AMERICAN ACADEMY OF OPHTHALMOLOGY®

Prevalence of Diabetic Retinopathy in Indigenous and Non-Indigenous Australians

A Systematic Review and Meta-analysis

Mark A. Chia, MBBS, MMed,[1,2] Joshua R. Taylor, MD,[2] Kelsey V. Stuart, MBBCh, MSc,[1] Anthony P. Khawaja, PhD, FRCOphth,[1] Paul J. Foster, PhD, FRCSEd,[1] Pearse A. Keane, MD, FRCOphth,[1] Angus W. Turner, MSc, FRANZCO[2,3]

Topic: This systematic review and meta-analysis summarizes evidence relating to the prevalence of diabetic retinopathy (DR) among Indigenous and non-Indigenous Australians.

Clinical Relevance: Indigenous Australians suffer disproportionately from diabetes-related complications. Exploring ethnic variation in disease is important for equitable distribution of resources and may lead to identification of ethnic-specific modifiable risk factors. Existing DR prevalence studies comparing Indigenous and non-Indigenous Australians have shown conflicting results.

Methods: This study was conducted following Joanna Briggs Institute guidance on systematic reviews of prevalence studies (PROSPERO ID: CRD42022259048). We performed searches of Medline (Ovid), EMBASE, and Web of Science until October 2021, using a strategy designed by an information specialist. We included studies reporting DR prevalence among diabetic patients in Indigenous and non-Indigenous Australian populations. Two independent reviewers performed quality assessments using a 9-item appraisal tool. Meta-analysis and meta-regression were performed using double arcsine transformation and a random-effects model comparing Indigenous and non-Indigenous subgroups.

Results: Fifteen studies with 8219 participants met criteria for inclusion. The Indigenous subgroup scored lower on the appraisal tool than the non-Indigenous subgroup (mean score 50% vs. 72%, $P = 0.04$). In the unadjusted meta-analysis, DR prevalence in the Indigenous subgroup (30.2%; 95% confidence interval [CI], 24.9–35.7) did not differ significantly ($P = 0.17$) from the non-Indigenous subgroup (23.7%; 95% CI, 16.8–31.4). After adjusting for age and quality, DR prevalence was higher in the Indigenous subgroup ($P < 0.01$), with prevalence ratio point estimates ranging from 1.72 to 2.58, depending on the meta-regression model. For the secondary outcomes, prevalence estimates were higher in the Indigenous subgroup for diabetic macular edema (DME) (8.7% vs. 2.7%, $P = 0.02$) and vision-threatening DR (VTDR) (8.6% vs. 3.0%, $P = 0.03$) but not for proliferative DR (2.5% vs. 0.8%, $P = 0.07$).

Conclusions: Indigenous studies scored lower for methodological quality, raising the possibility that systematic differences in research practices may be leading to underestimation of disease burden. After adjusting for age and quality, we found a higher DR prevalence in the Indigenous subgroup. This contrasts with a previous review that reported the opposite finding of lower DR prevalence using unadjusted pooled estimates. Future epidemiological work exploring DR burden in Indigenous communities should aim to address methodological weaknesses identified by this review. *Ophthalmology 2023;130:56-67 © 2022 by the American Academy of Ophthalmology. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).*

Supplemental material available at www.aaojournal.org.

Diabetes prevalence is rapidly increasing, contributing to significant morbidity and mortality in both Indigenous and non-Indigenous Australians.[1] The burden of diabetes affects Indigenous Australians disproportionately, with diabetes-associated death being 6 times the national average.[2] The basis of this is likely to be multifactorial, including earlier onset, increased prevalence of risk factors, and barriers to best practice care. Diabetic retinopathy (DR) is one of the most common complications of diabetes and the leading cause of preventable blindness in working-aged Australians.[3,4] Some reports indicate that diabetes-related visual loss is up to 5 times higher among Indigenous Australians.[5]

Existing studies have reported conflicting findings on DR prevalence in Indigenous diabetic patients compared with their non-Indigenous counterparts. A nonsystematic review on the topic found that DR prevalence was actually lower among Indigenous diabetic patients; however, the prevalence of diabetic macular edema (DME) was higher.[6] One

https://doi.org/10.1016/j.ophtha.2022.07.024
ISSN 0161-6420/22

suggested explanation was a relative resistance during the initial stages of DR but with a subset progressing quickly to vision-threatening DR (VTDR). Although a formal risk of bias assessment was not performed, the authors pointed out methodological differences between Indigenous and non-Indigenous studies, as well as relevant differences in the characteristics of cohorts.

More recently, several additional Australian DR prevalence studies have been published, including 2 population-based studies that reported the opposite finding of increased DR prevalence in Indigenous Australians.[7,8] Understanding ethnic variation in disease prevalence is important for identifying key health priorities to policymakers to reduce health inequity. Epidemiological studies may lead to the identification of ethnic-specific modifiable risk factors that can be targeted to reduce morbidity.

Previous systematic reviews have identified ethnic variation in DR prevalence for other populations;[9,10] however, our literature search did not identify systematic reviews on this topic performed in Australia. This review aims to evaluate key differences in methodology, characteristics, and DR prevalence outcomes between Indigenous and non-Indigenous Australian cohorts.

Methods

We performed a systematic review and meta-analysis following recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement, as well as guidance specific to prevalence studies from the Joanna Briggs Institute (JBI).[11,12] The review protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO; ID: CRD42022259048). Protocol deviations were considered minor and are outlined in Appendix A (available at www.aaojournal.org). This study adhered to the tenets of the Declaration of Helsinki and was exempt from Institutional Review Board approval since it only involved the review and synthesis of existing literature.

Eligibility Criteria for Considering Studies for This Review

The inclusion criteria were defined according to the Condition, Context, Population framework.[12] (1) Condition: We included studies reporting DR prevalence among patients with type 2 diabetes or any diabetes type. The decision to include mixed cohorts was based on preliminary searches that found that many DR prevalence studies do not distinguish between diabetes types. We expected that type 2 diabetic patients would comprise the majority of mixed diabetic cohorts.[13] Diabetes was defined broadly using any method including physician diagnosis, laboratory tests, diabetes treatment, or self-report. For DR assessment, we required the use of an objective measure as part of the study including clinical examination or retinal photography but not self-report. We excluded studies that selected for diabetic subgroups such as children, type 1 diabetes, or gestational diabetes. (2) Context: We included studies with last collected data after January 2000 to reflect prevalence rates and detection methods over the past 20 years. (3) Population: We included studies conducted in Australian populations including Indigenous cohorts, non-Indigenous cohorts, or the general Australian population. For general population studies that did not report Indigenous status, we expected the proportion of Indigenous participants to be low and considered this before inclusion, although no exclusions were made on this basis. We included population-based studies, community-based studies,[14] or clinic-based studies but excluded nonscreening populations derived from specialist centers requiring a referral. Reviews and commentaries were excluded.

Search Methods for Identifying Studies

We performed database searches of Medline (Ovid), EMBASE, and Web of Science from inception to October 2021 using a search strategy designed by an information specialist (Appendix B, available at www.aaojournal.org). CENTRAL and CINAHL were considered low-yield databases because of the focus on randomized trials and allied health research, respectively.[15] Reference lists of included studies and relevant reviews were manually screened. To include gray literature, we performed searches of Trove (National Library of Australia), Google Scholar, Australian Bureau of Statistics, Australian Institute of Health and Welfare, and the Australian Indigenous Health Infonet (Appendix B). There were no restrictions on language or publication status.

Study Selection

Records retrieved from database searches were compiled in Endnote X9, and the deduplication function was used to identify potential duplicates. All duplicates were manually reviewed before exclusion. Two reviewers (M.A.C. and J.R.T.) independently screened titles and abstracts using Rayyan software to identify reports requiring full-text review. Reviewers then independently evaluated full-text reports against inclusion criteria. Disagreements were resolved by discussion or arbitration with a third reviewer (A.W.T.) where necessary.

