Incidence and Risk Factors for Blindness in Adults With Diabetes: The Israeli National Diabetes Registry (INDR)

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• PURPOSE: To estimate the 3-year incidence of blindness among diabetes patients aged ≥18 years; to compare blindness incidence rates of persons with and without diabetes; and to investigate risk factors associated with diabetic retinopathy (DR), age-related macular degeneration (ARMD), glaucoma, and cataract-related blindness.
• DESIGN: Cohort study.
• METHODS: The Israeli National Diabetes Registry for 2012 was cross-linked with the database of blindness certifications obtained from the National Registry of the Blind. Blindness was defined as the receipt of an official certificate of blindness (a visual acuity of 3/60 or worse, or a visual field loss of < 20 degrees in the better eye.) Incidence rates of blindness, overall and by main cause of blindness, were calculated for the years 2013-2015. Standardized morbidity ratios (SMRs) for 2013 were calculated, using the nondiabetic population as a reference. A multinomial logistic model was used to identify covariates associated with the incidence of blindness by main cause of blindness.
• RESULTS: The 3-year incidence rates were 31.0 and 8.4 per 10 000 for overall and DR-related blindness, respectively. The SMR for overall blindness in people with diabetes was significantly higher than in the general nondiabetic population (1.39; 95% confidence interval: 1.27–1.53); however, the SMRs for ARMD, glaucoma, and cataract were not statistically significant. Poor metabolic control, insulin treatment, long diabetes duration, and chronic kidney disease were associated with DR-related blindness. Low socioeconomic status (SES) was associated with both cataract and DR-related blindness.
• CONCLUSIONS: Optimum metabolic control of diabetes is important for prevention of DR-related blindness. SES-related disparities in blindness risk should be explored and reduced by directing efforts to provide appropriate treatment for all diabetic patients in order to prevent unnecessary blindness. (Am J Ophthalmol 2019;200:57–64. © 2018 Published by Elsevier Inc.)

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DIABETIC RETINOPATHY (DR) IS A WELL-KNOWN specific microvascular complication of diabetes, and is the leading cause of preventable blindness before the age of 74 years.[1,2] The prevalence of DR among people with diabetes was reported to range from 10% to over 90%, depending on the population, the methods used to screen for DR, the type, and the duration of diabetes.[3,4] According to the World Health Organization (WHO), 75% of patients with a 20-year history of diabetes have some degree of retinopathy.[5] However, in developed countries the annual incidence of diabetic blindness can be reduced to 1% or less.[6] Some ocular conditions such as cataract and glaucoma were also found to be associated with hyperglycemia and diabetes, whereas a higher risk of age-related macular degeneration (ARMD) was not consistently found to be associated with diabetes.[7,8]

Compared to the overall population, individuals with diabetes are at an increased risk of blindness.[7] With the continuous increase of life expectancy among patients with diabetes, the number of individuals with diabetes-related visual impairments and blindness is also expected to increase.[9] Therefore, detecting risk factors for diabetes-related blindness is of high importance. Few studies so far have explored the associations between various risk factors and blindness among diabetic patients.[10,11]

The objectives of the present study were as follows: (1) to estimate the 3-year incidence of blindness among patients with diabetes aged 18 and above, overall and by main cause of blindness; (2) to compare blindness incidence rates of persons with and without diabetes; and (3) to investigate risk factors associated with the incidence of DR, ARMD, glaucoma and cataract-related blindness among patients with diabetes aged 18 and above, using data from the National Registry of the Blind and the Israeli National Diabetes Registry (INDR).

METHODS

• SUBJECTS AND STUDY DESIGN: The INDR was established in 2012 and is managed by the Israel Center for Disease Control. The INDR receives an annual dataset of prevalent cases of diabetes from each of the 4 health maintenance organizations (HMOs) that provide medical services to all Israeli permanent residents (except military

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personnel and prisoners). The dataset reported to the INDR includes individual coded de-identified data on HMO members who met 1 of the following criteria in the previous year: (1) a single test of glycated hemoglobin (HbA1c) greater than or equal to 6.5%; (2) serum glucose concentrations of 200 mg/dL or higher in 2 tests performed at least 1 month apart; (3) at least 3 purchases of hypoglycemic medications (including insulin) in different months. The INDR does not have information about diabetes type. The INDR dataset for 2012 was cross-linked with the database of blindness certifications obtained from the National Registry of the Blind. All diabetic patients with certified blindness obtained before 2013 were excluded. Owing to the fact that diabetes-induced blindness in persons below age 18 is almost nonexistent, we excluded patients below the age of 18.

The study was approved by the Sheba Medical Center Ethics Committee. As the data were obtained from government computerized registers that serve regulatory purposes, an individual consent form was not required.

• **DATA COLLECTION:** Demographic data available for all participants included age, sex, and socioeconomic status (SES). SES was determined according to the poverty index of the area of residence defined by the Israeli Bureau of Statistics from the 2008 national census data collection. The poverty index, ranging from 1 (lowest) to 10 (highest), is based on several parameters, including household income, educational qualifications, crowding, material conditions, and car ownership.[12] Participants were classified into 3 categories of SES: low (1-3), intermediate (4-7), and high (8-10).

