• Meta-Analysis •

Prevalence of diabetic retinopathy in Iran: a systematic review and Meta-analysis

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Abstract

• AIM: To estimate the overall prevalence of diabetic retinopathy (DR) in Iran by a systematic review and Meta-analysis.

• METHODS: We conducted a search of all published literature on diabetic patients for the prevalence of DR using Web of Sciences, PubMed, Scopus, Google Scholar, and national electronic databases SID, Magiran, and Iranmedex from their inception until September 2016 with standard keywords. Pooled estimates of the DR prevalence and the corresponding 95% confidence intervals (CI) were calculated using random effects models.

• RESULTS: Thirty-one studies involving 23 729 patients with type I and II diabetes were included. The publication bias assumption for prevalence of DR was rejected by Begg and Egger tests (P=0.825, P=0.057, respectively). The results of Cochran test and I^2 statistics showed considerable heterogeneity for prevalence of DR (Q=1278.21, d.f.=30, P<0.001 and I^2=97.7%). The prevalence of DR, non-proliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR) in Iranian diabetic patients were 41.9% (95% CI: 35.6-48.2), 32.2% (95% CI: 28.7-35.8), and 13.2% (95% CI: 8.3-18.1), respectively.

• CONCLUSION: The prevalence of DR in Iran appears a little high. NPDR was more common. This study highlights the necessity for DR screening and management in diabetic patients in Iran.

• KEYWORDS: diabetic retinopathy; Iran; prevalence; Meta-analysis; systematic review

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INTRODUCTION

Diabetic retinopathy (DR) is a major cause of visual impairment and blindness among working aged adults worldwide[1]. As the prevalence of diabetes in adults of working-age increases[2], a parallel increase in DR as common complication of diabetes might be expected. There are two types of diabetic retinopathy: non-proliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR). NPDR, also known as background retinopathy, is the early stage of the disease in which symptoms will be mild or non-existent. PDR is the more advanced form of the DR and mainly occurs when abnormal new blood vessels grow on the surface of the retina[1,3]. The known risk factors for DR are duration of diabetes, hyperglycemia, hypertension and dyslipidemia[1,3-4]. Previous research indicated that the risk of vision loss due to DR could be reduced by tight control of serum glucose and blood pressure[4].

A recent systematic review of 35 population-based studies around the world showed that the prevalence of DR and PDR among people with diabetes was 34.6% and 7.0%, respectively[5]. Moreover, both DR and PDR prevalence were higher in people with type I compared with type II diabetes[5]. Despite the importance of this issue, and its significant impact on the health care systems and the rising prevalence of diabetes notably in working-age adults, there are no overall precise estimates of the DR prevalence in Iran, particularly based on the two main type of DR (*i.e.* NPDR and PDR). Previous individual researches have shown considerable variability in DR prevalence estimates among adults with both type I and II diabetes, with rates ranging from 10.4% to 76.4%[6-36].

Due to the considerable heterogeneity among the reported prevalence rate of DR in previous individual studies and significant impact of DR on the health-care systems, the broader and more precise estimate of the prevalence of DR is necessary for strategic plan and health policy. We therefore performed a systematic review and Meta-analysis of all published studies to estimate the overall prevalence rate of DR as well as NPDR and PDR among adult diabetic persons in Iran.

MATERIALS AND METHODS

Search Strategy This Meta-analysis was conducted according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) checklist[37]. We conducted a literature search of published papers in September 2016 using international and national electronic databases Web of Science, PubMed, Scopus, Google Scholar, Magiran, SID, and Iranmedex. Key words included "diabetic retinopathy", "prevalence" and "Iran". We also checked the reference lists of the included article for further relevant articles. No language or time restriction was applied to the searches.

Inclusion and Exclusion Criteria The following inclusion criteria were used to select studies for the Meta-analysis: 1) studies with prevalence estimates of DR, 2) studies of any language and time. We excluded the following studies: 1) intervention or treatment studies, 2) studies in newly diagnosed diabetic patients, 3) repeated or overlapping studies, and 4) no usable data reported.

Data Extraction and Quality Assessment Two authors (Maroufizadeh S and Almasi-Hashiani A) independently extracted the following data from the included studies: first author's name, year of publication, location, year of study, sample size, type of diabetes, sex ratio, age, duration of diabetes and prevalence estimate of DR, NPDR and PDR. Two reviewers (Maroufizadeh S and Hosseini M) independently performed the quality assessment based on the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist.