Data Collection and Risk of Bias Assessment

Two reviewers (M.A.C. and J.R.T.) independently performed data extraction in duplicate using standardized data collection forms. We sought information on study design, collection period, setting, recruitment methods, diabetes definition, DR definition, participant characteristics, risk factors, and reported outcomes. All corresponding authors were contacted by email to request missing data.

The primary outcome was the prevalence of DR among diabetic patients, defined according to an objective grading method. Secondary outcomes were the prevalence of DME, proliferative DR (PDR), and VTDR, defined as PDR or DME.

Risk of bias assessments were performed by 2 reviewers (J.R.T. and M.A.C.) using the JBI Checklist for Prevalence Studies.[16] Using the accompanying guidance to the checklist, we first agreed on a system for applying the tool to studies of DR prevalence (Appendix C, available at www.aaojournal.org). Studies were then assessed independently, with disagreements resolved by discussion or arbitration. We assigned an overall quality score to each study using equal weightings for all checklist items. Although such aggregate scores have been discouraged for interventional studies, their utility when meta-analyzing prevalence studies has been emphasized.[17] We also performed a post hoc analysis to show that our quality rankings were robust to subjective variation in domain weights (Appendix D, available at www.aaojournal.org), which is a major criticism of aggregate quality scores. We used the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach to assess the overall quality of evidence.[18] Because of the absence of guidance on certainty assessment for prevalence estimates, we applied a framework intended for incidence estimates in the context of prognostic studies.[19]

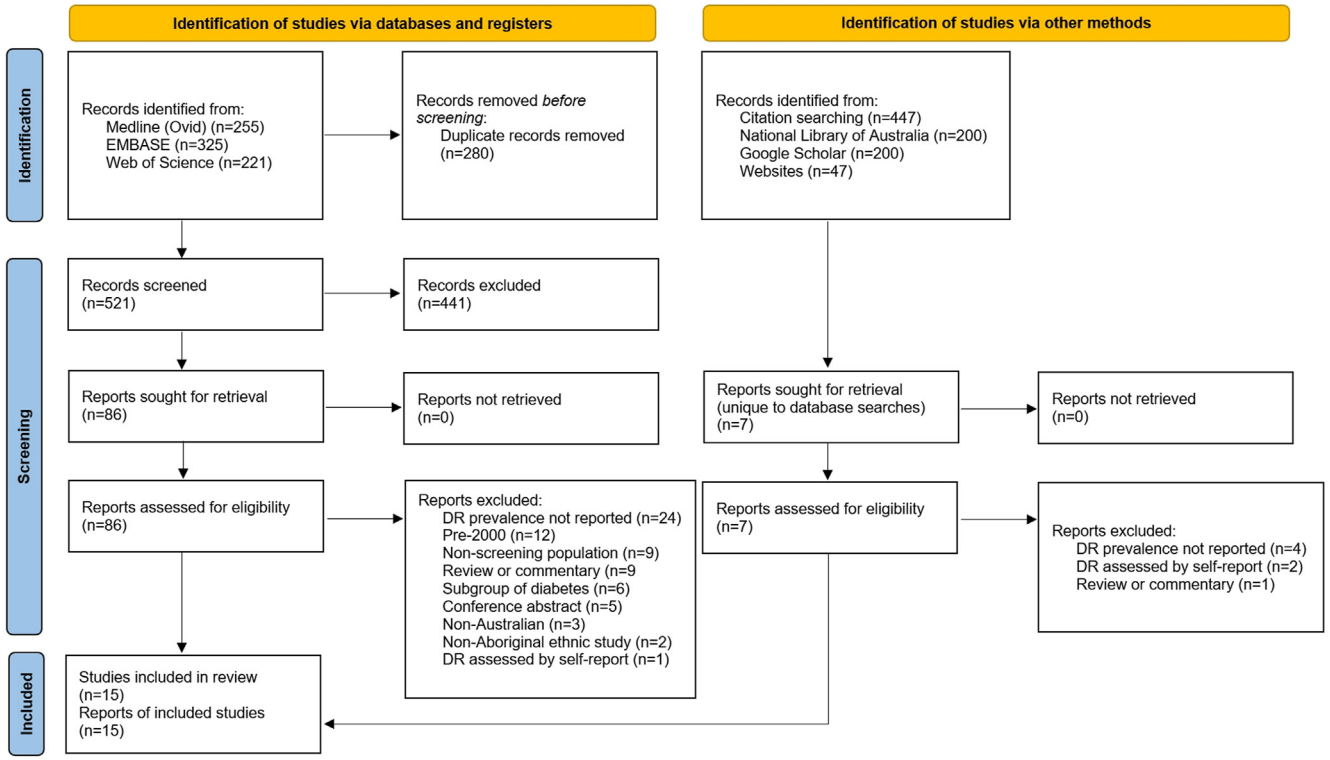


Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of study selection. DR = diabetic retinopathy.

Data Synthesis and Analysis

The primary meta-analysis was a subgroup analysis comparing DR prevalence between Indigenous and non-Indigenous subgroups. We pooled prevalence estimates by performing Freeman−Tukey double arcsine transformation to address variance instability and normality assumptions.[17] A random-effects model was chosen in accordance with JBI guidance to allow for between-study variation.[12] The 95% confidence intervals (CIs) were calculated using the score statistic.[12,20] We expected individual prevalence estimates to vary considerably between studies and selected statistical methods that are commonly applied to account for this variation when meta-analyzing prevalence studies.[20] Heterogeneity between studies was assessed by Cochran Q test and the I^2 statistic; however, it is noted that, because of the nature of proportional data, high I^2 statistics are expected and should be interpreted conservatively.[21]

In addition to the primary subgroup analysis, we further explored heterogeneity by performing meta-regression using the following prespecified covariates: median year of data collection, quality score, age, female proportion, diabetes duration (continuous), rural versus metropolitan, national versus local, retinal photo versus clinical examination, self-reported versus objective diabetes diagnosis, and population based versus nonpopulation based (binary categorical). We first performed univariable meta-regression by applying logarithmic transformation to meet parametric assumptions of normality.[22] We then performed multivariable meta-regression by including each covariate separately in the regression model along with Indigenous status. We limited the number of covariates in the regression model to 2 to maintain an approximate covariate to study cohort ratio of 1:10, as has been commonly advised.[23]

Prespecified sensitivity analyses were performed by excluding low-quality studies and studies with sample sizes < 200. We used 2 thresholds to define lower-quality studies: those with a quality score < 50% and those with nonpopulation-based recruitment. In accordance with recent guidance, publication bias was not formally assessed on the basis that underlying assumptions do not necessarily hold true for prevalence studies.[21] Statistical analysis was conducted in Stata, version 15, with meta-analysis and meta-regression performed using the "metaprop" and "metareg" functions.

