The Prevalence of and Factors Associated With Diabetic Retinopathy in the Australian Population

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OBJECTIVE — To determine the prevalence and factors associated with diabetic retinopathy in the Australian population and to estimate the time difference between disease onset and clinical diagnosis of type 2 diabetes.

RESEARCH DESIGN AND METHODS — The Australian Diabetes, Obesity and Lifestyle study (AusDiab) included 11,247 adults aged ≥25 years in 42 randomly selected areas of Australia. Retinopathy was assessed in participants identified as having diabetes (based on self-report and oral glucose tolerance test), impaired fasting glucose, and impaired glucose tolerance and in a random sample with normal glucose tolerance. Data were available for 2,177 participants.

RESULTS — Overall, 15.3% of those with diabetes had retinopathy. The prevalence of retinopathy was 21.9% in those with known type 2 diabetes (KDM) and 6.2% in those newly diagnosed (NDM). The prevalence of proliferative diabetic retinopathy (PDR) was 2.1% in those with KDM. No cases of PDR were found in those with NDM. Untreated vision threatening retinopathy (presence of PDR or macular edema) was present in 1.2% ($n = 4$). Factors associated with retinopathy were duration of diabetes, HbA_{1c}, and systolic blood pressure. Using linear extrapolation of the prevalence of retinopathy with diabetes duration, the onset of diabetes in this population was approximately the time of diagnosis.

CONCLUSIONS — This is one of the first national studies of diabetic retinopathy in a developed country. The prevalence of retinopathy was similar to that in other population-based studies. Vision threatening retinopathy was relatively rare; however, four untreated cases were identified. Regular screening for diabetic retinopathy and more aggressive management of modifiable risk factors could reduce the numbers of people who develop vision-threatening retinopathy.

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Diabetic retinopathy is a common complication of diabetes and despite the availability of effective treatment, it remains one of the leading causes of visual loss (1–5). Internationally there have been many studies assessing the prevalence of retinopathy, though few have looked at both those with previously and newly diagnosed diabetes (6–8), and only one from a developed country has used a nationally representative population (9). Several factors have consistently been identified by both cross-sectional and prospective studies as risk factors in the development of diabetic retinopathy: duration of diabetes, systolic blood pressure (SBP), glycemic control, and urinary albumin (7,10). Other factors, including BMI, smoking, serum lipids, and C-peptide, have shown varying results (7, 10–13).

By the time of clinical diagnosis of type 2 diabetes, some individuals already show evidence of diabetic retinopathy (7,14–16), indicating that diabetes may have been present for several years. Extrapolating the relationship between duration of diabetes and prevalence of retinopathy back to a prevalence of zero, previous studies have estimated that the actual onset of diabetes is up to 12 years before clinical diagnosis (15). The AusDiab study, with its large, nationally representative sample, provides an ideal setting in which to investigate the prevalence of and factors associated with diabetic retinopathy, as well as the relationship between retinopathy and diabetes duration.

RESEARCH DESIGN AND METHODS

— The population, methods, and response rates of the Australian Diabetes, Obesity and Lifestyle study (AusDiab) are found in detail elsewhere (17). In brief, AusDiab was a population-based study of 11,247 people aged ≥25 years, from 42 randomly selected urban and rural areas of Australia. A stratified cluster sampling method was used, involving seven strata (the six states and the Northern Territory), and clusters were

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Abbreviations: AusDiab, Australian Diabetes, Obesity and Lifestyle study; FPG, fasting plasma glucose; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; KDM, known diabetes; Melbourne VIP, Melbourne Visual Impairment Project; NDM, newly diagnosed diabetes; NGT, normal glucose tolerance; NPDR, nonproliferative diabetic retinopathy; OGTT, oral glucose tolerance test; SBP, systolic blood pressure.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Prevalence of retinopathy according to glucose tolerance status: the AusDiab study*

	n	Mean age (years) ± SD	Prevalence of retinopathy (%) (95% CI)
KDM*	333	63 ± 11	21.9 (17.6–26.8)
NDM	370	61 ± 13	6.2 (4.0–9.2)
IGT and IFG combined	1,027	58 ± 13	6.7 (5.3–8.4)
NGT	415	50 ± 14	5.8 (3.7–8.5)

*Excludes type 1 diabetes.

