



Incidence and Determinants of Intraocular Lens Implantation in Type 2 Diabetes: The Fremantle Diabetes Study Phase II

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OBJECTIVE

To compare the incidence of intraocular lens (IOL) implantation for cataracts between people with and without type 2 diabetes and to determine associated risk factors in those with type 2 diabetes.

RESEARCH DESIGN AND METHODS

Participants with type 2 diabetes ($n = 1,499$) from the community-based observational Fremantle Diabetes Study Phase II (FDS2) were age, sex, and zip code matched 1:4 with residents without diabetes. IOL implantation status was ascertained between entry (2008–2011) and the end of 2016 using validated data linkage. Age-specific incidence rates and incidence rate ratios (IRRs) for cataract surgery were calculated. Predictors of IOL implantation in FDS2 participants were assessed using proportional hazards and competing risk regression modeling.

RESULTS

The crude IRR (95% CI) for cataract surgery in FDS2 participants (mean \pm SD age 62.8 ± 10.8 years at entry) versus the matched group without diabetes was 1.50 (1.32–1.71), with the highest relative risk in those aged 45–54 years at the time of surgery (7.12 [2.05–27.66]). Competing risk analysis showed that age at entry, diabetes duration, serum HDL cholesterol, serum triglycerides, a severe hypoglycemic episode in the past year, and Asian and southern European ethnicity increased the risk of cataract surgery in participants with type 2 diabetes ($P \leq 0.025$).

CONCLUSIONS

People with type 2 diabetes, especially those in younger age-groups, are at a significantly increased risk of cataract surgery than matched people without diabetes. Multifaceted prevention strategies should be incorporated as part of routine care. As well as limiting ultraviolet light exposure, these might include lipid-modifying treatment and strategies to avoid severe hypoglycemia.

Cataracts are lens opacities that impair clarity of vision. They are the leading cause of visual impairment in the elderly in developed countries and the leading cause of blindness worldwide (1,2). A meta-analysis has shown that compared with people without diabetes, those with type 2 diabetes have almost double the odds of developing any type of cataract (3). Putative underlying mechanisms include increased oxidative stress through activation of the polyol pathway (4).

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The only approved cataract treatment is surgical extraction with implantation of an intraocular lens (IOL), allowing visual rehabilitation. Increasing surgical demand has highlighted the need for cataract prevention (5), especially because surgery is expensive and can worsen other preexisting ocular complications in type 2 diabetes (6). Risk factors for cataracts complicating type 2 diabetes, including those that are potentially modifiable, have been assessed in only a few longitudinal studies. The available data are inconsistent, and none of the studies have addressed the influence of the competing risk of death (7–22).

Although cataracts are strongly associated with increasing age and suboptimal glycemic control, the contributions of diabetes treatment, serum lipids, smoking, and blood pressure are less clear (7–22). The primary aim of this study, therefore, was to determine the incidence of and risk factors for IOL implantation for visually significant cataracts in well-characterized community-based people with type 2 diabetes. The secondary aim was to compare the incidence of IOL implantation between people with and without type 2 diabetes from the same community.

RESEARCH DESIGN AND METHODS

Participants and Approvals

The Fremantle Diabetes Study Phase II (FDS2) is a prospective, longitudinal, observational study of people with diabetes from a zip code–defined urban community of 157,000 people in the state of Western Australia (WA). Residents within the catchment area with a physician-confirmed diabetes diagnosis and those who had participated in FDS1 but had relocated were eligible. Sample characteristics, including classification of diabetes type and details of those not recruited, have been described previously (23). Briefly, 4,639 people with diabetes were identified, and 1,668 (36%) were recruited together with 64 FDS1 participants. Of these 1,732 people, 1,551 (89.5%) had type 2 diabetes, of whom 1,499 were resident within the FDS2 study area and included in the current analysis. The South Metropolitan Area Health Service human research ethics committee (East Perth, WA, Australia) approved FDS2, and written

informed consent was obtained from each participant.

Participants in FDS2 were age, sex, and zip code matched to four deidentified people without diabetes randomly selected using the WA electoral roll and, for those age <18 years, using birth registrations. Because it is compulsory for Australian adult citizens to vote, all residents within the FDS2 catchment area should be listed on the electoral roll. Zip code matching was performed because of variations in socioeconomic/demographic status within the catchment area. Data related to the matched residents, who had never been coded with diabetes on any WA health database before study entry, were available through the WA Data Linkage System, including the Hospital Morbidity Data Collection from which the Charlson comorbidity index (CCI) was calculated for the 5-year period before entry (24), and through death registrations.

