Insulin Use and Risk of Diabetic Macular Edema in Diabetes Mellitus: A Systemic Review and Meta-Analysis of Observational Studies

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Background: Diabetes mellitus is a common and serious disorder. A search of the literature reveals no comprehensive quantitative assessment of the association between insulin use and incidence of diabetic macular edema. Therefore, we performed a meta-analysis of observational studies to evaluate the effect of insulin use on the risk of developing macular edema.

Material/Methods: Comparative studies published until May 2014 were searched through a comprehensive search of the Medline, Embase, and the Cochrane Library electronic databases. A systematic review and quantitative analysis of comparative studies reporting the effect of insulin use on the incidence of macular edema was performed. All analyses were performed using the Review Manager (RevMan) v.5 (Nordic Cochrane Centre, Copenhagen, Denmark).

Results: A total of 202 905 individuals were included in the present meta-analysis. In a random-effects meta-analysis, the use of insulin was found to be associated with increased risk of macular edema (RR, 3.416; 95% CI, 2.417–4.829; I^2, 86.6%). Analysis that just included high-quality studies showed that insulin use increased the risk of macular edema (RR, 2.728; 95% CI, 1.881–3.955; I^2=77.7%). In cohort studies (RR, 4.509; 95% CI, 3.100–6.559; I^2, 77.7%) but not in case-control studies (RR, 1.455; 95% CI, 0.520 to 4.066; I^2, 95.9%), increased incidence of macular edema was observed.

Conclusions: The results of this meta-analysis of observational studies demonstrate that insulin use is a risk factor for diabetic macular edema. However, available data are still sparse, and in-depth analyses of the assessed associations in the context of additional longitudinal studies are highly desirable to enable more precise estimates and a better understanding of the role of insulin use in incidence of diabetic macular edema.

MeSH Keywords: Case-Control Studies • Cohort Studies • Insulins • Insulins • Macular Edema • Meta-Analysis

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Background

Diabetes mellitus is a common and serious disorder. Mostly because of chronic complications associated with the condition, diabetes mellitus accounts for over $100 billion in annual health care expenditures in the U.S. alone [1]. By 2030, an estimated 350 million people will have diabetes worldwide [2]. Diabetic retinopathy is the most important ocular complication in patients with diabetes mellitus and previous epidemiology studies have reported that the prevalence rate of diabetic retinopathy ranges between 6% and 18.4% [3]. Some patients with diabetic retinopathy develop macular edema [4,5]. Macular edema is one of the major causes of vision loss in individuals with diabetes and its development depends, in part, on the breakdown of the blood-retinal barrier. Diabetic macular edema is the major cause of vision loss associated with diabetic retinopathy. Worldwide, there are approximately 93 million people with diabetic retinopathy, 17 million with proliferative diabetic retinopathy, and 21 million with diabetic macular edema. The overall prevalence of DME is 6.81% (6.74–6.89) for DME in people with diabetes worldwide [7], accounting for 12% of new cases of blindness annually [8]. According to studies of the natural history of DME, 24% of eyes with DME will lose at least 3 lines of vision within 3 years.

The prevalence of diabetic macular edema depends on the type and duration of diabetes. In patients with type I diabetes, DME occurs in the first 5 years following diagnosis of diabetes, with the prevalence gradually increasing to 40% over 30 years. Around 5% of type II diabetes patients had diabetic macular edema when diabetes was diagnosed, gradually increasing to 30% within 25–30 years [6]. Several systemic risk factors have been identified in population-based epidemiological studies. In patients <age 30, independent risk factors for diabetic macular edema included duration of diabetes, proteinuria, sex, history of cardiovascular disease, use of diuretics, and elevated HbA1C [7]. In patients >30 years old, the incidence of diabetic macular edema is associated with longer duration of diabetes, elevated systolic blood pressure, and elevated glycosylated hemoglobin [8]. Proteinuria was positively associated with insulin dependence but not in those that were not using insulin. The prevalence of diabetic macular edema was also significantly associated with high serum cholesterol levels in patients with type I diabetes [9]. A sharp reduction (from 2.3% and 0.9%) in the prevalence of diabetic macular edema was noted in a Wisconsin population with better blood glucose control over 2 decades, confirming that chronic hyperglycemia is a critical factor in the pathogenesis of diabetic macular edema [10]. A cross-sectional study enrolling patients with type 2 diabetes who agreed to undergo blood sampling showed that exogenous insulin therapy is a independent risk factor for macular edema (p<0.05; odds ratio=3.8) [11]. Several observational studies were conducted to investigate the association between insulin use and macular edema incidence; however, the results were inconsistent [12–14]. To the best of our knowledge, there has been no comprehensive quantitative assessment of the association between insulin use and diabetic macular edema incidence. Therefore, we performed a meta-analysis of observational studies to evaluate the effect of insulin consumption on the risk of developing macular edema.

