) demonstrated no significant effect. Use of rosiglitazone (OR = 3.12; 95% CI = 1.30-7.49) affected the incidence of macular edema. Our results show that insulin, meglitinide, and rosiglitazon will increase the risk of macular edema while sulfonylureas shows a prospective effect. A series of well-designed studies with large samples are required to confirm our existing conclusions.

Keywords: Type 2 diabetes mellitus, macular edema, risk factor, meta-analysis

Introduction

The number of patients with diabetes mellitus (T2DM), caused by insulin resistance with a relative insulin deficiency, is presumed to double by 2030 [1]. T2DM has caused enormous public health and economic loss, thus, it is currently one of the most challenging problems to all nations [2]. Diabetic retinopathy and/or diabetic macular edema are frequent and specific microvascular complications. Unlike diabetic retinopathy, which is usually asymptomatic in the early stage, macular edema is the leading cause of visual loss and legal blindness in patients with DM [3]. T2DM is usually treated with oral anti-diabetic medications (ADM) or insulin injection, however, there is currently no cure for DM. Several kinds of adverse effects including increased risk of cardiovascular mortality [4], hypoglycemia [5], and so forth [6] have been reported in ADM use. Coincidentally, ADM use is regarded to be associated with risk of macular edema. Except for longstanding diabetes, poor glycemic control, and presence of diabetic retinopathy and hypertension, insulin use is one of the risk factors of macular edema [7]. Besides, thiazolinedione (TZD) use, which is thought to be associated with risk of bladder cancer [8] and bone fracture [9], could modify risk of macular edema as reported by Idris I [10]. However, in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study with a total of 3537 participants, no association between TZD use and incidence of macular edema was detected [11]. At present, the relationship between ADM intake (including insulin injection and oral AMD) and incidence of macular edema is still unclear. Considering the limitations of preclinical researches about association between ADM use and risk of macular

edema and the absence of understanding of the pathogenesis of macular edema, a summary and quantitative synthesis of the existing clinical data would potentially provide important understanding.

Meta-analysis is an effective statistical tool in uncovering inconspicuous trends in a single study by pooling independent but similar research, increasing the level of confidence of the conclusions. Herein, we conducted a meta-analysis of all relevant studies to identify the association between ADM use and risk of macular edema.

Methods

Literature search and data extraction

This current meta-analysis was reported according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [12] and Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines [13]. A comprehensive search was conducted in MEDLINE, EMBASE, and Web of Science up through May 2016. The search terms ("hypoglycemic agents" OR "insulin" OR "thiazolidinediones" OR "pioglitazone" OR "rosiglitazone" OR "glitazone" OR "metformin" OR "sulfonylurea compounds") AND ("macular edema" OR "macular oedema") were obtained. References of relevant articles were detected for additional publications. No language restriction was set for this meta-analysis. Contacting corresponding authors was conducted when additional information was needed. Studies would be included in this meta-analysis when the following inclusion criteria were met: 1) a cohort, case-control, or randomized controlled trials (RCT) design; 2) evaluated the relationship between any ADM and risk of macular edema; 3) provided the odds ratios (ORs) or relative risks (RRs) or hazard ratios with 95% confidence intervals (CI), standard errors or sufficient data to calculate them.

The following data was extracted from each included study: name of the first author, study design, country where the study was conducted, study period, follow up time, amount of all participants, detailed settings of case and control groups, matching or adjusted items, and ORs with 95% CI evaluating the relationship between ADM use and risk of macular edema. When ORs were not provided in the studies, the initial data was obtained to evaluate them. The extractions were conducted by two reviewers (W. Zhu and Y. Wu), independently, and checked after the first extraction. Any disagreement regarding data extraction was resolved by the two reviewers.

Quality assessment

The methodological quality of each included study was also evaluated by two reviewers (W. Zhu and Y. Wu), independently. The Newcastle-Ottawa Quality Assessment Scale (NOS) was obtained for cohort and case-control studies [14] while the Cochrane collaboration tool was obtained for assessment of bias of the RCT [15]. NOS was used to evaluate selection, comparability, and outcome or expose cohort or case-control studies. The maximum score of NOS was 9* and studies with over 6* were considered to be of relatively higher quality. The Cochrane collaboration tool contains a total of 7 domains including random sequence generation, allocation concealment, blinding of participants, blinding of outcome assessment, follow up, selective reporting, and other bias.

Statistical analysis

The ORs and 95% CI were extracted or calculated from each study and then used in this quantitative meta-analysis. Expected heterogeneity of various study designs, case group settings, and population differences existed, so we used the random-effects model to calculate ORs through pooling the data together. Statistical heterogeneity among the included studies was evaluated by both X^2 and I^2 tests. When $P<0.1$ or $I^2>50\%$, heterogeneity was considered statistically significant. To detect possible sources of heterogeneity and deepen the understanding of association between ADM and risk of macular edema, subgroup analysis by study design, region, follow up duration, and adjustment status was also conducted. For oral ADM, relationship between each type of ADM use and risk of macular edema was detected independently and more detailed analyses were conducted on a certain drug (TZD in this study).

To detect the robustness of conclusions in this study, sensitivity analyses were conducted by two different methods. First, we conducted a