based on census collector districts. The sample size was based on estimates to identify a national diabetes prevalence of 7% (an estimate based on the results of previous surveys and the expectation that the diabetes rate had increased over time). Of those who completed the household interview, 55.3% (n = 11,247) attended the biomedical examination. People identified through the AusDiab study as having diabetes (known and newly diagnosed by oral glucose tolerance test [OGTT] in the survey), impaired fasting glucose (IFG), and impaired glucose tolerance (IGT) and a random sample of people with normal glucose tolerance (NGT) were invited to attend the complications survey. Participants with NGT were selected using a systematic random sample selecting every *n*th person. The value of *n* was dependent on the number of people expected on the day of testing, in order to obtain a sample size of 10 per day. Of 2,773 participants invited to the complications component, 2,476 attended (overall response rate 89%, 91% in those with diabetes and 88% in those without diabetes). Diabetes classification was based on plasma glucose results, using the 1999 World Health Organization diabetes classification (18). Diabetes was diagnosed on the basis of fasting plasma glucose of ≥7.0 mmol/l, 2-h plasma glucose of ≥11.1 mmol/l, or current treatment with insulin or oral hypoglycemic medication. Participants diagnosed with diabetes through the AusDiab study were categorized as newly diagnosed diabetes (NDM). Those with self-reported diabetes and either on current treatment (insulin or oral hypoglycemic medication) or with diabetic glucose values were categorized as having known diabetes (KDM). Type 1 diabetes was assigned to those who started insulin treatment within 2 years of diagnosis (if diabetes onset was at age 40 years or later, current BMI also had to be <27 kg/m^2) (19). All other cases were classified as type 2. IGT was defined on the basis of fasting plasma glucose of <7.0 mmol/l and 2-h plasma glucose of ≥7.8 and <11.1 mmol/l, and IFG on the basis of fasting plasma glucose of ≥6.1 and <7.0 mmol/l and 2-h plasma glucose of <7.8 mmol/l. There were 431 people with KDM, 424 with NDM, 1,155 with IGT or IFG, and 466 with NGT. Thirty-two of the 431 with KDM had type 1 diabetes and were included only in the overall prevalence of retinopathy and excluded from further analyses. After exclusion of participants who were unable to be photographed or whose photographs were not gradable, data were available for 2,177 participants. The participants with diabetes (KDM or NDM) for whom photos were available were significantly younger (62 vs. 67 years; $P < 0.001$) and less likely to be male (51% vs 60%; $P = 0.018$) than those for whom photos were not available (either because of nonattendance or nongradable photos).

Retinal photographs were taken using a nonmydriatic retinal camera (Canon CR6–45NM) with an adapter fitted with a Sony three-chip charge-coupled device color camera and OptoMise PRO software on a Pentium 2 processor–based computer. Images were stored as uncompressed tagged image format files (TIFF) giving resolution of 768 by 576 pixels with 24-bit color displayed on a standard 17-inch monitor. Photographs were taken in two fields per eye, macula centered and nasal to disc. No dilating drops were used. One assessor, masked to all participant information, graded the photographs. Level of retinopathy was defined according to a simplified version of the Wisconsin grading system (20) (classification was based on the grading of the worst eye). Nonproliferative diabetic retinopathy (NPDR) was defined as the presence of at least one definite retinal hemorrhage and/or microaneurysm. Macular edema was defined as hard exudate within one disc diameter of the center of the macula. Vision-threatening retinopathy was defined by the presence of proliferative retinopathy or macular edema. A random sample of 167 retinal photographs (with and without retinopathy) were regraded (by the same assessor) to assess the internal validity of the grading. Overall there was a high degree of agreement between the first and second grading of retinopathy (κ = 0.732, unweighted).

Plasma glucose, fasting serum total cholesterol, HDL cholesterol, and triglycerides were determined by enzymatic methods (Olympus AU600 analyzer). Urinary albumin and creatinine were also determined by enzymatic methods (Olympus AU600 analyzer). HbA_{1c} was determined in whole blood using boronate affinity high-performance liquid chromatography (Bio-Rad Variant Hemoglobin Testing System). The normal range for HbA_{1c} was 4.2–6.3%. C-peptide was measured by radioimmunoassay with Linco human C-peptide kits (Linco, St. Charles, MO). Blood pressure was measured in a supine position in the right arm, using a standard mercury sphygmomanometer, using the first and fifth Korotkoff sounds to the nearest 2 mmHg. Participants rested for 10 min before testing. Hypertension was defined as present if SBP was ≥140 mmHg, diastolic blood pressure was ≥90 mmHg, or the participant reported current treatment for hypertension. Height and weight were measured in light clothing by a trained observer. BMI was calculated as weight (kg)/height (m)^2. Information on alcohol consumption, smoking, medication, and history of diabetes were obtained by interview.

