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Risk factors associated with incident cataracts and cataract surgery in the Age Related Eye Disease Study (AREDS). AREDS Report Number 32

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Abstract

Objective—To investigate potential risk factors associated with incident nuclear, cortical, and posterior subcapsular (PSC) cataracts and cataract surgery in participants in the Age-Related Eye Disease Study (AREDS).

Design—Clinic-based prospective cohort study.

Participants—Persons (N=4425), aged 60 to 80 years of age enrolled in a controlled clinical trial of antioxidant vitamins and minerals, AREDS, for age-related macular degeneration (AMD) and cataract.

Methods—Lens photographs were graded centrally for nuclear, cortical, and PSC opacities using the AREDS System for Classifying Cataracts. Type-specific incident cataracts were defined as an increase in cataract grade from none or mild at baseline to a grade of moderate at follow-up, with also a grade of at least moderate at the final visit, or cataract surgery. Cox regression analyses were used to assess baseline risk factors associated with type specific opacities and cataract surgery.

Main Outcome Measures—Moderate cataract was defined as a grade of ≥4.0 for nuclear opacity, ≥10% involvement within the full visible lens for cortical opacity, and ≥5% involvement

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This article contains online-only material. The following should appear online-only: Tables 1 to 3.

of the central 5 mm circle of the lens for PSC opacity. These were graded on baseline and annual lens photographs.

Results—A clinic-based cohort of 4425 persons aged 55–80 years at baseline was followed for an average of 9.8 ± 2.4 years. The following associations were found: increasing age with increased risk of all types of cataract and cataract surgery; males with increased risk of PSC and decreased risk of cortical cataracts; non-whites with increased risk of cortical cataract; hyperopia with decreased risk of PSC, nuclear cataract, and cataract surgery; Centrum use with decreased risk of nuclear cataract; diabetes with increased risk of cortical, PSC cataract, and cataract surgery; higher educational level with decreased risk of cortical cataract; and smoking with increased risk of cortical cataract and cataract surgery. Estrogen replacement therapy in female participants increased the risk of cataract surgery.

Conclusions—Our findings are largely consistent with the results of previous studies, providing further evidence for possible modifiable risk factors for age-related cataract.

Introduction

Age-related cataract is the leading cause of blindness throughout the world,[1,2] and a leading cause of low-vision in the United States.[3] Cataract also remains the most expensive eye disease requiring care in the United States, accounting for over 60% of annual eye-related Medicare spending.[4] The number of people with cataract in the United States is estimated to increase from 20 million in 2000 to 30 million in 2020.[5] Identifying risk factors may help to identify prevention and treatment options that may ultimately lessen the economic and public health burden of this disease.

The Age-Related Eye Disease Study (AREDS) was designed in part to evaluate the natural course of age-related cataract. Previous studies have evaluated risk factors associated with cataract including educational status,[6,7] smoking,[8] diabetes,[9,10] sunlight exposure,[11–13] body mass index,[14–16] drug use,[17–19] and estrogen replacement therapy.[20–22] The AREDS, which followed a large geographically diverse clinic population for nearly 10 years, provides data that complement the results from long-term population-based studies. Data about possible risk factors were collected at baseline and lens photographs were taken annually and graded at a central location.[23] This study examines associations between non-nutritional risk factors and the incidence of nuclear, cortical, and posterior subcapsular (PSC) cataracts, as well as cataract surgery in the AREDS population. Our findings offer possible insights into the pathophysiology of this multifactorial disease, strengthening the case for previously identified potential risk factors and suggesting new associations for further investigation.

Patients and Methods

Study Population

The AREDS was a randomized clinical trial that evaluated the effect of selected nutritional supplements at high doses on the incidence and progression of AMD and cataracts. Details of the study design and methods have been published elsewhere but will be described briefly here.[24] There were 4757 participants enrolled in AREDS from 11 eye care centers specializing in retinal diseases from 1992 through 1998. The Institutional Review Board for each clinical center approved the protocol, and informed consent was obtained from all participants. Enrollment required the media to be sufficiently clear for visualization and photographic documentation of the macula, thus excluding participants with more extensive opacities from enrollment, except in those cases when advanced AMD could be detected at baseline in the presence of lens opacities. All participants were also required to have at least one eye with a visual acuity of 20/30 or better.

For this report, participants who had cataract surgery before the study and participants who had a missing value for any of the covariates were excluded, leaving 4425 participants for analysis. For each of the type specific analyses, participants who had a cataract severity grade of moderate for that type at baseline were also excluded.

Procedures

Questionnaires were used at baseline to collect demographic information, history of smoking and sunlight exposure, body mass index (BMI), weight change since age 20 (gain or loss), medical history, history of specific prescription drugs and non-prescription medication use, and history of vitamin and mineral use. Details on methods of evaluation have been published in an earlier AREDS report.[25] Annual ophthalmic examinations included manifest refraction, best-corrected visual acuity, intraocular pressure, slit-lamp biomicroscopy, and ophthalmoscopy. Height, weight, and blood pressure were measured. Participants were asked about interim cataract surgery at 6 month intervals.