Statistical Analysis All statistical analyses were performed using STATA version 13.0 (Stata Corp, College Station, TX, USA). Statistical heterogeneity among the studies was assessed by the Cochrane Q test and I^2 statistic[38]. For the Cochrane Q test, P<0.10 was considered statistically significant for heterogeneity. The I^2 statistic indicates the percentage of total variation across studies due to heterogeneity rather than chance. I^2 values of 25%, 50% and 75% correspond to low, moderate and high heterogeneity, respectively[38]. The Meta-analysis was performed with a random effect model, considering the remarkable heterogeneity among studies. Meta regression was conducted to explore the sources of between-study heterogeneity, including year of study and sample size. We conducted sensitivity analyses by excluding each study at a time from the Meta-analysis, in order to examine its influence on the pooled estimate. The Galbraith plot was also used to detect the potential sources of heterogeneity[39]. The Funnel plot and Begg's rank correlation and Egger's weighted regression tests were used to assess publication bias[40-41]. Finally, cumulative Meta-analysis was also conducted to investigate whether the magnitude of prevalence rate changes markedly with time of study.

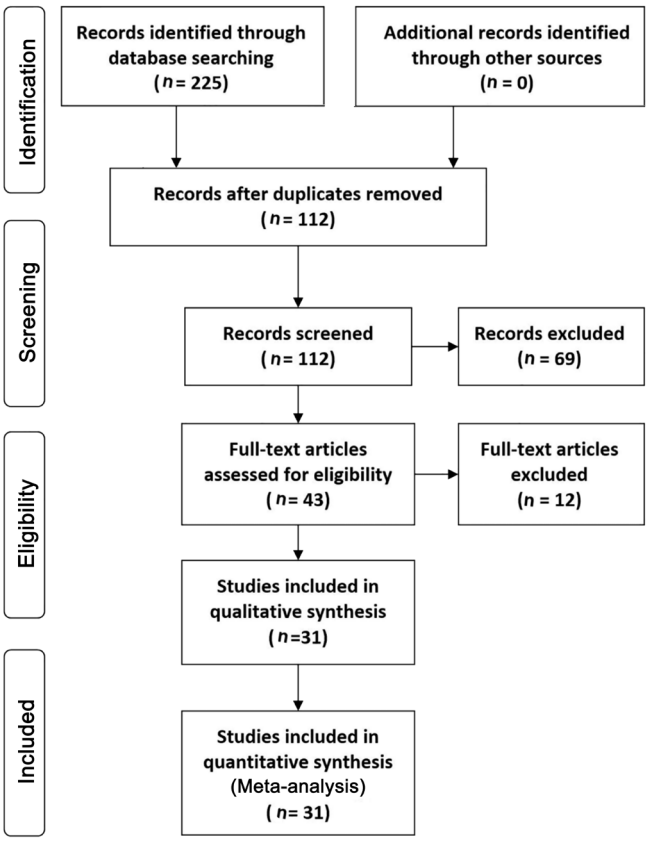

Figure 1 Flow diagram of the literature search for studies included in Meta-analysis.

RESULTS

Study Selection Figure 1 shows the results of the literature search and selection process based on the PRISMA flow chart for systematic reviews[37]. A total of 225 potentially relevant articles were identified from the initial searches. After removing duplicates, 112 articles remained. We excluded 69 articles by screening titles and abstracts, and retrieved the full texts of 43 remaining articles. Finally, 31 studies met the inclusion criteria and were included in this Meta-analysis (Figure 1).

Study Characteristics The characteristics of included studies are presented in Table 1. These studies were published between 2003 (Janghorbani *et al*[6]) and 2016 (Eslami *et al*[36]). The sample size of included articles varied from 46 (Soleymanian *et al*[33]) to 3734 (Hosseini *et al*[21]), with a total of 23 729 cases.

Evaluation of Heterogeneity and Meta-analysis The results of Cochran's Q test and I^2 statistics indicated substantial heterogeneity among the included studies for DR (Q=1278.21, d.f.=30, P<0.001 and I^2=97.7%), PDR (Q=65.63, d.f.=15, P<0.001 and I^2=77.1%) and NPDR (Q=42.95, d.f.=15, P<0.001 and I^2=65.1%), and thus random effects model was used for analysis. The pooled prevalence of DR was 41.9% (95% CI: 35.6-48.2). As seen in Figure 2, the lowest and highest prevalence of DR was reported by Ghodsi *et al*[30] in Fasa (southern of Iran) (10.4%, 95% CI: 4.5-16.3) and Faghih-Imani *et al*[11] in Isfahan (center of Iran) (76.4%, 95% CI: 72.1-

Table 1 Description of the studies included in the Meta-analysis mean (%)