The study was approved by the ethics committee of the International Diabetes Institute. Informed consent for the study was obtained from all participants.

Statistical Methods

The data analysis was performed with Stata version 7.0 for Windows (Stata, College Station, TX) and SPSS version 10.0.5 for Windows (SPSS, Chicago, IL). Descriptive information for each of the variables was derived and distribution assessed. Those with newly diagnosed diabetes were given a diabetes duration of zero years. Univariate associations with

Table 2—*Characteristics of the population with type 2 diabetes, according to retinopathy status: the AusDiab study*

	Retinopathy	No retinopathy	*P*
n	96	607	
Age (years)	65 ± 11	62 ± 12	0.016
Male (%)	45	51	0.241
Fasting plasma glucose (mmol/l)	10.2 ± 4.5	7.9 ± 2.4	<0.001
HbA_{1c} (%)	7.4 (5.9–8.5)	6.0 (5.6–6.8)	<0.001
Known diabetes (%)	76	43	<0.001
Duration of diabetes (years)*	7 (0–15)	0 (0–4)	<0.001
On insulin or tablets (%)	82	65	0.004
BMI (kg/m^2)	30.3 ± 5.6	30.2 ± 6.1	0.984
Cholesterol (mmol/l)	5.5 ± 1.0	5.7 ± 1.0	0.115
Triglycerides (mmol/l)	1.8 (1.3–2.6)	1.9 (1.3–2.7)	0.572
Current smoker (%)	11	9	0.574
Hypertension (%)	72	66	0.288
SBP (mmHg)	148 ± 24	140 ± 18	<0.001
DBP (mmHg)	78 ± 10	79 ± 10	0.415
C-peptide (ng/ml)	3.2 ± 1.7	3.8 ± 1.7	0.001
Urinary albumin:creatinine ratio (mg/mmol)	1.72 (0.8–6.3)	0.97 (0.6–2.3)	<0.001

Data are mean ± SD or median (interquartile range).*Newly diagnosed participants given duration of zero. DBP, diastolic blood pressure.

retinopathy were assessed using *t* tests for metric variables (Mann-Whitney test was used for triglycerides, urinary albumin: creatinine ratio, and diabetes duration) and χ^2 tests for categorical variables. From the univariate analyses, variables with *P* values ≤0.25, as well as established risk factors, were considered for entry into a logistic regression model to predict retinopathy. Where two variables were very similar, one was selected for inclusion in modeling.

The relationship between retinopathy and duration of diabetes was assessed using a weighted linear regression model. Participants were grouped according to diabetes duration (in 2-year intervals), and each group was weighted by the reciprocal of the variances $p(1-p)/n$, where n is the size of the group and p is the frequency of retinopathy. For this analysis, the population was limited to those with previously diagnosed type 2 diabetes.

RESULTS — Overall, 15.3% of those with diabetes (known and newly diagnosed, types 1 and 2) and 24.5% of those with KDM had retinopathy (in at least one eye). Those with type 1 diabetes are excluded from further analyses and the prevalence of retinopathy by glucose tolerance status in the remaining participants is shown in Table 1. The prevalence of retinopathy was almost four times higher in those with type 2 KDM (21.9%) than in those with NDM (6.2%). In those with KDM, the prevalence of NPDR was 19.8% and PDR was 2.1%. In those with NDM there were no cases of PDR. Evidence of laser treatment was present in 3.0% of KDM participants (n = 10) and was bilateral in 2.4% (n = 8). Macular edema was present in 3.3% (n = 11) of KDM participants, bilateral in 1.5% (n = 5). All 7 participants with PDR and 7 of the 11 participants with macular edema had undergone laser treatment. Untreated vision-threatening retinopathy was present in 1.2% (n = 4).

The characteristics of the population (according to retinopathy status) are shown in Table 2. Factors significantly associated with retinopathy were duration of diabetes, HbA_{1c}, SBP, urinary albumin: creatinine ratio, fasting plasma glucose (FPG), C-peptide, and insulin/hypoglycemic tablet use.

The prevalence of retinopathy increased with duration of diabetes (KDM only) (duration 0–4 years, –9.2%; 5–9 years, –23.1%; 10–19 years, –33.3%; and ≥20 years, –57.1%). The prevalence of retinopathy increased with increasing HbA_{1c} (shown in quartiles) (HbA_{1c} <5.6%, –8.5%; HbA_{1c} 5.6%–6.1%, –6.6%; HbA_{1c} 6.2%–7.2%, –11.2%; and HbA_{1c} ≥7.3%, –29.1%). Among those with retinopathy, 21.9% had untreated hypertension.