Clinical Assessment

All FDS2 participants underwent detailed face-to-face assessment at study entry and then biennially (23). Each assessment included questionnaires that covered health care utilization, medical conditions, medication use, and socioeconomic, demographic, and lifestyle data. Treatment history, BMI, age at diagnosis, nature of initial presentation, case record, and/or self-identification were used to determine diabetes type (25). Participants with type 2 diabetes were not treated with insulin and diagnosed at ≥ 60 years of age or were diagnosed at age <60 years and not initially treated with insulin (25). Severe hypoglycemic episodes (requiring second-party assistance) in the year preceding study entry were ascertained from self-report.

A physical examination was conducted by trained nurses according to a standard protocol, including visual acuity measured using a Bailey-Lovie chart at a distance of 3 m in a well-lit room and fundus photography. Biochemical tests were performed on fasting samples using standard automated methods in a single nationally accredited laboratory (25). Plasma N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentrations were measured by commercial assay. Estimated glomerular filtration rate (eGFR) was calculated using the Chronic

Kidney Disease Epidemiology Collaboration equation (26).

Ascertainment of Cataract Surgery and Mortality

The Hospital Morbidity Data Collection and death registrations capture all hospitalizations (including IOL procedures, which are classified as same-day admissions) and deaths, respectively, in WA. These sources were accessed for FDS2 participants and matched individuals without diabetes through the WA Data Linkage System. The data were used to determine IOL status from relevant ICD-9-CM and ICD-10-AM diagnosis/procedure codes (Supplementary Table 1) and follow-up time to end of 2016. The admission date was considered the date of IOL implantation. The diagnosis and procedure codes were checked for consistency; a participant with a cataract diagnosis code was expected to have had an IOL procedure because patients usually are not hospitalized for cataracts alone. When a cataract diagnosis was made without an IOL procedure code and where an IOL procedure was performed without a cataract diagnosis, the coding was checked from available information.

Statistical Analysis

Statistical analyses were conducted using SPSS for Windows version 22.0 (IBM Corporation, Armonk, NY) and Stata 15.1 (StataCorp, College Station, TX) software. Data are presented as proportions, means \pm SDs, geometric means (SD range), or medians with interquartile ranges (IQRs). For independent samples, two-way comparisons for categorical variables were by Fisher exact test; for normally or log-normally distributed continuous variables, by independent samples *t* test; and for variables not conforming to normal or log-normal distribution, by Mann-Whitney *U* test. A two-tailed significance level of $P < 0.05$ was used.

Age- and sex-specific incidence rates (IRs) for first IOL implantation for the FDS2 cohort were compared with the matched group without diabetes, and incident rate ratios (IRRs) were calculated during follow-up to first IOL implantation, death, or end of 2016, whichever came first. Because of the small number of cataract surgeries in younger people, 10-year age-groups from age 45 years were selected.

To determine the effect of diabetes on first IOL implantation for cataract, cause-specific hazard ratios (csHRs) from Cox proportional hazards modeling (forward conditional modeling $P < 0.05$ for entry and $P > 0.10$ for removal) as well as subdistributional hazard ratios (sdHRs) from Fine and Gray modeling, which allows for the competing risk of death, were generated 1) with type 2 diabetes as the sole independent variable and 2) with adjustment for explanatory/confounding variables. Because of the presence of covariates strongly associated with age, age was used as the time scale, with left truncation at study entry. Because the cohort without diabetes was deidentified, limited variables were available for adjustment in this group (age, sex, and comorbidities defined by the CCI). The proportional hazards assumption was checked using time-varying covariates. When this assumption was violated, a time-varying interaction of the covariate with $\ln(\text{age as time scale})$ was included in the model. The 8-year cumulative incidence of IOL implantation for cataracts by diabetes status was determined from an unadjusted Fine and Gray competing risk model, using time from study entry as the time scale.

To identify the determinants of IOL implantation in the FDS2 cohort, multivariate modeling was performed. Baseline

risk factors for incident IOL implantation and all-cause death were explored using all variables available from FDS2 assessments. Variables were considered for model entry on the basis of clinical relevance and $P < 0.20$ in bivariate analysis.

