Pseudoexfoliation Syndrome and the Long-Term Incidence of Cataract and Cataract Surgery: The Blue Mountains Eye Study

GOWRI L. KANTHAN, PAUL MITCHELL, GEORGE BURLUTSKY, ELENA ROCHTCHINA, AND JIE JIN WANG

• PURPOSE: To assess whether the pseudoexfoliation syndrome (PXS) is associated with the long-term incidence of cataract or cataract surgery.
• DESIGN: Population-based cohort study.
• METHODS: The Blue Mountains Eye Study examined 3654 persons 49 years of age and older at baseline; 2564 were re-examined after 5 or 10 years, or both. PXS was recorded at the baseline eye examination by an ophthalmologist. Masked graders assessed lens photographs using the Wisconsin Cataract Grading System. Generalized estimating equation regression models were used to examine the association between PXS and cataract by eye.
• RESULTS: Eyes with PXS had a significantly greater prevalence of cortical cataract ($P = .02$) and nuclear cataract ($P < .0001$) than eyes without PXS. The association between PXS and cortical cataract, however, did not persist after further adjustment for age, gender, smoking, diabetes, steroid use, myopia, socioeconomic status, and open-angle glaucoma (odds ratio [OR], 0.89; 95% confidence interval [CI], 0.53 to 1.46), whereas the association between PXS and nuclear cataract persisted after adjustment for the above confounders (OR, 1.90; 95% CI, 1.04 to 3.48). In addition, significant associations were found between the presence of PXS at baseline and the 10-year incidence of either nuclear cataract ($P < .0001$) or cataract surgery ($P < .0001$). These associations persisted after adjustment for the potential confounders listed above (OR, 3.25; 95% CI, 1.38 to 7.65; and OR, 4.09; 95% CI, 2.25 to 7.44; respectively). No significant cross-sectional or longitudinal associations were found between PXS and posterior subcapsular cataract.
• CONCLUSIONS: Long-term follow-up data from this population-based older cohort suggest that the presence of PXS is associated with an increased risk of nuclear cataract and cataract surgery. (Am J Ophthalmol 2013;155: 83–88. © 2013 by Elsevier Inc. All rights reserved.)

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CATARACT IS THE MOST FREQUENT EYE DISEASE IN the elderly population.[1] Despite recent improvements in surgical techniques and subsequent outcomes,[2] cataract remains the leading cause of mild to moderate visual impairment in the developed world.[3]

Pseudoexfoliation syndrome (PXS) is characterized by the production and progressive accumulation of a fibrillar extracellular material in ocular and extraocular tissues.[4,5] In the eye, PXS is characterized clinically by small white deposits of material in the anterior segment, most commonly on the pupillary border and anterior lens capsule. It is the most common identifiable cause of open-angle glaucoma, and in some countries accounts for most open-angle glaucoma cases.[6]

Findings from previous cross-sectional studies examining the association between PXS and cataract have been inconsistent.[7–14] Nevertheless, both the prevalence of PXS and cataract are strongly associated with age, and PXS is known to be associated with open-angle glaucoma,[6] which, together with glaucoma surgery, can be independent risk factors for cataract.[15–17] Therefore, the apparent association between PXS and cataract, reported by some previous studies could be the result of the confounding effects of age and open-angle glaucoma. In addition, longitudinal studies are needed to establish a causal association between preceding exposures and subsequent development of cataract.

We aimed in this study to assess associations between the presence of PXS at baseline examinations of the Blue Mountains Eye Study cohort and the prevalence and long-term incidence of cataract and cataract surgery, after adjusting for several potential confounders, including open-angle glaucoma.

METHODS

• STUDY POPULATION: Details of the Blue Mountains Eye Study population and its methods are reported elsewhere.[1,17–19] In brief, the Blue Mountains Eye Study is a population-based cohort study of vision and common eye diseases in an urban older population comprising 2 postcode areas in the Blue Mountains region, west of Sydney, Australia. This geographically well-defined area has a stable population that is reasonably representative of

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Australia in socioeconomic status and other measures. All residents 49 years of age or older of these 2 postcode areas were eligible and were invited to participate in the survey.