Clinical parameters included duration of diabetes, insulin treatment, smoking status, body mass index (BMI), prevalence of chronic kidney disease (CKD), levels of HbA1c, low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C). Duration of diabetes was defined according to the year the participant started to purchase hypoglycemic medication and was classified into 2 categories of ≤10 or >10 years. BMI was calculated as weight in kilograms divided by the square of height in meters. Obesity was defined as BMI ≥ 30 kg/m^2. Poor glucose control was defined as HbA1c <7%. Poor LDL-C control was defined as LDL-C level ≥100 mg/dL and poor HDL-C control was defined as HDL-C levels ≤40 mg/dL for men and ≤50 mg/dL for women. CKD was defined in accordance with the National Kidney Foundation definition as an estimated glomerular filtration rate of less than 60 mL/min/1.73 m^2 of body-surface area, estimated using the Modification of Diet in Renal Disease formula.[13] Smoking was determined on the basis of self-reported data obtained by the HMO.

• **INFORMATION ON BLINDNESS:** The National Registry of the Blind is managed by the Ministry of Social Affairs since 1987. Blindness is defined in Israel as best-corrected visual acuity of less than 1/60 or central visual field not more than 10 degrees in the less impaired eye. Severe visual impairment is defined as visual acuity of less than 3/60 but of 1/60 or better, or a corresponding visual field of less than 10-19 degrees in the less impaired eye. Legal blindness encompasses both blindness and severe visual impairment.[14] The certification process includes a thorough assessment by a senior ophthalmologist who determines the cause for the visual loss.[15] If 2 or more causes of blindness were present, the disease with the most significant and irreversible pathology was assigned as the main cause of blindness. It can be assumed that the vast majority of blind individuals in Israel are diagnosed and registered, thanks to the universal free access to widely available healthcare in Israel, including all ophthalmologic services,[15] and the considerable advantages conferred by their registration. Incident blindness for this study was defined as the receipt of an official certificate of blindness by the National Registry of the Blind between January 1, 2013, and December 31, 2015. In addition to overall blindness, we examined the incident blindness by main causes including ocular DR, glaucoma, cataract, ARMD, and other causes, which included retinitis pigmentosa, optic atrophy, myopic maculopathy, problems with retina, vitreous hemorrhage, retinitis, and other ocular neuropathies.

• **DATA ANALYSIS:** The rates of incident blindness certifications overall and by main cause, per 10 000 adults with diabetes, were calculated for the years 2013-2015. Confidence intervals (95% CI) were estimated using Wilson's approximation. The rates were calculated for the overall diabetic population and stratified by age and sex. Expected blindness cases in 2013 were calculated by age groups, and standardized morbidity ratios (SMRs) were calculated, using as a reference the nondiabetic Israeli general population for the same year. Poisson approximation was used to calculate the 95% CIs for SMRs.[16] Comparison of variables between causes of blindness groups was performed using Kruskal-Wallis test and χ^2 test for continuous and categorical variables, respectively. A multinomial logistic model was used to identify covariates associated with blindness related to ARMD, DR, glaucoma,a and cataract among diabetic patients. The categories of the outcome variable were ARMD, DR, glaucoma, cataract, and no blindness as reference category. All analyses were performed using a 95% CI. Covariates for which there was evidence of a univariate association with the outcome ($P < .2$) were retained in the multivariate model. Goodness of fit in the final model was checked using minus 2 log-likelihood ratios. Statistical analysis was performed using SAS Enterprise Guide 7.12 (SAS Institute Inc, Cary, North Carolina, USA).

RESULTS

THERE WERE 458 728 PATIENTS AGED 18 AND ABOVE REGISTERED in the INDR in 2012; 6541 of these were identified with prevalent blindness and excluded (Figure). During

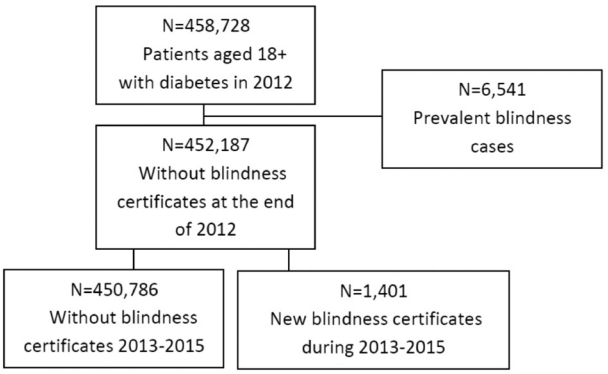

FIGURE. Study flowchart.

the period between January 1, 2013, and December 31, 2015, 1401 new blindness certificate recipients were registered, of whom 49.0% (n = 687) were male; mean age was 71.6 ± 11.9 years and 72.7 ± 11.7 years for male and female patients, respectively. Clinical and demographic characteristics of patients aged 18 and above with diabetes are shown in Table 1. In brief, the mean age was 64.9 ± 13.0 years. With regard to metabolic control, 52.3% had HbA1c ≤7% and 65.0% had LDL levels ≤100 mg/dL. A total of 14.5% of the participants were classified as low SES, 71.3% intermediate SES, and 14.2% high SES.