RESULTS

Participant Disposition

The disposition of FDS2 participants and matched people without diabetes is shown in Fig. 1. Procedure and diagnosis codes were inconsistent on 22 occasions. Ten people (three in FDS2 and seven matched individuals without diabetes) had a cataract diagnosis code that was not associated with an IOL procedure code, suggesting incorrect coding, and were excluded. Twelve people (four in FDS2 and eight matched individuals without diabetes) underwent IOL implantation for refractive error and were censored at the time of surgery. Three hundred thirteen FDS2 participants and 856 matched people who had undergone cataract surgery before commencing the study also were excluded.

Baseline Characteristics and IOL Implantation IRs

The 1,183 FDS2 participants without prior cataract surgery had a mean \pm SD

age of 62.8 ± 10.8 years at study entry, 52.6% were male, and their median (IQR) diabetes duration was 8.7 years (2.0–14.0). During 6,949 person-years of follow-up from baseline (median [IQR] 6.4 years [4.9–7.5]), 311 (26.3%) were hospitalized for first IOL implantation (IR 44.76 [95% CI 39.92–50.02] per 1,000 person-years).

The 5,133 matched people without diabetes and no prior cataract surgery had a mean age of 63.4 ± 11.1 years at the time their matched FDS2 participants were recruited, and 52.6% were male. Although there was some loss of matched individuals because of the exclusion of those with prior IOL implantation, incorrect coding for IOL, or censoring, no statistically significant difference was found in age or sex by diabetes status ($P \geq 0.97$). During 31,136 person-years of follow-up (median 6.6 years [IQR 5.5–7.7]), 928 (18.1%) had a first cataract surgery (IR 29.81 [95% CI 27.92–31.79] per 1,000 person-years). During follow-up, hospitalization data were used to identify matched residents without diabetes at baseline who were diagnosed with diabetes after baseline. There were 475 individuals who developed diabetes during follow-up. Of these, 180 had cataract surgery before or at the time of diabetes diagnosis and were included as an IOL implantation end point