Certified photographers obtained color photographs of the lenses of participants at baseline, at the 2-year follow up visit, and annually thereafter using specially modified Topcon slit-lamp cameras (Topcon Corp, Tokyo, Japan) and Neitz retroillumination cameras (Neitz Instruments Co, Ltd, Tokyo, Japan).

The Age Related Eye Disease System for Classifying Cataracts was used by certified examiners at a central reading center to assess the presence and severity of cataracts.[23] Nuclear opacities were graded using a series of 7 standard photographs with increasingly severe opacification. A grid overlay on the retroillumination photographs was used to estimate the area of lens involvement for PSC and cortical lens opacities. For each type of cataract, specific cut-points were used to define progression to clinically significant cataracts.

Outcome

Moderate cataract was defined here as a grade of ≥4.0 for nuclear, ≥10% involvement within the full visible lens for cortical, and ≥5% involvement of the central 5 mm circle of the lens for PSC. An event was defined as a type-specific opacity progression from a baseline grade of mild (which is less than moderate opacity) or no lens opacity to either 1) a grade of moderate at the final visit following a grade of moderate at any visit or 2) cataract surgery following a grade of moderate at any visit. Cataract surgery, as determined by history and clinical exam, was also analyzed separately.

Statistical Modeling and Analysis

Models were developed separately for each type of opacity and for cataract surgery using Cox proportional hazards regression analysis.[26] The Wei-Lin-Weissfeld method for analyzing repeated measures was applied to take into account the correlation between the two eyes of each participant.[27] We evaluated risk factors previously found to be significantly associated with cataract development. Baseline factors included: age, sex, race, weight change since age 20, smoking status, education, diabetes history, refractive error, sunlight exposure, iris color, anti-inflammatory drug use, thyroid hormone drug use, Centrum use, estrogen use (for women only), AMD category of severity, and opacity-specific baseline grade. We also evaluated the effect of other types of opacity at the time of the type specific events. The variables were defined as in AREDS Report 5.[25]

To develop the final models, we first included all the variables that were significant in age- and sex-adjusted models at a p-value of 0.15. In a multi-step process, variables were entered or removed from the model by comparing the −2 log of the maximized likelihood between

the model with the variable and the model without the variable.[28] We used a p-value of 0.10 for comparing models and obtained a final model that best fits the data. Estrogen replacement therapy among women was evaluated by including it in the final model, restricted to women. From the final models we computed hazard ratios and 95% confidence intervals to assess the effects of the variables. A p-value of 0.05 was considered statistically significant.

The analyses were done using the PHREG procedure of SAS version 9.2 (SAS Institute, Cary, NC).

Results

Baseline characteristics

Table 1, available at http://aaojournal.org, depicts the baseline demographic characteristics of the participants for each analysis. The number of participants analyzed was 4425, 4018, 3934, and 4210, for cataract surgery, nuclear, cortical, and PSC cataract, respectively. Approximately 96% of the study participants were white and 56% were female. The mean age (± standard deviation) was 69 ± 5 years. Eight percent had diabetes and about 12% used nonsteroidal anti-inflammatory drugs (NSAID) or thyroid hormone drugs. All participants were offered Centrum, and two-thirds of the study population elected to take it. Table 2, available at http://aaojournal.org, describes baseline characteristics by eye including iris color, refractive error, and baseline opacity type.

Significant associations with incident cataracts or cataract surgery

Hazard ratios (HR) and 95% confidence intervals (CI) for the risk factors considered in this analysis are shown from the age- and sex-adjusted model (Table 3) and from the final multivariable models (Table 4). Unless otherwise specified, the hazard ratios reported below reflect the fully-adjusted final models, and 95% confidence intervals are provided.

Nuclear cataract—Nuclear cataract was found to be associated with increasing age (HR 1.07, CI 1.06, 1.09), mild nuclear cataract at baseline (HR 6.10, CI 5.30, 7.01), and mild and moderate PSC cataract at follow up (HR 1.46, CI 1.22, 1.75, and HR 1.46, CI 1.19, 1.79, respectively). Those participants who were non-myopic (HR 0.76, CI 0.63, 0.92), using Centrum (HR 0.83, CI 0.73, 0.94), or who had moderate cortical cataract at follow-up (HR 0.55, CI 0.46, 0.66) were less likely to develop moderate nuclear cataracts. The increased risk of nuclear cataracts in females was borderline significant (HR 1.12, CI 0.99, 1.28). While risk factors such as education level, smoking status, iris color, and AMD category achieved statistical significance in the univariate analyses that were adjusted for age and sex (Table 3, available at http://aaojournal.org), they were no longer significant after adjusting for all other covariates in the final model (Table 4).