Material and Methods

Study identification

This meta-analysis was conducted following the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines [15], and the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines [16]. A literature search was carried out using PubMed (1966 to May 2014), Embase (1947 to May 2014), and Cochrane Library Central database (1967 to May 2014). There were no restrictions on origin or languages. Search terms included: "insulin", "antihyperglycemic" in combination with "macular edema" or "diabetic retinopathy". The reference lists of each comparative study included in this meta-analysis and previous reviews were manually examined to identify additional relevant studies.

Study selection

Two reviewers independently selected eligible case-control and cohort studies that investigated insulin use and macular edema risk. Disagreement between the 2 reviewers was settled by discussing with the third reviewer. Inclusion criteria were: (i) used a case-control or cohort study design; (ii) evaluated the association between insulin use and macular edema risk; (iii) presented odds ratio (OR), relative risk (RR), or hazard ratio (HR) estimates with 95% confidence interval (CI). When there were multiple publications from the same population, only data from the most recent report were included in the meta-analysis and the remaining were excluded. Studies reporting different measures of RR (e.g., risk ratio, rate ratio, hazard ratio, and odds ratio) were included in the meta-analysis. In practice, these measures of effect yield a similar estimate of RR.

Data extraction

The following data were collected by 2 reviewers independently using a purpose-designed form: name of first author, publication date, country of the population studied, study design, study period, number of cancer cases and subjects, sex, the study-specific adjusted ORs, RRs, or HRs with their 95% CIs for the insulin use and risk of macular edema, and confounding factors for matching or adjustments.
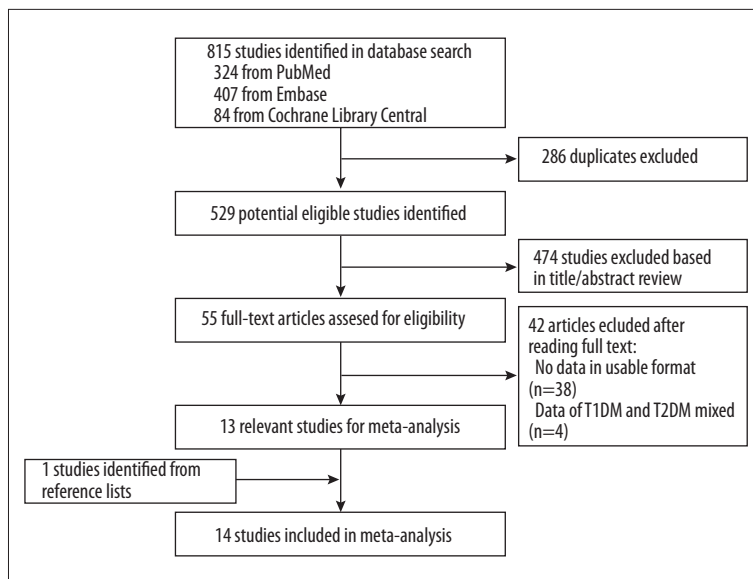
Figure 1. Flow chart of the literature search. The literature search was conducted in Medline, EMBASE, and Cochrane Library. The reference lists of the relevant studies were also reviewed.

Methodological quality assessment

We used the Newcastle-Ottawa scale to assess the methodologic quality of cohort and case-control studies [17]. The Newcastle-Ottawa scale contains 8 items in 3 categories: selection (4 items, 1 star each), comparability (1 item, up to 2 stars), and exposure/outcome (3 items, 1 star each). A "star" presents a "high-quality" choice of individual study. Hence, the full score was 9 stars, and a high-quality study was defined as a study with ≥6 awarded stars.