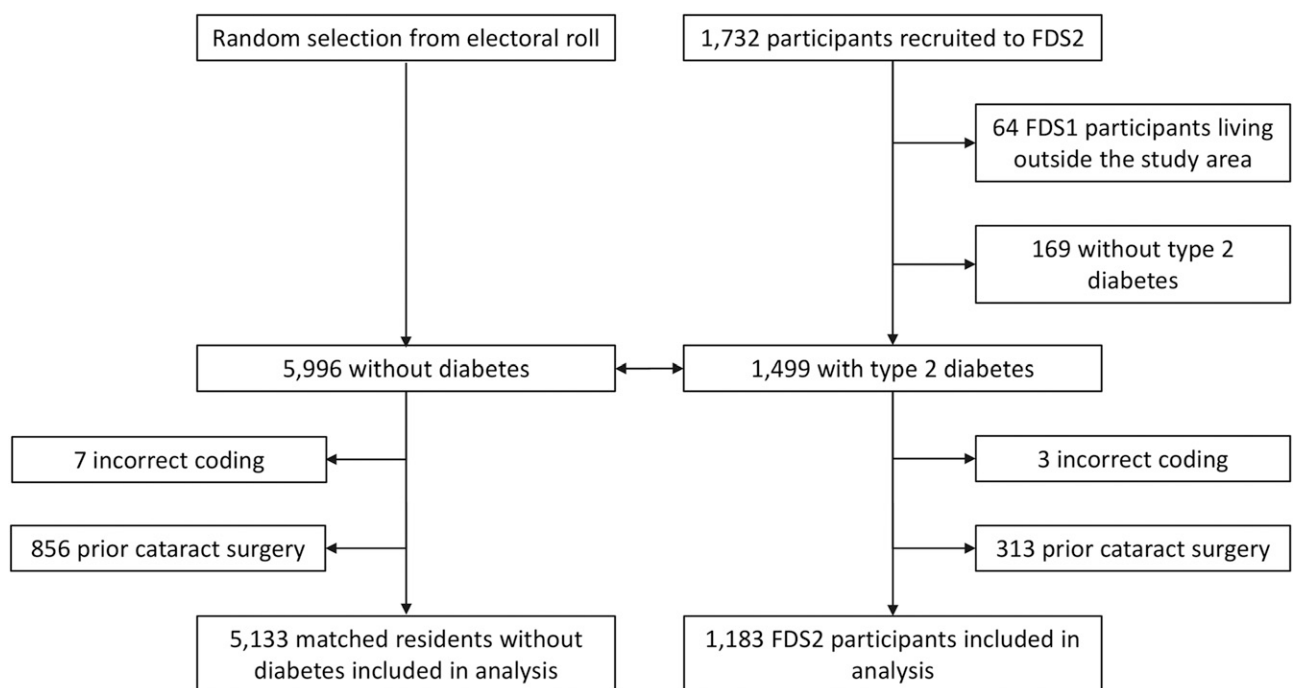


Figure 1—CONSORT (Consolidated Standards of Reporting Trials) diagram showing participants included in analyses.

and 295 were censored at the time of diabetes diagnosis.

The crude IRR for first IOL implantation in FDS2 participants with type 2 diabetes versus the matched cohort was 1.50 (95% CI 1.32–1.71; $P < 0.001$). Age-specific IRs and IRRs for cataract surgery from age 45 years are shown in Table 1. Within age-specific subgroups, the IRR decreased with increasing age from seven times higher in the 45–54-year age-group to 32% higher in the 75–84-year age-group. All age-groups showed a significantly higher rate in the FDS2 participants compared with the matched cohort apart from those age ≥ 85 years. No significant difference was found in the crude IRR between males and females in the FDS2 cohort (0.93 [95% CI 0.75–1.16]), but males had a significantly lower IR than females in the cohort without diabetes (IRR 0.87 [0.77–0.99]).

Type 2 Diabetes and IOL Implantation Incidence

Because diabetes status violated the proportional hazards assumption for both IOL implantation incidence and all-cause death, diabetes \times ln(age as time scale) was added to each model, and the regression coefficients and 95% CIs were calculated (Supplementary Table 2). With increasing age, the risk of incident IOL implantation and all-cause death in those with type 2 diabetes was attenuated toward the risk in those without diabetes (Supplementary Fig. 1). Type 2 diabetes increased the csHR of IOL implantation 3.82 times in those 50 years of age at census compared with only 1.28 times in 80-year-olds in the unadjusted Cox model and the sdHR 3.76

times in 50-year-olds compared with 1.23 times in 80-year-olds in the unadjusted Fine and Gray model. After adjustment for baseline age, sex, and CCI, the respective HRs ranged from 3.67 to 1.28 in the Cox model and 3.49 to 1.30 in the Fine and Gray model. In the adjusted Fine and Gray model, male sex decreased the risk of cataract surgery (sdHR 0.79 [95% CI 0.71–0.89]; $P < 0.001$). The unadjusted HR for all-cause death was 4.51 times higher in 50-year-olds with type 2 diabetes versus no diabetes and 1.06 times higher in 80-year-olds. After adjustment, these HRs reduced to 2.94 and 0.90, respectively. The 8-year cumulative IR (95% CI) of IOL implantation for cataract surgery was 29.3% (26.4–32.3) in those with type 2 diabetes and 20.0% (18.8–21.2) in those without diabetes (Supplementary Fig. 2).

Predictors of First IOL Implantation in the FDS2 Cohort

Baseline bivariate associations by incident IOL status are shown in Table 2 for the FDS2 type 2 diabetes cohort. Compared with those without incident IOL implantation, those who had cataract surgery were older and more likely to be Indigenous Australian, current smokers, on insulin, and on antihypertensive and lipid-modifying medications; to have ischemic heart disease and peripheral sensory neuropathy; and to have had a prior severe hypoglycemic event. They had a higher daily alcohol intake, urinary albumin-to-creatinine ratio, serum HDL cholesterol (HDL-C) concentration, and supine systolic blood pressure. They were more likely to have a lower

BMI, supine diastolic blood pressure, and eGFR. No statistically significant difference was found in the proportion who died during follow-up between those who underwent and did not undergo cataract surgery (13.1% and 10.3%, respectively; $P = 0.23$).

Because diabetes duration violated the proportional hazards assumption for IOL implantation incidence, diabetes duration \times ln(age as time scale) was added to each model and regression coefficients with 95% CIs calculated (Table 3). Independent predictors of first cataract surgery obtained from the Cox model and the Fine and Gray model are shown together with the Cox model for all-cause death. Death during follow-up was predicted by age at study entry, heart rate, current smoking, male sex, NT-proBNP, and CCI (excluding diabetes-specific components). None of these were significant predictors of incident cataract surgery in the Cox model. In the Fine and Gray model, age at study entry and all the variables in the Cox model were statistically significant predictors of cataract surgery.