The mean annual incidence rates for overall, ARMD, DR, glaucoma and cataract-related blindness per 10 000 adults with diabetes were 10.3, 3.2, 2.8, 1.4, and 0.5, respectively (Table 2). Incidence increased gradually with age; notably, the incidence rate in the oldest age group was 4 times higher than in the youngest age group. ARMD was the most frequent cause of incident blindness in those aged 75+ (51%) and DR was the main cause in patients aged 55-64 (53.1%) (Table 2).

The SMR for overall blindness in people with diabetes was significantly higher than in the general nondiabetic population (1.39; 95% CI: 1.27–1.53); however, the SMRs for ARMD, glaucoma, and cataract were not significantly different.

Table 3 summarizes the participants' clinical and demographic characteristics stratified by cause of blindness. Patients with blindness attributable to DR were younger (67.7 ± 10.8 years) than patients with blindness attributable to cataract (71.8 ± 10.6 years), ARMD (79.9 ± 7.0 years), and glaucoma (75.3 ± 10.5 years); and were more likely to have diabetes duration longer than 10 years, to use insulin, to have CKD, and to have poor glucose and poor HDL control. Diabetic patients with blindness owing to DR or cataract were more likely to live in low-SES areas compared to patients with blindness owing to other causes. Patients with blindness owing to glaucoma and cataract were less likely than patients with blindness owing to other causes to be obese.

TABLE 1. Clinical and Demographic Characteristics of Patients Aged 18 and Above With Diabetes: Israel National Diabetes Registry (INDR), 2012

Characteristic	Total (N = 452 187)
Age (y), mean ± SD	64.9 ± 13.0
Sex	
Male	224 690 (49.7)
Female	227 497 (50.3)
Smoking	
Yes	65 708 (15.0)
No	373 926 (85.0)
Obesity	
BMI ≥ 30 kg/m^2	188 090 (47.1)
BMI < 30 kg/m^2	211 337 (52.9)
Glucose control	
HbA1c ≤ 7%	214 477 (52.3)
HbA1c > 7%	195 788 (47.7)
LDL-C control	
≤100 mg/dL	262 114 (65.0)
>100 mg/dL	140 903 (35.0)
HDL-C control[a]	
Yes	192 439 (46.3)
No	223 409 (53.7)
Diabetes duration (years)	
>10	116 307 (27.2)
≤10	310 914 (72.8)
Insulin treatment	
Yes	86 032 (19.0)
No	366 155 (81.0)
CKD	
Yes	76 371 (18.2)
No	342 186 (81.8)
SES[b]	
Low	65 076 (14.5)
Intermediate	320 432 (71.3)
High	63 899 (14.2)

BMI = body mass index; CKD = chronic kidney disease; HbA1c = glycated hemoglobin (A1c); HDL-C= high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; SES = socioeconomic status.

Data are number (%) of cases, unless otherwise indicated.

[a]>40 mg/dL for men, >50 mg/dL for women.

[b]SES was determined according to the poverty index of the census enumeration area as defined by the Israeli Bureau of Statistics for the 2008 national census (low = 1-3; intermediate = 4-7; high = 8-10).

Table 4 presents the associations of various demographic and clinical characteristics with the incidence of ARMD, DR, glaucoma, and cataract-related blindness. DR-related blindness was associated with age group 55-64 years (odds ratio [OR] = 1.80, 95% CI: 1.26–2.56), poor glucose control (OR = 2.14, 95% CI: 1.56–2.92), poor LDL control (OR = 1.41, 95% CI: 1.12–1.77), insulin treatment (OR = 5.69, 95% CI: 4.30–7.54), long diabetes duration (OR = 1.93, 95% CI: 1.50–2.48), CKD (OR = 3.15,

TABLE 2. Incidence Rates[a] of Blindness Among Patients With Diabetes by Age and Cause of Blindness