Cortical cataract—Higher risk of cortical cataract was associated with increasing age (HR 1.05, CI 1.03, 1.06), diabetes (HR 1.31, CI 1.04, 1.66), weight change of middle quintiles (HR 1.20, CI 1.00, 1.43) and top quintile (HR 1.35, CI 1.09, 1.67) compared to lowest quintile, smoking status of current versus never (HR 1.41, CI 1.09, 1.83), and mild cortical cataract at baseline (HR 5.17, CI 4.29, 6.22). Decreased risk was found in those who were male (HR 0.83, CI 0.72, 0.95), white (HR 0.56, CI 0.42, 0.75), had college education (HR 0.77, CI 0.66, 0.91), or had mild (HR 0.79, CI 0.68, 0.92) or moderate (HR 0.43, CI 0.34, 0.54) nuclear cataract at follow-up.

PSC cataract—Increased risk of PSC cataract was associated with increasing age (HR 1.06, CI 1.04, 1.08), male sex (HR 1.32, CI 1.11, 1.58), diabetes (HR 1.71, CI 1.29, 2.27),

increased weight change (highest quintile versus lowest quintile, HR 1.48, CI 1.10,1.97), thyroid hormone use (HR 1.37, CI 1.00, 1.87), mild PSC cataract at baseline (HR 9.94, CI 8.00, 12.35), mild and moderate nuclear cataract at follow-up (HR 1.66, CI 1.29, 2.14, and HR 1.70, CI 1.24, 2.31, respectively), and mild and moderate cortical cataract at follow-up (HR 1.28, CI 1.04, 1.57, and HR 1.69, CI 1.33, 2.17, respectively). Hyperopia was the only significant factor associated with a decreased risk of PSC cataract (HR 0.78, CI 0.61, 0.99).

Cataract surgery—The risk of cataract surgery is associated with increasing age (HR 1.06, CI 1.05, 1.08), diabetes (HR 1.45, CI 1.19, 1.75), having smoked in the past versus never having smoked (HR 1.18, CI 1.05, 1.33), use of non-steroidal anti-inflammatory medications (HR 1.17, 95%CI 1.00, 1.38), and presence of any cataract at baseline. Risk of cataract surgery was inversely associated with hyperopia (HR 0.66, CI 0.57, 0.77) and severe AMD (HR 0.64, CI 0.52, 0.77). Males were less likely to undergo cataract surgery in the age- and sex-adjusted model (HR 0.86, CI 0.77, 0.96), but this was borderline statistically significant in the fully adjusted model (p=0.06). In the final multivariable model, women who had used estrogen replacement therapy at some point ("ever") regardless of duration were found to be at increased risk for cataract surgery compared with those who had never used this therapy (HR 1.22, CI 1.04, 1.43).

Discussion

Risk factors associated with baseline nuclear and cortical cataracts were presented in a previous AREDS report.[25] Using data from up to 12 years of follow-up on this same population, we identified many risk factors that were significantly associated with incident age-related nuclear, cortical and PSC cataracts. Most of our results support previous studies in associating risk with factors such as age, sex, race, education, diabetes, weight change, refraction, smoking, and multivitamin use. Results for some risk factors that have been previously reported, such as sunlight exposure and iris pigmentation, were not statistically significant in this analysis. Slight variations in cataract grading definitions may contribute to some of the different findings between studies.

Associated Risk Factors

Age—Consistent with previous reports of various study populations,[9,29–31] increasing age was a significant risk factor for all types of cataracts and cataract surgery, even after adjusting for all major covariates. The effects of aging may reflect contributions from several factors, such as the accumulation of damage from the environment, the deterioration of defense and repair mechanisms, and genetic predisposition.

Sex and estrogen replacement therapy—Our finding that females are at increased risk of cortical cataract is consistent with previous population-based studies.[6,29,32–34] We also found decreased risk associated with female sex for PSC cataract, which is novel. These findings remain significant even after adjusting for mortality. The association between PSC cataract and male sex may be a chance finding or it may be a true association related to the characteristics of the AREDS population. AREDS participants tended to be older on average than the participants in population-based studies. Probably because of the older age of AREDS participants and the large sample size, we noted a high rate of PSC cataract, providing more power to evaluate this relatively rare type of opacity (Koo, Chang, et al., manuscript in preparation). A separate analysis of the women in our study showed that estrogen replacement therapy had no significant effect on risk of any type of opacity, although it was in the direction of protection for nuclear and cortical cataract, but not for PSC cataract. Estrogen replacement did, however, increase the risk of cataract surgery in the final multivariable analyses.