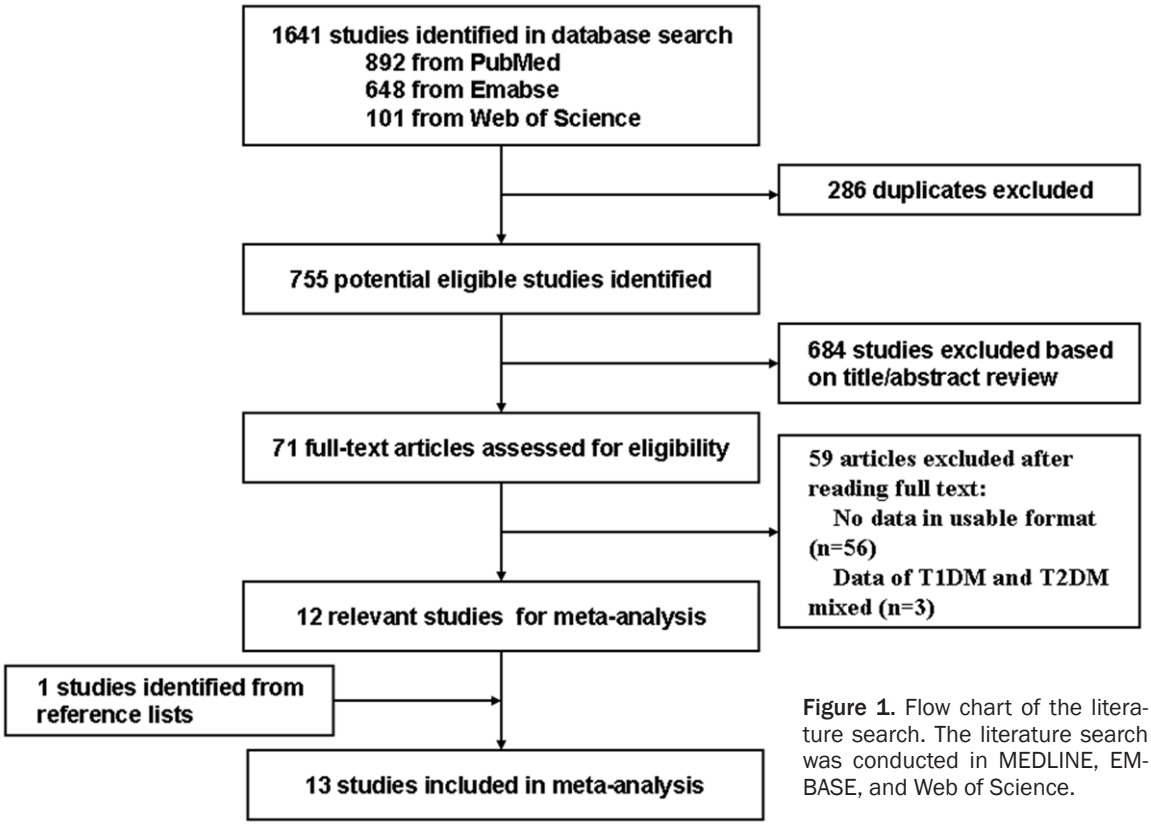

Figure 1. Flow chart of the literature search. The literature search was conducted in MEDLINE, EMBASE, and Web of Science.

sensitivity analysis by excluding the included studies one by one. Second, studies with relative poorer methodological quality (NOS scale <6*) were excluded from the meta-analysis. Potential publication bias was assessed through visually evaluating Begg's funnel plot and Egger's test. In this meta-analysis, all analyses were conducted using Stata software package (version 11.0; Stata Corp., College Station, TX).

Results

Search results and study characteristics

Figure 1 shows the flow diagram for selection of included studies. The initial 1,641 articles (892 from MEDLINE, 648 from Embase, and 101 from Web of Science) were identified through systemic search. After excluding 286 duplicates and 684 unrelated studies, 71 full-text articles were assessed for eligibility. Among the 59 excluded full-text articles, 56 studies provided unusable data and 3 studies were about both T1DM and T2DM. One more paper was identified from the reference lists and, ultimately a total of 13 studies were included in this meta-analysis [10, 16-27].

Detailed characteristics of included studies are shown in **Table 1**. A total of 305,809 individuals were included in this current meta-analysis. Among the 13 included studies, there were 8 cohort studies, 4 case-control studies, and 1 RCT. Ten studies demonstrated a prospective design and the remaining 3 studies demonstrated a retrospective design. Geographic distributions of the study sites were 5 studies in Europe, 6 studies in the America, and 2 studies in Asia. The follow up durations of included studies were different. The longest period was over 20 years while the shortest was less than 1 year. Among the 12 cohort or case-control studies, 8 studies showed a relative higher quality and the mean sacle of all the non-RCT studies was 6.41 (standard deviation: 1.56). The included RCT didn't show high risk of bias in any domain, according to the Cochrane collaboration tool.

Quantitative synthesis

Insulin use and macular edema: Meta-analysis of all relevant studies on the risk of macular edema in patients with T2DM, use of insulin

Table 1. Characteristics of included studies

Study, Publication yera	Country	Follow-up (year)	Sample size	Study design	Setting	Case group (Percentage of all participants)	Control group	Adjusted/matched	Study Quality*
Bertram B, 1997	German	<1	496	Cohort Prospective	Hospital based	Insulin (30.53%) Oral ADM (40.57)	Diet	NA	6
Leske MC, 2003	Barbados	4	410	Cohort Prospective	Population based	Insulin (2.92%) Oral ADM (46.10%)	Diet	NA	5
Klein R, 1995	USA	10	773	Cohort Prospective	Population based	Insulin (43.86%) Oral ADM (37.26%)	Diet	Age, sex, age of diagnosis, smoking, history of aspirin use, cardiovascular disease	8
Aroca PR, 2004	Spain	4	93	C-C Prospective	Hospital based	Insulin (NA)	No insulin	Age, sex, duration of DM	4
Romero-Aroca P, 2006	Spain	<1	132	Cohort Prospective	Hospital based	Insulin (35.36%) Oral ADM (63.63%)	Diet	Age, sex, duration of DM, arterial hypertension	7
Lee SJ, 2006	Korea	<1	496	C-C Prospective	Population based	Insulin (11.51%) Oral ADM (72.37%)	Diet	Age, sex, BMI, hypertension	5
Hirai FE, 2008	USA	20	2366	Cohort Prospective	Population based	Insulin (49.26%)	No insulin	Age, sex, BMI, HbAlc, CVD history, hypertension	8
Shen LQ, 2008	USA	3	282	C-C Retrospective	Hospital based	Rosiglitazone (43.97%)	No glitazone	Age, sex, race, duration of DM, HbA1c, blood pressure, use of antihypertensive drugs, pedal edema	7
Fong DS, 2009	USA	1	143257	Cohort Prospective	Population based	TZD (8.37%) Insulin, other oral ADM (NA)	No relevant drug	Age and HbA1c, and excludes patients without drug benefit, no eye exam and HbA1c<7.0	8
Home PD, 2009	International	7	4447	RCT Prospective	Population based	Metformin or sulfonylurea with rosiglitazone (49.92%)	Metformin and sulfonylurea	NR	-
Motola D, 2012	USA	4	49589	C-C Retrospective	Population based	Biguanides (26%), Ulfo-nylureas (22%), Exenatide (18%) TZDs (16%)	No relevant drug	NA	5
Idris I, 2012	UK	10	103368	Cohort Retrospective	Population based	TZD (3.12%)	No TZD	Age, sex, BMI, blood pressure, HbA1c, HDL, LDL	8
Arulanandham A, 2012	India	3	100	Cohort Prospective	Hospital based	TZD (50%)	No glitazone	NA	6

C-C: case-control; RCT: randomized-controlled trials; Y: year; M: month; ADM: anti-diabetic medication; TZD: thiazolinedione; NA: not available; DM: diabetes mellitus; BMI: body mass index; HDL: high densitv lipoprotein; LDL: low-density lipoprotein. *The study quality was assessed by the Newcastle-Ottawa Quality Assessment Scale (nine stars).