Data synthesis and analysis

Heterogeneity was assessed using the Cochran Q and I^2 statistics. For the Q statistic, a P value<0.10 was considered statistically significant for heterogeneity; for the I^2 statistic, heterogeneity was interpreted as absent (I^2: 0–25%), low (I^2: 25.1–50%), moderate (I^2: 50.1–75%), or high (I^2: 75.1–100%) [18]. Subgroup analyses were carried out according to: (i) study quality, (ii) study design (cohort versus case-control studies), (iii) geographic location (Europe vs. Asia vs. North America), and (iv) number of adjustment factors (n ≥5 vs. n ≤6). Pooled RR estimates and corresponding 95% CIs were calculated using the inverse variance method. Considering that this is a meta-analysis based on observational studies, regardless of whether heterogeneity was significant (I^2 ≥50%), the summary estimate based on the random-effects model (DerSimonian-Laird method) was reported, which assumes that the studies included in the meta-analysis had varying effect sizes. We carried out sensitivity analyses by excluding 1 study at a time to explore whether the results were strongly influenced by a specific study. Publication bias was assessed using Begg and Mazumdar adjusted rank correlation test and the Egger regression asymmetry test. All analyses were performed using Stata version 11.0 software (StataCorp, College Station, TX).

Results

Identification and selection of studies

The initial 815 articles (324 from PubMed, 407 from Embase and 84 from Cochrane Library Central) were identified. After 286 duplicates and 474 unrelated articles were excluded, 55 full-text articles were assessed for eligibility. From these 55 articles, we excluded 4 articles that did not report the incidence of macular edema and 38 articles that did not report the data in usable format. One reference was included from reviewing the reference lists of the related articles. A total of 14 studies were included in this study [12-14, 19-29]. Figure 1 shows the flow of search results.

Study characteristics and quality

A total of 202 905 individuals were included in the present current meta-analysis. The characteristics of these included studies were shown in Table 1. Among the 14 included studies, 3 studies were case-control studies and 11 were cohort studies. Geographic distribution of all included studies was 6 in the Americas, 6 in Europe and 2 in Asia. The duration of all the studies differed – the longest was about 20 years and the shortest was less than 1 year.

Thirteen studies among all the included studies provided adjusted RR/OR value and the adjusted factors (e.g., age, sex, and diabetes mellitus duration) were different in each study. To evaluate the methodological qualities of the included studies, we used the Newcastle-Ottawa scale. The Newcastle-Ottawa scale assessment score of most studies was >6 (mean: 6.71; standard deviation: 1.83) and 2 studies got less than 6 because of too few data sources or due to methodological design. All the results are presented in Table 2.

Table 1. Study characteristics of included studies.

Name	Country	Study duration	Follow-up	case/control	Hospital/ population	DM type	Adjusted factors
Henricsson M.	Sweden	1997	3.1±1.3 Y	2414	Hospital based Cohort study	2	Age, smoking, antihypertensive treatment
Bertram B.	German	1997	<1 Y	496	Hospital based Cohort study	2	Age, treatment
Klein R.	USA	1979–1980	10 Y	891	Population based Cohort study	2	Age,sex,age of diagnosis, smoking history,aspirin use, cardiovascular disease
Leske M.C.	Barbados	2003	4	410	Population based Cohort study	2	Age of onset, systolic blood pressure, treatment with insulin, and oral medication
Aroca P.R.	Spain	2000–2004	4	93	Hospital based case-control study	2	Age,sex,duration of DM
Romero-Aroca P.	Spain	2004.1–2004.6	11 M	123	Hospital based Cohort study	2	Age,sex,duration of DM, arterial hypertension
Lee S.J.	Korea	2002.9–2004.3	< 1 Y	496	Population based Cohort study	2	Age,sex,BMI,hypertension
Hirai F.E.	USA	1980–1982	20 Y	2366	Population based Cohort study	1,2	Age,sex,BMI,HbAlc,CVD history,hypertension
Shen L.Q.	USA	2002.5.1–2003.5.31	2.8 Y	282	Population based Cohort study	2	Age,sex, race, duration of DM, HbA1c, blood pressure, use of antihypertensive drugs, pedal edema
Liu L.Y.	China	2001–2005	32 M	1974	Hospital based Case-control study	1,2	Age, sex
Fong D.S.	USA	2002–2006	1 Y	143257	Population based Cohort study	2	age and HgA1c, and excludes patients without drug benefit, no eye exam and HgA1c 7.0
Motola D.	USA	2005.1–2008.10	4 Y	49589	Population based Case-control study	2	NA
Idris I.	UK	2000.1.1– 2009.11.30	10 Y	103368	Population based Cohort study	2	Age, sex, BMI, blood pressure, HbA1c, HDL, LDL
Bertelsen G.	Norway	2007.10–2008.11	1 Y	514	Population based Cohort study	2	Sex, blood pressure, BMI, cholesterol, somking