Results

Study Selection

Of 801 records identified by database searching, 86 were selected for full-text assessment (Fig 1). An additional 7 unique full-text records were identified through non−database searching. Of these, 15 studies enrolling 8219 diabetic participants were included in our systematic review and meta-analysis.[7,8,24–36]

Study Characteristics

The characteristics of included studies are presented in Table 1, and the funding sources are shown in Appendix E (available at www.aaojournal.org). There were 9 studies of Indigenous participants, 4 studies containing both Indigenous and non-Indigenous cohorts, and 2 studies of the general Australian population that did not distinguish between Indigenous status. One of the general studies reported an Indigenous proportion of 0.8%.[35] The other also had an estimated Indigenous proportion of < 1%

Table 1. Characteristics of Included Studies

Study	Name	Period	Location	Sampling	DR Method	Population Characteristics	Outcomes
Indigenous							
Murray (2005a)[24]	Kimberley Eye Program	1999–2004	Kimberley region, WA (Remote)	Clinic-based	Retinal photo	Mean age (SD): 50.6 yrs (13) Female: 62%	DR, DME, VTDR, PDR
Durkin (2006)[25]	South Australian Eye Health Program	1999–2004	Multiple regions, SA (Remote)	Clinic-based	Clinical examination	Mean age (SD): 42.0 yrs (20.1) Female: 62%	DR, DME, VTDR
Maple-Brown (2008)[26]	Darwin Region Urban Indigenous Diabetes Study	2003–2005	Darwin, NT (Regional)	Community-based	Retinal photo	Mean age (SD): 53 yrs (10) Female: 76% Median diabetes duration (IQR): 8.0 yrs (3.5–14.5)	DR
Clark (2010)[27]	Goldfields Eye Health Survey	1995–2007	Goldfields region, WA (Remote)	Community-based	Clinical examination	Mean age (SD): 48.0 yrs (12.9) Female: 59%	DR, DME, VTDR, PDR
Landers (2010)[28]	Central Australia Ocular Health Study	2005–2008	Central Australia, NT (Remote)	Clinic-based	Clinical examination	Mean age (SD): 48.4 yrs (14.6) Female: 63%	DR, DME, VTDR, PDR
Spurling (2010)[29]	Inala Indigenous Health Service	2007–2009	Brisbane, QLD (Metro)	Clinic-based	Retinal photo	Median age (range): 52 yrs (24–78) Female: 55% Median diabetes duration (range): 6 yrs (1–37)	DR, VTDR
Xie (2011)[30]	National Indigenous Eye Health Study	2008	National sample	Community-based	Retinal photo	Median age (IQR): 53 yrs (47–61) Female: 60% Mean diabetes duration (IQR): 9 yrs (13)	DR, DME
Moynihan (2017a)[31]	Kimberley DR Screening Program	2010–2014	Kimberley region, WA (Remote)	Clinic-based	Retinal photo	Mean age (SD): 52.6 yrs (14.1) Female: 56%	DR, PDR
Keel (2017a)[7]	National Eye Health Survey	2015–2016	National sample	Population-based	Retinal photo	Mean age (SD): 58.1 yrs (9.8) Female: 62% Mean diabetes duration (SD): 11.0 yrs (11.9)	DR, DME, VTDR, PDR
Brazionis (2018)[32]	TEAMSnet Substudy	2014–2016	Alice Springs, NT (Remote)	Clinic-based	Retinal photo	Mean age (SD): 48.2 yrs (13.3) Female: 67% Mean diabetes duration (SD): 8.6 yrs (7.5)	DR, DME, VTDR, PDR
O'Halloran (2018)[33]	Lions Outback Vision	2014–2015	Perth, WA (Metro); Port Hedland, WA (Remote)	Clinic-based	Retinal photo	Mean age (range): 53.5 yrs (18–84) Female: 47%	DR, DME
Drinkwater (2020a)[8]	Fremantle Diabetes Study II	2008–2011	Perth, WA (Metro)	Population-based	Retinal photo	Mean age (SD): 53.8 yrs (11.4) Female: 65% Median diabetes duration (IQR): 7.4 yrs (3.0–16.0)	DR
Quinn (2020)[34]	TEAMSnet Substudy	2013–2015	Top End Region, NT (Remote)	Clinic-based	Retinal photo	Median age (range): 53 yrs (29–79) Female: 61%	DR, DME, VTDR, PDR
Non-Indigenous							
Tapp (2003)[35]	Australian Diabetes Study	1999–2001	National sample	Population-based	Retinal photo	Mean age (SD): 62.4 yrs (11.9) Female: 50% Median diabetes duration (IQR): 7 yrs (0–15)	DR, DME, VTDR, PDR
Murray (2005b)[24]	Kimberley Eye Program	1999–2004	Kimberley Region, WA (Remote)	Clinic-based	Retinal photo	Mean age (SD): 54.6 yrs (12.6) Female: 32%	DR, DME, VTDR, PDR

(*Continued*)

Table 1. (Continued.)

Study	Name	Period	Location	Sampling	DR Method	Population Characteristics	Outcomes
Cugati (2006)[36]	Blue Mountain Eye Study II	1997–2000	Sydney, NSW (Metro)	Population-based	Retinal photo	Mean age (SD): 68.1 yrs (8.1) Female: 49% Median diabetes duration: 7.5 yrs	DR, PDR
Moynihan (2017b)[31]	Kimberley DR Screening Program	2010–2014	Kimberley Region, WA (Remote)	Clinic-based	Retinal photo	Mean age (SD): 57.4 yrs (12.6) Female: 31%	DR, PDR
Keel (2017b)[7]	National Eye Health Survey	2015–2016	National sample	Population-based	Retinal photo	Mean age (SD): 68.4 yrs (8.9) Female 43% Mean diabetes duration (SD): 10.0 yrs (12.0)	DR, DME, VTDR, PDR
Drinkwater (2020b)[8]	Fremantle Diabetes Study II	2008–2011	Perth, WA (Metro)	Population-based	Retinal photo	Mean age (SD): 67.3 yrs (10.5) Female 49% Median diabetes duration (IQR): 8.7 yrs (2.8–15.3)	DR

DR = diabetic retinopathy; DME = diabetic macular edema; IQR = interquartile range; NSW = New South Wales; NT = Northern Territory; PDR = proliferative diabetic retinopathy; QLD = Queensland; SA = South Australia; SD = standard deviation; TEAMSnet = Telehealth Eye and Associated Services Network Study; VTDR = vision-threatening diabetic retinopathy; WA = Western Australia. Note. The a and b in referenced studies do not indicate separate studies – they indicate a single study that has been divided into (a) Indigenous and (b) non-Indigenous cohort.

based on census data;[36] therefore, we classified both as non-Indigenous cohorts. We considered the 4 studies with both Indigenous and non-Indigenous data as being composed of separate cohorts, resulting in 13 Indigenous cohorts and 6 non-Indigenous cohorts. Data from all studies were collected between 1999 and 2016. Three studies used a national sample frame, and the remainder involved a mixture of metropolitan and rural settings. Four of 6 non-Indigenous cohorts used population-based sampling, but only 2 of 13 Indigenous cohorts were population based. Three studies used clinical examination rather than retinal photography to grade DR, all being Indigenous studies. The mean or median ages of the Indigenous cohorts tended to be lower than those of the non-Indigenous cohorts (range, 42–58 versus 55–68 years).

Quality Assessment

Risk of bias graphs are shown in Figure 2, presented separately for the Indigenous and non-Indigenous subgroups to enable comparison. Complete quality assessments for each study are presented in Table S2 (available at www.aaojournal.org). The mean quality score for the Indigenous subgroup was lower than for the non-Indigenous subgroup (50% vs. 72%, $P = 0.04$). Both subgroups scored poorly on the checklist items pertaining to sample size calculations and assessment of coverage bias. Checklist items where the non-Indigenous subgroup notably outperformed the Indigenous subgroup included (1) selection of an appropriate sample frame, (2) use of appropriate sampling methods (population-based sampling), and (3) reporting of adequate response rates. The use of population-based sampling was a good indicator of the highest quality studies overall, with the 4 population-based studies being the only ones to achieve quality scores better than 75%. The overall certainty of evidence was assessed as low using the GRADE framework as detailed in Table S3 (available at www.aaojournal.org).

