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Jin, G., Xiao, W., Ding, X., Xu, X., An, L., Congdon, N., Zhao, J., & He, M. (2018). Prevalence of and Risk Factors for Diabetic Retinopathy in a Rural Chinese Population: The Yangxi Eye Study. *Investigative ophthalmology & visual science*, 59(12), 5067-5073. <https://doi.org/10.1167/iovs.18-24280>

Published in:

Investigative ophthalmology & visual science

Document Version:

Publisher's PDF, also known as Version of record

Queen's University Belfast - Research Portal:

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Prevalence of and Risk Factors for Diabetic Retinopathy in a Rural Chinese Population: The Yangxi Eye Study

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Submitted: March 10, 2018
Accepted: September 8, 2018

Citation: Jin G, Xiao W, Ding X, et al. Prevalence of and risk factors for diabetic retinopathy in a rural Chinese population: the Yangxi Eye Study. *Invest Ophthalmol Vis Sci*. 2018;59:5067-5073. <https://doi.org/10.1167/iovs.18-24280>

PURPOSE. To investigate the prevalence and determinants of diabetic retinopathy (DR) among older adults in rural Southern China.

METHODS. Using random cluster sampling, persons aged 50 years or older were randomly selected in rural Yangxi County, Guangdong Province, China. All participants underwent a standardized interview, fundus photography, and point of service glycosylated hemoglobin A1c (HbA1c) testing. Diabetes mellitus (DM) was diagnosed based on confirmed medical history or HbA1c $\geq 6.5\%$. Fundus photographs were graded for DR and diabetic macular edema (DME) based on the United Kingdom National Diabetic Eye Screening Program guidelines. Prevalence of and risk factors for DR and vision-threatening diabetic retinopathy (VTDR) were evaluated.

RESULTS. Among 5825 subjects who participated (90.7% response rate) in the Yangxi Eye Study, 562 (9.6%) were diagnosed with DM, including 79 (14.1%) known and 483 new (85.9%) cases. Among DM cases, 476 (84.7%) had gradable fundus photos. The prevalence of any DR and VTDR were 8.19% (95% confidence interval [CI] 5.9-11.0) and 5.25% (95% CI 3.43-7.66), respectively. These figures were 23.9% and 12.7% for known and 5.43% and 3.95% for new DM cases. Risk factors for any DR were higher HbA1c level (OR [odds ratio] per unit 1.34, $P < 0.001$), longer duration of DM (OR per year = 2.29, $P < 0.001$) and having previously undergone cataract surgery (OR 4.11, $P < 0.030$).

CONCLUSIONS. Our study found a lower prevalence of DR among adults 50 years and older than in previously reports. Perhaps this difference can be explained by the short duration of most cases.

Keywords: prevalence, risk factors, diabetic retinopathy, rural China

The total number of people with diabetes mellitus (DM) in China is projected to rise from 171 million in 2000 to 366 million by 2030, meaning that China will become the country with the largest diabetes population in the world.¹ Diabetic retinopathy (DR), a common complication of diabetes, is the leading cause of blindness in the working age population worldwide.²⁻⁴ The global prevalence of DR grew 64% from 1990 to 2010, virtually all due to increases in low- and middle-income countries, but few population-based data from such settings have been published.⁵⁻⁸ Reports from upper-income countries are comparatively plentiful,⁸⁻²⁰ and substantial regional variation has been identified.²¹

China is the world's most populous country, with one-half of its 1.4 billion people living in rural areas.²² However, population-based data on the prevalence of DM and DR in China remained limited,²³⁻²⁷ particularly in rural areas, where only a single study has been conducted, in Handan, northern China, more than 10 years ago. With the diabetes population

increasing rapidly in China,^{28,29} an up-to-date study on the rural prevalence of DR is needed by policy makers to assess the current magnitude of the disease and requirements for service delivery. Additional population-based data would also help quantify regional variation in a large country such as China, where genetic background, lifestyle, and quality of and access to healthcare services differ considerably from region to region.

In the current study, we investigated the age- and sex-specific prevalence of DM and DR and potential predictors in a large, population-based cohort in rural southern China.