Author	Location	Year	Sample size	Prevalence			Age (a)	Duration of disease (a)
				DR	NPDR	PDR		
Janghorbani *et al* (2003)[6]	Isfahan	1992-2001	549	45.3	-	-	44.6 (9.3)	5.9 (5.7)
Manaviat *et al* (2004)[7]	Yazd	2000-2001	590	39.3	33.9	5.4	54.9 (10.2)	10.2 (6.6)
Aghadoost *et al* (2005)[8]	Kashan	2002-2003	200	36.0	31.0	5.0	51.2 (-)	12.0 (-)
Ghasemi *et al* (2005)[9]	Tehran	1998-2002	253	69.6	48.6	21.0	60.8 (11.6)	11.1 (7.8)
Mazarei *et al* (2005)[10]	Ghazvin	2000-2001	94	52.1	34.0	18.1	55.0 (15.8)	7.5 (3.4)
Faghih-Imani *et al* (2005)[11]	Isfahan	2004	500	76.4	-	-	49.6 (-)	-
Ramezani *et al* (2006)[12]	Tehran	1998-2002	288	56.6	29.9	26.7	53 (15.9)	11.2 (8.0)
Akbarzadeh *et al* (2006)[13]	Hamadan	1999	2000	13.1	-	-	<40: 28.3%	<10: 51.6%
Abdollahi *et al* (2007)[14]	Tehran	[1]2007	181	37.6	-	-	55.5 (11.7)	9.9 (6.7)
Naseripoor *et al* (2006)[15]	Kermanshah	1993-1999	610	32.9	-	-	47.2 (15.7)	6.1 (5.2)
Shafiepour *et al* (2006)[16]	Sari	2005	540	34.2	31.8	2.4	52.66 (11.5)	8.4 (6.3)
Shahbazian *et al* (2006)[17]	Ahvaz	2004	200	43.5	31.0	12.5	51.8 (5.8)	9.6 (6.9)
Esteghamati *et al* (2007)[18]	Tehran	[1]2007	66	36.4	-	-	57.0 (9.5)	14.44 (6.8)
Davari *et al* (2008)[19]	Birjand	2006-2007	359	37.3	26.7	10.6	51.2 (15.2)	<5: 66.6%
Manaviat *et al* (2008)[20]	Yazd	[1]2008	199	70.3	45.2	25.1	54.2 (11.0)	10.3 (6. 9)
Hosseini *et al* (2009)[21]	Isfahan	2009	3734	54.0	-	-	52.2 (10.5)	7.00 (6.00)
Javadi *et al* (2009)[22]	Tehran	2007	634	37.8	27.6	10.2	59.3 (12.0)	<10: 67.7%
Hosseini *et al* (2012)[23]	Qom	2005-2006	261	39.1	27.6	11.5	52.2 (11.5)	9.1 (7.1)
Salehi *et al* (2012)[24]	Tehran	2005	367	32.7	-	-	57.5 (9.8)	7.3 (6.1)
Dehghan *et al* (2013)[25]	Yazd	2011	529	30.0	-	-	57.0 (9.8)	6.4 (6.3)
Kohian *et al* (2013)[26]	Shahroud	1999-2002	625	29.3	23.4	5.9	47.9 (11.7)	<6: 74.6
Mahmoudi *et al* (2013)[27]	Saqqez	2011	1563	12.1	-	-	53.6 (11.8)	-
Tazhibi *et al* (2014)[28]	Isfahan	2003	3535	53.4	-	-	52.57 (10.3)	7.1 (6.7)
Yaghoubi *et al* (2014)[29]	Mashhad	2011	342	30.4	22.2	8.2	55.05 (9.1)	<10: 47.4%
Ghodsi *et al* (2014)[30]	Fasa	2009-2013	978	10.4	-	-	51.8 (12.9)	9.3 (6.0)
Azizi-Soleiman *et al* (2015)[31]	Isfahan	[1]2015	1782	57.2	-	-	50.3 (9.6)	5.8 (5.9)
Rasoulinejad *et al* (2015)[32]	Babol	2006-2010	1562	63.4	36.9	26.5	54.6 (10.6)	10.6 (7.3)
Soleymanian *et al* (2015)[33]	Tehran	2008-2011	46	39.1	-	-	48.9 (11.9)	7.2 (5.6)
Bonakdaran *et al* (2015)[34]	Mashhad	[1]2015	235	35.0	27.2	7.7	54.8 (9.4)	7.5 (6.1)
Vahabi *et al* (2015)[35]	Tehran	[1]2015	623	37.9	-	-	59.9 (11.5)	7.2 (6.0)
Eslami *et al* (2016)[36]	Hamadan	2013-2014	284	54.2	39.1	15.1	-	<10: 35.6%

DR: Diabetic retinopathy; NPDR: Non-proliferative diabetic retinopathy; PDR: Proliferative diabetic retinopathy. [1]Year of publication.