At baseline examinations (1992 through 1994), 4433 eligible residents were identified, of whom 3654 (82.4%) were interviewed and examined. Baseline differences between participants and nonparticipants were reported previously.[18] All surviving participants were invited for re-examination after 5 years (1997 through 1999) and 10 years (2002 through 2004), with 2335 (75.1% of survivors) and 1952 (75.6% of survivors) returning for re-examinations at these times, respectively. Altogether, 2564 participants were followed-up at least once since their baseline examinations.

Comparisons of participants and nonparticipants at each follow-up examination have been reported previously.[1] Nonparticipants were significantly younger ($P < .0001$), were more likely to be current smokers ($P < .0001$), and were more likely to have been diagnosed with diabetes ($P = .049$). They also were more likely to report lower job prestige index ($P = .041$) and were less likely to live in their own home ($P = .0006$) than those who participated in follow-up examinations.[1]

The study was approved by the University of Sydney and Western Sydney Area Health Service Human Research Ethics Committees. Written informed consent was obtained from all participants.

• **PROCEDURES:** An interviewer-administered questionnaire was used to collect detailed demographic and medical history data at each visit. All participants underwent detailed eye examinations. Slit-lamp lens photographs of each eye were obtained using Ektachrome 200 color film (Kodak, Rochester, New York, USA) on a Topcon SL-7E photograph slit-lamp camera (Topcon, Tokyo, Japan) to assess the presence of nuclear cataract. Retroillumination lens photographs were obtained using a Neitz CT-R cataract camera (Neitz Instruments, Tokyo, Japan) to assess the presence of cortical cataract and posterior subcapsular (PSC) cataract.

Presence of pseudoexfoliation was recorded at baseline eye examination as described previously.[19] After pupil dilatation, a detailed high-magnification slit-lamp assessment of the anterior segment was performed by means of a narrowed slit beam by 1 observer (P.M.) on all participants. The anterior lens surface from each eye was scanned from left to right, looking specifically for early signs of PXS, including pregranular radial lines,[20,21] as well as established granular deposits. Presence of specific anterior segment abnormalities was recorded, including the presence of exfoliative material on the anterior lens surface or on the pupil margin, with the latter useful in pseudophakic eyes.

Intraocular pressure was measured using applanation tonometry. Glaucoma was diagnosed from characteristic visual field loss combined with optic disc cupping and rim thinning without reference to intraocular pressure.[19] Refractive error was assessed using autorefraction, followed by subjective best-corrected refraction. At the 5-year and 10-year follow-up visits, participants were re-examined in approximately the same order as that at baseline, using the same procedures and equipment.

The Wisconsin Cataract Grading System,[22] first developed in 1990 for use in the Beaver Dam Eye Study, was followed closely in performing masked grading of all lens photographs obtained at each visit. Intergrader and intragrader reproducibility of the lens photograph grading was assessed using quadratic weighted κ statistics and was shown to be within an acceptable range in our study.[1,23]

Incident cataract was defined as the appearance of nuclear, cortical, or PSC cataract subtypes in bilaterally phakic participants, in which the corresponding cataract subtype was not present in either eye at baseline. Similarly, incident cataract surgery was defined as cataract surgery performed in either eye of participants who were bilaterally phakic at baseline.

Progression of nuclear cataract was defined as an increase of 1.0 or more in the grading score of nuclear opacity. Progression of cortical cataract was defined as an increase of at least 10% of the lens area affected by the cortical cataract. Progression of PSC cataract was defined as an increase of at least 2% of the lens area affected by PSC cataract.

• **STATISTICAL ANALYSIS:** SAS software (SAS Institute, Cary, North Carolina, USA) was used for data analysis. Generalized estimating equation regression models and eye-specific data were used to assess associations between the presence of pseudoexfoliation at baseline and the prevalence and 10-year incidence of cortical, nuclear, and PSC cataract or cataract surgery. Potential confounders adjusted for included age, gender, diabetes, smoking, steroid use, myopia, socioeconomic status, and open-angle glaucoma. Supplemental analyses using competing risk models considering competing event of death also were performed using subject-specific data and the SAS macros function.[24] Findings are presented as odds ratios (ORs) with 95% confidence intervals (CIs).

