AMERICAN ACADEMY OF OPHTHALMOLOGY®

Global Prevalence of Diabetic Retinopathy and Projection of Burden through 2045

Systematic Review and Meta-analysis

Zhen Ling Teo, MBBS, MRCS (Edin),[1,] Yih-Chung Tham, PhD,[1,2,*] Marco Yu, PhD,[1,2,*] Miao Li Chee, BSc,[1] Tyler Hyungtaek Rim, MD, PhD,[1,2] Ning Cheung, MD,[1,2] Mukharram M. Bikbov, MD, PhD,[3] Ya Xing Wang, MD,[4] Yating Tang, MD, PhD,[5] Yi Lu, MD, PhD,[5] Ian Y. Wong, MD, FRCOphth,[6,9] Daniel Shu Wei Ting, MD, PhD,[1,2] Gavin Siew Wei Tan, MD, PhD,[1,2] Jost B. Jonas, MD,[7] Charumathi Sabanayagam, MD, PhD,[1,2] Tien Yin Wong, MD, PhD,[1,2,8,‡] Ching-Yu Cheng, MD, PhD[1,2,8,‡]*

Topic: To provide updated estimates on the global prevalence and number of people with diabetic retinopathy (DR) through 2045.

Clinical Relevance: The International Diabetes Federation (IDF) estimated the global population with diabetes mellitus (DM) to be 463 million in 2019 and 700 million in 2045. Diabetic retinopathy remains a common complication of DM and a leading cause of preventable blindness in the adult working population.

Methods: We conducted a systematic review using PubMed, Medline, Web of Science, and Scopus for population-based studies published up to March 2020. Random effect meta-analysis with logit transformation was performed to estimate global and regional prevalence of DR, vision-threatening DR (VTDR), and clinically significant macular edema (CSME). Projections of DR, VTDR, and CSME burden were based on population data from the IDF Atlas 2019.

Results: We included 59 population-based studies. Among individuals with diabetes, global prevalence was 22.27% (95% confidence interval [CI], 19.73%−25.03%) for DR, 6.17% (95% CI, 5.43%−6.98%) for VTDR, and 4.07% (95% CI, 3.42%−4.82%) for CSME. In 2020, the number of adults worldwide with DR, VTDR, and CSME was estimated to be 103.12 million, 28.54 million, and 18.83 million, respectively; by 2045, the numbers are projected to increase to 160.50 million, 44.82 million, and 28.61 million, respectively. Diabetic retinopathy prevalence was highest in Africa (35.90%) and North American and the Caribbean (33.30%) and was lowest in South and Central America (13.37%). In meta-regression models adjusting for habitation type, response rate, study year, and DR diagnostic method, Hispanics (odds ratio [OR], 2.92; 95% CI, 1.22−6.98) and Middle Easterners (OR, 2.44; 95% CI, 1.51−3.94) with diabetes were more likely to have DR compared with Asians.

Discussion: The global DR burden is expected to remain high through 2045, disproportionately affecting countries in the Middle East and North Africa and the Western Pacific. These updated estimates may guide DR screening, treatment, and public health care strategies. *Ophthalmology 2021;■:1−12 © 2021 by the American Academy of Ophthalmology*

Supplemental material available at www.aaojournal.org.

The International Diabetes Federation (IDF) estimated the global population with diabetes mellitus (DM) to be 463 million in 2019 and projected it to be 700 million by 2045.[1] As the most common and specific complication of DM,[2] diabetic retinopathy (DR) also is one of the leading causes of preventable blindness in the adult working population.[3−6] The Global Burden of Disease Study found that in adults 50 years of age and older, DR was the fifth leading cause of blindness and of moderate and severe vision impairment.[7] In particular, the age-standardized global prevalence for blindness resulting from diabetic eye disease has increased by 14.9% to 18.5% from 1990 to 2020.[7] With a rapidly aging global population, increasing lifespan of people living with DM, and lifestyle changes leading to an increased risk for DM, a higher burden of DR and demand for eye care and treatment are expected. Thus, up-to-date and accurate estimation of the prevalence of DR is critical in the formulation of health policies and for allocation of adequate resources to address this global problem.

A previous meta-analysis on the global prevalence of DR was conducted more than a decade ago using data up to 2008 from 35 population-based studies.[8] A need exists for contemporary data because several important changes regarding the epidemiologic features of DR have emerged in recent years. First, a declining trend for DR prevalence

https://doi.org/10.1016/j.ophtha.2021.04.027
ISSN 0161-6420/21

has been suggested,[9–11] especially in developed countries. This is likely a result of increased awareness and improved systemic control for patients with DM.[11] Second, most studies included in the last meta-analysis were derived from populations of European ancestry.[8] Since 2008, a substantial increase has occurred in the number of population-based studies in other regions, particularly in Asia, which accounts for approximately half of the global DM population.[1,12] The top 2 countries with the highest number of people with DM are both in Asia—China (116 million) and India (77 million)[1]—reflecting the rapid economic growth and urbanization in Asia over the past decade with significant lifestyle and dietary changes.[12,13] Thus, these recent data from Asia should be included to provide better and contemporary estimates of the global prevalence and burden of DR. Third, diabetic macular edema is the most common form of DR causing moderate vision loss.[10] However, the global prevalence of diabetic macular edema has not been described previously. Data on diabetic macular edema is important for global health care guidelines and resource planning, particularly in the context of increasing use of intraocular anti–vascular endothelial growth factor therapy, which may not be available or accessible to all countries.[14,15]

To address these important gaps, we aimed to re-evaluate and re-estimate the global prevalence of DR and to provide future projections of the number of people with DR, vision-threatening DR (VTDR), and clinically significant macular edema (CSME) through 2045. These findings are important in the planning of DR public health policies and screening and management strategies for DR worldwide.

Methods

Systematic Review Process

We conducted a systematic review and meta-analysis to determine the prevalence of DR, VTDR, and CSME, in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines[16] (Appendix A, available at www.aaojournal.org). A systematic search using PubMed, Medline, Web of Science, and Scopus was conducted to identify studies on DR, VTDR, and CSME prevalence. We included a combination of key words such as *diabetic retinopathy*, *prevalence*, *global prevalence*, and *population* and specific region and country names used in all fields including title, abstract, and medical subject headings (Appendix B, available at www.aaojournal.org). We included publications in the English language published up to March 20, 2020. Further literature search consisted of reviewing the reference lists of relevant articles such as previous country or region-based systematic reviews and meta-analyses providing DR prevalence. This adopted strategy identified all articles used in previous reviews.[8,17-19]

In addition, we further obtained original unpublished DR, VTDR, and CSME data from Asian population studies via the Asian Eye Epidemiology Consortium. The Asian Eye Epidemiology Consortium is a collaborative network of population-based studies across Asia.[20,21] Within this network, unpublished DR data were obtained from 3 epidemiologic studies that fulfilled our study selection criteria and previously published their methodologies: the Tai Zhou Eye Study,[22] the Hong Kong Eye Study,[23] and the Ural Eye and Medical Study.[24] The IRB/ethics committee at each institution approved this study. All research adhered to the tenets of the Declaration of Helsinki. The requirement for informed consent was waived because of the retrospective nature of the study.