80.7), respectively. In addition, the pooled prevalence rates of NPDR (Figure 3) and PDR (Figure 4) were 32.2% (95% CI: 28.7-35.8), 13.2% (95% CI: 8.3-18.1), respectively.

Meta Regression Meta regression was used to explore the sources of between-study heterogeneity, including year of study and sample size. According to the results, prevalence of DR, PDR and NPDR was not related to year of study (all $P>0.05$) and sample size (all $P>0.05$).

Publication Bias As seen in Figures 5, 6 and 7, the funnel plots showed symmetry, demonstrating the absence of publication bias among the included studies. The Begg's and Egger's tests also confirmed the absence of publication bias among the included studies for prevalence of DR ($P=0.825$ and $P=0.075$, respectively), PDR ($P=0.471$ and $P=0.103$, respectively) and NPDR ($P=0.964$ and $P=0.527$, respectively).

Sensitivity Analysis To evaluate the influence of each individual study, we performed sensitivity analyses by excluding each study from the Meta-analyses and comparing the point estimates before and after excluding each specific individual study. Based on the sensitivity analysis, exclusion of individual studies did not change the results substantially, with pooled prevalence of DR ranging from 40.7% (when excluding Faghih-Imani *et al*[11]) and 43.01% (when excluding Ghodsi *et al*[30]). And also, after sensitivity analysis, pooled prevalence

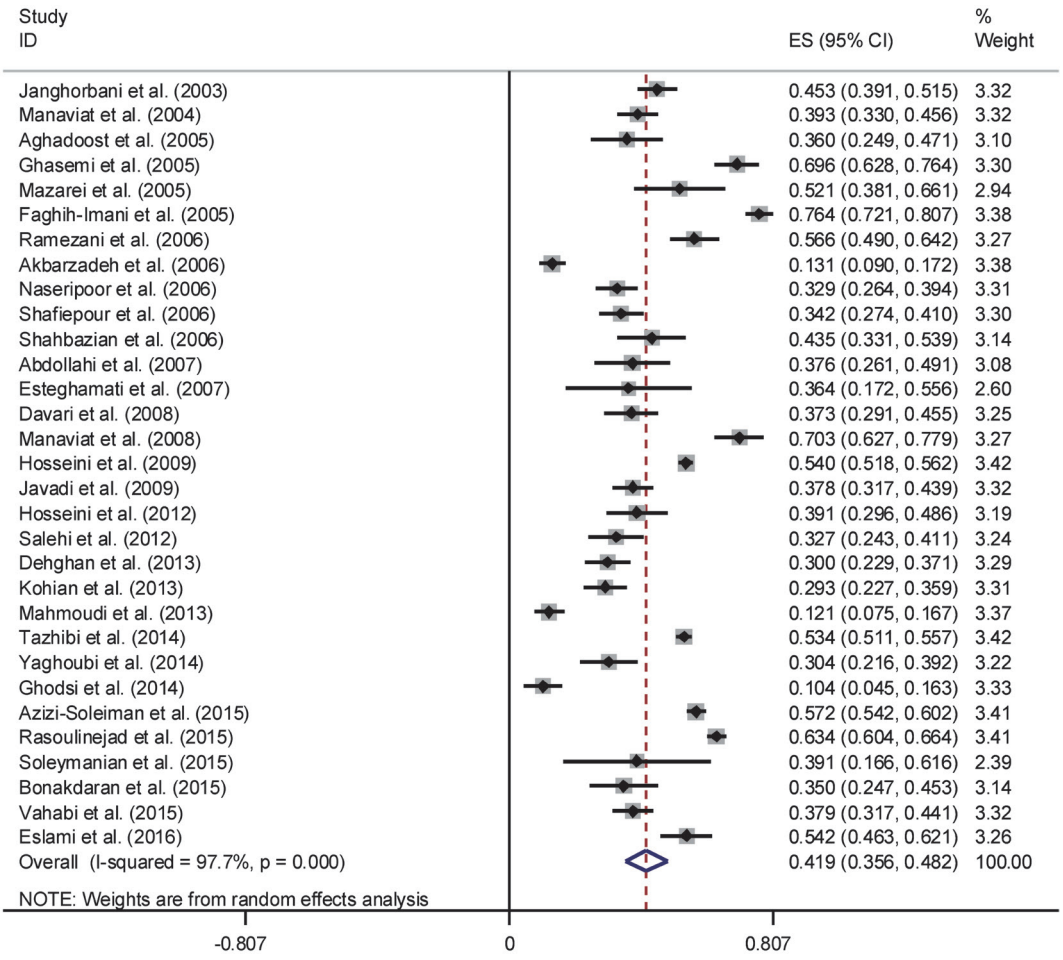

Figure 2 Forest plot showing prevalence of diabetic retinopathy among diabetic patients in Iran.