RESULTS

TABLE 1 SHOWS THE EYE-SPECIFIC PREVALENCE OF PXS stratified by age and gender. Of the 7308 eyes examined at baseline, 120 (1.64%) had PXS. In men, 38 (1.20%) of 3164 eyes had PXS, and in women, 82 (1.98%) of 4144 eyes had PXS. The prevalence of PXS increased steadily with age from 0% in the youngest group (49 to 54 years of age) to 6.25% in the oldest group (85 years of age and older) of the study population.

Table 2 shows the cross-sectional association between PXS and either cataract or cataract surgery at the baseline examination. Eyes with PXS had a significantly greater

TABLE 1. Prevalence of Pseudoexfoliation Syndrome in the Blue Mountains Eye Study Population

	Male		Female		Total	
Age Group (y)	n/N[a]	%	n/N[a]	%	n/N[a]	%
49 to 54	0/430	0	0/540	0	0/970	0
55 to 64	6/1026	0.58	13/1318	0.99	19/2344	0.81
65 to 74	17/1054	1.61	31/1364	2.27	48/2418	1.99
75 to 84	14/558	2.51	22/746	2.95	36/1304	2.76
85 and older	1/96	1.04	16/176	9.09	17/272	6.25
Total	38/3164	1.20	82/4144	1.98	120/7308	1.64

[a]Number of eyes with pseudoexfoliation/total number of eyes.

prevalence of both cortical cataract ($P = .02$) and nuclear cataract ($P < .0001$) compared with eyes without PXS. The association between PXS and cortical cataract prevalence, however, did not persist after further adjustment for age, gender, smoking, diabetes, steroid use, myopia, socioeconomic status, and open-angle glaucoma (OR, 0.89; 95% CI, 0.53 to 1.46), whereas the association between PXS and nuclear cataract prevalence persisted after further adjustment for the above confounders (OR, 1.90; 95% CI, 1.04 to 3.48). No significant associations were found between PXS and the prevalence of either PSC cataract or cataract surgery ($P = .18$ and $P = .14$, respectively).

Table 3 shows the associations between PXS at baseline and the 10-year incidence of the 3 cataract subtypes and cataract surgery. No associations were found between PXS and the incidence of cortical or PSC cataract ($P = .18$ and $P = .19$, respectively). However, baseline PXS was associated significantly with the 10-year incidence of nuclear cataract ($P < .0001$). This association persisted after adjusting for age, gender, smoking, diabetes, steroid use, myopia, socioeconomic status, and open-angle glaucoma (OR, 3.25; 95% CI, 1.38 to 7.65). In addition, PXS was associated significantly with the 10-year incidence of cataract surgery ($P < .0001$). This association also persisted after adjusting for the potential confounders listed above (OR, 4.09; 95% CI, 2.25 to 7.44). When we repeated the analysis after excluding eyes with glaucoma, the association of PXS with nuclear cataract (adjusted OR, 3.22; 95% CI, 1.38 to 7.55) and cataract surgery (adjusted OR, 3.91; 95% CI, 2.10 to 7.26) remained significant. Furthermore, when the analysis was repeated using person-specific data, similar associations were observed between PXS and nuclear cataract (OR, 3.20; 95% CI, 1.37 to 7.48) and cataract surgery (OR, 4.12; 95% CI, 2.27 to 7.49; Table 4). Competing risk models incorporating the probability of competing event of death provided the same risk estimates for the associations (data not shown).

No significant associations were observed between PXS at baseline and the long-term progression of the different cataract subtypes (Table 5).

DISCUSSION

IN THIS COHORT STUDY OF OLDER AUSTRALIANS, WE found that the presence of pseudoexfoliation at baseline was significantly associated with increased prevalence and long-term incidence of nuclear cataract, as well as the long-term incidence of cataract surgery in affected eyes.