Race—Although the AREDS population was 96% white, we found race to be significantly associated with the incidence of cortical cataract, with decreased risk in white participants compared to non-white participants, who were mostly African Americans. This finding agrees with data from the Barbados Eye Study, which studied a population that was 93% black and found higher risk of cortical opacities (relative risk (RR) 3.2, CI 1.7–6.2) among black participants compared to white participants.[33] Similarly, the Salisbury Eye Evaluation (SEE) project, in which 26.4% of the population was black, showed a higher risk of cortical cataract in black participants than white participants (odds ratio (OR) 4.0, CI 3.3–4.8).[35] These previous studies did not adjust for diabetes, which may be an important confounder, but data from our fully-adjusted model suggest that race has an effect beyond diabetes. Several prevalence studies have shown that cataracts are more likely to be a cause of vision impairment in blacks than in whites.[36,37] The SEE project also found that white participants were more likely to undergo cataract surgery than the black participants (OR 2.8, CI 1.9, 4.2).[35] Our study showed a borderline significant higher risk of cataract surgery among white participants (HR 1.39, CI 0.98, 1.95). Limited access to health care among non-white populations must be considered as a potential contribution to these racial disparities in visual impairment and cataract surgery rates.

Education—Higher educational levels have been associated with decreased risk of cataract in studies of different populations throughout the world.[6,7,38–42] Our findings are consistent with these previous reports: having graduated from college was associated with decreased risk of cortical cataract in the final model, and was protective for both cortical and nuclear cataract in the age- and sex-adjusted model. The mechanism underlying this association remains unknown, although education is often used as a marker of socioeconomic status and may reflect a wide variety of lifestyle differences and environmental exposures. It is also worth noting that our data showed no association between educational level and rates of cataract surgery.

Smoking—In the AREDS population, current smokers had a significantly higher risk of cortical cataract and former smokers had a higher risk of cataract surgery compared to those who had never smoked. These findings agree with many large cross-sectional and prospective studies.[8,43] It has even been shown that there is a dose-response relationship and that smoking cessation can decrease the risk of cataract.[43] Overall, smoking is one of the most consistently noted modifiable risk factors for cataract progression.

Diabetes—After adjusting for all significant covariates, patients with diabetes were found to have significantly higher risk of cortical and PSC cataracts as well as cataract surgery. Diabetes has been associated with increased risk of cortical and PSC cataracts in several previous studies.[6,10,41,44] Our results for diabetes as a risk factor for cataract surgery differed from the data presented in the Blue Mountains Eye Study (BMES) which showed no significant risk for cataract surgery in diabetics.[45] Longer duration of diabetes may increase the risk of cataract. Though there is much evidence supporting an association between age-related cataracts and diabetes, the increased opportunity for detection of cataracts in the diabetic population due to high referral rates for annual retina exams may also play a role.

Weight Change—Our analysis showed weight change to be a significant risk factor for both PSC and cortical cataract, in agreement with previous studies.[16,45] In the fully adjusted model, participants who had gained or lost 53 or more pounds (≥24 kilograms, the top quintile) compared to those with a weight change of 10 or fewer pounds (≤4.5kg, the bottom quintile) since age 20 were at increased risk of moderate PSC and cortical cataract. Risk of moderate cortical cataract was also higher in participants who had gained or lost more than

10 but less than 53 pounds since age 20. We found no association with nuclear cataract, and previous reports show conflicting results regarding nuclear cataract. The Physicians' Health Study reported increased risk of nuclear cataracts with increased body mass index (BMI)[15] but the SEE Project[14] and the Lens Opacities Case-Control Study[41] reported increased risk associated with low body mass. The Physicians Health Study also showed increased risk of cataract surgery with increased BMI,[15] but in our study, weight change was a significant risk factor for cataract surgery only in the age- and sex-adjusted model.

Refraction—In our study, baseline myopia (≤ −1.0D) was associated with an increased risk of nuclear and PSC cataracts and cataract surgery when compared to hyperopia. Many large population studies have reported associations between refractive error and risk of cataract and/or cataract surgery.[41,46–48] Overall, our findings agree with the results of these previous studies. Both the Blue Mountains Eye Study (BMES)[48] and the SEE Project[46] reported a significantly increased risk of nuclear and PSC cataracts in patients with myopia. In addition, the BMES also reported an increased risk of cataract surgery in those with any severity of myopia. At the 5 year follow-up, the Beaver Dam Eye Study observed a significant increased risk of cataract surgery with myopia in their age- and sex-adjusted analysis (OR 1.89; CI 1.18, 3.04) but a non-significant increased risk in their multivariable analyses (OR 1.60, CI 0.96, 2.64).[47]

Multivitamin use (Centrum)—We found that Centrum use was associated with decreased risk of nuclear cataract. Although one large prospective study of women found no benefit with multivitamin use,[24] the results of our current analysis agree with several observational studies[38,41,49–51] and randomized clinical trials.[52,53] One of these trials had also shown significantly increased risk of PSC with Centrum use,[52] but neither our age- and sex-adjusted model nor the fully-adjusted model shows any significant association between PSC cataract and Centrum use. Our findings are consistent with an earlier report based on propensity score analysis of cataract and Centrum use in the AREDS population.[54] Identifying which ingredients or combinations contribute to the protective effect of Centrum on nuclear cataract remains an area of active investigation.

