CHAPTER 21

EPIDEMIOLOGY OF OCULAR FUNCTIONS AND DISEASES IN PERSONS WITH DIABETES

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SUMMARY

Visual impairment (visual acuity poorer than 20/40) in those with type 2 diabetes was estimated to affect 937,000 Americans age ≥40 years in data collected in the 1990s. While data from the National Health and Nutrition Examination Surveys collected in 1999–2004 and 2005–2008 suggest that this prevalence is declining, the prevalence of visual impairment is about two to three times as high in persons with diabetes as in those without the disease. Prevalence estimates for those with type 1 diabetes suggest that they too have a disproportionate prevalence of visual impairment compared to those without diabetes. Diabetic retinopathy is one of the five most common causes of severe visual impairment (visual acuity of 20/200 or worse) in the U.S. population. There are important differences in the distribution of low vision (best-corrected visual acuity of <20/40 in the better eye, excluding those who were blind) attributable to diabetic retinopathy by racial/ethnic group with 4.9%, 14.5%, and 13.0% of whites, blacks, and Hispanics, respectively, being affected. For blindness (best corrected visual acuity <20/200 in the better seeing eye), the corresponding prevalences are 5.4%, 7.3%, and 14.3% for the three races/ethnicities. The risk of visual impairment increases with increasing duration of diabetes for both type 1 and type 2 diabetes. Among risk factors that affect vision in persons with diabetes, the level of glycemia is the most important. In prevalence data from the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) for persons with type 1 diabetes, those in the highest quartile of glycosylated hemoglobin (A1c) were about four times as likely to experience doubling of the visual angle (a loss of 15 or more letters on the LogMar Chart, e.g., a change in visual acuity in the better eye of 20/20 to 20/40 or 20/30 to 20/60 or worse) over 10 years as those with A1c in the lowest quartile. For those with type 2 diabetes, the effect across quartiles was about 1.5 times. Fortunately, treatments are available for some specific ocular complications that have a direct effect on visual acuity.

The decreased visual acuity that is the most important functional effect of diabetes on the eye is largely attributable to anatomic pathologic conditions, such as diabetic retinopathy, diabetic macular edema, cataract, glaucoma, and corneal disease. Of these, the most important, due to the chance of permanent decreased vision, are severe diabetic retinopathy (i.e., proliferative diabetic retinopathy [PDR]) and diabetic macular edema. In the WESDR, a largely white cohort, 71% of persons with type 1 diabetes and 47% of persons with type 2 diabetes had retinopathy, 23% and 6% had PDR, and 11% and 8%, respectively, had macular edema at the baseline examination (1980–1982). Risk factors for development and progression of diabetic retinopathy and incidence of PDR include longer duration of diabetes, higher level of glycemia, greater body mass index, higher blood pressure, and the presence of nephropathy. Hispanics and blacks have higher prevalences of retinopathy compared to whites due, at least in part, to differences in health care access. Panretinal photocoagulation for treatment of PDR and focal and grid laser photocoagulation for clinically significant macular edema (CSME) have reduced the risk of severe vision loss by as much as 90%. Intravitreal injections of anti-vascular endothelial growth factor for CSME have shown efficacy in randomized controlled clinical trials in diminishing the effects of these retinal complications on vision and are expected to result in further prevention of visual loss. However, these treatments are expensive and associated with the risk of complications. While the prevalence of severe diabetic retinopathy is likely to be somewhat lower currently than in the past, evidence from cohorts defined in the early years of the 21st century suggests that this condition has not been overcome, and with the likely increases in the number of youths and adults with type 2 diabetes, diabetic retinal outcomes will continue to be important health burdens.

Vision loss associated with diabetic retinopathy has been associated with poorer health-related quality of life. Guidelines for screening for PDR and macular edema have been developed. Studies have shown the efficacy and cost-effectiveness of such screening, yet some groups, such as Hispanics, are not getting timely dilated eye examinations as recommended in the guidelines.

Aside from aging, diabetes is the most common risk factor for cataract. Cataract surgery with implant of artificial intra-ocular lenses is highly successful in restoring vision when cataract is the primary reason for decreased vision in those with diabetes. However, the surgery can have side effects or complications inherent in intra-ocular surgery that are more common in those with diabetes than in those without it. In addition, cataract surgery is a major health care cost because of its frequency, and when resources are scarce, surgery may be delayed, prolonging the time and inconvenience of decreased vision associated with cataracts.

Received in final form October 15, 2014.

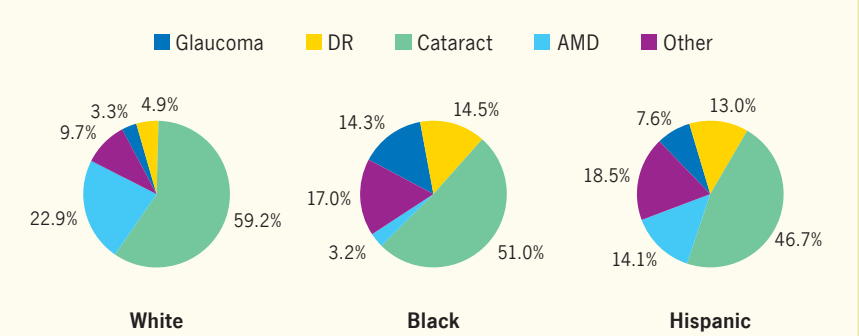
The need for surveillance and care for those with diabetic ocular complications is likely to increase with the projected increase in the number of people with diabetes. In addition, changes in therapy, both general medical and specific ocular, are changing care patterns. Therefore, to anticipate health care needs and costs, and as part of a comprehensive public health program to diminish the disabilities associated with ocular problems related to diabetes, ongoing collection of population-based data on this subject is needed.

IMPAIRMENT OF VISION AND BLINDNESS RELATED TO DIABETES

PREVALENCE

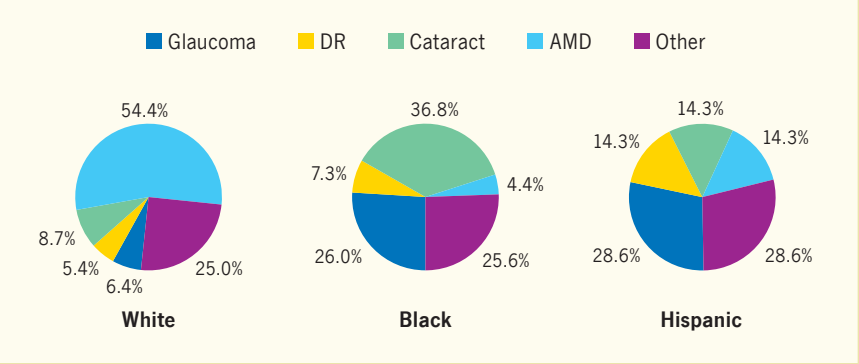
In 2004, estimates of the cause of severe visual impairment and low vision in adults in the United States were reported by the Eye Diseases Prevalence Research Group (1). Using prevalence data pooled from eight epidemiologic cohort studies that collected and reported data in the 1980s and 1990s in which best corrected visual acuity was ascertained after refraction, the authors estimated that 937,000 Americans with diabetes age ≥40 years had severe visual impairment, for an estimated prevalence of 0.78% (95% confidence interval [CI] 0.63%–0.94%) in the general U.S. population. The relative proportions of persons with low vision (corrected visual acuity of poorer than 20/40 in the better seeing eye, excluding persons who were blind) and blindness (corrected visual acuity of poorer than 20/200 in the better seeing eye) attributed to diabetic retinopathy varied by race/ethnicity, with the lowest estimated prevalence in whites (4.9% and 5.4%, respectively) compared to blacks (14.5% and 7.3%, respectively) and Hispanic persons (13.0% and 14.3%, respectively) (Figures 21.1 and 21.2).

FIGURE 21.1. Causes of Low Vision (Best Corrected Visual Acuity <6/12 [<20/40] in the Better Seeing Eye), Excluding Persons Categorized as Being Blind (Best Corrected Visual Acuity <6/60 [<20/200]), by Race/Ethnicity, U.S., 2004



AMD, age-related macular degeneration; DR, diabetic retinopathy.

FIGURE 21.2. Causes of Blindness (Best-Corrected Visual Acuity <6/60 [<20/200]), by Race/Ethnicity, U.S., 2004



AMD, age-related macular degeneration; DR, diabetic retinopathy.

The National Health and Nutrition Examination Surveys (NHANES) provided estimates of the prevalence of visual impairment in 1999–2002 in persons with diabetes in the United States age ≥12 years (2). In those data, the prevalence of any visual impairment in persons with diabetes was 11.3% (95% CI 6.9%–15.7%) compared to 6.2% (95% CI 5.8%–6.6%) in persons without diabetes. In a different publication using NHANES data from 1999–2004, persons with diabetes were more likely to have visual impairment than persons of the same age without diabetes (3). The prevalence of visual impairment not correctable with refraction ("uncorrectable visual impairment") among adults in the United States with diabetes who were age ≥20 years was 3.8% (moderate visual impairment 2.9%, severe visual impairment 1.0%), and among those without diabetes, it was 1.4% (moderate 1.2%, severe 0.3%). These estimates of visual impairment are lower than those reported by the Eye Diseases Prevalence Research Group (1), even when restricting the NHANES data to those age ≥40 years. This difference may be due, in part, to the sampling frame of the NHANES that included only community-dwelling persons and excluded those who were unable to see or were institutionalized.

In a study of 725 African Americans age 3–80 years with type 1 diabetes examined from January 1, 1999, to December 31, 2001, visual impairment was present in 79 (11.0%) and legal blindness in 22 (3.1%) of the participants (4). Diabetic retinopathy was responsible for 90.9% of the blindness. The prevalence of visual impairment was significantly associated with older age and female sex, and only weakly with less education.

Of 6,357 Los Angeles Latino Eye Study (LALES) participants who were examined from February 2000 to May 2003,

821 individuals had a history of type 2 diabetes and a history of treatment for it (5). Of these, 101 (12.3%) had visual impairment.

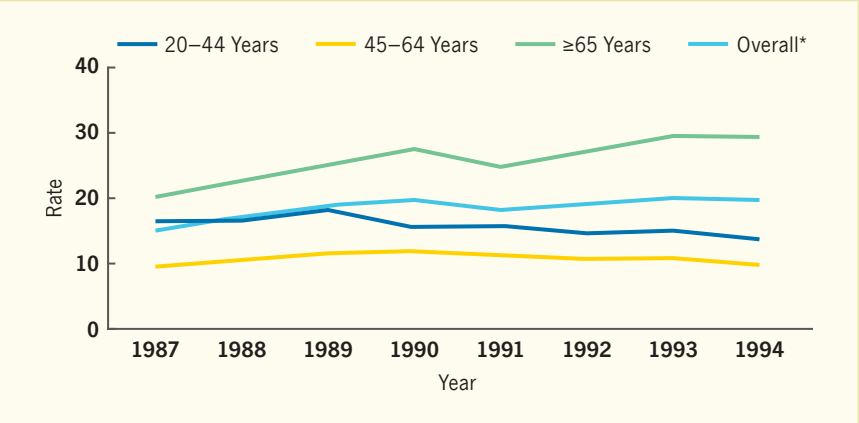
Using data from the National Health Interview Survey (NHIS), a periodic survey of self-reported visual function involving a probability sample of 40,695 adults age ≥65 years in the United States in 2000–2006, Jones *et al.* found that approximately 26% of older adults who were blind reported having diabetes compared with approximately 15% of those with no visual impairment (age-sex-adjusted odds ratio [OR] 1.73) (6).

Changes in Prevalence of Visual Impairment by Period of Diagnosis of Diabetes

During the period between 1987 and 1994, blindness caused by diabetes in Massachusetts was reported for 2,990 persons (annual mean number of persons reporting blindness: 374, range: 340–397); 60% were age ≥65 years, 30% were age 45–64 years, and 10% were age 20–44 years (7). In 1994, the overall prevalence of blindness caused by diabetes recorded on the Massachusetts Commission for the Blind register was 3,434 cases; the annual mean for 1987–1994 was 2,994 (range: 2,298–3,536). Persons age ≥65 years accounted for 67% of cases, persons age 45–64 years for 23%, and persons age 20–44 years for 10%. The mean age-standardized annual prevalence of blindness was 18.5 per 1,000 persons with diabetes (range: 15.3–20.2), and the age-standardized women-to-men rate ratio was 1.4:1. During 1987–1994, the overall age-standardized prevalence increased 28% (Figure 21.3). *Morbidity and Mortality Weekly Reports* (7) showed that the prevalence of blindness decreased 17% among persons age 20–44 years but increased substantially (46%) among persons age ≥65 years.

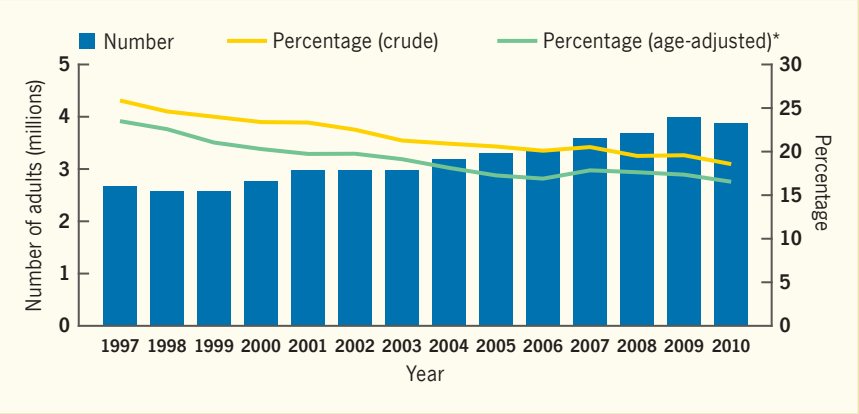
Data from the NHIS 1997–2010 indicated an increase in the number of adults with diagnosed diabetes reporting visual impairment (8). Figure 21.4 shows the number of adults age ≥18 years

FIGURE 21.3. Annual Prevalence Rate of Blindness Caused by Diabetes, by Age, Massachusetts, 1987–1994



Per 1,000 persons with diabetes. Age-standardized to the estimated number of persons with diabetes in Massachusetts in 1987.
* For persons age ≥20 years. Blindness caused by diabetes is rare in persons age <20 years.
SOURCE: Reference 7

FIGURE 21.4. Number of Adults Age ≥18 Years With Diabetes and Visual Impairment and Percentage of Adults Age ≥18 Years With Diabetes Who Also Reported Visual Impairment, U.S., 1997–2010



Diabetes and visual impairment are self-reported.
* Based on the 2000 U.S. standard population.
SOURCE: Reference 8

with self-reported diabetes and visual impairment (bars). From 1997 to 2010, the number of adults with self-reported diabetes and visual impairment increased from 2.7 million to 3.9 million ($p<0.001$).

Although the number of persons with diabetes reporting visual impairment grew, the age-adjusted percentage of adults with diagnosed diabetes who reported visual impairment declined significantly, from 23.7% in 1997 to 16.7% in 2010 (lines in Figure 21.4). During this 14-year period, age-adjusted prevalence of visual impairment declined significantly in diabetic men and women, whites, and Hispanics, and in diabetic persons with some college or higher education. Visual impairment also declined in those diagnosed with diabetes for ≥3 years and among those age ≥45 years (8).

In the population-based Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR), a modification of the Early Treatment Diabetic Retinopathy Study (ETDRS) protocol was used for the measurement of best corrected visual acuity at all examinations over a 25-year period from 1980–1982 to 2005–2007. The study involved both persons with type 1 diabetes and persons with type 2 diabetes at the first three examinations but only persons with type 1 diabetes

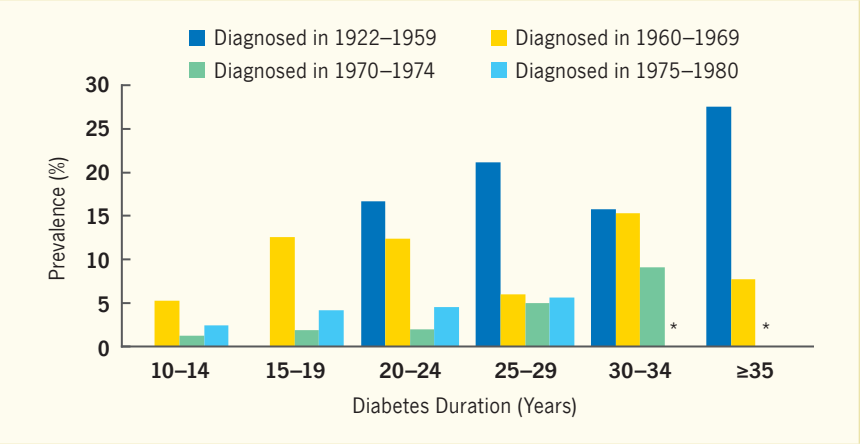
thereafter because of the high mortality in persons with type 2 diabetes in the cohort after 10 years of follow-up. Prevalence of visual impairment is often examined by duration of diabetes. However, population-based cohorts examined at multiple intervals over a long period of time, such as the WESDR, allow for the additional opportunity to explore whether period of diagnosis of type 1 diabetes affects this relation. In the WESDR, for any specific duration of type 1 diabetes, those who were diagnosed with type 1 diabetes in a more recent period were less likely to be visually impaired than those diagnosed in an earlier period (OR per category 0.91, 95% CI 0.88–0.93, p<0.0001). This association remained while adjusting for glycosylated hemoglobin (A1c), blood pressure level, and other related factors (9). In the WESDR, the influence of diabetes duration on visual impairment declined in more recent periods of diagnosis of diabetes (Figure 21.5) (9,10).

In the Beaver Dam Eye Study (BDES), a study primarily of whites, for any specific duration of type 2 diabetes, those who were diagnosed with type 2 diabetes in a more recent period were less likely to be visually impaired than those diagnosed in an earlier period (OR per 10 years 0.7, 95% CI 0.5–0.9, p=0.0054) (R. Klein, B. E. K. Klein, K. E. Lee, unpublished data). This observation remained while adjusting for A1c, blood pressure level, and other related factors.

INCIDENCE

In the WESDR, the mean decrease in visual acuity (as measured by the number of letters that persons with type 1 diabetes read correctly) over the 25-year period of the study was similar in the right (-6.7±18.9, equivalent to approximately one line of vision on the LogMar chart) and left (-7.6±18.0, p=0.46) eyes (11). Those with shorter duration of type 1 diabetes lost fewer letters during the 25-year period than those who had a longer duration of diabetes at baseline (Figure 21.6), but this trend was not statistically significant. For right eyes, the decrease in letters correctly identified varied from -3.9±17.0 letters in

FIGURE 21.5. Improvement in Prevalence of Visual Impairment, by Duration of Diabetes and Period of Diagnosis, WESDR



For a specific duration of diabetes, persons with recently diagnosed type 1 or type 2 diabetes have a lower prevalence of visual impairment, defined as a best corrected visual acuity of 20/40 or worse in the better eye, compared with patients who received a diagnosis in earlier periods. WESDR, Wisconsin Epidemiologic Study of Diabetic Retinopathy.
* Numbers were too few to establish a reliable estimate.
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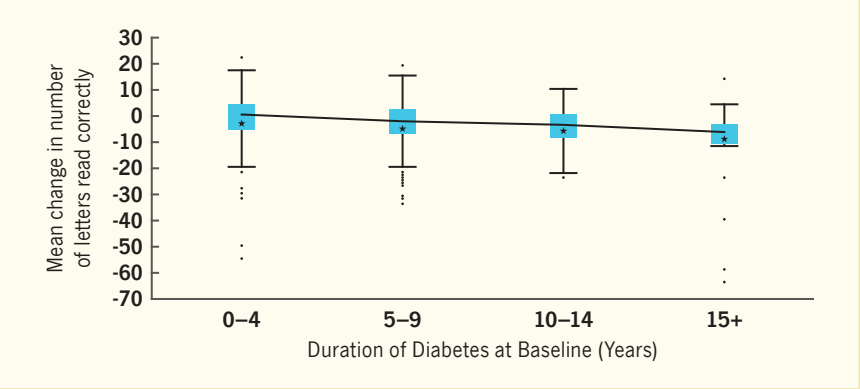
FIGURE 21.6. Twenty-Five-Year Change in the Mean Number of Letters Correctly Read in Right Eyes, by Duration of Diabetes at the Baseline Examination, WESDR, 1980–1982 to 2005–2007



Box extends from 25th to the 75th percentiles with line at median. Mean change indicated by star. WESDR, Wisconsin Epidemiologic Study of Diabetic Retinopathy.
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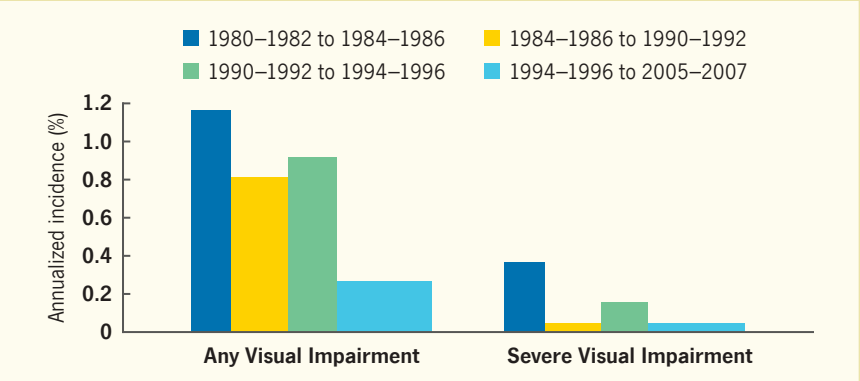
FIGURE 21.7. Estimated Annualized Rates for Incidence of Any and Severe Visual Impairment for Four Study Periods, WESDR



Width of bar corresponds to length of period. The length of the interval varied over the study; the widths of the bars in the figure vary to reflect this. WESDR, Wisconsin Epidemiologic Study of Diabetic Retinopathy.
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TABLE 21.1. Twenty-Five-Year Cumulative Incidence of Any and Severe Visual Impairment and Doubling of the Visual Angle in Better Eye, by Age and Duration of Diabetes, WESDR, 1980–1982 to 2005–2007

	ANY VISUAL IMPAIRMENT				DOUBLING OF THE VISUAL ANGLE				SEVERE VISUAL IMPAIRMENT			
			Cumulative Incidence (%)				Cumulative Incidence (%)				Cumulative Incidence (%)	
	N at Risk	N Events	Event	Risk of Dying Before Event	N at Risk	N Events	Event	Risk of Dying Before Event	N at Risk	N Events	Event	Risk of Dying Before Event
All age groups (years)	874	105	13.3	27.3	939	126	15.1	30.3	920	21	2.5	36.6
0–9	24	0	0.0	0.0	25	0	0.0	0.0	25	0	0.0	0.0
10–14	77	3	5.5	13.7	80	4	7.6	13.3	80	1	2.3	15.6
15–19	145	5	3.8	20.6	147	10	7.8	19.1	147	1	1.0	22.1
20–24	145	16	13.0	11.0	153	26	19.9	11.8	153	5	3.4	16.1
25–29	129	18	14.7	22.2	136	19	14.8	24.7	135	4	3.2	31.8
30–34	131	16	14.7	28.7	140	14	11.8	33.9	137	0	0.0	36.0
≥35	223	47	21.9	48.8	258	53	21.6	54.0	243	10	4.2	67.0
Diabetes duration (years)												
0–2	74	5	8.5	8.8	75	6	10.6	8.7	75	0	0.0	14.6
3–4	82	5	9.1	14.1	83	6	10.1	13.9	83	1	1.6	14.1
5–9	232	15	8.0	16.3	237	23	12.4	15.3	237	1	0.6	18.3
10–14	159	14	9.3	18.5	164	21	13.8	19.7	164	3	1.9	24.2
15–19	114	18	16.7	29.0	130	23	18.5	32.2	127	8	6.8	29.8
20–24	73	11	16.2	44.2	81	13	17.4	47.3	78	5	6.9	53.7
25–29	63	9	15.4	60.8	76	12	16.7	59.6	70	3	4.3	69.4
≥30	77	28	37.2	55.7	93	22	24.5	69.6	86	0	0.0	90.9

The 25-year cumulative incidence of any VI and severe VI in the better eye in the population, accounting for the competing risk of death, was 13% (95% CI 11%–16%) and 3% (95% CI 1%–4%), respectively. For right eyes, the 25-year cumulative incidence of any VI and severe VI in the population was 22% (95% CI 19%–25%) and 6% (95% CI 4%–7%), respectively, whereas for left eyes, it was 21% (95% CI 18%–24%) and 6% (95% CI 4%–8%), respectively. CI, confidence interval; VI, visual impairment; WESDR, Wisconsin Epidemiologic Study of Diabetic Retinopathy.

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persons with <5 years of type 1 diabetes to -9.3±24.6 letters (nearly two lines of vision) in persons with ≥15 years of type 1 diabetes at baseline. Similar relationships were found for left eyes.

In the WESDR cohort with type 1 diabetes, the 25-year cumulative incidence of any and severe visual impairment in the better eye, accounting for the competing risk of death, was 13.3% (95% CI 11%–16%) and 2.5% (95% CI 1%–4%), respectively (Table 21.1) (11). Using the World Health Organization (WHO) definitions, the 25-year cumulative incidence of moderate visual impairment (best-corrected visual acuity in the better eye of <20/80 and >20/200) and blindness (best-corrected visual acuity in the better eye of <20/400) was 3.0% and 1.2%, respectively. The difference in cumulative incidence between the WESDR and the WHO may reflect, in part, the differences in the definitions of categories of impairment. Additionally, the WESDR data are from persons with type 1 diabetes, while the WHO data are based largely on persons with type 2 diabetes. Therefore, it is not possible to determine how much of the differences are related to type of diabetes as opposed to age or other risk factors, as well as potential health care disparities.

In the WESDR, cumulative incidence of any visual impairment and severe visual impairment in the better eye and risk of death increased with age and duration of diabetes (Table 21.1). Figure 21.7 illustrates estimates of the annual incidence of any and severe visual impairment over the four study intervals (11). The estimates were similar for any visual impairment except for the last period, where it was markedly lower; a similar temporal pattern was found for severe visual impairment. To evaluate whether the lower annualized incidence in the last period was real or influenced by averaging over a longer interval, the annualized incidence was examined between the 1980–1982 and 1990–1992 examinations. This annualized incidence of 0.65 (data not shown) for any visual impairment is still higher than the annualized incidence of 0.28 over the comparable interval (1995–1996 to 2005–2007).