Early evidence for a possible association between PXS and cataract came from clinic-based case-control studies.[23–26] Several population-based cross-sectional studies also have examined the association between PXS and cataract with inconsistent findings.[7–14] A cross-sectional study conducted in Finland reported that PXS was associated with cataract only in men.[9] Another Finnish study reported lens opacities twice as frequently in eyes with PXS than in fellow eyes without PXS.[12] A study from Saudi Arabia showed that eyes with PXS had significantly more advanced cataract changes than eyes without this sign.[8] In a study of an Australian Aboriginal population, 81% of participants with PXS had cataract.[7] In the eastern Mediterranean area of Turkey, persons with PXS had a significantly higher prevalence of cataract than persons without PXS.[14] A population-based cross-sectional study in south India reported that nuclear cataract was more prevalent in persons with PXS than in persons without PXS.[10] In another south Indian population, 26% of persons with PXS were found to be blind in both eyes, and 89% of this blindness was the result of cataract.[11] The Kandy Eye Study also reported a significant association between PXS and the prevalence of nuclear cataract in a central Sri Lankan population.[13] In the Framingham Eye Study, PXS was associated with more frequent senile lens changes, but this relationship was not statistically significant.[25] Cross-sectional data from the Melbourne Visual Impairment Project, however, did not show any significant association between PXS and cataract after multivariate adjustment.[26]

Very few longitudinal studies have examined the relationship between PXS and cataract.[27] A 5-year follow-up study examining the development of lens opacities in 63 patients with unilateral PXS found that eyes with PXS developed significantly higher levels of lens opacity compared with fellow eyes without PXS.[27]

An association between PXS and the development of cataract is biologically plausible. Electron microscopic examination of the iris vasculature in eyes with PXS revealed multiple abnormalities, including deposits of pseudoexfoliation material lying adjacent to the vascular endothelial wall, thin vessel basement membrane, sometimes even interrupted, extreme reduction of vessel lumina through increased volume of the endothelial cells and fenestration of the vascular endothelial wall.[28] Another study showed that the rate of aqueous flow through the anterior chamber was lower in eyes affected by PXS than in control eyes.[29] A third study confirmed impairment of

TABLE 2. Associations between Pseudoexfoliation Syndrome and the Prevalence of Cataract, by Eye

Cataract Type	PXS Absent n/N[a]	PXS Absent %	PXS Present n/N[a]	PXS Present %	Univariate *P* Value	Multivariate Adjusted[b] Odds Ratio (95% Confidence Interval)
Cortical	1182/6604	17.90	28/105	26.67	**.02**	0.89 (0.53 to 1.46)
Nuclear	705/4525	15.58	26/82	31.71	**<.0001**	**1.90 (1.04 to 3.48)**
Posterior subcapsular	258/6632	3.89	7/110	6.36	.18	NI
Cataract surgery	323/7175	4.50	2/120	1.67	.14	NI

NI = not included in the multivariate-adjusted model as the univariate model was not statistically significant; PXS = pseudoexfoliation syndrome.

Significant *P* values (<.05) appear in boldface.

[a]Number of eyes with cataract/number of eyes at risk.

[b]Adjusted for age, gender, diabetes, steroid use, smoking, myopia, socioeconomic status, and open-angle glaucoma.

TABLE 3. Associations between Baseline Pseudoexfoliation Syndrome and the Long-Term Incidence of Cataract, by Eye

Cataract Type	PXS Absent n/N[a]	PXS Absent %	PXS Present n/N[a]	PXS Present %	Univariate *P* Value	Multivariate Adjusted[b] Odds Ratio (95% Confidence Interval)
Cortical	641/3808	10.62	2/31	4.44	.18	NI
Nuclear	658/2730	16.04	15/26	45.45	**<.001**	**3.25 (1.38 to 7.65)**
Posterior subcapsular	191/4196	2.84	0/39	0.0	.19	NI
Cataract surgery	564/4841	11.65	26/56	46.43	**<.0001**	**4.09 (2.25 to 7.44)**

NI = not included in the multivariate-adjusted model as the univariate model was not statistically significant; PXS = pseudoexfoliation syndrome.

Significant *P* values (< .05) appear in boldface.

[a]Number with cataract/number at risk.

[b]Adjusted for age, gender, diabetes, steroid use, smoking, myopia, socioeconomic status, and open-angle glaucoma.