Insulin use and risk of macular edema

Figure 2 shows the relationship between insulin use and risk of macular edema. In a random-effects meta-analysis, the use of insulin was related with increased risk of macular edema (RR, 3.416; 95% CI, 2.417–4.829; I2, 86.6%). Table 3 shows the effects of insulin use and edema risk in subgroup analysis by adjustment status, study type, country, diabetes mellitus types, and duration. Analysis that just included the high-quality studies showed that insulin use increased that risk of macular edema (RR, 2.728; 95% CI, 1.881–3.955; I²=77.7%). Increased incidence of macular edema was observed in co-hort studies (RR, 4.509; 95% CI, 3.100–6.559; I², 77.7%) but not in case-control studies (RR, 1.455; 95% CI, 0.520–4.066; I²,

95.9%). When subgroup analyses were conducted according to the study designs, significant associations were detected in prospective studies (RR, 3.85; 95% CI, 2.637–5.620; I²=83.5) and retrospective studies (RR, 2.420; 95% CI, 0.867–6.753; I²=91.3). When the data source was considered, the population-based (RR, 2.726; 95% CI, 1.709–4.349; I²=82.7) and hospital based studies (RR, 4.934; 95% CI, 2.475–9.837; I²=91.4) showed a significant association between insulin use and risk of macular edema. However, the results were not changed in the subgroup analyses by follow-up duration and number of adjustment factors.

A significant heterogeneity was observed when all the 14 studies were included (I², 86.6%; P<0.866). However, the

Table 2. Quality assessment of included studies#.

Author, year	Quality assessment criteria			
	Selection	Comparability	Outcome/exposure	Overall quality
Henricsson M., 1997	***	**	***	8
Bertram B., 1997	***	*	**	6
Klein R., 1995	***	**	***	8
Leske M.C., 2003	***	*	**	6
Aroca P.R., 2004	**	*	**	5
Romero-Aroca P., 2006	***	**	**	7
Lee S.J., 2006	***	**	**	7
Hirai F.E., 2008	**	*	**	5
Shen L.Q., 2008	***	**	**	7
Liu L.Y., 2007	***	**	**	7
Fong D.S., 2009	***	**	***	8
Motola D., 2012	***	*	**	6
Idris I., 2012	***	**	***	8
Bertelsen G., 2013	***	*	**	6

the methodological qualities of the included studies were assessed using the Newcastle-Ottawa scale.
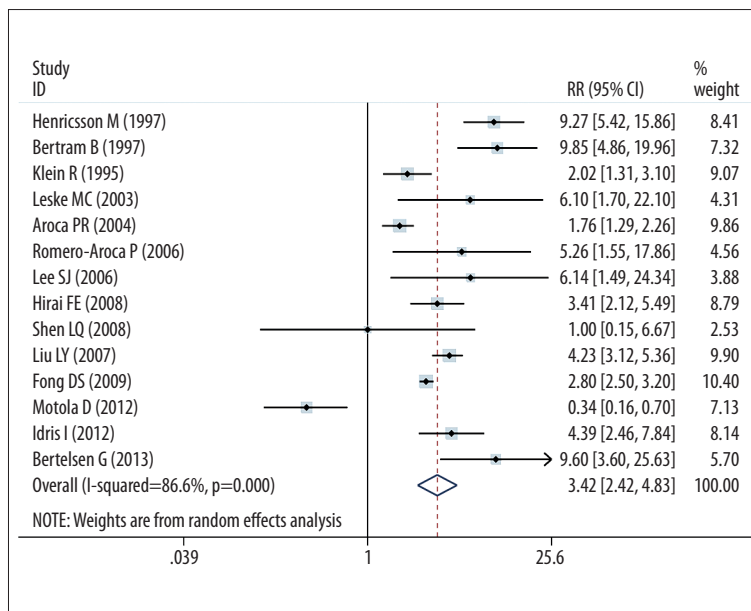