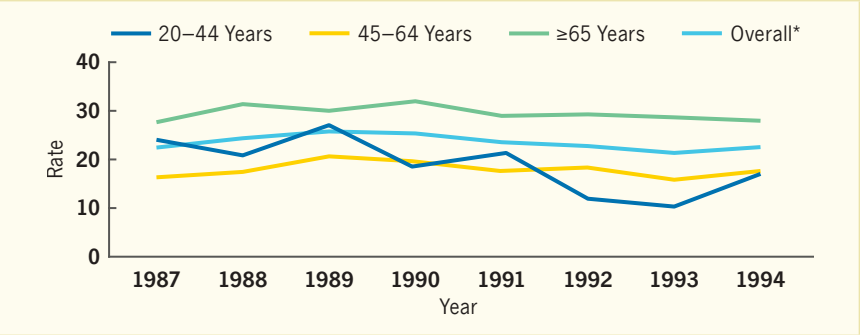
Based on 25-year follow-up data from the WESDR, it was estimated that of the 515,000 to 1.3 million Americans thought to have type 1 diabetes in 2005–2006, approximately 66,950–169,000 persons with type 1 diabetes would develop visual impairment, of whom 15,400–39,000 would develop severe visual impairment. The decrease from earlier periods in annualized incidence of visual impairment between the examinations in 1995–1996 and 2005–2006 suggests that applying these findings from earlier examinations to persons who currently have type 1 diabetes may overestimate the number of persons who will develop visual impairment over the next 25 years.

In Massachusetts, from 1987 to 1994 (7), the mean age-standardized annual incidence of blindness was 2.4 per 1,000 persons with diabetes (range: 2.1–2.6), and the age-standardized women-to-men rate ratio was 1.4:1. Overall, the incidence of blindness remained stable between 1987 and 1994 (Figure 21.8); however, for both men and women age 20–44 years, the incidence of blindness decreased over the interval by approximately 29%.

Of 835 persons in the LALES with type 2 diabetes at baseline, 21 (2.5%) developed incident visual impairment over a 4-year period (2000–2003 to 2004–2007) (12). While adjusting for age and other factors, persons with type 2 diabetes had double the odds of developing visual impairment compared to persons without diabetes.

Aside from the studies cited above, few other contemporary studies have examined the incidence of visual impairment in a cohort of persons with diabetes in the United States. Incidence data on visual impairment from studies done in earlier

FIGURE 21.8. Annual Incidence Rate of Blindness Caused by Diabetes, by Age, Massachusetts, 1987–1994



Per 1,000 persons with diabetes. Age-standardized to the estimated number of persons with diabetes in Massachusetts in 1987.
* For persons age ≥20 years. Blindness caused by diabetes is rare in persons age <20 years.
SOURCE: Reference 7

TABLE 21.2. Ten-Year Incidence of Doubling of the Visual Angle, by Participant Characteristics at the Baseline Examination, WESDR, 1980–1982, 1984–1986, and 1990–1992

	TYPE 1 DIABETES			TYPE 2 DIABETES					
				Taking Insulin			Not Taking Insulin		
CHARACTERISTICS	Value	N (%)	P-Value	Value	N (%)	P-Value	Value	N (%)	P-Value
Sex	Men	443 (9.6)	0.73	Men	217 (25.7)	<0.05	Men	222 (15.7)	<0.05
	Women	437 (8.8)		Women	255 (38.1)		Women	272 (25.6)	
A1c (%)	6.0–10.8	211 (3.3)	<0.0001	6.9–10.1	110 (24.5)	<0.005	6.2–8.5	115 (21.5)	0.49
	10.9–12.2	210 (7.6)		10.2–11.8	105 (25.7)		8.6–9.8	121 (19.5)	
	12.3–14.1	214 (11.5)		11.9–13.4	105 (38.6)		9.9–11.5	120 (15.2)	
	14.2–23.3	201 (15.0)		13.5–19.2	111 (40.3)		11.7–23.6	102 (31.9)	
Systolic BP (mmHg)	78–110	217 (6.3)	<0.0001	80–128	116 (20.9)	<0.0001	94–132	105 (22.4)	0.09
	111–120	242 (6.6)		129–144	131 (27.3)		133–145	155 (16.8)	
	121–134	223 (6.6)		145–160	128 (33.7)		146–161	119 (17.5)	
	135–221	191 (18.9)		161–263	97 (63.4)		162–236	114 (34.7)	
Diastolic BP (mmHg)	42–71	231 (3.6)	<0.0001	45–69	101 (41.8)	0.40	47–72	76 (33.2)	<0.005
	72–78	223 (9.6)		70–77	124 (30.9)		73–79	129 (28.7)	
	79–85	204 (7.6)		78–86	125 (20.6)		80–87	141 (18.0)	
	86–117	214 (16.4)		87–129	122 (39.3)		88–121	144 (13.7)	
Proteinuria	Absent	690 (6.2)	<0.0001	Absent	390 (29.4)	<0.005	Absent	438 (20.2)	0.19
	Present	156 (20.8)		Present	63 (51.5)		Present	40 (32.5)	
Smoking history*	Never	384 (9.1)	0.16	Never	248 (36.1)	0.29	Never	283 (25.2)	<0.05
	Former	116 (12.4)		Former	154 (29.9)		Former	145 (18.8)	
	Current	199 (14.4)		Current	70 (27.5)		Current	66 (9.7)	
Pack-years smoked*	0	385 (9.4)	<0.05	0	249 (35.9)	0.13	0	283 (25.2)	<0.05
	<5	96 (9.7)		<10	51 (35.2)		<10	56 (18.8)	
	5–14	92 (11.6)		10–19	44 (25.0)		10–19	28 (9.7)	
	≥15	124 (18.3)		20–39	51 (34.4)		20–39	43 (25.2)	
				≥40	76 (24.6)		≥40	82 (23.9)	
Macular edema†	Absent	717 (10.6)	<0.0001	Absent	353 (35.8)	<0.0001	Absent	448 (28.0)	<0.0001
	Present	47 (40.0)		Present	51 (60.7)		Present	15 (53.3)	
Retinopathy†	Level 10	297 (4.8)	<0.0001	Level 10	178 (36.0)	<0.0001	Level 10	337 (26.6)	<0.005
	Level 21	159 (7.5)		Level 21	65 (36.0)		Level 21	74 (35.8)	
	Level 31	84 (11.6)		Level 31	49 (28.2)		Level 31	32 (23.4)	
	Level 37	100 (12.6)		Level 37	66 (52.5)		Level 37	24 (47.2)	
	Level 43	53 (19.2)		Level 43	43 (56.2)		Level 43	11 (51.5)	
	Level 47	25 (16.0)		Level 47	14 (38.8)		Level 47–53	8 (50.0)	
	Level 53	12 (58.3)		Level 53	8 (37.5)		Level 60–85	5 (20.0)	
	Level 60	30 (21.3)		Level 60	10 (52.0)				
	Level 65	74 (44.1)		Level 65	26 (69.2)				
	Level 70	26 (48.1)		Level 70	4 (50.0)				
	Level 85	13 (53.8)		Level 85	8 (81.2)				

Conversions for A1c values are provided in *Diabetes in America Appendix 1 Conversions.* BP, blood pressure; WESDR, Wisconsin Epidemiologic Study of Diabetic Retinopathy.
* In persons with type 1 diabetes, limited to those age ≥18 years.
† In right eye.
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periods can be found in previous editions of *Diabetes in America* (13,14). The reader is also referred to a 2003 study from the Steno Clinic of persons with type 1 diabetes that found lower incidence of visual impairment than in the past (15).

RISK FACTORS FOR DEVELOPMENT OF VISION LOSS AND LEGAL BLINDNESS

Severity of Retinopathy and Macular Edema

Two advanced stages of retinal disease, proliferative diabetic retinopathy (PDR) and macular edema, are important causes of visual impairment in persons with diabetes. The epidemiology of diabetic retinopathy is described in detail in the next section. Diabetic macular edema occurs in individuals with type 1 diabetes, as well as those with type 2 diabetes. When present, it is more often a cause of severe visual impairment in individuals with type 2 diabetes (9.2%) than in those with type 1 diabetes (2.3%) (16).

TABLE 21.3. Ten-Year Incidence of Blindness in the Right Eye, by Retinopathy Level at the Baseline Examination, WESDR, 1980–1982 to 1990–1992

BASELINE RETINOPATHY LEVEL IN THE RIGHT EYE	TYPE 1 DIABETES		TYPE 2 DIABETES			
			Taking Insulin		Not Taking Insulin	
	N	%	N	%	N	%
10	297	0.3	170	6.8	327	5.5
21	158	0.6	61	11.7	70	15.6
31	82	2.6	47	0	31	3.2
37	100	3.1	63	15.3	23	21.7
43	53	9.6	43	22.7	11	18.2
47	25	0	14	21.4		
47–53					8*	37.5
53	12	16.7	6	16.7		
60	23	0	9	0		
60–85†					3*	0
65	72	19.3	23	23.5		
70	21	36.5	4	0		
P-value‡		<0.0001		<0.05		<0.01

WESDR, Wisconsin Epidemiologic Study of Diabetic Retinopathy.
* Because of small numbers, levels 47–53 and 60–85 were grouped in the type 2 diabetes group not taking insulin.
† Too few eyes with retinopathy level 85 to reliably estimate percentage with 10-year incidence of blindness.
‡ Based on a test for trend.
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Data describing impaired vision attributed to retinopathy by race/ethnicity in the United States from the Eye Disease Prevalence Research Group are presented in Figures 21.1 and 21.2 (1). In the Baltimore Eye Survey, legal blindness in persons with diabetes attributed to diabetic retinopathy was equally prevalent in whites (6%) and in blacks (5%) who were age ≥40 years, although these prevalences were based on small numbers (17).

Prior to the widespread use of panretinal photocoagulation, the risk of legal blindness associated with severe retinopathy was high; of 51 persons with type 1 diabetes at the Steno Hospital in Denmark, 50% were legally blind after 5 years in a report from 1967 (18). In the Diabetic Retinopathy Study, a randomized controlled clinical trial of panretinal photocoagulation begun in 1971, the 2- and 3-year cumulative incidences of visual acuity of poorer than 5/200 at two or more consecutive follow-up visits in untreated eyes were 16% and 26%, respectively, in eyes with PDR with high-risk characteristics for visual loss (19). In that trial, scatter photocoagulation reduced severe visual acuity loss by approximately 50% compared to no treatment throughout 5 years of follow-up. In the ETDRS, a trial conducted from 1979 to 1985, the 5-year cumulative incidence of visual acuity of poorer than 5/200 in eyes with macular edema differed by the severity of coexisting retinopathy. For those with less severe retinopathy (mild to moderate nonproliferative diabetic retinopathy [NPDR]) who received delayed focal treatment, the incidence was 3%; for those with more severe diabetic retinopathy (severe NPDR or early PDR), the incidence was 7% after treatment (20).

In the WESDR, the 10-year cumulative incidence of doubling of the visual angle (for example, best corrected visual acuity changing from 20/20 to 20/40 or from 20/30 to 20/60) (Table 21.2) and severe visual impairment (Table 21.3) increased with severity of diabetic retinopathy and the presence of macular edema in both persons with type 1 diabetes and persons with type 2 diabetes in those taking and not taking insulin (21). In 2010, the WESDR reported that while adjusting for other risk factors, each step of increasing diabetic retinopathy severity at baseline was associated with a 14% increased risk of developing visual impairment over a 25-year period in persons with type 1 diabetes (Table 21.4) (11).

Glycemic Control and Other Systemic Risk Factors

In univariable analyses, the 25-year cumulative incidence of any visual impairment in the WESDR in persons with type 1 diabetes was associated with having higher A1c, higher systolic or diastolic blood pressure, having hypertension, having gross proteinuria, being a current smoker, and having more pack-years smoked while having diabetes (11). In multivariable analyses that adjusted for duration of type 1 diabetes, the severity of diabetic retinopathy, presence of cataract, and having macular edema at baseline, the risk of visual impairment was associated with higher A1c, having hypertension, and currently smoking (versus never smoking), but not proteinuria (Table 21.4). When severity of diabetic retinopathy was excluded from the model, gross proteinuria was associated with incident visual impairment (hazard ratio [HR] 1.74, 95%

CI 1.07–2.84, p=0.03). The relative importance of the risk factors for doubling of the visual angle over 10 years was similar for persons with type 2 diabetes. However, the A1c at the baseline examination was not related to doubling of the visual angle in persons with type 2 diabetes (data not shown). This may be a result of selective survival, i.e., those with type 2 diabetes with high A1c who developed visual impairment were more likely to die from renal and cardiovascular disease (CVD) and not be seen at follow-up compared to those with high A1c who did not develop visual impairment. To date, no reports have been published on the relationship of intensive glycemic control and long-term incidence of visual impairment in type 1 diabetes from the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications study (DCCT/EDIC) group.

The 25-year cumulative incidence of visual impairment in the WESDR was significantly associated with hypertension at baseline (11). The cumulative risk for doubling of the visual angle over 9 years in the United Kingdom Prospective Diabetes Study (UKPDS) was 37% lower in the intensive blood pressure control group compared with the less intensive blood pressure control group (relative risk [RR] 0.63, 95% CI 0.42–0.92, p=0.002) (22).

Age and Duration of Diabetes

In data from 1988, the incidence of blindness (visual acuity of 20/200 or worse) in all persons in the WESDR was associated with increasing age in persons with type 1 diabetes and persons with type 2 diabetes who were taking insulin (Table 21.5) (23). A similar relationship between blindness and duration of diabetes was also seen in both persons with type 1 diabetes and persons with type 2 diabetes (Table 21.6) (23). The association between severe visual impairment and duration of diabetes has been reported from other studies as well (24,25,26,27). Risk factors for self-reported visual functions (the National Eye Institute Visual Function Questionnaire [NEI-VFQ-25]), as well as for performance-based visual function measures, were obtained from persons

TABLE 21.4. Associations With the 25-Year Cumulative Incidence of Any Visual Impairment, WESDR, 1980–1982 to 2005–2007

RISK FACTORS	ADJUSTING ONLY FOR DURATION OF DIABETES		MULTIVARIATE*	
	HR (95% CI)	P-Value	HR (95% CI)	P-Value
Sex (male)	1.10 (0.75–1.61)	0.62		
A1c (%)				
Per 1%	1.33 (1.21–1.46)	<0.001	1.28 (1.16–1.42)	<0.001
9.5–10.5 vs. <9.5	1.61 (0.80–3.23)	0.18		
10.6–12.0 vs. <9.5	1.83 (0.93–3.60)	0.08		
12.1–19.5 vs. <9.5	4.33 (2.32–8.07)	<0.001		
Proteinuria present	2.90 (1.92–4.37)	<0.001	NS	
Retinopathy severity				
Level 21 vs. Level 10	1.62 (0.77–3.44)	0.21		
Level 31–37 vs. Level 10	1.86 (0.92–3.78)	0.08		
Level 43–53 vs. Level 10	3.19 (1.50–6.77)	0.003		
Level 60+ vs. Level 10	8.26 (4.22–16.17)	<0.001		
15-level retinopathy severity, per 2 steps	1.35 (1.25–1.46)	<0.001	1.14 (1.03–1.27)	0.01
Macular edema present	2.66 (1.61–4.39)	<0.001	NS	
Cataract present	3.68 (2.37–5.70)	<0.001	2.49 (1.53–4.04)	<0.001
History of glaucoma present	3.92 (0.96–16.03)	0.06	NS	
Systolic blood pressure, per 10 mmHg	1.40 (1.27–1.55)	<0.001		
Diastolic blood pressure, per 10 mmHg	1.53 (1.27–1.83)	<0.001		
Hypertension present	2.74 (1.82–4.12)	<0.001	1.72 (1.05–2.83)	0.03
Smoking history†				
Past vs. never	1.24 (0.72–2.11)	0.44	NS	
Current vs. never	1.69 (1.09–2.61)	0.02	1.63 (1.01–2.61)	0.04
Pack-years smoked†				
<5	0.90 (0.49–1.65)	0.73		
5–14 vs. none	1.26 (0.68–2.31)	0.46		
≥15 vs. none	2.26 (1.36–3.74)	0.002		
Pack-years smoked, per 1 SD†	1.38 (1.17–1.64)	<0.001		
Body mass index, per 1 SD	1.08 (0.89–1.30)	0.44		

Conversions for A1c values are provided in *Diabetes in America Appendix 1 Conversions.* A1c, glycosylated hemoglobin; CI, confidence interval; HR, hazard ratio; NS, not statistically significant; SD, standard deviation; WESDR, Wisconsin Epidemiologic Study of Diabetic Retinopathy.

* All variables included in a single model. Information from measured blood pressure, pack-years smoked, categorical retinopathy severity, and categorical A1c level were included in the variables of hypertension present, smoking history, 15-level retinopathy severity, and A1c per 1%, respectively. Sex and body mass index were not significant in the model only adjusting for duration of diabetes and thus not included in the final multivariate model.

† Restricted to those age ≥18 years.

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TABLE 21.5. Four-Year Incidence of Blindness in Diabetic Persons, by Age at Baseline Examination, WESDR, 1980–1986

BASELINE AGE (YEARS)	TYPE 1 DIABETES		TYPE 2 DIABETES			
			Taking Insulin		Not Taking Insulin	
	N	%	N	%	N	%
0–9	25	0				
10–19	222	0				
20–29	282	1.8				
30–44	242	2.1	26	0	19	0
45–54	97*	3.1*	86	1.2	52	1.9
55–64			137	1.5	148	2.7
65–74			160	3.1	177	0
≥75			56	12.5	94	8.5
P-value†	<0.025		<0.001		0.05	

WESDR, Wisconsin Epidemiologic Study of Diabetic Retinopathy.

* Sample size and rate for age ≥45 years.

† Based on a test for trend.

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with long-term type 1 diabetes in the WESDR. The NEI-VFQ-25 scores were independently associated with older age, as well as complications of long-term type 1 diabetes (28).

Sex

Data from the model reporting areas showed that the highest rates of legal blindness attributed to diabetes occurred in nonwhite women; nonwhite men and white women were intermediate, and white men had the lowest rates (29). Sex was not associated with the cumulative incidence of visual impairment in the WESDR (HR men vs. women 1.10, 95% CI 0.75–1.61) (11).

EFFECT OF VISUAL IMPAIRMENT ON QUALITY OF LIFE IN PERSONS WITH DIABETES

Visual acuity may not optimally measure the ability of an individual to perform specific tasks, and it does not measure a person's self-assessment of well-being, expectations, and needs. The NEI-VFQ-25 is an instrument developed to assess the effects of visual impairment due to various ocular diseases on an individual's self-perception of his/her quality of life. In the WESDR, those with poorer visual acuity were more likely to have lower vision-related quality of life than those with better visual acuity (Figure 21.9 and Table 21.7) (28). In multivariate models, strong cross-sectional associations were found between best-corrected visual acuity and the NEI-VFQ-25 subscale and composite scores (Table 21.7).

In a follow-up of the WESDR cohort with type 1 diabetes, doubling of the visual angle over a 10-year period was related to negative changes in the NEI-VFQ-25 scores after adjusting for confounders (30). The most important changes were observed in subscales, such as general vision, mental health, role difficulty, and driving. However, changes in retinopathy status were not related to changes in any subscale after 10 years (Table 21.8) (30).

In the Pittsburgh Epidemiology of Diabetes Complications Study, Lloyd *et al.* (31) found an association of poor vision related to diabetic retinopathy with poorer quality of life. Tranos *et al.* (32) and Okamoto *et al.* (33) both reported some amelioration by laser treatment or vitrectomy, respectively, of the impairment of quality of life associated with decreased vision in those with diabetes.

Health-related quality of life was assessed by the NEI-VFQ-25 and the Medical Outcomes Study 12-item Short Form Health Survey (SF-12) in persons with type 2 diabetes who participated in the baseline examination of the LALES (34). In that study, more severe diabetic retinopathy was associated with worse health-related quality of life scores on all of the NEI-VFQ-25 and SF-12 subscales ($p<0.05$), independent of visual impairment. The decline in health-related quality of life was modest in those with minimal to mild NPDR and became significantly steeper with more severe retinopathy (moderate NPDR to PDR) (Table 21.9). The domains with the most significant impact were for vision-related daily activities, dependency, and mental health. In a study of persons with type 2 diabetes attending patient focus groups, Coyne *et al.* showed an association of visual impairment in persons with moderate and severe NPDR with poor health-related quality of life in areas of independence, mobility, leisure, and self-care activities (35).

TABLE 21.6. Four-Year Incidence of Blindness in Diabetic Persons, by Duration of Diabetes at Baseline Examination, WESDR, 1980–1986

BASELINE DURATION (YEARS)	TYPE 1 DIABETES		TYPE 2 DIABETES			
			Taking Insulin		Not Taking Insulin	
	N	%	N	%	N	%
0–4	157	0	78	0	204	2.9
5–9	232	0	83	3.6	151	2.0
10–14	162	1.2	78	2.6	54	1.9
15–19	117	5.1	106	3.8	54	5.6
20–24	73	2.7	75	2.7	27*	0*
25–29	61	4.9	28	10.7		
≥30	66	0	17	5.9		
P-value†		<0.005		0.056		0.93

WESDR, Wisconsin Epidemiologic Study of Diabetic Retinopathy.
* Sample size and rate for duration of diabetes ≥20 years.
† Based on a test for trend.
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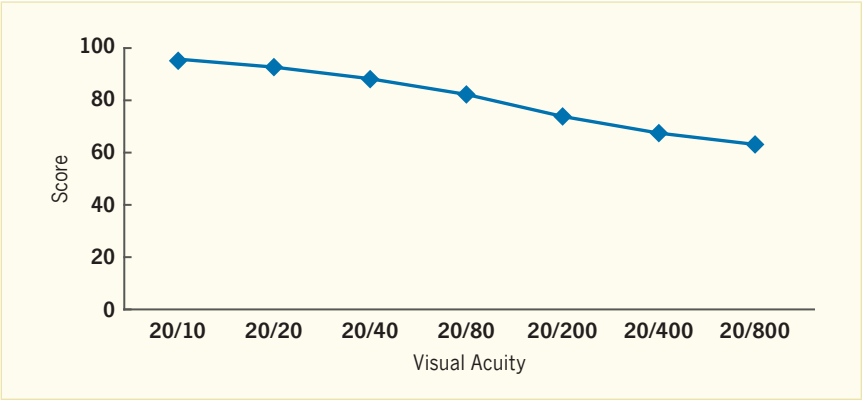
FIGURE 21.9. Independent Effect of Visual Acuity on the Total National Eye Institute Visual Function Questionnaire-25 Score, WESDR, 1997–1998



Adjusted for age, retinopathy level, loss of tactile sensation, pack-years smoked, SF-36 (36-Item Short-Form Health Survey) physical component summary, and SF-36 mental component summary. The National Eye Institute Visual Function Questionnaire-25 (NEI-VFQ-25) is a 25-item questionnaire that measures vision-related quality of life. WESDR, Wisconsin Epidemiologic Study of Diabetic Retinopathy.

TABLE 21.7. NEI-VFQ-25 Composite and Select Subscale Scores by Various Characteristics, WESDR, 1997–1998

CHARACTERISTICS	N	MEAN±SD					N	MEAN±SD
		NEI-VFQ-25 Composite	General Vision	Near Vision	Far Vision	Mental Health		Driving
Renal failure status								
None	418	90.9±12.2	81.4±15.0	89.1±16.3	89.2±16.1	87.0±15.6	396	88.1±20.3
Creatinine ≥177 µmol/L (2 mg/dL)	23	85.0±13.1	73.9±18.5	81.5±16.1	82.7±14.9	79.5±22.4	22	82.7±14.2
Dialysis or transplant	53	74.7±16.2	65.7±18.1	72.9±20.2	66.0±18.1	67.5±24.1	51	63.2±34.1
Amputations								
Absent	581	89.8±12.5	80.6±15.2	88.6±15.9	87.4±16.9	85.5±16.9	550	86.2±21.5
Present	21	64.1±20.8	57.1±23.9	59.9±27.7	63.7±23.2	59.4±32.1	19	52.2±36.2
Visual acuity								
≥20/20	412	92.6±9.2	83.5±14.2	91.5±13.4	91.2±13.5	88.8±13.5	400	90.4±15.5
20/25 to 20/32	145	85.0±14.1	75.3±13.3	83.1±18.0	81.3±16.9	79.3±20.9	132	79.9±23.4
20/40 to 20/80	31	69.6±17.8	63.9±15.0	68.3±19.6	61.9±22.3	63.4±26.6	23	46.3±36.7
≤20/100	10	53.6±28.3	44.0±29.5	46.7±32.2	46.3±30.9	58.1±28.4	10	26.3±42.8
Retinopathy severity								
None	13	95.0±6.1	86.2±12.6	93.6±7.0	94.2±9.9	93.9±8.7	12	94.0±6.3
Mild	209	94.1±8.3	85.8±12.6	94.2±11.4	93.7±12.2	90.0±11.6	198	92.8±13.1
Moderate	131	92.6±9.1	82.6±14.3	90.7±13.1	92.1±11.8	87.9±15.0	129	91.2±15.4
PDR	257	82.7±16.4	73.4±17.0	80.6±20.2	77.8±20.1	78.3±21.8	238	75.4±28.6
Macular edema								
Absent	414	92.9±8.5	83.8±13.2	92.2±12.3	91.7±13.1	88.8±13.3	392	91.6±12.8
Present	131	82.8±14.6	72.4±15.0	79.6±18.6	78.7±17.7	77.7±20.4	122	76.7±26.5
Lens status								
No significant cataract	442	91.2±11.4	81.5±14.9	89.9±14.9	89.3±15.6	87.0±15.9	423	88.8±18.6
Cataract ≥ standard	25	81.3±15.5	73.6±17.0	74.3±19.0	76.7±21.3	76.1±18.6	23	76.3±23.9
Cataract surgery	50	80.2±16.5	72.0±17.1	77.6±21.9	76.1±20.2	76.4±22.1	45	68.8±32.6

NEI-VFQ-25, 25-item National Eye Institute Visual Function Questionnaire, a measure of vision-related quality of life; PDR, proliferative diabetic retinopathy; SD, standard deviation; WESDR, Wisconsin Epidemiologic Study of Diabetic Retinopathy.