The effect of diabetes duration on the risk of incident IOL implantation by age (as time scale) in people whose other risk factors (age at study entry, HDL-C, triglycerides, severe hypoglycemia, ethnicity) were the same is illustrated in Supplementary Fig. 3. With increasing age, the risk of incident IOL implantation in those with diabetes duration of 20 years was attenuated toward the risk in those with newly diagnosed diabetes. Diabetes duration of 20 years increased the csHR of IOL by 7.58 times in those 50 years of age at census compared

Table 1—Age-specific IR, IRR, and IR difference per 1,000 person-years of first cataract surgery for people with type 2 diabetes (FDS2) versus matched people without diabetes

	Age-group (years)					
	45–54	55–64	65–74	75–84	≥ 85	All ≥ 45
FDS2						
With IOL procedure (n)	8	38	128	119	13	306
Person-years of follow-up	870.86	2,187.37	2,385.83	1,147.05	87.89	6,679
IR	9.19	17.37	53.65	103.74	147.91	45.82
No diabetes						
With IOL procedure (n)	5	77	357	432	56	927
Person-years of follow-up	3,874.93	9,274.65	10,676.03	5,482.11	662.81	29,970.53
IR	1.29	8.30	33.44	78.80	84.49	30.93
IRR	7.12	2.09	1.60	1.32	1.75	1.48
95% CI	2.05–27.66	1.38–3.12	1.30–1.97	1.07–1.62	0.88–3.24	1.30–1.69
IR difference	7.90	9.07	20.21	24.94	63.42	14.88
95% CI	1.43–14.36	3.24–14.90	10.29–30.13	4.88–45.01	–19.97 to 146.82	9.38–20.39

Table 2—Baseline characteristics of FDS2 participants with no prior cataract surgery by IOL status to end of 2016

	No history of IOL implantation during follow-up	IOL during follow-up	P value
n (%)	872 (73.7)	311 (26.3)	
Age (years)	60.6 ± 10.5	68.7 ± 9.2	<0.001
Male sex	53.4	50.2	0.32
Ethnic background			0.020
Anglo-Celtic	51.5	52.4	0.79
Southern European	10.9	14.5	0.10
Other European	7.0	7.7	0.70
Asian	4.2	6.1	0.21
Indigenous Australian	9.4	4.2	0.003
Mixed/other	17.0	15.1	0.48
Private health insurance	60.4	61.1	0.89
Duration of diabetes (years at study entry)	5.0 (1.6–12.0)	11.0 (4.0–11.0)	<0.001
Diabetes treatment			0.001
Diet	27.6	20.9	
Oral agents	55.1	52.4	
Insulin ± oral agents	17.3	26.7	
Fasting glucose (mmol/L)	7.3 (6.2–9.1)	7.3 (6.2–9.1)	0.97
HbA _{1c} (%)	6.8 (6.2–7.8)	6.9 (6.2–7.7)	0.70
HbA _{1c} (mmol/mol)	51 (44–62)	52 (44–61)	0.70
Minor hypoglycemic episode in past year	22.3	24.4	0.43
Severe hypoglycemic episode in past year	3.2	6.8	0.012
Self-monitors blood glucose	83.1	84.2	0.72
BMI (kg/m ²)	31.9 ± 6.3	30.7 ± 6.1	0.005
Supine SBP (mmHg)	143 ± 21	147 ± 21	0.001
Supine DBP (mmHg)	81 ± 12	78 ± 11	<0.001
On antihypertensive medication	67.4	77.2	0.003
ACE inhibitor	66.1	55.9	0.002
ARB	30.0	31.8	0.57
β-Blocker	17.9	22.5	0.08
Calcium channel blocker	19.4	25.4	0.028
On lipid-modifying medication	62.5	72.3	0.002
Statins	61.8	71.4	0.002
Fibrates	2.3	1.9	0.82
Corticosteroid use	0.8	1.6	0.32
Asthma medications	8.1	8.7	0.72
Total cholesterol (mmol/L)	4.4 ± 1.1	4.4 ± 1.2	0.54
Serum HDL-C (mmol/L)	1.2 ± 0.3	1.3 ± 0.4	<0.001
Serum triglycerides (mmol/L)	1.5 (0.9–2.6)	1.6 (0.9–2.7)	0.80
Urinary albumin-to-creatinine (mg/mmol)	2.7 (0.7–9.7)	3.8 (0.9–16.6)	<0.001
eGFR (CKD-EPI) category (mL/min/1.73 m ²)			<0.001
≥90	51.4	28.9	
60–89	38.3	52.6	
45–59	6.1	9.4	
30–44	3.0	6.2	
15–29	1.1	1.3	
<15	0	1.6	
Plasma NT-proBNP (pmol/L)	54.0 (13.3–219.2)	93.3 (24.4–356.8)	<0.001
Ischemic heart disease	22.1	30.5	0.003
Cerebrovascular disease	5.3	8.4	0.05
Peripheral sensory neuropathy	51.3	62.5	0.001
Alcohol (standard drinks/day)	0.3 (0–1.2)	0.1 (0–1.2)	0.025
Current smoker	13.0	8.0	0.023
Eye test in past year	78.7	82.8	0.15
Visual acuity <6/19	1.0	2.3	0.15

