Meta Analysis

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Prevalence of diabetic retinopathy in the Eastern Mediterranean Region: a systematic review and meta-analysis

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Abstract

Objectives: Individual studies in the Eastern Mediterranean Region (EMR) have shown the high prevalence of diabetic retinopathy. We conducted a meta-analysis to yield an estimate of the prevalence of diabetic (type 1 and 2) retinopathy in the EMR. Additionally, we explored its potential modulators.

Methods: Two-step screening of relevant articles published from 1 January 2000 to 13 December 2019 was carried out. An estimation of summary proportions, subgroup analysis, meta-regression, and publication bias assessment were performed.

Results: One hundred nine articles were included in the meta-analysis, involving 280,566 patients. The prevalence of diabetic retinopathy was 31% (95% confidence interval [CI] = 28, 33). The highest and lowest diabetic retinopathy prevalence rates were observed in low human development index (HDI) countries (63.6; 95% CI = 52.4, 74.0) and very high HDI countries 22.6 (95% CI = 20.5, 24.7), respectively.

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Conclusions: The prevalence of diabetic retinopathy is high in the EMR. Our results provide important information for diverse healthcare surveillance systems in the EMR to implement the modifiable risk factors, diabetes screening to decrease undiagnosed diabetes, early detection of retinopathy, and proper diabetes care to decrease untreated diabetes.

Keywords
Prevalence, epidemiology, meta-analysis, diabetic retinopathy, diabetes mellitus, diabetes complication, diabetic angiopathy, vascular disease, Eastern Mediterranean Region, systematic review

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Introduction

Diabetes mellitus is one of the most prevalent metabolic disorders that has reached epidemic proportions worldwide, exerting a substantial burden on healthcare services. Based on International Diabetes Federation (IDF) reports, approximately 537 million people had diabetes in 2021, and this rate is projected to increase to 643 million people by 2030 and 783 million by 2045.[1] Approximately 87.5% of people with undiagnosed diabetes live in low- and middle- income countries. Countries with a high prevalence of undiagnosed diabetes show an increased incidence of diabetic complications.[1] Undiagnosed or untreated complications will inevitably affect the patients' quality of life and become a burden for the health system.[2]

Diabetic retinopathy is a chronic diabetic complication and a leading cause of blindness and vision disabilities worldwide.[3] This complication develops in almost all patients with type 1 by two decades after diagnosis and approximately 80% of those with type 2 diabetes.[4] Different risk factors are associated with retinopathy in patients with diabetes; the most important factors are age, duration of diabetes, high blood pressure, high body mass index, hyperglycemia, and hypercholesterolemia.[6–9]

The Eastern Mediterranean Region (EMR) is a sub-community of the World Health Organization (WHO) with countries located in southwest Asia, Western Asia, and North Africa, including a range of low-, middle-, and high-income countries.[10–12] There is an increasing trend in the prevalence of type 2 diabetes in middle- and low-income countries.[13] As the WHO stated, the EMR has the highest prevalence of diabetes worldwide, with 43 million people living with the disease in 2014 (14% versus 9% global prevalence among people aged ≥ 18 years).[10] Additionally, several regional studies indicated a wide range of diabetes prevalence rates in the EMR, such as 14.1% in Iran[12] and 32.8% in Saudi Arabia.[15] Similarly, the prevalence of diabetes complications is dramatically increasing in the EMR.[16] In a systematic review from Pakistan, the prevalence of diabetic retinopathy was 28%, ranging from 10.6% to 91.3%.[17] A meta-analysis from Iran showed an overall prevalence of diabetic retinopathy of 37.8%.[18] In addition, several studies from Saudi Arabia,[19,20] Kuwait,[21] and Jordan[22] reported that diabetic retinopathy is highly prevalent (27.8% to 36.4%, 50%, and 48.4%, respectively).

One mission of surveillance services in decreasing the burden of retinopathy on the health system and patients is to provide information regarding the prevalence of diabetic retinopathy for healthcare policy-making.[23] Systematic epidemiologic data

are vital for government health legislation to implement early detection and efficient intervention; however, to the best of our knowledge, no study has evaluated the prevalence of diabetic retinopathy in the EMR. Therefore, we conducted a systematic review and meta-analysis of relevant studies published since 2000 to estimate the incidence of diabetic (type 1 and 2) retinopathy in the EMR.

Materials and methods

We followed the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) 2020 guideline and checklist.[24] We did not prospectively register this trial but registered it retrospectively at Research Registry (registration number: reviewregistry1362; registered on 18 May 2022). The study protocol was approved by the Ethics Committee of Shiraz University of Medical Sciences (code: IR.SUMS.REC.1398.818). Because this meta-analysis used the results of published studies, which did not contain individual data, informed consent was not applicable.

Search strategy

This meta-analysis of effect estimates was designed and conducted in January 2020 to estimate the prevalence of retinopathy in patients with both type 1 and type 2 diabetes in the EMR. We searched for the relevant keywords in the title and abstract of articles from Medline/PubMed, Scopus, Embase, Web of knowledge, and Google Scholar (gray literature) to identify the target studies published from 1 January 2000 to 13 December 2019. The keywords list is provided in Appendix 1. Additionally, the references of systematic reviews and meta-analyses were manually searched to include all relevant articles. The articles list was collected in EndNote X9.

Selection criteria

The first screening was conducted based on the title, abstract, and quality assessment by two independent researchers (S.D-KH and P.A-CH). The second screening was performed by scanning the entire manuscript. An article was included if it studied the prevalence of retinopathy among patients with diabetes in a normal population. In cases of conflict, a third researcher (A.H) made the final decision whether to include or exclude an article. The Joanna Briggs Institute checklist for systematic reviews was used for methodological quality assessment (possibility of bias in design, conduct, and analysis) of included studies.[25] The result of the quality assessment is presented in Appendix 2.

Data extraction

All targeted statistics were entered into a checklist prepared as a spreadsheet. This checklist included the first author's name, publication year, recruitment time span, country, sample size, proportion (%) and upper and lower 95% confidence intervals (CIs) of retinopathy, range of participants' age, mean duration of diabetes, and method of diagnosis.

Statistical analysis

Statistical analysis was carried out by R (v3.4.1, www.r-project.org) using metafor[26] and meta[27] packages. We followed a recently published paper for the meta-analysis of proportions.[28] Our codes are provided in Appendix 3.

For calculating the summary effect size, we applied the random-effects model because both between-study variance (tau;^{2} true effect sizes related to population characteristics) and within-study variance (due to the random sampling error) exist in most series of observational studies on a specific topic. Additionally, results

obtained by the random-effects model are more generalizable. The random-effects model was carried out using the restricted maximum likelihood method. Moreover, we applied the double-arcsine transformation method to make the included studies follow a normal distribution to obtain more accurate estimates of summary proportions and statistical analyses.

Heterogeneity consists of two distinct components: the between-study variance (tau;[2] real variation) and the within-study variance (sampling error). Because a considerable variation (heterogeneity) in the summary proportion usually exists, we visually inspected the output forest plot (studies with 95% CIs non-overlapping with the 95% CIs of the summary effect), performed X^2 tests (general heterogeneity), and calculated I^2 statistics (the proportion of heterogeneity refers to the between-study variance). It is worth noting that our estimated I^2 was 99.77% (95% CI = 99.70, 99.83), which means that approximately all heterogeneity could be attributed to the between-study variance. Therefore, we carried out subgroup analyses or meta-regression to explore different potential mediators of this heterogeneity of the effect sizes, including the Human Development Index (HDI; a relative measure of the living standards in human societies)[29], publication year, and mean duration of diagnosed diabetes. For subgroup analysis, the random-effects model was used to obtain summary effect sizes within each subgroup, and then a fixed-effects model was used to test whether these effects differed significantly from each other.