TABLE 21.8. Multivariable Analysis of Change in the NEI-VFQ-25, WESDR, 1995–1996 to 2005–2007

VARIABLE	COMP	OH*	GV	OP*	NA	DA	SF	MH	RD	DP	DR	CV	PV
Age, per 1 year	0.02	-0.09	-0.03	-0.15	0.11	-0.16	0.06	0.22	0.12	0.20	0.02	-0.08	0.24
Sex, vs. female	-0.76	-4.48	2.82	0.09	-1.89	-0.08	-3.42†	-4.52‡	-3.00‡	-1.73	0.01	-0.34	-1.07
Employment, vs. full/part time job													
Retired	-1.24	-7.59	1.05	-0.26	0.03	1.42	-2.21	-1.11	-8.59‡	-5.46‡	-1.21	1.54	-7.05
Not working	-4.50‡	-6.52	1.74	3.14	-2.50	-3.60	-3.12‡	-9.60‡	-10.51†	-4.30	-5.99	-3.36	-11.60‡
Other	0.82	1.40	0.82	2.69	4.57	3.56	-0.50	-0.79	-6.77†	0.89	7.17	2.48	1.81
A1c, per 1 unit %	0.57	-1.65‡	-0.29	0.70	0.46	0.57	0.26	1.44‡	0.97	1.15	0.85	0.45	1.24
Diabetes duration, per 1 year	-0.01	-0.12	0.24	-0.11	-0.11	0.10	0.15	-0.18	0.28	0.06	-0.06	-0.01	-0.31
CVD, vs. none	-2.52	1.79	-0.47	1.63	-4.23‡	-2.42	-1.64	-0.09	-6.95†	-1.69	-6.95‡	-2.12	-6.58‡
Nephropathy, vs. none	-1.73‡	1.39	-1.94	-1.46	-1.76	-1.09	-1.95	1.78	-2.45	-0.23	-3.45	-3.87‡	-2.77
Neuropathy, vs. none	0.18	-2.02	0.16	-0.42	0.98	-1.10	-0.56	-1.19	-0.85	-0.35	1.86	0.17	0.58
Amputation, vs. none	1.98	-5.87	-3.57	-3.03	0.49	1.69	2.43	3.43	-1.73	1.04	-0.67	-2.56	6.48
Diabetic retinopathy, vs. no change													
Improvement	0.37	1.63	-3.77	1.09	-0.60	-0.08	-1.39	0.78	1.82	-0.75	-0.40	2.34	1.59
Progression	0.69	1.20	0.22	-1.81	-0.44	-1.20	-0.29	-0.13	1.34	4.01	3.68	1.93	0.41
Visual acuity, per three line decrease	-5.69†	2.72	-6.46†	-4.05‡	-6.88†	-6.17†	-3.06†	-10.19†	-6.90†	-6.06†	-10.43†	-0.06	-1.27

(-) sign, decrease in 1 score unit in domain change; A1c, glycosylated hemoglobin; Comp, composite score; CV, color vision; CVD, cardiovascular disease; DA, distant activities; DP, vision-specific dependency; DR, driving; GV, general vision; MH, vision-specific mental health; NA, near activities; NEI-VFQ-25, 25-item National Eye Institute Visual Function Questionnaire, a measure of vision-related quality of life; OH, overall health; OP, ocular pain; PV, peripheral vision; RD, vision-specific role difficulty; SF, vision-specific social functioning; WESDR, Wisconsin Epidemiologic Study of Diabetic Retinopathy.

* Models also adjusted for body mass index.

† $p<0.01$

‡ $p<0.05$

SOCIODEMOGRAPHIC AND ECONOMIC RELATIONSHIPS OF IMPAIRED VISION IN PERSONS WITH DIABETES

Few data are available describing the socioeconomic and psychosocial characteristics of diabetic persons who have impaired vision and need rehabilitative services. In the WESDR, men with type 1 diabetes age ≥25 years who had PDR and who were employed at baseline were more likely to become unemployed 4 years later (36). Women with type 1 diabetes who had impaired vision at baseline had an increased 4-year incidence of divorce or separation (36). Psychological distress in diabetic persons with either stable or fluctuating decreases in vision, even when mild, has been thought to be a result of physical inactivity and inability to manage their diabetes (37,38). Rehabilitation programs consisting of education concerning diabetes self-management skills, nutrition counseling, and exercise programs have been shown to lead to significant improvements in psychological profiles in diabetic patients with fluctuating vision or loss of vision (39).

In 2009, Schmier *et al.* (40) provided estimates of costs associated with visual impairment in persons with diabetes. The use of low vision assistive devices (e.g., magnifier, white cane) and caregiving services increased with decreasing levels of visual acuity. The estimated yearly cost of these devices and caregiving services ranged from $641 for those with visual acuity (presumably of the better eye) of 20/20 or better to $48,162 for those with visual acuity of 20/80 or worse. These estimates did not include costs of reduced productivity, output loss, societal burdens of rehabilitation, or other local expenses. Based on the WESDR estimates of prevalence of blindness among persons with diagnosed diabetes in the United States in 1980–1982, there was an estimated annual cost of approximately $500 million per year (16).

The Behavioral Risk Factor Surveillance System is an annual, state-based, random-digit-dialed telephone survey of the noninstitutionalized U.S. civilian population age ≥18 years that provides sociodemographic and other information on health behaviors, chronic illness, and access to health care. Diabetic retinopathy was one of the conditions included in the query about specific eye diseases. In data from at least one year (from 2006–2009) in 21 states, a substantial percentage of visually impaired persons did not seek eye care because of lack of insurance (41).

Occupational therapists have become involved in working with visually impaired persons with diabetes (42). Occupational therapy is necessary for independent living, including dispensing medication accurately.

TABLE 21.9. NEI-VFQ-25 Composite and Driving Difficulty Subscale Scores and the SF-12 Physical and Mental Component Subscale Scores at Each Severity Level of Diabetic Retinopathy, LALES, 2000–2003

DR SEVERITY CONCATENATED SCALE STEPS	ETDRS SCORE* IN THE 2 EYES	NEI-VFQ-25				SF-12			
		Driving Difficulty Subscale		Composite		Physical Component		Mental Component	
		Score†	Slope‡	Score†	Slope‡	Score†	Slope‡	Score†	Slope‡
1	10/10	87.02		84.02		44.85		49.24	
2	20/<20	86.53	-0.49	83.76	-0.27	44.31	-0.55	48.98	-0.25
3	20/20	86.26	-0.28	83.52	-0.24	43.95	-0.35	48.85	-0.13
4	31/<31	86.02	-0.24	83.27	-0.25	43.64	-0.31	48.73	-0.12
5	31/31	85.78	-0.24	83.01	-0.26	43.35	-0.29	48.61	-0.12
6	37/<37	85.55	-0.23	82.72	-0.28	43.08	-0.27	48.49	-0.12
7	37/37	85.32	-0.23	82.40	-0.32	42.83	-0.25	48.37	-0.12
8	43/<43	84.97	-0.35	82.00	-0.40	42.58	-0.25	48.19	-0.18
9	**43/43**	**81.98**	**-2.99**	**80.21**	**-1.80**	**41.64**	**-0.94**	**47.73**	**-0.46**
10	47/<47	78.39	-3.59	77.66	-2.54	40.62	-1.01	47.06	-0.68
11	47/47	75.20	-3.19	75.31	-2.35	39.73	-0.89	46.41	-0.65
12	53/<53	72.15	-3.05	73.05	-2.26	38.89	-0.85	45.77	-0.64
13	53/53	68.70	-3.44	70.50	-2.55	37.97	-0.92	45.06	-0.71
14	60+/<60+	65.35	-3.35	68.04	-2.46	37.03	-0.93	44.38	-0.68
15	60+/60+	61.90	-3.46	65.53	-2.51	36.07	-0.97	43.69	-0.69

DR, diabetic retinopathy; ETDRS, Early Treatment Diabetic Retinopathy Study; LALES, Los Angeles Latino Eye Study; NEI-VFQ-25, 25-item National Eye Institute Visual Function Questionnaire, a measure of vision-related quality of life; NPDR, nonproliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy; SF-12, Medical Outcomes Study 12-item Short Form Health Survey, a measure of health-related quality of life.

* ETDRS scores correspond to the following clinical severity levels: Level 10–13, no DR; level 14–31, mild NPDR; level 35–47, moderate NPDR; level 53–59, severe NPDR; level ≥60, PDR. The relationship changes significantly at the DR Severity Concatenated Scale step 9 (43/43), which corresponds to bilateral moderate NPDR (boldface).

† The NEI-VFQ-25 and SF-12 scores have been adjusted for covariates.

‡ For the relationship between severity of DR and the NEI-VFQ-25 and SF-12 quality-of-life scores.

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VISUAL ACUITY AS A PREDICTOR OF DEATH

Among persons with type 1 diabetes in the WESDR, after adjusting for age and sex, persons with a visual acuity of 20/200 or worse in their better eye at baseline had a 5-year survival rate of 56% compared with 94% in persons whose visual acuity was better than 20/40 in the better eye (43). Poorer 5-year survival was also seen in persons with type 2 diabetes with poorer visual acuity at baseline (31% compared with 76% in those with better visual acuity at baseline). The relationship between survival and visual acuity remained after adjusting for other factors associated with mortality.

Further follow-up of the WESDR cohort for a mean of 14–16 years after the baseline examination showed that severe visual impairment was consistently associated with all-cause mortality in people with type 1 or type 2 diabetes (44). In the ETDRS, the probability of death in persons with type 1 diabetes or type 2 diabetes increased with decreasing visual acuity (45).

These studies suggest that poor vision associated with diabetic retinopathy is a risk indicator that should alert primary care givers to the need to detect and treat accompanying early systemic complications in order to minimize their effects on mortality.

DIABETIC RETINOPATHY

Diabetic retinopathy is characterized by specific alterations in the appearance of the retina. The earliest change that can be seen with the aid of the ophthalmoscope is the retinal microaneurysm. Retinal blot hemorrhages and hard exudates follow. Cotton-wool spots, intraretinal microvascular abnormalities, venous beading, and venous reduplication are other lesions that signal the onset of the ischemic hypoxic nonproliferative phase of diabetic retinopathy. Increasing hypoxia may result in the expression of growth factors and the development of PDR, characterized by the growth of abnormal blood vessels and fibrous tissue from the optic nerve head or from the inner retinal surface elsewhere. Swelling of the macular region of the retina, called macular edema, may occur in the presence of either NPDR or PDR. It is a result of leakage of fluid due to breakdown of the blood-retinal barrier and the failure of the retinal pigment epithelium to pump the fluid out of the retina.

PREVALENCE

The prevalences of diabetic retinopathy, PDR, and macular edema are thought to be decreasing. In 1980–1982, the prevalence of diabetic retinopathy in persons with type 1 diabetes and type 2 diabetes in the WESDR was 71% and 47%, for PDR it was 23% and 6%, and for macular edema it was 11% and 8%, respectively. Estimates of retinopathy were higher in persons with type 2 diabetes in the WESDR than in persons with type 2 diabetes in other cohorts included in the analysis by the Eye Diseases Prevalence Research Group (Table 21.10). The crude prevalence of any diabetic retinopathy reported among persons with type 2 diabetes in that study was 40%, and the crude prevalence of severe vision-threatening retinopathy (pre-proliferative and PDR or macular edema) was 8% (46).

In 2004, the Eye Diseases Prevalence Research Group estimated that 4 million diabetic persons age ≥40 years had diabetic retinopathy, of whom approximately 900,000 had signs of vision-threatening retinopathy (Table 21.11) (46). Updated estimates of the prevalence of diabetic retinopathy in the United States are available from the NHANES 2005–2008. The estimated prevalences of diabetic retinopathy and vision-threatening retinopathy were 29% (95% CI 25%–33%) and 4% (95% CI 3%–6%) among adults in the United States with diabetes, respectively (Table 21.12) (47). Approximately 4.2 million persons with type 2 diabetes age ≥40 years were estimated to have diabetic retinopathy, of whom 650,000 had signs of vision-threatening retinopathy.

Changes in the way diabetes is managed (14,26,48,49,50,51,52,53,54,55,56,57,58,59,60,61,62,63,64,65,66,67,68,69,70,71,72,73,74,75,76,77,78,79,80,81,82,83,84,85,86) are thought to be responsible for the lower prevalence of diabetic retinopathy in more recent compared to early epidemiologic studies of persons with diabetes (87). For example, in the WESDR, self-monitoring of blood glucose in persons with type 1 diabetes increased from 72% in 1984–1986 to 91% in 2005–2007, and a higher proportion of persons used three or more injections of insulin per day (4% in 1980–1982 vs. 85% in 2005–2007). While adjusting for duration of diabetes, WESDR data also revealed a lower prevalence of PDR (4% lower per more recent time period) in those diagnosed with type 1 diabetes more recently than those diagnosed longer ago (Figure 21.10).

The lower prevalence of diabetic retinopathy in persons diagnosed with type 1 diabetes more recently was associated with a 25% drop in the mean A1c from 10.1% (87 mmol/mol) to 7.6% (60 mmol/mol) and a 29% increase in those achieving American Diabetes Association guidelines of A1c <7.0% (<53 mmol/mol) (from 4% to 33%) over the same period (87). However, these relationships remained when adjusting for hypertension and A1c levels over time, suggesting other factors may be related to this change.

In the Wisconsin Diabetes Registry Study (88), among an incipient cohort of individuals diagnosed with type 1 diabetes between 1987 and 1992, the prevalence of PDR at 15 or 20 years of diabetes was appreciably lower than for those with the same duration of type 1 diabetes in the most recent study period in the WESDR (2005–2007). In contrast, the prevalence of PDR was not found to be related to period of diagnosis of diabetes over a 25-year period in the Pittsburgh Epidemiology of Diabetes Complications Study (89).

Changes in the management of glycemia with improvement in glycemic control in persons with type 2 diabetes have also been reported. Between 1999–2000 and 2005–2006, increases in the use of more than one oral hypoglycemic agent (90,91) were thought to result in decreases in the mean A1c. The number of persons achieving A1c <7.0% increased by approximately 40%. This would be expected to have resulted in decreases in the prevalence and severity of diabetic retinopathy in persons with type 2 diabetes in the last

TABLE 21.10. Studies Included in Estimates of the Prevalence of Diabetic Retinopathy

VARIABLE	Barbados Eye Study, Barbados, West Indies	BDES, Beaver Dam, Wisconsin	BMES, Blue Mountain, Australia	Melbourne VIP, Melbourne, Australia	Proyecto VER, Nogales and Tucson, Arizona	SAHS, San Antonio, Texas*	SLVDS, San Luis, Colorado	WESDR, Southern Wisconsin
Years study conducted	1988–1992	1988–1990	1992–1994	1991–1998	1999–2000	1985–1987	1984–1988	1980–1982
No. participants with diabetes†	615	410	252	233	899	351	360	1,313
Photographic fields taken‡	1 and 2	1–7	1–5	1 and 2	1, 2, and 4	1–7	1, 2, and 4	1–7
Age (years)								
40–49	19.2	6.6	0.0	9.9	17.8	31.2	22.9	7.4
50–64	47.2	36.3	38.9	40.8	44.6	66.7	55.8	35.9
65–74	26.3	34.9	36.5	31.7	25.4	12.5	31.4	33.8
≥75	7.3	22.2	24.6	17.6	12.2	NA	NA	22.8
Sex								
Women	63.4	56.8	47.2	43.8	63.0	58.7	56.4	53.2
Men	36.6	43.2	52.8	56.2	37.0	41.3	33.6	46.8
Race/ethnicity								
White	NA	100.0	100.0	100.0	NA	19.4	35.3	100.0
Black	100.0	NA	NA	NA	NA	NA	NA	NA
Hispanic	NA	NA	NA	NA	100.0	80.6	64.7	NA
Crude prevalence								
Mild NPDR	19.8	22.9	21.0	16.3	36.6	18.2	20.6	36.6
Moderate NPDR	8.0	10.0	4.4	6.9	1.7	13.7	10.3	6.8
Severe NPDR/PDR	1.0	2.2	3.6	4.3	6.0	4.3	4.4	6.9
Macular edema	8.6	1.2	4.8	2.2	8.9	2.6	3.3	5.1
DR of any type	28.8	35.1	29.0	27.5	44.3	36.2	35.3	50.3
VTDR	9.1	3.2	6.4	4.3	8.9	5.3	6.4	10.0

Data are given as percentage of persons unless otherwise indicated. BDES, Beaver Dam Eye Study; BMES, Blue Mountains Eye Study; DR, diabetic retinopathy; NA, not applicable; NPDR, nonproliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy; SAHS, San Antonio Heart Study; SLVDS, San Luis Valley Diabetes Study; VER, Vision Evaluation Research; VIP, Visual Impairment Project; VTDR, vision-threatening diabetic retinopathy; WESDR, Wisconsin Epidemiologic Study of Diabetic Retinopathy.

* Persons with type 2 diabetes only.

† The number of persons reported for each study in this table reflects the number contributing to the estimates in the current chapter and not necessarily the total number of participants in the original study as published.

‡ The photographic fields are described in: Early Treatment Diabetic Retinopathy Study Research Group: Grading diabetic retinopathy from stereoscopic color fundus photographs—an extension of the modified Airlie House classification. ETRDS report number 10. *Ophthalmology* 98(Suppl):786–806, 1991.

TABLE 21.11. Estimated Prevalence of Diabetic Retinopathy, by Age, Sex, and Race/Ethnicity, U.S., 2004

	N OF PERSONS (IN THOUSANDS)			TOTAL POPULATION	
SEX AND AGE (Years)	White	Black	Hispanic	Persons With DR (95% CI)	Prevalence per 100 Persons (95% CI)
Any retinopathy					
Women					
40–49	165	52	36	265 (185–344)	1.23 (0.86–1.60)
50–64	474	138	118	767 (656–879)	3.55 (3.04–4.07)
65–74	390	64	44	513 (432–594)	5.08 (4.28–5.89)
≥75	431	46	39	533 (432–633)	5.08 (4.12–6.04)
Subtotal	1,460	300	237	2,078 (1,890–2,266)	3.26 (2.97–3.56)
Men					
40–49	198	43	49	324 (239–410)	1.54 (1.13–1.95)
50–64	567	81	109	815 (689–941)	4.02 (3.40–4.65)
65–74	464	28	38	555 (457–653)	6.69 (5.50–7.87)
≥75	231	20	34	291 (222–360)	4.77 (3.63–5.90)
Subtotal	1,460	172	230	1,985 (1,791–2,180)	3.57 (3.22–3.92)
Women and men					
40–49	363	95	85	589 (472–706)	1.38 (1.11–1.66)
50–64	1,041	219	227	1,582 (1,414–1,751)	3.78 (3.38–4.18)
65–74	854	92	82	1,068 (940–1,195)	5.81 (5.11–6.50)
≥75	662	66	73	824 (7.02–946)	4.96 (4.23–5.70)
Total	2,920	472	467	4,063 (3,793–4,334)	3.40 (3.18–3.63)

Table 21.11 continues on the next page.

TABLE 21.11. (continued)

SEX AND AGE (Years)	N OF PERSONS (IN THOUSANDS) White	Black	Hispanic	TOTAL POPULATION Persons With DR (95% CI)	Prevalence per 100 Persons (95% CI)
Vision-threatening retinopathy					
Women					
40–49	85	14	4	73 (30–117)	0.34 (0.14–0.54)
50–64	111	46	26	193 (147–238)	0.89 (0.68–1.10)
65–74	76	27	8	115 (83–147)	1.14 (0.82–1.46)
≥75	60	20	6	90 (52–128)	0.86 (0.49–1.22)
Subtotal	299	107	44	471 (391–551)	0.74 (0.61–0.87)
Men					
40–49	28	10	9	53 (26–80)	0.25 (0.13–0.38)
50–64	158	28	22	223 (165–281)	1.10 (0.82–1.39)
65–74	80	2	10	97 (64–131)	1.17 (0.77–1.57)
≥75	45	5	5	55 (26–84)	0.90 (0.43–1.38)
Subtotal	311	45	46	428 (351–506)	0.77 (0.63–0.91)
Women and men					
40–49	80	24	13	126 (75–177)	0.30 (0.18–0.42)
50–64	269	74	48	416 (342–489)	0.99 (0.82–1.17)
65–74	156	29	18	212 (166–259)	1.15 (0.90–1.41)
≥75	105	25	11	145 (97–193)	0.86 (0.59–1.16)
Total	610	152	90	899 (788–1,011)	0.75 (0.66–0.85)

All estimates are based on the 2000 U.S. Census population. The estimates were derived from models using an unweighted average of the pooled age- and sex-specific rates for white, black, and Hispanic persons. Additional tables are available from *http://www.nei.nih.gov/eyedata*. Estimates for the prevalence of diabetic retinopathy in the total U.S. population include estimates for other races (Asian, Native American, Alaska Native, Native Hawaiian, and other Pacific Islander, and any other race/ethnicity) and those designating more than one race on the 2000 U.S. Census form. CI, confidence interval; DR, diabetic retinopathy.

TABLE 21.12. Estimated Prevalence of Diabetic Retinopathy and Vision-Threatening Diabetic Retinopathy in Adults With Diabetes Age ≥40 Years, by Age, Sex, and Race/Ethnicity, U.S., 2005–2008

CHARACTERISTICS	N*	N†	WEIGHTED SIZE, IN THOUSANDS‡	POPULATION WITH DIABETES % (95% CI)	P-Value	U.S. POPULATION % (95% CI)	P-Value
Crude prevalence of diabetic retinopathy							
Total	1,006	324	4,202	28.5 (24.9–32.5)		3.8 (3.2–4.5)	
Age (years)					0.64		<0.001
40–64	575	189	2,588	28.0 (23.0–33.6)		3.1 (2.4–3.9)	
≥65	431	135	1,613	29.5 (25.4–33.9)		6.1 (5.1–7.3)	
Sex					0.04		0.046
Male	504	173	2,257	31.6 (26.8–36.8)		4.3 (3.5–5.3)	
Female	502	151	1,944	25.7 (21.7–30.1)		3.3 (2.7–4.1)	
Race/ethnicity					0.008		<0.001
Non-Hispanic white	396	107	2,507	26.4 (21.4–32.2)		2.9 (2.2–3.9)	
Non-Hispanic black	306	119	1,006	38.8 (31.9–46.1)		9.6 (7.7–11.9)	
Mexican American	197	70	401	34.0 (26.7–42.1)		6.7 (5.4–8.4)	
Other	107	28	286	19.7 (12.5–29.7)		3.3 (2.3–4.7)	
Crude prevalence of vision-threatening diabetic retinopathy							
Total	1,006	62	655	4.4 (3.5–5.7)		0.6 (0.5–0.8)	
Age (years)					0.41		0.009
40–64	575	36	376	4.1 (2.8–5.8)		0.4 (0.3–0.7)	
≥65	431	26	278	5.1 (3.5–7.3)		1.0 (0.7–1.5)	
Sex					0.67		0.81
Male	504	24	298	4.2 (2.8–6.1)		0.6 (0.4–0.9)	
Female	502	38	356	4.7 (3.2–6.9)		0.6 (0.4–0.9)	

Table 21.12 continues on the next page.

TABLE 21.12. (continued)

CHARACTERISTICS	N*	N†	WEIGHTED SIZE, IN THOUSANDS‡	POPULATION WITH DIABETES		U.S. POPULATION	
				% (95% CI)	P-Value	% (95% CI)	P-Value
Race/ethnicity					0.006		<0.001
Non-Hispanic white	396	13	304	3.2 (2.0–5.1)		0.4 (0.2–0.6)	
Non-Hispanic black	306	28	241	9.3 (5.9–14.4)		2.3 (1.5–3.6)	
Mexican American	197	16	85	7.3 (3.9–13.3)		1.4 (0.8–2.7)	
Other	107	5	22	1.6 (0.6–3.8)[1]		0.3 (0.1–0.6)	

CI, confidence interval; NHANES, National Health and Nutrition Examination Survey.
* Number of participants with diabetes in the NHANES 2005–2008.
† Number of participants with diabetes who had diabetic retinopathy or vision-threatening diabetic retinopathy in the NHANES 2005–2008.
‡ Weighted total number of U.S. adult population who had diabetic retinopathy or vision-threatening diabetic retinopathy.
[1] Relative standard error >30%

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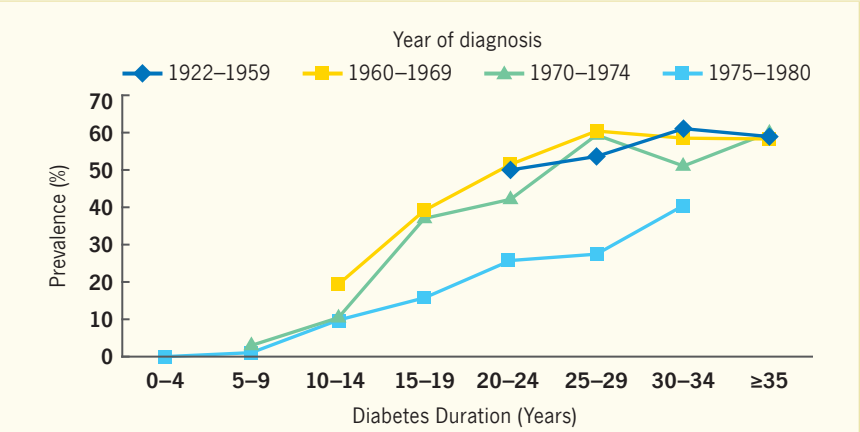
decade. Compared to persons with type 2 diabetes in the WESDR cohort studied 8 years earlier (1980–1982), duration-specific prevalences of NPDR and PDR were lower in the BDES cohort. The prevalence of diabetic retinopathy reported in the NHANES was higher at the 2005–2008 examination than at the 1988–1994 examination (47,62). This would suggest an increasing burden of diabetic retinopathy and PDR in the U.S. population. However, the comparisons of these estimates are not likely to be valid because of changes in methods of assessment of diabetic retinopathy between the two NHANES studies (one image of one standard fundus photo field of one eye in 1988–1994 compared to two fields of both eyes in 2005–2008).