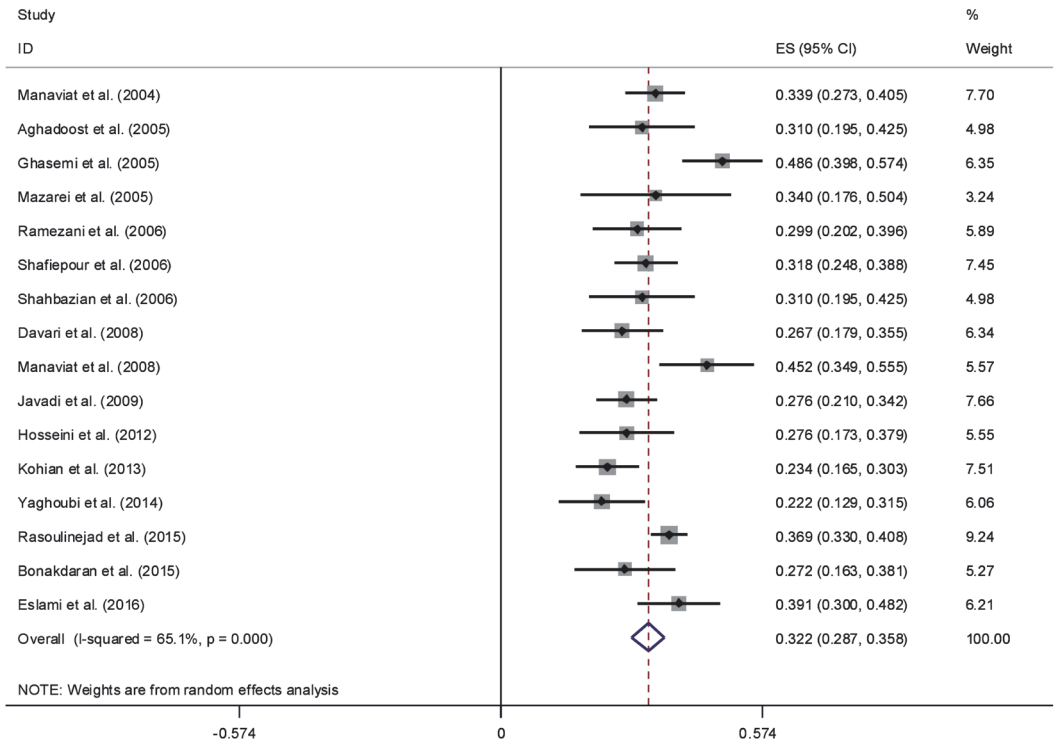

Figure 3 Forest plot showing prevalence of non-proliferative diabetic retinopathy among diabetic patients in Iran.

of PDR ranging from 12.27% (when excluding Ramezani *et al*[12]) to 14.02% (when excluding Shafiepour *et al*[16]) and the pooled prevalence of NPDR ranging from 31.17% (when excluding Ghasemi *et al*[9]) to 32.9% (when excluding Davari *et al*[19]).