TABLE 4. Associations between Baseline Pseudoexfoliation Syndrome and the Long-Term Incidence of Cataract, by Person

Cataract Type	PXS Absent n/N[a]	PXS Absent %	PXS Present n/N[a]	PXS Present %	Univariate *P* Value	Multivariate Adjusted[b] Odds Ratio (95% Confidence Interval)
Cortical	395/1773	22.3	4/24	16.7	.51	NI
Nuclear	380/1241	30.6	11/18	61.1	**.0055**	**3.20 (1.37 to 7.48)**
Posterior subcapsular	139/2002	6.9	0/28	0.0	.14	NI
Cataract surgery	344/2406	14.3	21/42	50.0	**<.0001**	**4.12 (2.27 to 7.49)**

NI = not included in the multivariate-adjusted model as the univariate model was not statistically significant; PXS = pseudoexfoliation syndrome.

Significant *P* values (< .05) appear in boldface.

[a]Number with cataract/number at risk.

[b]Adjusted for age, gender, diabetes, steroid use, smoking, myopia, and socioeconomic status.

the blood-aqueous barrier in eyes affected with PXS at the level of the iris and, to a lesser extent, at the level of the ciliary body.[30] Lens metabolism depends on the aqueous. Alterations in the iris vasculature and blood-aqueous barrier could affect the composition of the aqueous and subsequently could affect the lens metabolism, resulting in cataract formation.

Some studies have suggested that open-angle glaucoma is a possible risk factor for cataract.[15–17] In addition, it is possible that medical or surgical treatment for glaucoma

TABLE 5. Associations between Baseline Pseudoexfoliation Syndrome and the Long-Term Progression[a] of Cataract, by Eye

Cataract Type	PXS Absent		PXS Present		Univariate
	n/N[b]	%	n/N[b]	%	*P* Value
Cortical	275/1251	22.0	3/12	25.0	.80
Nuclear	378/706	53.5	5/8	62.5	.61
Posterior subcapsular	35/1232	2.8	0/12	0.0	.55

PXS = pseudoexfoliation syndrome.
[a]Defined as an increase of 1.0 or more in the grading score of nuclear opacity or an increase of at least 10% of the lens area affected by the cortical cataract or an increase of at least 2% of the lens area affected by posterior subcapsular cataract.
[b]Number with cataract/number at risk.

also may increase the risk of cataract.[31] Because PXS is a risk factor for open-angle glaucoma,[6] glaucoma may confound the association between PXS and cataract. Nevertheless, the association found in our study between PXS and nuclear cataract and cataract surgery remained significant after adjusting for open-angle glaucoma. In addition, when we repeated the analysis after excluding eyes with glaucoma, the association of PXS with nuclear cataract and cataract surgery remained significant. This suggests that PXS may contribute to the development of cataract through a pathway different from that responsible for elevated intraocular pressure or open-angle glaucoma and the need for glaucoma treatment.

It is also possible that people with PXS are likely to visit their eye care providers on a regular basis because of other complications such as glaucoma. Therefore, their lens opacities would have been more likely to be diagnosed and operated on at an earlier stage. Nevertheless, such detection bias cannot explain the association found between PXS and nuclear cataract, because the diagnosis of nuclear cataract was made via masked photographic grading of lens photographs in the study.

Patients with PXS are at increased risk of intraoperative and postoperative complications from cataract surgery. PXS causes zonular fragility, leading to a higher risk of dropped lens. In addition, eyes with PXS dilate poorly, making surgery technically difficult. As a result, eyes with PXS have a significantly higher rate of operative complications such as capsular rupture, zonular dehiscence, and vitreous loss.[4] Furthermore, PXS has been shown to increase the incidence of posterior capsular opacification after cataract surgery.[32] The present study shows that PXS also may increase the incidence of cataract and cataract surgery.

We did not find any significant associations between PXS and long-term progression of cataract (Table 5). This is possibly the result of the effect of cataract surgery, because most eyes that had significant progression of cataract over the long term would have undergone cataract surgery, and hence would have been excluded from the analysis for cataract progression.

We presented eye-specific data to provide evidence supporting a longitudinal association between pre-existing PXS and subsequent development of cataract in the same eye. Nevertheless, when we repeated the analysis using person-specific data, the findings were similar (Table 4). Similarly, when competing risk models were used incorporating the probability of competing event of death, the findings remained unchanged.