FIGURE 21.10. Relationship of Prevalence of Proliferative Diabetic Retinopathy to Duration of Type 1 Diabetes, by Period of Diabetes Diagnosis, WESDR



WESDR, Wisconsin Epidemiologic Study of Diabetic Retinopathy.

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In addition, changes in diagnostic criteria for defining the presence of type 2 diabetes in the population (fasting blood glucose ≥125 mg/dL [≥6.94 mmol/L] or A1c ≥6.5% [≥48 mmol/mol] in 2005–2008 compared to fasting blood glucose of ≥140 mg/dL [≥7.77 mmol/L] in 1988–1994) may have resulted in some of the difference. In analyses conducted for *Diabetes in America, 3rd edition,* based on the NHIS, the self-report of a diagnosis of diabetic retinopathy was statistically significantly lower in 2008 compared to 2002 (7.7% vs. 10.4%) (Table 21.13). Age-sex-specific and race/ethnicity prevalences of diabetic retinopathy were generally lower in most groups in 2008 compared to 2002 (Table 21.13). The comparisons of prevalence between the two periods are limited because they were not adjusted for duration of type 2 diabetes, an important factor associated with the prevalence of diabetic retinopathy.

TABLE 21.13. Percent of Persons With Retinopathy Among Adults Age ≥40 Years With Diabetes, by Age, Sex, and Race/Ethnicity, U.S., 2002 and 2008

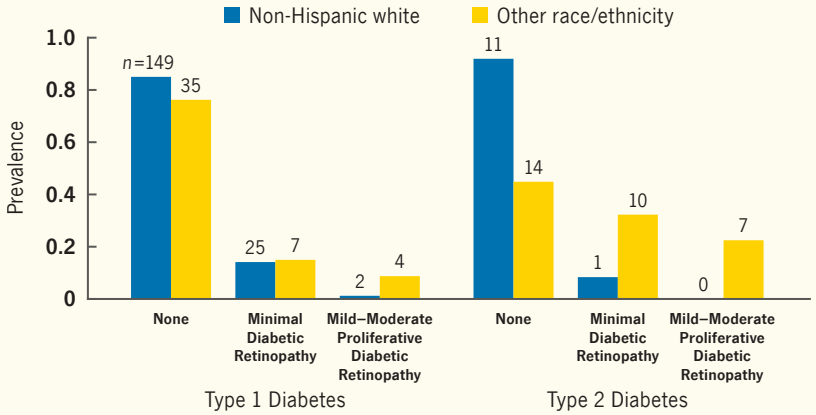
CHARACTERISTICS	PERCENT (STANDARD ERROR)	
	2002	2008
Overall	10.4 (0.84)	7.7 (0.73)*
Men, age (years)		
40–64	10.2 (1.68)	7.9 (1.39)
65–74	10.2 (2.38)	5.0 (1.69)[1]
≥75	6.0 (1.86)[1]	7.2 (2.33)[1]
Women, age (years)		
40–64	9.5 (1.37)	7.5 (1.26)
65–74	14.9 (2.41)	10.2 (2.52)
≥75	12.1 (2.17)	7.6 (2.22)
Race/ethnicity		
Non-Hispanic white	9.4 (0.94)	7.3 (0.91)
Non-Hispanic black	11.5 (1.78)	7.9 (1.76)
All Hispanic	13.3 (3.21)	7.5 (1.77)
Mexican American	14.3 (4.41)[1]	6.3 (2.09)[1]
Non-Hispanic Asian	17.9 (6.89)[1]	7.3 (2.35)[1]

Diabetes status and retinopathy are based on self-reported diagnosis.
* P-value compared to analogous 2002 estimate <0.05
[1] Relative standard error >30%–40%

SOURCE: National Health Interview Surveys 2002 and 2008

The number of youths with type 2 diabetes is growing (92), but few data are available describing the prevalence and severity of diabetic retinopathy in this group. A 2012 pilot study reported the prevalence and correlates of diabetic retinopathy in a racially/ethnically diverse sample of 222 youths with type 1 diabetes or type 2 diabetes. The prevalence of diabetic retinopathy was 17% for persons with type 1 diabetes and 42% in persons with type 2 diabetes (OR 1.50, 95% CI 0.58–3.88, p=0.40) adjusted for age, duration, sex, race/ethnicity, parental education, and A1c (93). For persons with type 1 diabetes and persons with type 2 diabetes, crude prevalence of both minimal diabetic retinopathy and mild-to-proliferative diabetic retinopathy was lower among non-Hispanic white individuals compared with those of other races/ethnicities (Figure 21.11).

FIGURE 21.11. Prevalence of Diabetic Retinopathy by Severity Within Subgroups of Diabetes Type and Race/Ethnicity, 2009–2010



Prevalence and severity of diabetic retinopathy among participants in the SEARCH for Diabetes in Youth diabetic retinopathy pilot study: n=222 with type 1 diabetes and n=43 with type 2 diabetes, mean age 16.0 years (standard deviation 4.4) and 21.1 years (standard deviation 2.8), respectively. For proliferative diabetic retinopathy: n=0 for type 1 diabetes and n=1 for type 2 diabetes.

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INCIDENCE

A number of population-based studies have reported incidence of diabetic retinopathy in the United States (26,83,94, 95,96,97,98,99,100,101,102,103,104, 105,106,107). The incidences of diabetic retinopathy, PDR, and macular edema over 4-year and 10-year intervals in persons with type 1 diabetes and type 2 diabetes in the WESDR were presented in the previous edition of *Diabetes in America* (14). In brief, for the cohort with type 1 diabetes, 59% and 89% developed diabetic retinopathy, 41% and 76% progressed by two or more steps on the concatenated ETDRS severity scale, 11% and 30% developed PDR, and 4% and 14% developed clinically significant macular edema (CSME) over the 4- and 10-year periods, respectively (95,97). Persons with type 1 diabetes had a higher 10-year incidence of any retinopathy (89% vs. 71%), progression of retinopathy by two or more

TABLE 21.14. Twenty-Five-Year Cumulative Rate for Progression of Retinopathy, Incidence of Proliferative Diabetic Retinopathy, and Improvement of Retinopathy, by Age and Diabetes Duration, WESDR, 1980–1982 to 2005–2007

	PROGRESSION OF RETINOPATHY				INCIDENCE OF PDR				IMPROVEMENT OF RETINOPATHY			
			Cumulative Progression (%)				Cumulative Incidence (%)				Cumulative Incidence (%)	
	N at Risk	N Events	Event	Risk of Dying Before Event	N at Risk	N Events	Event	Risk of Dying Before Event	N at Risk	N Events	Event	Risk of Dying Before Event
All groups	734	586	83.1	9.2	734	285	42.2	15.0	403	69	17.8	30.3
Age (years)												
0–9	27	21	100.0	0.0	27	1	5.9	0.0	0			
10–14	80	75	95.5	1.3	80	28	43.3	9.5	5	1	20.0	0.0
15–19	143	126	91.7	3.7	143	55	41.6	8.5	58	7	12.3	24.5
20–24	132	113	87.2	3.3	132	65	51.4	6.6	86	12	14.3	12.7
25–29	101	86	89.3	2.3	101	45	48.1	8.0	68	11	17.3	30.4
30–34	103	78	80.1	6.7	103	37	39.9	13.9	59	9	16.0	31.0
≥35	148	87	60.2	31.2	148	54	37.7	38.3	127	29	23.7	45.3
Diabetes duration (years)												
0–2	77	64	88.6	1.3	77	13	19.3	5.8	5	2	40.0	60.0
3–4	83	71	92.8	0.0	83	24	39.1	10.1	5	1	20.0	0.0
5–9	231	206	92.3	2.3	231	94	44.4	7.8	96	10	10.6	18.5
10–14	141	122	89.2	4.6	141	80	59.4	8.4	113	14	13.0	20.5
15–19	81	63	80.9	9.5	81	36	47.5	14.3	70	12	18.7	34.7
20–24	43	26	62.1	22.4	43	16	38.9	24.7	42	8	19.7	38.0
25–29	37	22	61.5	24.5	37	16	44.4	33.1	35	13	37.1	31.2
≥30	41	12	29.3	65.2	41	6	14.6	74.8	37	9	24.7	72.5

PDR, proliferative diabetic retinopathy; WESDR, Wisconsin Epidemiologic Study of Diabetic Retinopathy.

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TABLE 21.15. Twenty-Five-Year Cumulative Incidence of Macular Edema and Clinically Significant Macular Edema, by Age and Duration of Diabetes, WESDR, 1980–1982 to 2005–2007

	INCIDENCE OF MACULAR EDEMA				INCIDENCE OF CLINICALLY SIGNIFICANT MACULAR EDEMA			
			Cumulative Incidence (%)				Cumulative Incidence (%)	
	N at Risk	N Events	Event	Risk of Dying Before Event	N at Risk	N Events	Event	Risk of Dying Before Event
All groups	818	213	28.6	25.3	841	128	16.6	29.0
Age (years)								
0–9	24	4	23.2	0.0	24	4	23.2	0.0
10–14	77	18	28.8	10.4	77	12	19.0	12.4
15–19	142	34	26.1	13.7	143	23	17.7	15.2
20–24	141	39	29.7	11.9	143	25	18.4	13.5
25–29	111	40	39.9	15.7	117	23	21.1	21.3
30–34	122	33	29.9	21.0	125	19	16.5	25.1
≥35	201	45	23.4	57.5	212	22	11.0	63.0
Diabetes duration (years)								
0–2	74	11	17.7	9.6	74	6	10.2	11.5
3–4	80	19	29.2	10.0	80	10	14.4	11.9
5–9	234	72	34.0	9.3	235	56	26.4	11.8
10–14	142	50	37.7	14.1	146	25	18.1	16.0
15–19	100	24	26.1	30.2	103	12	12.3	35.1
20–24	60	20	36.0	38.8	68	12	19.5	45.0
25–29	54	10	19.1	59.8	57	6	10.7	63.6
≥30	74	7	9.6	82.8	78	1	1.3	88.3

WESDR, Wisconsin Epidemiologic Study of Diabetic Retinopathy.

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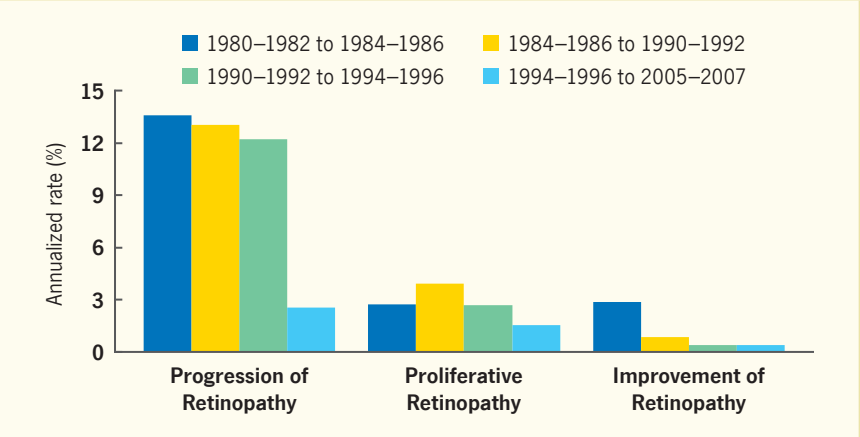
steps (76% vs. 60%), and progression to PDR (30% vs. 16%) compared to those with type 2 diabetes (96). Nonetheless, estimates of the number of incident cases in the 10-year period were higher in the group with type 2 diabetes than in the group with type 1 diabetes. This difference is due to the higher prevalence of persons with type 2 diabetes compared to those with type 1 diabetes.

The 25-year cumulative incidence of diabetic retinopathy in the WESDR cohort with type 1 diabetes, accounting for the competing risk of death, was 97% (108). For progression of diabetic retinopathy of two or more steps, it was 83% (95% CI 80%–86%), while for progression to PDR, it was 42% (95% CI 39%–46%). High-risk characteristics (e.g., the extent and location of the retinal new vessels, presence of preretinal or vitreal hemorrhage) for severe vision loss developed in 38% of those who developed PDR (Table 21.14) (108). The 25-year incidence of macular edema was 29% (95% CI 25%–32%), and the 25-year cumulative incidence of CSME was 17% (95% CI 14%–19%) (Table 21.15) (109). Using competing risk of death in estimating the 25-year cumulative incidence resulted in lower estimates than the methods used previously in the WESDR.

The WESDR also examined persons with type 1 diabetes with active PDR but without Diabetic Retinopathy Study high-risk characteristics (DRS-HRC) in at least one eye (ETDRS level 65) at baseline. Of this group, 31% developed DRS-HRC (levels 71 and 75) in at least one eye, and 7% progressed beyond DRS-HRC to the most severe stage of PDR associated with severe loss of vision (level 85) over the 25-year follow-up. Of 38 persons with DRS-HRC in at least one eye who were reexamined, 40% (n=15) had progressed to level 85, the most severe stage resulting in severe visual impairment, in at least one eye, and 13% (n=5) had progressed to level 85 in both eyes (108,109). Based on these findings,

FIGURE 21.12. Estimated Annualized Rates for Progression of Diabetic Retinopathy, Incidence of Proliferative Diabetic Retinopathy, and Improvement of Retinopathy for Four Study Periods in Persons With Type 1 Diabetes, WESDR



WESDR, Wisconsin Epidemiologic Study of Diabetic Retinopathy.

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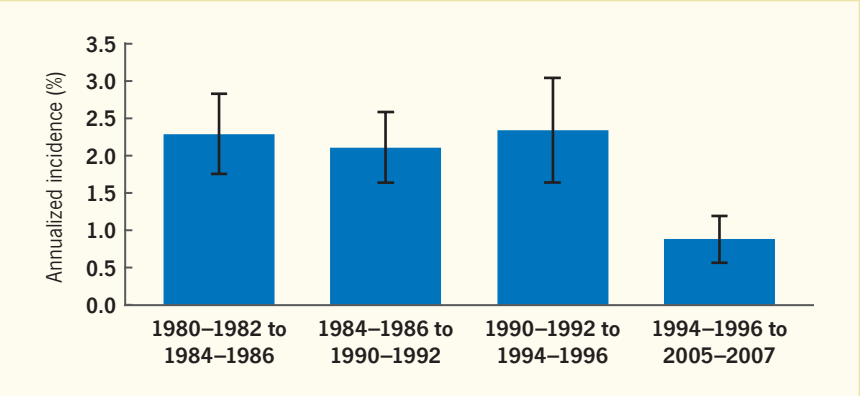
of the 515,000 to 1.3 million Americans thought in 2010 to have type 1 diabetes, it is estimated that over the next 25 years, 185,000–466,000 will develop PDR, of whom 63,000–159,000 will develop PDR with DRS-HRC and 149,000–377,000 will develop macular edema, of whom 88,000–221,000 will develop CSME.

Progression of diabetic retinopathy by two or more steps, incidence of PDR, improvement of retinopathy (Figure 21.12), and incidence of macular edema (Figure 21.13) were all lower in persons with type 1 diabetes in the WESDR who were examined more recently than those examined earlier in the course of the study.

Similar to decreases in the prevalence of diabetic retinopathy, the decrease in progression of diabetic retinopathy has been attributed to improved glycemic control, better treatment of high blood pressure, and better treatment of high lipid levels over the duration of the study. In the WESDR, in persons with type 1 diabetes, the annualized estimates for the progression of diabetic retinopathy (4.5% vs. 2.5%), the incidence of PDR (3.4% vs. 1.5%), and the incidence of CSME (1.0% vs. 0.4%) were higher in the first 12 years of the study (1980–1992) than in the latter 13 years of the study (1994–2007) (9,11,108,109). In the WESDR, an effect of period of diagnosis was observed for a specific duration of type 1 diabetes, with fewer persons with the same duration of type 1 diabetes developing PDR among those diagnosed more recently than in the past (108).

Few data are available showing similar decreases in the incidence of diabetic retinopathy in persons with type 2 diabetes. A study involving Medicare data from two different cohorts (one followed from 1994 to 1999 and the other from 2000 to 2005) of individuals age ≥65 years and newly diagnosed with type 2 diabetes showed decreases in the cumulative incidences of diabetic retinopathy, PDR, and macular edema of 17%, 23%, and 9%, respectively, in the more recently diagnosed cohort (110).

FIGURE 21.13. Estimated Annualized Rates for Incidence of Macular Edema for Four Study Periods in Persons With Type 1 Diabetes, WESDR



Error bars indicate 95% confidence intervals.

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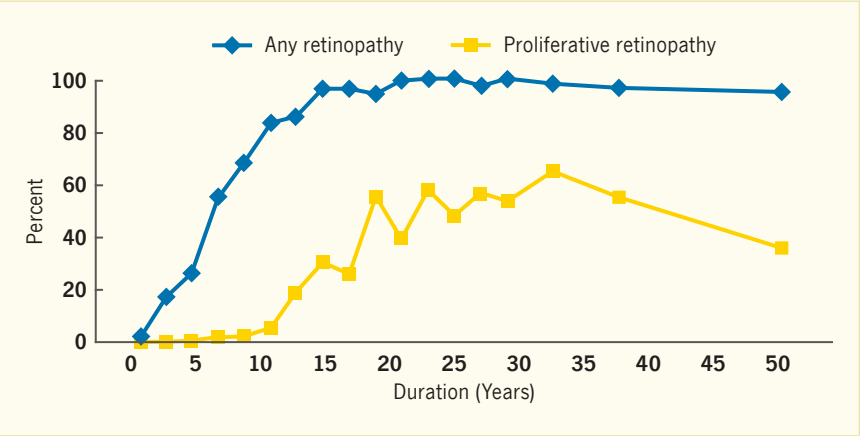
FIGURE 21.14. Prevalence of Any Retinopathy and Proliferative Diabetic Retinopathy in Persons With Type 1 Diabetes Diagnosed at Age <30 Years, by Duration of Diabetes, WESDR, 1980–1982



WESDR, Wisconsin Epidemiologic Study of Diabetic Retinopathy.

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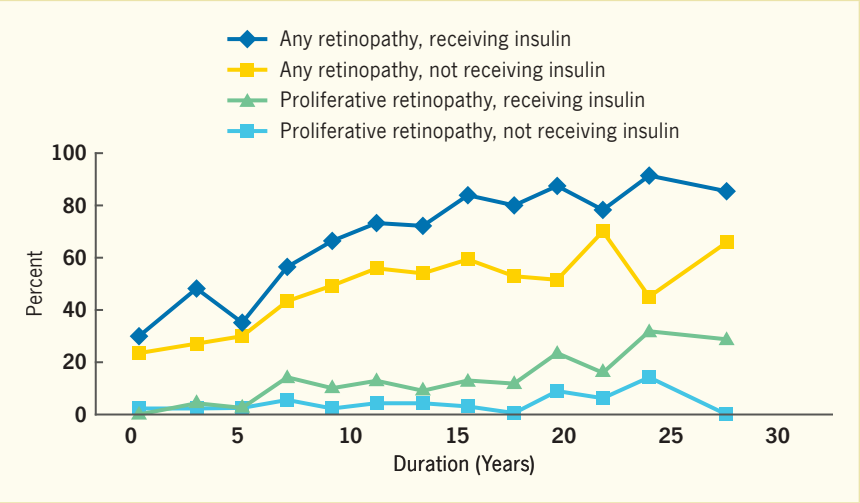
FIGURE 21.15. Prevalence of Any Retinopathy and Proliferative Retinopathy in Patients With Type 2 Diabetes Diagnosed at Age ≥30 Years, by Duration of Diabetes, WESDR, 1980–1982



WESDR, Wisconsin Epidemiologic Study of Diabetic Retinopathy.

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RISK FACTORS FOR DIABETIC RETINOPATHY

Duration of Diabetes

Frequency and severity of diabetic retinopathy increase with longer duration of type 1 diabetes and type 2 diabetes (111). The prevalence of diabetic retinopathy in persons with type 1 diabetes in the WESDR varied from 14% in men and 24% in women 3–4 years after diagnosis to nearly 100% at 30 years after diagnosis. With increasing duration of diabetes, a higher proportion of those with diabetic retinopathy have PDR (111). For example, among persons with type 1 diabetes duration of 19–20 years, 50% of men and 33% of women had PDR. In contrast, virtually at the time of diagnosis of type 2 diabetes, diabetic retinopathy is more common compared to those diagnosed with type 1 diabetes (Figures 21.14 and 21.15) (111,112). This difference is thought to be due to the longer period of time between the actual onset and diagnosis of type 2 diabetes than found in persons with type 1 diabetes. Harris *et al.* used diabetic retinopathy prevalence data from persons with type 2 diabetes at different durations of diabetes and extrapolated backward to the time when prevalence of retinopathy was estimated to be zero (113). They estimated that the onset of detectable diabetic retinopathy occurred approximately 4–7 years before diagnosis of type 2 diabetes in these cohorts. The changes made in 2002 in diagnostic criteria for defining type 2 diabetes and screening guidelines (114,115) would be expected to shorten the time between onset and detection.

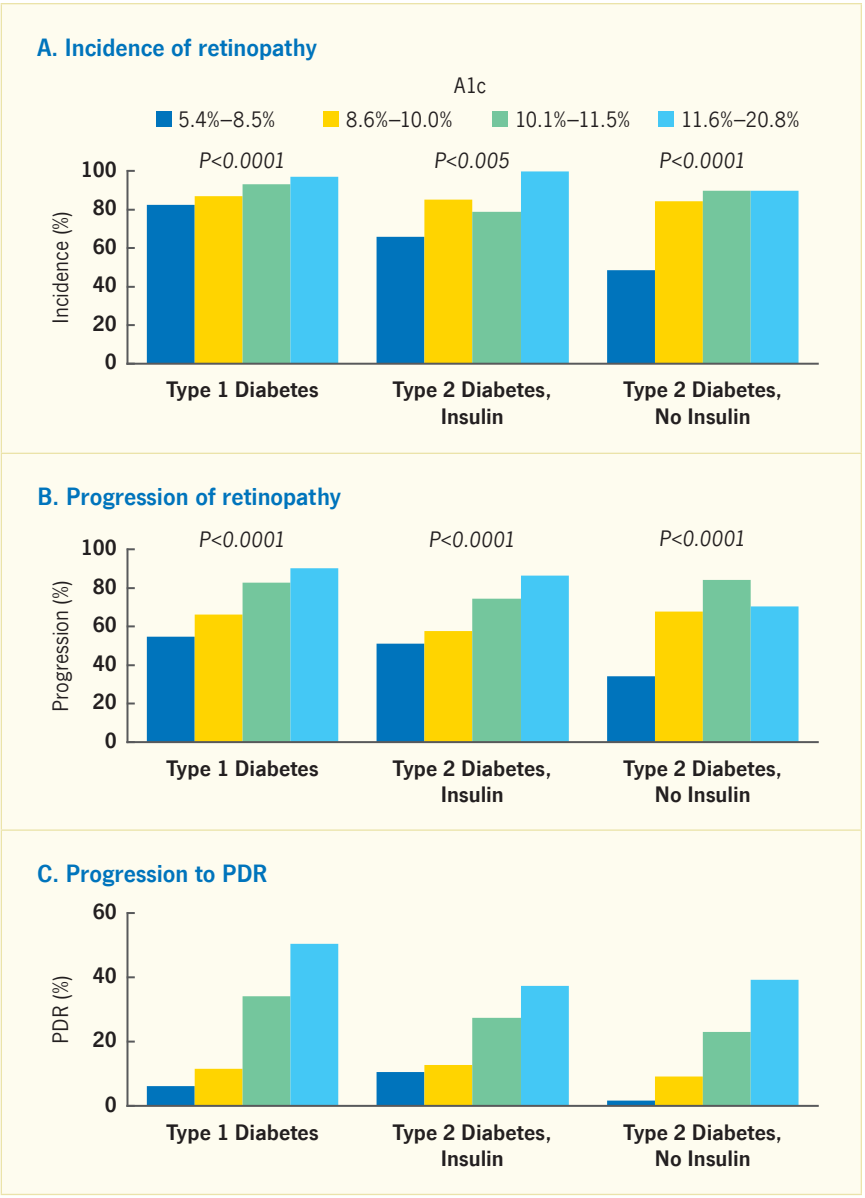
The relationships of the 4- and 10-year incidences of diabetic retinopathy and PDR with duration of type 1 diabetes and type 2 diabetes are described in detail in the previous edition of *Diabetes in America* (14). In brief, incidence of diabetic retinopathy increased with longer duration of diabetes (95,97,98), with the risk of developing diabetic retinopathy after 10 years of type 1 diabetes reaching 74%. The 4-year incidence of PDR varied from 0% during the first 3 years after diagnosis of diabetes to 28% in those with 13–14 years of diabetes. Thereafter, the

TABLE 21.16. Relationship of Increasing Duration of Type 1 Diabetes to the Prevalence and 25-Year Cumulative Incidence of Proliferative Diabetic Retinopathy in Persons With Type 1 Diabetes, WESDR, 1980–1982 to 2005–2007

DURATION OF TYPE 1 DIABETES (YEARS)	N	PREVALENCE OF PDR (%)	25-YEAR CUMULATIVE INCIDENCE OF PDR (%)*
<25	814	15	44
25–49	177	56	28
≥50	5	40	
Total	996	23	42

PDR, proliferative diabetic retinopathy; WESDR, Wisconsin Epidemiologic Study of Diabetic Retinopathy.
* Accounting for competing risk of death.
SOURCE: R. Klein and B.E.K. Klein, personal communication

FIGURE 21.16. Relation of (A) Incidence of Retinopathy, (B) Progression of Retinopathy, and (C) Progression to Proliferative Diabetic Retinopathy Over a 10-Year Period to A1c Levels by Quartile at Baseline, by Diabetes Type and Insulin Use, WESDR, 1980–1982, 1984–1986, and 1990–1992



Conversions for A1c values are provided in *Diabetes in America Appendix 1 Conversions.* A1c, glycosylated hemoglobin; PDR, proliferative diabetic retinopathy; WESDR, Wisconsin Epidemiologic Study of Diabetic Retinopathy.
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incidence remained stable (95). This trend was also found in a cohort of patients with type 1 diabetes followed at the Joslin Clinic (116).