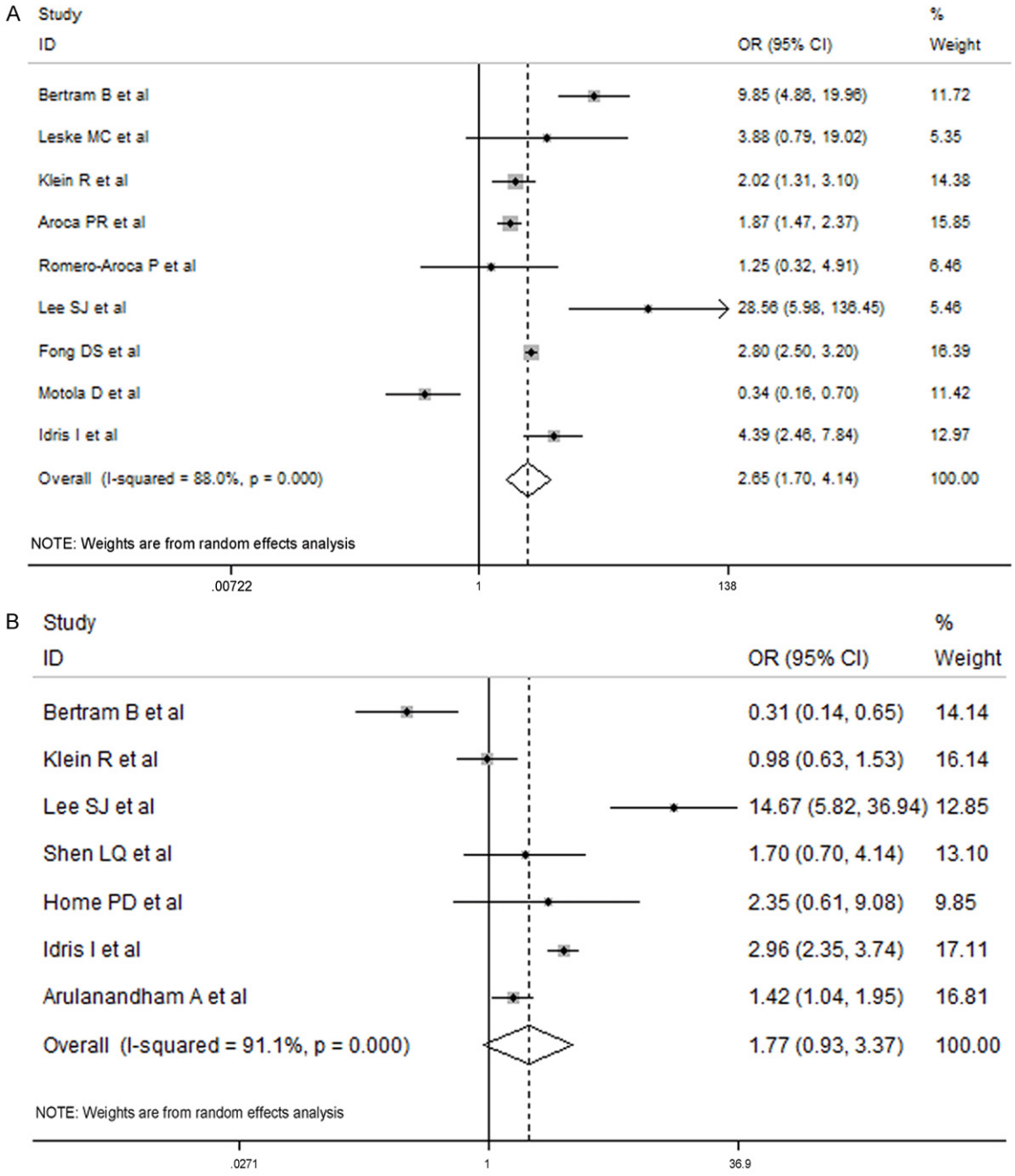

Figure 2. A. Forest plot of the association between insulin use and risk of macular edema. B. Forest plot of the association between oral anti-diabetic medications use and risk of macular edema.

showed certain relation with risk of macular edema (OR = 2.65; 95% CI = 1.70-4.14; $P<0.001$) (**Figure 2A**). This result was permanent across different study designs, follow up periods, and adjusted status of DM duration and HbA1c. However, significant heterogeneity was detected ($I^2 = 88.0\%$; $P<0.001$). A subgroup analysis was conducted to avoid the influence of inter-study heterogeneity (**Table 2**). Association between insulin use and risk of macular edema was not significant when retrospective studies (1.23 [0.10 to 15.15]), hospital based studies (2.99 [0.87 to 10.34]), and studies in America (1.57 [0.70 to 3.54]) were summarized. The entities of different study designs and geographic and ethnic differences could contribute

Table 2. Summary RRs of subgroup analyses of the effects of insulin or oral ADM on the incidence of macular edema*

Subgroups	Insulin					Oral ADM				
	N	OR	95% CI	Heterogeneity		N	OR	95% CI	Heterogeneity	
				P	I^2				*P*	I^2
Study design										
Cohort	6	**3.34**	**2.15-5.15**	**0.003**	**72.3**	4	1.13	0.53-2.40	**0**	**93.8**
C-C	3	**2.21**	**1.83-4.06**	**0**	**93.6**	2	4.97	0.60-41.15	**0.001**	**90.8**
RCT	0					1	2.35	0.60-41.15	**0**	**91.1**
Setting										
Prospective	7	**3.14**	**2.07-4.75**	**0**	**82.4**	5	1.61	0.66-3.96	**0**	**90.8**
Retrospective	2	1.23	0.10-15.15	**0**	**96.5**	2	**2.67**	**1.73-4.10**	0.235	29.1
Setting										
Population	6	**2.56**	**1.32-4.99**	**0**	**88.6**	4	**3.01**	**1.19-7.61**	**0**	**86.2**
Hospital	3	2.99	0.87-10.34	**0**	**86.7**	3	0.91	0.34-2.46	**0**	**90.9**
Region										
Europe	4	**3.38**	**1.43-7.9**	**0**	**87.8**	3	1.27	0.25-6.45	**0**	**93.8**
America	4	1.57	0.70-3.54	**0**	**88**	2	1.12	0.71-1.78	0.281	13.9
Asia	1	**28.56**	**5.98-138.45**	-	-	2	4.38	0.45-43.02	**0**	**95.5**
Follow-up										
<10 Y	7	**2.6**	**1.46-4.63**	**0**	**90.3**	5	1.85	0.63-5.37	**0**	**90.3**
>10 Y	2	**2.9**	**1.38-6.21**	**0.035**	**77.6**	2	1.73	0.59-5.13	**0**	**94.6**
DM duration										
Adjusted	2	**1.85**	**1.46-2.33**	0.569	0	1	1.7	0.70-4.14	**0**	**91.1**
Non-adjusted	7	**3.17**	**1.68-6.01**	**0**	**87.8**	6	1.79	0.83-3.65	**0**	**92.6**
HbA1c										
Adjusted	2	**3.2**	**2.14-4.77**	0.137	54.8	2	2.67	1.73-4.10	0.235	29.1
Non-adjusted	7	**2.57**	**1.21-5.47**	**0**	**88.9**	5	1.61	0.66-3.95	**0**	**90.8**