Figure 2. Forest plot of insulin use and risk of diabetic macular edema. The size of the shaded square is proportional to the percent weight of each study. The horizontal lines represent 95% CIs. The diamond data markers indicate the pooled ORs. A random-effects model was obtained.

heterogeneity was significant when the study design, data source, follow-up duration, and number of the adjusted factors were accounted for. However, when the subgroup analyses was conducted by location, we found that the studies conducted in Asia showed no significant association between insulin use and risk of macular edema (I^2=0.0%, P=0.607). However,

considering that only 2 of the studies in this meta-analysis were in Asian populations, the relatively low number of included studies might be the reason for the non-significant result. A sensitivity analysis was conducted after 2 studies that got Newcastle-Ottawa Scale <6 were excluded and no change was observed (RR, 2.728; 95% CI, 1.881–3.955; I^2, 77.7%). No

Table 3. Subgroup analysis of insulin use and macular edema incidence with combined RR.

	No. of studies	Pooled estimate		Tests of heterogeneity	
		RR	95% CI	P value	I² (%)
All studies	14	3.416	2.417 to 4.829	<0.001	86.6
High-quality studies (scores ≥7)	10	2.728	1.881 to 3.955	<0.001	77.7
Study design					
Cohort	11	4.509	3.100 to 6.559	<0.001	77.0
Case-control	3	1.455	0.520 to 4.066	<0.001	95.9
Data source					
Population based	9	2.726	1.709 to 4.349	<0.001	82.7
Hospital based	5	4.934	2.475 to 9.837	<0.001	91.4
Geographic location					
Europe	6	5.560	2.579 to 11.985	<0.001	89.8
Asia	2	4.288	3.287 to 5.592	0.607	0.0
North America	6	1.928	1.087 to 3.420	<0.001	86.0
DM type					
T2DM	12	4.520	2.444 to 8.362	<0.001	85.4
T1DM and T2DM	2	2.486	1.510 to 4.094	<0.001	90.6
Follow-up duration					
≤5 years	11	3.567	2.297 to 5.539	<0.001	89.1
>5 years	3	3.026	1.918 to 4.774	0.076	61.3
Design					
Prospective	8	3.850	2.637 to 5.620	<0.001	83.5
Retrospective	5	2.420	0.867 to 6.753	<0.001	91.4
Number of adjustment factors					
n ≤5 confounders	8	3.663	1.842 to 7.283	<0.001	91.7
n ≥6 confounders	6	3.136	2.284 to 4.308	0.03	59.4

RR – relative risk; CI – confidence interval.

significant publication bias was found in the 14 selected studies, see Figure 3 (Begg's funnel plot, symmetrical; Begg's test, P for bias=0.381; Begg's test, P for bias=0.606).

Discussion

To the best of our knowledge, this is the first meta-analysis evaluating the association between insulin use and macular edema risk. The present meta-analysis included 14 observational studies currently available (11 cohort studies and 3 case-control studies), involving a total of 202 905 participants. There

was statistically significant heterogeneity among the 14 included studies investigating the association between insulin use and macular edema risk, so a random-effects model was chosen over a fixed-effects model. Finally, we found that insulin use significantly increase the macular edema risk. Sensitivity analysis indicated that the omission of any 1 study did not alter the magnitude of observed effect, suggesting the stability of our findings. Moreover, the results of Begg's test and Egger's test did not support the existence of major publication bias.

In general, insulin use is one of the most important therapies for diabetes mellitus [30,31]. Insulin provides a better effect in
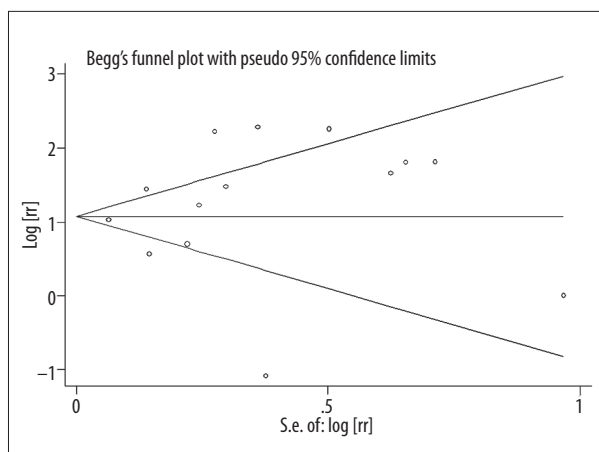
Figure 3. Funnel plot of all the included studies.