Data are %, mean ± SD, geometric mean (SD range), or median (IQR). ARB, angiotensin receptor blocker; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; DBP, diastolic blood pressure; SBP, systolic blood pressure.

Table 3—Models of independent predictors of first incident cataract surgery and the competing event of death in FDS2 participants

Outcome and baseline variable	Cox model coefficient (95% CI)	P value	Fine and Gray model coefficient (95% CI)	P value
First cataract surgery				
Main				
Age at study entry (increase of 1 year)			0.069 (0.038–0.100)	<0.001
Diabetes duration (increase of 1 year)	0.830 (0.415–1.244)	<0.001	0.773 (0.392–1.154)	<0.001
Serum HDL-C (increase of 0.1 mmol/L)	0.063 (0.025–0.101)	0.001	0.077 (0.043–0.110)	<0.001
Ln(serum triglycerides) (mmol/L) [†]	0.476 (0.221–0.730)	<0.001	0.473 (0.227–0.720)	<0.001
Severe hypoglycemic episode in past year	0.927 (0.478–1.377)	<0.001	0.794 (0.349–1.238)	<0.001
Asian ethnicity	0.635 (0.146–1.124)	0.011	0.696 (0.209–1.183)	0.005
Southern European ethnicity	0.379 (0.057–0.702)	0.021	0.342 (0.043–0.641)	0.025
Time varying				
Diabetes duration × ln(age at census)	−0.186 (−0.283 to −0.090)	<0.001	−0.173 (−0.262 to −0.084)	<0.001
All-cause death				
Age at study entry (increase of 1 year)	−0.099 (−0.176 to −0.022)	0.011		
Heart rate (increase of 1 beat/min)	0.025 (0.013–0.037)	<0.001		
Ln(plasma NT-proBNP) (pmol/L) [†]	0.389 (0.275–0.502)	<0.001		
Current smoker	1.076 (0.618–1.534)	<0.001		
Male sex	0.514 (0.164–0.863)	0.004		
CCI ≥3 [‡]	0.643 (0.187–1.100)	0.006		

[†]A 2.72-fold increase in serum triglycerides or plasma NT-proBNP corresponds to an increased risk of 1 in ln(serum triglycerides) or ln(plasma NT-proBNP), respectively. [‡]CCI was calculated from data during the 5-year period before the study, excluding diabetes-specific variables.

with 1.32 times in 80-year-olds in the Cox model and the sdHR by 6.66 times in 50-year-olds compared with 1.31 times in 80-year-olds in the Fine and Gray model.

CONCLUSIONS

The results confirm a greater risk of cataract surgery in people with type 2 diabetes than in matched people without diabetes, especially in younger age-groups. Sex was not a risk factor for IOL implantation within our type 2 diabetes cohort, but females had a higher risk in our pooled sample after adjusting for diabetes status, age, and CCI. Our competing risk analysis has identified previously reported and novel independent risk factors for cataract surgery in people with type 2 diabetes. Known risk factors comprised age at baseline, diabetes duration, serum triglycerides, and both Asian and southern European ethnicity. A prior severe hypoglycemic episode and an increased serum HDL-C were novel predictors. This risk factor profile provides some insights into the pathophysiology of cataracts and offers potential opportunities for interventions that may reduce the risk of cataracts severe enough to warrant IOL implantation.