Medications: non-steroidal anti-inflammatory drugs, including aspirin, and thyroid hormone use—The relationship between nonsteroidal anti-inflammatory drugs (NSAIDs) and cataract remains unclear; several earlier studies suggested a beneficial effect of NSAIDs or aspirin on cataract or cataract surgery rates[18,55,56] but many other studies have found no association.[46–48,57,58] In an earlier case-control analysis of baseline risk factor associations with cataract in the AREDS, a decreased risk of nuclear cataract was associated with NSAIDs, including aspirin, and an increased risk of cortical cataract was associated with thyroid hormone use.[25] In the current analysis, however, NSAIDs were associated with increased risk of cataract surgery, but not with any specific opacity type, and thyroid hormone use was associated with increased risk of PSC cataract, but not cortical cataract. Previous reports on NSAID use and cataract risk have been conflicting,[59,60] and the association with thyroid hormone use requires further investigation. Our current study is notable for having a higher overall rate of PSC than previous studies (Koo, Chang, et al., manuscript in preparation), adding statistical power and potentially accounting for the absence of this observation in other longitudinal studies. Possible confounding variables such as the underlying reasons for NSAID use are not available in our data, and further investigation is needed.

Age-related macular degeneration (AMD)—The multivariable analysis showed a statistically significant decrease in risk for cataract surgery associated with category 4 AMD, but this did not persist for the other categories of AMD. This is likely due to the fact that

AREDS investigators, who are retinal specialists, may have played a role in determining who would be eligible for cataract surgery. Previous studies have shown associations with cataract and AMD,[61,62] but we saw no consistent association between AMD and any specific opacity type in our analysis, in agreement with the BMES.[63]

Associations between opacity types—Our current analysis showed that PSC cataract was significantly associated with mild and moderate nuclear and cortical cataract at follow-up, in both the univariate and the final multivariable model. Similarly, patients with mild or moderate PSC cataract at follow-up had increased risk of nuclear cataract, although there was no significant association with the incidence of cortical cataract. Patients with moderate nuclear cataract at follow-up were less likely to develop cortical cataract, and conversely, patients with mild or moderate cortical cataract at follow-up were less likely to develop nuclear cataract. Few studies have investigated associations between opacity types, and there has been no consistent association between nuclear and cortical cataract.[64] It is known that the various opacity types share some common risk factors, such as age and sex, so it is difficult to determine whether the association between opacities reflects confounding or whether the pathophysiology of one type actually influences the other.

Our findings in this report are largely consistent with previous studies, lending further support to the importance of modifiable risk factors including smoking, education, diabetes, weight change, and multivitamin use. Other consistently noted risk factors include age, sex, race, and refraction. A higher risk of PSC cataract in our study population may account for new and conflicting associations found with sex which warrant further investigation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Baseline characteristics by person

		CataractSurgery		Nuclear		Cortical		PSC	
		N	%	N	%	N	%	N	%
Total		4425	100.0	4018	100.10	3934	100.0	4210	100.0
Agegroup	<65	970	21.9	935	23.3	926	23.5	943	22.4
	65-<70	1499	33.9	1393	34.7	1346	34.2	1429	33.9
	70+	1956	44.2	1690	42.1	1662	42.2	1838	43.7
Sex	Female	2483	56.1	2229	55.5	2186	55.6	2367	56.2
	Male	1942	43.9	1789	44.5	1748	44.4	1843	43.8
Race	Non-White	196	4.4	169	4.2	145	3.7	177	4.2
	White	4229	95.6	3849	95.8	3789	96.3	4033	95.8
Smoke	Never	1983	44.8	1810	45.0	1764	44.8	1895	45.0
	Former	2112	47.7	1922	47.8	1881	47.8	2008	47.7
	Current	330	7.5	286	7.1	289	7.3	307	7.3
Education	Highschool or Less	1554	35.1	1374	34.2	1327	33.7	1450	34.4
	SomeCollege	1336	30.2	1224	30.5	1211	30.8	1286	30.5
	CollegeGraduate	1535	34.7	1420	35.3	1396	35.5	1474	35.0
Weightchange	Lowestquintile [a]	828	18.7	749	18.6	750	19.1	796	18.9
	Middlequintiles	2710	61.2	2450	61.0	2414	61.4	2566	61.0
	Topquintile [b]	887	20.0	819	20.4	770	19.6	848	20.1
Sunlightexposure	Lowestquintile	876	19.8	790	19.7	761	19.3	828	19.7
	Middlequintiles	2664	60.2	2417	60.2	2377	60.4	2541	60.4
	Topquintile	885	20.0	811	20.2	796	20.2	841	20.0
Diabetes	No	4069	92.0	3693	91.9	3628	92.2	3871	91.9
	Yes	356	8.0	325	8.1	306	7.8	339	8.1
Anti-inflammatory drug use	No	3909	88.3	3547	88.3	3475	88.3	3720	88.4
	Yes	516	11.7	471	11.7	459	11.7	490	11.6
Thyroid hormone druguse	No	4108	92.8	3723	92.7	3645	92.7	3904	92.7