To visualize studies' effects and their CIs, we generated a forest plot. It is worth noting that by visual inspection of another forest plot (Appendix 4) that sorted the studies according to their precisions (using standard error), the nine largest studies were considered outliers, which confirmed the high overall heterogeneity. However, we performed a quantitative test to determine if the outlying studies were truly outliers. It was carried out by externally studentized residuals, which consider a study as an outlier if its absolute value is larger than 3, and leave-one-out estimates for the amount of heterogeneity, which consider a study as an outlier if its exclusion leads to a considerable influence on the summary proportion. In the externally studentized residuals test, we did not find any study with an absolute value of larger than 3 (Appendix 5). Moreover, the leave-one-out diagnostic test did not find any influential outlier (Appendix 6–9).

We generated a funnel plot and carried out objective tests for publication bias, including Egger's regression test and the rank correlation test, which are powerful for large meta-analyses involving more than 75 studies. However, it should be noticed that in epidemiology studies, papers reporting either low proportions or high proportions are likely to be published. Therefore, exploring the publication bias might not be applicable in meta-analyses of observational studies. $p < 0.05$ was considered statistically significant.

Results

Search results

We initially identified 4096 citations. After discarding duplicates (automatic: 930; manually: 198) and publications before 2000, 2974 studies were screened based on the title and abstract, which resulted in 153 articles for the second round of screening. In addition, 43 studies were manually added. After reading 196 full texts, 87 papers were discarded, and 109 remaining articles were entered into the meta-analysis. The reasons for excluding the 87 articles were: (1) studies outside of the EMR (n = 21), not normal population (n = 9), not reporting the prevalence of retinopathy

(n = 6), reporting the incidence of retinopathy (n = 3), review or meta-analysis study (n = 13), non-English papers (n = 7), full text unavailable (n = 5), unclear results (n = 5), and irrelevant papers (n = 18). The flowchart of data retrieval is shown in Figure 1.

Description of the included studies

The basic characteristics of the included studies in the meta-analysis are shown in Table 1. Our dataset consisted of 109 studies that were published from 2000 to 2019 and contained population-based or secondary- or tertiary-care-based data on the prevalence of retinopathy in patients with diabetes in the EMR. The sample sizes of the included studies ranged from 51 to 64,351 patients, with a combined total of 280,566 patients. Twelve (11.01%) studies included undiagnosed subjects with type 2 diabetes, while the remaining studies were only conducted on known cases of type 2 and/or type 1 diabetes. The prevalence of diabetic retinopathy was reported for only patients with type 1 diabetes in three (2.75%) studies, only patients with type 2 diabetes in 61 (55.96%) studies, and both type 1 and 2 diabetes separately in 11 (10.09%) studies. Additionally, in 27 (24.77) studies, the prevalence of diabetic retinopathy was not provided for each type of diabetes separately, even though the study had been conducted

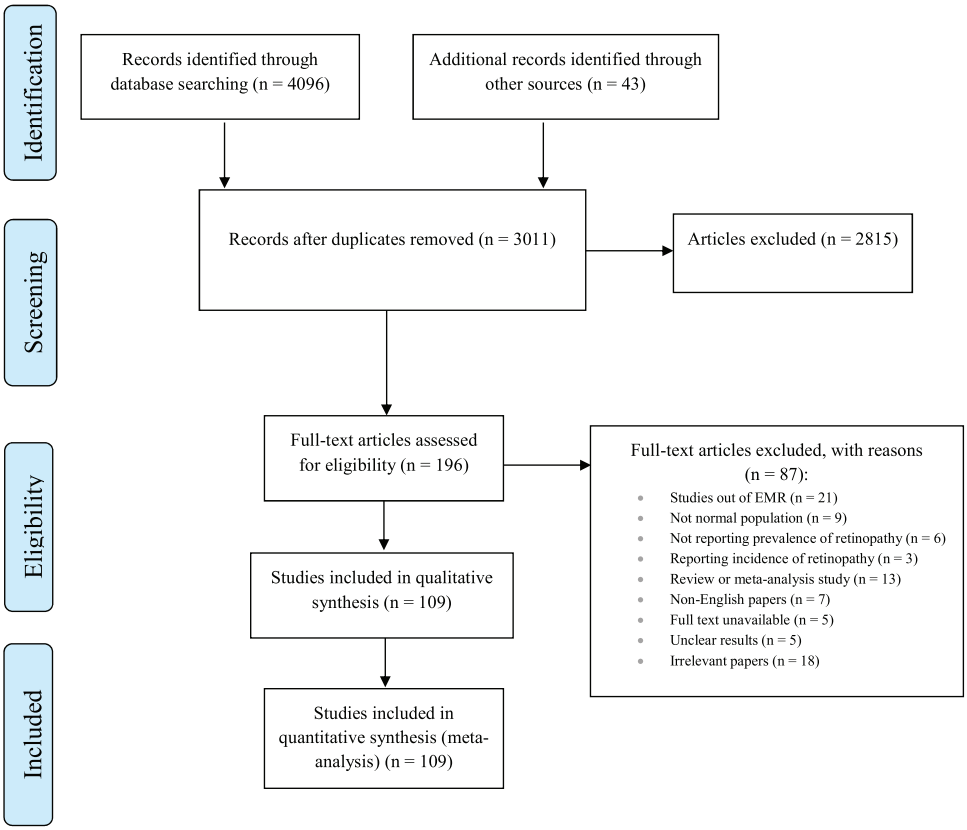

Figure 1. Flowchart of search and screening results (PRISMA-2020-Flow-Diagram).
EMR, Eastern Mediterranean Region.

Table 1. Basic characteristics of the studies included in the review.