Diabetes is an established risk factor for cataracts. A meta-analysis found an odds ratio of 1.97 (95% CI 1.45–2.67) in people with versus those without diabetes (3), which is comparable to the crude

IRR of 1.50 (95% CI 1.32–1.71) for IOL implantation in our sample. A recent U.K. retrospective observational registry study found an IRR of 1.6 (1.5–1.6) for cataract surgery for individuals with newly diagnosed diabetes of unspecified type compared with those without diabetes (21), also close to the crude IRR of 1.50 in the current study. However, the IRs for cataract surgery for both those with (12.4 per 1,000 person-years) and without (7.9 per 1,000 person-years) diabetes were lower in the U.K. study (21) compared with FDS2 (44.8 and 29.8 per 1,000 person-years, respectively). This finding likely reflects the much greater ultraviolet light exposure in Australia than in the U.K.

The Age-Related Eye Disease Study (AREDS) conducted since 1992 in 11 U.S. sites found a 10-year cumulative IR for cataract surgery of 33.6% in people with diabetes and 26.2% in people without diabetes after adjusting for the competing risk of death (27). In the Blue Mountains Eye Study (BMES), which was an Australian study commenced in 1992, the equivalent figures were 20.9% and 17.5% (28). Our 8-year cumulative IRs were 29.3% in FDS2 participants and 20.0% in the matched residents without diabetes. By extrapolating our results, the 10-year cumulative IRs in FDS2 would be 36.6% and 25.0%, respectively, similar to those in AREDS but higher than in BMES. Given that the mean age in BMES was close to that in FDS2 (62.2 vs. 62.8 years),

age does not explain the increased incidence of IOL implantation in the FDS2 participants and matched individuals without diabetes. Our results may reflect a temporal difference in access to care and a declining visual acuity threshold for cataract surgery in Australia, with some patients now having surgery with a visual acuity <6/9 (29). The BMES was conducted at a time when IOL implantation may have been performed at levels of visual impairment that were greater than those in contemporary Australia. Although AREDS also was conducted contemporaneously with BMES, AREDS participants who underwent annual examinations at eye centers may have had greater access to care than BMES participants.

The increased IRR for cataract surgery in younger compared with older people with versus without type 2 diabetes in the current study also was found in a U.K. study of older people with diabetes (most of whom would likely have had type 2 diabetes) in which there was a progressive decrease in IRR (95% CI) from 13.5 (9.0–21.2) in those 45–54 years of age to 1.5 (1.4–1.6) in those 75–84 years of age (21). The consistent age-specific data from these two studies strongly suggest that an early diagnosis of diabetes has a particularly deleterious effect on cataract development compared with a diagnosis later in life.

There is evidence that females are more likely to develop cataracts in the

general population (27,30). We found this association for cataract surgery in a pooled analysis, but sex did not predict IOL implantation in FDS2 participants with type 2 diabetes in an adjusted competing risk model. Only one longitudinal study that assessed risk factors for nuclear cataracts in people with type 2 diabetes found a significant positive association with female sex (11), whereas many others have not (7–10,12–15, 20–22). Overall, these data suggest that the development of cataracts requiring IOL implantation in type 2 diabetes is not influenced by sex.

Aging contributed to lens breakdown and epithelial cell migration *in vitro* (31) and to cataract development in many longitudinal studies of type 2 diabetes (7,8,10–12,14,15,20). Similarly, longer diabetes duration increased the risk of cataracts in two cohort studies (10,21), with a 10% increase in risk of posterior subcapsular cataract for every year of type 2 diabetes (10). Becker et al. (21) showed that compared with those within 2 years of diagnosis, people with diabetes duration 2–4.9 years and ≥ 10 years had adjusted odds ratios of 1.24 and 5.14, respectively. Our study found a time-varying increased risk of IOL implantation with longer duration in a fully adjusted competing risk model in which the effect of longer diabetes duration was attenuated by older age at census. At 50 years of age, sdHRs were 6.66, 4.15, 2.58, and 1.61 for diabetes durations of 20, 15, 10, and 5 years compared with newly diagnosed diabetes with all other risk factors being equal, whereas the equivalent sdHRs were much less at 1.31, 1.22, 1.14, and 1.07 at 80 years of age. Although other studies have reported no association with duration (11,12), the weight of evidence suggests that diabetes duration, perhaps as a surrogate for long-term glycemic exposure, contributes to cataract development in type 2 diabetes, especially in relatively young patients.