Duration of diabetes, age, sex, HbA_{1c}, cholesterol, SBP, C-peptide, and the urinary albumin:creatinine ratio were entered into a logistic regression model. Duration of diabetes, HbA_{1c}, and SBP were shown to be independently associated with retinopathy (Table 3).

Figure 1 shows the association between duration of diabetes, HbA_{1c}, SBP, and the prevalence of retinopathy in those with previously diagnosed diabetes. In those with a duration of diabetes <4 years, the prevalence of retinopathy was similar in each tertile of HbA_{1c} (Fig. 1*A*). For longer durations, however, the influence of HbA_{1c} was strong. Duration of diabetes was important at all levels of HbA_{1c}. SBP made no difference to the prevalence of retinopathy in those with a duration <4 years and had increasing impact with longer duration of diabetes (Fig. 1*B*). SBP had no impact on the prevalence of retinopathy in the lower two tertiles of

Table 3—*Independent factors associated with retinopathy: the AusDiab study*

	KDM and NDM		KDM	
	Odds ratio (95% CI)	*P*	Odds ratio (95% CI)	*P*
Duration of diabetes (per 10 years)	2.50 (1.81–3.44)	<0.001	2.24 (1.55–3.22)	<0.001
HbA_{1c} (per 1%)	1.38 (1.19–1.58)	<0.001	1.38 (1.16–1.64)	<0.001
SBP (per 10 mmHg)	1.26 (1.11–1.42)	<0.001	1.20 (1.02–1.40)	0.024

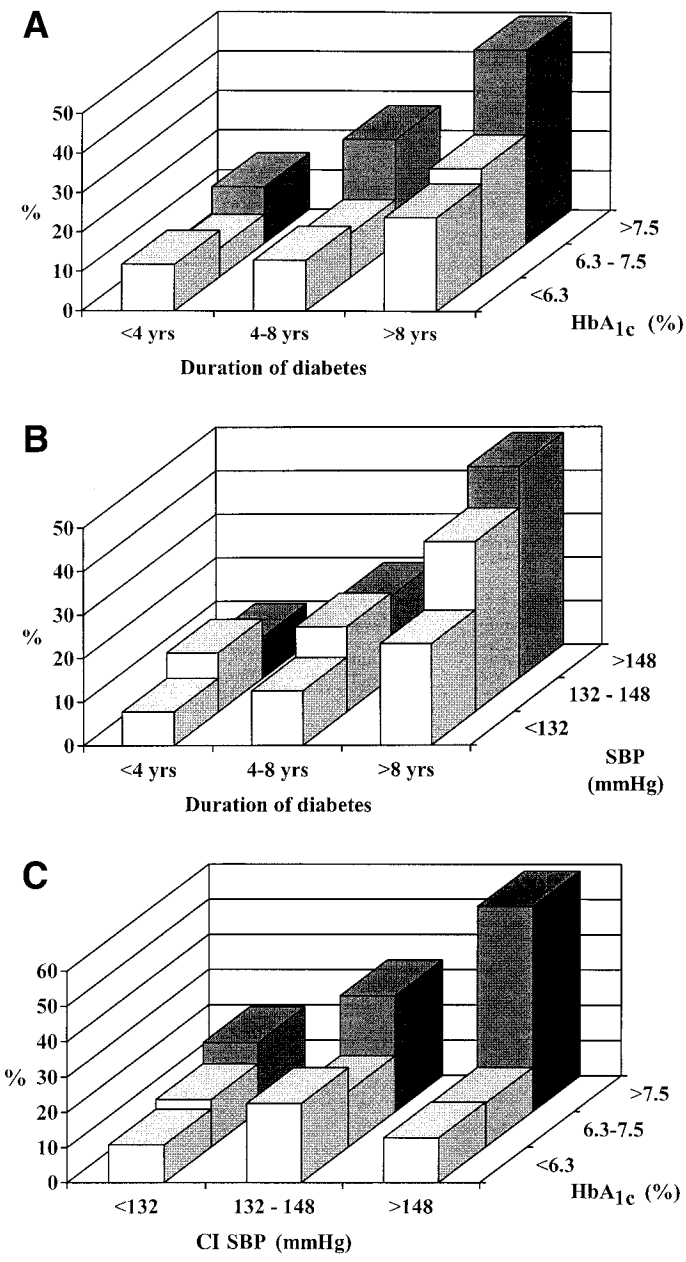

Figure 1—*Prevalence of retinopathy in the AusDiab study (KDM only) by tertiles of duration of diabetes and HbA_{1c} (A), duration of diabetes and SBP (B), and SBP and HbA_{1c} (C).*

HbA_{1c} and had increasing impact in the highest tertile of HbA_{1c} (Fig. 1*C*).