#	Author, Year	Country, HDI	Time period	UDDM included	Diabetes type	N	PDR (%)	Age (year)	Mean duration	Diagnosis tool	Stage of DR (N)				
											Mild NPDR	Moderate NPDR	Severe NPDR	PDR	ME
1	Khanedkar, 2005[29]	Oman, VH	2002	–	1 & 2 [Y]	2,520	14	NA	NA	C1,3	NA	NA	NA	NA	NA
2	Din, 2006[30]	Pakistan, M	2002	–	1 & 2 [Y]	108	15.7	30–70	NA	C1	6	5	2	1	3
3	Humera Ishaq, 2016[31]	Pakistan, M	2013–2014	–	2	154	42.86	50.59 ± 10.24	NA	C1	NA	NA	NA	NA	NA
4	Taleb, 2008[32]	Lebanon, H	2005–2007	–	2	235	33	57.7 ± 10.6	8.2 ± 6.6	C1	NA	NA	NA	NA	NA
5	Harb, 2018[33]	Lebanon, H	2006–2016	–	2	484	24.6	NA	8.3 ± SD?	C1	30	32	14	43	81
6	Shaikh, 2008[34]	Pakistan, M	2003	+	NA	660	15.3	≥30	NA	C1	NA	NA	NA	NA	NA
7	Alaboud, 2016[35]	Saudi Arabia, VH	2014	–	2	748	14.7	25–97	NA	NA	NA	NA	NA	NA	NA
8	Al-Agha, 2015[36]	Saudi Arabia, VH	2013–2014	–	1	228	4.4	10.99 ± SD?	NA	NA	NA	NA	NA	NA	NA
9	Esteghamati, 2017[37]	Iran, H	2015–2016	–	1 & 2 [N]	30,202	21.9	≥18	NA	NA	NA	NA	NA	NA	NA
10	Hajar, 2015[18]	Saudi Arabia, VH	2011–2012	–	NA	740	27.8	≥50	NA	C1	NA	NA	NA	NA	NA
11	Alvi, 2016[38]	Pakistan, M	2011–2012	–	1 & 2 [Y]	8,742	20.3	19–102	0.5	C1,2	NA	NA	NA	NA	NA
12	Ali, 2013[39]	Pakistan, M	2011–2012	+	2	113	24.79	30–70	0.5	C1	NA	NA	NA	NA	NA
13	Memon, 2014[40]	Pakistan, M	2009–2011	–	1 & 2 [Y]	10,768	24.7	53.18 ± SD?	NA	C1,2	1209	386	52	129	852
14	Javanbakht, 2012[41]	Iran, H	NA	–	2	3,472	40.4	59.4 ± 11.7	8.08 ± 6.7	NA	NA	NA	NA	NA	NA
15	Hussain, 2013[42]	Pakistan, M	2011–2012	–	2	300	23.9	49.04 ± 0.69	7.17 ± 0.38	C1	NA	NA	NA	NA	NA
16	Valizadeh, 2016[43]	Iran, H	2015	–	2	206	45.1	60.4 ± 3	13 ± SD?	NA	NA	NA	NA	NA	NA
17	Janghorbani, 2003[44]	Iran, H	1992–2001	–	NA	549	45.35	45.7 ± 9.3	6.9 ± 5.7	C1	NA	NA	NA	NA	NA
18	Khandekr, 2015[45]	Saudi Arabia, VH	2013–2014	–	1 & 2 [Y]	51	52	24-89	3.6 ± 4.2	NA	NA	NA	NA	5	4
19	Al-Zuabi, 2005[46]	Kuwait, VH	2002–2004	+	2	92	7.6	≥51	0.5	C2	NA	NA	NA	NA	NA
20	Safi, 2019[47]	Iran, H	2018	–	1 & 2 [N]	604	40	53 ± 14	9 ± 7	C1,2	NA	NA	NA	NA	NA
21	Rahman khan, 2010[48]	Saudi Arabia, VH	2007–2009	–	1 & 2 [Y]	473	30	≥18	8.61 ± 5.96	C5	NA	NA	NA	NA	NA
22	Mehhana, 2017[49]	Lebanon, H	2004	–	2	462	39.18	57.27 ± 10.91	8.39 ± 7.38	C1,3,5,6,7	62	18	14	8	NA
23	Katibeh, 2014[50]	Iran, H	2012–2013	–	NA	529	29.5	40-80	NA	C1,2,5	NA	NA	NA	NA	NA
24	Aidenloo, 2016[51]	Iran, H	2012–2013	–	2	327	32.6	54.7 ± 8.4	7.3 ± 0.6	C2	NA	NA	NA	NA	NA
25	Jammal, 2013[52]	Jordan, H	2009–2011	+	2	127	7.9	49.7 ± 10	0.5	C1	NA	NA	NA	NA	NA
26	Alberto, 2016[53]	Saudi Arabia, VH	2012–2013	–	1 & 2 [N]	126	61	38-87	14.9 ± SD?	NA	NA	NA	NA	NA	NA
27	Ahmed, 2016[19]	Saudi Arabia, VH	2008–2013	–	2	401	36.4	54.6 ± 12.3	9.2 ± SD?	C2,3,5	84	29	16	17	NA
28	Ageely, 2019[54]	Saudi Arabia, VH	2017	–	2	281	32.4	≥18	NA	NA	NA	NA	NA	NA	NA
29	Elwali, 2017[55]	Sudan, L	2015	–	1 & 2 [N]	316	82.6	58.7 ± 10.5	NA	C1,5	NA	NA	NA	126	140
30	Abro, 2019[56]	Pakistan, M	2005–2016	–	2	28,601	15.8	52.5 ± 11.3	8.2 ± 7.5	C1,2	NA	NA	NA	NA	NA
31	Sultan, 2019[57]	Pakistan, M	2017	–	2	709	17.5	49.93 ± 12.51	9.01 ± 7.71	C5	NA	NA	NA	NA	NA

(continued)

Table 1. Continued.