In accord with previous general population studies, Asian and southern European ethnicity were associated with an increased risk of cataract surgery in the current study. The Singapore Epidemiology of Eye Diseases Study found a higher prevalence of cataracts in people of Asian ethnicity compared with participants in the BMES (32). An Australian study showed that southern

European-born participants had a higher risk of cortical and mixed cortical-nuclear cataracts than Australian-born participants after adjusting for age (33), perhaps reflecting genetic predisposition (32).

The relationship among lipids, cataract development, and the need for IOL implantation in type 2 diabetes may be complex. A Taiwanese study found that serum triglycerides > 2 mmol/L were associated with a more than doubling of the risk of any cataract (7). Consistent with this observation, we found a highly significant association between serum triglycerides and IOL implantation after adjusting for the competing risk of death. Serum concentrations of triglycerides and HDL-C typically are inversely related, but HDL-C also was independently and positively associated with increased cataract surgery risk in people with type 2 diabetes in the current study. This association has not been reported previously in observational studies. Indeed, a higher serum HDL-C was protective in females in the Beaver Dam Eye Study, although this was not specifically in type 2 diabetes (34). Preclinical studies also have suggested that triglycerides increase the risk of cataracts but that HDL-C may be protective (35).

Participants in the current study had higher serum HDL-C concentrations than previous studies examining the risks of cataracts in people with diabetes (18,36), including the Beaver Dam Eye Study (34) (median 1.1 vs. 1.3 mmol/L in FDS2), suggesting that a deleterious effect of high HDL-C may have been missed in other studies. It is possible that chronic raised HDL-C levels accumulate within the lens with other lipids (37) and that diabetes-associated alterations in HDL-C structure may inhibit its efflux (38). Of note, people with the cholesteryl ester transfer protein gene variant rs2303790, which codes for higher serum HDL-C concentrations, have an increased risk of cataract development compared with people without the mutation (39). Fibrates reduce serum triglycerides and increase HDL-C, which would, on the basis of our data, have opposing influences on cataract formation and thus a likely net neutral effect on IOL implantation. Consistent with this hypothesis, no effect of fenofibrate treatment on cataract development was found in people with type 2 diabetes in the Action to

Control Cardiovascular Risk in Diabetes (ACCORD) Eye Study (19).

We found that a self-reported severe hypoglycemic episode in the year before recruitment doubled the risk of cataract surgery in our participants with type 2 diabetes. This association has not been reported previously in adults, but ketotic hypoglycemia has been associated with cataract development in children (40). Preclinical studies have shown that low glucose levels can induce the unfolded protein response, which leads to cataract development (35). These observations suggest that prior severe hypoglycemia, perhaps as a marker of increased frequency and severity of hypoglycemia, may contribute to cataract development in type 2 diabetes.

The strengths of the current study include a relatively large sample size, a representative community-based cohort, comprehensive assessments, use of a single nationally accredited laboratory, and ascertainment of outcomes from a well-validated data linkage system. In addition, this is the first longitudinal study of IOL implantation for cataracts complicating type 2 diabetes to account for the competing risk of death.

The current study had limitations. First, we relied on hospital coding to ascertain IOL implantation events, which carried the possibility of data recording errors and insufficient detail to ascertain cataract type. Second, cataract surgery may only reflect lens opacities severe enough to impair visual acuity significantly, although the visual acuity threshold prompting surgery may vary between individuals and medical practitioners. Third, because regular ophthalmic review is part of recommended type 2 diabetes management, it is possible that the prevalence of cataracts was underestimated in the matched people without diabetes who are not routinely screened. Finally, no data were available to assess ultraviolet light exposure.

In conclusion, we have shown that type 2 diabetes increases the risk of cataract surgery, particularly in younger people, a subgroup in which multifaceted cataract-prevention strategies could be of substantial benefit. In people with type 2 diabetes, those who have longer diabetes duration, are older, or are of Asian/southern European descent are

at a higher risk of IOL implantation. We identified severe hypoglycemia and hypertriglyceridemia as potentially modifiable risk factors for cataract surgery. Intensified lipid-modifying management and individualized strategies to reduce hypoglycemia thus may be useful in preventing or delaying cataracts in type 2 diabetes.

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