Strengths of this study include its long-term follow-up of participants with reasonable surveillance rates, consistency of the methods used at the baseline and follow-up examinations to assess cataract, and documentation of many potential confounders that were able to be adjusted for in analyses. In addition, cataract was diagnosed via photographic grading of lens photographs, whereas all other information of the participants was masked to the graders. Limitations of our study also should be noted. Although our study sample had a reasonably large number of participants, only a small proportion of subjects had PXS. Our study thus might have lacked adequate power to detect weak associations between PXS and cortical or PSC cataract. The association found in our study between PXS and nuclear cataract and cataract surgery should be interpreted with caution, and confirmation from other studies is needed. Although we adjusted for age, gender, smoking, diabetes, myopia, socioeconomic status, steroid use, and open-angle glaucoma, other unknown confounders could not be ruled out.

In summary, long-term follow-up data from this older Australian population-based cohort suggest that PXS may be a risk factor for both nuclear cataract and cataract surgery. The biological plausibility for an association between PXS and the development of cataract, together with the consistency in findings between our study and those of previous cross-sectional studies from other populations, provide further and stronger evidence to support this association.

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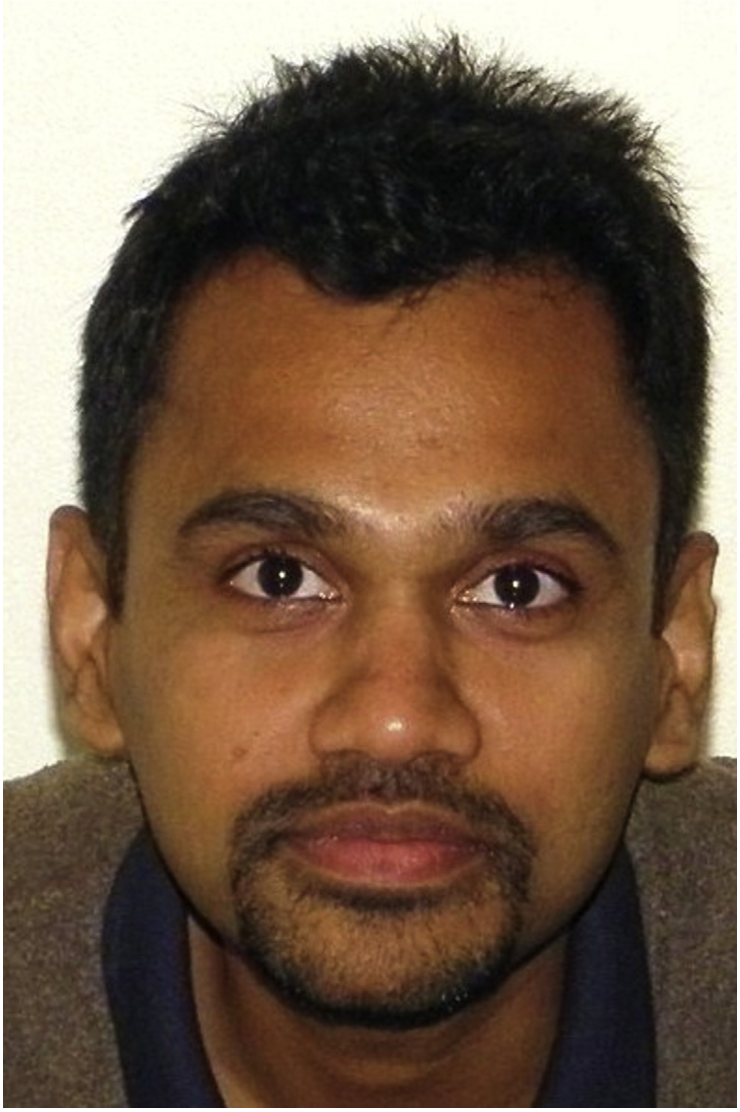

Biosketch

Gowri L. Kanthan completed his medical degree at the University of New South Wales and subsequently completed two Masters degrees in Clinical Epidemiology and Ophthalmic Science. He worked as an ophthalmology registrar at Canberra Hospital for a year. He is currently a PhD candidate at the University of Sydney, Australia. His current research aims at determining the long-term incidence of cataract in the Blue Mountains Eye Study population and exploring the risk factors for incident cataract.