#	Author, Year	Country, HDI	Time period	UDDM included	Diabetes type	N	PDR (%)	Age (year)	Mean duration	Diagnosis tool	Stage of DR (N)				
											Mild NPDR	Moderate NPDR	Severe NPDR	PDR	ME
32	Zia, 2016[58]	Pakistan, M	2011–2012	–	2	678	0.56	51.81 ± 11.43	7.23 ± 6.75	NA	NA	NA	NA	NA	NA
33	El-Gendi, 2018[59]	Egypt, H	2014–2016	–	1 & 2 [N]	67	62.7	57 ± 12.5	NA	C1,5	NA	NA	NA	NA	NA
		Sudan, L	2014–2016	–	1 & 2 [N]	86	26.7	51.8 ± 11.1	NA	C1,5	NA	NA	NA	NA	NA
		Yemen, L	2014–2016	–	1 & 2 [N]	56	87.5	52.5 ± 12	NA	C1,5	NA	NA	NA	NA	NA
34	Ahsan, 2015[60]	Pakistan, M	2009–2010	–	2	366	27.3	48.5 ± 8.02	9.17 ± 6.51	C2	NA	NA	NA	NA	NA
35	Morsy, 2019[61]	Saudi Arabia, VH	2017	–	1 & 2 [N]	234	27.35	12-65	NA	C1	NA	NA	NA	NA	NA
36	Bamashmus, 2009[62]	Yemen, L	2004	–	1 & 2 [N]	350	55	54.4 ± 11.8	9.9 ± 7.77	C1,5	NA	NA	45	60	77
37	Abdelfattah, 2014[63]	Egypt, H	2012	–	1 & 2 [N]	71	52.11	54.53 ± 15.03	NA	NA	NA	NA	NA	NA	NA
38	Hyassat, 2014[64]	Jordan, H	2011–2012	–	2	1,105	23	57.1 ± 10.3	5.1 ± SD?	NA	NA	NA	NA	NA	NA
39	Al-Otaiby, 2017[65]	Saudi Arabia, VH	2015–2016	–	1 & 2 [N]	400	48.8	NA	NA	C1	NA	NA	NA	NA	NA
40	Al-Till, 2005[66]	Jordan, H	NA	–	1 & 2 [N]	986	64.1	55.3 ± 12.5	11.9 ± 6.3	C1,2,5,6,7	NA	NA	NA	NA	NA
41	Khandekar, 2009[67]	Oman, VH	2006	–	1 & 2 [N]	418	7.9	52.23 ± 12.51	NA	C5	NA	NA	NA	NA	NA
42	Kamaleldeen, 2018[68]	Egypt, H	2012–2014	–	1	180	1.1	13.82 ± 3.23	6 ± 3.08	C1,2	NA	NA	NA	NA	NA
43	AL-Amir, 2008[69]	Jordan, H	2006–2007	–	2	1,000	34.1	57.8 ± 9.9	9.6 ± 7.6	C1,5	121	71	53	96	78
44	Bamashmus, 2009[70]	Yemen, L	2004	–	1 & 2 [N]	228	51.1	50.01 ± 12.0	NA	C1,5	NA	NA	NA	NA	NA
45	Costanion, 2014[71]	Lebanon, H	2008–2009	–	2	187	16.6	44.7 ± 14.9	NA	NA	NA	NA	NA	NA	NA
46	El Samahy, 2015[72]	Egypt, H	2010–2013	–	1 & 2 [N]	600	1.83	13.29 ± 5.05	6.37 ± 3.64	C1	NA	NA	NA	NA	NA
47	Rahman KHan, 2014[73]	Saudi Arabia, VH	2012–2013	–	2	506	2.96	57.44 ± SD?	10.2 ± 5.96	C1	6	7	NA	2	NA
48	El-Shafei, 2011[74]	Qatar, VH	2009	–	1 & 2 [N]	540	23.5	≥40	12.88 ± 9.06	C1,2,5	NA	NA	NA	NA	NA
49	Kahloun, 2014[75]	Tunisia, H	2007–2011	–	1 & 2 [N]	2,320	26.3	54.5 ± SD?	7.6 ± SD?	C1,2,5,6,7	530	280	251	156	402
50	Rabiu, 2015[21]	Jordan, H	NA	–	1 & 2 [N]	1,040	48.4	≥50	NA	C1	NA	NA	NA	NA	NA
51	Heydari, 2012[76]	Iran, H	2008–2010	–	1 & 2 [N]	1,022	23.6	55.7 ± 12.2	6.85 ± SD?	C1,5	NA	NA	NA	NA	NA
52	Mehravar, 2016[77]	Iran, H	2014	–	2	562	28.1	61.62 ± 10.49	12.82 ± 6.61	C1	NA	NA	NA	NA	NA
53	Khandekar, 2004[78]	Oman, VH	NA	–	1 & 2 [N]	2,063	15.07	NA	NA	C1,5	NA	NA	NA	NA	NA
54	Rahman, 2011[79]	Pakistan, M	NA	–	1 & 2 [N]	200	51	48.3 ± 13	8.5 ± 5.6	C1,4,5	NA	NA	NA	NA	NA
55	Wahab, 2008[80]	Pakistan, M	2006	+	2	130	15	43.2 ± 10.2	0.5	C1	NA	NA	NA	NA	NA
56	Shera, 2004[81]	Pakistan, M	NA	–	2	500	43	55.2 ± 10.6	7 ± SD?	C1	NA	NA	NA	NA	NA
57	Al-Akily, 2011[82]	Yemen, L	2001–2005	–	1 & 2 [N]	694	53	53.9 ± 11.52	10.3 ± 7.7	C1,3,4,5,6	NA	NA	NA	NA	NA
58	Iqbal, 2009[83]	Pakistan, M	2005	+	2	100	9	47 ± SD?	0.5	C1	NA	NA	2	1	NA
59	Yasir, 2019[84]	Saudi Arabia, VH	2014-2017	–	1 & 2 [N]	395	33.7	≥40	NA	C1,5,6	NA	NA	NA	NA	NA
60	Al-Rubeaan, 2015[85]	Saudi Arabia, VH	NA	–	2	50,464	19.7	59.7 ± 12.78	13.4 ± 8.24	C1,4	9.1	NA	NA	5367	2880

(continued)

Table 1. Continued.

#	Author, Year	Country, HDI	Time period	UDDM included	Diabetes type	N	PDR (%)	Age (year)	Mean duration	Diagnosis tool	Stage of DR (N)				
											Mild NPDR	Moderate NPDR	Severe NPDR	PDR	ME
61	Farasat, 2017[86]	Pakistan, M	2010	+	2	200	33	50.69	0.5	C1	NA	NA	NA	NA	NA
62	Szabo, 2015[87]	UAE, VH	2009–2011	–	2	150	6	58.3 ± 12.2	14.4 ± 7.7	NA	NA	NA	NA	NA	NA
63	Javadi, 2009[88]	Iran, H	2007	–	1 & 2 [N]	634	37	58.16 ± 11.98	NA	C1,5	114	42	19	65	38
64	Al-Maskari, 2007[89]	UAE, VH	2003–2004	–	1 & 2 [Y]	513	19	53.3 ± 13.01	NA	C2,5,7	NA	NA	NA	NA	NA
65	Al Kahtani, 2016[90]	Saudi Arabia, VH	2000–2010	–	1 & 2 [Y]	64,351	17.5	55.92 ± 14.5	13.17 ± 8.05	NA	NA	NA	NA	6146	2914
66	Uddin, 2018[91]	Pakistan, M	2015–2016	+	2	891	15.9	47.7 ± 10.6	0.5	C1	NA	NA	NA	NA	NA
67	Khandekar, 2003[92]	Oman, VH	2000–2001	–	1 & 2 [Y]	2,249	14.39	NA	NA	C1,5,7	NA	NA	NA	67	149
68	Nizamani, 2017[93]	Pakistan, M	2014–2015	–	1 & 2 [N]	1,6760	17	>15	NA	C1,4	NA	NA	NA	NA	NA
69	Jelinek, 2017[94]	UAE, VH	2014–2015	–	2	490	13.26	60 ± 11.3	NA	NA	NA	NA	NA	NA	NA
70	Akhter, 2017[95]	Pakistan, M	2014–2015	–	1 & 2 [N]	876	7.8	53.1 ± 11.9	7.6 ± 7.1	NA	NA	NA	NA	NA	NA
71	Alfadda, 2006[96]	Saudi Arabia, VH	2001–2003	–	2	99	25.3	56.6 ± 12	11.8 ± 7.7	NA	NA	NA	NA	NA	NA
72	Alwakeel, 2008[97]	Saudi Arabia, VH	1989–2004	–	2	1,952	16.7	58.4 ± 14.2	10.4 ± 7.5	NA	NA	NA	NA	NA	NA
73	Ahmed, 2019[98]	Sudan, L	2015	–	1 & 2 [N]	316	83.3	NA	NA	NA	NA	NA	NA	NA	NA
74	Awadalla, 2017[99]	Sudan, L	NA	–	2	424	72.6	20-75	NA	NA	NA	NA	NA	NA	NA
75	Awadalla, 2017[99]	Sudan, L	NA	–	2	316	51.6	58 ± 10	NA	NA	NA	NA	NA	NA	NA
76	Niroomand, 2016[100]	Iran, H	2014	–	2	200	60.5	60.17 ± 13.56	13.06 ± SD?	NA	NA	NA	NA	NA	NA
77	Salti, 2009[22]	Lebanon, H	2004–2007	–	2	557	35	56.4 ± 11.7	9.2 ± 6.9	C1,5,7	NA	NA	NA	45	42
78	Azizi-Soleiman, 2015[101]	Iran, H	2003–2014	–	2	1,429	56.3	NA	NA	C1,5,7	NA	NA	NA	NA	NA
79	Solaymani, 2012[102]	Iran, H	2007–2008	–	2	140	36.42	53.49 ± 9.72	8.88 ± 6.06	C1,5,7	NA	NA	NA	8	35
80	Al-Ghamdi, 2012[103]	Saudi Arabia, VH	NA	–	2	852	34.5	63.3 ± SD?	NA	C1,2	NA	NA	NA	NA	NA
81	Saadi, 2007[104]	UAE, VH	2005–2006	–	2	245	54.2	>18	NA	C1	NA	NA	NA	NA	NA
82	Abdolghani, 2018[105]	Saudi Arabia, VH	2015–2016	–	2	360	23.3	18-75	NA	NA	NA	NA	NA	NA	NA
83	Ghaem, 2018[106]	Iran, H	2015–2016	–	1 & 2 [N]	478	32.8	56.64 ± 12.45	11.37 ± 9	NA	82	44	18	13	NA
84	Basit, 2005[107]	Pakistan, M	1996–2001	–	2	2,199	15.9	NA	NA	C1	NA	NA	NA	NA	NA
85	Faghih-Amini, 2005[108]	Iran, H	2004	–	1	500	76.4	49.59 ± SD?	NA	NA	NA	NA	NA	NA	NA
86	Shafiqur-Rahman, 2004[109]	Pakistan, M	2002	NA	NA	185	55	48.3 ± 13.3	8.5 ± 5.6	C1	NA	NA	NA	NA	NA
87	Afghani, 2007[110]	Pakistan, M	1997–2001	+	NA	8,227	22.29	≥40	NA	C1	NA	NA	NA	NA	NA
88	Esteghamati, 2007[111]	Iran, H	NA	–	2	66	36.4	57 ± 9.5	14.44 ± 6.78	NA	NA	NA	NA	NA	NA
89	Al-Adsani, 2007[112]	Kuwait, VH	2000–2005	–	2	165	40	48.99 ± 10.05	8.03 ± 7.04	C1,2	35	NA	NA	5	17
90	Askarishahi, 2012[113]	Iran, H	2008	–	2	459	40.7	55 ± 9.9	10.5 ± 6.4	C1,5	NA	NA	NA	NA	NA
91	Aamir, 2012[114]	Pakistan, M	2011	–	2	2,123	38.34	57.4 ± 22	NA	C1,2	NA	NA	NA	NA	NA