the hypoglycemic effect and it can protect the insular function [32]. However, in the long-term outcome of patients with diabetes, we found that insulin use is associated with increased risk of various cancers with the development of insulin use. For example, in a meta-analysis using data from 12 published epidemiologic studies (7 case-control and 5 cohort studies) published before January 2014, it was reported that insulin use increased the risk of colorectal cancer [33]. Findings of significantly harmful effects of insulin, reported mainly in case-control studies, may stem from study design differences and number of included studies. Several studies reported that insulin use increased the risk of diabetic retinopathy. In this prospective, non-interventional, cross-sectional case-control study, 729 subjects from Los Angeles County University of Southern California Medical Center (LAC + USC), Los Angeles, CA, were enrolled. It was found that insulin use increased the risk of proliferative diabetic retinopathy (OR, 1.85; 95% CI, 1.13–3.03) [34]. Considering that diabetic macular edema is a common cause of visual impairment in diabetic patients, the association between insulin use and risk of macular edema needs advanced research [35]. In both case-control and cohort studies, there are strong and independent associations between insulin use and risk of macular edema [22–24]. There are various biases in observational studies. Recently, there have been no randomized controlled trials investigating the effect of insulin use on the incidence of macular edema. In this meta-analysis, through pooling 14 observational studies, we found that insulin use is a risk factor for macular edema.

The pathogenesis of diabetic macular edema remains to be completely defined because it is caused by a complex pathological process with many contributing factors [36]. Dysfunction of the inner and outer retinal barriers leads to accumulation of sub- and intra-retinal fluid in the inner and outer plexiform layers [37]. Vascular endothelial growth factor (VEGF) has generally been accepted as the main factor that disrupts the inner blood-retinal barrier (BRB) function, making it an important

target for pharmaceutical intervention [38,39]. A study in diabetic mice found that insulin treatment resulted in increased vascular leakage, apparently mediated by betacellulin and signaling via the epidermal growth factor (EGF) receptor. In addition, treatment with EGF receptor inhibitors reduced retinal vascular leakage in diabetic mice on insulin. These findings provide unique insight into the role of insulin signaling in mediating retinal effects in diabetes, and open new avenues for treating the retinal complications of diabetes mellitus [40]., An *in vitro* study showed that PLGF-1 induced a reversible decrease in transepithelial resistance and enhanced tritiated insulin flux. These effects were specifically abolished by an antisense oligonucleotide directed at VEGF receptor 1. Exposure of ARPE-19 cells to hypoxic conditions or to insulin induced upregulation of PLGF-1 expression along with increased transcellular permeability. The PLGF-1-induced RPE cell permeability involved the MEK signalling pathway [41].

The strengths of this study are: (1) we adopted a relatively comprehensive literature search strategy in the acquisition of studies to consider for inclusion. To avoid missing includable articles, we searched the database with keywords of "insulin" and "antihyperglycemic" in combination with "macular edema". (2) Most of the studies included in this meta-analysis demonstrated relatively high quality. The results of the sensitivity analysis and the publication bias detection suggest that the conclusions of the present study are quite robust (3). We performed consummate analyses, including detailed subgroup analyses and sensitivity analyses. The careful analyses provide more detailed data on the relation between insulin use and risk of diabetic macular edema.

As with any meta-analysis of observational studies, ours has several limitations. First, some of the studies followed a case-control study design and thus had recall and selection bias, which are inherent in retrospective studies. This study is limited in that, although subgroup analysis by study design was conducted, the robustness was limited by including too few cohort studies. Second, data on the formulations and methods of insulin use are limited in this study. There points all indicate the need for further well-designed studies.

Conclusions

The results from this meta-analysis of observational studies demonstrate that insulin use is a risk factor for diabetic macular edema. However, available data are still sparse, and indepth analyses of the assessed associations in the context of additional longitudinal studies are highly desirable to enable more precise estimates and a better understanding of the role of insulin use in incidence of diabetic macular edema.

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