Age Group	Overall		ARMD		DR		Glaucoma		Cataract		Other[b]	
	N (%)	Rate (95% CI)	N (%)	Rate (95% CI)	N (%)	Rate (95% CI)	N (%)	Rate (95% CI)	N (%)	Rate (95% CI)	N (%)	Rate (95% CI)
3-year blindness rates												
18-54	106 (7.6)	12 (10.1–14.2)	2 (1.9)	0.2 (0.3–0.8)	54 (50.9)	6.1 (4.9–7.8)	7 (6.6)	0.8 (0.6–1.6)	3 (2.8)	0.3 (0.3–1.0)	40 (37.7)	4.5 (3.5–6.0)
55-64	260 (18.6)	20.3 (18.1–22.6)	10 (3.9)	0.8 (0.6–1.4)	138 (53.1)	10.8 (9.3–12.5)	22 (8.5)	1.7 (1.3–2.5)	14 (5.4)	1.1 (0.8–1.8)	76 (29.2)	5.9 (4.9–7.3)
65-74	351 (25.1)	28.5 (25.8–31.2)	77 (21.9)	6.3 (5.2–7.7)	11 (31.6)	9.0 (7.6–10.6)	48 (13.7)	3.9 (3.1–5.1)	18 (5.1)	1.5 (1.1–2.3)	97 (27.6)	7.9 (6.6–9.4)
75+	684 (48.8)	60.9 (56.7–64.9)	349 (51.0)	31.1 (28.2–34.0)	79 (11.6)	7.0 (5.8–8.6)	109 (15.9)	9.7 (8.2–11.5)	31 (4.5)	2.8 (2.1–3.8)	116 (17.0)	10.3 (8.8–12.2)
Overall crude rate												
	1401 (100.0)	31.0 (29.5–32.4)	438 (31.3)	9.7 (8.9–10.5)	338 (27.3)	8.4 (7.7–9.2)	186 (13.3)	4.1 (3.6–4.7)	66 (4.7)	1.5 (1.2–1.8)	329 (23.5)	7.3 (6.6–8.0)
Overall age-standardized incidence rate												
				3.1 (2.8–3.5)		7.1 (5.9–8.2)		1.9 (1.4–2.3)		0.7 (0.4–1.0)		5.4 (4.4–6.5)
Mean annual incidence rates												
		10.3 (9.8–10.8)		3.2 (3.0–3.5)		2.8 (2.3–3.1)		1.4 (1.2–1.6)		0.5 (0.4–0.6)		2.4 (2.2–2.7)

ARMD = age-related macular degeneration; CI = confidence interval; DR = diabetic retinopathy.

[a]Rates per 10 000 adults with diabetes.

[b]Includes retinitis pigmentosa, optic atrophy, myopic maculopathy, problems with retina, vitreous hemorrhage, retinitis, and other neuropathy.

95% CI: 2.46–4.03), and low and intermediate SES (OR = 3.78, 95% CI: 2.37–6.04 and OR = 1.86, 95% CI: 1.20–2.89, respectively). No significant association was found with sex, poor HDL control, or smoking. Besides age, ARMD-related blindness was only associated with current smoking (OR = 1.79, 95% CI: 1.28–2.50). Cataract-related blindness was significantly associated with low SES (OR = 7.84, 95% CI: 2.26–27.21) and an association of borderline significance was found with diabetes duration (OR = 1.65, 95% CI: 0.93–2.92). Glaucoma-related blindness was inversely associated with female sex (OR = 0.48, 95% CI: 0.34–0.67); no association was found between metabolic control characteristics and glaucoma-related blindness.

DISCUSSION

TO OUR KNOWLEDGE, THIS IS THE FIRST STUDY IN ISRAEL TO describe national rates of registered blindness among patients with diabetes and to assess risk factors for blindness attributable to DR and other ocular conditions in adults with diabetes.

In this study the overall incidence rate of blindness among people with diabetes aged 18 years and above was low and similar to data published in other reports from high-income countries.[17–19] Compared to the general nondiabetic population, individuals with diabetes in our study were at a 40% increased risk of blindness. The mean annual incidence rates were 10.3 and 2.8 per 10 000 persons for overall and DR-related blindness, respectively. In comparison, in a study conducted in England in 2013, the incidence of blindness certification in the diabetic population aged 16 years and above was estimated at 12.1 per 10 000 persons.[18] In Ireland, the incidence of blindness attributable to DR in 2013 was 1.5 per 10 000 (95% CI 0.8–2.5) adults with diabetes aged 18-69 years.[20]

Comparisons of blindness incidence rates between studies are difficult. First, few countries maintain nationwide blindness registries and these registries differ in their definitions for blindness. The definition of blindness in Israel is less strict than that of the WHO (visual acuity <3/60).[14] In general, definitions of blindness in Israel are more comparable with those of Western Europe.[18] Secondly, most registries have not estimated overall blindness rates specifically among patients with diabetes.[21–23] Lastly, in some of the studies age ranges were limited to the working-age population.[20,23]

Population-based studies carried out during the past 20 years have revealed that cataract, glaucoma, macular degeneration, uncorrected refractive error, and diabetic retinopathy are the most common causes of blindness and vision impairment worldwide.[24] There was a decline in the incidence of blindness from all treatable or potentially preventable causes, such as glaucoma, diabetic retinopathy,

TABLE 3. Clinical and Demographic Characteristics of Blind Patients With Diabetes Stratified by Cause of Blindness