ADM: anti-diabetic medication. *The results which were statistically significant were in bold.

to the result of non-significant association in the three subgroups above. The differential results of subgroup analysis might also partially explain the source of heterogeneity in this meta-analysis. However, heterogeneity in most subgroup analysis was statistically significant except the two adjusted subgroups. However, use of insulin was also significantly associated with risk of macular edema and the pooled OR value of 3 independent studies was 2.61 (95% CI = 1.67-4.06).

Oral ADM and macular edema: The pooled data of 7 studies demonstrated that oral ADM was not associated with risk of macular edema (OR = 1.77; 95% CI = 0.93-3.37) as shown in **Figure 2B**. However, significant heterogeneity was detected (I^2 = 91.1%, P<0.001) as well. Detailed results of subgroup analysis are presented in **Table 2**. In general, subgroup meta-analysis demonstrated no significant results, however, results of the pooled data are: from retrospective studies (OR = 2.67; 95% CI = 1.73-4.10), population based studies (OR = 3.01; 95% CI = 1.19-7.61), and studies adjusted for HbA1c (OR = 2.67; 95% CI = 1.73-4.10). Three subgroups showed non-significant heterogeneity and detailed results are presented in **Table 2**.

When types of oral ADM were considered, the use of TZD (OR 2.19; [95% CI 1.49 to 3.21]) and meglitinide (OR = 2.20; 95% CI = 1.15-4.20) were risk factors for macular edema, use of sulfonylureas (OR = 0.83; 95% CI = 0.69-0.99) might be a protective factor while metformin (OR = 0.94; 95% CI = 0.79-1.13), and acarbose (OR = 1.30; 95% CI = 0.92-1.84) use were unrelated with risk of macular edema (**Figure 3**). However, except for the TZD, the number of studies about the remaining 4 ADM was quite limited (1 or 2), therefore, the results should be considered with caution.

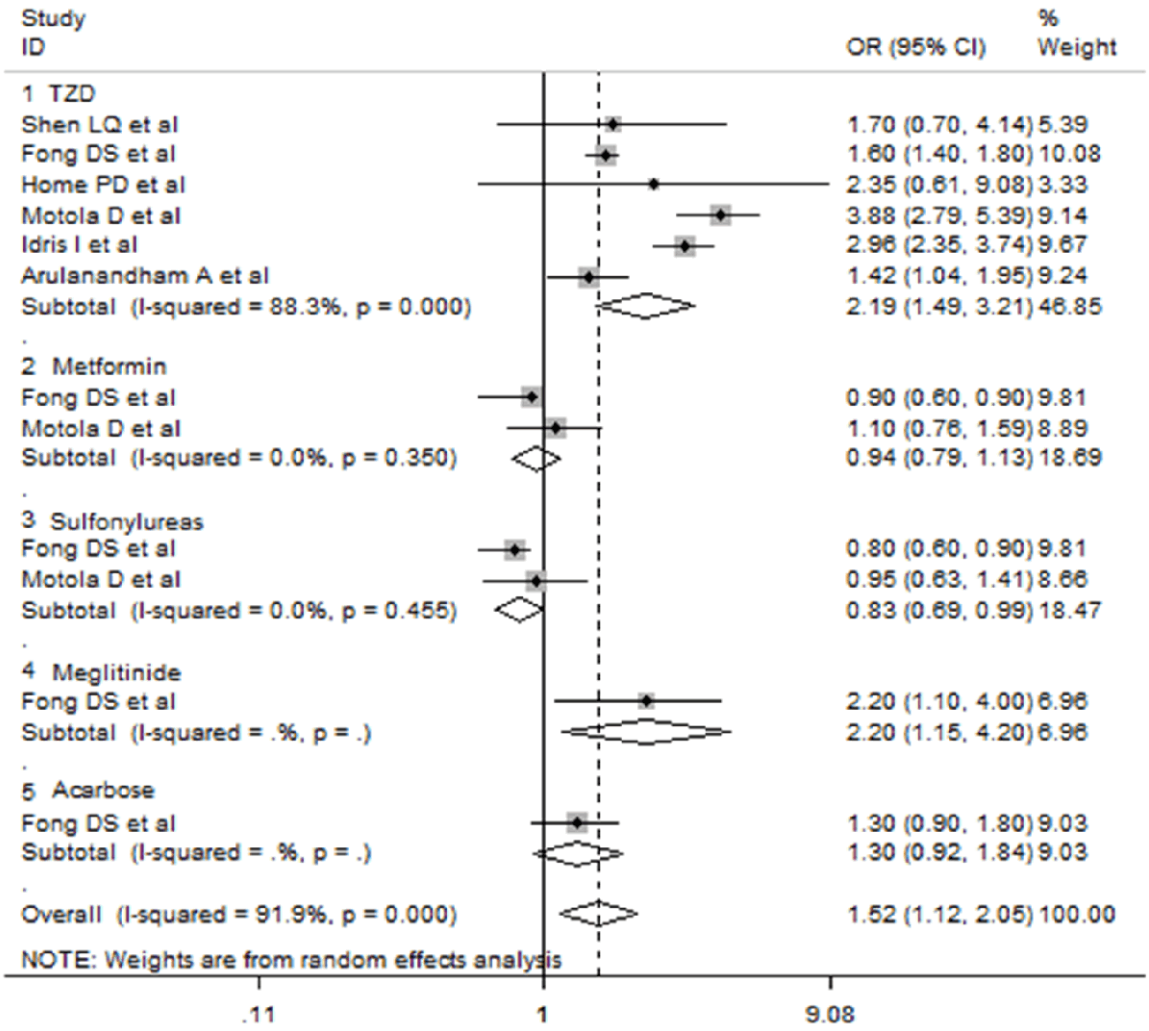

Figure 3. Subgroup analyses by the types of the oral anti-diabetic medications. Associations between the types of the medications (TZD, meglitinide, sulfonylureas, metformin, and acarbose) and risk of macular edema are presented. The size of the shaded square is proportional to the percent weight o f each study. TZD: thiazolinedione.