Inclusion and Exclusion Criteria for Literature Search

We included studies with the following criteria: (1) population-based study; (2) clear definition on random or clustered sampling procedure; (3) 60% or more participation rate of the eligible population; (4) provided DR, VTDR, or CSME prevalence, or a combination thereof, amongst the DM group(s); (5) provided a clear definition of DM with at least 1 of the following used for DM diagnosis: fasting blood glucose $\geq$ 7 mmol/l, random blood glucose of more than 11.1 mmol/l, oral glucose tolerance test results of 11.1 mmol/l or more, glycated hemoglobin findings of 6.5% (48 mmol/mol) or more, self-reporting of physician-diagnosed DM, existing DM treatment, and medical records; and (6) DR defined by the presence of retinal hemorrhages, microaneurysms, cotton-wool spots, panretinal photocoagulation laser scars, or a combination thereof found on color fundus photographs, dilated slit-lamp examination by an ophthalmologist, or a combination thereof. We excluded studies that (1) were clinical trials or hospital-based or clinic-based studies, (2) were duplicates, (3) did not have full-text articles, (4) solely reported on type 1 DM in pediatric populations, and (5) had a response rate of less than 60%. Based on the above criteria, 2 reviewers (Z.L.T., Y.-C.T.) independently selected the studies for final inclusion. Disagreements between the 2 were resolved and adjudicated by the senior author (C.-Y.C.).

Quality Assessment

Funnel plots and Begg and Mazumdar tests (for DR, VTDR, and CSME) were performed to determine potential publication bias among included studies. Overall, no significant publication bias was found for DR ($P = 0.633$; Fig S1, available at www.aaojournal.org), but publication bias was significant for VTDR ($P = 0.022$; Fig S2A, available at www.aaojournal.org) and CSME ($P = 0.007$; Fig S3A, available at www.aaojournal.org). The 2 studies identified with potential publication bias in VTDR were the Bhaktapur Glaucoma Study and the Central India Eye and Medical Study; 2 other studies identified with publication bias in CSME were the Beijing Eye Study and the Tromso Eye Study. These studies were removed in the VTDR and CSME analyses, respectively. After removing these studies, the revised funnel plots for VTDR and CSME showed no significant publication bias ($P \geq 0.073$; Figs S2B and S3B, respectively). The quality of included studies was assessed using a modified version of the risk of bias tool modified from the Grades of Recommendation, Assessment, Development and Evaluation approach developed by Hoy et al[25] (Appendix C, available at www.aaojournal.org). The tool assessed both external and internal validity via the following domains: representation of the national population, nonresponse bias, distinction between type 1 and type 2 diabetes, DR diagnosis method, consistency in data collection, and year of data collection. Studies were assessed and given a total risk score from 0 to 6, with 0 representing good quality. Studies with a score of 4 or more were classified as having higher risk of bias.

Data Extraction

A data extraction spreadsheet was used to collect information on study and participant characteristics. For each included study, we extracted the following data: country of studied population, year that the study was conducted, habitation type (urban, rural, or mixed), participation response rate, ethnicity of study participants (European ancestry, Asian, Middle Easterner, Hispanic, or African ancestry), number of patients with DM, number of patients with DR, number of patients with VTDR, number of patients with CSME, DR grading system, DM diagnostic method, and DR diagnostic method. Current and projected global and regional DM numbers (up to 2045) were extracted from the IDF Atlas 2019.[26] The IDF performed an extensive systematic review up to 2018, including publications of multiple languages and data from national health databases. The Analytical Hierarchy Process scoring system was used to evaluate the data, and population data from the United Nations was used. Details of the IDF methodology have been reported previously[1] and are described further in Appendix D (available at www.aaojournal.org). We classified countries based on the Ninth IDF Atlas into 7 world regions: Africa, Europe, Middle East and North Africa (MENA), North America and the Caribbean (NAC), South and Central America (SACA), South East Asia (SEA), and Western Pacific (WP; Appendix D). The IDF regional classification was used in this study to allow for DR projection to be in concordance with the IDF projection of DM. This allows for better regional and country-specific policy planning. In addition, the IDF regions took into account the World Bank-defined income group characteristics to classify countries further based on epidemiologic and socioeconomic similarities,[1] which are important factors for DM burden and management. We did not use the 7 super regions as used in the Global Burden of Disease Study because no data were available on region or country-specific DM projections (in terms of forecasted DM numbers, which are crucial for this study's purpose).

Diabetic Retinopathy Definition and Assessment

We found that most studies defined DR according to either the Early Treatment Diabetic Retinopathy Study classification,[27] the American Association of Ophthalmology International Clinical Diabetic Retinopathy Disease Severity Scale,[28] or the Scottish Diabetic Retinopathy Grading Scheme.[29] In this study, DR represents any DR, including VTDR and CSME. Vision-threatening DR was defined as the presence of severe nonproliferative DR, proliferative DR, CSME, or a combination thereof according to the Eye Diseases Prevalence Research Group definition.[30] Clinically significant macular edema was defined as (1) thickening of the retina at or within 500 μm of the center of the macula, (2) hard exudate at or within 500 μm of the center of the macula associated with thickening of adjacent retina, or (3) a zone of retinal thickening 1 disc area or larger, any part of which is within 1 disc diameter of the center of the macula according to the Early Treatment Diabetic Retinopathy Study definition.[27] Studies that provided only CSME data without a breakdown of severe nonproliferative DR and proliferative DR data were not included in VTDR analysis and were included only in the CSME analysis.

Statistical Analysis

All statistical analyses were performed using R statistical software version 3.4.4 (R Foundation for Statistical Computing). A P value of less than 0.05 was considered statistically significant.

Pooling of Diabetic Retinopathy Prevalence. To estimate the regional pooled prevalence, random-effects meta-analysis was performed by binomial likelihood maximization under a generalized linear mixed model and with logit transformation.[31] Pooled prevalence was estimated using back transformation. Test for heterogeneity (I^2 index) was performed to determine significant differences in prevalence estimates between studies.

Future Projection Estimates of Diabetic Retinopathy, Vision-Threatening Diabetic Retinopathy, and Clinically Significant Macular Edema in 2030 and 2045. The IDF Atlas 2019 provides up-to-date estimates on current DM population data (20−79 years of age) and projection of global and regional DM numbers until 2045.[1] For the projection estimates of the number of people with DR, VTDR, and CSME in 2030 and 2045, we incorporated the IDF DM population projection data into our pooled prevalence estimate of DR, VTDR, and CSME for each region. In brief, this was modeled by performing the binomial-normal hierarchical model fitting with Markov chain Monte Carlo simulations (using a sample size of 10 000 based on WinBUGS software version 14.3; Appendix E, available at www.aaojournal.org).

In this projection estimate, region-specific DR, VTDR, and CSME prevalence rates within people with DM were assumed to be constant over the next 25 years through year 2045. This was because, based on meta-regression analysis, we observed that the year of study was not associated significantly with DR prevalence for each region (Appendix F, available at www.aaojournal.org). This observation indicated a constant trend of prevalence across all regions from 1980 through 2017 among the eligible studies included in this review.