	ARMD (N = 438)	DR (N = 382)	Glaucoma (N = 186)	Cataract (N = 66)	Other[a] (N = 329)	*P* Value
Age (y), mean ± SD	79.9 ± 7.0	67.7 ± 10.8	75.3 ± 10.5	71.8 ± 10.6	68.8 ± 12.4	<.001
Sex						
Male	192 (43.8)	176 (46.1)	114 (61.3)	33 (50.0)	172 (52.3)	<.001
Female	246 (56.2)	206 (53.9)	72 (38.7)	33 (50.0)	157 (47.7)	
Smoking						
Yes	51 (11.9)	44 (11.7)	19 (10.4)	9 (13.9)	41 (12.9)	.921
Obesity						
BMI ≥30 kg/m^2	160 (40.2)	166 (46.5)	51 (30.5)	19 (31.7)	132 (44.4)	<.001
Glucose control						
HbA1c ≤7%	235 (57.9)	58 (16.3)	94 (57.7)	29 (49.2)	141 (45.8)	<.001
LDL-C control						
≤100Lmg/dl	289 (71.4)	206 (61.7)	111 (66.1)	44 (73.3)	193 (65.7)	.058
HDL-C control[b]						
Yes	216 (51.8)	136 (38.6)	84 (49.4)	28 (46.7)	144 (47.1)	.007
Diabetes duration						
>10 y	151 (36.9)	237 (62.0)	68 (39.3)	30 (45.5)	110 (35.0)	<.001
Insulin treatment						
Yes	69 (15.8)	276 (72.3)	41 (22.0)	14 (21.2)	95 (28.9)	<.001
CKD						
Yes	143 (33.7)	167 (45.9)	58 (33.7)	17 (27.0)	74 (23.3)	<.001
SES[c]						
Low	32 (7.3)	115 (30.1)	15 (8.1)	20 (30.3)	52 (15.8)	<.001
Intermediate	333 (76.4)	236 (61.8)	145 (78.0)	43 (65.2)	238 (72.3)	
High	71 (16.3)	31 (8.1)	26 (14.0)	3 (4.6)	39 (11.9)	

ARMD = age-related macular degeneration; BMI = body mass index; CKD = chronic kidney disease; DR = diabetic retinopathy; HbA1c = glycated hemoglobin (A1c); HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; SES = socioeconomic status.

Data are number (%) of cases, unless otherwise indicated.

[a]Includes: retinitis pigmentosa, optic atrophy, myopic maculopathy, problems with retina, vitreous hemorrhage, retinitis and other neuropathy.

[b]>40 mg/dL for men, >50 mg/dL for women.

[c]SES was determined according to the poverty index of the census enumeration area as defined by the Israeli Bureau of Statistics for the 2008 national census (low = 1-3; intermediate = 4-7; high = 8-10).

ARMD, and cataract in Israel over the last decade. However, DR is the most common ocular complication associated with diabetes[2] and is the leading cause of preventable blindness before the age of 74 years.[1] In the present study, among people with diabetes, ARMD was the most frequent cause of incident blindness in the 75+ age group and DR was the main cause in those aged 55-64.

According to our study, age between 55 and 64 years, duration of diabetes, insulin treatment, and poor glycemic control were independently associated with DR-related blindness among patients with diabetes. This is consistent with previous studies that found that duration of diabetes is one of the major nonmodifiable risk factors, and that higher HbA1c is one of the main modifiable risk factors, for the development and progression of DR.[10,25,26] The Diabetes Control and Complications Trial and United Kingdom Prospective Diabetes Study were 2 clinical trials that showed that tight glycemic control (HbA1c ≤7) could reduce the risk of DR development and progression in both type 1 diabetes and type 2 diabetes patients, respectively.[27] A recent meta-analysis involving participants with type 2 diabetes from 7 trials showed that intensive glycemic control reduced the risk of DR by 20%.[28] Chronic exposure to hyperglycemia combined with other risk factors such as hypertension are believed to initiate a cascade of biochemical and physiological changes that ultimately lead to microvascular damage and retinal dysfunction.[1] Optimum control of blood glucose and blood pressure remains the foundation for reduction of the risk of DR development and progression.

In our study, poor control of LDL-C was found to be significantly associated with DR-related blindness, whereas HDL-C was not. Various studies have reported inconsistent results regarding the effects of blood lipids on the development and progression of DR.[29,30] In the Madrid Diabetes Study, which included 3443 persons with type 2 diabetes, higher levels of LDL-C increased the 4-year risk of DR by 8-fold.[31] The Hoorn study demonstrated no relationship

TABLE 4. Adjusted Multinomial Logistic Regression[a] of Risk Factors Associated With Age-Related Macular Degeneration, Diabetic Retinopathy, Glaucoma, and Cataract-Related Blindness