MATERIALS AND METHODS

Study Population

The Yangxi Eye Study is a population-based, cross-sectional study of Han Chinese age 50 years or older living in a rural setting in southern China. As part of the 2014 China Nine-



Province Survey, this study of visual impairment and blindness was designed to report the prevalence and clinical characteristics of eye diseases, including DR and age-related macular degeneration.³⁰ From August to November 2014, based on data from the Residence Administrative Committee, 6425 eligible subjects were identified using cluster random sampling from 268 geographically defined basic sampling units. The subjects underwent full ocular examinations. The research followed the tenets of the Declaration of Helsinki, written informed consent was obtained from all the participants, and the study was approved by the Institutional Review Board of Zhongshan Ophthalmic Center (Guangzhou, China).

Study Procedures

Eligible participants, persons age 50 years and older who had been living in the catchment area for at least 6 months, were recruited based on a household registry and door-to-door enumeration. A standard questionnaire conducted by trained interviewers was used to collect past medical history regarding DM, including the date of confirmed diagnosis and current use of medications. Glycosylated hemoglobin A1c (HbA1c) was analyzed using a point-of-care device (Afinion AS100; Axis-Shield, Norway). New diabetes mellitus (NDM) was diagnosed by HbA1c $\geq 6.5\%$, as recommended by the American Diabetes Association,³¹ and known diabetes mellitus (KDM) was defined as a self-reported history of physician diagnosis or current drug treatment for diabetes. A systemic examination was performed by a trained nurse, including the measurement of blood pressure and height and weight for the computation of body mass index (BMI).

Basic eye examinations were performed after the interview and the aforementioned systemic examination, according to standardized protocol. Visual acuity was assessed with Early Treatment Diabetic Retinopathy Study (ETDRS) charts.³² The presenting visual acuity (PVA) of each eye with habitual correction where available was recorded, and the best corrected visual acuity (BCVA) was assessed with noncycloplegic automated refraction (KR-8900; Topcon, Tokyo, Japan) in those with PVA $< 6/12$ in either eye. Slit-lamp biomicroscopy and direct ophthalmoscopy were performed by trained ophthalmologists to identify and record abnormalities of the anterior and posterior segments.

Fundus photography was undertaken for each eye in all participants using a digital non-mydratic fundus camera (FundusVue; Crystalvue, Inc., Ltd., Taoyuan City, Taiwan), consisting of NHS screening program standard field 1 (centered on the optic disc) and field 2 (centered on the fovea).³³ Pupils were dilated by applying compound tropicamide eye drops (each milliliter contains 5 mg tropicamide and 5 mg phenylephrine hydrochloride), 3 drops in each eye.

Diabetic Retinopathy Grading

Retinal photographs were graded by trained graders according to the United Kingdom National Diabetic Eye Screening Program (UK NDESP) guidelines.³³ DR was graded as R0, R1, R2, R3a, or R3s. R0 was defined as no DR and R1 as background DR with at least one of the following features: microaneurysm(s) or HMA (a term used when it is difficult to distinguish between a microaneurysm and a dot hemorrhage); retinal hemorrhage(s); venous loop(s); any exudate in the presence of other non-referable features of DR; or any number of cotton wool spots in the presence of other non-referable features of DR. R2 was defined as pre-proliferative DR with at least one of the following features: venous beading, venous reduplication, multiple blot hemorrhages, or intraretinal microvascular abnormality. R3 was classified into two groups:

R3a was defined as active proliferative retinopathy with at least one of these features: new vessels on the disc, new vessels elsewhere, pre-retinal or vitreous hemorrhage, or pre-retinal fibrosis with or without retinal traction. R3s was defined as stable post-treatment retinopathy, with evidence of previous peripheral retinal laser treatment. R3s was rare in this study's setting and was therefore combined with R3a to report the prevalence of R3.

Diabetic macular edema (DME) was graded as M0 or M1. M0 was defined as no maculopathy, and M1 had at least one of the following features: exudate within 1 disc diameter of the center of the fovea, or a collection of exudates within the macula. Vision-threatening DR (VTDR) was considered to be present if any feature(s) of M1, R2, or R3 were found. Photographs were classified as ungradable if quality precluded classification according to the above system.