Meta-Regression Modelling. To evaluate factors associated with the prevalence of DR and VTDR, the meta-regression model was used to model the logit of prevalence for DR and VTDR. We first performed a nonadjusted model followed by a multiple adjusted model, adjusting for region, habitation type, response rate, year of study, and DR diagnostic method. We did not concurrently include ethnicity and world region in the same model as covariates because of high collinearity between the two. We did not adjust for age and gender in the main multivariate model because only 27 studies reported complete age data and only 49 studies reported complete gender data. Random effects were incorporated in the models to account for between-study variability.

Results

Figure S4 (available at www.aaojournal.org) shows the article selection process for studies included in the final meta-analysis. In brief, a total of 3433 individual records were identified during the initial search, of which 81 relevant articles were selected. After further reviewing the full text of these selected articles, 25 articles were excluded. Meanwhile, unpublished DR data was obtained from a further 3 studies that were affiliated with the Asian Eye Epidemiology Consortium and met our selection criteria. Ultimately, 59 studies were included in the final analysis (Table S1, available at www.aaojournal.org).

Summary of Included Studies

The final included data (59 studies from 27 countries) consisted of 9685 patients with DR among 40 857 individuals with DM (age range, 20−87 years). We further extracted VTDR data from 51 of the 59 studies comprising 1789 patients with VTDR (of 36 091 individuals with DM) and CSME data from 41 studies comprising 1145 patients with CSME (of 27 125 individuals with DM). By IDF world regions, 17 study populations were from the WP, 14 were from SEA, 12 were from NAC, 7 were from the MENA, 6

were from Europe, 2 were from SACA, and 1 was from Africa. Detailed characteristics of the studies are described in Table S1. Of the included studies, 56 reported complete data on region, habitation type, response rate, year of study, and DR diagnosis method and were used as adjusted covariates in the meta-regression modeling for DR. Of the 56 studies, a subset of 50 provided ethnicity information, 49 reported gender proportion data, and 27 provided mean age data. Meanwhile, 49 studies were used for VTDR-related meta-regression analysis and 39 studies were used for CSME-related meta-regression analysis (results described below).

Global Prevalence and Numbers of Diabetic Retinopathy, Vision-Threatening Diabetic Retinopathy, and Clinically Significant Macular Edema in 2020

Figure S5 (available at www.aaojournal.org) shows the pooled prevalence of DR, VTDR, and CSME globally and by region. The prevalence of DR was estimated to be 22.27% (95% confidence interval [CI], 19.73%−25.03%) globally within the DM population. The global number of adults with DR in 2020 was estimated to be 103.12 million (95% CI, 91.34−115.90 million; Table 1; Fig 1). Meanwhile, the prevalence of VTDR was estimated to be 6.17% (95% CI, 5.43%−6.98%) within the DM population, and the number of adults with VTDR was estimated to be 28.54 million (95% CI, 25.12−32.34 million) in 2020 globally (Table 1). The global prevalence of CSME was estimated to be 4.07% (95% CI, 3.42%−4.82%) within the DM population, with a global CSME population of 18.83 million (95% CI, 15.82−22.32 million; Table 1).

Regional Variations in Diabetic Retinopathy, Vision-Threatening Diabetic Retinopathy, and Clinically Significant Macular Edema Prevalence

Analysis of the 59 included studies showed that NAC (33.30%; 95% CI, 25.29%−42.40%) and MENA (32.90%; 95% CI, 26.06−40.55%) regions showed significantly higher DR prevalence than other regions (Table 1; Fig S6, available at www.aaojournal.org). In the meta-regression analysis adjusting for response rate, habitation type, year of study, and DR diagnostic method, individuals with DM residing in NAC (odds ratio [OR], 2.33; 95% CI, 1.39−3.92) and the MENA (OR, 2.72; 95% CI, 1.58−4.68) showed significantly higher odds of DR compared with those residing in the SEA region (Table 2).

Although pooled DR prevalence also was high in Africa at 35.90% (95% CI, 29.48%−42.87%), meta-regression analysis showed only marginally significantly higher odds of DR in Africa compared with SEA ($P = 0.055$; Table 2). Diabetic retinopathy prevalence for the remaining regions were as follows: the WP, 19.20% (95% CI, 14.16%−25.50%); Europe, 18.75% (95% CI, 13.69%−25.12%); SEA, 16.99% (95% CI, 14.13%−20.28%); and SACA, 13.37% (95% CI, 6.13%−26.74%; Table 1; Fig 1; Fig S6).

For VTDR (51 studies), the top 3 regions were Africa (14.36%; 95% CI, 10.10%−20.01%), the MENA (8.19%; 95% CI, 5.11%−12.87%), and NAC (7.82%; 95% CI, 5.34%−11.31%; Table 1; Fig S7, available at www.aaojournal.org). Meta-regression analysis adjusting for response rate, habitation type, year of study, and DR diagnostic method (Table 2) showed that individuals with DM residing in these top 3 regions demonstrated significantly higher odds of having VTDR compared with those in SEA: Africa (OR 4.32; 95% CI, 1.35−13.79), NAC (OR 2.94; 95% CI, 1.73−4.98), and the MENA (OR 2.34; 95% CI, 1.36−4.01; Table 2). The VTDR prevalences for the remaining regions are as follows: SACA, 5.83% (95% CI, 4.15%−8.13%); the WP, 5.54% (95% CI, 4.53%−6.76%); Europe, 5.49% (95% CI, 4.63%−6.51%); and SEA, 3.53% (95% CI, 2.45%−5.05%; Fig S7).

For CSME (41 studies), the MENA showed the highest CSME prevalence at 6.06% (95% CI, 3.59%−10.06%; Table 1; Fig S8, available at www.aaojournal.org). Meta-regression analysis showed that individuals with diabetes residing in the MENA were significantly more likely to have CSME (OR, 2.48; 95% CI, 1.33−4.61) compared with those residing in SEA (Table 2). North America and the Caribbean had an estimated CSME prevalence of 4.89% (95% CI, 2.92%−8.08%) and was also found to have significantly higher odds of CSME (OR, 2.82; 95% CI, 1.48−5.39) compared with SEA (Table 2). The CSME prevalences for the remaining regions are as follows: Europe, 5.29% (95% CI, 4.18%−6.68%); SACA, 4.92% (95% CI, 3.39%−7.08%); Africa, 4.10% (95% CI, 2.06%−7.99%); the WP, 3.23%; 95% CI, 2.26%−4.59%); and SEA, 2.30% (95% CI, 1.44%−3.67%; Fig S8).