The relationship of the 25-year cumulative incidence of PDR (accounting for competing risk of death) by duration and age has been reported for persons with type 1 diabetes in the WESDR (108). The study showed that the cumulative incidence remained relatively constant across ages and durations due to the increase in the competing risk of death with increasing age or duration of diabetes (Table 21.14).

Longer duration of type 1 diabetes (25–49 years) was associated with higher prevalence of PDR (56% vs. 15%) but lower incidence (28% vs. 44%) than in persons with <25 years of type 1 diabetes in the WESDR. This suggests that even with no evidence of PDR in persons with type 1 diabetes, there is still substantial risk of developing PDR late in the course of diabetes (Table 21.16). Improved survival of persons with type 1 diabetes may have influenced this finding.

Of those with type 2 diabetes in the WESDR, 2% of those with <5 years and 5% of those with ≥15 years of diabetes who were not taking insulin at baseline had developed signs of PDR by the 4-year follow-up (97).

Glycemia

The role of hyperglycemia in the pathogenesis of diabetic retinopathy was not confirmed until 1980 (117). However, long-term follow-up of the WESDR cohort of persons with type 1 and type 2 diabetes showed a strong relationship of glycemia as measured by A1c to the incidence and progression of diabetic retinopathy (Figure 21.16) (118,119). Furthermore, intensive glycemic control has been shown to reduce these diabetic retinopathy endpoints (120,121,122,123). Figure 21.16 and Tables 21.17 and 21.18 indicate that 25 years after the WESDR baseline examination, both progression of retinopathy and incident PDR were significantly associated with level of glycemia. The odds ratios per 1% higher A1c were 1.32 and 1.38 for progression of diabetic retinopathy of two or more steps and incidence of PDR, respectively (108).

The DCCT involved 1,441 patients with type 1 diabetes randomized between 1983 and 1989 to intensive or conventional glycemic intervention. There was an average follow-up of 6.5 years (range 3–9 years) after randomization and an average difference in A1c of nearly 2% between the intensive and conventional treatment groups for both the primary prevention (defined by the absence of diabetic retinopathy at baseline) and secondary prevention (defined by the presence of microaneurysms only to moderate or severe NPDR levels). The trial showed a statistically significant reduction in risk of sustained progression of diabetic retinopathy by three or more steps by 76% in the primary prevention group and 54% in the secondary prevention group (Figure 21.17 and Table 21.19) (124). In addition, when both cohorts were combined, the intensive therapy group also had a 47% reduction in risk of developing severe NPDR or PDR and a 51% reduction in treatment with panretinal photocoagulation (Table 21.19). The incidence of CSME in the group assigned to intensive therapy was lower than in the group assigned to conventional

TABLE 21.17. Associations With Progression of Diabetic Retinopathy in Type 1 Diabetes, WESDR, 1980–1982 to 2005–2007

		UNIVARIATE		MULTIVARIATE*	
RISK VARIABLE	LEVEL	HR (95% CI)	P-Value	HR (95% CI)	P-Value
Sex	Male	1.30 (1.11–1.54)	0.002	1.33 (1.11–1.58)	0.002
Age at diagnosis (years)	10–19 vs. <10 20–29 vs. <10	1.00 (0.82–1.21) 0.85 (0.68–1.06)	0.97 0.15		
A1c	Per 1%	1.29 (1.24–1.35)	<0.001	1.32 (1.26–1.38)	<0.001
A1c quartiles (%)	9.5–10.5 vs. <9.5 10.6–12.0 vs. <9.5 12.1–19.5 vs. <9.5	1.72 (1.34–2.21) 2.42 (1.91–3.06) 3.65 (2.87–4.65)	<0.001 <0.001 <0.001		
Proteinuria	Present	1.01 (0.76–1.33)	0.97		
Retinopathy severity level†	21 vs. 10 31–37 vs. 10 43–53 vs. 10	1.01 (0.80–1.27) 1.20 (0.95–1.51) 1.11 (0.83–1.48)	0.94 0.13 0.48		
15-level retinopathy severity	Per 2 steps	1.05 (0.99–1.12)	0.12	0.92 (0.86–0.99)	0.03
Systolic blood pressure	Per 10 mmHg	1.05 (0.99–1.11)	0.14		
Diastolic blood pressure	Per 10 mmHg	1.05 (0.97–1.13)	0.22		
Hypertension	Present	1.11 (0.86–1.44)	0.42		
Smoking history	Past vs. never Current vs. never	0.98 (0.74–1.29) 1.23 (0.99–1.54)	0.88 0.07		
Education	Per 4 years	0.98 (0.90–1.06)	0.62		
Body mass index	Per 4 kg/m^2	1.08 (1.00–1.17)	0.04	1.16 (1.07–1.26)	<0.001

Conversions for A1c values are provided in *Diabetes in America Appendix 1 Conversions.* A1c, glycosylated hemoglobin; CI, confidence interval; HR, hazard ratio; WESDR, Wisconsin Epidemiologic Study of Diabetic Retinopathy.
* All variables included in a single model. Missing rows indicate that variable was not significant and thus not included in the final multivariate model.
† Diabetic retinopathy is based on modified Early Treatment of Diabetic Retinopathy Study Severity Scale.
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therapy; however, this difference was not statistically significant. Intensive insulin treatment in the DCCT reduced but did not prevent the incidence and progression of diabetic retinopathy in persons without signs of retinopathy at baseline. The study showed that intensive therapy was more beneficial when started earlier in the course of type 1 diabetes, with the 9-year cumulative incidence of sustained three-step progression in the intensive therapy group being lower in eyes with minimal to early NPDR at baseline compared to eyes with more severe NPDR at baseline (11.5% to 18.2% vs. 43.8%). Researchers estimated that intensive therapy would result in a "gain of 920,000 years of sight, at an additional cost of $4.0 billion over the lifetime" of the 120,000 persons with type 1 diabetes in the United States at the time who met DCCT eligibility criteria (120).

TABLE 21.18. Associations With Incident Proliferative Diabetic Retinopathy in Type 1 Diabetes, WESDR, 1980–1982 to 2005–2007

		UNIVARIATE		MULTIVARIATE*	
RISK VARIABLE	LEVEL	HR (95% CI)	P-Value	HR (95% CI)	P-Value
Sex	Male	1.02 (0.81–1.28)	0.89		
Age at diagnosis (years)	10–19 vs. <10 20–29 vs. <10	0.94 (0.72–1.23) 0.94 (0.69–1.28)	0.67 0.67		
A1c	Per 1%	1.37 (1.30–1.45)	<0.001	1.38 (1.31–1.46)	<0.001
A1c quartiles (%)	9.5–10.5 vs. <9.5 10.6–12.0 vs. <9.5 12.1–19.5 vs. <9.5	2.91 (1.89–4.48) 4.08 (2.73–6.10) 6.29 (4.23–9.33)	<0.001 <0.001 <0.001		
Proteinuria	Present	2.12 (1.53–2.92)	<0.001	1.83 (1.31–2.56)	<0.001
Retinopathy severity†	21 vs. 10 31–37 vs. 10 43–53 vs. 10	1.84 (1.27–2.67) 4.19 (3.03–5.80) 6.75 (4.66–9.76)	0.001 <0.001 <0.001		
15-level retinopathy severity	Per 2 steps	1.56 (1.45–1.68)	<0.001		
Systolic blood pressure	Per 10 mmHg	1.21 (1.12–1.32)	<0.001	1.14 (1.04–1.25)	0.005
Diastolic blood pressure	Per 10 mmHg	1.30 (1.16–1.46)	<0.001		
Hypertension	Present	1.73 (1.25–2.40)	<0.001		
Smoking history	Past vs. never Current vs. never	0.91 (0.61–1.35) 1.22 (0.91–1.63)	0.63 0.18		
Education	Per 4 years	1.05 (0.94–1.19)	0.38		
Body mass index	Per 4 kg/m^2	1.17 (1.05–1.30)	0.0004	1.21 (1.07–1.36)	0.002

Conversions for A1c values are provided in *Diabetes in America Appendix 1 Conversions*. A1c, glycosylated hemoglobin; CI, confidence interval; HR, hazard ratio; WESDR, Wisconsin Epidemiologic Study of Diabetic Retinopathy.
* All variables included in a single model. Missing rows indicate that variable was not significant and thus not included in the final multivariate model.
† Diabetic retinopathy is based on modified Early Treatment of Diabetic Retinopathy Study Severity Scale.
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FIGURE 21.17. Cumulative Incidence of a Sustained Change in Retinopathy in Persons With Type 1 Diabetes Receiving Intensive or Conventional Therapy in (A) the Primary Prevention and (B) the Secondary Prevention Arms of the Diabetes Control and Complications Trial, 1983–1993

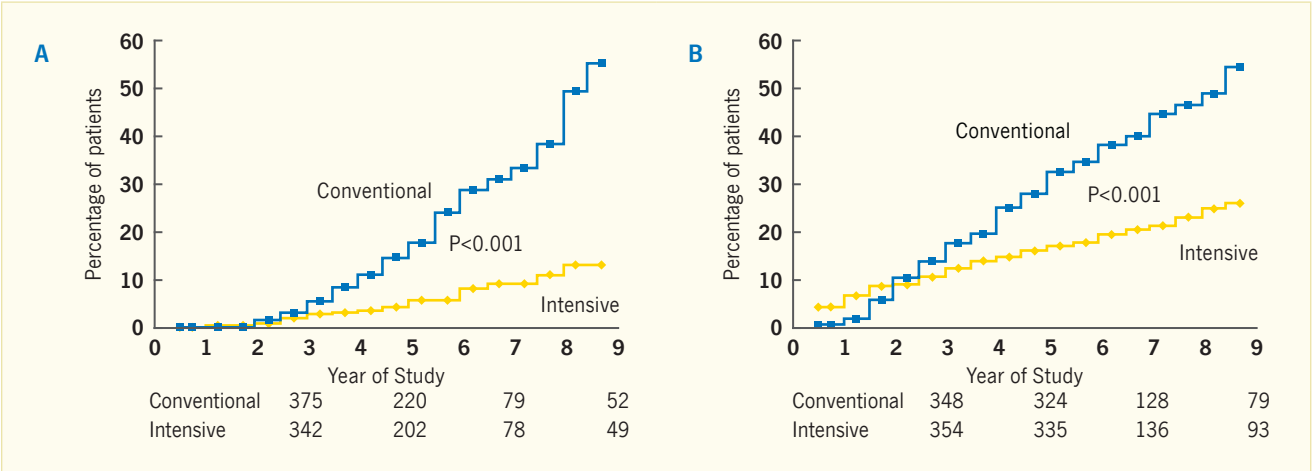

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TABLE 21.19. Development and Progression of Long-Term Complications of Diabetes in the Study Cohorts and Reduction in Risk With Intensive Compared With Conventional Therapy, DCCT

	PRIMARY PREVENTION			SECONDARY PREVENTION			BOTH COHORTS*
	Conventional Therapy	Intensive Therapy	Risk Reduction	Conventional Therapy	Intensive Therapy	Risk Reduction	Risk Reduction
COMPLICATIONS	Rate/100 Patient-Years		% (95% CI)	Rate/100 Patient-Years		% (95% CI)	% (95% CI)
≥3-step sustained retinopathy	4.7	1.2	76 (62–85)†	7.8	3.7	54 (39–66)†	63 (52–71)†
Macular edema‡				3.0	2.0	23 (-13–48)	26 (-8–50)
Severe NPDR or PDR‡				2.4	1.1	47 (14–67)§	47 (15–67)§
Laser treatment‡‖				2.3	0.9	56 (26–74)†	51 (21–70)§

Rates shown are absolute rates of the development and progression of complications per 100 patient-years. Risk reductions represent the comparison of intensive with conventional treatment, expressed as a percentage and calculated from the proportional-hazards model with adjustment for baseline values as noted. CI, confidence interval; DCCT, Diabetes Control and Complications Trial; NPDR, nonproliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy.

* Stratified according to the primary prevention and secondary prevention cohorts. Primary prevention cohort defined by the absence of diabetic retinopathy at baseline. Secondary prevention cohort defined by the presence of microaneurysms only to moderate or severe nonproliferative retinopathy levels.

† P≤0.002 by the two-tailed rank-sum test.

‡ Too few events occurred in the primary prevention cohort to allow meaningful analysis of this variable.

§ P<0.04 by the two-tailed rank-sum test.

‖ Denotes the first episode of laser therapy for macular edema or proliferative retinopathy.

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Data from the WESDR have shown that A1c and blood pressure only explain a small proportion of the progression of retinopathy (an R^2 of 11%) and the incidence of proliferative retinopathy (an R^2 of 11%) in persons with type 1 diabetes (R. Klein and B.E.K. Klein, unpublished data). It has been estimated from DCCT data that while A1c levels accounted for more than 95% of the difference in retinopathy levels and other complications between the intensive and conventional treatment groups in that trial, A1c levels accounted for only 11% of the overall risk of retinopathy with "genetic and environmental influences" being other likely factors explaining the variance (125). Others have hypothesized that wide temporal fluctuations in blood glucose, rather than A1c values, which represent only a 3-month average, may better explain the variance in diabetic retinopathy, although some data from the DCCT seem to refute this contention (126).

Other novel factors not usually measured in population-based cohort studies may explain some of the variance of who develops PDR. In a cross-sectional study of people with ≥50 years of type 1 diabetes seen at the Joslin Clinic, 43% remained free of PDR (127). In this group, blood glucose control was not related to the incidence of PDR. Subjects with high plasma carboxymethyl-lysine and pentosidine, two markers of advanced glycation endproducts (AGEs), were more likely to develop PDR, suggesting a possible role of AGEs in the development of PDR.

After 4 years of additional follow-up of the DCCT cohort, the study was stopped. Although A1c levels converged in the intensive and conventional groups, the protective effect of decreased incidence and progression of diabetic retinopathy by intensive glycemic control earlier was maintained in the intensive group (121,128,129). This phenomenon has been labeled "metabolic memory" and has also been found in persons with type 2 diabetes in the UKPDS (130).

The UKPDS was a randomized controlled clinical trial involving 3,867 patients newly diagnosed with type 2 diabetes (122,123,131). After 12 years of follow-up, the study showed a 21% reduction in the rate of progression of diabetic retinopathy and a 29% reduction in the need for laser photocoagulation in the intensive versus the conventional glycemic treatment group, although no difference in vision outcomes was observed between conventional and intensive treatments. Economic analyses of the clinical trial data suggested that intensive glucose control increased treatment costs but substantially reduced complication costs and increased the time free of such complications (131).

The development of new treatment modalities for achieving glycemic control permitted evaluation of near normalization of glycemic level on the incidence of CVD, as well as on diabetic retinopathy. In the Veterans Affairs Diabetes Trial (VADT), 1,791 military veterans with an average age of 60 years and an average duration of 11 years of type 2 diabetes were randomly assigned to receive either intensive or standard blood glucose control. The aim in the intensive therapy group was to achieve an absolute reduction of 1.5 percentage points in A1c compared with the standard therapy group. After a follow-up of 7.5 years (median 5.6 years) and despite reaching their glycemic goal (median A1c at 6 months: 6.9% [52 mmol/mol] in the intensive therapy group and 8.4% [68 mmol/mol] in the standard therapy group), no statistically significant differences were observed in any of the retinopathy outcomes between the two treatment groups (incidence of diabetic retinopathy 42% vs. 49%, p=0.27; progression of retinopathy by two or more steps on the ETDRS severity scale 17% vs. 22%, p=0.07; progression to PDR 4% vs. 5%, p=0.27) or in progression to CSME (3%

vs. 5%, p=0.31) in the intensive versus standard treatment groups, respectively (132,133).

In the Action to Control Cardiovascular Risk in Diabetes (ACCORD), intensive treatment (targeted A1c <6.0% [<42 mmol/mol]) versus standard treatment (targeted A1c 7.0%–7.9% [53–63 mmol/mol]) was examined to determine effects on the risk of morbidity and mortality from CVD (primary endpoint). The study also examined the effect of intensive treatment on the incidence of microvascular events, such as the incidence of photocoagulation treatment for diabetic retinopathy and incidence of microalbuminuria and macroalbuminuria over a 5-year period (secondary endpoints). In the entire study population, the mean age was 60 years, with an average duration of 10 years of type 2 diabetes (134). In the eye substudy, using the grading of fundus photographs to assess intensive glycemic control, a 33% reduction in the relative risk of progression of diabetic retinopathy from 7.3% with intensive glycemic therapy versus 10.4% with standard therapy (adjusted OR 0.67, 95% CI 0.51–0.87, p=0.003) in a relatively short period (4 years) was reported (135). The ACCORD was stopped early because of higher mortality in those in the intensive treatment group than in the standard treatment group. A third clinical trial, the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) of persons with type 2 diabetes, showed no statistically significant effect of glycemic control on retinopathy outcomes (136).

The results of these clinical trials show that intensive therapy for controlling glycemia should be the primary public health care strategy aimed at reducing the risk of visual loss from diabetic retinopathy in persons with poorly controlled diabetes. The data from the DCCT and UKPDS provide further support for the American Diabetes Association guidelines of a target A1c <7.0% and suggest that this level of glycemic control, when achieved early after diagnosis of diabetes, may have long-term benefit in terms of reducing the incidence and progression of diabetic retinopathy (137). However, although there has been improvement in A1c levels since the completion of these trials, data from the NHANES (138,139,140) and the WESDR (87,141) show that few persons with diabetes actually reach this targeted level of glycemic control. The data from the ACCORD indicate that lowering the A1c to <6% protected against retinopathy, but achieving such levels with the current technology in patients with longstanding type 2 diabetes who have or who are at risk of CVD may be hazardous (142,143). "In these persons, negative metabolic memory" may result from chronic exposure to hyperglycemia, reducing the possible efficacy of good glycemic control (144).

When taken together, the results from the UKPDS, VADT, ACCORD, and ADVANCE suggest the need for early identification of type 2 diabetes and control of hyperglycemia. The decision to employ intensive glucose management in patients with longer-term type 2 diabetes is dependent on the duration of diabetes, preexisting macrovascular disease, and hypoglycemic unawareness, as well as on significant comorbidities, and A1c goals should account for these factors and be individualized for each patient (145).

Age at Diagnosis

While adjusting for A1c levels, age at diagnosis was not related to the incidence or progression of diabetic retinopathy in either of the diabetes groups followed in the WESDR (95,97).

Puberty

Diabetic retinopathy is infrequent prior to age 13 years, irrespective of the duration of type 1 diabetes, and increases thereafter (111). In the WESDR, the 4-year incidence of diabetic retinopathy rose with age in children who were age 10–12 years at baseline (95). Four-year rates of progression of diabetic retinopathy in persons with type 1 diabetes continued to rise steadily with age until age 20 years, after which there was a gradual decline. No child age <13 years at baseline in the WESDR was found to have PDR at the 4-year follow-up. These findings form the rationale for guidelines for not screening for diabetic retinopathy in children with type 1 diabetes prior to puberty (114).

Menarchal status, a crude marker of puberty, is related to the prevalence and severity of diabetic retinopathy (146). In the WESDR, independent of duration of type 1 diabetes and other risk factors, those who were postmenarchal were three times as likely to have diabetic retinopathy as those who were premenarchal. The incidence of diabetic retinopathy has been shown to be higher after puberty than before, independent of duration or glycemic control of type 1 diabetes (147,148,149). Changes that occur after puberty (e.g., increases in insulin-like growth factor 1, growth hormone, sex hormones, and blood pressure), as well as poorer glycemic control (due to increased insulin resistance, poorer compliance, and/or inadequate insulin dosage), may explain the higher risk of developing diabetic retinopathy after puberty.

Early age at menarche has been linked to elevated risk of type 2 diabetes (150,151), and early menarche is associated with unfavorable metabolic traits, such as increased body mass index (BMI) and increased (log) insulin (152), but only limited information is available on the prevalence or incidence of retinopathy in women associated with early-onset type 2 diabetes or with the adverse phenotypes related to puberty status.

Blood Pressure

High blood pressure has been thought to increase risk of the incidence and progression of diabetic retinopathy. In the WESDR, blood pressure was a significant predictor of the incidence of diabetic retinopathy in persons with type 1 diabetes (100). While adjusting for other risk factors, such as retinopathy severity, A1c, and duration of diabetes at baseline, higher blood pressure was significantly associated with incidence and progression of diabetic retinopathy in those with type 1 diabetes. However, in the WESDR, neither systolic nor diastolic blood pressures was found to be related to the 10-year

incidence and progression of retinopathy in those with type 2 diabetes (153). The UKPDS reported that incidence of diabetic retinopathy was associated with systolic blood pressure in persons with type 2 diabetes. In the WESDR, a 10 mmHg rise in diastolic blood pressure was associated with a 330% increased 4-year risk of macular edema in those with type 1 diabetes and a 210% increased risk in those with type 2 diabetes (154).

Some randomized clinical trials have examined whether control of blood pressure reduced the risk of the incidence and progression of diabetic retinopathy. The UKPDS sought to determine whether lowering blood pressure was beneficial in reducing macrovascular and microvascular complications associated with newly diagnosed type 2 diabetes (155). One thousand forty-eight patients with hypertension (mean blood pressure 160/94 mmHg) were randomized to a regimen of intensive control of blood pressure with either captopril (an angiotensin-converting enzyme inhibitor) or atenolol (a beta blocker) and another 390 patients to less intensive control of their blood pressure. The aim in the group randomized to intensive control of blood pressure (by the standards at the beginning of the clinical trial) was to achieve blood pressure values <150/<85 mmHg. The aim in the group randomized to less intensive control was to achieve blood pressure values <180/<105 mmHg. The UKPDS showed that blood pressure control resulted in a 35% reduction in retinal photocoagulation compared to conventional control, presumably due to a lower incidence of macular edema. Furthermore, for each 10 mmHg decrease in mean systolic blood pressure, there was a 13% reduction in microvascular complications. No evidence was found of a threshold in lowering blood pressure for any diabetic retinopathy endpoint (156). After 7.5 years of follow-up, a 34% reduction in the rate of progression of diabetic retinopathy and a 47% reduction in doubling of the visual angle were observed. Atenolol and captopril were equally effective in reducing the risk of developing microvascular complications, suggesting that blood pressure reduction itself was more important than the type of medication used to reduce it. The effects of blood pressure control were independent of those of glycemic control. These findings support the recommendations for blood pressure control in patients with type 2 diabetes as a means of preventing vision loss from diabetic retinopathy.

The ACCORD trial was formulated to test whether a therapeutic strategy that aimed for systolic blood pressure of <120 mmHg would reduce CVD events compared to a strategy that yielded a systolic blood pressure of <140 mmHg in persons with type 2 diabetes in the context of good glycemic control (135). The ACCORD Eye study involved 1,263 participants who were involved in the ACCORD Blood Pressure study and had both baseline and year 4 follow-up data available for analyses. After 1 year, the baseline median systolic blood pressure decreased significantly (from 133 to 117 mmHg) in the group receiving intensive blood pressure therapy compared to the group receiving standard blood pressure therapy. No statistically significant difference in the progression of diabetic retinopathy was found between the groups (10% in the group undergoing intensive blood pressure control compared to 9% in the group undergoing standard blood pressure control, adjusted OR 1.23, 95% CI 0.84–1.79, p=0.29) (135). The rates of moderate vision loss were also similar between the two treatment arms (28% and 25%) in the intensive therapy group and the standard therapy group, respectively (adjusted HR 1.17, 95% CI 0.96–1.42, p=0.12).

The ADVANCE study also found no beneficial effect of intensive blood pressure control on progression of diabetic retinopathy (157). These findings from the ACCORD, ADVANCE, and UKPDS suggest that the benefit to diabetic retinopathy of treating blood pressure is likely limited to those with type 2 diabetes with levels that would be considered high and that there is no obvious effect of lowering blood pressure that is in the normal range or in those with only slightly elevated blood pressure in persons with type 2 diabetes. Because of differences in design, similar conclusions cannot be drawn from the randomized controlled clinical trials in persons with type 1 diabetes.

Some randomized controlled clinical trials have examined whether specific antihypertensive agents have a protective effect in preventing the progression of diabetic retinopathy independent of its effect on blood pressure (158,159,160,161,162,163). The Epidemiology and Prevention of Diabetes Controlled Trial of Lisinopril in Insulin-Dependent Diabetes Mellitus (EUCLID) study examined whether lisinopril, an angiotensin-converting enzyme inhibitor, reduced the incidence and progression of diabetic retinopathy in a group of normotensive patients with type 1 diabetes, independent of blood pressure level (158). A statistically significant 50% reduction in the progression of diabetic retinopathy was observed in those taking lisinopril, which remained after adjustment for glycemic control. Progression to PDR was also reduced, although the relation was not statistically significant. No significant interaction with blood glucose control was noted. These findings suggest that angiotensin-converting enzyme inhibitors might have a beneficial effect independent of lowering blood pressure (159).

The DIabetic REtinopathy Candesartan Trials (DIRECT) consisted of three randomized double-masked, parallel, placebo-controlled studies that aimed to determine the impact of treatment with candesartan, an angiotensin II type 1 receptor blocker, on the incidence and progression of diabetic retinopathy over a 4-year period (160,161,164). The DIRECT-Prevent 1 involved prevention of incident diabetic retinopathy, while the DIRECT-Protect 1 involved protection against progression of diabetic retinopathy in normoalbuminuric normotensive individuals with type 1 diabetes. The third trial, the DIRECT-Protect 2, aimed to show whether candesartan protected against progression of diabetic retinopathy in persons with type 2 diabetes who were normoalbuminuric and either normotensive or only mildly hypertensive (162,164). In the DIRECT-Prevent 1, candesartan had

a borderline effect (p=0.0508), reducing the incidence of diabetic retinopathy by two or more steps on the ETDRS severity scale by 18%. In post-hoc analyses, candesartan reduced the incidence of diabetic retinopathy by three or more steps by 35% (HR 0.65, 95% CI 0.40–0.87) in the DIRECT-Prevent 1. In the DIRECT-Protect 1 and 2, candesartan had no statistically significant effect on the progression of diabetic retinopathy in persons with minimal to moderate NPDR at baseline. Thus, the DIRECT did not achieve the prespecified primary endpoint in any of the three trials.