Since data regarding the use of TZD and risk of macular edema was relatively more abundant, subgroup analysis was conducted. TZD use was associated with risk of macular edema in both cohort (OR = 1.90; 95% CI = 1.24-2.90]) and case-control studies (OR = 2.88; 95% CI = 1.31-6.25), while association was not significant in RCT (OR = 2.35; 95% CI = 0.81-9.08) (**Figure 4A**). Through advanced analyses, it was the use of rosiglitazone (OR = 3.12; 95% CI = 1.30-7.49) rather than the use of pioglitazone (OR = 1.72; 95% CI = 0.65-4.55) that affected the incidence of macular edema. Significant heterogeneity was detected in each subgroup in the stratified analyses of TZD use and risk of macular edema.

Sensitivity analysis and publication bias

After included studies in this meta-analysis were excluded one by one, association between insulin or oral ADM use and risk of macular edema was not statistically altered. Meanwhile, after removing studies with relatively poor methodological quality, the pooled ORs about insulin and oral ADM use were 3.32 (95% CI = 2.09-5.27) and 1.302 (95% CI = 0.71-2.40), respectively.

No significant publication bias was found in the effect of insulin use (Egger's test, $P = 0.967$) and oral ADM (Egger's test, $P = 0.688$) on the risk of macular edema. **Figures 5** and **6** show

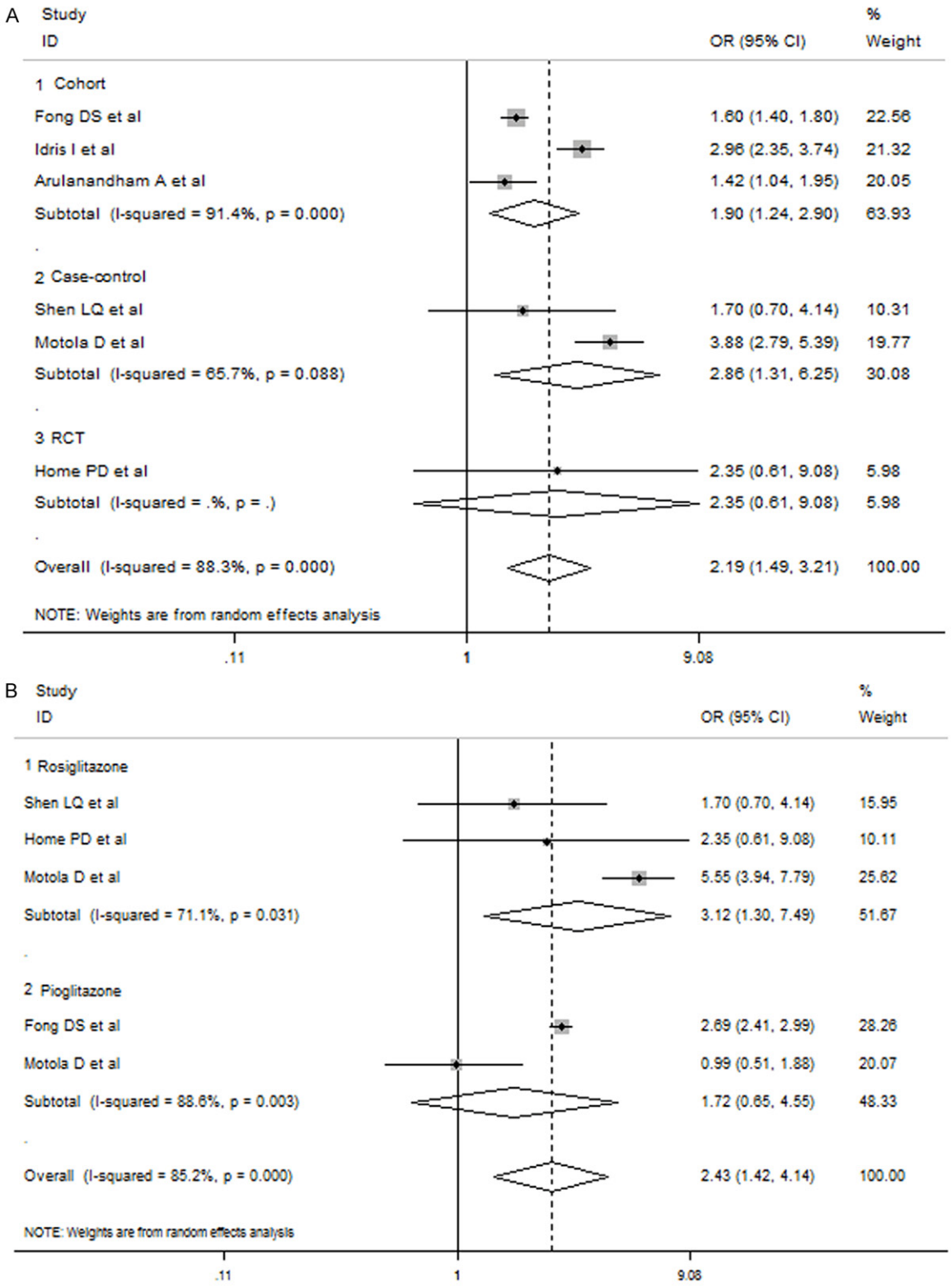

Figure 4. Subgroup analyses of the association between TZD use and risk of macular edema. A. Subgroup analyses stratified by the study designs (cohort, case-control, and RCT). B. Subgroup analyses stratified by the subtypes of the TZD (rosiglitazone and pioglitazone). TZD: thiazolinedione; RCT: randomized-controlled trials.