Variations in Diabetic Retinopathy, Vision-Threatening Diabetic Retinopathy, and Clinically Significant Macular Edema Prevalences across Ethnicities

Figure S9 (available at www.aaojournal.org) illustrates the variation in the prevalence of DR, VTDR, and CSME across ethnic groups. Hispanics showed the highest DR prevalence at 47.40% (95% CI, 45.29%−49.52%) followed by Middle Easterners (32.90%; 95% CI, 26.06%−40.55%), people of African ancestry (31.01%; 95% CI, 26.10%−36.38%), people of European ancestry (23.71%; 95% CI, 17.13%−31.84%), and Asians at 17.94% (95% CI, 14.77%−21.61%; Fig S10, available at www.aaojournal.org). For VTDR, people of African ancestry showed the highest VTDR prevalence at 10.90% (95% CI, 7.87%−14.91), followed by Hispanics (8.26%; 95% CI, 5.77- 11.71%), Middle Easterners (8.19%; 95% CI, 5.11%−12.87%), people of European ancestry (5.87%; 95% CI, 4.44%−7.72%), and Asians (4.06%; 95% CI, 3.22%−5.11%). For CSME, Middle Easterners showed the highest CSME prevalence at 6.06% (95% CI, 3.59%−10.06%), followed by Hispanics (5.71%; 95% CI, 4.81%−6.78%), people of European ancestry (4.65%; 95% CI, 3.60%−5.99%), people of African ancestry (4.10%; 95% CI, 2.06%−7.99%), and Asians (2.67%; 95% CI, 2.01%−3.54%).

In meta-regression analysis adjusting for response rate, habitation type, year of study, and DR diagnostic method, compared with Asians, Hispanics with diabetes were 2.92 times (OR, 2.92; 95% CI, 1.22−6.98) more likely to have DR, and Middle Easterners were 2.44 times (OR, 2.44; 95% CI, 1.51−3.94) more likely to have DR (Table 2). Similarly, compared with Asians, Hispanics (OR, 2.71; 95% CI, 1.30−5.67), people of African ancestry (OR, 2.58; 95% CI, 1.24−5.38), and Middle Easterners (OR, 1.84; 95% CI, 1.20−2.82) were more likely to have VTDR (Table 2). We found that Hispanics (OR, 3.93; 95% CI, 1.74−8.88) and Middle Easterners (OR, 2.27; 95% CI, 1.43−3.60) also were observed to have higher odds of CSME compared with Asians with diabetes (Table 2).

Table 1. Prevalence and Number of Adults with Diabetic Retinopathy, Vision-Threatening Diabetic Retinopathy, and Clinically Significant Macular Edema in 2020

	Diabetic Retinopathy		Vision-Threatening Diabetic Retinopathy		Clinically Significant Macular Edema	
World Region	*Prevalence (%)*	*No. (in Millions)*	*Prevalence (%)*	*No. (in Millions)*	*Prevalence (%)*	*No. (in Millions)*
SEA	16.99 (14.13–20.28)	14.95 (12.42–17.81)	3.53 (2.45–5.05)	3.15 (2.15–4.44)	2.30 (1.44–3.67)	2.08 (1.26–3.22)
Africa	35.90 (29.48–42.87)	6.99 (5.73–8.33)	14.36 (10.10–20.01)	2.83 (1.97–3.90)	4.10 (2.06–7.99)	0.85 (0.40–1.56)
Europe	18.75 (13.69–25.12)	11.25 (8.12–14.93)	5.49 (4.63–6.51)	3.28 (2.74–3.88)	5.29 (4.18–6.68)	3.16 (2.47–3.98)
MENA	32.90 (26.06–40.55)	18.07 (14.28–22.28)	8.19 (5.11–12.87)	4.59 (2.80–7.09)	6.06 (3.59–10.06)	3.43 (1.96–5.54)
NAC	33.30 (25.29–42.40)	15.89 (12.03–20.16)	7.82 (5.34–11.31)	3.78 (2.54–5.37)	4.89 (2.92–8.08)	2.40 (1.38–3.83)
SACA	13.37 (6.13–26.74)	4.47 (1.93–8.51)	5.83 (4.15–8.13)	1.87 (1.31–2.58)	4.92 (3.39–7.08)	1.58 (1.07–2.25)
WP	19.20 (14.16–25.50)	31.50 (22.97–41.56)	5.54 (4.53–6.76)	9.06 (7.36–11.03)	3.23 (2.26–4.59)	5.34 (3.68–7.47)
Global	22.27 (19.73–25.03)	103.12 (91.34–115.90)	6.17 (5.43–6.98)	28.54 (25.12–32.34)	4.07 (3.42–4.82)	18.83 (15.82–22.32)

MENA = Middle East and North Africa; NAC = North America and Caribbean; SACA = South and Central America; SEA = South East Asia; WP = Western Pacific.
Data are presented as percentage or number (95% confidence interval).