		CataractSurgery		Nuclear		Cortical		PSC	
		N	%	N	%	N	%	N	%
	Yes	317	7.2	295	7.3	289	7.3	306	7.3
Centrum use	No	1494	33.8	1351	33.6	1313	33.4	1417	33.7
	Yes	2931	66.2	2667	66.4	2621	66.6	2793	66.3
Estrogenuse (women only)	total	2465	100.0	2213	100.0	2171	100.0	2350	100.0
Estrogenuse – Current[c]	No	1877	76.1	1673	75.6	1631	75.1	1781	75.8
	Yes	588	23.9	540	24.4	540	24.9	569	24.2
Estrogenuse – Ever [d]	No	1656	67.2	1467	66.3	1430	65.9	1567	66.7
	Yes	809	32.8	746	33.7	741	34.1	783	33.3
AMDcategory [e]	1	1082	24.5	1008	25.1	963	24.5	1027	24.4
	2	1007	22.8	920	22.9	913	23.2	966	22.9
	3	1489	33.6	1347	33.5	1329	33.8	1421	33.8
	4	847	19.1	743	18.5	729	18.5	796	18.9

[a] weightchange ≤ 4.5kg since age 20

[b] weightchange ≥ 24 kgsince age 20

[c] womenwho werecurrent users of estrogenreplacement therapy at baseline and whohad morethan 5 lifetime years ofregular use

[d] women whohave ever used estrogen replacementtherapy, regardlessof duration (“Ever”)

[e] AMD Category:**1** : fewif anydrusen; **2** :extensive small drusen, pigment abnormalities, orat least 1 intermediate size druse; **3** :at least one largedruse and/or extensive intermediate drusen, or geographic atrophy (GA) not involving the center of the macula; **4**:GA involving center of maculaor neovascular maculopathy inone eye orvisual acuity <20/32 due to AMD inone eye.

PSC =posterior subcapsular;AMD = Age-relatedmacular degeneration; GA = geographic atrophy.

Table 2

Baseline characteristics by eye

		Cataract Surgery	Nuclear	Cortical	PSC
		%	%	%	%
Total eyes		100.0	100.0	100.0	100.0
Iris color	Light	27.3	27.7	28.0	27.6
	Other	60.1	59.9	60.0	60.0
	Dark	12.6	12.4	12.0	12.4
Refractive error	≤-1.0D	17.2	16.3	17.2	16.6
	Other	49.0	49.6	49.3	49.5
	≥1.0D	33.9	34.1	33.5	33.9
Nuclear cataract at baseline	≤2	52.8	58.5	54.5	54.1
	>2, <4	38.1	41.5	37.1	37.6
	≥4	9.1		8.2	8.2
Cortical cataract at baseline	0	33.6	34.1	37.8	34.1
	>0, <10%	55.5	55.4	62.2	55.7
	≥10%	10.9	10.4		10.2
PSC cataract at baseline	<0.1	93.7	94.3	94.4	95.1
	≥0.1, <5%	4.9	4.6	4.6	4.9
	≥5%	1.4	1.0	1.0	

D = Diopter; PSC = Posterior Subcapsular.