Figure 2 shows the prevalence of retinopathy by duration of diabetes (in 2-year intervals). Using a linear regression model, the onset of diabetes was estimated to be approximately the time of clinical diagnosis. The baseline was set at a prevalence of 5.8%, as some retinopathy is due to other causes and in this population was present in 5.8% of those with NGT.

CONCLUSIONS — This is one of the first national studies of diabetic retinopathy in a developed country and one of the few population-based studies of diabetic retinopathy to include an OGTT, allowing for identification of all of those with undiagnosed diabetes. The current study showed that the prevalence of retinopathy was 15.3% (KDM and NDM, types 1 and 2), –24.5% in those with KDM (types 1 and 2) and 6.2% in those with NDM. The prevalence of retinopathy in this population was similar to that found in other population-based studies (9,21–24). In a population-based study of retinopathy from Victoria (the Melbourne Visual Impairment Project [Melbourne VIP]), the prevalence of retinopathy was 29.1% in those with self-reported diabetes (age limited to ≥40 years, types 1 and 2 diabetes) (21). The difference in prevalence between the Melbourne VIP and AusDiab studies disappeared once duration of diabetes was accounted for (Melbourne VIP duration, 0–4 years 9.0% and ≥ 20 years 55.2%; AusDiab study [age limited ≥40 years, types 1 and 2 diabetes], 0–4 years –9.7% and ≥20 years –60.5%). In the Blue Mountains Eye Study (16), the prevalence of retinopathy was 35.5% based on self-reported diabetes and FPG values (age range limited to those ≥49 years, types 1 and 2 diabetes). Limiting the age range of the current study to those ≥49 years with known diabetes, the prevalence of retinopathy was 24.4%. The largest study of diabetic retinopathy in Australia was the Newcastle Diabetic Retinopathy Study, which was a clinic-based study conducted over 11 years (1977 to 1988) (25). At the conclusion of the study, the prevalence of retinopathy was 35%. Differences in sampling (clinic versus population based) could explain the difference in prevalence between the Newcastle Diabetic Retinopathy Study and the current study. In addition, the method of retinal photography used in Newcastle (7-field 30° photography) is more sensitive than 2-field 45° digital imaging used in this study (26). The sensitivity of a single 45° nonmydriatic digital image has been reported to be 78% for the detection of any retinopathy compared to the gold standard of 7-field 30° photography (27).

Internationally, the prevalence of retinopathy has varied widely depending on the methodology and population sample. In a recent large nationally representative population from the United States, the prevalence of retinopathy was 18.2% (type 2 diabetes, non-Hispanic whites) (9), which is very similar to the prevalence in the current study. The prevalence of retinopathy in those with IGT, IFG, and NGT has varied between populations (8,28). The prevalence of retinopathy in the AusDiab population in those with IGT, IFG, and NGT was similar to that shown in the Blue Mountains Eye Study (28). The Blue Mountains Eye Study

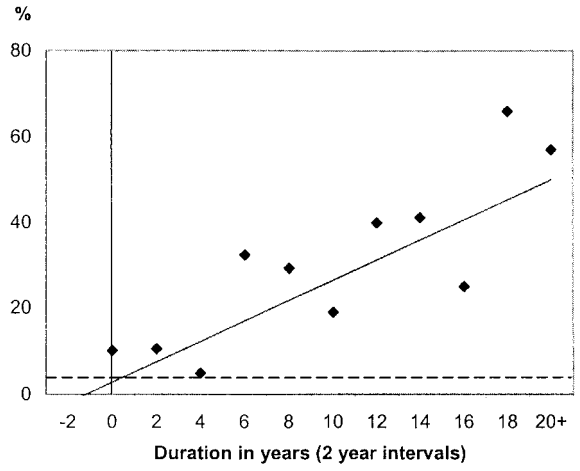

Figure 2—*Prevalence of retinopathy by duration of diabetes: the AusDiab Study (KDM only). ----, Prevalence of retinopathy in those with NGT.*

showed retinopathy to be present in 9.8% of those with NGT and significantly related to hypertension (28).