Diabetic Retinopathy Prevalence

The forest plot for the primary meta-analysis comparing DR prevalence between Indigenous and non-Indigenous subgroups is presented in Figure 3. The pooled prevalence for the Indigenous subgroup (30.2%; 95% CI, 24.9–35.7) did not differ significantly ($P = 0.17$) from the non-Indigenous subgroup (23.7%; 95% CI, 16.8–31.4), although there was evidence of considerable heterogeneity in both pooled estimates ($I^2 = 95.0\%$ and 93.5%, $P < 0.01$). Of the 4 studies reporting within-study comparisons, 3 studies found that DR prevalence was higher among Indigenous participants. The fourth contained only a small non-Indigenous cohort and was likely underpowered to detect such a difference.[31] Inspection of the forest plot revealed a trend of higher DR prevalence among more recent studies in both subgroups.

To further examine heterogeneity, we performed meta-regression to investigate the impact of various prespecified covariates on prevalence estimates, as previously outlined. Median year of data collection was the only significant modifier of DR prevalence in the univariable meta-regression (Table S4, available at www.aaojournal.org), with higher prevalence among more recent studies (exp(Effect estimate) = 1.04; 95% CI, 1.01–1.07; $P = 0.01$, adjusted $R^2 = 35.2\%$).

In the multivariable models, Indigenous status was a significant modifier of DR prevalence after adjusting separately for age, quality, and use of population-based sampling (Table 2). Prevalence ratio point estimates comparing Indigenous with non-Indigenous subgroups ranged from 1.72 to 2.58 depending on the multivariable model. The proportion of between-study variance explained by the multivariable models (adjusted R^2) ranged between 45% and 50%. The remaining nonsignificant models are

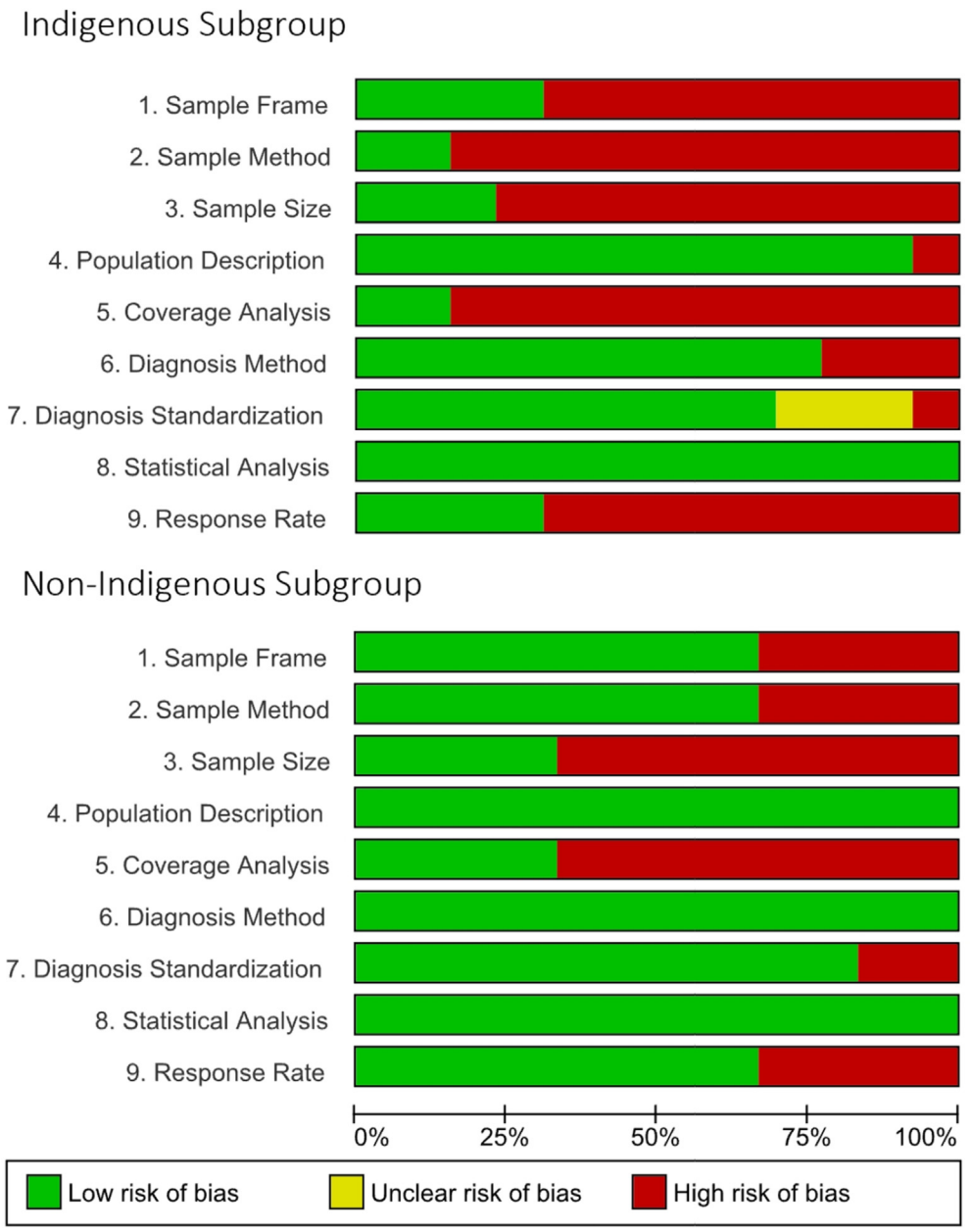


Figure 2. Risk of bias graphs for Indigenous and non-Indigenous subgroups using the Joanna Briggs Institute critical appraisal checklist for prevalence studies. The 4 studies with both Indigenous and non-Indigenous data are represented in both graphs.

presented in Table S4, and the forest plot for the quality adjusted model is displayed in Figure 4.

Secondary Outcomes and Sensitivity Analysis

Pooled prevalence estimates were higher in the Indigenous subgroup than in the non-Indigenous subgroup for the secondary outcomes DME (8.7% vs. 2.7%, $P = 0.02$) and VTDR (8.6% vs. 3.0%, $P = 0.03$) but not for PDR (2.5% vs. 0.8%, $P = 0.07$; Table 3). In the sensitivity analysis excluding low-quality studies, there were significant subgroup differences for all secondary outcomes but not for the primary outcome of any DR (Table 3). In the sensitivity analysis that only included population-based studies (also interpreted as the highest-quality studies), subgroup differences were significant for all primary and secondary outcomes. These findings are consistent with the meta-regression models showing that Indigenous status was a significant modifier of DR prevalence after adjusting for quality and population-based sampling. Five cohorts were excluded by the small sample sensitivity analysis, but there were no unique findings compared with the original analysis (Table 3).

We performed an additional post hoc sensitivity analysis in which we included only the 4 studies with both Indigenous and non-Indigenous cohorts. We calculated prevalence ratios between the 2 cohorts for each study to isolate quality differences and pooled these to produce a summary prevalence ratio of 1.58 (95%