(continued)

Table 1. Continued.

#	Author, Year	Country, HDI	Time period	UDDM included	Diabetes type	N	PDR (%)	Age (year)	Mean duration	Diagnosis tool	Stage of DR (N)				
											Mild NPDR	Moderate NPDR	Severe NPDR	PDR	ME
92	Bonakdaran, 2015[115]	Iran, H	NA	–	2	235	34.8	54.8 ± 9.4	7.52 ± 6.1	C1	NA	NA	NA	NA	NA
93	Dehghan, 2015[116]	Iran, H	NA	+	NA	529	29.6	54.11 ± 10.06	NA	C1,2,5	67	52	24	16	25
94	Najafi, 2013[117]	Iran, H	2011–2012	–	2	243	17.69	55.8 ± 10.33	9.08 ± 7.9	NA	NA	NA	NA	NA	NA
95	Amini, 2008[118]	Iran, H	2001–2004	+	2	710	9	48.8 ± 9.8	0.5	C1	NA	NA	NA	NA	NA
96	Hosseini, 2014[119]	Iran, H	2011–2012	–	2	305	35.7	53.9 ± 1	8.2 ± 7.1	C1	NA	NA	NA	NA	NA
97	AlamKhanzada, 2011[120]	Pakistan, M	2009–2010	–	2	244	40.94	45 ± 11.5	13 ± 4.5	C1,4,5	NA	NA	NA	NA	NA
98	Manaviat, 2004[121]	Iran, H	2000–2001	–	2	590	39.7	54.9 ± 10.2	10.2 ± 6.6	C1,4,5,6	113	71	16	32	52
99	Manaviat, 2008[122]	Iran, H	NA	–	2	199	70.35	54.16 ± 11.2	NA	C1,2,5	34	34	22	50	NA
100	Sohail, 2014[123]	Pakistan, M	2009–2010	–	2	202	56.9	52.9 ± 10.5	8.5 ± 5.1	C1	NA	NA	NA	NA	NA
101	Khalid, 2015[124]	Pakistan, M	2014–2015	–	2	340	17	47.55 ± 9.13	NA	C1,5	23	17	10	7	NA
102	Shaikh, 2010[125]	Pakistan, M	2008–2010	–	2	200	25.5	38-70	NA	C1	NA	NA	NA	NA	NA
103	Hassan, 2010[126]	Pakistan, M	2004–2005	–	2	500	41.4	NA	NA	NA	NA	NA	NA	NA	NA
104	Rasoulinejad, 2015[127]	Iran, H	2006–2010	–	1 & 2 [N]	1,562	64.1	54.6 ± 10.6	9.6 ± 7	C5	NA	NA	NA	NA	NA
105	Macky, 2011[128]	Egypt, H	2007–2008	–	1 & 2 [Y]	1,325	20.5	49 ± 12.9	NA	C1,5,6	NA	NA	NA	NA	NA
106	Hussain, 2011[129]	Pakistan, M	2008–2009	–	1 & 2 [Y]	1,524	12	20–70	NA	C1,3,5,6	NA	NA	NA	NA	NA
107	Janghorbani, 2017[130]	Iran, H	2001–2004	–	2	1,566	36.46	50.6 ± 12.3	7.6 ± 6.9	C1,2	NA	NA	NA	NA	NA
108	Jsnghorbani, 2006[131]	Iran, H	2000–2003	–	2	810	33.38	52.7 ± 9.9	8.2 ± 6.8	C2	NA	NA	NA	NA	NA
109	Khazaei, 2010[132]	Iran, H	2002	+	2	200	11	NA	NA	C1	NA	NA	NA	NA	NA

Codes [1]: VH (very high); H (high); M (medium); L (low).

Codes [2]: C1 (Dilated fundus examination (ophthalmoscopy)); C2 (Retinal photography); C3 (Digital stereoscopic retinal imaging); C4 (Angiography); C5 (Slit lamp biomicroscopy); C6 (Visual acuity); C7 (Tonometry).

Codes [3]: D (diagnosed diabetes); nD (newly diagnosed diabetes).

Codes [4]: [Y] (P_{DR} reported for both type I and II diabetes, separately); [N] (P_{DR} not reported for both type I and II diabetes, separately).

Abbreviations: NPDR, non-proliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy; ME, macular edema; UDDM, undiagnosed diabetes; SD, standard deviation.