The prevalences of proliferative retinopathy and macular edema were similar to those shown in previous studies (21,23,29). Four cases of untreated vision-threatening retinopathy were found in this study. The detection of people with untreated vision-threatening retinopathy (defined by the presence of PDR or macula edema) is of concern, given that it is recommended that all people with diabetes have their eyes examined every 1 to 2 years (30).

Independent factors associated with retinopathy were duration of diabetes, SBP, HbA_{1c}, and FPG (FPG was included in a separate model from HbA_{1c}, data not shown). Diabetes duration has been shown to be an independent risk factor for retinopathy in many studies (11,21). Duration of diabetes reflects total glycemic control and risk factor exposure over time (7). Although C-peptide was lower in those with retinopathy than those without, its significance disappeared once duration of diabetes was added to the model. Hypertension has frequently been shown to be a risk factor in the development of retinopathy (7,10,31). In the present study, elevated SBP had an increasing impact with longer duration of diabetes and higher HbA_{1c} values (Fig. 1*B* and *C*). The U.K. Prospective Diabetes Study showed a 34% reduction in the progression of retinopathy (by two steps on the early detection of diabetic retinopathy study chart) in those treated intensively for hypertension (4). The current study showed that of those with retinopathy, 21.9% had untreated hypertension. Improved monitoring and control of hypertension in those with diabetes could reduce the number of people developing diabetic retinopathy (31). Studies of diabetic retinopathy have consistently shown HbA_{1c}, a measure of glycemic control, to be a risk factor for retinopathy (6,21,32). Serum lipids were not shown to be associated with retinopathy in this study. The reported associations of serum lipids with retinopathy have not been consistent; however, two large studies, the Early Treatment Diabetic Retinopathy study and the Wisconsin Epidemiological study, showed serum lipids to be associated with an increased risk of hard exudate formation (13,33), but not with other features of retinopathy.

The estimated onset of diabetes in this population was approximately the reported time of clinical diagnosis. The prevalence of retinopathy in the first 5 years after clinical diagnosis of diabetes remained constant, and then the prevalence of retinopathy began to rise (Fig. 2). This finding is consistent with studies assessing the development of diabetic retinopathy in type 1 diabetes. That is, diabetic retinopathy is relatively rare until ~4 years after the onset of diabetes (34), although the Diabetes Control and Complications Trial showed 54.2% of those with type 1 diabetes with duration <5 years had retinopathy (diagnosed by fundus photography and fluorescein angiography) (35). Previous studies using the same methodology as the current study have shown the onset of type 2 diabetes to occur ~4 to 7 years before clinical diagnosis (15,36). However, those studies had not accounted for retinopathy due to other causes unrelated to diabetes and assumed that the prevalence in the normal population was zero (28). In the present study, the baseline was raised to 5.8% to account for the prevalence of retinopathy in those with NGT. Raising the baseline prevalence of the study by Harris et al. (15) to 5%, the onset of diabetes would have been ~2 years before diagnosis for rural Western Australia and 4 years before diagnosis for Southern Wisconsin. Thus it appears that within the AusDiab population, the clinical diagnosis of diabetes may have been made slightly earlier in the history of the disease than in other previously reported populations.

The current study has a few limitations. Duration of diabetes was based on self-report, without confirmation from medical records. The impact of lowering the fasting diagnostic threshold for diabetes could have meant that more early diabetes cases were included in this sample. This would have had a minimal effect, as the AusDiab study was conducted in 1999–2000, and the new threshold was only formally adopted in 1999 (37). It is possible that a few people with NDM and assumed to have type 2 diabetes may have been misclassified, and actually had latent autoimmune diabetes of adults. Participants with diabetes (KDM or NDM) for whom photos were available were significantly younger and less likely to be male than were those without photos. The female bias is unlikely to have affected prevalence estimates, as there was no association between retinopathy and sex, but the age difference probably caused a slight underestimation of prevalence.

In summary, this was the first national, population-based study of diabetic retinopathy in Australia. The study showed prevalence of and factors associated with diabetic retinopathy similar to those shown in other population-based studies. It is of concern that cases of untreated vision-threatening retinopathy and cases of retinopathy with untreated hypertension were identified. The prevalence of diabetes is reaching epidemic proportions and with this the numbers of people with diabetic complications will continue to rise (38). Diabetic retinopathy is both a treatable and often preventable condition. Regular screening for diabetic retinopathy and more aggressive management of glycemia and hypertension could reduce the numbers of people who develop vision-threatening retinopathy.

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