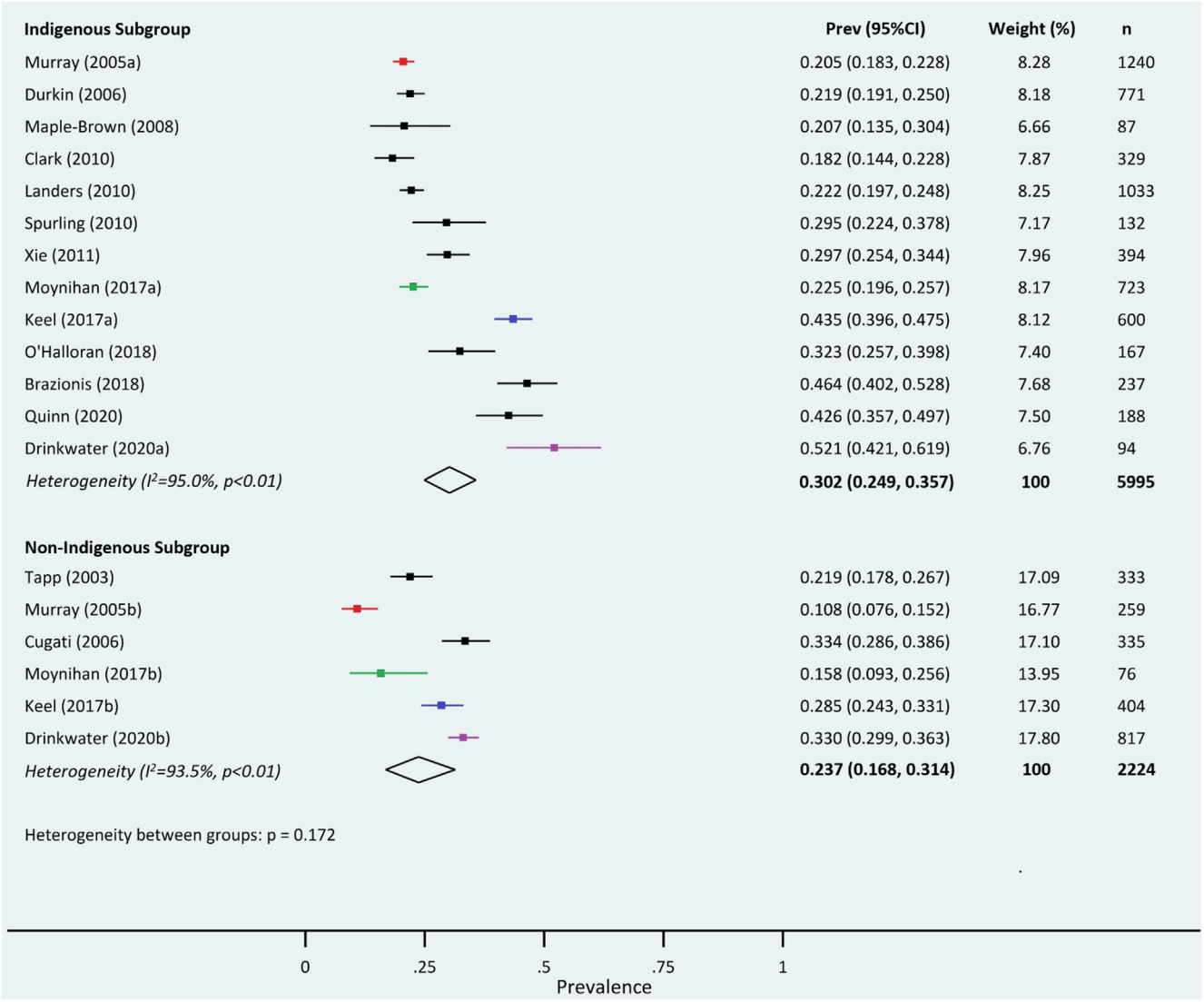


Figure 3. Forest plot of diabetic retinopathy prevalence between Indigenous and non-Indigenous subgroups. Studies reporting within-study comparisons are color-coded for clarity. CI = confidence interval. The a and b in referenced studies do not indicate separate studies — they indicate a single study that has been divided into (a) Indigenous and (b) non-Indigenous cohort.

CI, 1.39–1.79) (Fig S5, available at www.aaojournal.org). This pooled prevalence ratio was comparable to the estimate derived from our quality-adjusted meta-regression model (Table 2).

Discussion

According to our literature search, this is the first systematic review and meta-analysis of DR prevalence in Australia. Our review specifically aimed to identify differences in methodology, characteristics, and outcomes between Indigenous and non-Indigenous subgroups. We found that Indigenous diabetic cohorts tended to be younger and that quality scores of Indigenous studies were lower. In our unadjusted meta-analysis, there were no significant differences in DR prevalence between subgroups. However, after adjusting separately for age and quality in our meta-regression model, DR prevalence was higher in the Indigenous subgroup, with prevalence ratios ranging from 1.7 to 2.6.

Our key findings differ substantially from a previous nonsystematic review of DR prevalence by Kaidonis et al,[6] which found the opposite effect of reduced DR prevalence among Indigenous studies (23.6% vs. 28.9%, $P < 0.01$). Methodological aspects of this earlier review that may explain discrepancies include (1) absence of meta-regression techniques adjusting for relevant covariates, (2) use of informal pooling methods that more closely reflect fixed-effects meta-analysis and therefore fail to account for between-study variation, (3) inclusion of a large non-Indigenous study that likely oversampled type 1 diabetic patients and contributed > 80% of the pooled subgroup estimate, and (4) a different inclusion period spanning 1990 to 2013.

Table 2. Multivariable Meta-regression Models with Significant Modifiers when Combined with Indigenous Status

Meta-regression Model	Prevalence Ratio [95% CI]	*P* Value	Adjusted R^2
Age and Indigenous status		0.005	45.0%
Non-Indigenous	Reference		
Indigenous	2.58 [1.52–4.37]	0.002	
Age (continuous)	1.06 [1.02–1.09]	0.002	
Quality and Indigenous status		0.004	46.8%
Non-Indigenous	Reference		
Indigenous	1.72 [1.20–2.47]	0.006	
Quality (continuous)	1.16 [1.07–1.26]	0.002	
Population-based and Indigenous status		0.003	49.6%
Non-Indigenous	Reference		
Indigenous	1.84 [1.27–2.66]	0.003	
Nonpopulation-based	Reference		
Population-based	1.94 [1.36–2.77]	0.001	

CI = confidence interval.
Adjusted R^2 may be interpreted as the proportion of variance explained by the model.

Kaidonis et al[6] highlight the differing age structure of Indigenous Australians as being an important consideration when interpreting their findings. Indigenous Australians are known to develop diabetes at an earlier age and to experience premature mortality compared with non-Indigenous Australians. Direct comparisons with non-Indigenous cohorts may lead to underestimation of Indigenous DR prevalence because many may have otherwise developed DR had they reached the life expectancy of their non-Indigenous counterparts.[6]

To explore the effect of recently recommended meta-analytical techniques more directly, we applied our own pooling methods to the data extracted by Kaidonis et al[6] (Fig S6, available at www.aaojournal.org). In the random-effects meta-analysis, the DR prevalence point estimate remained lower in the Indigenous subgroup, but the effect was no longer significant (25.9% vs. 28.8%, $P = 0.39$). After adjusting for age (Fig S7, available at www.aaojournal.org), the DR prevalence point estimate became higher in the Indigenous subgroup, although the difference remained nonsignificant (33.5% vs. 19.7%, $P = 0.28$).

Despite finding lower prevalence of any DR, Kaidonis et al[6] report similar or higher rates of severe DR outcomes including DME, VTDR, and PDR. This was consistent with our own findings, which showed that relative differences in prevalence were larger for severe outcomes. Early diabetes onset has been identified as a risk factor for DR severity, independent of diabetes duration and glycemic control, potentially suggesting inherent tissue susceptibility to hyperglycemic damage.[37] It is possible that Indigenous patients tend to develop this more aggressive phenotype, causing rapid progression to VTDR. Access to health care and attitudes toward Western medicine may be additional important contributing factors.[38] Despite recent improvements, screening rates for DR in Indigenous patients fall well short of the general population, raising the possibility that poor risk factor control may accelerate DR progression in Indigenous Australians.[5]

Although our findings differed from those of Kaidonis et al,[6] key results are consistent with 2 recent, high-quality, population-based studies reporting comparisons by Indigenous status, both of which are included in the present review. The National Eye Health Survey and the Fremantle Diabetes Study II both found higher DR prevalence among Indigenous participants.[7,8] Considering methodological differences between studies, consistency of within-study comparisons among high-quality studies adds strength to our conclusions.