Table 3

Age- and sex-adjusted hazard ratios and 95% confidence intervals

RiskFactor	Exposure	Surgery	Nuclear	Cortical	PSC
Age	Oneyear increase	**1.10 (1.09,1.11)***	**1.11 (1.10,1.12)***	**1.05 (1.04,1.07)***	**1.09 (1.07,1.11)***
Sex	Male	**0.86 (0.77,0.96)***	**0.81 (0.72,0.92)***	**0.82 (0.72,0.94)***	**1.20 (1.01,1.41)***
Race	White	1.01(0.75, 1.35)	1.10(0.79, 1.55)	**0.52 (0.39,0.69)***	1.20(0.72, 2.00)
Education[a]	Somecollege	1.02(0.89, 1.16)	0.89(0.77, 1.03)	0.90(0.77, 1.05)	0.85(0.69, 1.04)
	Collegegraduate	0.96(0.84, 1.09)	**0.79 (0.68,0.92)***	**0.74 (0.63,0.87)***	0.86(0.70, 1.05)
Smokingstatus [b]	Former	**1.17 (1.05,1.31)***	1.04(0.91, 1.19)	1.04(0.91, 1.19)	1.09(0.91, 1.31)
	Current	1.22(0.97, 1.52)	**1.45 (1.15,1.83)***	**1.33 (1.04,1.72)***	1.31(0.93, 1.84)
Diabetes	Yes	**1.43 (1.19,1.72)***	1.08(0.86, 1.36)	**1.39 (1.11,1.74)***	**1.70 (1.30,2.21)***
Weightchange [c]	Middlequintiles	1.10(0.95, 1.27)	0.96(0.82, 1.13)	1.13(0.95, 1.35)	1.21(0.96, 1.52)
	Topquintile	**1.24 (1.04,1.47)***	1.02(0.84, 1.25)	**1.38 (1.12,1.70)***	**1.59 (1.21,2.08)***
Sunlightexposure [c]	Middlequintiles	0.96(0.84, 1.10)	0.90(0.77, 1.05)	0.98(0.83, 1.16)	0.98(0.79, 1.22)
	Topquintile	0.87(0.73, 1.03)	0.85(0.70, 1.04)	1.06(0.87, 1.30)	0.92(0.70, 1.20)
Iriscolor [d]	Other	**1.16 (1.03,1.31)***	1.04(0.91, 1.19)	**1.18 (1.02,1.37)***	1.07(0.89, 1.29)
	Dark	1.19(0.99, 1.42)	**1.34 (1.10,1.63)***	**1.55 (1.25,1.91)***	1.25(0.94, 1.65)
Refractiveerror [e]	Other	**0.61 (0.53,0.70)***	1.00(0.84, 1.20)	1.10(0.91, 1.32)	0.81(0.65, 1.02)
	≥1.0D	**0.59 (0.51,0.69)***	**0.79 (0.65,0.95)***	0.97(0.80, 1.19)	**0.78 (0.62,0.99)***
Centrumuse	Yes	**0.90 (0.80,1.00)***	**0.84 (0.74,0.95)***	0.93(0.81, 1.07)	0.96(0.81, 1.15)
Anti-inflammatorydrug use	Yes	1.10(0.94, 1.29)	0.93(0.77, 1.12)	0.90(0.73, 1.11)	1.11(0.88, 1.42)
Thyroidhormone use	Yes	1.02(0.84, 1.25)	1.03(0.83, 1.28)	1.04(0.82, 1.33)	**1.39 (1.04,1.85)***
Estrogenuse [b]	Current	1.12(0.95, 1.31)	0.90(0.74, 1.09)	0.86(0.71, 1.05)	1.15(0.88, 1.50)
	Ever	**1.18 (1.02,1.37)***	0.97(0.81, 1.15)	0.92(0.77, 1.10)	1.21(0.94, 1.55)
AMD category[f]	2	0.95(0.81, 1.11)	**0.82 (0.68,0.97)***	0.94(0.79, 1.13)	1.12(0.88, 1.43)
	3	1.08(0.93, 1.25)	0.89(0.76, 1.04)	0.98(0.83, 1.16)	1.04(0.82, 1.31)
	4	**0.79 (0.66,0.95)***	0.95(0.79, 1.15)	0.90(0.73, 1.11)	1.14(0.88, 1.48)
Nuclearcataract at baseline [g]	>2, <4	**1.70 (1.52,1.90)***	**6.05 (5.28,6.95)***		
	≥4	**3.48 (2.95,4.10)***			
Corticalcataract at baseline [h]	>0, <10%	**1.41 (1.26,1.58)***		**5.23 (4.35,6.30)***	

RiskFactor	Exposure	Surgery	Nuclear	Cortical	PSC
	≥10%	**2.16 (1.82,2.56)***			
PSC cataractat baseline [i]	≥0.1,<5%	**2.88 (2.44,3.39)***			**10.42 (8.46,12.82)***
	≥5%	**7.59 (5.57,10.34)***			
Nuclearcataract at follow - up[g]	>2, <4			**0.81 (0.69,0.94)***	**1.67 (1.29,2.15)***
	≥4			**0.42 (0.34,0.53)***	**1.99 (1.48,2.67)***
Corticalcataract at follow - up[h]	>0, <10%		1.08(0.95, 1.23)		**1.38 (1.13,1.70)***
	≥10%		**0.56 (0.46,0.67)***		**1.88 (1.49,2.36)***
PSC cataractat follow -up[i]	≥0.1,<5%		**1.48 (1.25,1.76)***	0.91(0.74, 1.11)	
	≥5%		**1.47 (1.21,1.78)***	1.00(0.79, 1.27)	

Age- and sex-adjusted hazard ratios and 95% confidence intervals for models that use both eyes (Wei-Lin-Weissfeld method). Hazard ratios significant at $p \leq 0.05$ appear in bold and are marked with an asterisk. D = Diopter; AMD = Age-related Macular Degeneration; PSC = Posterior Subcapsular.