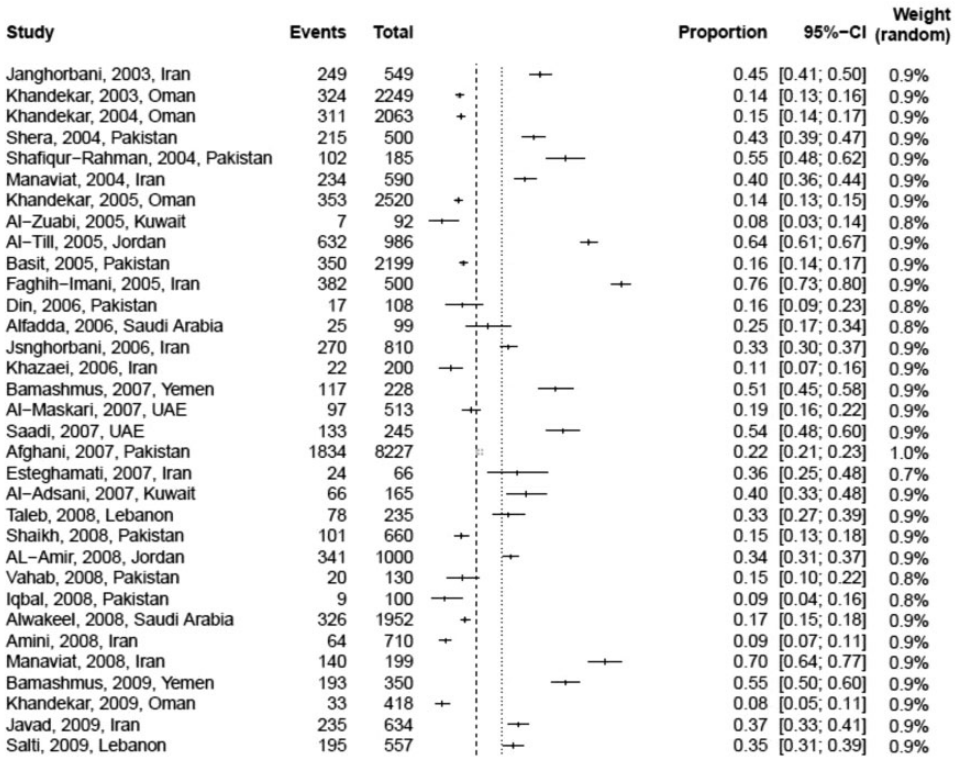

Figure 2. Forest plot of 109 studies.
CI, confidence interval.

on both types. Judgement for the remaining seven (6.42%) studies was not feasible. Furthermore, 13 (11.93%) and 7 (6.42%) studies provided the classified prevalence of diabetic retinopathy according to the stage (i.e., non-proliferative diabetic retinopathy and proliferative diabetic retinopathy) and the presence of macular edema in addition to the stage of diabetic retinopathy, respectively.

Results of the meta-analysis

Heterogeneity. The output of heterogeneity analysis showed that tau^2 was 0.05 (95% CI = 0.04, 0.06), I^2 was 99.77% (95% CI = 99.7, 99.83), and the Q-statistic was 13,537.27 ($p < 0.0001$), all of which suggested a high heterogeneity in the effect sizes. Additionally, the high value of I^2 indicated that almost all heterogeneity was related to the between-study variance (Figure 2).

Prevalence of retinopathy in diabetes. We found that the summary proportion was 0.31 (95% CI = 0.28, 0.33), which represented a 31% prevalence of diabetic retinopathy (Figure 2).

Prevalence of retinopathy in diabetes based on subgroup analysis by HDI. Low HDI countries and very high HDI countries had the highest and lowest diabetic retinopathy prevalence. Moreover, the recalculated prevalence of retinopathy was 0.254 (95% CI = 0.238, 0.270). In subgroup analysis by

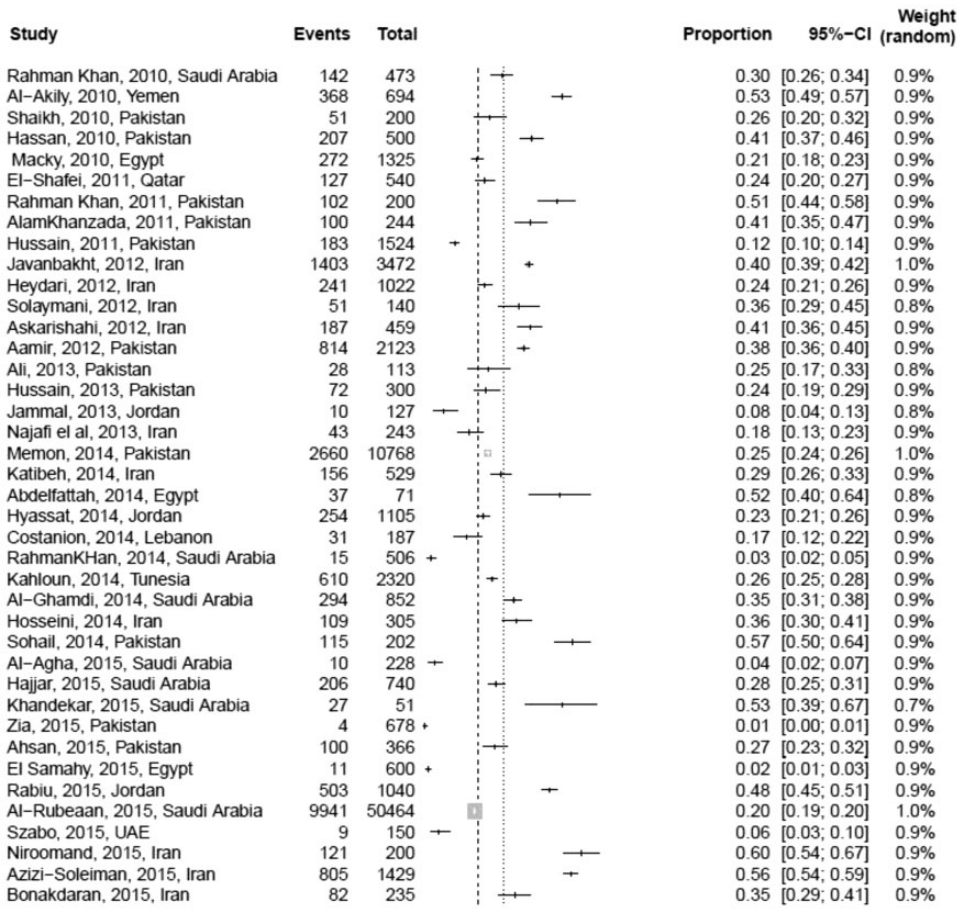

Figure 2. Continued.

HDI, the summary effect proportions were 0.636 (95% CI = 0.524, 0.740), 0.240 (95% CI = 0.211, 0.269), 0.339 (95% CI = 0.292, 0.388), and 0.226 (95% CI = 0.205, 0.247) for the four subgroups (low, medium, high, and very high), respectively. As a nature of our analysis (separate random-effects models in each subgroup), within-group estimates of tau^2 were 0.029 [Q (df = 8) = 280.461, $p < 0.001$], 0.008 [Q (df = 28) = 2231.918, $p < 0.001$], 0.029 [Q (df = 43) = 5009.601, $p < 0.001$], and 0.004 [Q (df = 28) = 1305.489, $p < 0.001$] for low, medium, high, and very high subgroups, respectively. We found that the difference between the four subgroup summary estimates was significant (QM (df = 3) = 0.45, $p < 0.001$), and HDI had a moderating effect on the prevalence of diabetic retinopathy and shared effect on the true heterogeneity in the proportion.

Results of the meta-regression

The meta-regression analysis was performed for three different variables, including HDI, publication year, and the mean duration of diagnosed diabetes.