There are several plausible explanations for our finding of reduced study quality among Indigenous studies. Because of the low proportion of Indigenous patients within urban settings, studies targeted at Indigenous participants are more likely to occur within remote Indigenous communities. Performing high-quality epidemiological research is often challenging in these settings. This is particularly true when exploring DR prevalence because specialized clinical skills and equipment are required. Because of the lack of permanent specialist services, research is frequently conducted through visiting services. Many of the important methodological differences we noted in the Indigenous subgroup may be explained by limitations of transient services, such as suboptimal sampling methods, limited sample frames, and unreliable diagnostic methods. Our findings raise the possibility that systematic differences in research practices may be leading to underestimation of disease burden in the Indigenous population, with potential flow-on effects on healthcare funding priorities.

Key strengths of our review include registration of a comprehensive protocol, a comprehensive search strategy, quality assessment using a prevalence-specific critical appraisal tool, adoption of widely recommended meta-analytical techniques, and the use of meta-regression to adjust for prespecified covariates.

Study Limitations

Our study has relevant limitations. First, we were not able to simultaneously adjust for all relevant covariates to explore the independent effect of Indigenous status. Diabetes duration and glycemic control are clearly related to DR;

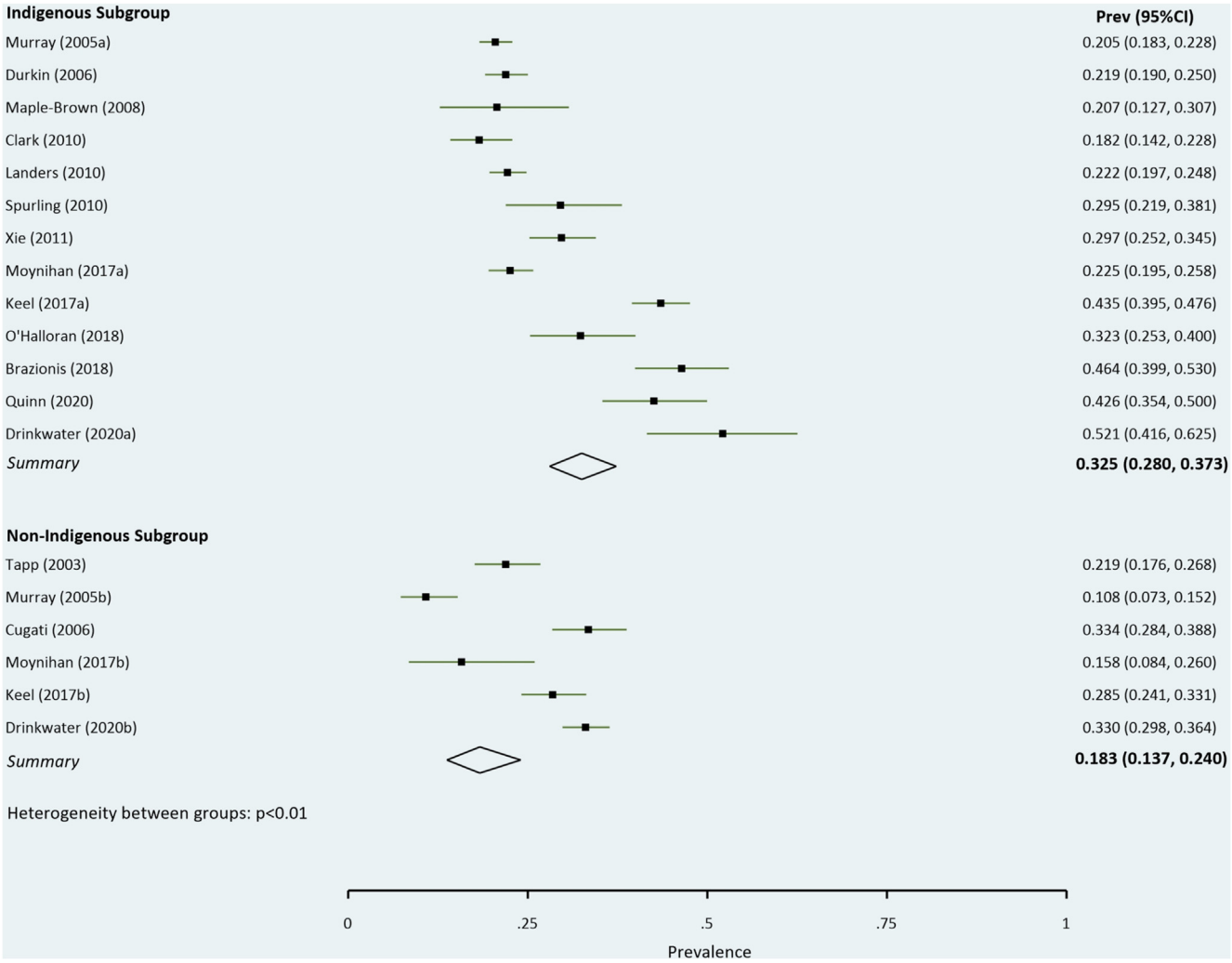


Figure 4. Forest plot of diabetic retinopathy prevalence between Indigenous and non-Indigenous subgroups after adjusting for quality score in a meta-regression model. CI = confidence interval. The a and b in referenced studies do not indicate separate studies — they indicate a single study that has been divided into (a) Indigenous and (b) non-Indigenous cohort.

therefore, it is likely that ethnic differences in these risk factors at least partially account for the effect of Indigenous status. Although we attempted to include diabetes duration in our meta-regression model, data were only available in half of the cohorts, and inconsistent summary measures were reported. It was therefore unsurprising that diabetes duration was not identified as a significant modifier, despite its known relation to DR.[6] Likewise, diabetes type and glycemic control were infrequently reported and could not be included in a meta-regression model.

Between-study methodological differences further limited our ability to examine the independent effect of Indigenous status. We attempted to account for these by exploring a range of potentially relevant covariates including quality score. However, because of the modest number of studies and the availability of study-level rather than patient-level data, we were not able to include > 2 covariates simultaneously.[23] The value of meta-analyzing prevalence studies is questioned by some because of a tendency for heterogeneity; however, many experts advocate for its benefits, and adoption is increasing, with a 10-fold increase in such studies over the past decade.[12,21]

Second, our subgroup analysis classified studies of the general Australian population as non-Indigenous cohorts. As previously outlined, this assumption affected only 2 studies, and in both cases, the expected Indigenous proportion was $< 1\%$; therefore, we expect any impact to be minor.

Conclusions

Future epidemiological work exploring DR prevalence in Indigenous communities should address common methodological weaknesses identified by this review. Researchers should aim to collect data on important risk factors, including diabetes type, diabetes duration, glycemic control, hypertension, and body mass index, which may lead to the

Table 3. Meta-analyses and Sensitivity Analyses of DR Prevalence

Meta-analyzed Outcomes	Indigenous Prevalence, % [95% CI]	Non-Indigenous Prevalence, % [95% CI]	*P* Value
Original analysis			
Any DR (primary outcome)	30.2 [24.9–35.7]	23.7 [16.8–31.4]	0.17
DME	8.7 [5.8–12.1]	2.7 [0.4–6.5]	0.02*
VTDR	8.6 [5.8–11.9]	3.0 [0.6–7.0]	0.03*
PDR	2.5 [1.2–4.4]	0.8 [0.1–1.9]	0.07
Sensitivity 1: Low quality excluded			
Any DR	38.3 [29.2–47.8]	29.2 [24.3–34.4]	0.09
DME	12.5 [8.8–16.7]	4.4 [3.1–6.1]	<0.01*
VTDR	12.4 [10.3–14.8]	4.9 [3.4–6.6]	<0.01*
PDR	4.7 [3.3–6.3]	1.6 [0.9–2.4]	<0.01*
Sensitivity 2: Population-based only			
Any DR	44.6 [40.9–48.4]	29.2 [24.3–34.4]	<0.01*
DME	14.7 [12.0–17.7]	4.4 [3.1–6.1]	<0.01*
VTDR	11.1 [8.8–13.9]	4.9 [3.4–6.6]	<0.01*
PDR	6.0 [4.4–8.2]	1.6 [0.9–2.4]	<0.01*
Sensitivity 3: Small sample excluded			
Any DR	27.5 [21.5–33.9]	25.1 [17.6–33.4]	0.64
DME	8.4 [5.4–11.9]	2.7 [0.4–6.5]	0.02*
VTDR	9.0 [6.0–12.6]	3.0 [0.6–7.0]	0.02*
PDR	2.3 [0.9–4.1]	1.0 [0.2–2.2]	0.20