	ARMD		DR		Glaucoma		Cataract	
	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Sex								
Female vs male	1.19 (0.96–1.48)	.11	1.13 (0.91–1.42)	.28	0.48 (0.34–0.67)	<.001	0.91 (0.54–1.54)	.73
Age groups								
18-54	Ref.		Ref.		Ref.		Ref.	
55-64	1.61 (0.31–8.27)	.57	1.80 (1.26–2.56)	.001	1.67 (0.64–4.31)	.29	3.06 (0.87–10.81)	.08
65-74	21.45 (5.25–87.65)	<.001	1.20 (0.82–1.76)	.34	4.52 (1.90–10.79)	<.001	3.45 (0.98–12.18)	.054
75+	116.0 (28.71–468.41)	<.001	0.92 (0.61–1.40)	.70	11.13 (4.71–26.31)	<.001	7.58 (2.17–26.54)	.002
Diabetes duration								
>10 y	0.95 (0.75–1.19)	.64	1.93 (1.50–2.48)	<.001	1.10 (0.77–1.58)	.60	1.65 (0.93–2.92)	.09
Poor glucose control								
HbA1c >7%	1.03 (0.82–1.29)	.79	2.14 (1.56–2.92)	<.001	0.84 (0.59–1.19)	.32	0.99 (0.57–1.73)	.97
Poor LDL-C control								
(≥100 mg/dL)	0.88 (0.70–1.12)	.30	1.41 (1.12–1.77)	.003	1.34 (0.95–1.88)	.10	0.78 (0.43–1.41)	.41
Poor HDL-C control								
(≤40 mg/dL for men, >50 mg/dL for women)	0.95 (0.77–1.17)	.61	1.02 (0.81–1.28)	.88	1.01 (0.73–1.40)	.94	1.03 (0.61–1.73)	.93
Insulin treatment								
Yes vs no	1.15 (0.86–1.55)	.35	5.69 (4.30–7.54)	<.001	1.44 (0.94–2.21)	.09	0.97 (0.49–1.93)	.93
Smoking								
Yes vs no	1.79 (1.28–2.50)	<.001	0.81 (0.56–1.15)	.235	0.97 (0.56–1.68)	.91	0.92 (0.38–2.19)	.85
CKD								
Yes vs no	0.89 (0.71–1.12)	.33	3.15 (2.46–4.03)	<.001	1.18 (0.82–1.69)	.37	0.90 (0.47–1.71)	.74
SES								
Low	0.95 (0.60–1.51)	.83	3.78 (2.37–6.04)	<.001	1.03 (0.52–2.03)	.93	7.84 (2.26–27.21)	.001
Intermediate	1.14 (0.85–1.52)	.39	1.86 (1.20–2.89)	.006	1.15 (0.73–1.81)	.55	2.78 (0.86–8.99)	.09
High	Ref.		Ref.		Ref.		Ref.	

ARMD = age-related macular degeneration; BMI = body mass index; CI = confidence interval; CKD = chronic kidney disease; DR = diabetic retinopathy; HbA1c = glycated hemoglobin (A1c); HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; SES = socioeconomic status.

[a]The categories of the outcome variable were ARMD, DR, glaucoma, cataract, and no blindness as reference category.

between total cholesterol, HDL-C, and triglyceride levels and the incidence of DR.[29] Tomić and associates[30] demonstrated no statistically significant differences in cholesterol levels between patients with different severity of DR.

In this study, smoking was not found to be associated with DR-related blindness. Previous studies have also shown inconsistent results regarding the association between smoking and DR.[10,27] There is some evidence that smoking may protect against the progression of retinopathy in patients with type 2 diabetes.[32]

In this study, lower SES was significantly associated with DR and cataract-related blindness. This can possibly be attributed to a number of factors. Poor control of HbA1c and blood pressure, as well as lack of awareness and limited access to treatment, have been shown to be associated with low SES.[33–35] In Israel, all citizens have medical insurance that provides a broad basket of medical services. Overall rates of eye examination among diabetes patients aged 18-84 years in Israel increased, from 63.8% in 2008 to 74.2% in 2013.[36] Regarding SES, the rates were slightly higher for patients exempt from medical copayments owing to poverty (75.5%) compared with those with no financial exemption (73.6%).[36] In light of this fact, we assume that the association between low SES and blindness is not owing to lack of detection, but rather because of lack of awareness of treatment options or limited access to treatments. Laser photocoagulation and treatment with anti–vascular endothelial growth factor (anti-VEGF) agents have improved vision outcomes and reduced the worsening of DR, macular edema, and ARMD. Randomized controlled trials have shown that early treatment can reduce an individual's risk of severe visual loss by 57%.[37] However, despite available screening and effective treatments such as laser and anti-VEGF therapy for preservation of vision, DR remains the third-leading cause of blindness in Israel.[38]

Duration of diabetes was associated with cataract-related blindness with borderline significance; this may be owing to insufficient statistical power. Other causes of blindness

were not associated with clinical parameters of diabetes in this study. Numerous studies have documented an association between diabetes and cataracts.[39–41] Deposits of advanced glycation end products in the lens have been postulated as one possible pathogenic mechanism for diabetic cataract. A few previous studies found positive associations between hyperglycemia and diabetes treated with insulin and glaucoma, but in this study such associations were not found.[7,42,43]

Our study has several methodologic strengths, including its good external validity, since data were obtained from nonselective nationwide registries and included information regarding both clinical and demographic variables for all patients with diabetes. However, some important issues need to be considered. First, our study did not have data on stages of DR and ARMD or types of cataract and glaucoma, which would have enabled us to account for the important contribution of these factors to blindness. Second, it was difficult to determine the exact time of onset of blindness, and we arbitrarily defined the time of occurrence of blindness as the year when the patient was registered as having legal blindness. In addition, we have no data about persons who became blind and died prior to the receipt of certification, but we expect that the number of blindness cases to be missed was very small. At any rate, it would mean that our findings might have slightly underestimated the true relation between diabetes and blindness. Finally, data on some variables that can be associated with blindness, such as hypertension, other comorbidities, treatments and type of diabetes were missing in our analysis.