The ADVANCE study aimed to show whether lowering of blood pressure via a combination of perindopril and indapamide provided additional benefit beyond intensive glycemic control in preventing macrovascular and microvascular complications of diabetes (157). Although mean systolic and diastolic blood pressure reduction by 5.6 mmHg and 2.2 mmHg, respectively, was achieved, there was no reduction in the 4-year incidence or progression of diabetic retinopathy (5.2% in both treatment and placebo groups).

The Renin-Angiotensin System Study (RASS) was a multicenter controlled trial involving normotensive patients with type 1 diabetes and normoalbuminuria who were randomly assigned to receive losartan, enalapril, or placebo and followed for 5 years (163). The RASS showed that compared with placebo, the odds of diabetic retinopathy progression by two or more steps was reduced by 65% with enalapril (OR 0.35, 95% CI 0.14–0.85) and by 70% with losartan (OR 0.30, 95% CI 0.12–0.73), independent of changes in blood pressure.

These clinical trial data show a protective effect on incidence of diabetic retinopathy by angiotensin inhibitors or receptor blockers in normotensive, normoalbuminuric persons with no retinopathy and an inconsistent effect on progression in those with early to moderate NPDR. It is not known why the RASS, DIRECT, and ADVANCE did not consistently show a beneficial effect of specific angiotensin-converting enzyme treatment on diabetic retinopathy outcomes.

Proteinuria and Diabetic Nephropathy

Diabetic nephropathy and diabetic retinopathy have been consistently shown to be associated in epidemiologic studies (59,63,68,70,85,98,111,112,165,166). Abnormalities in rheological, platelet, and lipid metabolism found in persons with diabetic nephropathy have been hypothesized to have a role in the pathogenesis of diabetic retinopathy. Persons with type 1 diabetes in the WESDR with gross proteinuria at baseline had approximately twice the risk of PDR developing over 4 years compared to those without (166). After adjusting for other risk factors, the relationship was attenuated and of borderline significance. For those in the WESDR with type 2 diabetes taking insulin, while adjusting for risk factors, the relative risk was 2, and for those not taking insulin, it was 1.

In the Pittsburgh Epidemiology of Diabetes Complications study, while adjusting for other risk factors, those with type 1 diabetes who had microalbuminuria or overt nephropathy at entry in the study were more likely to develop PDR over a 2-year follow-up than those without microalbuminuria (167). However, in that study, diabetic nephropathy at baseline was not associated with diabetic retinopathy progression. Based on these findings, gross proteinuria appears to behave as a risk indicator for PDR in persons with type 1 diabetes. These findings suggest that patients with type 1 diabetes and signs of nephropathy may benefit from being more closely followed with ophthalmologic examinations with pupil dilation. However, no clinical trial data have shown that interventions that prevent or slow diabetic nephropathy will do the same for the progression of diabetic retinopathy.

Serum Lipids and Lipid Lowering

Hard exudate, a lipoprotein deposit in the retina, is often associated with macular edema and CSME resulting in visual impairment (23). Elevated plasma triglycerides and lipids in some studies have been shown to be related to the presence of retinal hard exudates (168). Serum total cholesterol has been shown to be directly associated with the prevalence and incidence of retinal hard exudates in persons with type 1 diabetes and type 2 diabetes (169). Having the epsilon4 allele polymorphism of the apolipoprotein E gene was associated with a higher prevalence of severe retinal hard exudates in Mexican persons with type 2 diabetes (170).

Most data showing the efficacy of statins on macular edema are from small pilot studies (135,171,172,173). One of the few larger trials to examine this relationship is the ACCORD Lipid study. In the trial, persons with type 2 diabetes were randomized to be treated with either fenofibrate or placebo. The protocol included the use of open-label background simvastatin therapy administered in accordance with current guidelines (20–40 mg/day, depending on observed low-density lipoprotein (LDL) cholesterol values and whether the participant had had a clinical cardiovascular event). The rate of progression of diabetic retinopathy at 4 years was 6.5% in the fenofibrate treatment group compared to 10.2% in the placebo group (adjusted OR 0.60, 95% CI 0.42–0.87, p=0.006). These findings are consistent with those of the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study, a randomized trial of monotherapy with fenofibrate, which showed a significant reduction in the need for laser therapy for either macular edema or PDR in the fenofibrate treatment group compared with the placebo group (3.4% vs. 4.9%, p<0.001) (174). These findings suggest a beneficial effect of the use of fenofibrate therapy in diabetic patients with elevated triglycerides at risk of progression of diabetic retinopathy and macular edema.

Body Mass Index

Studies have shown BMI to have an inconsistent association with diabetic retinopathy (48,85,111,175,176,177, 178,179). Obesity, as defined by BMI, is hypothesized to have a deleterious effect on diabetic retinopathy by increasing

levels of inflammation (180). While adjusting for other factors, greater BMI at baseline was associated with progression of diabetic retinopathy (OR per 4 kg/m^2 1.16, 95% CI 1.07–1.26, p<0.001) and progression to PDR (OR 1.21, 95% CI 1.07–1.36, p=0.002) but not incidence of macular edema over 25 years of follow-up in persons with type 1 diabetes in the WESDR. In the same study, BMI was inversely related to the presence or severity of diabetic retinopathy over 10 years of follow-up only in persons with type 2 diabetes not using insulin (177). Persons with type 2 diabetes who were underweight at baseline (BMI <20 kg/m^2 for both sexes) were three times as likely to develop diabetic retinopathy as those whose were of normal weight (BMI 20–27.7 kg/m^2 for men; BMI 20–27.2 kg/m^2 for women). This finding may be due to those with type 2 diabetes who were underweight having more severe diabetes. Persons with type 2 diabetes who were obese at baseline (BMI >31.0 kg/m^2 for men; BMI >32.1 kg/m^2 for women) were 35% more likely to have progression of diabetic retinopathy and 41% more likely to develop PDR than persons who were of normal weight at baseline; however, these associations did not reach statistical significance.

Metabolic Syndrome

The metabolic syndrome, defined by conditions described above (e.g., obesity, dyslipidemia, and high blood pressure) was cross-sectionally associated with retinopathy (OR 1.68, 95% CI 1.44–1.96) while adjusting for age, sex, race, education, smoking status, and alcohol consumption. Retinopathy in that study was shown to be related to higher blood pressure, fasting glucose, higher triglyceride levels, and lower high-density lipoprotein (HDL) cholesterol in people without hypertension or diabetes (181). A cross-sectional association of the metabolic syndrome with retinopathy was also found in the NHANES III but the relationship was not independent of diabetes status (182). There are few population-based data regarding the relationship of the metabolic syndrome to the incidence of retinopathy (183).

Age

Persons in the WESDR with type 2 diabetes who were taking insulin were less likely to develop or have any progression of diabetic retinopathy over 4 years if they were younger. However, older persons with type 2 diabetes (age ≥75 years) had decreased progression to PDR over a 10-year period compared to younger persons (age 30–44 years) at baseline (97). Improvement of diabetic retinopathy (regression) tended to increase with age (97). Few persons with type 2 diabetes age ≥75 years developed PDR over the 10 years of follow-up in the WESDR. These findings are consistent with those of other population-based studies (26,48,83) and reflect less severe disease in people who develop type 2 diabetes later in life. They might also be a result of selective survival (i.e., older persons who develop severe retinopathy are more likely to die and not participate at follow-up examinations).

Sex

After adjusting for other factors, a consistent difference in the prevalence, incidence, and progression of diabetic retinopathy has not been observed between men and women with type 1 diabetes or type 2 diabetes (95,97,98,100,111,112).

Hormonal and Reproductive Exposures in Women

Sex hormones have been hypothesized to heighten the risk of developing retinopathy after puberty, consistent with the higher incidence of diabetic retinopathy following menarche described earlier (146). However, increased estrogen levels do not seem to explain this finding. Neither use of oral contraceptives (which contain estrogens, as well as progestins) nor use of hormone replacement therapy appears to increase the risk of retinopathy (184,185).

Pregnancy, a condition associated with high levels of estrogens, is associated with accelerated progression of retinopathy. Klein *et al.* (186) followed two groups of women of similar age and duration of type 1 diabetes, one pregnant and the other not pregnant, for a time interval roughly equal to the length of the pregnancy; the pregnant women were more likely than the nonpregnant women to develop retinopathy if they had not previously had it, and for those who had already developed retinopathy, it was more likely to increase in severity. This association remained even while adjusting for glycemia and blood pressure levels. This may occur in women with type 2 diabetes, as well as women with type 1 diabetes (187). Others have reported similar findings (188,189). Additionally, progression of diabetic retinopathy was found to be more likely to occur in diabetic women with preeclampsia than in those without (190). Although glycemia and blood pressure levels are important factors related to progression of retinopathy in pregnant women (191), as well as nonpregnant women, pregnancy in all likelihood accelerates the process. Progression of retinopathy in pregnancy was found by other investigators to be related to prior duration of diabetes (192,193). Though not a novel finding, as duration of diabetes is a risk factor for progression of diabetic retinopathy regardless of pregnancy status, it may be helpful to keep in mind when developing follow-up plans for eye care during pregnancy.

Women with moderate to severe NPDR may consider laser treatment before becoming pregnant to protect against progression of diabetic retinopathy during pregnancy (194); however, no clinical trials have yet tested the efficacy of this approach. Diabetic macular edema that occurs during pregnancy is another potentially sight-threatening complication that may benefit from laser treatment, but it is not known how many women might experience remission of macular edema after giving birth (195).

Limited data point to the possibility that insulin-like growth factor 1 levels in serum are associated with progression of diabetic retinopathy during pregnancy (196,197). In a study of the vasoconstrictor endothelin-1, which is elevated in persons with hypertension and diabetes, diabetic women had higher levels of endothelin-1 in pregnancy than nondiabetic women in the same trimester, but it was

not related to severity of diabetic retinopathy (198). However, due to its small sample size, this study cannot be considered conclusive.

The number of past pregnancies was unrelated to the severity of diabetic retinopathy in women with type 1 diabetes in the WESDR (185). Another study in Finland similarly found that second and subsequent pregnancies did not affect severity of retinopathy (199). These data may be interpreted to suggest that pregnancy imparts a transient increased risk for incidence or progression of retinopathy. However, since more severe or more complicated diabetes can result in decreased fertility, it is possible that women with diabetes who sustain multiple pregnancies are more robust or have lower levels of risk factors for progression of retinopathy.

Smoking

Smoking causes tissue hypoxia by increasing blood carbon monoxide levels; it also increases platelet aggregation and adhesiveness, two mechanisms hypothesized to be involved in the pathogenesis of diabetic retinopathy (200,201). However, data from the WESDR and from most other epidemiologic studies have shown no relationship between smoking and the incidence or progression of diabetic retinopathy (48,63,70,85,202,203,204,205). In the WESDR, the amount of cigarettes smoked at baseline was univariately associated with the 25-year cumulative incidence of macular edema (OR for ≥15 pack-years vs. none 1.67, 95% CI 1.03–2.69, p=0.04). However, when adjusting for other factors, this association was no longer statistically significant.

Regardless of the absence of an association with diabetic retinopathy, persons with diabetes should be counseled not to smoke because of an increased risk of developing cancer, as well as cardiovascular and respiratory diseases. In the WESDR, after adjusting for other risk factors, persons with type 1 diabetes who smoked were nearly 2.5 times more likely and persons with type 2 diabetes who smoked were approximately 1.5 times more likely to die sooner than persons who did not smoke (43).

Alcohol Consumption

In the WESDR, alcohol consumption was associated with a lower prevalence of PDR in persons with type 1 diabetes (206). However, no relationship was found between alcohol consumption and the 6-year incidence of diabetic retinopathy, its progression by two or more steps, or its progression to PDR or macular edema in persons with type 1 or type 2 diabetes (207). Data from other studies also did not show a consistent relation of alcohol consumption to the incidence and progression of diabetic retinopathy (69,74,208,209,210,211). The lack of a consistent positive relationship of alcohol consumption with the incidence and progression of diabetic retinopathy is contrary to expectations, as moderate alcohol consumption improves glycemic control, reduces inflammation, and decreases platelet aggregation and adhesiveness. All of these mechanisms are hypothesized to exert possible protective effects in reducing the incidence and progression of diabetic retinopathy (212,213,214). While adjusting for other risk factors, reduced mortality from CVD was found in persons with type 2 diabetes in the WESDR who consumed an average of one serving of alcohol per day (215). If there are no contraindications, modest alcohol consumption (e.g., one glass of wine per day) may have a protective effect against CVD in persons with diabetes.

Physical Activity

Only weak evidence has been found showing a benefit of physical activity in reducing the incidence and progression of diabetic retinopathy in type 1 or type 2 diabetes (178,216,217,218,219). Physical activity's beneficial effect on glycemic control would be expected to result in a lower incidence of diabetic retinopathy (219). No relationship was observed between participating in team sports in high school or college and a history of laser treatment or blindness in persons with type 1 diabetes (178); physical activity in youth did not relate to complications of diabetes (217,218). In the WESDR, participation in team sports by women diagnosed with type 1 diabetes before age 14 years was inversely associated with the incidence of PDR (216). Physical activity or leisure time energy expenditure was not associated with the presence or severity of diabetic retinopathy in men. Additionally, physical activity was not associated with either an increased or decreased risk of progression of diabetic retinopathy or the development of PDR over a 6-year interval in persons with type 1 diabetes (220). However, in the Atherosclerosis Risk in Communities (ARIC) Study, while adjusting for other factors, persons with type 2 diabetes and a history of work-related physical activity above the median level were less likely to have diabetic retinopathy (OR 0.69, 95% CI 0.51–0.93) compared to those below the median (221).

Race/Ethnicity

A growing number of epidemiologic studies have compared the prevalence of diabetic retinopathy among different racial/ethnic groups in the United States. Data from the New Jersey 725 study cohort showed that the prevalence of any retinopathy and severe diabetic retinopathy in African Americans was similar to the prevalence of diabetic retinopathy in whites with type 1 diabetes in the WESDR (Table 21.20) (80,81,222). At the 6-year follow-up of the same African American cohort, 56% showed progression of diabetic retinopathy, 15% showed progression to PDR, and 16% developed macular edema (104). This was similar to incidence and progression found in whites in the WESDR (95,96).

Retinopathy has been consistently shown to be more frequent in African Americans than in whites with type 2 diabetes in the NHANES 1988–1994 and 2005–2008 (Table 21.12) (47,62), the ARIC study (223), the Cardiovascular Health Study (224), the Multi-Ethnic Study of Atherosclerosis (MESA) (225), and by the Eye Diseases Prevalence Research Group (46). In the NHANES 1988–1994, this difference between the racial/ethnic groups was shown to be due, in part, to poorer

glycemic control (A1c >8.3% [>67 mmol/mol], 37% vs. 30%), higher systolic blood pressure (>142 mmHg, 42% vs. 32%), and longer duration of diabetes (>14 years, 29% vs. 23%) in blacks than whites (62). When these factors were entered into multivariate models, the prevalence of diabetic retinopathy was no longer statistically significantly different between blacks and whites. Similarly, the higher prevalence of diabetic retinopathy in the ARIC study (28% vs. 17%) and in the MESA (37% vs. 25%) in blacks compared to whites was no longer statistically significant while adjusting for differences in blood pressure and glycemic control between the racial/ethnic groups (223,225). These data provide evidence that efforts to better control blood glucose and blood pressure in diabetic African Americans might be beneficial for narrowing the differences in prevalence of diabetic retinopathy in blacks and whites.

Mexican Americans have been shown to have more severe diabetic retinopathy and higher prevalence of diabetic retinopathy than non-Hispanic whites (46,47,58,59,62,86,225,226). In the NHANES 1988–1994 and 2005–2008, the MESA, Proyecto Vision Evaluation and Research (VER), and the LALES, diabetic retinopathy was more prevalent in Mexican Americans with type 2 diabetes compared to non-Hispanic whites age ≥40 years (62,86,225,226). In the NHANES 1988–1994, the higher prevalence of diabetic retinopathy in Mexican Americans (OR 2.15, 95% CI 1.15–4.04) compared to non-Hispanic whites remained statistically significant while adjusting for A1c and blood

TABLE 21.20. Estimated Prevalence of Diabetic Retinopathy in Persons With Type 1 Diabetes, by Age, Sex, and Race, WESDR and New Jersey 725 Study, 2004

SEX AND AGE (YEARS)	PREVALENCE PER 100 INDIVIDUALS (95% CI)	
	White	Black
Any retinopathy*		
Women		
18–39	79.6 (74.7–83.8)	71.4 (65.8–76.4)
40–49	95.8 (84.8–99.0)	94.8 (85.2–98.3)
≥50	98.9 (84.3–99.9)	95.8 (57.5–99.7)
Men		
18–39	75.9 (70.7–80.5)	67.5 (60.7–73.6)
40–49	96.0 (85.4–99.0)	97.1 (82.3–99.6)
≥50	93.9 (82.7–98.0)	92.3 (60.9–98.9)
Vision-threatening diabetic retinopathy†		
Women		
18–39	22.0 (17.7–27.0)	21.0 (16.6–26.2)
40–49	50.0 (36.2–63.8)	50.0 (37.4–62.6)
≥50	52.3 (37.7–66.4)	95.8 (57.5–99.7)
Men		
18–39	26.8 (22.0–32.1)	24.5 (19.0–30.9)
40–49	74.0 (60.2–84.3)	65.7 (48.8–79.4)
≥50	50.0 (36.2–63.8)	53.8 (28.2–77.6)

CI, confidence interval; WESDR, Wisconsin Epidemiologic Study of Diabetic Retinopathy.
* Any retinopathy is defined as a retinopathy severity level of 14 or greater, clinically significant macular edema, or both.
† Vision-threatening diabetic retinopathy is defined as a retinopathy severity level of 50 or greater, clinically significant macular edema, or both.
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TABLE 21.21. Estimated Annual Incidence of Diabetic Retinopathy in Population-Based Studies

STUDY POPULATION AND LOCATION	YEAR OF STUDY		AGE RANGE (Years)	NUMBER OF PHOTOGRAPHIC FIELDS GRADED	CRUDE ANNUAL INCIDENCE OF DR*		CRUDE ANNUAL INCIDENCE OF DR BY DIABETES DURATION (YEARS) PERCENT (95% CI)*			
	Baseline	Follow-Up			N	Percent (95% CI)	<5†	5–9	10–14	≥15
Latinos										
Los Angeles, U.S.	2000–2003	2004–2007	≥40	7	421	7.1 (4.6–9.6)	5.6 (2.9–8.3)	7.7 (1.4–14.1)	12.5 (2.9–22.1)	10.5 (0.0–21.3)
San Luis Valley, U.S.	1984–1988	1988–1992	20–74	3	116	5.2 (1.2–9.2)	Did not stratify results by duration of diabetes			
African ancestry										
Barbados	1988–1992	1992–1997	40–84	2	306	7.5 (5.0–10.0)	5.7 (2.5–8.9)	12.7 (4.3–21.1)	10.0 (0.0–21.8)	7.2 (0.0–18.2)
Non-Hispanic white										
Wisconsin, U.S.	1980–1982	1984–1986	≥30	7	320	8.6 (5.5–11.7)	7.8 (3.5–12.0)	8.1 (2.7–13.4)	9.5 (0.0–20.1)	12.9 (2.1–23.6)
San Luis Valley, U.S.	1984–1988	1988–1992	20–74	3	53	6.6 (0.0–13.2)	Did not stratify results by duration of diabetes			
Blue Mountains, Australia	1992–1994	1997–1999	≥49	5	90	4.4 (0.2–8.7)	Did not stratify results by duration of diabetes			
Melbourne, Australia	1992–1994	1997–1999	≥40	2	73	2.2 (0.0–5.6)	Did not stratify results by duration of diabetes			

CI, confidence interval; DR, diabetic retinopathy; N, number at risk for incidence of DR with definite diabetes at baseline.
* Incidence of DR defined as absence of retinopathy in both eyes for persons with definite diabetes at baseline and presence of any retinopathy in either eye at follow-up. Crude annual incidence estimated from 4-year incidence for studies in Los Angeles, San Luis Valley, Barbados, and Wisconsin, and 5-year incidence for studies in Melbourne and Blue Mountains.
† Includes persons who were newly diagnosed with diabetes at the time of baseline examination.
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pressure level (46), suggesting other factors may be responsible for these differences. In the NHANES 2005–2008, vision-threatening retinopathy was approximately 3.5 (95% CI 1.05–12.56) times as prevalent in Mexican Americans compared to non-Hispanic whites (47). Beyond levels of glycemic and blood pressure control, differences in prevalence and severity of diabetic retinopathy among different racial/ethnic groups might be a result of variations in how long it takes to diagnose type 2 diabetes in specific groups after its onset and how type 2 diabetes was defined. These differences also may be due to the degree of gene sharing with Native Americans, a group with a high prevalence of diabetic retinopathy (see below).

Only the LALES has provided data on the incidence and progression of diabetic retinopathy in Mexican Americans with type 2 diabetes (106). The 4-year incidences of diabetic retinopathy and CSME were 34% and 7%, respectively, and progression of diabetic retinopathy by two or more steps and progression from NPDR to PDR were 39% and 5%, respectively. While the annualized incidence over a 4-year period in the LALES (7%) is comparable to that found in the WESDR (9%), it is higher than the annualized incidence in most other contemporaneous studies of whites with type 2 diabetes, including two in Australia (Table 21.21) (106).

In studies conducted in the 1970s, Native Americans were reported to have higher prevalence of severe diabetic retinopathy for a given duration of type 2 diabetes compared to whites (49,55). However, a study in Pima Indians in Arizona reported lower cumulative incidence and progression of diabetic retinopathy (17% and 18%, respectively) than in whites with type 2 diabetes (227).

Few data are available on the prevalence and none on the incidence of diabetic retinopathy in Asian Americans and other racial/ethnic groups (52,56,57,225). In the MESA, the prevalences of diabetic retinopathy in Chinese Americans and whites were similar (26% vs. 25%), but prevalences of CSME and PDR were higher in Chinese Americans (3% and 5%, respectively) than in whites (2% and 2.6%, respectively) with type 2 diabetes (225). More data on the prevalence and incidence of retinopathy in Chinese and other Asian American groups are needed.

Genetic Factors

In identical twins, the time of appearance of diabetic retinopathy and its severity are more likely to be similar than in dizygotic twins (228). This suggests a possible role of genetic factors in the development of diabetic retinopathy. Familial clustering studies also suggest that genetic factors may contribute to the susceptibility to diabetic retinopathy (229,230). The polygenic heritability for PDR was approximately 25% in the Family Investigation of Nephropathy and Diabetes-Eye study sample (231). In a cohort of Pima Indians with type 2 diabetes in Starr County, Texas, the heritability was 18% (232). However, few single nucleotide polymorphisms have been shown to be strongly or consistently associated with diabetic retinopathy. This may be due, in part, to relationships of glycemia and blood pressure to retinopathy, which are controllable by intensive treatment, resulting in a stronger effect than genetic factors on whether diabetic retinopathy develops and progresses. Another reason may be that the earliest stages of diabetic retinopathy, manifest by the presence of retinal microaneurysms and blot hemorrhages, are not specific to glycemia. They may also be manifestations of other conditions, such as severe hypertension. Thus, their presence in the absence of signs of more severe retinopathy (e.g., intra-retinal microvascular abnormalities, retinal venous beading) and proliferative disease may also contribute to weaker, less consistent relationships of candidate genes with early diabetic retinopathy compared to more severe diabetic retinopathy (233).

Associations of diabetic retinopathy with mitochondrial DNA mutations (234), polymorphisms of the aldose reductase gene (235,236), endothelial nitric oxide synthase gene (237), paraoxonase (an enzyme that prevents oxidation of LDL cholesterol) gene (238), TNF-beta NcoI gene (239), epsilon4 allele of apolipoprotein E gene (170), intercellular adhesion molecule-1 (240), alpha2beta1 integrin gene (involved with platelet function) (241), and cytokine vascular endothelial growth factor gene have been shown in some studies but have not been consistently replicated (242,243,244,245).

Socioeconomic Status

More education and higher income would be expected to be associated with lower incidence and progression of diabetic retinopathy secondary to better understanding and management of the disease and its complications and increased accessibility to better medical care, respectively. However, inconsistent relationships between socioeconomic status and retinopathy severity have been reported (36,85,86,104,246,247). Haffner *et al.* (246) did not find a relationship between socioeconomic status (measured using a combination of the Duncan Index, educational attainment, and income) and severe diabetic retinopathy in 343 Mexican Americans and 79 non-Hispanic whites with type 2 diabetes in San Antonio, Texas. West *et al.* (85) also did not observe a relationship between diabetic retinopathy severity and education level in a population of Oklahoma Indians with type 2 diabetes. However, in the Proyecto VER cohort of Mexican Americans with type 2 diabetes, low income, once adjusted for other factors, was cross-sectionally associated with PDR (OR 3.93, 95% CI 1.31–11.80) (86). In the New Jersey 725, low socioeconomic status was significantly associated with the 6-year incidence of macular edema but not incidence or progression of diabetic retinopathy. In that study, education, income, medical or eye care, and health insurance status at baseline were not significantly different between persons with and without macular edema at follow-up. Except for an association of lower 4-year incidence of PDR in women with type 1 diabetes age ≥25 years with more education, socioeconomic status (as measured by higher education level

and Duncan Socioeconomic Index score) was otherwise not associated with risk of developing PDR in the WESDR (36). The absence of a relationship of socioeconomic status and diabetic retinopathy severity in the WESDR and San Antonio studies may be related to the lack of an association of socioeconomic status to glycemic control in these cohorts.

COMORBIDITY AND MORTALITY

In the WESDR, the risk of developing macrovascular systemic complications (e.g., heart attack, stroke, lower limb amputation) and microvascular complications was higher in those with PDR compared to those with no or minimal diabetic retinopathy at baseline (Table 21.22) (248). In those with type 1 diabetes, while adjusting for age and sex, diabetic retinopathy severity was associated with all-cause and ischemic heart disease mortality. In persons with type 2 diabetes, diabetic retinopathy severity was associated with all-cause and ischemic heart disease mortality and stroke (44). While adjusting for systemic factors, the relations remained only for all-cause and stroke mortality in persons with type 2 diabetes. These findings suggest that severe diabetic retinopathy is an indicator for increased risk of death from ischemic heart disease and may identify individuals who should be under care for CVD. This association has been reported by others (249,250,251). The higher risk of CVD in persons with more severe diabetic retinopathy may be partially due to the association of severe retinopathy with CVD risk factors, such as hyperglycemia, hypertension, platelet aggregation, and diabetic nephropathy with chronic kidney disease.