DR was graded based on the worse-affected eye for each participant, as previously described.³⁴ In particular, if one eye was ungradable and the other was gradable, the participant would be classified based on the gradable eye.

As called for in the NDESP protocol,³³ two trained, experienced graders graded each image independently, based on the protocol as outlined. If there was any discrepancy between them, the image was reassessed by a senior grader (ophthalmologist), whose decision was final. These graders were trained and certified in the UK NDESP national screening program online course³⁵ and had worked as service providers for a national diabetes screening program run by the Chinese Ministry of Health. The interobserver agreement between the graders was good (weighted κ 0.84 for retinopathy and 0.73 for DME).

Statistical Analyses

Overall, age-specific and sex-specific prevalence of DR and its component signs were assessed. Chi-square and Mann-Whitney *U* tests were used to compare characteristics between sexes and different age groups. Multivariate-adjusted logistic regression analysis of risk factors for the development of DR was also performed. The impact of diabetes on vision impairment was assessed, and prevalence of visually significant comorbid eye disease were compared between groups with and without diabetes. According to WHO criteria, visual impairment was categorized as: $< 6/18$ – $6/60$ (moderate visual impairment), $< 6/60$ – $6/120$ (severe visual impairment), and $> 6/120$ (blindness).³⁶ All data analyses were performed using Stata 14.0 software (Stata Corp., College Station, TX, USA). *P* value < 0.05 was considered statistically significant.

RESULTS

Of 6425 eligible participants, 5825 (90.7%) took part in the study. Hb1Ac results were available for 5742 (98.6%) participants, and medical history data available for 5744 (98.6%). A total of 562 persons (9.6%) were diagnosed with DM, including 79 (14.1%) known DM (KDM) and 483 (85.9%) new DM (NDM) cases. Among the DM cases, 476 (84.7%; mean age 65.7 ± 9.48 years, 37.2% men) had gradable photos in at least 1 eye, including 34 persons were graded as non-VTDR in one eye and ungradable in the fellow eye (Fig. 1). Characteristics of all persons with DM are shown in Supplementary Table S1. Participants without gradable photos were significantly older ($P = 0.012$) and significantly more likely to have PVA $< 6/18$ ($P < 0.001$). Characteristics of NDM and KDM participants with gradable fundus photographs are shown in Table 1.

Table 2 shows the age- and sex-specific prevalence of DR among participants with DM. The overall prevalence of DR in

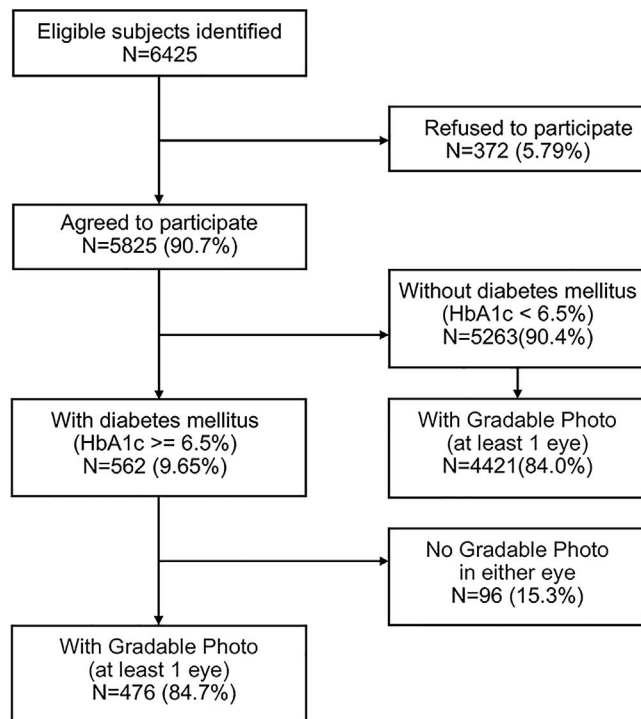


FIGURE 1. Flowchart of participants included and excluded from analysis for diabetes and diabetic retinopathy in the Yangxi Eye Study.

this cohort was 8.19% (95% CI, 5.9%–11.0%). VTDR was present in 5.25% (95% CI, 3.43%–7.66%), and M1 in 3.58% (95% CI, 2.10%–5.67%) of participants with DM. The prevalence of DR, M1 and VTDR did not differ significantly by age or sex (Table 2).