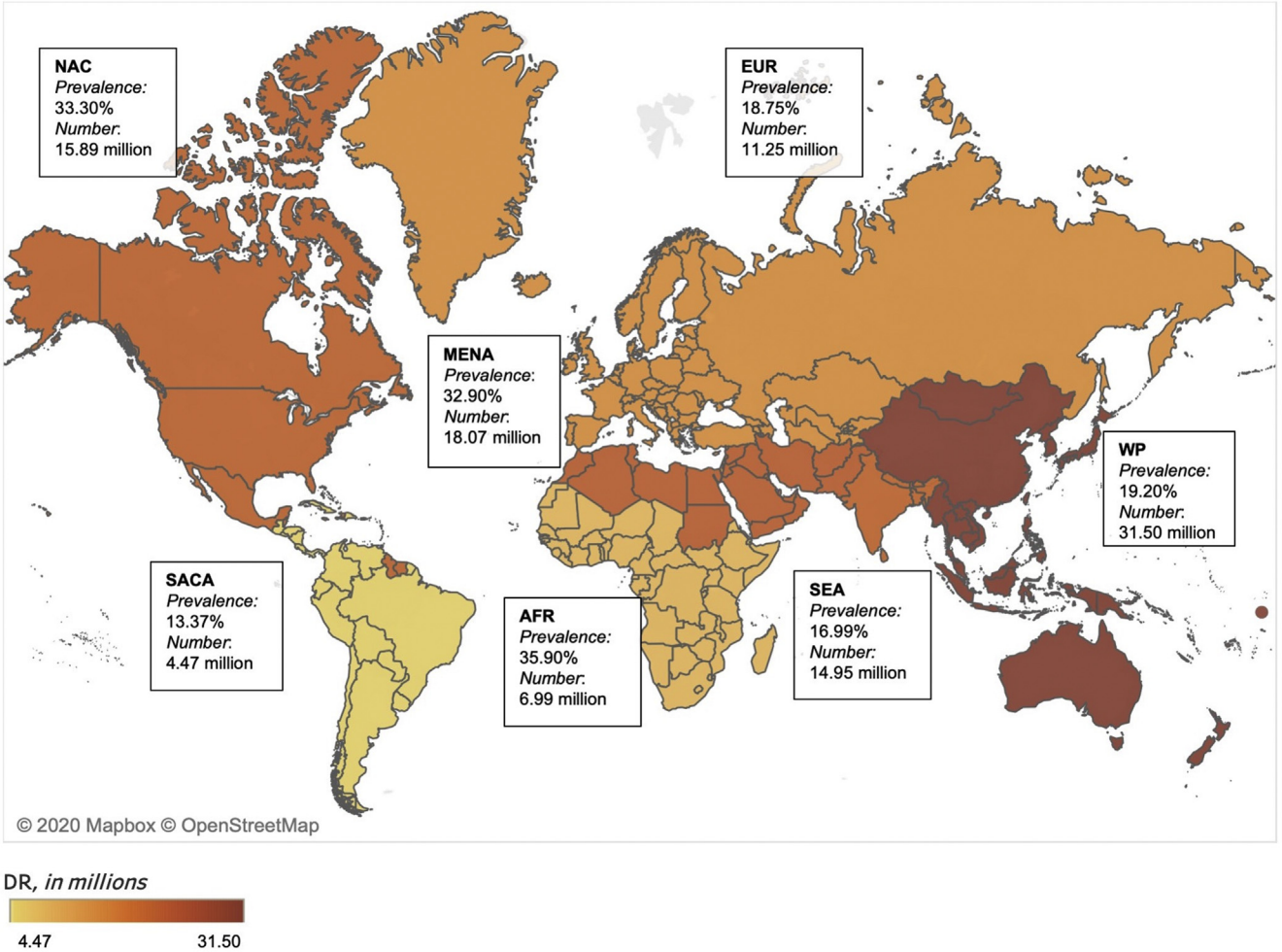

Figure 1. Global map showing diabetic retinopathy (DR) prevalence and numbers by International Diabetes Foundation world regions in 2020. AFR = Africa; EUR = Europe; MENA = Middle East and North Africa; NAC = North America and Caribbean; SACA = South and Central America; SEA = South East Asia; WP = Western Pacific.

Table 2. Factors Associated with Diabetic Retinopathy, Vision-Threatening Diabetic Retinopathy, and Clinically Significant Macular Edema (Multivariate Analysis)

	Diabetic Retinopathy*		Vision-Threatening Diabetic Retinopathy†		Clinically Significant Macular Edema‡	
	Adjusted Odds Ratio§ (95% CI)	*P Value*	*Adjusted Odds Ratio§ (95% CI)*	*P Value*	*Adjusted Odds Ratio§ (95% CI)*	*P Value*
Region						
SEA	Reference					
Africa	3.32 (0.97–11.33)	0.055	**4.32 (1.35–13.79)**	**0.013**	1.23 (0.30–5.14)	0.773
Europe	1.45 (0.76–2.75)	0.258	1.63 (0.76–3.48)	0.209	1.59 (0.60–4.18)	0.349
MENA	**2.72 (1.58–4.68)**	**< 0.001**	**2.34 (1.36–4.01)**	**0.002**	**2.48 (1.33–4.61)**	**0.004**
NAC	**2.33 (1.39–3.92)**	**0.001**	**2.94 (1.73–4.98)**	**< 0.001**	**2.82 (1.48–5.39)**	**0.002**
SACA	0.93 (0.38–2.30)	0.880	1.43 (0.44–4.67)	0.557	1.93 (0.52–7.13)	0.326
WP	1.40 (0.84–2.31)	0.196	**1.77 (1.03–3.05)**	**0.039**	1.22 (0.60–2.50)	0.586
Ethnicity‖						
Asian	Reference					
African ancestry	1.94 (0.83–4.57)	0.127	**2.58 (1.24–5.38)**	**0.011**	1.20 (0.37–3.92)	0.762
European ancestry	1.35 (0.89–2.04)	0.162	1.50 (0.99–2.27)	0.054	1.72 (0.98–3.01)	0.058
Hispanic	**2.92 (1.22–6.98)**	**0.016**	**2.71 (1.30–5.67)**	**0.008**	**3.93 (1.74–8.88)**	**0.001**
Middle Eastern	**2.44 (1.51–3.94)**	**< 0.001**	**1.84 (1.20–2.82)**	**0.005**	**2.27 (1.43–3.60)**	**< 0.001**
Habitation type						
Rural	Reference					
Urban	1.05 (0.68–1.62)	0.837	0.95 (0.62–1.47)	0.822	1.35 (0.78–2.34)	0.291
Mixed	0.85 (0.54–1.34)	0.495	0.85 (0.55–1.32)	0.463	1.05 (0.57–1.92)	0.878
Response rate	1.00 (0.98–1.02)	0.818	1.01 (0.99–1.03)	0.569	1.01 (0.99–1.04)	0.271
Year of study conducted	0.99 (0.97–1.01)	0.398	1.01 (0.99–1.03)	0.413	1.01 (0.98–1.04)	0.386
Diagnostic method						
Clinical fundus examination only	Reference					
CFP (1–2 fields)	0.98 (0.63–1.52)	0.924	0.90 (0.56–1.43)	0.644	1.18 (0.63–2.21)	0.597
CFP (3–7 fields)	1.38 (0.88–2.17)	0.158	0.68 (0.43–1.06)	0.088	**0.55 (0.31–0.98)**	**0.044**
Age, per decade¶	**2.41 (1.20–4.82)**	**0.013**	0.83 (0.32–2.16)	0.704	1.71 (0.42–7.04)	0.455
Gender#						
Male	Reference					
Female	0.10 (0.00–2.41)	0.158	**0.05 (0.00–0.99)**	**0.049**	0.17 (0.00–5.83)	0.324
Mydriatic CFP**						
No	Reference					
Yes	1.10 (0.65–1.85)	0.721	1.21 (0.68–2.13)	0.514	1.57 (0.66–3.74)	0.307

CFP = color fundus photography; CI = confidence interval; CSME = clinically significant macular edema; DR = diabetic retinopathy; MENA = Middle East and North Africa; NAC = North America and Caribbean; SACA = South and Central America; SEA = South East Asia; VTDR = vision-threatening diabetic retinopathy; WP = Western Pacific.
Boldface indicates statistical significance of $P < 0.05$.
*Analysis performed on only 56 studies with DR and adjustment covariates data available.
†Analysis performed on only 49 studies with VTDR data available.
‡Analysis performed on only 39 studies with CSME data available.
§Meta-regression models were adjusted by region (but excluded from model when evaluating ethnicity as exposure), habitation type, response rate, year study conducted, and DR diagnosis method.
‖Analysis performed on 50 studies, 44 studies, and 34 studies with ethnicity information available for DR, VTDR, and CSME analyses, respectively.
¶Analysis performed on 27 studies, 23 studies, and 21 studies with mean age information available for DR, VTDR, and CSME analyses, respectively.
#Analysis performed on 49 studies, 43 studies, and 39 studies with gender proportion information available for DR, VTDR, and CSME analyses, respectively.
**Analysis performed on 39 studies, 35 studies, and 26 studies that used CFP for DR diagnosis for DR, VTDR, and CSME analyses, respectively.

Effect of Diabetic Retinopathy Diagnostic Method and Dilated Fundus Photography on Diabetic Retinopathy, Vision-Threatening Diabetic Retinopathy, and Clinically Significant Macular Edema

We further evaluated the effects of diagnostic method and dilated fundus photography on the estimates of DR, VTDR, and CSME prevalence. Multivariate logistic regression showed that the use of different diagnostic methods generally did not have significant effects on the odds of DR, VTDR, or CSME (except for the use of 3–7 fields of color fundus photographs on CSME, which was of borderline significance [$P = 0.044$]; Table 2). In addition, in a subset of 39 studies that used color fundus photography for diagnosis, multivariate logistic regression showed that dilated fundus photography had no significant effect on the odds of DR, VTDR, or CSME (Table 2).