In conclusion, the results of this nationwide study demonstrate that diabetes is still a significant risk for blindness; therefore, efforts to optimize the metabolic control of diabetes and improve the treatment of early stages of DR should be continued. In addition, the SES-related disparities in the risk of DR and cataract-related blindness need to be addressed, by directing efforts to enhance accessibility of appropriate treatment for all diabetic patients, thus contributing to the prevention of unnecessary blindness, especially among the underprivileged diabetic population.

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REFERENCES

1. Klein BE. Overview of epidemiologic studies of diabetic retinopathy. *Ophthalmic Epidemiol* 2007;14(4):179–183.
2. Cheung N, Mitchell P, Wong TY. Diabetic retinopathy. *Lancet* 2010;376(9735):124–136.
3. Yau JW, Rogers SL, Kawasaki R, et al. Global prevalence and major risk factors of diabetic retinopathy. *Diabetes Care* 2012;35(3):556–564.
4. Klein R, Knudtson MD, Lee KE, Gangnon R, Klein BE. The Wisconsin Epidemiologic Study of Diabetic Retinopathy: XXII the twenty-five-year progression of retinopathy in persons with type 1 diabetes. *Ophthalmology* 2008;115:1859–1868.
5. World Health Organization. Prevention of Blindness from Diabetes Mellitus. Report of WHO consultation in Geneva, Switzerland, 9-11 November 2005. Available at: http://www.who.int/blindness/Prevention%20of%20Blindness%20from%20Diabetes%20Mellituswith-cover-small.pdf. Accessed December 24, 2017.
6. Stefansson E. Prevention of diabetic blindness. *Br J Ophthalmol* 2006;90(1):2–3.
7. Jeganathan VS, Wang JJ, Wong TY. Ocular associations of diabetes other than diabetic retinopathy. *Diabetes Care* 2008;31(9):1905–1912.
8. Mitchell P, Wang JJ. Diabetes, fasting blood glucose and age-related maculopathy: The Blue Mountains Eye Study. *Aust N Z J Ophthalmol* 1999;27(3-4):197–199.
9. Saaddine JB, Honeycutt AA, Narayan KM, Zhang X, Klein R, Boyle JP. Projection of diabetic retinopathy and other major eye diseases among people with diabetes mellitus: United States, 2005-2050. *Arch Ophthalmol* 2008;126(12):1740–1747.
10. Hippisley-Cox J, Coupland C. Development and validation of risk prediction equations to estimate future risk of blindness and lower limb amputation in patients with diabetes: cohort study. *BMJ* 2015;351:h5441.
11. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 1998;352(9131):837–853.
12. 2008 Census of Population and Housing Jerusalem (ISR): Israel Central Bureau of Statistics; 2008.
13. Brosius FC 3rd, Hostetter TH, Kelepouris E, et al. Detection of chronic kidney disease in patients with or at increased risk of cardiovascular disease: a science advisory from the American Heart Association Kidney and Cardiovascular Disease Council; the Councils on High Blood Pressure Research, Cardiovascular Disease in the Young, and Epidemiology and Prevention; and the Quality of Care and Outcomes Research Interdisciplinary Working Group: developed in collaboration with the National Kidney Foundation. *Circulation* 2006;114(10):1083–1087.
14. Avisar R, Friling R, Snir M, Avisar I, Weinberger D. Estimation of prevalence and incidence rates and causes of blindness in Israel, 1998-2003. *Isr Med Assoc J* 2006;8(12):880–881.
15. Farber MD. National Registry for the Blind in Israel: estimation of prevalence and incidence rates and causes of blindness. *Ophthalmic epidemiol* 2003;10(4):267–277.