CI = confidence interval; DME = diabetic macular edema; DR = diabetic retinopathy; PDR = proliferative diabetic retinopathy; VTDR = vision-threatening diabetic retinopathy.
*$P < 0.05$.

identification of ethnic-specific modifiable risk factors. Longitudinal studies exploring progression of DR severity have the potential to establish new biomarkers identifying high-risk individuals to be targeted for increased disease surveillance. These types of longitudinal studies are difficult to perform but offer important advantages over cross-sectional studies when exploring the impact of glycemic control and diabetes duration. Although the challenges of epidemiological research within Indigenous communities are well described, the commencement of Australia's first dedicated remote eye center provides promising research potential.[39]

Our systematic review and meta-analysis found a higher rate of DR prevalence among Indigenous Australians after adjusting for age and quality score, in contrast to an earlier review. Strategies for improving access to high-quality and culturally appropriate services for Indigenous patients remain a critical healthcare priority for Australia.

Footnotes and Disclosures

Originally received: March 25, 2022.
Final revision: July 5, 2022.
Accepted: July 19, 2022.
Available online: August 2, 2022. Manuscript no. OPHTHA-D-22-00525

[1] NIHR Biomedical Research Centre, Moorfields Eye Hospital NHS Foundation Trust and UCL Institute of Ophthalmology, London, United Kingdom.

[2] Lions Outback Vision, Lions Eye Institute, Nedlands, Western Australia, Australia.

[3] University of Western Australia, Perth, Western Australia, Australia.

Disclosure(s):

All authors have completed and submitted the ICMJE disclosures form.

The author(s) have made the following disclosure(s): A.P.K.: Consultant or lecturer – AbbVie, Aerie, Allergan, Google Health, Heidelberg, Novartis, Reichert, Santen, Thea.

P.J.F.: Consultant – Alphasights, GLG, Google Health, Guidepoint, PwC, Santen. P.A.K.: Consultant or lecturer – DeepMind, Roche, Novartis, Apellis, Bitfount, Heidelberg, Topcon, Allergan, Bayer; Stock – Big Picture Medical.

M.A.C.: Recipient of a General Sir John Monash Scholarship.

K.V.S.: Recipient of a UCL Overseas Research Scholarship.

K.V.S., P.J.F.: Grant support – Fight for Sight, London (1956A) and The Desmond Foundation.

A.P.K., P.J.F., P.A.K.: Research costs and salary support – UK Department of Health through the National Institute for Health and Care Research grant for a biomedical research center at Moorfields and UCL Institute of Ophthalmology. The sponsor or funding organization had no role in the design or conduct of this research.

Presented in part at: Association for Research in Vision and Ophthalmology Annual Meeting, May 1–4, 2022, Denver, Colorado.

HUMAN SUBJECTS: No human subjects were included in this study. No Institutional Review Board approval required. 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 used in this study.

Author Contributions:

Conception and design: Chia, Taylor, Khawaja, Turner

Data collection: Chia, Taylor

Analysis and interpretation: Chia, Taylor, Stuart, Khawaja, Foster, Keane, Turner

Obtained funding: N/A

Overall responsibility: Chia, Taylor, Stuart, Khawaja, Foster, Keane, Turner

Abbreviations and Acronyms:
CI = confidence interval; **DME** = diabetic macular edema; **DR** = diabetic retinopathy; **JBI** = Joanna Briggs Institute; **PDR** = proliferative diabetic retinopathy; **VTDR** = vision-threatening diabetic retinopathy.

Keywords:
Diabetic retinopathy, Prevalence, Indigenous Australians, Aboriginal, Systematic review.

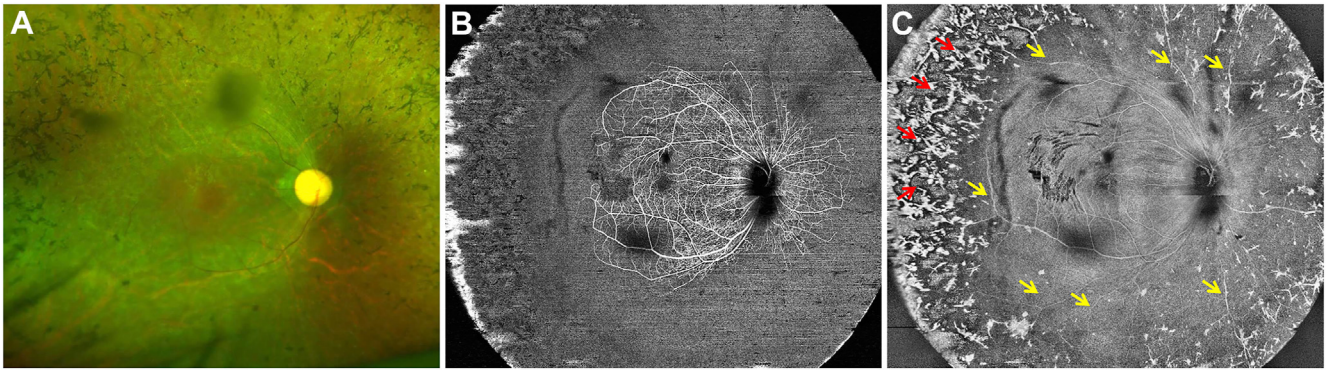
Correspondence:
Mark A. Chia, MBBS, MMed, Institute of Ophthalmology, University College London, 11-43 Bath Street, London EC1V 9EL, UK. E-mail: mark.a.chia@outlook.com.