Cumulative Meta-analysis Cumulative Meta-analysis was

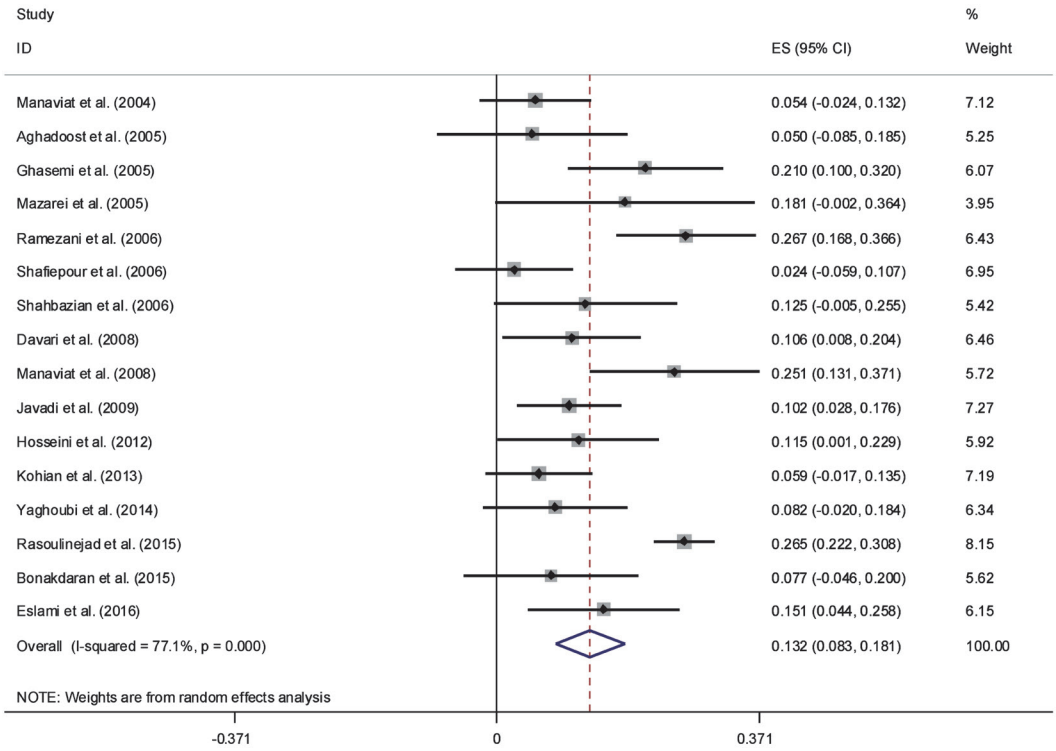

Figure 4 Forest plot showing prevalence of proliferative diabetic retinopathy among diabetic patients in Iran.

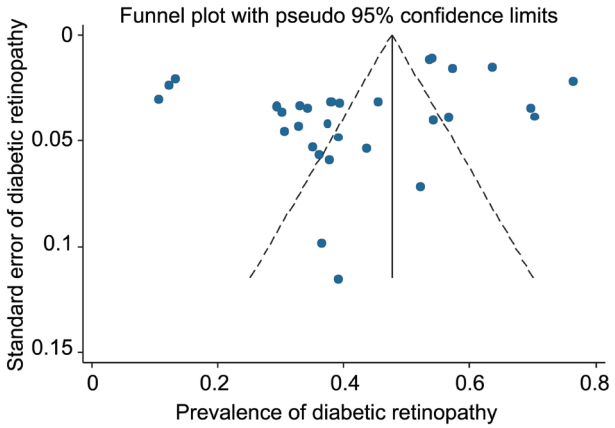

Figure 5 Funnel plot for assessing publication bias in Meta-analysis for diabetic retinopathy.

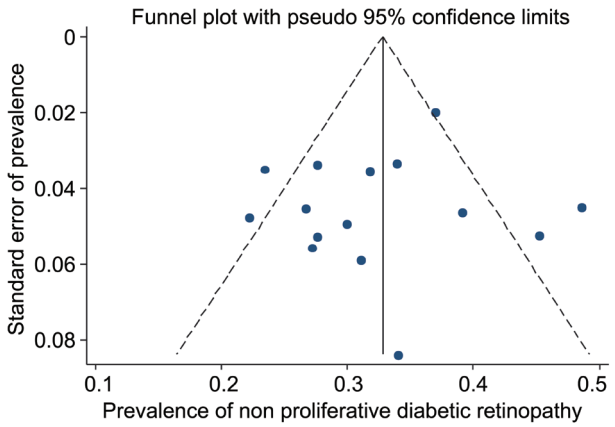

Figure 6 Funnel plot for assessing publication bias in Meta-analysis for non-proliferative diabetic retinopathy.

also performed by sorting the studies based on publication time. As shown in Figures 8, 9 and 10, cumulative Meta-

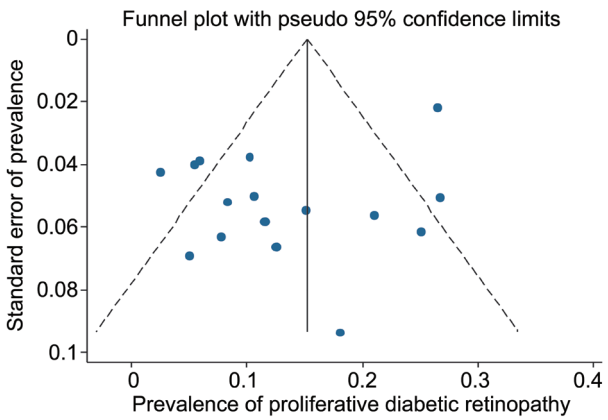

Figure 7 Funnel plot for assessing publication bias in Meta-analysis for proliferative diabetic retinopathy.

analysis of DR prevalence revealed that the overall prevalence estimates were stable and that the 95% CIs narrowed with accumulation of data over time.