Effect of Age and Gender on Diabetic Retinopathy, Vision-Threatening Diabetic Retinopathy, and Clinically Significant Macular Edema

Multivariate meta-regression subgroup analysis revealed that the OR of DR was 2.41 (95% CI, 1.20–4.82; $P = 0.013$) with each decade increase in age, after adjusting for world region, habitation

Table 3. Projection of the Number of People with Diabetic Retinopathy, Vision-Threatening Diabetic Retinopathy, and Clinically Significant Macular Edema in 2030 and 2045

World Region	Diabetic Retinopathy, No. in Millions (95% CI)		Vision-Threatening Diabetic Retinopathy, No. in Millions (95% CI)		Clinically Significant Macular Edema, No. in Millions (95% CI)	
	2030	*2045*	*2030*	*2045*	*2030*	*2045*
SEA	19.62 (16.18–23.37)	26.06 (21.64–31.08)	4.13 (2.79–5.82)	5.48 (3.76–7.77)	2.73 (1.64–4.23)	3.62 (2.22–5.64)
Africa	10.29 (8.36–12.28)	16.93 (13.91–20.19)	4.16 (2.86–5.75)	6.84 (4.78–9.44)	1.24 (0.58–2.30)	2.04 (0.98–3.77)
Europe	12.46 (9.03–16.50)	12.89 (9.23–17.17)	3.64 (3.04–4.30)	3.76 (3.13–4.45)	3.51 (2.74–4.40)	3.63 (2.81–4.56)
MENA	25.05 (19.75–30.79)	35.47 (27.98–43.66)	6.36 (3.86–9.77)	9.01 (5.48–13.89)	4.74 (2.70–7.62)	6.72 (3.84–10.85)
NAC	18.75 (14.15–23.83)	21.11 (15.95–26.83)	4.46 (2.98–6.36)	5.02 (3.36–7.16)	2.84 (1.63–4.55)	3.18 (1.83–5.12)
SACA	5.69 (2.44–10.82)	6.96 (3.00–12.99)	2.37 (1.66–3.30)	2.90 (2.04–3.97)	2.01 (1.36–2.87)	2.46 (1.67–3.46)
WP	37.98 (27.76–50.13)	41.08 (30.03–54.40)	10.93 (8.89–13.32)	11.81 (9.58–14.43)	6.43 (4.43–9.03)	6.96 (4.78–9.84)
Global	129.84 (115.30–145.60)	160.50 (143.70–178.60)	36.05 (31.63–41.15)	44.82 (39.20–51.33)	23.50 (19.69–27.97)	28.61 (23.85–34.29)

CI = confidence interval; MENA = Middle East and North Africa; NAC = North America and Caribbean; SACA = South and Central America; SEA = South East Asia; WP = Western Pacific.

type, response rate, year of study, and DR diagnostic method (Table 2). However, the effect of age on VTDR and CSME prevalence was not statistically significant ($P \geq 0.704$; Table 2). Subgroup multivariate meta-regression analysis showed that gender had no significant effect on DR or CSME prevalence ($P \geq 0.158$), whereas the effect of gender on VTDR was marginally significant ($P = 0.049$; Table 2). Habitation type, response rate, and year of study did not have significant effects on DR, VTDR, or CSME prevalence ($P \geq 0.271$; for univariate analyses, Table 2 and Table S2 [available at www.aaojournal.org]).

Quality Assessment: Sensitivity Analysis Excluding Studies with Higher Risk of Bias

Quality assessment using the risk-of-bias tool showed that 3 studies (the Hoorn Study,[32] the Tehran Eye Study,[33] and the Taipei Ta An Study[34]), had a score of 4 or more and were deemed to be of higher risk of bias (Table S3, available at www.aaojournal.org). Sensitivity analysis excluding these 3 studies showed that findings remained largely similar (Table S4A, B, available at www.aaojournal.org).

Projection of Number of Individuals with Diabetic Retinopathy, Vision-Threatening Diabetic Retinopathy, and Clinically Significant Macular Edema in 2030 and 2040

In 2020, the total number of adults with DR was estimated to be 103.12 million globally (95% CI, 91.34−115.90 million), with the highest numbers in the WP region (31.50 million), followed by the MENA (18.07 million) and NAC (15.89 million; Table 1; Fig 1). For VTDR, the total number was estimated to be 28.54 million (95% CI, 25.12−32.34 million) in 2020, and similarly with the largest numbers in the WP (9.06 million), followed by the MENA (4.59 million) and NAC (3.78 million; Table 1). For CSME, the total number was estimated to be 18.83 million (95% CI, 15.82−22.32 million) in 2020, with corresponding highest numbers in the WP (5.34 million) followed by the MENA (3.43 million) and Europe (3.16 million; Table 1). In further meta-regression analysis by region subgroups, we found no statistically significant trend in DR prevalence over time (based on study year) across all regions ($P \geq 0.084$; results not shown in tables; Fig S11, available at www.aaojournal.org).

Hence, while assuming the rate of DR prevalence to be constant over the next 25 years, we estimated that the global number of adults with DR would increase by 25.9% to 129.84 million (95% CI, 115.30−145.60 million) in 2030 and by 55.6% to 160.50 million (95% CI, 143.70−178.60 million) in 2045 (Table 3). Much of the projected increase in DR numbers is attributable to significant increases in the MENA, SEA, and WP regions. The WP will remain as the region with the greatest number of people with DR in 2045, with an increment of 9.58 million from 2020. Across world regions, the MENA is projected to have the most drastic increase in DR cases by 96.3% (17.4 million) from 2020 to 2045. However, it is projected that the NAC, Europe, and SACA regions will show small increments in DR cases from 2020 to 2045.

Projection of the number of people with VTDR and CSME also was performed while assuming the rate of prevalence to be constant over the next 25 years. We estimated that the global number of adults with VTDR will increase by 26.3% to 36.05 million (95% CI, 31.63−41.15 million) in 2030 and by 57.0% to 44.82 million (95% CI, 39.20−51.33 million) in 2045. The global number of adults with CSME will increase by 24.8% to 23.50 million (95%

CI, 19.69−27.97 million) in 2030 and by 51.9% to 28.61 million (95% CI, 23.85−34.29 million) in 2045.

Discussion

Our study provides comprehensive and up-to-date evaluations of the current global DR prevalence with the largest meta-analysis to date. Our study provides novel estimates on global and regional CSME prevalence and future projection of the number of people with DR, VTDR, and CSME globally and regionally. From a global prevalence of 22.27% for DR, 6.17% for VTDR, and 4.07% for CSME, we estimated that there will be 103.12 million people with DR, 28.54 million people with VTDR, and 18.83 million people with CSME in 2020. The number of people with DR, VTDR, and CSME is projected to rise to 160.50 million, 44.82 million, and 28.61 million, respectively, in 2045, disproportionately affecting individuals with DM residing in the MENA and WP regions. The demand for DR and CSME treatment will continue to rise significantly in the future.