16. Breslow NE, Day NE. (1987) Statistical methods in cancer research. The design and analysis of cohort studies. *IARC Sci Publ* 1987;(82):1–406.
17. Agardh E, Agardh CD, Hansson-Lundblad C. The five-year incidence of blindness after introducing a screening programme for early detection of treatable diabetic retinopathy. *Diabet Med* 1993;10(6):555–559.
18. Lin S, Gupta B, James N, Ling RH. Visual impairment certification due to diabetic retinopathy in North and Eastern Devon. *Acta Ophthalmol* 2017;95(8):e756–e762.
19. Hall HN, Chinn DJ, Sinclair A, Styles CJ. Epidemiology of blindness attributable to diabetes in Scotland: change over 20 years in a defined population. *Diabet Med* 2013;30(11): 1349–1354.
20. Tracey ML, McHugh SM, Fitzgerald AP, Buckley CM, Canavan RJ, Kearney PM. Trends in blindness due to diabetic retinopathy among adults aged 18-69 years over a decade in Ireland. *Diabetes Res Clin Pract* 2016;121:1–8.
21. Trautner C, Haastert B, Richter B, Berger M, Giani G. Incidence of blindness in southern Germany due to glaucoma and degenerative conditions. *Invest Ophthalmol Vis Sci* 2003; 44(3):1031–1034.
22. Yong VK, Morgan WH, Cooper RL, et al. Trends in registered blindness and its causes over 19 years in Western Australia. *Ophthalmic Epidemiol* 2006;13(1):35–42.
23. Cedrone C, Culasso F, Cesareo M, et al. Incidence of blindness and low vision in a sample population: the Priverno Eye Study, Italy. *Ophthalmology* 2003;110(3):584–588.
24. Bourne RR, Stevens GA, White RA, et al. Causes of vision loss worldwide, 1990-2010: a systematic analysis. *Lancet Glob Health* 2013;1(6):e339–349.
25. Sabanayagam C, Yip W, Ting DS, Tan G, Wong TY. Ten emerging trends in the epidemiology of diabetic retinopathy. *Ophthalmic Epidemiol* 2016;23(4):209–222.
26. Matthews DR, Stratton IM, Aldington SJ, et al. Risks of progression of retinopathy and vision loss related to tight blood pressure control in type 2 diabetes mellitus: UKPDS 69. *Arch Ophthalmol* 2004;122(11):1631–1640.
27. Stratton IM, Kohner EM, Aldington SJ, et al. UKPDS 50: risk factors for incidence and progression of retinopathy in Type II diabetes over 6 years from diagnosis. *Diabetologia* 2001;44(2): 156–163.
28. Hemmingsen B, Lund SS, Gluud C, et al. Intensive glycaemic control for patients with type 2 diabetes: systematic review with meta-analysis and trial sequential analysis of randomised clinical trials. *BMJ* 2011;343:d6898.
29. van Leiden HA, Dekker JM, Moll AC, et al. Risk factors for incident retinopathy in a diabetic and nondiabetic population: the Hoorn study. *Arch Ophthalmol* 2003;121(12):245–251.
30. Tomić M, Ljubić S, Kaštelan S, Gverović Antunica A, Jazbec A, Poljičanin T. Inflammation, haemostatic disturbance, and obesity: possible link to pathogenesis of diabetic retinopathy in type 2 diabetes. *Mediators Inflamm* 2013; 2013:818671.
31. Salinero-Fort MA, San Andres-Rebollo FJ, de Burgos-Lunar C, Arrieta-Blanco FJ, Gomez-Campelo P. Four-year incidence of diabetic retinopathy in a Spanish cohort: the MADIABETES study. *PLoS One* 2013;8(10):e76417.
32. Omae T, Nagaoka T, Yoshida A. Effects of habitual cigarette smoking on retinal circulation in patients with type 2 diabetes. *Invest Ophthalmol Vis Sci* 2016;57(3): 1345–1351.
33. Wang W, Yan W, Muller A, Keel S, He M. Association of Socioeconomics With Prevalence of Visual Impairment and Blindness. *JAMA Ophthalmol* 2017;135(12):1295–1302.
34. Huang OS, Tay WT, Tai ES, et al. Lack of awareness amongst community patients with diabetes and diabetic retinopathy: the Singapore Malay eye study. *Ann Acad Med Singapore* 2009;38(12):1048–1055.
35. Islam FM, Chakrabarti R, Islam SZ, Finger RP, Critchley C. Factors associated with awareness, attitudes and practices regarding common eye diseases in the general population in a rural district in Bangladesh: the Bangladesh Population-based Diabetes and Eye Study (BPDES). *PLoS One* 2015; 10(7):e0133043.
36. Manor O, Shmueli A, Ben-Yehuda A, Paltiel O, Calderon R, Jaffe DH. National Program for Quality Indicators in Community Healthcare in Israel Report, 2008-2010. Jerusalem, Israel: School of Public Health and Community Medicine, Hebrew University-Hadassah; 2012.
37. Grading diabetic retinopathy from stereoscopic color fundus photographs–an extension of the modified Airlie House classification. ETDRS report number 10. Early Treatment Diabetic Retinopathy Study Research Group. *Ophthalmology* 1991;98(5 Suppl):786–806.
38. Skaat A, Chetrit A, Belkin M, Kinori M, Kalter-Leibovici O. Time trends in the incidence and causes of blindness in Israel. *Am J Ophthalmol* 2012;153(2):214–221.
39. Pirie A. Epidemiological and biochemical studies of cataract and diabetes. *Invest Ophthalmol* 1965;4:629–637.
40. Mukesh BN, Le A, Dimitrov PN, Ahmed S, Taylor HR, McCarty CA. Development of cataract and associated risk factors: the Visual Impairment Project. *Arch Ophthalmol* 2006;124(1):79–85.
41. Negahban K, Chern K. Cataracts associated with systemic disorders and syndromes. *Curr Opin Ophthalmol* 2002;13(6): 419–422.
42. Yanagi M, Kawasaki R, Wang JJ, Wong TY, Crowston J, Kiuchi Y. Vascular risk factors in glaucoma: a review. *Clin Exp Ophthalmol* 2011;39(3):252–258.
43. Topouzis F, Wilson MR, Harris A, et al. Risk factors for primary open-angle glaucoma and pseudoexfoliative glaucoma in the Thessaloniki eye study. *Am J Ophthalmol* 2011; 152(2):219–228.e1.