Table 3 shows the prevalence of DR in those with KDM and NDM. Compared with NDM subjects, KDM subjects had significantly higher prevalence of any DR (23.9% vs. 5.43%, $P < 0.001$) and VTDR (12.7% vs. 3.95%, $P = 0.002$) but not M1 (5.63% vs. 3.22%, $P = 0.312$). Both the presence and severity of DR increased significantly with longer duration of diabetes (Fig. 2). Any DR was present in 40% of KDM participants with a 10-year history of diabetes, compared to 5.43% of NDM participants ($P < 0.001$).

TABLE 1. Characteristics of New Diabetes Mellitus and Known Diabetes Mellitus in the Yangxi Eye Study

	Total (n = 476)	NDM (n = 405)	KDM (n = 71)	P Value
		Mean (Standard Deviation)		
Age (years)	65.7 ± 9.48	65.7 ± 9.61	65.5 ± 8.75	0.838
Body mass index (kg/m ²)	23.9 ± 4.03	23.9 ± 4.15	24.1 ± 3.28	0.802
Systolic blood pressure (mm Hg)	147.4 ± 24.7	146.5 ± 25.1	152.3 ± 22.4	0.071
Diastolic blood pressure (mm Hg)	76.5 ± 13.5	76.5 ± 13.8	77.0 ± 11.7	0.744
HbA1c (%)	7.62 ± 1.77	7.46 ± 1.52	8.48 ± 2.65	<0.001
Spherical equivalent (right eye)	0.22 ± 1.77	0.13 ± 1.81	0.66 ± 1.46	0.027
		Number (%)		
Male	177 (37.2)	155 (38.3)	22 (31.0)	0.241
Hypertension	296 (62.2)	243 (60.0)	53 (74.7)	0.019
Self-reported hypertension	65 (13.7)	42 (10.4)	23 (32.4)	<0.001
Education (high school or higher)	8 (1.68)	8 (1.98)	0 (0.00)	0.232
Previous cataract surgery (at least 1 eye)	22 (4.63)	21 (5.20)	1 (1.41)	0.161
PVA <6/18a	72 (15.5)	61 (15.5)	11 (15.5)	0.998

Table 4 shows the associations of various potential determinants of any DR and of VTDR. In multivariate analysis, factors significantly associated with any DR were higher HbA1c (OR, 1.34 per 1% increase, $P < 0.001$) and longer diabetes duration (OR, 2.29 per year increase, $P < 0.001$). HbA1c (OR, 1.32 per 1% increase, $P < 0.002$) and longer diabetes duration (OR, 1.82 per year increase, $P < 0.019$) were also risk factors for VTDR.

A total of 546 (97.2%) participants with DM completed assessment of PVA, as did 5021 without DM (95.4%). The prevalence of moderate and severe visual impairment and blindness among those with diabetes was 3.66% (95% CI, 2.25%–5.60%), 1.28% (95% CI, 0.52%–2.62%), and 2.38% (95% CI, 1.27%–4.04%), respectively, and did not differ significantly from rates among those without diabetes (Table 5). Visual impairment associated with glaucoma was significantly higher among participants with DM than without DM, but the rates for cataract and refractive error did not differ significantly by DM status.

DISCUSSION

In the current study, we chose to use the UK NDESP classification to assess the severity of DR because our graders had been trained and certified using this system. Although the UK NDESP classification system differs from research grading systems such as that used in the ETDRS,³⁷ it is capable of classifying referral DR and VTDR cases, has been widely used in DR screening programs, and is less resource-intensive and time-consuming for patients.^{34,38,39} In these respects, it was more suitable in this low-resource setting.