Adults with type 1 diabetes with poor glycemic control have been shown to manifest a distinctive pattern of cognitive dysfunction characterized primarily by poor performance on tasks requiring psychomotor speed (252,253,254). Patients with diabetic retinopathy were more likely to manifest psychomotor slowing than patients without retinopathy (255,256,257). The relationship of diabetic retinopathy to cognitive dysfunction in persons with type 2 diabetes has not been consistently shown (258,259,260).

TABLE 21.22. Relative Risk for the Prevalence and 4-Year Incidence of Myocardial Infarction, Stroke, and Amputation of Lower Extremity Associated With Presence of Proliferative Diabetic Retinopathy, Corrected for Age, WESDR, 1980–1982 and 1984–1986

	RELATIVE RISK (95% CONFIDENCE INTERVAL)		
	Myocardial Infarction	Stroke	Amputation of Lower Extremity
Type 1 diabetes			
Prevalence	3.5 (1.5–7.9)	2.6 (0.7–9.7)	7.1 (2.6–19.7)
Incidence	4.5 (1.3–15.4)	1.6 (0.4–5.7)	6.0 (2.1–16.9)
Type 2 diabetes, taking insulin			
Prevalence	0.8 (0.4–1.4)	1.2 (0.6–2.4)	4.2 (2.3–7.9)
Incidence	1.2 (0.5–3.4)	2.9 (1.2–6.8)	3.4 (0.9–13.2)
Type 2 diabetes, not taking insulin			
Prevalence	0.3 (0–2.4)	2.9 (0.9–9.4)	5.2 (0.6–45.0)
Incidence	1.5 (0.2–12.5)	6.0 (1.1–32.6)	7.0 (0.8–64.4)

WESDR; Wisconsin Epidemiologic Study of Diabetic Retinopathy.

SOURCE: Reference 248, copyright © 1992 American Diabetes Association, reprinted with permission

NEW MEDICAL INTERVENTIONS FOR TREATMENT

Since the last edition of *Diabetes in America* was published, findings from randomized controlled clinical trials have provided evidence showing the efficacy of treatments in addition to hypoglycemic agents to prevent or retard progress of retinal complications of diabetes (135,158,163,174,261). Angiotensin-converting enzyme inhibitors targeting the renin-angiotensin system and the lowering of uncontrolled blood pressure have been shown in some studies (e.g., the RASS, EUCLID, and UKPDS) to reduce the risk of progression of diabetic retinopathy, as noted above (155,158,163). Fenofibrates have also been shown to reduce the incidence and progression of diabetic retinopathy, possibly through a reduction of triglycerides (174). However, randomized controlled clinical trials of inhibitors of aldose reductase, protein kinase C, and metalloproteinases have not shown efficacy in preventing the incidence and progression of diabetic retinopathy in persons with diabetes (262). Controlled clinical trials showing the efficacy of intravitreally administered vascular endothelial growth factor inhibitors and steroids in the treatment of PDR and diabetic macular edema are presented elsewhere (261).

PUBLIC HEALTH APPLICATIONS OF EPIDEMIOLOGIC DIABETIC RETINOPATHY DATA

In the past, many diabetic persons with severe diabetic retinopathy were not receiving optimal eye care, including dilated eye examinations. Based on these observations, guidelines for these examinations were developed and implemented (114,263,264). The guidelines specify that after the initial screening examination, "subsequent examinations for both type 1 diabetes and type 2 diabetes patients should be repeated annually by an ophthalmologist or optometrist who is knowledgeable and experienced in diagnosing the presence of diabetic retinopathy, and is aware of its management" (114).

Three studies (265,266,267) estimated the cost-effectiveness of strategies for detecting diabetic retinopathy. Data from these analyses suggest that screening for diabetic retinopathy and obtaining ophthalmologic care result in significant savings for persons with type 1 diabetes. One analysis (267) predicted an annual savings of an estimated $240.5 million and 138,390 person-years of sight for a 60% screening and treatment rate implementation level; if all patients were to receive appropriate eye care, the predicted savings would exceed $400 million and 230,000 person-years of sight in persons with type 1 diabetes. Another analysis (29) also found that targeting persons with type 1 diabetes and

those with type 2 diabetes taking insulin could achieve cost savings. Conversely, the incremental number of sight-years to be gained in those with type 2 diabetes not taking insulin, even by annual ophthalmologic examination with fundus photography, was reported to be small. Despite being an important cause of vision loss, macular edema was not included in the analysis.

New analyses of NHANES and NHIS data on eye examinations among persons with diabetes were conducted for *Diabetes in America*. In the NHANES 2005–2008, 92.7% and 98.8% of those age ≥40 years with diagnosed diabetes and PDR ascertained by grading of retinal fundus photographs self-reported having had their pupils dilated within 1 year and 2 years, respectively, of being examined (Table 21.23). Comparisons of race/ethnicity and severity of diabetic retinopathy related to the time since the pupils were self-reported to be dilated among people age ≥40 years with diagnosed diabetes are limited due to small sample size. In the NHIS 2008, in non-Hispanic white persons with self-reported retinopathy with vision loss, 79% of those with self-reported diabetes said they had seen an eye doctor in the last 12 months, and 82% had had their pupils dilated within the last year (Table 21.24). Compared with non-Hispanic whites, Hispanics with retinopathy with vision loss were less likely and non-Hispanic blacks with vision loss were more likely to have seen an eye doctor or have had their pupils dilated within the last 12 months.

Despite a strong effort to improve compliance with the American Diabetes Association guidelines, compliance remains poor due to specific physician and patient factors (268,269,270). In one study, 52% of primary care physicians reported that they performed in-office ophthalmoscopy, 90% of which was through undilated pupils, an approach shown in other studies to have limited sensitivity for detecting vision-threatening retinopathy (268). Of persons in the WESDR cohort who had not had a dilated eye examination in the previous year, 31% of those with type 1 diabetes and 35% of those with type 2 diabetes reported not being told by their primary care physicians that they needed one (269). Patient factors also explain some of the lack of adherence to guidelines for dilated eye examinations. In the WESDR, among those not having a dilated eye examination in the previous year, 79% and 71% of those with type 1 diabetes and type 2 diabetes, respectively, reported not having had one because they had no problems with their eyes, and 32% and 11% said they were too busy. These data suggest the importance of educating persons with diabetes about the asymptomatic nature of diabetic retinopathy and the benefits of a dilated eye examination. This has become an important priority of the National Eye Institute (National Eye Health Education Program) and other specialty organizations (271). Another barrier to seeing an eye doctor is cost. Moss *et al.* (269) found that 30% of persons with type 1 diabetes and 12% of those with type 2 diabetes said they could not afford an eye examination.

Reexamination of WESDR data by Batchelder and Barricks (272) led them to conclude that based on the "…remarkably low incidence of treatable conditions over 4 years for patients with retinopathy levels 21 or less and over 10 years for patients with no retinopathy at their baseline examination" that "these data do not suggest any difference in effectiveness for screening intervals of 1, 2, 3 or even 4 years for this group of low-risk patients." Others, also using models, have suggested in those with type 2 diabetes

TABLE 21.23. Age- and Sex-Standardized Percent Distribution of Time Since Pupils Were Last Dilated Among People Age ≥40 Years With Diagnosed Diabetes, by Retinopathy Status and Race/Ethnicity, U.S., 2005–2008

RACE/ETHNICITY AND RETINOPATHY STATUS	TIME SINCE PUPILS WERE LAST DILATED PERCENT (STANDARD ERROR)			
	<1 Year	1–<2 Years	≥2 Years	Never
Overall				
No retinopathy	61.1 (2.93)	15.0 (3.09)	19.1 (2.52)	4.8 (1.06)
Non-proliferative retinopathy	65.0 (3.50)	13.3 (3.14)	14.9 (2.70)	6.8 (2.72)[1]
Proliferative retinopathy	92.7 (3.32)	6.1 (2.94)[2]	[3]	[3]
Non-Hispanic white				
No retinopathy	60.7 (3.81)	16.0 (4.07)	20.5 (3.55)	2.8 (1.28)[2]
Non-proliferative retinopathy	60.3 (5.78)	14.8 (4.89)[1]	18.8 (5.48)	[3]
Proliferative retinopathy	[3]	[3]	[3]	[3]
Non-Hispanic black				
No retinopathy	66.6 (4.92)	15.6 (3.78)	12.7 (2.19)	5.1 (1.71)[1]
Non-proliferative retinopathy	65.7 (4.84)	12.9 (3.93)[1]	19.1 (4.38)	[3]
Proliferative retinopathy	92.5 (4.79)	[3]	[3]	[3]
All Hispanic				
No retinopathy	58.4 (4.07)	10.7 (2.58)	18.4 (3.67)	12.5 (2.66)
Non-proliferative retinopathy	62.1 (9.32)	7.3 (1.91)	5.8 (1.68)	24.8 (8.60)[1]
Proliferative retinopathy	77.5 (9.51)	[3]	[3]	[3]
Mexican American				
No retinopathy	49.7 (5.63)	12.9 (2.95)	24.9 (5.57)	12.5 (2.92)
Non-proliferative retinopathy	58.0 (6.70)	10.3 (3.70)[1]	10.6 (2.81)	21.1 (4.50)
Proliferative retinopathy	75.9 (18.47)	[3]	[3]	[3]

Time since pupils were last dilated and diabetes status are based on self-report. Retinopathy status is based on retinal imaging. Standardized to the National Health Interview Survey 2008 population with diabetes using age categories 40–64, 65–74, and ≥75 years.

[1] Relative standard error >30%–40%

[2] Relative standard error >40%–50%

[3] Relative standard error >50%; estimate is too unreliable to present.

SOURCE: National Health and Nutrition Examination Surveys 2005–2008

without retinopathy, examinations every 2 years rather than annually would be adequate to detect vision-threatening retinopathy (273). The National Committee for Quality Assurance Health Plan Employer Data and Information Set 1999 draft recommended examinations for retinopathy every other year for persons who meet the following criteria: no evidence of retinopathy in the previous year's eye examination, no insulin use, and A1c <8.0% (<64 mmol/mol) (274). However, the WESDR data showed that in persons with type 2 diabetes without retinopathy at baseline, 4 per 1,000 developed PDR and 10 per 1,000 persons developed CSME over a 4-year period (95,96,97).

In 2011, Rein *et al.* examined whether biennial eye evaluation or telemedicine screening are cost-effective alternatives to current recommendations for the estimated 10 million people age 30–84 years with diabetes with no or minimal diabetic retinopathy (275). They showed that "biennial eye evaluation was the most cost-effective treatment option when the ability to detect other eye conditions was included in the model" (Table 21.25). Telemedicine was most cost-effective when other eye conditions were not considered or when telemedicine was assumed to detect refractive error. The current annual eye evaluation recommendation was costly compared with either treatment alternative. Self-referral was most cost-effective "up to a willingness to pay of U.S. $37,600, with either biennial or annual evaluation most cost-effective at higher willingness to pay levels." They concluded that annual eye evaluations were costly and added little benefit compared with biennial eye examinations.

TABLE 21.24. Age- and Sex-Standardized Percent Who Have Seen an Eye Doctor in the Past 12 Months and Time Since Pupils Were Last Dilated Among Adults Age ≥40 Years With Diagnosed Diabetes, by Retinopathy Status and Race/Ethnicity, U.S., 2008

RACE/ETHNICITY AND RETINOPATHY STATUS	PERCENT (STANDARD ERROR)			
	Saw an Eye Doctor in the Past 12 Months	Time Since Pupils Last Dilated		
		< 1 Year	1–<2 Years	≥2 Years
Non-Hispanic white				
No retinopathy	61.3 (1.93)	63.6 (1.69)	13.9 (1.37)	18.9 (1.54)
Retinopathy without vision loss	85.7 (5.58)	74.7 (7.72)	12.9 (6.41)[2]	12.5 (5.54)[2]
Retinopathy with vision loss	78.8 (6.44)	82.0 (6.21)	12.3 (5.49)[2]	[3]
Non-Hispanic black				
No retinopathy	50.1 (2.91)	59.6 (2.98)	18.4 (2.72)	17.3 (2.37)
Retinopathy without vision loss	84.5 (8.59)	78.6 (9.85)	[3]	[3]
Retinopathy with vision loss	85.3 (8.66)	97.7 (2.54)	[3]	[3]
All Hispanic				
No retinopathy	56.6 (4.01)	61.7 (4.07)	13.7 (2.67)	13.5 (2.24)
Retinopathy without vision loss	60.4 (1.36)	60.4 (1.36)	[3]	[3]
Retinopathy with vision loss	55.3 (11.60)	61.3 (11.11)	29.1 (9.22)[1]	[3]
Mexican American				
No retinopathy	52.4 (5.26)	57.9 (5.57)	15.2 (3.69)	12.7 (2.71)
Retinopathy without vision loss	54.9 (3.27)	54.9 (3.27)	[3]	[3]
Retinopathy with vision loss	47.4 (13.74)	47.4 (13.74)	[3]	[3]
Non-Hispanic Asian				
No retinopathy	61.6 (6.22)	71.2 (5.83)	11.1 (3.64)[1]	11.1 (4.04)[1]
Retinopathy without vision loss	[3]	66.4 (19.18)	[3]	[3]
Retinopathy with vision loss	[3]	[3]	[3]	[3]

Time since pupils were last dilated does not add to 100% because some participants have never had their pupils dilated. Diabetes status, retinopathy status, seen eye doctor in the past 12 months, and times since pupils were last dilated are based on self-report. Standardized to the National Health Interview Survey 2008 population with diabetes using age categories 40–64, 65–74, and ≥75 years.

[1] Relative standard error >30%–40%

[2] Relative standard error >40%–50%

[3] Relative standard error >50%; estimate is too unreliable to present.

SOURCE: National Health Interview Survey 2008

TABLE 21.25. Costs, Quality-Adjusted Life Years, and Cost-Effectiveness of Different Diabetic Retinopathy Screening and Treatment Alternatives Considering the Impacts of Diabetic Retinopathy Alone and the Impacts of Diabetic Retinopathy, Age-Related Macular Degeneration, Glaucoma, and Uncorrected Refractive Error

SCENARIOS	OUTCOMES		ICER		INB GIVEN WTP=$50,000 PER QALY GAINED			
	Total Cost (CI)	QALYs (CI)	Versus Self-Referral	Probability Cost-Effective	Versus Self-Referral	Probability Cost-Effective	Versus Next Most Expensive Option	Probability Cost-Effective
Self-referral at visual loss	$7,368 ($6,127–$8,610)	10.1646 (10.1643–10.1648)						
Annual telemedicine	$10,711 ($9,045–$12,378)	10.2254 (10.2251–10.2256)	$54,979		-$303 (-$3,185–$2,579)	0.37		
Biennial evaluation	$11,004 ($8,515–$13,493)	10.2614 (10.2612–10.2617)	$37,531	$8,107	$1,208 (-$2,497–$4,912)	0.93	$1,511 (-$2,619–$5,640)	0.98
Annual evaluation	$12,177 ($9,213–$15,141)	10.2700 (10.2698–10.2703)	$45,586	$136,170	$466 (-$3,714–$4,645)	0.70	-$742 (-$6,169–$4,685)	0.15

Productivity losses refer only to those that occur as a result of eye evaluations, dilation, or treatment of diabetic retinopathy; they do not include losses from visual impairment as these are incorporated in QALY losses. All costs are expressed in U.S. dollars. AMD, age-related macular degeneration; CI, confidence interval; ICER, incremental cost effectiveness ratio = change in QALYs – change in costs; INB, incremental net benefit = WTP × change in QALYs – change in costs; QALY, quality-adjusted life year; URE, uncorrected refractive error; WTP, willingness to pay.

SOURCE: Reference 275, copyright © 2011 John Wiley & Sons, reprinted with permission

Based on data from the NHANES 2002, an estimated 61 million adults in the United States were at high risk of vision loss (had diabetes, had a reported vision or eye problem, or were age ≥65 years) (276). In those at high risk of vision loss, the probability of having an eye examination with pupil dilation increased with age, education, and income ($p<0.01$). It was higher among the insured, women, persons with diabetes, and persons with vision or eye problems ($p<0.01$). The preferred epidemiologic data on prevalence and severity of retinopathy are based on detection by trained graders using standardized protocols to grade stereoscopic color fundus photographs. Newer screening approaches, including digital cameras with central reading centers, are being used for the screening of diabetic patients not under the care of an ophthalmologist. A meta-analysis conducted in 2011 showed that protocols that include retinal photography by a photographer without specific training and without using dilating eye drops (the outreach model) are not more likely to miss cases of diabetic retinopathy than protocols using mydriasis and a skilled photographer with eye qualifications (277). Further epidemiologic studies and controlled clinical trials are needed to evaluate the interval and type of ophthalmic screening in persons with diabetes without diabetic retinopathy in various health care settings. Such studies would provide better evidence of the efficacy of specific approaches to validate new guidelines and screening approaches.

OTHER OCULAR COMPLICATIONS

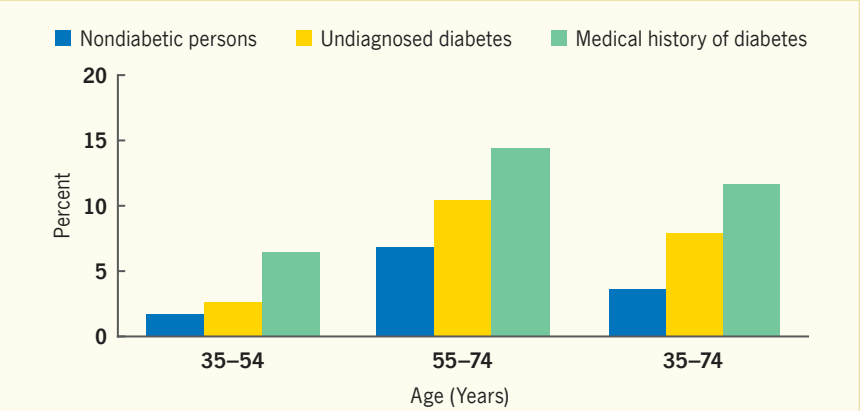
CATARACTS AND CATARACT EXTRACTION

Cataracts occur frequently in older persons in the United States and were a cause of decreased vision in persons with type 2 diabetes in the WESDR (16). Data from the NHIS 1976–1980, as well as new analyses of data from the NHIS 2002 and 2008 conducted for *Diabetes in America*, indicate that persons with diabetes who were age ≥40 years were more likely to report cataract than persons of similar age without diabetes (Figure 21.18 and Table 21.26). Prevalences increased with age in both groups. Women were more likely to report having cataract than men. Non-Hispanic whites had higher prevalences of cataract than non-Hispanic blacks, Hispanic, and non-Hispanic Asian populations. Similar trends were present in 2008 (Table 21.26). Prevalence of cataract (or senile lens changes) determined at an ophthalmologic examination in the NHANES 1970–1975 and the Framingham Eye Study 1973–1975 populations also increased with increasing age (Figure 21.19) (278).

In the WESDR, cataract was determined by slit-lamp examination and graded by comparison with standard photographs (279). Among persons with type 1 diabetes and persons with type 2 diabetes, the prevalence of cataract was slightly higher in women than in men.

Lens opacities of any sort are often referred to as cataract, despite the fact that different anatomic locations in the

FIGURE 21.18. Prevalence of Self-Reported History of Cataracts, by Diabetes Status and Age, U.S., 1976–1980



Undiagnosed diabetes determined by oral glucose tolerance test; nondiabetic status ascertained by medical history and oral glucose tolerance test.
SOURCE: Reference 14

TABLE 21.26. Percent With Cataract Among Adults Age ≥40 Years, by Age, Sex, Race/Ethnicity, and Diabetes Status, U.S., 2002 and 2008

CHARACTERISTICS	PERCENT (STANDARD ERROR)			
	2002		2008	
	Diabetes	No Diabetes	Diabetes	No Diabetes
Overall	29.3 (1.25)	12.6 (0.30)	31.0 (1.30)	14.9 (0.39)
Men, age (years)				
40–64	10.8 (1.51)	3.1 (0.28)	10.0 (1.72)	3.9 (0.35)
65–74	33.9 (3.41)	23.3 (1.45)	42.7 (4.04)	27.0 (1.82)
≥75	59.3 (4.30)	47.2 (2.02)	70.2 (4.63)	52.7 (2.39)
Women, age (years)				
40–64	15.2 (1.76)	3.8 (0.26)	15.8 (1.82)	5.2 (0.40)
65–74	52.1 (3.31)	33.1 (1.47)	54.4 (3.83)	35.6 (1.73)
≥75	63.8 (3.51)	54.2 (1.37)	70.2 (3.24)	66.9 (1.66)
Race/ethnicity				
Non-Hispanic white	33.6 (1.55)	14.1 (0.34)	34.8 (1.69)	16.9 (0.49)
Non-Hispanic black	20.2 (2.37)	8.6 (0.57)	24.4 (2.33)	9.8 (0.76)
All Hispanic	20.6 (2.83)	5.6 (0.58)	20.2 (2.26)	8.2 (0.90)
Mexican American	20.1 (3.24)	5.0 (0.60)	17.7 (2.87)	6.6 (1.02)
Non-Hispanic Asian	13.1 (5.21)[1]	6.0 (1.40)	29.4 (7.26)	9.0 (1.31)

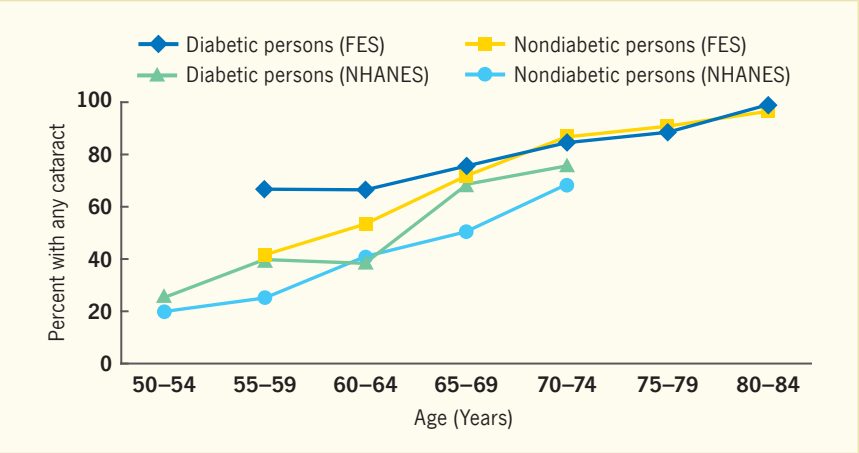
Diabetes status and cataract are based on self-reported diagnosis. All p-values >0.05 comparing 2002 and 2008 estimates for people with diabetes.
[1] Relative standard error >30%–40%
SOURCE: National Health Interview Surveys 2002 and 2008

lens may be involved. Many studies do not specify subtypes of cataract. However, differences in the prevalence and severity of specific lens opacities in persons with diabetes have been reported. In the BDES, lenses were photographed with cameras designed to image specific sites of lens opacities (280). Photographs were graded according to standard protocols, and graders were masked to subject characteristics. In that study, cortical opacities were significantly more common among persons with type 2 diabetes in all four age categories compared with the rest of the Beaver Dam population (280). Posterior subcapsular cataract was also numerically more common in persons with diabetes, but the increase was not significant in all age groups. Longer duration of diabetes was associated with increased odds of all subtypes of age-related cataract but was significant only for cortical cataract; A1c was not significantly associated with any type of cataract. With regard to risk factors for prevalent cataract in persons with diabetes in the WESDR, multivariate analyses indicated that age and duration of diabetes were the most important risk factors in cross-sectional analyses (Table 21.27) (279), with the severity of diabetic retinopathy associated with a small but significant additional increase in risk.

In persons with type 1 diabetes, diuretic use and A1c were also associated with increased risk of cataract. In persons with type 2 diabetes, diuretic use, intraocular pressure, smoking status (current/past/never), and diastolic blood pressure were associated with increased risk of cataract.

In a case-control study from Laxa, Iceland, cataract prevalence was determined by slit lamp examinations using the Lens Opacities Classification System II (281). The mean age of those with diabetes (cases) was 69 years, and for the controls, it was 70 years. Cortical, posterior subcapsular, and nuclear cataract prevalences were 65.5%, 42.5%, and 48%, respectively, in persons with type 2 diabetes. In those with diabetes, cortical cataract was significantly more common, and prevalence of posterior subcapsular cataract was associated with A1c.

FIGURE 21.19. Prevalence of Senile Lens Changes in Diabetic and Nondiabetic Persons, by Age



FES, Framingham Eye Study, 1973–1975; NHANES, First National Health and Nutrition Examination Surveys, 1970–1975.

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TABLE 21.27. Logistic Regression of Risk Factors for Cataract, WESDR, 1980–1982

RISK FACTOR	ENTROPY*	CHANGE IN ENTROPY
Type 1 diabetes		
Duration	0.38	0.38
Age at examination	0.41	0.03
Retinopathy	0.43	0.02
Diuretic (never, ex-user, current user)	0.43	0.01
A1c	0.44	0.01
Type 2 diabetes		
Age at examination	0.20	0.20
Retinopathy	0.22	0.02
Diuretic (never, ex-user, current user)	0.23	0.01
Intraocular pressure	0.24	0.01
Smoking	0.25	0.01
Diastolic blood pressure	0.25	0.003

Type 1 diabetes, diabetes diagnosed at age <30 years, n=618 no cataract, n=219 with cataract; type 2 diabetes, diabetes diagnosed at age ≥30 years, n=145 no cataract, n=968 with cataract. A1c, glycosylated hemoglobin; WESDR, Wisconsin Epidemiologic Study of Diabetic Retinopathy.

* In order to evaluate the goodness of fit of the model to the data, an index, "entropy," is used. Entropy is a function of the log likelihood of the current model compared with a model in which no variables had been considered, i.e., the prevalence. This index is analogous to the R^2 values for multiple linear regression.