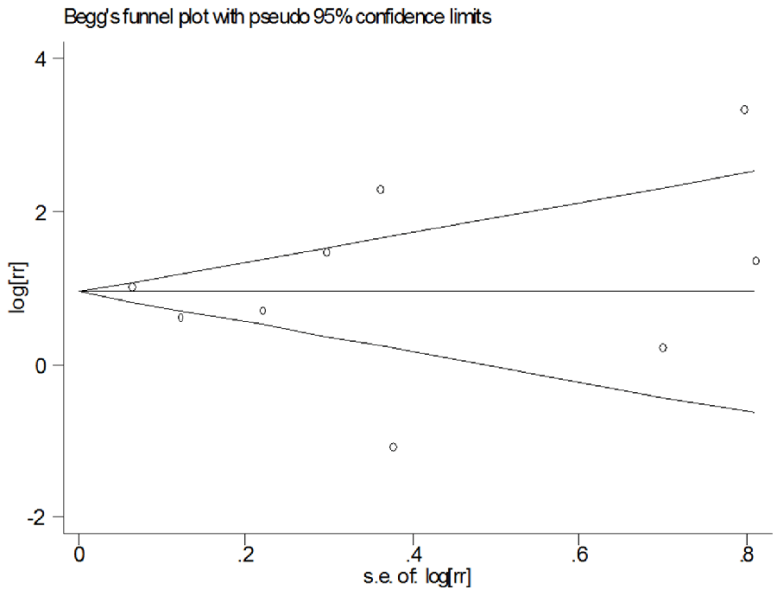

Figure 5. Funnel plot showing insulin use and risk of macular edema. On the Y axis, the log relative risk (RR) are shown for each trial; on the X axis, the standard error (SE) for each log relative risk is shown as a proxy for study size.

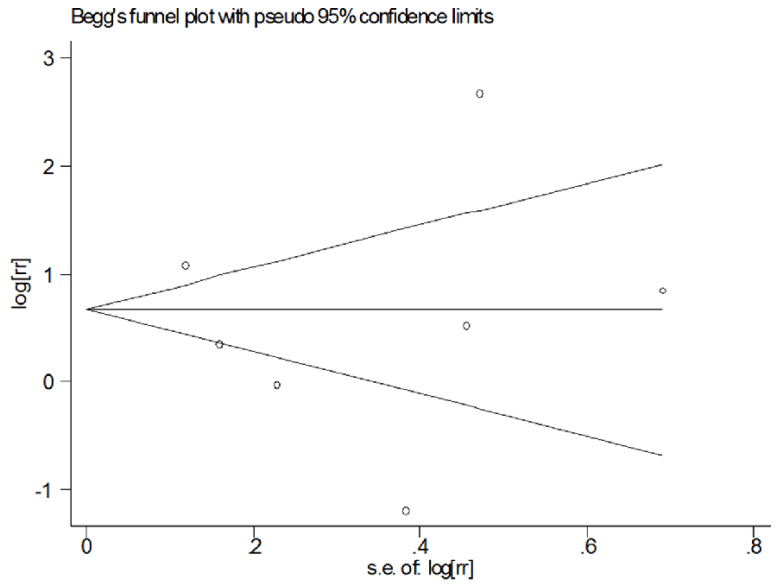

Figure 6. Funnel plot showing TZD use and risk of macular edema. On the Y axis, the log relative risk (RR) are shown for each trial; on the X axis, the standard error (SE) for each log relative risk is shown as a proxy for study size.

that, by funnel plot, no publication bias was detected.

Conclusions

In this current meta-analysis, enrolling 13 independent studies on the association between ADM use and risk of macular edema, we found that insulin use shows over 2.5 times increased association with incidence of macular edema whereas oral ADM intake is probably not associated with macular edema incidence. Among oral AMDs, TZD and meglitinide are associated with double increase in the risk of macular edema while sulfonylureas use is associated with a fifth reduction in that. However, the relatively lacking number of included studies on ADM subtypes (apart from the TZD) weakens the stability of our conclusions. According to advanced subgroup analysis, among the TZD subtypes, it is the use of rosiglitazone rather than the use of pioglitazone that modifies incidence of macular edema. The robustness of the conclusions in this current meta-analysis is proven by sensitivity analysis through two independent methods. Furthermore, there was no significant publication bias detected in any of the analyses.

In this meta-analysis, we found that insulin use is associated with risk of macular edema., however, the association is not significant in respective (number of studies = 2), hospital based (number of studies = 3) studies, and studies in America (n = 4). The difference in respective and hospital based studies might be explained by the relative poorer methodological quality and shortage in the amount of included studies. Geographic and ethnic differences might partly explain the non-significant association in subgroup analysis of studies in America.

Insulin use has been regarded as a risk factor of macular edema by several large sample cohort studies [10, 24], consistent with this meta-analysis. However, the understanding of etiological and physiopathological mechanisms of insulin in the incidence of macular edema is not completely clear. We hypothesize that insulin use is more frequently adopted by patients with longer duration of DM and poorer glycemic control, which are risk factors for macular edema. However, even intensive insulin therapy is associated with long-term benefits in the prevention and control of diabetic retinopathy. Several studies have demonstrated that in the first two years after initiation of intensive insulin therapy, diabetic retinopathy would transiently worsen. Macular edema, as a more rapid complication, is significantly associated with the severity of diabetic retinopathy [18] and the early worsening effect couldn't be excluded from possible contribution on the development and progression of macular edema. When physiopathological mechanisms are considered, insulin could influence retinal blood flow, angiogenesis, and vascular tone, perhaps modifying the risk of macular edema [28]. Besides, insulin use could induce the expression of vascular endothelial growth factor (VEGF) and insulin and insulin-like growth factor-1 (IGF-1) [29, 30]. VEGF could break down the blood-retina barrier and effect central subfield thickness measurements [31, 32]. IGF-1 might not be associated with the progression of macular edema directly but it could have an effect through inducing expression of VEGF [31, 33].

In general, oral ADM may not be associated with risk of macular edema, according to our meta-analysis. However, each kind of oral ADM has a specific effect. TZD is the most frequently discussed to be associated with risk of macular edema. Several cases reports of macular edema induced by TZD use have been reported [34, 35] while a further case reported a spontaneous resolution of CSME and visual acuity improvement on discontinuation of TZD [36]. However, the following retrospective analyses of patients with T2DM tend to exclude association between TZD use and risk of macular edema or central subfield retinal thickness of [37, 38]. The conclusions of these studies were suggestive, limited by the retrospective and small sample size. In 2009, a prospective cohort study with over 100,000 participants demonstrated that TZD use would modify risk of macular edema [24]. This conclusion is confirmed by this current meta-analysis. However, in our meta-analysis, we found that only rosiglitazone use affected as a modifier. It was pretty interesting and potentially important and should be further studied by advanced studies. To our knowledge, no specialized designed studies on the effect of other oral ADMs have been identified. Summarizing all of the existing data, meglitinide and sulfonylureas have shown harmful and protective effects, respectively. The results were quite questionable considering the absence of adequate study numbers, however, some significant suggestions regarding association between oral ADMs and macular edema are provided in this meta-analysis.