A number of studies have been carried out on DR prevalence worldwide to date. A retrospective study pooling of 35 population-based studies from the United States, Australia, Europe, Asia, and other countries and regions over the past 30 years (1980–2008) reported that the mean prevalence of DR and VTDR were 34.6% and 7.0%, respectively, among persons with DM.²¹ The prevalence of DR and VTDR identified in our study was much lower than reported in developed countries in Europe,^{12,40–43} the United States,^{9,10,13,14,44} Australia,^{11,45,46} and Asia (Singapore).¹⁵ Interestingly, reported prevalence of any DR from another low- to middle-income country (India: 10.3%–18.0%)^{8,16} was more in line with our own findings in rural China. However, our observed prevalence of any DR was also lower than has been

TABLE 2. Age- and Sex-Specific Prevalence of Diabetic Retinopathy in the Yangxi Eye Study

DR Grade	Total (n = 476)	Age Group (years) % (95% CI)			P Value	Sex % (95% CI)		P Value
		50–59 (n = 136)	60–69 (n = 179)	70+ (n = 161)		Men (n = 177)	Women (n = 299)	
Any DR	8.19 (5.9–11.0)	8.09 (4.11–14.0)	9.50 (5.63–14.8)	6.83 (3.46–11.9)	0.669	6.21 (3.14–10.8)	9.36 (6.8–13.2)	0.226
R0	91.8 (89.0–94.1)	91.9 (86.0–95.9)	90.5 (85.2–94.4)	93.2 (88.1–96.5)	0.669	93.8 (89.2–96.9)	90.6 (86.8–93.7)	0.226
R1	5.88 (3.94–8.39)	5.89 (2.57–11.3)	7.26 (3.92–12.1)	4.35 (1.77–8.75)	0.522	5.08 (2.35–9.43)	6.35 (3.87–9.75)	0.569
R2	1.89 (0.87–3.56)	1.03 (0.18–5.21)	1.68 (0.35–4.82)	2.48 (0.68–6.24)	0.787	0.56 (0.01–3.11)	2.68 (1.16–5.20)	0.102
R3	0.42 (0.05–1.51)	0.73 (0.02–4.03)	0.56 (0.01–3.07)	0 (0–2.27)	0.582	0.56 (0.01–3.11)	0.33 (0.01–1.85)	0.720
M1	3.58 (2.10–5.67)	2.94 (0.81–7.36)	4.47 (1.95–8.62)	3.12 (1.02–7.14)	0.716	1.69 (0.35–4.87)	4.70 (2.59–7.76)	0.088
VTDR	5.25 (3.43–7.66)	4.41 (1.64–9.36)	6.15 (3.11–10.7)	4.97 (2.17–9.56)	0.777	2.82 (0.92–6.46)	6.69 (4.13–10.1)	0.068

TABLE 3. Prevalence of Diabetic Retinopathy in Those With Known Diabetes Mellitus and Newly Diagnosed Diabetes Mellitus in the Yangxi Eye Study

DR Grading	Total (n = 476)	KDM (n = 71)	NDM (n = 405)	OR (95% CI)*	P Value
	n (%)	n (%)	n (%)		
Any DR	39 (8.19)	17 (23.9)	22 (5.43)	5.48 (2.74–11.0)	<0.001
R1	28 (5.88)	10 (14.1)	18 (4.44)	3.94 (1.73–8.98)	0.001
R2	9 (1.89)	6 (8.45)	3 (0.74)	12.5 (3.06–51.4)	<0.001
R3	2 (0.42)	1 (1.41)	1 (0.25)	5.78 (0.36–93.3)	0.163
M1	17 (3.58)	4 (5.63)	13 (3.22)	1.80 (0.57–5.67)	0.312
VTDR	25 (5.25)	9 (12.7)	16 (3.95)	3.53 (1.49–8.34)	0.002

* Logistic regression analysis with KDM as the dependent variable for the type of DR and ME.