References

1. Saeedi P, Petersohn I, Salpea P, et al. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: results from the International Diabetes Federation Diabetes Atlas, 9th edition. *Diabetes Res Clin Pract*. 2019;157:107843.
2. Burrow S, Ride K. Review of diabetes among Aboriginal and Torres Strait Islander people. *Australian Indigenous HealthInfoNet*; 2016. https://ro.ecu.edu.au/ecuworkspost2013/2226. Accessed March 3, 2022.
3. Cheung N, Wong TY. Diabetic retinopathy and systemic vascular complications. *Prog Retin Eye Res*. 2008;27:161–176.
4. Crossland L, Askew D, Ware R, et al. Diabetic retinopathy screening and monitoring of early stage disease in Australian general practice: tackling preventable blindness within a chronic care model. *J Diabetes Res*. 2015;2016:e8405395.
5. Foreman J, Keel S, Xie J, et al. *National Eye Health Survey Report*. Melbourne: Centre for Eye Research Australia; 2016. https://www.vision2020australia.org.au/wp-content/uploads/2019/06/National-Eye-Health-Survey_Full-Report_FINAL.pdf. Accessed February 1, 2022.
6. Kaidonis G, Mills RA, Landers J, et al. Review of the prevalence of diabetic retinopathy in Indigenous Australians. *Clin Exp Ophthalmol*. 2014;42:875–882.
7. Keel S, Xie J, Foreman J, et al. The prevalence of diabetic retinopathy in Australian adults with self-reported diabetes. *Ophthalmology*. 2017;124:977–984.
8. Drinkwater JJ, Davis WA, Davis TM, et al. Differences in retinopathy prevalence and progression between Anglo-Celt and Aboriginal Australians: The Fremantle Diabetes Study Phase II. *Intern Med J*. 2022;52:590–598.
9. Yang Q-H, Zhang Y, Zhang X-M, et al. Prevalence of diabetic retinopathy, proliferative diabetic retinopathy and non-proliferative diabetic retinopathy in Asian T2DM patients: a systematic review and meta-analysis. *Int J Ophthalmol*. 2019;12:302–311.
10. Sivaprasad S, Gupta B, Crosby-Nwaobi R, et al. Prevalence of diabetic retinopathy in various ethnic groups: a worldwide perspective. *Surv Ophthalmol*. 2012;57:347–370.
11. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ*. 2009;339:b2535–b2535.
12. Munn Z, Moola S, Lisy K, et al. Methodological guidance for systematic reviews of observational epidemiological studies reporting prevalence and cumulative incidence data. *Int J Evid Based Healthc*. 2015;13:147–153.
13. Chatterjee S, Khunti K, Davies MJ. Type 2 diabetes. *Lancet*. 2017;389:2239–2251.
14. Leung BM, McDonald SW, Kaplan BJ, et al. Comparison of sample characteristics in two pregnancy cohorts: community-based versus population-based recruitment methods. *BMC Med Res Methodol*. 2013;13:149.
15. Borges Migliavaca C, Stein C, Colpani V, et al. How are systematic reviews of prevalence conducted? A methodological study. *BMC Med Res Methodol*. 2020;20:96.
16. Munn Z, Moola S, Riitano D, et al. The development of a critical appraisal tool for use in systematic reviews addressing questions of prevalence. *Int J Health Policy Manag*. 2014;3:123–128.
17. Barendregt JJ, Doi SA, Lee YY, et al. Meta-analysis of prevalence. *J Epidemiol Community Health*. 2013;67:974–978.
18. Balshem H, Helfand M, Schünemann HJ, et al. GRADE guidelines:3. Rating the quality of evidence. *J Clin Epidemiol*. 2011;64:401–406.
19. Iorio A, Spencer FA, Falavigna M, et al. Use of GRADE for assessment of evidence about prognosis: rating confidence in estimates of event rates in broad categories of patients. *BMJ*. 2015;350:h870–h870.
20. Nyaga VN, Arbyn M, Aerts M. Metaprop: a Stata command to perform meta-analysis of binomial data. *Arch Public Health*. 2014;72:39.
21. Barker TH, Migliavaca CB, Stein C, et al. Conducting proportional meta-analysis in different types of systematic reviews: a guide for synthesisers of evidence. *BMC Med Res Methodol*. 2021;21:189.
22. Ferrari AJ, Somerville AJ, Baxter AJ, et al. Global variation in the prevalence and incidence of major depressive disorder: a systematic review of the epidemiological literature. *Psychol Med*. 2013;43:471–481.
23. Borenstein M, Hedges LV, Higgins JP, et al. *Introduction to Meta-analysis*. Chichester, UK: John Wiley and Sons; 2009.
24. Murray RB, Metcalf SM, Lewis PM, et al. Sustaining remote-area programs: retinal camera use by Aboriginal health workers and nurses in a Kimberley partnership. *Med J Aust*. 2005;182:520–523.
25. Durkin SR, Casson R, Newland HS, et al. Prevalence of trachoma and diabetes-related eye disease among a cohort of adult Aboriginal patients screened over the period 1999–2004 in remote South Australia. *Clin Exp Ophthalmol*. 2006;34:329–334.
26. Maple-Brown L, Cunningham J, Dunne K, et al. Complications of diabetes in urban Indigenous Australians: The DRUID study. *Diabetes Res Clin Pract*. 2008;80:455–462.
27. Clark A, Morgan WH, Kain S, et al. Diabetic retinopathy and the major causes of vision loss in Aboriginals from remote Western Australia. *Clin Exp Ophthalmol*. 2010;38:475–482.
28. Landers J, Henderson T, Abhary S, et al. Prevalence and associations of diabetic retinopathy in indigenous Australians within central Australia: the Central Australian Ocular Health Study. *Clin Exp Ophthalmol*. 2010;38:393–397.
29. GKP Spurling, Askew DA, Hayman NE, et al. Retinal photography for diabetic retinopathy screening in Indigenous primary health care: the Inala experience. *Aust N Z J Public Health*. 2010;34:S30–S33.

30. Xie J, Arnold A-L, Keeffe J, et al. Prevalence of self-reported diabetes and diabetic retinopathy in indigenous Australians: the National Indigenous Eye Health Survey. *Clin Exp Ophthalmol*. 2011;39:487−493.
31. Moynihan V, Turner A. Coordination of diabetic retinopathy screening in the Kimberley region of Western Australia. *Aust J Rural Health*. 2017;25:110−115.
32. Brazionis L, Jenkins A, Keech A, et al. Diabetic retinopathy in a remote Indigenous primary healthcare population: a Central Australian diabetic retinopathy screening study in the Telehealth Eye and Associated Medical Services Network project. *Diabet Med*. 2018;35:630−639.
33. O'Halloran RA, Turner AW. Evaluating the impact of optical coherence tomography in diabetic retinopathy screening for an Aboriginal population. *Clin Exp Ophthalmol*. 2018;46:116−121.
34. Quinn N, Yang F, Ryan C, et al. Screening for diabetic retinopathy and reduced vision among Indigenous Australians in Top End primary care health services: a TEAMSnet sub-study. *Intern Med J*. 2021;51:1897−1905.
35. Tapp RJ, Shaw JE, Harper CA, et al. The prevalence of and factors associated with diabetic retinopathy in the Australian population. *Diabetes Care*. 2003;26:1731−1737.
36. Cugati S, Kifley A, Mitchell P, et al. Temporal trends in the age-specific prevalence of diabetes and diabetic retinopathy in older persons: population-based survey findings. *Diabetes Res Clin Pract*. 2006;74:301−308.
37. Wong J, Molyneaux L, Constantino M, et al. Timing is everything: age of onset influences long-term retinopathy risk in type 2 diabetes, independent of traditional risk factors. *Diabetes Care*. 2008;31:1985−1990.
38. Copeland S, Muir J, Turner A. Understanding Indigenous patient attendance: a qualitative study. *Aust J Rural Health*. 2017;25:268−274.
39. Chia MA, Turner AW. Benefits of integrating telemedicine and artificial intelligence into outreach eye care: stepwise approach and future directions. *Front Med*. 2022;9:835804.

Pictures & Perspectives



Ultrawide-field Swept Source-OCT Angiography of Retinitis Pigmentosa

A 42-year-old man diagnosed with retinitis pigmentosa (RP) underwent widefield Optos imaging and swept-source OCT angiography (SS-OCTA) (24 × 20 mm SS-OCTA; BM-400K BMizar, TowardPi Medical Technology) examination. **A**, Fundus image revealed classic features of RP, including intraretinal pigmentation, waxy pallor of the optic disc, and attenuated retinal blood vessels. **B**, The retinal flow image displayed perfusion limited to the posterior pole with vascular remodeling at the borders. **C**, The retinal structure image showed intraretinal pigmentation outside the arcade (red arrows) and the empty shells of nonperfused "ghost" vessels (yellow arrows) (Magnified version of Fig **A**-**C** is available online at www.aaojournal.org).

Fang Zheng, MD
Jingliang He, MD
Xiaoyun Fang, MD

Eye Center, The Second Affiliated Hospital Zhejiang University School of Medicine, Zhejiang University, Hangzhou, China