Key Strengths and Findings

A key strength of this current systematic review lies in the significantly more comprehensive and up-to-date estimates as compared with the last review conducted a decade ago.[8] This was coupled with critical appraisal of study quality including only population-based studies with response rates of 60% or more and strict application of inclusion and exclusion criteria. Substantial improvement occurred in the number of included studies from 35 to 59, with a substantial increment of data from Asian populations, specifically the WP (from 9 to 17 studies) and SEA (from 2 to 14 studies). With the inclusion of 40 new studies and better Asian representation compared with the previous review, our findings provide more up-to-date estimates. Importantly, we included a notably higher number of studies from China and India, which have the highest numbers of people with DM (China, 116 million; India, 77 million).[1] In this review, we included 7 studies from China and 11 from India, a substantial improvement compared with the previous review, which consisted of 2 studies from China and 3 from India.[8] Further novelties of our study are the inclusion of studies from all regions including the MENA, SACA, and Africa, areas from which previously no studies were included, and the inclusion of a recent study from Russia (which is the first Russian population-based study reporting on DR prevalence).[35] We classified studies according to IDF regions, with most regions well represented by a sufficient number of studies with large sample sizes. The most up-to-date DM data from the IDF Atlas 2019 also was used to provide robust DR population estimates.

Our study estimated the pooled global prevalence of DR and VTDR to be 22.27% and 6.17%, respectively, lower than the previous estimates of 34.6% and 10.2% by Yau et al.[8] Differences in estimates may be the result of a combination of factors. First, as discussed earlier, our analysis consisted of a more extensive and recent evidence base from Asia, including many new studies from the WP and SEA, which have lower DR prevalence than other regions, as shown in our results. Second, also changes have been made in the definition of DM over time. For example, DM now includes the use of hemoglobin A1c of more than 6.5% (48 mmol/mol)[36,37] as a diagnostic criterion. The updated DM diagnostic criteria and improvement in standards of care in DM[38] allow for earlier DM diagnosis, stricter glycemic control, and consequently better prevention of complications that have resulted in lower rates of other diabetes-related complications, including microangiopathy and nephropathy.[39] This could explain the lower DR prevalence found in our study compared with previous estimates by Yau et al.[8] Third, significant public interest exists regarding DM in Asia,[12] which has led to national policies for primary prevention of DM and screening for high-risk populations in many Asian countries (e.g., Singapore,[40] India,[41] and China[42]), potentially leading to earlier diagnosis of DM and a corresponding lower prevalence of DM-related complications. Finally, some studies with low response rates included in the previous analysis[8] were excluded in the current review; these studies have a relatively high DR prevalence perhaps because of a selection artifact.[43-45] Hence, the current study estimates are likely to represent more accurate and up-to-date prevalence estimates.

Our study further provides regional and ethnic variations in DR, VTDR, and CSME prevalence estimates that are not currently available. We observed significant regional variation, with people with DM living in NAC and the MENA having higher odds of DR and CSME and those in Africa, the MENA, NAC, and the WP having higher odds of VTDR. Similar regional variation was seen in DM prevalence where prevalence is estimated to be the highest in the MENA (13.9%) followed by NAC (13.0%) in 2045.[1] These 2 regions correspondingly showed higher DR prevalence in the current findings (Fig S12, available at www.aaojournal.org). These regional estimates can aid further in region-specific health care policy planning. Similarly, we reported a significantly higher DR, VTDR, and CSME prevalence among Hispanics and Middle Easterners compared with Asians. The previous review by Yau et al[8] similarly reported a lower DR prevalence among Asians. In addition, both our review and the study of Yau et al[8] found that people of African ancestry have the highest prevalence of VTDR. Similarly, the National Health and Nutrition Examination Survey found higher VTDR prevalence among Hispanic and Black individuals. The top 3 ethnic groups (Hispanics, Middle Easterners, and people of African ancestry) correspondingly were from the 3 regions with the highest DR prevalence (Africa, NAC, and the MENA). It is interesting that these ethnic groups showed significantly higher odds of DR and VTDR, despite being from different countries and regions (e.g., Middle Easterners were from Egypt, Iran, Jordan, and Saudi Arabia; people of African ancestry were from Africa and NAC). This potentially suggests that the effect of ethnicity as a risk factor for DR and VTDR may transcend geographical regions.

Projection of Global Number of People with Diabetic Retinopathy and Clinically Significant Macular Edema

We have attempted to project the number of people with DR over time globally and by regions. Across all regions, IDF estimated that both DM prevalence and numbers will rise steadily from 2019 to 2045[1] (Appendix G, available at www.aaojournal.org). Substantial regional variation was found, with the MENA projected to have the greatest increase in DM prevalence (by 2.9%) and SEA projected to have the greatest increase in absolute DM population size (by 65.2 million) by 2045.[26] However, the WP will remain as the region with the largest DM population (212.2 million) by 2045.[26]

By 2045, the MENA is expected to have the greatest increase in DR population by 96.3% (17.4 million). This is because its DM population is estimated to increase drastically from 54.8 million in 2019 to 107.6 million in 2045,[1] with DM prevalence in the MENA rising the most across all regions, from 12.8% to 15.7% in 2045.[26]

Meanwhile, although the estimated DR prevalence in the WP (19.20%) is lower than in some regions, the WP currently has the largest DR population in absolute numbers and is projected to continue to do so with a DR population size of 41.08 million in 2045, an increase of 9.58 million patients with DR from 2020. This is because of the sheer number of people with DM residing in the WP, which is expected to grow to 212.2 million in 2045,[1,26] leading to the largest absolute number of patients with DR in a world region, currently and in the future.

We estimated that the global DR population will increase by 55.6% (57.4 million) from 2020 to 2045. This is mainly attributed to the rapidly growing global DM population especially in Africa, the MENA, and the WP.[1] Our findings show that DR population size is tightly correlated with DM population size and suggest the need for more resources for DM and DR management, particularly in these regions. With the rising DM population, attention should be paid to prevent complications such as DR.

Diabetic macular edema is now known to be the main cause of moderate vision loss among individuals with DM globally[46] but estimates of CSME prevalence have not been available previously. Our study provides novel estimates of CSME prevalence globally and projections of the number of adults with CSME. We estimated that the global number of adults with CSME will rise by 51.9% to 28.61 million in 2045. This suggests the need to improve access to CSME treatment such as intravitreal anti−vascular endothelial growth factor therapy or laser treatment.