TABLE 4. Risk Factors for Presence of Any Diabetic Retinopathy in the Yangxi Eye Study

Factors	Any DR				VTDR			
	Age–Sex Adjusted		Multivariate Adjusted		Age–Sex Adjusted		Multivariate Adjusted	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Male	0.64 (0.31–1.33)	0.233	0.85 (0.38–1.91)	0.700	0.40 (0.15–1.10)	0.076	0.46 (0.16–1.31)	0.143
Age (per 10 years)	0.92 (0.61–1.39)	0.688	0.73 (0.44–1.21)	0.225	1.06 (0.64–1.76)	0.822	0.93 (0.52–1.64)	0.794
Systolic BP (per mm Hg)	1.16 (1.02–1.32)	0.028	1.11 (0.96–1.30)	0.159	1.13 (0.96–1.33)	0.128	-	-
Diastolic BP (per mm Hg)	0.85 (0.65–1.10)	0.214	-	-	0.75 (0.54–1.04)	0.085	-	-
BMI† (per kg/m ²)	0.93 (0.84–1.03)	0.168	0.98 (0.87–1.10)	0.747	0.90 (0.79–1.02)	0.102	0.97 (0.85–1.12)	0.692
HbA1c, (per 1%)	1.44 (1.26–1.65)	<0.001	1.34 (1.16–1.56)	<0.001	1.40 (1.20–1.64)	<0.001	1.32 (1.11–1.56)	0.002
Duration of DM (per year)	2.43 (1.68–3.54)	<0.001	2.29 (1.51–3.47)	<0.001	1.93 (1.23–3.03)	0.004	1.82 (1.11–2.99)	0.019
Hypertension	1.67 (0.79–3.52)	0.182	-	-	1.86 (0.71–4.90)	0.209	-	-
Duration of hypertension (per year)	0.58 (0.34–1.01)	0.054	-	-	0.19 (0.03–1.47)	0.112	-	-
Use of insulin or hypoglycemic drugs	1.00 (0.18–5.58)	0.998	-	-	-	-	-	-
Education (middle school or higher)	0.51 (0.12–2.21)	0.364	-	-	0.46 (0.06–3.54)	0.454	-	-
Cataract surgery (at least 1 eye)	3.22 (0.99–110.5)	0.052	4.11 (1.15–14.7)	0.030	3.73 (0.97–14.4)	0.056	4.42 (1.07–18.2)	0.040
Spherical equivalent (per diopter)	1.12 (0.89–1.42)	0.312	-	-	1.01 (0.78–1.31)	0.943	-	-

TABLE 5. Impact of Diabetes on Visual Impairment and Visually Significant Comorbid Eye Disease in the Yangxi Eye Study

Visual Impairment	All	With Diabetes	Without Diabetes	Unadjusted Comparison P Value	Adjusted Comparison* P Value
Moderate visual impairment† n (%)	228 (4.10)	20 (3.66)	208 (4.14)	0.651	0.599
Severe visual impairment‡ n (%)	56 (1.01)	7 (1.28)	49 (0.98)	0.495	0.633
Blindness§ n (%)	96 (1.72)	13 (2.38)	83 (1.65)	0.223	0.288
Cataract associated with VA <6/18 in either eye	278 (5.00)	33 (6.04)	245 (4.84)	0.254	0.779
Glaucoma associated with VA <6/18 in either eye	8 (0.14)	3 (0.55)	5 (0.10)	0.008	0.025
Refractive error associated with VA <6/18 in either eye	26 (0.47)	1 (0.18)	25 (0.50)	0.306	0.341

* Adjusting for age and sex.

† Presenting visual acuity <6/18 and ≥6/60 in the better-seeing eye.

‡ Presenting visual acuity <6/60 but ≥3/60 in the better-seeing eye.

§ Presenting visual acuity <3/60 in the better-seeing eye.

Diabetic Retinopathy Prevalence in Rural China

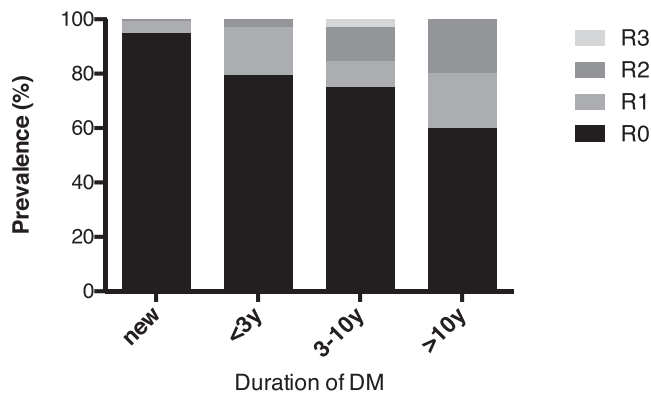


FIGURE 2. Prevalence of types of diabetic retinopathy by known duration of diabetes mellitus in the Yangxi Eye Study.