DISCUSSION

It is very important to estimate the prevalence of DR as it is a key indicator of systemic diabetic microvascular complications, which, in turn, is a crucial indicator of the impact of diabetes on patients. Furthermore, it is adequately essential to create an extensive and more accurate estimate of the prevalence of DR, particularly for its two main type (*i.e.* NPDR and PDR), so it can be used for guiding public health education and managing the clinical aspects of this disease in a favorable way. The better management of DR and diabetes, and overall increased screening for diabetes, may have caused the incidence and prevalence DR to decline over time[42].

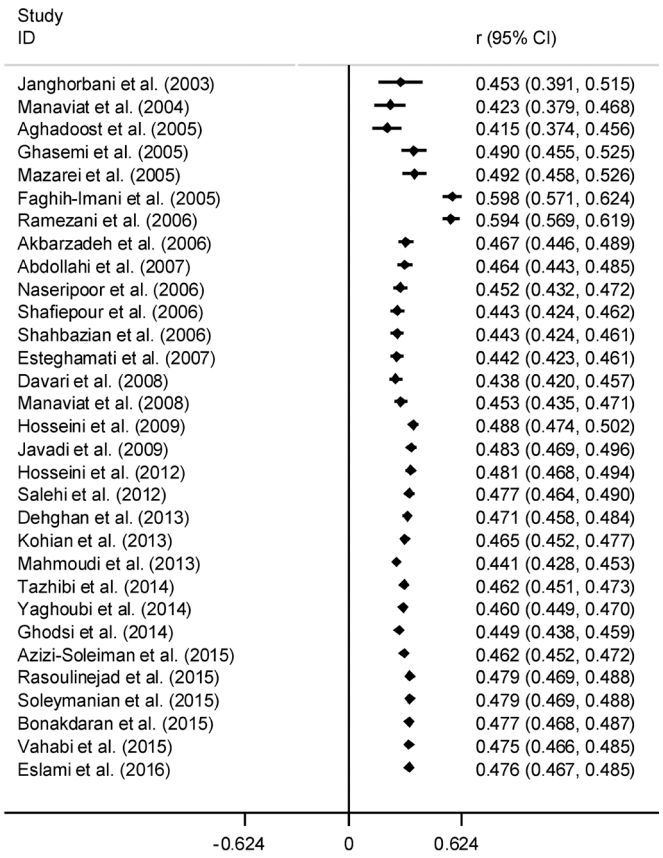

Figure 8 Cumulative Meta-analysis of diabetic retinopathy by sorting the studies based on publication time.

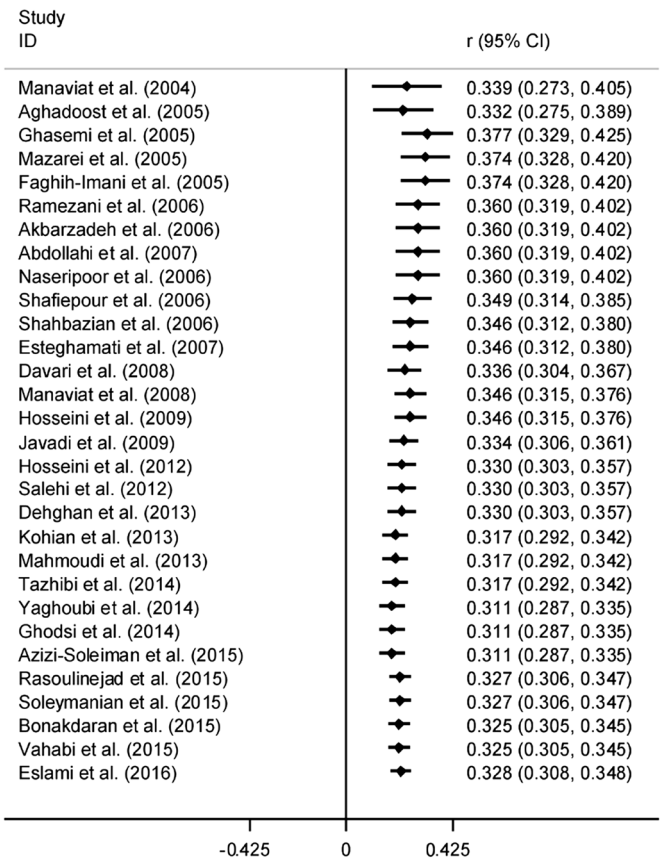

Figure 9 Cumulative Meta-analysis of non-proliferative diabetic retinopathy by sorting the studies based on publication time.

With the expected increased prevalence of type 2 diabetes in the population, in part due to increasing rates of obesity and decreasing physical activity, the burden of diabetic retinopathy might be expected to increase as well[5,43]. However, improved access to screening tools and treatment of diabetic retinopathy may reduce the burden of diabetes-related vision loss.