Study Limitations

Our review has some limitations. First, in Africa and SACA, the limited studies may be insufficient to represent the region entirely. In addition, the limited studies in Africa likely resulted in insufficient statistical power in analysis, leading to statistically insignificant higher odds of DR, despite Africa having the highest DR prevalence estimate. Second, in the projection of DR, we were unable to include age as a covariate in our analysis because of limited age-related data provided by studies. Third, most studies defined CSME by stereoscopic fundus photography, before OCT (a sensitive and more accurate technique to detect CSME[47]) was used widely; thus, this may underestimate our CSME estimates. In addition, we were unable to provide diabetic macular edema estimates that include nonclinically significant macular edema because of limited data from studies. Fourth, the change in prevalence over time is difficult to quantify, especially given the nature of a disease in which environmental and behavioral factors play a significant role. Nonetheless, our meta-regression analysis by region showed that the year of study had no significant effect on DR prevalence (Fig S11; $P \geq 0.084$ for all regions); thus, constant prevalence rates were used for projection of numbers. Fifth, the duration and systemic control of DM are important risk factors for DR. However, among the included studies, few provided data in this regard, and when reported, these may not be completely reliable because methods to obtain these measurements vary greatly. Despite insufficient data to analyze this in detail, we cannot entirely rule out the impact of duration and control of DM on the current estimates. Longer duration of DM likely is associated with higher prevalence of DR, which may explain in part the higher prevalence in NAC where DM has been a consistent top chronic disease and individuals with DM are living longer.[48] However, the higher prevalence of DR in Africa and the MENA may be attributed to poor control of DM, because as previous reports indicate high proportions of untreated DM in Africa (69.2%)[1] and high rates of poorly controlled DM in the MENA countries (approximately 50%).[49,50] Hence, future analysis that can incorporate information on duration and control status of DM further would help to improve the accuracy of these estimates.

Sixth, 34 of 59 studies provided data on the proportion of ungradable fundus, which ranged between 0.4% and 22%. Diabetes mellitus, especially when poorly controlled, increases the risk of cataract formation,[51] which may lead to significant cataract that may obscure the fundal view. This could represent an underestimation of DR prevalence in regions with poor access to cataract surgery. However, only 3 studies had more than 10% of ungradable fundus, and thus this is unlikely to affect our estimates significantly. Finally, we acknowledge that a significant difference exists between the DR prevalence among individuals with type 1 DM (T1DM) and type 2 DM (T2DM), but most included studies did not provide data on DR prevalence by diabetes types. This is because accurate differentiation between the 2 types requires sophisticated laboratory tests, which generally is not feasible in large-scale population studies. To our knowledge, for the same reason, separate global estimates of diabetes prevalence for T1DM and T2DM, in particular in adults, do not exist.[47,52] Nevertheless, it is important to note that although complete data on DR prevalence by diabetes types are not available, this would not have affected the overall DR prevalence estimates substantially in the study population. Sensitivity analysis excluding studies that did not provide information on the proportion of T1DM and T2DM showed similar prevalence

results (Table S5, available at www.aaojournal.org). To evaluate formally how the prevalence of DR changes with varying proportions of T1DM and T2DM, we performed a simulation analysis (Appendix H, available at www.aaojournal.org) that shows that the estimate on global prevalence of DR would still fall within the 95% CI of our original estimate when 93% or more of DM cases are T2DM in populations. Because T2DM accounts for more than 90% to 95% for all diabetes cases, in the population older than 20 years (age range of this study), the proportion of T2DM cases likely would be even higher than 90% to 95% (thus fulfilling the cutoff of ≥93%). Therefore, this limitation would not have affected our DR prevalence estimates substantially in people older than 20 years.

In conclusion, our study provides more precise and contemporary estimates of the global prevalence of DR, VTDR, and CSME, with projections of the present and future burden up to 2045. Our findings suggest that approximately 1 in 5 persons with diabetes worldwide have DR. Although the current prevalence estimates for VTDR are lower than earlier estimates, the total number of people losing vision as a result of DR may continue to rise. Our findings also suggest the continual need for high-quality population-based studies of DR, especially in Africa and SACA. Findings and estimates from this study may aid in the planning of global, regional, and country-specific health care strategies to prevent diabetes-related vision loss.

Footnotes and Disclosures

Originally received: January 10, 2021.
Final revision: April 20, 2021.
Accepted: April 23, 2021.
Available online: ■■■. Manuscript no. D-21-00059.

[1] Singapore National Eye Centre, Singapore Eye Research Institute, Singapore, Republic of Singapore.

[2] Duke-NUS Medical School, Singapore, Republic of Singapore.

[3] Ufa Eye Research Institute, Ufa, Bashkortostan, Russia.

[4] Beijing Institute of Ophthalmology, Beijing Key Laboratory of Ophthalmology and Visual Sciences, Beijing Tongren Eye Center, Beijing Tongren Hospital, Capital Medical University, Beijing, China.

[5] Department of Ophthalmology, Eye and ENT Hospital of Fudan University, Shanghai, China.

[6] Department of Ophthalmology, University of Hong Kong Li Ka Shing Faculty of Medicine, Hong Kong, China.

[7] Department of Ophthalmology, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany.

[8] Yong Loo Lin School of Medicine, National University of Singapore, Singapore, Republic of Singapore.

[9] Department of Ophthalmology, Hong Kong Sanatorium and Hospital, Hong Kong SAR, China.

*These authors contributed equally as first authors.

‡Both authors contributed equally as senior authors.

Disclosure(s):
All authors have completed and submitted the ICMJE disclosures form.

Daniel Shu Wei Ting, an editorial board member of this journal, was recused from the peer-review process of this article and had no access to information regarding its peer-review.

The author(s) have no proprietary or commercial interest in any materials discussed in this article.

Supported by the National Medical Research Council, Singapore, Republic of Singapore (grant nos.: NMRC/CIRG/1417/2015 and NMRC/CIRG/1488/2018).

HUMAN SUBJECTS: No human subjects were included in this study. The IRB/ethics committee at each institution approved this study. All research adhered to the tenets of the Declaration of Helsinki. The requirement for informed consent was waived because of the retrospective nature of the study.

No animal subjects were included in this study.

Author Contributions:

Conception and design: T.Y.Wong, Cheng

Analysis and interpretation: Sabanayagam, T.Y.Wong, Cheng

Data collection: Teo, Tham, Yu, Chee, Rim, Cheung, Bikbov, Wang, Tang, Lu, I.Y.H.Wong, Ting, Tan, Jonas, Sabanayagam, T.Y.Wong, Cheng

Obtained funding: N/A

Overall responsibility: Teo, Tham, Yu, Chee, Rim, Cheung, Bikbov, Wang, Tang, Lu, I.Y.H.Wong, Ting, Tan, Jonas, Sabanayagam, T.Y.Wong, Cheng

Abbreviations and Acronyms:
CI = confidence interval; **CSME** = clinically significant macular edema; **DM** = diabetes mellitus; **DR** = diabetic retinopathy; **IDF** = International Diabetes Federation; **MENA** = Middle East and North Africa; **NAC** = North America and the Caribbean; **OR** = odds ratio; **SACA** = South and Central America; **SEA** = South East Asia; **T1DM** = type 1 diabetes mellitus; **T2DM** = type 2 diabetes mellitus; **VTDR** = vision-threatening diabetic retinopathy; **WP** = Western Pacific.

Keywords:
Diabetes mellitus, Diabetic retinopathy, Population, Prevalence, Systematic review.

Correspondence:
Ching-Yu Cheng, MD, PhD, Singapore Eye Research Institute, The Academia, 20 College Road, Discovery Tower Level 6, Singapore, 169856, Republic of Singapore. E-mail: chingyu.cheng@duke-nus.edu.sg.

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