reported in other population-based studies conducted in China (Supplementary Table S2), with values ranging from 9.9% to 43.1%.^{23–27}

There are several possible explanations for the low prevalence of DR observed in the current study: First, different characteristics of the study populations might contribute to the discrepancy. The ratio between KDM to NDM was 1:5 in the current study, which is substantially lower than that identified in developed countries or the findings from the Handan Eye Study conducted in northern rural China (ratio = 1:2),^{11,12,47,48} presumably due to relatively poor access to care in our study setting. Given the fact that DR was much less common in NDM patients,²⁷ presumably due to their shorter mean duration and possibly lesser severity of disease, this is a likely explanation for the low prevalence of DR observed in our study. Second, race, which is considered an independent risk factor for DR, is another possible reason.^{21,49} Many studies have investigated the relationship between ethnicity and DR, with typical associations to be dependent on differences in the control of established risk factors.^{14,50} However, some studies have identified ethnicity as an independent risk factor for DR that could not otherwise be explained.^{44,51} Third, regional differences between northern and southern China, secondary to lifestyle, environmental differences and variations in access to care, may be another factor contributing to the discrepancy. Regional differences within the same ethnic group—for example, between Indian migrants to Singapore and those remaining in India—have also been reported in the Singapore Indian Eye Study.¹⁸

We identified both HbA1c and longer duration of DM as risk factors for both DR and VTDR, but no such association was present for age, BMI, hypertension, and insulin use. Our findings for HbA1c and DM duration are consistent with previous studies.^{15,17,27,52} HbA1c reflects glycemic levels over the past 3 months, and DM duration is an index of cumulative damage to the microvascular system. Therefore, it is biologically plausible that these factors may be linked causally with the presence and severity of DR.

Strengths of this study include the population-based design with large sample size, high participation rate, and the use of recommended HbA1c testing (shown to be more accurate in assessment of DM than is random plasma glucose³¹). Limitations of the study must also be addressed: First, although the UK NDESP grading system was suitable for this rural Chinese setting, differences in photographic protocol and cutoffs limit our comparison with studies based on other systems. Second, data on other biomarkers that are potentially important in the DR pathway (including genetic factors and blood lipids) were not collected here; therefore, an assessment of their effects on

DR is not possible. Third, consistent with previous studies,^{15,27} we used nonstereoscopic digital photography, which may affect the accuracy for DME classification, where stereoscopic findings can be important.

In conclusion, prevalence of DR and VTDR among persons with diabetes in this population was far lower than has been reported previously in rural China.²⁷ The four-fold difference (between 10% and 40%) has important implications for human resource and equipment needs across the very large populations of rural China. Furthermore, the high proportion of previously undiagnosed diabetes observed in our study suggests that further efforts are needed to improve access to basic healthcare in at least some parts of rural China. Additional studies are required to confirm these findings elsewhere and elucidate reasons for possible regional variations in DM and DR prevalence across China.

Acknowledgments

The authors thank the National Institute of Hospital Administration of the Chinese National Health and Family Planning Commission, funded under ORBIS International North Asia (Beijing, China) contract no. 1541.

Supported by the National Institute of Hospital Administration, the Chinese National Health and Family Planning Commission and ORBIS International. Mingguang He receives support from the Fundamental Research Funds of the State Key Laboratory in Ophthalmology, Science and Technology Planning Project of Guangdong Province 2013B20400003, and the University of Melbourne Research Accelerator Program and the CERA Foundation. The Centre for Eye Research Australia receives Operational Infrastructure Support from the Victorian State Government. Nathan Congdon is supported by the Ulverschroft Foundation (UK). The sponsors had no role in study design, data collection, analysis, decision to publish, or preparation of the manuscript.

Disclosure: **G. Jin**, None; **W. Xiao**, None; **X. Ding**, None; **X. Xu**, None; **L. An**, None; **N. Congdon**, None; **J. Zhao**, None; **M. He**, None

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