The slope of the estimated regression line suggested that HDI had a significant

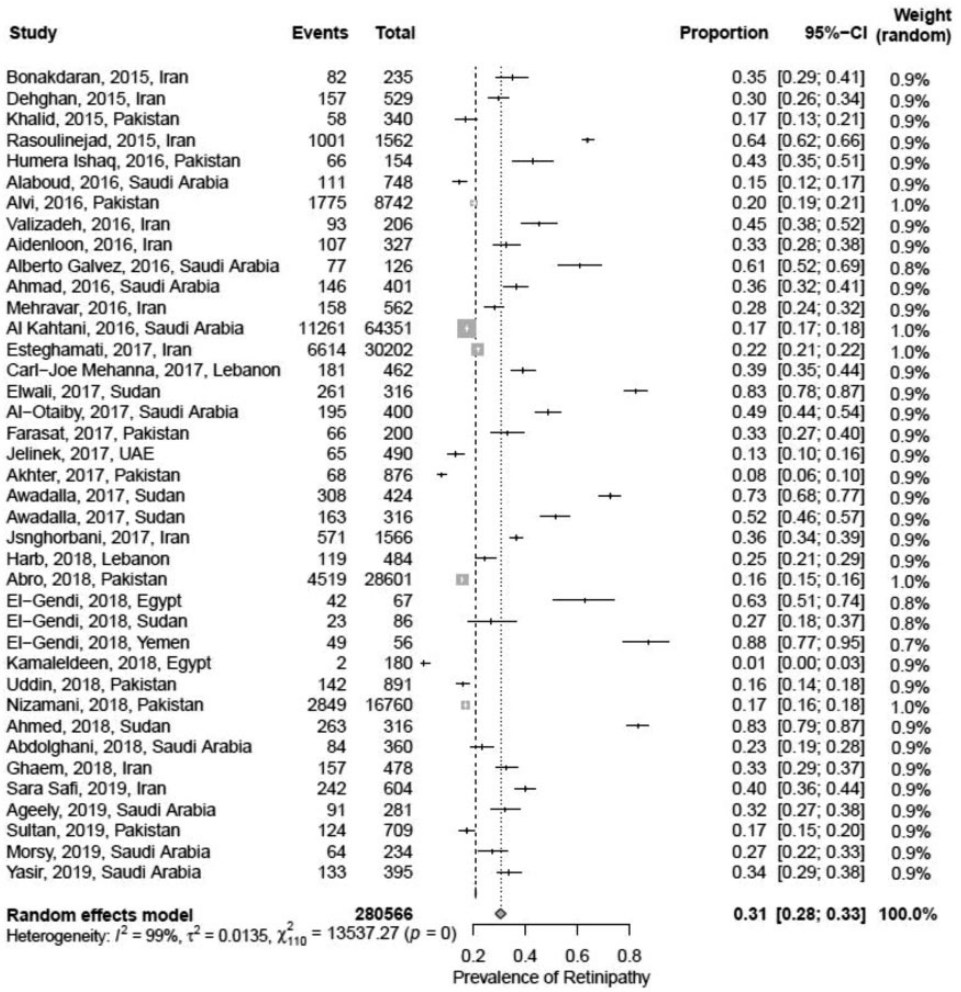

Figure 2. Continued.

negative moderating effect on the prevalence of retinopathy in diabetes (results of the test of modulators: [QM (df = 1) = 27.016, $p < 0.0001$]; slope coefficient: [−0.069, $Z = -5.198$, $p < 0.0001$]) (Figure 3).

The slope of the estimated regression line for publication year was almost horizontal, suggesting that it was not a significant modulator of the prevalence of retinopathy in diabetes (results of the test of modulators: [QM (df = 1) = 0.184, $p = 0.6679$]; slope coefficient: [0.001, $Z = 0.429$, $p = 0.668$]) (Figure 4).

The slope of the estimated regression line for the mean duration of diagnosed diabetes suggested that it had a significant positive moderating effect on the prevalence of retinopathy in diabetes (results of the test of modulators: [QM (df = 1) = 19.752, $p < 0.0001$]; slope coefficient: [0.019, $Z = 4.444$, $p < 0.0001$]) (Figure 5).

Importantly, in all meta-regression plots, most studies were outside the 95% CI

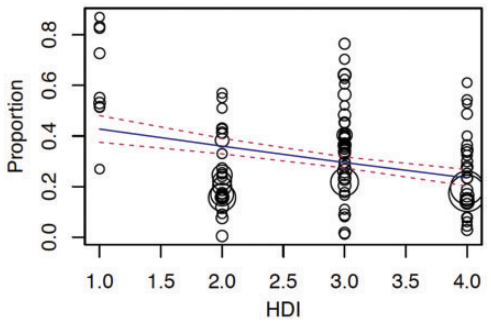

Figure 3. The scatter plot of HDI and the effect sizes [Note for interpretation: Each study was represented by a circle with a size proportional to the study size.]
HDI, Human Development Index

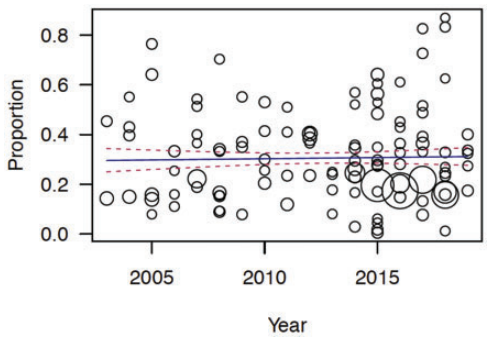

Figure 4. The scatter plot of publication year and the effect sizes [Note for interpretation: Each study was represented by a circle with a size proportional to the study size.]

boundaries, indicating the presence of unknown or missed parameters affecting the prevalence of retinopathy in diabetes. A zero-to-negligible value of R^2, which represents the amount of between-study heterogeneity explained by a modulator, supported this claim ($R^2_{HDI} = 0.00$, $R^2_{\text{publication year}} = 1.33\%$, $R^2_{\text{mean duration of diagnosed diabetes}} = 0.00$).

Publication bias

Visual inspection of the funnel plot of proportions against sample sizes showed that our data were asymmetrical (Figure 6). Additionally, Egger's test showed that the

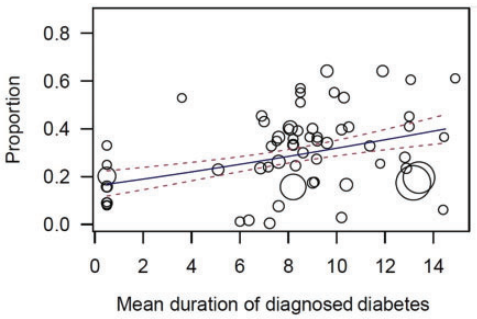

Figure 5. The scatter plot of the mean duration of diagnosed diabetes and the effect sizes [Note for interpretation: Each study was represented by a circle with a size proportional to the study size.]

funnel plot was significantly asymmetrical ($Z = 2.321$, $p = 0.020$). Furthermore, the funnel plot of proportions against sample sizes showed that a small-study effect was present in our meta-analysis (Appendix 10). However, the rank correlation test did not find any association between the sample size and the reported prevalence of diabetic retinopathy of each study (Kendall's tau $= 0.057$, $p = 0.375$).