The independent etiological and physiopathological mechanisms of oral ADMs on risk of macular edema were insufficient. Use of TZD, regarded as a risk factor of macular edema, could induce edema as well. This side effect might contribute to the development of macular edema. Furthermore, induced VEGF expression in TZD users could partially explain the mechanism [39]. Considering the lack of attention on other oral ADMs on macular edema, relevant preclinical studies are absent. A series of laboratory studies are needed, perhaps providing a new view of the issues.

To the best of our knowledge, this is the first meta-analysis identifying association between ADMs and risk of macular edema. Strengths of this meta-analysis include the comprehensive search of literatures and simultaneous assessment of all ADMs (including insulin and oral ADMs) on risk of macular edema. Comprehensive search of literatures and a detailed check of the relevant references provide an integral inclusion of all possible studies. Through analyzing the effect of all ADMs, the difference between the effects of insulin use and oral ADMs on risk of macular edema was identified. Furthermore, the respective role of each subtype of ADMs was also studied and our understanding was further detailed.

However, there are several limitations of our meta-analysis. First, as the effects of oral ADM subtypes are different, pooling subtypes together might result in certain heterogeneity. We adopted oral ADM as an independent influ-

encing factor because the oral ADM is a term independent of insulin injection and the effect of oral ADM on risk macular edema were reported in several studies. Insulin use is now regarded as a risk factor of macular edema. This is meaningful in studying the modifying effects of oral ADMs. In this meta-analysis, effects of the subtypes of oral ADMs were studied as well and, thus, the analysis is abundant and complete. Second, as we know, the RCT design could exclude potential biases and get confident conclusions. However, in this meta-analysis, only 1 RCT was identified through a comprehensive search of the literature. Besides, in the only RCT, incidence of macular edema was not included in the main outcomes and it would provide less persuasive results. Well-designed RCTs reporting the association of ADMs and risk of macular edema are wanted, intensively. Third, although adequate studies were included in this meta-analysis, the sample sizes of some of the included studies were insufficient and the results may be unreliable.

In conclusion, insulin use is a risk factor of macular edema while oral ADM use isn't a modifying factor. Rosiglitazon, a subtype of TZDs, is associated with increased risk of macular edema. The effects of other types of oral ADMs were specified and the results should be considered with great caution. Considering the existing limitations of this meta-analysis, a series of well-designed studies with large samples are required to confirm the existing conclusions.

Acknowledgements

This work was supported in whole or in part by the National Science Foundation for Young Scientists of China (Grant No. 81700804), Foundation for Young Scholars of Suzhou, China (Grant No. kjxw2015044), and Foundation for Young Medical Talents of Jiangsu Province, 2016, (Grant No. QNRC2016211). The sponsors and funding organizations had no role in the design or conduct of this research.

Disclosure of conflict of interest

None.

Abbreviations

ADM, anti-diabetic medications; T2DM, type 2 diabetes mellitus; RCT, randomized controlled study; OR, odds ratio; RR, relative risk; IGF-1, insulin-like growth factor-1; TZD, thiazolinedione; NOS, Newcastle-Ottawa Scale; VEGF, vascular endothelial growth factor.

Address correspondence to: Jiong Lu, Department of Ophthalmology, Changshu No.2 People's Hospital, Changshu, China. E-mail: cslujiong@163.com

References

[1] Hayes J, Anderson R and Stephens JW. Sitagliptin/metformin fixed-dose combination in type 2 diabetes mellitus: an evidence-based review of its place in therapy. Drug Des Devel Ther 2016; 10: 2263-2270.

[2] Li R, Xing J, Mu X, Wang H, Zhang L, Zhao Y and Zhang Y. Sulodexide therapy for the treatment of diabetic nephropathy, a meta-analysis and literature review. Drug Des Devel Ther 2015; 9: 6275-6283.

[3] Vos RC, van Avendonk MJ, Jansen H, Goudswaard AN, van den Donk M, Gorter K, Kerssen A and Rutten GE. Insulin monotherapy compared with the addition of oral glucose-lowering agents to insulin for people with type 2 diabetes already on insulin therapy and inadequate glycaemic control. Cochrane Database Syst Rev 2016; 9: CD006992.

[4] Wang HB, Zeng P, Yang J, Yang J and Liu XW. Paclitaxel-eluting stents versus sirolimus-eluting stents in patients with diabetes mellitus undergoing percutaneous coronary intervention: a systematic review and meta-analysis of randomized controlled trials. Intern Emerg Med 2016; 11: 1005-13.

[5] Lee AK, McEvoy JW, Hoogeveen RC, Ballantyne CM and Selvin E. Severe hypoglycemia and elevated high-sensitivity cardiac troponin T in older adults with diabetes: the ARIC study. J Am Coll Cardiol 2016; 68: 1370-1371.

[6] DeWitt DE and Hirsch IB. Outpatient insulin therapy in type 1 and type 2 diabetes mellitus: scientific review. JAMA 2003; 289: 2254-2264.

[7] Kendall C and Wooltorton E. Rosiglitazone (Avandia) and macular edema. CMAJ 2006; 174: 623.

[8] Mamtani R, Haynes K, Bilker WB, Vaughn DJ, Strom BL, Glanz K and Lewis JD. Association between longer therapy with thiazolidinediones and risk of bladder cancer: a cohort study. J Natl Cancer Inst 2012; 104: 1411-1421.