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TABLE 21.28. Age- and Sex-Standardized Percent With Eye Disease Among Adults Age ≥40 Years, by Diabetes Status, U.S., 2005–2008

DIABETES STATUS	PERCENT (STANDARD ERROR)		
	Self-Reported Cataract Surgery	Self-Reported Glaucoma	Early Age-Related Macular Degeneration*
Diagnosed diabetes†	16.1 (1.05)‡	9.1 (0.98)‡	5.6 (0.71)
No diabetes§	10.0 (1.37)	2.9 (0.79)	6.0 (1.10)

Standardized to the National Health Interview Survey 2008 total population using age categories 40–64, 65–74, and ≥75 years.

* Based on retinal imaging.

† Based on self-reported previous diabetes diagnosis.

‡ P-value compared to no diabetes group <0.05.

§ Based on glycosylated hemoglobin (A1c) <5.7%, fasting glucose <100 mg/dL, and 2-hour glucose <140 mg/dL; conversions for glucose and A1c values are provided in *Diabetes in America Appendix 1 Conversions.*

SOURCE: National Health and Nutrition Examination Surveys 2005–2008

Cataract extraction is common in persons with diabetes. In prevalence data from the WESDR, 3.6% of those with type 1 diabetes and 8.7% of those with type 2 diabetes had undergone such surgery (279). Prevalence of surgery increased with current age in both groups, but there appears to be an effect above that contributed by age. Cataract extraction was a major endpoint in the UKPDS. Intensive glycemic control was associated with a nonsignificant reduction in risk of this endpoint (OR 0.76, 95% CI 0.53–1.08) (122). In a new analysis of NHANES 2005–2008 data for *Diabetes in America*, age- and sex-standardized self-reported cataract surgery was more prevalent among persons with diagnosed diabetes than in nondiabetic persons (Table 21.28). Long-term incidence data are sparse with regard to cataract surgery among diabetic patients. Table 21.29 indicates the 10-year incidence of such surgery in subjects in the WESDR (282).

Current age is systematically associated with increased incidence of cataract surgery (Table 21.30) (282). Multivariate analyses of risk factors for incidence of cataract surgery were performed on data from the WESDR (Table 21.31) (282). For persons with type 1 diabetes, older age, past history of laser therapy, presence of proteinuria, higher A1c, and taking aspirin daily were associated with increased risk of cataract surgery. For persons with type 2 diabetes, use of insulin was associated with increased risk of cataract surgery.

Cataract surgery is very successful in improving vision in persons with diabetes even in the presence of diabetic retinopathy (283). In persons with diabetes but no macular edema prior to cataract surgery, macular edema did not develop within 16 weeks of surgery, but 10% (95% CI 5%–18%) of eyes with non-central-involved diabetic macular edema at baseline progressed to central-involved macular edema (284). History of treatment for diabetic macular edema was significantly associated with central-involved development of macular edema (p<0.001) (284). Visual acuity was better after cataract surgery in all study participants, but the

TABLE 21.29. Ten-Year Incidence of Cataract Surgery in Persons With Diabetes, WESDR, 1980–1992

	N	INCIDENCE (%) (95% CI)
Type 1 diabetes (age ≥18 years)	685	8.5 (6.2–10.8)
Type 2 diabetes	925	24.9 (21.3–28.5)

Type 1 diabetes, diabetes diagnosed at age <30 years; type 2 diabetes diagnosed at age ≥30 years. CI, confidence interval; WESDR, Wisconsin Epidemiologic Study of Diabetic Retinopathy.

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TABLE 21.30. Ten-Year Incidence of Cataract Surgery in Persons With Diabetes, by Age, WESDR, 1980–1992

AGE (YEARS)	N AT RISK	INCIDENCE (%)
Type 1 diabetes		
18–24	218	3.7
25–34	262	6.1
35–44	113	9.7
≥45	92	27.6
Type 2 diabetes		
30–54	184	14.7
55–64	283	21.0
65–74	309	31.7
≥75	149	44.3

Test for trend with age: type 1 diabetes (diabetes diagnosed at age <30 years, p<0.0001), type 2 diabetes (diabetes diagnosed at age ≥30 years, p<0.0005). WESDR, Wisconsin Epidemiologic Study of Diabetic Retinopathy.

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TABLE 21.31. Odds Ratios for 10-Year Incidence of Cataract Surgery for a Specified Change in Baseline Characteristic, WESDR, 1980–1992

CHARACTERISTICS	CHANGE	ODDS RATIO (95% CI)	P-VALUE
Type 1 diabetes			
Age	10 years	2.35 (1.73–3.20)	<0.0001
Laser history	present	3.28 (1.44–7.45)	<0.005
Proteinuria	present	3.21 (1.43–7.20)	<0.005
A1c	1%	1.21 (1.02–1.45)	<0.05
Aspirin/day	taking	2.44 (1.02–5.84)	<0.05
Type 2 diabetes			
Age	10 years	1.79 (1.47–2.18)	<0.0001
Insulin	taking	2.11 (1.43–3.11)	<0.0005

Type 1 diabetes, diabetes diagnosed at age <30 years; type 2 diabetes, diabetes diagnosed at age ≥30 years. A1c, glycosylated hemoglobin; CI, confidence interval; WESDR, Wisconsin Epidemiologic Study of Diabetic Retinopathy.

SOURCE: Reference 14

TABLE 21.32. Age- and Sex-Standardized Percent With Eye Disease Among Adults Age ≥40 Years, by Diabetes Status, U.S., 2002 and 2008

	PERCENT (STANDARD ERROR)			
	2002		2008	
EYE DISEASE	Diabetes	No Diabetes	Diabetes	No Diabetes
Diabetic retinopathy	10.2 (0.87)	NA	7.7 (0.75)*	NA
Cataracts	23.8 (1.01)	13.2 (0.26)	25.5 (1.11)	15.8 (0.32)
Glaucoma	6.4 (0.67)	2.8 (0.14)	6.5 (0.66)	2.9 (0.18)
AMD	2.0 (0.29)	1.9 (0.12)	3.2 (0.44)*	2.4 (0.16)

All relative standard errors ≤30%. Diabetes status and eye disease are based on self-reported diagnosis. Standardized to the National Health Interview Survey 2008 total population using age categories 40–64, 65–74, and ≥75 years. AMD, age-related macular degeneration; NA, not applicable.

* P-value compared to analogous 2002 estimate <0.05.

SOURCE: National Health Interview Surveys 2002 and 2008

improvement was not as great in those who developed central macular edema. The incidence of operative complications appears to be increased in persons with diabetes (285). Endophthalmitis appears to be more common after complicated intraocular surgery in those with diabetes than others (286,287).

In summary, cataract and cataract surgery are more prevalent in persons with diabetes. While the level of glycemia significantly influences the risk of cataract, it is likely that even with optimal glycemic control, there will be increased risk associated with diabetes. Ophthalmologists, as well as health care planners, must be mindful of the costs of care associated with cataract, cataract surgery, and rehabilitation in persons with diabetes.

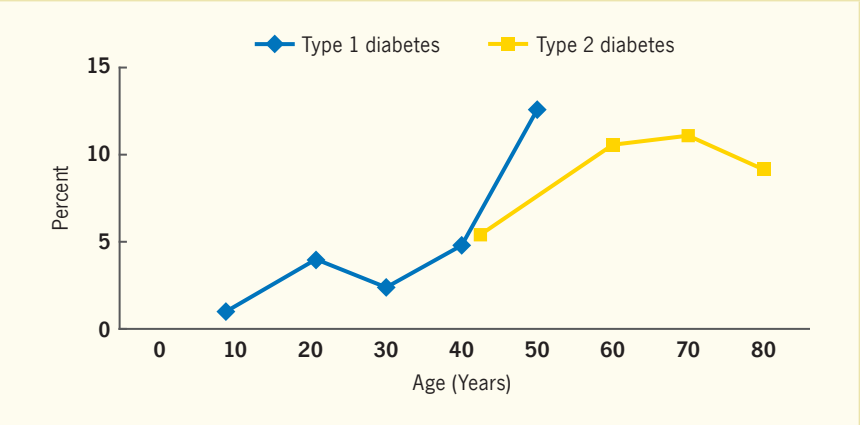
OPEN ANGLE GLAUCOMA

Glaucoma is a condition in which there is evidence of optic nerve damage attributed to intraocular pressure that is presumably too high for a particular eye. Prevalence data from the NHIS 2002 and 2008 analyzed for *Diabetes in America* indicate that persons with diabetes self-reported glaucoma more commonly than nondiabetic persons in the U.S. population (Table 21.32).

Glaucoma has been defined in various ways in different studies. Some researchers include as cases all those with a history of glaucoma irrespective of treatment status. Some include only those with a history of medical or surgical intervention, while others depend on defined objective criteria. Another consideration to bear in mind when reviewing published data is that some studies do not distinguish between the various types of glaucoma (open angle, closed angle, neovascular, or other primary or secondary types of glaucoma).

In the BDES, definite glaucoma was defined by the presence of at least two of the following three characteristics: abnormal visual field, large or asymmetric cupping of the optic nerve, and an intraocular pressure >21 mmHg (288). Probable glaucoma was defined as a history of

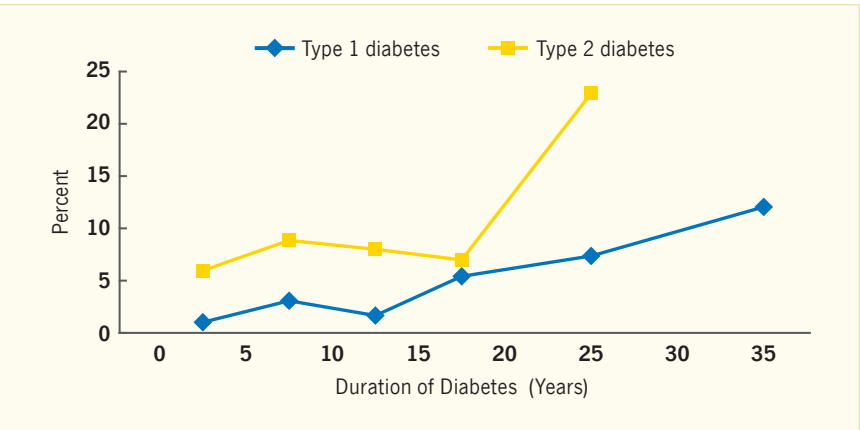
FIGURE 21.20. Ten-Year Incidence of History of Glaucoma in Persons With Type 1 and Type 2 Diabetes, by Age, WESDR, 1980–1982 to 1990–1992



Test for trend: p<0.001 for type 1 diabetes; p<0.005 for type 2 diabetes. WESDR, Wisconsin Epidemiologic Study of Diabetic Retinopathy.

SOURCE: Reference 14

FIGURE 21.21. Ten-Year Incidence of History of Glaucoma in Persons With Type 1 and Type 2 Diabetes, by Diabetes Duration, WESDR, 1980–1982 to 1990–1992



Test for trend: p<0.001 for type 1 diabetes; p<0.005 for type 2 diabetes. WESDR, Wisconsin Epidemiologic Study of Diabetic Retinopathy.

SOURCE: Reference 14

medical treatment or surgery for glaucoma with fewer than two of the above criteria. In a multiple logistic regression model, after adjusting for age and sex, the relationship of the presence of type 2 diabetes to glaucoma was evaluated. Diabetes was significantly associated with prevalence of definite glaucoma (adjusting for age and sex) (288).

In the WESDR, self-reported incidence of glaucoma was evaluated in both type 1 diabetes and type 2 diabetes. Follow-up evaluations were done 4 and 10 years after the original evaluation. Using the product limit method to adjust for study attrition, the 10-year incidence of glaucoma in the group with type 1 diabetes was estimated to be 3.7% (95% CI 2.3%–5.1%). The estimated incidence in the group with type 2 diabetes not taking insulin was 6.9% (95% CI 3.9%–9.8%); in those taking insulin, it was 11.8% (95% CI 7.9%–15.7%) (14). The 10-year incidence of glaucoma varied with age (Figure 21.20). In persons with type 1 diabetes, as well as persons with type 2 diabetes, incidence increased with age, although the relationship was only significant in those with type 1 diabetes. The decrease noted at the oldest age in persons with type 2 diabetes may reflect the high mortality in this group (14).

The relationship of duration of diabetes to glaucoma can be seen in Figure 21.21. The relationship was significant in both persons

with type 1 diabetes and those with type 2 diabetes. To evaluate the effects of several characteristics on the presence of glaucoma, multiple logistic regression analyses were used. The variables included were age, sex, A1c, duration of diabetes, systolic blood pressure, diastolic blood pressure, BMI, and presence of proteinuria. In persons with type 1 diabetes, only age was significantly related to glaucoma; the odds ratio was 1.7 (95% CI 1.2–2.3) per 10-year increase in age. For persons with type 2 diabetes, only duration of diabetes was associated with a significantly increased risk (OR 1.8, 95% CI 1.3–2.6) per 10-years duration (14).

Zhang *et al.* reported that Mexican Americans age 45–74 years who had diabetes had higher prevalence of glaucoma than nondiabetic Mexican Americans (289). Chopra *et al.* examined cross-sectional data from the LALES on the association between diabetes and glaucoma (290). They found an odds ratio of 1.40 (95% CI 1.03–1.80) for glaucoma associated with diabetes, and longer duration of type 2 diabetes was associated with greater odds of having glaucoma present. In contrast, in a population-based study of Mexican Americans in Arizona, glaucoma was not associated with the presence of type 2 diabetes (291). Graw *et al.* reported a significant increase in risk of glaucoma in persons treated with insulin and other medications for diabetes (OR 5.8, 95% CI 1.3–21.8) (292).

The metabolic syndrome has been linked to glaucoma. Newman-Casey *et al.* (293) used data from a national medical plan with 2,182,315 beneficiaries to examine the association of glaucoma to diabetes with or without hypertension. The cohort included 55,090 individuals with at least one diagnosis of open angle glaucoma. The hazard ratio for glaucoma was 1.35 (95% CI 1.21–1.50) for those with diabetes only and 1.48 (95% CI 1.39–1.58) for those with diabetes and hypertension.

In summary, these data suggest an increased risk of open angle glaucoma associated with diabetes. In addition, among persons with type 2 diabetes, increasing duration of diabetes is associated with increased risk. Although some of this excess may be related to greater surveillance of persons with diabetes, it is unlikely to explain the entirety. Pathologic mechanisms responsible for increased glaucoma risk should be investigated. Population-based incidence data using objective diagnostic criteria are needed to evaluate the actual incidence of glaucoma and anticipate the need for care.

CORNEAL LESIONS AND DRY EYE

Aside from dry eye, few population-based data are available on corneal disease in people with and without diabetes. Saini and Khandalavla demonstrated in a case-control study in India that mean corneal epithelial fragility values were higher in persons with type 2 diabetes than in controls without diabetes (294). Rosenberg *et al.* (295) using confocal microscopy demonstrated in another case-control study that there was a reduction in the number of long nerve fiber bundles in persons with type 1 diabetes and mild to moderate neuropathy and that mechanical sensitivity was reduced in those with severe neuropathy. The corneal epithelium was thinner in those with severe neuropathy than in persons with diabetes without neuropathy. The authors speculated that this may lead to recurrent erosions, a painful condition that usually impairs vision and the ability to accomplish vision-related tasks until the erosion heals.

Few epidemiologic data have been reported on the prevalence and incidence of corneal lesions associated with diabetes. However, clinical reports suggest that corneal ulcers occur more commonly in persons with type 1 diabetes than in those without (296), and ophthalmic surgeons have noted that persons with diabetes are predisposed to significant corneal complications requiring treatment after undergoing pars plana vitrectomy (297,298,299).

Dry eye is diagnosed largely by the history of a scratchy or burning sensation of the eye. Occasionally, it is associated with short-term changes in vision. Usually, this is a minor annoyance, but it can cause considerable distress when it is extreme and can affect quality of life. Dry eye is more common in persons with diabetes than in those without (300,301). This is thought to be due to ocular surface disorders that are more common in persons who have diabetes (302). In prevalence data from the population-based BDES, Moss *et al.* reported an odds ratio of 1.38 (95% CI 1.03–1.86) for a history of dry eye in the presence of diabetes (303).

Contact lens use in the presence of diabetes is associated with lower corneal endothelial cell count than occurs in persons with diabetes who do not use contact lenses and in individuals without diabetes who do not wear contact lenses (304). Endothelial cells are needed to maintain normal (low) hydration of the cornea that is important in maintaining clarity of vision. However, March *et al.* reported no significant difference in complications of contact lens wearers between 254 persons with diabetes and an equal number of controls (305).

NONARTERITIC ANTERIOR ISCHEMIC OPTIC NEUROPATHY

Nonarteritic anterior ischemic optic neuropathy (NAION) is an uncommon condition occurring in about 8,000 persons each year in the United States (306). It typically occurs in persons age ≥50 years and often manifests as decreased vision in one eye noted upon awakening. The vision may be obscured in the upper or lower half of vision, or it may be obscured throughout the field of vision. The condition is painless. Vision improves over the next 6 months or so in about half the cases. NAION has been thought to be related to cardiovascular risk factors. Some speculate that crowding of neurons at the optic nerve is a predisposing characteristic.

Lee *et al.* studied Medicare records of 25,515 patients with diabetes and an equal number of age- and sex-matched nondiabetic controls (307). They found that after adjusting for covariates, persons with diabetes had a 40% increased risk of developing NAION compared to persons without diabetes (OR 1.40, 95% CI 1.12–1.75). Further, a repeat episode of NAION

TABLE 21.33. Prevalence of Visual Impairment and Selected Eye Diseases Among Persons Age ≥50 Years With and Without Diagnosed Diabetes, by Selected Characteristics, U.S., 2002

	PERCENT (95% CONFIDENCE INTERVAL)				
	Glaucoma		Age-Related Macular Degeneration		Diabetic Retinopathy*
CHARACTERISTICS	Diabetes	No Diabetes	Diabetes	No Diabetes	Diabetes
Age (years)					
50–64	4.9 (3.0–6.8)	1.9 (1.5–2.3)	1.1 (0.4–1.8)	0.7 (0.4–0.9)	9.7 (7.3–12.1)
≥65	11.7 (9.4–13.9)	7.0 (6.2–7.8)	4.7 (3.2–6.2)	5.6 (4.8–6.3)	10.8 (8.6–13.0)
Total (unadjusted)	8.4 (6.9–9.9)	4.1 (3.7–4.5)	3.0 (2.1–3.8)	2.7 (2.4–3.0)	10.3 (8.6–11.9)
Sex					
Men	7.0 (5.0–8.9)	4.0 (3.3–4.7)	2.7 (1.6–3.9)	2.3 (1.8–2.8)	8.7 (6.4–11.0)
Women	9.1 (6.9–11.2)	4.5 (3.9–5.0)	2.8 (1.8–3.9)	3.4 (2.9–3.8)	11.8 (9.5–14.1)
Race/ethnicity					
Non-Hispanic white	6.8 (5.1–8.5)	4.1 (3.6–4.5)	3.2 (2.2–4.1)	3.2 (2.8–3.7)	9.4 (7.5–11.2)
Other†	11.4 (8.4–14.4)	5.2 (4.2–6.2)	1.4 (0.4–2.4)	1.1 (0.5–1.8)	12.0 (8.8–15.2)
Education level					
<High school	9.3 (6.6–12.0)	5.3 (4.2–6.3)	1.7 (0.8–2.6)	2.6 (2.0–3.3)	12.1 (8.8–15.4)
≥High school	7.3 (5.6–9.1)	4.0 (3.5–4.5)	3.3 (2.2–4.5)	3.0 (2.6–3.5)	9.4 (7.5–11.3)
Health insurance					
Yes	8.3 (6.7–9.8)	4.3 (3.9–4.8)	2.8 (2.0–3.6)	2.9 (2.6–3.3)	10.2 (8.5–11.9)
No	6.6 (-0.9–14.1)	0.6 (0.2–0.9)	3.3 (-2.9–9.4)	1.1 (-0.2–2.3)	9.9 (2.4–17.5)
Total (age-adjusted)	8.0 (6.5–9.5)	4.3 (3.8–4.7)	2.8 (2.0–3.5)	2.9 (2.5–3.3)	10.2 (8.5–11.8)

Sex, race/ethnicity, education level, and health insurance status are age-adjusted according to the 2000 U.S. standard population.
* Not applicable for persons without diabetes.
† Numbers for racial/ethnic populations other than non-Hispanic white were combined because, when analyzed separately, data were too small for meaningful analysis.
SOURCE: Reference 321

was more likely to occur in persons with diabetes than in those without (308). It is not known whether the actual level of glycemic control influences risk, although if its etiology is vascular, one might anticipate that this is so.

RETINAL VEIN OCCLUSION

Retinal vein occlusion has been estimated to affect about 1% of the population age >50 years and can lead to loss of visual acuity in the affected eye (309,310). Diabetes has been recognized as a risk factor for retinal vein occlusions (311,312,313,314). Central vein occlusion is associated with decreased vision and may be complicated by retinal neovascularization requiring laser photocoagulation. Cugati *et al.* (314) reported that in persons age <70 years, retinal vein occlusion was associated with increased cardiovascular mortality.

RETINAL ARTERIOLAR EMBOLI

Retinal emboli are often found in the retinal arterioles, and their appearance can vary from dull to highly refractile. In about 75% of persons, the emboli arise from atherosclerotic plaques in the carotid artery (315). Most emboli are transient and are often asymptomatic. They are estimated to occur in 1%–1.5% of the population age ≥40 years (316,317). In the BDES, persons with type 2 diabetes had a twofold higher prevalence of retinal emboli than people without diabetes. However, in two other populations, this association was not found (318,319).

AGE-RELATED MACULAR DEGENERATION

Age-related macular degeneration (AMD) is the most common cause of severe visual impairment in people age ≥65 years. It is characterized by large soft drusen, yellow round deposits under the retinal pigment epithelium in its early stages and, in some persons, with the development of two advanced stages—one an atrophy of the outer retinal layers, referred to as geographic atrophy, and the other a development of subretinal new vessels with exudation and bleeding, referred to as exudative AMD.

Few reports have been published on the association of AMD with diabetes. Klein *et al.* found a significant increase in exudative AMD in men age ≥75 years in prevalence data from the BDES (RR 10.2, 95% CI 2.4–43.7) (320). In prevalence data from the NHIS 2002, AMD (early and late stages) was not consistently associated with diabetes (Table 21.33) (321). In non-Hispanic whites, those with diabetes reported similar prevalence of AMD as those without diabetes. In the BDES cohort, neither diabetes status nor the severity of diabetic retinopathy was associated with the incidence of AMD (322). However, using Medicare claims data, Hahn *et al.* (323) reported the 10-year incidence of geographic atrophy and exudative AMD from 1995–2005 in beneficiaries age >69 years with newly diagnosed diabetes (N=6,621), NPDR (N=1,307), and PDR (N=327) compared with other persons within each group, as well as with matched nondiabetic controls for each group. After adjusting for covariates, NPDR was associated with an increased risk of incident geographic atrophy (HR 1.24, 95% CI 1.08–1.43) and exudative AMD (HR 1.68, 95% CI 1.23–2.31). PDR was associated with significantly increased risk of exudative AMD (HR 2.15, 95% CI 1.07–4.33). Diabetes without retinopathy was not associated with advanced stages of AMD.

OTHER OCULAR FINDINGS ASSOCIATED WITH DIABETES

Diabetic papillopathy is an uncommon finding in persons with type 1 diabetes often occurring in the presence of severe hyperglycemia. It is characterized by swelling of the optic nerve and may be accompanied by a mild decrease in vision.

Dysfunction of other cranial nerves, especially cranial nerves 1, 4, and 6, can lead to ocular movement disorders and double vision, as well as malfunction of the eyelids. These problems tend to resolve on their own, and management usually is limited to patching an eye until muscle function returns so that double vision is not a problem. If the lid is closed due to third nerve palsy, it protects the cornea from drying changes and diminishes the problems attendant upon diplopia.

LIST OF ABBREVIATIONS

A1c. . . . . glycosylated hemoglobin
ACCORD . . . . . Action to Control Cardiovascular Risk in Diabetes
ADVANCE . . . . Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation
AGE . . . . . advanced glycation endproduct
AMD. . . . . age-related macular degeneration
ARIC. . . . . Atherosclerosis Risk in Communities study
BDES. . . . . Beaver Dam Eye Study
BMI . . . . . body mass index
CI. . . . . confidence interval
CSME. . . . . clinically significant macular edema
CVD . . . . . cardiovascular disease
DCCT. . . . . Diabetes Control and Complications Trial
DIRECT . . . . . DIabetic REtinopathy Candesartan Trials
DRS-HRC. . . . Diabetic Retinopathy Study high-risk characteristics
ETDRS. . . . . Early Treatment of Diabetic Retinopathy Study
EUCLID . . . . . Epidemiology and Prevention of Diabetes Controlled trial of Lisinopril in Insulin-dependent Diabetes
HR . . . . . hazard ratio
LALES . . . . . Los Angeles Latino Eye Study
LDL . . . . . low-density lipoprotein
MESA. . . . . Multi-Ethnic Study of Atherosclerosis
NAION . . . . . nonarteritic anterior ischemic optic neuropathy
NEI-VFQ-25 . . . National Eye Institute Visual Functioning Questionnaire 25
NHANES . . . . . National Health and Nutrition Examination Survey
NHIS . . . . . National Health Interview Survey
NPDR. . . . . nonproliferative diabetic retinopathy
OR . . . . . odds ratio
PDR . . . . . proliferative diabetic retinopathy
RASS . . . . . Renin-Angiotensin System Study
RR . . . . . relative risk
SF-12 . . . . . Medical Outcomes Study 12-item Short Form Health Survey
UKPDS. . . . . United Kingdom Prospective Diabetes Study
VADT . . . . . Veterans Affairs Diabetes Trial
VER . . . . . Proyecto Vision Evaluation and Research
WESDR . . . . . Wisconsin Epidemiologic Study of Diabetic Retinopathy
WHO . . . . . World Health Organization

CONVERSIONS

Conversions for A1c and glucose values are provided in *Diabetes in America Appendix 1 Conversions.*

ACKNOWLEDGMENTS/ FUNDING

Drs. Klein and Klein were supported by a grant from the National Eye Institute (EY016379 and EY06594) and an unrestricted grant from Research to Prevent Blindness, New York, NY.

DUALITY OF INTEREST

Drs. Klein and Klein reported no conflicts of interest.

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