Discussion

To our knowledge, this is the first meta-analysis on the prevalence of diabetic retinopathy, irrespective of the type of diabetes, in the EMR, including 109 population-based studies. Most studies included in the meta-analysis were from Iran (28 articles) and Pakistan (28 articles), followed by Saudi Arabia (18 articles), while we could not find any publication that matched our inclusion criteria on the prevalence of diabetic retinopathy from Afghanistan, Bahrain, Iraq, Syria, Somalia, Morocco, Palestine, Djibouti, and Libya. Based on the analysis, the high between-study heterogeneity in this study might indicate a regional difference in the prevalence of diabetic retinopathy in the EMR. In other words,

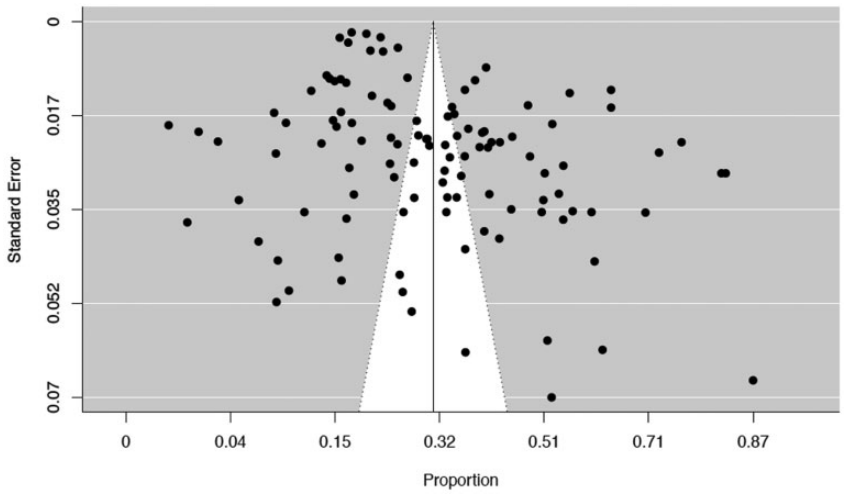

Figure 6. The funnel plot of effect size against standard error [Note for interpretation: Each dot denotes a study, the vertical line denotes the summary effect size, and the two limit lines denote the 95% confidence intervals of the summary effect size.]

the effectiveness of health surveillance and early detection in these countries vary.

On the basis of the data from 109 studies and approximately 280,000 participants with diabetes, the prevalence of diabetic retinopathy was estimated to be 31% in the EMR, which was higher than the global 25.2% estimation reported by IDF in 2019[134] and the 22.27% reported in another meta-analysis in 2021.[135] Furthermore, although the regional classifications by WHO (EMR) and IDF (MENA) are different despite a large overlap, our estimation was comparable to the 33.8% and 32.90% in MENA reported by the above-mentioned studies, respectively.[134,135] However, these estimations did not yield a weighted (according to the country population proportions) summary prevalence of diabetic retinopathy and might be underestimated.

Based on subgroup analysis and meta-regression, HDI was negatively correlated with the prevalence of diabetic retinopathy. The very high HDI countries in the EMR, all of which were "Gulf Cooperation Council (GCC)" countries, had the lowest diabetic retinopathy prevalence rate in the EMR of 22.6%, which is similar to the estimations from Europe (18.75%) and the Western Pacific (19.20%), lower than those from North America and the Caribbean (33.30%) and Africa (35.90%), and higher than those from South East Asia (16.99%) and South and Central America (13.37%).[134] In a low-income developing country with a poor healthcare system (i.e., screening and diabetes care), the risk of retinopathy would be higher in patients with diabetes. Another, perhaps counter-intuitive, point worth mentioning is that the summary proportion in the medium HDI subgroup was higher than that of the high HDI subgroup. One possible explanation may be that Pakistan was the only member in our medium HDI subgroup; therefore, we should consider the situation of the healthcare system and delivery in Pakistan. Public health resources in Pakistan are mostly located in urban regions, which provide a better quality of life in general for their citizens. In addition, owing to the cost associated with poor

transportation systems, most of the rural population cannot go to these public health centers.[136,137] Moreover, the majority of included studies sampled the urban community, which may influence the prevalence of diabetic retinopathy obtained for this category.

The results of meta-regression did not show a statistically significant association between the publication year and prevalence of diabetic retinopathy in the EMR. Thus, the year of study was not a cause of variability in the results. Indeed, publication year cannot properly represent the exact prevalence trend.[138] The regression line is fitted on the pooled data from different countries in each publication year, which can severely introduce selection bias as this is not longitudinal, and the regression line is the result of a sum of data from variable numbers of studies from different sets of countries at each publication year. However, if we consider the publication year as a relative indicator of changes in diabetic retinopathy prevalence in the EMR, one can interpret that this apparently stable trend during the past 20 years in the EMR might imply an interplay between various opposing factors that has ultimately kept the retinopathy rate constant in the EMR. For example, although GCC countries have made progress in recent years and developed their healthcare systems, the rate of diabetes is noticeable because of the several fundamental risk factors of diabetic retinopathy, including rapid industrialization and globalization, sedentary lifestyle, and dramatically decreased physical activity levels.[139] Additionally, several EMR countries have encountered serious economic and political issues because of warfare, sanctions, and refugees, which have drastically compromised the healthcare system.

Another remarkable and important point is that although the meta-regression plots demonstrated correlations of HDI, publication year, and diabetes duration with diabetic retinopathy, most studies were outside of 95% CI boundaries in all three plots. This result indicated the presence of several unknown and missed parameters that define the prevalence of diabetic retinopathy in a region and could not be considered because of the nature of our study.

It is worth noting that the asymmetry in the publication bias assessment might not necessarily indicate publication bias as other parameters that interfere with the inclusion of small studies may contribute to this asymmetry in observational studies.[140] First, we previously showed a high between-study heterogeneity, and a substantial number of studies fell outside of the two limit lines in the forest plot, which confirmed the high heterogeneity. In other words, this high between-study heterogeneity might be due to particular reasons. Second, we excluded small studies in foreign languages, which may have resulted in the so-called English language bias. Third, irrespective of the sensitive search strategy, gray literature search, and manual search in references for relevant studies, citation bias might have been present.

Several studies in the EMR showed a high prevalence of undiagnosed diabetes.[138,141,142] This is important because when treatment starts immediately, especially in the pre-diabetes stage of type 2 diabetes, the risk of diabetes complications decreases. These have implications for our study. In particular, most of the included studies in this meta-analysis were carried out on different sample populations of known type 2 diabetes cases. Therefore, this meta-analysis might have underestimated the prevalence of diabetic retinopathy in the EMR. Moreover, we showed that the longer the duration of diabetes, the higher the prevalence of diabetic retinopathy. The duration of diabetes is a major risk factor in developing diabetic retinopathy.[143] Furthermore, the development of diabetic

retinopathy is related to uncontrolled conditions, such as glycemic control, systolic hypertension, and dyslipidemia, which are prevalent in the EMR.[144,145] For example, the prevalence of uncontrolled diabetes is high (about 60%) among patients with diabetes in the EMR.[13,146] Taking these challenges into account, addressing the healthcare burden of this group would be difficult. In particular, although diabetic retinopathy is a well-known complication with comprehensive and universal identification and control protocols, financial barriers, insufficient health system services (all three levels), and limited skilled practitioners in most countries of the EMR are obstacles for the active and efficient follow-up of all patient populations and communications and consultations to make patients with diabetes aware of the importance of annual check-ups and follow-up protocols even at asymptomatic phases.

Conclusion

Our study provided the first pooled analysis to estimate the prevalence of diabetic retinopathy in the EMR. On the basis of the data from 109 studies and approximately 280,000 participants with diabetes, the prevalence of diabetic retinopathy was estimated to be high as 31% in the EMR. We showed that a longer duration of diagnosed diabetes and worse healthcare systems (using HDI as its proxy) were correlated with a higher rate of diabetic retinopathy. Our results implicate the importance of diabetes screening, periodic examinations for retinopathy, diabetes care, and risk factor controls.

Declaration of conflicting interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Author contributions

All authors conceived the study and were responsible for designing the protocol. AH, MA, and AM designed the study. SS performed the literature search and, together with SPA and SD, selected the studies and extracted the relevant information. All authors synthesized the data. AH and SPA wrote the first draft of the paper. AH, AM, and MA provided critical guidance on the analysis and overall direction of the study. All authors critically revised successive drafts of the paper and approved the final version.

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