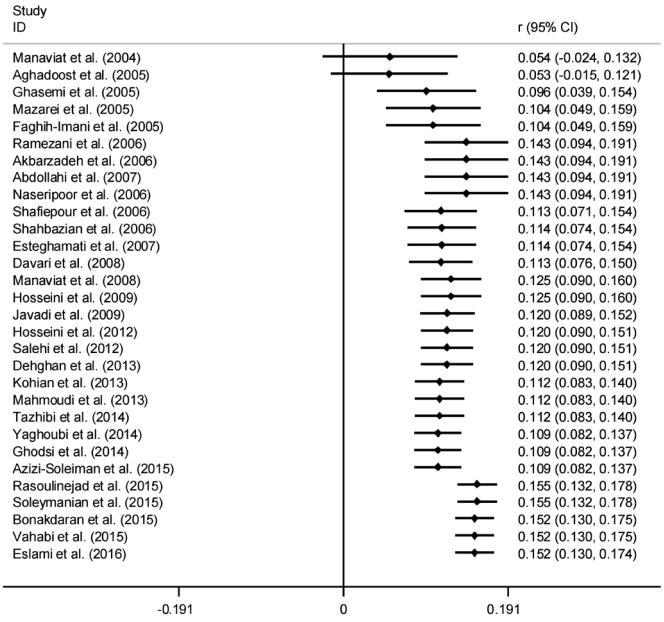

Figure 10 Cumulative Meta-analysis of proliferative diabetic retinopathy by sorting the studies based on publication time.

To the best of our knowledge, this is the first systematic review and Meta-analysis of DR prevalence in Iran. In this Meta-analysis, a total of 31 studies with 23 729 people with diabetes were included. In the present study, the overall prevalence of DR using the random effect model was 41.9%, which is higher than what was reported in United Arab Emirates (19.0%)[44], India (21.7%)[45], Mainland China (23.0%)[46], Peru (23.1%)[47], Puerto Rico (37.7%)[48], but lower than what was reported in adult Latinos (46.9%)[49].

As indicated in the findings, there was considerable heterogeneity among included studies. Some of these differences between individual studies regarding DR prevalence, may be due to the differences in time periods of the studies. Also, in this Meta-analysis, it is possible that the prevalence rates of DR have been affected by the dissimilarity of studies concerning the ophthalmologic definitions and examination methodologies. However, the pooled prevalence rates of DR were also estimated by random-effects model. Furthermore, DR susceptibility may also vary among different ethnic groups[5]. Although the prevalence of DR in this Meta-analysis is higher than the previously reported global estimates of 34.6% reported by Yau *et al*[5], several factors make it difficult to compare the estimates.

The present study has several strengths that should be mentioned. The major strengths of our study were the large sample size of diabetic patients, which enabled us to estimate the overall prevalence of DR from different prevalence studies. Second,

the funnel plot and the Begg and Egger's tests did not support the presence of publication bias, providing further indication of the robustness of our results. Nevertheless, our study has some limitations that should be noted when interpreting the findings. First, considerable heterogeneity was observed among studies. Therefore, even if we used random effects model to take heterogeneity into account, our overall estimates should be interpreted with caution. Second, we could not conduct Meta-regression for other sources of between-study heterogeneity-hyperglycemia, hypertension and dyslipidemia-since we did not have data on these risk factors. These factors have been found to be related to DR. Finally, the absence of studies from the South, South East, and North West of Iran could also affect the generalizability of our findings.

In Iran, the prevalence of DR, especially PDR, appeared a little high. Furthermore, with the aging of the population and the increasing prevalence of diabetes among working-aged adults, the number of individuals of DR will likely increase. Our data provide policy makers updated information for use in effective screening of DR, planning eye care services, management of DR risk factors and rehabilitation.

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Authors' Contributions: Maroufizadeh S, Almasi-Hashiani A and Omani Samani R contributed to conceive and design of the study. Maroufizadeh S and Almasi-Hashiani A performed the literature search, data extraction and quality assessment. Maroufizadeh S, Almasi-Hashiani A and Hosseini M performed data analysis and interpretation. Maroufizadeh S, Almasi-Hashiani A and Hosseini M were responsible for data extraction and the accuracy of the data analysis. Maroufizadeh S, Almasi-Hashiani A, Hosseini M and Sepidarkish M drafted the manuscript and Omani Samani R reviewed it.

Conflicts of Interest: Maroufizadeh S, None; **Almasi-Hashiani A,** None; **Hosseini M,** None; **Sepidarkish M,** None; **Omani Samani R,** None.

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