[9] Colhoun HM, Livingstone SJ, Looker HC, Morris AD, Wild SH, Lindsay RS, Reed C, Donnan PT, Guthrie B, Leese GP, McKnight J, Pearson DW, Pearson E, Petrie JR, Philip S, Sattar N, Sullivan FM and McKeigue P. Hospitalised hip fracture risk with rosiglitazone and pioglitazone

use compared with other glucose-lowering drugs. Diabetologia 2012; 55: 2929-2937.
[10] Idris I, Warren G and Donnelly R. Association between thiazolidinedione treatment and risk of macular edema among patients with type 2 diabetes. Arch Intern Med 2012; 172: 1005-1011.
[11] Ambrosius WT, Danis RP, Goff DC Jr, Greven CM, Gerstein HC, Cohen RM, Riddle MC, Miller ME, Buse JB, Bonds DE, Peterson KA, Rosenberg YD, Perdue LH, Esser BA, Seaquist LA, Felicetta JV, Chew EY; ACCORD Study Group. Lack of association between thiazolidinediones and macular edema in type 2 diabetes: the ACCORD eye substudy. Arch Ophthalmol 2010; 128: 312-318.
[12] Moher D, Liberati A, Tetzlaff J and Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ 2009; 339: b2535.
[13] Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, Moher D, Becker BJ, Sipe TA and Thacker SB. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis of observational studies in epidemiology (MOOSE) group. JAMA 2000; 283: 2008-2012.
[14] Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol 2010; 25: 603-605.
[15] Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, Savovic J, Schulz KF, Weeks L and Sterne JA. The cochrane collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011; 343: d5928.
[16] Bertram B. [Prevalence of patients with diabetes mellitus without and with retinopathy in an ophthalmology practice]. Ophthalmologe 1997; 94: 401-404.
[17] Leske MC, Wu SY, Hennis A, Nemesure B, Hyman L and Schachat A. Incidence of diabetic retinopathy in the Barbados eye studies. Ophthalmology 2003; 110: 941-947.
[18] Klein R, Klein BE, Moss SE and Cruickshanks KJ. The Wisconsin epidemiologic study of diabetic retinopathy. XV. The long-term incidence of macular edema. Ophthalmology 1995; 102: 7-16.
[19] Aroca PR, Salvat M, Fernandez J and Mendez I. Risk factors for diffuse and focal macular edema. J Diabetes Complications 2004; 18: 211-215.
[20] Romero-Aroca P, Fernandez-Ballart J, Almena-Garcia M, Mendez-Marin I, Salvat-Serra M and Buil-Calvo JA. Nonproliferative diabetic retinopathy and macular edema progression after phacoemulsification: prospective study. J Cataract Refract Surg 2006; 32: 1438-1444.
[21] Lee SJ and Choi MG. Association of manganese superoxide dismutase gene polymorphism (V16A) with diabetic macular edema in Korean type 2 diabetic patients. Metabolism 2006; 55: 1681-1688.
[22] Hirai FE, Knudtson MD, Klein BE and Klein R. Clinically significant macular edema and survival in type 1 and type 2 diabetes. Am J Ophthalmol 2008; 145: 700-706.
[23] Shen LQ, Child A, Weber GM, Folkman J and Aiello LP. Rosiglitazone and delayed onset of proliferative diabetic retinopathy. Arch Ophthalmol 2008; 126: 793-799.
[24] Fong DS and Contreras R. Glitazone use associated with diabetic macular edema. Am J Ophthalmol 2009; 147: 583-586 e581.
[25] Home PD, Pocock SJ, Beck-Nielsen H, Curtis PS, Gomis R, Hanefeld M, Jones NP, Komajda M and McMurray JJ. Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): a multicentre, randomised, open-label trial. Lancet 2009; 373: 2125-2135.
[26] Motola D, Piccinni C, Biagi C, Raschi E, Marra A, Marchesini G and Poluzzi E. Cardiovascular, ocular and bone adverse reactions associated with thiazolidinediones: a disproportionality analysis of the US FDA adverse event reporting system database. Drug Saf 2012; 35: 315-323.
[27] Arulanandham A, Raju A, Pradeep Rajkumar L, Lakshminarayanan B, Gayathri T and Bothiraj B. Prevalence of clinically significant macular edema [CSME] among glitazone users and non-users of type-2 DM patients with diabetic retinopathy. Int J Drug Dev & Res 2012; 4: 132-137.
[28] Anfossi G, Russo I, Doronzo G and Trovati M. Relevance of the vascular effects of insulin in the rationale of its therapeutical use. Cardiovasc Hematol Disord Drug Targets 2007; 7: 228-249.
[29] Poulaki V, Qin W, Joussen AM, Hurlbut P, Wiegand SJ, Rudge J, Yancopoulos GD and Adamis AP. Acute intensive insulin therapy exacerbates diabetic blood-retinal barrier breakdown via hypoxia-inducible factor-1alpha and VEGF. J Clin Invest 2002; 109: 805-815.
[30] Merante D, Menchini F, Truitt KE and Bandello FM. Diabetic macular edema: correlations with available diabetes therapies--evidence across a qualitative review of published literature from MEDLINE and EMBASE. Drug Saf 2010; 33: 643-652.
[31] Hartnett ME, Tinkham N, Paynter L, Geisen P, Rosenberg P, Koch G and Cohen KL. Aqueous vascular endothelial growth factor as a predictor of macular thickening following cataract

surgery in patients with diabetes mellitus. Am J Ophthalmol 2009; 148: 895-901 e891.
[32] Querques G, Lattanzio R, Querques L, Del Turco C, Forte R, Pierro L, Souied EH and Bandello F. Enhanced depth imaging optical coherence tomography in type 2 diabetes. Invest Ophthalmol Vis Sci 2012; 53: 6017-6024.
[33] Josifova T, Schneider U, Henrich PB and Schrader W. Eye disorders in diabetes: potential drug targets. Infect Disord Drug Targets 2008; 8: 70-75.
[34] Nyssen V, Hautenauven F, Lekeu Hinostroza JP and Guagnini AP. [Diabetic edematous maculopathy associated with rosiglitazone treatment: report of a case]. Bull Soc Belge Ophtalmol 2009; 39-44.
[35] Oshitari T, Asaumi N, Watanabe M, Kumagai K and Mitamura Y. Severe macular edema induced by pioglitazone in a patient with diabetic retinopathy: a case study. Vasc Health Risk Manag 2008; 4: 1137-1140.
[36] Liazos E, Broadbent DM, Beare N and Kumar N. Spontaneous resolution of diabetic macular oedema after discontinuation of thiazolidenediones. Diabet Med 2008; 25: 860-862.
[37] Tatti P, Arrigoni F, Longobardi A, Costanza F, Di Blasi P and Merante D. Retrospective analysis of rosiglitazone and macular oedema in patients with type 2 diabetes mellitus. Clin Drug Investig 2008; 28: 327-332.
[38] Tarbett AK, VanRoekel RC, Howard RS and Vigersky RA. The use of optical coherence tomography to determine the effect of thiazolidinediones on retinal thickness in patients with type 2 diabetes. J Diabetes Sci Technol 2011; 5: 945-951.
[39] Emoto M, Anno T, Sato Y, Tanabe K, Okuya S, Tanizawa Y, Matsutani A and Oka Y. Troglitazone treatment increases plasma vascular endothelial growth factor in diabetic patients and its mRNA in 3T3-L1 adipocytes. Diabetes 2001; 50: 1166-1170.