[a] Referent: high school or less;

[b] Referent: never;

[c] Referent: lowest quintile;

[d] Referent: light iris color;

[e] Referent: ≤−1.0D;

[f] Referent: AMD category 1;

[g] Referent: Nuclear cataract grade ≤ 2;

[h] Referent: 0% of visible lens area;

[i] Referent: <0.1% of central 5 mm.

Table 4

Hazard ratios and 95% confidence intervals for the final models

Risk Factor	Exposure	Surgery	Nuclear	Cortical	PSC
Age	One year increase	**1.06 (1.05, 1.08)***	**1.07 (1.06, 1.09)***	**1.05 (1.03, 1.06)***	**1.06 (1.04, 1.08)***
Sex	Male	0.90 (0.80, 1.01)	0.89 (0.78, 1.01)	**0.83 (0.72, 0.95)***	**1.32 (1.11, 1.58)***
Race	White	1.39 (0.98, 1.95)		**0.56 (0.42, 0.75)***	
Education[a]	Some college			0.87 (0.74, 1.02)	
	College graduate			**0.77 (0.66, 0.91)***	
Smoking[b]	Former	**1.18 (1.05, 1.33)***		1.01 (0.88, 1.17)	
	Current	1.14 (0.89, 1.46)		**1.41 (1.09, 1.83)***	
Diabetes	Yes	**1.45 (1.19, 1.75)***		**1.31 (1.04, 1.66)***	**1.71 (1.29, 2.27)***
Weight change[c]	Middle quintiles			**1.20 (1.00, 1.43)***	1.25 (0.98, 1.60)
	Top quintile			**1.35 (1.09, 1.67)***	**1.48 (1.10, 1.97)***
Refractive error[d]	Other	**0.68 (0.59, 0.79)***	**0.83 (0.69, 0.99)***		0.90 (0.71, 1.13)
	≥1.0D	**0.66 (0.57, 0.77)***	**0.76 (0.63, 0.92)***		**0.78 (0.61, 0.99)***
Centrum use	Yes		**0.83 (0.73, 0.94)***		
Anti-inflammatory drug use	Yes	**1.17 (1.00, 1.38)***			
Thyroid hormone use	Yes				**1.37 (1.00, 1.87)***
Estrogen use[b]	Current	1.16 (0.99, 1.37)	0.89 (0.73, 1.09)	0.85 (0.69, 1.04)	1.19 (0.90, 1.59)
	Ever	**1.22 (1.04, 1.43)***	0.95 (0.80, 1.14)	0.93 (0.77, 1.12)	1.24 (0.95, 1.61)
AMD category[e]	2	0.96 (0.82, 1.13)			
	3	1.06 (0.92, 1.22)			
	4	**0.64 (0.52, 0.77)***			
Nuclear cataract at baseline[f]	>2, <4	**1.71 (1.53, 1.92)***	**6.10 (5.30, 7.01)***		
	≥4	**3.28 (2.77, 3.89)***			
Cortical cataract at baseline[g]	>0, <10%	**1.39 (1.24, 1.56)***		**5.17 (4.29, 6.22)***	
	≥10%	**2.12 (1.77, 2.54)***			
PSC cataract at baseline[h]	≥0.1, <5%	**2.54 (2.15, 2.99)***			**9.94 (8.00,12.35)***
	≥5%	**5.28 (3.73, 7.46)***			
Nuclear cataract at follow-up[f]	>2, <4			**0.79 (0.68, 0.92)***	**1.66 (1.29, 2.14)***

Risk Factor	Exposure	Surgery	Nuclear	Cortical	PSC
	≥4			**0.43 (0.34, 0.54)***	**1.70 (1.24, 2.31)***
Cortical cataract at follow-up[g]	>0, <10%		1.07 (0.94, 1.22)		**1.28 (1.04, 1.57)***
	≥10%		**0.55 (0.46, 0.66)***		**1.69 (1.33, 2.17)***
PSC cataract at follow-up[h]	≥0.1, <5%		**1.46 (1.22, 1.75)***		
	≥5%		**1.46 (1.19, 1.79)***		

Hazard ratios and 95% confidence intervals for the final multivariable models that use both eyes (Wei-Lin-Weissfeld method) for cataract surgery, nuclear, cortical, and PSC cataract. Hazard ratios significant at $p \leq 0.05$ appear in bold and are marked with an asterisk. D = Diopter; AMD = Age-related Macular Degeneration; PSC = Posterior Subcapsular.

[a] Referent: high school or less;

[b] Referent: never;

[c] Referent: lowest quintile;

[d] Referent: ≤ −1.0D;

[e] Referent: AMD category 1;

[f] Referent: Nuclear cataract grade ≤ 2;

[g] Referent: 0% of visible lens area;

[h] Referent: <0.1% of central 5 mm.